University of Southampton

Department of Chemistry

The Total Synthesis of Tetrahydrolipstatin

by

Joanne Lerpiniere

A thesis submitted for
the degree of
Master of Philosophy

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To my husband, Phil and my Mum and Dad.

"Chemistry, especially, has always had irresistible attractions for me, from the enormous, the illimitable power which the knowledge of it confers. Chemists, I assert it emphatically, might sway, if they pleased, the destinies of humanity."

Wilkie Collins.

Contents.

Acknowledgements.

I would like to thank all my colleagues within the chemistry department especially those I shared a laboratory with, for there support and assistance. My special thanks go to Andy Kohler for proof reading this work.

I gratefully acknowledge the Science and Engineering Research Council for financially supporting this project.

Finally my deepest gratitude is to my husband, Phil, whose support and guidance has been so invaluable to me.

Abbreviations.

Ac	Acetate.
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binapthyl.
Bn	Benzyl.
b.p.	Boiling point.
Bu	Butyl.
Bz	Benzoyl.
CAN	Ceric ammonium nitrate.
Cbz	Carbobenzyloxy.
CI	Chemical ionisation.
DCC	1,3-Dicyclohexylcarbodiimide.
DCM	Dichloromethane.
DEAD	Diethyl azodicarboxylate.
DiBAIH	Di-*iso*-butylaluminium hydride.
DIPT	Di-*iso*-propyl tartrate.
DMAP	4-Dimethylaminopyridine.
DME	Ethylene glycol dimethyl ether.
DMF	N,N-Dimethylformamide.
DMSO	Methylsulphoxide.
Et	Ethyl.
h	Hour.
HMPA	Hexamethylphosphoramide.
i -	*iso*-.
IR	Infra red.
L	Ligand.
LDA	Lithium di-*iso*-propylamide.
MCPBA	*meta*-Chloroperbenzoic acid.
Me	Methyl.

min	Minutes.
mol. sieves	Molecular sieves.
m. p.	Melting point.
MRNi	Modified Raney nickel.
m/s	Mass spectrum.
NMR	Nuclear magnetic resonance.
NOE	Nuclear Overhauser effects.
OTf	Trifluoromethanesulphonate.
p	*Para.*
P	Unspecified protecting group.
Ph	Phenyl.
Pr	Propyl.
PPTS	Pyridinium *p*-toluenesulphonate.
Py	Pyridine.
rt	Room temperature.
Sia	Siamyl.
s-	*secondary*-.
t-	*tertiary*-.
TBAF	Tetrabutylammonium fluoride.
TBDMS	*tert*-Butyldimethylsilyl.
TBHP	*tert*-Butyl hydroperoxide.
THF	Tetrahydrofuran.
THP	Tetrahydropyranyl.
TLC	Thin layer chromatography.
TMS	Trimethylsilyl.
Tosyl	*p*-Toluenesulphonyl.
Ts	See tosyl.

UNIVERSITY OF SOUTHAMPTON.

ABSTRACT

FACULTY OF SCIENCE

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The Total Synthesis of Tetrahydrolipstatin

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An asymmetric synthesis of tetrahydrolipstatin, a pancreatic lipase inhibitor, is described. The β-lactone moiety of tetrahydrolipstatin was prepared *via* a Lewis acid induced cycloaddition of a homochiral hydroxy aldehyde to a silyl ketene. Subsequent manipulation of the silylated β-lactone formed, afforded tetrahydrolipstatin. Three routes to the homochiral hydroxy aldehyde are described, each method using different procedures to induce the chirality of the hydroxyl group. The most elegant and preferred procedure for the formation of the homochiral hydroxy aldehyde, induces the chirality enantioselectively using a Sharpless asymmetric epoxidation of an allylic alcohol.

Preface.

The research described in this thesis was carried out at the University of Southampton between October 1989 and September 1992. No part of this thesis has previously been submitted for a degree at this or any other University, except where specific acknowledgement has been made.

Chapter One

Chapter One.

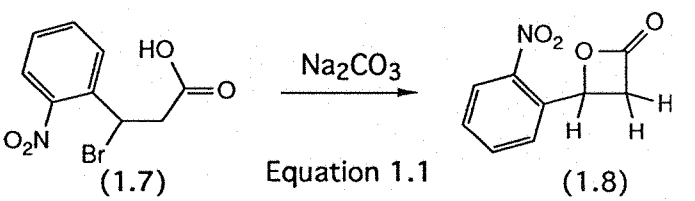
Methods of Formation of β-Lactones.

History of β-Lactones.

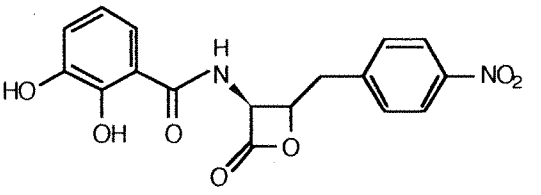
The β-lactone moiety, or 2-oxetanone, consists of a highly strained four-membered heterocyclic ring. They differ from five and six membered lactones, in both their reactivity and methods of formation. Unlike δ- and γ-lactones, they can not be formed by thermal dehydration of the corresponding hydroxy acids. The presence of a highly reactive carbonyl group in such a strained structure makes these compounds particularly susceptible towards nucleophilic attack. β-Lactones are also readily thermolysed with loss of carbon dioxide to form the corresponding olefin. Two excellent reviews dealing with the formation and reactions of β-lactones have been published[1,2].

The simplest 2-oxetanone, β-propiolactone, is readily available commercially and for this reason much of the work in the literature has concentrated on the reactions and properties of this β-lactone. Although for many years β-lactones have been considered important in polymer science, it is only recently that the pharmaceutical industry has become interested in these types of structures. This current interest stems from the recent discovery of a series of biologically active natural products containing four membered lactones, for example obafluorin (1.1)[3], lipstatin (1.2)[4,5], valilactone (1.3)[6], L-659,699 (or 1233A) (1.4)[7] and ebelactones A and B (1.5 and 1.6)[8,9] (figure 1.1).

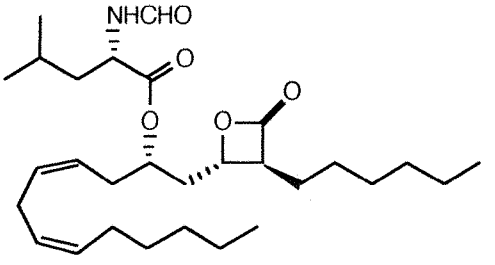
The first isolation of a β-lactone was reported in 1883 by Einhorn, who treated β-bromo-*o*-nitrohydrocinnamic acid (1.7) with sodium carbonate to afford the β-lactone (1.8) in 40% yield (equation 1.1)[10]. Although β-lactones had been postulated before this time as intermediates in a large number of reactions, their thermal instability had prevented their isolation.



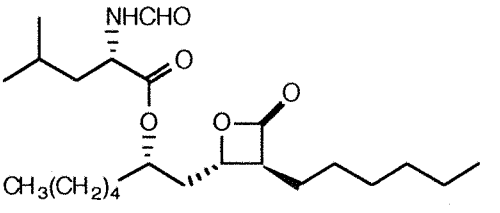
(1.7) Equation 1.1 (1.8)



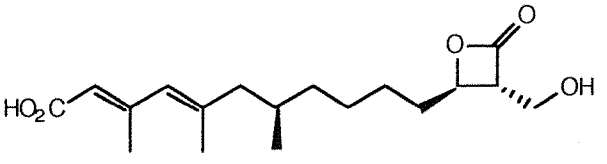
Obafluorin (1.1)



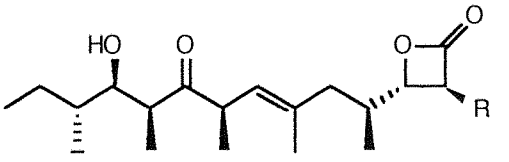
Lipstatin (1.2)



Valilactone (1.3)



L-659,699 (1.4)
(1233A)



Ebelactone A R = Me (1.5)
Ebelactone B R = Et (1.6)

Figure 1.1

Since then a great deal of work has been done on the preparation and reactions of 2-oxetanones. Much of the work has centred on the decarboxylation and polymerisation of β-lactones. 2-Oxetanones readily decarboxylate at elevated temperatures stereospecifically to form substituted olefins. With the development of new synthetic methods for the stereoselective formation of β-lactones, this opens up the possibility of using β-lactones as latent olefins, which are held in a fixed conformation. As the reaction is almost quantitative, this offers a good alternative to the Wittig reaction, especially for the synthesis of tri- and tetra-substituted alkenes[11-14].

The polymerisation of β-lactones is an area of research that has received a great deal of attention. The polymerisation can be induced using a variety of initiators, which can be either acidic or basic. The mechanism of the polymerisation reaction is thought to be ionic and can be either anionic or cationic depending upon the initiator[15,16]. The majority of the published work has concentrated on anionic polymerisation. Some

oxetanones, particularly β-propiolactone, are known to polymerise explosively without the need for an initiator.

Formation of β-Lactones.

Many new synthetic methods for the formation of β-lactones have been published, but few have found wide application in synthetic work. There are only three general methods for the formation β-lactones:-

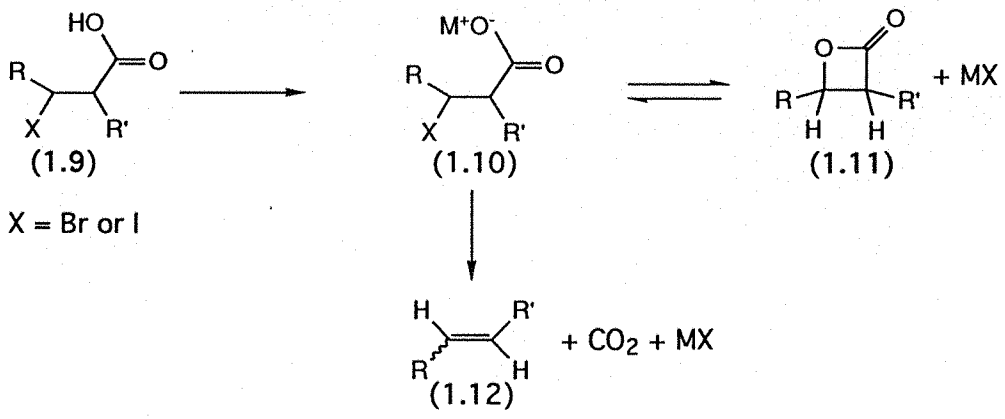
i) The treatment of β-halogeno acids with basic reagents.

ii) The cycloacylation of β-hydroxy acids.

iii) The cycloaddition of ketenes with carbonyl compounds, this reaction is usually facilitated by the addition of a Lewis acid.

β-Lactones from β-Halogeno Acids.

The first β-lactone to be isolated was made by treating β-bromo-*o*-nitrohydrocinnamic acid with sodium carbonate. Treatment of the halogeno acid with a base causes a displacement of the halogen *via* an S_N2 mechanism resulting in an inversion of configuration at the site of attack. The very early work on β-lactones relied on this method of formation, using either β-bromo or β-iodo acids as the starting materials. The ring closure was accomplished using a wide variety of bases varying from potassium acetate to sodium hydroxide, although the most widely used reagents were sodium hydroxide, sodium carbonate in water or moist silver oxide in ether[2]. As β-lactones can be easily hydrolysed in alkaline conditions, care must be taken to ensure that only enough base is used to form the salt of the acid. Excess base also tends to increase the amount of α,β-unsaturated acid formed by dehydrohalogenation of the β-halogeno acid. Another and often more important side reaction is the tendency of the β-halogeno acid (1.9) to decompose to the ethylene (1.12) producing carbon dioxide and the metal halide (scheme 1.1)[2]. This type of



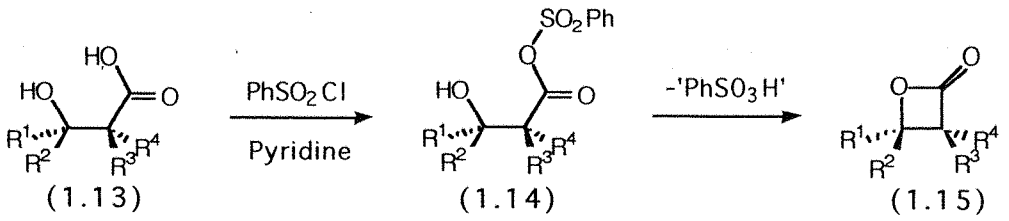
Scheme 1.1

displacement method is now rarely used and has been generally superseded by cycloacylation.

β-Lactones from the Cycloacylation of β-Hydroxy Acids.

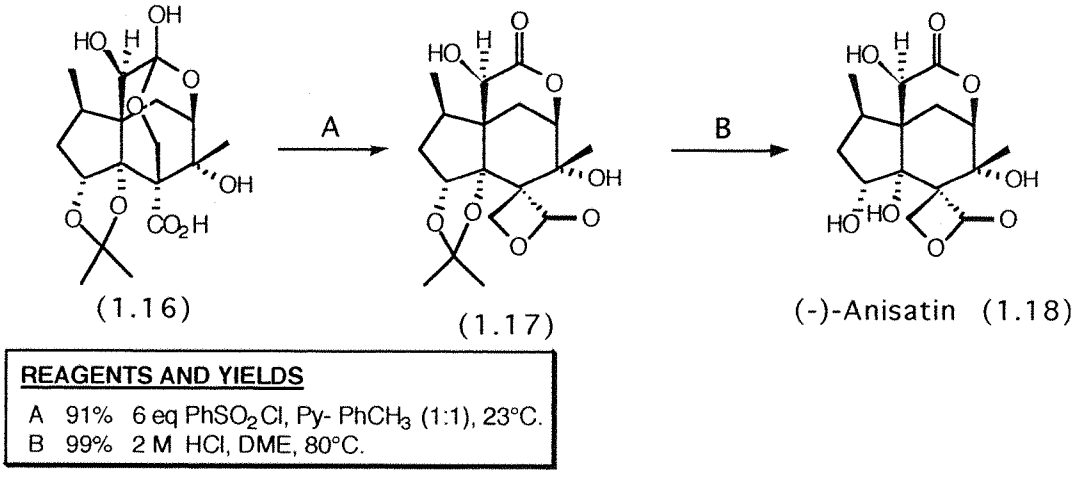
The ring closure of hydroxy acids, induced by activation of the acid group to attack, has now replaced the above method as the main route to the formation of β-lactones. Modern organic chemistry and more especially medicinal chemistry requires reactions in which the stereochemistry of the product can be easily controlled and predicted. There are in the literature, many methods reported for the formation of chiral β-hydroxy acids and this is one reason for the popularity of the cycloacylation method.

Of all the methods for inducing the cyclisation of the hydroxy acids the most reliably high yielding and therefore the most popular method was developed by Adam and co-workers in 1972 by adapting a procedure of Brewster-Ciotti for the formation of esters[12]. Brewster-Ciotti had prepared esters, derived from acid sensitive alcohols or carboxylic acids, by treating the acids with benzenesulphonyl chloride in pyridine in the presence of the alcohol[17]. Adam found that this method could be extended to the formation of 2-oxetanones. By modifying the work up procedure they were able to form β-lactones from β-hydroxy acids in high yields (scheme 1.2). The mechanism is presumed to involve the formation of a mixed anhydride (1.14) which is then attacked



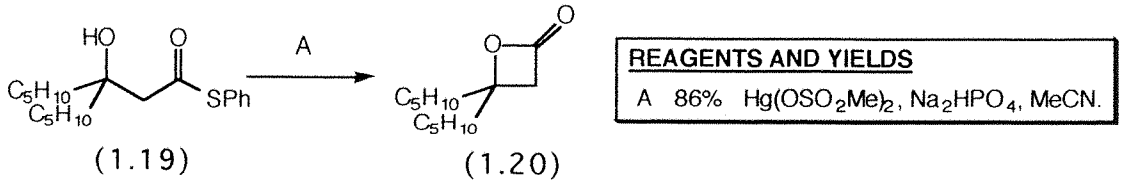
Scheme 1.2

by the hydroxyl group, this results in a retention of configuration at the ring junctions. This procedure was used by Niwa and co-workers in the synthesis of (-)-anisatin[18], a neurotoxic sesquiterpenoid containing a spiro-β-lactone (scheme 1.3) and by Barbier and co-workers in the synthesis of tetrahydrolipstatin (see later).



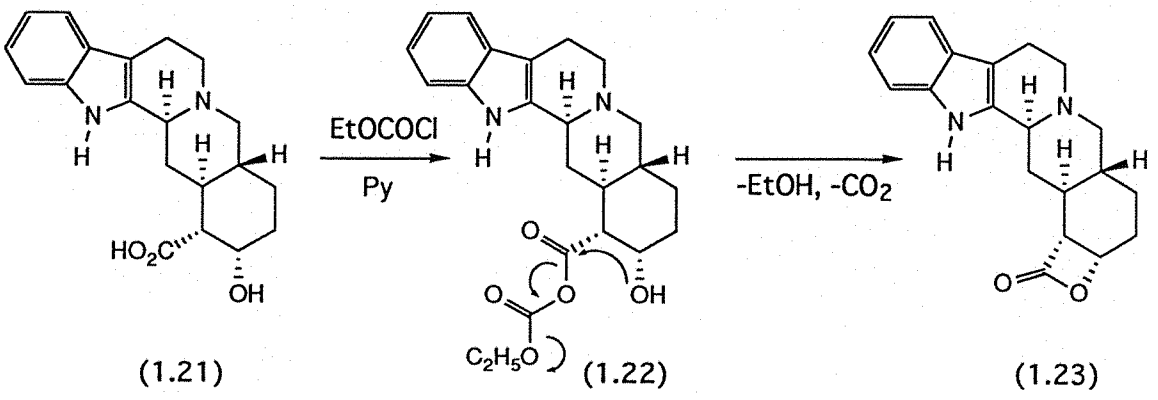
Scheme 1.3

Other methods of inducing cycloacylation by the activation of β-hydroxy acids have been reported; these include the transformation of the acids into benzenethio esters and the activation of the acid with ethyl choroformate, tosyl chloride or 4-bromobenzenesulphonyl chloride. In the first of these the carboxylic acid was converted into the benzenethio ester (1.19), which was then treated with two equivalents of mercury (II) methanesulphonate in the presence of sodium hydrogen



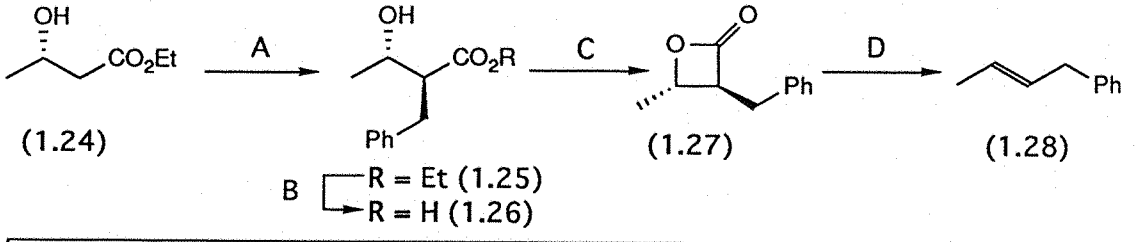
Equation 1.2

phosphate, after ten minutes the β-lactone was formed in good yield (equation 1.2)[19]. The use of ethyl chloroformate to activate the carbonyl to attack was reported in 1958 by Diassi and co-workers in the formation of β-yohimbine (1.23) from yohimbine[20]. They treated yohimbine (1.21), a β-hydroxy acid, with ethyl chloroformate in



Scheme 1.4

pyridine to form the required β-lactone in 35% yield (scheme 1.4). Another high yielding method of activating the carbonyl group towards cycloacylation was reported in 1984 by Fráter and co-workers (scheme 1.5)[21]. Fráter, whilst working on the



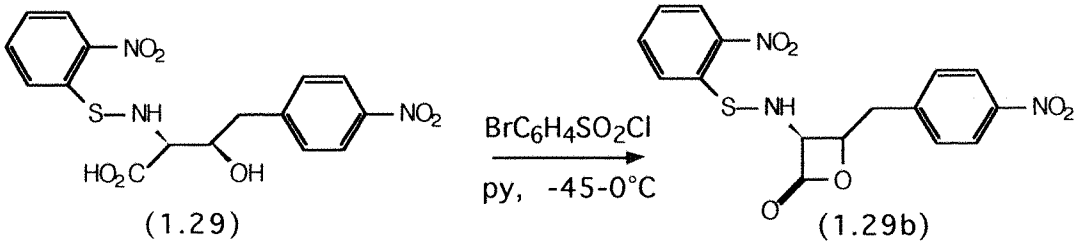
REAGENTS AND YIELDS

A 82% i) 2 eq LDA, THF, -50- -20°C. ii) BnBr, HMPA, 0°C.
B 85% KOH, H_2O-EtOH (1:1).
C 82% TsCl, Py, -5- 0°C.
D 85% 150-160°C.

Scheme 1.5

stereoselective α-alkylation of chiral β-hydroxy esters, chose to determine the configuration of the alkylated product by forming the β-lactone. Hydrolysis of the ester followed by treatment of the hydroxy acid with tosyl chloride in pyridine formed the β-lactone (1.27) in 82% yield. From the coupling in the proton NMR and more particularly from the analysis of the pyrolysis product (1.28) they were able to determine the stereochemistry of the product of α-alkylation of a chiral β-hydroxy

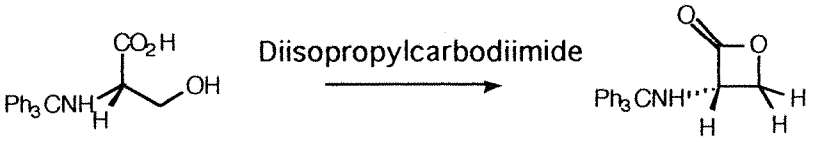
ester. In 1992 Vederas and co-workers synthesised (+)-obafluorin (1.1), an antibiotic natural product containing a β-lactone moiety, from the β-hydroxy acid. The cyclisation was accomplished by treating the hydroxy acid (1.29) with 4-bromobenzenesulphonyl chloride in pyridine, to afford the β-lactone (1.29b) in yields of between 45 and 56% (equation 1.3)[22].



(1.29) (1.29b)

Equation 1.3

Serine is a readily available naturally occurring β-hydroxy acid and a variety of methods for converting serine into β-lactones have been reported. In 1959 Sheehan *et al.* reported the cyclisation of N-trityl-L-serine (1.30) with 1,3-diisopropylcarbodiimide in 15% yield (equation1.4)[23]. Sheehan's method was



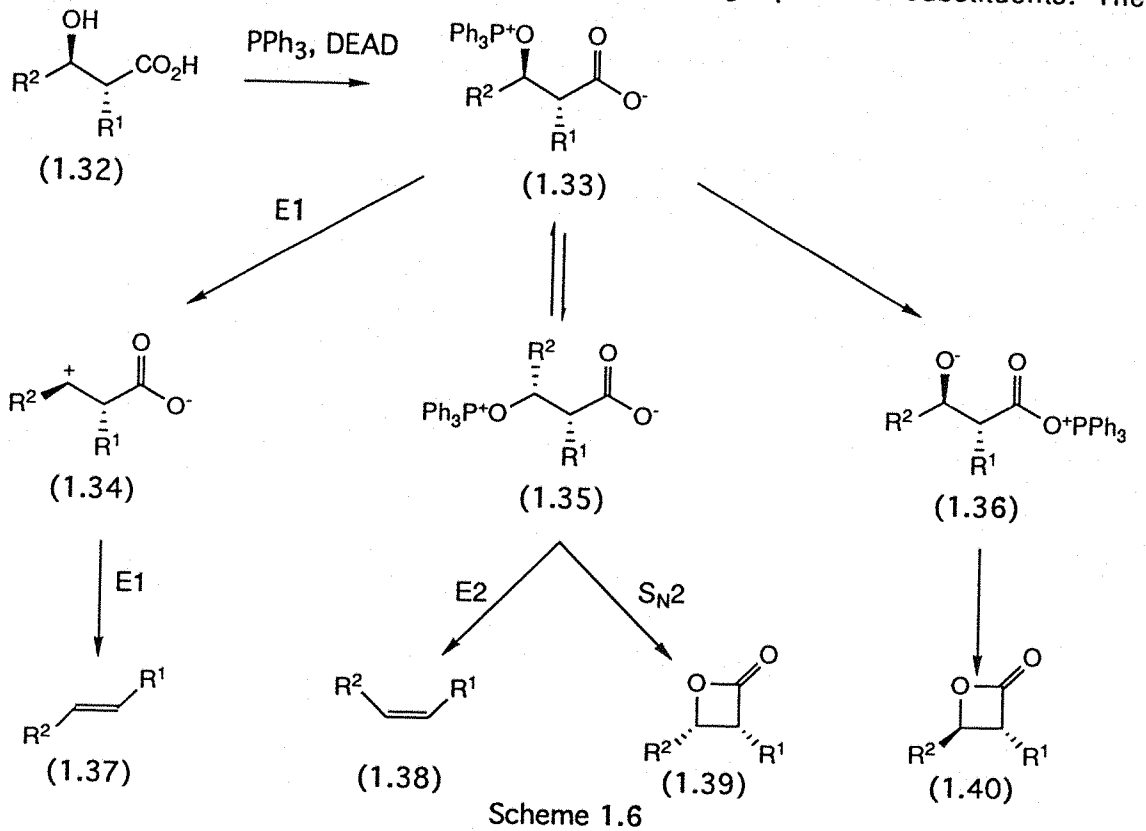
(1.30) (1.31)

Equation 1.4

later modified by using 4-dimethylaminopyridine as a catalyst and 1,3-diisopropylcarbodiimide[24] or 1,3-dicyclohexylcarbodiimide[25] as the activating reagent, but neither of these methods resulted in a significant increase in the yield. Serine can be cyclised in high yields, up to 81%, using Mitsunobu conditions at low temperature, to form the β-lactone[26].

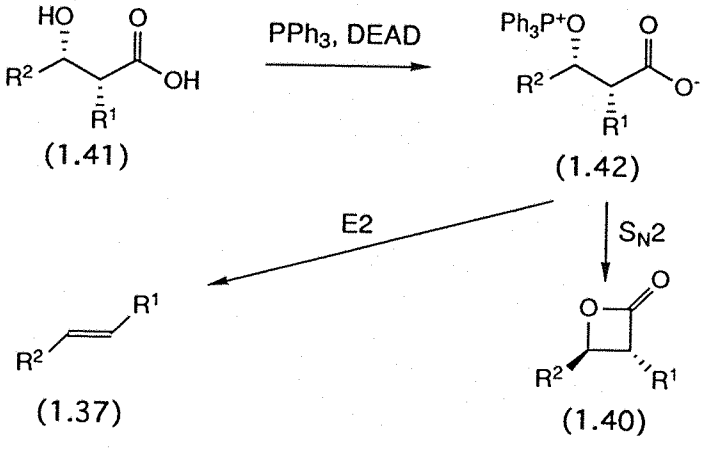
Other methods for the formation of β-lactones from hydroxy acids have been reported but these have not been generally applied to synthetic work. Mulzer and co-workers in 1979 reported the formation of β-lactones from β-hydroxy acids using Mitsunobu conditions[27]. In their work they found that *threo*-hydroxy acids (1.32)

formed a mixture of the (*E*)- and (*Z*)-alkenes and the *cis*- and *trans*-β-lactones (scheme 1.6), the ratio of the products depending upon the substituents. The



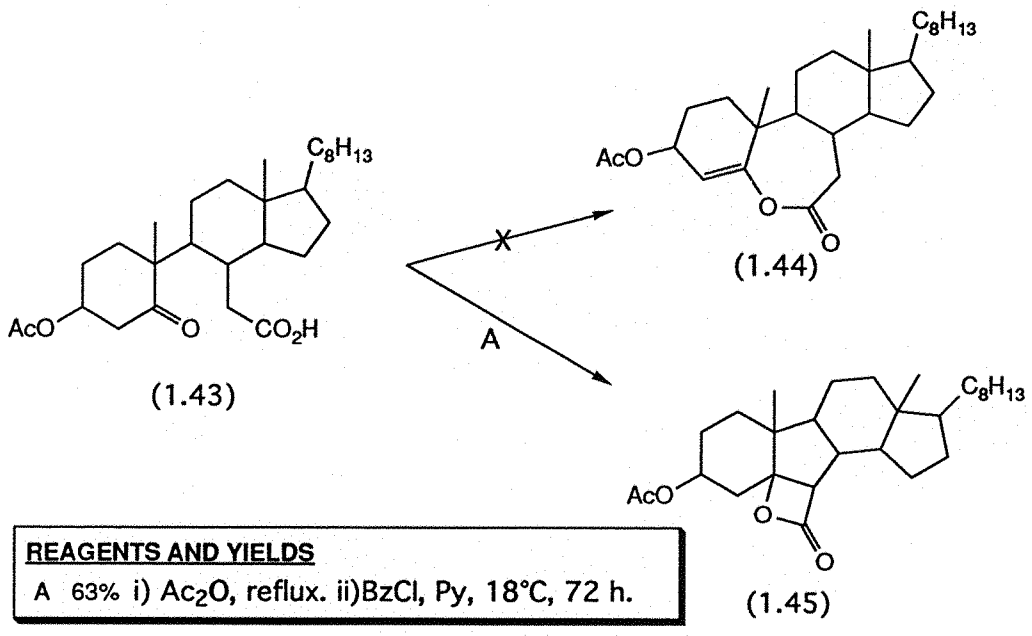
Scheme 1.6

mechanism involves a competition between activation of the hydroxyl (1.35) or carbonyl (1.36) group, and if R^2 has a high +M effect, such as phenyl, the zwitterionic structure (1.34). The *erythro*-hydroxy acids (1.41) react exclusively by hydroxyl group activation and therefore only give the (*E*)-alkene and the *trans*-β-lactone (scheme 1.7).



Scheme 1.7

In 1948 Sorm and co-workers inadvertently formed a β-lactone upon treating (1.43) with benzoyl chloride in pyridine. They assigned the product as the seven membered lactone (1.44)[28]. Later Boswell repeated this work and proved the product had been incorrectly assigned and in fact the β-lactone (1.45) had been formed (scheme 1.8)[29].

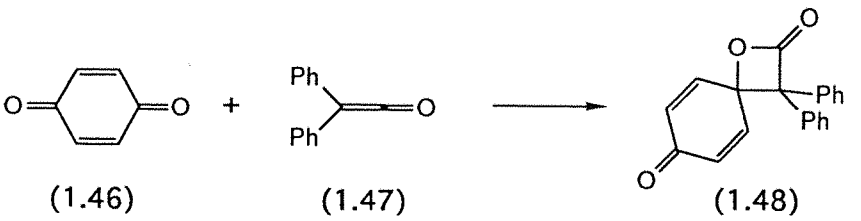


REAGENTS AND YIELDS
A 63% i) Ac_2O, reflux. ii)BzCl, Py, 18°C, 72 h.

Scheme 1.8

β-Lactones from Cycloaddition.

The third general method for the formation of β-lactones is the cycloaddition of carbonyl compounds with ketenes. The first example of this reaction was reported in 1908 by Staudinger who reacted aldehydes with diphenyl ketene at elevated temperatures. On maintaining the temperature between 120 and 180°C, until the evolution of carbon dioxide had ceased, they isolated diphenylethylenes as the sole products[30]. It was postulated that a β-lactone had been formed, which on heating had undergone decarboxylation to form the isolated products. Later, in 1911, Staudinger and Bereza reported the isolation of the β-lactone (1.48) from the reaction between benzoquinone and diphenyl ketene, the reaction occurred at room temperature without the need for any catalyst (scheme 1.9)[31].

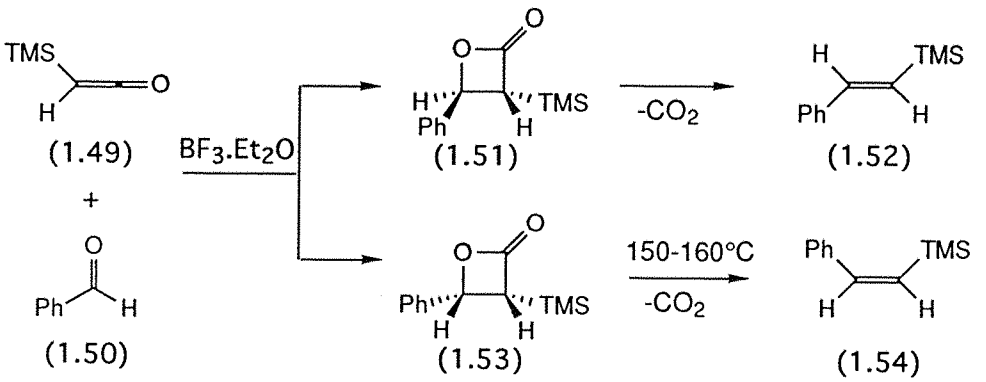


(1.46) (1.47) (1.48)

Scheme 1.9

In the forties and fifties a great deal of work was published, especially in the patent literature, on the reaction between carbonyl compounds and ketenes to form β-lactones[2]. This method is still used as the industrial process for the formation of β-propiolactone, from ketene and formaldehyde. Although no catalyst is required when using diphenylketene, the cycloaddition reaction generally requires the addition of a catalyst. A wide range of catalysts have been used, from dry Fuller's earth to urananyl chloride, but the most frequently used are Lewis acids such as boron trifluoride etherate or zinc chloride. Both ketones and aldehydes can react with ketene but more active Lewis acids are required to catalyse the reaction with ketones.

In 1974 Zaitseva and co-workers reported the reaction between trimethylsilyl-ketene and benzaldehyde in the presence of boron trifluoride etherate to form a mixture of the *cis*- and *trans*-β-lactones (1.53 and 1.51). On heating these underwent decarboxylation to give the corresponding trimethylstyrylsilanes (scheme 1.10)[32]. This work was followed up in 1978 by the same group, who reported the



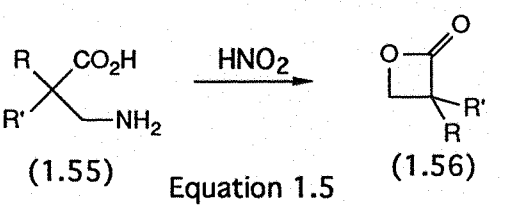
Scheme 1.10

reaction of both silyl and germylketenes with a wide range of aldehydes and ketones[33]. Shortly after this publication, a second group reported similar work[34]. This work will

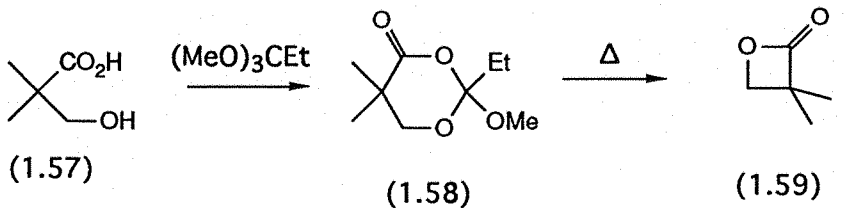
be covered in more detail later.

Other Methods for the Formation of β-Lactones.

Other methods for the formation of β-lactones have been published but these methods have been less generally applied in synthetic work. In 1961 Testa and co-workers synthesised 2-oxetanones by treating α-substituted β–aminopropionic acids (1.55) with nitrous acid (equation 1.5)[35]. Later Blume and co-workers formed β-lactones by thermolysis of 4-oxo-1,3-dioxane (1.58). The dioxane was formed by the uncatalysed reaction of β-hydroxy acids with an *ortho*-ester at



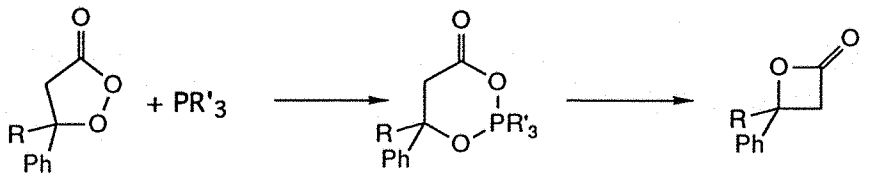
(1.55) Equation 1.5 (1.56)



(1.57) (1.58) (1.59)

Scheme 1.11

50-100°C (scheme 1.11)[36]. In 1969 Adam reported the formation of β-lactones from the reaction of β-peroxy lactones with phosphines (scheme 1.12)[37].

