UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

Mastere of Philosophy

DIASTEREOFACIAL SELECTIVITY IN THE LEWIS ACID PROMOTED [2+2] CYCLOADDITION BETWEEN AN ALKYL(TRIALKYLSILYL)KETENE AND CHIRAL ALDEHYDES : 1,2 - AND 1,3 ASYMMETRIC INDUCTION

by Béatrice PELOTIER

September 1995

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ABSTRACT

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DIASTEREOFACIAL SELECTIVITY IN THE LEWIS ACID PROMOTED [2+2] CYCLOADDITION BETWEEN AN ALKYL(TRIALKYLSILYL)KETENE AND CHIRAL ALDEHYDES : 1,2- AND 1,3-ASYMMETRIC INDUCTION

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A review of the preparation and reactivity of β-lactones is followed by an account of the possible mechanisms regarding the [2+2] cycloaddition between ketenes and unsaturated compounds.

The [2+2] cycloadditions of an alkyl(trimethylsilyl)ketene, *n*-hexyl(trimethylsilyl)ketene, with α-alkoxy-, α-methyl, β-alkoxy and α-methyl-β-alkoxy aldehydes in the presence of $EtAlCl_2$ or $BF_3.Et_2O$ were performed and showed a high diastereoselectivity. The 1,3-asymmetric induction observed in [2+2] cycloadditions with β-alkoxyaldehydes leads to one major isomer whose stereochemistry was proved by X-ray crystallographic analysis. Assuming the ketene to be the nucleophilic species, the results were explained in terms of facial selectivity directed by the α- and β-substituents, leading to 1,2- or 1,3-asymmetric induction.

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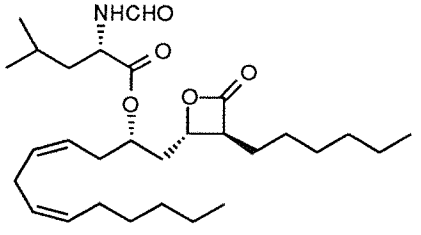
CONTENTS

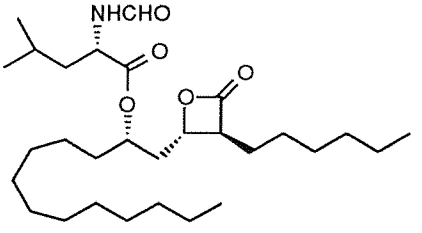
INTRODUCTION

Over these last years, the chemistry of *ß*-lactones aroused a growing interest, due in particular to the discovery of a new family of biologically active molecules possessing the *ß*-lactone moiety. The potential of *ß*-lactones as synthesis intermediates is also developing in parallel with a better understanding of the stereoselectivity problems in asymmetric synthesis.

Among the numerous syntheses of natural *ß*-lactones already achieved, only that of the lipstatin[1] (**A**) and tetrahydrolipstatin[2] (**B**) have involved a [2+2] cycloaddition between an alkyl(trialkylsilyl)ketene and an aldehyde promoted by a Lewis acid. The scope and potential of this reaction have not yet been investigated. Therefore, we launched a systematic study of the Lewis acid promoted [2+2] cycloaddition of *n*-hexyl(trimethylsilyl)ketene with various chiral *α*- and *ß*-substituted aldehydes in order to investigate the diastereoselectivity of the reaction.



A



B

After reviewing the preparation and reactivity of *ß*-lactones, attention will be focussed on [2+2] cycloadditions of ketenes with different unsaturated compounds, including a brief look at their possible mechanisms. This is followed by the results and discussion of the experimental work carried out on [2+2] cycloadditions.

CHAPTER I

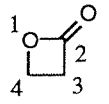
β - Lactones : preparation and reactivity

ß-Lactones : preparation and reactivity[3]

I.1 - Presentation

I.1.1 - Nomenclature

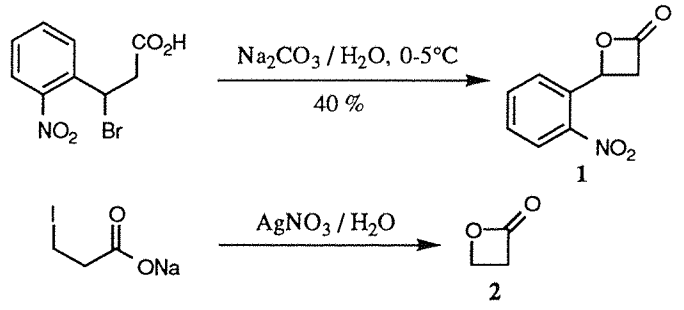
ß-Lactones, four-membered heterocycles, are also called propiolactones or 2-oxetanones. The ring atoms will be numbered as indicated in Figure 1.



- Figure 1 -

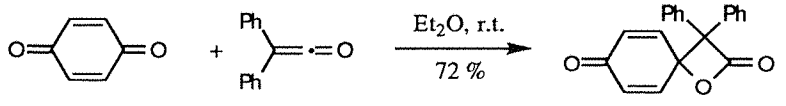
I.1.2 - History

In 1880, Erlenmeyer postulated that a ß-lactone was an intermediate formed during the preparation of styrene from 3-bromo-3-phenylpropionic acid[4]. Three years later, Einhorn isolated the first crystalline substituted ß-lactone **1**, 4-(2-nitrophenyl)-2-oxetanone[5]. The simplest but less stable ß-lactone **2**, 2-oxetanone, was first prepared in 1916 by Johanson[6] (Scheme 1).



- Scheme 1 -

The formation of a ß-lactone by [2+2] cycloaddition between a ketene and a carbonyl group was achieved for the first time by Staudinger in 1911[7]. He observed a reaction between benzoquinone and diphenylketene, in the absence of a catalyst (Scheme 2).

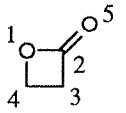


- Scheme 2 -

I.1.3 - Structure

1.3.1 - Theoretical methods

Bond lengths and angles of 2-oxetanone have been assessed by semi-empirical (AM1)[3], *ab initio* (6-31G**)[8], and molecular mechanics (MM2)[9] calculations, leading to values (Table 1) close to the experimental data (electron diffraction, X-ray) obtained for more complex *ß*-lactones[10].



	AM1	6-31G**	MM2
C_2O_5	1.213	1.172	1.208
O_1C_2	1.403	1.342	1.365
C_2C_3	1.522	1.519	1.518
C_3C_4	1.551	1.533	1.544
C_4O_1	1.471	1.438	1.436
$O_1C_2O_5$	123.1	128.4	
$C_3C_2C_5$	143.1	137.5	
$C_2C_3C_4$	84.3	82.9	82.0
$O_1C_4C_3$	90.1	89.9	91.2
$C_2O_1C_4$	91.7	93.1	91.7
$O_1C_2C_3$	93.1	94.1	95.1

Table 1 - Bond lengths (Å) and angles (deg) for 2-oxetanone.

The MM2 calculations showed that the heterocycle is planar and adopts an eclipsed conformation, contrary to many cyclobutane derivatives, whose 4-membered ring is twisted. According to Allinger, this is due to the ester type resonance stabilization.

1.3.2 - Molecular spectroscopy

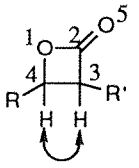
The infrared spectrum of *ß*-lactones presents a characteristic absorption band at ν = 1840-1810 cm^{-1}, due to the carbonyl stretching.

In 1979, the study of proton nuclear magnetic resonance (^1H NMR) spectra of 3,4-disubstituted 2-oxetanones led Mulzer[11] to the following conclusions (Figure 2) :

- the *cis* and *trans* coupling constants are : $^3J_{cis}$ = 6.5 Hz, $^3J_{trans}$ = 4-4.5 Hz
- the chemical shifts of the protons are always ordered :

δ(3-H)*cis* > δ(3-H)*trans* > δ(4-H)*cis* > δ(4-H)*trans*

These values are in accordance with the attribution achieved by Abraham for 2-oxetanone, ten years previously[12] : $^3J_{cis}$ = 6.93 Hz and $^3J_{trans}$ = 4.61 Hz.



- Figure 2 -

Carbon nuclear magnetic resonance (^{13}C NMR) spectra of several natural β-lactones provide the average chemical shifts values for the ring carbon atoms : 171-172 ppm (C_2), 49-57 ppm (C_3), 75-83 ppm (C_4).

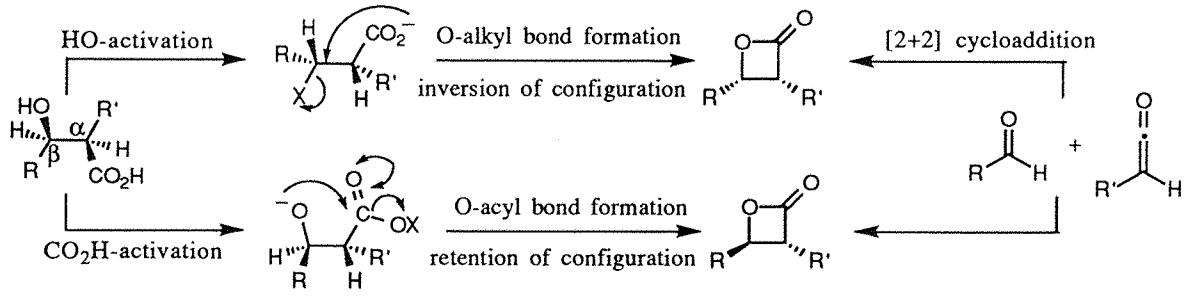
Oxygen nuclear magnetic resonance (^{18}O NMR) spectroscopy of 2-oxetanone and 4-methyl-2-oxetanone has also been performed[13]. The values (in ppm) are given in Figure 3.

- Figure 3 -

I.2 - Preparation of the β-lactone moiety

The first β-lactones were obtained either by cyclisation of β-halo acid salts or by [2+2] cycloaddition between ketenes and carbonyl groups[14]. Since attention has been concentrated on the synthesis of natural β-lactones, methods have largely diversified and can be classified within 3 main groups :

- lactonization *via* oxygen-acyl bond formation
- lactonization *via* oxygen-alkyl bond formation
- [2+2] cycloaddition



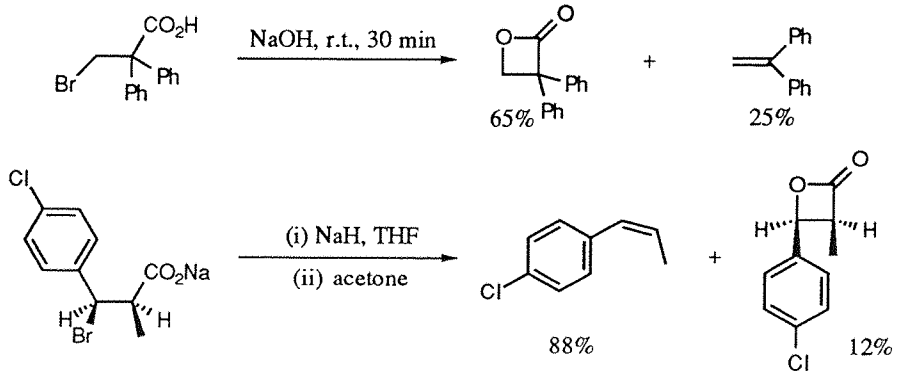
- Scheme 3 -

I.2.1 - Lactonization *via* oxygen-alkyl bond formation

This cyclisation involves β-substituted carboxylic acids and takes place with inversion of configuration at the β-carbon (Scheme 3).

2.1.1 - From β-halocarboxylic acid salts

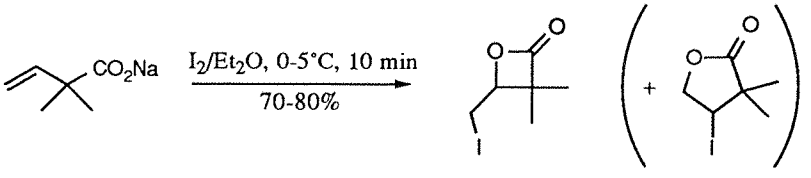
This is the oldest known method to prepare β-lactones. The acid salt is generated *in situ* by action of a mild base on the acid and the lactonization occurs at room temperature. It can be performed either in aqueous[15] (the most common case) or non-aqueous[16] media but is now abandoned because of the competitive formation of olefins (Scheme 4).



- Scheme 4 -

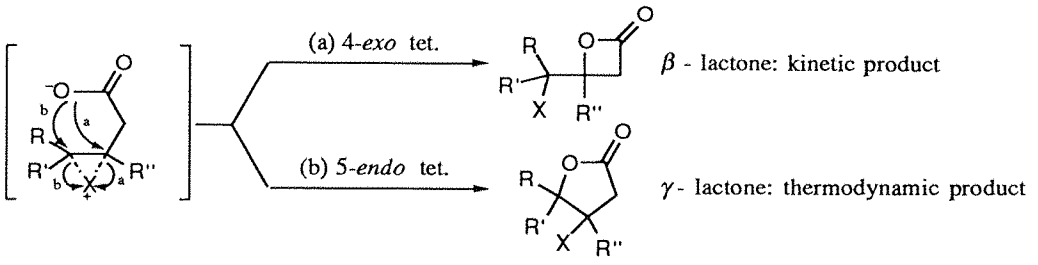
2.1.2 - From β,γ unsaturated carboxylic acids

In 1971, Barnett discovered that β-lactones could be formed preferentially (kinetic products) instead of γ-lactones (thermodynamic products) in the halolactonization of β,γ-unsaturated carboxylic acids by controlling the reaction time (Scheme 5)[17,18].



- Scheme 5 -

The halonium ion intermediate undergoes a nucleophilic attack by the carboxyl group in a 4-*exo*-tet ring closure process rather than a 5-*endo*-tet process as predicted by Baldwin's rules[19] (Scheme 6).

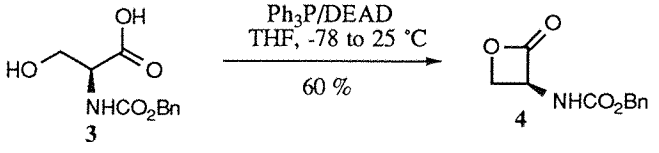


- Scheme 6 -

2.1.3 - From *β*-hydroxy carboxylic acids

The Hydroxy Group Activation (HGA) required by this method can be achieved under Mitsunobu conditions (PPh_3 / DEAD) but competition with the Carbonyl Group Activation (CGA) may occur, therefore leading to the opposite isomer[20].

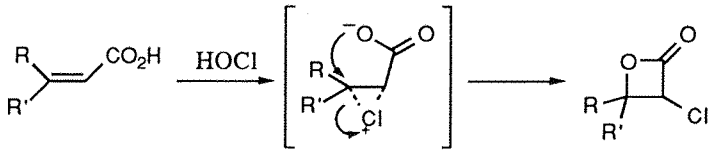
Nevertheless, this method has been successfully applied to the preparation of serine *β*-lactones. For example, the serine *β*-lactone **4** was prepared in 60 % yield from *N*-(benzyloxycarbonyl)-L-serine **3**[21] (Scheme 7).



- Scheme 7 -

2.1.4 - From other substrates

β-Amino acids in the presence of sodium nitrite in acetic acid[22] and *α,β*-unsaturated acids in the presence of hypochlorous acid[23] (Scheme 8) also yield respectively *β*-lactones and *α*-chloro-*β*-lactones.



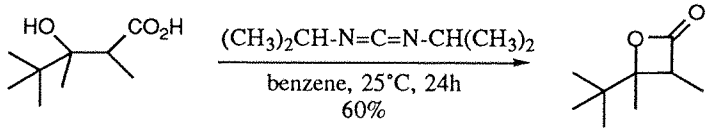
- Scheme 8 -

I.2.2 - Lactonization *via* oxygen-acyl bond formation

This method requires a Carboxy Group Activation (CGA) to allow an intramolecular nucleophilic attack by the oxygen atom of the hydroxy group. The resulting oxygen-acyl bond formation occurs with retention of configuration at the *β*-carbon (*cf* Scheme 3).

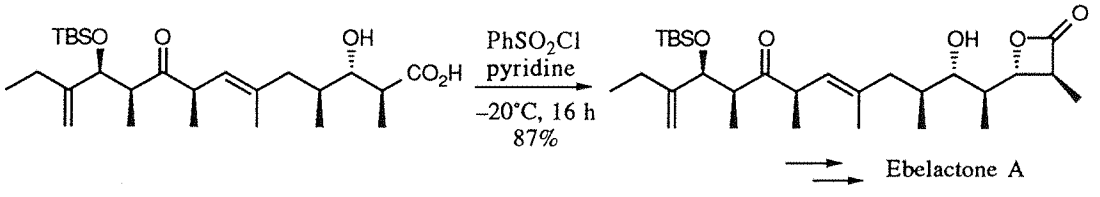
2.2.1 - From *ß*-hydroxy carboxylic acids

The lactonization of *ß*-hydroxy carboxylic acids has been achieved with ethyl chloroformate in pyridine and carbodiimide reagents, which activate the carbonyl group by forming a mixed anhydride. The former was used by Diassi in a synthesis of yohimbic acid lactone[24], while Wetmore lactonized 3-hydroxy-2,3,4,4-tetramethylpentanoic acid with *N,N'*-diisopropylcarbodiimide in benzene[25] (Scheme 9).



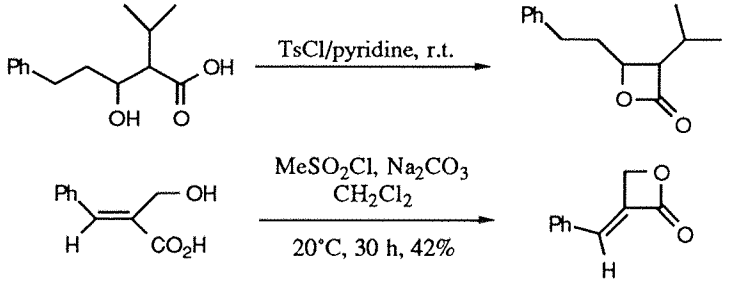
- Scheme 9 -

Sulfonyl chlorides are the most popular and effective lactonization agents because they are compatible with a wide variety of substituents. The couple benzenesulfonyl chloride / pyridine was first introduced by Adam[26] in 1972, and has since been applied to many syntheses of natural *ß*-lactones, such as ebelactone A[27] (Scheme 10), antibiotic 1233A[28] and tetrahydrolipstatin[29].



- Scheme 10 -

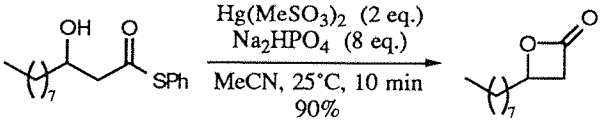
Tosylchloride / pyridine[30], *p*-bromobenzenesulfonyl chloride / pyridine[31] and methanesulfonyl chloride / Na_2CO_3 / dichloromethane[32] have also been successful (Scheme 11).



- Scheme 11 -

2.2.2 - From ß-hydroxy acid derivatives including transition-metal complexes

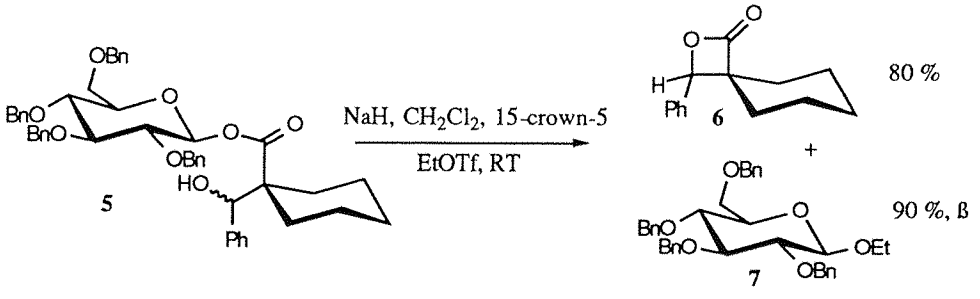
In 1976, Masamune prepared ß-lactones from ß-hydroxy thiol esters in the presence of a mercury salt, Hg(II) methanesulfonate, in good yields[33] (Scheme 12).



- Scheme 12 -

Danheiser proposed a similar method which consists of a classical aldol reaction between a thiol ester and a carbonyl compound leading to a ß-alcoholate thiol ester. This latter one then spontaneously lactonizes[34].

More recently, ß-lactones could also be obtained from ß-hydroxy esters. Thus, spiro ß-lactone **6** was formed along with ß-glucoside **7** from ß-hydroxy ester **5** in the presence of crown ether[35] (Scheme 13).

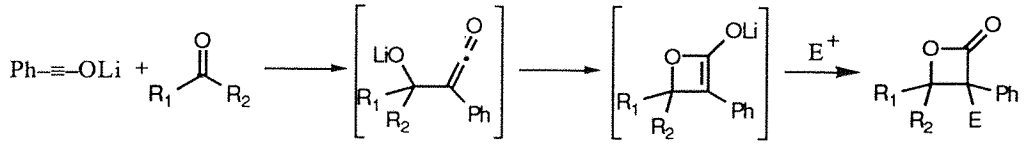


- Scheme 13 -

ß-lactones were also prepared *via* transition-metal complexes, using palladium for the catalysed carbonylation of halo alcohols[36] and iron chiral auxiliary [CpFe(CO)(PPh_3)] for a directed aldol condensation[37]. ß-Hydroxy carbonylmetal complexes thus formed could then react to give ß-lactones.

2.2.3 - From ß-hydroxylithiated ketenes

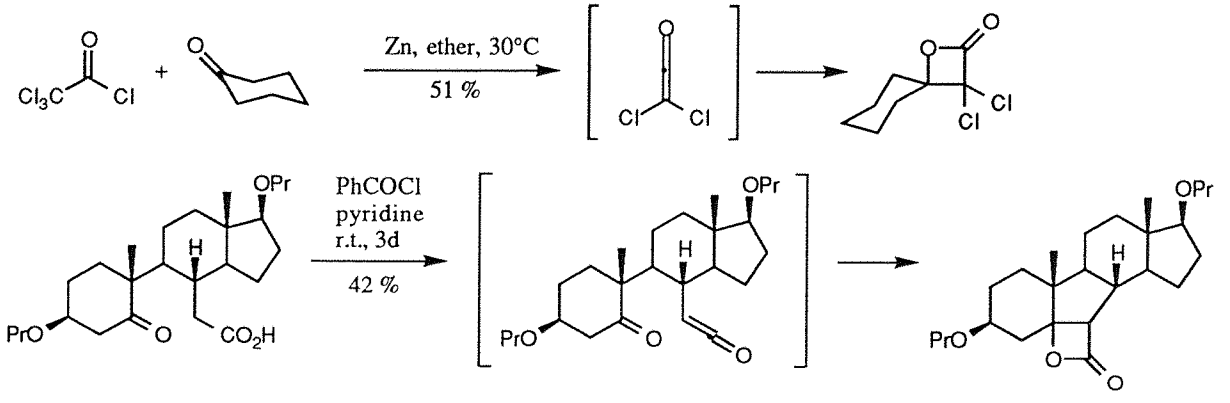
Lithium alkynolates react with carbonyl compounds to form ß-hydroxylithiated ketenes. The resulting ß-lactone lithium enolates can then be quenched with different electrophiles, such as water or alkylating agents[38] (Scheme 14).



- Scheme 14 -

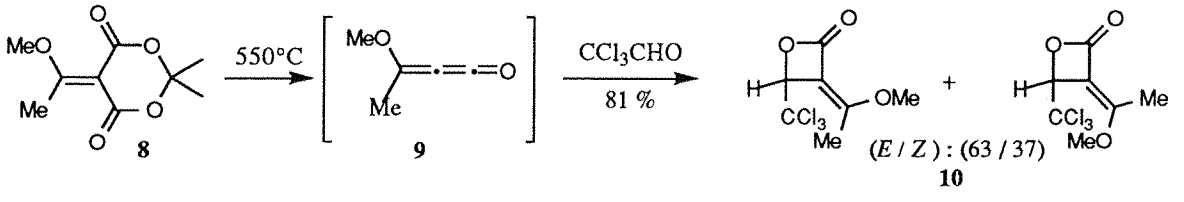
I.2.3 - [2+2] cycloaddition

Due to the instability of the first available ketenes, this method was not exploited in synthesis and most of the examples involved intermolecular[39] or intramolecular[40] [2+2] cycloadditions with ketenes generated *in situ* (Scheme 15).



- Scheme 15 -

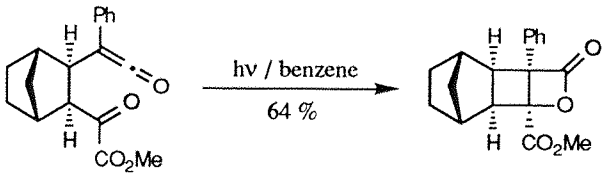
Methylene *ß*-lactones, a synthetically useful class of *ß*-lactones, have also been prepared in this way from methyleneketenes. Thus, heterosubstituted methyleneketene **9** generated through the pyrolysis of Meldrum's acid derivative **8** yielded a mixture of (*E*) and (*Z*) isomers of heterosubstituted α-methylene *ß*-lactone **10**[41] (Scheme 16).



- Scheme 16 -

Conversely, (trialkylsilyl)ketenes[42] and (trialkylgermyl)ketenes[43] are very stable compounds, easily stored and handled. Their cycloaddition with aldehydes in the presence of a Lewis acid yields a mixture of *cis*- and *trans*-*ß*-lactones whose ratio is dependent on the aldehyde and the Lewis acid used, but is usually in favor of the *cis*-isomer.

Photochemistry is also a useful means of forming *ß*-lactones. Thus, Christl showed that γ-oxoketenes could lead to 2-oxetanones by photolysis[44] (Scheme 17).

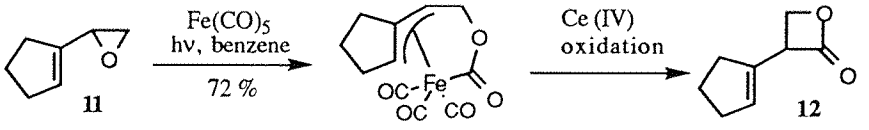


- Scheme 17 -

I.2.4 - Miscellaneous

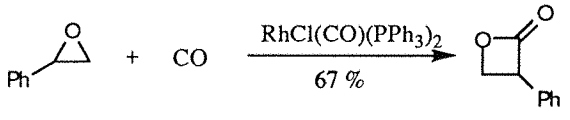
2.4.1 - Transition-metal promoted reactions

Other methods involving transition-metal complexes have been reported for the preparation of *ß*-lactones. Thus, Ley obtained *ß*,*γ*-unsaturated *ß*-lactone **12**, *via* π-allyltricarbonyliron lactone complex from vinyl oxirane **11** and ironpentacarbonyl[45] (Scheme 18).



- Scheme 18 -

The C-H insertion reaction of diazomalonates catalysed by rhodium(II) acetate $[Rh_2(OAc)_4]$[46] also leads to *ß*-lactones. Used as catalysts, $Rh_4(CO)_{12}$ allows the cyclocarbonylation of substituted propargyl alcohols[47] and $[RhCl(CO)(PPh_3)_2]$ the carbonylation of oxiranes[48] such as styrene epoxide (Scheme 19).

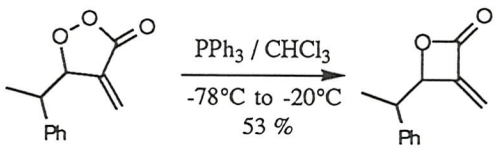


- Scheme 19 -

Finally, ruthenium(VIII) oxide, RuO_4, was used to oxidize oxetanes into 2-oxetanones[49].

2.4.2 - Deoxygenation of *ß*-peroxylactone

This original method was introduced by Adam in 1969 and allowed the obtention of the first *α*-methylene *ß*-lactones by deoxygenation of *α*-methylene *ß*-peroxylactones with triphenylphosphine[50] (Scheme 20).

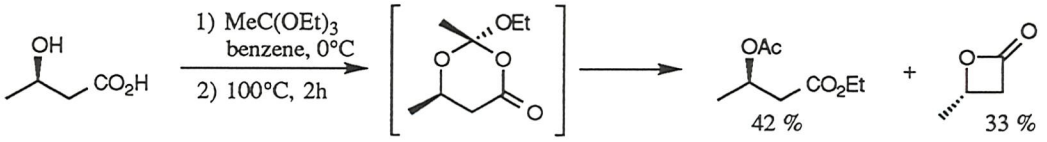


- Scheme 20 -

2.4.3 - Others

The epoxidation of allenes yielded β-lactones by a Baeyer-Villiger oxidation of the cyclopropanone intermediates[51].

When heated, 4-oxo-1,3-dioxanes undergo ring contraction[52] as illustrated in Scheme 21.

