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Synthesis of the Aglycones of Pseudopterosins.

Alessandro Pontiroli

A thesis submitted for the degree of Doctor of Philosophy

September 1997

University of Glasgow

FACULTY OF SCIENCE

CHEMISTRY

ABSTRACT

Doctor of Philosophy

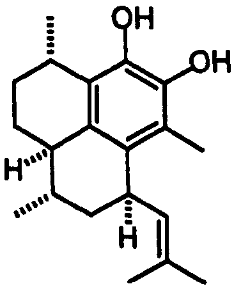
SYNTHESIS OF THE AGLYCONES OF PSEUDOPTEROSINS

by Alessandro Pontiroli

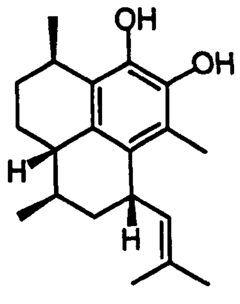
The stereocontrolled and efficient syntheses of the aglycones of the potent anti-inflammatory pseudopterosins A-F and K-L have been achieved starting from convenient monoterpenic units and using a novel benzannulation protocol partially developed in our laboratories.

For the synthesis of the K-L compounds a completely substrate-controlled stereoselective route was devised starting from commercial isopulegol using a sequence of epoxidation and Lewis acid-promoted oxirane opening followed by benzannulation and Friedel-Crafts type sulphone displacement to generate the tricyclic structure of **3.2.1.13**.

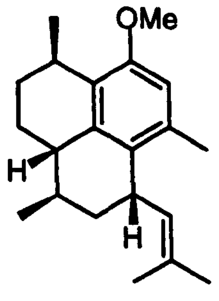
The route to pseudopterosins A-E started from (–)-citronellal and employed catalytic asymmetric reduction of α,β-unsaturated ester **8.2.1.5**. After the formation of the aromatic ring, the second approach was convergent to the enantiomers of intermediates used in the first route. Oxidation with Fremy's salt led to the unstable aglycones of the natural compounds under mild conditions.



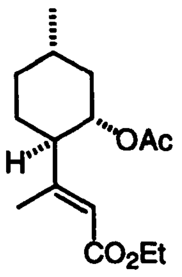
Pseudopterosins A-F aglycone



Pseudopterosins K-L aglycone



3.2.1.13



8.2.1.5

This thesis is dedicated to the memory of Ercole Rovati,
my beloved uncle.

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Preface

The research described in this thesis was carried out under the supervision of Professor P.J. Kocienski at the University of Southampton between September 1994 and October 1996 and then at the University of Glasgow between November 1996 and September 1997. No part of this thesis has been previously submitted for a degree at this or any other University except where specific acknowledgement has been made.

Acknowledgements.

I would like to thank my supervisor, Prof. Philip Kocienski, for his advice and support over the last three years.

I would also like to thank Dr. David Harrowven for helpful discussions and for providing me access to a copy of Dr. Carpino's thesis.

Very special thanks also to:

Dr. John Langley for mass spectroscopy work, Mrs Joan Street for high resolution NMR spectra and Dr. Gillian Reid for X-ray analysis at the University of Southampton;

Mr. Anthony Ritchie for mass spectroscopy work, Mr. Jim Gall for high resolution NMR spectra and Mrs Kim Wilson for elementary analysis at the University of Glasgow;

the Collegio Ghislieri of Pavia and the Università di Pavia (Italy) for their generous financial support;

all the past and present members of the Kocienski group for their company and assistance during the last three hectic years;

the many friends and colleagues at Southampton and Glasgow Universities that made my time most enjoyably spent;

my family and friends overseas for their invaluable support and long-distance help.

Abbreviations.

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobis(isobutyronitrile)
9-BBN	9-borabicyclo[3.3.1]nonane
BOM	benzyloxymethoxy
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
CI	chemical ionisation
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DMAD	dimethylacetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EI	electronic impact
ESI	electrospray
Et	ethyl
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LDA	lithium di*iso*propylamide
LHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectroscopy
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
mp	melting point
Ms	methanesulphonyl
NBS	*N*-bromosuccinimide
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhH	benzene
PhMe	toluene
Piv	pivaloate
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzoic
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTSA	*para*-toluenesulfonic acid
Pv	pivaloyl
Pyr	pyridine
rt	room temperature
sia	siamyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tris	2,4,6-tri*iso*propylphenyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet

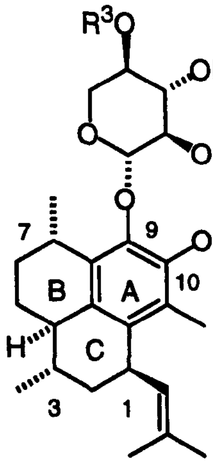
Chapter 1

Isolation and biological action of pseudopterosins.

1.1 Discovery and isolation of pseudopterosins and analogues.

Marine organisms are an invaluable source of molecules with relevant biological activities. The class of diterpene monosaccharides named pseudopterosins were discovered from the sea whip of the genus *Pseudopterogorgia* in 1986. Four compounds were initially extracted from *P.elisabethae* collected in the Bahamas sea and denominated pseudopterosins A-D[1] (scheme **1.1.1**). Their structure was determined by X-ray crystallographic analysis of pseudopterosin C, the only crystalline compound. The absolute configuration of the aglycone portion could be assigned after determining that of the sugar fragment. The structures of the other three compounds were determined by spectral analysis and conversion to the corresponding peracetylated compounds.

Scheme **1.1.1**

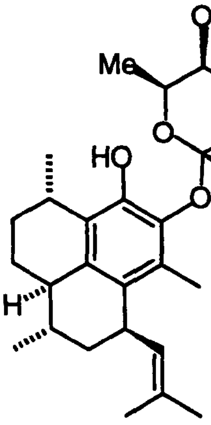


1.1.1.1 Pseudopterosin A : $R^1 = R^2 = R^3 = H$
1.1.1.2 Pseudopterosin B : $R^1 = Ac$, $R^2 = R^3 = H$
1.1.1.3 Pseudopterosin C : $R^2 = Ac$, $R^1 = R^3 = H$
1.1.1.4 Pseudopterosin D : $R^3 = Ac$, $R^1 = R^2 = H$

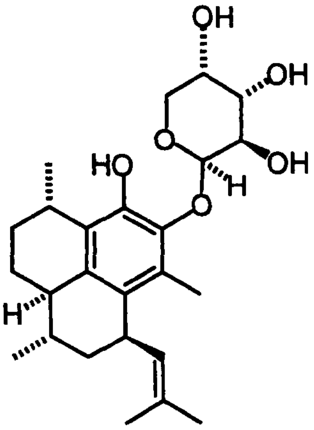
Common features are the tricyclic skeleton with an hexasubstituted aromatic ring, a D-xylose or monoacetylated xylose attached to one of the two phenolic oxygens and four stereogenic centers on the aglycone portion. All the metabolites displayed remarkable anti-inflammatory and analgesic activity, equivalent in potency to the industry standard indomethacin[2] but showed acute toxicity in mice. The mechanism of action appeared to be unique but not disclosed in full; however, cellular studies[2,3] revealed that pseudopterosins inhibit leukotriene biosynthesis rather than cyclooxygenases, unlike most non-steroidal anti-inflammatory agents.

In 1990, the same group[4] reported the discovery and characterisation of eight novel members of the family, named pseudopterosins E-L (scheme **1.1.2**), from *P.elisabethae* organic extracts.

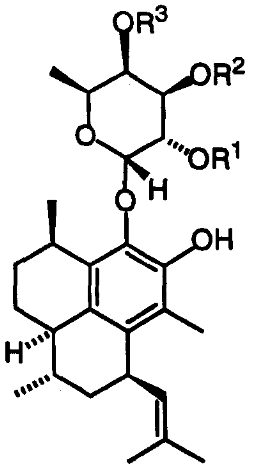
Scheme **1.1.2**



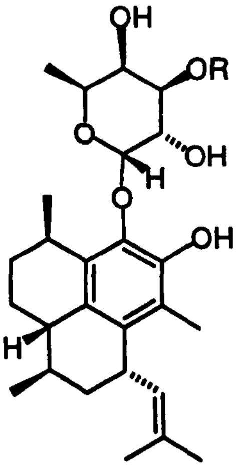
1.1.2.1 Pseudopterosin E



1.1.2.2 Pseudopterosin F



1.1.2.3 Pseudopterosin G : R^1 = R^2 = R^3 = H
1.1.2.4 Pseudopterosin H : R^1 = Ac, R^2 = R^3 = H
1.1.2.5 Pseudopterosin I : R^2 = Ac, R^1 = R^3 = H
1.1.2.6 Pseudopterosin J : R^3 = Ac, R^1 = R^2 = H



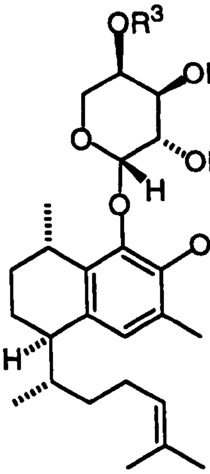
1.1.2.7 Pseudopterosin K : R = H
1.1.2.8 Pseudopterosin L : R = Ac

Pseudopterosins E and F display the same aglycones as the previously discovered compounds but their sugar portions, α-L-fucose and α-D-arabinose respectively, are attached to the C10 oxygen. Pseudopterosins G and its monoacetates (compounds H-J) are C9 α-L-fucose glycosides; the aglycone of the molecules is a C7 epimer of the corresponding partial components of compounds A - F.

Pseudopterosins K and L are the major constituents of the organic extracts of *P.elisabethae* collected in the Bahamas sea and their C9 α-L-fucosylated aglycones are enantiomeric to those of the A-F members of the family.

All these compounds, and in particular pseudopterosin E, possess superior anti-inflammatory properties and lower toxicity ($LD_{50} > 300$ mg/Kg for **1.1.2.1**) than the previously discovered analogues.

Scheme **1.1.3**

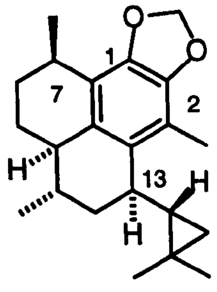


1.1.3.1 Secopseudopterosin A : $R^1 = R^2 = R^3 = H$
1.1.3.2 Secopseudopterosin B : $R^1 = Ac$, $R^2 = R^3 = H$
1.1.3.3 Secopseudopterosin C : $R^2 = Ac$, $R^1 = R^3 = H$
1.1.3.4 Secopseudopterosin D : $R^3 = Ac$, $R^1 = R^2 = H$

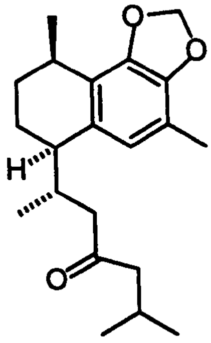
In more recent years, other compounds bearing relevant structural similarities with pseudopterosins have been discovered. The bicyclic terpene glycosides named secopseudopterosins A-D (scheme **1.1.3**) were isolated in 1987 from *Pseudopterogorgia Kallos*[5] and have antimicrobial (*Staphilococcus aureus* growth inhibitor) as well as potent anti-inflammatory and analgesic activity.

Higa and coworkers[6] isolated the compounds named helioporins A-G (scheme **1.1.4**) from the blue coral *Heliopora coerulea* in 1993. The structure of helioporin A showed close similarity with those of pseudopterosins G-J while compounds B-G are related to secopseudopterosins aglycones. Helioporins A and B were inactive in the apical anti-inflammatory assay but exhibited antiviral activity against HSV1 while compounds C-G show cytotoxicity against P 338.

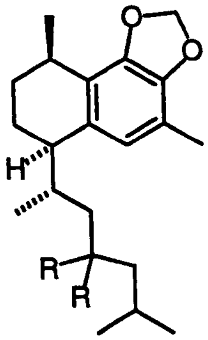
Scheme **1.1.4**



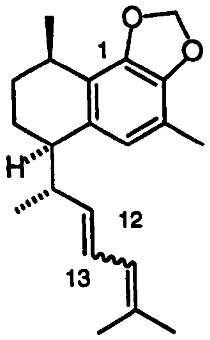
1.1.4.1 Helioporin A



1.1.4.2 Helioporin B



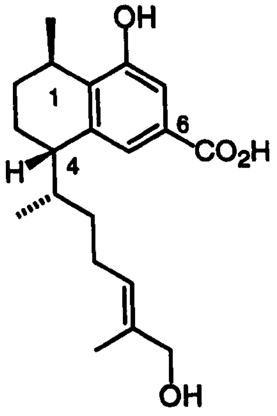
1.1.4.3 Helioporin C : R = O
1.1.4.4 Helioporin D : R = H



1.1.4.5 Helioporin E : $\Delta^{12,13}$ *Z*
1.1.4.6 Helioporin F : $\Delta^{12,13}$ *E*

Dihydroxyserrulatic acid was isolated[7,8] from a completely different source, the leaves of the Australian shrub *Eremophila serrulatae*, in 1978 (scheme **1.1.5**). This compound has in common with secopseudopterosins a 1,4,6-trisubstituted-8-hydroxytetralin as central unit and a prenyl side chain but showed no relevant biological activity.

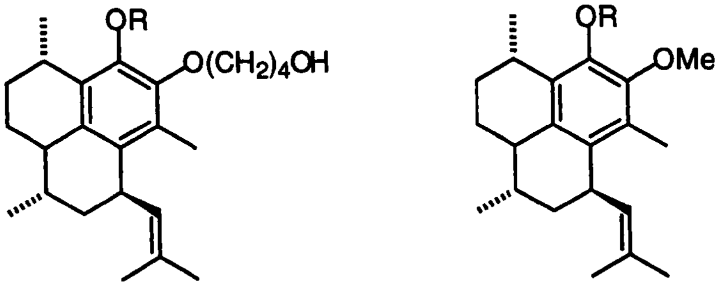
Scheme **1.1.5**



Dihydroxyserrulatic acid

A range of semi-synthetic pseudopterosins ethers were recently patented as potential analgesic, vulnerary and anti-inflammatory agents[9,10]. In particular, pseudopterosin A derivatives **1.1.6.1**, named **WF-336**, and **1.1.6.2** (scheme **1.1.6**) were found to be particularly active during *in vivo* tests in mice and in pig.

Scheme **1.1.6.**



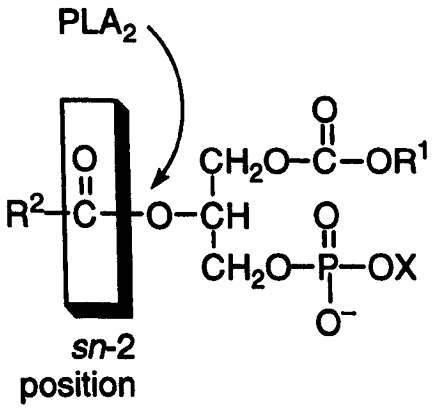
1.1.6.1 WF-336 : R = D-xylose **1.1.6.2: R = D-xylose**

1.2 Biological activities of pseudopterosins.

The pseudopterosins are among the most potent non-steroidal anti-inflammatory agents but their mechanism of action has not been characterised in full detail.

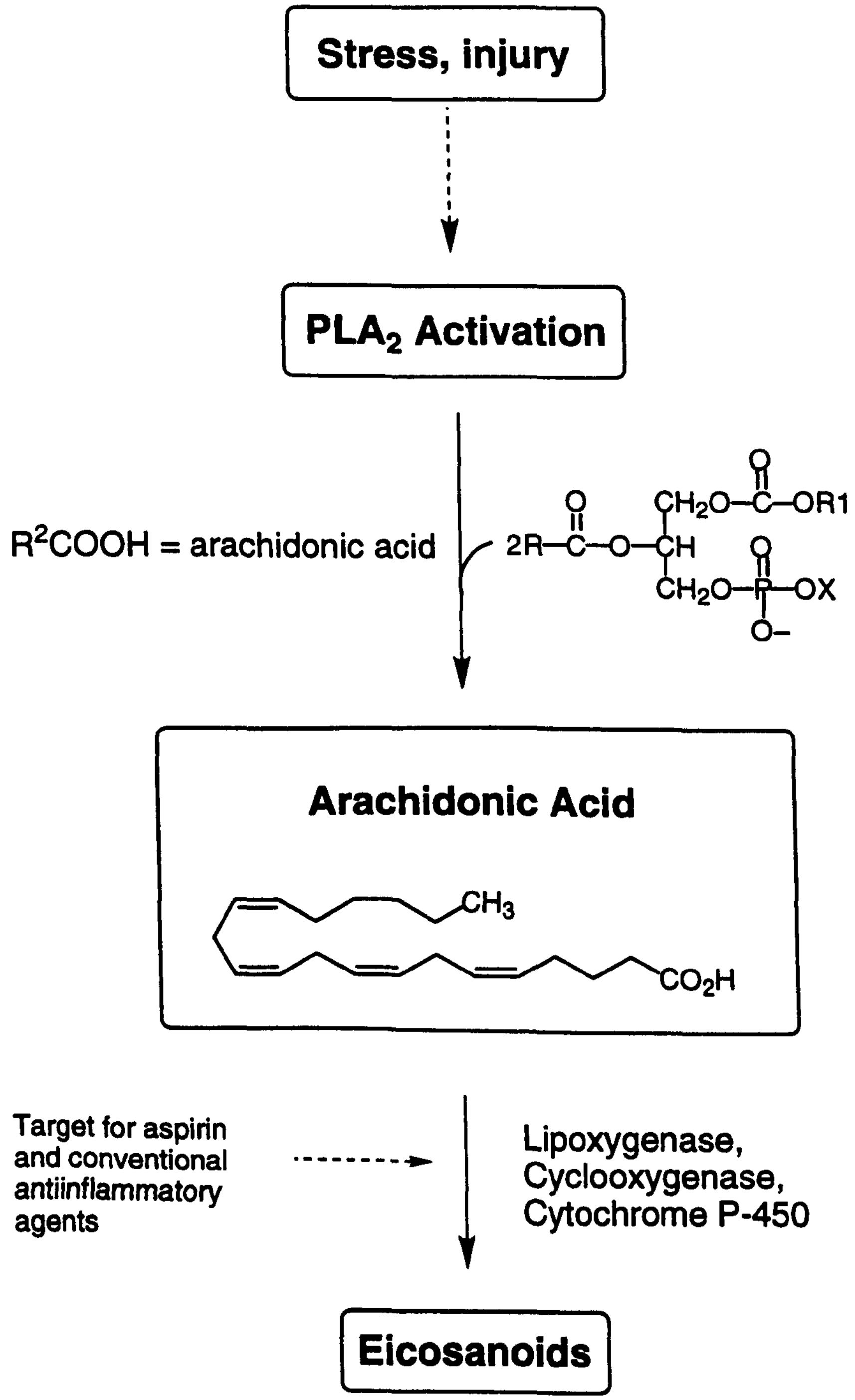
The inflammatory response is mediated by the biosynthesis of eicosanoids derived from arachidonic acid, such as leukotrienes, prostaglandins and thromboxanes, as well as other agents released locally in response to an irritant[11-13]. Phospholipases A_2 (PLA_2) are calcium-dependent enzymes that specifically catalyse the hydrolysis of esters at the *sn*-2 position of a phospholipid (scheme **1.2.1**) releasing a free fatty acid.

Scheme **1.2.1**



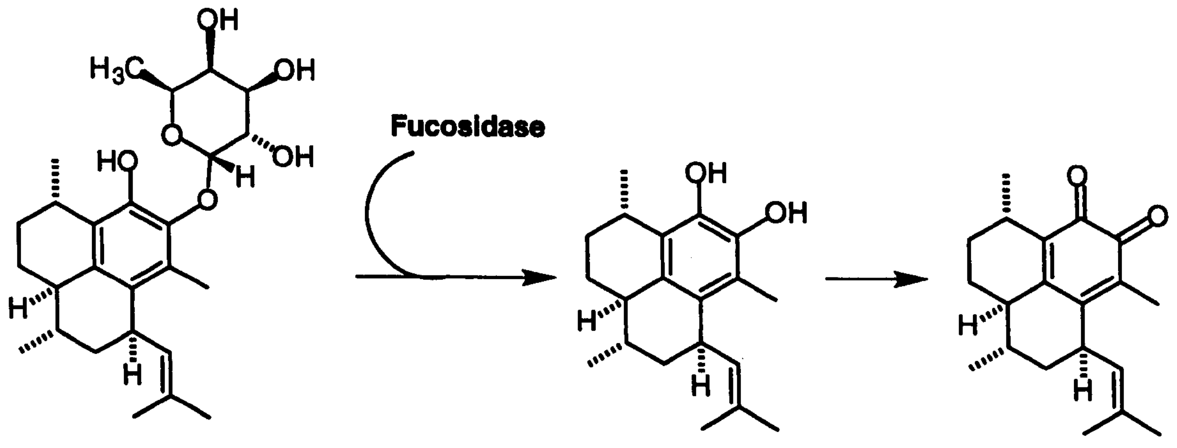
The increased production of eicosanoids in response to a variety of stimuli is believed to be controlled by the release of their precursor, arachidonic acid, which is mainly stored in phospholipids. Production of arachidonic acid from the action of PLA_2 on membrane phospholipids provides the substrate for the pathway of eicosanoid biosynthesis known as the "arachidonic acid cascade" (scheme **1.2.2**). Because eicosanoids are potent mediators of inflammation, selective inhibition of their biosynthesis can be expected to modify the inflammatory response.

Scheme **1.2.2**


Stress, injury
PLA2 Activation
R2COOH = arachidonic acid
2R–C(=O)–O–CH
CH2O–C(=O)–OR1
CH2O–P(=O)(O–)–OX
Arachidonic Acid
CH3
CO2H
Target for aspirin and conventional antiinflammatory agents
Lipoxygenase, Cyclooxygenase, Cytochrome P-450
Eicosanoids

Pharmaceutical agents such as indomethacin and aspirin inhibit the cyclo-oxygenase pathway responsible for the conversion of arachidonic acid into prostaglandins, thus blocking the cascade without preventing the release of the acid. Pseudopterosins appear to block the eicosanoids biosynthesis by inhibition of both PLA_2 and 5-lipoxygenase. Pseudopterosin A and E were initially tested[2] and found to inhibit a range of PLA_2 from various sources. A subsequent study led to the conclusion that the *ortho*-quinone **1.2.3.1** derived from oxidation of the aglycone is the active form of these molecules (scheme **1.2.3**). The glycosides are active *in vivo* (in mice) and in whole cells but in crude enzyme preparations they require the presence of fucosidase, suggesting that the molecules are active only after cleavage of the sugar portion. Notably, **1.2.3.1** is active towards a wider range of PLA_2 than the natural glycosides.

Scheme **1.2.3.**



1.1.2.1 Pseudopterosin E

1.2.3.1

Finally, comparative studies[2] suggested that the cell-type selectivity of pseudopterosins may be a function of the glycoside moiety, possibly a novel example of drug targeting.

Chapter 2
Previous syntheses.

2.1 Introduction.

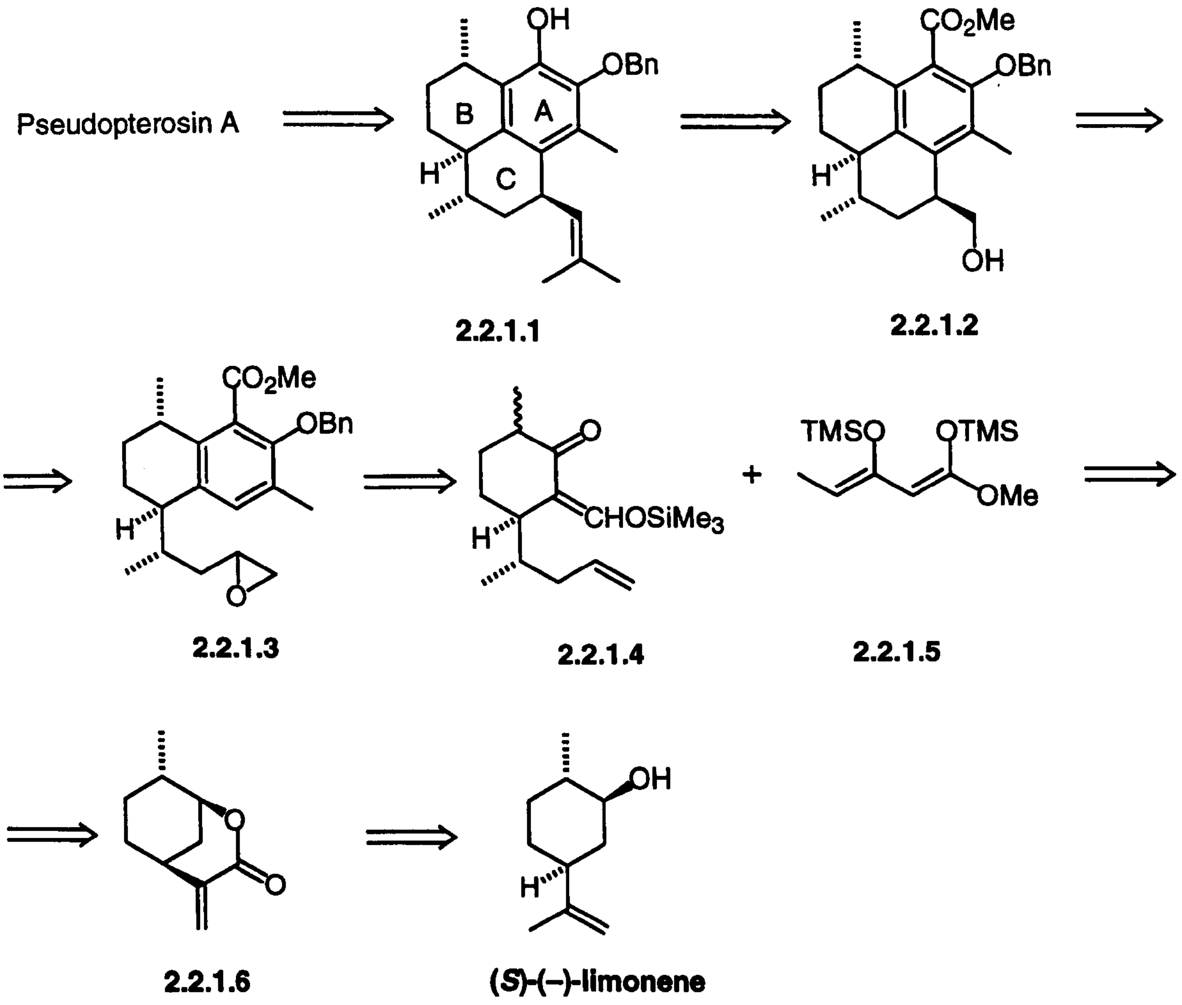
Since the discovery of the first four members of the class, various total and partial syntheses of pseudopterosins and analogues have been reported, the interest of chemists being drawn by the challenging structural features as well as by the relevant biological activities of these compounds.

Two main strategic approaches have been devised for the synthesis of the aglycone. The first is based on functionalisation of suitable monoterpenic starting materials, taking advantage of pre-existing stereocenters to introduce chiral centers in a substrate-controlled manner. The major task in this approach is the formation of the hexasubstituted aromatic ring. The alternative strategy employs functionalised tetralins as starting materials and the stereocenters are introduced on the side chain *via* asymmetric synthesis using organometallic reagents. The published syntheses of pseudopterosins and analogues are briefly illustrated in the following paragraphs.

2.2 The Broka total synthesis of pseudopterosin A.

The first reported synthesis of pseudopterosin A was published by Broka and coworkers in 1988[14]. The retrosynthetic analysis for their approach is highlighted in scheme **2.2.1**. Monoprotected catechol **2.2.1.1** was chosen as the precursor for the final glycosidation step. Baeyer-Villiger oxidation of the corresponding α-hydroxybenzoate was envisioned to provide the catechol unit. It was also expected that Friedel-Crafts type ring closure of epoxide **2.2.1.3** could provide stereocontrol in the closure of ring C of pseudopterosins, due to the induction from the neighbouring stereocenters. The approach chosen for the crucial construction of the aromatic ring was Mukaiyama reaction of α,β-unsaturated enone **2.2.1.4** with diene **2.2.1.5** according to the procedure of Chan and Broadbridge[15].

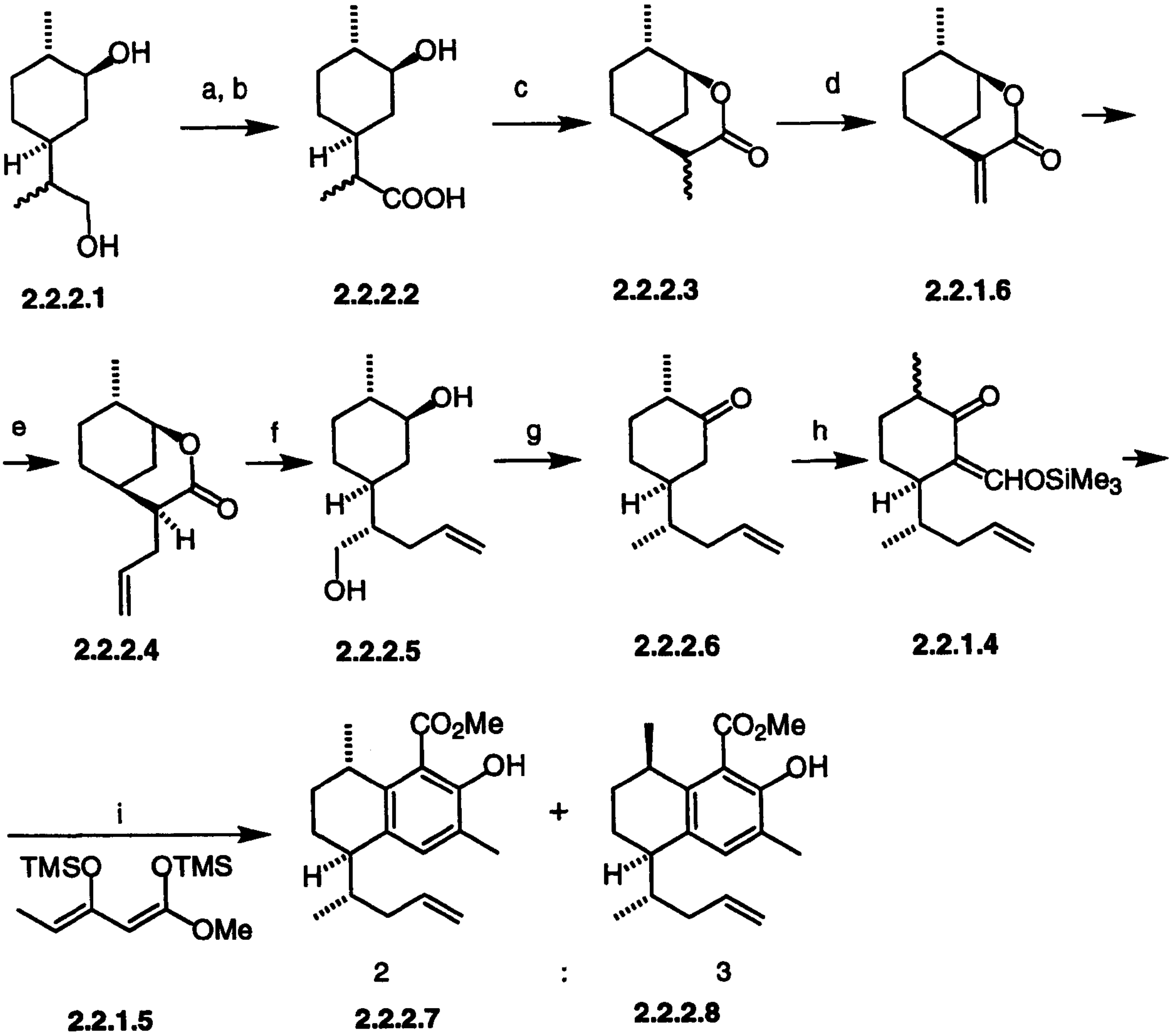
Scheme **2.2.1.**


Pseudopterosin A
OH
OBn
A
B
C
H
2.2.1.1
CO2Me
OBn
H
OH
2.2.1.2
CO2Me
OBn
H
O
2.2.1.3
O
CHOSiMe3
H
2.2.1.4
+
TMSO
OTMS
OMe
2.2.1.5
O
O
2.2.1.6
OH
H
(S)-(–)-limonene

Introduction of the desired stereochemistry at the C3 sterocenter could conceivably be achieved by substrate-controlled 1,4-addition of an organometallic vinyl reagent to enone **2.2.1.6**. This bicyclic compound can easily derived from the monoterpenic skeleton of (*S*)-(–)-limonene.

Initial hydroboration of the commercially available (*S*)-(–)-limonene displayed poor stereoselectivity. The resulting mixture of diols **2.2.2.1** was transformed in four steps to lactone **2.2.1.6** which underwent a 1,4-Michael addition with vinyl cuprate in the presence of TMSCl to yield the intermediate silylated enol ether. Protonation from the least hindered face during work-up allowed control of the stereocenter next to the carbonyl group to yield **2.2.2.4** as a single isomer. Subsequent hydrolysis and conversion to ketone **2.2.2.6**, homologation and protection yielded the silylated enol ether **2.2.1.4** with loss of stereochemistry at the α-position to the ketone. After Mukaiyama reaction with diene **2.2.1.5** followed by aromatisation, compounds **2.2.2.7** and the epimer **2.2.2.8** were obtained in 2:3 ratio respectively and separated by chromatography.

Scheme **2.2.2.**



2.2.2.1 **2.2.2.2** **2.2.2.3** **2.2.1.6**

2.2.2.4 **2.2.2.5** **2.2.2.6** **2.2.1.4**

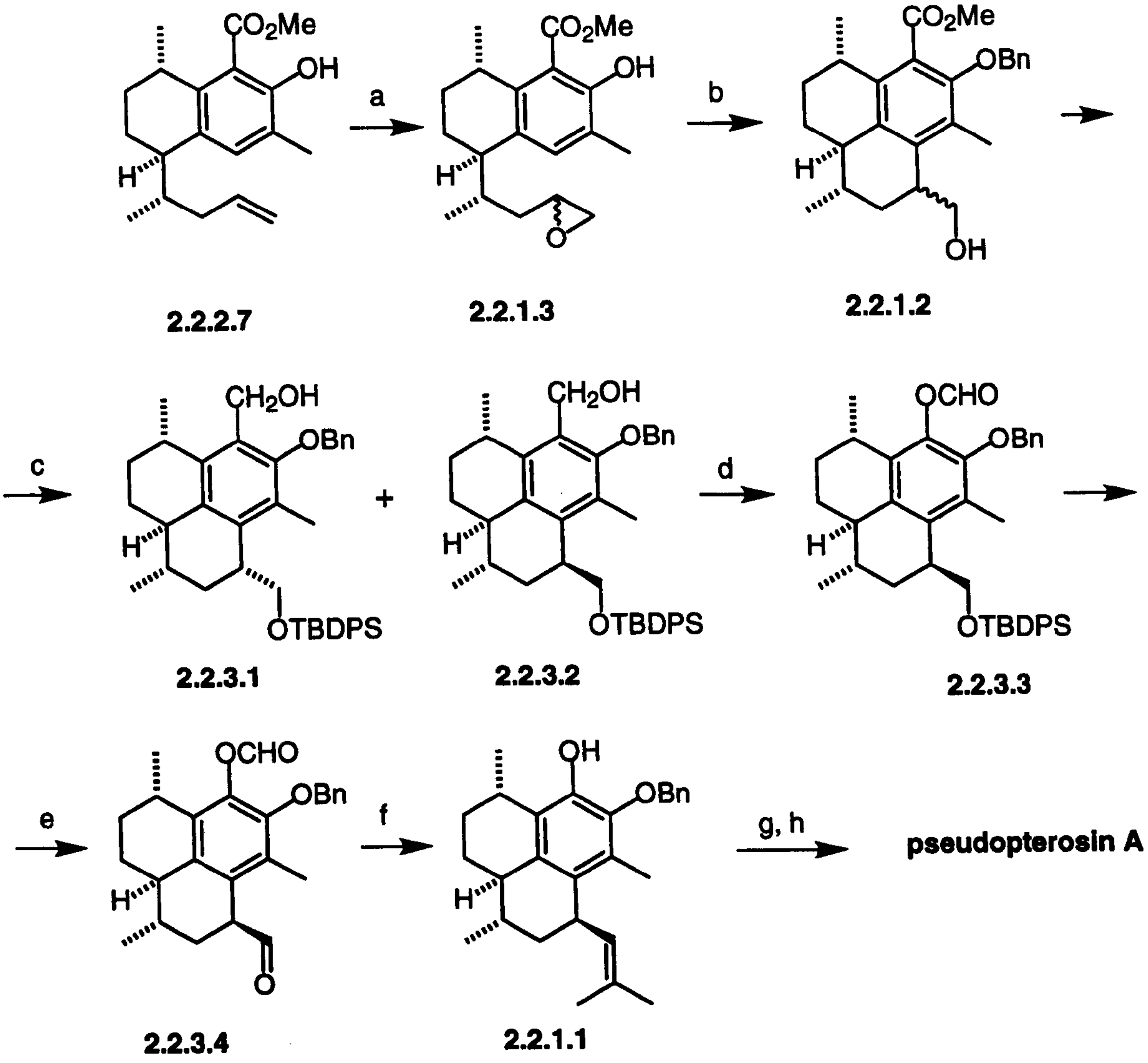
2.2.1.5 **2.2.2.7** **2.2.2.8**

Yields, reagents and conditions :

a	-	(i) PvCl, Pyr; (ii) DHP, PPTS, CH_2Cl_2; (iii) KOH; (iv) PCC, NaOAc, CH_2Cl_2
b	90%	(ii) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene; (ii) AcOH (aq), 80°C
c	67%	*p*-TsOH, PhMe, reflux
d	91%	(i) LDA, PhSeCl; (ii) H_2O_2
e	79%	CH_2=CHMgBr, CuI-DMS, TMSCl, THF, –40°C
f	84%	LAH, THF
g	63%	(i) $PhSO_2Cl$, DMAP, Et_3N, CH_2Cl_2; (ii) $LiBHEt_3$, THF; (iii) PCC
h	85%	(i) HCO_2Et, NaH, dioxane; (ii) TMSCl, Et_3N
i	66%	(i) **2.2.1.5**, $TiCl_4$; (ii) NaOMe, MeOH

The subsequent epoxidation of **2.2.2.7** (scheme **2.2.3**) occurred without stereoselectivity, then the Friedel-Crafts ring closure yielded again a 1.1:1 mixture of epimers **2.2.3.1** and **2.2.3.2** which could be separated by HPLC after protection of the primary hydroxyl group.

Scheme **2.2.3.**



Yields, reagents and conditions :

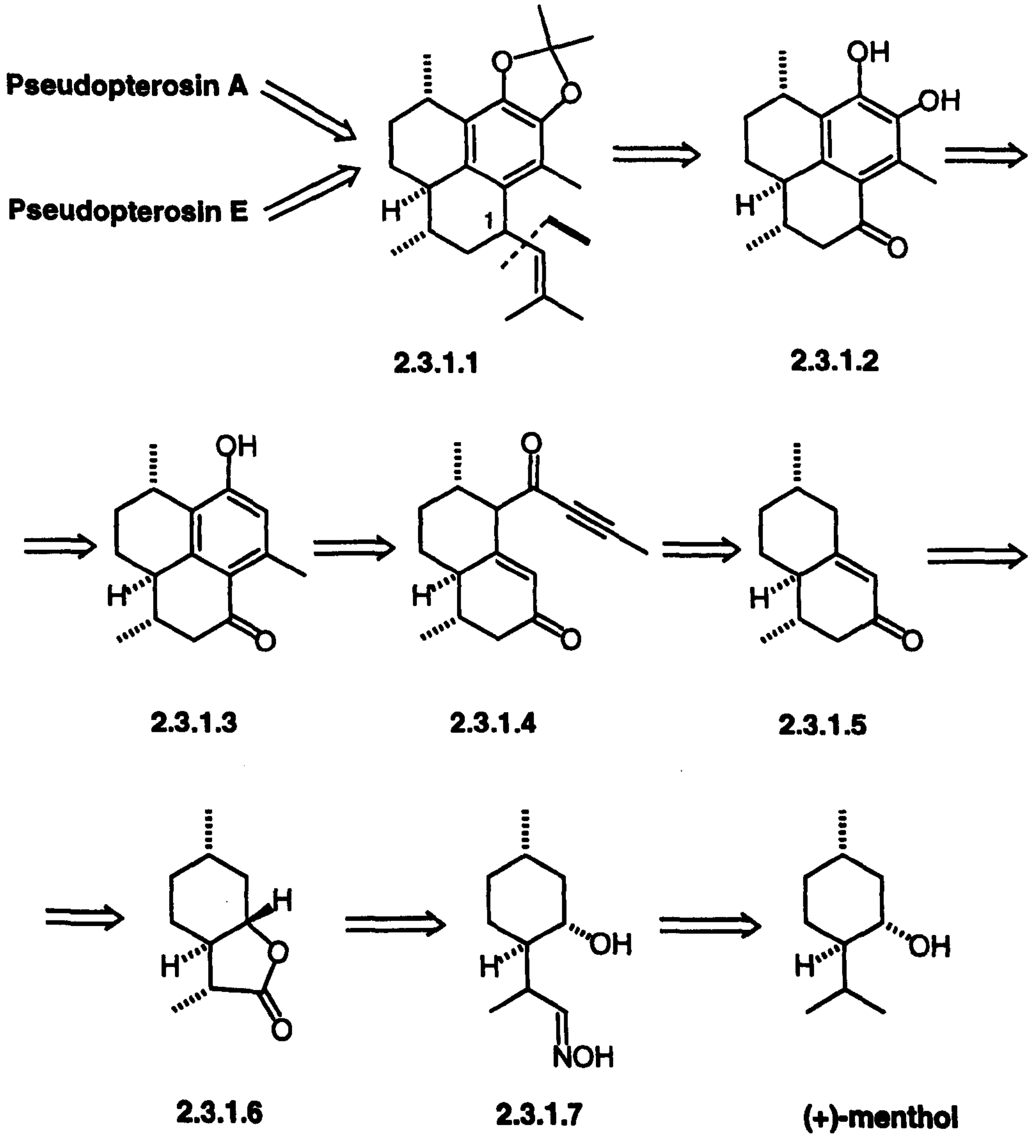
a	64%	MCPBA, $NaHCO_3$, $CHCl_3$, 55°C
b	88%	(i) $SnCl_4$, CH_2Cl_2, rt; (ii) BnBr, DMSO, K_2CO_3
c	75%	(i) TBDPSCl, imidazole, DMF; (ii) DIBAL, CH_2Cl_2, 20°C
d	88%	(i) PCC, CH_2Cl_2; (ii) MCPBA, Na_2HPO_4, $CHCl_3$, 20°C
e	86%	(i) TBAF, AcOH, THF; (ii) Swern oxidation
f	82%	(i) $Me_2C(Li)CO_2Li$, THF, 20°C; (ii) (dimethylamino)formaldehyde dineopentyl acetal
	-	4,4′-methylenebis(2,6-di-*tert*-butylphenol), 55°C, 3 days
g	51%	1-Bromo-2,3,4-triacetyl-D-xylose, AgOTf, tetramethylurea, CH_2Cl_2, 20°C
h	73%	KOH, MeOH; (ii) Li/NH_3, THF

Three further steps completed the synthesis of pseudopterosin A aglycone which was finally coupled with 1-bromo-2,3,4-triacetyl-D-xylose to obtain the target molecule after removal of the protecting groups. The synthesis proved lengthy and involved loss of control at various stereocenters: this resulted in difficult separations and considerable reduction in the overall yield.

2.3 The Corey total synthesis of pseudopterosins A and E.

A superior enantiospecific approach to pseudopterosins A and E was reported by Corey and Carpino in 1989[16]. Their retrosynthetic analysis (scheme **2.3.1**) indicated compound **2.3.1.1** as common precursor to both natural products.

Scheme **2.3.1.**

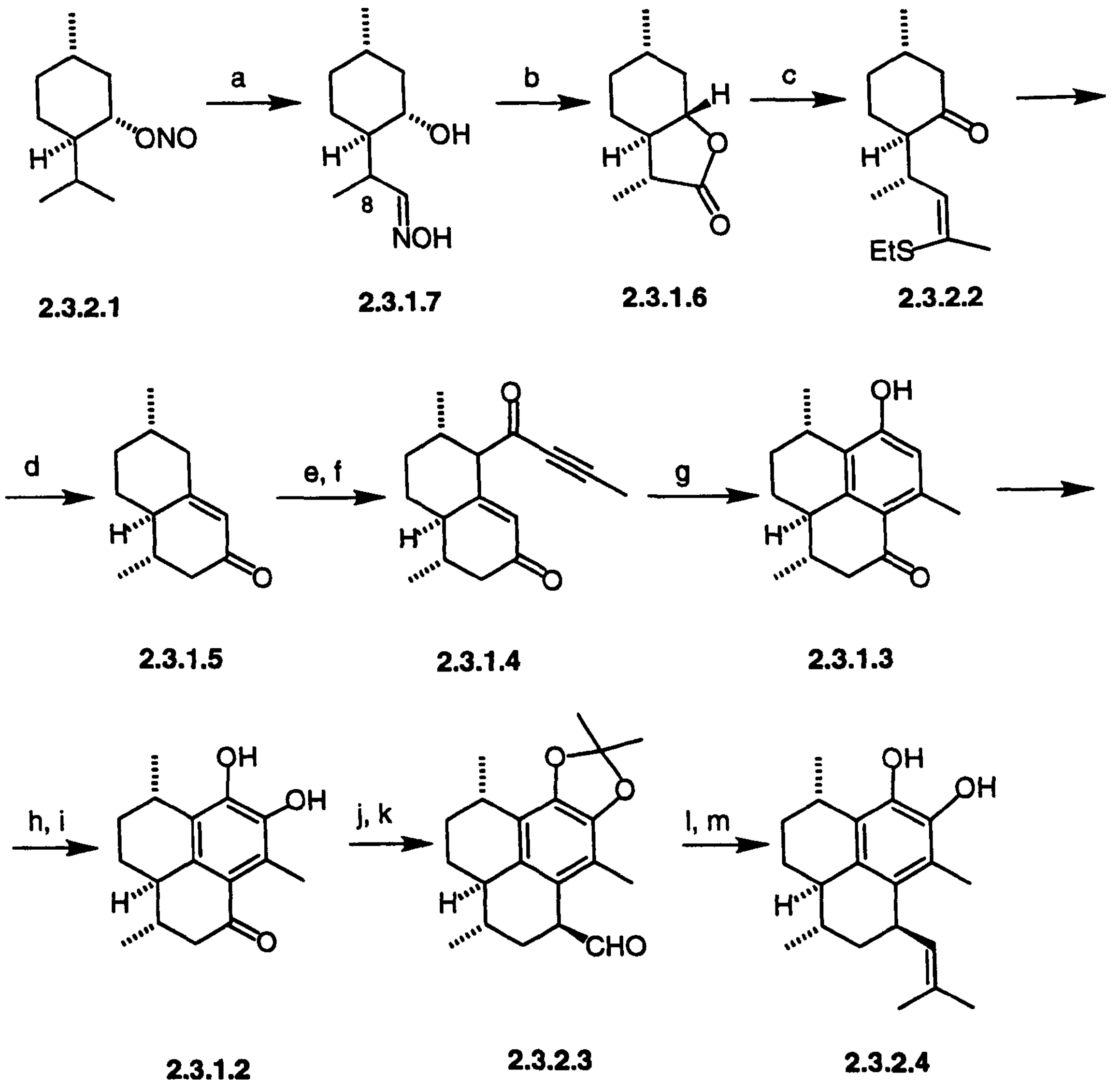

Pseudopterosin A
Pseudopterosin E
H
1
2.3.1.1
OH
OH
H
O
2.3.1.2
OH
H
O
2.3.1.3
O
H
O
2.3.1.4
H
O
2.3.1.5
H
H
O
O
2.3.1.6
H
OH
NOH
2.3.1.7
H
OH
(+)-menthol

After disconnection at C1 to reveal the key intermediate **2.3.1.2**, the overall strategy chosen for the synthesis of the tricyclic unit was again the building of the aromatic ring after introduction of the stereocenters on a monoterpenic unit rather than using an aromatic template as starting material. The authors relied mainly on induction of chirality to control the newly formed stereocenters and were aware that the oxidation of a phenol to catechol in the late stages of the synthesis could be troublesome.

Aromatisation of bicyclic enone **2.3.1.4** was to be employed as a concise route to the highly functionalised ring of **2.3.1.3**. Disconnection of the side chain bearing the propargylic ketone identified bicyclic **2.3.1.5** as a suitable precursor. It was expected that the introduction of the stereocenter at C3 (pseudopterosins numbering) could be directed exploiting conformational strain in bicyclic lactone **2.3.1.6**, easily accessible from **2.3.1.7**.

The synthesis began with photolysis of (1*S*, 2*R*, 5*S*)-(+)-menthol nitrite ester **2.3.2.1** (scheme **2.3.2**) to yield oxime **2.3.1.7** as a 5:1 mixture of epimers at C8. The correct stereochemistry at the newly formed center was introduced exploiting the cyclic constraint of a γ-lactone ring. **2.3.1.7** underwent a sequence of hydrolysis of the oxime function, oxidation of the lactol and isomerisation to the desired C8 configuration *via* enolisation with LDA to afford **2.3.1.6** as a single stereoisomer in good overall yield. Synthesis of key 1,5-diketone **2.3.1.4** was achieved *via* a sequence of five reactions in 40% overall yield. The tricyclic system of pseudopterosins was then easily formed treating alkyne 1,5-dione **2.3.1.4** with KH in THF to form the substituted aromatic ring. Oxidation of phenol **2.3.1.3** proved challenging: after extensive experimentation, a three-step procedure was the only viable method. Treatment with benzenesulfinic anhydride and HMDS converted **2.3.1.3** into the corresponding *ortho*-quinone imine[17] which was then hydrolysed with AcOH/H_2O in presence of perchloric acid. Reduction of the resulting quinone with excess $Na_2S_2O_4$ yielded **2.3.1.2** in 74% overall yield. After protection of the sensitive catechol unit by the isopropylidene group, side chain extension *via* methylenation of the ketone and Lewis acid-promoted rearrangement of the epoxide thus formed **2.3.2.3** as a 10:1 mixture of axial and equatorial aldehydes. Wittig reaction and hydrolysis of the protecting group yielded catechol **2.3.2.4** as an oil, identical to the aglycones of pseudopterosins A-E by ^{1}H-NMR and TLC analysis.

Scheme 2.3.2.

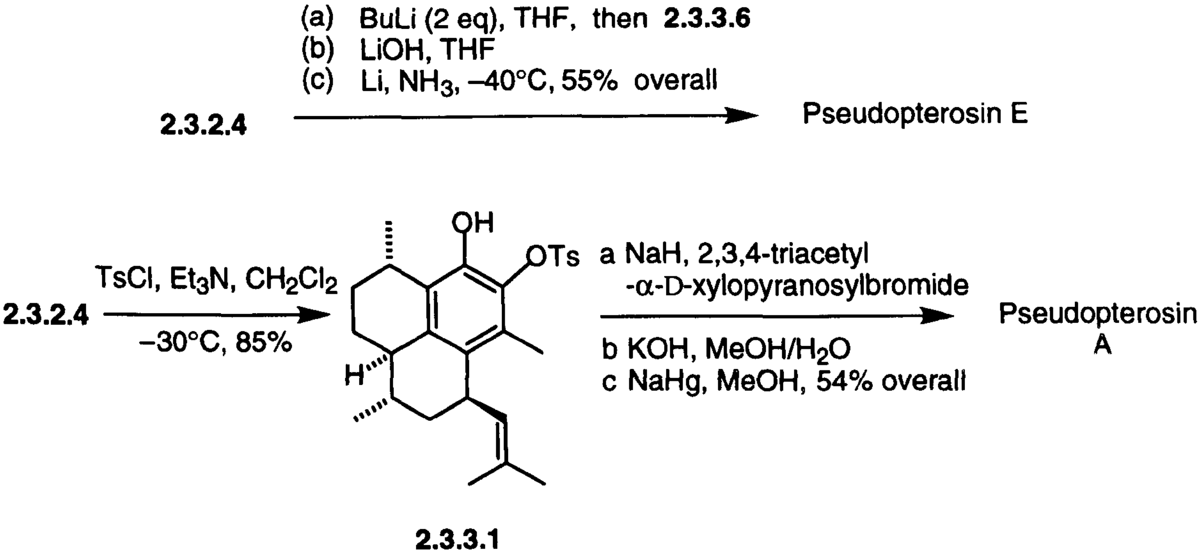

2.3.2.1
a
ONO
H
OH
8
NOH
2.3.1.7
b
H
O
O
2.3.1.6
c
O
EtS
2.3.2.2
d
O
2.3.1.5
e, f
O
O
2.3.1.4
g
OH
O
2.3.1.3
h, i
OH
OH
O
2.3.1.2
j, k
O
O
CHO
2.3.2.3
l, m
OH
OH
2.3.2.4

Yields, reagents and conditions :

a	90%	hv
b	60%	(i) $NaHSO_3$, 50°C; (ii) Br_2, $CaCO_3$,THF/H_2O; (iii) LDA, THF, 0°C; (iv) NH_4Cl
c	-	(i) DIBAL-H, CH_2Cl_2, –78°C; (ii) $Ph_3P{=}C(CH_3)SEt$, DMSO;(iii) DMSO, TFAA, Et_3N
d	40%	(i) $HgCl_2$, CH_3CN/H_2O, 50°C; (v) $NaOCH_3$, CH_3OH, 23°C
e	97%	KH, THF-HMPA, then TMSCl
f	61%	(i) 2-Butynal, TMSOTf, CH_2Cl_2, –78°C, then H_2O; (ii) PCC, CH_2Cl_2, 23°C
g	70%	KH, THF, 23°C
h	79%	Benzeneseleninic anhydride, HMDS, PhH, 23°C
i	71%	(i) AcOH (aq.), $HClO_4$ (cat), 23°C; (ii) $NaHSO_3$, H_2O
j	87%	2,2-Dimethoxypropane, PPTS, $CHCl_3$
k	76%	(i) $Me_2S{=}CH_2$, THF, 23°C; (ii) $BF_3{\bullet}OEt_2$, CH_2Cl_2, –30°C → 23°C
l	81%	$Ph_3P{=}CHMe_2$, THF, 0°C
m	71%	HCl (aq.), MeOH, THF, 70°C

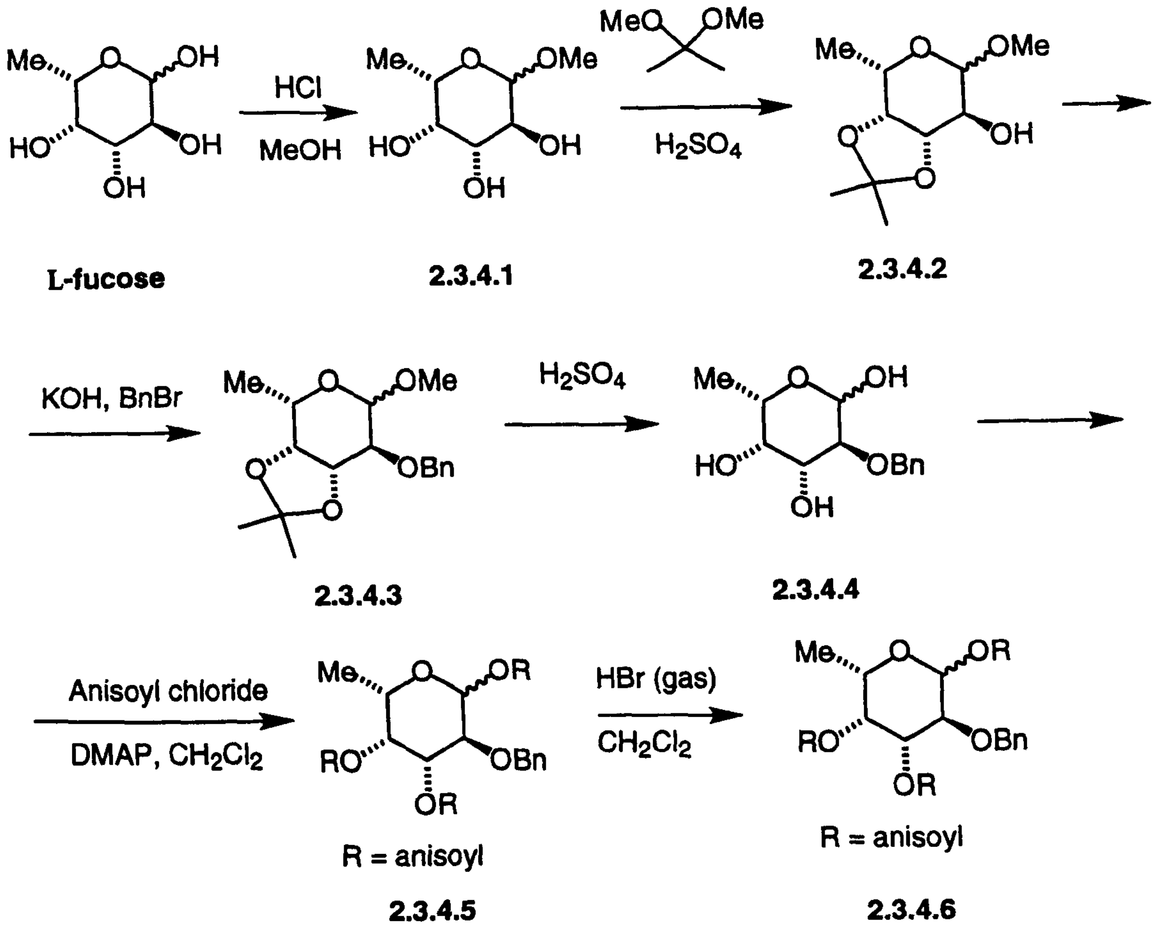
The different steric hindrance of the two hydroxyl groups at C9 and C10 was exploited for selective glycosylation on the route to pseudopterosins A and E (scheme **2.3.3**). The C9 position is in close proximity to an isopropyl group and hence the C10 hydroxyl is biased to react faster with electrophiles. Hence, for the synthesis of pseudopterosin A the more reactive C10 position was protected as the tosylate, **2.3.3.1** was then treated with NaH in CH_3CN followed by 2,3,4-triacetyl-α-D-xylopyranosyl bromide *in situ* to give the corresponding 10-tosyl-9-triacetyl-β-xylopyranoside. Removal of acetyl and tosyl protecting groups and chromatographic separation afforded pseudopterosin A in 54% yield.

Scheme **2.3.3.**


(a) BuLi (2 eq), THF, then 2.3.3.6
(b) LiOH, THF
(c) Li, NH3, –40°C, 55% overall
2.3.2.4
Pseudopterosin E
TsCl, Et3N, CH2Cl2
2.3.2.4
–30°C, 85%
OH
OTs
H
a NaH, 2,3,4-triacetyl -α-D-xylopyranosylbromide
b KOH, MeOH/H2O
c NaHg, MeOH, 54% overall
Pseudopterosin A
2.3.3.1

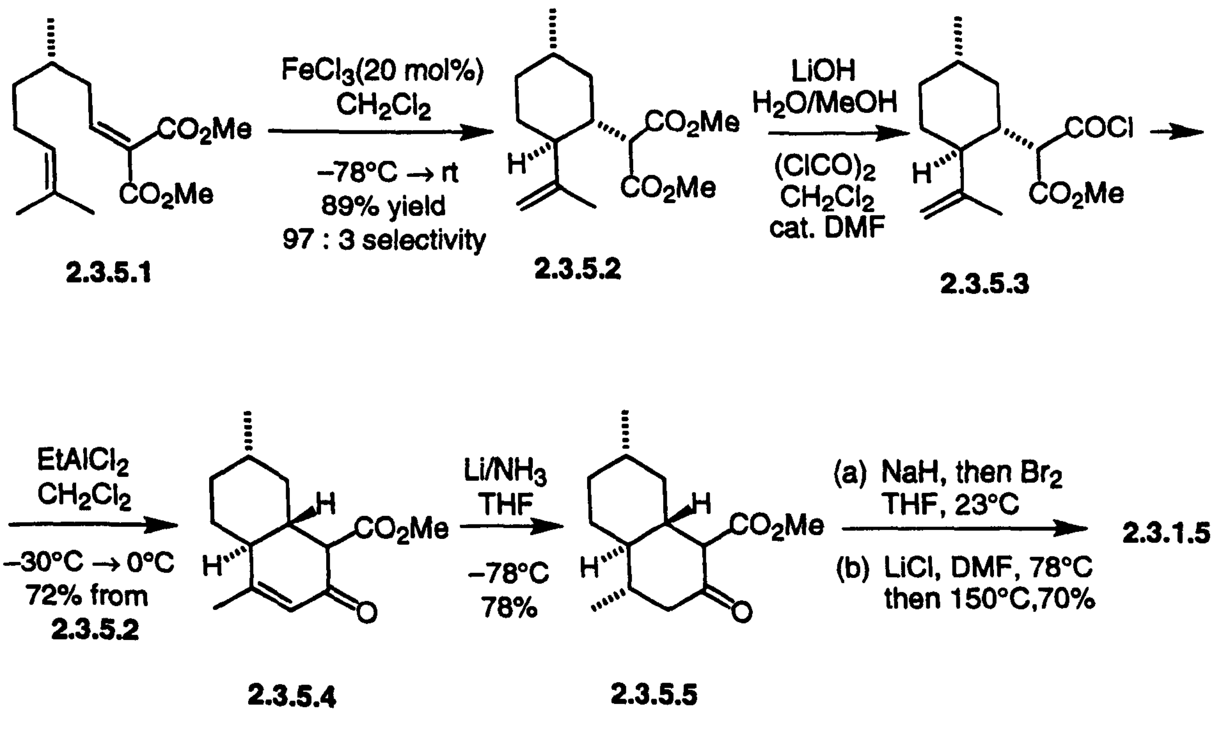
Pseudopterosin E was synthesised by direct attachment of the L-fucose unit *via* a novel protocol, as preliminary studies on this reaction carried out by Prof. Fenical suggested that known methods for the formation of α-aryl glycosides would not yield satisfactory results. Deprotonation of the aglycone with 2 equivalents of BuLi and reaction with glycosyl bromide **2.3.4.6** proceeded with very good selectivity but low yields. Sequential cleavage of the ester and ether protecting groups cleanly produced pseudopterosin E in 53% overall yield from the aglycone. The preparation of **2.3.4.6** is depicted in scheme **2.3.4.**

Scheme **2.3.4.**


L-fucose
HCl
MeOH
2.3.4.1
MeO OMe
H₂SO₄
2.3.4.2
KOH, BnBr
2.3.4.3
H₂SO₄
2.3.4.4
Anisoyl chloride
DMAP, CH₂Cl₂
R = anisoyl
2.3.4.5
HBr (gas)
CH₂Cl₂
R = anisoyl
2.3.4.6

An improved approach to intermediate **2.3.1.5** was reported by the same authors[18] in 1990 (scheme **2.3.5**). The (*S*)-citronellal derivative **2.3.5.1** underwent FeCl3-catalysed ene reaction and the cyclic diester thus obtained was transformed into keto ester **2.3.5.4** in two steps.

