Synthetic Studies on the Pseudopterosins and *trans*-4-Methyl-L-Proline

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To my family

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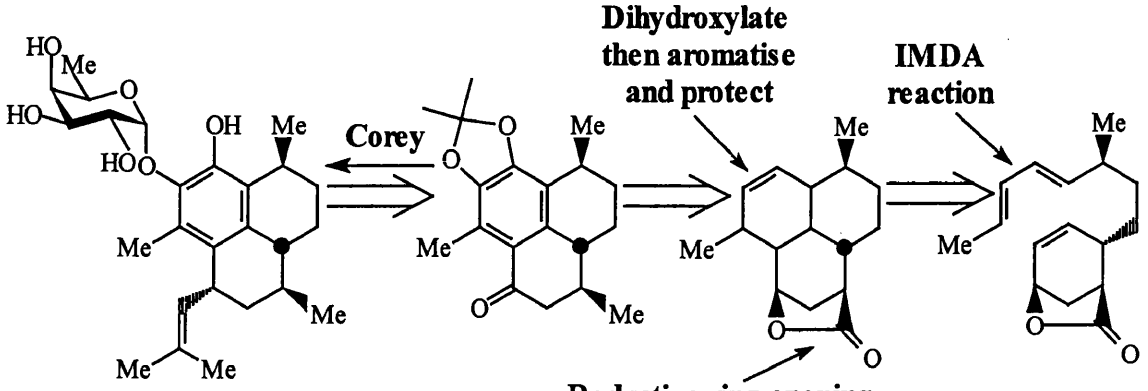
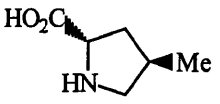
Abstract

The Pseudopterosin family of diterpene glycosides was isolated in 1986 from the Caribbean sea-plume *Pseudopterogorgia elisabethea.* Pseudopterosin E is one of the most potent anti-inflammatory agents currently know, being fifty times more active than indomethacin in preventing phorbol myristate acetate topically-induced inflammation in the mouse ear oedema model.



In the first section of this thesis, an attempted synthetic strategy towards Pseudopterosin E is reported. Our initial retrosynthesis adopted an intramolecular Diels-Alder reaction (IMDA) to form the tricarbocyclic core of the natural product. It was envisaged that elaboration of the IMDA product would lead to a key intermediate in the Corey *et al.* synthesis of Pseudopterosin E. The remainder of our synthesis would be after Corey.

Free *trans*-4-methyl-L-proline was first obtained from Worcester Pearmain apples in 1952. It is a constituent part of several natural products; Grisemelycin, Mycoplanecin A, and the Monamycins, all of which have potent biological activity profiles.



***trans*-4-METHYL-L-PROLINE**

In the second section of this thesis, several synthetic approaches to *trans*-4-methyl-L-proline are reported.

Acknowledgements

I would like to thank;

Professor Hale for his patient supervision and guidance for the past three years.

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Mike Cocksedge at The London School of Pharmacy for determining accurate mass measurements.

My family, without whose support this thesis could not have been prepared.

Abbreviations

acac	acetylacetonate anion
Ac	acetyl
AIBN	α,α'-azobisisobutyronitrile
al.	*alia*
aq	aqueous
atm	atmospheres
Bn	benzyl
Boc	(*t*-butoxycarbonyl)
BOM	benzyloxymethyl
Bu	butyl
cat	catalytic
CA	chiral auxiliary
Chem. Abs.	Chemical Abstracts
CI	chemical ionisation
conc	concentrated
DBAD	di-*t*-butyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DME	dimethoxyethane
DMF	dimethylformamide
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine

DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNP	2,4-dinitrophenyl
dppp	1,3-bis(diphenylphosphino)propane
ED_{50}	effective dose in 50% of subjects tested
ee	enantiomeric excess
ether	diethyl ether
Et	ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
hr(s)	hour(s)
HRMS	high resolution mass spectrometry
IC_{50}	concentration of a drug that reduces a response to another drug or target enzyme by 50%
ir	infra red
LDA	lithium diisopropylamide
LiCA	lithium isopropylcyclohexylamide
Lit.	literature
m-CPBA	3-chloroperbenzoic acid
Me	methyl
MHz	megahertz
min(s)	minute(s)
MOM	methoxymethyl

mp	melting point
MPLC	medium pressure liquid chromatography
m/z	mass/charge ratio
Ms	methanesulfonyl
NADP(H)	nicotinamide dinucleotide (phosphate)
NBS/NCS	*N*-bromosuccinimide/*N*-chlorosuccinimide
n/i/t	normal/iso/tertiary
NMO	4-methylmorpholine *N*-oxide
nmr	nuclear magnetic resonance
o/m/p	ortho/meta/para
petrol	petroleum ether 40-60 °C
PDC/PCC	pyridinium dichromate/pyridinium chlorochromate
Ph	phenyl
PhFl	9-(9-phenylfluorenyl)
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
psi	pounds/inch^2
R_f	retention factor
R	general alkyl group
rt	room temperature
satd	saturated
sec(s)	second(s)
TBAF	tetra-*n*-butylammonium fluoride

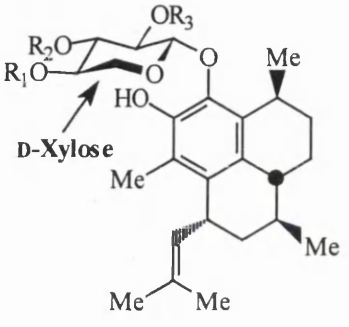
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TM	trade mark
TMEDA	*N,N,N',N'*,-tetramethylethylenediamine
TMS	trimethylsilyl
p-Ts	*p*-toluenesulfonyl
Z	benzyloxycarbonyl

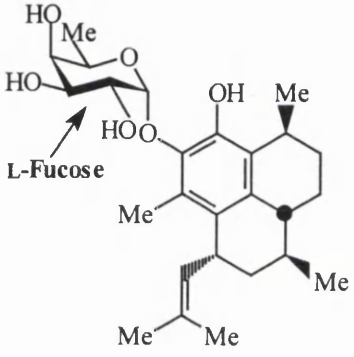
CHAPTER 1
The Pseudopterosins

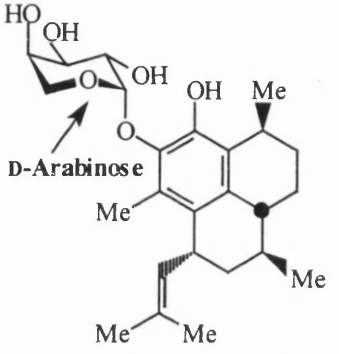
1.0 Introduction

The Pseudopterosin family of diterpene glycosides (Fig. 1) was isolated in 1986[1] and 1990[2] by Fenical *et al.* from the Caribbean sea-plume *Pseudopterogorgia elisabethea.*

Fig. 1



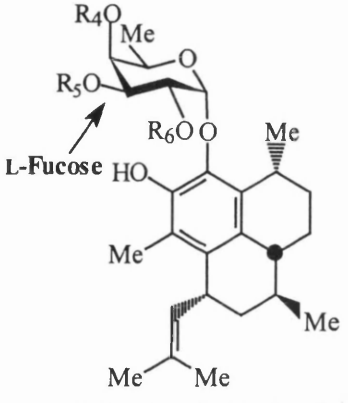


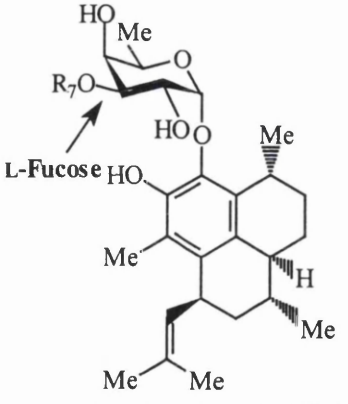


PSEUDOPTEROSIN A; R_1=R_2=R_3=H
PSEUDOPTEROSIN B; R_1=Ac,R_2=R_3=H
PSEUDOPTEROSIN C; R_2=Ac,R_1=R_3=H
PSEUDOPTEROSIN D; R_3=Ac,R_1=R_2=H

PSEUDOPTEROSIN E

PSEUDOPTEROSIN F





PSEUDOPTEROSIN G; R_4=R_5=R_6=H
PSEUDOPTEROSIN H; R_4=Ac,R_5=R_6=H
PSEUDOPTEROSIN I; R_5=Ac,R_4=R_6=H
PSEUDOPTEROSIN J; R_6=Ac,R_4=R_5=H

PSEUDOPTEROSIN K; R_7=H
PSEUDOPTEROSIN L; R_7=Ac

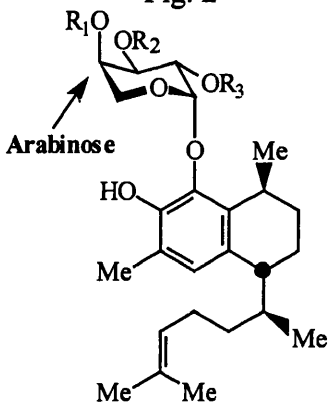
Pseudopterogorgia elisabethea

Structurally, the family is united by a common aglycone unit, *albeit* with differing absolute and relative stereochemistry, attached to a variety of sugars, and their acetylated congeners, in a regio- and stereospecific manner.

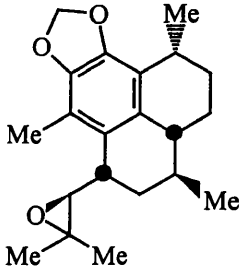
Biologically, they are potent anti-inflammatory and analgesic agents with Pseudopterosin C achieving commercial success in Resilience™, an anti-ageing cream marketed by Estée Lauder.

Structurally related natural products are the *seco*-pseudopterosins[3], also isolated from *Pseudopterogorgia elisabethea* by Fenical *et al.*, and the Helioporins[4] obtained from *Heliopora coerulea* in 1993 by Higa *et al.* (Fig 2).

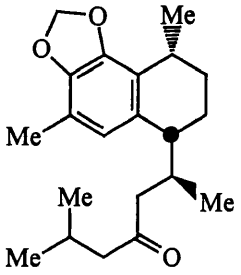
Fig. 2



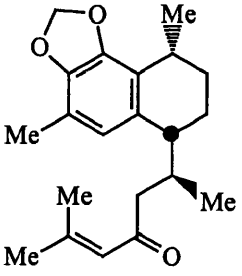
***seco*-PSEUDOPTEROSIN A; R_1=R_2=R_3=H**
***seco*-PSEUDOPTEROSIN B; R_3=Ac,R_1=R_2=H**
***seco*-PSEUDOPTEROSIN C; R_2=Ac,R_1=R_3=H**
***seco*-PSEUDOPTEROSIN D; R_1=Ac,R_2=R_3=H**



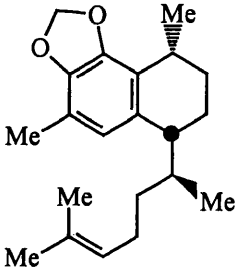
HELIOPORIN A



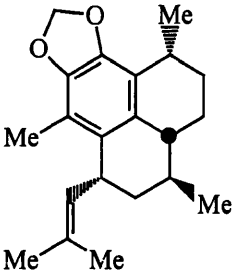
HELIOPORIN B



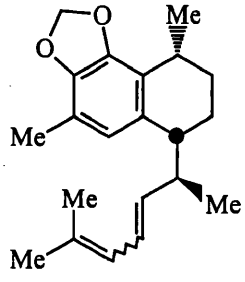
HELIOPORIN C



HELIOPORIN D



HELIOPORIN E



HELIOPORIN F (*Z*)
HELIOPORIN G (*E*)

1.1 Isolation and Structural Determination

Marine soft corals of the subclass *Octorallia* are ubiquitous in the tropical waters of the Atlantic ocean and the Caribbean sea[5]. Known as sea-whips, sea-fans, sea-plumes, and as gorgonian corals (order *Gorgonacea*, phylum *Cnidaria*), they account for an estimated 38% of the known fauna in the Caribbean with over 195 reported species[6].

There are 15 species of the genus *Pseudopterogorgia* documented which are best characterised as sea-plumes owing to their large, highly and finely branched plumose and physically soft forms[5]. The natural product chemistry of *Pseudopterogorgia* species was first studied in 1968 and led to the isolation of complex mixtures of sesquiterpene hydrocarbons from *Pseudopterogorgia americana*[7]. Since then, natural product isolation programmes have found that they are a rich source of terpenoids[8] and secosterols[9] and they have been described as one of the most chemically prolific of the octocorals of the tropical Atlantic ocean[2].

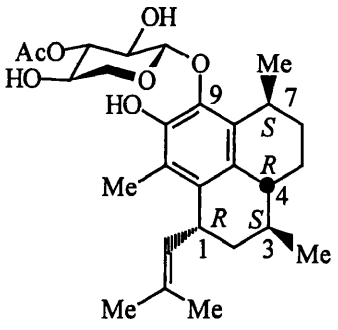
Fenical *et al.* have focused attention on representatives of this genus which are found in deeper water and which are less conspicuous[1]. In 1982, *Pseudopterogorgia elisabethea* was collected near Crooked Island in the Bahamas at depths of –15 to –35 metres. The animals were homogenised and the gorgonian cake was repeatedly extracted with $CHCl_3$ and EtOAc. Purification of the crude residue by rapid-elution chromatography and HPLC yielded Pseudopterosins A-D (Fig 1). Pseudopterosin C was the major component accounting for 7.5% of the organic extract, whilst Pseudopterosins A, B, and D occupied less than 1% of the organic extract each.

For Pseudopterosin C, a molecular formula of $C_{27}H_{38}O_7$ was established from the HRMS and ^{13}C nmr spectrum, indicating that the molecule was highly unsaturated. A peak at 1725 cm^{-1} in the ir spectrum suggested that Pseudopterosin C contained a

monoacetate unit and the ^{1}H nmr spectrum contained five methyl peaks, in addition to the acetyl peak, and three hydroxyl peaks. The 'Methyl Count' in the ^{1}H nmr spectrum suggested a diterpenoid carbon skeleton. Furthermore, the ^{13}C nmr spectrum showed peaks characteristic of an isopropylidene group. The presence of an acetate group, polyhydroxylation, and a carbon count five in excess of a diterpenoid molecule indicated that Pseudopterosin C contained an acetylated pentose sugar. Comparison of the spectral data established that Pseudopterosins B and D were isomeric monoacetates and that Pseudopterosin A was the unacetylated congener. Extensive ^{1}H nmr spin-decoupling experiments established that the sugar moiety was a β-xylopyranose and the positions of acetylation for Pseudopterosins B-D. In addition, when subjected to acid hydrolysis Pseudopterosin A liberated D-xylose.

The full structural assignment of Pseudopterosin C was achieved by X-ray crystallography where the aglycone unit was found to be a tricyclic diterpene ring system based on the rare amphilectane[10] skeleton. As the absolute stereochemistry of the sugar moiety was known, and the X-ray data gave the relative stereochemistry of the molecule as a whole, the absolute stereochemistry of Pseudopterosin C could be assigned (Fig. 3). The aromatic ring is planar and the two carbocyclic rings are in the half-chair conformation. The methyl at C-7 is pseudoaxial whilst the methyl at C-3 is pseudoequatorial. The isopropylidene group and the bridgehead hydrogen (C-4) are pseudoaxial. The 3-*O*-acetyl-β-D-xylopyranose moiety is attached at the C-9 hydroxyl and is in a chair conformation with all the substituents occupying equatorial positions. The absolute stereochemical structures of the remaining Pseudopterosins were defined by analogy.

Fig. 3



PSEUDOPTEROSIN C

When a Bermudan extract of *Pseudopterogorgia elisabethea* was examined, the animals were found to contain six additional members of the family[2], namely Pseudopterosins E-J (Fig. 1).

Using techniques similar to those just described, both Pseudopterosin E and F were found to contain the same agylcone unit as for Pseudopterosins A-D, though long range ^{1}H-^{13}C correlation nmr spectra suggested that the sugar was attached to the C-10 hydroxyl. The sugar component of Pseudopterosin E was identified as an α-fucose, and thought to be an α-L-fucose as only L-fucose is found in marine organisms[11]. Furthermore, this structure was confirmed through a concomitant total asymmetric synthesis by Corey[12] (*vide infra*). Chemical degradation of Pseudopterosin F revealed that the sugar component was a D-arabinose and X-ray crystallography confirmed the structure. The sugar unit of Pseudopterosin G was determined to be an α-L-fucose attached to the C-9 position of an aglycone which is epimeric at the C-7 methyl to those previously described. Pseudopterosins H-J are the monoacetate isomers of Pseudopterosin G.

Interestingly, when *Pseudopterogorgia elisabethea* was collected at Great Abaco Island in the Bahamas, the animals were found to contain Pseudopterosins K and L exclusively without even trace amounts of the other Pseudopterosins[2].

The sugar moiety of Pseudopterosin K is an α-L-fucose attached to the C9 position of an agylcone that was found to be enantiomeric to those in Pseudopterosins A-F. Pseudopterosin L is the 3-*O*-acetyl-α-L-fucoside version of Pseudopterosin K.

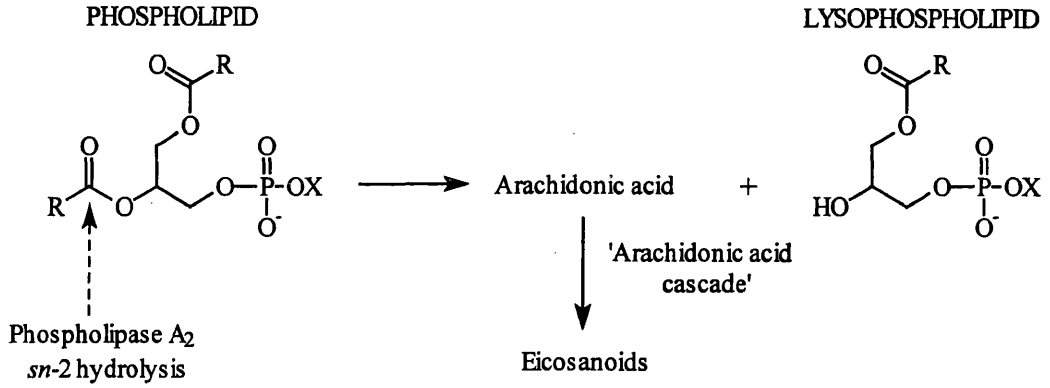
In summary, the Pseudopterosin class of tricarbocyclic diterpene glycosides has been isolated by Fenical *et al.* and their structures have been determined using a combination of chemical, physical, and spectral techniques.

1.2 Pharmacology

Human inflammatory ailments such as gout, psoriasis, and oedemas can be extremely painful[13].

The inflammatory response is mediated by the biosynthesis of eicosanoids, such as leukotrienes, prostaglandins, and thromboxanes, from arachidonic acid[14] (Fig. 4).

Fig. 4



The production of arachidonic acid is catalysed by phospholipase A_2, an enzyme for ester hydrolysis at the *sn*-2 position of a phospholipid. The resulting arachidonic acid is then metabolised by many biosynthetic pathways, known collectively as the 'arachidonic acid cascade', to produce eicosaniods. Of these, the most potent chemotactic eicosanoids are the leukotrienes, which increase the permeability of local venules and capillaries resulting in fluid leaking into the interstitial spaces causing oedema[15]. Any selective inhibition of phospholipase A_2 or any of the main pathways within the 'arachidonic acid cascade' by a substrate can be expected to modify the inflammatory response[16]. For example, indomethacin, a typical non-steroidal anti-inflammatory agent, inhibits the cyclo-oxygenase pathway responsible for the production of prostaglandins[17].

Often, the painful nature of the inflammation is not due to the inflammation *per se* but to the tissue destructive events of neutrophils (polymorphonuclear leukocytes) [18].

Neutrophils, phagocytic cells released by non-specific immune systems, help to destroy foreign antigens, invading microorganisms, and damaged tissue structures. Once activated, neutrophils congregate at the site of the offending agent and undergo degranulation to release a complex armamentarium. Among the most damaging of the tissue ravaging agents released are hypochlorous acid[19] and chloramines[20]. Both types of oxidant are formed through a cascade of reactions that commences with the reduction of molecular oxygen to $O_2^{\cdot-}$ by NADPH oxidase[21] (Scheme 1). The $O_2^{\cdot-}$ then undergoes distmutation to hydrogen peroxide[22], much of which then fuels the myleperoxidase system in its oxidation of chloride ion to hypochlorous acid. The chloramines are thought to be generated by oxidation of amines within the intracellular granules by some of the liberated hypochlorous acid[23]. Unfortunately, neutrophils often display little discriminatory ability to distinguish between damaged tissue and healthy tissue that is merely inflamed, as in the leukotriene mode of action described above. The unnecessary destructive attack by neutrophils on inflamed tissue is one of the causes of pain in inflammatory illnesses[24].

Scheme 1

$$2O_2 + NADPH \rightarrow 2O_2^{\cdot-} + NADP + H^+$$

$$2O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2$$

$$H_2O_2 + Cl^- + H^+ \rightarrow HOCl + H_2O$$

$$RNH_2 + HOCl \rightarrow RNHCl + H_2O$$

Recent pharmacological characterisation by Jacobs[25] *et al.* of Pseudopterosin A and E has shown that they are potent anti-inflammatory and analgesic agents.

When administered topically against phorbol 12-myristate 13-acetate induced mouse ear oedema both Pseudopterosin A and E exhibited high levels of inhibition at low concentrations (ED_{50} = 8 μg/ear and 38 μg/ear respectively). Both are significantly more potent than indomathecin (ED_{50} = 80 μg/ear), the current industry standard. When administered systematically (intraperitoneally) Pseudopterosin A and E inhibited

inflammation in a dose-dependent manner (ED_{50} = 32 μg/ear and 14 μg/ear respectively) confirming an anti-inflammatory effect and ruling out a non-specific counter irritant effect. Increasing dosage levels led to a maximum inhibition of 90% at 100 mg/kg for both compounds, but at these high doses the mice appeared severely agitated suggesting a possible neurological effect.

In vivo, analgesic effects for Pseudopterosin A and E were determined against phenyl-*p*-benzoquinone-induced writhing (ED_{50} = 4 mg/kg and 14 mg/kg, ip, respectively) and, for Pseudopterosin E, against zymosian-induced eicosanoid production in murine peritoneal exudates (ED_{50} = 24 mg/kg for 6-keto-prostaglandin $-F_{1\alpha}$ and ED_{50} = 24 mg/kg for leukotriene C_4). These data suggest a direct effect on the lipoxygenase and cyclo-oxygenase enzymes in the 'arachidonic acid cascade'. However, the observed four-fold increase between ED_{50} values for zymosian writhing (4 mg/kg) and eicosanoid production (26-31 mg/kg) indicate that other mechanisms contribute to the analgesic effects of the Pseudopterosins.

In vitro, Pseudopterosin A inhibited both prostaglandin E_2 (IC_{50} = 4 μM) and leukotriene C_4 (IC_{50} = 1 μM) in a concentration-dependent manner. In contrast, Pseudopterosin E was inactive (< 40% inhibition) suggesting *in vivo* metabolism that allows Pseudopterosin E to inhibit zymosian-induced eicosanoid production *in vivo*. Furthermore, both Pseudopterosin A and E have no significant effect on phospholipase A_2 activity nor do they effect phospholipase A_2-regulated surface expression of CD11b in human neutrophils.

The mode of action of the Pseudopterosins remains unclear, though early work of Faulkner *et al.* has established that the aglycone unit is the active form of the drug[15].

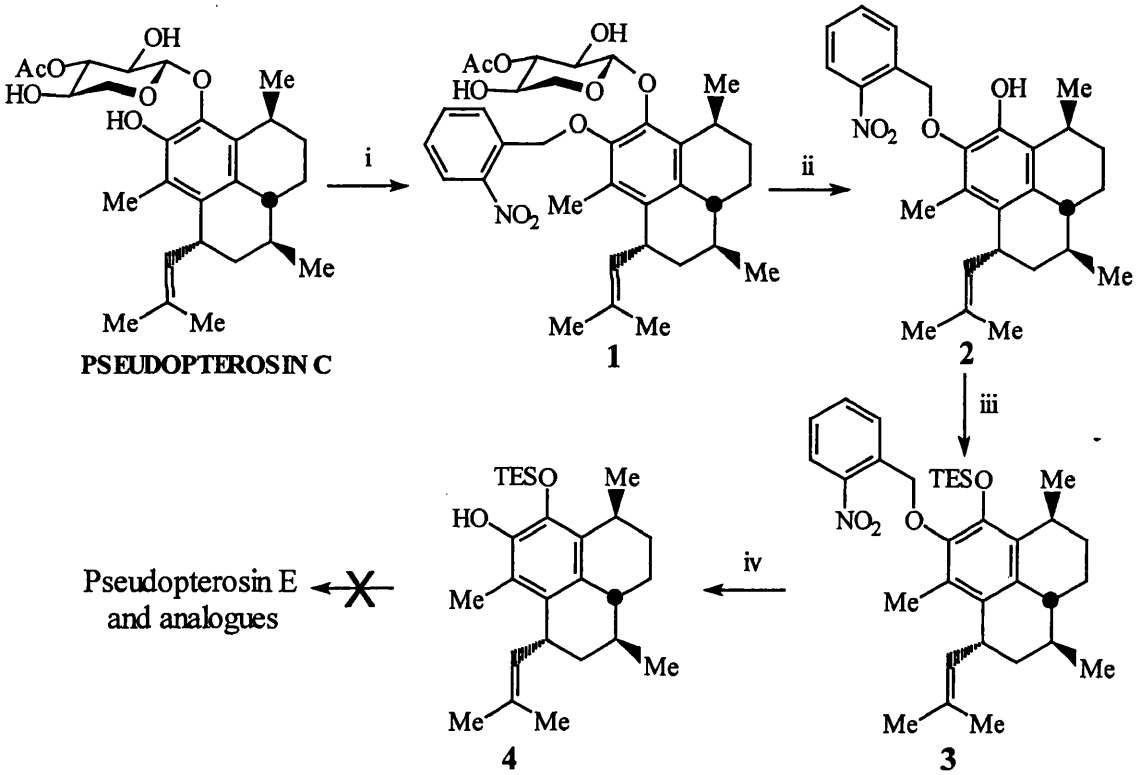
In summary, these combined data suggest that the Pseudopterosins mediate their anti-inflammatory effect by the inhibition of eicosanoid production through a

phospholipase A_2 and cyclo-oxygenase independent mechanism. Crucially, they have been shown to inhibit the most potent of the chemotactic eicosanoids, namely the leukotrienes.

1.3 Promulgated Synthetic Approaches to the Pseudopterosins

The first reported synthetic work on the Pseudopterosins was an attempted inter-conversion of Pseudopterosin C (the most abundant Pseudopterosin) to Pseudopterosin E (the most biologically active Pseudopterosin) by Fenical[2] *et al.* (Scheme 2).

Scheme 2



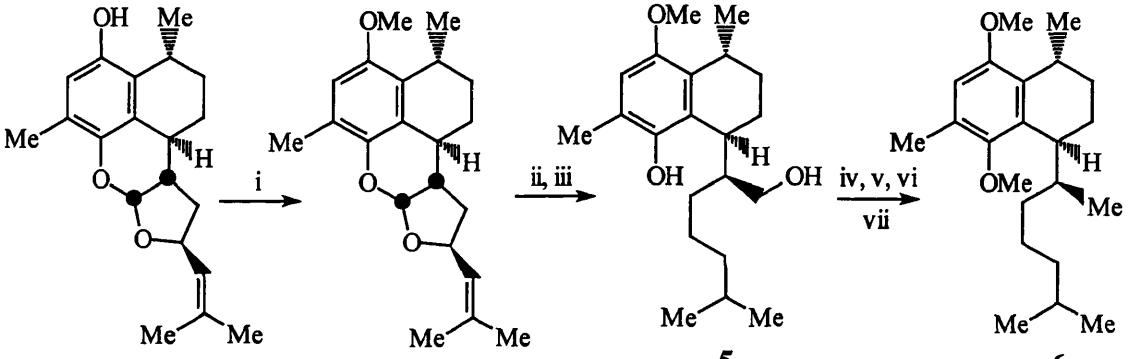
(i) K_2CO_3, *o*-nitrobenzyl chloride, acetone, rt, 9 hrs, 67%; (ii) 1N (aq) HCl, MeOH, 60 °C, 48 hrs, 86%; (iii) TESCl, imidazole, DMF, rt for 1 hr, then 60 °C for 5 hrs, 96%; (iv) hν, Girard's reagent T, MeOH: DCM 2:1, rt, 6 hrs, 91%.

Pseudopterosin C reacted readily with *o*-nitrobenzyl chloride to form the ether **1**. Acid hydrolysis of the 3-*O*-acetyl-D-xylose unit gave the phenol **2**, which was then protected as the triethylsilyl ether **3**. Photolysis of the *o*-nitrobenzyl ether unmasked the C-10 hydroxyl affording **4**, which could have been glycosidated with a variety of protected

sugars to yield Pseudopterosin E and analogues. Despite many attempts at C-10 glycosidation, the yields were always very low. Optimisation of the reaction conditions was not pursued by Fenical, in light of a successful synthesis of Pseudopterosin E by Corey[13] *et al.*, though the use of orthogonal protecting groups in this manner could lead to a large assemblage of Pseudopterosin analogues.

Massey-Westropp[26] and Cowin have developed an expedient route to *seco*-Pseudopterosin analogues from the naturally occurring diterpene Serrulatenol (Scheme 3).

Scheme 3



(i) NaH, MeI, DMSO, rt, 48 hrs, 72%; (ii) Li-NH_3, THF, EtOH, -78 °C, 5 mins; (iii) H_2, PtO_2, EtOAc, rt, 71% for two steps; (iv) NaH, MeI, DMSO, rt, 48 hrs, 48%; (v) MsCl, pyridine, 0 °C, overnight; (vi) NaI, acetone, reflux, overnight, 85% for two steps; (vii) *n*-Bu_3SnH, AIBN, PhH, reflux, 16 hrs, 38%.

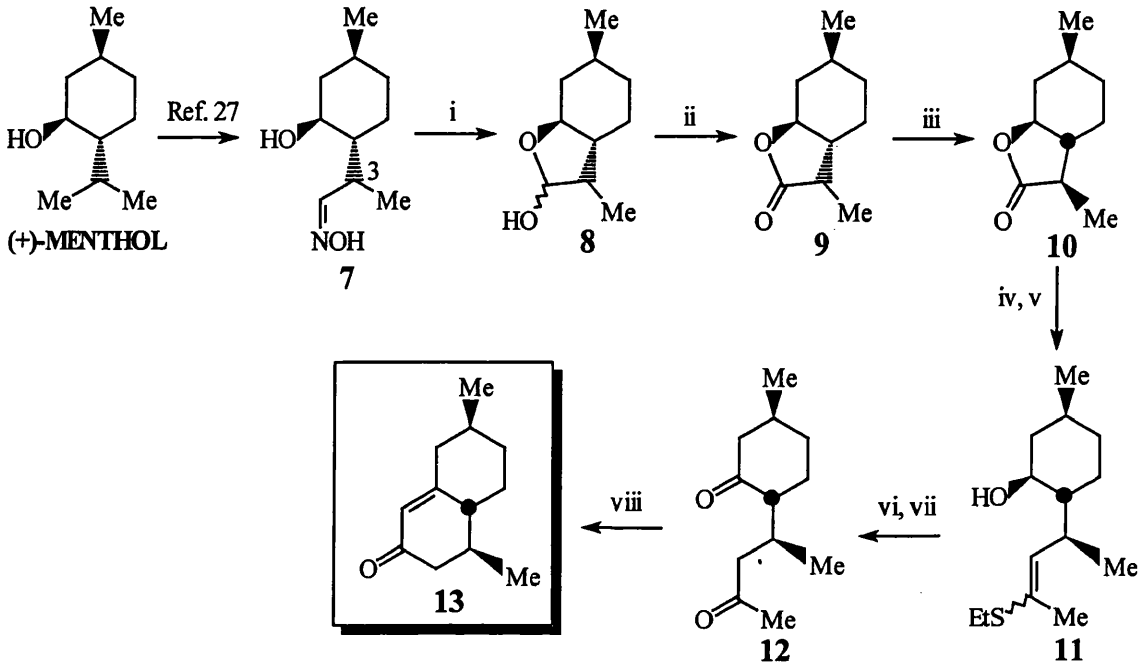
Serrulatenol was methyl protected and exposed to Li-NH_3 in EtOH followed by hydrogenation to afford **5**. Selective phenol methylation and subsequent deoxygenation under standard conditions led to **6** in very low overall yield (8% for 7 steps). Though **6** is somewhat different to the *seco*-Pseudopterosin aglycone, Massey-Westropp and Cowin intend to prepare derivatives of **6** for biological assay.

1.3.1 The Corey Asymmetric Total Syntheses of Pseudopterosin A and E

Corey[13] and Carpino achieved the asymmetric total synthesis of Pseudopterosins A and E in 1989. The oxime **7** (Scheme 4), available from (+)-menthol as a 5:1 *R*:*S*

mixture of diastereomers[27] at C-3 (Pseudopterosin numbering), was hydrolysed with 5 equivalents of $NaHSO_3$ to form the lactol **8** which was oxidised to the lactone **9** with Br_2 in THF/H_2O.

Scheme 4

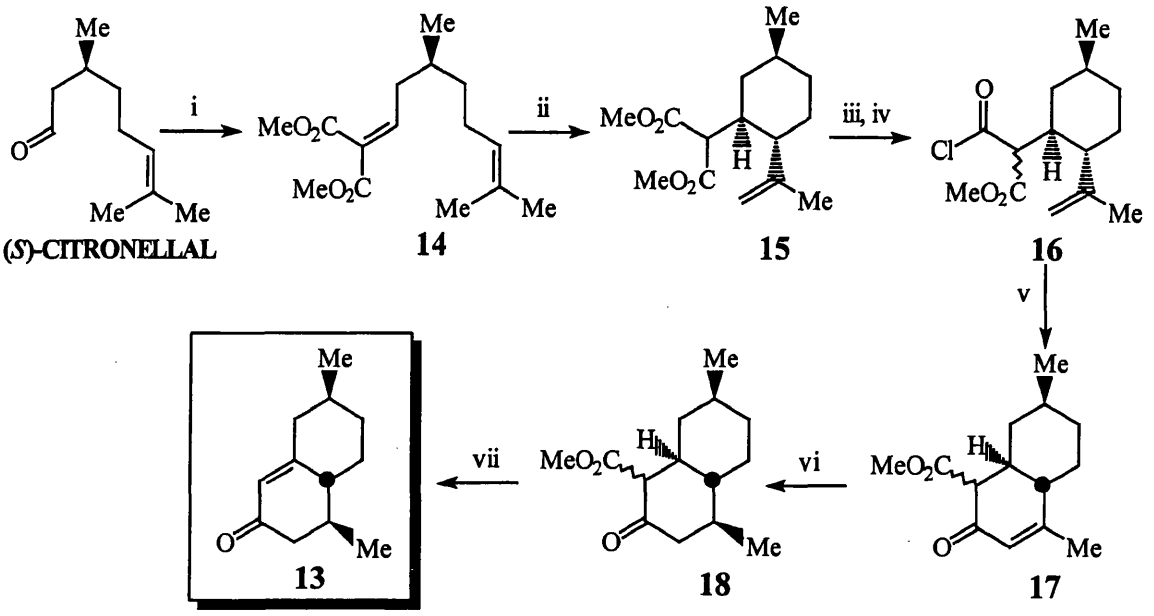


(i) $NaHCO_3$, H_2O, 50 °C, 4 hrs; (ii) Br_2, $CaCO_3$, THF, H_2O, rt, 1.5 hrs; (iii) LDA, THF, 0 °C, 2 hrs, 60% for 3 steps; (iv) DIBAL, DCM, -78 °C, 2 hrs; (v) $Ph_3PC(Me)SEt$, DMSO, rt, 24 hrs; (vi) $(CF_3CO)_2O$, Et_3N, DCM, -65 °C, 1 hr; (vii) $HgCl_2$, MeCN, H_2O, 50 °C, 1 hr; (viii) NaOMe, MeOH, rt, 12 hrs, 40% for 4 steps.

Complete isomerisation at C-3 (Pseudopterosin numbering) to the *R* configuration was achieved by aqueous quench of the enolate formed by the action of LDA on **9** to afford the γ-lactone **10** in good yield. Reduction of **10** with DIBAL in DCM and subsequent Wittig chain extension with $Ph_3PC(Me)SEt$ in DMSO gave rise to **11**. Swern oxidation of **11** with $(CF_3CO)_2O$ followed by thioether cleavage with $HgCl_2$ afforded the 1,5-diketone **12**, which, on exposure to NaOMe in MeOH, yielded the octalone **13** *via* an Aldol cyclisation, condensation reaction.

In a later report[28] (1990), Corey and Carpino showed that the octalone **13** can be made in a more expedient manner starting from commercially available (*S*)-citronellal (Scheme 5).

Scheme 5

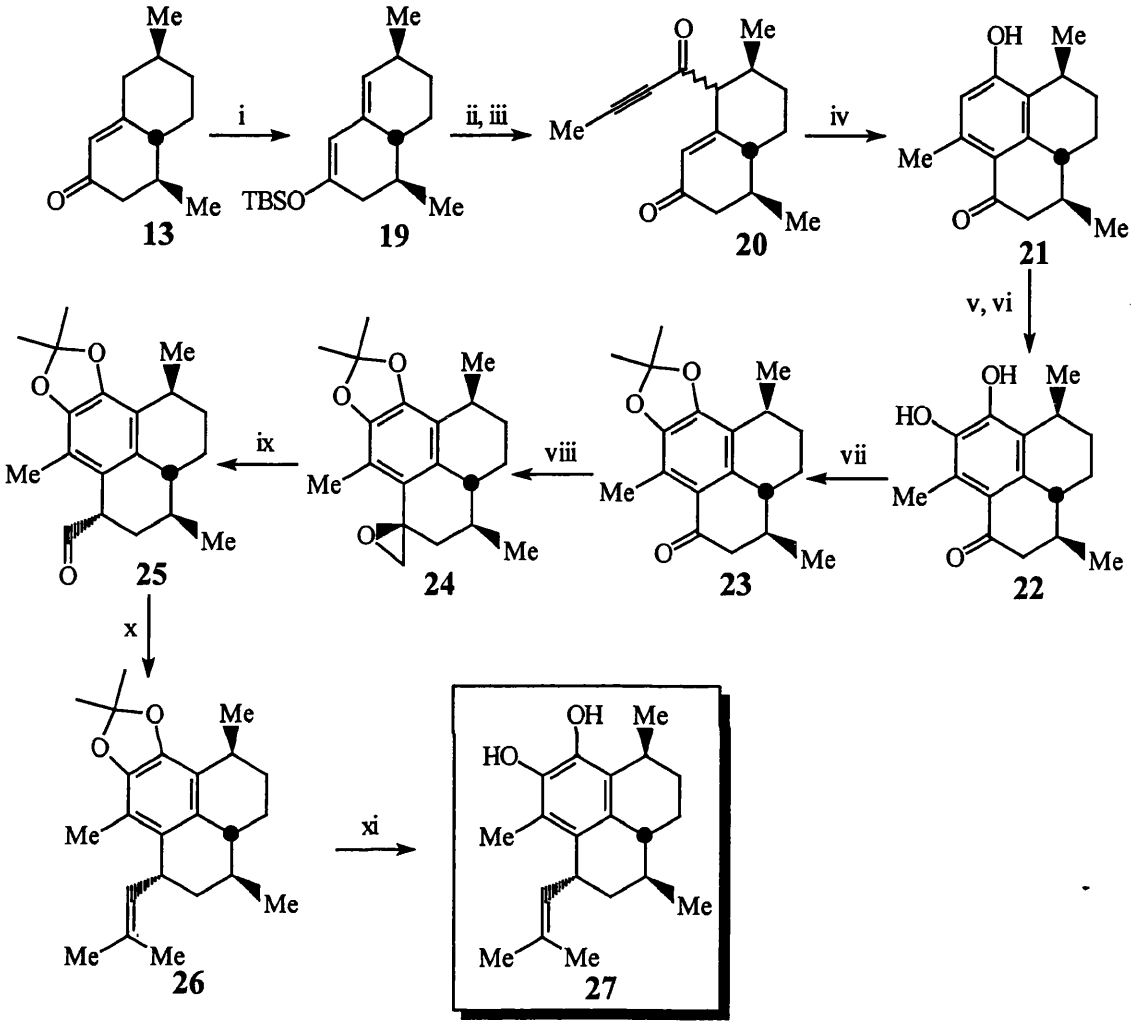


(i) $CH_2(CO_2Me)_2$, piperidinium acetate, rt, 12 hrs; (ii) $FeCl_3$, DCM, -78 °C, 3 hrs, then rt, 1 hr, 89%; (iii) 1M (aq) LiOH, MeOH, rt, 12 hrs; (iv) $(COCl)_2$, DCM, DMF, rt, 2 hrs; (v) $EtAlCl_2$, DCM, -30 °C to rt, 24 hrs, 72% for 3 steps; (vi) Li-NH_3, THF, -78 °C, 10 mins, 78%; (vii) NaH, THF, rt, 3 hrs, then Br_2; crude residue, LiCl, DMF, 80 °C, 3 hrs, then 125 °C, 3 hrs, 70%.

The unsaturated malonic ester **14**, obtained from the reaction of (*S*)-citronellal with dimethyl malonate and piperidinium acetate, formed the cyclic diester **15** upon exposure to $FeCl_3$ in DCM with excellent yield (89%) and diastereoselectivity (97:3)[29]. Mono-saponification of **15** with 1.2 equivalents of LiOH and reaction of the resulting mono-acid with oxalyl chloride in DCM resulted in the formation of the mono-acid chloride **16**. The acid chloride **16** reacted with 3 equivalents of $EtAlCl_2$ in DCM to afford the unsaturated β-keto ester **17** in excellent (72%) yield overall from the cyclic diester **15**. The saturated β-keto ester **18** was formed by lithium metal reduction of **17** at low temperature and was transformed to the octalone **13** by a novel two-step procedure. Namely, **18** was reacted with NaH in THF to afford the sodio derivative which was quenched with Br_2. The crude isolated product was heated with a 6% solution of LiCl in DMF for several hours to give the octalone **13**, which was identical in all respects to the previously synthesised material.

Reaction of the octalone **13** with KH in THF and trapping of the thermodynamic enolate with TBSCl gave the dienol silyl ether **19** (Scheme 6).

Scheme 6



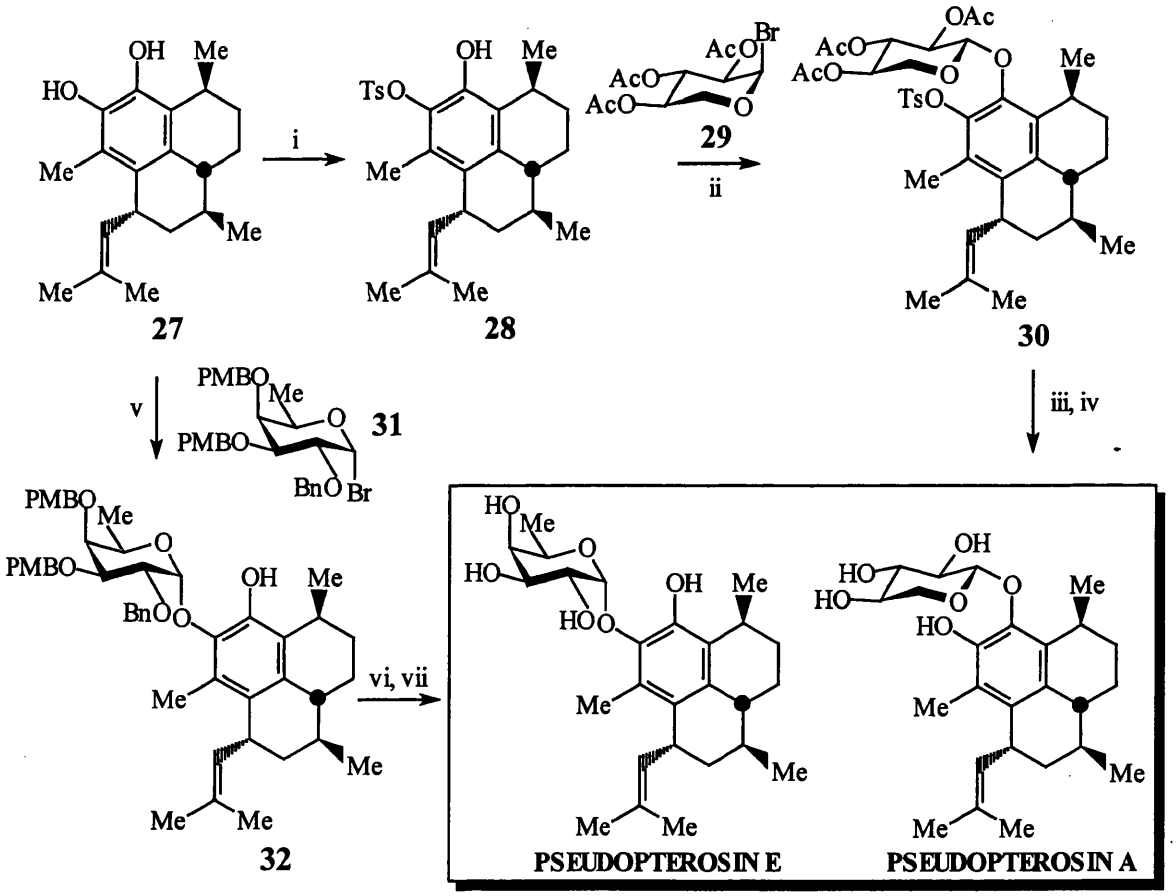
(i) KH, TBSCl, THF, HMPA, rt, 12 hrs, 97%; (ii) 2-Butynal, TBSOTf, DCM, -78 °C, 3 hrs; (iii) PCC, 4Å molecular sieves, DCM, rt, 3 hrs, 61% for two steps; (iv) KH, THF, rt, 24 hrs, 70%; (v) $(PhSeO)_2O$, HMDS, PhH, rt, 12 hrs, 79%; (vi) Acetic acid, $HClO_4$, H_2O, rt, 2 hrs, 71%; (vii) 2,2-Dimethoxypropane, pyridinium tosylate, $CHCl_3$, 70 °C, 12 hrs, 87%; (viii) Me_2SCH_2, THF, rt; (ix) BF_3-OEt, DCM, -30 °C to rt, 1 hr, 76% for two steps; (x) Ph_3PCMe_2, THF, 0 °C, 1 hr, 81%; (xi) 1:1:1 10% (aq) HCl:THF:MeOH, 70 °C, 12 hrs, 71%.

Slow addition of **19** in DCM to butynal and TMSOTf in DCM at -78 °C and oxidation of the resulting propargylic alcohol with PCC gave the diketone **20**. Treatment of **20** with KH in THF gave the phenol **21** in which the tricyclic core of the Pseudopterosins is formed by a novel aromatic annulation procedure. *Ortho*-hydroxylation of the phenol **21** was achieved under Barton conditions to give the catechol **22**, which was protected

under standard conditions. The ketone **23** was methenylated on the lesser sterically hindered face of the ketone with Me_2SCH_2 in THF and the resulting epoxide **24** was ring-opened with BF_3-OEt in DCM to form the aldehyde **25** stereoselectively. Wittig reaction of **25** with Ph_3PCMe_2 in THF and exposure of **26** to mild acid conditions led to the formation of the Pseudopterosin A-F aglycone **27** identical in all respects to a sample obtained from degradation of the natural products.

With the unsatisfactory glycosidation experiences of Fenical[2] *et al.* in mind, Corey and Carpino first investigated the reactive nature of **27** (Scheme 7).

Scheme 7



(i) TsCl, Et_3N, DCM, -30 °C to rt, 2 hrs, 85%; (ii) NaH, **29**, MeCN, rt; (iii) KOH, MeOH, H_2O, rt, 1 hr; (iv) 6% NaHg, MeOH, 54% for three steps; (v) *n*-BuLi, **31**, THF, rt; (vi) LiOH, THF, MeOH; (vii) Li-NH_3, THF, 53% for three steps.

Crucially, they found that **27** reacts with 1 equivalent of TsCl in DCM in the presence of Et_3N exclusively at the C-10 hydroxyl of the aglycone to afford **28** in very good (85%) yield.

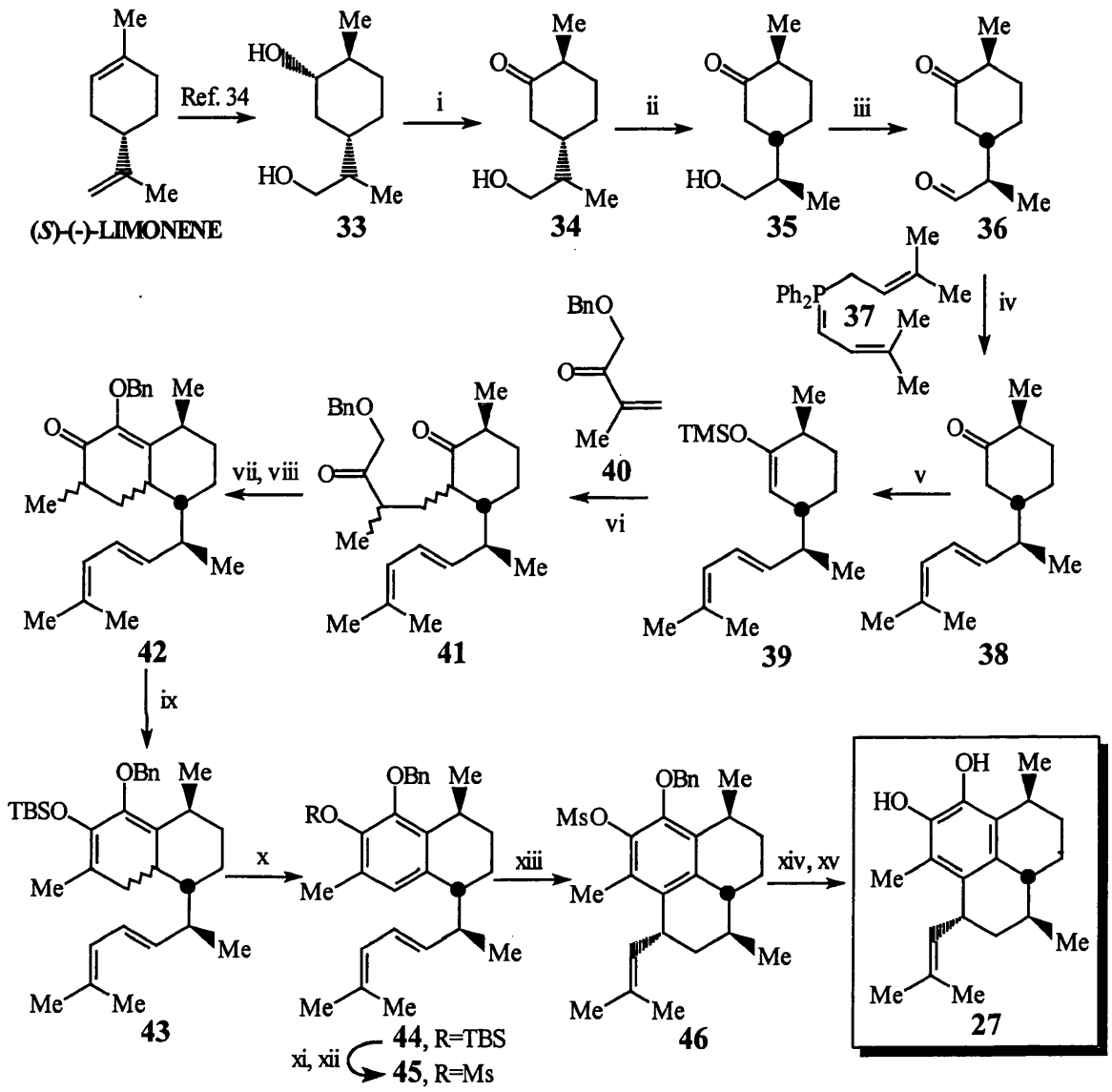
With this knowledge in hand, **28** was deprotonated with NaH in MeCN and reacted with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[30] **29** to produce **30** stereoselectively. Removal of the acetyl and tosyl groups furnished synthetic Pseudopterosin A, which was identical in all respects to the natural product.

Deprotonation of **27** with 2 equivalents of *n*-BuLi in THF and reaction with the α-L-bromofucose derivative[31] **31** led regio- and stereoselectively to **32**, which on deprotection afforded synthetic Pseudopterosin E identical in all respects to the natural product. As the absolute stereochemistry of the fucose component of Pseudopterosin E had not been determined from the natural product, Corey and Carpino have also synthesised the D-fucoside of **27** and have demonstrated that this is not the natural product.

Recently (1998), Corey[32] and Lazerwith have reported a novel synthetic route to the agylcone unit **27** starting from commercially available (*S*)-(-)-limonene (Scheme 8). The diol **33** was obtained from hydroboration of (*S*)-(-)-limonene and alkaline peroxide oxidation as a 1:1 mixture of diastereomers[33] at C-3 (Pseudopterosin numbering). NaOCl mediated selective oxidation of the secondary hydroxyl in acetic acid formed the hydroxy ketone **34**. Exposure of **34** to isopropenyl acetate in isopropyl ether with Amano PS lipase as a catalyst resulted in selective acetylation of the (3*S*)-alcohol and allowed for isolation of the desired (3*R*)-alcohol **35** in 36% yield. Oxidation of **35** afforded the keto-aldehyde **36**, which, under the Wittig-Vedejs *E*-selective conditions with ylide **37**[34], gave rise to **38** as a single diastereomer in good yield. Mukaiyama-type aldol coupling of **39**, produced from **38** under standard conditions, with the α,β-

unsaturated enone **40**[35] using $SnCl_4$ as the catalyst gave **41** as a gross mixture of diastereomers.

Scheme 8



(i) NaOCl, acetic acid, H_2O, rt, 3 hrs, 86%; (ii) Amano PS lipase, isopropenyl acetate, isopropyl ether, rt, 23 hrs, 36%; (iii) 6% (aq) NaOCl, TEMPO, KBr, DCM, 0 °C, 1.5 hrs, 92%; (iv) **37**, DME, -60 °C, 10 mins, 85%; (v) LDA, TMSCl, DME, -78 °C, 5 mins, 100%; (vi) **40**, $SnCl_4$, DCM, -78 °C, 40 mins, 58% with 22% recovered starting material; (vii) KOH, EtOH, 0 °C, 1 hr, 70%; (viii) $SOCl_2$, pyridine, rt, 1.5 hrs, 70%; (ix) LDA, TBSOTf, THF, -78 °C, 15 mins, then 0 °C, 15 mins, 100%; (x) MnO_2, methylcyclohexane, 70 °C, 16 hrs; (xi) TBAF, THF, rt, 5 mins, 86% for two steps; (xii) MsCl, Et_3N, DCM, -30 °C to rt, 15 mins, 96%; (xiii) MsOH, DCM, -78 °C to -50 °C for 10 hrs, 100%; (xiv) MeMgBr, THF, 0 °C, 18 hrs, 97%; (xv) BBr_3, DCM, 0 °C, 5 mins, 83%.

Aldol cyclisation of **41** with ethanolic KOH afforded the α,β-unsaturated enone **42** upon dehydration of the aldol product with $SOCl_2$-pyridine. Aromatisation of the newly formed ring was achieved in good yield by the action of activated MnO_2 in

methylcyclohexane at 70 °C on the TBS enol ether **43**, obtained from **42** under standard conditions. The transformation **43** to **44** represents a novel aromatisation protocol and appears to be general for cyclohexadienes. Desilylation of **44** with TBAF in THF and mesylation under standard conditions afforded **45**. This mesylate cyclised diastereoselectively (25:1) and in high yield to **46** when treated with 5 equivalents of $MeSO_3H$ in DCM at -50 °C. The mesyl group was removed with MeMgBr in THF and the benzyl group was cleaved with BBr_3 in DCM to reveal the Pseudopterosin aglycone **27**. This material was identical in all respects to the compound made by Corey and Carpino and, therefore, constitutes a formal asymmetric synthesis of Pseudopterosin A and E.

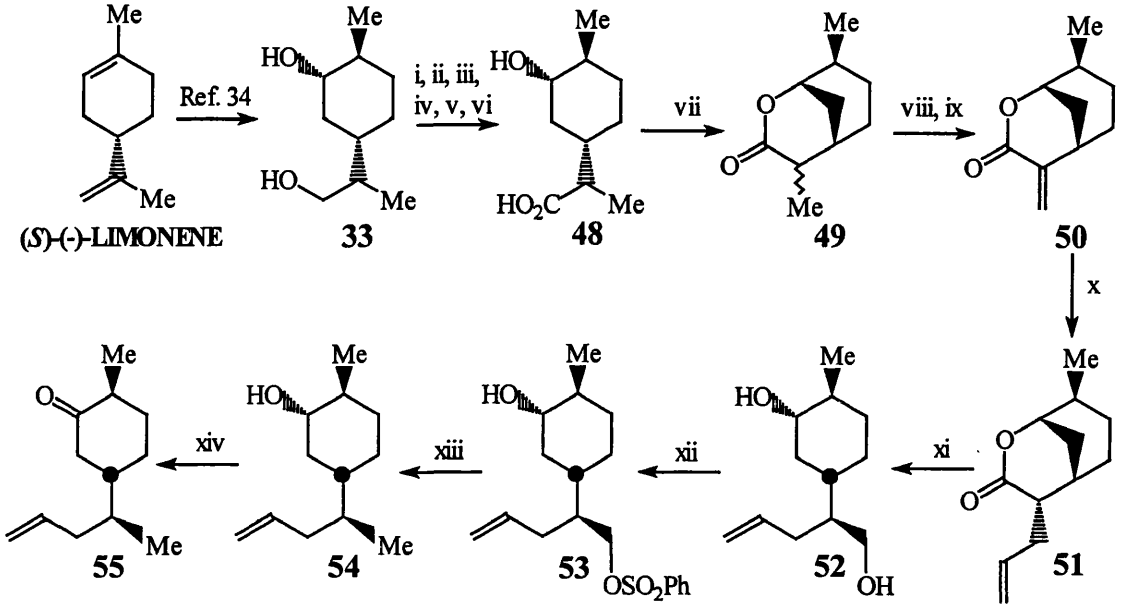
In summary, Corey *et al.* have developed several stereocontrolled synthetic routes to Pseudopterosin A and E starting from (+)-menthol (A, 23 steps, ~1% overall yield; E, 22 steps, ~1% overall yield) and (*S*)-citronellal, and to the Pseudopterosin A-F aglycone from (*S*)-(-)-limonene (15 steps, 11% overall).

1.3.2 The Broka Asymmetric Total Synthesis of Pseudopterosin A

In 1987 Broka[36] *et al.* reported a synthesis of Pseudopterosin A which starts with the diol **33**[34,37], obtained from (*S*)-(-)-limonene (Scheme 9). Routine functional group interconversion leads to the hydroxy acid **48** in excellent yield, which was lactonised under standard conditions. Selenation-oxidation of the lactone **49** afforded the α,β-unsaturated lactone **50** as a single diastereomer. Vinyl cuprate addition to **50** in the presence of TMSCl resulted in the formation of **51** stereoselectively, thereby setting the C-3 (Pseudopterosin numbering) stereocentre to the desired configuration, in good yield. Ring opening of **51** to the diol **52** with $LiAlH_4$ in THF followed by selective sulfonylation with $PhSO_2Cl$ gave rise to **53**, which was then treated with $LiEt_3BH$ in

THF to afford **54**. PCC oxidation of **54** in DCM gave the hydroxy ketone **55** as a single diastereomer.

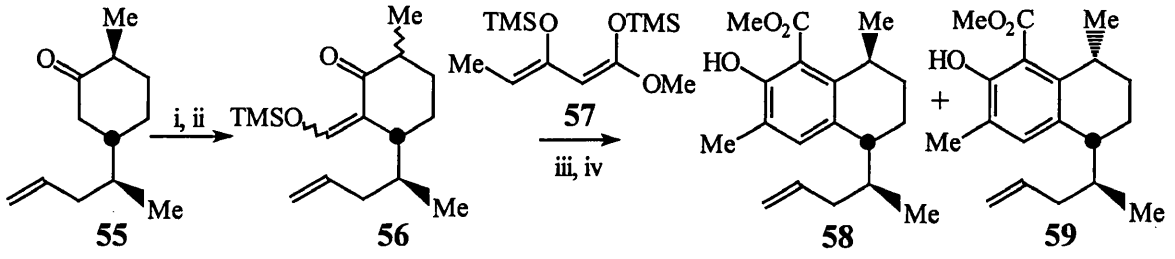
Scheme 9



(i) PivCl, pyridine; (ii) DHP, PPTS, DCM; (iii) KOH, H_2O; (iv) PCC, NaOAc, DCM; (v) $NaClO_2$, *t*-BuOH, H_2O, 2-methyl-2-butene; (vi) Acetic acid, H_2O, 80 °C, 90% for six steps; (vii) *p*-TsOH, PhMe, reflux, 67%; (viii) LDA, PhSeCl, HMPA; (ix) H_2O_2, 91% for two steps; (x) Vinyl magnesium bromide, CuI-DMS, TMSCl, THF, -40 °C, 79%; (xi) $LiAlH_4$, THF, rt, 84%; (xii) $PhSO_2Cl$, Et_3N, DMAP, DCM; (xiii) $LiEt_3BH$, THF; (xiv) PCC, DCM, 63% for three steps.

Installation of the aromatic nucleus of the natural product was realised under the Chan-Brownbridge conditions[38] (Scheme 10).

Scheme 10



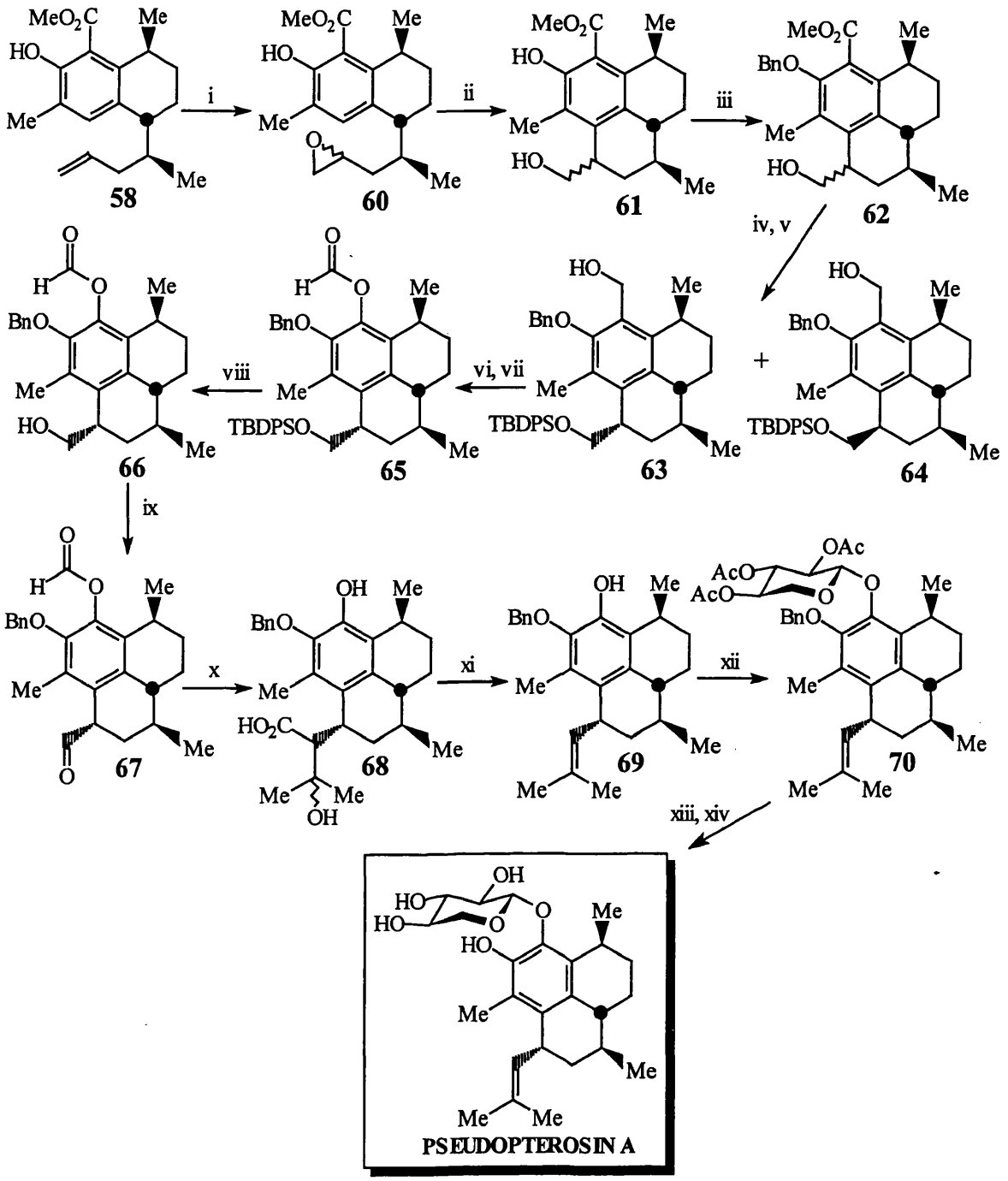
(i) NaH, HCO_2Et, dioxane; (ii) TMSCl, Et_3N, hexane, 85% for two steps; (iii) **57**, $TiCl_4$, DCM, -78 °C; (iv) NaOMe, MeOH, 66% for two steps.

Unfortunately, conversion of **55** to the required silyl enone **56** resulted in loss of stereochemistry at C-7 (Pseudopterosin numbering). Reaction of **56** with the diene **57**[39]

and subsequent aromatisation with NaOMe gave the phenols **58** and **59** (**58**:**59**, 2:3). Preparative TLC allowed for the isolation of the desired epimer **58**.

The synthesis was completed starting with peracid oxidation of **58** to give **60** as an inseparable mixture of epoxides (Scheme 11). Freidel-Crafts alkylation on **60** using $SnCl_4$ as the Lewis acid formed the third ring of the amphilectane skeleton gave **61** and selective benzylation of the phenol hydroxyl formed **62** in excellent yield. Silylation of the primary hydroxyl and DIBAL reduction of the methyl ester led to **63** and **64** (**63**:**64**, 1.1:1), which were separated by preparative TLC. PCC oxidation of **63** followed by Baeyer-Villiger oxidation with *m*-CPBA in $CHCl_3$ led to the formyl compound **65**. Desilylation to **65** could be achieved with TBAF at pH=7 without formyl hydrolysis to form **66**. Swern oxidation of the alcohol **66** with $(COCl)_2$ afforded the aldehyde **67** with no detectable epimerisation. Reaction of **67** with the di-lithio anion of isobutyric acid in THF and subsequent treatment of the crude reaction residue with (dimethylamino)formaldehyde dineopentyl acetal[40] led to the formation of **69**, presumably *via* the β-hydroxy acid **68**. AgOTf mediated glycosidation of **69** with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[31] **29** gave **70** stereoselectively in 51% yield. Removal of the acetyl and benzyl protecting groups led to synthetic Pseudopterosin A, which was identical in all respects to the natural product.

Scheme 11



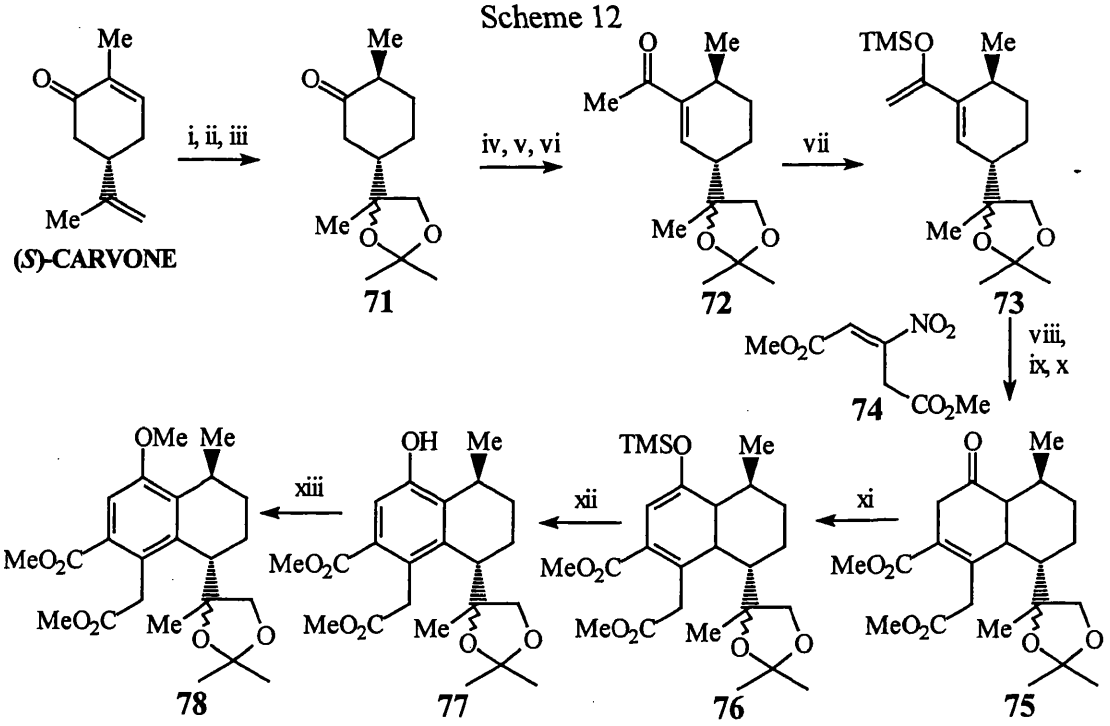
(i) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 55 °C, 64%; (ii) $SnCl_4$, DCM; (iii) BnBr, K_2CO_3, DMSO, 88% for two steps; (iv) TBDPSCl, imidazole, DMF, 45 °C; (v) DIBAL, DCM, rt, 75% for two steps; (vi) PCC, DCM; (vii) *m*-CPBA, Na_2HPO_4, $CHCl_3$, rt, 3 hrs, 88% for two steps; (viii) TBAF, acetic acid, THF; (ix) $(COCl)_2$, Et_3N, DMSO, -60 °C to -40 °C, 86% for two steps; (x) $Me_2C(Li)CO_2Li$, THF, rt, 30 mins; (xi) (dimethylamino)formaldehyde dineopentyl acetal, 4,4'-methylenebis(2,6-di-*t*-butylphenol), $CHCl_3$, 55 °C, 3 days, 82% for two steps; (xii) 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide, AgOTf, tetramethylurea, DCM, rt, 51%; (xiii) KOH, MeOH; (xiv) Li-NH_3, THF, 73% for two steps.

In summary, Broka *et al.* have produced a synthesis of Pseudopterosin A starting from (*S*)-(-)-limonene (26 steps, <1% overall yield).

1.3.3 The Kozikowski Asymmetric Synthesis of a late Pseudopterosin Intermediate

In 1991 Kozikowski[41] *et al.* published a Diels-Alder approach, starting from (*S*)-carvone, to the tricarbocyclic core of the Pseudopterosins (Scheme 12). The ketone **71** was obtained from (*S*)-carvone under standard conditions and was converted to **72** by the Shapiro reaction with acetaldehyde as the electrophile and PDC to oxidise the resulting alcohol in good yield. Reaction of **72** with LiHMDS in THF and trapping of the enolate with TMSCl generated the silyloxydiene **73**. Treatment of **73** with neat dienophile **74** and hydrolysis of the primary reaction product with 2N (aq) HCl and elimination of the nitro group with DBU in THF afforded **75** in 52 % yield. Conversion of the ketone **75** to the silyl enol ether **76** and aromatisation of the resulting cyclohexadiene ring with DDQ led to the formation of the phenol **77**, which was methylated with Me_2SO_4 in the presence of Bu_4NI in good overall yield.

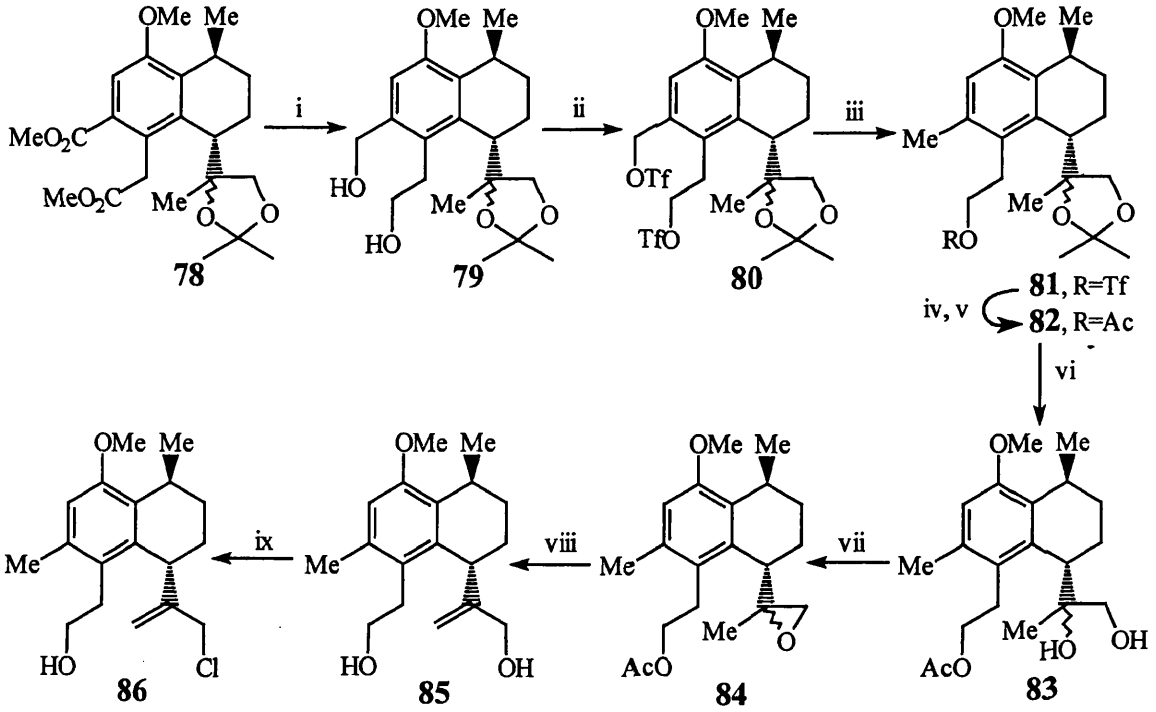
Scheme 12



(i) Li-NH_3, *t*-BuOH, THF, -30 °C, 72%; (ii) NMO, OsO_4, *t*-BuOH, THF, H_2O, rt, 10 hrs, 95%; (iii) 2,2-dimethoxypropane, PPTS, DCM, rt, 24 hrs, 90%; (iv) $TrisNHNH_2$, MeOH, 10 mins, 81%; (v) *n*-BuLi, hexane:TMEDA 1:1, -78 °C, 2 hrs, 0 °C, 1 hr with MeCHO, 57%; (vi) PDC, DCM, rt, overnight, 71%; (vii) LiHMDS, TMSCl, THF, -78 °C to 0 °C, 40 mins, 99%; (viii) **74**, 3,5-di-*t*-butylcatechol, 0 °C for 30 mins, rt for 15 hrs; (ix) 2N (aq) HCl, THF, 0 °C, 5 mins; (x) DBU, THF, 0 °C for 30 mins, rt for 1 hr, 52% for three steps; (xi) TMSI, HMDS, Et_3N, 1,2-dichloroethane, rt, 2 hrs; (xii) DDQ, PhH, rt, overnight, 68% for two steps; (xiii) Me_2SO_4, K_2CO_3, Bu_4NI, acetone, dark, reflux, 15 hrs, 95%.

The diol **79** (Scheme 13), produced by DIBAL reduction of **78**, was converted to the bistrifluoromethanesulfonate **80** and subjected to hydrogenolysis in the presence of trace TFA. The thus formed trifluoromethanesulfonate **81** was converted to the acetate **82** under standard conditions. Removal of the acetonide protecting group with acetic acid in THF/H_2O and treatment of the diol **83** with tosyl chloride and Et_3N in DCM followed by DBU produced the epoxide **84**. Eliminative ring-opening of the epoxide **84**, and concomitant acetyl hydrolysis, with aluminium isopropoxide in PhMe heated at reflux produced the allylic alcohol **85** in 94% yield, which was converted to the allylic chloride by the action of NCS in Me_2S.

Scheme 13

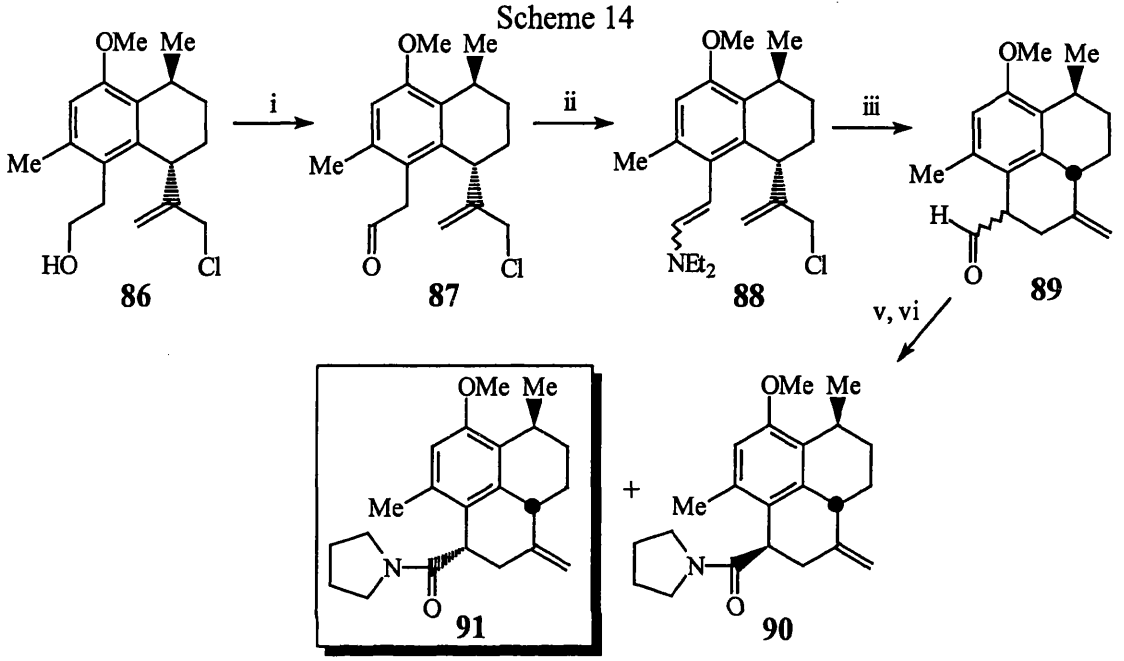


(i) DIBAL, Et_2O, -78 °C, 30 mins, then rt, 2 hrs, 78%; (ii) $(TfO)_2O$, Et_3N, DCM, 0 °C, 2 hrs; (iii) H_2, 10% Pd-C, TFA, 50 °C, overnight; (iv) K_2CO_3, MeOH, rt 30 mins, 85% for three steps; (v) Ac_2O, Et_3N, DMAP, DCM, rt, overnight, 98%; (vi) AcOH:THF:H_2O 3:1:1, 80 °C, 20 hrs, 82%; (vii) TsCl, Et_3N, DMAP, DCM, rt, 20 hrs then DBU, rt, 5 hrs, 95%; (viii) Al(O-*i*-Pr)$_3$, PhMe, 120 °C, 20 hrs, 94%; (ix) NCS, Me_2S, DCM, -15 °C, 5 mins, then 0 °C, 2 hrs, 84%.

The tricyclic core of the Pseudopterosin aglycone was synthesised by enamine ring closure of **88** (Scheme 14). Alcohol **86** was oxidised with PDC in DCM and the resulting aldehyde **87** was reacted with TMS-diethylamine (hetero-Peterson olefination)

to form the enamine **88**. When crude **88** was heated at 85 °C in EtOH, cyclisation occurred to give **89** as a 3:2 mixture of desired to undesired diastereomers at C-1 (Pseudopterosin numbering). Chromatographic separation was achieved by conversion of **89** to the pyrrolidine derivatives **90** and **91**.

Scheme 14



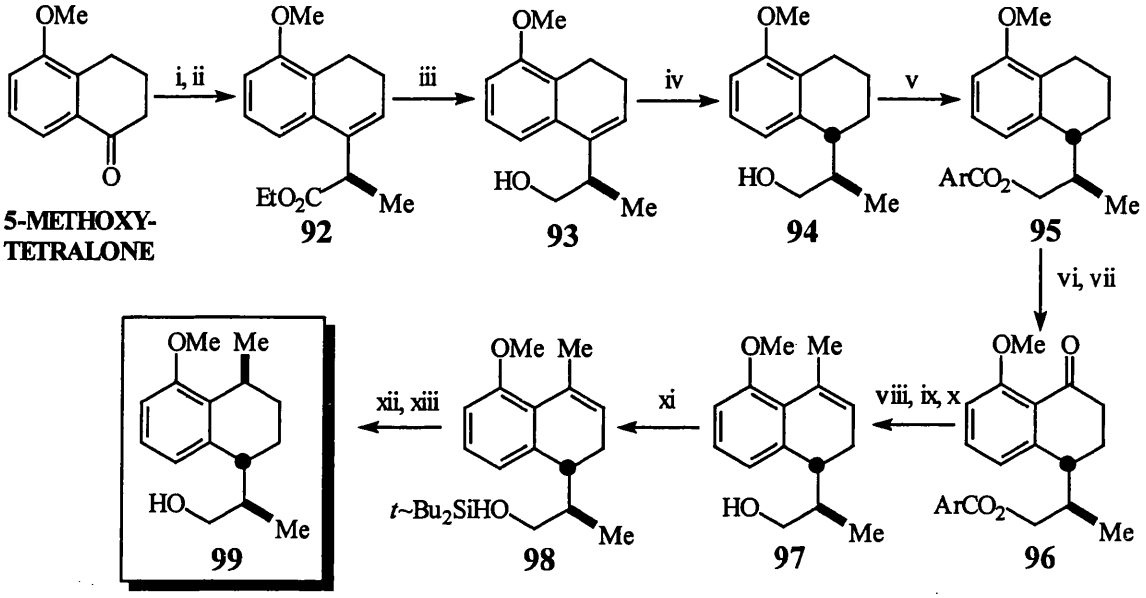
(i) PDC, DCM, rt, overnight, 76%; (ii) TMS-diethylamine, *p*-TsOH, rt, 24 hrs; (iii) EtOH, NaI, 85 °C, 15 hrs, then EtOH:H_2O 4:1, 85 °C, 12 hrs, 75% for two steps; (v) $NaOCl_2$, 2-methyl-2-butene, 1M (aq) KH_2PO_4:*t*-BuOH 1:2, rt, overnight; (vi) pyrrolidine, Et_3N, 2-chloro-1-methylpyridinium iodide, DCM_2 45 °C, 2 hrs, 52% for two steps.

In summary, Kozikowski *et al.* have reported the synthesis of an advanced intermediate which could be used in a synthetic strategy to the Pseudopterosins and analogues. To date, this work has not been elaborated nor has the stereochemistry at C-1 (Pseudopterosin numbering) been confirmed.

1.3.4 The McCombie Racemic Synthesis of the Pseudopterosin A-F and seco-*Pseudopterosin Aglycones*

In 1991 McCombie *et al.* published racemic syntheses of the *seco*-Pseudopterosin[42] and Pseudopterosin A-F[43] aglycones both starting from 5-methoxytetralone with the alcohol **99** as a key intermediate (Scheme 15).

Scheme 15



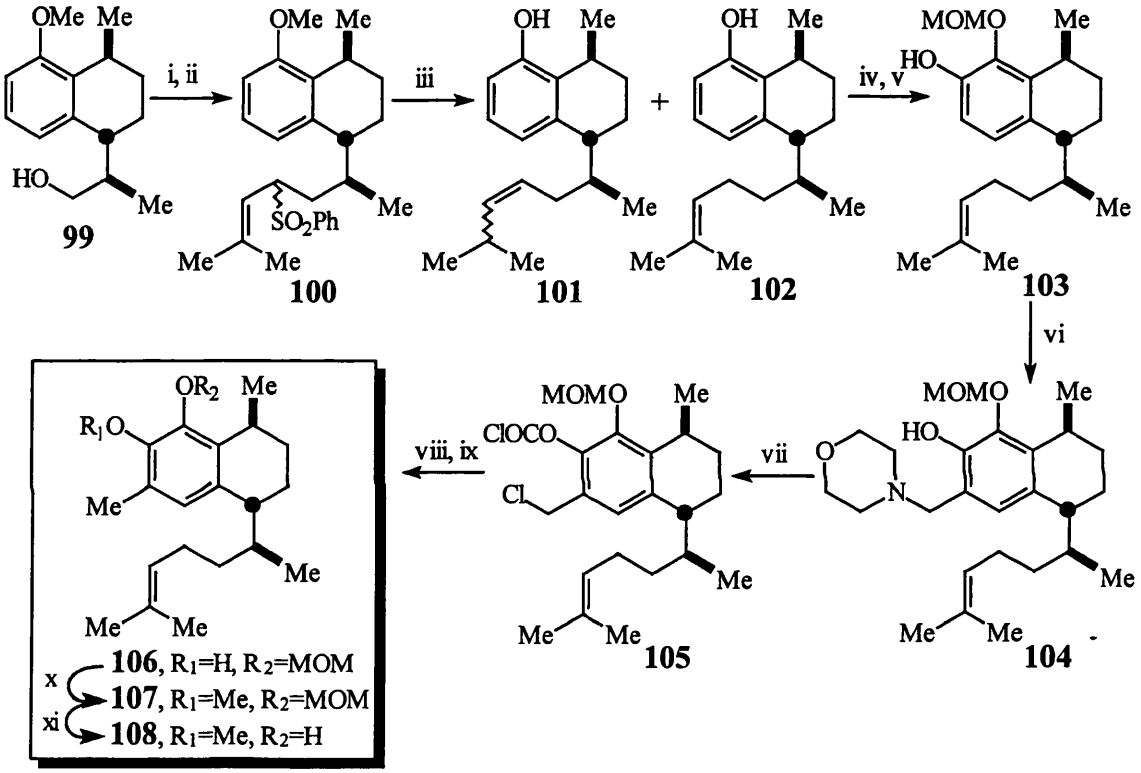
(i) Zn, $MeCH(Br)CO_2Et$, TMSCl, THF, 65 °C; (ii) MsOH, 1,2-dichloroethane, 80 °C; (iii) $NaH_2Al(OCH_2CH_2OMe)$, Et_2O, 75-85% for three steps; (iv) H_2, $ClRh(PPh_3)$, *t*-BuOK, 60 psi, THF, rt, 50 hrs; (v) *p*-$NO_2C_6H_4COCl$, pyridine, 86% for two steps; (vi) $K_2S_2O_8$, $CuSO_4$, *sym*-collidine, $MeCN:H_2O$ 1:1, 80 °C, 1.5 hrs; (vii) PCC, Celite™, DCM, 63% for two steps; (viii) NaOMe; (ix) $MeCeCl_2$, THF, -70 °C to rt; (x) TsOH, 72% for three steps; (xi) *t*-Bu_2SiHCl, imidazole, DMF, rt; (xii) Syringe pump addition (16-20 hrs) of **96** in DCM to 0.1M TFA in DCM; (xiii) TBAF, THF, rt, 65-75% for three steps.

Reformatski reaction and subsequent dehydration of 5-methoxytetralone, gave the ester **92**, which was reduced to the homoallylic alcohol **93** with Red-Al in Et_2O in good overall yield. The dihydronaphthalene **93** has a strongly preferred solution conformation, which minimises *peri*-ArH interactions and allows for stereoselective reduction of the diastereotopic faces of the double bond. This was achieved under the Thompson conditions to afford **94** in >95:5 stereoselectivity. Conversion of the alcohol **94** to the *p*-nitrobenzoate and recrystalisation secured **95** as a single compound. Treatment of **95** with $K_2S_2O_8$ and $CuSO_4$ with *sym*-collidine, followed by further oxidation with PCC in DCM, led to the ketone **96**. Hydrolysis of the *p*-nitrobenzoate and reaction of the carbonyl group with $MeCeCl_2$ resulted in the olefin **97** after dehydration. Stereoselective reduction of **98**, produced from **97** under standard conditions, was realised *via* an intra-molecular 'ionic hydrogenation' reaction mediated

by TFA and subsequent desilylation gave **99** of >95% isomeric purity and in 65-75% yield from **97**.

The *seco*-Pseudopterosin aglycone was obtained (Scheme 16) as follows: conversion of **99** to the tosylate and sulfone displacement with $Me_2C{=}CHCH(Li)SO_2Ph$ in THF led to **100** as a mixture of diastereomers.

Scheme 16



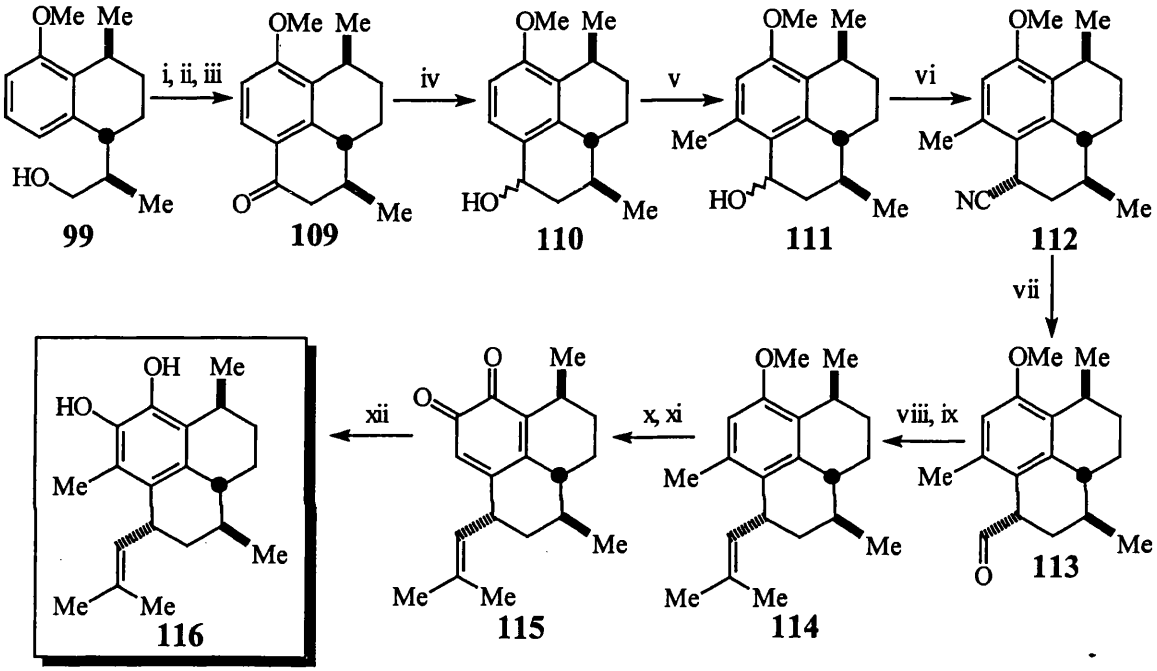
(i) TsCl, pyridine, rt; (ii) $Me_2C{=}CHCH(Li)SO_2Ph$, THF, -70 °C to rt; (iii) Li-$EtNH_2$; (iv) MOMCl, Hünigs base; (v) *t*-BuLi, Et_2O, 0 °C, then $B(OMe)_3$, H_2O_2-H_2O-K_2CO_3; (vi) CH_2O, morpholine, H_2O, EtOH, 80 °C; (vii) $Cl_3COCOCl$, *sym*-collidine, Hünigs base, 0 °C to rt, 6 hrs; (viii) $NaBH_4$, DMSO; (ix) NaOH, H_2O, EtOH; (x) K_2CO_3, MeI, acetone; (xi) TsOH, MeOH.

Desulfonylation with Li in $EtNH_2$ with concomitant demethylation led to **102** with trace amounts of the by-product **101**. The phenol was MOM protected, metalated with *t*-BuLi, and worked-up with $B(OMe)_3$ followed by H_2O_2-H_2O-K_2CO_3 to give the catechol ether **103**. Mannich reaction produced **104**, which was converted to the chloromethyl compound **105** with $Cl_3COCOCl$. Reduction of **105** followed by hydrolysis afforded **106**, which was *O*-methylated under standard conditions to cede **107**. Hydrolysis of the

MOM ether provided **108**, identical to a sample obtained from degradation of the natural product.

The Pseudopterosin A-F aglycone was obtained (Scheme 17) as follows: alcohol **99** was transformed to the tricyclic ketone **109** under standard conditions and subsequent reduction led to **110** as a mixture of diastereomers.

Scheme 17



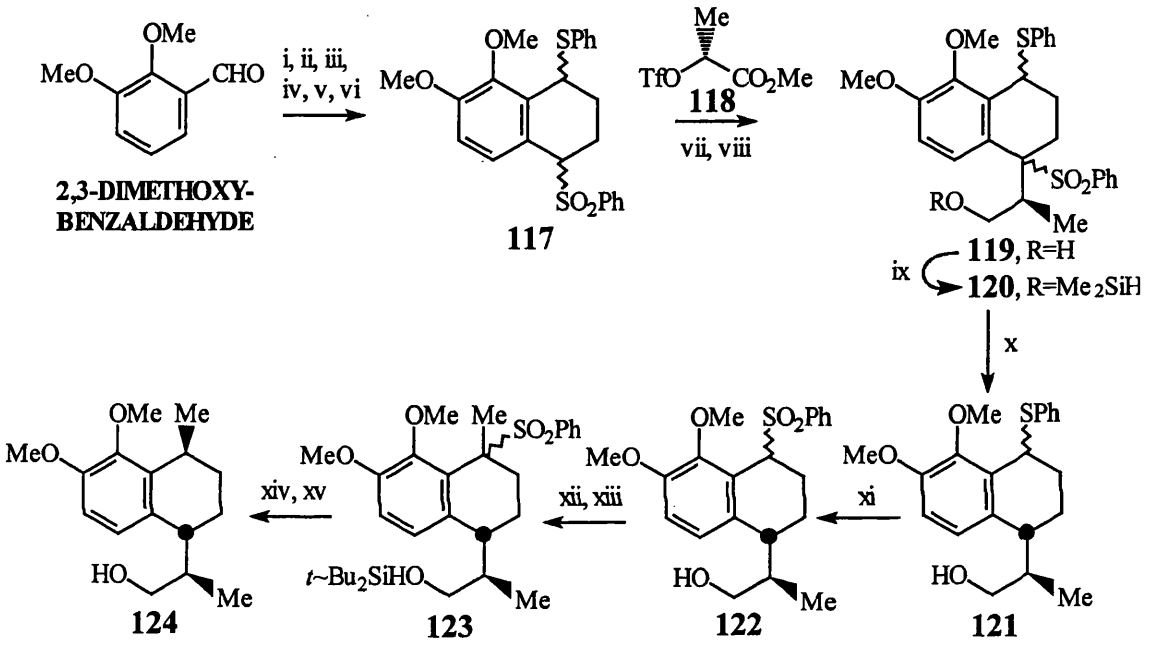
(i) TsCl, pyridine, rt; (ii) NaCN, DMSO, 65 °C; (iii) MsOH, 1,2-dichloroethane, 85 °C, 2 hrs, then NaOAc, H_2O, 85 °C, 2 hrs, 60-70% for three steps; (iv) $NaBH_4$; (v) *t*-BuLi, Et_2O, pentane, 35 °C, then MeI, 0 °C; (vi) Et_2AlCN, BF_3-OEt, DCM, -70 °C, 60-70%; (vii) *i*-Bu_2AlH, PhMe, -70 °C; (viii) $Me_2C(Li)SO_2Ph$, THF, -70 °C; (ix) Na-Hg, K_2HPO_4, MeOH, 55% for three steps; (x) BBr_3, 2,6-di-*t*-butylpyridine, DCM, 0 °C; (xi) $ON(SO_3K)_2$, KH_2PO_4, acetone-H_2O, 0 °C; (xii) $Na_2S_2O_4$, H_2O, DCM.

Alkoxide-directed metalation with *t*-BuLi in Et_2O of **110** and reaction with MeI installed the aromatic methyl of the natural product. Reaction of **111** with Et_2AlCN with BF_3-OEt as the Lewis acid afforded **112** in good yield and high stereoselectivity (16:1). The nitrile **112** was reduced to the aldehyde **113** and Julia olefination with the sulfone Me_2CSO_2Ph gave **114**. Demethylation with BBr_3, and oxidation with $ON(SO_3K)_2$ yielded the *o*-quinone **115**, which was reduced to the Pseudopterosin aglycone **116** with

$Na_2S_2O_4$ in H_2O. Synthetic **116** was identical to a sample obtained from degradation of Pseudopterosin E.

In an update[44] of their earlier work, McCombie *et al.* report an asymmetric synthesis of the key alcohol **124** starting from 2,3-dimethoxybenzaldehyde (Scheme 18).

Scheme 18



(i) $EtO_2CCH_2CH_2ZnI$, $ClTi(O\text{-}i\text{-}Pr)_3$; (ii) PhSH, MsOH; (iii) $(COCl)_2$; (iv) $SnCl_4$; (v) $LiAlH_4$; (vi) $PhSO_2Na$, TFA, ~65% for six steps; (vii) LDA, THF, 70-75%; (viii) $LiAlH_4$; (ix) Me_2SiHCl; (x) $EtAlCl_2$, DCM, -70 °C; (xi) OXONE™; (xii) MeI; (xiii) $t\text{-}Bu_2SiHCl$; (xiv) $EtAlCl_2$, rt; (xv) F^-.

The sulfone **117**, obtained in 65% overall yield, was alkylated with the triflate **118**, and the crude alkylation product was reduced to the alcohol **119**. Conversion of **119** to the dimethylsilyl ether **120** and subsequent treatment with $EtAlCl_2$ in DCM at -70 °C led to **121** stereoselectively. Sulfide oxidation yielded **122**, which was methylated then *O*-silylated under standard conditions. Treatment of **123** with $EtAlCl_2$ at room temperature produced **124** after fluoride treatment.

