UNIVERSITY
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DEPARTMENT OF CHEMISTRY

A Novel Asymmetric [2+2] Cycloaddition and its Application to the Total Synthesis of 1233A

A thesis submitted in part fulfilment
for the degree of Doctor of Philosophy

by

Brian William Dymock

September 1997

Declaration

I declare that all of the work contained within this thesis was performed by myself unless otherwise stated. This thesis was submitted for examination in September 1997 and examined in December 1997.

Brian William Dymock

signed

Glasgow, December 1997

To my wife, Mei...

UNIVERSITY OF GLASGOW

ABSTRACT

FACULTY OF SCIENCE
DEPARTMENT OF CHEMISTRY

Doctor of Philosophy

A Novel Asymmetric [2+2] Cycloaddition and
its Application to the Total Synthesis of 1233A

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The first enantioselective [2+2] cycloaddition of aldehydes with (trimethylsilyl)ketene is discovered and developed using chirally modified Lewis acids. In order to demonstrate the utility of the new methodology, the total synthesis of the cholesterol biosynthesis inhibitor 1233A was undertaken. Background biochemistry on cholesterol biosynthesis and coronary heart disease is discussed followed by previous syntheses of the target molecule.

The stereoselective synthesis of 1233A was completed using four key steps: (i) a cobalt semicorrin catalysed enantioselective reduction of an α,β-unsaturated ester; (ii) a copper-mediated coupling of a vinyl iodide with a vinyl stannane; (iii) a novel [2+2] cycloaddition of an aldehyde with (trimethylsilyl)ketene and (iv) a β-lactone aldol-type reaction quenching with carbon dioxide to install the final carbon of 1233A.

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Preface

The research described in this thesis was carried out under the supervision of Professor P. J. Kocienski at the University of Southampton between October 1994 and January 1997 and then at the University of Glasgow between February 1997 and September 1997. No part of this thesis has been previously submitted for a degree at this or any other university, except where specific acknowledgement has been made. Part of this thesis has been previously published:

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Abbreviations

Ac	acetyl
ADP	adenosine diphosphate
Allyl	2-propenyl
Anal.	combustion analysis
Ar	aryl
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	1,1′-bi-2-naphthol
BINOL	2,2′-*bis*-(diphenylphosphino-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
BT	benzothiazole
BTSH	2-mercaptobenzothiazole
Bu	butyl
BuLi	*n*-butyllithium
c	concentration in g/100 mL (for optical rotation)
CI	chemical ionisation
CLSR	chiral lanthanide shift reagent
d	days
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicycano1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	di*iso*-propyl azodicarboxylate
DIBALH	di*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*′-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
eq	equivalents

ES	electrospray
Et	ethyl
FGI	functional group interconversion
h	hours
Hex	hexyl
HOMO	highest occupied molecular orbital
hυ	light
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
i	*iso*
imid	imidazole
IPA	*iso*-propylalcohol
IR	infrared
KHMDS	potassium methyldisilazide
L	ligand
LDA	lithium di*iso*-propylamide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar/metal
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methyoxyethoxymethyl
MHz	megahertz
min	minutes
mL	millilitres
mmol	millimoles
mp	melting point
Ms	methanesulfonyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
n	normal
NMP	*N*-methylpyrrolidinone
NMR	nuclear magentic resonance
Nuc	nucleophile
PDC	pyridinium dichromate
Ph	phenyl

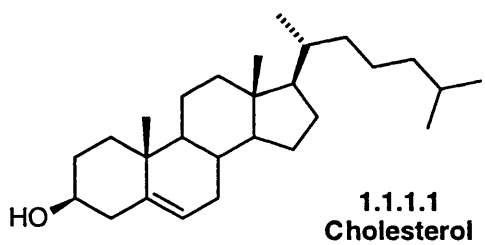
P_i	inorganic phosphate
Piv	pivaloyl
PMA	phosphomolybdic acid
PMBOM	*para*-methoxybenzyloxymethyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr	pyridine
quant	quantitative
R	alkyl
rt	room temperature
s	secondary
t	*tert*
TADDOL	tartrate-derived diol
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*-propylsilyl
TLC	thin layer chromoatography
TMS	trimethylsilyl
TPAP	tertrapropylammonium perruthenate
Tr	trityl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	leaving group

Chapter 1

Introduction, Biological Background and Biosynthesis of Antibiotic 1233A

1.1 Introduction

Coronary heart disease (CHD) is the major cause of death in most industrialised nations, causing more deaths than all forms of cancer combined. [1] One of the main causes of CHD is atherosclerosis, a progressive disease of the major coronary arteries which is characterised by the formation of fatty plaques of cholesterol, lipids and other cellular debris in the arteries. In much the same fashion as water pipes in a heating system "fur-up" with old age, the cross-sectional area of the artery is reduced, the flexibility of the artery wall is diminished and the heart is forced to work much harder as a consequence. The disease is asymptomatic for many years as the lesion matures but the onset of symptoms can be rapid and fatal. Hypercholesterolemia is well recognised as a major independent risk factor for coronary disease[2] and a number of studies have shown that reducing elevated levels of serum cholesterol in man leads to a reduction in the incidence of coronary-related deaths. [3,4]



1.1.1.1
Cholesterol

Figure 1.1.1

1.2 Cholesterol Biosynthesis

In humans, 70% of cholesterol is derived from *de novo* synthesis in the liver and developments in the past decade have shown that one of the most effective approaches to lowering serum cholesterol levels is by inhibiting sterol biosynthesis. [5]

Cholesterol is of interest both as a membrane component, modulating the fluidity of eukaryotic membranes, and as a precursor of many signal molecules.[6] Steroid hormones such as progesterone, testosterone and cortisol are derived from cholesterol. The biosynthesis of cholesterol exemplifies a fundamental mechanism for the assembly of extended carbon skeletons from

five-carbon units. The "Jekyl and Hyde" nature of cholesterol is aptly expressed by Brown and Goldstein: [7]

"Cholesterol is the most highly decorated small molecule in biology. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol. Ever since it was isolated from gallstones in 1784, cholesterol has exerted an almost hypnotic fascination for scientists from the most diverse areas of science or medicine...
Cholesterol is a Janus-faced molecule. The very property that makes it useful in cell membranes, namely its absolute insolubility in water, also makes it lethal".

All 27 carbon atoms of cholesterol are derived from *acetyl Coenzyme A.* Coenzyme A is a central molecule in metabolism. The "A" stands for *acetylation.* It is a universal carrier of acyl groups. The structure of Coenzyme A is shown[8] (Scheme 1.2.1).

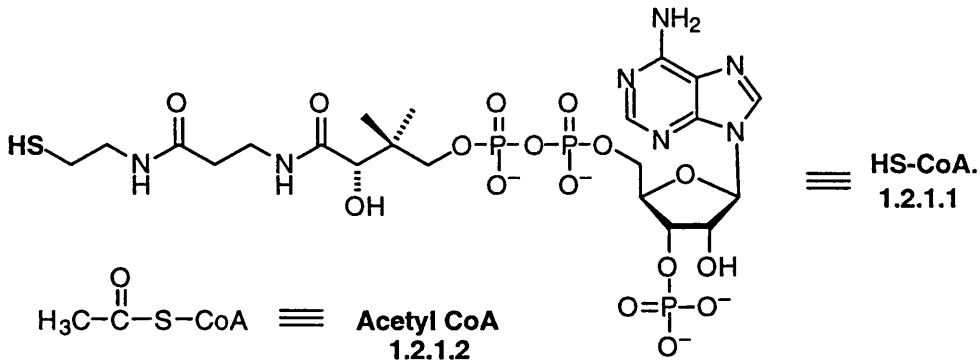
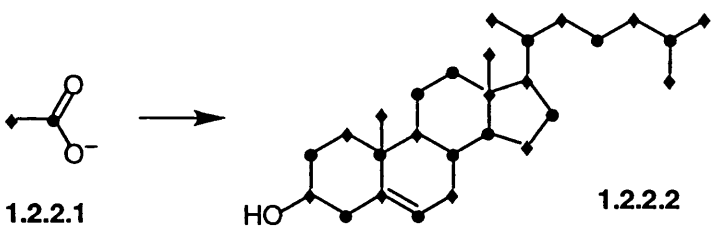


Figure 1.2.1

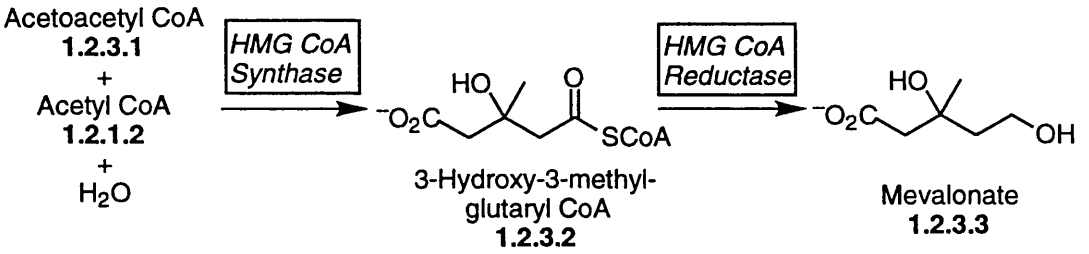
The terminal sulfhydryl group in CoA is the reactive site. The acetyl unit is linked to CoA by a thioester bond; this derivative is called acetyl CoA. The hydrolysis of a thioester bond is thermodynamically more favourable than an oxygen ester because sulfur is larger and more diffuse than oxygen and does not efficiently share the electrons of the carbonyl group. Consequently acetyl CoA has a high acetyl group transfer potential.

Cholesterol has been synthesised using acetate labelled in either its methyl or carboxyl carbon. Degradation of such labelled cholesterol allowed the origin of each atom of the cholesterol molecule to be determined[9] (Scheme 1.2.2).



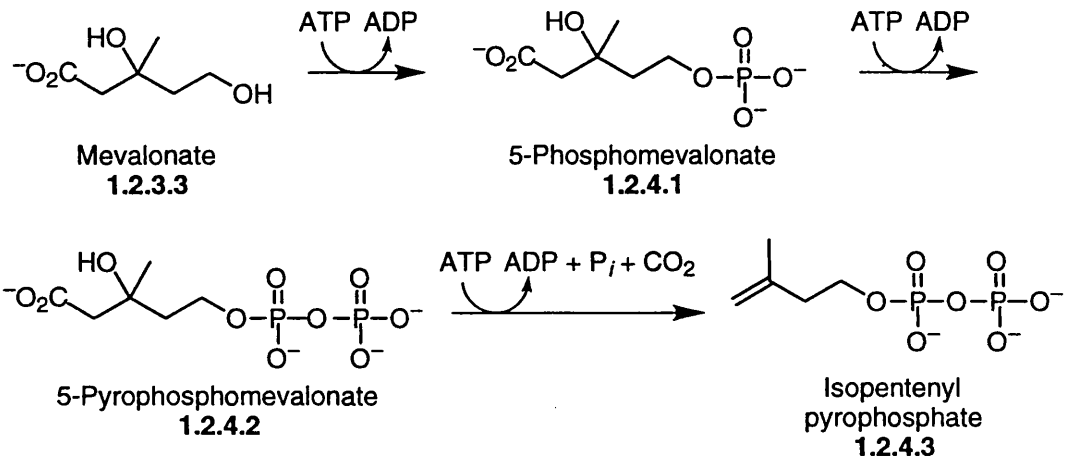
Scheme 1.2.2

The biosynthesis of cholesterol starts with the formation of 3-hydroxy-3-methylglutaryl CoA (3-HMG CoA) from acetyl CoA and acetoacetyl CoA catalysed by the enzyme *HMG CoA synthase*. 3-HMG CoA is then reduced to *mevalonate* by *HMG CoA reductase*. The synthesis of mevalonate is the committed step in cholesterol formation[6] (Scheme 1.2.3).



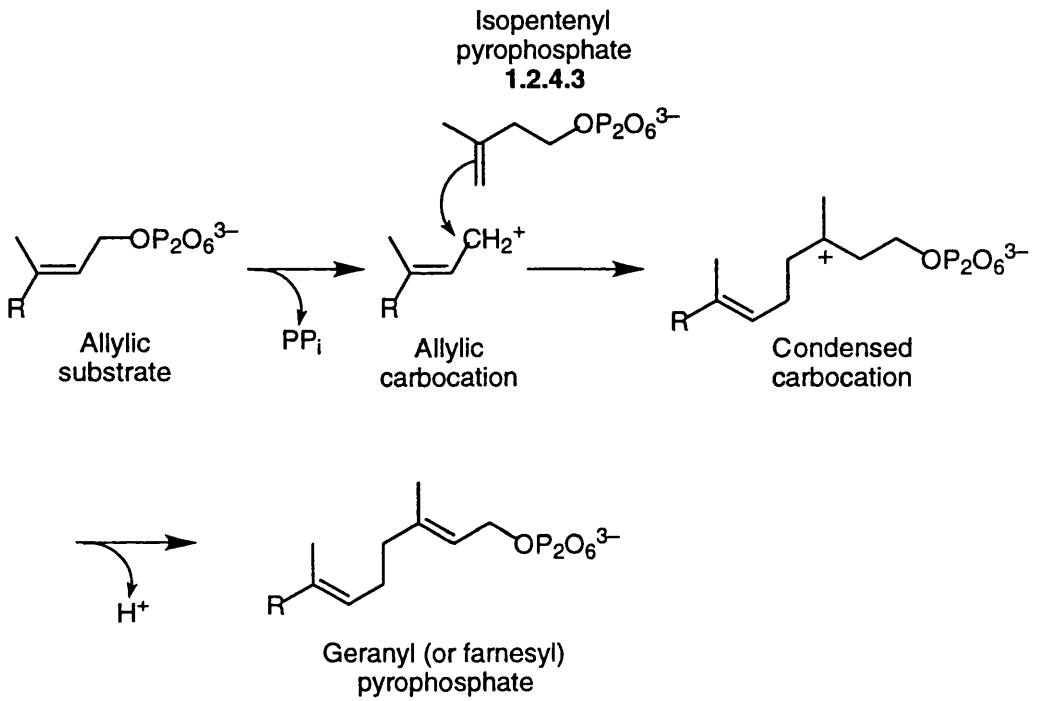
Scheme 1.2.3

Mevalonate is converted into *3-isopentenyl pyrophosphate* by three consecutive reactions involving ATP (Scheme 1.2.4).



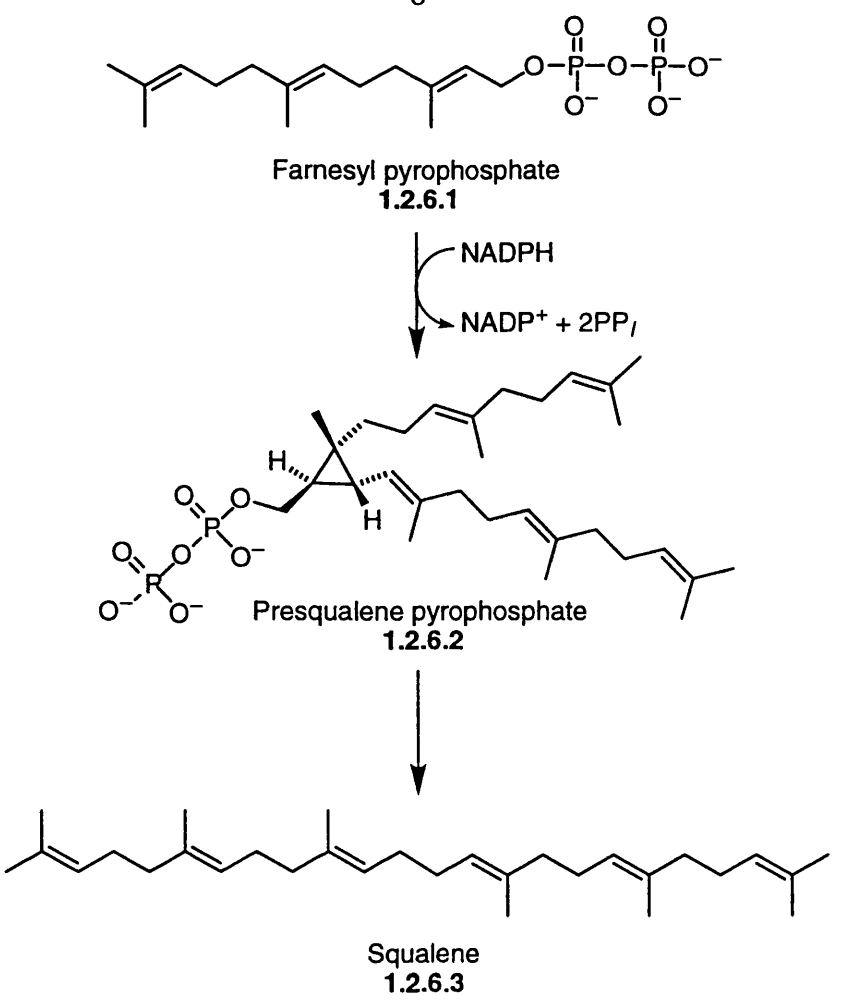
Scheme 1.2.4

Isomerisation of isopentenyl pyrophosphate to *dimethylallyl pyrophosphate* is followed by condensation of these C_5 units to form a C_{10} compound: *geranyl pyrophosphate*. An allylic carbocation formed from dimethylallyl pyrophosphate is attacked by isopentenyl pyrophosphate. A similar reaction then occurs to convert geranyl pyrophosphate to the C_{15} compound *farnesyl pyrophosphate* (Scheme 1.2.5).



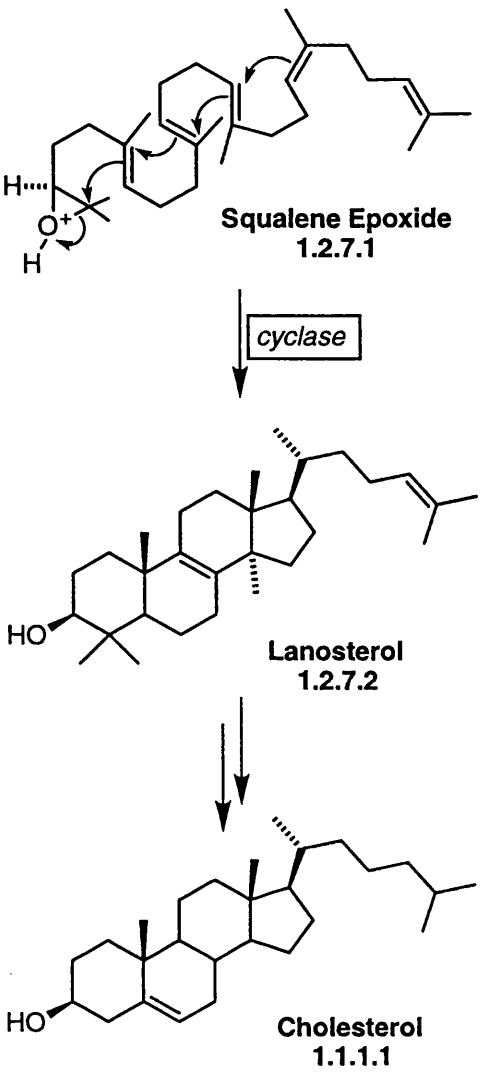
Scheme 1.2.5

Reductive condensation of two molecules of farnesyl pyrophosphate leads to the formation of *squalene*, a C_{30} compound. This reaction proceeds through the cyclopropane intermediate *presqualene pyrophosphate*[10] (Scheme 1.2.6).



Scheme 1.2.6

The final stage of cholesterol biosynthesis starts with the cyclisation of squalene. *Squalene epoxide* is formed from squalene in the presence of molecular oxygen, then a *cyclase* enzyme catalyses a remarkable cyclisation to form lanosterol. The squalene epoxide molecule is believed to be folded in a conformation which allows one double bond after another to react as a nucleophile with a cationic centre which develops nearby in the molecule. [6] A cationic centre behaves as a Lewis acid towards the π-electrons of an adjacent double bond which in turn creates a new cationic centre. This process continues until cyclisation is complete. Finally, lanosterol is converted into cholesterol by the removal of three methyl groups, the reduction of one double bond by NADPH and the migration of the other double bond (Scheme 1.2.7).



Scheme 1.2.7

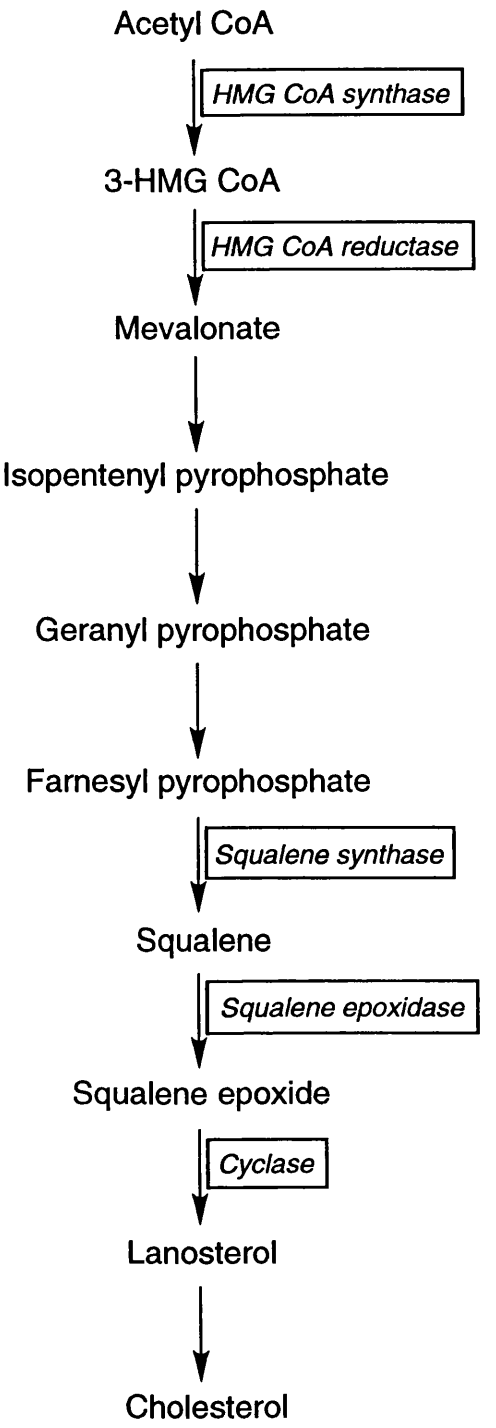
Scheme 1.2.8 shows the general scheme for the biosynthesis of cholesterol.

1.3 Cholesterol Transport[6]

Cholesterol is transported in body fluids in the form of *lipoprotein particles*. The protein components of these macromolecular aggregates have two roles:

(i) They solubilise hydrophobic lipids for transport to cells.
(ii) They contain cell targeting apparatus, essential for molecular recognition on arrival at a cell.

Lipoproteins are classified according to density. *Low-density lipoprotein* (*LDL*), the major carrier of cholesterol in blood, has a diameter of 22 nm and a mass of approximately 3 million daltons. It contains a core of some 1500 esterified cholesterol molecules surrounded by a shell of phospholipids and



Scheme 1.2.9

unesterified cholesterols. The role of LDL is to transport cholesterol to peripheral tissues and regulate *de novo* cholesterol synthesis at these sites. Although cholesterol is essential for the growth and viability of cells in higher organisms, high serum levels of cholesterol cause disease and death by contributing to the formation of atherosclerotic plaques in arteries throughout the body. It is evident that cholesterol metabolism must be precisely regulated. In general, cells outside the liver obtain cholesterol from the plasma, rather than

synthesising it *de novo*. Their primary source of cholesterol is the low density lipoprotein. The steps in the uptake of cholesterol by the LDL pathway are:

(i) The LDL particle binds to a specific receptor protein on the cell surface.
(ii) The receptor–LDL complex is internalised by *endocytosis*–the process by which a living cell takes up molecules bound to its surface.
(iii) *Lysosomes*, which carry a wide array of degradative enzymes, hydrolyse the protein component of the LDL to free amino acids and also hydrolyse the cholesterol esters. The receptor from the surface of the LDL is returned to the membrane and recycled.
(iv) The released unesterified cholesterol can then be used for membrane biosynthesis. Alternatively it can be re-esterified for storage inside the cell.

The LDL receptor on the surface of cells is subject to a feedback regulation: when cholesterol is abundant inside the cell, new LDL receptors are not synthesised, and so the uptake of additional cholesterol from plasma LDL is blocked. The cholesterol from these LDL particles may then be deposited as a component of plaques on arterial walls.

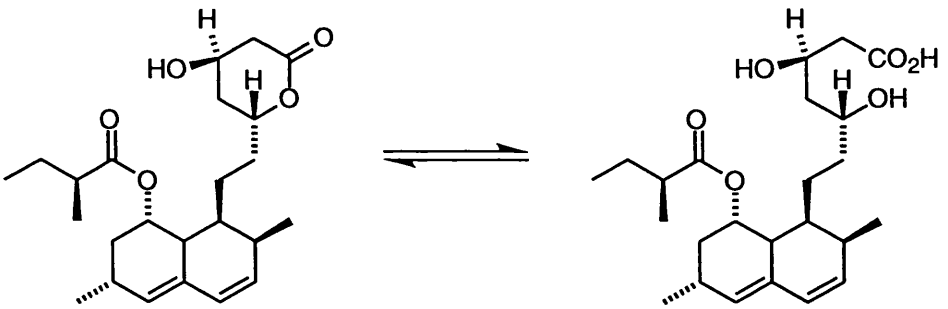
Pioneering studies of *familial hypercholesterolemia* by Brown and Goldstein revealed the physiological importance of the LDL receptor.[11] The total concentration of cholesterol and LDL in the plasma is markedly elevated in this genetic disorder (300 mg/dL *c.f.* desirable level of 175 mg/dL). In familial hypercholesterolemia, cholesterol is deposited on various tissues because of the high concentration of LDL–cholesterol in the plasma. More harmful, however, is the deposition of cholesterol in atherosclerotic plaques causing arterial narrowing and leading to heart attacks. The molecular defect in most cases of familial hypercholesterolemia is an absence or deficiency of functional receptors for LDL.

The production of LDL receptors is controlled by the cell's need for cholesterol. When cholesterol is required, the amount of mRNA for LDL receptor rises and more receptor is found on the cell surface. This state can be induced by inhibiting cholesterol biosynthesis. Current drug therapy involves inhibition of HMG-CoA reductase by *lovastatin* (also called *mevinolin*, see scheme 1.4.1).[12]

The consequent increase in the number of LDL receptors on liver cells leads to a decrease in the LDL level in blood. Plasma cholesterol levels decrease by as much as 50% in many patients.

1.4 Drug Therapy

There is much interest in drugs which inhibit cholesterol levels because atherosclerosis is the leading cause of death in industrialised societies.[2]
Current drug therapy is dominated by inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR). In clinical studies such inhibitors effectively reduce serum cholesterol levels in a dose-related manner and a recent study has demonstrated that lowering raised cholesterol levels in patients with coronary heart disease improves survival.[13]
One such drug is *lovastatin* (also called *mevinolin*) which effectively blocks cholesterol biosynthesis (K_i = 1 nM) (Scheme 1.4.1). The consequent increase in the number of LDL receptors on liver cells leads to a decrease in the LDL level in blood.



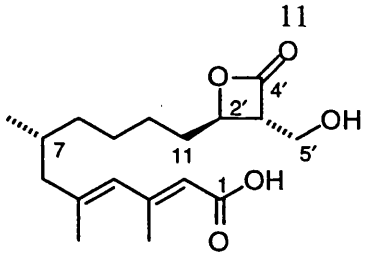
Prodrug lactone
1.4.1.1

Inhibitor lovastatin
1.4.1.2

Scheme 1.4.1

1.5 Antibiotic 1233A

Another suitable enzyme for inhibition is 3-HMG CoA synthase. **Antibiotic 1233A (1.5.1.1)** (Figure 1.5.1) inhibits this enzyme specifically and irreversibly.[14-16] 1233A was first isolated from *Cephalosporium sp.* in 1970.[17-19] However, since it has also been independently isolated from two other sources, it is also known as F-244 (isolated from *Scopulariopsis sp.*)[20] and L-

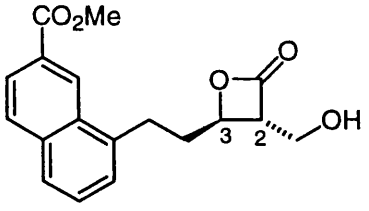


Antibiotic 1233A 1.5.1.1

Figure 1.5.1

659,699 (isolated from *Fusarium sp.*). [21] The structure of 1233A has been known since its isolation but its relative and absolute configuration were only established in 1988 from a combination of chemical degradation and NMR spectroscopic studies. [22] The 2-oxetanone ring was shown to be essential for enzyme inhibitory activity since a series of γ-lactone, cyclobutanone and oxetane analogues were found to be inactive. [23,24] This conclusion is in accord with several reports concerning the mechanism of inhibition which involves acylation of the enzyme by ring opening of the 2-oxetanone moiety by an active site cysteinyl sulfhydryl group. [25-29] Not only has the β-lactone moiety been shown to be essential for enzyme inhibition but the length of the side chain also plays an important role. [29,30]

Very recently Omura *et al* reported a study which demonstrated that the specific absolute configuration (2*R*, 3*R*) of the 2-oxetanone **1.5.2.1** (DU-6622) was required for most potent inhibitory activity against HMG-CoA synthase. [31] Omura synthesised all four possible diastereoisomers of **1.5.2.1** and tested each one separately.

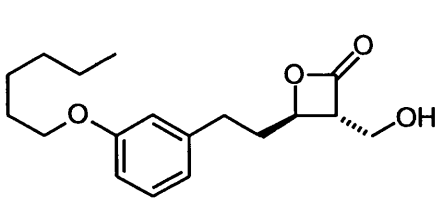


(2*R*, 3*R*) DU-6622 1.5.2.1

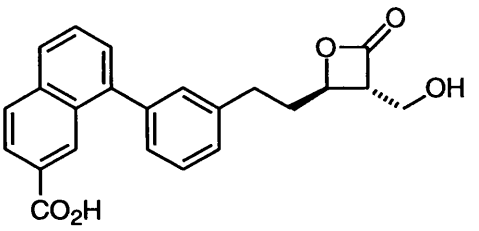
Figure 1.5.2

Compound **1.5.2.1** is actually more active than **1.5.1.1** *in vitro* (IC_{50}: 0.098 μM and 0.20 μM, respectively). Another interesting result is that the (2*S*, 3*R*) isomer is more potent than the (2*S*, 3*S*) isomer which is more potent than the (2*R*, 3*S*) isomer (IC_{50} values: 9.4 μM, 31 μM and 360 μM, respectively). This suggests that the C3 geometry of the 2-oxetanone is more important for inhibitory activity than the C2 geometry.

Although **1.5.2.1** is very active, it induced a considerable increment in serum triglyceride levels. In an effort to find a more selective inhibitor, Omura has developed a number of other synthetic 2-oxetanones which retain the same lactone motif as the natural product but have similar activity *in vitro* and *in vivo* with little or no effect on triglyceride levels.[32-34] Figure 1.5.3 shows



1.5.3.1
IC_{50} = 0.74 μM

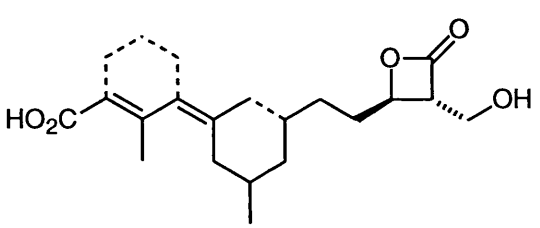


1.5.3.2
IC_{50} = 0.13 μM

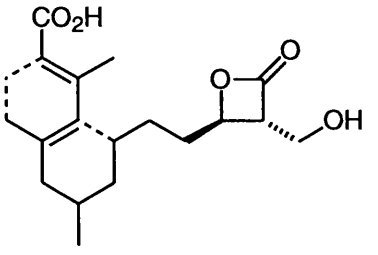
Figure 1.5.3

two highly active compounds synthesised by Omura. **1.5.3.1** possesses a hexyl ether on the *meta-* position of the aromatic ring.[33] This compound possessed good activity *in vitro* and *in vivo* (80.1% @ 500 mg/kg *versus* 83.0% @ 500 mg/kg for 1233A) but also had no effect on triglyceride levels. An ethyl group spacer between the 2-oxetanone and aromatic system was required for good inhibitory activity on all analogues investigated. Compound **1.5.3.2** has a more complex aromatic system but possesses very high activity *in vitro* and significant *in vivo* inhibition (51.7% @ 200 mg/kg in the mouse liver *versus* 83% @ 500 mg/kg for 1233A).[34]

The central tenet which underpins the design of these inhibitors lies in a hypothetical folded structure of the 1233A side-chain (for an example, see Figure 1.5.4). The high activities of some side-chain mimics suggest that these analogues may interact with the enzyme in a similar way to the 1233A side-chain.



1.5.4.1



1.5.4.2

Figure 1.5.4

The biosynthesis of antibiotic 1233A was studied by feeding ^{13}C-labelled precursors to the producing organism *Scopulariopsis* sp. F-244.[35] ^{13}C NMR spectroscopy established that 1233A is derived from 4 methionines and 7 acetates (Figure 1.5.5).

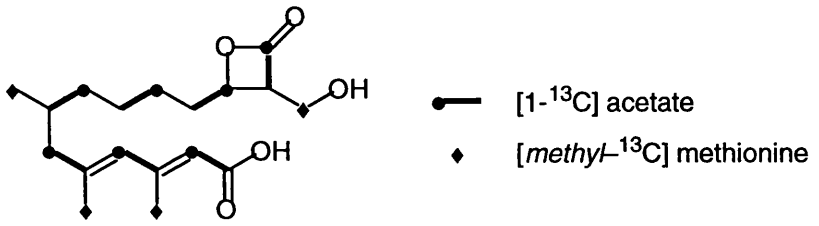


Figure 1.5.5

Seven acetates are condensed to form a hexaketide and 4 methyl residues from methionine are introduced into the main skeleton. The 2-oxetanone is derived from the α-carboxylic acid of the hexaketide. Since methionine was efficiently incorporated into 1233A, radio labelled 1233A was prepared biosynthetically by feeding [^{14}C]methionine to the producing organism. As a result, [^{14}C]1233A was obtained with high specific radioactivity (27.2 μCi/μmol). This enabled study of the direct interaction between HMG-CoA synthase and [^{14}C]1233A which led to the conclusion that [^{14}C]1233A specifically binds HMG-CoA synthase covalently.

1.6 Conclusions

In this chapter, the biological stage has been set for the total synthesis of the HMG-CoA synthase inhibitor 1233A. There is much known about the mechanisms involved in the formation of atherosclerotic plaques and the importance of this area will continue for many years with such high death rates attributable to coronary heart disease. Drug therapy appears to be a good alternative to surgical intervention and already analogues of 1233A are appearing in efforts to produce compounds which may one day become superior pharmaceuticals.

Chapter 2

Previous Syntheses of 1233A

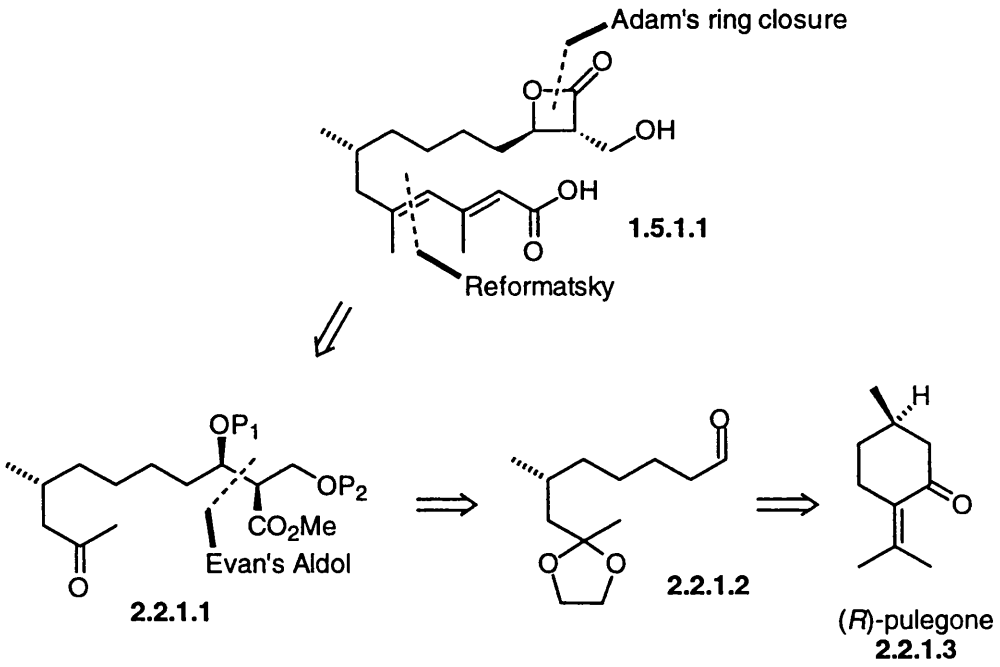
2.1 Introduction

To date there have been three total syntheses of 1233A and two formal syntheses published in the literature. The following discussion presents the salient points from these syntheses.

2.2 The Merck Total Synthesis

Antibiotic 1233A was first synthesised in 1988 by a group from Merck, Sharp and Dohme. [36]

Retrosynthetic analysis (Scheme 2.2.1) shows that 2-oxetanone formation could be effected *via* ring-closure and the diene could be constructed *via* a Reformatsky reaction. An Evan's aldol reaction should install the stereogenic centres of the 2-oxetanone ring and the aldehyde (**2.2.1.2**) could be made from (*R*)-pulegone (**2.2.1.3**).

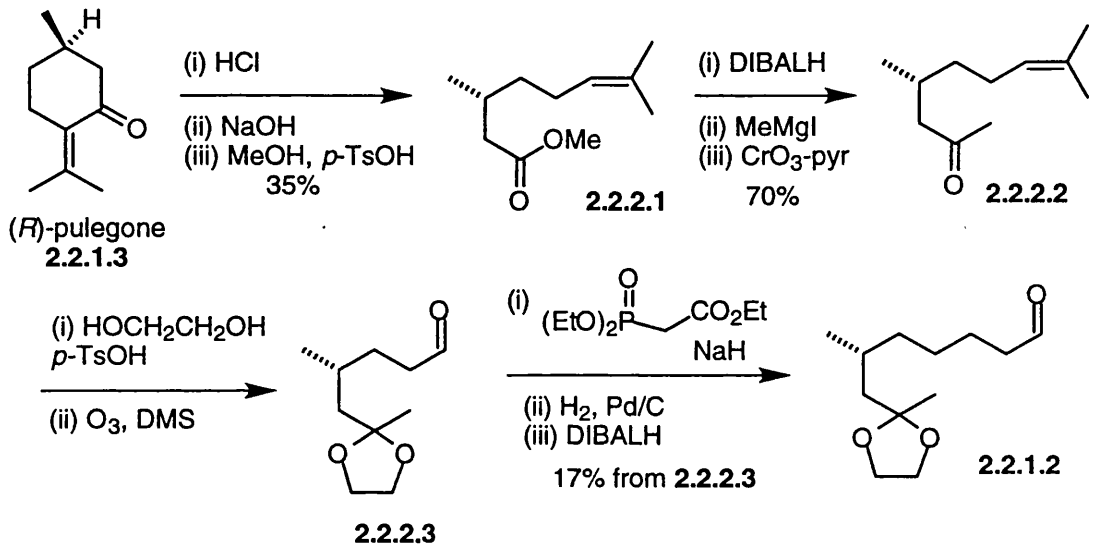


Scheme 2.2.1

Synthesis

Schemes 2.2.2 and 2.2.3 show the approach taken in practice. The key step was a highly diastereoselective Evans aldol[37] reaction between an *N*-crotonyloxazolidinone (**2.2.3.1**) and aldehyde **2.2.1.2**. Aldehyde **2.2.1.2** was prepared from (*R*)-(+)-pulegone (**2.2.1.3**) (Scheme 2.2.2). After ring-opening,

DIBALH reduction, methyl magnesium iodide addition to the resultant aldehyde and oxidation with chromium trioxide-pyridine in dichloromethane, the methyl ketone **2.2.2.2** was obtained in 70% yield. Protection of the ketone as the ketal and ozonolysis revealed aldehyde **2.2.2.3** which was then chain extended with a Horner-Wadsworth-Emmons reaction followed by olefin and ester reduction.

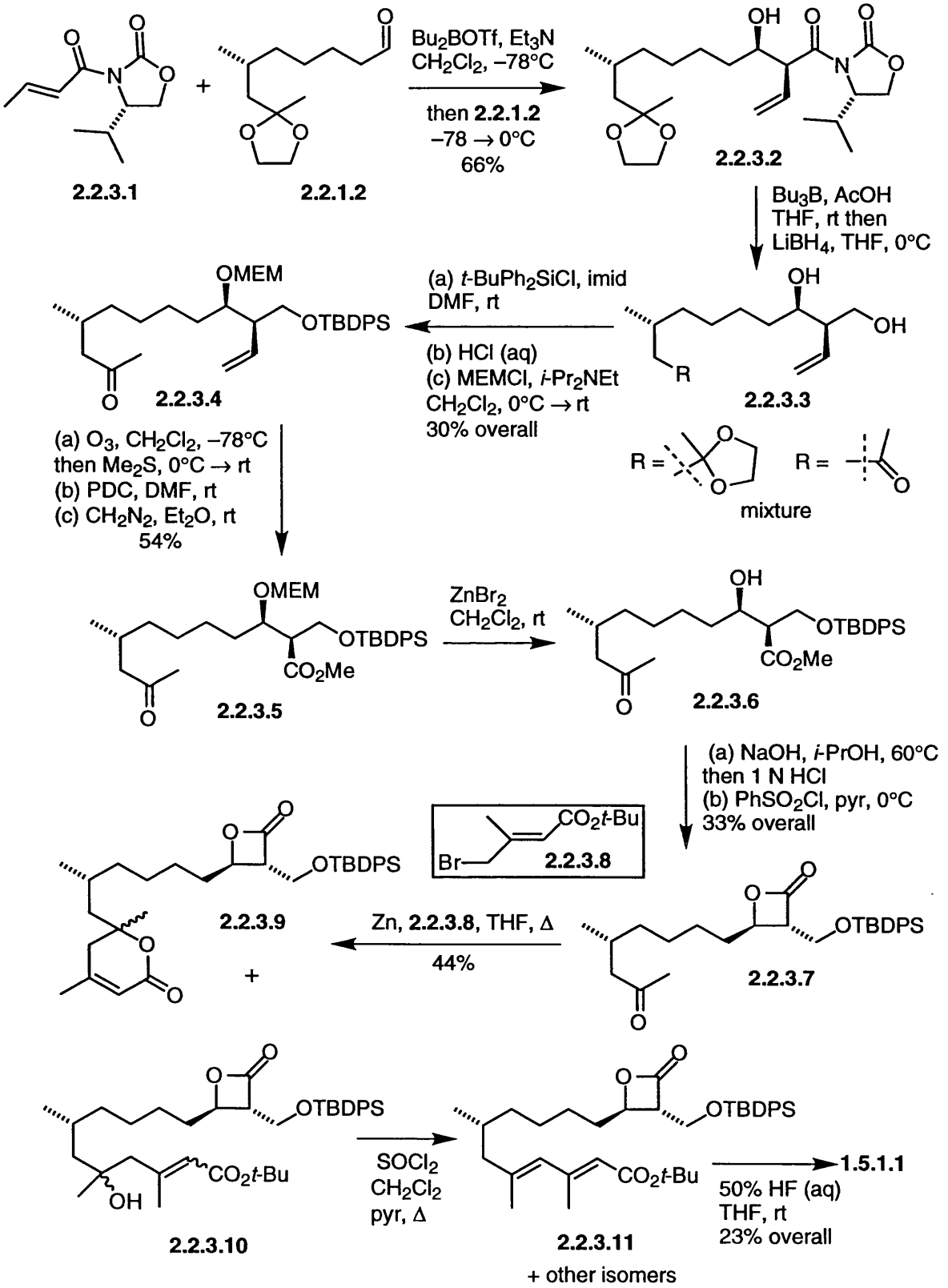


Scheme 2.2.2

Thus, upon treatment with dibutylboron trifluoromethanesulfonate (Bu_2BOTf) and triethylamine, oxazolidinone **2.2.3.1** gave the corresponding boron enolate which smoothly added to aldehyde **2.2.1.2.** After silylation (TBS) of the product GC analysis revealed 94% diastereoselection.

Removal of the chiral auxiliary in **2.2.3.2** gave a mixture of protected and unprotected ketones which were silylated together before treatment with hydrochloric acid. Methoxyethoxymethyl (MEM) protection gave olefin **2.2.3.4** in 30% overall yield. Conversion of the double bond in **2.2.3.4** to ester **2.2.3.5** was achieved *via* ozonolysis, oxidation with PDC and methylation with diazomethane in 54% overall yield. Lewis acid removal of the MEM protecting group to give **2.2.3.6** was followed by 2-oxetanone formation employing the classical Adams ring closure procedure: [38] sodium hydroxide cleavage of the methyl ester and conversion of the crude acid to a mixed anhydride with benzene sulfonyl chloride invited attack from the adjacent hydroxyl group forming four-membered ring compound **2.2.3.7** in 48% yield. This sequence is a common factor in all the total syntheses of 1233A detailed in the literature.

Finally, the diene portion is attached with a Reformatsky reaction between lactone **2.2.3.7** and bromide **2.2.3.8** to give *trans* 2-oxetanone **2.2.3.10** and lactone **2.2.3.9**. After separation of the desired **2.2.3.10**, dehydration and



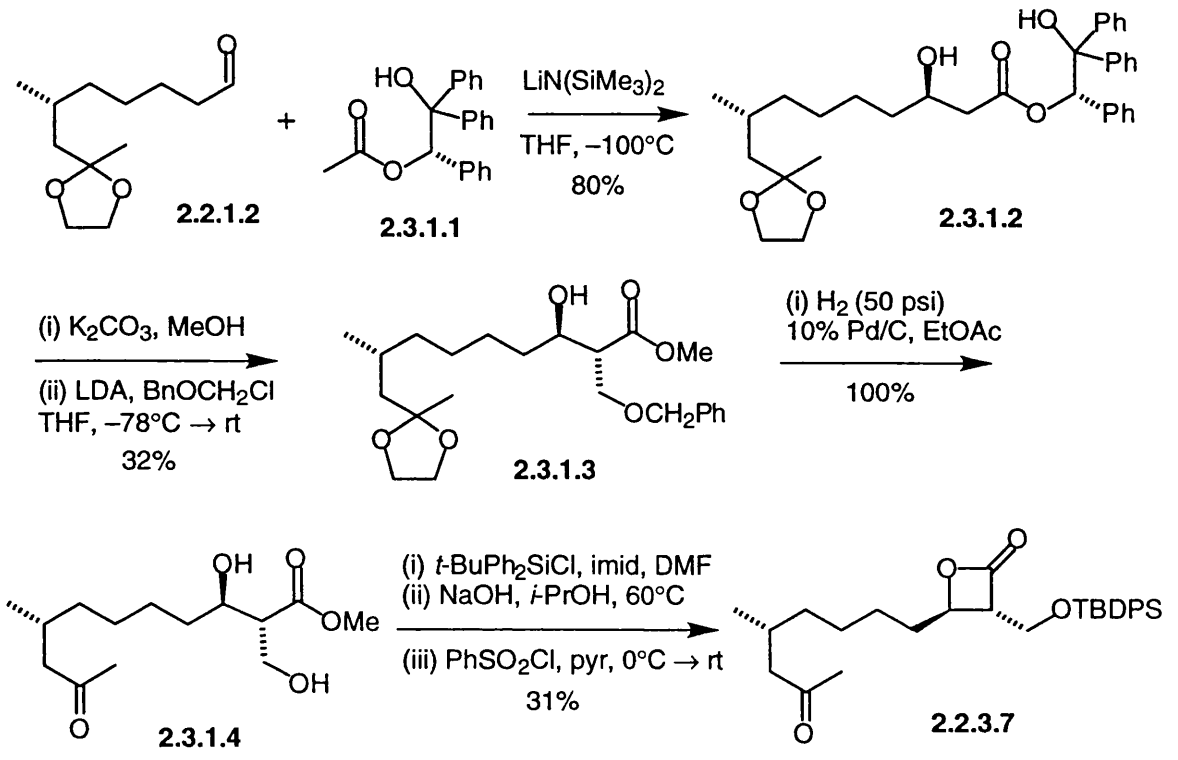
Scheme 2.2.3

simultaneous deprotection of the *tert*-butyl ester and *tert*-butyldimethylsilyl groups with aqueous HF gave **1.5.1.1** in an overall yield of <1%.

Although the initial key step to install the chiral centres of the oxetanone proceeded efficiently using Evans chemistry, subsequent manipulations resulted in mixtures of isomers and rather low yields. In particular, the last few steps are rather arduous: the Reformatsky reaction, in addition to being complicated by unreacted starting material, produced two products: the desired tertiary alcohol **2.2.3.10** and α,β-unsaturated lactone **2.2.3.9**. **2.2.3.10** is a mixture of four isomers which are subsequently separated, after dehydration, using preparative TLC which required seven elutions! At 23 steps this synthesis is also lengthy for a molecule containing 18 carbons and 3 stereocentres.

2.3 The Wattanasin Formal Synthesis

Scheme 2.3.1 shows an alternative synthesis, by Wattanasin *et al*, of advanced intermediate **2.2.3.7** from the Merck synthesis[39] therefore constituting a formal total synthesis. Hence the first and key step uses the enolate of Braun's chiral acetate[40] **2.3.1.1**. Condensation of this enolate with aldehyde **2.2.1.2** derived from (*R*)-(+)-citronellol led to β-hydroxy ester **2.3.1.2** which was transformed to the desired *trans*-2-oxetanone **2.2.3.7**.



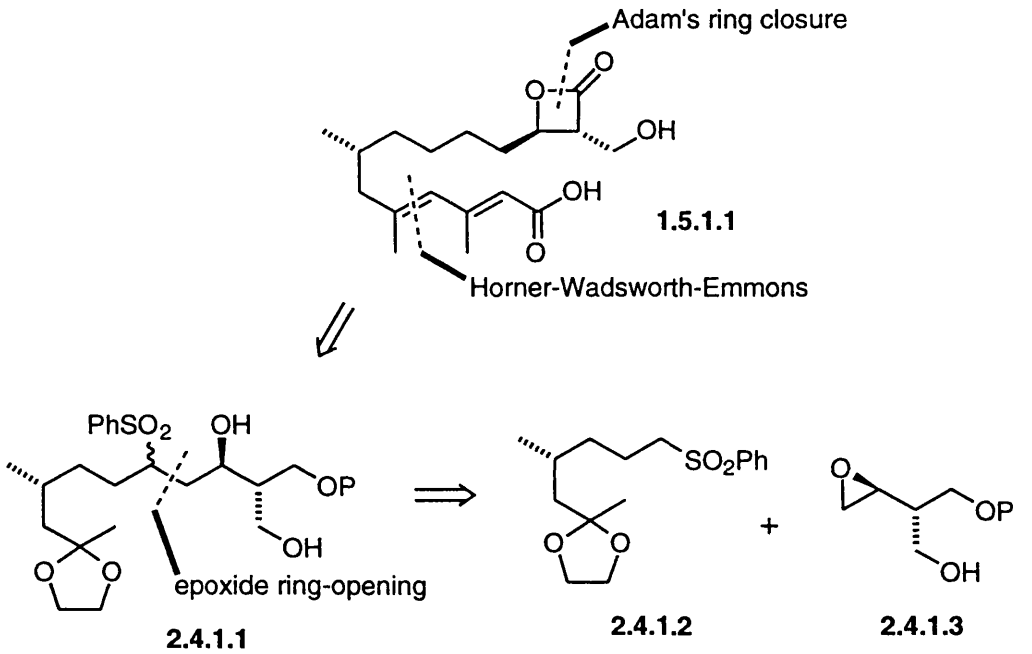
Scheme 2.3.1

Overall yield was 8% (*c.f.* Merck, above, with 0.4% overall yield for the same compound).

2.4 The Mori Total Synthesis

Mori has prepared 1233A making use of the chirality generated from an enzymatic reaction.[41]

Retrosynthetic analysis starts with the classical Adam's ring closure of the 2-oxetanone ring (Scheme 2.4.1). A Horner-Wadsworth-Emmons reaction should furnish the desired olefin. Functional group addition of a phenyl vinyl sulfone in the position *beta* to the secondary alcohol to give **2.4.1.1** should allow an epoxide ring-opening disconnection hence revealing the key carbon-carbon bond forming process between sulfone **2.4.1.2** and epoxide **2.4.1.3**.

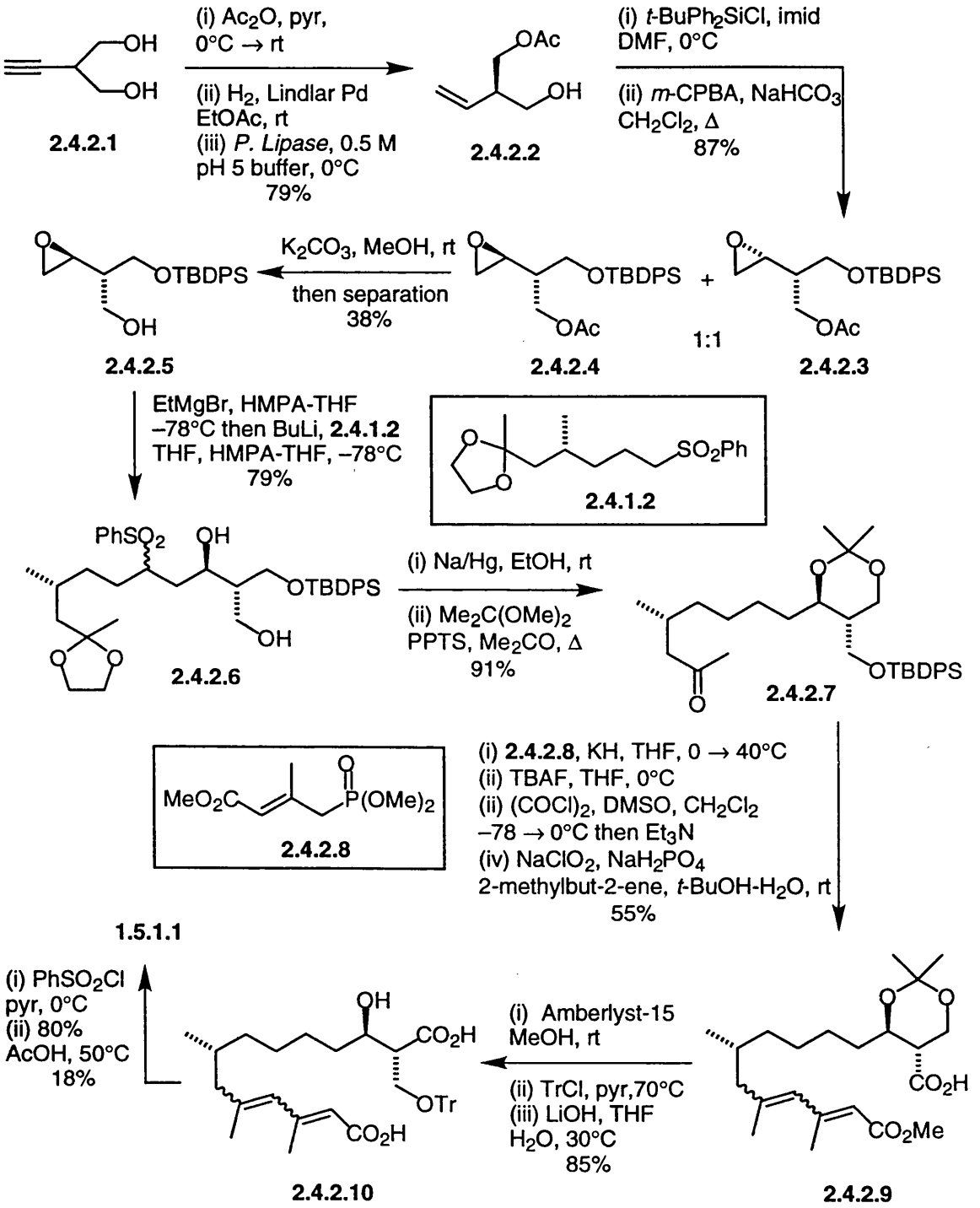


Scheme 2.4.1

Synthesis

Mori's approach starts with the preparation of homochiral alcohol **2.4.2.2** employing a pancreatic lipase-induced asymmetric hydrolysis of the *meso*-diester derived from the starting *meso*-acetylenic diol **2.4.2.1** (Scheme 2.4.2). After hydroxyl protection the terminal olefin is epoxidised with *meta*-chloroperbenzoic acid. Unfortunately this reaction produces two epoxide diastereoisomers **2.4.2.3** and **2.4.2.4** in a 1:1 ratio. Other epoxidation

conditions, such as the Sharpless epoxidation, were tried but no improvement in diastereoselectivity was found. However chromatographic separation was possible, after deacetylation with potassium carbonate in methanol, to give



Scheme 2.4.2

alcohol **2.4.2.5**. The key coupling reaction was then performed with addition of the anion of phenyl sulfone **2.4.1.2** (prepared in 6 steps from (*R*)-citronellic acid) to the epoxide derived from **2.4.2.5**. HMPA was required to effect smooth coupling in 79% yield. Desulfurisation and diol protection with

concomitant removal of the ketal protecting group prepared the molecule for a Horner-Wadsworth-Emmons reaction. Hence, reaction of **2.4.2.7** with the potassium anion of phosphonate **2.4.2.8** produced a mixture of isomers containing 70% of the desired (*E*, *E*) diene and 30% of a mixture of other geometrical isomers.

Subsequent manipulations led to trityl protected β-hydroxy acid **2.4.2.10** which was ring-closed as in previous examples using Adam's protocol. Separation of the various diastereoisomers and removal of the trityl group with acetic acid gave **1.5.1.1** in an overall yield of <1% over 19 steps.

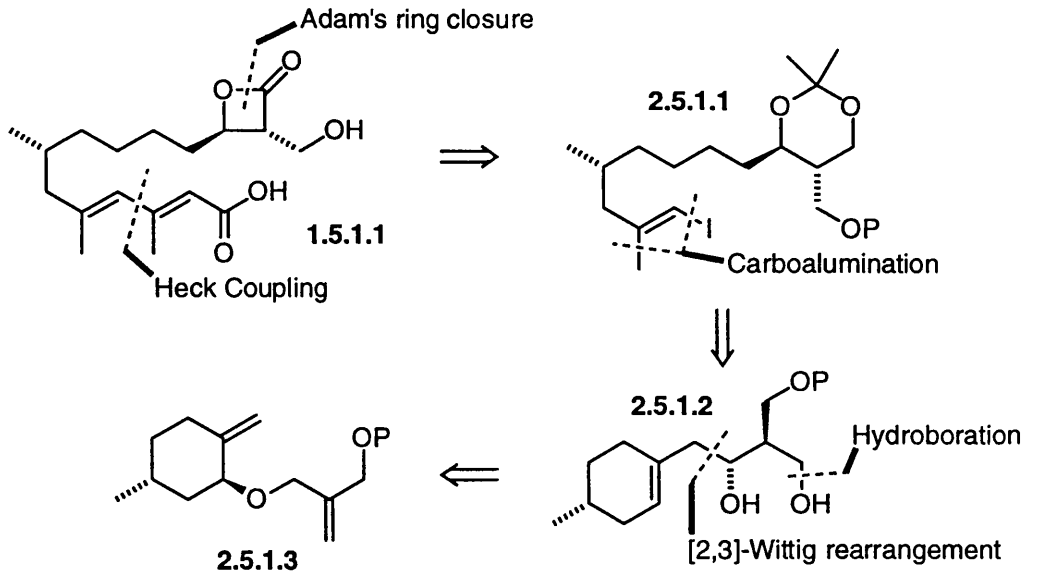
This synthesis is similar in terms of efficiency to Merck's approach. It is long at 19 steps and complicated by mixtures of isomers at key points such as the epoxidation of **2.4.2.2** to **2.4.2.4** and the Horner-Wadsworth-Emmons reaction. The key coupling between sulfone **2.4.1.2** and epoxide **2.4.2.5**, although not directly forming any new stereocentres present in the natural product, was a noteworthy highlight.

At this juncture the difficulties experienced with these syntheses clearly demonstrate the deceptive complexity of 1233A and the challenges still remaining for the modern synthetic organic experimentalist.

2.5 The Wovkulich Total Synthesis

Of the three total syntheses to date the Wovkulich approach is the most recent, published in 1993, utilising two diastereoselective processes: a [2,3] Wittig rearrangement and a hydroboration.[42]

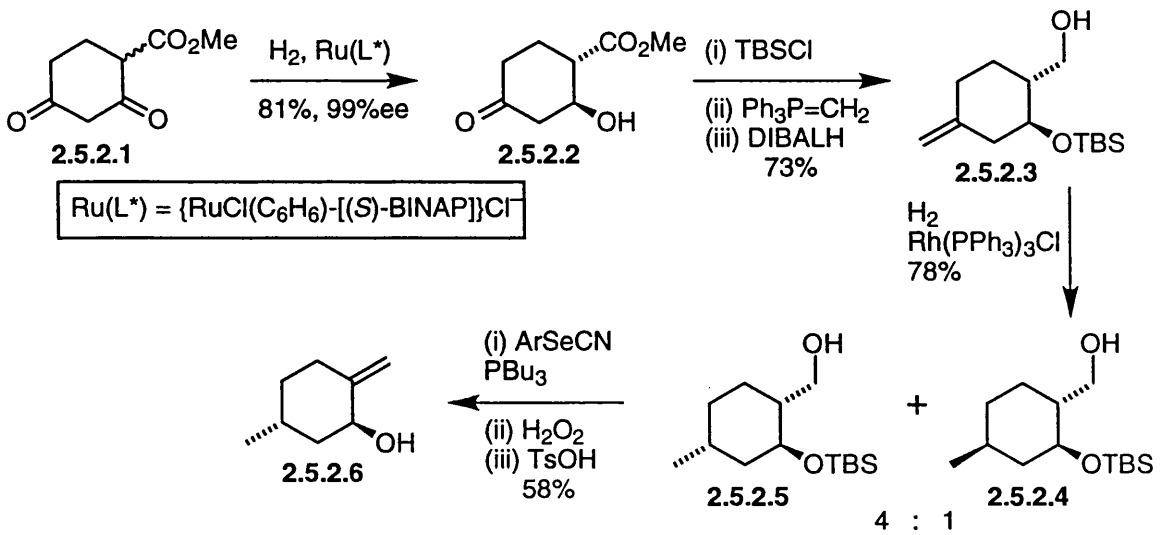
Retrosynthetic analysis starts again with the Adam's ring-closure and a Heck reaction which should form the desired diene (Scheme 2.5.1). Classical Negishi carboalumination to form vinyl iodide **2.5.1.1** followed by some functional group manipulation may allow an opportunity to perform a diastereoselective hydroboration and a [2,3]-Wittig rearrangement, key steps in creating the motif in **2.5.1.2** to lay the stereochemical foundations for building 1233A.



Scheme 2.5.1

Synthesis

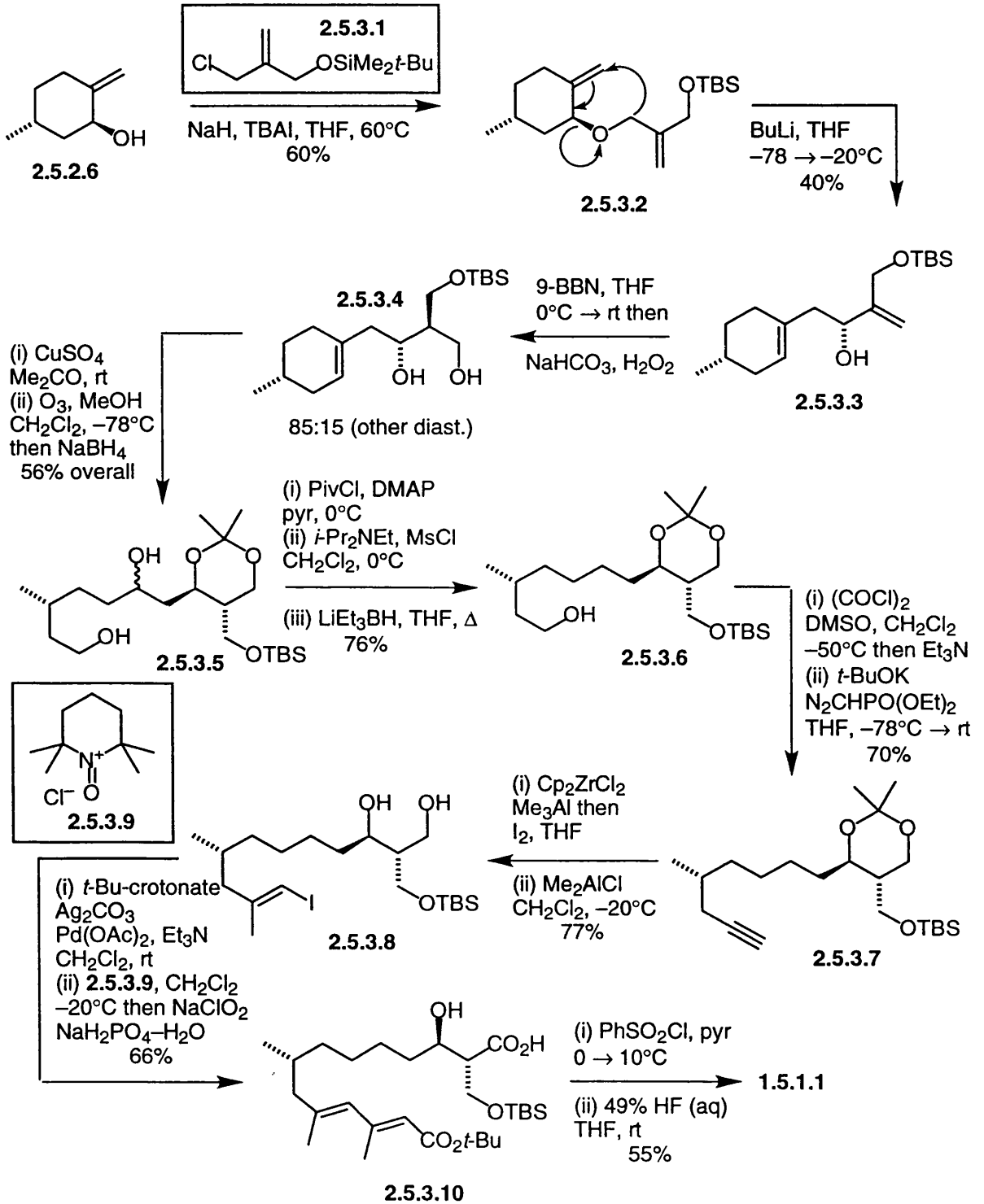
Asymmetric hydrogenation of diketo ester **2.5.2.1** gave *β*-hydroxy ester **2.5.2.2** in 99% ee and 81% yield (Scheme 2.5.2). Silyl protection, Wittig methylenation and DIBALH reduction of the ester led to olefin **2.5.2.3** which was further reduced with a rhodium catalysed hydrogenation. This last step resulted in the formation of two products: the desired alcohol **2.5.2.5** constituted 80% of the mixture and was separated from the undesired **2.5.2.4**. Selenium induced elimination and acid catalysed desilylation gave the alcohol **2.5.2.6** in 27% overall yield for the 8 steps from **2.5.2.1**.



Scheme 2.5.2

The key transformation was a diastereoselective [2,3] rearrangement of *bis*-allylic ether **2.5.3.2** to allylic alcohol **2.5.3.3** (Scheme 2.5.3). Although the

yield is only 40% and some unidentifiable by-products are also formed, the product is isolated as a single diastereoisomer. Some of the problems with this step may stem from a lack of regioselectivity at the initial deprotonation step (*i.e.* require selective deprotonation of CH_2OC_6 *versus* CH_2OTBS).Hydroboration of the rearranged compound with 9-BBN and hydrogen peroxide resulted in a 85:15 mixture of diastereoisomers in favour of



Scheme 2.5.3

the desired diol **2.5.3.4**. This mixture was protected as the acetonide before the isomers were separated. However the minor diastereomer was not wasted: convenient re-equilibration under thermodynamic conditions ($CuSO_4$, acetone, TsOH) produced a mixture of three isomers enriched in the desired one (after re-silylation). In this way isomeric material could be salvaged.

Cleavage of the cyclohexene ring *via* ozonolysis with reductive work-up gave **2.5.3.5**. Selective pivaloyl protection of the primary alcohol and removal of the unwanted hydroxyl group (mesylation and treatment with super-hydride) gave alcohol **2.5.3.6** (the pivaloyl group is lost in the hydride reduction). Swern oxidation and homologation of the resultant aldehyde employing Gilbert's (diazomethyl)phosphonate conditions[43,44] set up terminal acetylene **2.5.3.7**, an appropriate substrate for a classical Negishi carboalumination with iodine quench. [45] The (*E*) vinyl iodide **2.5.3.8** was then coupled with *tert*-butyl crotonate in the key Heck reaction catalysed by palladium acetate under newly developed conditions employing 1.1 equivalents of silver carbonate in dichloromethane. Only a few per cent of unwanted (*Z*, *E*) isomer was formed. Remarkably, with DMF or THF as solvents the reaction required 5-8 days to progress anywhere near completion! No explanation was offered for this solvent effect and no other studies were carried out with other non-complexing solvents.

Oxidation of the resultant diol with *N*-oxammonium chloride (**2.5.3.9**) gave an unstable hydroxy aldehyde which was immediately further oxidised to hydroxy acid **2.5.3.10** with sodium chlorite. Ring closure again with Adam's protocol and deprotection (aqueous HF, THF) afforded the natural product **1.5.1.1** in 2% overall yield.

Wovkulich's synthesis of 1233A is linear and not short at 24 steps but the overall yield of 2% is reasonable when compared with previous approaches discussed above. However the first key step, [2,3]-Wittig rearrangement, only gave 40% of the desired product and the second key step produced mixtures of diastereoisomers. Although some of these isomers could be re-processed by equilibration, it is still somewhat inelegant and laborious to proceed with a reaction which is not selective synthetically (*i.e.* would require either very easy separation or no separation at all). Chiral pool materials are relied on heavily in the above approaches but Wovkulich has started with a catalytic asymmetric hydrogenation of diketone **2.5.2.1**, a more efficient and forward-thinking

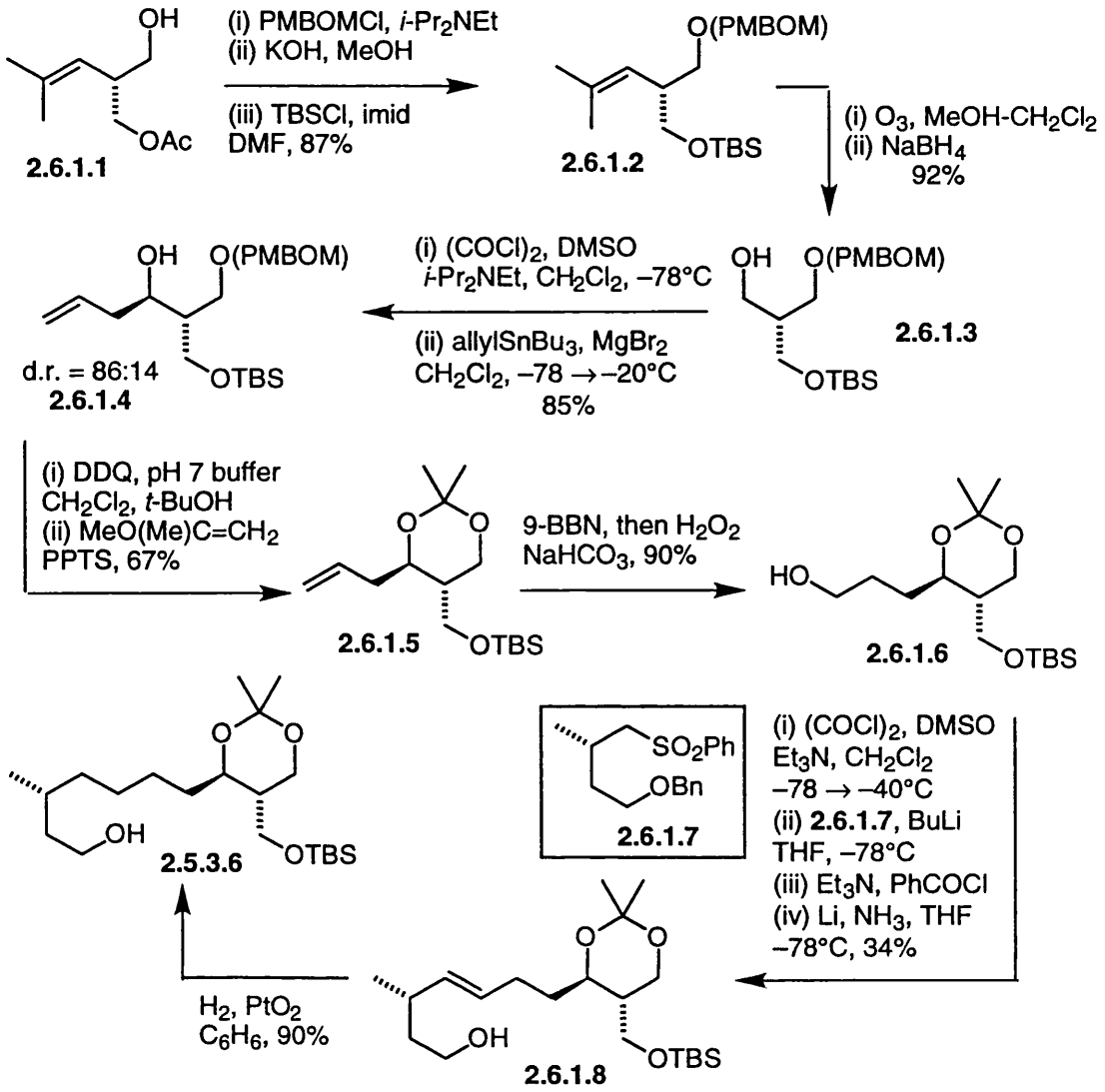
strategy. Finally the palladium catalysed Heck cross-coupling, although requiring a large excess of *tert*-butyl crotonate (35 equivalents), was very satisfying since installation of hindered multi-substituted olefin systems with most commonly used methodologies (*e.g.* Wittig, dehydration) are almost always accompanied by significant quantities of geometrical isomers.

2.6 The Guanti Formal Synthesis

Only three years ago, Guanti published a synthesis[46] of advanced intermediate **2.5.3.6** from the Wovkulich synthesis therefore constituting a formal total synthesis.

The starting alcohol **2.6.1.1** was prepared from the corresponding diol by an enantioselective PPL catalysed monoacetylation (96% ee). Protection of the alcohol as it's *para*-methoxybenzyloxymethyl (PMBOM), exchange of the acetate for TBS and ozonolysis with reductive work-up gave primary alcohol **2.6.1.3**. Swern oxidation allowed a diastereoselective Lewis acid catalysed allylation providing secondary alcohol **2.6.1.4** with a diastereomeric ratio of 86:14. After removal of the PMBOM group with DDQ, acetonide formation and hydroboration of the terminal olefin, another Swern oxidation was performed to give an aldehyde which was the electrophilic partner in the key step: addition of the anion of sulfone **2.6.1.7** (derived from (*R*)-methyl 3-hydroxy-2-methylpropanoate in 8 steps, 69% yield) to the aldehyde followed by *in situ* benzoylation of the intermediate β-hydroxy sulfone and elimination to the olefin **2.6.1.8** with lithium in liquid ammonia. This route was found to produce an acceptable yield (34% from **2.6.1.5**) compared to other standard work-up procedures e.g. elimination of the benzoyl derivative with sodium amalgam.

Platinum catalysed hydrogenation of the 9:1 *E*:*Z* mixture of alkenes produced the target intermediate **2.5.3.5** in 11% overall yield (*c.f.* Wovkulich's overall yield for the same intermediate of 3%).



Scheme 2.6.1

2.7 Conclusions

In this chapter, syntheses of the cholesterol biosynthesis inhibitor 1233A already published in the literature have been discussed. It is clear that, although these works possess some originality and reach their goals, there is still much to be improved. Particularly, the synthesis of the 2-oxetanone core has been approached in similar ways and there have been very few stereoselective methods towards the diene moiety.

Chapter 3

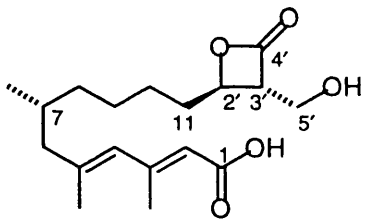
Structural Features and Retrosynthetic Analysis of 1233A

3.1 Introduction

This chapter will discuss the structural features of 1233A and the possible approaches to a total synthesis. These approaches will employ both novel and very recently published methodology. The goal is to make real contributions to the field of organic synthesis by designing a concise and stereocontrolled route to the target.

3.2 Structure Features of 1233A

1233A is an oxygenated natural product consisting of a strained *trans* disubstituted 2-oxetanone ring. On carbon 3′, α to the ring carbonyl, resides a hydroxymethyl group. On carbon 4′ there is a straight chain of 11 carbons terminating in a carboxylic acid. In the centre of this chain resides an isolated chiral methyl group. A hexasubstituted diene unit is in conjugation with the terminal acid moiety, posing a considerable challenge to the synthetic chemist.



Antibiotic 1233A 1.5.1.1

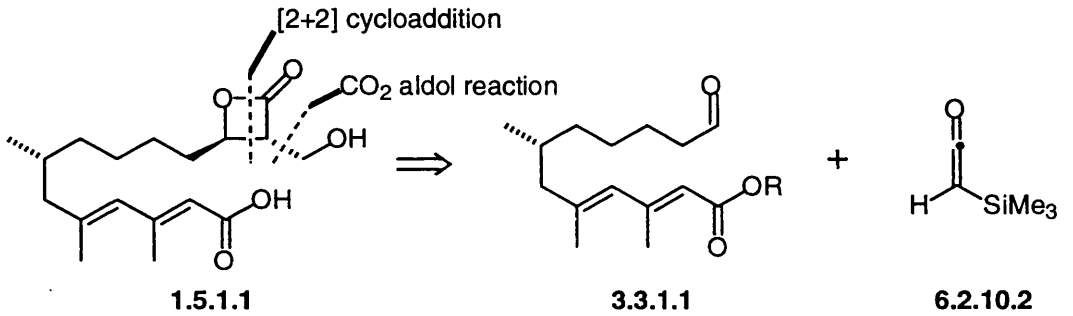
Figure 3.2.1

3.3 Retrosynthetic Analysis

In the previous two chapters, biological data and previous total syntheses were discussed. Therefore it becomes clear that 1233A possesses usefulness through the inherent reactivity of the 2-oxetanone ring and that this structural feature may only be synthesised with difficulty using predominately ring closure strategies. Hence the oxetanone motif poses the most significant synthetic challenge since there is a real need for more efficient and generally applicable methodologies.

Past tactics have entirely relied upon the ring-closing methodology of Adams[38] (see Chapter 2). A new approach would be disconnection of *both* the indicated bonds in Scheme 3.3.1. An asymmetric [2+2] cycloaddition of a silylketene

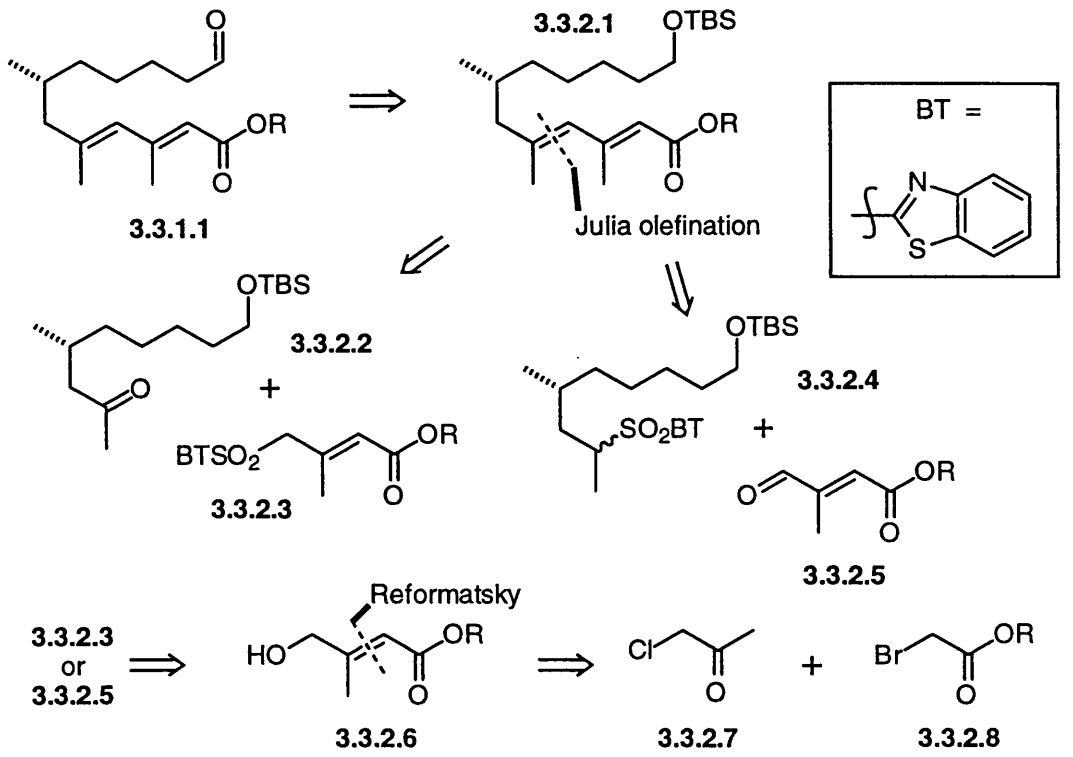
with an aldehyde should accomplish this transformation. The history and development of this chemistry is fully detailed in chapters 6 and 7 and at this point it should be made clear that this methodology was developed *before* the synthesis of the natural product was undertaken. Before such a cycloaddition, retrosynthetic removal of the hydroxymethyl group will be necessary. Quenching a β-lactone-derived enolate with carbon dioxide in an aldol-type process could lead to an acid which could be reduced to the desired hydroxymethyl group. This chemistry had to be investigated before any work towards the natural product could be undertaken (see Chapter 8).



Scheme 3.3.1

Aldehyde **3.3.1.1** then becomes the next target for analysis. Shielding of the reactive aldehyde as a silyl protected alcohol (e.g. TBS) leads to consideration of possible disconnections towards the diene moiety. Wovkulich reported a stereoselective Heck reaction (see Chapter 2) which seems quite efficient (although a few per cent of an unwanted isomer was isolated), but it would be worthwhile to consider other interesting routes using new methodology.

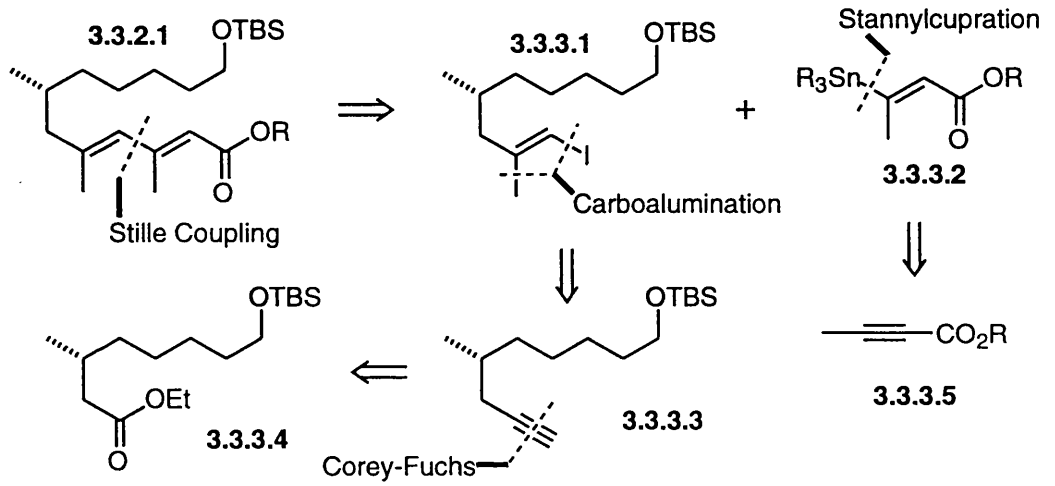
A Julia olefination strategy[47] (see Chapter 4) would be one possibility where either ketone **3.3.2.2** and sulfone **3.3.2.3** or sulfone **3.3.2.4** and aldehyde **3.3.2.5** could be coupled together (Scheme 3.3.2).



Scheme 3.3.2

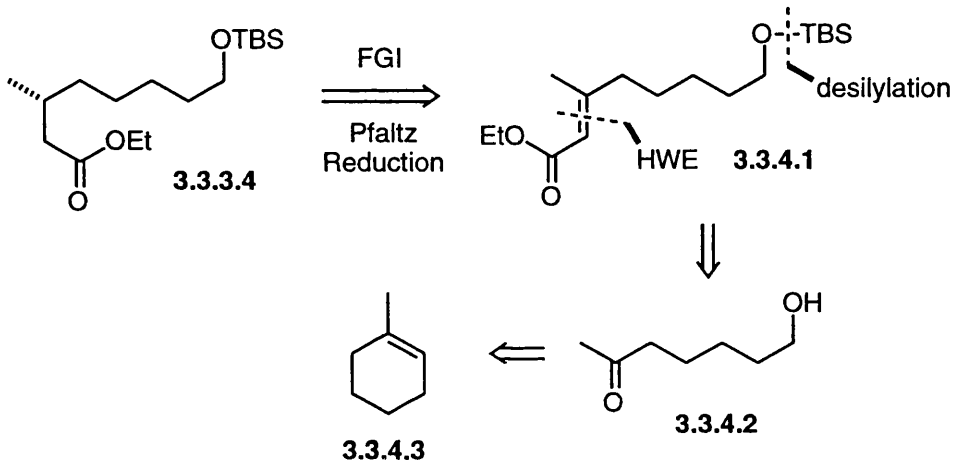
Sulfone **3.3.2.3** and aldehyde **3.3.2.5** should be available from common intermediate **3.3.2.6** which itself can be synthesised *via* a Reformatsky reaction of the appropriate α-bromo ester **3.3.2.8** with chloroacetone. [48]

Failing this, one alternative could be the Stille coupling[49,50] of vinyl stannane **3.3.3.2** with vinyl iodide **3.3.3.1**. This disconnection is shown in Scheme 3.3.3: vinyl iodide **3.3.3.1** would almost certainly be available through the Negishi carboalumination[45] (see Wovkulich's total synthesis, Chapter 2) and vinyl stannane **3.3.3.2** could be accessed with a stannylcupration[51] of the desired ester of tetrolic acid. Acetylene **3.3.3.3**, the carboalumination substrate, could be formed with a Corey-Fuchs homologation[52] of the corresponding aldehyde. An oxidation state change leads to the key intermediary chiral ester **3.3.3.4**.



Scheme 3.3.3

In order to install the isolated chiral methyl group in ester **3.3.3.4** it would be more efficient to employ a catalytic asymmetric reaction instead of using a chiral pool approach as in some past syntheses of 1233A. Cobalt semi-corrin catalysed reduction of α, β-unsaturated esters to give β-chiral saturated esters was developed by Pfaltz[53] in the 1980's (see Chapter 4). This reaction, which has received little attention in the literature, is extremely efficient requiring only 1 mol% of the catalyst which is commercially available. The disconnection to α, β-unsaturated ester **3.3.4.1** is shown in Scheme 3.3.4.



Scheme 3.3.4

Retrosynthetic cleavage of the double bond in **3.3.4.1** with, perhaps, a Horner-Wadsworth-Emmons[54] reaction leads to 7-hydroxyheptan-2-one (**3.3.4.2**). This seven carbon starting material is not commercially available but could be synthesised easily (*via* ozonolysis and selective reduction of the aldehyde group) after a reconnection reveals 1-methyl-cyclohexene (**3.3.4.3**).

The above analysis will, of course, change as laboratory work progresses.

3.4 Conclusions

In this chapter a retrosynthetic analysis of the cholesterol biosynthesis inhibitor 1233A has been detailed employing a plethora of metal mediated reactions, including a novel [2+2] cycloaddition of an aldehyde with a silylketene and a catalytic enantioselective reduction.

Chapter 4

The Use of a Cobalt Semicorrin Catalysed Enantioselective Reduction for the Synthesis of Chiral Ester 3.3.3.4

4.1 Introduction

This chapter will discuss the approach towards the synthesis of the first chiral key intermediate: β-chiral ester **3.3.3.4** (Figure 4.1.1).

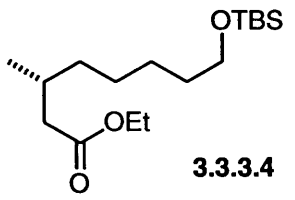
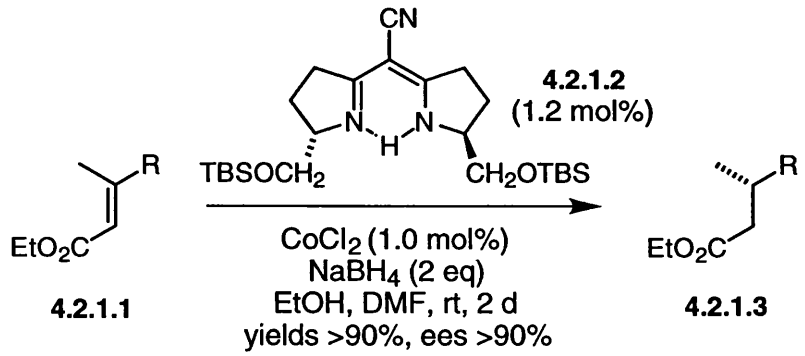


Figure 4.1.1

4.2 The Cobalt Semicorrin Catalysed Enantioselective Reduction

Over the past two decades, asymmetric catalysis has evolved into a dynamic and rapidly growing area of research. As a result, powerful synthetic catalysts have become available which exhibit levels of enantioselectivity previously considered beyond reach for non-enzymatic processes.[55] The impressive enantioselectivities that have been achieved are exemplified by combining a catalytically active metal with different types of chiral ligands, for example, ruthenium-BINAP hydrogenation,[56,57] Sharpless epoxidation[58,59] and now the Pfaltz conjugate reduction of an α,β-unsaturated ester with cobalt semi-corrin catalyst **4.2.1.2** (Scheme **4.2.1**).[53,60]



Scheme 4.2.1

A new stereogenic centre is created if the olefin portion is tri- or tetra-substituted. The configuration of the product may be controlled at will by using either the natural or unnatural ligands derived from L- or D-pyroglutamic acid. Alternatively, the ligand is available commercially albeit at a premium. The

product configuration may also be controlled by changing the geometry of the olefin substrate: the opposite product enantiomer is obtained by changing from (*E*) to (*Z*) if the same catalyst is used. Hence, this chemistry is very flexible and therefore the more accessible substrate isomer may be used with the appropriate catalyst to give the desired product.