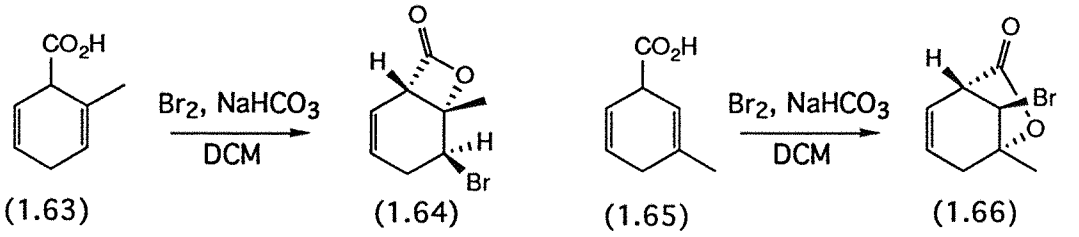


(1.60) (1.61) (1.62)

Scheme 1.12

Halolactonisation of β,γ-unsaturated acids to form β-lactones has also been accomplished. Bromolactonisation has proved to be more successful than iodolactonisation, achieving quite acceptable yields. This reaction has the possibility of forming either the β- or γ-lactone. Good yields of the β-lactone were obtained except

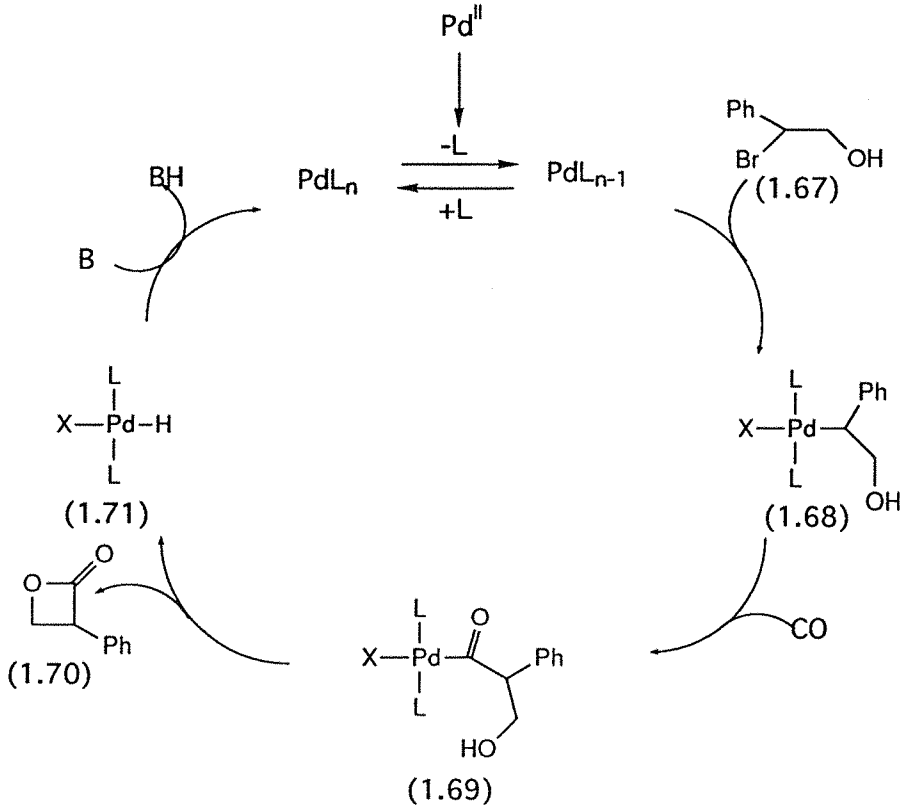
where the substitution at the γ-carbon can assist the development of carbonium character at the γ-carbon. For example 2-methyl-1,4-dihydrobenzoic acid (1.63) forms the β-lactone, where as 3-methyl-1,4-dihydrobenzoic acid (1.65) forms the γ-lactone (scheme 1.13)[38].



(1.63) (1.64) (1.65) (1.66)

Scheme 1.13

In 1980 Stille reported the formation of a variety of β-lactones and $\Delta^{\alpha,\beta}$-butenolides from palladium-catalysed carbonylation of halo alcohols (scheme 1.14)[39]. The synthesis of β-lactone (1.70) was reported from



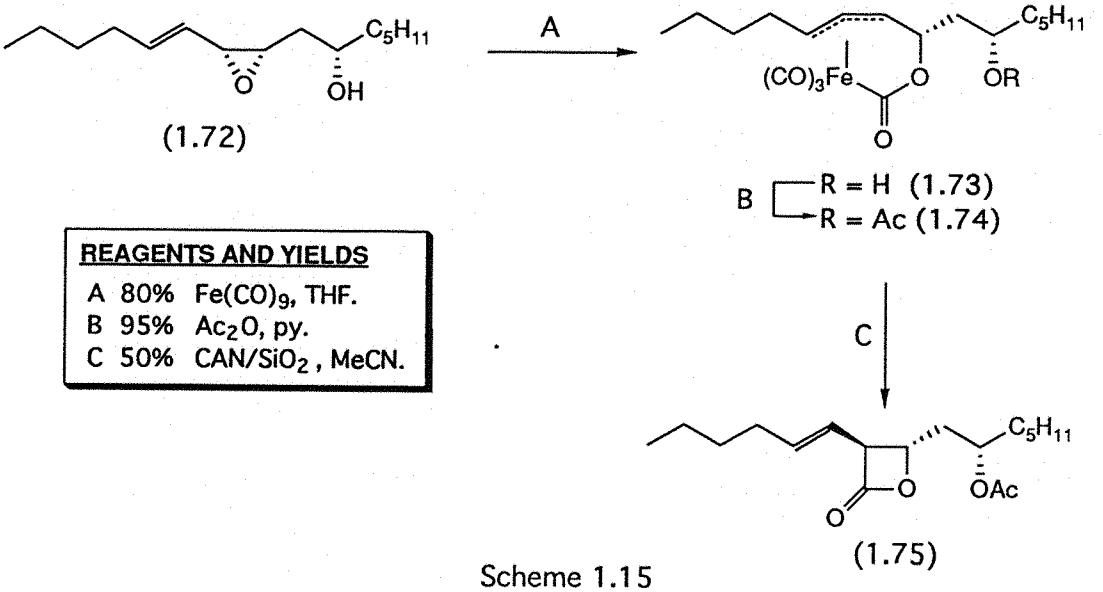
Scheme 1.14

2-bromo-2-phenylethanol (1.67) in 63% yield. Oxidative addition of the bromide (1.67) to palladium (0) followed by insertion of carbon monoxide into the palladium-carbon sigma bond afforded (1.69). This underwent reductive elimination

to generate the β-lactone. Reaction of the palladium complex with the base regenerated the palladium (0), allowing the completion of the catalytic cycle.

Another synthesis of β-lactones using organometallics was reported in 1991 by Davies and co-workers, who published an asymmetric synthesis of homochiral β–lactones using an iron chiral auxiliary. Formation of the β-hydroxy acyl complex from a homochiral iron acetyl complex with pivalaldehyde proceeded stereoselectively. Oxidation of this complex with bromine in dichloromethane at low temperature gave the β-lactone in 65% yield (see later)[40].

At about the same time Ley and co-workers reported the formation of β-lactones from the oxidation of a π-allyl iron carbonyl lactone complex (scheme 1.15)[41].



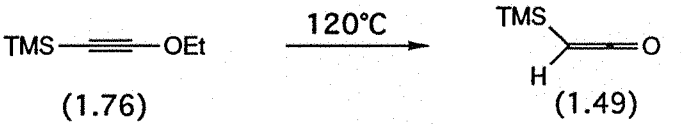
Scheme 1.15

Treatment of the alkenyl epoxide (1.72) with diiron nonacarbonyl afforded in 80% yield the π-allyltricarbonyliron complex as two separable isomers in a ratio of 4:1. The desired *exo*-isomer (1.73) was formed as the major component. Initial attempts to oxidise this complex, with ceric ammonium nitrate in buffered ethanol, afforded the β-lactone in 26% yield. A number of different solvents and oxidants were used in an attempt to improve the yield, without success. But on protection of the free hydroxyl group as the acetate, the oxidation, with ceric ammonium nitrate, proceeded smoothly to afford the *trans*-β-lactone (1.75) in 50% yield. Further elaboration afforded

valilactone (1.3), a β-lactone natural product.

Formation of β-Lactones from Silyl Ketenes.

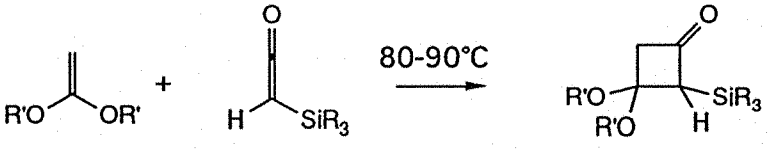
Ketenes are, in general, very unstable compounds, especially towards oxidation, and tend to dimerise readily. For this reason they are usually generated *in situ*. Silyl ketenes are considerably more stable, although they are still very reactive and have been used as acylating agents for hindered amines and tertiary alcohols[42]. Trimethylsilyl ketene (1.49) was first prepared in 1964 by the pyrolysis of (trimethylsilyl)ethoxyacetylene (equation 1.6)[43]. Trimethylsilyl ketene does not dimerise on heating and can be stored for long periods of time.



(1.76) (1.49)

Equation 1.6

In 1974 Zaitseva and co-workers reported the cycloaddition of trialkylsilyl ketenes with ketene dialkyl acetals (1.77) to form 1,3-cyclobutanedione acetals in yields of 45-50% (scheme 1.16)[44]. The reaction was found to proceed slowly at room temperature but within two to four hours at 80-90°C.



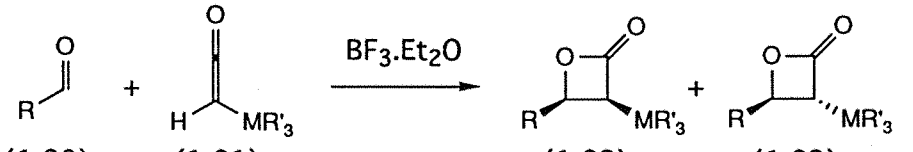
(1.77) (1.78) (1.79)

Scheme 1.16

Later in 1974 the same group published a communication outlining work on the cycloaddition of trialkylsilyl ketenes to carbonyl compounds. They described the reaction between benzaldehyde and trimethylsilyl ketene in the presence of boron trifluoride etherate at -50°C (scheme 1.10)[32]. From the proton NMR spectrum, of the reaction mixture, they deduced that two products had been formed in a 2:1 ratio. They assigned the major product as the *cis*-isomer (1.53) and the minor product as the *trans*-isomer (1.51). On warming to 50°C a decrease in the amount of the *trans*-isomer was observed. Distillation of this mixture yielded

trimethyl-*trans*-styrylsilane (13%)(1.52) and *cis*-4-phenyl-3-(trimethylsilyl) -2-oxetanone (62%)(1.53). The *cis*-β-lactone decarboxylated upon heating to 150-160°C to form the trimethyl-*cis*-styrylsilane (1.54).

In 1978 Zaitseva published a full paper on the cycloaddition of carbonyl compounds to trialkylsilyl ketenes (scheme 1.17)[33]. A series of aldehydes were reacted with



(1.80) (1.81) (1.82) (1.83)

Scheme 1.17

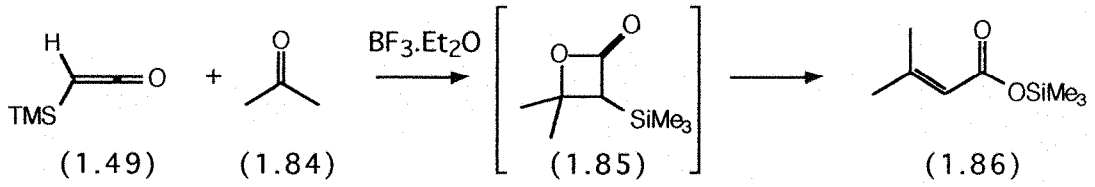
trialkyl silyl and germyl ketenes to determine the importance of different substituents on the ease of formation of oxetanones and to examine the ratio of the *cis*- to *trans*-isomers obtained (see table 1). From the table it can be seen that

MR'_3	R	Temperature (°C)	Reaction time	Yield %	Ratio cis: trans
Me_3Si	Cl_3C	90-100	4 h	69	20: 80
Me_3Si	Cl_3C	-50	20 h	64	30: 70
Me_3Si	Cl_3C	-78	15 h	32	40: 60
Me_3Si	Br_3C	10	2 h	53	0: 100
Me_3Si	Br_3C	-50	2 h	35	20: 80
$MeEt_2Si$	Cl_3C	80-90	2 h	63	0: 100
Et_3Si	Cl_3C	100	6 h	45	0: 100
$Me_2(ClCH_2)Si$	Cl_3C	-50	1.5 h	51	20: 80
$Me_2(ClCH_2)Si$	Br_3C	-10	10 min	64	0: 100
Me_3Ge	Cl_3C	50	5 h	67	0: 100
Me_3Si	H	20	40 min	30	
Me_3Si	Me	20	30 min	64	60: 40
Me_3Si	Me	-78	2 h	42	50: 50
Me_3Si	Et	20	20 min	68	60: 40
Me_3Si	*n*-Pr	20	20 min	62	60: 40
Me_3Si	*i*-Pr	20	20 min	90	60: 40
Me_3Si	*i*-Bu	20	20 min	86	60: 40
Me_3Ge	Me	-78	20 min	75	60: 40

Table 1

(chloromethyl)dimethylsilyl ketene and trimethylgermyl ketene are more reactive than trialkylsilyl ketene and often afford a greater stereoselectivity. Attempts to react trimethylsilyl ketene with ketones were largely unsuccessful. Only in the case of

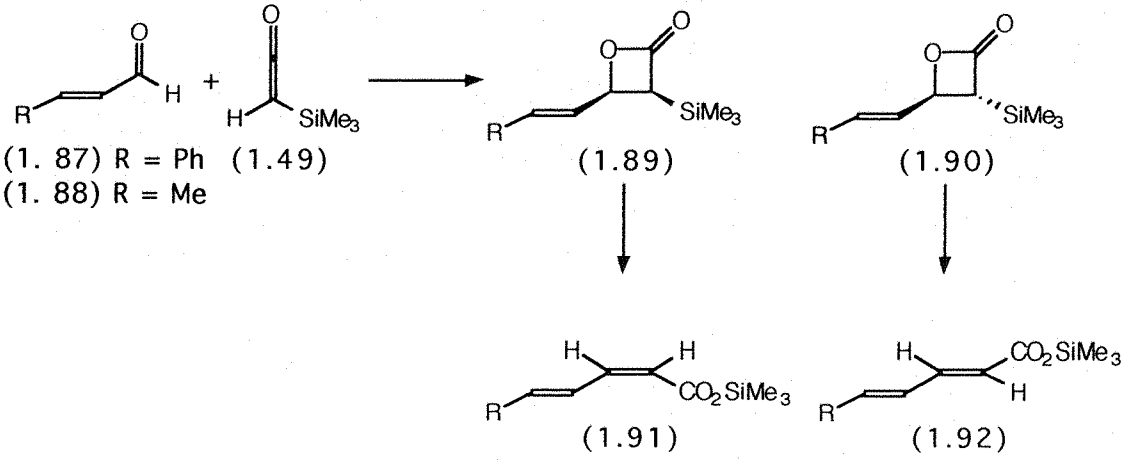
acetone was anything isolated (scheme 1.18). Even after ten hours at 50°C starting material was still recovered. After removal of the starting materials trimethylsilyl 3-methyl-2-butenoate (1.86) was isolated in 28% yield.



(1.49) (1.84) (1.85) (1.86)

Scheme 1.18

A few years later Brady reported the cycloaddition of trimethylsilyl ketene with α,β-unsaturated aldehydes. Reacting trimethylsilyl ketene with either (*E*)-cinnamaldehyde (1.87) or (*E*)-crotonaldehyde (1.88) resulted in the formation of the corresponding β-lactones, but on distillation the silicon group migrated from the carbon to the oxygen and the oxetanone opened to yield the trimethylsilyl dienoate esters (scheme 1.19)[34].



(1. 87) R = Ph (1.49)
(1. 88) R = Me

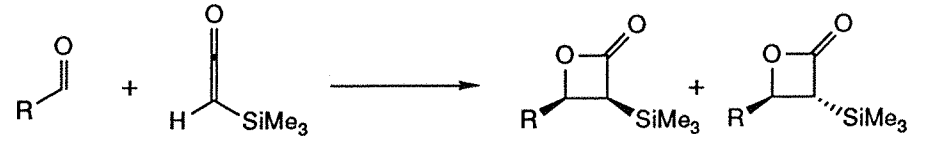
(1.89) (1.90)

(1.91) (1.92)

Scheme 1.19

Much more recently Maruoka and co-workers reported a communication outlining their work on the stereocontrolled cycloaddition of trimethylsilyl ketene and aldehydes in the presence of methylaluminium bis(4-bromo-2,6-ditert-butylphenoxide) (MABR)(1.96)[45]. A range of aldehydes and Lewis acids were examined (table 2). As can be seen from the table, high levels of stereoselectivity were recorded for simple aldehydes, where the *cis*-β-lactone was formed almost exclusively. Aldehydes with

more bulky substituents, such as pivalaldehyde, showed a preference for formation of the *trans* -isomer.

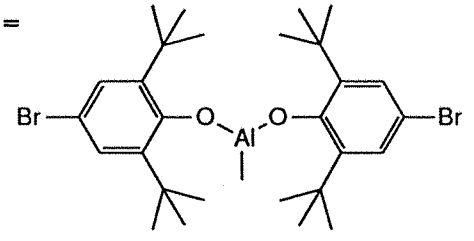


(1.93) (1.49) (1.94) (1.95)

Scheme 1.20

R	Lewis acid (equivalent)	Temperature (°C)	Reaction Time (h)	Yield %	Ratio cis: trans
Et	$BF_3.OEt_2$	-20	3.5	42	70: 30
Et	Et_2AlCl (1)	-78	1.5	71	92: 8
Et	$SnCl_4$ (1)	-78	2	6	92: 8
Et	MABR (1)	-78	2	82	100: 0
c-C_6H_{11}	$BF_3.OEt_2$	-20	1	52	41: 59
c-C_6H_{11}	MABR (1)	-78	1	88	90: 10
t-Bu	$BF_3.OEt_2$	-20	0.5	42	4: 96
t-Bu	MABR (1)	-20	0.5	53	21: 79
Ph	$BF_3.OEt_2$	-20	3.5	44	100: 0
Ph	MABR (0.2)	-20	1	57	100: 0

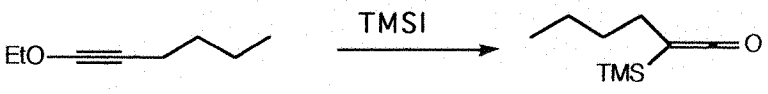
MABR =



(1.96)

Table 2

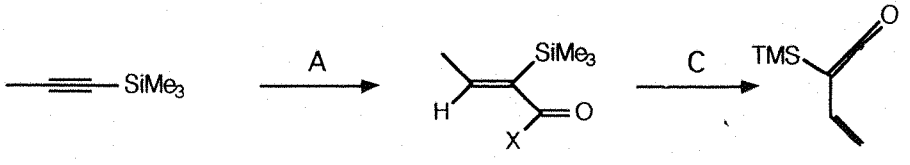
Most of the work in the literature has examined only unsubstituted trialkylsilyl or germyl ketenes. One of the reasons for this is the difficulty in preparing substituted silyl ketenes. In 1979 Sakurai and co-workers reported the first route to alkyl trimethylsilyl ketenes[46]. They had developed a new method of forming trimethylsilyl iodide *in situ* from the reaction of hexamethyldisilane with iodine. In the same paper they reported a route to silyl ketenes. Using their method they generated TMSI *in situ,* to which they added 1-ethoxyhexyne. After heating to 70°C for forty six hours they isolated *n*-butyl trimethylsilyl ketene (1.98) in 57% yield (equation 1.7).



(1.97) (1.98)

Equation 1.7

In 1980 (Trimethylsilyl)vinyl ketene (1.102) was prepared from (*Z*)-2-(trimethylsilyl)-2-butenoyl chloride formed from 1-(trimethylsilyl)propyne[47]. Treatment of the propyne (1.99) with di-*iso*-butylaluminium hydride and methyl lithium followed by carbon dioxide formed (*Z*)-2-(trimethylsilyl)-2-butenoic acid in 68% yield. Formation of the potassium salt followed by treatment with oxalyl chloride yielded the acid chloride (1.101) which on treatment with triethylamine formed the vinylsilylketene in 39-50% yield from the acid (scheme 1.21). Danheiser

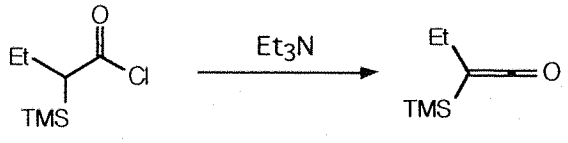


(1.99) B → X = OH (1.100), X = Cl (1.101) (1.102)

REAGENTS AND YIELDS		
A	68%	i) DiBAlH, MeLi, Et_2O - Hexane, ii) CO_2.
B		Oxalyl chloride, DMF, 0-25°C.
C	50%	Et_3N, pentane, reflux.

Scheme 1.21

then used this vinylsilyl ketene in Diels-Alder reactions with various olefins and acetylenes. The same method was later used by Baigrie and co-workers to synthesise ethyl(trimethylsilyl)ketene (1.104) from (trimethylsilyl)butanoyl chloride (Equation 1.8)[48].

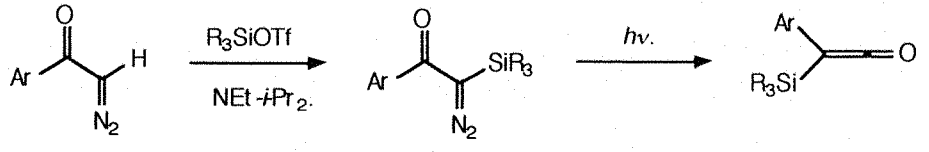


(1.103) (1.104)

Equation 1.8

One further route to the formation of substituted silylketenes was published in 1985[49]. Maas reported the synthesis of arylsilylketenes from silylated α-diazo

carbonyl compounds (scheme 1.22). Two examples were given where the arylsilyl ketenes were obtained by unsensitised irradiation of the diazo compounds in benzene. The yields were 37% and 94% respectively.



(1.105) Ar = Ph, R = Et (1.107) (1.108)
(1.106) Ar = 2-thienyl, R = *i*-Pr

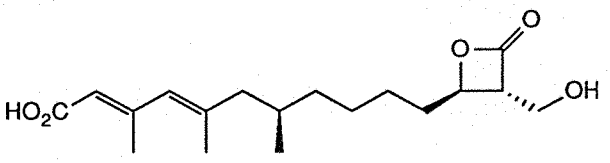
Scheme 1.22

Chapter Two

Chapter Two.

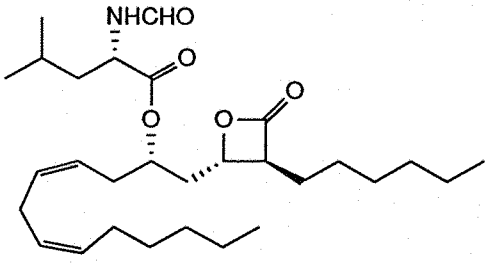
Previous Syntheses of Tetrahydrolipstatin.

In the last twenty years a series of biologically active, fatty acid derived β-lactone natural products have been isolated. The structure of the first of these, antibiotic L-659,699 (1.4), also known as 1233A, (figure 2.1), was assigned in 1970 by Aldridge and co-workers[7].

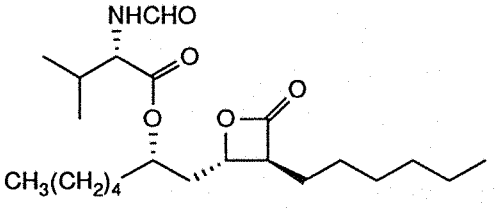


L-659,699 (1.4)
(1233A)
Figure 2.1

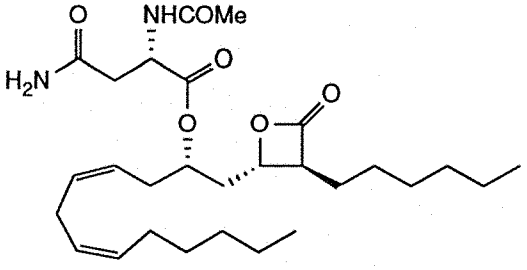
Since then lipstatin (1.2)[4], valilactone (1.3)[6] esterastin (2.1)[50,51] and ebelactones A (1.5) and B (1.6)[8,9] have been isolated and characterised (figure 2.2). All are of



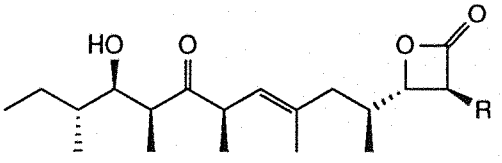
Lipstatin (1.2)



Valilactone (1.3)



Esterastin (2.1)

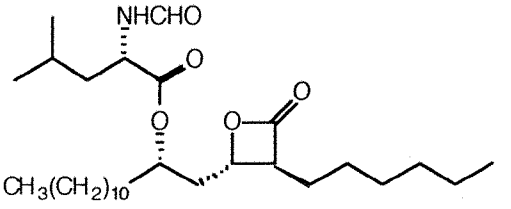


Ebelactone A R = Me (1.5)
Ebelactone B R = Et (1.6)

Figure 2.2

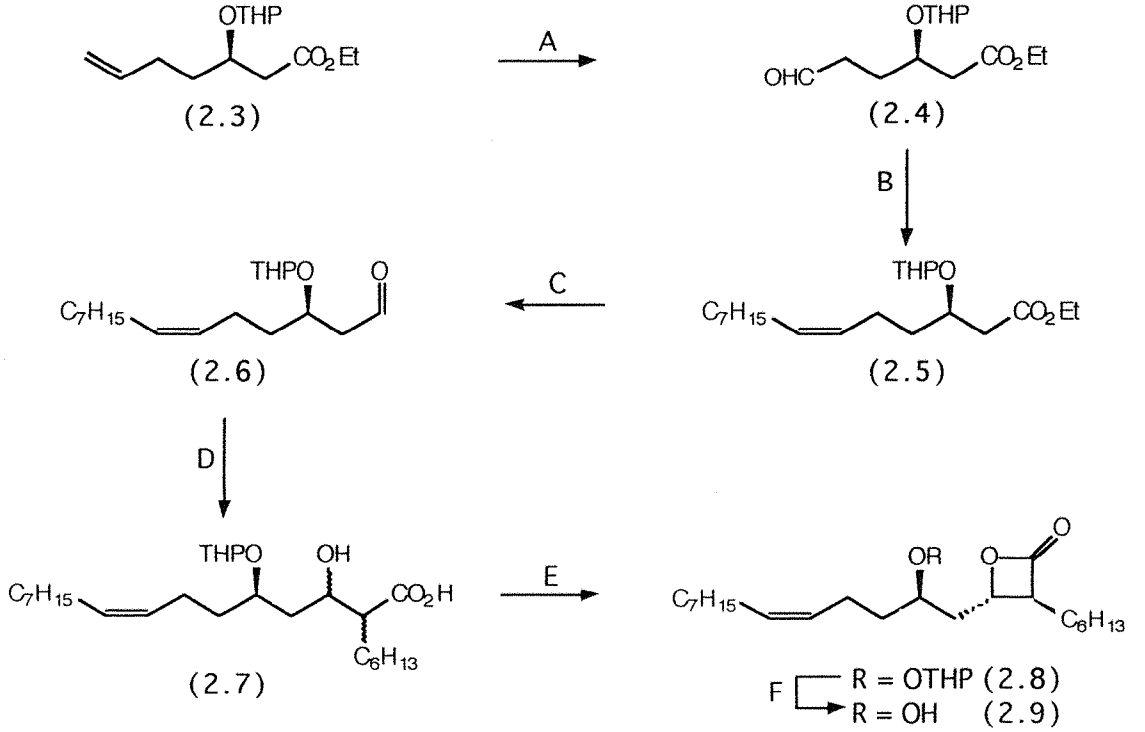
pharmacological interest. L-659,699 is an inhibitor of HMG-CoA synthase and of cholesterol biosynthesis. Esterastin, valilactone and the ebelactones were found to inhibit esterase and lipase. Ebelactones A and B were found to inhibit N-formylmethionine aminopeptidase and produce enhanced immune responses. Esterastin suppressed immune responses and valilactone was found to have no effect.

Lipstatin is a potent, selective and irreversible inhibitor of pancreatic lipase, a key enzyme in intestinal fat digestion, isolated from *Streptomyces toxytricini*. Catalytic hydrogenation of lipstatin yielded tetrahydrolipstatin (2.2) (figure 2.3) which was shown to possess the same biological activity. The potential antiobesity activity[52-54] of tetrahydrolipstatin, led a team at Hoffman-La Roche to develop several synthetic routes.



Tetrahydrolipstatin (2.2)
Figure 2.3

The first route, published by Barbier and Schneider in 1987, served to establish the absolute stereochemistry of tetrahydrolipstatin (scheme 2.1)[55]. Starting from known ethyl (*R*)-3-hydroxy-6-heptenoate, the hydroxyl group was protected as the



Tetrahydrolipstatin (2.2)

REAGENTS AND YIELDS

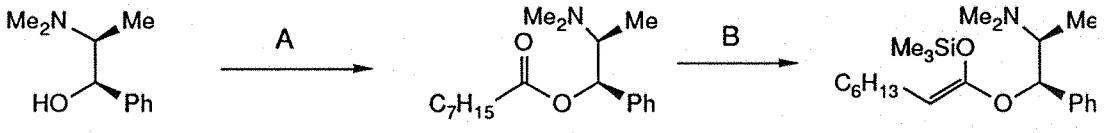
A	-	i) O_3, AcOEt, -78°C. ii) H_2, Pd/C.
B	24%	$C_8H_{17}PPh_3Br$, *n*-BuLi, THF, -40°C- rt.
C	69%	DiBAlH, DCM, -78°C.
D	-	$C_7H_{15}CO_2H$, LDA, THF, -50°C.
E	-	$PhSO_2Cl$, py, 0°C.
F	11%	PPTS, EtOH, 50°C.
G	50%	(*S*)-N-formylleucine, PPh_3, DEAD, THF.
H	60%	H_2, Pd/C, THF.

Scheme 2.1

tetrahydropyranyl (THP) ether (2.3). Ozonolysis of the double bond afforded aldehyde (2.4), which was used without further purification. The crude aldehyde underwent a Wittig reaction upon treatment with octyl(triphenyl)phosphonium bromide to afford the alkene (2.5) in 24% yield from (2.3). Reduction of the ethyl ester with di-*iso*-butylaluminium hydride (DiBAlH) afforded the aldehyde (2.6), which underwent an aldol condensation with the anion of lithium octanoate to yield hydroxy acid (2.7). Cyclisation of this hydroxy acid was performed with benzenesulphonyl chloride in pyridine to form β-lactone (2.8), as a mixture of four diastereomers, which were carried through to the next reaction without purification. After removal of the tetrahydropyranyl group, the four isomers were separated by chromatography, to afford the required *trans*-isomer (2.9) in 11% yield. Esterification of this isomer with (*S*)-N-formylleucine under Mitsunobu conditions followed by catalytic hydrogenation afforded tetrahydrolipstatin.

In the same paper Barbier and Schneider reported a non-stereoselective synthesis of tetrahydrolipstatin, in which achiral starting materials were used to form the hydroxy β-lactone as a mixture of eight racemic diastereomers.

Later in 1987 a second paper was published by the same group, detailing a stereoselective synthesis of tetrahydrolipstatin[56]. The stereochemistry of the ring was established using a titanium tetrachloride mediated condensation of a ketene silyl acetal with an aldehyde. The homochiral ketene silyl acetal was formed from (-)-N-methylephedrine (scheme 2.2). The aldehyde was obtained from the known

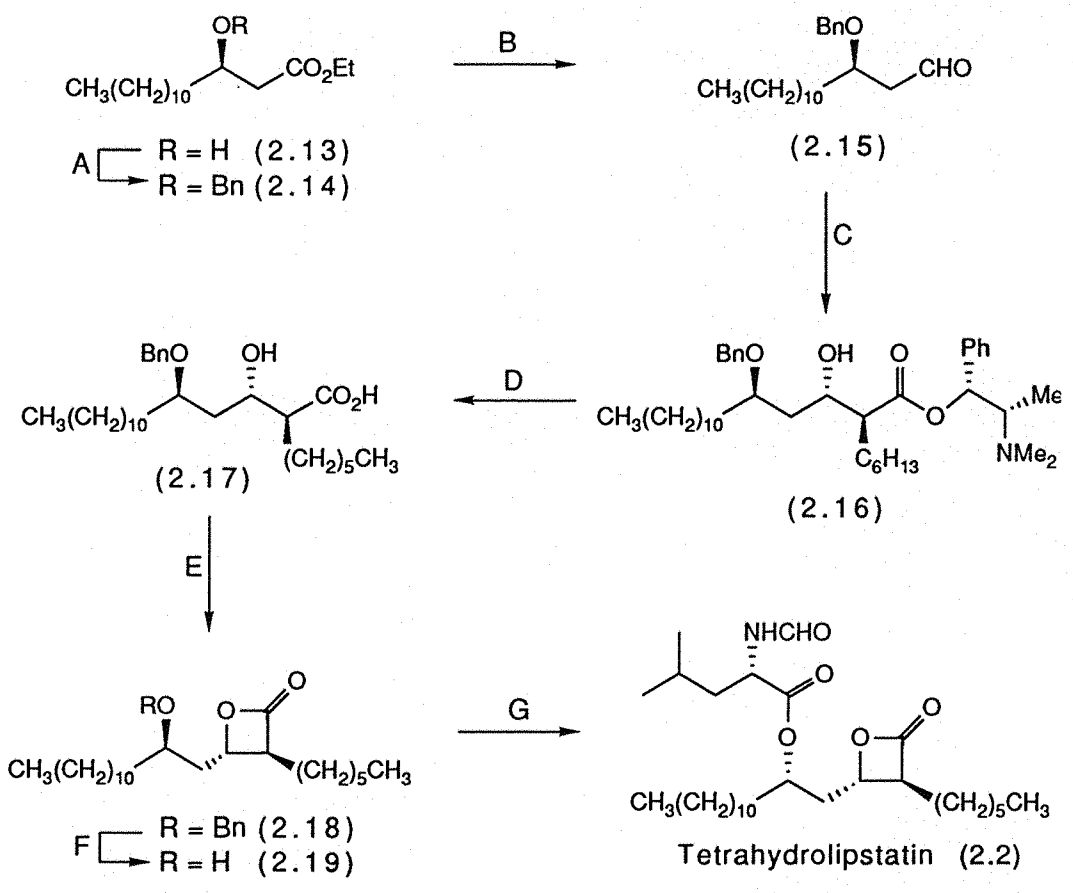


(2.10) (2.11) (2. 12)

REAGENTS AND YIELDS		
A	89%	$C_7H_{15}COCl$, *t*-BuOMe.
B	-	i) LDA, THF, -78°C. ii) TMSCl, -78°C- rt.

Scheme 2.2

homochiral hydroxy ester (2.13)[57]. This was protected, under acidic conditions, as the benzyl ether using benzyltrichloroacetimidate[58] before being reduced to the aldehyde



REAGENTS AND YIELDS

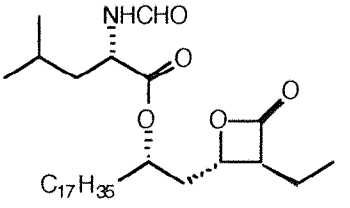
A	78%	$CCl_3C(NH)OBn$, CF_3CO_2H, DCM, C_6H_{11}, rt.
B	82%	DiBAlH, DCM, -78°C.
C	40%	(2.12), $TiCl_4$, DCM, -78°C.
D	64%	i) KOH, MeOH, reflux. ii) HCl.
E	61%	$PhSO_2Cl$, py, 0°C.
F	70%	H_2, Pd/C, THF.
G	77%	(*S*)-N-formylleucine, PPh_3, DEAD, THF, 0°C.