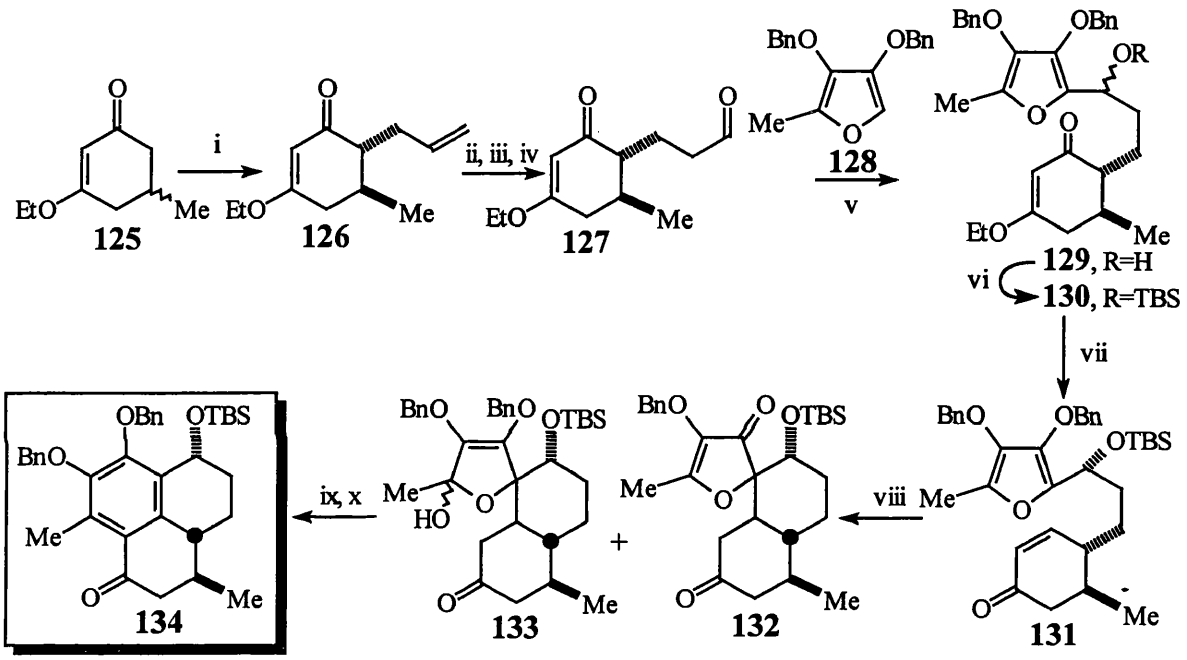
In summary, McCombie *et al.* have achieved racemic syntheses of a *seco*-Pseudopterosin aglycone derivative and the Pseudopterosin aglycone (25 steps) *via* a

common intermediate. Furthermore, they have produced an advanced intermediate for an asymmetric total synthesis of these compounds.

1.3.5 The Jung Racemic Synthesis of a Late Pseudopterosin Intermediate

The Jung[45] and Siedem (1993) approach to the Pseudopterosins starts with the readily available β-ethoxyenone **125**[46] (Scheme 19).

Scheme 19



(i) LDA, allyl bromide, THF, HMPA, -78 °C, 95%; (ii) Sia_2BH; (iii) H_2O_2, NaOH; (iv) $(COCl)_2$, Et_3N, DMSO, 56% for three steps; (v) **128**, *n*-BuLi, THF, 0 °C, added to **127**, THF, -78 °C; (vi) TBSCl, imidazole, DMF, 53% for two steps; (vii) DIBAL, PhMe, -78 °C, then SiO_2, 70%; (viii) $SnCl_4$, PhMe, -78 °C, 1 hr, **133** 58% and **132** 36%; (ix) *t*-BuOK, *t*-BuOH; (x) TBSCl, imidazole, DMF, 60% for two steps.

Alkylation of **125** under standard conditions with allyl bromide gave **126** in good yield and stereoselectivity (7.5:1). Hydroboration-oxidation of the double bond with disiamylborane followed by Swern oxidation with $(COCl)_2$ furnished the aldehyde **127** in good yield. The lithium anion of furan **128**[47] was reacted with **127** to form the secondary alcohol **129** as a 1:1 mixture of diastereomers, which was silylated to give **130**. DIBAL reduction of **130** not only unmasked the desired enone unit in **131** but also equilibrated the benzylic centre α to the furan ring to one diastereomer as shown.

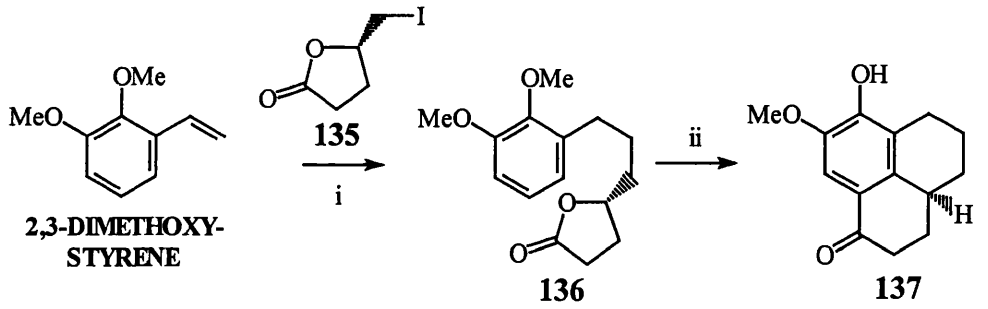
Attempted intramolecular Diels-Alder reactions of **131** under thermal and Lewis acid conditions all failed to give the desired product **134**. Instead, the major products of the reaction were the novel intramolecular Michael adducts **133** (58%) and **132** (36%), as exemplified for $SnCl_4$. The hemiacetal **133** was converted to the desired phenalene **134** upon the action of *t*-BuOK in *t*-BuOH (with re-silylation of the unsilylated analogue of **134**).

In summary, Jung and Siedem have developed a novel Michael addition strategy to substituted phenalenes and have prepared a late intermediate which could be used in a racemic synthesis of Pseudopterosin A.

1.3.6 The Harrowven Cascade Approach to the Pseudopterosin Tricyclic Core

In 1994 Harrowven[48] *et al.* reported initial model studies on the construction of the amphilectane skeleton of the Pseudopterosins *via* a tandem Friedel-Crafts alkylation, Friedel-Crafts acylation protocol (Scheme 20).

Scheme 20



(i) **135**, Bu_3SnH, AIBN, PhH, reflux, 3 hrs, then KF, H_2O, 48%; (ii) $TiCl_4$, DCM, reflux, 36 hrs, 74%.

Unification of the iodolactone **135**[49] and 2,3-dimethoxystyrene under tin mediated radical conditions led to the simple analogue **136** to be used in test reactions. Gratifyingly, when $TiCl_4$ was used as the Lewis acid, there was a smooth tandem Friedel-Crafts alkylation, Friedel-Crafts acylation reaction accompanied by *para*-demethylation to afford **137**. It appears that alkylation occurs with inversion of

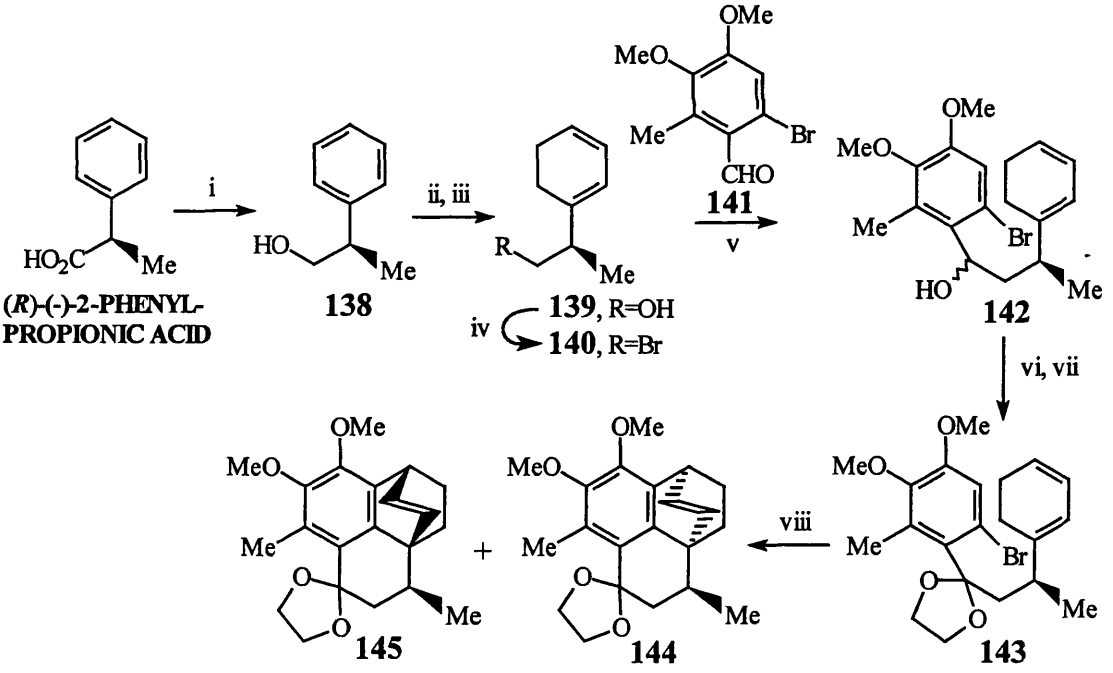
configuration, based on the optical activity of **137**, though this is not confirmed neither has the ee of the reaction been determined.

In summary, Harrowven *et al.* have achieved a rapid and concise entry into the Pseudopterosin aglycone *via* a novel synthetic tactic which also allows for differentiation of the two catechol groups.

1.3.7 The Buszek Asymmetric Synthesis of the Pseudopterosin A-F Aglycone

The Buszek[50] and Bixby approach (1995) to the Pseudopterosin A-F aglycone starts with commercially available (*R*)-(-)-2-phenylpropionic acid, which is reduced to the alcohol **138** with $LiAlH_4$ in THF (Scheme 21).

Scheme 21



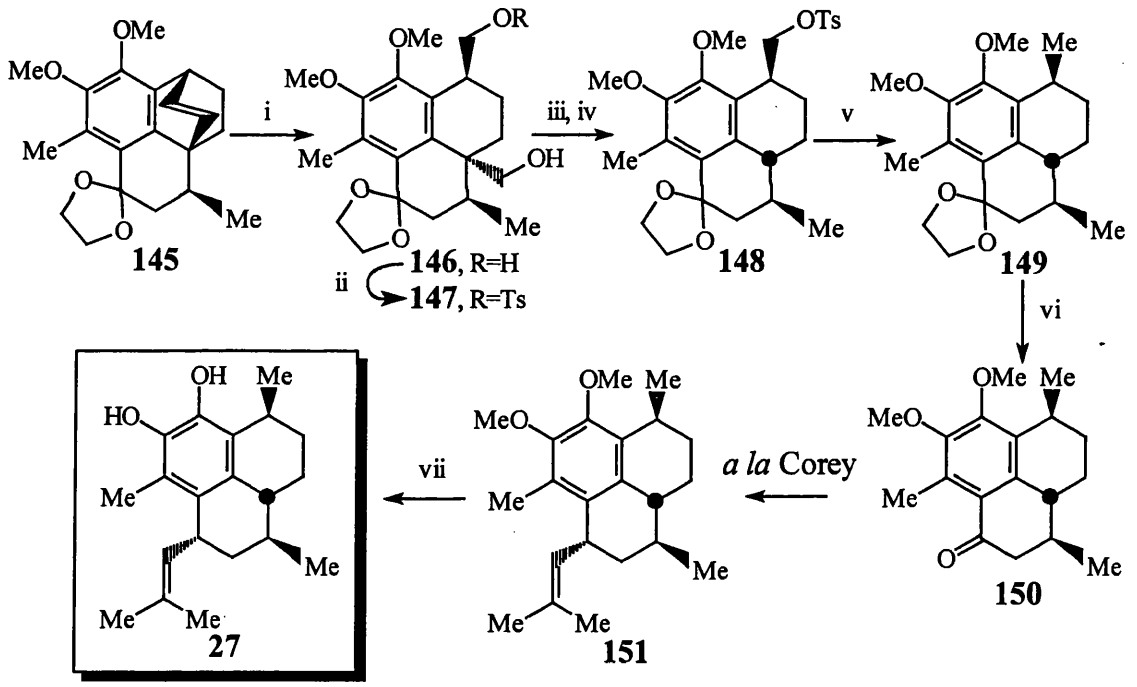
(i) $LiAlH_4$, THF, 65 °C, 12 hrs; (ii) Na-NH_3, EtOH, -78 °C, 6 hrs; (iii) *t*-BuOK, DMSO, -65 °C to rt, 2 hrs; (iv) NBS, PPh_3, pyridine, DCM, rt, 1 hr, 48% for four steps; (v) Mg, THF, rt to 0 °C, then add to **141**, THF, 0 °C, 78%; (vi) $(COCl)_2$, Et_3N, DMSO, DCM, -78 °C to rt, 1 hr; (vii) $(TMSOCH_2)_2$, TMSOTf, DCM, -78 °C, 4 hrs, 81% for two steps; (viii) LDA, THF, -78 °C, 2 hrs, then slow warming to rt over 12 hrs, 63-71%.

Birch reduction of **138** followed by *t*-BuOK induced isomerisation led to the 1-substituted cyclohexadiene **139**, which was brominated with NBS/Ph_3P in DCM

containing pyridine to afford **140** in good overall yield. Grignard addition of **140** to the known aldehyde **141**[51] led to **142** as a mixture of diastereomers. Swern oxidation with $(COCl)_2$ to the ketone and protection as the 1,3-dioxolane under Noyori conditions gave **143**. The key step in this sequence is the intramolecular benzyne Diels-Alder reaction[52] of **143**, yielding **144** and **145** (**144**:**145** 42:58), in which the tricyclic core of the natural product is produced.

The desired diastereomer **145** was readily separated by chromatography and oxidative cleavage of the ethylene bridgehead gave the diol **146** in good yield (Scheme 22).

Scheme 22



(i) a. NMO, 10% OsO_4 in PhMe, acetone:H_2O 9:1, rt, 2.5 hrs, b. $NaIO_4$, THF:H_2O 1:1, rt, 4 hrs, then $NaBH_4$, 85%; (ii) TsCl, pyridine, 0 °C to rt, 6 hrs, 83%; (iii) Dess-Martin periodinane, DCM, rt, 2 hrs; (iv) $(Ph_3P)_3RhCl$, PhCN, rt to 160 °C, 0.5 hrs, 76% for two steps; (v) $LiAlH_4$, THF, reflux, 18 hrs, 68%; (vi) PPTS, acetone, H_2O, 12 hrs, 100%; (vii) TMSI, $CHCl_3$, 35 °C, 48 hrs, .

Selective protection of the less hindered alcohol gave the tosylate **147**. Dess-Martin periodinane oxidation of the remaining alcohol and decarbonylation of the resulting aldehyde with Wilkinson's catalyst led to **148** in 76% yield. Hydride displacement of the tosylate using $LiAlH_4$ in THF heated at reflux afforded **149**, which was deketalised

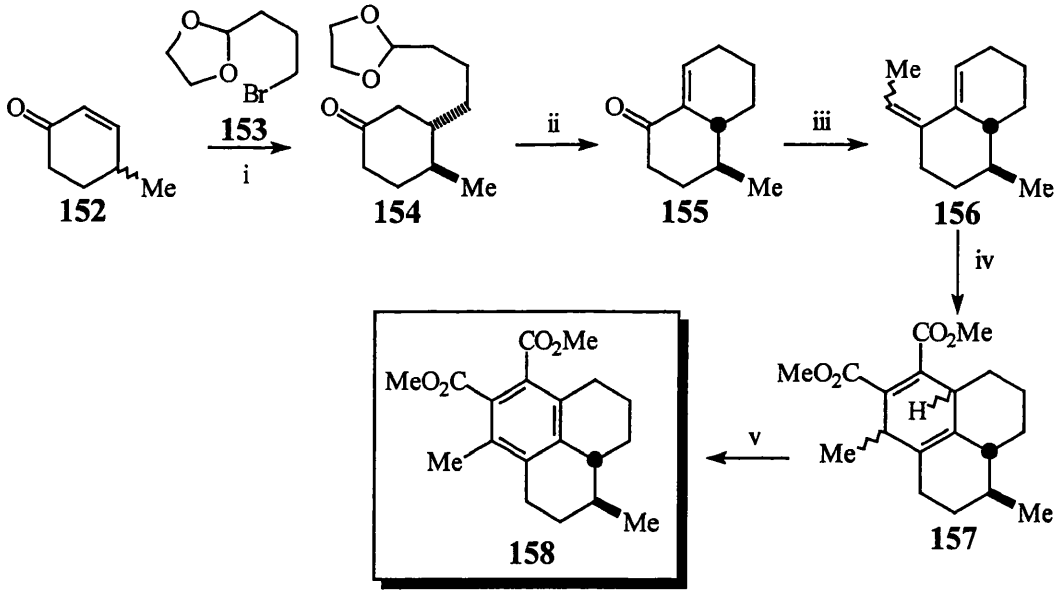
with PPTS in warm acetone/H_2O to give the hexahydrophenalen-1-one **150**. The isopropylidene unit was installed using the chemistry of Corey[13] (Scheme 6) giving **151** and the methyl ethers were cleaved with TMSI to afford the aglycone **27**, identical in all respects to a sample obtained by degradation of the natural products.

In summary, Buszek and Bixby have used a novel intramolecular benzyne Diels-Alder strategy in an expedient asymmetric synthesis of the Pseudopterosin A-F aglycone (18 steps, 3% overall yield).

1.3.8 The Frejd Approach to the Pseudopterosin Tricyclic Core

Frejd[53] *et al.* have reported (1995) a rapid creation of the tricyclic core of the Pseudopterosins starting from the known racemic enone **152**[54] (Scheme 23).

Scheme 23



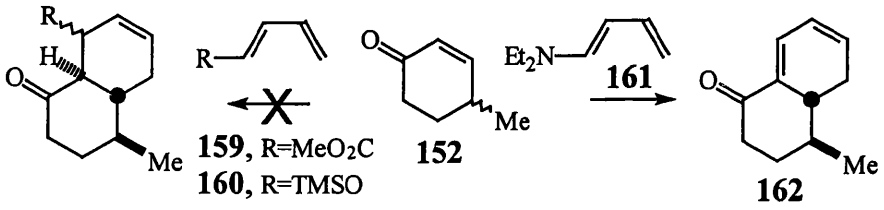
(i) **153**, Mg, THF, rt, ultrasound for 50 mins, then cool to -78 °C, CuBr, Me_2S, 1 hr, then **152**, THF, -78 °C for 9 hrs, rt for 1 hr, 63%; (ii) HCl, THF, 80 °C, 6 hrs, 59%; (iii) Ph_3PCHMe, Et_2O, -78 °C for 4 hrs, rt for 0.5 hrs, 53%; (iv) Dimethyl acetylenedicarboxylate, $AlCl_3$, DCM, 0 °C, 2 hrs; (v) DDQ, DMF, 140 °C, 37 hrs, 38% for two steps.

Cuprate addition of the bromodioxolane **153**[55] to **152** formed the Michael addition product **154** as predominately the *trans* diastereomer (*trans*:*cis* 97:3). Acid hydrolysis of **154** induced an aldol cyclisation, condensation reaction to give the methyloctalone

155, which reacted with Ph_3PCHMe to give diene **156** as a mixture of geometric isomers (*Z*:*E* 2:1). Lewis acid catalysed Diels-Alder reaction of **156** with dimethyl acetylenedicarboxylate proceeded smoothly to afford **157** and the resulting cyclohexadiene ring was aromatised with DDQ to give **158**.

Frejd *et al.* also comment on the remarkable inactivity of the enone **152** as a dienophile in the Diels-Alder reaction (Scheme 24).

Scheme 24



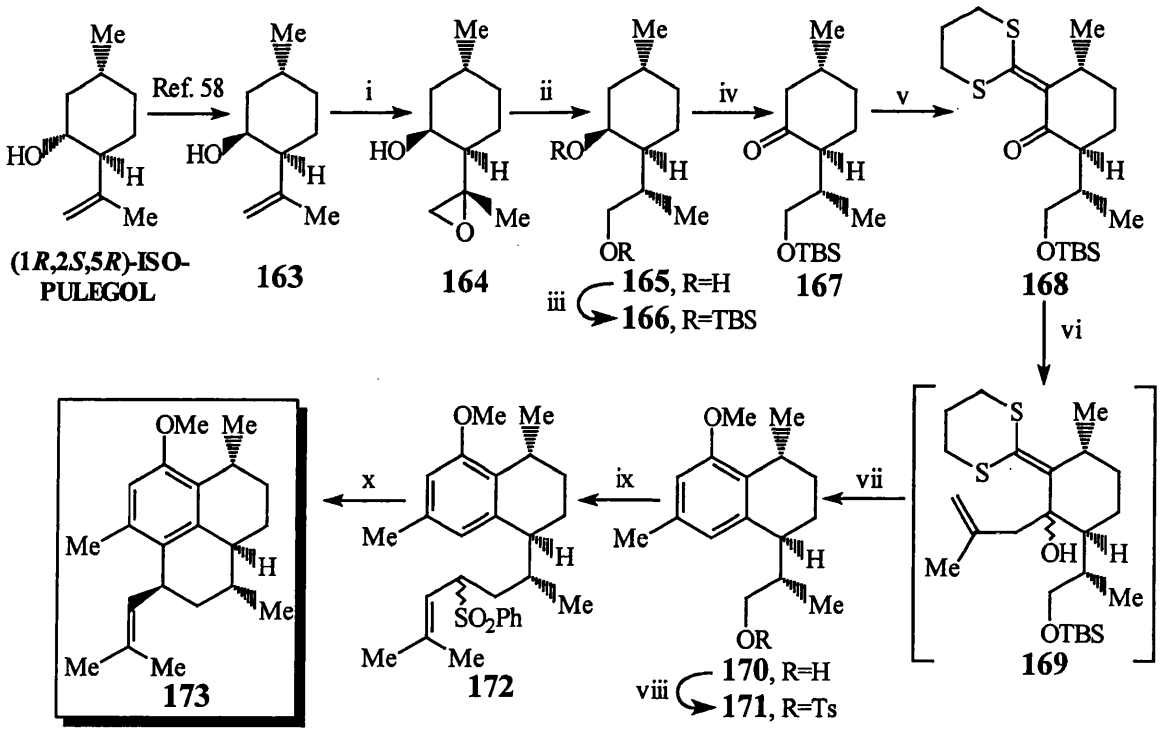
Specifically, **152** failed to react with both **159** and **160** even under very forcing conditions, and reacted only in low yield with **161** ultimately affording **162**.

In summary, Frejd *et al.* have developed a rapid assembly of a possible intermediate for the preparation of the Pseudopterosins and analogues. Furthermore, an asymmetric synthesis could be realised starting from the known enone (*S*)-**152**[56].

1.3.9 The Kocienski Asymmetric Syntheses of the Pseudopterosin K and L C-10 Deoxyaglycone and the Pseudopterosin G Aglycone Dimethyl Ether Enantiomer

In the first[57] (1996) of two publications, Kocienski *et al.* report a stereoselective synthesis of the Pseudopterosin K and L C-10 deoxyaglycone starting from (1*S*,2*S*,5*R*)-neoisopulegol **163**[58] (Scheme 25). Hydroxyl directed epoxidation of **163**, obtained from commercially available from (1*S*,2*S*,5*R*)-isopulegol, affords the oxirane **164**, which is ring opened with clean inversion of configuration with $NaBH_3CN$ and BF_3-OEt to produce **165**. Silyl protection of the primary hydroxyl to yield **166** followed by Swern oxidation of the secondary hydroxyl gave the ketone **167**.

Scheme 25



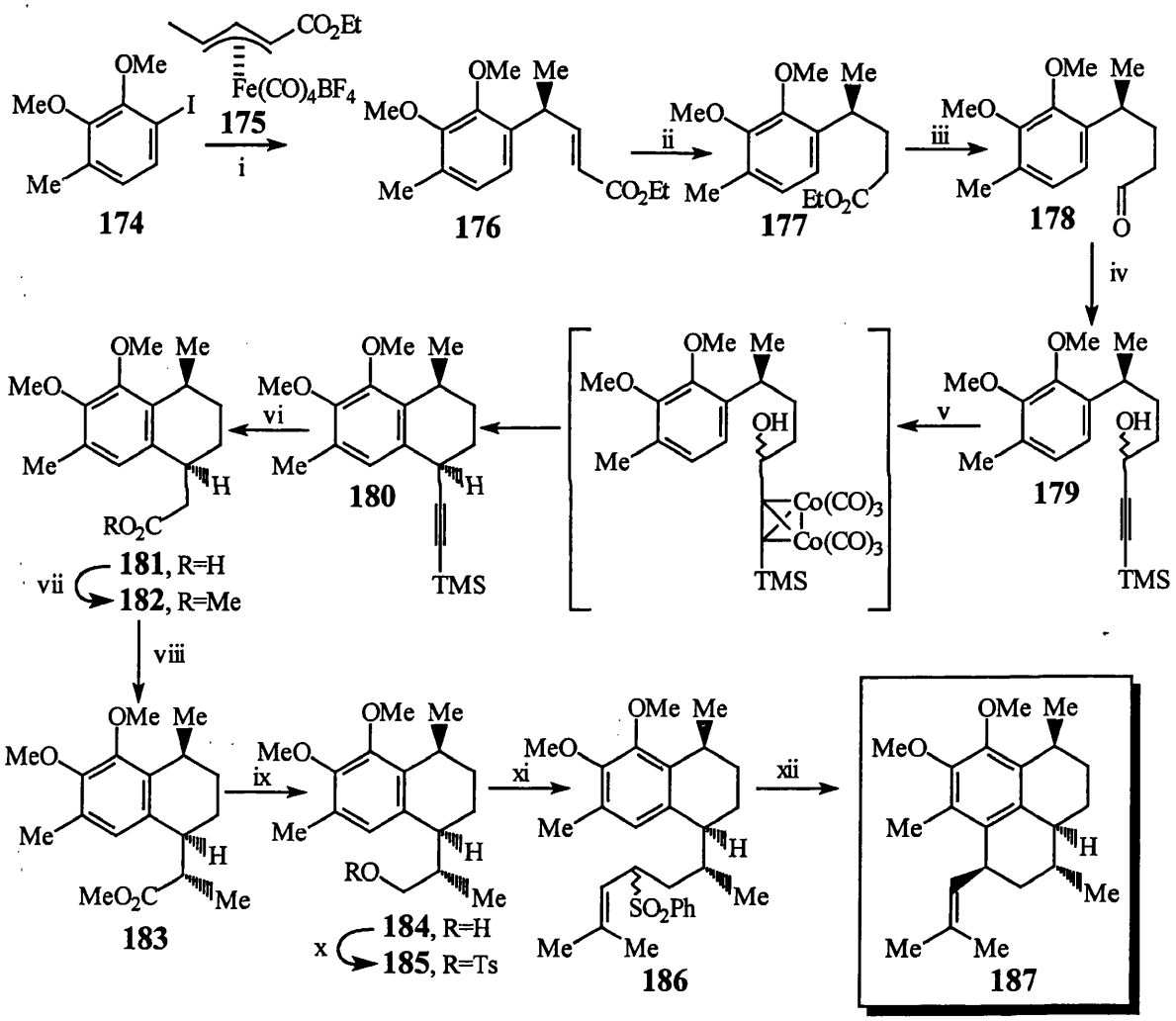
(i) $VO(acac)_2$, *t*-BuOOH, PhH, rt, 88%; (ii) $NaBH_3CN$, BF_3-OEt, THF, 79%; (iii) TBSCl, imidazole, DMF, rt, 84%; (iv) Swern oxidation, 88%; (v) a. LiHMDS, DMPU, THF, -78 °C, b. CS_2, -78 °C to 0 °C, c. LiHMDS, -78 °C, d. $Br(CH_2)_3Br$, -78 °C to rt, 71%; (vi) Methallylmagnesium chloride, THF, 0 °C; (vii) BF_3-OEt_2, MeOH, THF, -40 °C to rt, 63% for two steps; (viii) TsCl, DMAP, Et_3N, 0 °C to rt, 86%; (ix) Me_2C=CHCH(Li)SO_2Ph, THF, -78 °C to rt, 91%; (x) $EtAlCl_2$, THF, -78 °C to rt, 79%.

Conversion of **167** to the α-oxoketenedithioacetal **168** was mediated by a one-pot, four step procedure involving the reaction of the lithium enolate of **167** with CS_2 followed by a second enolisation and trapping of the intermediate ketene dithiolate with 1,3-dibromopropane to give **168** in 71% yield. Creation of the aromatic ring of the natural product, with concomitant desilylation, was realised under the Dieter-Ila-Junjappa conditions[59], where **168** was reacted with methallylmagnesium chloride and the resulting crude alcohol **169** was treated with BF_3-OEt_2 in MeOH and THF to afford **170** in good yield. Tosylation of the pendent alcohol yielded **171**, which was reacted with Me_2C=CHCH(Li)SO_2Ph to produce **172** as a ~1:1 mixture of diastereomers. Treatment of **172** with $EtAlCl_2$ in THF at -78 °C returned the tricycle **173** as a 10:1 mixture of diastereomers (10 steps, 15% overall yield). In addition, as *ent*-**163**[60] is readily available

from (*S*)-citronellal, this synthetic route could also furnish the Pseudopterosin A-F aglycone.

In a later[61] (1998) report, Kocienski *et al.* disclose an asymmetric route to the enantiomer of the Pseudopterosin G aglycone dimethyl ether **187** starting from the iodide **174**[62] (Scheme 26).

Scheme 26



(i) a. *n*-BuLi, THF:Et_2O 5:1, -100 °C, b. $ZnBr_2$, -100 °C to -70 °C, c. CuCN.2LiCl, -70 °C, d. **175**, -70 °C to 0 °C, 60%; (ii) Mg, MeOH, 5 °C, 3 hrs, 90%; (iii) DIBAL, DCM, -80 °C, 1 hr, 87%; (iv) TMSethynylmagnesium bromide, 0 °C, 15 mins, 89%; (v) a. $Co_2(CO)_8$, DCM, rt, 1 hr, b. BF_3-OEt, -20 °C, 3 hrs, c. $Fe(NO_3)_3.9H_2O$, MeOH, rt, 3 hrs, 86%; (vi) a. $(C_5H_{11})_2BH$, THF, 5 °C, 1 hr, b. H_2O_2, NaOH, MeOH, 30-50 °C, 1 hr, 65%; (vii) Tetramethylguanidine, MeI, PhMe, rt, 95%, (viii) a. LDA, THF, -40 °C, b. MeI, 85%; (ix) $LiAlH_4$, THF, 0 °C, 92%; (x) TsCl, Et_3N, DMAP, DCM, 86%; (xi) Me_2C=CHCH(Li)SO_2Ph, THF, 3 hrs, 75%; (xii) $EtAlCl_2$, DCM, -30 °C, 3 hrs, 90%.

Zinc-cuprate addition of **174** to the homochiral (*E*)-[(2,3,4-η^3)-1-ethoxy-1-oxo-3-pentenyl]tricarbonyliron (1-) tetrafluoroborate complex **175**[63] led to **176** stereoselectively (>95:5) in 60% yield. Treatment of **176** with Mg in MeOH gave **177** followed by DIBAL reduction in DCM of the ester group to the unsaturated aldehyde **178**. Reaction of **178** with TMSethynylmagnesium bromide afforded **179** as a 1:1 mixture of diastereomers. Protection of the triple bond with $Co_2(CO)_8$, and Nicholas cyclisation of the resulting complex with BF_3-OEt_2, formed **180** stereoselectively (95:5). Hydroboration-oxidation of the silylalkyne led to the carboxylic acid **181**, which was esterified with iodomethane. Treatment of the ester **182** with LDA followed by MeI leads to **183**, where α-alkylation was in good yield and diastereocontrol (10:1). Installation of the final ring and stereogenic centre of the natural product was achieved as published previously by Kocienski *et al.* Namely, reduction of the ester **183** to the alcohol **184** followed by tosylation to **185**. Sulfone displacement with Me_2C=CHCH(Li)SO_2Ph yields **186**, which cyclises under Lewis acid conditions to give the enantiomer of the Pseudopterosin G aglycone dimethyl ether **187**.

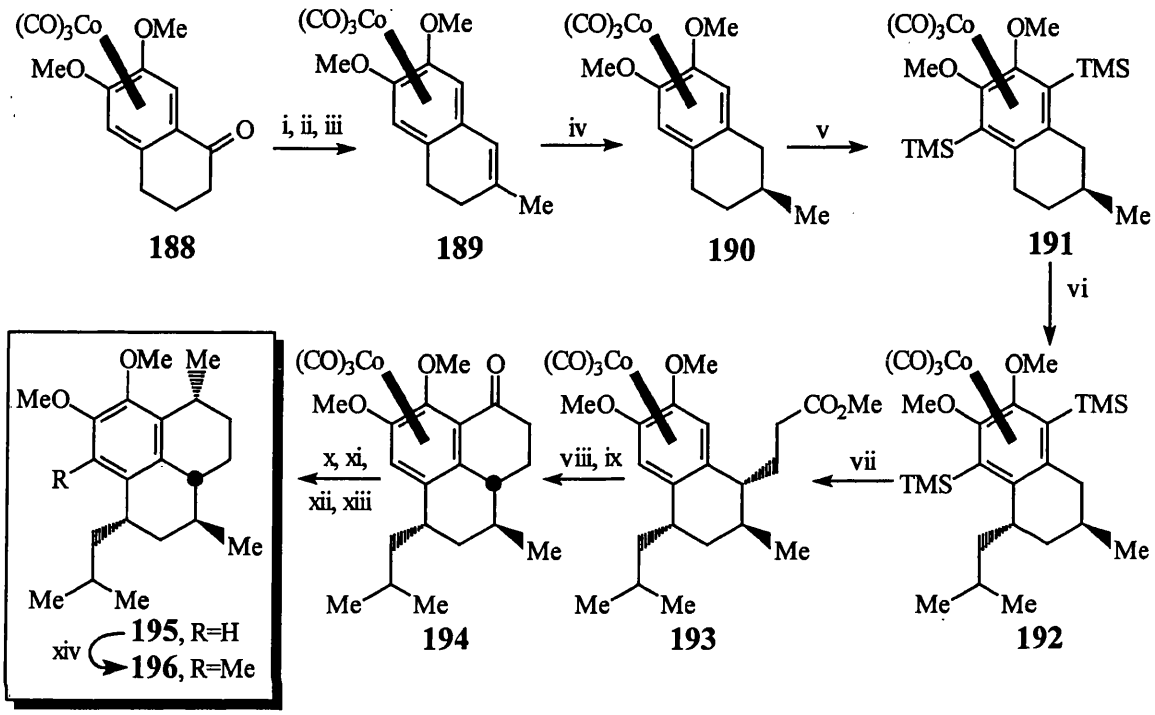
In summary, Kocienski *et al.* have synthesised the Pseudopterosin G aglycone in a stereocontrolled manner (12 steps, 4.5% overall yield).

*1.3.10 The Schmalz Asymmetric Syntheses of the 14,15-Dihydro-Pseudopterosin G Aglycone Dimethyl Ether, the 18-nor-*seco*-Pseudopterosin Aglycone Dimethyl Ether, the Pseudopterosin A-F Aglycone, the* seco*-Pseudopterosin Aglycone, and the Related Natural Product Helioporin D*

Since 1994 Schmalz *et al.* have exploited the chemistry of the homochiral complexes of the type **188**[64] (Scheme 27) in their synthetic work on the Pseudopterosins.

Their first report[65] was of an asymmetric synthesis of the 14,15-dihydro-Pseudopterosin G aglycone dimethyl ether **196** (Scheme 27).

Scheme 27



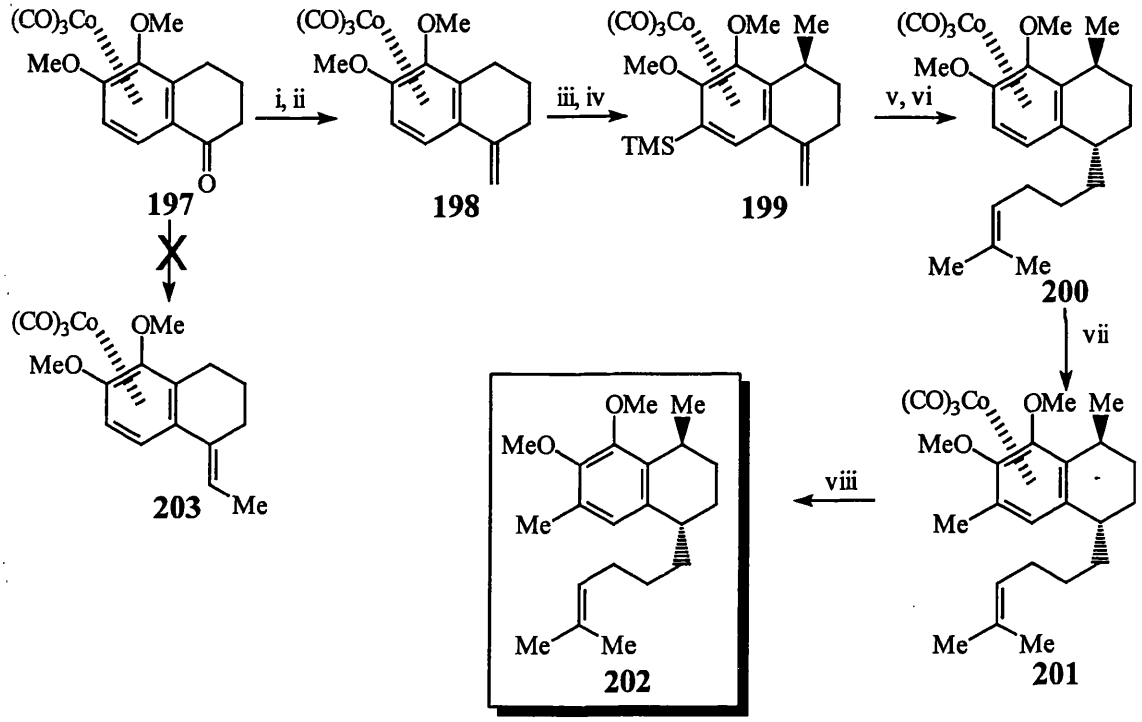
(i) LiHMDS, THF, -78 °C, 15 mins, then MeI, HMPA, rt, 2.5 hrs; (ii) $NaBH_4$, MeOH, DCM, rt, 1 hr; (iii) 3% TsOH on SiO_2, PhH, rt, 4 hrs, 83% for three steps; (iv) H_2, Rh/Al_2O_3, ethyl acetate:AcOH 50:1, rt, 30 hrs; (v) Lithium-2,2',6,6'-tetramethylpiperidide, TMSCl, THF, -40 °C to rt, 1 hr, 80% for two steps; (vi) *n*-BuLi, THF:HMPA 25:1, -50 °C to 0 °C, 3 hrs, then ICH_2CHMe_2, -30 °C to rt, 2 hrs, 84%; (vii) *n*-BuLi, THF:HMPA 20:1, -55 °C to 0 °C, 2 hrs, then $CH_2=C(TMS)CO_2Me$, -75 °C to 0 °C, 30 mins, then 2N (aq) HCl, 0 °C, 5 mins, then TBAF, THF, rt, 15 hrs, 67%; (viii) NaOH, MeOH, H_2O, rt, 20 hrs; (ix) PPA, rt, 3 hrs, then 70 °C, 3 hrs, 60% for two steps; (x) $NaBH_4$, MeOH, DCM, rt, 3 hrs; (xi) Ac_2O, pyridine, DMAP, rt, 18 hrs; (xii) Me_3Al, DCM, -78 °C to 0 °C, 3 hrs, 48% for three steps; (xiii) hν, air, Et_2O, rt, 95%; (xiv) *n*-BuLi, TMEDA, hexane, 0 °C to 40 °C, 2 hrs, then MeI, 0 °C to rt, 17 hrs.

Conversion of **188** to **189** was achieved in good yield under standard conditions. Rh-catalysed hydrogenation of **189** (from the face opposite to the metal) gave **190** diastereoselectively, and the resulting methyl compound was bis-silylated. Treatment of **191** with *n*-BuLi in THF followed by isobutyl iodide furnished **192** regio- and stereoselectively. A lithiation/Michael addition strategy using methyl-α-TMSacrylate[66] afforded **193**, after treatment with TBAF, as a single diastereomer. Hydrolysis of the ester unit and Friedel-Crafts type cyclisation gave the tricyclic compound **194**.

Installation of the final stereogenic centre of the molecule was achieved under Uemura conditions[67] and oxidative decomplexation led to **195** (12 steps, 10% overall yield), which was methylated under standard conditions, *albeit* with extensive *O*-demethylation, to afford the 14,15-dihydro-Pseudopterosin G aglycone dimethyl ether **196.**

Synthesis of the 18-nor-*seco*-Pseudopterosin aglycone dimethyl ether[68] **202** starts with Peterson olefination of **197** to give the *exo*-alkene **198** (Scheme 28).

Scheme 28



(i) $TMSCH_2CeCl_2$, THF, -75 °C to rt, 0.5 hrs, 96%; (ii) KH, THF, rt, 10 mins, 93%; (iii) *n*-BuLi, THF, -78 °C, 0.5 hrs, then TMSCl, 94%; (iv) *n*-BuLi, THF:HMPA 70:1, -50 °C to 0 °C, 0.5 hrs, then MeI, -30 °C to 0 °C, 0.5 hrs, 96%; (v) 4-methyl-3-pentenyllithium, THF, -60 °C to 0 °C, then 0.5N (aq) HCl, 0 °C to rt, 94%; (vi) TBAF, THF, H_2O, rt, 15 mins, 75%; (vii) *n*-BuLi, THF, -70 °C to -40 °C, 2 hrs, then MeI, -40 °C to 0 °C, 15 mins, 94%; (viii) hν, air, Et_2O, 98%.

Reaction of **198** with *n*-BuLi in THF followed by TMSCl with subsequent treatment of *n*-BuLi followed by MeI yielded **199** as a single diastereomer. Michael addition of homoprenyllithium to **199** led, after TBAF treatment, to a 75% isolated yield of **200** with a 7% isolated yield of the *cis*-diastereomer (stereoselectivity of addition 10:1).

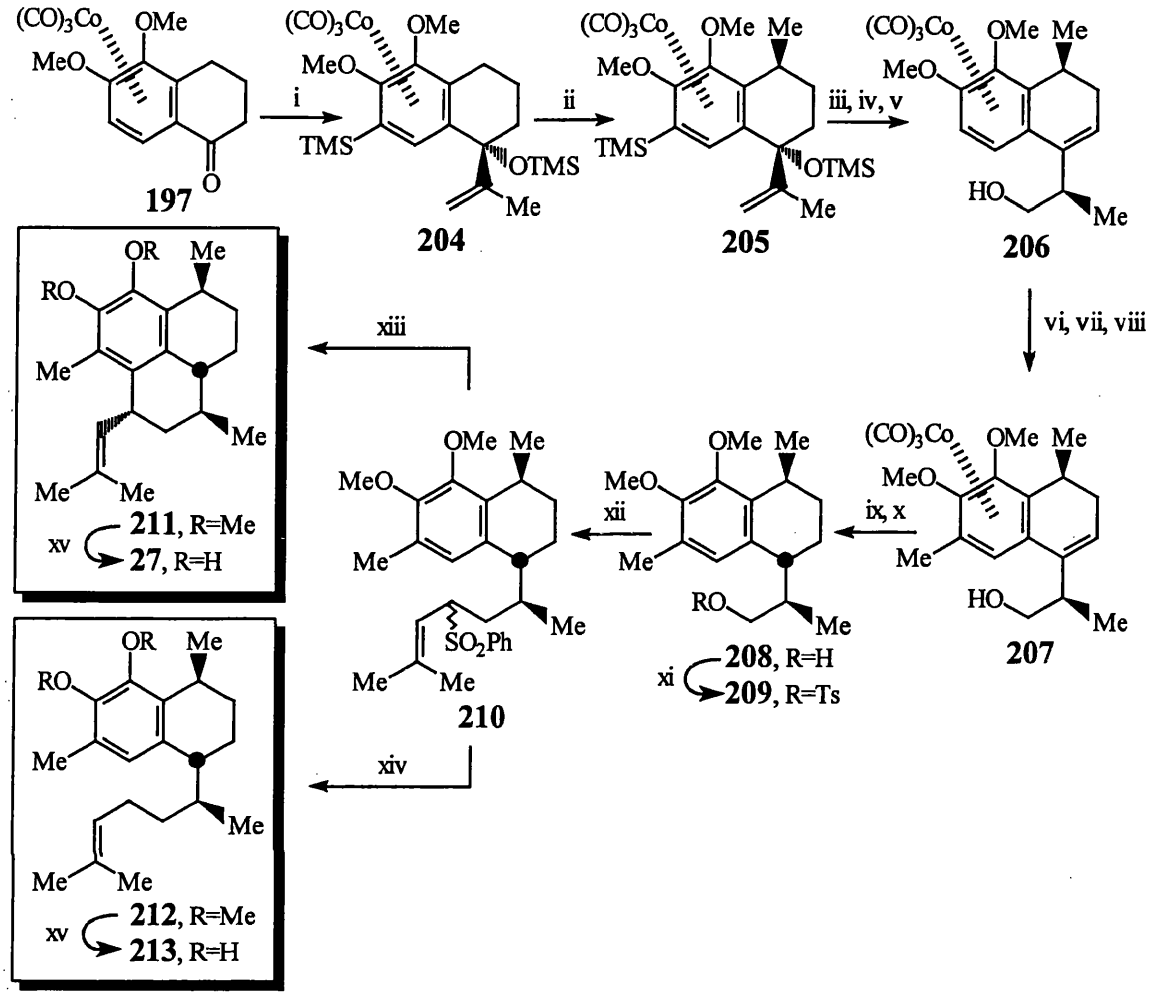
Aromatic methylation of **200** was performed under standard conditions to provide **201**, which was submitted to photochemical decomplexation to afford **202** (8 steps, 55% overall yield). De-*O*-methylation of **202** was achieved using BCl_3 in DCM, though the product proved to be air-sensitive. Unfortunately, the synthesis of the *seco*-Pseudopterosin aglycone using this route was inappropriate as direct ethylidenation of **197** to provide the required starting material **203** was difficult.

The Schmalz *et al.* synthesis of the aglycones of the Pseudopterosins A-F and the *seco*-Pseudopterosins using **197** as the chiral building block was finally realised in 1997[69] (Scheme 29). Isoprenyllithium attack onto **197** with TMSCl quench led to the bis-silylated product **204** stereoselectively. Deprotonation/methylation of **204** afforded **205** diastereoselectively in quantitative yield. Diastereoselective hydroboration of the isoprenyl side-chain preceded desilylation with TBAF in THF and elimination of the resulting benzylic OH to give **206** a single compound. The aromatic methyl was introduced under standard conditions, *albeit* requiring temporary silyl protection of the pendant hydroxyl, to afford **207** in excellent yield. Treatment of **207** with SmI_2 in THF followed by oxidative decomplexation led to **208** almost quantitatively, which was tosylated under standard conditions to afford **209**. Tosyl displacement with $Me_2C{=}CHCH(Li)SO_2Ph$ gave **210**, a late common intermediate for both the Pseudopterosin A-F and the *seco*-Pseudopterosin aglycone, as a mixture of diastereomers.

Cyclisation of **210** with $EtAlCl_2$ in DCM gave the tricycle **211**, which was de-*O*-methylated with LiSEt in THF to afford the Pseudopterosin A-F aglycone **27**.

Reductive desulfonylation of **210** with $LiEt_3BH$ followed by de-*O*-methylation of **212** also with LiSEt in THF produced the *seco*-Pseudopterosin aglycone **213**.

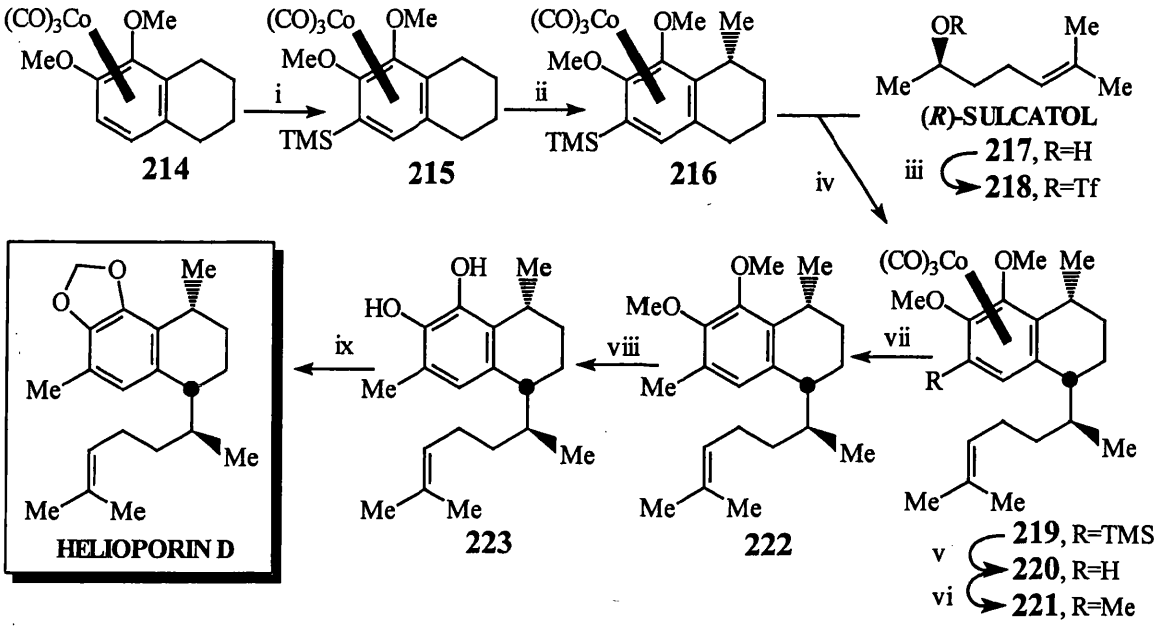
Scheme 29



(i) isopropenyllithium, THF, -70 °C to -40 °C, 1 hr, then rt, 1 hr, then TMSCl, -30 °C, 0.5 hrs, 87%; (ii) *n*-BuLi, THF, HMPA, -35 °C to 0 °C, 2 hrs, then MeI, -20 °C, 0.5 hrs, 99%; (iii) $BH_3.Me_2S$, THF, 30 °C, 15 hrs, then NaOH, H_2O_2; (iv) TBAF, THF, 0 °C, 1 hr; (v) *p*-TsOH, SiO_2, PhH, rt, 2 hrs, 71% for three steps; (vi) TBSCl, imidazole, DMF, rt, 1.5 hrs; (vii) *n*-BuLi, THF, -75 °C to -40 °C, 2 hrs, then MeI, -65 °C, 10 mins, then rt, 1 hrs; (viii) TBAF, THF, rt, 1 hr, 95% for three steps; (ix) SmI_2, THF:HMPA 15:1, H_2O, 0 °C, 2.5 hrs, then rt, 0.5 hrs, 98%; (x) hν, air, Et_2O; (xi) *p*-TsCl, Et_3N, DMAP, DCM, 35 °C, 6 hrs, 92% for two steps; (xii) $Me_2C{=}CHCH(Li)SO_2Ph$, THF, -78 °C to -45 °C, 1.5 hrs, then 0 °C, 0.5 hrs, 90%; (xiii) $EtAlCl_2$, DCM, -78 °C to -30 °C, then rt, 0.5 hrs, 95%; (xiv) $LiEt_3BH$, $PdCl_2(dppp)$, THF, 0 °C, 1.5 hrs, then rt, 0.5 hrs, 98%; (xv) LiSEt, DMF, 160 °C, 2 hrs, 95%.

To further demonstrate the synthetic application of piano-stool complexes as starting materials in asymmetric total synthesis, Schmalz *et al.* have also prepared[70] Helioporin D (Fig. 2), a cytotoxic natural product structurally related to the *seco*-Pseudopterosin aglycone (Scheme 30). Protection of the acidic aryl position of **214** allows for regio- and stereoselective deprotonation/methylation of **215** to produce **216** in excellent yield.

Scheme 30



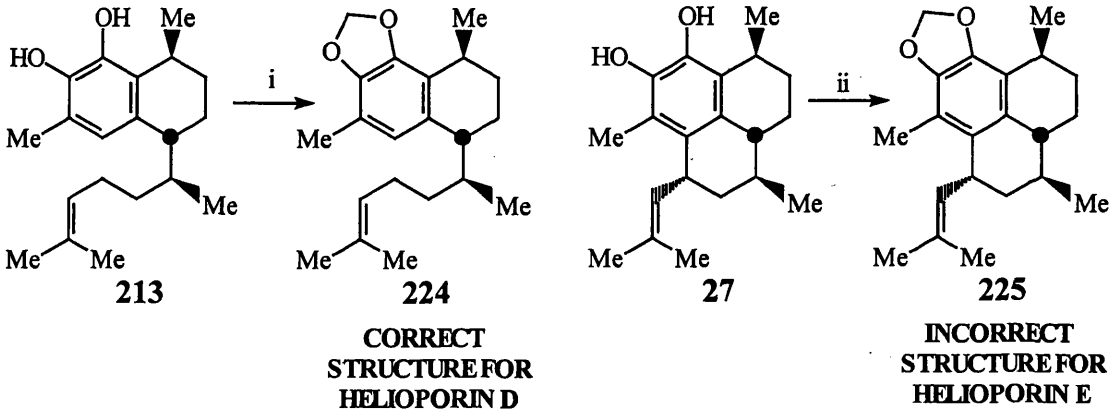
(i) *n*-BuLi, TMSCl, THF, 91%; (ii) *n*-BuLi, MeI, THF, 93%; (iii) *n*-BuLi, hexane, 0 °C, then add to Tf_2O, DCM, -20 °C; (iv) *s*-BuLi, THF, -70 °C to -20 °C, 75 mins, then add crude **218** in hexane, DCM, -65 °C to rt, 1.5 hrs, 85%; (v) TBAF, THF, 0 °C, 100%; (vi) *n*-BuLi, THF, -70 °C to -20 °C, 70 mins, then MeI, -40 °C to rt, 1.5 hrs, 95%; (vii) hν, air, Et_2O, 100%; (viii) LiESt, DMF, reflux, 2 hrs, 95%; (ix) CsF, DCM, DMF, reflux, 3 hrs, 88%.

Treatment of **216** with *s*-BuLi in THF followed by addition of the triflate **218**[71], prepared from (*R*)-sulcatol **217**, results in the diastereoselective (92:8) formation of **219**, which was desilylated with TBAF in THF to form **220**. *Ortho*-lithiation/methylation gave **221** and oxidative decomplexation afforded **222**, which was de-*O*-methylated with LiESt in THF to give **223** in almost quantitative yield. Formation of the methylenedioxy bridge was achieved with CsF in DCM to yield Helioporin D as described by Higa *et al.* (8 steps, 45% overall yield).

However, high field ^1H and ^{13}C nmr revealed that the synthetic and natural materials were different[72]. Reasoning that, as the relative stereochemistry of the Pseudopterosin agylcones as a whole vary only at C-7, Schmalz *et al.* installed the methylenedioxy bridge on their previously synthesised *seco*-Pseudopterosin aglycone material (Scheme 31). The material thus derived **224** was shown to be identical to natural Helioporin D. Confusingly, when the Pseudopterosin A-F aglycone was

converted to the methylenedioxy compound **225** (Scheme 31), the possibility of a C-7 epimeric structure for Helioporin E was ruled out. The full stereostructural assignment of the Helioporins has yet to be determined (those in Fig. 2 are after Higa *et al.*)

Scheme 31



213 **224** **27** **225**

CORRECT STRUCTURE FOR HELIOPORIN D

INCORRECT STRUCTURE FOR HELIOPORIN E

(i) CsF, DCM, DMF, reflux, 91%; (ii) CsF, DCM, DMF, reflux, 83%.

In summary, Schmalz *et al.* have developed the use of chiral arene-$Cr(CO)_3$ complexes for the asymmetric synthesis of the Pseudopterosin A-F aglycone (15 steps, 43% overall yield) and the seco-Pseudopterosin aglycone (15 steps, 44% overall yield) as well as various analogues. Furthermore, the stereoselective predictability and reliability of this chemistry has allowed for the asymmetric synthesis of the correct structure for Helioporin D.

1.4 Concluding Remarks

There have been many elegant, direct, and efficient syntheses of the Pseudopterosins many of which embrace novel synthetic methodology in their realisation.

Pharmacologists have proposed that the nature of the relative and absolute stereochemistry of the Pseudopterosin aglycone is of vital importance to the activity[73]. Ideally, pharmacologists would like to draw structure-activity relationships between the 16 possible diastereomers of Pseudopterosin E (the most biologically active

Pseudopterosin). As nature cannot provide these compounds, synthesis must. However, none of the above syntheses are flexible enough to allow for the predictable synthesis of aglycone diastereomers.

As a result, the primary aim of our synthetic programme was to develop an efficient, practical route to Pseudopterosin E, which would ultimately be applicable to the synthesis of the 16 possible diastereomers of the Pseudopterosin A-F aglycone. With these materials in hand a full structure-activity relationship for the Pseudopterosins could be determined.

CHAPTER 2
The Pseudopterosins: Results and Discussion

2.0 Retrosynthesis

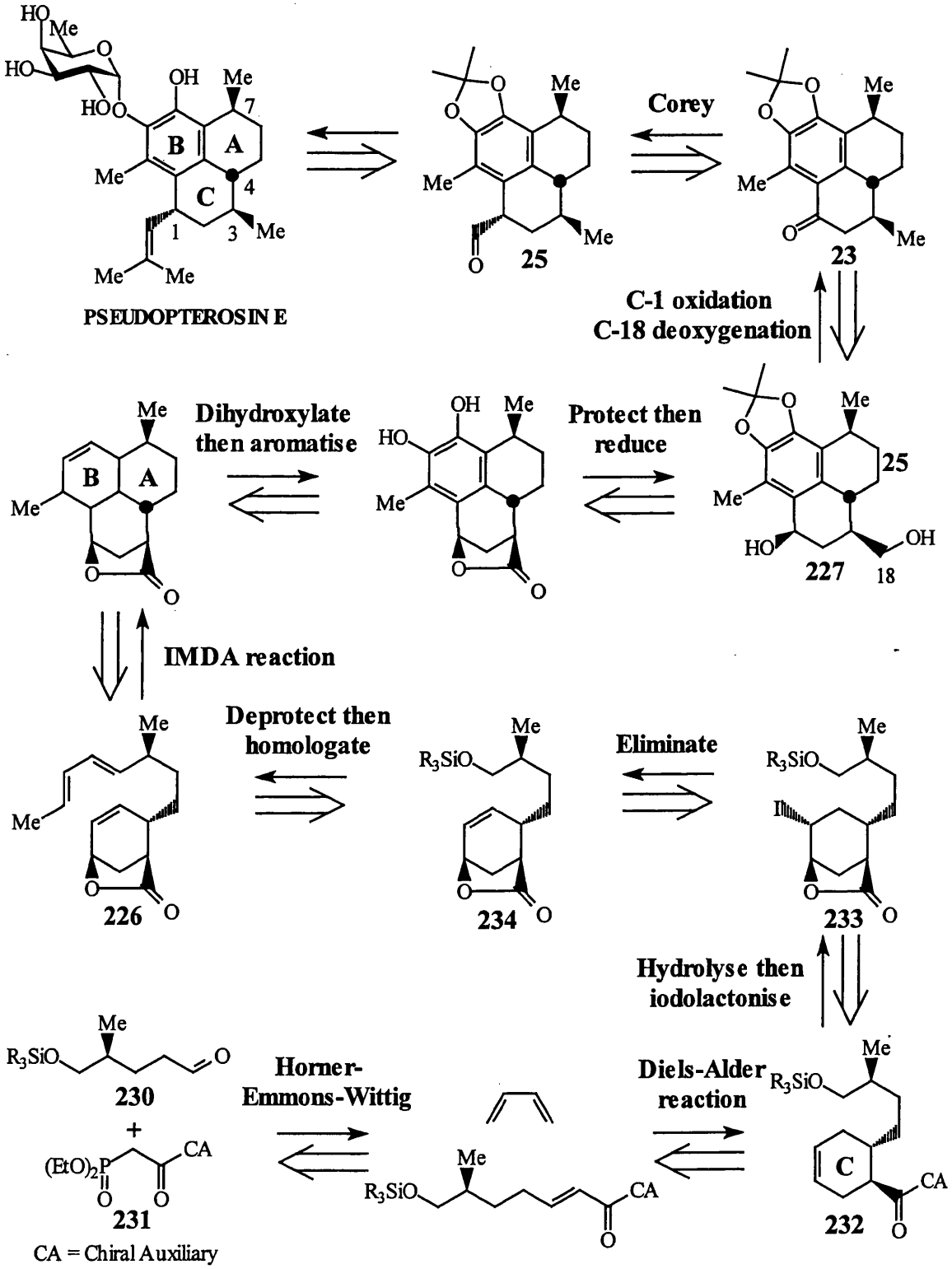
Our retrosynthesis envisages an intramolecular Diels-Alder (IMDA)[75] reaction on a substrate of the type **226** (Scheme 32), in which the A and B rings of the tricarbocyclic core of the Pseudopterosins would be created. Dihydroxylation of the resulting double bond and aromatisation of the B ring would lead to the hexasubstituted aromatic ring of the natural product. It should be noted that all of the stereochemistry derived from the IMDA reaction is destroyed in the steps that introduce the aromatic nucleus. Protection of the catechol unit and reductive ring opening of the lactone would afford the diol **227**. Oxidation of the secondary alcohol and deoxygenation at the primary alcohol would give the ketone **23**, a key intermediate in the Corey[13] syntheses of Pseudopterosins A and E. As adumbrated, the remaining steps in our synthesis would be after Corey *via* the aldehyde **25**.

The triene **226** could be synthesised starting with the Horner-Emmons-Wittig condensation of the known aldehyde **230**[76] with a phosphonate of the type **231**. The resulting enone could be subjected to a low temperature Lewis acid mediated Diels-Alder reaction with 1,3-butadiene[77] to form **232**, where the C ring and the stereogenic centres at C-3 and C-4 of the natural product have been created. Hydrolysis of the chiral auxiliary followed by iodolactonisation would cede **233**, where elimination of HI would introduce the dienophilic double bond of the triene **226**. Deprotection of the silyl ether **234**, followed by oxidation of the resulting alcohol to the aldehyde and Wittig homologation, would install the remaining double bonds to afford the triene **226**.

The primary aim of this synthetic programme was to develop an efficient, stereocontrolled synthesis of Pseudopterosin E, which would ultimately be applicable to

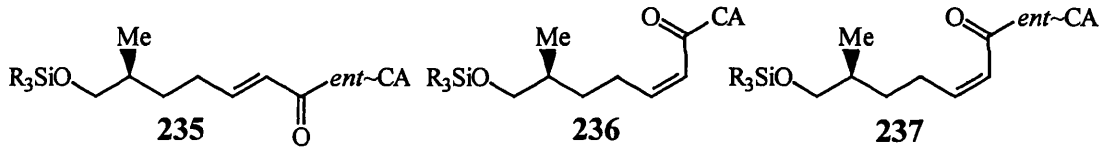
the synthesis of the 16 possible diastereomers of the Pseudopterosin A-F aglycone. For this to be achieved our synthesis must flexible enough to accept changes in stereochemistry of intermediates without affecting the overall synthetic route.

Scheme 32



Our retrosynthesis could allow this goal to be attained for the following reasons;

- The methyl C-7 stereogenic centre is derived from the starting aldehyde **230**. Both enantiomers of **230** can be synthesised from commercially available material *via* the same synthetic route[76] (*vide infra*).
- The methyl C-3 and bridgehead C-4 stereogenic centres are set in a chiral auxiliary directed Diels-Alder reaction to afford **232**. To make the diastereomer of **232**, with the same (*trans*) relative configuration but opposite absolute configuration, would require **235** as the starting material. To make the diastereomers with *cis* relative configuration would require **236** and **237** as starting materials for the Diels-Alder reaction with 1,3-butadiene. Judicious use of both chiral auxiliaries and *cis/trans* enones should allow for the synthesis of all the possible diastereomers of **232** using the same reaction conditions.



235 **236** **237**

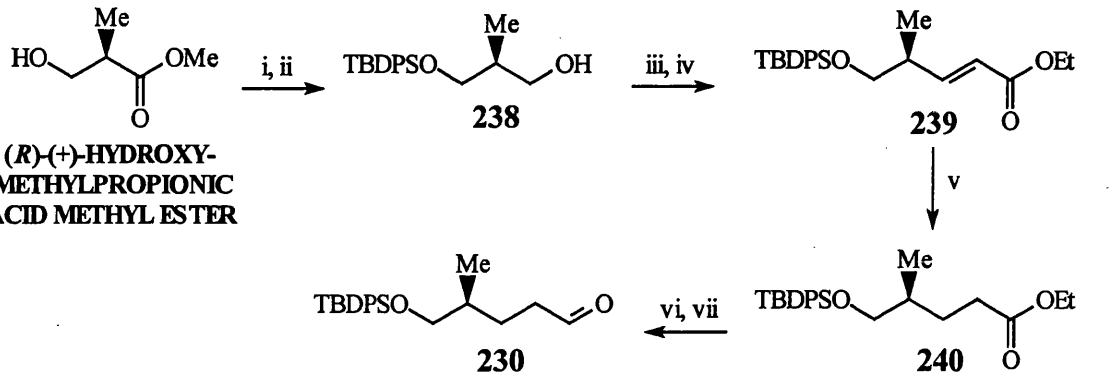
- The C-1 stereogenic centre is to be set using the chemistry of Corey to provide the aldehyde **25** (Scheme 6). Though there is no direct control over the creation of this stereogenic centre (under the Corey route the stereochemistry of this centre is set by the influence of the molecule as a whole), the resulting aldehyde could be used to obtain both epimers. Exposure of **25** to mild base should selectively epimerise the C-1 centre (the α-aldehydic proton being quite acidic) without affecting the other benzylic positions. Separation of the resulting diastereomers would provide the required materials.

In this manner, our retrosynthesis can accommodate the synthesis of the 16 diastereomers of Pseudopterosin E required by pharmacologists for structure-activity investigations.

2.1 Synthesis of the Starting Materials

Synthesis of the aldehyde **230**[76] starts with protection of commercially available (Sigma) (*R*)-(+)-3-hydroxy-2-methylpropionic acid methyl ester and DIBAL reduction of the crude residue to afford the alcohol **238** in good yield (Scheme 33).

Scheme 33

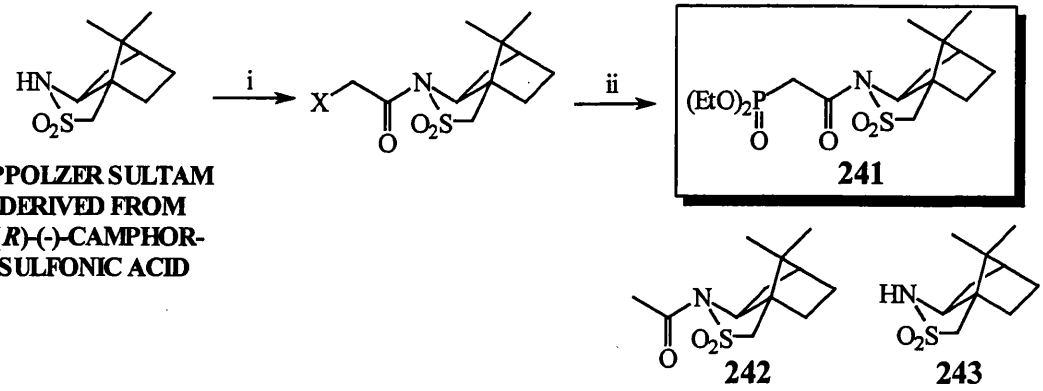


(i) TBDPSCl, Et_3N, DMAP, DCM, rt, 18 hrs; (ii) DIBAL, DCM, -78 °C, 0.5 hrs, 98% for two steps; (iii) $(COCl)_2$, DMSO, DCM, -78 °C, 1.5 hrs, then Et_3N, rt, 20 mins, 92%; (iv) Ph_3PCHCO_2Et, DCM, rt, 18 hrs, 97%; (v) H_2, Pd-C, EtOAc, rt, 0.5 hrs, 99%; (vi) DIBAL, DCM, -78 °C, 0.5 hrs, 99%; (vii) $(COCl)_2$, DMSO, DCM, -78 °C, 1.5 hrs, then Et_3N, rt, 30 mins, 95%.

Swern oxidation with $(COCl)_2$ of **238** followed by Wittig reaction with Ph_3PCHCO_2Et in DCM gave the α,β-unsaturated ester **239**, which was hydrogenated under standard conditions to cede **240** in excellent yield. DIBAL reduction of **240** in DCM followed by Swern oxidation furnished **230** in 7 steps and 81% overall yield. The synthesis of *ent*-**230** using this reaction sequence can be realised starting with (*S*)-(-)-hydroxymethylpropionic acid methyl ester (Sigma).

For the phosphonate, the chiral auxiliary of choice was the Oppolzer sultam, as used in the Oppolzer *et al.* synthesis of Pulo'upone[78]. However, although *N*-acylation with both bromo- and chloroacetyl chloride was facile (Scheme 34), subsequent conversion to the phosphonoacetate **241** under Arbusov conditions was low yielding (6%). Instead, the major reaction products were **242** (43%) and **243** (33%), appearing to come from direct attack of triethylphosphite on the halogen.

Scheme 34

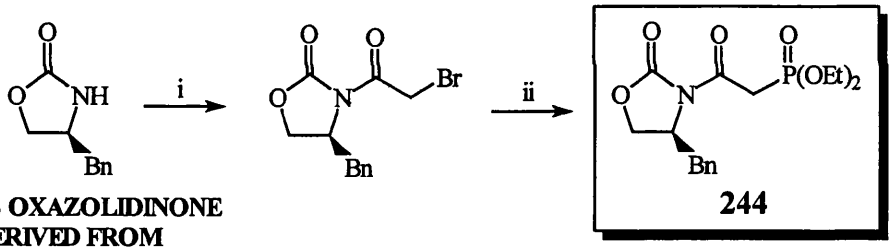


OPPOLZER SULTAM DERIVED FROM (*R*)-(-)-CAMPHOR-SULFONIC ACID

(i) X=Br: NaH, bromoacetyl chloride, 0 °C, 1.5 hrs, 91%; X=Cl: *n*-BuLi, chloroacetyl chloride, -78 °C to rt, 1 hr, 80%; (ii) X=Br: $P(OEt)_3$, 150 °C, 21 hrs, **241** 6%, **242** 43%, **243** 33%.

Fortunately, synthesis of the phosphonate derived from the Evans oxazolidinone **244** (Scheme 35), as used by Broka and Ehrler in the synthesis of Bengamides B and E[79], was achieved readily on a variety of scales (max. 150g).

Scheme 35



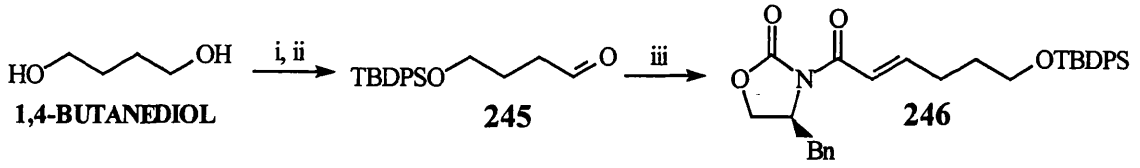
EVANS OXAZOLIDINONE DERIVED FROM L-PHENYALANINE

(i) *n*-BuLi, bromoacetyl chloride, THF, -78 °C, 1 hr; (ii) $P(OEt)_3$, PhMe, 50 °C, 3 days, 80% for two steps.

2.2 Triene Synthesis

Before embarking on the synthesis, it was necessary to determine if compounds of the type **247** were stable under Lewis acid conditions, particularly as (*R*)-(+)-hydroxymethylpropionic acid methyl ester was somewhat expensive (>£1 per g). To this end, condensation of **245**[148], available readily from 1,4-butanediol, with the phosphonate **244** gave the enone **246**, suitable for test reactions (Scheme 36). It was found that **246** was stable to the action of Me_2AlCl in DCM/hexanes at 0 °C for several hours but was destroyed upon exposure to $EtAlCl_2$ under the same conditions.

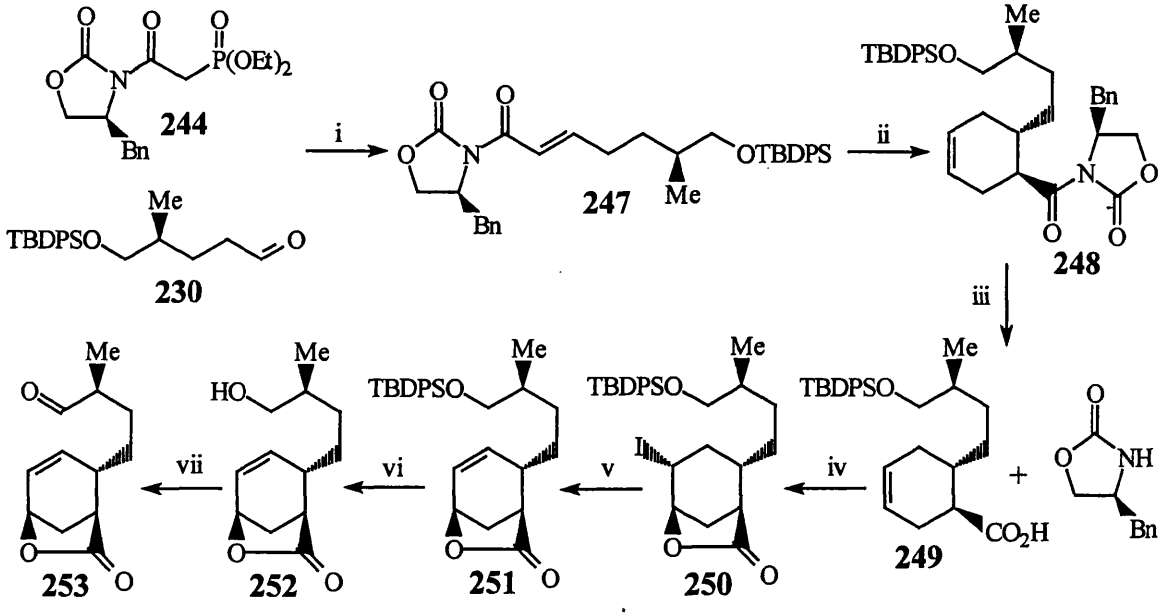
Scheme 36



(i) NaH, TBDPSCl, THF, rt, 1.5 hrs, 99%; (ii) $(COCl)_2$, DMSO, DCM, -78 °C, 1.5 hrs, then Et_3N, rt, 30 mins, 99%; (iii) **244**, LiCl, Hünigs base, MeCN, rt, 5 mins, then **246**, MeCN, rt, 2 days, 93%.

With this knowledge in hand, the attempted synthesis of triene **226** begins with condensation of **244** with **230** under Roush-Masamune conditions[80] leading to the formation of **247** (Scheme 37) as a single diastereomer of $[\alpha]_D^{21}$ +31.5 (c=0.43 in DCM) with suitable combustion analysis (found C 73.43, H 7.33, N 2.54; $C_{34}H_{41}NO_4Si$ requires C 73.48, H 7.44, N 2.52) and HRMS (found *m/z* 556.2826; $C_{34}H_{42}NO_4Si$ $[MH]^+$ requires *m/z* 556.2883).

Scheme 37



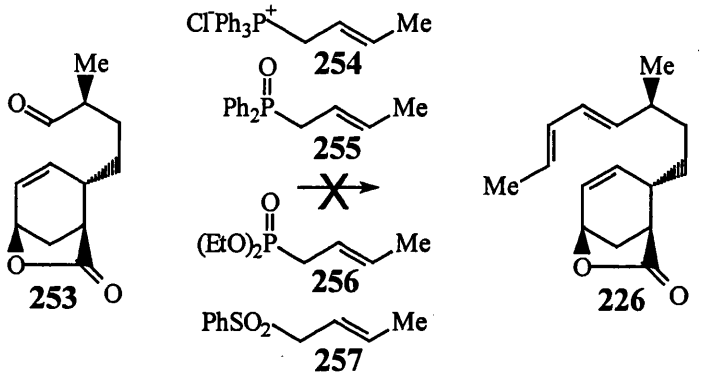
(i) **244**, LiCl, Hünigs base, MeCN, rt, 40 mins, then **230**, MeCN, rt, 18 hrs, 82%; (ii) 1,3-Butadiene, Me_2AlCl, DCM, hexanes, -40 °C, 20 mins, then -10 °C, 3 days, 72%; (iii) LiOH, H_2O_2, THF:H_2O 1:1, rt, 18 hrs, 88%; (iv) $NaHCO_3$, KI, I_2, DCM:H_2O ~16:1, 0 °C, 3 hrs, 85%; (v) DBU, DCM, reflux, 24 hrs, 95%; (vi) TBAF, THF, rt, 4 hrs, 96%; (vii) $(COCl)_2$, DMSO, DCM, -78 °C, 1 hr, then Et_3N, rt, 20 mins, 95%.

Evidence for the *trans* nature of the double bond in **247** could not be obtained from coupling constants in the ^1H nmr as the double bond peaks were superimposed by the

aromatic peaks of the benzyl unit of the molecule. When **247** was reacted with 1,3-butadiene at low temperature under the influence of Me_2AlCl these conditions afforded **248** as a single diastereomer according to nmr analysis after 3 days at -10 °C. This is at the limit of the reaction conditions as 1,3-butadiene boils at -4 °C (on large scale a well-ventilated fume-hood is essential as, under balloon pressure, a significant proportion of 1,3-butadiene escapes from the reaction vessel). Lithium hydroperoxide hydrolysis in THF/H_2O of the amide bond in **248** gave the acid **249** as a ~7:1 (nmr) mixture of diastereomers at the acid centre. (It seems that, under the base conditions of the hydrolysis, some exchange of the α-acidic proton is occurring to give the diastereomeric mixture). Unfortunately, owing to hydrolysis of the carbamate unit in **248**, a small amount of the oxazolidinone is not recovered under the reaction conditions. However, 88% was deemed to be acceptable recovery and this material is fully recyclable. Bartlett iodolactonisation of **249** gave the iodolactone **250** in good (85%) yield and DBU, in DCM heated at reflux, mediated elimination of HI and ceded **251** as a single diastereomer (according to nmr analysis), the minor diastereomer having been 'purified-out'. Installation of the diene unit of triene **226** began with a TBAF in THF induced *O*-desilylation of **251** to yield the alcohol **252**, which under Swern oxidation conditions with $(COCl)_2$ gave the aldehyde **253**.

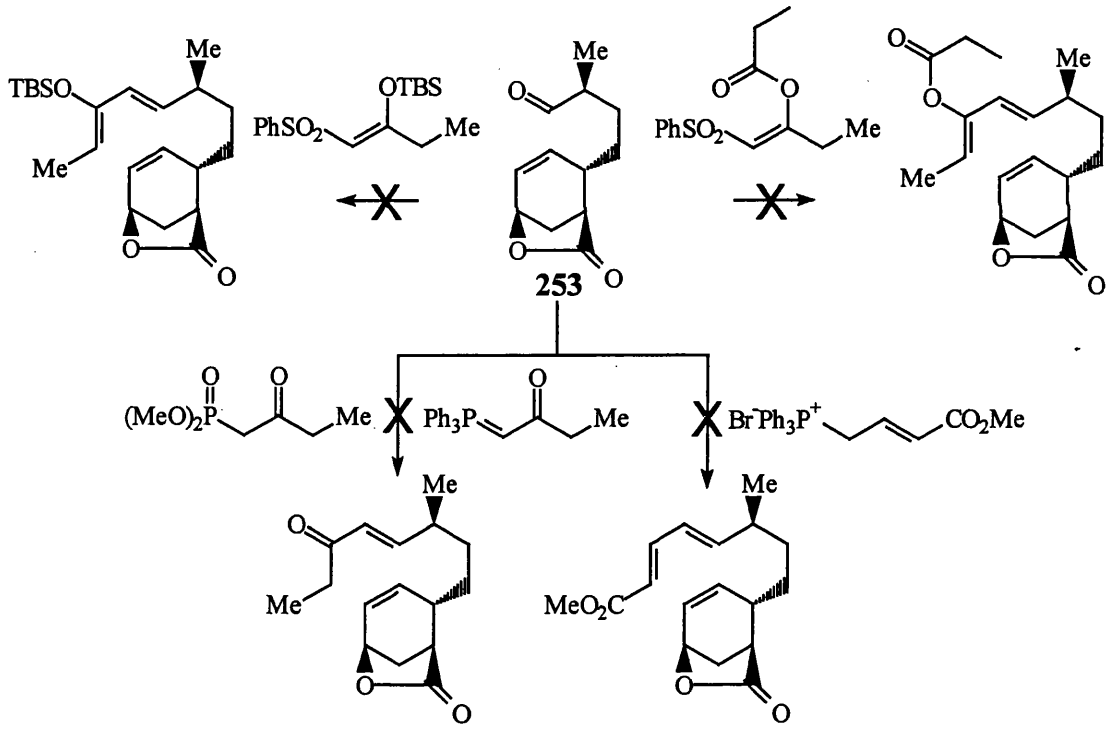
Unfortunately, the aldehyde **253** proved quite unstable and initial attempts to introduce the crotonyl unit of the triene **226** with the known phosphonium salt **254**[82] and phosphine oxide **255**[83] led to multiple products by tlc (Scheme 38). Under the milder Horner-Emmons-Wittig reaction conditions with the phosphonate **256**[84] complete consumption of the aldehyde **253** to several products (tlc) was observed. The same was true for attempted Julia olefination with the known sulfone **257**[85].

Scheme 38



Reaction of **253** with a variety of other Wittig[86,87,88] and Julia[89] reagents also failed to yield the desired products (*vide infra*) despite much experimentation (Scheme 39).

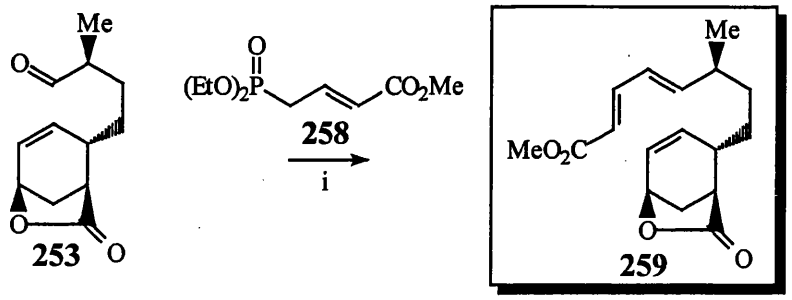
Scheme 39



Presumably, the aldehyde **253** is rather base sensitive and several base-induced decay pathways can be envisaged.

Fortunately, exposure of **253** to the known phosphonate **258**[90] under standard Roush-Masamune conditions[80] (Scheme 40) resulted in the clean formation of the triene **259** in modest (40%) yield.

Scheme 40

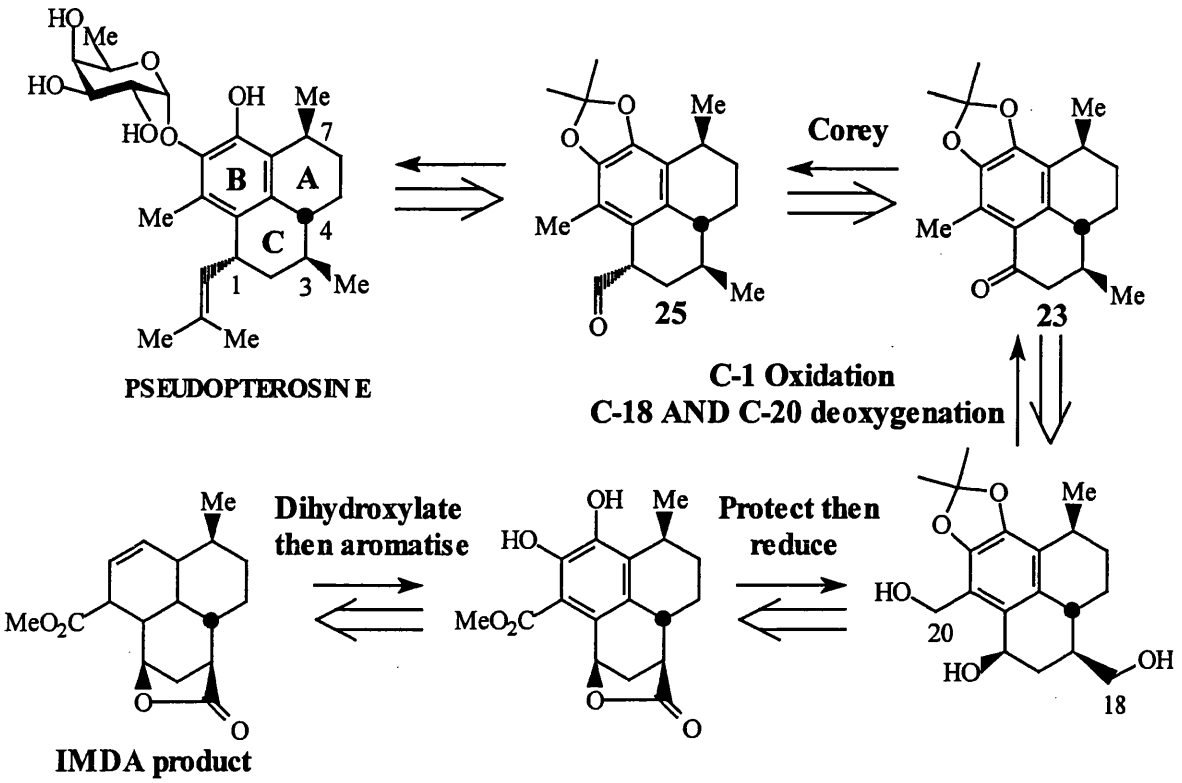


(i) **258**, LiCl, Hünigs base, MeCN, rt, 30 mins, then **253**, MeCN, rt, 48 hrs, 40%.

Though the yield for this reaction is low, the preceding steps to **259** are all high yielding and can be performed on large scale, which allows for synthesis of **259** on a multigram scale. Triene **259** was a single compound (nmr), of *E,E* configuration in the diene unit ($^3J_{HH}$ values of 10.5 and 15.5), with $[\alpha]_D^{19}$ +69.9 (c=0.29 in DCM) and the HRMS (FAB) found *m/z* 313.1406 ($C_{17}H_{22}O_4Na$ $[MNa]^+$ requires *m/z* 313.1416).

The inclusion of an ester group at C-20 (Pseudopterosin numbering) affects the synthetic plan only slightly (Scheme 41) and does not increase the number of steps. Specifically, the aromatic methyl unit of the natural product was to be unmasked by reduction then deoxygenation of the methyl ester group. These two steps were already present in the original retrosynthetic plan (cf Scheme 32).

Scheme 41

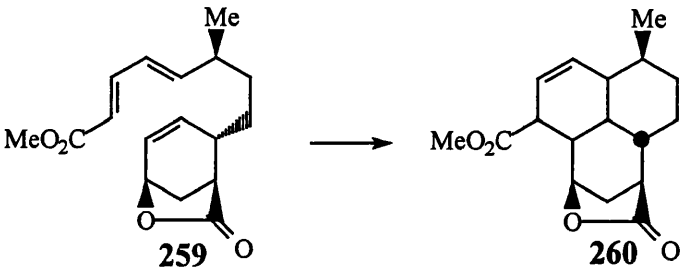


With gram quantities on **259** in hand, attempts at the IMDA reaction were initiated.

2.3 Attempted IMDA Reaction of 259

Table 1 outlines the thermal, Lewis acid, and radical-cation[91] conditions under which the IMDA reaction of **259** was attempted. To our delight, one of the first conditions tested (entry 2) resulted in an 8% (3mg) yield of a compound tentatively ascribed as the desired IMDA product **260**. Although the ^{1}H nmr (Appendix 2) seems to show that the IMDA product has been formed as a ~3:1 mixture of diastereomers at the ester position, the material was too unstable for further characterisation (decayed whilst the ^{13}C nmr was acquiring). Furthermore, this result could not be reproduced in order to obtain more of the putative IMDA product.

Table 1



THERMAL
1. PhMe, Sealed Tube, 120 °C, 60 hrs, no reaction.
2. PhMe, Sealed Tube, 190-200 °C, 60 hrs, 8%.
3. $(HOCH_2)_2$, Sealed Tube, 150 °C, 3 days, no reaction.
4. *o*-Xylene, Sealed Tube, 200 °C, 5 days, no reaction.
5. Xylenes, Sealed Tube, 250 °C, 4 days, no reaction.
LEWIS ACID
6. $SnCl_4$ (0.1 equivalents), DCM, -100 °C, 35 mins, then -78 °C, 1 hr, no reaction.
7. $SnCl_4$, (1.1 equivalents), DCM, -78 °C, 2 hrs, no reaction.
8. Me_2AlCl (5.0 equivalents), DCM, -78 °C, 1 hr, no reaction.
9. $EtAlCl_2$ (5.0 equivalents), DCM, rt, 6 hrs, no reaction.
RADICAL-CATION
10. $(p\text{-BrPh})_3NSbCl_6$, 2,6-di-*t*-butylpyridine, DCM, 0 °C, 30 mins, then rt, 3 hrs, no reaction

However, this was an extremely encouraging finding. The starting triene **259** is not an ideal precursor for the IMDA reaction. The presence of an electron-withdrawing group on the diene unit is not desirable; in most IMDA reactions the diene unit is electron-rich and the dienophile unit is electron-poor[92]. In addition, the newly created cyclohexane ring in the product contains four substituents in pseudoaxial positions, resulting in an highly sterically encumbered product. The supposed production of **260** in

spite of unfavourable electronic and steric factors was a great stimulus to further investigation of the IMDA reaction of **259**.

The use of ethylene glycol[93] (entry 3) or xylenes[94] (entries 4 and 5), both well-known IMDA sealed tube reaction solvents, failed to effect the desired transformation even at temperatures up to 250 °C.

Various Lewis acid conditions were equally unsuccessful (entries 6-9). At temperatures between -100 °C to room temperature several IMDA reaction attempts, using $SnCl_4$, Me_2AlCl, and $EtAlCl_2$, all returned the starting triene.

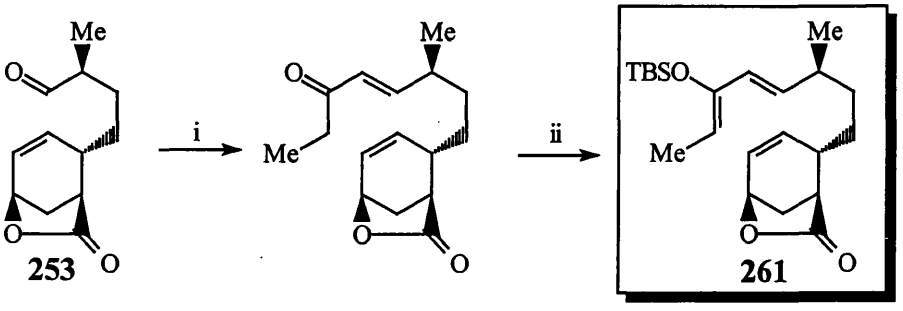
Despite the fact that the diene component of **259** is neither cyclic nor in the *s*-cis conformation and contains an electron withdrawing group, a cation-radical IMDA reaction was also attempted (entry 10), but with no success[91].

In the face of these disappointing findings, the major spur to continue on an IMDA route was the early (unconfirmed) successful IMDA reaction of **259**. To develop our synthetic strategy, it was necessary to determine if steric or electronic arguments were the major adverse factors for the inactivity of **259** in the IMDA reaction.

2.4 Synthetic Probe of the Steric vs Electronic Inactivity of 259

The triene **261**, which contains an electron-rich diene unit, was made in extremely low yield from the aldehyde **253** (Scheme 42).

Scheme 42

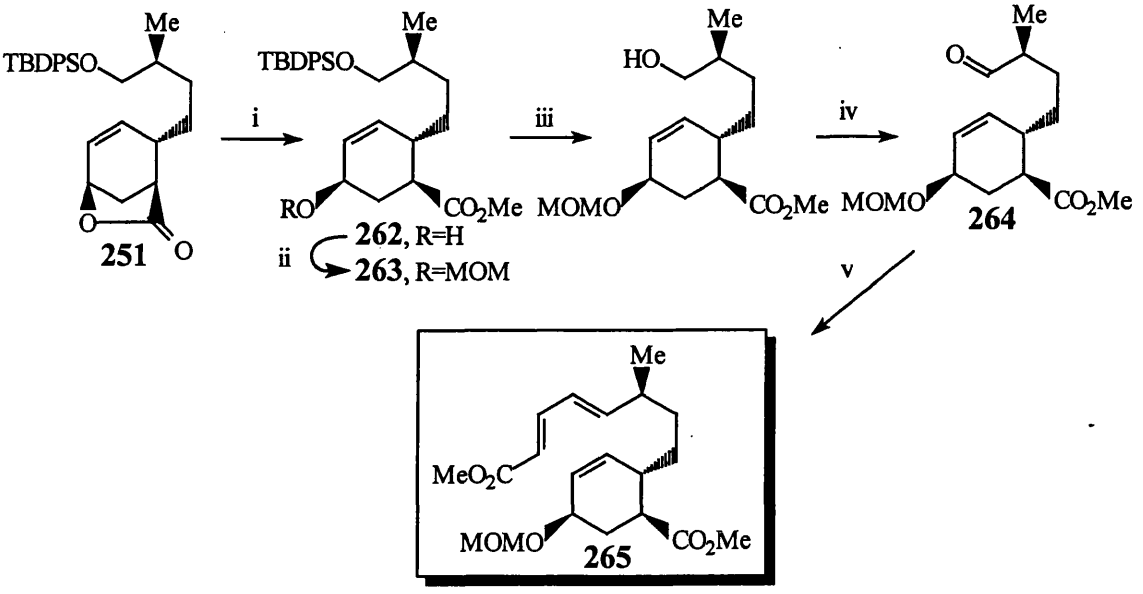


(i) $Ph_3PCHC(O)CH_2Me$, DCM, rt, 33 hrs, 26%; (ii) Et_3N, DCM, rt, 8 mins, then TBSOTf, DCM, rt, 25 mins, 33%.

Wittig homologation with the known phosphorane $Ph_3PCHC(O)CH_2Me$[95] in DCM followed by silyl enol ether formation under standard conditions led to the formation of **261** by ^1H nmr. The synthesis of **261** allows for a probe of electronic factors in the diene moiety between **261** and **259** whilst keeping the steric factors inherent in the lactone group constant.

Methanolysis of **251** at -15 °C led to the alcohol **262** with no detectable (nmr) epimerisation at C-3 (Pseudopterosin numbering) and **262** was protected as the methoxymethyl ether **263** (Scheme 43).

Scheme 43

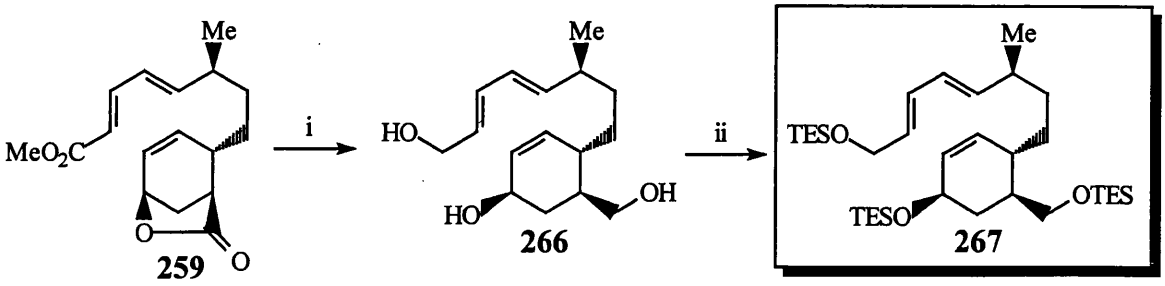


(i) NaOMe, MeOH, -15 °C, 16 mins; (ii) MOMCl, Hünigs base, DCM, rt, 4 hrs, 98% for two steps; (iii) TBAF, THF, rt, 18 hrs, 72%; (iv) $(COCl)_2$, DMSO, DCM, -78 °C, 1 hr, then Et_3N, rt, 40 mins, 94%; (v) **258**, LiCl, Hünigs base, MeCN, rt, 7 mins, then **264**, MeCN, rt, 72 hrs, 90%.

Installation of the diene component was realised as for **259**. Namely, silyl deprotection of **263** with TBAF in THF followed by Swern oxidation with $(COCl)_2$ of the resulting alcohol to the aldehyde **264**. Horner-Emmons-Wittig homologation gave **265** (^1H nmr and LRMS) in good overall yield. The triene **265** allows for a probe of steric factors between **265** and **259** whilst keeping the electronic factors of the diene unit constant.

Finally, DIBAL reduction of **259** followed by triple silyl protection of the crude triol **266** ceded the triene **267** in good yield (Scheme 44).

Scheme 44



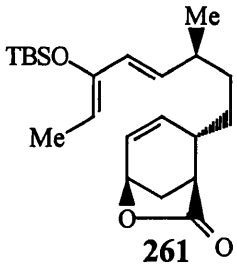
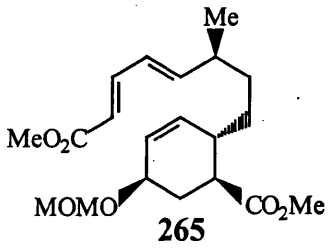
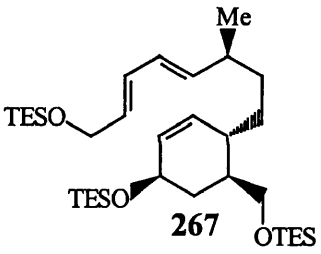
(i) DIBAL, DCM, -78 °C, 1 hrs; (ii) TESCl, imidazole, DCM, rt, 50 mins, 66% for two steps.

The triene **267** was made as a standard for this set of IMDA attempts as it is moderately sterically hindered (as a result of using the TES protecting group) and contains a diene unit which is neither electron-rich nor electron-poor.

Table 2 summarises the IMDA reaction conditions to which the trienes **261**, **265**, and **267** were submitted.

Unfortunately, these results seem to imply that adverse steric factors are of paramount importance. Even the electron-rich diene moiety in **261** is unable to effect the required IMDA reaction under either thermal or radical-cation conditions (Lewis acid conditions are not appropriate as these would cleave the TBS enol ether). Ring-opening of the lactone group also seems to have little effect on reactivity. For **265**, where no IMDA reaction was observed, the inference is that, whilst steric strain in the putative product has been relieved, the electron-poor diene is not a sufficient driving force for the IMDA reaction. Only **267** showed any sign of reactivity, *albeit* in a complex (decay) manner.

Table 2

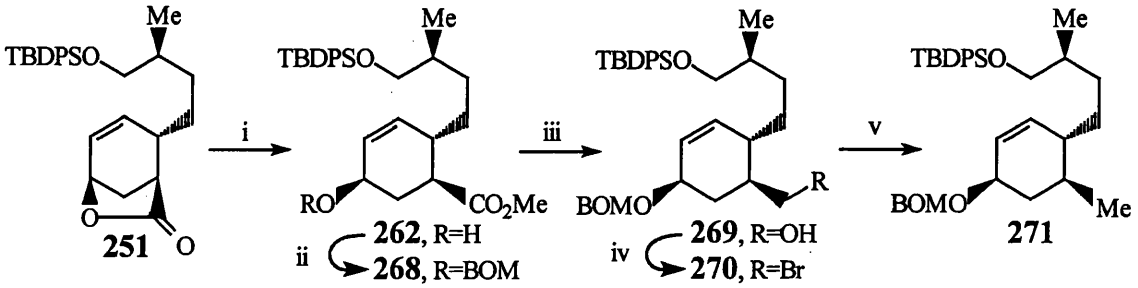
TRIENE	*THERMAL*	*LEWIS ACID*	*RADICAL-CATION*
 **261**	PhMe, Sealed Tube, 200 °C, 6 days, no reaction.	Not applicable	$(p\text{BrPh})_3\text{NSbCl}_6$ 2,6-di-*t*-butyl pyridine, DCM, 0 °C, 10 mins, then rt, 4 hrs, no reaction.
 **265**	PhMe, Sealed Tube, 150 °C, 4 days, no reaction.	Me_2AlCl, DCM, -78 °C to rt, 6 hrs, no reaction.	Not applicable.
 **267**	PhMe, Sealed Tube, 150 °C, 5 days, complex reaction (tlc).	Not applicable.	$(p\text{BrPh})_3\text{NSbCl}_6$ 2,6-di-*t*-butyl pyridine, DCM, 0 °C, 20 mins, then rt, 1.5 hrs, no reaction.