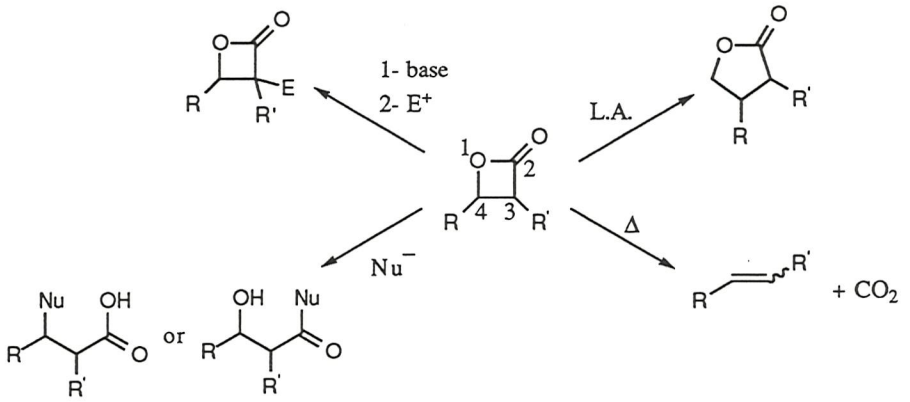


- Scheme 21 -

I.3 - Reactivity

It is only in recent years that chemists have used β-lactones as intermediates, due in particular to stereochemical problems being solved. The unusual reactivity of this strained ring gives rise to 4 main transformations (Scheme 22) :

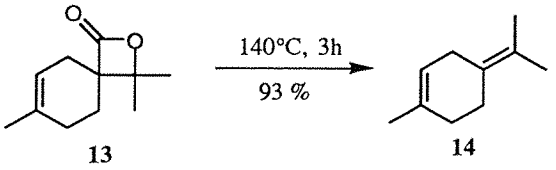
- decarboxylation
- Lewis acid promoted rearrangement
- nucleophilic attack
- enolate formation and reaction towards electrophiles



- Scheme 22 -

I.3.1 - Decarboxylation

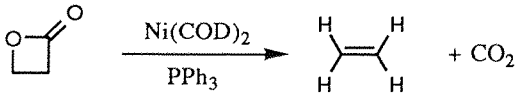
The thermal decomposition of *β*-lactones usually takes place between 80 and 160°C and leads to olefins *via* a stereospecific *cis*-elimination, i.e. *cis*-*β*-lactones yield (*Z*) olefins and *trans*-*β*-lactones yield (*E*) olefins[16]. Theoretical studies showed that the rate of decarboxylation is higher for *trans*-derivatives[42,53] and for 2-oxetanones bearing an electron-donor substituent at the C_4 position[54]. This method has been exploited in the synthesis of steroids[40], benzofurans, isoflavones[55], allenes[56] and terpenes[57]. For example, the thermolysis of *β*-lactone **13** yielded terpinolene **14** in 93 % yield (Scheme 23).



13 **14**

- Scheme 23 -

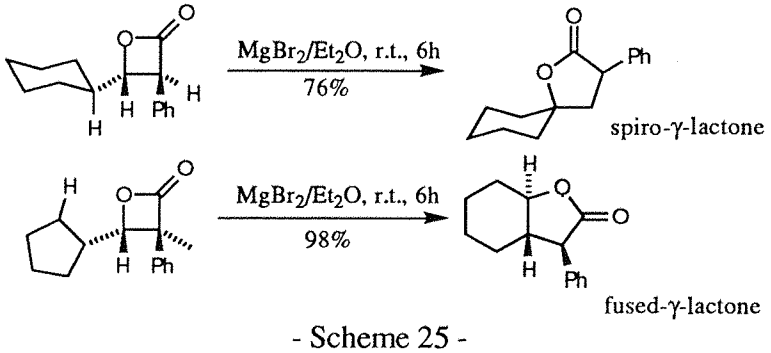
Decarboxylation is also possible under catalytic conditions as reported by Yamamoto for 2-oxetanone (Scheme 24)[58].



- Scheme 24 -

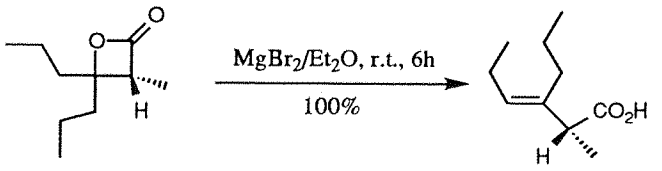
I.3.2 - Lewis acid promoted rearrangement

The dyotropic Wagner-Meerwein rearrangement of *β*-lactones into *γ*-lactones promoted by BF_3 was first reported by Borrmann in 1967[59]. Later, Black and Fields studied this new route to substituted *γ*-lactones[60] and concluded that it occurred by a concerted mechanism. They also found that $MgBr_2.Et_2O$ is superior to other catalysts (*p*-TsOH, $ZnCl_2$, $BF_3.Et_2O$, $Ti(OPr\text{-}i)_4$), that the obtention of either a spiro or a fused *γ*-lactone is a function of the ring size[61] (Scheme 25), and that the fused *γ*-lactone products have a *trans* ring fusion.



- Scheme 25 -

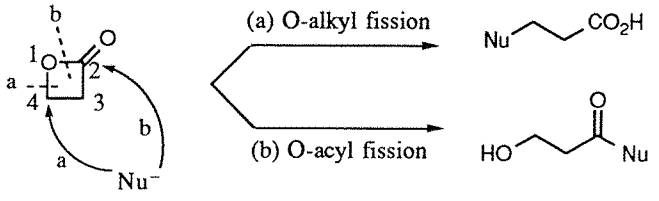
However, 4,4-disubstituted-2-oxetanones yield β,γ-unsaturated carboxylic acids by E1-type elimination[62] (Scheme 26), and not γ-lactones.



- Scheme 26 -

I.3.3 - Reactions with nucleophiles

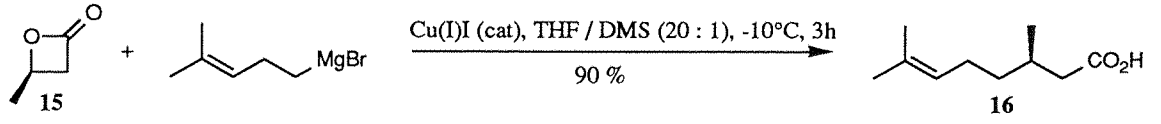
β-Lactones possess two electrophilic centers, therefore nucleophilic attack occurs either by oxygen-alkyl or oxygen-acyl bond cleavage (Scheme 27).



- Scheme 27 -

3.3.1 - Grignard, organolithium and organocuprate reagents

In the absence of Cu(I) salts, organomagnesium and organolithium compounds react with β-lactones according to mechanism (b)[14] (Scheme 27). More interestingly, organocuprates or organomagnesiums in the presence of Cu(I) attack β-lactones at C-4 position or C-2' position for 4-vinyl-2-oxetanones allowing respectively a 3-carbon[63] or 5-carbon[64] homologation through a SN2 or SN2' mechanism. Homoterpenic carboxylic acid **16** could then be prepared from (+)-(*R*)-4-methyl-2-oxetanone **15** with clean inversion of configuration using copper(I) iodide as catalyst[65] (Scheme 28).

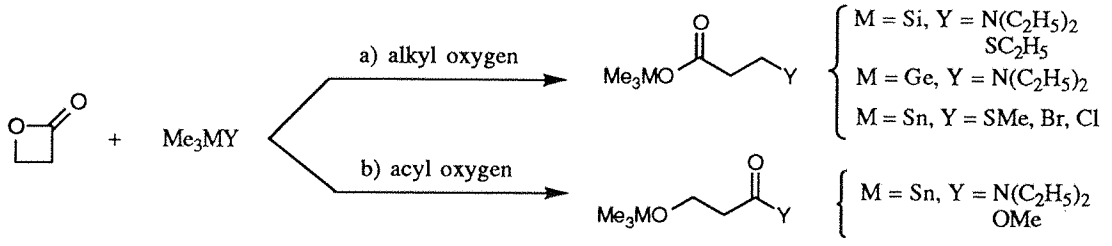


- Scheme 28 -

3.3.2 - Group IV organometallic compounds

Itoh studied the reactivity of Group IV organometallic compounds on 2-oxetanone and found that (trimethylsilyl)dialkylamines, (trimethylgermyl)dialkylamines and methyl

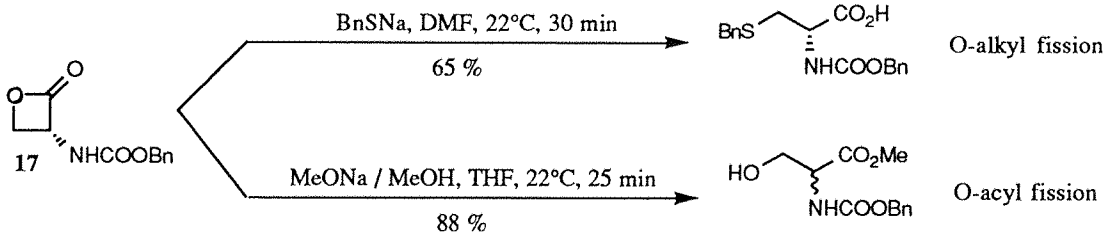
trimethyltin sulfide induce oxygen-alkyl bond cleavage whereas oxygen-tin compounds react at the carbonyl group[66] (Scheme 29).



- Scheme 29 -

3.3.3 - Group V and group VI nucleophiles

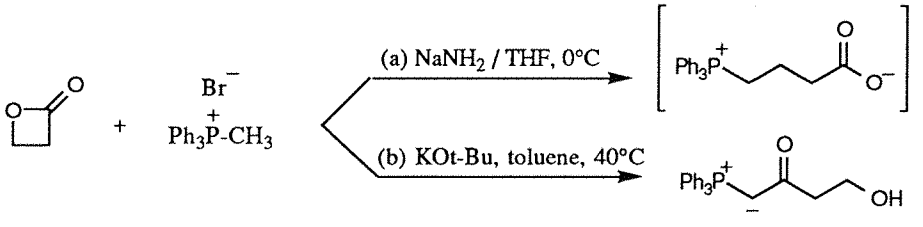
The ring opening varies according to the solvent[67], the substrate and the nature of the nucleophile. Many studies[68,69,70,71] have been performed with serine and threonine β-lactones as substrates as they can lead to new optically pure amino acids. In the case of *N*-protected serine β-lactone **17**, Vederas et al. showed that most nucleophiles (halogen, sulphur, nitrogen reagents) react through O-alkyl fission whereas hard nucleophiles such as methoxide attack at the carbonyl site[68] (Scheme 30).



- Scheme 30 -

3.3.4 - Ylides

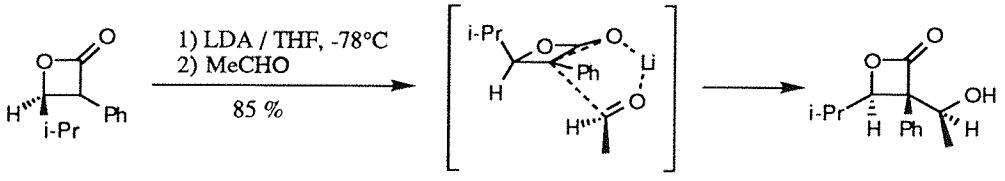
Depending on the reaction conditions, ylides can attack either electrophilic site of β-lactones. The reaction of 2-oxetanone and methylene triphenylphosphorane generated under different basic conditions led Kise et al.[72] (a) and Le Corre and Le Roux[73] (b) to differents adducts (Scheme 31).



- Scheme 31 -

I.3.4 - Enolate formation and reaction towards electrophiles

Deprotonation of β-lactones by lithium diisopropylamide at low temperature was demonstrated in 1980 by Mulzer, who made the resulting β-lactone enolate react with different electrophiles[74,75]. The stability of the enolates increases with the substitution, therefore α,β-disubstituted β-lactones proved to be very stable[76] at high temperature whereas nonsubstituted β-lactones could not be alkylated[74]. Interestingly, α,β-disubstituted β-lactone enolates can react diastereoselectively with aldehydes, which attack from the less hindered side and chelate the lithium ion[77] (Scheme 32).



- Scheme 32 -

I.4 - Conclusion

Despite the numerous methods to prepare β-lactones, [2+2] cycloadditions and lactonizations from β-hydroxy carboxylic acids and their derivatives remain the most widely used. The reactivity of β-lactones should know a great development in the forthcoming years in reason of the reactivity of the strained 4-membered ring both towards electrophiles and nucleophiles.

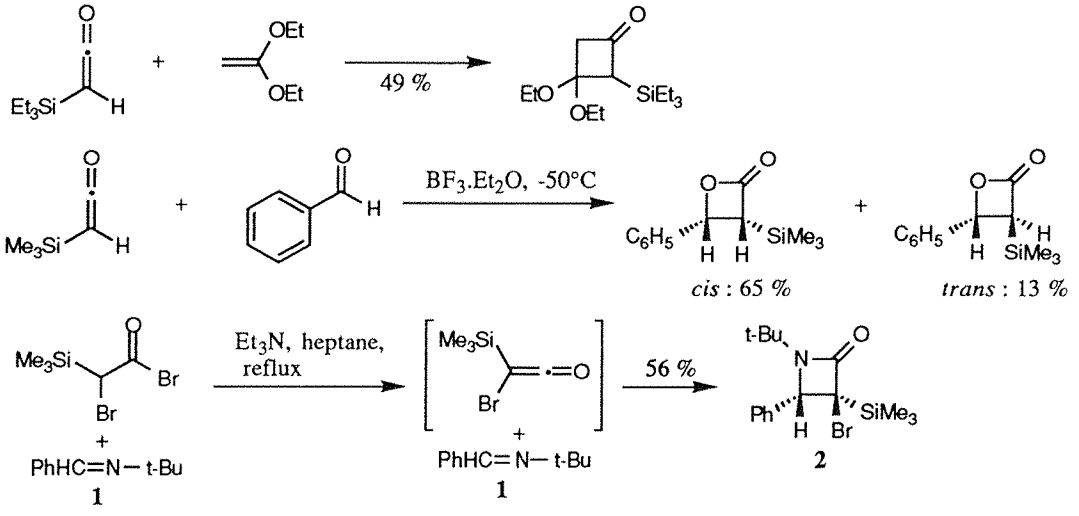
CHAPTER II

[2+2] Cycloadditions involving ketenes

[2+2] Cycloadditions involving ketenes

H.1 - History

The first cycloaddition between a ketene and a carbonyl group was carried out near the beginning of this century, as we have already mentioned (*cf* I.1), and was performed by Staudinger[7] a few years after he discovered the existence of ketenes in 1905[78]. Trimethylsilylketene was first synthesized by Shchukovskaya et al.[79] in 1965 and since then silylketenes have been involved in [2+2] cycloadditions with different unsaturated compounds. Zaitseva first demonstrated their reactivity towards olefins[80] in 1974 and towards carbonyl compounds[81] one year later (Scheme 33). The [2+2] cycloaddition between a silylketene and an imine was afterwards introduced by Brady[82] who obtained *β*-lactam **2** from imine **1** and bromo(trimethylsilyl)ketene generated *in situ* (Scheme 33).



- Scheme 33 -

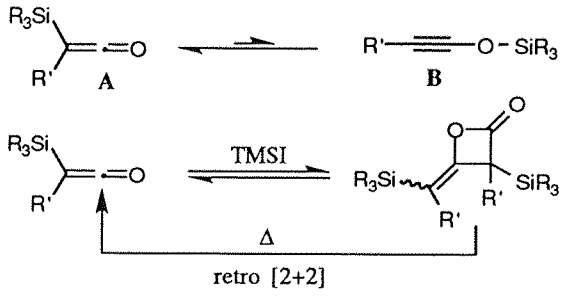
The first [2+2] cycloaddition between an alkyl(trialkylsilyl)ketene and an aldehyde was achieved in 1989 by Pons and Kocienski in a synthesis of tetrahydrolipstatin[2].

II.2 - Alkyl(trialkylsilyl)ketenes

II.2.1 - Structure

The ketene structure is easily detected by infrared spectroscopy with the characteristic absorption band of the carbonyl stretching at $\nu = 2100\text{-}2000\ cm^{-1}$.

Alkyl(trialkylsilyl)ketenes **A** are very stable species (*cf* II.2.2) therefore the equilibrium with their tautomeric form **B** is strongly in favor of the ketene. Nevertheless, dimerization (catalysed by TMSI) is observed (IR : $\nu = 1780$ cm^{-1}), in particular during the preparation of the ketene[83], but the process is slow and reversible upon heating (Scheme 34).

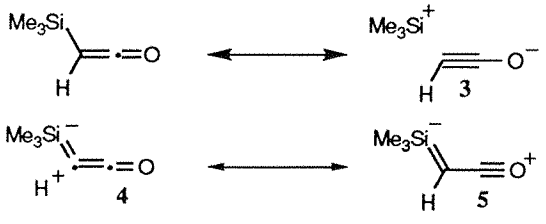


- Scheme 34 -

II.2.2 - Stability

Alkyl(trialkylsilyl)ketenes and silylketenes in general were found to be remarkably stable compared to their alkylketene analogs, and therefore more resistant to dimerization and cycloadditions.

Two hypotheses were proposed to explain the stability of silylketenes: Brady and Cheng[84] assumed a σ-π donation from the C-Si bond to the carbonyl p orbital, leading to the resonance structure **3**, whereas Runge[85] concluded by CNDO/S calculations that a back-donation from the ketene π system to the d orbital of the silicon atom occurs. The resulting resonance structures **4** and **5** in this latter case entail a negative charge on the silicon and a partial Si-C double bond character (Scheme 35).



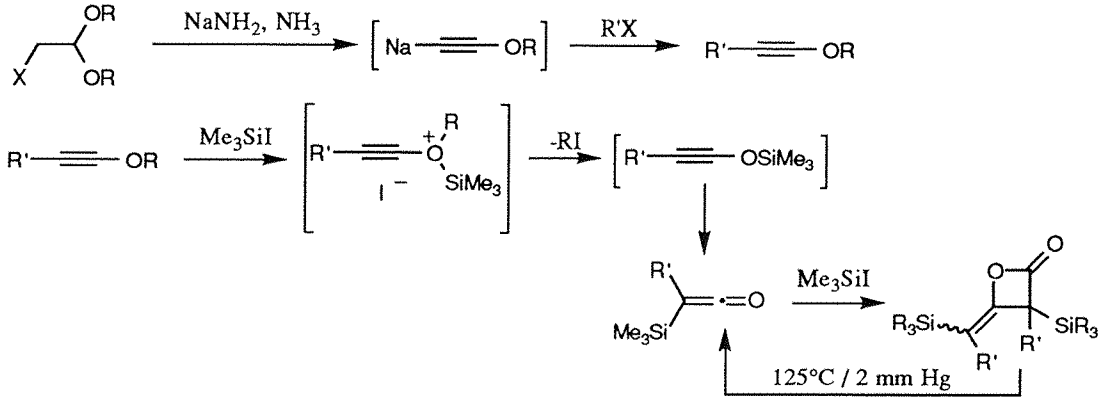
- Scheme 35 -

These interpretations were dismissed in 1991 when Tidwell carried out comprehensive *ab initio* studies on substituent effects on ketene stability[86]. He compared the stabilizing effect of π-acceptor substituents and IIIrd period elements with their IInd period counterparts. Thus, the ketene $(H_3Si)CH=C=O$ was calculated to be 10.9 kcal/mol more stable than methylketene $(H_3C)CH=C=O$. This is due to the electropositive character of the silicon but also to the ability of the silicon to stabilize an adjacent negative charge.

II.2.3 - Preparation

2.3.1 - From (trialkylsilyloxy)alkynes

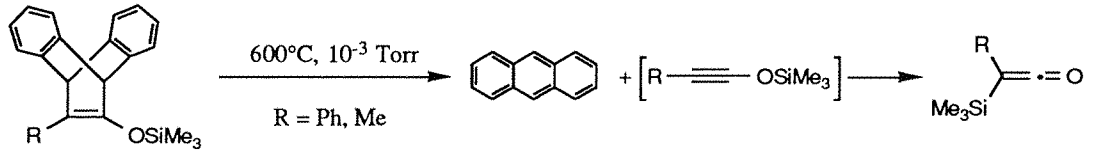
Alkyl(trialkylsilyl)ketenes are obtained by thermal rearrangement of (trialkylsilyloxy)alkynes, which can be generated in different ways. The currently most common method to form (trimethylsilyloxy)alkynes is by reaction of the corresponding alkoxyalkynes with trimethylsilyl iodide[87], the alkoxyalkyne being itself prepared by successive β-eliminations of haloacetaldehyde dialkyl acetal in the presence of sodium amide[88] (Scheme 36).



- Scheme 36 -

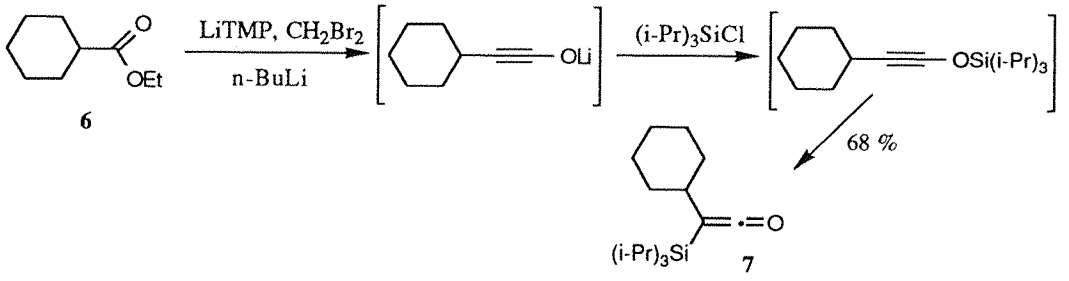
Using this method, alkyl(trialkylmetal)ketenes (metal = germyl, stannyl) and bis(trialkylmetal)ketenes may also be obtained[87].

The retro Diels-Alder reaction of ethenoanthracenic silylated enol ethers under high temperature and low pressure yields (trialkylsilyloxy)alkynes , which spontaneously isomerize to the ketenes[89] (Scheme 37).



- Scheme 37 -

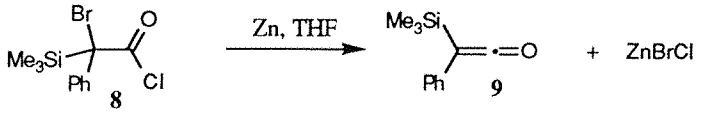
(Trialkylsilyloxy)alkynes were also formed by trapping of lithium ynolates, prepared either from alkynyltosylates[90] or (n-1) homologue esters[91]. Thus, cyclohexyl (triisopropylsilyl)ketene **7** was obtained from ethyl cyclohexylmethanoate **6** by trapping of the intermediate lithium ynolate with triisopropylsilyl chloride (Scheme 38).



- Scheme 38 -

2.3.2 - From acyl chlorides

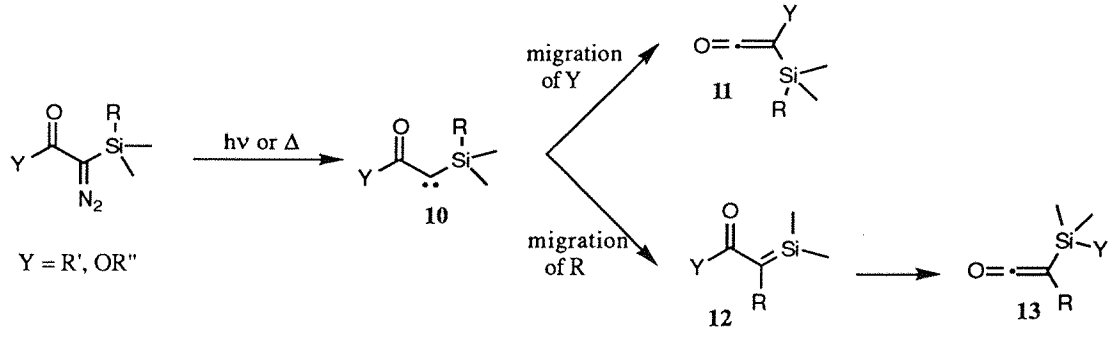
Dehydrohalogenation of acyl chlorides using tertiary amines and reductive elimination of α-halo acyl chlorides in presence of zinc are classical methods to generate ketenes, which have been successfully applied in the synthesis of alkyl(trialkylsilyl) ketenes[92,93]. For instance, zinc dehalogenation of phenyl(trimethylsilyl)bromoacetyl chloride **8** yielded the highly stable ketene **9**, phenyl(trimethylsilyl)ketene (Scheme 39).



- Scheme 39 -

2.3.3 - From acyl silylcarbenes

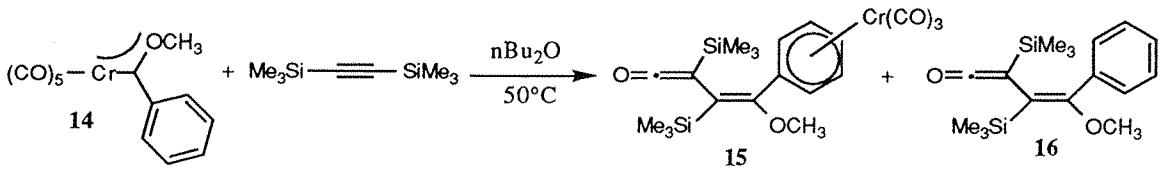
Photochemical or thermal decomposition of α-diazoketones and α-diazoesters is known to yield ketenes through a Wolff rearrangement of intermediate acylcarbenes. The same result was observed with α-diazo-β-trialkylsilyl-ketones[94] and -esters[94,95] providing either ketene **11** or silene **12** according to the migrating group, *via* acylsilylcarbenes **10**. The silene **12** then spontaneously isomerizes to ketene **13** (Scheme 40).



- Scheme 40 -

2.3.4 - From alkynes

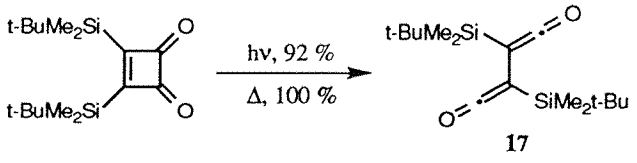
Metal-complex induced olefination and carbonylation of alkynes also constitute a source of alkyl(trialkylsilyl)ketenes. Thus, pentacarbonyl[methoxy(phenyl)carbene] chromium **14** reacts with bis(trimethylsilyl)acetylene on warming in dibutylether to give tricarbonyl [4-methoxy-4-phenyl-2,3-bis(trimethylsilyl)-1,3-butadiene]chromium **15** and the metal-free vinylketene derivative **16** in a head-to-tail addition process[96] (Scheme 41).



- Scheme 41 -

2.3.5 - From cyclobutenediones

The photolysis or thermolysis of cyclobutenediones allowed the preparation of the first stable bis(trialkylsilyl)ketenes. Bis(tert-butyldimethylsilyl)ketene **17** was obtained in very good yields in both cases[97] (Scheme 42).



- Scheme 42 -

II.3 - Mechanisms of [2+2] cycloadditions

II.3.1 - Introduction

According to the theory of conservation of orbital symmetry expressed by Woodward and Hoffmann[98], [2+2] cycloadditions are thermally forbidden reactions. Overlap integrals between the highest occupied molecular orbital (HOMO) of one molecule and the lowest unoccupied molecular orbital (LUMO) of the other partner are of opposite sign, which makes the suprafacial approach impossible (Figure 4).

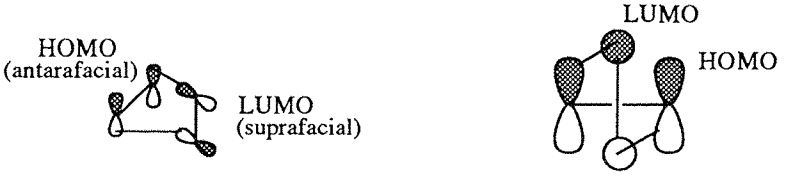
- Figure 4 -

Yet, these reactions occur and many studies have been undertaken to understand their mechanism. The current computer facilities offered to the chemist allow the execution of high-level calculations and the proposal of sound theories. Unfortunately, [2+2] cycloadditions between silylketenes and carbonyl compounds did not give rise to many theoretical studies, therefore we will also focus our attention on cycloadditions of ketenes with unsaturated compouds, in order to draw an analogy.

II.3.2 - Cycloadditions of ketenes

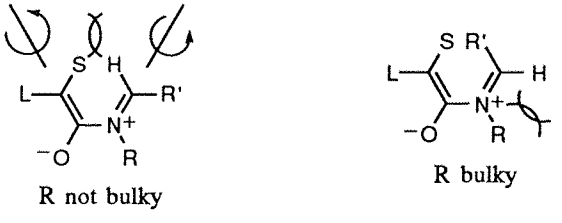
3.2.1 - With imines

Using the Frontier Orbital theory, Houk extended Woodward's rationale[98] to the reactivity of ketenes with imines and proposed a supra-antara approach of the two partners with orthogonal molecular planes[99] (Figure 5). This mechanism was postulated in particular for cases in which the nucleophilicity of the nitrogen lone pair of the imine was strongly diminished by the inductive electron-withdrawing effect of the substituents.



- Figure 5 -

Recent experimental work[100,101] and theoretical studies[102] suggest a two-step nonconcerted mechanism involving a zwitterionic intermediate. In the first step, the nucleophilic nitrogen lone pair attacks the central carbon atom of the ketene, the dihedral angle $C_4N_1C_2C_3$ varying from 40° to 180°. The zwitterion is formed in such a way that the steric interactions between the substituents are minimized (Figure 6); a subsequent conrotatory ring closure yields the *β*-lactam.