The semi-corrin ligand which is complexed to cobalt is conformationally rigid with the chirality elements in close proximity to the co-ordinating metal centre. This is a central tenet of Pfaltz's approach to enantioselective catalysis and has borne much fruit.

The semi-corrin ligand may also be used for the copper catalysed enantioselective cyclopropanation of olefins with diazo compounds.[53]

4.3 Synthesis of Trisubstituted Olefin 3.3.4.1

In order to carry out the cobalt catalysed enantioselective reduction a stereocontrolled synthesis of trisubstituted α,β-unsaturated ester **3.3.4.1** was required. From the discussion above it is clear that to obtain the desired (*R*) configuration of **3.3.3.4** an (*E*) olefin will be required using the ligand **4.2.1.2** derived from natural L-glutamic acid. Two approaches were investigated: a Horner-Wadsworth-Emmons reaction and a carbocupration reaction.

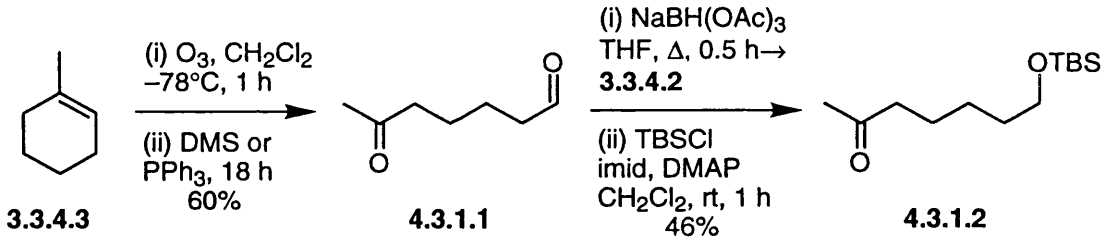
4.3.1 The Horner-Wadsworth-Emmons Approach to α,β-Unsaturated Ester 3.3.4.1.

4.3.1.1 Synthesis of Ketone 4.3.1.2 *via* Ozonolysis of 1-Methylcyclohexene

The now classical reaction between a carbonyl compound and a phosphorus ylid revolutionised organic synthesis after its original publication in 1949.[61] Alkenes became readily available and since they were invariably embedded in the structure of many natural products they were on the target list of many synthetic chemists. Inevitably this widespread use led to many improved versions of the original reaction. One of these improvements was the use of phosphonates instead of phosphoranes.[54] Generally, phosphorane derived ylids give (*Z*) olefins and olefination with phosphonate carbanions gives (*E*)

products. The phosphonate variation has come to be known as the *Horner-Wadsworth-Emmons modification* of the Wittig olefination.

In order to obtain (*E*) stereoselectivity in the synthesis of **3.3.4.1** the Horner-Wadsworth-Emmons (HWE) reaction could be applied . A reaction between a protected 7-hydroxyheptan-2-one (**4.3.1.2**) and the anion of triethylphosphonoacetate should yield **3.3.4.1**. Therefore the first objective was to prepare **4.3.1.2**. Although alcohol **3.3.4.2** is known in the literature, these published methods are not synthetically useful since yields were low and the product was often obtained as complex mixtures with other side-products.[62,63] An alternative approach could be the ozonolytic ring-opening of 1-methylcyclohexene (**3.3.4.3**) with reductive work up followed by selective reduction of the aldehyde. Scheme 4.3.1 shows the result of this chemistry.



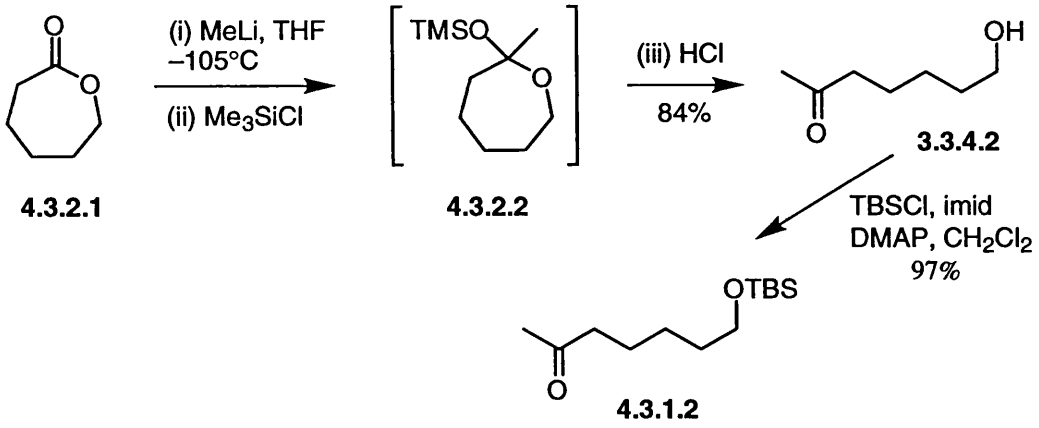
Scheme 4.3.1

Ozonolysis of **3.3.4.3** at −80°C in dichloromethane with reductive work-up (dimethylsulfide or triphenylphosphine) gave a 60% yield of aldehyde **4.3.1.1**. Selective reduction of the aldehyde carbonyl with two equivalents of sodium triacetoxyborohydride in refluxing THF furnished alcohol **3.3.4.2** in 70% yield. Silylation of **3.3.4.2** proceeded uneventfully giving protected ketone **4.3.1.2**, the HWE substrate, in a moderate 65% yield. However, preparation of **4.3.1.2** *via* this three step procedure was laborious and low yielding (27% overall) and the ozonide derived from **3.3.4.3** was found to only slowly decompose under the reductive conditions and in one case actually detonated on distillation (after probably inadequate reductive treatment) so a more practical route was sought.

4.3.1.2 Synthesis of Ketone 4.3.1.2 *via* Ring-Opening of ε-Caprolactone

In 1993 Overman published procedure allowing transformation of an ester to the analogous methyl ketone *via* methyllithium addition.[64] It is logical to

extend this method to lactones thereby providing access to hydroxy methyl ketones. Hence, **3.3.4.2** could be accessed by a ring-opening reaction of the very cheap ε-caprolactone with methyl lithium at –105°C (Scheme **4.3.2**).



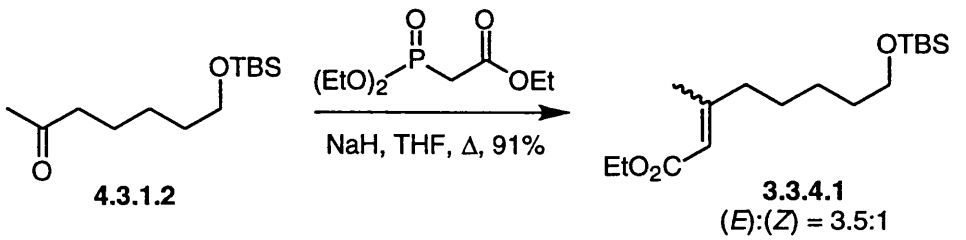
Scheme 4.3.2

Temperature control is essential to prevent methyl ketone formation during the reaction and hence double addition of a methyl group. (In previous studies, **4.3.2.1** was ring-opened with methyl lithium and also methyl magnesium chloride; as expected, a statistical mixture of unreacted starting material, desired product and tertiary alcohol (from double addition) were isolated.) The second stage, after addition of the methyl group to the carbonyl, is the trapping of the anion intermediate with trimethylsilyl chloride. In this way, the mono-addition product may be warmed to 0°C and hydrolysed with dilute hydrochloric acid resulting in a satisfying 84% isolated yield of **3.3.4.2**. Protection with *tert*-butyldimethylsilyl chloride produced an almost quantitative yield (97%) of ketone **4.3.1.2**. This improvement in yield was most likely due to better quality **3.3.4.2** stemming from a more efficient and cleaner preparation. The ring-opening reaction was performed on a 0.1 mole scale. Overall yields for this improved process are 81%, a three-fold improvement over the initial route.

4.3.1.3 The Horner-Wadsworth-Emmons Reaction

Having access to suitable quantities of ketone **4.3.1.2** provided the opportunity to explore the HWE reaction for the synthesis of **3.3.4.1**. Using

triethylphosphonoacetate with sodium hydride in refluxing THF gave 91% of the desired product (Scheme **4.3.3**).



Scheme 4.3.3

Unfortunately, **3.3.4.1** was isolated as a 3.5:1 mixture of (*E*):(*Z*) geometrical isomers. Various conditions were explored to attempt to improve this isomeric ratio:

(i) Conducting the reaction at a lower temperature (rt, 18 h).
(ii) The influence of tertiary amine bases and added salts on enolate formation and stabilisation has been well documented. [65]
(iii) Use of differently substituted phosphonates.

Attempt (i) resulted in no change in ratio or yield and (ii) gave no reaction. (iii) was tried with several phosphonates: ethyldi*iso*-propylphosphonate was the best but only offered a marginal improvement in (*E*):(*Z*) ratio to 5:1. The greater cost and slim gain in isomer ratio was, on balance, judged to be unworthy of pursuit. Despite the above disappointments, the (*E*) and (*Z*) isomers were separable with careful chromatography: various batches of different purities were obtained; repeatedly chromatographing these batches with the same column of silica gel in a recycling fashion eventually resulted in production of pure (*E*) isomer **3.3.4.1**. Chromatographic separation in this manner is not entirely practical and somewhat laborious therefore a more efficient preparation of **3.3.4.1** was sought.

4.3.2 The Carbocupration Approach to α,β-Unsaturated Ester 3.3.4.1.

Organocuprate methodology represents an important niche in organic synthesis. Organocuprates $R_2CuLi{\bullet}LiI$, prepared from two equivalents of lithium reagent and a copper (I) salt CuX (typically X = I, Br, CN) are indispensable reagents

for selective carbon-carbon bond formation. [66,67] A fundamental problem with these reagents is that only one of the R groups is utilised in synthetic applications. Hence the ultimate goal in organocuprate chemistry would be a reactive cuprate with a cheap, non-toxic non-transferable ligand. Previous work towards this goal has comprised of two basic approaches using a non transferable ligand which is:

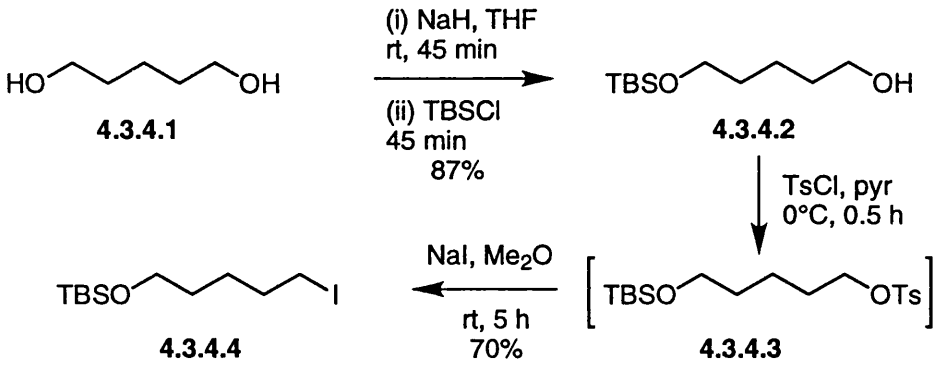
(i) bonded to Cu at an sp or sp^2 carbon (e.g. alkynyl[68] or 2-thienyl, [69,70] respectively) or
(ii) attached to Cu *via* a heteroatom such as S, [71] N, [72,73] or P. [72-75]

These approaches have all been less than ideal. The best solution to date appears to be RCu(Th)Li•LiI (Th = 2-thienyl) but this is often not reactive enough and the thienyl group is sometimes transferred.
However, recently, Bertz published a new approach[76] based on his earlier work investigating the effect of TMS on the acceleration of organocuprate conjugate addition. [77] Incorporating a β-silyl group into the cuprate structure was expected to give a highly reactive cuprate since, in this position, the silicon stabilises the transition state. Indeed when the *trimethylsilylmethyl* ($TMSCH_2$) group is one of the cuprate ligands and the other is the alkyl group to be transferred, a cuprate of unparalleled reactivity is produced. To illustrate the stoichiometry, these new reagents may be written as $R(TMSCH_2)CuLi•LiX$. They have been shown to be:

(i) highly reactive (even more reactive than the corresponding homocuprates);
(ii) thermally stable at room temperature;
(iii) economical with respect to the transferred group.

Two important reactions of cuprates were studied by Bertz: conjugate addition and ketone formation from acid chlorides.
Application of this new work to the synthesis of **3.3.4.1** was envisioned using a carbocupration of the commercially available acetylene compound ethyl tetrolate (also known as ethyl-2-butynoate (**4.3.5.3**)). Temperature control is essential to obtain entirely kinetic product. [78] Since kinetic addition will be *syn*

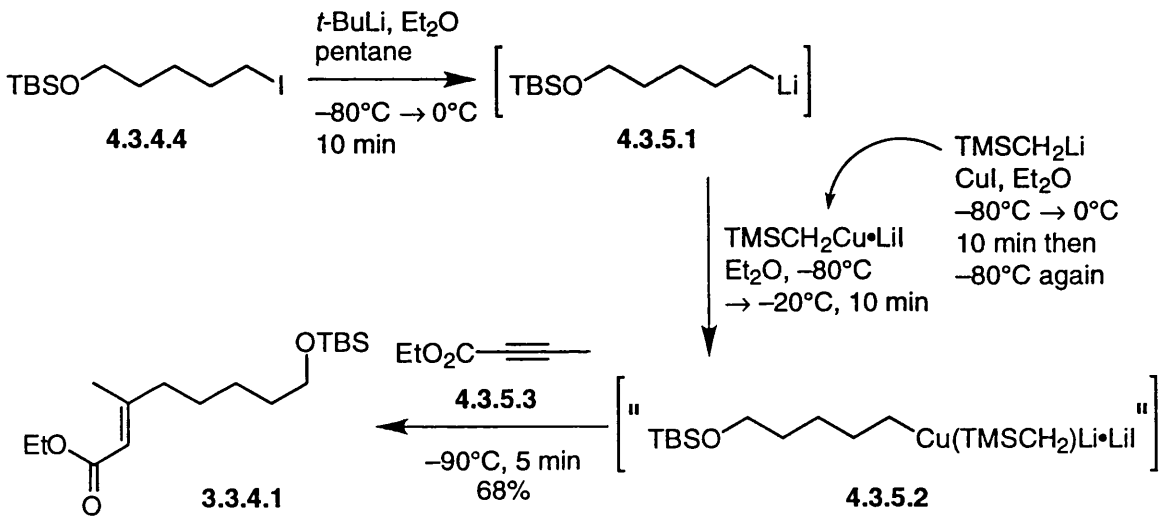
across the acetylene, the transferred ligand must be the more complex chain which may be derived from iodide **4.3.4.4** (Scheme **4.3.4**).



Scheme 4.3.4

Hence mono-TBS protection of pentan-diol using sodium hydride in THF and TBSCl gives alcohol **4.3.4.2.** [79] Mono-protection of diols is usually accompanied by the *bis*-protected product and some unreacted starting material but when sodium hydride is used, the mono-sodium anion precipitates from solution and slowly reacts with the TBSCl giving only protection of one alcohol. Subsequent tosylation and displacement with iodide gives the desired iodide **4.3.4.4.** [80]

The cuprate derived from commercially available trimethylsilylmethyl lithium was prepared from copper (I) iodide (the best results are obtained with freshly purified copper (I) iodide) in ether then added to lithium derivative **4.3.5.1**. Lithiation of **4.3.4.4** with *tert*-butyllithium in ether/pentane solvent was necessary since THF resulted in almost complete Wurtz coupling.

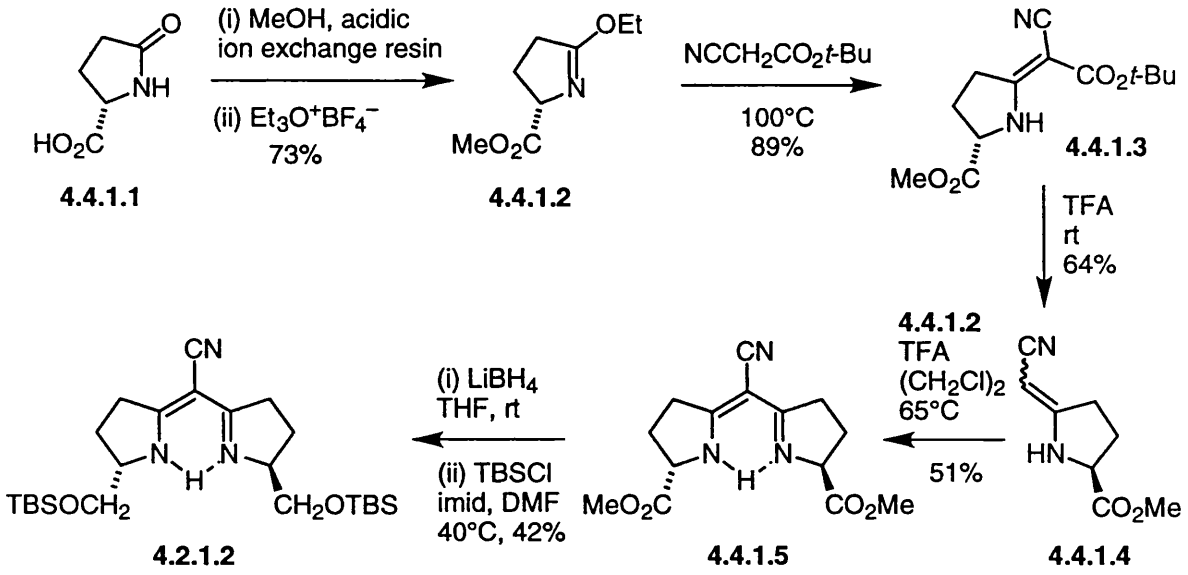


Scheme 4.3.5

This mixed cuprate **4.3.5.2** is quite thermally stable and may be annealed at 0°C. After cooling to –90°C (internal temperature) the ethyl tetrolate (**4.3.5.3**) may be added (Scheme 4.3.5). Maintaining the internal temperature at –90°C or below is essential for good stereocontrol. The reaction is complete before any TLC analysis can be performed and is quenched at the low temperature. Moderate yields of the product (68%) are obtained but importantly the (*E*) isomer is formed exclusively. Although chromatographic separation of the (*E*) and (*Z*) isomers is possible, as stated above, it is not practical so this cuprate methodology represents a significant improvement with both a reduction in the number of synthetic steps from known compounds and an improvement in overall efficiency.

4.4 Synthesis of Chiral Ester 3.3.3.4 *via* the Cobalt Semicorrin Catalysed Enantioselective reduction.

Due to its expense, commercially available ligand **4.2.1.2** had to be synthesised using the developed method of Pfaltz. [53] Scheme **4.4.1** shows this chemistry which starts with an esterification of either L- or D-pyroglutamic acid (**4.4.1.1**).



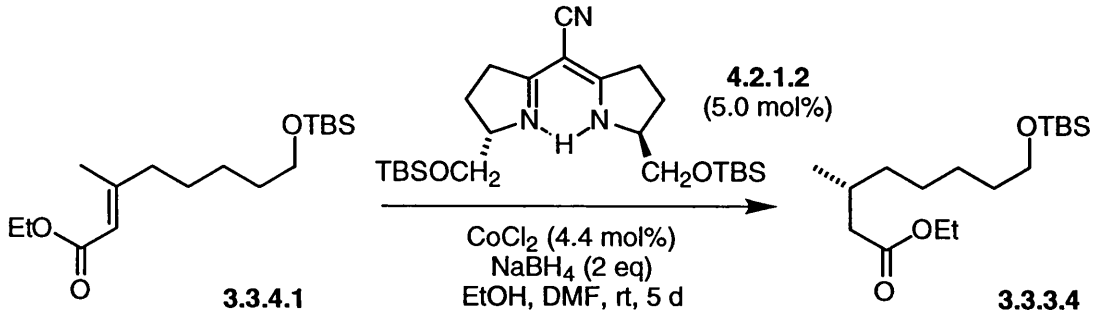
Scheme 4.4.1

L-pyroglutamic acid is more cheaply available from L-glutamic acid by refluxing in water overnight. Iminoester formation with triethyloxonium tetrafluoroborate gives **4.4.1.2**. Only part of **4.4.1.2** is taken forward for

treatment with *tert*-butylcyanoacetate followed by trifluoroacetic acid. The resulting 1:1 mixture of vinyl cyanides **4.4.1.4** was then coupled with the other portion of iminoester **4.4.1.2**, giving the first semi-corrin intermediate, *bis*-methyl ester **4.4.1.5**. For the enantioselective conjugate reduction reactions, it is necessary to convert these methyl ester groups into TBS substituted hydroxymethyls. Hence, reduction of the methyl esters with lithium borohydride in THF followed by TBSCl and imidazole in DMF at 40°C gave ligand **4.2.1.2** (42% yield for the last two steps; lit.[53]= 43%). For the reduction to succeed it is imperative that crystalline *bis*-ester **4.4.1.5** be obtained. Careful chromatography of **4.4.1.5** will result in material pure enough to be crystallised. However, in the reduction step, fresh or active but properly stored commercially available lithium borohydride solution in THF should be used to ensure successful conversion.

With large quantities of ligand **4.2.1.2** and olefin **3.3.4.1** in hand the reduction reaction could be attempted. At first, in order to generate material for evaluation of future steps, the reduction was carried out racemically with a standard palladium catalysed hydrogenation in ethyl acetate. A sample of the racemate is important in order to determine the eventual enantiomeric excess of the asymmetric process.

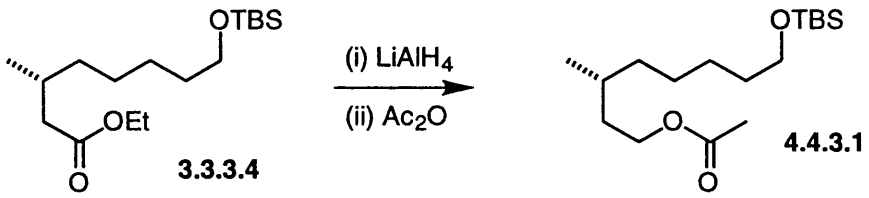
Initial attempts at the enantioselective reduction were successful but the reaction had not progressed to completion using 1.2 mol% of ligand **4.2.1.2** and 1.0 mol% of cobalt chloride. In this example the starting olefin and product were inseparable using TLC and it was reasonable to assume that any unreacted starting material would be either impossible or very difficult to remove from subsequent products. Hence the quantities of ligand and metal were increased to 5.0 mol% and 4.4 mol% and the reaction time was increased from 2 to 5 days in an effort to push the reduction to completion.



Scheme 4.4.2

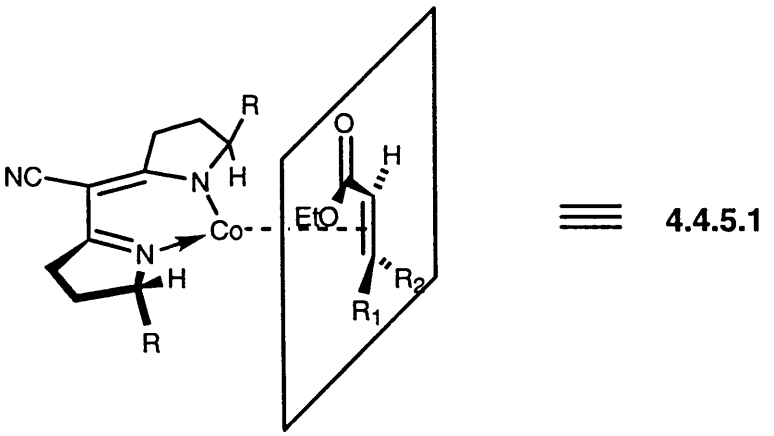
To our delight, these measures furnished a 96% yield of chiral ester **3.3.3.4** which was analytically pure after purification by chromatography (Scheme **4.4.2**).

Analysis of **3.3.3.4** with the chiral lanthanide shift reagent Eu(hfc)$_3$, [81] after reduction and acetylation of **3.3.3.4** to **4.4.3.1** according to Pfaltz[53] revealed that the product was of >90% ee or >20:1 ratio of enantiomers in favour of the desired (*R*) enantiomer (Scheme 4.4.3).



Scheme 4.4.3

Pfaltz has postulated a mechanism for the reduction involving initial formation of an *in situ* prepared Co(II)-semicorrin complex which is reduced by sodium borohydride to a Co(I)-semicorrin complex. This complex could then attack the electrophilic C=C π-system of the α-β-unsaturated ester substrate. This could lead to a cobalt π-complex such as **4.4.4.1** (Figure 4.4.4) or, *via* addition to the

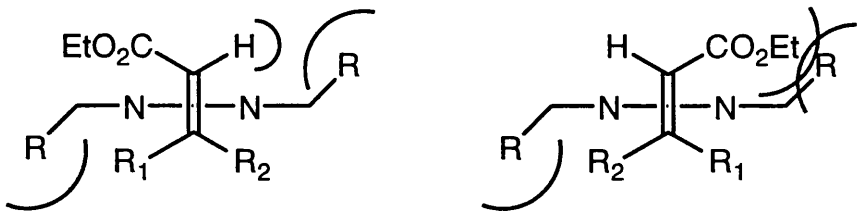


complex **4.4.4.1**

Figure 4.4.4

β-position, to a cobalt (III)-alkyl compound. Experiments with deuterium-labelled reagents has shown that the β-H atom of the product stems from the borohydride ($NaBD_4$ in EtOH/DMF) and that the α-H atom stems from ethanol ($NaBH_4$ in EtOD/DMF). An interpretation of these results could be that hydride transfer from $NaBH_4$ to a cobalt π-complex or to a cobalt-alkyl

intermediate is followed by intramolecular hydride shift to the β-carbon of the substrate. This may lead to a cobalt enolate which is protonated by the solvent. This would predict that the β-H atom is introduced on the same side of the C=C double bond which initially interacts with the cobalt. The observed enantioselectivities may be rationalised by referring to the hypothetical π-complexes in figure 4.4.5.



4.4.5.1 **4.4.5.2**

Figure 4.4.5

In **4.4.5.1** the ester group occupies a sterically non-congested area of space around the co-ordination sphere with the small H-atom placed in a sterically more crowded environment. In **4.4.5.2** the transition state is likely to be less stable since there is a strong steric interaction between the ester group and substituent of the semi-corrin ligand. Although experimental facts concerning the mechanism of this reaction are scarce, this model does explain the observed enantioselection in the reduction of **3.3.4.1** to **3.3.3.4**.

4.5 Conclusions

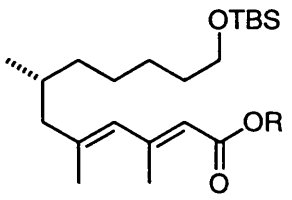
In this chapter, a practical, catalytic, enantioselective synthesis of the first key intermediate in our synthesis of 1233A has been discussed. Several routes to ketone **4.3.1.2** were explored but rejected in favour of a new cuprate protocol which only requires one equivalent of the transferred ligand. The resulting α,β-unsaturated ester **3.3.4.1** underwent the Pfaltz asymmetric cobalt semi-corrin catalysed reduction to give **3.3.3.4** in almost quantitative yield and high enantiomeric excess.

Chapter 5

The Use of a Copper (I) Thiophenecarboxylate Mediated Coupling for the Synthesis of Diene 3.3.2.1

5.1 Introduction

This chapter will discuss approaches towards the synthesis of the diene moiety **3.3.2.1** in the target 1233A (Figure 5.1.1 and see Chapter 3).

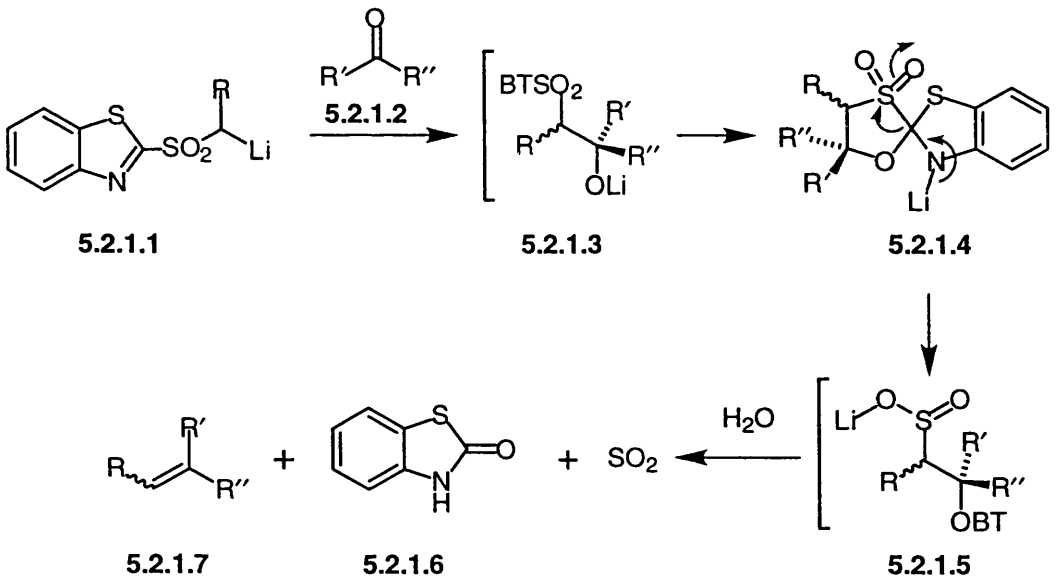


3.3.2.1

Figure 5.1.1

5.2 The Julia Olefination Approach for the Synthesis of Diene 3.3.2.1

Reaction of an α-metallated benzothiazolylsulfone (**5.2.1.1**) with an aldehyde or ketone (**5.2.1.2**) produces a β-lithioxy sulfone (**5.2.1.3**) which may undergo elimination to alkene **5.2.1.7** *via* **5.2.1.4** and **5.2.1.5** (Scheme 5.2.1).



5.2.1.1 **5.2.1.3** **5.2.1.4**

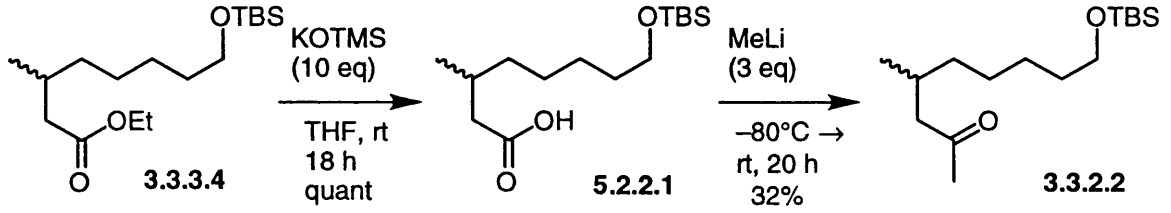
5.2.1.7 **5.2.1.6** **5.2.1.5**

Scheme 5.2.1

This one-pot reaction was reported in 1991 by Julia[47,82,83] and is known as the *one-pot-Julia olefination*. This reaction was used to synthesise diene **3.3.2.1** according to the previously described retrosynthetic analysis (Chapter 3). There are two permutations of reagents that may be combined in order to give

the same product: either ketone **3.3.2.2** and sulfone **3.3.2.3** OR aldehyde **3.3.2.5** and sulfone **3.3.2.4** (see Scheme 3.3.2).

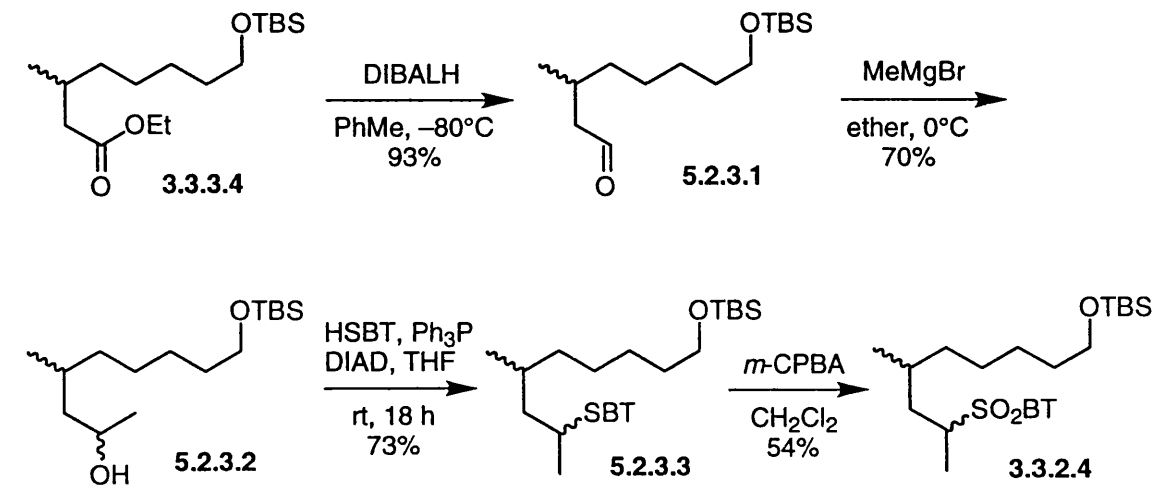
This chemistry was investigated using racemic compounds. Ketone **3.3.2.2** was synthesised from racemic ester **3.3.3.4** (from a Palladium catalysed hydrogenation of α,β-unsaturated ester **3.3.4.1**, see Chapter 4). Hence saponification of **3.3.3.4** with potassium trimethylsilanolate furnished a quantitative yield of acid **5.2.2.1** (Scheme 5.2.2).



Scheme 5.2.2

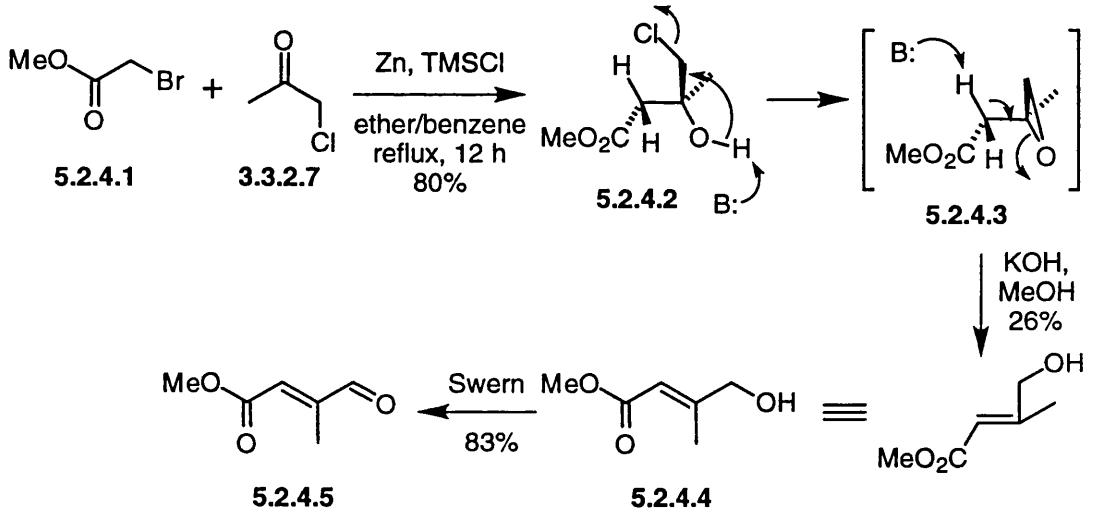
This reagent was used by Barrett to saponify an ester in the presence of sensitive silyl-protecting groups. [84] Treatment of acid **5.2.2.1** with three equivalents of methyl lithium led to the desired ketone **3.3.2.2**. Although the overall yield was low, sufficient quantities of **3.3.2.2** could be prepared in order to investigate the Julia olefination.

Sulfone **3.3.2.4** was also prepared from racemic ester **3.3.3.4** (Scheme 5.2.3). Initial functional group transformation of the ester to aldehyde **5.2.3.1** with DIBALH (see later discussion, Section 5.3.1.1) was followed by a methyl magnesium bromide Grignard addition to furnish alcohol **5.2.3.2** as a mixture of diastereoisomers. The benzothiazolyl group was installed in a 2 step procedure: Mitsunobu substitution of alcohol **5.2.3.2** with mercaptobenzothiazole led to sulfide **5.2.3.3** which was oxidised in moderate yield with *m*-CPBA to the desired sulfone **3.3.2.4**.

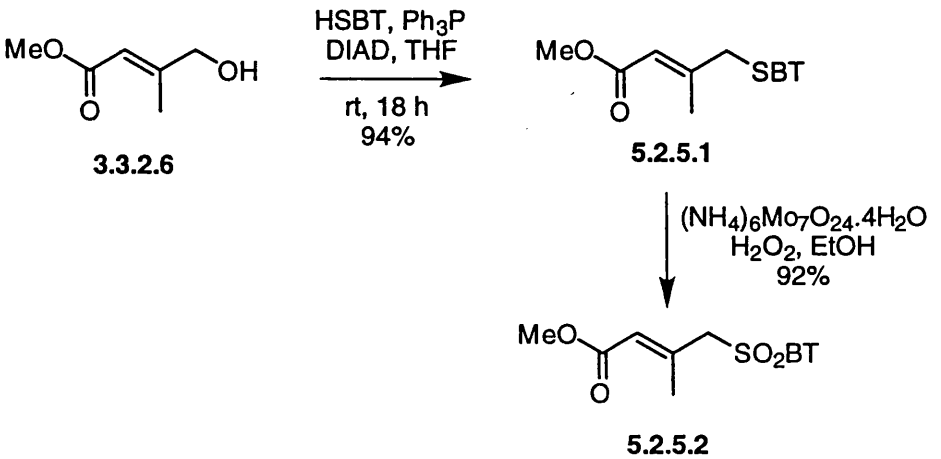


Scheme 5.2.3

Compounds **5.2.5.2** and **5.2.4.5** were prepared from common intermediate **5.2.4.4**. This compound was prepared by the method of Epstein[48] as one double bond isomer in 2 steps *via* Reformatsky reaction between methyl-bromoacetate (**5.2.4.1**) and chloroacetone (**3.3.2.7**) to give **5.2.4.2** in 80% yield (Scheme 5.2.4). Base induced stereospecific elimination proceeds *via* epoxide **5.2.4.3** to give **5.2.4.4** in the rather low yield of 26%. Although low yielding, this procedure was suitable for scale-up so that enough material could be generated for subsequent reactions. Swern oxidation of **5.2.4.4** gives **5.2.4.5** in 83% yield. Mitsunobu reaction of **5.2.4.4** with mercaptobenzothiazole, as above, followed by ammonium molybdate oxidation gave **5.2.5.2** in excellent yield (Scheme 5.2.5).



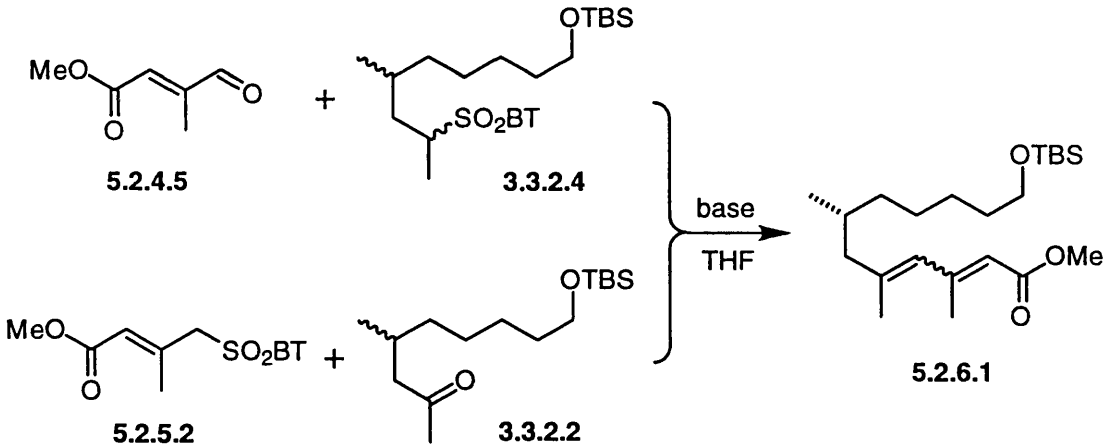
Scheme 5.2.4



Scheme 5.2.5

With the four required starting materials in hand, the investigation into the applicability of the Julia olefination for the synthesis of the diene portion of 1233A could commence. Table 5.2.6 shows the coupling of reagents to produce diene **5.2.6.1** (equivalent to **3.3.2.1**, R = Me). Unfortunately, both a low yield and poor selectivity were observed in entries 1 and 2, employing aldehyde **5.2.4.5**. No reaction was detected with the third entry, using ketone **3.3.2.2**. This could be due to the lower reactivity of the ketone present in **3.3.2.2**. Interestingly, the ratio of isomers produced in the successful case could be significantly influenced in favour of the desired (*E*, *E*) diene with the alternative base potassium hexamethyldisilazide.

However, since there are no documented examples of high control in the synthesis of trisubstituted alkenes with the Julia olefination, it was unlikely that any further perseverance with this approach would have resulted in complete stereocontrol. Therefore another method will be required in order to achieve an efficient diene installation.



Entry	Reactants	Base	Yield	Ratio (*E*, *E*):(*E*,*Z*)
1	**5.2.4.5 + 3.3.2.4**	LDA	40	1:1
2	**5.2.4.5 + 3.3.2.4**	KHMDS	35	2:1
3	**5.2.5.2 + 3.3.2.2**	LDA	0	–

Table 5.2.6

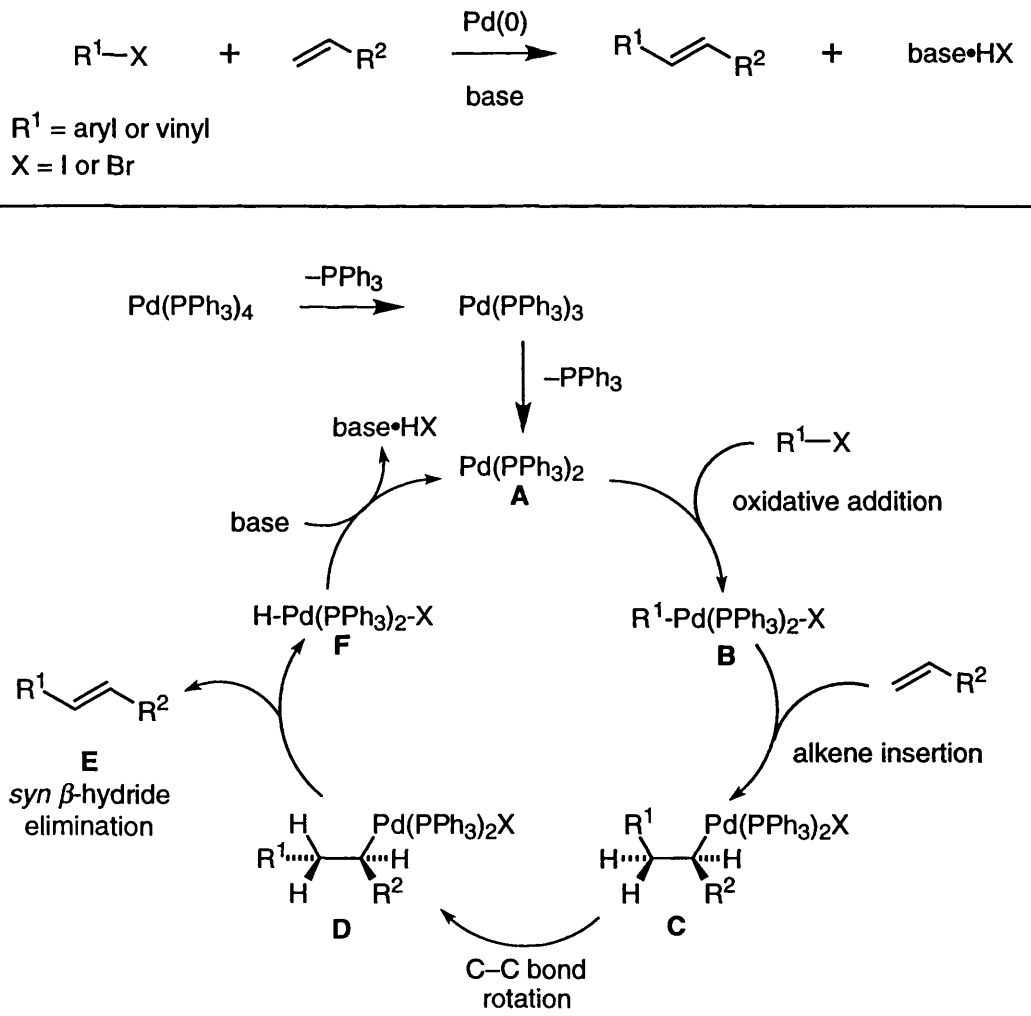
5.3 Palladium Catalysed Coupling protocols for Diene Synthesis

Palladium catalysed organic reactions have revolutionised contemporary organic synthesis. With the ability to form strategic bonds under extremely mild conditions, organic chemists have indeed found themselves a powerful

weapon. Two coupling protocols which may be carried out with some of the many available palladium catalysts are the Heck and Stille couplings.

5.3.1 The Heck Reaction

One highlight from the Wovkulich total synthesis of 1233A was an efficient synthesis of the diene moiety employing a palladium catalysed Heck reaction (see Chapter 2). This powerful carbon-carbon bond forming process is one of a plethora of palladium catalysed organic reactions which are believed to proceed *via* an oxidative addition of a coordinatively unsaturated 14-electron Pd^0 species **A** with an alkenyl or aryl halide (typically iodine) bond to give 16-electron complex **B** (Scheme 5.3.1).



Scheme 5.3.1

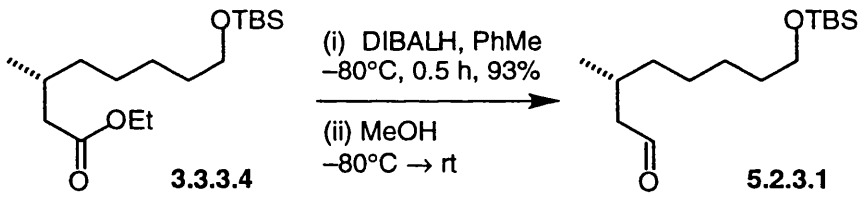
This is followed by insertion of the alkene or arene into the Pd-C bond generating intermediate **C** *via* a 4-centre transition state. This insertion occurs as a *syn* addition and it should be noted that the organic ligand from the palladium becomes bonded to the less hindered carbon of the olefin. In order to

create the necessary *syn* relationship between the Pd and β-hydride, a bond rotation of **C** occurs to give **D**, which may then eliminate to give **F** and the coupled product **E**. Finally a base-assisted reductive elimination of HX from **F** occurs to regenerate the Pd^0 catalyst.

Wovkulich used a vinyl iodide and *tert*-butyl crotonate (see Scheme 2.5.3) to achieve his transformation. Incorporation of this chemistry into our 1233A synthesis would constitute a useful exercise if only to generate material for investigation of future steps. Later, if successful, an alternative approach to the diene moiety could be developed if resources permit.

5.3.1.1 Synthesis of Iodide 3.3.3.1

Iodide **3.3.3.1** (see Scheme 3.3.3) would be required for coupling to *tert*-butyl crotonate. Synthesis of **3.3.3.1** could be approached as outlined in Chapter 3.. Hence DIBALH reduction of ester **3.3.3.4** produced aldehyde **5.2.3.1** smoothly in 93% yield (Scheme 5.3.2).

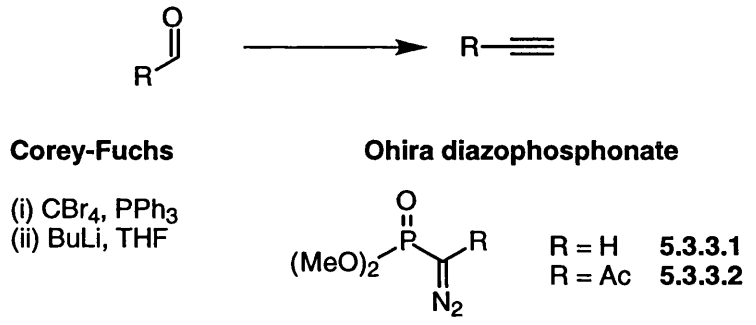


Scheme 5.3.2

A problem often associated with DIBALH reductions of esters is over-reduction to the undesired alcohol. Although some structures are predisposed towards over-reduction, e.g. β-oxygenated esters, this problem could also be due to unreliable TLC analysis. These reactions are typically closely analysed at low temperature for any alcohol formation. If this happens, the experimentalist often adds another equivalent of DIBALH thereby completely reducing the substrate to the alcohol which would be subsequently oxidised back to the required aldehyde (*e.g.* Swern). However, when the synthesis of aldehyde **5.2.3.1** was carried out, some alcohol was detected in the initial TLC analysis of the reaction mixture which was at –80°C. No more DIBALH was added, instead the reaction was quenched and worked-up in a standard fashion (see Experimental section for complete details) to reveal alcohol-free crude product. It is unlikely that any alcohol present would be washed into the aqueous layer

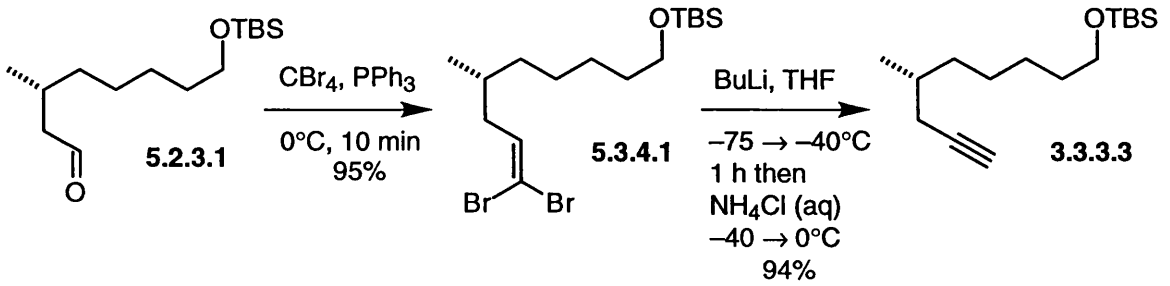
since the molecule is quite lipophilic, and considering the very high yield of purified product, it must be concluded that the TLC analysis of the reaction mixture indicated what was in the considerably warmer capillary and not what was actually in the reaction mixture itself.

Aldehyde **5.2.3.1** then had to be converted into a one-carbon homologated terminal acetylene which would be the substrate for a Negishi carboalumination (see similar steps in the Wovkulich synthesis of 1233A, see Chapter 2). Two methods were considered for achieving this goal: the Corey-Fuchs procedure[52] and Ohira's diazophosphonate reagent[85] (Scheme 5.3.3).



Scheme 5.3.3

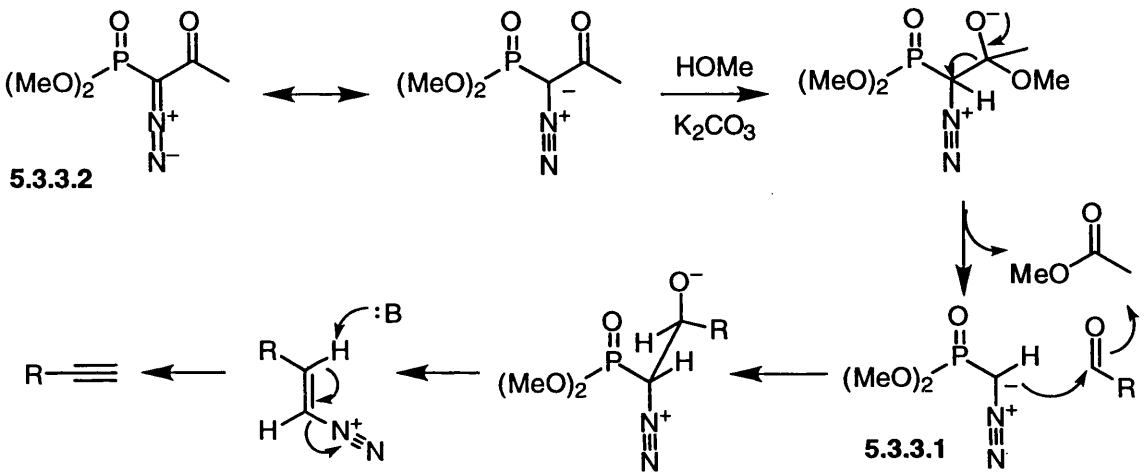
The former approach was used initially: treatment of aldehyde **5.2.3.1** with a previously prepared mixture of carbon tetrabromide and triphenylphosphine in dichloromethane solvent at 0°C for only a few minutes yielded the one-carbon homologated geminal dibromide **5.3.4.1** in almost quantitative yield. This compound then underwent elimination of HBr using *n*-butyl lithium in THF at low temperature. Protonolysis of the resulting lithium acetylide salt furnished terminal alkyne **3.3.3.3** in a satisfying overall yield of 89% (Scheme 5.3.4).



Scheme 5.3.4

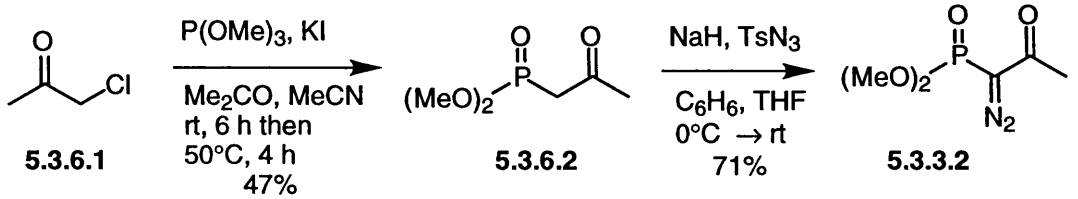
One of the disadvantages associated with this series of reactions is that there are 2 steps to be performed in order to install only one extra carbon. If this were true of the whole target molecule the synthesis would run up to 36 steps, a clearly undesirable scenario! Another problem is that the first step requires 2 equivalents of the reagent derived from CBr_4 and PPh_3 which has 1:2

stoichiometry, respectively. Therefore product isolation becomes arduous since there are 4 equivalents of phosphorus related compounds to be removed. Although the second step is not problematic (BuLi, THF, 80°C) it is always preferable to avoid low temperatures and expensive organolithium reagents. Having considered the above points, the diazophosphonate method could serve as an improvement. Two reagents may be used to accomplish the same transformation: either **5.3.3.1** or **5.3.3.2**. The latter has been shown to give higher yields, although **5.3.3.1** is formed in solution as the active reactant probably through loss of methyl acetate (see Scheme 5.3.5).



Scheme 5.3.5

In situ formation of **5.3.3.1** in this manner probably enhances the yield by supplying a more reactive form of **5.3.3.1** directly where it can be consumed. Following previously published work, the phosphonate **5.3.3.2** could be easily prepared (Scheme 5.3.6).



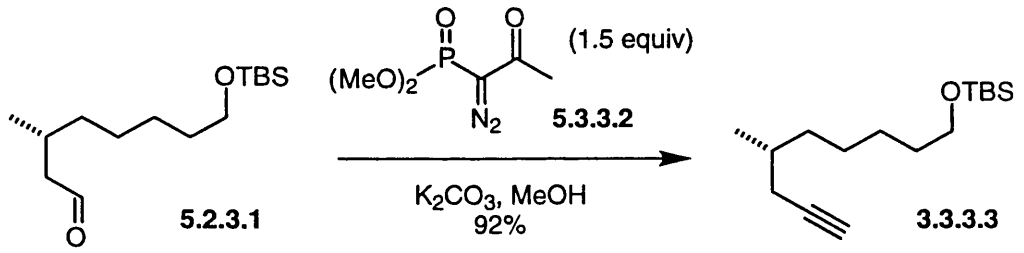
Scheme 5.3.6

An Arbuzov reaction with trimethylphosphite, chloroacetone (**5.3.6.1**) and potassium iodide in hot acetone/acetonitrile produced phosphonate **5.3.6.2** in 47% yield according to Noyori.[86] Formation of diazo compounds requires a suitable source of electrophilic nitrogen, usually tosyl azide. This compound

has an explosive character under extremes of pressure or temperature so caution was exercised. Its synthesis is very simple: tosyl chloride is mixed with sodium azide in aqueous ethanol and the product forms as a colourless oil which may be collected *neat* with a separating funnel. [87] After drying the product, no further purification is necessary and the reagent may be stored indefinitely in the refrigerator, at which temperature it forms colourless crystals.

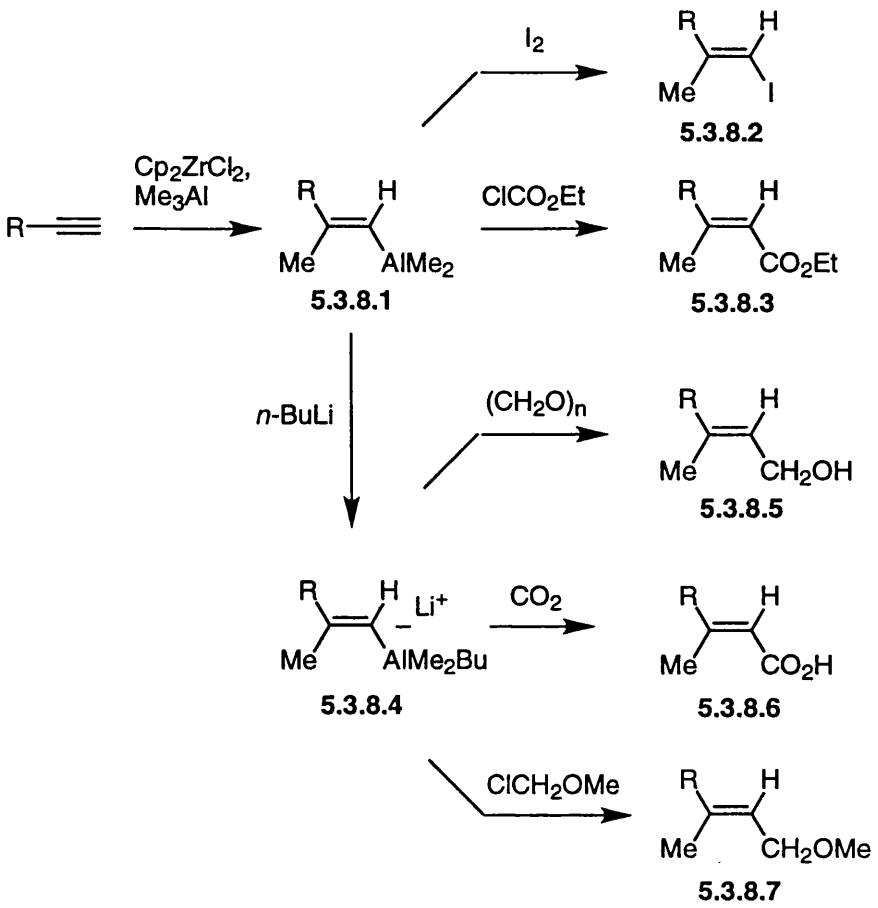
Treatment of **5.3.6.2** with sodium hydride in benzene/THF then with tosyl azide gave diazophosphonate **5.3.3.2**. If this reaction is carried out in THF alone, the de-acetylated product **5.3.3.1** is formed instead. This was not a great problem since **5.3.3.1** also homologates aldehydes to acetylenes but with a lower yield (56% *versus* 92%).

Reaction of aldehyde **5.2.3.1** with **5.3.3.2** in the presence of anhydrous potassium carbonate in dry methanol gave acetylene **3.3.3.3** in 92% yield (Scheme 5.3.7). Circumvention of an unnecessary Corey-Fuchs process has therefore been successfully achieved.



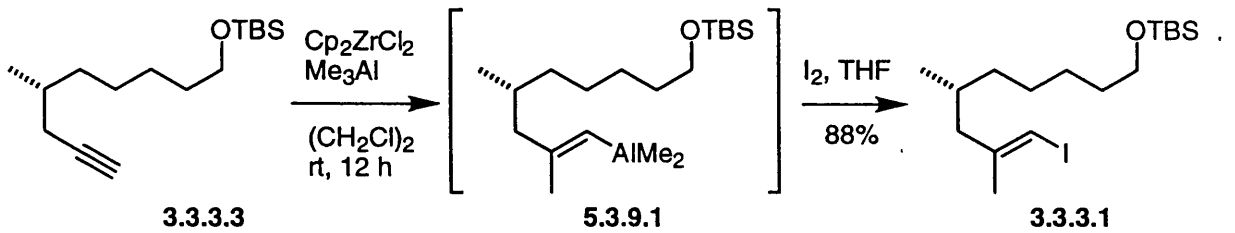
Scheme 5.3.7

Negishi's now classical carboalumination of acetylenes occupies a special niche in organic synthesis. The stereocontrolled functionalisation of an acetylene is itself of high utility but with many electrophiles to choose from the array of accessible functional groups is vast. Scheme 5.3.8 shows a few of the possibilities for one-carbon functionalisation. After carboalumination of alkyne **3.3.3.3** with zirconocene dichloride and trimethylaluminium, the intermediate vinyl alane **5.3.8.1** may be quenched with iodine giving vinyl iodide **5.3.8.2** or with a chloroformate to install an extra carbon atom as in compound **5.3.8.3**. **5.3.8.1** may be made more reactive by forming the ate complex **5.3.8.4** with *n*-butyl lithium. This complex may then be elaborated with a number of carbon electrophiles: paraformaldehyde gives allylic alcohol **5.3.8.5**; a carbon dioxide quench gives acid **5.3.8.6** and methoxymethylchloride (MOMCl) results in allylic ether **5.3.8.7**.



Scheme 5.3.8

For the synthesis of iodide **3.3.3.1** the intermediary vinyl alane **5.3.9.1** will need to be quenched with iodine, a rapid and most efficient protocol. Indeed the *syn* addition of the trimethylaluminium to alkyne **3.3.3.3** proceeded smoothly at room temperature (Scheme 5.3.9).



3.3.3.3 5.3.9.1 3.3.3.1

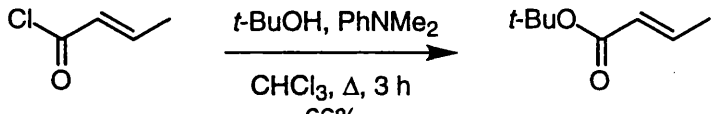
Scheme 5.3.9

Iodine quench was straightforward at –20°C giving a yield of 88% after chromatography. Many vinyl iodides are unstable in storage but **3.3.3.1**, if pure, did not appreciably decompose even over several months.

5.3.1.2 The Use of a Heck Coupling for Diene 3.3.2.1

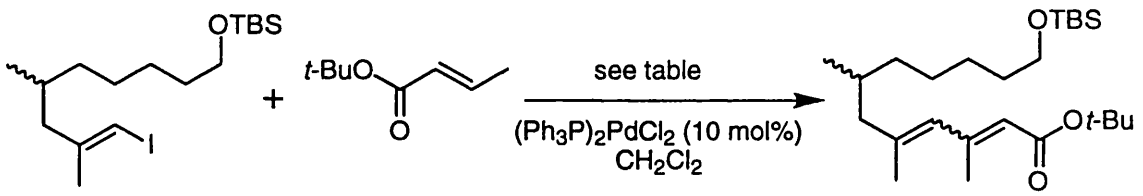
Having developed a high yielding and practical route to the required vinyl iodide **3.3.3.1**, all that remained was to prepare sufficient quantities of *tert*-butyl crotonate[88] (**5.3.10.2**) before the palladium catalysed Heck coupling could be attempted.

According to the method of McCloskey for *tert*-butyl ester synthesis, **5.3.10.2** was synthesised from crotyl chloride (**5.3.10.1**) in 66% yield (Scheme 5.3.10).



5.3.10.1 **5.3.10.2**

Scheme 5.3.10



3.3.3.1 **5.3.10.2** **5.3.11.1**

Entry	Equiv of 5.3.10.2	Silver Additive (Equiv)	Equiv of EtOH	Yield (%)	(*E*, *E*) : (*Z*, *E*)
1	7	Ag_2CO_3 (1.05)	65	89	1.2:1
2	21	$AgNO_3$ (1.1)	20	>95*	2.4:1
3	20	Ag_2CO_3 (1.16)	11	>95*	1.9:1
4	40	Ag_2CO_3 (1.13)	23	>95*	2:1

* = crude yield

Table 5.3.11

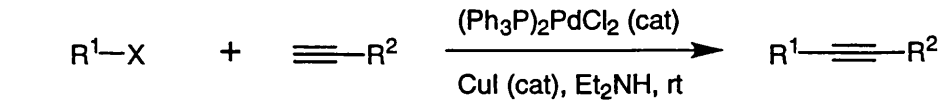
The Heck reaction was investigated with racemic iodide **3.3.3.1** and **5.3.10.2**. Initially, a modified reaction of Wovkulich[42] was used, instead of "re-inventing the wheel" due to the similarity between the vinyl iodides **2.5.3.8** and **3.3.3.1**. Entry 1 shows the conditions and results of this attempt using silver carbonate as the additive (see Table 5.3.11).

Although the yield was high (89%), crucially, the ratio of geometrical isomers was only 1.2:1 in favour of the desired (*E*, *E*) diene. The undesired (*Z*, *E*) isomer was inseparable by chromatography even after desilylation to the primary alcohol (TBAF, THF, rt). In an effort to increase the ratio of isomers, a different added silver salt was examined: silver nitrate influenced the reaction in a favourable manner but only up to 2.4:1 (Entry 2). Also in this case a larger excess of **5.3.10.2** was used (21 equivalents) since the literature example of Wovkulich used such a quantity. A closer look at the importance of the crotonate and added silver salt revealed that there are probably contributing factors from both variables since the ratio of 1.9:1 in entry 3 lies between that of entries 1 and 2. Finally, a reaction very similar to the literature example was conducted (Entry 4) but to no avail: a 2:1 ratio resulted. Clearly the goal of a highly stereoselective Heck approach towards the diene moiety may not be easily realised. The stability of the product was tested by resubmitting it to the reaction conditions and heating it in the presence of palladium catalyst and silver salts. No change in the initial ratio of diene isomers was observed. This suggests that the difference in product isomer ratios between **5.3.11.1** and **2.5.3.7** could be due to substrate structure. Therefore an alternative method will be required to synthesise diene **5.3.11.1** with complete stereocontrol.

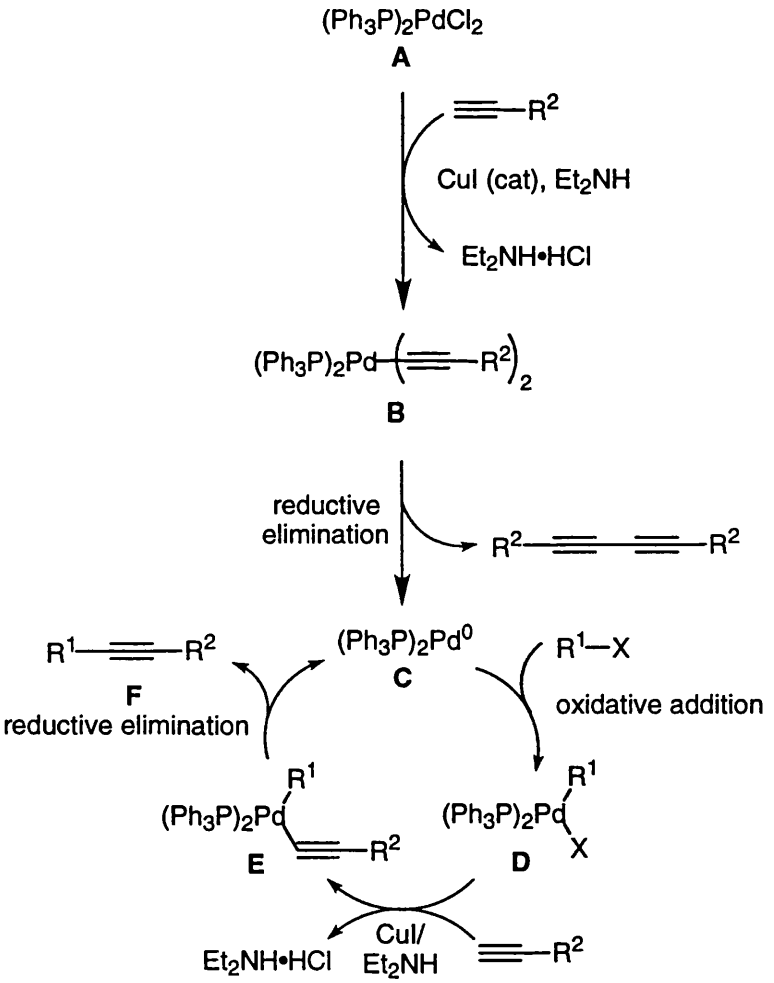
5.3.2 The Sonogashira-Negishi Approach to Diene 3.3.2.1

In 1975 Sonogashira *et al* demonstrated that terminal alkynes react smoothly with bromoalkenes, iodoarenes and bromopyridines in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and copper (I) iodide in diethylamine at room temperature. [89,90] This very mild Pd^0/Cu^L-catalysed linking of sp and sp^2 centres has proved most useful in complex natural product syntheses and in recognition of the valuable contribution of Sonogashira *et al* it is often referred to as the *Sonogashira coupling* reaction. Scheme 5.3.12 shows the presumed catalytic cycle: the active catalyst, *bis* (triphenylphosphine)palladium (0) could be formed *in situ* through sequential copper (I) iodide-catalysed *bis*-alkynylation and reductive elimination reactions (**A** → **B** → **C**). Coordinatively unsaturated 14-electron complex **C** participates in an oxidative addition reaction with the aryl or vinyl halide to give the 16-electron complex **D**. A copper (I)-catalysed alkynylation of **D** then furnishes aryl- or vinylalkynyl palladium (II) complex **E**. Finally, a terminating reductive

elimination step reveals the coupled product **F** and regenerates the active palladium (0) catalyst. These reactions are also successful starting with a palladium (0) catalyst, *e.g.* $Pd(PPh_3)_4$, as may be expected from the postulated mechanism.



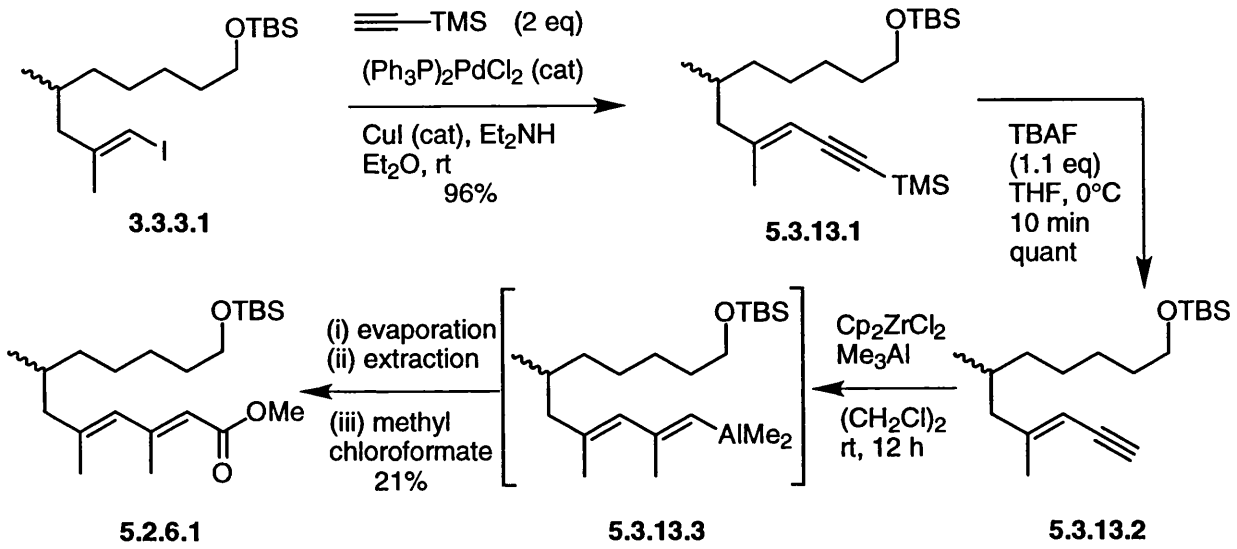
R^1 = aryl, vinyl or pyridyl
X = I or Br



Scheme 5.3.12

Notably, the Sonogashira coupling of a haloalkene of defined stereochemistry with an alkyne proceeds with retention of alkene geometry. For an application to the synthesis of 1233A, this would be ideal for extending the structure of iodide **3.3.3.1**. A further Negishi carboalumination of the resulting alkyne, quenching with a chloroformate (see Scheme 5.3.8), should result in the desired diene with complete stereocontrol.

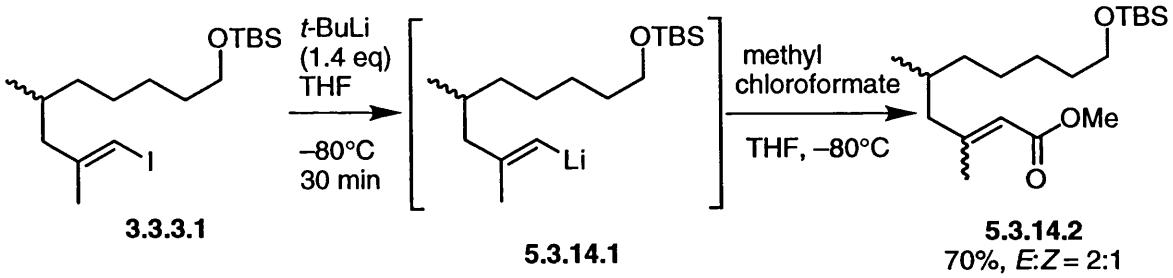
Scheme 5.3.13 highlights the foray into this chemistry. The standard Sonogashira coupling with **3.3.3.1** and trimethylsilylacetylene was very successful yielding 96% of the coupled product **5.3.13.1** (Scheme 5.3.13).



Scheme 5.3.13

Only 7.6 mol% of CuI and 3.4 mol% of $(Ph_3P)_2PdCl_2$ were required in ether/diethylamine for 12 h. **5.3.13.1** was selectively desilylated with a controlled amount of TBAF in quantitative yield to give terminal alkyne **5.3.13.2** which underwent carboalumination under Negishi's conditions to give vinyl alane **5.3.13.3**, as in the synthesis of **3.3.3.1**. The experimental procedure for quenching a vinyl alane such as **5.3.13.3** with a chloroformate is more complex than for the iodine quench: the solvent from the carboalumination (1,2-dichloroethylene) must be evaporated *in vacuo* under inert gas conditions then an extraction with multiple aliquots of petrol must be performed before the vinyl alane may be quenched with chloroformate. Happily, this sequence of reactions proved successful but unfortunately only a 21% yield of diene **5.2.6.1** was obtained.

Although a low yield, stereochemical analysis with ^1H NMR of **5.2.6.1** indicated complete stereocontrol had been achieved. Attempts at repetition, or formation of the *ate* complex (*c.f.* Scheme **5.3.8**), in order to increase the chemical yield were fruitless. An alternative use of vinyl alane **5.3.13.3** could be iodine quench followed by lithiation and then chloroformate quench. This idea was tested on vinyl iodide **3.3.3.1** (Scheme 5.3.14).



3.3.3.1 5.3.14.1 5.3.14.2
70%, *E*:*Z* = 2:1

Scheme 5.3.14

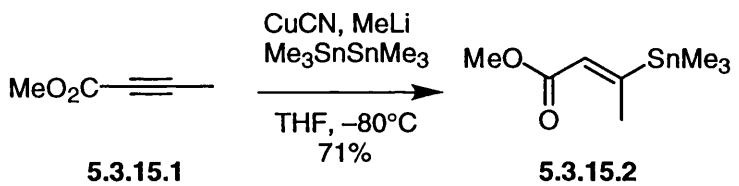
Lithiation at low temperature with *tert*-butyllithium was followed by reaction of vinyl lithium **5.3.14.1** with methyl chloroformate. The configurational stability of the sp^2 anion in **5.3.14.1** was thought to be questionable due to the π-system being trisubstituted and, disappointingly, this proved to be the stumbling block: a good chemical yield of α,β-unsaturated ester **5.3.14.2** was achieved but the stereochemical integrity of the double bond was destroyed.

A criticism of this Sonogashira-Negishi strategy is that it is somewhat linear Importantly, this approach could not be considered an improvement on Wovkulich's synthesis of 1233A (see Chapter 2) which uses the more convergent Heck reaction strategy. Therefore another tactic was required.

5.3.3 The Stille Coupling Approach to Diene 3.3.2.1

The final palladium catalysed reaction to be used in this study is the ubiquitous Stille coupling of an alkenyl stannane and vinyl iodide. This reaction has been used extensively in organic synthesis for more than a decade and adequate reviews are available.[49,50] Mechanistically, there are broad similarities with the other Pd-catalysed reactions discussed above, particularly the Heck coupling (Scheme 5.3.1) where the alkene may be replaced by an organotin reagent.

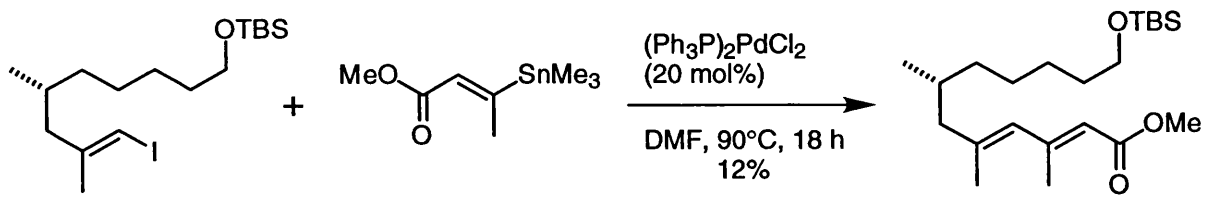
For the synthesis of diene **3.3.2.1**, the vinyl iodide would need to be coupled with an appropriate vinyl tin reagent. Scheme 5.3.15 shows the synthesis of such a suitable compound. A stannylcupration reaction of methyl tetrolate **5.3.15.1** (methyl 2-butynoate) according to Piers[91] or Lipshutz[51] produced a 71% yield of trimethylstannyl ester **5.3.15.2** (Scheme 5.3.15).



5.3.15.1 5.3.15.2

Scheme 5.3.15

With both partners now in hand, the coupling reaction could be attempted. Employing *bis*-(triphenylphosphine) palladium dichloride in DMF solvent the reaction was only narrowly successful, progressing slowly even at higher temperatures (Scheme 5.3.16).



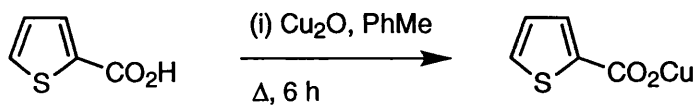
3.3.3.1 **5.3.15.2** **5.2.6.1**

Scheme 5.3.16

The product was isolated in only 12% yield from a mixture of many other products. However, retention of geometry at both sp^2 centres occurred so the reaction still had some promise. At this stage, however, the chemistry in the following section was also being explored with considerable success, resulting in efforts towards the Stille approach ceasing.

5.4 A Novel Copper (I) Thiophenecarboxylate Coupling for Diene 3.3.2.1

Recently Liebeskind reported that copper (I) thiophenecarboxylate (**5.4.1.2**) cleanly and rapidly couples vinyl or aryl stannanes with vinyl iodides in high yield *with no palladium catalyst present.*[92] This landmark publication has opened a multitude of possibilities with cheap copper in place of expensive and often capricious palladium catalysts. Liebeskind reports that the reagent is easily and rapidly prepared on large scale from cheap thiophene carboxylic acid (**5.4.1.1**) and copper (I) oxide.

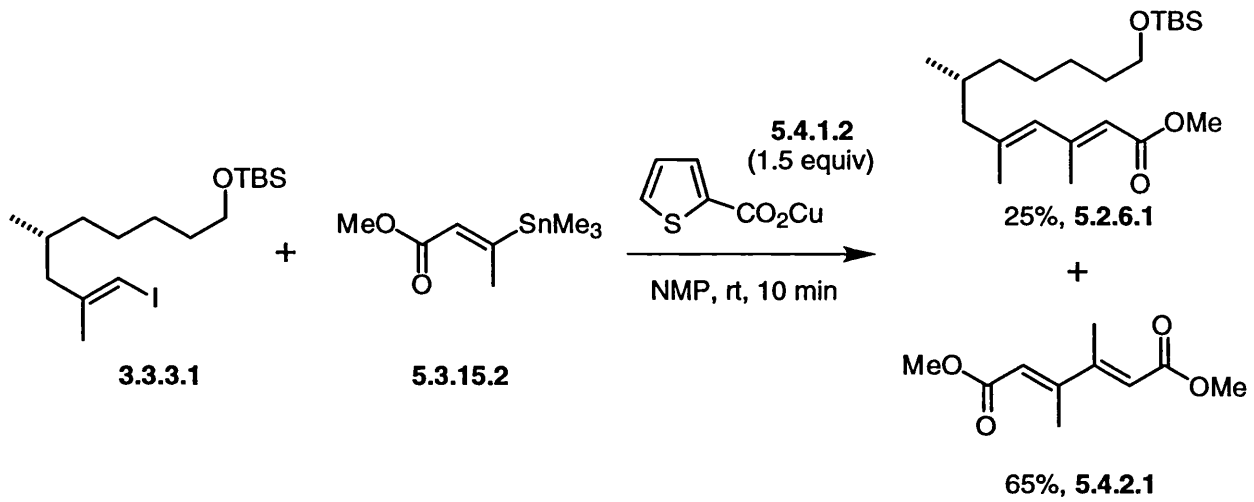


5.4.1.1 **5.4.1.2**

Scheme 5.4.1

In our hands the preparation of **5.4.1.2** was indeed facile. It was found that only 6 hours reflux time was required and after filtration and washing with ether (a large quantity of ether was required so soxhlet extraction was sometimes used),

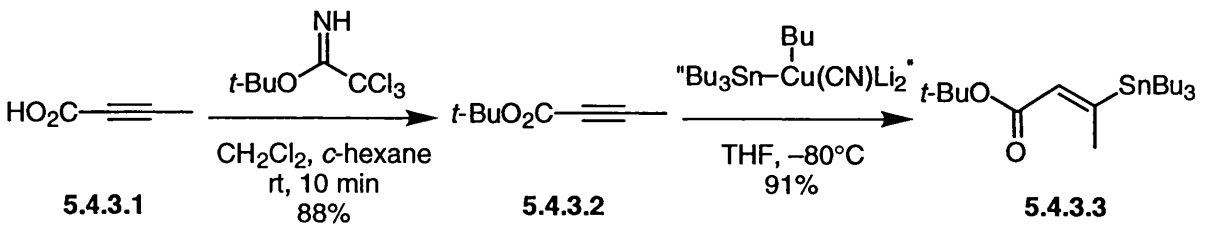
which removes copper (II) salts. The resulting tan powder could be ground into a finer powder with higher activity. In this form **5.4.1.2** was an extremely effective mediator (1.5 equivalents) for the coupling of vinyl stannane **5.3.15.2** with iodide **3.3.3.1** in *N*-methylpyrrolidinone solvent in a matter of minutes at room temperature! Complete retention of double bond geometry was achieved therefore providing diene **5.2.6.1** as one isomer (Scheme **5.4.2**).



Scheme 5.4.2

In initial studies, shown in scheme 5.4.2, a severe drawback was encountered: the vinyl stannane self-coupled to a such an extent that it was the major product (65% of **5.4.2.1** *versus* only 25% of diene **5.2.6.1**)

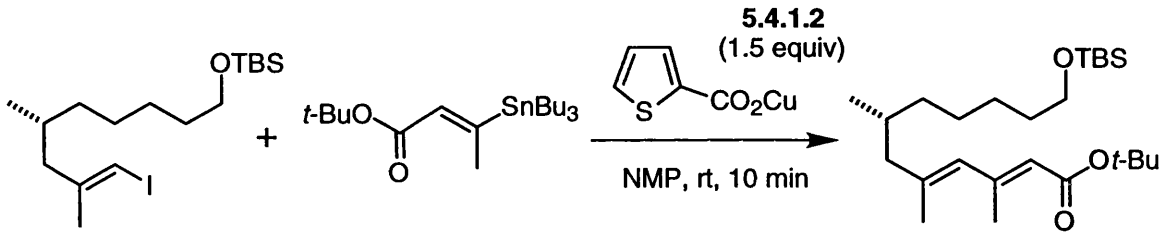
In order to prevent self coupling of **5.3.15.2** and promote cross-coupling to the desired diene, more equivalents of iodide **3.3.3.1** were employed. Additionally, changing the tin substitution from trimethyl to tributyl was thought to be worthwhile since the bulkier tributyltin group should react slower. Hence, the synthesis of the tribuylstannane **5.4.3.3** is depicted in Scheme 5.4.3 (*c.f.* Scheme 5.3.15).



Scheme 5.4.3

A *tert*-butyl ester was employed to facilitate deprotection later in the synthesis. *Tert*-butyltrichloroacetimidate[93] was the ideal reagent for esterification of tetrolic acid (**5.4.3.1**). In this extremely efficient and rapid reaction, **5.4.3.1** appeared to act as its own catalyst since no Lewis acid was required to induce reaction. The stannylcupration of **5.4.3.2** proceeded most efficiently to give an excellent yield of the desired (*E*)-vinyl stannane. From a practical perspective, the (*E*)-isomer of **5.4.3.3** was much more polar than the (*Z*)-isomer, which eluted near the solvent front with unreacted tributyltin hydride in 2% ether:petrol. This always ensured remarkably facile purification of (*E*)-stannane even if, in some cases, the stannylcupration reaction was not stereoselective.

Implementing the measures above proved quite successful: up to 7.5 equivalents of **3.3.3.1** were used to couple to stannane **5.4.3.3** with yields up to 75%. Although unreacted **3.3.3.1** could be recovered in good yield, this strategy was still unsatisfactorily atom efficient particularly since the excess component was the more valuable and took longer to prepare in large quantities. However, further experimentation reduced the required amount of iodide to only 2 equivalents with an 85% yield of **5.3.11.1** (Scheme 5.4.4).

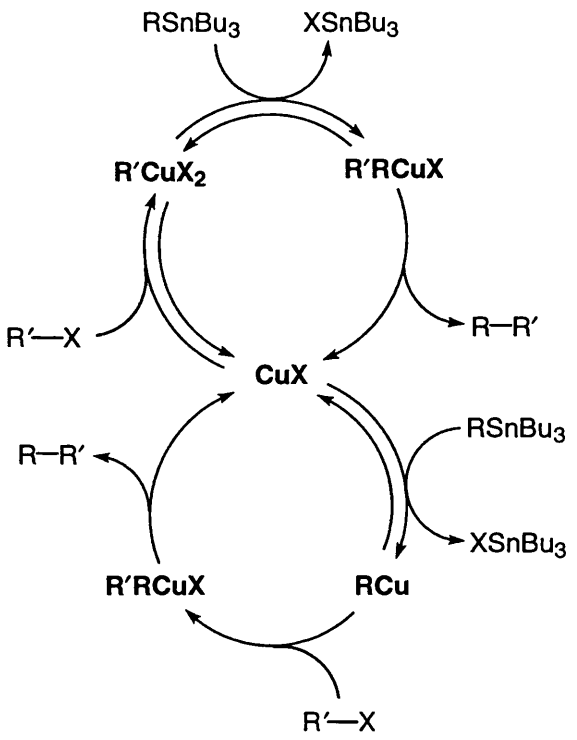


3.3.3.1 (2 eq) **5.4.3.3** 85%, **5.3.11.1**

Scheme 5.4.4

With 1 equivalent of **3.3.3.1** the yield is a reasonable 56% but since any unreacted iodide may be fully recovered, the best compromise is using 2 equivalents and obtaining the higher yield.

Mechanistically, the first step could be either transmetallation of Sn to Cu or oxidative insertion of Cu into the C–I bond (Scheme 5.4.5).



Scheme 5.4.5

Since considerable self-coupling of stannane **5.4.3.3** is observed, the lower cycle in scheme 5.4.5 illustrates the likely mechanism involved in the synthesis of **5.3.11.1** *i.e.* initial transmetallation of copper for tin giving a vinyl copper species which may oxidatively insert into the CX bond of the vinyl halide to give a R′RCuX intermediate. Product expulsion could then occur with generation of CuX.

Liebeskind investigated the effect of tin halide accumulation by monitoring a test system using GLC.[92] An initial rapid rate was followed by a considerable rate retardation as the reaction approached 50% completion. Significantly, the addition of 1 equivalent of Bu_3SnCl into an identical test system only produced a trace of product. These observations are consistent with a *reversible* transmetallation of tin to copper that is retarded by the formation of increasing concentrations of Bu_3SnX.

If a reaction *catalytic* in copper were to be considered, control over all halide species introduced into the reaction would be necessary in order to ensure production of impotent tin halides. Therefore both the copper (I) salt (CuX) and the organic halide (R′X) must possess a moiety, X, that produces the same form of Bu_3SnX. Effective copper catalysis may eventually be feasible if a viable reaction partner, R′X, can be found that both participates in efficient

coupling with $RSnBu_3$ and possesses a group, X, that leads to an unreactive form of Bu_3SnX.

Nevertheless, the stoichiometric quantities of **5.4.1.2** required to mediate the reaction which produces diene **5.3.11.1** does not present a problem. On the contrary, this chemistry has circumvented what was appearing to be an insurmountable obstacle: the stereocontrolled, high yielding and practical synthesis of the diene portion of the natural product 1233A.

5.5 Conclusions

Five separate assaults were made on the challenge of preparing the diene moiety of 1233A: the Julia olefination, the Heck reaction, the Sonogashira-Negishi approach, the Stille coupling and finally a copper (I) mediated coupling first reported by Liebeskind. The first two methods resulted in good yields but poor stereocontrol. Complete command of double-bond geometry was achieved in methods 3 and 4 but yields were diabolical. Only the copper (I) mediated coupling of vinyl stannane **5.4.3.3** with iodide **3.3.3.1** resulted in complete control of stereochemistry *and* a high yield.

Chapter 6

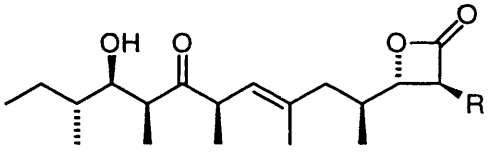
Overview of β-Lactone, Silylketene and Chiral Lewis Acid Chemistry

6.1 Introduction

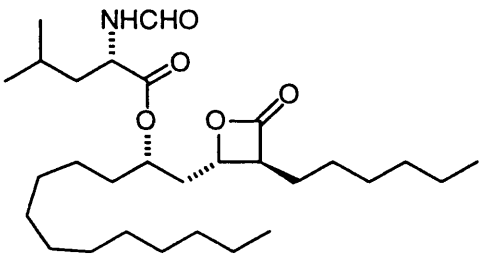
This chapter will discuss relevant key developments in the literature in the fields of interest: synthesis of β-lactones, chemistry of silylketenes and chiral Lewis acid catalysed reactions.