The major conclusion drawn from this work is that the IMDA reaction in this particular system is very susceptible to steric factors. To this end, the synthesis of a triene of the type **265** but with an electron-rich diene unit could be desirable. To do this represents a significant departure from our original retrosynthesis, which envisaged an IMDA reaction early in the synthetic plan with subsequent elaboration to the required ketone **23**. Conceptually, our new synthetic plan would contain an IMDA reaction late in the route on a triene as similar in structure as the desired ketone **23** as possible. In this way, we hope to minimise steric interactions in the IMDA reaction product.

2.5 Synthesis of a 'Late' Triene with an Electron-Rich Diene Unit

Methanolysis of **251** at 0 °C led to the alcohol **262,** which was protected as the benzyloxymethyl ether **268** (Scheme 45).

Scheme 45

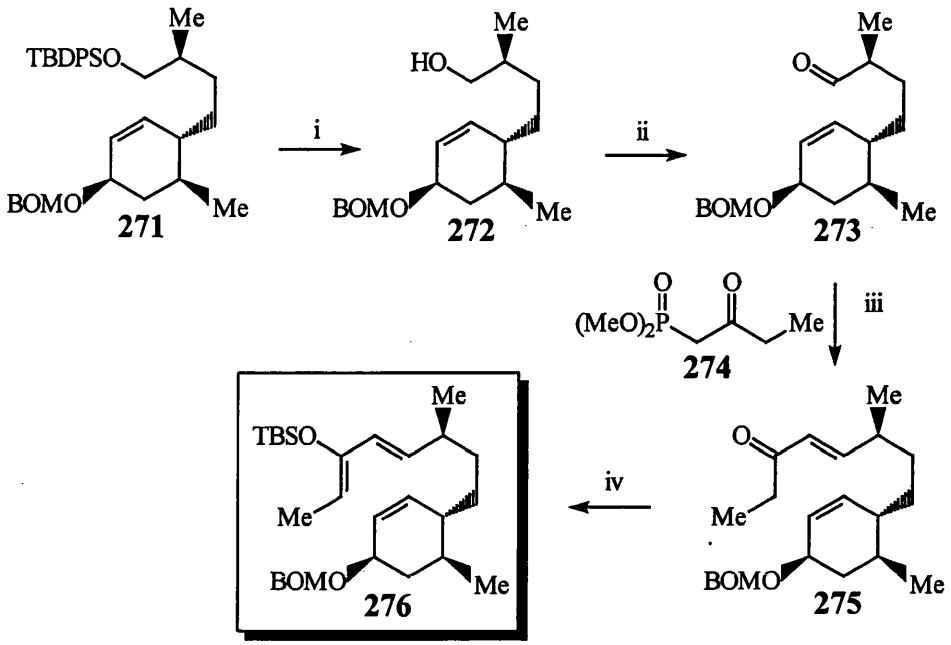


(i) NaOMe, MeOH, 0 °C, 26 mins; (ii) BOMCl, Hünigs base, DCM, rt, 2 days, 95% for two steps; (iii) DIBAL, DCM, 0 °C, 31 mins, 85%; (iv) CBr_4, Ph_3P, THF, rt, 3.5 hrs, 94%; (v) Bu_3SnH, AIBN, PhMe, reflux, 62.5 hrs, 95%.

DIBAL reduction of the methyl ester in DCM gave the alcohol **269** in good yield. Bromination of **269** was realised with CBr_4 and Ph_3P in THF and Bu_3SnH reduction of the bromide **270** revealed the C-3 methyl (Pseudopterosin numbering) of the natural product.

Desilylation of **271** with TBAF in THF led to the alcohol **272**, which was oxidised under Swern conditions with $(COCl)_2$ to afford the aldehyde **273** (Scheme 46). Horner-Emmons-Wittig reaction, again under Roush-Masamune conditions[80], with the known phosphonate **274**[86] ceded the enone **275** in excellent yield. (The earlier homologation problems associated with installing the diene unit were overcome by ring-opening of the lactone group). Treatment of **275** with Et_3N and TBSOTf in DCM produced the triene **276** in virtually quantitative yield. Triene **276** appears to be a single geometric isomer (nmr) having $[\alpha]_D^{18}$ +19.0 (c=0.28 in DCM) and a peak in the HRMS at *m/z* 523.3030 ($C_{30}H_{48}O_3SiK$ $[MK]^+$ requires *m/z* 523.3010).

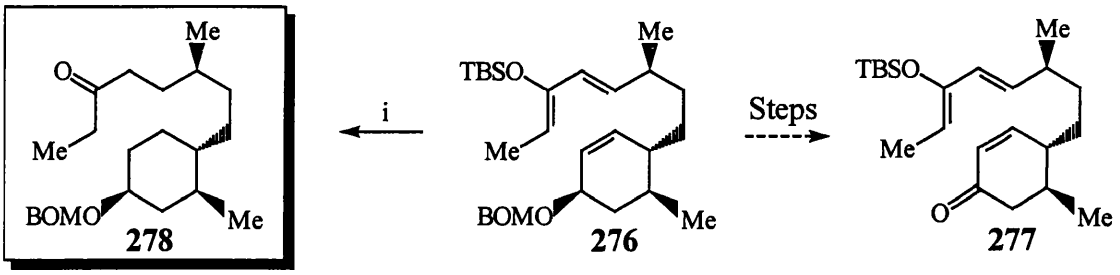
Scheme 46



(i) TBAF, THF, rt, 20 hrs, 86%; (ii) $(COCl)_2$, DMSO, DCM, -78 °C, 1 hr, then Et_3N, rt, 1 hr; (iii) **274**, LiCl, Hünigs base, MeCN, rt, 4 mins, then **273**, MeCN, rt, 48 hrs, 93%; (iv) TBSOTf, Et_3N, DCM, rt, 18 mins, 98%.

Though this triene was thought to be reasonably similar in structure to the ultimately required ketone **23** a bid was made to further activate the molecule for the IMDA reaction (Scheme 47).

Scheme 47



(i) H_2, 10% Pd-C, THF, H_2O, rt, 2 hrs, 91%.

It was intended to synthesise **277**, which contains an electron-poor dienophile unit. Unfortunately, several hydrogenation attempts led only to the formation of **278**. Though hydrogenolysis of BOM protecting groups in the presence of carbon-carbon double bonds is well precedented,[96] in this case relief of ring strain seems to favour the production of **278** – as evidenced *inter alia* by a peaks in the ^1H nmr characteristic of

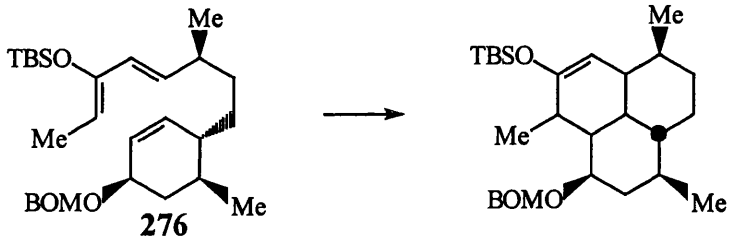
the $MeCH_2CO$ group (δ_H 0.95, 3H, t, *J* 7.5, **Me**CH_2CO and δ_H 2.34, 2H, q, *J* 7.5, $MeCH_2CO$) and a peak in the HRMS at *m/z* 375.2887 ($C_{24}H_{39}O_3$ $[MH]^+$ requires *m/z* 375.2899).

With **276** in hand, further investigation into a synthetic route based on an IMDA reaction to the tricarbocylic core of the Pseudopterosins could be tackled.

2.6 Attempted IMDA Reaction of 276

Triene **276** was subjected to the reaction conditions outlined in Table 3.

Table 3



276

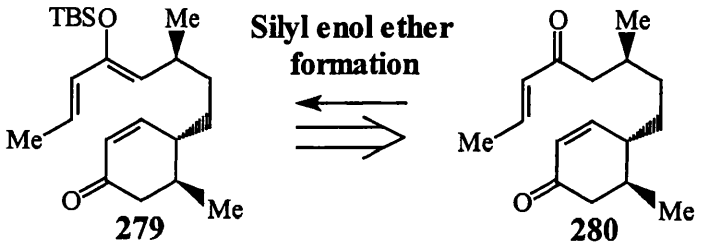
THERMAL	*RADICAL-CATION*
1. PhMe, Sealed Tube, 200 °C, 2 days, clean conversion to the enone **275**. 2. PhMe, Sealed Tube, 200 °C, 7 hrs, in the presence of trace TBSCl and Et_3N, clean conversion to the enone **275**. 3. H_2O, 50 °C, 5 hrs, then reflux, 8 hrs, no reaction.	(pBrPh)$_3$NSbCl$_6$, 2,6-di-*t*-butylpyridine, DCM, 0 °C, 10 mins, then rt, 5 hrs, no reaction.

Under our standard thermal reaction conditions (entry 1) **276** decayed very cleanly to the starting enone **275**, even with trace amounts of TBSCl and Et_3N in the reaction vessel. Prolonged exposure of **276** to H_2O at reflux[97] also failed to induce the IMDA reaction, as did standard radical-cation conditions.

At this stage, it was decided that an IMDA based strategy to the tricarbocyclic core of the Pseudopterosin aglycone could not form part of a viable synthetic route to this family of natural products.

The major reason for abandoning this work was our inability to make the triene **279** (Scheme 48), an ideal precursor for the IMDA reaction having an electron-poor dienophile and electron-rich diene with the optimal regiochemistry for addition.

Scheme 48



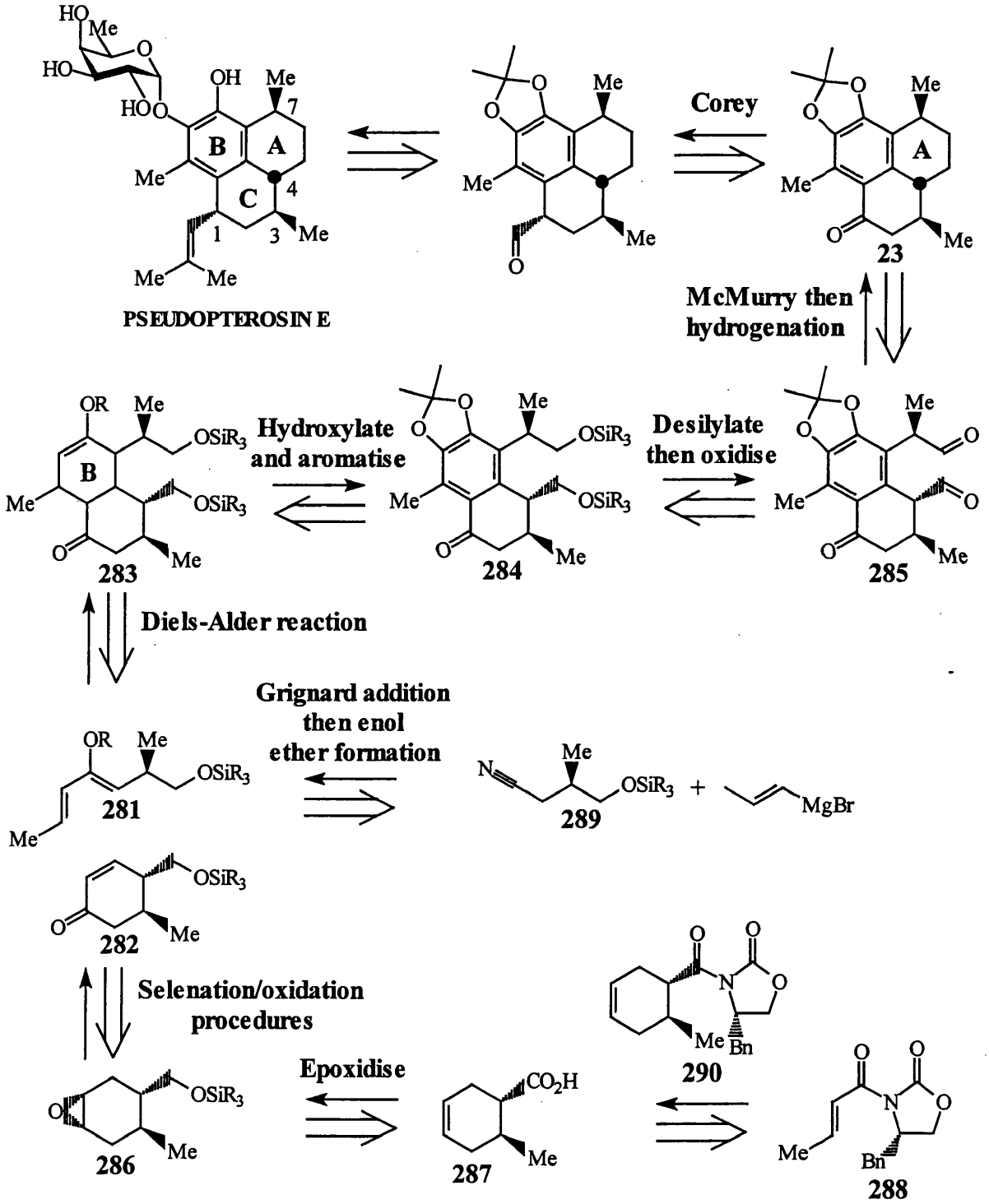
Intuitively, **279** could be formed from the di-enone **280**, though only in an highly regioselective silyl enol ether formation reaction (there are four possible deprotonation sites in **280**). It was felt that a reaction of this type would not be synthetically convenient, particularly on large-scale.

However, it appeared logical, as both diene and dienophile could not be created together in the same reaction pot, that an *inter*molecular Diels-Alder reaction approach would solve this synthetic problem.

2.7 New Retrosynthesis: An Intermolecular Diels-Alder Approach

Diels-Alder unification of the diene **281** with the enone **282** would form the enol ether **283** (Scheme 49).

Scheme 49



Hydroxylation of **283** followed by aromatisation of the B-ring would, after suitable protection, install the hexasubstituted benzene ring of the natural product. Double deprotection of **284** followed by double oxidation of the resulting diol would give the di-aldehyde **285**. McMurry reaction of **285** would, on hydrogenation of the newly formed double bond, create the A-ring of the desired ketone **23**.

The enone **282** could be derived from the epoxide **286** according to Sharpless[98] *et al.*, the epoxide in turn being produced from the known cyclohexene acid **287**[99]. This acid was synthesised by Clive *et al.* in a low temperature, Lewis acid mediated, chiral auxiliary directed Diels-Alder reaction of **288** with 1,3-butadiene (*vide infra*).

The known cyano compound **289**[100], obtained from (*S*)-(-)-hydroxymethylpropionic acid methyl ester, was chosen as a favourable starting material for the diene **281**.

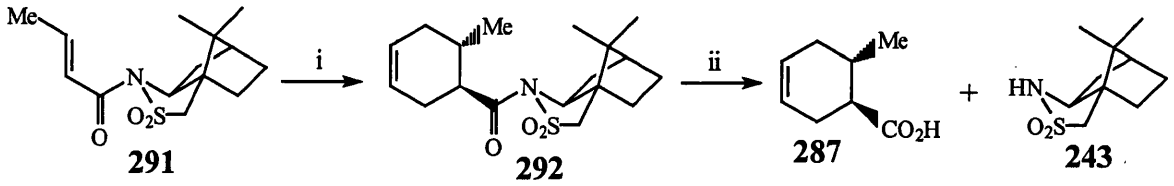
In this new retrosynthesis the stereogenic centres of the molecule are planned to be set as in the IMDA route. Namely, C-1 after Corey, C-3 and C-4 *via* a chiral auxiliary, and C-7 from a commercially available homochiral starting material. As a result, the primary aim of this project can still be realised.

2.8 Synthesis of the Dienophile

Clive[99] *et al.* and Sonnet[101] *et al.* report the asymmetric synthesis of **287** (called trimedlure, a synthetic attractant for the Mediterranean fruit fly) using the Evans oxazolidinone as the chiral auxiliary. However, both comment on inconvenient hydrolysis protocols needed to obtain the acid in pure form with good chiral auxiliary recovery. Presumably, direct hydrolysis of the amide bond in **290** is accompanied by hydrolysis of the oxazolidinone. However, use of the more hydrolytically robust Oppolzer sultam as the chiral auxiliary should allow for a direct synthesis of trimedlure.

To this end, our synthesis of **287** starts with the known butenoyl compound **291** (Scheme 50), as used by Oppolzer *et al.* in the synthesis of Loganin[102].

Scheme 50



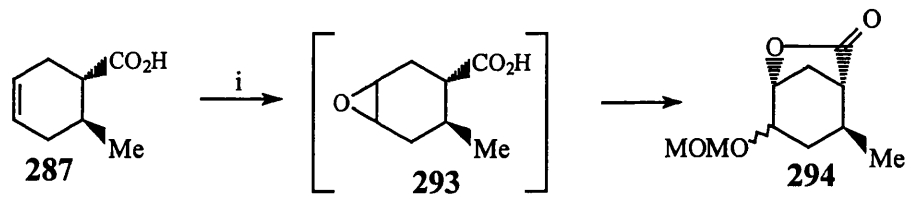
291 **292** **287** **243**

(i) 1,3-Butadiene, $EtAlCl_2$, DCM, -20 °C, 3 days, 98%; (ii) LiOH, H_2O_2, THF:H_2O 1:1, rt, 5 hrs, **287** 89%, **243** 87%.

Prolonged exposure (3 days) of **291** to 1,3-butadiene in DCM at -20 °C in the presence of $EtAlCl_2$ produced **292** as a single compound (nmr) with mp 187-190 °C, $[\alpha]_D^{21}$+154.1 (c=0.27 in DCM) and a peak in the HRMS at *m/z* 338.1783 ($C_{18}H_{28}NO_3S$ $[MH]^+$ requires *m/z* 338.1790). Lithium hydroperoxide hydrolysis of **292** gave synthetic trimedlure in good yield (89%) with clean recovery of the chiral auxiliary (87%). The recovered Oppolzer sultam was of sufficient purity to be used again in the preparation of **287**.

Initial attempts at stereoselective epoxidation of **287** focused upon the use of *m*-CPBA, where the participation of the carboxy group would direct epoxidation onto the same face of the molecule as the acid centre (Scheme 51).

Scheme 51



287 **293** **294**

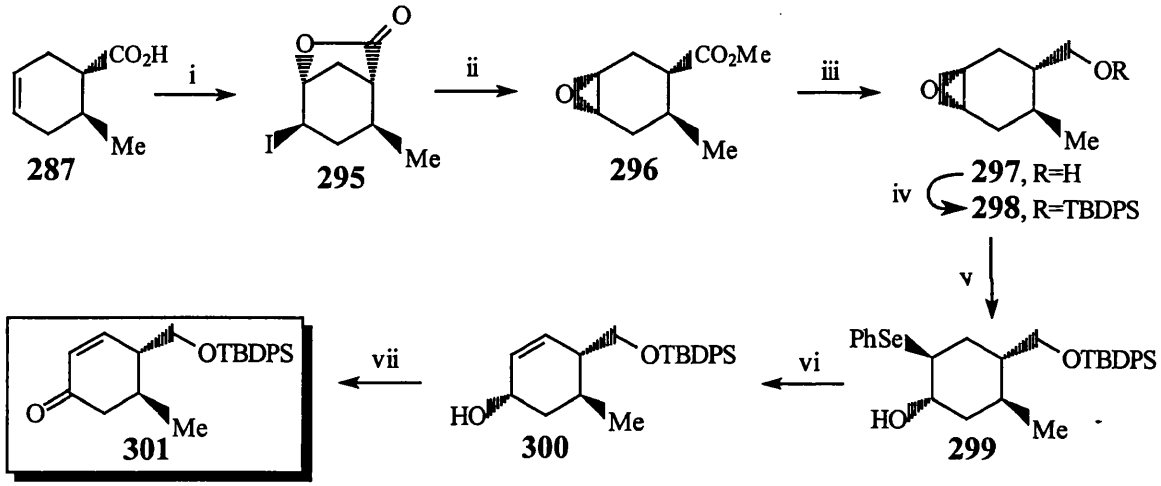
(i) *m*-CPBA, PhMe, 0 °C, 3 hrs, then Et_3N, 30 °C, 4 hrs, then MOMCl, 30 °C, 2.5 hrs, 89%.

Unfortunately, the epoxy acid **293** could not be separated from the reaction co-product (*m*-chlorobenzoic acid) by standard techniques. In order to ascertain the degree of stereoselectivity on epoxidation, trimedlure was converted to the lactone ether **294** in a

one-pot, three step procedure. Specifically, treatment of **287** with *m*-CPBA at 0 °C for 3 hrs effected epoxidation, lactonisation was then induced by the action of Et_3N at 30 °C for 4 hrs and the resulting alcohol was trapped as the MOM ether **294** in good overall yield (89%). The lactone **294** was isolated as an inseparable, 1:1 mixture of diastereomers (nmr) at the centre indicated, implying that there was no direction of epoxidation by the carboxyl unit of **287**.

A stereoselective epoxidation of **287** was achieved starting with Bartlett iodolactonisation in moderate (62%) yield (Scheme 52).

Scheme 52



(i) $NaHCO_3$, KI, I_2, DCM:H_2O 1:1, 0 °C, 5 hrs, 62%; (ii) NaOMe, MeOH, $CHCl_3$, -5 °C to 0 °C, 15 mins, 88%; (iii) $LiBH_4$, THF, -78 °C to 0 °C, 2 hrs, then rt, 17.5 hrs, 90%; (iv) TBDPSCl, Et_3N, DMAP, DCM, rt, 15.5 hrs, 99%; (v) $(PhSe)_2$, $NaBH_4$, EtOH, rt, 5 mins, then **298**, EtOH, reflux, 3 hrs, 86%; (vi) $NaIO_4$, THF:H_2O 1:1, rt, 16 hrs, 92%; (vii) MnO_2, PhMe, reflux with azeotropic removal of H_2O (Dean-Stark), then **300**, PhMe, reflux, 1 hr, 92%.

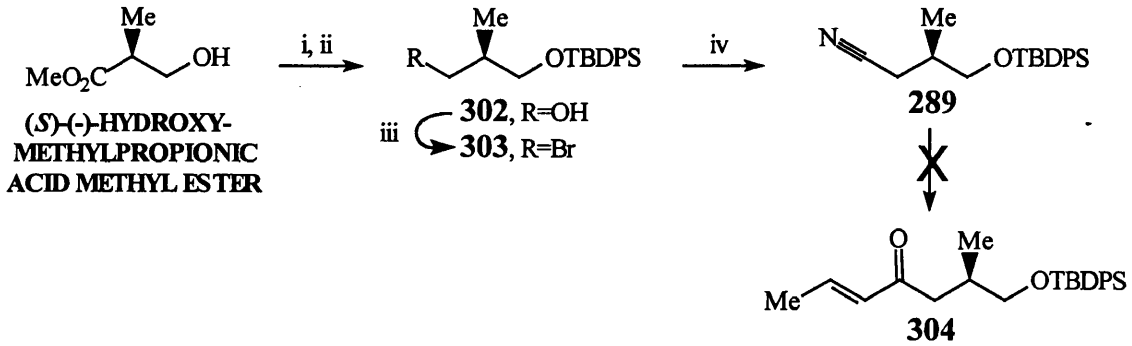
The known iodolactone **295**[103] was then exposed to NaOMe at -5 °C to 0 °C for 15 mins to cede the epoxide **296** as a single compound (nmr) and reduction of the methyl ester **296** to the alcohol **297** was realised with $LiBH_4$ at low temperature. In both steps no loss of stereochemical integrity was observed (by nmr) at the C-4 (Pseudopterosin numbering) stereocentre. Silyl protection of **297** under standard conditions gave rise to **298** as a white crystalline solid (mp 175-177 °C). C-2 ring opening of the epoxide was readily achieved under the conditions of Sharpless[98] to give the selenol **299** as an oil,

which was smoothly converted to the allylic alcohol **300** by the action of $NaIO_4$ in THF and H_2O. Several one-pot procedures for the direct conversion of **298** to **300** were examined and it was found that the overall yield was greater if the intermediate selenol **299** was isolated and purified prior to oxidation/elimination. Oxidation of **300** using pre-dried MnO_2 gave the dienophile **301** in 7 steps from **287**, 35 % overall yield. The dienophile **301** was an oil with $[\alpha]_D^{22}$ +38.3 (c=0.39 in DCM) and a peak in the HRMS at *m/z* 401.190 ($C_{24}H_{30}O_2SiNa$ $[MNa]^+$ requires *m/z* 401.1913).

2.9 Synthesis of the Diene

Synthesis of the known cyano compound **289**[100] starts with silyl protection of (*S*)-(-)-hydroxymethylpropionic acid methyl ester followed by DIBAL reduction to the alcohol **302** (Scheme 53).

Scheme 53



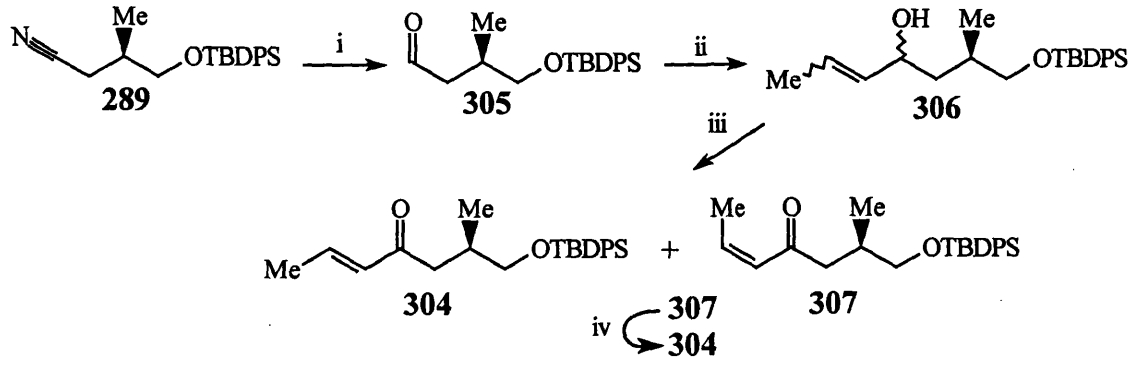
(i) TBDPSCl, Et_3N, DMAP, DCM, rt, 4.5 hrs; (ii) DIBAL, DCM, 0 °C, 38 mins, 99% for two steps; (iii) CBr_4, Ph_3P, THF, rt, 96%; (iv) NaCN, DMF, 90 °C, 1.5 hrs, 94%.

Bromination to **303** and cyanation under standard conditions furnished **289** in good overall yield. Unfortunately, **289** was found unsuitable as an intermediate for the synthesis of the enone **304**, even when the Grignard reagent was exposed to **289** in the presence of CuBr[74].

Conversion of **289** to the aldehyde **305**[100] with DIBAL (Scheme 54) at low temperature in DCM allowed for the addition of propenylmagnesium bromide to form

306 as an inseparable mixture of the four possible diastereomeric alcohols (propenylmagnesium bromide is supplied as a mixture of geometric isomers by Aldrich).

Scheme 54

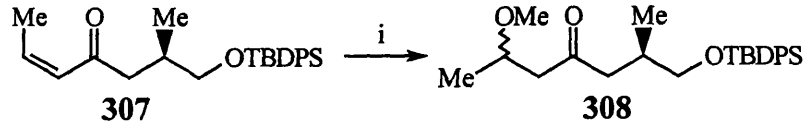


(i) DIBAL, DCM, -78 °C, 1 hr, 99%; (ii) 1-Propenylmagnesium bromide, THF, -78 °C, 45 mins, 99%; (iii) PDC, DMF, rt, 13 hrs, **304** 47%, **307** 52%; (iv) Et_3N, THF, rt, 18 hrs, 95%.

PDC oxidation of **306** in DMF gave 1.1:1 *cis*:*trans* mixture of enones, which were separated easily by flash column chromatography. Gratifyingly, treatment of the *cis* isomer **307** with Et_3N in THF at rt overnight effected double bond isomerisation to the *trans* compound **304** in excellent yield. Taking this isomerisation into account, the yield of the desired trans enone **304** is 96% from **306**.

Quite by surprise, when the same isomerisation was attempted with NaOMe in MeOH, conjugate addition of methoxide occurred to afford **308** as an inseparable 1:1 mixture of diastereomers (nmr) where indicated (Scheme 55).

Scheme 55

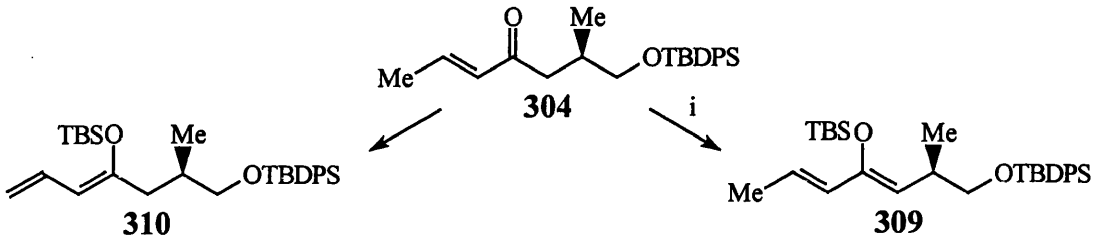


(i) NaOMe, MeOH, rt, 20 hrs, 95%.

The *trans* isomer **304** also acts as a Michael acceptor of methoxide under the same reaction conditions, giving the identical product in 96% yield.

Initial attempts to synthesise the required diene **309** focused on the action of lithium bases (LDA and LiHMDS) on **304** and trapping of the resulting enolate with TBSOTf. In all cases, and when Et_3N was utilised as the base, the product was the terminal diene **310** (Scheme 56). This diene is the more stable of the two as the oxygen lone-pair is fully delocalised over the double bonds.

Scheme 56



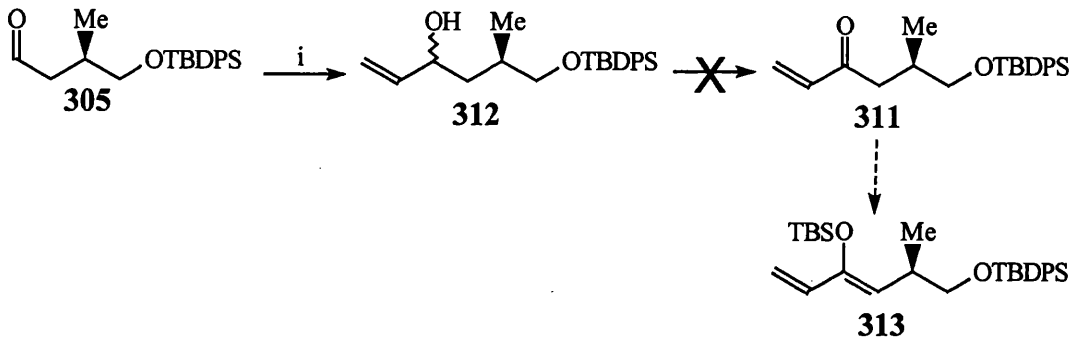
(i) NaHMDS, THF, -78 °C, 7 mins, then TBSOTf, THF, -78 °C, 16 mins, 72%.

The desired diene **309** was only produced by treating **304** in THF with NaHMDS at low temperature and trapping the resulting enolate with TBSOTf in 72% yield – and was characterised *inter alia* by the presence of a low field methyl doublet in the ^1H nmr (δ_H 1.71, 3H, d, *J* 5.5, **Me**C(H)=) and a peak in the HRMS at *m/z* 495.3122 ($C_{30}H_{47}O_2Si_2$ $[MH]^+$ requires *m/z* 495.3115).

Combined with the earlier isomerisation observation, it appears that the enones **304/307** exhibit unusual reactivity when in the presence of Na^+. There is no immediately obvious explanation for this.

The use of the enone **311** as a precursor for the diene would have avoided the production of regio-isomeric dienes (Scheme 57). However, though the synthesis of the allylic alcohol **312** was facile, subsequent oxidation to the enone **311** failed under a wide variety of oxidation protocols (PDC in DMF, MnO_2 in Et_2O, Swern conditions with $(COCl)_2$, Magtrieve™ in DCM, and TPAP/O_2 in DCM).

Scheme 57



(i) Vinylmagnesium bromide, THF, -78 °C to 0 °C, 1 hr, 99%.

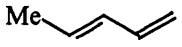
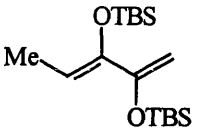
Ultimately, the use of the diene **313** was rejected, as this would require the installation of the aromatic methyl group of the natural product at a later stage thereby increasing the number of synthetic steps.

Having established gram scale routes to both the diene and dienophile, the key step of this synthesis could then be investigated.

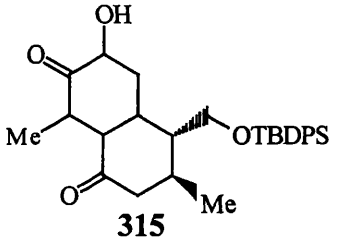
2.10 Attempted Intermolecular Diels-Alder Reaction

With the warning of Fredj[53] *et al.* on the reluctance of enones of the type **301** to be willing participants in the Diels-Alder reaction in mind, test reactions with simpler dienes were first attempted (Table 4). Early results using piperylene as the diene confirmed the findings of Fredj *et al.* under a variety of thermal and Lewis acid conditions.

Table 4

DIENE	*THERMAL*	*LEWIS ACID*
 *Piperylene*	PhH, Sealed Tube, 150 °C, 4 days, no reaction.	1. Me_2AlCl, DCM, -78 °C, 1 hr, -40 °C, 2 hrs, 0 °C, 1 hr, rt, 17 hrs, no reaction. 2. $ZnCl_2$, PhMe, 0 °C, 1.5 hrs, rt, overnight, no reaction. 3. $SnCl_4$, Et_2O, -78 °C, 1.5 hrs, -20 °C, 2 hrs, no reaction.
 **314**	PhMe, Sealed Tube, 190 °C, 15.5 hrs, clean conversion to an unstable compound.	Not applicable.

However, under thermal conditions, the di-enol ether **314**[104] reacted cleanly (tlc) to give an extremely unstable product. Based solely on the available data (^{1}H nmr and ir) the product was assigned as **315**, where addition has occurred with concomitant loss of the silyl groups from the diene.

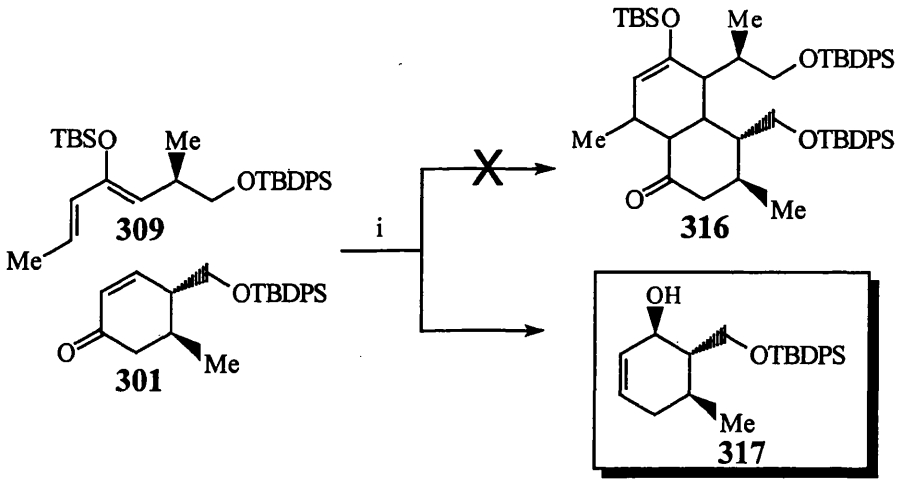


315

Unfortunately, exposure of freshly prepared **315** to either DDQ in dioxane or MnO_2 in PhMe failed to transform the molecule to a more stable compound.

As a test reaction, this was a promising result and the diene **309** and dienophile **301** were submitted to the same reaction conditions (Scheme 58).

Scheme 58



(i) PhMe, trace HMDS, Sealed Tube, 190 °C, 3 days, 95%.

Reaction to the desired product **316** did not occur. Instead, the allylic alcohol **317** was produced of $[\alpha]_D^{22}$ +26.7 (c=0.47 in DCM) with a peak in the HRMS at *m/z* 403.2087 ($C_{24}H_{32}O_2SiNa$ $[MNa]^+$ requires *m/z* 403.2069). Identification of this compound was greatly helped by our previous synthesis of the isomeric compound **300**. During the course of the reaction the diene **309** reverted (tlc) to the enone **304**. The formation of **317** was a quite unexpected result.

Of paramount importance is the discovery that the desired product was not formed during the course of this reaction.

Given the relative instability of the diene **309** and the inactivity of the enone **301**, it was decided to abandon work on this project.

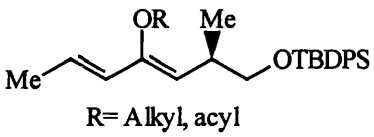
2.11 Conclusions and Future Work

The primary aim of this project was to develop an efficient, stereocontrolled synthesis of Pseudopterosin E, which would ultimately be applicable to the synthesis of the 24 possible diastereomers of the Pseudopterosin A-F aglycone.

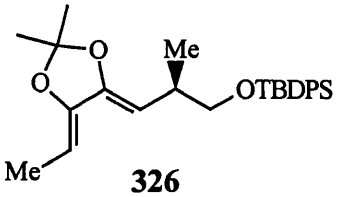
In order to achieve this, synthetic routes in which the Diels-Alder reaction was the key step were investigated. It was found that, though the synthesis of many Diels-

Alder reaction precursors was facile, the actual reaction itself proved problematic. Despite employing a broad variety of well characterised literature procedures known to effect the Diels-Alder reaction, little success was achieved.

The use of a more stable diene system, such as **325** or **326,** could allow for the unification of diene and dienophile.



325



326

In the course of this work a practical (particularly on large scale) synthetic route to the natural product trimedlure **287** was developed.

Cyclisation with NaH in DMF then TFA/DCM deprotection should then cede *trans*-4-methyl-L-proline.

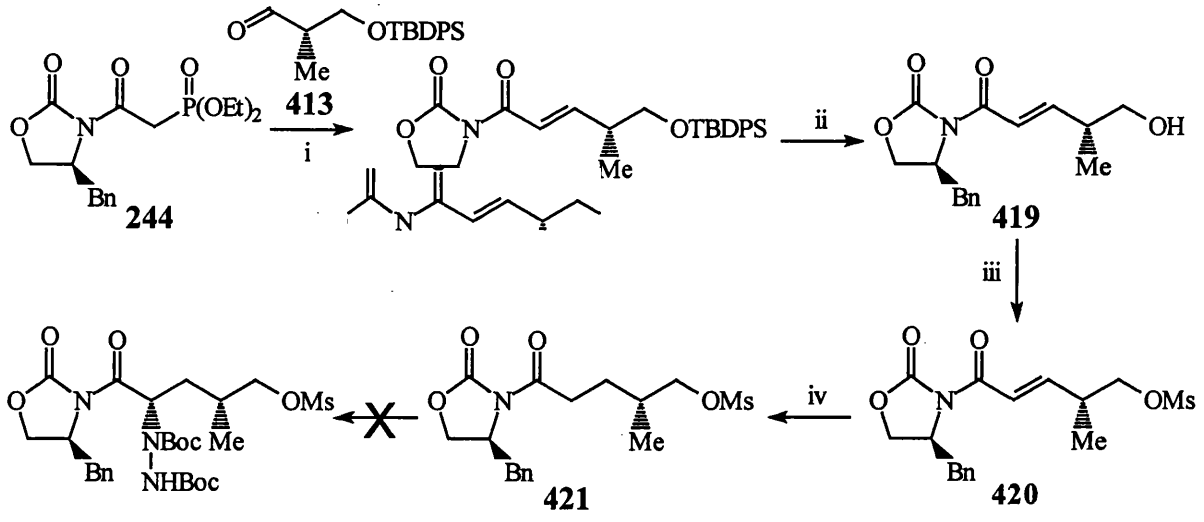
Both the starting materials were synthesised during the course of our work on the Pseudopterosins (**244** Scheme 35, *ent*-**413** Scheme 33).

In this retrosynthesis the C-4 stereogenic centre of *trans*-4-methyl-L-proline is derived from the chiral pool and the C-2 stereocentre is set in a chiral auxiliary directed hydrazination reaction. By building the molecule this way, it should be possible to avoid the production of C-4 diastereomers as observed in our earlier work (in this case the *N*-acyl side of **414** chain does not contain competing chelation sites). Futhermore, careful use of the two starting materials **244** and **413** *and* their enantiomers should allow for the asymmetric synthesis of the four possible diastereomers of 4-methyl-proline.

4.1 Syntheses of 414 and Attempted Hydrazination

Horner-Emmons-Wittig condensation of **244** with **413** afforded **418** as a single diastereomer in good yield (Scheme 79).

Scheme 79

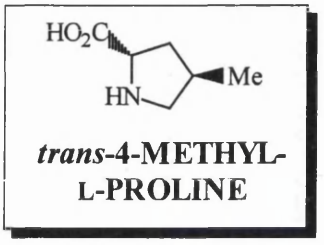


(i) **244**, LiCl, Hünigs base, MeCN, rt, 10 mins, then **413**, MeCN, rt, 13 hrs, 86%; (ii) 40% (aq) HF, MeCN:THF 1:1, rt, 24 hrs, 97%; (iii) MsCl, Et_3N, DCM, 0 °C, 31 mins, 94%; (iv) H_2, 10% Pd-C, MeOH, rt, 13.5 hrs, 97%.

CHAPTER 3:
trans-4-Methyl-L-Proline

3.0 Introduction

Free *trans*-4-methyl-L-proline was first isolated from young Worcester Pearmain apples by Hulme and Arthington in 1952[105].



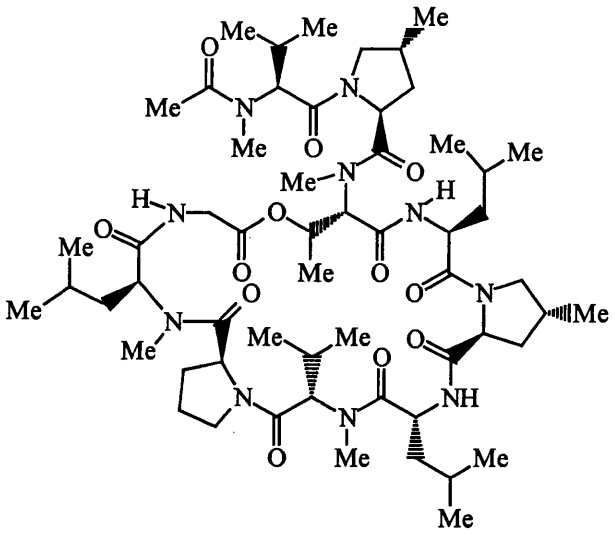
***trans*-4-METHYL-L-PROLINE**

The structure of this novel imino acid was predicted on the basis of extensive chromatographic techniques in comparison to L-proline and confirmed by a synthesis of Steward *et al.* at Cornell[106].

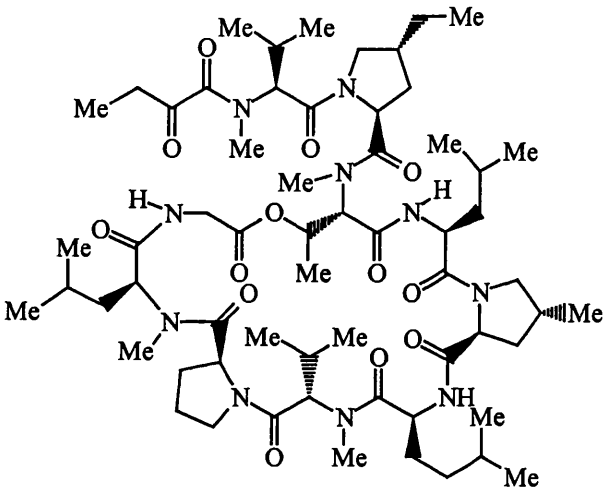
To date, *trans*-4-methyl-L-proline has been found to be a constituent part of several natural products (Scheme 60).

- Grisemelycin, an octadepsipeptide, was isolated in 1971 by Terlain and Thomas (Rhône-Poulenc Laboratories, France) from the bacteria *Stremptomyces cœlicus* and *Stremptomyces griseus*[107]. It contains two *trans*-4-methyl-L-proline residues and has several minor congeners containing either three proline residues or three *trans*-4-methyl-L-proline residues, or two proline and one *trans*-4-methyl-L-proline residues. The natural product is active against mycobacteria and Gram-positive microorganisms.
- In 1983 the structurally related natural product Mycoplanecin A was isolated from *Actinoplanes awajinensis* by several workers of the Sankyo Corporation of Japan[108].

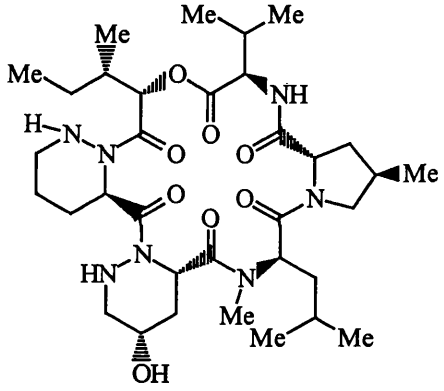
Scheme 60



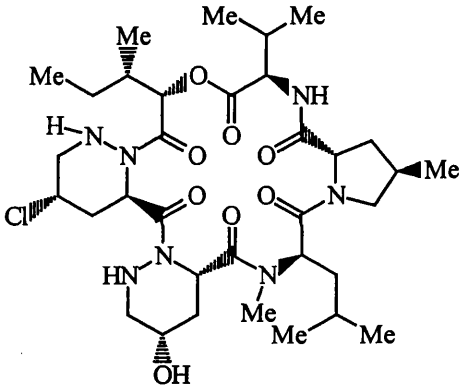
GRISELIMYCINE



MYCOPLANECIN A



MONAMYCIN D_1



MONAMYCIN H_1

In addition to a *trans*-4-methyl-L-proline residue the molecule also includes a *trans*-4-ethyl-L-proline residue. The compound is active against molds, yeasts, and mycobacteria including *Mycobacterium tuberculosis* whilst exhibiting low toxicity (mice can tolerate oral administrations of up to 3,000 mg/kg).

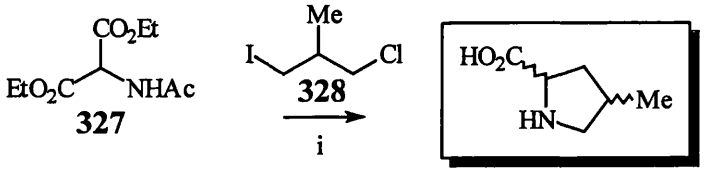
- The Monamycins, a family of fifteen hexadepsipeptides, were first isolated by Hassall and Magnus from *Streptomyces jamaicensis* in 1959[109]. Structural elucidation of Monamycin D_1 and H_1 was reported by Hassall *et al.* in 1971[110]. They are active against Gram-positive bacteria with some immunosuppressant activity.

Though *trans*-4-methyl-L-proline for itself has little or no biological significance, a convenient fabrication is essential in any synthetic programme towards the more (biologically) interesting compounds Grisemelycin, Mycoplanecin A, and the Monamycins[111].

3.1 Promulgated Syntheses of trans-*4-Methyl-L-Proline*

Whilst trying to make 4-hydroxyleucine, Dakin[112] reports the unexpected synthesis of racemic 4-methylproline, which pre-dates the Hume isolation of *trans*-4-methyl-L-proline (Scheme 61).

Scheme 61

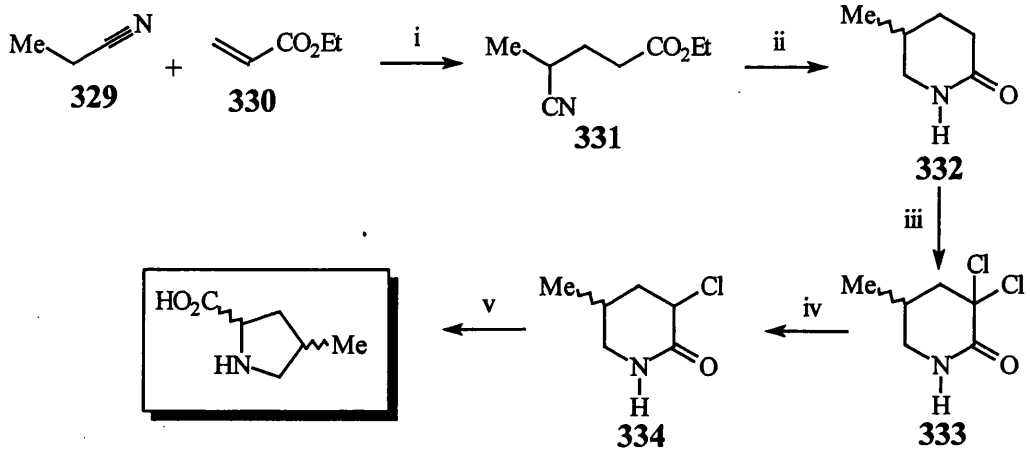


(i) Na, EtOH, dioxane, rt, then **328**, dioxane, reflux, 9 hrs, then hot EtOH.

Condensation of the sodio derivative of acetylaminomalonic acid ethyl ester **327** with 1,3-chloroiodoisobutane **328** followed by hydrolysis and treatment of the crude residue with hot absolute alcohol affords 4-methylproline in low overall yield (?%).

In 1962 Kariyone[113] also published a racemic synthesis of 4-methylproline, starting from the Michael condensation of propionitrile **329** with ethyl acrylate **330** (Scheme 62). Raney nickel reduction of **331** afforded the 5-methyl-2-piperidone **332**, which was chlorinated in $CHCl_3$ in the presence of both PCl_5 and $SOCl_2$. Reduction (Raney nickel) of **333** gave the mono-chloropiperidone **334**, which cyclised to form 4-methylproline when exposed to $Ba(OH)_2$ mediated hydrolysis (ignoring the extremely low yielding formation of **331**; 4 steps, 23% overall yield).

Scheme 62



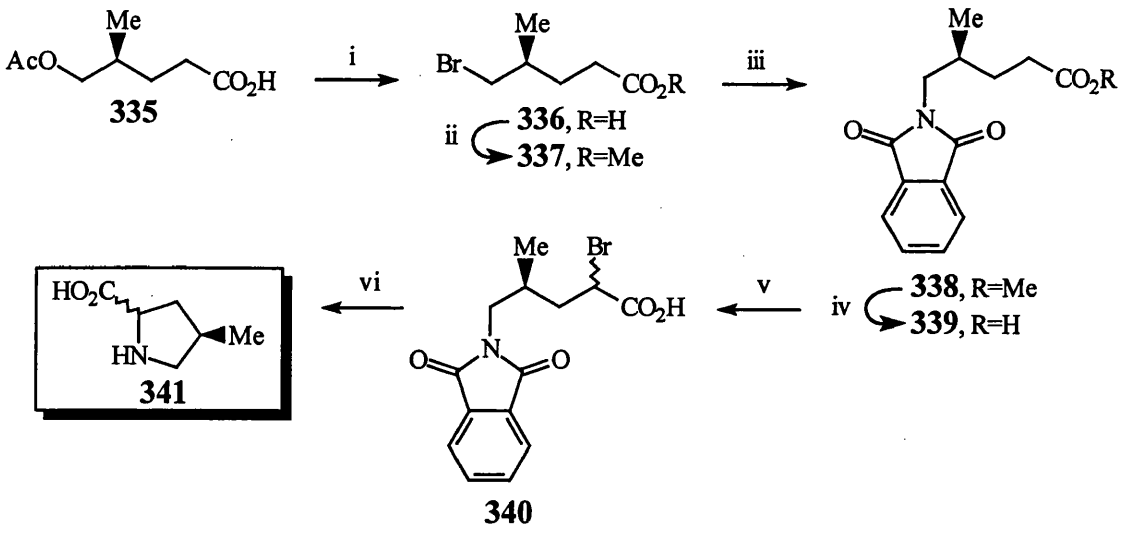
(i) *t*-BuOK, *t*-BuOH, Sealed Tube, 180 °C, 10 hrs, 9%; (ii) H_2, Raney nickel, Et_3N, EtOH, 80 atm., 130 °C, 3 hrs, 86%; (iii) PCl_5, $SOCl_2$, $CHCl_3$, rt, 30 mins, 86%; (iv) H_2, Raney nickel, Et_3N, EtOH, rt, 69%; (v) $Ba(OH)_2$, H_2O, reflux, 3.5 hrs, then H_2SO_4, reflux, 0.5 hrs, then rt, overnight, 46%.

Slight variation to this chemistry also allows for the synthesis of racemic 2-methylproline.

3.1.1 The Dalby, Kenner, and Sheppard Synthesis of trans-*4-Methyl-L-Proline and* cis-*4-Methyl-D-Proline*

The first synthesis of *trans*-4-methyl-L-proline was realised by Dalby, Kenner, and Sheppard[114] in 1962 and starts with the homochiral acid **335**, an industrial by-product (Scheme 63). Exposure of **335** to HBr and H_2SO_4 in MeOH effected bromination to **336**. After esterification, **337** was condensed with potassium phthalimide in DMF to cede **338**, which was subjected to acid hydrolysis to afford **339**. α-Bromination of **339** proceded with little stereoselectivity, giving **340** as a mixture of C-2 diastereomers (the extent of diastereoselectivity varied from experiment to experiment). Cyclisation under base conditions afforded a mixture of *trans*-4-methyl-L-proline and of *cis*-4-methyl-D-proline **341**.

Scheme 63



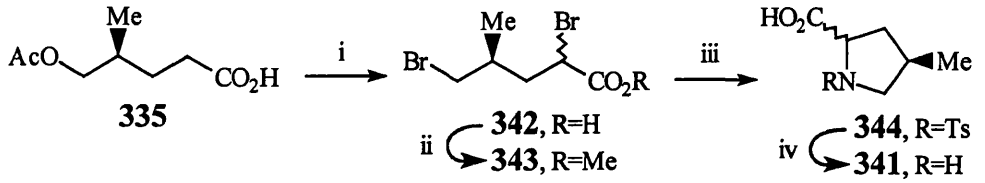
(i) 48% (aq) HBr, conc. H_2SO_4, 90 °C, 7 hrs, 60%; (ii) conc. H_2SO_4, MeOH, reflux, 20 hrs, 80%; (iii) Potassium phthalimide, DMF, 90 °C, 3 hrs, 98%; (iv) 2N (aq) HCl, reflux, 2.5 hrs, 72%; (v) Red phosphorus, Br_2, CCl_4, reflux, 4 hrs, 72%; (vi) NaOH, H_2O, rt, 4 days, 43%.

The two imino acids were separated either;

1. By exposure of the mixture **341** to $Cu(CO)_2$, which induced preferential crystallisation of the copper salt of *trans*-4-methyl-L-proline. Separation of the two salts was then possible and they were converted to pure *trans*-4-methyl-L-proline and pure *cis*-4-methyl-D-proline on Dowex 50-exchange resins with ammonia to afford the two products (17% isolation of *trans*-4-methyl-L-proline), or
2. By destructive oxidation of the *cis*-4-methyl-D-proline component of the mixture **341** with the enzyme D-amino acid oxidase in the presence of O_2, which allowed for the isolation of pure *trans*-4-methyl-L-proline (45% isolation of *trans*-4-methyl-L-proline).

An alternative, less efficient route to the mixture **341** was also given, starting with di-bromination of **335** (Scheme 64). Esterification of **342** in MeOH heated at reflux containing conc. H_2SO_4 yielded **343**. Condensation of **343** with potassium *p*-toluenesulfonamide gave the tosyl compound **344**, after saponification. Cleavage of the tosyl group with HBr in AcOH gave the mixture **341** in low overall yield.

Scheme 64



(i) Red phosphorous, Br_2, CCl_4, reflux, 4 hrs; (ii) conc. H_2SO_4, MeOH, reflux, 18 hrs, 26% for two steps; (iii) Potassium *p*-toluenesulphonamide, DMF, 90 °C, 4.5 hrs; NaOMe, MeOH, 90 °C, 2.5 hrs; NaOH, dioxane, H_2O, reflux, 2 hrs, 11% for three steps; (iv) HBr, AcOH.

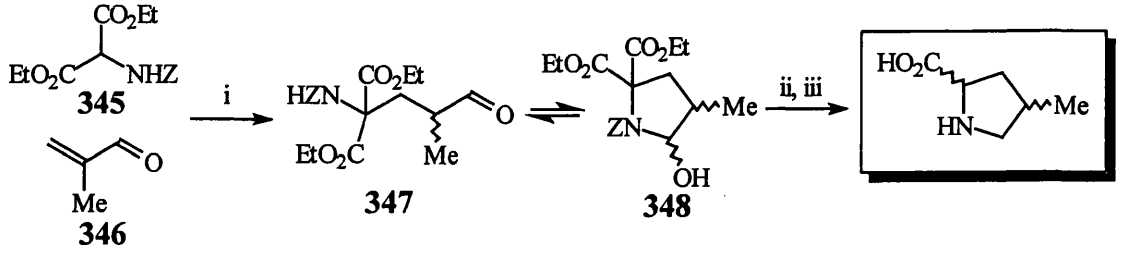
They also outline another approach to 4-methylproline, extended by Cox, Johnson, and Mauger[115] (*vide infra*).

In summary, Dalby, Kenner, and Sheppard have synthesised *trans*-4-methyl-L-proline from a commercial by-product (Phthalimido route; 7 steps, 5% overall yield).

3.1.2 The Cox, Johnson, and Mauger Racemic Synthesis of 4-Methylproline

As alluded to by Dalby, Kenner, and Sheppard[114], Michael addition of the sodio derivative of diethyl benzyloxycarbonylaminomalonate **345** to α-methacrolein **346** afforded **347**, which is in equilibrium with the cyclic form **348** (Scheme 65).

Scheme 65



(i) **345**, Na, EtOH, rt, then add **346**, EtOH, 30 mins; (ii) H_2, 10% Pd-C, EtOH, rt, 82% for two steps; (iii) 6N (aq) HCl, reflux, 3 hrs, 80%.

Reduction of **348** (H_2 over 10% Pd-C) in EtOH followed by exposure to 6N (aq) HCl produced racemic 4-methylproline (3 steps, 66% overall yield).

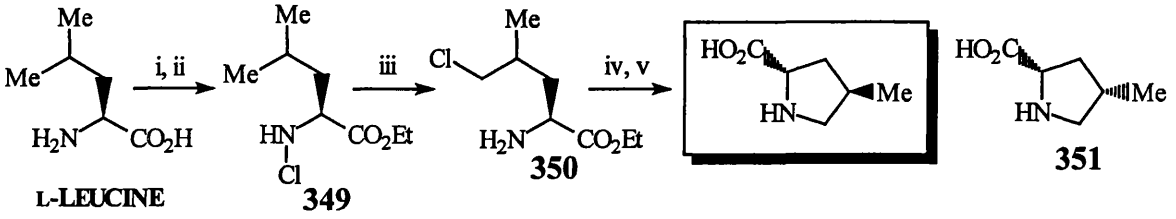
Depending upon the aldehyde used as a Michael acceptor, a wide variety of racemic proline derivatives may be synthesised by this chemistry. Specifically, 3-

phenylproline and 3-methylproline are available from cinnamaldehyde and crotonaldehyde respectively.

3.1.3 The Lavergne Synthesis of trans- *and* cis-*4-Methyl-L-Proline*

Lavergne[116] *et al.* make use of the Hoffmann-Löffler-Freytag reaction in their synthesis of *trans*-4-methyl-L-proline and *cis*-4-methyl-L-proline **351** starting from L-leucine (Scheme 66).

Scheme 66



(i) $SOCl_2$, EtOH, reflux, 10 hrs, 70%; (ii) *t*-BuOCl, PhH, <5 °C, 1.5 hrs, 90%; (iii) 15W Rayonet Lamp, conc. H_2SO_4, KI, acetone, 0 °C, 40 hrs; (iv) NaOH, MeOH, reflux, 2 hrs; (v) HCl, Dowex 50 Column, 38% for three steps.

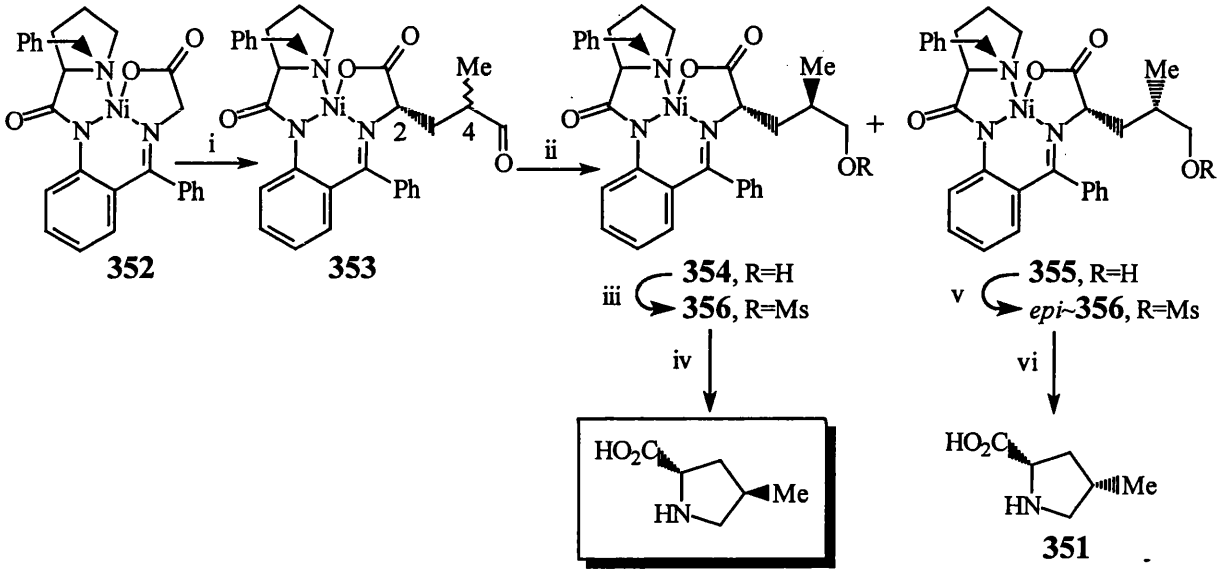
Esterification of L-leucine followed by *N*-chlorination using *t*-BuOCl in PhH gave the Hoffmann-Löffler-Freytag precursor **349** in good yield. Irradiation of **349** effected the desired chlorine transposition and cyclisation was achieved by exposure of **350** to NaOH to give a mixture of *trans*-4-methyl-L-proline and *cis*-4-methyl-L-proline **351** (1:1 mixture of diastereomers). Separation of the diastereomers was realised as described by Dalby, Kenner, and Sheppard[114] (5 steps, 24% overall yield).

This chemistry can also be applied to the asymmetric syntheses of L-proline, *trans*-3-methyl-L-proline and *cis*-3-methyl-L-proline starting from L-norvaline, L-alloisoleucine, and L-isoleucine respectively.

3.1.4 The Belekon Synthesis of trans- *and* cis-*4-Methyl-L-Proline: A General Route to 3-, 4-, and 5-alkylprolines*

In 1988 Belekon[117] *et al.* reported the use of the Ni(II) Shiff complex **352** (formed from the reaction of glycine and (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone in the presence of $Ni(NO_3)_2$) in the synthesis of both *trans*-4-methyl-L-proline and *cis*-4-methyl-L-proline **351** (Scheme 67).

Scheme 67



(i) α-Methacrylaldehyde, Et_3N, MeOH, 60 °C, 72 hrs, 98%; (ii) MSA-1 resin (BH_4^- form), MeOH, rt, **354** 23%, **355** 63%; (iii) MsCl, pyridine, DCM, rt; (iv) 3N (aq) HCl, MeOH, 80 °C, 70% for two steps; (v) MsCl, pyridine, DCM, rt; (vi) 3M (aq) HCl, MeOH, 80 °C, 74% for two steps.

Treatment of **352** in MeOH with Et_3N followed by α-methacrylaldehyde gave a 2:1 (2*S*,4*S*):(2*S*,4*R*) mixture of diastereomers and a minor (11%) quantity of the 2-(*R*) diastereomers. Reduction of **353** with MSA-1 resin (BH_4^- form) allowed for chromatographic separation of the epimeric alcohols **354** and **355**. Conversion of **354** to the mesylate and subsequent treatment of **356** with 3N (aq) HCl cleaved the Ni(ii) complex with concomitant cyclisation to form *trans*-4-methyl-L-proline (4 steps, 16% overall yield) in >95% ee at the newly created amino stereogenic centre. Similarly, *cis*-

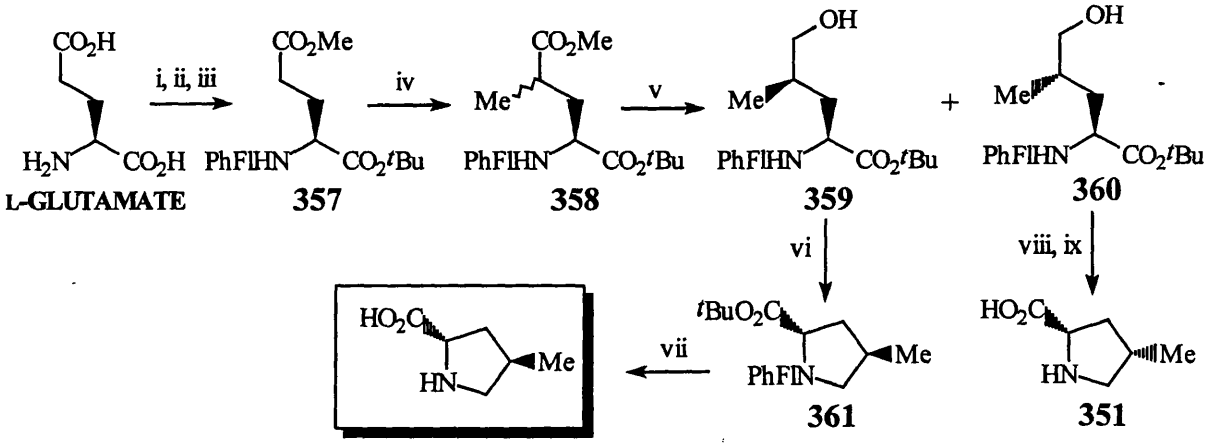
4-methyl-L-proline **351** can be synthesised from the alcohol **355** via the mesylate *epi*-**356**.

Furthermore, condensation of the complex **352** with acryaldehyde, (*E*)-crotonaldehyde, (*E*)-cinnamaldehyde, and methyl vinyl ketone leads to the production of (*S*)- and (*R*)-proline, *trans*-3-methyl-L-proline, *trans*- and *cis*-3-phenyl-L-proline, and *trans*- and *cis*-5-methyl-L-proline respectively accompanied by trace amounts of the D-series. Belokon *et al.* indicate that the synthetic limitation to this chemistry is only the availability of suitably substituted acryaldehydes.

3.1.5 The Rapoport Synthesis of trans- *and* cis-*4-Methyl-L-Proline: A General, Chirospecific Route to 4-Substituted Prolines*

The Rapoport[118] *et al.* synthesis (1989) of *trans*-4-methyl-L-proline and *cis*-4-methyl-L-proline **351** begins with global protection of L-glutamate (Scheme 68).

Scheme 68



(i) Ref. 119; (ii) $TMSCl$, $CHCl_3$, reflux, 2 hrs, then Et_3N, $Pb(NO_3)_2$, 9-bromo-9-(phenylfluorenyl), $CHCl_3$, rt, 87 hrs, 84%; (iii) *O*-*t*-Butyl-*N*,*N*'-diisopropylurea, DCM, rt, 16 hrs, 75%; (iv) KHMDS, THF, -78 °C, 1 hr, then MeI, THF, -78 °C, 3 hrs, 94%; (v) $LiAlH_4$, THF, -78 °C, 4 hrs, **359** 24%, **360** 66%; (vi) CBr_4, Ph_3P, THF, rt, 1 hr, 89%; (vii) TFA, DCM, 16 hrs, 87%; (viii) CBr_4, Ph_3P, THF, rt, 1 hr, 88%; (ix) TFA, DCM, 16 hrs, 90%.

The 9-(9-phenylfluorenyl) protecting group was chosen so as to prevent racemisation at the α-amino acid stereogenic centre, and the two acid groups were differentiated as the

t-butyl and methyl esters. Treatment of **357** in THF with KHMDS at low temperature selectively generated the distal enolate ester, which was quenched with MeI to afford **358** in good yield as a 1:3 *R*:*S* inseparable mixture of diastereomers with minor amounts (3%) of the dialkylated product. Separation of the diastereomers was achieved by MPLC after low temperature $LiAlH_4$ reduction to the alcohols **359** and **360**. Cyclisation of **359** under Mitsunobu conditions (CBr_4 and Ph_3P in THF containing Hünigs Base) gave **361**, which was deprotected with TFA in DCM to afford *trans*-4-methyl-L-proline (6 steps, 11% overall yield). Similarly, *cis*-4-methyl-L-proline **351** can also be produced.

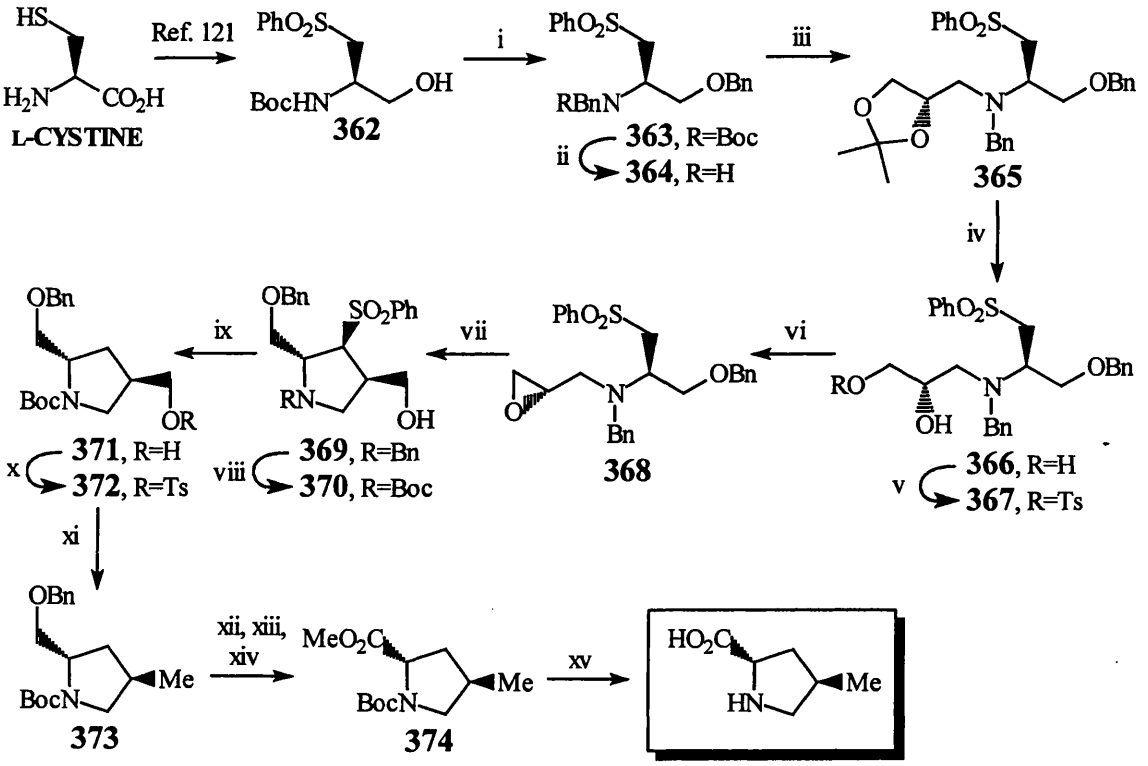
Alkylation with electrophiles other than MeI was also realised using similar chemistry, which allowed the syntheses of *trans*- and *cis*-4-propyl-L-proline, *trans*- and *cis*-4-cyanomethyl-L-proline, and *trans*- and *cis*-4-phenyl-L-proline.

3.1.6 The Sasaki Asymmetric Synthesis of trans*-4-Methyl-L-Proline: A General Asymmetric Route to 4-Substituted Prolines*

To date, the only totally stereocontrolled synthesis of *trans*-4-methyl-L-proline is that of Sasaki[120] *et al.* published in 1998. Global benzylation of **362**, obtained from cysteine under standard conditions, followed by hydrolysis of the Boc group in **363** gave the dibenzyl compound **364** in good yield (Scheme 69). Reductive *N*-alkylation of **364** with (2*R*)-2,3-*O*-isopropylideneglyceraldehyde[121] using $NaBH(OAc)_3$ in 1,2-dichloroethane gave **365** in excellent yield. Hydrolysis of the isopropylidene group with 4N (aq) HCl ceded the diol **366**, which was monotosylated to **367** and cyclised with K_2CO_3 in wet DMF to afford the epoxide **368**. Cyclisation of **368** was achieved using KHMDS as the base in THF at low temperature with $Ti(O\text{-}i\text{-}Pr)_4$ as a Lewis acid additive in 73% yield. The *N*-benzyl protecting group in **369** was exchanged for an *N*-

Boc group without any *O*-benzyl deprotection. Exposure of **370** to 6% Na-Hg amalgam in MeOH effected desulfonylation in quantitative yield to give **371**. Tosylation of the pendent alcohol group in **371** to afford **372** was followed by $NaBH_4$ reduction in DMSO to install the methyl unit of the final product. Hydogenolysis of **373** followed by TEMPO/NaOCl oxidation and diazomethane esterification of the resulting acid gave the methyl ester **374** in good overall yield. Treatment of **374** with HCl and propylene oxide afforded *trans*-4-methyl-L-proline (15 steps, 26% overall yield).

Scheme 69



(i) NaH, THF, 0 °C, 30 mins, then BnBr, *n*-Bu_4NI, THF, 0 °C, 24 hrs, 86%; (ii) 3N (aq) HCl, EtOAc, rt, 1 hr, 95%; (iii) (2*R*)-2,3-*O*-isopropylideneglyceraldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, overnight, 97%; (iv) 4N (aq) HCl, THF, rt, 3 hrs, 94%; (v) TsCl, pyridine, 0 °C, 24 hrs, 85%; (vi) K_2CO_3, wet DMF, rt, 24 hrs, 99%; (vii) KHMDS, Ti(O-*i*-Pr)$_4$, THF, -70 °C, 2 hrs, 73%; (viii) H_2, 10% Pd-C, Boc_2O, MeOH, rt, 3 hrs, 95%; (ix) 6% Na-Hg, Na_2HPO_4, MeOH, 0 °C, 2 hrs, 100%; (x) TsCl, DMAP, pyridine, 0 °C, 30 mins, then rt, 24 hrs, 85%; (xi) $NaBH_4$, DMSO, 45 °C, 16 hrs, 87%; (xii) H_2, 10% Pd-C, MeOH, rt, 18 hrs, 92%; (xiii) TEMPO, NaOCl, KBr, 5% (aq) $NaHCO_3$, acetone, 0 °C, 2 hrs; (xiv) CH_2N_2, 88% for two steps; (xv) 1N (aq) HCl, reflux, 3 hrs, then propylene oxide, EtOH, heat, 100%.

The motivation for this work was to make homochiral *trans*-4-methyl-L-proline to act as a proline-leucine chimera in peptidomimetic studies. With this chemistry,

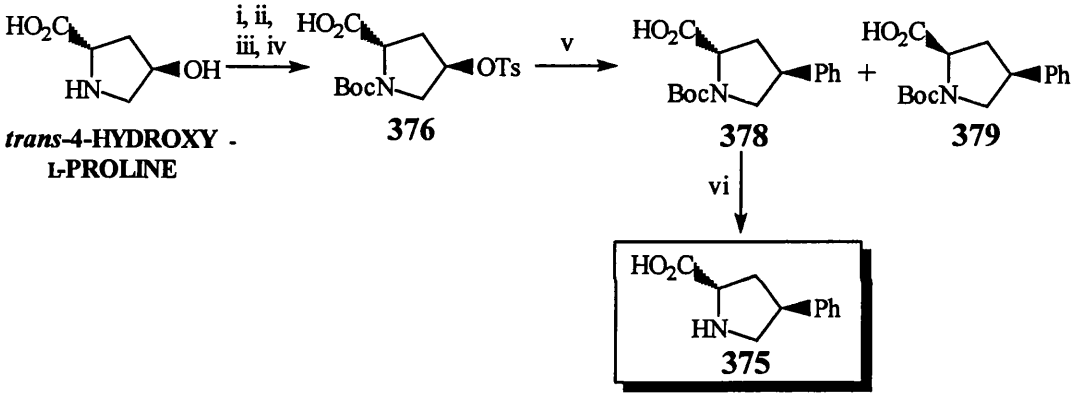
Sasaki *et al.* have also synthesised proline-lycine, proline-arginine, and proline-glutamic acid chimeras.

3.2 Synthetic Approaches to trans*-4-Alkyl-L-Prolines*

Several asymmetric syntheses of *trans*-4-alkyl-L-prolines start from the commercially available material *trans*-4-hydroxy-L-proline.

Thottathil[122] and Moniot achieved a rapid synthesis of *trans*-4-phenyl-L-proline **375** *via* cuprate addition of phenyl lithium to the tosylate **376** (Scheme 70).

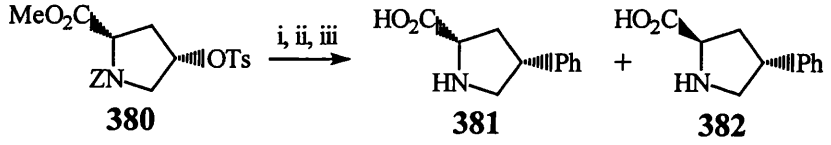
Scheme 70



(i) Boc_2O, KOH; (ii) BzCl, Et_3N; (iii) TsCl, pyridine; (iv) H_2, Pd-C; (v) PhLi, CuBr.DMS, Et_2O, THF, 0 °C, 1 hr, 90% overall, **378** 67%; (vi) TFA.

The overall yield of phenyl addition (**378** + **379**) was 90% with net retention of configuration at C-4 being observed for both products. A single crystallisation of the crude reaction mixture from chloroform gave pure *N*-Boc-*trans*-4-phenyl-L-proline **378** in 67% yield and this was deprotected with TFA. Furthermore, when the *cis* tosylate **380** was subjected to the same cuprate reaction conditions (Scheme 71), net retention of configuration was also observed giving the mixture of products **381** and **382** in 82% yield (**381**:**382** 2:3).

Scheme 71



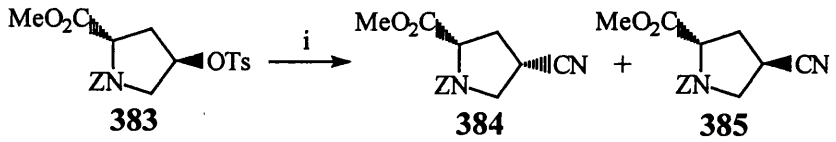
380 **381** **382**

(i) Ph_2CuLi; (ii) NaOH, H_2O; (iii) H_2, Pd-C, 82% for three steps.

Thottathil and Moniot propose that the D-imino acid products come from secondary reaction processes under the reaction conditions. (When pure **378** was treated with Ph_2CuLi in Et_2O/THF at 0 °C for 1 hr, a 2:1 mixture of **378** and **379** resulted).

Smith[123] *et al.* have disclosed that when **383**, the *trans* epimer of **380**, was exposed to KCN in the presence of dibenzo-16-crown-6 (Scheme 72), the cyano compounds **384** and **385** were produced in low yield (**384** 33%, **385** 15%).

Scheme 72



383 **384** **385**

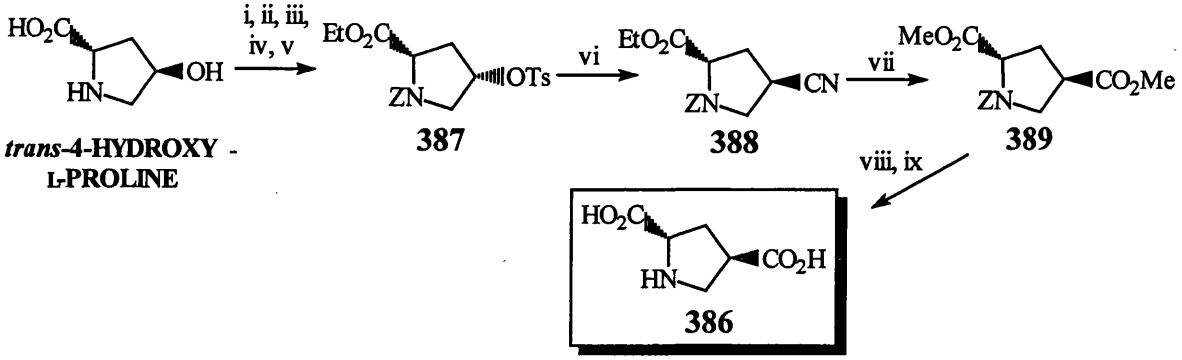
(i) KCN, dibenzo-18-crown-6, MeCN, reflux, 44 hrs, **384** 33%, **385** 15%.

In this case, the major product of the reaction has net inversion of configuration at C-4 and no D-imino acid production was observed. Smith *et al.* have exploited compound **383** as a precursor to several 4-substituted-L-prolines (such as ethers, sulfides, fluorides, and azides) under this chemistry.

In a separate report, Bridges[124] *et al.* publish a synthesis of *trans*-L-pyrrolidine-2,4-dicarboxylate **386** using similar chemistry to set the C-4 stereogenic centre (Scheme 73). Conversion of *trans*-4-hydroxy-L-proline to the *cis* tosyl compound **387** was realised in high overall yield (66%) under standard conditions. Treatment of **387** with NaCN in DMSO at elevated temperature formed **388** in 70% yield (cf Scheme 72). Pinner reaction of **388** gave the dimethyl ester **389**, which was triple deprotected to afford **386**. Using this synthetic approach, starting either from *trans*-4-hydroxy-L-

proline or *cis*-4-hydroxy-D-proline, the three other possible diastereomers of **386** can be produced in good yield.

Scheme 73

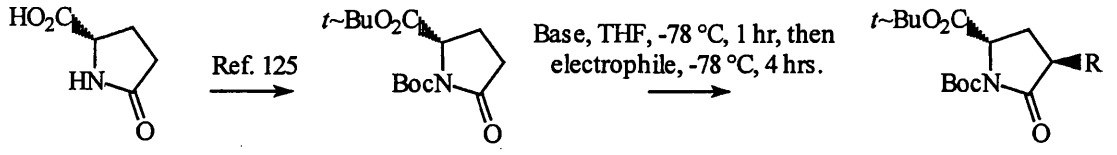


(i) BnO_2CCl, $NaHCO_3$, PhMe, H_2O, rt, 16 hrs, 98%; (ii) Jones reagent, acetone, isopropanol, rt, 2.5 hrs; (iii) $NaBH_4$, MeOH, H_2O, -5 °C, 20 hrs; (iv) *p*-TsOH, EtOH, reflux, 36 hrs, 83% for three steps; (v) *p*-TsCl, pyridine, rt, 7 days, 80%; (vi) NaCN, DMSO, 80 °C, 3 hrs, 70%; (vii) HCl, MeOH, rt, 4 days, 94%; (viii) NaOH, THF, H_2O, rt, 55 mins, 100%; (ix) H_2, 10% Pd-C, MeOH, Parr shaker bottle, 48-50 psi, 0.5 hrs, 75%.

L-Pyroglutamic acid has also proved useful in the synthesis of *trans*-4-alkyl-L-proline residues.

Baldwin[125] *et al.* have found that treatment of *N*-Boc-pyroglutamic acid *t*-butyl ester **390** with a lithium base in THF at low temperature followed by quench of the resulting enolate with an electrophile produces the *trans*-4-alkyl products **391** stereoselectively (Scheme 74)

Scheme 74



L-PYROGLUTAMIC ACID

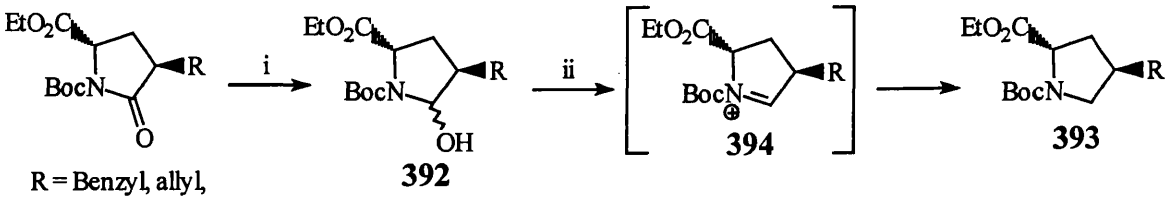
390

391

BASE	*ELECTROPHILE*	*PRODUCT*	*YIELD*
LDA	PhCHO	R = -(OH)CHPh	62%
LiHMDS	PhCHO	R = -(OH)CHPh	69%
LiCA	EtCHO	R = -(OH)Et	28%
LiHMDS	$H_2CCHCHO$	R = -(OH)$CHCH_2$	79%
LDA	BnBr	R = -Bn	51%
LDA	MeI	No alkylation	0%

The relatively low yields for these alkylations were due to competing processes, such as dialkylation (at C-4 and/or C-2) and ring cleavage. Of particular note was the failure of MeI to act as a suitable electrophile for this chemistry. Hon[126] *et al.*, Langlois[127] *et al.*, and Young[128] *et al.* have used this chemistry to produce several other 4-substituted-pyroglutamates. Hon[126] *et al.* also show that *trans* to *cis* interconversion can be realised under standard deprotonation/reprotonation conditions. Final conversion to the imino acid was best achieved by Pedregal and Runao[129] *et al.* by exposure of the *trans*-4-substituted-L-pyroglutamate to $LiEt_3BH$ in THF at low temperature followed by treatment of the crude hemiaminal **392** with BF_3-OEt_2 and Et_3SiH (Scheme 75).

Scheme 75



R = Benzyl, allyl, cyanomethyl.

392

394

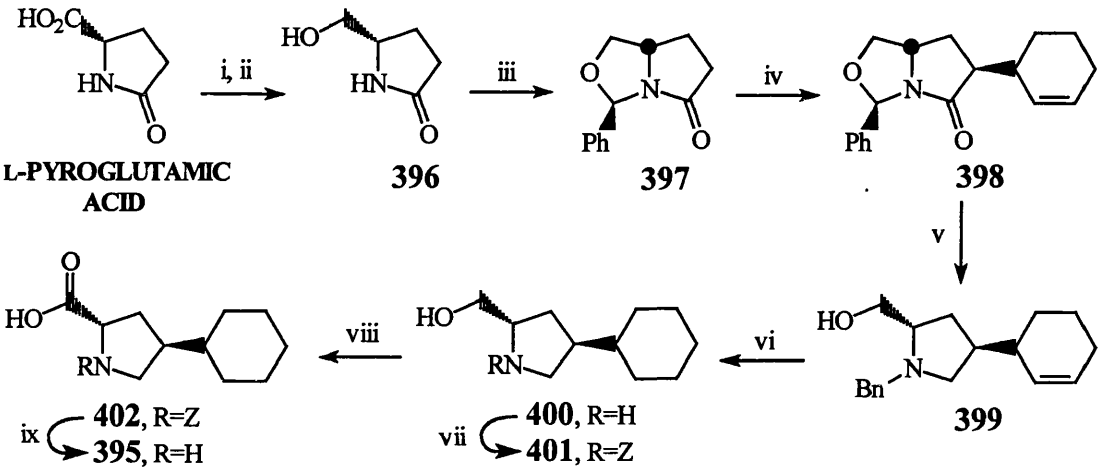
393

(i) $LiEt_3BH$, THF, -78 °C, 30 mins; (ii) Et_3SiH, DCM, -78 °C, then BF_3-OEt_2, DCM, -78 °C, 2 hrs, 70-85% for two steps.

The 4-alkyl prolines **393** thus formed, *via* the *N*-acyliminiums **394**, have been produced without affecting the stereochemical integrity of the molecule.

L-Pyroglutamic acid was used as the chiral template by Thottathil[130] *et al.* in the synthesis of *trans*-4-cyclohexyl-L-proline **395** (Scheme 76).

Scheme 76



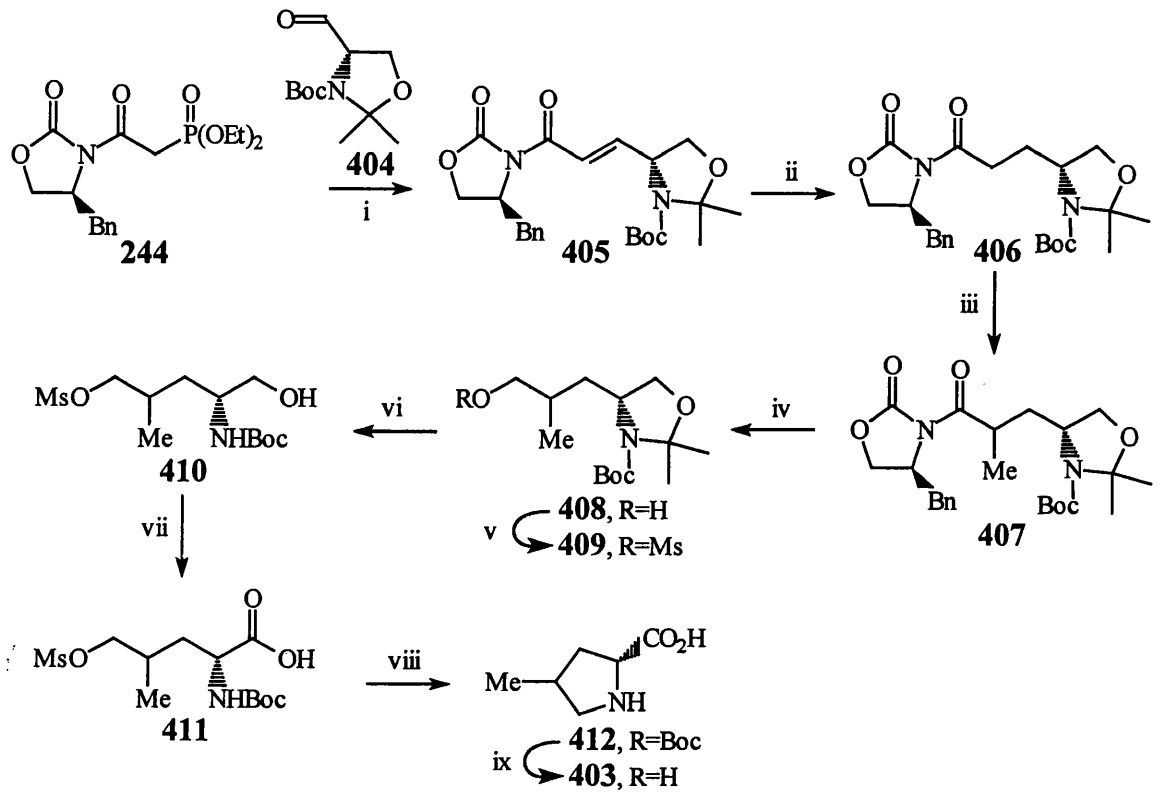
(i) ROH, acid; (ii) $NaBH_4$; (iii) PhCHO, *p*-TsOH, PhMe, reflux, Dean-Stark, 9 hrs, 86%; (iv) LDA, THF, -78 °C, 30 mins, then 3-bromocyclohexene, THF, -20 °C, 20 mins; (v) $LiAlH_4$, THF, reflux, 1 hr; (vi) H_2, 10% Pd-C, ethyl acetate, AcOH, rt, 45 psi, 2 hrs, 65% for three steps; (vii) ZCl, K_2CO_3, THF, H_2O, 0 °C, 15 mins; (viii) Jones reagent, acetone, -5 °C, 6 hrs; (ix) H_2, 10% Pd-C, MeOH, rt, 2 hrs, 78% for three steps.

Reaction of **396**, obtained from L-pyroglutamic acid, with benzaldehyde in PhMe heated at reflux gave the bicyclic *N,O*-acetal **397** as a single diastereomer. Alkylation of **397** in THF using LDA as the base and 3-bromocyclohexene as the electrophile afforded **398**. $LiAlH_4$ reduction followed by hydrogenolysis of **399** gave the fully reduced compound **400**. Temporary protection of the amine allowed for Jones oxidation of the alcohol **401** to the acid **402**, which was hydrogenated to cede *trans*-4-cyclohexyl-L-proline **395**.

3.3 The Hale Approach to 4-Methyl-D-Proline

Hale[131] *et al.* have shown that 4-methyl-D-proline **403** can be made starting with the Horner-Emmons-Wittig condensation of the phosphonate **244**[79] with the Garner aldehyde **404**[132] (Scheme 77)

Scheme 77



(i) **244**, Hünigs base, LiCl, MeCN, rt, 76 mins, then **404**, MeCN, rt, 5 hrs, 88%; (ii) H_2, 10% Pd-C, EtOH, rt, 2.5 hrs, 67%; (iii) LiHMDS, THF, MeI, -78 °C to 0 °C, 2 hrs, then 0 °C, 4.5 hrs, 75%; (iv) $LiEt_3BH$, THF, -78 °C, 3 hrs, 91%; (v) MsCl, Et_3N, DCM, rt, 19 hrs, 96%; (vi) PPTS, MeOH, rt, 8 hrs, 89%; (vii) $RuCl_3$, $NaIO_4$, CCl_4:H_2O:MeCN 2:2:3, rt, 1 hr, 75%; (viii) NaH, DMF, rt, 8 hrs; (ix) TFA, DCM, rt, 18 hrs, 100% for two steps.

Exposure of **405** to 10% Pd-C in EtOAc under H_2 allowed for hydrogenation of the enone in good yield. Alkylation of the LiHMDS derived enolate of **406** in THF with MeI afforded **407**. Owing to the presence of rotamers in **407** the degree of stereoselectivity of methylation could not be determined at this stage. Superhydride reduction of **407** in THF cleaved the chiral auxiliary and gave the alcohol **408**, which was converted to the mesylate **409** under standard conditions. The isopropylidene protecting group was removed by the action of PPTS in MeOH and the resulting alcohol **410** was oxidised to the acid **411** with $RuCl_3$ and $NaIO_4$ in a solution of CCl_4:H_2O:MeCN 2:2:3. Cyclisation of **411** was induced with NaH in DMF to give **412**, which was deprotected with TFA in DCM to afford 4-methyl-D-proline **403**. Although

this material appeared to be a single compound with spectral data consistant to *trans*-4-methyl-D-proline, conversion to the *N*-DNP derivative revealed that a 3.4:1 *cis*:*trans* mixture had been formed. Presumably, the nitrogen, and possibly the oxygen, of the Garner aldehyde moiety of **406** in someway chelates to lithium on enolate formation, thereby over-riding the directing effect of the oxazolidinone auxiliary and favouring the production of the *cis* compound.

3.4 Concluding Remarks

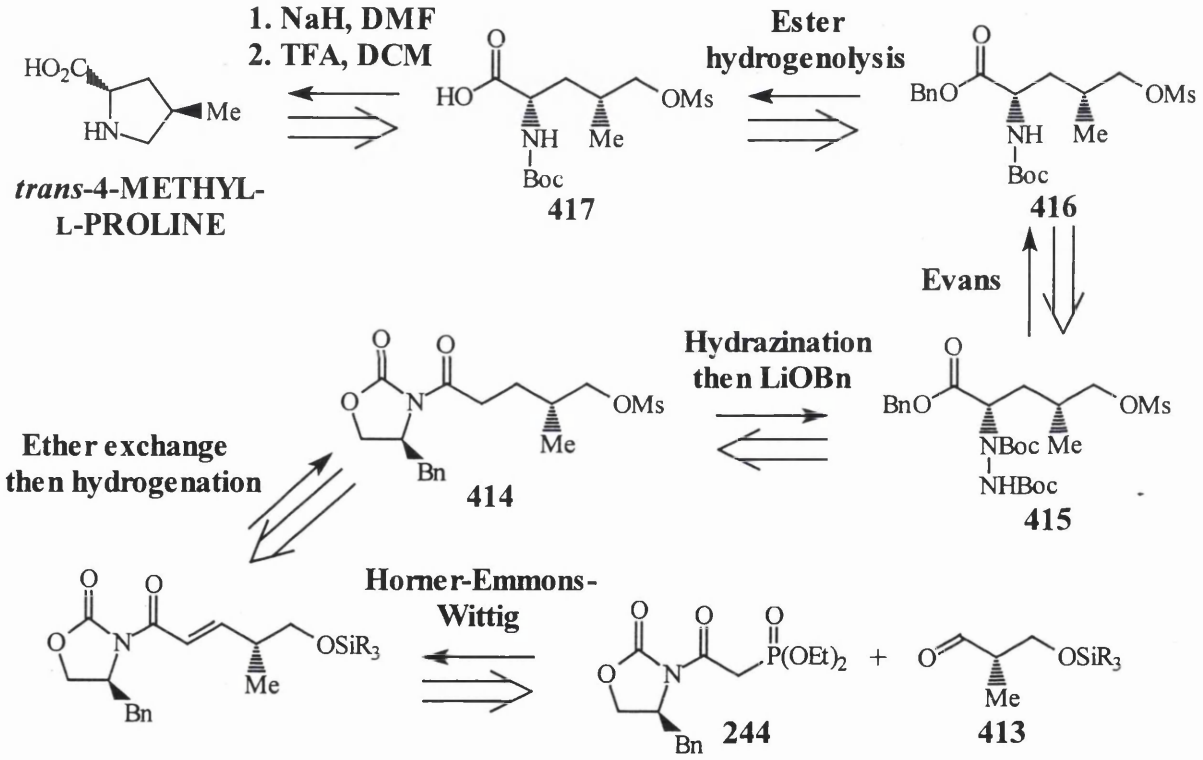
To build on the previous work in the group, it was decided develop a synthetic strategy to *trans*-4-methyl-L-proline which relied on the successful transformations already achieved.

CHAPTER 4
trans-4-Methyl-L-Proline: Results and Discussion

4.0 Reterosynthesis

Our retrosynthesis of this deceptively simple molecule starts with Horner-Emmons-Wittig condensation of the known aldehyde **413**[76] with the known phosphonate **244**[79] (Scheme 78).

Scheme 78



Silyl ether to mesyl ester interconversion followed by hydrogenation would give **414**. A chiral auxiliary directed hydrazination reaction with di-*t*-butyl azodicarboxylate (DBAD) followed by cleavage of the oxazolidinone with LiOBn would afford the ester **415** diastereoselectively. Under the conditions of Evans[133], treatment of **415** with TFA in DCM then Raney Ni hydrogenolysis followed by reprotection would yield the *N*-Boc amine **416**. Ester hydrogenolysis of **416** would afford the acid **417**, the enantiomer of the key intermediate **411** (Scheme 77) in the Hale *et al.* synthesis of 4-methyl-D-proline.

Cyclisation with NaH in DMF then TFA/DCM deprotection should then cede *trans*-4-methyl-L-proline.