Scheme **2.3.5.**

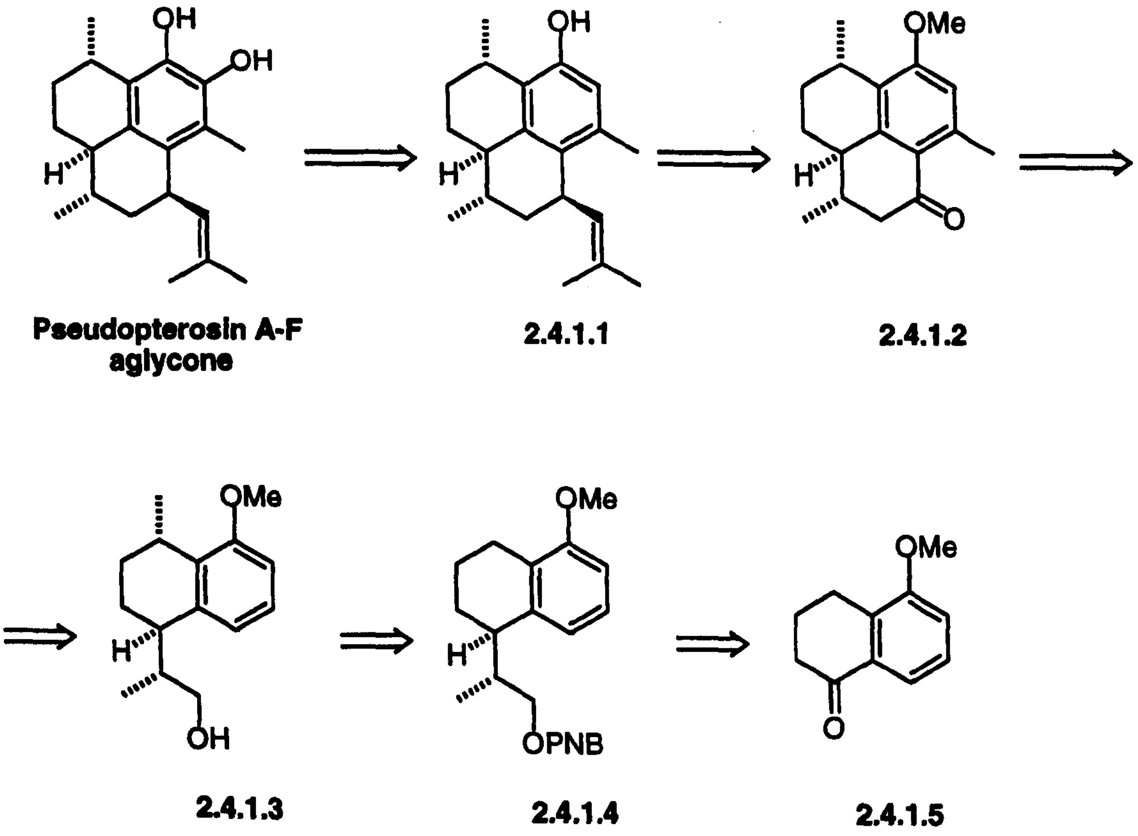

2.3.5.1
FeCl₃(20 mol%)
CH₂Cl₂
−78°C → rt
89% yield
97 : 3 selectivity
2.3.5.2
LiOH
H₂O/MeOH
(ClCO)₂
CH₂Cl₂
cat. DMF
2.3.5.3
EtAlCl₂
CH₂Cl₂
−30°C → 0°C
72% from
2.3.5.2
2.3.5.4
Li/NH₃
THF
−78°C
78%
2.3.5.5
(a) NaH, then Br₂
THF, 23°C
(b) LiCl, DMF, 78°C
then 150°C,70%
2.3.1.5

Introduction of the new stereocenters at C3 was again carried out *via* hydrogenation, exploiting the strain of the α,β-unsaturated cyclic enone to obtain **2.3.5.5**; a two-step procedure consisting of reaction with NaH, quenching with bromine and heating the product in the presence of LiCl gave desired **2.3.1.5** in 70% yield from **2.3.5.5**.

2.4 The McCombie synthesis of pseudopterosins A-F aglycones.

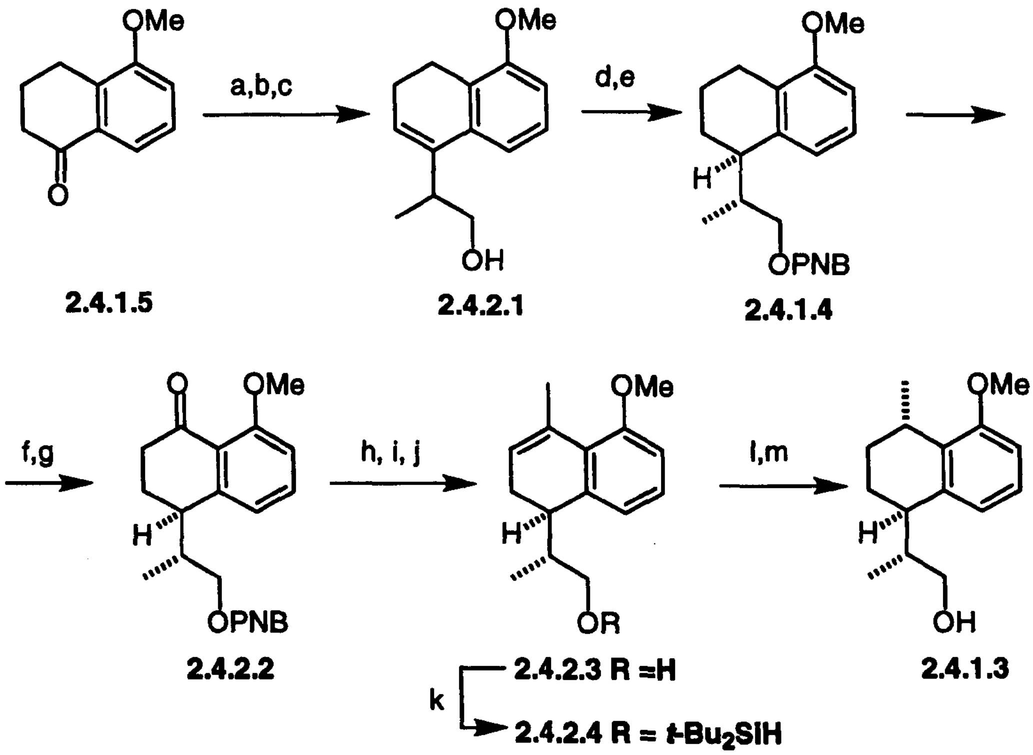
An innovative synthesis of the racemic aglycones of pseudopterosins A-F was published by S. W. McCombie and coworkers in 1991[19,20]. The retrosynthetic analysis (scheme **2.4.1**) is based on the oxidation of phenol **2.4.1.1.** in the latest stage of the route. Disconnection of the side chain at C1 leads to ketone **2.4.1.2**, similar to Corey's pivotal tricyclic intermediate. In this case the overall strategy is based on an aromatic starting material, **2.4.1.5**, which is commercially available. Introduction of relative stereochemistry would take advantage of substrate induction once the first centres had been established and the process was designed as a non-enantioselective approach.

Scheme **2.4.1**.



Racemic alcohol **2.4.2.1** (scheme **2.4.2**) was obtained after Reformatsky reaction followed by dehydration and reduction of the ester group to a hydroxyl. The free carbinol was exploited to direct hydrogenation of the double bond under homogeneous catalysis conditions (selectivity > 95:5 in favour of the desired isomer). Methylation of the secondary benzylic position was attained by selective oxidation and addition of an organocerium reagent to yield **2.4.2.3**. The correct stereochemistry was set *via* an intramolecular version of ionic hydrogenation[21] by treating silyl ether **2.4.2.4** with trifluoroacetic acid to secure **2.4.1.3** in 65-75% yield and >95% isomeric purity.

Scheme **2.4.2**

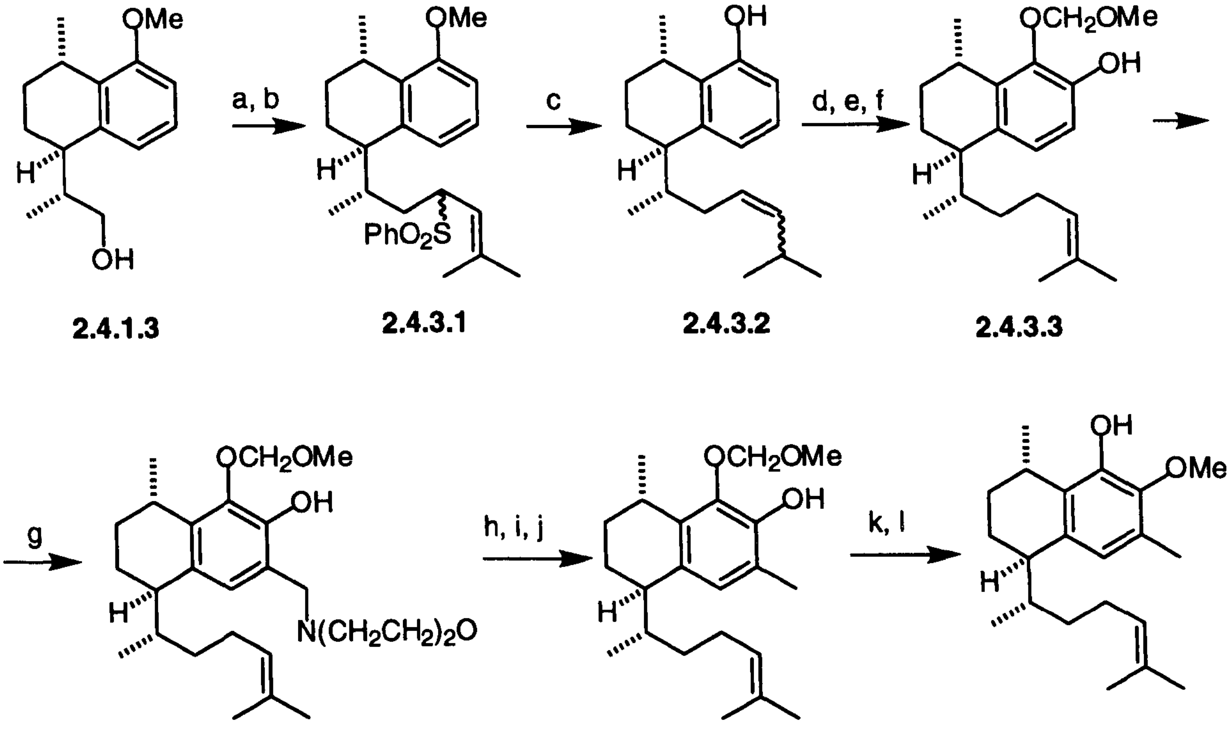


Yields, reagents and conditions

(a)	-	Zn, $MeCHBrCO_2Et$, TMSCl, THF, 65°C
(b)	-	MsOH, $(ClCH_2)_2$
(c)	75%	Red-Al
(d)	-	$(Ph_3P)_3RhCl$, *t*-BuOK, H_2 (60 psi), THF
(e)	80%	PNBCl, Pyr
(f)	80%	$K_2S_2O_8$, $CuSO_4$,*sym*-collidine, $MeCN/H_2O$
(g)	63%	PCC, celite, CH_2Cl_2
(h)	-	NaOMe
(i)	-	$MeCeCl_2$
(j)	72%	TsOH
(k)	-	$(t\text{-Bu})_2SiHCl$, imidazole, DMF
(l)	-	TFA, CH_2Cl_2
(m)	65%	TBAF, THF, 23°C

Conversion of **2.4.1.3** to a derivative of the secopseudopterosins aglycone was easily accomplished (scheme **2.4.3**). After attachment of the unsaturated side chain, the second oxygen on the aromatic ring of **2.4.3.3** was introduced *via* *ortho*-directed metallation, quenching with $B(OMe)_3$ and oxidation, prior to methylation *via* a Mannich reaction. Conversion to **2.4.3.6** allowed spectral comparison with material derived from natural secopseudopterosins.

Scheme **2.4.3.**



2.4.1.3 **2.4.3.1** **2.4.3.2** **2.4.3.3**

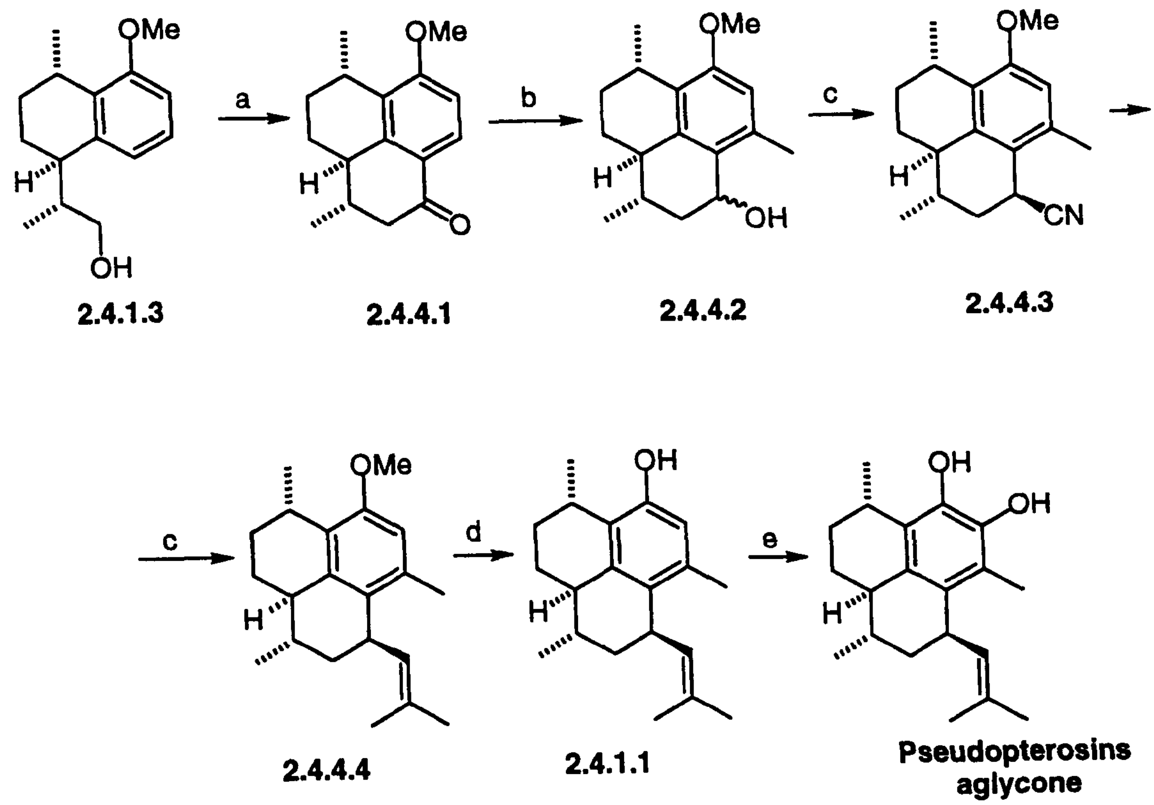
2.4.3.4 **2.4.3.5** **2.4.3.6**

Reagents and conditions :

a TsCl, Pyr
b $Me_2C{=}CHCH(Li)SO_2Ph$, THF, −70°C → 23°C
c Li, $EtNH_2$
d $MeOCH_2Cl$, *i*-Pr_2NEt
e *t*-BuLi, Et_2O, 0°C, then $B(OMe)_3$
f H_2O_2, K_2CO_3, H_2O
g Aq. CH_2O, morpholine, EtOH, 80°C
h CCl_3OCOCl, *sym*-collidine
- CH_2Cl_2, 0°C
i $NaBH_4$, DMSO
j NaOH, H_2O
k MeI, K_2CO_3, acetone
l TsOH, MeOH

For the synthesis of pseudopterosins aglycone, **2.4.1.3** (scheme **2.4.4**) was transformed into tricyclic ketone **2.4.4.1**, then reduced to the corresponding epimeric alcohols. Experiments under several conditions failed to attain the alkylation at C1 with the desired stereochemistry. However, reaction of the methylated intermediate **2.4.4.2** with Et_2AlCN and $SnCl_4$ or $BF_3{\bullet}OEt_2$ in CH_2Cl_2 afforded nitrile **2.4.4.3** as the major isomer in 70% yield.

Scheme **2.4.4.**



Yields, reagents and conditions :

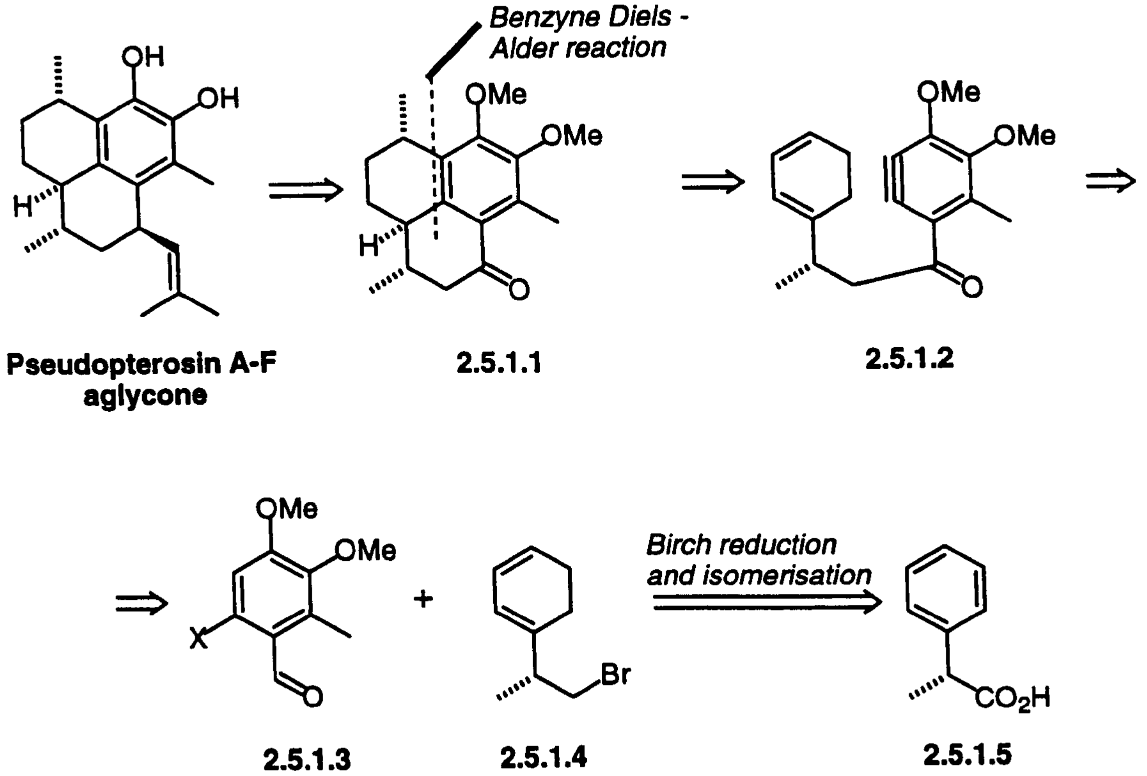
a 60% (i) TsCl, Pyr; (ii) NaCN, DMSO, 65°C;(iii) MsOH, $(ClCH_2)_2$; (iv) NaOAc, H_2O, 85°C
b 60% (i) $NaBH_4$; (ii) *t*-BuLi, Et_2O, pentane, 35°C; (iii) MeI, 0°C; (iv) Et_2AlCN, $SnCl_4$
c 55% (i) DIBAL-H, toluene, –70°C; (ii) $PhSO_2C(Li)Me_2$, THF, –70°C; (iii) Na-Hg, MeOH
d - BBr_3, 2,6-dibutylpyridine, CH_2Cl_2, 0°C
e - (i) $ON(SO_3K)_2$, KH_2PO_4, acetone/H_2O; (ii) $Na_2S_2O_4$, CH_2Cl_2/H_2O

Notably, the presence of the methyl on the aromatic ring showed no influence, whereas changing the configuration of the CH_3 group at C3 position resulted in the formation of the undesired pseudoequatorial nitrile as the main product, probably due to conformational effects. Conversion of the nitrile into the isobutenyl sidechain and cleavage of the methoxy group led to **2.4.1.1**. The phenol was then oxidised to the sensitive *ortho*-quinone (Fremy's salt, KH_2PO_4, acetone-H_2O, 0°C) which was immediately reduced to the unstable aglycone of the natural products. The synthetic aglycone and its diacetate were spectroscopically and chromatographically identical to material derived from pseudopterosin E. The overall low yield of the synthesis stems mainly from the necessity of overcoming conformational effects in the introduction of new stereocenters and makes the approach inefficient.

2.5 The Buszek and Bixby synthesis.

The most recent total synthesis of pseudopterosins A-F aglycone was reported by K. R. Buszek and D. L. Bixby in 1995[22]. Their original strategy is illustrated in scheme **2.5.1**. The key steps involved intramolecular benzyne Diels-Alder cycloaddition (IMBDA) between the tethered cyclohexadiene and the aromatic portion of **2.5.1.2**.

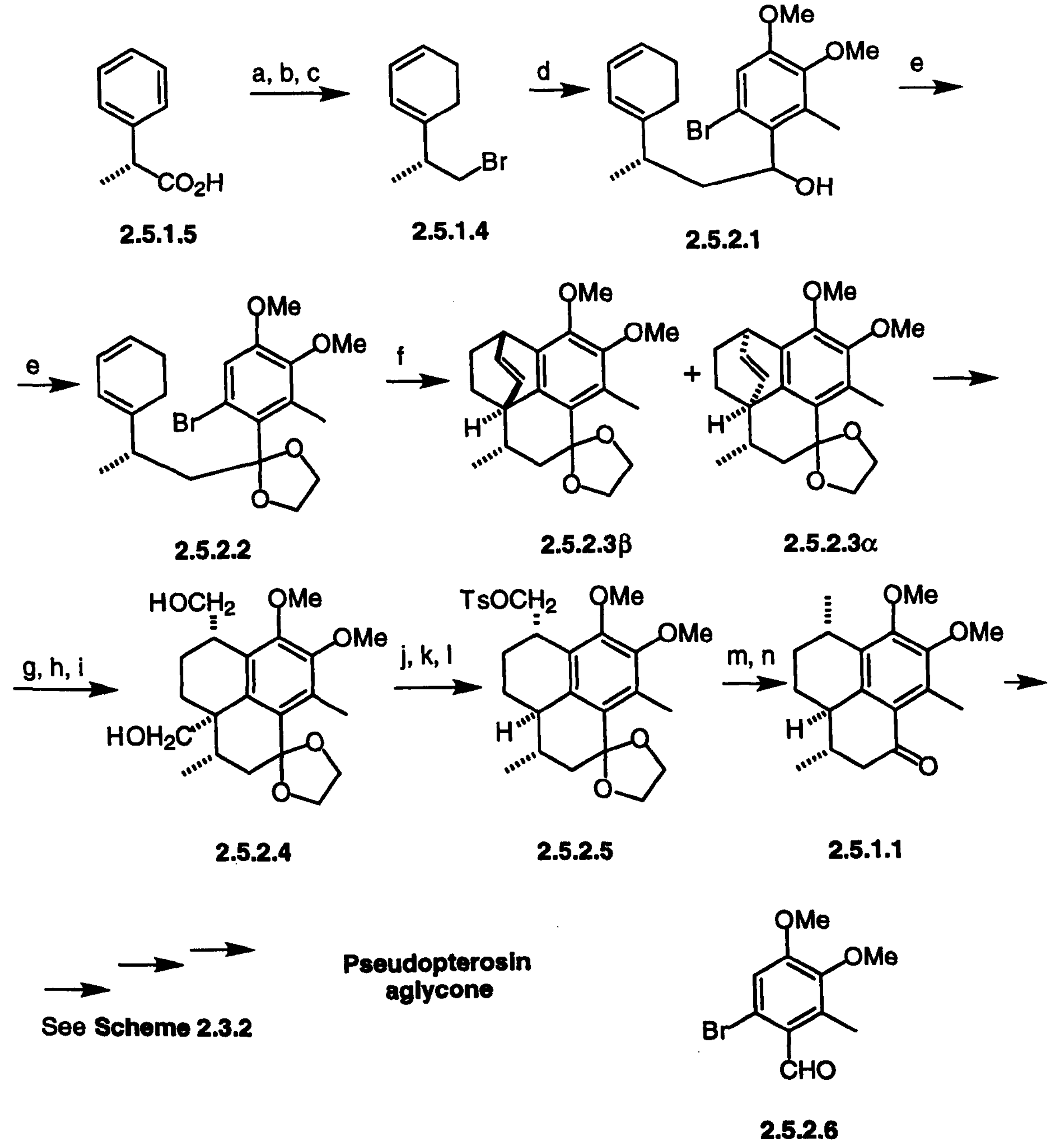
Scheme **2.5.1**.


Benzyne Diels - Alder reaction
OH
OH
H
OMe
OMe
O
Br
X
CO2H
+
Birch reduction and isomerisation
Pseudopterosin A-F aglycone
2.5.1.1
2.5.1.2
2.5.1.3
2.5.1.4
2.5.1.5

Easy disconnection at the protected carbonyl reveals aldehyde **2.5.1.3** and diene **2.5.1.4**. The cyclohexadiene can be easily obtained from the chiral starting material **2.5.1.5** after Birch reduction and base-catalysed isomerisation of the 1,3-diene to the conjugated system.

Their concise synthesis is shown in scheme **2.5.2**. The alcohol derived from reduction of commercially available (*R*)-(–)-2-phenylpropionic acid (**2.5.1.5**) was subjected to Birch reduction followed by base-induced isomerisation to yield the corresponding 1,3-diene. The Grignard reagent derived from bromide **2.5.1.4** was then added to the known aldehyde **2.5.2.6** (prepared in 7 steps from 2-methylpiperonal) to give the key intermediate **2.5.2.2** after oxidation and protection of the ketone.

Scheme **2.5.2.**


a, b, c
d
e
f
g, h, i
j, k, l
m, n
OMe
OMe
Br
OH
CO2H
CHO
HOCH2
HOH2C
TsOCH2
H
2.5.1.5
2.5.1.4
2.5.2.1
2.5.2.2
2.5.2.3β
2.5.2.3α
2.5.2.4
2.5.2.5
2.5.1.1
2.5.2.6
See Scheme 2.3.2
Pseudopterosin aglycone

Yields, reagents and conditions :

a	-	$LiAlH_4$, THF, 65°C
b	-	(i) Na-NH_3, EtOH, −78°C; (ii) *t*-BuOK, DMSO, 65°C
c	48%	PPh_3, NBS, Pyr, CH_2Cl_2
d	78%	Mg, THF then **2.5.2.6**, THF, 0°C
e	81%	(i) Swern oxidation; (ii) $(TMSOCH_2)_2$, TMSOTf (cat.), CH_2Cl_2, −78°C
f	63%	LDA, THF, −78°C →rt
g	-	NMO, OsO_4 (cat.), PhMe, acetone, H_2O
h	-	$NaIO_4$
i	85%	$NaBH_4$
j	83%	TsCl, Pyr
k	-	Dess-Martin periodinane, CH_2Cl_2
l	76%	$(PPh_3)_3RhCl$, PhCN, reflux
m	68%	$LiAlH_4$, THF, 65°C
n	100%	PPTS, acetone, H_2O

MM2 calculations predicted that the desired α-face approach transition state would be preferred over the alternative β-face approach to avoid steric interaction between the stereogenic methyl group at C3 and the terminal hydrogen of the diene. However, the intramolecular benzyne Diels-

Alder reaction led to a 58:42 mixture of diastereoisomers **2.5.2.3α** and **2.5.2.3β**. Separation by chromatography afforded **2.5.2.3α** as a single isomer, identified *via* NOE difference ^{1}H NMR experiments. Oxidative cleavage of the ethylene bridge followed by decarbonylation protocol led to **2.5.2.5**. After hydride reduction of the tosylate group of **2.5.2.5** and deprotection, introduction of the unsaturated side chain was carried out following the method of Corey[16] (see scheme **2.3.2**). Deprotection of the methoxy group with TMSI concluded the enantiospecific synthesis of pseudopterosin A and E aglycone. Lack of stereoselectivity in the cycloaddition step and the use of a very expensive chiral starting material are the major drawbacks of this otherwise elegant and concise approach.

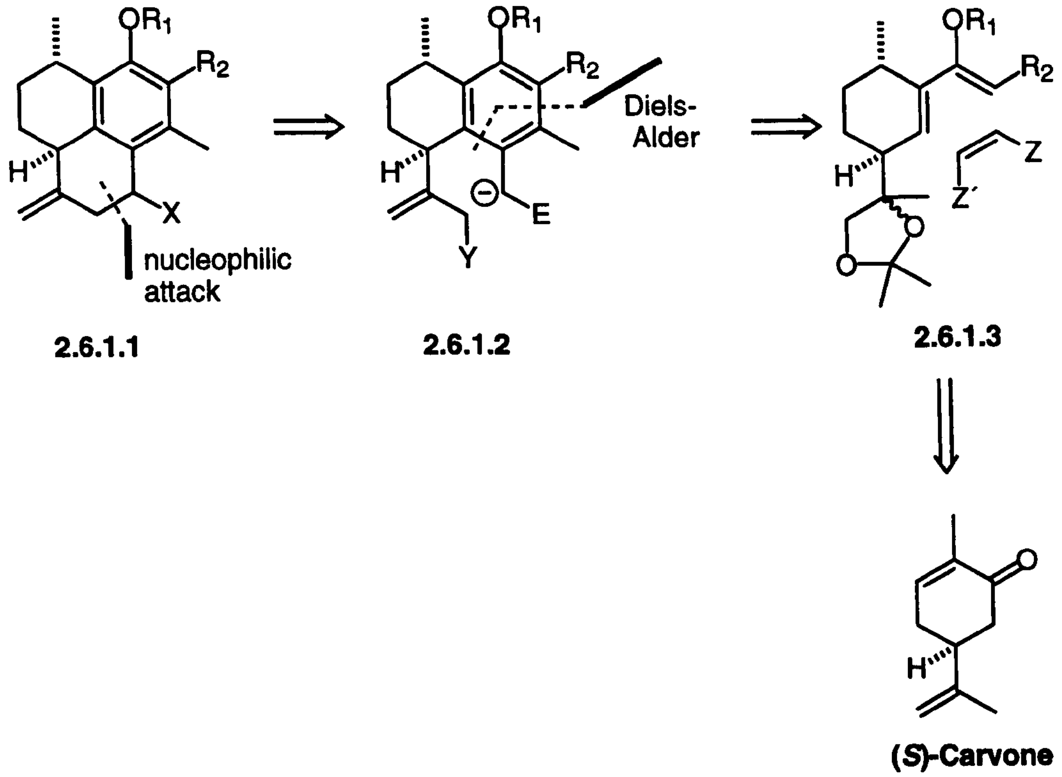
2.6 The Kozikowski and Wu partial synthesis.

Several partial syntheses of pseudopterosins and analogues have been published since 1991, proving the interest of several organic chemists in this class of compounds.

The first partial synthesis by Kozikowski and Wu[3] (scheme **2.6.1**) was conceived as a flexible approach to the natural compounds as well as to selected analogues with a view to exploring the structure-biological activity relationships of these compounds.

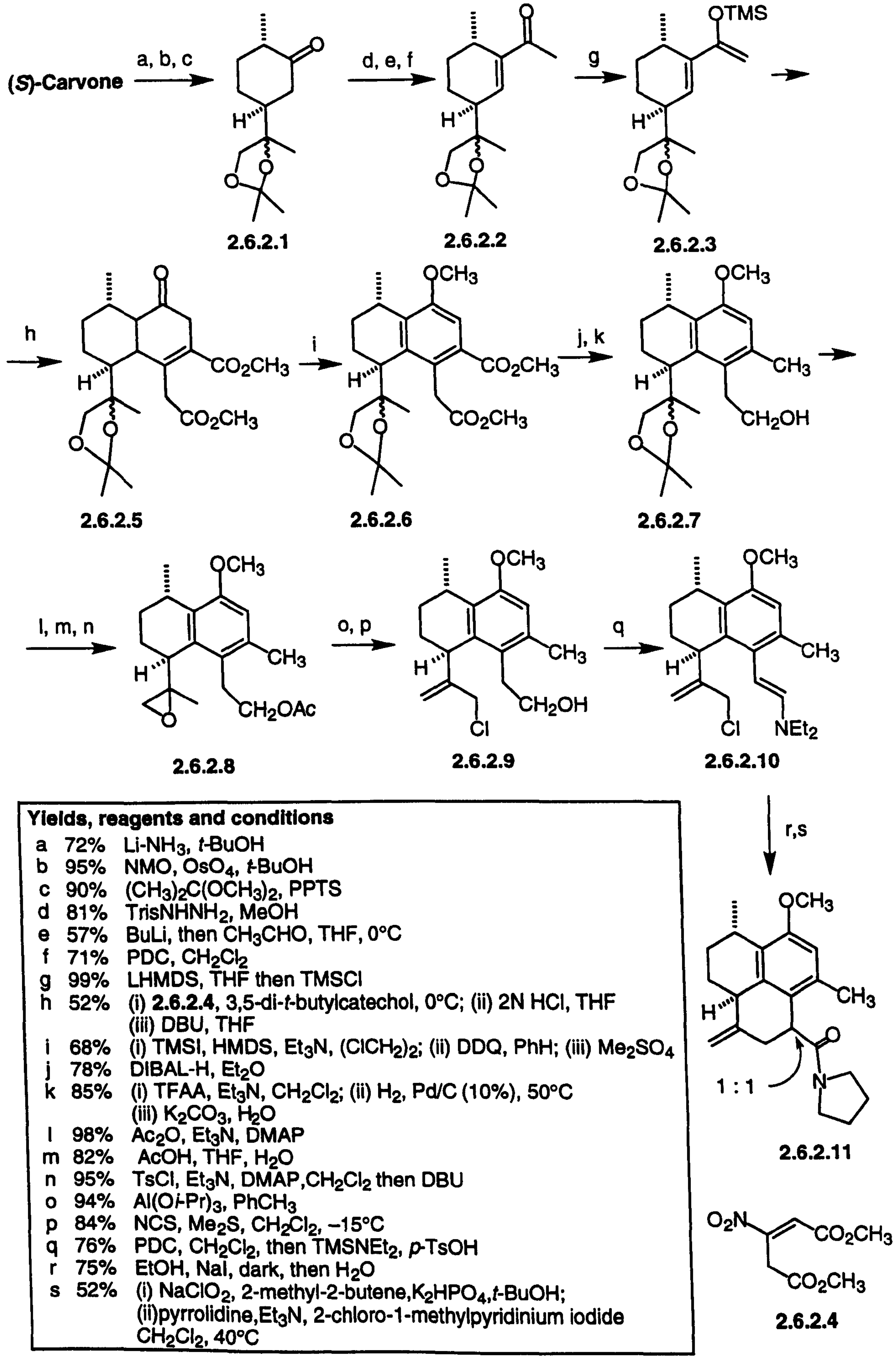
It was envisioned that alkene **2.6.1.1** would be a suitable precursor for a range of pseudopterosins analogues. Its synthesis was based on nucleophilic addition for the closure of ring C of pseudopterosins and intramolecular Diels-Alder for the formation of the aromatic core. Diene **2.6.1.3** could be derived from (*S*)-carvone.

Scheme **2.6.1**


OR1
R2
X
H
nucleophilic attack
2.6.1.1
Diels-Alder
E
Y
2.6.1.2
Z
Z'
2.6.1.3
(S)-Carvone

Scheme **2.6.2** shows the overall sequence. Key diene **2.6.2.3** was prepared after a series of transformations including Shapiro reaction of ketone **2.6.2.1**. Reaction of **2.6.2.3** with dienophile **2.6.2.4** (prepared in four steps from methyl-3-bromopropiolate) followed by aromatisation led to bicylcic **2.6.2.6**. After a rather lengthy series of manipulations of the side chains, intramolecular reactions of enamine **2.6.2.10** formed ring C of the desired intermediate. Amide **2.6.2.11** was formed as a 1:1 mixture of diastereoisomers which could then be separated by chromatography.

Scheme **2.6.2.**



2.6.2.1, **2.6.2.2**, **2.6.2.3**, **2.6.2.5**, **2.6.2.6**, **2.6.2.7**, **2.6.2.8**, **2.6.2.9**, **2.6.2.10**, **2.6.2.11**, **2.6.2.4**

Yields, reagents and conditions

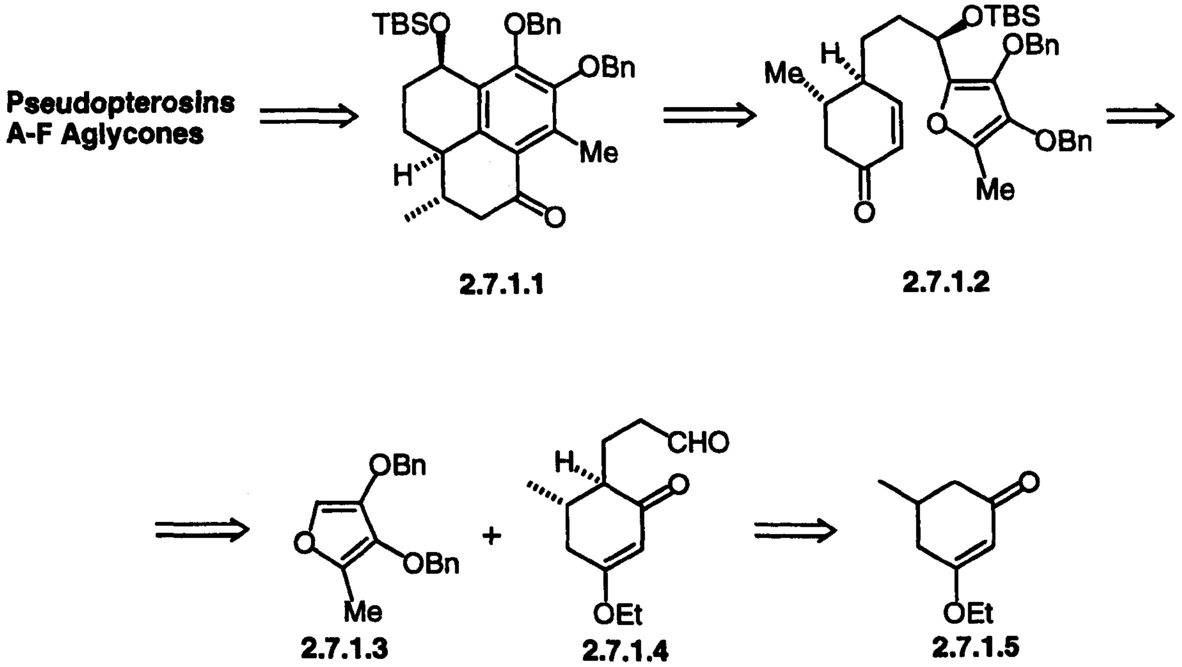
a	72%	Li-NH_3, *t*-BuOH
b	95%	NMO, OsO_4, *t*-BuOH
c	90%	$(CH_3)_2C(OCH_3)_2$, PPTS
d	81%	$TrisNHNH_2$, MeOH
e	57%	BuLi, then CH_3CHO, THF, 0°C
f	71%	PDC, CH_2Cl_2
g	99%	LHMDS, THF then TMSCl
h	52%	(i) **2.6.2.4**, 3,5-di-*t*-butylcatechol, 0°C; (ii) 2N HCl, THF (iii) DBU, THF
i	68%	(i) TMSI, HMDS, Et_3N, $(ClCH_2)_2$; (ii) DDQ, PhH; (iii) Me_2SO_4
j	78%	DIBAL-H, Et_2O
k	85%	(i) TFAA, Et_3N, CH_2Cl_2; (ii) H_2, Pd/C (10%), 50°C (iii) K_2CO_3, H_2O
l	98%	Ac_2O, Et_3N, DMAP
m	82%	AcOH, THF, H_2O
n	95%	TsCl, Et_3N, DMAP,CH_2Cl_2 then DBU
o	94%	Al(O*i*-Pr)$_3$, $PhCH_3$
p	84%	NCS, Me_2S, CH_2Cl_2, −15°C
q	76%	PDC, CH_2Cl_2, then $TMSNEt_2$, *p*-TsOH
r	75%	EtOH, NaI, dark, then H_2O
s	52%	(i) $NaClO_2$, 2-methyl-2-butene,K_2HPO_4,*t*-BuOH; (ii)pyrrolidine,Et_3N, 2-chloro-1-methylpyridinium iodide CH_2Cl_2, 40°C

This approach was long and the lack of stereocontrol at C1 (aglycone numbering) affected the overall efficiency.

2.7 The Jung and Siedem partial synthesis.

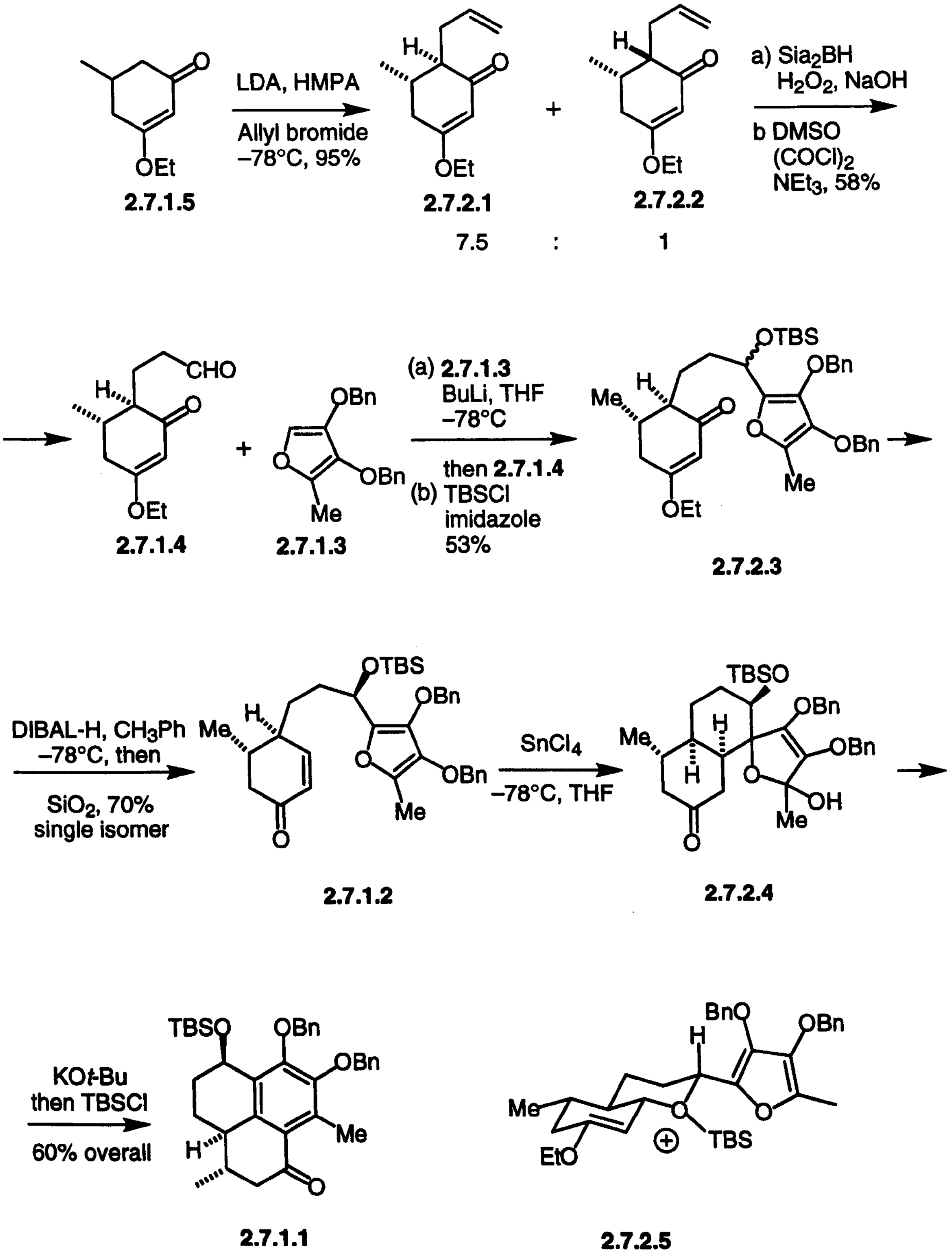
A novel and concise approach was presented by M. E. Jung and C. S. Siedem[23] in 1993 (scheme **2.7.1**). Their strategy was based on the key transformation of the functionalised furanyl derivative **2.7.1.2** into phenalene **2.7.1.1**. Intramolecular Diels-Alder or Michael addition followed by aromatisation were considered as benzannulation methods.

Scheme **2.7.1.**


Pseudopterosins A-F Aglycones
TBSO
OBn
OBn
Me
H
O
2.7.1.1
OTBS
OBn
Me
H
O
O
OBn
Me
2.7.1.2
OBn
O
OBn
Me
2.7.1.3
+
CHO
H
O
OEt
2.7.1.4
O
OEt
2.7.1.5

The concise synthesis (scheme **2.7.2**) started from racemic enol ether **2.7.1.5** which was readily transformed into aldehyde **2.7.1.4** after allylation followed by hydroboration and oxidation. **2.7.1.4** was added to the lithium anion of known furan **2.7.1.3** and the enone **2.7.2.3** was obtained after protection. DIBAL-H reduction at –78°C followed by elimination on silica gel yielded **2.7.1.2** as a single isomer.

Scheme **2.7.2.**

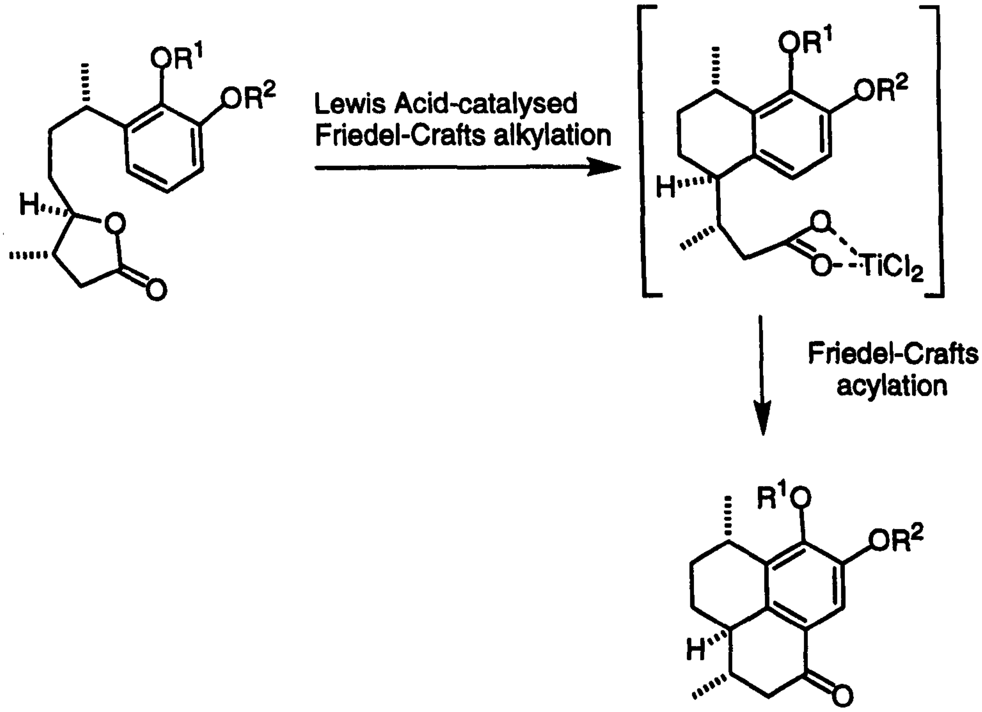

OEt
2.7.1.5
LDA, HMPA
Allyl bromide
−78°C, 95%
H
O
OEt
2.7.2.1
+
H
O
OEt
2.7.2.2
7.5 : 1
a) Sia$_2$BH
H$_2$O$_2$, NaOH
b DMSO
(COCl)$_2$
NEt$_3$, 58%
H
CHO
O
OEt
2.7.1.4
+
OBn
O
OBn
Me
2.7.1.3
(a) 2.7.1.3
BuLi, THF
−78°C
then 2.7.1.4
(b) TBSCl
imidazole
53%
OTBS
OBn
Me
H
O
O
OBn
Me
OEt
2.7.2.3
DIBAL-H, CH$_3$Ph
−78°C, then
SiO$_2$, 70%
single isomer
OTBS
OBn
Me
H
O
OBn
Me
O
2.7.1.2
SnCl$_4$
−78°C, THF
TBSO
OBn
Me
H
H
OBn
O
OH
Me
O
2.7.2.4
KOt-Bu
then TBSCl
60% overall
TBSO
OBn
OBn
Me
H
O
2.7.1.1
BnO
OBn
H
Me
EtO
O
⊕
TBS
O
2.7.2.5

The authors explained the selectivity through the formation of an allylic carbocation formed by dehydration of the carbinol formed after reduction with DIBAL-H, consequently trapped by the silyl ether to give **2.7.2.5**. Equilibration *via* a stabilised furfuryl carbocation and hydrolysis led to **2.7.1.2**. The preference of the furan ring to be equatorial in **2.7.2.5** results in the formation of **2.7.1.2** as a single isomer. The resulting enone failed to undergo intramolecular Diels-Alder, leading to the recovery of the product of Michael addition between the electon-rich furan ring and the unsaturated system. A delicate balance between Diels-Alder, retroaldol and Michael addition is probably responsible for these results. Treatment of **2.7.2.4** with base led to aldol reaction followed by aromatisation and partial loss of the TBS group. Silylation of the mixture finally afforded desired phenalene **2.7.1.1**. The approach, although overall concise and original, is only partial and developed towards racemic compounds. This route highlights the numerous regio- and stereochemical issues to be taken into account when planning synthetic approaches to these structures.

2.8 The Harrowven tandem approach.

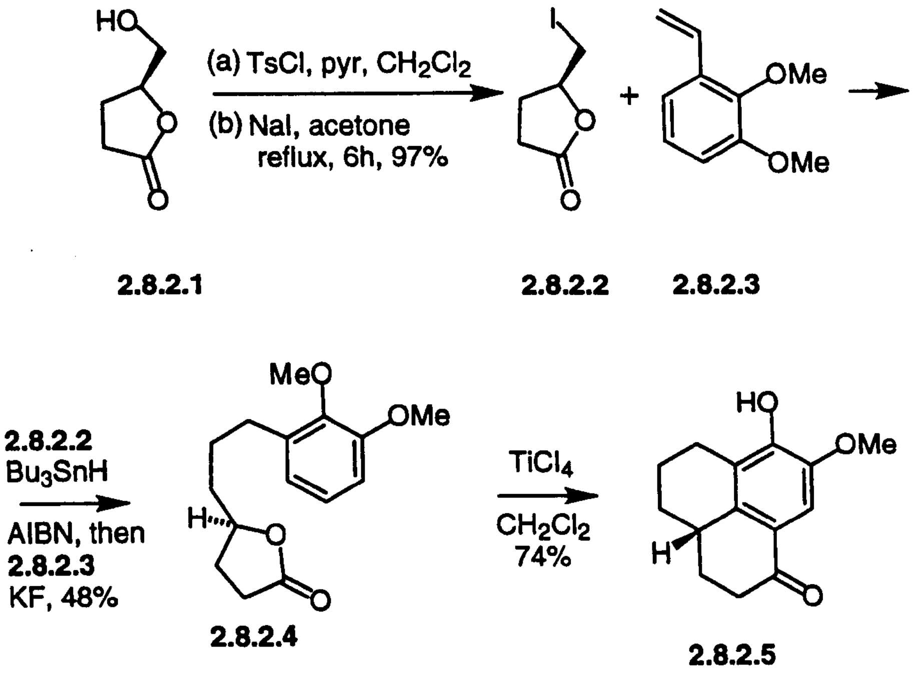
An original approach to the hexahydrophenalene system of pseudopterosins aglycones was presented in 1994 by Harrowven *et al*[24]. They envisaged that a sequence of Friedel-Crafts alkylation and Friedel-Crafts acylation reaction could easily afford the tricyclic system of the target molecules (scheme **2.8.1**).

Scheme **2.8.1**.



Scheme **2.8.2** describes their partial route. Treatment of **2.8.2.4** with a Lewis acid to give tricyclic **2.8.2.5** proceeded with good yield but substantial loss of stereocontrol at the secondary benzylic position.

Scheme **2.8.2.**


(a) TsCl, pyr, CH2Cl2
(b) NaI, acetone
reflux, 6h, 97%
2.8.2.1
2.8.2.2
2.8.2.3
OMe
OMe
2.8.2.2
Bu3SnH
AIBN, then
2.8.2.3
KF, 48%
MeO
OMe
2.8.2.4
TiCl4
CH2Cl2
74%
HO
OMe
2.8.2.5

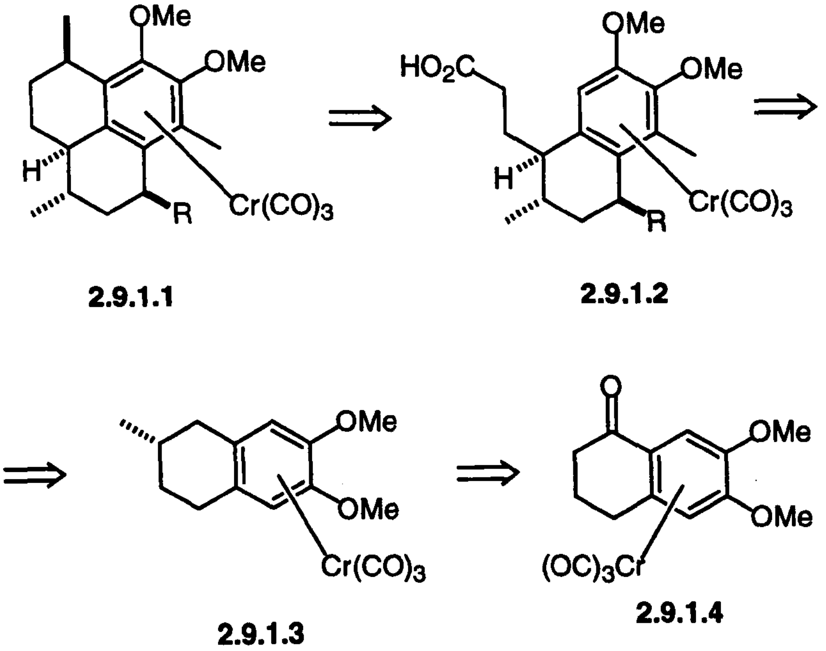
Although extremely concise, so far this route has approached only analogues of Corey's key intermediates and has not yet tackled the issue of introducing the remaining two stereocenters.

2.9 The Schmalz approaches to pseudopterosins and analogues.

The strategy devised by H.-G. Schmalz and coworkers is based on the reactivity of arene-$Cr(CO)_3$ complexes as sources of chirality and activation for aromatic precursors of pseudopterosins and analogues. The presence of the metal stabilises both carbanions and carbocations at benzylic positions as well as activating the aromatic ring towards nucleophilic substitution.

In their first commmunication[25] published in 1994, the substituted tetrahydronaphthalene skeleton was derived from Cr-complexed tetralone **2.9.1.4** (scheme **2.9.1**) after a series of asymmetric alkylations. The stereoselective transformations were directed by the presence of the bulky ligand on one face of the molecule.

Scheme **2.9.1.**

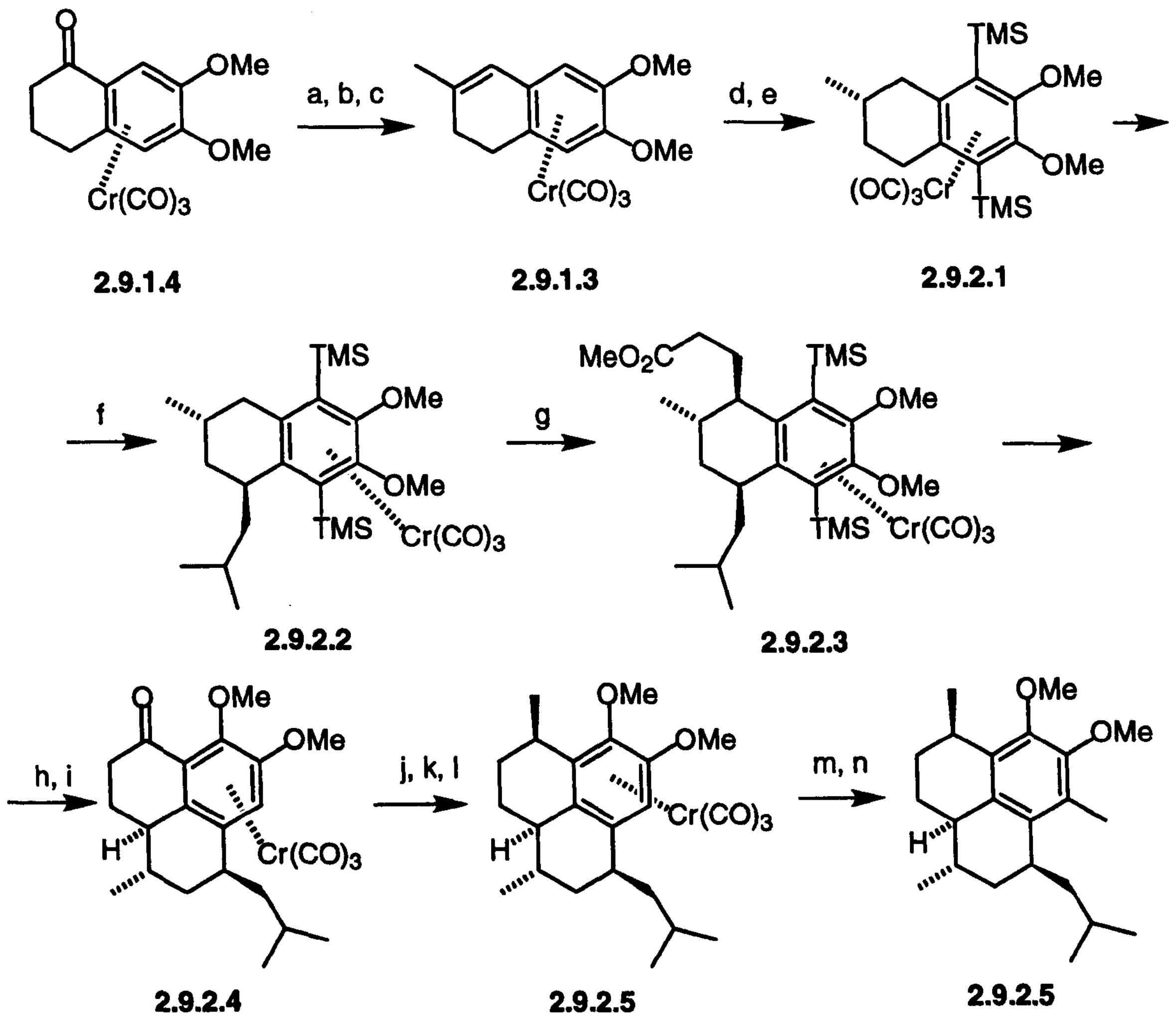


2.9.1.1 **2.9.1.2**

2.9.1.3 **2.9.1.4**

Their original synthesis (scheme **2.9.2**) starts from nonracemic **2.9.1.4** (>97% *ee*). **2.9.2.1** was obtained after a sequence of alkylation, dehydration and hydrogenation of the alkene from the least hindered face to introduce the first chiral center before protection. The remaining two stereocenters in **2.9.2.3** were introduced with complete regio- and stereocontrol by direct alkylation of one of the benzylic positions and Michael addition of the anion generated on the other. The final key cyclisation and stereoselective introduction of the benzylic methyl group completed the synthesis of **2.9.2.6**, a partially saturated analogue of pseudopterosin G aglycone and helioporin E.