6.2 Overview of β-Lactone Chemistry

The past decade has seen considerable developments in the field of β-lactone chemistry. This interest is, in part, due to the presence of the β-lactone moiety in many natural products such as 1233A, the immunostimulants ebelactone A (**6.2.1.1**) and B (**6.2.1.2**)[94-96] and tetrahydrolipstatin (**6.2.1.3**), the non-natural saturated analogue of lipstatin[97,98] (Scheme 6.2.1).



R = Me Ebelactone A (**6.2.1.1**)
R = Et Ebelactone B (**6.2.1.2**)

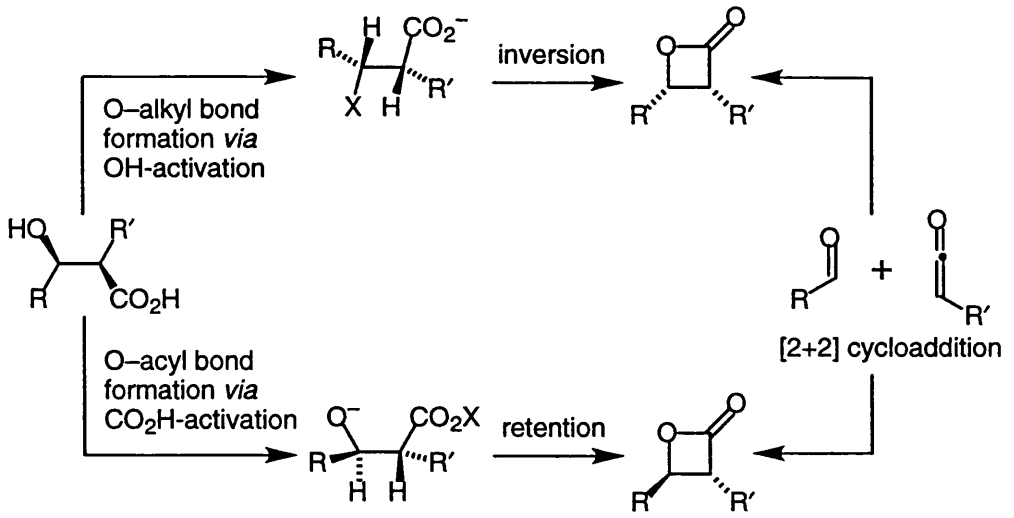


Tetrahydrolipstatin (**6.2.1.3**)

Scheme 6.2.1

The latter is a pancreatic lypase inhibitor and is being developed as a treatment for obesity. Such potentially attractive possibilities have also led to exploitation of the inherent strain in the 4-membered ring. Thus useful synthetic reactions, not seen with esters or larger ring lactones, may be performed with β-lactones. There are three principal methods for formation of a β-lactone ring (Scheme 6.2.2):

(i) lactonisation *via* oxygen–alkyl bond formation
(ii) lactonisation *via* oxygen–acyl bond formation
(iii) [2+2] cycloaddition



Scheme 6.2.2

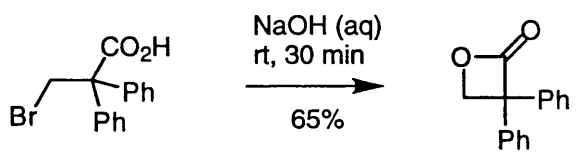
A short overview of β-lactone synthesis now follows but a more comprehensive discussion may be found in recent reviews by Pommier and Pons. [97,99]

6.2.1 Lactonisation *via* Oxygen–Alkyl Bond Formation

An intramolecular displacement reaction by the carboxyl group of a β-substituted carboxylic acid results in the formation of a β-lactone ring with inversion of configuration at the carbon which bore the leaving group (Scheme 6.2.2). Three of the more popular ring-closing methods for achieving this goal are from:

(i) β-halocarboxylic acid salts
(ii) β-γ-unsaturated carboxylic acids
(iii) β-hydroxy carboxylic acids

The first of these is the oldest known method for preparing β-lactones. The acid salt is prepared *in situ* from the acid in a mild base and then cyclisation proceeds at room temperature. Scheme 6.2.3 shows the example of bromo-acid **6.2.3.1** being lactonised into **6.2.3.2** in 65% yield. [100]

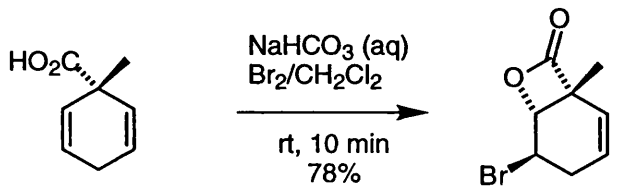


6.2.3.1 **6.2.3.2**

Scheme 6.2.3

Due to frequent problems with loss of CO_2 to form the olefin (see later), the use of β-haloacid salts has been superseded by better methods.

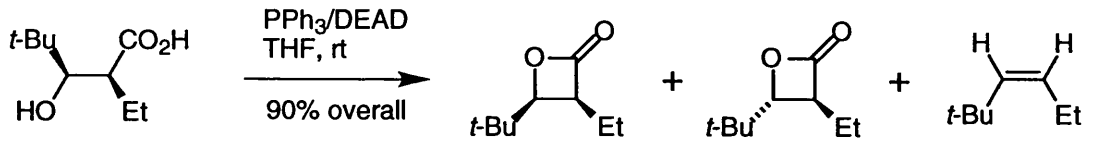
Treatment of β-γ-unsaturated carboxylic acids with halogens induces a halolactonisation reaction. The kinetic products of these reactions may be formed under specific conditions. An intermediary halonium ion is attacked either *via* a 4-*exo*-tet or 5-*endo*-tet cyclisation forming either a β-lactone or the thermodynamically preferable γ-lactone. The formation of lactone **6.2.4.2** from acid **6.2.4.1** adequately illustrates this method.[101]



6.2.4.1 **6.2.4.2**

Scheme 6.2.4

β-Hydroxy acids may also ring-close under Mitsunobu conditions: PPh_3/DEAD. Regioselective attack of the triphenylphosphine is the problem with this technique: generally, mixtures of isomers and decarboxylation products will be formed, such as in the reaction of acid **6.2.5.1** (Scheme **6.2.5**).



6.2.5.1 **44%, 6.2.5.2** **44%, 6.2.5.3** **12%, 6.2.5.4**

Scheme 6.2.5

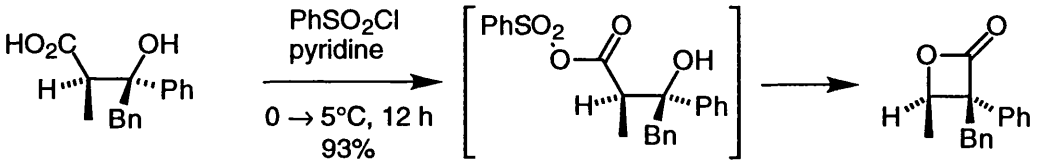
6.2.2 Lactonisation *via* Oxygen–Acyl Bond Formation

This method involves activation of the carboxyl group which then undergoes attack by an oxygen atom in the β-position. The principle reaction substrates are:

(i) β-hydroxy carboxylic acids
(ii) β-hydroxy acid derivatives

(iii) β-hydroxy lithiated ketenes

The first of these includes the most popular method for preparing the β-lactone moiety in natural product syntheses, introduced by Adam in 1972.[38] Activation of the carboxyl group, by formation of a mixed anhydride with benzenesulfonyl chloride, is followed by attack of the hydroxy group to give the 4-membered ring. Thus, β-lactone **6.2.6.3** is prepared in excellent yield from **6.2.6.1** *via* mixed anhydride **6.2.6.2** (Scheme 6.2.6).[38]

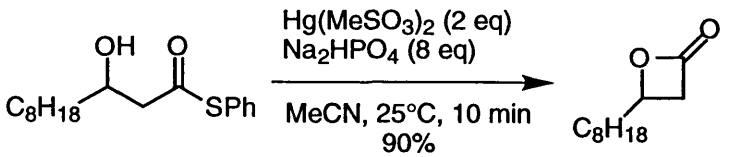


6.2.6.1 **6.2.6.2** **6.2.6.3**

Scheme 6.2.6

Other sulfonyl chlorides have been successfully applied: tosyl chloride, *p*-bromobenzenesulfonyl chloride and methanesulfonyl chloride.

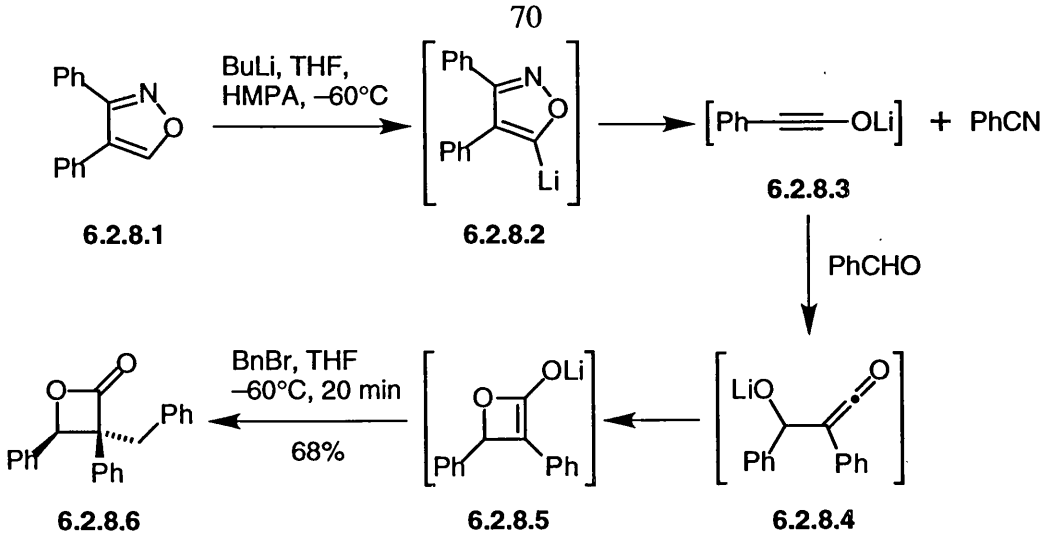
One example of a β-hydroxy acid derivative is thiol ester **6.2.7.1** which was ring-closed to **6.2.7.2** with mercury (II) methanesulfonate/disodium hydrogen phosphate in acetonitrile (Scheme 6.2.7).[102]



6.2.7.1 **6.2.7.2**

Scheme 6.2.7

Lithium alkynolates (lithioketenes) react with carbonyl compounds and yield β-lactones *via* β-hydroxy lithiated intermediates such as **6.2.8.4** in the preparation of **6.2.8.6**.[103,104]

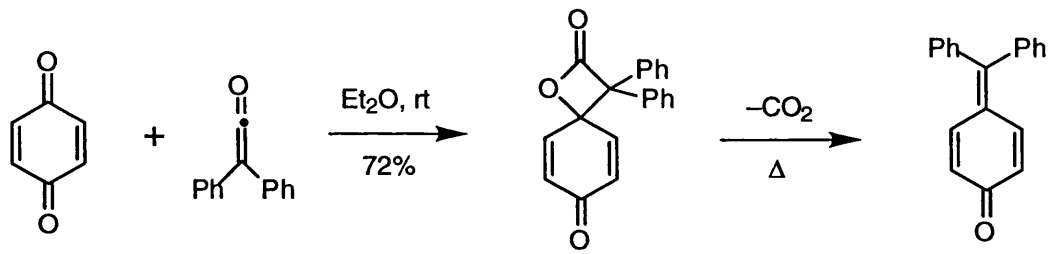


6.2.8.1 6.2.8.2 6.2.8.3 6.2.8.4 6.2.8.5 6.2.8.6

Scheme 6.2.8

6.2.3 Lactonisation *via* [2+2] Cycloaddition

As demonstrated in scheme 6.2.2, the [2+2] cycloaddition of an aldehyde or ketone may lead to a β-lactone. This reaction was first introduced in 1911 by Staudinger[105] who observed a reaction between benzoquinone (**6.2.9.1**) and diphenylketene (**6.2.9.2**) which led to the olefin **6.2.9.4** *via* β-lactone **6.2.9.3**.



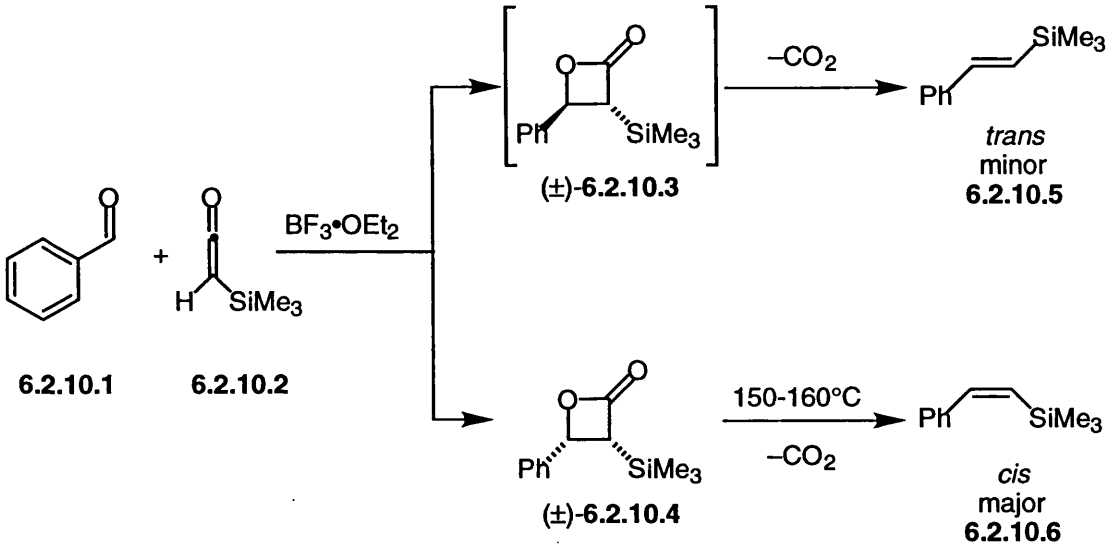
6.2.9.1 6.2.9.2 6.2.9.3 6.2.9.4

Scheme 6.2.9

Decarboxylation is a synthetically useful reaction of β-lactones and will be discussed later in this chapter. Staudinger did not require a catalyst but similar reactions with ketene itself do require catalysts. However the instability of many ketenes and the problems of preparation meant that this method has been seldom used in synthesis.

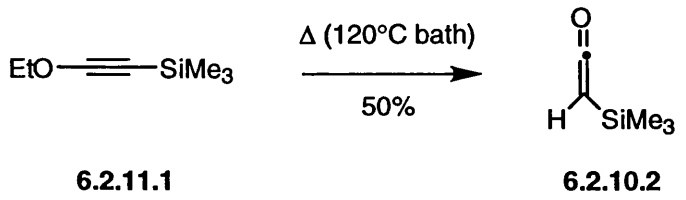
Ketenes may be generated *in situ* by several methods including the elimination of HCl from acyl chlorides using tertiary amines[106,107] and the reductive elimination of α-halo acyl chlorides with zinc.[108,109]

However, these methods are not practical particularly on large scale. In 1975, Russian chemist Zaitseva published the first preparation of the β-lactone moiety *via* a Lewis acid catalysed [2+2] cycloaddition between an aldehyde and the remarkably stable but reactive (trimethylsilyl)ketene **6.2.10.2** (Scheme 6.2.10).[110]



Scheme 6.2.10

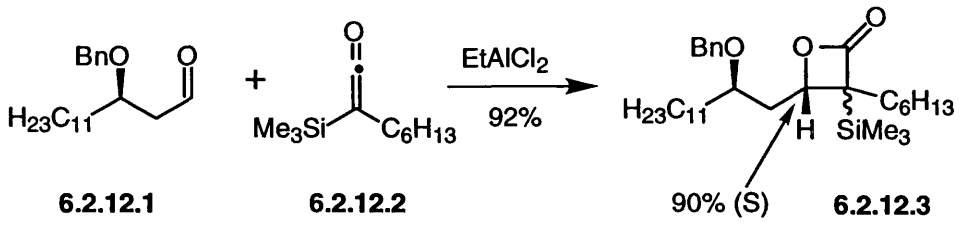
First discovered in 1965 by Shchukovskaya,[111] **6.2.10.2** may be prepared on a large scale by pyrolysis of ethoxy(trimethylsilyl)acetylene (**6.2.11.1**) in 65% yield (Scheme 6.2.11). **6.2.10.2** may be handled in air and stored for protracted periods of time with no loss of effectiveness.



Scheme 6.2.11

The practical advantages are self-evident when a comparison is made with ketene itself: ketene is a reactive gas which is prepared with specialised equipment and must be used immediately whereas (trimethylsilyl)ketene is a stable mobile oil which is easily handled, purified and stored with no special precautions.

Since Zaitseva's initial publication, the [2+2] cycloaddition of aldehydes and silylketenes received very little attention until the late 1980's when Kocienski and Pons reported a concise synthesis of tetrahydrolipstatin (**6.2.1.3**), a pancreatic lipase inhibitor (see Scheme 6.2.1).[112] The key step was a diastereoselective [2+2] cycloaddition of aldehyde **6.2.12.1** with *n*-hexyl(trimethylsilyl)ketene (**6.2.12.2**) giving silyl-β-lactone **6.2.12.3** (Scheme 6.2.12).

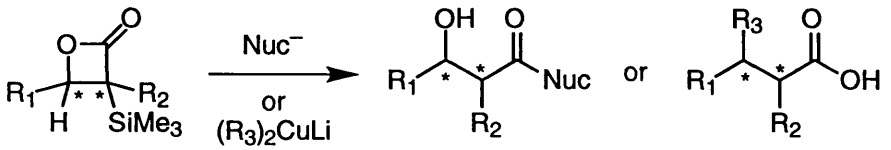


6.2.12.1 **6.2.12.2** **6.2.12.3**

Scheme 6.2.12

Consideration of all the points from the above discussion indicates clearly that efforts towards the β-lactone moiety of 1233A should be channelled in the direction of an asymmetric [2+2] cycloaddition between an aldehyde and a silylketene.

Finally, a short word on the utility of β-lactones themselves as motifs for further elaboration to useful organic fragments. The β-lactone moiety may be considered as an internally protected aldol adduct and hence is useful since the acyl-oxygen bond may be selectively cleaved by nucleophilic attack at the carbonyl[113](Scheme 6.2.13). Additionally, these strained 4-membered rings may be cleaved at the alkyl-oxygen bond with cuprates[114,115] giving rise to useful chiral acids.



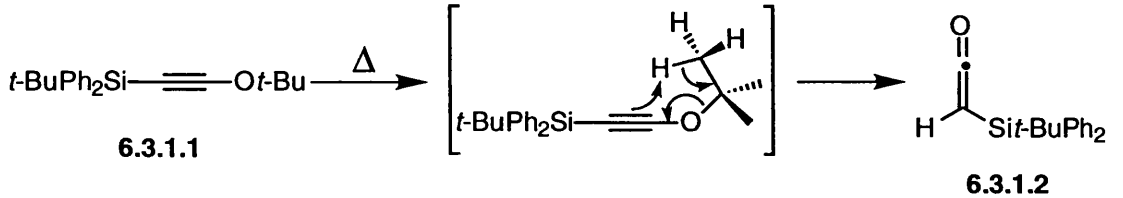
Scheme 6.2.13

6.3 Silylketenes: Synthesis and Reactivity

The following is a short introduction of some relevant works from the literature describing silylketene chemistry. A comprehensive overview concerning all aspects of ketene chemistry is available.[116]

6.3.1 (Trialkylsilyl)ketenes

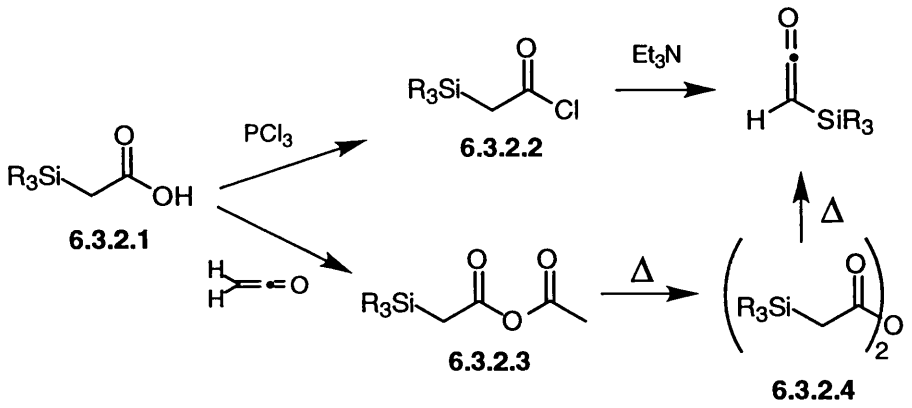
As detailed above, the first synthesis of trimethylsilylketene (**6.2.10.2**) was in 1965 by Shchukovskaya (see Scheme 6.2.11). Throughout the past 2 decades, Zaitseva has explored the chemistry of various silyl and germyl ketenes.[117-127] As yet stannyl ketenes have not been prepared with the exception of *bis*(trialkylstannyl)ketenes prepared by treatment of alkoxy(trialkylstannyl)acetylenes with a trialkylmetal bromide in the presence of $MgBr_2$.[128,129] However, there has been very little activity in this area.
The trichloro and triethylsilyl, *tris*(deuteromethyl)silyl,[130,131] trimethylgermyl and triethylgermyl ketenes[132] and the (–)-(methyl-1-naphthylphenylsilyl) ketene,[133] the first optically active silylketene, have also been made.
Trialkylsilyloxyalkynes were also seen as intermediates in the formation of trialkylsilylketenes by the retro-Diels-Alder reaction of silyl enol ethers of ethenoanthracenes[134] by thermolysis of 2-trimethylsilyl-4,5-dihydrofurane.[135] Acetylenic *tert*-butyl ethers provide a substrate which may be thermolysed under conditions notably milder than those used for the corresponding ethyl ethers, above. Hence, the pyrolysis of 1-*tert*-butoxy(*tert*-butyldiphenylsilyl)acetylene (**6.3.1.1**) permits the preparation of (*tert*-butyldiphenylsilyl)ketene (**6.3.1.2**)[136] (Scheme 6.3.1).



6.3.1.1 **6.3.1.2**

Scheme 6.3.1

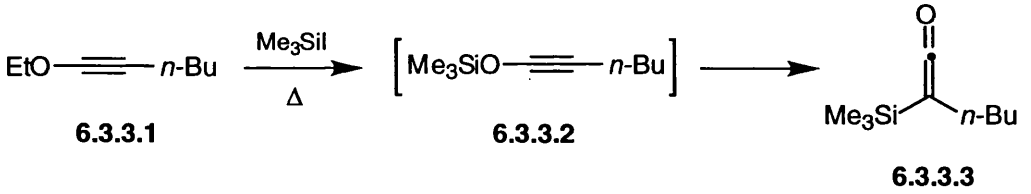
(Trialkylsilyl)acetic acids **6.3.2.1** may be used for the preparation of (trialkylsilyl)ketenes by either formation of acid chloride **6.3.2.2** and dehydrochlorination with triethylamine or formation of anhydride **6.3.2.3** and thermolysis *via* anhydride **6.3.2.4**[137-139] (Scheme 6.2.14).



Scheme 6.3.2

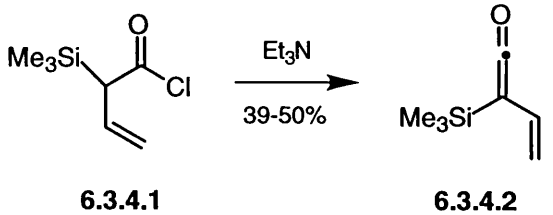
6.3.2 Aryl-, Alkyl- and Alkoxy-(Trialkylsilyl)ketenes

One practical method for preparing these more complex ketenes is the thermal rearrangement of (trialkylsilyloxy)alkynes which may be obtained from alkoxyalkynes in the presence of trimethylsilyl iodide[140-142]. Following this approach, butyl(trimethylsilyl) ketene **6.3.3.3** was obtained in 57% yield by treatment of ethoxyhexyne **6.3.3.1** with trimethylsilyl iodide (TMSI) and rearrangement of the intermediary (trimethylsilyl)oxyhexyne **6.3.3.2** (Scheme 6.3.3).[143]



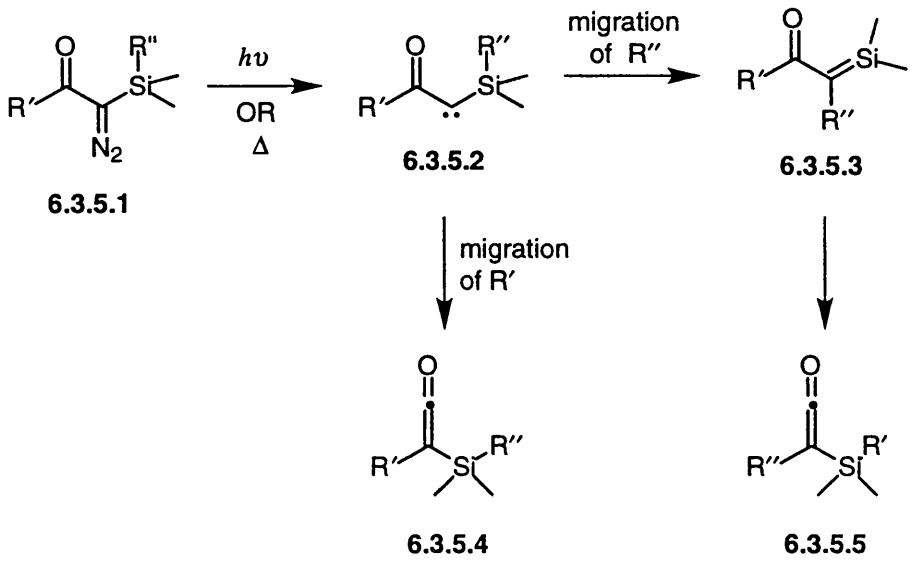
Scheme 6.3.3

Other alkyl(trialkylmetal)ketenes may be prepared with this general method.[144] Others may be obtained by the action of Et_3N on acid chlorides, *e.g.* preparation of vinylketene **6.3.4.2** from acid chloride **6.3.4.1** (Scheme 6.3.4).[145]



Scheme 6.3.4

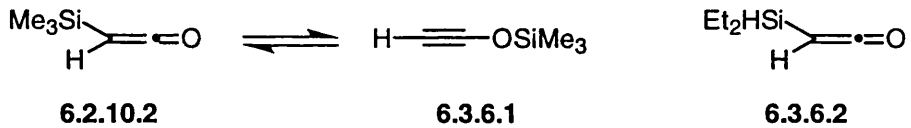
This method has been used to synthesise bromo(trimethylsilyl)ketene. [146] Thermal[147] or photochemical[148] decomposition of (trialkylsilyl)diazoacetates and trialkylsilyldiazoketones is also a source of alkyl(trialkylsilyl)ketenes and alkoxy(trialkylsilyl)ketenes, *via* the Wolff rearrangement (Scheme 6.3.5).



Scheme 6.3.5

6.3.3 Structure and Stability of Silylketenes

Initially the structure of silylketenes were thought to have major contributions from the tautomers **6.2.10.2** and **6.3.6.1** (Scheme 6.3.6). [111]

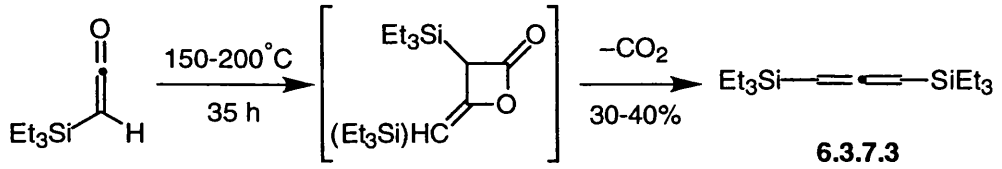


Scheme 6.3.6

On the basis of NMR and IR studies this hypothesis was abandoned in favour of the ketene structure **6.2.10.2**: [130,131] the chemical shift for the ketene proton in **6.3.6.2** (δ = 1.65 ppm, doublet) was in the region for an acetylene (δ = 1.53 ppm for ethoxyacetylene) but a doublet could only be formed by the ketene structure of type **6.2.10.2**.

Silylketenes are quite stable, regarding dimerisation[122,149-151] and can be stored for prolonged periods. It is therefore necessary to heat (trimethylsilyl)ketene (**6.2.10.2**) at 150-200°C for 35 h before formation of 30-40% of allene **6.3.7.3**,

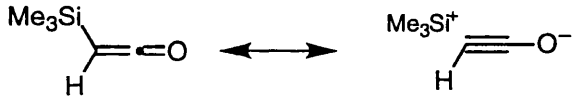
formed by decarboxylation of cyclodimerisation product **6.3.7.2**, is observed[122] (Scheme 6.3.7).



6.3.7.1 **6.3.7.2** **6.3.7.3**

Scheme 6.3.7

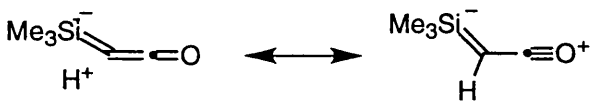
This stability, confirmed by calculation, is due to the electropositive silicon and its ability to stabilise an adjacent negative charge. However ethoxy(triphenylsilyl)ketene is very reactive: the destabilising effect of the ethoxy group opposes the stabilisation due to silicon. Two hypotheses were initially offered in explanation: Brady and Cheng[152] proposed *s-p* donation *via* the C-Si bond (Scheme 6.3.8).



6.2.10.2 **6.3.8.1**

Scheme 6.3.8

Alternatively, Runge[153] used CNDO/S calculations to propose a retrodonation of the π-system of the ketene to the d-orbitals of silicon as in the proposed resonance structures **6.3.9.1** and **6.3.9.2** where a negative charge on silicon and a C=Si double bond (silene) are present (Scheme 6.3.9).



6.3.9.1 **6.3.9.2**

Scheme 6.3.9

In 1991, Tidwell carried out a theoretical *ab initio* study/calculation on the influence of the nature of the substituents on the stability of ketenes.[154,155] These calculations showed that stability was imparted by electropositive substituents (σ-donation). This hypothesis proposes an important contribution

from structure **6.3.8.1** which would affect the geometry of the silyl ketene (Scheme 6.3.8, above).

This is in discord with the C=C and C=O bond lengths calculated by Tidwell[154] for (trimethylsilyl)ketene and methyl ketene. In addition, d-π conjugation (Scheme 6.3.9) is not considered important in the effects of silyl substituents.[156] In conclusion, the electropositive character of silicon is the apparent principle cause of the stabilisation of silylketenes.

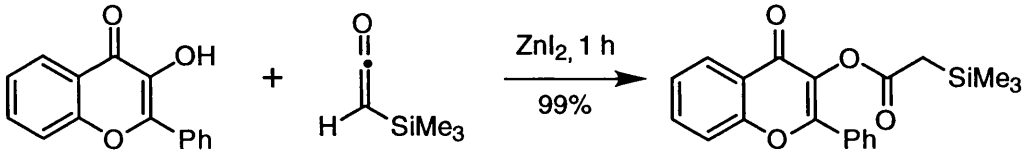
6.3.4 Reactivity of Silylketenes

Silylketenes react, in good yields, with a large variety of heteroatomic or carbon nucleophiles. They also undergo a number of useful cycloaddition reactions. There now follows some key studies from the literature which are of interest in the present context.

6.3.4.1 Reaction of Silylketenes with Heteroatomic and Carbon Nucleophiles and Others

Under neutral conditions, nucleophilic addition to (trimethylsilyl)ketene is slow[155] due to the stability of these compounds. However, with a little acid or base, the reactivity of the ketene is considerably augmented. This is due to the ability of the silicon atom to stabilise a negative charge at the α-position (with base) or a positive charge, β,with acid. (Trialklsilyl)ketenes react well with alcohols[130,131,133,147,157,158], amines[130,131,159,160] and hydroxylamines.[161] The use of Lewis acids, such as $BF_3{\bullet}OEt_2$,[151] $ZnCl_2$ or ZnI_2[162] in the condensation of alcohols with silylketenes, increases the rate of reaction.

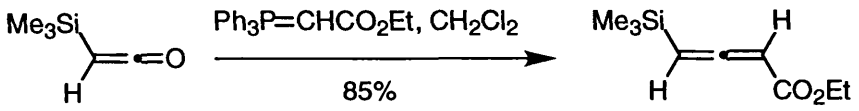
Other α-silyl acetates, such as **6.3.10.2**, have been prepared in excellent yield by Kita *et al*[162](Scheme 6.3.10).



6.3.10.1 **6.2.10.2** **6.3.10.2**

Scheme 6.3.10

In the presence of stabilised phosphorus ylids, (trimethylsilyl)ketenes undergo a Wittig-type reaction. With this method, the ester allene **6.3.11.1** has been prepared in 85% yield[151] (Scheme 6.3.11).



6.2.10.2 **6.3.11.1**

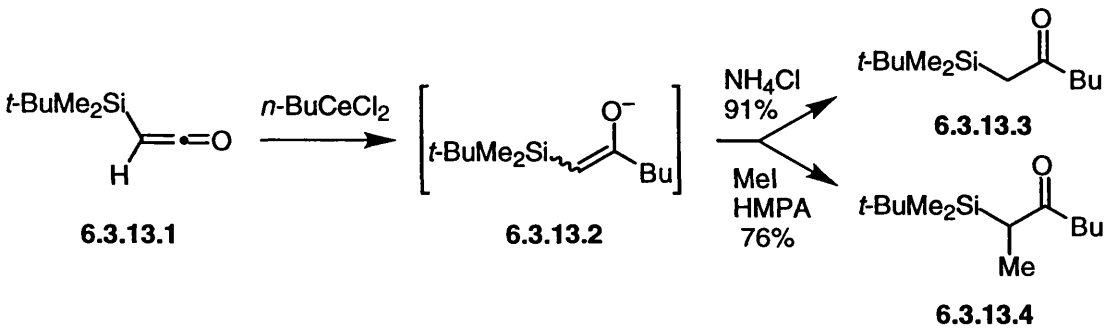
Scheme 6.3.11

Condensation of *n*-butyl lithium with ketene **6.3.12.1** followed by addition of chlorotrimethylsilane, gives silyl vinyl ether **6.3.12.2** as the (*Z*)-isomer[163] (Scheme 6.3.12).

6.3.12.1 **6.3.12.2**

Scheme 6.3.12

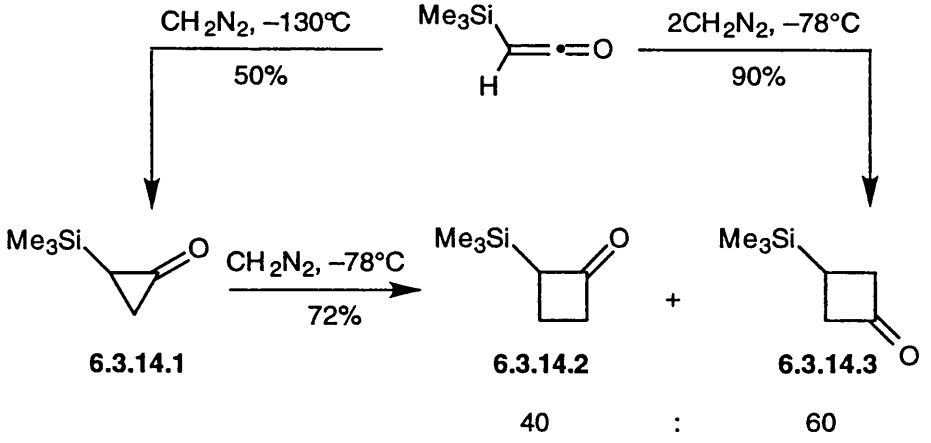
Addition of reactive organocerium compounds to silylketenes gives, *via* the intermediate enolate, compounds **6.3.13.3** and **6.3.13.4**.[164]



6.3.13.1 **6.3.13.2** **6.3.13.3** **6.3.13.4**

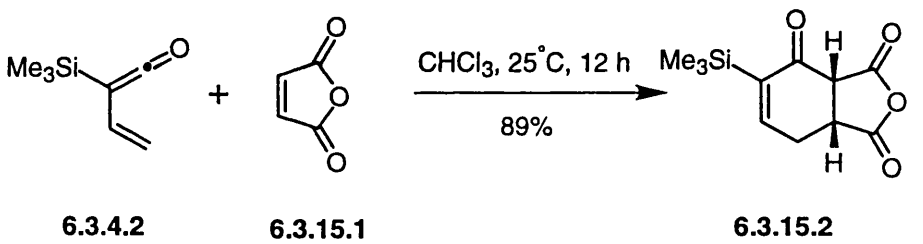
Scheme 6.3.13

The reactivity of trialkylsilylketenes with diazomethane has been largely studied by Zaitseva *et al*[120,126,165] In the presence of diazomethane, (trimethylsilyl)ketene gives cyclobutanones **6.3.14.2** and **6.3.14.3** *via* cyclopropanone **6.3.14.1**[118] (Scheme 6.3.14).



Scheme 6.3.14

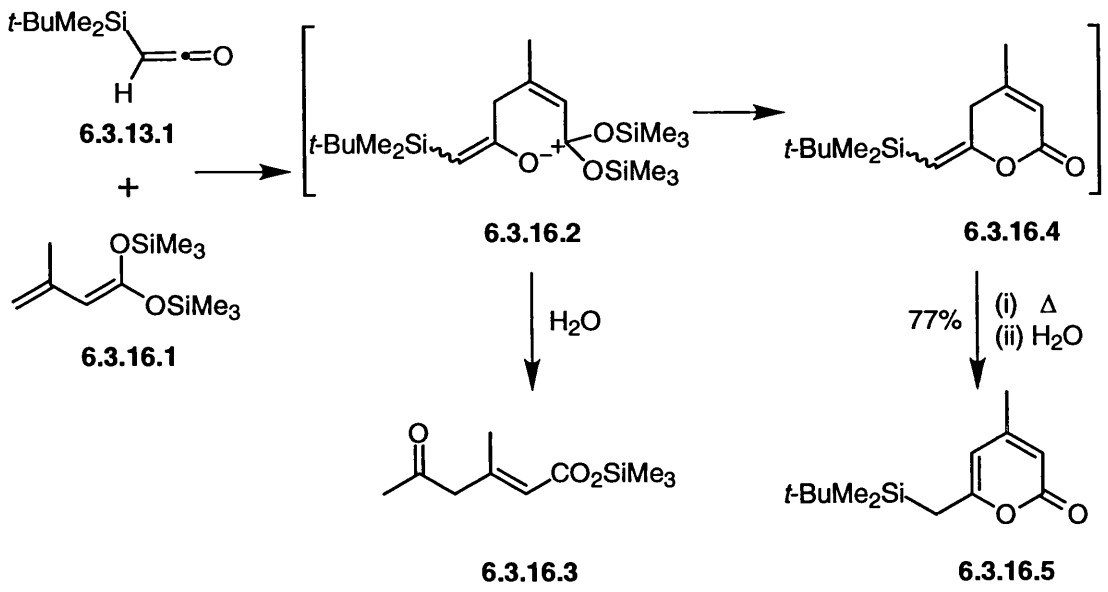
In 1980, Danheiser *et al* published results concerning the use of vinyl(trimethylsilyl)ketene (**6.3.4.2**) as a diene in the Diels-Alder reaction. In the presence of maleic anhydride this ketene gives, with good yield, cycloadduct **6.3.15.2**[145](Scheme 6.3.15).



6.3.4.2 **6.3.15.1** **6.3.15.2**

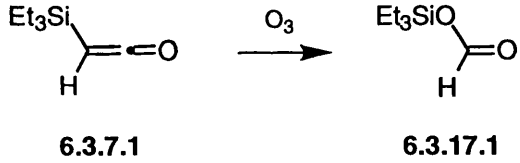
Scheme 6.3.15

Silylketenes also react as dieneophiles in [4+2] cycloaddition reactions. Recently, the [4+2] cycloaddition of trialkylsilylketenes and electron rich 1,3-dienes was studied. Experiments showed that the reaction was a stepwise process: initially, nucleophilic attack of **6.3.16.1** on the sp carbon of **6.3.13.1** gave betaine intermediate **6.3.16.2**. Stopping the reaction at this stage gave acyclic ether **6.3.16.3**. If the reaction is allowed to continue at higher temperature, **6.3.16.2** cyclizes to dihydropyranone **6.3.16.4** which isomerises to give pyranone **6.3.16.5**[166] (Scheme 6.3.16).



Scheme 6.3.16

Ozonolysis of (trialkylsilyl)ketenes gives the corresponding trialkylsilylformates[167] (e.g. Scheme 6.3.17).



Scheme 6.3.17

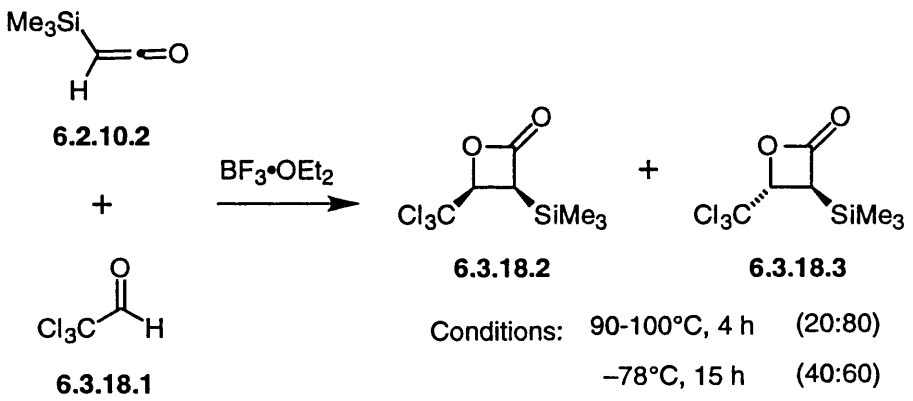
6.3.4.2 [2+2] Cycloadditions of Silylketenes

The [2+2] cycloaddition of ketenes with olefins, imines or carbonyl compounds is a frequently used reaction for the preparation of cyclobutanones,[168,169] β-lactams,[170] or β-lactones,[99] respectively.

The first [2+2] cycloaddition between a silylketene and a carbonyl compound was described by Zaitseva *et al* in 1975.[110] Hence, in the presence of a catalytic amount of $BF_3 \cdot OEt_2$, trimethylsilylketene (**6.2.10.2**) and benzaldehyde (**6.2.10.1**), at –50°C, gave a 1:2 mixture of *trans* and *cis* 4-phenyl-3-trimethylsilyl-2-oxetanones (**6.2.10.3** and **6.2.10.4**, respectively) (see Scheme 6.2.10, above). When the reaction mixture is heated at 50°C for 6 h, a decrease in the proportion of the *trans* isomer is observed. Distillation of the crude reaction product gives 13% of *trans*-(trimethylsilyl)styrene **6.2.10.5** and 65% of *cis* 4-phenyl-3-trimethylsilyl-2-oxetanone **6.2.10.4**. *cis*-

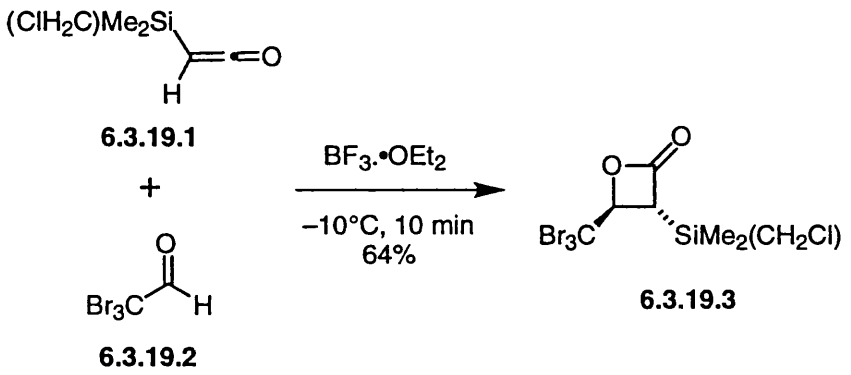
(Trimethylsilyl)styrene **6.2.10.6** is only obtainable on heating **6.2.10.4** to 150-160°C.

In an investigation to determine the influence of the structure of the reactants on the ease of formation of 2-oxetanones and on the relative proportions of the *cis* and *trans* isomers, Zaitseva enlarged her study of the number of ketenes and carbonyl compounds. [119] Studied substrates include formaldehyde and analogues (acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde), chloral and bromal and some ketones. In the absence of a catalyst, (trimethylsilyl)ketene doesn't react with chloral. In summary, the use of BF_3•OEt_2 complex allows isolation of both *cis* and *trans* isomers of the 2-oxetanone in various proportions, dependant on the reaction conditions (Scheme 6.3.18).



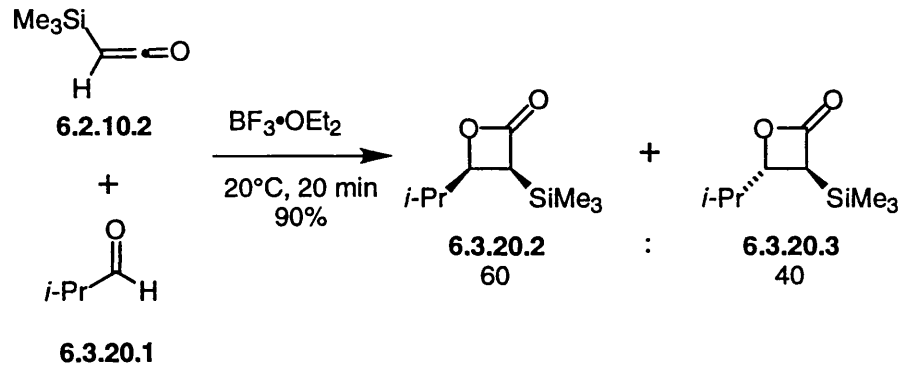
Scheme 6.3.18

The use of the more reactive [(chloromethyl)dimethylsilyl]ketene (**6.3.19.1**) in the cycloaddition reaction with chloral and bromal allows the exclusive isolation of the corresponding *trans* 2-oxetanone[119] (Scheme 6.3.19).



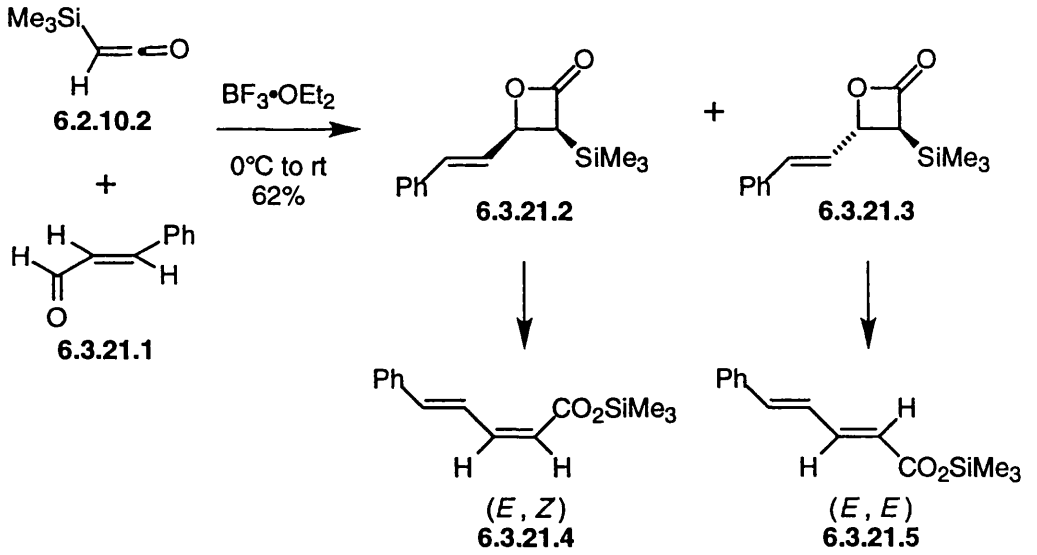
Scheme 6.3.19

The cycloaddition of (trimethylsilyl)ketene with isobutyraldehyde gives the corresponding *cis* and *trans* 4-alkyl-2-oxetanones in the ratio 60:40 and with 90% yield (Scheme 6.3.20).



Scheme 6.3.20

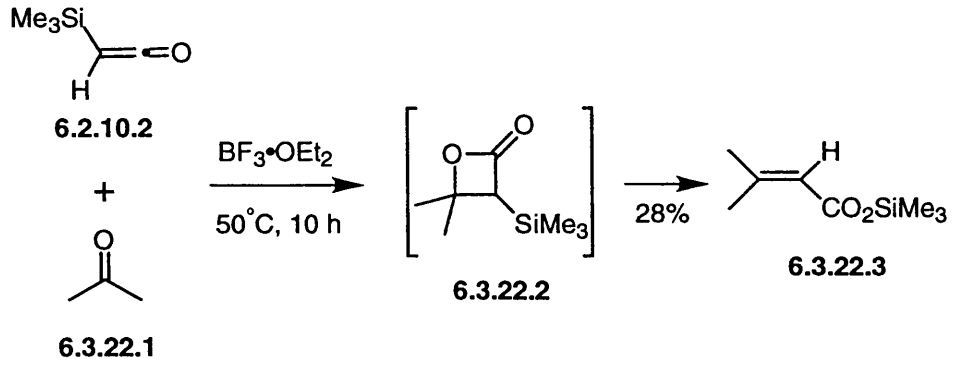
Reaction of α,β-unsaturated aldehydes and (trimethylsilyl)ketene also gives 2-oxetanones. One example is shown in Scheme 6.3.21: on distillation of the crude β-lactone products, the TMS group migrates from carbon to oxygen giving the corresponding α,β-unsaturated silyl esters.



Scheme 6.3.21

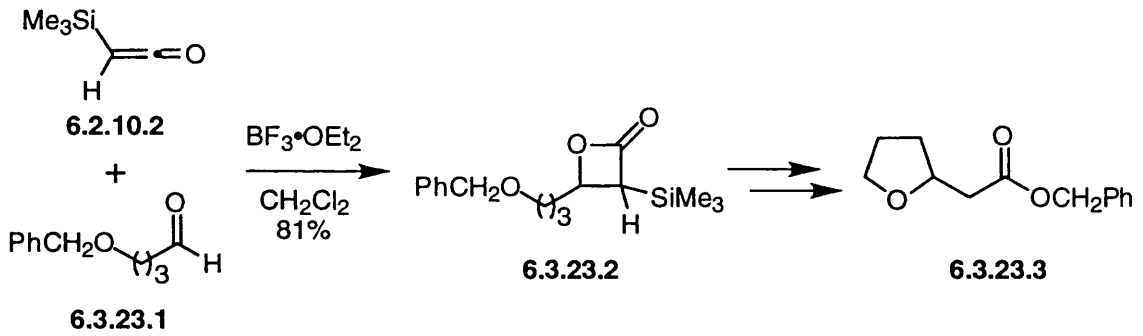
Zaitseva *et al* has used other ketones (acetone, butanone, cyclohexanone, pinacolone, acetophenone) which are less reactive than aldehydes in the cycloaddition with ketenes. [119] With acetone, reactions were monitored by IR. After 10 h at 50°C, formation of a 2-oxetanone (1830cm^{-1}) and an α,β-unsaturated ester (1700 and 1650 cm^{-1}) were observed. Distillation of the

crude reaction mixture allowed isolation of trimethylsilyl-2-butenoate **6.3.22.3** in 28% yield (Scheme 6.3.22).



Scheme 6.3.22

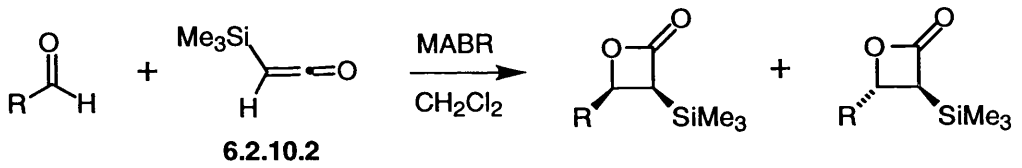
In synthesis, the use of the [2+2] cycloaddition between silylketenes and carbonyl compounds has not been fully exploited. However, in 1988 Mead *et al* reported the preparation of silyl-β-lactones as precursors to tetrahydrofurans[171,172] (Scheme 6.3.23).



Scheme 6.3.23

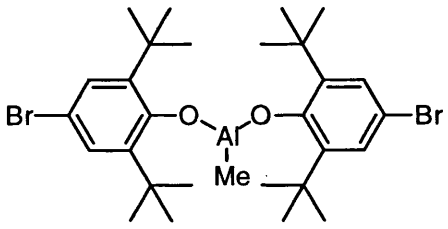
Another elegant synthetic use of these [2+2] cycloaddtions has been provided by Kocienski *et al* in a synthesis of tetrahydrolipstatin, the pancreatic lipase inhibitor (see Scheme 6.2.1, above). Here, the cycloaddition was performed with *n*-hexyl(trimethylsilyl)ketene (**6.2.12.2**) and aldehyde **6.2.12.1** (see Scheme 6.2.12, above).

Recently, Yamamoto *et al*[173] observed, in the presence of methylaluminium *bis* (4-bromo-2,6-di-*tert* -butylphenoxide) (MABR), *cis* stereoselectivity for the cycloaddition between (trimethylsilyl)ketene and aldehydes (Scheme 6.3.24).



6.2.10.2

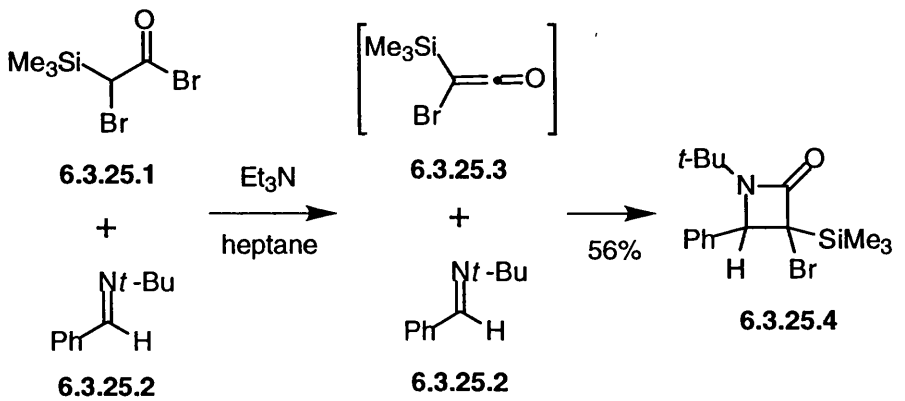
Aldehyde (R)	Lewis Acid (equiv)	Conditions (°C, h)	% yield (*cis*/*trans*)
CH_2CH_3	BF_3•OEt_2	–20°C, 3.5 h; 0°C	42 (70:30)
	MABR (1.0)	0.5 h; –78°C, 2 h	82 (100:0)
c-C_6H_{11}	BF_3•OEt_2	–20°C, 1 h; 0°C, 0.5 h	52 (41:59)
	MABR (1.0)	–78°C, 1 h; –40°C, 1.5 h	88 (90:10)



MABR
6.3.24.1

Scheme 6.3.24

One possible synthesis of the β-lactam moiety is the cycloaddition between a ketene and an imine. This reaction can be done with certain ketenes and silylketenes. The first cycloaddition between silylketenes and imines was described by Brady in 1976.[146] Prepared *in situ* by the action of triethylamine on acid bromide **6.3.25.1**, bromo(trimethylsilyl)ketene (**6.3.25.3**) and *N-tert* -butylbenzylimine (**6.3.25.2**) give *N-tert* -butyl(trimethylsilyl)-β-lactam **6.3.25.4** (Scheme 6.3.25).



Scheme 6.3.25

It should be stressed, however, that the [2+2] cycloaddition of an imine with a silylketene is not a general process as for aldehydes; usually electron withdrawing groups are required on both the ketene and the imine hence severely reducing the scope of this potentially useful reaction.
The situation is somewhat similar with the preparation of the cyclobutanone moiety *via* [2+2] cycloaddition of an alkene with a silylketene. There are very few examples in the literature and no further discussion is pertinent in the present context.

In conclusion, silylketenes are compounds of remarkable stability and utility. Many methods of preparation allow synthesis of a wide range of these ketenes. They react with electrophiles (Lewis acid catalysed), alcohols, water and nucleophilic carbon giving a diverse choice of organic fragments. [2+2] Cycloaddition is an important reaction of silylketenes. Of particular importance are the results of Zaitseva which show carbonyl compounds possessing electrophilic character react rapidly, hinting at the nucleophilic character of the ketene moiety.

6.4 Chiral Lewis Acids In Synthesis

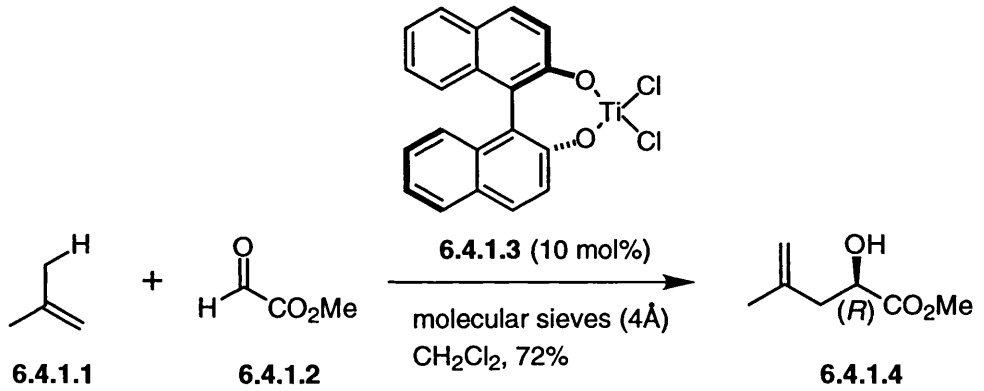
6.4.1 Introduction

A Lewis acid is defined as *a molecule capable of receiving an electron pair into the shell of one of its atoms*. Such acids may form stable complexes with Lewis bases which are defined as *molecules with an electron pair capable of entering such a shell to create an electron pair bond.* Some examples of Lewis acids are BF_3, $AlCl_3$, $ZnBr_2$, $TiCl_4$,and $SnCl_4$.[174]
Among the Lewis acid-catalysed reactions, those involving the formation of complexes between carbonyl compounds and Lewis acids are particularly important since these complexes play a fundamental role in organic and bioorganic chemistry. In asymmetric synthesis, the key carbon-carbon bond forming reactions which are catalysed by Lewis acids are: the carbonyl-ene reaction , the Mukaiyama aldol reaction (silyl enol ether additions to aldehydes or ketones), the Sakurai reaction (allylsilanes or allylstannanes additions to aldehydes and to conjugated enones) and the Diels-Alder reaction. These

reactions may be enantioselective and catalysed by chirally modified Lewis acids. Some examples of recent enantioselective chiral Lewis acid catalysed processes now follow.

6.4.2 The Carbonyl-Ene Reaction

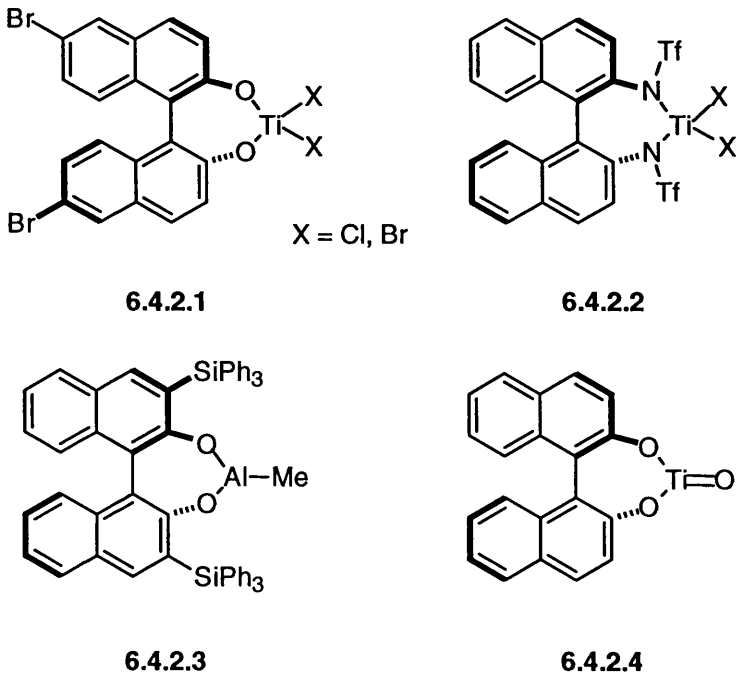
A review is available detailing the carbonyl-ene reaction up until 1992.[175] An asymmetric example of this reaction is Mikami's titanium binolate (**6.4.1.3**) catalysed addition of 2-butene (**6.4.1.1**) to methyl glyoxalate (**6.4.1.2**) forming homoallylic alcohol **6.4.1.4** in 72% yield and 95% ee[176,177] (Scheme 6.4.1).



6.4.1.1 **6.4.1.2** **6.4.1.4**

Scheme 6.4.1

This popular BINOL ligand was further modified in 1994 leading to titanium based chiral Lewis acids such as bromine substituted **6.4.2.1**, *bis*-triflamide

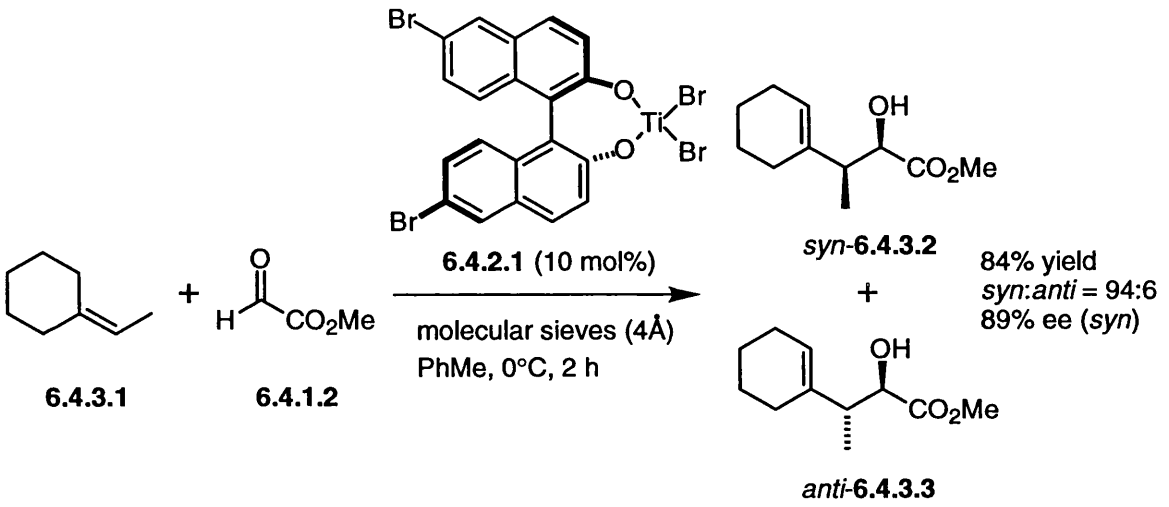


6.4.2.1 **6.4.2.2**

6.4.2.3 **6.4.2.4**

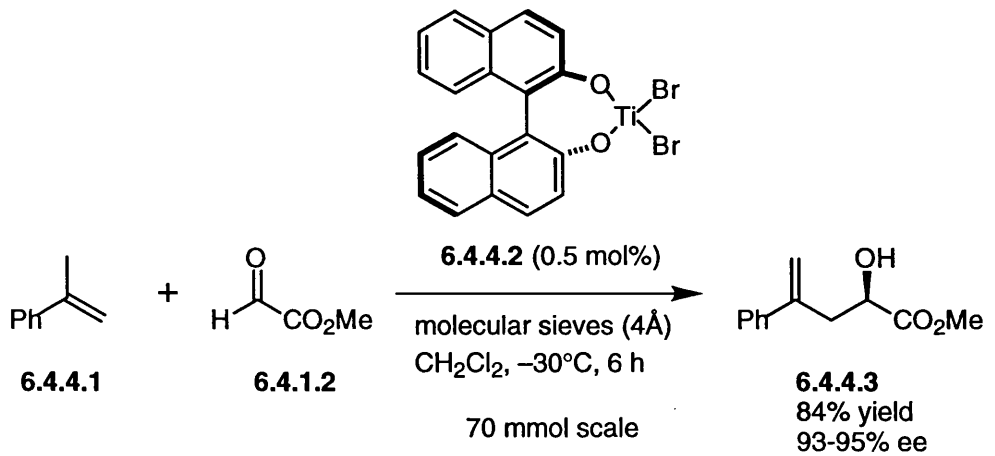
Figure 6.4.2

6.4.2.2[178] and earlier in 1990, the unusual oxotitanium species **6.4.2.4**, used by Mukaiyama himself but only reaching 85% ee.Very bulky *ortho*-triphenylsilyl-substituted aluminium Lewis acid **6.4.2.3** was used as the catalyst (20 mol%) for the addition of but-2-ene to pentafluorobenzaldehyde[179] (Figure 6.4.2). Catalysts **6.4.2.1** and **6.4.2.2** as well as **6.4.1.3** were shown to be effective for the addition of tri-substituted olefins to methyl glyoxylate in up to 89% ee and 94:6 d.e.[178] (Scheme 6.4.3).



Scheme 6.4.3

Catalytic quantities of as little as 0.5 mol% have been used in a highly practical ene reaction between α-methylstyrene (**6.4.4.1**) and methyl glyoxalate (**6.4.1.2**), carried out on a 70 mmol scale and detailed in *Organic Syntheses*[180] (Scheme 6.4.4).



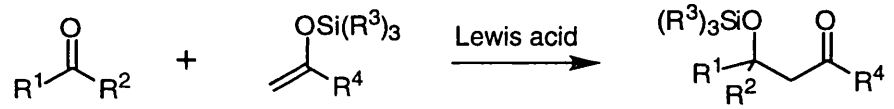
Scheme 6.4.4

This catalyst possesses, significantly, bromine substitution on the titanium atom (*c.f.* dichloro catalyst **6.4.1.3**). Judicious choice of either dichloro or dibromo chiral catalysts may provide ene products in high enantiomeric purity.

A review on the many applications of the chiral binaphthyl unit in asymmetric synthesis is available.[181] Chiral titanium complexes and their additions to carbonyl groups has also been reviewed.[182]

6.4.3 The Mukaiyama Aldol Reaction

Lewis acid induced reaction of a silyl enol ether with aldehydes and ketones, an aldol cross-coupling reaction, is commonly referred to as the Mukaiyama aldol reaction after the name of its discoverer.[183-187] This extremely mild method of effecting carbon-carbon bond formation involves transfer of the silicon atom from the oxygen of the enol ether component to the oxygen atom of the electrophilic aldehyde or ketone partner (see Scheme 6.4.5).

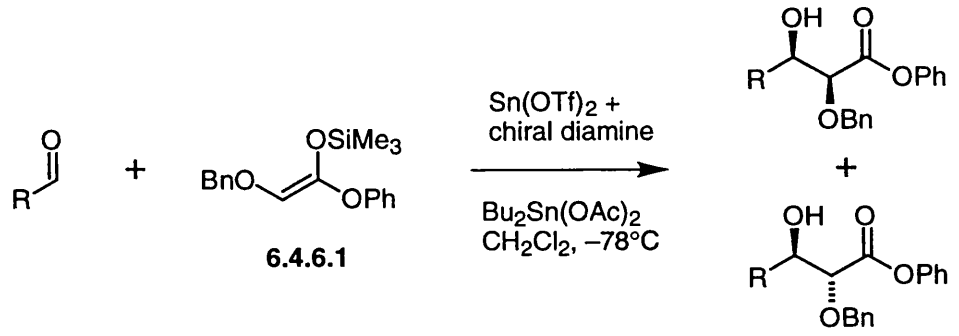


Scheme 6.4.5

An in-depth mechanistic investigation of this reaction has been reported by Bosnich and Hollis.[188] They found that trimethylsilyltriflate (TMSOTf) is a very powerful catalyst for the reaction. TMSOTf is often produced *via* hydrolysis of other species originally thought to be catalysts themselves e.g. $[Ti(Cp)_2(OTf)_2]$.

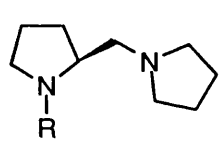
Since the Mukaiyama coupling is such a powerful bond forming process, it has been extensively studied for catalysis by chirally modified Lewis acids. This approach has been very successful, leading to a number of stereoselective processes.[189-191]

Illustrative of the advances already made in this field is Kobayashi's chiral Lewis acid-controlled synthesis of both individual diastereomers, in high enantiomeric excess from the same starting material, as a function of choice of chiral Lewis acids. The reaction studied was the tin(II) Lewis acid coupling of enol silane **6.4.6.1** with various aldehydes giving *syn* and *anti* 2,3-dihydroxy ester derivatives (Scheme 6.4.6).

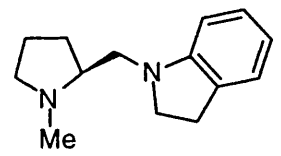


R	chiral diamine	yield (%)	*syn*/ *anti*	ee (%)
Ph	**6.4.6.4**	85	95/5	91
C_5H_{11}	**6.4.6.4**	90	94/6	94
CH_3CH=CH	**6.4.6.4**	89	>99/1	98
PhCH=CH	**6.4.6.4**	89	>99/1	98
2-furyl	**6.4.6.4**	88	>99/1	94
Ph	**6.4.6.2**	80	9/91	90
C_5H_{11}[a]	**6.4.6.3**	88	8/92	92
CH_3CH=CH	**6.4.6.2**	51	7/93	92
PhCH=CH[a]	**6.4.6.2**	63	12/88	94
2-furyl	**6.4.6.3**	77	12/88	91

[a] Bu_3SnF was used instead of $Bu_2Sn(OAc)_2$



R = Et **6.4.6.2**
R = Pr **6.4.6.3**

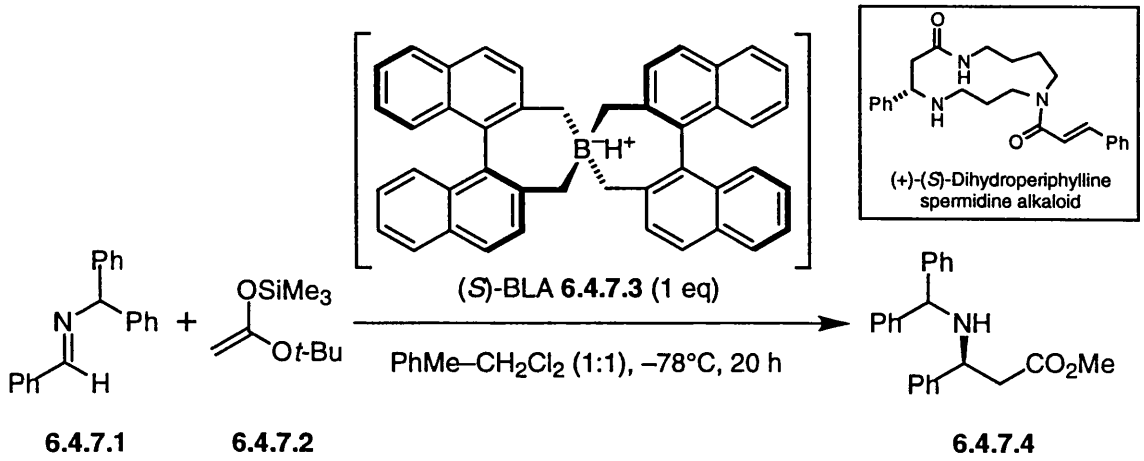


6.4.6.4

Table 6.4.6

From the table it can be seen that almost complete control over the *syn*:*anti* ratio has been achieved with very high enantiomeric excesses of the major products. Another 10 diamines were also studied but the 3 shown were superior.

Yamamoto achieved 96% ee for a chiral BLA (Bronsted acid assisted chiral Lewis acid) promoted aldol-type reaction of silyl enol ether **6.4.7.2** with imine **6.4.7.1**[192] (Table 6.4.7).



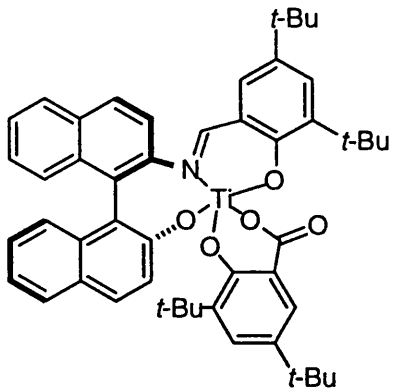
6.4.7.1 6.4.7.2 6.4.7.4

Scheme 6.4.7

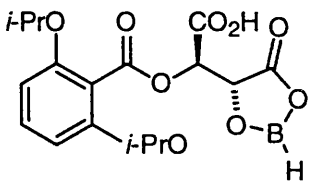
This unusual concept of a BLA is very effective but in this case one whole equivalent of **6.4.7.3** is required which is considerable since 2 molecules of BINOL are required per molecule of **6.4.7.3**.

Yamamoto utilised **6.4.7.4** in the synthesis of the spermidine alkaloid (+)-(*S*)-dihydroperiphylline.

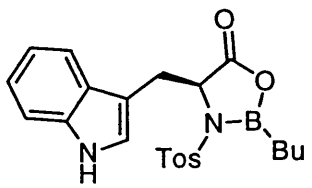
Bulky 5-coordinate titanium chiral Lewis acid **6.4.8.1**[191] and four boron-centred Lewis acids **6.4.8.2**[193,194], **6.4.8.3**[195], **6.4.8.4**[196] and **6.4.8.5**[197,198] have also been used for the Mukaiyama aldol reaction (Figure 6.4.8).



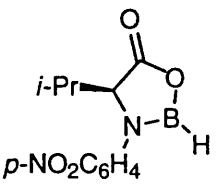
6.4.8.1



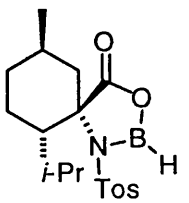
6.4.8.2



6.4.8.3



6.4.8.4

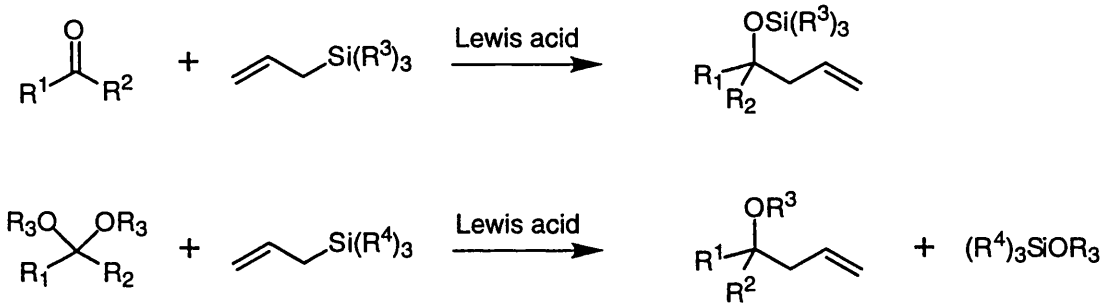


6.4.8.5

Figure 6.4.8

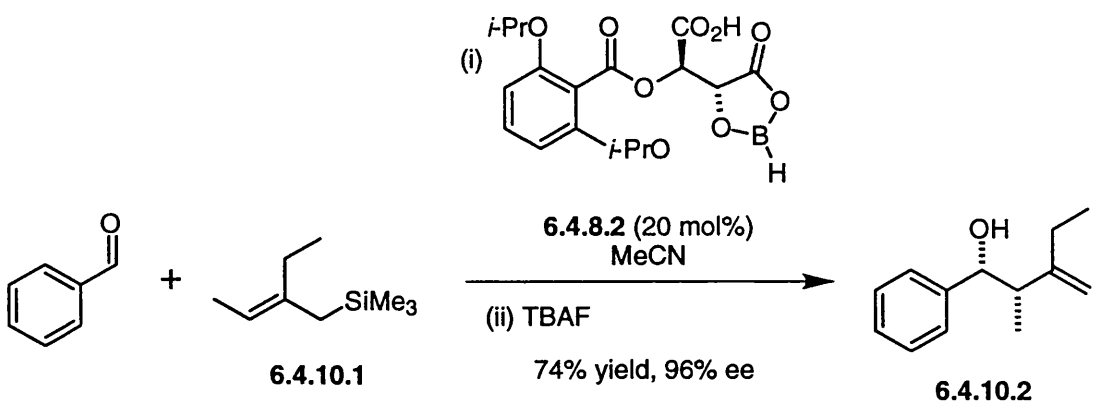
6.4.4 The Sakurai Reaction

An reaction analogous to the Mukaiyama, but as yet less versatile, is that reported by Sakurai and now known by that name. [199,200] He found that Lewis acids promoted the reaction of allylic silanes with aldehydes, ketones, acetals, ketals and orthoesters as shown in Scheme 6.4.9.



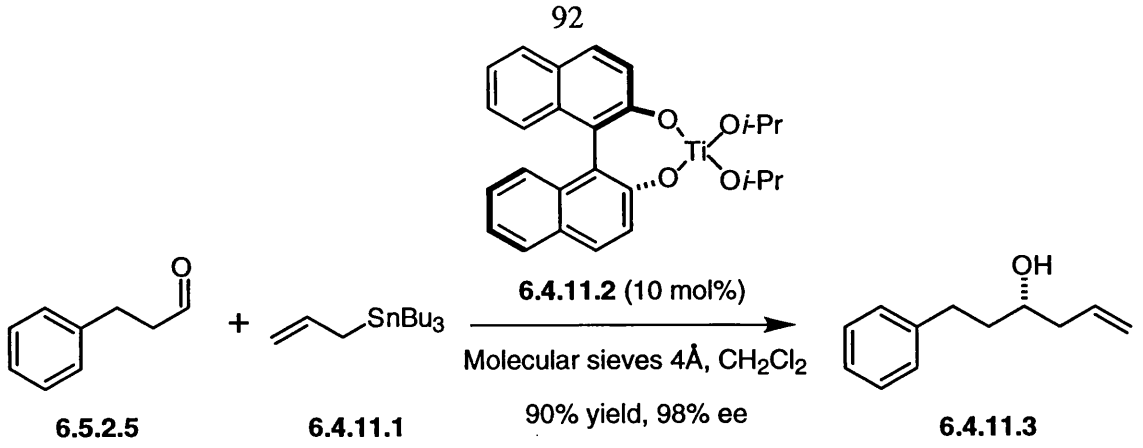
Scheme 6.4.9

Mechanistically, the Sakurai reaction is similar to the Mukaiyama aldol reaction[188] and may be catalysed by simliar Lewis acids.
For example, the boron Lewis acid **6.4.8.2** was employed by Yamamoto to accomplish a 96% ee for the reaction shown in Scheme 6.4.10. [201,202]



Scheme 6.4.10

With allylstannanes, the reaction is known as the Keck allylation, named after its discoverer. An example of the achievable level of stereocontrol is shown in Scheme 6.4.11. [203]



Scheme 6.4.11

Although the Sakurai reaction is a useful process, it is far outweighed by the next reaction.

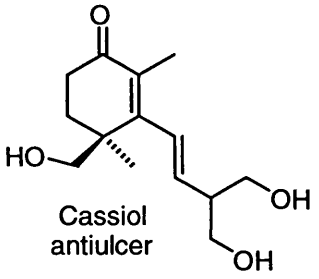
6.4.5 The Diels-Alder Reaction

The [4+2] cycloaddtion to form a 6-membered ring is a standard method which is known as the Diels-Alder reaction. It allows, in principle, the formation of four contiguous stereogenic centres. Relative stereochemistry is usually well defined because of the formation of a cyclic transition state arising from orbital interactions, with endo approach.[204]

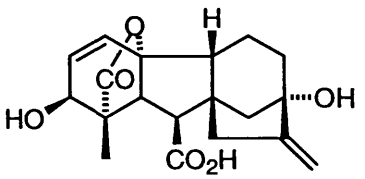
Useful reviews are available on the catalytic asymmetric Diels-Alder reaction.[205-207] A few examples of more recent and useful applications of chiral Lewis acids to the Diels-Alder reaction now follows.

In 1994, Corey reported the use of boron-centred Lewis acids **6.4.12.3** and **6.4.8.3**, which are derived from cheap and easily recyclable *N*-(*p*-tolylsulfonyl)tryptophan, in syntheses of the antiulcer substance cassiol and the plant growth regulator gibberellic acid (Scheme 6.4.12).[208]

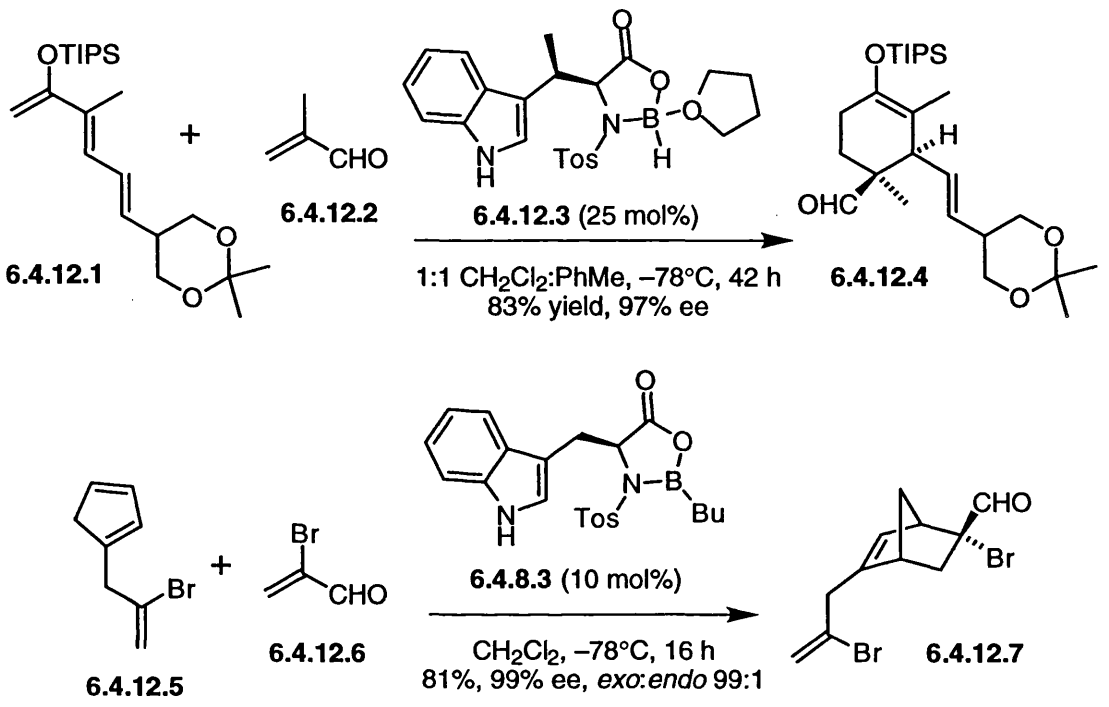
Hence, [4+2] cycloaddition of diene **6.4.12.1** with 2-methylacrolein (**6.4.12.2**), catalysed by boron chiral Lewis acid **6.4.12.3**, leads to cyclohexene **6.4.12.4** in an impressive 83% yield and 97% ee. **6.4.12.4** is then further elaborated to Cassiol in short order. In the same paper, Corey goes on to apply previously described catalyst **6.4.8.3** to the synthesis of key bicyclic intermediate **6.4.12.7** for the synthesis of Gibberellic acid. Cycloaddition of cyclopentadiene **6.4.12.5** with bromoacrolein (**6.4.12.6**) proceeds in a stunning 81% yield and 99% ee with additional superb control over the *exo*:*endo* ratio.



Cassiol
antiulcer

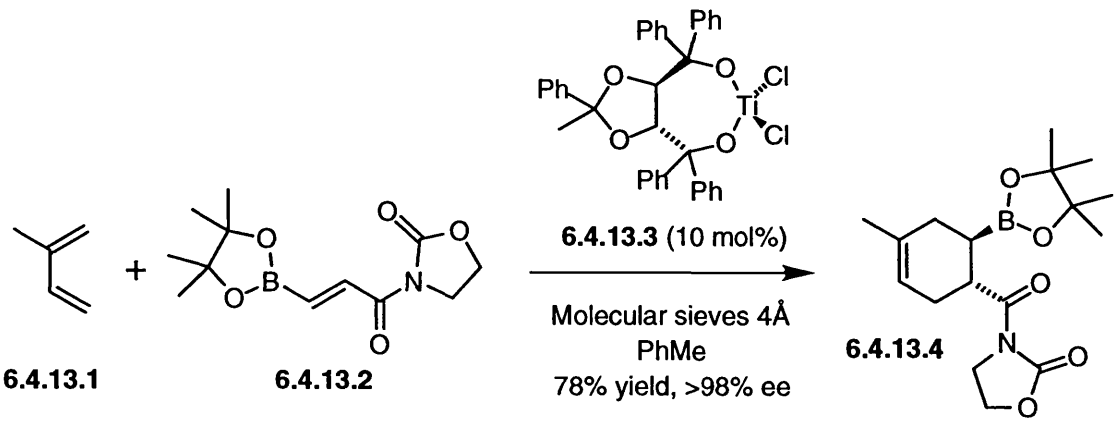


Gibberellic Acid
plant growth regulator



Scheme 6.4.12

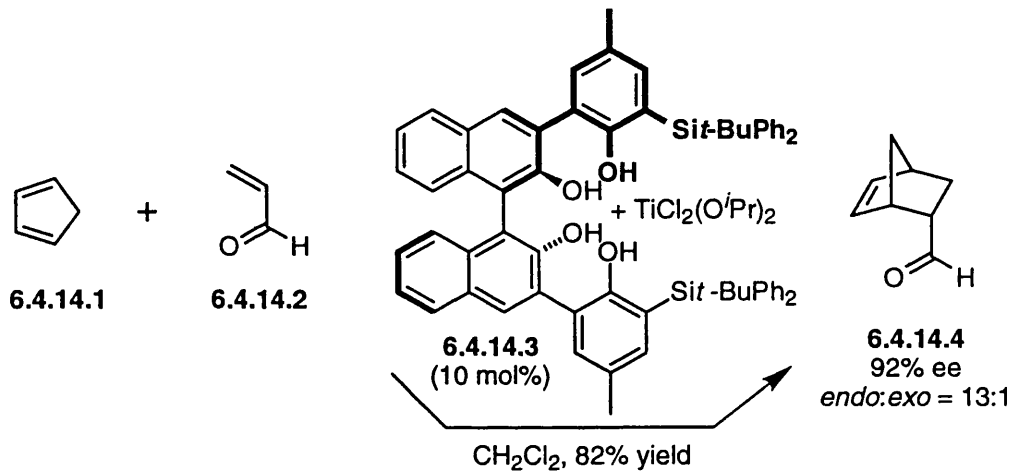
Tartrate-derived diols (TADDOLS) have also found use as ligands for chiral Lewis acids of titanium.[209-211] In 1992, Narasaka described an approach to chiral boron species **6.4.13.4** through an enantioselective Diels-Alder reaction catalysed by Ti-TADDOLate **6.4.13.3**.[211]



Scheme 6.4.13

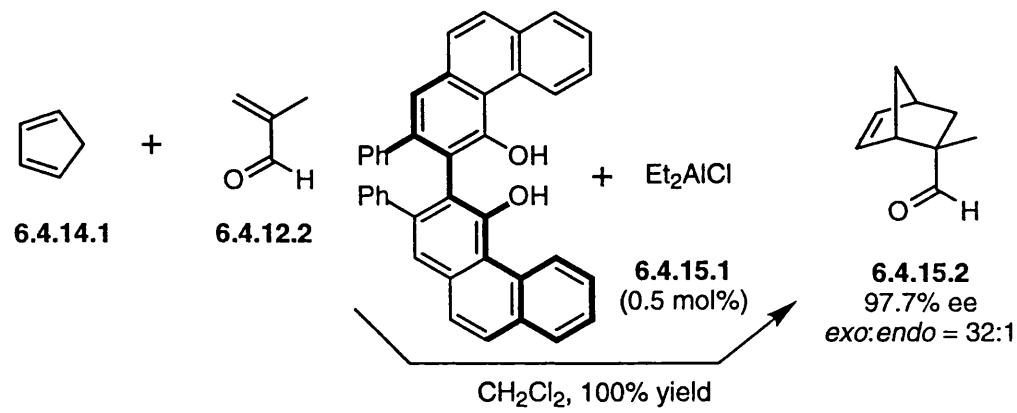
There has been much work carried out with TADDOLS. Recent studies which have expanded our understanding of these reactions have been carried out by Seebach *et al*[209] and DiMare *et al.* [210]

Further examples of impressive BINOL derivatives (*c.f.* Figure 6.4.2) have been reported by Yamamoto[212] and Wulff. [213] Scheme 6.4.14 shows Yamamoto's extremely bulky ligand **6.4.14.3** which, when complexed with titanium, gives an 82% yield and 92% ee for the cycloaddition of cyclopentadiene (**6.4.14.1**) with acrolein (**6.4.14.2**). The product **6.4.14.4** is a mixture of 13:1 of *endo*:*exo* isomers.



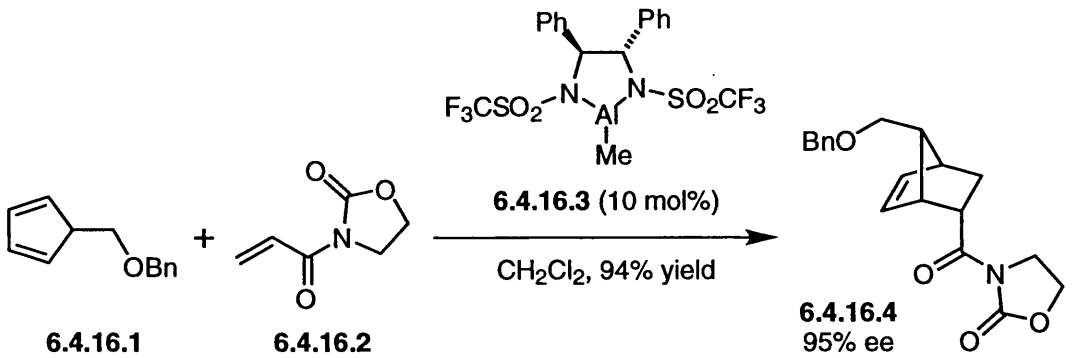
Scheme 6.4.14

Wulff has applied chiral *bis*-phenanthrene **6.4.15.1** with diethylaluminium chloride (only 0.5 mol% of chiral Lewis acid!) for the cycloaddition of cyclopentadiene with 2-methylacrolein (Scheme 6.4.15). A quantitative yield, high ee and *exo*:*endo* ratio make this reaction very attractive indeed.



Scheme 6.4.15

In 1989 Corey *et al* reported chirally modified aluminium Lewis acid **6.4.16.3** for use in the Diels-Alder reaction of cyclopentadiene **6.4.16.1** with dieneophile **6.4.16.2**.[214] The product **6.4.16.4** was elaborated to a key intermediate in Corey's prostaglandin synthesis.