Scheme 2.3

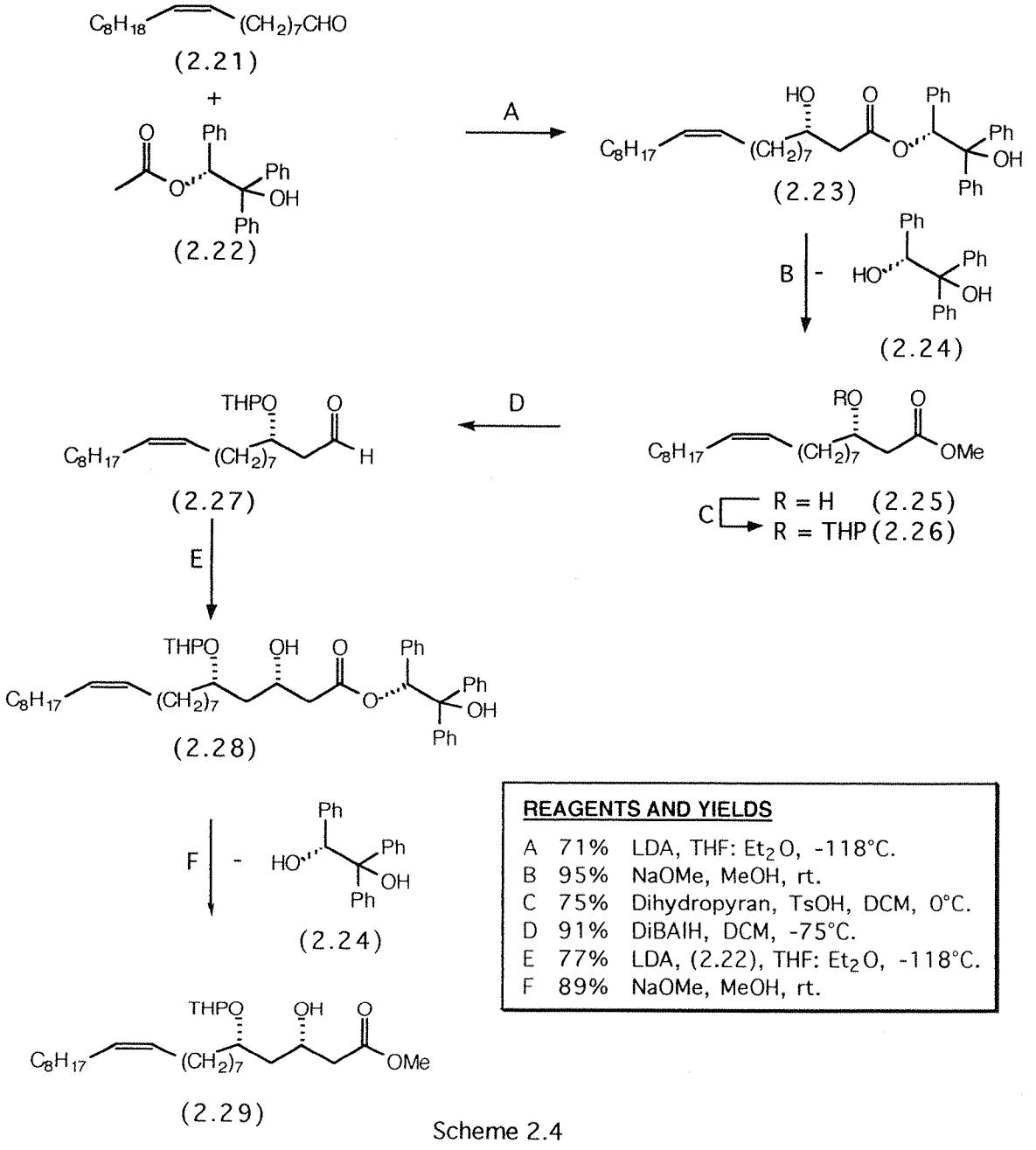
with DiBAlH (scheme 2.3). Condensation of the aldehyde with the ketene silyl acetal (2.12) in the presence of titanium tetrachloride yielded the hydroxy ester as a mixture of two diastereomers, of which the major product (2.16) was the required isomer. Separation of the mixture, *via* chromatography, afforded the desired isomer (2.16) in 40% yield. Hydrolysis of this isomer furnished the hydroxy acid (2.17) which was ring-closed, using benzenesulphonyl chloride in pyridine, in 61% yield. Hydrogenolysis of the benzyl ether afforded the hydroxy lactone (2.19) which was esterified under Mitsunobu conditions to furnish tetrahydrolipstatin. Although this route obviously represented a significant improvement upon the previous synthesis, the scheme relied on a bulky chiral auxiliary to set up the stereochemistry of the ring and even then the

reaction only gave 40% of the desired isomer.

In the same paper a synthesis of an analogue of tetrahydrolipstatin (figure 2.4) was reported. This analogue (2.20) differed from tetrahydrolipstatin only in the number of carbons in the alkyl side chains. The fulcrum of this route was the condensation of an aldehyde with an acetate unit, esterified with a homochiral diol obtained from mandelic acid. By repeating this condensation twice the stereochemistry of the ring and the ester group was established with reasonable control (scheme 2.4). (*Z*)-9-Octadecenal was condensed with



(2.20)
Figure 2.4

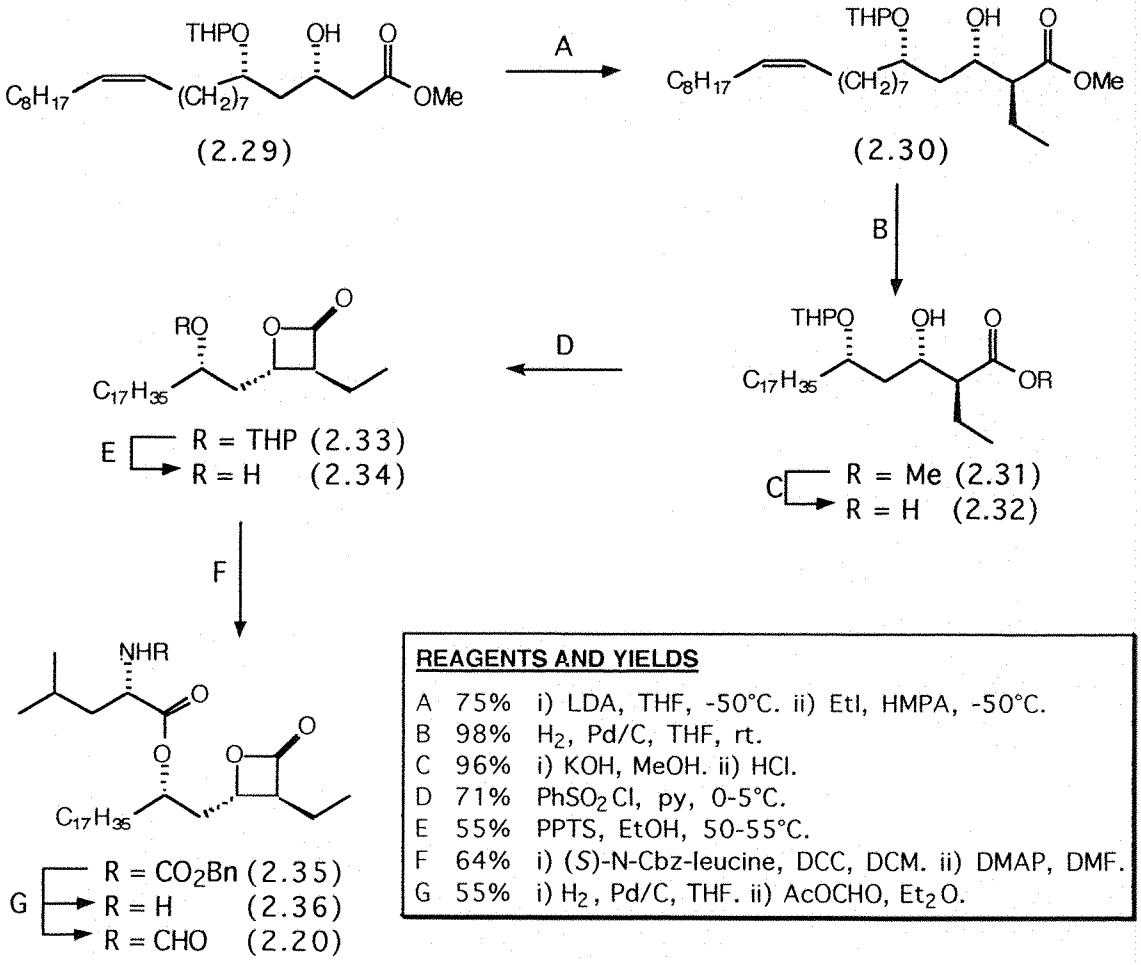


REAGENTS AND YIELDS

A	71%	LDA, THF: Et_2O, -118°C.
B	95%	NaOMe, MeOH, rt.
C	75%	Dihydropyran, TsOH, DCM, 0°C.
D	91%	DiBAlH, DCM, -75°C.
E	77%	LDA, (2.22), THF: Et_2O, -118°C.
F	89%	NaOMe, MeOH, rt.

Scheme 2.4

the lithium dianion of the optically active ester (2.22) to furnish adduct (2.23). Transesterification with methanol afforded the methyl ester (2.25). During transesterification (*R*)-1,2,2-triphenyl-1,2-ethanediol (2.24) was formed as white crystals which could be filtered off and recycled. Protection of the hydroxyl group as the tetrahydropyranyl ether followed by reduction of the ester afforded aldehyde (2.27). Condensation of the aldehyde with acetate (2.22), as before, afforded hydroxy ester (2.28) as a mixture of two diastereomers in a ratio of 4:1. The major isomer was identified as the desired compound by NMR spectroscopy and the ester was carried through as a mixture. Transesterification with methanol furnished the methyl ester (2.29) and the chiral diol (2.24), which can be recycled. Having established two chiral centres, stereoselective alkylation with ethyl iodide yielded (2.30), in what was assumed to be a



REAGENTS AND YIELDS

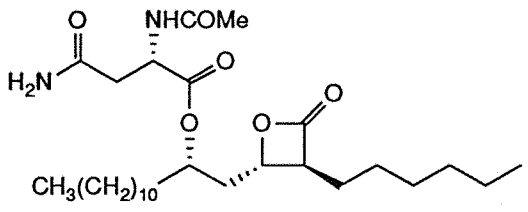
A	75%	i) LDA, THF, -50°C. ii) EtI, HMPA, -50°C.
B	98%	H_2, Pd/C, THF, rt.
C	96%	i) KOH, MeOH. ii) HCl.
D	71%	$PhSO_2Cl$, py, 0-5°C.
E	55%	PPTS, EtOH, 50-55°C.
F	64%	i) (*S*)-N-Cbz-leucine, DCC, DCM. ii) DMAP, DMF.
G	55%	i) H_2, Pd/C, THF. ii) AcOCHO, Et_2O.

Scheme 2.5

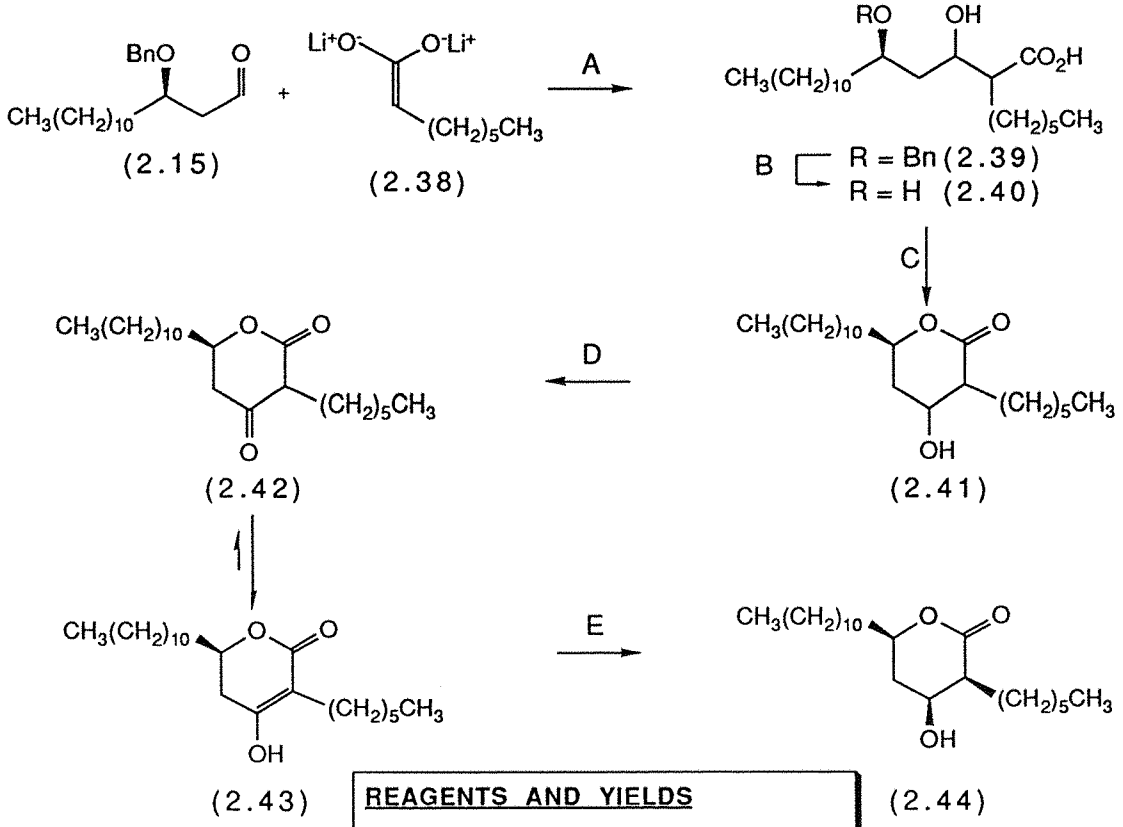
high *erythro/threo* ratio (scheme 2.5). Hydrogenation of the olefin, followed by saponification afforded the hydroxy acid (2.32). Cyclisation as before, with benzenesulphonyl chloride, furnished the β-lactone in 71% yield. Upon cleavage of the

tetrahydropyranyl ether, the hydroxy lactones could be separated, by chromatography. As they had assumed, the *trans*-isomer was the main product which could separated from the *cis*-isomer by recrystallisation. The hydroxy lactone (2.34) was then esterified with (*S*)-N-(benzyloxycarbonyl)leucine. Hydrogenolysis of the Cbz group followed by formylation yielded the target compound (2.20). This route had one advantage over the previous synthesis in that the chiral auxiliary, derived from mandelic acid, could be easily recycled.

In 1988 Barbier and Schneider published a highly stereoselective synthesis of tetrahydrolipstatin and tetrahydroesterastin (2.37)(figure 2.5)[59]. The key to this synthesis was the formation of a β-keto-γ-lactone which was hydrogenated stereoselectively to the hydroxy-γ-lactone



Tetrahydroesterastin (2.37)
Figure 2.5

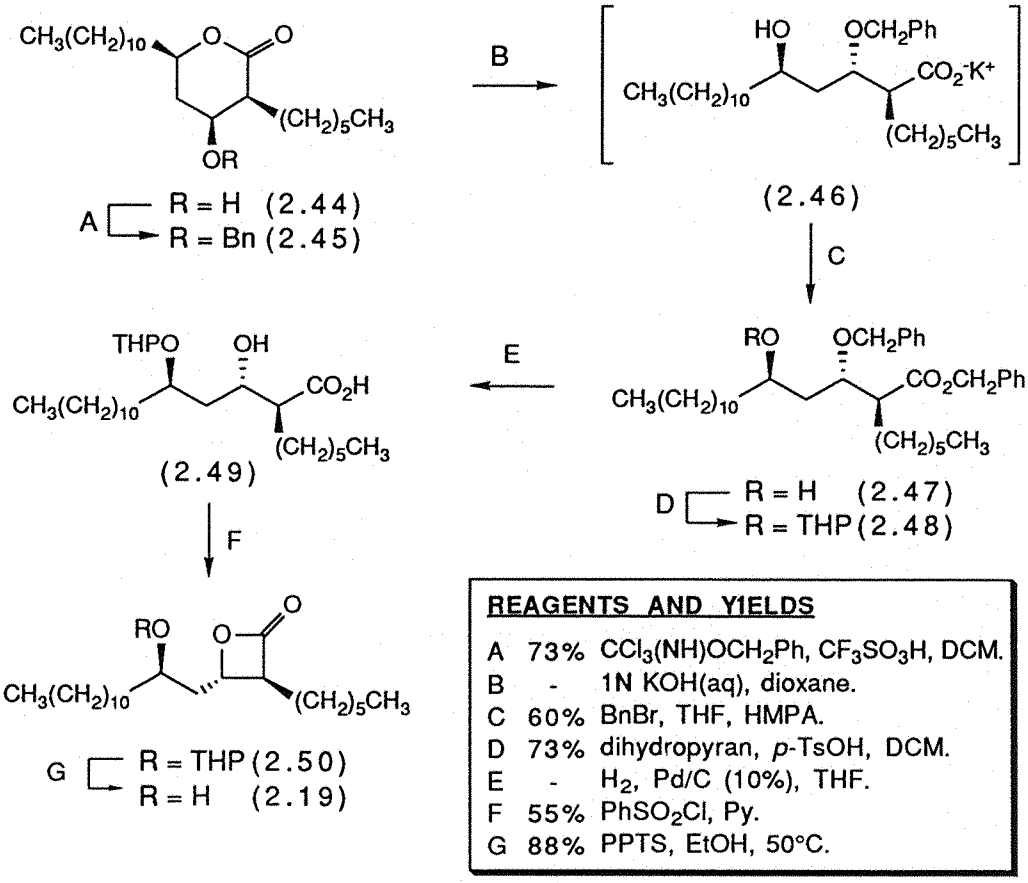


REAGENTS AND YIELDS

A	-	$C_7H_{15}CO_2H$, LDA, THF, -50°C.
B	-	H_2, Pd/C (10%), THF.
C	-	*p*-TsOH, $CHCl_3$.
D	-	Jones' reagent.
E	84%	H_2, PtO_2, EtOAc, 50 bar.

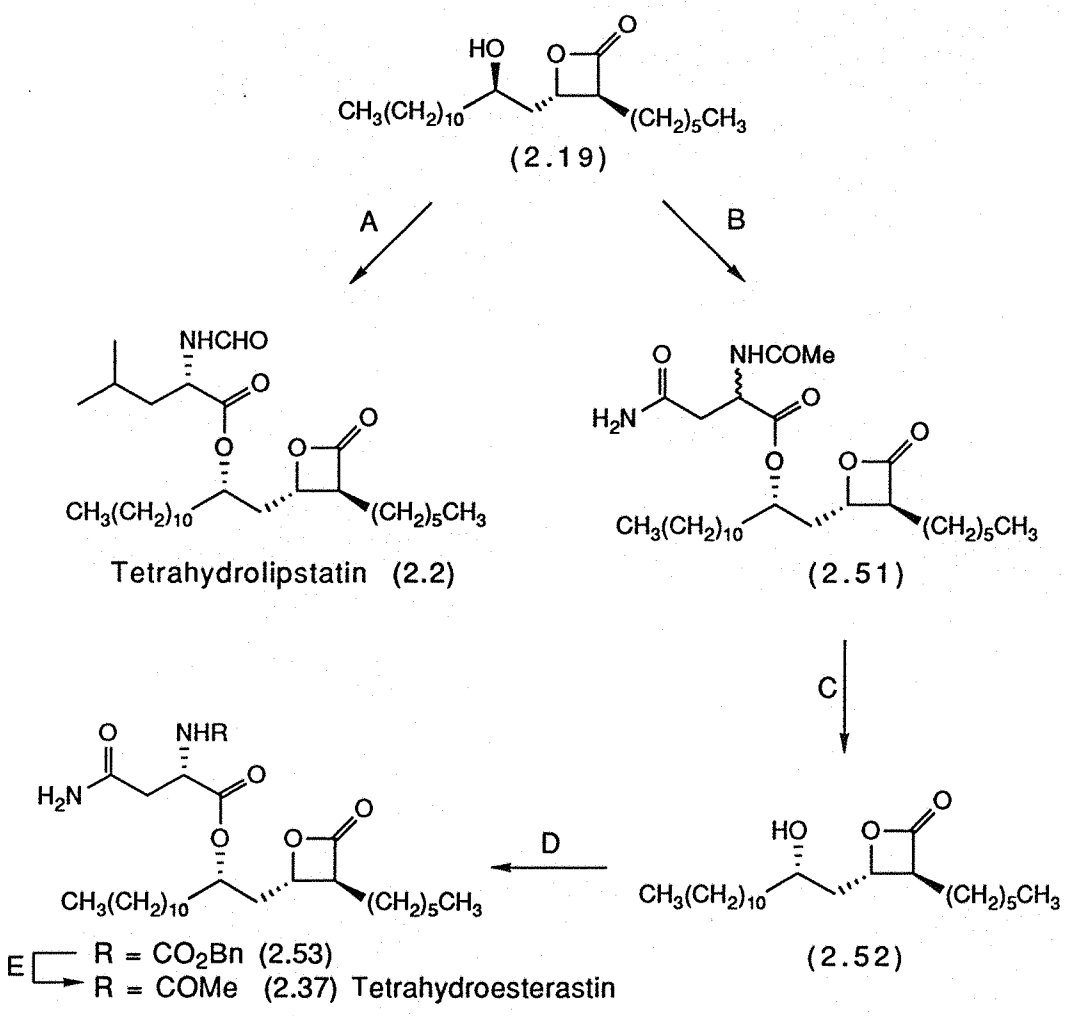
Scheme 2.6

(scheme 2.6). The benzyl-protected hydroxy aldehyde (2.15), used in an earlier synthesis[56], was condensed with dilithium octanoate to yield the hydroxy acid (2.39) as a mixture of four diastereomers. Without separation, the benzyl ether was cleaved and the resulting dihydroxy acid was cyclised to the γ-lactone (2.41). Oxidation of the hydroxyl group afforded the β-keto-γ-lactone (2.42), which in chloroform exists mainly as the enol (2.43). Hydrogenation of the double bond resulted in the formation of hydroxy δ-lactone (2.44) as one single crystalline isomer. The stereocentres were now established in the correct absolute stereochemistry for tetrahydrolipstatin. The free hydroxyl group was protected as the benzyl ether before the γ-lactone was cleaved with



Scheme 2.7

potassium hydroxide (scheme 2.7). Treatment of the potassium salt with benzyl bromide resulted in the formation of the benzyl ester (2.47). Protection of the free hydroxyl group as the tetrahydropyranyl ether followed by hydrogenation to remove the benzyl groups yielded the β-hydroxy acid (2.49). Cyclisation with benzenesulphonyl chloride afforded the β-lactone as one isomer. Cleavage of the tetrahydropyranyl ether afforded the



REAGENTS AND YIELDS

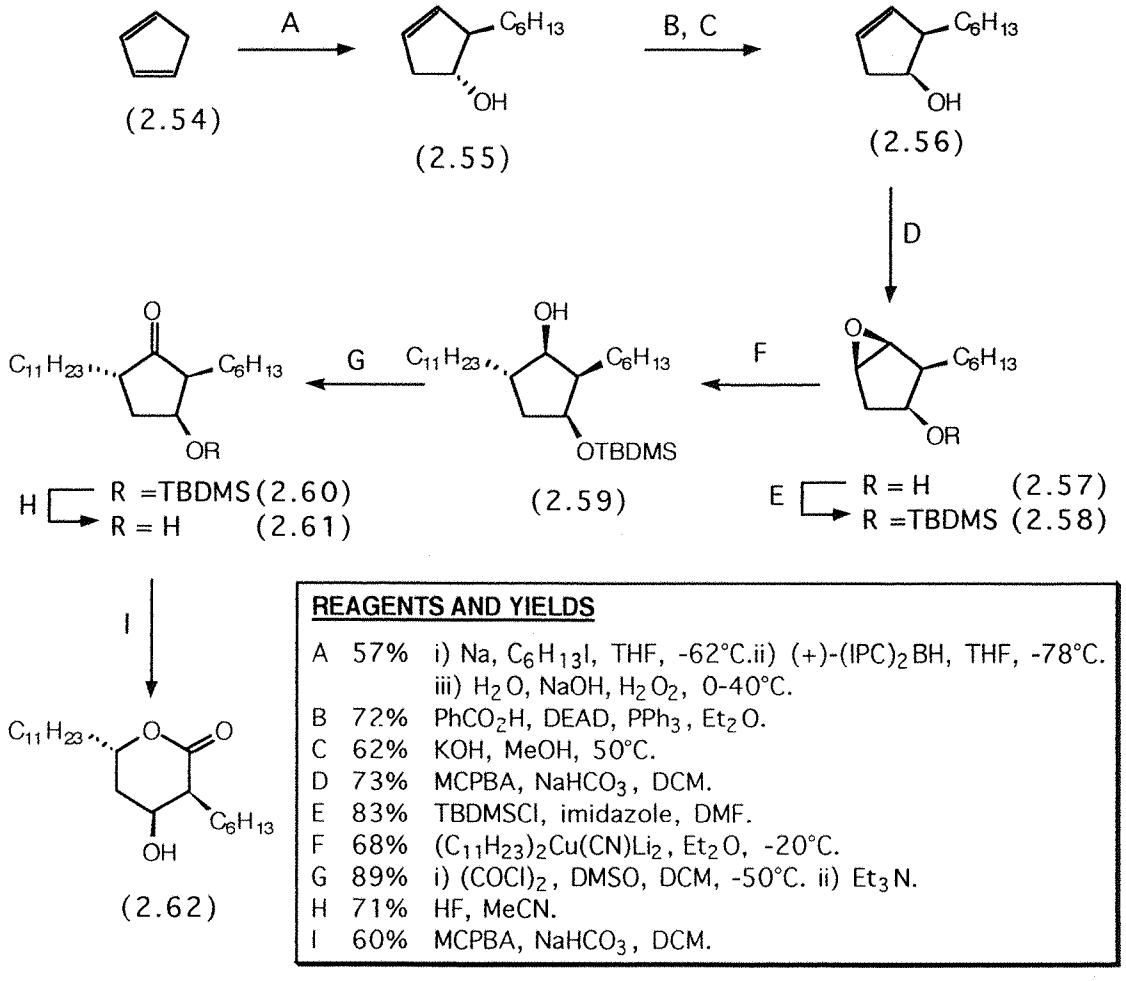
A 80% (*S*)-N-formylleucine, PPh_3, DEAD, THF, 0°C.
B 38% (*S*)-N-acetylaspargine, PPh_3, DEAD, THF, 0°C.
C 63% 0.02 N NaOH (aq), dioxane.
D 33% (*S*)-N-(benzyloxycarbonyl)asparagine, pivaloyl chloride, Et_3N, DMF, -5°C.
E 98% i) H_2, Pd/C, THF. ii) MeCOCl, Et_3N, THF.

Scheme 2.8

hydroxy lactone (2.19). This was then carried forward to tetrahydrolipstatin and tetrahydroesterastin (scheme 2.8). Esterification with (*S*)-N-formylleucine under Mitsunobu conditions, as before, afforded tetrahydrolipstatin in good yield. Unfortunately attempts to form tetrahydroesterastin were not as successful; esterification of the hydroxy lactone under identical conditions with (*S*)-N-acetylasparagine resulted in racemisation of the amino acid. The racemised amino acid derivative was removed to afford hydroxy β-lactone (2.52). This was then esterified using a mixed anhydride to give (2.53). Cleavage of the benzyloxycarbonyl protecting group followed by acetylation of the

amine afforded tetrahydroesterastin. The formation of tetrahydrolipstatin, using this route, although highly stereoselective, involved a lengthy and inelegant method of setting up the stereochemistry.

Much more recently a further synthesis of tetrahydrolipstatin has been reported by a different group at Hoffmann-La Roche[60]. The key steps in this synthesis rely on a one pot cyclopentadiene alkylation and asymmetric hydroboration to establish the stereochemistry. Cyclopentadiene was alkylated with hexyl iodide and then hydroborated *in situ* with (+)-di-*iso*-pinocampheylborane, to afford after oxidative work up (1*R*, 2*R*)-2-hexyl-3-cyclopentenol (2.55) with 96% enantiomeric excess in 57% yield (scheme 2.9). Inversion of the hydroxyl group configuration, using Mitsunobu



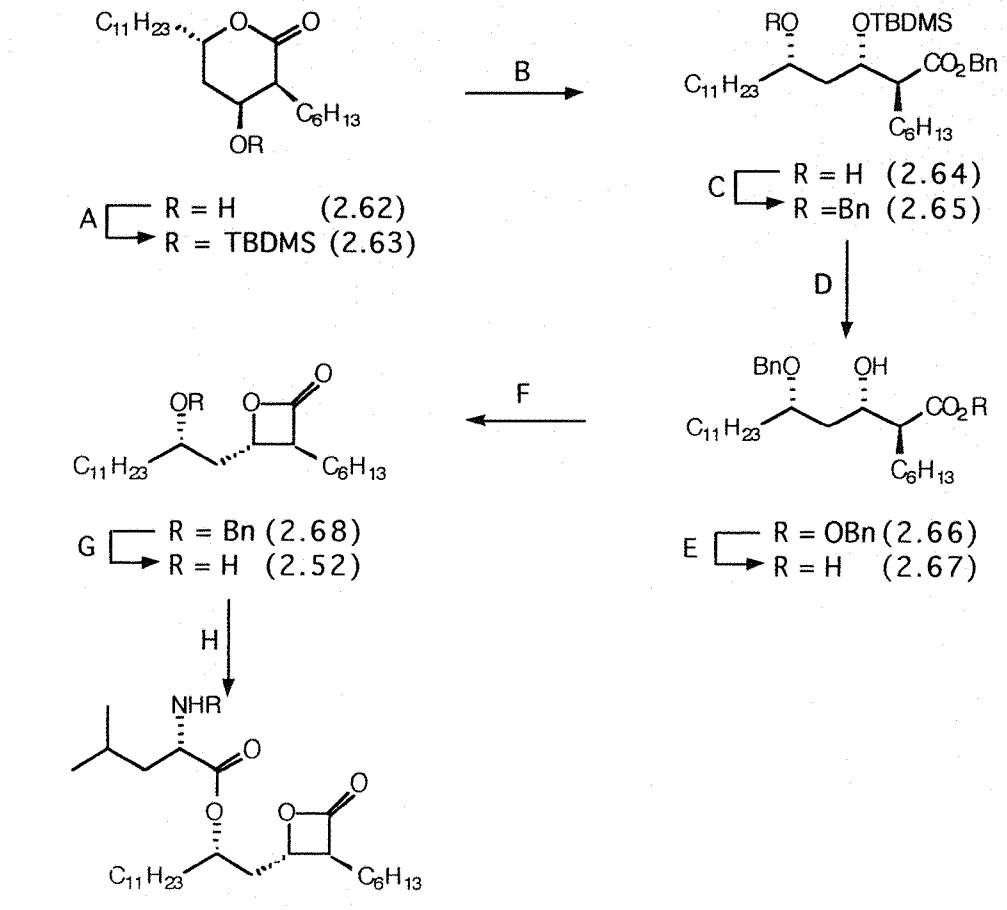
REAGENTS AND YIELDS

A	57%	i) Na, $C_6H_{13}I$, THF, -62°C.ii) (+)-$(IPC)_2BH$, THF, -78°C. iii) H_2O, NaOH, H_2O_2, 0-40°C.
B	72%	$PhCO_2H$, DEAD, PPh_3, Et_2O.
C	62%	KOH, MeOH, 50°C.
D	73%	MCPBA, $NaHCO_3$, DCM.
E	83%	TBDMSCl, imidazole, DMF.
F	68%	$(C_{11}H_{23})_2Cu(CN)Li_2$, Et_2O, -20°C.
G	89%	i) $(COCl)_2$, DMSO, DCM, -50°C. ii) Et_3N.
H	71%	HF, MeCN.
I	60%	MCPBA, $NaHCO_3$, DCM.

Scheme 2.9

conditions, set the hydroxyl group in the correct absolute stereochemistry required for tetrahydrolipstatin. Hydroxyl group directed *meta*-chloroperbenzoic acid (MCPBA) epoxidation afforded epoxide (2.57) with all the stereocentres established in a *cis* relationship. The alcohol was protected as the silyl ether, before the epoxide was

regioselectively opened with a cyanocuprate. The alcohol formed was transformed to the ketone (2.60) using a Swern oxidation. The next step in the synthesis was to be the Baeyer-Villiger oxidation to form the γ-lactone. Attempts to oxidise (2.60) were completely unsuccessful, although a wide variety of reagents were used, but on removal of the silicon protecting group the oxidation proceeded smoothly with MCPBA to afford the desired γ-lactone (2.62) as the only product. The hydroxyl group was reprotected as the silyl ether (2.63) before the lactone was hydrolysed with potassium hydroxide and the potassium salt obtained was treated with benzyl bromide to afford the benzyl ester



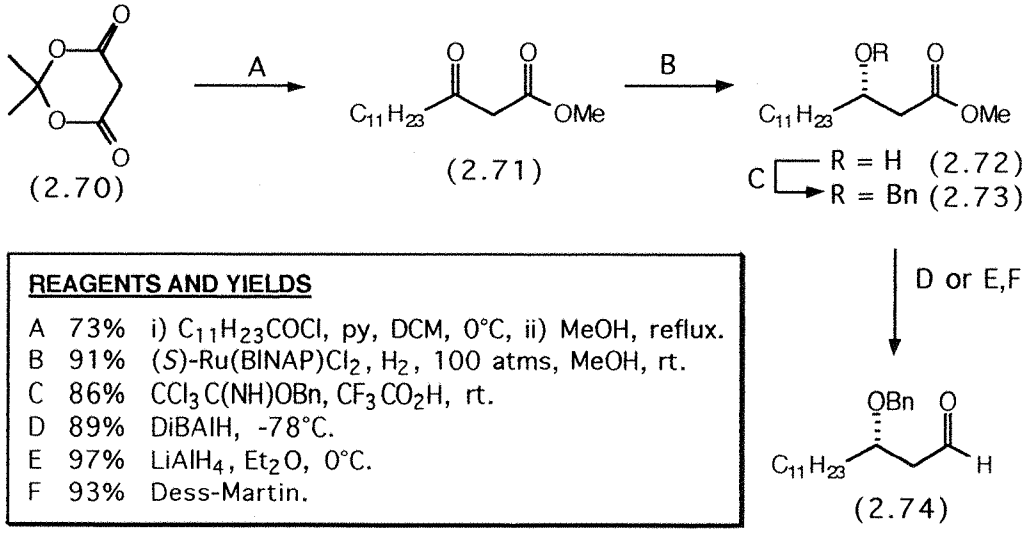
REAGENTS AND YIELDS

A	90%	TBDMSCl, $(i\text{-pr})_2$NEt, DMF.
B	81%	KOH,BnBr, dioxane.
C	71%	$Cl_3C(NH)OBn$, CF_3CO_2H, C_6H_{12}, DCM, 0°C.
D	94%	HF, MeCN, THF, 0°C.
E	99%	NaOH, EtOH, 50°C.
F	69%	$PhSO_2Cl$, py.
G	95%	H_2, Pd/C, THF.
H	85%	i) (*S*)-N-Cbz-leucine, DCC, THF, 4°C. ii) DMAP.
I	72%	i) H_2, Pd/C, THF. ii)AcOCHO.

Scheme 2.10

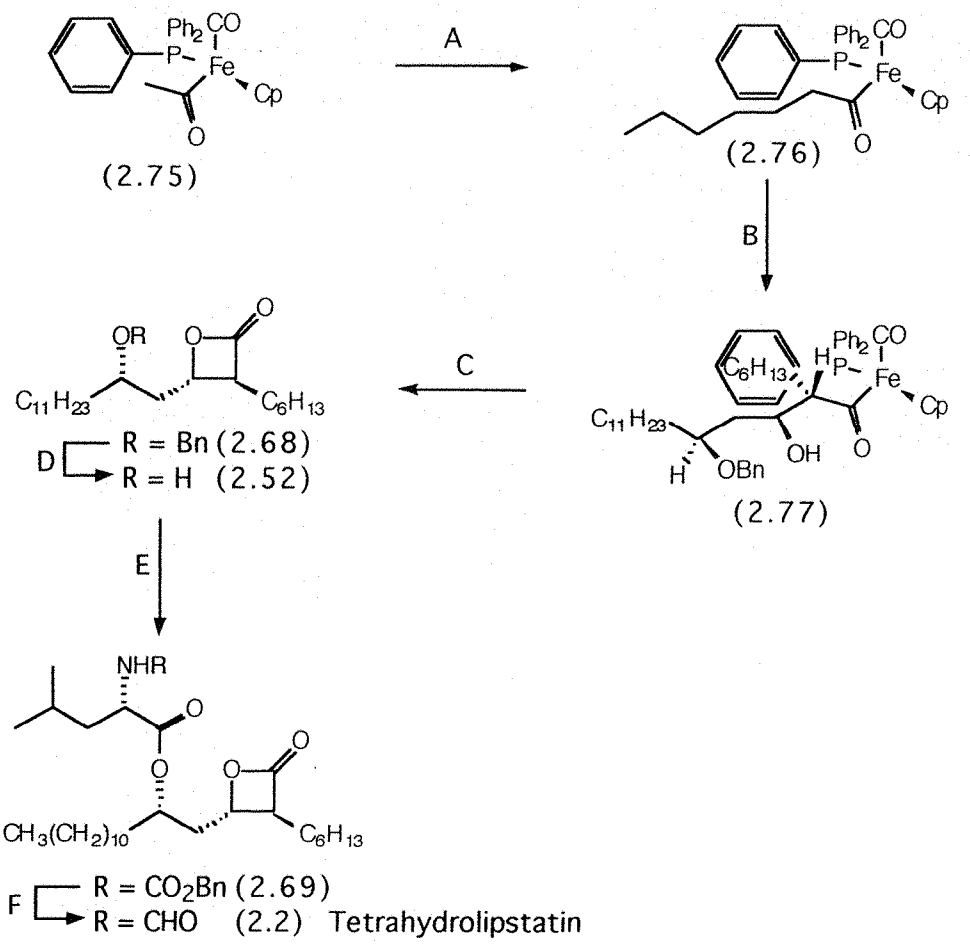
(scheme 2.10). Protection of the free hydroxyl group as the benzyl ether under acidic conditions[58] followed by selective deprotection yielded the β-hydroxy acid (2.67). Cyclisation with benzenesulphonyl chloride in pyridine gave the benzyl protected β-lactone. Deprotection followed by DCC esterification with N-Cbz protected leucine formed the protected leucine derivative. This was easily transformed to tetrahydrolipstatin by hydrogenolysis of the Cbz protecting group, followed by N-formylation.

In 1991 Davies and co-workers reported an asymmetric synthesis of tetrahydrolipstatin using a route to β-lactones developed in their laboratories[61]. The key step in the scheme involved the formation of a β-hydroxy acyl complex attached to an iron chiral auxiliary, which upon oxidation afforded the homochiral β-lactone. Starting from dodecanoyl chloride, condensation with Meldrum's acid followed by decarboxylation in methanol afforded the β-keto ester (2.71)(scheme 2.11). Catalytic hydrogenation using



Scheme 2.11

Noyori's conditions[62], i.e. $Ru(BINAP)Cl_2$, formed chiral β-hydroxy ester (2.72) in high yield with greater than 99% enantiomeric excess. The hydroxyl group was protected as the benzyl ether using benzyltrichloroacetimidate[58]. The ester was then reduced to the aldehyde (2.74) either directly using di-*iso*-butylaluminiumhydride or in two stages using lithium aluminium hydride followed by oxidation of the alcohol using the Dess-Martin reagent. Alkylation of the commercially available (*S*)-iron acetyl complex with hexyl iodide afforded the (*S*)-iron octanoyl complex (2.76)(scheme 2.12).