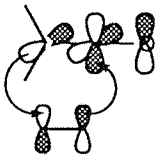


- Figure 6 -

For ketenes bearing an electronegative substituent, the electronic effects could predominate over the steric interactions so that the substituent would occupy the position of the smallest group in order to stabilize a partial positive charge on the nitrogen atom.

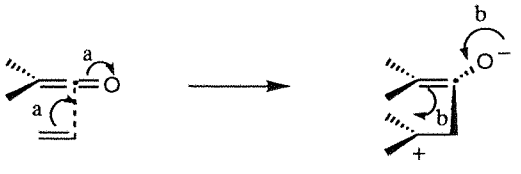
3.2.2 - With olefins

The [2+2] cycloaddition between an olefin and a ketene is the most studied reaction from a theoretical point of view. As for the imines, some authors[103,104] speculate a concerted $[\pi 2_s+\pi 2_a]$ cycloaddition in which the ketene is the antarafacial component. Others[105] suggest a "push-pull" mechanism based upon the interaction between the alkene π^* and both the nucleophilic π_{C-C} and the electrophilic $\pi^*_{C=O}$ of the ketene (Figure 7).



- Figure 7 -

Computational techniques (AM1[106], 6-31G*[107]) have recently allowed the proposal of a concerted nonsynchronous $[\pi 2_s+(\pi 2_s+\pi 2_s)]$ mechanism. The study of the [2+2] cycloaddition between ketene and ethylene shows that the central carbon atom of the ketene uses the $\pi^*_{C=O}$ orbital for electrophilic interaction and the $\pi_{C=C}$ orbital for nucleophilic interaction with the olefin, which involves the movement of 4 electron pairs occurring in two separate but simultaneous processes (Figure 8).



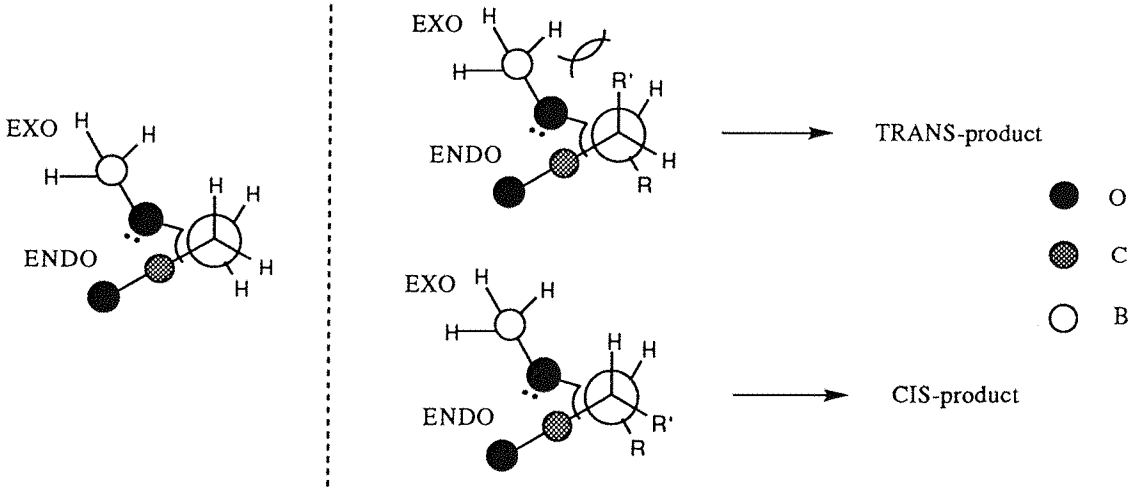
- Figure 8 -

3.2.3 - With carbonyl compounds

The reactivity of ketenes in [2+2] cycloaddition reactions with carbonyl compounds seems to be more complex and more difficult to predict. In a series of experiments carried out with various substituted benzaldehydes, dichloroketene behaved in a nucleophilic manner as reported by Krabbenhoft[54] whereas halocyanoketenes uniquely react with electron-rich carbonyl groups according to Moore[108]. In the first case, a $[\pi 2_s+(\pi 2_s+\pi 2_s)]$ mechanism has been invoked while in the second case the characterization of a zwitteronic intermediate suggested a nonconcerted dipolar process.

The [2+2] cycloaddition between ketene and formaldehyde was recently studied from a theoretical point of view by Rajzmann[109] and Cossio and Ugalde[110]. Using the semi-empirical AM1 method, Rajzmann concluded a nonconcerted mechanism, in which the oxygen atom of the aldehyde first attacks the electrophilic ketene. On the contrary, *ab initio*

MP2/6-31G* and HF/6-31G* calculations favoured a concerted [$\pi 2_s+(\pi 2_s+\pi 2_s)$] mechanism whose main interaction involves the ketene's HOMO and the LUMO of the aldehyde. Interestingly, Cossio and Ugalde also modeled the [2+2] cycloaddition of nonactivated ketenes (nonsubstituted or bearing an electron-donor substituent) with formaldehyde catalysed by BH_3. Using SCRF calculations that takes into account the influence of the solvent, they found that the presence of a Lewis acid decreases the activation energy and induces a rather asynchronous mechanism. The more favoured transition structure (Figure 9) explains the *cis*-diastereoselectivity observed in most cases for this kind of cycloaddition.

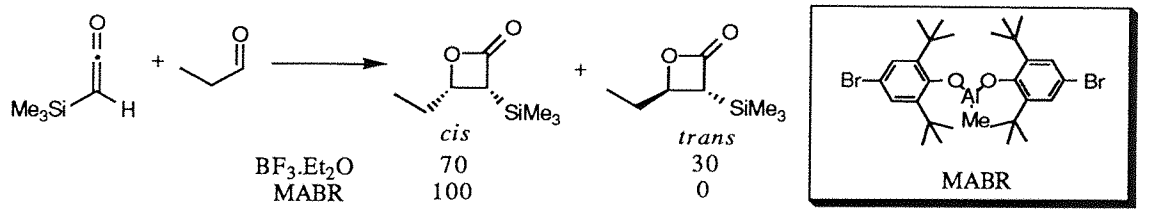


- Figure 9 -

In this structure, BH_3 occupies the *exo* position so that the aldehyde oxygen atom lone pair in the *endo* position stabilizes the electron-deficient ketene moiety. One can reasonably assume that the alkyl-chain of the aldehyde prefers the *trans* relationship with the Lewis acid, therefore two transition states are possible depending on the ketene substituent placement. The conformation leading to a *trans* ß-lactone is disfavoured for steric reasons. In particular, the more bulky the catalyst, the higher the *cis*-diastereoselectivity.

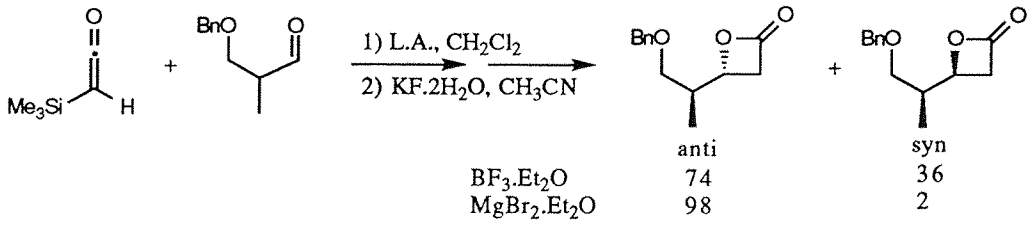
II.3.3 - Cycloadditions of silylketenes

[2+2] Cycloadditions between a silylketene and a carbonyl compound have received very little attention from a theoretical point of view. Due to the high stability and lower reactivity of these ketenes, the reaction often requires the presence of a Lewis acid. This catalyst may play a determining role both on the mechanism and the stereoselectivity. Thus, Yamamoto performed highly diastereoselective cycloadditions between trimethylsilylketenes and various aldehydes with the very bulky methyl-aluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) or MABR[111] (Scheme 43).



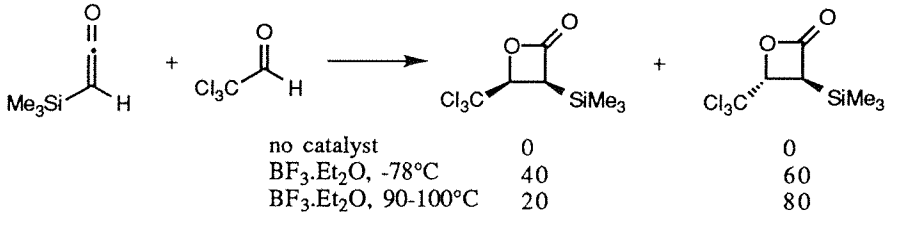
- Scheme 43 -

More recently, Romo suggested that chelating Lewis acids can control the selectivity of cycloadditions with α-alkoxy or β-alkoxy aldehydes : the bidentate Lewis acid $MgBr_2.Et_2O$ was indeed found to be more selective than the monodentate $BF_3.Et_2O$[112] (Scheme 44).



- Scheme 44 -

Using the same Lewis acid, Zaitseva performed a series of experiments in order to determine the influence of the structure of the aldehyde[113]. Thus, [2+2] cycloadditions between (trimethylsilyl)ketene and chloral under different conditions led to the following results :



- Scheme 45 -

Interestingly, under the same reaction conditions (20°C, 20-30 min), (trimethylsilyl)ketene cycloadds formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde and isovaleraldehyde with the same selectivity (*cis* / *trans* : 60 / 40) but in different yields according to the alkyl chain. In general, yields were found to be lower (≈65 %) for linear-chain aldehydes and much lower for formaldehyde (30 %) than for the branched-chain ones (≈90 %).

II.3.4 - Summary

Theoretical calculations indicate that the initially proposed $[\pi 2_s+\pi 2_a]$ mechanism is incorrect. Alternatives include (a) a two-step nonconcerted mechanism involving a zwitterionic intermediate (as in the [2+2] cycloadditions of imines and carbonyl compounds), in which the ketene is an electrophilic species, or (b) a concerted $[\pi 2_s+(\pi 2_s+\pi 2_s)]$ mechanism in the course of which the formation of the two new bonds is either non synchronous (with olefins) or quite synchronous (with aldehydes).

CHAPTER III

[2+2] Cycloadditions : Results and Discussion

[2+2] Cycloadditions : Results and Discussion

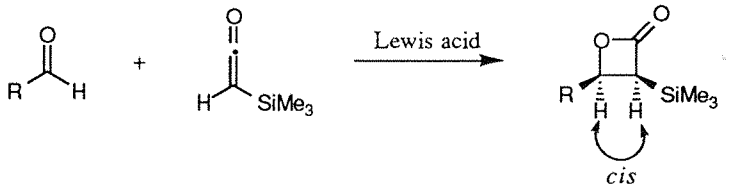
III.1 - Introduction

The [2+2] cycloaddition between silylketenes and aldehydes raises two stereochemical issues :

a) the inherent facial bias in the ketene component in the absence of substituents

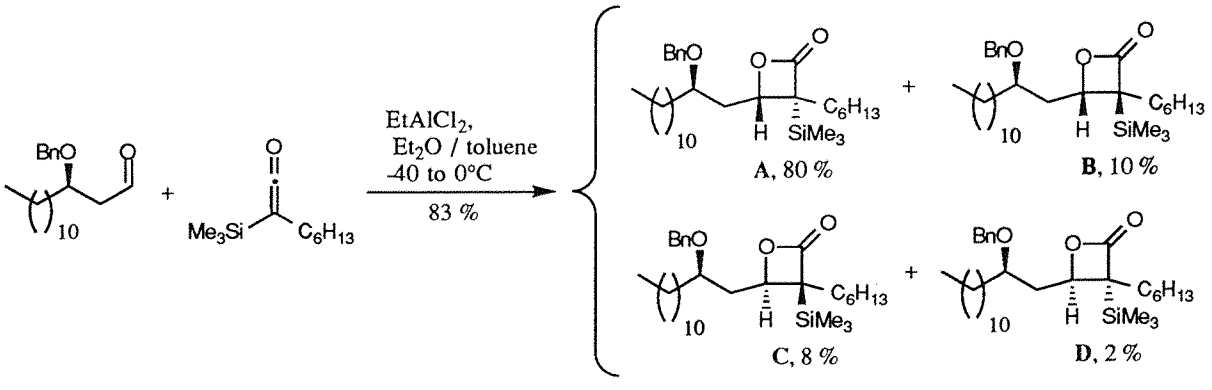
b) the facial bias exerted by substituents near the aldehyde

The cycloaddition of trimethylsilylketene with carbonyl compounds shows a very strong bias in favor of the *cis* β–lactone (Scheme 46), as demonstrated by Zaitseva[113], Yamamoto[111] and Dymock's[114] work.



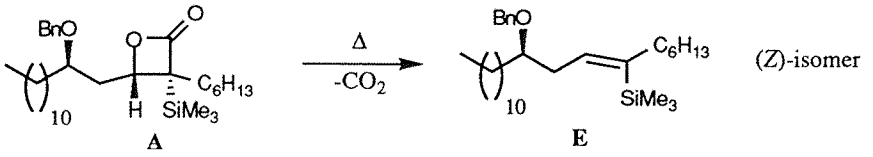
- Scheme 46 -

The absence of a substituent on the silicon-bearing carbon allows an easy assay of stereochemistry by NMR spectroscopy, the vicinal coupling constants being J_{cis} = 6.5 Hz and J_{trans} = 4-4.5 Hz. However, in the case of alkyl-substituted silylketenes, the diastereoselectivity cannot be determined by direct methods. Nevertheless, the synthesis of tetrahydrolipstatin[83] was significant because it demonstrated that both a high facial bias and excellent 1,3-asymmetric induction were possible using an hexyl(trimethylsilyl)ketene (Scheme 47).



- Scheme 47 -

Although the 1,3-asymmetric induction was conclusively proven by correlation with the natural product, lipstatin, the sense of the facial bias exerted by the ketene could only be inferred by further transformations. Thus, the major diastereoisomer **A** was pyrolysed and a n.O.e. study of the resultant alkenylsilane **E** suggested that the trimethylsilyl group and the alkyl chain are in a *syn* relationship, assuming retention of configuration in the thermal extrusion of CO_2 (Scheme 48).



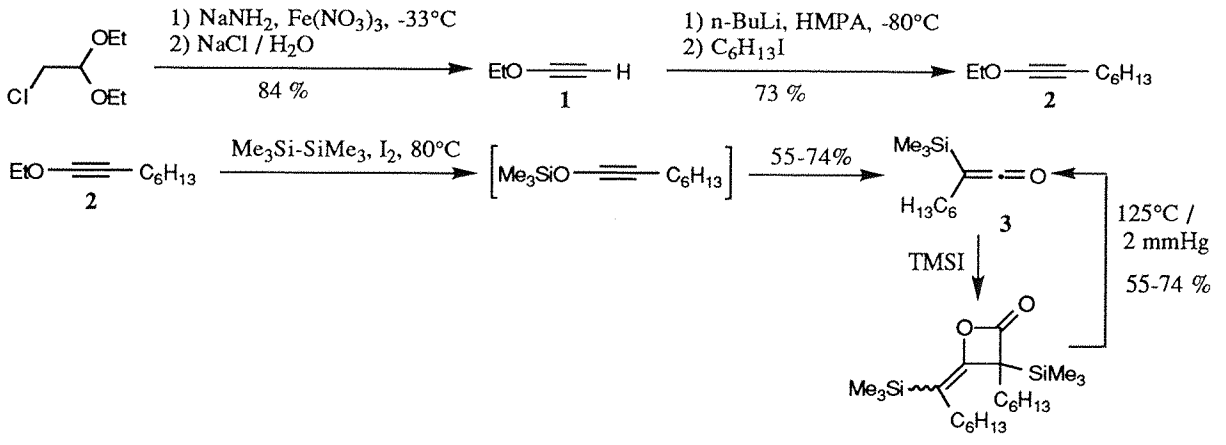
- Scheme 48 -

The syntheses of tetrahydrolipstatin and lipstatin were noteworthy because they demonstrated that even with more complex aldehyde and silylketene components, high stereoselectivities were still possible in Lewis acid-catalysed [2+2] cycloadditions. Not only was the preference for placing the trimethylsilyl group of the ketene and the alkyl group of the aldehyde in a *syn*-relationship maintained despite the bulky hexyl chain, but also, for the first time, high levels of 1,3-asymmetric induction were observed by a *ß*-alkoxysubstituent in the aldehyde component. With the ultimate aim of broadening the scope of the cycloaddition as well as understanding its mechanism, the objectives of our work were (a) to determine whether the asymmetric induction of the aldehyde in the above case could be generalised and (b) to prove unequivocally the facial bias exerted by the alkyl silylketene by direct methods.

III.2 - Preparation of starting reactants

III.2.1 - *n*-Hexyl(trimethylsilyl)ketene

n-Hexyl(trimethylsilyl)ketene **3** was obtained in three steps from chloroacetaldehyde diethyl acetal in 45 % overall yield (Scheme 49). The preparation of 1-ethoxy-1-octyne was improved by the isolation and purification of ethoxyacetylene **1** by quenching the ethoxyethynylsodium with water instead of the alkylating agent. 1-Ethoxy-1-octyne **2** was then formed by alkylation of the ethoxyacetylene. The one-pot preparation led to a very low yield and was therefore abandoned. *n*-Hexyl(trimethysilyl)ketene was obtained by reaction of 1-ethoxy-1-octyne with iodotrimethylsilane generated *in situ.* (by reaction of hexamethyldisilane with iodine), according to a similar procedure described by Sakurai[115] for the obtention of *n*-butyl(trimethylsilyl)ketene.

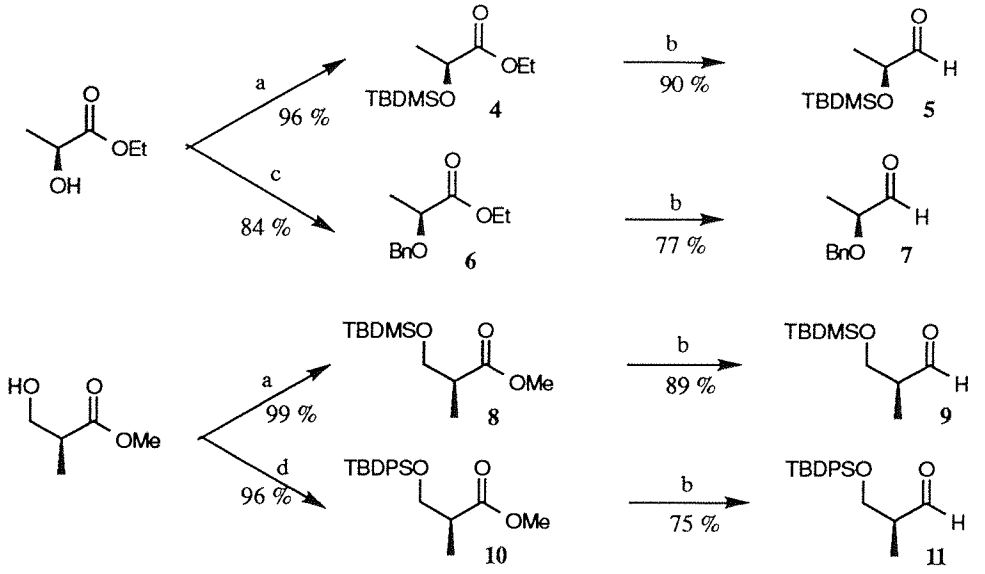


- Scheme 49 -

Relatively good yields (60-74 %) are observed for the last step, provided that the reaction takes place under *rigorously* anhydrous conditions and with exclusion of light. The addition of copper is also important as it traps the excess iodine generated by decomposition of the iodotrimethylsilane, thus avoiding or lowering the irreversible formation of impurities (IR : $\nu = 1586, 1635\ cm^{-1}$). The *n*-hexyl(trimethylsilyl)ketene generated can be detected by infrared spectroscopy of the crude reaction mixture but it dimerises under these conditions in the presence of iodotrimethylsilane. Once the iodotrimethylsilane is removed on workup, the dimer can be thermolysed to the monomer by Kügelrohr distillation, leading to the desired hexyl(trimethylsilyl)ketene as a pale yellow oil which was stable to storage at –20°C for weeks.

III.2.2 - Aldehydes

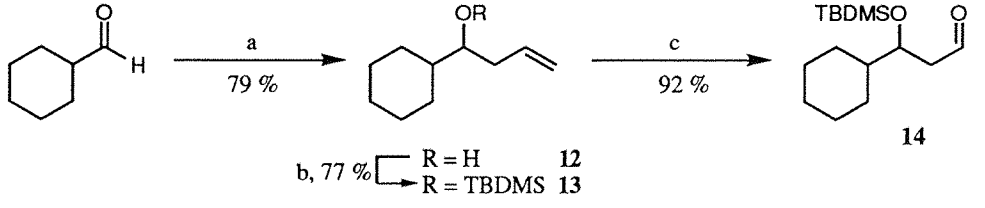
The α- and β-alkoxyaldehyde derivatives **5** and **7** were prepared in good overall yield in two steps from ethyl (*S*)-lactate by protection of the hydroxyl function as its *tert*-butyldimethylsilyl ether and benzyl ether derivative respectively followed by DIBAlH reduction (Scheme 50). Similar chemistry was used to transform the commercial methyl (*S*)-(+)-3-hydroxy-2-methylpropionate to the β-silyloxyaldehydes **9** and **11**.



Reagents and conditions
a) TBDMSCl, imidazole, DMAP, DCM, r.t., 2h
b) DiBAlH, DCM, -85°C, 15 min
c) 2,2,2-benzyltrichloroacetimidate, CF_3SO_3H, cyclohexane, DCM, r.t., 4h
d) TBDPSCl, imidazole, DMAP, DCM, r.t., 3h

- Scheme 50 -

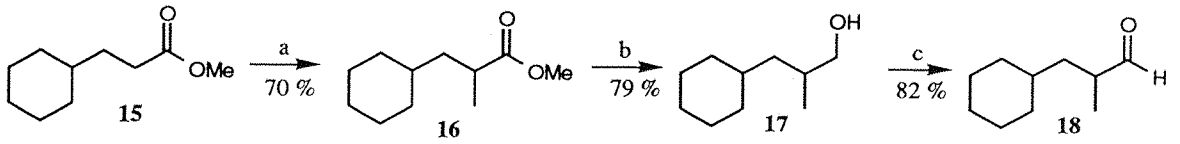
The *ß*-silyloxyaldehyde **14** was prepared from cyclohexanecarboxaldehyde by Grignard reaction with allylmagnesium bromide followed by protection of the resulting alcohol **12** and ozonolysis of the alkene **13** (Scheme 51).



Reagents and conditions
a) allylmagnesium bromide, Et_2O, -35°C, 1.5h; sat. aq. NH_4Cl sol.
b) TBDMSCl, imidazole, DMAP, DCM, r.t., 2h
c) O_3, MeOH, DCM, -60°C, 1h; DMS, r.t., 12h

- Scheme 51 -

A different strategy was adopted for the synthesis of 2-methyl-3-cyclohexylpropanal **18** due to purification problems. The alkylation of ester **15** yielded the expected *α*-methyl ester along with minor amounts of dimethylated product and starting material. The polarity of these three components and of aldehyde **18** being very similar required careful purification. The reduction of **16** to the alcohol **17** followed by a Swern oxidation was in this case more efficient than a direct DIBAlH reduction (Scheme 52).



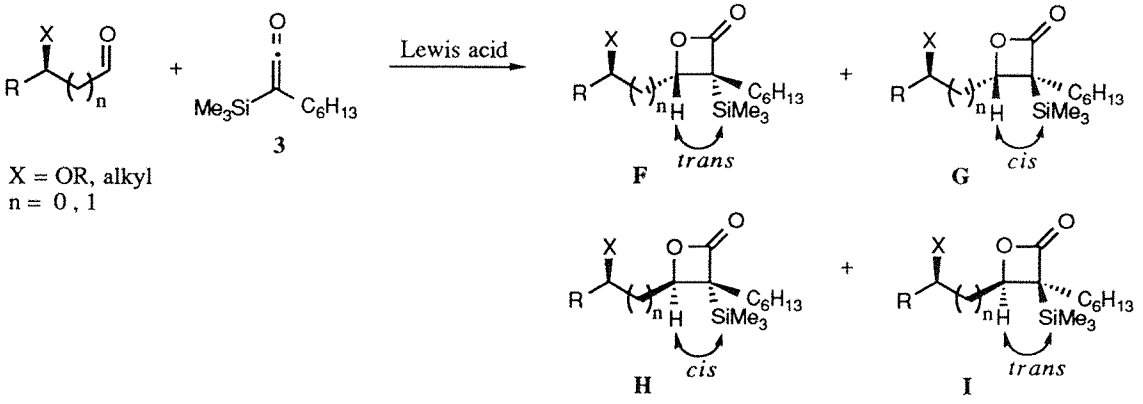
Reagents and conditions
a) LDA, THF, -60°C to -40°C, 1h; MeI, -78°C to -60°C, 1h
b) $LiAlH_4$, Et_2O, 0°C, 15 min
c) DMSO, oxalyl chloride, DCM, -50°C; **17**, *N*-methylmorpholine, -50°C, 5 min, 0°C, 1h

- Scheme 52 -

III.3 - [2+2] Cycloadditions

III.3.1 - Presentation

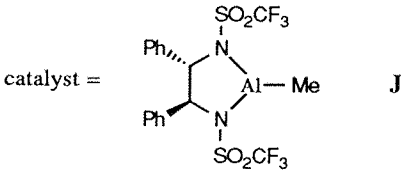
The [2+2] cycloaddition of *n*-hexyl(trimethylsilyl)ketene with α- and / or β-substituted aldehydes in the presence of different Lewis acids yielded β-lactones as a mixture of isomers. The existing stereogenic centre on the aldehyde induces the creation of two new stereogenic centres and the obtention of four possible diastereoisomers (Scheme 53).



- Scheme 53 -

The isomers **F** and **G** result from the attack of the alkyl silylketene on the *Re* face of the aldehyde whereas isomers **H** and **I** are formed by two different approaches of the ketene on the *Si* face of the aldehyde.

Our study was restricted to three Lewis acids: $EtAlCl_2$, $BF_3.Et_2O$ and the homochiral alane **J**, prepared by the method of Pikul and Corey[116] (Figure 10).



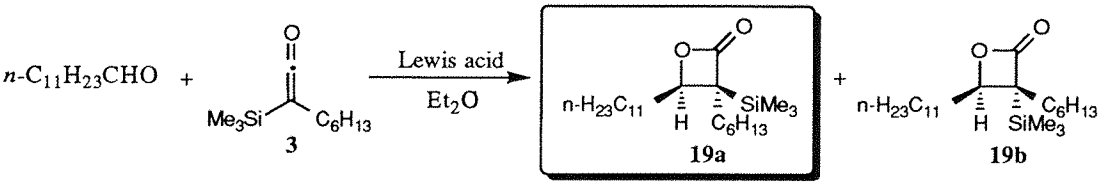
- Figure 10 -

III.3.2 - Results

• [2+2] Cycloaddition of *n*-hexyl(trimethylsilyl)ketene with dodecanal

In order to assess our methodology with simple systems, we began with a study of the cycloaddition of hexyl(trimethylsilyl)ketene with dodecanal, to investigate the facial bias of the reaction unobstructed by substituents. As can be seen from Scheme 54, $EtAlCl_2$ (2 eq.) showed good selectivity (d.r. = 95:5) with diminished selectivity being observed with $BF_3.Et_2O$ (d.r. = 73:27). The aluminium catalyst was also more reactive than the boron catalyst in parallel with earlier studies in the tetrahydrolipstatin series[2,83]. Although determination of the d.r. by NMR spectroscopy was easy, the stereochemistry could not be definitively determined. Therefore the assignment of stereochemistry of the cycloadducts **19a,b** was based on analogy with precedent[83]; i.e., we assumed that the TMS group is *cis* to the alkyl chain in the aldehyde for the major diastereoisomer and *trans* for the minor one.

The results depicted in Scheme 54 prove for the first time that high facial bias in the [2+2] cycloaddition of alkyl(trimethylsilyl)ketenes with simple aldehydes is possible.