Scheme **2.9.2.**

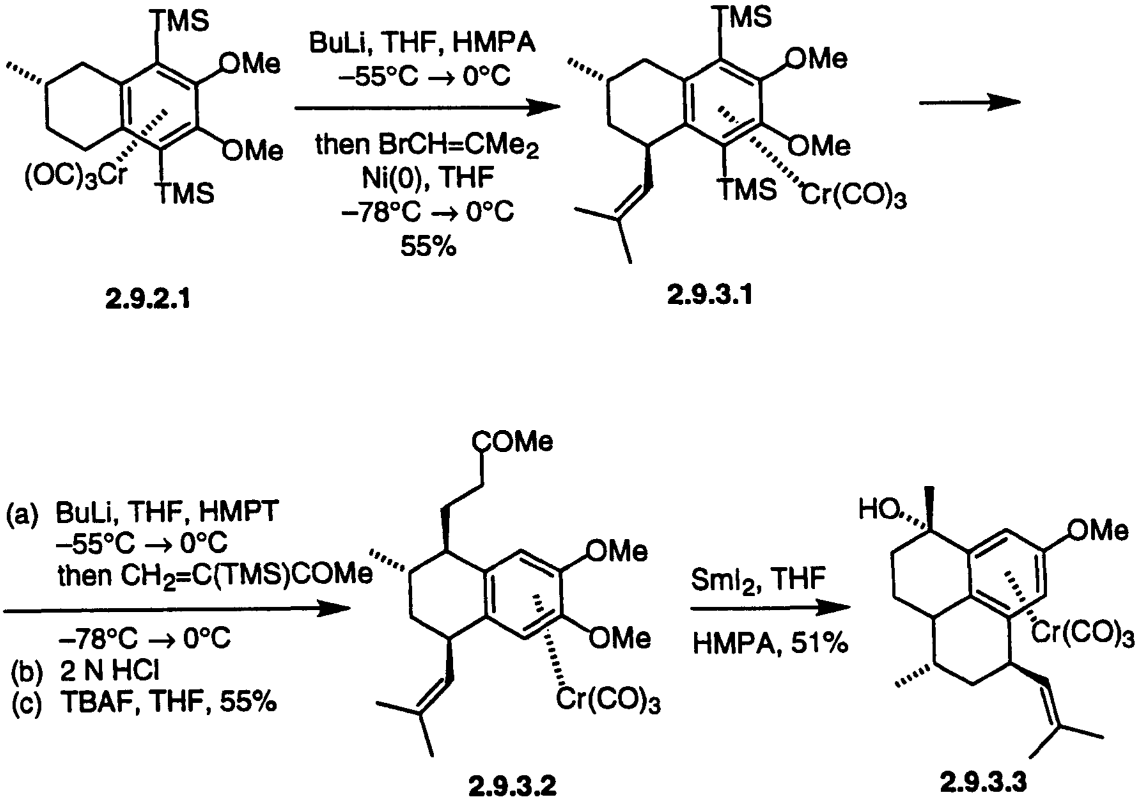


Yields, reagents and conditions :

a	-	LHMDS, THF, –78°C then MeI, HMPT
b	-	$NaBH_4$, MeOH, CH_2Cl_2
c	83%	*p*-TsOH on SiO_2, C_6H_6
d	-	5 bar H_2, cat Rh/Al_2O_3, AcOEt, AcOH
e	80%	Lithium-2,2,6,6-tetramethylpiperidide, TMSCl, THF
f	84%	BuLi, THF, HMPT, –50°C → 0°C then ICH_2CHMe_2, THF, –30°C → 0°C
g	67%	(i) BuLi, THF, HMPT, –55°C → 0°C, then CH_2=C(TMS)CO_2Me (ii) 2N HCl, 0°C; (iii) TBAF, THF
h	-	NaOH, MeOH, H_2O
i	60%	Polyphosphoric acid, rt → 70°C
j	-	$NaBH_4$, MeOH, CH_2Cl_2
k	-	Ac_2O, pyr, DMAP
l	48%	$AlMe_3$, CH_2Cl_2, –78°C → 0°C
m	-	hv, air, Et_2O
n	-	BuLi, TMEDA, then MeLi

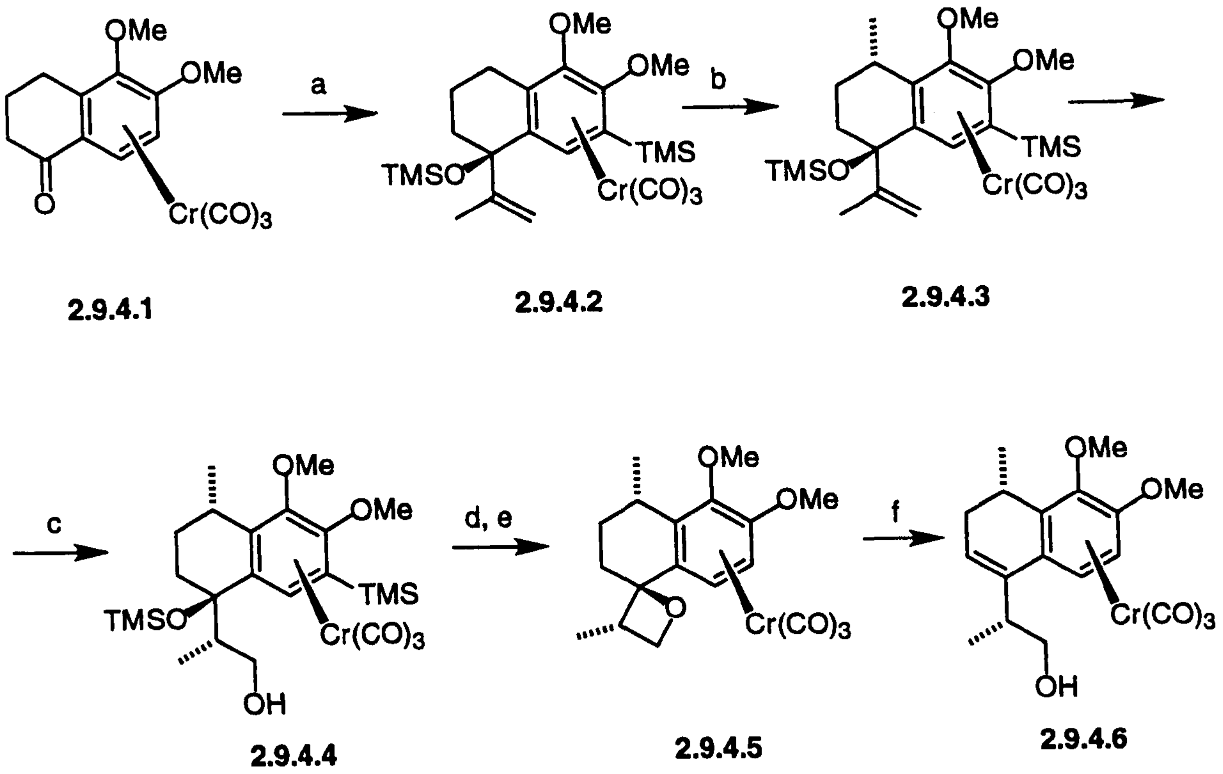
A modification of this procedure[26] allowed the synthesis of **2.9.3.3**, an advanced precursor with an unsaturated butylidene side chain (scheme **2.9.3**). Stereoselective vinylation of **2.9.2.1** and attachment of the carbonyl side chain of **2.9.3.2** were effected in a fashion similar to that used in their preceding paper. A novel radical addition to the chromium-complexed aromatic ring led to **2.9.3.3** as a single diasteroisomer after loss of methanol upon aromatisation.

Scheme **2.9.3.**


TMS
OMe
OMe
(OC)3Cr
TMS
2.9.2.1
BuLi, THF, HMPA
−55°C → 0°C
then BrCH=CMe2
Ni(0), THF
−78°C → 0°C
55%
TMS
OMe
OMe
TMS
Cr(CO)3
2.9.3.1
(a) BuLi, THF, HMPT
−55°C → 0°C
then CH2=C(TMS)COMe
−78°C → 0°C
(b) 2 N HCl
(c) TBAF, THF, 55%
COMe
OMe
OMe
Cr(CO)3
2.9.3.2
SmI2, THF
HMPA, 51%
HO
OMe
Cr(CO)3
2.9.3.3

A different protocol, again based on the same overall strategy, was employed[27] for the synthesis of functionalised tetrahydronaphthalene derivative **2.9.4.6** (scheme **2.9.4**). The well-precedented introduction of the two side chains starting from **2.9.4.1** led to unsaturated **2.9.4.3** as a single isomer. Stereoselective hydroboration of the terminal double bond proved another advantage of the arene-Cr complexes. As only one face of the molecule is strongly hindered, the free rotation of the side chain is restrained and the borane attacks the π system from the most accessible side. A number of hydride sources were examined for the opening of the oxetane **2.9.4.5** to yield the corresponding tetrahydronaphthalene system but the elimination product **2.9.4.6** was obtained instead.

Scheme **2.9.4.**

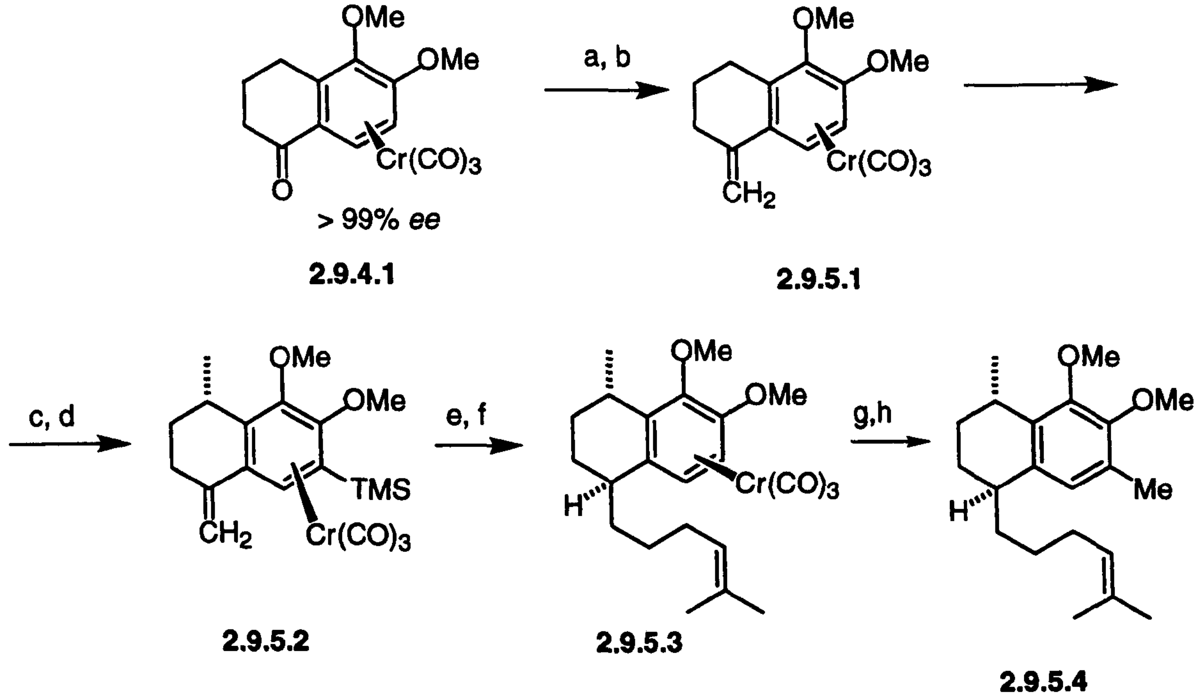


Yields, reagents and conditions :

(a)	75%	Isopropenyl lithium, THF, –70°C → 0°C, then TMSCl, –30°C → 0°C
(b)	87%	BuLi, THF, HMPA, –35°C → 0°C, then MeI, THF, –20°C → 0°C
(c)	52%	(i) BH_3•SMe_2, THF, 28°C; (ii) H_2O, 0°C; (iii) H_2O_2, NaOH
(d)	-	*p*-TsCl, Pyr
(e)	63%	TBAF, THF
(f)	50%	BF_3•OEt

The latest approach to secopseudopterosins *via* arene Cr-(CO)3 complexes was published by the same group in 1997[28]. The approach is based on the consideration that attack of an organolithium reagent on the exocyclic double bond of complex **2.9.5.2** (scheme **2.9.5**) followed by diastereoselective protonation from the least hindered face should afford preferentially a *trans* product. **2.9.5.3** was obtained with very good diastereoselectivity (10:1) following this protocol. The synthesis of secopseudopterosins aglycone analogue **2.9.5.4** was achieved in a straightforward manner and with high yield. Introduction of the remaining stereocenter on the side chain, however, remains a major untackled issue in this approach.

Scheme **2.9.5**

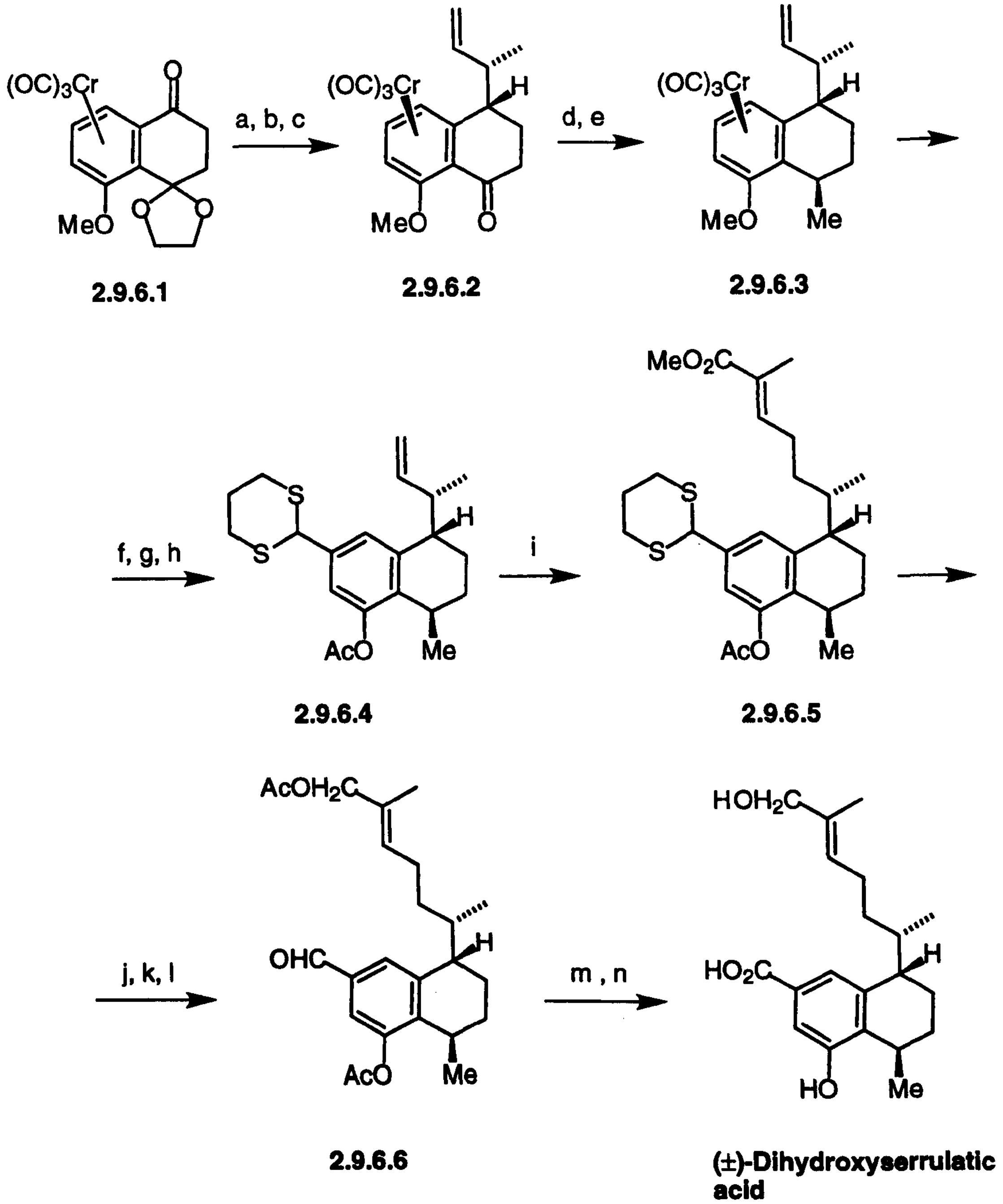

OMe
OMe
Cr(CO)3
O
> 99% *ee*
2.9.4.1
a, b
OMe
OMe
Cr(CO)3
CH2
2.9.5.1
c, d
OMe
OMe
TMS
CH2
Cr(CO)3
2.9.5.2
e, f
OMe
OMe
Cr(CO)3
H
2.9.5.3
g,h
OMe
OMe
Me
H
2.9.5.4

Yields, reagents and conditions:

(a)	-	$TMSCH_2CeCl_2$, THF, −75°C- rt
(b)	85%	KH, THF
(c)	-	BuLi, THF, −78°C, then TMSCl
(d)	-	BuLi, THF/HMPT, −50 → 0°C then MeI, −30°C
(e)	90%	homoprenyllithium, THF, −60 → 0°C then HCl
-	-	10:1 mixture of isomers
(f)	75%	TBAF, THF, H_2O, then chromatography
(g)	94%	BuLi, THF, −70 → −40 °C, then MeI
(h)	98%	hν, air

The use of chiral Cr-arene complexes appears to be an interesting approach to the system but so far only the synthesis of analogues of the natural pseudopterosins and helioporins has been achieved. Also noteworthy is the total synthesis of (+)-dihydroxyserrulatic acid by Uemura and coworkers[29], the first to employ Cr-arene complexes to control stereochemical issues. Their synthesis is shown in scheme **2.9.6.** Unsaturated side chain of **2.9.6.2** was introduced *via* stereoselective reaction of the corresponding stabilised benzylic cation with (*E*)-crotyltrimethylsilane. Nucleophilic attack and ionic hydrogenolysis yielded methylated tetralin **2.9.6.3** as a single isomer.

Scheme **2.9.6.**


(OC)3Cr
MeO
a, b, c
(OC)3Cr
H
MeO
O
d, e
(OC)3Cr
H
MeO
Me
f, g, h
S
S
H
AcO
Me
i
MeO2C
S
S
H
AcO
Me
j, k, l
AcOH2C
OHC
H
AcO
Me
m , n
HOH2C
HO2C
H
HO
Me

2.9.6.1 **2.9.6.2** **2.9.6.3**

2.9.6.4 **2.9.6.5**

2.9.6.6 **(±)-Dihydroxyserrulatic acid**

Yields, reagents and conditions :

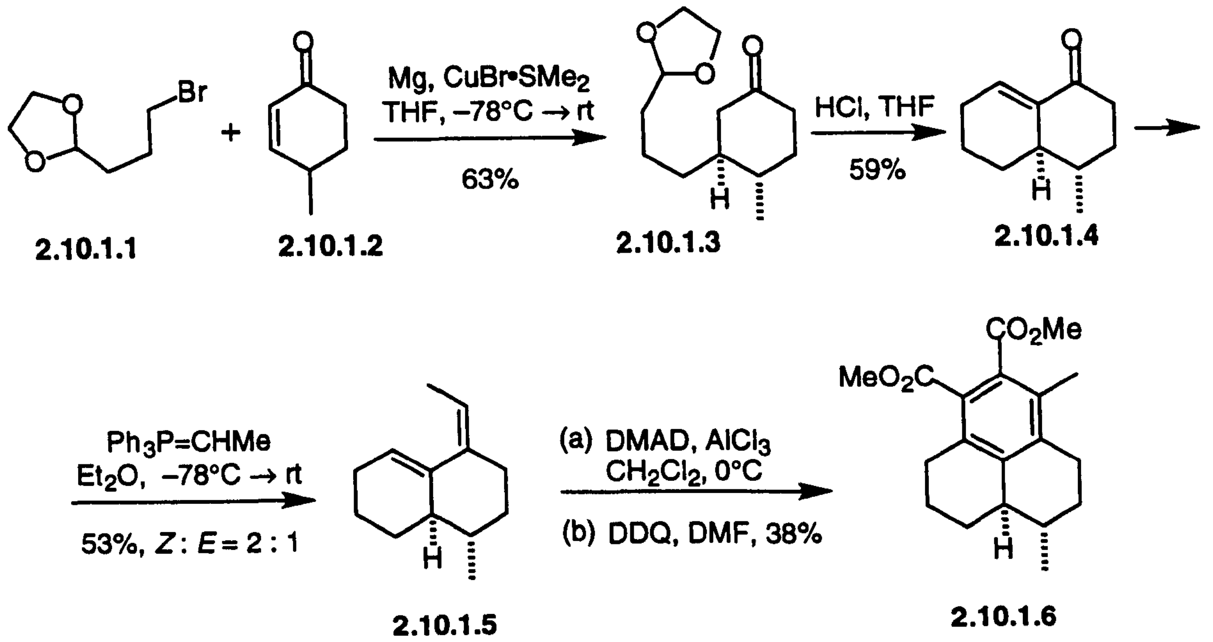
a	95%	$LiAlH_4$	i	77%	9-BBN, then $PdCl_2(dppf)$, K_2CO_3
b	98%	Ac_2O, Pyr			*E*-methyl-β-bromomethacrylate
c	72%	(*E*)-$MeCH=CHCH_2SiMe_3$	j	90%	DIBAL-H, CH_2Cl_2
		$BF_3 \bullet OEt_2$	k	98%	Ac_2O, Pyr
d	60%	MeLi	l	69%	HgO, $BF_3 \bullet OEt_2$, H_2O
e	-	Et_3SiH, CF_3CO_2H	m	85%	NaCN, MnO_2, MeOH, AcOH
f	50%	2-Lithio-1,3-dithiane, then I_2	n	60%	NaOH, MeOH, H_2O
g	95%	EtSH, NaH, DMF			
h	96%	Ac_2O, Pyr			

Introduction of the remaining benzylic C1 unit *via* aromatic nucleophilic addition and extension of the side chain followed by minor transformations yielded (±)-dihydroxyserrulatic acid in 13 steps from the complexed tetralin **2.9.6.1.**

2.10 The Frejd studies towards pseudopterosin A.

A synthetic approach to pseudopterosin A was published by Frejd *et al*[30] in 1996. The functionalised aromatic ring was built through Diels-Alder cycloaddition between dimethylacetylenedicarboxylate (DMAD) and the suitable diene **2.10.1.5** (scheme **2.10.1**) followed by aromatisation.

Scheme **2.10.1.**


Br
+
Mg, CuBr•SMe$_2$
THF, –78°C → rt
63%
H
HCl, THF
59%
H
2.10.1.1
2.10.1.2
2.10.1.3
2.10.1.4
Ph$_3$P=CHMe
Et$_2$O, –78°C → rt
53%, Z : E = 2 : 1
H
(a) DMAD, AlCl$_3$
CH$_2$Cl$_2$, 0°C
(b) DDQ, DMF, 38%
CO$_2$Me
MeO$_2$C
H
2.10.1.5
2.10.1.6

Although this route is simple and straightforward, the lack of enantioselectivity and stereocontrol in the formation of the diene makes it unsatisfactory in its present shape.

2.11 Conclusions.

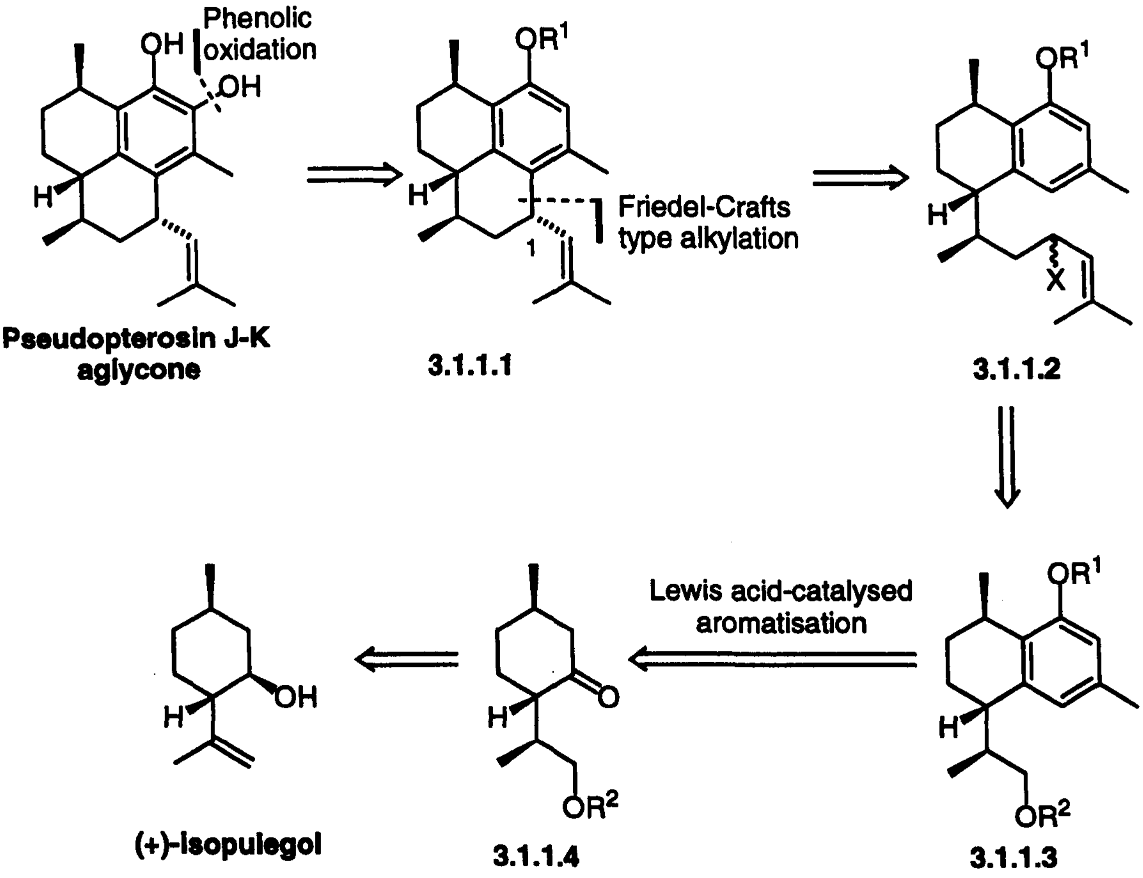
The wealth of total syntheses and approaches to analogues of pseudopterosins show the keen interest of researchers in these compounds. Despite the biological importance of these natural products, however, none of the published routes is sufficiently concise and stereoselective to make it suitable for the synthesis of large quantities of final compounds. Stereocontrol and introduction of the correct functionalities on the aromatic ring appear the major obstacles encountered to date.

Chapter 3
The Kocienski group approach.

3.1 Retrosynthetic analysis.

Studies towards pseudopterosins in Professor P. J. Kocienski's group were carried out by Dr. S. Gill and Dr. A. Kohler starting in 1987. The retrosynthetic analysis for this approach (scheme **3.1.1**) started from the oxidation of phenol **3.1.1.1** to the natural product aglycone in the last stage of the synthesis to avoid problems with the instability of the target. It was predicted that the center at C1 of pseudopterosin could be introduced with stereocontrol using a Friedel-Crafts type alkylation of the electron-rich oxygenated aromatic ring.

Scheme **3.1.1**


Phenolic oxidation
OH
OH
H
Pseudopterosin J-K aglycone
OR1
H
1
Friedel-Crafts type alkylation
3.1.1.1
OR1
H
X
3.1.1.2
OR1
H
OR2
3.1.1.3
Lewis acid-catalysed aromatisation
H
O
OR2
3.1.1.4
OH
H
(+)-Isopulegol

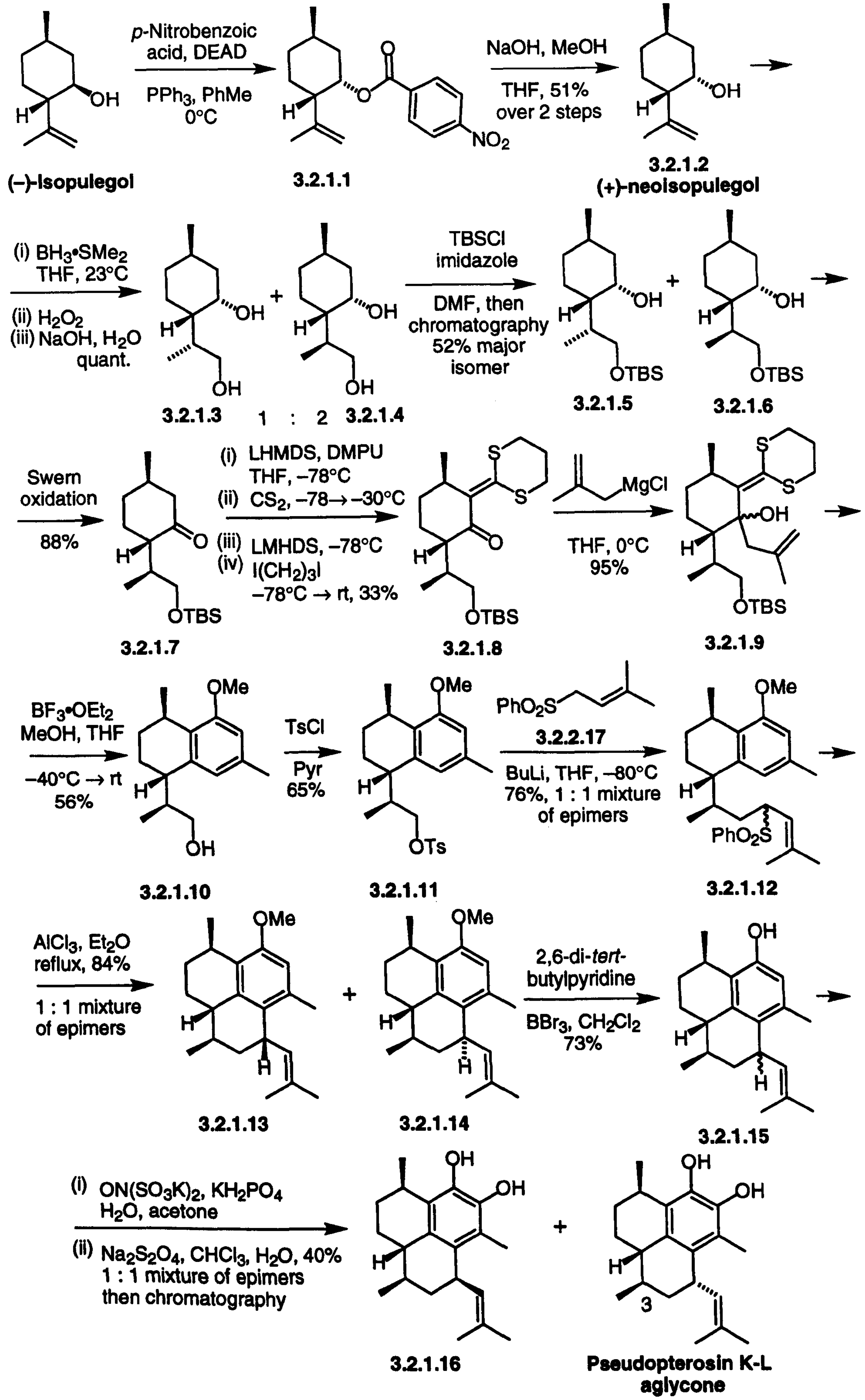
For the pivotal intermediate **3.1.1.3** a non-aromatic precursor was chosen, anticipating that the anisole ring with the desired substitution pattern could be built *via* a protocol published by Dieter *et al*[31]. Following this strategy, two stereocenters of the final target could be derived from commercially available (–)-isopulegol and the remaining two would be ensured exploiting substrate control.

3.2.1 The first Kocienski group approach.

Scheme **3.2.1** depicts the first approach to pseudopterosins K and L aglycone, presented in 1994 after extensive studies[32]. The synthesis started with chromatographic separation of (–)-isopulegol from the commercial mixture of isomers (mainly the desired compound and neoisopulegol in 3:2 ratio). Direct hydroboration of the monoterpene yielded the 1,4-diol with the undesired configuration at the C3 stereocenter of pseudopterosins. Inversion of the secondary alcohol of isopulegol had then to be performed under Mitsunobu conditions. After easy cleavage of the *p*-nitrobenzoic ester, hydroboration of the newly formed neoisopulegol (**3.2.1.2**) yielded a mixture of diols **3.2.1.3** and **3.2.1.4** in a 2:1 ratio in favour of the desired diastereoisomer. Despite several attempts varying conditions and reagents, this ratio could not be improved and the isomers had to be separated by chromatography after selective protection of the primary hydroxy group as TBS ether. Swern oxidation provided ketone **3.2.1.8**, the starting material for the aromatisation procedure which will be described in detail in chapter 5. Synthesis of the unstable cyclic α-oxoketene dithioacetal **3.2.1.8** proved a capricious reaction and was achieved with unsatisfactory yield (33% at best) and with formation of a number of side products which made purification extremely difficult. Aromatisation was then achieved after 1,2-addition of methallyl magnesium chloride and treatment of unstable **3.2.1.9** with $BF_3 \cdot OEt_2$ in the presence of MeOH. Reaction of analogous acyclic dithioacetals led exclusively to the formation of thioanisole products and conversion of these substrates to the oxygenated analogues proved lengthy and unpractical.

After tosylation of **3.2.1.10**, allylic sulfone **3.2.1.12** was obtained as a 1:1 mixture of epimers after alkylation with the lithium anion derived from 3-methyl-1-phenylsulphonylbut-2-ene (**3.2.1.17**). Closure of ring C of pseudopterosins was then achieved in good yield upon treatment of **3.2.1.12** with $AlCl_3$ in Et_2O at reflux, although a 1:1 mixture of inseparable diastereoisomers was formed.

Scheme **3.2.1**.


p-Nitrobenzoic acid, DEAD
PPh3, PhMe
0°C
(–)-Isopulegol
3.2.1.1
NO2
NaOH, MeOH
THF, 51% over 2 steps
3.2.1.2
(+)-neoisopulegol
(i) BH3•SMe2 THF, 23°C
(ii) H2O2
(iii) NaOH, H2O
quant.
3.2.1.3
1 : 2
3.2.1.4
TBSCl
imidazole
DMF, then chromatography
52% major isomer
OTBS
3.2.1.5
3.2.1.6
Swern oxidation
88%
3.2.1.7
(i) LHMDS, DMPU THF, –78°C
(ii) CS2, –78→–30°C
(iii) LMHDS, –78°C
(iv) I(CH2)3I –78°C → rt, 33%
3.2.1.8
MgCl
THF, 0°C
95%
3.2.1.9
BF3•OEt2
MeOH, THF
–40°C → rt
56%
OMe
3.2.1.10
TsCl
Pyr
65%
OTs
3.2.1.11
PhO2S
3.2.2.17
BuLi, THF, –80°C
76%, 1 : 1 mixture of epimers
3.2.1.12
AlCl3, Et2O
reflux, 84%
1 : 1 mixture of epimers
3.2.1.13
3.2.1.14
2,6-di-tert-butylpyridine
BBr3, CH2Cl2
73%
3.2.1.15
(i) ON(SO3K)2, KH2PO4 H2O, acetone
(ii) Na2S2O4, CHCl3, H2O, 40%
1 : 1 mixture of epimers
then chromatography
3.2.1.16
3
Pseudopterosin K-L aglycone

The final steps of the synthesis were carried out following the procedure reported by McCombie *et al*[19]. After cleavage of the methoxy group to afford free phenol **3.2.1.15**, oxidation with Fremy's salt followed by reduction of the corresponding intermediate quinone to the catechol yielded a 1:1 mixture of pseudopterosin K-L aglycone and its C1 epimer in a disappointing 40% yield. The two diastereoisomers could be partially separated after repeated column chromatography.

3.3 Conclusions.

The first Kocienski group synthesis presented several drawbacks:

- the initial chromatographic separation on commercial isopulegol was costly and not practical;

- Mitsunobu inversion as first step was expensive and purification of the product from triphenylphosphine oxide was troublesome on a large scale;

- poor stereocontrol in the hydroboration of **3.2.1.2** to **3.2.1.3** and **3.2.1.4** led to yet another difficult chromatographic separation and loss of a significant share of the material;

- key formation of cyclic α-oxoketene dithioacetal **3.2.1.8** was achieved in low yields and with poor reproducibility;

- total lack of stereocontrol in the ring C closure step and poor yield in the oxidation step lowered unacceptably the overall efficiency.

With these observations in mind, we set to improve the previously outlined synthesis before investigating an entirely new approach.

Chapter 4

Stereoselective synthesis of the ketone precursor for the benzannulation reaction.

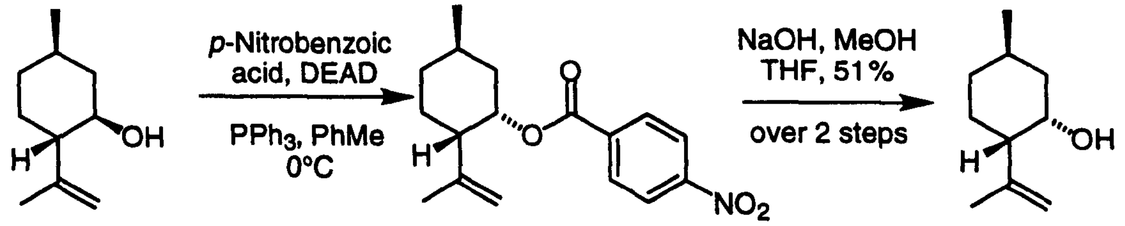
4.1 Introduction.

In this section we report our first attempts to improve the practicability and stereocontrol in the synthesis of diol **3.2.1.4**. We predicted that securing an easy access to significant amounts of this intermediate was essential to be able to investigate the aromatisation step and the stereochemical issues in the later stages of the synthesis.

4.2 Mitsunobu inversion of isopulegol.

We encountered our first difficulties while attempting to scale up the Mitsunobu inversion of isopulegol to neoisopulegol *p*-nitrobenzoate (scheme **4.2.1**). This transformation is smoothly achieved in good yield on medium scale (up to 5 grams of alcohol) while on larger scale it seems to stop after conversion of only 30% of the starting material. Recovery of the product from unreacted triphenylphosphine-DEAD adduct (a thick orange oil) in these conditions is also extremely difficult.

Scheme **4.2.1**.



(−)-Isopulegol

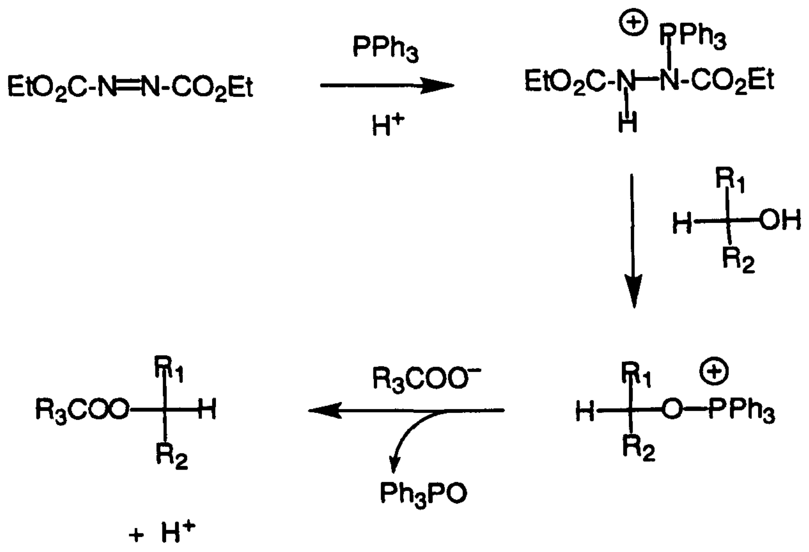
3.2.1.1

3.2.1.2
(+)-neoisopulegol

It is reported [33] that transformation of this kind can be capricious and the yields vary greatly depending on the substrate. The highly exothermic nature of the reaction can be responsible for the irreproducibility on large scale. Changing solvent from toluene to benzene or THF and using 1.8 equivalents of DEAD instead of 1.2 did not improve the yield on large scale. The mechanism for this reaction is reported in scheme **4.2.2**.

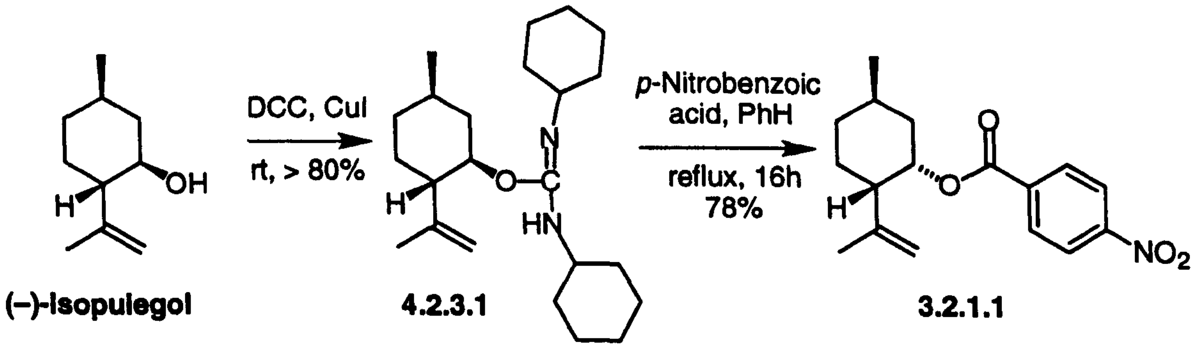
We eventually found a viable alternative in the method reported by Kaulen *et al* [34] in 1987 (scheme **4.2.3**).

Scheme **4.2.2**



Formation of the adduct **4.2.3.1** between isopulegol and dicyclohexylcarbodiimide (DCC) in presence of Cu(I) was followed by reaction with *p*-nitrobenzoic acid to provide crystalline ester **3.2.1.1** in good overall yield (> 72%).

Scheme **4.2.3.**



This inversion could be reproduced on up to 15 g scale but initial chromatographical separation of commercial isopulegol was still necessary.

4.3 Hydroboration of isopulegol and neoisopulegol.

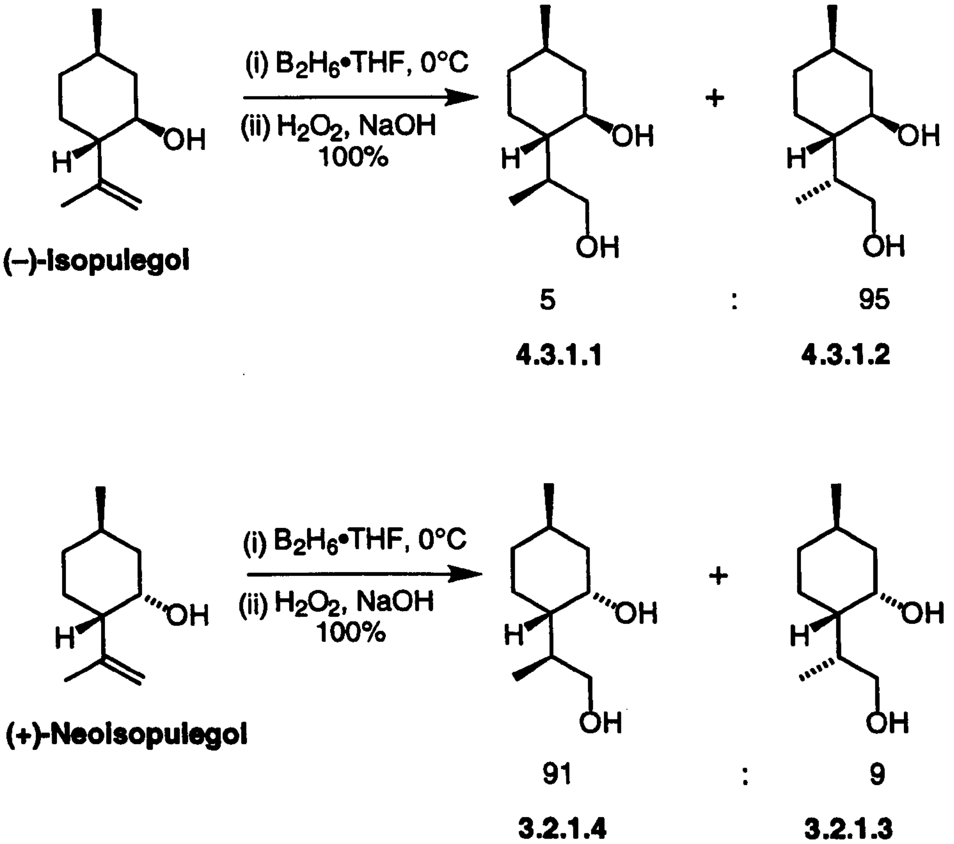
Lack of stereocontrol in the hydroboration step was still the major problem in the first steps of the synthesis.

Hydroboration of isopulegol and neoisopulegol was first reported by Schulte-Elte and Ohloff in 1967[35]. Direct hydroboration of (+)-isopulegol (scheme **4.3.1**) leads to diols **4.3.1.1** and **4.3.1.2** in 5:95 ratio.

(scheme **4.3.1**) leads to diols **4.3.1.1** and **4.3.1.2** in 5:95 ratio. Unfortunately, the major product has the wrong relative configuration for our final target.

Reaction of (–)-neoisopulegol under the same conditions reportedly led to a mixture of **3.2.1.4** and **3.2.1.3** in 91:9 ratio. In this case, the isomer with relative configuration suitable for the synthesis of pseudopterosins is obtained as the major component.

Scheme **4.3.1.**

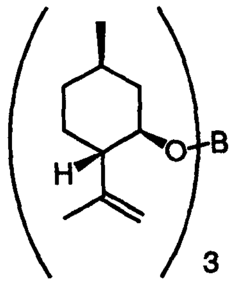


Schulte-Elte and Ohloff investigated the mechanism and the origins of selectivity conducting the hydroboration of the preformed trialkylboronic ester of isopulegol (scheme **4.3.2**). As the same ratio of diastereoisomers was obtained, they inferred that **4.3.2.1** was the intermediate in the hydroboration of isopulegol. This experiment suggested the postulated mechanism reported in scheme **4.3.2**.

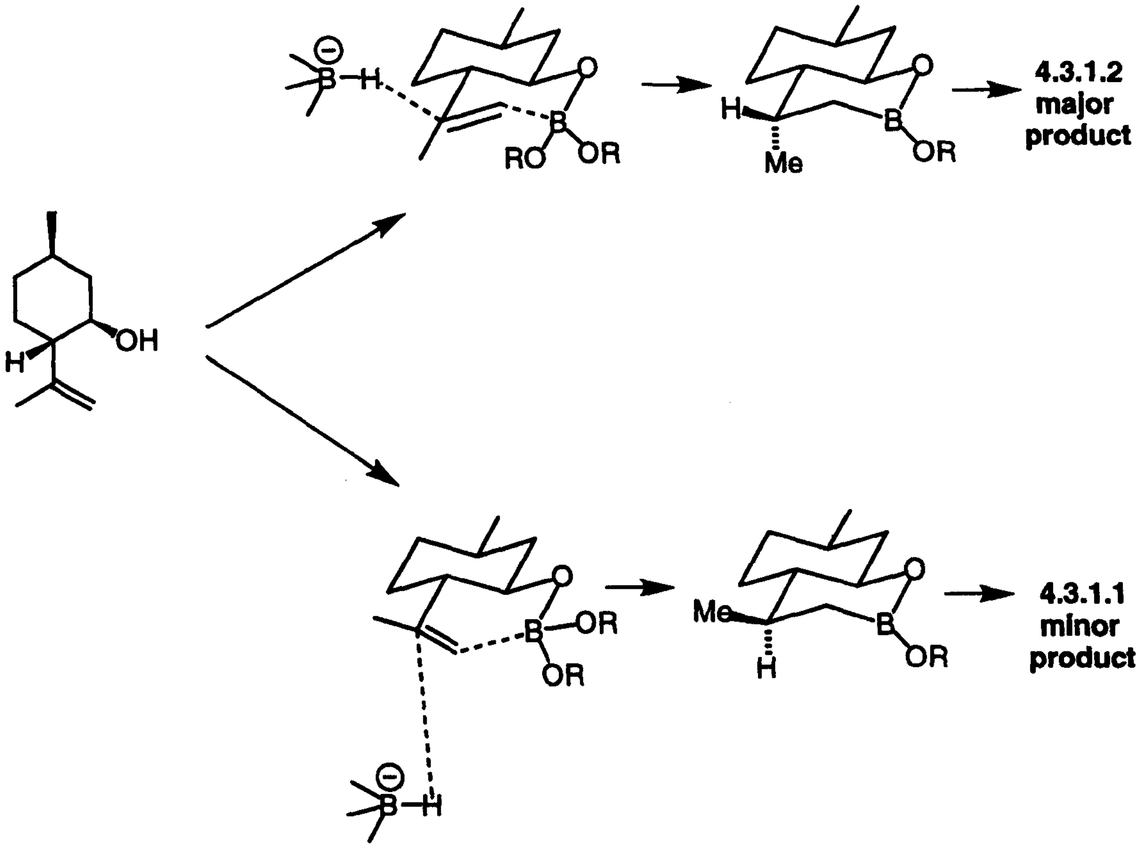
In our hands, the selectivity reported in the original paper could never be reproduced and the best ratio obtained was 2.5:1 in favour of desired **3.2.1.4**. Our first attempts to improve this far from ideal situation involved the screening of different hydroborating agents and reaction conditions.

neoisopulegol the results were disappointing. The best obtained ratio was 2 :1 in favour of **3.2.1** and changing reaction conditions (different temperatures, times and order of addition of reagents) or using $BH_3 \bullet SMe_2$ could not improve the stereochemical outcome. When 9-BBN was employed, the undesired isomer **3.2.1.3** was obtained as the predominant product (3:1 ratio).

Scheme **4.3.2**.



4.3.2.1


B
H
O
B
RO
OR
H
Me
B
OR
4.3.1.2
major
product
OH
H
O
B
OR
OR
B
H
Me
H
B
OR
4.3.1.1
minor
product

For the first part of our studies, we agreed to employ this route, even with poor stereocontrol, keeping in mind that further studies had to be undertaken after investigating the challenging problems in the later stages of the synthesis.

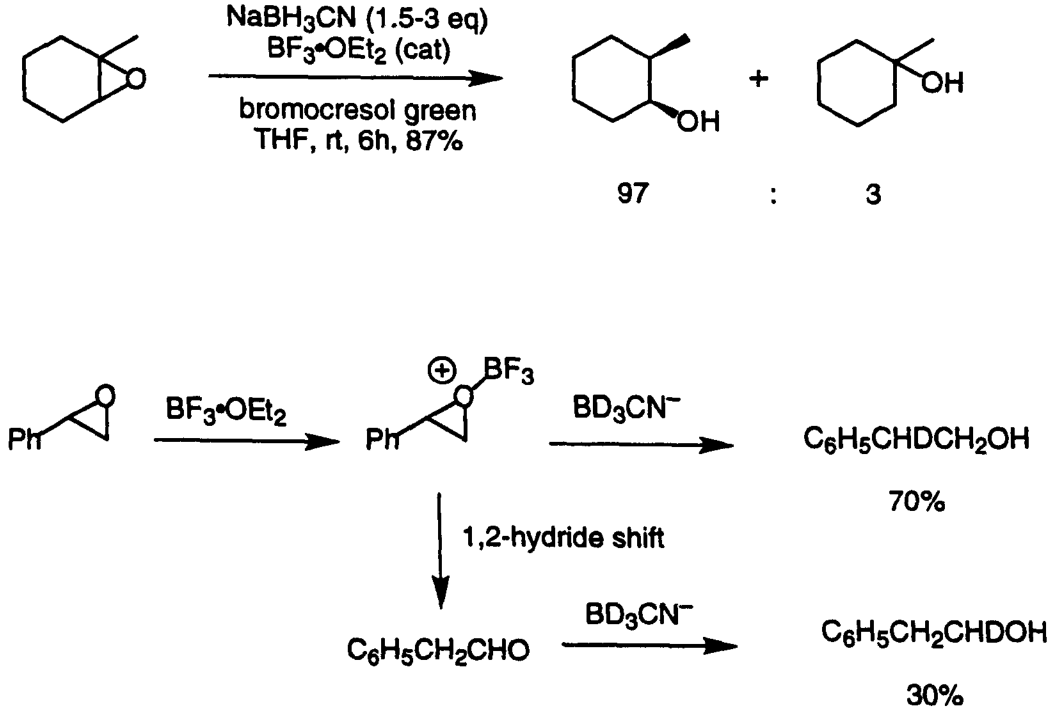
4.4 Synthesis of diol 3.2.1.4 *via* epoxidation - NaBH3CN oxirane opening sequence.

The decisive improvement came through when we investigated the possibility of introducing the C3 center *via* a sequence of directed epoxidation and regioselective oxirane ring opening.

The substrate-directed epoxidation of homoallylic alcohols is a well-studied transformation[37] and we were confident that some degree of stereoselectivity was achievable after some experimentation. For the overall sequence to be stereoselective, however, S_N2-type delivery of an hydride to the most hindered terminus of the epoxide would have to take place with high regio- and stereocontrol.

Various methods for the regiospecific opening of terminal epoxides are known[38-41] but many of these procedures are not stereoselective. Hutchins *et al.* [42]reported in 1981 an elegant method for this kind of tranformations (scheme **4.4.1**).

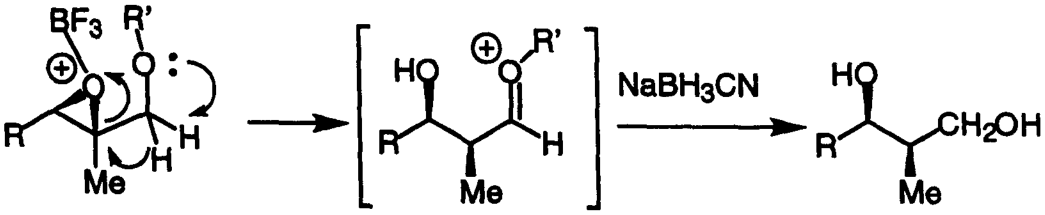
Scheme **4.4.1**.


NaBH3CN (1.5-3 eq)
BF3•OEt2 (cat)
bromocresol green
THF, rt, 6h, 87%
O
OH
+
OH
97
:
3
Ph
O
BF3•OEt2
⊕
BF3
Ph
BD3CN⁻
C6H5CHDCH2OH
70%
1,2-hydride shift
C6H5CH2CHO
BD3CN⁻
C6H5CH2CHDOH
30%

Various epoxides were transformed into the corresponding primary alcohols in good yields by treatment with $NaBH_3CN$ in THF solution buffered between pH 3.8 and 5.4 by addition of $BF_3 \cdot OEt_2$. The reaction was subsequently employed in the synthesis of natural products[43-45] with stereoselectivity but no mechanism was ever proposed for it. $BF_3 \cdot OEt_2$ can stereoselectivity but no mechanism was ever proposed for it. $BF_3 \bullet OEt_2$ can coordinate to the oxygen atom of the epoxide weakening the C-O bond and creating partial carbocationic character prior to S_N2-type attack. Complexation with Lewis acid is essential for the reaction to proceed as epoxides are inert to treatment with $NaBH_3CN$ in basic or neutral media. Whatever the complexing Lewis acid, the final effect is stabilisation of the incipient positive charge on the most substituted position[46]. Delivery of the hydride takes place with complete inversion of configuration. Therefore opening of the epoxide does not occur *via* a completely cationic intermediate, which would lead to scrambling of stereochemistry. This pathway is partially supported by investigations made by the authors of the original paper[42]. They reported that treatment of styrene oxide with $NaBD_3CN$ afforded mainly 2-deuterio-2-phenylethanol, alongside with 30% of alcohol carrying deuterium at the C1 position.

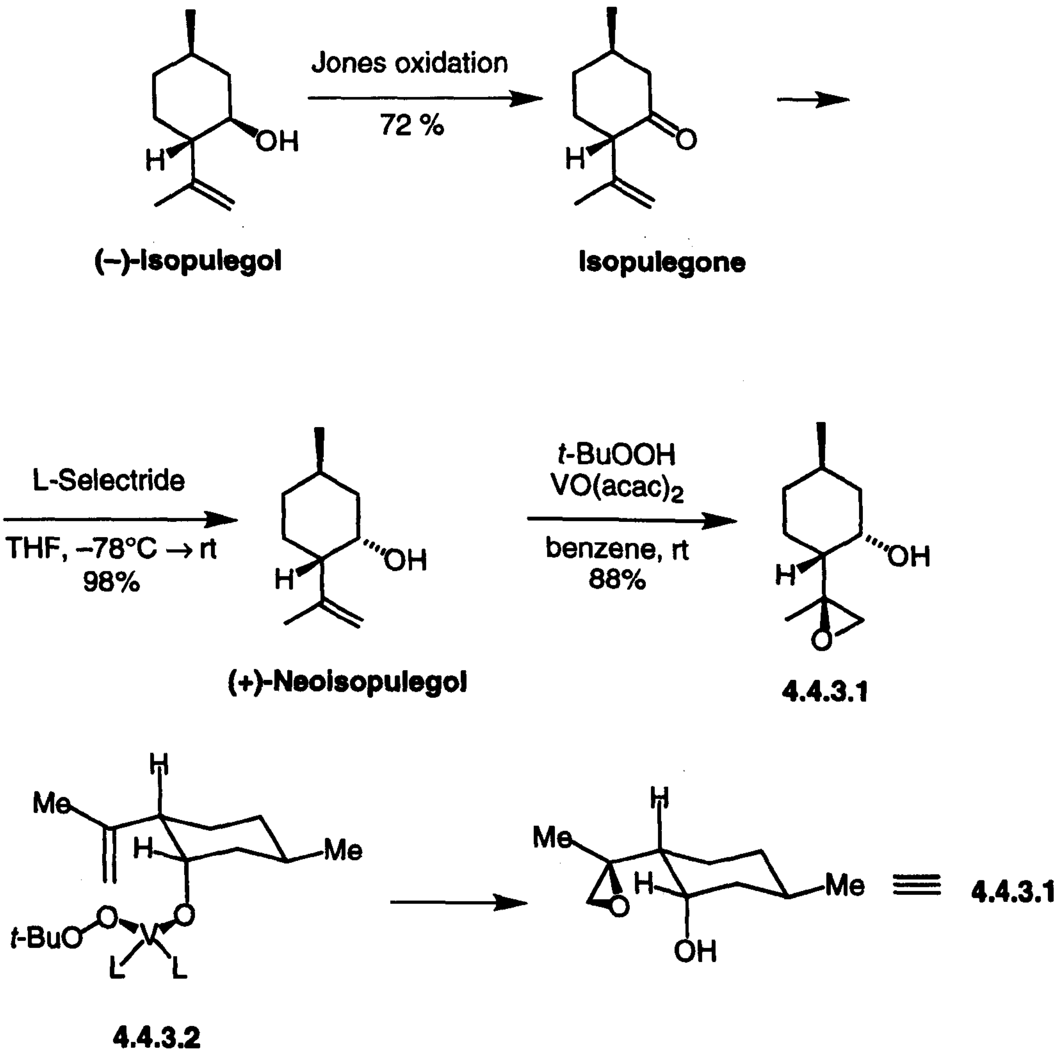
The minor product arose from an alternative pathway. After complexation of the oxirane with $BF_3 \bullet OEt_2$, an intramolecular 1,2-hydride shift can occur with inversion of configuration at the most substituted center to generate the corresponding aldehyde (scheme **4.4.2**). The carbonyl group is then reduced by the external hydride source. Transformations of this kind have been more recently reported[47-50]. Both pathways are plausible, although the 1,2-hydride shift seems the most commonly accepted for non-benzylic epoxides. This could be proved by treating the allylic substrates with $NaBD_3CN$ but none of the authors reported experiments using deuterium labelling.

Scheme **4.4.2.**



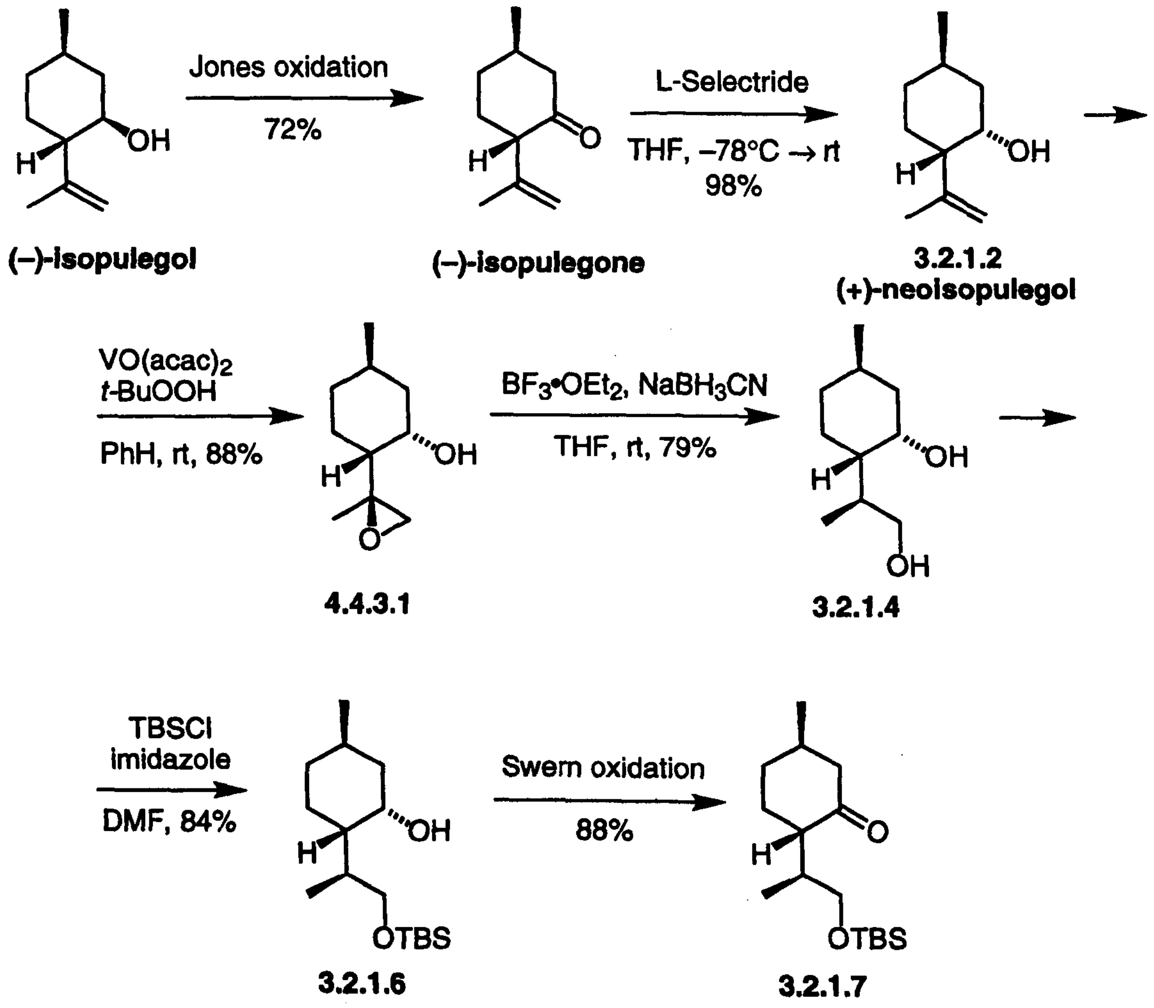
We then set to apply these conditions to our substrate but direct epoxidation of isopulegol with MCPBA or $VO(acac)_2$ gave a 1:1 mixture of diastereoisomers. Friedrich and Bohlmann[51] reported in 1988 that hydroxyl-directed epoxidation of neoisopulegol with $VO(acac)_2$ leads to **4.4.3.1** (Scheme **4.4.3**) with complete stereocontrol. This intermediate displays the correct stereochemistry to be transformed into diol **3.2.1.4** after reductive opening with inversion. The proposed[37] intermediate for this epoxidation is **4.4.3.2** and the axial position of the hydroxyl group is crucial for stereodifferentiation. We could reproduce this transformation with excellent stereocontrol (no trace of isomers by ^1H and ^{13}C NMR) to obtain crystalline **4.4.3.1** in 88% yield.

Scheme **4.4.3.**


Jones oxidation
72 %
OH
H
O
(−)-Isopulegol
Isopulegone
L-Selectride
THF, −78°C → rt
98%
t-BuOOH
VO(acac)2
benzene, rt
88%
(+)-Neoisopulegol
4.4.3.1
Me
H
t-BuO
O
V
L
4.4.3.2
≡ 4.4.3.1

Although transformation of **4.4.3.1** into **3.2.1.4** was never reported before, we were pleased to find that the ring opening takes place smoothly under Lewis-acid catalysis to produce the corresponding diol as a single stereoisomer. Comparison with ^1H and ^{13}C NMR spectra of the product with those of previously obtained **3.2.1.4** and **3.2.1.3** proved that the reduction occurs with complete inversion to afford the desired stereoisomer in high yield. Besides, Friedrich and Bohlmann reported in the same paper an ingenious and straightforward inversion of isopulegol to neoisopulegol. A two-step sequence of oxidation to isopulegone and reduction to the axial overall yield. This route is ideal to our purposes as it allows us to start from commercial isopulegol (containing up to 33% of neoisopulegol) without the initial chromatography separation on large scale. The final sequence is shown in scheme **4.4.3**.

Scheme **4.4.3.**


Jones oxidation
72%
L-Selectride
THF, –78°C → rt
98%
VO(acac)2
t-BuOOH
PhH, rt, 88%
BF3•OEt2, NaBH3CN
THF, rt, 79%
TBSCl
imidazole
DMF, 84%
Swern oxidation
88%
OH
H
O
OTBS
(–)-isopulegol
(–)-isopulegone
3.2.1.2
(+)-neoisopulegol
4.4.3.1
3.2.1.4
3.2.1.6
3.2.1.7

Selective protection of the primary hydroxyl group of **3.2.1.4** as its TBS ether and Swern oxidation to ketone **3.2.1.7** easily completed the synthesis of our precursor for the construction of the aromatic ring.

4.5 Conclusions.

After extensive experimentation, it became clear that approach to diol **3.2.1.4** *via* hydroboration was inadequate because of lack of stereocontrol. However, our completely reshaped route involving epoxidation and reduction with $NaBH_3CN$ in presence of BF_3•OEt_2 provided excellent selectivity and good yield. These results and the alcohol inversion *via* reduction of isopulegone allowed us to synthesise efficiently up to 4 g of ketone **3.2.1.7**.