REAGENTS AND YIELDS

A	97%	i) *n*-BuLi, -78°C. ii) $C_6H_{13}I$, -78°C - rt.
B	92%	i) *n*-BuLi, -78°C. ii) $EtAlCl_2$, -40°C, iii) (2.74), -98°C.
C	57%	Br_2, DCM, -78°C.
D	99%	H_2, Pd/C, DCM, rt.
E		i) (*S*)-N-Cbz-Leucine, DCC, DCM, 0°C. ii) DMAP, rt.
F	77%	i) H_2, Pd/C. ii) AcOCHO, DCM, rt.

Scheme 2.12

Treatment of this complex with *n*-butyl lithium followed by transmetallation with diethylaluminium chloride formed the diethylaluminium enolate. Addition of the benzyl protected hydroxy aldehyde generated the (*S,S,S,S*)-aldol product (2.77), with less than 5% of the other diastereomers. Oxidation with bromine in dichloromethane at low temperature afforded, after chromatography, β-lactone (2.68) in 57% yield. Cleavage of the benzyl ether followed by esterification with N-Cbz protected Leucine afforded, after protecting group manipulation, tetrahydrolipstatin in 77% yield.

Chapter Three

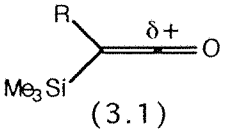
Chapter Three.

Formation of Tetrahydrolipstatin *via* Cycloaddition.

As was reported in the previous chapter, most of the past syntheses of tetrahydrolipstatin relied on the method reported by Adam and co-workers in 1972 for the formation of the β-lactone ring. Benzenesulphonyl chloride in pyridine has also been used in the synthesis of other recently discovered β-lactone natural products such as ebelactone A (1.5)[63] and L-659,699 (1233A)(1.4)[64].

In our approach to the synthesis of tetrahydrolipstatin, we wished to explore a totally different method for the formation of the β-lactone ring. We planned to make use of the work reported by Zaitseva and co-workers on the [2+2] cycloaddition of silyl ketenes to aldehydes, as previously discussed in chapter one[28]. Zaitseva and later Brady[34] had reported the reaction between silyl ketenes and aldehydes, in the presence of a Lewis acid, to afford silylated β-lactones.

Ketenes are in general highly reactive molecules that dimerise readily. Silyl ketenes are much more stable than ketenes; they can be stored for many months and do not readily dimerise. The stability induced by the silicon group is likely to be a result of both steric and electronic factors. One of the problems encountered when working with ketene, is the strong tendency of ketene to dimerise. The additional steric bulk created by the trimethylsilyl group should reduce the tendency of the silyl ketene to dimerise. The silyl ketene will also be stabilised by an electronic effect. In silyl ketenes the charges are distributed such that a partial positive charge exists on a carbon that is in a position beta to the silyl group (figure 3.1) and this charge can be stabilised by the trimethylsilyl group.

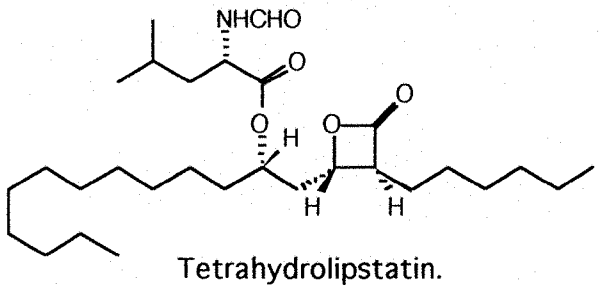


(3.1)
Figure 3.1

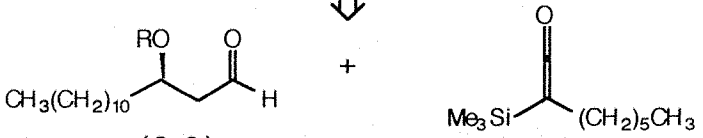
We wished to explore the possibility of using the cycloaddition reaction of an aldehyde to a silyl ketene, reported by Zaitseva and co-workers, to develop a simple, general stereoselective method for the formation of β-lactone rings. Earlier work in our group on the synthesis of tetrahydrolipstatin has been reported[65]. The cycloaddition of an aldehyde and silyl ketene formed the mainstay of this synthesis and we wished to further develop

and improve on this work.

Retrosynthetic analysis, using this cycloaddition approach gave two targets, homochiral protected hydroxy aldehyde (3.2) and *n*-hexyltrimethylsilyl ketene (3.3) (scheme 3.1). The homochiral hydroxy aldehyde is a known compound and has been



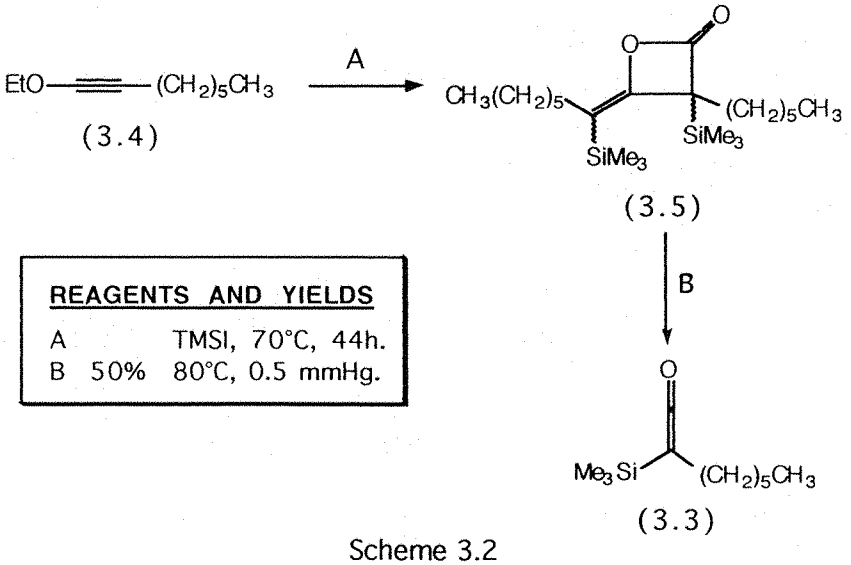
Tetrahydrolipstatin.



(3.2) (3.3)

Scheme 3.1

prepared *via* a number of different methods in the literature. *n*-Hexyltrimethylsilyl ketene, however, was not known until reported by Pons and Kocienski. As has already been discussed in chapter one, there are few literature methods reported for the formation of substituted silyl ketenes. Pons and Kocienski made use of a procedure developed by Sakurai (equation 1.7) to form their desired silyl ketene (3.3)[46]. Treatment of 1-ethoxyoctyne (3.4) with trimethylsilyl iodide, formed *in situ* from hexamethyldisilane and iodine, afforded, after distillation, hexyltrimethylsilyl ketene (3.3) in 50% yield (scheme 3.2).

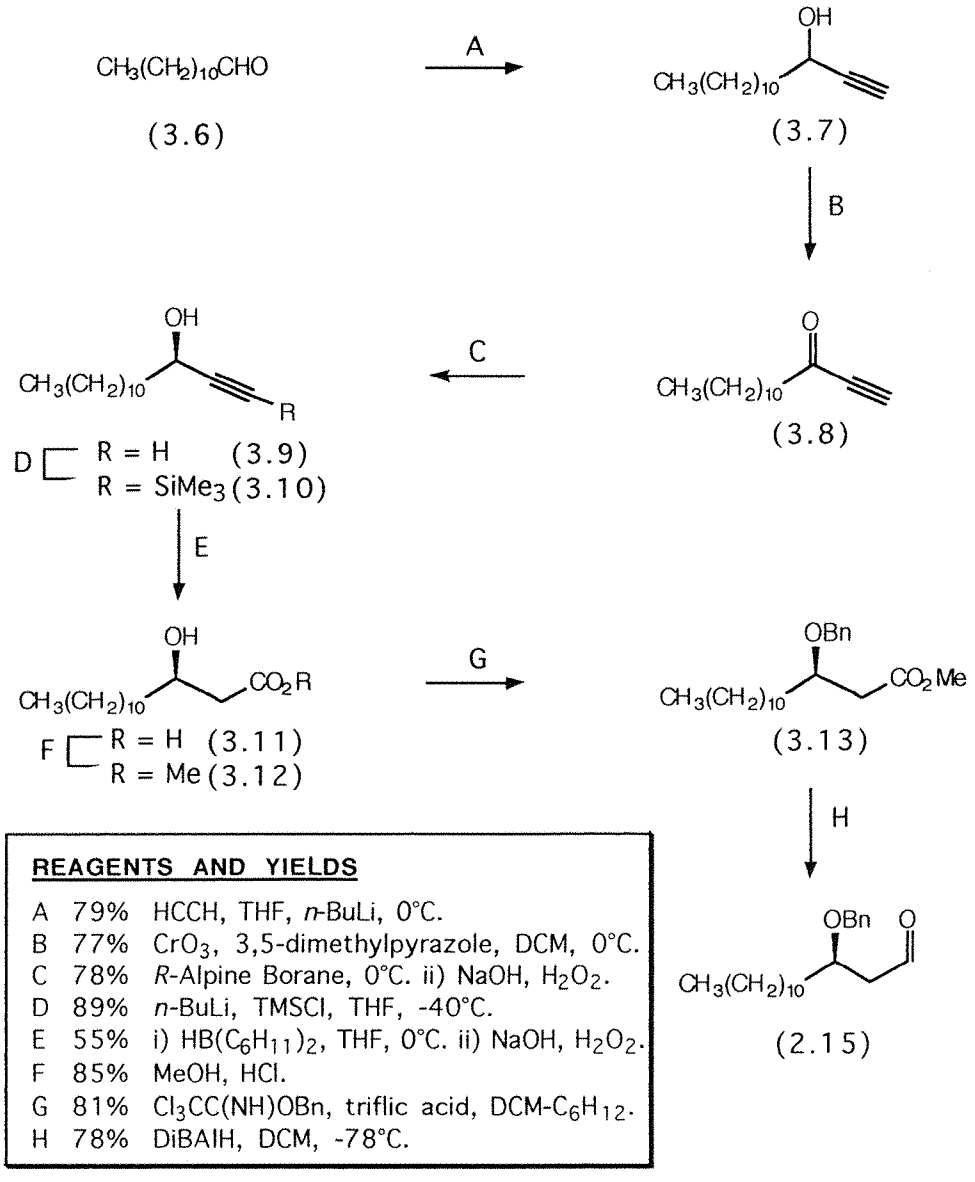


(3.4) (3.5) (3.3)

REAGENTS AND YIELDS		
A		TMSI, 70°C, 44h.
B	50%	80°C, 0.5 mmHg.

Scheme 3.2

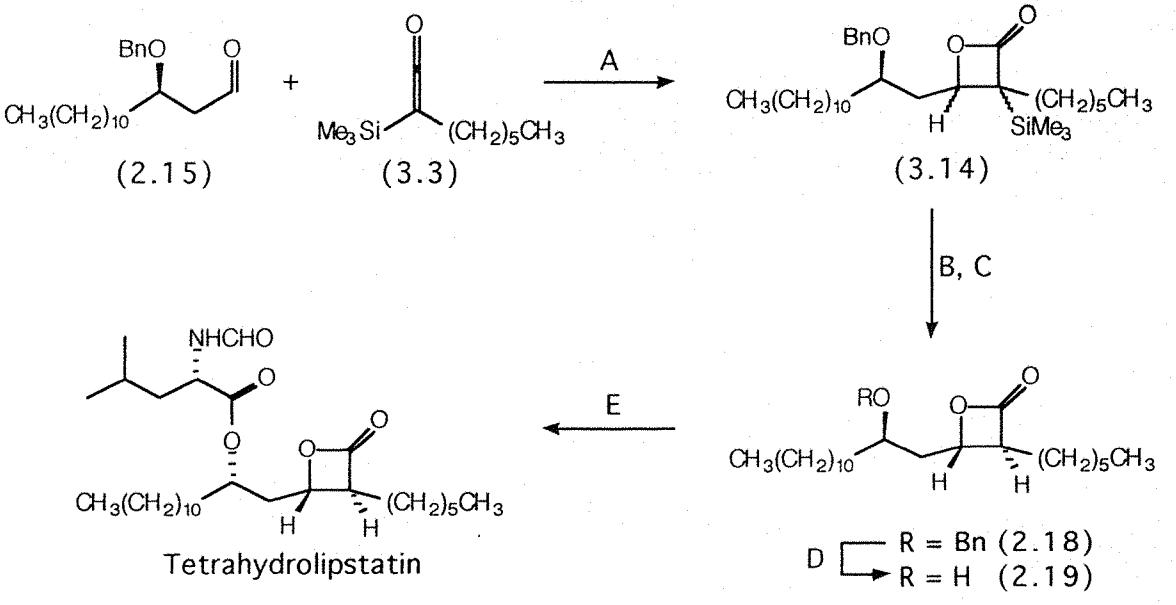
Pons and Kocienski synthesised the homochiral aldehyde (2.15) using an asymmetric borane reduction of the ynone (3.8). Further elaboration converted the acetylene into the required aldehyde functionality (scheme 3.3). The ynone was formed from a chromium



Scheme 3.3

trioxide oxidation of the propargylic alcohol (3.7) obtained from the addition of lithium acetylide to lauraldehyde (3.6). Reduction of the ketone using *R*-Alpine Borane afforded, after oxidation, the propargylic alcohol (3.9) in 78% yield and 84% enantiomeric excess, as measured from the ^{19}F NMR of the Mosher's ester derivative[66]. Deprotonation of the alkyne followed by treatment with chlorotrimethylsilane formed the trimethylsilylacetylene (3.10). Hydroboration of this acetylene with two equivalents of dicyclohexylborane afforded, after oxidation, carboxylic acid (3.11) in 55% yield[67]. The

acid was esterified, with methanol, before the hydroxyl group was protected as the benzyl ether using benzyltrichloroacetimidate[58]. The methyl ester (3.13) could then be reduced with di-*iso*-butylaluminium hydride to afford the desired aldehyde in 78% yield. The aldehyde obtained from this route then underwent cycloaddition with the silyl ketene (3.3), in the presence of boron trifluoride etherate, to afford the silylated β-lactone (3.14) as a diastereomeric mixture (scheme 3.4). Desilylation with



REAGENTS AND YIELDS

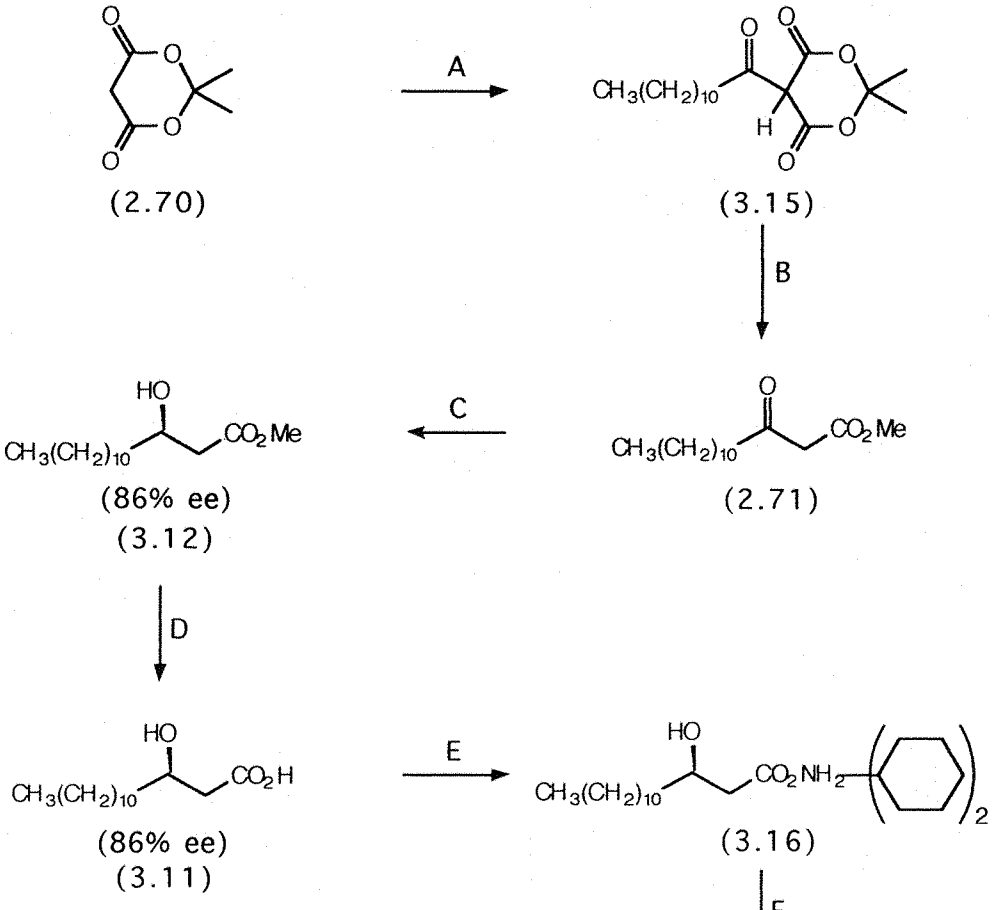
A	83%	$BF_3.Et_2O$, Et_2O, -15°C.
B	84%	TBAF, THF, -80°C.
C	55%	Separation.
D	88%	H_2, Pd/C, THF.
E	73%	(*S*)-N-formylleucine, PPh_3, DEAD, THF, 0°C.

Scheme 3.4

tetrabutylammonium fluoride afforded the β-lactone as a mixture of four diastereomers, which could be separated by chromatography to afford the desired isomer (2.18) in 55% yield. Cleavage of the benzyl protecting group followed by esterification, under Mitsunobu conditions, with (*S*)-N-formylleucine afforded tetrahydrolipstatin in good yield. This approach to the formation of the β-lactone is marred by the poor stereoselectivity obtained in the cycloaddition, resulting in the need for a careful chromatographic separation. The other drawback to this synthesis was the long and inelegant route used to form the homochiral hydroxy aldehyde.

There were in the literature a number of other methods for the formation of aldehyde

(2.15). The same aldehyde had been used in two of the Hoffman La-Roche syntheses of tetrahydrolipstatin[56]. Barbier and co-workers had formed the aldehyde from the reduction of the homochiral hydroxy ester (scheme 2.3), obtained using a method reported by Nakahata and coworkers[57]. Nakahata and co-workers had developed a method of forming homochiral β-hydroxy acids, which employed an enantioface-differentiating hydrogenation of the corresponding β-keto ester using a modified Raney nickel catalyst. In the paper they reported the formation of a series of optically pure β-hydroxy acids of varying alkyl chain length, one of which was the correct structure for use in the synthesis of tetrahydrolipstatin (scheme 3.5). The β-keto ester was formed from the



Scheme 3.5

reaction between dodecanyl chloride and 2,2-dimethyl-1,3-dioxane-4,6-dione (2.70) to form (3.15), which on heating in methanol underwent decarboxylation to afford methyl-3-oxotetradecanoate (2.71). Treatment of the β-keto ester with the tartaric acid, sodium bromide modified Raney nickel at 100°C at 100 Kg/cm^2 afforded the hydroxy ester (3.12) in 86% enantiomeric excess. Hydrolysis of the methyl ester afforded the hydroxy acid (3.11). The acid could be obtained enantiomerically pure by performing three preferential recrystallisations of the dicyclohexylammonium salt. Using this method, Barbier and co-workers were able to obtain the required hydroxy ester on a reasonable scale with 98% enantiomeric excess. Protection of the hydroxyl group as the benzyl ether under acidic conditions using benzyl-2,2,2-trichloroacetimidate[58] followed by reduction of the ester using di-*iso*-butylaluminium hydride afforded the required aldehyde in reasonable yields (scheme 2.3).

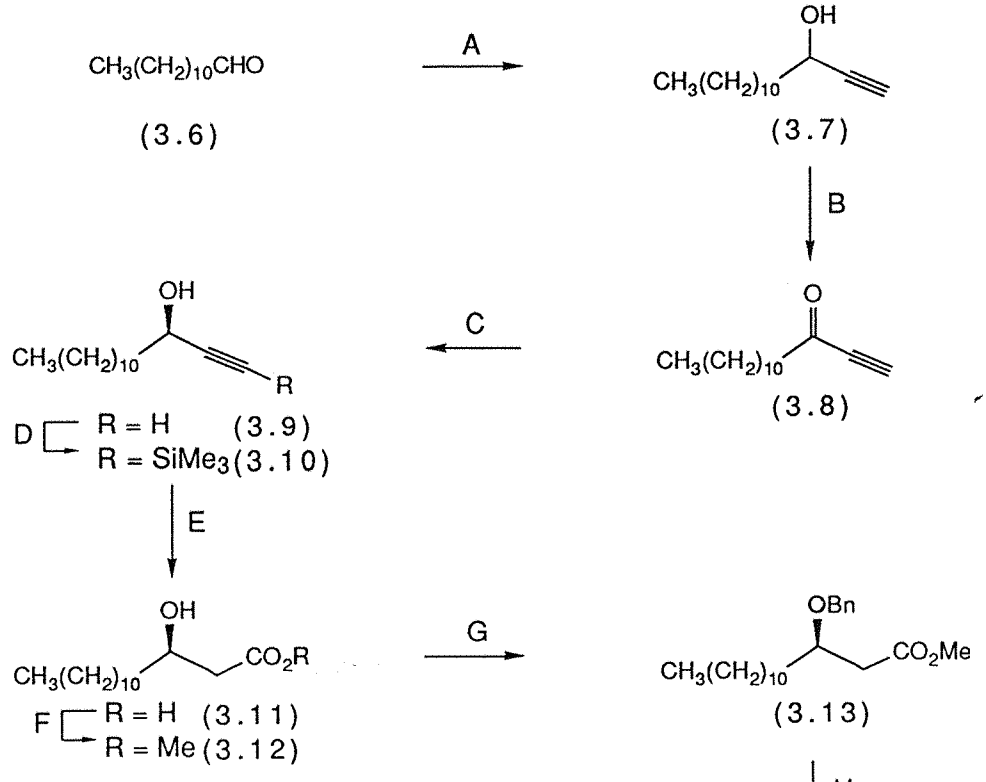
An alternative method for the formation of homochiral hydroxy aldehydes was used by Davies and co-workers in their reported synthesis of tetrahydrolipstatin (see chapter 2)[61]. They made use of Noyori's work on the enantioselective hydrogenation of β-keto esters using $Ru(BINAP)Cl_2$[62]. The β-keto ester (2.71) was formed in two steps from dodecanyl chloride as described above, by Nakahata. Hydrogenation of (2.71) at 100 atmospheres in the presence of (*S*)-$Ru(BINAP)Cl_2$, formed *in situ* from (*S*)-Ru $(BINAP)(OAc)_2$[68], afforded (*S*)-(-)-methyl 3-hydroxytetradecanoate (2.72) in 91% yield and greater than 99% enantiomeric excess (scheme 2.11). The ester could then be reduced to the aldehyde in one of two ways. The first method consisted of a straight forward reduction of the ester in one step using di-*iso*-butylaluminium hydride. Alternatively the reaction could be completed in two steps, using lithium aluminium hydride to reduce the ester to the alcohol followed by a Dess Martin oxidation of the alcohol to the aldehyde. Both routes afforded the aldehyde (2.74) in good yield.

Chapter Four

Chapter Four.

The Synthesis of the Homochiral Hydroxy Aldehyde.

As discussed in the previous chapter, a key compound in our proposed synthesis of tetrahydrolipstatin was to be the homochiral protected hydroxy aldehyde (3.2). Our initial route to this compound simply involved repeating the method reported by Pons[65], which was discussed in the previous chapter. Although we were able to repeat the route with comparable yields (scheme 4.1), we encountered some problems when repeating the reactions on multigram scales. The most troublesome reaction in the scheme was the chromium trioxide-3,5-dimethylpyrazole oxidation of the propargylic alcohol (3.7) to the ynone (3.8). As the scale increased, the yield of the reaction dropped considerably and



REAGENTS AND YIELDS

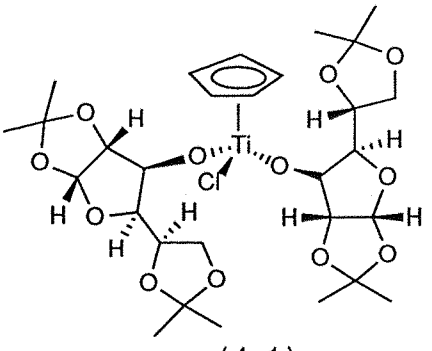
A	67%	HCCH, THF, *n*-BuLi, 0°C.
B	76%	CrO_3, 3,5-dimethylpyrazole, DCM, 0°C.
C	81%	*R*-Alpine Borane, 0°C. ii H_2O_2, NaOH.
D	61%	*n*-BuLi, TMSCl, THF, -40°C.
E	75%	i) $HB(C_6H_{11})_2$, THF, 0°C. ii) NaOH, H_2O_2.
F	60%	MeOH, HCl.
G	77%	$Cl_3CC(NH)OBn$, triflic acid, DCM-C_6H_{12}.
H	67%	DiBAlH, DCM, -78°C.

Scheme 4.1

practical problems were encountered in removing the chromium residues.

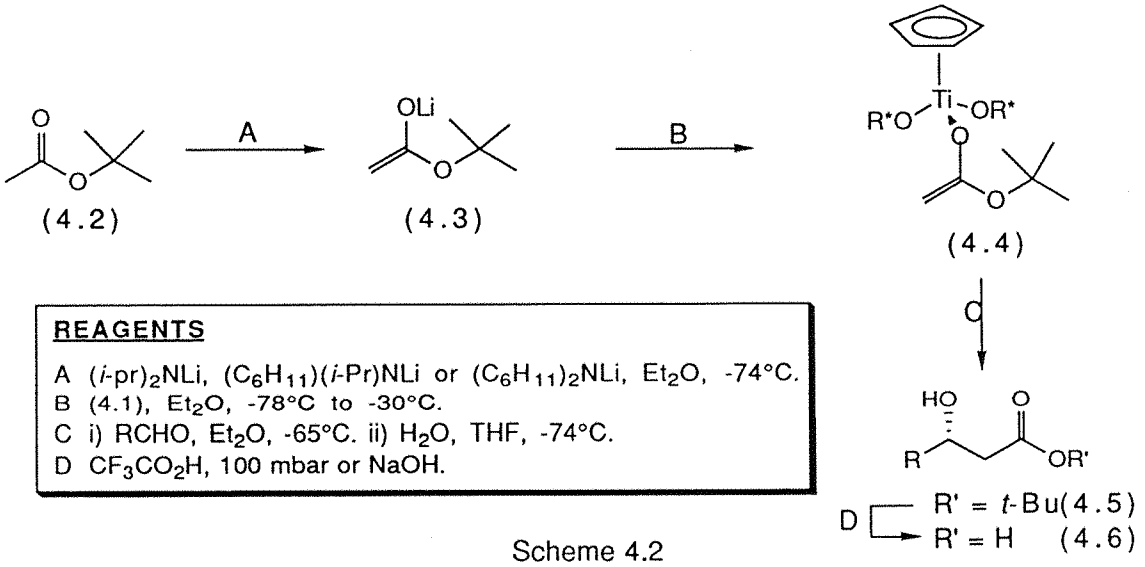
Although it would probably have been possible to avoid this problem by changing the oxidation conditions, it was felt that the scheme, generally, could be improved. The initial steps in the scheme offer a most inelegant method for the formation of the homochiral hydroxyl group. In the first step the propargylic alcohol (3.7) is formed without any stereocontrol, this is then oxidised to the ketone before being reduced to reform the alkynol (3.9) this time with an 84% enantiomeric excess. The ynone (3.8) was reduced using nearly two equivalents of *R*-Alpine Borane. The use of nearly two equivalents of a reducing agent to induce stereochemistry cannot be considered an ideal procedure, especially so early in the synthesis. Producing the aldehyde on a reasonable, multigram scale would become very expensive.

It therefore became necessary to devise an alternative route to the protected homochiral hydroxy aldehyde (3.2). In 1989 a research group at Ciba-Geigy reported a new route to β-hydroxy esters[69], using their recently developed titanium-carbohydrate complex (figure 4.1)[70,71]. The reaction consisted of an aldol reaction between a *tertiary*-butyl acetate group bound to the titanium complex (4.4) and an aldehyde. Using this procedure they were able to produce hydroxy esters (4.5) with 90-95% optical purity (scheme 4.2). This scheme offered an interesting and concise route to our chiral



(4.1)

Figure 4.1



(4.2) (4.3) (4.4)

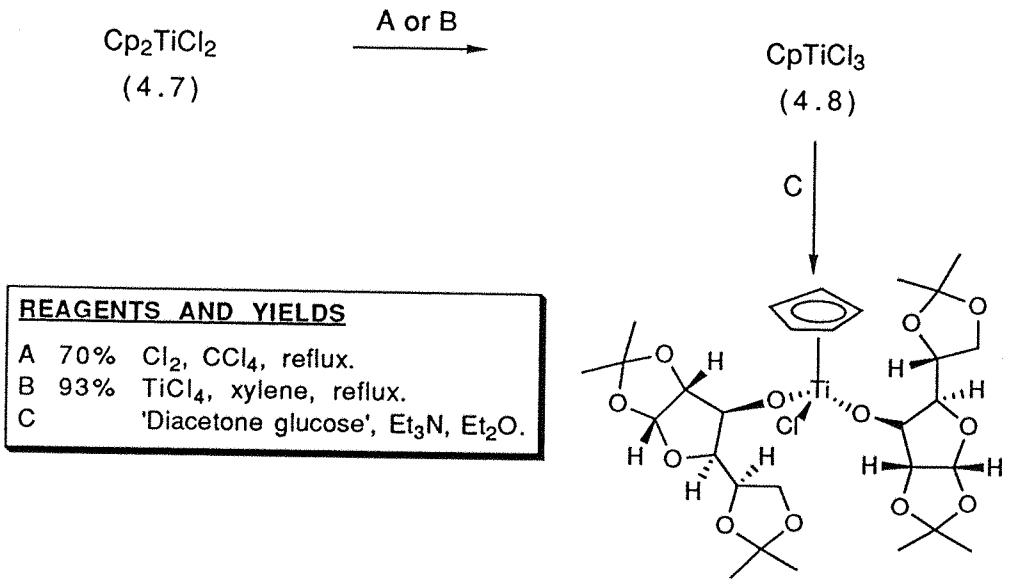
REAGENTS

A $(i\text{-pr})_2NLi$, $(C_6H_{11})(i\text{-Pr})NLi$ or $(C_6H_{11})_2NLi$, Et_2O, -74°C.
B (4.1), Et_2O, -78°C to -30°C.
C i) RCHO, Et_2O, -65°C. ii) H_2O, THF, -74°C.
D CF_3CO_2H, 100 mbar or NaOH.

Scheme 4.2

hydroxy aldehyde, as reduction of the *t*-butyl ester, using di-*iso*-butylaluminium hydride, would afford the homochiral hydroxy aldehyde.

The air sensitive titanium-carbohydrate complex (4.1) was generated from the reaction of cyclopentadienyltitanium trichloride with 1,2,5,6-di-*iso*-propylidene-D-glucose (diacetone-D-glucose) (scheme 4.3). The cyclopentadienyltitanium trichloride

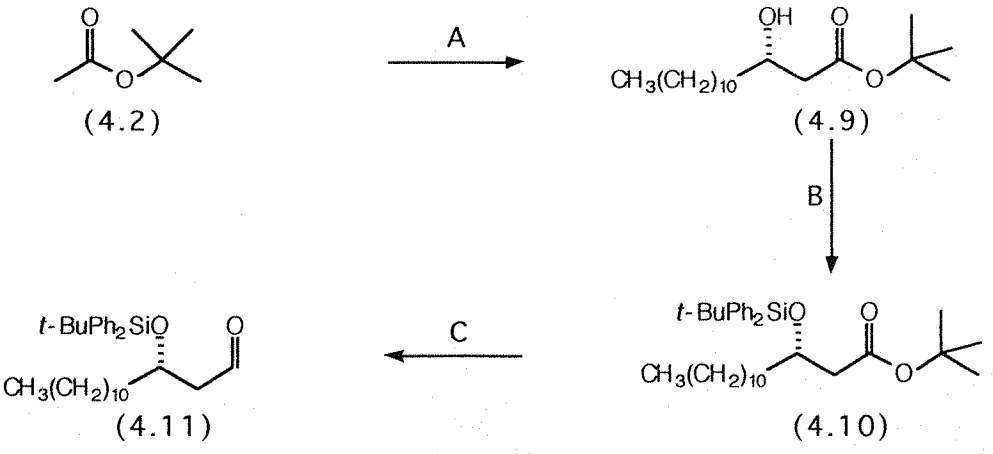


(4.1)

Scheme 4.3

(4.8) could be formed from bis(cyclopentadienyl)titanium dichloride (titanocene dichloride) using two different methods[72] . The first route involved bubbling chlorine gas through a refluxing solution of titanocene dichloride (4.7) in carbon tetrachloride. The second method consisted simply of refluxing a mixture of titanium tetrachloride and titanocene dichloride in xylene. Of the two methods the second was usually the method of choice, due to its practical simplicity. Both reactions had to be conducted carefully ensuring the complete absence of oxygen or moisture. Treatment of cyclopentadienyltitanium trichloride (4.8) with diacetone-D-glucose in the presence of triethylamine resulted in the formation of the titanium-carbohydrate complex (4.1). After removal of triethylamine hydrochloride, the complex could be stored as a stock solution in diethyl ether or toluene. The molarity was calculated assuming quantitative formation of the complex.

Having formed the titanium-carbohydrate complex, it could be used to induce stereocontrol in the aldol reaction between *t*-butyl acetate (4.2) and dodecanal (scheme

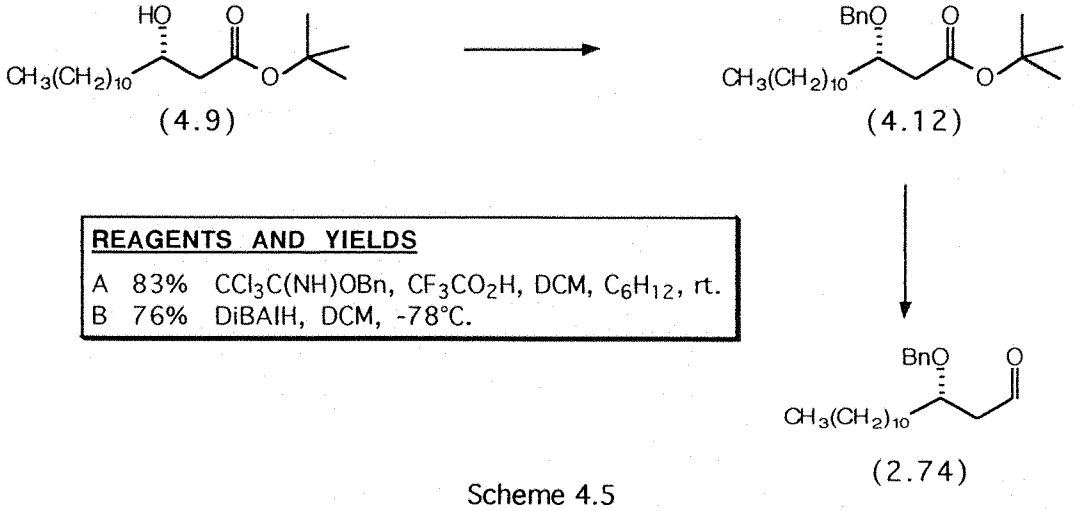


REAGENTS AND YIELDS

A 89% i) $(C_6H_{11})_2NLi$, Et_2O, -78°C. ii) (4.1), Et_2O, -78°C to -30°C iii) $C_{11}H_{23}CHO$, Et_2O, -65°C. iv) H_2O, THF, -65°C.
B 94% *t*-$BuPh_2SiCl$, imidazole, DMF.
C 70% DiBAlH, DCM, -78°C.

Scheme 4.4

4.4). Lithiation of the acetate (4.2) with lithium dicyclohexylamide followed by transmetallation with the titanium complex (4.1) afforded the enolate (4.4), as shown in scheme 4.2. The titanium acetate complex (4.4) then underwent an aldol reaction with lauraldehyde to furnish, after work up, the hydroxy ester (4.9) in 89% yield. The enantiomeric excess was measured, by formation of the Mosher's ester[66], as 82%. The hydroxyl group could then be protected as the *tertiary*-butyl dimethylsilyl (scheme 4.4) or benzyl ether (scheme 4.5) before the *tert*-butyl ester was reduced to the aldehyde using di-*iso*-butylaluminium hydride.