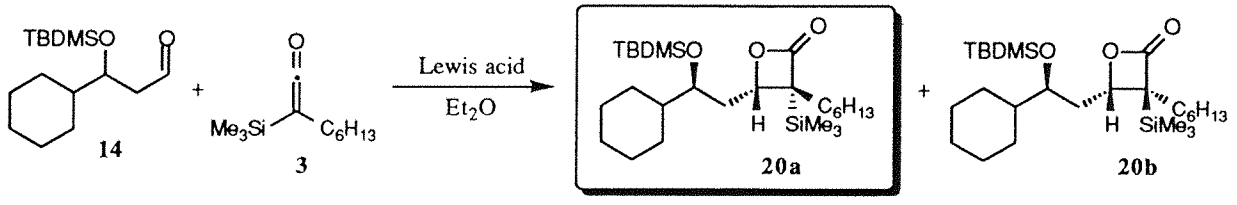
Lewis Acid (eq)	3 (eq)	T	Time	Yield	19a : 19b
$EtAlCl_2$ (1.3)	2	-20°C	2h	52 %	95 : 5
$BF_3.Et_2O$ (1.8)	1.4	0°C	4h	24 %	73 : 27

- Scheme 54 -

• [2+2] Cycloaddition of *n*-hexyl(trimethylsilyl)ketene with aldehyde **14**

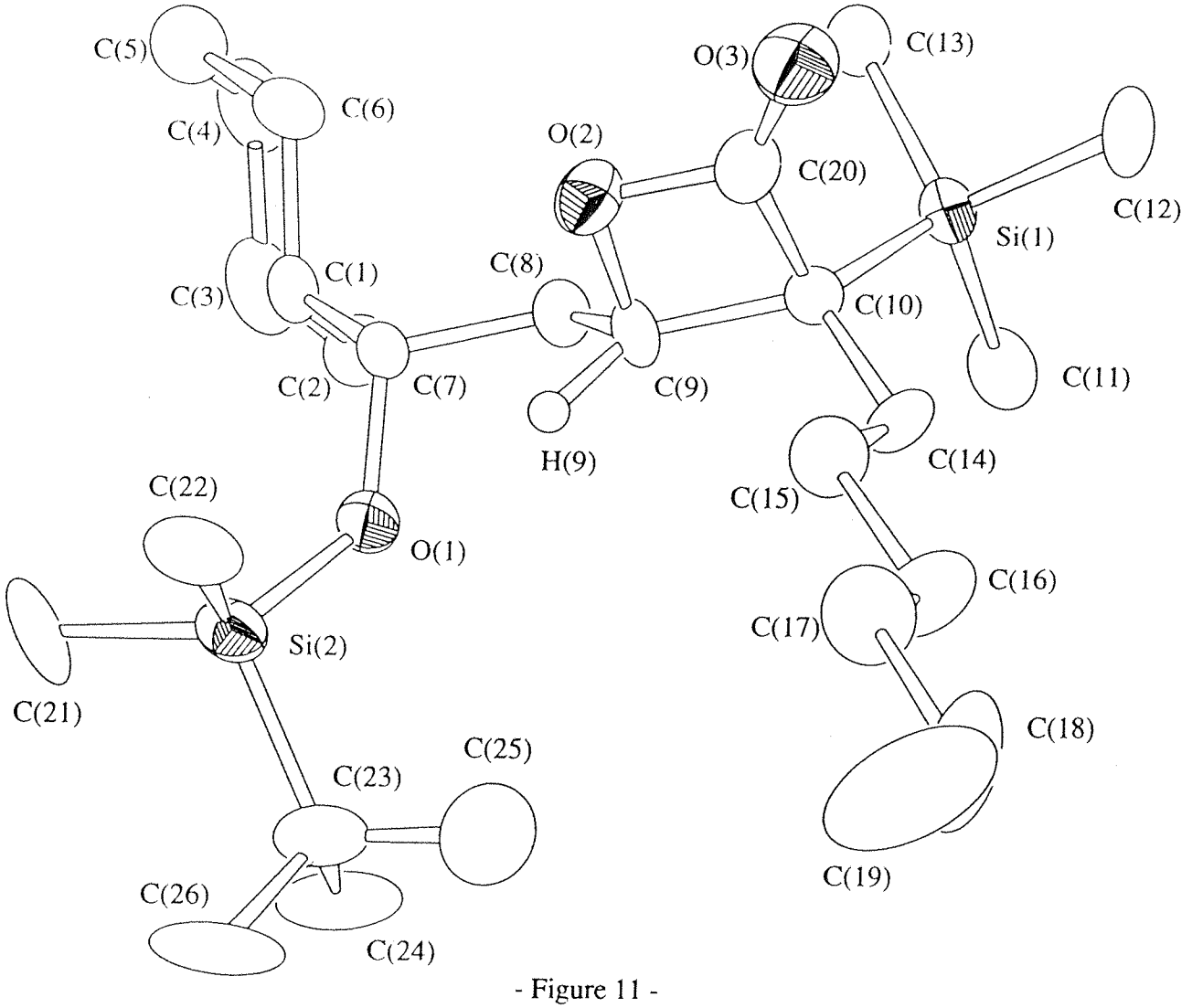
The cycloaddition of silylketene **3** and the *racemic ß*-silyloxy aldehyde **14** (Scheme 55) once again demonstrates the superior reactivity and efficiency of $EtAlCl_2$ compared with either $BF_3.Et_2O$ or the homochiral catalyst **J**. Although 8 diastereoisomers were possible (i.e., 4 pairs of enantiomers), the reaction, in fact, gave only two diastereoisomeric products (d.r. = 91:9) in detectable amounts by NMR analysis of the crude reaction mixture. The relative stereochemistry of the major crystalline derivative was revealed by X-ray

crystallographic analysis (Figure 11). With the exception of H_9, all of the hydrogen atoms have been omitted for clarity. The C_{10}-Si_1 bond from the ketene is *syn* to the C_8-C_9 bond of the aldehyde alkyl chain, the steric hindrance being lowered by the length of the C-Si bond ($d(Si_1-C_{10})$ = 1.905 Å and $d(C_{10}-C_{14})$ = 1.533 Å). The absolute configuration of the carbon C_7 is (*R*) for this enantiomer.These results show that a *β*-alkoxy substituent causes an excellent 1,3-asymmetric induction as the ketene attacked only the *Re* face of the aldehyde.



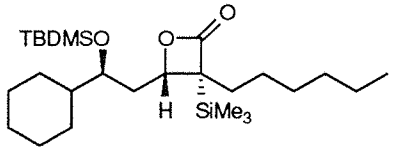
Lewis Acid (eq)	3 (eq)	T	Time	Yield	20a : 20b
$EtAlCl_2$ (1.1)	1.3	-25°C	1h	81 %	91 : 9
$BF_3.Et_2O$ (1.1)	1.3	0°C	2.5h	49 %	63 : 37
catalyst A (0.5)	1.3	-30°C	3h	85 %	50 : 50

- Scheme 55 -

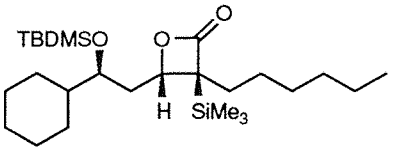


- Figure 11 -

Full characterisation of the stereochemistry of the minor isomer **20b** was precluded because we could not obtain a pure sample despite several recrystallisations from the initial 63 : 37 mixture of isomers derived from the $BF_3.Et_2O$-catalysed reaction. Its stereochemistry is assumed to be the same as that of the second most abundant isomer obtained in the synthesis of tetrahydrolipstatin[83] (Figure 12). This prediction is also based on a comparison of the chemical shifts of the C_3 proton on the β-lactone ring of the corresponding isomers in the tetrahydrolipstatin series in which $\Delta\delta = 0.08$ ppm is observed. Thus, the chemical shifts of the hydroxy derivatives of **A** and **B** are respectively 4.723 and 4.643 ppm (500 MHz) whereas the diastereoisomers **20a,b** are recorded at 4.62 and 4.54 ppm (270 MHz).



major isomer (X-ray structure)



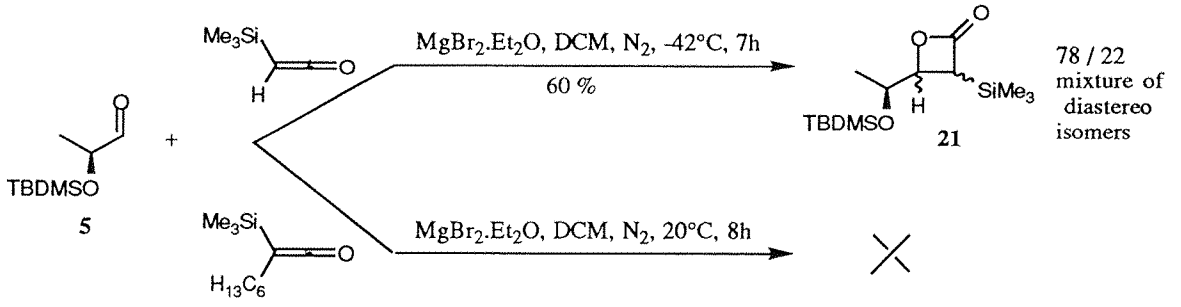
minor isomer

- Figure 12 -

The definitive assignment of the relative stereochemistry of adduct **20a** proves for the first time the sense of the facial bias exerted by the alkyl(silyl)ketene in the [2+2] cycloaddition with β-alkoxy aldehydes and confirms the stereochemical assignments inferred from chemical transformations in the synthesis of the tetrahydrolipstatin[83].

• <u>[2+2] Cycloaddition of *n*-hexyl(trimethylsilyl)ketene with aldehydes **5** and **7**</u>

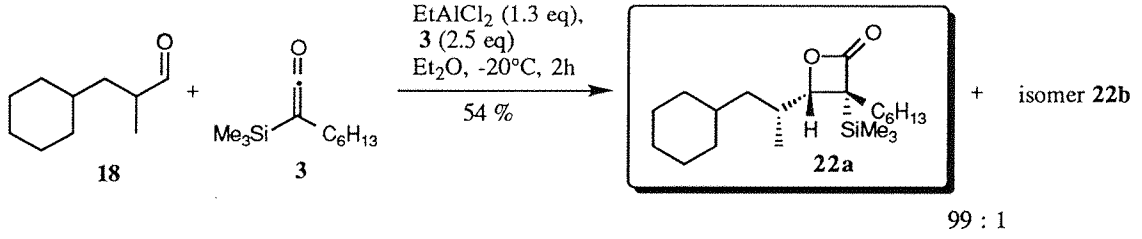
No β-lactone could be obtained from α-alkoxy aldehydes **5** and **7** in the presence of $EtAlCl_2$ (**5**, **7**) or $BF_3.Et_2O$ (**5**). The reaction was also unsuccessful with 2 equivalents of Lewis acid. When our work was nearly complete, Romo[112] reported successful [2+2] cycloadditions of aldehyde **7** with trimethylsilylketene in the presence of the bidentate Lewis acid $MgBr_2.Et_2O$. We first confirmed Romo's results using trimethylsilylketene and then repeated the experiment with *n*-hexyltrimethylsilylketene and the aldehyde **5** (Scheme 56). Again no β-lactone was obtained. These results suggest that *n*-hexyltrimethylsilylketene is less reactive than trimethylsilylketene.



- Scheme 56 -

• [2+2] Cycloaddition of *n*-hexyl(trimethylsilyl)ketene with aldehyde **18**

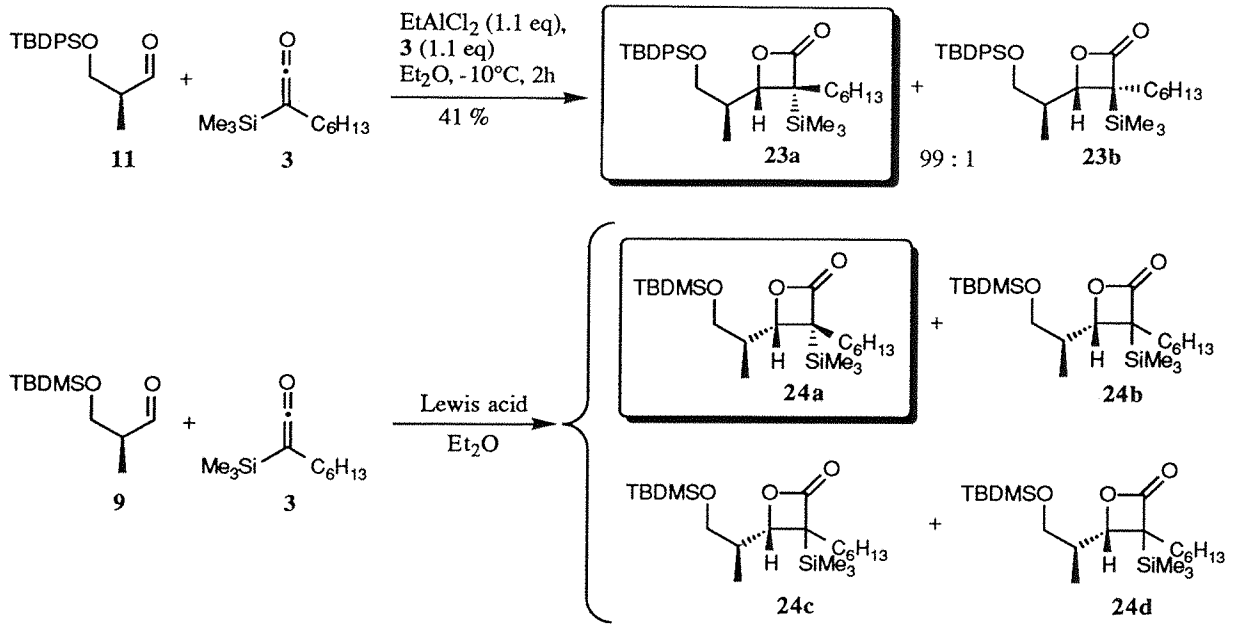
The reaction of hexyl(trimethylsilyl)ketene **3** with the *racemic* aldehyde **18** in the presence of $EtAlCl_2$ (Scheme 57) was moderately efficient (54% yield) but very stereoselective (d.r. = 99:1) according to NMR analysis. Thus, contrary to α-alkoxy aldehydes, α-alkyl aldehydes can react with alkyl(silyl)ketenes with high 1,2-asymmetric induction, which suggests that steric hindrance is not the main reason for the lack of reactivity in the previous [2+2] cycloaddition. The rationale for the stereochemical assignment of adduct **22a** will be discussed in III.4.



- Scheme 57 -

• [2+2] Cycloaddition of *n*-hexyl(trimethylsilyl)ketene with aldehydes **9** and **11**

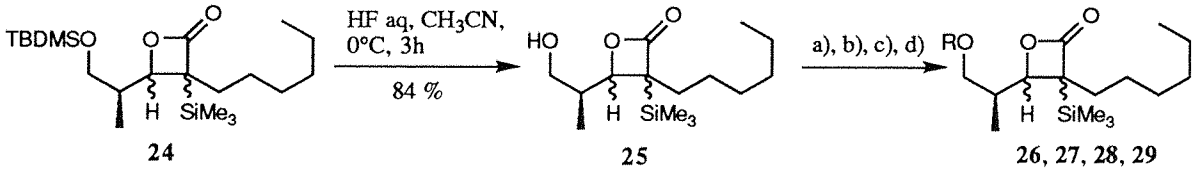
The cycloaddition of hexyl(trimethylsilyl)ketene **3** with aldehydes **9** and **11** was of interest to determine the combined effect of a β-silyloxy substituent (which usually gives good to excellent yields) with the beneficial steric effect of an α-alkyl group (*vide supra*). As can be seen from the results depicted in Scheme 58, the yields in the $EtAlCl_2$-catalysed reaction were modest at best but the stereoselectivity was again excellent. Interestingly, $BF_3.Et_2O$ appeared to catalyse the cycloaddition but no β-lactone could be isolated from the crude reaction mixture.



Lewis Acid (eq)	3 (eq)	T	Time	Yield	24a : 24b : 24c : 24d
$EtAlCl_2$ (1.1)	1.3	-15°C	2h	56 %	95 : 1 : 2 : 2
$BF_3.Et_2O$ (1.1)	1.4	-5°C	6h	0 %	-
catalyst A (0.5)	1.3	-40°C	3h	51 %	81 : 17 : 1 : 1

- Scheme 58 -

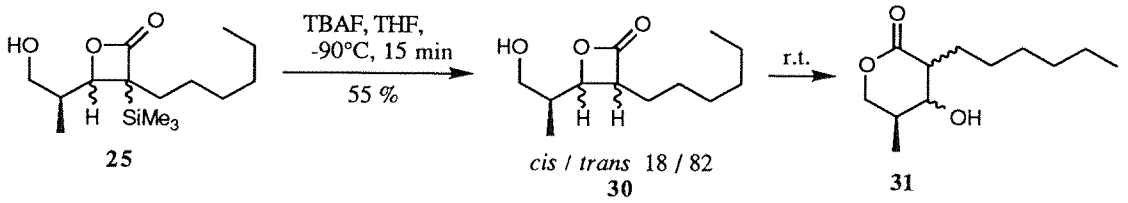
In order to determine the structure of the major isomer **24a**, attempts were made to obtain a crystalline derivative without changing the stereochemical configuration. Therefore the hydroxyl group was deprotected using hydrofluoric acid in acetonitrile and derivatised with different acyl and sulfonyl chlorides (Scheme 59). None of these attempts to obtain a crystalline derivative were successful.



Reagents and conditions
a) 3,5-dinitrobenzoylchloride, pyridine, THF, r.t., 12h, 47 % **26**
b) TsCl, Et_3N, DMAP, DCM, r.t., 20h, 65 % **27**
c) p-bromobenzenesulfonylchloride, Et_3N, DMAP, DCM, r.t., 20h, 72 % **28**
d) (-)-10-camphorsulfonylchloride, Et_3N, DMAP, DCM, r.t., 48h, 61 % **29**

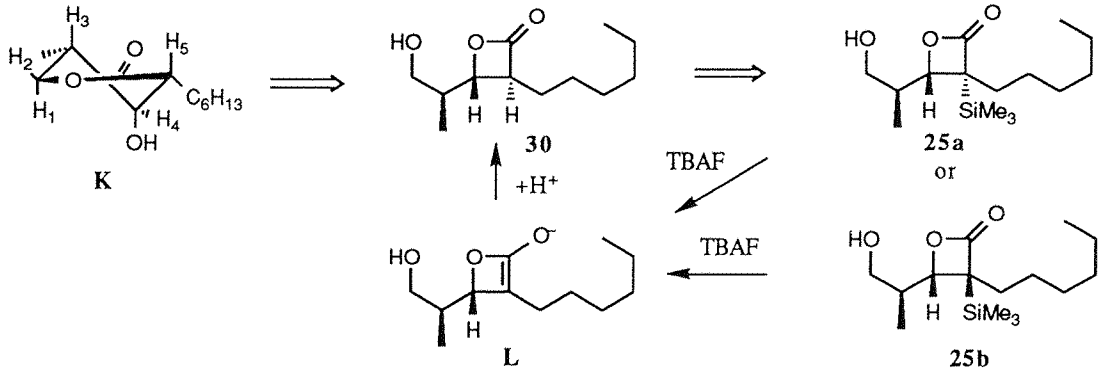
- Scheme 59 -

Desilylation of the hydroxy-β-lactone **25** , using tetrabutylammonium fluoride at –90°C, yielded the *trans*-β-lactone **30** which slowly rearranged at room temperature by intramolecular transesterification to give the crystalline δ–lactone **31** (Scheme 60) whose stereochemistry could be determined by ^1H NMR spectroscopy.



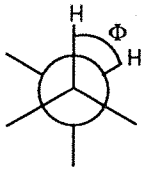
- Scheme 60 -

An MM2 calculation (Chem 3D®) suggested that lactone **31** exists in a twisted chair conformation **K** as shown in Scheme 61 in which the methyl and hexyl groups occupy pseudo-equatorial positions. Accordingly, the high value for the $J_{1,3}$ coupling constant ($J_{1,3}$ = 9.3 Hz) indicated that hydrogen atom H_3 is in the axial position. As $J_{3,4}$ = 3.8 Hz, H_4 cannot occupy the axial position ($J_{ax\text{-}ax}$ = 9-13 Hz), from which one can deduce the (*S*) configuration of the carbon atom bearing the hydroxy group. Finally, the fact that H_4 and H_5 are known to be in a *trans* relationship in *ß*-lactone **30** implies an axial H_5 atom.



- Scheme 61 -

The dihedral angles determined by calculation were applied to the Karplus equation and led to the following vicinal coupling constants (J^0 = 8.5 Hz, J^{180} = 9.5 Hz, standard values) which is in good agreement with the experimental coupling constants (Figure 12).



H_1-C_6-C_5-H_3 = 169.8°, J_{13} = 8.92 Hz
H_3-C_5-C_4-H_4 = -66.0°, J_{34} = 1.12 Hz
H_4-C_4-C_3-H_5 = 54.5°, J_{45} = 2.58 Hz

- Figure 12 -

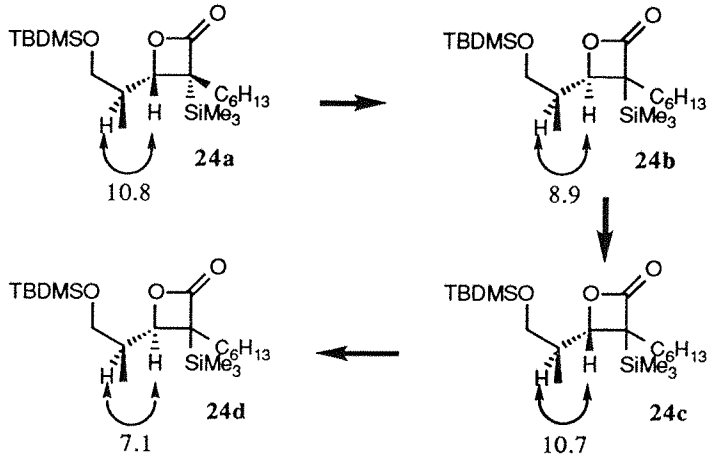
The stereochemistry of the remaining stereogenic centre in *ß*-lactone **25** could not be proven because under the C-desilylation conditions, both possible diastereoisomers **25a** or **25b** could proceed to the observed product *via* the corresponding enolate **L** (Scheme 61). Our preference for structure **25a** placing the silyl group at C_3 and the alkyl group at C_4 in a *cis* relationship is based on extrapolation from earlier results (*vide supra*).

The stereochemistry of minor β-lactones **24b**, **24c** and **24d** was deduced by consideration of the coupling constants between H_3 and H_4 for **24a-d** (Table 3).

β-lactone	**24a**	**24b**	**24c**	**24d**
$J_{3,4}$	10.8	8.9	10.7	7.1

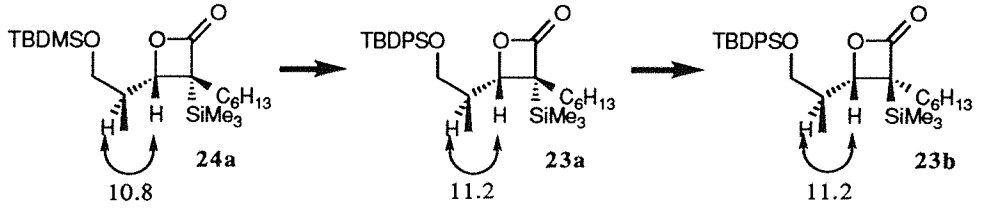
Table 3 - Coupling constants $J_{3,4}$ for β-lactones **24**

This data shows that the relative configuration of H_3 and H_4 in diastereoisomers **24a,c** and **24b,d** is identical. Taken together the NMR data and the assumed stereochemistry at C_3 for diastereoisomer **24a** leads to the following stereochemical assignments for all four diastereoisomers (Scheme 62).



- Scheme 62 -

A similar rationale with β-lactones **23a** and **23b** allowed assignment of their stereochemistry : **23a** was deduced from **24a** by analogy and **23b** from **23a**, knowing that $J_{3,4}$(**23a**) = $J_{3,4}$(**23b**) = 11.2 Hz (Scheme 63).

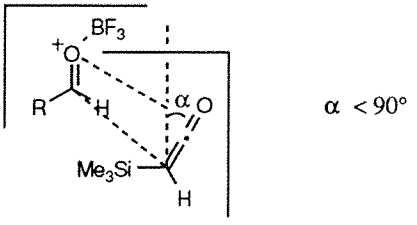


- Scheme 63 -

This last cycloaddition reveals a strong 1,2-asymmetric induction with α-alkyl-β-alkoxy substituted aldehydes, which is believed to be in the opposite sense to that with α-alkyl substituted aldehydes (*cf* cycloaddition with aldehyde **18**). A discussion of the stereochemistry of the cycloaddition is given below.

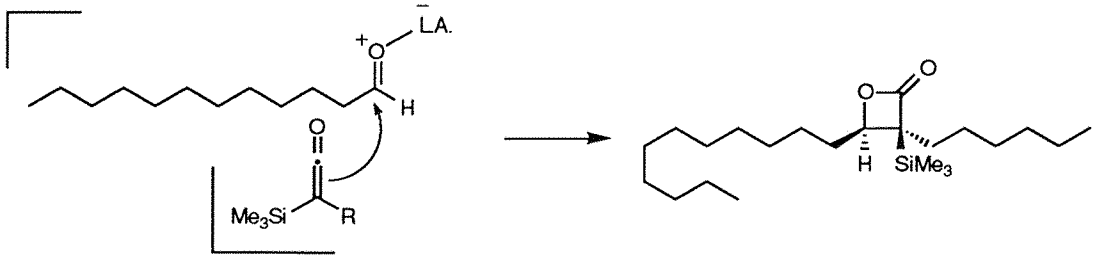
III.4 - Discussion

As discussed above, the mechanism of [2+2] cycloadditions between unsaturated compounds and ketenes has not yet been elucidated. Although the [2+2] cycloaddition between a ketene and a carbonyl compound is comparable to the ketene-imine cycloaddition regarding the electronic nature of the atoms involved, no *anti* approach could be found by *ab initio* [110] or semi-empirical[109] calculations. The role of the ketene and the aldehyde is highly dependent on the nature of their substituents : thus, Krabbenhoft concluded that dichloroketene was nucleophilic[54] whereas Moore concluded that chlorocyanoketene was electrophilic[108]. In the case of silylketenes, the experimental and theoretical evidence[83] is largely in favor of a nucleophilic ketene and an electrophilic aldehyde, which is corroborated by recent unpublished results[117] based on AM1 calculations concerning the BF_3-catalysed [2+2] cycloaddition between a silylketene and different aldehydes. These calculations predict the reactants to approach with parallel molecular planes in a *syn* fashion (Figure 13).



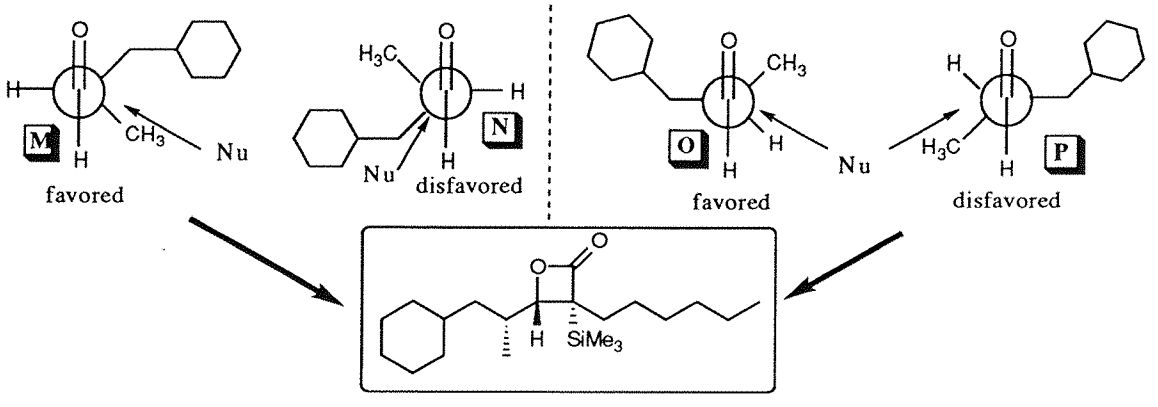
- Figure 13 -

Fortified by this evidence, our results will be interpreted by considering the nucleophilic attack of the alkyl(trialkylsilyl)ketene on the electrophilic carbonyl moiety activated by chelation with the Lewis acid. The [2+2] cycloaddition of *n*-hexyl(trimethylsilyl)ketene with dodecyl aldehyde yields essentially one diastereoisomer as expected by the consideration of steric effects. The Si-C bond (d = 1.7 Å) is longer than a C-C bond (d = 1.4 Å) thereby favoring a *syn* approach of the trimethylsilyl group and the alkyl chain, leading to one major diastereoisomer (a pair of enantiomers) according to the carbonyl face attacked by the ketene (Figure 14).



- Figure 14 -

The introduction of substituents onto the alkyl chain of the aldehyde induced a high diastereofacial selectivity. The stereochemical determination of the major isomer allowed an interpretation of these results taking into account the role of both the Lewis acid and the hydroxyl substituent. In the case of α-methyl substituted aldehyde **18**, the facial selectivity can be predicted by the Anh-Eisenstein model[118], which assumes an attack of the nucleophile antiperiplanar to the largest group of the stereogenic centre or to the ligand with the lowest σ^* orbital. According to the Cieplak hypothesis[119], C-H bonds are more electron-donating than C-C bonds therefore σ^*(C-H) is lower than σ^*(C-C). Thus, if the selectivity is imposed by electronic effects, the conformer **M** is prefered to the conformer **N**, by favorable interaction between the nucleophilic ketene and the closest substituent of the α-carbon atom (Figure 15). Nevertheless, it is believed that steric effects may couterbalance the σ^*-orbital energies[120] so that the antiperiplanar position is occupied by the largest group, which leads to the comparison of transition structures **O** and **P**. For the same reasons as above, the structure **O** is favored over **P**. However, both models predict the same stereochemical outcome.