Chapter 5

Transformations of ketones into phenols and catechols.

5.1 Introduction.

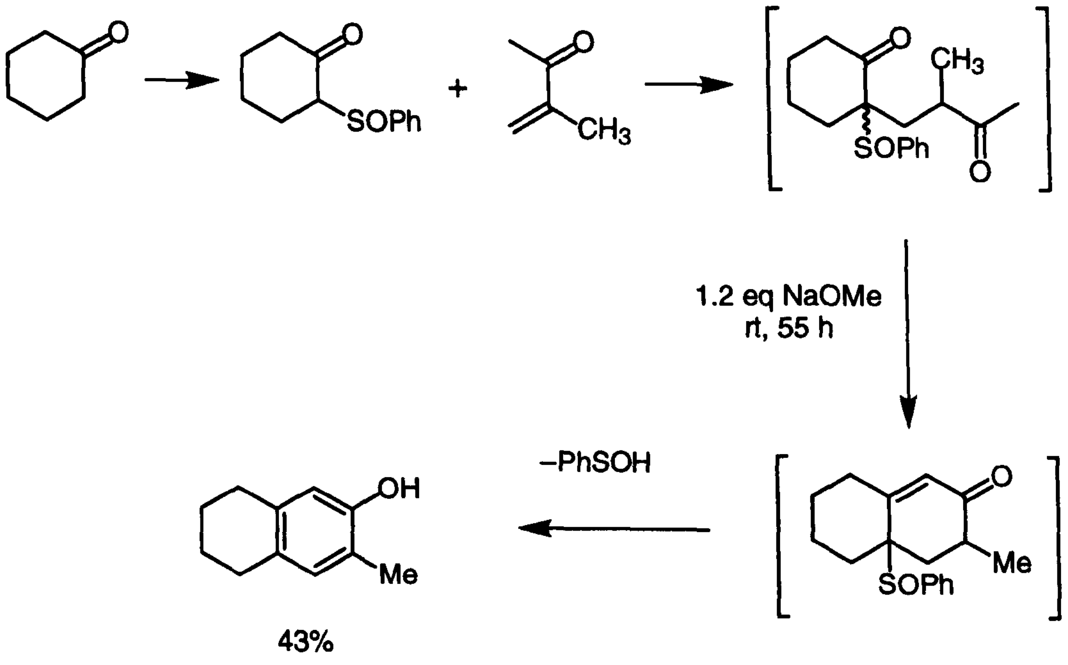
Building an aromatic ring with the substitution pattern suitable for pseudopterosins is a significant synthetic challenge. Although various methods for the construction of aromatic rings starting from aliphatic ketones have been reported, a standard procedure for the transformation has not been established to date. Some of these methods have already been reported in chapter 2. The approaches to pseudopterosins by Buszeck[22], Kozikowski[3] and Jung[23] exploit Diels-Alder cycloadditions to build the functionalised phenols while Corey[16] and Broka[14] used a sequence of Michael addition on terpenoid precursors followed by aromatisation.

A short review of the methods for this transformation reported in literature is presented in the following paragraphs.

5.2 Annulations based on Michael and aldol additions.

Boger and Mulican[52] reported a mild and versatile phenol formation in 1980. The process is basically a Robinson annulation of β-ketosulfoxide with a vinyl ketone, followed by mild elimination of phenylsulfenic acid to give the corresponding phenol (scheme **5.2.1**).

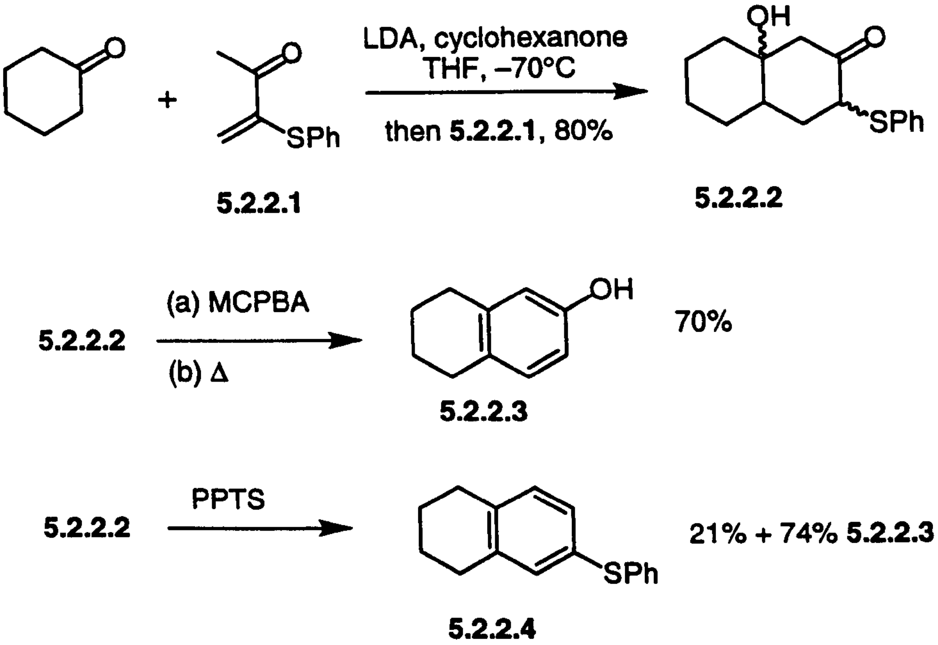
Scheme **5.2.1**.



The entire transformation proceeds under extremely mild conditions (0-25°C) to give the aromatic ring without isolation of any of the intermediates albeit yields are generally modest (30-58%) and only cyclohexanone was used as the ketone partner.

Another approach to fused phenols based on Michael addition was developed by Takaki *et al*[53,54]. Robinson annulation of various ketones with enone **5.2.2.1** (scheme **5.2.2**) led to bicyclic **5.2.2.2**. Oxidation of the thioether group followed by thermal elimination led to the corresponding bicyclic phenols whereas treatment of **5.2.2.2** with PPTS yielded the thioanisoles deriving from double dehydration in minor yield.

Scheme **5.2.2**.

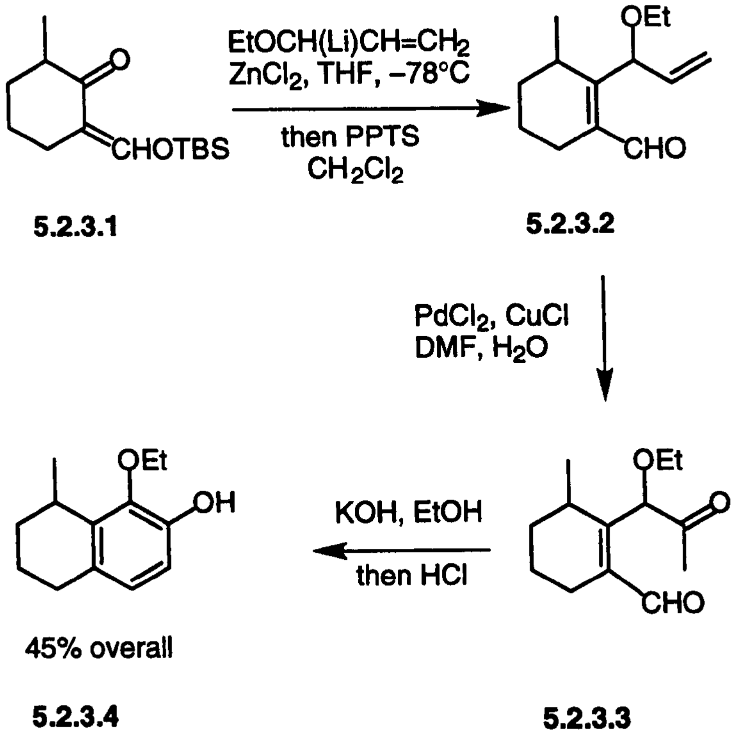


A similar method was published by Corey and Palam in 1997[55] for the synthesis of monoterpene catechols but in this case the rather lengthy sequence (5 steps) and low overall yield make it unpractical.

An interesting synthesis of catechol monoethers from hydroxymethylene ketones was devised by Tius *et al* [56,57]. Their rather elaborate route began with 1,2-addition of a allylic lithium reagent to α-keto enol ether **5.2.3.1** (scheme **5.2.3**), followed by conversion to the corresponding enal (**5.2.3.2**) by treatment with anhydrous pyridinium tosylate and Pd-catalysed oxidation of the terminal olefin to ketone. One-pot intramolecular aldol reaction and dehydration led cleanly to the desired catechol ether in acceptable overall yield (43 - 78%).

However, the transformation proved to be capricious, mainly due to the concurrent formation of β-hydroxy aldehydes rather than unsaturated aldehydes in the desilylation step and to poor stereoselectivity in the Pd-catalysed oxidation.

Scheme **5.2.3**.

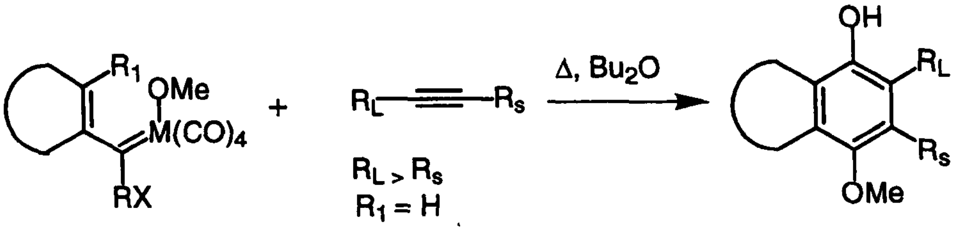

CHOTBS
EtOCH(Li)CH=CH2
ZnCl2, THF, -78°C
then PPTS
CH2Cl2
OEt
CHO
5.2.3.1
5.2.3.2
PdCl2, CuCl
DMF, H2O
OEt
OH
KOH, EtOH
then HCl
OEt
CHO
45% overall
5.2.3.4
5.2.3.3

Unfortunately, all these annulations are unsuitable to our purpose as the C-O bonds would be formed on the same side as the starting carbonyl group, thus with the unsuitable regiochemistry for pseudopterosins starting from ketone **3.2.1.7**. A route *via* Michael addition could be employed starting from other monoterpene units, such as dihydrocarvone.

5.3 Synthesis of catechols *via* chromium carbene complexes.

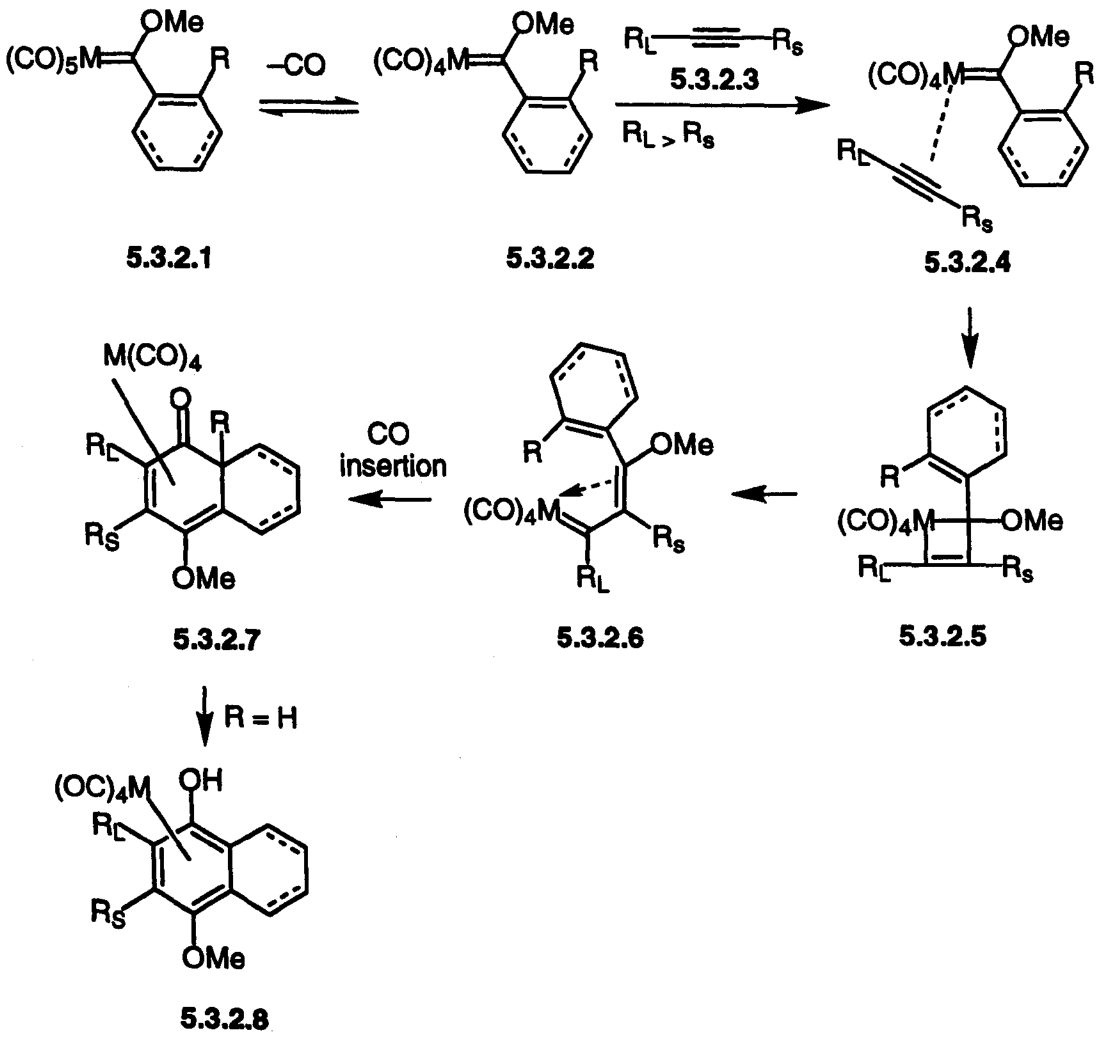
The benzannulation of Fischer-type chromium carbene complexes with alkynes, known as the Dötz annulation (scheme **5.3.1**), is a well known reaction with vast utility [58,59].

Scheme **5.3.1**.


R1
OMe
M(CO)4
RX
+
RL
Rs
RL > Rs
R1 = H
Δ, Bu2O
OH
RL
Rs
OMe

The commonly accepted mechanism for this [3+2+1] addition is illustrated in scheme **5.3.2**. The first postulated step is the reversible dissociation of a carbon monoxide ligand from the metal center, followed by coordination of the alkyne to give **5.3.2.4**. The regioselectivity of the reaction is determined at this step by steric factors. The smallest substituent on asymmetric alkynes places itself next to the carbene ligand in the most stable conformer of the alkyne complex **5.3.2.4** and finally occupies the position α to the methoxy group in the hydroquinone monoether. A carbon-carbon bond is then formed between the carbene and one terminus of the triple bond to give **5.3.2.5**. Electrocyclic ring opening of the highly strained **5.3.2.5** leads to vinyl complex **5.3.2.6**.

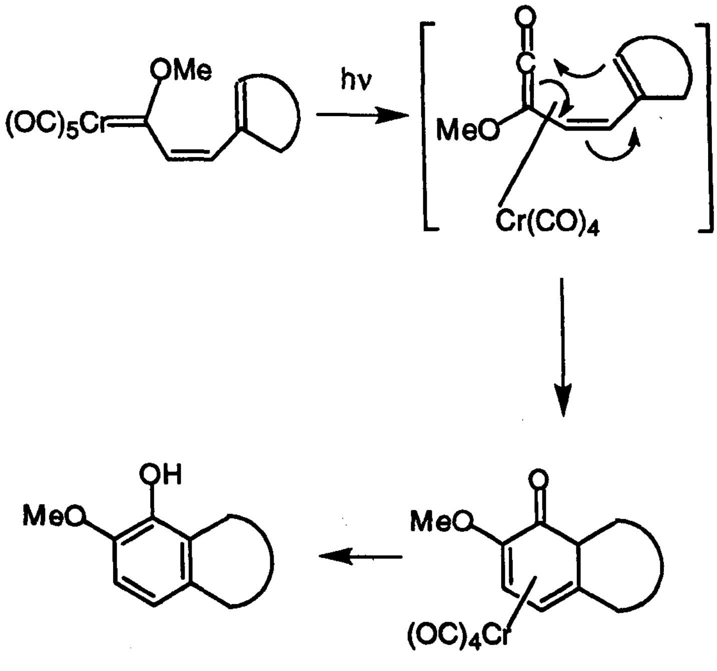
Scheme **5.3.2**.


OMe
(CO)5M
R
-CO
5.3.2.1
OMe
(CO)4M
R
5.3.2.2
RL
Rs
5.3.2.3
RL > Rs
OMe
(CO)4M
R
RL
Rs
5.3.2.4
R
(CO)4M
OMe
RL
Rs
5.3.2.5
R
OMe
(CO)4M
Rs
RL
5.3.2.6
CO
insertion
M(CO)4
O
R
RL
Rs
OMe
5.3.2.7
R = H
(OC)4M
OH
RL
Rs
OMe
5.3.2.8

The benzannulated product **5.3.2.7** is formed either *via* insertion of CO into the vinyl carbene followed by electrocyclic ring closure, as postulated by Dötz, or *via* the mechanism proposed by Casey, in which the order of the two steps is reversed. The final product is generally obtained in good yield and with fair to good regioselectivity. In any example, only aromatic rings with the hydroxy and methoxy substituents in *para* relation are obtained, under both thermal and photochemical conditions.

An alternative route to the synthesis of substituted catechols is the photochemical intramolecular benzannulation of (Z)-dienyl(alkoxy)chromium carbene complexes[60,61] (scheme **5.3.3**). The proposed mechanism proceeds *via* a ketene intermediate which undergoes electrocyclisation to form the aromatic ring in a one-pot process.

Scheme **5.3.3**.

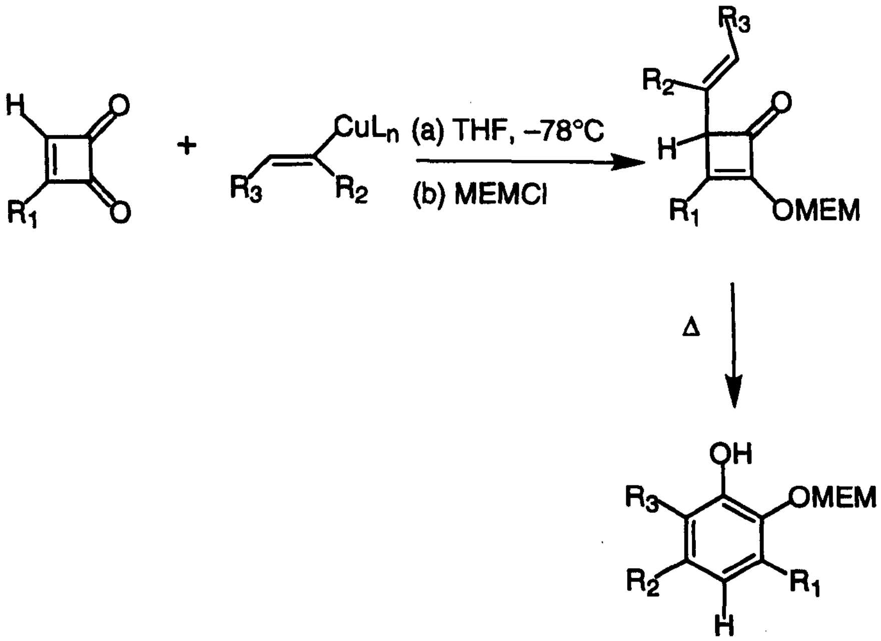


The catechols are generally obtained in good yield (40 - 90%) and excellent regioselectivity but so far only aromatic starting materials have been employed, perhaps due to lack of reactivity when aliphatic dienyl complexes were subject to photolysis.

5.4 Synthesis of substituted catechols *via* conjugated addition of organocopper reagents to cyclobutenediones and thermal rearrangement.

Liebeskind and Gurski reported in 1993 an interesting approach to highly substituted catechol monoethers[62]. A variety of symmetrically and unsymmetrically substituted cyclobutenediones were treated with vinyl-, aryl- and heteroarylcuprates to obtain the corresponding enolates (scheme **5.4.1**). After protection as MEM ether, thermal rearrangement smoothly affords the monoprotected catechols in high yields (64 - 94%).

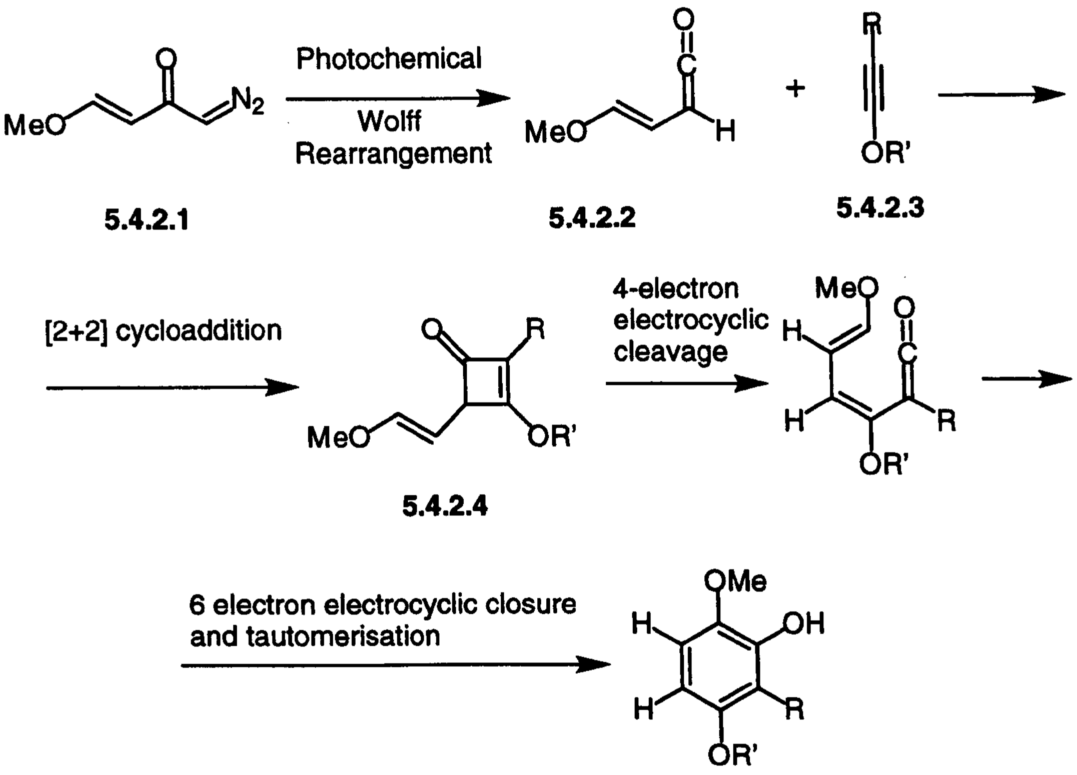
Scheme **5.4.1**.



The recent developments in the synthesis of cyclobutenediones and the very mild conditions of this method make it particularly attractive for large scale synthesis of substituted catechols.

Another method involving cyclobutanones as intermediates had been earlier published by Danheiser *et al*[63,64]. Diazoketone **5.4.2.1** was easily photolised to vinyl ketene **5.4.2.5** which undergoes a cascade of pericyclic reactions to yield the desired benzene 1,2,4-triol derivative with yields around 55%. Despite the remarkable simplicity of this one-pot sequence, the starting α-diazoketones are not readily accessible and the presence of the third hydroxyl group could lead to problems on the route to pseudopterosins.

Scheme **5.4.2.**

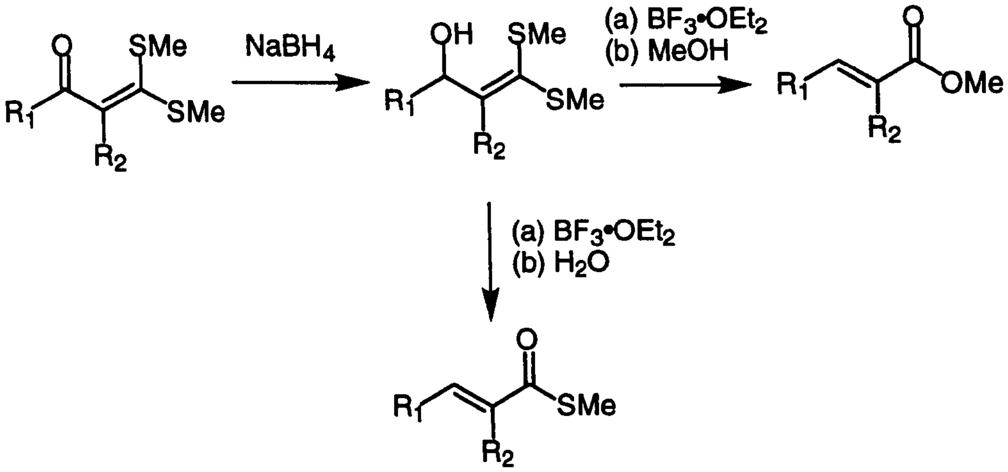

Photochemical
Wolff Rearrangement
[2+2] cycloaddition
4-electron electrocyclic cleavage
6 electron electrocyclic closure and tautomerisation
MeO
N_2
H
R
OR'
OMe
OH

5.4.2.1 **5.4.2.2** **5.4.2.3** **5.4.2.4**

5.5 The Dieter annulation.

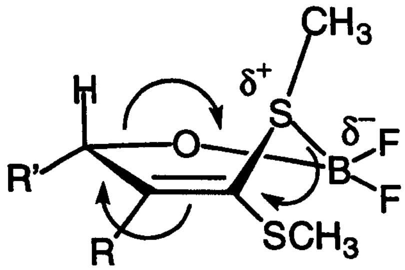
A simple and straightforward method to form aromatic rings from ketones and aldehydes is based on the α-oxoketene dithioacetal chemistry developed by Dieter and coworkers[31,65]. Ketene dithioacetals conjugated to carbonyl groups can be readily prepared by reaction of the corresponding active methylene compound with carbon disulfide in presence of a base followed by alkylation, usually in a one-pot protocol. Further elaboration of the products by reduction, 1,2- or 1,4-nucleophilic addition or deprotonation provides access to a wealth of products including heterocycles, 1,3-enones and thioesters. Junjappa *et al*[66] reported in 1983 that reduction of the ketone functionality of α-oxoketene dithioacetals followed by treatment with Lewis acids in presence of methanol leads cleanly to 1,3-carbonyl transposition with loss of the thioalkyl groups (Scheme **5.5.1**).

Scheme **5.5.1**.



The mechanism proposed by the authors involves coordination of the alcohol oxygen and of one of the sulphur atoms by boron, resulting in a 6-membered boat-like transition state (scheme **5.5.2**).

Scheme **5.5.2**.

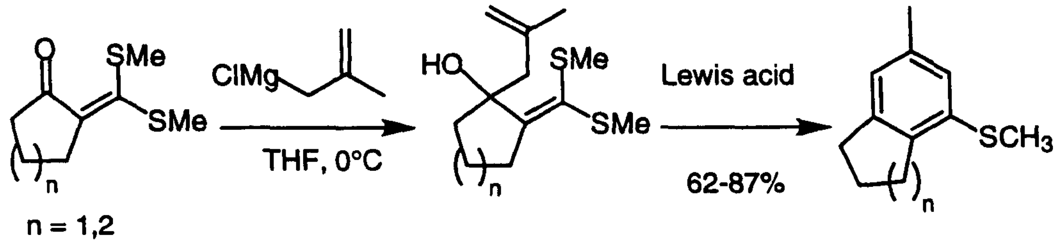


Methanolysis of these intermediates would lead to α,β-unsaturated esters while reactions in presence of water afford thioesters in good yield. Boron-assisted solvolysis of ketene dithioacetals had been previoulsy reported by Corey and Chen[67].

Junjappa[68] and Dieter[69] reported independently in 1984 that 1,2-addition of methallylmagnesium chloride to α-oxoketene dithioacetals followed by treatment of the carbinol with HBF_4 in THF leads to benzannulation reactions instead of 1,3-carbonyl transposition (scheme **5.5.3**). The resulting thioanisole was obtained in good yield, even when different Lewis acids ($HgCl_2$ in CH_3CN, BF_3•OEt_2 in benzene) were employed.

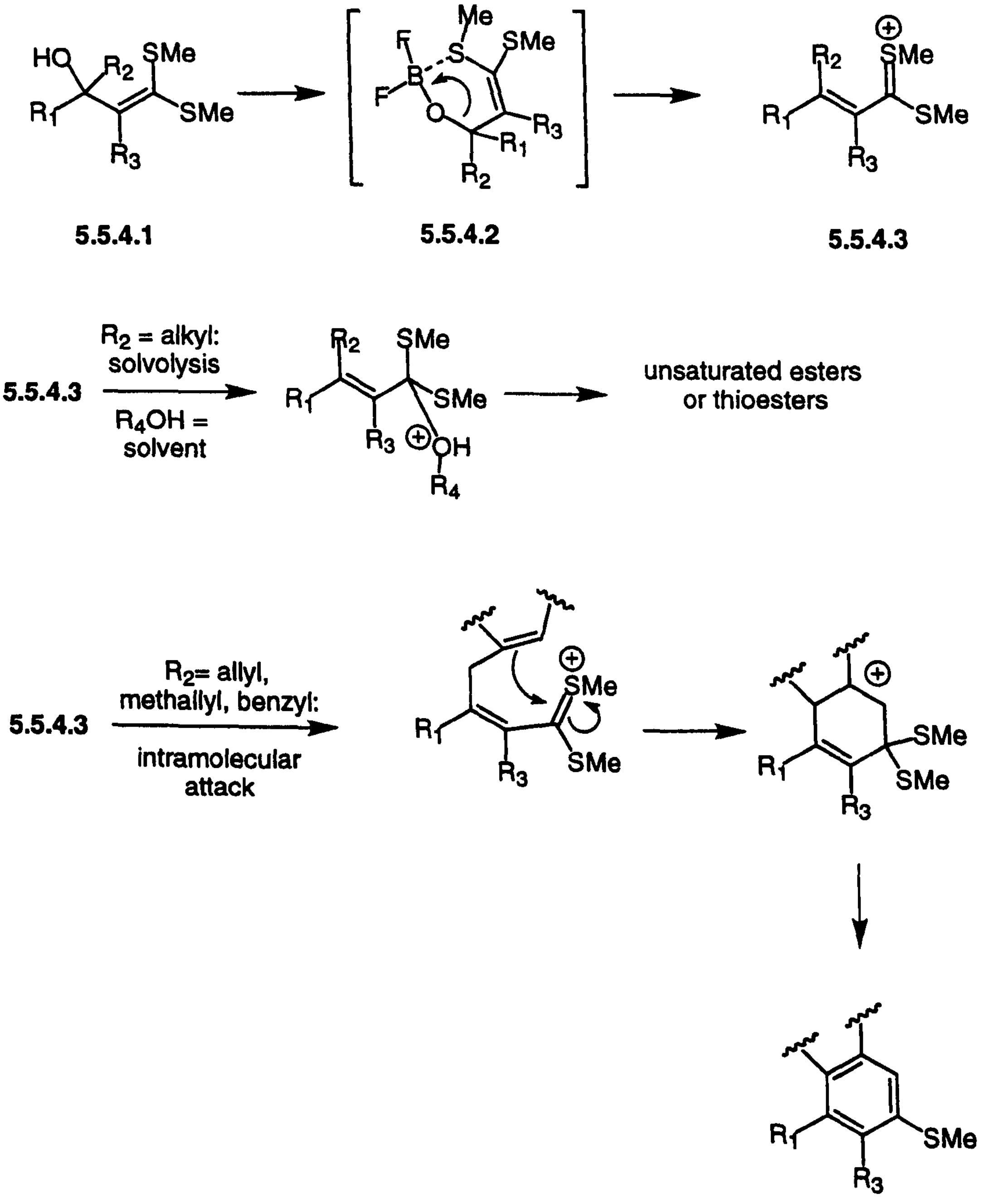
This protocol was then applied to a variety of substrates, although dithioacetals obtained from open-chain ketones led to moderate yields of annulated thiophenols. In all examples only sulphurated arenes were obtained.

Scheme **5.5.3**.


SMe
SMe
n
n = 1,2
ClMg
THF, 0°C
HO
SMe
SMe
n
Lewis acid
62-87%
SCH3
n

The mechanism is likely to proceed *via* a boat-like intermediate, in analogy to the 1,3-carbonyl transposition (scheme **5.5.4**), to form cationic species of type **5.5.4.3**.

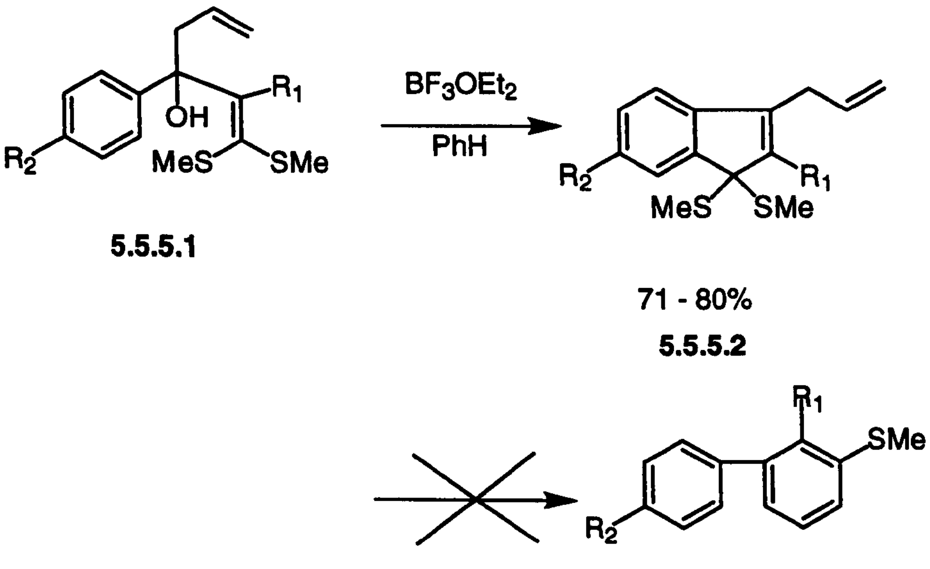
Scheme **5.5.4**.


HO
R2
SMe
R1
SMe
R3
Me
F
S
SMe
B
F
O
R3
R1
R2
R2
SMe
R1
SMe
R3
5.5.4.1
5.5.4.2
5.5.4.3
5.5.4.3
R2 = alkyl:
solvolysis
R4OH =
solvent
R2
SMe
R1
SMe
R3
OH
R4
unsaturated esters
or thioesters
5.5.4.3
R2= allyl,
methallyl, benzyl:
intramolecular
attack
R1
SMe
R3
SMe
R1
SMe
SMe
R3
R1
SMe
R3

The presence of a nucleophilic group (alkene or phenyl) on the side chain and the use of a non-nucleophilic solvent lead to intramolecular attack rather than solvolysis. Loss of an alkylthio group after coordination to the Lewis acid and aromatisation are the driving forces for the process.

The importance of conformational effects on the outcome of this cyclisation was outlined by Junjappa[70] *et al.* Treatment of α-hydroxy dithioketene acetals **5.5.5.1** (scheme **5.5.5**) with $BF_3 \cdot OEt_2$ in benzene afforded the corresponding 3-allyl-1,1-bis(methylthio)-2-alkylindene **5.5.5.2** instead of the benzannulation products **5.5.5.3**.

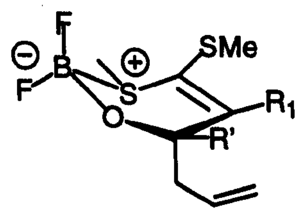
Scheme **5.5.5**.



5.5.5.1

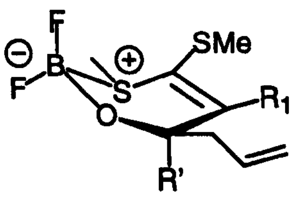
71 - 80%
5.5.5.2

5.5.5.3



5.5.5.4a

$R_1 = H, R' = R_1 = -(CH_2)_n-$



5.5.5.4b

$R' = Ph, R_1 = alkyl$

The authors rationalised this behaviour through the transition state **5.5.5.4a** and **5.5.5.4b**. When the side groups R^1 and R´ have low steric bulk, the alkyl chain occupies preferentially the quasi-axial position to minimise 1,2-steric interaction (**5.5.4.4a**). This conformation promotes interaction between the π system of the alkene and the endocyclic double bond leading to the benzannulation. If R^1 = alkyl and R' is a bulky phenyl group (**5.5.4.4b**) the allylic group is forced into the pseudo-equatorial position, pointing away from the adjacent π system. The aromatic ring then attacks the developing stabilised carbocation on the bismethylthio acetal position and leads to the formation of indene-type products.

This type of cyclisation has been widely exploited by Junjappa and coworkers[71] for the synthesis of alkyl aryl thioethers and heterocycles in generally good yields.

5.6 Conclusions.

Review of the literature concerning the transformation of ketones into phenols and catechols highlights a good number of methods, although most of these are rather lengthy and have low yields or poor selectivity. Synthesis of hydroquinones rather than of catechols is generally favoured and this limits the application to the synthesis of pseudopterosins aglycone.

Work on the Dieter benzannulation and its modifications within Professor Kocienski's group with a view to applying this protocol to the synthesis of pseudopterosins initiated in 1987. The following chapter describes the past studies and our contribution to the project.

Chapter 6

Application of the Dieter aromatisation to the synthesis of pseudopterosin aglycone.

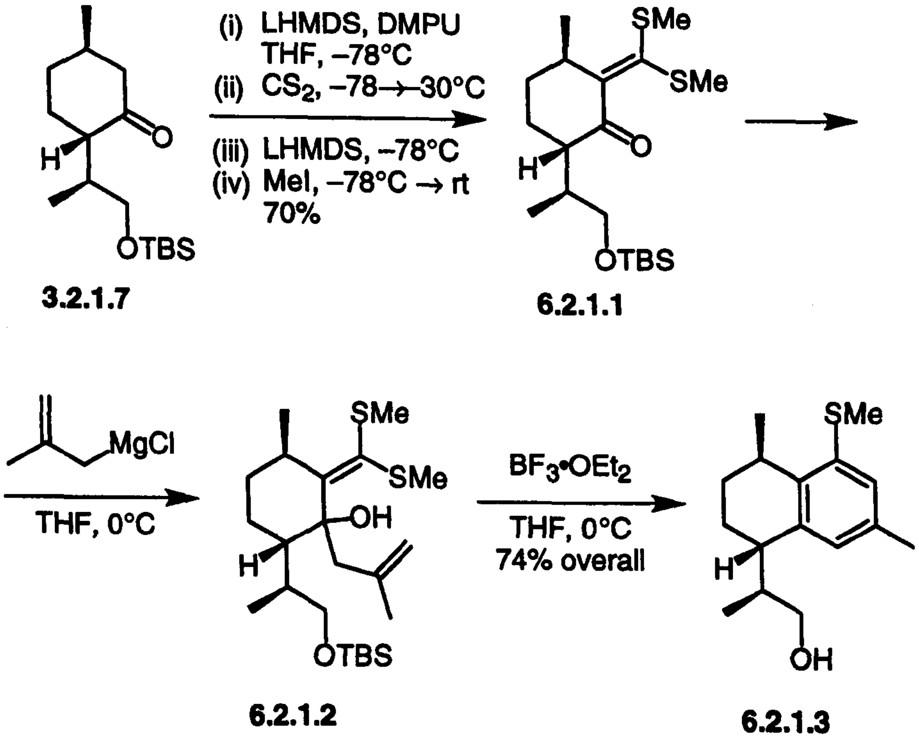
6.1 Introduction.

Progresses in the construction of the pseudopterosins aromatic ring from ketone **3.2.1.7** were reported by Dr. S. Gill and Dr. A. Kohler in their Ph.D. theses[32,72] at the University of Southampton. At the end of these studies, however, the efficiency of this transformation was far from ideal. Formation of the cyclic dithioketene acetal **3.2.1.8** could only be achieved in low yield (< 33%) and resulted in a complex mixture of products. Achieving reproducibility and higher yields in this transformation was our primary target for the overall improvement of the synthesis.

6.2 The previous studies towards pseudopterosins using the Dieter annulation.

Studies concerning the Dieter annulation for the synthesis of pseudopterosins began in 1987. Starting from Dieter's initial report on annulation of pulegone[69] Gill could achieve the synthesis of dithioketene acetal **6.2.1.1** (scheme **6.2.1**) after optimisation of experimental conditions.

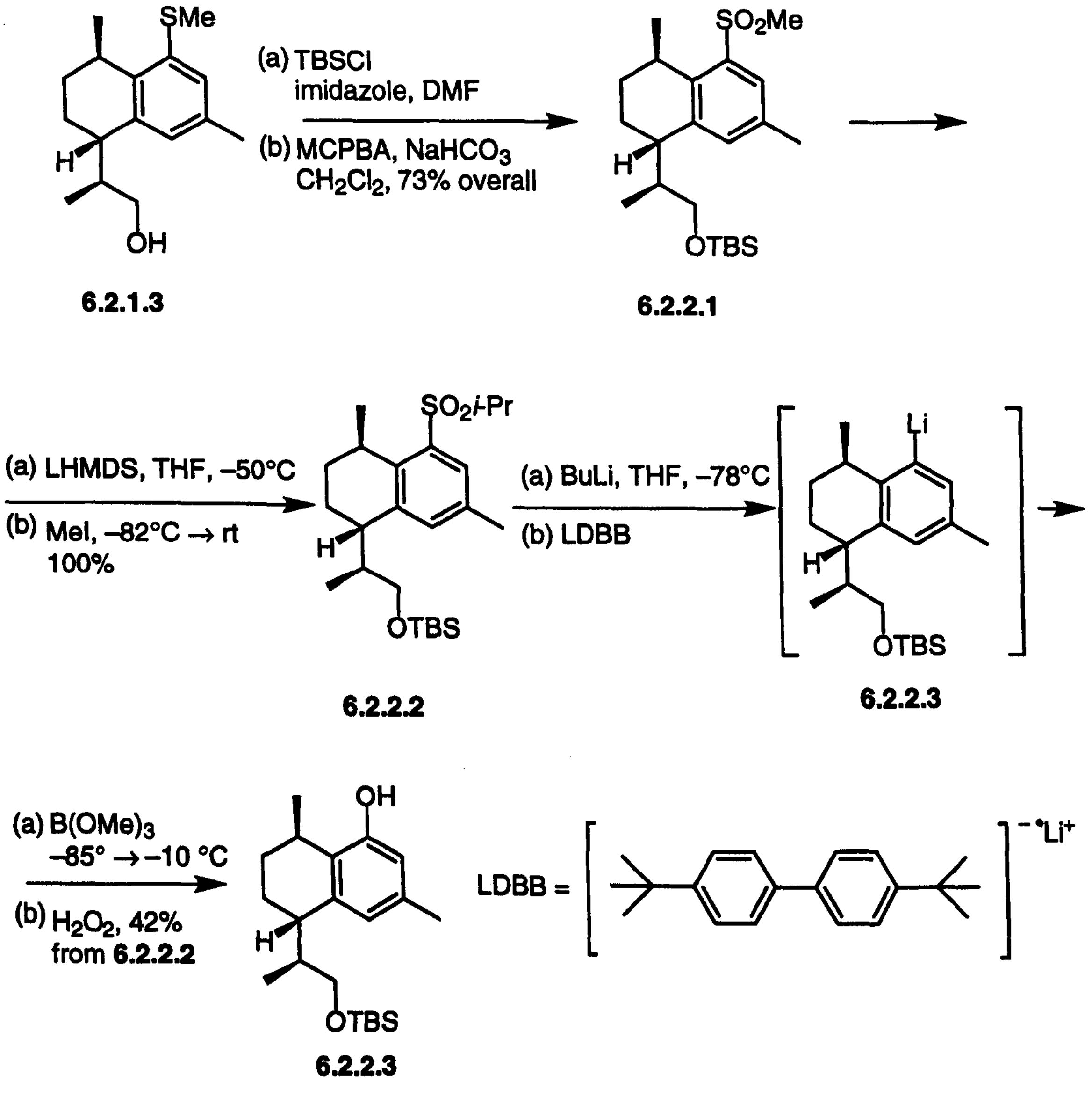
Scheme **6.2.1.**


H
O
OTBS
3.2.1.7
(i) LHMDS, DMPU THF, −78°C
(ii) CS2, −78→−30°C
(iii) LHMDS, −78°C
(iv) MeI, −78°C → rt
70%
SMe
SMe
O
H
OTBS
6.2.1.1
MgCl
THF, 0°C
SMe
SMe
OH
H
OTBS
6.2.1.2
BF3•OEt2
THF, 0°C
74% overall
SMe
H
OH
6.2.1.3

Treatment of **6.2.1.1** with methallylmagnesium chloride in THF yielded the unstable carbinol **6.2.1.2**, which was readily transformed into thioanisole **6.2.1.3** in high overall yield. Formation of hydrogen fluoride from reaction of water produced in the cyclisation and $BF_3 \bullet OEt_2$ resulted in convenient cleavage of the TBS ether in one pot.

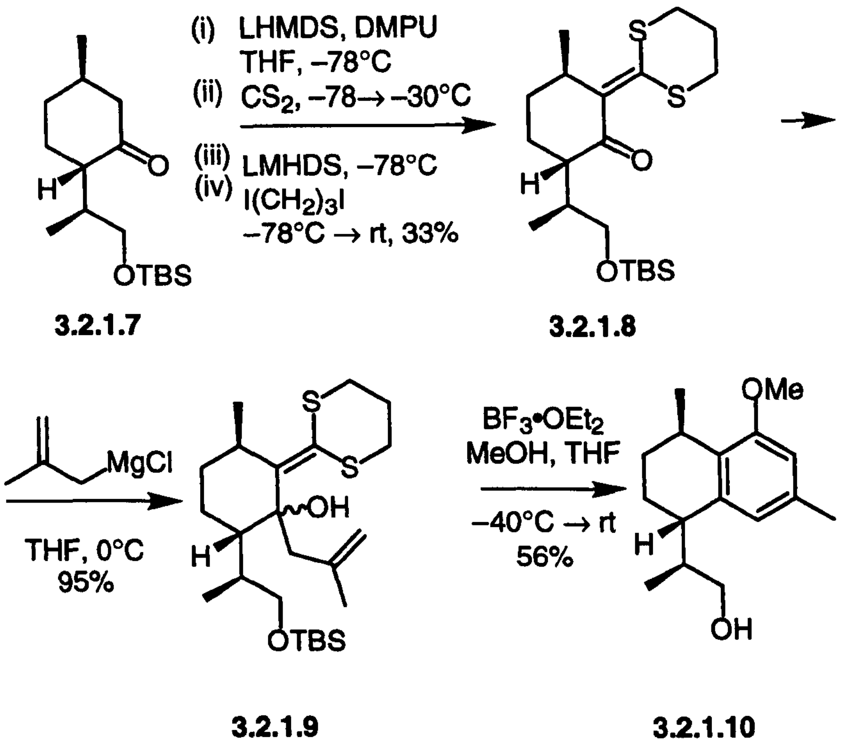
Transformation of the thioanisole into the corresponding oxygenated arene proved to be challenging. A direct approach could not be found despite many attempts and the only viable method was the four-step procedure reported in scheme **6.2.2**. The sequence was rather lengthy and too unreproducible to be of any synthetic use.

Scheme **6.2.2**.


SMe
H
OH
6.2.1.3
(a) TBSCl imidazole, DMF
(b) MCPBA, NaHCO3 CH2Cl2, 73% overall
SO2Me
H
OTBS
6.2.2.1
(a) LHMDS, THF, −50°C
(b) MeI, −82°C → rt 100%
SO2i-Pr
H
OTBS
6.2.2.2
(a) BuLi, THF, −78°C
(b) LDBB
Li
H
OTBS
6.2.2.3
(a) B(OMe)3 −85° → −10 °C
(b) H2O2, 42% from 6.2.2.2
OH
H
OTBS
6.2.2.3
LDBB =
−•Li+

A decisive advance was made by Dr. L. Qun, a visiting researcher in Southampton during 1989/1990. He discovered that employing cyclic dithioacetals and carrying out the reaction in presence of methanol leads to the direct formation of anisoles (scheme **6.2.3**).

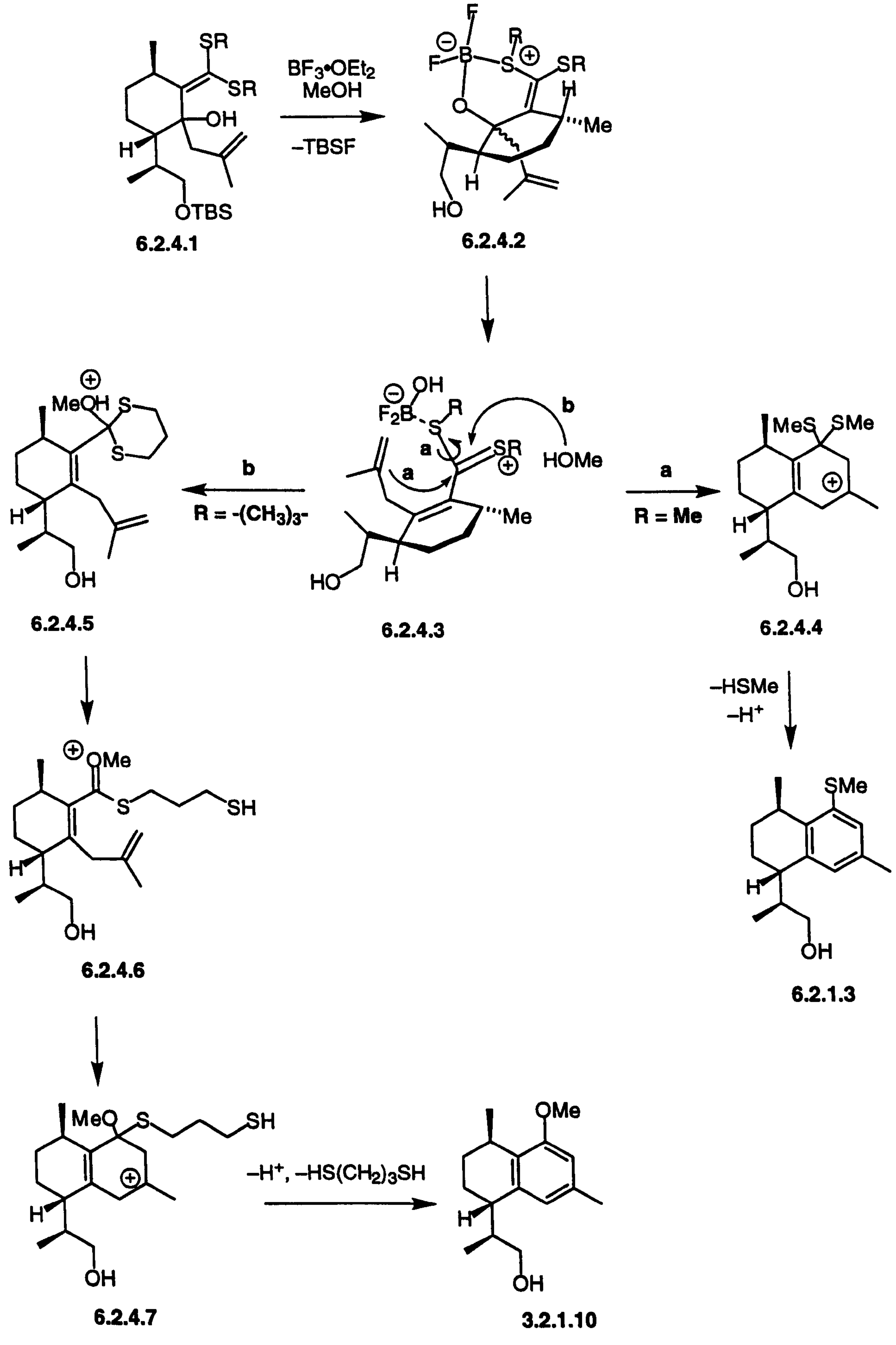
Scheme **6.2.3.**


(i) LHMDS, DMPU
THF, −78°C
(ii) CS2, −78→ −30°C
(iii) LMHDS, −78°C
(iv) I(CH2)3I
−78°C → rt, 33%
OTBS
H
O
S
S
3.2.1.7
3.2.1.8
MgCl
THF, 0°C
95%
OH
BF3•OEt2
MeOH, THF
−40°C → rt
56%
OMe
3.2.1.9
3.2.1.10

The reason why reaction of cyclic acetals afford oxygenated arenes is not completely clear. The studies on conformational effects reported in chapter **5.5** [71] may suggest a tentative explanation (scheme **6.2.4**).

After chelation by the electrophilic boron atom and loss of the tertiary hydroxy, cationic species **6.2.4.3** is rapidly formed. It is likely, however, that the bulky Lewis acid remains in the sphere of coordination of the sulphur atom on the dithioketene acetal moiety. At this stage two situations are possible. If R = methyl, the C-S bond could rotate freely to minimise interaction between the substituents on the sulphur and the alkene on the side chain. This would lead to a rapid nucleophilic attack and formation of the bicyclic dithioacetal **6.2.4.4**, leading ultimately to thioanisoles. In the case of a cyclic acetal, the 1,3-dithiane ring limits the number of conformations that the substituents can adopt. Steric hindrance might disfavour the direct cyclisation and nucleophilic attack from methanol can take place at a competitive rate. Attack by the alkene on the cationic center leads then to anisole **3.2.1.10** after aromatisation.

Scheme **6.2.4**.



BF₃•OEt₂
MeOH
–TBSF
SR
SR
OH
H
OTBS
F
R
SR
Me
HO
HOMe
a
b
R = -(CH₃)₃-
R = Me
MeOH
OH
MeS SMe
–HSMe
–H⁺
SMe
OMe
SH
–H⁺, –HS(CH₂)₃SH

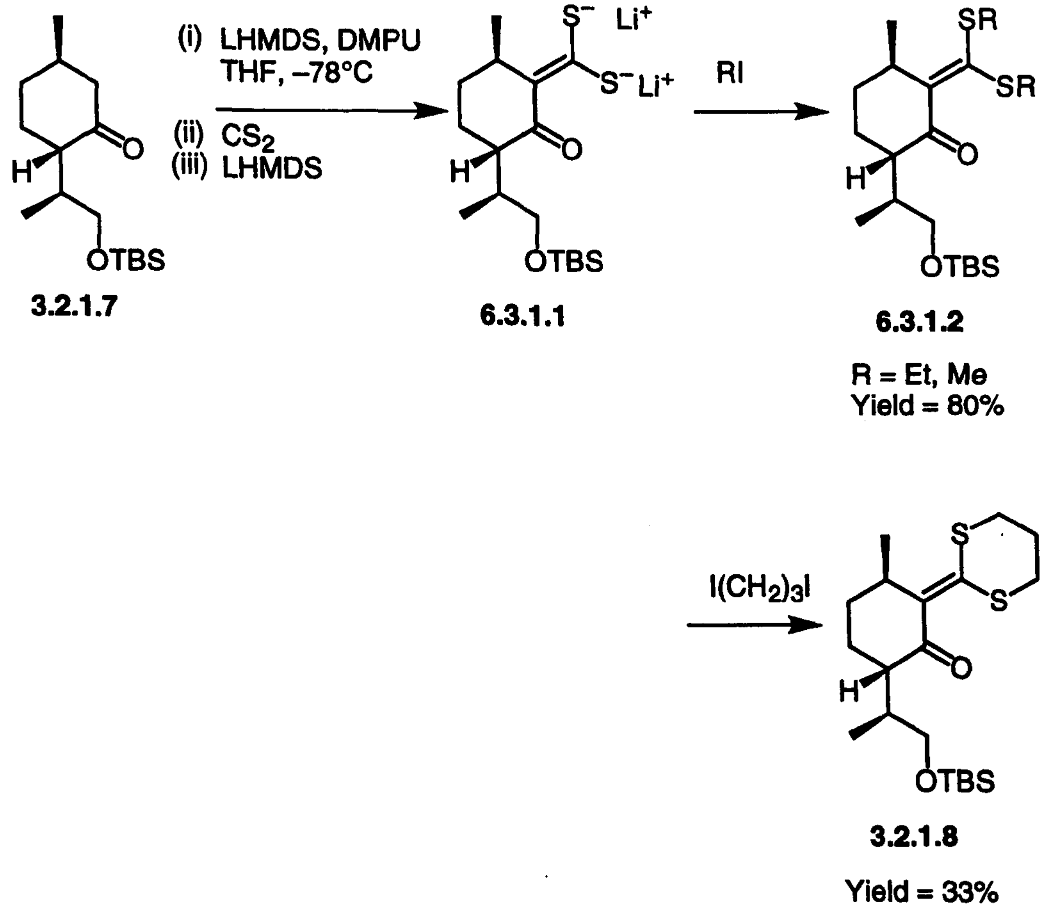
6.2.4.1 **6.2.4.2** **6.2.4.5** **6.2.4.3** **6.2.4.4** **6.2.4.6** **6.2.1.3** **6.2.4.7** **3.2.1.10**

This modification of the Dieter procedure, however, suffered from a major drawback. The synthesis of cyclic dithioketene acetals is scarcely documented and with these substrates Gill and Kohler could not obtain yields greater than 33% with poor reproducibility. Besides, none of the starting material could be recovered. At this stage, this procedure was unsuitable to be used in an efficient multi-step synthesis.

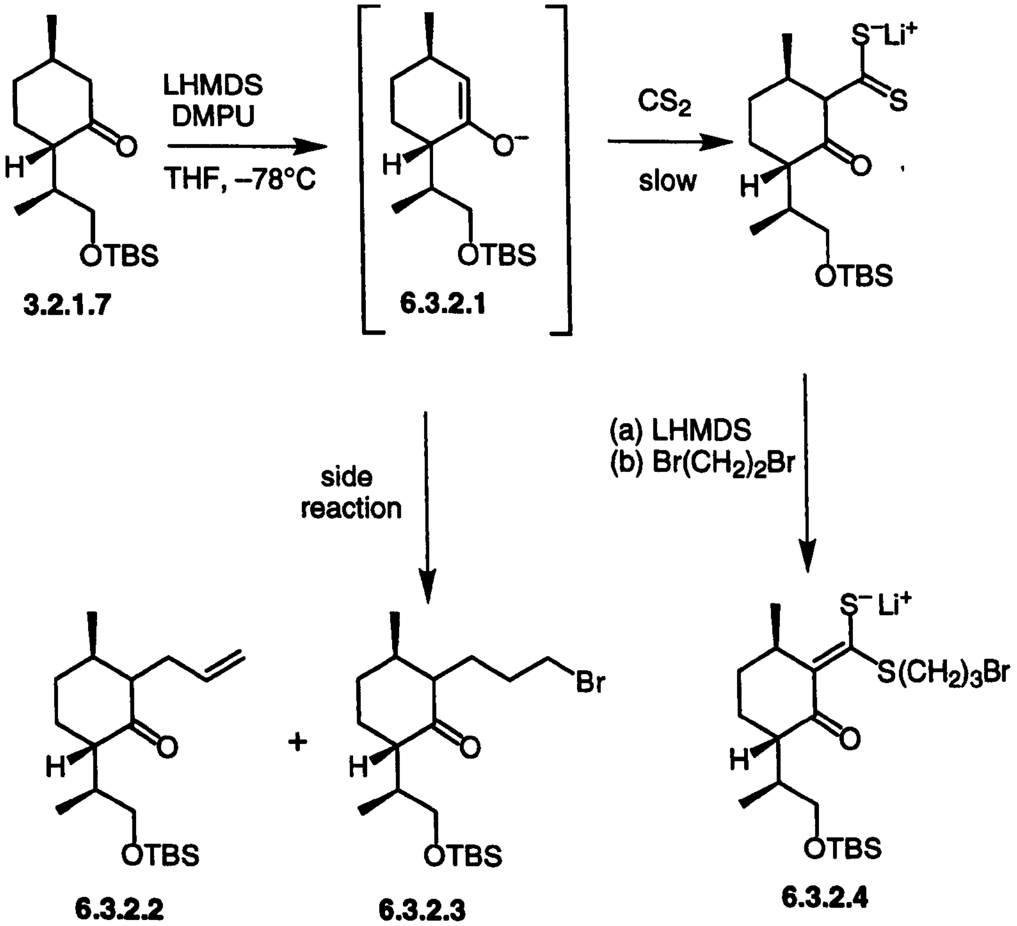
6.3 Improving the synthesis of cyclic dithioketene acetal 3.2.1.8.

At the beginning of our studies, it was assumed that problems with the closure of the 1,3-dithiane ring could be the cause of the low yield and complex mixture of products recovered. Acyclic dithioketene acetals could be formed in higher yield (up to 80%) by quenching the intermediate dianion with with MeI or EtI (scheme **6.3.1**).

Scheme **6.3.1.**



This reaction is rather delicate from the experimental point of view. The enolate formed from **3.2.1.7** at –78°C was stirred for 30 min at the same temperature in presence of DMPU. Neat CS_2 was then added and the orange solution warmed to –30°C over 2 hours, before cooling to –78°C again. A second equivalent of base was added to form the dianion. After 25 min at the same temperature, a solution of the dihalide was finally added and the reaction mixture allowed to warm to room temperature over 16 hours. Scheme **6.3.2**.



The initial experiments using increasing dilution in the final double alkylation step to facilitate intramolecular attack did not lead to any improvement. Using 1,3-dibromopropane instead of 1,3-diiodopropane, however, made the reaction cleaner and more reproducible but the yields remained below 35%. On the other hand, experimentation with acyclic ketals and more thiophilic Lewis acids (Sn(OTf)$_2$, HgCl$_2$) in the cyclisation step resulted only in the recovery of thioanisoles.

The solution to our problems was finally found when more starting material had been made available from improvement in early stages of the synthesis. Scaling up the dithioketene acetal preparation allowed us to isolate the side products, identified as a mixture of **6.3.2.2** and **6.3.2.3** (scheme **6.3.2**) by IR (unconjugated carbonyl, no band of thiols) and ^{1}H NMR. Monoalkylated α,β-unsaturated products of the type **6.3.2.4** or the corersponding thioesters could not be detected by IR (no C=S or conjugated C=O bands) and ^{13}C NMR (no signals for the C=CS$_2$ or thioester systems).