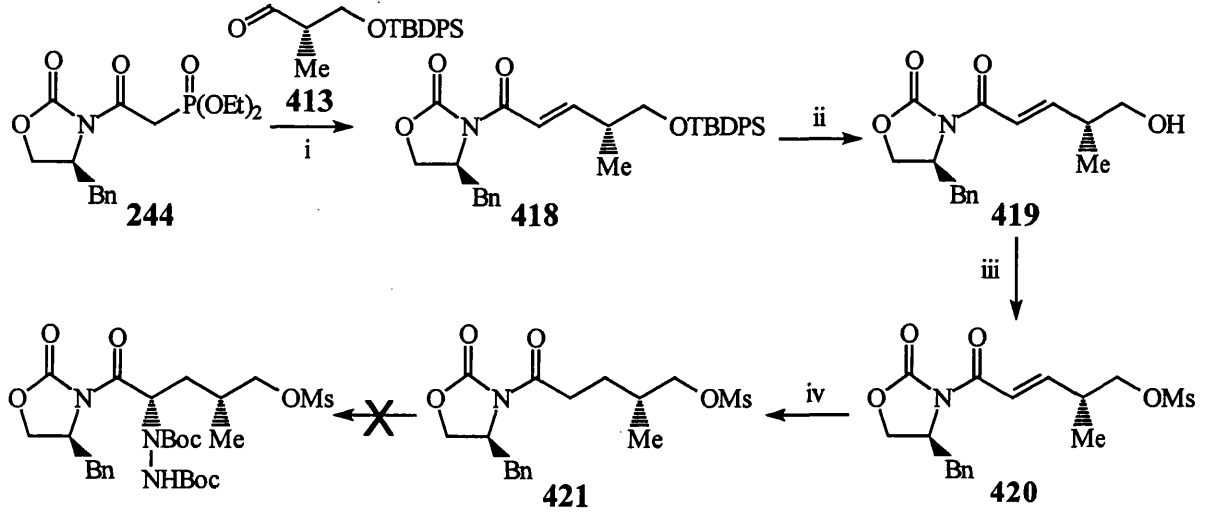
Both the starting materials were synthesised during the course of our work on the Pseudopterosins (**244** Scheme 35, *ent*-**413** Scheme 33).

In this retrosynthesis the C-4 stereogenic centre of *trans*-4-methyl-L-proline is derived from the chiral pool and the C-2 stereocentre is set in a chiral auxiliary directed hydrazination reaction. By building the molecule this way, it should be possible to avoid the production of C-4 diastereomers as observed in our earlier work (in this case the *N*-acyl side of **414** chain does not contain competing chelation sites). Futhermore, careful use of the two starting materials **244** and **413** *and* their enantiomers should allow for the asymmetric synthesis of the four possible diastereomers of 4-methyl-proline.

4.1 Syntheses of 414 and Attempted Hydrazination

Horner-Emmons-Wittig condensation of **244** with **413** afforded **418** as a single diastereomer in good yield (Scheme 79).

Scheme 79



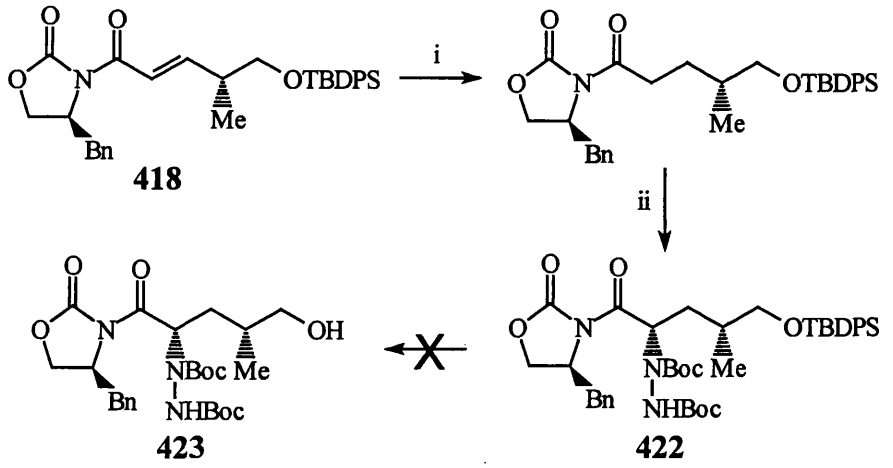
(i) **244**, LiCl, Hünigs base, MeCN, rt, 10 mins, then **413**, MeCN, rt, 13 hrs, 86%; (ii) 40% (aq) HF, MeCN:THF 1:1, rt, 24 hrs, 97%; (iii) MsCl, Et_3N, DCM, 0 °C, 31 mins, 94%; (iv) H_2, 10% Pd-C, MeOH, rt, 13.5 hrs, 97%.

Exposure of **418** to 40% (aq) HF in MeCN/THF for 24 hrs effected clean desilylation and the resulting alcohol **419**[81] was mesylated under standard conditions to cede **420**. Hydrogenation of **420** gave the hydrazination precursor **421** in virtually quantitative yield. The ir spectrum of **421** contained peaks at 1777 and 1697 cm^{-1} indicative of the $O(C=O)CH_2$ and O(C=O)N carbonyl groups respectively, with a peak in the HRMS at 370.1337 ($C_{17}H_{24}NO_6S$ $[MH]^+$ requires *m/z* 370.1324) and $[\alpha]_D^{24}$ +37.8 (c=0.25 in DCM).

Unfortunately, hydrazination of **421** was unsuccessful using either LDA or LiHMDS as the base for enolate formation. Complete consumption of **421** to several products was observed (tlc) with both bases, presumably owing to competing deprotonation on the methyl group of the mesylate.

As a way around this a route in which hydrazination preceded silyl ether to mesyl ether interconversion was investigated. To this end, hydrogenation of **418** followed by hydrazination using LDA gave the *N,N'*-Boc-hydrazino compound **422** (Scheme 80), as characterised *inter alia* by a peak in the HRMS at *m/z* 782.3840 ($C_{42}H_{57}N_3O_8Si$ $[MNa]^+$ requires *m/z* 782.3813).

Scheme 80



(i) H_2, 10% Pd-C, MeOH, rt, 2 hrs; (ii) LDA, THF, -78 °C, 32 mins, then DBAD, DCM, -78 °C, 49 mins, 78% for two steps.

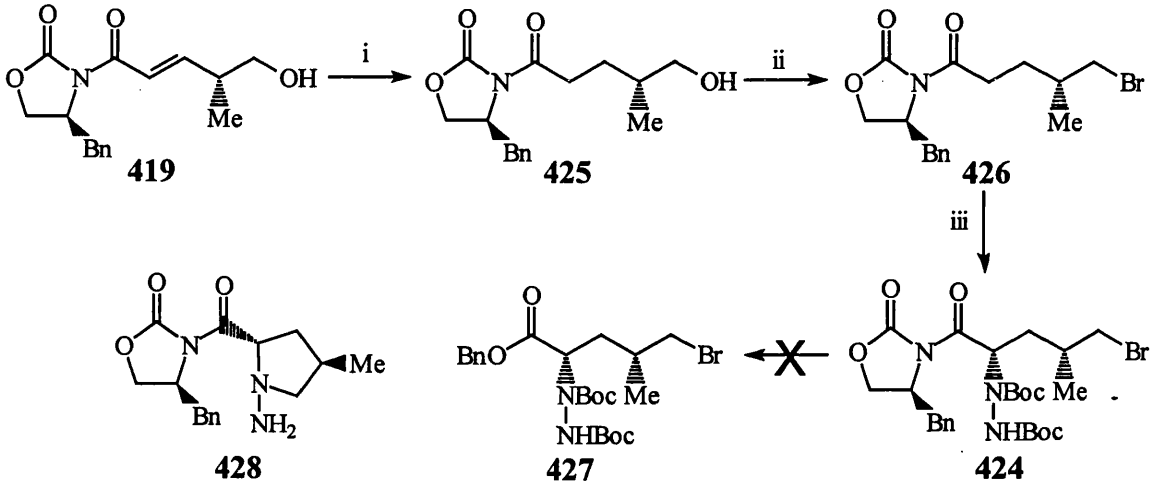
Unfortunately, desilylation with either TBAF in THF or 40% (aq) HF in MeCN/THF gave rise to several products (tlc) and failed to yield the desired alcohol **423**.

With these results in mind, it was decided to adopt a synthetic route to a cyclisation precursor having an alternative leaving group to OMs.

4.2 Synthesis of the Bromide 424

Hydrogenation of **419** afforded the alcohol **425**, which was brominated using CBr_4/Ph_3P in THF to cede the hydrazination precursor **426**[81] (Scheme 81).

Scheme 81



(i) H_2, 10% Pd-C, EtOAc, rt, 32 mins, 99%; (ii) CBr_4, Ph_3P, THF, rt, 37 mins, 83%; (iii) LDA, THF, -78 °C, 1 hr, then DBAD, DCM, -78 °C, 1 hr, 90%.

Exposure of **426** to LDA in THF at low temperature followed by enolate quench with DBAD in DCM afforded **424** in excellent yield – the HRMS (FAB) found *m/z* 606.1811; $C_{26}H_{38}BrN_3O_7Na$ $[MNa]^+$ requires *m/z* 606.1791.

In keeping with the original plan, LiOBn mediated cleavage of the oxazolidinone was attempted but to no avail. It appeared that competing bromide displacement and/or elimination precluded the synthesis of **427**.

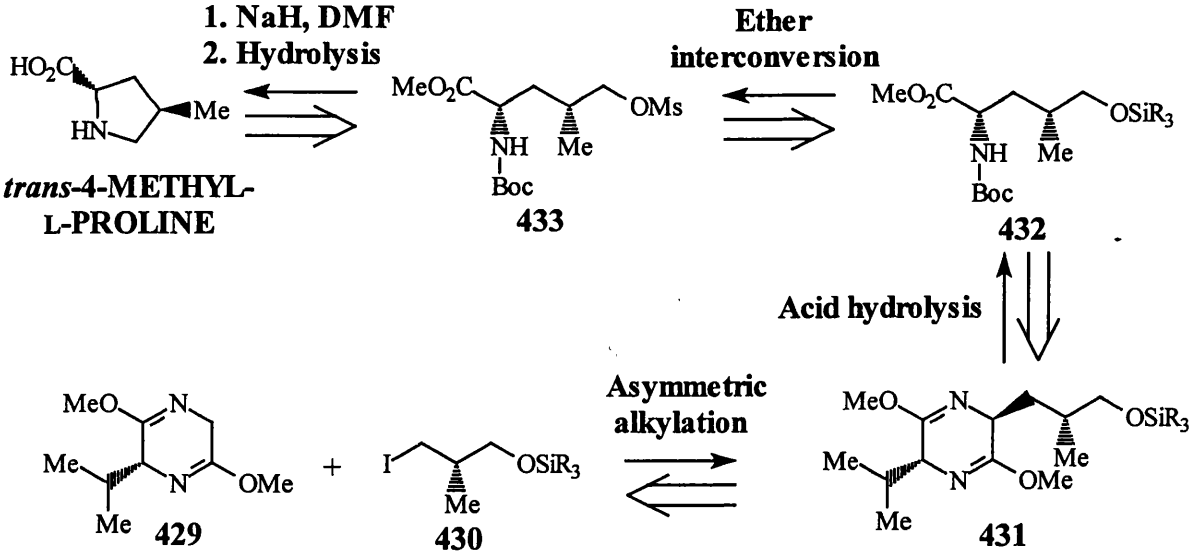
It was expected that exposure of **424** to TFA in DCM followed by mild base conditions ($NaHCO_3$ in DCM/H_2O) would afford the bicyclic compound **428**. Unfortunately, this proved not to be the case.

Given the series of difficulties encountered with this chemistry, specifically the failure to make **415** (Scheme 78), it was decided to investigate a new synthetic route to *trans*-4-methyl-L-proline.

4.3 New Retrosynthesis

The approach of Schöllkopf[134] *et al.* for the synthesis of α-amino acids was adopted in this new retrosynthesis (Scheme 82).

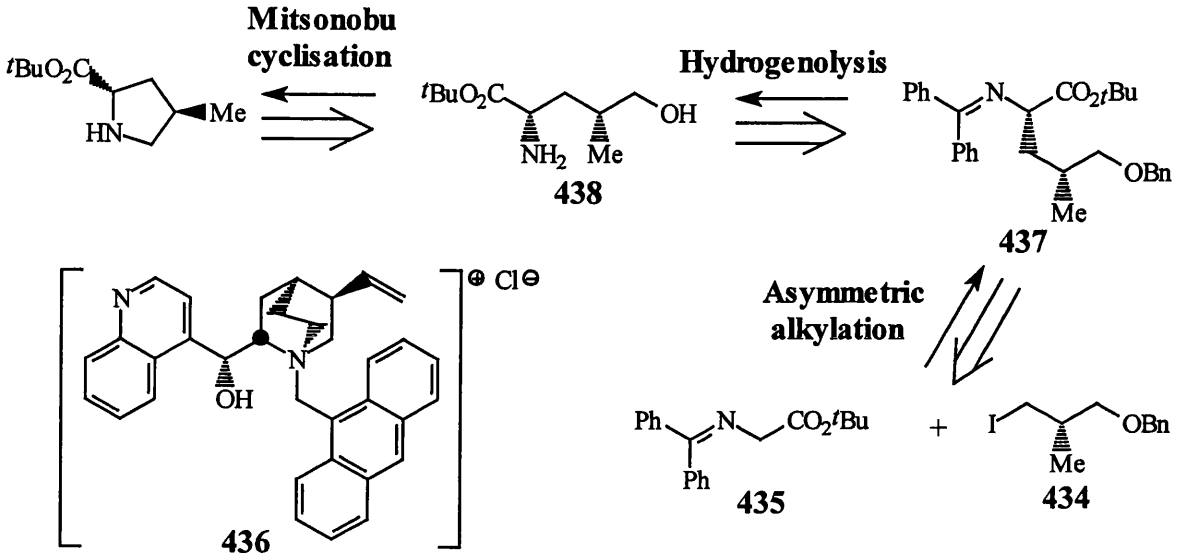
Scheme 82



Alkylation of the bis-lactim ether **429**[135] (derived from D-valine) with the iodide **430**[136] should afford **431** diastereoselectively. Acid hydrolysis of **431** would give **432**, after *N*-Boc protection. Silyl to mesyl ester interconversion would result in the cyclisation precursor **433**. Exposure of **433** to NaH in DMF followed by acid hydrolysis would afford *trans*-4-methyl-L-proline.

Similarly, the Schiff Base asymmetric alkylation chemistry of O'Donnell[137] *et al.* (as extended by Lygo[138] *et al.*, Corey[139] *et al.*, and Katsuki[119] *et al.*) could be used to set the imino acid stereogenic centre of *trans*-4-methyl-L-proline (Scheme 83).

Scheme 83



Alkylation of the iodide **434**[140] to the imine **435**[137] in the presence of the (-)-cinconidine derived catalyst **436**[138] would result in the formation of **437** with good diastereoselectivity. Hydrogenation of **437** would give the aminol **438**, which could be cyclised under Mitsu nobu conditions to afford *trans*-4-methyl-L-proline *t*-butyl ester.

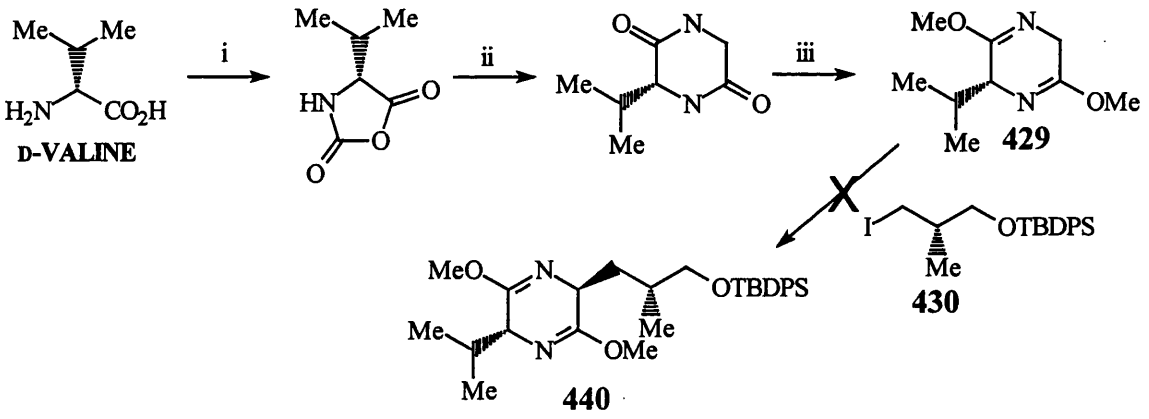
In principle, either of these proposed routes could give an efficient and expedient synthesis of *trans*-4-methyl-L-proline.

4.4 The Schöllkopf Approach

The bis-lactim ether **429** was produced from D-Valine according to Schöllkopf[135] *et al.* in good overall yield (Scheme 84). Treatment of **429** with *n*-BuLi in THF at low temperature followed by the iodide **430**, prepared from (*S*)-(-)-hydroxymethylpropionc acid methyl ester (Scheme 85), failed to deliver the desired

product **440**. After aqueous work-up, both the bis-lactim ether **429** and the iodide **430** were recovered cleanly.

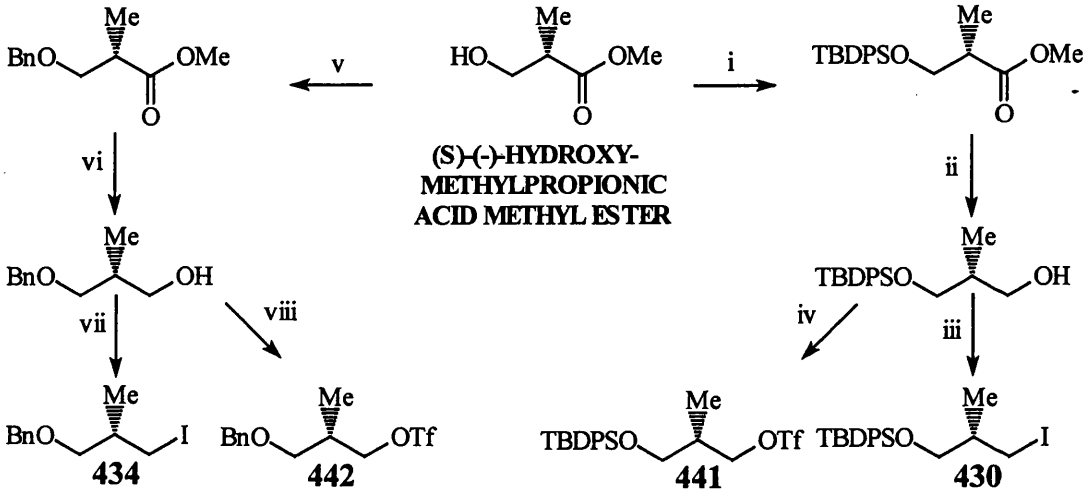
Scheme 84



(i) Phosgene, THF, PhMe, 40 °C, 2 hrs, then rt, 1 hr; (ii) $HO_2CCH_2NH_2.HCl$, Et_3N, $CHCl_3$, -70 °C, 3 hrs, then PhMe, reflux, 14 hrs, 92% for two steps; (iii) $[Me_3O]BF_4$, DCM, rt, 3 days, 100%.

Alkylation with the triflate **441**[141] was also found to be unsuccessful and these results were mirrored by the benzyl protected congeners **434**[140] and **442**[142] (Scheme 85).

Scheme 85



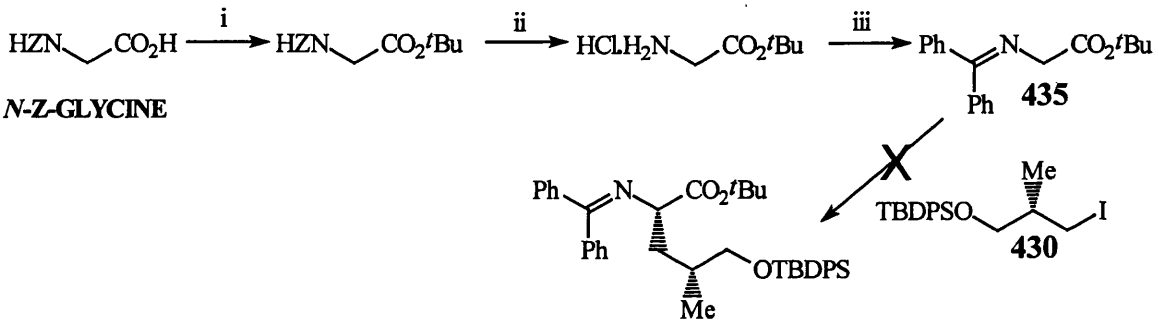
(i) TBDPSCl, Et_3N, DMAP, DCM, rt, 15 hrs; (ii) DIBAL, DCM, 0 °C, 41 mins, 86% for two steps; (iii) I_2, Ph_3P, imidazole, PhMe, rt, 2 hrs, 93%; (iv) Tf_2O, Et_3N, DCM, rt, used crude; (v) Benzyl 2,2,2-trichloroacetimidate, TFA, cyclohexane, DCM, rt, 23 hrs; (vi) DIBAL, DCM, 0 °C, 38 mins, 86% for two steps; (vii) I_2, Ph_3P, imidazole, PhMe, rt, 59%; (viii) Tf_2O, Et_3N, DCM, rt, 2 hrs, used crude.

It appears that the branching methyl group in the electrophiles presents a sufficient steric block to alkylation and it was decided to investigate the O'Donnell-Lygo-Corey approach for the synthesis of *trans*-4-methyl-L-proline.

4.5 The O'Donnell-Lygo-Corey Approach

The known glycine imine **435** was made according to O'Donnell[137] in excellent yield (Scheme 86).

Scheme 86

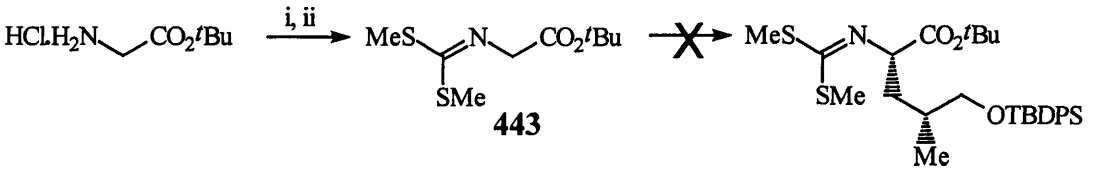


(i) Isobutylene, conc. H_2SO_4, DCM, rt, -78 °C, then rt, 5 days, 91%; (ii) H_2, 10% Pd-C, EtOH, rt, 19.5 hrs, then conc. HCl, 91%; (iii) Benzophenone imine, DCM, rt, 36 hrs, 66%.

Attempted alkylation under the phase-transfer conditions of Lygo[138] *et al.* with the iodide **430** failed to effect unification of the two materials. When the triflate **441** was used in the reaction the alcohol *ent*-**238** (Scheme 35) was produced virtually quantitatively.

In order to increase the nucleophilicity of the imine component, the dithiol imine **443** of Hoppe[143] *et al.* was investigated as an alkylation precursor, again without success (Scheme 87).

Scheme 87



(i) CS_2, Et_3N, $CHCl_3$, rt, 1.5 hrs, then MeI, reflux, 1.5 hrs; (ii) Crude residue, K_2CO_3, MeI, acetone, reflux, 2 hrs, 63% for two steps.

As with the Schöllkopf approach, it appears that the presence of a branching methyl group presents an adequate barrier to alkylation.

4.6 Conclusions and Future Work

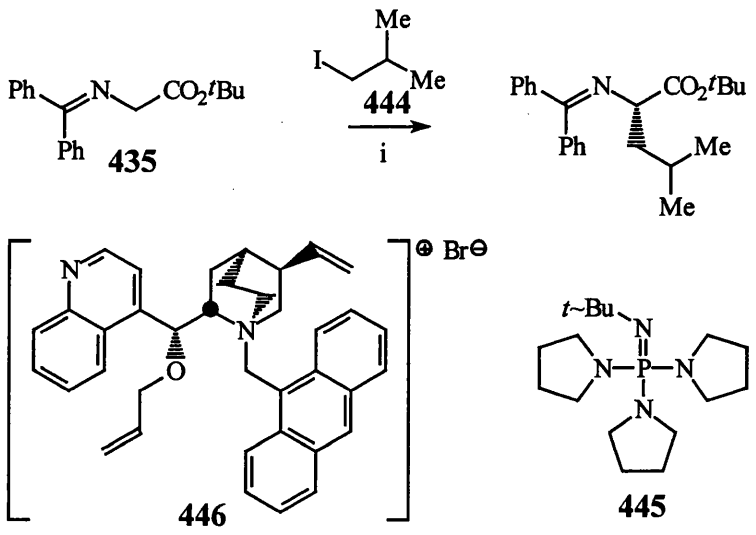
Four routes *inter alia* to *trans*-4-methyl-L-proline were investigated during the course of this work.

Unfortunately, the hydrazino route, used in our earlier work on the synthesis of 4-methyl-D-proline, was unfruitful in this case. Though both stereogenic centres could be set to the correct absolute configuration using this chemistry, cyclisation to the imino acid was found to be problematic.

In our hands, the O'Donnell-Lygo-Corey approach did not allow for the synthesis of *trans*-4-methyl-L-proline, though our work highlighted the problem of using β-branched alkyl iodides as the electrophilic component for alkylation.

Shortly after this work was completed O'Donnell[144] *et al.* reported the efficient asymmetric (ee > 97%) alkylation of the imine **435** with the alkyl iodide **444** under *homogenous* reaction conditions using the Schwesinger base **445**[145] in the presence of the cinchonidine derived catalyst **446** (Scheme 88).

Scheme 88



(i) DCM, -50 °C, 24 hrs, 97%.

By using the iodide **441** in this reaction, the O'Donnell-Lygo-Corey approach could still furnish *trans*-4-methyl-L-proline.

CHAPTER 5
EXPERIMENTAL SECTION

5.0 Experimental Techniques

^{1}H nmr spectra were recorded on the following spectrometers; Brüker AMX 300 (300 MHz), Varian VXR 400 (400 MHz), Brüker AMX 400 (400 MHz), and Brüker AMX 500 (500 MHz). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane. Abbreviations used in the description of multiplicities are: s (singlet), d (doublet), t (triplet), q (quartet), app (apparent), m (multiplet), and br (broad). Coupling constants (*J*) are quoted to the nearest 0.5 Hz (for 300 and 400 MHz spectra) and 0.1 Hz (for 500 MHz spectra).

^{13}C nmr spectra were recorded on the following spectrometers; Brüker AMX 300 (75.4 MHz), Varian VXR 400 (100.5 MHz), Brüker AMX 400 (100.5 MHz), and Brüker AMX 500 (125.8 MHz).

Peaks in the nmr data were assigned with the aid of COSY (correlated spectroscopy), DEPT (distortionless enhancement through polarisation transfer), and C-H correlation spectra where obtained.

Infrared (ir) spectra were recorded on a Perkin-Elmner 1600 Series FTIR spectrophotometer, where adsorption maxima are given in wavenumbers (cm^{-1}) and are classified as s (strong), m (medium), w (weak), and br (broad).

Mass spectra (MS) were recorded on the following machines; FAB and CI, VG ZAB-SE, and EI, VG-7070. *m/z* values are reported in Daltons with the percentage abundance in parentheses.

High resolution mass spectra (HRMS) were recorded at The London School of Pharmacy.

Combustion analyses were determined in the department.

Optical rotations were measured on a Polaar AA Series automatic polarimeter and the specific rotation $[\alpha]_D^t$ of the sample is quoted at concentration c (g/100ml) and temperature t (°C).

Melting points were determined on a Reichert Hotstage Microscope apparatus and are corrected.

Thin layer chromatography (tlc) was performed on Merck 12 PLC 20x20cm silca gel 60 F_{254} 0.2mm precoated plates. Product spots were visualised by the quenching of UV fluoresence (if appropriate) then stained and heated with one, some, or all of the following solutions: (i) 5% (w/v) *dodeca*-molybdophosphoric acid in ethanol, (ii) *p*-Anisaldehyde (15ml), sulfuric acid (15ml), and acetic acid (15ml) in EtOH (250ml), (iii) 0.3% ninhydrin in *n*-BuOH with 3% acetic acid, (iv) 0.5% (aq) $PdCl_2$ with a drop of conc HCl, and (v) 0.5% 2,4-dinitrophenylhydrazine in 2M (aq) HCl.

Preparative layer chromatography was performed on Merck 12 PLC 20x20cm silca gel 60 F_{254} 2.0mm precoated plates

Flash chromatography purification was performed on Fluka silica gel 60 for column chromatography for flash chromatography according to the method of Still[146] *et al.* using the solvent systems given.

All solvents were purified and distilled by standard procedures[147] before use. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 60-80 °C.

For radical reactions, benzene and toluene were degassed by passing a rapid flow of nitrogen through the solvent for 30-60 mins before use, depending on scale, and the purity of tri-*n*-butyltin hydride was ascertained to be approx 80% by proton nmr (by

comparison of the intensity of the SnH peak with the relative intensity of the butyl peaks).

S-(-)- and *R*-(+)-Hydroxymethylpropionic acid methyl ester (Sigma) were dried from benzene prior to use (3 x Xml of benzene per Xml of reagent).

All other reagents were used as supplied by the manufacturers.

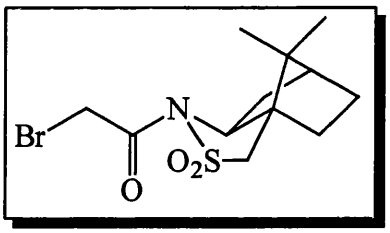
All known compounds were made as promulgated, are referenced, and gave identical spectral data to that reported.

(1*S*,6*S*)-6-Methyl-3-cyclohexene-1-carboxylate **287**[99] was synthesised under novel conditions and the data is given for information.

Reactions were conducted under an inert (nitrogen) atmosphere, at balloon pressure, using three-way taps, unless otherwise stated.

Experimental Procedures

(7*R*)-2-Bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone



To a stirred solution of (7*R*)-10,10-dimethyl-3-thia-4-aza-tricyclo[5.2.1.0^{0,0}]decane 3,3-dioxide (1.14g, 5.30mmol) in THF (50ml) at 0 °C was added NaH (60% dispersion in oil, 318mg, 7.95mmol) over 10 mins. The ice/water bath was removed and stirring was continued for 1 hr during which time the reaction mixture heated to rt. Bromoacetyl chloride (0.89ml, 10.63mmol) was then added dropwise over 20 mins. The resulting mixture was stirred at rt for 1.5 hrs. The reaction mixture was quenched carefully with

H_2O (100ml) and extracted (3x100ml DCM). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 20:1→10:1→5:1) to afford the title compound as a clear oil (1.62g, 91%).

R_f 0.31 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.95 (3H, s, Me-10), 1.13 (3H, s, Me-10), 1.31-1.43 (2H, m), 1.83-1.92 (3H, m), 2.05 (1H, dd, *J* 7.5, 13.0, NCHC**H**α), 2.09-2.13 (1H, m, NCHC**H**β), 3.44 (1H, d, *J* 14.0, NSO_2CH**H**), 3.49 (1H, d, *J* 14.0, NSO_2C**H**H), 3.89 (1H, dd, *J* 5.0, 7.5, C**H**N), 4.17 (1H, d, *J* 13.0, BrCH**H**), 4.30 (1H, d, *J* 13.0, BrC**H**H).

δ_C (100.5 MHz Varian, $CDCl_3$) 19.84 (Me-10), 20.70 (Me-10), 26.39 (**C**H_2), 32.75 (**C**H_2), 32.81 (**C**H_2), 37.89 (**C**H_2), 44.76 (**C**H), 47.85, 48.97, 52.66 (**C**H_2), 65.42 (**C**H), 164.46 (**C**O).

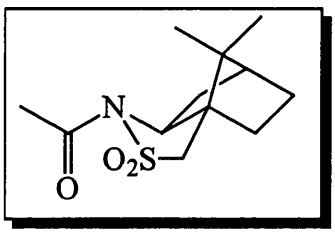
ν_{max} (thin film) 3050-2950 (s, C-H), 1702 (s, C=O), 1457 (w), 1381 (s), 1314 (w), 1255 (m), 1171 (m, SO_2-N), 1098 (m, S=O), 849 (w), 751 (w).

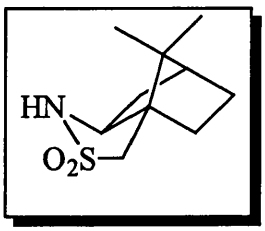
m/z (FAB) 358/360 ([M($^{79/81}$Br)Na]$^+$, 15), 336/338 ([M($^{79/81}$Br)H]$^+$, 100), 307 (15), 289 (17), 228 (16), 216 (45%).

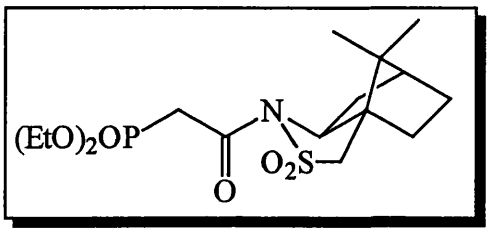
HRMS (FAB) found *m/z* 336.0279; $C_{12}H_{19}BrNO_3S$ $[MH]^+$ requires *m/z* 336.0269.

$[\alpha]_D^{24}$ -29.4 (c=0.30 in DCM).

(7*R*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone 242, (7*R*)-10,10-dimethyl-3-thia-4-aza-tricyclo[5.2.1.0^{0,0}]decane 3,3-dioxide 243, and (7*R*)-[2-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-2-oxo-ethyl]-phosphonic acid diethyl ester 241[78]







A stirred solution of (7*R*)-2-Bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone (420mg, 1.25mmol) in $POEt_3$ (236μl, 1.38mmol) was heated at 150 °C for 21 hrs. After cooling to rt, the reaction mixture was diluted with EtOAc (100ml) and washed with H_2O (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→5:1→0:1) to afford (7*R*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone **242** as a white crystaline solid (121mg, 43%), (7*R*)-10,10-dimethyl-3-thia-4-aza-tricyclo[5.2.1.0^{0,0}]decane **243** as a white crystaline solid (90mg, 33%), and (7*R*)-[2-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-2-oxo-ethyl]-phosphonic acid diethyl ester **241** as a clear oil (29mg, 6%).

(7*R*)-1-(10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone 242

R_f 0.38 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.93 (3H, s, Me-10), 1.11 (3H, s, Me-10), 1.30-1.37 (2H, m), 1.83-1.88 (3H, m), 2.02 (1H, dd, *J* 7.5, 14.0, NCHC**H**α), 2.09-2.10 (1H, m,

NCHCHβ), 2.33 (3H, s, **Me**CO), 3.38 (1H, d, *J* 14.0, NSO_2CHH), 3.45 (1H, d, *J* 14.0, NSO_2CHH), 3.80 (1H, dd, *J* 5.0, 7.5, **CH**N).

δ_C (100.5 MHz Varian, $CDCl_3$) 19.82 (Me-10), 20.76 (Me-10), 23.13 (**Me**CO), 26.38 (CH_2), 32.76 (CH_2), 38.33 (CH_2), 44.58 (**CH**), 47.69, 48.31, 52.69 (CH_2), 65.9 (**CH**), 168.52 (**CO**).

ν_{max} (KBr disc) 3050-2830 (s, C-H), 1688 (s, C=O), 1513 (w), 1456 (m), 1426 (m), 1378 (m), 1326 (s, SO_2), 1293 (s), 1250 (s), 1167 (m, SO_2–N), 1140 (m), 1116 (m), 1090 (m), 1040 (m), 986 (m), 878 (w), 839 (w), 768 (m).

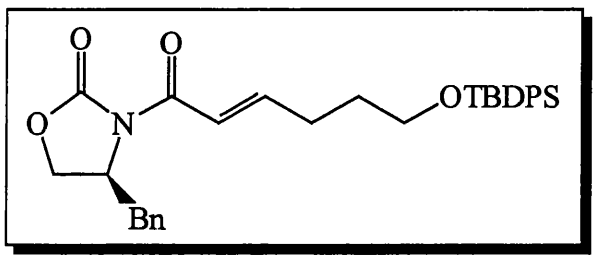
m/z (FAB) 280 ($[MNa]^+$, 12), 258 ($[MH]^+$, 100), 214 (11), 135 (20), 93 (10%).

HRMS (FAB) found *m/z* 258.1171; $C_{12}H_{20}NO_3S$ $[MH]^+$ requires *m/z* 258.1164.

$[\alpha]_D^{19}$ -62.8 (c=0.28 in DCM).

mp 135-137 °C.

(4*S*,2'*E*)-4-Benzyl-3-[6'-(*t*-butyl-diphenyl-silanyloxy)-hex-2'-enoyl]-oxazolidin-2-one 246



To a stirred solution **244**[79] (3.59g, 11.02mmol) in MeCN (10ml) containing LiCl (933mg, 22.02mmol) at rt was added Hünigs base (9.60ml, 55.06mmol) over 1 min and the resulting mixture was stirred at rt for 5 mins. A solution of 4-(*t*-butyl-diphenyl-silanyloxy)-butaldehyde **245**[145] (5.86g, 16.52mmol) in MeCN (10ml) was then added dropwise over 2 mins and the resulting mixture was stirred at rt for 2 days. The reaction mixture was diluted with Et_2O (200ml), washed with 10% (aq) HCl (200ml), and then

satd (aq) NaCl (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as an orange, yellow oil (5.42g, 93%).

R_f 0.37 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.73-1.80 (2H, m, $CH_2\mathbf{CH_2}CH_2OSiR_3$), 2.39-2.46 (2H, m, $\mathbf{CH_2}CH_2CH_2OSiR_3$), 2.78 (1H, dd, *J* 9.5, 13.5, PhCH**H**), 3.32 (1H, dd, *J* 3.0, 13.5, PhC**H**H), 3.71 (2H, appt, *J* 3.0, $\mathbf{CH_2}OSiR_3$), 4.13-4.21 (2H, m, $\mathbf{CH_2}O(CO)$), 4.70-4.74 (1H, m, C**H**N), 7.19-7.68 (17H, m, Ph superimposing alkenic protons).

δ_C (100.5 MHz Varian, $CDCl_3$) 19.16 ($\mathbf{C}Me_3$), 26.08 ($C\mathbf{Me_3}$), 29.27 ($\mathbf{C}H_2CH_2CH_2OSiR_3$), 30.96 ($CH_2\mathbf{C}H_2CH_2OSiR_3$), 37.84 ($Ph\mathbf{C}H_2$), 55.25 (**C**HN), 63.00 ($\mathbf{C}H_2OSiR_3$), 66.02 ($\mathbf{C}H_2O(CO)$), 120.37, 127.24, 128.87, 129.39, 129.50, 129.55, 133.72, 135.34, 135.49, 151.48, 153.34, 164.94.

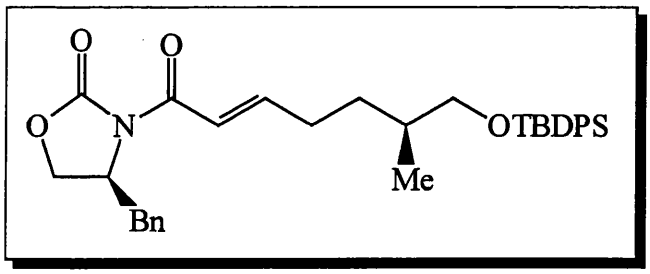
ν_{max} (thin film) 3070-2850 (s, C-H), 1783 (s, N(C=O)CH), 1682 (s, O(C=O)N), 1635 (s, HC=CH), 1537 (w), 1473 (m), 1428 (m), 1388 (s), 1357 (s), 1288 (s), 1211 (s), 1107 (s), 1007 (s), 823 (m), 738 (s), 704 (s), 613 (s).

m/z (FAB) 550 ($[MNa]^+$, 36), 464 (89), 450 (100), 416 (9), 351 (29), 293 (71), 230 (30%).

HRMS (FAB) found *m/z* 550.2377; $C_{32}H_{37}NO_4Si$ $[MNa]^+$ requires *m/z* 550.2390.

$[\alpha]_D^{17}$ +83.8 (c=0.22 in DCM).

(4*S*,2'*E*,6'*S*)-4-Benzyl-3-[7'-(*t*-butyl-diphenyl-silanyloxy)-6'-methyl-hept-2'-enoyl]-oxazolidin-2-one 247



To a stirred solution **244**[79] (13.7g, 38.5mmol) in MeCN (50ml) containing LiCl (3.28g, 77.17mmol) at rt was added Hünigs base (33.8ml, 192.6mmol) over 10 min and the resulting mixture was stirred at rt for 30 mins. A solution of **230**[76](15.0g, 42.38mmol) in MeCN (50ml) was then added dropwise over 10 mins and the resulting mixture was stirred at rt for 18 hrs. The reaction mixture was diluted with Et_2O (200ml), washed with 10% (aq) HCl (100ml), and then satd (aq) NaCl (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a clear oil (19.3g, 82%).

R_f 0.54 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.97 (3H, d, *J* 6.5, Me), 1.09 (9H, s, *t*-Bu), 1.32-1.35 (1H, m, C**H**Me), 1.58-1.71 (2H, m, C**H**$_2$CHMe), 2.23-2.31 (2H, m, C**H**$_2$CHCH), 2.78 (1H, dd, *J* 9.5, 13.5, PhCH**H**), 3.33 (1H, dd, *J* 3.0, 13.5, PhC**H**H), 3.45-3.52 (2H, m, C**H**$_2$OSiR$_3$), 4.14-4.21 (2H, m, C**H**$_2$O(CO)), 4.70-4.74 (1H, m, C**H**N), 7.15-7.69 (17H, m, Ph superimposing alkenic protons).

δ_C (100.5 MHz Varian, $CDCl_3$) 16.69 (**Me**CH), 19.33 (**C**Me$_3$), 26.92 (C**Me**$_3$), 38.43 (**C**H$_2$CHCH), 42.47 (CH$_2$**C**H$_2$CHMe), 42.65 (**C**HMe), 37.88 (Ph**C**H$_2$), 55.31 (**C**HN), 66.07 (**C**H$_2$OSiR$_3$), 68.46 (**C**H$_2$O(CO)), 120.25, 127.28, 127.63, 127.69, 128.93, 129.46, 129.57, 129.68, 133.87, 135.61, 152.00, 168.08.

ν_{max} (thin film) 3070-2850 (s, C-H), 1781 (s, N(C=O)CH), 1682 (m, O(C=O)N), 1634 (m, HC=CH), 1455 (w), 1428 (m), 1389 (m), 1355 (m), 1211 (m), 1112 (s), 1030 (m), 824 (w), 741 (m), 702 (s).

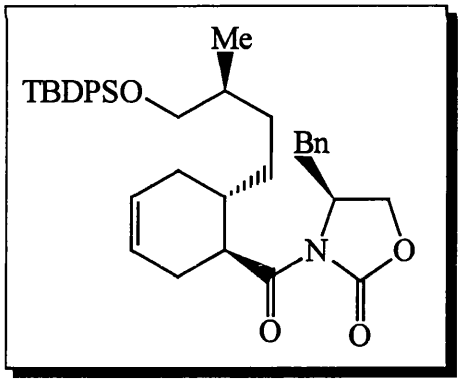
m/z (FAB) 578 ($[MNa]^+$, 4), 498 ($[M-(t\text{-Bu})]^+$, 45), 478 (67), 321 (11), 259 (13), 199 (63), 135 (100), 91 (35%).

HRMS (FAB) found *m/z* 556.2862; $C_{34}H_{42}NO_4Si$ $[MH]^+$ requires *m/z* 556.2883.

Combustion analysis found C 73.43, H 7.33, N 2.54; $C_{34}H_{41}NO_4Si$ requires C 73.48, H 7.44, N 2.52.

$[\alpha]_D^{21}$ +31.5 (c=0.43 in DCM).

(4*S*,1'*S*,6'*S*,3''*S*])-4-Benzyl-3-{6'-[4''-(*t*-butyl-diphenyl-silanyloxy)-3''-methyl-butyl]-cyclohex-3'-enecarbonyl}-oxazolidin-2-one 248



To freshly condensed 1,3-butadiene (approx 8ml, approx 150mmol) at -40 °C was added **247** (8.3g, 14.95mmol) in DCM (81ml) over 10 mins. Me_2AlCl (1.0M in hexanes, 74.77ml, 74.77mmol) was then added over 10 mins. The resulting mixture was stirred at -10 °C for 3 days. The reaction mixture was diluted with DCM (500ml) and quenched at 0 °C with 10% (aq) Rochelles salt (500ml). The quenched reaction mixture was stirred vigorously for 1.5 hrs during which time it heated to rt. The now clear layers were separated and the aqueous layer was extracted (3x500ml DCM). The combined organic

layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1) to afford the title compound as a clear oil (6.59g, 72%).

R_f 0.63 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.91 (3H, d, *J* 5.5, Me), 1.05 (9H, s, *t*-Bu), 1.10-2.40 (10H, m), 2.75 (1H, dd, *J* 9.5, 13.5, PhCH**H**), 3.23 (1H, dd, *J* 3.0, 13.5, PhC**H**H), 3.45 (1H, dd, *J* 6.0, 10.0, CH**H**OSiR_3), 3.49 (1H, dd, *J* 5.5, 10.0, C**H**HOSiR_3), 3.75-3.80 (1H, m, CH_2C**H**(CO)), 4.01 (1H, dd, *J* 7.5, 9.0, BnCHCH**H**(CO)), 4.11 (1H, dd, *J* 3.0, 9.0, BnCHC**H**H(CO)), 4.55-4.65 (1H, m, C**H**N), 5.70 (2H, apps, **H**C=C**H**), 7.19-7.67 (15H, m, Ph).

δ_C (100.5 MHz Brucker, $CDCl_3$) 17.28 (CH**Me**), 19.26 (**C**Me_3), 26.82 (C**Me**$_3$), 28.76 (**C**H_2), 29.66 (**C**H_2), 30.05 (**C**H_2), 31.48 (**C**H_2), 35.15 (**C**H), 35.99 (**C**H), 37.79 (Ph**C**H_2), 42.93 (CH_2**C**H(CO)), 55.30 (**C**HN), 65.85 (CH**C**H_2(CO)), 68.34 (**C**H_2OSiR_3), 124.49, 126.12, 127.29, 127.53, 128.86, 129.42, 133.75, 134.75, 135.22, 135.55, 152.97, 176.44.

ν_{max} (thin film) 3030-2850 (s, C-H), 1781 (s, N(C=O)CH), 1696 (s, N(C=O)O), 1462 (m), 1429 (m), 1385 (s), 1205 (s), 1108 (s), 938 (w), 823 (m), 740 (m), 702 (s), 661 (m).

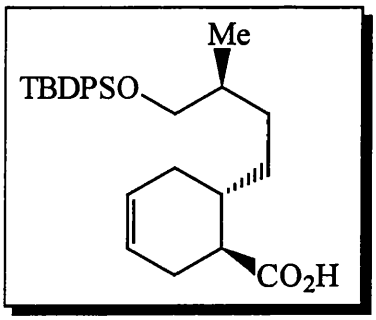
m/z (FAB) 632 ($[MNa]^+$, 100), 552 ($[M-(t\text{-Bu})]^+$, 9), 199 (37), 135 (52), 91 (42%).

HRMS (FAB) found *m/z* 610.3372; $C_{38}H_{48}NO_4Si$ $[MH]^+$ requires *m/z* 610.3353.

Combustion analysis found C 74.48, H 7.79, N 2.10; $C_{38}H_{47}NO_4Si$ requires C 74.84, H 7.77, N 2.30.

$[\alpha]_D^{21}$ +16.1 (c=0.41 in DCM).

(1*S*,6*S*,3'*S*)-6-[4'-(*t*-Butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enecarboxylic acid 249



To a stirred solution of **248** (5.59g, 8.91mmol) in THF (81ml) and H_2O (81ml) at rt was added LiOH (95%, 1.94g, 44.55mmol) and H_2O_2 (8.1ml, 89.12mmol) in single portions. The resulting mixture was stirred at rt for 18 hrs. The reaction mixture was acidified to pH = 2 with cHCl and extracted (3x100ml DCM). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 3:1→1:1) to afford the title compound as a clear oil (4.12g, 99%) and as a ~7:1 mixture of diastereoisomers and (4*S*)-4-benzyl-oxazolidin-2-one as a white crystaline solid (1.62g, 88%).

R_f 0.42 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.89 (3H, d, *J* 6.5, Me), 1.04 (9H, s, *t*-Bu), 1.60-1.72 (6H, m), 1.86-1.90 (1H, m), 2.21-2.39 (4H, m, $CH_2CH{=}CHCH_2$), 3.44 (1H, dd, *J* 5.5, 10.0, $CHHOSiR_3$), 3.47 (1H, dd, *J* 5.5, 10.0, $CHHOSiR_3$), 5.64 (2H, apps, HC=CH), 7.24-7.66 (10H, m, Ph), (minor diastereomer; 0.86 (d, *J* 6.5)).

δ_C (100.5 MHz Brucker, $CDCl_3$) 17.10 (CHMe), 19.32 (CMe_3), 26.88 (CMe_3), 27.57 (CH_2), 29.48 (CH_2), 30.03 (CH_2), 31.39 (CH_2), 34.92 (CH), 36.00 (CH), 44.97 ($CHCO_2H$), 68.50 (CH_2OSiR_3), 124.35 (=CH), 126.05 (=CH), 127.56 (Ph), 129.49 (Ph), 134.04 (Ph), 135.61 (Ph), 182.7 (C=O), (minor diastereomer; 26.55, 27.84, 29.54, 34.46, 35.52, 127.71, 129.58, 129.60, 129.64, 134.01, 134.78).

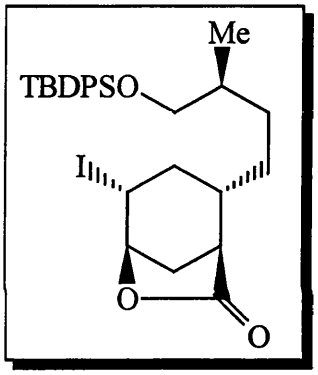
ν_{max} (thin film) 3800-2850 (s, O-H and C-H), 1704 (s, C=O), 1465 (m), 1428 (m), 1251 (m), 1200 (m), 1108 (s), 941 (w), 823 (m), 740 (m), 702 (s).

m/z (FAB) 473 ($[MNa]^+$, 51), 433 ($[MH-(H_2O)]^+$, 3), 355 (3), 315 (69), 239 (11), 199 (82), 135 (100), 91 (78%).

HRMS (FAB) found *m/z* 451.2651; $C_{28}H_{39}O_3Si$ $[MH]^+$ requires *m/z* 451.2668.

$[\alpha]_D^{19}$ +56.5 (c=0.29 in DCM).

(1*S*,2*S*,4*R*,5*R*,3'*S*)-2-[4'-(*t*-Butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-4-iodo-6-oxa-bicyclo[3.2.1]octan-7-one 250



To a stirred solution of **249** (4.1g, 9.23mmol) in DCM (852ml) and H_2O (52ml) at 0 °C in a flask open to air and protected from light was added $NaHCO_3$ (2.36g, 27.68mmol), KI (2.25g, 13.85mmol), and I_2 (3.49g, 13.85mmol) in single portions. The resulting mixture was stirred at 0 °C for 3 hrs. The reaction mixture was diluted with Et_2O (200ml) and washed with satd (aq) Na_2SO_3 (200ml), and then satd (aq) NaCl (200ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 30:1) to afford the title compound as a clear oil (4.42g, 85%).

R_f 0.70 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.87 (3H, d, *J* 7.0, Me), 1.01 (9H, s, *t*-Bu), 1.40-1.50 (2H, m, CH_2CH_2CHMe), 1.60-1.70 (1H, m, CH_2CH_2CHMe), 1.7-1.8 (2H, m,

CH_2CH_2CHMe), 1.97-2.01 (2H, m, H-5β and H-6), 2.15-2.25 (1H, H-2α), 2.52-2.63 (2H, m, H-1 and H-2β), 2.75 (1H, d, *J* 12.5, H-5α), 3.44-3.52 (2H, m, CH_2SiOR_3), 4.32-4.37 (1H, m, H-4), 4.81-4.86 (1H, m, H-3), 7.31-7.63 (10H, m, Ph).

δ_C (100.5 MHz Brucker, $CDCl_3$) 16.51 (**Me**CH), 19.09 (CMe_3), 19.61 (**C**H), 26.99 (CMe_3), 27.8 (CH_2), 29.70 (CH_2), 30.70 (CH_2), 32.02 (CH_2), 34.45 (**C**H), 35.27 (**C**H), 41.88 (**C**H), 68.37 (CH_2OSiR_3), 81.26 (**C**HI), 127.49 (Ph), 129.42 (Ph), 133.70 (Ph), 135.41 (Ph), 178.36 (**C**O).

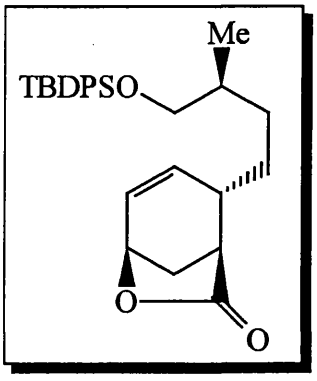
ν_{max} (thin film) 3000-2850 (s, C-H), 1787 (s, C=O), 1464 (m), 1319 (w), 1157 (s), 1108 (s), 963 (w), 906 (w), 820 (w), 740 (w), 702 (s).

m/z (FAB) 599 ($[MNa]^+$, 4), 577 ($[MH]^+$, 18), 519 ($[M-(t\text{-Bu})]^+$, 31), 499 (100), 421 (24), 393 (26), 373 (88), 361 (22), 349 (17), 338 (23), 315 (85%).

HRMS (FAB) found *m/z* 577.1645; $C_{28}H_{38}IO_3Si$ $[MH]^+$ requires *m/z* 577.1635.

$[\alpha]_D^{19}$ +8.6 (c=0.23 in DCM).

(1*S*,2*S*,5*R*,3'*S*)-2-[4'-(*t*-Butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-6-oxa-bicyclo[3.2.1]oct-3-en-7-one 251



To a stirred solution of **250** (4.4g, 7.54mmol) in DCM (125ml) at rt was added DBU (1.26ml, 8.30mmol) dropwise over 5 mins. The resulting mixture was heated at reflux for 24 hrs. After cooling to rt, the reaction mixture was diluted with EtOAc (200ml) and washed with H_2O (200ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in*

vacuo. The residue was purified by flash column chromatography (petrol:ethyl acetate; 30:1) to afford the title compound as a clear oil (3.21g, 95%).

R_f 0.53 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.90 (3H, d, *J* 6.5, Me), 1.05 (9H, s, *t*-Bu), 1.18-1.27 (1H, m, $CH_2CH\mathbf{H}CHMe$), 1.40-1.48 (2H, m, $C\mathbf{H}_2CH_2CHMe$), 1.51-1.60 (1H, m, $CH_2C\mathbf{H}HCHMe$), 1.61-1.67 (1H, m, C**H**Me), 2.07 (1H, d, *J* 11.0, H-2β), 2.26-2.31 (1H, m, H-2α), 2.40-2.45 (1H, m, H-6), 2.71-2.74 (1H, m, H-1), 3.48 (2H, d, *J* 6.0, $C\mathbf{H}_2OSiR_3$), 4.70-4.72 (1H, appt, *J* 5.5, H-3), 5.74 (1H, dd, *J* 3.5, 9.5, H-5), 6.15 (1H, m, H-4), 7.34-7.66 (10H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) 16.76 (**Me**CH), 19.31 (**C**Me_3), 26.89 (C**Me**$_3$), 30.38 ($\mathbf{C}H_2CH_2CHMe$), 31.00 ($CH_2\mathbf{C}H_2CHMe$), 31.07 (C-2), 35.64 (**C**HMe), 38.73 (C-6), 42.15 (C-1), 68.43 ($\mathbf{C}H_2OSiR_3$), 73.76 (C-3), 127.61 (Ph), 128.54 (C-5), 129.58 (Ph), 133.84 (Ph), 134.76 (C-4), 135.59 (Ph), 179.61 (**C**O).

ν_{max} (thin film) 3050-2850 (s, C-H), 1777 (s, C=O), 1633 (w), 1590 (w), 1465 (m), 1428 (m), 1388 (m), 1330 (m), 1181 (m), 1145 (s), 1110 (s), 1014 (m), 956 (m), 907 (m), 821 (m), 742 (s), 703 (s), 613 (s).

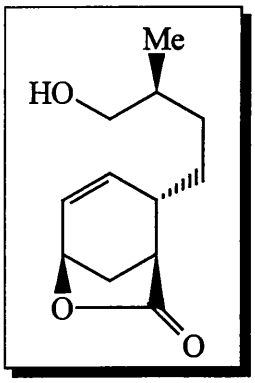
m/z (FAB) 499 (25), 479 (46), 449 ($[MH]^+$, 23), 421 ($[(MH)-(CO)]^+$, 18), 403 ($[M-(CO_2H)]^+$, 391 ($[M-(t\text{-}Bu)]^+$, 30), 371 (28), 353 (19), 347 (37), 327 (21), 319 (33), 313 (100%).

HRMS (FAB) found *m/z* 449.2506; $C_{28}H_{37}O_3Si$ $[MH]^+$ requires *m/z* 449.2512.

$[\alpha]_D^{20}$ +33.4 (c=0.45 in DCM).

(1*S*,2*S*,5*R*,3'*S*)-2-[4'-Hydroxy-3'-methyl-butyl]-6-oxa-bicyclo[3.2.1]oct-3-en-7-one

252



To **251** (790mg, 1.75mmol) at rt was added TBAF (1.0M in THF, 5.33ml, 5.24mmol) dropwise over 30 secs. The resulting mixture was stirred at rt for 4 hrs then *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→1:1) to afford the title compound as a clear oil (354mg, 96%).

R_f 0.28 (petrol:ethyl acetate; 1:1).

δ_H (500 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.7, Me), 1.21-1.31 (2H, m), 1.41-1.59 (3H, m) 1.60-1.71 (1H, m, C**H**Me), 2.14 (1H, d, *J* 11.4, H-2β), 2.35 (1H, appddd, *J* 5.2, 11.4, 16.5, H-2α), 2.49-2.52 (1H, m, H-6), 2.80 (1H, dd, *J* 1.2, 5.2, H-1), 3.49 (1H, dd, *J* 3.8, 10.5, CH**H**OH), 3.53 (1H, d, *J* 6.0, 10.5, C**H**HOH), 4.76 (1H, appt, *J* 8.5, H-3), 5.79 (1H, dd, *J* 3.4, 9.5, H-5), 6.20-6.23 (1H, m, H-4).

δ_C (125.8MHz, $CDCl_3$) 16.42 (**Me**CH), 30.41 (**C**H_2), 31.01 (**C**H_2), 31.08 (C-2), 35.67 (**C**HMe), 38.71 (C-6), 42.10 (C-1), 67.97 (**C**H_2OH), 73.76 (C-3), 128.75 (C-5), 134.67 (C-4), 179.53 (**C**O).

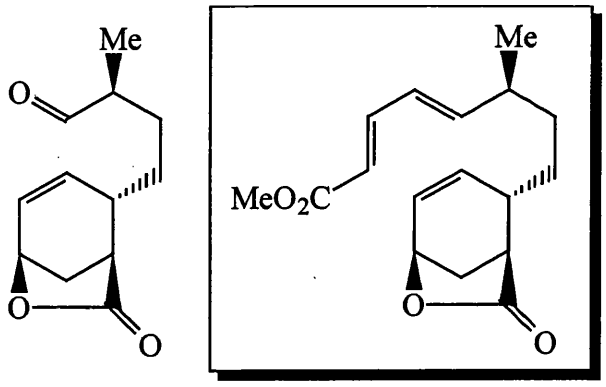
ν_{max} (thin film) 3410 (br s, O-H), 3050-2850 (s, C-H), 1765 (s, C=O), 1462 (m), 1250 (m), 1109 (s), 845 (m), 702 (s).

m/z (FAB) 211 ($[MH]^+$, 7), 176 (12), 154 (100), 136 (48), 125 (10), 109 (13%).

HRMS (FAB) found *m/z* 211.1335; $C_{12}H_{19}O_3$ $[MH]^+$ requires *m/z* 211.1334.

$[\alpha]_D^{22}$ +113.3 (c=0.17 in DCM).

(2*E*,4*E*,6*S*,1'*S*,2'*S*,5'*R*)-6-Methyl-8-(7'-oxo-6'-oxa-bicyclo[3.2.1]oct-3'-en-2'-yl)-octa-2,4-dienoic acid methyl ester 259



To a stirred solution of DMSO (4.2ml, 58.78mmol) in DCM (38ml) at -78 °C was added oxalyl chloride (3.7ml, 41.94mmol) dropwise over 2 mins. The resulting mixture was stirred at -78 °C for 31 mins. A solution of **252** (1.75g, 8.39mmol) in DCM (38ml) was then added dropwise over 3 mins. The resulting mixture was stirred at -78 °C for 31 mins. Et_3N (29.4ml, 209.7mmol) was then added over 2 mins and the CO_2/acetone bath was removed. The resulting mixture was stirred for 17 mins. The reaction mixture was quenched with H_2O (100ml) and extracted (3x100ml DCM). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 5:1→1:1) to afford a clear oil presumed to be the aldehyde **253** (1.65g, 95%). To a stirred solution of phosphonate **258**[90] (2.90g, 6.56mmol) in MeCN (33.6ml) containing LiCl (585mg, 11.96mmol) at rt was added Hünigs base (5.2ml, 29.96mmol) dropwise over 2 mins. The resulting mixture was stirred at rt for 30 mins. A solution of aldehyde **253** (1.25g, 5.99mmol) in MeCN (33.6ml) was then added dropwise over 8 hrs. The resulting mixture was stirred at rt for 48 hrs. The reaction mixture was diluted with EtOAc (100ml) and washed with 10% (aq) HCl (100ml), and then satd (aq) NaCl (200ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column

chromatography (petrol:ethyl acetate; 10:1→7:1) to afford the title compound as a clear oil (698mg, 40%).

R_f 0.73 (petrol:ethyl acetate; 1:1).

δ_H (400 MHz Varian, $CDCl_3$) 1.00 (3H, d, *J* 6.5, **Me**CH), 1.34-1.45 (4H, m), 2.04 (1H, d, *J* 11.0, H-2β), 2.20-2.28 (1H, ddd, *J* 5.0, 11.0, 16.5, H-2α, superimposing 1H, m, MeC**H**), 2.37-2.40 (1H, m, H-6), 2.67 (1H, dd, *J* 1.5, 5.0, H-1), 3.67 (3H, s, CO_2**Me**), 4.67 (1H, appt, *J* 5.5, H-3), 5.67-5.70 (1H, m, H-5), 5.75 (1H, d, *J* 15.5, CHCHCHC**H**CO_2Me), 5.89 (1H, dd, *J* 6.0, 15.5, C**H**CHCHCHCO_2Me), 6.09 (1H, dd, *J* 6.0, 10.5, CHC**H**CHCHCO_2Me), 6.12-6.15 (1H, m, H-4), 7.18 (1H, dd, *J* 10.5, 15.5, CHCHC**H**CHCO_2Me).

δ_C (100.5 MHz Varian, $CDCl_3$) 19.90 (**Me**CH), 30.62 (**C**H_2), 30.95 (**C**H_2), 34.23 (**C**H_2), 37.15 (**C**H), 38.41 (C-6), 42.12 (C-1), 51.35 (CO_2**Me**), 73.71 (C-3), 119.22 (=**C**H), 127.06 (=**C**H), 128.74 (=**C**H), 134.18 (=**C**H), 144.91 (=**C**H), 158.31 (=**C**H), 167.43 (**C**O_2Me), 179.39 (**C**O_2CH).

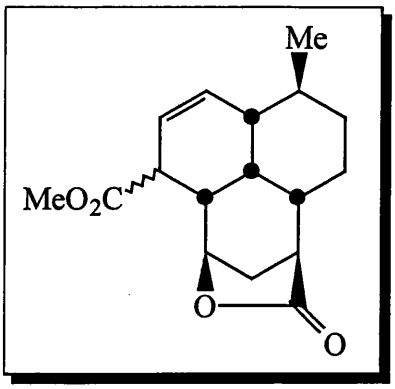
ν_{max} (thin film) 2860-2300 (m, C-H), 1774 (s, (C=O)OCH), 1716 (s, (C=O)OMe), 1641 (s, C=C), 1438 (m), 1257 (s), 1145 (s), 1009 (s), 954 (s), 907 (m), 759 (m).

m/z (FAB) 313 ($[MNa]^+$, 8), 291 ($[MH]^+$, 41), 259 (46), 231 (13), 213 (10), 185 (17), 145 (32), 107 (56), 91 (100%).

HRMS (FAB) found *m/z* 313.1406; $C_{17}H_{22}O_4Na$ $[MNa]^+$ requires *m/z* 313.1416.

$[\alpha]_D^{19}$ +69.9 (c=0.29 in DCM).

Possible tricycle 260



A solution of **259** (32mg, 0.11mmol) in PhMe (20ml) was transferred to an Ace pressure tube under N_2 and the tube was sealed tightly. The sealed tube was heated at 120 °C for 60 hrs and then at 190-200 °C for 60 hrs. After cooling to rt, the sealed tube was opened carefully and the reaction mixture was *conc in vacuo*. The residue was purified by preparatory plate chromatography (petrol:ethyl acetate; 3:1) to afford a residue which was purified by flash column chromatography (petrol:ethyl acetate; 3:1) to afford the title compound as a clear oil (3mg, 8%) and as a ~3:1 mixture of diastereoisomers.

R_f 0.45 (petrol:ethyl acetate; 3:1).

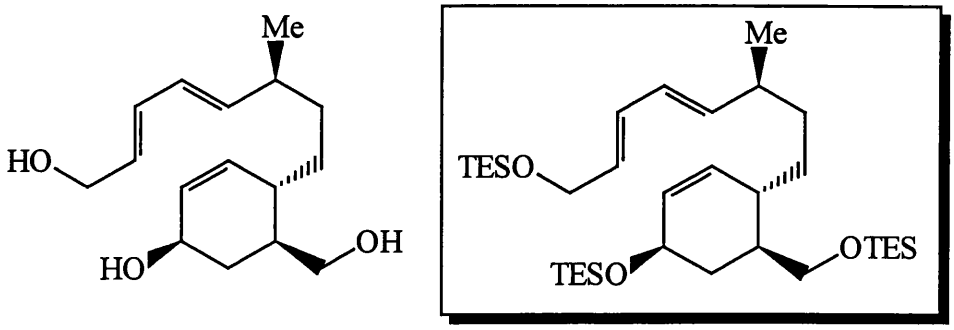
δ_H (400 MHz Varian, $CDCl_3$) 1.00 (3H, d, *J* 6.5, **Me**CH), 1.06-1.30 (2H, m), 1.73-2.38 (8H, m), 2.70-2.83 (2H, m), 3.19-3.23 (1H, m), 3.72 (3H, s, CO_2**Me**), 4.65-4.68 (1H, m), 5.98-6.03 (1H, m), 6.17-6.21 (1H, m), (minor diastereomer, 1.04 (d, *J* 6.5), 3.77 (s, CO_2**Me**)).

ν_{max} (thin film) 3382 (br s, wet sample), 2860-2300 (m, C-H), 1779 (s, (C=O)OCH), 1735 (s, (C=O)OMe), 1458 (m), 1158 (s).

m/z (APCI, NH_3) 291 ($[MH]^+$, 23), 259 (30), 245 (42), 231 (19), 213 (10), 185 (100), 149 (12%).

HRMS (FAB) found *m/z* 313.1430; $C_{17}H_{22}O_4Na$ $[MNa]^+$ requires *m/z* 313.1416.

(3*S*,4*S*,6*R*,3'*S*,4'*E*,6'*E*)-3-[3'-Methyl-8'-(triethyl-silanyloxy)-octa-4',6'-dienyl]-4-(triethyl-silanyloxymethyl)-6-(triethyl-silanyloxy)-cyclohexene 267



To a stirred solution of **259** (361mg, 1.25mmol) in DCM (26ml) at -78 °C was added DIBAL (1.5M in hexanes, 4.9ml, 7.48mmol) dropwise over 4 mins. The CO_2/acetone bath was replaced with an ice/water bath and the resulting mixture was stirred for 30 mins. The reaction mixture was cooled to -78 °C and quenched carefully with 10% (aq) Rochelles salt (100ml). The resulting mixture was diluted with DCM (75ml) and stirred vigorously for 1 hr during which time it heated to rt. The now clear layers were separated and the aqueous layer was extracted (3x50ml EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo* to afford a clear oil presumed to be the triol **266** (259mg, 78%). To a stirred solution of **266** (259mg, 0.97mmol) in DCM (20ml) containing imidazole (332mg, 4.87mmol) at 0 °C was added a solution of TESCl (0.33ml, 1.95mmol) in DCM (5ml) dropwise over 3 mins. The resulting mixture was stirred at 0 °C for 46 mins. The reaction mixture was diluted with Et_2O (100ml) and poured onto ice cold H_2O (100ml). The aqueous layer was extracted (1x100ml Et_2O) and the combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 1:0→30:1) to afford the title compound as a clear oil (378mg, 66%).

R_f 0.64 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.45-0.54 (18H, m, $SiCH_2CH_3$), 0.71-0.88 (30H, m, $SiCH_2CH_3$ superimposing **Me**CH), 1.02-1.43 (6H, m), 1.83-2.00 (3H, m), 3.32 (1H, dd, *J* 7.0, 10.0, saturated CH**H**OTES), 3.57 (1H, dd, *J* 4.0, 10.0, saturated C**H**HOTES), 4.06 (2H, d, *J* 5.5, unsaturated CH_2OTES), 4.10-4.14 (1H, m, C**H**OTES), 5.35-6.10 (6H, m, alkenic protons).

δ_C (75.4 MHz, $CDCl_3$) 4.37, 4.43, 4.83, 5.75, 6.45, 6.72, 6.76, 6.79, 20.69 (**Me**CH), 30.74 (CH_2), 33.22 (CH_2), 36.05 (CH_2), 36.60 (CH), 37.14 (CH), 39.80 (CH), 63.29 (CH_2OTES), 65.19 (CH_2OTES), 67.73 (CHOTES), 128.00 (=CH), 128.12 (=CH), 130.04 (=CH), 130.65 (=CH), 131.90 (=CH), 140.16 (=CH).

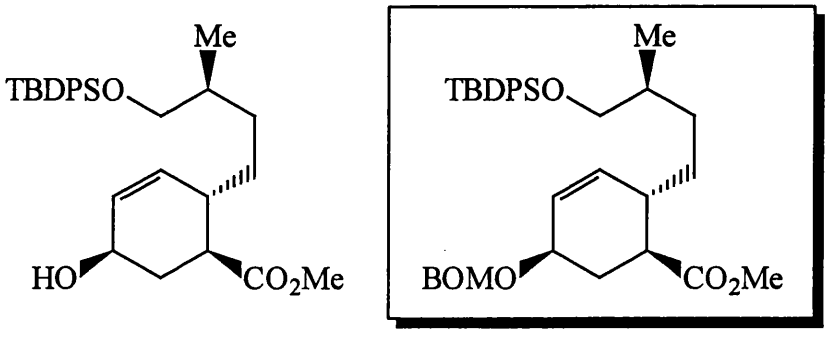
ν_{max} (thin film) 3000-2870 (s, C-H), 1459 (m), 1414 (w), 1380 (w), 1239 (m), 1084 (s), 1010 (s), 798 (m), 741 (s), 669 (w).

m/z (FAB) 607 ($[M-H]^+$, 24), 580 (13), 492 (13), 476 (100), 464 (42), 448 (94), 435 (23), 419 (21), 407 (21%).

HRMS (FAB) found *m/z* 607.4370; $C_{34}H_{67}O_3Si_3$ $[M-H]^+$ requires *m/z* 607.4398.

$[\alpha]_D^{24}$ +87.6 (c=0.20 in DCM).

(1*S*,2*S*,5*R*,3'*S*)-5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enecarboxylic acid methyl ester 268



To a stirred solution of **251** (1.93g, 4.31mmol) in MeOH (198ml) at 0 °C was added NaOMe (0.4M in MeOH, 10.8ml, 4.31mmol) dropwise over 3 mins. The resulting

mixture was stirred at 0 °C for 23 mins. The reaction mixture was diluted with EtOAc (200ml) and washed with H_2O (200ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo* to afford a yellow oil presumed to be the alcohol **262**. To a stirred solution of the crude alcohol **262** (assuming 100% conversion, 2.10g, 4.31mmol) in DCM (50ml) at rt was added Hünigs base (1.6ml, 8.75mmol) dropwise over 1 min. The resulting mixture was stirred at rt for 4 mins. BOMCl (60% assay, 2.3ml, 8.75mmol) was added dropwise over 2 mins. The resulting mixture was stirred at rt for 2 days. The reaction mixture was diluted with DCM (100ml) and washed with H_2O (100ml). The aqueous layer was extracted (1x100ml EtOAc) and the combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 20:1) to afford the title compound as a clear oil (2.46g, 95% over two steps).

R_f 0.80 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, **Me**CH), 1.09 (9H, s, *t*-Bu), 1.21-2.22 (7H, m), 2.46-2.54 (2H, m, **CHCH**CO_2Me), 3.49 (1H, dd, *J* 6.0, 9.9, CH**H**OSiR_3), 3.52 (1H, dd, *J* 5.8, 9.9, **CH**HOSiR_3), 3.69 (3H, s, CO_2**Me**), 4.22-4.24 (1H, m, BOMOC**H**), 4.72 (2H, apps, Ph**C**H_2O), 4.86-4.96 (2H, m, O**C**H_2O), 5.68-5.76 (2H, m, alkenic protons), 7.30-7.70 (15H, m, Ph).

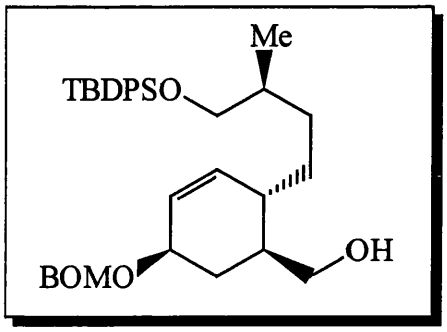
δ_C (75.4 MHz, $CDCl_3$) 16.94 (**Me**CH), 19.29 (**C**Me_3), 26.85 (C**Me**$_3$), 29.43 (**C**H_2), 31.40 (**C**H_2), 32.68 (**C**H_2), 36.00 (**C**H), 37.61 (**C**H), 44.30 (**C**H), 51.70 (CO_2**Me**), 68.42 (**C**H_2OSiR_3), 69.88 (Ph**C**H_2O), 72.48 (BOMO**C**H), 91.32 (O**C**H_2O), 127.55 (Ph), 127.72 (Ph), 127.80 (Ph), 127.85 (Ph), 128.09 (Ph), 128.43 (Ph), 129.49 (HC=**C**H), 132.47 (Ph), 133.97 (Ph), 135.59 (H**C**=CH), 175.14 (**C**O).

ν_{max} (thin film) 3040-2850 (s, C-H), 1736 (s, C=O), 1457 (m), 1430 (m), 1273 (m), 1163 (s), 1110 (s), 995 (s), 824 (m), 741 (s), 702 (s), 612 (s).

m/z (FAB) 639 ([MK]$^+$, 1), 573 ([M-(TBDPS)]$^+$, 58), 464 (43), 385 (75), 307 (64), 289 (65), 239 (63%).

$[\alpha]_D^{19}$ +31.9 (c=0.29 in DCM).

(1*S*,2*S*,5*R*,3'*S*)-{5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enyl}-methanol 269



To a stirred solution of **268** (2.46g, 4.27mmol) in DCM (45ml) at -78 °C was added DIBAL (1.5M in hexanes, 8.5ml, 12.81mmol) dropwise over 2 mins. The CO_2/acetone bath was replaced with an ice/water bath and the resulting mixture was stirred for 31 mins. The reaction mixture was cooled to -78 °C and quenched carefully with 20% (aq) Rochelles salt (250ml). The resulting mixture was diluted with DCM (200ml) and stirred vigorously for 38 mins during which time it heated to rt. The now clear layers were separated and the aqueous layer was extracted (2x100ml EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→3:1) to afford the title compound as a clear oil (1.99g, 85%).

R_f 0.33 (petrol:ethyl acetate; 10:1).

δ_H (500 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.6, Me), 1.08 (9H, s, *t*-Bu), 1.20-1.78 (8H, m), 1.93 (1H, br s, O**H**), 2.07-2.13 (1H, m), 3.48 (1H, dd, *J* 6.1, 9.8, CH**H**OH), 3.52 (1H, dd, *J* 5.7, 9.8, C**H**HOH), 3.57 (1H, dd, *J* 7.0, 10.6, CH**H**OSiR$_3$), 3.69 (1H, dd, *J* 4.1,

10.6, C**H**HOSiR$_3$), 4.18-4.26 (1H, m, BOMOC**H**), 4.61-4.70 (2H, m, PhC**H**$_2$), 4.86-4.97 (2H, m, OC**H**$_2$O), 5.75-5.81 (2H, m, **H**C=C**H**), 7.31-7.75 (15H, m, Ph).

δ_C (100.5 MHz Brucker, $CDCl_3$) 16.98 (**Me**CH), 19.30 (**C**Me$_3$), 26.85 (C**Me**$_3$), 30.04 (**C**H$_2$), 30.13 (**C**H$_2$), 30.82 (**C**H$_2$), 35.97 (**C**H), 36.74 (**C**H), 38.26 (**C**H), 65.38 (**C**H$_2$OSiR$_3$), 68.53 (Ph**C**H$_2$O), 69.46 (**C**H$_2$OSiR$_3$), 71.02 (BOMO**C**H), 93.21 (O**C**H$_2$O), 127.13 (Ph), 127.56 =**C**H), 127.70 (Ph), 127.88 (Ph), 128.43 (Ph), 129.50 (Ph), 133.99 (Ph), 134.13 (Ph), 135.60 (=**C**H), 137.78 (Ph).

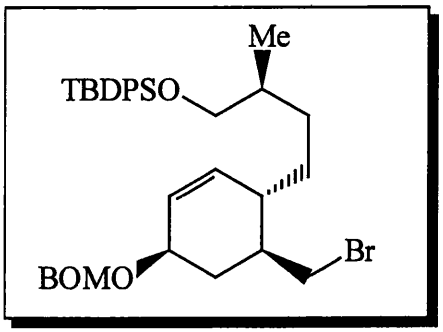
ν_{max} (thin film) 3423 (br m, O-H), 3000-2850 (s, C-H), 1726 (m), 1460 (m), 1428 (m), 1388 (m), 1277 (m), 1109 (s), 1037 (s), 823 (m), 740 (s), 702 (s).

m/z (FAB) 595 ([MNa]$^+$, 14), 494 (11), 466 (16), 436 (19), 414 (31), 392 (72), 377 (34), 329 (37), 307 (77), 289 (100), 269 (56), 239 (72), 227 (46), 212 (77%).

HRMS (FAB) found *m/z* 595.3245; $C_{36}H_{48}O_4SiNa$ [MNa]$^+$ requires *m/z* 595.3220.

$[\alpha]_D^{17}$ +53.2 (c=0.19 in DCM)

(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-bromomethyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 270



To a stirred solution of **269** (1.35g, 2.46mmol) in THF (30ml) at rt was added PPh_3 (1.95g, 7.39mmol) and CBr_4 (2.46g, 7.39mmol) in single portions. The resulting mixture was stirred at rt for 3.5 hrs during which time a bright yellow precipitate formed. The reaction mixture was *conc in vacuo*. Et_2O was added to the residue and the

white precipitate which formed on cooling the flask to 0 °C was filtered-off. The filtrate was *conc in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate; 20:1) to afford the title compound as a clear oil (1.40g, 94%).

R_f 0.78 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.95 (3H, d, *J* 6.5, Me), 1.09 (9H, s, *t*-Bu), 1.13-1.79 (7H, m), 2.16-2.23 (2H, m), 3.46-3.56 (4H, m, CH_2Br superimposing CH_2OSiR_3), 4.27-4.30 (1H, m, BOMOCH), 4.60-4.80 (2H, m, $PhCH_2O$), 4.86 (1H, d, *J* 7.0, OCHHO), 4.90 (1H, d, *J* 7.0, OCHHO), 5.68-5.58 (2H, m, HC=CH), 7.30-7.70 (15H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 17.07 (MeCH), 19.33 (CMe_3), 26.91 (CMe_3), 29.43 (CH_2), 30.03 (CH_2), 33.35 (CH_2), 36.00 (CH), 38.49 (CH), 38.53 (CH_2Br), 38.57 (CH), 68.38 (CH_2SiOR_3), 69.48 ($PhCH_2O$), 71.74 (BOMOCH), 93.24 (OCH_2O), 127.61 (Ph), 127.72 (Ph), 127.97 (Ph), 128.35 (Ph), 128.46 (Ph), 129.56 (=CH), 132.75 (Ph), 133.96 (=CH), 135.63 (Ph), 137.86 (Ph).

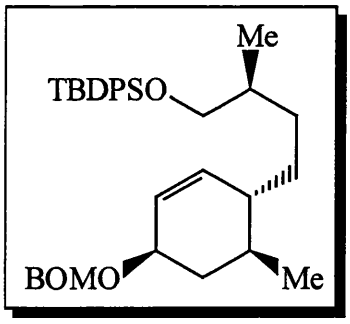
ν_{max} (thin film) 3070-2850 (s, C-H), 1590 (w), 1461 (m), 1428 (m), 1389 (m), 1163 (m), 1109 (s), 1042 (s), 823 (m), 740 (m), 702 (s), 612 (m).

m/z (FAB) 657/659 ($[M(^{79}Br/^{81}Br)Na]^+$, 7), 497/499 (100) 471 (32), 437 (22), 391 (28%).

HRMS (FAB) found *m/z* 657.2383; $C_{36}H_{47}O_3BrSiNa$ $[MNa]^+$ requires *m/z* 657.2376.

$[\alpha]_D^{21}$ +24.4 (c=0.44 in DCM).

(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 271



To a stirred solution of **270** (1.08g, 1.85mmol) in PhMe (25ml) at rt was added tri-*n*-butyltin hydride (1.0ml, 3.70mmol) and AIBN (20mg, 0.09mmol) in single portions. The resulting mixture was heated at reflux for 14.5 hrs. AIBN (approx 20mg, 0.09mmol) was added in a single portion and heating at reflux was continued for 48 hrs. After cooling to rt, the reaction mixture was *conc in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate; 1:0→40:1) to afford the title compound as a clear oil (926mg, 95%).

R_f 0.41 (petrol:ethyl acetate; 10:1).

δ_H (500 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.6, ring Me), 1.00 (3H, d, *J* 6.5, chain Me), 1.08 (9H, s, *t*-Bu), 1.12-2.08 (9H, m), 3.48 (1H, dd, *J* 6.1, 9.8, CH**H**OSiR_3), 3.52 (1H, dd, *J* 5.7, 9.8, C**H**HOSiR_3), 4.30-4.33 (1H, m, BOMOC**H**), 4.65-4.70 (2H, m, PhC$\mathbf{H}_2$), 4.86 (1H, d, *J* 7.0, OCH**H**O), 4.89 (1H, d, *J* 7.0, OC**H**HO), 5.67-5.74 (2H, m, **H**C=C**H**), 7.31-7.75 (15H, m, Ph), (minor diastereomer; 0.93 (d, *J* 6.6), 3.35-3.42 (m), 3.48-3.50 (m), 4.24-4.30 (m), 4.65-4.70 (m superimposed by PhC$\mathbf{H}_2$), 4.84-4.90 (m)).

δ_C (100.5 MHz Brucker, $CDCl_3$) 17.10 (ring Me), 19.30 (**C**Me_3), 19.89 (chain Me), 26.86 (C**Me**$_3$), 28.90 (**C**H_2), 29.84 (**C**H_2), 32.15 (**C**H), 36.15 (**C**H), 38.70 (**C**H_2), 43.04 (**C**H), 68.49 (**C**H_2OSiR_3), 69.51 (Ph**C**H_2), 73.30 (BOMO**C**H), 93.13 (O**C**H_2O), 127.54

(=CH), 127.90 (Ph), 128.41 (Ph), 128.61 (Ph), 129.47 (Ph), 130.87 (Ph), 133.71 (Ph), 134.04 (Ph), 135.61 (=CH), 137.95 (Ph).

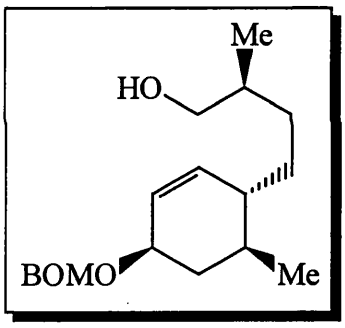
ν_{max} (thin film) 3040-2850 (s, C-H), 1590 (w), 1726 (w), 1459 (m), 1428 (m), 1385 (m), 1270 (m), 1110 (s), 1042 (s), 823 (m), 740 (m), 702 (s).

m/z (FAB) 579 ($[MNa]^+$, 4), 420 (24), 392 (26), 377 (16), 357 (21), 335 (15), 301 (21), 289 (31), 259 (27), 239 (87), 227 (45), 211 (64%).

HRMS (FAB) found *m/z* 579.3254; $C_{36}H_{48}O_3SiNa$ $[MNa]^+$ requires *m/z* 579.3270.

$[\alpha]_D^{24}$ +11.3 (c=0.46 in DCM).

(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butan-1-ol 272



To **271** (926mg, 1.84mmol) at rt was added TBAF (1.0M in THF, 5.51ml, 5.51mmol) dropwise over 45 secs. The resulting mixture was stirred at rt for 20 hrs then *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→5:1) to afford the title compound as a clear oil (501mg, 86%).

R_f 0.24 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.7, ring Me), 1.02 (3H, d, *J* 6.5, chain Me), 1.19-2.20 (10H, m), 3.45 (1H, dd, *J* 6.4, 10.5, CH**H**OH), 3.55 (1H, dd, *J* 5.6, 10.5, C**H**HOH), 4.29-4.33 (1H, m, BOMOC**H**), 4.64 (1H, d, *J* 11.8, PhCH**H**), 4.68 (1H, d, *J* 11.8, PhC**H**H), 4.85 (1H, d, *J* 7.0, OCH**H**O), 4.89 (1H, d, *J* 7.0, OC**H**HO), 5.67-5.75

(2H, m, **HC=CH**), 7.30-7.74 (5H, m, Ph), (minor diastereomer; 0.94 (d, *J* 6.7), 3.57-3.60 (m), 4.22-4.28 (m), 4.77 (d, *J* 7.0), 4.79 (d, *J* 7.0)).

δ_C (125.8 MHz, $CDCl_3$) 16.78 (ring Me), 19.92 (chain Me), 29.36 (**CH**), 29.83 ($\mathbf{CH_2}$), 32.09 (**CH**), 36.15 (**CH**), 38.57 ($\mathbf{CH_2}$), 39.19 ($\mathbf{CH_2}$), 68.10 ($\mathbf{CH_2}$OH), 69.34 (Ph$\mathbf{CH_2}$), 73.25 (BOMO**CH**), 91.15 (O$\mathbf{CH_2}$O), 127.65 (=**CH**), 127.90 (Ph), 128.42 (Ph), 128.85 (Ph), 133.52 (=**CH**), 137.93 (Ph).

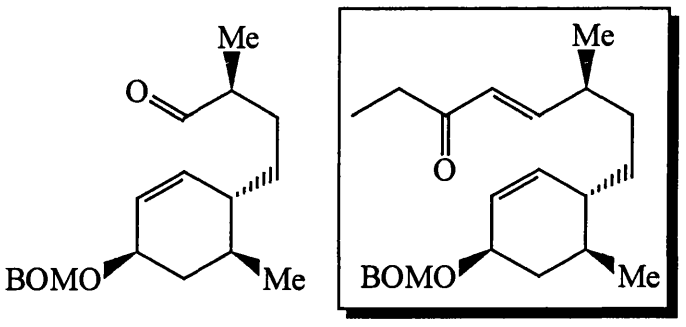
ν_{max} (thin film) 3423 (br m, O-H), 3030-2860 (s, C-H), 1725 (w), 1457 (m), 1380 (m), 1273 (m), 1164 (m), 1107 (m), 1041 (s), 737 (m), 697 (m).

m/z (FAB) 341 ($[MNa]^+$, 79), 307 (46), 287 (39), 279 (100), 249 (41), 243 (45), 234 (47), 227 (57%).

HRMS (FAB) found *m/z* 341.2080; $C_{20}H_{30}O_3Na$ $[MNa]^+$ requires *m/z* 341.2093.

$[\alpha]_D^{22}$ +18.6 (c=0.29 in DCM).

(4*E*,6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-3'-enyl)-6-methyl-oct-4-en-3-one 275



To a stirred solution of DMSO (0.58ml, 7.98mmol) in DCM (5ml) at -78 °C was added oxalyl chloride (0.53ml, 5.69mmol) dropwise over 30 secs. The resulting mixture was stirred at -78 °C for 29 mins. A solution of **272** (362mg, 1.14mmol) in DCM (5ml) was then added dropwise over 45 secs. The resulting mixture was stirred at –78 °C for 28 mins. Et_3N (4.0ml, 28.46mmol) was then added and the CO_2/acetone bath was removed.

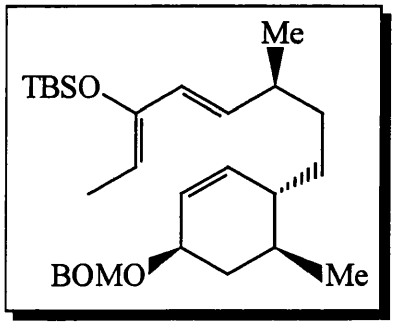
The resulting mixture was stirred for 57 mins. The reaction mixture was quenched with H_2O (100ml) and extracted (3x100ml DCM). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→5:1) to afford a clear oil presumed to be the aldehyde **273** (358mg, 99%). To a stirred solution of phosphonate **274**[95] (270mg, 1.38mmol) in MeCN (4.1ml) containing LiCl (571mg, 1.48mmol) at rt was added Hünigs base (0.61ml, 3.70mmol) dropwise over 30 secs. The resulting mixture was stirred at rt for 4 mins. A solution of the aldehyde **273** (234mg, 0.74mmol) in MeCN (4.1ml) was then added dropwise over 30 secs. The resulting mixture was stirred at rt for 48 hrs. The reaction mixture was diluted with EtOAc (100ml) and washed with 10% (aq) HCl (100ml), and then satd (aq) NaCl (200ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 20:1→10:1) to afford the title compound as a clear oil (253mg, 93%).

R_f 0.72 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.80-0.91 (1H, m), 0.97 (3H, d, *J* 6.5, ring Me), 1.10 (3H, d, *J* 6.5, **Me**$CHCH_2$), 1.14 (3H, t, *J* 7.5, chain Me), 1.15-1.60 (5H, m), 1.71-1.80 (1H, m), 2.00-2.08 (1H, m), 2.22-2.33 (1H, m), 2.58 (2H, q, *J* 7.5, $MeCH_2CO$), 4.27-4.31 (1H, m, BOMOC**H**), 4.64 (1H, d, *J* 12.0, PhCH**H**O), 4.66 (1H, d, *J* 12.0, PhC**H**HO), 4.85 (1H, d, *J* 7.0, OCH**H**O), 4.88 (1H, d, *J* 7.0, OC**H**HO), 5.64-5.75 (2H, m, **H**C=C**H**), 6.08 (1H, d, *J* 16.0, CHC**H**CO), 6.70 (1H, dd, *J* 8.0, 16.0, C**H**CHCO), 7.31-7.46 (5H, m, Ph).

This compound was taken forward onto the next step without further characterisation.

(1*Z*,2*E*,4*S*,1'*S*,4'*R*,6'*S*)-[6-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-1-ethylidene-4-methyl-hex-2-enyloxy]-*t*-butyl-dimethyl-silane 276



To a stirred solution of **275** (199mg, 0.54mmol) in DCM (7ml) at rt was added Et_3N (0.36ml, 2.69mmol) dropwise over 1 min. The resulting mixture was stirred at rt for 4 mins. TBSOTf (0.26ml, 1.08mmol) was added dropwise over 1 min and the resulting mixture was stirred at rt for 13 mins. The reaction mixture was diluted with Et_2O (100ml) and washed with H_2O (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1) to afford the title compound as a clear oil (256mg, 98%).

R_f 0.55 (petrol:ethyl acetate; 10:1).

δ_H (500 MHz, $CDCl_3$) 0.12 (6H, s, Si**Me**$_2$), 0.97 (3H, d, *J* 6.5, ring Me), 1.08 (12H, s, *t*-Bu superimposing chain **Me**), 1.00-1.55 (6H, m), 1.66 (3H, d, *J* 7.0, **Me**CH=), 1.70-2.30 (3H, m), 4.20-4.33 (1H, m, BOMOC**H**), 4.58-4.67 (2H, m, PhC**H**$_2$), 4.75 (1H, d, *J* 7.0, MeC**H**C(OTBS)), 5.84 (1H, d, *J* 7.0, OCH**H**O), 4.86 (1H, d, *J* 7.0, OC**H**HO), 5.52-5.87 (4H, m, alkenic protons), 7.30-7.80 (5H, m, Ph).

δ_C (100.5 MHz Brucker, $CDCl_3$) –3.54 (Si**Me**$_2$), 11.72 (**Me**CH=), 19.95 (**C**Me$_3$), 21.08 (chain Me), 26.00 (**C**H$_2$), 26.56 (C**Me**$_3$), 30.34 (ring Me), 32.27 (**C**H$_2$), 33.34 (**C**H), 36.94 (**C**H), 38.61 (**C**H$_2$), 42.71 (**C**H), 69.31 (Ph**C**H$_2$O), 73.27 (BOMO**C**H), 93.14 (O**C**H$_2$O), 107.56 (Me**C**HC(OTBS)), 127.21 (=**C**H), 127.64 (Ph), 127.90 (=**C**H), 128.40 (=**C**H), 128.66 (Ph), 133.52 (=**C**H), 134.19 (Ph).

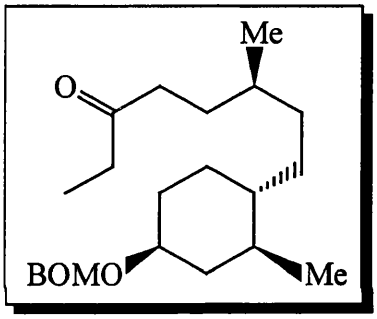
ν_{max} (thin film) 3000-2850 (m, C-H), 1724 (m), 1674 (m), 1626 (m), 1458 (m), 1379 (m), 1272 (m), 1111 (s), 1040 (s), 838 (m), 740 (m), 701 (m).

m/z (APCI, NH_3) 485 ($[MH]^+$, 20), 451 (15), 416 (60), 399 (100), 341 (24), 321 (51), 250 (16), 233 (31), 132 (31), 108 (23), 91 (18%).

HRMS (FAB) found *m/z* 523.3030; $C_{30}H_{48}O_3SiK$ $[MK]^+$ requires *m/z* 523.3010.

$[\alpha]_D^{18}$ +19.0 (c=0.28 in DCM).

(6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-2'-methyl-cyclohexyl)-6-methyl-octan-3-one 278



To a stirred solution of **276** (60mg, 0.12mmol) in THF (5ml) and H_2O (5ml) at rt was added with care Pd/C (40mg, 10 wt % palladium on activated carbon) and the reaction flask was then evacuated and flooded with hydrogen four times. The resulting suspension was then stirred vigorously under hydrogen at rt for 2 hrs. The reaction mixture was filtered through a thin plug of Celite™ and the filtrate was diluted with EtOAc (50ml) and washed with H_2O (50ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1→30:1) to afford the title compound as a clear oil (41mg, 91%).

R_f 0.70 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.76 (3H, d, *J* 5.5, ring Me superimposing 2H, m), 0.81 (3H, d, *J* 6.5, chain Me), 0.95 (3H, t, *J* 7.5, **Me**CH_2CO superimposing 2H, m), 1.01-1.99

(11H, m), 2.21-2.30 (2H, m, CH_2CH_2CO), 2.34 (2H, q, *J* 7.5, $MeCH_2CO$), 3.41-3.50 (1H, BOMOCH), 4.51 (2H, s, $PhCH_2$), 4.71 (2H, s, OCH_2O), 7.17-7.25 (5H, m, Ph).

δ_C (100.5 MHz Brucker, $CDCl_3$) 7.88 ($MeCH_2CO$), 19.64 (ring Me), 20.07 (chain Me), 29.92 (CH_2), 30.10 (CH_2), 30.44 (CH_2), 32.93 (CH_2), 32.96 (CH_2), 33.48 (CH), 35.42 (CH_2CH_2CO), 35.85 ($MeCH_2CO$), 40.07 (CH_2), 42.01 (CH), 43.40 (CH), 69.25 ($PhCH_2O$), 75.64 (BOMOCH), 92.55 (OCH_2O), 127.64 (Ph), 127.88 (Ph), 128.40 (Ph), 138.05 (Ph), 212.14 (CO).

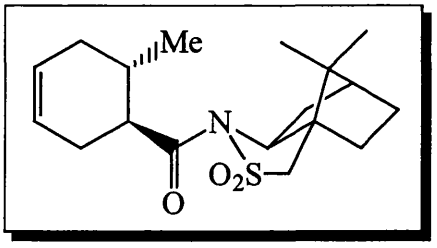
ν_{max} (thin film) 3040-2850 (s, C-H), 1718 (m, C=O), 1674 (w), 1458 (m), 1377 (m), 1254 (m), 1158 (m), 1109 (s), 1045 (s), 837 (m), 778 (m), 736 (m), 698 (m).

m/z (FAB) 397 ($[MNa]^+$, 24), 392 (19), 375 ($[MH]^+$, 7), 307 (11), 289 (13), 265 (14), 253 (16), 237 (100), 219 (56%).

HRMS (FAB) found *m/z* 375.2887; $C_{24}H_{39}O_3$ $[MH]^+$ requires *m/z* 375.2899.

$[\alpha]_D^{24}$ +10.7 (c=0.24 in DCM).

(7*R*,1'*S*,6'*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-(6'-methyl-cyclohex-3'-enyl)-methanone 292



To freshly condensed 1,3-butadiene (approx 68ml, approx 1260mmol) at –20 °C was added **291**[102] (35.67g, 126.48mmol) in DCM (245ml) over 20 mins. A solution of $EtAlCl_2$ (1.0M in hexanes, 189.73ml, 189.73mmol) was then added over 30 mins. The resulting mixture was stirred at –20 °C for 3 days. The reaction was diluted with DCM (1l) and quenched at 0 °C with 10% (aq) Rochelles salt (1.5l). The quenched mixture

was vigorously stirred for 1.5 hrs during which time it heated to rt. The resulting mixture was filtered through a thin plug of Celite™ and the filtrate was stirred for a further 1 hr at rt. The now clear layers were separated and the aqueous extracted (3x500ml EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1) to afford the title compound as a white crystaline solid (41.54g, 98%).

R_f 0.29 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.90 (6H, m, 1xMe-10 superimposing **Me**CH), 1.07 (3H, s, 1xMe-10), 1.30-1.37 (2H, m), 1.67-1.89 (4H, m), 1.92-2.10 (5H, m), 2.29-2.34 (1H, m, **CH**(CO)), 2.85 (1H, dt, *J* 5.5, 10.5, NCHCH**H**-α), 3.38 (1H, d, *J* 14.0, NSO_2CHH), 3.45 (1H, d, *J* 14.0, NSO_2CHH), 3.86 (1H, t, *J* 6.5, $NCHCH_2$), 5.57 (2H, apps, **H**C=C**H**).