Scheme 6.4.16

6.5 Conclusions

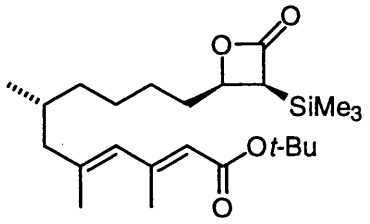
In this chapter, a cursory survey of recent literature has been discussed for areas relevant to the forthcoming methodology study: β-lactone and silylketene chemistry have been introduced followed by an overview of some important chiral Lewis acid mediated C–C bond forming processes.

Chapter 7

The Discovery of a Novel, Enantioselective Chiral Lewis Acid Catalysed [2+2] Cycloaddition of Aldehydes with (Trimethylsilyl)ketene and its Application to the Construction of the β-Lactone Portion of 1233A

7.1 Introduction

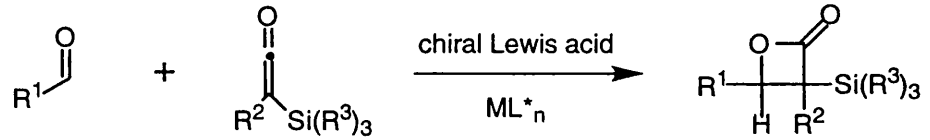
This chapter will discuss the discovery of the first enantioselective [2+2] cycloaddition of achiral aldehydes with (trimethylsilyl)ketene. Application of this new methodology for the synthesis of the β-lactone moiety in 1233A will then be tackled. Figure 7.1.1 shows the target compound **7.1.1.1** derived from the new methodology.



7.1.1.1

Figure 7.1.1

Before any piece of scientific research is to be undertaken, it is wise to survey the literature works on the subject and outline a sensible plan in order to maximise the possibility of success in the shortest possible time.
Firstly, the problem itself should be clearly defined: in this case a [2+2] cycloaddition of an aldehyde with a silylketene producing a 4-membered β-lactone ring, the reaction being catalysed by a chirally modified Lewis acid, ML^*_n (Scheme 6.5.1).



Scheme 7.1.2

For a methodology study to bear fruit, a coherent plan must be formulated which takes into consideration all the variables present in the initial problem. From scheme 7.1.2, the variables are: the aldehyde, the silylketene, the Lewis acid (which metal? which ligand?) and any reaction parameters such as solvent and temperature. Of course the reactions should be conducted under conditions as similar to each other as possible so accurate comparisons of any results may be made. After consideration, the plan of action was set:

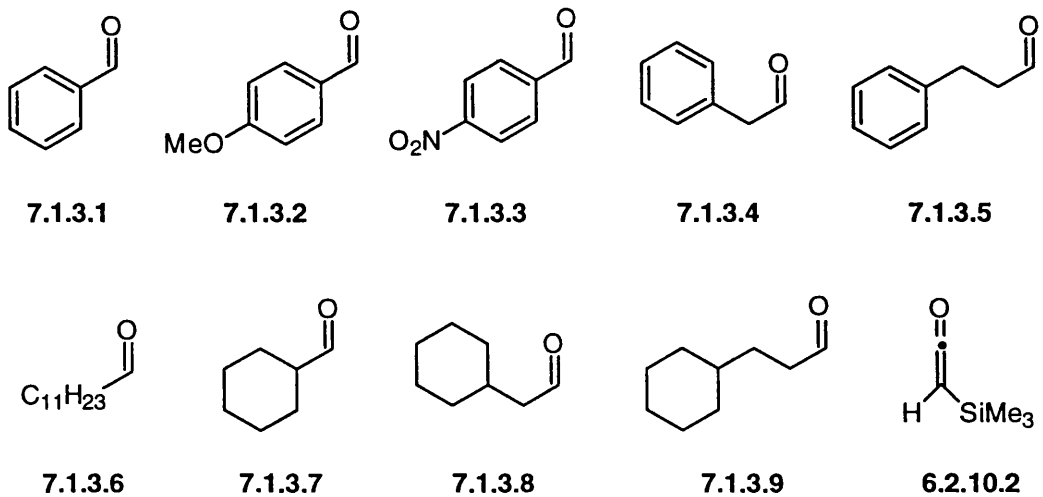
(i) Select 3 or 4 achiral aldehyde substrates.

(ii) Select one silylketene.

(iii) Develop model [2+2] cycloadditions with available achiral Lewis acids *e.g.* BF_3, $EtAlCl_2$.

(iv) Chirally modify the Lewis acid in order to make the reaction enantioselective.

(Trimethylsilyl)ketene (**6.2.10.2**) was chosen as a simple and easy to prepare ketene (see Scheme 6.2.11) but also because of ease of analysis of the cycloadducts (see below). The aldehydes were chosen as in figure 7.1.3. This selection will be used for various studies depending on the outcome of their cycloadditions with **6.2.10.2**. The aromatic aldehydes **7.1.3.1**, **7.1.3.2** and **7.1.3.3** could yield some mechanistic information due to the differences in the electronic distribution within the carbonyl group. The other 2 aromatic ring-containing aldehydes, **7.1.3.4** and **7.1.3.5**, could be of use in a chiral study examining the importance of the proximity of an aromatic ring to the reacting centres. Dodecanal (**7.1.3.6**) is a simple long-chain aldehyde, arguably the greatest challenge for an enantioselective reaction due to the lack of any sterically encumbering groups. Cyclohexane carboxaldehyde (**7.1.3.7**) is a simple α-branched aldehyde and the influence of the saturated ring could be studied with **7.1.3.8** and **7.1.3.9**.



7.1.3.1 **7.1.3.2** **7.1.3.3** **7.1.3.4** **7.1.3.5**

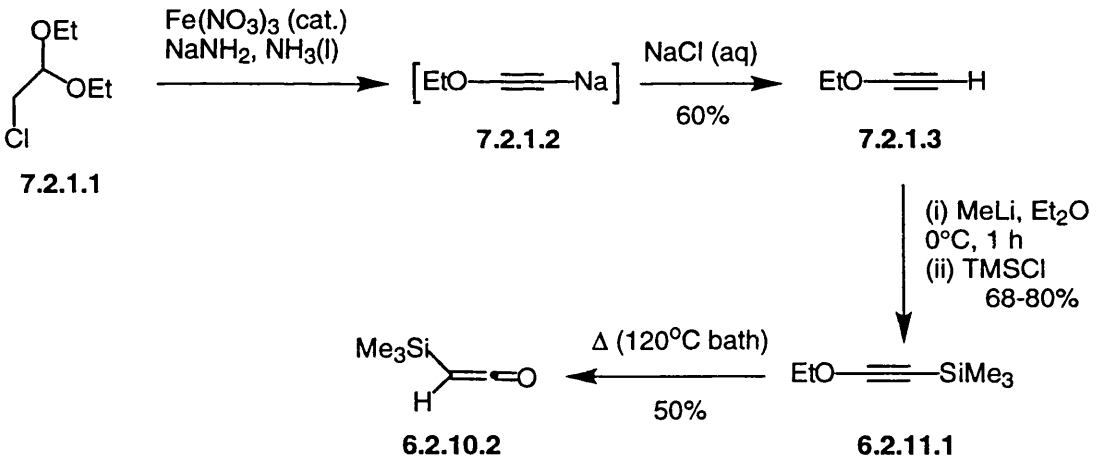
7.1.3.6 **7.1.3.7** **7.1.3.8** **7.1.3.9** **6.2.10.2**

Figure 7.1.3

The following discussion will chronicle efforts to synthesise the ketene, explore model studies with achiral Lewis acids and then bring these studies to a point where various chiral ligands can be tested for enantioselectivity.

7.2 Preparation of (Trimethylsilyl)ketene (6.2.10.2)

The most practical method for the preparation of **6.2.10.2** involves pyrolysis of (trimethylsilyl)ethoxyacetylene (**6.2.11.1**)[111,151] which is formed by quenching of metallated ethoxyacetylene with trimethylsilyl chloride. Although ethoxyacetylene (**7.2.1.3**) is commercially available, it is expensive and often requires purification before use, so it must be prepared freshly[215] rendering the synthesis of **6.2.10.2** a 3 step procedure. In order to increase the efficiency of this synthesis, two attempts at quenching an *in situ* formed metallated ethoxyacetylene with TMSCl were carried out: firstly, formation of **7.2.1.2** from chloroacetaldehyde diethylacetal (**7.2.1.1**)[215] and quenching with TMSCl to hopefully give **6.2.11.1**; secondly, formation of lithiated ethoxyacetylene from **7.2.1.1** and methyl lithium and quenching with TMSCl. Unfortunately, neither process was successful so without further investigation **6.2.10.2** was prepared from the literature method[111,151] (Scheme 7.2.1).

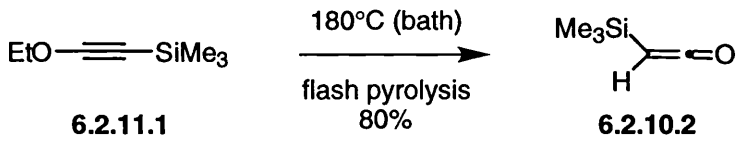


Scheme 7.2.1

Preparation of **7.2.1.3** by treatment of **7.2.1.1** with 3 equivalents of sodamide in liquid ammonia gave a 60% yield. Lithiation of acetylene **7.2.1.3** and quenching with TMSCl gave **6.2.11.1** in 68% yield. This low yield is probably due to loss of some product on evaporation of the solvent *in vacuo*. Crude **6.2.11.1** was pyrolysed at 120°C: **6.2.10.1** distilled at 79-82°C in 50% yield. The product was redistilled through a 10cm Vigreux column in order to remove all traces of **6.2.11.1** which were detectable in the crude NMR and IR of **6.2.10.2**. Overall yield from **7.2.1.3** was only 25% (lit.[151] 65%).

The key step in this preparation is the pyrolysis of trimethylsilyl

ethoxyacetylene **6.2.11.1** to the ketene **6.2.10.2**. Observations led to the conclusion that the method of achieving the pyrolysis reaction by heating **6.2.11.1** at 120°C was resulting in significant decomposition. Since it takes a finite time for any liquid to be completely vaporised by boiling, and the product ketene is thermally unstable under the pyrolysis conditions, it was necessary to devise a method of pyrolysis where the materials were exposed to high temperatures for shorter periods of time. Such a technique is flash pyrolysis: acetylene **6.2.11.1** was added dropwise *via* syringe into an empty, dry distillation flask immersed in a silicone oil bath at 180°C (Scheme 7.2.2).



6.2.11.1 **6.2.10.2**

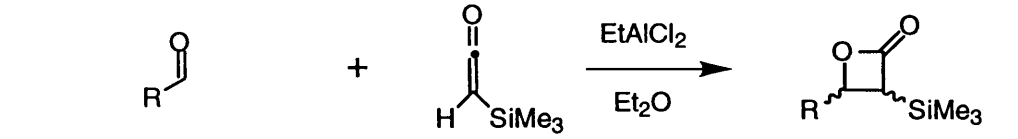
Scheme 7.2.2

6.2.11.1 pyrolysed rapidly (or "flashed") and could be condensed as normal. The rate of addition of **6.2.11.1** into the hot flask equalled the rate of condensation of the product **6.2.10.2** so that only a small amount of material was boiling at any one time, minimising decomposition dramatically. A lower temperature bath gave incomplete conversion. Any traces of unreacted **6.2.11.1** may be removed with a simple Kugelrohr distillation at atmospheric pressure. Using this technique, the yield of ketene increased to 50% overall from ethoxyacetylene.

7.3 Model [2+2] Cycloadditions

Note: All reactions were conducted with 1.2-1.5 equivalents of ketene unless otherwise stated.

Initial attempts at [2+2] cycloaddition with **6.2.10.2** were made with the aryl aldehydes benzaldehyde **7.1.3.1** and *para*-nitrobenzaldehyde **7.1.3.3** (Table 7.3.1).



R = Ph, *p*-NO_2-C_6H_4 **7.1.3.1** **7.1.3.3** **6.2.10.2** R = Ph, *p*-NO_2-C_6H_4

Entry	Aldehyde (R =)	Eq of **6.2.10.2**	Yield (%)	*cis:trans* ratio
1	Ph	0.9	ND[a]	-
2	*p*-NO_2-C_6H_4	1.2	ND[a]	-

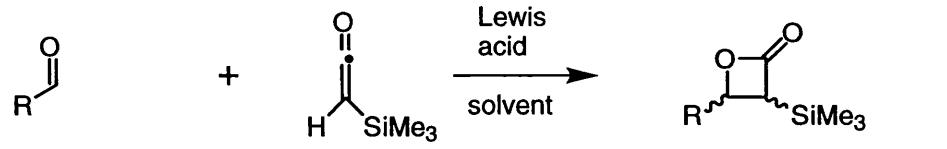
ND = not determined; [a]Polar material formed.

Table 7.3.1

Conducted in ether solvent and using ethylaluminium dichloride as Lewis acid,[216] these reactions were quenched with water at 0°C, after consumption of starting material. Cycloaddition took place as evidenced by isolation of polar products: α,β-unsaturated carboxylic acids or silylstyrene decarboxylation products (see Mechanistic Considerations, below). An *in situ* formed 2-oxetanone has probably further reacted either under the reaction conditions or during work-up.[145] Considering that Zaitseva[110] and more recently Brady[168] worked without solvent and directly distilled the product 2-oxetanones from the reaction mixture, it may be concluded that these aryl aldehydes are unsuitable as models under the chosen conditions although their relative reaction rates will later become useful when the mechanism is considered.

Some of the other aldehydes from figure 7.1.3 were more successful (Table 7.3.2).

Table 7.3.2 shows that dodecanal (**7.1.3.6**) cycloadds in moderate to good yield with both $EtAlCl_2$ and BF_3•OEt_2 as the Lewis acid mediator (entries 1 and 4), the former in a variety of solvents (entries 1-3). However, the ratio of *cis:trans* product isomers are quite different: with the aluminium Lewis acid total *cis* selectivity was observed but with boron, this selectivity was completely destroyed. This difference may be due to the greater steric bulk of the aluminium. (see later mechanistic discussions for an explanation)



R = $C_{11}H_{23}$ **7.1.3.6**
c-hex **7.1.3.7**
$PhCH_2CH_2$ **7.1.3.5**

6.2.10.2

R = $C_{11}H_{23}$ **7.3.2.1**
c-hex **7.3.2.2**
$PhCH_2CH_2$ **7.3.2.3**

Entry	Aldehyde (R =)	Lewis acid (1.1 eq)	Solvent	Yield (%)[a]	*cis:trans* ratio
1	$C_{11}H_{23}$	$EtAlCl_2$	Et_2O	68	100:0
2	$C_{11}H_{23}$	$EtAlCl_2$	CH_2Cl_2	54	100:0
3	$C_{11}H_{23}$	$EtAlCl_2$	PhMe	52	100:0
4	$C_{11}H_{23}$	$BF_3{\bullet}OEt_2$	Et_2O	81	53:47
5	$C_{11}H_{23}$	$AlCl_3$	Et_2O	56	100:0
6	$C_{11}H_{23}$	Me_3Al	CH_2Cl_2	15[c]	77:23
7	*c*-Hex	$EtAlCl_2$	Et_2O	17[b]	-
8	$PhCH_2CH_2$	$EtAlCl_2$	PhMe	62	81:19
9	$PhCH_2CH_2$	Me_3Al	CH_2Cl_2	18[d]	100:0

Notes: [a] refers to yield after column chromatography unless otherwise stated; [b] Isolated yield of decarboxylated product (silyl alkene); [c] 19% of decarboxylated product (silyl alkene) also isolated in addition to Me attack on the carbonyl; [d] major product was 4-phenyl butan-2-ol derived from Me attack on the aldehyde carbonyl (64%).

Table 7.3.2

A few other aluminium Lewis acids were also examined since this metal appears to give better stereoselectivity. Trimethylaluminium was found to give side products *e.g.* addition of a methyl group to the carbonyl of the aldehyde (entries 6 and 9). $AlCl_3$ also performed well for **7.1.3.6** (entry 5). For cyclohexane carboxaldehyde (**7.1.3.7**) only polar products were isolated as for the aromatic aldehydes discussed above. However, a suitable model reaction with dodecanal has been found for initial forays into enantioselective reactions.

7.4 Development of a Suitable Method of Analysis of the Product Enantiomers

The products of a typical [2+2] cycloaddition with aldehydes and silylketenes may be composed of up to 4 stereoisomers: two *cis* and two *trans* enantiomers.

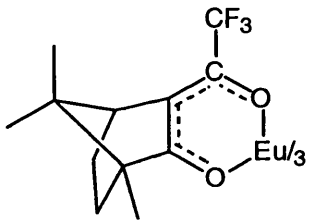
Since the *cis* and *trans* geometrical isomers are separable by chromatography, the problem is reduced to determining the ratio of enantiomers in each sample of *cis* and/or *trans*-β-lactones. Available modern methods include:[217]

(i) NMR Methods
  (a) Chiral Lanthanide Shift Reagents (CLSRs)
  (b) Chiral Solvents
  (c) Chiral Solvating Agents

(ii) Chemical Derivatisation

(iii) Chiral Chromatography

Since (iii) was not readily available at the outset of this study and (ii) requires and extra chemical step, methods (i) were investigated. Initially, the CLSR **7.4.1.1** (Figure 7.4.1) was tested at varying product/CLSR ratios.[81]

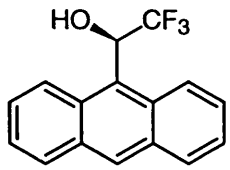


7.4.1.1

Figure 7.4.1

As this ratio increased, increasing line-broadening was observed in the ^{1}H NMR spectrum at 270 or 360 MHz but no enantiomeric signals became sufficiently separate for an accurate integration analysis. Chiral solvents are expensive and infrequently of use and were not studied. However, option (i) (c) proved to be of some utility: a chiral solvating agent is a substance whose chirality influences solute spectral behaviour.[218] Typically, these agents are added to an achiral solvent containing the solute (racemic, enantiomerically enriched or even a single enantiomer). Model analyses were probed with racemic β-lactones: on addition of 1 equivalent of (*S*)-(–)-BINOL to the deuteriochloroform NMR solution of β-lactone enantiomers, the doublets at approximately δ3.3 (J = 6.1Hz for the *cis* isomer) for the CHTMS proton became sufficiently separate for an accurate integration analysis (±10% ee) at 360 MHz (compound **7.3.2.1**). This method was employed for analyses in initial studies (see notes under the following tables) but often the ^{1}H NMR spectrum required resolution enhancement in order to effectively fully separate

the signals of interest. A resolution enhanced spectrum cannot be accurately integrated therefore greater errors are introduced into the enantiomer analysis. However, it was later found that Pirkle's anthracene derivative (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**7.4.2.1**) (figure 7.4.2) was more effective.



7.4.2.1

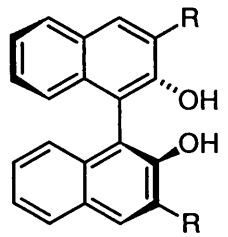
Figure 7.4.2

When 2 equivalents of **7.4.2.1** were added to the deuteriochloroform or deuteriobenzene solutions of the target β-lactone, effective separation of the CHTMS doublet was usually obtained without resolution enhancement.
Later, in the chiral studies discussed below, chiral HPLC chromatography became available. Notes below tables indicate which methods have been used for the determination of ee.

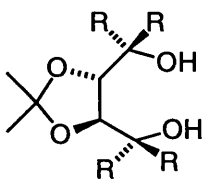
7.5 Studies Towards an Enantioselective [2+2] Cycloaddition

7.5.1 Introduction

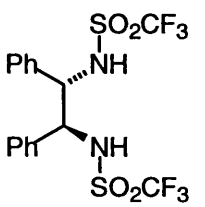
In situ formed chirally modified Lewis acids have been found to efficiently direct many carbon-carbon bond forming reactions (see Chapter 6). Ligands used with aluminium include the binaphthyls **7.5.1.1**-**7.5.1.3**,[219,220] tartrate derived diols **7.5.1.4**-**7.5.1.6**[209-211] and *bis*-sulfonamides such as **7.5.1.7**[221] or **7.5.1.8**[222,223] (see Figure 7.5.1).



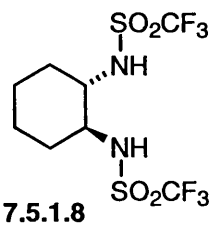
R = H **7.5.1.1**
R = Me **7.5.1.2**
R = $SiPh_3$ **7.5.1.3**



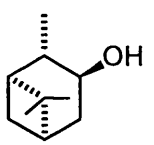
R = Ph **7.5.1.4**
R =1-naphthyl **7.5.1.5**
R = 2-naphthyl **7.5.1.6**



7.5.1.7

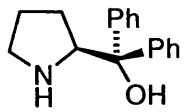


7.5.1.8



7.5.1.9

7.5.1.10



7.5.1.11

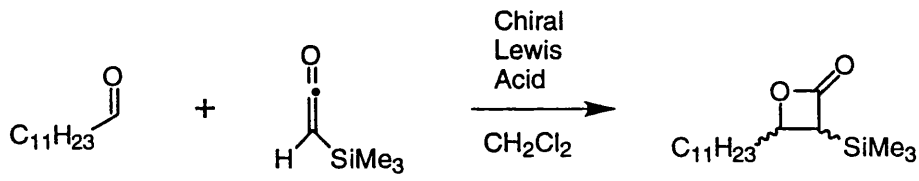
Figure 7.5.1

Potentially, the aluminium Lewis acid could be complexed with any chiral alcohol, e.g. **7.5.1.9** or **7.5.1.10**, diol, aminol, *e.g.* **7.5.1.11** (easily accessible from L-proline) or diamine.

Since there is an adequate supply of these chiral ligands the object of this work is not to redesign new catalysts but to simply utilise existing ones in order to create a chiral Lewis acid which might enantioselectively catalyse the [2+2] cycloaddition in question.

7.5.2 Results of Preliminary Chiral Study

Dodecanal was identified, above, as a suitable model for initial chiral studies. Using a selection of chiral ligands from figure 7.5.1, some successful enantioselective reactions were carried out. Table 7.5.2 shows these results which amount to the first ever enantioselective chiral Lewis acid catalysed reactions of aldehydes with a silylketene.



7.1.3.6 **6.2.10.2** **7.3.2.1**

Entry	Chiral Lewis acid	Yield (%)	*cis:trans* ratio	ee[a] (%)
1	$EtAlCl_2$/**7.5.1.1**[b]	83[d]	100:0	11
2	$EtAlCl_2$/**7.5.1.4**[b]	11	100:0	10
3	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$/**7.5.1.8**[b]	0	-	-
4	$EtAlCl_2$/**7.5.1.8**[b]	48[e]	100:0	0
5	$EtAlCl_2$/**7.5.1.9**[b]	69[f]	100:0	22
6	$EtAlCl_2$/**7.5.1.10**[b]	61	100:0	18
7	$EtAlCl_2$/**7.5.1.10**[c]	4[f]	0:100	ND

[a] ees were determined by 360MHz ^1H NMR: addition of 1 equivalent of (*S*)-(–)-BINOL to the NMR solution and integration of the CHTMS doublets; [b] 1:1 ratio; [c] 1:2 ratio; [d] Yield based on recovered aldehyde; [e] Also 11% of the aldehyde + product mixture(1:1). [f] Also 65% of R^*OCOCH_2TMS; ND = not determined.

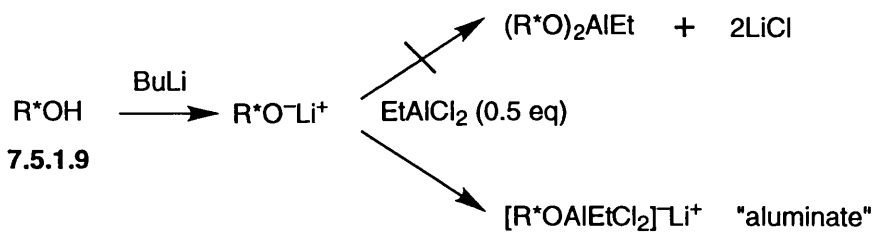
Table 7.5.2

However, as suspected from previous work,[216] the titanium system was just too strong and destroyed the products as they formed.

All chiral ligands were used in stoichiometric quantities. The first attempt was with (S)-(-)-BINOL **7.5.1.1**: this chiral diol was complexed with $EtAlCl_2$ (liberating HCl) at –30°C then dodecanal was added and finally the ketene **6.2.10.2** (entry 1). The reaction yielded 56% of exclusively *cis*-2-oxetanone **7.3.2.1** (and 18% recovered aldehyde, 83% yield of product based on recovered starting material). A slight enantioselective effect of 11% ee was detected using chiral BINOL in the ^1H NMR *i.e.* 55.5% of one enantiomer and 44.5% of the other. Although very slight this experiment is highly significant since it demonstrates that the reactions can be conducted enantioselectively. Some BINOL-derived side products were also isolated but not fully identified.

Further studies with the tartrate derived diol **7.5.1.4** (TADDOL) (entry 2) gave a very poor reaction but the isolated product exhibited a slight ee of about 10%. *Bis*-sulfonamide **7.5.1.8**[222] was studied with a titanium Lewis acid but resulted in no reaction (entry 3). Although the $EtAlCl_2$ complexed **7.5.1.8** resulted in some desired product with exclusive *cis* selectivity, disappointingly there was no enantioinduction (entry 4).

Chiral alcohols (+)-*iso*-pinocampheol **7.5.1.9** and (–)-menthol **7.5.1.10** were available and experiments were conducted with 1 equivalent of each with $EtAlCl_2$ (entries 5 + 6, respectively). These cycloadditions progressed rapidly and resulted in good yields of cycloadduct with slightly better enantioselection than **7.5.1.1** (22 and 18% for **7.5.1.9** and **7.5.1.10**, respectively). The alcohols were also acylated in good yield by the ketene **6.2.10.2** to give α-silyl esters derived from the chiral alcohol, a typical reaction of alcohols with silylketenes (see Chapter 6). This previously reported[221] side reaction could be due to the presence of HCl in the reaction mixture rendering the chiral aluminium complex formation reversible. Therefore eliminating HCl from the equation may prevent acylation of the alcohol. One attempt is shown in Scheme 7.5.3.



Scheme 7.5.3

Lithiation of the alcohol **7.5.1.9** with *n*-butyl lithium then reaction with $EtAlCl_2$ in ether did not result in the expected product with liberation of lithium chloride (a driving force for completion of complexation) but instead gave a solid gel which could be an aluminate complex. Other methods of preventing acylation of the chiral alcohols could be use of Me_3Al or Et_3Al (liberation of methane or ethane) or formation of the trimethylsilyl protected alcohol and removal of volatile trimethylsilyl chloride (bp 57°C) by distillation on reaction with $EtAlCl_2$ in a suitable solvent, *e.g.* toluene.

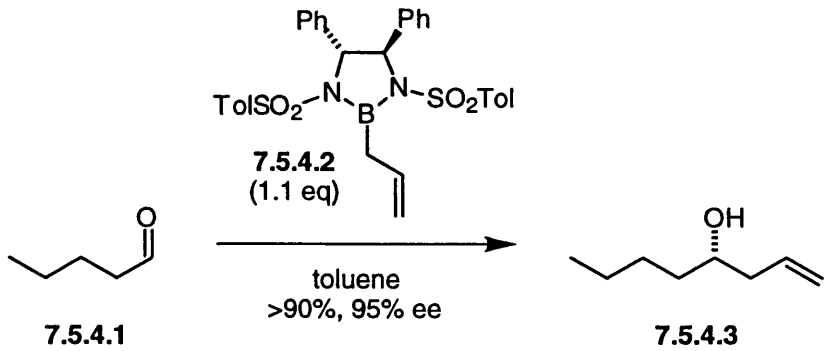
Enantioselectivity is likely to be improved if two chiral alcohol units modify the Lewis acid so the [2+2] cycloaddition was also attempted with 2 equivalents of **7.5.1.10** (with 1 equivalent of $EtAlCl_2$) but resulted in large quantities of α-silyl ester derived from the chiral alcohol and very little 2-oxetanone product.

7.5.3 Discovery that Chiral Lewis Acids Derived from 7.5.1.7 Catalyse the [2+2] Cycloaddition with High Enantioselectivity

Recently Corey has developed a new class of chiral Lewis acid catalyst **6.4.16.3** (see Scheme 6.4.16) for the Diels-Alder reaction. [214,224] These catalysts are aluminium derivatives of *bis*-sulphonamide **7.5.1.7** and have been fully characterised (including X-ray studies) by Corey. [225] In our [2+2] cycloaddition, such catalysts were found to be useful due to rapid screening of ligands through ease of ligand synthesis. Such attributes are lacking in many other ligands such as BINOLs or TADDOLs (see Chapter 6). The following sections will discuss previous applications of *bis*-sulfonamide ligands in asymmetric synthesis, the preparation of the ligands and the development and optimisation of chiral catalysts for the [2+2] cycloaddition of aldehydes and silylketenes.

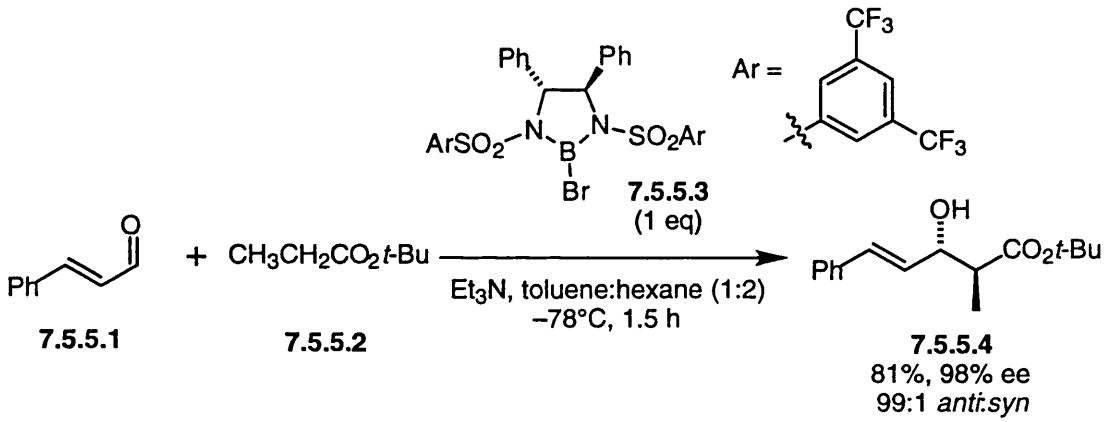
7.5.3.1 Previous Methodology with *Bis*-sulfonamides as Ligands for Chiral Lewis Acids

Good precedent for their use is evidenced in their application to several stereoselective processes. Firstly, Corey reported the above Diels-Alder chemistry which led to enantioselective and diastereoselective allylations of aldehydes mediated by stoichiometric quantities of boron-centred *bis*-sulfonamide **7.5.4.2** (Scheme 7.5.4). [226]



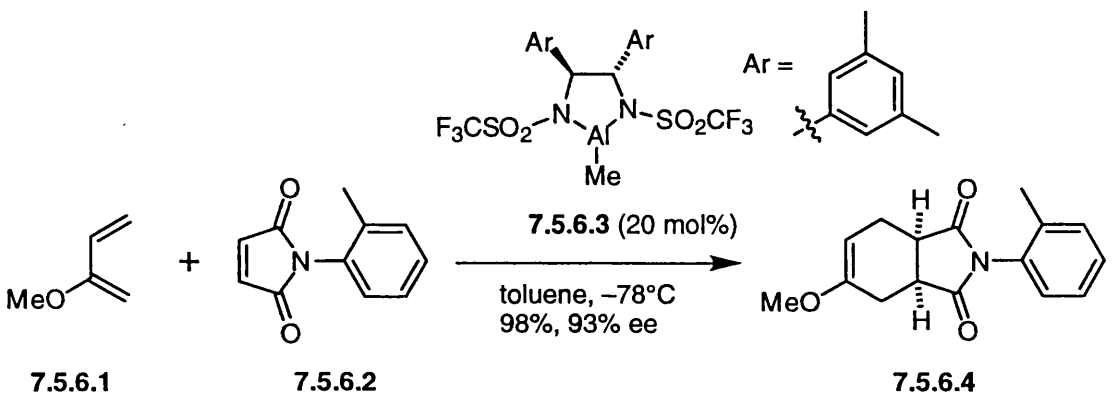
Scheme 7.5.4

Highly stereoselective aldol reactions may be performed with propionate ester enolates and aldehydes mediated by boron-centred chiral Lewis acid **7.5.5.3** (Scheme 7.5.5). [227,228]



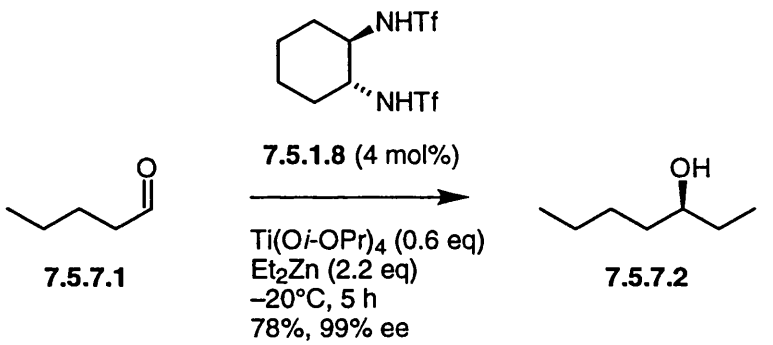
Scheme 7.5.5

The first example of an enantioselective Diels-Alder reaction of an achiral C_{2v}-symmetric dienophile and an achiral diene was reported by Corey in 1994. In this instance, the aryl groups from the parent diamine were modified with 3,5-dimethyl substitution to give catalyst **7.5.6.3** which catalysed the [4+2] cycloaddition of diene **7.5.6.1** with the dienophile **7.5.6.2** in 98% yield and 93% ee (Scheme 7.5.6). [229]



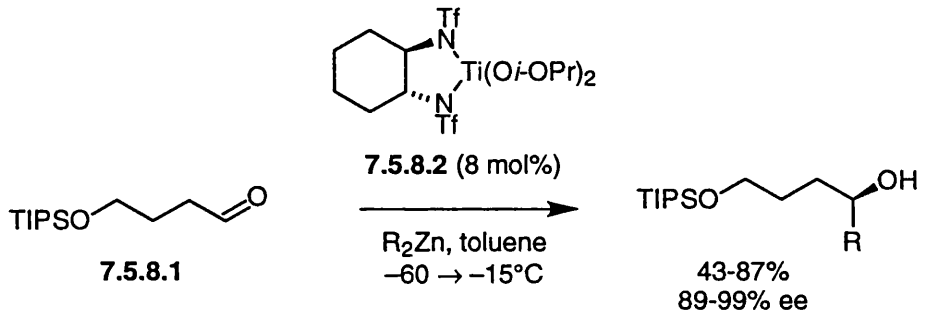
Scheme 7.5.6

Another reaction which is possible to influence enantioselectively with *bis*-sulfonamides is the addition of alkyl groups to aldehydes using a titanium-dialkylzinc system. [222] The example shown in scheme 7.5.7 is impressive since almost complete control of the product stereochemistry is achieved with linear pentanal.



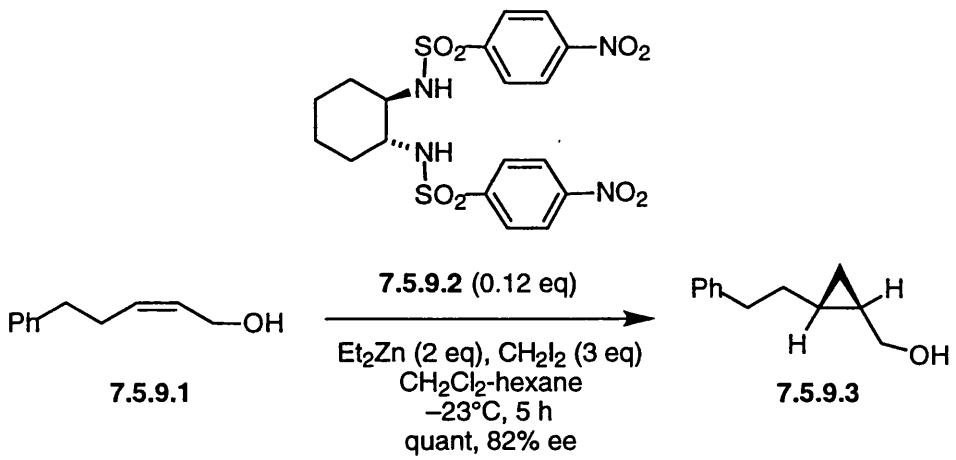
Scheme 7.5.7

In a similar vein, Knochel has prepared 1,4-diols by the catalytic enantioselective addition of functionalized dialkylzincs to γ-oxyaldehydes. For example TIPS protected 4-hydroxybutanal (**7.5.8.1**) undergoes addition from a variety of organozincs in the presence of 8 mol% of titanium chiral Lewis acid **7.5.8.2** (Scheme 7.5.8). [223]



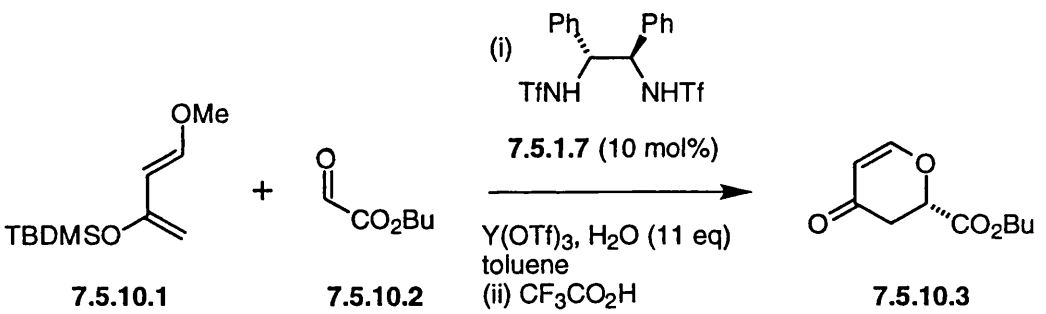
Scheme 7.5.8

More recently, Kobayashi has demonstrated good enantioselectivity for the Simmons-Smith cyclopropanation of allylic alcohols catalysed by various *bis*-sulfonamide-zinc-complexed species. One of the better examples is shown in scheme 7.5.9 where 0.12 equivalents of *para*-nitrobenzenesulfonamide **7.5.9.2** was employed giving a quantitative yield and 82% ee. [230,231]



Scheme 7.5.9

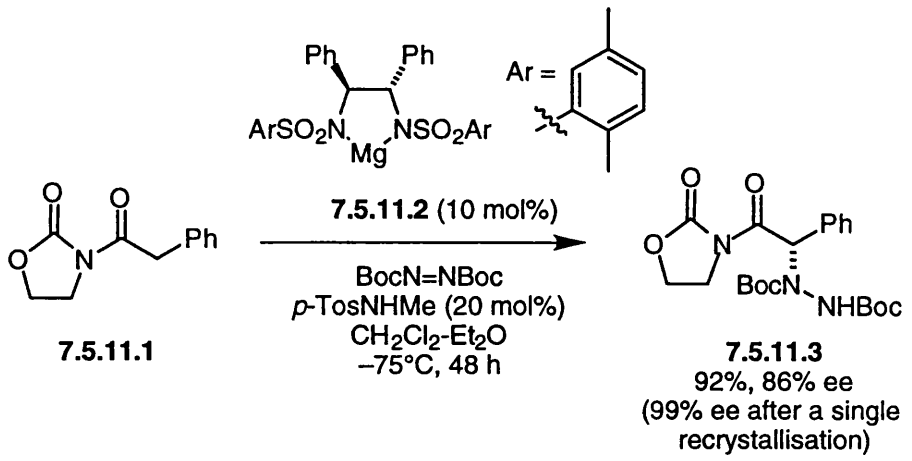
Lanthanide-*bis*-triflamides have been employed for the hetero-Diels-Alder reaction of Danishefsky's diene **7.5.10.1** with butyl glyoxalate (**7.5.10.2**) [232] (Scheme 7.5.10).



Scheme 7.5.10

The lanthanide-*bis*-sulfonamide complex is formed by deprotonation of the acidic sulfonamide protons with sodium hydride then addition of the lanthanide triflate (ytterbium triflate gave the best results). The interesting point about this study is the beneficial influence of water as an additive in increasing not only the enantioselectivity but also the chemical yield. Other reactions catalysed by lanthanide complexes in the presence of water have been studied. [233]

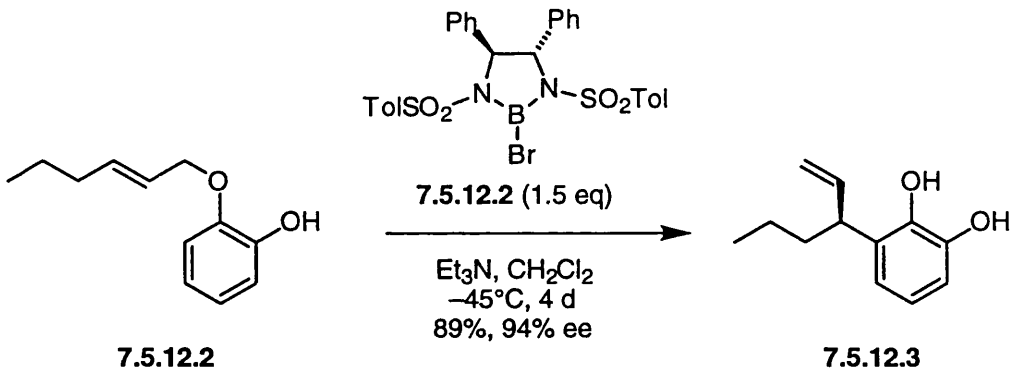
Very recently, Evans reported the application of chiral magnesium-*bis*-sulfonamide **7.5.11.2** for the enantioselective amination of *N*-acyloxazolidinones such as **7.5.11.1**[234] (Scheme 7.5.11).



Scheme 7.5.11

The product **7.5.11.3** may be upgraded to >99% ee after only a single recrystallisation. The role of the *N*-methyl-*p*-toluenesulfonamide has not been completely elucidated but a kinetic study revealed a first-order dependence of this addend on the reaction rate.

Finally, also very recently, an enantioselective Claisen rearrangement was reported using boron chiral Lewis acid **7.5.12.2**[235] (Scheme 7.5.12).



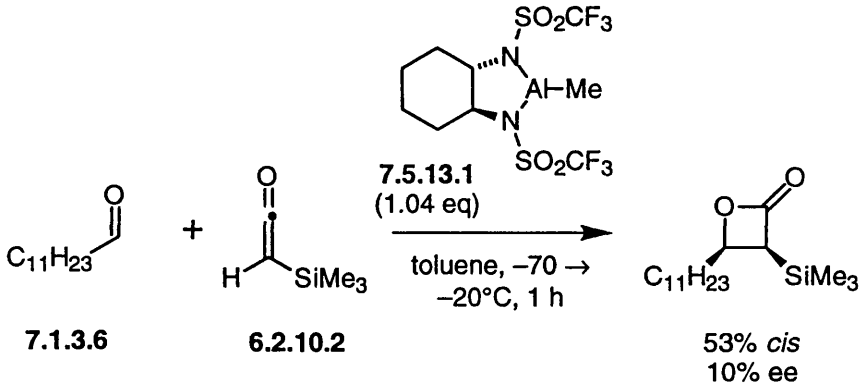
Scheme 7.5.12

This chemistry has the considerable disadvantages of requiring stoichiometric quantities of **7.5.12.2** and being very slow.

7.5.3.2 Synthesis of the *Bis*-sulfonamide Ligands

Hope was initially offered when an opportunity was taken to evaluate this class of Lewis acid by experimentation with aluminium cyclohexane *bis*-triflamide

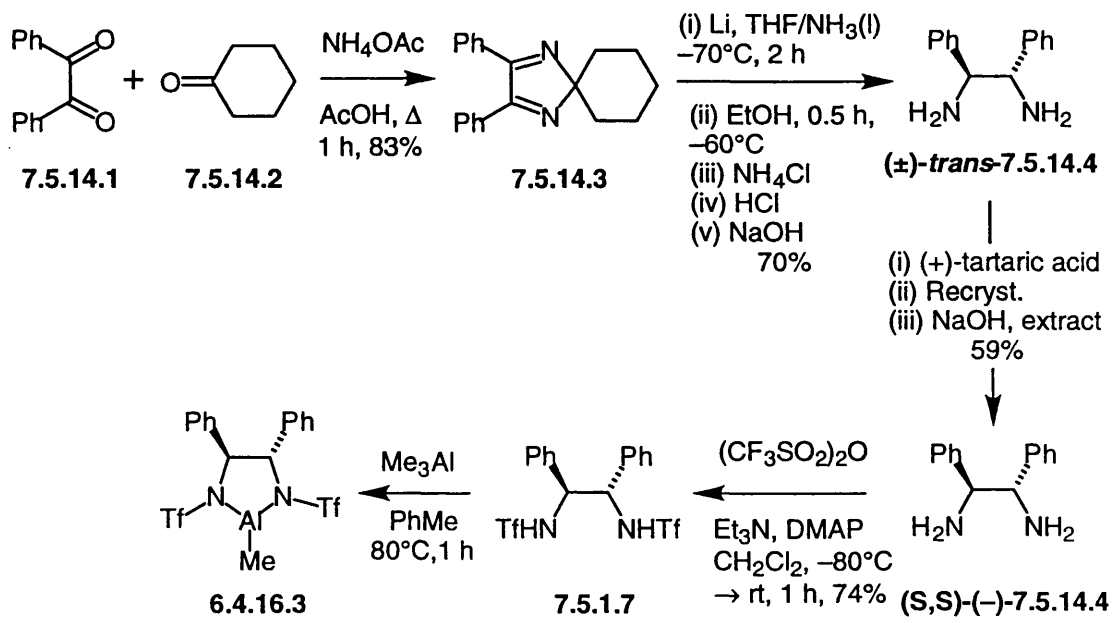
7.5.13.1 for the [2+2] cycloaddition of dodecanal with (trimethylsilyl)ketene (**6.2.10.2**) (Scheme 7.5.13, *c.f.* Table 7.5.2, entry 4).



Scheme 7.5.13

Lewis acid **7.5.13.1** was formed by addition of 1 equivalent of trimethylaluminium in toluene to the *bis*-triflamide **7.5.1.8** and heating at 80°C for 1 h (Corey conditions[214]). Scheme 7.5.13 shows that **7.5.13.1** successfully mediated the reaction of dodecanal (**7.1.3.6**) with **6.2.10.2** in 53% yield but importantly a slight enantiomeric excess was detected (BINOL added to ^{1}H NMR and analysis of CHTMS doublets). With this result in hand, the synthesis of Corey's 1,2-diphenylethylene diamine-based ligand could be attempted. The phenyl groups could be important electronically and sterically. [236]

Hence the synthesis of parent diamine **7.5.14.4** was undertaken as in scheme 7.5.14. [237,238]



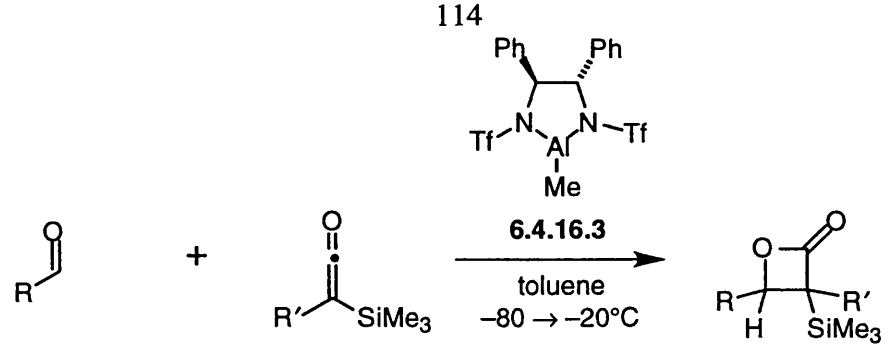
Scheme 7.5.14

Spiro-imidazole intermediate **7.5.14.3** was obtained by reaction of 1 equivalent each of benzil (**7.5.14.1**), cyclohexanone (**7.5.14.2**) and ammonium acetate in refluxing acetic acid (83% yield after recrystallisation from hexane). **7.5.14.3** was stereoselectively reduced with lithium metal in 1:1 THF: liquid ammonia to give exclusively the *trans* racemic diamine (±)-**7.5.14.4** in 70% yield. Resolution of (±)-**7.5.14.4** with (+)-tartaric acid in 2 recrystallisations followed by extraction of the free amine from aqueous sodium hydroxide solution yielded the optically pure (S,S)-(–)-**7.5.14.4**. This compound along with its enantiomer is commercially available but prohibitively expensive. At this stage any sulphonamide desired may be prepared from **7.5.14.4** by reaction with the appropriate sulphonyl chloride or anhydride. Initially the triflamide **7.5.1.7** was prepared since this has been studied widely by Corey. Aluminoimidazoline **6.4.16.3** forms easily when **7.5.1.7** is exposed to trimethylaluminium in toluene. It was subsequently found that heating this mixture to 80°C (as for Corey's conditions[214] was not necessary in order to form the catalyst: stirring at room temperature for 10 minutes results in evolution of methane). A toluene solution of **6.4.16.3** may be stored under an inert atmosphere and used when required but it is a simpler matter to prepare the catalyst *in situ*.

Modifications to the catalyst structure proved to be facile. The sulfone of choice may be attached to the parent chiral diamine **7.5.14.4** using standard methodology (sulfonyl chloride (2 equivalents), triethylamine (3 equivalents) and catalytic DMAP in dichloromethane at rt). Some non-C_2-symmetric variants were also prepared. For these, addition of one equivalent of sulfonyl chloride followed by the other after consumption of the first was necessary to avoid mixtures of products (see later).

7.5.3.3 [2+2] Cycloadditions Catalysed by 6.4.16.3 with a Range of Aldehydes

Cycloaddition reactions were studied with **6.4.16.3** as chiral Lewis acid. Firstly the reaction of dodecanal (**7.1.3.6**) with **6.2.10.2** was investigated with 1.01 equivalents of **6.4.16.3** (Table 7.5.15, entry 1).



R = $C_{11}H_{23}$ **7.1.3.6**
$PhCH_2CH_2$ **7.1.3.5**
$PhCH_2$ **7.1.3.4**
Ph **7.1.3.1**
c-$hexCH_2CH_2$ **7.1.3.9**
c-$hexCH_2$ **7.1.3.8**
c-hex **7.1.3.7**
p-$NO_2C_6H_4$ **7.1.3.3**
p-$MeOC_6H_4$ **7.1.3.2**

R′ = H **6.2.10.2**
C_6H_{13} **6.2.12.2**

R =	R′ =	
$C_{11}H_{23}$	H	**7.3.2.1**
$PhCH_2CH_2$	H	**7.3.2.3**
$PhCH_2$	H	**7.5.15.1**
Ph	H	**6.2.10.4**
c-$hexCH_2CH_2$	H	**7.5.15.2**
c-$hexCH_2$	H	**7.5.15.3**
c-hex	H	**7.3.2.2**
p-$NO_2C_6H_4$	H	**7.5.15.4**
p-$MeOC_6H_4$	H	**7.5.15.5**
$PhCH_2CH_2$	C_6H_{13}	**7.5.15.6**
$PhCH_2$	C_6H_{13}	**7.5.15.7**
c-$hexCH_2CH_2$	C_6H_{13}	**7.5.15.8**

Entry	RCHO (R =)	Ketene (R′ =)	Equivalents of **6.4.16.3**	Yield (%)[a]	*Cis:Trans*	ee[h] (%) (*cis*)
1	$C_{11}H_{23}$	H	1.01	53	100:0	0
2	$C_{11}H_{23}$	H	0.51	52	100:0	<5
3	$C_{11}H_{23}$	H	0.20[c]	53	100:0	<5
4	$PhCH_2CH_2$	H	0.20	81	95:5	15
5	$PhCH_2$	H	0.20	81	84:16	15
6	Ph	H	0.20	70[d]	100:0	20
7	*c*-$HexCH_2CH_2$	H	0.20	75	97:3	5
8	*c*-$HexCH_2$	H	0.20	73	96:4[e]	10
9	*c*-Hex	H	0.20	71	88:12	0
10	*p*-$NO_2C_6H_4$	H	0.20	75[i]	100:0	f
11	*p*-$MeOC_6H_4$	H	0.20	67[g]	-	-
12	$PhCH_2CH_2$	C_6H_{13}	0.20	77	86:14	ND
13	$PhCH_2$	C_6H_{13}	0.20	73	82:18	ND
14	*c*-$HexCH_2CH_2$	C_6H_{13}	0.20	ND	ND	ND

Notes: ND: not determined; [a] refers to yield after column chromatography unless otherwise stated; [b] 19% of decarboxylated product (silyl alkene) also isolated; [c] no reaction with 15, 10 or 1 mol%; [d] crude β-lactone isolated but hydrolysed on silica to give 70% of the α,β-unsaturated acid; [e] inseparable 96:4 mixture characterised; [f] decomposed on treatment with BINOL; [g] yield of α,β-unsaturated acid derived from β-lactone; [h] ee s were determined by 360MHz ^{1}H NMR: addition of 1 equivalent of (*S*)-(−)-BINOL to the NMR solution and integration of the CHTMS doublets; [i] yield of crude product.

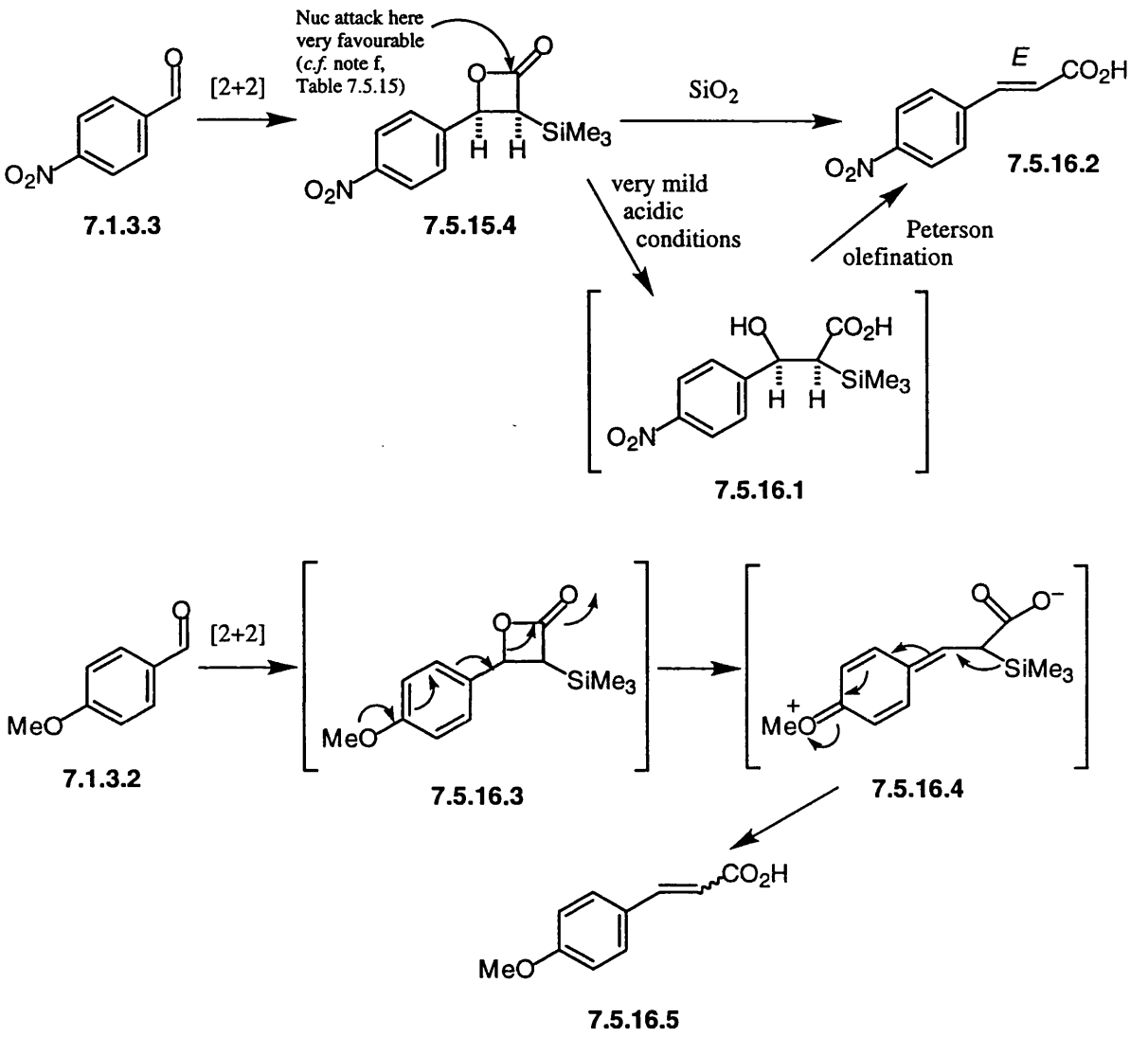
Table 7.5.15

Complete reaction was achieved rapidly and with 100% *cis* selectivity (although no enantioselectivity). When a catalytic quantity of **6.4.16.3** was employed (50 then 20 mol%, entries 2 and 3 and see note c) it was discovered that the reaction progressed efficiently with no loss in yield, *cis*:*trans* selectivity or reaction rate. Hence the reaction has successfully been made catalytic. In fact these reactions progressed more rapidly and cleanly than studies with achiral Lewis acids such as $EtAlCl_2$.

Considering the relative Lewis acidity of the catalyst with Lewis basicity of the aldehyde starting material and β-lactone product may help in our understanding of the catalytic cycle. Strong Lewis acids such as $EtAlCl_2$ and Me_3Al co-ordinate strongly to the Lewis basic sites on the aldehyde *and* β-lactone carbonyl groups. Hence a full equivalent of Lewis acid is required for complete conversion to the product. For a successful catalyst, effective binding to the aldehyde substrate is required in order to induce reaction but the products should bind less tightly so that the Lewis acid may detach itself and thereby become available to initiate another cycle. In the case of **6.4.16.3**, tempering of the Lewis acidity of the aluminium centre by the *bis*-sulfonamide ligand seems to have occurred in a favourable direction so that its interaction with the weakly Lewis basic β-lactone carbonyl has been rendered small enough so that the **6.4.16.3** molecule remains free to assist the reaction of a second molecule of aldehyde with the ketene, etc. In addition there is likely to be an unfavourable steric factor involved in the interaction between the β-lactone and the catalyst.

Successful reactions were also achieved with the other aldehydes chosen for the study (see Figure 7.1.3). This series compares aldehydes with electronically and sterically significant groups at varying positions (0, 1 and 2 carbon spacers) relative to the carbonyl group. All reactions progressed rapidly and remarkably cleanly. The product β-lactones were isolated in good yield by chromatography and fully characterised. Most yields were greater than 70% and useful *cis*:*trans* ratios were obtained (entries 4-9). Evidence supporting the mild nature of the catalyst is offered in entry 10: *para*-nitrobenzaldehyde (**7.1.3.3**) gave a 75% yield of β-lactone **7.5.15.4**. This product was sufficiently sensitive to react with BINOL during the ee analysis! However the electronically challenging *para*-methoxybenzaldehyde (**7.1.3.2**) was not so fortunate: only β-lactone derived products were isolated, perhaps due to the higher temperature required to induce cycloaddition with such an unreactive carbonyl.

In order to understand these differences a mechanistic argument can be put forward for the greater instability of the expected product **7.5.16.3** compared to **7.5.15.4** (Scheme 7.5.16).



Scheme 7.5.16

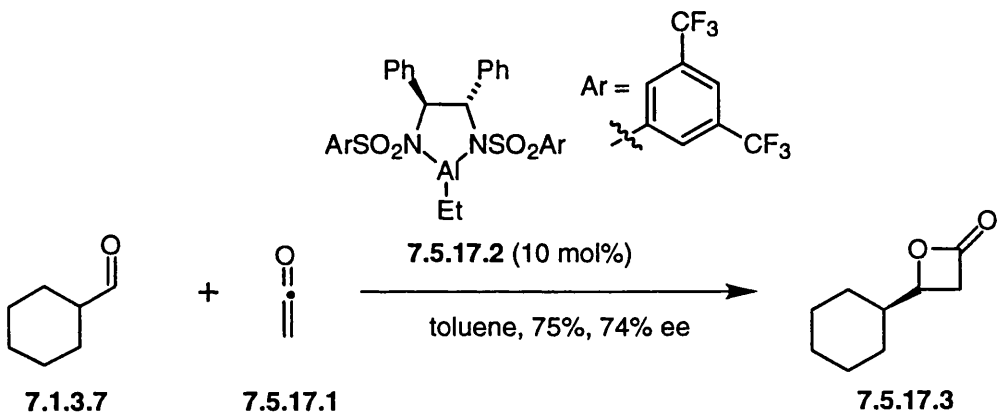
The strong electron donating character of the methoxy group in the *para* position pushes electrons through the aromatic ring in **7.5.16.3**. This results in **7.5.16.4** which loses TMS to give **7.5.16.5**, the driving force being aromatisation and formation of the lower energy fully conjugated system. Of course, the highly reactive nature of the carbonyl group in **7.5.15.4** is due to the powerful electron withdrawing nitro group on the aromatic ring. The decomposition is probably due to Peterson olefination (**7.5.16.1** → **7.5.16.2**).

Studies with hexyl(trimethylsilyl)ketene (**6.2.12.2**) were also carried out (entries 12-14). Some of this material was available from studies on

tetrahydrolipstatin (**6.2.1.3**). Reactions are still clean (although slower, taking about 1 h) and high yielding although the *cis* or *trans* stereochemistry is unknown due to loss of coupling constant information with replacement of the CHTMS proton with a six-carbon chain.

The best enantiomeric excesses so far are only around 20% so some modification of the catalyst structure will be necessary.

At this point we became aware of a publication detailing the [2+2] cycloaddition of some aldehydes with ketene itself employing aluminium modified with *bis*-sulfonamides (Scheme 7.5.17). [221]



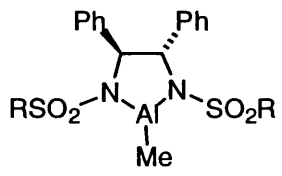
Scheme 7.5.17

Although this work uses ketene (**7.5.17.1**) which is a reactive gas and requires special equipment for its preparation, the principle of aluminium modified with a *bis*-sulfonamide ligand was established confirming that our work was progressing in a positive direction. The use of an ethyl group on aluminium will also be explored later.

7.5.3.4 Optimisation of the Aluminoimidazoline Structure

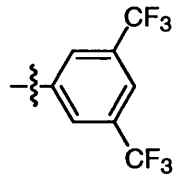
7.5.3.4.1 Study of the Sulfone Group

Figure 7.5.18 shows the structural analogues of **6.4.16.3** tested in table 7.5.19. Aromatic sulfones were realistically the best choice for ease of synthesis and fine-tuning of the steric and electronic properties of the catalyst.

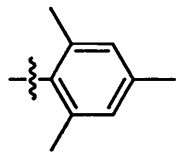


(*S*, *S*) or (*R*, *R*)

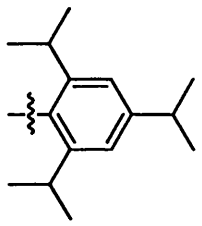
R =



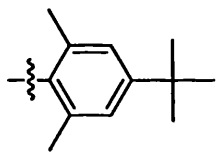
7.5.18.1 (*S*, *S*)



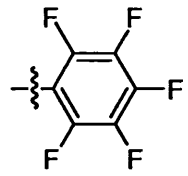
7.5.18.2 (*R*, *R*)



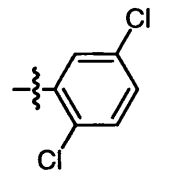
7.5.18.3 (*S*, *S*)



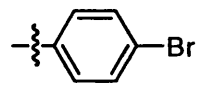
7.5.18.4 (*S*, *S*)



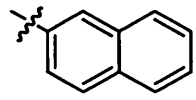
7.5.18.5



7.5.18.6



7.5.18.7



7.5.18.8

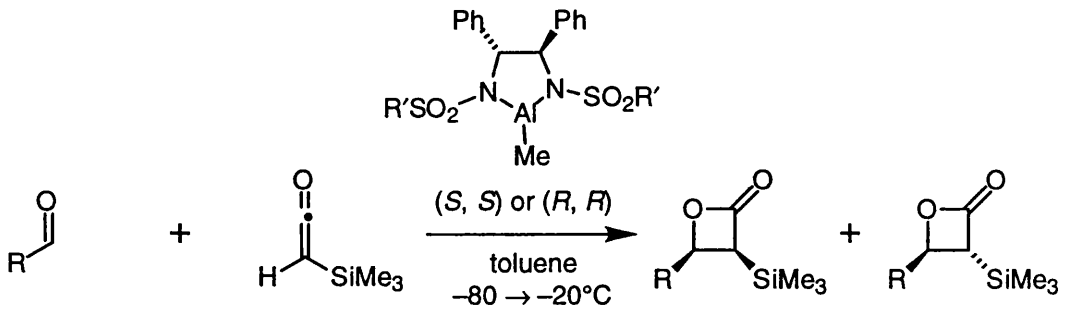
7.5.18.9 (*S*, *S*)

Table 7.5.18

The nine sulfonamide ligands in scheme 7.5.18 were prepared easily from enantiomerically pure diamine **7.5.14.4** and the appropriate sulfonyl chloride (Et_3N and catalytic DMAP in dichloromethane) in 90% yield. Some sulfonyl chlorides also had to be prepared (see Experimental Section).

Unfortunately some ligands were so insoluble in a range of organic solvents (petrol, toluene, ether, dichloromethane, THF, ethyl acetate) that they were effectively useless for application as chiral modifiers of trimethylaluminium. These *bis*-sulfonamides would have given catalysts **7.5.18.5** to **7.5.18.8**. It appears that already valuable information has been gained on the nature of the ligand which will be required for a successful catalyst: aromatic nuclei directly substituted with a halogen appear to be generally useless due to solvation problems. This is almost as disappointing as the failure of naphthyl substituted **7.5.18.8** since the larger "plates" of the naphthyl group may have been powerful

directors in the catalyst epicentre. However, the remaining ligands did not present any immediate problems with their physical properties.



R = $C_{11}H_{23}$ **7.1.3.6** **6.2.10.2**
$PhCH_2CH_2$ **7.1.3.5**
$PhCH_2$ **7.1.3.4**
c-hex **7.1.3.7**
p-$MeOC_6H_4CH_2$ **7.5.19.1**

R = $C_{11}H_{23}$ **7.3.2.1**
$PhCH_2CH_2$ **7.3.2.3**
$PhCH_2$ **7.5.15.1**
c-hex **7.3.2.2**
p-$MeOC_6H_4CH_2$ **7.5.19.2**

Entry	RCHO (R =)	Catalyst (mol%)	Yield	*cis:trans*	ee[b] (%) (*cis*)	Abs. Config.[f]
1	$PhCH_2$	**7.5.18.1** (25)	48	80:20	0[c]	-
2	$PhCH_2CH_2$	**7.5.18.1** (21)	44	90:10	5[c]	ND
3	*c*-Hex	**7.5.18.1** (20)	ND	77:23	20[c]	ND
4	$PhCH_2$	**7.5.18.2** (44)[a]	43	100:0	58[d]	(*S*, *R*)
5	$PhCH_2CH_2$	**7.5.18.2** (61)[a]	43	100:0	44[d]	(*S*, *R*)
6	*c*-Hex	**7.5.18.2** (98)[a]	57	95:5	64[d]	(*S*, *R*)
7	$PhCH_2$	**7.5.18.3** (100)	-	-	-	(*R*, *S*)
8	$PhCH_2$	**7.5.18.4** (50)	56	83:17	83[d]	(*R*, *S*)
9	$PhCH_2CH_2$	**7.5.18.4** (30)	80	90:10	44[d]	(*R*, *S*)
10	*c*-Hex	**7.5.18.4** (33)	32	85:15	68[d]	(*R*, *S*)
11	$C_{11}H_{23}$	**7.5.18.4** (29)	67	94:6	47[e]	(*R*, *S*)
12	*p*-$MeOC_6H_4CH_2$	**7.5.18.4** (30)	77	99.3:0.7	83[e]	(*R*, *S*)
13	$PhCH_2$	**7.5.18.9** (50)	29	91:9	9	ND

ND = not determined; [a] (*R*, *R*) catalyst; [b] ee determined as indicated; [c] ee determined by ^{1}H NMR analysis of the C*H*TMS doublet in the presence of 1 equivalent of (*R*)-(+)-BINOL; [d] ee determined by chiral HPLC (Daicel Chiralpak AD, 2% *iso*-propyl alcohol-hexane, 1.0 mL/min, 210 nm); [e] ee determined by ^{1}H NMR analysis of the C*H*TMS doublet in the presence of 2 equivalents of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol; [f] absolute configurations determined by independent synthesis (see later).

Table 7.5.19

The results from Table 7.5.19 are very encouraging. Optimum enantiomeric excesses were obtained with catalyst **7.5.18.4** which possesses a 4-*tert*-butyl-2,6-dimethyl substituted benzene sulfonamide (entries 8-12). Aldehydes with an aromatic group in the α-position such as phenylacetaldehyde (**7.1.3.4**) and *para*-methoxyphenylacetaldehyde (**7.5.19.1**) gave an ee of 83% (entries 8 and 12). This is a ratio of enantiomers of 11:1, which is approaching synthetic utility.

When the aromatic ring is moved further away from the aldehyde carbonyl, into the β-position, a drop in enantioselectivity to 44% ee is suffered (entry 9). This is somewhat disappointing since the obvious conclusion is that some form of π-stacking is occurring between the phenyl rings of the substrate and the catalyst.[239]

Even with the most challenging linear chain of dodecanal (**7.1.3.6**), an ee of 47% has been achieved (entry 11). The simple alkyl-α-substituted aldehyde cyclohexane carboxaldehyde (**7.1.3.7**) yielded 64-68% ee with either catalysts **7.5.18.2** or **7.5.18.4** (entries 6 and 10), suggesting that a sterically encumbered aldehyde is of some benefit but not as extensive as an α-positioned aromatic nucleus.

The steric limits of the system have been reached with 2,4,6-tri*iso*-propylbenzene-derived catalyst **7.5.18.3**: no reaction occurred even with one whole equivalent of Lewis acid (entry 7).

As previously published with ketene (**7.5.17.1**), an ee of 74% was obtained with chiral catalyst **7.5.18.1** (with an ethyl group on Al, see Scheme 7.5.17). However, with (trimethylsilyl)ketene (**6.2.10.2**) poor results were obtained (with a methyl group on Al, entries 1-3). Alkyl substitution on Al will be explored in a later section.

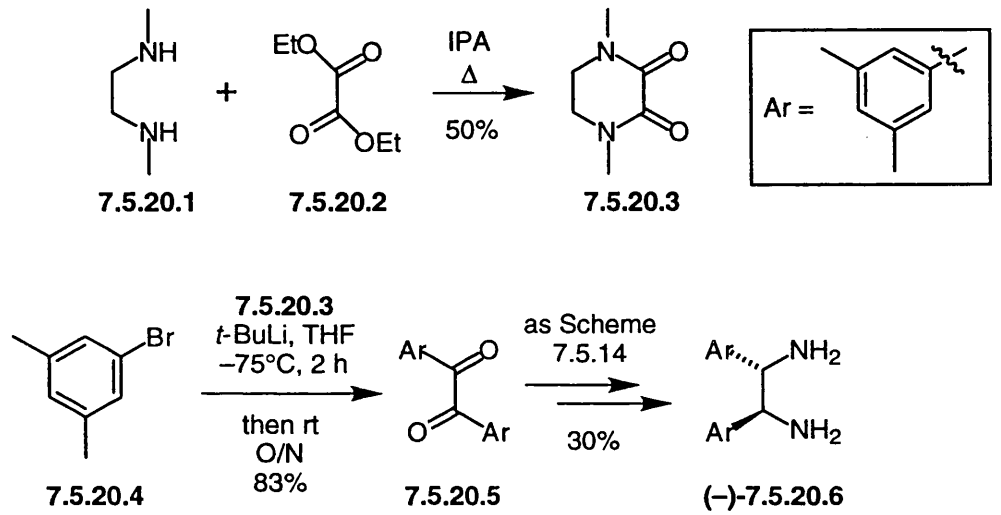
In conclusion, a vast step forward has been achieved in the quest for a generally applicable enantioselective catalyst for the [2+2] cycloaddition of aldehydes with (trimethylsilyl)ketene. However, there are other features of the catalyst which remain to be investigated and these studies now follow.

7.5.3.4.2 Study of the Parent Phenyl Ring

A study of the phenyl groups of the sulfonamide sub-structure of the catalyst revealed the importance of the type and position of the substitution. Similarly, on the western side of the catalyst there reside 2 phenyl rings originating with

the parent diamine **7.5.14.4**. In light of the importance of the nature of the sulfonamide it would be desirable to examine more closely the effect of simple substitutions on these rings.

Recently, Corey published some general experimental procedures leading to substituted benzils[236] which could then be further elaborated to the chiral diamine of interest. Using this chemistry 3,5-dimethyl-substituted benzil **7.5.20.5** was prepared and elaborated to the diamine **7.5.20.6** (Scheme 7.5.20).



Scheme 7.5.20

Similar chemistry was attempted with the α-naphthyl group in place of 3,5-dimethylphenyl but this was found to be overly impractical with low yields and insoluble intermediates.

Figure 7.5.21 shows the catalysts studied with the new substitution and Table 7.5.22 exhibits the results.

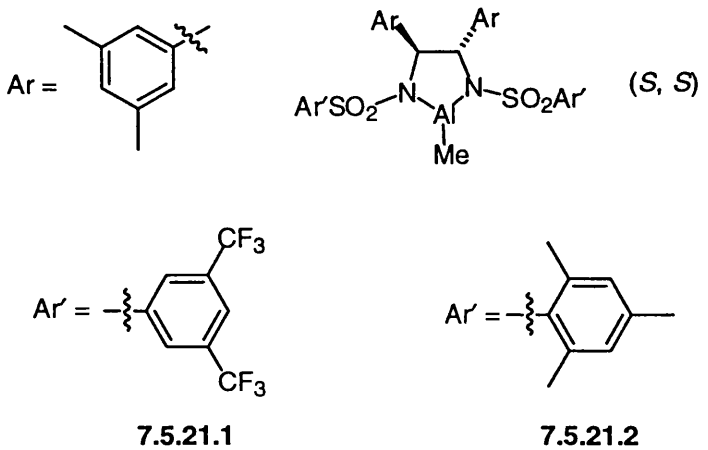
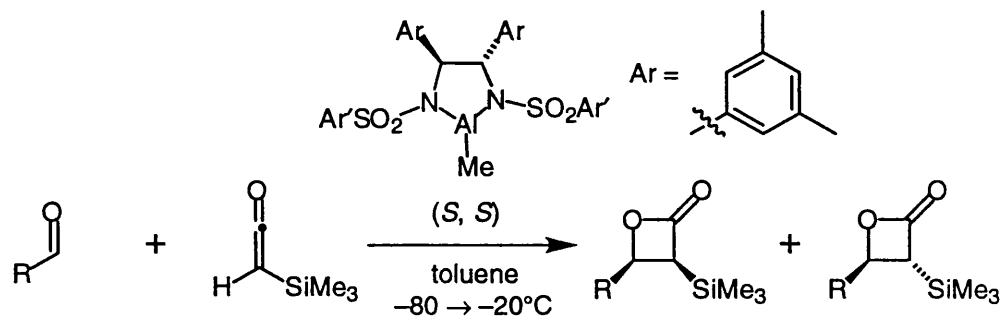


Figure 7.5.21

Although only 2 catalysts were looked at in this C_2-symmetric series, enough data has been gathered to draw some conclusions.



R = $PhCH_2CH_2$ **7.1.3.5** **6.2.10.2**
$PhCH_2$ **7.1.3.4**
c-hex **7.1.3.7**

R = $PhCH_2CH_2$ **7.3.2.3**
$PhCH_2$ **7.5.15.1**
c-hex **7.3.2.2**

Entry	RCHO (R =)	Catalyst (mol%)	Yield	*cis:trans*	ee[b] (%) (*cis*)	Abs. Config.[d]
1	$PhCH_2$	**7.5.21.1** (21)	76	76:24	22[c]	ND
2	$PhCH_2CH_2$	**7.5.21.1** (23)	66[a]	90:10	8[c]	ND
3	*c*-Hex	**7.5.21.1** (39)	15	73:27	0[c]	ND
4	$PhCH_2$	**7.5.21.2** (30)	61	93:7	75[c]	(*R*, *S*)
5	$PhCH_2CH_2$	**7.5.21.2** (58)	46	97:3	40[c]	(*R*, *S*)
6	*c*-Hex	**7.5.21.2** (49)	36	100:0	55[c]	(*R*, *S*)

ND = not determined; [a] isolated yield of *cis* isomer only; [b] ee determined as indicated; [c] ee determined by ^1H NMR analysis of the C*H*TMS doublet in the presence of 2 equivalents of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol; [d] absolute configurations determined by independent synthesis (see later).

Table 7.5.22

A slight improvement in ee from 58 to 75% was found with catalyst **7.5.21.2** with phenylacetaldehyde (entry 4, *c.f.* entry 4 in Table 7.5.19) but the changes in the other results were not statistically significant.

These small improvements do not justify the extra effort required to synthesise these ligands.

7.5.3.4.3 Study of the Substitution at Aluminium

Since the metal atom in the catalyst is at the centre of the system, it would be reasonable to expect profound changes to occur on alteration of the group bonded directly to the aluminium centre.

Figure 7.5.23 shows the catalysts tested and table 7.5.24 shows results obtained with various alkyl substitutions on some of the catalysts.

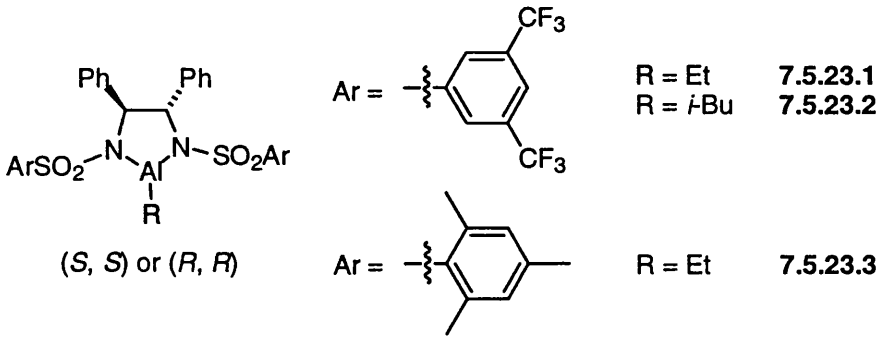
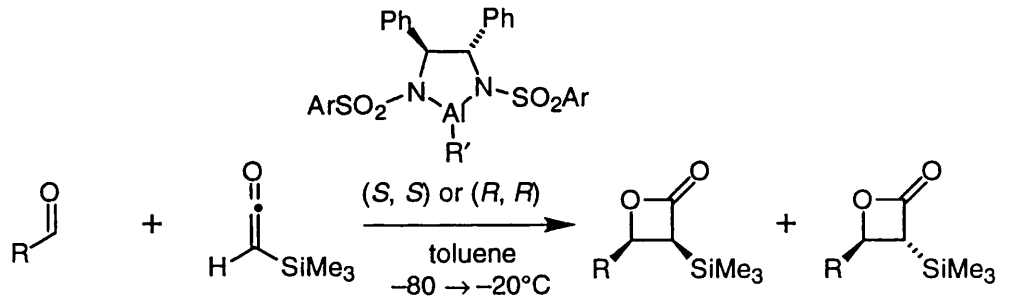


Figure 7.5.23

Available trialkylaluminiums Et_3Al and *i*-Bu_3Al were used to derivatise two catalyst ligands leading to catalysts **7.5.23.1-3**. Experimental procedures were identical to that for the Me_3Al derived catalysts. Table 7.5.24 shows the reactions progressed in variable yields but with good *cis:trans* ratios.



R = $PhCH_2CH_2$	**7.1.3.5**	**6.2.10.2**	
$PhCH_2$	**7.1.3.4**		
c-hex	**7.1.3.7**		
$C_{11}H_{23}$	**7.1.3.6**		

R = $PhCH_2CH_2$	**7.3.2.3**
$PhCH_2$	**7.5.15.1**
c-hex	**7.3.2.2**
$C_{11}H_{23}$	**7.3.2.1**

Entry	RCHO (R =)	Catalyst (mol%)	Yield	*cis:trans*	ee[d] (%) (*cis*)	Abs. Config.[f]
1	$PhCH_2$	**7.5.23.1** (50)	59[a]	79:21	47[e]	ND
2	$PhCH_2$	**7.5.23.2** (20)	41[b]	80:20	36	ND
3	$PhCH_2CH_2$	**7.5.23.2** (21)	72	92:8	24	ND
4	*c*-Hex	**7.5.23.2** (21)	8[c]	100:0	54	ND
5	$C_{11}H_{23}$	**7.5.23.2** (40)	60	92:8	15	ND
6	$PhCH_2CH_2$	**7.5.23.3** (78)	35	90:10	37[e]	(*S*, *R*)

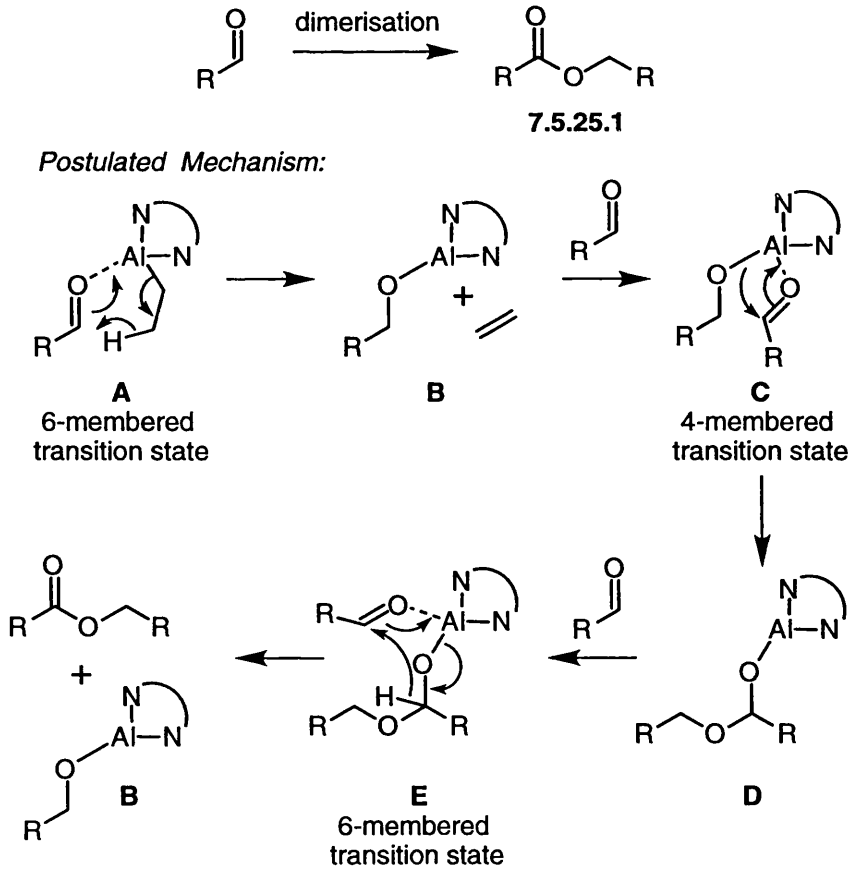
ND = not determined; [a] +20% aldehyde dimer; [b] +33% aldehyde dimer; [c] +52% aldehyde dimer; [d] ee determined by ^1H NMR analysis of the C*H*TMS doublet in the presence of 2 equivalents of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol unless otherwise noted; [e] ee determined by chiral HPLC (Daicel Chiralpak AD, 2% *iso*-propyl alcohol-hexane, 1.0 mL/min, 210 nm); [f] absolute configurations determined by independent synthesis (see later).

Table 7.5.24

Enantiomeric excesses were moderate and variable, the highest being cyclohexane carboxaldehyde with catalyst **7.5.23.2** (54% ee, entry 4). As hoped, this is probably a result of increased steric interaction at aluminium in the transition state (*c.f.* only 20% ee for entry 3 in table 7.5.19 using the methylalumino catalyst **7.5.18.1**).

Other comparisons which may be made are the one result with catalyst **7.5.23.1** of 47% ee (entry 1, *c.f.* 0% ee for entry 1 in table 7.5.19). This result is a significant improvement but not as enantioselective as catalyst **7.5.18.4** (83% ee, entry 8 in table 7.5.19). Using *iso*-butyl (catalyst **7.5.23.2**) instead of ethyl (catalyst **7.5.23.1**) led to a slight drop to 37% ee, so these selectivities are not based on steric interactions alone.

Clearly there is another mechanism operating in these reactions, possibly a redox process suggested by the isolation of aldehyde dimer **7.5.25.1** (Scheme 7.5.25).



Scheme 7.5.25

This unusual self-coupling of an aldehyde was not entirely unexpected due to the presence of protons in the β-position with respect to the aluminium atom.

This dimerisation was a severe problem with the three catalysts in this section. A postulated mechanism is shown in scheme 7.5.25. Initial co-ordination of an aldehyde molecule to the catalyst (**A**) may be followed by reductive transferral of the β-proton to the aldehyde carbonyl with expulsion of ethylene (or *iso*-butylene in the case of **7.5.23.2**). The product shown in **B** may be further co-ordinated with another aldehyde molecule to give **C**. From here, product **D** could be formed *via* a 4-membered transition state. Yet another aldehyde molecule could co-ordinate to the aluminium giving **E** and the product could then detach *via* another 6-membered transition state, leaving the third aldehyde molecule connected as in structure **B** and ready to start another cycle.
This mechanism is, of course, unsubstantiated but nonetheless the problem of aldehyde dimerisation renders the ethyl and *iso*-butyl groups less useful than the simpler methyl group.
Therefore, the best way forward would be further investigation of the sulfonamide groups, perhaps non-C_2-symmetric analogues.

7.5.3.4.4 Non-C_2-Symmetric Variants: a Novel Class of Chiral Lewis Acid

If two different sulfonamides are engineered into one catalyst, the new catalyst will have reduced symmetry *i.e.* be non-C_2-symmetric. Although more complex, this is a new class of chiral Lewis acid. If one sulfonamide was larger than the other, there may be exclusively one avenue of approach for the reagents, in effect, an asymmetric box.
Figure 7.5.26 shows the various non-C_2-symmetric catalysts prepared.

The extremely bulky 2,4,6-tri*iso*-propyl benzene group was used along with four other groups to create a small selection of non-C_2-symmetric catalysts for testing in the [2+2] cycloaddition. These ligands were prepared by a similar procedure to the C_2-symmetric ones: the first sulfonyl chloride was added and allowed to be consumed before the second sulfonyl chloride was added. In this way, undesired C_2-symmetric by-products were minimised. See the experimental section for more details. The trifluoromethyl group, which previously produced the most active C_2-symmetric catalyst was used as the first test group with the bulky *iso*-propyl ligand. Table **7.5.27**, entry 1, shows that

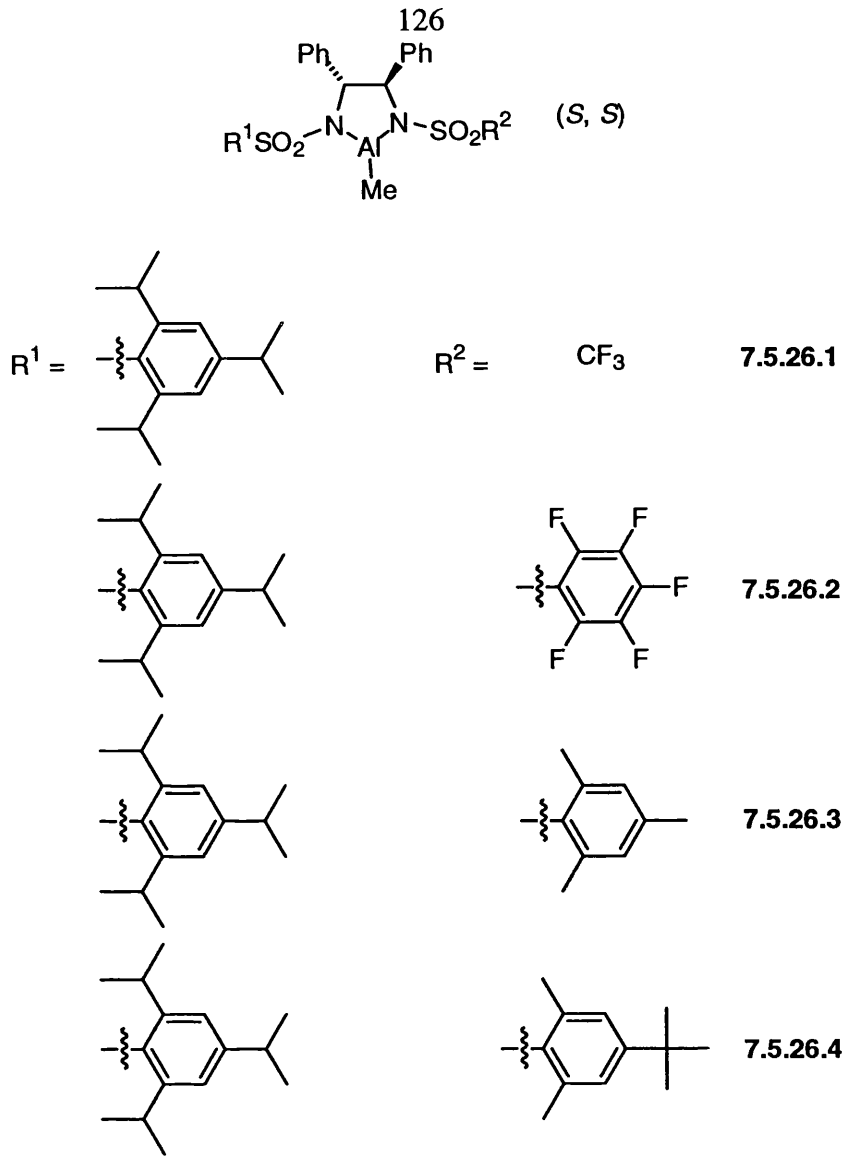
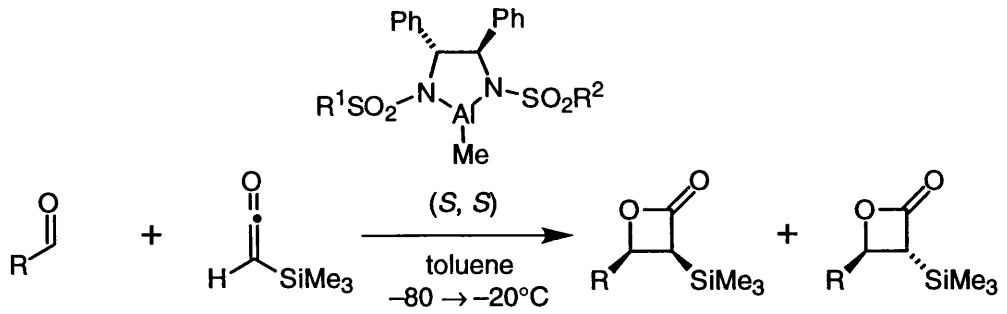


Figure 7.5.26

this catalyst gives a moderate 57% yield and good *cis*:*trans* ratio but the ee was only 17%.