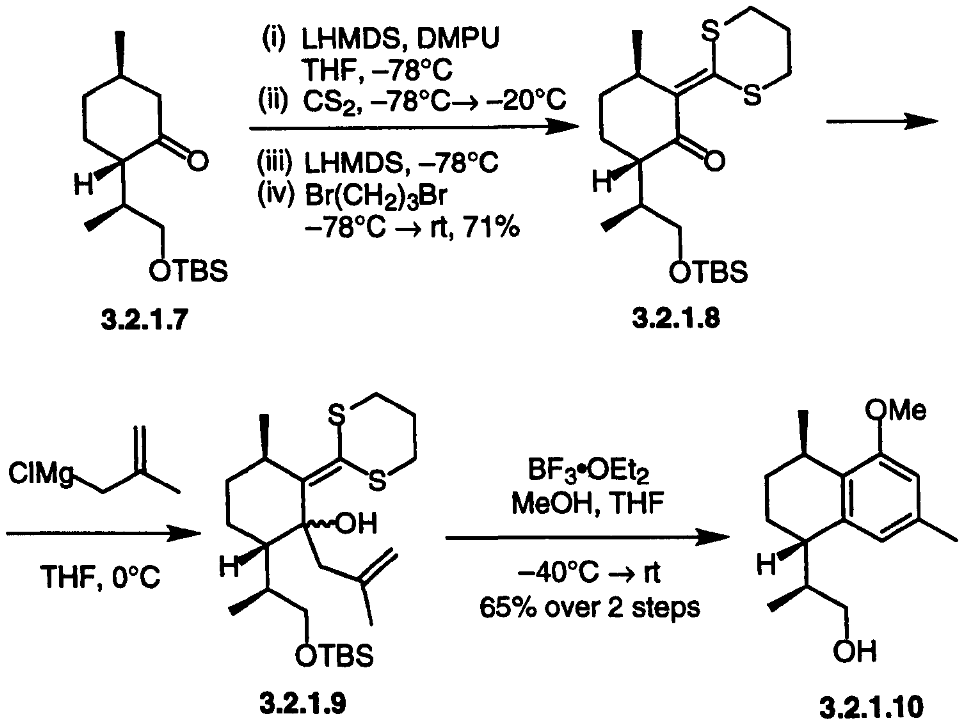
This ruled out the hypothesis that the closure of the 1,3-dithiane was the main problem.

A plausible explanation for the formation of alkylated products **6.3.2.2** and **6.3.2.3** is that unreacted enoate **6.3.2.1** is still present when the dihalide is added at the end of the one-pot procedure. Direct attack of the enolate on the halide leads to these side products, possibly after the action of the second equivalent of base. Therefore, poor reactivity during the nucleophilic attack on CS_2 is responsible for the low yield of the reaction. It is probable that the formation of the enolate is quite sluggish at temperatures below –30°C and CS_2 polymerises in presence of the base. Formation of tars were always detected using the unoptimised conditions. Addition of a second equivalent of base and warming up to room temperature could result in more effective enolisation and attack on the halide.

To prove our hypothesis, the experimental protocol was altered. After addition of CS_2 at –78°C, the solution was allowed to warm to higher temperature (–20°C) and stirred for 90 min at this temperature before cooling down again. Formation of polymeric material began to appear upon longer periods at –20°C. This procedure brought dramatic improvement. The yield more than doubled (from 33% to 71%) and the reaction was clean and reproducible. This also eliminated the need for repeated column chromatography to get rid of side products and minimised decomposition of the dithioketene acetal in the purification process. This resulted in higher yields and better reproducibility in the subsequent Grignard addition and cyclisation steps.

The optimised procedure was reliable also on a larger scale (starting from 2.4 g of **3.2.1.7**). Best overall yields were obtained when the three reactions from **3.2.1.7** to **3.2.1.10** were performed in rapid succession (within 3 days). The sulphurated intermediates are unstable and should not be stored for more than 3-4 days, even at –25°C. The final yields and conditions for the synthesis of anisole **3.2.1.10** from ketone **3.2.1.7** are illustrated in scheme **6.3.3**.

Scheme **6.3.3.**


(i) LHMDS, DMPU
THF, –78°C
(ii) CS_2, –78°C→ –20°C
(iii) LHMDS, –78°C
(iv) $Br(CH_2)_3Br$
–78°C → rt, 71%
O
H
OTBS
S
S
3.2.1.7
3.2.1.8
ClMg
THF, 0°C
OH
3.2.1.9
BF_3•OEt_2
MeOH, THF
–40°C → rt
65% over 2 steps
OMe
OH
3.2.1.10

6.4 Conclusions.

The Dieter benzannulation of **3.2.1.7** is the pivotal step of our approach to pseudopterosins. After observations on the recovered side products and considerations on the mechanism of the α-oxoketene dithioacetal formation, significant improvement of yield and reproducibility were achieved. This made the overall synthesis reliable and suitable for the production of larger quantities of key intermediates. The following chapter describes the final steps towards pseudopterosins K-L aglycone.

Chapter 7
Conclusion of the first approach.

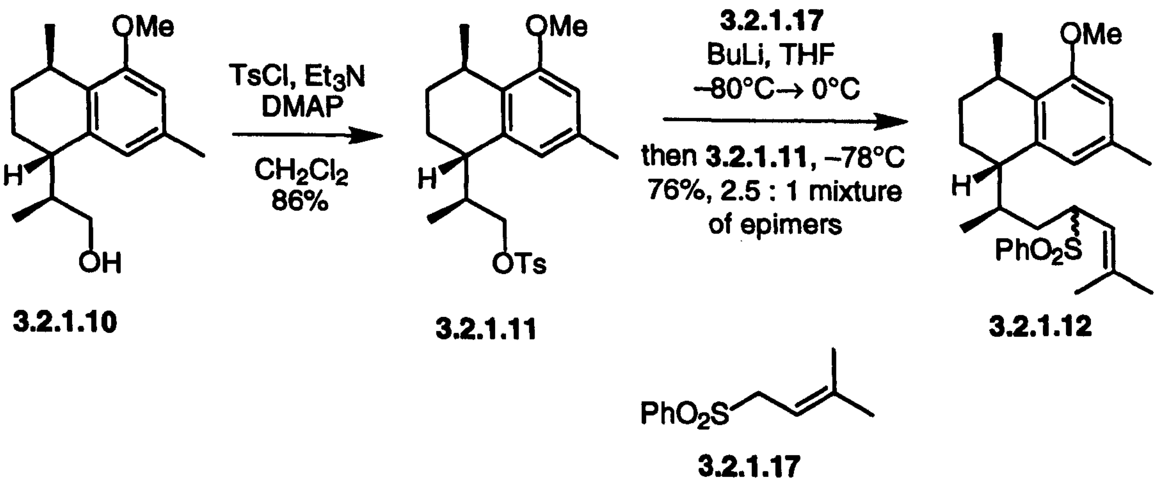
7.1 Introduction.

The final stages of the synthesis offered significant challenges. Reaction of sulfone **3.2.1.12** with $AlCl_3$ afforded a 1:1 mixture of diastereomeric **3.2.1.13** and **3.2.1.14** in Dr Kohler's hands. This result was clearly unacceptable and affected the overall yield and feasibility of the approach. The final oxidation step was also unsatisfactory because of the yield and of the complex mixture of products obtained.

7.2 Formation of tricyclic 3.2.1.13 and 3.2.1.14.

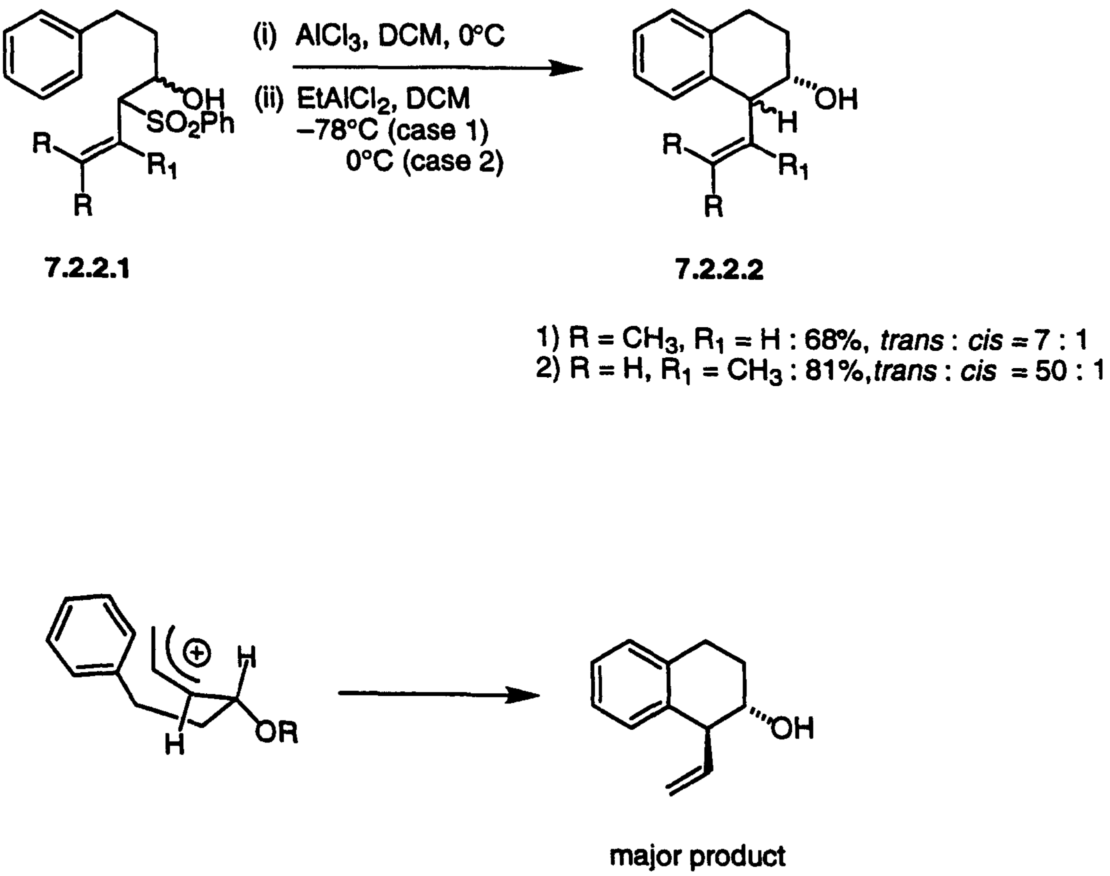
Treatment of alcohol **3.2.1.10** with TsCl and Et_3N in presence of catalytic DMAP yielded tosylate **3.2.1.11** in high yield (scheme **7.2.1**). Previously reported conditions employing excess pyridine proved unpractical and inefficient.

Scheme **7.2.1**.



For the alkylation of **3.2.1.11** with the anion generated from **3.2.1.17** and BuLi we adopted a slightly modified procedure. After addition of the base to the sulfone at –78°C, the yellow solution was allowed to warm up to 0°C before addition of the tosylate at –78°C. The mixture of epimeric sulfones **3.2.1.12** was obtained in higher yields but the ratio differed from that previously reported. Dr. Kohler recovered a 1:1 mixture of epimers and reported that partial separation of epimers was possible *via* selective recrystallisation. This enabled him to conduct experiments on the subsequent cyclisation starting from a single isomer. He claimed that different epimers of **3.2.1.12** treated with $AlCl_3$ in Et_2O at reflux led to different mixtures of tricyclic **3.2.1.14** and **3.2.1.13**. This suggested an S_N2-type mechanism for the cyclisation. However, we obtained the sulfones in 2:1 mixture as a pale yellow oil and despite several attempts we could never crystallise them, even after several days at –25°C. The epimeric composition might have an influence on the physical state of the mixture. Our studies on the cyclisation were even more interesting. An extensive review of the literature on sulphones as nucleophilic - electrophilic synthones ("chemical chameleons" according to B.M. Trost[73]) disclosed a relevant example published in 1986[74] (scheme **7.2.2**). After complexation of the hydroxy group with the first Lewis acid, displacement of the sulphone was promoted by $EtAlCl_2$ in DCM at low temperature. Excellent diastereoselectivity and high yield were easily achieved on these simple substrates.

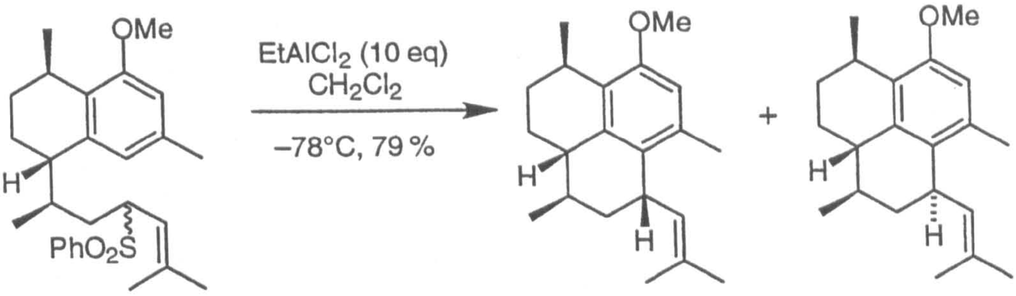
Scheme **7.2.2.**



(i) AlCl3, DCM, 0°C
(ii) EtAlCl2, DCM
-78°C (case 1)
0°C (case 2)
OH
SO2Ph
R
R1
7.2.2.1
7.2.2.2
H
1) R = CH3, R1 = H : 68%, trans : cis ≈ 7 : 1
2) R = H, R1 = CH3 : 81%, trans : cis = 50 : 1
⊕
OR
major product

The authors[75] rationalised their results through an ionic mechanism as reported in scheme **7.2.2**. Once the allylic carbocation is generated, steric effects rather than configuration at the neighbouring stereocenter are responsible for the stereochemical outcome.

Scheme **7.2.3**.

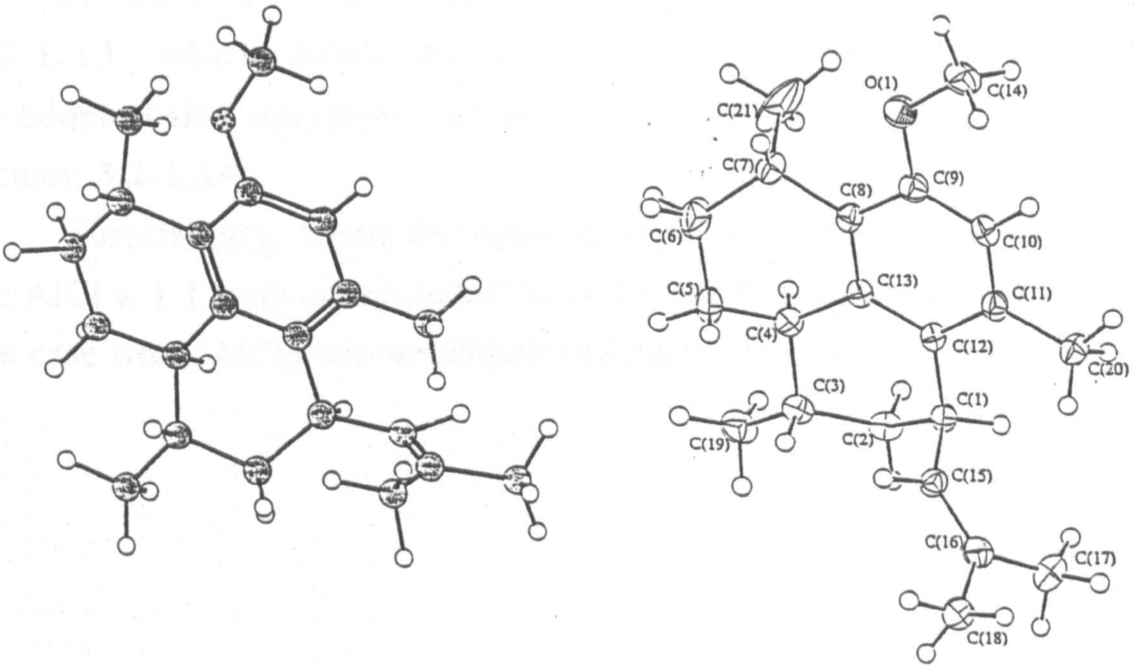

OMe
EtAlCl$_2$ (10 eq)
CH$_2$Cl$_2$
−78°C, 79 %
H
PhO$_2$S
OMe
H
H
+
OMe
H
H

3.2.1.12 **3.2.1.13** **3.2.1.14**

3.2.1.13 : 3.2.1.14 = 9.8 : 1

We applied their conditions to our highly substituted system with very good results (scheme **7.2.3**). The tricyclic products were obtained in 79% yield and the diastereomeric ratio was now 9.8:1. Choice of Lewis acid, solvent and temperature affected dramatically the selectivity. Certain assignment of the relative configuration was not possible from NMR data. Partial separation of the diastereoisomers on repeated column chromatography allowed us obtain a pure sample of the major isomer as a white crystalline solid. After recrystallisation from *i*-PrOH, the product was submitted for X-ray analysis. We were delighted to find that our major product had the relative configuration required for the pseudopterosins aglycone, as depicted in scheme 7.2.4.

Scheme **7.2.4**

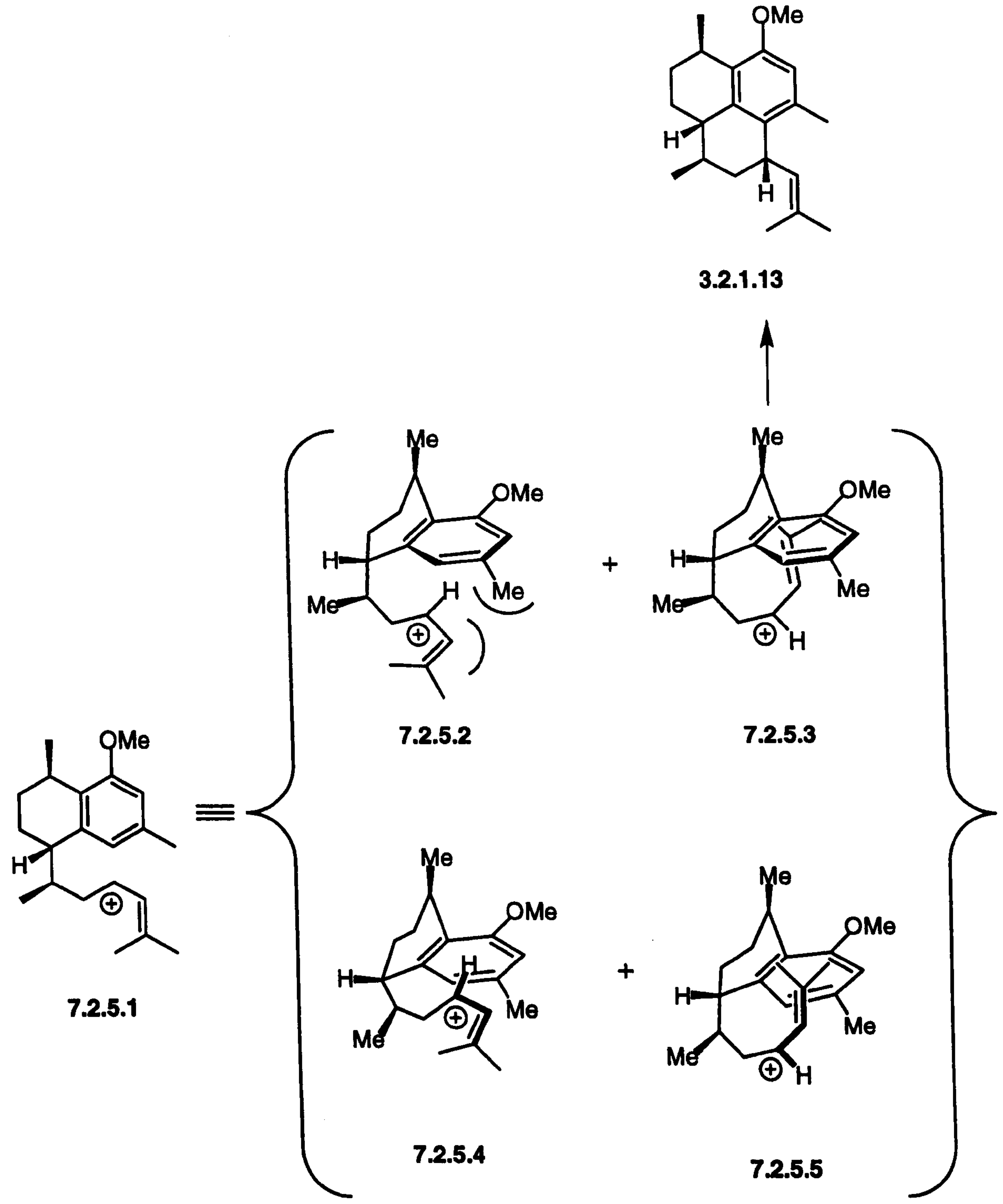

O(1)
C(14)
C(21)
C(7)
C(8)
C(9)
C(6)
C(10)
C(5)
C(13)
C(11)
C(4)
C(12)
C(20)
C(3)
C(1)
C(19)
C(2)
C(15)
C(16)
C(17)
C(18)

The fact that the diastereomeric ratio of the products does not reflect that of the starting mixture of sulfones is significant to understand the mechanism. Displacement of the sulfone can take place either *via* an S_N2- or an S_N1-type mechanism. The S_N2 pathway involves inversion of configuration at the allylic center, so starting from a 2.5:1 mixture of epimeric sulfones we should obtain a 2.5:1 mixture of products. The distribution of **3.2.1.13** and **3.2.1.14** clearly indicates that the mechanism should be closer to an S_N1 displacement, in which case a planar cationic intermediate is formed before the nucleophilic attack takes place. Electrophilic aromatic substitution can take place *via* four conformers (scheme **7.2.5**). Ring B adopts preferentially a half-chair conformation in which the C4 side chain and the C7 methyl occupy pseudoequatorial positions. Therefore, the unsaturated side chain must be on the same face of the system as the C3-C4 bond and this rules out conformers **7.2.5.4** and **7.2.5.5**. The folded transition state **7.2.5.3** is slightly higher in energy (2 kcal/mol according to MM2 calculations) than **7.2.5.2** but does not suffer from severe steric congestion. The extended cation form **7.2.5.2** has lower energy but is disfavoured because of steric hindrance between the methyl group on the aromatic ring and those on the side chain. Minor hindrance is present in **7.2.5.3**, as the C7 methyl and the isopropylidene groups are on different faces of the molecule. Moreover, π-π interactions[76] between electrons on the unsaturated side chain and the aromatic ring are also possible and this would bring further stabilisation to **7.2.5.3**.

Friedel-Crafts type electrophilic attack in **7.2.5.3** leads to the desired **3.2.1.13**, which bears the suitable relative configuration for the pseudopterosins aglycone, while reaction of **7.2.5.2** affords the minor isomer **3.2.1.14**.

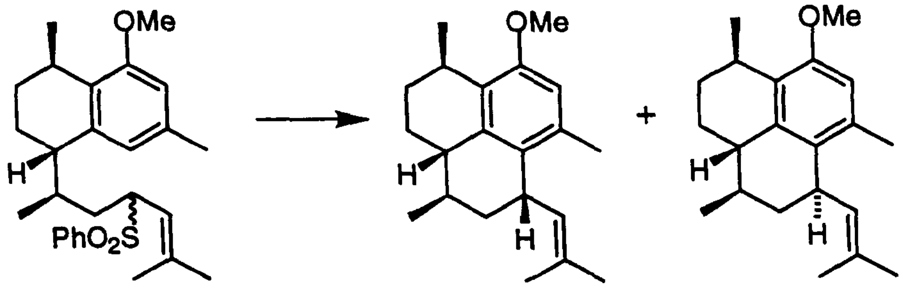
Surprisingly, when the same mixture of sulfones was treated with Et_2AlCl a 1:1 ratio of epimeric **3.2.1.13** and **3.2.1.14** was obtained, as in the case when $AlCl_3$ was employed (scheme **7.2.6**).

Scheme 7.2.5.



A possible interpretation for this behaviour is that the Lewis acid may coordinate to with the leaving group which then can form a tight ion pair with the allylic carbocation. Extra steric effects might thus be introduced and influence the distribution of transition states. Formation of these complexes would depend on nature of Lewis acid, solvent and temperature. The combination of strength and coordinating ability of the metal center would be ideal only when $EtAlCl_2$ is used. We also noticed than a red colour developed only in Et_2AlCl-catalysed reaction and not when $EtAlCl_2$ was used, indicating the formation of different species in solution.

Scheme **7.2.6.**



3.2.1.12 **3.2.1.13** **3.2.1.14**

Conditions:	Ratio **3.2.1.13** : **3.2.1.14**
$AlCl_3$, Et_2O reflux:	1 : 1
$EtAlCl_2$, CH_2Cl_2, −78°C → rt	9.8 : 1
Et_2AlCl, CH_2Cl_2, −78°C → rt	1 :1

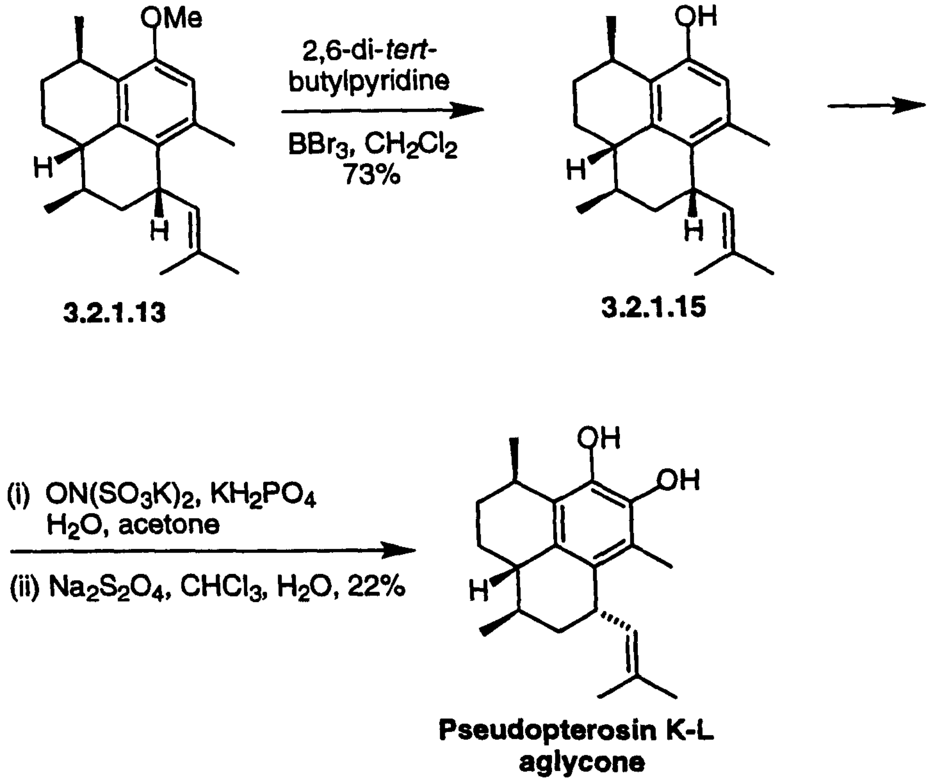
Similar dependence of the reaction outcome from the Lewis acid employed has been reported by numerous researchers[73,77].

7.3 Formation of pseudopterosins aglycone.

Cleavage of the methoxy group of **3.2.1.13** was achieved in good yield using BBr_3 and 2,6-di-*tert*-butylpyridine over 30 min. Longer exposure to these reaction conditions resulted in partial epimerisation at the C7 benzylic center.

The final oxidation proved problematic, as we partially expected. The Fremy's salt oxidation used by McCombie *et al*[19] in their synthesis was never achieved in the yield that they reported. The best we could obtain was 22% using freshly prepared potassium nitrosodisulfonate and KH_2PO_4 buffer in acetone/H_2O at rt followed by reduction with sodium dithionite (scheme **7.3.1**).

Scheme 7.3.1.

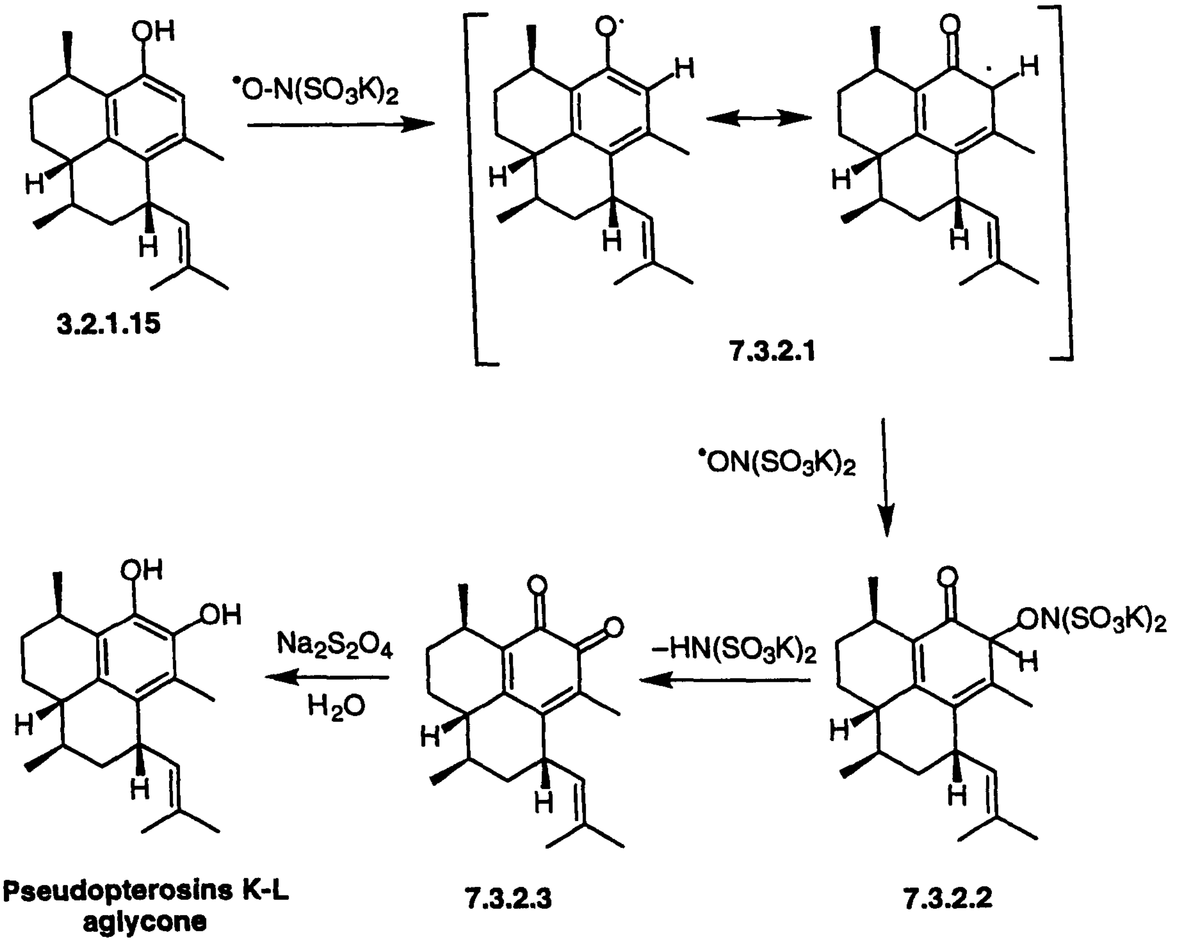

OMe
2,6-di-*tert*-butylpyridine
BBr3, CH2Cl2
73%
OH
H
H
3.2.1.13
3.2.1.15
(i) ON(SO3K)2, KH2PO4
H2O, acetone
(ii) Na2S2O4, CHCl3, H2O, 22%
OH
OH
H
Pseudopterosin K-L
aglycone

Unreacted starting material and a number of side products were always recovered. The mechanism[78] for this oxidation is reported in scheme 7.3.2.

The first step is deprotonation of the phenol to form the corresponding radical 7.3.2.1. Reaction with a second equivalent of potassium nitrosodisulfonate leads to the quinone derivative 7.3.2.2, rapidly hydrolised to *ortho*-quinone 7.3.2.3.

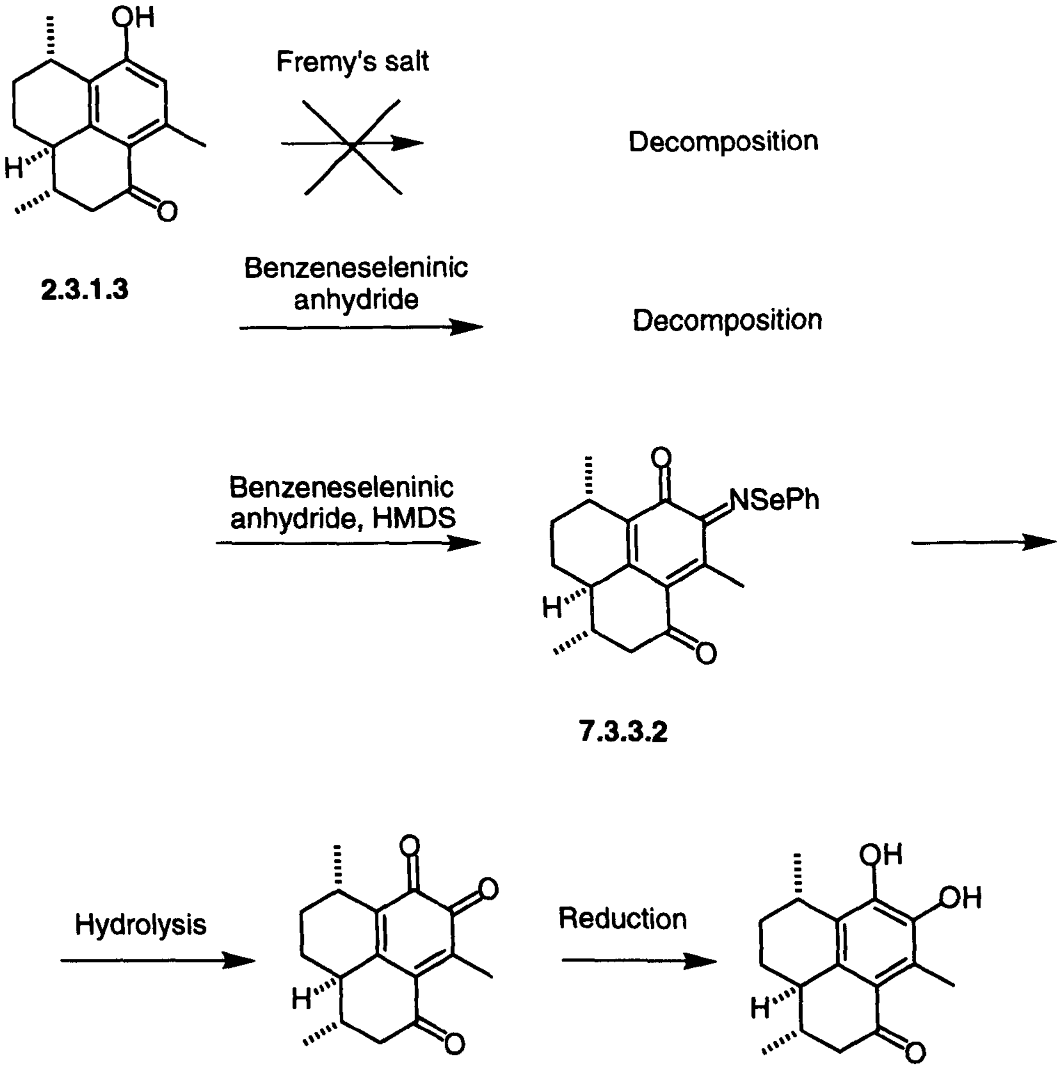
Fremy's salt oxidation usually leads to a mixture of *ortho*- and *para*-quinones if both positions are available. The 1,4-dicarbonyl product is generally the major obtained. In these case the *para* position is blocked and the *ortho*-quinone should be the only product.

Scheme **7.3.2.**


OH
•O-N(SO3K)2
H
H
3.2.1.15
O·
H
H
H
O
·H
H
H
7.3.2.1
•ON(SO3K)2
OH
OH
H
H
Pseudopterosins K-L aglycone
Na2S2O4
H2O
O
O
H
H
7.3.2.3
-HN(SO3K)2
O
ON(SO3K)2
H
H
H
7.3.2.2

A possible explanation for the low yield of this transformation is that the radical **7.3.2.1** can undergo a number of side reactions. In particular, the presence of the double bond on the side chain might trigger a series of rearrangements and eventual aromatisation to a naphthalene derivative. Similar problems were encountered by Corey and Carpino[79] during their synthesis (scheme **7.3.3**). Treatment of **2.3.1.3** with Fremy's salt led to unexpected side reactions, while alternative reaction with benzeneseleninic anhydride yielded addition products. The problem was solved using Barton's method[17] for the oxidation of phenols. Phenylselenoimine **7.3.3.2** was formed by reaction of **2.3.1.3** with benzeneseleninic anhydride and HMDS and was then hydrolysed to the quinone. Reduction cleanly yielded catechol **2.3.1.2**.

Scheme **7.3.3**


OH
H
O
Fremy's salt
Decomposition
Benzeneseleninic anhydride
Decomposition
Benzeneseleninic anhydride, HMDS
O
NSePh
H
O
Hydrolysis
O
O
H
O
Reduction
OH
OH
H
O

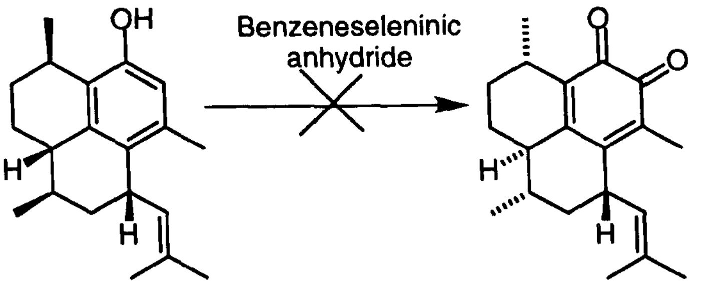
2.3.1.3

7.3.3.2

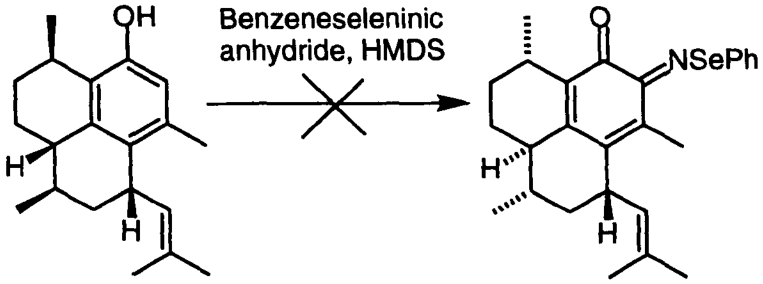
2.3.1.2

When we tried this method on our phenol bearing the unsaturated side chain (scheme **7.3.4**), none of the desired organoselenium compound was obtained while several unstable side products were formed. Reaction with benzeneseleninic anhydride alone did not lead to better results.

Scheme **7.3.4.**


OH
Benzeneseleninic anhydride
O
O
H
H

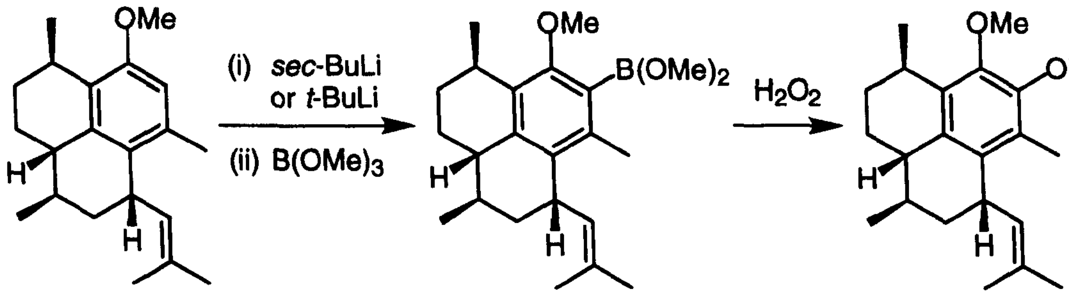
3.2.1.15 **7.3.4.1**


OH
Benzeneseleninic anhydride, HMDS
O
NSePh
H
H

3.2.1.15 **7.3.4.2**

We then tried an alternative approach based on heteroatom-directed *ortho*-metallation of the aromatic ring. In principle, treatment of methoxyarene **3.2.1.13** with *sec*- or *tert*-BuLi (scheme **7.3.5**) should lead to deprotonation on the aromatic position, directed by the presence of a methoxy[38] or a MEM[21] group. Quenching of the carbanion thus formed with $B(OMe)_3$ and oxidation with H_2O_2 should lead to the desired monoprotected catechol derivative **7.3.5.2**.

Scheme **7.3.5.**


OMe
(i) sec-BuLi or t-BuLi
(ii) B(OMe)3
B(OMe)2
H2O2
OH
H

3.2.1.13 **7.3.5.1** **7.3.5.2**

All our attempts were thwarted: even after treatment with *tert*-BuLi and reflux for several hours in Et_2O, the reaction failed. The starting material was recovered unchanged and failed incorporation of deuterium after quenching with D_2O proved that abstraction of the proton was not taking place. Changing the protecting group to MEM group was also unsuccessful. At this stage, the final oxidation was still our major problem, although it could be achieved in low yield and with poor reproducibility.

7.4 Conclusions.

The overall formal synthesis of pseudopterosins K-L aglycone has been radically changed by our contribution and is now a feasible and reproducible approach.

The main improvements are:

- synthesis of neoisopulegol *via* reduction of isopulegone is easier than the Mitsunobu inversion and is suitable to the production of large quantities of early precursors from commercial technical isopulegol;

- introduction of the C3 stereocenter *via* stereoselective epoxidation and Lewis acid-catalysed oxirane opening provides complete control and therefore avoids the problem of unpractical separation by chromatography;

- the yield of the dithioketene acetal formation has been increased from 33 to 71% and the reaction is now clean and reproducible;

- selectivity in the closure of ring C of pseudopterosins has been enhanced from 1:1 to 9.8:1 in favour of the desired isomer and X-ray analysis confirmed its structure.

The main problem at this stage remained the final oxidation step, still capricious and with low yields, although formal synthesis was achieved as **3.2.1.15** is a common intermediate to McCombie's synthesis.

Rather than repeating again our synthesis, we decided to undertake a new approach, this time targeted to the synthesis of the more biologically active pseudopterosin E. Our studies and the completion of our second route are described in the following chapter.

Chapter 8

A new approach to pseudopterosin E.

8.1 Introduction.

In order to achieve a feasible approach to pseudopterosins A-F aglycones we formulated these three goals:

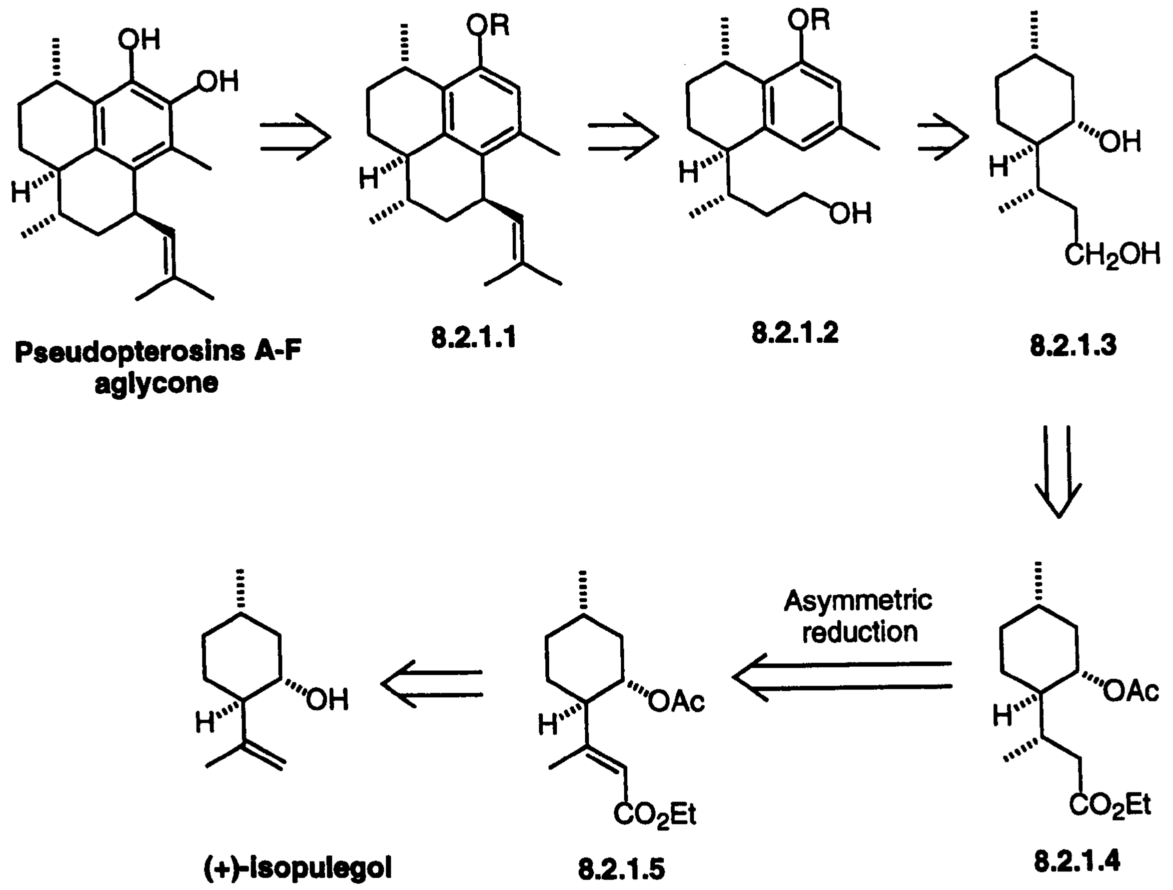
- to apply our annulation method to different substrates and demonstrate its wider scope;
- to undertake further investigations on the closure of ring C;
- to improve the synthesis of the final catechol.

8.2 General strategy.

The general framework of the new approach was again based on the construction of the aromatic ring starting from monoterpenic precursors (scheme **8.2.1**). We envisioned that the C3 stereocenter could be introduced *via* asymmetric catalytic reduction of an α,β-unsaturated ester. Benzannulation using our modification of the Dieter procedure would lead us to **8.2.1.2**, a C1 homologue of **3.2.1.10**. Final ring closure and oxidation could afford the aglycone.

This route would also increase the flexibility of our approach with a view to the synthesis of bioactive analogues. Our aim was also to make the synthesis more straightforward by eliminating the initial conversion of isopulegol to neoisopulegol. This is quite important as (+)-isopulegol cannot be derived from the cheap technical isopulegol but must be obtained from less affordable enantiopure starting material (up to 100 times more expensive).

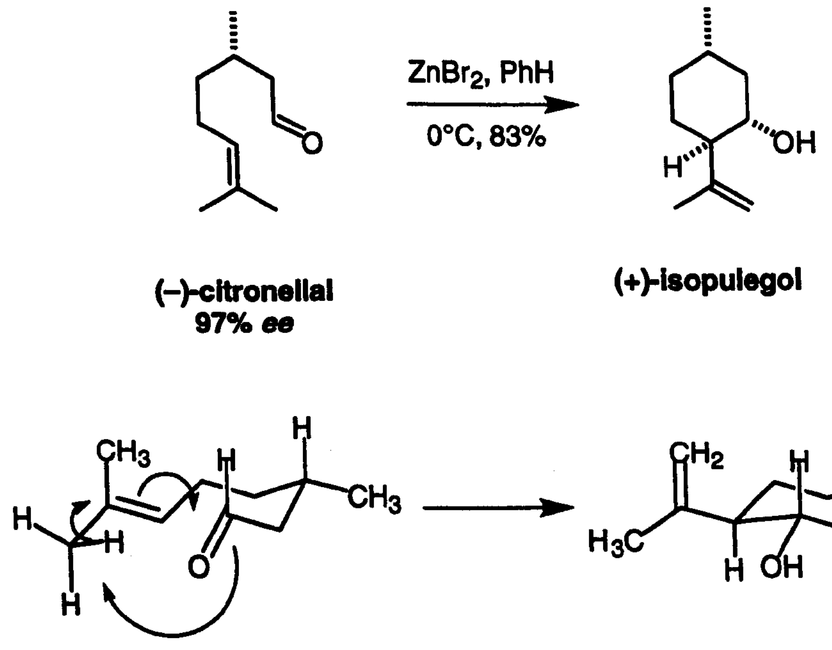
Scheme **8.2.1**.


OH
OH
H
OR
H
OR
H
OH
H
OH
CH2OH
Pseudopterosins A-F aglycone
8.2.1.1
8.2.1.2
8.2.1.3
OH
H
OAc
H
CO2Et
Asymmetric reduction
OAc
H
CO2Et
(+)-isopulegol
8.2.1.5
8.2.1.4

8.3 Synthesis of α,β-unsaturated ester 8.2.1.5.

A simple way to synthesise (+)-isopulegol from *l*-citronellal was published in 1978 by Nakatami *et al*[80] (scheme **8.3.1**).

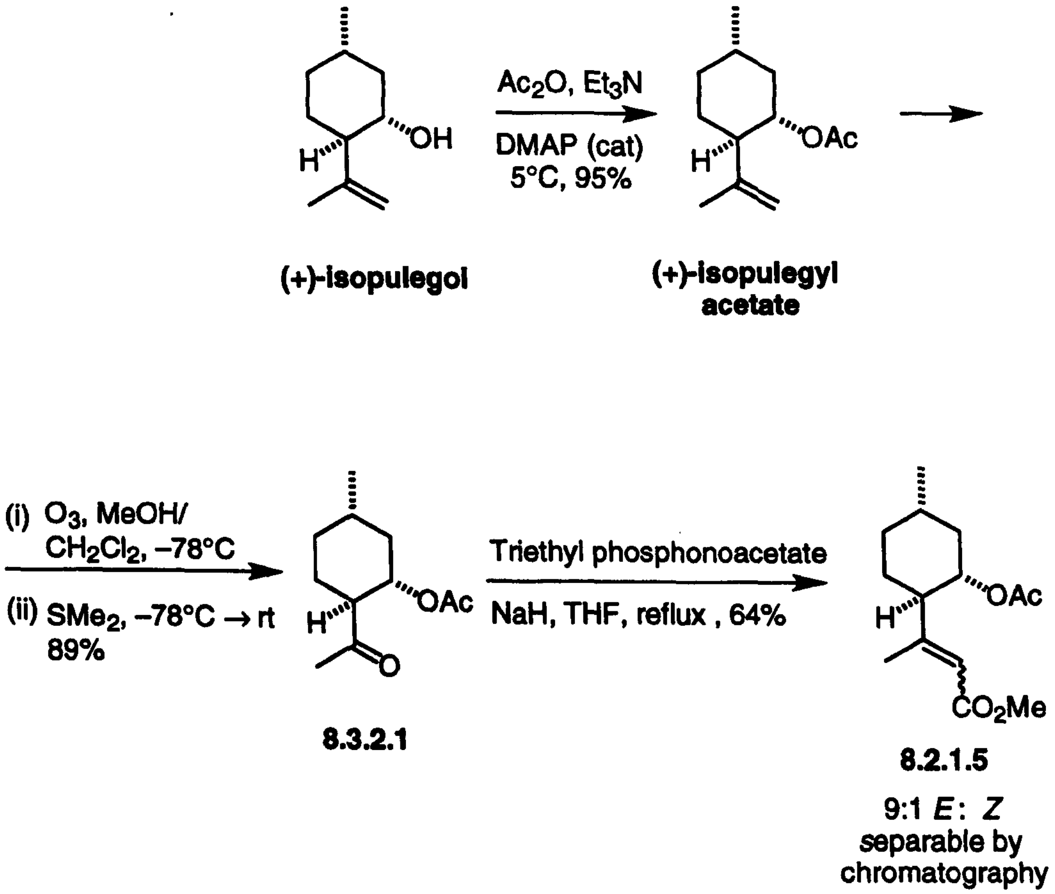
Scheme **8.3.1**.


O
ZnBr2, PhH
0°C, 83%
OH
H
(–)-citronellal
97% ee
(+)-isopulegol
CH3
H
H
CH3
H
H
H
O
CH2
H
H
CH3
H3C
H
OH

Treatment of (–)-citronellal in benzene with $ZnBr_2$ at 0°C yields (+)-isopulegol in good yield and very good stereoselectivity. The six-membered transition state for this type I ene reaction (according to Oppolzer's classification[81] is presented in scheme **8.3.1**. Placing the methyl group in equatorial position dictates the relative stereochemistry of the two newly formed stereocenters.

The product was formed with very good stereocontrol (83% isopulegol) starting from commercial citronellal available in 97% *ee* (scheme **8.3.2**). After transformation into the known acetate (95% yield), ozonolysis easily afforded ketone **8.3.2.1**.

Scheme **8.3.2**.



H
OH
Ac2O, Et3N
DMAP (cat)
5°C, 95%
H
OAc
(+)-Isopulegol
(+)-Isopulegyl acetate
(i) O3, MeOH/ CH2Cl2, –78°C
(ii) SMe2, –78°C → rt
89%
H
OAc
O
8.3.2.1
Triethyl phosphonoacetate
NaH, THF, reflux, 64%
H
OAc
CO2Me
8.2.1.5
9:1 E: Z
separable by chromatography

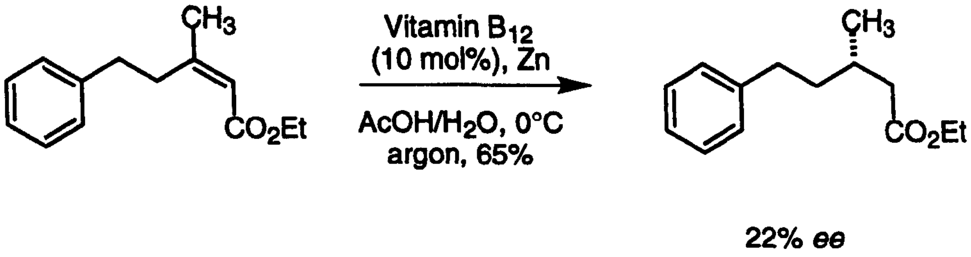
Wadsworth-Emmons reaction of **8.3.2.1** with triethyl phosphonoacetate led to α,β-unsaturated ester **8.2.1.5** as a 9:1 mixture of *E* and Z isomers. The moderate yield is mainly due to the unexpected volatility of the product and to base-catalysed side reactions. The minor *Z* isomer could be separated by column chromatography and the stereochemistry of the major product was established by NOE experiments. Our efforts to improve the yield varying times and temperature of the reaction were fruitless. We also tried to change the hydroxyl protecting group to a TBS ether, a benzoate and a pivaloate to decrease the volatility of the product but in all these cases the reaction proved sluggish (< 50% conversion after 5 days in THF at reflux) and with lower stereoselectivity (3:1 *E* :*Z*).

8.4 The Pfaltz asymmetric reduction of α,β-unsaturated esters.

After securing the substrate for the asymmetric reduction in four steps from citronellal, we considered the methods for an efficient transformation. The asymmetric reduction of α,β-unsaturated esters has great potential in organic synthesis but, surprisingly, very few methods are known in literature.

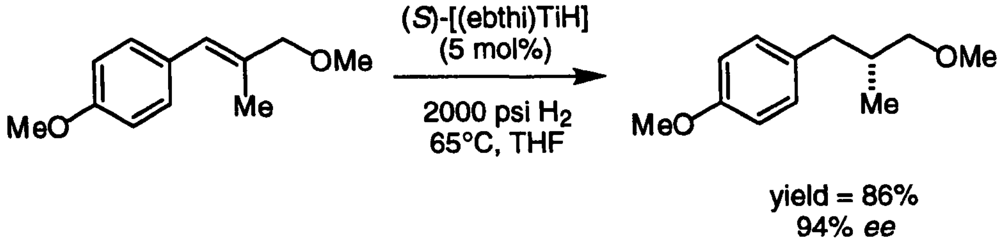
The use of Cob(I)alamine, the Co(I) form of vitamin B_{12}, for the reduction of organic substrates only led to modest *ee*'s[39] (scheme **8.4.1**).

Scheme **8.4.1**.



Various methods have been developed for the asymmetric hydrogenation of α-*N*-acylamido-α,β-unsaturated acids or esters using Ru or Rh catalysis with chiral phosphines[82]. Hydrogenation of some unsaturated carboxylic acids has also been achieved with the same methods in high *ee*. However, there are very few examples of asymmetric hydrogenation of unsaturated carboxylic systems without an electron-withdrawing group in the α-position. A recent development was published by Buchwald and coworkers in 1990[83].

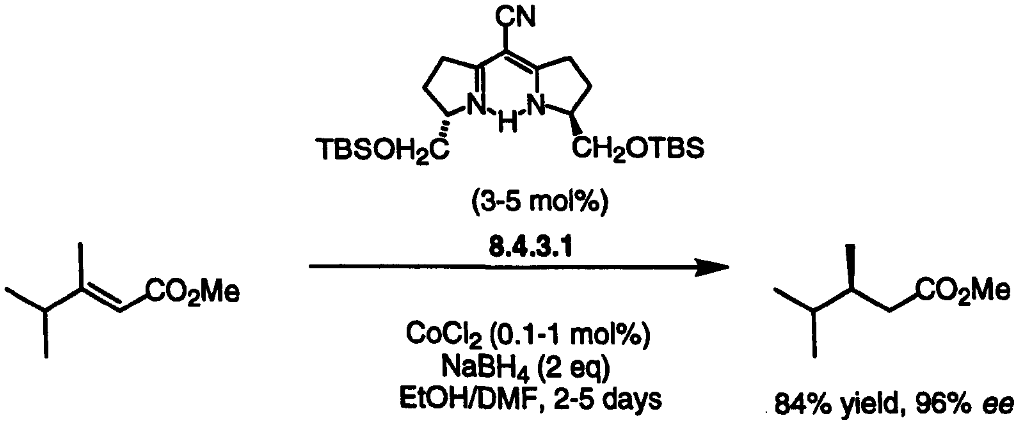
Scheme **8.4.2.**


(S)-[(ebthi)TiH]
(5 mol%)
2000 psi H2
65°C, THF
MeO
Me
OMe
yield = 86%
94% ee

Hydrogenation of the trisubstituted olefins was achieved in good yield and *ee* > 92% with homochiral ethylenebis(tetrahydroindenyl)titanocene (ebthi) catalyst generated *in situ*. (scheme **8.4.2**). This procedure, however, was not applied to α,β-unsaturated esters and all substrates reported are benzylic olefins, although these are not stated prerequisites.

Andreas Pfaltz and coworkers[84,85] devised a very interesting method for the reduction of α,β-unsaturated esters based on semicorrin ligand-Co catalysis. Their procedure (scheme **8.4.3**) consists of treatment of the substrate with 2 eq of $NaBH_4$ in EtOH/DMF in presence of the semicorrin ligand **8.4.3.1** (1-5 mol%) and $CoCl_2$ (0.1-1 mol%).

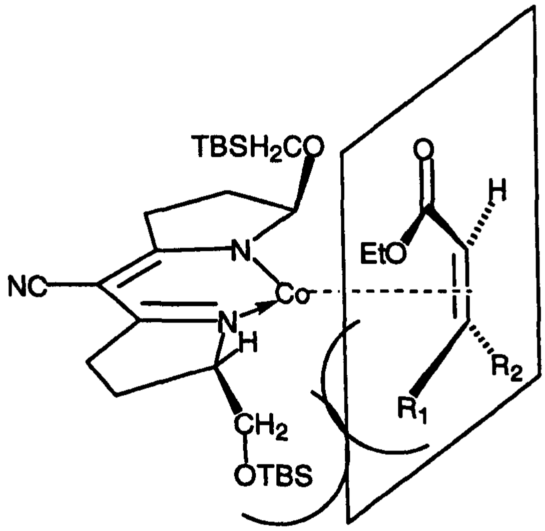
Scheme **8.4.3.**


CN
N
H
N
TBSOH2C
CH2OTBS
(3-5 mol%)
8.4.3.1
CO2Me
CoCl2 (0.1-1 mol%)
NaBH4 (2 eq)
EtOH/DMF, 2-5 days
CO2Me
84% yield, 96% ee

The reduction is usually achieved with excellent yield (>95% after 2-3 days) and *ee* (>92%). Both enantiomers of the catalyst are available from glutamic acid and, depending on the geometry of the substrate double bond, stereocenters are generated with either *R* or *S* configuration.

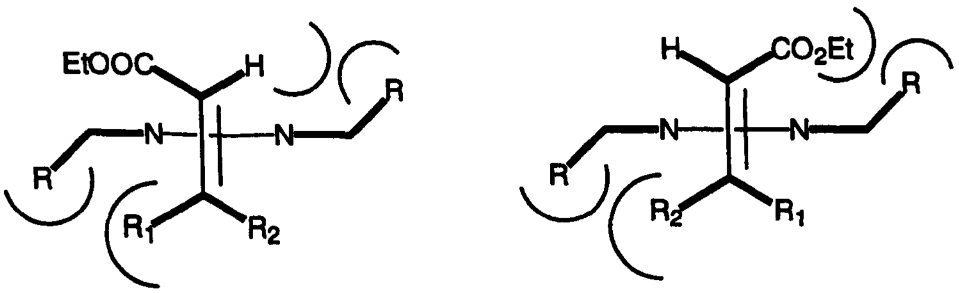
Although no studies were performed on the mechanism of this reaction, the authors presented a speculative rationale for the stereoselectivity. According to their hypothesis, Co(II) is complexed by the ligand and reduced by $NaBH_4$ to a Co(I) species. The electron-deficient double bond of the substrate then coordinates to the metallic center in the fashion shown in scheme **8.4.4**.

Scheme **8.4.4**.



Hydride transfer from $NaBH_4$ to Co is followed by an intramolecular hydride shift to the β-atom of the substrate, leading to a cobalt enolate. Delivery of hydride to the β-position of the unsaturated ester takes place from the face of the C=C bond which is bound to the catalyst. Enantioselectivity is determined by steric interactions between the carboxylic group and the substituents on the side chains of the catalyst (scheme **8.4.5**). **8.4.5.1a** is the favoured transition state, leading to the major product.

Scheme **8.4.5**.