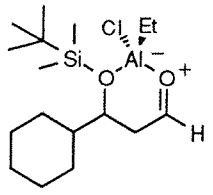


- Figure 15 -

The replacement of the α-methyl substituent by a protected hydroxyl group totally changed the reactivity as in this case no β-lactone could be obtained, whatever the hydroxy protecting group. This lack of reactivity is possibly due to the electron-withdrawing inductive effect of the oxygen atom α to the carbonyl, which lowers the basicity of the lone pairs of the carbonyl oxygen. Thus, the Lewis acid may chelate less strongly to the aldehyde resulting in diminished electrophilicity, whereupon reaction only takes place with the more reactive trimethylsilylketene.

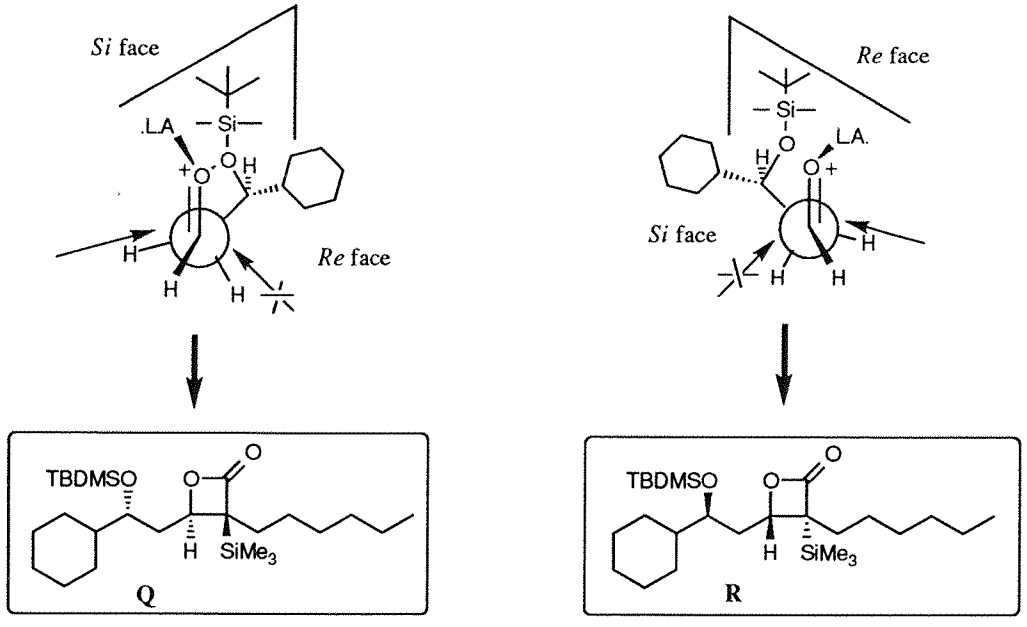
Conversely, a hydroxyl substituent β to the carbonyl moiety enhances the reactivity, as proved by the [2+2] cycloaddition between *n*-hexyl(trimethylsilyl)ketene and 3-cyclohexyl-3(*tert*-butyldimethylsilyloxy)propanal. In this case, the oxygen atom is too far away to exert an electron-withdrawing effect on the carbonyl oxygen, but can more favorably interact with the latter or with the Lewis acid. Chelation may be excluded for

$BF_3.Et_2O$ but not totally with $EtAlCl_2$, as the substitution of one chlorine atom by the carbonyl oxygen atom cannot be ruled out (Figure 16).



- Figure 16 -

However, in the hypothesis of non chelating Lewis acids, the conformation of the transition state can still be fixed by electrostatic interaction between the two oxygen atoms, which would explain the observed facial selectivity. Thus, the nucleophilic attack of the ketene occurs on the opposite side to the bulky cyclohexyl substituent, by the *Re* face of the (*S*) enantiomer (Figure 17), leading to two enantiomeric *ß*-lactones **Q** and **R** whose structure is proven by crystallographic analysis.

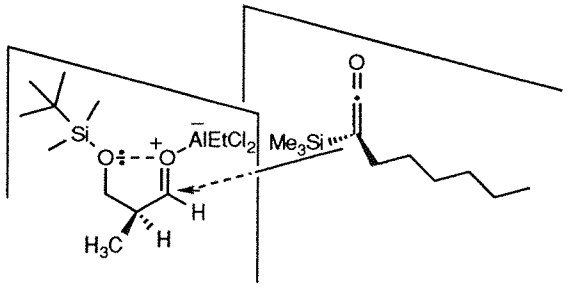


- Figure 17 -

The cyclohexyl ring gives rise to total facial selectivity as the minor isomer of this cycloaddition results from a different approach of the ketene on the same side of the aldehyde, providing only two diastereoisomers. This role was played by a linear alkyl chain in the aldehyde used for the synthesis of tetrahydrolipstatin and the obtention of four diastereoisomers (80 / 10 / 8 / 2) reveals a decrease of the selectivity due to the lower steric hindrance of the hexyl substituent.

The merged influence of a *α*-methyl and a *ß*-hydroxy substituent was studied with aldehyde **9**, (*S*)-2-methyl-3-(*tert*-butyldimethylsilyloxy)propanal. The failure of $BF_3.Et_2O$ to

catalyse the cycloaddition may result from the donor inductive effect of the methyl group which diminishes the electrophilicity of the carbonyl moiety and offsets the activation by the weaker Lewis acid. The results of the cycloaddition of aldehyde **9** using $EtAlCl_2$ are in accordance with the previous interpretation regarding the eclipsed conformation of the two oxygen atoms. The steric influence of the methyl group on the approach of the ketene is consistent with an increase of the diastereoselectivity (99 % of the major isomer): the methyl substituent is indeed closer to the site of the nucleophilic attack than the cyclohexyl ring and therefore enhances the differentiation between the faces of the carbonyl group (Figure 18).



- Figure 18 -

The use of a bulky chiral catalyst shows a significant decrease in the facial selectivity (81 / 17, *cf* III.3.2). In this case, the high steric hindrance prevents any electrostatic interaction between the two oxygen atoms; moreover, the reaction of homochiral catalyst in the presence of chiral aldehydes may be adversely affected by mis-matched pairing.

III.5 - Conclusions

We have made several useful observations on the scope and stereochemistry of the cycloaddition which are likely to extend its synthetic utility :

1. The inherent stereoselectivity observed in the cycloaddition of trimethylsilylketene to aldehydes is also observed with *n*-hexyltrimethylsilylketene and is the same in both cases.
2. The X-ray structure obtained for adduct **20a** constitutes the first direct proof of the facial bias exerted by an alkyl silylketene in the [2+2] cycloaddition with *ß*-alkoxy aldehydes.
3. The asymmetric induction in the tetrahydrolipstatin case was not unique. Other *ß*-alkoxy and *α*-alkyl substituents in the aldehyde component can also give rise to synthetically useful levels of 1,3- and 1,2-asymmetric induction.
4. The sense of the 1,2-asymmetric induction of *α*-alkyl substituted aldehydes may be governed and totally reversed by the presence or the absence of a *ß*-alkoxy group.

5. α-Alkoxy substituents in the aldehyde component prevent the [2+2] cycloaddition with alkyl silylketenes from taking place. Since TMS ketene is known to react with α-alkoxy aldehydes, it would appear that the alkyl silylketenes are the reactive species.

Unfortunately, we were not able to make a meaningful contribution to a general mechanism of the cycloaddition because we were not able to prove conclusively the stereochemistry at C_3 in the β-lactone adducts by either NMR spectroscopy or X-ray analysis in every case. Insufficient time did not allow us to extend the range of cases studied or further explore the effect of a wider range of Lewis acids or solvents. Nor was the unique ability of aluminium catalysts to promote high stereoselectivity and efficiency probed. There is much that remains to be done.

CHAPTER IV

Experimental

Experimental

IV.1 - General experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus and under nitrogen atmosphere. Solvents were dried by distillation from the drying agent : sodium and benzophenone for diethyl ether and tetrahydrofuran, calcium hydride for dichloromethane, dimethylformamide, pyridine, triethylamine and cyclohexane.

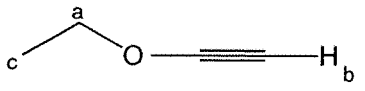
All reactions were magnetically stirred and monitored by TLC with Macherey-Nagel Duren Alugram Sil G/UV_{254} aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised with UV and / or phosphomolybdic acid in ethanol. Column chromatography was performed on Merck Kieselgel 60 (0.04-0.063 mm, 230-400 mesh) and run under pressure. Petrol refers to petroleum ether b_p 40-60°C.

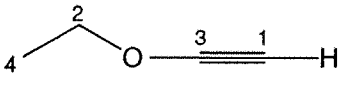
IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer, using NaCl plates or quartz cell. ^1H NMR spectra were recorded in Fourier Transform mode on Jeol GX-270 and ^{13}C NMR spectra on a Brücker AC-300, using $CDCl_3$ as solvent. Mass spectra were run on a VG 70-250-SE spectrometer.

IV.2 - Procedures and spectroscopic data

Ethoxyacetylene (1)

A 1L 2-necked round-bottom flask fitted with a cold finger condenser was immersed in a liquid nitrogen / acetone bath at –40°C and charged with liquid ammonia (500 mL). A little piece of sodium was added, followed by ferric nitrate (350 mg). The rest of the sodium (30 g, 1.3 mol) was then added portionwise over a period of 2.5 h. The reaction mixture was stirred under reflux until all the sodium had reacted as indicated by the change of colour from dark blue to dark grey. A pressure-equalized dropping-funnel was fitted to the reaction vessel and chloroacetaldehyde diethyl acetal (60 mL, 0.4 mol) added dropwise over 1 h. The reaction mixture was stirred under reflux for a further 4 h. The ammonia was evaporated by replacing the cold bath with a water bath at 20°C. The flask was fitted with a distillation apparatus and the reaction was quenched by dropwise addition of a saturated aqueous solution of sodium chloride (250 mL). The distillation of the crude product was carried out (B_P = 43-44°C / 760 mm Hg), yielding pure colourless ethoxyacetylene (23.7 g, 0.338 mol, 84 %).





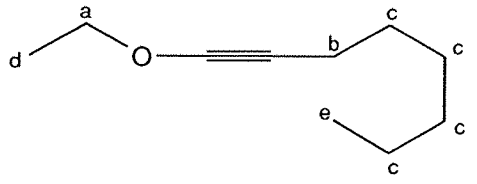
C_4H_6O, MW = 70.09

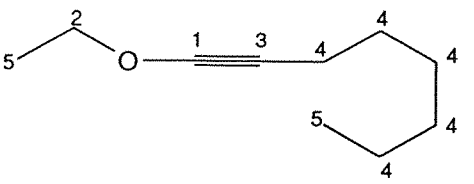
^{1}H NMR (270 MHz, $CDCl_3$)
H_a : 4.13 (2H, q, J = 7.1 Hz)
H_b : 1.53 (1H, s)
H_c : 1.39 (3H, t, J = 7.1 Hz)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 91.0
C_2 : 74.7
C_3 : 26.6
C_4 : 14.4

1-Ethoxy-1-octyne (2)

A 500 mL 3-necked round-bottom flask, fitted with a magnetic stirrer and a dropping funnel, was charged with ethoxyacetylene (6.31 g, 90 mmol) in dry THF (100 mL) under nitrogen at –85°C. n-Butyllithium (2.3 M in hexanes, 45 mL, 104 mmol) was added dropwise and the mixture was stirred for 1 h. Hexamethylphosphoramide (35 mL, 198 mmol) was then added dropwise maintaining the temperature at –80°C and the reaction was stirred for a further 30 min. 1-Iodohexane (10.6 mL, 72 mmol) in dry THF (15 mL) was added and the solution allowed to warm up to r.t. and stirred for 24 h. The mixture was hydrolysed with water (100 mL), stirred for 1 h and the organic layer was extracted with ether (3 x 200 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was distilled (bp 60°C / 2 mm Hg) to afford pure colourless 1-ethoxy-1-octyne (8.14 g, 52.8 mmol, 73 %).





$C_{10}H_{18}O$, MW = 154.25

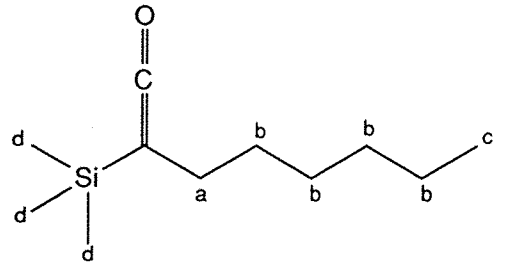
IR (film) : ν = 2957 s, 2931 s, 2858 s, 2272 s, 1467 m, 1443 m, 1223 s, 1010 s cm^{-1}

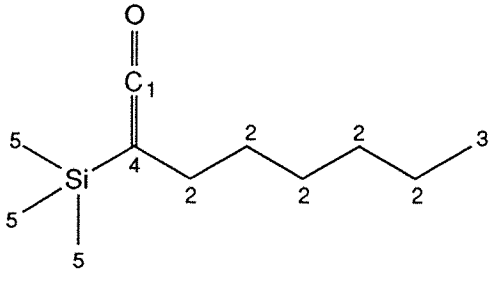
^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.02 (2H, q, J = 7.1 Hz)
H_b : 2.11 (2H, t, J = 6.8 Hz)
H_c : 1.46-1.27 (8H, m)
H_d : 1.35 (3H, t, J = 7.1 Hz)
H_e : 0.89 (3H, t, J = 6.8 Hz)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 89.4
C_2 : 74.0
C3 : 37.6
C_4 : 31.6, 29.9, 28.7, 22.8, 17.4
C_5 : 14.5, 14.2

_n_-Hexyl(trimethylsilyl)ketene (3)

A flame-dried 50 mL 2-necked flask fitted with a reflux condenser and a sealed tube was charged with hexamethyldisilane (1.83 g, 12.5 mmol). The mixture was heated to 80°C whereupon iodine (2.89 g, 11.4 mmol) was slowly added in 100 mg portions. The purple solution was heated at 80°C for a further 1 h until it becomes light brown. The mixture was then cooled to r.t. and powdered copper (100 mg) was added, followed by 1-ethoxy-1-octyne (2.93 g, 19 mmol). The mixture was heated at 70°C for 48 h. The excess of iodotrimethylsilane was removed *in vacuo* and the crude product was distilled using a Kugelrohr apparatus (bp 125°C / 2 mm Hg) to yield *n*-hexyl(trimethylsilyl)ketene (2.79 g, 14.1 mmol, 74 %) as a pale yellow oil.





$C_{11}H_{22}OSi$, MW = 198.38

IR (film) : ν = 2957 s, 2927 s, 2857 s, 2086 s, 1467 m, 1251 s, 840 s cm^{-1}

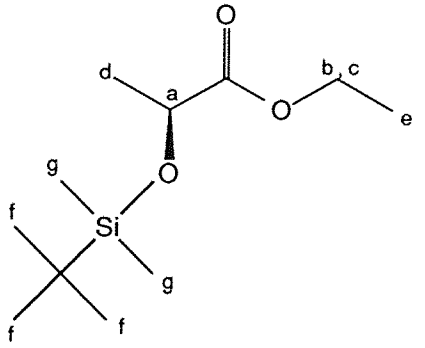
^1H NMR (270 MHz, $CDCl_3$)
H_a : 1.91 (2H, t-like)
H_b : 1.56-1.20 (8H, m)
H_c : 0.90 (3H, distorted t, J = 7.1 Hz))
H_d : 0.16 (9H, s)

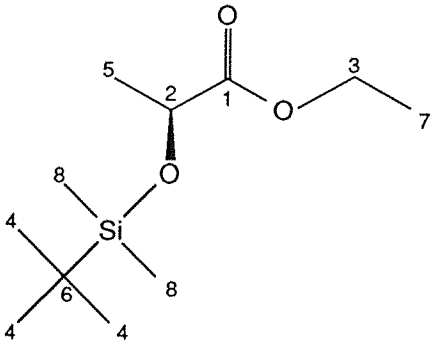
^{13}C NMR (270 MHz, $CDCl_3$)
C_1 : 182.5
C_2 : 31.8, 31.7, 29.0, 22.8, 22.3
C_3 : 14.2
C_4 : 13.0
C_5 : –0.7 (3C)

LRMS (CI mode, NH_3) m/z = 199 [$(M+H)^{+\bullet}$, 85 %], 90 (100).

Ethyl (*S*)-2-(*tert*-butyldimethylsiloxy)propanoate (4)

tert-Butyldimethylsilyl chloride (1.75 g, 11.5 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of imidazole (2.72 g, 40 mmol), ethyl (*S*)-lactate (1.19 g, 10 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) in CH_2Cl_2 (17 mL) under nitrogen at r.t.. Once the addition was complete, the solution was stirred for a further 2 h. The solvent was then removed *in vacuo* and the cloudy white mixture was poured into H_2O / Et_2O (20 / 20 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 10 mL).The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. A flash chromatography (ether / hexanes 2 : 98) yielded a colourless oil as the pure protected ester (2.23 g, 9.6 mmol, 96 %).





$C_{11}H_{24}O_3Si$, MW = 232.40

$[\alpha_D]$ (24°C) = –29.3° (*c* = 1.20 in $CHCl_3$)

IR (film) : *v* = 2957 s, 2931 s, 2898 s, 2858 s, 1755 s, 1473 m, 1373 m, 1257 s, 1190 m, 1148 s, 833 s, 779 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.31 (1H, q, J = 6.8 Hz)
H_b : 4.21 (1H, 1/2 ABX, qd, J_{AB} = 3.7 Hz, J = 7.1 Hz)
H_c : 4.17 (1H, 1/2 ABX, qd, J_{AB} = 3.7 Hz, J = 7.1 Hz)
H_d : 1.40 (3H, d, J = 6.8 Hz)
H_e : 1.28 (3H, t , J = 7.1 Hz)
H_f : 0.91 (9H, s)
H_g : 0.11 (3H,s)
0.08 (3H, s)

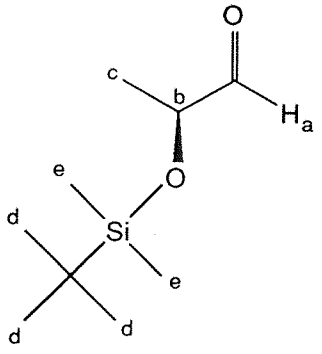
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 174.3
C_2 : 68.6
C_3 : 60.9
C_4 : 25.9 (3C)
C_5 : 21.5
C_6 : 18.5
C_7 : 14.3
C_8 : -4.8 (2C)

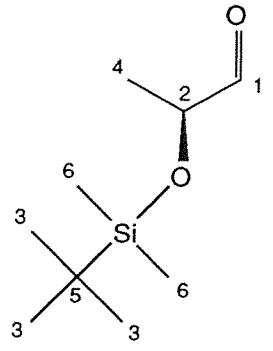
LRMS (CI mode, NH_3) *m/z* = 250 [$(M+NH_4)^{+\bullet}$, 20 %], 233 [$(M+H)^{+\bullet}$, 100 %], 217 (17), 175 (44), 159 (16), 35 (20).

(*S*)-2-(*tert*-Butyldimethylsiloxy)propanal (5)

DiBAlH (1.5 M in toluene, 1.43 mL, 2.15 mmol) was slowly added to a stirred solution of ethyl (*S*)-2-(*tert*-butyldimethysiloxy)propanoate (500 mg, 2.15 mmol) in dry CH_2Cl_2 (4 mL) under nitrogen at –85°C. The resulting solution was stirred for 15 min and hydrolysed with an aqueous saturated solution of ammonium chloride (0.6 mL) and hydrochloric acid (1M, 1.1 mL). The ammonium salts were filtered on silica, the filtrate was dried over

$MgSO_4$ and concentrated *in vacuo*. A column chromatography (ether / hexanes 2 : 98) yielded the pure aldehyde (365 mg, 1.94 mmol, 90 %).





$C_9H_{20}O_2Si$, MW = 188.34

$[\alpha_D]$ (24°C) = –11.3° (c = 1.05 in $CHCl_3$)

IR (film) : ν = 2931 s, 2888 s, 2858 s, 1741 s, 1473 m, 1374 m, 1255 s, 1141 s, 837 s, 778 s cm^{-1}

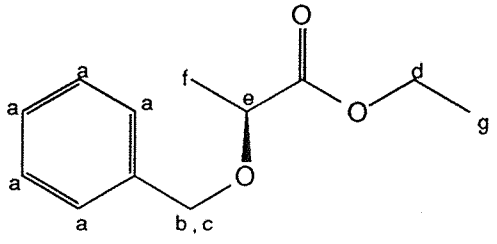
^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.61 (1H, d, J =1.3 Hz)
H_b : 4.10 (1H, dq, J = 6.9, 1.3 Hz)
H_c : 1.27 (3H, d, J = 6.9 Hz)
H_d : 0.91 (9H, s)
H_e : 0.10 (3H, s)
0.09 (3H, s)

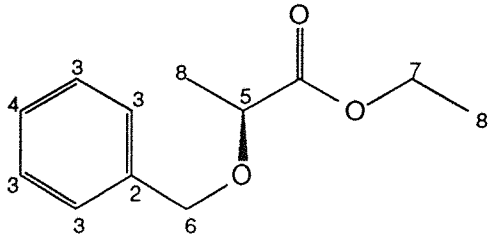
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 204.3
C_2 : 74.0
C_3 : 25.9 (3C)
C_4 : 18.6
C_5 : 18.3
C_6 : –4.6, –4.7

LRMS (CI mode, NH_3) m/z = 206 [$(M+NH_4)^{+\bullet}$, 61 %], 189 [$(M+H)^{+\bullet}$, 62 %], 173 (29), 159 (45), 131 (100), 90 (22), 74 (19), 35 (44).

Ethyl (*S*)-2-(benzyloxy)propanoate (6)

Triflic acid (70 µL, 0.8 mmol) was added to a stirred solution of ethyl (*S*)-lactate (1.41 g, 12 mmol) and 2,2,2-benzyltrichloroacetimidate (4.5 mL, 24 mmol) in dry cyclohexane (9 mL) and dry CH_2Cl_2 (9 mL) under nitrogen at r.t.. The mixture was stirred for 4 h. The crystalline trichloroacetamide was then removed by filtration and the filtrate washed with an aqueous saturated solution of sodium bicarbonate (50 mL) and water (50 mL). The organic layer was dried over Na_2SO_4 and the solvents removed *in vacuo*. The residue was purified by chromatography on silica gel (ether / hexanes 2 : 98) to give the protected ester (2.08 g, 10 mmol, 83 %).





$C_{12}H_{16}O_3$, MW = 208.26

$[\alpha_D]$ (24°C) = –70.7° (c = 2.02 in MeOH)

IR (film) : ν = 3063 m, 3029 m, 2984 s, 2938 s, 1746 s, 1496 m, 1454 s, 1372 m,1270 s, 1198 s, 1143 s, 1065 s, 1026 s, 907 w, 860 w, 737 s, 698 s cm^{-1}

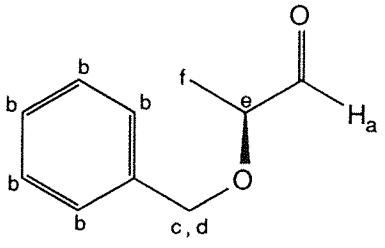
^1H NMR (270 MHz, $CDCl_3$)
H_a : 7.40-7.30 (5H, m)
H_b : 4.71 (1H, 1/2 AB, d, J_{AB} = 11.8 Hz)
H_c : 4.46 (1H, 1/2 AB, d, J_{AB} = 11.8 Hz)
H_d : 4.23 (2H, qd, J = 7.1, 1.3 Hz)
H_e : 4.06 (1H, q, J = 6.9 Hz)
H_f : 1.45 (3H, d, J = 6.9 Hz)
H_g : 1.31 (3H, t, J = 7.1 Hz)

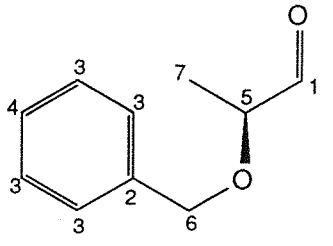
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 173.4
C_2 : 137.7
C_3 : 128.5 (2C), 128.1 (2C)
C_4 : 128.0
C_5 : 74.2
C_6 : 72.1
C_7 : 61.0
C_8 : 18.9, 14.4

LRMS (CI mode, NH_3) m/z = 226 [$(M+NH_4)^{+\bullet}$, 100 %], 209 [$(M+H)^{+\bullet}$, 17], 100 (30), 91 (20).

(*S*)-2-(Benzyloxy)propanal (7)

DiBAlH (1.5 M in toluene, 1.28 mL, 1.92 mmol) was slowly added to a stirred solution of ethyl (*S*)-2-(benzyloxy)propanoate (400 mg, 1.92 mmol) in dry CH_2Cl_2 (4 mL) under nitrogen at –85°C. The resulting solution was stirred for 15 min and hydrolysed with an aqueous saturated solution of ammonium chloride (0.5 mL) and hydrochloric acid (1M, 1 mL). The ammonium salts were filtered on silica, the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ether / hexanes 1 : 99) yielded the pure aldehyde (244 mg, 1.49 mmol, 77 %).





$C_{10}H_{12}O_2$, MW = 164.21

$[\alpha_D]$ (24°C) = –19.9° (c = 2.0 in MeOH)

IR (film) : ν = 3063 m, 3029 m, 2982 s, 2935 s, 2870 s, 2710 w, 1734 s, 1496 m, 1455 s, 1374 m, 1306 w, 1204 m, 1128 s, 1028 m, 907 w, 846 w, 737 s, 698 s cm^{-1}

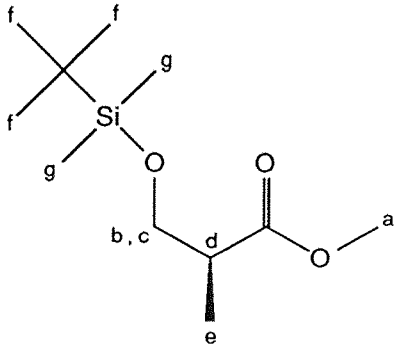
^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.68 (1H, d, J = 1.9 Hz)
H_b : 7.40-7.30 (5H, m)
H_c : 4.67 (1H, d, J_{AB} = 11.8 Hz)
H_d : 4.61 (1H, d, J_{AB} = 11.8 Hz)
H_e : 3.91 (1H, dq, J = 6.9, 1.7 Hz)
H_f : 1.34 (3H, d, J = 6.9 Hz)

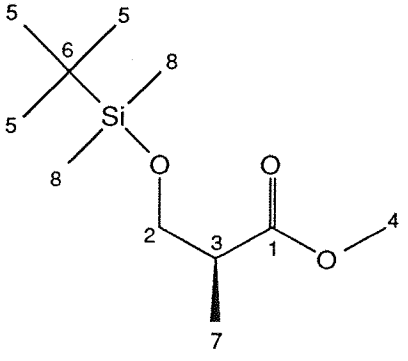
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 203.7
C_2 : 137.5
C_3 : 128.8 (2C), 128.3 (2C)
C_4 : 128.1
C_5 : 79.6
C_6 : 72.2
C_7 : 15.5

LRMS (CI mode, NH_3) : *m/z* = 182 [$(M+NH_4)^{+\bullet}$, 100 %], 108 (30).

Methyl (*S*)-2-methyl-3-(*tert*-butyldimethylsiloxy)propanoate (8)

tert-Butyldimethylsilyl chloride (3.62 g, 24 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of imidazole (5.8 g, 85 mmol), methyl (*S*)-2-methyl-3-(hydroxy)-2-methylpropanoate (2.32 mL, 21 mmol) and 4-dimethylaminopyridine (137 mg, 1.1 mmol) in CH_2Cl_2 (25 mL) under nitrogen at r.t.. Once the addition was complete, the cloudy white solution was stirred for a further 2 h. The solvent was removed *in vacuo*, the residue treated with hexanes (20 mL) and stored overnight at 0°C. The resulting precipitate was filtered and the filtrate was evaporated to give a colourless oil. The crude product was purified by flash chromatography using 2 % ether / hexanes as eluent to afford pure ester (4.91 g, 21 mmol, 100 %).