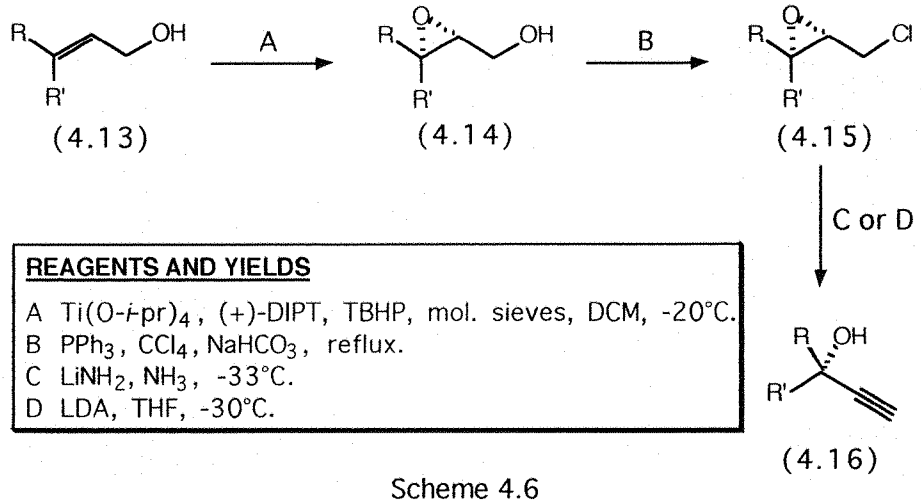
REAGENTS AND YIELDS

A 83% $CCl_3C(NH)OBn$, CF_3CO_2H, DCM, C_6H_{12}, rt.
B 76% DiBAlH, DCM, -78°C.

Scheme 4.5

This procedure offered a concise route to the homochiral hydroxy aldehyde but, as with the previous scheme, made use of a stoichiometric quantity of the chiral reagent to control the stereochemistry and achieved no better stereocontrol than the Pons route. Although the chiral starting material in this case, glucose, is inexpensive. The real difficulty in this scheme lay in the manufacture of the large quantities of the titanium complex needed. Problems arose in the handling and filtering of the moisture sensitive titanium reagents, on large scale, under inert conditions. It was decided that an alternative route was needed.

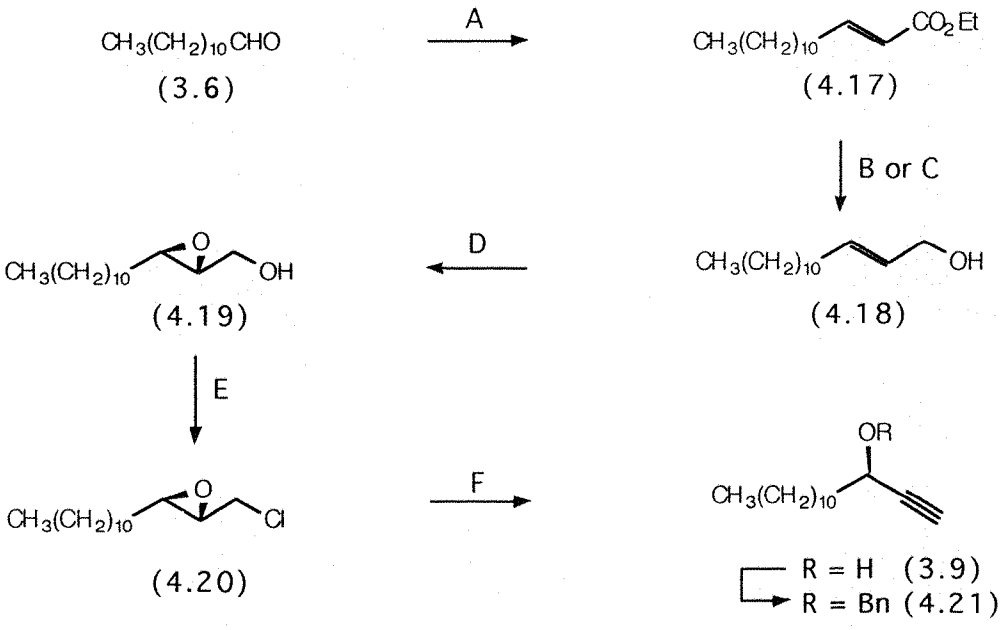
In 1990 Yadav and co-workers reported a method for the synthesis of chiral propargylic alcohols[73]. The main feature of this scheme was the rearrangement of a chiral epoxychloride (4.15) to a chiral propargylic alcohol (4.16) using lithium di-*iso*-propyl amine or lithium amide (scheme 4.6). The epoxy chloride was obtained



Scheme 4.6

from the corresponding epoxy alcohol (4.14) which could be easily obtained from the Sharpless epoxidation[74] of the allylic alcohol (4.13). We devised a synthesis to form our desired aldehyde incorporating this work by Yadav.

Our final route to the homochiral hydroxy aldehyde, depicted in scheme 4.7, started from lauraldehyde (3.6), which underwent a Wittig reaction with (carboethoxy)methylene triphenylphosphorane to form the α,β-unsaturated ethyl ester (4.17). The phosphorane was commercially available, but could easily be synthesised in large quantities[75]. The ester (4.17) was then reduced to the alcohol (4.18) using either two equivalents of di-*iso*-butyl aluminium hydride or lithium aluminium hydride. Although the first reagent gave higher yields, the second method was experimentally



REAGENTS AND YIELDS

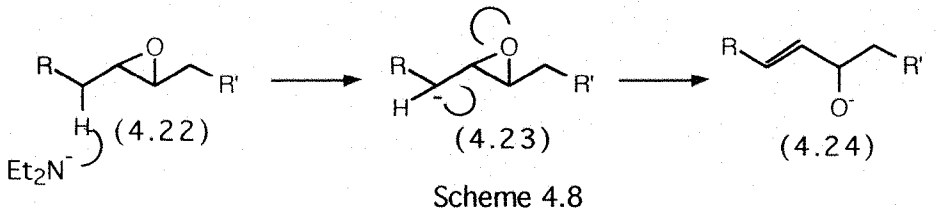
A	99%	Ph_3PCHCO_2Et, $PhCH_3$, reflux.
B	98%	DiBAlH, DCM, -78°C.
C	60%	$LiAlH_4$, PhH, 60°C.
D	90%	(-)-DIPT, $Ti(O\text{-}i\text{-}pr)_4$, TBHP, mol. sieves, DCM, -20°C.
E	87%	PPh_3, $NaHCO_3$, CCl_4, reflux.
F	98%	LDA, THF, -30°C.
G	90%	NaH, BnBr, DMF.

Scheme 4.7

easier and therefore preferable for larger scale work. Sharpless epoxidation of the allylic alcohol proceeded smoothly to furnish the epoxy alcohol, as a solid, in 90% yield. To deduce the enantiomeric excess obtained using this scheme, the epoxy alcohol was esterified with O-acetylmandelic chloride. By proton and carbon-13 NMR spectroscopy the product was found to be enantiomerically pure, within the limits of detection. Treatment of the epoxy alcohol (4.19) with triphenyl phosphine in refluxing carbon tetrachloride with a catalytic quantity of sodium bicarbonate afforded the epoxy chloride (4.20), as a solid, in 90% yield. Treatment of the epoxy chloride with three equivalents of lithium di-*iso*-propylamine (LDA) at -30°C furnished the homochiral alkynol (3.9) as a low melting solid. In our early work we then protected the hydroxyl group as the benzyl ether (4.21) (scheme 4.7).

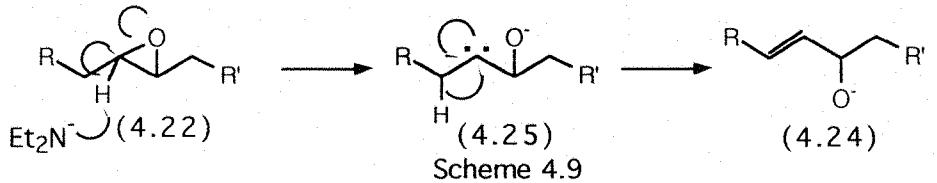
The mechanism for the opening of epoxides to afford the allylic alcohols, with lithium diethylamide has been examined in the literature by Cope and co-workers[76]. In their work they reported that two possible mechanisms for the opening of the epoxide can occur.

The first of these involves deprotonation of the carbon α to the oxirane ring, followed by ring opening (scheme 4.8). The second possible mechanism involves the removal of one of



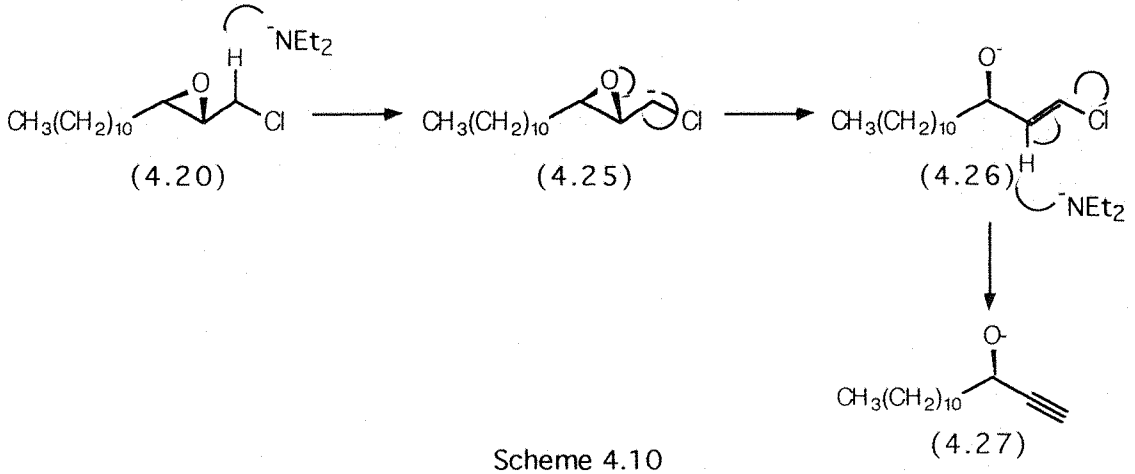
Scheme 4.8

the protons on the oxirane ring to form a carbene, which then undergoes a 1,2-hydride shift to form the allylic alcohol (scheme 4.9). Cope has shown that the carbene



Scheme 4.9

mechanism occurs in systems such as *cis*-cyclooctene oxide and *cis*-cyclodecene oxide, he reasoned that this was due to steric effects which existed in the medium ring epoxides[77]. In aliphatic epoxides such as *cis*- and *trans*-4-octene oxide the carbanion mechanism was shown to predominate. Therefore, the mechanism for the transformation of the epoxy chloride (4.20) to the propargylic alcohol (3.9) is likely to proceed through a carbanion intermediate (scheme 4.10).

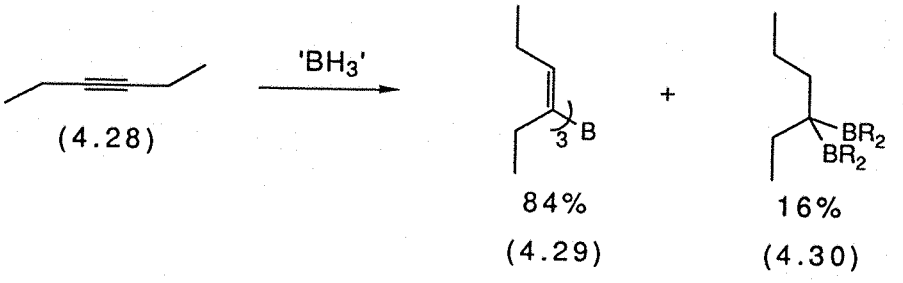


Scheme 4.10

Having generated the hydroxy alkyne (3.9) our next task was to transform this to the hydroxy aldehyde. This had already been achieved by Pons and Kocienski in their synthesis of tetrahydrolipstatin (scheme 3.3). In their route, transformation of the propargylic alcohol to the hydroxy aldehyde had occurred in four steps with a total yield of 32%. The

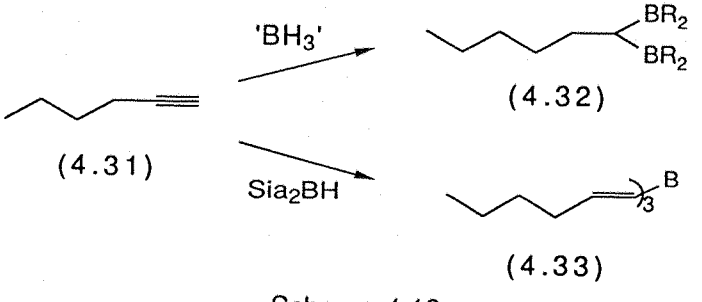
acetylene was deprotonated before being treated with trimethylsilyl chloride to afford the silyl acetylene (3.10). Hydroboration with two equivalents of dicyclohexylborane furnished, after oxidation, the carboxylic acid (3.11). Formation of the methyl ester followed by reduction with di-*iso*-butylaluminium hydride afforded the aldehyde. This seemed to be an unnecessarily lengthy approach to this transformation, as hydroboration of an acetylene with one equivalent of a borane reagent should result in the formation, after oxidation, of an aldehyde in one step.

Some work on the hydroboration of internal and terminal acetylenes was published by Brown and Zweifel in 1961[78]. They treated 3-hexyne and 1-hexyne with borane and analysed the products by gas chromatography (schemes 4.11 and 4.12). From these

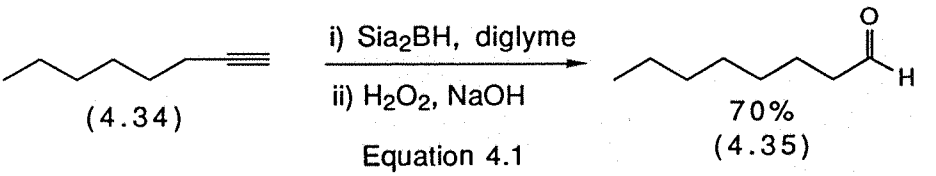


Scheme 4.11

experiments they deduced that the terminal acetylenes (4.31) preferentially underwent dihydroboration (4.32) where as the major product with the internal acetylene was the monohydroborated derivative (4.29). Repeating the hydroboration of the terminal acetylene using disiamylborane, a sterically hindered hydroborating reagent made *in situ*, they were able to generate the monohydroborated product (4.33) almost quantitatively, as shown by gas chromatographic analysis (scheme 4.12). Repeating this procedure on 1-octyne (4.34) they obtained, after careful oxidation, octanal (4.35) in 70% yield (equation 4.1). The oxidation was accomplished by the addition of hydrogen peroxide



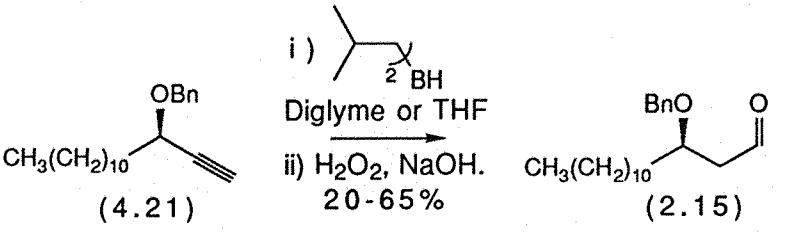
Scheme 4.12



Equation 4.1

whilst maintaining the pH of the reaction mixture between seven and eight. Later, in 1972, Brown and Gupta published a communication on the use of catecholborane for the monohydroboration of alkynes[79]. In this paper they stated that this reaction could be used to make aldehydes but no examples were given.

We attempted to reproduce the hydroboration of the benzyl protected propargylic alcohol (4.21) with disiamylborane in diglyme or tetrahydrofuran as described by Zweifel[78]. Unfortunately in our hands the reaction proved to be highly capricious, affording yields of between 20 and 65% (equation 4.2). The bulk of the remainder being

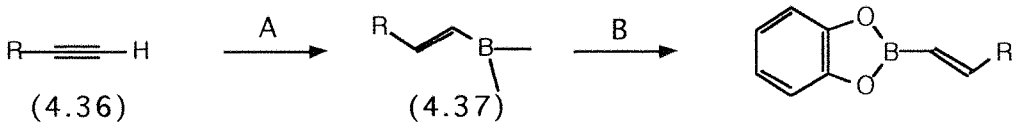


Equation 4.2

the starting material. Attempts to drive the reaction to completion by adding further equivalents of borane reagent only resulted in a reduction of the yield and an increase in the amount of the alcohol side product isolated. This was probably due to the formation of the dihydroborated product. Zweifel had reported that the dihydroboration product of 1-hexyne (4.32) when oxidised afforded 1-hexanol as the major product and concluded that the dihydroboration product must undergo rapid hydrolysis to lose one of the carbon-boron bonds before the oxidation takes place.

Due to the low yields encountered on using disiamyl borane, we repeated the hydroboration of the alkyne using other sterically hindered hydroborating reagents. We used a variety of other borane reagents, including catecholborane, 9-BBN and dicyclohexylborane. Unfortunately, no significant improvement in the yield of the aldehyde was observed. While this work was in progress a paper was published by Periasamy and co-workers, which outlined the use of borane-N,N-diethylaniline complex in catalysing the reaction of catecholborane with alkynes[80]. Upon treating alkynes with

catecholborane in the presence of 10 mol.% of borane-N,N-diethylaniline at 25°C they were able to produce aldehydes in yields of between 65-81%. Periasamy and co-workers proposed that the mechanism involved the initial formation of alkenyl borane (4.37), which would undergo rapid exchange with the alkoxyborane to form the alkenyl catecholborane (scheme 4.13). Their mechanism was based on work reported in 1971 by

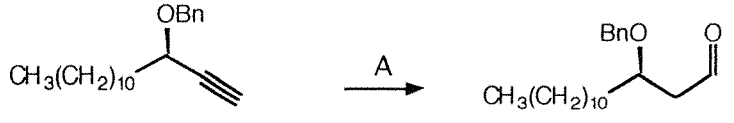


(4.36) (4.37) (4.38)

REAGENTS
A BH_3.N,N-diethylaniline.
B Catecholborane.

Scheme 4.13

Brown and Gupta[81], which described the exchange reaction that occurred between triaryloxyboranes and trialkyl boranes in the presence of catalytic amounts of borane, to afford alkylaryloxyboranes. When we repeated the hydroboration of our acetylene (4.21) using catecholborane and adding a catalytic amount of borane-N,N-diethylaniline we obtained the aldehyde (2.15) in reasonable yields after twenty-four hours at room temperature (equation 4.3).



(4.21) (2.15)

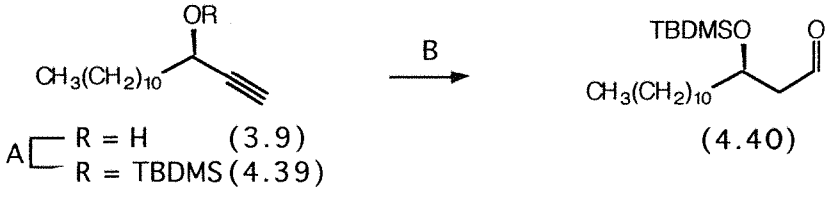
REAGENTS AND YIELDS
A 71% i) Catecholborane, BH_3.N,N-diethylaniline, THF, 23°C.
ii) H_2O_2, NaOH, 50°C.

Equation 4.3

Having now solved the problem of driving the reaction to completion, our next difficulty arose from the oxidation of the borane to form the aldehyde. In the work by Zweifel they had formed the aldehyde by adding hydrogen peroxide, whilst maintaining the pH between seven and eight by the addition of sodium hydroxide. This was not always practical on a small scale, so we tried to make use of other oxidative conditions.

Periasamy and co-workers, in their work on borane-N,N-diethylaniline, had used sodium acetate and hydrogen peroxide. Unfortunately on repeating this work we found that some of the acetic acid formed stayed in the organic phase on workup and on concentration caused the benzyloxy aldehyde to undergo elimination to form the α,β-unsaturated aldehyde. So it appeared that our problem was compounded, as our molecule was sensitive to both acidic and basic conditions. We also tried to make use of other known reagents for borane oxidation such as sodium percarbonate[82] and sodium perborate[83] without any improvement to the yield of the aldehyde. Finally we were forced to return to using hydrogen peroxide and sodium hydroxide and monitoring the pH very carefully upon addition of the reagents and throughout the oxidation.

Later in our work we switched to using a silicon protecting group for the hydroxy acetylene. We found that the hydroboration occurred smoothly using catecholborane, without the need for borane-N,N-diethylaniline, but we continued to use the hydrogen peroxide, sodium hydroxide work up (scheme 4.14). A possible reason for the difference



REAGENTS AND YIELDS

A 99% *t*-$BuMe_2SiCl$, imidazole, DMF.
B 69% i) Catecholborane, THF, reflux. ii) H_2O_2, NaOH, 50°C.

Scheme 4.14

in reactivity between the benzyl and silyl protected hydroxy acetylene could be explained by the difference in the ability of the ether oxygen to act as a Lewis base. Schreiber has reported that the oxygen atom in a benzyl ether acts as a stronger Lewis base than the oxygen atom in a silyl ether[84]. This finding may offer an explanation as to why the benzyl-protected propargylic alcohol (4.21) is less reactive towards hydroboration than the silyl-protected hydroxy alkyne (4.39). If the oxygen atom in the benzyl ether is a strong enough Lewis base to co-ordinate the borane reagent, this may hinder the borane reagent from performing the hydroboration. The silyl ether possessing less Lewis

basicity is possibly unable to co-ordinate the borane reagent and this may account for the difference in the reactivity of the benzyl and silyl protected hydroxy acetylene.

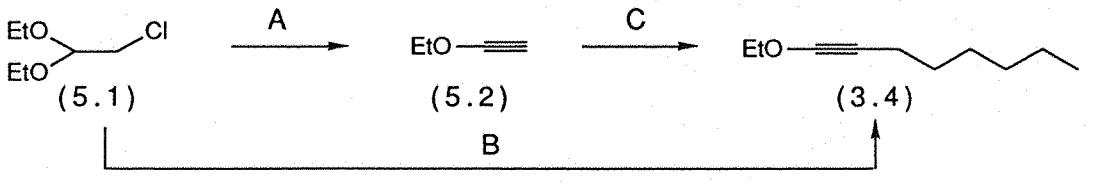
We had now developed a route to the homochiral hydroxy aldehyde, which induced the chirality at the hydroxyl group using a catalytic asymmetric procedure. Our scheme avoided many of the problems encountered with the Pons route. Due to the high stereoselectivity of the Sharpless reaction and the isolation of a series of crystalline compounds during the scheme, we were able to obtain the final product, the hydroxy aldehyde, enantiomerically pure. This was an obvious improvement over the 84% enantiomeric excess obtained in the Pons route. We encountered no experimental difficulties on increasing the scale of the reactions up to thirty grams.

Chapter Five

Chapter Five.

Formation of *n*-Hexyltrimethylsilyl Ketene.

The methods available in the literature for the formation of substituted silyl ketenes have already been discussed in chapter one. We chose to form silyl ketene (3.3) using the method described by Pons and Kocienski in their synthesis of tetrahydrolipstatin (scheme 3.2). Pons had synthesised the silyl ketene using an adaptation of a procedure reported by Sakurai[46]. Treatment of 1-ethoxy-1-octyne (3.3) with trimethylsilyl iodide, generated *in situ*, afforded *n*-hexyltrimethylsilyl ketene in 50% yield (scheme 3.2). The 1-ethoxy-1-octyne[85] (3.3) could be formed in one of two ways. Firstly, deprotonation of ethoxy acetylene (5.2) with *n*-butyl lithium followed by treatment with hexyl iodide in tetrahydrofuran and hexamethylphosphoramide (HMPA) at low temperature afforded ethoxy octyne (5.2) in 97% yield (scheme 5.1). The ethoxy acetylene (5.2) could be



REAGENTS AND YIELDS

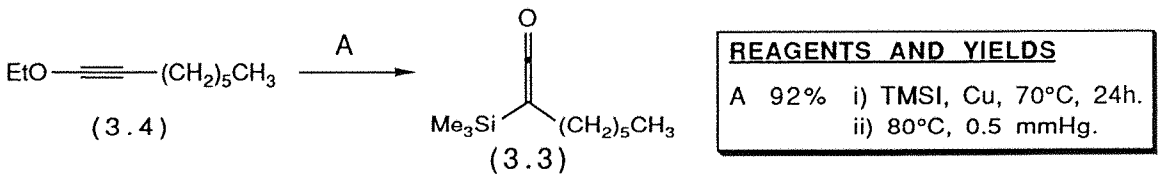
A 17% $NaNH_2$, NH_3, -30°C. ii) $NaCl/H_20$.
B 43% i) $NaNH_2$, NH_3, -30°C. ii) $C_6H_{11}I$.
C 97% i) *n*-BuLi, THF, HMPA. ii) $C_6H_{11}I$.

Scheme 5.1

obtained from commercial sources or from the treatment of chloroacetaldehyde diethyl acetal (5.1) with sodamide[86] (scheme 5.1). 1-Ethoxy-1-octyne could also be generated in one step by treating chloroacetaldehyde diethyl acetal (5.1) with sodamide in liquid ammonia and quenching the reaction with hexyl iodide instead of aqueous sodium chloride (scheme 5.1).

The silyl ketene (3.2) was obtained by treating 1-ethoxy-1-octyne (3.4) with trimethylsilyl iodide (scheme 5.2). The trimethylsilyl iodide was produced *in situ* by heating together hexamethyldisilane and iodine. On cooling, 1-ethoxy-1-octyne (3.4)

was added and the neat reaction mixture was heated at 70°C for forty-four hours. Careful monitoring of the reaction by infra red spectroscopy revealed that as the reaction proceeded the absorption band due to the acetylene (2272 cm^{-1}) diminished and at the same time a band at 2086 cm^{-1} was observed. This band was due to formation of the silyl ketene. As the reaction neared completion the ketene absorption was seen to diminish and a band at 1781 cm^{-1} was seen to increase in intensity, this band was believed to be due to the ketene dimer (3.5). On completion of the reaction, the excess trimethylsilyl iodide was removed *in vacuo* and the dimer was thermolysed (80°C, 0.5 mmHg) to afford the silyl ketene. A side product of the reaction, which was occasionally seen, was thought to be formed by the reaction of residual iodine, either left in the reaction mixture after formation of the trimethylsilyl iodide or formed by the breakdown of the trimethylsilyl iodide under the reaction conditions. Although the side product was never isolated or characterised, its presence could be easily detected by its characteristic infra red band at 1252 cm^{-1}. The presence of this impurity interfered with the cycloaddition reaction resulting in a low yield of the β-lactone. It became obvious that it was necessary to ensure that all the iodine had been consumed before the acetylene was added and to ensure that any iodine generated during the course of the reaction by the breakdown of trimethylsilyl iodide was removed. The most obvious solution was to add copper to the reaction before the addition of the acetylene. The addition of copper, either as clean copper wire or as the powder, resulted in a considerable improvement to the reaction preventing the formation of the troublesome side product and reducing the reaction time from forty-four to twenty-four hours. The suppression in the formation of the side products also resulted in an increase in the yield from 50% to 92% (equation 5.1). This was obviously a vast improvement and meant that we now had a high yielding and reliable method for the formation of the silyl ketene.



(3.4) (3.3)

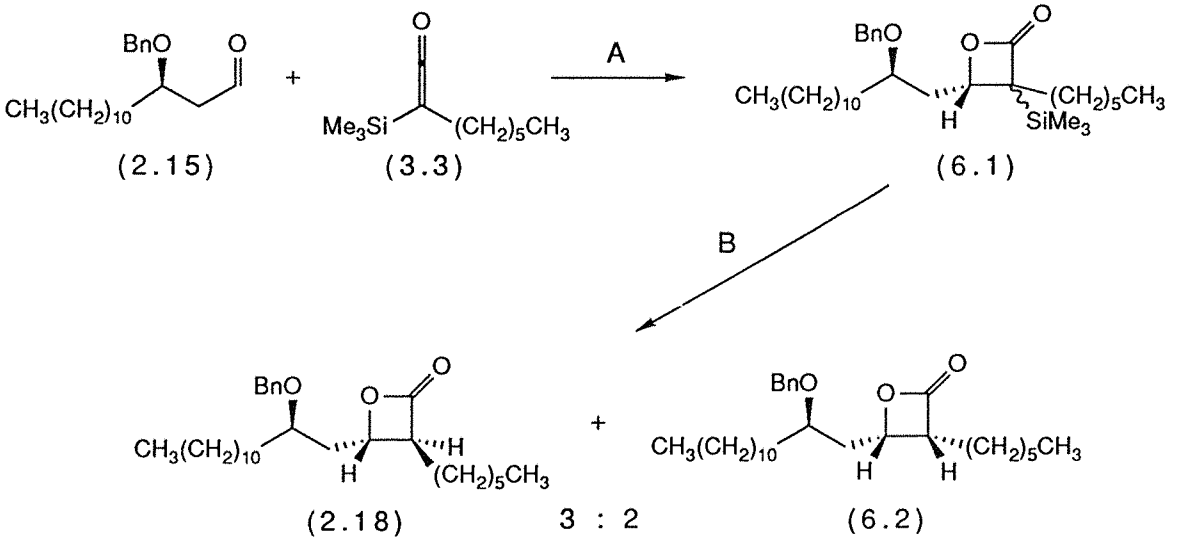
Equation 5.1

Chapter Six

Chapter Six.

Formation of Tetrahydrolipstatin.

As has been previously discussed in chapter three, we intended to synthesise tetrahydrolipstatin using a cycloaddition reaction between a homochiral hydroxy aldehyde and a silyl ketene. Chapters four and five described how we had developed high yielding methods for the production of the silyl ketene and the homochiral hydroxy aldehyde, both on reasonable scales. We now turned our attention to using these compounds in the cycloaddition reaction. Pons and Kocienski had reported the cycloaddition of the aldehyde (2.15) to the silyl ketene (3.3) in the presence of boron trifluoride etherate (scheme 3.4)[65]. Although the cycloaddition proceeded smoothly, desilylation afforded the β-lactone as a mixture of four diastereomers, the desired isomer (2.18) accounting for 55% of the mixture. Our initial work on the cycloaddition involved simply repeating the procedure described by Pons. We obtained the β-lactone with comparable yields to those reported by Pons (scheme 6.1). Unfortunately in our hands the silylated β-lactone (6.1) proved to be

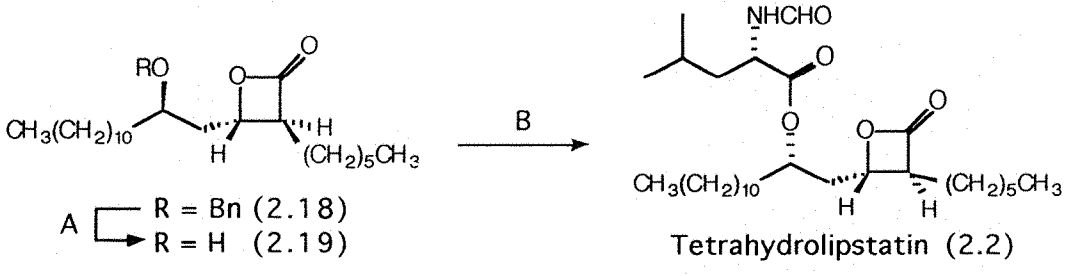


REAGENTS AND YIELDS		
A	-	$BF_3.Et_2O$, Et_2O, -15°C.
B	72%	TBAF, THF, -80°C.

Scheme 6.1

unstable on silica. Purification of this material, by column chromatography, resulted in some of the β-lactone (6.1) undergoing desilylation. Therefore, we isolated a mixture of the silylated and desilylated β-lactone from the column. We assumed that the desilylation on silica was caused by the presence of trace amounts of fluoride residues, derived from the boron trifluoride etherate, which remained present in the crude reaction mixture after work up. We attempted to alleviate this problem by washing the organic phase, obtained after extracting the reaction mixture, with a dilute solution of sodium bicarbonate. Unfortunately this resulted in a decrease in the yield and did not prevent some desilylation still occurring on chromatography. To avoid this problem we usually carried the reaction mixture, from the cycloaddition, through to the next step, crude. Therefore the mixture of diastereomers was subjected to desilylation using tetrabutylammonium fluoride, to afford after five minutes the β-lactone in good yield. Chromatographic separation revealed two diastereomers, the *trans*-(2.18) and *cis*-(6.2) isomers, in a ratio of 3:2 in favour of the *trans*-isomer. Although Pons had reported the formation of four diastereomers, we were only able to detect and isolate two diastereoisomers.

The desilylated lactones (2.18 and 6.2) could easily be carried through to tetrahydrolipstatin and its epimer (scheme 6.2 and 6.3). Hydrogenation of the benzyl

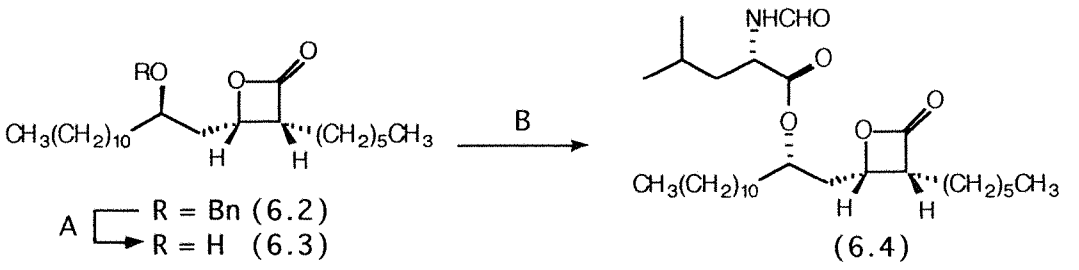


REAGENTS AND YIELDS

A 59% H_2, Pd/C, EtOAc.
B 79% (*S*)-N-formylleucine, PPh_3, DEAD, THF.

Scheme 6.2

protecting group afforded the free hydroxyl group. Esterification, under Mitsunobu conditions, with (*S*)-N-formylleucine afforded tetrahydrolipstatin (2.2) and the diastereomer (6.4).

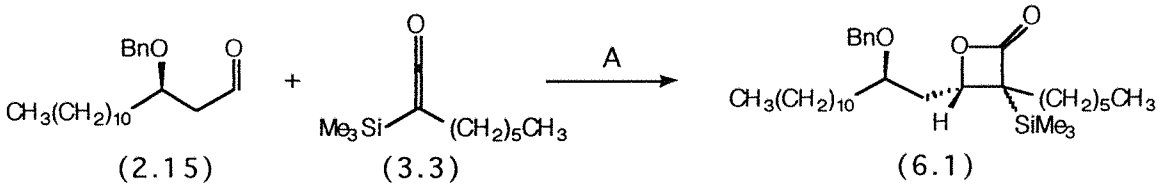


REAGENTS AND YIELDS

A 58% H_2, Pd/C, THF.
B 84% (*S*)-N-formylleucine, PPh_3, DEAD, THF.

Scheme 6.3

At this stage, in an attempt to improve the yield of the cycloaddition, we decided to explore the use of other Lewis acids. Continuing to use the benzyl protected hydroxy aldehyde (2.15), we performed the cycloaddition, with silyl ketene (3.3), at -40°C using ethylaluminium dichloride (scheme 6.4). The reaction proceeded cleanly to afford,



REAGENTS AND YIELDS

A 83% $EtAlCl_2$, DCM, -40°C.

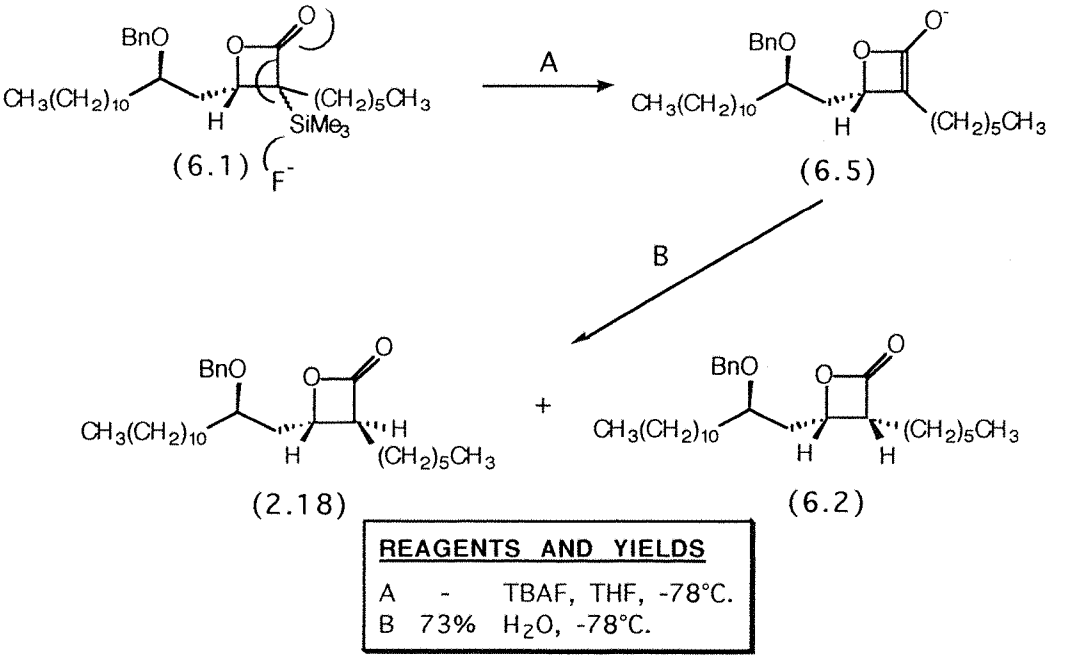
Scheme 6.4

after column chromatography, the silylated β-lactone (6.1). The use of ethylaluminium dichloride as the Lewis acid, instead of boron trifluoride etherate, allowed us to isolate the silylated β-lactone, as little or no desilylation occurred on chromatography.