δ_C (75.4 MHz, $CDCl_3$) 19.20, 19.58, 20.82, 26.39, 28.44, 29.51, 30.48, 32.74, 32.93, 38.47, 47.31, 47.68, 48.17, 53.19, 64.94, 124.48, 126.73, 175.19.

ν_{max} (KBr disc) 3000-2837 (s, C-H), 1738 (s, C=O), 1682 (s, C=C), 1459 (m), 1399 (m), 1321 (s, SO_2), 1274 (m), 1238 (s), 1208 (s), 1169 (m, SO_2–N), 1129 (s), 1060 (s, S=O), 1000 (m), 769 (m), 740 (w), 713 (w), 662 (w), 539 (s), 502 (w).

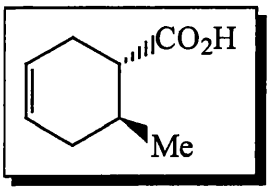
m/z (FAB) 360 ($[MNa]^+$, 2), 338 ($[MH]^+$, 100), 135 (31), 121 (35), 107 (66), 95 (100), 79 (78), 67 (72), 55 (89%).

HRMS (FAB) found *m/z* 338.1783; $C_{18}H_{28}NO_3S$ $[MH]^+$ requires *m/z* 338.1790.

$[\alpha]_D^{21}$ +154.1 (c=0.27 in DCM).

mp 187-190 °C.

(1*S*,6*S*)-6-Methyl-3-cyclohex-3-enecarboxylic acid 287[99]



To a solution of **292** (35g, 104.17mmol) in THF (812ml) and water (812ml) at rt in a flask which was open to air was added LiOH (21.8g, 520.8mmol) and H_2O_2 (70ml, 1041.6mmol) in single portions. The resulting mixture was stirred vigorously at rt for 5 hrs. The reaction mixture was extracted (3x150ml Et_2O) and the combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was recrystalised from EtOH to afford (7*R*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5,5-dioxide as a white crystaline solid (19.60g, 87%). The aqueous layer was acidified to pH = 2 with conc HCl, extracted (3x150ml EtOAc), and the combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo* to afford the title compound as a clear oil (14.01g, 89%).

R_f 0.19 (petrol:ethyl acetate; 3:1).

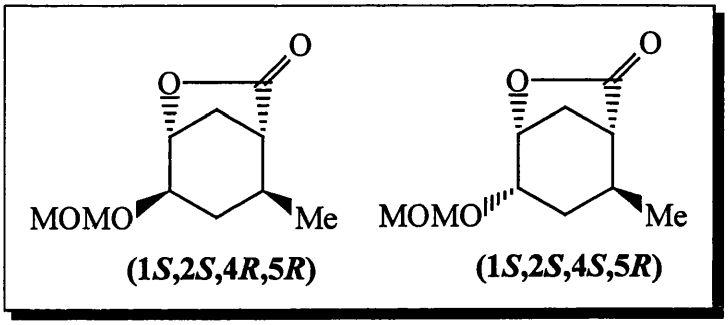
δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.5, Me), 1.71-1.78 (1H, m, MeC**H**CHCO$_2$H), 1.92-1.97 (1H, m, MeCHC**H**CO$_2$H), 2.16-2.33 (4H, m, 2xC**H**$_2$), 5.67 (2H, apps, **H**C=C**H**), 11.0-11.6 (1H, br s, CO$_2$**H**).

δ_C (75.4 MHz, $CDCl_3$) 19.69 (Me), 28.35 (**C**H$_2$), 30.25 (Me**C**HCHCO$_2$H), 32.83 (**C**H$_2$), 46.77 (MeCH**C**HCO$_2$H), 124.47 (=**C**H), 126.27 (=**C**H), 182.56 (**C**=O).

ν_{max} (thin film) 3600-2350 (br s, OH and C-H), 1698 (s, C=O), 1596 (w), 1574 (m), 1417 (m), 1306 (s), 1264 (s), 1074 (m), 898 (m), 749 (s), 720 (s).

$[\alpha]_D^{22}$ +41.6 (c=0.19 in DCM); Lit. Value $[\alpha]_D^{24}$ +76.7 (c=9.78, $CHCl_3$).

(1*S*,2*S*,4*R*,5*R*)-4-Methoxymethoxy-2-methyl-6-oxa-bicyclo[3.2.1]octan-7-one and (1*S*,2*S*,4*S*,5*R*)-4-methoxymethoxy-2-methyl-6-oxa-bicyclo[3.2.1]octan-7-one 294



To a stirred solution of **287** (119mg, 0.87mmol) in PhMe (30ml) at 0 °C was added *m*-CPBA (50%, 329mg, 0.96mmol) in a single portion. The resulting mixture was stirred at 0 °C for 3 hrs. Et_3N (1.19ml, 8.75mmol) was added to the reaction mixture at 0 °C. The resulting mixture was heated at 30 °C for 4 hrs. MOMCl (146µl, 1.92mmol) was then added slowly to the reaction mixture at 30 °C over 20 mins. The resulting mixture was stirred at 30 °C for 2.5 hrs. The reaction mixture was diluted with EtOAc (200ml) and washed with 5% (aq) KOH (100ml), and then satd (aq) NaCl (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a clear oil (157mg, 89%) and as an inseparable 1:1 mixture of the two diastereoisomers above.

R_f 0.74 (petrol:ethyl acetate; 1:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.80-0.84 (3H, 2xd, *J* 6.5, 6.5, **Me**CH), 1.31-2.28 (6H, m), 3.06-3.15 (2H, m), 3.35-3.57 (3H, m, **Me**OCH_2), 5.12-5.17 (2H, m, MeO**C**H_2).

δ_C (100.5 MHz Brucker, $CDCl_3$) 19.07 and 19.18 (**C**H_3), 26.36 (**C**H), 26.76 (**C**H_2), 28.42 (**C**H_2), 29.56 (**C**H), 31.91 (**C**H_2), 32.73 (**C**H_2), 43.19 (**C**H), 45.98 (**C**H), 50.05 (**C**H), 51.05 (**C**H), 51.91 (**C**H), 52.24 (**C**H), 57.34 and 57.38 (**C**H_3), 90.02 and 90.08 (**C**H_2), 174.28 and 174.75 (**C**O).

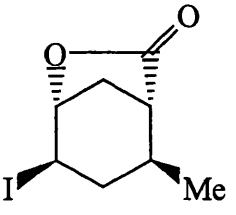
ν_{max} (thin film) 3000-2850 (m, C-H), 1740 (s, C=O), 1435 (w), 1371 (w), 1312 (m), 1243 (m), 1215 (m), 1159 (s), 1134 (s), 1094 (s), 1077 (s), 988 (s), 964 (s), 931 (m), 822 (m), 785 (m).

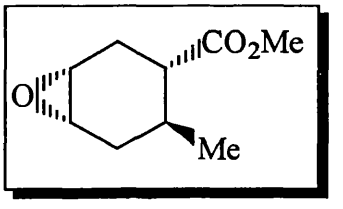
m/z (FAB) 201 ($[MH]^+$, 100), 185 (37), 171 (14), 163 (19), 137 (25), 109 (15%).

HRMS (FAB) found *m/z* 201.1120; $C_{10}H_{17}O_4$ $[MH]^+$ requires *m/z* 201.1127.

$[\alpha]_D^{19}$ +23.2 (c=0.34 in DCM).

(1*S*,3*S*,4*S*,6*R*)-4-Methyl-7-oxa-bicyclo[4.1.0]heptane-3-carboxylic acid methyl ester 296





To a solution of **287** (200mg, 1.43mmol) in DCM (6ml) and water (6ml) at 0 °C in a flask open to air and protected from light was added $NaHCO_3$ (360mg, 4.29mmol), KI (354mg, 2.14mmol), and I_2 (541mg, 2.14mmol) in single portions. The resulting mixture was stirred at 0 °C for 5 hrs. The reaction mixture was quenched with satd (aq) Na_2SO_3 (200ml) and extracted (3x50ml DCM). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 3:1) to afford yellow, white crystals presumed to be the iodolactone **295** (232mg, 62%). To the iodolactone **295** (202mg, 0.76mmol) in $CHCl_3$ (7ml) at –5 °C was added NaOMe (0.4M in MeOH, 1.90ml, 0.78mmol) dropwise over 2 mins. The resulting mixture was stirred for a further 15 mins during which time the cooling bath heated to 0 °C. The reaction mixture was diluted with EtOAc (100ml) and washed with satd (aq) NaCl (50ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo*. The residue was purified by flash column chromatography

(petrol:ethyl acetate; 3:1) to afford the title compound as a clear oil (112mg, 88%) *albeit* contaminated with a trace amount of an inseparable aromatic contaminant.

R_f 0.24 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.6, **Me**CH), 1.40 (1H, 2xdd, *J* 1.7, 11.0), 1.81-1.88 (1H, m), 1.96 (1H, dt, *J* 6.6, 10.8, MeC**H**), 2.08-2.23 (3H, m), 3.15-3.18 (2H, m, C**H**(O)C**H**), 3.67 (3H, s, CO_2**Me**), (minor peaks owing to the contaminant; 1.05 (s), 7.39-7.68 (m)).

δ_C (75.4 MHz, $CDCl_3$) 19.26 (**Me**CH), 26.75, 27.03, 33.01, 45.97, 50.29, 51.46 (**C**H(O)CH), 51.47 (CO_2**Me**), 52.49 (CH(O)**C**H),, 175.48 (**C**O_2Me), (minor peaks owing to the contaminant; 14.16, 37.26, 67.47, 68.54, 127.68, 129.71, 133.08, 135.50).

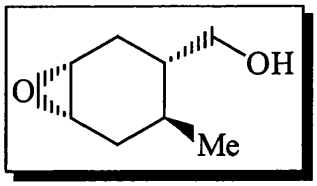
ν_{max} (thin film) 3000-2900 (s, C-H), 1735 (s, C=O), 1435 (s), 1376 (m), 1318 (s), 1261 (s), 1171 (s), 1147 (s), 1110 (m), 1080 (m), 1024 (m), 988 (m), 903 (w), 864 (w), 825 (m), 785 (m), 744 (w), 706 (m), 669 (w).

m/z (FAB) 171 ($[MH]^+$, 44), 165 (25), 153 (76), 139 (91), 121 (65), 111 (97), 107 (100%).

HRMS (FAB) found *m/z* 171.1024; $C_9H_{15}O_3$ $[MH]^+$ requires *m/z* 171.1021.

$[\alpha]_D^{24}$ +93.2 (c=0.15 in DCM).

(1*S*,3*S*,4*S*,6*R*)-(4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-yl)-methanol 297



To a solution of **296** (6.63g, 38.94mmol) in THF (300ml) at –78 °C was added $LiBH_4$ (96%, 1.96g, 85.66mmol) in a single portion. The CO_2/acetone bath was removed and replaced with an ice/water bath and stirring was continued for 2 hrs during which time

the reaction mixture heated to 0 °C. The ice/water bath was then removed and stirring was continued for 17.5 hrs during which time the reaction mixture heated to rt. The reaction mixture was quenched carefully at 0 °C with H_2O (200ml) and extracted (3x100ml EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1→1:1) to afford the title compound as a white crystaline solid (4.99g, 90%).

R_f 0.18 (petrol:ethyl acetate; 1:1).

δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.4, Me), 1.26-1.49 (3H, m), 1.90 (1H, q, *J* 12.9), 2.16-2.21 (1H, m), 2.45 (1H, dt, *J* 3.9, 13.4), 2.61 (1H, br s, O**H**), 3.55 (1H, dd, *J* 5.5, 10.7, CH**H**OH), 3.61-3.72 (1H, m, HC(O)C**H**), 3.74 (1H, dd, *J* 4.6, 10.7, C**H**HOH), 4.02-4.10 (1H, m, **H**C(O)CH).

δ_C (75.4 MHz, $CDCl_3$) 18.42 (Me), 35.46 (**C**HMe), 36.58 (**C**H_2), 41.52 (HC(O)**C**H), 44.39 (**C**HCH_2OH), 46.78 (**C**H_2), 64.52 (**C**H_2OH), 75.95 (H**C**(O)CH).

ν_{max} (thin film) 3363 (br s, OH), 3000-2865 (s, C-H), 1435 (s), 1358 (s), 1238 (s), 1155 (s), 1052 (s), 925 (s), 703 (s).

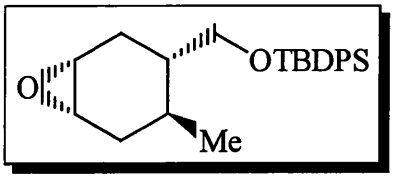
m/z (EI @ 70 eV) 143 ($[MH]^+$, 2), 125 ($[(MH)-(H_2O)]^+$, 100), 107 (74), 95 (44), 91 (23), 81 (37), 69 (26), 54 (95), 41 (66), 37 (27%).

HRMS (CI) found *m/z* 160.1337; $C_8H_{18}O_2$ $[MNH_4]^+$ requires *m/z* 160.1337.

$[\alpha]_D^{19}$ +25.6 (c=0.27 in DCM).

mp 147-151 °C.

(1*S*,3*S*,4*S*,6*R*)-(4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-ylmethoxy)-*t*-butyl-diphenyl-silane 298



To a stirred solution of **297** (4.71g, 33.17mmol) in DCM (250ml) at 0 °C was added Et_3N (13.3ml, 99.52mmol) over 1 min and DMAP (202mg, 1.65mmol) in a single portion. The resulting mixture was stirred for 4 mins at 0 °C before TBDPSCl (10ml, 36.94mmol) was added over 2 mins. The ice/water bath was removed and stirring was continued for 15.5 hrs during which time the reaction mixture heated to rt. The reaction mixture was diluted with Et_2O (200ml) and washed with satd (aq) $NaHCO_3$ (250ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 30:1) to afford the title compound as a white crystalline solid (12.46g, 99%) and as a ~10:1 mixture of diastereoisomers.

R_f 0.80 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, Me), 1.14 (9H, s, *t*-Bu), 1.21-1.41 (1H, m), 1.37-1.53 (1H, m), 1.90 (1H, q, *J* 12.7), 2.25 (1H, dt, *J* 4.3, 12.3), 2.45-2.52 (2H, m), 3.62 (1H, dd, *J*, 5.4, 10.2, CH**H**OSiR_3), 3.67 (1H, dd, *J* 3.1, 10.2, C**H**HOSiR_3), 3.73-3.78 (1H, dt, *J* 4.5, 10.8, CH(O)C**H**), 4.08-4.14 (1H, dt, *J* 4.5, 10.0, C**H**(O)CH), 7.42-7.82 (10H, m, Ph), (minor diastereomer; 0.83 (d, *J* 6.5), 3.18-3.53 (m)).

δ_C (75.4 MHz Varian, $CDCl_3$) 18.35, 18.96, 26.53, 35.26, 36.72, 42.19, 44.58, 46.78, 65.18, 76.13, 127.65, 129.56, 134.77, 135.15, (minor diastereomer; 19.29, 26.86, 34.34, 41.22, 52.15, 53.11, 65.53, 129.72, 135.15).

ν_{max} (thin film) 3418 (br s, wet plate), 3070-2850 (s, C-H), 1960 (w), 1891 (w), 1590 (w), 1468 (m),1428 (m), 1389 (m), 1362 (m), 1258 (m), 1159 (m), 1110 (s), 1003 (m), 938 (w), 821 (s), 740 (s), 703 (s), 606 (s).

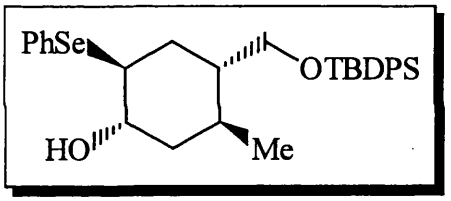
m/z (FAB) 403 ($[MNa]^+$, 4), 381 ($[MH]^+$, 16), 323 ($[(M)-(t\text{-Bu})]^+$, 21), 303 (10), 245 (13), 199 (100), 183 (20), 135 (73), 125 (13), 107 (37), 95 (16), 75 (19%).

HRMS (FAB) found *m/z* 403.2087; $C_{24}H_{32}O_2SiNa$ $[MNa]^+$ requires *m/z* 403.2069.

$[\alpha]_D^{21}$ +21.4 (c=0.36 in DCM).

mp 175-177 °C.

(1*S*,2*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-2-phenylselanyl-cyclohexanol 299



To a bright yellow solution of $(PhSe)_2$ (2.26g, 19.66mmol) in EtOH (162ml) at rt was added $NaBH_4$ (1.48g, 39.33mmol) in approx 100mg portions over 1 min. The resulting mixture was stirred at rt for 4 mins during which time the yellow colour of the solution dissipated. A solution of **298** (12.46g, 32.77mmol) in EtOH (64ml) was added over 5 mins and the resulting mixture was heated at reflux for 3 hrs. Upon cooling to rt, the reaction mixture was diluted with EtOAc (500ml) and washed with satd (aq) NaCl (300ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1→20:1) to afford the title compound as a pale, yellow oil (15.18g, 86%).

R_f 0.54 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.6, Me), 1.07 (9H, s, *t*-Bu), 1.59-1.67 (2H, m), 1.78-1.94 (3H, m), 2.07 (1H, s, **OH**), 2.16-2.2 (1H, m, **CH**CH_2OSiR_3), 3.31-3.34 (1H, m, PhSe**CH**), 3.64 (1H, dd, *J* 6.8, 10.1, **CH**$HOSiR_3$), 3.69 (1H, dd, *J* 4.6, 10.1, **CH**$HOSiR_3$), 3.90 (1H, apps, **CH**OH), 7.25-7.68 (15H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 19.28 (**Me**CH), 19.62 (**C**Me_3), 26.85 (C**Me**$_3$), 27.62, 28.75, 36.38, 41.46, 50.74 (PhSe**CH**), 65.62 (**C**H_2OSiR_3), 68.82 (**C**HOH), 127.04 (Ph), 127.62 (Ph), 128.98 (Ph), 129.57 (Ph), 131.88 (Ph), 133.47 (Ph), 134.50 (Ph), 135.58 (Ph).

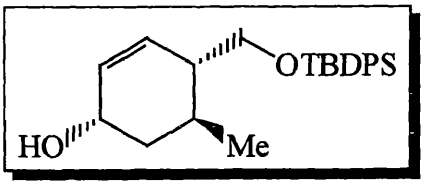
ν_{max} (thin film) 3380 (br s, OH), 3070-2900 (s, C-H), 1587 (w), 1473 (m), 1429 (m), 1110 (s), 821 (m), 740 (s), 702 (s).

m/z (FAB) 671 ($[MHCs]^+$, 7), 415 (10), 355 (16), 327 (22), 281 (47), 239 (46%).

HRMS (FAB) found *m/z* 671.0835; $C_{30}H_{39}O_2SeSiCs$ $[MHCs]^+$ requires *m/z* 671.0861.

$[\alpha]_D^{18}$ +10.5 (c=0.35 in DCM).

(1*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)–cyclohex-2-enol 300



To a solution of **299** (4.0g, 7.45mmol) in THF (32ml) at rt in a flask open to air was added a solution of $NaIO_4$ (6.37g, 29.80mmol) in H_2O (32ml) in a single portion. The resulting mixture was stirred at rt for 16 hrs. The reaction mixture was diluted with Et_2O (200ml) and washed with satd (aq) $NaHCO_3$ (500ml). The aqueous layer was extracted (2x100ml Et_2O) and the combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 3:1→1:1) to afford the title compound as a white foam (2.61g, 92%).

R_f 0.17 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.94 (9H, s, *t*-Bu), 1.03 (3H, d, *J* 6.8, Me), 1.62-1.84 (3H, m), 2.94-2.98 (1H, m, **CH**CH_2OSiR_3), 3.44 (1H, appt, *J* 8.2, CH**H**$OSiR_3$), 3.56 (1H, dd, *J* 4.5, 10.3, CH**H**$OSiR_3$), 4.20 (1H, br s, O**H**), 5.52 (1H, m, **CH**OH), 7.35-7.94 (12H, m, Ph superimposing alkenic protons).

δ_C (75.4 MHz, $CDCl_3$) 19.09 (**Me**CH), 19.71 (**C**Me_3), 21.34, 26.75 (C**Me**$_3$), 28.09, 36.25, 41.29, 65.22 (**C**H_2OSiR_3), 66.19 (**C**HCH_2OSiR_3), 66.84 (**C**HOH), 125.31, 127.64, 129.06, 129.64, 132.08, 133.25, 135.04, 142.39.

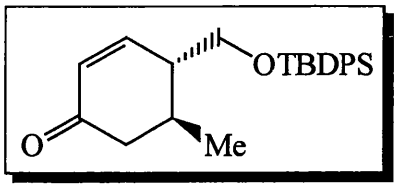
ν_{max} (thin film) 3382 (br s, OH), 3070-2900 (s, C-H), 1589 (w), 1428 (m), 1308 (w), 1110 (s), 1019 (s), 912 (w), 821 (m), 739 (s), 702 (s).

m/z (FAB) 403 ($[MNa]^+$, 8), 363 ($[(MH)-(H_2O)]^+$ 33), 323 (8), 269 (14), 229 (19), 199 (92), 183 (26), 165 (30), 154 (67), 135 (100), 121 (38%).

HRMS (FAB) found *m/z* 403.2087; $C_{24}H_{32}O_2SNa$ $[MNa]^+$ requires *m/z* 403.2069.

$[\alpha]_D^{22}$ +32.0 (c=0.27 in DCM).

(4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone 301



A suspension of MnO_2 (1.77g, 20.36mmol) in PhMe (20ml) was heated at reflux for 2.5 hrs with azeotropic removal of water (Dean-Stark apparatus). A solution of **300** (177mg, 0.47mmol) in PhMe (5ml) was added over 5 secs and the resulting suspension was heated at reflux for 1 hr. After cooling to rt, the reaction mixture was filtered through a thin plug of Celite™ and the filtrate was *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a clear oil (2.61g, 92%).

R_f 0.71 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) 0.98 (3H, d, *J* 5.8, Me), 1.09 (9H, s, *t*-Bu), 2.14-2.26 (3H, m), 2.48 (1H, d, *J* 12.4), 3.71 (1H, dd, *J* 5.9, 10.1, CH**H**OSiR_3), 3.88 (1H, dd, *J* 4.0, 10.1, **CH**HOSiR_3), 6.09 (1H, dd, *J* 2.2, 10.2, C**H**CH(CO)), 7.02 (1H, dd, *J* 2.2, 10.1, CHC**H**(CO)), 7.33-7.72 (10H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 19.28 (**Me**CH), 19.44 (**C**Me_3), 26.82 (C**Me**$_3$), 31.03, 45.19, 46.18, 64.02 (**C**H_2OSiR_3), 127.76 (Ph), 129.69 (Ph), 129.82 (Ph), 133.23 (CH**C**H(CO)), 135.59 (Ph), 152.48 (**C**HCH(CO)), 199.91 (**C**=O).

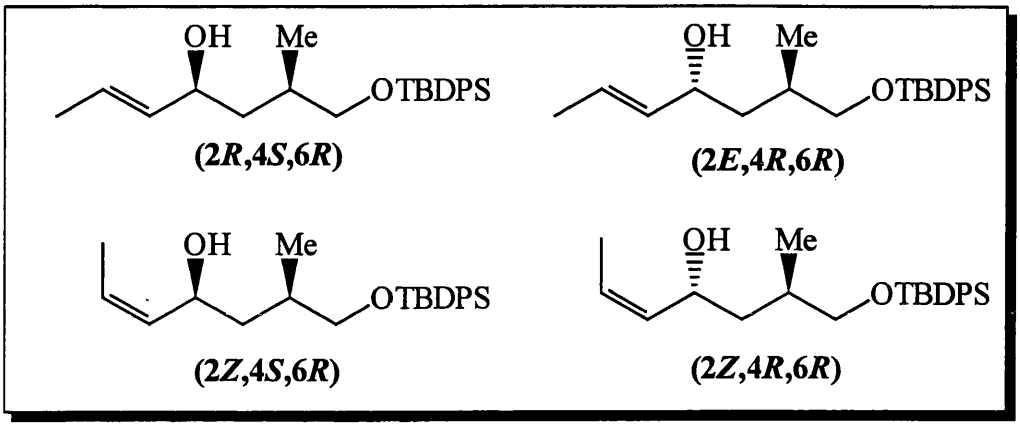
ν_{max} (thin film) 3070-2850 (s, C-H), 1680 (s, C=O), 1468 (m), 1427 (m), 1392 (m), 1247 (w), 1109 (s), 1000 (m), 867 (m), 823 (m), 741 (m), 703 (s).

m/z (FAB) 401 ($[MNa]^+$, 4), 378 ($[MH]^+$, 4), 377 ($[M-H]^+$, 9), 321 ($[M-(t\text{-Bu})]^+$, 24), 239 (11), 197 (45), 165 (22), 135 (100), 105 (23), 91 (18%).

HRMS (FAB) found *m/z* 401.1904; $C_{24}H_{30}O_2SiNa$ $[MNa]^+$ requires *m/z* 401.1913.

$[\alpha]_D^{22}$ +38.3 (c=0.39 in DCM).

(2*E*,4*S*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol, (2*E*,4*R*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol (2*Z*,4*S*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol, and (2*Z*,4*R*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol 306



To a solution of **305**[100] (487mg, 1.56mmol) in THF (15 ml) at –78 °C was added 1-propenylmagnesium bromide (0.5M in THF, 4.7ml, 2.34mmol) over 3 mins. The CO_2/acetone bath was removed and replaced with an ice/water bath and the resulting mixture was stirred for 41 mins. The reaction mixture was quenched at 0 °C by the rapid addition of H_2O (100ml) and extracted (3x50ml Et_2O). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 15:1) to afford the title compound as a clear oil (589mg, 99%) and as a inseparable 1:1:1:1 mixture of the four possible diastereoisomers.

R_f 0.51 (petrol:ethyl acetate; 3:1).

δ_H (500 MHz, $CDCl_3$) complex owing to diastereomers 0.95-1.00 (3H, 4xd, *J* 6.8, 6.8, 6.8, 6.8, **Me**CHCH$_2$), 1.12 (9H, s, *t*-Bu), 1.33-1.95 (3H, m, **CH$_2$CH**Me), 1.67-1.73 (3H, 4xd, *J* 6.9, 7.0, 6.9, 6.9, **Me**CHCH), 2.1-2.3 (1H, br s, **OH**), 3.55-3.61 (2H, m, CH$_2$OSiR$_3$), 4.15-4.69 (1H, m, **CH**OH), 5.43-5.73 (2H, m, **HC=CH**), 7.70-7.82 (10H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) complex owing to diastereomers 13.17, 13.25, 17.40, 17.46, 19.21, 26.80, 32.23, 32.31, 33.09, 41.49, 41.63, 42.14, 42.24, 65.28, 65.69, 68.96, 69.32, 69.41, 70.96, 71.22, 125.48, 125.94, 126.10, 126.57, 127.60, 129.58, 133.51, 133.54, 133.99, 134.29, 134.67, 134.77, 135.58.

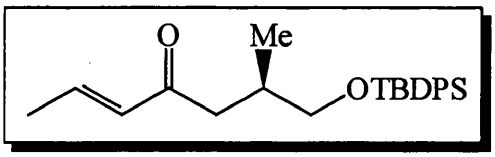
ν_{max} (thin film) 3381 (br s, OH), 3072-2840 (s, C-H), 1590 (m), 1427 (m), 109 (s), 642 (s).

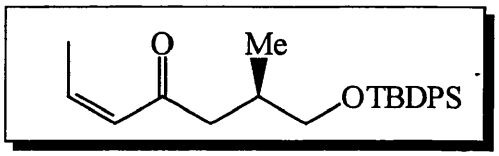
m/z (FAB) 405 ($[MNa]^+$, 2), 383 ($[MH]^+$, 5), 365 ($[M-(t\text{-Bu})]^+$, 9), 325 (4), 303 (3), 239 (6), 199 (53), 183 (11), 135 (37), 109 (100), 67 (19%).

HRMS (FAB) found *m/z* 383.2415; $C_{24}H_{35}O_2Si$ $[MH]^+$ requires *m/z* 383.2406.

$[\alpha]_D^{22}$ +10.2 (c=0.42 in DCM).

(2*E*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 304 and (2*Z*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 307





To a solution of **306** (80mg, 0.21mmol) in DMF (10ml) at rt was added PDC (236mg, 0.63mmol) in a single portion and the resulting mixture was stirred vigorously at rt for 13 hrs. The reaction mixture was quenched with H_2O (10ml) and extracted (3x15ml Et_2O). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1) to afford the title compounds as clear oils (*E*; 37mg, 52%: *Z*; 41mg, 47%: *E*:*Z*; 1:1.1).

(2*E*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 304

R_f 0.50 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.92 (3H, d, *J* 6.5, **Me**CHCH$_2$), 1.07 (9H, s, *t*-Bu), 1.89 (3H, d, *J* 6.0, **Me**CHCH), 2.29 (2H, m, CH**H**CO, superimposing MeC**H**CH$_2$), 2.82 (1H, dd, *J* 6.0, 16.0, C**H**HCO), 3.48 (1H, dd, *J* 6.5, 10.0, CH**H**SiOR$_3$), 3.55 (1H, dd, *J* 6.5, 12.0, C**H**HOSiR$_3$), 6.13 (1H, d, *J* 14.0, C**H**CH(Me)), 6.84 (1H, appdd, *J* 6.0, 14.0, CHC**H**(Me)), 7.36-7.67 (10H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 16.75 (**C**Me$_3$), 18.20 (**Me**CHCH$_2$), 19.28 (**Me**CHCH), 26.84 (C**Me**$_3$), 32.51 (CH$_2$**C**HMe), 43.68 (**C**H$_2$CO), 68.34 (**C**H$_2$OSiR$_3$), 127.61 (Ph), 129.57 (Ph), 132.35 (**C**HCH(Me)), 133.73 (Ph), 135.57 (Ph), 142.44 (CH**C**H(Me)), 200.22 (**C**O).

ν_{max} (thin film) 3072-2840 (s, C-H), 1696 (m, C=O), 1670 (m, C=O), 1633 (m, C=C), 1513 (w), 1428 (m), 1365 (m), 1251 (m), 1109 (s), 971 (m), 824 (m), 740 (m), 703 (s).

m/z (FAB) 381 ($[MH]^+$, 26), 339 (16), 323 ($[M-(t\text{-Bu})]^+$, 100), 303 (50), 199 (64), 135 (53), 69 (30%).

HRMS (FAB) found *m/z* 381.2256; $C_{24}H_{33}O_2Si$ $[MH]^+$ requires *m/z* 381.2250.

$[\alpha]_D^{20}$ +15.5 (c=0.45 in DCM).

(2*Z*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 307

R_f 0.35 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.95 (3H, d, *J* 6.5, **Me**CHCH$_2$), 1.06 (9H, s, *t*-Bu), 2.11 (3H, d, *J* 5.5, **Me**CHCH), 2.23 (2H, m, CH**H**(CO) superimposing MeC**H**CH$_2$), 2.75 (1H, m, C**H**H(CO)), 3.48 (1H, dd, *J* 5.5, 10.0, CH**H**OSiR$_3$), 3.55 (1H, dd, *J* 6.0, 10.0, C**H**HOSiR$_3$), 6.17 (2H, apps, **H**C=C**H**), 7.36-7.68 (10H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 15.83 (**C**Me$_3$), 16.73 (**Me**CHCH$_2$), 19.25 (**Me**CHCH), 26.81 (C**Me**$_3$), 32.23 (CH$_2$**C**HMe), 47.95 (**C**H$_2$CO), 68.22 (**C**H$_2$OSiR$_3$), 127.58 (Ph), 127.97 (**C**HCH(Me)), 129.54 (Ph), 133.69 (Ph), 135.53 (Ph), 142.50 (CH**C**H(Me)), 201.54 (**C**O).

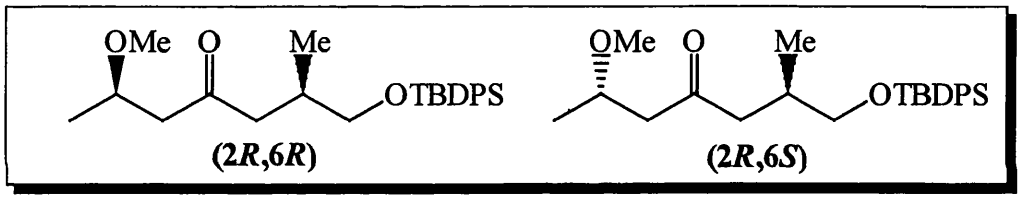
ν_{max} (thin film) 3072-2840 (s, C-H), 1692 (m, C=O), 1620 (m, C=C), 1512 (w), 1468 (m), 1427 (m), 1389 (m), 1365 (m), 1250 (m), 1109 (m), 936 (w), 824 (m), 740 (m), 703 (s), 612 (s).

m/z (FAB) 381 ($[MH]^+$, 6), 339 ($[M-(CHCH(Me))]^+$, 7), 323 ($[M-(t\text{-Bu})]^+$, 80), 303 (34), 199 (100), 135 (100), 125 (55), 69 (44%).

HRMS (FAB) found *m/z* 381.2256; $C_{24}H_{33}O_2Si$ $[MH]^+$ requires *m/z* 381.2250.

$[\alpha]_D^{21}$ +21.9 (c=0.36 in DCM).

(2*R*,6*R*)-1-(*t*-Butyl-diphenyl-silanyloxy)-6-methoxy-2-methyl-heptan-4-one and (2*R*,6*S*)-1-(*t*-butyl-diphenyl-silanyloxy)-6-methoxy-2-methyl-heptan-4-one 308



To a stirred solution of **307** (53mg, 0.14mmol) in MeOH (6ml) at rt was added NaOMe (0.4M in MeOH, 0.53ml, 0.21mmol) dropwise over 1 min. The resulting mixture was stirred at rt for 16 hrs. The reaction mixture was quenched with H_2O (50ml) and extracted (3x50ml EtOAc). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 40:1→20:1) to afford the title compounds as a clear oil (51mg, 86%) and as an inseparable 1:1 mixture of the two possible diastereoisomers.

R_f 0.27 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.91 (3H, d, *J* 6.5, **Me**CHCH$_2$), 1.07 (9H, s, *t*-Bu), 1.16 (3H, 2xd, *J* 6.0, 6.0, **Me**CHOMe), 2.20-2.29 (2H, m, CH**H**CHOMe superimposing CH**H**CHMe), 2.38 (1H, appdt, C**H**Me), 2.67-2.73 (2H, m, C**H**HCHOMe superimposing

CHHCHMe), 3.29-3.30 (3H, 2xs, OMe), 3.44 (1H, dd, *J* 2.5, 6.0, CHHOSiR$_3$), 3.53 (1H, dd, *J* 2.5, 6.0, CHHOSiR$_3$), 3.81 (1H, m, CHOMe), 7.27-7.72 (10H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 16.70 and 16.73 (**Me**CHCH$_2$), 19.22 and 19.27 (**Me**CHOMe), 26.83 (*t*-Bu), 31.64 and 31.73 (**C**HMe), 47.60 (**C**H$_2$CHMe), 50.03 and 50.07 (**C**H$_2$CHOMe), 56.25 (OMe), 68.14 and 68.23 (**C**H$_2$OSiR$_3$), 73.14 and 73.23 (**C**HOMe), 127.62 (Ph), 129.59 (Ph), 133.68 (Ph), 135.56 (Ph), 209.14 and 209.18 (**C**O).

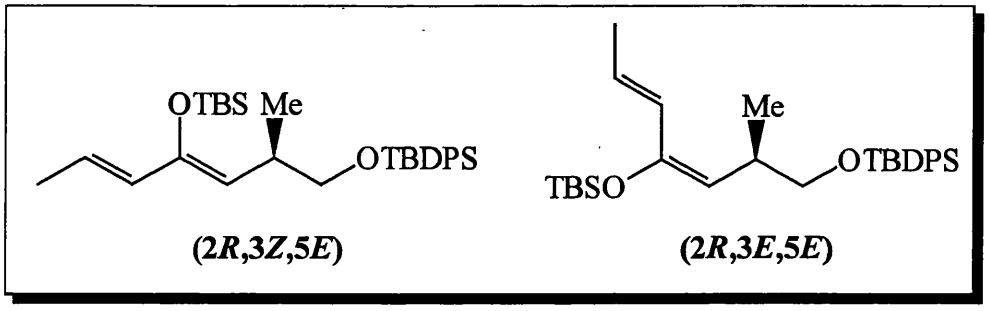
ν_{max} (thin film) 3072-2850 (s, C-H), 1713 (m, C=O), 1467 (m), 1428 (m), 1373 (m), 1110 (s), 823 (m), 741 (m), 703 (s).

m/z (FAB) 413 ([MH]$^+$, 16), 355 ([M-(*t*-Bu)]$^+$, 100), 339 (65), 323 (45), 303 (38), 297 (76), 277 (44), 239 (96), 219 (74), 213 (100), 207 (67%).

HRMS (FAB) found *m/z* 413.2504; $C_{25}H_{37}O_3Si$ [MH]$^+$ requires *m/z* 413.2512.

$[\alpha]_D^{20}$ +13.2 (c=0.2 in DCM).

(2*R*,3*Z*,5*E*)-(4-(*t*-Butyl-dimethyl-silanyloxy)-2-methyl-hepta-3,5-dienyloxy)-*t*-butyl-diphenyl-silane and (2*R*,3*E*,5*E*)-(4-(*t*-butyl-dimethyl-silanyloxy)-2-methyl-hepta-3,5-dienyloxy)-*t*-butyl-diphenyl-silane 309



(2*R*,3*Z*,5*E*) **(2*R*,3*E*,5*E*)**

To a stirred solution of **304** (287mg, 0.76mmol) in THF (7ml) at –78 °C was added NaHMDS (1.0M in THF, 0.84ml, 0.84mmol) dropwise over 1 min. The resulting mixture was stirred at –78 °C for 6 mins before a solution of TBSOTf (0.26ml, 1.14mmol) in THF (1ml) was added streamwise over approx 5 secs. The resulting

mixture was stirred at –78 °C for 16 mins. The reaction mixture was quenched with H_2O (50ml) and extracted (1x50ml EtOAc). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 400:1) to afford the title compound as a sparingly volatile oil (271mg, 72%) and as an inseparable 1:1 mixture of geometric isomers.

R_f 0.83 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, C_6D_6) 0.20-0.22 (6H, 4xs, Si**Me**$_2$), 1.07 (9H, s, ***t*-Bu**Ph_2Si), 1.08-1.19 (12H, m, ***t*-Bu**Me_2Si superimposing **Me**$CHCH_2$), 1.71 (3H, d, *J* 5.5, **Me**C(H)=), 3.19 (1H, m, Me**H**CH_2(CH)), 3.62-3.73 (2H, m, CH_2OSiR_3), 4.69 (1H, d, *J* 7.5, **CH**C(OTBS)CH), 6.00 (2H, apps, **H**C=C**H**), 7.35-7.96 (10H, m, Ph).

δ_C (125.8 MHz, C_6D_6) complex owing to geometric isomers, -4.40, -4.31, -3.61, -3.45, 0.70, 16.48, 16.58, 17.7, 17.81, 18.20, 18.62, 19.54, 19.60, 2.82, 25.96, 26.10, 26.19, 27.13, 33.60, 33.10, 34.67, 35.99, 41.02, 68.74, 68.90, 111.63, 111.88, 112.00, 115.53, 124.36, 127.47, 127.81, 128.20, 128.30, 128.51, 129.86, 129.91, 129.92, 130.75, 133.45, 134.40, 136.04, 136.08, 136.11, 148.65, 152.10, 155.08.

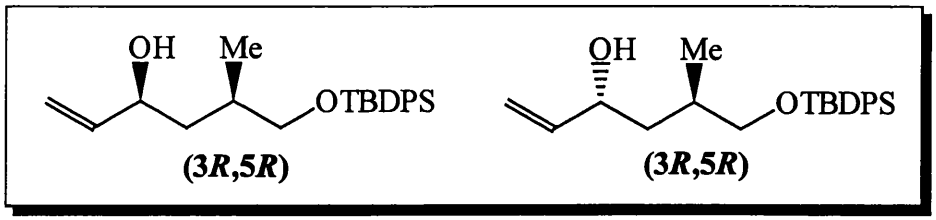
ν_{max} (thin film) 3075-2850 (s, C-H), 1644 (m with shoulder 2xC=C), 1590 (w), 1469 (m), 1427 (m), 1387 (m), 1360 (m), 1305 (m), 1255 (s), 1196 (m), 1111 (s), 1104 (s), 962 (m), 936 (m), 886 (m), 827 (s), 780 (s), 740 (m), 703 (s), 613 (s).

m/z (FAB) 495 ($[MH]^+$, 13), 438 ($[MH\text{-}(t\text{-Bu})]^+$, 63), 418 (18), 313 (21), 271 (100), 257 (37%).

HRMS (FAB) found *m/z* 495.3122; $C_{30}H_{47}O_2Si_2$ $[MH]^+$ requires *m/z* 495.3115.

$[\alpha]_D^{22}$ +9.6 (c=0.44 in DCM).

(3*S*,5*R*)-6-(*t*-Butyl-diphenyl-silanyloxy)-5-methyl-hex-1-en-3-ol and (3*R*,5*R*)-6-(*t*-butyl-diphenyl-silanyloxy)-5-methyl-hex-1-en-3-ol 312



To a stirred solution of **305**[100] (1.45g, 4.66mmol) in THF (46 ml) at –78 °C was added vinylmagnesium bromide (1.0M in THF, 7.0ml, 6.98mmol) over 1 min. The CO_2/acetone bath was removed and replaced with an ice/water bath and the resulting mixture was stirred for 1 hr. The reaction mixture was quenched at 0 °C by the careful addition of H_2O (100ml) and extracted (3x150ml Et_2O). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a clear oil (589mg, 99%) and as an inseparable 1:1 mixture of the two possible diastereomers.

R_f 0.24 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.82 (3H, d, *J* 7.0, Me), 0.97 (9H, s, *t*-Bu), 1.30-1.85 (3H, CH_2CHMe), 2.0-2.2 (1H, br s, OH), 3.32-3.50 (2H, m, CH_2COSiR_3), 4.01-4.16 (1H, m, CHOH), 4.99 (1H, appt, *J* 10.0, =CH**H**-(*trans*)), 5.15 (1H, dd, *J* 6.0, 17.0, =CH**H**-(*cis*)), 5.78 (1H, ddd, *J* 6.0, 10.0, 17.0, $HC=CH_2$), 7.28-7.63 (10H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) 17.55 (Me), 19.21 (CMe_3), 26.82(CMe_3), 32.12 and 33.18 (CHMe), 41.40 and 42.12 (CH_2CHMe), 68.93 and 69.50 (CH_2COSiR_3), 71.09 and 71.42 (CHOH), 114.08 and 114.50 ($=CH_2$), 127.64 (Ph), 129.64 (Ph), 133.48 (Ph), 135.60 (Ph), 141.25 and 141.63 ($HC=CH_2$).

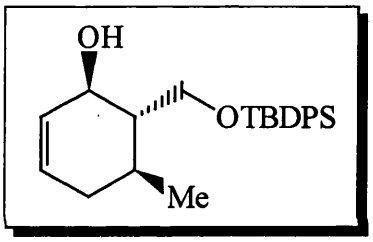
ν_{max} (thin film) 3382 (br s, OH), 3072-2850 (s, C-H), 1710 (m, HC=CH), 1589 (w), 1469 (m), 1427 (m), 1390 (m), 1363 (m), 1261 (m), 1189 (m), 1110 (s), 923 (m), 824 (m), 740 (m), 703 (s), 613 (s).

m/z (APCI, NH_3) 369 ($[MH]^+$, 9), 352 ($[(MH)-(H_2O)]^+$, 16), 339 (41), 279 (42), 239 (41), 201 (100), 179 (43), 129 (52%).

HRMS (FAB) found *m/z* 369.2246; $C_{23}H_{33}O_2Si$ $[MH]^+$ requires *m/z* 369.2250.

$[\alpha]_D^{21}$ +10.9 (c=0.27 in DCM).

(1*R*,5*S*,6*R*)-6-(*t*-Butyl-dipenyl-silanylyoxymethyl)-5-methyl-cyclohex-2-enol 317



Solutions of **301** (104mg, 0.27mmol) in PhMe (28ml) and **309** (271mg, 0.55mmol) in PhMe (10ml) were transferred to an Ace pressure tube under N_2 and the tube was sealed tightly. The sealed tube was heated at 190 °C for 3 days. After cooling to rt, the sealed tube was opened carefully and the reaction mixture was *conc in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate; 5:1) to afford the title compound as a yellow oil (97mg, 95%).

R_f 0.43 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Brucker, $CDCl_3$) 0.79 (3H, d, *J* 6.5, Me), 0.95 (9H, s, *t*-Bu), 1.11-1.76 (5H, m), 3.46 (1H, dd, *J* 6.5, 10.0, CH**H**OSiR$_3$), 3.66 (1H, dd, *J* 4.5, 10.0, C**H**HOSiR$_3$), 4.04 (1H, appd, *J* 3.5, C**H**OH), 5.78-5.82 (1H, m, **H**C=CHCHOH), 5.84 (1H, dd, *J* 1.5, 10.0, HC=C**H**CHOH), 7.30-7.57 (10H, m, Ph).

δ_C (75.4 MHz, $CDCl_3$) 19.31 (Me), 19.84 (**C**Me_3), 24.75, 26.86 (C**Me**$_3$), 38.76, 45.82, 64.19 (**C**HOH), 65.40 (**C**H_2OSiR_3), 127.64 (Ph), 128.96 (Ph), 129.62 (H**C**=CHCHOH), 133.26 (HC=**C**HCHOH), 133.68 (Ph), 135.61 (Ph).

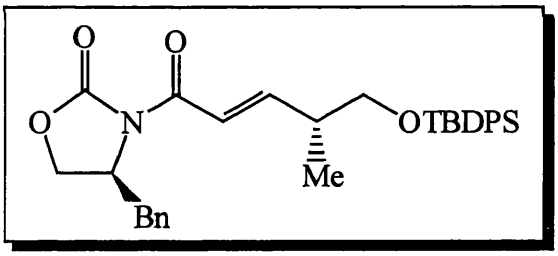
ν_{max} (thin film) 3341 (br s, OH), 3070-2850 (s, C-H), 1960 (w), 1891 (w), 1824 (w), 1737 (w), 1652 (w), 1590 (w), 1468 (s), 1428 (s), 1387 (m), 1256 (m), 1189 (m), 1110 (s), 1075 (s), 989 (s), 941 (m), 825 (s), 777 (s), 740 (s), 703 (s), 612 (s).

m/z (FAB) 403 ($[MNa]^+$, 1), 363 ($[(MH)-(H_2O)]^+$, 3), 199 (55), 153, (72%).

HRMS (FAB) found *m/z* 403.2087; $C_{24}H_{32}O_2SiNa$ $[MNa]^+$ requires *m/z* 403.2069.

$[\alpha]_D^{22}$ +26.7 (c=0.47 in DCM).

(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-(*t*-butyl-diphenyl-silanyloxy)-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 418



To a stirred solution of **244**[79] (5.98g, 16.84mmol) in MeCN (20ml) containing LiCl (1.30g, 30.59mmol) at rt was added Hünigs base (13.3ml, 76.53mmol) over 1 min and the resulting mixture was stirred at rt for 10 mins. A solution of **413**[76] (4.99g, 15.31mmol) in MeCN (20ml) was then added dropwise over 30 secs and the resulting mixture was stirred at rt for 13 hrs. The reaction mixture was diluted with Et_2O (200ml), washed with 10% (aq) HCl (100ml), and then satd (aq) NaCl (100ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a faint yellow oil (7.61g, 86%).

R_f 0.16 (petrol:ethyl acetate; 10:1).

δ_H (400 MHz Varian, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.12 (3H, d, *J* 7.0, Me), 2.67 (1H, m, MeC**H**), 2.82 (1H, dd, *J* 10.0, 13.5, PhCH**H**), 3.32 (1H, appdd, *J* 10.0, 13.5, PhC**H**H), 3.63 (2H, m, CH_2OSiR_3), 4.16 (2H, m, $CH_2O(CO)$), 4.72 (1H, m, C**H**N), 7.18-7.67 (17H, m, Ph superimposing alkenic protons).

δ_C (100.5 MHz Varian, $CDCl_3$) 15.70, 19.30, 28.85, 37.86, 39.70, 55.27, 55.33, 66.07, 67.59, 120.05, 127.29, 127.68, 128.94, 129.46, 129.66, 133.52, 135.38, 135.61, 153.90, 165.03.

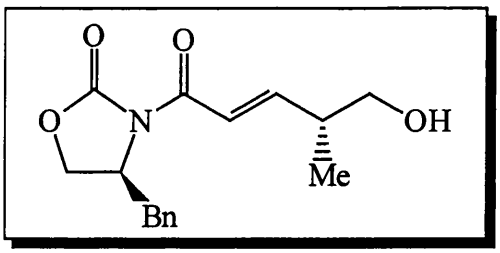
ν_{max} (thin film) 3070-2858 (s, C-H), 1779 (s, O(C=O)CH), 1681 (s, O(C=O)N), 1634 (s, HC=CH), 1589 (w), 1472 (m), 1454 (m), 1428 (m), 1386 (s), 1359 (s), 1255 (s), 1209 (s), 1104 (s), 1027 (m), 1006 (m), 983 (w), 824 (m), 805 (m), 741 (s), 702 (s), 614 (s).

m/z (FAB) 550 ($[MNa]^+$, 15), 528 ($[MH]^+$, 10), 470 (79), 450 (100), 416 (7), 376 (11), 356 (24), 338 (15), 293 (44), 197 (81%).

HRMS (FAB) found *m/z* 550.2377; $C_{32}H_{37}NO_4Si$ $[MNa]^+$ requires *m/z* 550.2390.

$[\alpha]_D^{18}$ +19.5 (c=0.30 in DCM).

(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 419



To a vigorously stirred solution of **418** (1.20g, 2.28mmol) in MeCN (10.3ml) and THF (10.3ml) at rt in a plastic container was added with care 40% (aq) HF (5.16ml) in a single portion. The resulting mixture was stirred vigorously at rt for 24 hrs. The reaction mixture was diluted with Et_2O (100ml) and quenched with care by the addition of solid

$NaHCO_3$ (10g) followed by the slow addition of water (100ml). The layers were separated and the aqueous layer extracted (2x50ml Et_2O). The combined organic layers were dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 5:1→1:1) to afford the title compound as a clear oil (671mg, 97%).

R_f 0.33 (petrol:ethyl acetate; 1:1).

δ_H (400 MHz Varian, $CDCl_3$) 1.11 (3H, d, *J* 7.0, Me), 2.09 (1H, br s, **OH**), 2.63 (1H, m, MeC**H**), 2.77 (1H, dd, *J* 9.5, 13.0, PhCH**H**), 3.30 (1H, appdd, *J* 3.0, 13.0, PhC**H**H), 3.64 (2H, m, CH_2OH), 4.20 (2H, m, $CH_2O(CO)$), 4.71 (1H, m, C**H**N), 7.18-7.67 (7H, m, Ph superimposing alkenic protons).

δ_C (100.5 MHz Varian, $CDCl_3$) 15.52, 37.75, 39.57, 36.66, 55.24, 66.10, 66.43, 120.68, 127.21, 128.84, 129.33, 135.22, 152.9, 164.92.

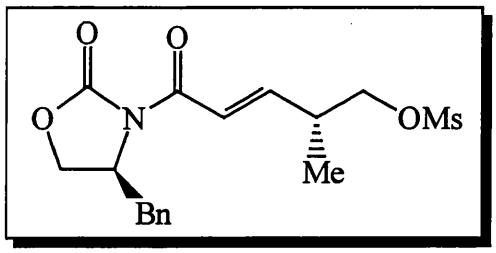
ν_{max} (thin film) 3443 (br s, OH), 3089-2875 (s, C-H), 1768 (s, O(C=O)CH), 1681 (s, O(C=O)N), 1633 (s, HC=CH), 1496 (m), 1480 (m), 1454 (s), 1360 (s), 1243 (s), 1103 (s, C-O), 1077 (s), 1040 (s), 1004 (s), 917 (m), 857 (m), 751 (s), 734 (s), 701 (s).

m/z (APCI, NH_3) 290 ($[MH]^+$, 100), 272 ($[MH-H_2O]^+$, 17), 260 (10), 210 (9), 178 (69), 117 (14%).

HRMS (FAB) found *m/z* 290.1399; $C_{16}H_{20}NO_4$ $[MH]^+$ requires *m/z* 290.1392.

$[\alpha]_D^{17}$ +16.2 (c=0.34 in DCM).

(2*R*,4'*S*,3*E*)-Methanesulfonic acid 5-(4'-benzyl-2'-oxo-oxazolidin-3'-yl)-2-methyl-5-oxo-pent-3-enyl ester 420



To a stirred solution of **419** (180mg, 0.62mmol) in DCM (5ml) at 0 °C was added Et_3N (0.26ml, 1.87mmol) followed by methanesulfonyl chloride (0.05ml, 0.69mmol) in single portions and the resulting mixture was stirred at 0 °C for 31 mins. The reaction mixture was diluted with Et_2O (50ml) and washed with water (50ml). The organic layer was dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 3:1→2:1) to afford the title compound as a faint yellow oil (215mg, 94%).

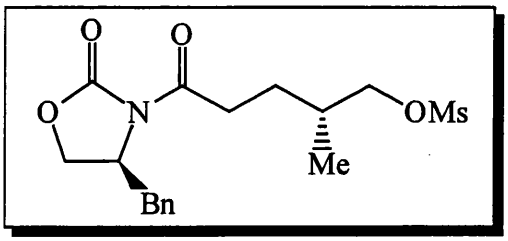
R_f 0.50 (petrol:ethyl acetate; 1:1).

δ_H (300 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.0, Me), 2.80 (1H, m, PhCH**H**), 2.92 (1H, m, MeC**H**), 3.04 (3H, s, $MeSO_2$), 3.33 (1H, m, PhC**H**H), 3.54 (4H, m, $CH_2O(CO)$ superimposing CH_2OMs), 4.83 (1H, m, C**H**N), 7.00-7.25 (7H, m, Ph superimposing alkenic protons).

ν_{max} (thin film) 3100-2939 (s, C-H), 1769 (s, O(C=O)CH), 1682 (s, O(C=O)N), 1643 (s, HC=CH), 1495 (w), 1455 (s), 1360 (s), 1211 (s), 1173 (s), 1107 (s), 1076 (m), 1054 (s), 964 (s), 837 (m), 751 (m), 706 (s).

m/z (FAB) 390 ($[MNa]^+$, 6), 368 ($[MH]^+$, 100), 272 ($[M-(OMs)]^+$, 28), 230 (5), 191 (9), 117 (20), 95 (78%).

(2*R*,4'*S*)-Methanesulfonic acid 5-(4'-benzyl-2'-oxo-oxazolidin-3'-yl)-2-methyl-5-oxo-pentyl ester 421



To a stirred solution of **420** (199mg, 0.55mmol) in MeOH (7ml) at rt was added with care Pd/C (30mg, 10 wt % palladium on activated carbon, Aldrich 20,569-9) and the reaction flask was evacuated and then flooded with hydrogen four times. The resulting suspension was stirred vigorously at rt under hydrogen for 13.5 hrs. The reaction mixture was filtered through a thin plug of Celite™ and the filtrate was *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 1:1) to afford the title compound as a clear oil (197mg, 97%).

R_f 0.18 (petrol:ethyl acetate; 3:1).

δ_H (300 MHz, $CDCl_3$) 1.06 (3H, d, *J* 7.0, Me), 1.60-2.20 (3H, m, C**H**$_2$C**H**Me), 2.83 (1H, dd, *J* 14.0, 19.0, PhCH**H**), 3.33 (3H, s, $MeSO_2$ superimposing 2H, m, N(CO)C**H**$_2$), 3.33 (1H, dd, *J* 10.0, 19.0, PhC**H**H), 4.20 (4H, m, C**H**$_2$O(CO) superimposing C**H**$_2$OMs), 4.75 (1H, m, C**H**N), 7.00-7.25 (5H, m, Ph).

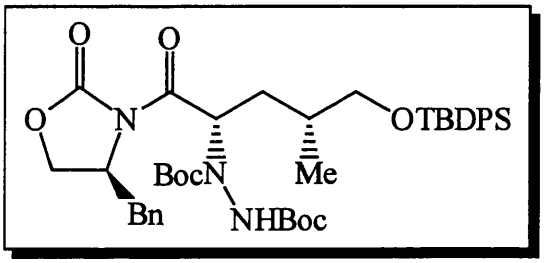
ν_{max} (thin film) 2937 (s, C-H), 1777 (s, O(C=O)CH_2), 1697 (s, O(C=O)N), 1454 (w), 1391 (m), 1352 (s), 1213 (m), 1173 (s), 1101 (w), 1053 (w), 961 (m), 839 (w), 748 (w), 705 (m).

m/z (FAB) 392 ($[MNa]^+$, 7), 370 ($[MH]^+$, 88), 274 ($[M-(OMs)]^+$, 71), 193 (15), 178 (100), 137 (34), 117 (44), 91 (48), 69 (39%).

HRMS (FAB) found *m/z* 370.1337; $C_{17}H_{24}NO_6S$ $[MH]^+$ requires *m/z* 370.1324.

$[\alpha]_D^{24}$ +37.8 (c=0.25 in DCM).

(4*S*,2'*S*,4'*R*)-4-Benzyl-3-[5'-(*t*-butyl-diphenyl-silanyloxy)-4'-methyl-2'-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)-pentanoyl]-oxazolidin-2-one 422



To a stirred solution of **418** (535 mg, 1.02mmol) in MeOH (15ml) at rt was added with care Pd/C (54mg, 10 wt % palladium on activated carbon, Aldrich 20,569-9) and the reaction flask was then evacuated and flooded with hydrogen four times. The resulting suspension was then stirred vigorously under hydrogen at rt for 2 hrs. The reaction mixture was filtered through a thin plug of Celite™ and the filtrate was *conc in vacuo* affording 504mg of residue. To a stirred solution of a portion of the residue (177mg) in THF (1ml) at –78 °C was added 0.5ml of a stock solution of LDA dropwise (prepared from adding *n*-BuLi (2.5M in hexanes, 1.48ml, 3.70mmol) to diisopropylamine (0.52ml, 3.70mmol) in THF (5ml) at –78 °C). The resulting mixture was stirred at –78 °C for 32 mins. A solution of DBAB (92mg, 0.40mmol) in DCM (2ml) at –78 °C was added over approx 5 secs and the resulting mixture was stirred at –78 °C for 49 mins during which time the yellow colour of the DBAD dissipated. The reaction mixture was quenched at –78 °C with glacial actetic acid (1ml) and partitioned with DCM (50ml) and pH 7 phosphate buffer (20ml). The aqueous layer was extracted (3x10ml DCM) and the combined organic layers were washed with satd (aq) $NaHCO_3$ (50ml), separated, dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a clear oil (207mg, 78% over two steps).

R_f 0.56 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) complex owing to rotamers, 0.89-1.07 (12H, m, *t*-BuSi, superimposing Me), 1.31-1.53 (18H, m, *t*-BuO), 1.62-2.20 (3H, m, CH_2CHMe), 2.70-3.49 (2H, m, $PhCH_2$), 3.51-3.58 (2H, m, CH_2OSiR_3), 4.09-4.16 (2H, m, $CH_2O(CO)$), 4.53-4.56 (1H, m, BnCHN), 5.85-6.00 (1H, br s, N(CO)CHNBoc), 6.50-6.75 (1H, br s, NH, rotamers), 7.17-7.68 (15H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) complex owing to rotamers.

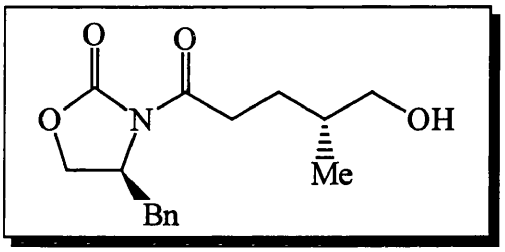
ν_{max} (thin film) 3385 (br s, N-H), 3000-2858 (s, C-H), 1789 (s, O(C=O)CH), 1713 (s, with two shoulders, 3xO(C=O)N), 1473 (m), 1428 (m), 1391 (s), 1367 (s), 1241 (s), 1152 (s), 1109 (s), 911 (w), 824 (w), 737 (m), 703 (s).

m/z (APCI, NH_3) 760 ($[MH]^+$, 28), 704 ($[(MH-(t\text{-}Bu))H]^+$, 20), 660 ($[(MH-(CO_2t\text{-}Bu))H]^+$, 100), 604 (73), 560 (49), 526 (23), 452 (60), 178 (70), 117 (21%).

HRMS (FAB) found *m/z* 782.3840; $C_{42}H_{57}N_3O_8Si$ $[MNa]^+$ requires *m/z* 782.3813.

$[\alpha]_D^{17}$ +18.1 (c=0.14 in DCM).

(4*S*,4'*R*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pentanoyl]-oxazolidin-2-one 425



To a stirred solution of **419** (250mg, 0.87mmol) in EtOAc (10ml) at rt was added with care Pd/C (25mg, 10 wt % palladium on activated carbon, Aldrich 20,569-9) and the reaction flask was then evacuated and flooded with hydrogen four times. The resulting suspension was then stirred vigorously under hydrogen at rt for 32 mins. The reaction mixture was filtered through a thin plug of Celite™ and the filtrate was *conc in vacuo.*

The residue was dried from benzene (3x5ml) *in vacuo* to afford the title compound as a clear oil (251mg, 99%).

R_f 0.32 (petrol:ethyl acetate; 1:1).

δ_H (400 MHz Varian, $CDCl_3$) 0.95 (3H, d, *J* 7.0, Me), 1.56 (1H, m, MeC**H**), 1.68-1.85 (2H, m, C**H**$_2$CHMe), 1.88, (1H, br s, O**H**), 2.75 (1H, dd, *J* 2.5, 13.0, PhCH**H**), 2.93 (2H, m, C**H**$_2$C(O)N), 3.24 (1H, dd, *J* 3.0, 13.0, PhC**H**H), 3.48 (2H, m, C**H**$_2$OSiR$_3$), 4.16 (2H, m, C**H**$_2$O(CO)), 4.64 (1H, m, C**H**N), 7.17-7.33 (5H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) 16.40, 27.19, 32.93, 35.15, 37.78, 55.08, 66.14, 67.12, 117.05, 128.85, 129.30, 135.10, 153.39, 173.46.

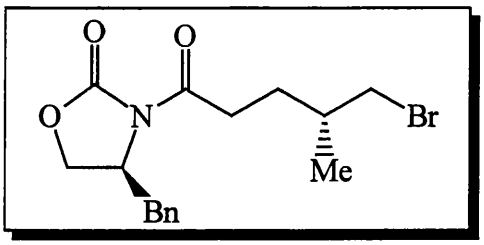
ν_{max} (thin film) 3417 (br s, OH), 3029-2874 (s, C-H), 1789 (s, O(C=O)CH_2), 1694 (s, O(C=O)N), 1454 (s), 1392 (s), 1357 (s), 1213 (s), 1098 (s), 1047 (s), 916 (w), 841 (w), 744 (s), 703 (s).

m/z (APCI, NH_3) 314 ($[MNa]^+$, 3), 274 ($[MH\text{-}H_2O]^+$, 78), 210 (12), 178 (100), 117 (27).

HRMS (FAB) found *m/z* 292.1562; $C_{16}H_{22}NO_4$ $[MH]^+$ requires *m/z* 292.1549.

$[\alpha]_D^{17}$ +36.4 (c=0.29 in DCM).

(4*S*,4'*R*)-4-Benzyl-3-[5'-bromo-4'-methyl-pentanoyl]-oxazolidin-2-one 426



To a stirred solution of **425** (206mg, 0.70mmol) in THF (7ml) at rt was added PPh_3 (548mg, 2.09mmol) and CBr_4 (693mg, 2.09mmol) in single portions. The resulting mixture was stirred at rt for 37 mins during which time a yellow precipitate formed. The reaction mixture was *conc in vacuo*, Et_2O was added to the residue and the white

precipitate which formed on cooling the flask to 0 °C was filtered off. The filtrate was *conc in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate; 20:1→10:1) to afford the title compound as a clear oil (206mg, 83%).

R_f 0.53 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) 1.04 (3H, d, *J* 6.0, Me), 1.62 (1H, m, MeC**H**), 1.66-1.89 (2H, m, CH_2CHMe), 2.78 (1H, dd, *J* 3.0, 13.0, PhCH**H**), 2.94 (2H, m, CH_2C(O)N), 3.27 (1H, dd, *J* 3.0, 13.0, PhC**H**H), 3.42 (2H, m, CH_2Br), 4.18 (2H, m, CH_2O(CO)), 4.65 (1H, m, C**H**N), 7.17-7.33 (5H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) 18.53, 29.04, 32.94, 34.41, 37.79, 40.63, 55.05, 66.16, 127.26, 128.86, 129.29, 135.11, 153.34, 172.66.

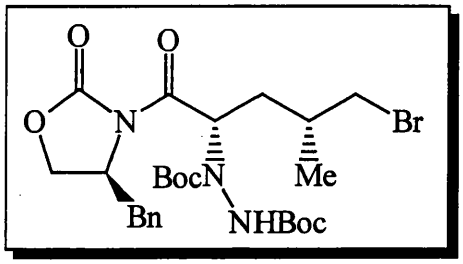
ν_{max} (thin film) 3063-2873 (s, C-H), 1789 (s, O(C=O)CH_2), 1695 (s, O(C=O)N), 1606 (w), 1486 (m), 1480 (m), 1454 (s), 1391 (s), 1353 (s), 1287 (s), 1211 (s), 1104 (s), 1076 (s), 1052 (s), 1052 (s), 1016 (m), 919 (w), 840 (w), 762 (s), 744 (s), 703 (s).

m/z (APCI, NH_3) 354/356 ($[M(^{79}Br/^{81}Br)H]^+$, 35), 274 ($[M-(HBr)]^+$, 36), 210 (20), 178 (100), 117 (16%).

HRMS (FAB) found *m/z* 354.0700; $C_{16}H_{21}BrNO_3$ $[MH]^+$ requires *m/z* 354.0705.

$[\alpha]_D^{18}$ +40.9 (c=0.39 in DCM).

(4*S*,2'*S*,4'*R*)-4-Benzyl-3-[5'-bromo-4'-methyl-2'-(*N*,*N*'-bis-(*t*-butoxycarbonyl) hydrazino)-pentanoyl]-oxazolidin-2-one 424



To a solution of diisopropylamine (0.05ml, 0.37mmol) in THF (0.5ml) at –78 °C was added *n*-BuLi (2.5M in hexanes, 0.15ml, 0.37mmol) dropwise over 10 secs. The resulting mixture was stirred at -78 °C for 8 mins. A solution of **426** (118mg, 0.33mmol) in THF (1.0ml) was added dropwise over 30 secs and stirring at –78 °C was continued for 58 mins. A solution of DBAB (92mg, 0.40mmol) in DCM (2ml) was then added dropwise over 20 secs and the resulting mixture was stirred at –78 °C for 58 mins during which time the yellow colour of the DBAD dissipated. The reaction was quenched at –78 °C with glacial actetic acid (1ml) and partitioned with DCM (20ml) and pH 7 phosphate buffer (50ml). The aqueous layer was extracted (2x20ml DCM) and the combined organic layers were washed with satd (aq) $NaHCO_3$ (50ml), separated, dried ($MgSO_4$), filtered, and *conc in vacuo.* The residue was purified by flash column chromatography (petrol:ethyl acetate; 10:1) to afford the title compound as a pale yellow oil (174mg, 90%).

R_f 0.46 (petrol:ethyl acetate; 3:1).

δ_H (400 MHz Varian, $CDCl_3$) complex owing to rotamers, 0.96-1.13 (3H, 3xd, *J* 6.5, 6.5, 6.5, Me), 1.23-1.57 (18H, m, *t*-BuO), 1.62-2.20 (3H, m, CH_2CHMe), 2.70-3.60 (4H, m, $PhCH_2$ and CH_2Br), 4.07-4.22 (2H, m, $CH_2O(CO)$), 4.53-4.56 (1H, m, BnCHN), 5.85-6.00 (1H, m, N(CO)CHNBoc), 6.75 (1H, br m, NH), 7.17-7.68 (5H, m, Ph).

δ_C (100.5 MHz Varian, $CDCl_3$) complex owing to rotamers.

ν_{max} (thin film) 3354 (br s, N-H), 3000-2933 (s, C-H), 1790 (s, O(C=O)CHN), 1731 (s, O(C=O)N), 1714 (s, O(C=O)N), 1682 (s, O(C=O)N), 1567 (w), 1480 (s), 1455 (s), 1393 (s), 1368 (s), 1248 (s), 1152 (s), 1110 (s), 1049 (s), 945 (w), 852 (m), 738 (s), 702 (s).

m/z (APCI, NH_3) 584/586 ($[M(^{79}Br/^{81}Br)H]^+$, 2), 528/530 ($[(M(^{79}Br/^{81}Br)H\text{-}(t\text{-Bu}))H]^+$, 3), 472/474 (36), 428/430 (56), 384/386 (73), 348 (5), 304 (9), 274 (18), 223 (13), 178 (100), 117 (24%).

HRMS (FAB) found *m/z* 606.1811; $C_{26}H_{38}BrN_3O_7Na$ $[MNa]^+$ requires *m/z* 606.1791.

$[\alpha]_D^{21}$ +21.2 (c=0.29 in DCM).

APPENDIX 1
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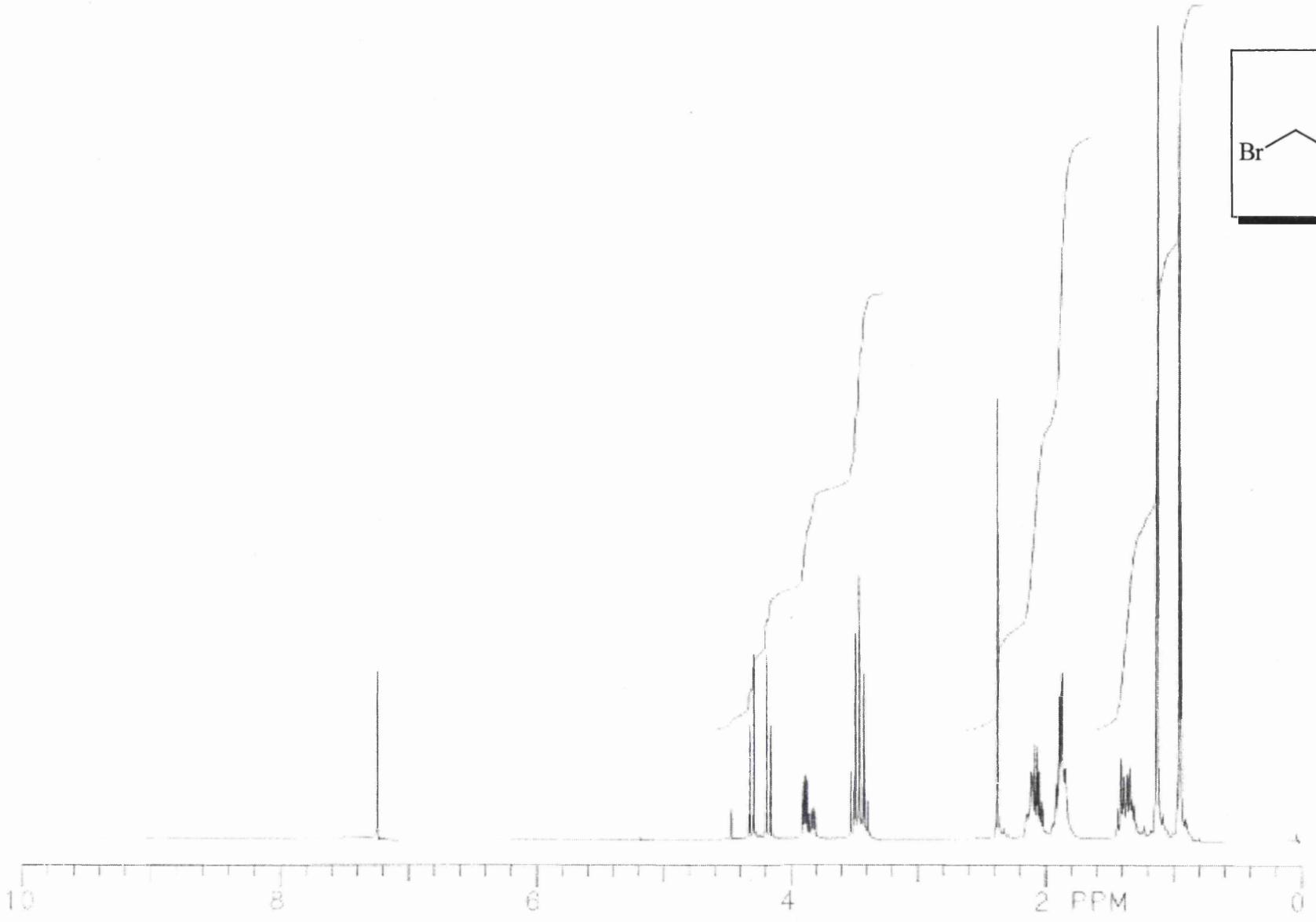
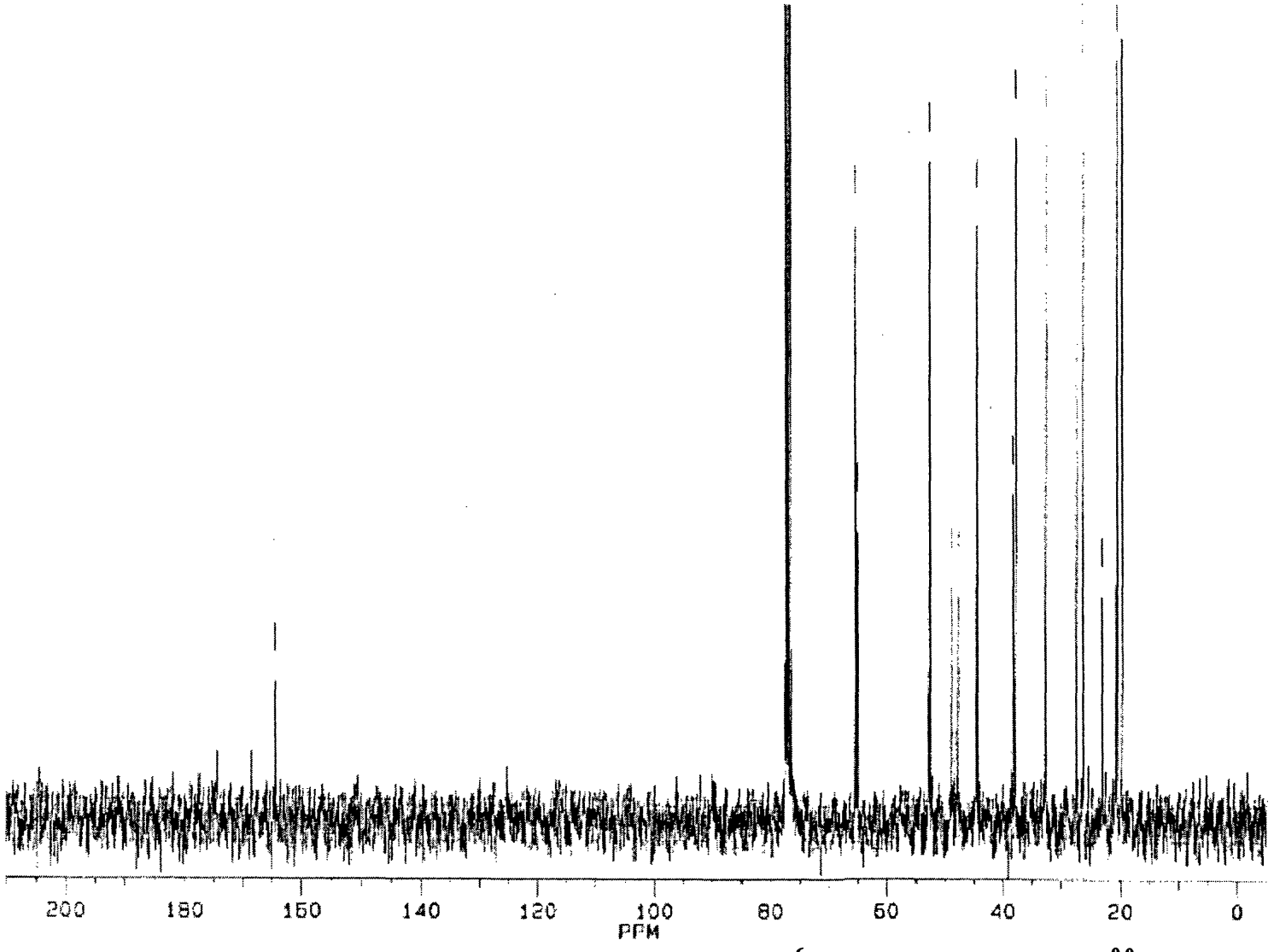
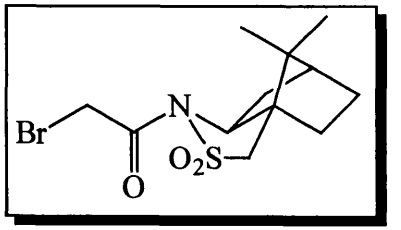
APPENDIX 2
SPECTRA

^{1}H nmr and ^{13}C nmr spectra are presented for each compound in Chapter 5 - Experimental Section and are given in the order they appear in the thesis.



(7*R*)-2-Bromo-1-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-ethanone





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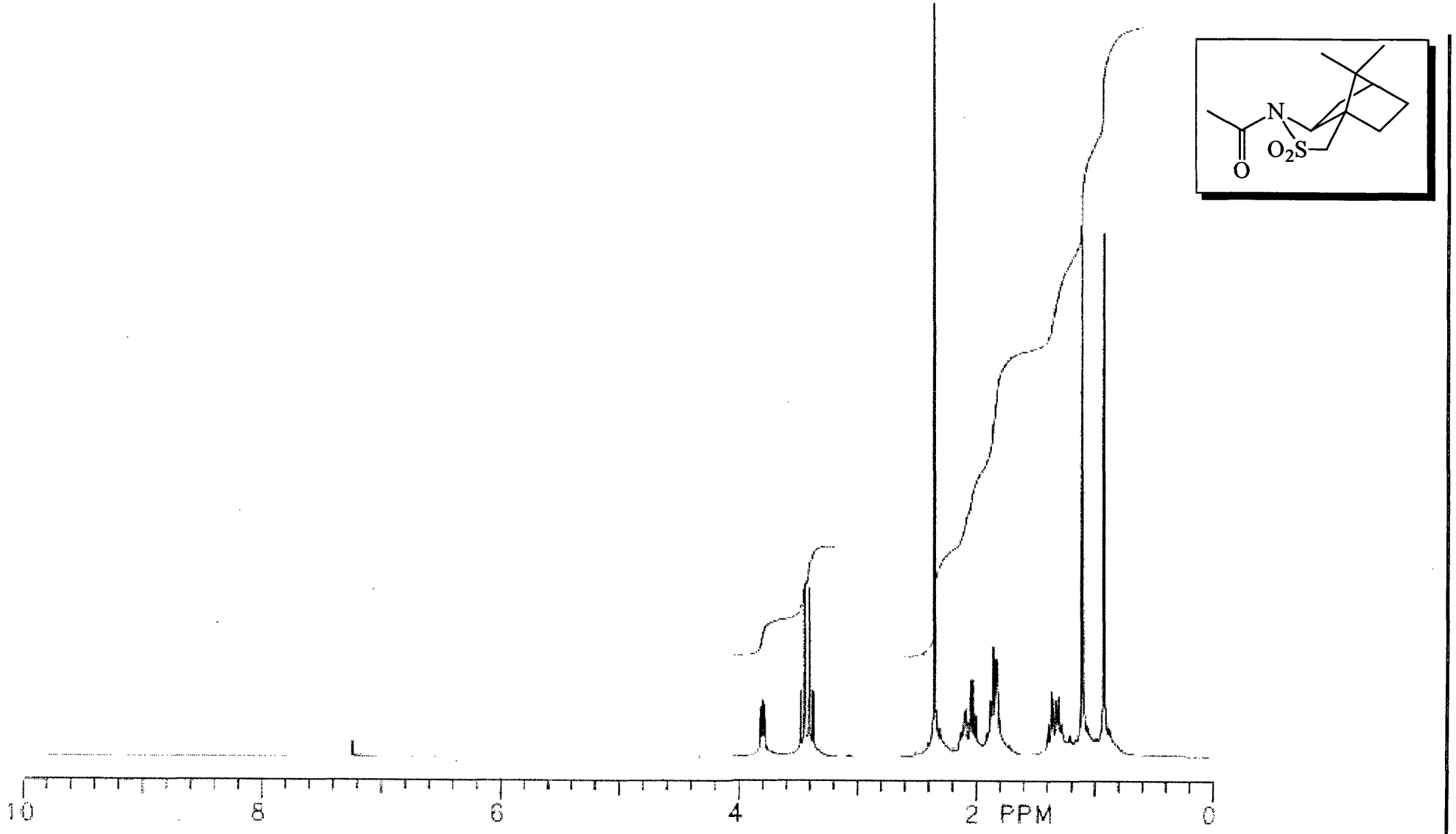

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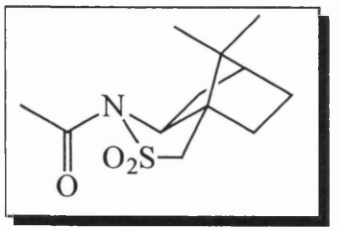

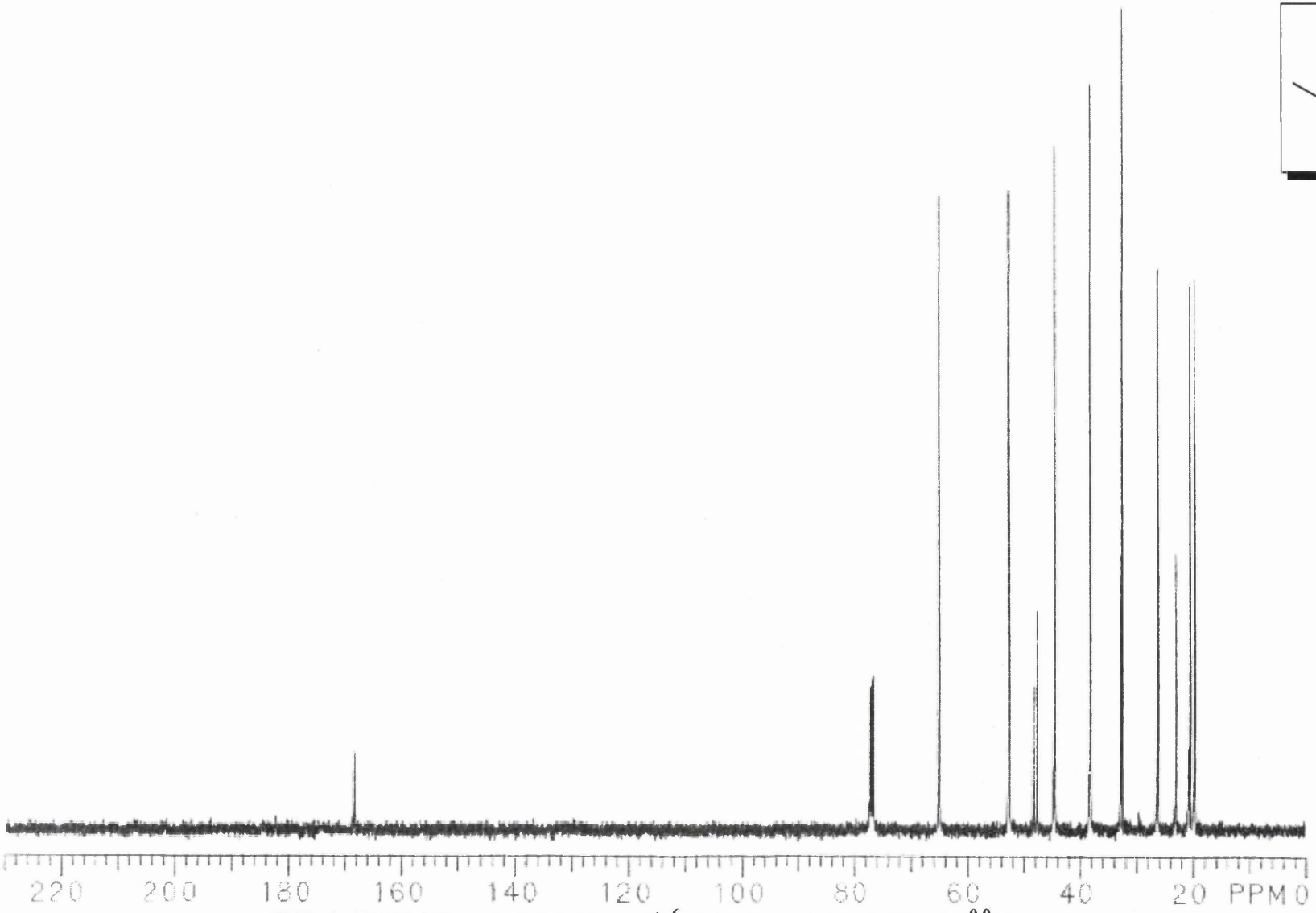

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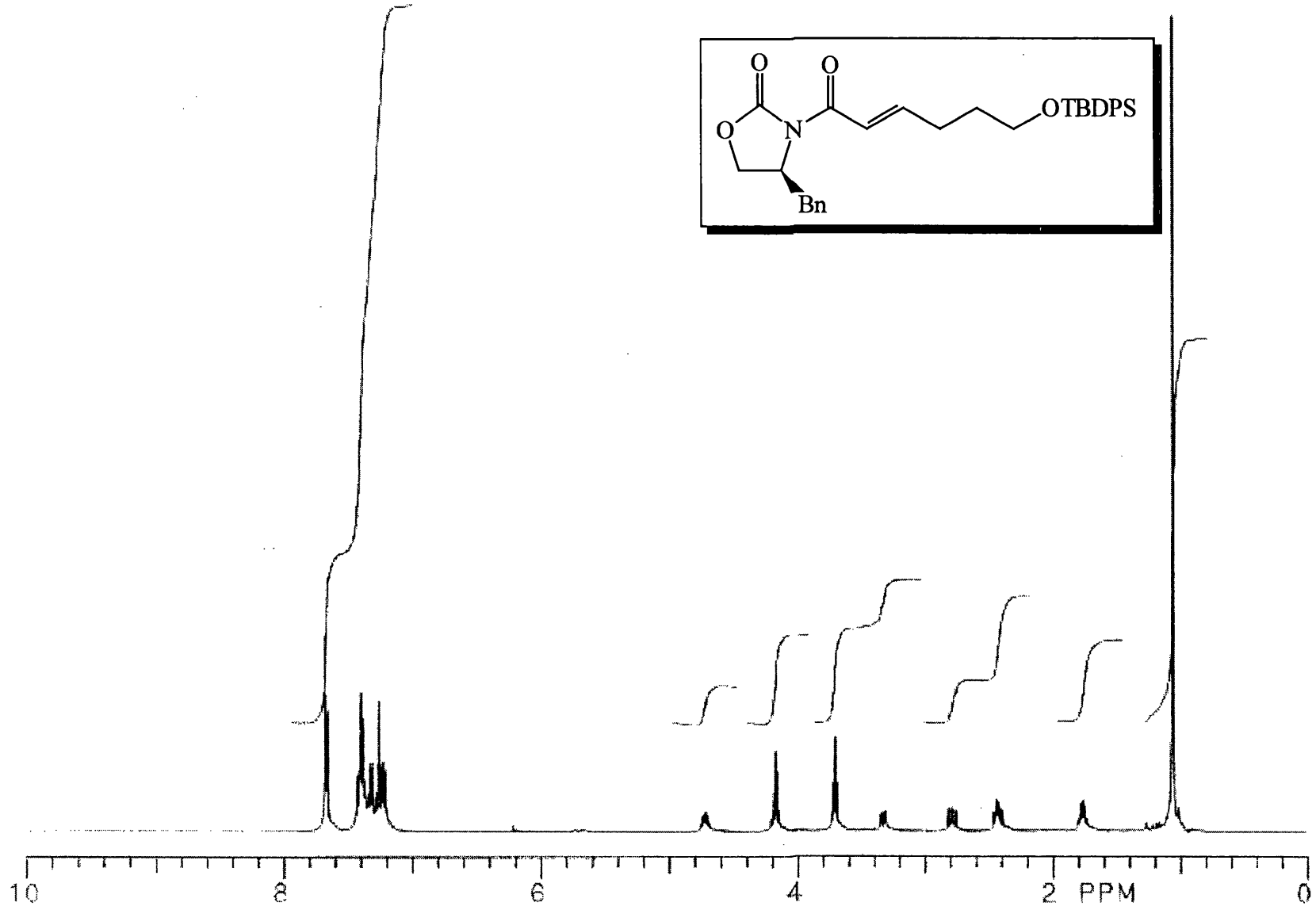

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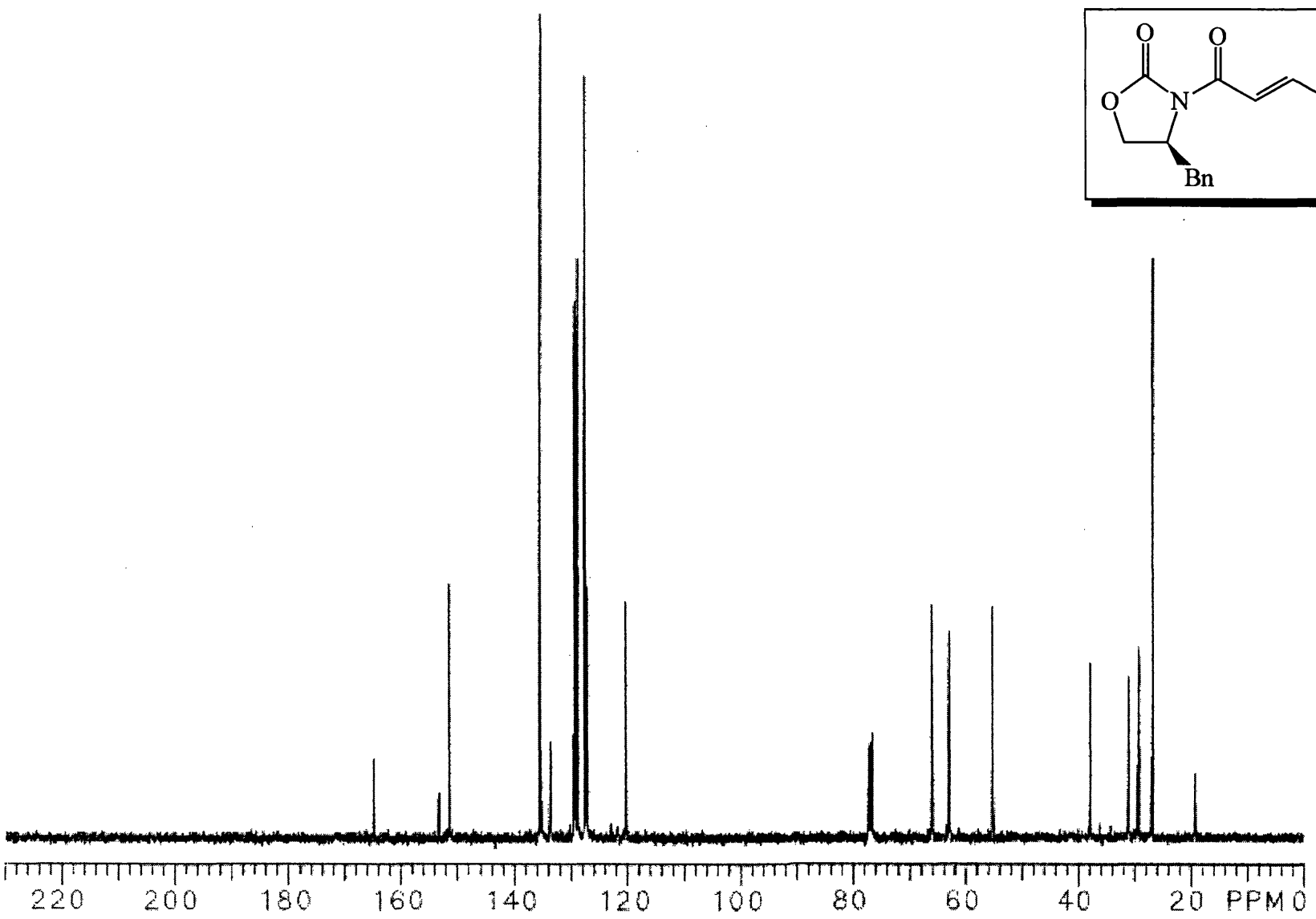

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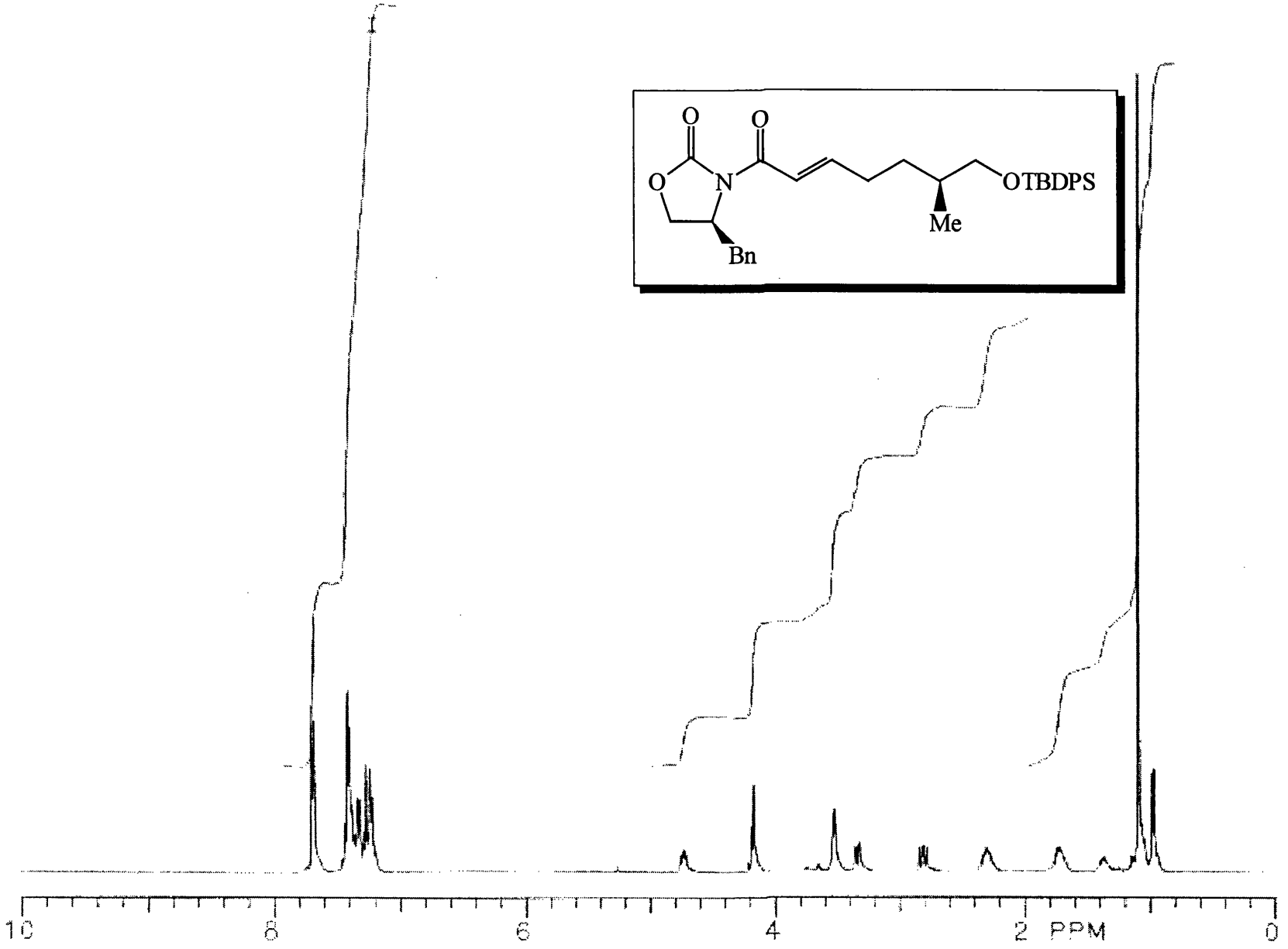
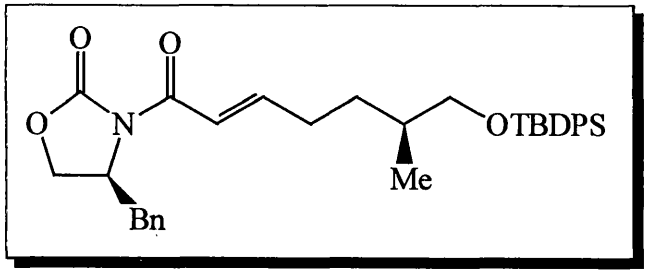


(4*S*,2'*E*,6'*S*)-4-Benzyl-3-[7'-(*t*-butyl-diphenyl-silanyloxy)-6'-methyl-hept-2'-enoyl]-oxazolidin-2-one 247



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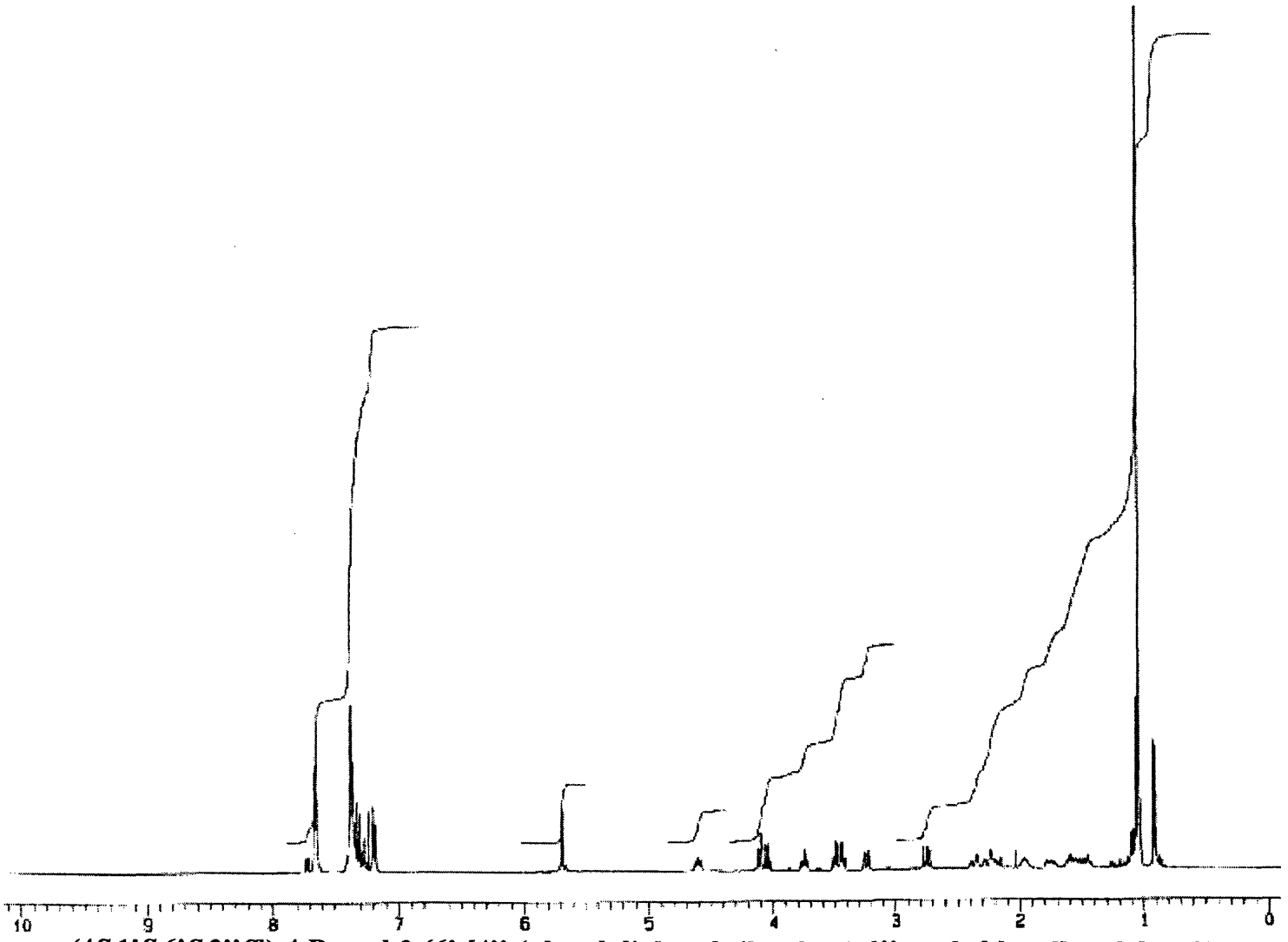