$C_{11}H_{24}O_3Si$, MW = 232.40

$[\alpha_D]$ (24°C) = +20.2° (*c* = 2.05 in $CHCl_3$)

IR (film) : *v* = 2955 s, 2885 s, 2858 s, 1744 s, 1472 s, 1389 m, 1362 m, 1257 s, 1199 s, 1098 s, 838 s, 777 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 3.68 (3H, s)
H_b : 3.78 (1H, dd, *J* = 9.7, 6.9 Hz)
H_c : 3.65 (1H, dd, *J* = 9.7, 5.9 Hz)
H_d : 2.65 (1H, quint.d, *J* = 6.9, 5.9 Hz)
H_e : 1.14 (3H, d, *J* = 6.9 Hz)
H_f : 0.88 (9H, s)
H_g : 0.05 (3H, s)
0.04 (3H, s)

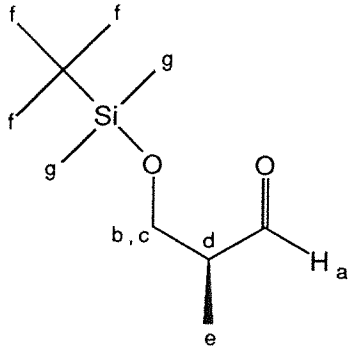
^{13}C NMR (270 MHz, $CDCl_3$)
C_1 : 175.6
C_2 : 65.4
C_3 : 51.6
C_4 : 42.7
C_5 : 25.9 (3C)
C_6 : 18.3
C_7 : 13.6
C_8 : –5.4 (2C)

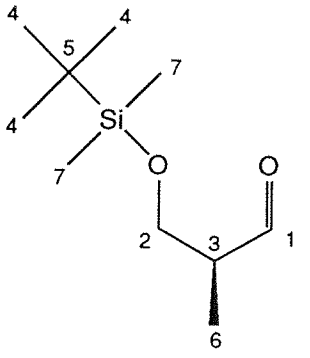
LRMS (CI mode, NH_3) *m/z* = 250 [$(M+NH_4)^{+\bullet}$, 4 %], 233 [$(M+H)^{+\bullet}$, 100 %], 175 (64), 106 (24

(*S*)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)propanal (9)

DiBAlH (1.5 M in toluene, 6.70 mL, 10 mmol) was slowly added to a stirred solution of methyl (*S*)-2-methyl-3-(*tert*-butyldimethysiloxy)propanoate (2.32 g, 10 mmol) in dry

CH_2Cl_2 (8 mL) under nitrogen at –85°C. The resulting solution was stirred for 15 min and hydrolysed with an aqueous saturated solution of ammonium chloride (2.9 mL) and hydrochloric acid (1M, 5.3 mL). The ammonium salts were then filtered on silica, the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. A column chromatography (ether / hexanes 2 : 98) yielded the pure aldehyde (1.80 g, 8.89 mmol, 89 %).





$C_{10}H_{22}O_2Si$, MW = 202.37

$[\alpha_D]$ (24°C) = +41.1° (*c* = 0.9 in $CHCl_3$)

IR (film) : ν = 2956 s, 2930 s, 2858 s, 2712 w, 1738 s, 1472 s, 1390 w, 1362 w, 1257 s, 1099 s, 839 s, 778 s cm^{-1}

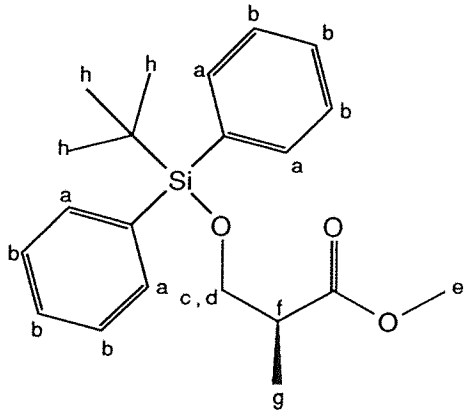
^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.74 (1H, d, *J* = 1.5 Hz)
H_b : 3.87 (1H, dd, *J* = 10.2, 5.2 Hz)
H_c : 3.81 (1H, dd, *J* = 10.2, 6.5 Hz)
H_d : 2.54 (1H, qddd, *J* = 7.1, 6.5, 5.2, 1.5 Hz)
H_e : 1.09 (3H, d, *J* = 7.1 Hz)
H_f : 0.88 (9H, s)
H_g : 0.06 (6H, s)

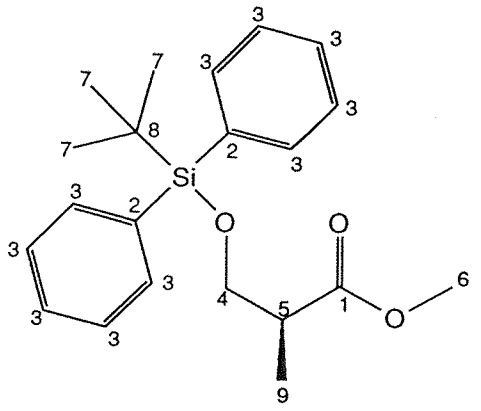
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 204.9
C_2 : 63.6
C_3 : 49.0
C_4 : 25.9 (3C)
C_5 : 18.4
C_6 : 10.4
C_7 : –5.4 (2C)

LRMS (EI mode) *m/z* = 202 [$M^{+\bullet}$, 0.5 %], 175 (18), 145 (100), 115 (76), 89 (21), 38 (75), 73 (16), 59 (16), 28 (63).

Methyl (*S*)-2-methyl-3-(*tert*-butyldiphenylsiloxy)propanoate (10)

tert-Butyldiphenylsilyl chloride (6.5 g, 24 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirred solution of imidazole (5.7 g, 80 mmol), methyl (*S*)-3-hydroxy-2-methylpropanoate (2.5 g, 21 mmol) and 4-dimethylaminopyridine (128 mg, 1.1 mmol) in CH_2Cl_2 (25 mL) under nitrogen at r.t.. Once the addition was complete, the cloudy white solution was stirred for a further 3 h. The solvent was removed *in vacuo* and the residue was treated with hexanes and stored at 0°C until a white precipitate settled. The precipitate was then filtered and washed with water (3x30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a clear liquid which was purified by column chromatography (ether / hexanes 1 : 99) yielding the ester (7.30 g, 20.5 mmol, 98 %).





$C_{21}H_{28}O_3Si$, MW = 356.54

$[\alpha_D]$ (20°C) = +23° (c = 7.8 in MeOH)

IR (film) : ν = 3071 m, 3050 m, 2932 s, 2858 s, 1741 s, 1472 m, 1428 m, 1389 m, 1362 m, 1257 m, 1199 s, 1112 s, 702 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 7.66-7.69 (4H, m)
H_b : 7.40-7.45 (6H, m)
H_c : 3.85 (1H, dd, J = 9.7, 6.9 Hz)
H_d : 3.74 (1H, dd, J = 9.7, 5.8 Hz)
H_e : 3.71 (3H, s)
H_f : 2.74 (1H, ddd, J = 7.1, 6.9, 5.8 Hz)
H_g : 1.18 (3H, d, J = 7.1 Hz)
H_h : 1.05 (9H, s)

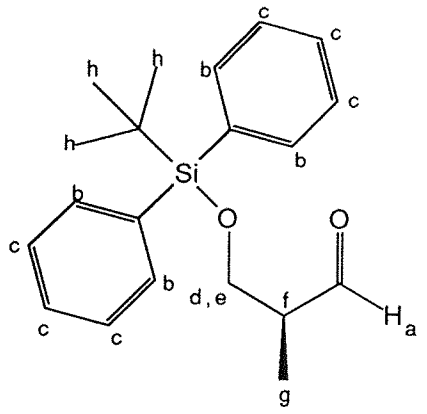
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 175.7
C_2 : 133.8 (2C)
C_3 : 135.9 (4C), 130.0 (2C), 128.0 (4C)
C_4 : 66.2
C_5 : 51.9
C_6 : 42.7
C_7 : 27.0 (3C)
C_8 : 19.5
C_9 : 13.8

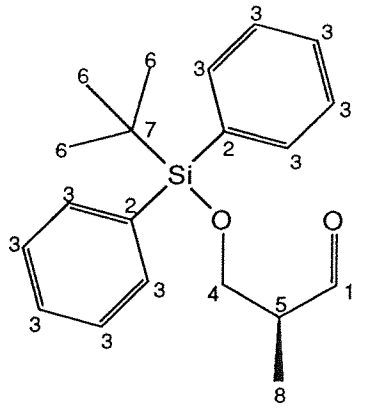
LRMS (FAB mode) m/z = 355 [$(M-H)^{+\bullet}$, 2 %], 299 (100), 279 (44), 213 (50), 197 (21), 183 (19) 151 (20), 135 (35), 89 (18).

(*S*)-2-Methyl-3-(*tert*-butyldiphenylsiloxy)propanal (11)

DiBAlH (1.5 M in toluene, 4.0 mL, 6 mmol) was slowly added to a stirred solution of methyl (*S*)-2-methyl-3-(*tert*-butyldiphenylsiloxy)propanoate (2.14 g, 6 mmol) in dry CH_2Cl_2 (8 mL) under nitrogen at –85°C. The resulting solution was stirred for 2 h and hydrolysed with an aqueous saturated solution of ammonium chloride (4.2 mL) and hydrochloric acid (1M, 7.6 mL). The ammonium salts were filtered on silica, the filtrate was dried over $MgSO_4$ and

concentrated *in vacuo*. On standing overnight, white crystals precipitated and were purified by recrystallisation in petrol (1.47 g, 4.5 mmol, 75 %).





$C_{20}H_{26}O_2Si$, MW = 326.52

$[\alpha_D]$ (20°C) = +30.7° (*c* = 1.0 in $CHCl_3$)

mp = 62-64°C

IR (film) : ν = 3071 m, 3049 m, 2932 s, 2858 s, 1738 s, 1472 s, 1428 s, 1391 m, 1362 m, 1112 s, 702 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.78 (1H, d, *J* = 1.7 Hz)
H_b : 7.68-7.64 (4H, m)
H_c : 7.46-7.38 (6H, m)
H_d : 3.92 (1H, dd, *J* = 10.4, 5.0 Hz)
H_e : 3.85 (1H, dd, *J* = 10.4, 6.3 Hz)
H_f : 2.62-2.55 (1H, ddq, *J* = 6.9, 6.3, 5.0 Hz)
H_g : 1.11 (3H, d, *J* = 6.9 Hz)
H_h : 1.05 (9H, s)

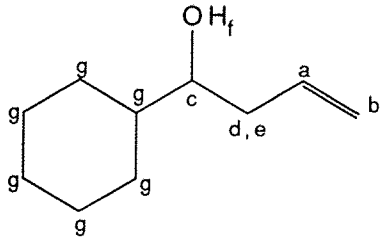
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 204.7
C_2 : 133.3 (2C)
C_3 : 135.8 (4C), 130.0 (2C), 127.9 (4C)
C_4 : 64.3
C_5 : 49.0
C_6 : 26.9 (3C)
C_7 : 19.4
C_8 : 10.5

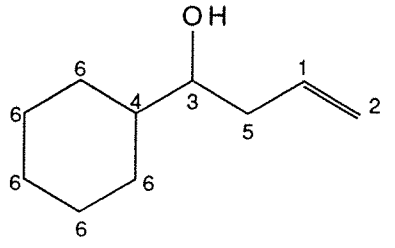
LRMS (FAB mode) *m/z* = 327 [$(M+H)^{+\bullet}$, 4 %],, 299 (28), 269 (81), 239 (48), 191 (56), 135 (100).

4-Cyclohexyl-4-(hydroxy)but-1-ene (12)

A flame-dried 100 mL 2-necked flask fitted with a magnetic stirrer and nitrogen line was immersed in a cold bath at –40°C and charged with allylmagnesium bromide (1.0 M in Et_2O, 30 mL, 30 mmol). Cyclohexanecarboxaldehyde (3.1 mL, 27 mmol) in dry Et_2O (15 mL)

was then added dropwise. The solution was stirred for 1.5 h between –40°C and –30°C, and hydrolysed with a saturated aqueous solution of ammonium chloride (20 mL). The organic layer was extracted with ether (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 3.53 g of crude product. A column chromatography on silica gel (ether / hexanes 5 : 95) yielded pure allylic alcohol (3.34 g, 21.6 mmol, 80 %).





$C_{10}H_{18}O$, MW = 154.25

IR (film) : ν = 3378 br m, 3075 m, 2925 s, 2853 s, 1641 m, 1450 m cm^{-1}

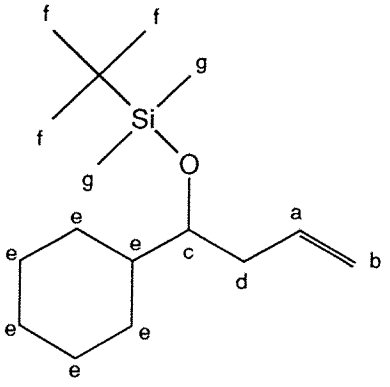
^1H NMR (270 MHz, $CDCl_3$)
H_a : 5.85 (1H, dddd, J = 17.8, 9.5, 8.0, 6.2 Hz)
H_b : 5.20-5.10 (2H, m)
H_c : 3.37 (1H, ddd, J = 9.1, 5.8, 3.4 Hz)
H_d : 2.35 (1H, 1/2 ABMX, dm, J_{AB} = 13.9 Hz)
H_e : 2.15 (1H, 1/2 ABMX, dtd, J_{AB} = 13.9 Hz, J = 8.0, 1.3 Hz)
H_f : 1.58 (1H, s)
H_g : 1.90-0.93 (11H, m)

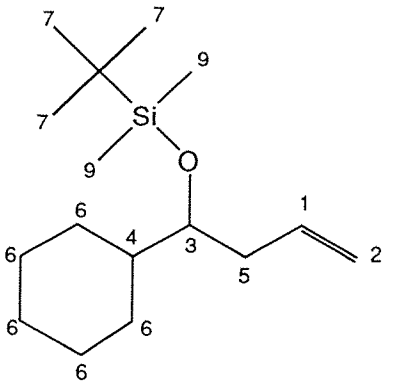
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 135.7
C_2 : 118.0
C_3 : 74.9
C4 : 43.2
C_5 : 39.0
C_6 : 29.2, 28.3, 26.7, 26.4, 26.3

LRMS (EI mode) m/z = 153 [$(M-H)^{+\bullet}$, 0.5 %], 136 [$(M-H_2O)^{+\bullet}$, 0.5 %], 113 (39), 95 (100), 67 (16), 55 (18), 41 (19).

4-Cyclohexyl-4-(*tert*-butyldimethylsilyloxy)but-1-ene (13)

tert-Butyldimethylsilyl chloride (2.60 g, 17.2 mmol) in dry CH_2Cl_2 (3 mL), was added to a stirred solution of imidazole (4.08 g, 60 mmol), 4-cyclohexyl-4-(hydroxy)but-1-ene (2.23 g, 15 mmol) and 4-dimethylaminopyridine (92 mg, 0.75 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen at r.t.. Once the addition was complete, the solution was stirred for a further 2 h. The reaction was quenched with water (20 mL) and extracted with ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* . A flash chromatography (ether / hexanes 1 : 99) yielded a colourless oil (3.03 g, 11.3 mmol, 75 %).





$C_{16}H_{32}OSi$, MW = 268.52

IR (film) : ν = 3077 w, 2929 s, 1855 s, 1641 w, 1472 m, 1450 m, 1360 m, 1255 s, 1069 s, 836 s, 774 s cm^{-1}

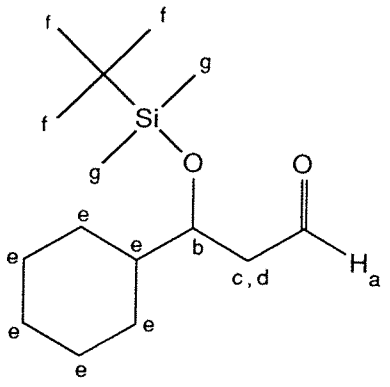
^1H NMR (270 MHz, $CDCl_3$)
H_a : 5.82 (1H, ddt, J = 16.7, 10.7, 7.2 Hz)
H_b : 5.08-4.99 (2H, m)
H_c : 3.46 (1H, br. q, J = 5.6 Hz)
H_d : 2.22 (2H, dddd, J = 7.2, 5.6, 2.7, 1.3 Hz)
H_e : 1.80-0.85 (11 H, m)
H_f : 0.90 (9H, s)
H_g : 0.05 (3H, s)
0.04 (3H, s)

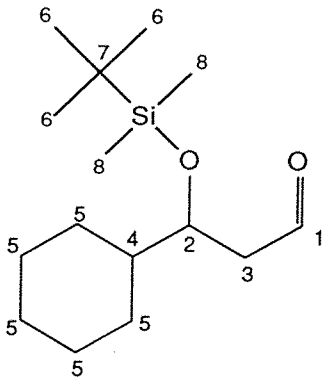
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 136.0
C_2 : 116.5
C_3 : 76.2
C_4 : 42.8
C_5 : 38.9
C_6 : 29.3, 28.1, 26.9, 26.7, 26.6
C_7 : 26.1 (3C)
C_8 : 18.3
C_9 : –4.0, –4.4

LRMS (CI mode, NH_3) m/z = 286 [$(M+NH_4)^{+\bullet}$, 2 %], 269 [$(M+H)^{+\bullet}$, 46 %], 253 (29), 227 (100), 211 (57), 169 (18), 137 (51), 116 (17), 95 (26), 74 (18).

3-Cyclohexyl-3-(*tert*-butyldimethylsilyloxy)propanal (14)

A 250 mL 3-necked flask was charged with 4-cyclohexyl-4-(*tert*-butyldimethyl silyloxy)but-1-ene (963 mg, 3.60 mmol) in MeOH (20 mL) and CH_2Cl_2(45 mL). The solution was cooled to –60°C whereupon ozone in a stream of oxygen was bubbled through the reaction mixture for 1 h. The ozone excess was removed by nitrogen current and dimethyl sulfide (5.3 mL, 72 mmol) was rapidly added. The agitation was stopped and the mixture allowed to warm to r.t.. After 12 h, the solvents were evaporated *in vacuo* and a flash chromatography (ether / petrol 3 : 97) led to a colourless aldehyde (897 mg, 3.32 mmol, 92 %).





$C_{15}H_{30}O_2Si$, MW = 270.49

IR (film) : ν = 2927 s, 2855 s, 2712 w, 1728 s, 1472 m, 1451 m, 1388 m, 1361 m, 1255 s, 836 s, 775 s cm^{-1}

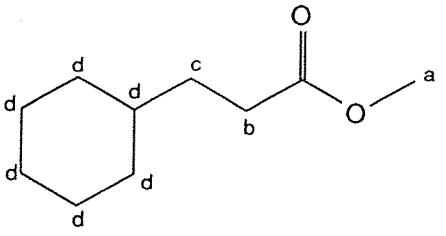
^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.80 (1H, dd, J = 3.0, 2.1 Hz)
H_b : 3.98 (1H, dt, J = 6.5, 4.8 Hz)
H_c : 2.55 (1H, ddd, J = 15.6 Hz, 3.0, 6.5 Hz)
H_d : 2.46 (1H, ddd, J = 15.6 Hz, 2.1, 4.8 Hz)
H_e : 1.85-0.90 (11H, m)
H_f : 0.88 (9H, s)
H_g : 0.07 (3H, s)
H_h : 0.05 (3H, s)

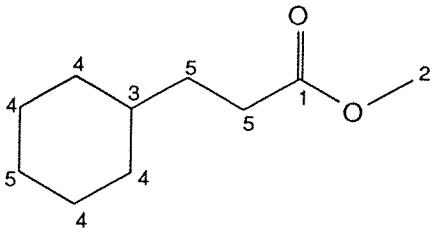
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 203.0
C_2 : 72.4
C_3 : 48.1
C_4 : 44.5
C_5 : 28.9, 28.3, 26.8, 26.5, 26.4
C_6 : 26.0 (3C)
C_7 : 18.3
C_8 : –4.3, –4.4

LRMS (CI mode, NH_3) m/z = 288 [$(M+NH_4)^{+\bullet}$, 4 %], 271 [$(M+H)^{+\bullet}$, 100 %], 227 (67), 213 (82), 169 (13), 131 (23), 121 (14), 95 (28), 74 (17).

Methyl 3-cyclohexylpropanoate (15)

Concentrated hydrochloric acid (10 mL) was added to a stirred solution of 3-cyclohexylpropionic acid (10.0 g, 64 mmol) in MeOH (150 mL). The mixture was heated to reflux and stirred overnight. The solvent was then evaporated and the cloudy solution was poured into H_2O / Et_2O (50 / 50 mL). The organic compound was extracted with ether (3 x 50 mL) and washed with an aqueous saturated solution of sodium bicarbonate (2 x 40 mL) and brine (40 mL). A flash chromatography (ether / hexanes 5 : 95) yielded the ester (10.1 g, 59.3 mmol, 93 %) as a colourless oil.





$C_{10}H_{18}O_2$, MW = 170.25

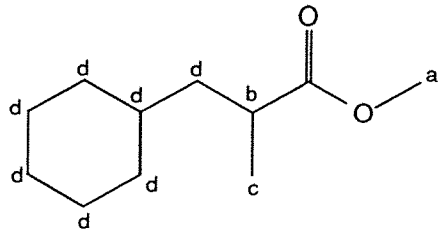
IR (film) : ν = 2923 s, 2851 s, 1740 s, 1449 s cm^{-1}

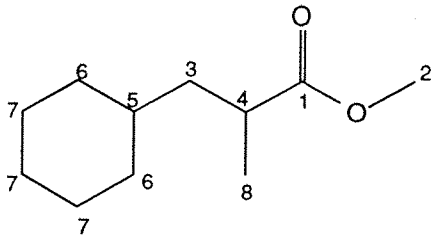
^1H NMR (270 MHz, $CDCl_3$)
H_a : 3.64 (3H, s)
H_b : 2.29 (2H, br.t, J = 7.5 Hz)
H_c : 1.50 (2H, br.q, J = 7.5 Hz)
H_d : 1.69-0.84 (11H, m)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 174.7
C_2 : 51.5
C_3 : 37.3
C_4 : 33.1 (2C), 26.3 (2C)
C_5 : 32.5, 31.8, 26.6

(±)-Methyl 2-methyl-3-cyclohexylpropanoate (16)

A 50 mL 3-necked round-bottomed flask fitted with a magnetic stirrer and nitrogen line was charged with a solution of diisopropylamine (2.37 mL, 16 mmol) in dry THF (10 mL) and cooled to -78°C. *n*-Butyllithium (2.17 M in hexane, 6 mL, 13 mmol) was then added before removing the cold bath. The mixture was allowed to warm to r.t. over 1 h, and cooled down again to –78°C. A solution of methyl 3-cyclohexylpropanoate (1.71 g, 10 mmol) in THF (5 mL) was quickly added and the mixture was stirred for 1 h between –60°C and –40°C, and then cooled to –78°C. Methyl iodide (1.25 mL, 20 mmol) was added dropwise and the reaction was stirred at –78°C for 1 h and allowed to warm up to –50°C over 1 h. Hydrolysis with water (15 mL) was then carried out. The solvents were evaporated under reduced pressure and the organic products were extracted with ether (3x10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (ether / hexanes 1 : 99) yielded the title compound as a colourless oil (1.29 g, 7.0 mmol, 70 %).





$C_{11}H_{20}O_2$, MW = 184.28

IR (film) : ν = 2922 s, 2852 s, 1738 s, 1449 s, 1377 m, 1255 m, 1194 s, 1167 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 3.67 (3H, s)
H_b : 2.61-2.50 (1H, m)
H_c : 1.13 (3H, d, J = 6.9 Hz)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 177.9
C_2 : 51.6
C_3 : 41.7

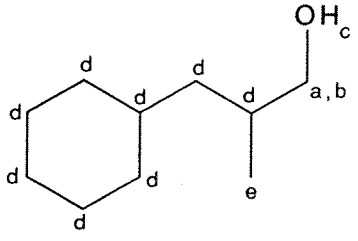
H_d : 1.80-0.80 (13H, m)

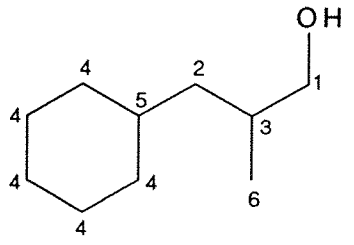
C_4 : 36.9
C_5 : 35.5
C_6 : 33.4, 33.3
C_7 : 26.7, 26.4, 26.3
C_8 : 17.7

LRMS (EI mode) *m/z* = 184 [$M^{+\bullet}$, 7 %], 153 [$(M\text{-}OCH_3)^{+\bullet}$, 9 %], 141 (51), 101 (42), 97 (16), 88 (100), 55 (27), 41 (19).

(±)-2-Methyl-3-cyclohexylpropanol (17)

To a suspension of lithium aluminium hydride (66 mg, 1.75 mmol) in dry Et_2O (5 mL) at –10°C was added (±)-methyl 2-methyl-3-cyclohexylpropanoate (423 mg, 2.3 mmol) dropwise under nitrogen. The reaction mixture was stirred for a further 15 min before being quenched by addition of water (0.07 mL), 15 % sodium hydroxide solution (0.07 mL) and water (0.2 mL). The mixture was allowed to warm to r.t. and stirred until the formation of a white precipitate. The solid was then filtered, washed with ether and the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (ether / hexanes 3 : 7) led to the alcohol (284 mg, 1.82 mmol, 79 %).





$C_{10}H_{20}O$, MW = 156.27

IR (film) : ν = 3330 br. m, 2922 s, 2849 s, 1456 s, 1374 m, 1036 s cm^{-1}

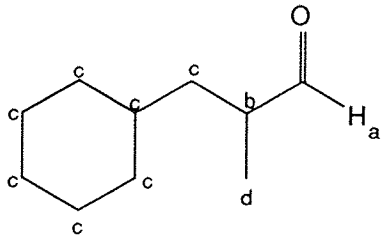
^1H NMR (270 MHz, $CDCl_3$)
H_a : 3.49 (1H, dd, *J* = 10.4, 5.4 Hz)
H_b : 3.37 (1H, dd, *J* = 10.4, 6.7 Hz)
H_c : 3.29 (1H, s)
H_d : 1.80-1.10 (14H, m)
H_e : 0.90 (3H, d, *J* = 6.8 Hz)

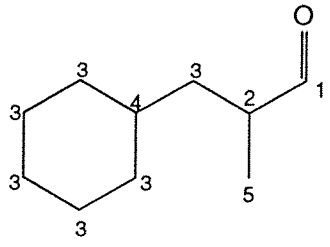
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 68.9
C_2 : 41.2
C_3 : 34.9
C_4 : 34.4, 33.2, 26.8, 26.6, 26.5
C_5 : 32.7
C_6 : 17.0

LRMS (EI mode) *m/z* = 138 [$(M\text{-}H_2O)^{+\bullet}$, 26 %], 109 (15), 96 (100), 83 (67), 69 (56), 55 (79), 41 (45), 32 (18), 28 (89).

(±)-2-Methyl-3-cyclohexylpropanal (18)

Dimethylsulfoxide (1.87 mL, 26.4 mmol) in dry CH_2Cl_2 (3.4 mL) was slowly added to a solution of oxalyl chloride (1.53 mL, 17.6 mmol) in dry CH_2Cl_2 (14.2 mL) between –60°C and –50°C. After 5 min, 2-methyl-3-cyclohexylpropanol (1.37 g, 8.8 mmol) in dry CH_2Cl_2 (1.7 mL) was added, resulting in the formation of a pale pink precipitate. The mixture was stirred at –50°C for 20 min before adding *N*-methylmorpholine (6.77 mL, 61.6 mmol), then stirred at –50°C for 5 min, at 0°C for 1 h and poured into an ice-cooled HCl solution (1 M, 5 mL). The organic layer was separated, washed with an aqueous saturated solution of sodium bicarbonate (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (ether / hexanes 5 : 95) gave the aldehyde as a pale yellow oil (1.11 g, 7.2 mmol, 82 %).





$C_{10}H_{18}O$, MW = 154.25

IR (film) : ν = 2923 s, 2852 s, 2708 w, 1727 s, 1450 m cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 9.58 (1H, d, J = 2.1 Hz)
H_b : 2.43 (1H, m)
H_c : 1.83-0.84 (13H, m)
H_d : 1.06 (3H, d, J = 7.0 Hz)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 205.7
C_2 : 43.9
C_3 : 38.4, 33.8, 33.1, 26.6, 26.4 (2C)
C_4 : 35.1
C5 : 13.9

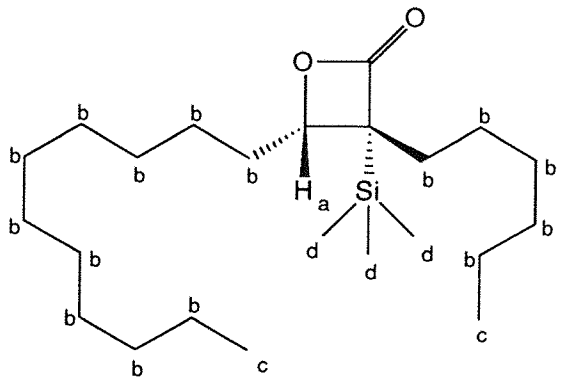
LRMS (EI mode) m/z = 152[$(M-H_2)^{+\bullet}$, 2 %], 127 (30), 97 (100), 87 (23), 74 (46), 55 (50), 41 (23).