Pentafluorobenzene derived **7.5.26.2** was even more disappointing yielding only 25% of a 10% ee product. However, this lack of success was short-lived since 2,4,6-trimethylbenzene-derived catalyst **7.5.26.3** (29 mol%) gave a useful 82% yield and 62% ee. This result compares well with the C_2-symmetric catalyst **7.5.18.2** (58% ee) although the extra bulk of the larger group in **7.5.26.3** has not had much impact. The other examples with **7.5.26.3** tell a similar story. Finally, with the most successful group from the C_2-symmetric series, 4-*tert*-2,6-dimethyl-butylbenzene, some better results were obtained. However, a similar story resulted: these catalysts gave remarkably similar



R = $PhCH_2CH_2$ **7.1.3.5** **6.2.10.2**
$PhCH_2$ **7.1.3.4**
c-hex **7.1.3.7**
$C_{11}H_{23}$ **7.1.3.6**
p-$MeOC_6H_4CH_2$ **7.5.19.1**

R = $PhCH_2CH_2$ **7.3.2.3**
$PhCH_2$ **7.5.15.1**
c-hex **7.3.2.2**
$C_{11}H_{23}$ **7.3.2.1**
p-$MeOC_6H_4CH_2$ **7.5.19.2**

Entry	RCHO (R =)	Catalyst (mol%)	Yield	*cis:trans*	ee[a] (%) (*cis*)	Abs. Config.[c]
1	$PhCH_2$	**7.5.26.1** (51)	57	90:10	17[b]	(*R*, *S*)
2	$PhCH_2$	**7.5.26.2** (48)	25	100:0	10[b]	(*R*, *S*)
3	$PhCH_2$	**7.5.26.3** (29)	82	79:21	62	(*R*, *S*)
4	$PhCH_2CH_2$	**7.5.26.3** (25)	85	90:10	30	(*R*, *S*)
5	*c*-Hex	**7.5.26.3** (51)	57	77:23	53	(*R*, *S*)
6	$PhCH_2$	**7.5.26.4** (30)	72	75:25	82	(*R*, *S*)
7	$PhCH_2CH_2$	**7.5.26.4** (29)	82	94:6	36	(*R*, *S*)
8	*c*-Hex	**7.5.26.4** (33)	43	69:31	67	(*R*, *S*)
9	$C_{11}H_{23}$	**7.5.26.4** (30)	67	82:18	48[b]	(*R*, *S*)
10	*p*-$MeOC_6CH_2$	**7.5.26.4** (29)	81	70:30	75[b]	(*R*, *S*)

[a] ee determined by chiral HPLC (Daicel Chiralpak AD, 2% *iso*-propyl alcohol-hexane, 1.0 mL/min, 210 nm) unless otherwise noted; [b] ee determined by ^1H NMR analysis of the C*H*TMS doublet in the presence of 2 equivalents of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol unless otherwise noted; [c] absolute configurations determined by independent synthesis (see later).

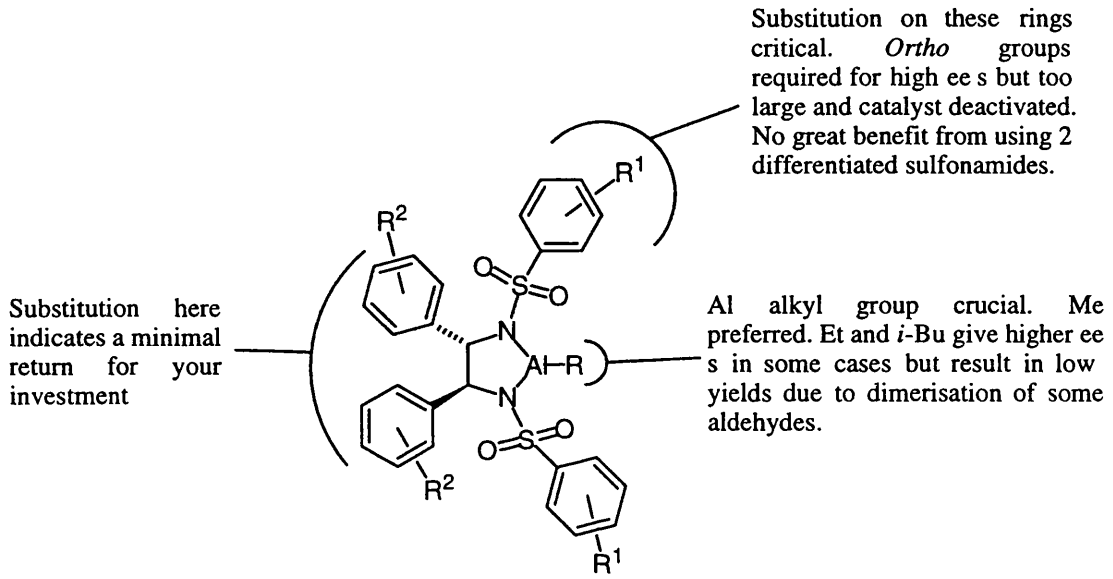
Table 7.5.27

enantioselectivities to the C_2-symmetric catalyst **7.5.18.4** (*c.f.* Table 7.5.19, entries 8-12).

In summary, these non-C_2-symmetric catalysts are no better or worse than their C_2-symmetric counterparts.

7.5.3.5 Conclusion of the *Bis*-sulfonamide Study

From the work done on the optimisation of the bis-sulfonamide catalyst, a pictorial summary aptly describes the results (Figure 7.5.28).



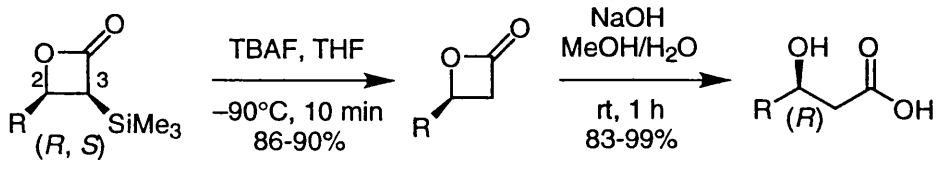
Scheme 7.5.28

7.6 Determination of the Absolute Stereochemistry of the Products

In order to draw any mechanistic conclusions and to relate the stereochemistry of a catalyst to the products, the absolute stereochemistry of the β-lactone products must be determined.

Since the products are novel there is no literature for comparisons. Therefore the products must be chemically derivatised to known compounds.

The method of choice consisted of initial desilylation (TBAF, THF, –90°C) of the silyl β-lactones **7.5.15.1**, **7.3.2.3** and **7.3.2.2** followed by selective acyl cleavage with sodium hydroxide[56] giving β-hydroxy acids **7.6.1.4** to **7.6.1.6** (Scheme 7.6.1).



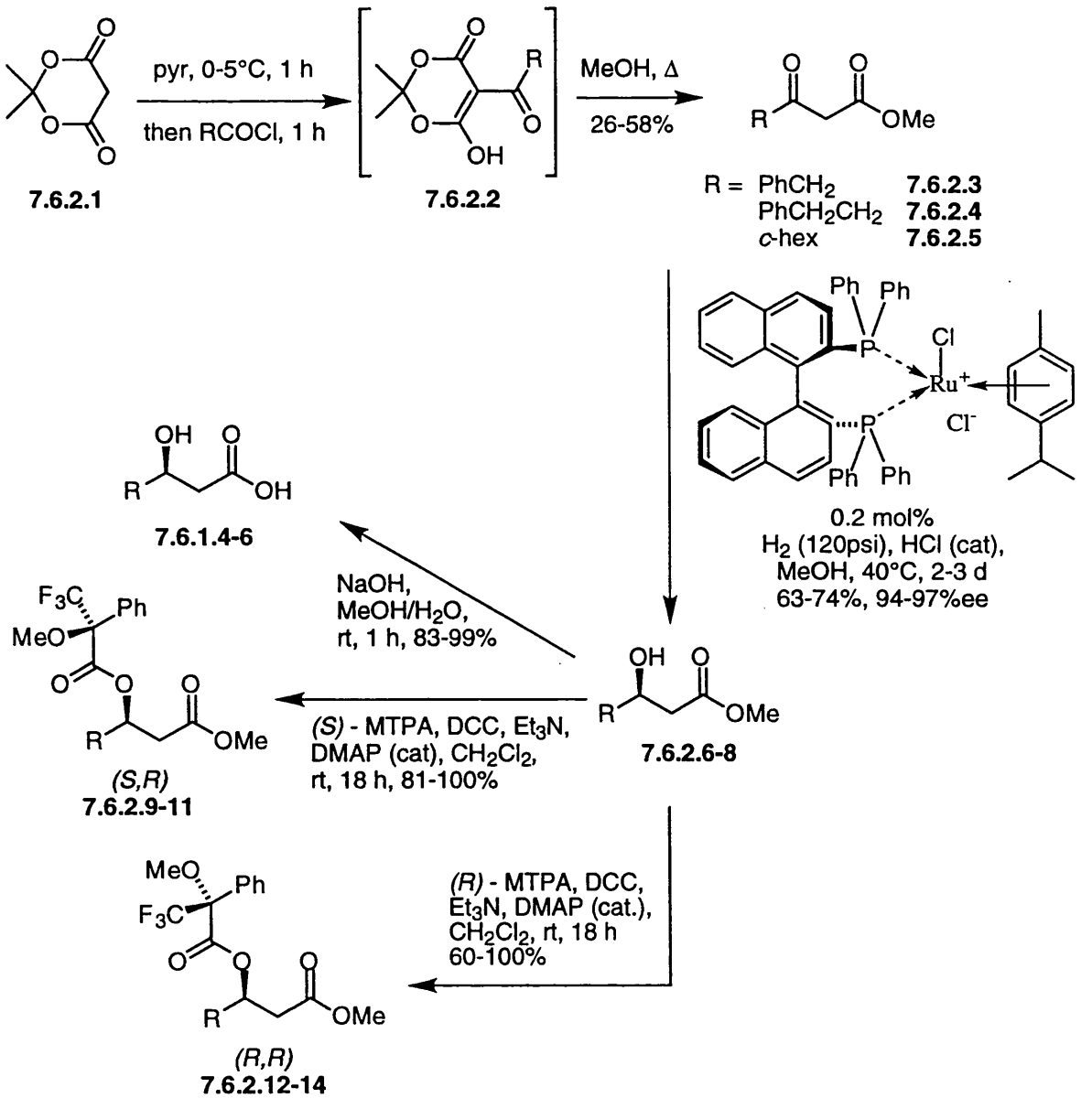
R =				
$PhCH_2$	**7.1.3.4**	**7.6.1.1**	**7.6.1.4**
$PhCH_2CH_2$	**7.1.3.5**	**7.6.1.2**	**7.6.1.5**
c-hex	**7.1.3.7**	**7.6.1.3**	**7.6.1.6**

(*R*) configuration from (*S*, *S*) catalyst
(*S*) configuration from (*R*, *R*) catalyst

Scheme 7.6.1

These hydroxy acids were independently synthesised by the route shown in Scheme 7.6.2. Acylation of Meldrum's acid **7.6.2.1** gave intermediate **7.6.2.2** which was methanolysed to the *β*-keto esters **7.6.2.3**, **7.6.2.4** and **7.6.2.5** in moderate yield. Catalytic, enantioselective reduction of the *β*-keto groups with [*(R)*-(+)-2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)-ruthenium chloride (0.2 mol%) led to good yields of chiral alcohols **7.6.2.6**, **7.6.2.7** and **7.6.2.8**.

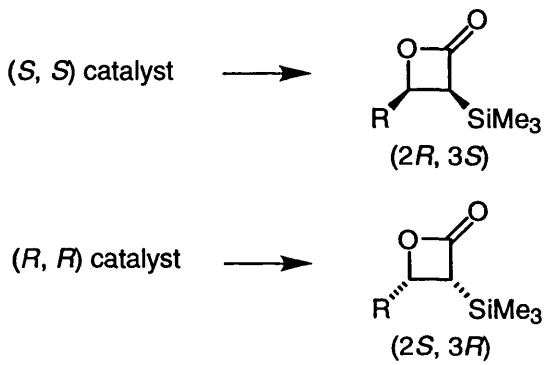
The enantioselectivities of these reductions were checked by ^{19}F NMR analysis of the MTPA esters of alcohols **7.6.2.6-8** and found to be 94-97%. Both MTPA esters of each alcohol were made in order to establish their absolute configurations. [240] Comparison of analogous reactions in the literature confirmed these assignments.



Scheme 7.6.2

Alkaline hydrolysis of methyl esters **7.6.2.6-8** with sodium hydroxide in aqueous methanol gave good yields of acids **7.6.1.4-6** which were compared with those derived from the [2+2] cycloaddition products. These compounds were found to have opposite signs of specific optical rotation therefore the assignments shown in the schemes could be made: (*R*, *R*) catalysts resulted in (2*S*, 3*R*) β-lactones and (*S*, *S*) catalysts gave (2*R*, 3*S*) β-lactones (Scheme 7.6.3).

Therefore it can be concluded that reaction takes place between the *Re* face of the aldehyde and the *Re* face of the ketene for catalysts with configuration *(R,R)* (*vice versa* for catalysts with *(S,S)* configuration) (Scheme 7.6.3).



Scheme 7.6.3

7.7 Mechanistic Considerations

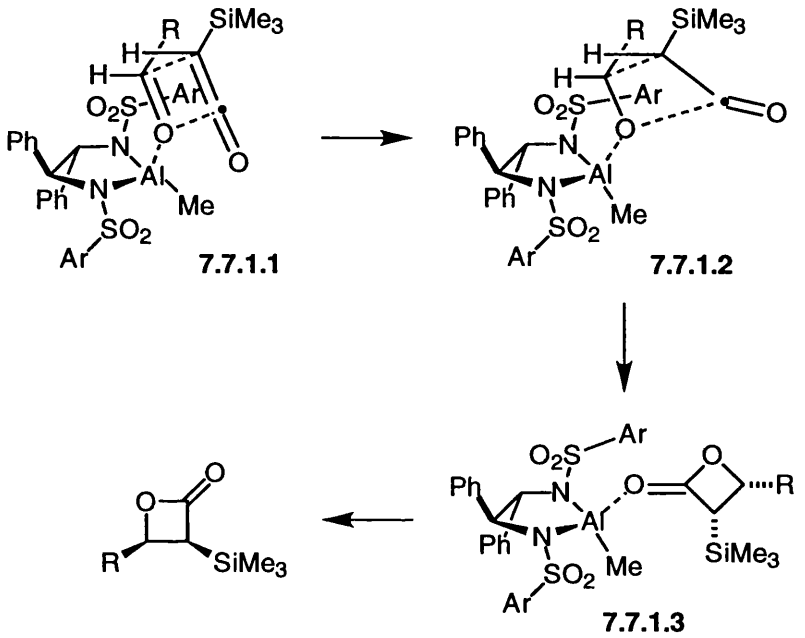
The mechanism of the [2+2] cycloaddition between a ketene and carbonyl compound or alkene is not well understood. However, a hypothesis may be made based on limited information.

One important piece of data derives from the ^{13}C NMR spectrum of (trimethylsilyl)ketene: the ketene carbon bearing the silicon atom has a chemical shift of 18 ppm. This is quite remarkable for a carbon atom which is considered similar to an alkene (δ100-120). Clearly, there resides a large share of electron density on this carbon, leading to the conclusion that the ketene is the nucleophilic partner in the cycloaddition.

Further evidence in support of this postulate is shown in scheme 7.5.16 where a more polarised carbonyl system (more δ+ carbonyl carbon) leads to an increase in reaction rate, *e.g. para*-nitrobenzaldehyde, whereas an aldehyde possessing a deactivated carbonyl (less δ+) is extremely sluggish, *e.g. para*-methoxybenzaldehyde.

If the assumption is made that the first bond to be formed is the C–C bond of the β-lactone and that the ketene is the nucleophilic partner, then the aldehyde must be co-ordinated to the Lewis acid. It is highly probable that the Lewis acid will co-ordinate with the Lewis basic lone pair of electrons of the carbonyl oxygen atom *anti* to the aldehyde R group in order to minimise unfavourable steric interactions. With a chirally modified Lewis acid, the additional dimension of chirality is added to the transition state.

Considering all these factors, an initial transition state **7.7.1.1** may be proposed (Scheme 7.7.1).



Scheme 7.7.1

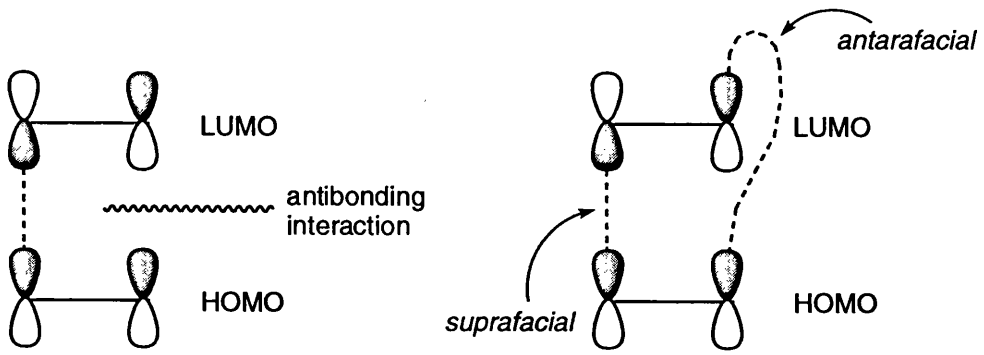
Complex **7.7.1.1** is depicted with the silylketene and aldehyde approaching in a *syn*-periplanar fashion with the silicon on the same side as the aldehyde R group.

If the silicon group were rotated through 180° a large steric interaction with the Lewis acid ligand would occur creating instability. Although some *trans* β-lactone is usually isolated, there is a strong preference for the *cis* isomer.

Theoretical studies by Pons *et al* [241] ,using AM1 and *ab initio* calculations, have shown that one favourable low energy pathway is a closed-shell, quasi-concerted but asynchronous process where priority is given to the C–C bond formation. This near coplanarity of the four participating atoms is in accord with recent *ab initio*[242,243] and semi-empirical calculations.[244] The

asynchronous but concerted nature of the process indicates that the two new bonds are formed at the same time but not to the same extent.
Structure **7.7.1.2** shows this postulate in an exaggerated manner. Completion of the bond forming process leads to co-ordinated β-lactone product **7.7.1.3**. On detachment of the product, the Lewis acid is available to once again enter the catalytic cycle.
Although scheme 7.7.1 explains the absolute stereochemistry of the products, there is still little evidence to support the mechanism.

Consideration of frontier orbital interactions leads to another postulate. In 1969 Woodward and Hoffman published their landmark work *The Conservation of Orbital Symmetry*.[245,246] Addition modes for specific π interactions were described as either *suprafacial* or *antarafacial*. The former has the bonds being made or broken on the same side of the reacting system whereas the latter has these bonds on opposite sides of the system. For [2+2] cycloadditions, approach of the orbitals along the geometrically most facile route produces only one orbital overlap (Scheme 7.7.2, left-hand diagram). Therefore, an antarafacial approach is necessary to enable the bonding orbitals for the other orbitals to overlap efficiently (Scheme 7.7.2, right-hand diagram).

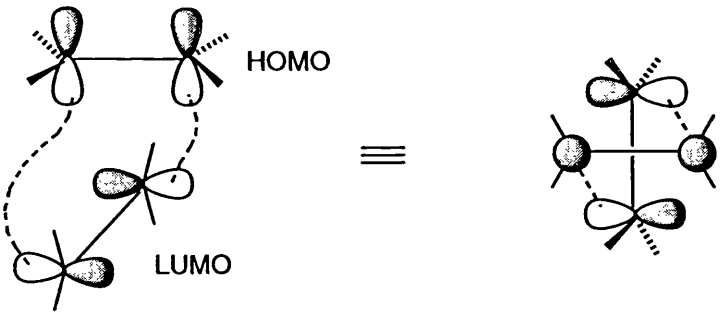


[2+2] cycloaddition –only one easily developed bonding overlap

[$\pi 2_a + \pi 2_s$] cycloaddition

Scheme 7.7.2

The required overlap can only be obtained if the two interacting π systems approach in an orthogonal style *i.e.* at approximate right-angles to each other (Scheme 7.7.3). The plan view shows this more clearly.

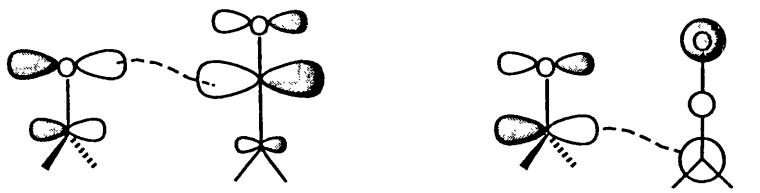


preferred geometry for a $[\pi 2_a + \pi 2_s]$ cycloaddition

plan view

Scheme 7.7.3

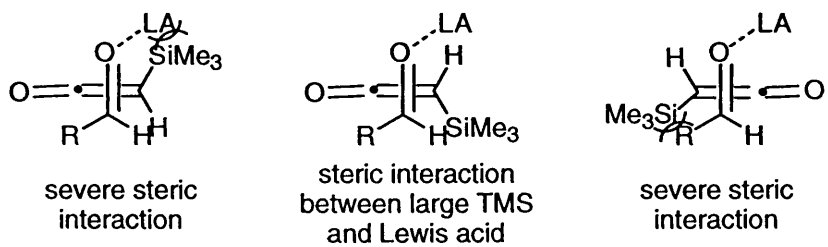
For the interaction between a carbonyl and ketene it is likely that contributions from both HOMO (carbonyl)/LUMO (ketene) and LUMO (carbonyl)/HOMO (ketene) are important[247] (Scheme 7.7.4).

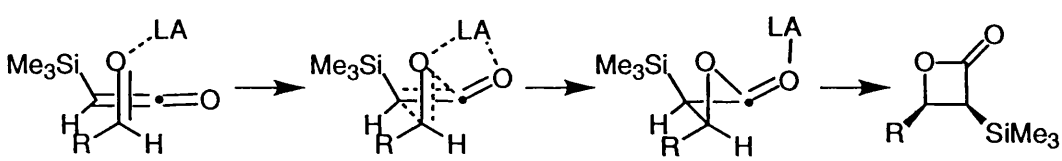


Both these interactions are likely to be important

Scheme 7.7.4

Applying these predicted geometries to the cycloaddition between an aldehyde and (trimethylsilyl)ketene results in 4 possible approaches (Scheme 7.7.5).



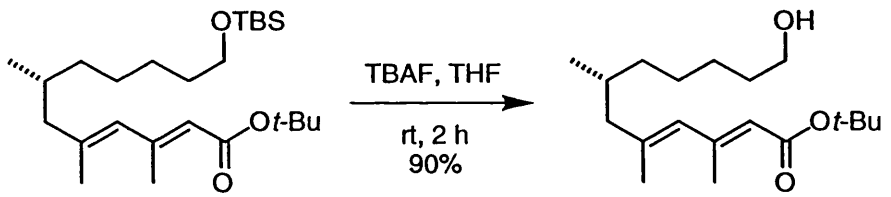


Scheme 7.7.5

Only one transition state geometry is likely to be heavily favoured. All the others are destabilised by unfavourable steric interactions between either the TMS group and Lewis acid or the TMS group and aldehyde R group. The favoured approach clearly places the bulky TMS group in an area of space as far away as possible from the larger groups.

7.8 Application of the [2+2] Cycloaddition to 1233A

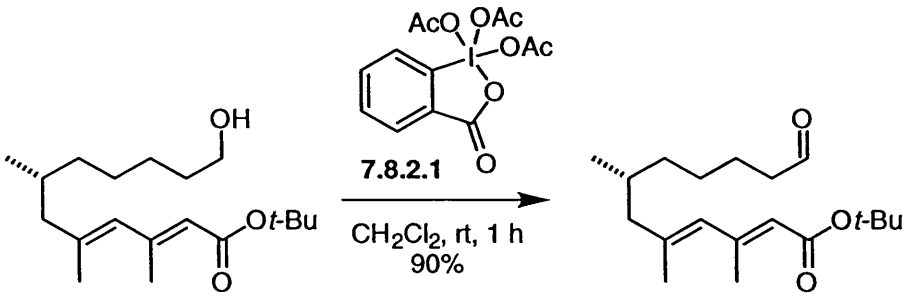
Conversion of the protected diene **5.3.11.1** into the required aldehyde for the [2+2] cycloaddition progressed smoothly. Two equivalents of TBAF in THF at room temperature yielded 90% of primary alcohol **7.8.1.1** (Scheme 7.8.1).



5.3.11.1 **7.8.1.1**

Scheme 7.8.1

Oxidation of **7.8.1.1** to the desired aldehyde was effected with the Dess-Martin periodinane reagent (**7.8.2.1**) which was prepared according to the literature.[248-250] This oxidation was complete in 1 hour and provided 90% of aldehyde **7.8.2.2** (Scheme 7.8.2).



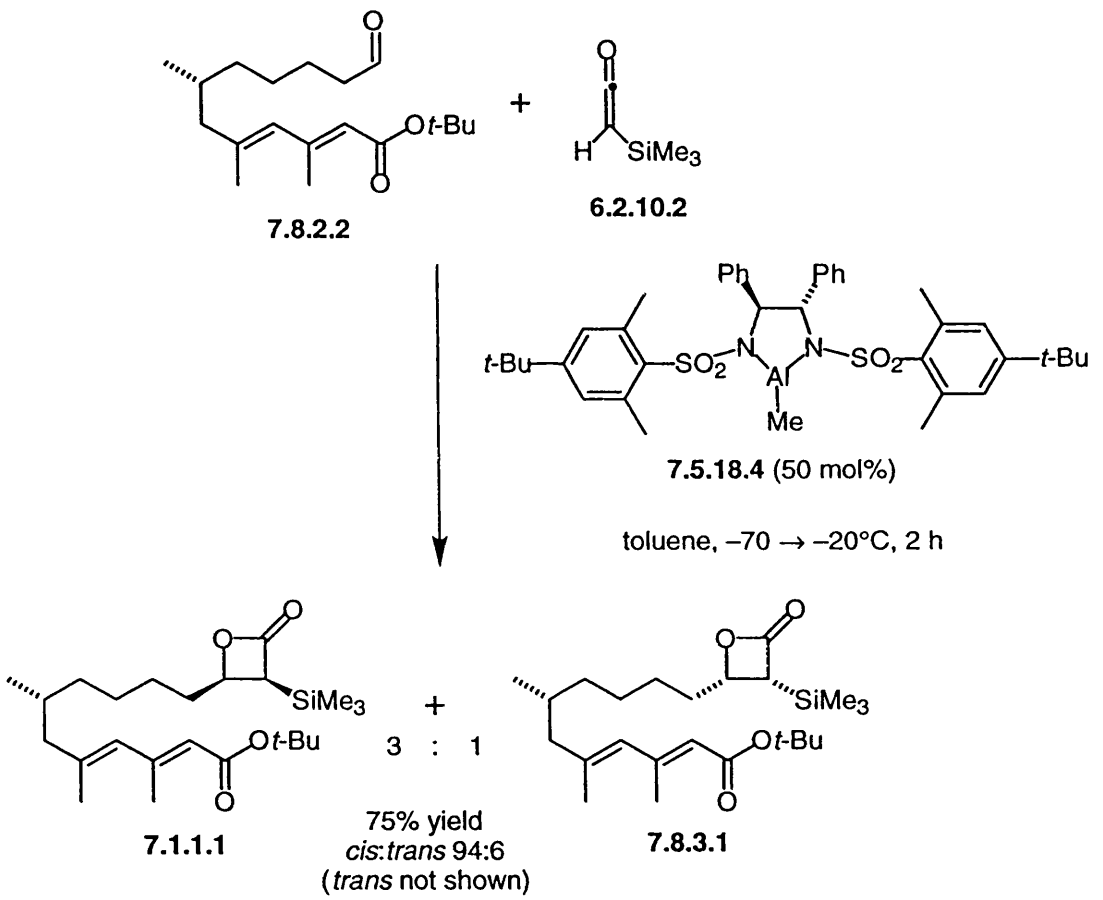
7.8.1.1 **7.8.2.2**

Scheme 7.8.2

Earlier model studies most closely resembling aldehyde **7.8.2.2** were with dodecanal (**7.1.3.6**). With C_2-symmetric catalyst **7.5.18.4** (29 mol%) a good

cis:*trans* ratio of 94:6 was obtained with a good yield (67%) and an ee of 47% (Table 7.5.19). Similarly, non-C_2-symmetric catalyst **7.5.26.4** (30 mol%) gave the same yield, a good *cis*:*trans* ratio and a 48% ee. It is reasonable to expect that **7.8.2.2** will behave similarly to dodecanal since the functionality in the chain is too distant to have any significant effect.

Indeed, when the enantioselective [2+2] cycloaddition was performed with **7.8.2.2** and (trimethylsilyl)ketene in the presence of 50 mol% of catalyst **7.5.18.4** in toluene, a smooth conversion to the desired product, with a trace of *trans* isomer, was obtained (Scheme 7.8.3).



Scheme 7.8.3

The *cis*:*trans* ratio was determined to be 94:6 by ^{1}H NMR analysis of the crude product. After column chromatography, a 67% yield of a mixture of **7.1.1.1** and **7.8.3.1** were obtained with the other 8% being a 1:1.3 *cis*:*trans* ratio. Since the signals were coincidental, even with resolution enhancement at high field, their ratio was determined using a previously described analysis of the C*H*TMS protons with Pirkle's chiral solvating agent (see Table 7.5.27 for more details). From this analysis it was found that a 50% ee had been achieved as expected.

This result should be correctly termed a 50% *diastereomeric excess* (de) due to the presence of the methyl group.
Unfortunately these isomers were inseparable using conventional flash chromatographic techniques. Therefore, it will be important to separate the isomers at some later stage in order to remove the unwanted diastereoisomer.

7.9 Conclusions

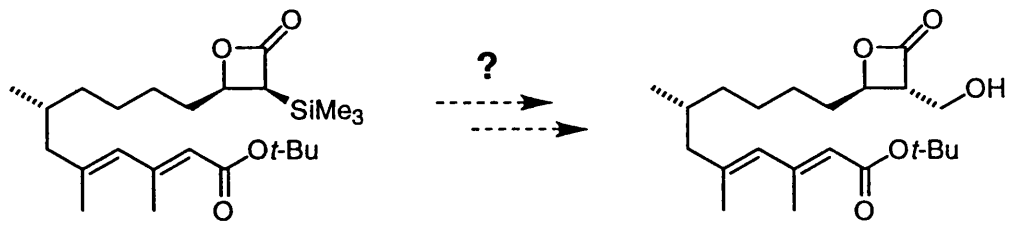
In this chapter, the first chiral Lewis acid catalysed enantioselective reactions have been developed between an aldehyde and (trimethylsilyl)ketene, attaining up to 83% ee. This new methodology has been applied successfully to the synthesis of the β-lactone portion of 1233A. In order to complete the synthesis of the natural product, all that remains is conversion of the silyl group for a hydroxymethyl and cleavage of the *tert*-butyl ester to reveal the free carboxylic acid.

Chapter 8

Conclusion of the Synthesis

8.1 Introduction

This chapter will discuss the remaining steps in the synthesis where, finally, the natural product 1233A will be revealed. At the end of this chapter the total synthesis will be shown on one page to clarify the overall strategy.
In this end game, the first problem to be tackled was conversion of the trimethylsilyl group on the β-lactone ring into a hydroxymethyl group with inversion of stereochemistry at the silicon-bearing carbon (Scheme 8.1.1).



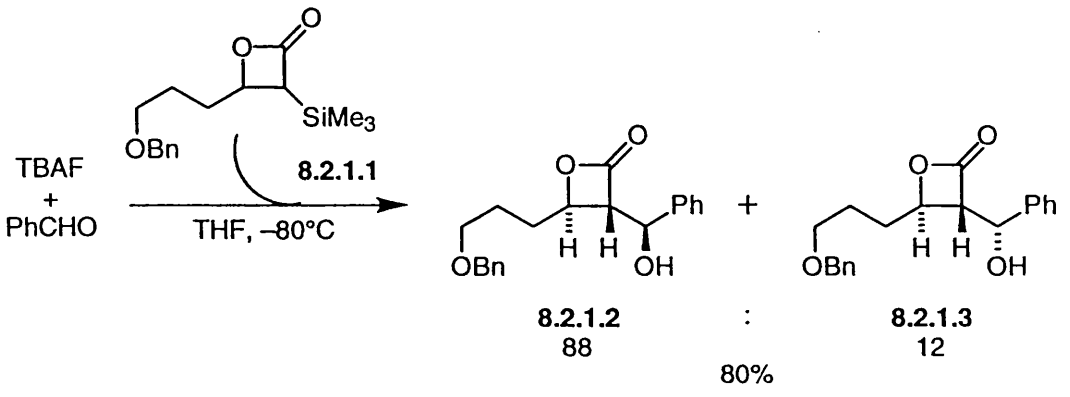
7.1.1.1 **8.1.1.1**

Scheme 8.1.1

Before any of the work so far described towards the natural product was undertaken, this problem had to be solved. This was necessary since there is no obvious method to employ for such a transformation. Using model β-lactones, various ideas were investigated.

8.2 Model Studies

The closest model to the natural product fragment **7.1.1.1** was dodecanal derived β-lactone **7.3.2.1**. Delving into the literature revealed only one piece of relevant work by Mead. [171,172,251] He described the aldol-type reaction of 3-trimethylsilyl-β-lactone **8.2.1.1** with benzaldehyde using TBAF (Scheme 8.2.1).

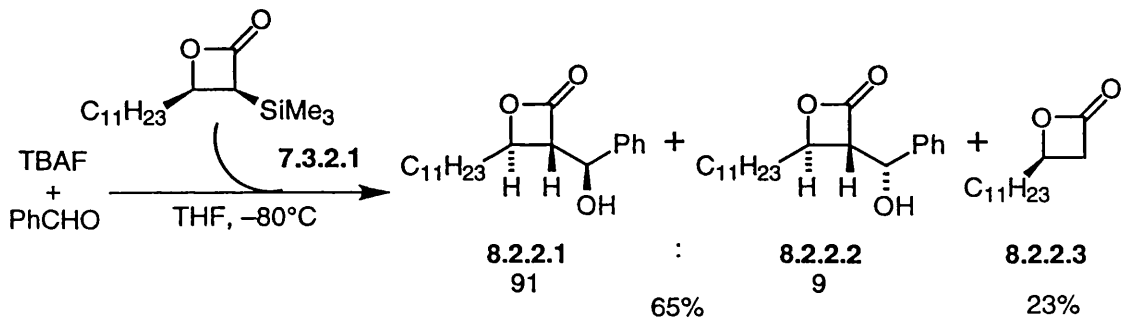


8.2.1.2 : **8.2.1.3**
88 12
80%

Scheme 8.2.1

After initial TBAF de-silylation, a β-lactone enolate is probably formed which is quenched predominately on the more sterically accessible side by the aldehyde giving a ratio of 88:12 for the products **8.2.1.2** and **8.2.1.3**. However, Mead warns that, unless the reaction is carefully conducted with slow addition of the β-lactone to the TBAF/benzaldehyde mixture, large quantities of de-silylated β-lactone are obtained (H-quenched β-lactone enolate).

Similarly, the model dodecanal-derived β-lactone **7.3.2.1** was transformed to a mixture of secondary alcohols **8.2.2.1** and **8.2.2.2** with some de-silylated material **8.2.2.3** (Scheme 8.2.2).



Scheme 8.2.2

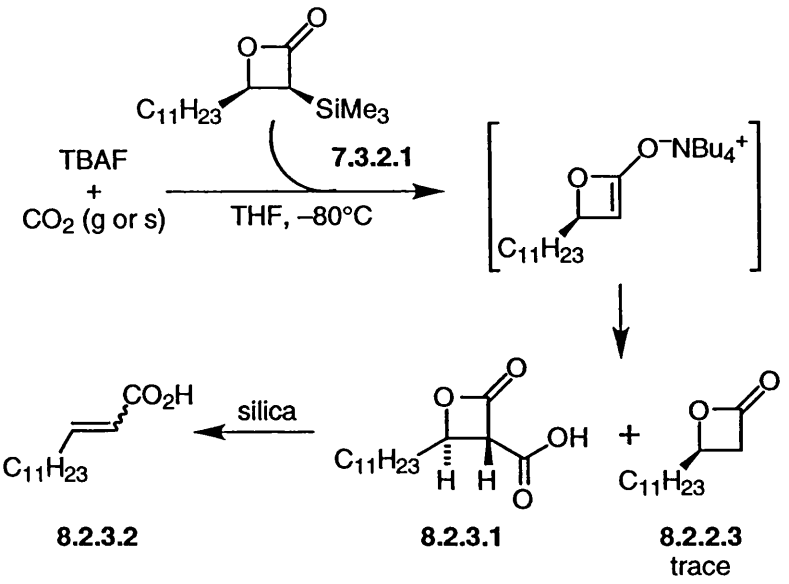
It appears to be quite difficult to totally suppress the formation of **8.2.2.3** but using a syringe pump to control the addition offers the best chance of success.

Having verified the literature precedent, attention was turned to the natural product sub-structure itself. Installation of a hydroxymethyl group would require a one-carbon electrophile, the most obvious being formaldehyde. Since formaldehyde is usually supplied as the hydrate, the polymeric form paraformaldehyde would have to be used. Unfortunately, when paraformaldehyde was used in the reaction, only de-silylated product **8.2.2.3** was isolated. Apparently, paraformaldehyde was not sufficiently reactive to quench the postulated β-lactone enolate derived from the TBAF de-silylation. Attempts at using gaseous formaldehyde, prepared from paraformaldehyde, were unsuccessful due to rapid polymerisation of the monomer.

Since TBAF induces the aldol reaction between two aldehydes possessing α-protons, a more elaborate strategy concerning a higher aldehyde followed by cleavage to leave a one carbon unit behind (*e.g.* periodate cleavage of a diol) was not easily implemented.

The next one-carbon electrophile to be tested was carbon dioxide. Obviously, the product of a CO_2 quench will be a carboxylic acid but these may be

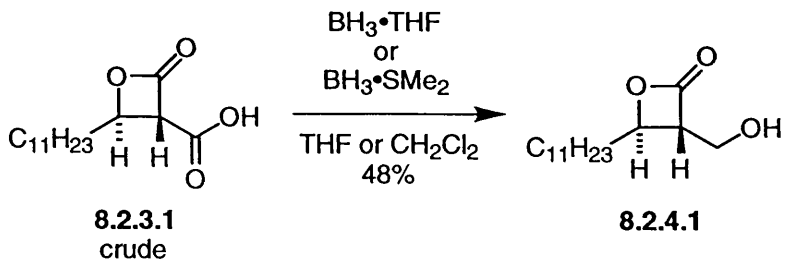
selectively reduced with borane. Thankfully CO_2 was sufficiently reactive to quench the β-lactone enolate but the product **8.2.3.1** was found to be unstable, undergoing decarboxylation when chromatographed on silica (Scheme 8.2.3).



Scheme 8.2.3

Fortunately there was only a trace of desilylated product, reflecting the reactive nature of the CO_2. With less reactive benzaldehyde a significant quantity of **8.2.2.3** was isolated. From a practical point of view it was found that either gaseous or solid CO_2 could be used. Either the gas from a cylinder of CO_2 was constantly bubbled through the reaction mixture or powdered dry ice was added in small quantities every 15 minutes.

Due to the instability of **8.2.3.1** it had to be freshly used crude. A smooth reduction with borane gave alcohol **8.2.4.1** in 48% yield over the 2 steps (Scheme 8.2.4).



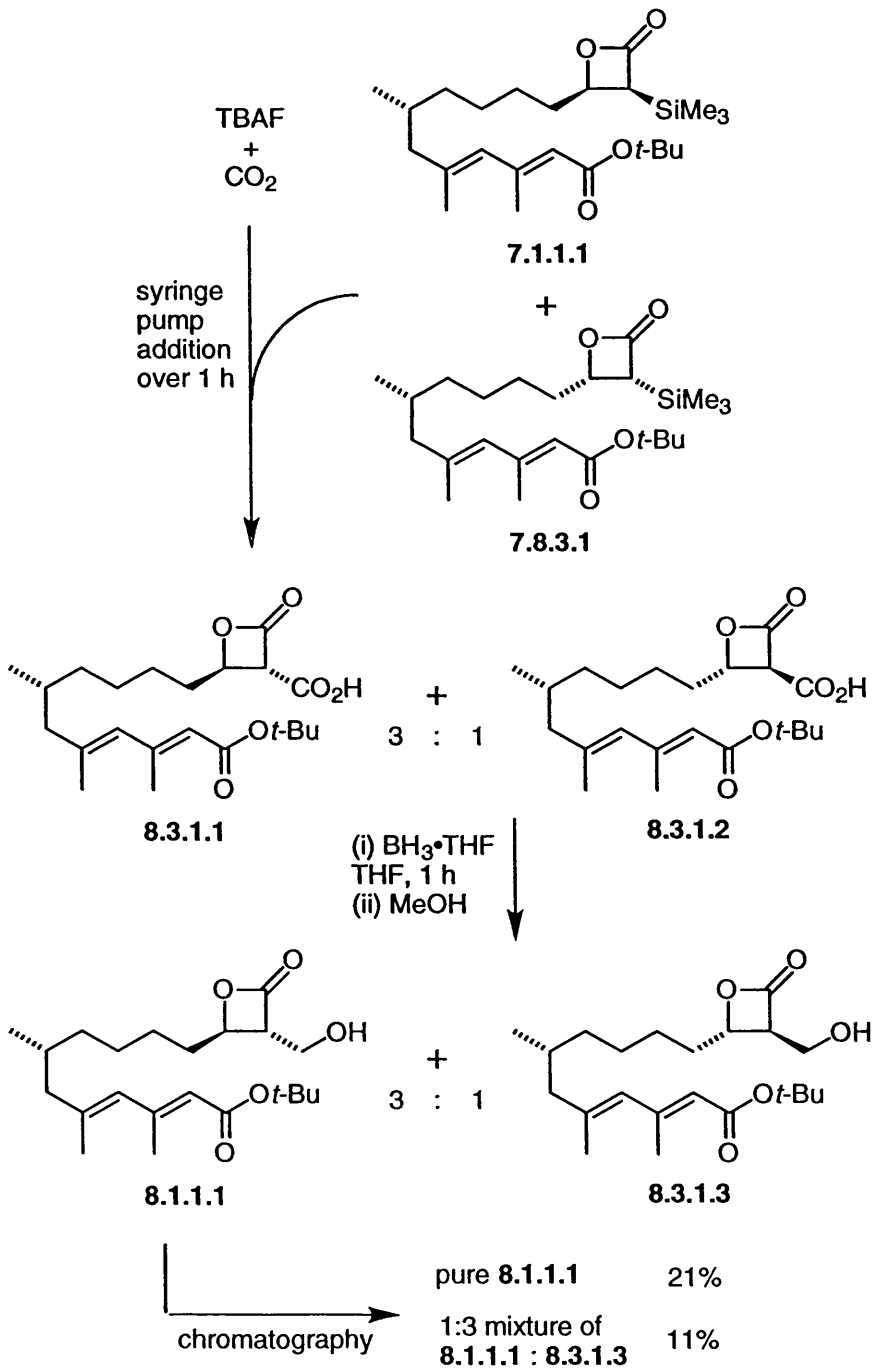
Scheme 8.2.4

Despite attempts with various borane species (BH_3•THF, BH_3•SMe_2) with different solvents (CH_2Cl_2, THF) and quenching procedures the yield could not

be improved. However a selective reduction of the carboxylic acid in the presence of the β-lactone has been achieved.

8.3 Application of the Carbon Dioxide Quench to 1233A

Application of the above methodology to the natural product synthesis progressed successfully although in slightly lower yield than with the model (Scheme 8.3.1).



Scheme 8.3.1

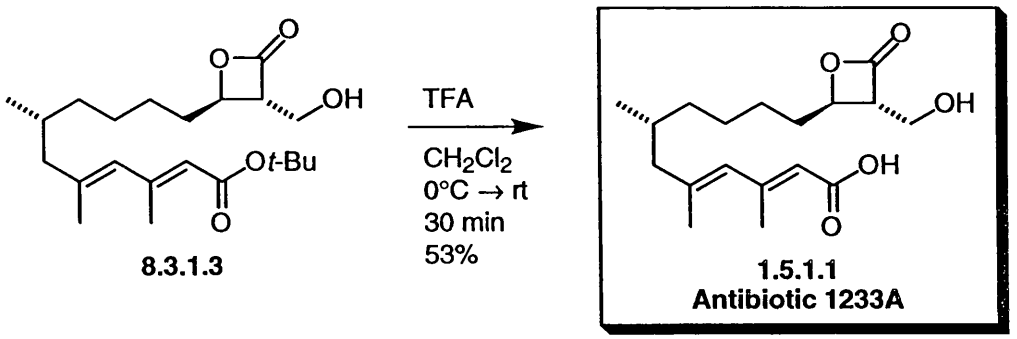
Acid mixture **8.3.1.1** and **8.3.1.2** was immediately reduced with BH_3•THF complex over 1 h. Experiments showed that using excess borane (> 2 equivalents) resulted in extensive hydroboration of the diene moiety. This problem was circumvented by optimising the quantity of borane required (1.6 equivalents or 4.8 hydride equivalents). Alcohol diastereomers **8.1.1.1** and **8.3.1.3** fortunately proved to be separable using standard flash chromatography. Overall yields for these two reactions ranged from 32-42% for 1.2 mmol and 0.13 mmol scale reactions respectively, after chromatographic separation. Using this route, 5 mg batches of pure 1233A *tert*-butyl ester **8.1.1.1** were prepared.

The CO_2 quenching procedure appears to proceed through a planar intermediate. Experiments have shown that when separate samples of *cis* and *trans* β-lactones are subjected to the same CO_2 reaction conditions, identical products result. Therefore it is not a simple inversion of configuration but an attack at the more sterically accessible side of a planar intermediate, most likely the β-lactone enolate proposed above.

8.4 Deprotection of the Ester Protecting Group

Earlier studies, not discussed until this point, centred on finding a suitable ester protecting group for the terminal dieneoic acid. Both methyl and allyl esters were considered: the methyl ester of 1233A was prepared but all attempts at revealing the free carboxylic acid in the presence of the β-lactone failed. These attempts included enzymatic techniques (*porcine pancreatic lipase* and *pig liver esterase* in various solvents and buffers) and lithium iodide in pyridine. In every case complete ring-opening of the β-lactone was observed with no trace of the desired product.

An allyl ester may be deprotected under mild conditions using palladium acetate. However when the allyl ester in the natural product series was prepared it was found, not unexpectedly, to be incompatible with the borane reducing conditions. Therefore the *tert*-butyl ester was employed as in previous syntheses of 1233A (see Chapter 2). Trifluoroacetic acid (TFA) was first used and found to successfully unmask the acid moiety rapidly but in disappointingly low yield (Scheme 8.4.1).



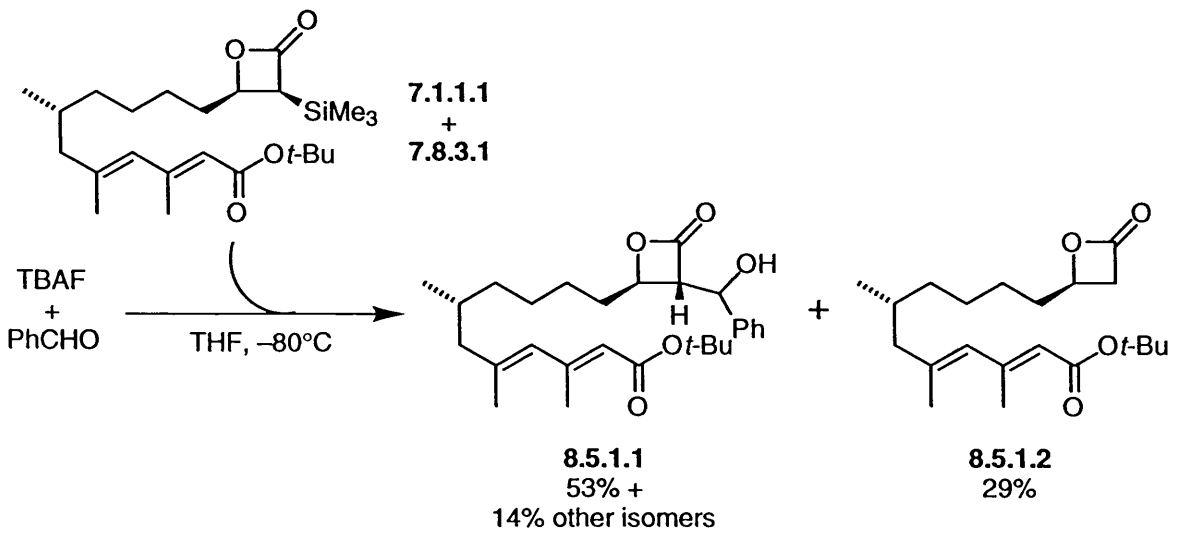
Scheme 8.4.1

Efforts to improve the yield included using a scavenger for the expunged *tert*-butyl cation. A large excess of 1,3-dimethoxybenzene (20 equivalents) succeeded only in slowing the reaction to about 2 hours duration with no effect on yield. Another commonly used reagent for the selective deprotection of *tert*-butyl esters is hydrofluoric acid. All attempts at using HF resulted in total recovery of the starting material, even when a fresh bottle was used! Strangely, Wovkulich used HF efficiently in his synthesis of 1233A (see Scheme 2.5.3). Limitations on quantities of material at such a late stage meant little experimentation could be done to improve the yield of the final step.

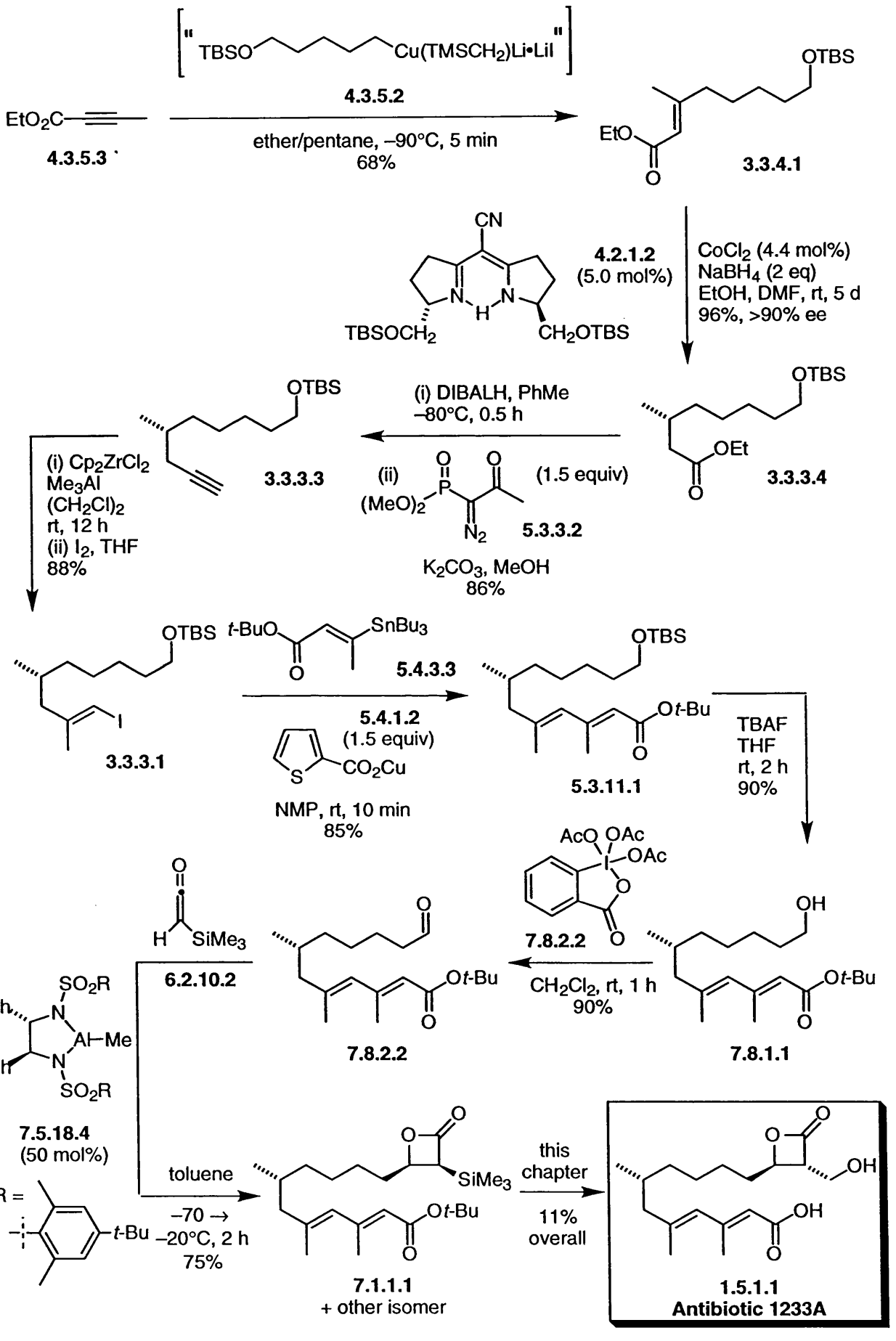
8.5 Synthesis of a Phenyl Analogue of 1233A

One advantage of total synthesis of complex molecules is the possibility of synthesising analogues of natural products for biological screening. In order to demonstrate the versatility of our route to 1233A, we endeavoured to synthesise the phenyl analogue of the hydroxymethyl side chain.

From the [2+2] cycloadduct **7.1.1.1** (along with diastereomeric impurity **7.8.3.1**) a benzaldehyde quench was used instead of CO_2 (Scheme 8.5.1).



Scheme 8.5.1



Overall Yield = 2.9% **Total Number of Steps = 12**

Scheme 8.6.1

Due to the less reactive nature of the benzaldehyde *versus* CO_2, some more proton quenched material **8.5.1.2** was isolated (29%). Nevertheless, the desired product **8.5.1.1** was isolated in 53% yield with 14% of a mixture of isomers. It was hoped that the product would be crystalline but this was not the case and no further attempt was made to establish the stereochemistry of **8.5.1.1**.

8.6 Conclusions

A short and stereoselective synthesis of 1233A has been achieved employing novel methodology for the enantioselective synthesis of β-lactone rings.
Scheme 8.6.1 depicts the shortest and most efficient route to the natural product. The overall number of steps is only 12 and overall yield is 2.9% which compares favourably with the previous total syntheses described in chapter 2. All these syntheses were lengthy (from 19 to 24 steps) and yields ranged from <1% to 2%. The crippling factor in our synthesis is the final 3 steps which proceed in only 11% yield. In addition, the selectivity of only 3:1 for the [2+2] cycloaddition step is not satisfactory. Fortunately, the isomers created were separable with ease rendering the synthesis, at least, practical.

Chapter 9

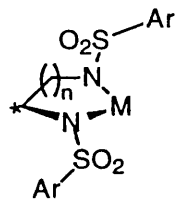
Future Work

9 Future Work

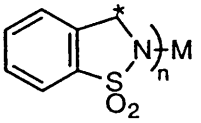
Some of the weaker steps in our synthesis of 1233A deserve further work. Particularly, the [2+2] cycloaddition step needs further development since there is great promise for a practical and synthetically generally useful process. Although enantiomeric excesses are good for aldehydes possessing α-aromatic substitution, the natural product example was only 50% diastereoselective. Linear aldehydes arguably pose the ultimate challenge in asymmetric synthesis and with better catalysts our [2+2] cycloaddition could be controlled at will.

The features of our catalyst which were important (see Chapter 7) could be used to design new better catalysts. For example, it would be wise to retain the metal–sulfonamide linkage since this system is easily synthesised using various metals and appears stable under the reaction conditions.

New ligands and metals could be investigated in a program of systematic study. *Mono*, *bi*, or *tri*-dentate ligands could be used with different metals such as magnesium, gallium or zinc. The general structures shown highlight some of these ideas (Figure 9.1).



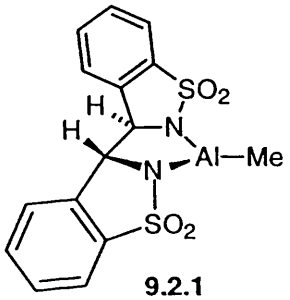
bidentate ring systems of various sizes (n =1, 2) with one chiral group but retaining the easily modified bis-sulfonamide



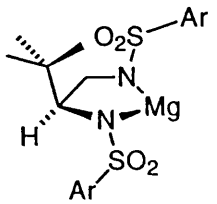
More rigid sulfonamide within a ring.

Figure 9.1

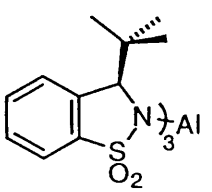
Some examples are shown in figure 9.2.



9.2.1



9.2.2

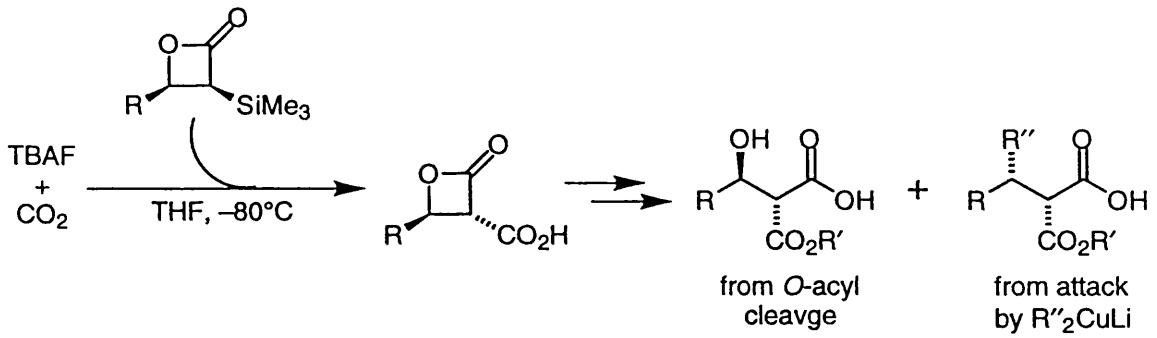


9.2.3

Figure 9.2

Complex **9.2.1** is similar to the Pfaltz catalyst **4.2.1.2** but, of course, doesn't possess any bulky groups close to the metal centre. This would be difficult to engineer into the structure without destroying the necessary sulfonamide moiety. Magnesium based **9.2.2** is a simple structure with a *tert*-butyl group in the position previously occupied by a phenyl ring. The extra bulk of the *tert*-butyl group could be significant if transition state **7.7.1.1** (Scheme 7.7.1) is envoked. A less rigid ligand structure, such as **9.2.3**, may also be worthwhile testing. Other metals, *mono* or *bidentate*, could be used, *e.g.* magnesium, so that rapid screening of metals would be possible using one ligand.

An innovation which has synthetic promise is the conversion of the silyl group to a carboxylic acid with inversion of configuration as in the final steps of the 1233A synthesis. Although attractive from a synthetic point of view, the yields were rather low. Further work could improve this chemistry and access to a wide range of chiral segments with contiguous stereogenic centres would be available through ring-opening of the β-lactone ring in two different ways (Scheme 9.3).



Scheme 9.3

The usefulness of β-lactones has been grossly underestimated, primarily due to difficulties in their synthesis, but with a robust asymmetric [2+2] cycloaddition this area of organic synthesis could be revolutionised.

Chapter 10

Experimental Section

10.1 General Experimental Details

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon or nitrogen. Organic extracts were dried over $MgSO_4$ unless otherwise specified and evaporated at electric pump (5-10 mmHg) or water pump (20 mmHg) using a Buchi rotary evaporator. Distillations in which the bath temperature is recorded were performed with a Kugelrohr apparatus.

Where appropriate, solvents and reagents were dried by standard methods,[252] *i.e.* by distillation from the usual drying agent prior to use: diethyl ether ("ether") and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Acetonitrile, pentane, cyclohexane, pyridine, benzene, dichloromethane, *N*,*N*-dimethylformamide, toluene, triethylamine, *N*-methylpyrrolidinone (NMP) and *tert*-butanol were distilled from CaH_2 and stored over 4 Å molecular sieves under nitrogen. Methanol was distilled from the corresponding magnesium alkoxide. Petroleum ether bp 40-60°C ("petrol") for chromatography was distilled from KOH before use. Trimethylsilyl chloride and benzaldehyde were distilled freshly before use. Dodecanal was purified by flash column chromatography and stored under nitrogen at –20°C. Iodine was sublimed at 0.5 mmHg and stored under nitrogen. Carbon tetrabromide was sublimed freshly before use. For best results, copper (I) iodide was extracted with THF in a soxhlet apparatus and stored in the dark. The Dess-Martin periodinane reagent was prepared according to the literature[250] and stored at –20°C under nitrogen. *tert*-Butyltrichloroacetimidate was prepared according to the literature procedure.[93] 4-*tert*-Butyl-2,6-dimethylbenzenesulfonyl chloride was prepared according to the general procedure.[253] (Trimethylsilyl)ketene was prepared by flash distillation of ethoxy(trimethylsilyl)acetylene at atmospheric pressure. Commercial organometallics were used as supplied and alkyllithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrazone.[254]

All reactions were magnetically stirred and were monitored by Thin Layer Chromatography (TLC) using Macherey-Nagel Düren Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thckness 0.25 mm. Compounds were visualised by UV (254 nm), then with 20 wt% phosphomolybdic acid (PMA) in ethanol with heating. Flash chromatography was performed on Merck silica gel 60 (0.04-0.063 mm, 230-400 mesh) and run under low pressure.[255]

Optical rotations were recorded on an Optical Activity AA-100 polarimeter at approximately 20°C.

Melting points were measured on a Griffin electrothermal apparatus and are uncorrected.

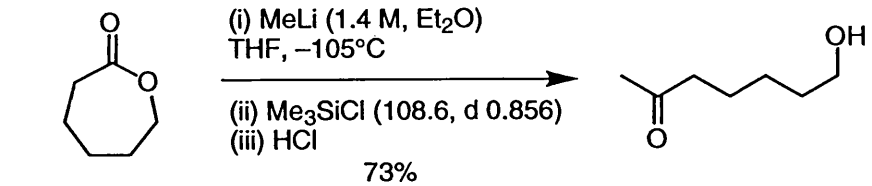
IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm^{-1} and defined as either strong (s), medium (m). Broad absorptions are designated (br). Weak absorptions are not reported.

Proton NMR spectra were recoreded in Fourier Transform mode on a Jeol JNX-GX-270 (270 MHz), Bruker AC 300 (300 MHz) or Bruker AM 360 (360 MHz) spectrometer in either chloroform-*d* or benzene-d_6. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.27) or benzene (δ = 7.18). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad.

Carbon-13 NMR spectra were recorded on a Jeol JNX-GX-270 (68 MHz), Bruker AC 300 (75 MHz) or Bruker AM 360 (90 MHz) spectrometer in either chloroform-*d* (δ = 77.2) or benzene-d_6 (δ = 128.7). Chemical shifts are reported in ppm relative to the solvent. Multiplicities were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. C-H coupling is indicated by an integer 0-3 in parenthesis following the ^{13}C chemical shift value denoting the number of coupled protons.

Mass spectra were run on a VG 70-250-SE or JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and where shown, the proposed signal assignment. All compounds submitted for mass spectral analysis were purified by either distillation or column chromatography and estimated to be at least 95% pure by NMR and thin layer chromatography.

7-Hydroxy-2-heptanone (3.3.4.2):



4.3.2.1
$C_6H_{10}O_2 = 114.2$

3.3.4.2
$C_7H_{14}O_2 = 130.2$

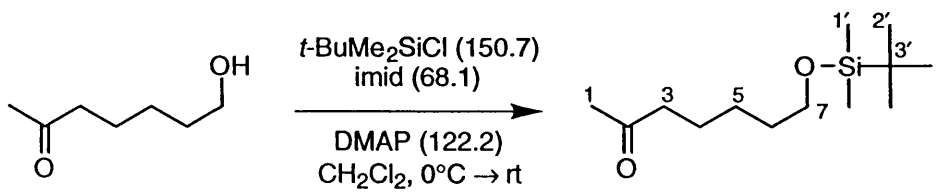
Methyl lithium (1.4 M in ether, 96 mL, 134.4 mmol) was added over 20 minutes to a mechanically stirred –105°C solution (liquid N_2 bath) of ε-caprolactone (**4.3.2.1**) (11.4 g, 100 mmol) in THF (450 mL). The internal temperature was maintained between –100 and –110°C at all times during the addition. The reaction was stirred for 20 minutes then trimethylsilyl chloride (39 mL, 33.4 g, 307 mmol, 3 eq) was added dropwise. The reaction was allowed to warm to 0°C and quenched with 2 N HCl (200 mL). The biphasic mixture was vigorously stirred for 1 h then poured onto sodium hydrogen carbonate (60 g). The phases were separated and the aqueous phase was concentrated *in vacuo* to remove THF then extracted with ethyl acetate (3 x 100 mL). The combined organic phases were then washed with brine (100 mL), dried, filtered and concentrated *in vacuo* to a colourless oil which was purified by short path distillation (10 mmHg, 122-126°C) to give **3.3.4.2** as a colourless oil (10.98 g, 84.3 mmol, 84%), exhibiting spectral characteristics according to the literature.[63]

IR (film): $\nu = 3411$ (br s), 2937 (s), 2867 (s), 1709 (s), 1414 (m), 1364 (m), 1269 (m), 1167 (m), 1053 (m) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.30$ (2H, m), 1.52 (4H, m), 2.08 (3H, s), 2.39 (2H, t, J = 7.5 Hz), 2.53 (1H, br s, OH), 3.55 (2H, t, $J = 6.9$ Hz).

^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 23.5$ (2), 25.3 (2), 29.9 (3), 32.4 (2), 43.6 (2), 62.4 (2), 209.5 (0).

7-[(*tert*-butyldimethylsilyl)oxy]-2-heptanone (4.3.1.2):



3.3.4.2
$C_7H_{14}O_2 = 130.2$

4.3.1.2
$C_{13}H_{28}O_2Si = 244.5$

To a solution of 7-hydroxy-2-heptanone (**3.3.4.2**) (4.18 g, 32.1 mmol) in CH_2Cl_2 (30 mL) at rt was added imidazole (6.5 g, 96.3 mmol, 3 eq) and DMAP (0.4 g, 3.27 mmol, 0.1 eq). The

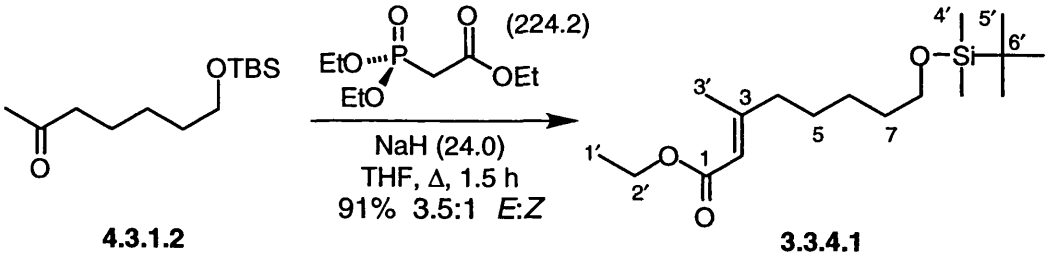
suspension was stirred at rt for 5 minutes then a solution of *tert*-butydimethylsilyl chloride (5.33 g, 35.4 mmol, 1.1 eq) in CH_2Cl_2 (20 mL) was added dropwise. The reaction was stirred at rt for 1 h then poured into 1 N HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to a colourless oil which was purified by column chromatography (SiO_2, petrol:Et_2O = 90:10) to give ketone **4.3.1.2** (7.61 g, 31.1 mmol, 97%) as a colourless oil. An analytical sample may be prepared by Kugelrohr distillation (110°C (bath) @ 10 mmHg).
We were unable to obtain a satisfactory microanalysis.

IR (film): ν = 2931 (s), 2858 (s), 1720 (s), 1472 (m), 1360 (m), 1255 (s), 1100 (s), 1006 (m), 836 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.01 (6H, s, H1′), 0.86 (9H, s, H2′), 1.30 (2H, m, H5), 1.52 (4H, m, H4,6), 2.10 (3H, s, H1), 2.40 (2H, t, J = 7.3 Hz, H3), 3.57 (2H, t, J = 6.3 Hz, H7).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.2 (3), 18.4 (0), 23.8 (2), 25.7 (2), 26.1 (3), 29.9 (3), 32.7 (2), 43.9 (2), 63.1 (2), 209.1 (0).

Ethyl (*E*)-8-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-2-octenoate (3.3.4.1):



4.3.1.2
$C_{13}H_{28}O_2Si$ = 244.5

3.3.4.1
$C_{17}H_{34}O_3Si$ = 314.5

Sodium hydride (5.5 g of 60% dispersion in oil ≡ 3.3 g NaH, 0.138 mol, 2.2 eq) was washed with dry petrol (3 x 20 mL) and dried under argon. THF (80 mL) was added and the suspension was cooled to 0°C. A solution of triethylphosphonoacetate (35.3 g, 0.157 mmol, 2.5 eq) in THF (40 mL) was added dropwise over 15 min. The resulting clear tan solution was warmed to rt and stirred for 5 min. Then a solution of the ketone (**4.3.1.2**) (15.4 g, 63 mmol) in THF (80 mL) was added dropwise. The reaction mixture was refluxed for 1.5 h then cooled to rt and poured into ether (500 mL) and water (200 mL). The aqueous phase was extracted with ether (100 mL). The combined ethereal extracts were washed with water (100 mL), brine (100 mL), dried, filtered and concentrated to a colourless oil (27.2 g) which was repeatedly chromatographed (SiO_2, petrol:Et_2O = 97:3) to give (*E*)-**3.3.4.1** (14.1 g, 44.5 mmol, 71%) and (*Z*)-**3.3.4.1** (4.0 g, 12.6 mmol, 20%) as colourless oils.
An analytical sample may be prepared by Kugelrohr distillation (110°C (bath) @ 0.5 mmHg).

Data for the (*E*) isomer:

IR (film): ν = 2933 (s), 2858 (s), 1718 (s), 1649 (s), 1472 (s), 1386 (m), 1367 (s), 1256 (s), 1222 (s), 1147 (s), 1100 (s), 1044 (m), 836 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 (6H, s, H4′), 0.88 (9H, s, H5′), 1.26 (3H, t, J = 7.2 Hz, H1′), 1.32-1.50 (6H, m, H5-7), 2.13 (2H, t, J = 8.8 Hz, H4), 2.14 (3H, d, J = 1.1 Hz, H3′), 3.59 (2H, t, J = 6.5 Hz, H8), 4.13 (2H, q, J = 7.2 Hz, H2′), 5.64 (1H, sextet, J = 1.1 Hz, H2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 (3), 14.6 (3), 18.5 (0), 18.8 (3), 25.6 (2), 26.1 (3), 27.3 (2), 32.7 (2), 41.0 (2), 59.5 (2), 63.1 (2), 115.7 (1), 160.2 (0), 167.0 (0).

LRMS (CI mode, NH_3): m/z = 315 [$(M+H)^+$, 95%], 286 (25), 269 (40), 257 [$(M+H-C_4H_9)^+$, 100].

Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.91; H, 10.94.

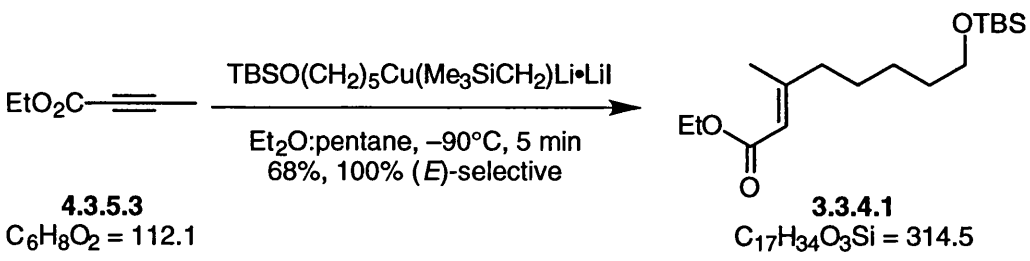
Data for the (*Z*) isomer:

IR (film): ν = 2932 (s), 2857 (s), 1714 (s), 1645 (s), 1474 (s), 1377 (m), 1256 (s), 1226 (s), 1146 (s), 1098 (s), 1045 (m), 1006 (m), 837 (s), 776 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.03 (6H, s, H4′), 0.87 (9H, s, H5′), 1.25 (3H, t, J = 7.2 Hz, H1′), 1.45 (6H, m, H5-7), 1.85 (3H, d, J = 1.1 Hz, H3′), 2.61 (2H, t, J = 6.8 Hz, H4), 3.59 (2H, t, J = 6.4 Hz, H8), 4.11 (2H, q, J = 7.1 Hz, H2′), 5.63 (1H, m, H2).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 14.5 (3), 18.5 (0), 25.3 (3), 25.6 (2), 26.1 (3), 28.2 (2), 32.9 (2), 33.5 (2), 59.5 (2), 63.3 (2), 116.2 (1), 160.6 (0), 166.5 (0).

Ethyl (*E*)-8-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-2-octenoate (3.3.4.1):



4.3.5.3
$C_6H_8O_2$ = 112.1

3.3.4.1
$C_{17}H_{34}O_3Si$ = 314.5

To a solution of 5-iodo-*O*-(*tert*-butyldimethylsilyl)-pentanol* (**4.3.5.3**) (377 mg, 1.15 mmol) in Et_2O (5 mL):pentane (3 mL) at –75°C was added *tert*-butyllithium (1.4 mL of a 1.7 M solution in hexanes, 2.38 mmol, 2 eq). The pale yellow solution was warmed to 0°C and

THF (200 μL, 2.46 mmol) was added. The mixture of 5-lithio-*O*-(*tert*-butyldimethylsilyl)-pentanol was stirred for 10 min then cooled to –20°C and added *via* cannula to another reaction flask containing a –80°C solution of trimethylsilylmethylcopper prepared as follows: to a suspension of copper (I) iodide (220 mg, 1.16 mmol) in Et_2O (10 mL) at –75°C was added trimethylsilylmethyllithium (1.15 mL of a 1.0 M solution in pentane, 1.15 mmol). The pale yellow mixture was warmed to 0°C and stirred for 10 min.

After addition of the alkyl lithium to the cuprate the resulting mixed cuprate was warmed to 0°C and stirred for 10 min. During this time the mixture became orange and finally pale tan. The solution was then cooled to –90°C and ethyl tetrolate (112 mg, 1.0 mmol) was added as a solution in Et_2O (0.5 mL + 2 x 0.5 mL rinses). The internal temperature was maintained at or slightly below –90°C during the addition. The reaction was stirred for 5 min then quenched (at –90°C) with saturated aqueous NH_4Cl solution (5 mL) and warmed to room temperature over 1 h. The mixture was poured into Et_2O (100 mL):water (50 mL). The organic phase was washed with water (2 x 25 mL) and brine (25 mL) then dried, filtered and concentrated *in vacuo* to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 97:3) to give (*E*)-**3.3.4.1** (214 mg, 0.68 mmol, 68%) as a colourless oil.

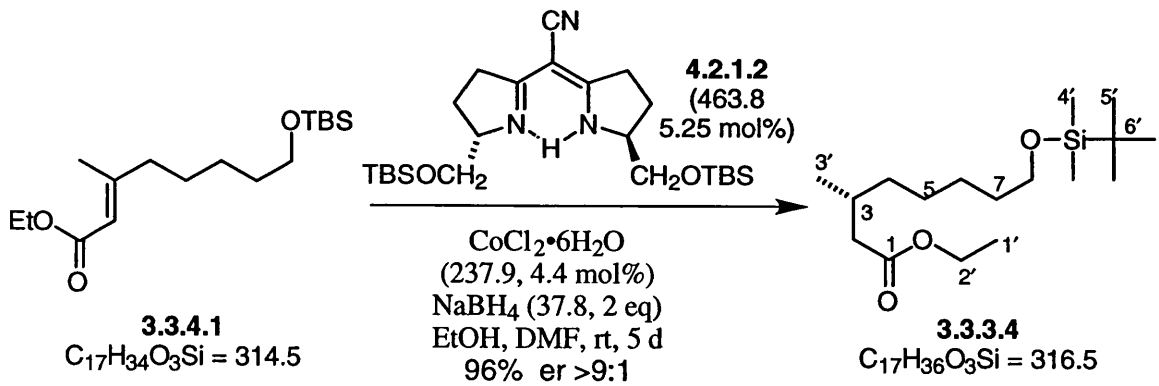
* prepared by mono TBS protection of pentan-diol then tosylation and treatment with sodium iodide in acetone:

P. G. McDougal, J. G. Rico, Y. Oh, B. D. Condon *J. Org. Chem.*, **1986**, *51*, 3388.

E. A. Mash, S. B. Hemperly, K. A. Nelson, P. C. Heidt, S. van Densen *J. Org. Chem.*, **1990**, *55*, 2045.

See preceeding experiment for characterisation data.

(*R*)-(+)-Ethyl 8-[(*tert*-butyldimethylsilyl)oxy]-3-methyloctanoate (3.3.3.4):



Into a glass tube fitted with a vacuum tight Young's tap was placed **3.3.4.1** (9.62 g, 30.6 mmol) in ethanol (12.5 mL) under argon. To the magnetically stirred solution was added cobalt chloride hexahydrate (319 mg, 1.34 mmol, 4.40 mol%) in ethanol (4 mL) followed by semi-corrin **4.2.1.2** (746 mg, 1.61 mmol, 5.26 mol%) in ethanol (5.5 mL). On addition of the semi-corrin the reaction mixture changed from a blue to a deep purple colour. To the

mixture was finally added a slightly turbid solution of sodium borohydride (2.315 g, 61.2 mmol, 2 eq) in DMF (19 mL). The now brown reaction mixture was thoroughly degassed *via* 4 freeze-thaw cycles then sealed under vacuum,* allowed to warm to rt and stirred for 5 days. After this time, the internal pressure was eased by careful opening of the teflon tap and water (100 mL) was added. The product was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL), brine (100 mL), dried and concentrated *in vacuo* to a brown oil which was chromatographed (SiO_2, petrol:Et_2O = 95:5) to give the ester **3.3.3.4** (9.31 g, 29.4 mmol, 96%) as a colourless oil (ee >90%, chiral lanthanide shift reagent, see Chapter 4).

* The sealed reaction mixture, under argon, was frozen in liquid nitrogen and evacuated with an oil pump (0.5 mmHg). After 5 min, the tube was re-sealed and allowed to warm to rt and thaw. Argon was re-introduced and the whole process repeated. The final cycle ends with the reaction mixture being sealed under vacuum while still frozen.

$[\alpha]_D$ = +2.8° (*c* = 3.42 in $CHCl_3$).

IR (film): ν = 2931 (s), 2857 (s), 1738 (s), 1255 (s), 1098 (s), 837 (s) cm^{-1}.

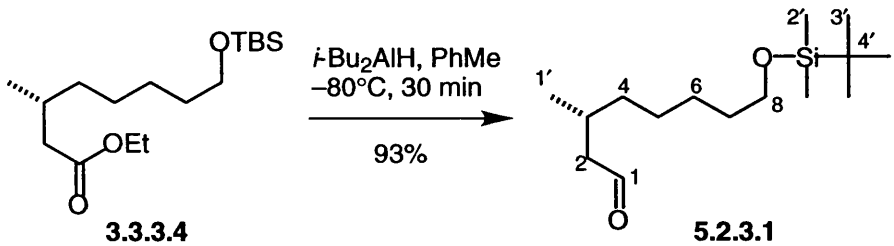
^1H NMR (270 MHz, $CDCl_3$): δ = 0.03 (6H, s, H4′), 0.88 (9H, s, H5′), 0.91 (3H, d, *J* = 6.3 Hz, H3′), 1.24 (3H, t, *J* = 7.1 Hz, H1′), 1.29 (6H, br m, H4-6), 1.48 (2H, m, H7), 1.90 (1H, br m, H3), 2.07 (1H, dd, *J* = 14.5, 7.9 Hz, H2), 2.27 (1H, dd, *J* = 14.3, 6.0 Hz, H2), 3.58 (2H, t, *J* = 6.9 Hz, H8), 4.11 (2H, q, *J* = 7.1 Hz, H2′).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 14.4 (3), 18.5 (0), 19.9 (3), 26.1 (3), 26.9 (2), 30.5 (1), 33.0 (2), 36.9 (2), 42.1 (2), 60.2 (2), 63.3 (2), 173.4 (0).

LRMS (CI mode, NH_3): *m/z* = 317 [$(M+NH_4)^+$, 100%], 259 (20), 57 (28).

Anal. Calcd for $C_{17}H_{36}O_3Si$: C, 64.51; H, 11.46. Found: C, 64.44; H, 11.57.

(*R*)-(+)-8-[(*tert*-butyldimethylsilyl)oxy]-3-methyloctanal (5.2.3.1):



3.3.3.4
$C_{17}H_{36}O_3Si$ = 316.5

5.2.3.1
$C_{15}H_{32}O_2Si$ = 272.5

Di*iso*-butylaluminium hydride (10.1 mL of a 1.5 M solution in toluene, 15.15 mmol) was added dropwise to a solution of ester **3.3.3.4** (4.7 g, 14.85 mmol) in toluene (60 mL) at –80°C. The reaction was stirred for 30 min then quenched by addition of methanol (40 mL). The mixture was warmed to 0°C then poured into a solution of sodium potassium tartrate (75 g) in water (300 mL). The mixture was stirred vigorously for 30 min then poured into Et_2O (300 mL) and brine (100 mL). The aqueous phase was extracted with Et_2O (100 mL) and combined organic layers were washed with brine (100 mL), dried and concentrated *in vacuo* to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 95:5) to give **5.2.3.1** as a colourless oil (3.812 g, 13.99 mmol, 94%).

$[\alpha]_D$ = +9.0° (*c* = 3.535 in $CHCl_3$).

IR (film): ν = 2930 (s), 2857 (s), 1728 (s), 1463 (s), 1387 (s), 1361 (m), 1255 (s), 1099 (s), 835 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.02 (6H, s, H2′), 0.87 (9H, s, H3′), 0.93 (3H, d, *J* = 6.7 Hz, H1′), 1.29 (6H, m, H4-6), 1.50 (2H, m, H7), 2.03 (1H, m, H3), 2.19 (1H, ddd, *J* = 15.8, 7.5, 2.3 Hz, H2), 2.37 (1H, ddd, *J* = 15.8, 5.6, 2.1 Hz, H2), 3.57 (H, t, *J* = 6.3 Hz, H8), 9.73 (1H, t, *J* = 2.3 Hz, H1).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.3 (3), 18.4 (0), 20.0 (3), 25.95 (2), 26.00 (3), 26.8 (2), 28.1 (1), 32.8 (2), 36.9 (2), 51.1 (2), 63.1 (2), 202.8 (0).

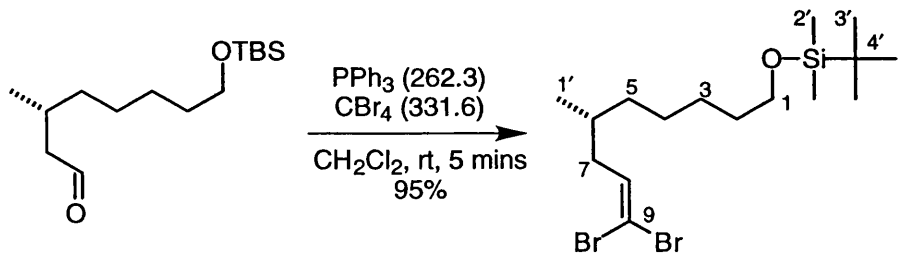
LRMS (CI mode, NH_3): *m/z* = 289 [$(M+NH_4)^+$, 100%].

Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.12; H, 11.84. Found: C, 66.19; H, 11.79.

An analytical sample may be prepared by Kugelrohr distillation (85°C (bath) @ 0.8 mmHg).

The aldehyde is not stable over days at room temperature but may be stored in the freezer for short periods.

(*R*)-(–)-*O*-(*tert*-butyldimethylsilyl)-9,9-dibromo-6-methyl-8-nonen-1-ol (5.3.3.1):



5.2.3.1
$C_{15}H_{32}O_2Si$ = 272.5

5.3.3.1
$C_{16}H_{32}Br_2OSi$ = 428.3

To a slightly turbid orange solution of triphenylphosphine (1.94 g, 7.40 mmol, 4 eq) and freshly sublimed carbon tetrabromide (1.22 g, 3.68 mmol, 2 eq) in CH_2Cl_2 (10 mL) at 0°C was added the aldehyde **5.2.3.1** (503 mg, 1.85 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 5 min then the solvent was removed *in vacuo* and the residue was chromatographed (SiO_2, petrol:Et_2O = 98:2) to give **5.3.3.1** as a colourless oil (752 mg, 1.76 mmol, 95%).

$[\alpha]_D = -1.6°$ (c = 3.45 in $CHCl_3$).

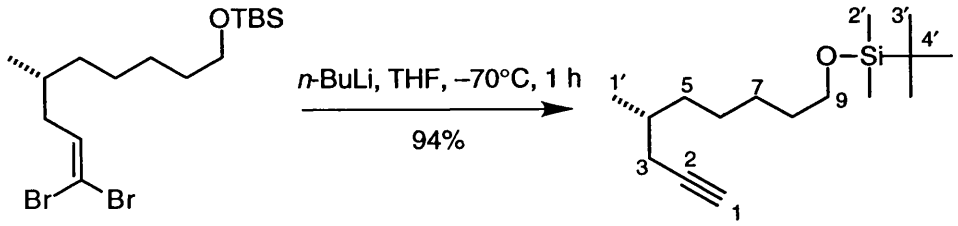
IR (film): ν = 2929 (s), 2856 (s), 1462 (m), 1255 (s), 1100 (s), 835 (s), 776 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.05 (6H, s, H2′), 0.90 (9H, s, H3′), 0.92 (3H, d, J = 6.5 Hz, H1′), 1.3-1.5 (9H, m, H2-6), 1.95 (1H, dt, J = 14.8, 7.4 Hz, H7), 2.10 (1H, ddd, J = 14.5, 7.1, 6.0 Hz, H7), 3.60 (2H, t, J = 6.4 Hz, H1), 6.40 (1H, t, J = 7.3 Hz, H8).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 18.5 (0), 19.7 (3), 26.2 (3), 27.0 (2 x 2), 32.6 (1), 33.0 (2), 36.7 (2), 40.3 (2), 63.4 (2), 89.1 (0), 137.9 (1).

LRMS (CI mode, NH_3): m/z = 446 [$(M+NH_4)^+$, 50%], 429 [$(M+H)^+$, 100], 388 [$(MNH_4–C_4H_9)^+$, 30], 349 [$(M–Br)^+$, 15], 317 (25), 265 (35).

(*R*)-(+)-*O*-(*tert*-butyldimethylsilyl)-6-methyl-8-nonyn-1-ol (3.3.3.3):



5.3.3.1
$C_{16}H_{32}Br_2OSi$ = 428.3

3.3.3.3
$C_{16}H_{32}OSi$ = 268.5

n-Butyllithium (7.4 mL of a 2.0 M solution in hexanes, 14.80 mmol, 3 eq) was added dropwise over 30 min to a –78°C solution of dibromide **5.3.3.1** (2.12 g, 4.95 mmol) in THF (20 mL). The yellow mixture was was stirred at –75°C for 1 h then warmed to –40°C when it was quenched with saturated aqueous ammonium chloride (20 mL). The biphasic mixture was warmed to 0°C and poured into Et_2O (100 mL) and water (50 mL). The aqueous phase was extracted with ether (20 mL) and combined organic layers were washed with brine (50 mL), dried and concentrated *in vacuo* to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 98:2) to give **3.3.3.3** as a colourless oil (1.25 g, 4.66 mmol, 94%).

$[\alpha]_D$ = +0.8° (*c* = 2.9 in $CHCl_3$).

IR (film): ν = 3314 (m), 2955 (s), 2923 (s), 2857 (s), 2118 (w), 1472 (m), 1255 (s), 1099 (s), 836 (s), 775 (s) cm^{-1}.

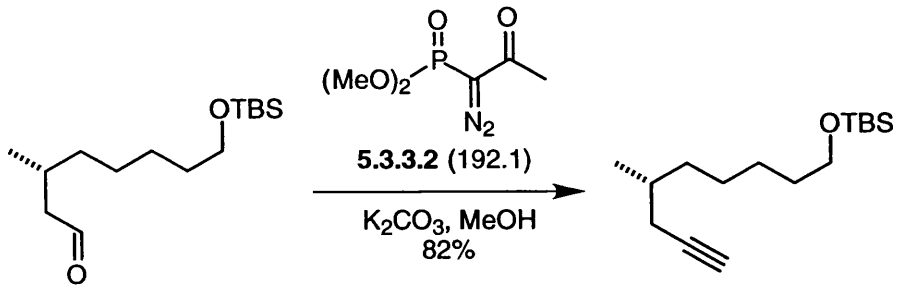
^1H NMR (270 MHz, $CDCl_3$): δ = 0.05 (6H, s, H2′), 0.89 (9H, s, H3′), 0.98 (3H, d, *J* = 6.9 Hz, H1′), 1.15-1.75 (9H, m, H4-8), 1.93 (1H, t, *J* = 2.5 Hz, H1), 2.05 (1H, ddd, *J* = 16.7, 6.6, 2.5 Hz, H3), 2.16 (1H, ddd, *J* = 16.7, 5.7, 2.5 Hz, H3), 3.60 (2H, t, *J* = 6.4 Hz, H9).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 18.5 (0), 19.6 (3), 25.9 (2, 2), 26.2 (3), 27.0 (2), 32.5 (1), 33.0 (2), 36.1 (2), 63.4 (2), 69.2 (0), 83.5 (1).

LRMS (CI mode, NH_3): *m/z* = 286 [$(M+NH_4)^+$, 15%], 269 [$(M+H)^+$, 100].

Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.69; H, 12.09.