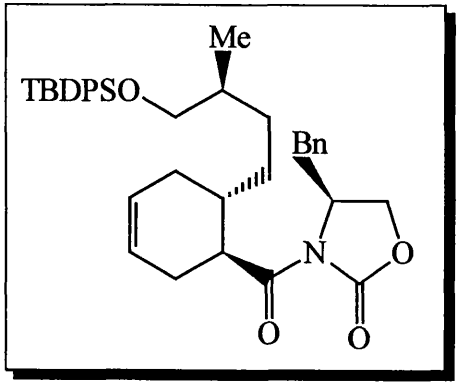

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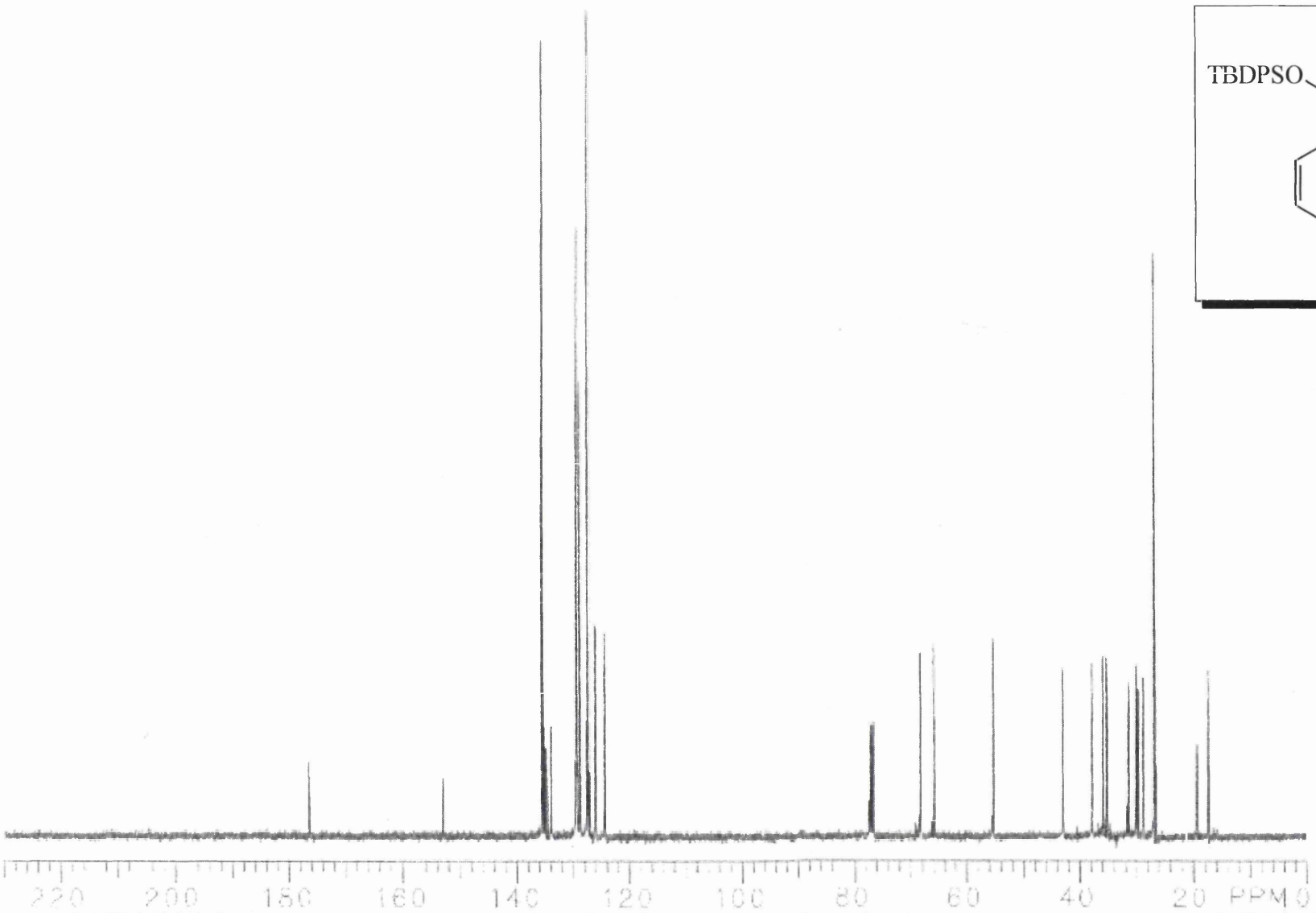

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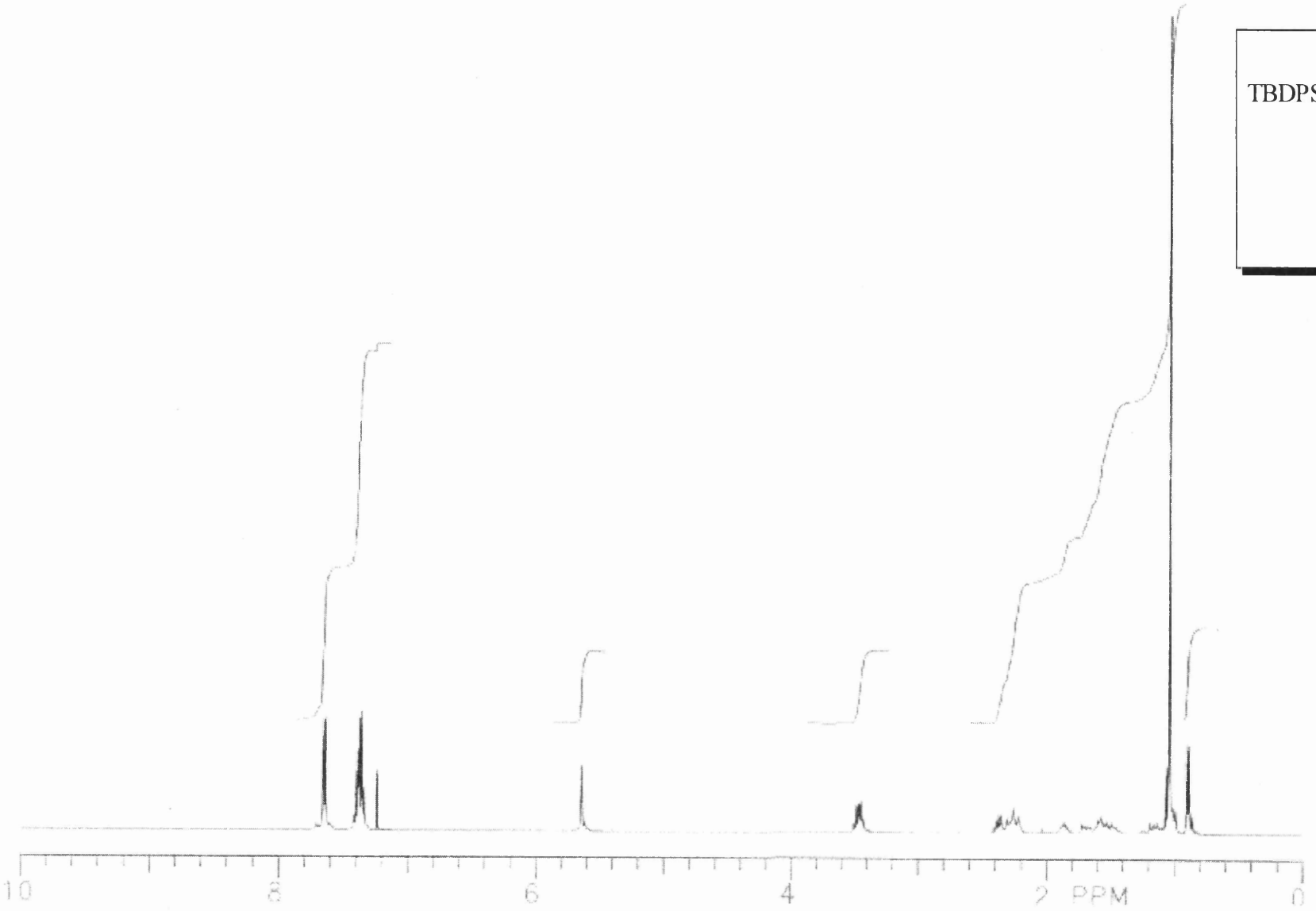

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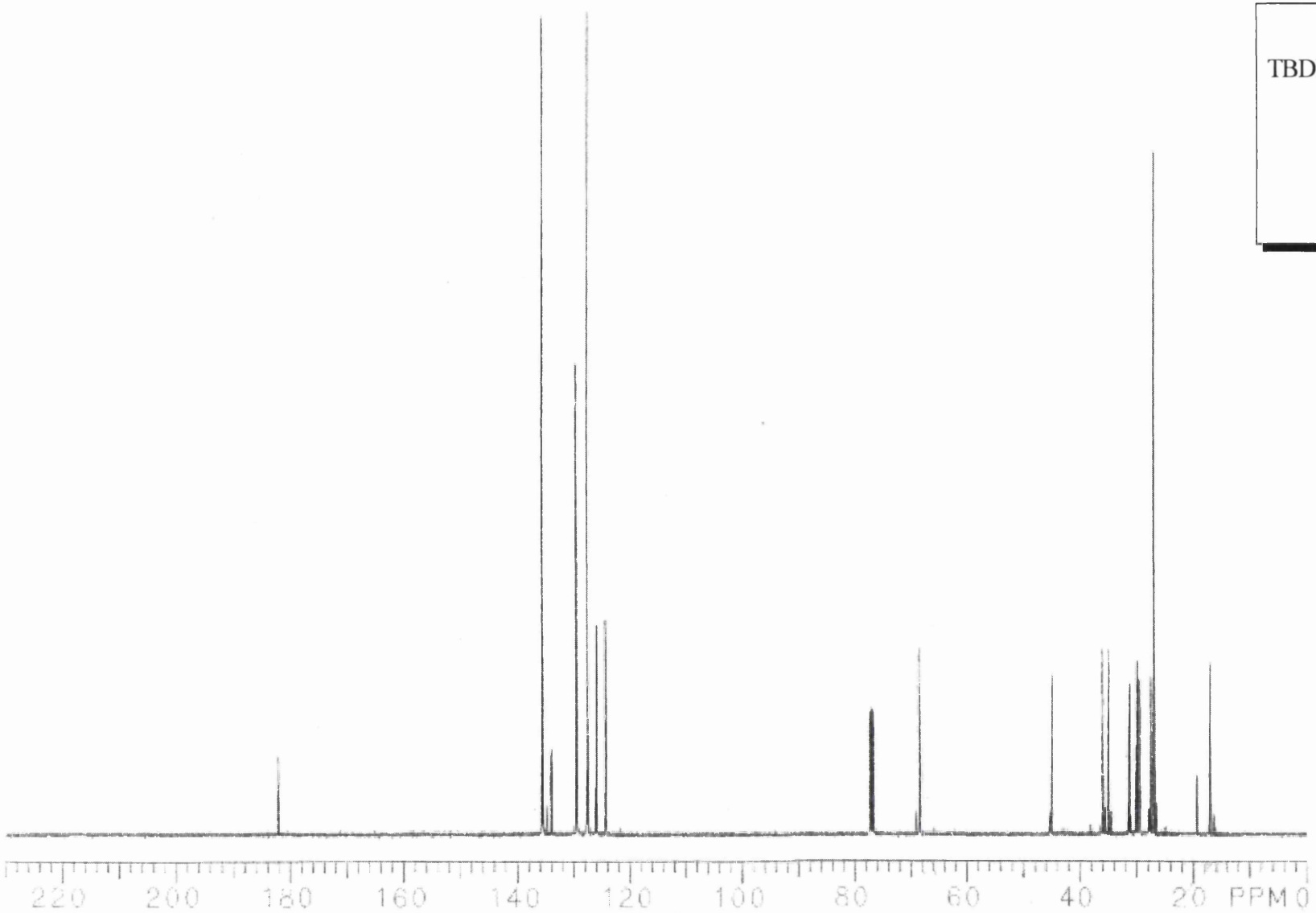

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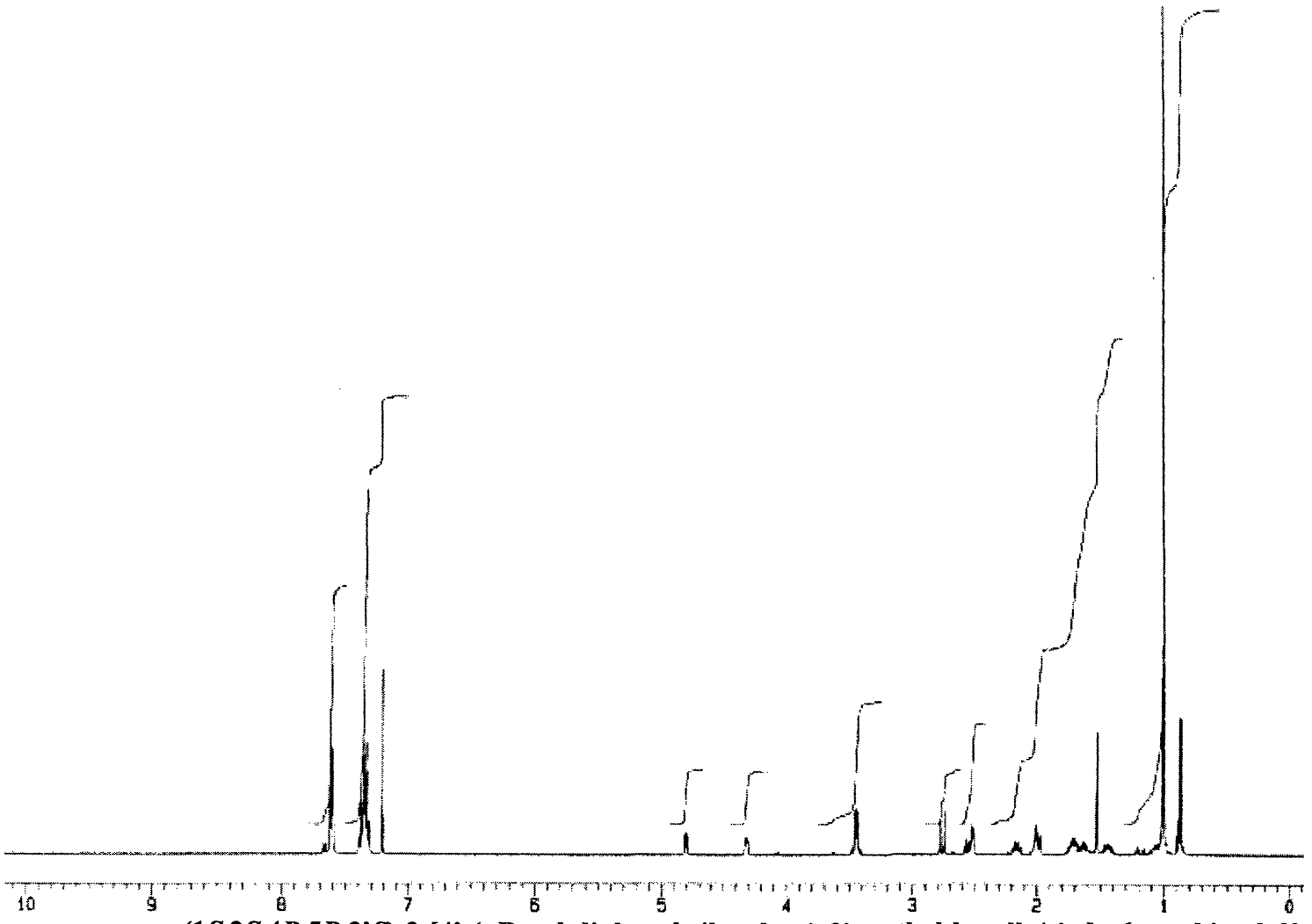

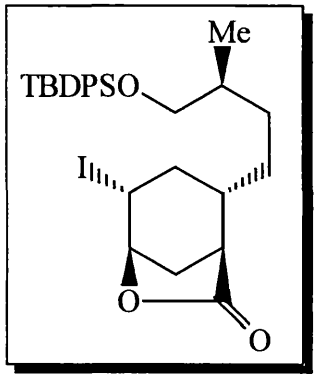

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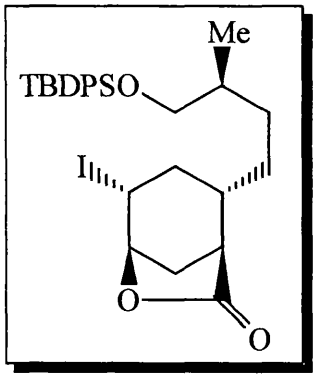

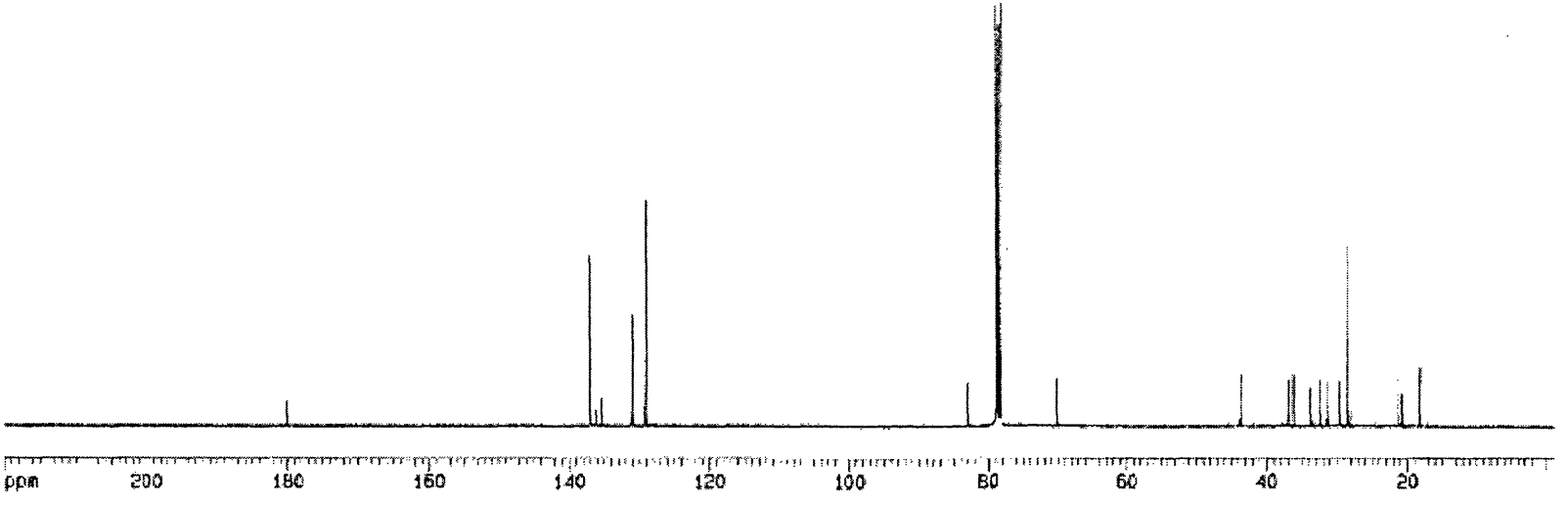

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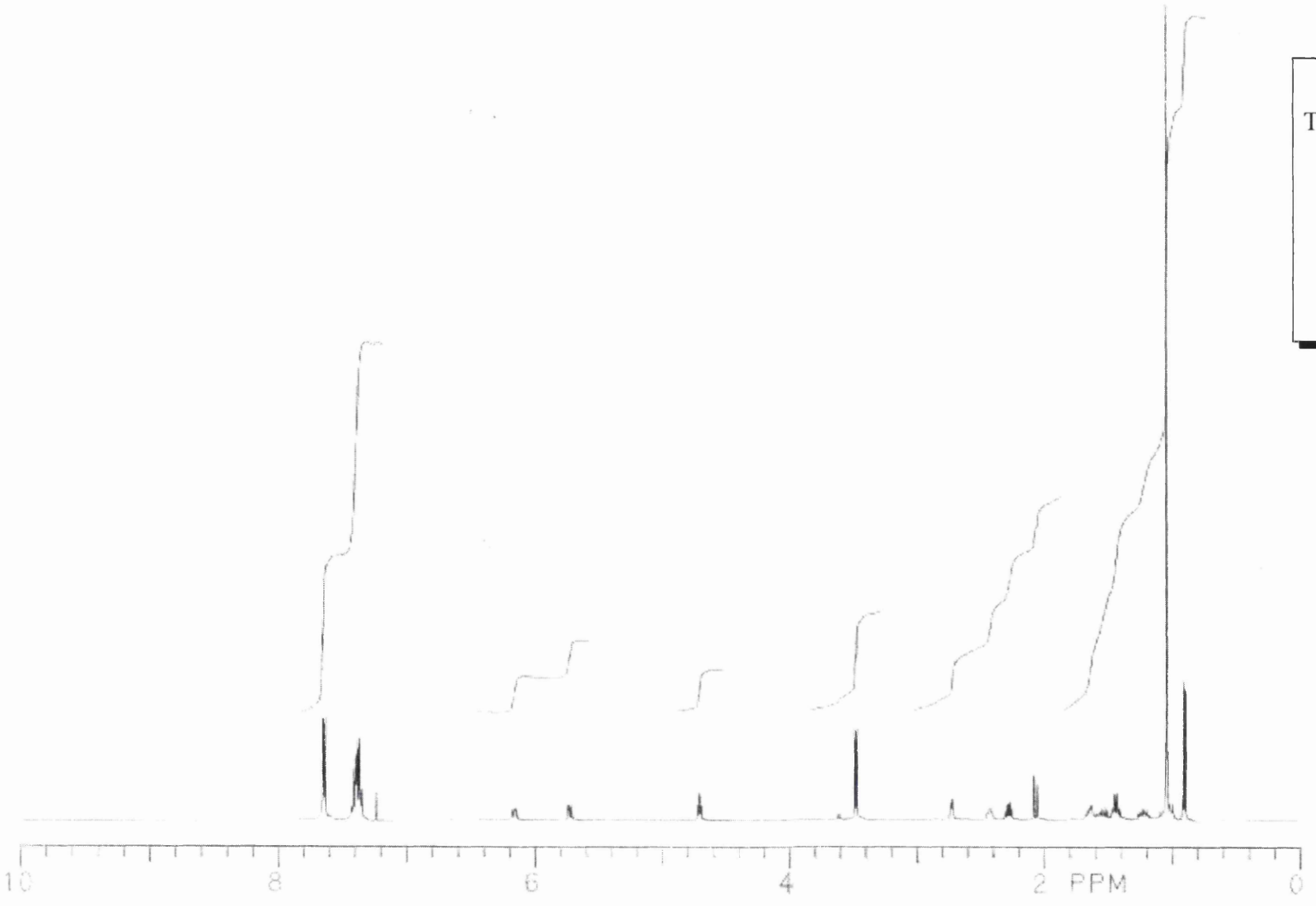

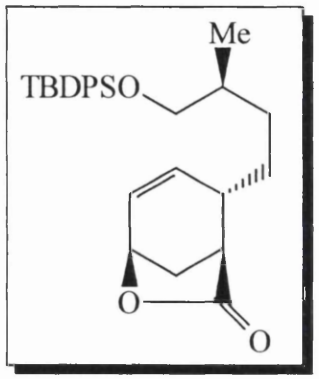

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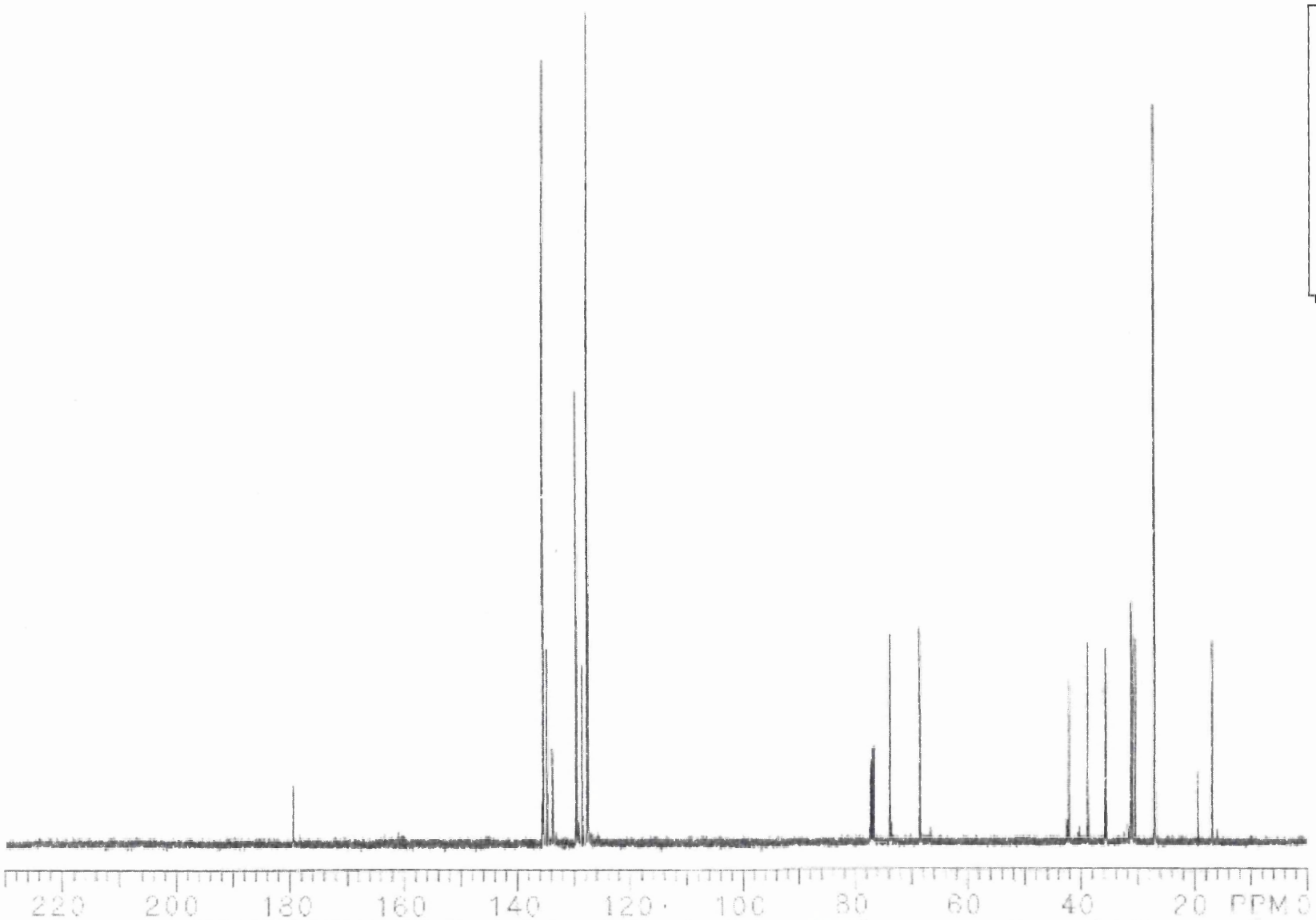

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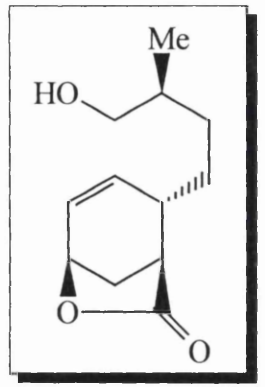
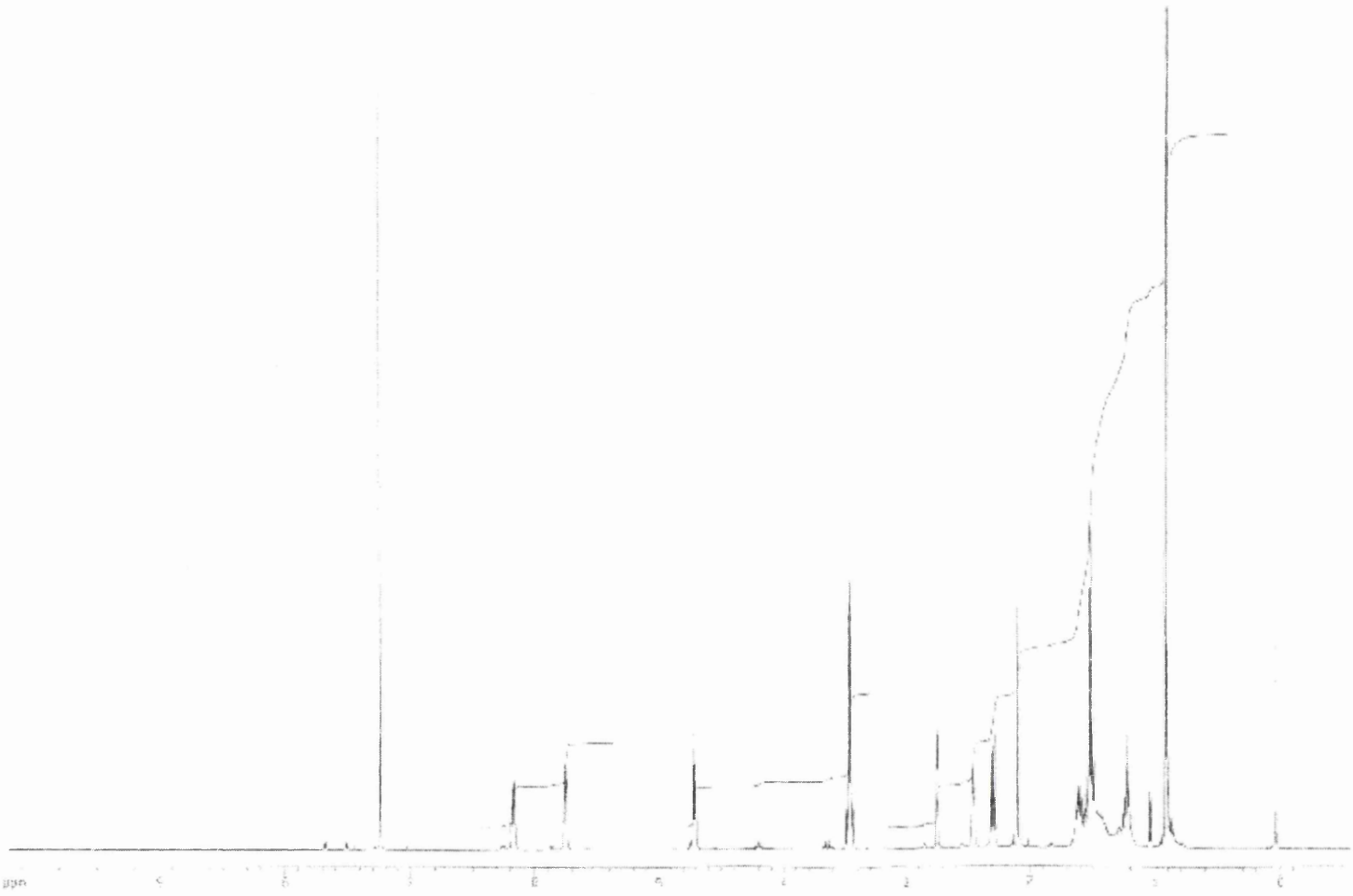
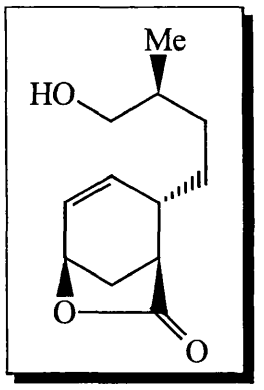
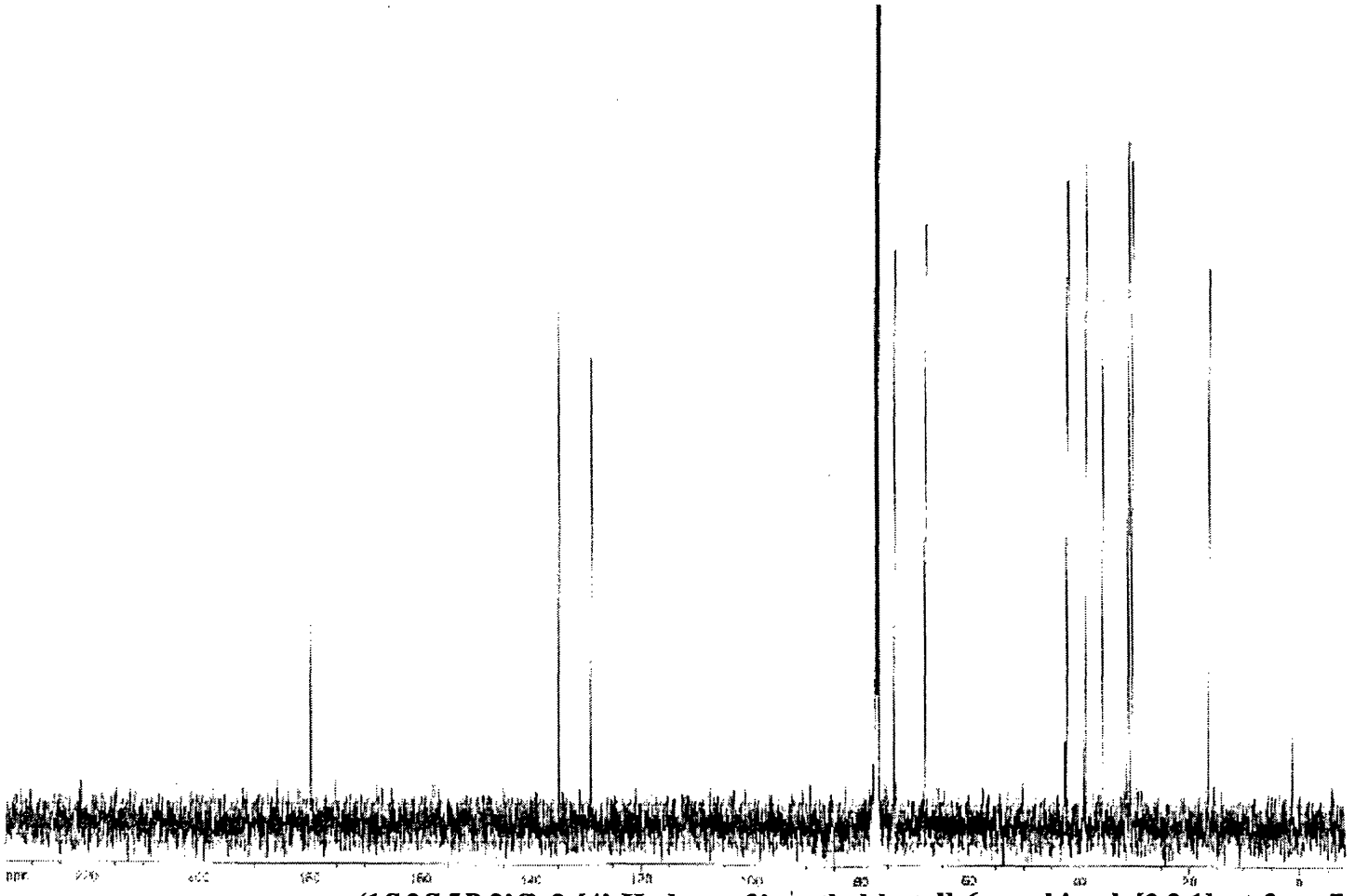


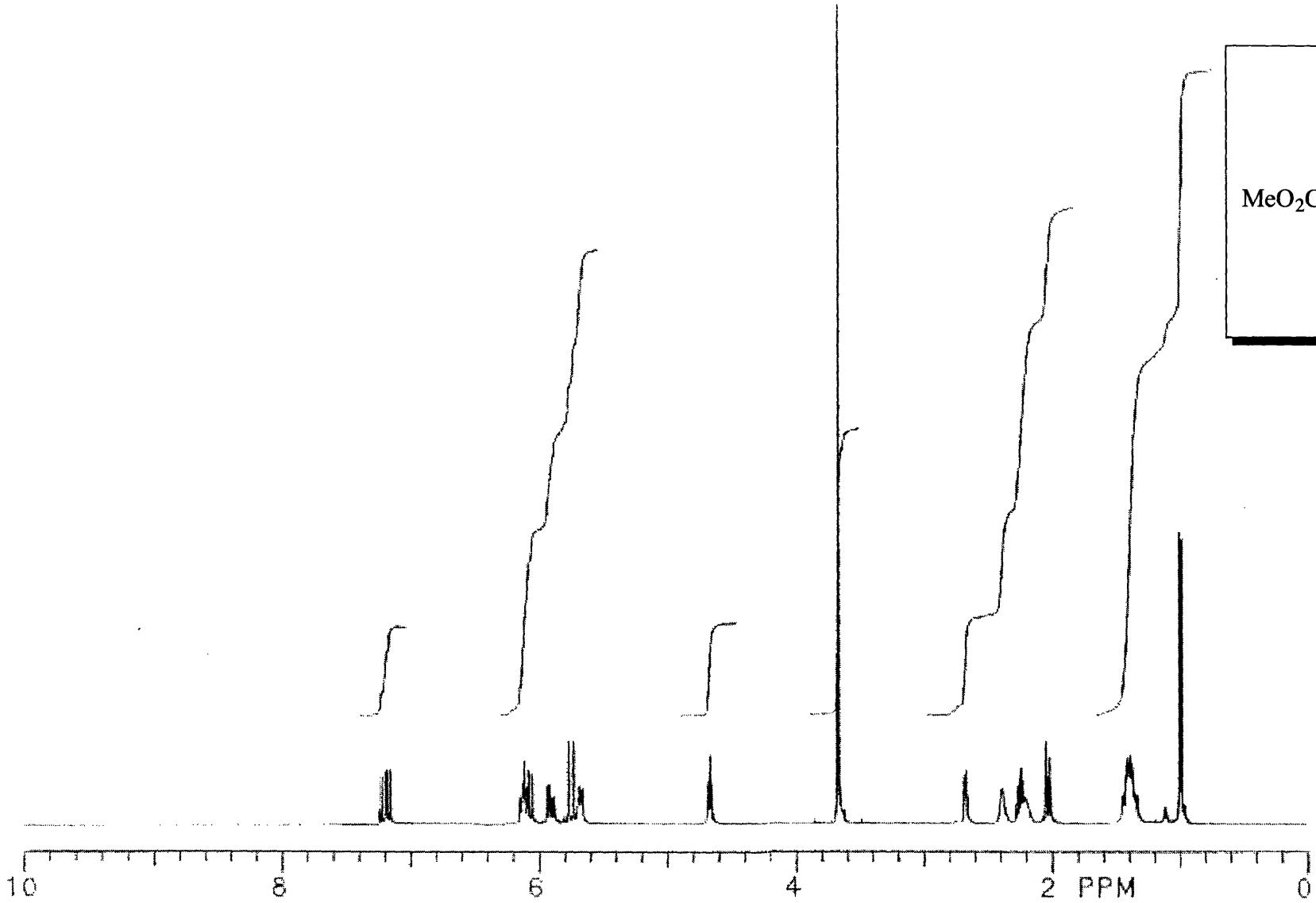


(1*S*,2*S*,5*R*,3'*S*)-2-[4'-Hydroxy-3'-methyl-butyl]-6-oxa-bicyclo[3.2.1]oct-3-en-7-one 252

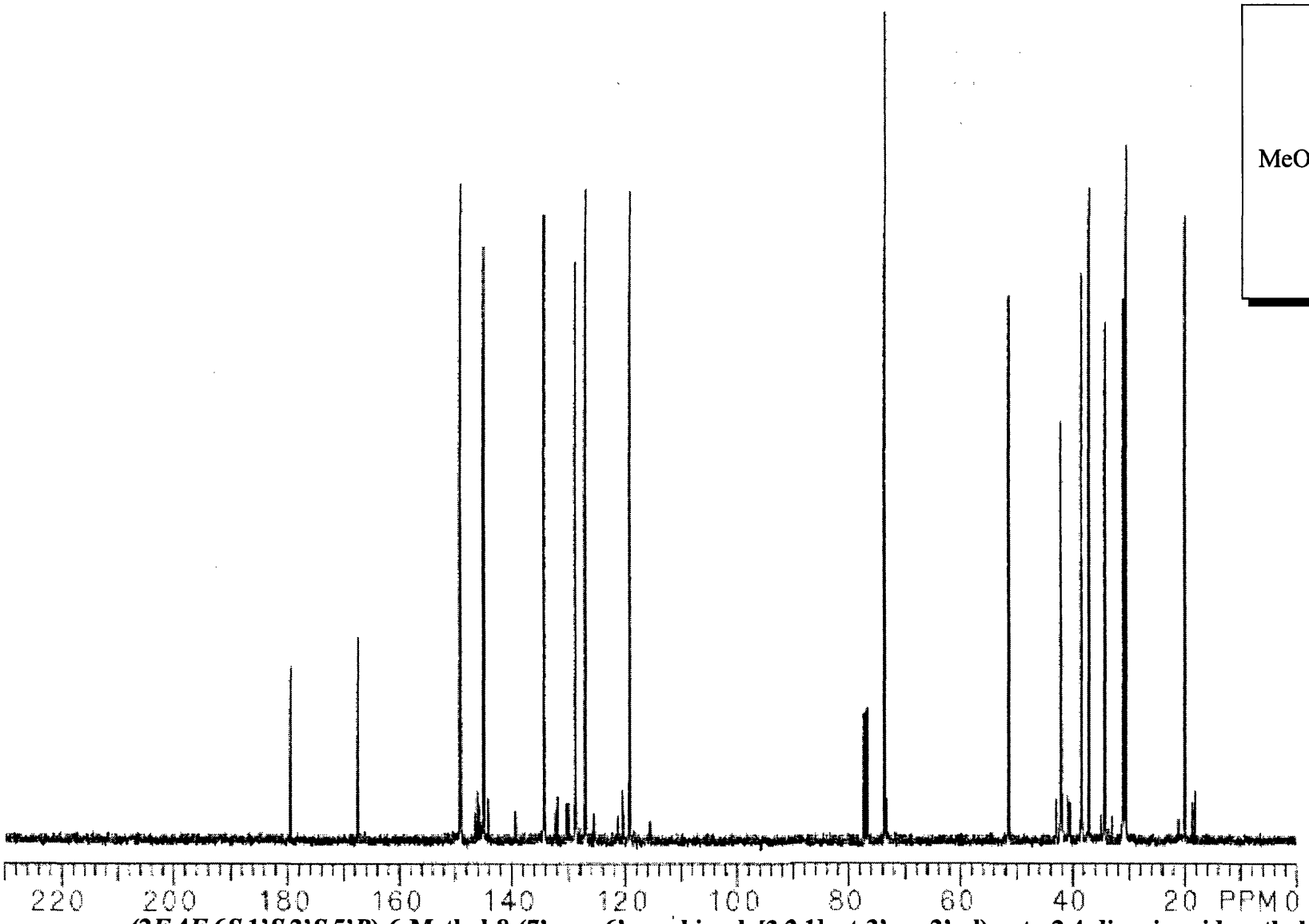


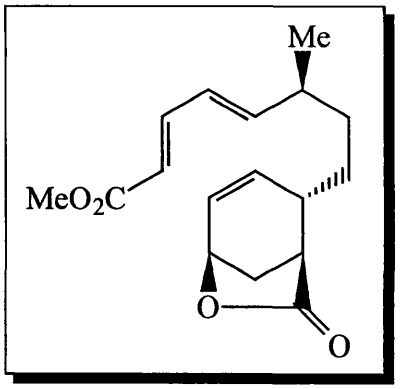


(1*S*,2*S*,5*R*,3'*S*)-2-[4'-Hydroxy-3'-methyl-butyl]-6-oxa-bicyclo[3.2.1]oct-3-en-7-one 252

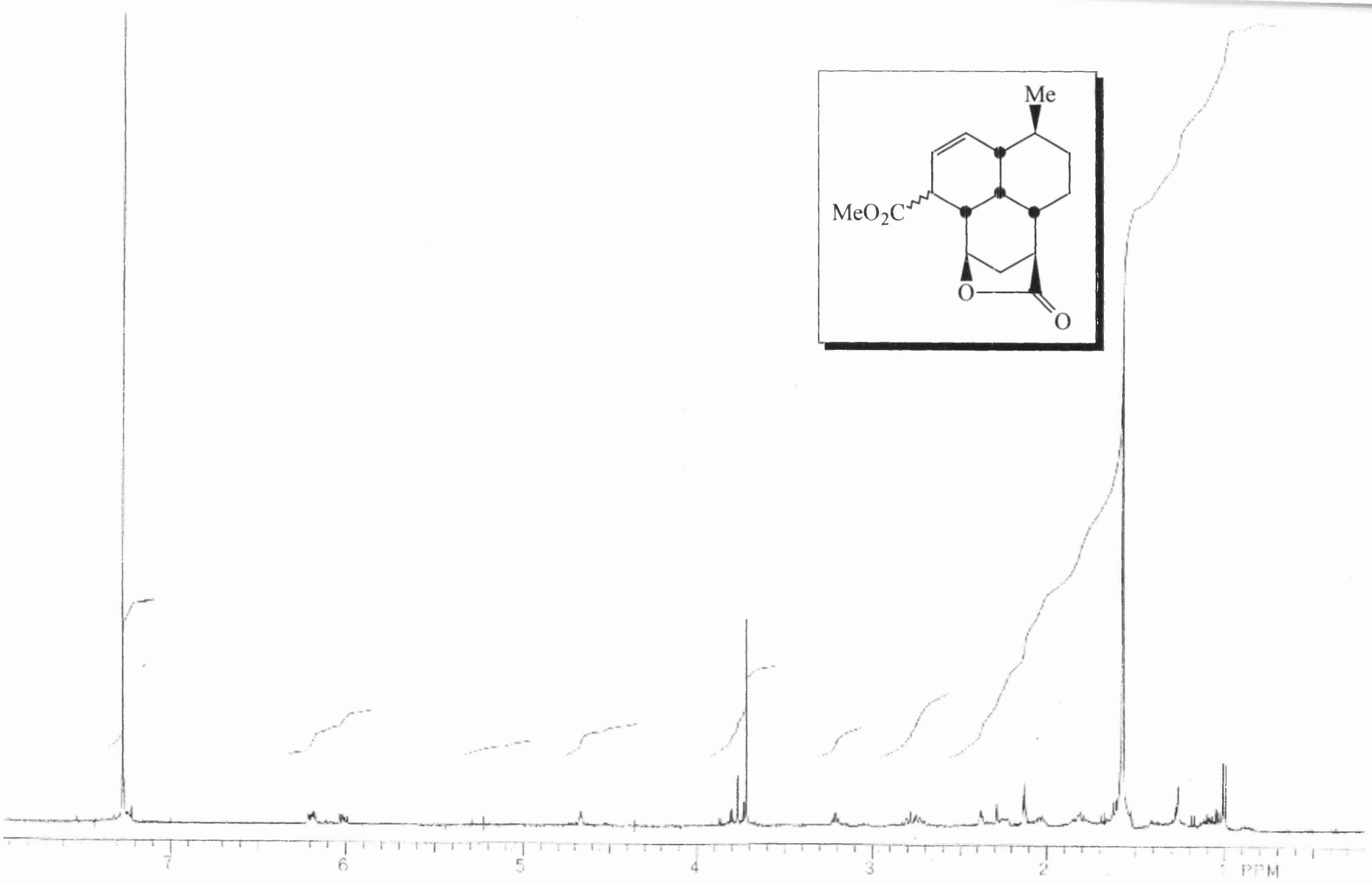


(2*E*,4*E*,6*S*,1'*S*,2'*S*,5'*R*)-6-Methyl-8-(7'-oxo-6'-oxa-bicyclo[3.2.1]oct-3'-en-2'-yl)-octa-2,4-dienoic acid methyl ester 259

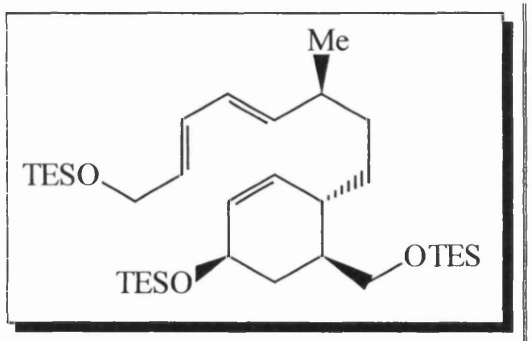


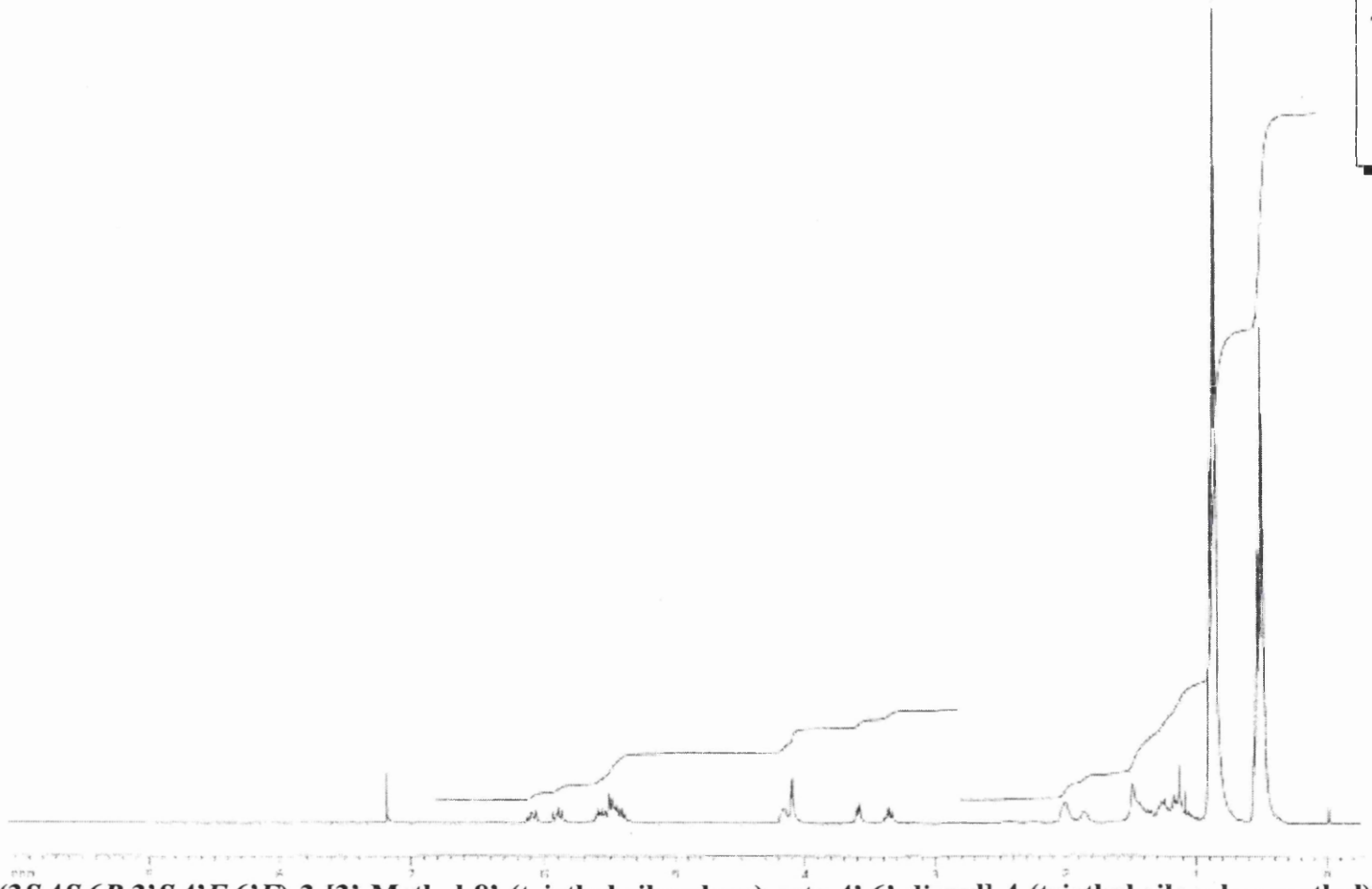


(2*E*,4*E*,6*S*,1'*S*,2'*S*,5'*R*)-6-Methyl-8-(7'-oxo-6'-oxa-bicyclo[3.2.1]oct-3'-en-2'-yl)-octa-2,4-dienoic acid methyl ester 259

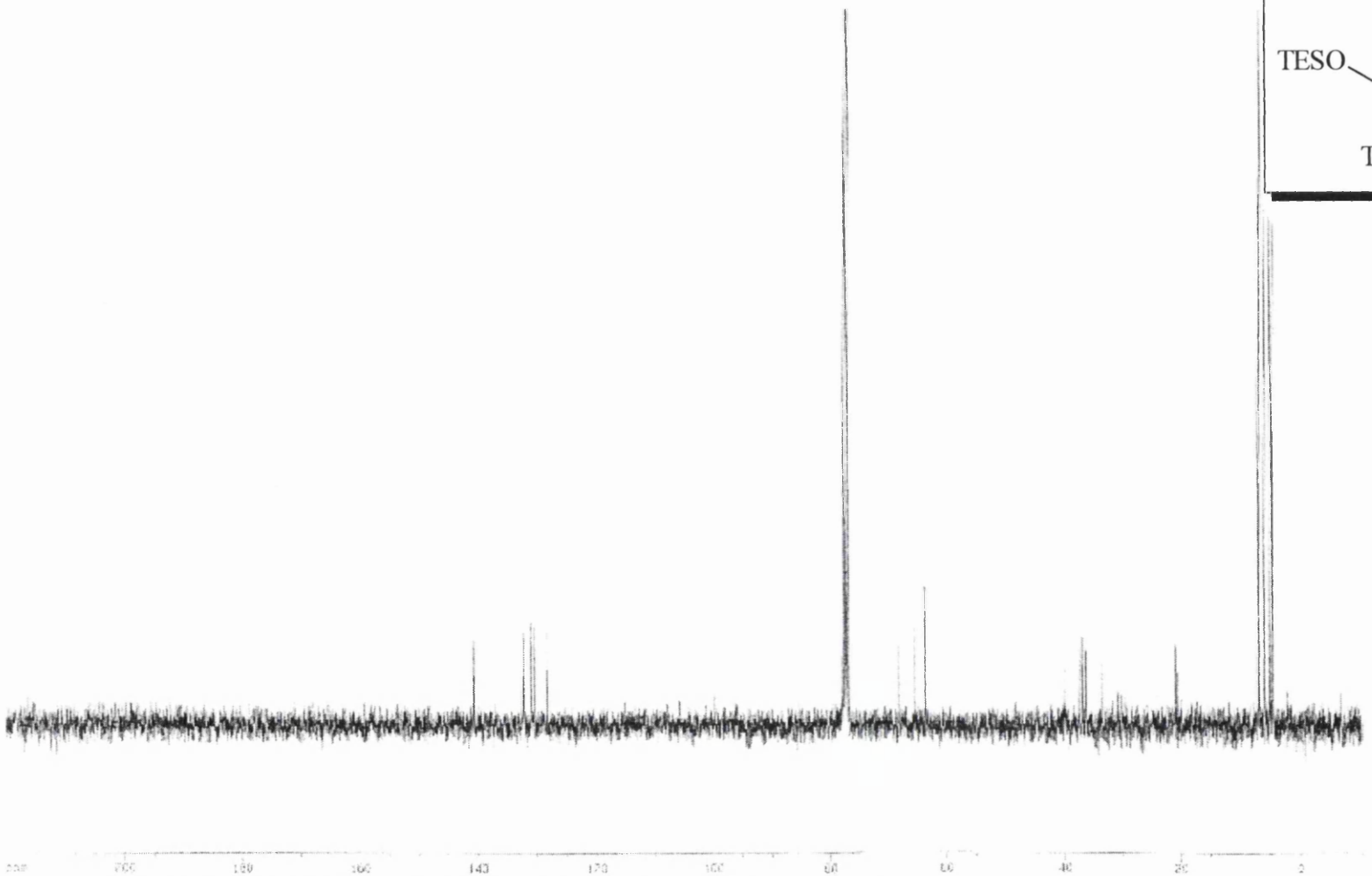


Possible tricycle 260



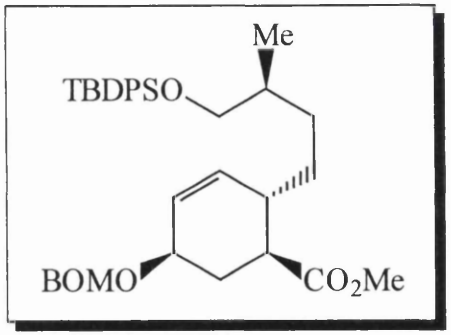


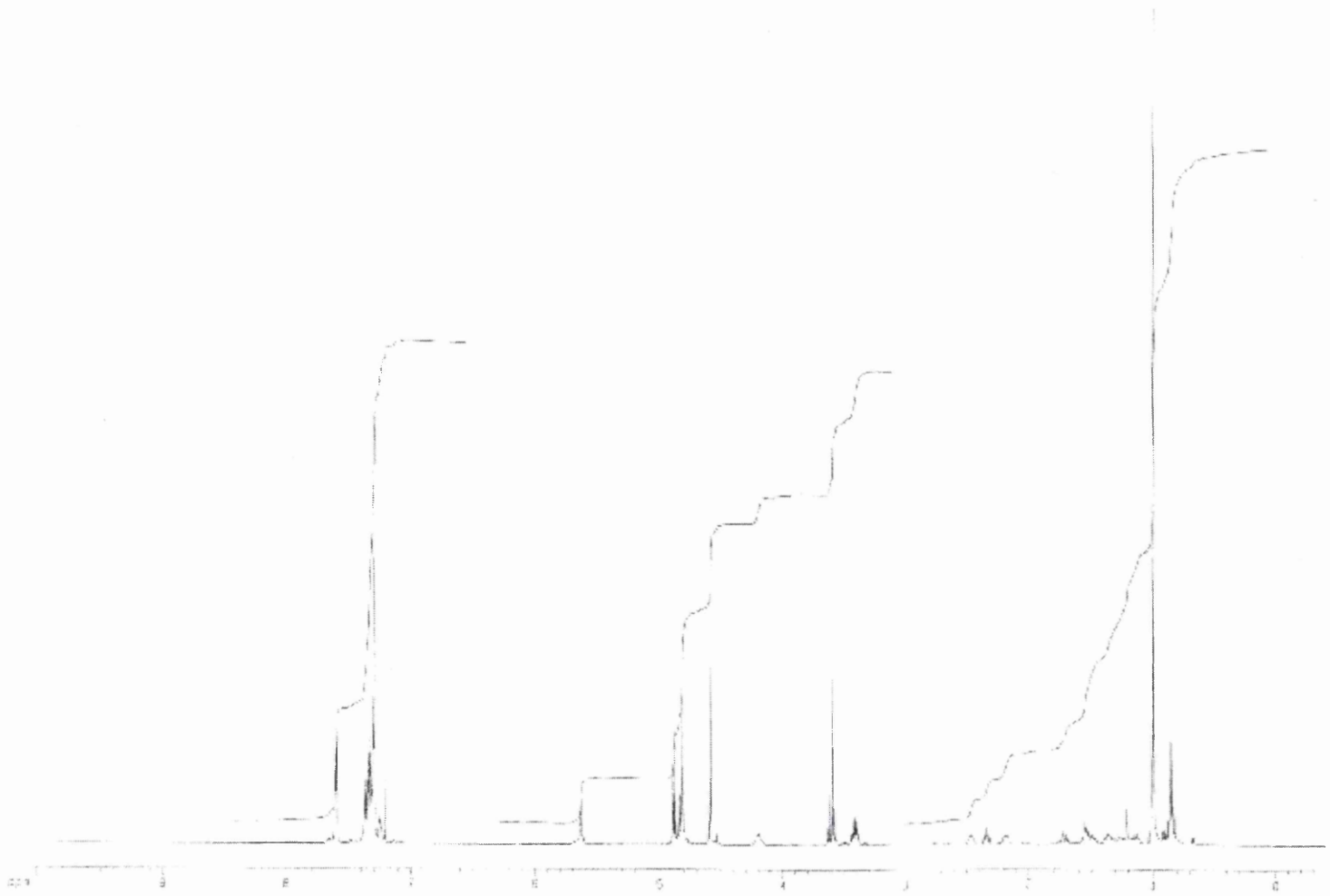
(3*S*,4*S*,6*R*,3'*S*,4'*E*,6'*E*)-3-[3'-Methyl-8'-(triethyl-silanyloxy)-octa-4',6'-dienyl]-4-(triethyl-silanyloxymethyl)-6-(triethyl-silanyloxy)-cyclohexene



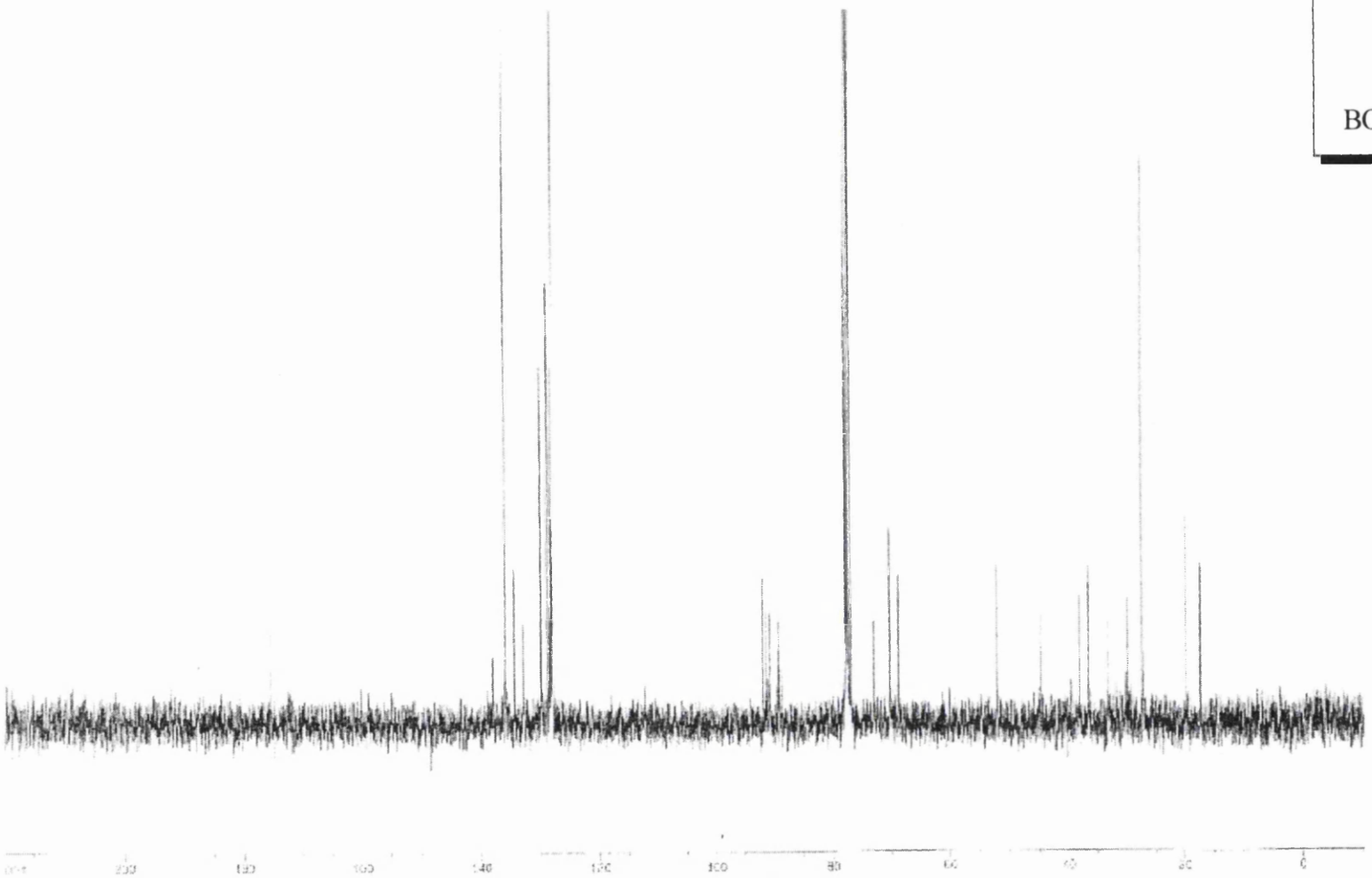
(3*S*,4*S*,6*R*,3'*S*,4'*E*,6'*E*)-3-[3'-Methyl-8'-(triethyl-silanyloxy)-octa-4',6'-dienyl]-4-(triethyl-silanyloxymethyl)-6-(triethyl-silanyloxy)-cyclohexene

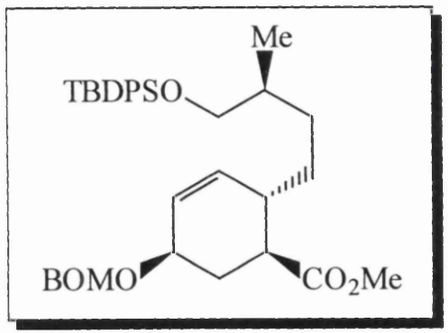
267



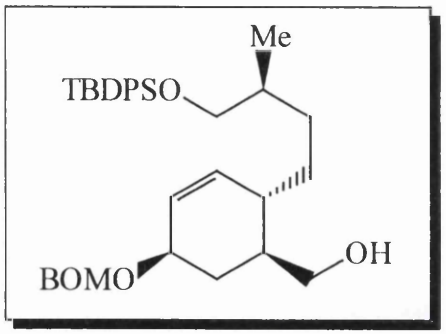


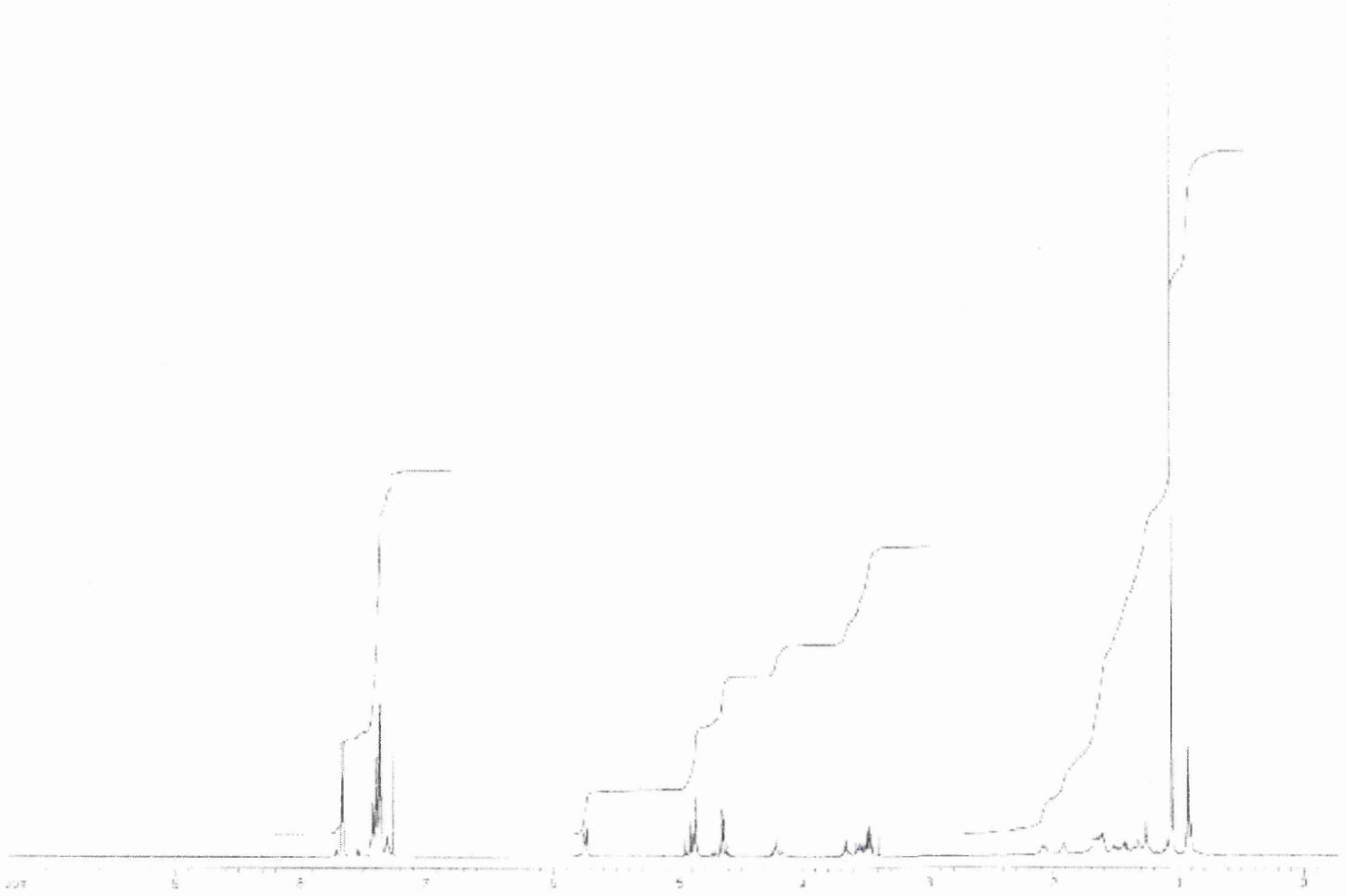
(1*S*,2*S*,5*R*,3'*S*)-5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enecarboxylic acid methyl ester 268



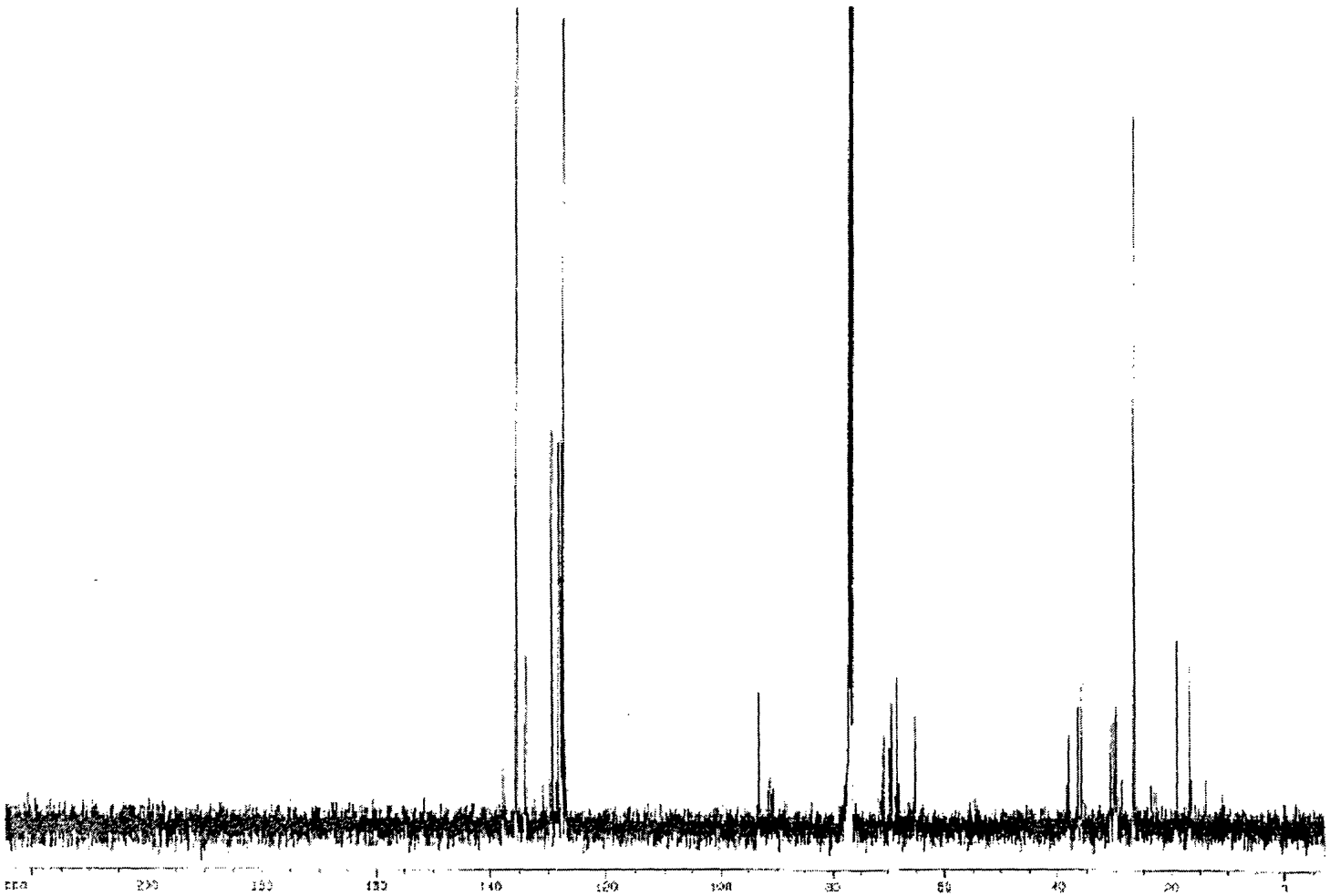


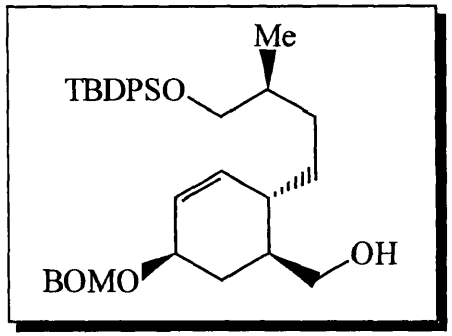
(1*S*,2*S*,5*R*,3'*S*)-5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enecarboxylic acid methyl ester 268



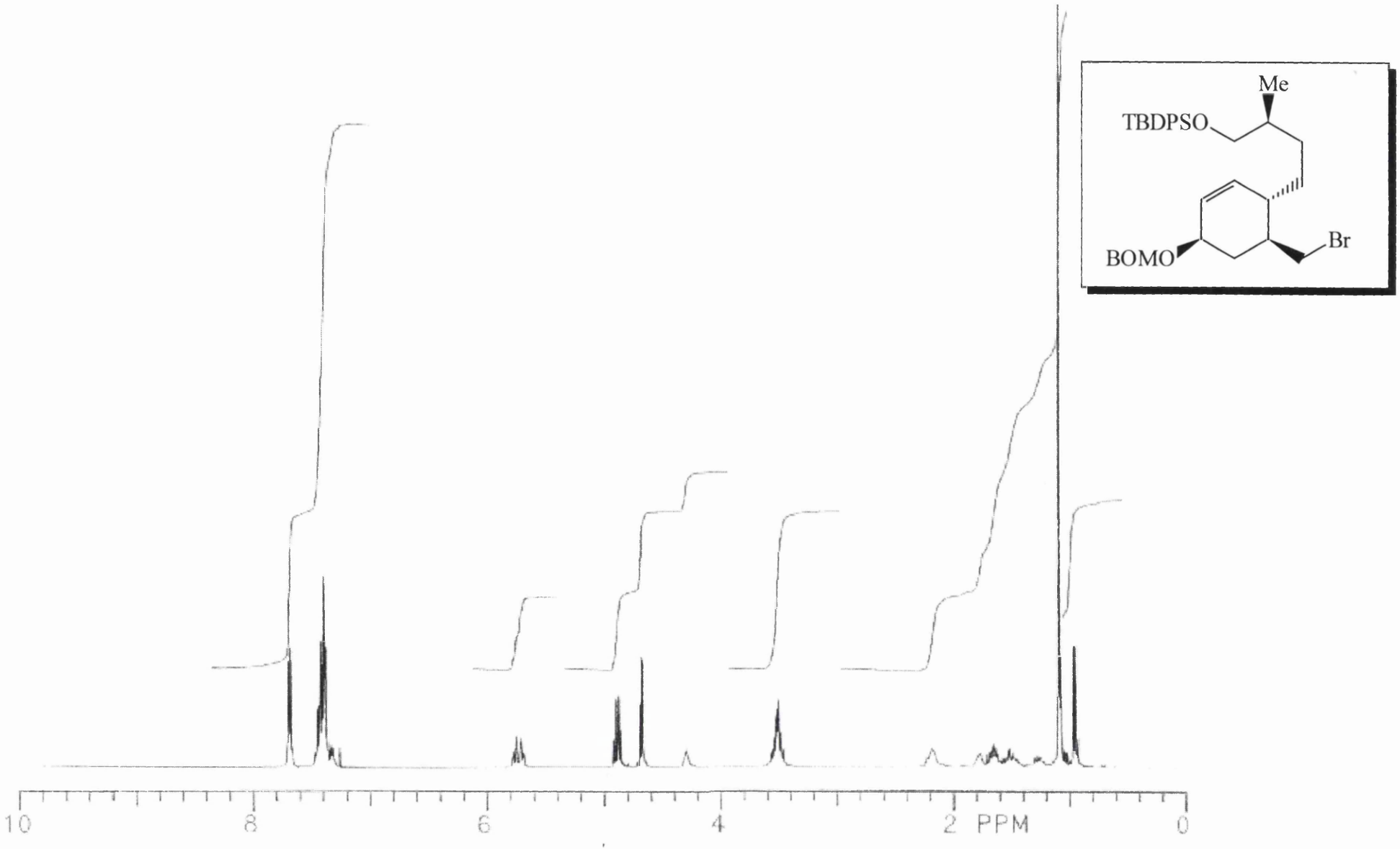


(1*S*,2*S*,5*R*,3'*S*)-{5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enyl}-methanol 269

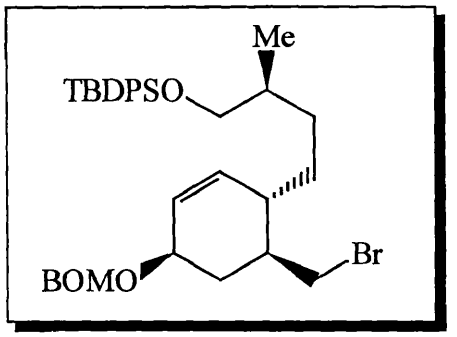


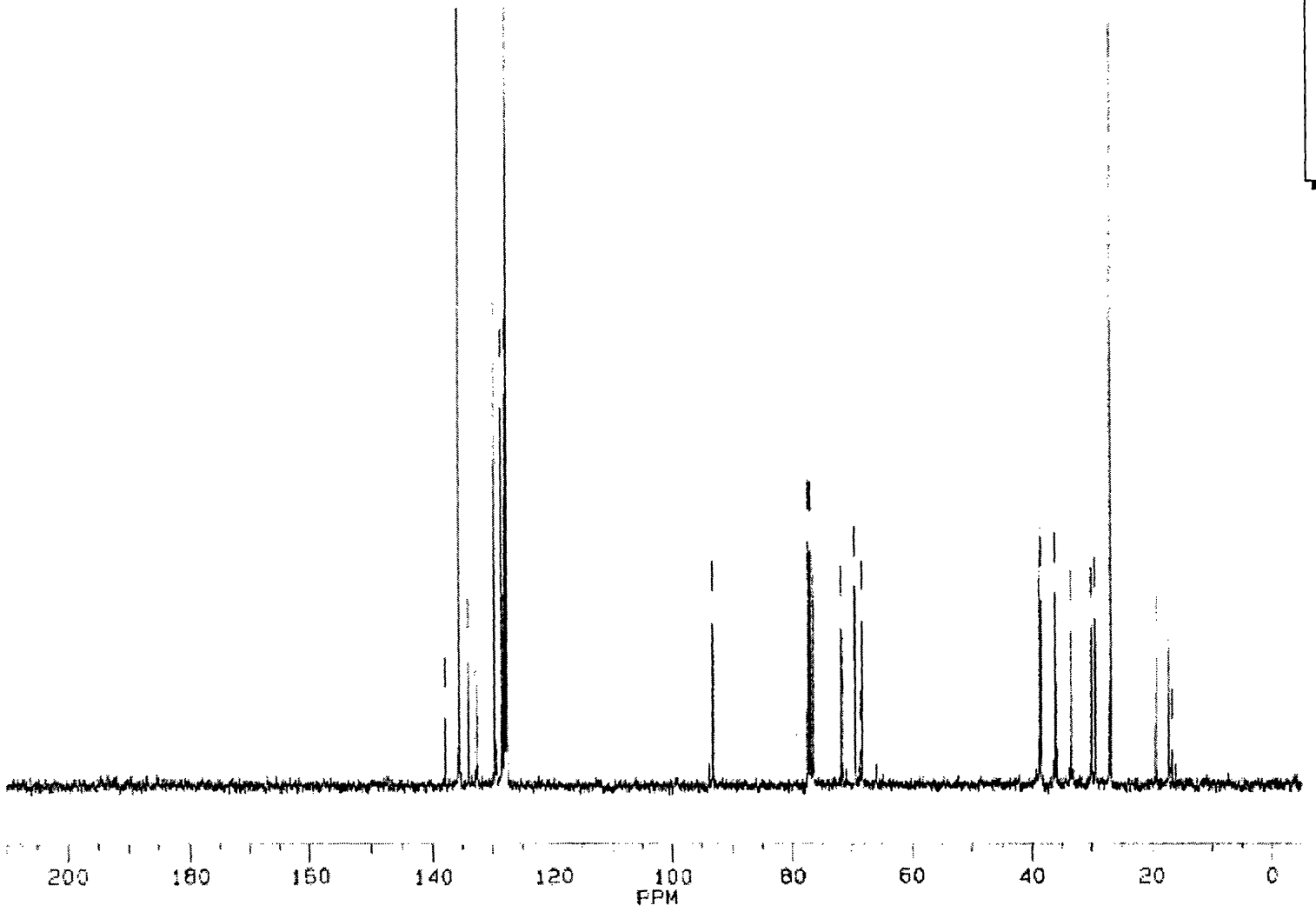


(1*S*,2*S*,5*R*,3'*S*)-{5-Benzyloxymethoxy-2-[4'-(*t*-butyl-diphenyl-silanyloxy)-3'-methyl-butyl]-cyclohex-3-enyl}-methanol 269

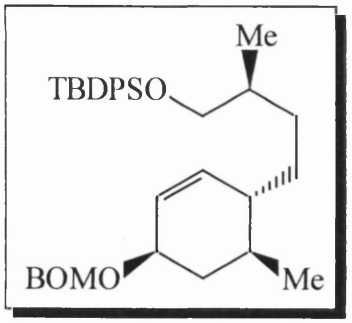


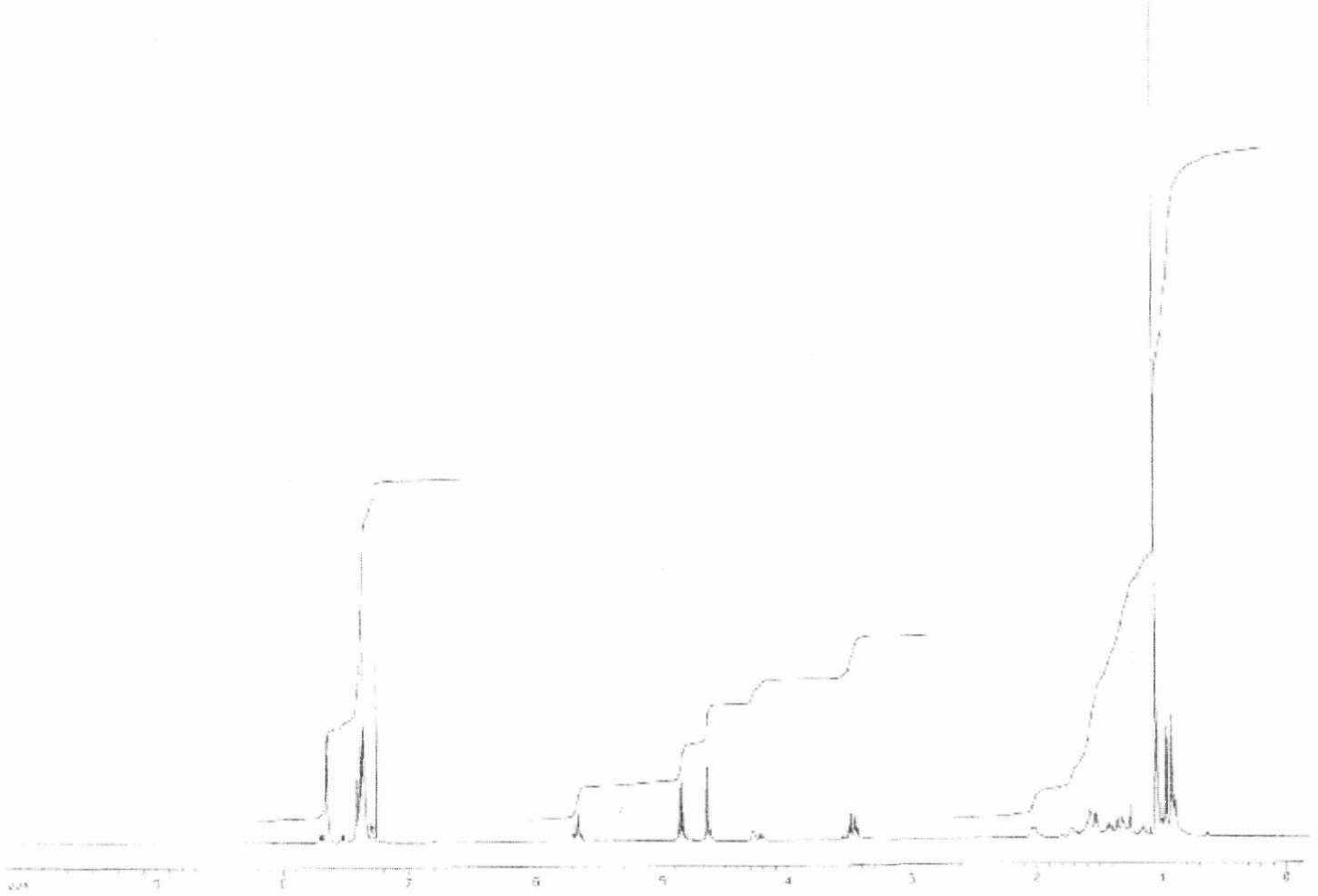
(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-bromomethyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 270



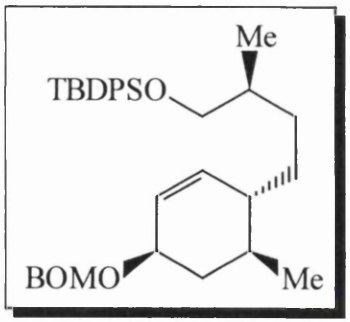


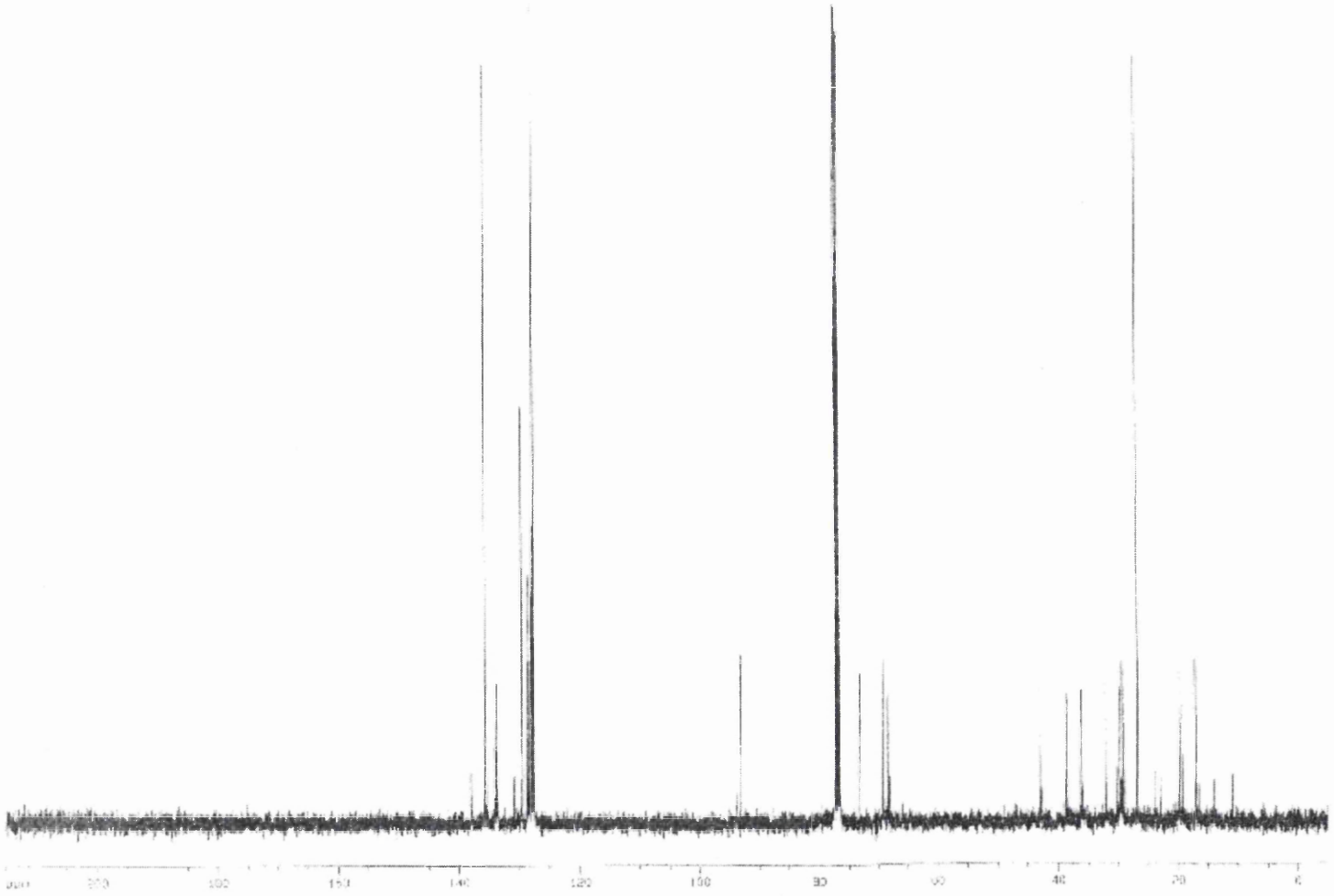
(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-bromomethyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 270



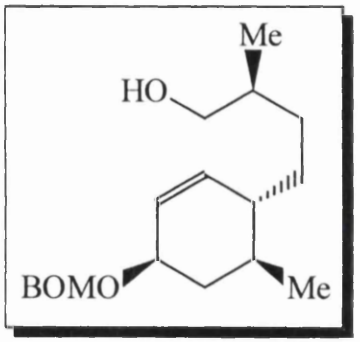


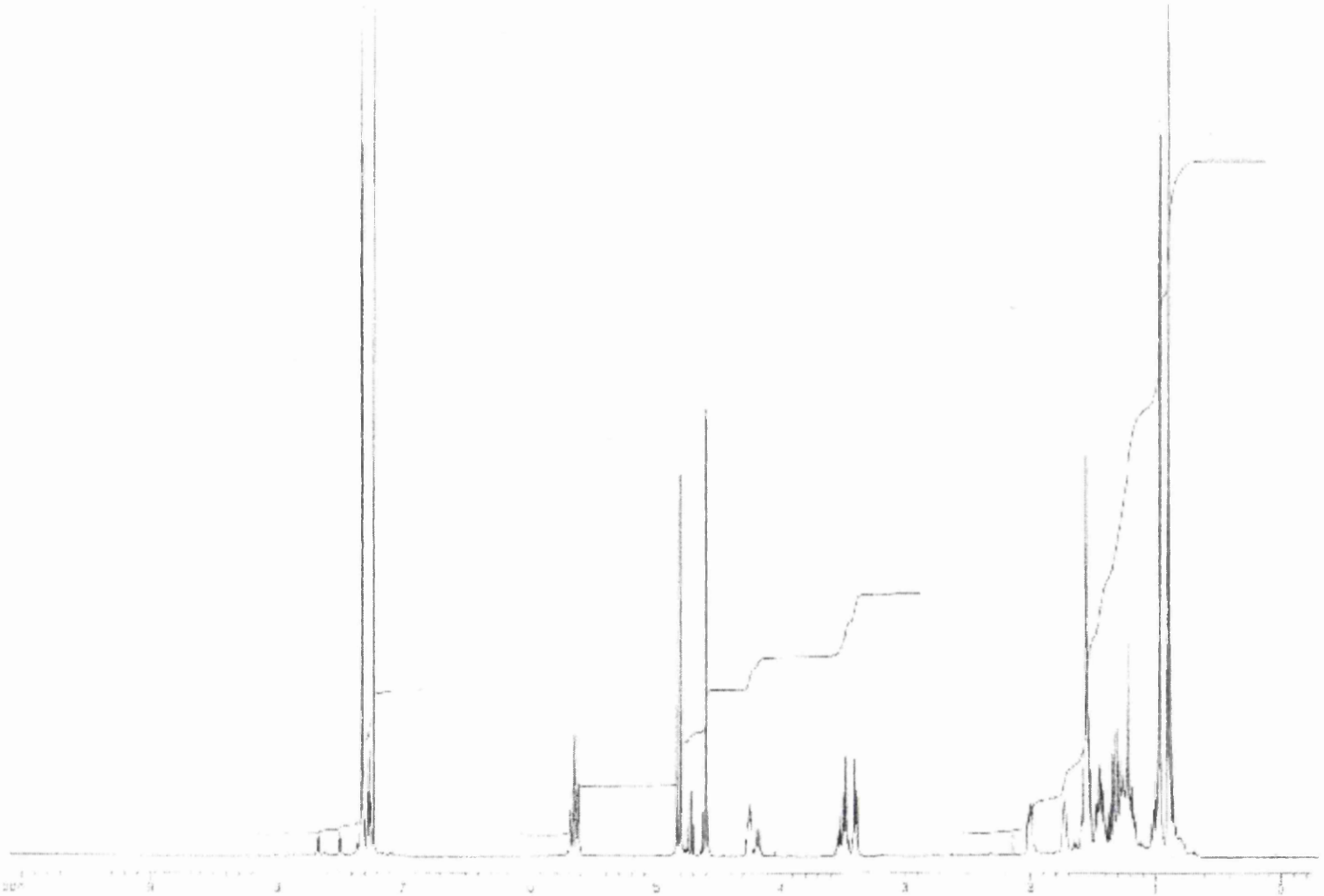
(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 271



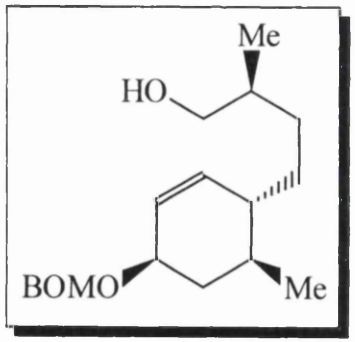


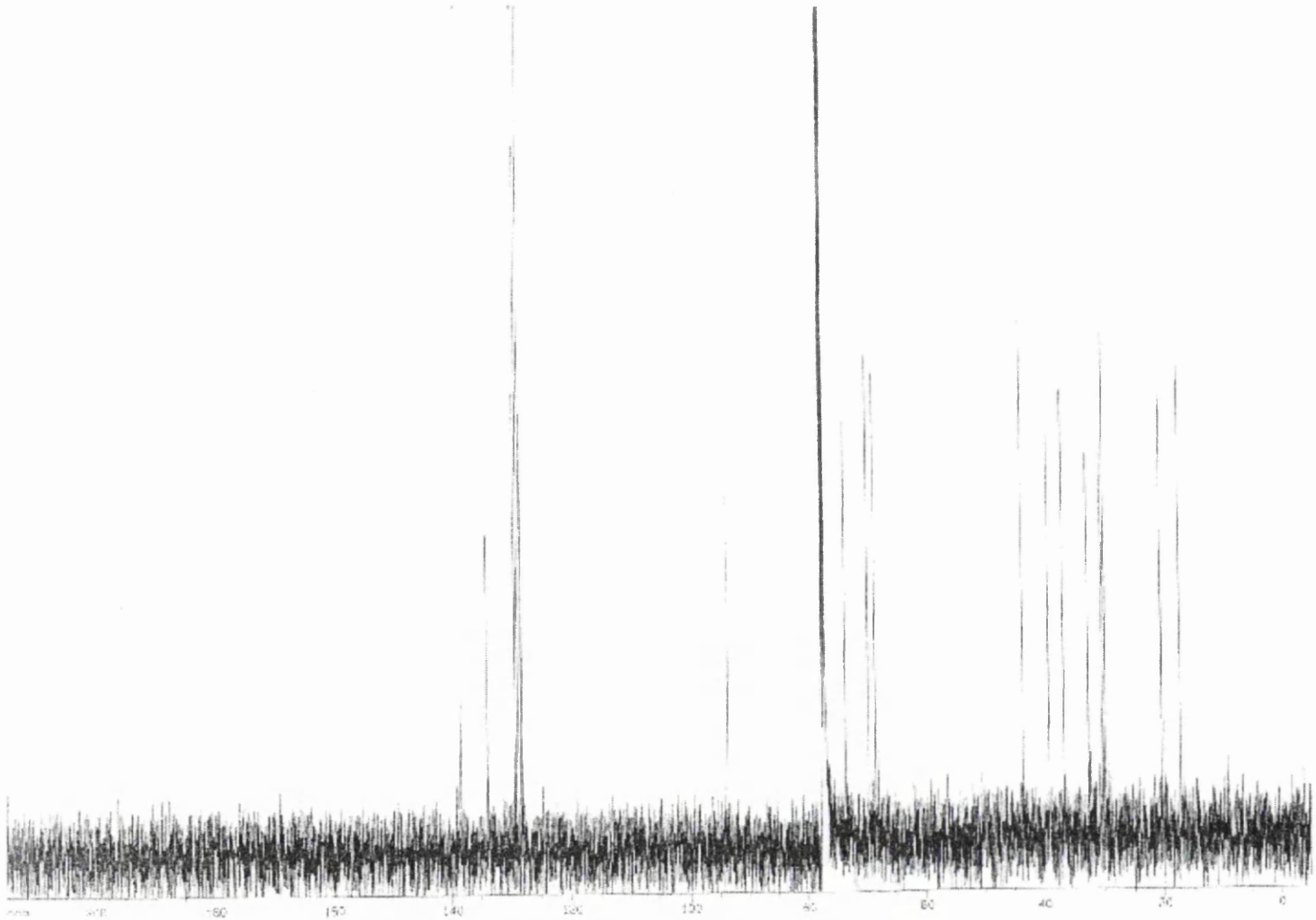
(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butoxy]-*t*-butyl-diphenyl-silane 271