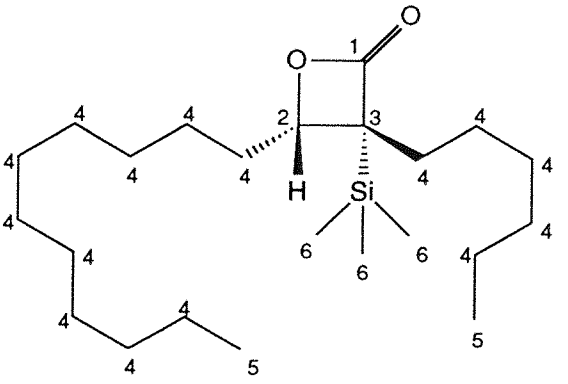
(±)-3-Hexyl-3-(trimethylsilyl)-4-undecyl-2-oxetanone (19)

A flame-dried 50 mL round-bottomed flask, fitted with a magnetic stirrer and nitrogen line, was charged with a solution of dodecanal (94 mg, 0.5 mmol) in dry Et_2O (2 mL) and cooled down to –55°C. Ethylaluminium dichloride (1 M in hexanes, 0.65 mL, 0.65 mmol) was added dropwise, maintaining the temperature below –50°C. The mixture was stirred for 15 min, cooled dohexyl (trimethylsilyl)ketene (198 mg, 1 mmol) in dry Et_2O (0.5 mL) was added. The reaction was allowed to warm up to –20°C and maintained between –30°C and –20°C for 1 h before adding water (3 mL). The crude product was extracted with ether (3x5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography on silica gel (ether / hexanes 1 : 99) yielded the title oxetanone (99 mg, 0.26 mmol, 52 %) as one major diastereoisomer.

Major isomer :

(3*R,4*S**)-3-hexyl-3-(trimethylsilyl)-4-undecyl-2-oxetanone**





$C_{23}H_{46}O_2Si$, MW = 382.71

IR (film) : ν = 2926 s, 2856 s, 1804 s, 1468 m, 1252 m, 845 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.34 (1H, dd, J = 10.2, 3.7 Hz)
H_b : 1.90-1.20 (32H, m)
H_c : 0.88 (6H, distorted t)
H_d : 0.22 (9H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 174.3
C_2 : 80.2
C_3 : 55.3
C_4 : 32.8, 32.0, 31.7, 30.9, 29.7 (3C) 29.6 (2C), 29.5, 29.4, 26.8, 26.4 22.8, 22.7
C_5 : 14.2, 14.1
C_6 : –1.2 (3C)

LRMS (CI mode, NH_3) *m/z* = 400 [$(M+NH_4)^{+\bullet}$, 30 %], 383 [$(M+H)^{+\bullet}$, 30 %], 293 (100), 264 (15), 245 (40), 173 (21), 90 (33), 73 (22).

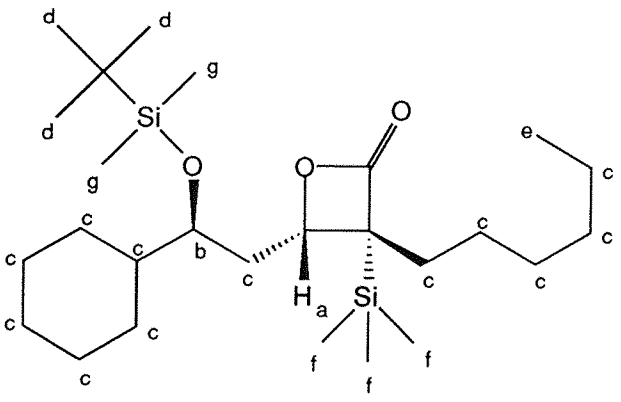
HRMS (CI mode, NH_3) : Found, $M^{+\bullet}$, 383.33. $C_{23}H_{46}O_2Si$ requires M, 382.71.

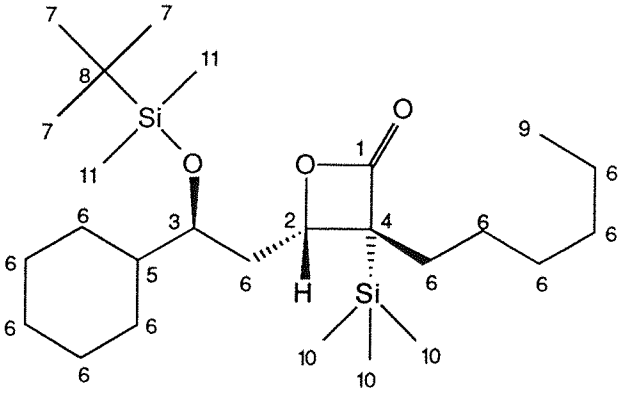
[2+2] Cycloaddition of aldehyde 14 with *n*-hexyl(trimethylsilyl)ketene (20)

A flame-dried 50 mL round-bottomed flask, fitted with a magnetic stirrer and nitrogen line, was charged with a solution of 3-(*tert*-butyldimethylsiloxy)-3-cyclohexylpropanal (1 eq) in dry Et_2O and cooled down to –50°C. The Lewis acid (1.1 eq) was added dropwise, maintaining the temperature below –40°C. The mixture was stirred for 5 min before adding a solution of *n*-hexyl(trimethylsilyl)ketene (1.3 eq) in Et_2O. The reaction was allowed to warm up, followed by TLC and stopped by addition of water. The extraction was carried out with Et_2O, the organic layer was dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The oxetanones were purified by column chromatography eluting with ether / hexanes (1 : 99) and were obtained as an inseparable mixture of diastereoisomers.

Major isomer :

(3*R,4*S**)-3-Hexyl-3-(trimethylsilyl)-4-[(*S**)-2'-(*tert*-butyldimethylsiloxy) -2'-cyclohexylethyl]-2-oxetanone**





$C_{26}H_{52}O_3Si_2$, MW = 468.87

mp = 86-88°C

IR (film) : ν = 2928 s, 2855 s, 1805 s, 1463 m, 1253 s, 1070 s, 844 s, 775 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.62 (1H, dd, J = 11.6, 1.9 Hz)
H_b : 3.73-3.66 (1H, m)
H_c : 1.95-1.05 (23H, m)
H_d : 0.91 (9H, s)
H_e : 0.89 (3H, t-like)
H_f : 0.22 (9H, s)
H_g : 0.08 (3H, s)
0.07 (3H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 174.5
C_2 : 76.4
C_3 : 72.7
C_4 : 54.5
C_5 : 44.8
C_6 : 35.7, 31.7, 30.6, 29.7, 29.0
27.1, 27.0, 26.8, 26.6, 26.3, 22.7
C_7 : 26.1 (3C)
C_8 : 18.3
C_9 : 14.2
C_{10} : –1.2 (3C)
C_{11} : –4.1, –4.6

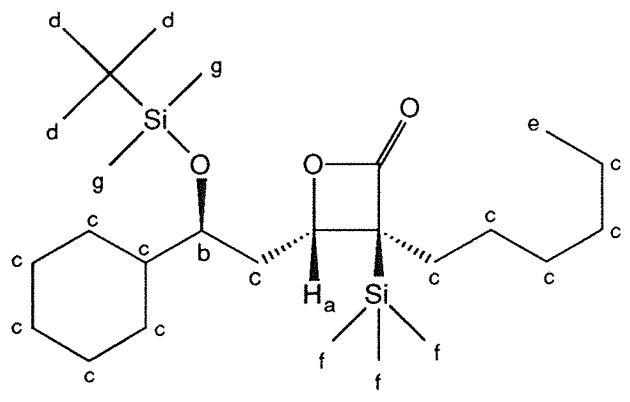
LRMS (CI mode, NH_3) m/z = 486 [$(M+NH_4)^{+\bullet}$, 2 %], 469 [$(M+H)^{+\bullet}$, 10 %], 337 (22) 271 (76), 227 (81), 213 (100).

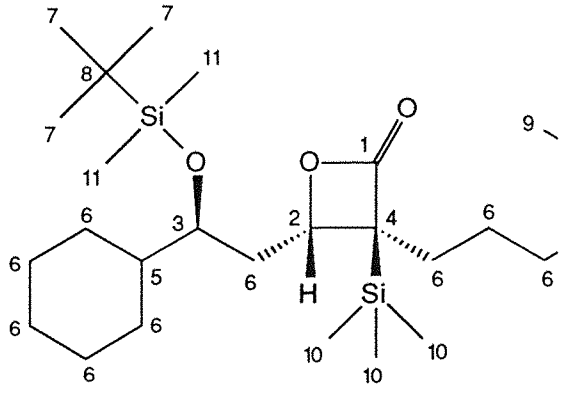
HRMS (EI mode) : Found, $M^{+\bullet}$, 468.34. $C_{26}H_{52}O_3Si_2$ requires M, 468.87.

Found : C 66.44 %, H 11.15 %. $C_{26}H_{52}O_3Si_2$ requires C 66.60 %, H 11.18 %.

Minor isomer :

(3*S,4*S**)-3-Hexyl-3-(trimethylsilyl)-4-[(*S**)-2'-(*tert*-butyldimethylsiloxy) -2'-cyclohexylethyl]-2-oxetanone**



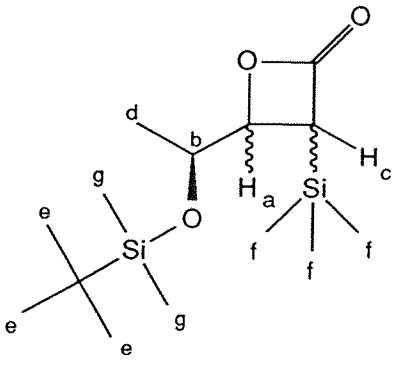


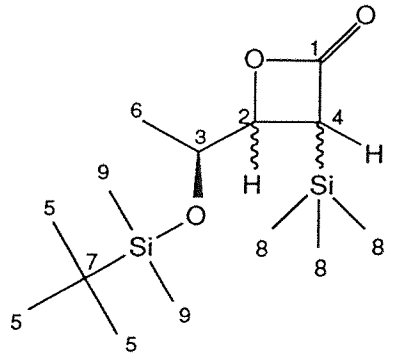
^{1}H NMR (270 MHz, $CDCl_3$)
H_a : 4.54 (1H, dd, J = 11.0, 2.1 Hz)
H_b : 3.78-3.70 (1H, m)
H_c : 1.95-1.05 (23H, m)
H_d : 0.91 (9H, s)
H_e : 0.88 (3H, distorted t)
H_f : 0.17 (9H, s)
H_g : 0.07 (3H, s)
0.06 (3H, s)

^{13}C NMR (270 MHz, $CDCl_3$)
C_1 : 176.1
C_2 : 73.9
C_3 : 72.2
C_4 : 53.0
C_5 : 45.0
C_6 : 31.9, 31.5, 30.1, 29.2, 27.9
27.5, 27.4, 26.8, 22.7, 22.5, 20.6
C_7 : 26.1 (3C)
C_8 : 18.3
C_9 : 14.4
C_{10} : –2.6 (3C)
C_{11} : –4.0, –3.2

[2+2] Cycloaddition of aldehyde 5 with trimethylsilylketene (21)

A flame-dried 50 mL round-bottom flask was charged with a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal (94 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) and cooled down to -40°C, before adding a solution of $MgBr_2.Et_2O$ (0.71 M in 25 % benzene / ether, 0.85 mL, 0.6 mmol) in CH_2Cl_2 (1 mL). After 15 min, a solution of trimethylsilylketene (69 mg, 0.6 mmol) in 1 mL of CH_2Cl_2 was added. The reaction mixture was stirred at -42°C under nitrogen for 7h and then quenched at that temperature by addition of 1 mL water. After warming up to r.t., the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (3x2 mL) and the combined organics were dried over $MgSO_4$, filtered and evaporated in vacuo. Column chromatography (petrol / ether 96 / 4) yielded 2-oxetanones as a 78 : 22 mixture of diastereoisomers (91 mg, 0.3 mmol, 60 %).





Major isomer :

$C_{14}H_{30}O_3Si_2$, MW = 302.56

IR (film) : ν = 2957 s, 2931 s, 2897 s, 2858 s, 1816 s, 1473 m, 1374 m, 1254 s, 1101 s, 839 s, 778 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.08 (1H, dd, J = 6.2, 4.1 Hz)
H_b : 3.92 (1H, quint., J = 6.2 Hz)
H_c : 2.95 (1H, d, J = 4.1 Hz)
H_d : 1.16 (3H, d, J = 6.2 Hz)
H_e : 0.89 (9H, s)
H_f : 0.18 (9H, s)
H_g : 0.08 (6H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 170.7
C_2 : 75.6
C_3 : 70.1
C_4 : 44.3
C_5 : 25.9 (3C)
C_6 : 18.9
C_7 : 18.2
C_8 : -2.8 (3C)
C_9 : -4.5, -4.6

Minor isomer :

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.16 (1H, dd, J = 6.4, 3.9 Hz)
H_b : 3.92 (1H, quint., J = 6.4 Hz)
H_c : 3.24 (1H, d, J = 3.9 Hz)
H_d : 1.16 (3H, d, J = 6.4 Hz)
H_e : 0.88 (9H, s)
H_f : 0.18 (9H, s)
H_g : 0.08 (6H, s)

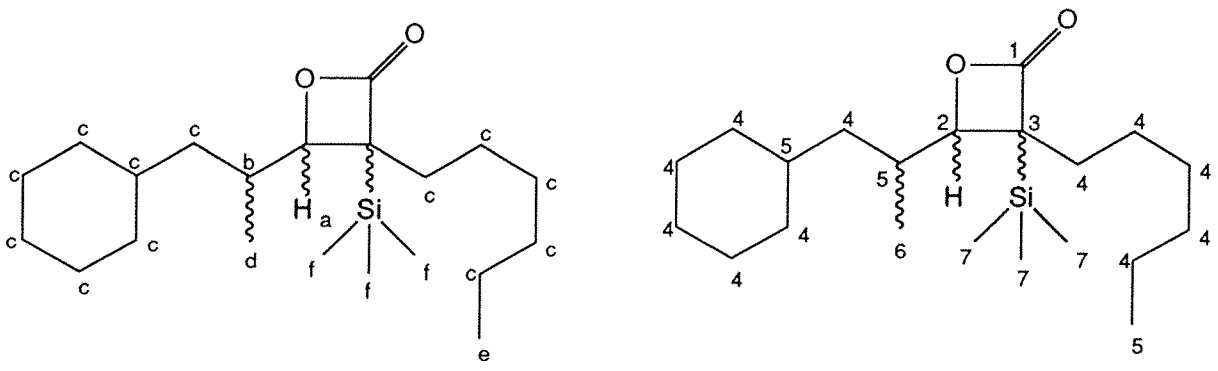
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 170.7
C_2 : 75.0
C_3 : 67.3
C_4 : 42.4
C_5 : 25.9 (3C)
C_6 : 18.9
C_7 : 18.7
C_8 : -2.8 (3C)
C_9 : -4.5, -4.6

(±)-3-Hexyl-3-(trimethylsilyl)-4-[1'-methyl-2'-cyclohexylethyl]-2-oxetanone (22)

A flame-dried 50 mL round-bottomed flask, fitted with a magnetic stirrer and nitrogen line, was charged with a solution of 2-methyl-3-cyclohexylpropanal (154 mg, 1.00 mmol) in dry Et_2O (3 mL) and cooled down to –55°C. Ethylaluminium dichloride (1 M in hexanes, 1.3 mL, 1.3 mmol) was added dropwise, maintaining the temperature below –50°C. The mixture was stirred for 15 min, cooled down to –60°C and a solution of *n*-hexyl (trimethylsilyl)ketene (496 mg, 2.5 mmol) in dry Et_2O (1 mL) was added. The reaction was allowed to warm up to –20°C and maintained between –30°C and –20°C for 2 h before adding water (5 mL). The crude

product was extracted with ether (3x10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography on silica gel (ether / hexanes 1 : 99) yielded the title oxetanone (189 mg, 0.54 mmol, 54 %) as one major diastereoisomer.

Major isomer :



$C_{21}H_{40}O_2Si$, MW = 352.64

IR (film) : ν = 2925 s, 2854 s, 1803 s, 1450 m, 1253 m, 1116 m, 845 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 3.97 (1H, d, J = 11.0 Hz)
H_b : 2.20-2.02 (1H, m)
H_c : 1.80-1.20 (23H, m)
H_d : 1.00 (3H, d, J = 6.4 Hz)
H_e : 0.88 (3H, distorted t)
H_f : 0.24 (9H, s)

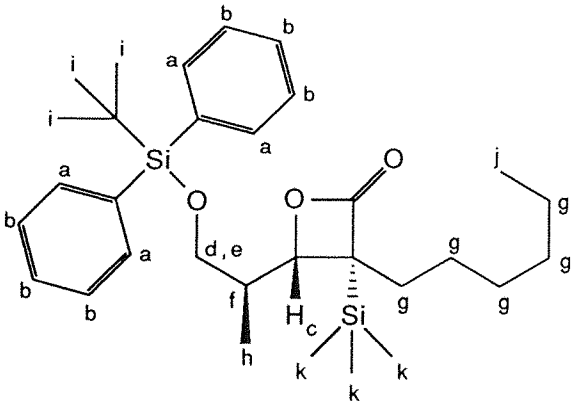
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 170.3
C_2 : 84.4
C_3 : 55.2
C_4 : 39.7, 35.4, 34.5, 32.3, 31.7, 29.
26.7 (2C), 26.5, 26.3, 22.7
C_5 : 34.8, 32.4
C_6 : 15.5, 14.1
C_7 : –1.1 (3C)

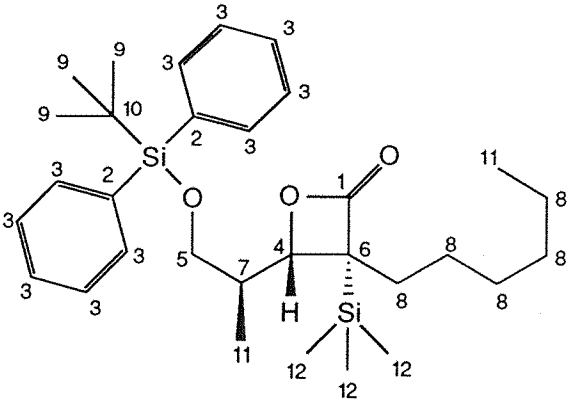
LRMS (FAB mode) m/z = 353 [$(M+H)^{+\bullet}$, 11 %], 337 [$(M-CH_3)^{+\bullet}$, 11 %], 263 (22), 199 (22), 95 (16), 73 (100).

HRMS (CI mode) : Found, $(M+NH4)^{+\bullet}$, 370.32. $C_{21}H_{40}O_2Si$, requires 370.68.

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*tert*-butyldiphenylsiloxy) ethyl]-2-oxetanone (23)

A flame-dried 50 mL round-bottomed flask, fitted with a magnetic stirrer and nitrogen line, was charged with a solution of (*tert*-butyldiphenylsiloxy)propanal (163 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) and cooled to –50°C. Ethylaluminium dichloride (1 M in hexanes, 0.65 mL, 0.65 mmol) was added dropwise, maintaining the temperature below –40°C. The mixture was stirred for 15 min and a solution of *n*-hexyl(trimethylsilyl) ketene (129 mg, 0.65 mmol) in dry CH_2Cl_2 (1 mL) was added. The reaction was allowed to warm up to –10°C over 2 h and was stopped by addition of water (5 mL). The crude product was extracted with ether (3x10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography on silica gel (ether / hexanes 1 : 99) yielded the title oxetanone (107 mg, 0.20 mmol, 40 %).





$C_{31}H_{48}O_3Si_2$, MW = 524.90

$[\alpha_D]$ (24°C) = +25.0° (c = 0.65 in $CHCl_3$)

IR (film) : ν = 3072 w, 3050 w, 2931 s, 2858 s, 1801 s, 1472 m, 1428 m, 1255 m, 1113 s, 845 s, 740 m, 702 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
- H_a : 7.68-7.63 (4H, m)
- H_b : 7.46-7.41 (6H, m)
- H_c : 4.43 (1H, d, J = 11.2 Hz)
- H_d : 3.59 (1H, dd, J = 10.0 Hz, 3.1 Hz)
- H_e : 3.50 (1H, dd, J = 10.0 Hz, 4.4 Hz)
- H_f : 2.20 (1H, dddq, J = 6.8, 11.2, 4.4, 3.1 Hz)
- H_g : 1.80-1.20 (10H, m)
- H_h : 1.21 (3H, d, J = 6.8 Hz)
- H_i : 1.10 (9H, s)
- H_j : 0.88 (3H, distorted t)
- H_k : 0.12 (9H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
- C_1 : 204.7
- C_2 : 133.1 (2C)
- C_3 : 135.7 (4C), 130.0 (2C), 127.8 (4C)
- C_4 : 80.1
- C_5 : 64.7
- C_6 : 55.4
- C_7 : 37.7
- C_8 : 31.7, 30.3, 29.7, 26.4, 22.8
- C_9 : 26.9 (3C)
- C_{10} : 19.5
- C_{11} : 14.2, 14.1
- C_{12} : –1.4 (3C)

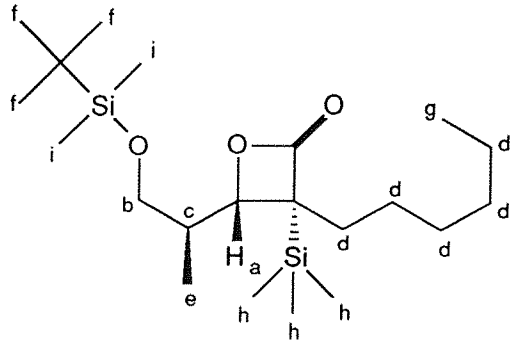
LRMS (EI mode) m/z = 509 [$(M\text{-}CH_3)^{+\bullet}$, 3 %], 467 (18), 299 (42), 269 (100), 239 (49), 199 (49), 191 (48), 183 (55), 135 (27), 105 (15), 73 (32).

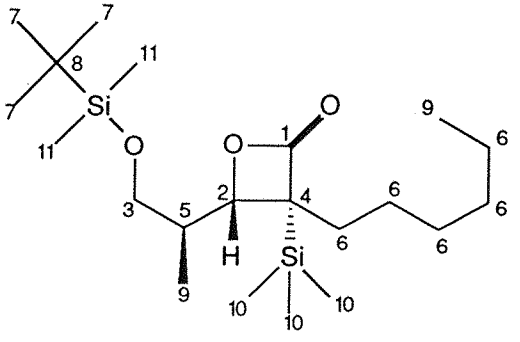
[2+2] Cycloaddition of aldehyde 9 with *n*-hexyl(trimethylsilyl)ketene (24)

A flame-dried 50 mL round-bottomed flask, fitted with a magnetic stirrer and nitrogen line, was charged with a solution of (*S*)-2-methyl-3-(*tert*-butyldimethylsiloxy)propanal (1 eq) in dry Et_2O and cooled down to –50°C. The Lewis acid (1.1 eq) was added dropwise, maintaining the temperature below –40°C. The mixture was stirred for 5 min before adding a solution of *n*-hexyl(trimethylsilyl)ketene (1.3 eq) in Et_2O. The reaction was allowed to warm up, followed by TLC and stopped by addition of water. The extraction was carried out with Et_2O, the organic layer was dried over magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo*. The oxetanones were purified by column chromatography eluting with ether / hexanes (1 : 99) and were obtained as an inseparable mixture of diastereoisomers.

Major isomer :

(3*R*,4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*tert*-butyldimethyl siloxy) ethyl]-2-oxetanone





$C_{21}H_{44}O_3Si_2$, MW = 400.76

$[\alpha_D]$ (24°C) = +26.9° (*c* = 0.7 in $CHCl_3$)

IR (film) : ν = 2956 s, 2931 s, 2858 s, 1802 s, 1463 m, 1254 s, 1115 s, 1033 m, 888 m, 840 s, 778 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.35 (1H, d, *J* = 10.8 Hz)
H_b : 3.53 (2H, d, *J* = 4.2 Hz)
H_c : 2.20 (1H, dtq, J = 6.6, 4.2, 10.8 Hz)
H_d : 1.80-1.20 (10H, m)
H_e : 1.09 (3H, d, *J* = 6.6 Hz)
H_f : 0.90 (9H, s)
H_g : 0.89 (3H, distorted t)
H_h : 0.23 (9H, s)
H_i : 0.06 (6H,s)

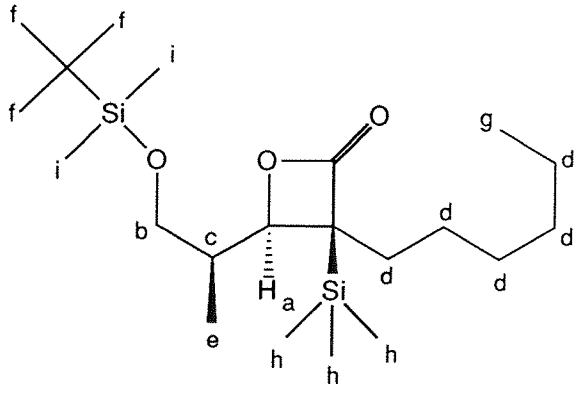
^{13}C NMR (270 MHz, $CDCl_3$)
C_1 : 174.2
C_2 : 80.5
C_3 : 64.7
C_4 : 55.5
C_5 : 37.5
C_6 : 31.8, 30.2, 29.7, 26.4, 22.7
C_7 : 26.0 (3C)
C_8 : 18.4
C_9 : 14.2, 13.9
C_{10} : –1.4 (3C)
C_{11} : –3.4 (2C)

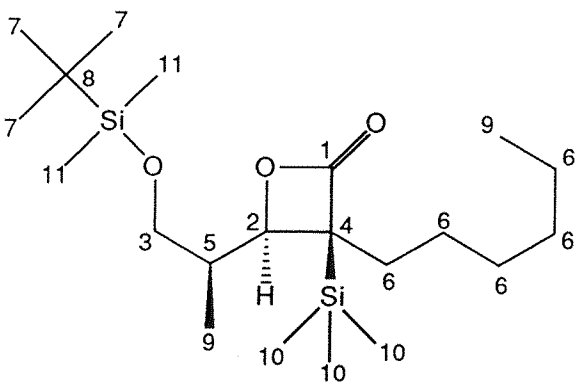
LRMS (FAB mode) *m/z* = 401 [$(M+H)^{+\bullet}$, 8 %], 311 (15), 145 (45), 115 (12), 89 (22), 73 (100).

HRMS (CI mode) : Found, $M^{+\bullet}$, 401.29. $C_{21}H_{44}O_3Si_2$, requires 400.76.

Minor isomer :

(3*S*,4*R*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*tert*-butyldimethylsiloxy) ethyl]-2-oxetanone



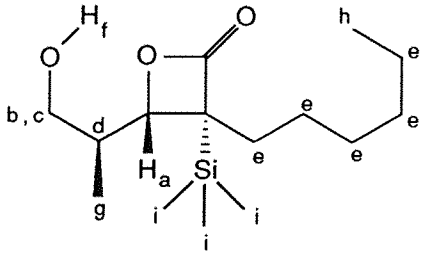


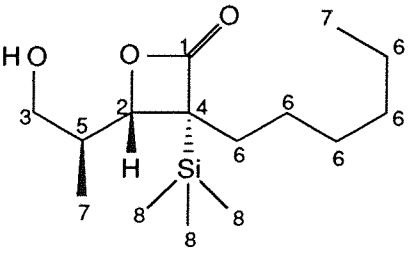
^{1}H NMR (270 MHz, $CDCl_3$)
H_a : 4.27 (1H, d, J = 8.9 Hz)
H_b : 3.53 (2H, d, J = 4.2 Hz)
H_c : 2.20 (1H, qtd, J = 6.6, 4.2, 8.9 Hz)
H_d : 1.80-1.20 (10H, m)
H_e : 1.10 (3H, d, J = 6.6 Hz)
H_f : 0.90 (9H, s)
H_g : 0.88 (3H, distorted t)
H_h : 0.17 (9H, s)
H_i : 0.05 (6H,s)

^{13}C NMR (270 MHz, $CDCl_3$)
C_1 : 174.2
C_2 : 77.8
C_3 : 64.4
C_4 : 53.0
C_5 : 36.4
C_6 : 31.6, 30.4, 27.4, 27.0, 25.9
C_7 : 26.0 (3C)
C_8 : 18.4
C_9 : 13.9, 13.6
C_{10} : –1.4 (3C)
C_{11} : –2.6 (2C)

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy) ethyl]-2-oxetanone (25)

Hydrofluoric acid (48 %, 1.6 mL, 50 mmol) was added to a stirred solution of 3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*tert*-butyldimethylsiloxy)ethyl]-2-oxetanone (400 mg, 1 mmol) in acetonitrile (10 mL) in a propylene bottle at 0°C. The resuting mixture was stirred for 3 h, diluted with ether (70 mL) and slowly poured into a saturated aqueous solution of sodium bicarbonate (70 mL). The organic layer was extracted with ether (2 x 20 mL), washed with water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica gel eluting with ether / petrol (3 : 7) to leave the title compound as a colourless oil (242 mg, 0.84 mmol, 84 %).