(*R*)-(+)-*O*-(*tert*-butyldimethylsilyl)-6-methyl-8-nonyn-1-ol (3.3.3.3):



5.2.3.1
$C_{15}H_{32}O_2Si$ = 272.5

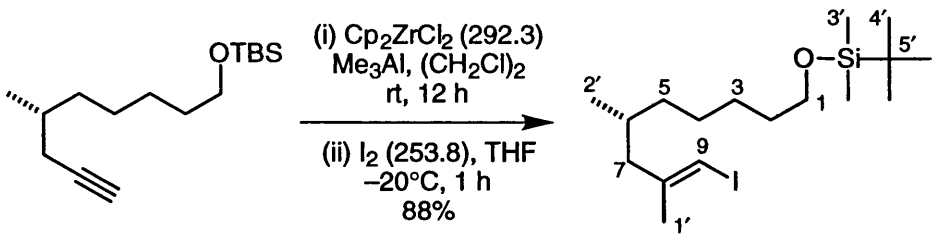
3.3.3.3
$C_{16}H_{32}OSi$ = 268.5

To a 0°C solution of aldehyde **5.2.3.1** (291 mg, 1.07 mmol) and 1-diazo-1-(dimethylphosphono)propan-2-one (**5.3.3.2**) (307 mg, 1.6 mmol, 1.5 eq) in dry methanol was added anhydrous K_2CO_3 (310 mg, 2.24 mmol, 2.1 eq). The yellow reaction mixture was warmed to rt and stirred for 14 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and extracted with petrol (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil which was chromatographed (SiO_2, petrol:Et_2O = 95:5) to give **3.3.3.3** as a colourless oil (236 mg, 0.879 mmol, 82%).

An analytical sample may be prepared by Kugelrohr distillation (50°C (bath) @ 0.5 mmHg).

The diazophosphonate was prepared according to:
P. Callant, L. D'Haenens, M. Vandewalle *Synth. Commun.*, **1984**, *14*, 155.

(*R*)-(*E*)-(–)-*O*-(*tert*-butyldimethylsilyl)-9-iodo-6,8-dimethyl-8-nonen-1-ol (3.3.3.1):



3.3.3.3
$C_{16}H_{32}OSi$ = 268.5

3.3.3.1
$C_{17}H_{35}IOSi$ = 410.45

To a suspension of zirconocene dichloride (1.09 g, 3.72 mmol, 1 eq) in 1,2-dichloroethane (10 mL) was added trimethylaluminium (5.6 mL of a 2.0 M solution in toluene, 11.2 mmol, 3 eq). The lemon yellow solution was stirred at rt for 15 min then the acetylene **3.3.3.3** (1.00 g, 3.72 mmol) in 1,2-dichloroethane (10 mL) was added. After stirring for 12 h the reaction had become a darker yellow colour. The reaction was cooled to –20°C and iodine (1.51 g, 5.95 mmol, 1.6 eq) added as a solution in THF (8 mL). The reaction was carefully quenched with 1:1 THF:H_2O (20 mL) at –10°C and warmed slowly to rt over 30 min. The mixture was poured into Et_2O (100 mL) and water (50 mL). The aqueous phase was extracted with Et_2O

(20 mL) and the combined organic layers were washed with brine (50 mL), dried and concentrated *in vacuo* to a colourless turbid oil which was chromatographed (SiO_2, petrol:Et_2O = 98:2) to give **3.3.3.1** as a colourless oil (1.35 g, 3.29 mmol, 88%).

$[\alpha]_D = -1.1°$ (c = 3.185 in $CHCl_3$).

IR (film): ν = 2928 (s), 2856 (s), 1462 (m), 1255 (s), 1099 (s), 836 (s), 775 (s) cm^{-1}.

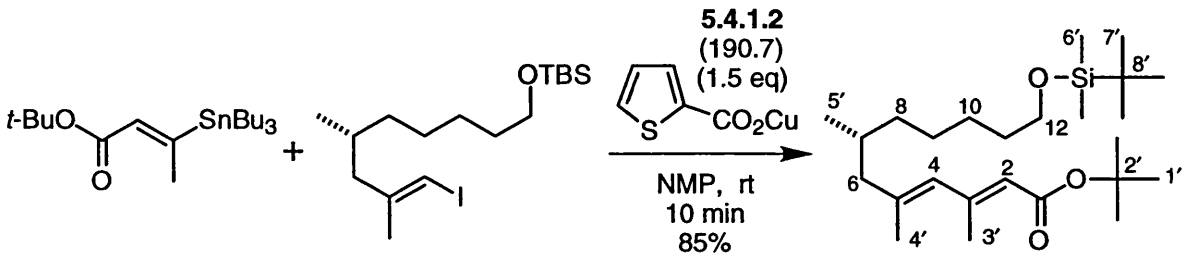
^1H NMR (270 MHz, $CDCl_3$): δ = 0.04 (6H, s, H3′), 0.81 (3H, d, J = 6.6 Hz, H2′), 0.90 (9H, s, H4′), 1.0-1.7 (9H, m, H2-6), 1.79 (3H, br s , H1′), 1.98 (1H, dd, J = 13.5, 8.4 Hz, H7), 2.19 (1H, dd, J = 13.5, 5.9 Hz, H7), 3.60 (2H, t, J = 6.3 Hz, H1), 5.82 (1H, s br, H9).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 18.5 (0), 19.5 (3), 23.9 (3), 26.2 (3, 2), 27.0 (2), 31.1 (1), 33.0 (2), 36.9 (2), 47.8 (2), 63.4 (2), 75.4 (1), 147.3 (0).

LRMS (CI mode, NH_3): m/z = 428 [$(M+NH_4)^+$, 40%], 411 [$(M+H)^+$, 100], 370 (70).

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 428.1823. $C_{17}H_{35}IOSi$ + NH_4 requires 428.1847 (error –5.3 ppm).

(*R*)-(*E*,*E*)-(–)-*tert*-Butyl-12-[(*tert*-butyldimethylsilyl)oxy]-3,5,7-trimethyl-2,4-dodecadieneoate (5.3.11.1):



5.4.3.3 $C_{20}H_{40}O_2Sn$ = 431.2

3.3.3.1 $C_{17}H_{35}IOSi$ = 410.45

5.3.11.1 $C_{25}H_{48}O_3Si$ = 424.7

To a solution of the iodide **3.3.3.1** (1.21 g, 2.95 mmol, 2 eq) in NMP (5 mL) was added copper (I) thiophenecarboxylate (422 mg, 2.21 mmol, 1.5 eq). To this suspension was added a solution of the vinyl tin **5.4.3.3** (632 mg, 1.47 mmol) in NMP (3 mL). The reaction mixture was stirred for 5 min then diluted with ether (50 mL) and filtered through a bed of celite. The resulting clear ethereal solution was washed with water (3 x 25 mL), brine (25 mL), dried, filtered and concentrated to a pale yellow oil which was chromatographed (SiO_2, petrol:Et_2O = 99:1 → 96:4) to yield the diene **5.3.11.1** (535 mg, 1.25 mmol, 85%) as a colourless oil and recovered iodide **3.3.3.1** (652 mg, 1.59 mmol, 93% recovery) as a colourless oil.

$[\alpha]_D = -11.2°$ (c = 3.12 in $CHCl_3$).

IR (film): ν = 2929 (s), 2856 (s), 1710 (s), 1625 (m), 1472 (m), 1462 (m), 1380 (m), 1366 (s), 1250 (s), 1141 (s), 1099 (s), 836 (s), 775 (s) cm^{-1}.

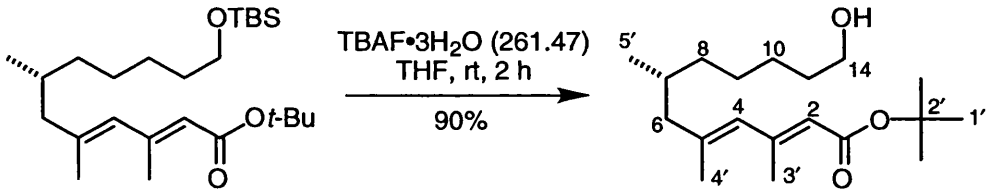
^1H NMR (270 MHz, $CDCl_3$): δ = 0.05 (6H, s, H6′), 0.82 (3H, d, J = 6.5 Hz, H5′), 0.89 (9H, s, H7′), 1.05-1.75 (9H, m, H7-11), 1.48 (9H, s, H1′), 1.98 (3H, d, J = 1.0 Hz, H4′), 1.80 (1H, dd, J = 13.0, 7.8 Hz, H6), 2.07 (1H, dd, J = 12.8, 5.6 Hz, H6), 2.19 (3H, d, J = 1.0 Hz, H3′), 3.60 (2H, t, J = 6.3 Hz, H12), 5.58 (1H, br s, H4), 5.66 (1H, br s, H2).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –5.1 (3), 18.3 (3), 19.4 (3, 3, 0), 26.0 (3), 26.1 (2), 26.8 (2), 28.3 (3), 30.9 (1), 32.9 (2), 36.9 (2), 49.0 (2), 63.2 (2), 79.4 (0), 119.3 (1), 129.5 (1), 140.5 (0), 152.7 (0), 166.7 (0).

LRMS (CI mode, NH_3): m/z = 442 [$(M+NH_4)^+$, 50%], 425 [$(M+H)^+$, 100], 386 [$(M+NH_4-C_4H_8)^+$, 5], 369 [$(M+H-C_4H_8)^+$, 10), 311 [$(M+H-C_8H_{18})^+$, 30).

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 442.3743. $C_{25}H_{48}O_3Si$ + NH_4 requires 442.3716 (error +6.0 ppm).

(*R*)-(*E*,*E*)-(–)-*tert*-Butyl-12-hydroxy-3,5,7-trimethyl-2,4-dodecadieneoate (7.8.1.1):



5.3.11.1
$C_{25}H_{48}O_3Si$ = 427.1

7.8.1.1
$C_{19}H_{34}O_3$ = 310.5

To a solution of the silyl ether **5.3.11.1** (210 mg, 0.494 mmol) in THF (7 mL) at 0°C was added a solution of TBAF•$3H_2O$ (314 mg, 1.2 mmol, 2.4 eq) in THF (3 mL). The yellow solution was warmed to rt, stirred for 1 h then quenched with water (1 mL). The organic phase was diluted with ether (5 mL) and the aqueous phase was extracted with ether (5 mL). Combined ethereal extracts were washed with brine (5 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 80:20 → 60:40) to yield the alcohol **7.8.1.1** (138 mg, 0.444 mmol, 90%) as a colourless oil.

$[\alpha]_D = -12.6°$ (c = 3.15 in $CHCl_3$).

IR (film): ν = 3365 (br s), 2929 (s), 2858 (s), 1708 (s), 1622 (s), 1456 (s), 1391 (s), 1367 (s), 1291 (m), 1240 (s), 1141 (s), 1043 (m), 888 (m) cm^{-1}.

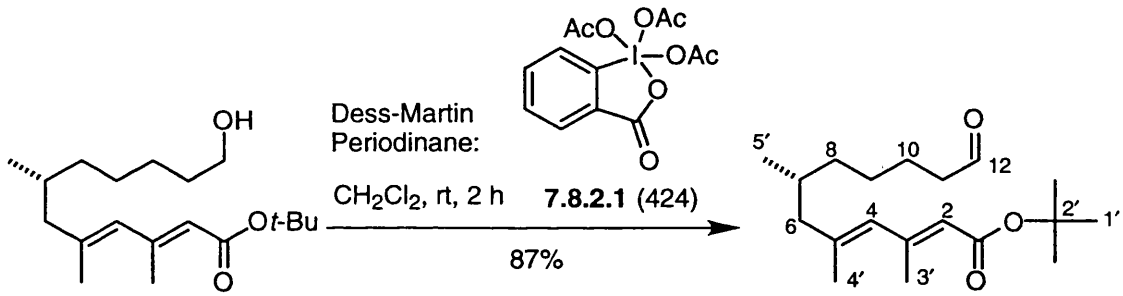
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.80 (3H, d, J = 6.5 Hz, H5′), 1.1-1.7 (9H, m, H7-11), 1.46 (9H, s, H1′), 1.76 (3H, d, J = 1.2 Hz, H4′), 1.79 (1H, dd, J = 12.7, 8.1 Hz, H6), 1.93 (1H, br s, OH), 2.05 (1H, dd, J = 12.7, 5.8 Hz, H6), 2.17 (3H, d, J = 1.2 Hz, H3), 3.61 (2H, t, J = 6.6 Hz, H12), 5.55 (1H, m, H4), 5.65 (1H, s br, H2).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.3 (3), 19.3 (3,3), 26.0 (2), 26.8 (2), 28.2 (3), 30.9 (1), 32.7 (2), 36.8 (2), 48.9 (2), 62.8 (2), 79.5 (0), 119.3 (1), 129.5 (1), 140.5 (0), 152.7 (0), 166.7 (0).

LRMS (CI mode, NH_3): m/z = 328 [$(M+NH_4)^+$, 100%], 311 [$(M+H)^+$, 90], 272 [$(M+NH_4-C_4H_8)^+$, 70], 255 [$(M+H-C_4H_8)^+$, 15).

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 328.2842. $C_{19}H_{34}O_3 + NH_4$ requires 328.2851 (error –2.7 ppm).

(*R*)-(*E*,*E*)-(–)-*tert*-Butyl-12-oxo-3,5,7-trimethyl-2,4-dodecadieneoate (7.8.2.2):



7.8.1.1
$C_{19}H_{34}O_3$ = 310.5

7.8.2.2
$C_{19}H_{32}O_3$ = 308.5

To a solution of the alcohol **7.8.1.1** (385 mg, 1.24 mmol) in CH_2Cl_2 (12 mL) was added the Dess-Martin periodinane (**7.8.2.1**) (873 mg, 2.06 mmol, 1.7 eq). The reaction mixture was stirred for 2 h then quenched with 1:1 saturated aqueous $Na_2S_2O_3$:saturated aqueous NH_4Cl (50 mL). The mixture was stirred vigorously for 10 min then the organic phase was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (25 mL) and the combined extracts were washed with saturated $NaHCO_3$ (5 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 90:10) to yield the aldehyde **7.8.2.2** (332 mg, 1.076 mmol, 87%) as a colourless oil.

$[\alpha]_D$ = –13.7° (c = 3.41 in $CHCl_3$).

IR (film): ν = 2931 (s), 2716 (m), 1728 (s), 1708 (s), 1622 (m), 1456 (m), 1391 (m), 1367 (m), 1239 (m), 1140 (s), 1016 (w), 889 (w) cm^{-1}.

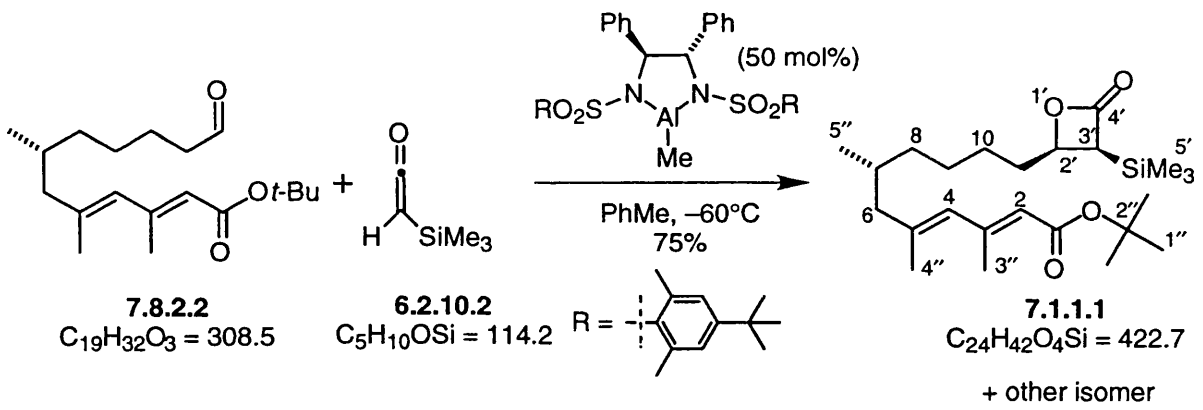
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.81 (3H, d, J = 6.4 Hz, H5′), 1.1-1.6 (7H, m, H7-10), 1.48 (9H, s, H1′), 1.78 (3H, d, J = 1.1 Hz, H4′), 1.81 (1H, dd, J = 12.8, 8.4 Hz, H6), 2.06 (1H, dd, J = 12.8, 5.6 Hz, H6), 2.19 (3H, d, J = 1.1 Hz, H3′), 2.43 (2H, dt, J = 6.2, 1.5 Hz, H11), 5.56 (1H, m, H4), 5.66 (1H, br s, H2), 9.77 (1H, t, J = 1.6 Hz, H12).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.5 (3), 19.5 (3), 19.6 (3), 22.5 (2), 26.8 (2), 28.5 (3), 31.0 (1), 36.7 (2), 44.1 (2), 49.1 (2), 79.7 (2), 119.5 (1), 129.8 (1), 140.5 (0), 152.8 (0), 166.9 (0), 202.9 (1).

LRMS (CI mode, NH_3): m/z = 326 [$(M+NH_4)^+$, 100%], 309 [$(M+H)^+$, 20], 270 [$(M+NH_4-C_4H_8)^+$, 70], 253 [$(M+H-C_4H_8)^+$, 5).

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 326.2692. $C_{19}H_{32}O_3$ + NH_4 requires 326.2692 (error –1.1 ppm).

(2′*R*,3′*S*)-7*R*)-(*E*,*E*)-(+)-*tert*-Butyl-11-[3′-trimethylsilyl-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoate (7.1.1.1):



7.8.2.2
$C_{19}H_{32}O_3$ = 308.5

6.2.10.2
$C_5H_{10}OSi$ = 114.2

7.1.1.1
$C_{24}H_{42}O_4Si$ = 422.7
+ other isomer

To a solution of the bis-sulfonamide **7.5.18.4** (342 mg, 0.517 mmol) in toluene (20 mL) was added trimethylaluminium (0.25 mL of a 2.0 M solution in toluene, 0.50 mmol). The chiral Lewis acid was stirred at rt for 10 min then cooled to –70°C when the aldehyde **7.8.2.2** (304 mg, 0.985 mmol) in toluene (5 mL + 2 x 1 mL rinses) was added dropwise. The mixture was stirred for 5 min then trimethylsilylketene (**6.2.10.2**) (146 mg, 1.28 mmol) in toluene (5 mL) was added dropwise. The reaction was stirred warming to 0°C over 2 h when it was quenched with saturated aqueous NH_4Cl (5 mL). The organic phase was diluted with ether (20 mL) and the aqueous phase was extracted with more ether (20 mL). The combined extracts were washed with 1 N HCl (10 mL), brine (20 mL), dried, filtered and concentrated to a colourless oil which was chromatographed (SiO_2, petrol:Et_2O = 95:5 → 80:20) to yield the *cis* β-lactones **7.1.1.1** and **7.8.3.1** (279 mg, 0.660 mmol, 67%) as a colourless oil (3:1 ratio of *cis* diastereoisomers in favour of **7.1.1.1**) and a 1:1.3 *cis*:*trans* mixture (32 mg, 0.076 mmol, 8%) also as a colourless oil. Total yield of β-lactone = 75%. *Cis*:*trans* = 94:6.

Data for *cis* isomer:

$[\alpha]_D = +17.1°$ ($c = 2.765$ in $CHCl_3$).

IR (film): ν = 2929 (s), 2862 (s), 1805 (s), 1705 (s), 1623 (s), 1456 (s), 1390 (s), 1367 (s), 1332 (m), 1292 (s), 1253 (s), 1141 (s), 1004 (m), 913 (m), 847 (s) cm^{-1}.

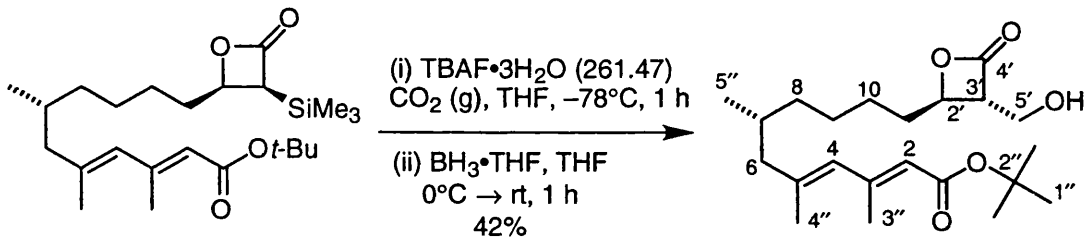
^1H NMR (270 MHz, $CDCl_3$): δ = 0.20 (9H, s, H5′), 0.80 (3H, d, J = 6.5 Hz, H5″), 1.0-1.6 (9H, m, H7-11), 1.45 (9H, s, H1″), 1.75 (3H, d, J = 1.2 Hz, H4″), 1.80 (1H, dd, J = 12.8, 7.8 Hz, H6), 2.03 (1H, dd, J = 12.8, 6.6 Hz, H6), 2.16 (3H, d, J = 1.2 Hz, H3″), 3.31 (1H, d, J = 6.1 Hz, H3′), 4.54 (1H, ddd, J = 9.2, 6.1, 4.8 Hz, H2′), 5.54 (1H, m, H4), 5.63 (1H, br s, H2).

^{13}C NMR (68 MHz, $CDCl_3$): δ = −1.0 (3), 18.4 (3), 19.4 (3), 19.5 (3), 26.7 (2, 2), 28.4 (3), 30.9 (1), 33.6 (2), 36.7 (2), 46.4 (1), 49.0 (2), 74.1 (1), 79.6 (0), 119.4 (1), 129.7 (1), 140.4 (0), 152.7 (0), 166.8 (0), 171.0 (0).

LRMS (CI mode, NH_3): m/z = 423 [$(M+H)^+$, 100%], 367 (18), 349 (30).

Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.43; H, 9.97.

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-(+)-*tert*-Butyl-11-[3′-hydroxymethyl-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoate (8.1.1.1):



7.1.1.1
$C_{24}H_{42}O_4Si$ = 422.7

8.1.1.1
$C_{22}H_{36}O_5$ = 380.5
+ mixture of isomers

Through a solution of TBAF trihydrate (105 mg, 0.402 mmol, 1.1 eq) in THF (10 mL) was bubbled CO_2 *via* a syringe needle for 10 min. The mixture was cooled to −78°C and CO_2 bubbling was continued. To this mixture was added the silyl β-lactone **7.1.1.1** (110 mg, 0.260 mmol) in THF (1.0 mL + 0.5 mL rinse) *via* a syringe pump over 1 h. CO_2 bubbling was stopped and the reaction warmed to rt then poured into 1 N HCl (10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried and concentrated to a colourless oil. Data for the crude carboxylic acid:

^1H NMR (200 MHz, $CDCl_3$): δ (selected signals) = 0.80 (3H, d, J = 6.4 Hz, $CHCH_3$), 1.47 (9H, s, $C(CH_3)_3$), 1.76 (3H, d, J = 1.0 Hz, $O_2CCH{=}CH{=}CCH_3$), 2.05 (1H, dd, J = 13.1, 6.0

Hz, $CH_3CCH_2CHCH_3$), 2.16 (3H, d, J = 1.0Hz, $O_2CCH{=}CCH_3$), 4.20 (1H, d, J = 4.3 Hz, $CHCO_2H$), 4.78 (1H, m, $CHCHCO_2H$), 5.56 (1H, br s, C=CH), 5.65 (1H, br s, C=CH), 8.64 (1H, vbr s, CO_2H).

LRMS (EI mode): m/z = 294 [$(M–CO_2–C_4H_8)^{+\bullet}$, 15%], 277 (14), 125 (100), 122 (30), 95 (15), 57 (13).
HRMS (EI mode): found, $(M–CO_2–C_4H_8)^{+\bullet}$, 294.1824. $C_{22}H_{34}O_6–CO_2–C_4H_8$ requires 294.1831 (error –2.4ppm).

The crude acid was split into 2 batches (c. 55mg each) for borane experiments. The following procedure is representative: to the crude acid (c. 55mg) in THF (5 mL) at 0°C was added borane THF complex (1.0 M in THF, 0.6 mL, 0.6 mmol, 1.6 eq). The reaction was warmed to rt and stirred for 1 h. The reaction was then quenched with methanol (5 mL) and stirred for 10 min. The volatiles were removed *in vacuo* and the resulting oil was chromatographed (SiO_2, petrol:Et_2O = 60:40 → 40:60) to yield the alcohol **8.1.1.1** (21 mg, 0.055 mmol, 42%, over 2 steps) as a colourless oil.

$[\alpha]_D$ = +9.2° (c = 1.515 in $CHCl_3$).

IR (film): ν = 3497 (s br), 2929 (s), 1824 (s), 1705 (s), 1623 (s), 1456 (s), 1367 (s), 1330 (m), 1240 (s), 1141 (s), 1043 (m), 885 (m), 834 (m) cm^{-1}.

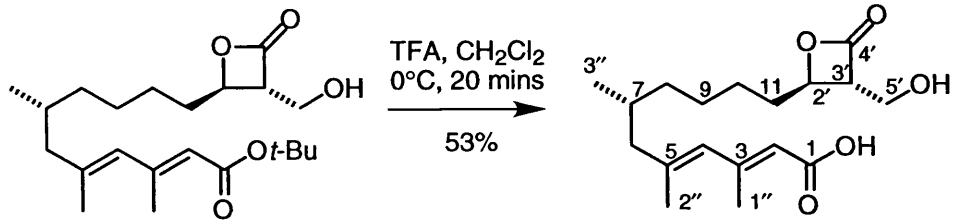
^1H NMR (270 MHz, $CDCl_3$): δ = 0.83 (3H, d, J = 6.4 Hz, H5″), 1.0-2.0 (9H, m, H7-11), 1.47 (9H, s, H1″), 1.78 (3H, d, J = 1.1 Hz, H4″), 1.83 (1H, dd, J = 12.8, 8.0 Hz, H6), 2.06 (1H, dd, J = 12.8, 6.2 Hz, H6), 2.19 (3H, d, J = 1.1 Hz, H3″), 3.39 (1H, q, J = 4.6 Hz, H3′), 3.88 (1H, dd, J = 11.5, 4.1 Hz, H5′), 4.03 (1H, dd, J = 11.7, 4.8 Hz, H5′), 4.58 (1H, ddd, J = 7.1, 5.7, 4.1 Hz, H2′), 5.57 (1H, br s, H4), 5.67 (1H, br s, H2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6 (3), 19.7 (3), 19.7 (3), 25.4 (2), 26.8 (2), 28.5 (3), 31.0 (1), 34.2 (2), 36.7 (2), 49.1 (1), 58.3 (2), 58.8 (1), 75.1 (1), 79.9 (0), 119.5 (1), 129.8 (1), 140.6 (0), 152.9 (0), 167.0 (0), 169.9 (0).

LRMS (EI mode): m/z = 324 [$(M–C_4H_8)^{+\bullet}$, 16%], 308 (15), 280 (5), 162 (10), 125 (100), 122 (24), 95 (17), 57 (28).

HRMS (EI mode): found, $(M–C_4H_8)^{+\bullet}$, 324.1933. $C_{18}H_{28}O_5$ requires 324.1937 (error –1.2 ppm).

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-11-[3′-hydroxymethyl-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic acid (1233A, 1.5.1.1):



8.1.1.1
$C_{24}H_{42}O_4Si$ = 422.7

1.5.1.1
$C_{18}H_{28}O_5$ = 324.4

To a solution of the ester **8.1.1.1** (33 mg, 0.0087 mmol) in CH_2Cl_2 (2 mL) at rt was added trifluoroacetic acid (1.5 mL). The reaction mixture was stirred at rt for 20 min then the volatiles were removed *in vacuo*. CH_2Cl_2 (2 mL) was added and evaporated. This was repeated twice and the crude product purified by chromatography (SiO_2, CH_2Cl_2:MeOH = 99:1 → 92:8) to give the natural product 1233A (**1.5.1.1**) (15 mg, 0.0046 mmol, 53%) as a colourless oil.

$[\alpha]_D$ = +28.8° (*c* = 0.25 in $CHCl_3$) (lit.[36] +28.6° (*c* = 0.62 in $CHCl_3$).

UV: λ_{max} = 271 nm (ε = 12,030) (lit.[18] 267nm, 12,150).

IR (film): ν = 3500-2500 (br s), 3389 (br s), 2925 (s), 2855 (s), 1820 (s), 1689 (s), 1614 (s), 1462 (m), 1379 (m), 1256 (m), 1142 (m) cm^{-1}.

LRMS (EI mode): *m/z* = 324 ($M^{+\bullet}$, 2%), 162 (8), 125 (100), 122 (24), 95 (22), 41 (27).

HRMS (EI mode): found, $M^{+\bullet}$, 324.1928. $C_{18}H_{28}O_5$ requires 324.1937 (error –2.7 ppm).

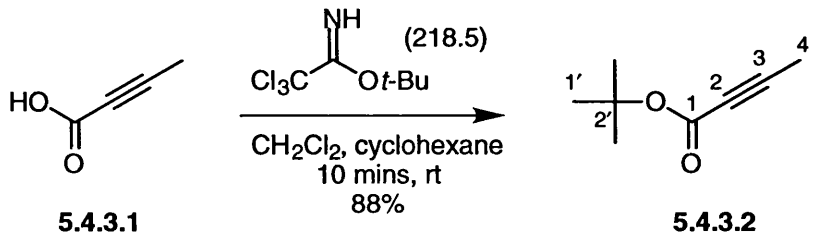
^{1}H NMR (diagnostic signals):

lit:[42] 200 MHz, $CDCl_3$; ref. TMS	Synthetic: 360 MHz, $CDCl_3$; ref. $CHCl_3$
0.83 (3H, d, J = 6.4 Hz)	0.85 (3H, d, J = 6.1 Hz, H3″)
1.80 (3H, s)	1.82 (3H, d, J = 1.1 Hz, H1″)
2.08 (1H, dd, J = 12.8, 6.3 Hz)	2.09 (1H, dd, J = 12.8, 6.4 Hz, H6)
2.23 (3H, s)	2.25 (3H, d, J = 1.1 Hz, H2″)
3.39 (1H, q, J = 4.2 Hz)	3.42 (1H, q, J = 4.3 Hz, H3′)
3.87 (1H, dd, J = 11.6, 4.0 Hz)	3.90 (1H, dd, J = 11.4, 4.0 Hz, H5′)
4.04 (1H, dd, J = 11.6, 5.0 Hz)	4.06 (1H, dd, J = 11.6, 4.6 Hz, H5′)
4.57 (1H, ddd, J = 7.0, 6.2, 4.5 Hz)	4.60 (1H, ddd, J = 7.3, 5.8, 4.1 Hz, H2′)
5.67 (1H, s)	5.69 (1H, s, H2)
5.71 (1H, s)	5.73 (1H, s, H4)

^{13}C NMR:

lit:[42] 50 MHz, $CDCl_3$; ref. TMS	Synthetic: 90 MHz, $CDCl_3$; ref. $CHCl_3$
18.5 (3)	18.7 (3)
19.4 (3)	19.6 (3)
19.9 (3)	20.2 (3)
25.1 (2)	25.4 (2)
26.6 (2)	26.8 (2)
30.9 (1)	31.1 (1)
33.9 (2)	34.2 (2)
36.5 (2)	36.8 (2)
48.9 (2)	49.2 (2)
58.0 (2)	58.3 (2)
58.6 (1)	58.8 (1)
74.9 (1)	75.1 (1)
116.6 (1)	116.6 (1)
129.5 (1)	129.7 (1)
142.1 (0)	142.3 (0)
157.0 (0)	157.2 (0)
169.8 (0)	169.9 (0)
171.7 (0)	171.0 (0)

***tert*-Butyl-2-butynoate (5.4.3.2):**



5.4.3.1
$C_4H_4O_2$ = 84.1

5.4.3.2
$C_8H_{12}O_2$ = 140.2

To a solution of tetrolic acid (**5.4.3.1**) (1.268 g, 15.08 mol) in CH_2Cl_2 (15 mL) at rt was added a solution of *tert*-butyltrichloroacetimidate (6.25 g, 28.60 mmol, 1.9 eq). The reaction was stirred for 10 min when the crystals of trichloroacetamide were filtered and washed with 1:1 ether:petrol (20 mL). The filtrate was concentrated to a yellow oil by distillation, at atmospheric pressure, then chromatographed (SiO_2, petrol:Et_2O = 95:5). The solvent was removed by distillation to give the ester **5.4.3.2** (1.58 g, 11.3 mmol, 75%) as a colourless oil. An analytical sample may be prepared by Kugelrohr distillation (100°C (bath) @ 20 mmHg). We were unable to obtain a satisfactory microanalysis.

IR (film): ν = 2981 (s), 2248 (s), 1708 (s), 1370 (m), 1281 (s), 1162 (s), 1073 (s), 843 (m), 755 (m) cm^{-1}.

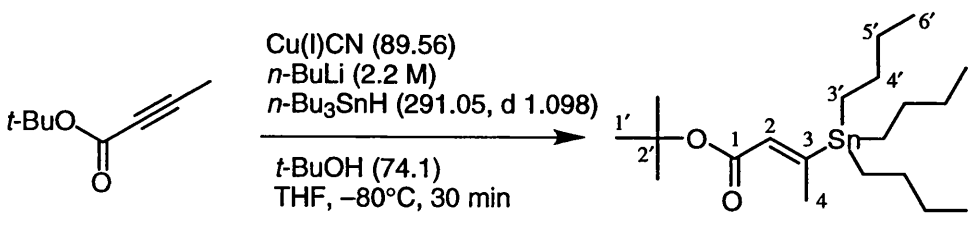
^1H NMR (200 MHz, $CDCl_3$): δ = 1.43 (9H, s, H1′), 1.91 (3H, s, H4).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 3.7 (3), 28.0 (3), 73.8 (0), 82.86 (0), 82.92 (0), 152.8 (0).

LRMS (EI mode): *m/z* = 83 [$(M-C_4H_9)^+\bullet$, 75%], 67 (100), 57 (65), 41 (40).

HRMS (CI mode, NH_3): found, $(M+H)^+$, 141.0910. $C_8H_{12}O_2$ + H requires 141.0916 (error –4.0 ppm).

***tert*-Butyl-3-(tributylstannyl)-2-butenoate (5.4.3.3):**



5.4.3.2
$C_8H_{12}O_3$ = 140.2

91%

5.4.3.3
$C_{20}H_{40}O_2Sn$ = 431.2

To a suspension of copper (I) cyanide (1.11 g, 12.4 mmol, 1.2 eq) in THF (30 mL) at –70°C was added *n*-BuLi (2.5 M in hexanes, 10.0 mL, 25.0 mmol, 2.5 eq). The mixture was

warmed to –30°C and stirred until homogeneous (10 min). The yellow mixture was cooled back to –70°C and tributyltin hydride (6.6 mL, 7.247 g, 24.9 mol, 2.5 eq) added neat. Slight foaming of the solution occurred. The stannyl cuprate was stirred for 5 min at –75°C then *tert*-butanol (920 mg, 12.42 mmol, 1.2 eq) added as a solution in THF (6 mL). More vigorous foaming occurred. To the now red mixture was added the acetylene **5.4.3.2** (1.45 g, 10.34 mmol) in THF (9 mL). The reaction was maintained at below –75°C for 30 min then quenched with a pH 8 solution of ammonia/saturated ammonium chloride (25 mL), warmed to rt and poured into ether/water. The emulsion was filtered through celite and the aqueous phase extracted with ether (2 x 100 mL). Combined ethereal layers were washed with brine (50 mL), dried and concentrated to a colourless oil whih was chromatographed (SiO_2, petrol:Et_2O = 99:1 → 96:4) to yield the product **5.4.3.3** (4.056 g, 9.4 mmol, 91%) as a colourless oil.

An analytical sample may be prepared by Kugelrohr distillation (100°C (bath) @ 0.5 mmHg).

IR (film): ν = 2958 (s), 2927 (s), 2872 (s), 2853 (s), 1711 (s), 1598 (m), 1457 (m), 1366 (s), 1341 (m), 1148 (s), 865 (m) cm^{-1}.

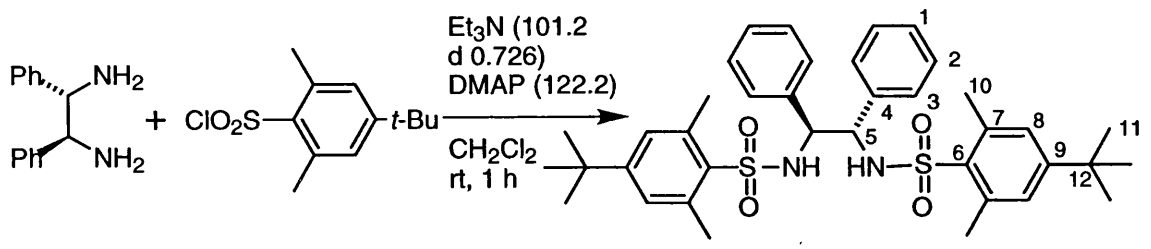
^1H NMR (360 MHz, $CDCl_3$): δ = 0.92 (15H, m, H5′, 6′), 1.32 (6H, m, H4′), 1.47 (6H, m, H3′), 1.49 (9H, s, H1′), 2.36 (3H, d, J = 1.8 Hz, H4), 5.86 (1H, q, J = 1.8 Hz, H2).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 9.6 (2), 13.8 (3), 22.3 (3), 27.5 (2), 28.5 (3), 29.2 (2), 79.9 (0), 130.2 (1), 164.4 (0), 166.7 (0).

LRMS (EI mode): *m/z* = 431 ($M^{+\circ}$, 10%), 375 (100), 319 (100), 263 (30), 233 (10), 205 (30), 177 (30), 135 (12), 121 (15), 57 (60), 41 (32).

Anal. Calcd for $C_{20}H_{40}O_2Sn$: C, 55.71; H, 9.35. Found: C, 55.73; H, 9.32.

(S,S)-(–)-*N,N'-bis*-(2,6-dimethyl-4-*tert*-butylbenzenesulfonyl)-1,2-diphenylethylenediamine (7.5.18.4):



7.5.14.4
$C_{14}H_{16}N_2$ = 212.3 $C_{12}H_{15}ClO_2S$ = 258.8

90%

7.5.18.4
$C_{38}H_{48}N_2O_4S_2$ = 660.9

To a solution of the diamine **7.5.14.4** (264 mg, 1.24 mmol) in CH_2Cl_2 (6 mL) at rt was added triethylamine (0.57 mL, 4.09 mmol) and DMAP (24 mg, 0.2 mmol). The colourless solution was stirred at rt and a solution of 4-*tert*-butyl-2,6-dimethylbenzenesulfonyl chloride (648 mg, 2.48 mmol) in CH_2Cl_2 (2 mL + 2 x 1 mL rinse) was added dropwise *via* syringe. The reaction stirred at rt for 1 h then poured into CH_2Cl_2/1 N HCl (1:1, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with brine (20 mL), dried, filtered and concentrated *in vacuo* to a solid foam which was chromatographed (SiO_2, petrol:Et_2O = 90:10 → 60:40) to give **7.5.18.4** as a white solid foam (738 mg, 1.12 mmol, 90%).

$[\alpha]_D = -89.0°$ (c = 0.52 in $CHCl_3$)

IR (CH_2Cl_2): ν = 3374 (s), 3053 (s), 2968 (s), 1596 (m), 1421 (m), 1321 (m), 1265 (s), 1174 (m), 1146 (m) cm^{-1}.

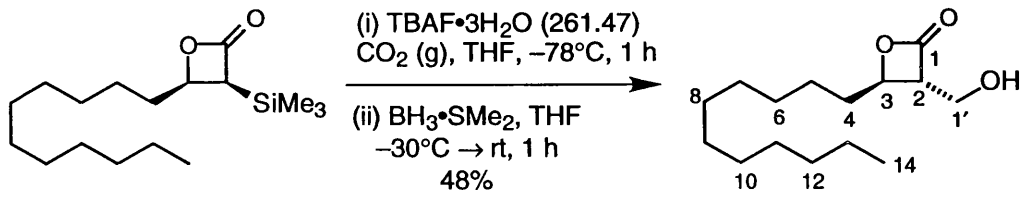
^1H NMR (270 MHz, $CDCl_3$): δ = 1.23 (18H, s, H11), 2.50 (12H, s, H10), 4.41 (2H, dd, J = 3.6, 2.0 Hz, H5), 6.00 (2H, dd, J = 3.6, 2.2 Hz, NH), 6.61 (4H, d, J = 6.8 Hz, H8), 6.86 (10H, m, H1-3).

^{13}C NMR (68 MHz, $CDCl_3$): δ = 23.3 (3), 31.0 (3), 34.6 (0), 62.5 (1), 127.4 (1), 127.8 (1), 128.0 (1), 128.2 (1), 134.1 (0), 136.3 (0), 138.8 (0), 155.0 (0).

LRMS (ES, +ve): m/z = 683 (MNa^+).

Anal. Calcd for $C_{38}H_{48}N_2O_4S_2$: C, 69.06; H, 7.32, N, 4.24. Found: C, 68.85; H, 7.19; N, 4.09.

***trans*-4-Dodecyl-3-(hydroxymethyl)-2-oxetanone (8.2.4.1):**



7.3.2.1
$C_{17}H_{34}O_2Si$ = 298.5

8.2.4.1
$C_{15}H_{28}O_3$ = 256.4

Through a solution of TBAF trihydrate (162 mg, 0.518 mmol, 1.1 eq) in THF (10 mL) was bubbled CO_2 *via* a syringe needle for 10 min. The mixture was cooled to –78°C and CO_2 bubbling was continued. To this mixture was added the silyl *β*-lactone **7.3.2.1** (149 mg, 0.499 mmol) in THF (1.0 mL + 0.5 mL rinse) *via* a syringe pump over 1 h. CO_2 bubbling was stopped and the reaction warmed to rt then poured into 1 N HCl (10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried and concentrated to a colourless oil. Data for the crude carboxylic acid:

IR (film): ν = 3413 (br s), 2924 (s), 2854 (s), 1823 (s), 1727 (s), 1641 (m), 1468 (m), 1381 (m), 1266 (m), 1130 (m) cm^{-1}.

LRMS (ES, –ve): *m/z* = 269 [$(M–H)^-$, 30%], [$(2M–H)^-$, 100].

To a portion of the crude acid (26 mg, 0.096 mmol) in THF (5 mL) at –30°C was added borane DMS complex (10 M, 0.08 mL, 0.8 mmol). The reaction was warmed to rt and stirred for 1 h. The reaction was then quenched with methanol (5 mL) and stirred for 14 h. The volatiles were removed *in vacuo* and the resulting oil was chromatographed (SiO_2, petrol:Et_2O = 90:10 → 60:40) to yield the alcohol **8.2.4.1** (12 mg, 0.049 mmol, 49%, over 2 steps) as a colourless oil.

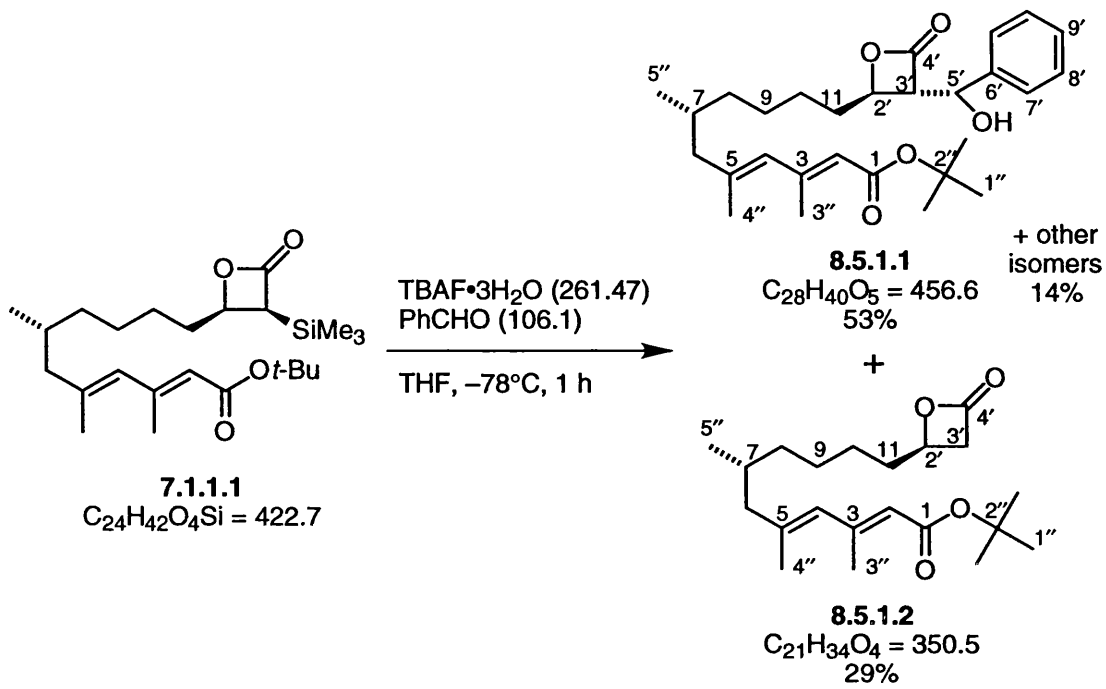
IR (film): ν = 3419 (br s), 2924 (s), 2854 (s), 1811 (s), 1462 (m), 1127 (m), 910 (m) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.90 (3H, t, *J* = 7.0 Hz, H14), 1.25 (18H, m, H5-13), 1.82 (2H, m, H4), 3.41 (1H, dt, *J* = 4.9, 4.1 Hz, H2), 3.89 (1H, dd, *J* = 11.7, 3.9 Hz, H1′), 4.07 (1H, dd, *J* = 11.5, 4.6 Hz, H1′), 4.59 (1H, ddd, *J* = 7.2, 6.1, 4.1 Hz, H3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3 (3), 22.8 (2), 25.0 (2), 29.3 (2), 29.5 (2), 29.57 (2), 29.62 (2), 29.7 (2, 2), 32.0 (2), 34.1 (2), 58.2 (2), 58.8 (1), 75.2 (1), 170.1 (0).

HRMS (ES, +ve): found, $M^{+\bullet}$, 256.2035. $C_{15}H_{28}O_3$ requires 256.2039 (error –1.4 ppm).

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-(+)-*tert*-Butyl-11-[3′-hydroxymethyl-1″-phenyl-4′-oxo-2′-oxetanyl]-3,5,7-trimethylundeca-2,4-dienoate (8.5.1.1) and **(3′*R*,7*R*)-(*E*,*E*)-(+)-*tert*-Butyl-11-(4′-oxo-2′-oxetanyl)-3,5,7-trimethylundeca-2,4-dienoate (8.5.1.2):**



7.1.1.1
$C_{24}H_{42}O_4Si$ = 422.7

8.5.1.1
$C_{28}H_{40}O_5$ = 456.6
53%

8.5.1.2
$C_{21}H_{34}O_4$ = 350.5
29%

A solution of TBAF trihydrate (94 mg, 0.36 mmol, 1.2 eq) in THF (4 mL) was cooled until turbid (–20°C) when benzaldehyde (159 mg, 1.5 mmol, 5 eq) in THF (2 mL) was added. The mixture was cooled to –80°C and a solution of β-lactone **7.1.1.1** (127 mg, 0.300 mmol) in THF (2 mL) was added over 45 min with a syringe pump. After the addition, the reaction was quenched at –70°C with saturated aqueous ammonium chloride (5 mL). The mixture was diluted with ether (10 mL) and water (5 mL), warmed to rt and poured into ether (25 mL) : water (10 mL). The aqueous phase was extracted with ether (10 mL) and combined extracts were dried, filtered and concentrated *in vacuo* to a colourless oil (278 mg) which was chromatographed (SiO_2, petrol:Et_2O = 90:10 → 70:30) to give **8.5.1.1** (72 mg, 0.158 mmol, 53%) as a yellow oil, a mixture of other product isomers (19 mg, 0.042 mmol, 14%) as a colourless oil and desilylated product **8.5.1.2** (30 mg, 0.086 mmol, 29%) as a colourless oil. Yield of desired products = 67%. Total yield 96%.

Data for **8.5.1.1**:

$[\alpha]_D$ = –8.9° (*c* = 3.7 in $CHCl_3$)

IR (film): ν = 3482 (br s), 2930 (s), 1822 (s), 1700 (s), 1652 (m), 1620 (m), 1456 (m), 1370 (m), 1242 (m), 1142 (s), 1018 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.77 (3H, d, J = 6.5 Hz, H5″), 0.90-1.6 (9H, m, H7-11), 1.48 (9H, s, H1″), 1.76 (3H, d, J = 1.1 Hz, H3″), 1.78 (1H, dd, J = 12.2, 7.8 Hz, H6), 2.00 (1H, dd, J = 12.2, 6.5 Hz, H6), 2.18 (3H, d, J = 1.1 Hz, H4″), 2.90 (1H, br s, OH), 3.50 (2H, t, J = 4.0 Hz, H3′), 4.72 (1H, ddd, J = 11.1, 7.1, 4.4 Hz, H2′), 5.24 (1H, d, J = 4.0 Hz, H5′), 5.57 (1H, br s, H2), 5.64 (1H, br s, H4), 7.35 (5H, m, H7′-9′).

^{13}C NMR (90 MHz, $CDCl_3$): δ= 18.5 (3), 19.5 (3), 19.6 (3), 24.8 (2), 26.7 (2), 28.4 (3), 30.9 (1), 34.2 (2), 36.6 (2), 49.0 (2), 63.9 (1), 69.2 (1), 73.8 (1), 79.8 (0), 119.5 (1), 125.4 (1), 128.3 (1), 128.9 (1), 129.8 (1), 140.5 (0), 141.0 (0), 152.9 (0), 167.0 (0), 169.8 (0).

LRMS (CI mode, NH_3): m/z = 474 [$(M+NH_4)^+$, 70%], 457 [$(M+H)^+$, 30), 418 [$(M-C_4H_8+NH_4)^+$,100], 356 [$(M-C_4H_8-CO_2+H)^+$, 60].

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 474.3228. $C_{28}H_{44}NO_5$ requires 474.3219 (error +1.9 ppm).

Data for **8.5.1.2**:

$[\alpha]_D = -1.5°$ (c = 1.45 in $CHCl_3$)

IR (film): ν = 2930 (s), 1830 (s), 1704 (s), 1622 (m), 1456 (m), 1368 (m), 1242 (m), 1142 (s) cm^{-1}.

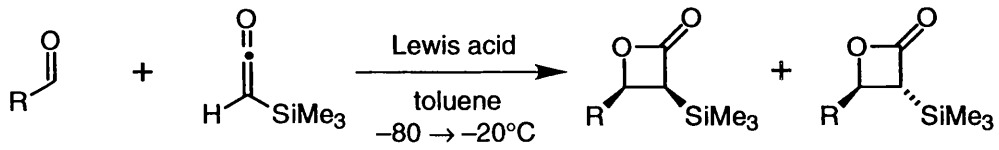
^{1}H NMR (360 MHz, $CDCl_3$): δ= 0.81 (3H, d, J = 6.5 Hz, H5″), 0.85-1.80 (9H, m, H7-11), 1.48 (9H, s, H1″), 1.77 (3H, d, J = 1.1 Hz, H3″), 1.81 (1H, dd, J = 12.4, 7.8 Hz, H6), 2.06 (1H, dd, J = 12.4, 6.4 Hz, H6), 2.18 (3H, d, J = 1.1 Hz, H4″), 3.05 (1H, dd, J = 16.2, 4.2 Hz, H3′), 3.50 (1H, dd, J = 16.2, 5.7 Hz, H3′), 4.50 (1H, dddd, J = 10.2, 7.3, 5.7, 4.2 Hz, H2′), 5.56 (1H, br s, H2), 5.66 (1H, br s, H4).

^{13}C NMR (50 MHz, $CDCl_3$): δ= 18.5 (3), 19.5 (3), 19.6 (3), 25.3 (2), 26.7 (2), 28.4 (3), 31.0 (1), 34.8 (2), 36.7 (2), 43.0 (2), 49.1 (2), 71.4 (1), 79.7 (0), 119.5 (1), 129.8 (1), 140.5 (0), 152.8 (0), 166.9 (0), 168.5 (0).

LRMS (CI mode, NH_3): m/z = 718 [$(2M+NH_4)^+$, 30%], 368 [$(M+NH_4)^+$, 100], 350 [$M+H)^+$,40], 312 (60).

HRMS (CI mode, NH_3): found, $(M+NH_4)^+$, 368.2801. $C_{21}H_{34}O_4 + NH_4$ requires 368.2801 (error +0.1 ppm).

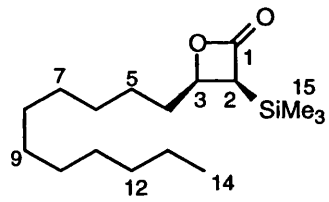
General Procedure for Cycloadditions



Into a flame-dried round-bottomed flask was placed a solution of the appropriate *bis*-sulfonamide in dry toluene (10 mL/mmol), under nitrogen at rt, to which was added trimethylaluminium (2.0 M in toluene). The complex was stirred at rt for 10 mins. After cooling the catalyst to –70°C the aldehyde was added as a solution in toluene. After 5 min, trimethylsilylketene (**6.2.10.2**) in toluene was added dropwise. The reaction was stirred at –70°C initially then warmed until conversion took place, as indicated by TLC, when it was quenched with saturated aqueous ammonium chloride. The aqueous phase was diluted with 1 N HCl (10 mL) then extracted with ether (2 x 10 mL). The combined organic phases were washed with brine then dried, filtered and concentrated *in vacuo* to give the crude product which was purified by flash column chromatography on silica gel eluting with petrol:Et_2O mixtures to give the pure *cis* -β-lactone and the recovered catalyst *bis*-sulfonamide ligand (up to 95% recovery). The *cis*:*trans* ratio was determined from the ^1H NMR of the crude product.

In some cases a stock solution of the chiral Lewis acid was used to facilitate performing several reactions at the same time. In these cases the molarity of the stock solution is given with the number of millimoles employed.

***cis*-4-Dodecyl-3-(trimethylsilyl)-2-oxetanone (7.3.2.1):**



Example (Table 7.5.15, entry 2):

The general procedure was followed with dodecylaldehyde (**7.1.3.6**) (143 mg, 0.78 mmol); ketene **6.2.10.2** (130 mg, 1.14 mmol); catalyst **6.4.16.3** (made from ligand **7.5.1.7** (190 mg, 0.40 mmol, 0.51 eq) and trimethylaluminium (0.2 mL of a 2.0 M solution in toluene, 0.40 mmol, 0.50 eq); chromatography (petrol:Et_2O = 96:4 → 92:8); total yield: 52%, *cis*:*trans* = 100:0.

IR (film): ν = 2925 (s), 2855 (s), 1806 (s), 1466 (m), 1253 (s), 1118 (s), 1003 (m), 847 (s) cm^{-1}.

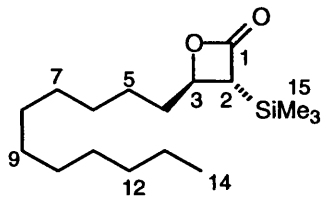
^1H NMR (270MHz, $CDCl_3$): δ = 0.22 (9H, s, H15), 0.88 (3H, t, J = 6.1 Hz, H14), 1.20-1.60 (18H, m, H5-13), 1.78 (2H, m, H4), 3.32 (1H, d, J = 6.1 Hz, H2), 4.57 (1H, ddd, J = 9.4, 6.1, 4.3 Hz, H3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.9 (3), 14.3 (3), 22.9 (2), 26.5 (2), 29.8→29.4 (6x2), 32.1 (2), 33.8 (2), 46.5 (1), 74.3 (1), 171.2 (0).

LRMS (CI mode, NH_3): *m/z* = 316 [$(M+NH_4)^+$, 100%], 299 [$(M+H)^+$, 18], 281 (97), 256 (8), 244 (6), 226 (25), 209 (57), 90 (44), 35 (55).

HRMS (CI mode): found, $(M+NH_4)^+$, 316.26718. $C_{17}H_{34}O_2Si + NH_4$ requires 316.2668 (error –1.2 ppm).

trans-4-Dodecyl-3-(trimethylsilyl)-2-oxetanone (7.3.2.1):

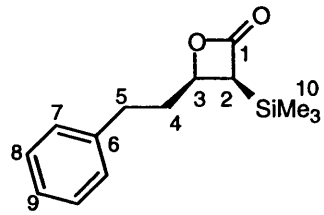


IR (film): ν = 2926 (s), 2855 (s), 1804 (s), 1466 (m), 1253 (s), 1125 (m), 1097 (m), 849 (s) cm^{-1}.

^1H NMR (270MHz, $CDCl_3$): δ = 0.17 (9H, s, H15), 0.87 (3H, t, *J* = 7.0 Hz, H14), 1.20-1.45 (18H, m, H5-13), 1.70 (1H, m, H4), 1.90 (1H, m, H4), 2.90 (1H, d, *J* = 4.0 Hz, H2), 4.24 (1H, dt, *J* = 9.0, 4.0 Hz, H3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.8 (3), 14.3 (3), 22.9 (2), 26.5 (2), 29.8→29.4 (6x2), 32.1 (2), 35.9 (2), 48.5 (1), 72.9 (1), 171.2 (0).

cis-4-(1′-Phenylethyl)-3-(trimethylsilyl)-2-oxetanone (7.3.2.3):



Example (Table 7.5.15, entry 4):
General procedure was followed with phenylpropionaldehyde (**7.1.3.5**) (145 mg, 1.08 mmol); ketene **6.2.10.2** (130 mg, 1.14 mmol); catalyst **6.4.16.3** (8 mL of 0.027 M in toluene, 0.22 mmol, 0.20 eq); chromatography (petrol:Et_2O = 90:10 → 80:20); total yield: 81%, *cis:trans* = 95:5.

IR (film): ν = 1801 (s), 1497 (m), 1455 (m), 1386 (m), 1298 (m), 1254 (s), 1114 (s), 1075 (m), 1000 (s), 847 (s) cm^{-1}.

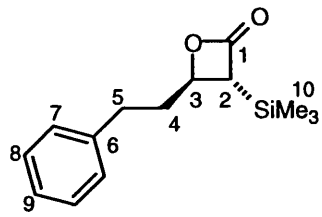
^1H NMR (270 MHz, C_6D_6): δ = 0.05 (9H, s, H10), 1.72 (1H, dddd, *J* = 13.8, 10.1, 7.8, 2.9 Hz, H4), 1.97 (1H, dddd, *J* = 13.8, 10.9, 8.6, 4.8 Hz, H4), 2.53 (1H, m, H5), 2.75 (1H, ddd, *J*

= 13.6, 9.2, 4.7 Hz, H5), 2.78 (1H, d, J = 6.2 Hz, H2), 4.12 (1H, ddd, J = 10.9, 6.2, 2.9 Hz, H3), 7.15 (5H, m, H7-9).

^{13}C NMR (68 MHz, C_6D_6): δ = –0.8 (3), 32.9 (2), 36.1 (2), 46.7 (1), 72.7 (1), 127.0 (1), 129.2 (1), 129.3 (1), 141.3 (0), 171.0 (0).

LRMS (CI mode, NH_3)): m/z = 321 [(M+TMS)$^+$, 15%], 291 (15), 266 [(M+NH_4)$^+$, 32], 249 [(M+H)$^+$, 22], 231 [(M+H–H_2O)$^+$, 62], 159 [(M+H–HOTMS)$^+$, 100], 134 (20).

trans-4-(1′-Phenylethyl)-3-(trimethylsilyl)-2-oxetanone (7.3.2.3):



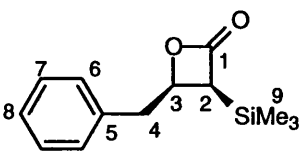
IR (film): ν = 2953 (m), 1805 (s), 1497 (m), 1455 (m), 1253 (s), 1107 (s), 849 (s) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.20 (9H, s, H10), 2.06 (1H, m, H4), 2.19 (1H, m, H4), 2.69 (1H, ddd, J = 14.0, 9.7, 6.5 Hz, H5), 2.80 (1H, ddd, J = 13.5, 10.0, 5.4 Hz, H5), 2.97 (1H, d, J = 4.0 Hz, H2), 4.30 (1H, ddd, J = 7.3, 5.4, 4.1 Hz, H3), 7.23 (5H, m).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –2.8 (3), 31.6 (2), 37.7 (2), 48.5 (1), 72.1 (1), 126.5 (1), 128.4 (1), 128.8 (1), 140.5 (0), 170.8 (0).

LRMS (CI mode, NH_3)): *m/z* = 266 [(M+NH_4)$^+$, 59%], 249 [(M+H)$^+$, 48], 233 (20), 159 [(M+H–HOTMS)$^+$, 100], 143 (13), 134 (17), 130 (18), 115 (10).

cis-4-(Phenylmethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.1):



Example (Table 7.5.15, entry 5):
The general procedure was followed with phenylacetaldehyde (**7.1.3.4**) (98 mg, 0.82 mmol); ketene **6.2.10.2** (130 mg, 1.14 mmol); catalyst **6.4.16.3** (6 mL of 0.027 M in toluene, 0.16 mmol, 0.20 eq); chromatography (petrol:Et_2O = 90:10); total yield: 81%, *cis*:*trans* = 84:16.

Recrystallised from pentane:CH_2Cl_2 (2:1) in the freezer (–18°C) to give colourless needles.

mp: 100-101.5°C
IR (CH_2Cl_2): ν = 2961 (m), 1803 (s), 1266 (s), 1111 (s), 1002 (m), 848 (s) cm^{-1}.

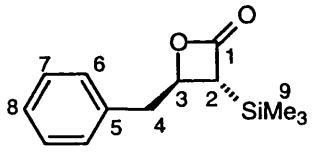
^{1}H NMR (270 MHz, C_6D_6): δ = 0.05 (9H, s, H9), 2.66 (1H, dd, J = 14.7, 3.1 Hz, H4), 2.79 (1H, d, J = 6.2 Hz, H2), 2.94 (1H, dd, J = 14.7, 10.4 Hz, H4), 4.32 (1H, ddd, J = 10.5, 6.2, 3.1 Hz, H3), 7.15 (5H, m, H6-8).

^{13}C NMR (68 MHz, C_6D_6): δ = –0.8 (3), 40.6 (2), 47.1 (1), 73.9 (1), 127.6 (1), 129.3 (1), 129.6 (1), 137.9 (0), 170.0 (0).

LRMS (CI mode, NH_3): m/z = 252 [$(M+NH_4)^+$, 21%], 235 [$(M+H)^+$, 20], 217 [$(M+H-H_2O)^+$, 70], 175 (10), 145 [$(M+H-HOTMS)^+$, 100].

Anal. Calcd for $C_{13}H_{18}O_2Si$: C, 66.62; H, 7.74. Found: C, 66.32; H, 7.67.

trans-4-(Phenylmethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.1):



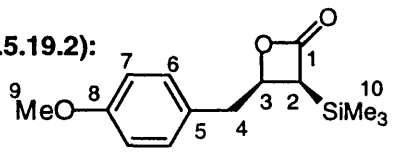
IR (film): ν = 2967 (m), 1806 (s), 1265 (s), 1108 (s), 1001 (m), 849 (s) cm^{-1}.

^{1}H NMR (270 MHz, C_6D_6): δ = 0.15 (9H, s, H9), 2.50 (1H, dd, J = 13.5, 8.3 Hz, H4), 2.72 (1H, d, J = 4.1 Hz, H2), 3.02 (1H, dd, J = 13.5, 5.6 Hz, H4), 4.16 (1H, ddd, J = 13.6, 7.7, 5.9 Hz, H3), 7.15 (5H, m, H6-8).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –3.1 (3), 42.0 (2), 48.1 (1), 72.7 (1), 127.5 (1), 129.0 (1), 129.4 (1), 135.4 (0), 170.5 (0).

LRMS (CI mode, NH_3): m/z = 252 [$(M+NH_4)^+$, 72%], 235 [$(M+H)^+$, 99], 217 [$(M+H-H_2O)^+$, 20], 145 [$(M+H-HOTMS)^+$, 100], 136 (28).

cis-3-(_p_-Methoxyphenylmethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.19.2):



Example (Table 7.5.27, entry 10):
The general procedure was followed with *para*-methoxyphenylacetaldehyde (**7.5.19.1**) (74 mg, 0.49 mmol); ketene **6.2.10.2** (74 mg, 0.65 mmol); catalyst **7.5.26.4** (made from *bis*-sulfonamide ligand (100 mg, 0.142 mmol, 0.29 eq) and trimethylaluminium (0.07 mL of a 2.0 M solution in toluene, 0.140 mmol, 0.29 eq); chromatography (petrol:Et_2O = 95:5); total yield: 81%, *cis*:*trans* = 70:30.

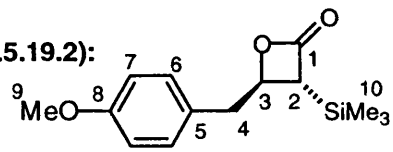
IR (CH_2Cl_2): ν = 2958 (m), 1799 (s), 1612 (m), 1514 (s), 1251 (s), 1114 (m), 844 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (9H, s, H10), 3.00 (1H, dd, J = 14.6, 3.6 Hz, H4), 3.09 (1H, dd, J = 14.7, 10.1 Hz, H4), 3.43 (1H, d, J = 6.1 Hz, H2), 3.80 (3H, s, H9), 4.78 (1H, ddd, J = 9.9, 6.2, 3.5 Hz, H3), 6.85 (2H, dm, J = 8.7 Hz, H6), 7.17 (2H, dm, J = 8.7 Hz, H7),

^{13}C NMR (68 MHz, $CDCl_3$): δ = –0.9 (3), 39.1 (2), 46.6 (1), 55.4 (3), 74.5 (1), 114.2 (1), 129.0 (0), 130.0 (1), 158.8 (0), 170.7 (0).

LRMS (ES, +ve): m/z = 815 [(3M+Na)$^+$], 551 [(2M+Na)$^+$, 100%], 546 [(2M+NH_4)$^+$], 460 , 282 [(M+NH_4)$^+$], 265 [(M+H)$^+$], 175.

trans-3-(_p_-Methoxyphenylmethyl)-2-(trimethylsilyl)-2-oxetanone (7.5.19.2):

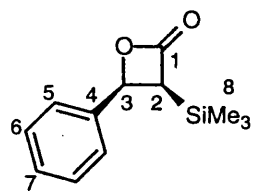


IR (CH_2Cl_2): ν = 2956 (m), 1806 (s), 1612 (m), 1514 (s), 1251 (s), 1102 (m), 1035 (m), 844 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (9H, s, H10), 2.87 (1H, dd, J = 13.7, 7.3 Hz, H4), 2.98 (1H, d, J = 4.0 Hz, H2), 3.25 (1H, dd, J = 13.8, 5.7 Hz, H4), 3.80 (3H, s, H9), 4.39 (1H, ddd, J = 7.3, 5.7, 2.4 Hz, H3), 6.88 (2H, dm, J = 8.7 Hz, H6), 7.14 (2H, dm, J = 8.7 Hz, H7)

^{13}C NMR (68 MHz, $CDCl_3$): δ = –3.1 (3), 41.0 (2), 47.9 (1), 55.5 (3), 72.8 (1), 114.4 (1), 127.3 (0), 130.4 (1), 159.0 (0), 170.6 (0).

cis-4-Phenyl-3-(trimethylsilyl)-2-oxetanone (6.2.10.4):



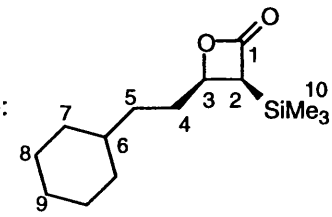
Example (Table 7.5.15, entry 6):
The general procedure was followed with benzaldehyde (**7.1.3.1**) (85 mg, 0.80 mmol); ketene **6.2.10.2** (113 mg, 0.99 mmol); catalyst **6.4.16.3** (2.1 mL of 0.0767 M in toluene, 0.16 mmol, 0.20 eq); chromatography (petrol:Et_2O = 90:10); total yield (crude): 84%, *cis*:*trans* = 100:0.

This compound was unstable and was not purified.

IR (film): ν = 1959 (m), 1801 (s), 1383 (s), 1253 (s), 1198 (s), 1148 (s), 849 (s) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = –0.08 (9H, s, H8), 3.73 (1H, d, J = 6.5 Hz, H2), 5.72 (1H, d, J = 6.5 Hz, H3), 7.30 (5H, m, H5-7).

***cis*-4-(1′-Cyclohexylethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.2):**



Example (Table 7.5.15, entry 7):
The general procedure was followed with cyclohexylpropionaldehyde (**7.1.3.9**) (106 mg, 0.76 mmol); ketene **6.2.10.2** (111 mg, 0.97 mmol); catalyst **6.4.16.3** (2 mL of 0.0767 M in toluene, 0.153 mmol, 0.20 eq); chromatography (petrol:Et_2O = 95:5); total yield: 75%, *cis*:*trans* = 97:3.

Recrystallised from pentane in the freezer (–20°C) to give colourless needles.

mp: 44-5°C.

IR (film): ν = 2922 (s), 2851 (s), 1798 (s), 1450 (m), 1387 (m), 1282 (m), 1253 (s), 1122 (s), 1005 (m), 846 (s) cm^{-1}.

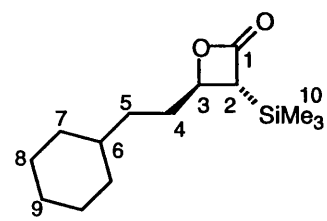
^1H NMR (270 MHz, $CDCl_3$): δ = 0.25 (9H, s, H10), 0.90 (2H, m, H9), 1.22 (5H, m, H4,5,7,8), 1.44 (1H, m, H6), 1.70 (7H, m, H4,5,7,8), 3.33 (1H, d, J =6.1 Hz, H2), 4.54 (1H, m, H3).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –0.9 (3), 26.4 (2), 26.7 (2, 2), 31.1 (2), 33.3 (2), 33.4 (2), 33.9 (2), 37.4 (1), 46.5 (1), 74.6 (1), 171.1 (0).

LRMS (CI mode, NH_3): *m/z* = 327 [$(M+TMS)^+$, 10%], 272 [$(M+NH_4)^+$, 35], 255 [$(M+H)^+$, 30], 237 [$(M+H–H_2O)^+$, 100], 165 [$(M+H–HOTMS)^+$, 95].

Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.07; H, 10.35.

***trans*-4-(1′-Cyclohexylethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.2):**

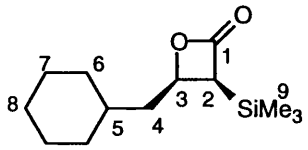


^1H NMR (270 MHz, $CDCl_3$): δ = 0.20 (9H, s, H10), 0.88 (2H, m, H4-9), 1.22 (5H, m, H4-9), 1.55 (1H, m, H4-9), 1.70 (7H, m, H4-9), 2.90 (1H, d, J =4.1 Hz, H2), 4.23 (1H, dt, J = 6.6, 4.1 Hz, H3).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –2.8 (3), 26.4 (2), 26.7 (2), 32.7 (2), 33.3 (2), 33.4 (2), 37.5 (1), 48.5 (1), 73.2 (1), 171.0 (0).

LRMS (CI mode, NH_3): *m/z* = 327 [(M+TMS)$^+$, 58%], 272 [(M+NH_4)$^+$, 31], 255 [(M+H)$^+$, 100], 239 [(M+H–H_2O)$^+$, 38], 212 (19), 195 (22), 165 (47), 154 (13), 143 (20), 114 (18).

cis-4-(1′-Cyclohexylmethyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.3):



Example (Table 7.5.15, entry 8):
The general procedure was followed with cyclohexylacetaldehyde (**7.1.3.8**) (101 mg, 0.80 mmol); ketene **6.2.10.2** (113 mg, 0.99 mmol); catalyst **6.4.16.3** (2.1 mL of 0.0767 M in toluene, 0.16 mmol, 0.20 eq); chromatography (petrol:Et_2O = 98:2); total yield: 73%, *cis*:*trans* = 96:4. Inseparable isomers. Characterised as mixture.

Recrystallised from pentane in the freezer (–20°C) to give colourless needles (note: crysyals dissolve in pentane at rt).

mp: 54-5°C.

IR (film): ν = 2925 (s), 2853 (s), 1802 (s), 1449 (m), 1385 (m), 1195 (s), 847 (s) cm^{-1}.

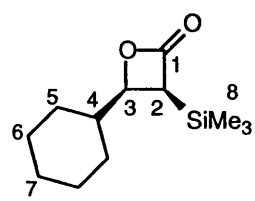
^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.22 (9H, s, H9), 0.95-1.65 (13H, m, H4-8), 3.33 (1H, d, *J* = 6.2 Hz, H2), 4.70 (1H, ddd, *J* = 10.7, 6.2, 2.9 Hz, H3).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –0.9 (3), 26.2 (2), 26.3 (2), 26.5 (2), 32.7 (2), 33.9 (2), 35.2 (2), 41.1 (1), 46.1 (1), 72.3 (1), 171.0 (0).

LRMS (CI mode, NH_3): *m/z* = 313 [(M+TMS)$^+$, 25%], 258 [(M+NH_4)$^+$, 40], 241 [(M+H)$^+$, 39], 223 [(M+HH_2O)$^+$, 99], 151 [(M+H–HOTMS)$^+$, 100].

Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.81; H, 10.01.

cis-4-Cyclohexyl-3-(trimethylsilyl)-2-oxetanone (7.3.2.2):



Example (Table 7.5.15, entry 9):
The general procedure was followed with cyclohexane carboxaldehyde (**7.1.3.7**) (82 mg, 0.73 mmol); ketene **6.2.10.2** (91 mg, 0.80 mmol); catalyst **6.4.16.3** (5.5 mL of 0.027 M in toluene,

0.15 mmol, 0.20 eq); chromatography (petrol:Et_2O = 92:8); total yield: 71%, *cis*:*trans* = 88:12.

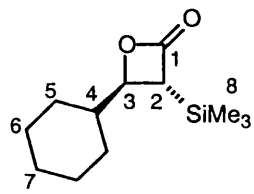
IR (film): ν = 2930 (s), 2854 (s), 1804 (s), 1451 (m), 1275 (s), 1253 (s), 1188 (m), 1128 (s), 848 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.25 (9H, s, H8), 0.90-1.70 (10H, m, H5-7), 1.99 (1H, d, *J* = 12.7 Hz, H4), 3.29 (1H, d, *J* = 6.0 Hz, H2), 4.21 (1H, dd, *J* = 10.4, 6.0 Hz, H3).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –0.6 (3), 25.3 (2), 25.4 (2), 26.1 (2), 28.8 (2), 29.2 (2), 40.9 (1), 46.2 (1), 78.2 (1), 171.2 (0).

LRMS (CI mode, NH_3): *m/z* = 299 [$(M+TMS)^+$, 10%], 244 [$(M+NH_4)^+$, 27], 227 [$(M+H)^+$, 40], 209 [$(M+H-H_2O)^+$, 70], 137 [$(M+H-HOTMS)^+$, 100].

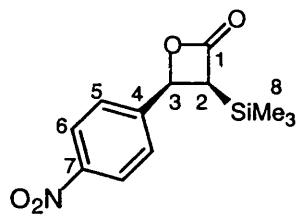
trans-4-Cyclohexyl-3-(trimethylsilyl)-2-oxetanone (7.3.2.2):



^1H NMR (270 MHz, $CDCl_3$): δ = 0.20 (9H, s, H8), 0.90-2.10 (11H, m, H4-7), 2.97 (1H, d, *J* = 4.1 Hz, H2), 3.93 (1H, dd, *J* = 8.1, 4.1 Hz, H3).

LRMS (CI mode, NH_3): *m/z* = 244 [$(M+NH_4)^+$, 28], 227 [$(M+H)^+$, 100], 211 [$(M+H-H_2O)^+$, 14], 137 [$(M+H-HOTMS)^+$, 36].

cis-4-(_p_-Nitrophenyl)-3-(trimethylsilyl)-2-oxetanone (7.5.15.4):



Example (Table 7.5.15, entry 10):
The general procedure was followed with *para*-nitrobenzaldehyde (**7.1.3.3**) (116 mg, 0.77 mmol); ketene **6.2.10.2** (107 mg, 0.94 mmol); catalyst **6.4.16.3** (2.0 mL of 0.0767 M in toluene, 0.15 mmol, 0.20 eq); chromatography (petrol:Et_2O = 95:5); total crude yield: 75%, *cis*:*trans* = 100:0.

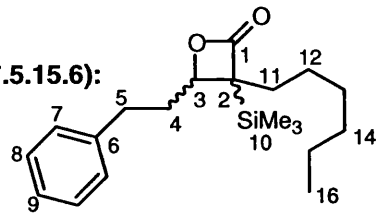
This compound was unstable and was not purified.

IR (film): ν = 2959 (m), 1822 (s), 1522 (s), 1348 (s), 1254 (s), 1199 (s), 1147 (s), 1108 (s), 853 (s) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = –0.02 (9H, s, H8), 3.91 (1H, d, J = 6.5 Hz, H2), 5.82 (1H, d, J = 6.6 Hz, H3), 7.38 (2H, d, J = 8.1 Hz, H5), 8.76 (2H, d, J = 8.1 Hz, H6).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –1.6 (3), 50.3 (1), 71.9 (1), 123.9 (1), 126.8 (1), 144.5 (0), 148.0 (0), 169.9 (0).

4-(1′-Phenylethyl)-3-(trimethylsilyl)-3-(*n*-hexyl)-2-oxetanone (7.5.15.6):



Example (Table 7.5.15, entry 12):
The general procedure was followed with phenylpropionaldehyde (**7.1.3.5**) (102 mg, 0.76 mmol); ketene **6.2.12.2** (186 mg, 0.94 mmol); catalyst **6.4.16.3** (2.0 mL of 0.0767 M in toluene, 0.15 mmol, 0.20 eq); chromatography (petrol:Et_2O = 100:0 → 96:4); total yield: 77%, *cis*:*trans* = 86:14.

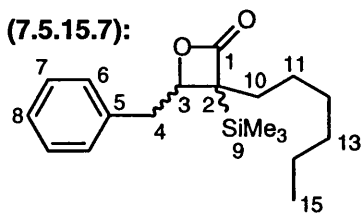
IR (CH_2Cl_2): ν = 2956 (s), 2930 (s), 2800 (m), 1795 (s), 1455 (m), 1252 (s), 1136 (m), 1120 (m), 1093 (m), 1072 (m), 847 (s) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ (selected signals) = 0.25 (9H, s, H10), 0.90 (3H, t, J = 7.0 Hz, H16), 1.30 (8H, br s, H12-15), 1.88 (2H, m, H11), 2.09 (1H, m, H4), 2.24 (1H, m, H4), 2.74 (1H, dd, J = 9.2, 7.0 Hz, H5), 2.90 (1H, dd, J = 9.7, 4.8 Hz, H5), 4.40 (1H, dd, J = 9.9, 3.0 Hz, H3), 7.30 (5H, m, H7-9).

^{13}C NMR (68 MHz, $CDCl_3$): δ = (–3.2 (3)), –1.2 (3), 14.2 (3), 22.7 (2), 26.3 (2), (26.8 (2)), (27.6 (2)), 29.7 (2), (30.2 (2)), 30.8 (2), (31.5 (2)), 31.7 (2), (32.1 (2)), 32.7 (2), (33.0 (2)), 34.6 (2), 55.2 (0), (76.2 (1)), 78.9 (1), 126.4 (1), 128.6 (1), 128.8 (1), 140.6 (0), (140.8 (0)), 174.0 (0).
(Entries in brackets refer to minor isomers.)

LRMS (CI mode, NH_3): *m/z* = 405 [$(M+TMS)^+$, 40%], 350 [$(M+NH_4)^+$, 17], 333 [$(M+H)^+$, 20], 243 [$(M+H–HOTMS)^+$, 100].

4-(1′-Phenylmethyl)-3-(trimethylsilyl)-3-(*n*-hexyl)-2-oxetanone (7.5.15.7):



Example (Table 7.5.15, entry 13):
The general procedure was followed with phenylacetaldehyde (**7.1.3.4**) (93 mg, 0.77 mmol); ketene **6.2.12.2** (173 mg, 0.87 mmol); catalyst **6.4.16.3** (2.0 mL of 0.0767 M in toluene, 0.15

mmol, 0.20 eq); chromatography (petrol:Et_2O = 100:0 → 99:1); total yield: 73%, *cis*:*trans* = 82:18.

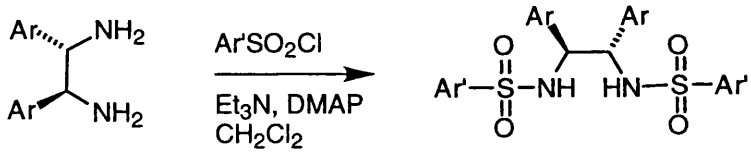
IR (film): ν = 2956 (s), 2930 (s), 2857 (m), 1802 (s), 1254 (s), 1112 (m), 1090 (m), 1070 (m), 847 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.35 (9H, s, H9), 0.95 (3H, t, J = 7.0 Hz, H15), 1.37 (8H, br s, H11-14), 1.93 (2H, m, H10), 3.05 (1H, dd, J = 14.5, 2.7 Hz, H4), 3.27 (1H, dd, J = 14.5, 10.9 Hz, H4), 4.62 (1H, dd, J = 10.9, 2.7 Hz, H3), 7.30 (5H, m, H6-8).

^{13}C NMR (68 MHz, $CDCl_3$): δ = –1.1 (3), 14.2 (3), 22.7 (2), 26.3 (2), 29.7 (2), 30.7 (2), 31.7 (2), 39.2 (2), 55.7 (0), 79.9 (1), 127.1 (1), 128.8 (1), 129.0 (1), 137.4 (0), 173.8 (0).

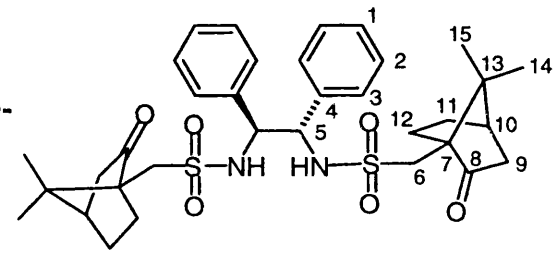
LRMS (CI mode, NH_3): *m/z* = 391 [$(M+TMS)^+$, 15%], 318 [$(M+H)^+$, 10], 229 [$(M+H-HOTMS)^+$, 100].

General Procedure for C_2-Symmetric Ligands



To a solution of the diamine in dry CH_2Cl_2 (5 mL/mmol), under nitrogen at rt, was added triethylamine (3 eq) and DMAP (10 mol%). The solution was stirred at rt and a solution of the sulfonyl chloride (2 eq) in CH_2Cl_2 was added dropwise. The reaction stirred at rt for 1 h then poured into CH_2Cl_2/1 N HCl (1:1). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to a solid foam which was purified by flash chromatography eluting with ether/petrol mixtures.

***(S,S)*-(+)-*N,N'*-*Bis*-((+)-10-camphorsulfonyl)-1,2-diphenylethylenediamine (for 7.5.18.9):**



The general procedure was followed with (*S*, *S*) diamine **7.5.14.4** (257 mg, 1.21 mmol); triethylamine (0.52 mL, 3.73 mmol); DMAP (20 mg, 0.16 mmol) and (+)-10-camphorsulphonyl chloride (611 mg, 2.44 mmol); chromatography (petrol:Et_2O = 50:50 → 0:100); yield: 37%, white solid foam.

mp: 90-110°C.

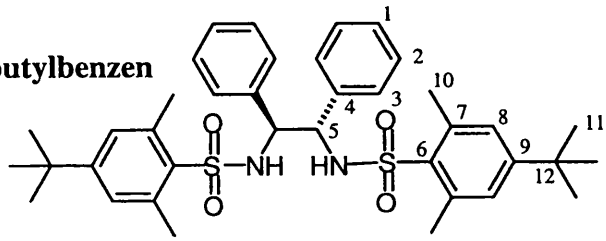
$[\alpha]_D$ = +30.6° (*c* = 0.575, $CHCl_3$).

IR (CH_2Cl_2): ν = 3297 (m), 1745 (s), 1266 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.72 (6H, s), 0.88 (6H, s), 1.40 (2H, ddd, *J* = 12.2, 9.2, 3.7 Hz), 1.75 (2H, ddd, *J* = 13.8, 9.1, 4.3 Hz), 1.94 (4H, m), 2.35 (2H, t, *J* = 4.3 Hz), 2.19 (1H, m), 2.24 (1H, m), 2.29 (1H, m), 2.37 (1H, m), 2.46 (2H, d, *J* = 14.8 Hz), 3.19 (2H, d, *J* = 15.0 Hz), 4.92 (2H, m), 6.27 (2H, m), 7.1-7.4 (10H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (3), 19.8 (3), 25.3 (2), 27.0 (2), 42.8 (1), 42.9 (2), 48.5 (0), 51.3 (2), 58.7 (0), 63.0 (1), 127.7 (1), 128.1 (1), 128.7 (1), 139.2 (0), 216.5 (0).
LRMS (ES, +ve): m/z = 1303 [$(2M+Na)^+$], 663 [$(M+Na)^+$].

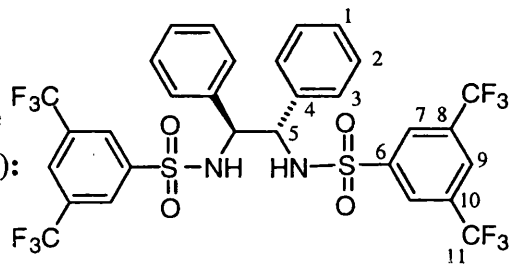
(*S,S*)-(–)-*N,N'-Bis*-(2,6-dimethyl-4-*tert*-butylbenzenesulfonyl)-1,2-diphenylethylene diamine (for 7.5.18.4):



The general procedure was followed with (*S*, *S*) diamine **7.5.14.4** (264 mg, 1.24 mmol) in CH_2Cl_2 (6 mL); triethylamine (0.57 mL, 4.09 mmol); DMAP (24 mg, 0.20 mmol) and 4-*tert*-butyl-2,6-dimethylbenzenesulfonyl chloride (648 mg, 2.48 mmol); chromatography (petrol:Et_2O = 90:10 → 60:40); yield: 90%, white solid foam.

See 1233A experimental for characterisation data.

(*S,S*)-(-)-*N,N'-Bis*-(3,5-*bis*-(trifluoromethyl)benzenesulfonyl)-1,2-diphenylethylenediamine (for 7.5.18.1):



The general procedure was followed with (*S*, *S*) diamine **7.5.14.4** (1.00g, 4.71 mmol); triethylamine (2.0 mL, 14.35 mmol); DMAP (60 mg, 0.49 mmol) and 3,5-*bis*-(trifluoromethyl)benzenesulfonyl chloride* (2.95g, 9.42 mmol); chromatography (petrol:Et_2O = 80:20 → 50:50); yield: 94%, white solid foam.

* prepared according to the procedure of: R. V. Hoffman *Org. Synth.* **1981**, *60*, 121.

mp 155-8°C.

$[\alpha]_D$ = –54.8°C (*c* = 1.025, $CHCl_3$).

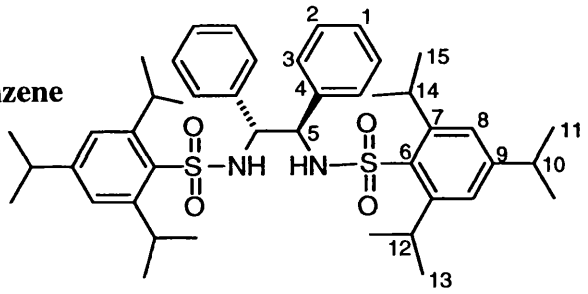
IR (CH_2Cl_2): ν = 3377 (s), 3051 (s), 2954 (s), 1266 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.93 (2H, dd, *J* = 5.0, 2.5 Hz, H5), 6.90 (10H, m, H1-3), 7.75 (2H, s, H9), 7.81 (2H, dd, *J* = 4.6, 2.3 Hz, NH), 7.99 (4H, s, H7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.7 (1), 120.4 (0), 124.4 (0), 125.7 (1), 127.2 (1), 128.0 (1), 128.4 (1), 128.6 (1), 132.2 (0), 132.7 (0), 134.5 (0), 143.5 (0).

This compound has been reported in the literature but no data was given.[221]

(*R*,*R*)-(+)-*N*,*N*′-*Bis*(2,4,6-tri*iso*-propylbenzene sulfonyl)-1,2-diphenylethylenediamine (for 7.5.18.3):



The general procedure was followed with (*R*, *R*) diamine **7.5.14.4** (530 mg, 2.50 mmol); triethylamine (1.0 mL, 7.17 mmol); DMAP (30 mg, 0.25 mmol) and 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (1.53g, 5.05 mmol); chromatography (petrol:Et_2O = 95:5 → 80:20); yield: 82%, white solid foam.

mp 90-100°C.

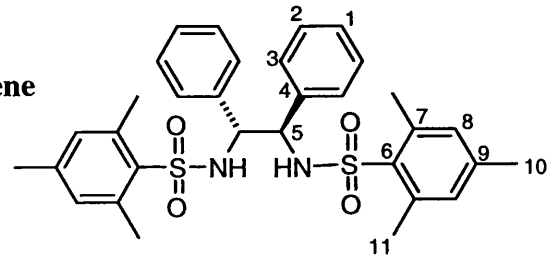
$[\alpha]_D$ = +96.5°C (*c* = 1.1, $CHCl_3$).

IR (CH_2H_2): ν = 2932 (s), 2859 (s), 2800 (s), 1741 (s), 1473 (s), 1375 (s), 1255 (s), 1137 (s), 1007 (s), 967 (m), 837 (s), 778 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (12H, d, *J* = 6.8 Hz, H13 or 15), 1.16 (12H, d, *J* = 6.8 Hz, H15 or 13), 1.21 (12H, d, *J* = 7.4 Hz, H11), 2.83 (2H, septet, *J* = 6.9 Hz, H10), 4.01 (4H, septet, *J* = 6.8 Hz, H12, 14), 4.48 (2H, dd, *J* = 3.6, 2.1 Hz, H5), 5.76 (2H, m, NH), 6.59 (4H, m, H1-3), 6.92 (6H, m, H1-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8 (3), 24.7 (3), 25.1(3), 29.9 (1), 34.3 (1), 62.0 (1), 123.6 (1), 127.6 (1), 127.9 (1), 128.3 (1), 132.9 (0), 137.3 (0), 150.3 (0), 153.0 (0).

(*R*,*R*)-(+)-*N*,*N*'-*Bis*(2,4,6-trimethylbenzene sulfonyl)-1,2-diphenylethylenediamine (for 7.5.18.2):



The general procedure was followed with (*R*, *R*) diamine **7.5.14.4** (558 mg, 2.63 mmol); triethylamine (1.1 mL, 7.89 mmol); DMAP (35 mg, 0.29 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (1.15g, 5.26 mmol); chromatography (petrol:Et_2O = 90:10 → 40:60); yield: 97%, white solid foam.

mp 90-5°C.

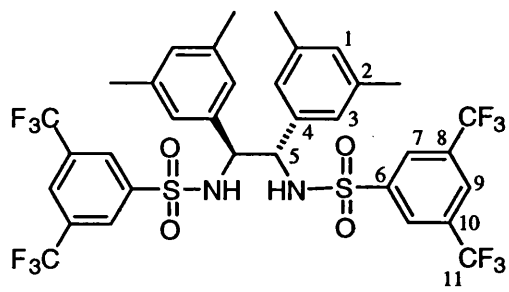
$[\alpha]_D$ = +58.0°C (*c* = 1.175, $CHCl_3$).