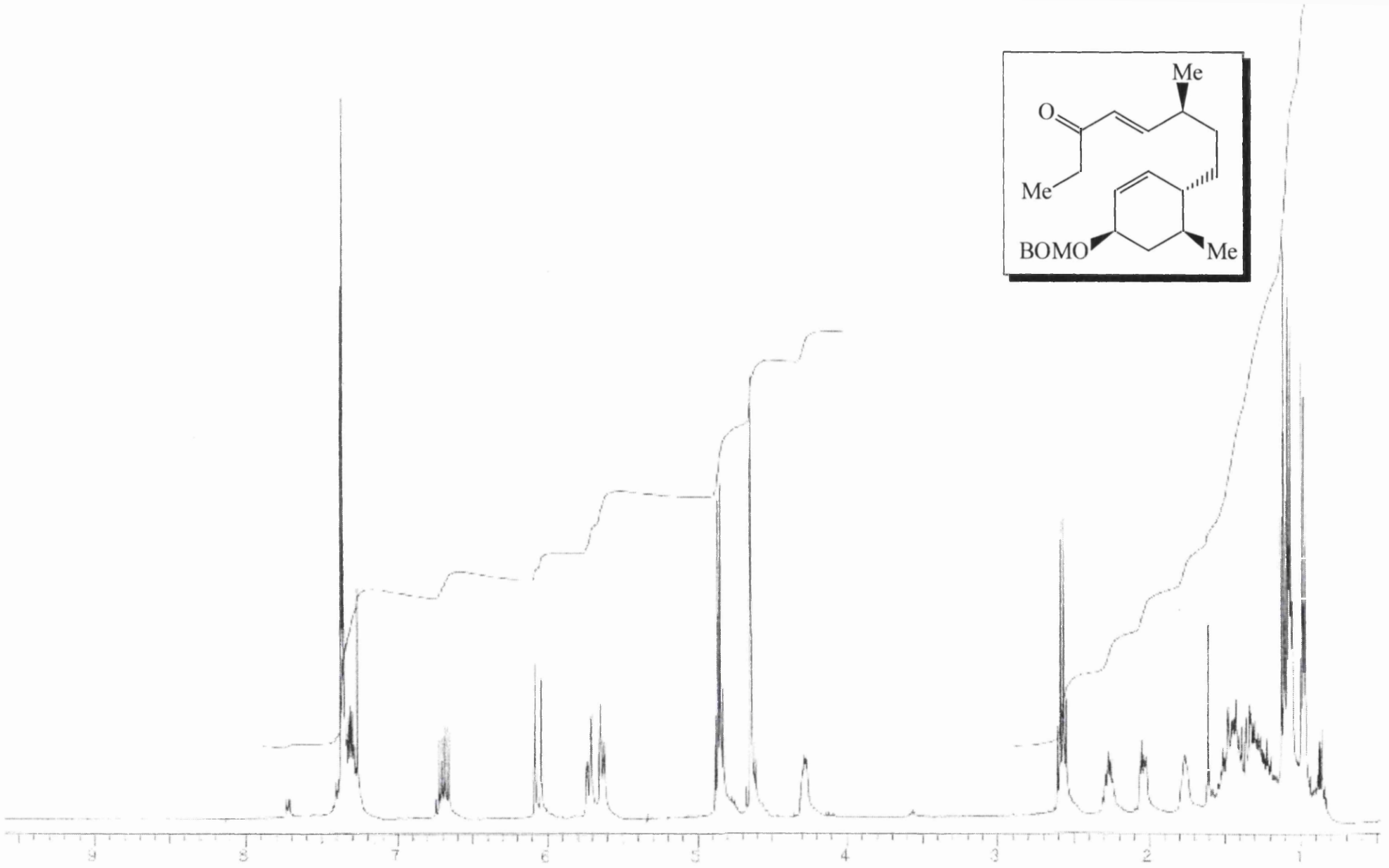


(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butan-1-ol 272

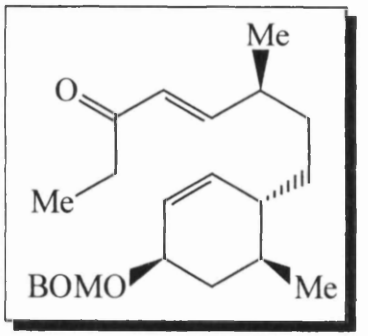


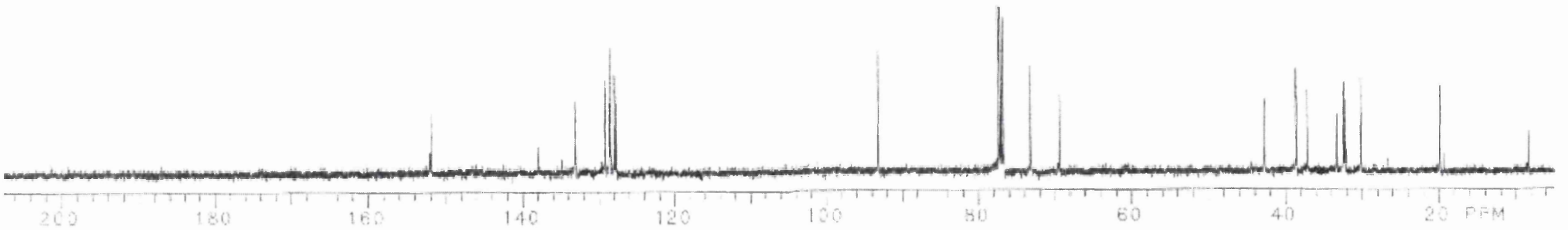


(2*S*,1'*S*,4'*R*,6'*S*)-[4-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-2-methyl-butan-1-ol 272

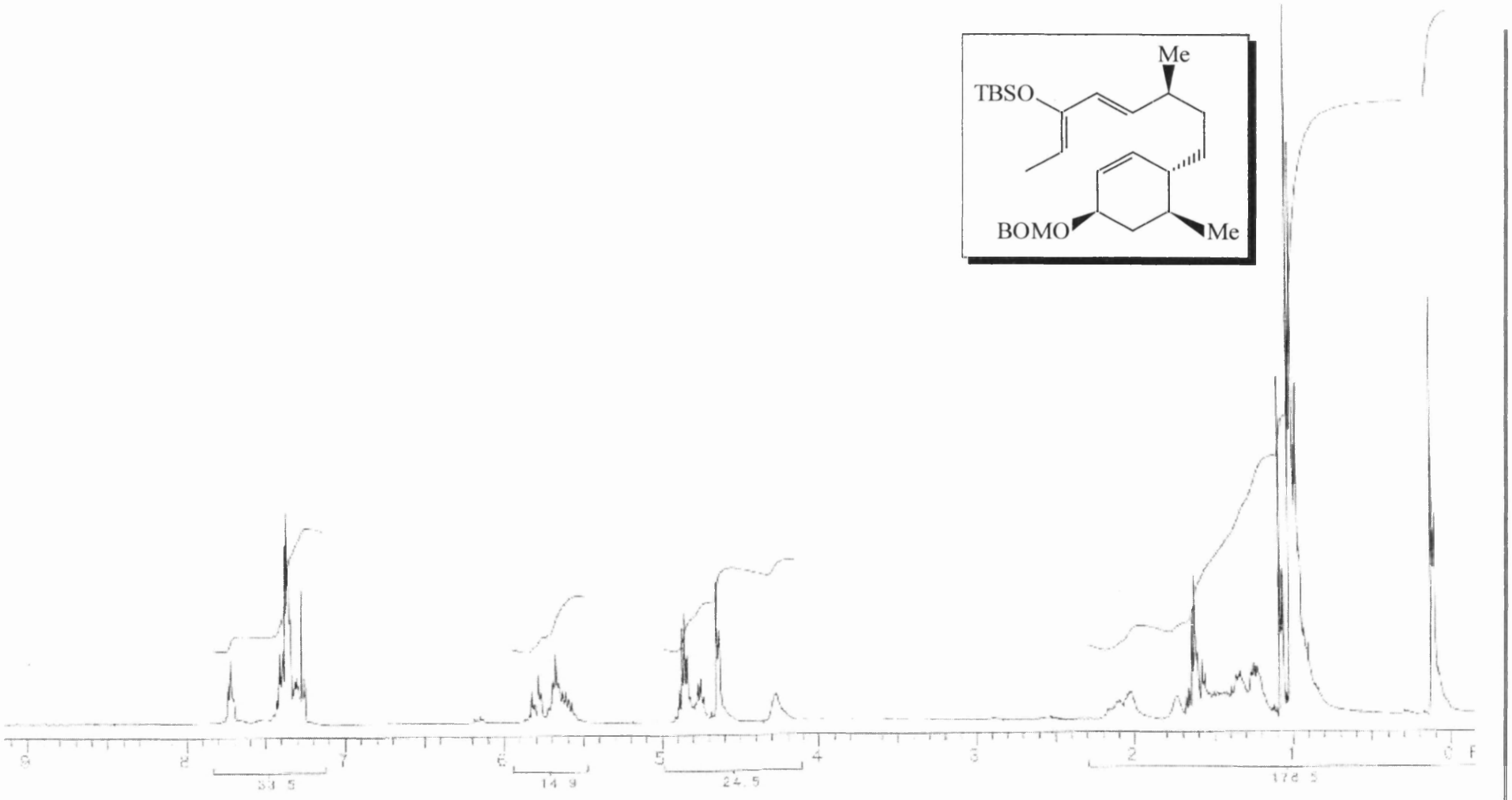


(4*E*,6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-3'-enyl)-6-methyl-oct-4-en-3-one 275

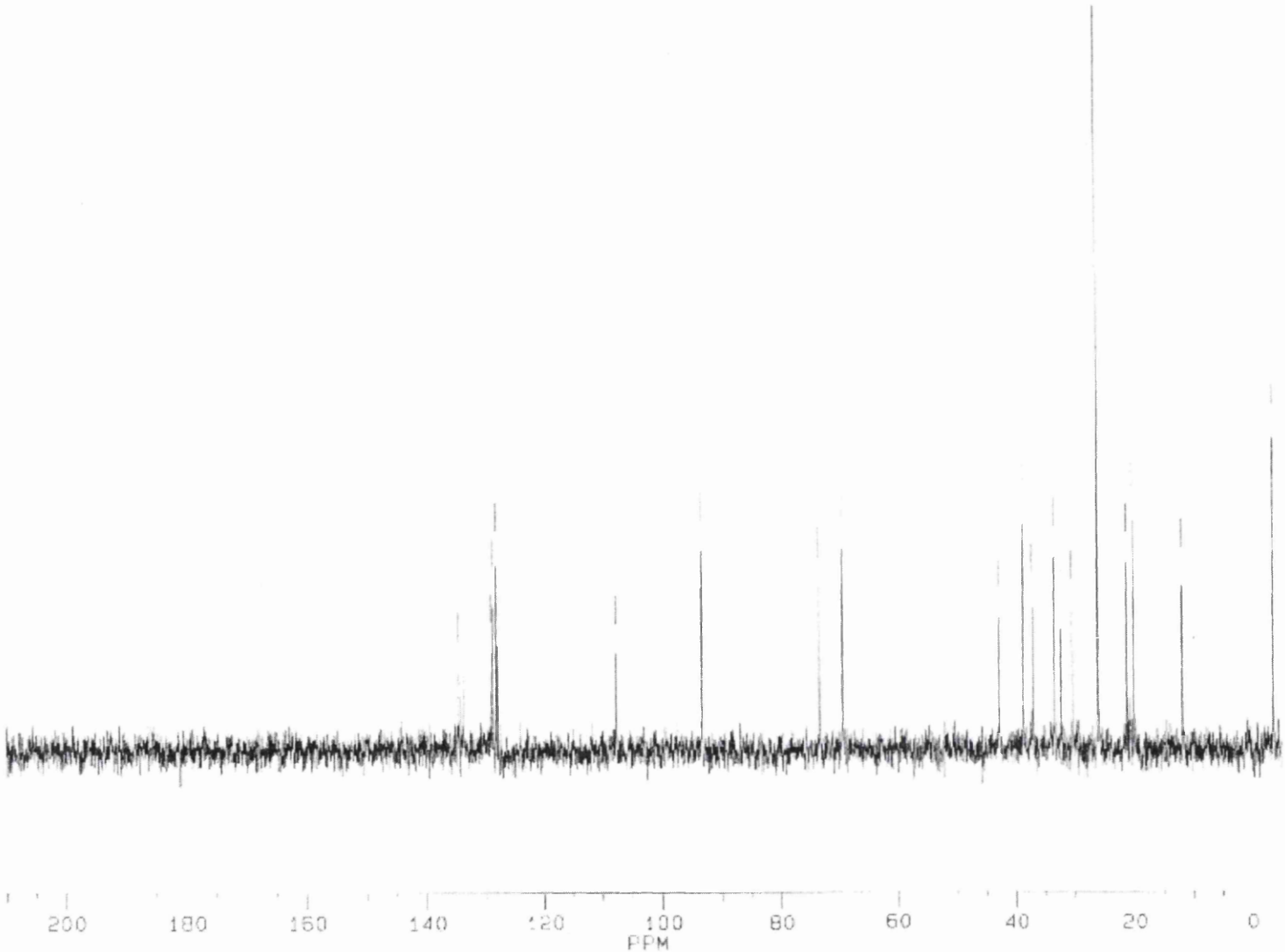




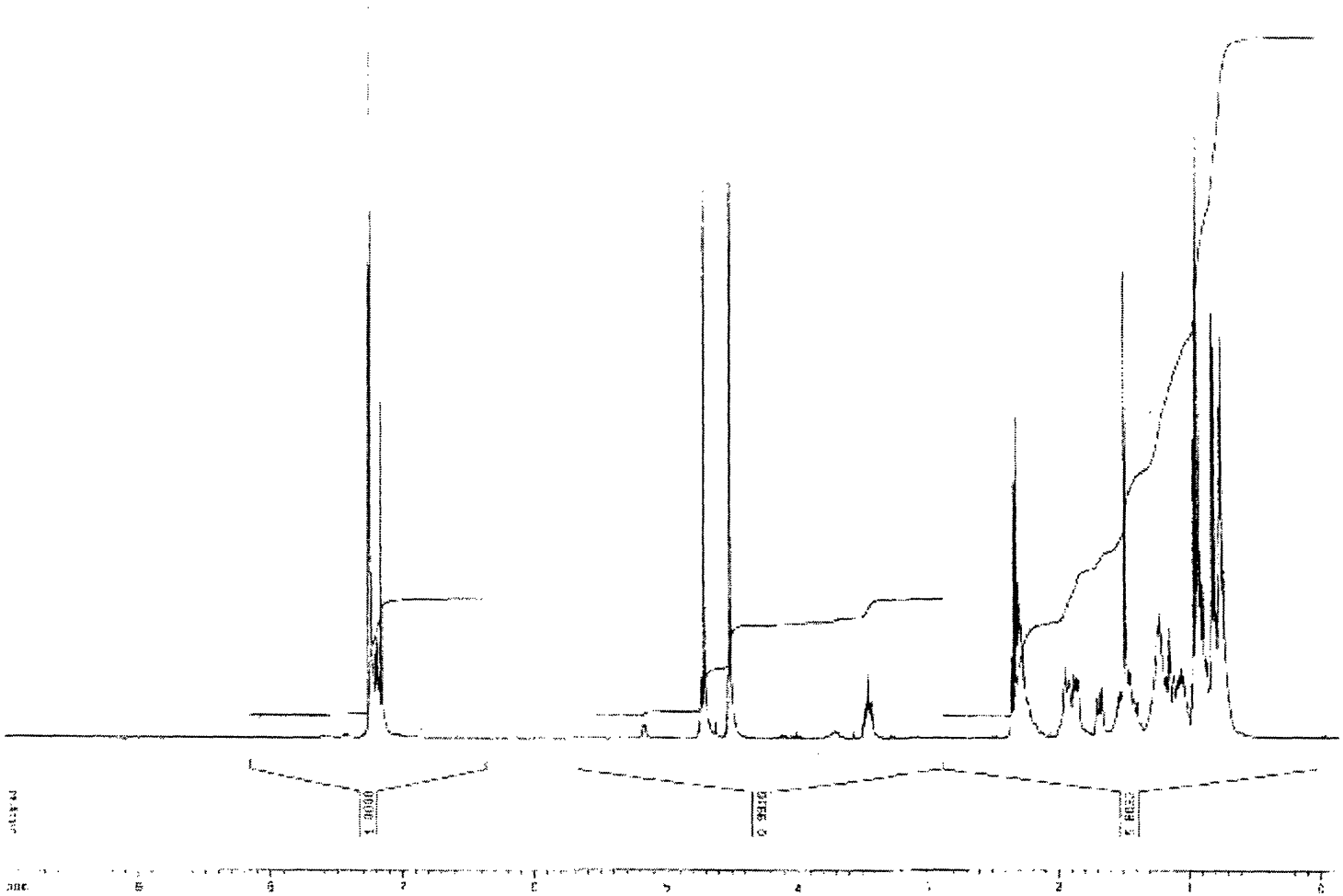
(4*E*,6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-3'-enyl)-6-methyl-oct-4-en-3-one 275

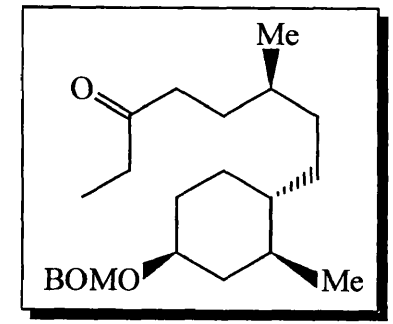


(1*Z*,2*E*,4*S*,1'*S*,4'*R*,6'*S*)-[6-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-1-ethylidene-4-methyl-hex-2-enyloxy]-*t*-butyl-dimethyl-silane 276

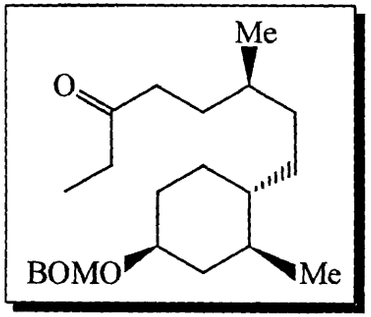


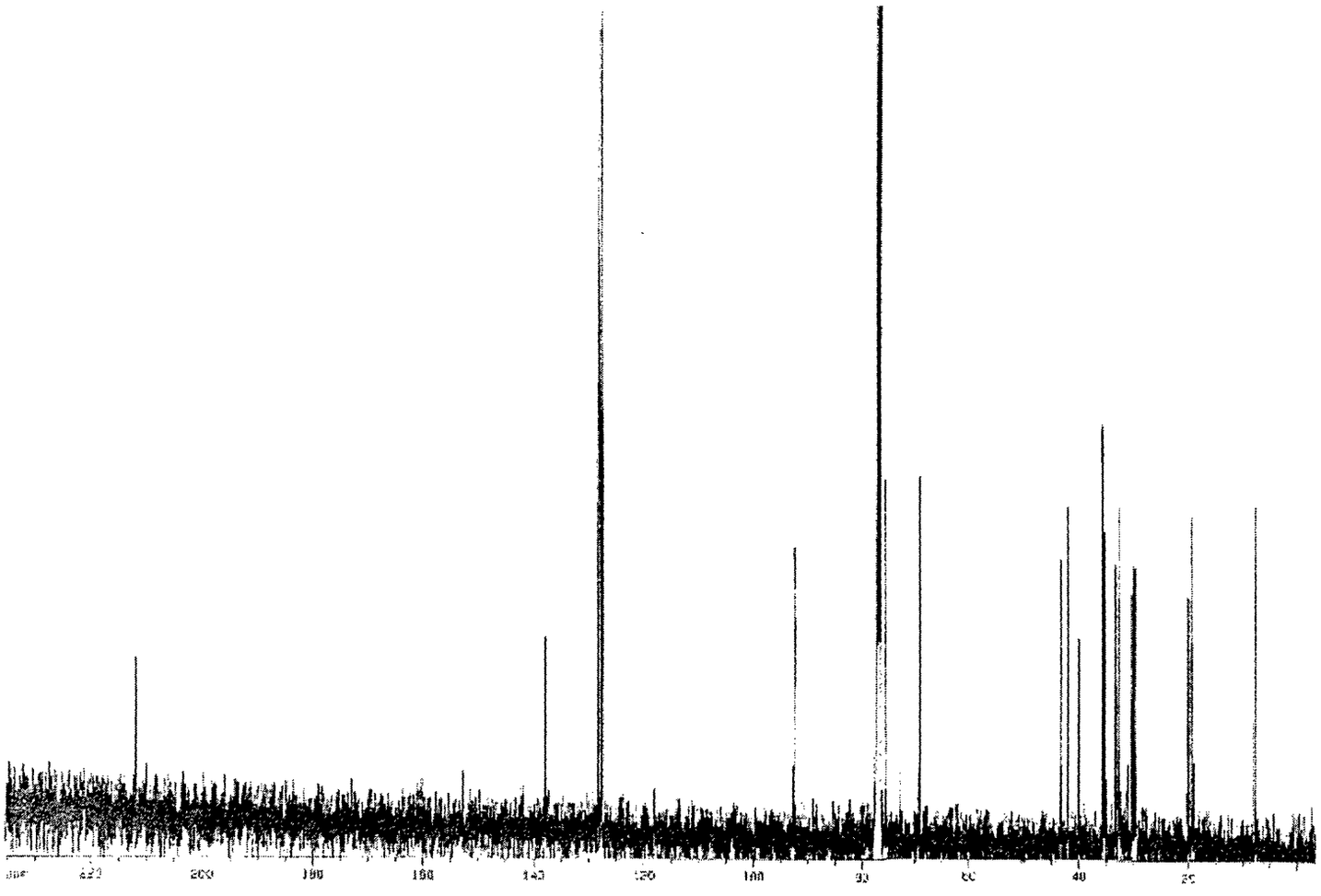
(1*Z*,2*E*,4*S*,1'*S*,4'*R*,6'*S*)-[6-(4'-Benzyloxymethoxy-6'-methyl-cyclohex-2'-enyl)-1-ethylidene-4-methyl-hex-2-enyloxy]-*t*-butyl-dimethyl-silane 276



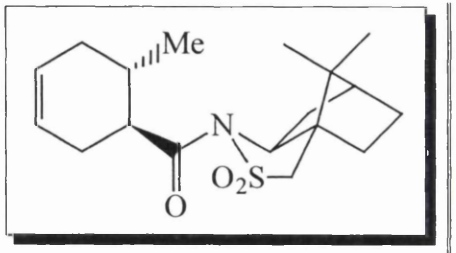


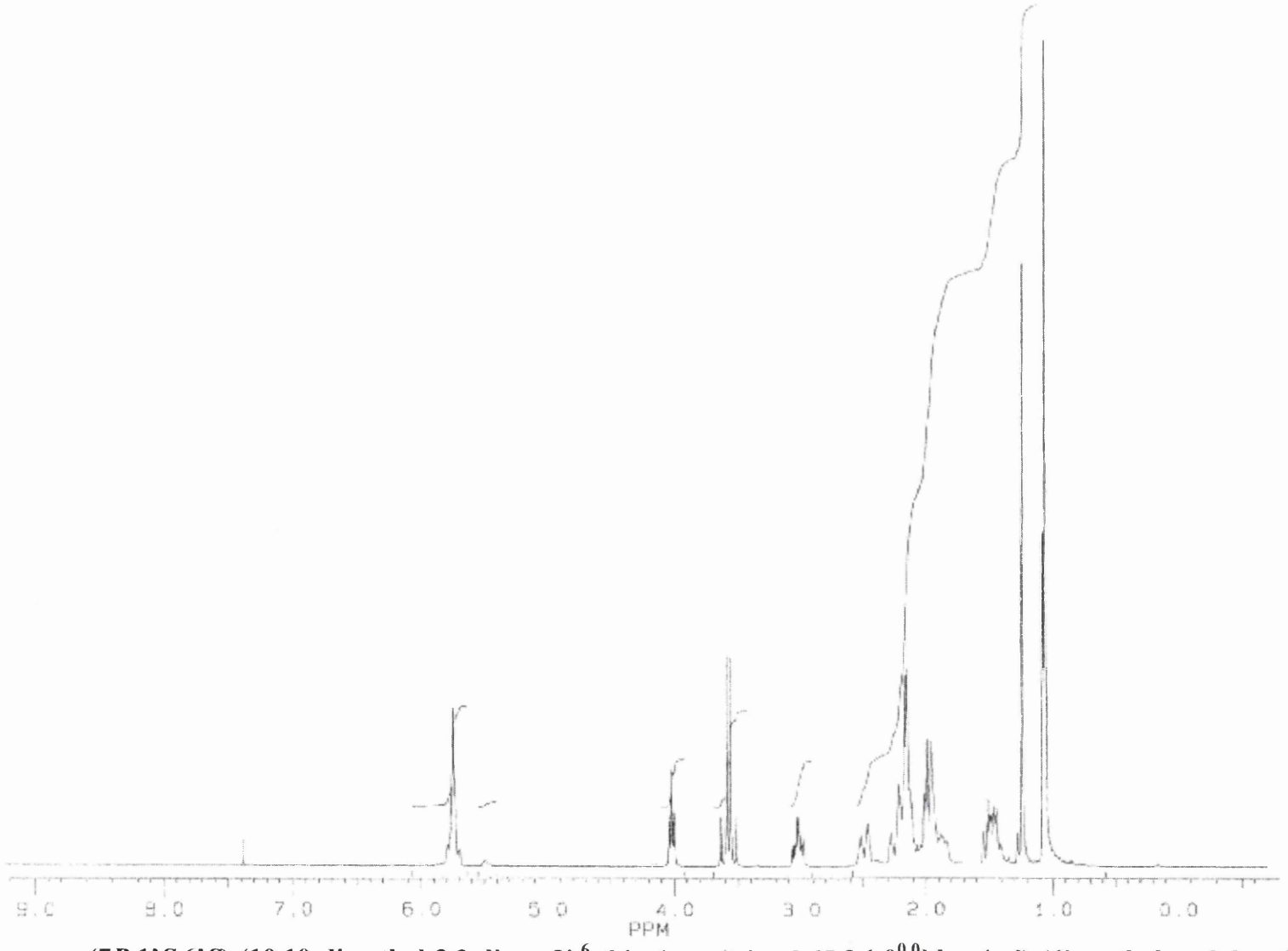
(6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-2'-methyl-cyclohexyl)-6-methyl-octan-3-one 278



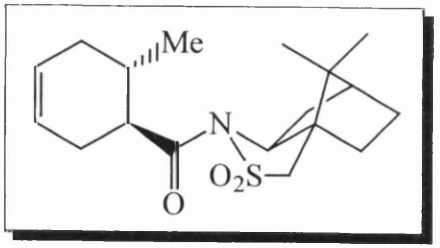


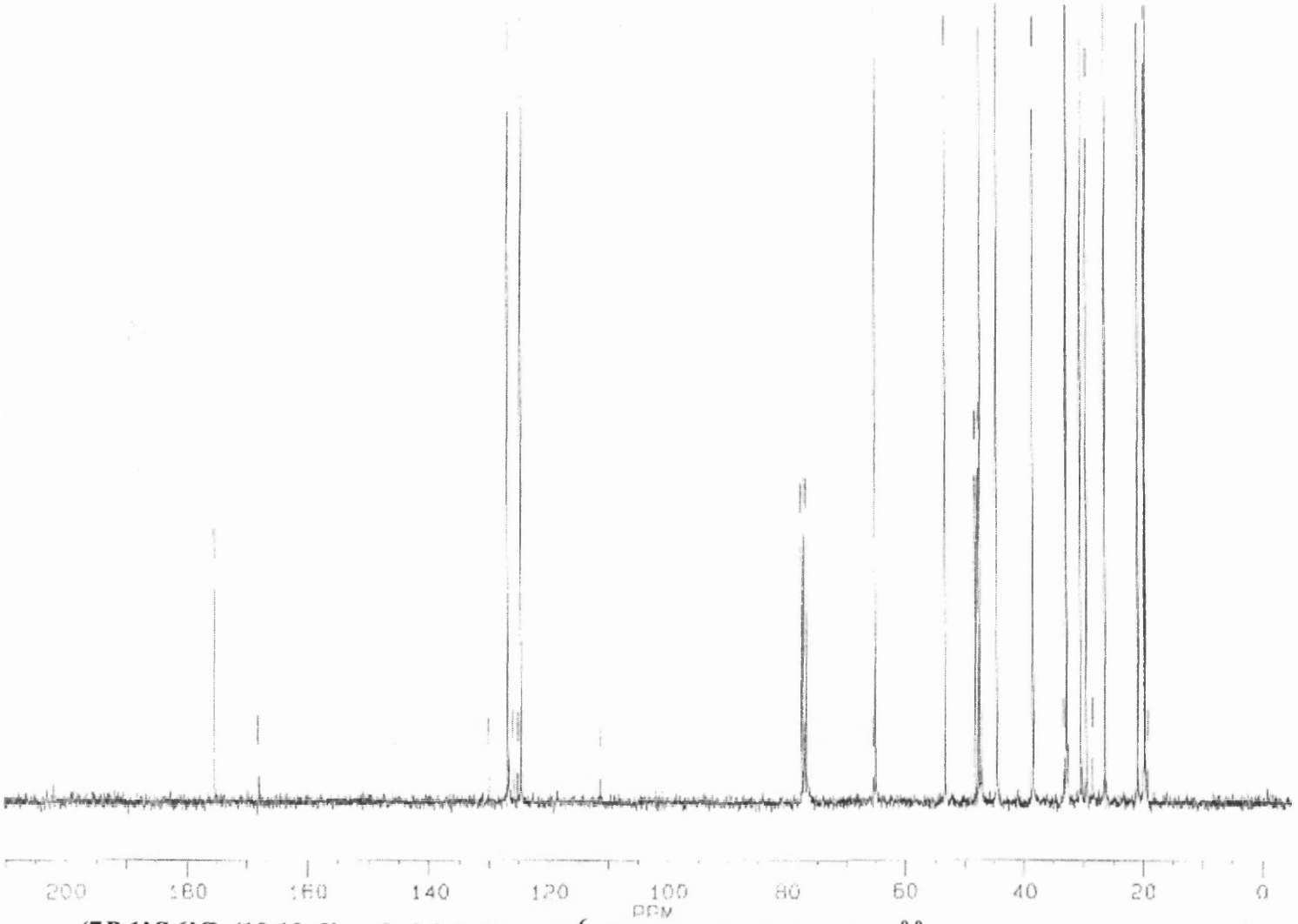
(6*S*,1'*S*,4'*R*,6'*S*)-8-(4'-Benzyloxymethoxy-2'-methyl-cyclohexyl)-6-methyl-octan-3-one 278



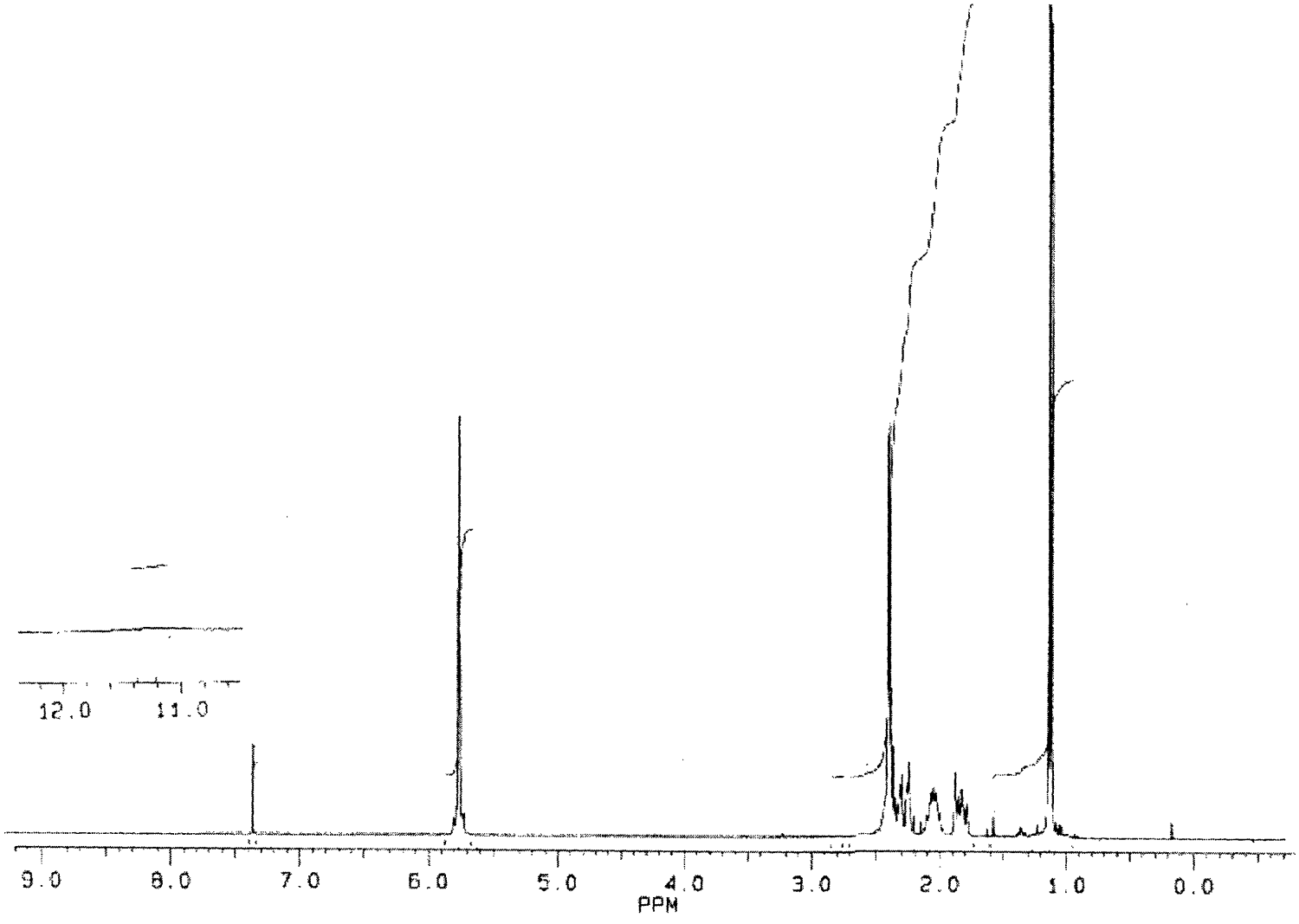


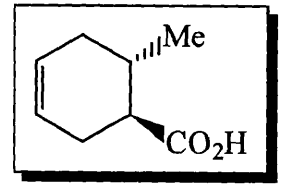
(7*R*,1'*S*,6'*S*)-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-(6'-methyl-cyclohex-3'-enyl)-methanone 292



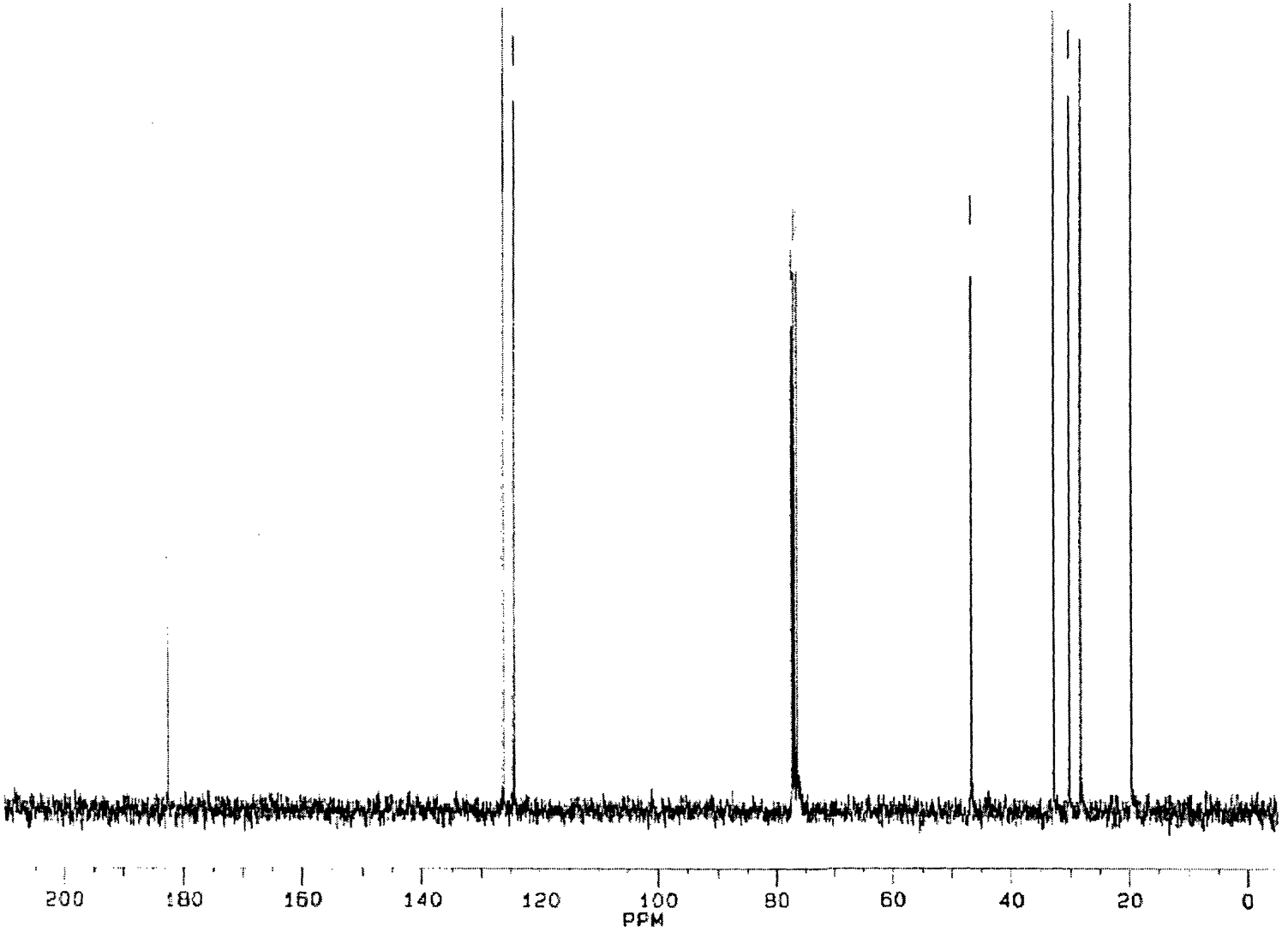


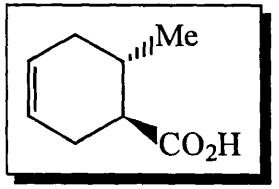
(7*R*,1'*S*,6'*S*)-(10,10-dimethyl-3,3-dioxo-3λ^{6}-thia-4-aza-tricyclo[5.2.1.0^{0,0}]dec-4-yl)-(6'-methyl-cyclohex-3'-enyl)-methanone 292



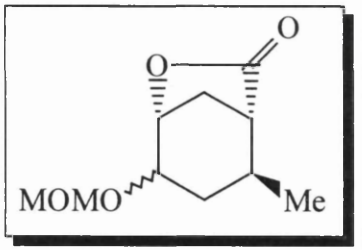


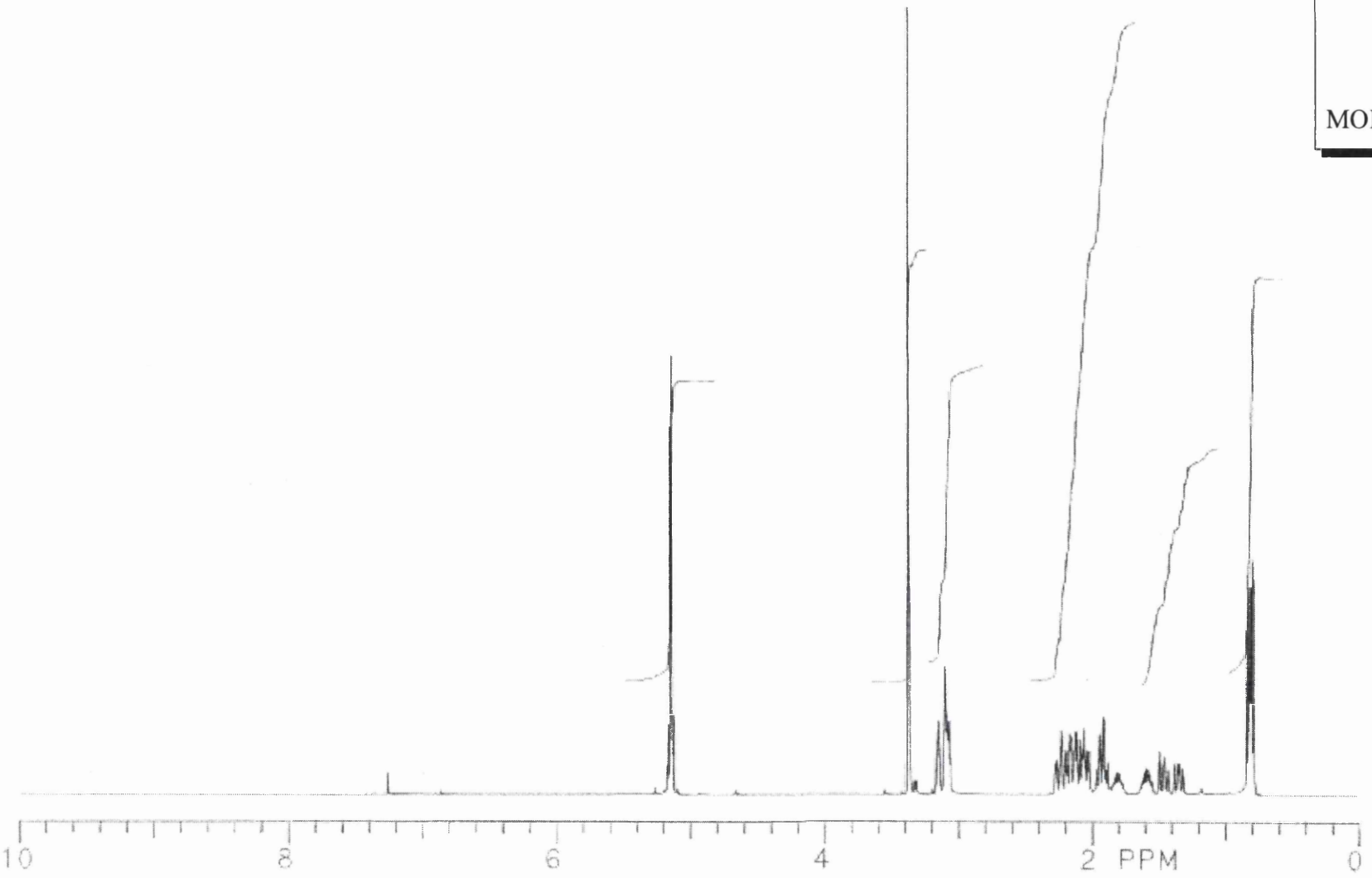
(1*S*,6*S*)-6-Methyl-3-cyclohex-3-enecarboxylic acid 287



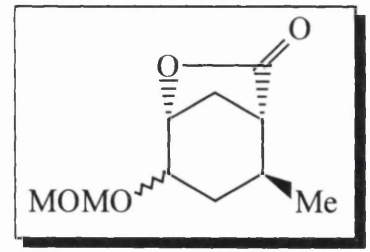


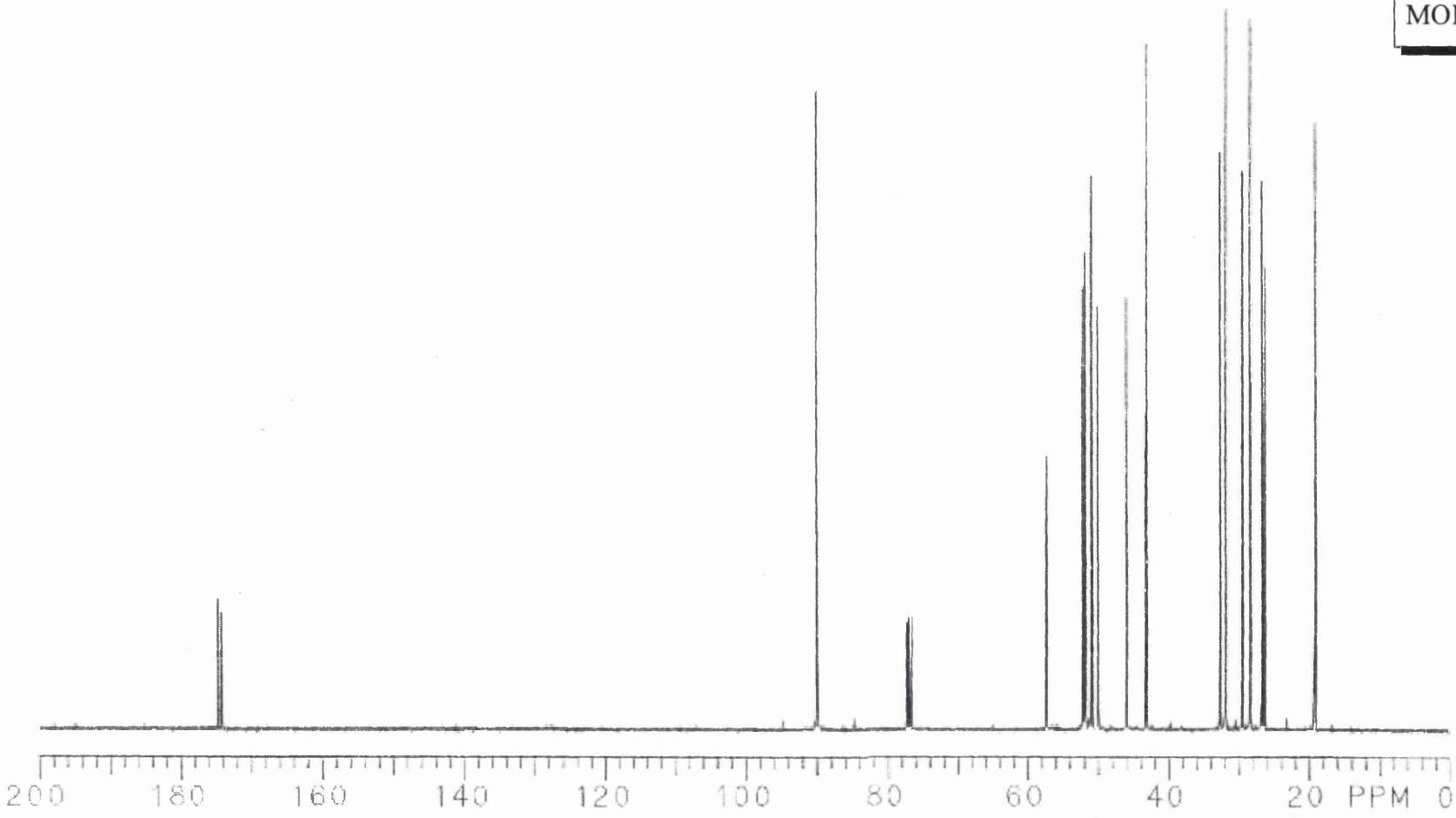
(1*S*,6*S*)-6-Methyl-3-cyclohex-3-enecarboxylic acid 287



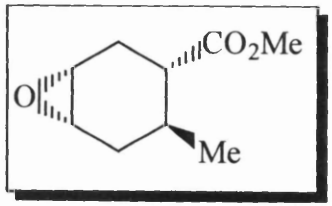


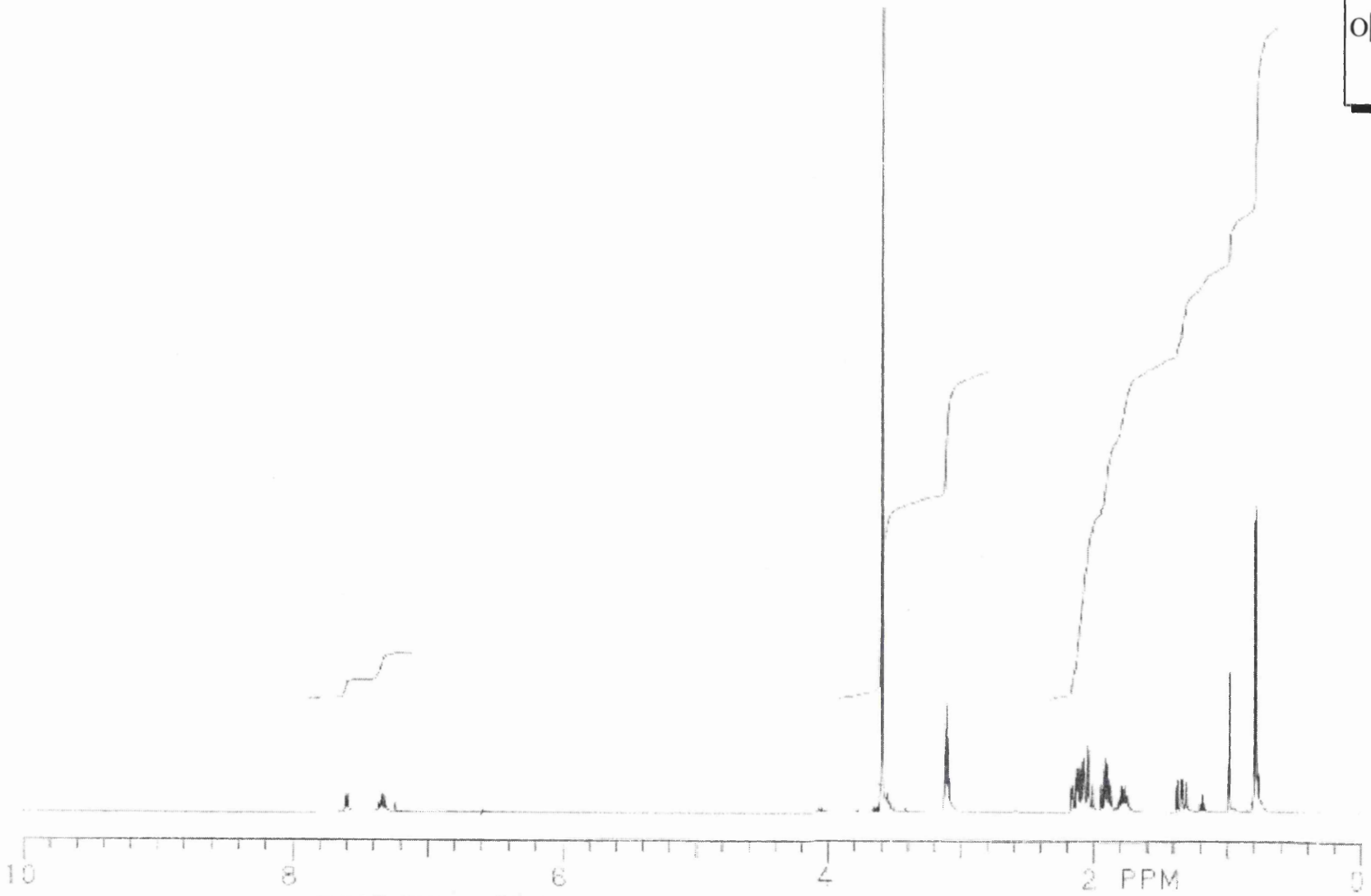
(1*S*,2*S*,4*R*,5*R*)- and (1*S*,2*S*,4*S*,5*R*)-4-Methoxymethoxy-2-methyl-6-oxa-bicyclo[3.2.1]octan-7-one 294



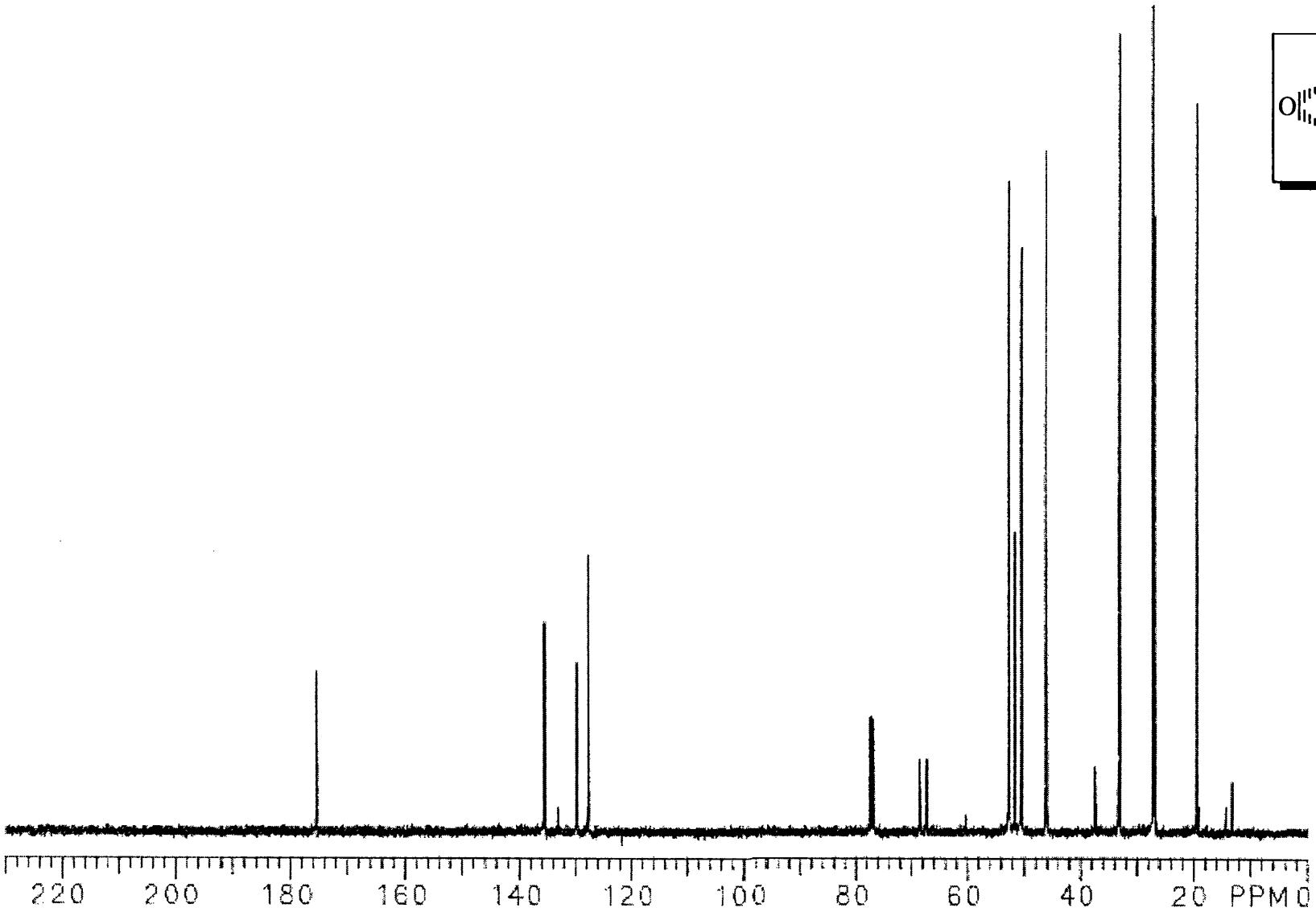


(1*S*,2*S*,4*R*,5*R*)- and (1*S*,2*S*,4*S*,5*R*)-4-Methoxymethoxy-2-methyl-6-oxa-bicyclo[3.2.1]octan-7-one 294

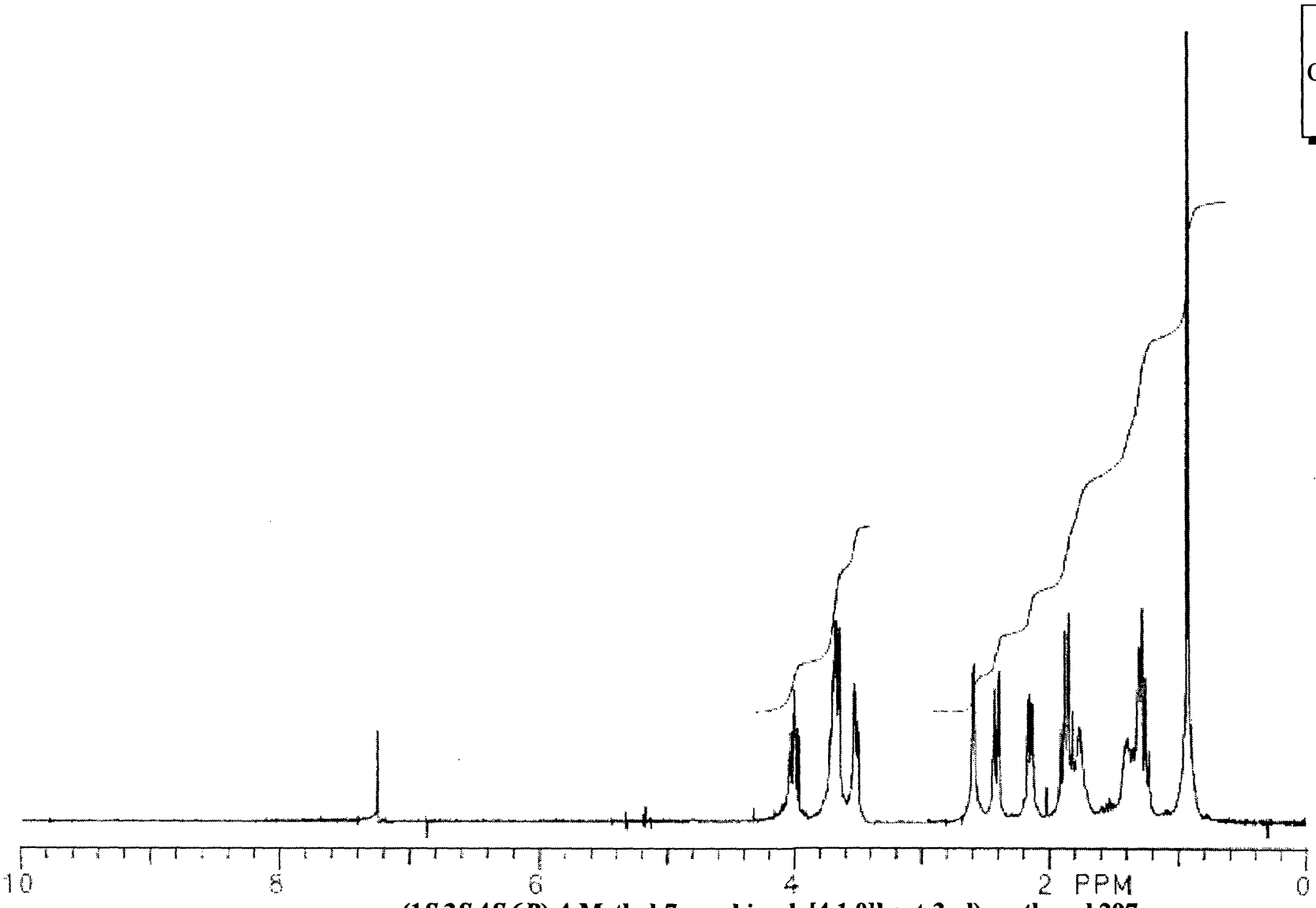




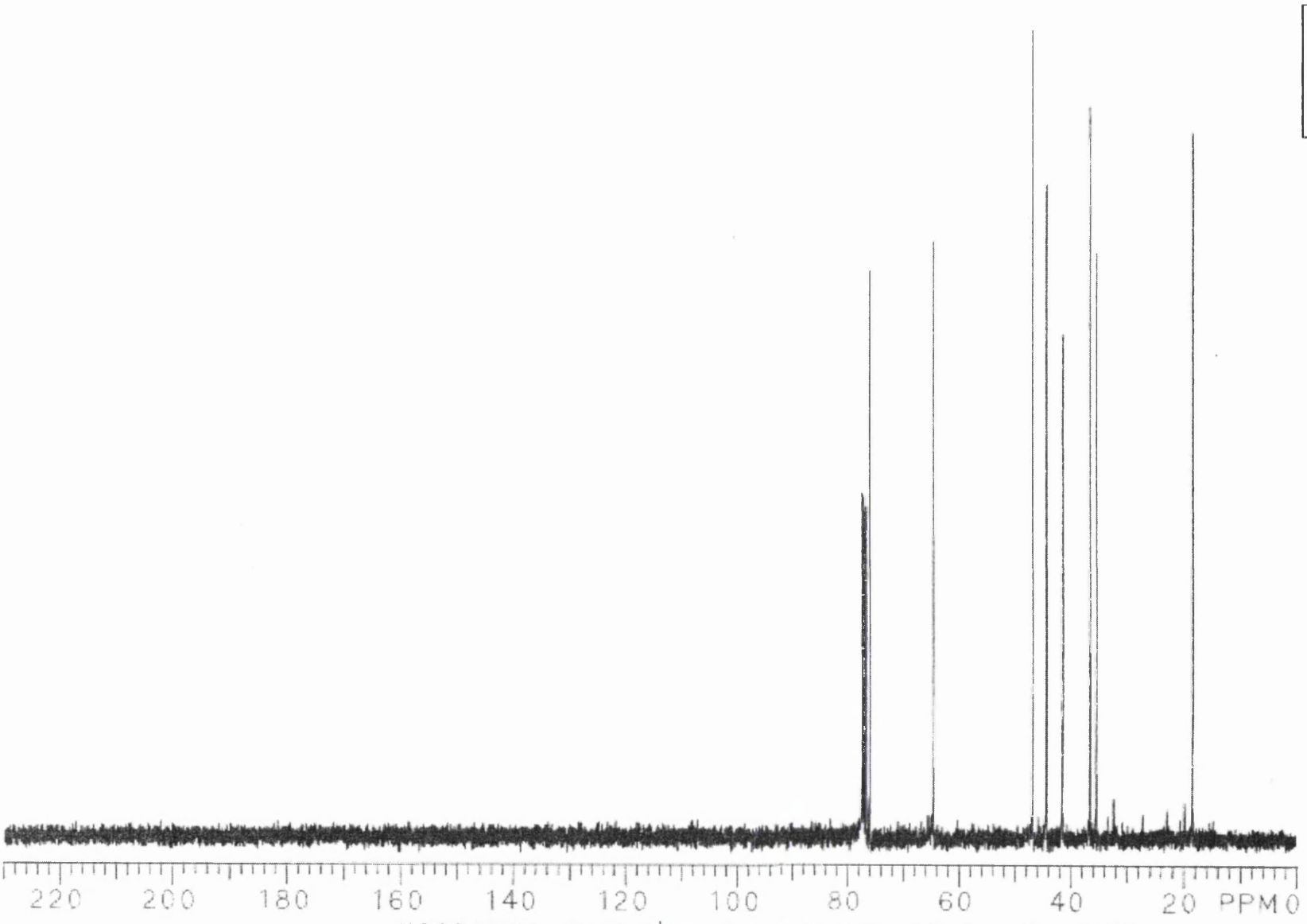
(1*S*,3*S*,4*S*,6*R*)-4-Methyl-7-oxa-bicyclo[4.1.0]heptane-3-carboxylic acid methyl ester 296



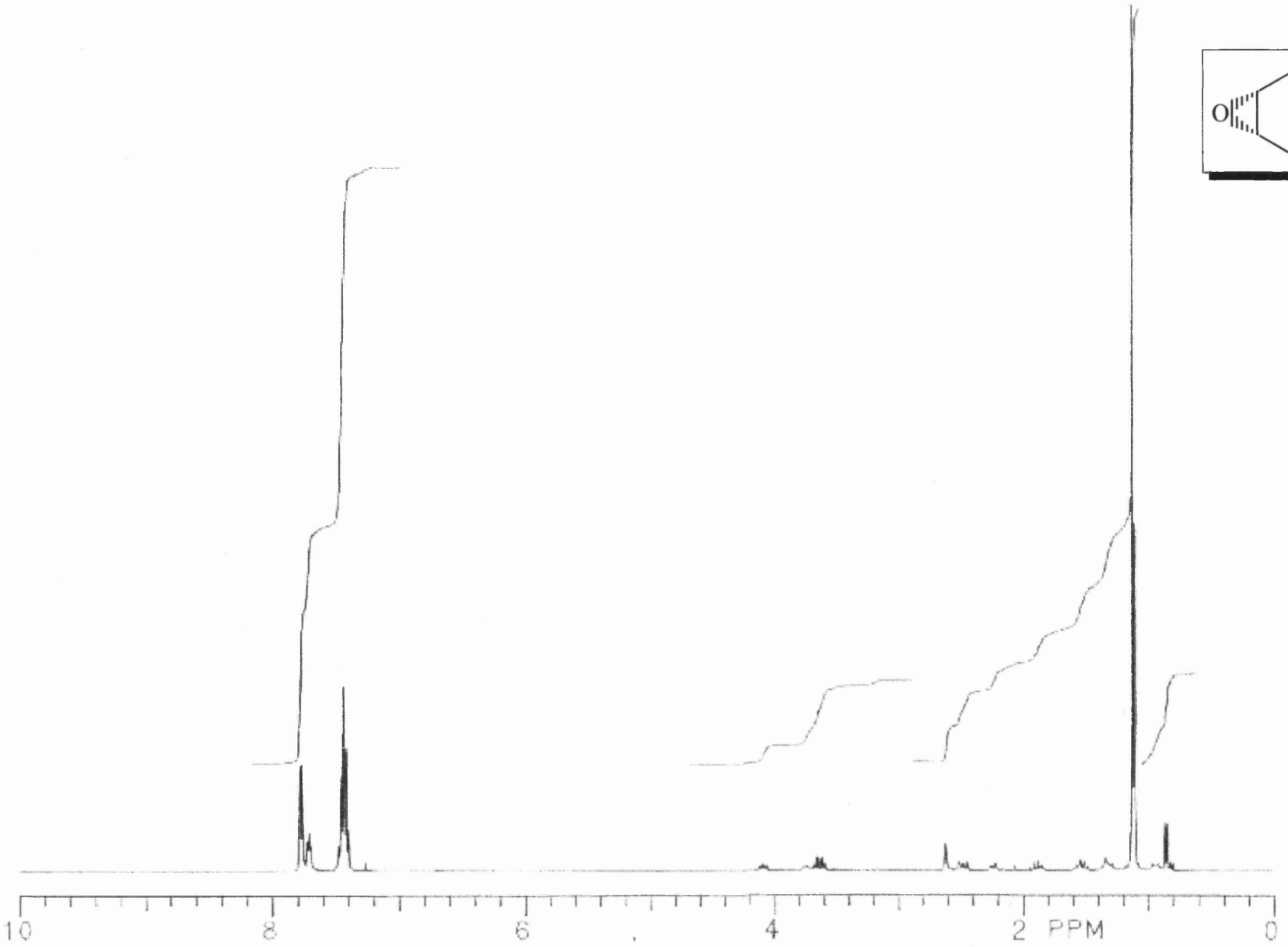
(1*S*,3*S*,4*S*,6*R*)-4-Methyl-7-oxa-bicyclo[4.1.0]heptane-3-carboxylic acid methyl ester 296



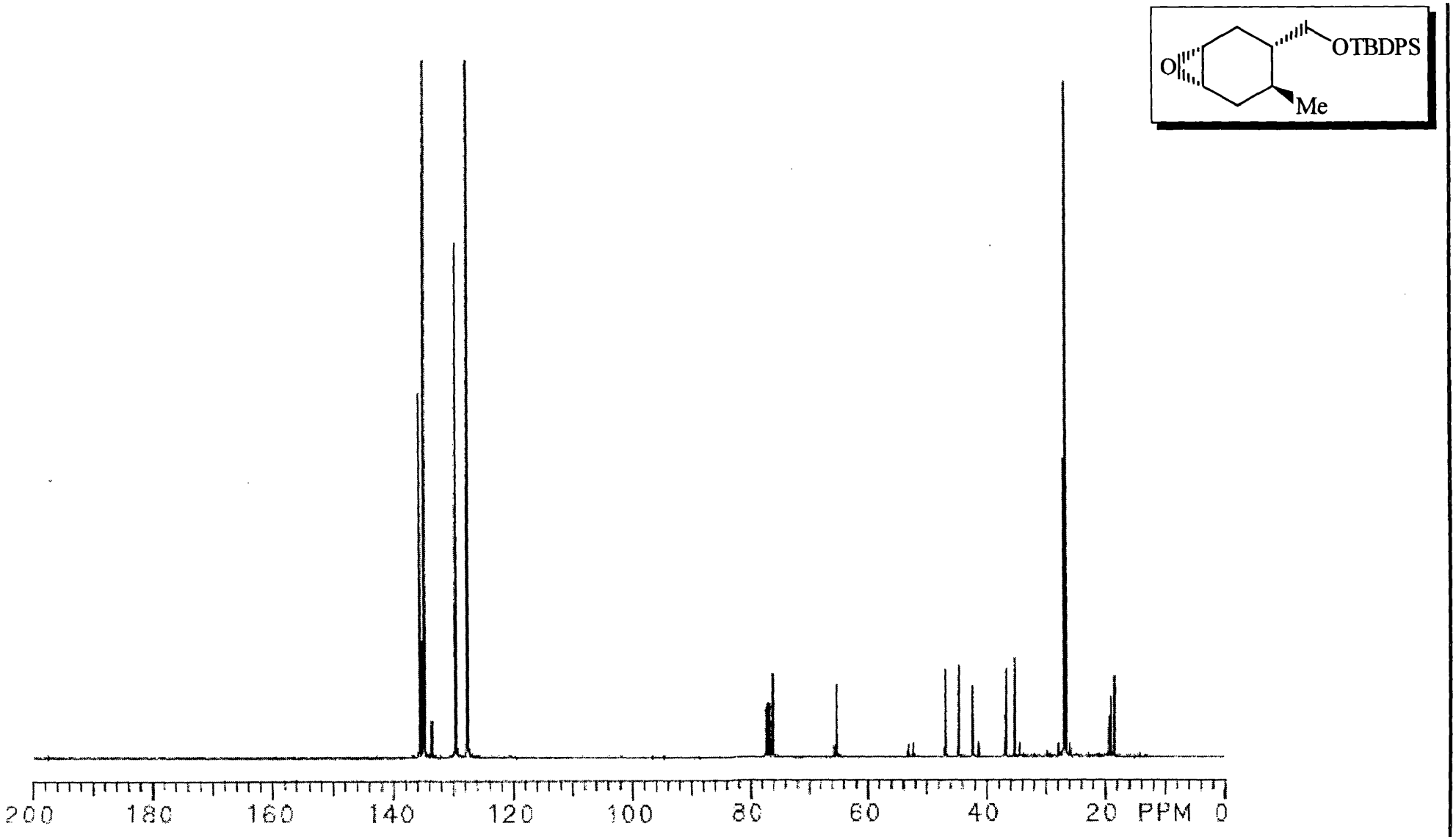
(1*S*,3*S*,4*S*,6*R*)-4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-yl)-methanol 297



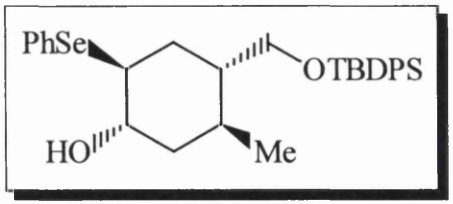
(1*S*,3*S*,4*S*,6*R*)-4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-yl)-methanol 297

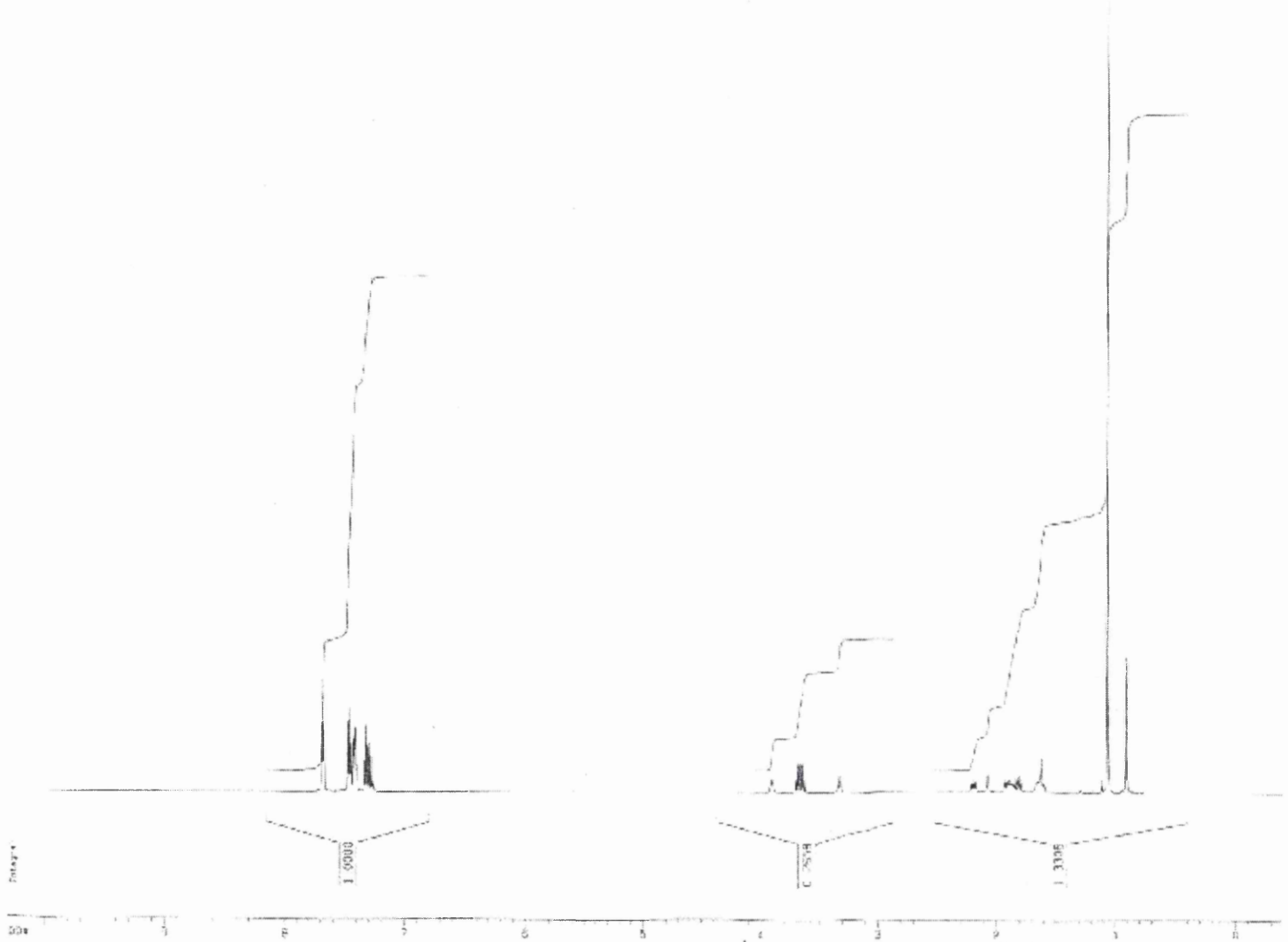


(1*S*,3*S*,4*S*,6*R*)-(4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-ylmethoxy)-*t*-butyl-diphenyl-silane 298

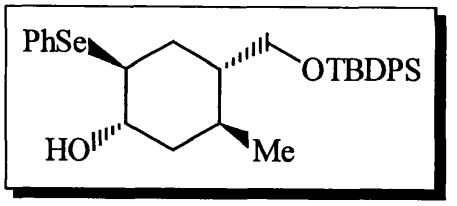


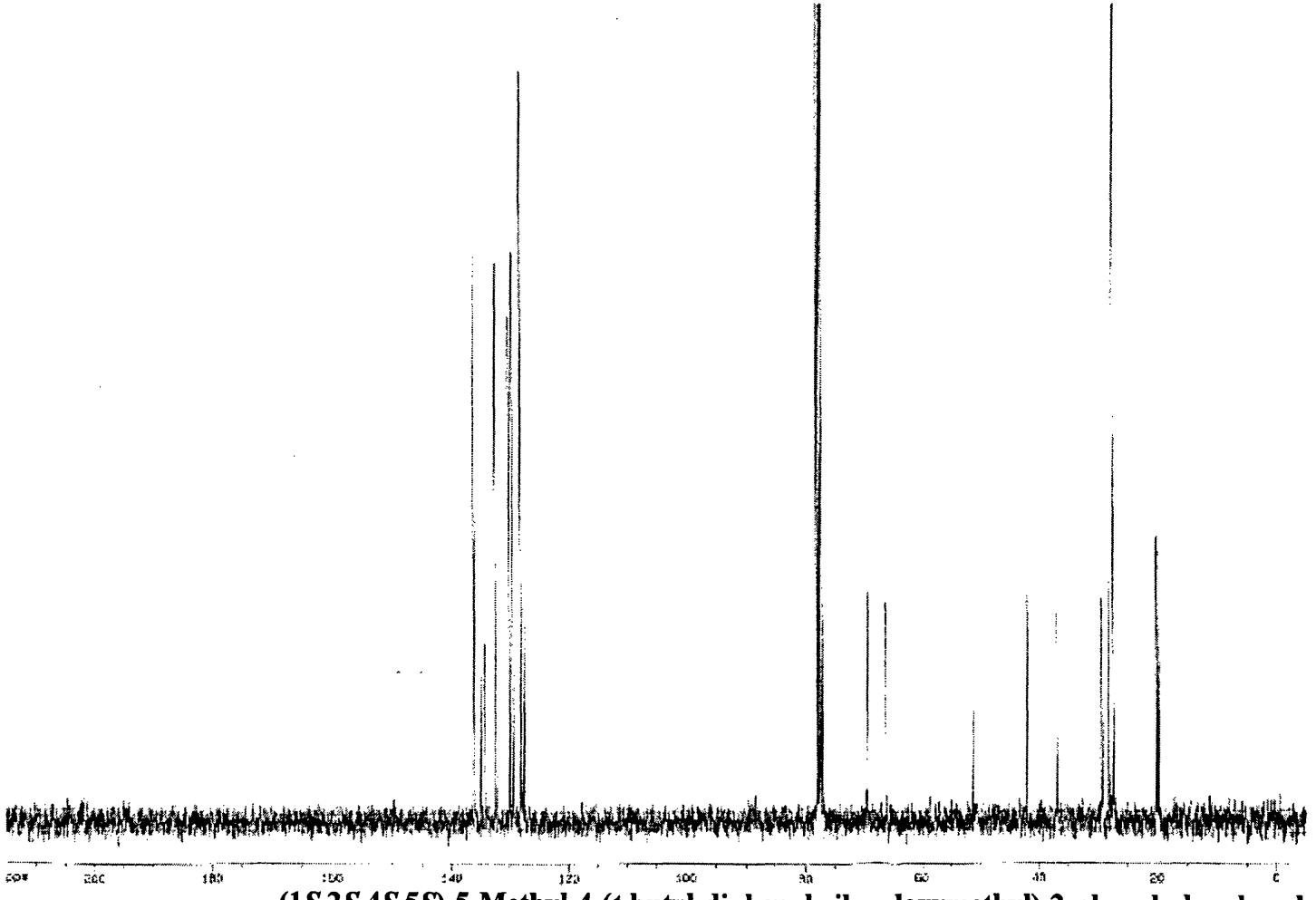
(1*S*,3*S*,4*S*,6*R*)-(4-Methyl-7-oxa-bicyclo[4.1.0]hept-3-ylmethoxy)-*t*-butyl-diphenyl-silane 298



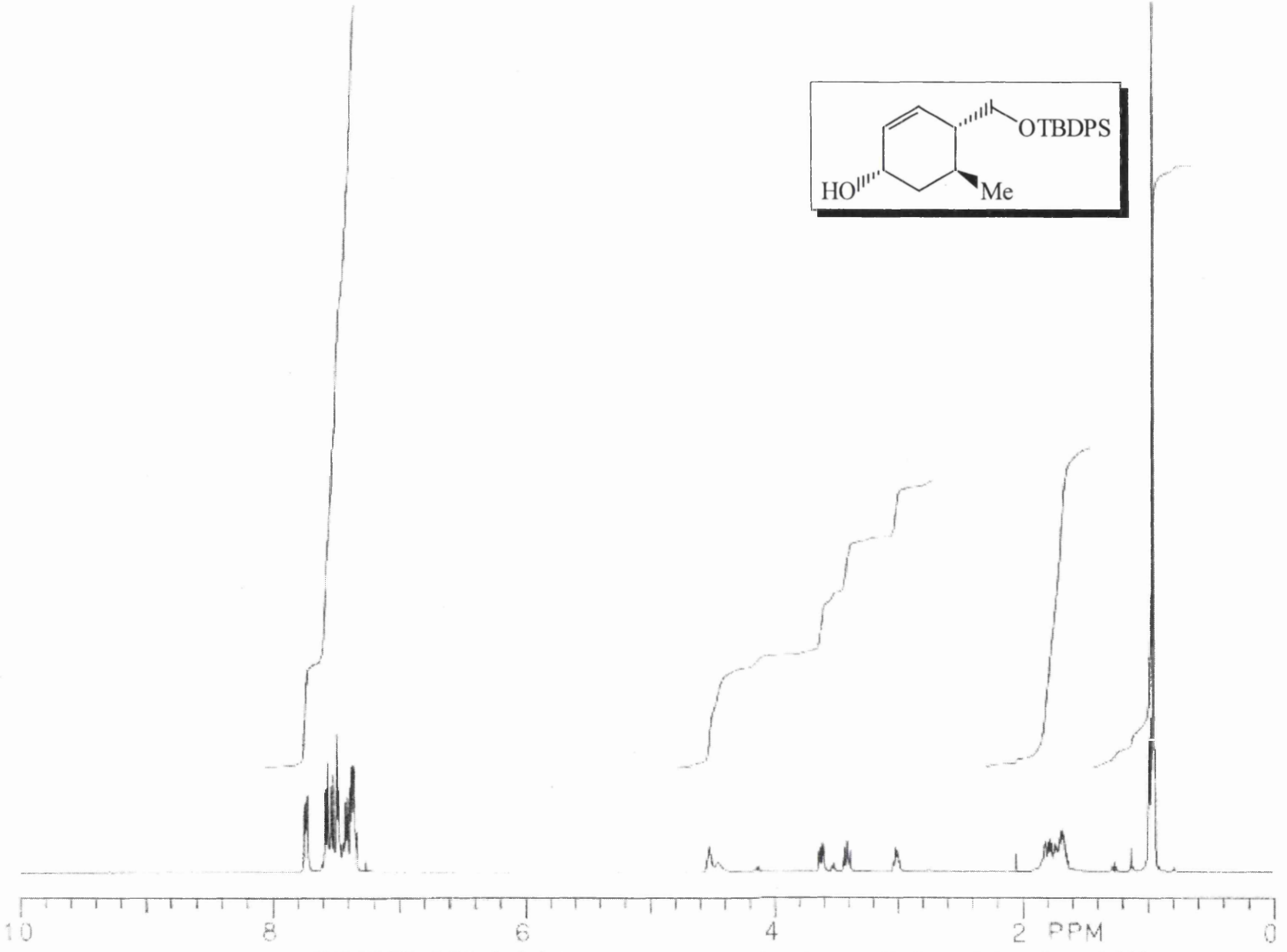


(1*S*,2*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-2-phenylselanyl-cyclohexanol 299

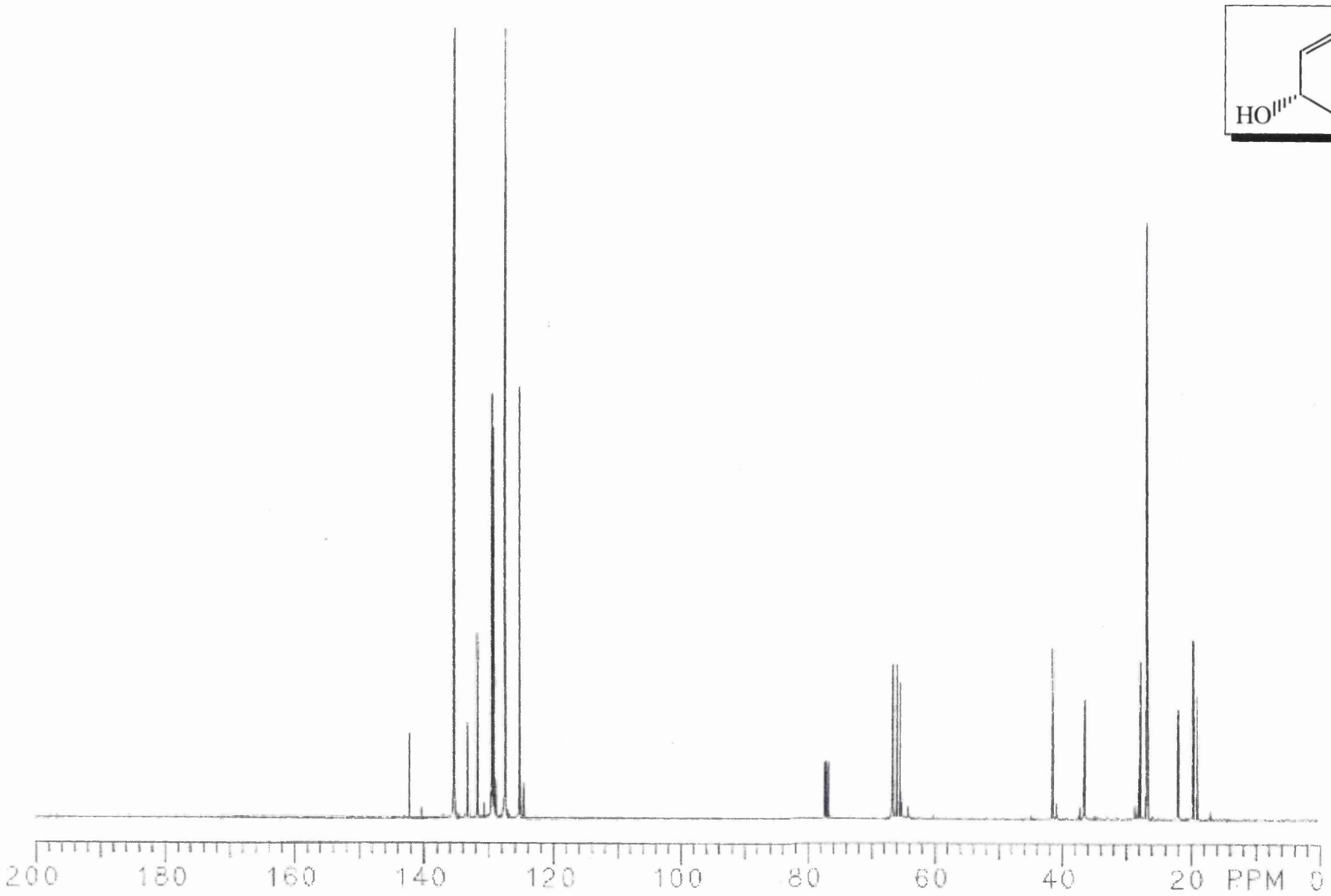




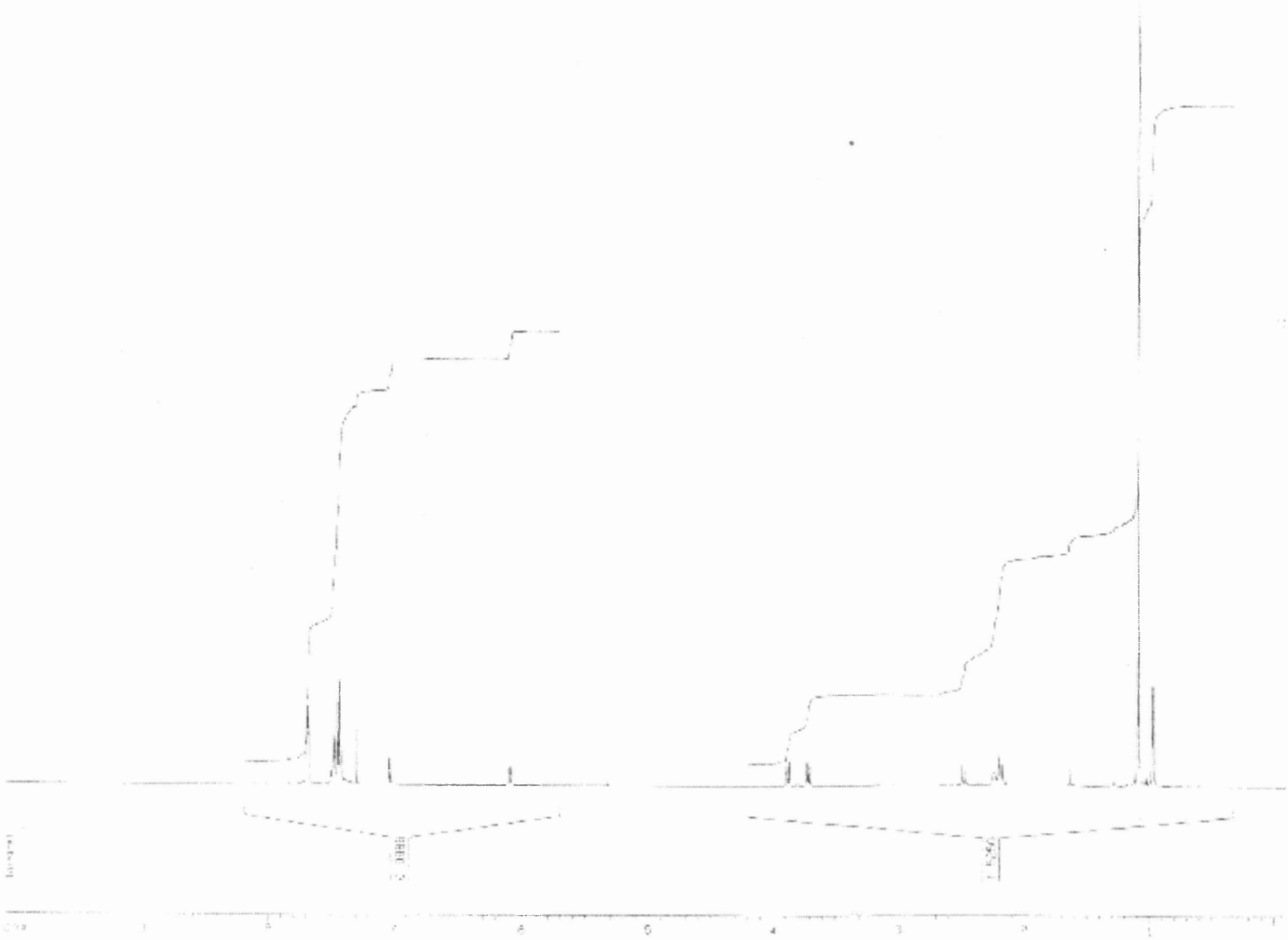
(1*S*,2*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-2-phenylselanyl-cyclohexanol 299

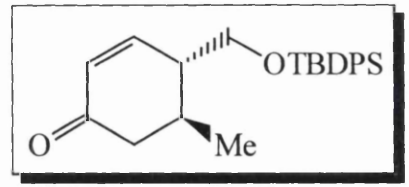


(1*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)–cyclohex-2-enol 300

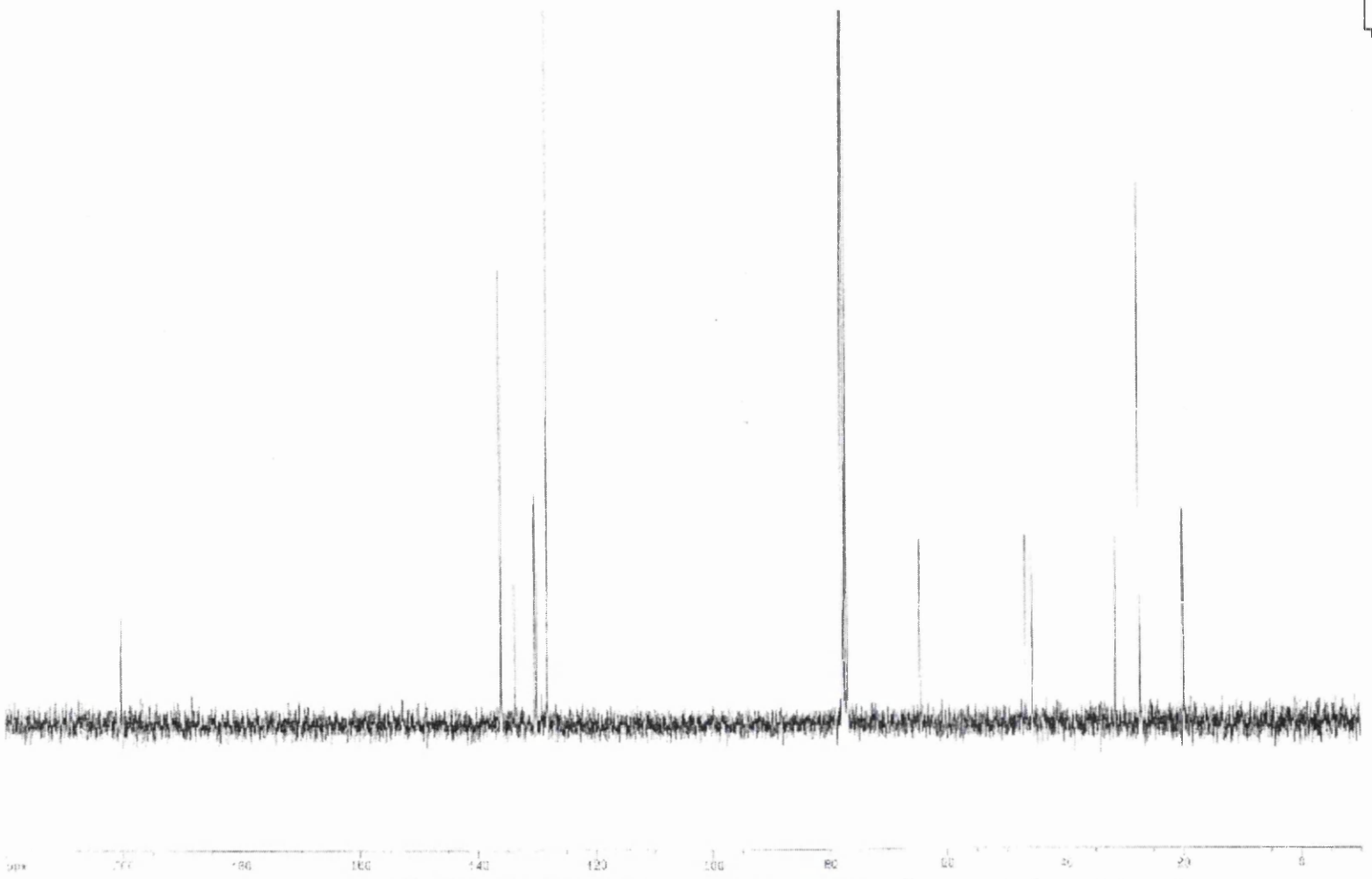


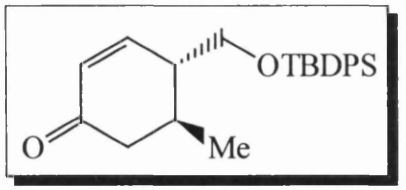
(1*S*,4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)–cyclohex-2-enol 300