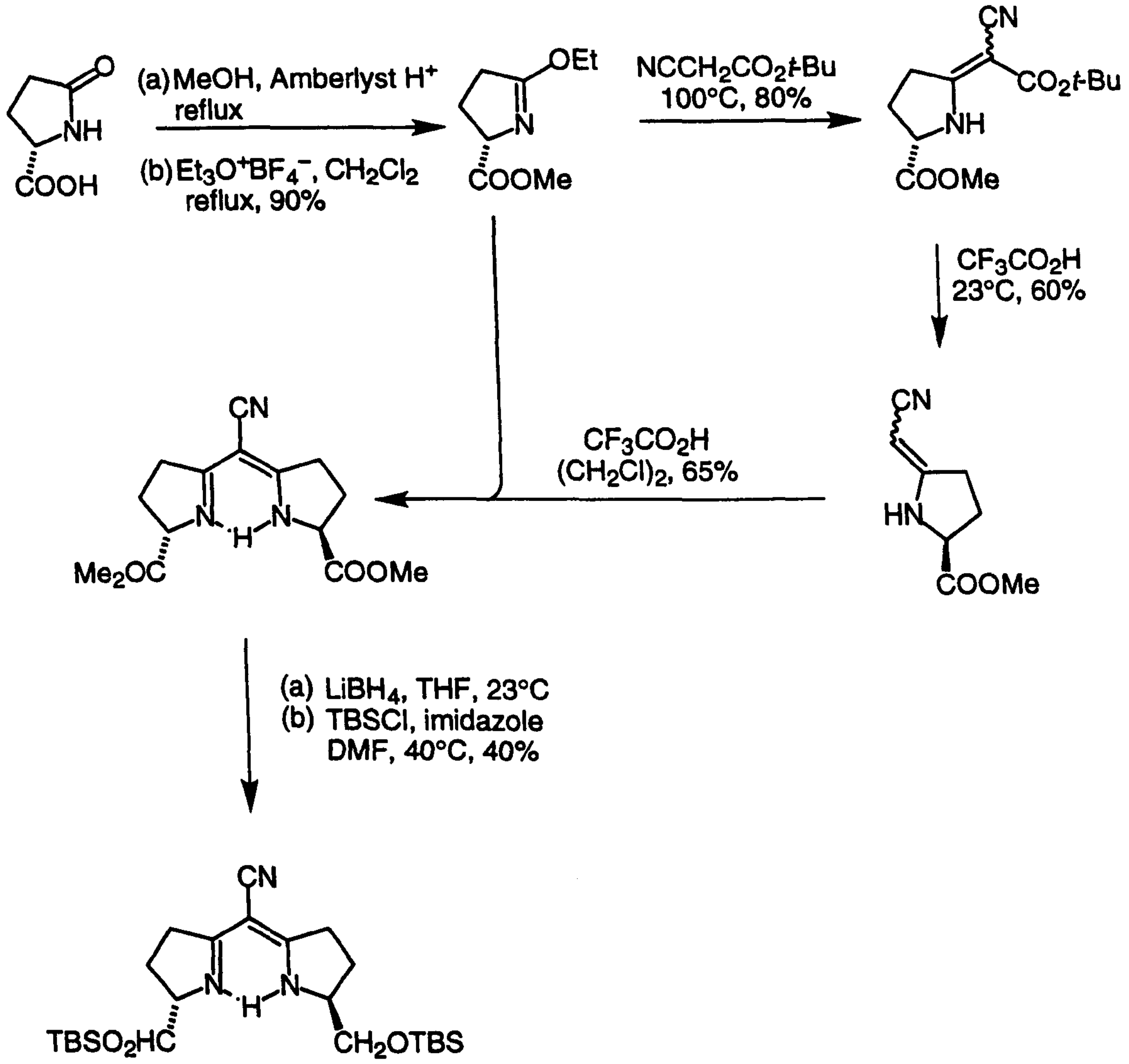
favoured
8.4.5.1a

disfavoured
8.4.5.1b

Only the β-hydrogen is introduced stereoselectively, while the α-hydrogen is derived from protonation of the enolate by the solvent. Reduction of analogue substrates with an α- instead of a β-substituent led to racemic products.

Preparation of the catalyst is reported in scheme **8.4.6**. Although relatively concise and starting from readily available enantiopure materials, this procedure gave very low yield (> 3% from pyroglutamic acid). Albeit commercially available, the catalyst is too expensive (£33.40 for 10 mg from Aldrich) for our purposes.

Scheme **8.4.6**.



COOH
NH
O
(a) MeOH, Amberlyst H+ reflux
(b) Et3O+BF4−, CH2Cl2 reflux, 90%
OEt
N
COOMe
NCCH2CO2t-Bu 100°C, 80%
CN
CO2t-Bu
NH
COOMe
CF3CO2H 23°C, 60%
CN
HN
COOMe
CF3CO2H (CH2Cl)2, 65%
CN
N
H
N
Me2OC
COOMe
(a) LiBH4, THF, 23°C
(b) TBSCl, imidazole DMF, 40°C, 40%
CN
TBSO2HC
CH2OTBS

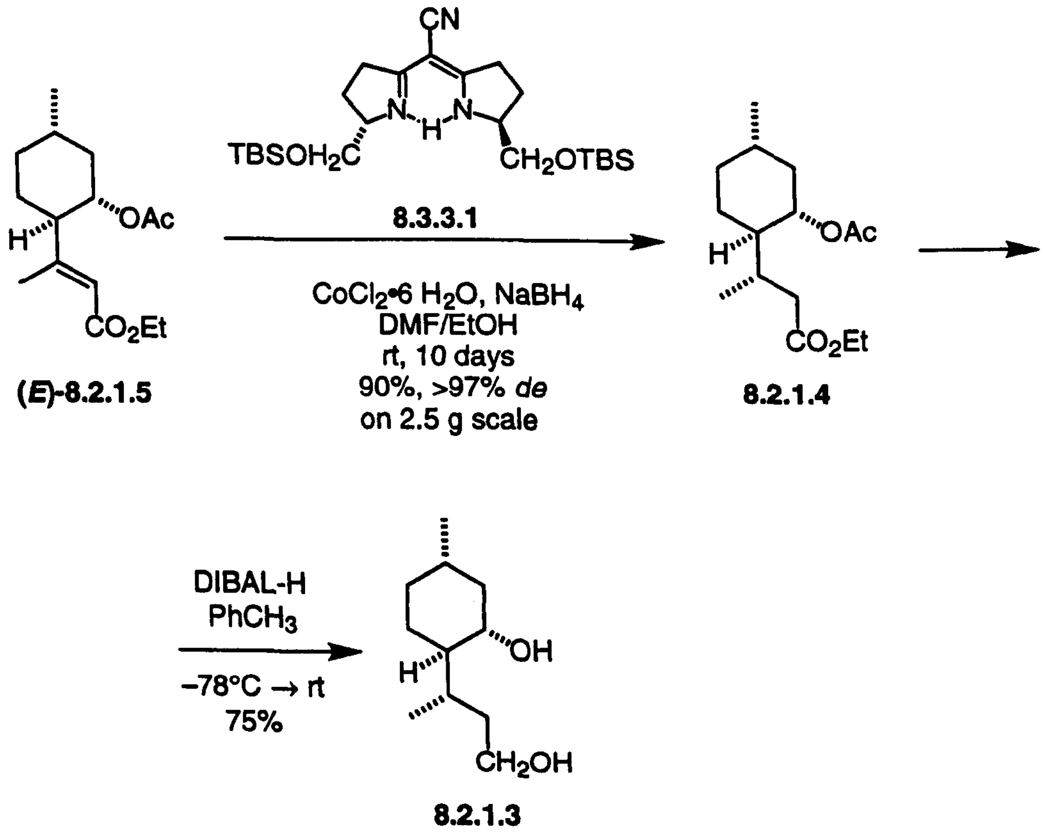
Pfaltz and coworkers employed their method only on very simple substrates, usually linear chains, that are very different from our diester **8.2.1.5**. We decided, however, to synthesise the catalyst and to apply this procedure to our α,β-unsaturated precursor of pseudopterosins.

8.5 Pfaltz reduction of 8.2.1.5.

Reduction of **8.2.1.5** using the Pfaltz method proceeded with very good yield (90%) and very good diastereoselectivity (>95%) using 8% of the catalyst. The main drawback, however, is that the reaction takes up to 15 days in a vacuum-sealed tube to go to completion on a 2.5 g scale and the catalyst could only partially be recovered. Our attempts to scale the transformation up starting from 8 g of the substrate were not successful: only 50% of conversion was obtained after 21 days and side reactions started to take place. The stereoselectivity, however, was not ffected. These problems could probably be overcome using a larger percentage of the catalyst but this would make the whole synthesis quite expensive and unpractical. To bypass this obstacle, we had to perform the asymmetric reduction in batches (up to 2.5 g each) although this is rather time demanding. Steric congestion around the double bond is probably responsible for the sluggish behaviour of the reaction.

Simple reduction of the double bond using MeOH and Mg[86] led to a 1:1 mixture of epimers, showing that no selectivity is achievable without an asymmetric process.

Scheme **8.5.1.**


CN
TBSOH₂C
CH₂OTBS
H
N
N
OAc
H
CO₂Et
(E)-8.2.1.5
8.3.3.1
CoCl₂•6 H₂O, NaBH₄
DMF/EtOH
rt, 10 days
90%, >97% de
on 2.5 g scale
OAc
H
CO₂Et
8.2.1.4
DIBAL-H
PhCH₃
-78°C → rt
75%
OH
H
CH₂OH
8.2.1.3

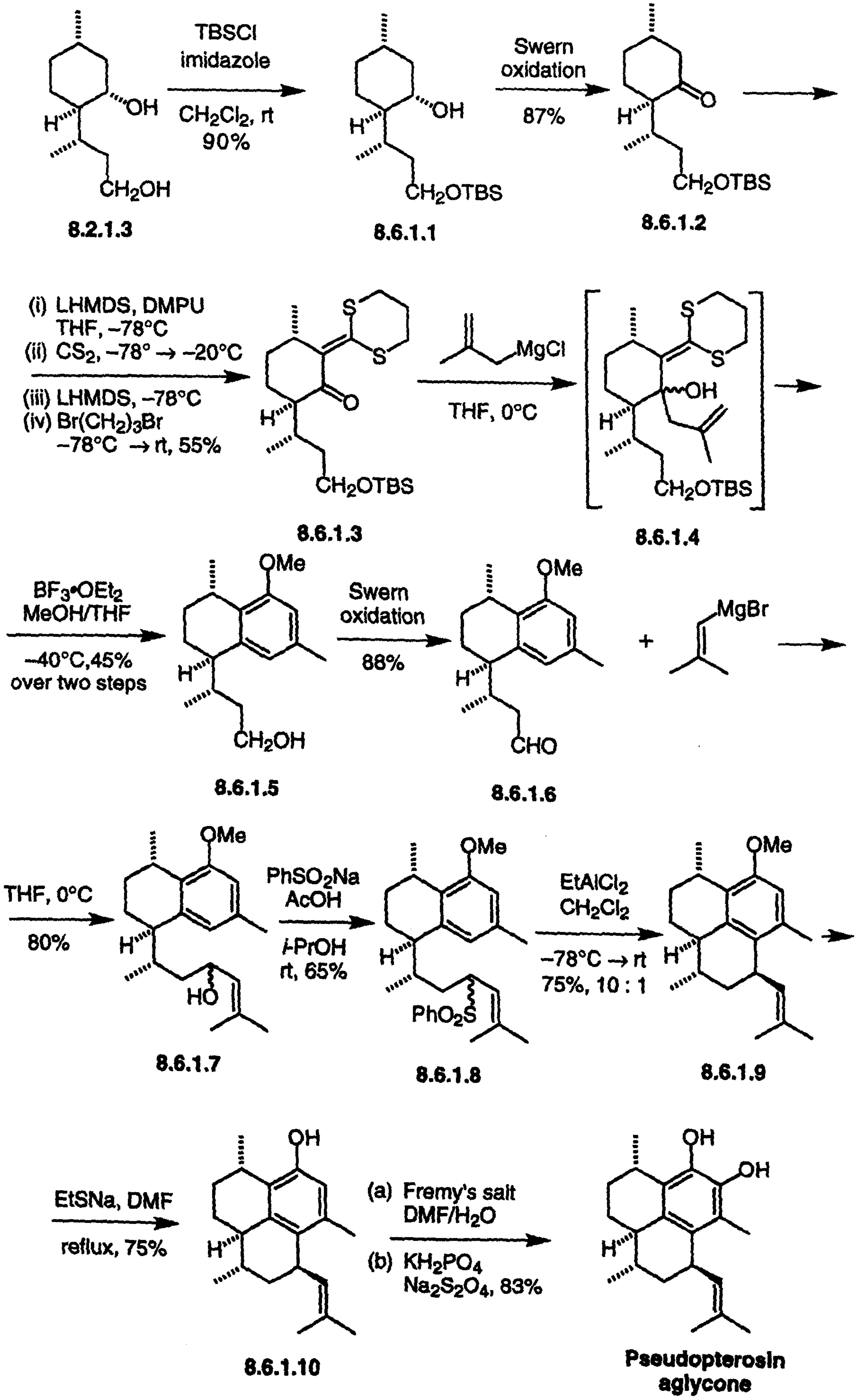
Reduction of the diester **8.2.1.4** to the diol **8.2.1.3** was carried out using DIBAL-H in good yield (scheme **8.5.1**). Reduction with $LiAlH_4$ led to lower yield (40-50%).

8.6 The second route to pseudopterosins.

The conclusion of our second approach is illustrated in scheme **8.6.1.** **8.6.1.5** was obtained alongside with 8% of impurities that could not be separated after repeated column chromatography. Transformation of **8.6.1.5** into **8.6.1.8**, enantiomer of **3.2.1 12**, was achieved in 3 steps. Allylic alcohol **8.6.1.7** was formed as a 2:1 mixture of epimers. Use of the organolithium reagent derived from 1-bromo-2-propene instead of the corresponding Grignard reagent led to lower yields (60%).
Presence of Lewis acid appears to be essential to obtain selectivity in the ring closure, as treatment of alcohol **8.6.1.7** with trifluoroacetic acid led to a 1:1 mixture of tricyclic products. Cyclisation of **8.5.2.7** with $EtAlCl_2$ following the procedure used in the first synthesis led to a mixture of diastereoisomers in a ratio consistent with our previous results. .

Cleavage of the methoxy group of **8.6.1.8** with sodium thioethoxide eliminated the problem of partial epimerisation of the benzylic center observed using BBr_3.

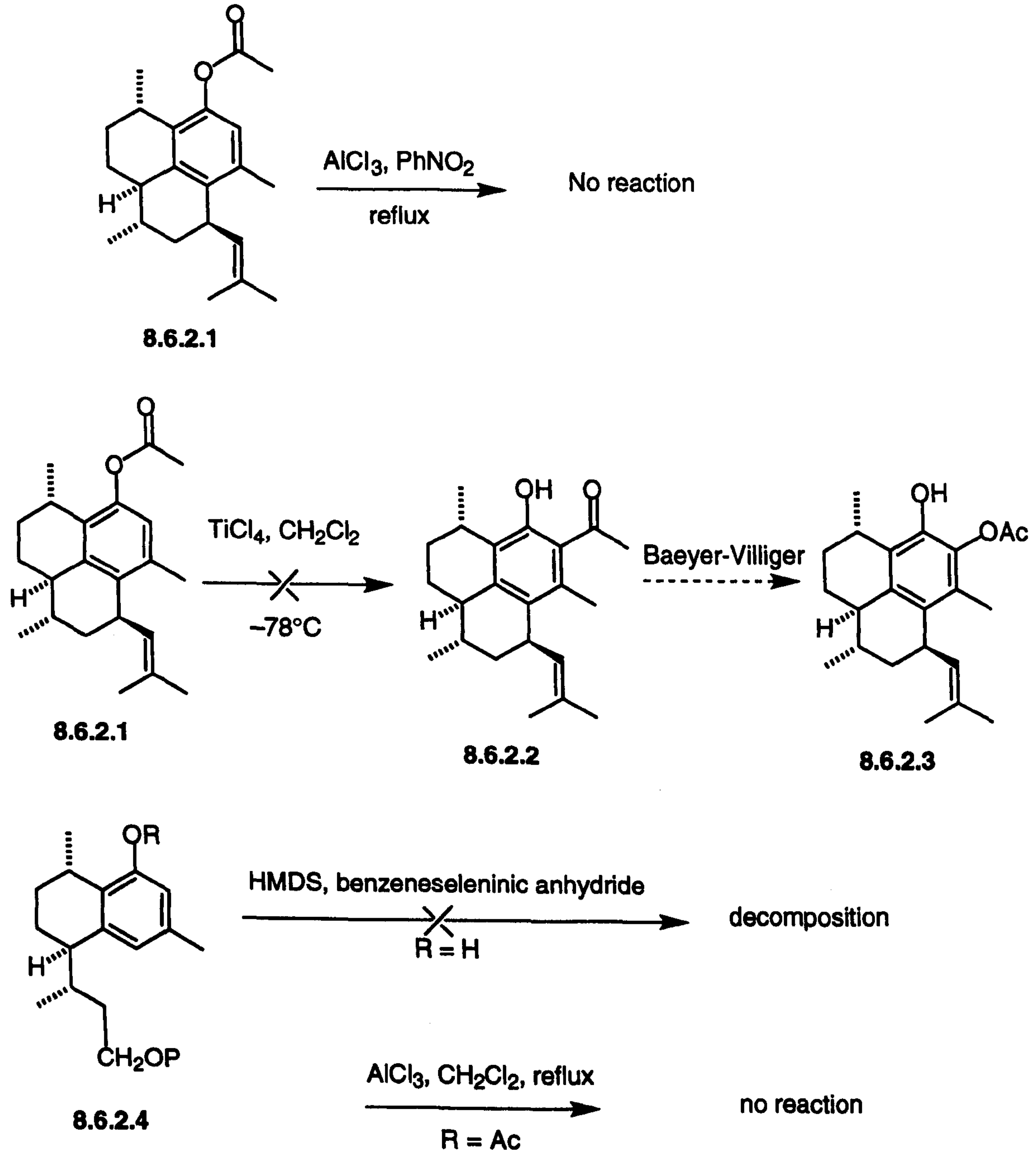
Scheme **8.6.1**.



OH
CH$_2$OH
H
8.2.1.3
TBSCl
imidazole
CH$_2$Cl$_2$, rt
90%
OH
CH$_2$OTBS
H
8.6.1.1
Swern
oxidation
87%
O
CH$_2$OTBS
H
8.6.1.2
(i) LHMDS, DMPU
THF, –78°C
(ii) CS$_2$, –78° → –20°C
(iii) LHMDS, –78°C
(iv) Br(CH$_2$)$_3$Br
–78°C → rt, 55%
S
S
O
H
CH$_2$OTBS
8.6.1.3
MgCl
THF, 0°C
S
S
OH
H
CH$_2$OTBS
8.6.1.4
BF$_3$•OEt$_2$
MeOH/THF
–40°C,45%
over two steps
OMe
H
CH$_2$OH
8.6.1.5
Swern
oxidation
88%
OMe
H
CHO
8.6.1.6
+
MgBr
THF, 0°C
80%
OMe
H
HO
8.6.1.7
PhSO$_2$Na
AcOH
i-PrOH
rt, 65%
OMe
H
PhO$_2$S
8.6.1.8
EtAlCl$_2$
CH$_2$Cl$_2$
–78°C → rt
75%, 10 : 1
OMe
H
8.6.1.9
EtSNa, DMF
reflux, 75%
OH
H
8.6.1.10
(a) Fremy's salt
DMF/H$_2$O
(b) KH$_2$PO$_4$
Na$_2$S$_2$O$_4$, 83%
OH
OH
H
Pseudopterosin
aglycone

Our studies on the final oxidation step were initially focused on strategies different from the use of Fremy's salt. We reasoned that acetylation of **8.6.1.10** (scheme **8.6.2**) followed by Fries rearrangement[87] and Baeyer-Villiger reaction would provide access to the monoacetylated catechol.

Scheme **8.6.2**.


$AlCl_3$, $PhNO_2$
reflux
No reaction
8.6.2.1
8.6.2.1
$TiCl_4$, CH_2Cl_2
–78°C
8.6.2.2
Baeyer-Villiger
OAc
8.6.2.3
OR
CH_2OP
8.6.2.4
HMDS, benzeneseleninic anhydride
R = H
decomposition
$AlCl_3$, CH_2Cl_2, reflux
R = Ac
no reaction

Unfortunately, treatment of **8.6.2.1** with $AlCl_3$ led to no reaction whereas $TiCl_4$ led to immediate decomposition even at –78°C (scheme **8.6.2**). Similar results were obtained when bicyclic substrates of the type **8.6.2.4** were employed.

We then returned to our initial approach and screened the various reaction conditions reported in literature for the Fremy's salt oxidation. Reactions of this kind are notoriously capricious and the correct solvent system has to be found for every substrate. Treatment of **8.6.1.10** with 10 eq of freshly prepared $(KSO_3)_2NO$ in H_2O/CH_2Cl_2 with Bu_4NHSO_4 as phase-transfer catalyst led to recovery of starting material. The transformation was finally achieved in good yield using the conditions very recently reported by Matsumoto *et al.*[88]. Reaction with Fremy's salt in DMF/H_2O in a flask protected from light was followed by reduction with sodium dithionite solution. The aglycone was obtained in 83% yield but it proved to be extremely unstable and prone to decomposition in $CDCl_3$ solution in the NMR tube. The quality of the ^{13}C-NMR spectra suffered from this but ^{1}H-NMR, HRMS and $[\alpha]_D$ are consistent with data reported in Dr Carpino's Ph. D. thesis[79] and McCombie synthesis[19]. Table **8.6.3** presents a comparison of selected ^{1}H NMR data relative to our synthetic aglycone and those reported by Dr. Carpino. ^{1}H NMR chemical shifts published by Fenical *et al.*[4] for the C10-monomethyl ether of pseudopterosin E aglycone are also shown.

Table **8.6.3**.

Observed ^{1}H spectrum for our synthetic aglycone: δ (360 MHz, $CDCl_3$) =	^{1}H spectrum reported by P.A. Carpino for the aglycone: δ (500MHz, $CDCl_3$) =	^{1}H spectrum of the C10-monomethyl ether of the aglycone: δ (360 MHz, $CDCl_3$) =
5.12 (1H, d, J = 9.1 Hz)	5.11 (1H, br d, J = 9.7 Hz)	5.12 (1H, d, J = 8.8 Hz)
5.07 (1H, br s)	5.03 (1H, br s)	-
4.87 (1H, br s)	4.89 (1H, br s)	-
3.62- 3.55 (1H, m)	3.57 (1H, m)	3.61 (1H, m)
2.04 (3H, s)	2.02 (3H, s)	2.05 (3H, s)
1.76 (3H, s)	1.75 (3H, s)	1.75 (3H, s)
1.70 (3H, s)	1.67 (3H, s)	1.67 (3H, s)
1.26 (3H, d, J = 7.1 Hz)	1.25 (3H,d, J = 7.03 Hz)	1.24 (3H,d, J = 7.2 Hz)
1.05 (3H, d, J = 6.1 Hz)	1.03 (3H, d, J = 6.2 Hz)	1.03 (3H, d, J = 6.2 Hz)

The ^{13}C data for the aglycone has never been reported in literature and Fenical[1] reported decomposition ot the intermediate *ortho*-quinone while attempting to purify it by HPLC.

Our first attempt to couple this catechol with glycosyl bromide **3.2.4.6** employed by Corey in his synthesis of pseudopterosin E failed. No reaction was observed after 2 days at room temperature in a sealed flask and the catechol decomposed. Alternative methods of glycosylation should be employed and the aglycone should be treated immediately after its synthesis.

8.7 Conclusions.

We achieved a synthesis of pseudopterosins A-F aglycone starting from *l*-citronellal. Our approach is direct and highly stereospecific but we encountered some problems on scaling up the Pfaltz reduction. Repeating this transformation in small batches (up to 2.5 g) partly solved this problem. The final oxidation is now viable in high yield even if the catechol is extremely unstable and should be protected immediately.

Chapter 9

Conclusions and aim for future work.

9.1 Overview of our syntheses.

We achieved two syntheses of pseudopterosins aglycones starting from readily available monoterpenes. These approaches secure facile entry to pseudopterosins A-F aglycone and its enantiomer, suitable for compounds K-L. The overall route for the first synthesis is reported in scheme **9.1.1**.

Our contribution to this synthesis provided:

- an easy access to (+)-isopulegol starting from commercial technical isopulegol *via* oxidation and reduction with L-Selectride, avoiding chromatography and in high yield;

- total stereocontrol on the introduction of the C3 center employing epoxidation and Lewis acid-catalysed oxirane opening instead of the unsatisfactory hydroboration approach;

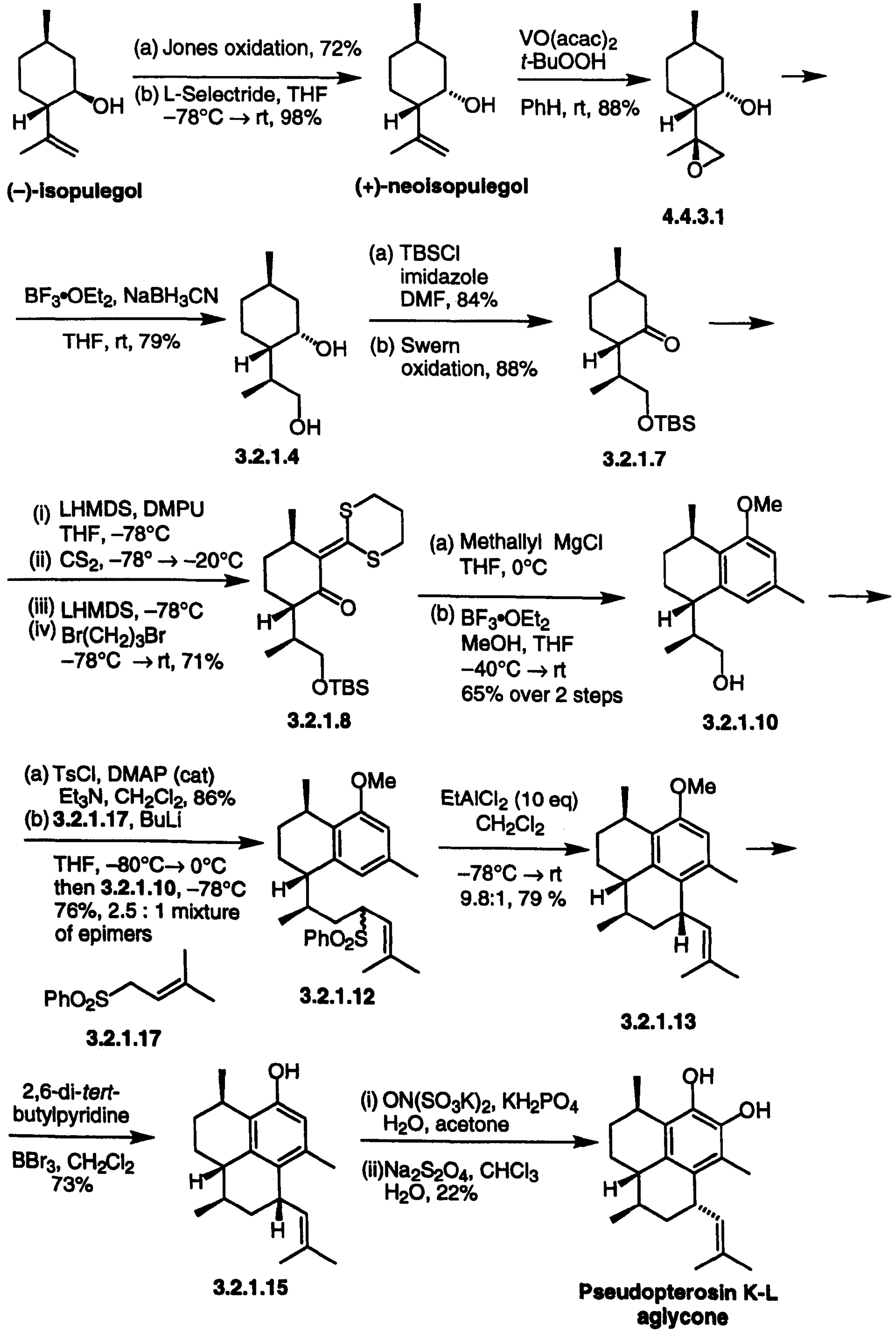
- improvement of yield (from 33 to 71%) and reproducibility in the first step of the annulation protocol after experimental observations on the mechanism of the dithioketene acetal formation;

- closure of ring C to yield the desired **3.2.1.13** in 9.8 : 1 ratio to the undesired **3.2.1.14**, improving dramatically the 1 : 1 ratio obtained in previous studies;

- confirmation of the structure of **3.2.1.13** by X-ray crystallographic analysis.

This approach was highly reliable and superior to the previously published syntheses in terms of overall yield (4.5% from isopulegol to **3.2.1.15**) and stereocontrol.

Scheme **9.1.1**.

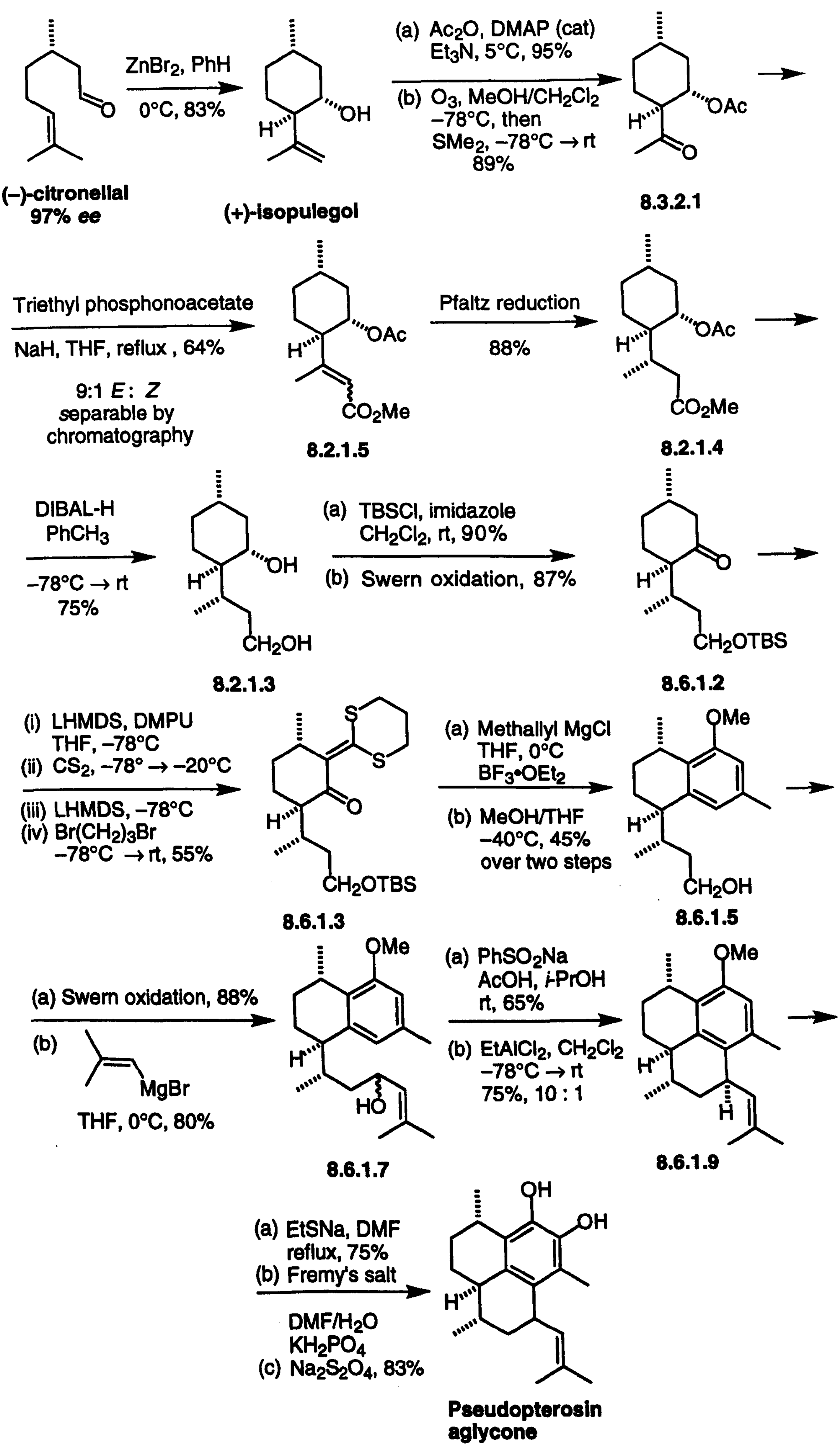

(a) Jones oxidation, 72%
(b) L-Selectride, THF −78°C → rt, 98%
(−)-isopulegol
(+)-neoisopulegol
VO(acac)2 t-BuOOH
PhH, rt, 88%
4.4.3.1
BF3•OEt2, NaBH3CN
THF, rt, 79%
3.2.1.4
(a) TBSCl imidazole DMF, 84%
(b) Swern oxidation, 88%
3.2.1.7
(i) LHMDS, DMPU THF, −78°C
(ii) CS2, −78° → −20°C
(iii) LHMDS, −78°C
(iv) Br(CH2)3Br −78°C → rt, 71%
3.2.1.8
(a) Methallyl MgCl THF, 0°C
(b) BF3•OEt2 MeOH, THF −40°C → rt 65% over 2 steps
3.2.1.10
(a) TsCl, DMAP (cat) Et3N, CH2Cl2, 86%
(b) 3.2.1.17, BuLi
THF, −80°C → 0°C then 3.2.1.10, −78°C 76%, 2.5 : 1 mixture of epimers
3.2.1.17
3.2.1.12
EtAlCl2 (10 eq) CH2Cl2
−78°C → rt 9.8:1, 79 %
3.2.1.13
2,6-di-tert-butylpyridine
BBr3, CH2Cl2 73%
3.2.1.15
(i) ON(SO3K)2, KH2PO4 H2O, acetone
(ii) Na2S2O4, CHCl3 H2O, 22%
Pseudopterosin K-L aglycone

Before improving the final oxidation step, we devised a novel approach to the synthesis of pseudopterosins A-F aglycone, as depicted in scheme **9.1.2**.

The introduction of the C3 stereocenter *via* Pfaltz reduction is the first example of application of such methodology to these substrates. Unfortunately, we encountered problems scaling up this transformation using more than 2.5 g of **8.2.1.5** and 8% or less of the catalyst. The reactions is excessively long (50% after 21 days), although the stereoselectivity is not effected.

The cyclisation step was effected in yields comparable with those obtained on different substrates, confirming the general applicability of our method. The synthesis is convergent to the sulphone intermediate used in our first approach, again in good diastereomerical purity. The final oxidation step was finally achieved in good yield using very recently published conditions. The target aglycone appears to be extremely unstable and prone to spontaneous decomposition within 1-2 days, so immediate protection or glycosylation is highly advisable in the future.

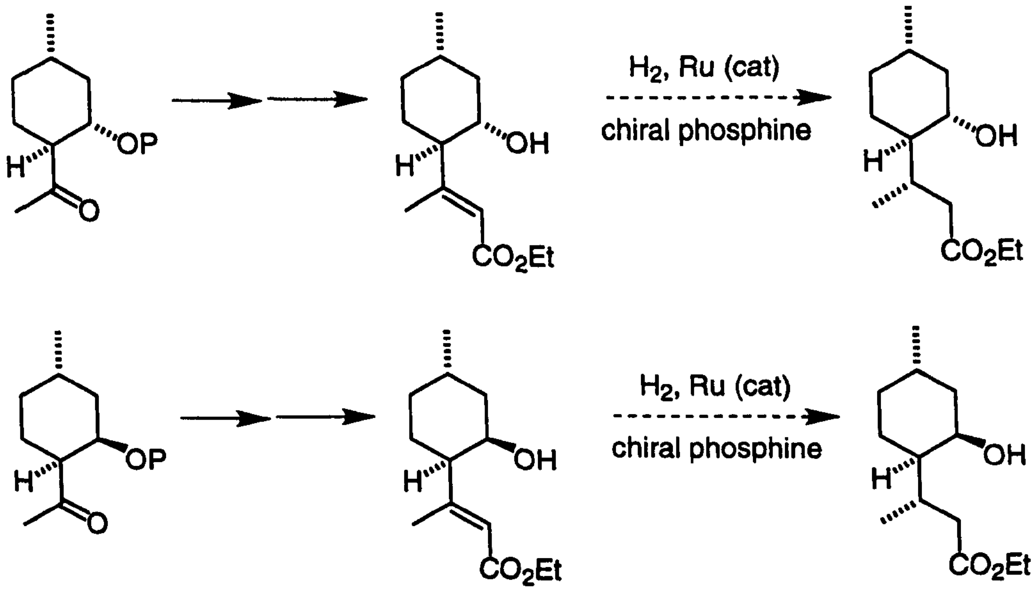
Scheme **9.1.2**.


(–)-citronellal
97% ee
ZnBr$_2$, PhH
0°C, 83%
(+)-isopulegol
(a) Ac$_2$O, DMAP (cat) Et$_3$N, 5°C, 95%
(b) O$_3$, MeOH/CH$_2$Cl$_2$ –78°C, then SMe$_2$, –78°C → rt 89%
8.3.2.1
Triethyl phosphonoacetate
NaH, THF, reflux, 64%
9:1 E : Z separable by chromatography
8.2.1.5
Pfaltz reduction
88%
8.2.1.4
DIBAL-H PhCH$_3$
–78°C → rt 75%
8.2.1.3
(a) TBSCl, imidazole CH$_2$Cl$_2$, rt, 90%
(b) Swern oxidation, 87%
8.6.1.2
(i) LHMDS, DMPU THF, –78°C
(ii) CS$_2$, –78° → –20°C
(iii) LHMDS, –78°C
(iv) Br(CH$_2$)$_3$Br –78°C → rt, 55%
8.6.1.3
(a) Methallyl MgCl THF, 0°C BF$_3$•OEt$_2$
(b) MeOH/THF –40°C, 45% over two steps
8.6.1.5
(a) Swern oxidation, 88%
(b) MgBr THF, 0°C, 80%
8.6.1.7
(a) PhSO$_2$Na AcOH, i-PrOH rt, 65%
(b) EtAlCl$_2$, CH$_2$Cl$_2$ –78°C → rt 75%, 10 : 1
8.6.1.9
(a) EtSNa, DMF reflux, 75%
(b) Fremy's salt DMF/H$_2$O KH$_2$PO$_4$
(c) Na$_2$S$_2$O$_4$, 83%
Pseudopterosin aglycone
OH
OAc
OMe
CO$_2$Me
CH$_2$OH
CH$_2$OTBS
H
O
S

9.2 Suggestions for future work.

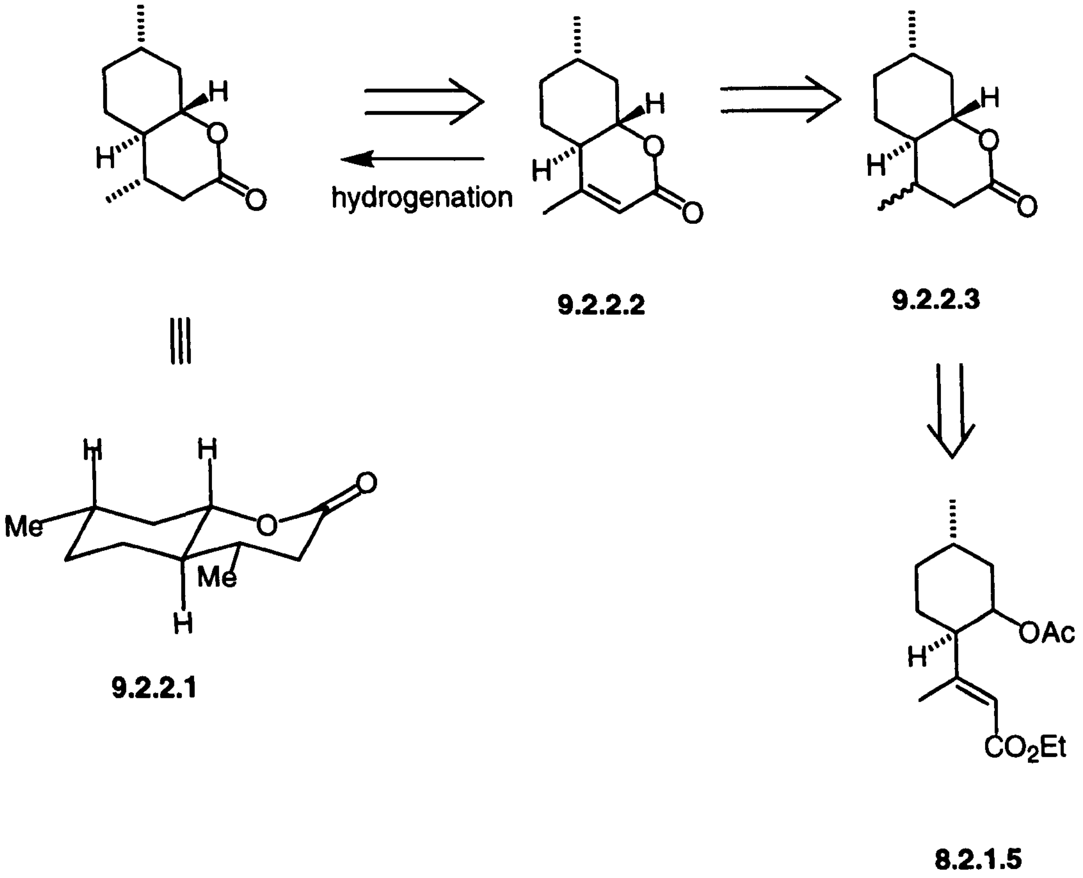
Alternatives to the Pfaltz reduction for the stereoselective reduction of α,β-unsaturated esters are not immediate to find. Direct hydrogenation of **8.2.1.5** led to a 1:1 mixture of C3 epimers, however Ru-catalysed hydrogenation of analogues with a free secondary hydroxyl group might lead to better selectivity (scheme **9.2.1**). Examples of this kind of transformation in the presence of chiral ligands have been presented and investigated by Brown[89]

Scheme **9.2.1**.



A less elegant alternative might involve the formation of an α,β-unsaturated lactone between the secondary hydroxyl group and the carboxylic moiety on the side chain. Hydrogenation of this intermediate should lead to the desired stereochemistry taking advantage of substrate control as **9.2.2.1** (scheme **9.2.2**) is the favoured all equatorial isomer. In our hands, reaction of **8.2.2.1** with the Still-Gennari reagent[90] failed to yield the *Z*-isomer required for the intramolecular lactonisation of **8.2.1.5**. *Z*-selectivity is usually achieved only starting from aldehydes. An alternative could be the sequence in scheme **9.2.3**, starting from non-stereocontrolled reduction of **8.2.1.5** with concomitant lactonisation (achieved with MeOH/Mg[86]). Reintroduction of the unsaturation could be effected *via* enolisation of the lactone, quenching with PhSeCl and elimination under oxidative conditions. This sequence should be effective, albeit not particularly concise.

Scheme **9.2.2.**

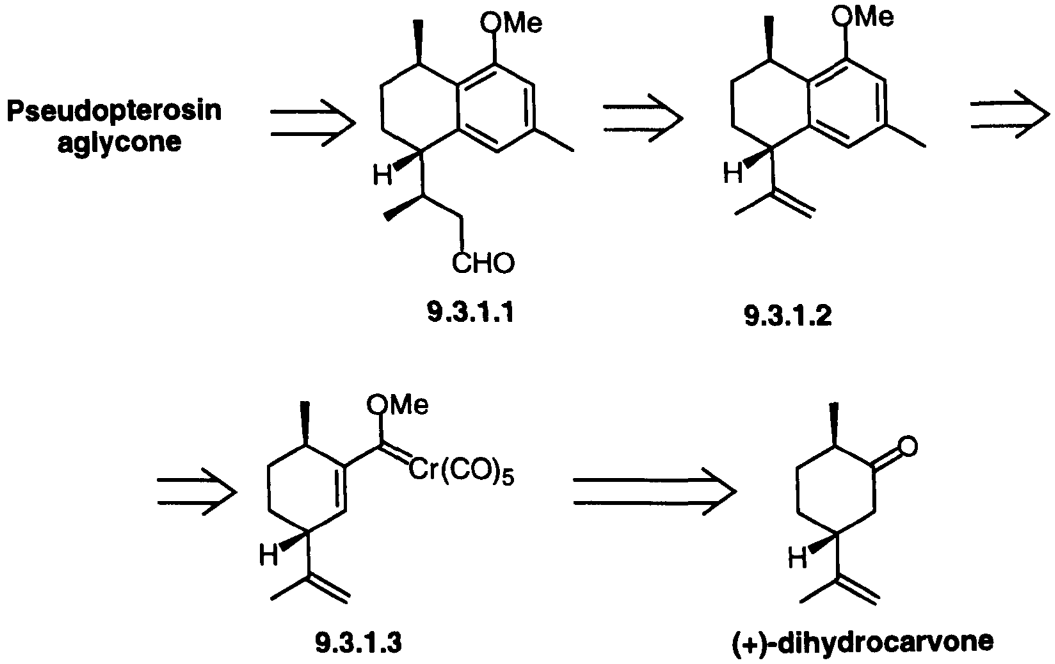


Hydrogenation of substrates analogous to **8.2.1.5** using ebthi-type catalysts[83] is also a conceivable alternative, although the lack of precedents and the not easily accessible catalyst does not make it particularly attractive. Reduction to the corresponding unsaturated diol and high-pressure hydrogenation in presence of chiral catalysts[82] might be more practicable, especially on large scale.

9.3 Alternative approaches in the Kocienski group.

Another approach to pseudopterosins aglycone was investigated in Prof. Kocienski's group by Dr. M. Signer and Dr. C. Aniès during the years 1995-1996. This route is convergent to the enantiomer of our intermediate **8.6.1.6** and starts from natural monoterpene (+)-dihydrocarvone. Cr-carbene complexes are used for the construction of the aromatic ring (scheme **9.3.1**).

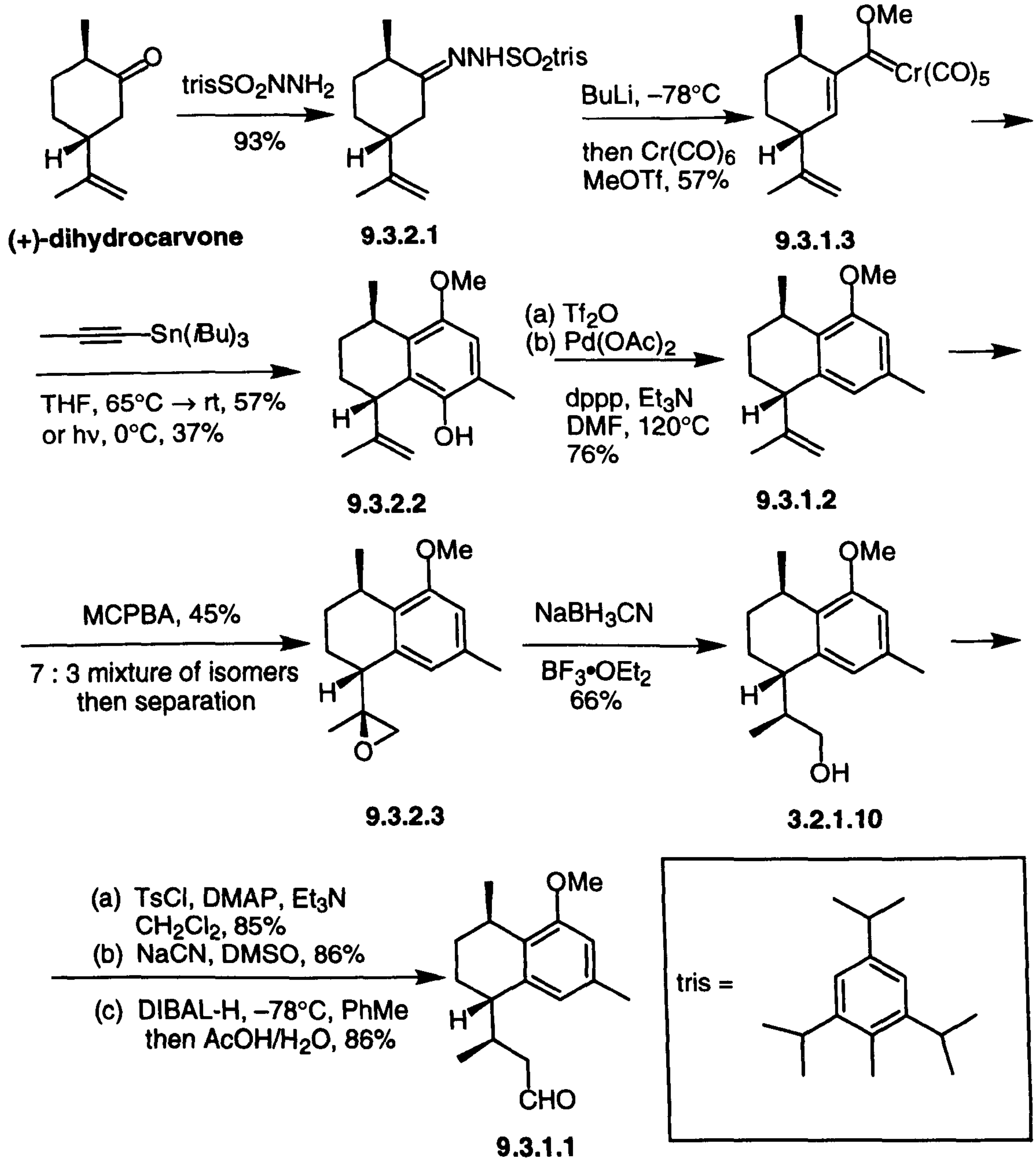
Scheme **9.3.1**.


Pseudopterosin aglycone
OMe
H
CHO
9.3.1.1
OMe
H
9.3.1.2
OMe
Cr(CO)5
H
9.3.1.3
O
H
(+)-dihydrocarvone

Although the bicyclic core is built in only five steps from dihydrocarvone (scheme **9.3.2**), introduction of the C3 stereocenter is again the major challenge. Jacobsen epoxidation[91] or a sequence of Sharpless[92] asymmetric dihydroxylation and epoxide formation from the diol could achieve the transformation of **9.3.1.2** to **9.3.2.3** more effectively.

An interesting modification to this approach would be to effect the aromatisation photochemically[60] starting from a (Z)-dienyl(alkoxy)chromium carbene complex (scheme **9.3.3**) to obtain a monosubstituted catechol instead of a protected hydroquinone.

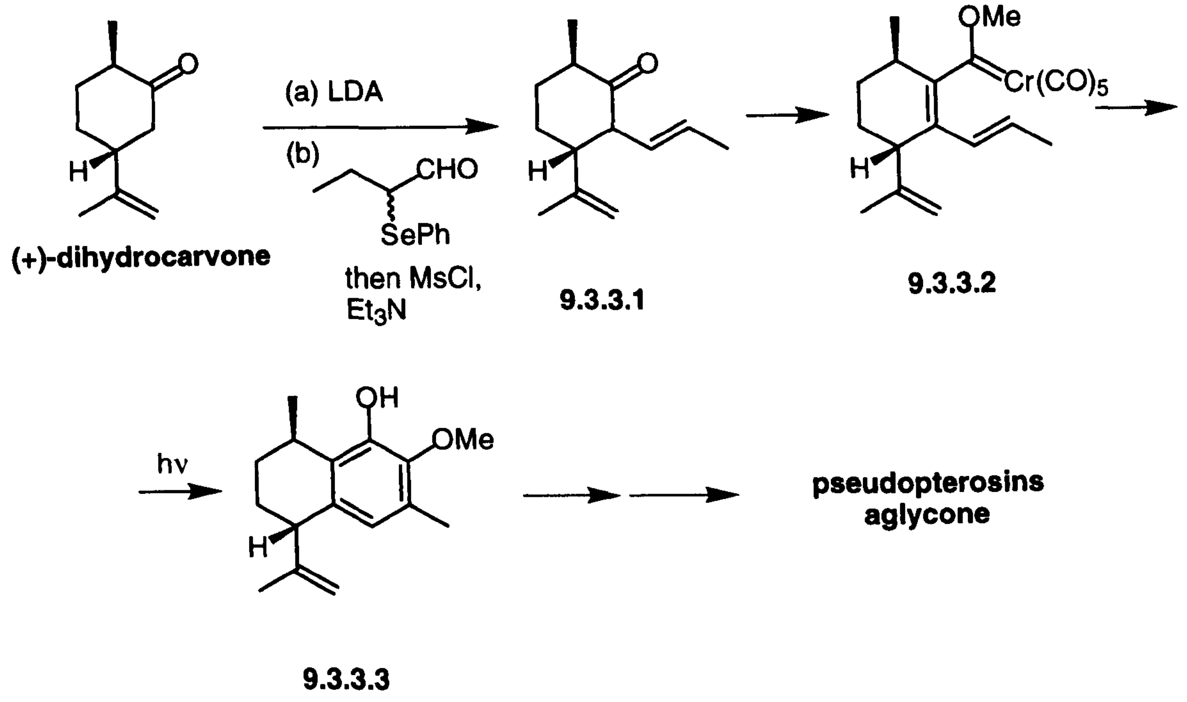
Scheme **9.3.2.**


trisSO2NNH2
93%
(+)-dihydrocarvone
NNHSO2tris
9.3.2.1
BuLi, -78°C
then Cr(CO)6
MeOTf, 57%
OMe
Cr(CO)5
9.3.1.3
Sn(*i*Bu)3
THF, 65°C → rt, 57%
or hv, 0°C, 37%
OMe
OH
9.3.2.2
(a) Tf2O
(b) Pd(OAc)2
dppp, Et3N
DMF, 120°C
76%
OMe
9.3.1.2
MCPBA, 45%
7 : 3 mixture of isomers
then separation
OMe
O
9.3.2.3
NaBH3CN
BF3•OEt2
66%
OMe
OH
3.2.1.10
(a) TsCl, DMAP, Et3N
CH2Cl2, 85%
(b) NaCN, DMSO, 86%
(c) DIBAL-H, -78°C, PhMe
then AcOH/H2O, 86%
OMe
CHO
9.3.1.1
tris =
H

This protocol might enable differentiation of the two hydroxyl groups on the aromatic ring and enhance the flexibility in the final glycosylation steps.

A suitable synthesis of β,γ-unsaturated ketones was described by D. Enders *et al*[93]. The presence of the terminal double bond could cause side reactions thus necessitating a protecting strategy.

Scheme **9.3.3.**



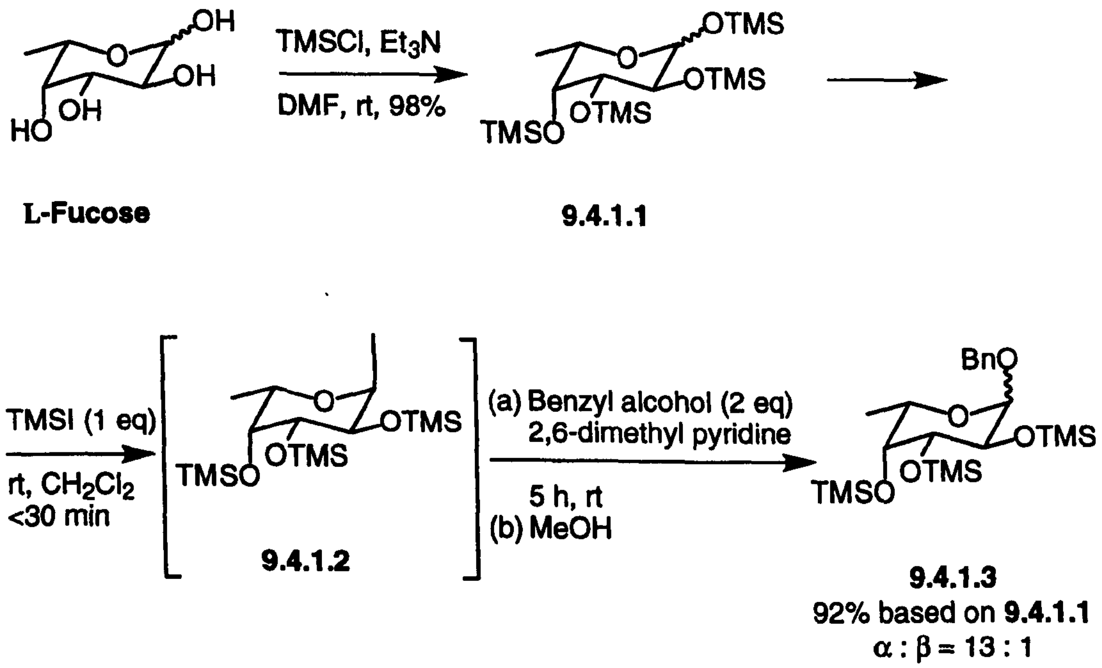
Approaches using coupling between squaric acid derivatives and cuprates[62] are also worth considering, especially for the lower toxicity of these compounds in comparison to CS_2 and $Cr(CO)_6$.

9.4 Approaches to glycosylation.

Total synthesis of natural pseudopterosins and bioactive analogues could be achieved by coupling the aglycones with suitable glycosyl units. Our attempts to synthesise pseudopterosin E using the method reported by Corey[16] failed and we had to postpone further investigations due to lack of time and to the instability of our aglycone. Extensive experimentations towards the glycosylation step might be needed, considering the wealth of literature on the synthesis of α-fucosides[94]. Fully protected glycosyl bromides of the type used by Corey are notoriously unstable and usually lead to inefficient reactions. Orthoesters-[95], imidates-[96] and thioethers-based methodologies are generally more effective and the corresponding glycosyl derivatives are easier to prepare. Both α- and β-glycosides are accessible *via* these methods. Removal of protecting groups, in most cases benzyl ethers, after coupling is almost always necessary.

A very simple procedure for α-fucosylation was published in 1996 by Uchiyama and Hindsgaul[97] (scheme **9.4.1**).
The iodide generated *in situ* from fully protected fucose **9.4.1.1** reacted with various alcohols to give α-glycosides in good yield and with no need for further activation.

Scheme **9.4.1.**


L-Fucose
TMSCl, Et_3N
DMF, rt, 98%
9.4.1.1
TMSI (1 eq)
rt, CH_2Cl_2
<30 min
9.4.1.2
(a) Benzyl alcohol (2 eq)
2,6-dimethyl pyridine
5 h, rt
(b) MeOH
9.4.1.3
92% based on 9.4.1.1
α : β = 13 : 1

One-pot deprotection and the short time of reaction make this method quite suitable for our purposes. However, only alcohols were employed in the original paper, so coupling with phenols and catechols should be investigated before attempting reaction with aglycones of pseudopterosins. Using substrates different from benzyl alcohol, up to 5 equivalents of **9.4.1.1** had to be used to obtain 47% conversion.

Enzymatic fucosylation[98] is also an interesting alternative, although rather costly.

9.5 Final conclusions.

Our two approaches to pseudopterosin are superior to those previously published for stereoselectivity and simplicity. We are confident that a wide range of pseudopterosins and biologically active analogues can be synthesised using our methodology as it is or with minor modifications. The problems we highlighted and solved on our routes should be of great help to other researchers in the synthesis of similar compounds. Finally, our modification of the Dieter procedure appears to be a general application for this challenging benzannulation.

Chapter 10
Experimental section.

10.1 General experimental.

All reactions requiring anhydrous conditions were carried out in flame-dried apparatus under inert atmosphere of dry nitrogen. All glass syringes, teflon stirring bars, cannulas and needles were dried in an oven at 120°C overnight prior to use and allowed to cool to rt in a desiccator in the presence of $CaCl_2$. Plastic syringes were stored in a desiccator under vacuum and in the presence of $CaCl_2$. Dry solvents were freshly distilled prior to use: THF and diethyl ether from sodium/benzophenone; dichloromethane and dimethylformamide from calcium hydride; benzene and toluene from sodium wire; methanol and isopropanol from the corresponding magnesium alkoxides. Petrol ether 40-60°C ("hexanes") was distilled before use.

Oxalyl chloride, carbon disulfide, ethanethiol, DMPU, acetyl chloride, $BF_3{\bullet}OEt_2$, 1,3-dibromopropane, methallyl chloride, 1-bromo-2-methylpropene and 2,6-di-*tert*-butyl-4-methylpyridine were freshly distilled prior to use. DMSO was distilled from calcium hydride and stored over 4Å molecular sieves under N_2. Triethylamine and HMDS were distilled from calcium hydride and stored over KOH under N_2. Molecular sieves were freshly activated by heating with a Bunsen flame until the evolution of water ceased and then cooled under a stream of dry N_2. Imidazole was recrystallised from dry benzene prior to use. Commercial toluenesulphonyl ("tosyl") chloride was recrystallised from $CHCl_3$. Triphenylphosphine was recrystallised from hexane. 4-Nitrobenzoic acid was crystallised from benzene and kept in a desiccator under vacuum.. Commercial solutions of alkyllithium reagents were titrated against solutions of diphenylacetic acid[99] or 1,3-diphenylacetone *p*-toluenesulphonyl hydrazone[100] in dry THF. All other reagents were used as supplied.

Fremy's salt was prepared according to the published procedure[78], stored under an atmosphere of NH_3 (NH_4Cl) in a desiccator and used within 3 days from preparation.

All reactions were magnetically stirred and were monitored by TLC using Macherey-Nagel Düren Alugram Sil G/UV_{254} pre-coated aluminium foil plates, layer thickness 0.25 mm. Compounds were visualised by UV, then with 20 wt.% PMA in ethanol. Organic solutions were concentrated using a Büchi Rotavapor R-114 at ca 20 mmHg between 20 and 60°C.

Flash chromatography was performed on Sorbisil silica gel 60 (40-60 mesh) or Merck silica gel 60 (-230 mesh) according to the general procedure of Still[101].

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

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

IR spectra were recorded in a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates or as solutions in chloroform when specified. Absorptions are reported as values in cm^{-1}. Strong, medium, weak and broad absorptions are designated s, m, w and br, respectively.

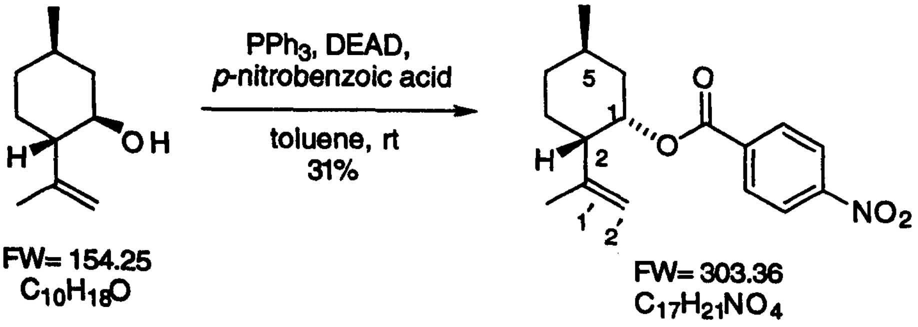
Proton NMR spectra were recorded in Fourier Tranform mode on Jeol JNX-GX-270 (270 MHz), Bruker AC 300 (300 MHz) or Bruker AM 360 (360 MHz) spectrometers. Spectra were obtained in $CDCl_3$ solutions and the chemicals shifts are reported as values in ppm relative to residual chloroform (δ = 7.27). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (app.) apparent. Coupling constants (*J*) are reported in Hertz.

Carbon-13 NMR spectra were recorded in Fourier Tranform mode on Jeol JNX-GX-270 (67.5 MHz), Bruker AC 300 (75 MHz) or Bruker AM 360 (90 MHz) spectrometers. Spectra were obtained in $CDCl_3$ solutions and the chemicals shifts are reported as values in ppm relative to residual chloroform (δ = 77.2). Multiplicities were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: (0) quaternary, (1) methine, (2) methylene, (3) methyl.

Mass spectra were run on a VG 70-250-SE spectrometer in electron ionisation (EI) or chemical ionisation (CI) mode or on a Micromass Platform quadrupole mass analyser (Micromass, Tudor Road, Altrincham, UK) with an electrospray ion source in positive ions detection mode (ESI+). Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and, where shown, the proposed signal assignment.

10.2 Experimental procedures and data.

(1*S*,2*S*,5*R*)-5-Methyl-2-(1-methylethenyl)-1-[(*p*-nitrobenzoyl)oxy]cyclohexane, (+)-neoisopulegyl *p*-nitrobenzoate (3.2.1.1).