IR (CH_2H_2 film) ν = 3312 (m), 1604 (m), 1456 (m), 1322 (s), 1266 (s), 1156 (s), 1056 (m), 921 (m), 738 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 2.20 (6H, s, H10), 2.44 (12h, s, H11, 12), 4.34 (2H, dd, *J* = 3.8, 2.0 Hz, H5), 5.78 (2H, dd, *J* = 3.6, 2.2 Hz, NH), 6.60 (4H, m, H2 or 3), 6.74 (4H, s, H8), 6.87 (4H, m, H2 or 3), 6.97 (2H, tt, *J* = 7.0, 1.6 Hz, H1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (3), 22.9 (3), 62.4 (1), 127.4 (1), 127.9 (1), 128.1 (1), 131.8 (1), 133.9 (0), 136.4 (0), 139.1 (0), 142.3 (0).

(*S*,*S*)-(+)-*N*,*N*'-*Bis*-(3,5-*bis*-(trifluoromethyl) benzenesulfonyl)-1,2-*bis*-(3,5-dimethyl phenyl)ethylenediamine (for 7.5.21.1):



The general procedure was followed with (*S*, *S*) diamine **7.5.20.6** (513 mg, 1.91 mmol); triethylamine (1.0 mL, 7.17 mmol); DMAP (20 mg, 0.164 mmol) and 3,5-*bis*-(trifluoromethyl)benzenesulfonyl chloride* (1.22g, 3.90 mmol); chromatography (petrol:Et_2O = 90:10 → 70:30); yield: 85%, white solid foam.

* prepared according to the procedure of: R. V. Hoffman *Org. Synth.* **1981**, *60*, 121.

mp 95-115°C (not crystallised).

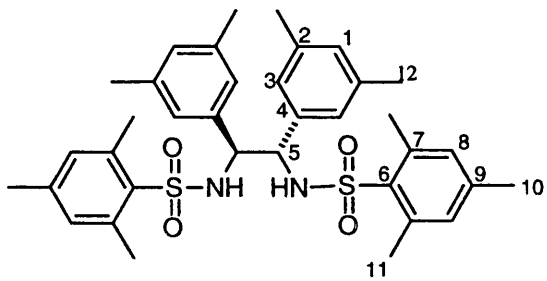
$[\alpha]_D$ = +53.0°C (*c* 1.3, $CHCl_3$).

IR (CH_2H_2): ν = 3254 (m), 1422 (m), 1360 (s), 1281, 1285 (s), 1164 (s), 1110 (m), 903 (m), 742 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.90 (12H, s, H12), 4.77 (2H, dd, J = 5.1, 2.4 Hz, H5), 6.27 (4H, s, H3), 6.45 (2H, s, H1), 7.52 (2H, dd, J = 4.9, 2.6 Hz, NH), 7.75 (2H, s, H9), 7.98 (4H, s, H7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (3), 62.3 (1), 120.6 (0), 124.2 (0), 125.6 (1), 125.8 (1), 126.9 (1), 129.9 (1), 134.3 (0), 137.9 (0), 143.6 (0).

(*S*,*S*)-(+)-*N*,*N'*-*Bis*-(2,4,6-trimethyl benzenesulfonyl)-1,2-*bis*-(3,5-dimethyl phenyl)ethylenediamine (for 7.5.21.2):



The general procedure was followed with (*S*, *S*) diamine **7.5.20.6** (414 mg, 1.54 mmol); triethylamine (0.65 ml, 4.66 mmol); DMAP (23 mg, 0.189 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (677 mg, 3.10 mmol); chromatography (petrol:Et_2O = 90:10 → 60:40); yield: 80%, white solid foam.

mp 94-7°C.

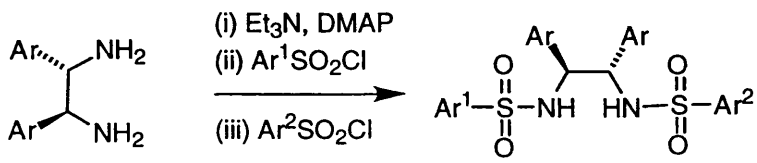
$[\alpha]_D$ = –71.6° (c = 0.64, $CHCl_3$).

IR (CH_2Cl_2): ν = 3054 (m), 2986 (m), 1605 (m), 1422 (m), 1322 (m), 1266 (s), 1156 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (12H, s, H12), 2.21 (6H, s, H10), 2.42 (12H, s, H11), 4.31 (2H, dd, J = 4.0, 1.9 Hz, H5), 5.56 (2H, dd, J = 3.7, 1.9 Hz, NH), 6.22 (4H, s, H3), 6.60 (2H, s, H1), 6.75 (4H, s, H8).

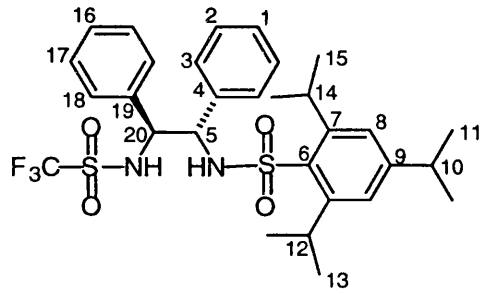
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (3), 21.1 (3), 22.8 (3), 62.0 (1), 125.4 (1), 129.4 (1), 131.7 (1), 134.2 (0), 136.1 (0), 137.4 (0), 139.1 (0), 142.0 (0).

General Procedure for Non-C_2-Symmetric Catalysts



To a solution of the diamine in dry CH_2Cl_2 (5 mL/mmol), under nitrogen at rt, was added triethylamine (3 eq) and DMAP (10 mol%). The solution was stirred at rt and a solution of the first sulfonyl chloride (1 eq) in CH_2Cl_2 was added dropwise. After 1 h at rt the second sulfonyl chloride was added as for the first and the reaction stirred at rt for a further 1 h then poured into CH_2Cl_2/1 N HCl (1:1). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to a solid foam which was purified by flash chromatography eluting with ether/petrol mxtures.

(S,S)-(–)-*N*-2,4,6-Tri*iso*-propylbenzenesulfonyl-*N'*-triflyl-1,2-diphenylethylenediamine (for 7.5.26.1):



The general procedure was followed with (*S*, *S*) diamine **7.5.14.4** (218 mg, 1.03 mmol); triethylamine (0.44 mL, 3.16 mmol); DMAP (10 mg, 0.08 mmol); 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (318 mg, 1.05 mmol) and triflic anhydride (305 mg, 1.08 mmol). NOTE: the reaction was cooled to –70°C before addition of the triflic anhydride then warmed slowly to rt. Chromatography (petrol:Et_2O = 50:50 → 0:100); yield: 64%, white solid foam.

IR (CH_2Cl_2): ν_{max} = 1265 (s) cm^{-1}.

$[\alpha]_D$ = –54.7° (*c* = 0.655, $CHCl_3$).

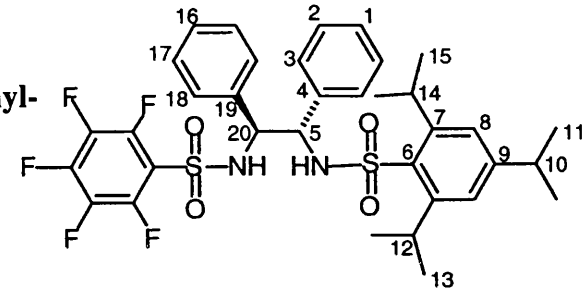
^{19}F NMR (282 MHz, $CDCl_3$): δ = 25.0 (ref.: C_6F_6 δ 0).

^1H NMR (270 MHz, $CDCl_3$): δ = 0.90 (6H, d, *J* = 6.8 Hz, H11), 1.22 (6H, d, *J* = 6.8 Hz, H13 or 15), 1.26 (6H, d, *J* = 6.8 Hz, H15 or 13), 2.86 (1H, septet, *J* = 6.9 Hz, H10), 3.99 (2H, septet, *J* = 6.9 Hz, H12, 14), 4.23 (1H, dd, *J* = 10.2, 7.7 Hz, H5), 4.89 (1H, dd, *J* = 10.2, 6.9 Hz, H20), 5.25 (1H, d, *J* = 7.5 Hz, C5 NH), 6.50 (2H, d, *J* = 7.1 Hz, H8), 7.05 (11H, m, H1-3, 16-18, C20 NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ= 23.5 (1), 23.7 (1), 23.9 (3), 25.2 (3), 29.9 (3), 34.2 (1), 62.2 (1), 63.1 (1), 119.0 (0)*, 123.8 (1), 127.07 (1), 127.13 (1), 128.3 (1), 128.5 (1), 128.8 (1), 128.9 (1), 131.8 (0), 136.2 (0), 137.4 (0), 150.2 (0), 152.0 (0).

* q, $J_{C\text{-}F}$ = 130 Hz

(*S,S*)-(–)-*N*-2,4,6-Tri*iso*-propylbenzenesulfonyl-*N'*-pentafluorobenzenesulfonyl-1,2-diphenyl ethylenediamine (for 7.5.26.2):



The general procedure was followed with (*S, S*) diamine **7.5.14.4** (421 mg, 1.98 mmol); triethylamine (0.84 mL, 6.03 mmol); DMAP (15 mg, 0.12 mmol); 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (601 mg, 1.98 mmol) and pentafluorobenzenesulfonyl chloride (528 mg, 1.98 mmol); chromatography (CH_2Cl_2); yield: 36%, white crystalline solid. Recrystallised from CH_2Cl_2 (250 mg in 5 mL) overlaid with petrol (2 mL). This solution was stood at rt for 1 h after which time the crystals were filtered and dried @ 0.5 mmHg @ 100°C to give white needles.

mp: 225°C.

$[\alpha]_D$ = –89.5° (*c* = 0.4, CH_2Cl_2).

IR (CH_2Cl_2): ν_{max} = 1265 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (6H, d, *J* = 6.7 Hz, H11, 13 or 15), 1.22 (6H, d, *J* = 6.9 Hz, H11, 13, or 15), 1.23 (6H, d, *J* = 6.6 Hz, H11, 13 or 15), 2.85 (1H, septet, *J* = 6.9 Hz, H10), 3.99 (2H, septet, *J* = 6.7 Hz, H12, 14), 4.48 (1H, dd, *J* = 10.3, 6.7 Hz, H5), 4.83 (1H, dd, *J* = 10.3, 6.6 Hz, H20), 5.49 (1H, d, *J* = 6.7 Hz, C5 NH), 6.60 (1H, d, *J* = 6.7 Hz, C20 NH), 6.95 (12H, m, H1-3, H8, 16-18).

^{13}C NMR (75 MHz, $CDCl_3$): δ= 23.7 (1), 23.8 (1), 24.4 (3), 25.2 (3), 30.0 (3), 34.3 (1), 61.7 (1), 63.0 (1), 123.8 (1), 127.5 (1), 127.6 (1), 128.2 (1), 128.4 (1), 128.5 (1), 128.7 (1), 132.4 (0), 135.7 (0), 136.2 (0), 150.3 (0), 153.5 (0).

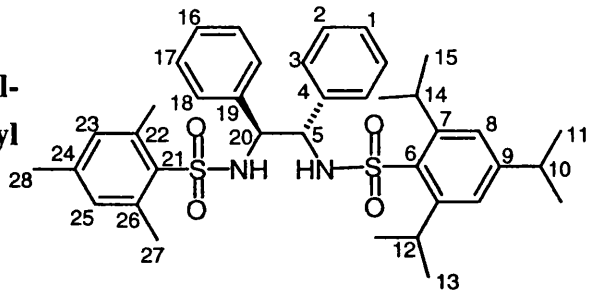
NB: C_6F_5: signals very weak.

^{19}F NMR (282 MHz, $CDCl_3$): δ = 1.77 (2F, m); 14.50 (1F, tt, *J* = 20.7, 6.5 Hz); 26.01 (2F, ddd, *J* = 27.8, 12.0, 7.9 Hz) (ref.: C_6F_6 δ 0).

LRMS (ES, +ve): *m/z* = 731 [(M+Na)$^+$], 1439 [(2M+Na)$^+$].

Anal. Calcd for $C_{35}H_{37}F_5N_2O_4S_2$: C, 59.31; H, 5.26.; N, 3.95; S, 9.05. Found: C, 59.27; H, 5.16; N, 3.71; S, 9.30.

(*S,S*)-(-)-*N*-2,4,6-Tri*iso*-propylbenzenesulfonyl-*N'*-2,4,6-trimethylbenzenesulfonyl-1,2-diphenyl ethylenediamine (for 7.5.26.3):



The general procedure was followed with (*S, S*) diamine **7.5.14.4** (257 mg, 1.21 mmol); triethylamine (0.52 mL, 3.73 mmol); DMAP (10 mg, 0.08 mmol); 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (368 mg, 1.22 mmol) and 2,4,6-dimethylbenzenesulfonyl chloride (267 mg, 1.22 mmol); chromatography (petrol:Et_2O = 50:50); yield: 79%, white solid foam.

$[\alpha]_D$ = -80.0° (*c* = 0.4, $CHCl_3$).

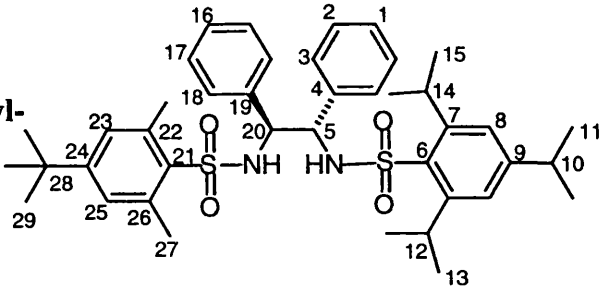
IR (CH_2Cl_2): ν_{max} = 1265 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (6H, d, *J* = 6.8 Hz, H15), 1.18 (6H, d, *J* = 6.6 Hz, H13), 1.20 (6H, d, *J* = 6.8 Hz, H11), 2.21 (3H, s, H28), 2.48 (6H, s, H27), 2.84 (1H, septet, *J* = 6.8 Hz, H10), 4.00 (2H, septet, *J* = 6.8 Hz, H12, 14), 4.42 (1H, dd, *J* = 10.1, 6.3 Hz, H5), 4.46 (1H, dd, *J* = 9.9, 4.7 Hz, H20), 5.66 (1H, d, *J* = 6.1 Hz, C5 NH), 6.15 (1H, d, *J* = 4.6 Hz, C20 NH), 6.56 (2H, d, *J* = 7.0 Hz,), 6.65 (2H, d, *J* = 7.0 Hz), 6.74 (2H, s, H1-3, 16-18), 6.82-6.98 (6H, m, H1-3, 16-18), 7.00 (2H, s, H1-3, 16-18).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.9 (3), 22.8 (3), 23.7 (3), 23.8 (3), 24.6 (3), 25.2 (3), 30.0 (1), 34.3 (1), 62.3 (1), 62.5 (1), 123.6 (1), 127.5 (1), 127.6 (1), 127.7 (1), 127.9 (1), 128.0 (1), 128.3 (1), 131.7 (1), 132.7 (0), 134.2 (0), 136.6 (0), 136.9 (0), 139.1 (0), 142.1 (0), 150.2 (0), 153.1 (0).

LRMS (ES, +ve): *m/z* = 1345 [(2M+Na)$^+$, 100), 683 [(M+Na)$^+$, 36], 662 [(M+H)$^+$, 20%].

(*S,S*)-(–)-*N*-2,4,6-Tri*iso*-propylbenzenesulfonyl-*N'*-2,6-dimethyl-4-*tert* -butylbenzenesulfonyl-1,2-diphenylethylenediamine (for 7.5.26.4):



The general procedure was followed with (*S, S*) diamine **7.5.14.4** (386 mg, 1.82 mmol); triethylamine (0.77 mL, 5.52 mmol); DMAP (24 mg, 0.20 mmol); 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (551 mg, 1.83 mmol) and 4-*tert*-butyl-2,6-dimethylbenzenesulfonyl chloride (478 mg, 1.83 mmol); chromatography (petrol:Et_2O = 95:5 → 60:40); yield: 79%, white solid foam.

mp: 95-100°C.

$[\alpha]_D = -89.9°$ ($c = 0.585$, $CHCl_3$).

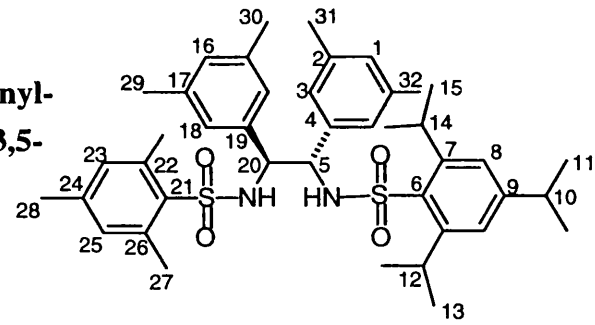
IR (CH_2Cl_2): ν_{max} = 3308 (m), 3054 (m), 2966 (s), 2871 (m), 1600 (m), 1456 (m), 1422 (m), 1321 (m), 1265 (s), 1150 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (6H, d, J = 6.7 Hz, H15), 1.19 (6H, d, J = 6.7 Hz, H13), 1.21 (6H, d, J = 6.7 Hz, H11), 1.24 (9H, s, H29), 2.51 (6H, s, H27), 2.84 (1H, septet, J = 6.9 Hz, H10), 4.01 (2H, septet, J = 6.9 Hz, H12, 14), 4.45 (2H, m, H5, 20), 5.68 (1H, m, C20 NH), 6.11 (1H, m, C5 NH), 6.59 (4H, t, J = 6.9 Hz, H8, 23, 25), 6.82 (2H, t, J = 6.9 Hz, H1-3, 16-18), 6.95 (8H, m, H1-3, 16-18).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (3), 23.78 (3), 23.81 (3), 24.6 (3), 25.2 (3), 30.0 (1), 31.1 (3), 34.3 (1), 34.6 (0), 62.2 (1), 62.4 (1), 123.6 (1), 127.5 (1), 127.6 (1), 127.7 (1), 127.9 (1), 128.0 (1), 128.1 (1), 128.3 (1), 132.9 (0), 134.1 (0), 136.4 (0), 137.0 (0), 138.8 (0), 150.3 (0), 153.1 (0), 154.9 (0).

LRMS (ES, +ve): m/z = 725 [$(M+Na)^+$, 100%].

(*S,S*)-(–)-*N*-2,4,6-Tri*iso*-propylbenzenesulfonyl-*N'*-2,4,6-trimethylbenzenesulfonyl-1,2-*bis*-(3,5-dimethylphenyl)-ethylenediamine:



The general procedure was followed with (*S, S*) diamine **7.5.20.6** (366 mg, 1.36 mmol); triethylamine (0.63 mL, 4.52 mmol); DMAP (24 mg, 0.20 mmol); 2,4,6-tri*iso*-propylbenzenesulfonyl chloride (412 mg, 1.36 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (303 mg, 1.38 mmol); chromatography (petrol:Et_2O = 90:10 → 70:30); yield: 41%, white solid foam.

mp: 90-94°C.

$[\alpha]_D = -90.5°$ ($c = 0.705$, $CHCl_3$).

IR (CH_2Cl_2): ν = 3310 (m), 2962 (s), 1602 (m), 1463 (m), 1424 (m), 1327 (m), 1265 (s), 1154 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.04 (6H, d, J = 6.8 Hz, H11), 1.16 (6H, d, J = 6.8 Hz, H13), 1.20 (6H, d, J = 6.8 Hz, H15), 1.96 (12H, s, H29-32), 2.20 (3H, s, H28), 2.43 (6H, s, H27), 2.84 (1H, septet, J = 7.2 Hz, H12), 3.95 (1H, septet, J = 7.2 Hz, H14), 4.37 (2H, m, H5, H20), 5.38 (1H, d, J = 5.3 Hz, C5 NH), 5.82 (1H, d, J = 4.3 Hz, C20 NH), 6.19 (4H, d, J = 12.4 Hz, H3, 18), 6.58 (2H, d, J = 6.9 Hz, H1, 16), 6.73 (2H, s, H8), 7.02 (2H, s, H23, 25).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (3), 21.1 (3), 21.2 (3), 22.7 (3), 23.7 (3), 24.7 (3), 25.0 (3), 30.0 (1), 34.3 (1), 61.6 (1), 62.1 (1), 123.6 (1), 125.4 (1), 125.6 (1), 129.3 (1), 129.5 (1), 131.6 (1), 133.1 (0), 134.5 (0), 136.2 (0), 136.7 (0), 137.3 (0), 137.6 (0), 139.1 (0), 141.8 (0), 150.2 (0), 152.8 (0).

LRMS (ES, +ve): *m/z* = 717 [$(M+H)^+$, 55%], 734 [$(M+NH_4)^+$, 65], 739 [$(M+Na)^+$, 55].

References

(1) American Heart Association. 1991 Heart and Stroke Facts. American Heart Association, Dallas, 1991.

(2) Gotto, A. M. Jr.; LaRosa, J. C.; Hunninghake, D.; Grundy, S. M.; Wilson, P. W.; Clarkson, T. B.; Hay, J. W.; Goodman, D. S. *Circulation* **1990**, *81*, 1721.

(3) Lipid Research Clinics Program *J. Am. Med. Assoc.* **1984**, *251*, 365.

(4) Lipid Research Clinics Program *J. Am. Med. Assoc.* **1984**, *251*, 351.

(5) Mahler, V. M. G.; Thompson, G. R. *Q. J. Med.* **1990**, *74*, 165.

(6) Stryer, L. *Biochemistry: Chapter 27: Biosynthesis of Membrane Lipids and Steroids;* 4th ed.; W. H. Freeman and Company: New York, 1995, pp 685.

(7) Brown, M.; Goldstein, J. *Nobel Lectures* **1985**,

(8) Stryer, L. *Biochemistry: Chapter 17: Metabolism;* 4th ed.; W. H. Freeman and Company: New York, 1995, pp 451.

(9) Bloch, K *Science* **1965**, *150*, 19.

(10) Watson, N. S.; Procopiou, P. A. *Progress in Medicinal Chemistry* **1996**, *33*, 331.

(11) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34.

(12) Goldstein, J. L.; S., Brown M. *Nature* **1990**, *343*, 425.

(13) Scandinavian Simvastatin Survival Study Group *Lancet* **1994**, *344*, 1383.

(14) Kumagai, H.; Tomoda, H.; Omura, S. *J. Antibiot.* **1990**, *43*, 397.

(15) Tomoda, H.; Kumagai, H.; Tanaka, Y.; Omura, S. *Biochim. Biophys. Acta.* **1987**, *922*, 351.

(16) Tomoda, H.; Kumagai, H.; Takahashi, Y.; Tanaka, Y.; Iwai, Y.; Omura, S. *J. Antibiot.* **1988**, *41*, 247.

(17) Aldridge, D. C.; Giles, D.; Turner, W. B. *J. Chem. Soc., Chem. Commun.* **1970**, 639.

(18) Aldridge, D. C.; Giles, D.; Turner, W. B. *J. Chem. Soc. (C)* **1971**, 3888.

(19) For a review of natural 2-oxetanones, see: Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729.

(20) Omura, S.; Tomoda, H.; Kumagai, H.; Greenspan, M. D.; Yudkovitz, J. B.; Chen, J. S.; Alberts, A. W.; Martin, I.; Mochales, S.; Monaghan, R. L.; Chabala, J. C.; Schwartz, R. E.; Patchett, A. A. *J. Antibiot.* **1987**, *40*, 1356.

(21) Greenspan, M. D.; Yudkovitz, J. B.; Lo, C. L.; Chen, J. S.; Alberts, A. W.; Hunt, V. M.; Chang, M. N.; Yang, S. S.; Thompson, K. L.; Chiang, Y. P.; Chabala, J. C.; Monaghan, R. L.; Schwartz, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7488.

(22) Chiang, Y. C. P.; Chang, M. N.; Yang, S. S.; Chabala, J. C.; Heck, J. V. *J. Org. Chem.* **1988**, *53*, 4599.

(23) Hashizume, H.; Ito, H.; Kanaya, N.; Nagashima, H.; Usui, H.; Oshima, R.; Kanao, M.; Tomoda, H.; Sunazuka, T.; Nagamistu, T.; Kumagai, H.; Omura, S. *Heterocycles* **1994**, *38*, 1551.

(24) Thompson, K. L.; Chang, M. N.; Chiang, Y. P.; Yang, S. S.; Chabala, J. C.; Arison, B. H.; Greenspan, M. D.; Hanf, D. P.; Yudkovitz, J. *Tetrahedron Lett.* **1991**, *32*, 3337.

(25) Greenspan, M. D.; Bull, H. G.; Yudkovitz, J. B.; Hanf, D. P.; Alberts, A. W. *Biochem. J.* **1993**, *289*, 889.

(26) Mayer, R. J.; Louis-Flamberg, P.; Elliot, J. D.; Fisher, M.; Leber, J. *Biochim. Biophys. Res. Commun.* **1990**, *169*, 610.

(27) Miziorka, H. M.; Behnke, C. E. *J. Biol. Chem.* **1985**, *260*, 13513.

(28) Tomoda, H.; Kumagai, H.; Tanaka, Y.; Omura, S. *J. Antibiot.* **1993**, *46*, 872.

(29) Sunazuka, T.; Tsuzuki, K.; Kumagai, H.; Tomoda, H.; Tanaka, H.; Nagashima, H.; Hashizume, H.; Omura, S. *J. Antibiot.* **1992**, *45*, 1139.

(30) Bell, K.; Saepudin, E.; Harrison, P. *Can. J. Chem.* **1996**, *74*, 24.

(31) Tomoda, H.; Kumagai, H.; Ogawa, Y.; Sunazuka, T.; Hashizume, H.; Nagashima, H.; Omura, S. *J. Org. Chem.* **1997**, *62*, 2161.

(32) Hashizume, H.; Ito, H.; Yamada, K.; Nagashima, H.; Kanao, M.; Tomoda, H.; Sunazuka, T.; Kumagai, H.; Omura, S. *Chem. Pharm. Bull.* **1994**, *42*, 512.

(33) Hashizume, H.; Ito, H.; Kanaya, N.; Yamada, K.; Nagashima, H.; Usui, H.; Oshima, R.; Kanao, M.; Tomoda, H.; Sunazuka, T.; Kumagai, H.; Omura, S. *Chem. Pharm. Bull.* **1994**, *42*, 1272.

(34) Hashizume, H.; Ito, H.; Morikawa, T.; Kanaya, N.; Nagashima, H.; Usui, H.; Tomoda, H.; Sunazuka, T.; Kumagai, H.; Omura, S. *Chem. Pharm. Bull.* **1994**, *42*, 2097.

(35) Kumagai, H.; Tomoda, H.; Omura, S. *J. Antibiot.* **1992**, *45*, 563.

(36) Chiang, Y. C. P.; Yang, S. S.; Heck, J. V.; Chabala, J. C.; Chang, M. N. *J. Org. Chem.* **1989**, *54*, 5708.

(37) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(38) Adam, W.; Baeza, J.; Ju-Chao, L. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

(39) Wattanasin, S.; Do, H. D.; Bhongle, N.; Kathawala, F. G. *J. Org. Chem.* **1993**, *58*, 1610.

(40) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.

(41) Mori, K.; Takahashi, Y. *Liebigs Ann. Chem.* **1991**, 1057.

(42) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.

(43) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(44) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans 1* **1977**, 869.

(45) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4096.

(46) Guanti, G.; Bauli, L.; Schmid, G. *Tetrahedron Lett.* **1994**, *35*, 4239.

(47) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, P.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.

(48) Epstein, W. W.; Sonntag, A. C. *J. Org. Chem.* **1967**, *32*, 3390.

(49) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

(50) Stille, J. K. *Angew. Chem., Int. Ed. Eng.* **1986**, *25*, 508.

(51) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.

(52) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(53) Pfaltz, A. In *Modern Synthetic Methods*; R. Scheffold, Ed.; Springer: Berlin, 1989; Vol. 5; pp 199.

(54) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(55) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; R. Scheffold, Ed.; Springer: Berlin, 1989; Vol. 5; pp 115.

(56) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596.

(57) Takaya, H.; Ohta, T.; Mashima, K.; Noyori, R. *Pure Appl. Chem.* **1990**, *62*, 1135.

(58) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(59) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; I. Ojima, Ed.; VCH Publishers: Weinheim, New York, 1993; pp 103.

(60) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

(61) Wittig, G.; Rieber, M. *Ann.* **1949**, *562*, 187.

(62) François, H.; Bex, H.; Lalande, G. *Bull. Soc. Chim. Fr.* **1965**, 3702.

(63) Barbry, D.; Faven, C.; Ajana, A. *Synth. Commun.* **1993**, 2647.

(64) Overman, L.; Rishton, G. M. *Org. Synth.* **1993**, *71*, 56.

(65) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(66) Bertz, S. H.; Fairchild, E. H. In *Encyclopedia of Reagents for Organic Synthesis*; L. Paquette, Ed.; Wiley: New York, 1995; Vol. 2; pp 1312.

(67) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(68) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(69) Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* **1982**, *23*, 3823.

(70) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.

(71) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

(72) Bertz, S. H.; Dabbagh, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1030.

(73) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 5824.

(74) Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119.

(75) Martin, S. F.; Fishpaugh, J. R.; Power, J. M.; Giolando, D. M.; Jones, R. A.; Nunn, C. M.; Cowley, A. H. **1988**, *110*, 7226.

(76) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

(77) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023.

(78) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

(79) McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(80) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Densen, S. *J. Org. Chem.* **1990**, *55*, 2045.

(81) Sullivan, G. R. *Top. Stereochem.* **1977**, *8*, 287.

(82) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.

(83) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.

(84) Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.
(85) Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155.
(86) Kitamura, M.; Tokumaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931.
(87) Ziegler, F . E.; Petersen, A. K. *J. Org. Chem.* **1994**, *59*, 2707.
(88) Vagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* **1990**, 2033.
(89) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(90) Sonogashira, K. In *Comp. Org. Synth.*; B. M. Trost and I. Fleming, Ed.; Pergamon Press: New York, 1991; Vol. 3; pp 521.
(91) Piers, E.; Wong, T.; Ellis, K. A. *Tetrahedron Lett.* **1992**, *70*, 2058.
(92) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
(93) Armstrong, A.; Brackenridge, I; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.
(94) Umezawa, H.; Takaaki, A.; Uotani, K.; Hamada, M.; Takeuchi, T.; Takahashi, S. *J. Antibiot.* **1980**, *33*, 1594.
(95) Uotani, K.; Naganawa, H.; Kondo, S.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1495.
(96) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288.
(97) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729.
(98) Pommier, A.; Pons, J-M.; Kocienski, P. J. ; Wong, L. *Synthesis* **1994**, 1294.
(99) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441.
(100) Zaugg, H. E. *J. Am. Chem. Soc.* **1950**, *72*, 2998.
(101) Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483.
(102) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.
(103) Schöllkopf, U.; Hoppe, I. *Angew. Chem.* **1975**, *87*, 814.
(104) Schöllkopf, U.; Hoppe, I. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 765.
(105) Staudinger, H.; Bereza, S. *Ann.* **1911**, *380*, 243.
(106) Borrmann, D.; Wegler, R. *Chem. Ber.* **1966**, *99*, 1245.
(107) Borrmann, D.; Wegler, R. *Chem. Ber.* **1967**, *100*, 1575.
(108) Brady, W. T.; Patel, A. D. *Synthesis* **1972**, 565.
(109) Brady, W. T.; Smith, L. *J. Org. Chem.* **1971**, *36*, 1637.
(110) Zaitseva, G. S.; Vinokurova, N. G.; Baukov, Yu. I. *Zh. Obshch. Khim* **1975**, *45*, 1398.
(111) Shchukovskaya, L. L.; Kol'tsov, A. I.; Lazarev, A. N.; Pal'chik, R. I. *Dokl. Akad. Nauk. SSSR* **1965**, *164*, 357.
(112) Pons, J. -M.; Kocienski, P. J. *Tetrahedron Lett.* **1989**, *30*, 1833.
(113) Ratemi, E. S.; Vederas, C. *Tetrahedron Lett.* **1994**, *35*, 7605.
(114) Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, *21*, 3377.
(115) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935.
(116) Tidwell, T. *Ketenes*; Wiley Interscience: 1995.
(117) Zaitseva, G. S.; Baukov, Yu. I.; Mal'tsev, V. V.; Lutsenko, I. F. *Zh. Obshch. Khim* **1974**, *44*, 1415.

(118) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1978**, *48*, 131.

(119) Zaitseva, G. S.; Vasil'eva, L. I.; Vinokurova, N. G.; Safronova, O. A.; Baukov, Yu. I. *Zh. Obshch. Khim. Engl. Trans.* **1978**, *48*, 1363.

(120) Zaitseva, G. S.; Krylova, G. S.; Perelygina, O. P.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1981**, *51*, 2252.

(121) Zaitseva, G. S.; Livantsova, L. I.; Bekker, R. A.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1983**, *53*, 2068.

(122) Zaitseva, G. S.; Livantsova, L. I.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1983**, *53*, 2254.

(123) Zaitseva, G. S.; Novikova, O. P.; Kostyuk, A. S.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1985**, *55*, 942.

(124) Zaitseva, G. S.; Kisin, A. V.; Fedorenko, E. N.; Nosova, V. M.; Livantsova, L. I.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1987**, *57*, 2049.

(125) Zaitseva *Zh. Obshch. Khim.* **1988**, *58*, 1675.

(126) Zaitseva, G. S.; Novikova, O. P.; Livantsova, L. I.; Kisin, A. V.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1990**, *60*, 1073.

(127) Zaitseva, G. S.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1991**, *61*, 1389.

(128) Ponomarev, S. V.; Erman, M. B.; Lebedev, S. A.; Pechurina, S. Ya.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1971**, *41*, 127.

(129) Ponomarev, S. V. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 675.

(130) Shchukovskaya, L. L.; Kol'tsov, A. I.; Lazarev, A. N.; Pal'chik, R. I. *Dokl. Akad. Nauk. SSSR* **1968**, *179*, 892.

(131) *Chem. Abstr.* **1967**, *67*, 36207.

(132) Ponomarev, S. V.; Pechurina, S. Ya.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1969**, *39*, 1171.

(133) Vodolazskaya, V. M.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1973**, *43*, 2088.

(134) Jabry, Z.; Lasne, M. -C.; Ripoll, J. -L. *J. Chem. Research (S)* **1986**, 188.

(135) Barton, T. J.; Groh, B. L. *J. Org. Chem.* **1985**, *50*, 158.

(136) Valentí, E.; Pericàs, M. A.; Serratosa, F. *J. Org. Chem.* **1990**, *55*, 395.

(137) Kudinova, V. V.; Veits, Yu. A.; Foss, V. L.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1969**, *39*, 2479.

(138) Kostyuk, A. S.; Dudukina, O. V.; Burlachenko, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1969**, *39*, 467.

(139) Kostyuk, A. S.; Boyadzhan, Zh. G.; Zaitseva, G. S.; Sergeev, V. N.; Savel'eva, N. I.; Baukov, Yu. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1979**, *49*, 1543.

(140) Smithers, R. H. *Synthesis* **1985**, 556.

(141) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332.

(142) Stalick, W. M.; Hazlett, R. N.; Morris, R. E. *Synthesis* **1988**, 287.

(143) Sakurai, H.; Shirahata, A.; Sasaki, K.; Hosomi, A. *Synthesis* **1979**, 740.

(144) Efimova, I. V.; Kazankova, M. A.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1985**, *55*, 1647.

(145) Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810.
(146) Brady, W. T.; Owens, R. A. *Tetrahedron Lett.* **1976**, *19*, 1553.
(147) Ando, W.; Sekiguchi, A.; Migita, T.; Kammula, S. L.; Green, M.; Jones Jr., M. *J. Am. Chem. Soc.* **1975**, *97*, 3818.
(148) Schneider, K.; Daucher, B.; Fronda, A.; Maas, G. *Chem. Ber.* **1990**, *123*, 589.
(149) Shchukovskaya, L. L.; Kol'tsov, A. I.; Lazarev, A. N.; Pal'chik, R. I. *Dokl. Akad. Nauk. SSSR* **1965**, *164*, 357.
(150) *Chem. Abstr.* **1965**, *63*, 18138.
(151) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607.
(152) Brady, W. T.; Cheng, T. C. *J. Org. Chem.* **1977**, *42*, 732.
(153) Runge, W. *Prog. Phys. Org. Chem.* **1981**, *13*, 315.
(154) Gong, L.; McAllister, A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, *113*, 6021.
(155) Allen, A. D.; Tidwell, T. T. *Tetrahedron Lett.* **1991**, *32*, 847.
(156) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.
(157) Zhao, D. -C.; Allen, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1993**, *115*, 10097.
(158) Knaus, E. E.; Coutts, R. T.; Kazakoff, C. W. *J. Chromatogr. Sci.* **1976**, *14*, 525.
(159) Coutts, R. T.; Jones, G. R.; Benderly, A.; Mak, A. L. C. *J. Chromatogr. Sci.* **1979**, *17*, 350.
(160) Kozyokov, V. P.; Feoktistov, A. E.; Mironov, V. F. *Zh. Obshch. Khim.* **1988**, *58*, 1056.
(161) Taylor, R. T.; Cassel, R. A. *Synthesis* **1982**, 672.
(162) Kita, Y. ; Sekihachi, J. -i.; Hayashi, Y.; Da, Y. -Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108.
(163) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.
(164) Kita, Y. ; Matsuda, S.; Kitagaki, S.; Tsuzuki, Y.; Akai, S. *Synlett* **1991**, 401.
(165) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *J. Organomet. Chem.* **1976**, *121*, C21.
(166) Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583.
(167) Brady, W. T.; Saidi, K. *Tetrahedron Lett.* **1978**, 721.
(168) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949.
(169) Ghosez, L. In *Stereoselective Synthesis of Natural Products*; W. Baitmann and E. Winterfeldt, Ed.; Oxford: Amsterdam, 1979; pp 93.
(170) Holden, K. G. In *Chemistry and Biology of β-Lactam Antibiotics*; R. B. Marin and M. Garman, Ed.; Academic Press, Inc: New-York-London, 1982.
(171) Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573.
(172) Mead, K. T.; Yang, H. -L. *Tetrahedron Lett.* **1989**, *30*, 6829.
(173) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1992**, 31.
(174) Santelli, M.; Pons, J. -M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996.
(175) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.
(176) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940.

(177) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.
(178) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693.
(179) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 3967.
(180) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Org. Synth.* **1992**, *71*, 14.
(181) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1991**, 503.
(182) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.
(183) Mukaiyama, T. In *Organic Reactions*John Wiley & Sons, Inc.: New York, 1982; Vol. 28; pp 203.
(184) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
(185) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011.
(186) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 989.
(187) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15.
(188) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.
(189) Mukaiyama, T.; Kobayashi, S. In *Stereocontrolled Organic Synthesis*; B. M. Trost, Ed.; Blackwell Scientific Publication: Boston, 1994; pp 37.
(190) Bach, T. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417.
(191) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837.
(192) Ishihara, K.; Kuroki, Y.; Yamamoto, H. *Synlett* **1995**, 41.
(193) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041.
(194) Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439.
(195) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.
(196) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927.
(197) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729.
(198) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9366.
(199) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295.
(200) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.
(201) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.
(202) Ishihara, K.; Mouri, M.; Gao, Q. Z.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.
(203) Keck, G. E.; Krishnamurty, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543.
(204) Fleming, I. In *Frontier Orbitals and Organic Chemical Reactions*John Wiley & Sons, Ltd.: Chichester, 1990; pp 131.
(205) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
(206) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.
(207) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.
(208) Corey, E. J.; Guzman-Perez, A.; Loh, T. -P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.
(209) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.
(210) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777.

(211) Narasaka, K.; Yamamoto, I. *Tetrahedron* **1992**, *48*, 5743.
(212) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938.
(213) Bao, J. M.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814.
(214) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.
(215) Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Sham, B. L. *Org. Synth.* **1963**, *coll. vol. IV*, 404.
(216) Pommier, A. PhD Thesis, l'Université de Droit, d'Economie et des Sciences d'Aix-Marseille III, 1994.
(217) Parker, D.; Taylor, R. J. In *Asymmetric Synthesis*; R. A. Aitken and S. N. Kilenyi, Ed.; Chapman & Hall: Cambridge, 1992; pp 33.
(218) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.
(219) Chapius, C.; Jurczak, J. *Helv. Chim. Acta.* **1987**, *70*, 436.
(220) Tamai, Y.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Perkin Trans 1* **1994**, 1549.
(221) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2281.
(222) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691.
(223) Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 5849.
(224) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209.
(225) Corey, E. J.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 7938.
(226) Corey, E. J.; Yu, C. -M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.
(227) Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715.
(228) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.
(229) Corey, E. J.; Sarshar, S.; Lee, D. -H. *J. Am. Chem. Soc.* **1994**, *116*, 12089.
(230) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575.
(231) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013.
(232) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. *Synlett* **1995**, 975.
(233) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851.
(234) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.
(235) Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4815.
(236) Corey, E. J.; Lee, D. -H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.
(237) Corey, E. J.; Pikul, S. *Org. Synth.* **1993**, *71*, 22.
(238) Corey, E. J.; Pikul, S. *Org. Synth.* **1993**, *71*, 30.
(239) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
(240) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(241) Pons, J. -M.; Oblin, M.; Pommier, A.; Rajzmann, M.; Liotard, D. *J. Am. Chem. Soc.* **1997**, *119*, 3333.
(242) Yamabe, S.; Minato, T.; Osamura, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 450.

(243) Lecea, B.; Arrieta, A.; Roa, G.; Ugalde, J. M.; Cossio, F. P. *J. Am. Chem. Soc.* **1994**, *116*, 9613.

(244) Pons, J. -M.; Pommier, A.; Rajzmann, M.; Liotard, D. *J. Mol. Struct. (Theochem)* **1994**, *119*, 361.

(245) Woodward, R. B.; Hoffman, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

(246) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag-Chemie/Academic: Weinheim, 1971, pp 781.

(247) Fleming, I. In *Frontier Orbitals and Organic Chemical Reactions*John Wiley & Sons, Ltd.: Chichester, 1990; pp 142.

(248) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(249) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(250) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(251) Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6832.

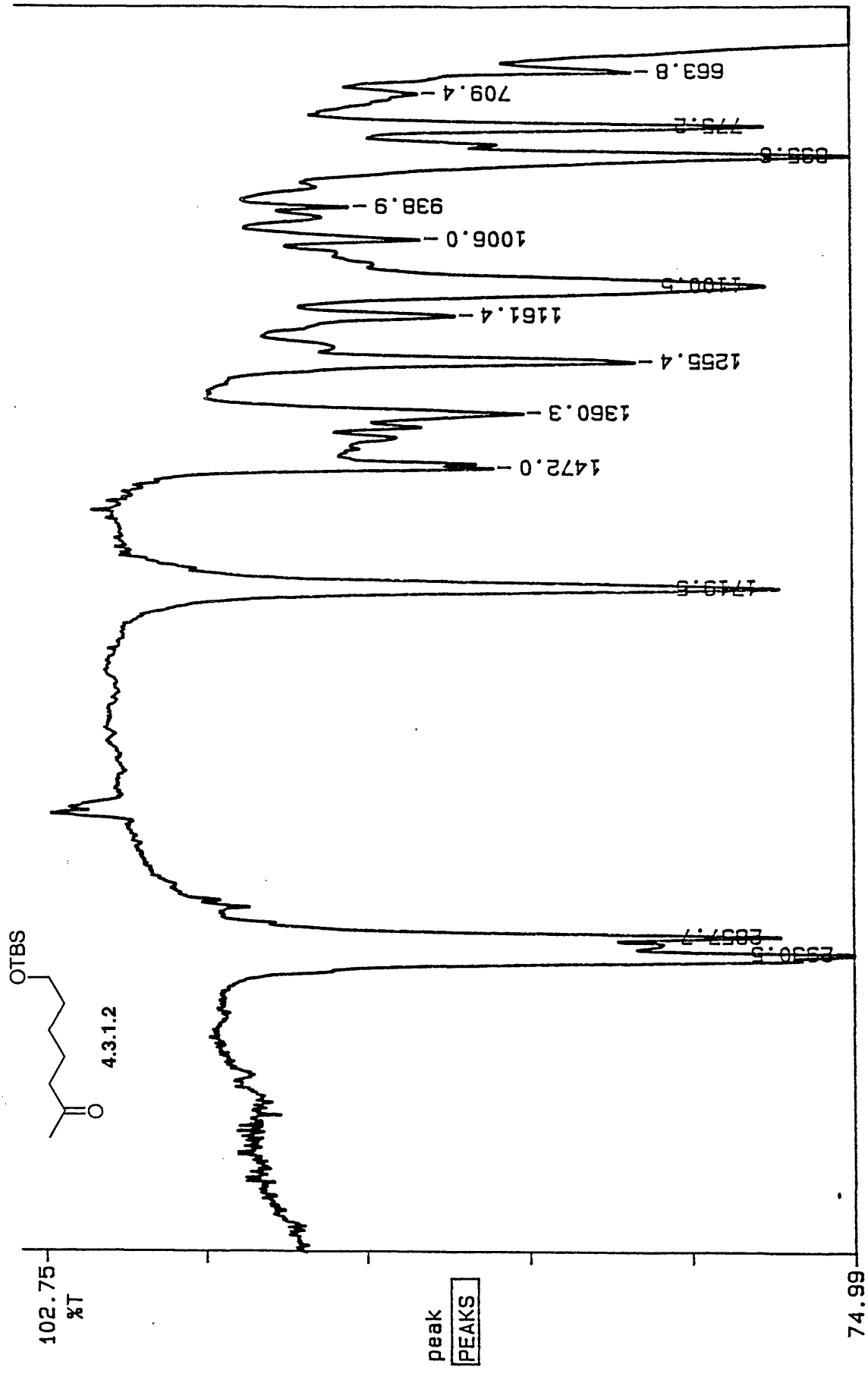
(252) Perrin, D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed.; Pergamon Press: 1988.

(253) Huntress, E. H.; Carten, F. H. *J. Am. Chem. Soc.* **1940**, *62*, 511.

(254) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C. *J. Organomet. Chem.* **1980**, *186*, 155.

(255) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Spectral Data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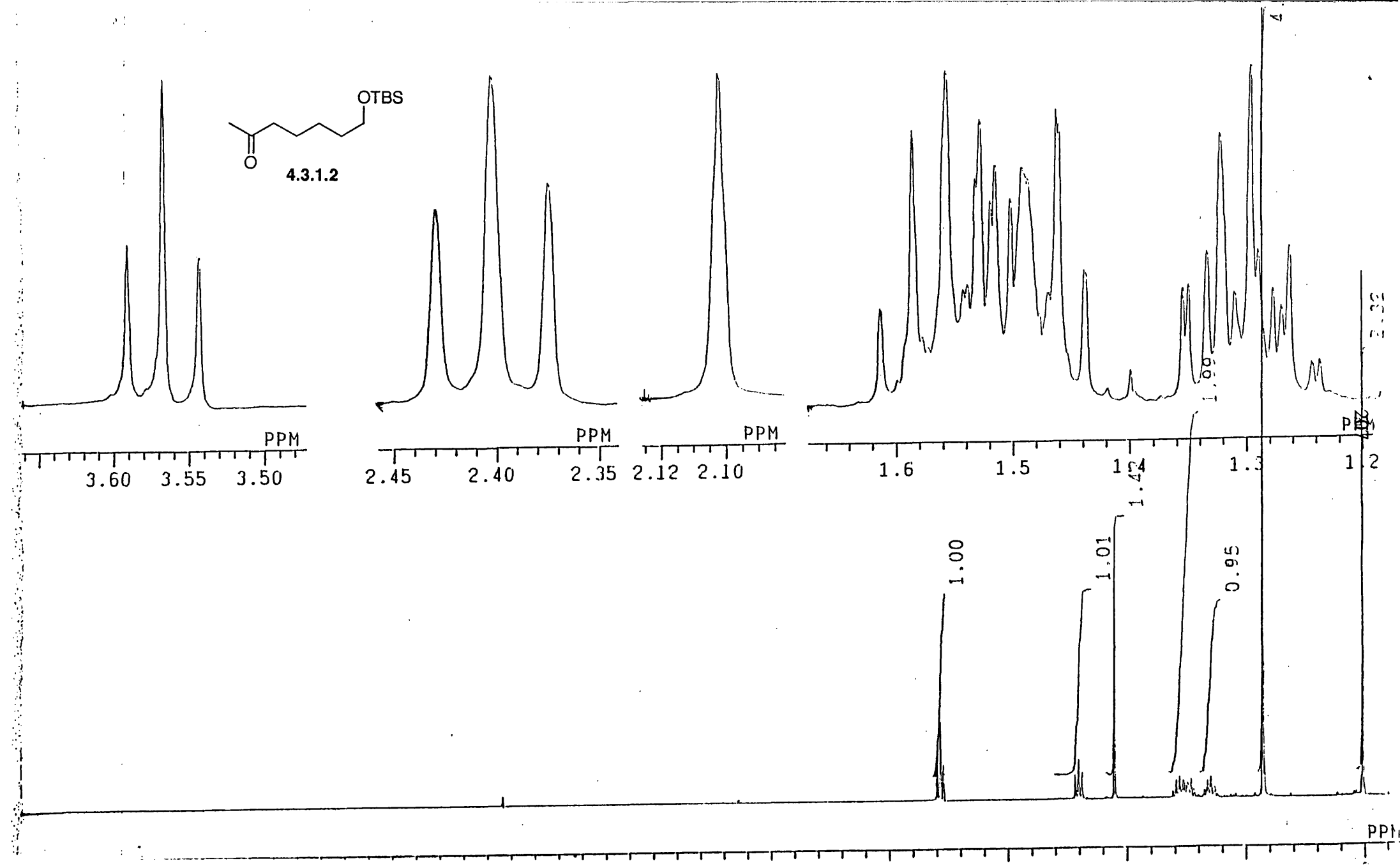
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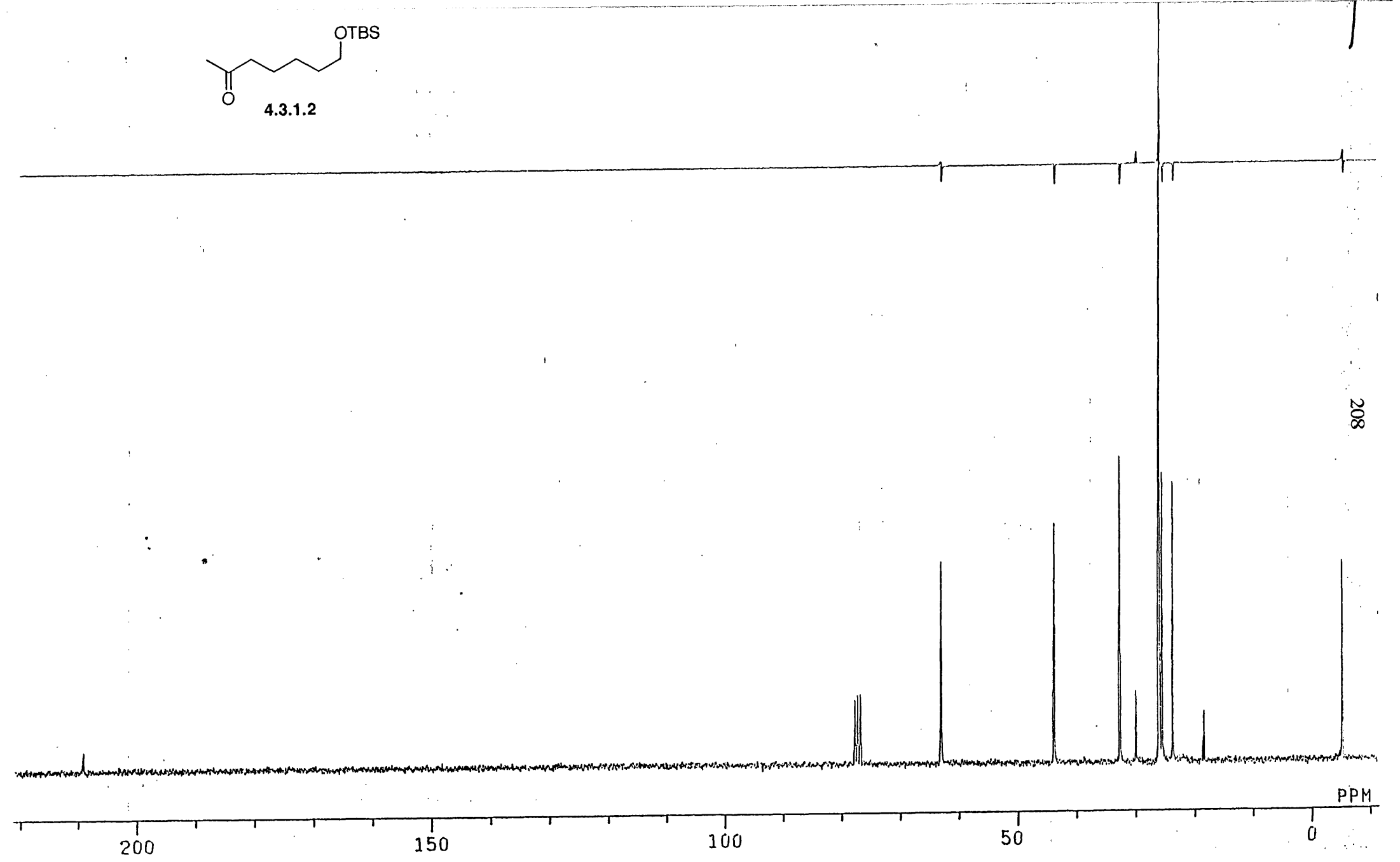
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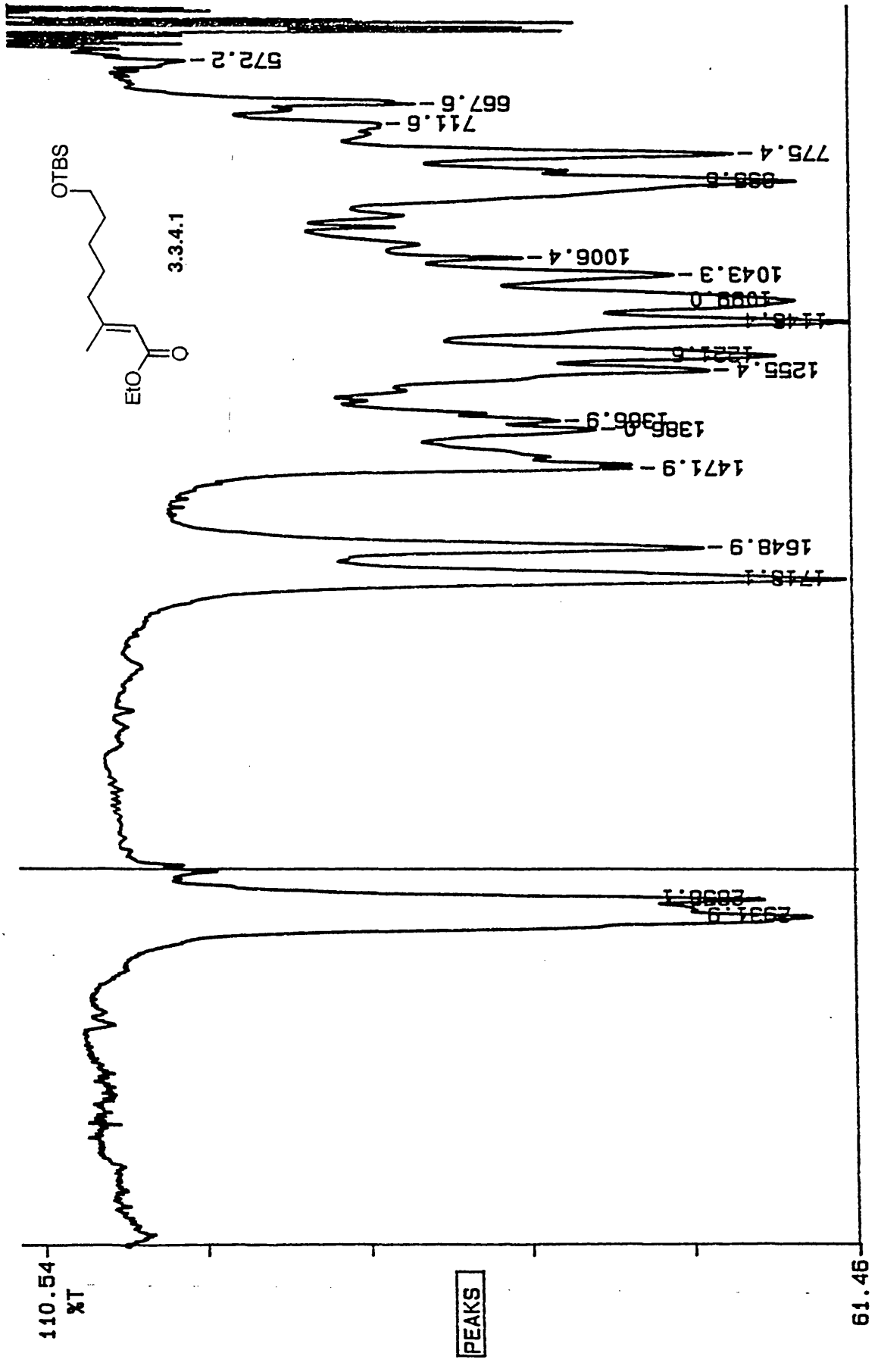
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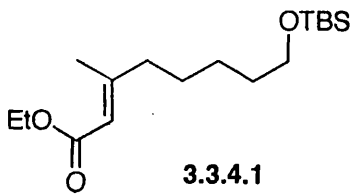
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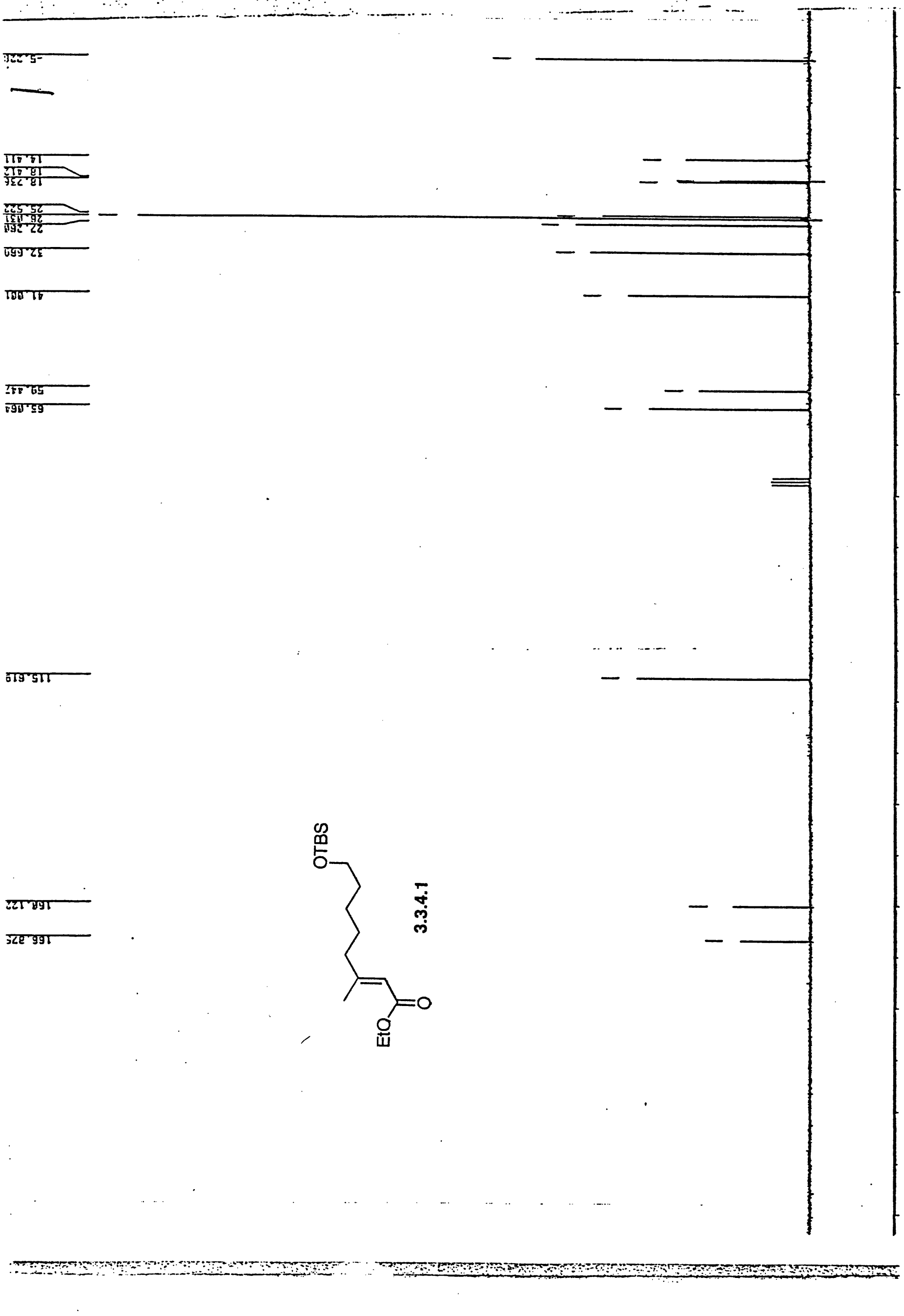
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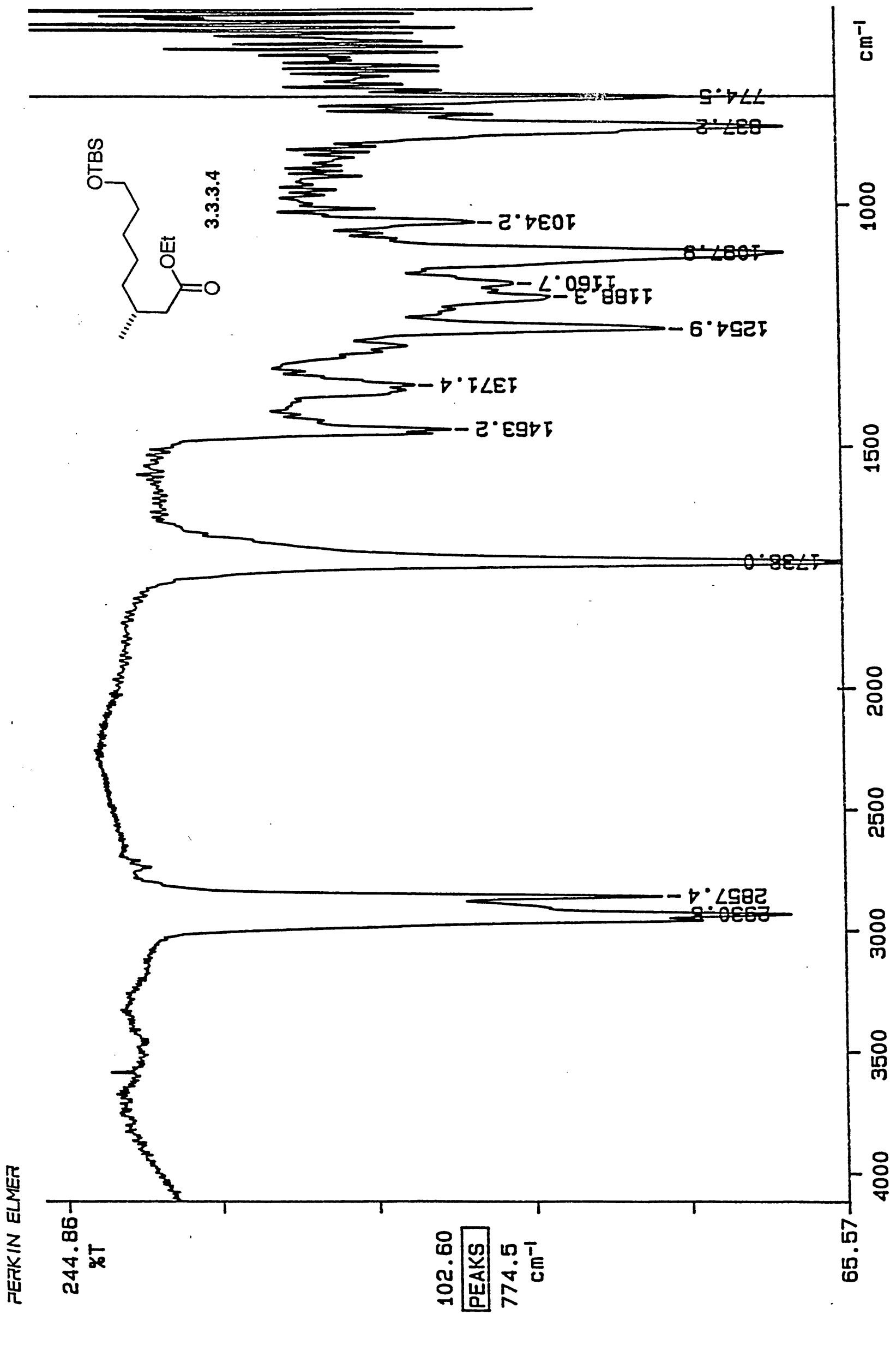
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3000
2500
2000
1500
1000
cm⁻¹
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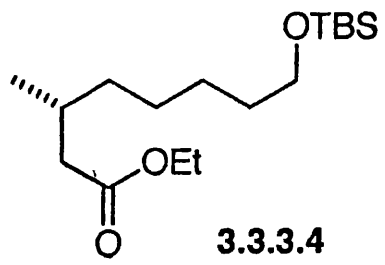
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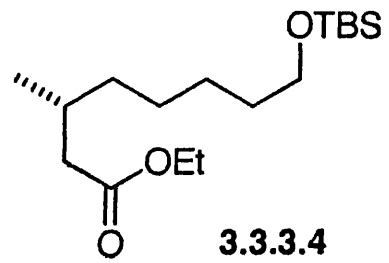

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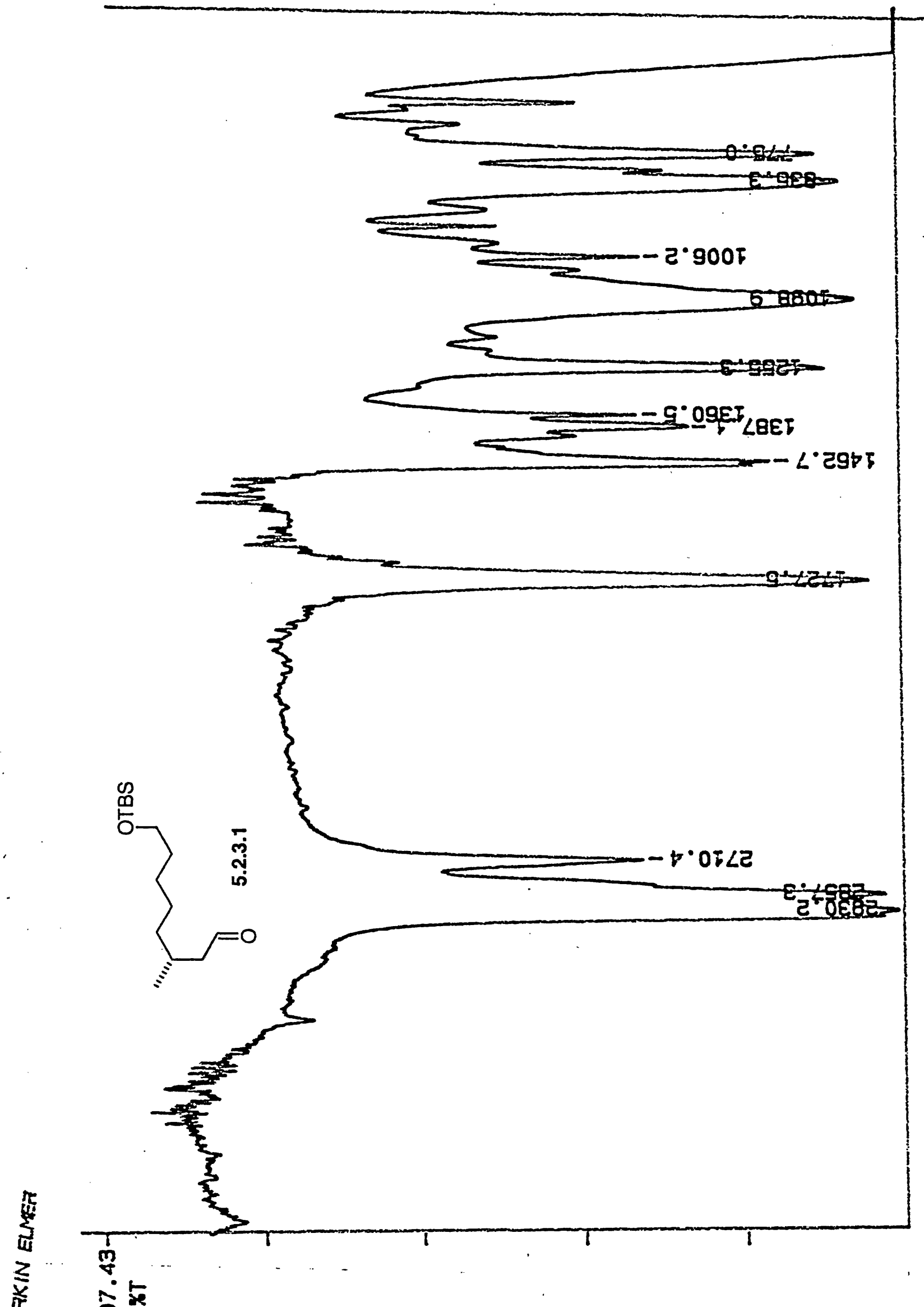
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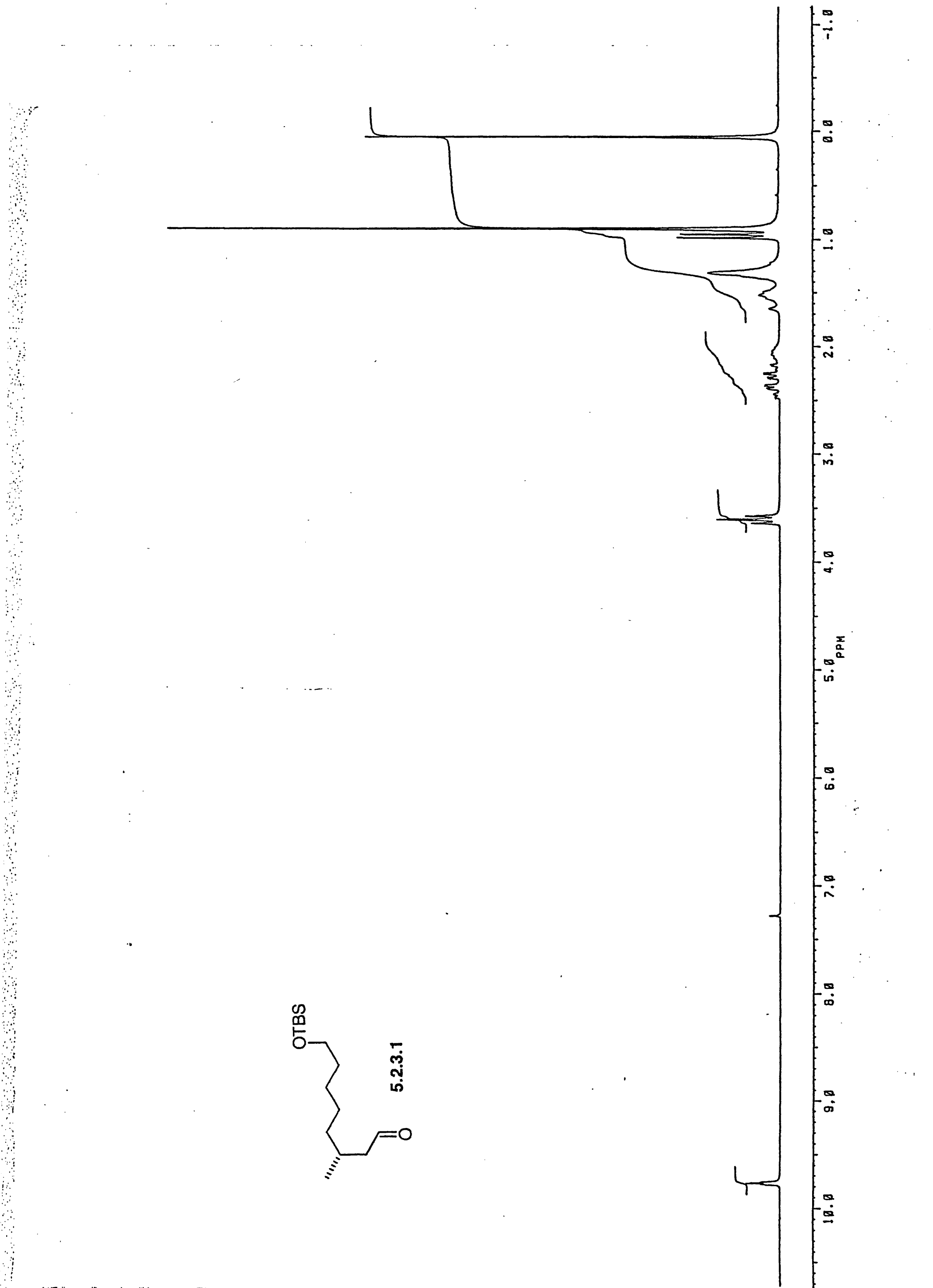
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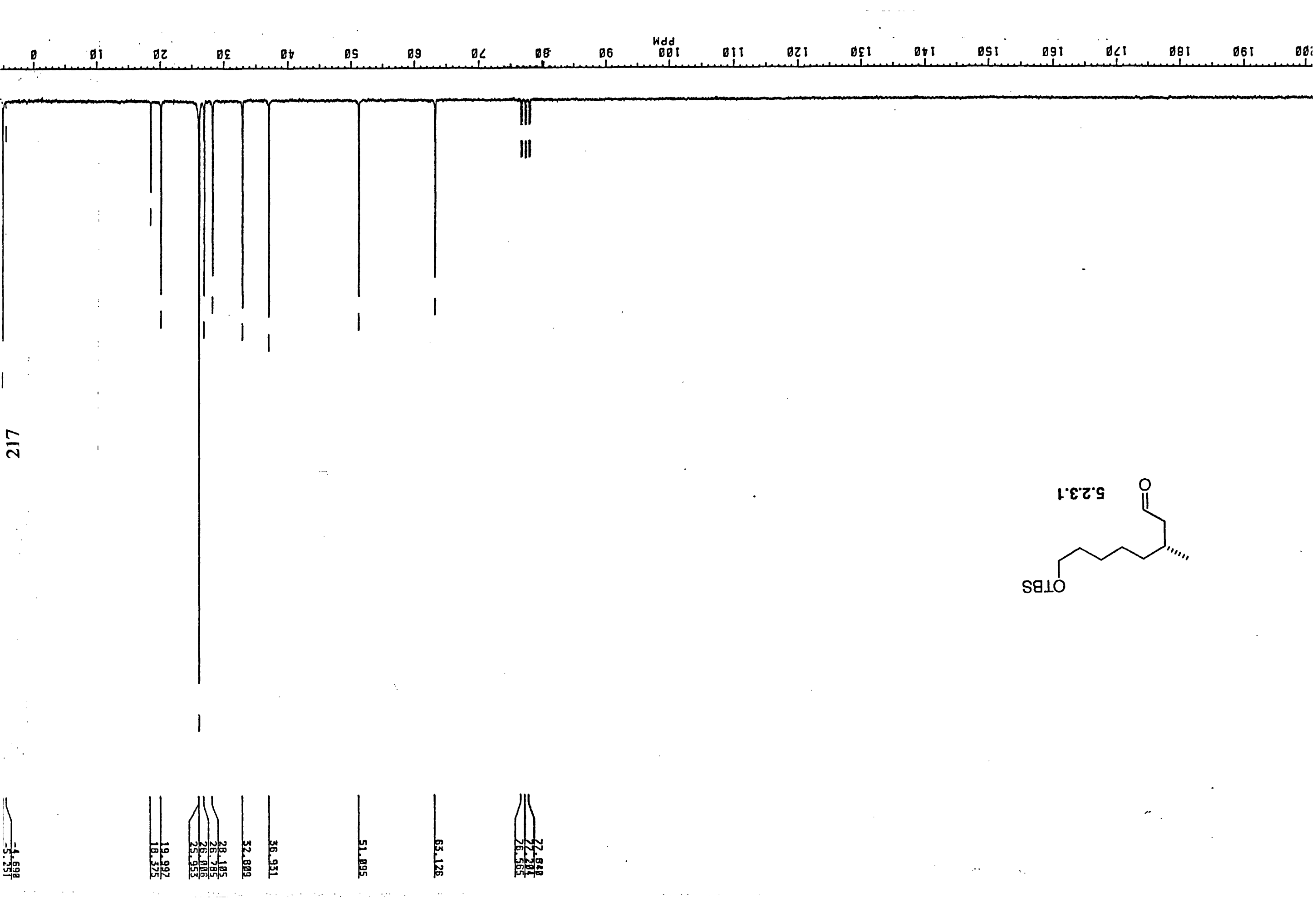
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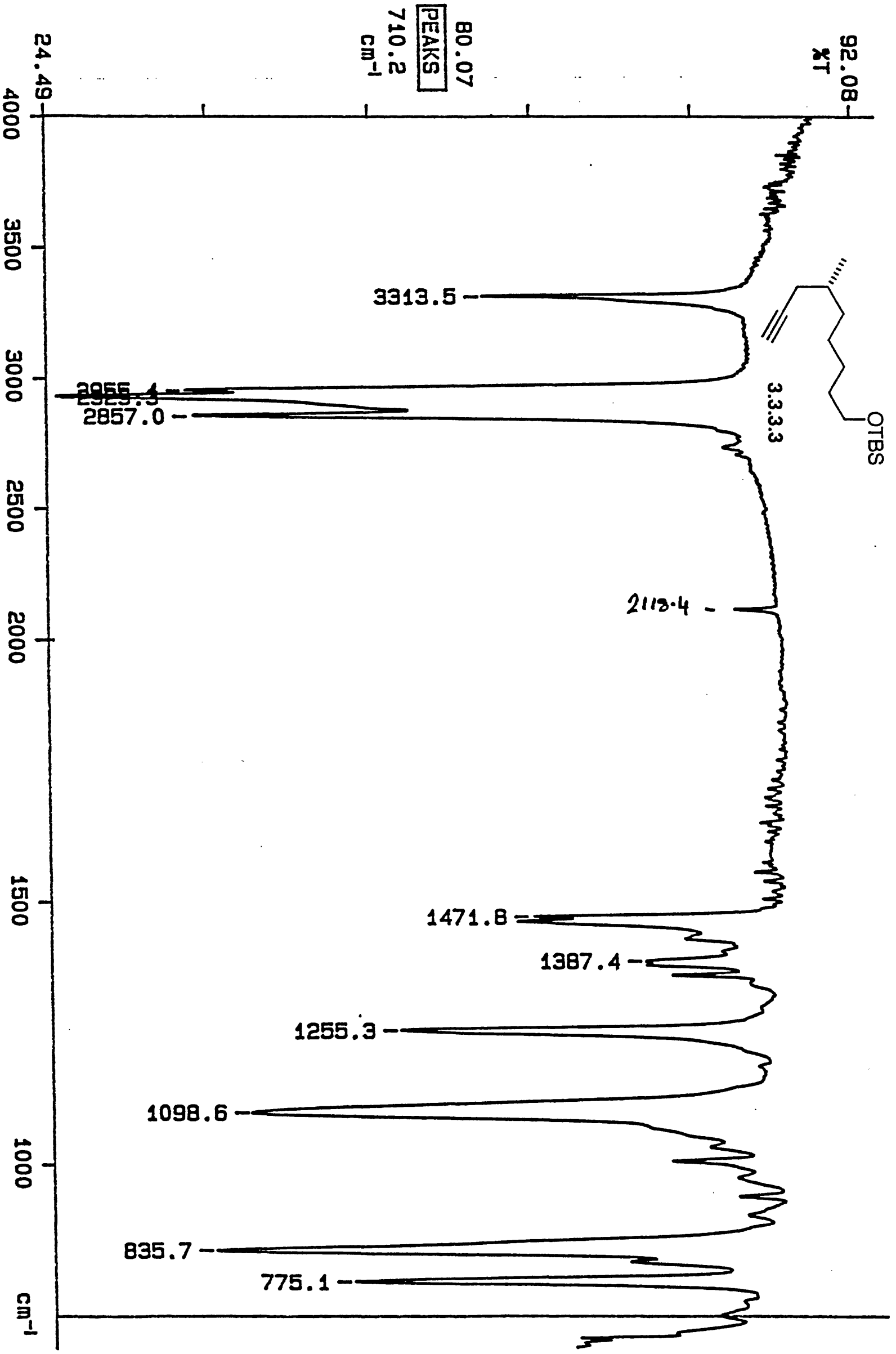
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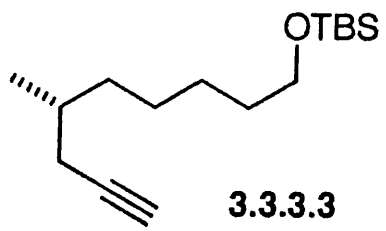

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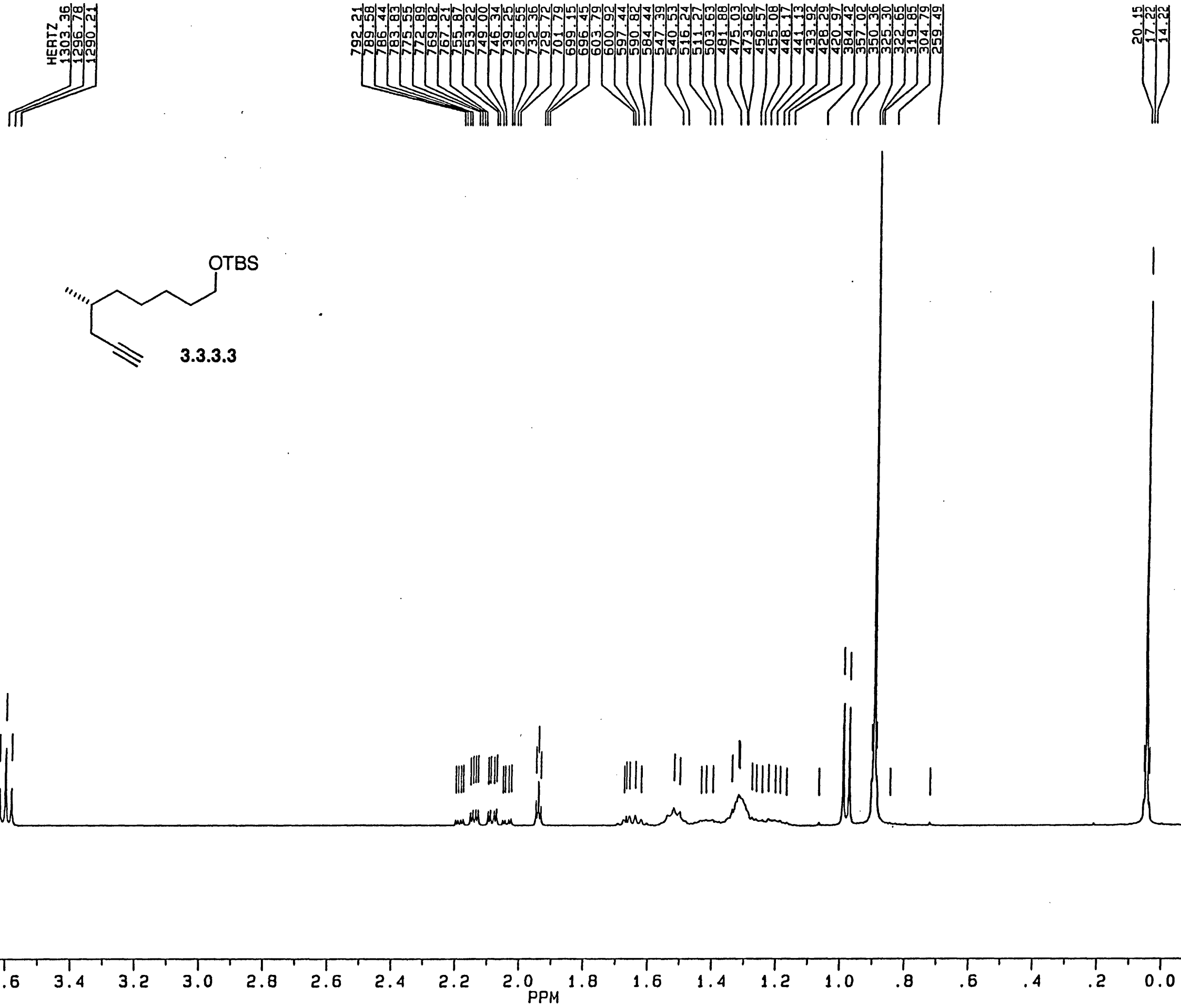
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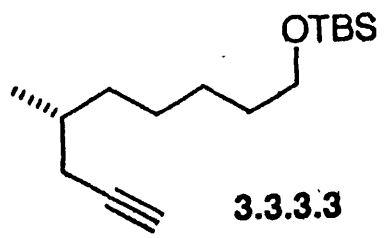

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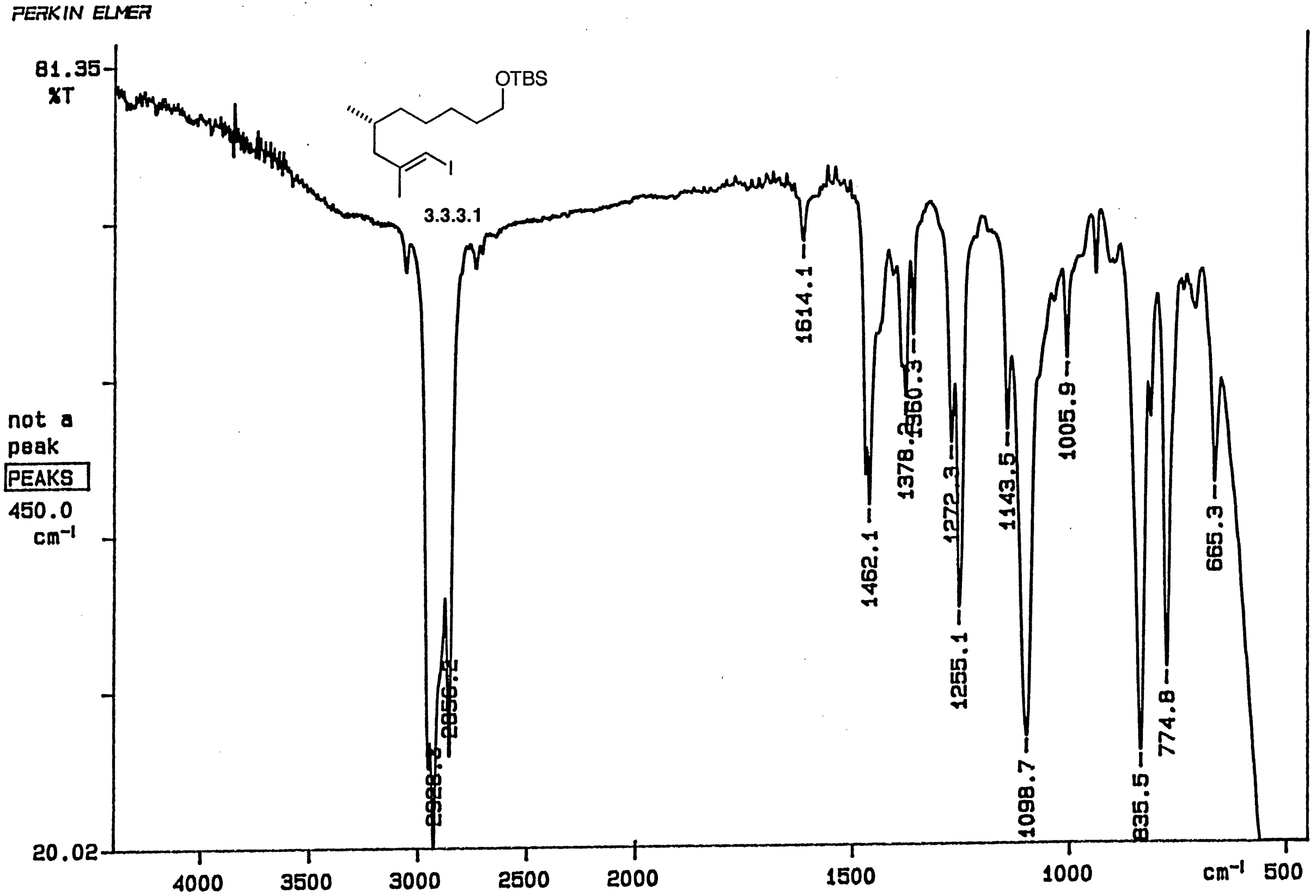
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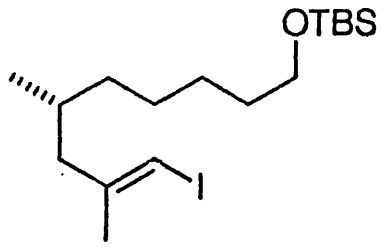

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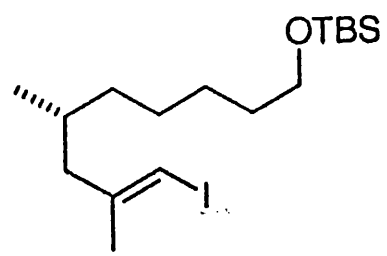