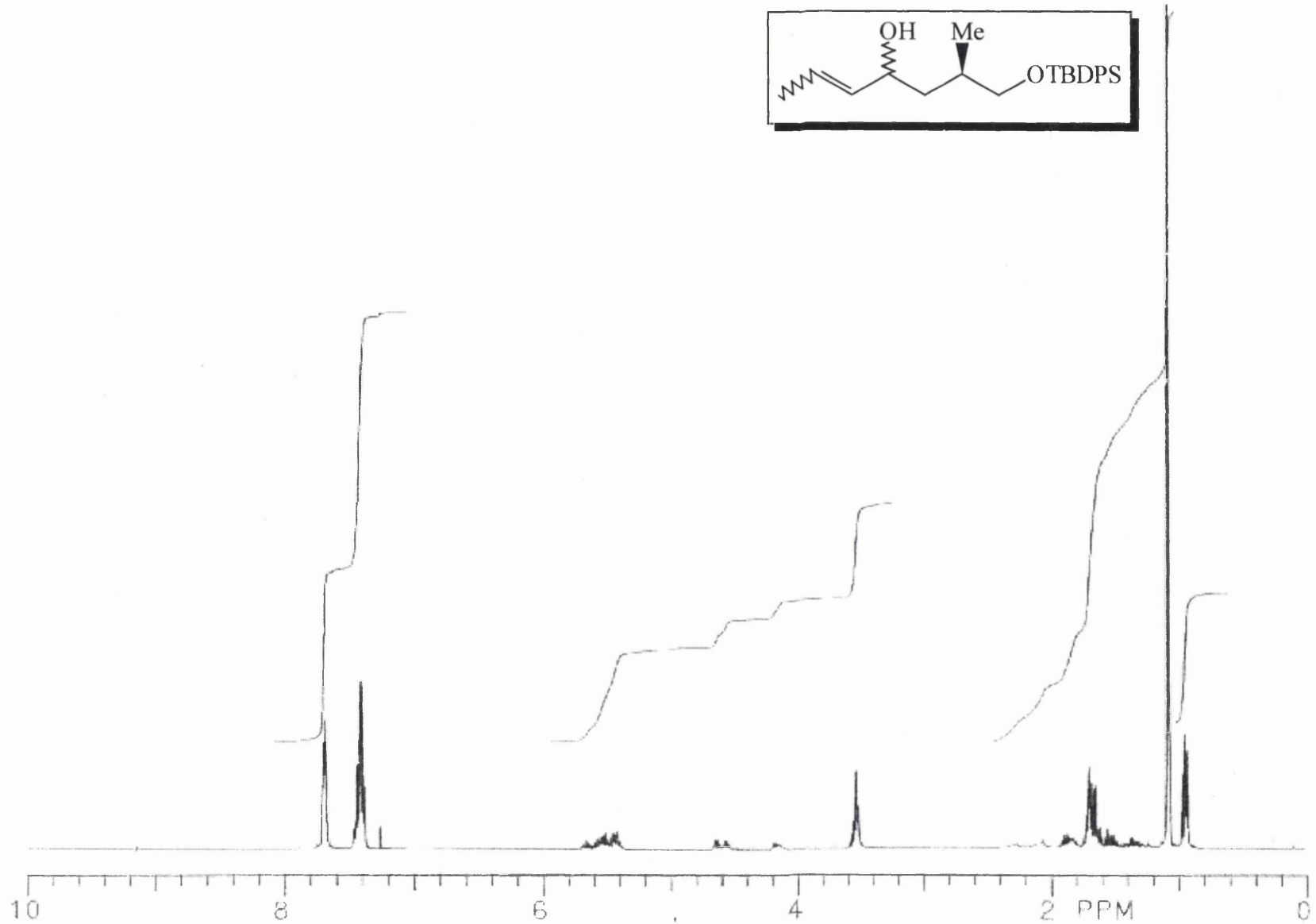


(4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone 301

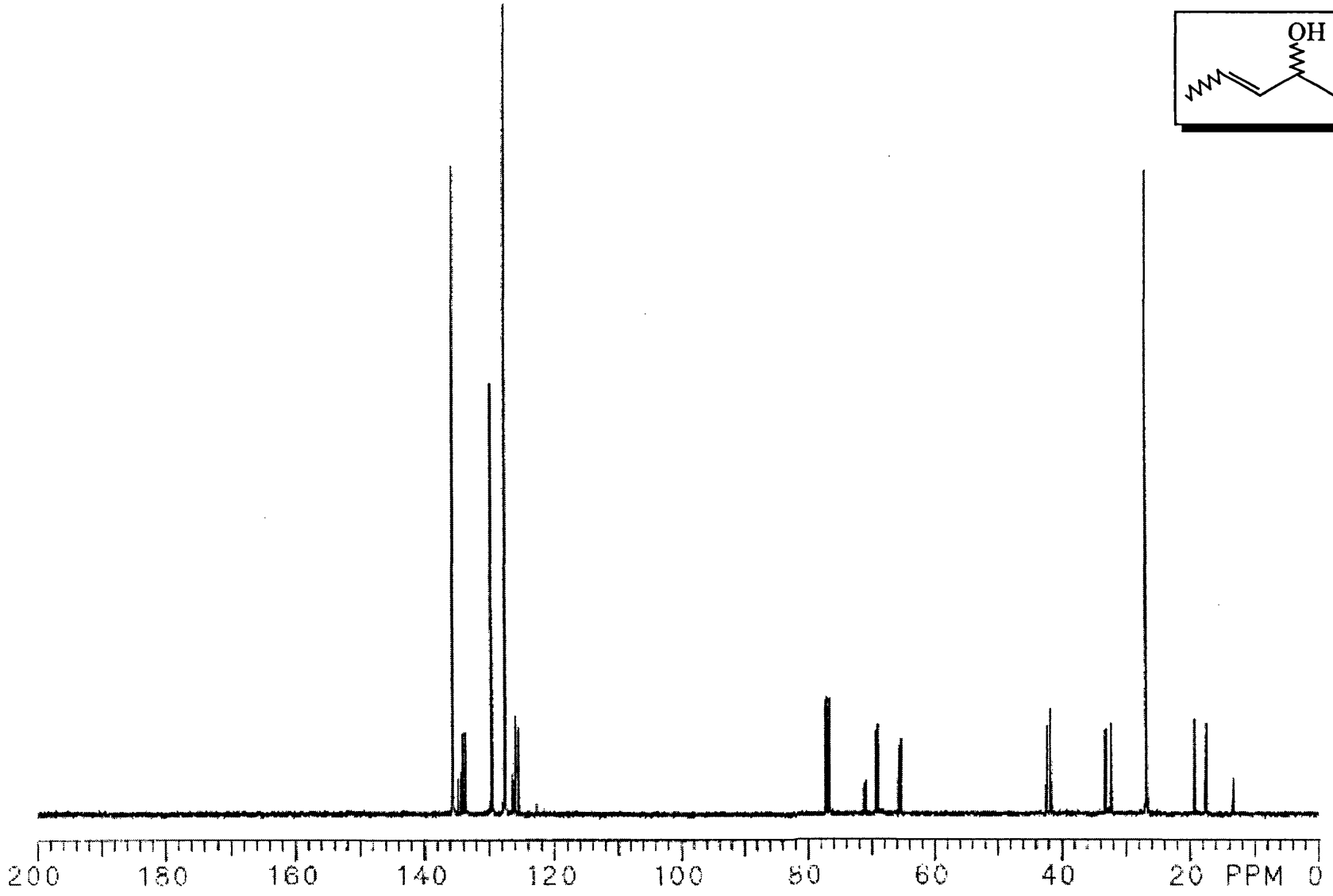




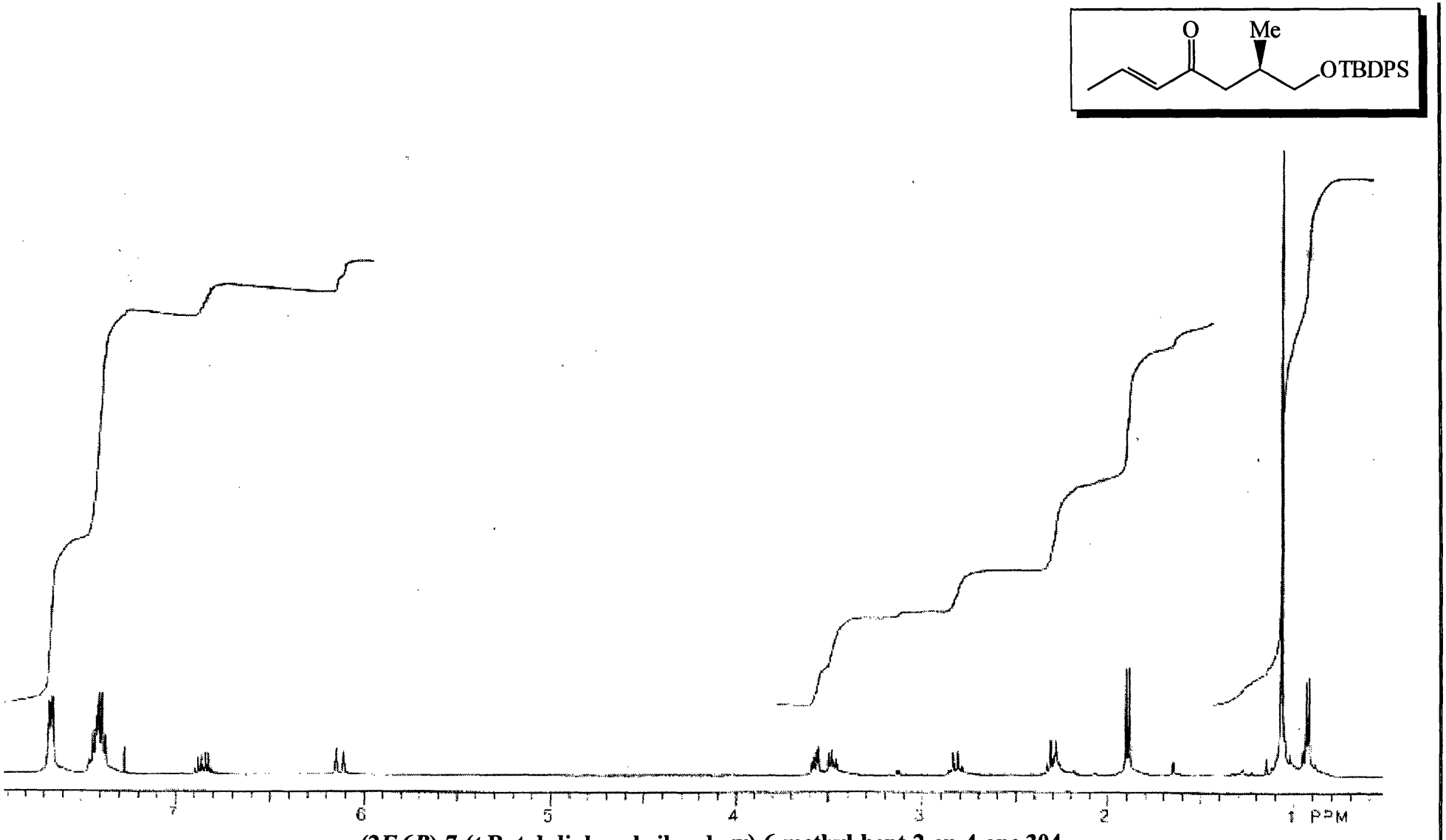
(4*S*,5*S*)-5-Methyl-4-(*t*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone 301



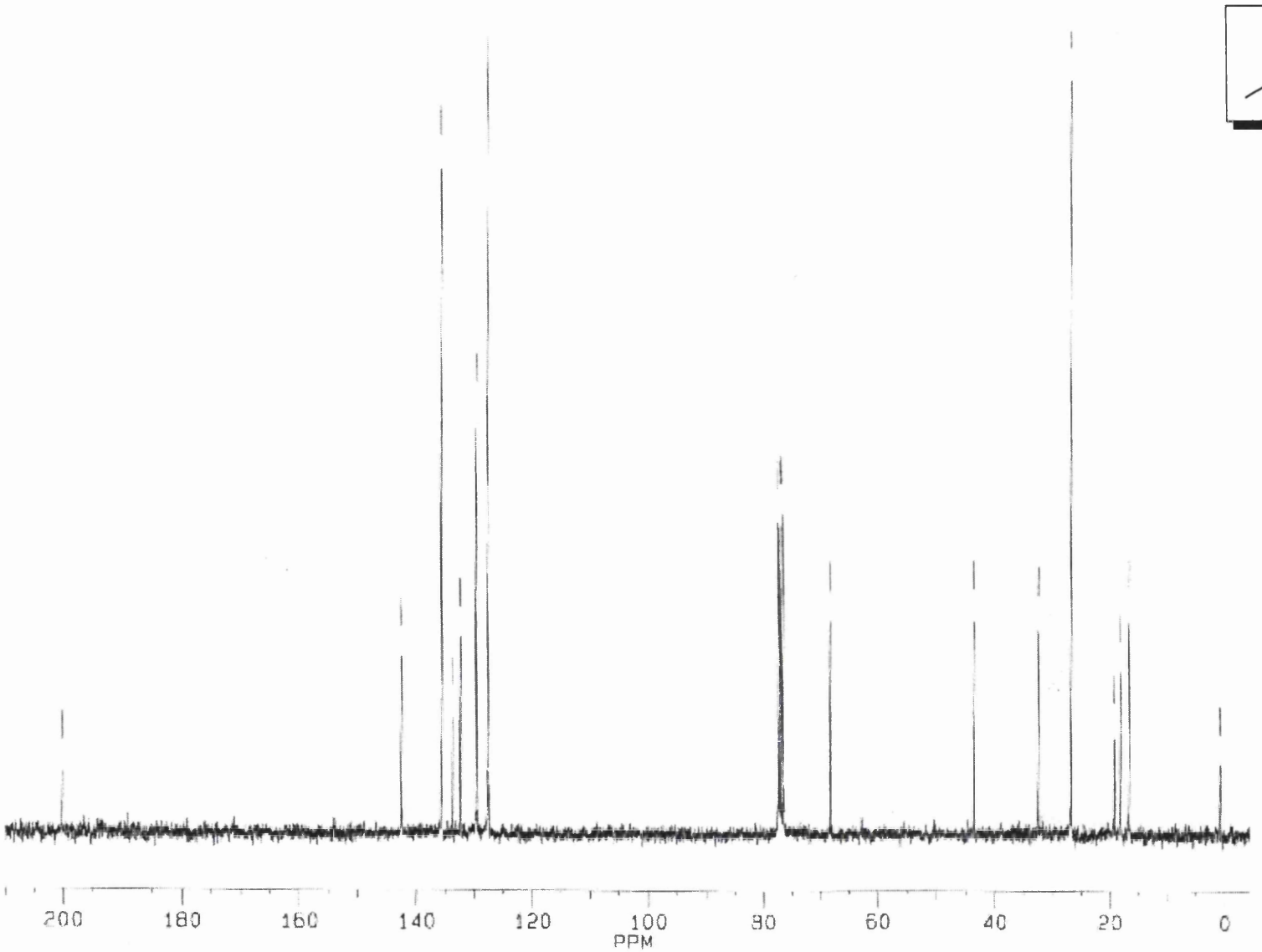
(2*E*,4*S*,6*R*)-, (2*E*,4*R*,6*R*)-, (2*Z*,4*S*,6*R*)-, and (2*Z*,4*R*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol 306



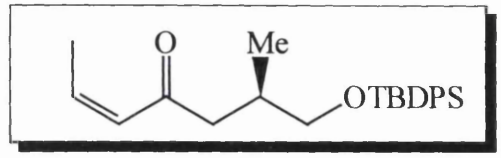
(2*E*,4*S*,6*R*)-, (2*E*,4*R*,6*R*)-, (2*Z*,4*S*,6*R*)-, and (2*Z*,4*R*,6*R*)-7-(*t*-butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-ol 306

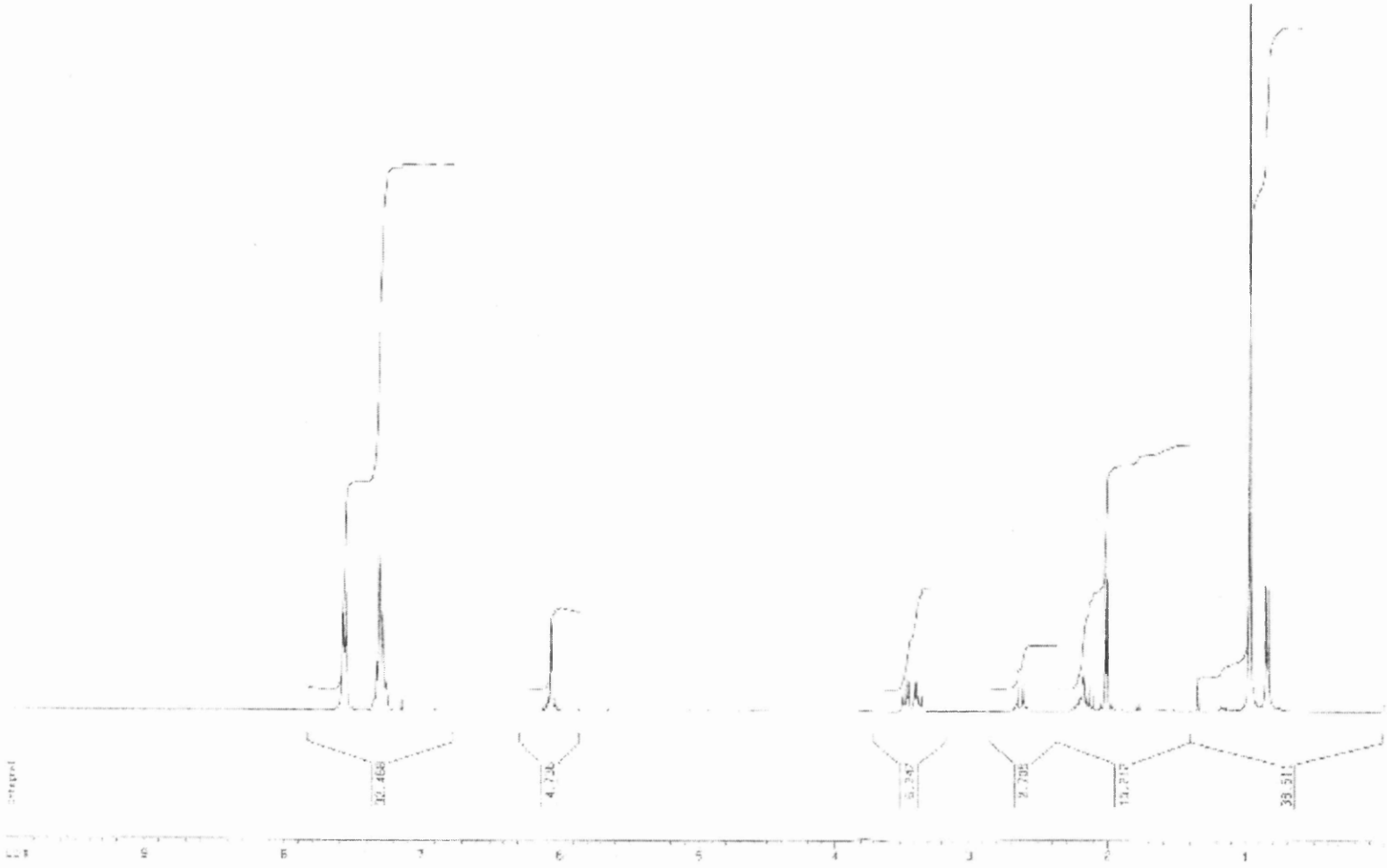


(2*E*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 304

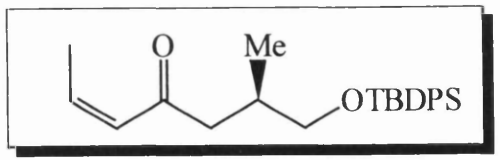


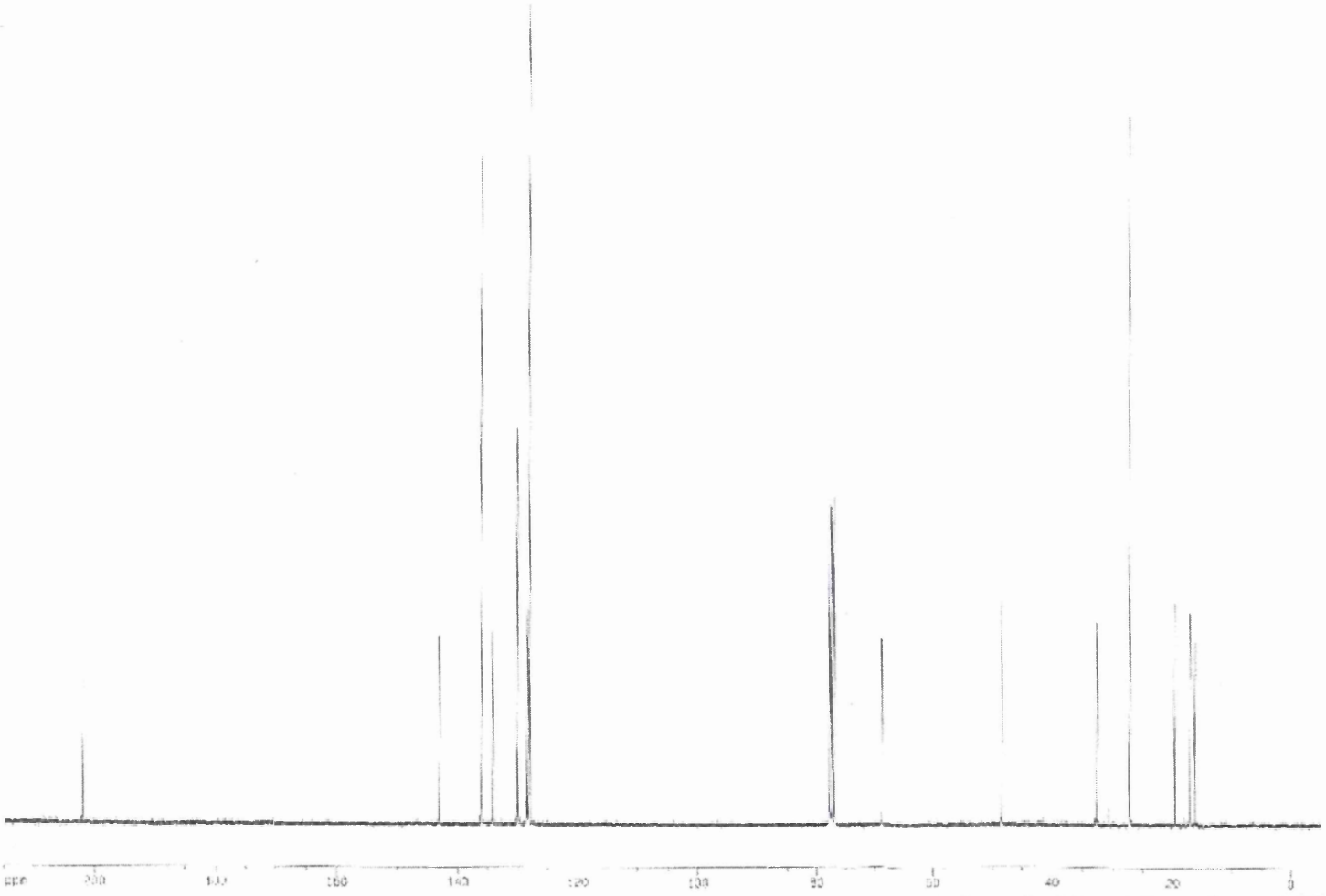
(2*E*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 304



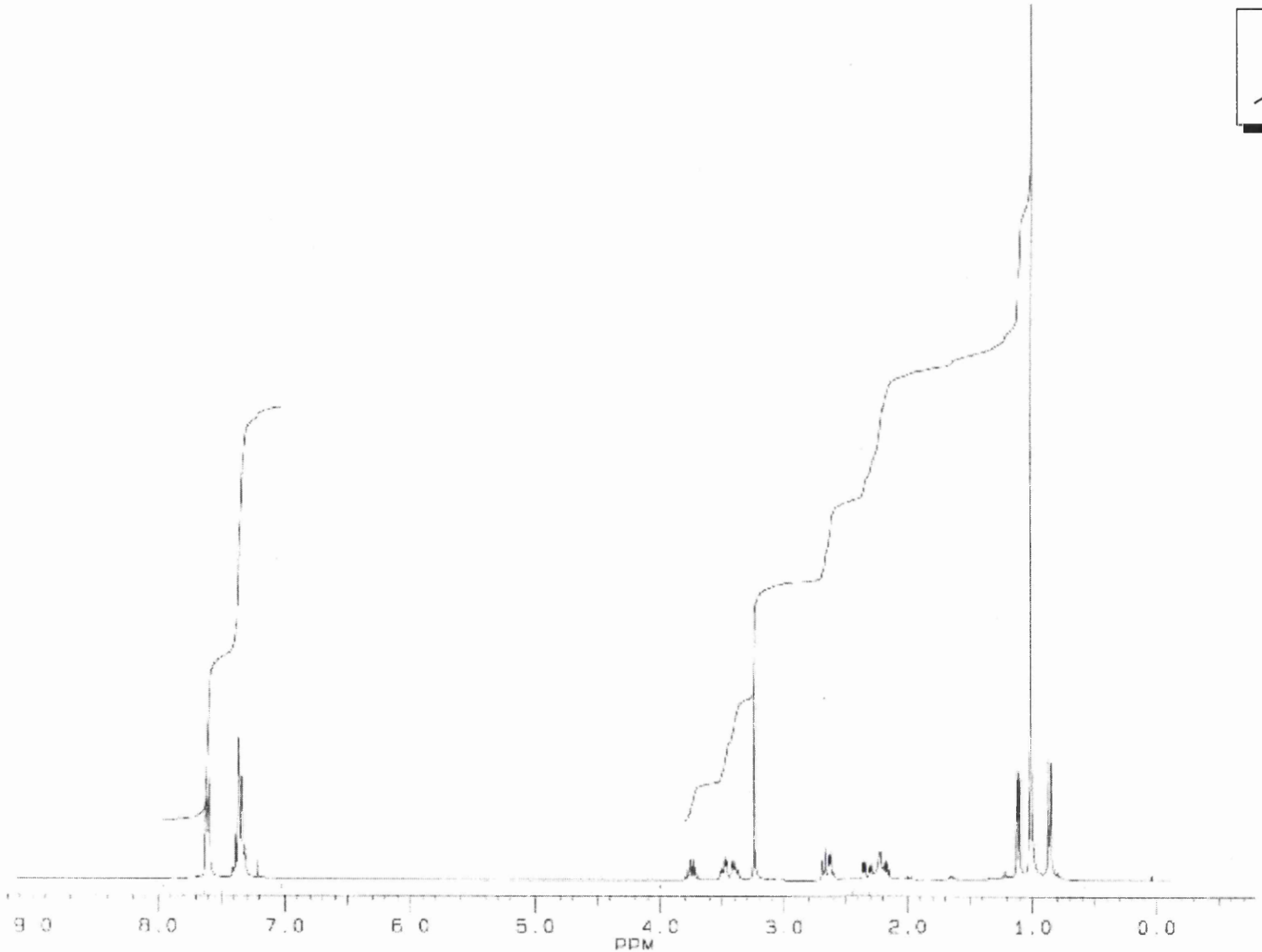


(2*Z*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 307

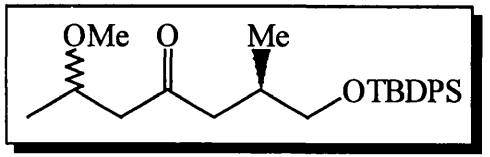


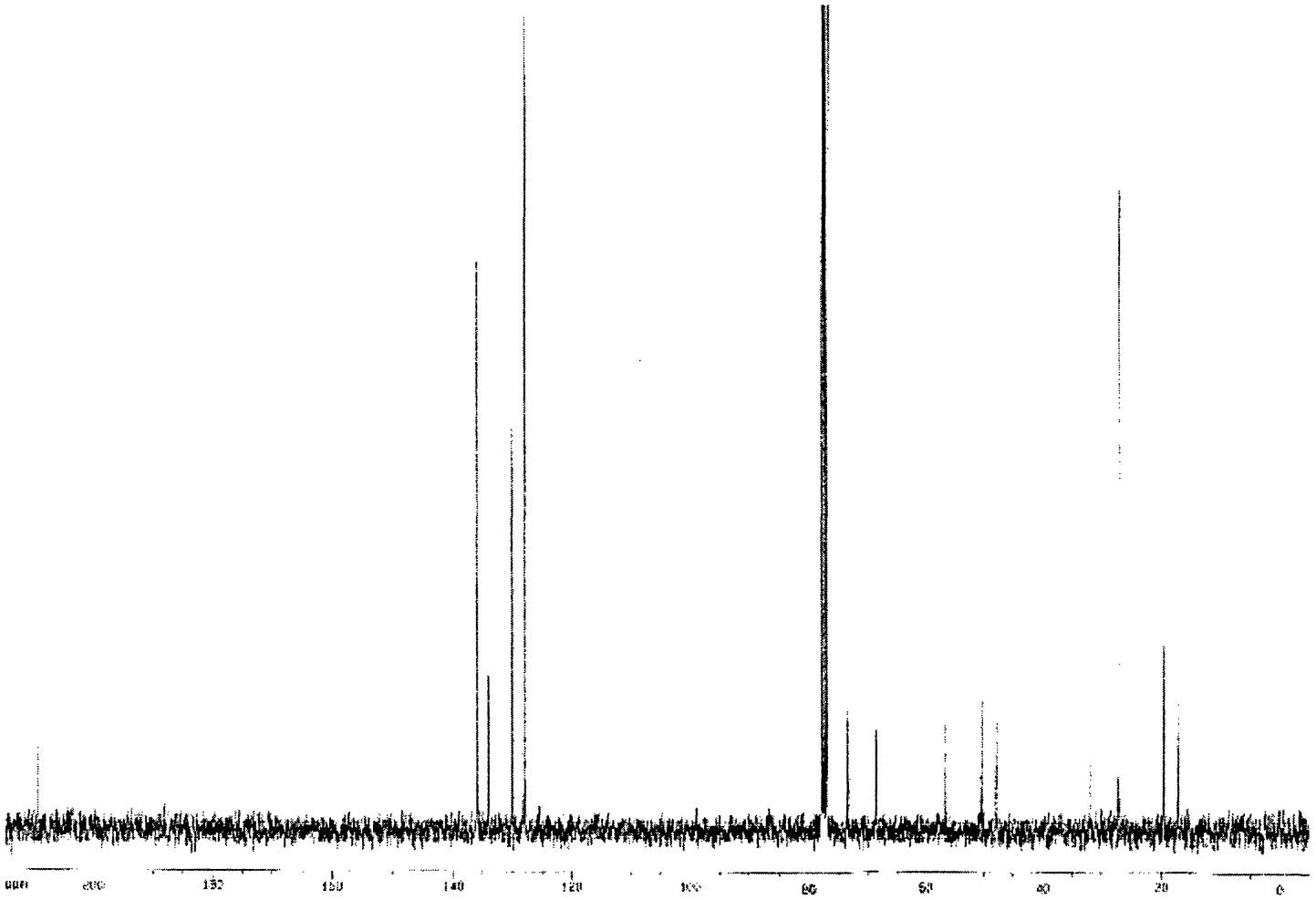


(2*Z*,6*R*)-7-(*t*-Butyl-diphenyl-silanyloxy)-6-methyl-hept-2-en-4-one 307

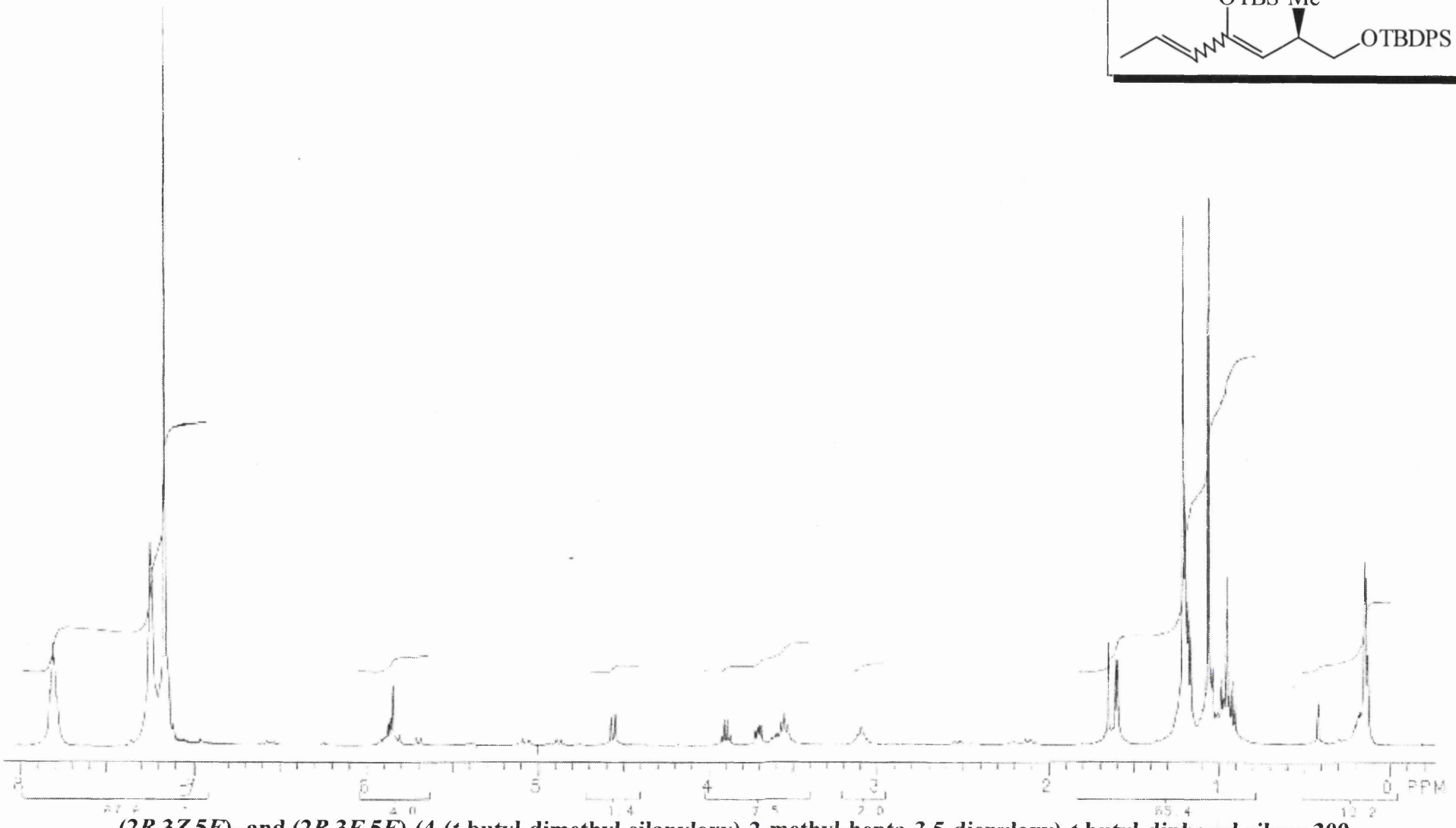


(2*R*,6*R*)- and (2*R*,6*S*)-1-(*t*-Butyl-diphenyl-silanyloxy)-6-methoxy-2-methyl-heptan-4-one 308

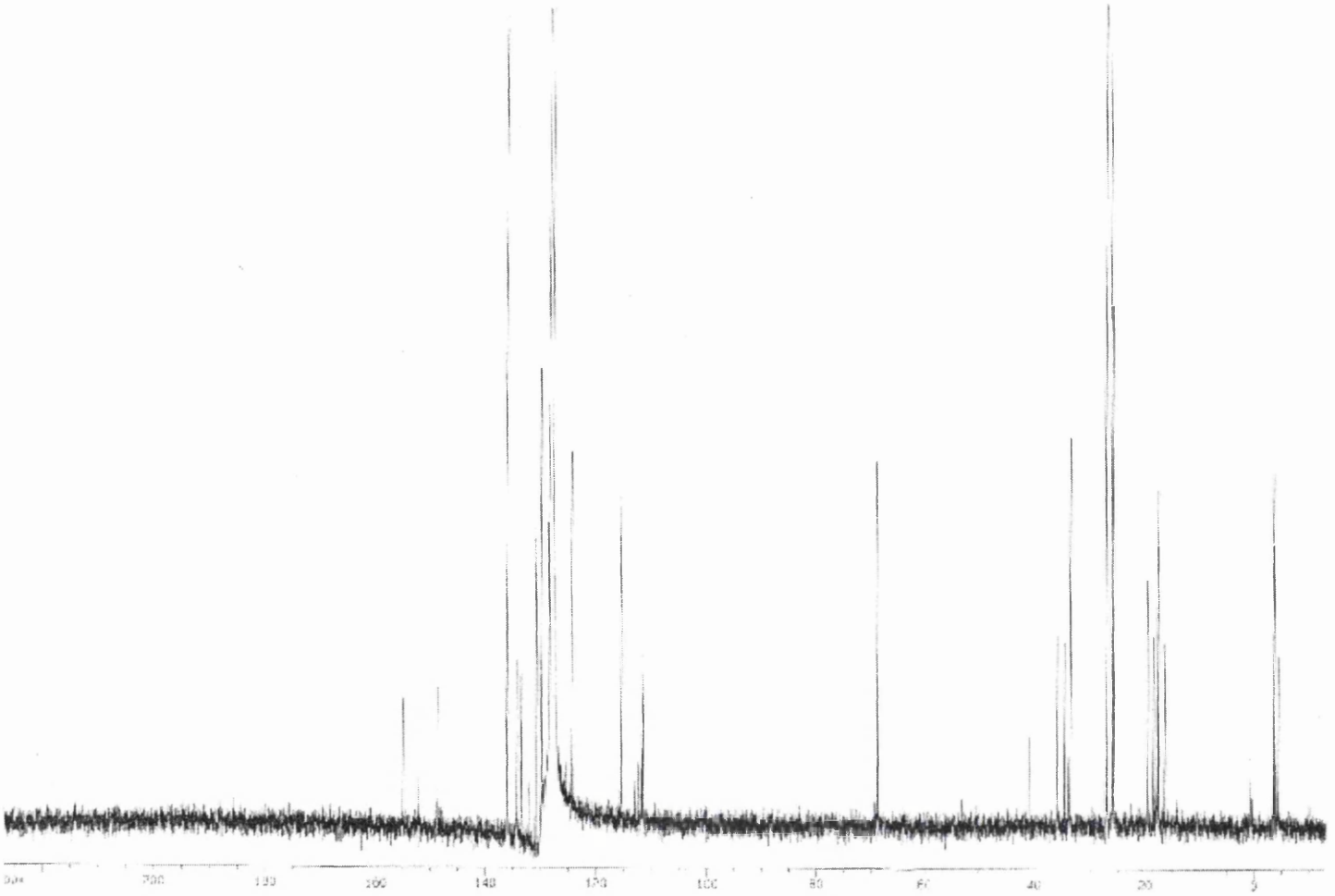




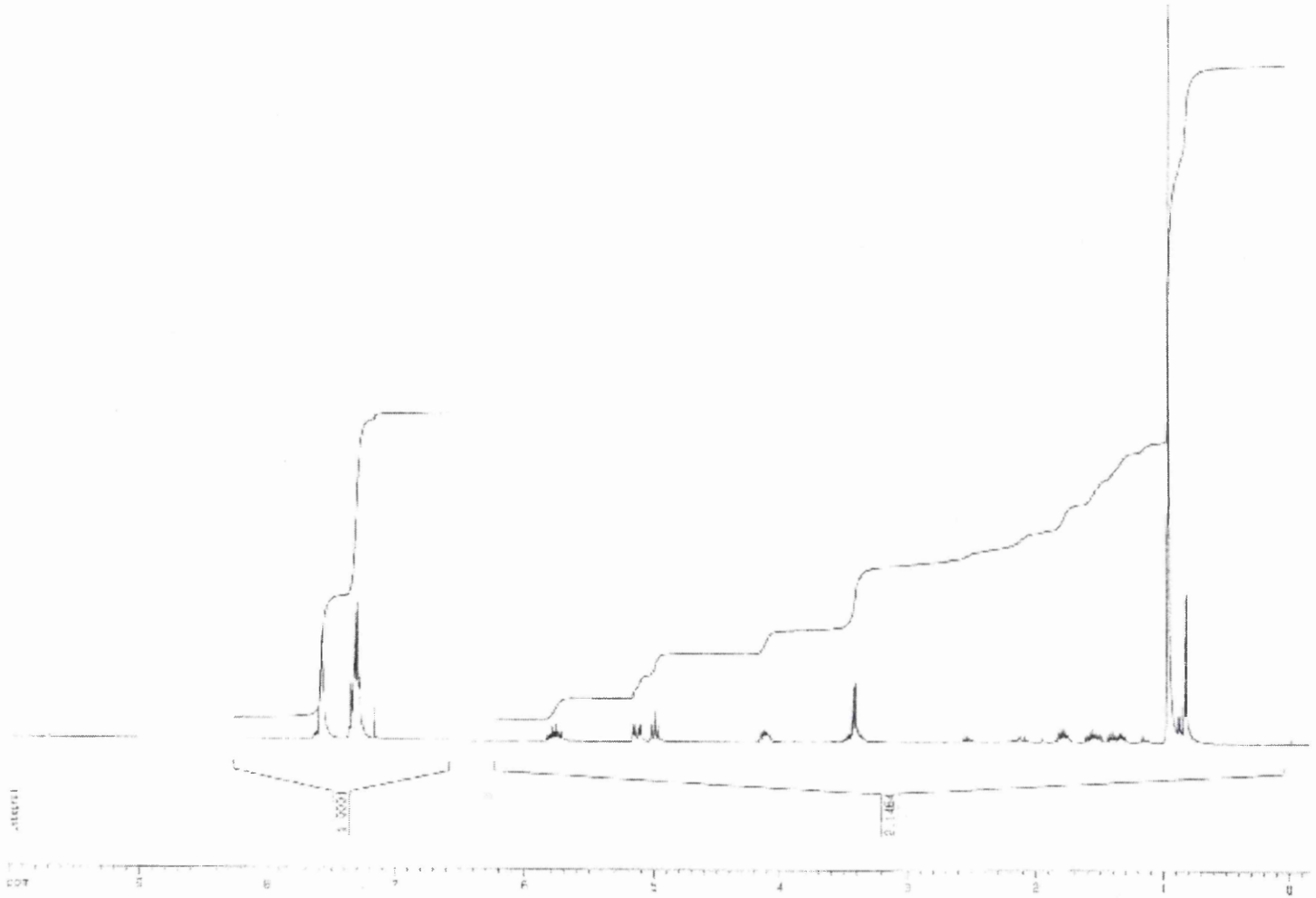
(2*R*,6*R*)- and (2*R*,6*S*)-1-(*t*-Butyl-diphenyl-silanyloxy)-6-methoxy-2-methyl-heptan-4-one 308



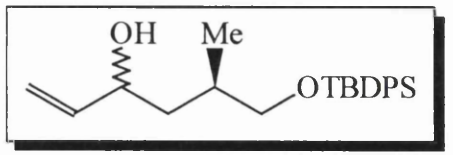
(2*R*,3*Z*,5*E*)- and (2*R*,3*E*,5*E*)-(4-(*t*-butyl-dimethyl-silanyloxy)-2-methyl-hepta-3,5-dienyloxy)-*t*-butyl-diphenyl-silane 309

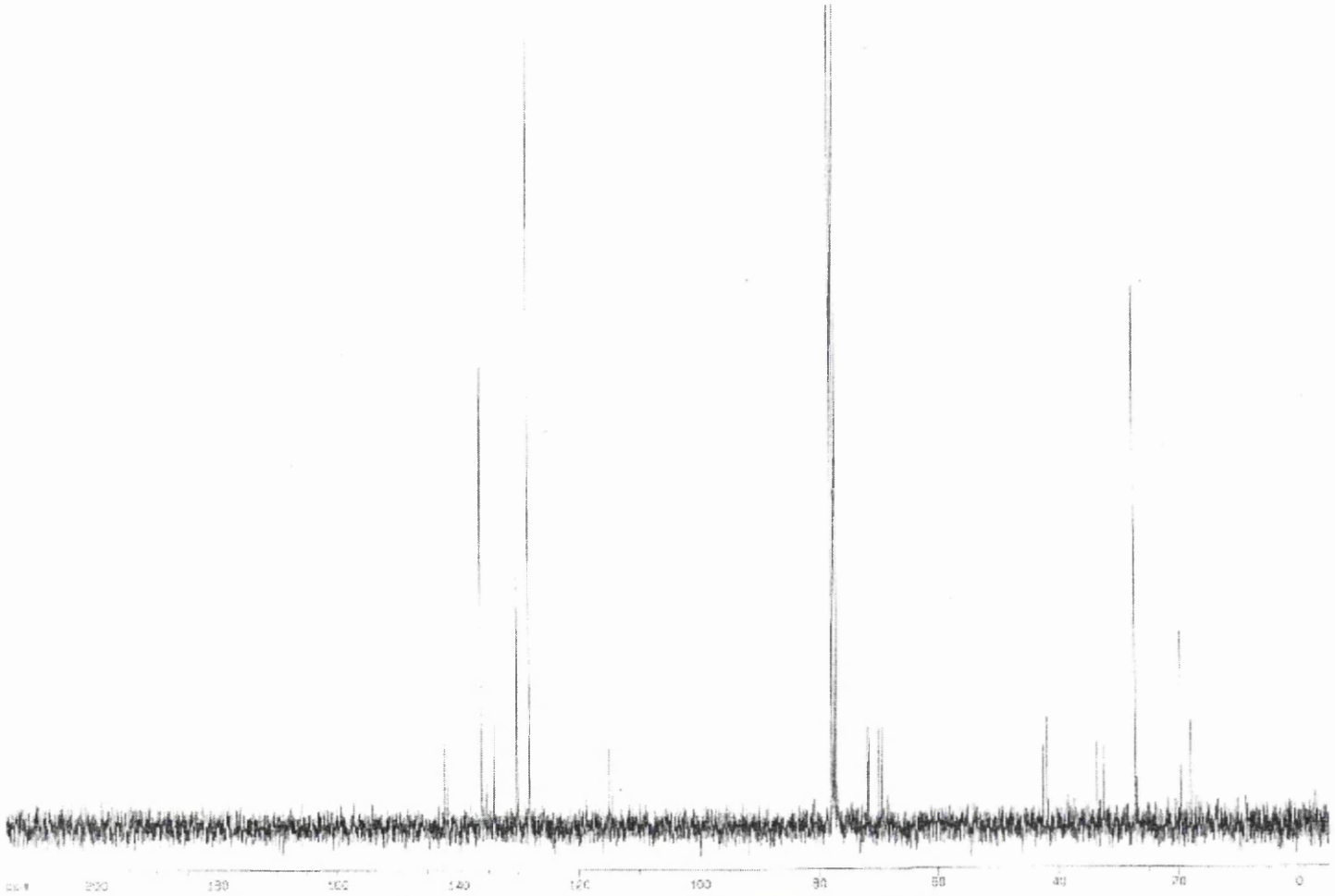


(2*R*,3*Z*,5*E*)- and (2*R*,3*E*,5*E*)-(4-(*t*-butyl-dimethyl-silanyloxy)-2-methyl-hepta-3,5-dienyloxy)-*t*-butyl-diphenyl-silane 309

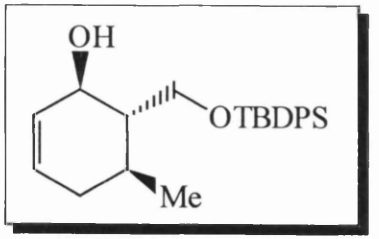


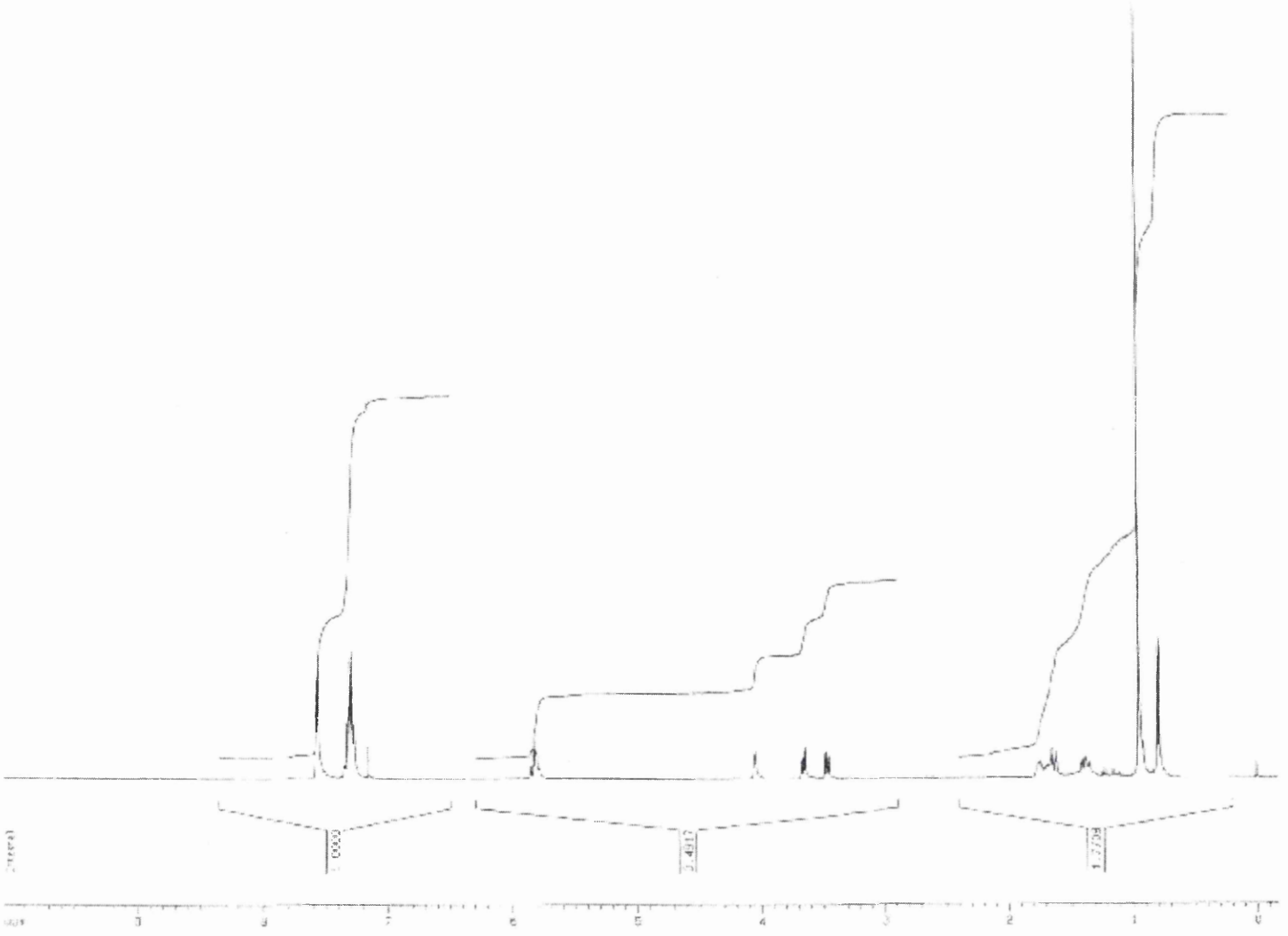
(3*S*,5*R*)- and (3*R*,5*R*)-6-(*t*-butyl-diphenyl-silanyloxy)-5-methyl-hex-1-en-3-ol 312



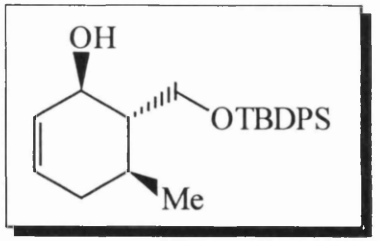


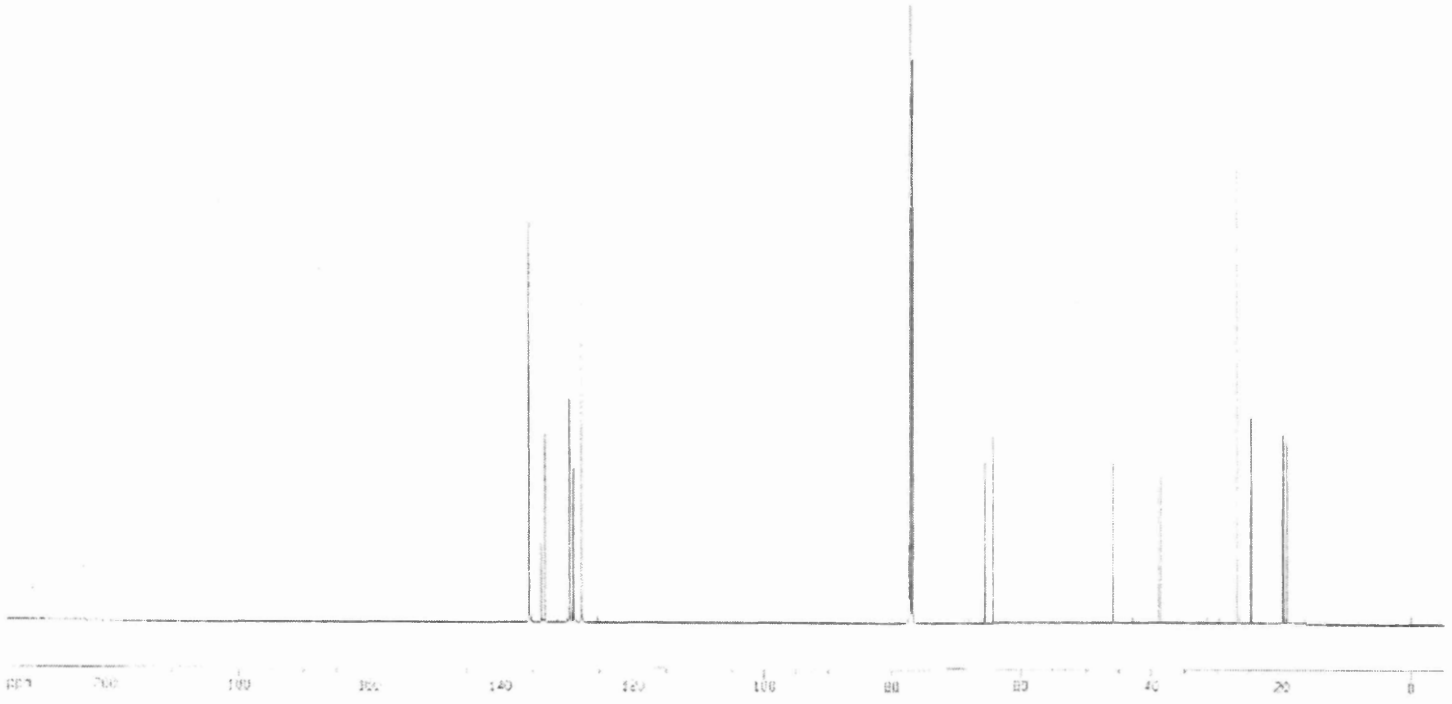
(3*S*,5*R*)- and (3*R*,5*R*)-6-(*t*-butyl-diphenyl-silanyloxy)-5-methyl-hex-1-en-3-ol 312



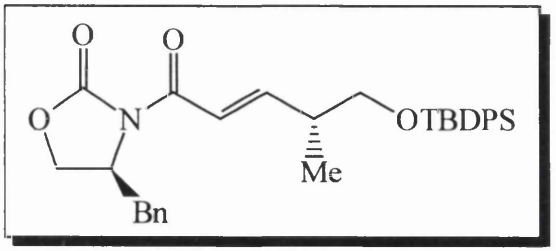


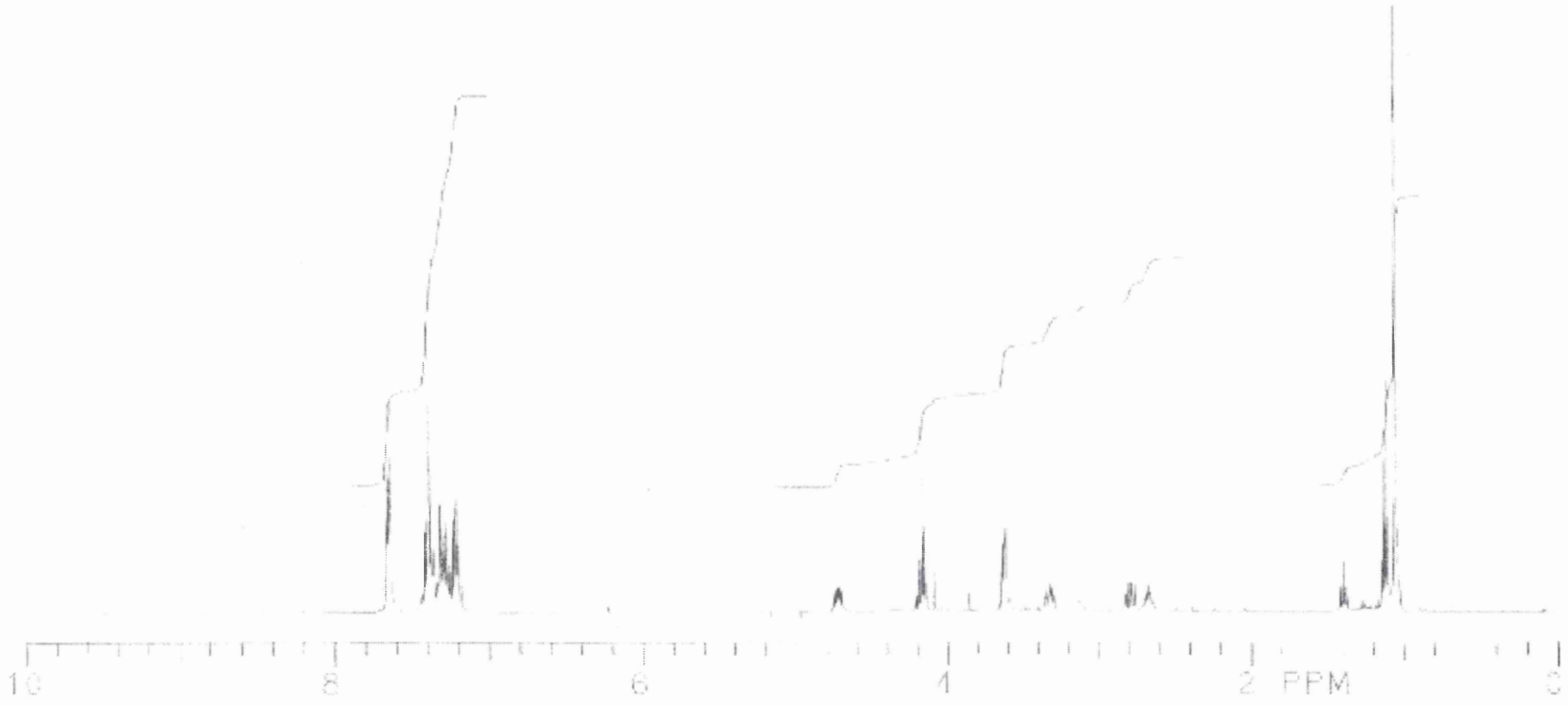
(1*R*,5*S*,6*R*)-6-(*t*-Butyl-dipenyl-silanylyoxymethyl)-5-methyl-cyclohex-2-enol 317



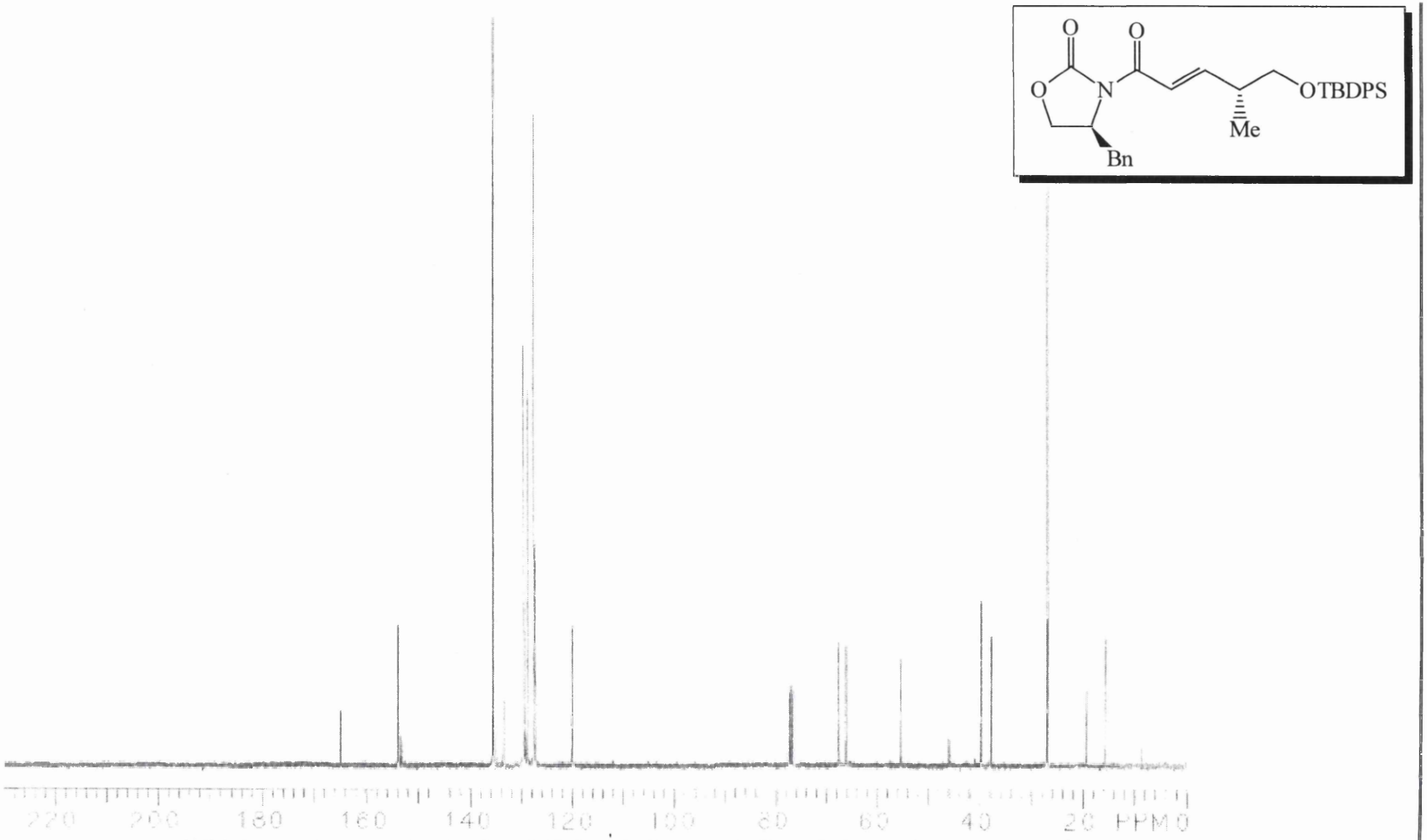


(1*R*,5*S*,6*R*)-6-(*t*-Butyl-dipenyl-silanylyoxymethyl)-5-methyl-cyclohex-2-enol 317

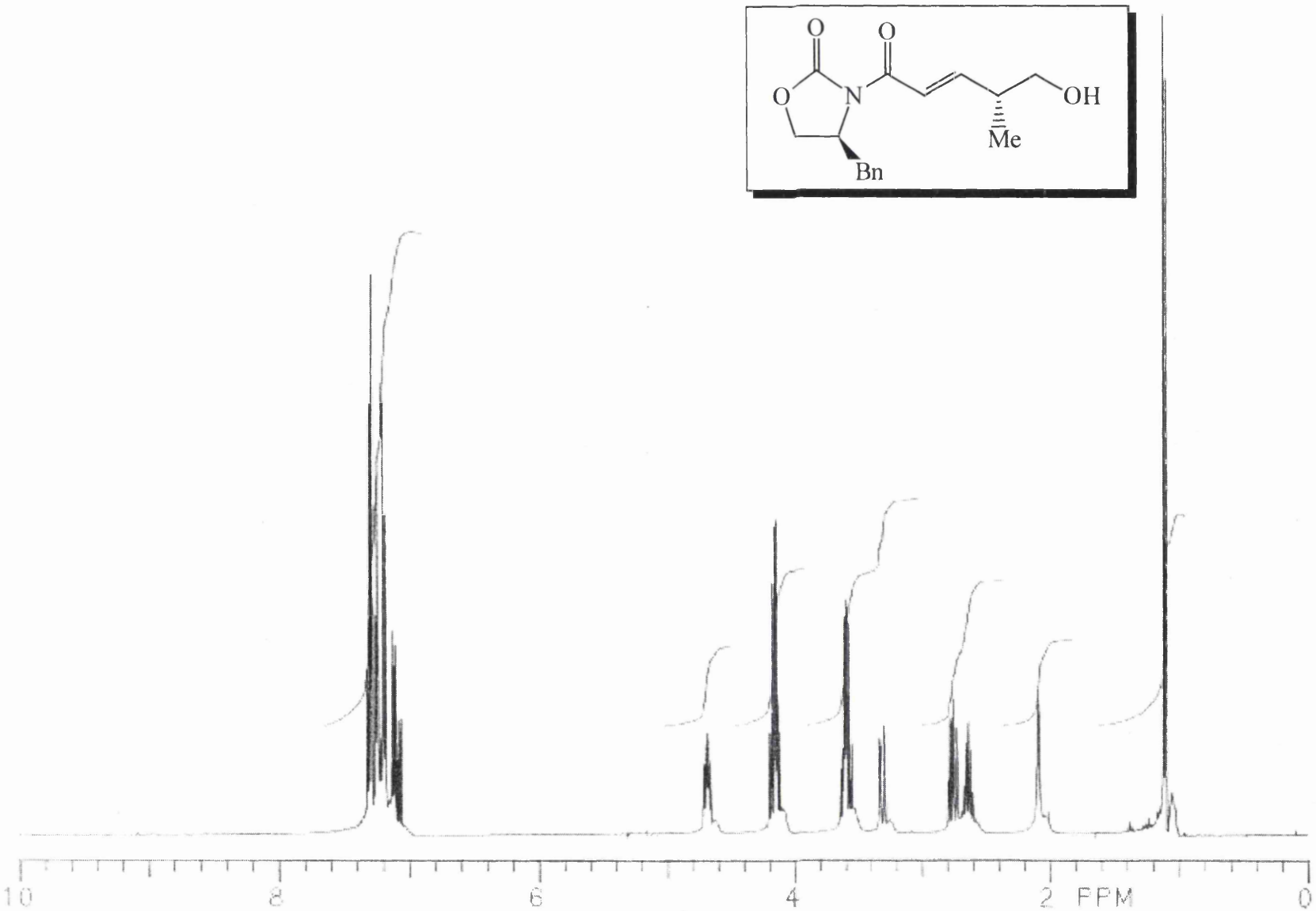




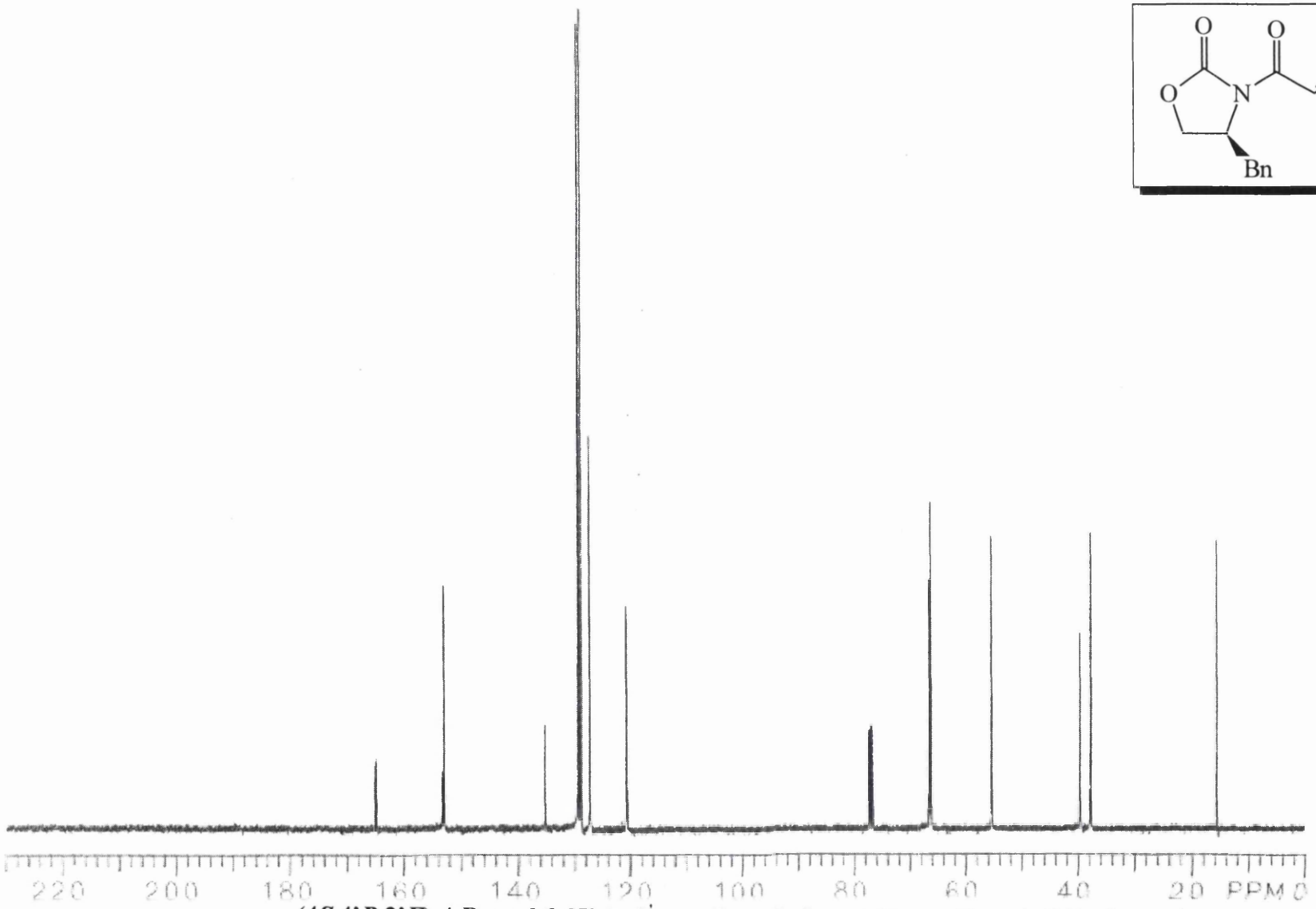
(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-(*t*-butyl-diphenyl-silanyloxy)-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 418



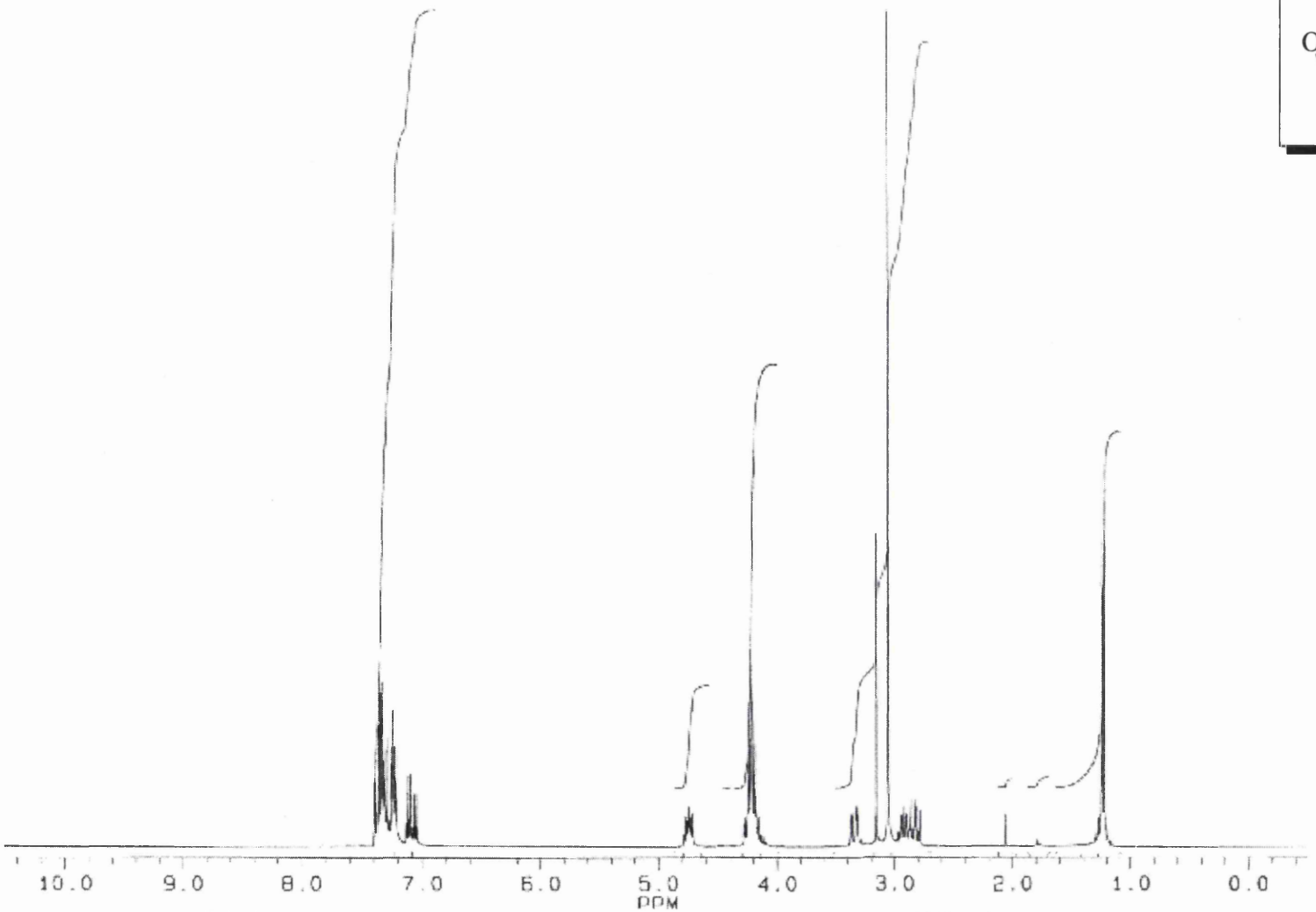
(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-(*t*-butyl-diphenyl-silanyloxy)-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 418

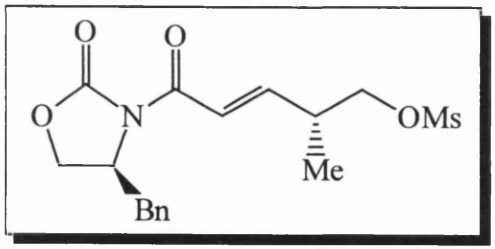


(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 419

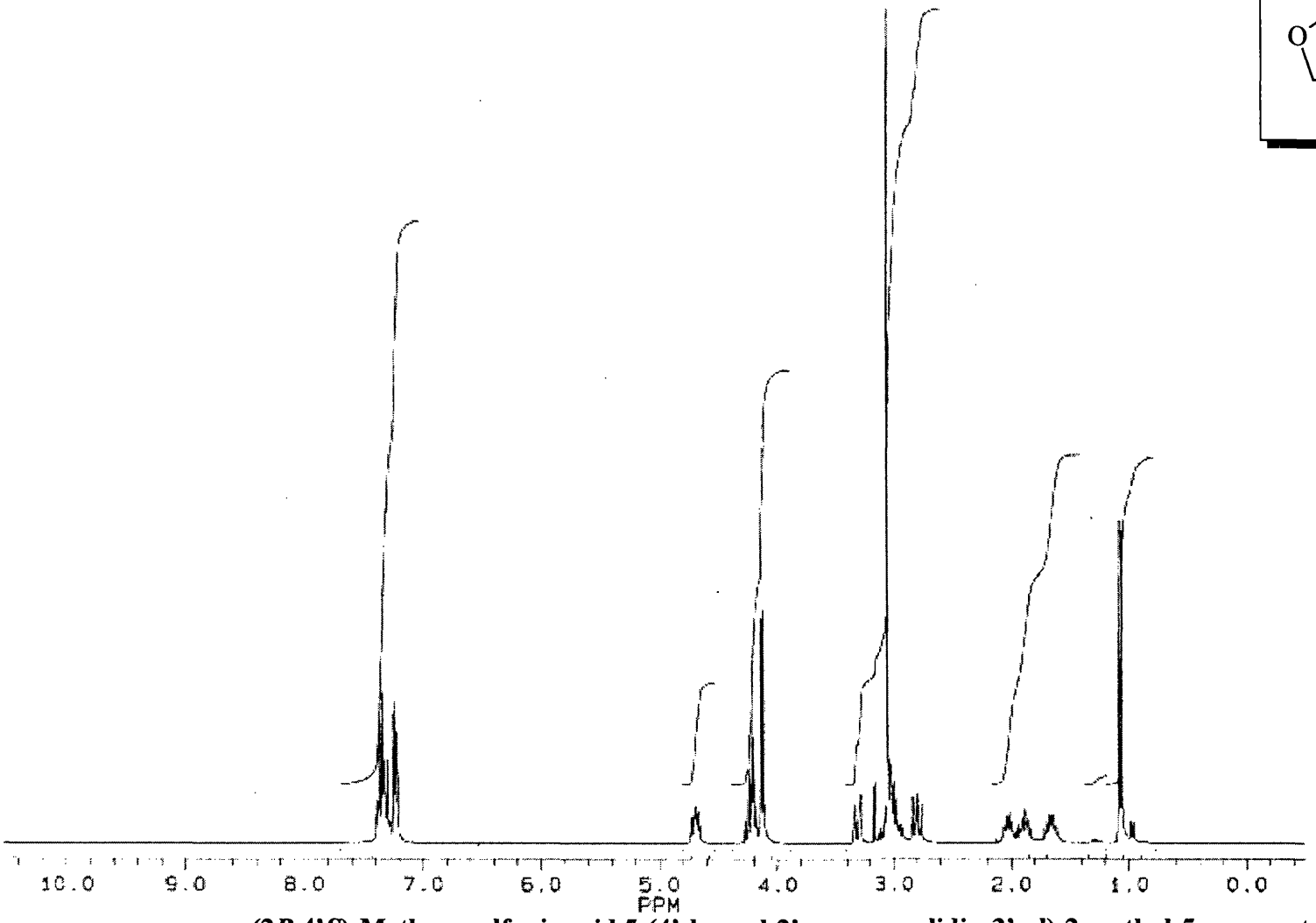


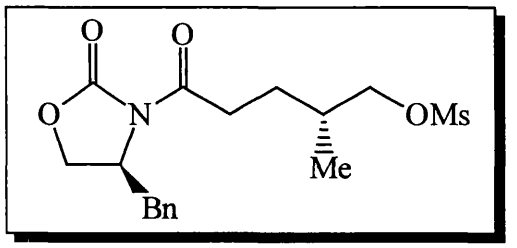
(4*S*,4'*R*,2'*E*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pent-2'-enoyl]-oxazolidin-2-one 419



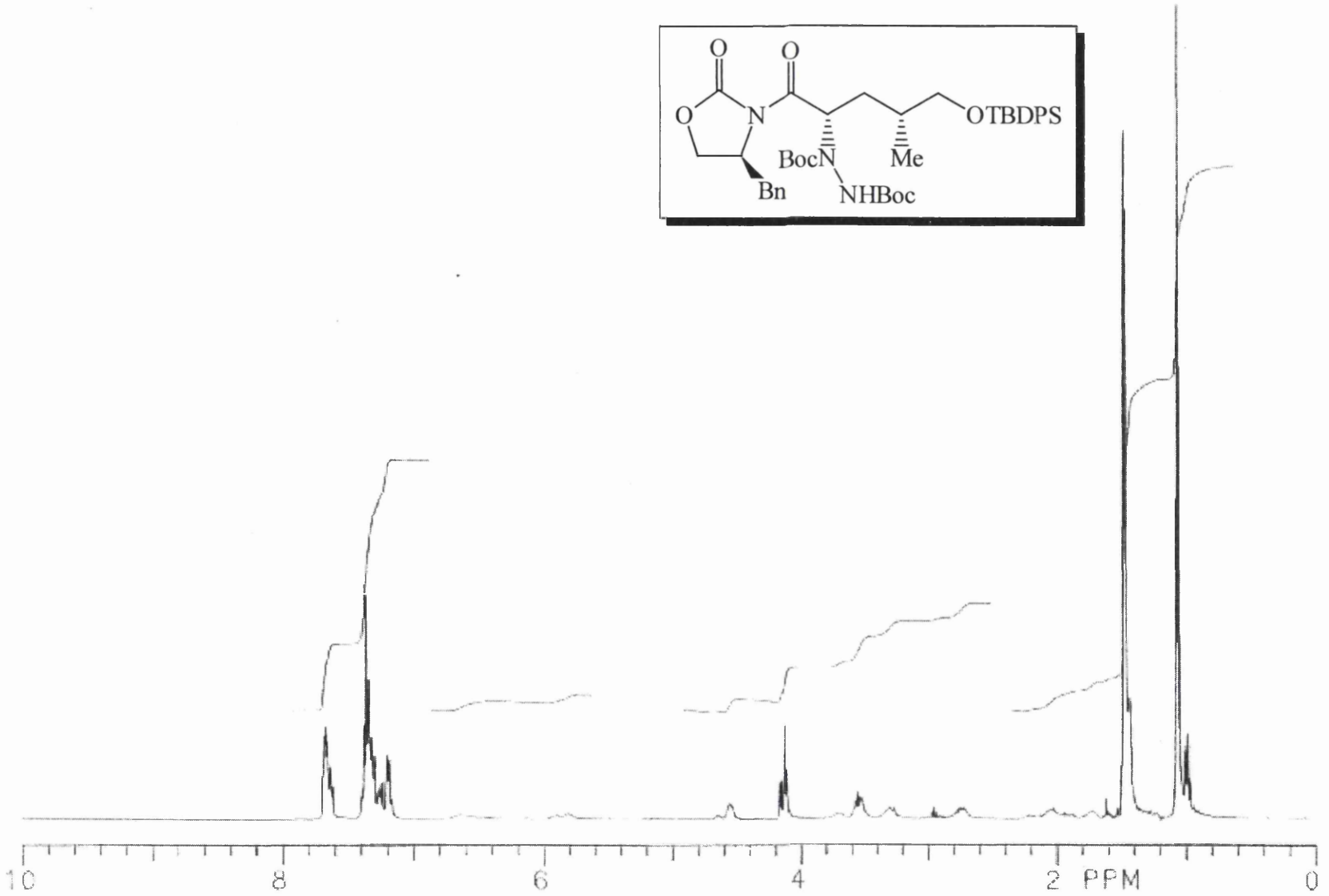


(2*R*,4'*S*,3*E*)-Methanesulfonic acid 5-(4'-benzyl-2'-oxo-oxazolidin-3'-yl)-2-methyl-5-oxo-pent-3-enyl ester 420

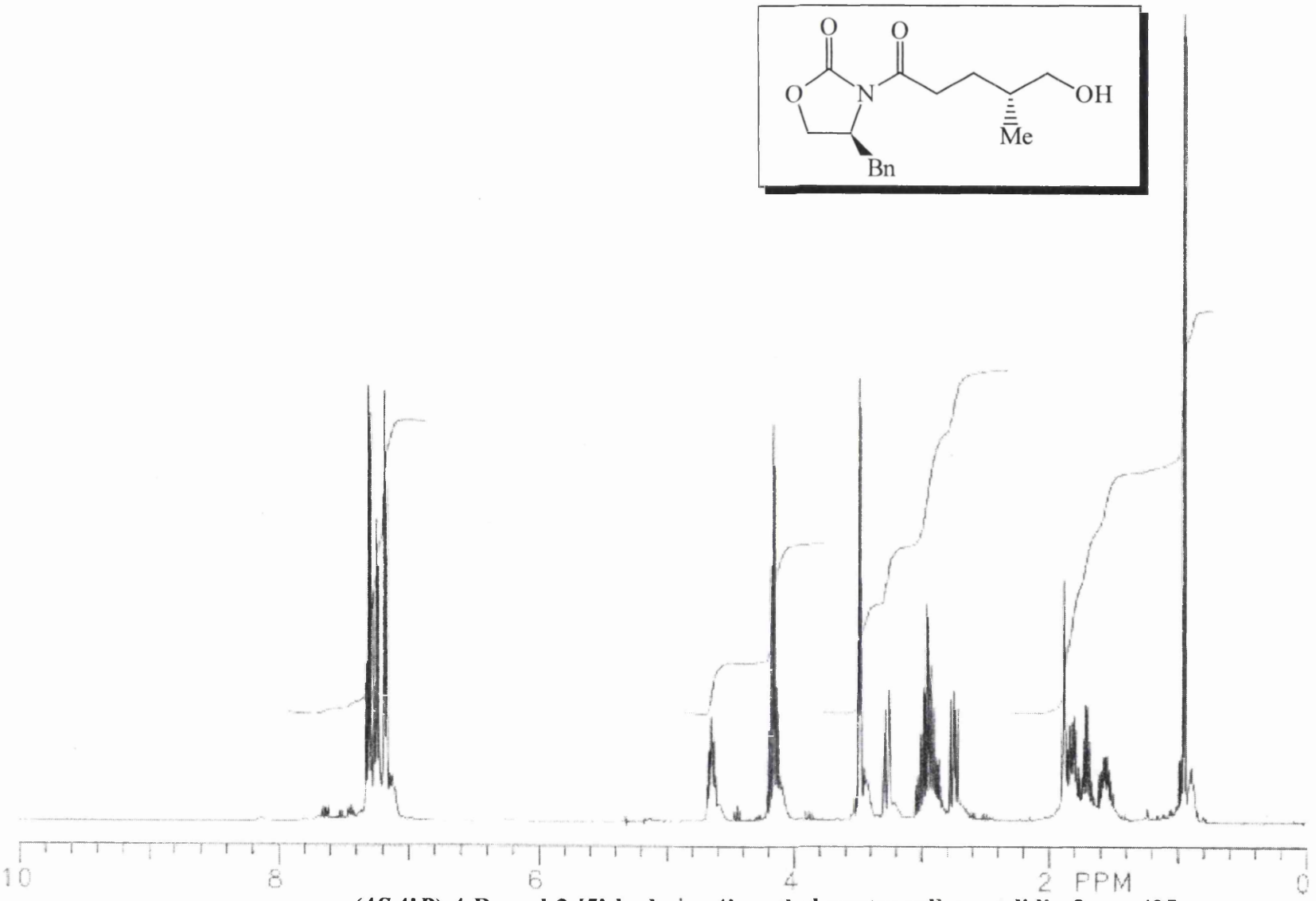




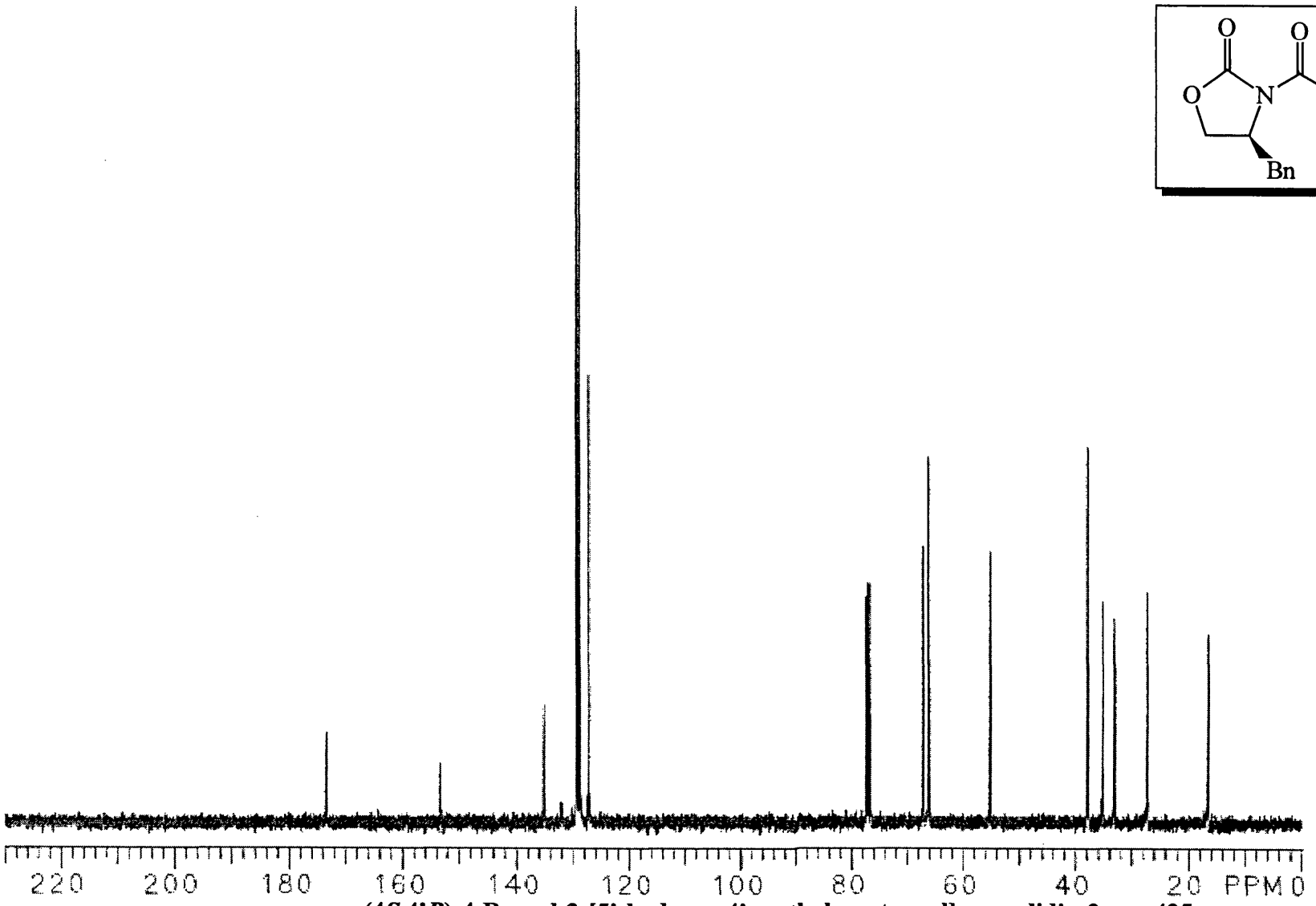
(2*R*,4'*S*)-Methanesulfonic acid 5-(4'-benzyl-2'-oxo-oxazolidin-3'-yl)-2-methyl-5-oxo-pentyl ester 421



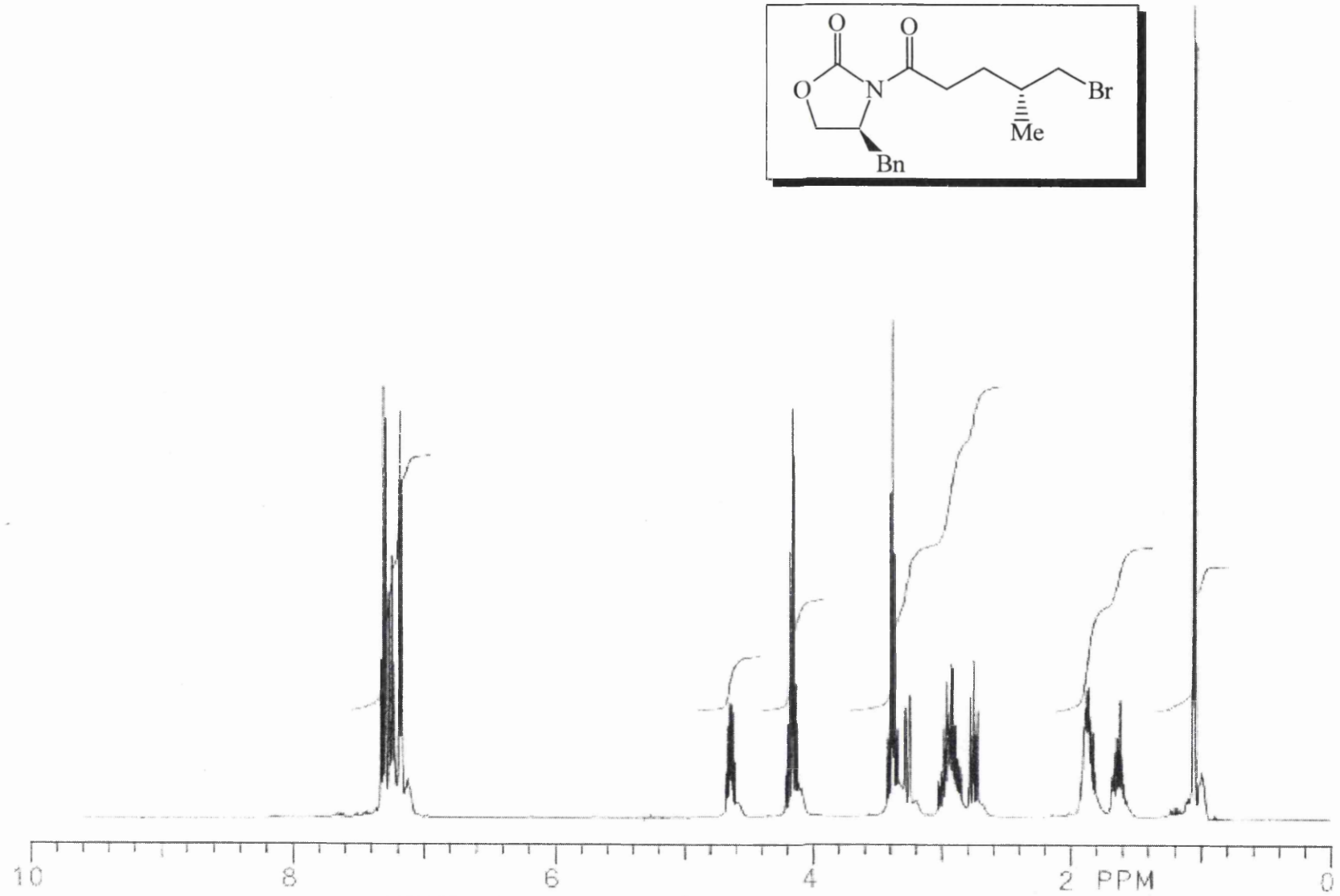
(4*S*,2'*S*,4'*R*)-4-Benzyl-3-[5'-(*t*-butyl-diphenyl-silanyloxy)-4'-methyl-2'-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)-pentanoyl]-oxazolidin-2-one
422



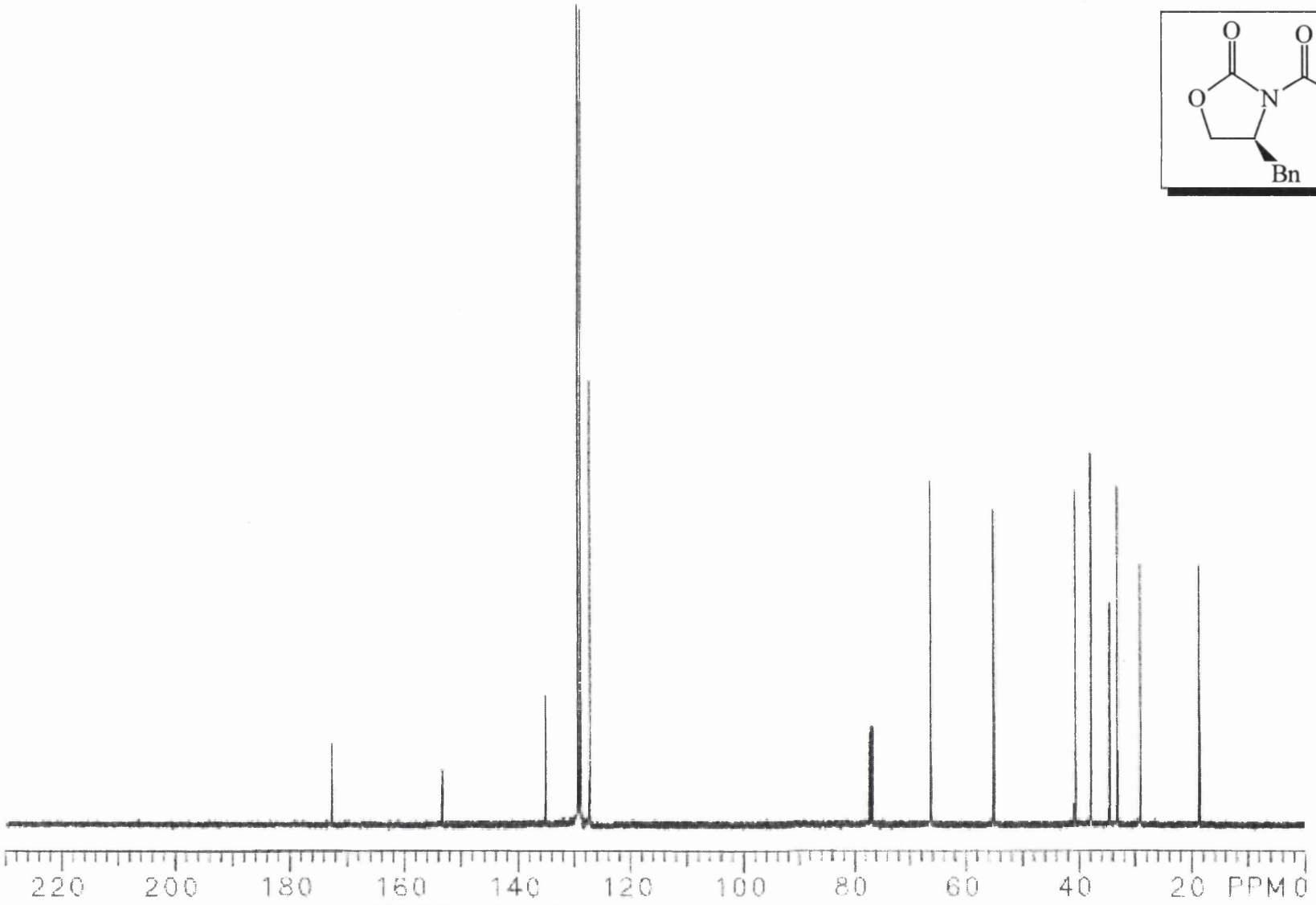
(4*S*,4'*R*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pentanoyl]-oxazolidin-2-one 425



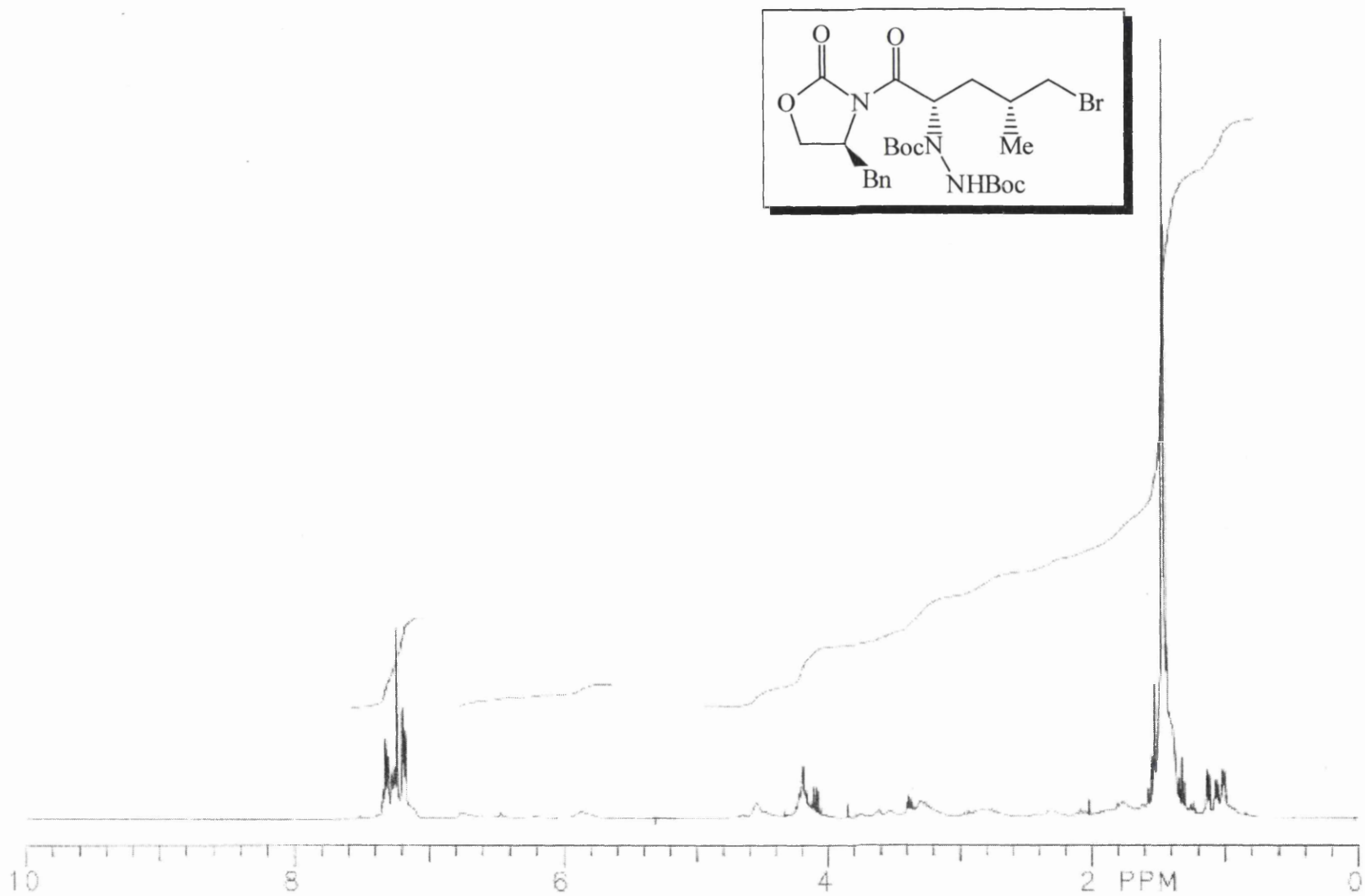
(4*S*,4'*R*)-4-Benzyl-3-[5'-hydroxy-4'-methyl-pentanoyl]-oxazolidin-2-one 425



(4*S*,[4*R*])-4-Benzyl-3-[5-bromo-4-methyl-1-oxopentyl]-2-oxazolidinone 426



(4*S*,[4*R*])-4-Benzyl-3-[5-bromo-4-methyl-1-oxopentyl]-2-oxazolidinone 426



(4*S*,2'*S*,4'*R*)-4-Benzyl-3-[5'-bromo-4'-methyl-2'-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)-pentanoyl]-oxazolidin-2-one 424