(–)-Isopulegol (14.5 g, 15.9 mL, 92.8 mmol) was added to a solution of PPh_3 (29.1 g, 110.8 mmol, 1.2 eq) and *p*-nitrobenzoic acid (18.55 g, 110.8 mmol, 1.2 eq) in toluene (350 mL). The mixture was cooled to 0°C in an ice bath and DEAD (19.3 g, 17.5 mL, 110.8 mmol, 1.2 eq) was slowly added over 40 min *via* syringe. The cooling bath was removed and the mixture stirred at rt for 16 h. The orange suspension was filtered and the filtrate washed with a saturated solution of $NaHCO_3$ (150 mL). The organic phase was separated and the aqueous layer extracted with toluene (75 mL x 3). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with Et_2O-hexanes (5:95) to give the title compound (9.29 g, 28.8 mmol, 31%) as pale yellow needles, mp 88-89°C (hexanes): $[\alpha]_D$= +14.7 (c = 2.77, $CHCl_3$)

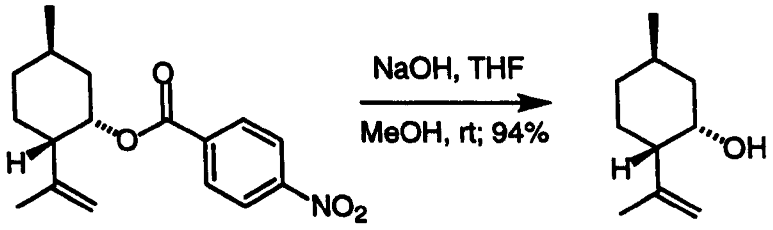
IR (nujol): ν = 2922 s, 2852 s, 1721 s (C=O), 1647 m, 1598 m, 1520 s, 1456 s, 1275 s, 1177 s, 1103 s, 717 s cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ= 8.28 (2H, d, AA′ portion of an AA′BB′ system, J_{AB}= 9.0 Hz, CH Ar), 8.17 (2H, d, BB′ portion of an AA′BB′ system, J_{AB}= 9.0 Hz, CH Ar), 5.55 (1H, m, C1H), 4.76 (1H, s, C2′H), 4.71 (1H, s, C2′H), 2.18 -2.02 (2H, m, $C6H_2$), 2.01-1.82 (1H, m, C2H), 1.78-1.65 (5H, m, C3′H + C3H + C4H), 1.31 (1H, ddd, J = 14.3, 12.1, 2.2, C3H), 1.08 (1H, dq, J = 11.8, 3.7, C4H), 0.92 (3H, d, J = 6.6 Hz, C5Me), 0.91 (1H, m, C5H)

^{13}C NMR (75 MHz, $CDCl_3$): δ= 164.0 (0), 150.5 (0), 146.0 (0), 136.5 (0), 130.8 (2C, 1), 123.7 (2C, 1), 111.2 (2), 72.4 (1), 47.1 (1), 39.3 (2), 34.6 (2), 27.1 (1), 25.4 (2), 22.6 (3), 22.2 (3).

Lit reference: Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron* **1993**, *49*, 6429.

(1*S*,2*S*,5*R*)-5-Methyl-2-(1-methylethenyl)-1-cyclohexanol; (+)-neoisopulegol (3.2.1.2).



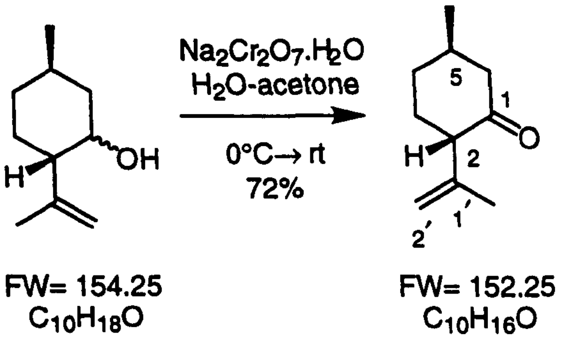
FW= 303.36
$C_{17}H_{21}NO_4$

FW= 154.25
$C_{10}H_{18}O$

To a solution of 9.00 g (29.7 mmol) of the isopulegyl *p*-nitrobenzoate in THF/MeOH (1:2 mixture, 100 mL) was added NaOH (2 M, 20 mL, 40 mmol). After 15 h at rt the solvents were removed *in vacuo* and water (25 mL) and ether (25 mL) were added. The organic phase was separated and the aqueous layer was extracted with Et_2O (35 mL x 3). The combined organic layers were washed with Na_2CO_3 (15 mL) and brine (15 mL) and dried over $MgSO_4$. The residue on evaporation was purified by column chromatography on silica gel eluting with Et_2O-hexanes (1:9) to give the title compounds as a colourless oil (4.1 g, 26.2 mmol, 94%): $[\alpha]_D = +26.8$ (*c* = 5.1, $CHCl_3$); lit.[35] $[\alpha]_D = +23.5$ (neat).

IR, ^1H NMR, ^{13}C NMR data consistent with those reported in literature[35]

(2*S*,5*R*)-5-Methyl-2-(1-methylethenyl)-1-cyclohexanone; (–)-isopulegone.



The oxidation was carried out according to the procedure of Friedrich and Bohlmann[51].To a solution of $Na_2Cr_2O_7.2H_2O$ (25.9 g, 86.7 mmol, 1 eq) in H_2O (80 mL) was added conc. H_2SO_4 (19 mL, 34.3 g, 8 eq) at a rate sufficient to maintain the temperature below 20°C with an ice bath. The solution was then cooled to 0°C and added to a solution of commercial technical grade isopulegol (25.5 g, 27.99 mL, 165.3 mmol, 1 eq) in acetone (200 mL) at 0°C. The temperature was kept between 5° and 10° C during the addition, then the ice bath was removed and the dark green mixture stirred at rt overnight. Acetone was partially removed by distillation and the organic phase extracted with Et_2O (2 x 75 mL), then AcOEt (2 x 50 mL) and the organic extracts washed with $NaHCO_3$ (45 mL) and then brine (25 mL). After drying over Na_2SO_4, the solvent was removed *in vacuo* and the residual dark brown solution distilled (bp = 121°C/16 mm Hg) to give the title ketone (18.1 g, 119.0 mmol, 72%) as a colourless oil.

IR (film): ν = 3074 w, 2928 s, 2869 s, 1712 s, C=O, 1648 w, 1456 m, 1375 w, 1191 w, 1126 w, 890 m cm^{-1}.

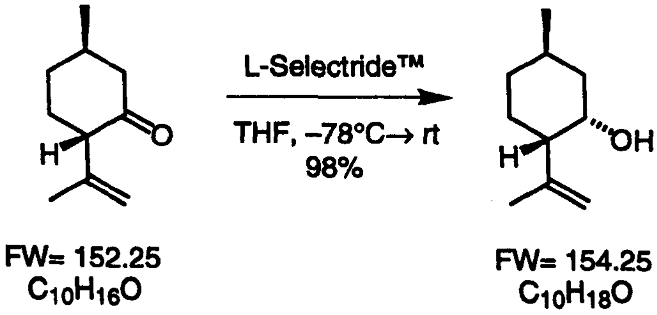
^{1}H NMR (300 MHz, CDCl$_3$): δ(ppm)= 4.92-4.88 (1H, dd, *J* = 2.5, 1.4 Hz, C2′H), 4.70-4.67 (1H, m, C2′H), 2.92 (1H, dd, *J*= 12.9, 5.5 Hz, C2H), 2.73-2.41 (1H, m, C3H0, 2.41-2.32 (1H, m, C6H), 2.26-1.76 (4H, m, C6H + C3H + C4H$_2$), 1.71 (3H, s, C1′Me), 1.50-1.22 (1H, m, C3H), 1.11 (3H, d, *J*= 6.2 Hz, C5Me).

^{13}C NMR (75 MHz, CDCl$_3$): δ(ppm)= 210.3 (0), 143.6 (0), 113.0 (2), 57.8 (1), 50.7 (2), 35.5 (1), 34.0 (2), 31.7 (3), 31.3 (2), 22.5 (3).

LRMS (ESI$^+$ mode, CH$_3$CN): *m/z* (%)= 153 [$(M+H)^+$, 100]

Spectroscopic data are consistent with those reported in literature[51]
Friedrich, D.; Bohlmann, F. *Tetrahedron* 1988, *44*, 1392.

(1*S*,2*S*,5*R*)-5-Methyl-2-(1-methylethenyl)-1-cyclohexanol; (+)-neoisopulegol.

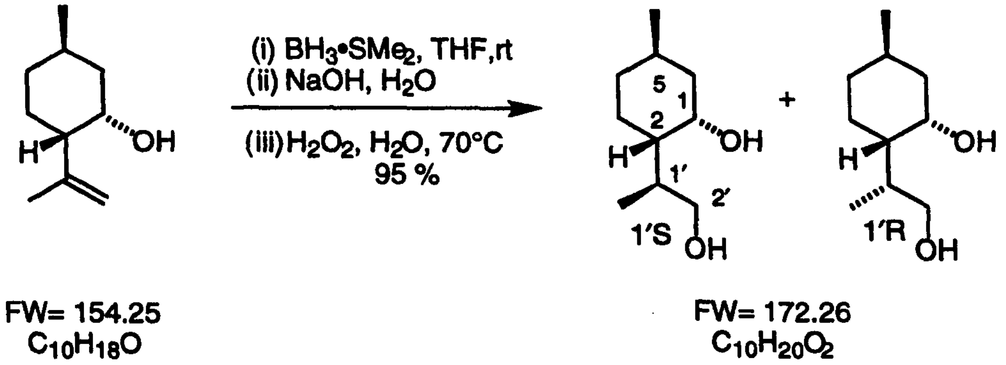


The reduction was carried out according to the procedure of Friedrich and Bohlmann[51]
A solution of (–)-isopulegone (18.11 g, 118.9 mmol, 1 eq) in dry THF (220 mL) was placed in a flame dried three necked flask fitted with thermometer, 250 mL pressure-equilibrating dropping funnel and condenser under Argon atmosphere and cooled to –75°C in an acetone/ dry ice bath. L-Selectride™ (1M solution in THF, 175 mL, 175 mmol, 1.47 eq) was added dropwise from the dropping funnel keeping a gentle evolution of gas and maintaining the temperature below –70°C. The solution was allowed to warm to rt over 8 h after the end of additions. The solution was cooled to +10°C in an ice bath and 3M NaOH aqueous solution (85 mL, 256.5 mmol, 2.21 eq) was slowly added from the dropping funnel followed by H$_2$O$_2$ 30% (85 mL,

256.5 mmol, 2.21 eq) maintaining the temperature between +15° and +35°C during the addition. After 15 min from the end of the addition, THF was partially removed at the rotavapor before addition of Et_2O (80 mL) and separation of the organic layer. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined ethereal phases washed with 2N HCl (40 mL) and brine (20 mL) before drying on Na_2CO_3/ Na_2SO_4. The solvent was then removed at the rotavapor and (+)-neoisopulegol obtained by distillation under reduced pressure (132°C/ 16 mmHg) as a colourless oil (17.98 g, 116.5 mmol, 98%).

Spectroscopic data are in agreement with those reported in literature: [35]
Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta* 1967, *50*, 153.
Procedure: Friedrich, D.; Bohlmann, F. *Tetrahedron* 1988, *44*, 1392.

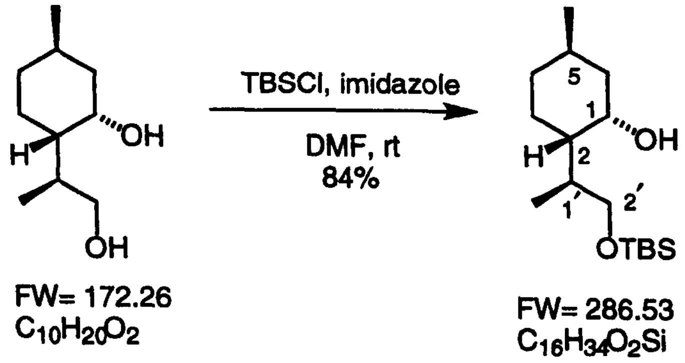
Hydroboration of Neoisopulegol



To a solution of neoisopulegol (5.4 g, 35 mmol) in dry THF (100 mL) was added dropwise over 40 min BH_3 (40 mL of 1.0 M solution in THF, 40 mmol, 1.14 eq) at a rate sufficient to maintain slow gas evolution. When the addition was complete, the clear solution was stirred at rt for 3 h, then NaOH (3 M, 17.4 mL, 52.2 mmol, 1.5 eq) was slowly added and the mixture then refluxed at 60°C for 2 h. The mixture was cooled in an ice bath and H_2O_2 (30%, 22 mL) was added dropwise at a rate sufficient to maintain the temperature below 30°C. After completing the addition, the reaction mixture was stirred for 1 h at rt and then refluxed overnight.

The bulk of THF was removed *in vacuo* and the residue was diluted with Et_2O (40 mL) and washed with brine (40 mL). After extraction of the aqueous phase with ether (35 mL x 3), the combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the residue purified by column chromatography on silica gel eluting with AcOEt-Et_2O (1:4) to give the title compound (5.85 g, 97%) as an inseparable 2:1 mixture of diastereoisomeric **(1*R*,2*S*,5*R*)-2-[(*S*)-2-Hydroxy-1-methylethyl]-5-methyl-1-cyclohexanol (3.2.1.4)** and **(1*R*,2*S*,5*R*)-2-[(*R*-2-Hydroxy-1-methylethyl]-5-methyl-1-cyclohexanol (3.2.1.3)** identified by comparison with the reported data[35] for IR, ^1H and ^{13}C NMR.

(2*S*,5*R*)-2-[(*S*)-2-[(*t*-Butyldimethylsilyl)oxy]-1-methylethyl]-5-methylcyclohexan-1-ol (3.2.1.6).



To a solution of **3.2.1.4** (3.50 g, 20.3 mmol) and imidazole (3.18 g, 46.74 mmol, 2.3 eq) in dry DMF (15 ml) was added TBSCl (3.37 g, 22.35 mmol, 1.1 eq). After 15 min the reaction mixture was poured into NH_4Cl (20 mL) and the product extracted into hexanes. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with Et_2O-hexanes (1:25) to give the title compound (4.89 g, 17.05 mmol, 84%) as a colourless oil: $[\alpha]_D = +7.1$ (c = 3.9 in $CHCl_3$).

IR (film): $\nu = 3440$ br, 2927 s, 2858 s, 1472 m, 1461 m, 1354 s, 1071 s, 961 m, 937 m, 836 s, 776 s, 666 m cm^{-1}.

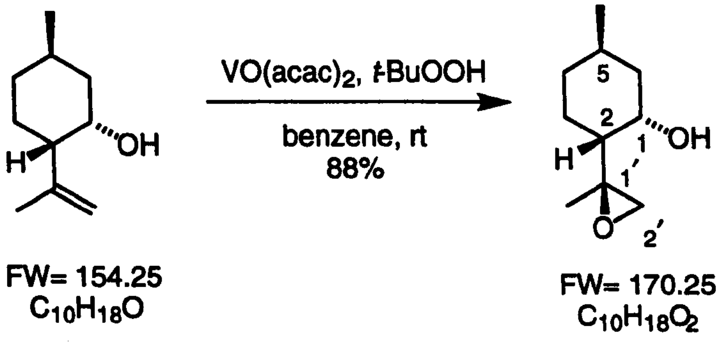
^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.07$ (1H, m, C1H), 3.66 (2H, overlapping br s, OH, and dd, A portion of an ABX system, $J_{AB} = 10.4$, $J_{AX} = 2.4$ Hz, C2'H_A), 3.52 (1H, dd, B portion of an ABX system, $J_{AB} = 10.4$, $J_{BX} = 6.2$ Hz, C2'H_B), 1.92-1.59 (6H, m, C6H_2 + C3H_2 + C4H_2), 1.29-0.98 (3H, m, C2H + C5H+C1'H), 0.94 (3H, d, $J = 6.4$ Hz, C1'Me), 0.91 (9H, s, *t*-Bu), 0.85 (3H, d, $J = 6.4$ Hz, C5Me), 0.08 (6H, s, $SiMe_2$).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 66.3$ (2), 66.2 (1), 46.9 (1), 41.9 (2), 38.4 (1), 35.6 (2), 26.3 (1), 26.0 (3C, 3), 25.8 (2), 22.6 (3), 18.4 (0), 16.3 (3), –5.5 (2C, 3).

LRMS (CI mode, NH_3): *m/z* (%)= 287 (MH^+, 100), 137 (48).

HRMS (CI mode, isobutane): found= 287.2414 $(MH)^+$, $C_{16}H_{35}O_2Si$ requires 287.2406.

(1*S*,2*R*,5*R*)-2-[(*R*)-1-Methyl-1,2-epoxyethyl]-5-methyl-1-cyclohexanol (4.4.2.1).



The reaction was carried out following the procedure reported by Friedrich and Bohlmann[51].

A solution of *tert*-butylhydroperoxide in isooctane (4.4 M, 11.2 mL, 49.3 mmol, 1.41 eq) was slowly added to a solution of vanadyl acetylacetonate (872 mg, 3.29 mmol, 0.094 eq) and isopulegol (5.93 mL, 5.40 g, 35.0 mmol) in benzene (65 mL) at rt. The colour of the solution changed from violet to brown during the addition. After 90 min the clear solution was poured into $NaHCO_3$ (70 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with with brine (15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes-Et_2O (1:1) to give the title compound (5.25 g, 30.8 mmol, 88%) as white crystals, mp 55–56°C.

^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) are in agreement with data reported by Friedrich and Bohlmann[51].

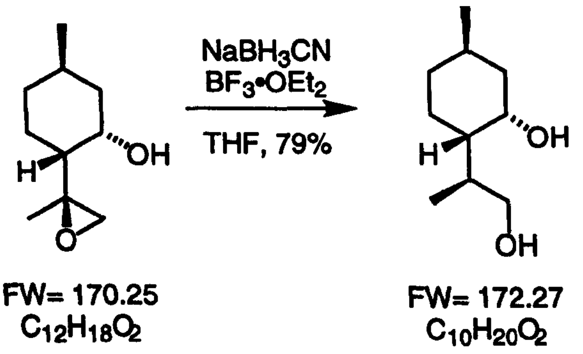
IR ($CHCl_3$) : ν = 3523 m, br (OH), 3007 m, 2927 s, 1457 m, 1405w, 1124 m, 946 m, 822 s cm^{-1}

^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm)= 4.30 (1H, m, C1H), 2.78 (1H,dd, *J*= 4.5, 0.6 Hz, C2'H), 2.68 (1H, s, OH), 2.47 (1H, d, *J*= 4.5 Hz, C2'H), 1.89- 1.68 (3H, m, C4H + C5H+C6H), 1.49- 1.37 (6H, m, C2H + $C3H_2$+C2'Me), 1.12- 0.80 (2H, m, C4H + C6H), 0.84 (3H, d, *J*= 6.4 Hz, C5Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm)= 68.0 (1), 60.4 (0), 51.5 (2), 44.4 (1), 42.1 (2), 34.6 (2), 25.6 (1), 22.3 (2C, 3+ 2), 21.9 (3).

LRMS (ESI$^+$ mode, CH_3CN): *m/z* (%)= 363[(2M+Na)$^+$, 15], 193[(M+Na)$^+$, 100], 153[(M-OH)$^+$, 12]

(1*R*,2*S*,5*R*)-2-[(*S*)-2-Hydroxy-1-methylethyl]-5-methyl-1-cyclohexanol (3.2.1.4).



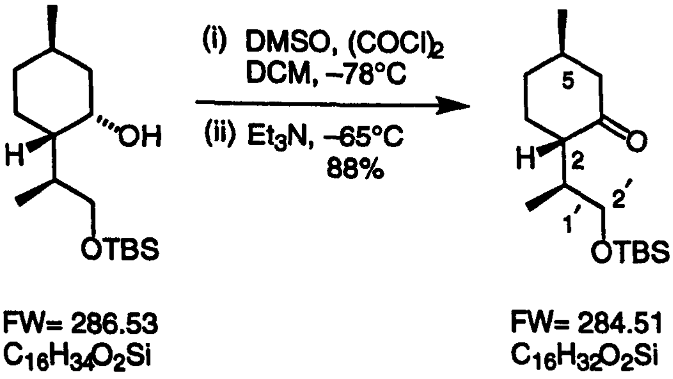
Sodium cyanoborohydride (4.47 g, 71.2 mmol, 3 eq) was added to a solution of epoxide **4.4.2.1** (4.04 g, 23.7 mmol) and a drop of bromocresol green in dry THF (5 mL). A solution of BF_3•OEt_2 in dry THF (0.8 M) was added dropwise until the colour changed to yellow. The reaction mixture was stirred for 12 h maintaining the yellow colour by dropwise addition of the BF_3•OEt_2 solution, then diluted with brine (35 mL) and extracted with AcOEt (5 x 35 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with AcOEt: hexanes (1:1) to give the title compound (3.24 g, 18.8 mmol, 79%) as a pale yellow oil. The product gave [α]$_D$, IR, ^{1}H NMR (300 MHz), and ^{13}C NMR (75 MHz) spectra consistent with data published by Schulte-Elte and Ohloff [35] $[\alpha]_D = +17.5$ ($c = 10$, $CHCl_3$), reported +17.0[35].

IR (film): ν = 3312 br (OH), 2912 s, 1456 s, 1376 m, 1367 w, 1305 w, 1106 w, 1065 m, 1035 s, 972 w, 936 w, 847 s cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm)= 4.16-4.10 (1H, m, C1H), 3.65 (1H, dd, A portion of an ABX system, J_{AB}= 10.8, J_{AX}= 2.9 Hz, C1′H_A), 3.54 (1H, dd, B portion of an ABX system, J_{AB}= 10.8, J_{BX}= 5.7 Hz, C1′H, C1′H_B), 3.33 (2H, br s, OH), 1.88-1.70 (4 H, m, C6H_2 + C3H_2), 1.64-1.54 (1H, m, C4H), 1.52-1.38 (1H, m, C4H), 1.28-1.10 (2H, m, C2H + C5H), 0.99 (3H, d, J = 7.1 Hz, C1′Me), 0.95 (1H, m, C1′H) 0.85 (3H, d, J = 6.2 Hz, C5Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 66.4 (1), 64.8 (2), 46.2 (1), 42.4 (2), 38.3 (1), 35.5 (2), 26.3 (1), 25.6 (2), 22.5 (3), 16.1 (3).

(2*S*,5*R*)-2-{(*S*)-2-[(*t*-Butyldimethylsilyl)oxy]-1-methylethyl}5-methylcyclohexan-1-one (3.2.1.7).



DMSO (1.02 g, 926 µl, 13.0 mmol, 2.5 eq) in CH_2Cl_2 (15 mL) was added dropwise to a solution of oxalyl chloride (0.80 g, 0.55 mL, 6.30 mmol, 1.2 eq) in dry CH_2Cl_2 (8 mL) at –72°C over 7 min. After 5 min alcohol **3.2.1.6** (1.50 g, 5.23 mmol) in CH_2Cl_2 (4 mL) was slowly added over 4 min at –65°C. After 90 min stirring at –65°C, Et_3N (2.18 g, 3 mL, 21.5 mmol, 4.1 eq) was added over 8 min and mixture allowed to warm to rt over 2 h. The white suspension was poured into vigorously stirred aq. NH_4Cl (15 mL) and extracted into hexanes (3 x 20 mL). The combined organic phases were washed with HCl (1.5 M, 10 mL) followed by brine (10 organic phases were washed with HCl (1.5 M, 10 mL) followed by brine (10 mL). The residue obtained on concentration *in vacuo* was purified by column chromatography on silica gel eluting with hexanes-Et_2O (95:5) to give the title compound (1.31 g, 4.60 mmol, 88%) as a pale yellow oil: $[\alpha]_D = -7.4$ ($c = 2.5$, $CHCl_3$).

IR (film): $\nu = 2955$ s, 2857 s, 1710 s, 1471 m, 1387 m, 1256 m, 1087 s, 836 s, 776 s cm^{-1}.

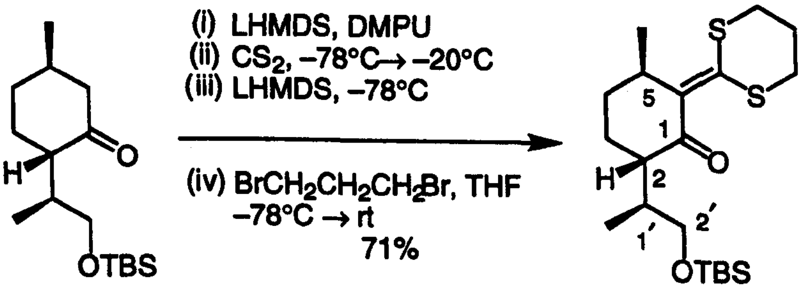
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 3.45 (2H, AB part of an ABX system, J_{AB}= 9.9, J_{BX}= 7.3, J_{AX}= 5.5 Hz, C2'H_{AB}), 2.43-2.2 (3H, m, C6H_2 + C2H), 2.05-1.80 (4H, m, C3H_2 + C1'H+C5H), 1.41-1.10 (2H, m, C4H_2), 1.02 (3H, d, J = 6.2 Hz, C1'Me), 0.88 (9H, s, *t*-Bu), 0.80 (3H, d, J = 7.0 Hz, C5Me), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 212.6 (0), 66.0 (2), 51.0 (2), 50.0 (1), 35.4 (1), 34.1 (2), 33.3 (1), 27.0 (2), 26.1 (3C, 3), 22.5 (3), 18.4 (0), 12.9 (3), –5.4 (3), –5.5 (3).

LRMS (CI^+ mode, NH_3): *m/z* (%)= 285 [$(M+H)^+$, 100], 227 (66), 153 (33).

HRMS (CI mode, NH_3): found $(M+H)^+$, 285.2249 $C_{20}H_{33}O_2Si$ requires 285.2250.

(2*S*,5*R*)-2-{(*S*)-2-[(*t*-Butyldimethylsilyl)oxy]-1-methylethyl}-5-methyl-6-(1,3-dithiane-2-ylidene)-cyclohexan-1-one (3.2.1.8).



FW= 286.51
$C_{16}H_{32}O_2Si$

FW= 400.72
$C_{20}H_{36}O_2SiS_2$

1.05 eq) was added slowly over 7 min. The mixture was warmed to rt over 30 min, then the clear solution was cooled again to –78°C and DMPU (1.06 mL, 1.11 g, 8.67 mmol, 1.05 eq) was added dropwise over 5 min. After stirring for 20 min at the same temperature, a solution of the ketone (2.35 g, 8.26 mmol) in THF (12 mL) was added dropwise over 10 min and the solution stirred at –78°C for a further 30 min before rapid addition of CS_2 (522 μL, 660 mg, 8.67 mmol, 1.05 eq). The orange solution was allowed to warm to –20°C over 2 h, stirred at this temperature for 90 min, and cooled again to –78°C before addition of a second portion of LHMDS solution in THF (1.05 eq) prepared as above. 1,3-Dibromopropane (885 μL, 1.75 g, 8.67 mmol, 1.05 eq) in THF (28 mL) was added after 30 min, the solution was allowed to warmed to rt over 13 h and then poured into aq. NH_4Cl (60 mL). The aqueous phase was separated, extracted with Et_2O (3 x 40 mL) and the combined organic layers washed with brine (20 mL) before drying over Na_2SO_4. The residue obtained on concentration *in vacuo* was purified by column chromatography on silica gel eluting with hexanes-Et_2O (4:1) to give the title compound (2.35 g, 5.86 mmol, 71%) as a dark orange oil: $[\alpha]_D$= +14.3 (c = 12, $CHCl_3$).

IR (film): ν = 2928 s, 2856 s, 1643s, 1472 s, 1418 m, 1281 m, 1255 m, 1087 s, 837 s, 775 s, 668 s cm^{-1}.

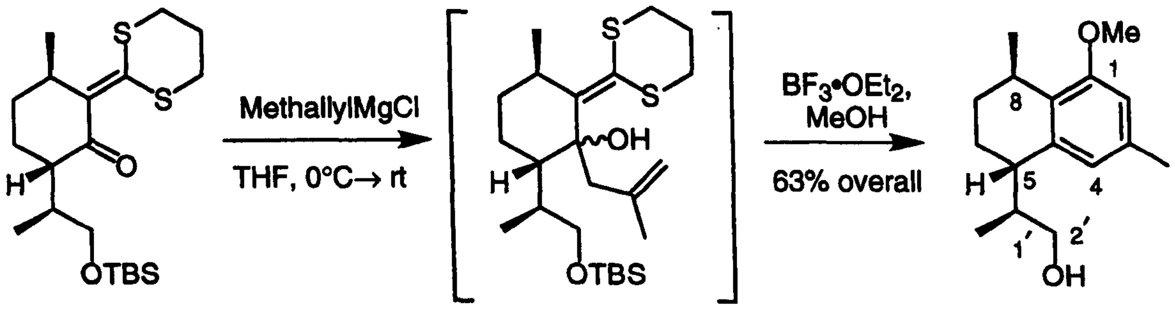
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 3.40 (2H, m, AB portion of ABX system, J_{AB}= 7.1 Hz, C2′H_2), 3.21 (1H, app. sextet, J = 6.4 Hz, C2H), 2.98 (2H, ddd, A_2 portion of $A_2BB'XY$ system, J_{AB}= 13.9, S-CH_2), 2.83 (1H, ddd, B portion of $A_2BB'XY$ system, J_{AB}= 13.9, J_{BX}= 7.7, J_{BY}= 7.3 Hz, S-CH_B), 2.75 (1H, ddd, B′ portion of $A_2BB'XY$ system, $J_{AB'}$= 13.9, $J_{B'X}$= 6.6, $J_{B'Y}$= 5.5 Hz, S-CH_B), 2.43 (1H, dd, J = 12.9, 6.2 Hz, C3H or C4H), 2.35 (1H, dd, J = 12.5, 6.6 Hz, C3H or C4H), 2.22-2.09 (2H, m, S-C-$\underline{CH_2}$), 2.03- 1.93 (1H, m, C5H or C1′H), 1.89-1.77 (1H, m, C5H or C1′H), 1.61-1.49 (1H, m, C4H or C3H), 1.46- 1.34 (1H, m, C4H or C3H), 1.11 (3H, d, J = 7.2 Hz, C1′Me, 0.86 (9H, s, *t*-Bu), 0.75 (3H, d, J = 6.5 Hz, C5Me), 0.02 (3H, s, SiMe), 0.01 (3H, s, SiMe).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ (ppm)= 200.4 (0), 150.8 (0), 137.1 (0), 66.1 (2), 48.7 (1), 36.1 (1), 33.9 (1), 29.3 (2), 29.1 (2), 28.9 (2), 26.1 (3), 23.9 (2), 20.3 (3), 19.8 (2), 18.4 (0), 12.7 (3), –5,2 (3), –5.3 (3).

LRMS (ESI^+ mode, CH_3CN): *m/z* (%)= 823 [$(2M+Na)^+$, 100], 423 [$(M+Na)^+$, 10], 401 [$(M+H)^+$, 16].

HRMS (CI mode, NH_3): found $(M+H)^+$, 401.2018; $C_{20}H_{36}O_2SiS_2$ requires 400.1926.

(5*S*, 8*R*)-1-Methoxy-3,8-dimethyl-5-[(*S*)-2-hydroxy-1-methylethyl)-5,6,7,8-tetrahydronaphthalene (3.2.1.10).



FW= 400.72
$C_{20}H_{36}O_2SiS_2$

FW= 456.83
$C_{24}H_{44}O_2SiS_2$

FW= 248.36
$C_{16}H_{24}O_2$

To a solution of α-oxoketene dithioacetal (4.09 g, 10.2 mmol) in THF (120 mL) was added methallylmagnesium chloride [prepared from methallyl chloride (7.03 mL, 6.46 g, 71.4 mmol, 7.0 eq) and Mg turnings (5.27 g, 217 mmol, 21 eq) in dry THF (286 mL)] over 15 min at 0°C *via* cannula. The cooling bath was removed and the mixture stirred at ambient temperature for 90 min, which caused the colour to change from dark to pale yellow. The reaction mixture was poured into aq. NH_4Cl (200 mL), extracted with ether (3 x 40 mL) and dried over Na_2SO_4. Concentration *in vacuo* gave alcohol **3.2.1.9** as a pale yellow oil (4.46 g) which was used immediately in the next step.

To a solution of $BF_3{\bullet}OEt_2$ (11.1 g, 9.83 mL, 78.2 mmol, 8 eq) in methanol (40 mL) at –40°C was added slowly crude alcohol **3.2.1.9** (4.46 g) in THF (10 mL). The mixture was allowed to warm to rt over 18 h. Saturated $NaHCO_3$ solution (45 mL) was added slowly and the mixture concentrated *in* *vacuo* to a slurry which was diluted with brine (15 mL) and extracted with ether (3 x 15 mL). The combined organic layers were dried over Na_2CO_3/ Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes-Et_2O (7:3) to give the title compound (1.61 g, 6.48 mmol, 63% from the **3.2.1.8**) as a yellow oil: $[\alpha]_D = -25.0$ ($c = 0.62$, $CHCl_3$).

IR (film): ν = 3354 s, br (OH), 3071 w, 2954 s, 2869 s, 1612 s, 1579 s, 1462 s, 1373 m, 1344 m, 1272 s, 1096 s, 1029 s, 893 m, 832 m cm^{-1}.

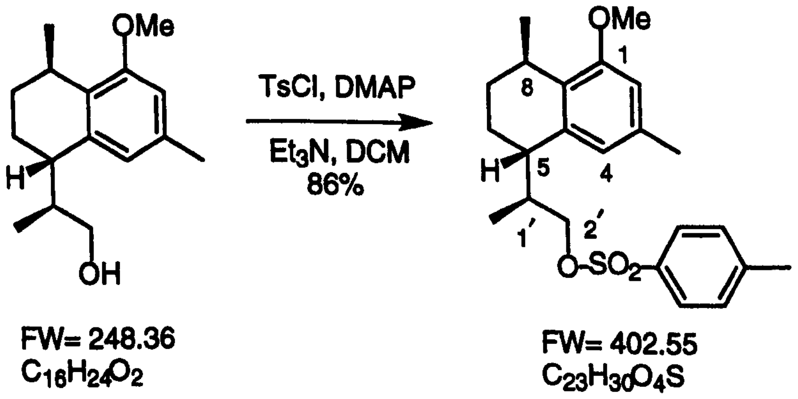
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.64 (1H, s, C4H), 6.53 (1H, s C2H), 3.82 (3H, s, OMe), 3.67 (1H, dd, J = 10.7, 6.6 Hz, C2′H), 3.56 (1H, dd, J = 10.7, 5.9 Hz, C2′H), 3.23- 3.13 (1H, m, C5H or C8H), 2.84- 2.74 (1H, m, C5H or C8H), 2.31 (3H, s, C3Me), 2.12- 2.04 (1H, m, C1′H), 1.91- 1.65 (3H, m, $C6H_2$ or $C7H_2$ + OH), 1.58-1.68 (2H, m, $C6H_2$ or $C7H_2$), 1.15 (3H, d, J = 6.8 Hz, C1′Me), 0.89 (3H, d, J = 7.0 Hz, C8Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 157.4 (0), 139.9 (0), 135.3 (0), 128.9 (0), 122.1 (1), 109.0 (1), 67.0 (2), 55.2 (3), 41.4 (1), 38.4 (1), 27.1 (2), 26.6 (1), 21.7 (3), 21.6 (3), 19.5 (2), 14.7 (3).

LRMS (EI mode): *m/z* (%)= 248 ($M^{+\bullet}$, 37), 189 [$(M-C_3H_7O)^{+\bullet}$, 100], 175 (26).

HRMS (EI mode): found $M^{+\bullet}$, 248.1774; $C_{16}H_{24}O_2$ requires 248.1776.

(5*R*, 8*R*)-1-Methoxy-3,8-dimethyl-5-[(*S*)-1-methyl-2-[(*p*-toluenesulfonyl)oxy]ethyl]-5,6,7,8-tetrahydronaphthalene (3.2.1.11).



To a solution of alcohol **3.2.1.10** (1.45 g, 5.84 mmol, 1 eq), DMAP (0.78g, 6.42 mmol, 1.1 eq) and NEt_3 (2.04 mL, 1.48 g, 14.6 mmol, 2.5 eq) in CH_2Cl_2 (40 mL) at 0°C was added solid TsCl (1.56 g, 8.18 mmol, 1.4 eq) portionwise over 10 min. The cooling bath was removed and the clear yellow solution stirred at r.t for 18 h before pouring into aq. NH_4Cl (50 mL). The organic layer was separated, the aqueous phase extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with HCl (2 M, 10 mL) and brine (10 mL), dried over Na_2CO_3/ Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purifued by column chromatography on silica gel eluting with hexanes-CH_2Cl_2 (1:4) to give the title compound (2.02 g, 5.02 mmol, 86%) as colourless needles, mp 69-70°C (hexanes): $[\alpha]_D$= +22.5 (c = 1.25, $CHCl_3$).

IR (film): ν = 2932 s, 2870 s, 1612 m, 1579 m, 1463 s, 1360 s, 1274 m, 1176 s, 1097 s, 965 s, 836 s, 791 s, 666 s cm^{-1}.

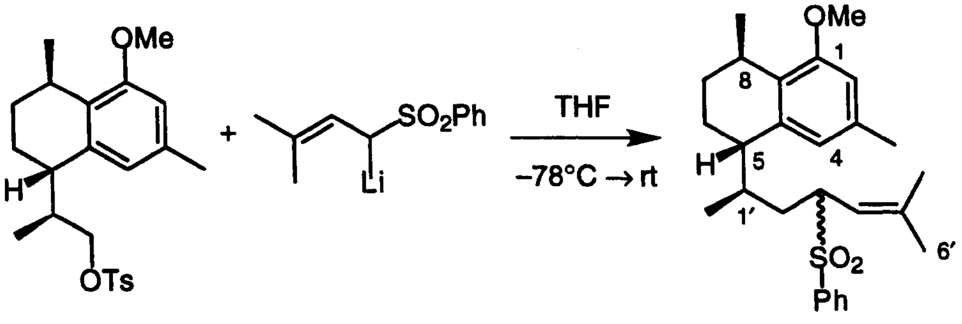
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.81 and 7.36 (2H each, d, J = 8.3 Hz, Ar AA'BB' system), 6.51 (1H, s, C4H), 6.44 (1H, s, C2H), 3.99 (2H, d, J = 5.9 Hz, C2'H_2), 3.82 (3H, s, OMe), 3.12- 3.08 (1H, m, C5H), 2.76- 2.71 (1H, m, C8H), 2.47 (3H, s, ArMe), 2.25 (3H, s, C3Me), 2.10 (1H, m, C1'H), 1.81- 1.75 (2H, m, C6H_2 or C7H_2), 1.58- 1.44 (2H, m, C6H_2 or C7H_2), 1.11 (3H, d, J = 7.0 Hz, C1'Me), 0.84 (3H, d, J = 7.0 Hz, C8Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 157.4 (0), 144.8 (0), 138.6 (0), 135.3 (0), 133.4 (0), 130.0 (2C, 1), 128.7 (0), 128.1 (2C, 1), 121.9 (1), 109.1 (1), 74.3 (2), 55.3 (3), 38.1 (1), 37.4 (1), 26.8 (2), 26.5 (1), 21.8 (3), 21.6 (3), 21.5 (3), 19.0 (2), 14.1 (3).

LRMS (EI mode): m/z (%)= 402 ($M^{+\bullet}$, 59), 230 [$(M-C_7H_8O_3S)^{+\bullet}$, 35], 215 (41), 189 (100), 173 (38), 91 (25).

Found: C, 68.40; H, 7.7%. $C_{23}H_{30}O_4S$ requires C, 68.63; H, 7.51; O, 15.90; S, 7.96.

(4*RS*, 5*S*, 8*R*)-1- Methoxy-3,8-dimethyl-5-[(1*S*)(1,5-dimethyl-3-phenylsulphonyl-4-hexenyl)-5,6,7,8,-tetrahydronaphthalene (3.2.1.12) .



FW= 402.55
$C_{23}H_{30}O_4S$

FW= 440.65
$C_{27}H_{36}O_3S$

To a solution of 3-methyl-1-(phenylsulfonyl)-2-butene (2.78g, 13.2 mmol, 4 eq) in THF (40 mL) at –78°C was added BuLi (1.58 M solution in hexanes, 8.36 mL, 13.2 mmol, 4 eq) over 10 min. The orange solution was warmed to –30°C over 2 h, then cooled again to –78°C, and a solution of tosylate **3.2.1.11** (1.33g, 3.30 mmol, 1 eq) in THF (24 mL) slowly added *via* cannula. The solution was allowed to warm to rt over 4 h and then poured into vigorously stirred aq. NH_4Cl (80 mL). The product was extracted into Et_2O (3 x 50 mL), and the combined organic layers washed with brine (25 mL) and dried over $MgSO_4$. The residue obtained after filtration and concentration *in vacuo* was purfied by column chromatography on silica gel eluting with Et_2O-hexanes (5:95) to give the title compound (1.10 g, 2.50 mmol, 76%) as a 2:1 mixture of epimers at C14 (^1H, ^{13}C NMR). Discernible signals relative to the minor isomer are marked with an asterisk (*). $[\alpha]_D$= +13.2 (*c* = 6, $CHCl_3$).

IR (film): ν = 3048 m, 2956 s, 2869 s, 1668 w, 1613 m, 1580 s, 1447 s, 1304 s, 1273 m, 1147 s, 1086 s, 743 s, 690 s cm^{-1}.

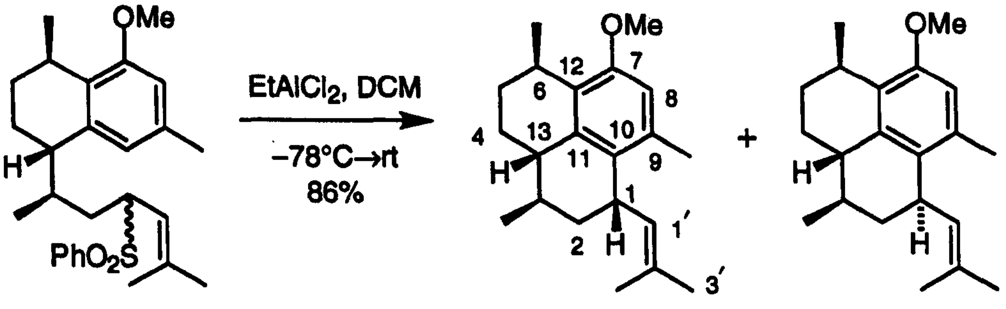
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.90- 7.78 (2H, m, Ph), 7.65- 7.59 (1H, m, Ph), 7.58- 7.48 (2H, m, Ph), 6.51 and 6.42* (2H, s, C2H and C4H), 5.00 and 4.92* (1H, dm, *J* = 10.3 Hz, C4′H), 3.88* and 3.79 (3H, s, OMe), 3.57 (1H, dt, *J* = 10.3, 3.3 Hz, C3′H), 3.05- 2.98 (1H, m, C8H or C5H), 2.56- 2.52* and 2.51- 2.48 (1H, m, C8H or C5H), 2.30- 2.10 (5H, m, C8Me + $C7H_2$ or $C6H_2$), 1.90- 1.88 (1H, m, C1′H), 1.73 and 1.69* (3H, s, $C6'H_3$), 1.69 and 1.59* (2H, m, C7H$_2$ or C6H$_2$), 1.52-1.46 (2H, m, C2′H$_2$), 1.19* and 1.08 (3H, d, J = 1.1 Hz, C5′Me), 1.13* and 1.11 (3H, d, J = 7.7 Hz, C1′Me), 0.80 and 0.68* (3H, d, J = 7.7 Hz, C8Me).

^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm)= 157.2* and 157.1 (0), 142.5* and 142.3 (0), 139.7 and 139.6* (0), 138.2 (0), 135.6 and 135.2* (0), 135.2 (0), 133.5* and 133.4, 133.4 (1), 129.4 (2C, 1), 128.8 (2C, 1), 121.8 (1), 117.8 and 117.5* (1), 108.8* and 108.7 (1), 64.0*, 63.3 (1), 55.3 (3), 41.8* and 38.1 (1), 36.5 and 36.2* (1), 33.4* and 32.0 (2), 29.9 (1), 27.6* and 27.4 (2), 26.0 (3), 21.9 (3), 21.2 (3), 19.2 (2), 18.7 and 18.1* (3), 17.9 and 15.7* (3).

LRMS (EI mode): *m/z* (%)= 440 (M$^{+\bullet}$, 29%), 299 [(M–PhSO$_2$)$^{+\bullet}$, 100], 216 [(M–C$_{10}$H$_{15}$SO$_2$)$^{+\bullet}$,48].

HRMS (EI mode): found M$^{+\bullet}$, 440.2377, $C_{27}H_{36}O_3S$ requires 440.2385

(3*R*, 6*R*, 13*S*)-7-Methoxy-3,6,9-trimethyl-1-(2-methyl-1-propenyl)-2,3,4,5,6,13-hexahydro-1*H*-phenalene (3.2.1.13 and 3.2.1.14).



FW= 440.65
$C_{27}H_{36}O_3S$

1*S*
FW= 298.47
$C_{21}H_{30}O$

1*R*
FW= 298.47
$C_{21}H_{30}O$

To a solution of sulfones **3.2.1.12** (264 mg, 0.6 mmol) in CH$_2$Cl$_2$ (15 mL) cooled to –78°C was added dropwise EtAlCl$_2$ (1 M in hexanes, 2.4 mL, 2.4 mmol, 4 eq) over 5 min. The brown solution was allowed to warm to rt overnight and then poured into HCl (2 M, 25 mL). The product was extracted into CH$_2$Cl$_2$ (3 x 25 mL) and the combined organic layers washed with NaHCO$_3$ (5 mL), brine (5 mL) and dried over Na$_2$SO$_4$. After filtration and concentration *in vacuo*, ^{1}H NMR analysis of the crude reaction mixture before chromatograpy revealed a 9.8:1 mixture of C1 epimers.

The major isomer could be separated by column chromatography on silica gel eluting with hexanes. (142 mg, 0.48 mmol, 79%), obtaiined as white needles, mp 95-96°C (2-propanol); $[\alpha]_D$= +16.8 ($CHCl_3$, c =0.57).

X-rays analysis identified the major isomer as **(1*S*, 3*R*, 6*R*, 13*S*)-7-Methoxy-3,6,9-trimethyl-1-(2-methyl-1-propenyl)-2,3,4,5,6,13-hexahydro-1*H*-phenalene (3.2.1.13).**

IR ($CHCl_3$): ν = 2923 s, 2856 s, 1593 s, 1575 s, 1464 s, 1379 m, 1320 m, 1273 m, 1216 m, 1177 m, 1101 m, 836 s cm^{-1}.

The ^{1}H NMR assignments were based on COSY experiments.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.63 (1H, s, C8H), 5.19 (1H, dm, J = 9.2 Hz, C1′H), 3.86 (3H, s, OMe), 3.69-3.64 (1H, m, C1H), 3.43 (1H, apparent sextet, J = 7.0 Hz, C6H), 2.22 (3H, s, C9Me), 2.21-2.10 (3H, m, C13H + C5H_2), 1.80 (3H, d, J = 1.3 Hz, C3′H_3), 1.73-1.60 (6H, m, C2H_2 + C3H + C2′Me), 1.58-1.45 (2H, m, C4H_2), 1.24 (3H, d, J = 7.0 Hz, C6Me), 1.12 (3H, d, J = 5.5 Hz, C3Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 154.9 (0), 138.7 (0), 134.6 (0), 129.8 (1), 129.6 (2C, 0), 128.4 (0), 110.8 (1), 55.4 (3), 43.5 (1), 39.4 (2), 35.2 (1), 30.6 (2), 30.1 (1), 28.2 (2), 26.6 (1), 25.9 (3), 23.3 (3), 21.3 (3), 19.7 (3), 17.8 (3).

LRMS (EI mode): *m/z* (%)= 298 ($M^{+\bullet}$, 87), 283 [$(M–CH_3)^{+\bullet}$, 100], 242 [$(M–C_4H_8,)^{+\bullet}$, 30], 227 [$(M-C_5H_{11})^{+\bullet}$, 33].

HRMS (EI mode): found $M^{+\bullet}$, 298.2295, $C_{21}H_{30}O$ requires 298.2297

X-ray analysis data are reported in appendix 1.

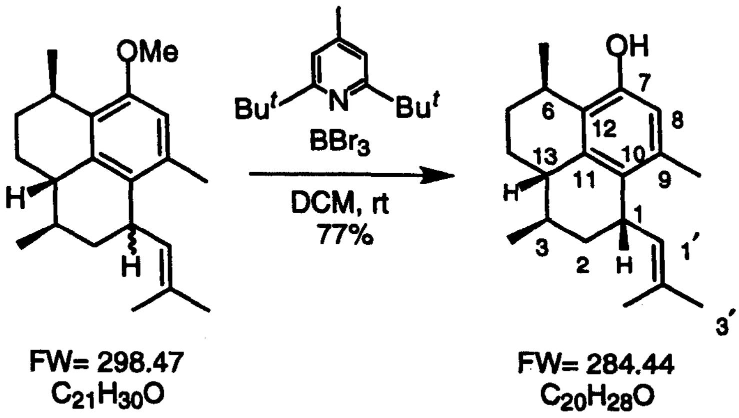
Data for the minor isomer:

(1*R*, 3*R*, 6*R*, 13*S*)-7-Methoxy-3,6,9-trimethyl-1-(2-methyl-1-propenyl)-2,3,4,5,6,13-hexahydro-1*H*-phenalene (3.2.1.14)

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.60 (1H, s, C8H), 4.99 (1H, dm, J = 9.6 Hz, C1'H), 3.86 (3H, s, OMe), 3.78- 3.72 (1H, m, C1H), 3.43 (1H, apparent sextet, J = 7.0 Hz, C6H), 2.23 (3H, s, C9Me), 2.21-2.10 (3H, m, C13H + $C5H_2$), 1.77 (3H, d, J = 1.5 Hz, $C3'H_3$), 1.73-1.60 (6H, m, $C2H_2$ + C3H+C2'Me), 1.58-1.45 (2H, m, $C4H_2$), 1.26 (3H, d, J = 6.6 Hz, C6Me), 1.08 (3H, d, J = 5.9 Hz, C3Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 155.6 (0), 140.7 (0), 135.1 (0), 131.3 (1), 130.0 (0) 129.8 (0), 127.9 (0), 111.1 (1), 55.2 (3), 45.0 (1), 40.2 (2), 36.7 (1), 34.2 (2), 31.9 (1), 28.3 (2), 27.8 (1), 25.6 (3), 23.8 (3), 20.8 (3), 20.3 (3), 17.7 (3).

(1*S*, 3*R*, 6*R*, 13*S*)-7-Hydroxy-3,6,9-trimethyl-1-[2-methyl-1-propenyl]-2,3,4,5,6,13-hexahydro-1*H*-phenalene (3.2.1.15).



To a solution of **3.2.1.14** (366 mg, 1.23 mmol) and freshly distilled 2,6-di-*tert*-butyl-4-methylpyridine (303 mg, 1.48 mmol, 1.2 eq) in CH_2Cl_2 (15 mL) was added dropwise BBr_3 (1.0 M solution in CH_2Cl_2, 2.46 mL, 2.46 mmol, 2 eq). The brown suspension was stirred for 30 min, then the mixture was poured into H_2O (50 mL), extracted with Et_2O (3 x 25 mL) and dried over Na_2CO_3/Na_2SO_4. The mixture was filtered, concentrated *in vacuo*, and the residue purified by column chromatography on silica gel eluting with hexanes followed by hexanes-Et_2O (95:5) to give the title compound (270 mg, 0.95 mmol, 77%) as a pale yellow oil: $[\alpha]_D$= +14.5 (c = 0.5 in $CHCl_3$).

IR ($CHCl_3$): ν = 3406 br (OH), 2922 s, 2868 s, 1585 s, 1455 s, 1096 m, 1043 m, 909 s, 843 s, 735 s cm^{-1}.

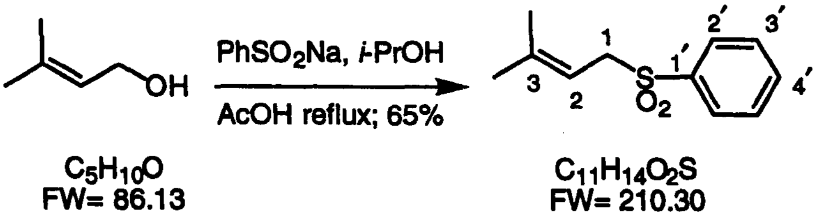
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.49 (1H, s, C8H), 5.15 (1H, dm, J = 8.0 Hz, C1'H), 5.05 (1H, s, OH), 3.61-3.58 (1H, m, C1H), 3.32-3.28 (1H, app. sextet, J = 7.0 Hz , C6H), 2.24-2.08 (6H, m, C13H + $C4H_2$ + C9Me), 1.81 (3H, s, $C3'H_3$), 1.75-1.72 (5H, m, C2'Me + $C2H_2$), 1.60-1.42 (3H, m, C3H + $C5H_2$), 1.24 (3H, d, J = 7.0 Hz, C6Me), 1.10 (3H, d, J = 5.8 Hz, C3Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 151.0 (0), 139.0 (0), 135.0 (0), 130.0 (2 C, 0+ 1), 129.7 (0), 126.0 (0), 115.4 (1), 43.6 (1), 39.3 (2), 35.1 (1), 30.8 (2), 29.9 (1), 28.1 (2), 26.9 (1), 25.8 (3), 23.1 (3), 21.1 (3), 19.1 (3), 17.7 (3).

LRMS (CI mode, NH_3): *m/z* (%)= 285 [$(M+H)^+$, 100], 134 (65), 35 (48).

HRMS (EI mode): found $M^{+\bullet}$, 284.2141, $C_{20}H_{28}O$ requires 284.2140.

3-Methyl-1-(phenylsulfonyl)-2-butene (3.2.1.17).



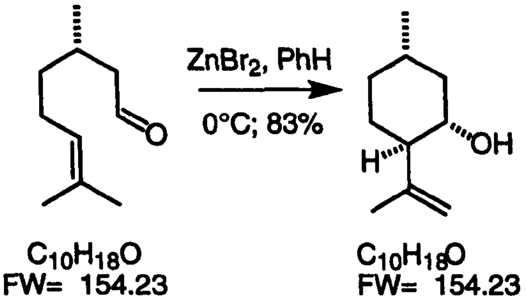
A mixture of 3-methyl-2-buten-1-ol (5.23 mL, 4.44 g, 51.5 mmol), glacial acetic acid (15 mL), 2-propanol (10 mL), sodium benzenesulfinate (10.1 g, 61.8 mmol, 1.2 eq) was stirred for 10 min at rt and then refluxed for 16 h. The mixture was diluted with AcOEt (40 mL) and the acetic acid neutralised with aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with AcOEt (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes-Et_2O (1:1) to give the title compound (7.04 g, 33.5 mmol, 65%) as white crystals, mp 50-51°C (2-propanol), lit.[102] mp = 50-51°C.

IR (film): ν = 3060 s, 2974 m, 2916 m, 1666 w, 1585 s, 1446 s, 1306 s, 1449 s, 1129 s, 1084 s, 963 m, 772 m, 739 s, 689 s cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm)= 7.89-7.84 (2, m, C3′H), 7.64 (1, tt, J =7.3, 1.6 Hz, C4′H), 7.53 (2, tt, J = 6.2, 1.6 Hz, C2′H), 5.17 (1, m, C2H), 3.78 (2, d, J = 7.7 Hz, C1H$_2$), 1.71 (3, d, J = 0.7 Hz, C3Me), 1.30 (3, d, J = 1.1 Hz, C3Me).

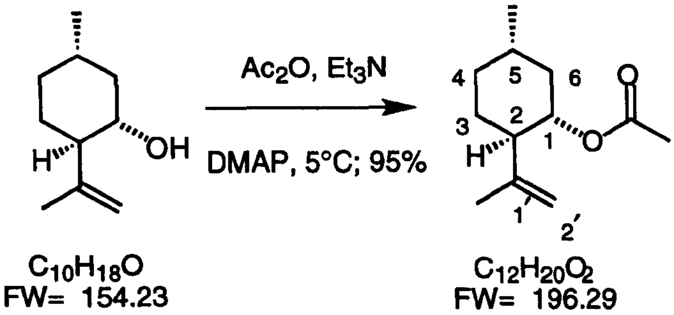
^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm)= 143.1 (0), 138.8 (0), 133.7 (1), 129.1 (1), 128.6 (1), 110.5 (1), 56.3 (2), 26.0 (3), 17.9 (3).

(+)-Isopulegol.



(–)-Citronellal (10.53 mL, 9.06 g, 58.7 mmol) was dissolved in dry benzene (30 mL) and cooled to 0°C in an ice bath. Powdered ZnBr$_2$ (13.33 g, 58.7 mmol, 1 eq) was added in small portions over 40 min keeping the temperature below 5°C. After complete addition , stirring was continued for 1 h, keeping the suspension in the ice bath, then the solid was filtered off by a sintered glass funnel. The solvent was removed under reduced pressure and the residue diluted with Et$_2$O (50 mL) and brine (30 mL). The aqueous layer was separated and extracted with Et$_2$O (3 x 35 mL). The organic layers was dried on Na$_2$SO$_4$, the solvent removed and the title compound was obtained after distillation (0.02 mmHg, 42-43°C) as a pale yellow oil (7.57 g, 49.1 mmol, 83%). $[\alpha]_D$= +17.1 (neat), reported 17.5 (neat)[80]. IR , ^{1}H and ^{13}C NMR spectra are consistent with data reported[80].

(1*S*,2*R*,5*S*)-1-Acetoxy-5-methyl-2-(1-methylethenyl)-cyclohexane, (+)-isopulegyl acetate.



DMAP (185 mg, 1.52 mmol, 0.031 eq) was dissolved in Ac_2O (9.28 mL, 10.0 g, 98.2 mmol, 2 eq), cooled to 0°C and added dropwise to a solution of (+)-isopulegol (8.31 mL, 7.57 g, 49.1 mmol) in Et_3N (13.78 mL, 9.94 g, 98.2 mmol, 2 eq) in an ice bath, keeping the temperature below 5°C during the addition (20 min). After 30 min the solution was allowed to warm to rt, stirred for 90 min and then poured onto crushed ice (100 g). The mixture was stirred for 15 min before Et_2O (100 mL) was added. The aqueous layer was then extracted with Et_2O (3 x 40 mL), the organic phases combined and washed with $NaHCO_3$ solution (20 mL), then brine (20 mL) and dried over Na_2SO_4 overnight. Distillation (12 mmHg, 134-135°C) gave the title acetate as a pale yellow oil (9.155 g, 46.6 mmol, 95%).

$[\alpha]_D$= +17.3 (*c* = 2, $CHCl_3$)

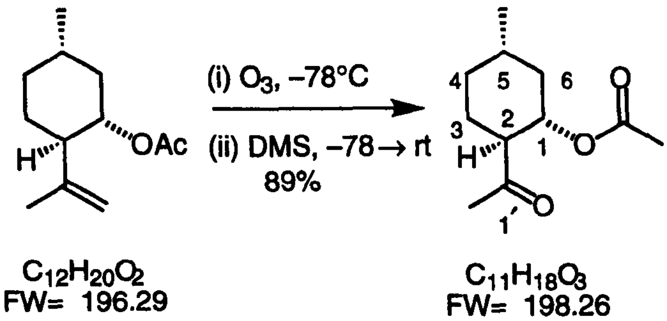
IR (thin film): ν = 3075 w, 2927 s, 2870 m, 1738 s,1647 m, 1457 m, 1373 m, 1244 s, 1028 s, 891 m cm^{-1}

1H NMR (270 MHz, $CDCl_3$): δ (ppm)= 4.78 (1H, td, *J* = 11.0, 4.4 Hz, C1H), 4.68 (2H, m, C2'H_2), 2.07 (1H, ddd, *J* = 12.4, 10.8,3.7 Hz, C6H), 2.00-1.90 (5H, m, OCO$\underline{Me}$ + C2H + C3H or C4H), 1.72-1.58 (4H, C1'Me + C3H or C4H), 1.56-1.45 (1, m, C5H), 1.34 (1H, app. dq, *J* = 13.1, 4.0 Hz, C3H or C4H), 1.04-0.79 (2H, m, C6H, C3H or C4H) 0.92 (3H, d, *J* = 6.6 Hz, C5Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.5 (0), 146.3 (0), 111.7 (1), 73.5 (1), 50.8 (1), 40.5 (2), 34.2 (2), 31.5 (1), 30.4 (2), 22.1 (3), 21.2 (3), 19.6 (3).

LRMS (ESI+ mode, CH_3CN): *m/z* (%)= 415 [$(2M+Na)^+$, 100], 219 [$(M+Na)^+$, 23]

(1*S*,2*S*,5*S*)-1-Acetoxy-2-acetyl-5-methylcyclohexane (8.3.2.1).



(+)-Isopulegyl acetate (9.15 g, 46.1 mmol) was dissolved in dry methanol (75 mL) and dry CH_2Cl_2 (25 mL), cooled to –78°C and O_3 was bubbled through the solution until the formation of a persistent blue colour. The mixture was flushed with N_2 for 15 min at –78°C before addition of dimethyl sulfide (16.8 mL, 14.3 g, 230.5 mmol, 5 eq). The solution was allowed to warm to rt over 10 h and the solvent was removed under reduced pressure. After addition of water (150 mL) and Et_2O (150 mL) the aqueous phase was separated, extracted with Et_2O (2 x 60 mL) and the organic phase washed with brine (30 mL) and dried on $MgSO_4$. Flash column chromatography (silica gel, hexanes-Et_2O 3:1) yielded the title compound as a colourless oil (8.13 g, 41.0 mmol, 89% yield).

$[\alpha]_D$= +76.3 (*c* = 2, $CHCl_3$)

IR (thin film): ν = 2930 s, 2870 m, 1738 s (C=O ester), 1715 s, (C=O ketone), 1455 m, 1371 s, 1241 s, 1204 m cm^{-1}.

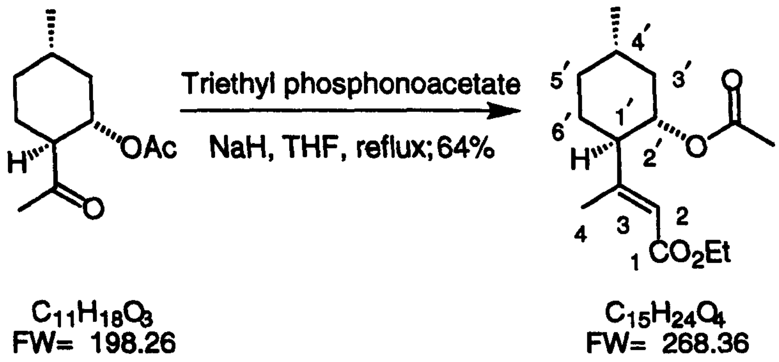
^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 4.91 (1H, td, *J* = 11.0, 4.4 Hz, C1H), 2.55 (1H, ddd, *J* = 10.9, 10.7, 3.8 Hz, C2H), 2.16-2.08 (4H, m, $C2'H_3$ + C6H), 1.97 (3H, s, OCOMe), 1.91 (1H, dq, *J* = 13.4, 3.4 Hz, C4H or C3H), 1.79-1.69 (1H, m, C3H or C4H), 1.65-1.53 (1H, m, C5H), 1.33 (1H, app. dq, J= 13.1, 3.6 Hz, C3H or C4H), 1.00-0.89 (2H, m, C6H+C3H or C4H), 0.93 (3H, d, *J* = 6.6 Hz, C5Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 210.0 (0), 170.3 (0), 73.4 (1), 55.7 (1), 39.6 (2), 33.5 (2), 31.0 (1), 29.2 (3), 27.9 (2), 22.0 (3), 21.3 (3).