$C_{15}H_{30}O_3Si$, MW = 286.49

$[\alpha_D]$ (24°C) = +49.0° (c = 1.0 in $CHCl_3$)

IR (film) : ν = 3498 br. m, 2932 s, 2859 s, 1802 s, 1779 s, 1461 m, 1255 m, 1117 m, 845 s cm^{-1}

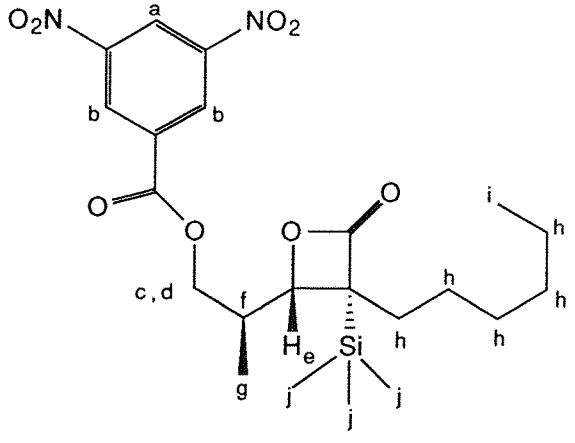
^{1}H NMR (270 MHz, $CDCl_3$)
H_a : 4.24 (1H, d, J = 11.2 Hz)
H_b : 3.62 (1H, dd, J = 10.4, 4.2 Hz)
H_c : 3.51 (1H, dd, J = 10.4, 6.0 Hz)
H_d : 2.24 (1H, dddq, J = 4.2, 6.0, 11.2, 6.6 Hz)
H_e : 1.80-1.30 (10H, m)
H_f : 1.52 (1H, br. s)
H_g : 1.14 (3H, d, J = 6.6 Hz)
H_h : 0.89 (3H, distorted t)
H_i : 0.24 (9H, s)

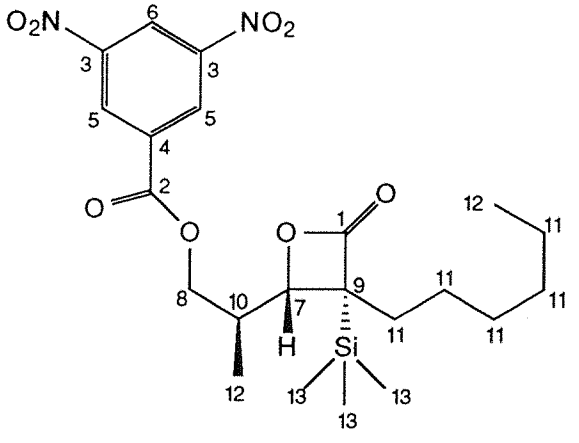
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 174.2
C_2 : 80.5
C_3 : 64.6
C_4 : 55.8
C_5 : 37.5
C_6 : 31.7, 30.3, 29.7, 26.5, 22.7
C_7 : 14.2, 13.7
C_8 : –1.4 (3C)

LRMS (CI mode, NH_3) m/z = 304 [$(M+NH_4)^{+\bullet}$, 23 %], 287 [$(M+H)^{+\bullet}$, 42 %], 269 (23), 256 (15) 197 (100), 166 (17), 90 (30), 73 (25).

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(3,5-dinitrobenzoyloxy)ethyl]-2-oxetanone (26)

To a solution of (3*S*, 4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy) ethyl]-2-oxetanone (213 mg, 0.74 mmol) in THF (12 mL) under nitrogen was added 3,5-dinitrobenzoyl chloride (205 mg, 0.89 mmol) followed by pyridine (78 µL, 0.96 mmol). The reaction was stirred at r.t. overnight. The mixture was poured into water (20 mL) and the extraction was carried out with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ether / hexanes 5 : 95) yielded the compound (169 mg, 0.35 mmol, 47 %) as a yellow oil.





$C_{22}H_{32}O_8N_2Si$, MW = 480.59

$[\alpha_D]$ (24°C) = +19.8° (c = 0.85 in $CHCl_3$)

IR (film) : ν = 3105 m, 2931 s, 2857 s, 1800 s, 1740 s, 1630 m, 1599 w, 1548 s, 1462 m, 1344 s,1279 s, 1164 s, 846 s, 730 s cm^{-1}

^{1}H NMR (270 MHz, $CDCl_3$)
H_a : 9.28 (1H, t, J = 2.1 Hz)
H_b : 9.16 (2H, d, J = 2.1 Hz)
H_c : 4.45 (1H, dd J = 11.1,3.9 Hz)

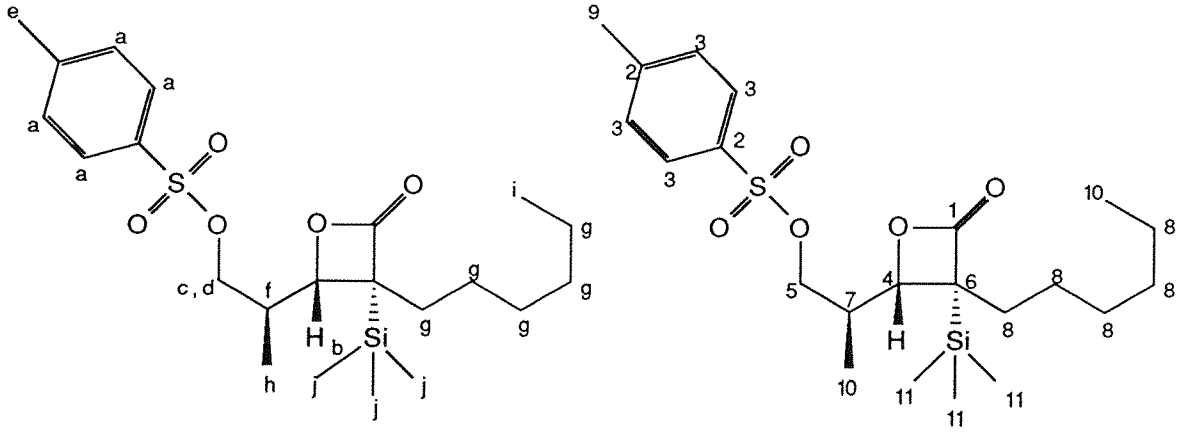
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 173.2
C_2 : 162.5
C_3 : 149.0 (2C)

H_d : 4.29 (1H, dd J = 11.1, 6.8 Hz)
H_e : 4.25 (1H, d, J = 11.0 Hz)
H_f : 2.60 (1H, dddq, J = 6.6, 11.0, 6.8, 3.9 Hz)
H_g : 1.29 (3H, d, J = 6.6 Hz)
H_h : 1.40-1.20 (10H, m)
H_i : 0.85 (3H, distorted t)
H_j : 0.29 (9H, s)

C_4 : 133.3
C_5 : 129.5 (2C)
C_6 : 123.0
C_7 : 79.1
C_8 : 67.7
C_9 : 56.0
C_{10} : 35.3
C_{11} : 31.7, 30.3, 29.6
26.5, 22.7
C_{12} : 14.4, 14.2
C_{13} : –1.3 (3C)

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*p*-toluenesulfonyloxy)ethyl]-2-oxetanone (27)

To a stirred solution of (3*S*, 4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy)ethyl]-2-oxetanone (53 mg, 0.18 mmol) and triethylamine (42 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) under nitrogen was added TsCl (60 mg, 0.31 mmol) at r.t.. 4-Dimethylaminoipyridine (5 mg) was then added and the mixture was stirred for 20 h. Water (1 mL) and Et_2O (1 mL) were added and the extraction was carried out with Et_2O (3x2 mL). The organic layer was washed with a saturated ammonium chloride solution (2x5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ether / hexanes 5 : 95) yielded the title compound (53 mg, 0.12 mmol, 65 %).



$C_{22}H_{36}O_5SiS$, MW = 440.68

$[\alpha_D]$ (24°C) = +24.6° (c = 1.1 in $CHCl_3$)

IR (film) : ν = 2931 s, 2858 s, 1798 s, 1598 m, 1468 m, 1366 m,1257 m, 1178 s, 908 s, 845 m, 733 s cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 7.78 (2H, br d, J = 8.2 Hz)
7.37 (2H, br d, J = 8.2 Hz)
H_b : 4.19 (1H, d, J = 10.8 Hz)
H_c : 3.91 (1H, dd, J = 9.5, 5.4 Hz)
H_d : 3.87 (1H, dd J = 9.5, 5.4 Hz)
H_e : 2.47 (3H, s)

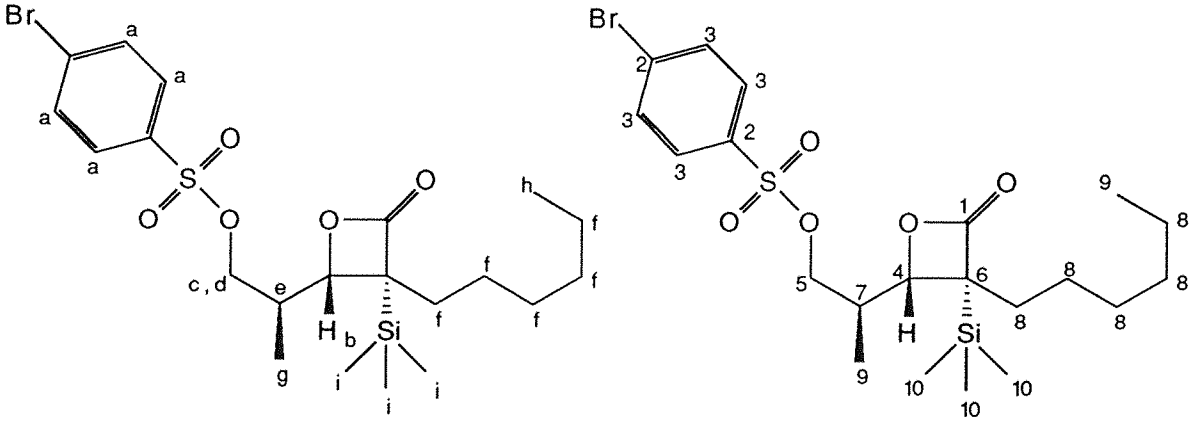
^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 173.4
C_2 : 145.5, 132.4
C_3 : 130.2 (2C), 128.1 (2C)
C_4 : 79.0
C_5 : 71.2
C_6 : 56.2

H_f : 2.40 (1H, dtq, J = 6.6, 5.4, 10.8 Hz)
H_g : 1.80-1.20 (10H, m)
H_h : 1.07 (3H, d, J = 6.6 Hz)
H_i : 0.91 (3H, distorted t)
H_j : 0.18 (9H, s)

C_7 : 35.0
C_8 : 31.7, 29.7, 29.5, 26.3, 22.8
C_9 : 21.9
C_{10} : 14.2, 13.4
C_{11} : –1.5 (3C)

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(*p*-bromobenzenesulfonyloxy) ethyl]-2-oxetanone (28)

To a stirred solution of (3*S*, 4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy)ethyl]-2-oxetanone (55 mg, 0.2 mmol) and triethylamine (61 µL, 0.44 mmol) in CH_2Cl_2 (2 mL) under nitrogen was added *p*-bromobenzenesulfonyl chloride (87 mg, 0.34 mmol) at r.t.. and 4-dimethylaminopyridine (20 mg) and the mixture stirred for 20 h. Water (2 mL) and Et_2O (2 mL) were poured into the mixture and the extraction was carried out with Et_2O (3x2 mL). The organic layer was washed with a saturated ammonium chloride solution (2x10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ether / hexanes 5 : 95) yielded the title compound (73 mg, 0.14 mmol, 72 %).



$C_{21}H_{33}O_5SiSBr$, MW = 505.55

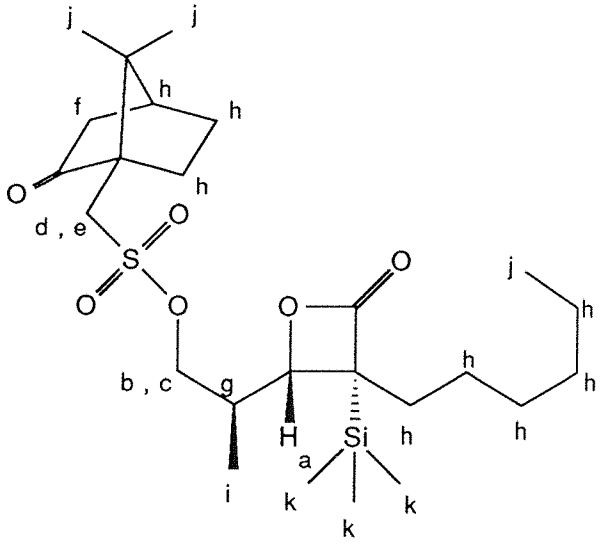
IR (film) : ν = 2931 s, 2857 s, 1801 s, 1577 m, 1468 m, 1392 m, 1369 m, 1255 m, 1189 s, 844 s 738 m cm^{-1}

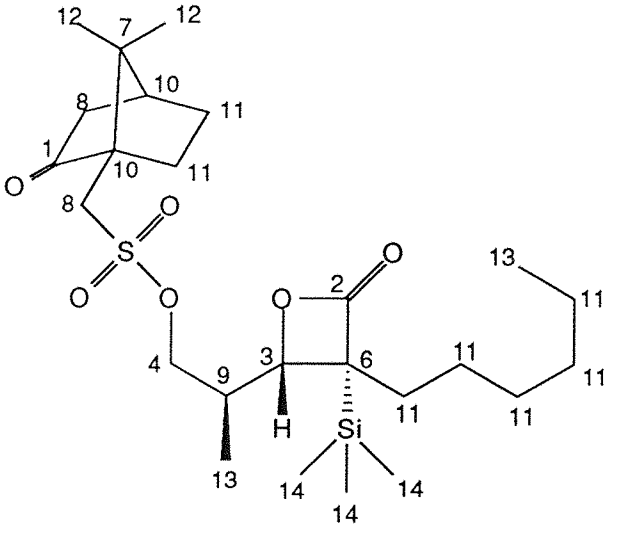
^1H NMR (270 MHz, $CDCl_3$)
H_a : 7.79-7.71 (4H, m)
H_b : 4.19 (1H, d, J = 10.8 Hz)
H_c : 3.95 (1H, dd, J = 9.5, 5.4 Hz)
H_d : 3.91 (1H, dd, J = 9.5, 5.4 Hz)
H_e : 2.45 (1H, dtq, J = 6.6, 5.4, 10.8 Hz)
H_f : 1.80-1.20 (10H, m)
H_g : 1.09 (3H, d, J = 6.6 Hz)
H_h : 0.91 (3H, distorted t)
H_i : 0.19 (9H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 173.1
C_2 : 134.4, 129.8
C_3 : 133.0 (2C), 129.6 (2C)
C_4 : 78.8
C_5 : 71.6
C_6 : 56.3
C_7 : 35.0
C_8 : 31.7, 29.7, 29.6, 26.4, 22.8
C_9 : 14.2, 13.5
C_{10} : –1.5 (3C)

(3*R*,4*S*)-3-Hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(-)-10-camphorsulfonyloxyethyl]-2-oxetanone (29)

To a stirred solution of (3*S*, 4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy)ethyl]-2-oxetanone (34 mg, 0.12 mmol) and triethylamine (24 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) under nitrogen was added (-)-10-camphorsulfonyl chloride (90 mg, 0.36 mmol) at r.t.. and 4-dimethylaminopyridine (10 mg) and the mixture stirred for 48 h. Water (1 mL) and Et_2O (1 mL) were poured into the mixture and the extraction was carried out with Et_2O (3x2 mL). The organic layer was washed with a saturated ammonium chloride solution (2x5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (ether / hexanes 5 : 95) yielded the title compound (36 mg, 0.07 mmol, 61 %).





$C_{25}H_{44}O_6SiS$, MW = 505.78

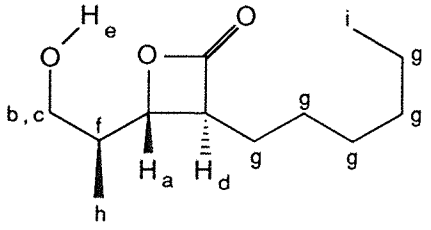
IR (film) : ν = 2929 s, 1799 s, 1746 s, 1461 m, 1363 m, 1259 m, 1169 m, 1114 m, 977 s, 844 m cm^{-1}

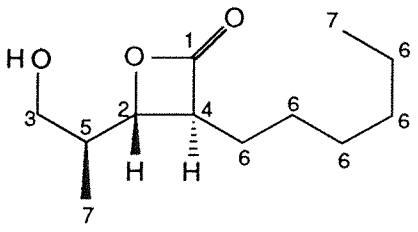
^1H NMR (270 MHz, $CDCl_3$)
- H_a : 4.28 (1H, d, J = 10.8 Hz)
- H_b : 4.24 (1H, 1/2 ABX, dd, J_{AB} = 9.8 Hz, J = 5.2 Hz)
- H_c : 4.18 (1H, 1/2 ABX, dd, J_{AB} = 9.8 Hz, J = 4.9 Hz)
- H_d : 3.56 (1H, 1/2 AB, d, J_{AB} = 15.0 Hz)
- H_e : 3.99 (1H, 1/2 AB, d, J_{AB} = 15.0 Hz)
- H_f : 2.53-2.33 (2H, m)
- H_g : 2.10 (1H, qddd, J = 6.6, 10.8, 5.2, 4.9 Hz)
- H_h : 2.20-1.20 (15H, m)
- H_i : 1.17 (3H, d, J = 6.6 Hz)
- H_j : 1.10 (3H, s)
  0.88 (6H, distorted t)
- H_k : 0.24 (9H, s)

^{13}C NMR (300 MHz, $CDCl_3$)
- C_1 : 214.6
- C_2 : 173.5
- C_3 : 78.8
- C_4 : 71.1
- C_5 : 58.1
- C_6 : 56.2
- C_7 : 48.3
- C_8 : 47.1, 42.7
- C_9 : 42.8
- C_{10} : 35.3
- C_{11} : 31.7, 29.7, 29.6, 27.0, 26.3, 25.1, 22.7
- C_{12} : 19.9, 19.8
- C_{13} : 14.2, 13.6
- C_{14} : -1.5 (3C)

(3*S*,4*S*)-3-Hexyl-4-[(*S*)-1'-methyl-2'(hydroxy)ethyl]-2-oxetanone (30)

To a stirred solution of (3*S*, 4*S*)-3-hexyl-3-(trimethylsilyl)-4-[(*S*)-1'-methyl-2'-(hydroxy)ethyl]-2-oxetanone (227 mg, 0.79 mmol) in THF (7 mL) at –90°C under nitrogen was slowly added a solution of TBAF (1.0 M in THF, 238 mg, 0.91 mmol) in THF (3 mL). Once the addition was complete, the mixture was stirred for a further 15 min at –90°C and then water (5 mL) was added. The extraction was carried out with Et_2O (3x20 mL) and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (ether / hexanes 3 : 7) yielded the product as a colourless oil (93 mg, 0.43 mmol, 55 %).





$C_{12}H_{22}O_3$, MW = 214.31

$[\alpha_D]$ (24°C) = +20.9° (*c* = 1.05 in $CHCl_3$)

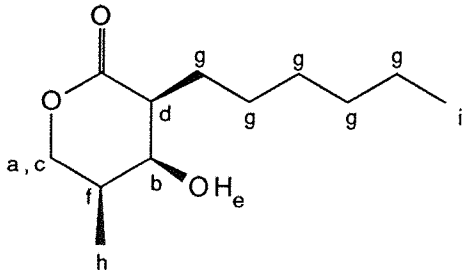
IR (film) : *v* = 3442 br m, 2927 s, 2860 s, 1822 s, 1463 m, 1124 m, 874 s cm^{-1}

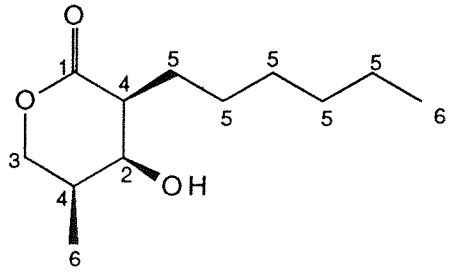
^1H NMR (270 MHz, $CDCl_3$)
- H_a : 4.20 (1H, dd, *J* = 7.3, 3.9 Hz)
- H_b : 3.65 (1H, dd, *J* = 10.8, 5.0 Hz)
- H_c : 3.55 (1H, dd, *J* = 10.8, 7.0 Hz)
- H_d : 3.42 (1H, td, *J* = 7.5, 3.9 Hz)
- H_e : 2.99 (1H, br s)
- H_f : 2.00 (1H, ddq, *J* = 6.8, 5.0, 3.9 Hz)
- H_g : 1.90-1.20 (10H, m)
- H_h : 1.02 (3H, d, *J* = 6.8 Hz)
- H_i : 0.86 (3H, distorted t)

^{13}C NMR (300 MHz, $CDCl_3$)
- C_1 : 172.3
- C_2 : 80.3
- C_3 : 64.3
- C_4 : 54.4
- C_5 : 39.4
- C_6 : 31.7, 29.2, 28.1, 26.9, 22.7
- C_7 : 14.2, 12.0

(3*S*,4*S*,5*S*)-3-Hexyl-4-(hydroxy)-5-methyl-2-oxanone (31)

This compound was obtained by intramolecular transesterification of (3*S*, 4*S*)-3-hexyl-4-[(S)-1'-methyl-2'-(hydroxy)ethyl]-2-oxetanone at r.t.. It was isolated by column chromatography (ether / petrol 5 : 5) and purified by recrystallisation in petrol to give brown crystals.





$C_{12}H_{22}O_3$, MW = 214.31

$[\alpha_D]$ (24°C) = –42.1° (c = 1.05 in $CHCl_3$)

mp = 50-52°C

IR (film) : ν = 3425 br m, 2926 s, 2856 s, 1726 s, 1462 m, 1262 m, 1164 m, 1111 m, 1043 m cm^{-1}

^1H NMR (270 MHz, $CDCl_3$)
H_a : 4.37 (1H, dd, J = 11.5, 5.8 Hz)
H_b : 3.91 (1H, t, J = 3.9 Hz)
H_c : 3.83 (1H, dd J = 11.5, 9.3 Hz)
H_d : 2.45 (1H, td, J = 6.9, 3.9 Hz)
H_e : 2.27 (1H, br s)
H_f : 2.14 (1H, qddd, J = 7.1, 9.3, 5.8, 3.9 Hz)
H_g : 2.00-1.20 (10H, m)
H_h : 1.07 (3H, d, J = 7.1 Hz)
H_i : 0.88 (3H, t, J = 6.6 Hz)

^{13}C NMR (300 MHz, $CDCl_3$)
C_1 : 173.9
C_2 : 72.8
C_3 : 70.3
C_4 : 43.9, 36.9
C_5 : 31.8, 29.4, 27.3, 25.7, 22.8
C_6 : 15.2, 14.2

LRMS (FAB mode) m/z = 215 [$(M+H)^{+\bullet}$, 100 %], 137 (25), 71 (19).

HRMS (CI mode) : Found, $(M+NH_4)^{+\bullet}$, 232.19. $C_{12}H_{22}O_3$, requires 232.35.

Found : C 67.00 %, H 10.40 %. $C_{12}H_{22}O_3$ requires C 67.25 %, H 10.35 %.

IV.3 - Crystallographic data

Air-stable colourless crystals were grown by recrystallisation from methanol and a suitable crystal mounted on a fibre for X-ray examination. Data were collected at 150 K using a Rigaku AFC7S diffractometer fitted with MoKα radiation and graphite monochromator. In addition to the usual Lorentz and polarisation corrections, a ψ-scan empirical absorption correction was applied (3 reflections. Transmission : 0.91 (min.); 1.00 (max)). The structure was solved using SHELXS-86[121] and refined by full-matrix least-squares minimising $\Sigma w\Delta^2$ using SHELX-76[122]. Most of the hydrogen atoms were identified from a difference electron density map and introduced into the model but not refined. Some six Me H-atoms (C(11) and C(19)) were not located and were included in calculated positions (d(C-H) = 1.08 Å). Neutral atom complex scattering factors were taken from SHELX-76.

Crystallographic data for $C_{26}H_{52}O_3Si_2$

molecular formula	$C_{26}H_{52}O_3Si_2$
molecular weight	468.9
crystallographic system	orthorhombic
space group	Pcba (no. 61)
a, Å	23.953 (3)
b, Å	22.097 (3)
c, Å	11.477 (4)
α, deg	90.0
β, deg	90.0
γ, deg	90.0
V, Å^3	6074.6 (3.5)
T, K	150
density (calculated), g cm^{-3}	1.025
Z	8
F (000), e	2080
crystal size, mm	0.80 x 0.25 x 0.10
type of data collection	ω-2θ
total no. of observations	5941
total no. of unique observations	4282
abs cor	ψ-scan
no. of data used in refinement	2190 (F > 3σ(F))
no. of parameters	287

no. of constraints	0
weighting scheme (w^{-1})	σ^2 (Fo)
λ, Å (Mo Kα)	0.71069
μ, cm^{-1}	1.05
max 2θ, deg	50
hkl limits	0 to 28, 0 to 26, 0 to -13
max |shift / esd|	0.3
R (F > 3σ(F))	0.084
wR (F > 3σ(F))	0.062

$R = \sum||Fo|-|Fc||/\sum|Fo|$; $wR = [\sum w(Fo-Fc)^2/\sum wFo^2]^{1/2}$

Bond lengths (Å) and angles (deg)

C(1) - C(2)	1.526	C(8) - C(9)	1.523
C(2) - C(3)	1.542	C(9) - C(10)	1.550
C(3) - C(4)	1.536	C(9) - O(2)	1.500
C(4) - C(5)	1.501	C(10) - C(20)	1.527
C(5) - C(6)	1.530	C(20) - O(2)	1.387
C(6) - C(1)	1.529	C(20) - O(3)	1.183
C(1) - C(7)	1.525	C(10) - C(14)	1.533
C(7) - C(8)	1.535	Si(1) - C(10)	1.905
C(7) - O(1)	1.447	Si(1) - C(11)	1.872
O(1) - Si(2)	1.648	Si(1) - C(12)	1.873
Si(2) - C(21)	1.887	Si(1) - C(13)	1.872
Si(2) - C(22)	1.864	C(14) - C(15)	1.525
Si(2) - C(23)	1.872	C(15) - C(16)	1.582
C(23) - C(24)	1.524	C(16) - C(17)	1.580
C(23) - C(25)	1.552	C(17) - C(18)	1.569
C(23) - C(26)	1.526	C(18) - C(19)	1.483

C(1) - C(2) - C(3)	110.9	C(24) - C(23) - C(26)	110.3
C(2) - C(3) - C(4)	111.5	C(25) - C(23) - C(26)	106.3
C(3) - C(4) - C(5)	112.6	C(8) - C(9) - C(10)	122.2
C(4) - C(5) - C(6)	109.9	C(8) - C(9) - O(2)	109.3
C(5) - C(6) - C(1)	111.9	C(9) - C(10) - Si(1)	121.2
C(6) - C(1) - C(2)	110.6	C(9) - C(10) - C(14)	114.5
C(2) - C(1) - C(7)	112.8	C(9) - C(10) - C(20)	83.8
C(6) - C(1) - C(7)	111.5	C(10) - C(20) - O(2)	95.4
C(1) - C(7) - O(1)	110.2	C(10) - C(20) - O(3)	138.6
C(1) - C(7) - C(8)	113.8	O(2) - C(20) - O(3)	126.0
O(1) - C(7) - C(8)	106.4	C(20) - O(2) - C(9)	90.7
C(7) - C(8) - C(9)	110.9	C(10) - Si(1) - C(11)	109.7
C(7) - O(1) - Si(2)	128.8	C(10) - Si(1) - C(12)	106.9
O(1) - Si(2) - C(21)	111.0	C(10) - Si(1) - C(13)	113.0
O(1) - Si(2) - C(22)	110.4	C(11) - Si(1) - C(12)	110.2
O(1) - Si(2) - C(23)	103.5	C(11) - Si(1) - C(13)	110.2
C(21) - Si(2) - C(22)	108.8	C(12) - Si(1) - C(13)	106.7
C(21) - Si(2) - C(23)	111.3	C(10) - C(14) - C(15)	115.2
C(22) - Si(2) - C(23)	111.7	C(14) - C(15) - C(16)	109.5
Si(2) - C(23) - C(24)	109.9	C(15) - C(16) - C(17)	109.6

Si(2) - C(23) - C(25)	112.0	C(16) - C(17) - C(18)	105.8
Si(2) - C(23) - C(26)	110.4	C(17) - C(18) - C(19)	108.1
C(24) - C(23) - C(25)	107.9		

ABBREVIATIONS

Ac	acetyl
Bn	benzyl
br	broad
Bu	butyl
CI	Chemical Ionization
COD	cyclooctadienyl
d	doublet
DCM	dichloromethane
DiBAlH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
d.r.	diastereoisomeric ratio
EI	Electron Impact
eq	equivalent
Et	ethyl
FAB	Fast Atom Bombardment
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
IR	infrared
L.A.	Lewis acid
LDA	lithium diisopropylamine
LiTMP	2,2,6,6-lithium tetramethylpiperidine
LRMS	low resolution mass spectroscopy
m	multiplet (NMR), medium (IR)
Me	methyl
m_p	melting point
MW	molecular weight
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
q	quartet
quint	quintet
R	alkyl
r.t.	room temperature

s	singulet (NMR), strong (IR)
SN	nucleophilic substitution
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
Ts	tosyl
U.V.	ultraviolet
w	weak

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