Although we had now developed a reasonably high yielding and easily reproducible method for forming the silylated β-lactone, the weak point in the synthesis was the poor diastereoselectivity obtained after desilylation of the silylated β-lactone (6.1). On removal of the trimethylsilyl group with tetrabutylammonium fluoride the *trans* to *cis* ratio was always 3:2 in favour of the *trans*-isomer. Various other desilylating reagents were used, in an attempt to increase this ratio in favour of the *trans*-isomer, but without success. Ammonium fluoride[87] in methanol afforded the *cis*- and *trans*-β-lactones in almost equal amounts. Hydrogen fluoride in acetonitrile failed to afford any of the

desilylated β-lactone and only starting material was isolated. From this last result we concluded that, in our molecule, the carbon-silicon bond could only be cleaved under basic conditions.

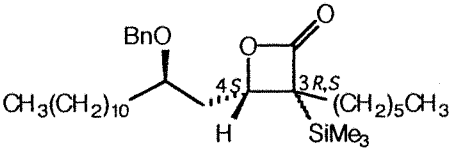
We assumed that the desilylation proceeded through a planar enolate structure (6.5). Protonation could then occur on either face to afford both the *cis*- and *trans*-isomers (scheme 6.5). The fact that we observed any stereocontrol, therefore, was unusual. A



Scheme 6.5

possible explanation for this facial selectivity is that the enolate formed (6.5), upon loss of the silicon group, does not adopt a planar configuration as would be expected, but adopts a distorted configuration which favours protonation occurring from the face that would result in the formation of the *trans* structure. The oxetene, formed on removal of the trimethylsilyl group (6.5), would be highly strained and likely to adopt a nonplanar structure so as to minimise the strain effect. In our system, this distorted conformation is adopted such as to favour protonation from the face that results in the desired *trans* isomer. Although the effect appears to operate in our favour, it is not particularly strong, resulting in a ratio of only 1.5:1 in favour of the *trans* isomer. Examples of nonplanar enolate structures have been reported by Seebach and co-workers[88,89]. They reported the crystal structures of two silyl enol ethers, which both showed pyramidalisation of the trigonal carbon in the same direction from which protonation occurred.

Upon desilylation of the silylated β-lactone we isolated only two diastereomers, the *cis*- and *trans*-β-lactones (2.18 and 6.2 respectively). As only two diastereomers were isolated we can assume that the cycloaddition reaction had resulted in the formation of the silylated β-lactone with the 4*S* configuration exclusively (see figure 6.1). In an attempt to rationalise this high stereoselectivity we examined the possible transition states formed in the reaction. To examine the mechanism for the cycloaddition reaction using the molecular orbital approach a number of assumptions must be made:-



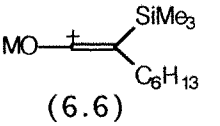
(6.1)

Figure 6.1

i) The cycloaddition reaction is concerted.

ii) The Lewis acid co-ordinates to the silyl ketene and not the aldehyde.

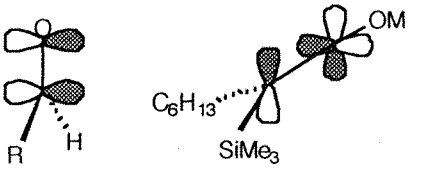
iii) The reacting species for the silyl ketene is the silicon-stabilised vinyl cation (6.6, figure 6.2).



(6.6)

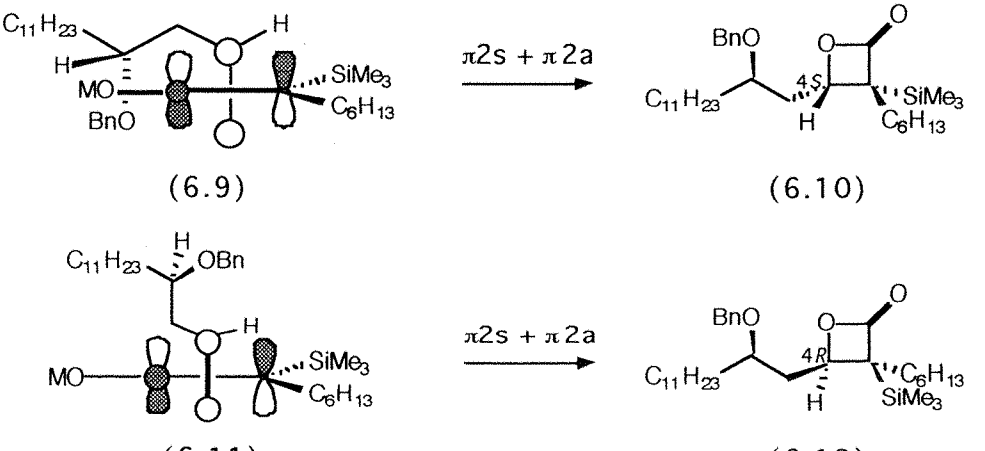
Figure 6.2

If we then examine the reaction, using a molecular orbital approach, between the HOMO of the aldehyde (6.7) and the LUMO of the silyl ketene (6.8)(figure 6.3). There are four possible transition states that can be adopted during the cycloaddition, two of these are so sterically hindered that for practical considerations they have been ignored in this discussion. Instead we have chosen to concentrate on the two remaining possible transition states (6.9) and (6.11) (scheme 6.6). Of these (6.9) would lead to the formation of (6.10), with the 4*S* stereochemistry, whilst (6.11) would



(6.7) (6.8)

Figure 6.3



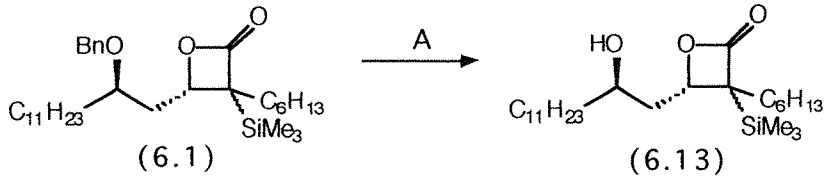
(6.9) (6.10)

(6.11) (6.12)

Scheme 6.6

lead to the 4*R* stereochemistry (6.12). As the only products isolated from the cycloaddition possessed the 4*S* stereochemistry, we can assume that the reaction must have proceeded through the transition state (6.9), i.e. where the Lewis acid is undergoing co-ordination to the benzyl ether. Therefore, we can conclude that the explanation for high stereoselectivity, obtained from the cycloaddition, lies in the co-ordination of the Lewis acid to both the silyl ketene and the ether group present in the aldehyde molecule.

To assist us further in understanding the mechanism of the cycloaddition, it would be helpful to know the chirality of both of the stereocentres created in the cycloaddition reaction. We already know that one of the stereocentres (carbon 4) is established in the *S* configuration (figure 6.1). But the other stereocentre, possessing the trimethylsily group, could not easily be assigned. On removal of the silyl group, the reaction proceeded through a planar structure and therefore all stereochemistry at that centre was lost. As the chiral centre we wished to examine (carbon 3), was a quaternary centre there was no easy way of establishing the stereochemistry. Our first idea was to form a crystalline derivative of the silylated β-lactone, from which we would, hopefully, be able to obtain an X-ray structure. We isolated the major diastereomer pure by column chromatography before removing the benzyl protecting group by hydrogenation, to afford the hydroxy silylated β-lactone (6.13) (equation 6.1). We then proceeded to form five ester



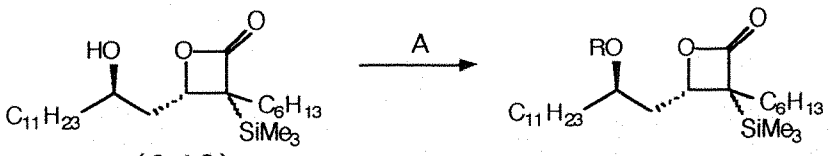
(6.1) (6.13)

REAGENTS AND YIELDS

A 52% H_2, Pd/C, THF.

Equation 6.1

derivatives of this compound (6.14 to 6.18)(equation 6.2, table 6.1). Although some of these compounds were solids, they were very waxy solids and did not give crystal structures that were suitable for x-ray analysis. We, therefore, ruled out this method of determining the structure and instead considered effecting a thermal extrusion of carbon dioxide from the lactone to afford the alkene, we then hoped that NOE studies would reveal the stereochemistry.



(6.13)

REAGENTS AND YIELDS

A See table 6.1

Equation 6.2

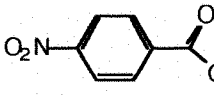
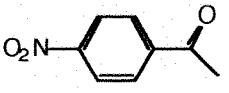
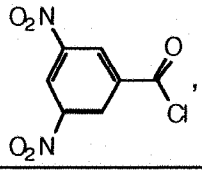
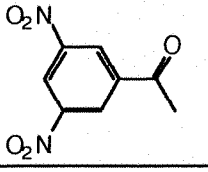
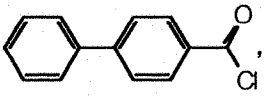
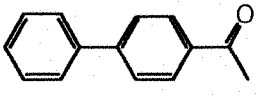
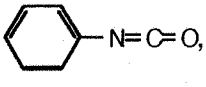
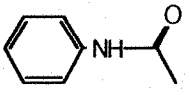
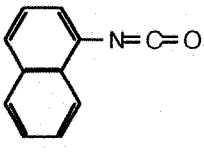
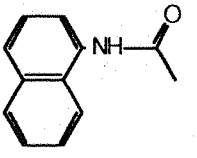
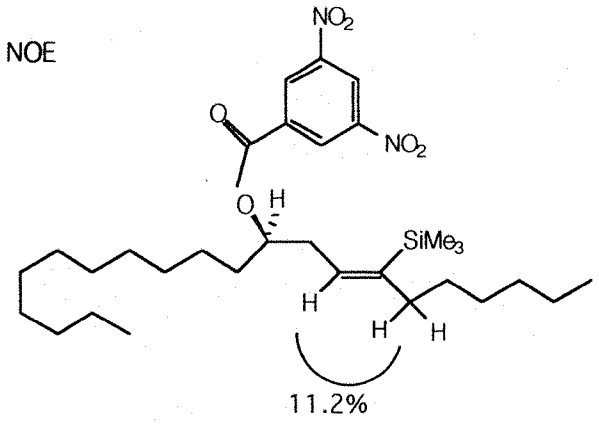
	Reagents	R =	Yields
(6.14)	 , py, THF, rt.		72%
(6.15)	 , py, THF, rt.		70%
(6.16)	 , py, DMAP, DCM, rt.		20%
(6.17)	 , py, 100°C.		94%
(6.18)	 , py, 100°C.		64%

Table 6.1

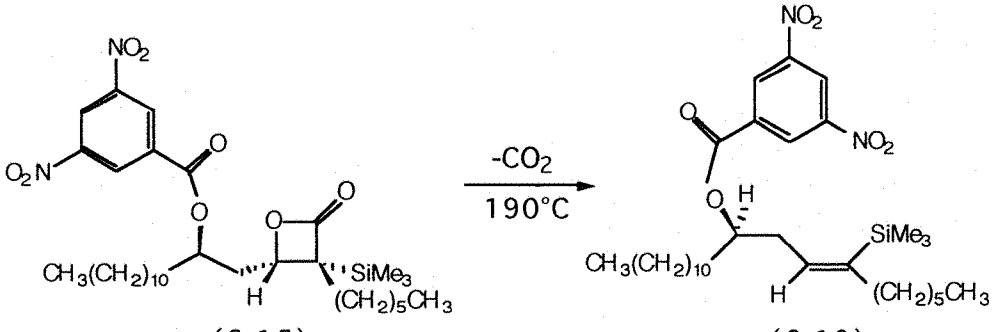
In 1966 Noyce and Banitt reported that β-lactones undergo decarboxylation to form olefins with stereospecific *cis*-elimination[11]. Zaitseva had reported the decarboxylation of silylated β-lactones (scheme 1.10)[32]. She had reported that the *trans*-β-lactone had decarboxylated readily on heating to 50°C to form the trimethylsilyl-*trans*-styrylsilane (1.52), but that the *cis*-lactone had required heating to 150-160°C before decarboxylation had occurred to form trimethylsilyl-*cis*-styrylsilane (1.53). We found it necessary to heat our β-lactone to 190°C before decarboxylation occurred. On isolating the alkene we were able to determine from NOE studies that the alkene existed in the *Z*-configuration (figure 6.4). From this we were able to deduce that the original silylated



(6.19)

Figure 6.4

β-lactone (6.15) must have existed in the configuration such that the two alkyl chains were *trans* to each other (equation 6.3).



(6.15) (6.19)

Equation 6.3

Up to this time all our work on the cycloaddition reaction had used the benzyl protected hydroxy aldehyde, but we found that the removal of the benzyl protecting group did not always proceed smoothly. Some trace impurity in the reaction mixture appeared to poison the catalyst and the palladium often had to be replaced several times before debenzylation occurred. We therefore made use of a different protecting group the *t*-butyldimethylsilyl ether. As has already been discussed in chapter four, this change was advantageous in the formation of the aldehyde, as the hydroboration to the aldehyde occurred far more readily with the silyl protected propargylic alcohol than with the benzyl protected alkynol.

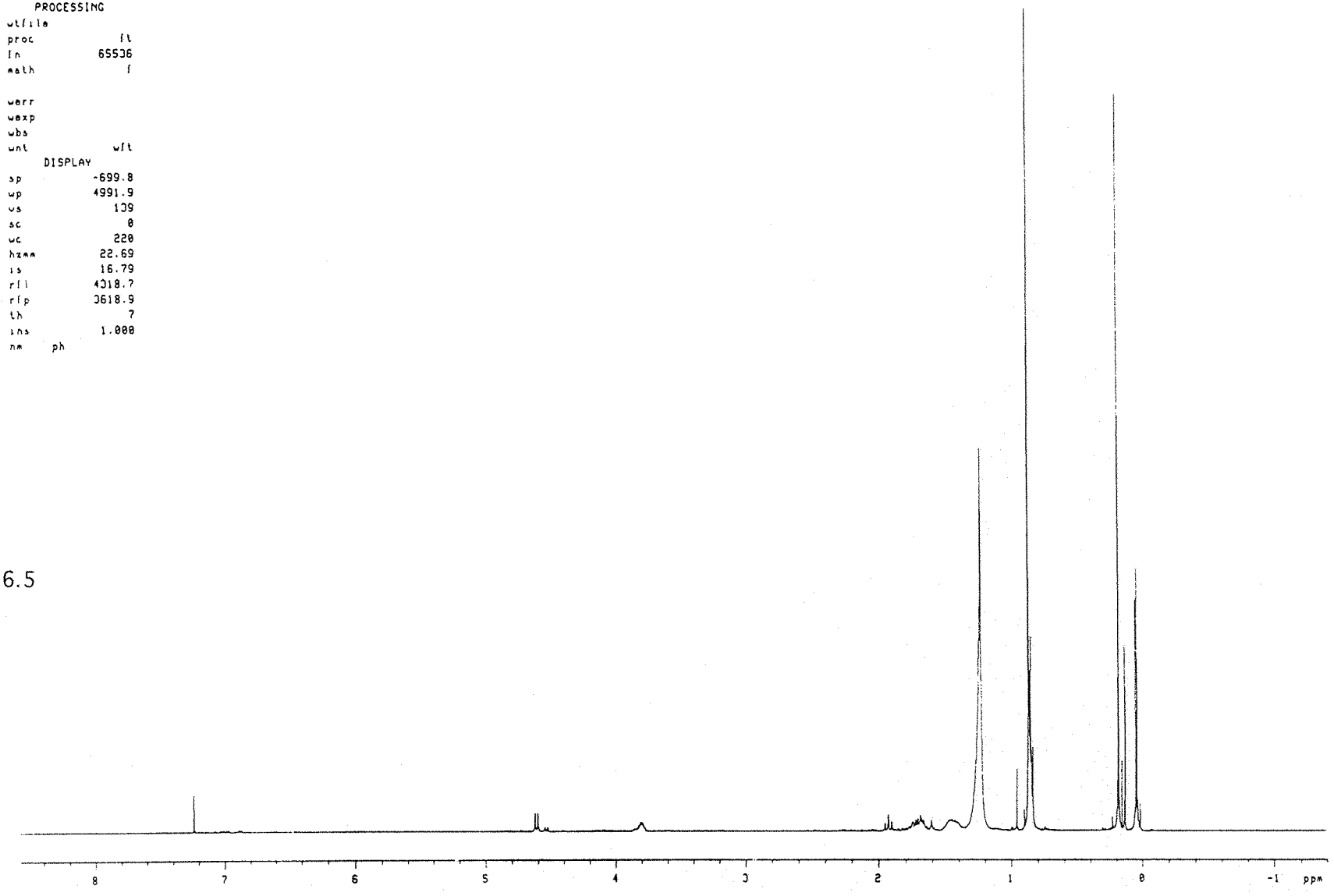
Cycloaddition of the silyl protected hydroxy aldehyde (4.40) proceeded smoothly to afford, after chromatography, the silylated β-lactone in 63% yield (scheme 6.7). Examination of the proton NMR spectrum (500 MHz), revealed four diastereomers, in the ratio of 75:7.5:15.5:2 (see figure 6.5 and 6.6). Again after desilylation we isolated

Jo herpiniere sample in CDCl3 at 20C, 1H

expl pulse sequence: s2pul JM5(1)

SAMPLE		DEC. & VT	
date	May 28 92	dn	H1
solvent	CDCl3	dof	0
file	exp	dm	nnn
ACQUISITION		dmm	c
sfrq	499.843	dmf	200
tn	H1	dpwr	38
at	3.282	temp	20.0
np	32768	PROCESSING	
sw	4991.9	wtfile	
fb	2800	proc	ft
bs	32	fn	65536
tpwr	63	math	f
pw	7.0		
dl	0	werr	
tof	-689.3	wexp	
nt	64	wbs	
ct	64	wnt	wft
alock	n	DISPLAY	
gain	not used	sp	-699.8
FLAGS		wp	4991.9
il	n	vs	139
in	n	sc	0
dp	y	wc	220
hs	nn	hzmm	22.69
		is	16.79
		rfl	4318.7
		rfp	3618.9
		th	7
		ins	1.000
		nm ph	

Figure 6.5



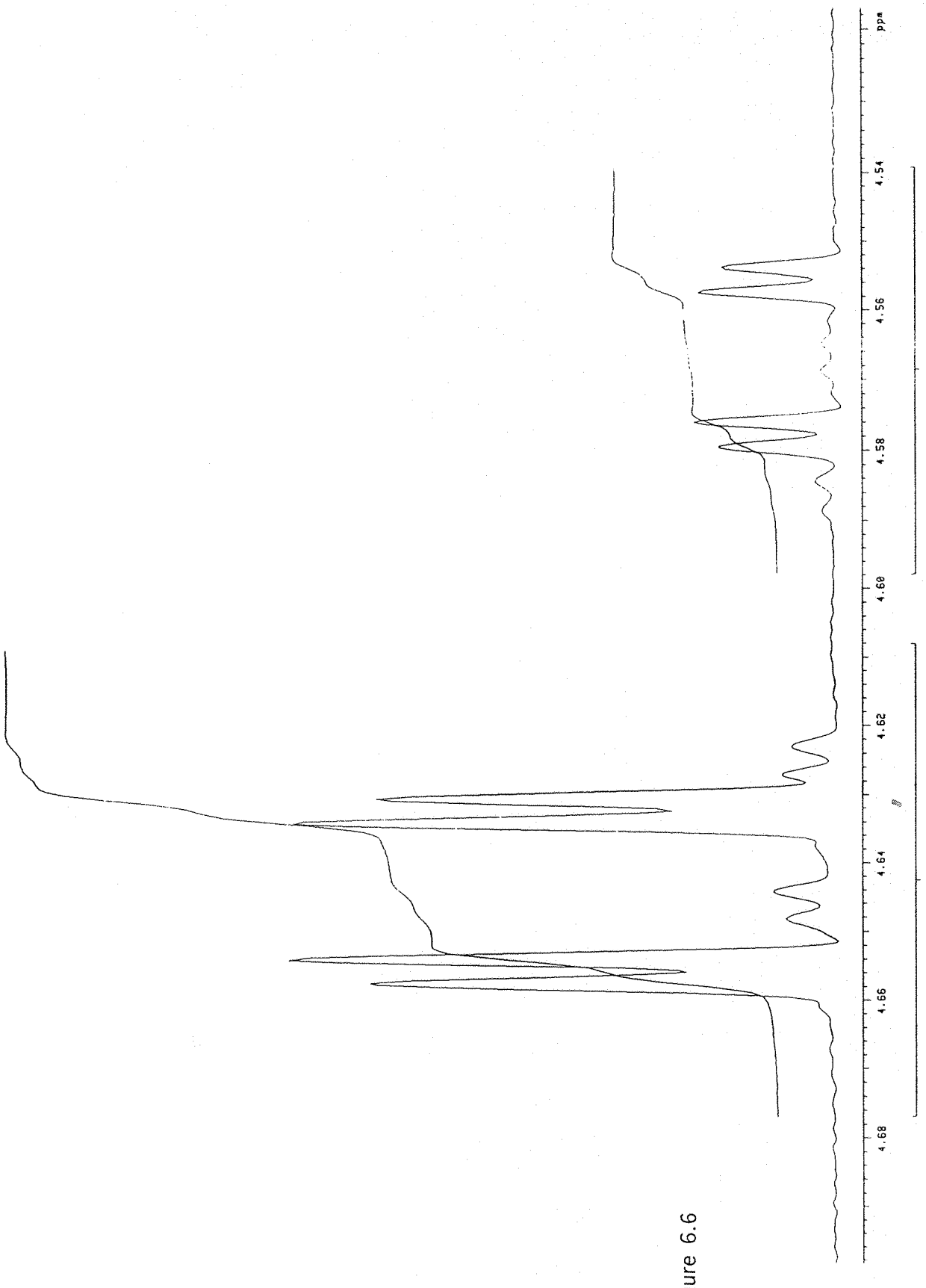
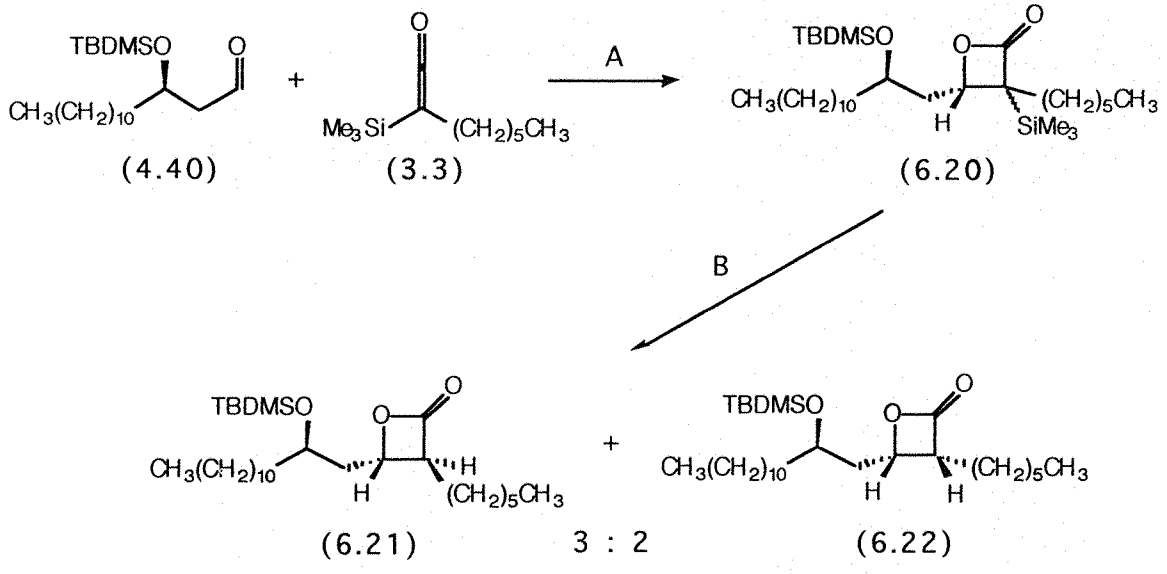

Jo herpiniere sample in CDCl3 at 20C, 1H
4.68
4.66
4.64
4.62
4.60
4.58
4.56
4.54
ppm

Figure 6.6



REAGENTS AND YIELDS

A 63% i) $EtAlCl_2$, Et_2O, -40°C. ii) (3.2), Et_2O, -40°C.
B 91% TBAF, THF, -78°C.

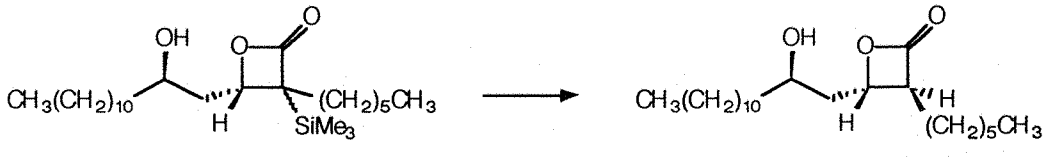
Scheme 6.7

the *trans*- and *cis*-isomers (6.21 and 6.22 respectively) in a 3:2 ratio, with a small amount of the other diastereoisomers. Of the four isomers seen by NMR we must assume that the two major isomers had the 4*S* stereochemistry required for tetrahydrolipstatin. As the desilylation step proceeds through a planar enolate structure, the stereochemistry of the quaternary centre is scrambled and therefore makes no difference to the final product.

Work on the mechanism of the reaction was proceeding during this time, by Pons and co-workers[90]. To assist in the elucidation of the mechanism, NMR experiments were carried out to determine which of the two starting materials, the aldehyde or ketene, underwent complexation with the Lewis acid. The experiments showed that on addition of boron trifluoride etherate, the aldehyde carbon shifted in the spectrum. But on addition of ethylaluminium dichloride, no effect was seen on the aldehyde carbon; instead, a broadening of the ketene carbon was observed. Although NMR experiments of this kind are not a totally reliable method of assigning mechanisms, as the intermediate seen in the NMR spectra may not necessarily participate in the reaction, the NMR results would tend to imply that when using boron trifluoride etherate the Lewis acid co-ordinated first to the aldehyde, but when using ethylaluminium dichloride as the Lewis acid, it co-ordinated

first to the silyl ketene. When we switched to using ethylaluminium dichloride as the Lewis acid, we had continued to use the same experimental procedure as we had used with boron trifluoride etherate, i.e.. addition of the Lewis acid to the aldehyde, followed a few minutes later by the addition of the silyl ketene. If the results from the NMR experiments were indeed a reliable indication of the mechanism, when using this procedure for the ethylaluminium dichloride reactions the first step would involve the complexation of the Lewis acid to the silyl ketene before the reaction would occur. It, therefore, seemed sensible to reverse the sequence of addition when using ethylaluminium dichloride, i.e.. adding the Lewis acid to the ketene before the addition of the aldehyde. We duly effected this procedural change and reported an improvement in the yield of the reaction, from 63 to 74% and a reduction in the reaction time, from fifty to twenty minutes.

Although we now had obtained a reasonable diastereoselectivity in the cycloaddition reaction, we still achieved poor stereoselectivity on desilylation of the silyl-β-lactone (6.20). Whilst researching different desilylation conditions in an attempt to improve the diastereoselectivity obtained from the desilylation reaction, we found that the hydroxy silylated β-lactone (6.13) underwent desilylation to afford only the *trans*-β-lactone (2.18) in 90% yield (equation 6.4). This result was very surprising and in an attempt



(6.13) (2.19)

REAGENTS AND YIELDS

A 90% TBAF, THF, -80°C.

Equation 6.4

to rationalise this result we examined the Chem 3D[91] model of the intermediate enolate (6.23). On examining the model (figure 6.7), it became apparent that the hydroxyl group was ideally situated to donate a proton to the enolate formed upon cleavage of the silicon-carbon bond (6.23) (scheme 6.8). The hydroxyl group would donate the proton to the face of the enolate that resulted in the formation of the *trans*-isomer (2.19). The hydrogen on the hydroxyl group is positioned 1.502 Å from the enolate carbon and is therefore perfectly situated for bonding. This result meant that we had now developed a

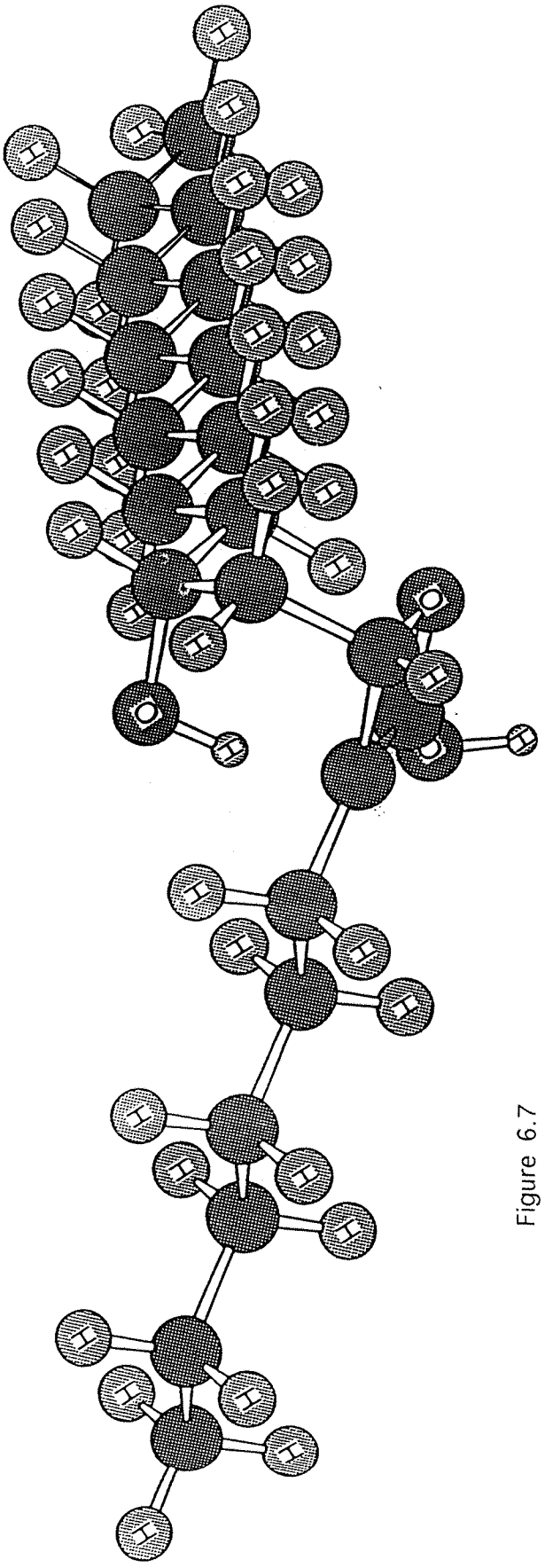
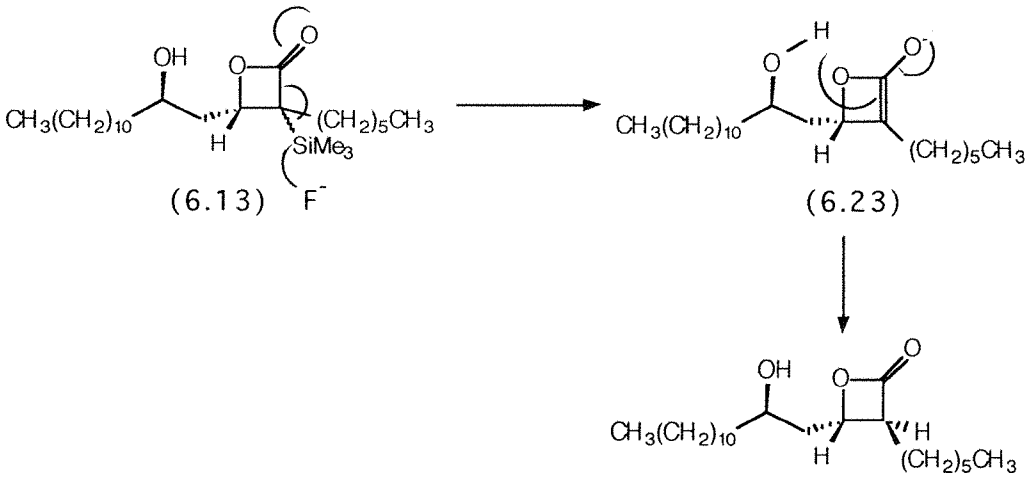


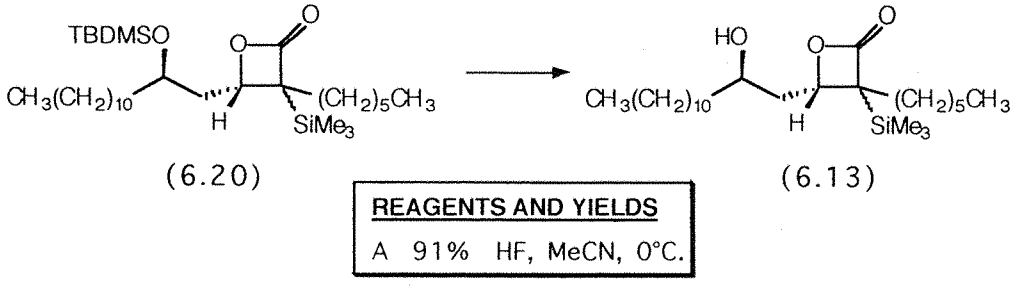
Figure 6.7



Scheme 6.8

highly stereoselective route to tetrahydrolipstatin, as by removing the the protecting group on the hydroxyl group before proceeding with the desilylation, we avoided all the problems of poor diastereocontrol, which we had encountered on desilylation of the protected hydroxy β-lactone.

Deprotection of the hydroxyl group before desilylation could easily be achieved when the protecting group was benzyl, by palladium catalysed hydrogenation (equation 6.1). But as our later work had relied on the use of a silicon protecting group, we were now faced with the problem of selective removal of one silicon group in the presence of another. Fortunately, as was demonstrated earlier in the synthesis, the trimethylsilyl-carbon bond was not cleaved under acidic conditions and this offered us a possible route to the hydroxy silyl-β-lactone, when using the silicon protected hydroxyl group. Treatment of the silyl ether with hydrogen fluoride in acetonitrile afforded the desired hydroxy silyl lactone (6.13) in good yield (equation 6.5). This could then be



Equation 6.5

desilylated with tetrabutylammonium fluoride to afford the *trans*-β-lactone (2.19) as the sole product (equation 6.4). Esterification under Mitsunobu conditions with

(*S*)-N-formylleucine (scheme 6.2) afforded tetrahydrolipstatin in good yield.

The discovery that the hydroxy silyl-β-lactone (6.13) underwent desilylation with excellent diastereoselectivity, to afford only the *trans*-β-lactone (2.18), meant that we had now developed a highly stereoselective synthesis of tetrahydrolipstatin. Having formed the protected hydroxy aldehydes (2.15 and 4.40) enantiomerically pure, using a catalytic asymmetric procedure, we then made use of this chirality to control all the remaining stereocentres in the molecule. The cycloaddition proceeded with reasonable diastereocontrol, when using both the benzyl and silyl protected hydroxy aldehyde. Removal of the protecting group followed by desilylation afforded the desired *trans*-β-lactone almost exclusively. Thus we had now developed a high yielding and stereoselective route to tetrahydrolipstatin.

Chapter Seven

Chapter Seven.

Experimental.

General.

All reactions requiring anhydrous conditions were conducted in flame dried apparatus, under a static atmosphere of nitrogen unless otherwise stated. All commercial reagents and solvents were used as obtained, except for the following which were purified by distillation from the drying agents stated in the brackets: benzene (sodium wire), $BF_3.Et_2O$ (CaH_2), dichloromethane (CaH_2), diethyl ether (sodium wire), DMF (CaH_2), HMPA (CaH_2), methanol ($Mg(OMe)_2$), pentane (CaH_2), petroleum ether (CaH_2), pyridine (CaH_2), THF (sodium/ benzophenone), toluene (sodium wire), triethylamine (CaH_2). Petrol refers to petroleum ether (40-60°C).

Thin layer chromatography was performed on Merck kieselgel 60 F254 precoated aluminium or glass backed plates. Chromatographic separation was performed using Merck kieselgel 60 (0.04-0.063 mm, 230-400 mesh).

Instrumentation.

Melting points were determined on a Griffin melting point apparatus and are uncorrected. Optical rotations were measured on an Optical Activity AA-100 polarimeter using 50 mm cells at ambient temperature. Infrared spectra were recorded on a Perkin-Elmer 1600 FT IR. Absorbtions are described as strong (s), medium (m), weak (w) and broad (br). ^1H NMR spectra were recorded at 270 MHz on a Jeol 270 MHz FT NMR, at 360 MHz on a Brucker AM 360 and at 500 MHz on a Varian 500. All spectra were run in $CDCl_3$ and the peak positions quoted against the δ-scale relative to an internal standard ($CHCl_3$, δ 7.27). The signals are assigned as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) or apparent quintet (app quin). ^{13}C NMR spectra were recorded at 67.5 MHz on a Jeol 270 MHz FT NMR, at 90 MHz on a Brucker AM 360. All spectra were run in $CDCl_3$ and the peak positions quoted against the δ-scale relative to the

central peak of $CDCl_3$ as an internal standard (δ 77.2). The multiplicities of the ^{13}C signals were determined using Distortionless Enhancement by Polarisation Transfer (DEPT) spectral editing techniques with second pulses at 90° and 135°. and are assigned by the number of attached protons (0, 1, 2, 3).