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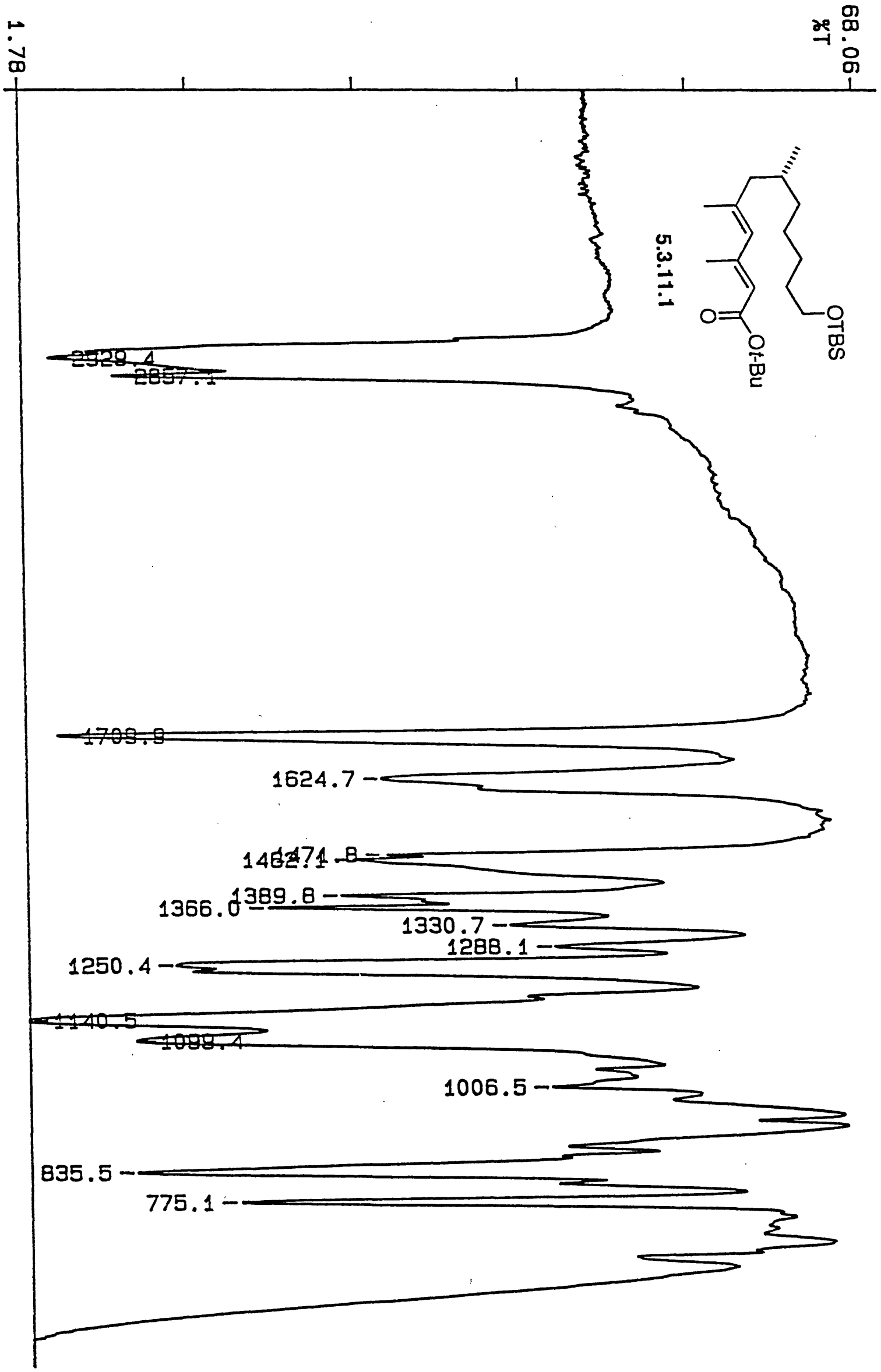
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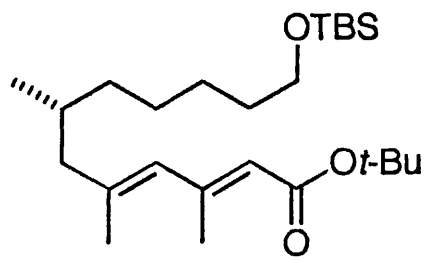
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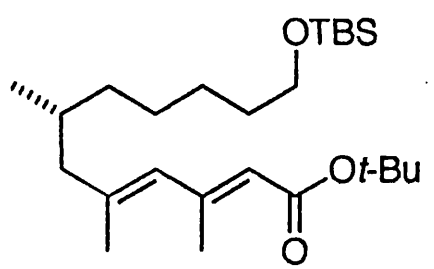

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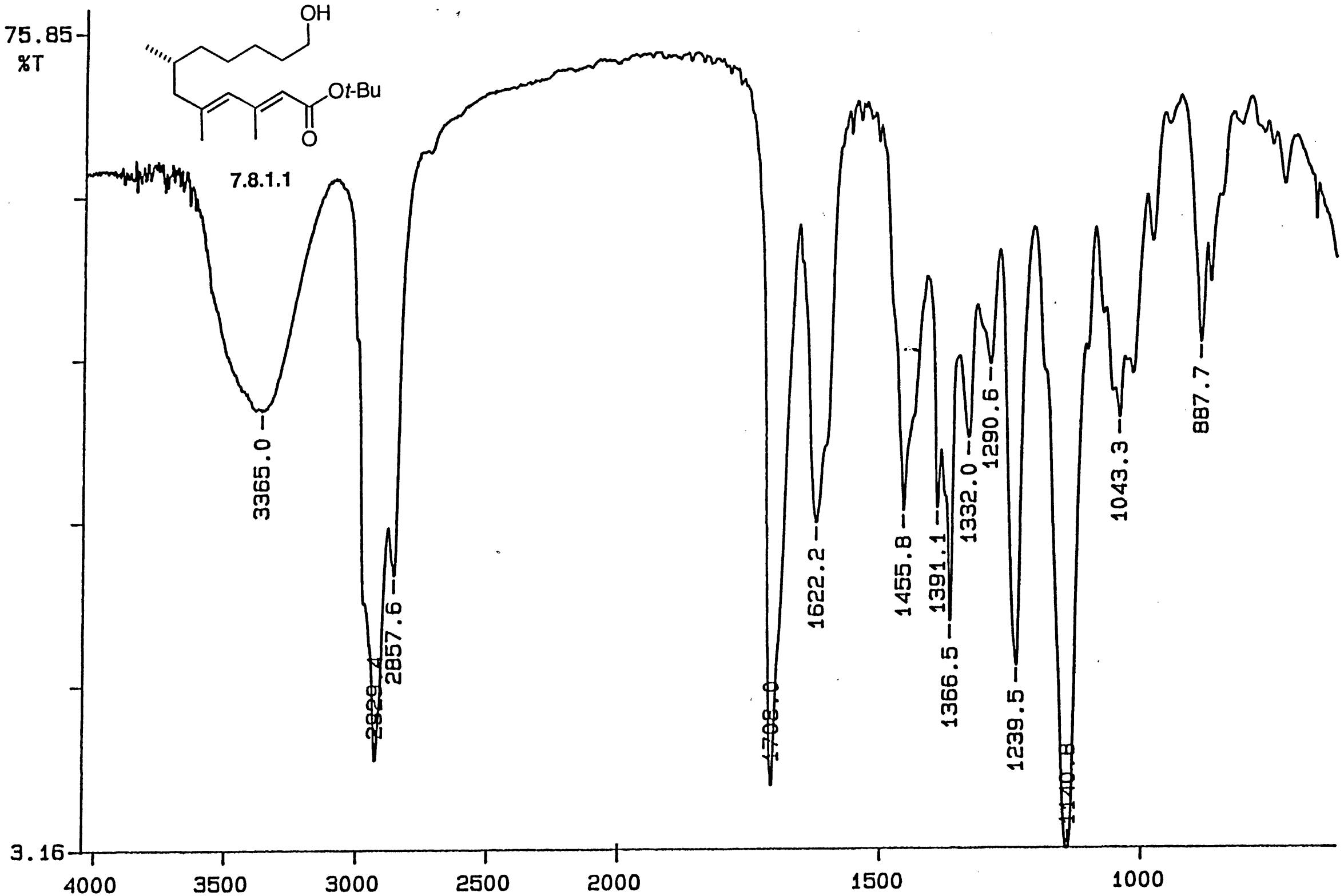
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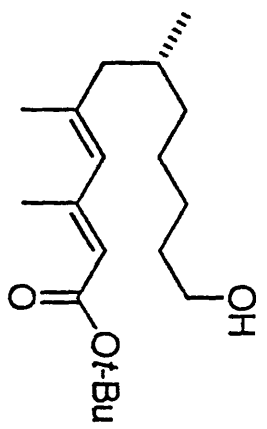
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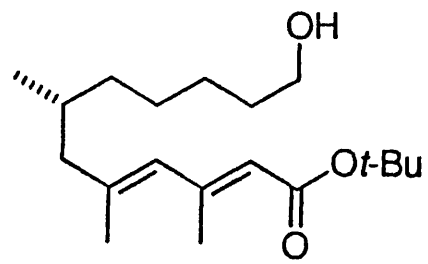
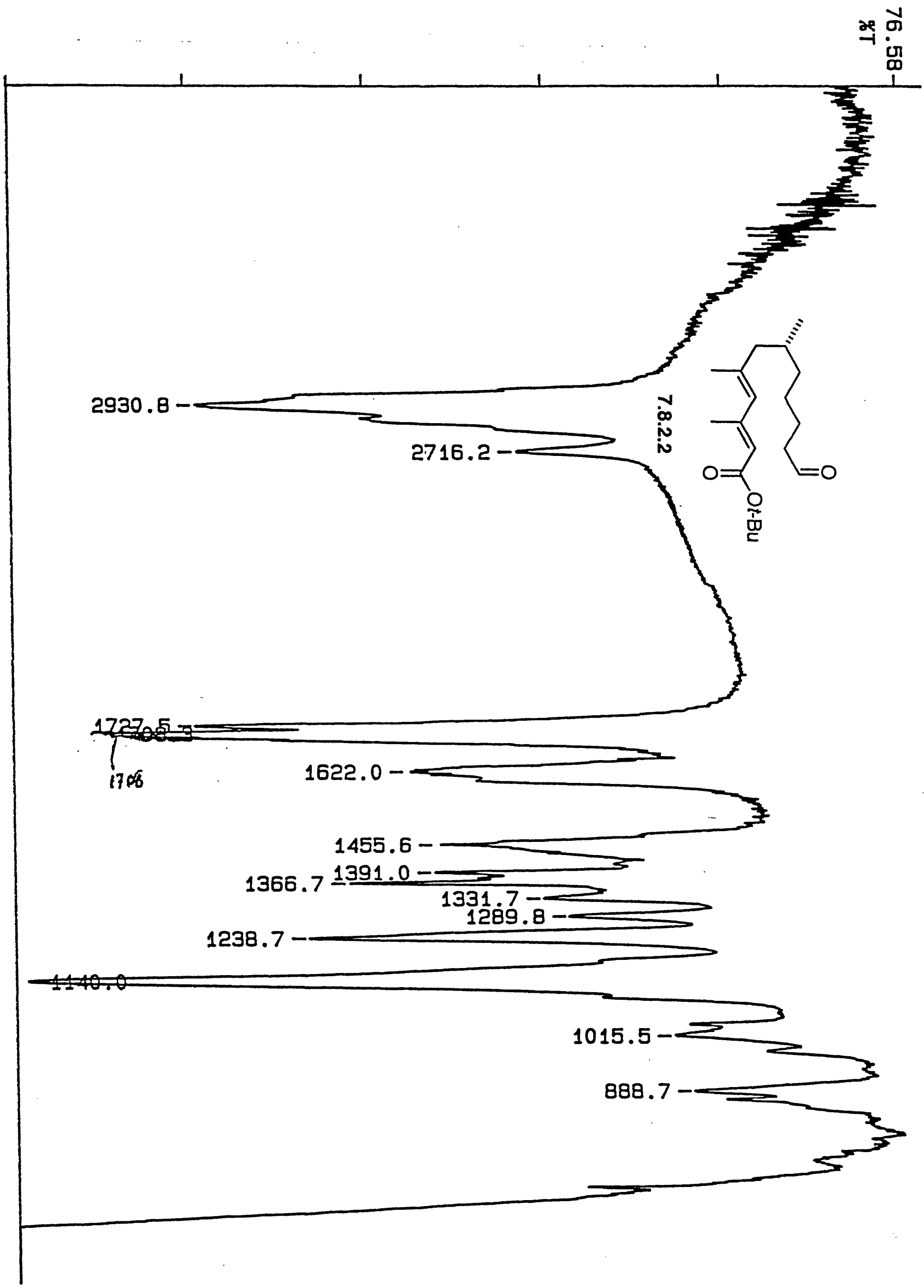
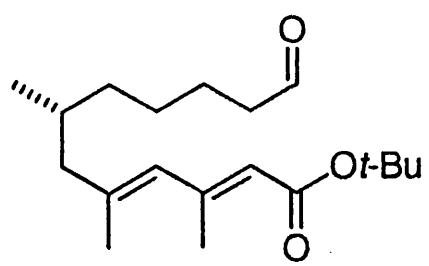
9
10
11
1.00
1.02
2.18
3.01
0.90
0.88
3.70
1.69
8.37
3.97
2.79

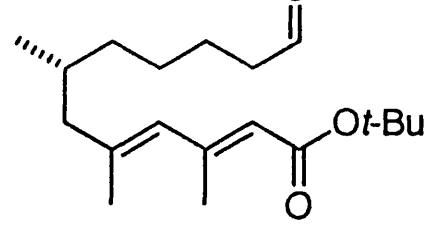


7.8.1.1


76.58
%T
2930.8
2716.2
7.8.2.2
O
O
O
O-t-Bu
1727.5
1706
1622.0
1455.6
1391.0
1366.7
1331.7
1289.8
1238.7
1140.0
1015.5
888.7



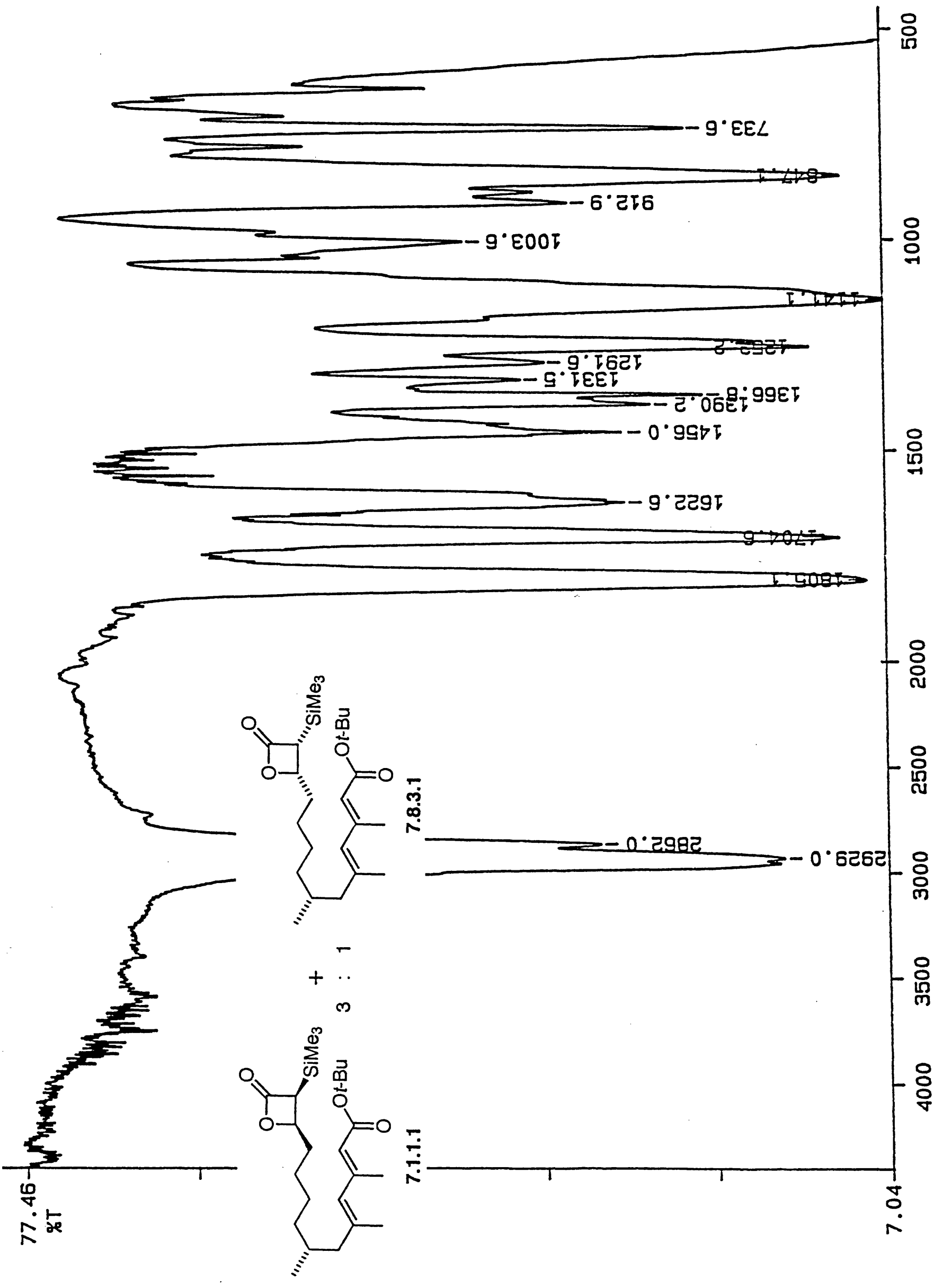
7.8.2.2

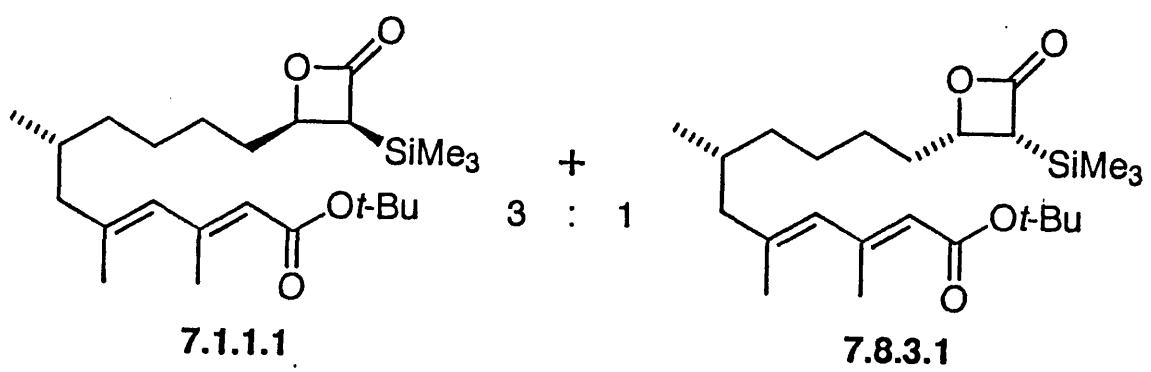


7.8.2.2

PPM

200 150 100 50 0


77.46
%T
2929.0
2862.0
1822.6
1704.6
1456.0
1390.2
1366.8
1331.5
1291.6
1252.2
1141.1
1003.6
912.9
847.1
733.6
1805.1
500
1000
1500
2000
2500
3000
3500
4000
7.04
7.8.3.1
7.1.1.1
SiMe3
Ot-Bu
3 : 1
+
SiMe3
Ot-Bu


SiMe3
Ot-Bu
O
O

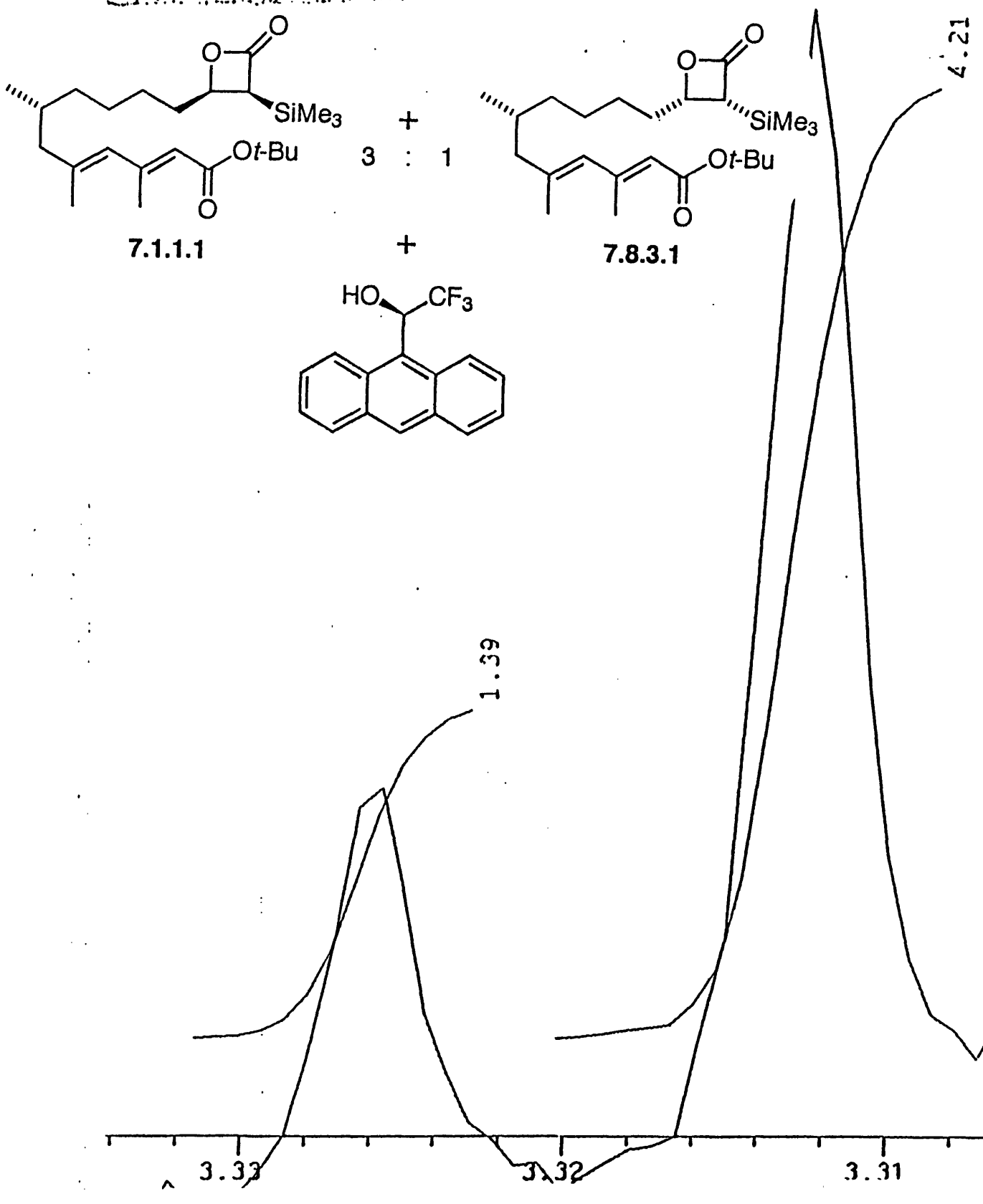
7.1.1.1

3 : 1

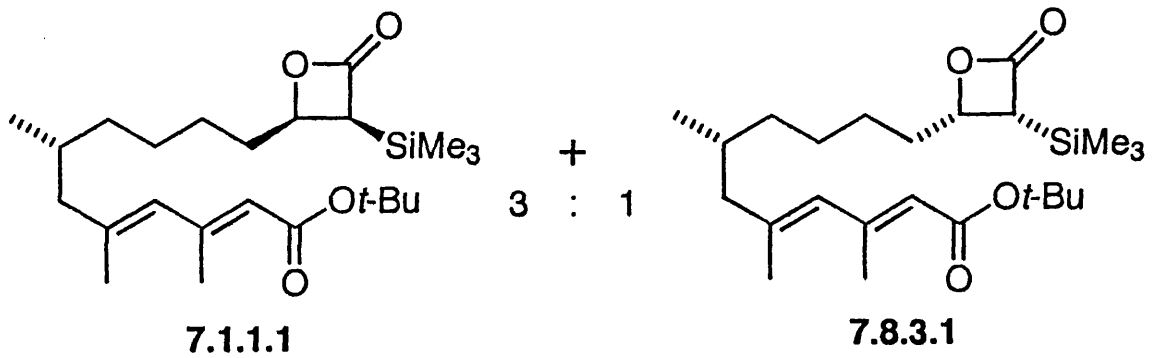
SiMe3
Ot-Bu
O
O

7.8.3.1

23.39
7.81
2.00
1.06
1.00
2.72
1.02
2.84
11
10
9
8
7
6
5
4
3
2
1
0


SiMe3
Ot-Bu
3 : 1
7.1.1.1
7.8.3.1
HO
CF3

4.21
4.48
1.39
1.00
3.33
3.32
3.31
3.30
PPM

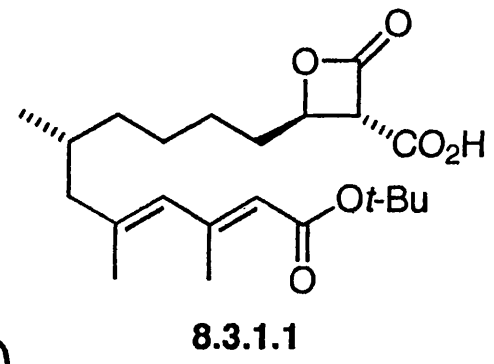


7.1.1.1

3 : 1

7.8.3.1

PERKIN ELMER



8.3.1.1

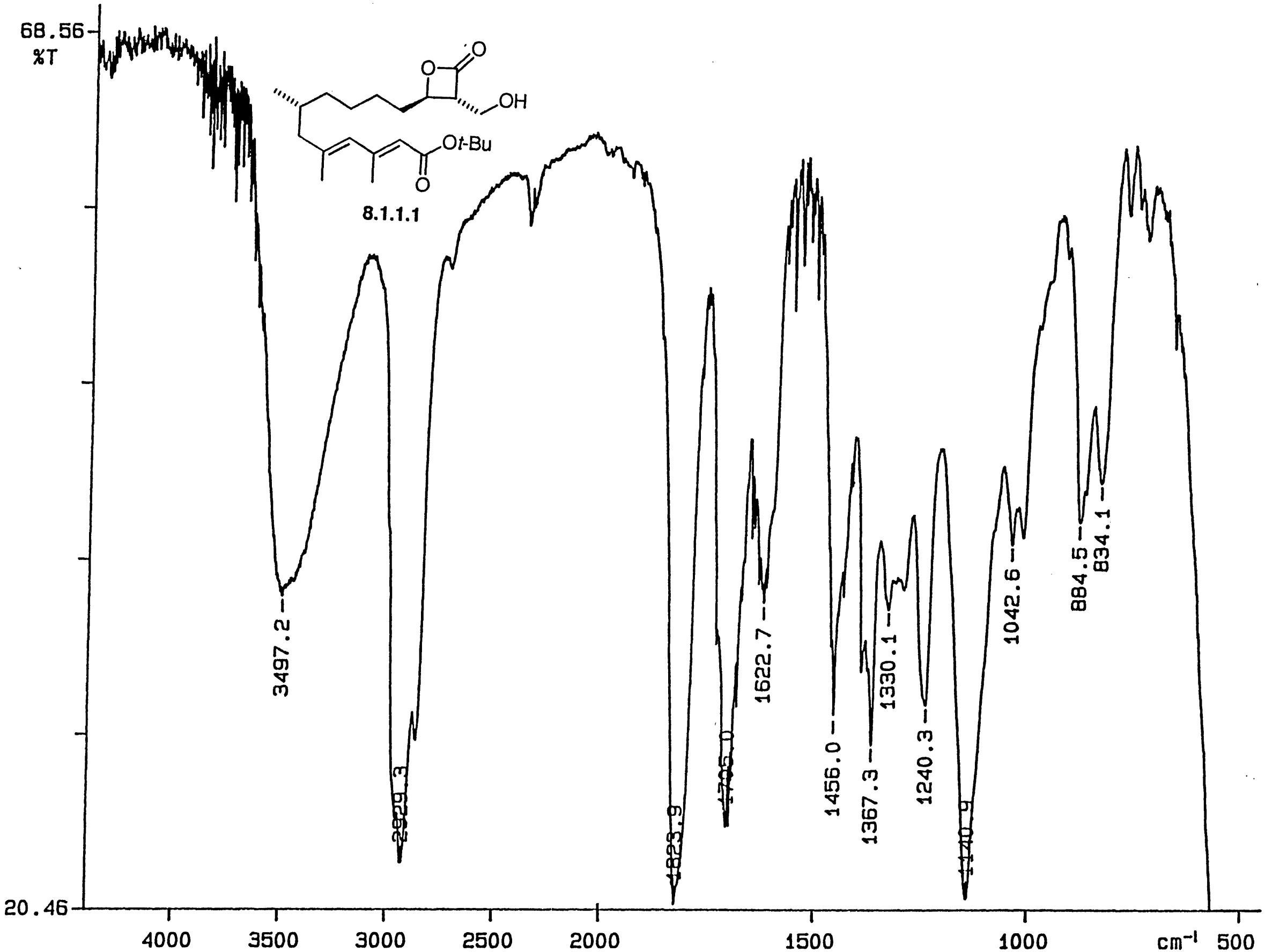
40.94
%T

not a
peak
PEAKS
463.6
cm-1

2923.9
1827.2
1731.5
1462.7
1381.7
1123.7
877.5
736.1

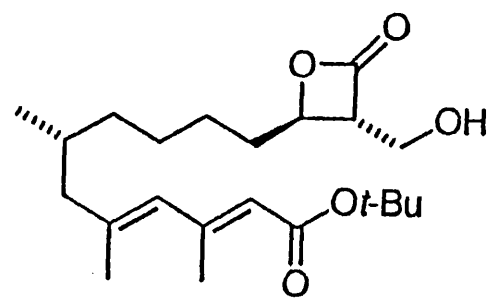
6.88

4000 3500 3000 2500 2000 1500 1000 cm-1 500

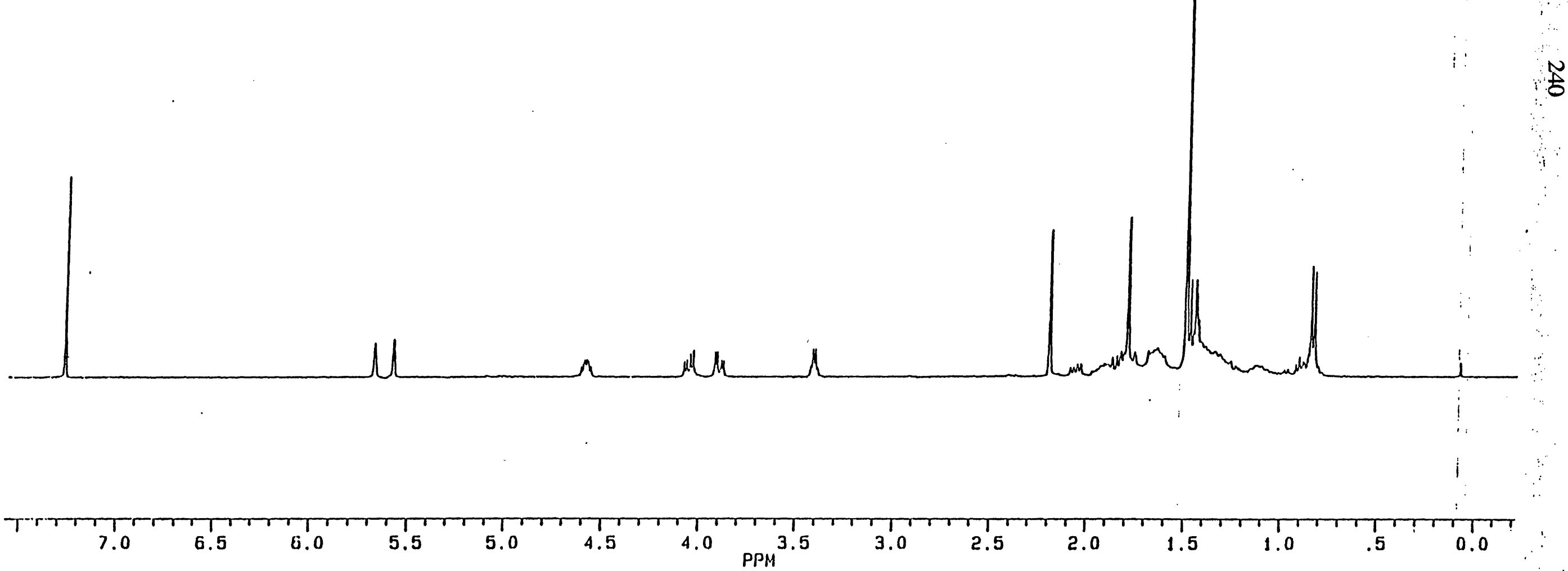

68.56
%T
20.46
3497.2
2929.3
1823.9
1705.0
1622.7
1456.0
1367.3
1330.1
1240.3
1140.9
1042.6
884.5
834.1
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

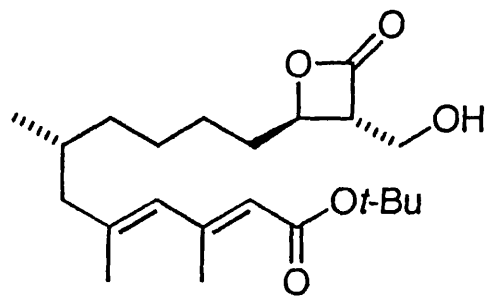
O
O
OH
Ot-Bu
O

8.1.1.1

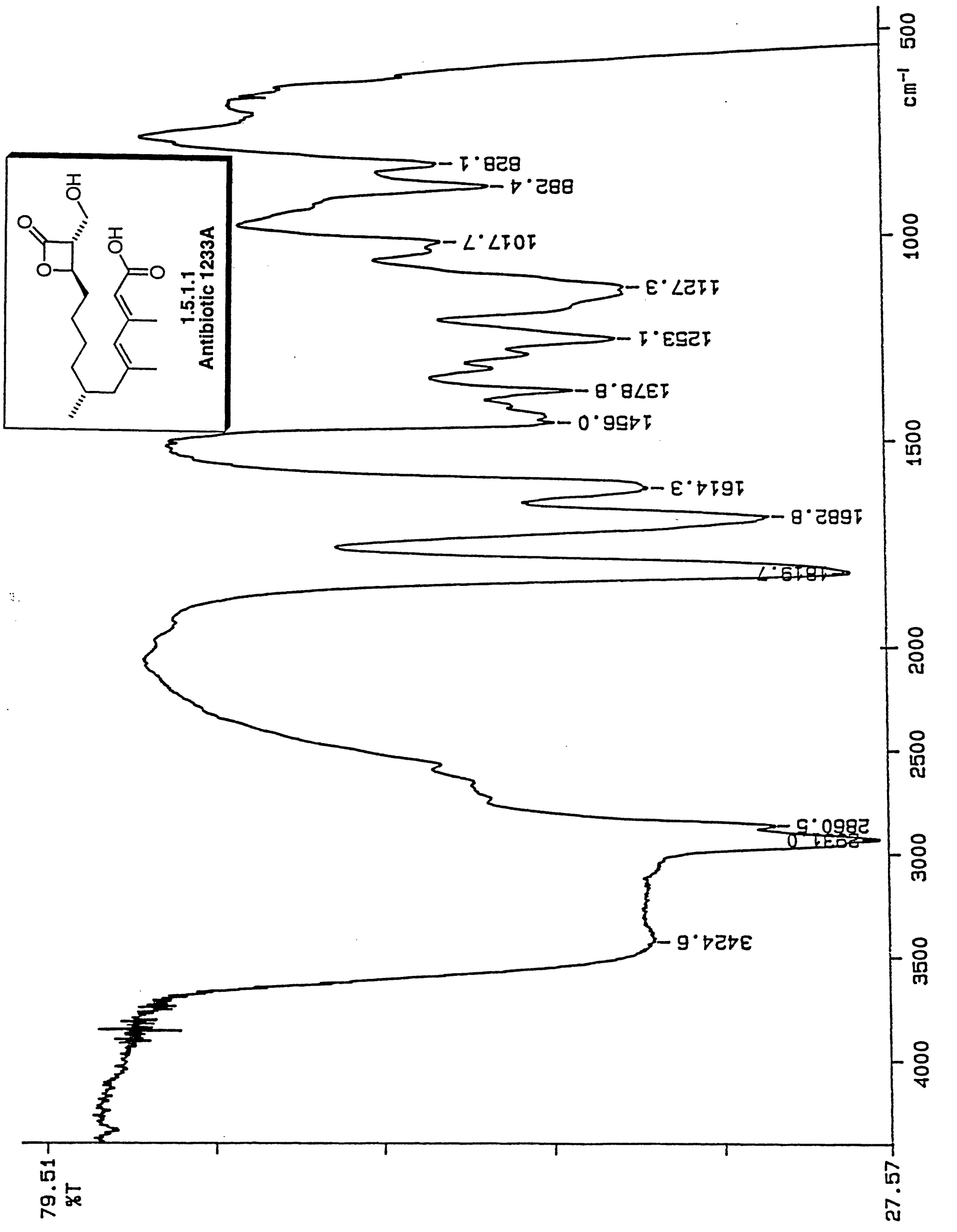


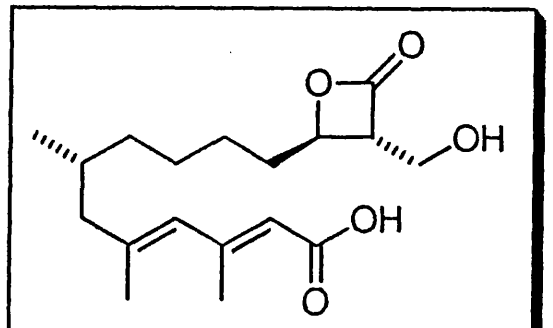
8.1.1.1



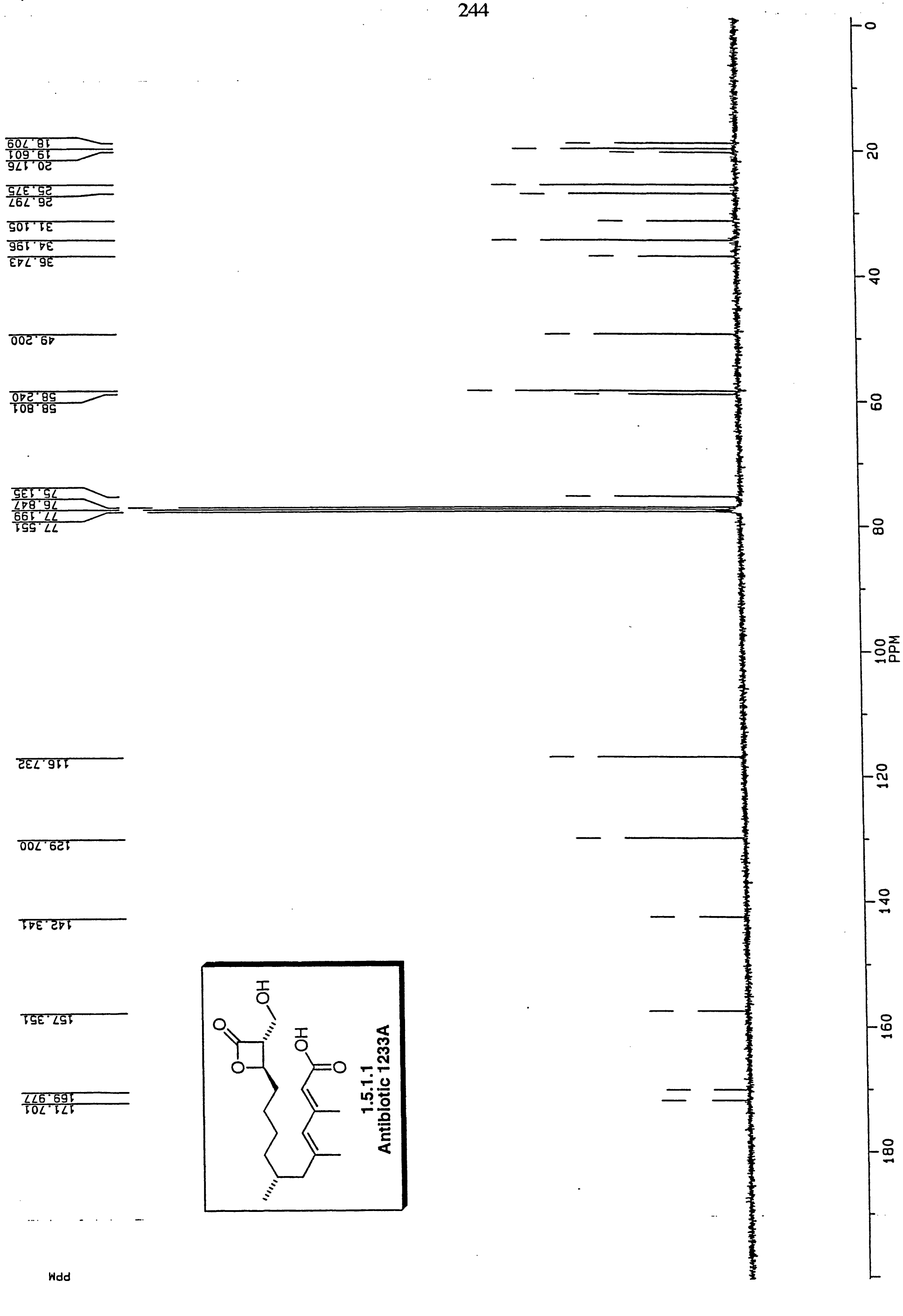


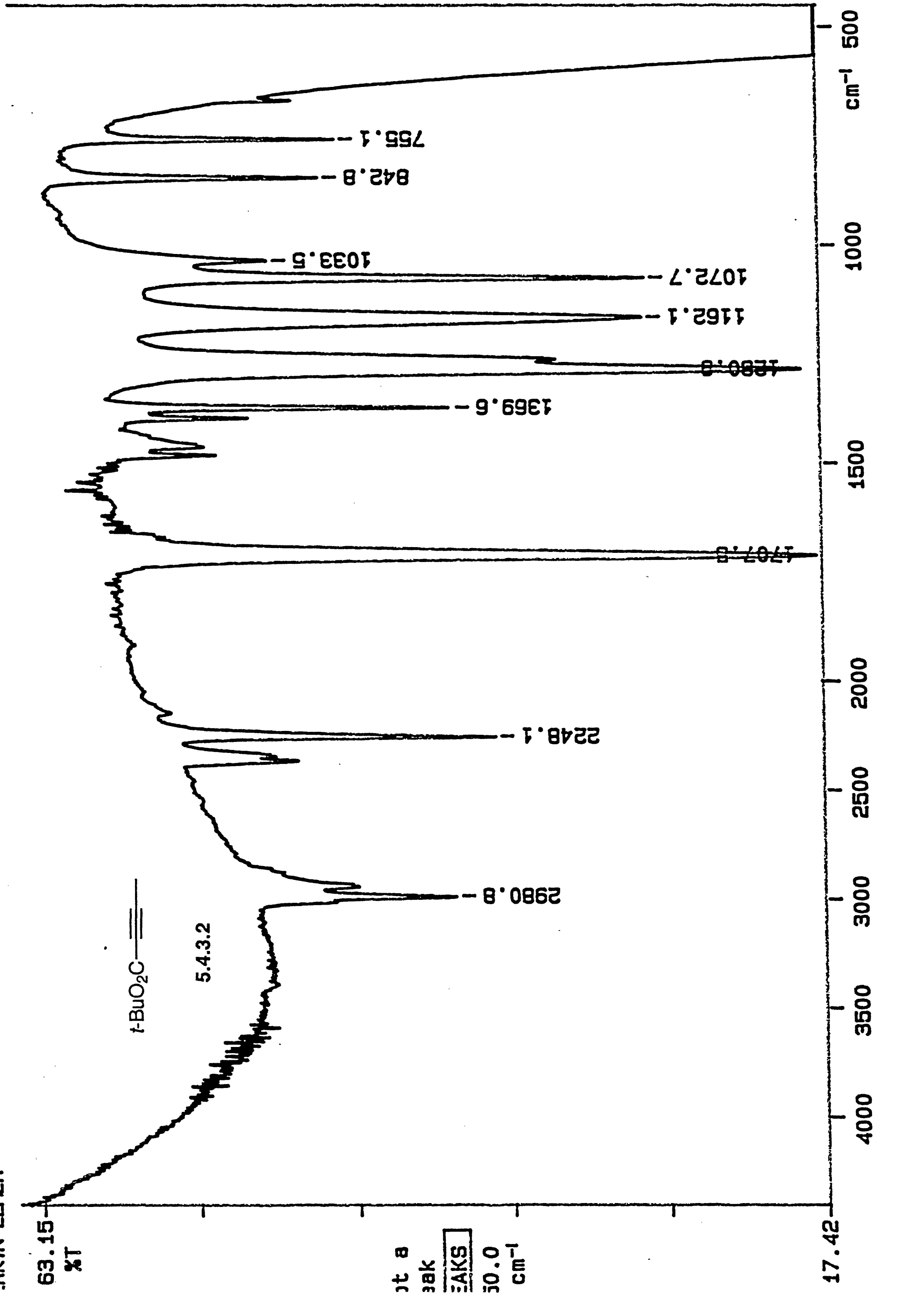
8.1.1.1


1.5.1.1
Antibiotic 1233A
OH
OH
O
O
O
cm⁻¹
500
1000
1500
2000
2500
3000
3500
4000
79.51
%T
27.57
828.1
882.4
1017.7
1127.3
1253.1
1378.8
1456.0
1614.3
1682.8
1819.7
2341.0
2860.5
3424.6



1.5.1.1
Antibiotic 1233A

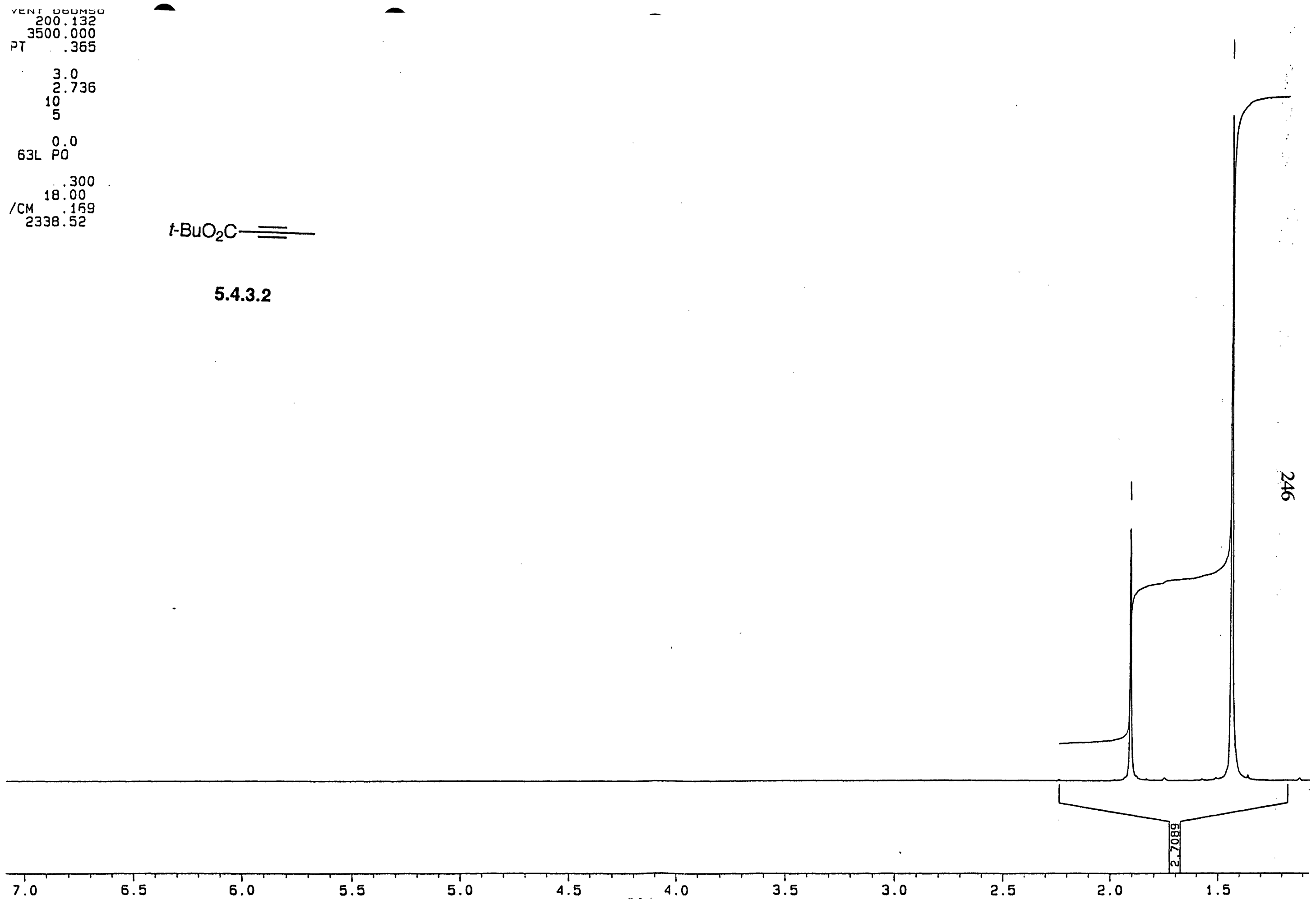

18.709
19.601
20.176
25.375
26.797
31.105
34.196
36.743
49.200
58.240
58.801
75.135
76.847
77.199
77.551
116.732
129.700
142.341
157.351
169.977
171.701
0
20
40
60
80
100
120
140
160
180
PPM
OH
O
O
OH
O
1.5.1.1
Antiblotic 1233A
PPM

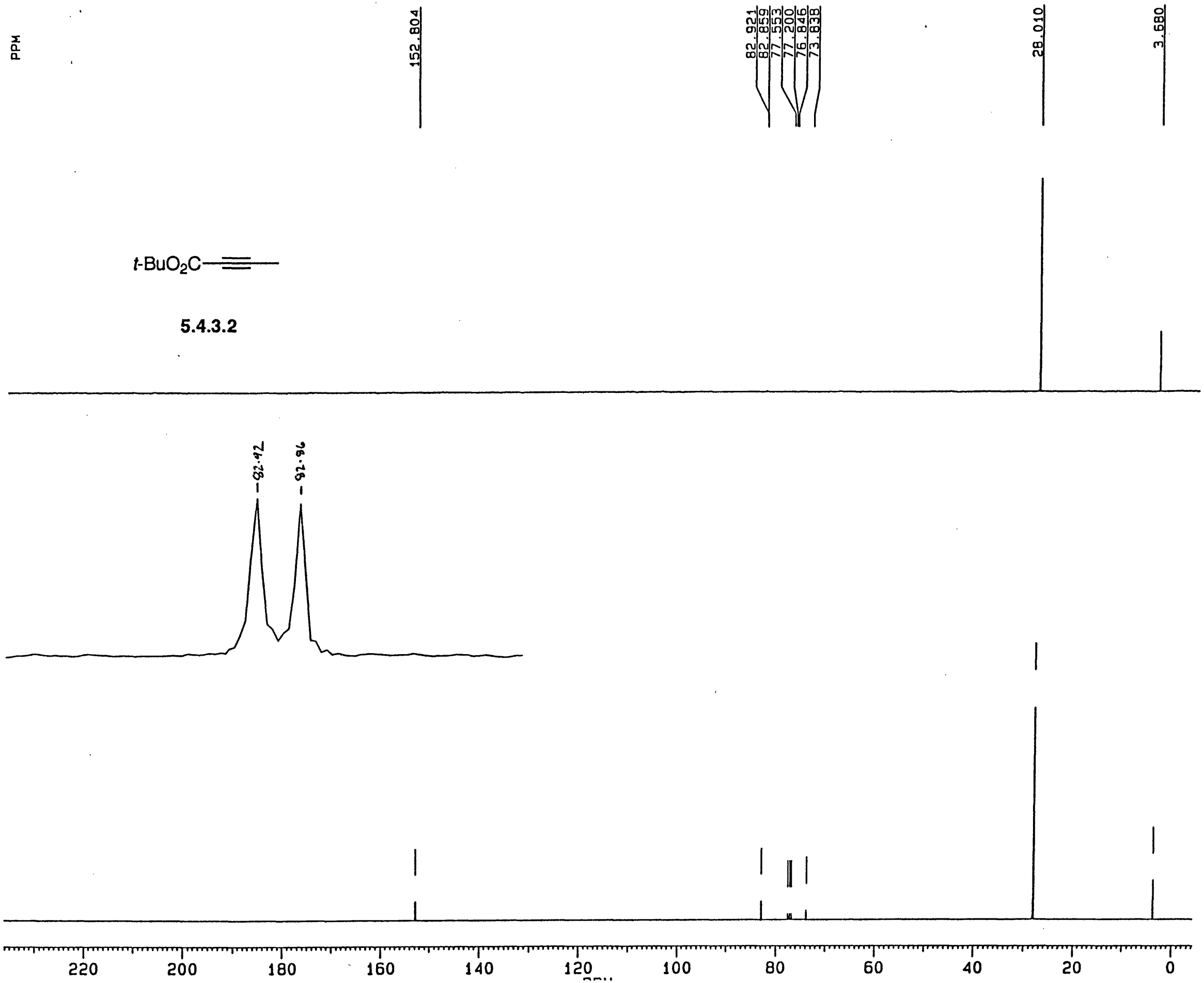

63.15
%T
17.42
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹
2980.8
2248.1
1707.8
1369.6
1280.8
1162.1
1072.7
1033.5
842.8
755.1
t-BuO2C
5.4.3.2

VENT DBDMSO
200.132
3500.000
PT .365
3.0
2.736
10
5
0.0
63L PO
.300
18.00
/CM .169
2338.52

t-BuO_2C—≡—

5.4.3.2





t-BuO_2C—≡—

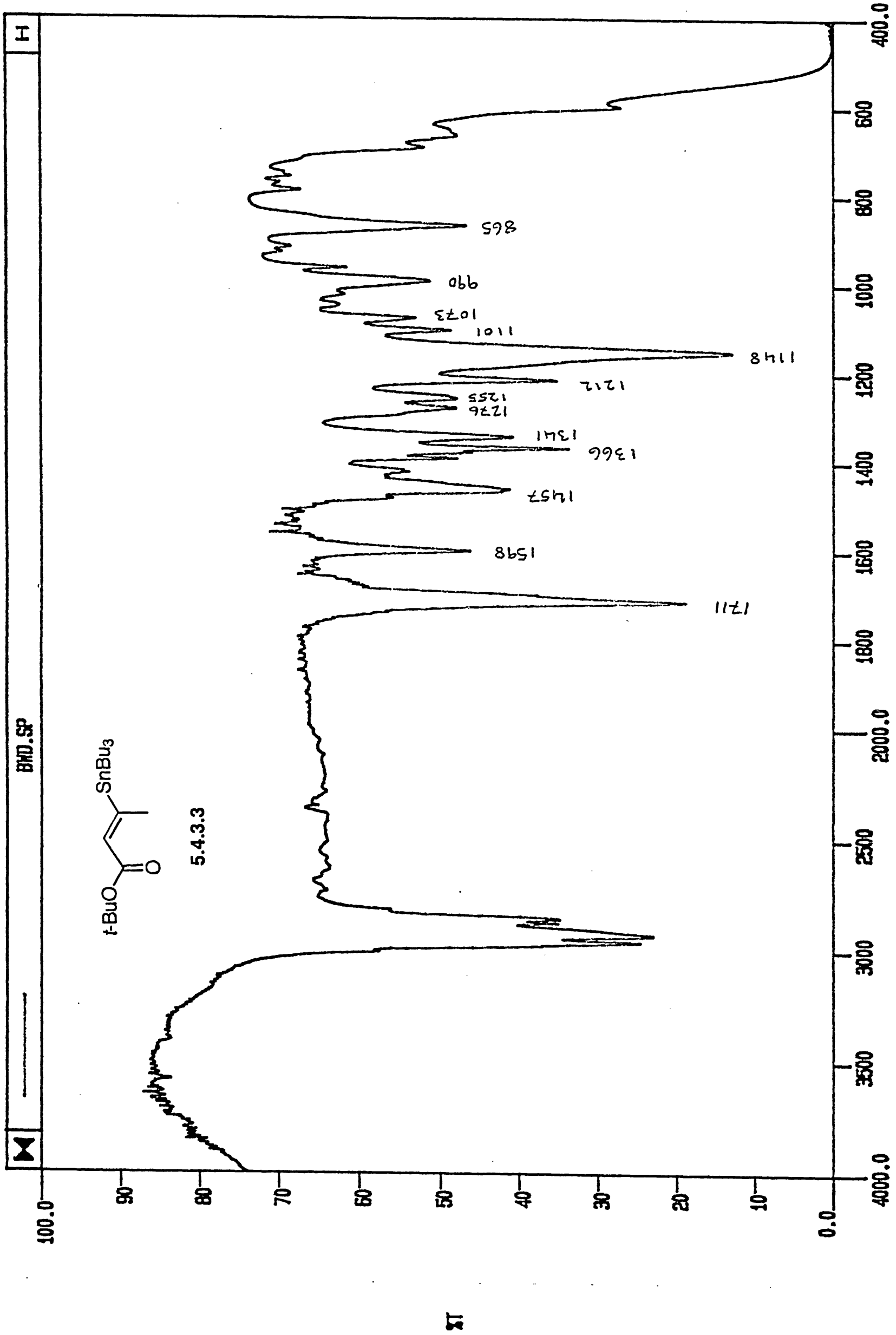
5.4.3.2

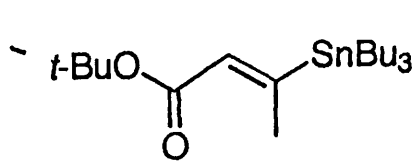
JN07BD.001
AU PROG:
DEPTA360
DATE 7-6-97
TIME 16:46

SF 90.556
SY 67.0
O1 15900.000
SI 65536
TD 32768
SW 22727.273
HZ/PT .694
PW 0.0
RD 0.0
AQ .721
RG 800
NS 1280
TE 298

FW 28500
O2 5593.000
DP 18H CPD

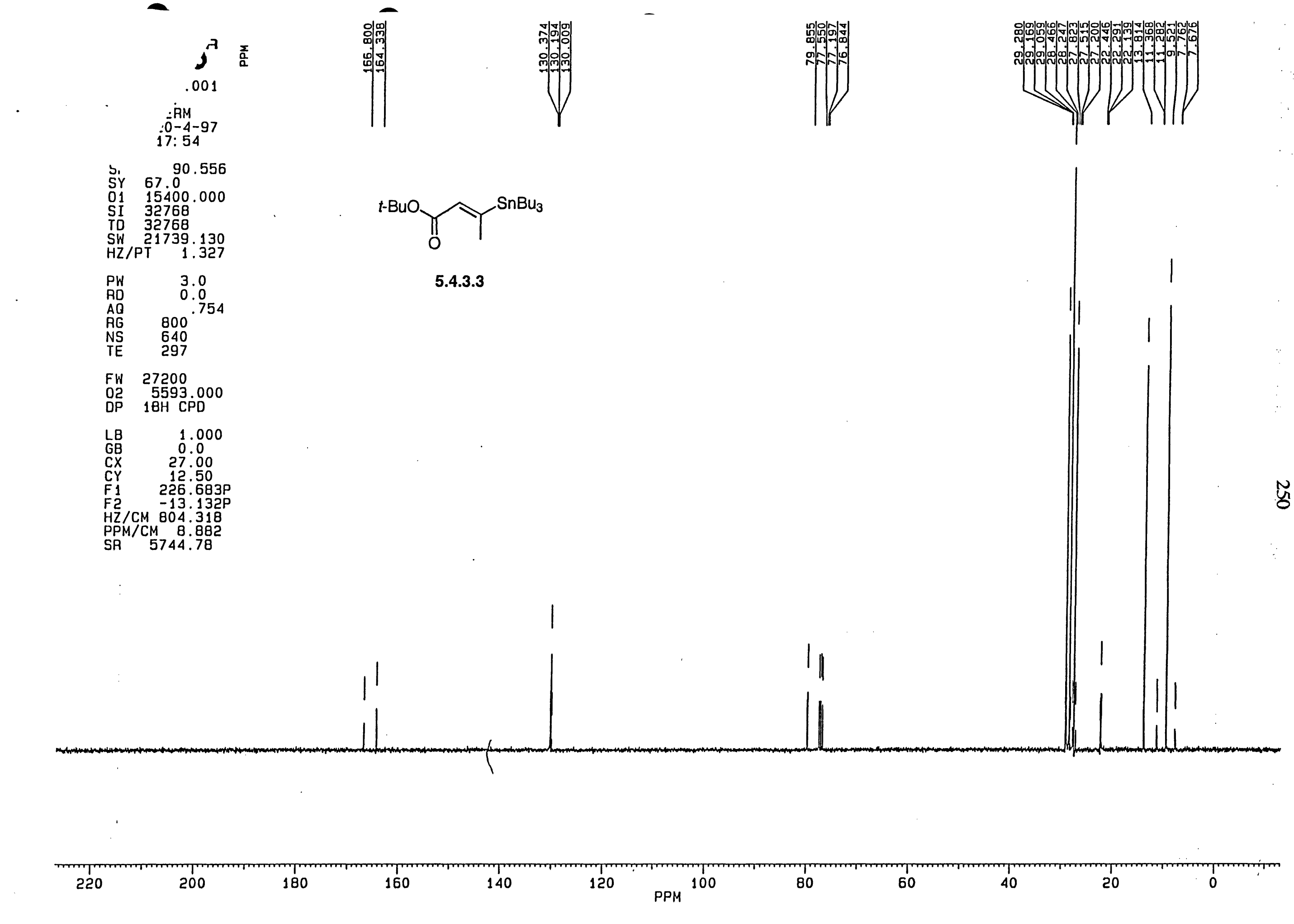
LB 1.000
GB 0.0
CX 23.00
CY 4.00
F1 236.120P
F2 -4.332P
HZ/CM 946.708
PPM/CM 10.454
SR 5751.22


H
BMD.SP
t-BuO
SnBu3
O
5.4.3.3
1711
1598
1457
1366
1341
1276
1255
1212
1148
1101
1073
990
865
100.0
90
80
70
60
50
40
30
20
10
0.0
4000.0
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
800
600
400.0
%T



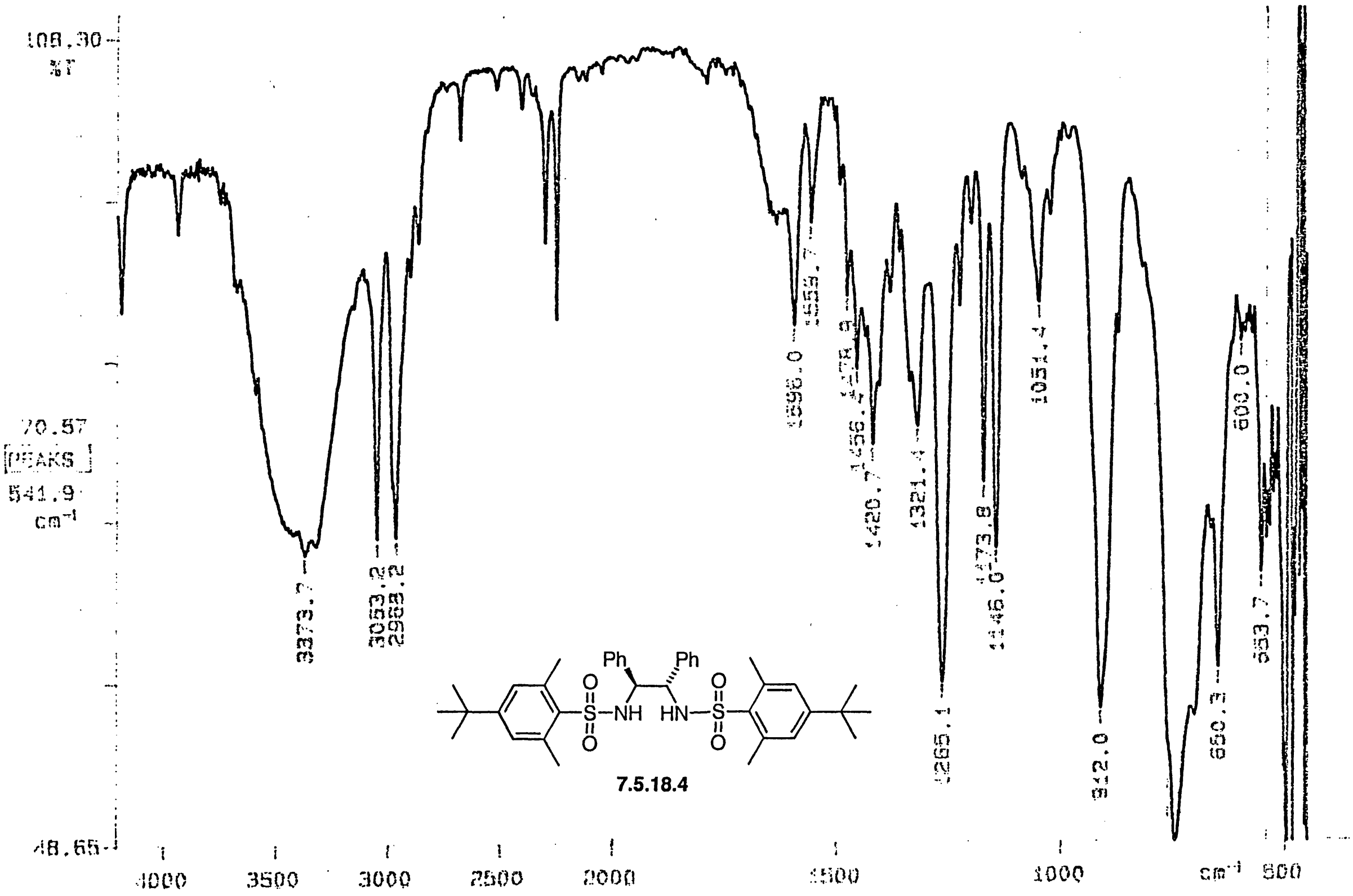
5.4.3.3

```
AP19B852.360
DATE 20-4-97
TIME 17:43

SF     360.134
SY 120.0
01    6300.000
SI   32768
TD   32768
SW    6024.096
HZ/PT     .368

PW        3.0
RD        0.0
AQ        2.720
RG       16
NS       16
TE      298

FW    7600
02    9280.000
DP   50L PO

LB         .300
GB         0.0
CX        27.00
CY        12.50
F1       14.816P
F2       -1.910P
HZ/CM  223.101
PPM/CM    .619
SR    3980.02
```

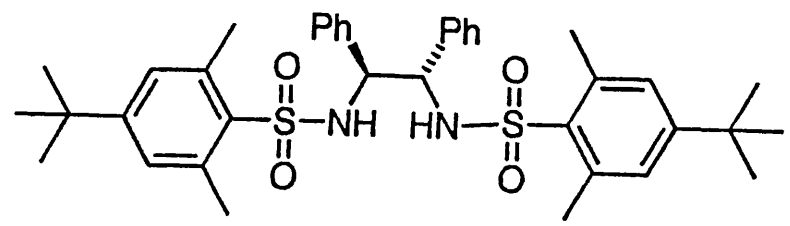

PPM
.001
:RM
:0-4-97
17:54
5. 90.556
SY 67.0
01 15400.000
SI 32768
TD 32768
SW 21739.130
HZ/PT 1.327
PW 3.0
RD 0.0
AQ .754
RG 800
NS 640
TE 297
FW 27200
02 5593.000
DP 18H CPD
LB 1.000
GB 0.0
CX 27.00
CY 12.50
F1 226.683P
F2 -13.132P
HZ/CM 804.318
PPM/CM 8.882
SR 5744.78
166.800
164.338
130.374
130.194
130.009
79.855
77.550
77.197
76.844
29.280
29.169
29.059
28.466
28.247
27.823
27.515
27.200
22.446
22.291
22.139
13.814
11.368
11.282
9.521
7.762
7.676
t-BuO
O
SnBu3
250
220
200
180
160
140
120
100
80
60
40
20
0
PPM

5.4.3.3

PERKIN ELMER

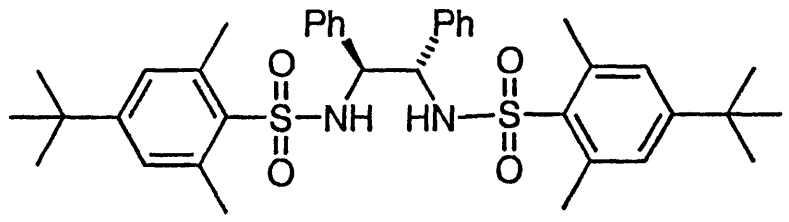


7.5.18.4

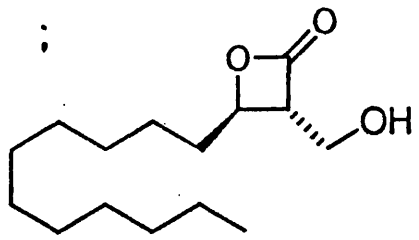

Ph
Ph
O
S
NH
HN
O
O
O

7.5.18.4

5.38
6.46
7.88
PPM
PPM
PPM
4.45
4.40
4.35
6.10
6.05
6.00
5.95
5.90
6.95
6.90
6.85
6.80
6.75
6.70
6.65
6.60
6.55
2.10
1.00
1.12
11
10
9
8
7
6
5
4
3
2
1
0



7.5.18.4



7.3.2.1

BRUKER

JA150S.233
AU PROG:
X00.AU
DATE 16-1-96

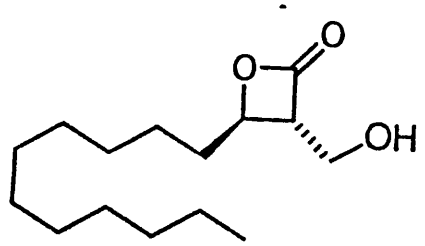
SF 300.133
SY 299.0
O1 5173.724
SI 16384
TD 16384
SW 6024.096
HZ/PT .735

PW 0.0
RD 0.0
AQ 1.3
RG 20
NS 16
TE 297

FW 7600
O2 3200.000
DP 63L PO

LB .300
GB 0.0
CX 35.00
CY 18.00
F1 9.200P
F2 -.799P
HZ/CM 85.743
PPM/CM .286
SR 3386.79

284



7.3.2.1

BRUKER

JA151S.233
AU PROG:
X02.AU
DATE 16-1-96

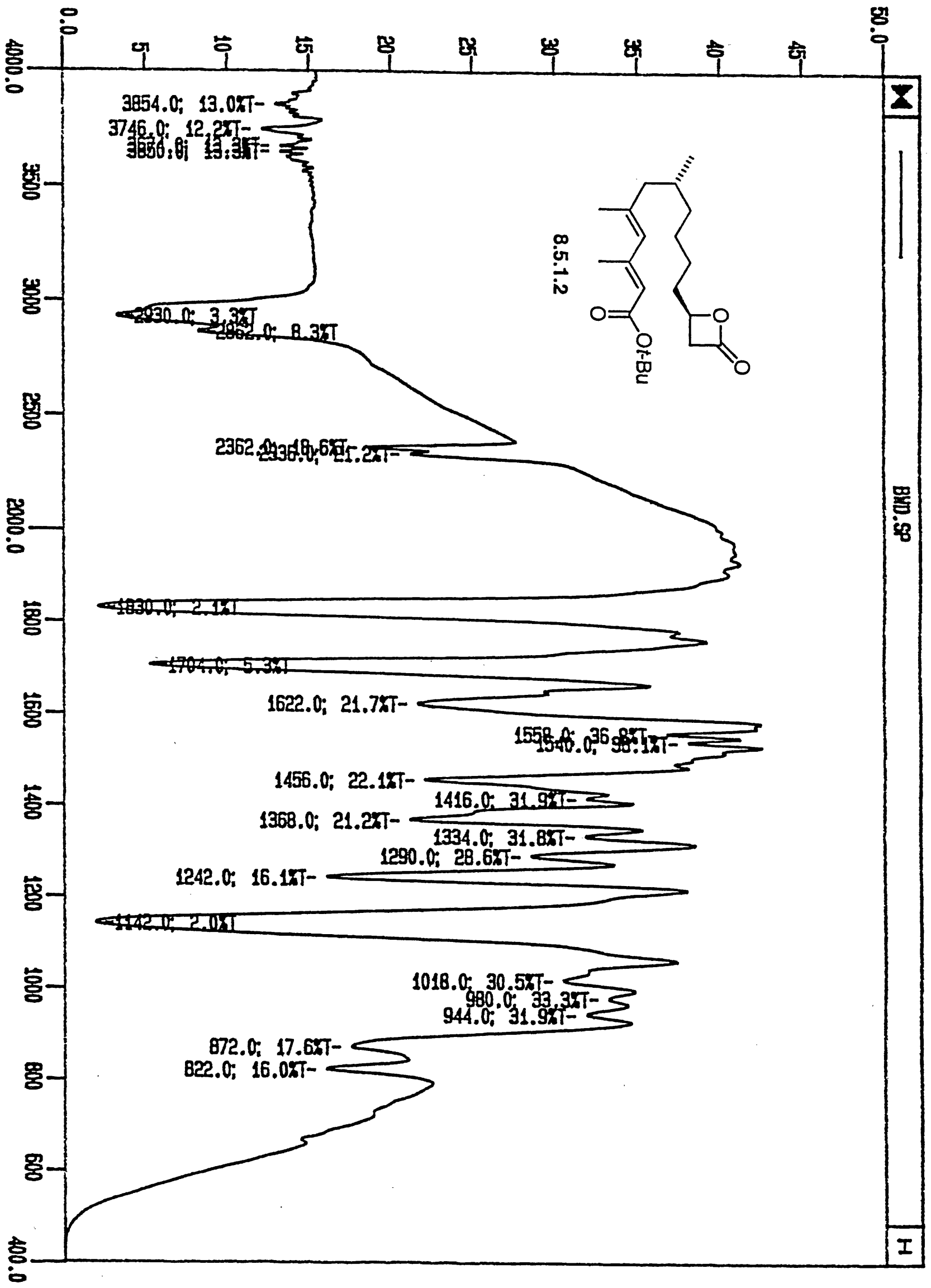
SF 75.469
SY 75.0
O1 6141.605
SI 32768
TD 32768
SW 18518.519
HZ/PT 1.130

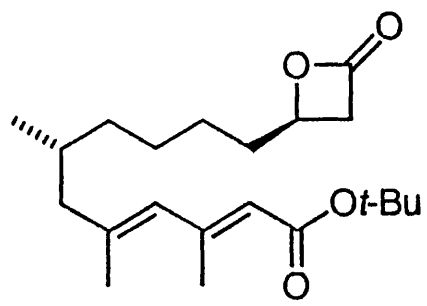
PW 0.0
RD 0.0
AQ .885
RG 400
NS 1024
TE 295

FW 23200
O2 4950.000
DP 16H DO

LB 2.000
GB 0.0
CX 35.00
CY 12.94
F1 230.014P
F2 -4.987P
HZ/CM 506.721
PPM/CM 6.714
SR -1416.58

PPM


8.5.1.2
Ot-Bu
O
O
O
3854.0; 13.0%T-
3746.0; 12.2%T-
2930.0; 3.3%T
2862.0; 8.3%T
2362.0; 48.6%T
2336.0; 21.2%T-
1830.0; 2.1%T
1704.0; 5.3%T
1622.0; 21.7%T-
1558.0; 36.8%T
1540.0; 38.1%T-
1456.0; 22.1%T-
1416.0; 31.9%T-
1368.0; 21.2%T-
1334.0; 31.8%T-
1290.0; 28.6%T-
1242.0; 16.1%T-
1142.0; 2.0%T
1018.0; 30.5%T-
980.0; 33.3%T-
944.0; 31.9%T-
872.0; 17.6%T-
822.0; 16.0%T-
4000.0
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
800
600
400.0
0.0
5
10
15
20
25
30
35
40
45
50.0
BMD.SP
H
CM-1



8.5.1.2

AG01BD1.001
AU PROG:
LONGTERM
DATE 1-8-97
TIME 16:42

SOLVENT CDCl3
SF 50.323
O1 28750.000
HZ/PT 1.453

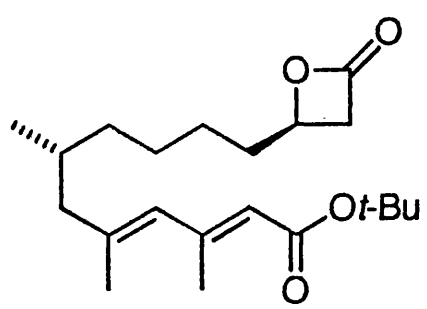
PW 3.0
AQ .688
RG 400
NS 2000

O2 3500.000
DP 21H CPD

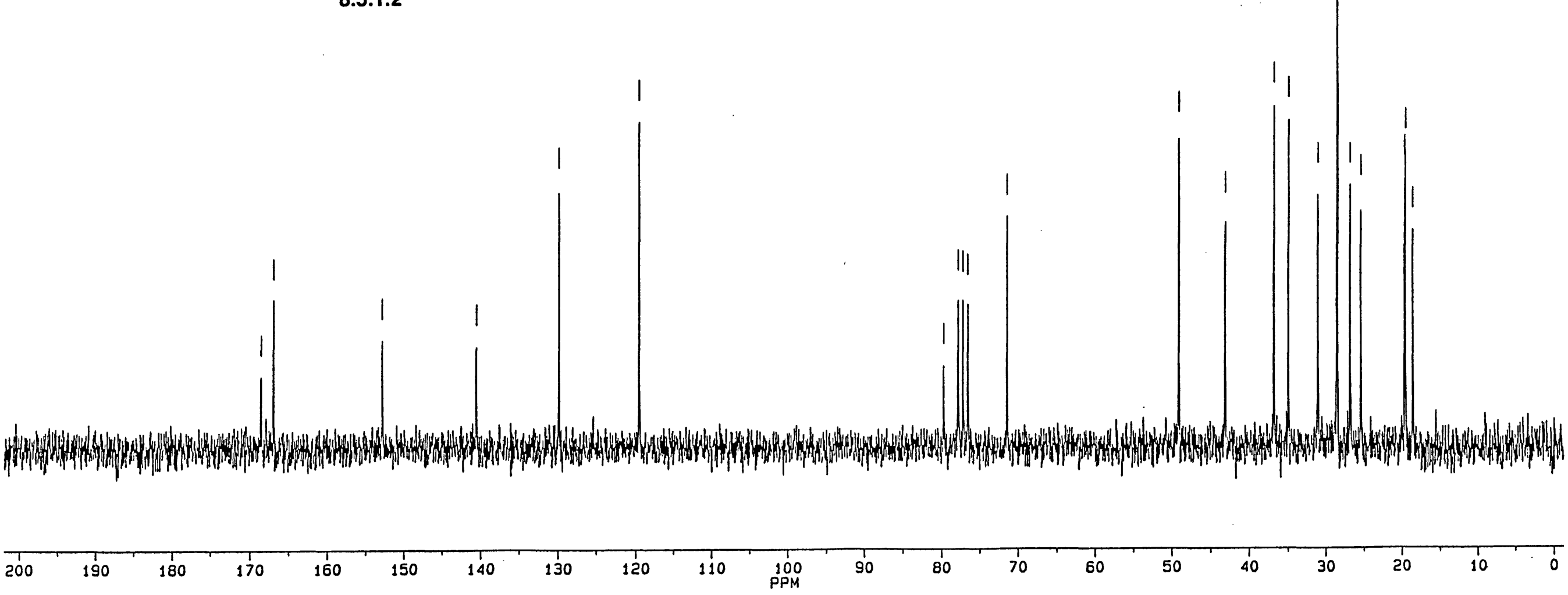
LB .300
CY 18.00
PPM/CM 5.349
SR 23310.10

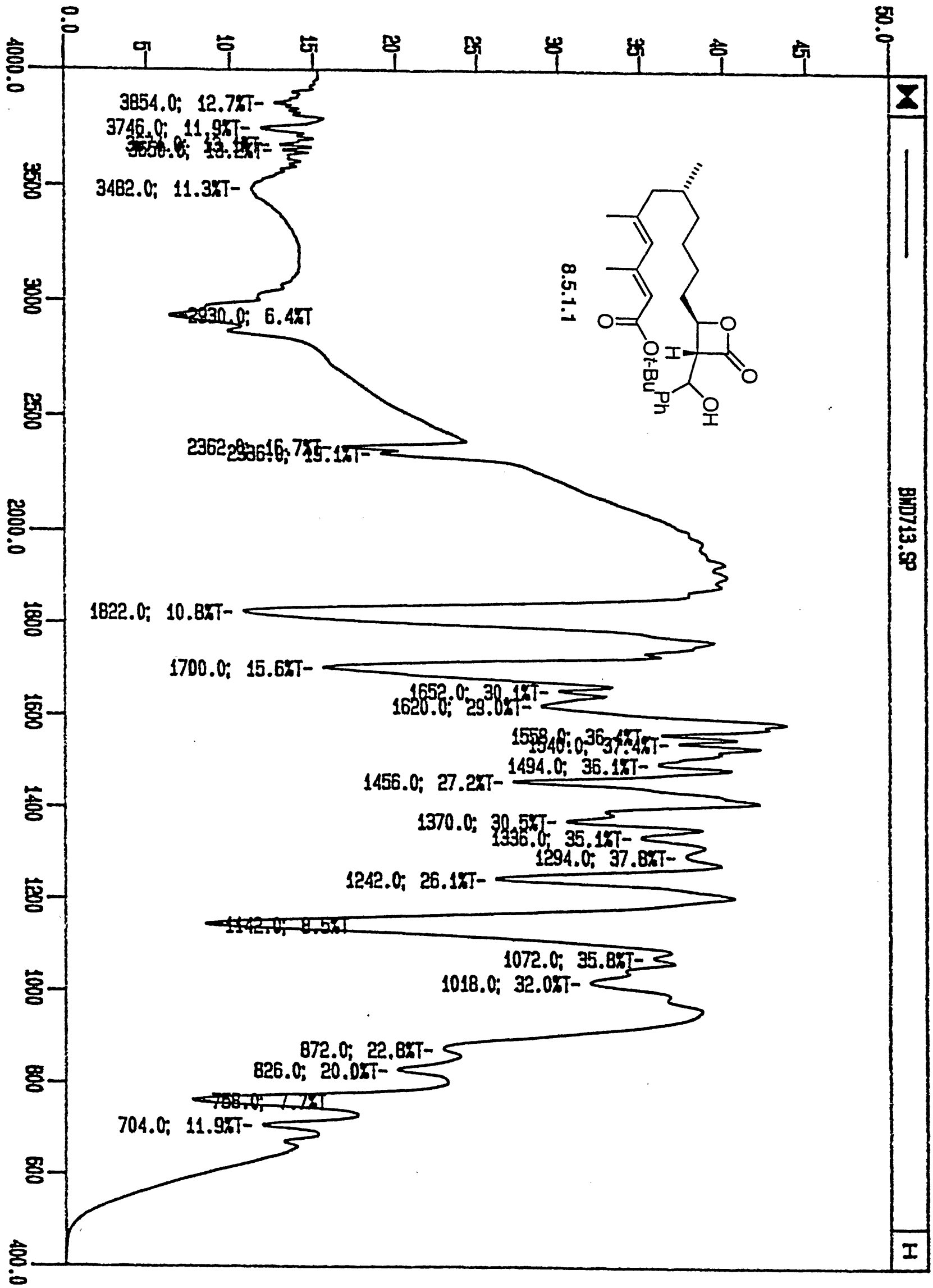
PPM

168.512
166.895
152.798
140.475
129.810
119.475
79.715
77.824
77.184
76.549
71.395
49.068
43.021
36.710
34.834
30.987
28.430
26.724
25.324
19.586
19.475
18.490

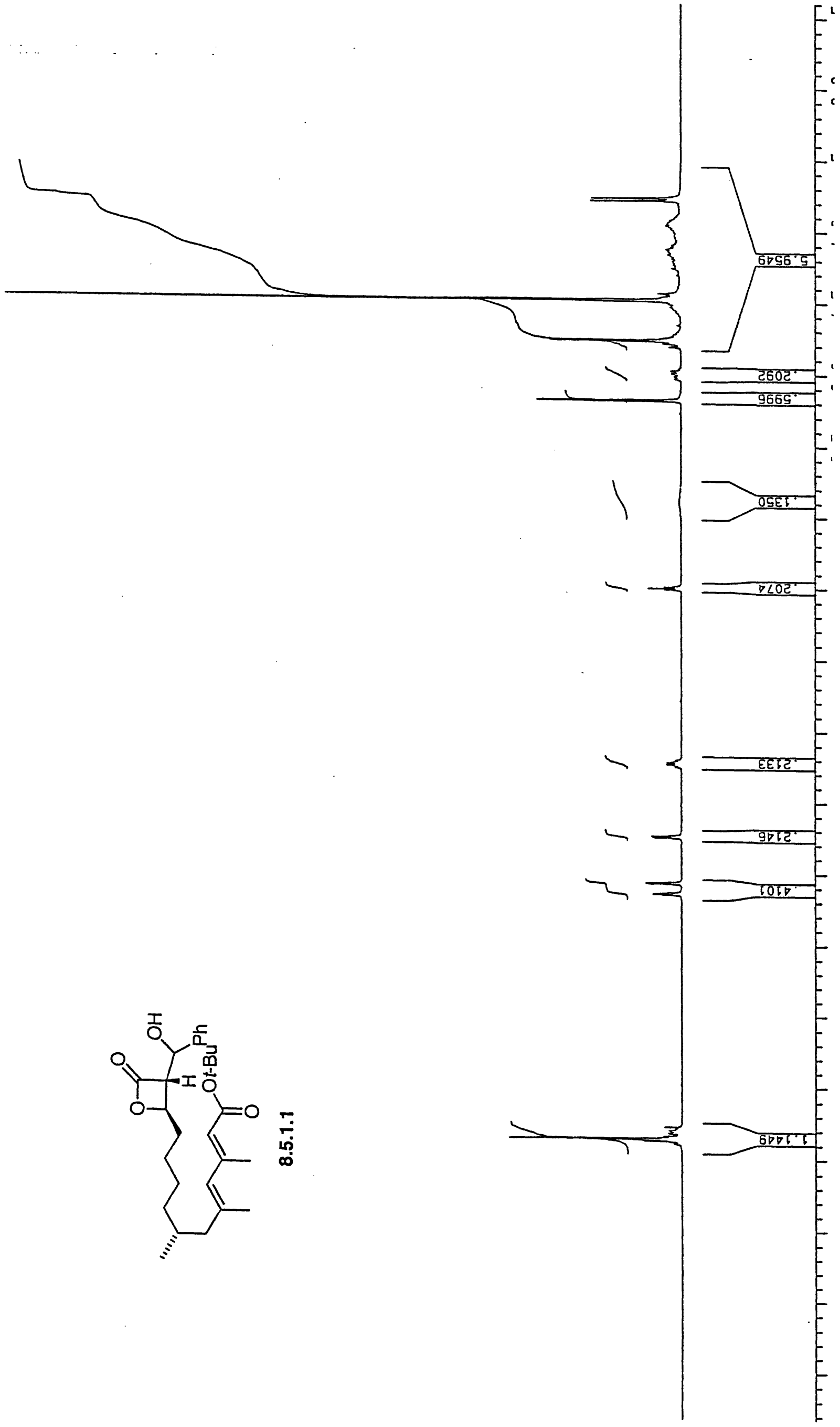


8.5.1.2



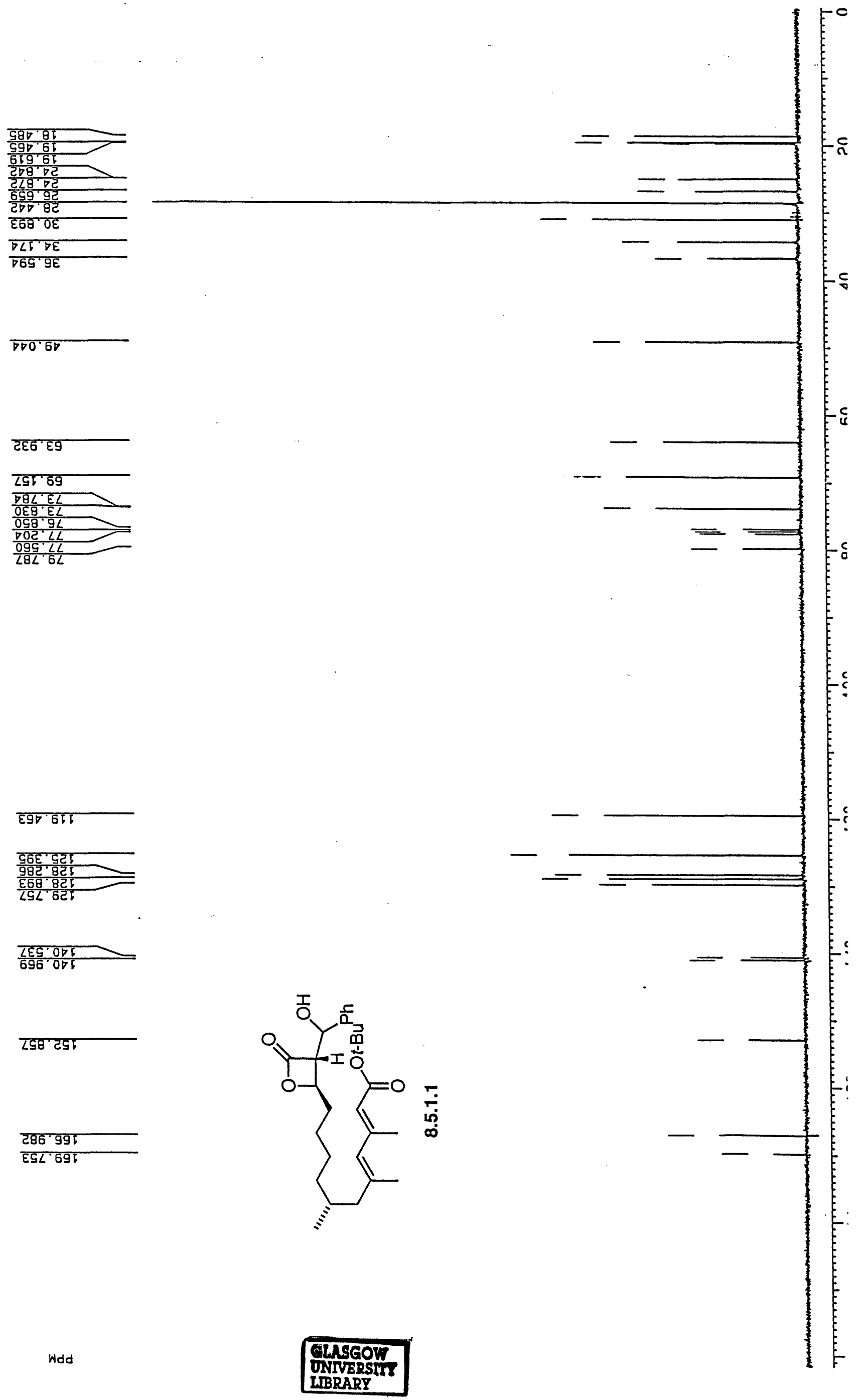

0.0
5
10
15
20
25
30
35
40
45
50.0
4000.0
3500
3000
2500
2000.0
1800
1600
1400
1200
1000
800
600
400.0
3854.0; 12.7%T-
3746.0; 11.9%T-
3482.0; 11.3%T-
2930.0; 6.4%T
1822.0; 10.8%T-
1700.0; 15.6%T-
1652.0; 30.1%T-
1620.0; 29.0%T-
1494.0; 36.1%T-
1456.0; 27.2%T-
1370.0; 30.5%T-
1336.0; 35.1%T-
1294.0; 37.8%T-
1242.0; 26.1%T-
1072.0; 35.8%T-
1018.0; 32.0%T-
872.0; 22.8%T-
826.0; 20.0%T-
704.0; 11.9%T-
8.5.1.1
O
O
H
Ot-Bu
Ph
OH
O
BMD713.SP
I

CH-1


5.9549
.2092
.5996
.1350
.2074
.2133
.2146
.4101
1.1449

OH
Ph
O
H
Ot-Bu
O
O

8.5.1.1



8.5.1.1