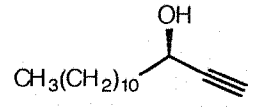
Experimental Procedures.

Tetradecyn-3-ol (3.7):- Dry acetylene was bubbled into THF (20 ml) at -78°C until saturation was reached. Whilst continuing a gentle flow of acetylene, *n*-BuLi (7 ml, 1.6 M, 11.2 mmol) was added slowly, maintaining the temperature at -78°C. The acetylene flow was removed and the reaction was stirred at -78°C for 20 min. Dodecanal (1.79 g, 9.7 mmol) in THF (2 ml) was added dropwise and the reaction mixture was stirred at -78°C for a further 2 h. The reaction mixture was quenched with water (2 ml). On warming to room temperature the reaction mixture was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (15% diethyl ether in petrol) yielded (3.7) as a low melting white solid (1.38 g, 6.57 mmol, 67%); IR (film) 3321 s, 2923 s, 2823 s, 2855 s, 2115 w, 1716 w cm^{-1}; ^1H NMR (270 MHz) δ_H 4.36 (1H, dt, J = 6.6, 1.9 Hz), 2.45 (1H, d, J = 1.9 Hz), 2.49-2.34 (1H, s, br), 1.75-1.63 (2H, m), 1.51-1.37 (2H, m), 1.37-1.16 (16H, s), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 85.2 (0), 72.9 (1), 62.4 (1), 37.8 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4 (2), 25.2 (2), 22.8 (2), 14.3 (3).

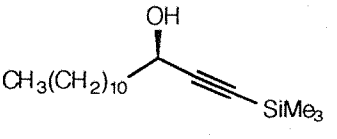
Tetradecyn-3-one (3.8):- To a suspension of chromium trioxide (5.66 g, 56.6 mmol) in DCM (120 ml) was added 3,5-dimethylpyrazole (3.75 g, 39.1 mmol) and the reaction was stirred at room temperature for 20 min. The mixture was cooled to 0°C and tetradecyn-3-ol (3.03 g, 14.4 mmol) in DCM (20 ml) was added rapidly. The reaction was stirred at 0°C for a further 14 h. The reaction was filtered and the filtrate concentrated. Rapid filtration through a short silica column yielded the crude product, which was concentrated and purified by flash chromatography (5% diethyl ether in petrol) to yield (3.8) as a colourless oil (2.285 g, 10.99 mmol, 76%); IR (film) 3303 m, 3258 m, 2924 s, 2855 s, 2094 s, 1682 s, 1466 m cm^{-1}; ^1H NMR (270 MHz) δ_H 3.20 (1H, s), 2.57 (2H, t, J = 7.4 Hz), 1.67 (2H, t, J = 7.0 Hz), 1.38-1.17 (16H, s), 0.88 (3H, t, J = 6.3 Hz); ^{13}C NMR (67.5 MHz) δ_C

187.6 (0), 81.7 (1), 78.4 (0), 45.6 (2), 32.1 (2), 29.8 (2), 29.6 (2), 29.5 (2), 29.5 (2), 29.1 (2), 23.9 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 226 ($(M+NH_4)^+$, 100%).

(*R*)-Tetradecyn-3-ol (3.9):- *R*-Alpine Borane (7 ml, 0.5 M in THF, 3.5 mmol) was concentrated *in vacuo* (40°C, 0.2 mm Hg). On removal of all the THF, the reaction mixture was cooled in ice before tetradecyn-3-one (404 mg, 1.94 mmol) was added dropwise and the mixture was stirred at 5°C for a further 30 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 14 h. Propionaldehyde (0.19 ml, 2.6 mmol) was added and the reaction was stirred for a further 1 h. The α-pinene was removed *in vacuo* (1 h, rt, 0.15 mm Hg) and the remaining mixture was dissolved in THF. The borane was oxidised by the addition of sodium hydroxide (1.6 ml, 3N) and hydrogen peroxide (1.6 ml, 30%). The reaction mixture was stirred at room temperature for 2 h before the mixture was extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (15% diethyl ether in petrol) yielded (3.9) as a yellow oil (332 mg, 1.58 mmol, 81%); $[\alpha]_D$ +3.32° (c. 1 in dioxane); IR (film) 3321 s, 2923 s, 2823 s, 2855 s, 2115 w, 1716 w cm^{-1}; ^1H NMR (270 MHz) δ_H 4.36 (1H, dt, J = 6.6, 1.9 Hz), 2.45 (1H, d, J = 1.9 Hz), 2.49-2.34 (1H, s, br), 1.75-1.63 (2H, m), 1.51-1.37 (2H, m), 1.37-1.16 (16H, s), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 85.2 (0), 72.9 (1), 62.4 (1), 37.8 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4 (2), 25.2 (2), 22.8 (2), 14.3 (3); m/z (CI, NH_3) 228 ($(M+NH_4)^+$, 100%); (Found : $(M+NH_4)^+$, 228.2326. $(C_{14}H_{26}O + NH_4)^+$ requires 228.2327).



(*R*)-1-Trimethylsilyltetradecyn-3-ol (3.10)- To a solution of (*R*)-tetradecyn-3-ol (245 mg, 1.17 mmol) in THF (3 ml), at -40°C, was added dropwise over 15 min *n*-BuLi (1.15 ml of a 2.5M solution in hexanes, 2.88 mmol).

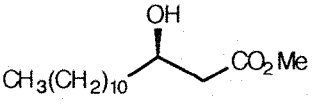


The reaction mixture was allowed to warm to -20°C and stirred at this temperature for 1 h. TMSCl (0.4 ml, 3.07 mmol) was added slowly and stirring continued for a further 30 min, before the mixture was allowed to warm to 10°C. H_2SO_4 (0.65 ml, 1.4M, 0.91 mmol) was added over 10 min and the reaction was stirred for a further 20 min. The mixture was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (6% diethyl ether in petrol) yielded (3.10) as a yellow oil (202 mg, 0.72 mmol, 61%); IR (film) 3632-3098 m, br, 2925 s, 2855 s, 2172 m, 1466 m, 1250 s, 1028 m, 843 s, 760 s cm^{-1}; ^1H NMR (270 MHz) δ_H 4.36 (1H, t, J = 6.6 Hz), 2.00 (1H, s), 1.74-1.64 (2H, m), 1.49-1.39 (2H, m), 1.46-1.18 (16H, s), 0.89 (3H, t, J = 6.6 Hz), 0.16 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 107.2 (0), 89.4 (0), 63.0 (1), 37.9 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4 (2), 25.3 (2), 25.3 (2), 22.9 (2), 14.3 (3), 0.1 (3); m/z (CI, NH_3) 300 ($(M+NH_4)^+$, 100%), 35 (61%).

(*R*)-3-Hydroxytetradecanoic acid (3.11):- To borane methyl sulphide complex (BMS) (1.6 ml of a 2M solution in THF, 24.6 mmol) in THF (0.7 ml) at 0°C was added dropwise cyclohexene (0.65 ml, 6.5 mmol) with vigorous stirring. Stirring was continued for a further 2.5 h at 0°C before the solvent was removed *in vacuo*. The white solid formed was dissolved in THF (2.1 ml) and cooled to 0°C. To this mixture was added (*R*)-1-trimethylsilyltetradecyn-3-ol (397 mg, 1.34 mmol) in THF (0.6 ml) over 10 min and stirring was continued at 0°C for a further 10 min. The mixture was warmed to room temperature and stirred for a further 1 h. The mixture was diluted in MeOH (0.7 ml) and recooled to 0°C before NaOH (0.7 ml of a 3M solution) and H_2O_2 (0.7 ml of a 30% solution) were added dropwise. After stirring for 5 min at 0°C the mixture was extracted with diethyl ether. The aqueous phase was acidified and re-extracted with diethyl ether. The organic fractions from the second extraction were dried ($MgSO_4$) and concentrated to yield (3.11) as a white solid (258 mg, 1.06 mmol, 75%); m.p. 70.5-73°C (lit. 72°C[57]); IR (film) 3707-3049 m, br, 2926 s, 2855 s, 1727 s,

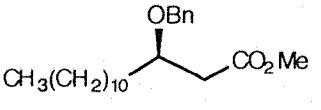
1462 m, 1383 m, 1262 m, 1120 m cm^{-1}; ^1H NMR (270 MHz) δ_H 6.6-5.7 (1H, s, br), 4.09-3.98 (1H, m), 2.59 (1H, dd, J = 16.6, 3.3 Hz), 2.48 (1H, dd, J = 16.6, 8.6 Hz), 1.58-1.39 (3H, m), 1.38-1.16 (18H, s), 0.89 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 177.5 (0), 68.2 (1), 41.1 (2), 36.7 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 25.6 (2), 22.9 (2), 14.3 (3).

(*R*)-3-Hydroxymethyltetradecanoate (3.12):-



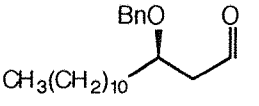
To (*R*)-3-hydroxytetradecanoic acid (1.51 g, 6.19 mmol) in methanol (24 ml) was added HCl (0.4 ml, 12N) and the was stirred for 2 h. The reaction mixture was poured into saturated brine and extracted with EtOAc, dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded a white solid, which was readily recrystallised (diethyl ether, petrol) to afford (3.12) as a white solid (963 mg, 3.73 mmol, 60%); IR (film) 3670-3106 m,br, 2923 s, 2852 s, 1739 s, 1439 m cm^{-1}; ^1H NMR (270 MHz) δ_H 4.07-3.94 (1H, m), 3.70 (3H, s), 2.94 (1H, d, J = 3.9 Hz), 2.51 (1H, dd, J = 16.4, 3.3 Hz), 2.43 (1H, dd, J = 16.4, 8.7 Hz), 1.58-1.37 (4H, m), 1.37-1.17 (16H, s), 0.89 (3H, t, J = 6.5 Hz); ^{13}C NMR (67.5 MHz) δ_C 173.7 (0), 68.2 (1), 51.9 (3), 41.3 (2), 36.7 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 25.6 (2), 22.8 (2), 14.3 (3).

(*R*)-3-Benzyloxymethyltetradecanoate (3.13):-

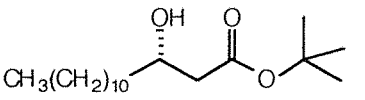


To a solution of (*R*)-3-hydroxymethyltetradecanoate (963 mg, 3.73 mmol) and benzyl 2,2,2-trichloroacetimidate (0.8 ml, 4.3 mmol) in DCM (6 ml) and cyclohexane (12 ml), cooled in ice, was added trifluoromethanesulfonic acid (32 μl, 0.36 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was filtered and the filtrate washed with sodium bicarbonate and water. The combined aqueous phases were re-extracted with DCM. The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (7% diethyl ether in petrol) afforded (3.13) as a pale yellow oil

(1.00 g, 2.88 mmol, 77%); IR (film) 3064 w, 3030 w, 2926 s, 2854 s, 1739 s, 1455 m, 1437 m, 734 s cm^{-1}; ^1H NMR (270 MHz) δ_H 7.39-7.26 (5H, m), 4.55 (2H, s), 3.94-3.83 (1H, m), 3.69 (3H, s), 2.64 (1H, dd, J = 15.1, 7.3 Hz), 2.50 (1H, dd, J = 15.1, 5.4 Hz), 1.68-1.51 (2H, m), 1.50-1.18 (18H, s), 0.91 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 172.4 (0), 138.7 (0), 128.5 (1), 127.9 (1), 127.7 (1), 76.3 (1), 71.7 (2), 51.8 (3), 40.0 (2), 34.6 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.5 (2), 25.3 (2), 22.9 (2), 14.3 (3).

(*R*)-3-Benzyloxytetradecanal (2.15):- To (*R*)-3-benzyloxymethyltetradecanoate (334 mg, 0.96 mmol) in DCM 

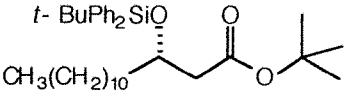
(3.3 ml) at -80°C was added dropwise DiBAlH (0.7 ml, 1.5M in toluene). After 30 min sat. NH_4Cl (0.23 ml) and HCl (0.46 ml, 2M) were added dropwise, maintaining the temperature below -75°C. After this addition, the reaction was allowed to warm to room temperature. The reaction mixture was filtered and the solid was washed with DCM. The filtrate was dried (Na_2SO_4) and concentrated. Flash chromatography (7% diethyl ether in petrol) yielded (2.15) as a colourless oil (205 mg, 0.64 mmol, 67%); IR (film) 3064 w, 3031 w, 2926 s, 2854 s, 2724 w, 1726 s, 1455 m, 1094 m, 1067 m, 734 m, 697 m cm^{-1}; ^1H NMR (270 MHz) δ_H 9.81 (1H, t, J = 2.2 Hz), 7.39-7.23 (5H, m), 4.55 (2H, dd, J = 15.6, 11.5 Hz), 4.00-3.91 (1H, symmetrical m), 2.69 (1H, ddd, 16.3, 7.2, 2.6 Hz), 2.58 (1H, ddd, J = 16.2, 4.8, 1.9 Hz), 1.78-1.44 (2H, m), 1.44-1.18 (18H, s), 0.90 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 201.9 (1), 138.4 (0), 128.6 (1), 128.0 (1), 127.9 (1), 74.5 (1), 71.4 (2), 48.5 (2), 34.4 (2), 32.1 (2), 29.8 (2), 29.8 (2), 29.5 (2), 25.3 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 336 ($(M+NH_4)^+$, 73%), 228 (100%).

***tert*-Butyl-(*S*)-3-hydroxytetradecanoate (4.9)**:- To cyclohexylamine (174 mg, 0.96 mmol) in 

diethyl ether (2 ml) at -25°C was added dropwise *n*-BuLi (0.52 ml of a 1.6 M solution in hexane, 0.8 mmol). After 30 min at this temperature the temperature was

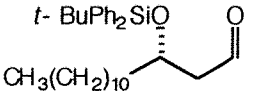
lowered to -78°C and a solution of *t*-butylacetate (83 mg, 0.72 mmol) in diethyl ether (0.5 ml) was added dropwise. After 30 min at -78°C chloro(cyclopentadienyl)bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) titanate (9.7 ml of a 0.1M solution in diethyl ether, 0.97 mmol) was added dropwise over 20 min. After stirring at this temperature for 2 h the reaction was warmed to -50°C. Lauraldehyde (132 mg, 0.72 mmol) in diethyl ether (0.4 ml) was added dropwise over 10 min. After 1.5 h the reaction was quenched at -50°C with 5M water in THF (1.6 ml), allowed to warm to room temperature and stirred for 1 h. The titanium residues were removed by filtration through celite. Concentration yielded a brown oil which was washed with NaCl and extracted with diethyl ether. The combined extracts were dried and concentrated to give a yellow oil. The glucose residue was hydrolysed by stirring with HCl (0.1M, 12 ml) at room temperature for 1 h. The reaction mixture was then re-extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (20% diethyl ether in petrol) yielded (4.9) as a brown oil (191 mg, 0.64 mmol, 89%). (>82% ee by MTPA ester[66]); IR (film) 3451 br, m, 1731 s, 1368 s, 1154 s cm^{-1}; ^1H NMR (270 MHz) δ_H 3.94 (1H, m), 3.15 (1H, s, br), 2.41 (1H, dd, J = 16.4, 3.3 Hz), 2.29 (1H, dd, J = 8.9, 16.4 Hz), 1.46 (9H, s), 1.25 (20H, s), 0.87 (3H, t, J = 7.2 Hz); ^{13}C NMR (67.5 MHz) δ_C 172. 8 (0), 81.3 (0), 68.3 (1), 42.4 (2), 36.6 (2), 32.1 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.5 (2), 28.3 (3), 25.6 (2), 22.8 (2), 14.3 (3).

***tert*-Butyl-(*S*)-3-*tert*-butyldiphenylsiloxy tetradecanoate (4.10)**:- To *t*-butyl-(*S*)-3-hydroxytetradecanoate (794 mg, 2.65 mmol) in dimethylformamide (17 ml) at room temperature was added imidazole (400 mg, 5.4 mmol) followed by *t*-butylchlorodiphenyl silane (760 mg, 2.7 mmol). After stirring overnight the reaction mixture was poured into water and extracted with petrol. The combined organic extracts were dried ($MgSO_4$) and concentrated to give a colourless oil. Flash chromatography (2% diethyl ether in petrol) yielded (4.10) as a colourless oil (1.334 g, 2.48

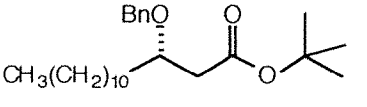


mmol, 94%); IR (film) 3071 m, 3049 m, 1732 s, 1590 w 1428 s, 1367 s, 1154 s, 1111 s, 702 s cm^{-1}; ^1H NMR (270 MHz) δ_H 7.71 (4H, dt, J = 8.2, 1.7 Hz), 7.34-7.48 (6H, m), 4.15 (1H, app quin, J = 6.1 Hz), 2.44 (1H, dd, J = 14.4, 5.8 Hz), 2.39 (1H, dd, J = 14.5, 6.6 Hz), 1.41 (9H, s), 1.52-1.14 (20H, m), 1.07 (9H, s), 0.89 (3H, t, J = 7.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 170.9 (0), 136.1 (1), 134.5 (0), 134.4 (0), 129.7 (1),127.6 (1), 80.3 (0), 70.7 (1), 43.5 (2), 36.9 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.6 (2), 28.3 (3), 27.2 (3), 24.8 (2), 22.9 (2), 19.5 (0), 14.4 (3).

(*S*)-3-*tert*-Butyldiphenylsilyloxytetradecanal (4.11):- To *t*-butyl-(*S*)-3-*t*-butyldiphenylsiloxytetradecanoate (102 mg, 0.19 mmol) in dichloromethane (0.6 ml) at -90°C was added dropwise DiBAlH (0.14 ml of a 1.5M solution in toluene, 0.21 mmol) After 10 min the reaction was quenched at -80°C by slow addition of a saturated NH_4Cl solution (0.05 ml) followed by HCl (0.1 ml, 2M). On warming to room temperature the mixture was filtered and washed with DCM. The filtrate was then dried (Na_2SO_4) and concentrated to yield a colourless oil. Flash chromatography (5% diethyl ether in petrol) yielded (4.11) as a colourless oil (62 mg, 0.13 mmol, 70%); IR (film) 3071 w, 3050 w, 2958 s, 2928s, 2856s, 2718 w, 1728 s, 1590 w, 1464 m, 1428 w, 1111 s, 702 s cm^{-1}; ^1H NMR (270 MHz) δ_H 9.74 (1H, t, J = 2.4 Hz), 7.74-7.64 (4H, m), 7.5-7.35 (6H, m), 4.21 (1H, app quin, J = 5.9 Hz), 2.51 (1H, d, J = 2.5 Hz), 2.49 (1H, d, J = 2.7 Hz), 1.61-1.44 (2H, m), 1.38-1.06 (18H, m), 1.06 (9H, s), 0.91 (3H, t, J = 6.9 Hz).

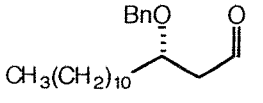


tert-Butyl-(*S*)-3-benzyloxytetradecanoate (4.12):- To *tert*-butyl-(*S*)-3-hydroxytetradecanoate (57 mg, 0.19 mmol) in DCM (0.3 ml) and cyclohexane (0.6 ml) was added benzyltrichloroacetimidate (38 μl, 0.20 mmol). The reaction was cooled in ice before trifluoromethanesulfonic acid (1 μl, 0.01 mmol) was added. The reaction mixture was



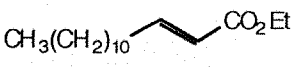
allowed to warm to room temperature and stirred for 4 h. The mixture was filtered and the filtrate washed with sodium bicarbonate and water. The combined aqueous phases were re-extracted with DCM. The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (7% diethyl ether in petrol) afforded (4.12) as a pale yellow oil (61.5 mg, 0.16 mmol, 83%); IR (film) 3065 w, 3031 w, 1731 s, 1456 m, 1367 s cm^{-1}; ^1H NMR (270 MHz) δ_H 7.32-7.27 (5H, m), 4.52 (1H, d, J = 11.4 Hz), 4.46 (1H, d, J = 11.4 Hz), 3.80 (1H, app quin, J = 6.2 Hz), 2.49 (1H, dd, J = 15.0, 7.3 Hz), 2.33 (1H, dd, J = 15.0, 5.5 Hz), 1.59-1.45 (2H, m), 1.41 (9H, s), 1.33-1.11 (18H, s), 0.83 (3H, t, J = 6.6 Hz); ^{13}C NMR (67.5 MHz) δ_C 171.4 (0), 138.8 (0), 128.4 (1), 127.9 (1), 127.6 (1), 80.6 (0), 76.5 (1), 71.6 (2), 41.4 (2), 34.5 (2), 32.1 (2), 29.8 (2), 29.5 (2), 28.2 (3), 25.4 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 408 ($(M+NH_4)^+$, 12%), 391 $(M+H)^+$, 4%), 352 (100%).

(*S*)-3-Benzyloxytetradecanal (2.74):- To *t*-butyl-(*S*)-3-benzyloxytetradecanoate (100 mg, 0.26 mmol) in

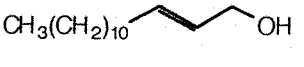


DCM (0.6 ml) at -78°C was added dropwise DiBAlH (0.17 ml, 1.5M in toluene, 0.26 mmol). After 15 min the reaction was quenched at -78°C by the slow addition of saturated NH_4Cl (0.05 ml) followed by HCl (0.1 ml), maintaining the temperature below -75°C. The reaction was warmed to room temperature and the aqueous phase was extracted with DCM. The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (7% diethyl ether in petrol) afforded (2.74) as a pale yellow oil (62 mg, 0.19 mmol, 76%); IR (film) 3031 w, 2925 s, 2854 s, 2723 w, 1726 s, 1455 m, 1067 m, 735 m, 697 m cm^{-1}; ^1H NMR (270 MHz) δ_H 9.71 (1H, s), 7.39-7.27 (5H, m), 4.52 (1H, d, J = 11.6 Hz), 4.46 (1H, d, J = 11.4 Hz), 3.89 (1H, app quin, J = 5.9 Hz), 2.62 (1H, ddd, J = 16.2, 7.1, 2.5 Hz), 2.56 (1H, ddd, J = 16.4, 4.8, 1.7 Hz), 1.76-1.40 (2H, m), 1.39-1.08 (18H, s), 0.85 (3H, t, J = 6.6 Hz); ^{13}C NMR (67.5 MHz) δ_C 201.9 (1), 138.4 (0), 128.6 (1), 128.0 (1), 127.9 (1), 74.5 (1), 71.4 (2), 48.4 (2), 34.3 (2), 32.1 (2), 29.8 (2), 29.7

(2), 29.5 (2), 25.2 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 336 ($(M+NH_4)^+$, 70%), 228 (51%), 35 (100%).

Ethyltetradec-2-eneoate (4.17):- To (carboethoxy)methylene triphenylphosphorane (3.12 g, 9.0 mmol) 

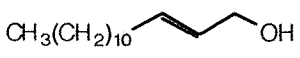
in toluene (30 ml) was added lauraldehyde (1.5 g, 8.2 mmol) and the mixture was refluxed for 10 h. Removal of the solvent *in vacuo* gave a white solid (Ph_3PO) which was removed by filtration and washed thoroughly with petrol. Concentration of the filtrate afforded a yellow oil. Distillation (b.p. 210°C, 0.03 mm Hg, lit 115°C, 2 Torr[92]) yielded (4.17) as a pale yellow oil (2.04 g, 8.0 mmol, 99%); IR (film) 1724 s, 1655 m, 1466 m, 1367 m, 1266 s, 1180 s, 1046 m cm^{-1}; ^1H NMR (270 MHz) δ_H 6.9 (1H, dt, J = 15.7, 7.0 Hz), 5.74 (1H, d, J = 15.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 2.14 (2H, q, J = 6.8 Hz), 1.41 (2H, m), 1.32-1.12 (19H, s), 0.84 (3H, t, J = 6.3 Hz); ^{13}C NMR (67.5 MHz) δ_C 166.8 (0), 149.5 (1), 121.3 (1), 60.1 (2), 32.3 (2), 32.0 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.5 (2), 29.3 (2), 28.1 (2), 22.8 (2), 14.3 (3), 14.2 (3).

Tetradec-2-enol (4.18):- To a solution of ethyltetradec-2-eneoate (1.77 g, 7.0 mmol) in DCM (80 ml) cooled 

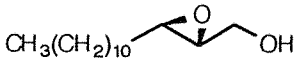
to -80°C, was added DiBAlH (12 ml of a 1.5 M solution in toluene, 18 mmol) dropwise over 30 min. The mixture was stirred at -80°C for 10 min before being quenched at -80°C by the slow addition of NH_4Cl (5 ml) followed by HCl (10 ml). The reaction was then allowed to warm to room temperature. The solid was removed by filtration and washed thoroughly with DCM. The filtrate was dried (Na_2SO_4) and concentrated. Flash chromatography (30% diethyl ether in petrol) yielded (4.18) as a colourless oil, which crystallised when stored at 5°C (1.45 g, 6.8 mmol, 98%); IR (film) 3624-3072 m, br, 2922 s, 2853 s, 1671 w, 1466 m, 1003 m, 969 m cm^{-1}; ^1H NMR (270 MHz) δ_H 5.70 (1H, app dt, J = 15.3, 5.6 Hz), 5.61 (1H, app dt, J = 15.3, 5.0 Hz), 4.09 (1H, d, J = 4.6 Hz), 2.04 (2H, q, J = 6.4 Hz),1.68 (1H, s), 1.47-1.12

(18H, s), 0.89 (3H, t, J = 6.6 Hz); ^{13}C NMR (67.5 MHz) δ_C 133.7 (1), 128.9 (1), 63.9 (2), 32.4 (2), 32.1 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4 (2), 29.3 (2), 22.8 (2), 14.3 (3); m/z (CI, NH_3) 230 ($(M+NH_4)^+$, 44%), 212 (M^+, 14%), 35 (100%); (Found : $(M+NH_4)^+$, 230.2484. $(C_{14}H_{28}O + NH_4)^+$ requires 230.2484).

Tetradec-2-enol (4.18):- To ethyltetradec-2-enoate (5.012 g, 19.7 mmol) in benzene (100 ml) was added Li-AlH_4 (903 mg, 23.7 mmol). The mixture was heated at 60°C for 20 h before cooling to room temperature. The mixture was quenched by slow addition of MeOH (5 ml) and water (2 ml). The inorganic solids were solubilised by the addition of HCl (25 ml of a 5% solution). The mixture was filtered and the filtrate extracted with diethyl ether. The organic phases were dried ($MgSO_4$) and concentrated to give a colourless oil. Flash chromatography (20% diethyl ether in petrol) yielded (4.18) as a colourless oil (2.51 g, 11.8 mmol, 60%). Spectroscopic data identical with above.

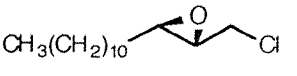


(2*R*, 3*R*)-*trans*-2-Hydroxymethyl-3-undecyl-oxirane (4.19):- This was prepared using the asymmetric epoxidation procedure developed by Sharpless[72]. To a suspension of molecular sieves (11.0 g, 4Å powder) in DCM at -20°C was added sequentially (-)-DIPT (749 mg, 3.2 mmol), titanium tetra-*iso*-propoxide (758 mg, 2.7 mmol) and *tert*-butyl hydroperoxide (23 ml of a 3.45 M solution in toluene, 80 mmol). The resulting mixture was stirred for 20 min at -20°C before tetradec-2-enol (11.33 g, 53.4 mmol) in DCM (20 ml) was added dropwise over 30 min. The mixture was left to warm to room temperature. The reaction mixture was poured into a freshly prepared solution of $FeSO_4$ (11.8 g) and tartaric acid (3.6 g) in water (36 ml) at 0°C. The resulting mixture was stirred for 20 min. The organic phase was separated and the aqueous phase was re-extracted with diethyl ether. The combined organic phases were stirred for 1 h with a solution of NaOH (30% w/v in brine). The mixture was extracted with

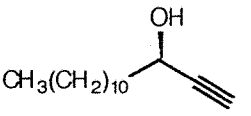


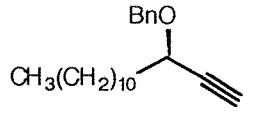
diethyl ether, dried (Na_2SO_4) and concentrated. Flash chromatography (50% diethyl ether in petrol) yielded (4.19) as a white crystalline solid (10.91 g, 47.9 mmol, 90%). This solid is readily recrystallised from hexane; m.p. 67-69°C; $[\alpha]_D$ +23.8° (c. 3 in $CHCl_3$); IR ($CHCl_3$) 3542-3295 m, 3014 m, 2928 s, 2856 s cm^{-1}; ^1H NMR (270 MHz) δ_H 3.92 (1H, d, J = 12.7 Hz), 3.61 (1H, d, J = 12.0 Hz), 2.96 (2H, m), 1.91 (1H, s), 1.56 (2H, t, J = 6.6 Hz), 1.52-1.38 (2H, m), 1.38-1.16 (16H, s), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (67.5 MHz) δ_C 61.9 (2), 58.6 (1), 56.2 (1), 32.1 (2), 31.7 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.5 (2), 26.1 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 246 ($(M + NH_4)^+$, 100%), 35 (71%); Anal. Found: C, 73.52; H, 12.49. Calc. for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36.

(2*S*, 3*R*)-*trans*-2-chloromethyl-3-Undecyl-oxirane (4.20):- A mixture of triphenylphosphine

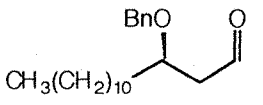


(12.24 g, 0.47 mol), (2*R*, 3*R*)-trans-2-hydroxymethyl-3-Undecyl-oxirane (10.29 g, 45 mmol) and sodium bicarbonate (0.85 g, 10.1 mmol) in CCl_4 (130 ml) was refluxed overnight. Removal of the solvent yielded a cream solid. Flash chromatography (2% diethyl ether in petrol) yielded (4.20) as a white solid (9.67 g, 39 mmol, 87%). This solid could be readily recrystallised from methanol; m.p 48-49°C; $[\alpha]_D$ +9.6° (c. 1 in $CHCl_3$); IR ($CHCl_3$) 3020 s, 2928 s, 2856 s cm^{-1}; ^1H NMR (270 MHz) δ_H 3.59 (1H, dd, J = 11.6, 5.8 Hz), 3.51 (1H, dd, J = 11.6, 5.2 Hz), 2.99 (1H, dt, J = 1.9, 5.1 Hz), 2.88 (1H, dt, J = 1.7, 5.1 Hz) 1.62-1.53 (2H, m), 1.49-1.38 (2H, m), 1.38-1.21 (16H, m), 0.88 (3H, t, J = 6.7 Hz); ^{13}C NMR (67.5 MHz) δ_C 59.4 (1), 57.3 (1), 45.0 (2), 32.1 (2), 31.6 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.5 (2), 26.0 (2), 22.9 (2), 14.3 (3); m/z 264 ($(M+NH_4)^+$, 100%); Anal. Found: C, 67.80; H, 11.01. Calc. for $C_{14}H_{27}ClO$ C: 68.13; H, 11.03.

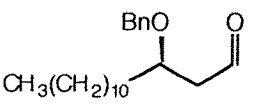
(*R*)-Tetradecyn-3-ol (3.9):- To di-*iso*-propylamine 
(127 mg, 1.25 mmol) in THF (2 ml) at -30°C was added *n*-BuLi (0.8 ml of a 1.6 M solution in hexanes, 1.26 mmol) dropwise. The reaction mixture was stirred for 1 h before the addition of (2*S-trans*)-3-undecyloxirane methylchloride (100 mg, 0.41 mmol) in THF (0.2 ml) dropwise. After 3 h the reaction was quenched at -30°C by the addition of NH_4Cl (0.02 ml). The mixture was extracted with DCM, washed with water and dried (Na_2SO_4). Flash chromatography (10% diethyl ether in petrol) yielded (3.9) as a cream low melting solid (83.5 mg, 0.40 mmol, 98%), which is readily recrystallised from pentane; m.p. 24-25°C; $[\alpha]_D$ +4.25° (c. 2 in $CHCl_3$); Spectral data identical with that reported before.

(*R*)-3-Benzyloxytetradec-1-yne (4.21):- Sodium 
hydride (725 mg, 60% in oil, 18.13 mmol) was washed twice with dry petrol before anhydrous DMF (30 ml) was added and the mixture was cooled in ice. (*R*)-tetradecyn-3-ol (3.48 g, 16.6 mmol) in DMF (20 ml) was added dropwise and stirred at 0°C for 1 h. Benzyl bromide (2.6 ml, 23.9 mmol) was added dropwise and the mixture was allowed to warm slowly to room temperature. The mixture was poured into water and extracted with petrol. The solution was dried (Na_2SO_4) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded (4.21) as a pale brown oil (4.48 g, 14.9 mmol, 90%); IR (film) 3309 m, 3065 w, 3032 w, 2929 s, 2854 s, 1496 w, 1455 m cm^{-1}; ^1H NMR (270 MHz) δ_H 7.43-7.30 (5H, m), 4.83 (1H, d, J = 11.8 Hz), 4.53 (1H, d, J = 11.8 Hz), 4.09 (1H, dt, J = 6.6, 1.9 Hz), 2.48 (1H, d, J = 1.9 Hz), 1.84-1.67 (2H, m), 1.55-1.40 (2H, m), 1.40-1.27 (16H, s), 0.90 (3H, t, J = 6.7 Hz); ^{13}C NMR (67.5 MHz) δ_C 138.1 (0), 128.5 (1), 128.2 (1), 127.9 (1), 83.2 (0), 73.9 (1), 70.7 (1), 68.6 (2), 35.8 (2), 32.1 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.5 (2), 29.5 (2), 25.4 (2), 22.9 (2), 14.3 (3); m/z (CI, NH_3) 318 ($(M+NH_4)^+$, 100%).

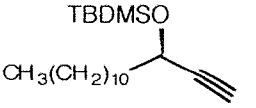
(*R*)-3-Benzyloxytetradecanal (2.15):- To 2-methyl-2-butene (47 mg, 0.67 mmol) in THF (0.5 ml) at 0°C was added BH_3.THF (0.33 ml of a 1 M solution , 0.33 mmol). The mixture was allowed to warm to room temperature before recooling in an ice/ salt bath. (*R*)-3-Benzyloxytetradec-1-yne (100 mg, 0.33 mmol) in THF (0.5 ml) was added rapidly keeping the temperature below 10°C. The reaction mixture was warmed to room temperature before recooling to 0°C. Oxidation was achieved by the addition of water (1.5 ml) and sodium percarbonate (158 mg, 1.19 mmol). The mixture was heated at 50°C for 1 h to complete oxidation. The mixture was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded (2.15) as a yellow oil (69 mg, 0.22 mmol, 65%); spectroscopic data identical with that reported earlier.



(*R*)-3-Benzyloxytetradecanal (2.15):-To (*R*)-3-benzyloxytetradec-1-yne (2.71 g, 9.03 mmol) in THF (5 ml) at 5°C was added catecholborane (9.1 ml, 9.1 mmol) dropwise. The reaction with catecholborane is slightly exothermic. BH_3.N,N, diethylaniline (148 mg, 0.9 mmol) was added to the mixture and the reaction was allowed to warm to room temperature. The reaction mixture was heated to 23°C for 24 h. The reaction was cooled in an ice bath before hydrogen peroxide (0.4 ml of a 30% solution) was added, whilst maintaining the pH between 7 and 8 by the addition of NaOH (2M). The mixture was heated to 50°C for 1 h to ensure complete oxidation. On cooling, the reaction was extracted with petrol. The organic phase was dried ($CaSO_4$) and concentrated. Flash chromatography (5% diethyl ether in petrol) yielded (2.15) as a pale yellow oil (2.03 g, 6.39 mmol, 71%). Spectroscopic data identical to that reported earlier.



(*R*)-3-*tert*-Butyldimethylsiloxytetradec-1-yne (4.39):- To (*R*)-3-hydroxytetradec-1-yne (1.19 g, 5.67 mmol) in anhydrous DMF (25 ml) was added imidazole (833 mg, 12.25 mmol) and

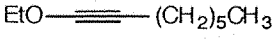


tert-butylchlorodimethysilane (939 mg, 6.23 mmol). The reaction mixture was stirred for 18 h. The mixture was poured into water and extracted with petrol. The organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (2% diethyl ether in petrol) yielded (4.39) as a pale yellow oil (1.81 g, 5.59 mmol, 99%); IR (film) 3312 m, 2927 s, 2856 s, 1464 m, 1252 m, 1096 m, 837 m, 777 m cm^{-1}; ^1H NMR (270 MHz) δ_H 4.34 (1H, dt, J = 6.5, 2.1 Hz), 2.37 (1H, d, J = 2.1 Hz), 1.72-1.63 (2H, m), 1.48-1.36 (2H, m), 1.36-1.19 (16H, s), 0.93-0.86 (12H, m), 0.14 (3H, s), 0.12 (3H, s); ^{13}C NMR (67.5 MHz) δ_C 86.0 (1), 72.0 (0), 63.0 (1), 38.8 (2), 32.2 (2), 29.9 (2), 29.8 (2), 29.8 (2), 29.6 (2), 29.5 (2), 26.0 (3), 25.4 (2), 22.9 (2), 18.4 (0), 14.3 (3), -4.4 (3), -4.9 (3); m/z (CI, NH_3) 342 ($(M+NH_4)^+$, 100%); (Found : $(M+NH_4)^+$, 342.3178. $(C_{20}H_{40}OSi + NH_4)^+$ requires 342.3192).

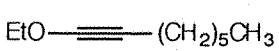
(*R*)-3-*tert*-Butyldimethylsiloxytetradecanal (4.40):- To (*R*)-3-*tert*-butyldimethylsiloxytetradec-1-yne (1.26 g, 3.89 mmol) in THF (6 ml) was added catecholborane (3.9 ml, 1.0 M in toluene, 3.9 mmol). The reaction mixture was heated to 60°C for 14 h. The reaction was diluted with THF (15 ml) and oxidised by the careful addition of hydrogen peroxide (8.7 ml) and sodium hydroxide (2M) maintaining the pH between 7 and 8.5. The reaction mixture was heated to 50°C for 1 h to ensure complete oxidation. On cooling to room temperature the reaction mixture was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (5% diethyl ether in petrol) afforded (4.40) as a pale yellow oil (923 mg, 2.70 mmol, 69%); $[\alpha]_D$ +3.0° (c. 2 in $CHCl_3$); IR (film) 2928 s, 2856 s, 2716 w, 1729 s, 1464 s, 1464 m, 1255 m, 1106 m, 837 s, 776 s cm^{-1}; ^1H NMR (270 MHz) δ_H 9.79 (1H, dd (app t), J = 2.51, 2.32 Hz), 4.17 (1H, app quin, J = 5.8 Hz), 2.50 (1H, d, J = 2.5 Hz), 2.48 (1H, d, J = 2.3 Hz), 1.58-1.42 (2H, m), 1.37-1.12 (18H, s), 0.96-0.78 (12H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (67.5 MHz) δ_C 202.4 (1), 68.4 (1), 50.9 (2),

38.0 (2), 32.0 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 25.9 (3), 25.2 (2), 22.8 (2), 18.1 (0), 14.2 (3), -4.3 (3), -4.6 (3); m/z (CI, NH_3) 360 ($(M+NH_4)^+$, 52%), 343 ($(M+H)^+$, 100%); (Found : $(M+H)^+$, 343.3004. $(C_{20}H_{42}O_2Si + H)^+$ requires 343.3032).

1-Ethoxyoct-1-yne (3.4):- To liquid ammonia (500 ml) at -30°C was added $Fe(NO_3)_3$ (150 mg, mmol). Sodium (11.24 g, 488 mmol) in 0.25 cm^3 pieces was added over 30 min. The reaction mixture was stirred at -30°C until no blue colour remained (approx. 2.5 h). Chloroacetaldehyde diethyl acetal (22 ml, 145 mmol) was added dropwise and the reaction was stirred at -30°C for a further 4 h. Hexyl iodide (17.5 ml, 118 mmol) was added dropwise and the reaction was stirred at -30°C overnight. The ammonia was allowed to evaporate before pentane (45 ml) was added. The reaction was quenched by the careful addition of a saturated NH_4Cl solution (110 ml). The aqueous layer was extracted with pentane, dried ($MgSO_4$) and concentrated. Distillation (30-32°C, 0.1 mm Hg, lit. 43°C, 0.5 mm Hg[85]) afforded (3.4) as a pale yellow oil (7.88 g, 51.2 mmol, 43%); spectral data identical with data reported previously[79].



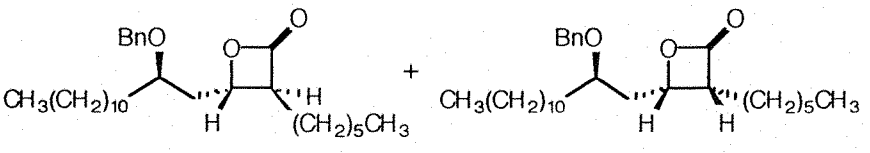
1-Ethoxyoct-1-yne (3.4):- To ethoxyacetylene (10.0 g, 50% w/w in hexane, 71.4 mmol) in THF (80 ml) at -80°C was added *n*-BuLi (32 ml of a 2.5M solution in hexane, 80 mmol). The reaction mixture was stirred for 1 h at -80°C before HMPA (27 ml, 155.2 mmol) was added. The reaction was stirred for a further 15 min at -80°C before hexyl iodide (10.02 g, 47 mmol) in THF (10 ml) was added dropwise over 20 min. The reaction mixture was then allowed to warm to room temperature. The reaction mixture was quenched with water (30 ml) and the aqueous phase was extracted with petrol. The combined organic fractions were dried ($MgSO_4$) and concentrated. Distillation (100°C, 12 mm Hg) afforded (3.4) as a colourless oil (7.04 g, 45.7 mmol, 97%); spectral data identical with that reported[79].



***n*-Hexyltrimethylsilyl ketene (3.3)**:- Hexamethyldisilane (3.5 ml, 17 mmol) was added to freshly resublimed iodine (4.35 g, 34 mmol) and the mixture was heated under argon at 80°C for 2 h[46]. On cooling to room temperature clean copper wire (300 mg) was added followed by 1-ethoxyoct-1-yne (3.49 g, 22.7 mmol). A white precipitate was formed which gradually turned a salmon pink. The reaction mixture was heated to 65°C for 24 h, whereupon the solid disappeared. The excess iodotrimethylsilane was removed (65°C, 20 mm Hg) and the residual oil was distilled (80°C, 0.5 mm Hg) to yield (3.3) as a pale yellow oil (4.14 g, 20.9 mmol, 92%); IR (film) 2957 s, 2928 s, 2857 s, 2086 s, 840 s cm^{-1}; ^1H NMR (270 MHz) δ_H 1.92 (2H, t, J = 7.1 Hz), 1.34-1.22 (8H, s), 0.90 (3H, t, J = 9.3 Hz), 0.16 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 183.2 (0), 32.1 (2), 29.9 (2), 29.8 (2), 29.6 (2), 22.9 (2), 22.2 (2), 14.3 (0), 13.1 (3), -0.7 (3).

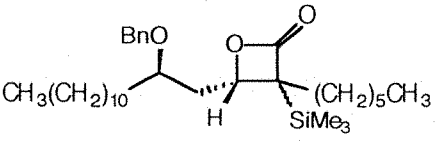
(3*R,S*, 4*S*)-4-[2-(Benzyloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (6.1):- To a solution of (*R*)-3-benzyloxytetradecanal (98 mg, 0.31 mmol) in anhydrous diethyl ether (1.2 ml) cooled to -18°C under an argon atmosphere was added dropwise freshly distilled $BF_3.Et_2O$ (40 µl, 0.31 mmol). After 10 min *n*-hexyltrimethylsilyl ketene (113 mg, 0.57 mmol) in anhydrous diethyl ether (0.2 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly over 4 h. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated to afford (6.1) as a yellow oil (205 mg, 129%) which was carried through to the next reaction without further purification.

(3*S*, 4*S*)-4-[(*R*)-2-(Benzyloxy)-1-tridecyl]-3-hexyl-2-oxetanone (2.18) and (3*R*, 4*S*)-4-[(*R*)-2-(benzyloxy)-1-tridecyl]-3-hexyl-2-oxetanone (6.2):-



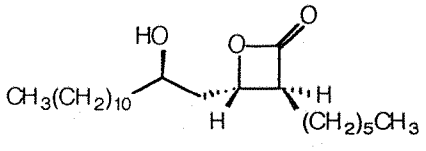
To a solution of crude 4-[2-(benzyloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (154 mg) in THF (1 ml) cooled to -80°C, was added dropwise TBAF (0.25 ml of a 1M solution in THF, 0.25 mmol). After 5 min the reaction was quenched at -80°C by the slow addition of water (1 ml). On warming to room temperature the mixture was extracted with diethyl ether, dried ($MgSO_4$) and concentrated to yield a yellow oil (111 mg). Flash chromatography (4% diethyl ether in petrol) afforded (2.18) as a pale yellow oil (44 mg, 0.09 mmol, 43% from (2.15)); $[\alpha]_D$ +0.5° (c. 2 in $CHCl_3$); IR (film) 1828 s, 1725 w, 1697 w, 1465 s, 1121 s cm^{-1}; ^{1}HMR (360 MHz) δ_H 7.39-7.24 (5H, m), 4.61 (1H, d, J = 9.47 Hz), 4.47-4.43 (2H, m), 3.61 (1H, app quin, J = 6.4 Hz), 3.22 (1H, dt, J = 7.6, 4.0 Hz), 1.94 (2H, t, J = 7.4 Hz), 1.81-1.47 (4H, m), 1.4-1.0 (26H, s), 0.88 (3H, t, J = 6.9 Hz), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 172.0 (0), 138.6 (0), 128.6 (1), 128.0 (1), 127.9 (1), 75.9 (1), 75.7 (1), 71.7 (2), 56.8 (1), 40.0 (2), 34.1 (2), 32.1 (2), 31.7 (2), 29.9 (2), 29.9 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.1 (2), 27.9 (2), 26.9 (2), 24.9 (2), 22.9 (2), 22.7 (2), 14.4 (3), 14.2 (3); m/z (CI, NH_3) 462 ($(M+NH_4)^+$, 100%), 445 ($(M+H)^+$, 27%) followed by (6.2) (30 mg, 0.06 mmol, 29%); IR (film) 1828 s, 1725 w, 1697 w, 1465 s, 1121 s cm^{-1}; ^{1}HMR (270 MHz) δ_H 7.41-7.25 (5H, m), 4.85 (1H, q, J = 8.5 Hz), 4.62 (1H, d, J = 11.4 Hz), 4.44-4.40 (2H, m), 3.61 (1H, app quin, J = 5.7 Hz), 1.96 (2H, t, J = 6.41 Hz), 1.81-1.46 (4H, m), 1.4-1.0 (26H, s), 0.88 (6H, m).

4-[2-(Benzyloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (6.1):- To a solution of (*R*)-3-

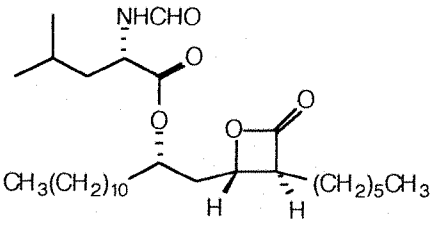


benzyloxytetradecanal (136 mg, 0.43 mmol) in anhydrous diethyl ether (1 ml) cooled to -40°C under an argon atmosphere was added dropwise freshly distilled $EtAlCl_2$ (0.05 ml, 0.47 mmol). After 10 min *n*-hexyltrimethylsilyl ketene (127 mg, 0.64 mmol) in anhydrous diethyl ether (1 ml) was added dropwise. The reaction was allowed to warm to 0°C slowly over 2 h. The reaction was quenched with water and extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5% diethyl ether in petrol) afforded (6.1) as a yellow oil (183 mg, 0.35 mmol, 83%); IR (film) 3424 w, br, 3031 w, 1805 s, 1698 m, 1496 w, 1456 m cm^{-1}; ^1H NMR (270 MHz) δ_H 7.44-7.25 (5H, m), 4.72-4.44 (3H, m), 3.69-3.58 (1H, m), 2.08-1.83 (2H, m), 1.83-1.48 (4H, m), 1.48-1.19 (26H, s), 0.89 (6H, t, J = 7.8 Hz), 0.24 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 174.2 (0), 138.5 (0), 128.5 (1), 128.0 (1), 127.9 (1), 76.3 (1), 76.2 (1), 72.2 (2), 54.7 (1), 53.2 (0), 37.9 (2), 34.4 (2), 32.0 (2), 31.7 (2), 30.4 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.4 (2), 29.2 (2), 26.1 (2), 25.0 (2), 22.8 (2), 22.6 (2), 14.2 (3), 14.1 (3), -1.4 (3).

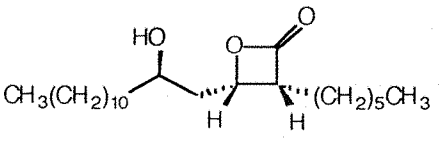
(3*S*, 4*S*)-3-Hexyl-4-[(*R*)-2-(hydroxy)-1-tridecyl]-2-oxetanone (2.19):- To a solution of 4-[2-(benzyloxy)-1-tridecyl]-3-hexyl-2-oxetanone (85 mg, 0.19 mmol) in ethylacetate (2 ml) was added Pd/C (10%, 30 mg). The mixture was placed under a hydrogen atmosphere and stirred overnight. On evacuation of the hydrogen the mixture was filtered through celite. Concentration afforded a white solid which was recrystallised from hexane to yield (2.19) as a white solid (40 mg, 0.11 mmol, 59%); m.p. 50.5-52°C (lit 57-59°C[56]); $[\alpha]_D$ -11.0° (c. 1 in $CHCl_3$); IR (CCl_4) 3480 s, br, 1820 s, 1120 s cm^{-1}; ^{1}HMR (270 MHz) δ_H 4.51 (1H, m), 3.81 (1H, m), 3.27 (1H, ddd, J = 8.2, 6.9, 4.1 Hz), 1.72-1.97 (4H, m), 1.67 (1H, br, s), 1.22-1.53 (28H, m), 0.88 (6H, t, J = 6.76 Hz); ^{13}C NMR (67.5 MHz) δ_C 171.9 (0), 75.8 (1), 68.6 (1), 56.7 (1), 42.0 (2), 38.3 (2), 37.8 (2), 32.1 (2), 31.7 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4



(2), 29.1 (2), 27.9 (2), 26.9 (2), 25.6 (2), 25.2 (2), 22.9 (2), 22.7 (2), 14.3 (3), 14.2 (3); m/z (CI, NH_3) 372 ($(M+NH_4)^+$, 100%), 354 (M^+, 22%).



(*S*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-2-oxetanyl)methyl]dodecyl-(*S*)-N-formylleucinate-tetrahydrolipstatin (2.2):- To a mixture of (3*S*, 4*S*)-3-hexyl-4-[(*R*)-2-(hydroxy)-1-tridecyl]-2-oxetanone (103 mg, 0.29 mmol), triphenylphosphine (92 mg, 0.35 mmol) and (*S*)-N-formylleucine (62 mg, 0.39 mmol) in THF (10 ml) cooled to 0°C, was added dropwise diethyl azodicarboxylate (62 μl, 0.51 mmol). After 1.5 h the mixture was warmed to room temperature and stirred for a further 2 h. Concentration afforded a yellow oil. The oil was taken up in a 50:50/ petrol: diethyl ether solution and the suspension formed was filtered. Concentration of the filtrate and flash chromatography (20% ethylacetate: petrol) yielded (2.2) as a white solid (113 mg, 0.23 mmol, 79%), which was recrystallised from pentane; m.p. 40-41°C; (lit. 41-42.5°C[56]) IR (CCl_4) 3436-3131 m, br, 1824 s, 1798 s, 1740 s, 1689 s cm^{-1}; ^{1}HMR (270 MHz) δ_H 8.22 (1H, s), 6.03 (1H, d, J = 8.7 Hz), 5.02 (1H, m), 4.68 (1H, ddd, J = 8.5, 8.5, 4.5 Hz), 4.29 (1H, m), 3.21 (1H, ddd, J = 7.8, 7.8, 4.0 Hz), 2.17 (1H, ddd, J = 14.8, 7.2, 7.2 Hz), 2.0 (1H, ddd, J = 14.8, 4.2, 4.1 Hz), 1.84-1.51 (8H, m), 1.48-1.18 (25H, s), 0.93 (6H, d, J = 6.2 Hz), 0.85 (6H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 172.1 (0), 170.9 (0), 160.8 (1), 74.9 (1), 72.9 (1), 57.2 (1), 49.7 (1), 41.7 (2), 38.8 (2), 34.2 (2), 32.0 (2), 31.6 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.4 (2), 29.1 (2), 27.7 (2), 26.8 (2), 25.2 (2), 25.0 (1), 23.0 (3), 22.8 (2), 22.6 (2), 21.9 (3), 14.2 (3), 14.1 (3); m/z (CI, NH_3) 513 ($(M+NH_4)^+$, 100%), 496 $(M+H)^+$, 32%), 35 (50%).



(3*R*, 4*S*)-3-Hexyl-4-[(*R*)-2-(hydroxy)-1-tridecyl]-2-oxetanone (6.3):-. To a solution of 4-[2-(benzyloxy)-1-tridecyl]-3-

hexyl-2-oxetanone (123 mg, 0.28 mmol) in THF (4 ml) was added Pd/C (10%, 31 mg). The mixture was placed under a hydrogen atmosphere and stirred overnight. On evacuation of the hydrogen the mixture was filtered through celite. Concentration, followed by flash chromatography (20% EtOAc : petrol) afforded (6.3) as a pale yellow oil (57 mg, 0.16 mmol, 58%); IR (film) 3648-3119 m, br, 2927 s, 2855 s, 1823 s, 1120 m cm^{-1}; ^{1}HMR (360 MHz) δ_H 4.89 (1H, ddd, J = 10.7, 6.51 2.5 Hz), 3.86-3.79 (1H, m), 3.64 (1H, dt, J = 8.3, 7.0 Hz), 2.13-1.96 (1H, s, br), 1.92-1.66 (2H, m), 1.54-1.46 (2H, m), 1.36-1.23 (28H, m), 0.88 (3H, t, J = 6.9 Hz), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 172.4 (0), 72.9 (1), 68.1 (1), 52.7 (1), 38.3 (2), 37.6 (2), 32.0 (2), 31.6 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.2 (2), 27.6 (2), 25.6 (2), 24.3 (2), 22.8 (2), 22.7 (2), 14.3 (3), 14.2 (3); m/z (CI, NH_3) 372 ($(M+NH_4)^+$, 100%), 355 ($(M+H)^+$, 38%).

(*S*)-1-[((2*S*, 3*R*)-3-Hexyl-4-oxo-2-oxetanyl)methyl]dodecyl-(*S*)-N-formylleucinate (6.4):- To a mixture of (3*R*, 4*S*)-3-hexyl-4-[(*R*)-2-(hydroxy)-1-tridecyl]-2-oxetanone (46 mg, 0.13 mmol), triphenylphosphine (42 mg, 0.16 mmol) and (*S*)-N-formylleucine (28 mg, 0.18 mmol) in THF (3 ml) cooled to 0°C was added dropwise diethyl azodicarboxylate (28 μl, 0.18 mmol). After 1.5 h the mixture was warmed to room temperature and stirred for a further 2 h. Concentration afforded a yellow oil. The oil was taken up in a 50:50/petrol: diethyl ether solution and the suspension formed was filtered. Concentration of the filtrate and flash chromatography (petrol: chloroform: dioxane/ 3:1:0.4) yielded (6.4) as a pale yellow oil (54 mg, 0.11 mmol, 84%); $[\alpha]_D$ -9.47° (c. 1 in $CHCl_3$); IR (CCl_4) 3436-3131 m, br, 1824 s, 1798 s, 1740 s, 1689 s cm^{-1}; ^{1}HMR (270 MHz) δ_H 8.22 (1H, s), 6.26 (1H, d, J = 8.1 Hz), 5.09 (1H, m), 4.69 (2H, m), 3.67 (1H, dd, J = 6.5, 3.0 Hz), 2.08-1.84 (2H, m), 1.81-1.45 (12H, m), 1.42-1.06 (21H, s), 0.94 (6H, d, J = 5.6 Hz), 0.86 (6H, t, J = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ_C 172.1 (0), 171.6 (0),

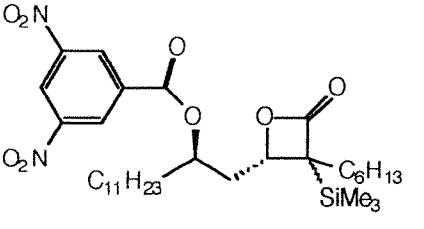
161.1 (1), 73.1 (1), 72.5 (1), 53.5 (1), 49.9 (1), 41.4 (2), 34.6 (2), 34.2 (2), 32.0 (2), 31.6 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.2 (2), 27.5 (2), 25.3 (2), 25.0 (1), 24.2 (2), 23.0 (3), 22.8 (2), 22.6 (2), 21.9 (3), 14.2 (3), 14.1 (3); m/z (CI, NH_3) 513 ($(M+NH_4)^+$, 100%), 496 $(M+H)^+$, 23%), 470 (27%), 86 (39%).

3-Hexyl-4-((*R*)-2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (6.13):- To 4-[2-(benzyloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (112 mg, 0.22 mmol) in THF (5 ml) was added Pd/C (10%, 10 mg). The reaction mixture was placed under a hydrogen atmosphere and stirred overnight. The mixture was filtered through celite and concentrated. Flash chromatography (30% diethyl ether in petrol) yielded (6.13) as a pale yellow oil (48 mg, 0.11 mmol, 52%); $[\alpha]_D$ -11.2° (c. 1 in $CHCl_3$); IR (film) 3612-3237 m, br, 2926 s, 2855 s, 1804 s, 1466 m, 1381 m, 1255 m, 1121 s, 846 s cm^{-1}; ^1H NMR (270 MHz) δ_H 4.72 (1H, dd, J = 11.2, 1.7 Hz), 3.88-3.76 (1H, m), 2.00 (1H, dt, J = 11.6, 2.3 Hz), 1.77 (5H, app q, J = 6.5 Hz), 1.56-1.21 (3H, m), 1.21-1.16 (24H, s), 0.89-0.79 (6H, m), 0.22 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 174.2 (0), 76.4 (1), 68.6 (1), 54.9 (0), 39.9 (2), 33.2 (2), 32.0 (2), 31.7 (2), 30.7 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.5 (2), 26.2 (2), 25.6 (2), 22.8 (2), 22.7 (2), 14.2 (3), 14.2 (3), -1.24 (3); m/z 444 ($(M+NH_4)^+$, 61%), 427 ($(M+H)^+$, 44%), 337 (100%); (Found : $(M+NH_4)^+$, 372.3485 .($C_{22}H_{42}O_3$ + $NH_4)^+$ requires 372.3478).

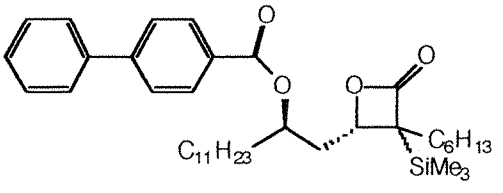
(*R*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyl-4-nitrobenzoate (6.14):- To 3-hexyl-4-(2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (16.5 mg, 0.04 mmol) in THF (1.5 ml) was added 4-

nitrobenzoyl chloride (7 mg, 0.04 mmol) followed by pyridine (3.6 mg, 0.04 mmol). The reaction mixture was stirred at room temperature overnight before being poured into water. The aqueous phase was extracted with diethyl ether and the organic fraction was dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded (6.14) as a pale yellow viscous oil (16 mg, 0.03 mmol, 72%); IR (film) 3112 w, 3080 w, 3055 w, 2926 s, 2855 s, 1805 s, 1725 s, 1608 m, 1530 s, 1466 m, 1350 m, 1274 s, 1116 s, 846 s, 720 s cm^{-1}; ^1H NMR (270 MHz) δ_H 8.30 (2H, dt, J = 9.1, 2.1 Hz), 8.21 (2H, dt, J = 9.1, 2.0 Hz), 5.28 (1H, app quin, J = 5.7 Hz), 4.52 (1H, dd, J = 10.9, 2.2 Hz), 2.36-2.25 (1H, m), 2.15 (1H, ddd, J = 14.4, 6.9, 2.2 Hz), 1.87-1.64 (4H, m), 1.44-1.18 (26H, s), 0.91-0.81 (6H, m), 0.23 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 173.5 (0), 164.3 (0), 150.7 (0), 135.7 (0), 130.8 (1), 123.7 (1), 75.6 (1), 74.0 (1), 65.9 (2), 55.7 (0), 36.9 (2), 34.1 (2), 32.0 (2), 31.6 (2), 30.5 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.6 (2), 29.5 (2), 29.4 (2), 26.2 (2), 25.3 (2), 22.8 (2), 22.6 (2), 14.2 (3), 14.1 (3), -1.32 (3).

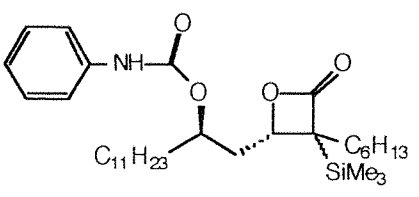
(*R*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyl-3,5-dinitrobenzoate (6.15):- To 3-hexyl-4-(2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (50 mg, 0.12 mmol) in THF (2 ml) was added 3,5-dinitrobenzoyl chloride (27.7 mg, 0.12 mmol) followed by pyridine (0.01 ml, 0.14 mmol). The reaction mixture was stirred at room temperature for 2 h before being poured into water. The aqueous phase was extracted with diethyl ether and the organic fraction was dried ($MgSO_4$) and concentrated. Flash chromatography (5% diethyl ether in petrol) yielded (6.15) as a pale yellow solid (51.1 mg, 0.08 mmol, 70%). Recrystallisation from isopropanol afforded a white solid; m.p. 59-61°C; IR 3105 w, 2957 s, 2927 s, 2856 s, 1805 s, 1730 s, 1629 m, 1548 s, 1345 s cm^{-1}; ^1H NMR (270 MHz) δ_H 9.24 (1H, s), 9.16 (2H, s), 5.42-5.28 (1H, m), 4.53 (1H,



d, J = 10.8 Hz), 2.46-2.31 (1H, m), 2.24-2.13 (1H, m), 1.98-1.63 (4H, m), 1.53-0.96 (26H, m), 0.95-0.76 (6H, m), 0.25 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 173.4 (0), 162.2 (0), 148.8 (0), 134.0 (0), 129.6 (1), 122.6 (1), 75.3 (1), 55.8 (0), 36.6 (2), 34.0 (2), 32.0 (2), 31.6 (2), 30.6 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.4 (2), 29.4 (2), 26.3 (2), 25.4 (2), 22.6 (2), 14.2 (3), 14.1 (3), -1.3 (3); m/z (CI, NH_3) 638 $(M+NH_4)^+$ (11%), 90 (100%).



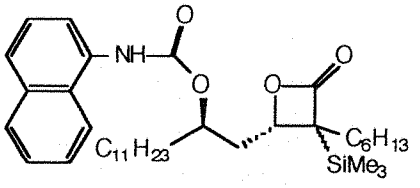
(*R*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyl-4-phenylbenzoate (6.16):- To 3-hexyl-4-(2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (43 mg, 0.10 mmol) in DCM (2 ml) was added 4-phenylbenzoyl chloride (22 mg, 0.10 mmol) followed by pyridine (0.01 ml, 0.14 mmol) and DMAP (1 mg, 8.0 μmol). The reaction mixture was stirred at room temperature overnight before being poured into water. The aqueous phase was extracted with diethyl ether and the organic fraction was dried ($MgSO_4$) and concentrated. Flash chromatography (5% diethyl ether in petrol) yielded (6.16) as a pale yellow solid (12.1 mg, 0.02 mmol, 20%); IR (film) 3061 w, 3032 w, 2959 s, 2928 s, 2857 s, 1807 s, 1724 s, 1276 s, 1120 s cm^{-1}; ^1H NMR (270 MHz) δ_H 8.13 (2H, d, J = 8.3 Hz), 7.66 (4H, dd, J = 13.2, 8.4 Hz), 7.58-7.37 (3H, m), 5.28 (1H, app quin, J = 5.9 Hz), 4.57 (1H, dd, J = 7.2, 2.9 Hz), 2.37-2.12 (2H, m), 1.91-1.64 (4H, m), 1.52-1.07 (26H, s), 0.99-0.78 (6H, m), 0.26 (9H, s).



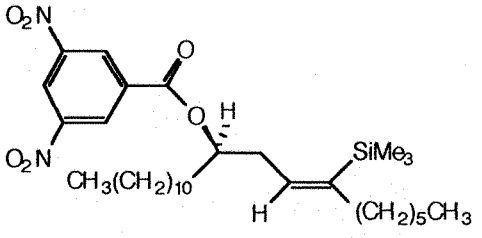
(*R*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyl-N-phenylcarbamate (6.17):- To 3-hexyl-4-(2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (34 mg, 0.08 mmol) in pyridine (0.6 ml) was added phenyl isocyanate (10.2 mg, 0.09 mmol). The reaction mixture was

heated to 100°C for 2 h. On cooling, the mixture was poured into water. The aqueous phase was extracted with diethyl ether and the organic fraction was dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded (6.17) as a colourless viscous oil (41 mg, 0.08 mmol, 94%), which was found to be contaminated. Attempts to further purify this product by column chromatography were unsuccessful; IR (film) 3448-3201 m, 3135 w, 3060 w, 2925 s, 2855 s, 1805 s, 1734 s, 1600 s, 1538 s, 1444 s, 1218 s, 1120 s, 846 s cm^{-1}; ^1H NMR (270 MHz) δ_H 7.44-7.29 (5H, m), 6.58 (1H, s), 5.04-4.93 (1H, m), 4.54 (1H, d, J = 10.6 Hz), 2.20-1.96 (2H, m), 1.83-1.56 (4H, m), 1.56-1.02 (26H, s), 1.02-0.76 (6H, m), 0.08 (9H, s).

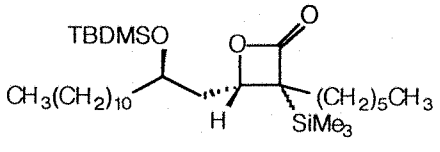
(*R*)-1-[((2*S*, 3*S*)-3-Hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyl-N-1-naphthylcarbamate (6.18):- To 3-hexyl-4-(2-hydroxy-1-tridecyl)-3-trimethyl-silyl-2-oxetanone (47 mg, 0.11 mmol) in pyridine (0.9 ml) was added 1-naphthyl isocyanate (19 mg, 0.11 mmol). The reaction mixture was heated to 100°C for 2 h. On cooling, the mixture was diluted with methanol and the reaction mixture was reheated to 100°C for 10 min. On cooling, the reaction was poured into water. The aqueous phase was extracted with diethyl ether and the organic fraction was dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) yielded (6.18) as a viscous oil (42 mg, 0.07 mmol, 64%); IR (film) 3660-3108 m, br, 3053 w, 2926 s, 2855 s, 1804 s, 1713 s, 1543 s, 1539 s, 1256 s, 1219 s, 1050 s, 847 s cm^{-1}; ^1H NMR (270 MHz) δ_H 7.92-7.85 (3H, m), 7.69 (1H, d, J = 8.3 Hz), 7.56-7.45 (3H, m), 6.97 (1H, s), 5.04 (1H, app quin, J = 5.9 Hz), 4.56 (1H, d, J = 10.0 Hz), 2.29-1.98 (2H, m), 1.83-1.58 (4H, m), 1.54-1.04 (26H, s), 0.89 (3H, t, J = 6.4 Hz), 0.86 (3H, t, J = 6.8 Hz), 0.25 (9H, s); ^{13}C NMR (67.5 MHz) δ_C 173.9 (0), 134.3 (0), 132.5 (0), 129.0 (1), 126.4 (1), 126.2 (1), 126.0 (1), 75.9 (1), 73.7 (1), 55.7 (0), 37.4 (2), 34.6 (2), 32.1



(2), 31.7 (2), 30.6 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.5 (2), 26.3 (2), 25.4 (2), 22.9 (2), 22.7 (2), 14.3 (3), 14.2 (3), -1.2 (3).



(*Z*)-(10*R*)-10-[(3,5-dinitrobenzoyloxy)-7-(trimethylsilyl)]-7-henecosene (6.19):- (*R*)-1-[((2*S*, 3*S*)-3-hexyl-4-oxo-3-trimethylsilyl-2-oxetanyl) methyl]dodecyldinitrobenzoate (7.6 mg, 0.01 mmol) in dekalin (0.5 ml) was heated to reflux (189-191°C) for 2 h. The reaction mixture was concentrated. Flash chromatography (2% diethyl ether in petrol) yielded (6.19) as a yellow oil (6.1 mg, 0.01 mmol, 86%); IR (film) 3104 w, 2958 s, 2926 s, 2855 s, 1730 s, 1628 m, 1548 s, 1460 m, 1344 s, 1276 s cm^{-1}; ^{1}H NMR (270 MHz) δ_H 9.24 (1H, t, J = 2.2 Hz), 9.15 (2H, d, J = 2.2 Hz), 5.92 (1H, dd, J = 7.8, 6.7 Hz), 5.29 (1H, tt, J = 7.3, 5.4 Hz), 2.60 (1H, dd, J = 14.8, 7.5 Hz), 2.55 (1H, dd, J = 12.1, 5.8 Hz), 2.05-1.98 (2H, m), 1.77 (2H, app quin, J = 7.4 Hz), 1.39-1.16 (26H, m), 0.88 (3H, t, J = 6.8 Hz), 0.84 (3H, t, J = 6.7 Hz), 0.16 (9H, s); ^{13}C NMR (90 MHz) δ_C 162.3 (0), 148.8 (0), 143.8 (0), 136.1 (1), 134.6 (0), 129.5 (1), 122.3 (1), 77.7 (1), 38.7 (2), 36.8 (2), 34.1 (2), 32.0 (2), 31.9 (2), 30.9 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.5 (2), 29.2 (2), 25.7 (2), 22.8 (2), 22.7 (2), 14.2 (3), 14.2 (3), 0.48 (3); unable to obtain a mass spectrum.



4-[2-(*tert*-Butyldimethylsiloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (6.20):-To (*R*)-3-*tert*-butyldimethylsiloxytetradecanal (216 mg, 0.63 mmol) in anhydrous diethyl ether (1.5 ml) at -40°C was added ethylaluminium dichloride. After 10 min *n*-Hexyltrimethylsilyl ketene (187 mg, 0.94 mmol) in anhydrous diethyl ether (0.5

ml) was added dropwise. The reaction mixture was allowed to warm slowly to 0°C. Whereupon the reaction was poured into water, extracted with petrol, dried ($MgSO_4$) and concentrated. Flash chromatography (3% diethyl ether in petrol) yielded (6.20) as four inseparable diastereoisomers (213 mg, 0.39 mmol, 63%) in a ratio of 75: 15.5: 7.5: 2; major isomer $[\alpha]_D$ +3.2° (c. 1 in $CHCl_3$); IR (film) 2958 s, 2928 s, 2857 s, 1809 s, 1464 m, 1255 m, 841 s cm^{-1}; ^{1}HMR (270 MHz) δ_H 4.64 (1H, dd, J = 11.5, 1.5 Hz), 3.94-3.77 (1H, m), 2.0 (1H, dt, J = 11.6, 2.3 Hz), 1.83-1.62 (2H, m), 1.58-1.39 (2H, m), 1.39-1.12 (27H, s), 0.94-0.79 (15H, m), 0.22 (9H, s), 0.12 (3H, s), 0.08 (3H, s); ^{13}C NMR (67.5 MHz) δ_C 174.5 (0), 76.1 (1), 68.9 (1), 54.5 (0), 39.6 (2), 38.3 (2), 32.1 (2), 31.7 (2), 30.6 (2), 29.9 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.5 (2), 26.3 (0), 26.0 (2), 24.7 (2), 22.8 (2), 22.6 (2), 22.6 (2), 14.3 (3), 14.1 (3), -1.26 (3); m/z (CI, NH_3) 558 ($(M+NH_4)^+$, 34%), 541 ($(M+H)^+$, 49%), 299 (100%).

4-[2-(*tert*-Butyldimethylsiloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (6.20):- To *n*-hexyltrimethylsilyl ketene (54 mg, 0.27 mmol) in anhydrous diethyl ether (0.5 ml) at -40°C was added ethylaluminium dichloride (0.18 ml, 1M in hexane, 0.18 mmol). After 10 min (*R*)-3-*tert*-butyldimethylsiloxytetradecanal (67 mg, 0.20 mmol) in anhydrous diethyl ether (0.3 ml) was added dropwise. The reaction was allowed to slowly warm to 0°C., whereupon the reaction was poured into water and extracted with petrol. The organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (3% diethyl ether in petrol) yielded (6.20) as four inseparable diastereoisomers (78 mg, 0.14 mmol, 74%) in a ratio of 82: 9: 8: 1; Spectral data identical to that reported before.

3-Hexyl-4-[(*R*)-2-hydroxy-1-tridecyl]-3-trimethylsilyl-2-oxetanone (6.13):- To 4-[2-(*tert*-butyldimethylsiloxy)-1-tridecyl]-3-trimethylsilyl-3-hexyl-2-oxetanone (24.6 mg, 0.05 mmol) in acetonitrile (2 ml) at 0°C was added a trace of HF (40% aq.). After 1 h the reaction was poured into water (5 ml) and extracted with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (10% diethyl ether in petrol) afforded (6.13) as a pale yellow oil (17.6 mg, 0.04 mmol, 91%); spectra identical with that reported before.

(3*S*, 4*S*)-3-Hexyl-4-[(*R*)-2-(hydroxy)-1-tridecyl]-2-oxetanone (2.19):- To 4-(2-hydroxy-1-tridecyl)-3-trimethylsilyl-3-hexyl-2-oxetanone (30.2 mg, 0.07 mmol) in THF (1 ml) at -90°C was added dropwise TBAF (0.07 ml, 1M in THF). After 5 min at -90°C the reaction mixture was quenched with water (0.5 ml) and allowed to warm to room temperature. On reaching room temperature the aqueous layer was extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Flash chromatography (20% diethyl ether in petrol) yielded (2.19) as a pale yellow solid (22.5 mg, 0.06 mmol, 90%), which was recrystallised from hexane; m.p. 50.5- 52°C; Spectra identical with that reported earlier.

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