LRMS (ESI^+ mode, CH_3CN): *m/z* (%)= 419 [$(2M+Na)^+$, 100], 221[$(M+Na)^+$, 48], 216 [$(M+NH_4)^+$, 62]

HRMS (CI mode, NH_3): found= 199.1332 $(MH)^+$, $C_{11}H_{19}O_3$ requires 199.1334.

Ethyl 3-[(1*R*,2*S*,4*S*)-2-acetoxy-4-methylcyclohex-1-yl]-but-2-enoate (8.2.1.5).



NaH (60% suspension in mineral oil, 705.6 mg, 17.64 mmol, 3.5 eq) was washed with dry hexane to remove the oil, suspended in dry THF (25 mL) and cooled to 0°C in an ice bath. Triethyl phosphonoacetate (4.00 mL, 4.520 g, 20.16 mmol, 4 eq) was slowly added over 35 min avoiding violent development of gas from the suspension. The ice bath was removed and the clear solution stirred at rt for 20 min before addition *via* cannula to a solution of ketone **8.3.2.1** (1.00 g, 5.04 mmol) in dry THF (25 mL). The solution was heated at reflux for 12 h, then poured into water (50 mL). The aqueous phase was extracted with ether (3 x 25 mL) and dried on $MgSO_4$. Flash column chromatography (SiO_2, petrol 9/ diethyl ether 1) yielded the title compound as a yellow oil (872 mg, 3.22 mmol, 64% yield). The compound was obtained as 9:1 mixture of isomers. The stereochemistry of the major product was confirmed by ^1H NMR NOE experiments.

$[\alpha]_D$= −3.4 (*c* = 2, $CHCl_3$)

IR (thin film): ν = 2930 (s), 2870 (m), 1736 (s, C=O esters), 1646 (s, C=C), 1453 (m), 1373 (s), 1242 (s), 1154 (s), 1027 (s), 868 (s) cm^{-1}

^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)= 5.66 (1H, d, *J* = 1.3 Hz, C2H), 4.83 (1H, dt, *J* = 10.8, 4.4 Hz, C2′), 4.11 (2H, q, *J* = 7.2 Hz, CH_2 ethyl), 2.18-2.08 (1H, m, C1′H), 2.06 (3H, d, *J* = 1.1 Hz, C3Me), 2.04- 1.92 (4H, m, C3′H + COOMe), 1.76- 1.64 (2H, m, C6′H + C5′H), 1.61-1.35 (2H, m, C4′H + C5′H), 1.23 (3H, t, *J* = 7.2 Hz, CH_3 ethyl), 1.00 (1H, q, *J* = 12.1 Hz, C4′H), 0.98- 0.80 (1H, m, C6′H) 0.90 (3H, d, *J* = 6.6 Hz,C4′Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.5 (0), 166.8 (0), 160.0 (0), 117.3 (1), 73.2 (2), 59.7 (2), 53.4 (1), 40.3 (2), 33.9 (2), 31.3 (1), 30.1 (2), 22.0 (3), 21.2 (3), 16.0 (3), 14.4 (3).

LRMS (CI^+ mode, NH_3): *m/z* (%)= 332 [$(M+Na+CH_3CN)^+$, 95], 291 [$(M+Na)^+$, 91].

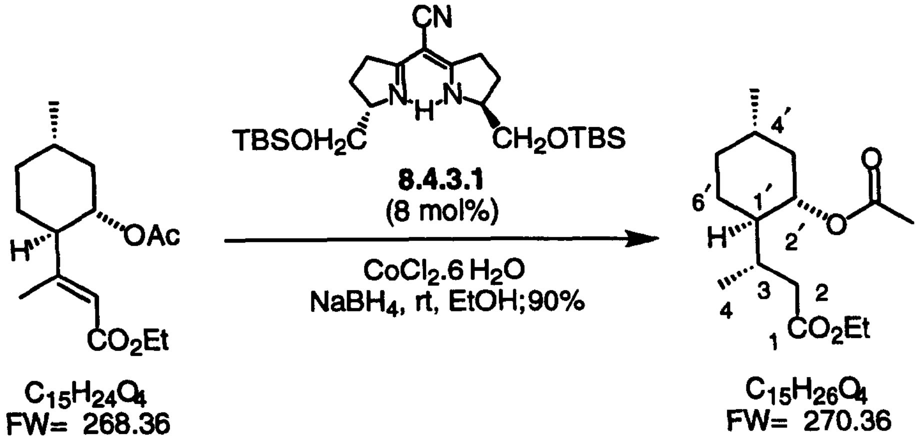
HRMS (CI mode, NH_3): found= 269.1769 $(M+H)^+$, $C_{15}H_{25}O_4$ requires 269.1753.

Data for the minor isomer:

^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm)= 5.65 (1H, s, C2H), 4.82 (1H, dt, *J* = 10.6, 4.4 Hz, C2′), 4.15 (2H, q, *J* = 7.1 Hz, CH_2 ethyl), 2.18-2.08 (1H, m, C1′H), 2.06 (3H, d, *J* = 1.1 Hz, C3Me), 2.04-1.92 (4H, m, C3′H + COOMe), 1.76-1.64 (2H, m, C6′H + C5′H), 1.61-1.35 (2H, m, C4′H + C5′H), 1.28 (3H, t, *J* = 7.1 Hz, CH_3 ethyl), 1.05-0.80 (2H, m, C3H + C6′H) 0.92 (3H, d, *J* = 6.6 Hz,C4′Me.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 170.7 (0), 166.2 (0), 160.0 (0), 118.5 (1), 73.3 (1), 59.7 (2), 53.4 (1), 43.8 (2), 33.8 (2), 31.4 (1), 29.5 (2), 22.0 (3), 20.4 (3), 15.3 (3), 14.4 (3).

(3*S*)-Ethyl 3-[(1*R*, 2*S*, 4*S*)-2-acetoxy-4-methylcyclohex-1-yl]-butanoate (8.2.1.4).



The catalyst **8.4.3.1** was prepared according to the procedure published by Pfaltz *et al*[85,103] and the reduction was carried following their protocol.
In a flask fitted with a vacuum-tight teflon stopper, a solution of the α,β-unsaturated ester **8.2.1.5** (670 mg, 2.5 mmol) in ethanol (1.0 mL) under N_2 was treated successively with $CoCl_2.6H_2O$ (42 mg, 0.175 mmol, 0.07 eq) in EtOH (0.27 mL) and semicorrin ligand **8.4.3.1** (93 mg, 0.2 mmol, 0.08 eq) in EtOH (0.52 mL) causing the colour to turn from blue-violet to dark blue. A solution of $NaBH_4$ (189 mg, 5.0 mmol, 2 eq) in DMF (1.5mL) was then added and the colour changed to brown. The suspension was then degassed at 0.01 mmHg by repeated (6) freeze-thaw cycles. The reaction mixture was stirred at 25°C for 6 days in the vacuum-sealed flask, then water (10 mL) was added and the mixture extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were washed with H_2O (15 mL) and dried on Na_2SO_4. After evaporation of the solvent at rotavapor, flash chromatography (silica gel, hexanes-Et_2O 4:1) yielded the title compound as a partially separable mixture with unreacted starting material. Level of conversion based on ^1H NMR-detected starting material= 90% (weight of the crude mixture= 739 mg, weight of the purified product= 592 mg, 2.2 mol, 87%).
The catalyst was partially recovered (54 mg) by exhaustive washing of the column with EtOAc.

$[\alpha]_D$= +35.7 (*c* = 2.5 , $CHCl_3$)

IR (thin film) : ν = 2953 s, 2929 s, 2870 s, 1735 s, COO esters, 1457 w, 1373 m, 1244 s, 1184 m, 1027 m cm^{-1}

The ^{1}H NMR assignments were based on COSY and 2D C-H correlation experiments.

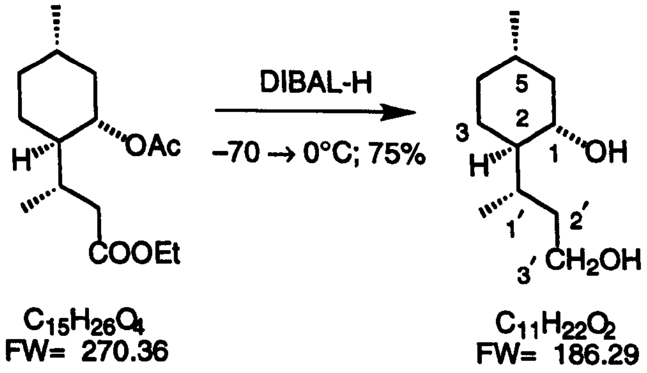
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 4.63 (1H, dt, J = 10.7, 4.4 Hz, C2′H), 4.10 (2H, q, J = 7.0 Hz, CH_2 ethyl), 2.36 (1H, dd, J = 14.9, 4.2 Hz, C5′H eq), 2.27-2.19 (1H, m, C4′H), 2.05 (3H, s, $OC{=}OCH_3$), 2.03-1.93 (2H, m, C5′H + C3′H eq), 1.76-1.64 (2H, m, C2H + C6′Heq), 1.53-1.40 (2H, m, C3H + C1′H), 1.24 (3H, t, J = 7.0 Hz, CH_3 ethyl), 1.02-0.82 (3H, m, C3′Hax + C6′Hax + C2H) 0.93 (3H, d, J = 7.0 Hz, C4′Me or $C4H_3$), 0.90 (3H, d, J = 6.6 Hz, C4′Me or $C4H_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 173.8 (0), 170.8 (0), 73.6 (1), 60.6 (2), 46.6 (1), 40.7 (2), 37.5 (2), 34.4 (2), 31.4 (1), 29.3 (1), 25.8 (2), 22.9 (3), 21.4 (3), 17.6 (3), 14.4 (3).

LRMS (ESI$^+$ mode, CH_3CN): m/z (%)= 563 [$(2M+Na)^+$, 100], 334 [$(M+Na+CH_3CN)^+$, 45], 293 [$(M+Na)^+$, 90].

HRMS (CI mode, NH_3): found= 271.1926 $(M+H)^+$, $C_{15}H_{27}O_4$ requires 271.1909.

(1*S*, 2*R*, 5*S*)-2-[(*S*)-3-hydroxy-1-methylpropyl]-5-methyl-1-cyclohexanol (8.2.1.3).



Diester **8.2.1.4** (562.3 mg, 2.08 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and cooled to −70°C. A 1.0 M solution of DIBAL-H in hexanes (11.3 mL, 11.3 mmol, 4.5 eq) was added dropwise over 15 min and the solution allowed to warm to 0°C over 1h. The mixture was then poured into an ice cold solution of sodium and potassium tartrate (10.5 g, 3.3 eq with respect to DIBAL-H) in water (15 mL) and CH_2Cl_2 (5 mL) and vigorously stirred for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 mL), the combined organic extracts washed with brine (5 mL) and dried on Na_2SO_4. Flash chromatography (silica gel, AcOEt-CH_2Cl_2 7:3) yielded the title diol as a white crystalline solid (290 mg after recrystallisation from petrol, 1.56 mmol, 75%). M.p.= 93-94°C

$[\alpha]_D$= +75.2 (c = 0.5, $CHCl_3$)

IR ($CHCl_3$ solution) : ν = 3265 br s, (OH), 2923 s, 2868 s, 1455 m, 1216 m, 1033 m, 758 s cm^{-1}

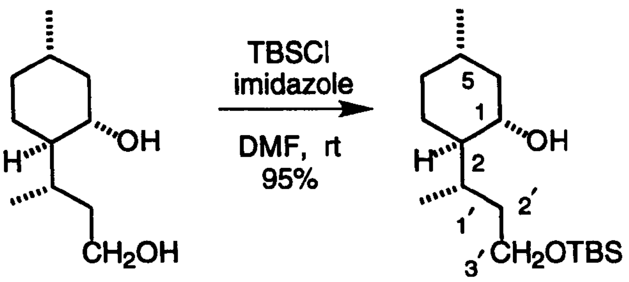
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 3.77 (1H, ddd, J = 10.6, 5.9, 4.6 Hz, C3′H_2), 3.77 (1H, app. dt, J = 9.9, 5.1 Hz, C3′H_2), 3.48 (1H, dt, J = 10.4, 4.6 Hz, C1H), 2.90-2.50 (2H, broad s, OH), 2.22-2.09 (1H, m, C5H), 2.01-1.95 (1H, m, C6H eq), 1.78-1.62 (3H, m, C3Heq + C2′H + C4eq), 1.50-1.38 (1H, m, C2′H), 1.29-1.12 (2H, m, C5H + C2H), 1.08-0.80 (3H, m, C6Hax + C3Hax + C4Hax), 0.95 (3H, d, J = 7.0 Hz, C5$\underline{Me}$ or C1′$\underline{Me}$), 0.92 (3H, d, J = 6.2 Hz, C5$\underline{Me}$ or C1′$\underline{Me}$).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 71.0 (1), 61.4 (2), 50.5 (1), 44.7 (2), 34.8 (2), 33.7 (2), 31.9 (1), 27.7 (1), 24.2 (2), 22.4 (3), 18.4 (3).

LRMS (ESI$^+$ mode, CH_3CN): m/z (%)= 454 [$(2M+2CH_3CN)^+$, 100], 334 [$(2M+CH_3CN)^+$, 73].

Found: C, 70.98; H, 11.75%. $C_{11}H_{22}O_2$ requires C, 70.92; H, 11.90; O, 17.18.

(1*S*,2*S*,5*R*)-2-[(*R*)-3-[(*t*-Butyldimethylsilyl)oxy]-1-methylpropyl]-5-methyl-1-cyclohexanol (8.6.1.1).



FW= 186.29
$C_{11}H_{22}O_2$

FW= 300.56
$C_{17}H_{36}O_2Si$

Diol **8.2.1.3** (4.2 g, 22.5 mmol) and imidazole (3.52 g, 51.7 mmol, 2.3 eq) were dissolved in dry DMF (35 ml) and solid TBSCl (3.74 g, 24.8 mmol, 1.1 eq) was then added. After 15 min, the reaction mixture was poured into NH_4Cl (40 mL) and the product extracted into hexanes (3 x 30 ml). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with Et_2O-hexanes (1:25) to give the title alcohol (6.42 g, 95%) as a colourless oil: $[\alpha]_D$= +29.1 (*c* = 2, $CHCl_3$).

IR (thin film): ν =3416 br, s, 2954 s, 2928 s, 2858 s, 1472 m, 1388 w, 1361 m, 1255 m, 1095 s, 836 s, 775 s cm^{-1}

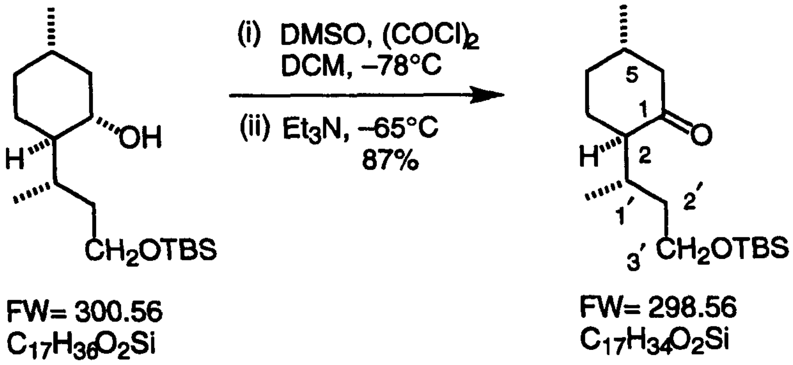
^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 3.72 (1H, ddd, *J* = 9.9, 6.2, 4.7 Hz, C3′H), 3.58 (1H, ddd, *J* = 9.9, 5.3, 5.3 Hz, C3′H), 3.45 (1H, m, C1H), 2.33 (1H, br. s, -OH), 2.14- 2.02 (1H, m, C5H), 2.01-1.90 (1H, dm, *J* = 12.0 Hz, C6Heq), 1.72- 1.59 (3H, m, C3Heq + C2′H + C4eq), 1.51-1.38 (1H, m, C2′H), 1.24- 1.10 (2H, m, C5H + C2H), 0.94- 0.88 (15H, m, Si-*t*-Bu + C5Me or C1′Me + C6Hax + C3Hax + C4Hax), 0.93 (3H, d, *J* = 7.2 Hz, C5Me or C1′Me) 0.05 (6H, s, $SiMe_2$).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 71.2 (1), 62.6 (2), 50.4 (1), 44.4 (2), 34.9 (2), 34.3 (2′) 31.9 (1), 28.3 (1), 26.2 (3, 3C), 24.5 (2), 22.4 (3), 18.6 (3), 18.5 (0), –5.3 (3, 2C).

LRMS (ESI+ mode, CH_3CN): *m/z* (%)= 342 [$(M+H+CHCN_3)^+$, 32], 301 [$(M+H)^+$, 78].

HRMS (CI mode, NH_3): found= 301.2547 $(M+H)^+$, $C_{17}H_{36}O_2Si$ requires 301.2563.

(2*S*,5*R*)-2-[(*R*)-3-[(*t*-Butyldimethylsilyl)oxy]-1-methylpropyl]-5-methyl-1-cyclohexanone (8.6.1.3).



DMSO (4.36 g, 3.96 ml, 55.8 mmol, 2.6 eq) in CH_2Cl_2 (15 mL) was added dropwise to a solution of oxalyl chloride (3.54 g, 2.40 mL, 27.9 mmol, 1.3 eq) in dry CH_2Cl_2 (80 mL) at −72°C over 10 min. After 20 min, alcohol **8.6.1.1** (6.45 g, 21.5 mmol) in CH_2Cl_2 (35 mL) was slowly added over 4 min at −65°C. After 90 min stirring at −65°C, Et_3N (8.90 g, 12.3 mL, 88.0 mmol, 4.1 eq) was added over 8 min and mixture allowed to warm to over 2 h. The white suspension was poured into vigorously stirred aq. NH_4Cl (50 mL) and extracted into hexanes (3 x 40 mL). The combined organic phases were washed with HCl (1.5 M, 30 mL) followed by brine (20 mL). The residue obtained on concentration *in vacuo* was purified by column chromatography on silica gel eluting with hexanes-Et_2O (95:5); the ketone was recovered as a pale yellow oil: $[\alpha]_D$= +27.6 (*c* = 1.1, $CHCl_3$)

IR (thin film): ν = 2928 s, 2858 s, 1712 s, 1462 s, 1380 w, 1255 s, 1104 s, 1005 w, 901 w, 836 s, 775 s, 663 w cm^{-1}

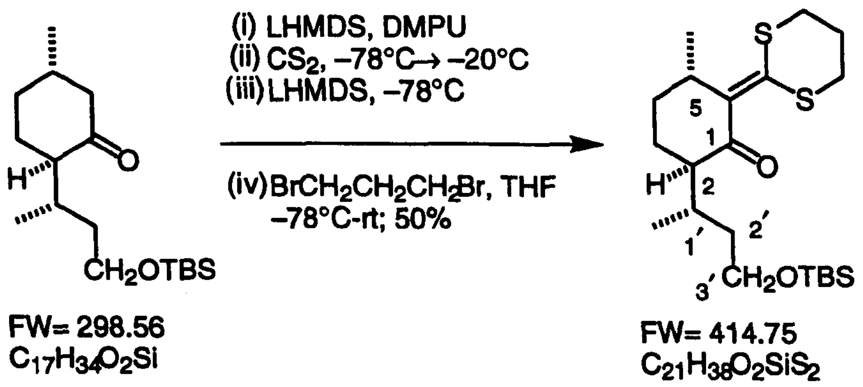
^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 3.68- 3.56 (2H, m, C1′H_2), 2.30 (1H, ddd, *J* = 12.9, 3.7, 2.2 Hz, C2H), 2.15- 2.09 (1H, m, C6H), 2.06- 1.77 (5H, m, C1′H + C3H + C4H_2 + C6H), 1.64- 1.56 (1H, m, C5H), 1.43 (1H, dq, *J* = 12.6, 3.0 Hz, C3H), 1.33- 1.22 (2H, m, C2′H_2), 0.98 (3H, d, J= 6.3 Hz, C5Me or C1′Me), 0.90 (3H, d, J= 6.9 Hz, C5Me or C1′Me), 0.86 (9H, s, Si*t*-Bu), 0.03 (3H, s, $SiMe_2$), 0.02 (3H, s, $SiMe_2$).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 211.9 (0), 62.1 (1), 55.2 (2), 51.0 (2), 36.4 (2), 35.3 (1), 34.1 (2), 28.6 (2), 28.4 (1), 26.1 (3, 3C), 22.4 (3), 18.4 (0), 17.7 (3), –5.2 (3, 2C).

LRMS (CI mode, NH_3): *m/z* (%)= 316 [$(M+NH_4)^+$, 15%], 299 [$(M+H)^+$, 100%], 241 [$(M–C_4H_9)^+$, 15%].

HRMS (CI mode, NH_3): found= 299.2416 $(M+H)^+$, $C_{17}H_{35}O_2Si$ requires 299.2406.

(2*R*,5*S*)-2-[(*R*)-3-[(*t*-Butyldimethylsilyl)oxy]-1-methylpropyl]-5-methyl-6-(1,3-dithiane-2-ylidene)-1-cyclohexanone (8.6.1.3).



A solution of HMDS (4.30 mL, 3.33 g, 20.6 mmol, 1.1 eq) in THF (25 mL) was cooled to –78°C and BuLi (1.38M in hexanes, 14.9 mL, 20.6 mmol, 1.1 eq) was added slowly over 10 min. The mixture was warmed to rt over 30 min , then the clear solution was cooled again to –78°C and DMPU (2.48 mL, 2.64 g, 20.6 mmol, 1.1 eq) was added dropwise over 5 min. After stirring for 20 min at the same temperature, a solution of ketone **8.6.1.2** (5.60 g, 18.8 mmol) in THF (20 mL) was added dropwise over 10 min and the solution stirred at –78°C for a further 30 min before rapid addition of CS_2 (1.24 mL, 1.57 g, 20.6 mmol, 1.1 eq). The orange solution was allowed to warm to –20°C over 2 h, stirred at this temperature for 90 min, and cooled again to –78°C before addition of a second portion of LHMDS solution in THF (1.05 eq) prepared as above. 1,3-Dibromopropane (885 µL, 1.75 g, 8.67 mmol, 1.05 eq) in THF (28 mL) was added after 30 min at the same temperature, the solution was warmed to rt over 16 h and then poured into aq. NH_4Cl (80 mL). The aqueous phase was separated, extracted with Et_2O (3 x 40 mL) and the combined organic layers washed with brine (30 mL) before drying over Na_2SO_4. The residue obtained after concentration *in vacuo* was purified by column chromatography on silica gel eluting with hexanes-Et_2O (4:1) to give the title ketene acetal (3.92 g, 9.45 mmol, 50%) as a dark orange oil: $[\alpha]_D = -46.2 (c = 1.1, CHCl_3)$

IR (thin film): ν = 2928 s, 2857 s, 1644 m, 1471 s, 1283 m, 1255 s, 1093 s, 836 s, 775 s cm^{-1}

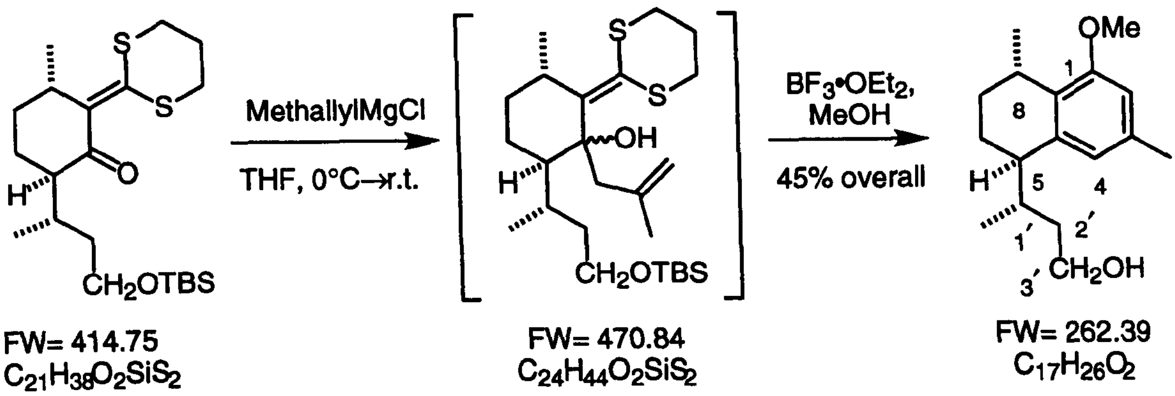
^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 3.64- 3.50 (2H, m, $C3'H_2$), 3.18 (1H, app. sextet, J= 6.4 Hz, C2H), 3.01 (2H, AA′ part of an AA′BB′XY system, J_{AB}= 13.8 Hz, $J_{A'B}$= 13.8 Hz, SCH_2), 2.91 (1H, ddd, B part of an AA′BB′XY system, J_{AB}= 13.8 Hz, J_{BX}= 8.6, J_{BY} =7.2 Hz, SCH_2), 2.71 (1H, ddd, B′ part of an AA′BB′XY system, J_{AB}= 13.8 Hz, J_{BX}= 6.6, J_{BY}= 4.8 Hz, SCH), 2.19-2.10 (2H, m, $SCH_2C\underline{H_2}$), 2.04- 1.96 (1H, m, C4H), 1.90- 1.71 (1H, m, C5H), 1.67- 1.54 (3H, m, $C2'H_2$ + C4H), 1.42- 1.24 (2H, m, $C3H_2$), 1.10 (3H, d, J = 6.9 Hz, $C1'\underline{Me}$), 0.90- 0.36 (13H, m, *t*-Bu+ $C5\underline{Me}$ + C1′H), 0.03 (3H, s, $SiMe_2$), 0.02 (3H, s, $SiMe_2$).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 200.6 (01), 150.0 (0), 137.4 (0), 61.9 (2), 53.5 (1), 36.7 (2), 34.2 (1), 31.1 (1), 29.1 (2), 28.8 (2), 26.1 (3, 3C), 23.9 (2), 22.7 (2), 21.3 (2), 20.2 (3), 18.4 (0), 18.0 (3), –5.1 (3, 2C).

LRMS (ESI^+ mode, CH_3CN): *m/z* (%)= 846 [$(2M+NH_4)^+$, 82], 415 [$(M+H)^+$, 100].

HRMS (CI mode, NH_3): found= 415.2141 $(M+H)^+$, $C_{21}H_{39}O_2S_2Si$ requires 415.2161.

(5*R*, 8*S*)-1-Methoxy-3,8-dimethyl-5-[(*R*)-3-hydroxy-1-methylpropyl)-5,6,7,8-tetrahydronaphthalene (8.6.1.5).



To a solution of α-oxoketene dithioacetal **8.6.1.3** (3.90 g, 9.4 mmol) in THF (100 mL) was added methallylmagnesium chloride [prepared from methallyl chloride (7.40 mL, 6.81 g, 75.2 mmol, 8.0 eq) and Mg turnings (5.4 g, 225.6 mmol, 24 eq) in dry THF (320 mL)] over 15 min at 0°C *via* cannula. The cooling bath was removed and the mixture stirred at rt for 2 h; the colour changed from dark to pale yellow. The reaction mixture was poured into aq. NH_4Cl (400 mL), extracted with ether (3 x 80 mL) and dried over Na_2SO_4. Concentration *in vacuo* gave the alcohol **8.6.1.4** as a pale yellow oil (4.80 g) which was used immediately in the next step.

To a solution of BF_3•OEt_2 (13.3 g, 11.6 mL, 94 mmol, 10 eq) in methanol (40 mL) at –40°C was added slowly a solution of crude alcohol **8.6.1.4** (4.80 g) in THF (40 mL). The mixture was allowed to warm to over 18 h. Saturated $NaHCO_3$ solution (60 mL) was added slowly and the mixture concentrated *in vacuo* to a slurry which was diluted with brine (40 mL) and extracted with ether (3 x 45 mL). The combined organic layers were dried over Na_2CO_3/ Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes-Et_2O (7:3) to give the title compound (1.12 g, 4.27 mmol, 45% over the two steps) as a yellow oil: $[\alpha]_D$= +32.9 (c = 3.0, $CHCl_3$).

The compound was contaminated with impurities (8%) that could not be removed after repeated column chromatography; ^{1}H NMR signals: 6.98 (s), 6.86 (s), 2.29 (s).

IR (thin film): ν = 3361 s, br, 2933 s, 2869 s, 1612 m, 1579 m, 1462 s, 13443 w, 1272 s, 1098 s, 1055 m, 832 m, 787 s, 764 m cm^{-1}.

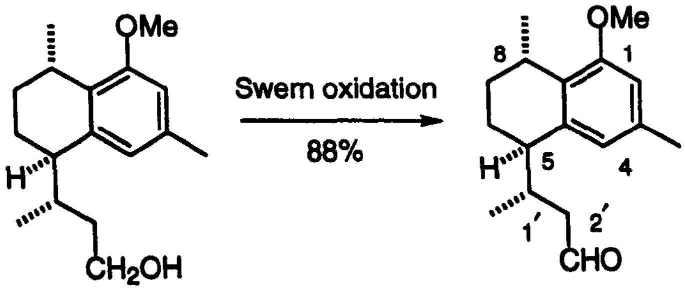
^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.66 (1H, s, C4H), 6.53 (1H, s, C2H), 3.83 (3H, s, OMe), 3.64- 3.56 (1H, A portion of an ABXY system, J_{AB}= 10.5 Hz, J_{BY}= 8.2, J_{AY}= 5.1 Hz, $C3'H_A$), 3.50- 3.42 (1H, B portion of an ABXY system, J_{AB}= 10.5 Hz, J_{BX}= J_{BY}= 7.3 Hz, $C3'H_B$), 3.20- 3.17 (1H, m, C5 or C8), 2.73- 2.62 (1H, m, C5 or C8), 2.33 (3H, s, C3Me), 2.22- 1.70 (4H, m, $C6H_2$ or $C7H_2$ + C2'), 1.65- 1.49 (2H, m, C6H or C7H + OH), 1.41- 1.28 (2H, m, C1'H + C6H or C7H), 1.18 (3H, d, J= 7.0 Hz, C1'Me), 1.04 (3H, d, J= 7.0 Hz, C5Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 157.1 (0), 140.1 (0), 135.0 (0), 128.8 (0), 121.9 (1), 108.6 (1), 61.8 (2), 55.1 (3), 42.2 (1), 36.4 (2), 35.4 (1), 27.5 (2), 26.5 (1), 21.7 (3), 21.4 (3), 19.2 (3), 18.9 (2).

LRMS (ESI$^+$ mode, CH_3CN): *m/z* (%)= 262 [M$^+$, 100].

HRMS (CI mode, NH_3): found = 263.2028, $C_{17}H_{27}O_2$ requires 263.2011.

(5*R*, 8*S*)-1-Methoxy-3,8-dimethyl-5-[(*R*)-3-oxy-1-methylpropyl)-5,6,7,8-tetrahydronaphthalene (8.6.1.6).



FW= 262.39
$C_{17}H_{26}O_2$

FW= 260.39
$C_{17}H_{24}O_2$

DMSO (204 mg, 0.186 ml, 2.62 mmol, 2.6 eq) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of oxalyl chloride (166 mg, 0.112 mL, 1.31 mmol, 1.3 eq) in dry CH_2Cl_2 (1.5 mL) at –70°C over 5 min. After 20 min alcohol **8.6.1.5** (262 mg, 1.0 mmol) in CH_2Cl_2 (2.6 mL) was slowly added over 4 min at –65°C. After 90 min stirring at –65°C, Et_3N (417 mg, .575 mL, 4.12 mmol, 4.1 eq) was added over 8 min and mixture allowed to warm to rt over 2 h. The white suspension was poured into vigorously stirred aq. NH_4Cl (10 mL) and extracted into hexanes (3 x 10 mL). The combined organic phases were washed with HCl (2 M, 3 mL) followed by brine (2 mL). The solution was concentrated at the rotavapor and purified by column chromatography on silica gel eluting with hexanes-Et_2O (95:5); the aldehyde was recovered as a pale yellow oil (230 mg, 0.88 mmol, 88%).$[\alpha]_D$= +32.9 (c = 3.0, $CHCl_3$)

IR (thin film): ν = 2928 s, 2870 s, 2717 w, 1725 s (C=O), 1612 m, 1579 m, 1463 s, 1273 s, 1098 s, 833 m, 733 m cm^{-1}.

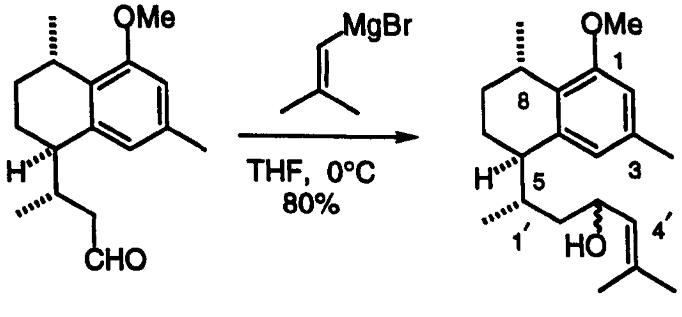
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 9.57 (1H, dd, J = 3.1, 1.2 Hz, CHO), 6.65 (1H, s, C4H), 6.53 (1H, s, C2H), 3.82 (3H, s, OMe), 3.20-3.12 (1H, m, C5 or C8), 2.74-2.69 (1H, m, C5 or C8), 2.64-2.57 (1H, m, C1´H), 2.34-2.29 (4H, m, C3Me + C2´H), 2.17 (1H, dd, J = 16.0, 10.3, 3.1 Hz, C2´H), 1.97-1.68 (3H, m, $C6H_2$ + C7H), 1.58-1.49 (1H, m, C7H), 1.14 (3H, d, J = 6.9 Hz, C1´H), 1.08 (3H, d, J = 6.8 Hz, C8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 203.2 (0), 157.3 (0), 139.2 (0), 135.6 (0), 129.0 (0), 121.9 (1), 109.1 (1), 55.3 (3), 48.0 (2), 41.5 (1), 33.9(1), 27.5 (2), 26.5 (1), 21.8 (3), 21.4 (3), 19.6 (3), 18.8 (2).

LRMS (EI mode): *m/z* (%)= 260 ($M^{+\bullet}$, 22), 216 [$(M-C_2H_4O)^{+\bullet}$, 16], 189 [$(M-C_4H_7O)^{+\bullet}$,100].

HRMS (EI mode): found $M^{+\bullet}$, 260.1781, $C_{17}H_{24}O_2$ requires 260.1776.

(2'*R*,5*R*, 8*S*)-1- Methoxy-3,8-dimethyl-5-(1,5-dimethyl-3-hydroxyl-4-hexenyl)-5,6,7,8,-tetrahydronaphthalene (8.6.1.7).



FW= 260.39
$C_{17}H_{24}O_2$

FW= 316.48
$C_{21}H_{32}O_2$

To a solution of aldehyde **8.6.1.6** (153 mg, 0.59 mmol) in dry THF (2mL) at 0°C was added 2-methylpropene-1-magnesium chloride prepared from 1-bromo-2-methylpropene (398 mg, 0.298 mL, 2.95 mmol, 5 eq) and Mg turnings (142 mg, 5.9 mmol, 10 eq) in dry THF (2 mL) *via* cannula over 5 min. The clear solution was allowed to warm to rt and stirred over 2h, then aq. NH_4Cl (5 mL) was added and the aqueous phase separated and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (2 ml) and dried on Na_2SO_4 before removal of the solvent *in vacuo* and column chromatography purification (silica gel, eluent hexanes-Et_2O 4:1→ 1:1). The title alcohol was recovered as a 2:1 mixture of epimers by ^1H and ^{13}C NMR (150 mg, 0.47 mmol, 80%). Discernible signals relative to the minor isomer are marked with an asterisk (*). $[\alpha]_D$= +21.2 (*c* = 5.0, $CHCl_3$).

IR (thin film): ν = 3360 br (OH), 2927 s, 2863 s, 1612 s, 1580 s, 1462 s, 1416 s, 1370 m, 1344m, 1271 s, 1097 s, 1043 s, 1370 m, 1344 m, 1271 s, 1097 s, 1043 s, 1016 s, 820 m, 800 cm^{-1}.

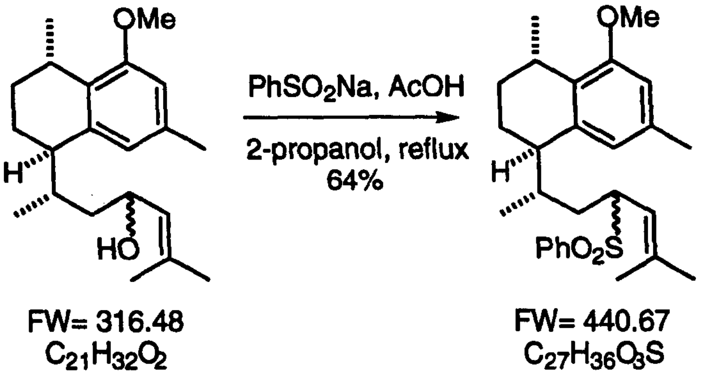
^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 6.66 and 6.60* (1H, s, C4H), 6.51 (1H, s, C2H), 5.09 (0.67H, dt, *J* = 8.5, 1.4 Hz, C4'H), 4.86* (0.33H, dt, *J* = 9.0, 1.4 Hz, C4'H), 4.34- 4.26 (1H, m, C3'H), 3.82 (3H, s, OMe), 3.17- 3.14 (1H, m, C5 or C8), 2.69- 2.60 (1H, m, C5 or C8), 2.31 (3H, s, C3Me), 2.23- 2.18 (1H, m, C1'H), 1.94- 1.86 (2H, m, $C6H_2$ or $C7H_2$), 1.78- 1.73 (2H, m, $C6H_2$ or $C7H_2$), 1.72* and 1.69 (3H, d, *J* = 1.2 Hz, C5'Me or C6'Me), 1.67* and 1.66 (3H, d, *J* = 1.2 Hz, C5'Me or C6'Me), 1.50- 1.43 and 1.40- 1.33* (2H, m, $C2'H_2$), 1.15 (3H, d, *J* = 6.9 Hz, C1'Me), 1.05 and 1.03* (3H, d, *J* = 6.8 Hz, C8Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 157.2 (0), 140.3* and 140.2 (0), 135.7 and 135.1 (0), 135.0 (0), 131.3 (0), 129.0 and 128.3* (1), 122.1 and 121.0* (1), 108.7 (1), 67.7* and 67.0 (1), 55.3 (3), 42.4 (1), 41.8 and 41.4* (2), 35.3* and 34.9 (1), 27.8* and 27.7 (2), 26.6 (1), 26.0* and 25.9 (3), 21.8 (3), 21.5 (3), 19.7 and 19.3* (3), 19.2* and 19.0 (2), 18.3* and 18.2 (3).

LRMS (EI mode): *m/z* (%)= 298 [$(M-H_2O)^{+\bullet}$, 8], 216 [$(M-C_6H_{12}O)^{+\bullet}$, 67], 189 [$(M-C_8H_{15}O)^{+\bullet}$,100].

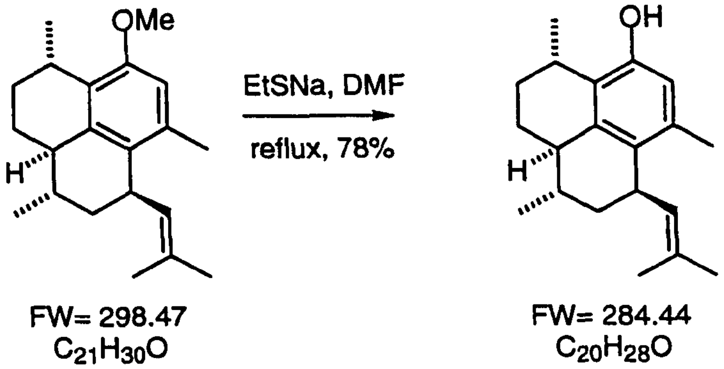
HRMS (EI mode): found $M^{+\bullet}$, 316.2402, $C_{21}H_{32}O_2$ requires 316.2402.

(2'*R*,5*R*, 8*S*)-1- Methoxy-3,8-dimethyl-5-(1,5-dimethyl-3-phenylsulphonyl-4-hexenyl)-5,6,7,8,-tetrahydronaphthalene (8.6.1.8).



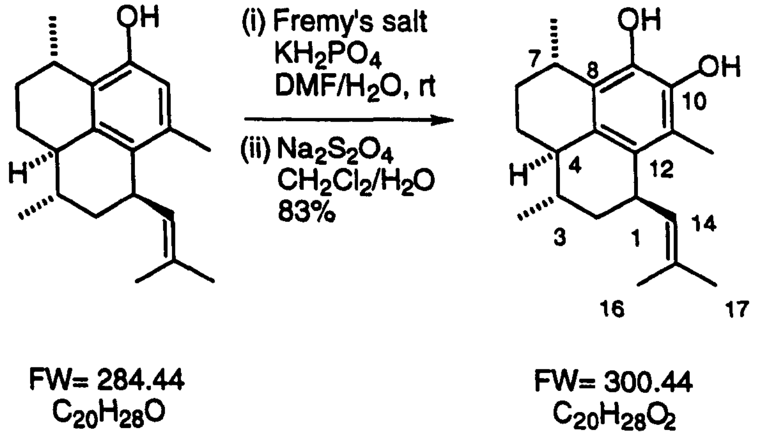
Solid $PhSO_2Na$ (579 mg, 3.52 mmol, 7.5 eq) was added to a solution of allylic alcohol **8.6.1.7**(150 mg, 0.47 mmol) in 2-propanol (5 mL). Glacial AcOH (0.5 mL) was added dropwise over 2 min, the suspension was stirred for 30 min at rt until all the solid had dissolved and then heated to reflux for 16 h. The pale yellow solution was then allowed to cool to rt, diluted with AcOEt (6 mL) and neutralised with aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with AcOEt (2 x 5 mL) and the organic phases dried over $MgSO_4$ before concentrating at the rotavapor. The residue was purified by column chromatography on silica gel eluting with hexanes- Et_2O 1:1 to afford the title sulfone as a yellow oil (132 mg, 0.3 mmol, 64 %) as a 2:1 mixture of epimers. ^1H and ^{13}C NMR data are consistent with those reported for **3.2.1.12**.

(1*R*, 3*S*, 6*S*, 13*R*)-7-Hydroxy-3,6,9-trimethyl-1-[2-methyl-1-propenyl]-2,3,4,5,6,13-hexahydro-1*H*-phenalene (8.6.1.10).


OMe
EtSNa, DMF
reflux, 78%
H
OH
H
FW= 298.47
C21H30O
FW= 284.44
C20H28O

A suspension of NaH (121 mg, 5 mmol, 20 eq) in dry DMF (2 mL) was added EtSH (311 mg, 0.37 mL, 5 mmol, 20 eq) in DMF (0.37 mL) at a rate sufficient to maintain slow gas evolution at 0°C. After 30 min from the end of the addition, a solution of **8.6.1.9** (75 mg, 0.25 mmol) in dry DMF (4 mL)was added *via* cannula. The clear yellow solution was heated at 155°C for 16 h before cooling to rt, diluting with Et_2O and pouring into aq. NH_4Cl (10 mL). After extraction of the aqueous phase with Et_2O (2 x 10 mL), and drying of the organic phase over Na_2SO_4, the solvent was removed *in vacuo* and column chromatography (silica gel, hexanes-Et_2O 4:1) yielded the title phenol as a colourless oil (56 mg, 0.197 mmol, 78%). ^1H and ^{13}C NMR data are consistent with those reported for **3.2.1.15**.

(1*R*, 3*S*, 6*S*, 13*R*)-7,8-Dihydroxy-3,6,9-trimethyl-1-[2-methyl-1-propenyl]-2,3,4,5,6,13-hexahydro-1*H*-phenalene, pseudopterosins A-F aglycone.


OH
(i) Fremy's salt
KH2PO4
DMF/H2O, rt
(ii) Na2S2O4
CH2Cl2/H2O
83%
H
OH
OH
7
8
10
4
12
H
3
1
14
16
17
FW= 284.44
C20H28O
FW= 300.44
C20H28O2

A solution of phenol **8.6.1.10** (55 mg, 0.16 mmol) in DMF (12 mL) was protected from light with aluminium foil and a solution of $(KSO_3)_2NO$ (518 mg, 19.3 mmol, 10 eq) and KH_2PO_4 (198 mg, 1.45 mmol, 7.54 eq) in H_2O (20 mL) was added *via* cannula over 15 min. The bright red solution was stirred at rt under N_2 for 16 h. The solution was then poured into 2N HCl (15 mL), extracted with Et_2O (3 x 5 mL) and the combined organic portions washed with brine (5 mL) before drying over Na_2SO_4. The crude was then dissolved in $CHCl_3$ (5 mL) and a freshly prepared saturated solution of $Na_2S_2O_4$ (10 mL) was added at rt. After vigorously stirring at rt for 15 min, the colour changed from dark orange to pale yellow. Et_2O (5 mL) was then added, the aqueous phase was separated and extracted with Et_2O (3 x 5 mL). After drying over Na_2SO_4 for 5 min, column chromatography afforded the unstable title compound as a yellow oil (48 mg, 0.16 mmol, 83%).

IR and ^1H NMR data are in agreement with those reported by A. Carpino[79] and McCombie[19]. Atom numbers in the NMR assignments and in the scheme above are given following the pseudopterosins numbering.

$[\alpha]_D$= +30.5 (c = 0.3, $CHCl_3$).

IR (thin film): ν = 3449 br (OH), 2923 s, 2857 s, 1446 s, 1374 m, 1295 s, 1189 m, 1106 m, 1041 m, 810 m cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ (ppm)= 5.12 (1H, d, J = 9.1 Hz, C14H), 5.07 (1H, br s, OH), 4.87 (1H, br s, OH), 3.62- 3.55 (1H, m, C1H), 3.23 (1H, app. sextet, J = 7.3 Hz, C7H), 2.25- 2.13 (3H, m, $C6H_2$ and C4H), 2.04 (3H, s, C11Me), 1.76 (3H, s, $C16H_3$), 1.70 (3H, s, $C17H_3$), 1.71- 1.41 (4H, m, $C2H_2$ and $C4H_2$), 1.26 (3H, d, J = 7.1 Hz, C7Me), 1.31- 1.20 (1H, m, C3H), 1.05 (3H, d, J = 6.1 Hz, C3Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm)= 140.0 (0), 139.9 (0), 130.4 (1), 130.3 (0), 130.0 (0), 126.0 (0), 125.7 (0), 120.0 (0), 43.3 (1), 39.7 (2), 35.5 (1), 31.1 (2), 30.1 (1), 28.4 (2), 27.5 (1), 25.8 (3), 23.2 (3), 21.2 (3), 17.8 (3), 11.0 (3).

LRMS (EI mode): m/z (%)= 300 ($M^{+\bullet}$, 100), 285 [$(M-CH_3)^{+\bullet}$, 75], 245 [$(M-C_4H_7)^{+\bullet}$,68], 244 [$(M-C_4H_8)^{+\bullet}$, 52], 229 [$(M-C_5H_{11})^{+\bullet}$, 36], 218 (28).

HRMS (EI mode): found $M^{+\bullet}$, 300.2071, $C_{20}H_{28}O_2$ requires 300.2089.

Appendix 1
X-ray data for 3.2.1.13

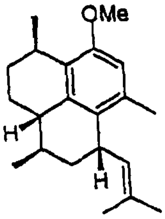
Sample: alp44 b25

P.O. # 2

X-ray Structure Report

for

A.Pontiroli



3.2.1.13

Uni. of Southampton

Tue Sep 19 1995

Introduction

This is the structural analysis of an organic compound produced as a step towards an end target. The purpose of running an x-ray diffraction pattern and solving the structure was to identify the relative stereochemistry of the iso-butene group. The cyclic carbon system was well defined in the starting data and side groups became clear once this had been set. Hydrogen atoms were placed on the structure using geometrically defined positions.

Experimental

Data Collection

A colourlesstablet tablet crystal of $C_{21}H_{30}O$ having approximate dimensions of 0.50 x 0.40 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 19 carefully centered reflections in the range $19.50 < 2\theta < 22.65°$ corresponded to amonoclinic cell with dimensions:

$a = 10.653(5)$ Å

$b = 9.082(7)$ Å $\qquad \beta = 101.27(5)°$

$c = 18.57(1)$ Å

$V = 1762(1)$ Å^3

For Z = 4 and F.W. = 298.47, the calculated density is 1.12 g/cm^3. The systematic absences of:

h0l: $l \neq 2n$

0k0: $k \neq 2n$

uniquely determine the space group to be:

$P2_1/c$ (#14)

The data were collected at a temperature of -123 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.28° with a take-off angle of 6.0°. Scans of $(1.42 + 0.35 \tan\theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 3083 reflections which were collected, 2894 were unique ($R_{int} = 0.041$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 3.6%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Mo-Kα radiation is 0.7 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.66 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 7.72816e-07).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1481 observed reflections ($I > 2.50\sigma(I)$) and 200 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.061$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma w Fo^2)]} = 0.070$$

The standard deviation of an observation of unit weight[4] was 2.39. The weighting scheme was based on counting statistics and included a factor ($p = 0.021$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.38 and -0.21 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SHELXS86: Sheldrick, G.M. (1985). In: "Crystallographic Computing 3" (Eds G.M. Sheldrick, C. Kruger and R. Goddard) Oxford University Press. pp. 175-189.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where $w = \frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$

$\sigma^2(Fo^2) = \frac{S^2(C+R^2B)+(pFo^2)^2}{Lp^2}$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{21}H_{30}O$
Formula Weight	298.47
Crystal Color, Habit	colourlesstablet, tablet
Crystal Dimensions	0.50 X 0.40 X 0.10 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	19 (19.5 - 22.6°)
Omega Scan Peak Width at Half-height	0.28°
Lattice Parameters	a = 10.653(5)Å b = 9.082(7) Å c = 18.57(1) Å β = 101.27(5)° V = 1762(1) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.125 g/cm^3
F_{000}	656.00
μ(MoKα)	0.66 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (factor = 3.59)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-123.0°C
Scan Type	ω-2θ
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.42 + 0.35 \tan\theta)^\circ$
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 3083 Unique: 2894 (R_{int} = 0.041)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.6618 - 1.0000) Decay (3.61% decline) Secondary Extinction (coefficient: 7.72816e-07)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.0210
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>2.50\sigma(I)$)	1481
No. Variables	200
Reflection/Parameter Ratio	7.41

Residuals: R; Rw	0.061 ; 0.070
Goodness of Fit Indicator	2.39
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.38 $e^-/\text{Å}^3$
Minimum peak in Final Diff. Map	-0.21 $e^-/\text{Å}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	-0.2915(3)	0.1658(4)	0.9460(2)	3.31(8)
C(1)	0.2319(4)	0.3399(5)	1.0069(2)	2.26(10)
C(2)	0.2829(4)	0.3548(5)	0.9352(2)	2.48(10)
C(3)	0.2591(4)	0.2165(5)	0.8887(2)	2.6(1)
C(4)	0.1138(4)	0.1910(5)	0.8650(2)	2.40(10)
C(5)	0.0827(4)	0.0344(5)	0.8363(2)	3.4(1)
C(6)	-0.0578(5)	0.0121(7)	0.8064(3)	5.6(2)
C(7)	-0.1522(4)	0.1018(5)	0.8406(2)	2.8(1)
C(8)	-0.0907(4)	0.1791(5)	0.9113(2)	2.17(10)
C(9)	-0.1640(4)	0.2084(5)	0.9638(2)	2.5(1)
C(10)	-0.1119(4)	0.2810(5)	1.0286(2)	2.4(1)
C(11)	0.0165(4)	0.3216(5)	1.0430(2)	2.39(10)
C(12)	0.0925(4)	0.2944(5)	0.9911(2)	1.99(9)
C(13)	0.0379(4)	0.2223(4)	0.9251(2)	2.00(9)
C(14)	-0.3696(4)	0.1921(6)	0.9993(3)	3.6(1)
C(15)	0.3110(4)	0.2307(5)	1.0581(2)	2.41(10)
C(16)	0.4066(4)	0.2613(5)	1.1156(2)	2.5(1)
C(17)	0.4470(4)	0.4133(6)	1.1402(2)	3.5(1)
C(18)	0.4772(4)	0.1373(5)	1.1605(2)	3.1(1)
C(19)	0.3240(4)	0.2274(6)	0.8219(2)	3.4(1)
C(20)	0.0703(4)	0.3993(5)	1.1146(2)	3.1(1)
C(21)	-0.2248(7)	0.2144(7)	0.7870(3)	8.7(2)
H(1)	-0.1684	0.2945	1.0676	4.2697
H(2)	0.2967	0.1163	1.0468	1.7238

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(3)	-0.3731	0.3076	1.0046	2.1297
H(4)	-0.4529	0.1594	0.9741	3.5524
H(5)	-0.3288	0.1417	1.0497	4.3155
H(6)	0.4427	0.4329	1.1912	6.0582
H(7)	0.5435	0.4292	1.1372	5.3053
H(8)	0.4079	0.5074	1.1156	7.0236
H(12)	0.4210	0.2374	0.8374	1.5143
H(13)	0.3080	0.1287	0.7931	4.5798
H(14)	0.3005	0.3277	0.7944	4.9816
H(15)	0.0007	0.4010	1.1482	6.2090
H(16)	0.1483	0.3496	1.1430	3.1472
H(17)	0.0909	0.5091	1.1066	2.9676
H(18)	-0.1792	0.3016	0.7717	14.5853
H(19)	-0.2644	0.1587	0.7442	9.7793
H(21)	0.1289	0.0064	0.7957	5.2293
H(22)	0.1049	-0.0470	0.8785	5.2907
H(23)	-0.0696	0.0109	0.7536	7.5802
H(24)	-0.0864	-0.1083	0.8035	13.8000
H(25)	0.2439	0.4481	0.9039	1.8870
H(26)	0.3753	0.3796	0.9475	3.6128
H(27)	0.0835	0.2615	0.8260	3.1668
H(28)	-0.2079	0.0308	0.8517	6.1121
H(29)	0.2437	0.4404	1.0323	2.0712
H(33)	-0.3089	0.2560	0.8164	23.5646

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(34)	0.2934	0.1284	0.9200	0.7923
H(35)	0.4483	0.0230	1.1466	10.2141
H(36)	0.5465	0.0907	1.1526	46.0221
H(37)	0.4618	0.1527	1.2077	7.3731

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.029(2)	0.054(2)	0.046(2)	-0.006(2)	0.014(1)	-0.008(2)
C(1)	0.029(2)	0.029(3)	0.028(2)	-0.001(2)	0.006(2)	-0.003(2)
C(2)	0.029(2)	0.031(3)	0.034(2)	-0.002(2)	0.007(2)	0.007(2)
C(3)	0.031(2)	0.040(3)	0.028(2)	0.005(2)	0.008(2)	0.006(2)
C(4)	0.034(2)	0.033(3)	0.024(2)	0.003(2)	0.006(2)	0.004(2)
C(5)	0.049(3)	0.041(3)	0.039(3)	0.000(2)	0.012(2)	-0.016(2)
C(6)	0.046(3)	0.110(5)	0.061(4)	-0.016(3)	0.024(3)	-0.050(4)
C(7)	0.040(2)	0.039(3)	0.027(2)	-0.004(2)	0.005(2)	-0.003(2)
C(8)	0.033(2)	0.025(3)	0.024(2)	0.000(2)	0.004(2)	0.001(2)
C(9)	0.030(3)	0.031(3)	0.034(3)	0.000(2)	0.007(2)	0.002(2)
C(10)	0.034(3)	0.029(3)	0.029(2)	0.005(2)	0.012(2)	0.000(2)
C(11)	0.038(3)	0.026(3)	0.025(2)	0.006(2)	0.005(2)	0.000(2)
C(12)	0.031(2)	0.025(3)	0.020(2)	0.002(2)	0.006(2)	0.004(2)
C(13)	0.032(2)	0.024(2)	0.021(2)	0.003(2)	0.007(2)	0.003(2)
C(14)	0.031(3)	0.059(4)	0.050(3)	-0.001(3)	0.020(2)	0.000(3)
C(15)	0.029(2)	0.036(3)	0.025(2)	0.000(2)	0.003(2)	0.000(2)
C(16)	0.030(2)	0.043(3)	0.026(2)	0.001(2)	0.011(2)	0.001(2)
C(17)	0.048(3)	0.047(3)	0.036(3)	-0.010(3)	0.002(2)	-0.005(2)
C(18)	0.046(3)	0.048(3)	0.023(2)	0.009(2)	0.004(2)	0.007(2)
C(19)	0.037(3)	0.057(4)	0.040(3)	0.003(2)	0.019(2)	0.005(3)
C(20)	0.044(3)	0.043(3)	0.028(2)	0.003(2)	0.001(2)	-0.009(2)
C(21)	0.161(7)	0.070(5)	0.059(4)	0.017(5)	-0.075(4)	-0.006(4)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
O(1)	C(9)	1.388(4)	O(1)	C(14)	1.432(5)
C(1)	C(2)	1.538(6)	C(1)	C(12)	1.514(5)
C(1)	C(15)	1.511(6)	C(1)	H(29)	1.02
C(2)	C(3)	1.518(6)	C(2)	H(25)	1.07
C(2)	H(26)	0.99	C(3)	C(4)	1.542(5)
C(3)	C(19)	1.537(6)	C(3)	H(34)	1.01
C(4)	C(5)	1.533(6)	C(4)	C(13)	1.526(5)
C(4)	H(27)	0.97	C(5)	C(6)	1.505(6)
C(5)	H(21)	1.01	C(5)	H(22)	1.07
C(6)	C(7)	1.526(6)	C(6)	H(23)	0.96
C(6)	H(24)	1.13	C(7)	C(8)	1.519(5)
C(7)	C(21)	1.528(7)	C(7)	H(28)	0.93
C(8)	C(9)	1.389(5)	C(8)	C(13)	1.400(5)
C(9)	C(10)	1.390(6)	C(10)	C(11)	1.391(5)
C(10)	H(1)	1.04	C(11)	C(12)	1.398(5)
C(11)	C(20)	1.516(6)	C(12)	C(13)	1.411(5)
C(14)	H(3)	1.05	C(14)	H(4)	0.97
C(14)	H(5)	1.06	C(15)	C(16)	1.353(5)
C(15)	H(2)	1.06	C(16)	C(17)	1.491(6)
C(16)	C(18)	1.512(6)	C(17)	H(6)	0.97
C(17)	H(7)	1.05	C(17)	H(8)	1.02
C(18)	H(35)	1.10	C(18)	H(36)	0.89
C(18)	H(37)	0.93	C(19)	H(12)	1.02
C(19)	H(13)	1.04	C(19)	H(14)	1.05

Table 3. Bond Lengths($\AA$) (continued)

atom	atom	distance	atom	atom	distance
C(20)	H(15)	1.06	C(20)	H(16)	1.00
C(20)	H(17)	1.04	C(21)	H(18)	1.00
C(21)	H(19)	0.97	C(21)	H(33)	1.20

Table 4. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(9)	O(1)	C(14)	117.6(3)	C(2)	C(1)	C(12)	110.7(3)
C(2)	C(1)	C(15)	110.7(3)	C(2)	C(1)	H(29)	106.7
C(12)	C(1)	C(15)	110.4(3)	C(12)	C(1)	H(29)	111.1
C(15)	C(1)	H(29)	107.0	C(1)	C(2)	C(3)	111.9(3)
C(1)	C(2)	H(25)	112.2	C(1)	C(2)	H(26)	108.9
C(3)	C(2)	H(25)	110.0	C(3)	C(2)	H(26)	111.5
H(25)	C(2)	H(26)	102.0	C(2)	C(3)	C(4)	109.5(3)
C(2)	C(3)	C(19)	110.8(4)	C(2)	C(3)	H(34)	108.9
C(4)	C(3)	C(19)	111.4(3)	C(4)	C(3)	H(34)	105.9
C(19)	C(3)	H(34)	110.2	C(3)	C(4)	C(5)	112.0(4)
C(3)	C(4)	C(13)	114.2(3)	C(3)	C(4)	H(27)	106.3
C(5)	C(4)	C(13)	108.6(3)	C(5)	C(4)	H(27)	109.5
C(13)	C(4)	H(27)	106.0	C(4)	C(5)	C(6)	112.6(4)
C(4)	C(5)	H(21)	113.0	C(4)	C(5)	H(22)	112.6
C(6)	C(5)	H(21)	106.6	C(6)	C(5)	H(22)	103.8
H(21)	C(5)	H(22)	107.6	C(5)	C(6)	C(7)	117.6(4)
C(5)	C(6)	H(23)	107.5	C(5)	C(6)	H(24)	112.7
C(7)	C(6)	H(23)	117.6	C(7)	C(6)	H(24)	110.0
H(23)	C(6)	H(24)	87.7	C(6)	C(7)	C(8)	113.5(4)
C(6)	C(7)	C(21)	112.1(5)	C(6)	C(7)	H(28)	102.9
C(8)	C(7)	C(21)	109.4(4)	C(8)	C(7)	H(28)	108.4
C(21)	C(7)	H(28)	110.2	C(7)	C(8)	C(9)	119.2(4)
C(7)	C(8)	C(13)	121.9(4)	C(9)	C(8)	C(13)	118.9(4)
O(1)	C(9)	C(8)	116.0(4)	O(1)	C(9)	C(10)	123.0(4

Table 4. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(8)	C(9)	C(10)	121.0(4)	C(9)	C(10)	C(11)	120.2(4)
C(9)	C(10)	H(1)	118.3	C(11)	C(10)	H(1)	121.2
C(10)	C(11)	C(12)	120.1(4)	C(10)	C(11)	C(20)	118.7(4)
C(12)	C(11)	C(20)	121.2(4)	C(1)	C(12)	C(11)	119.8(3)
C(1)	C(12)	C(13)	121.2(3)	C(11)	C(12)	C(13)	119.0(3)
C(4)	C(13)	C(8)	117.0(3)	C(4)	C(13)	C(12)	122.2(3)
C(8)	C(13)	C(12)	120.8(4)	O(1)	C(14)	H(3)	105.5
O(1)	C(14)	H(4)	102.4	O(1)	C(14)	H(5)	110.2
H(3)	C(14)	H(4)	107.7	H(3)	C(14)	H(5)	111.4
H(4)	C(14)	H(5)	118.5	C(1)	C(15)	C(16)	127.0(4)
C(1)	C(15)	H(2)	118.4	C(16)	C(15)	H(2)	114.4
C(15)	C(16)	C(17)	124.1(4)	C(15)	C(16)	C(18)	119.9(4)
C(17)	C(16)	C(18)	115.9(4)	C(16)	C(17)	H(6)	113.7
C(16)	C(17)	H(7)	109.7	C(16)	C(17)	H(8)	124.8
H(6)	C(17)	H(7)	105.0	H(6)	C(17)	H(8)	101.0
H(7)	C(17)	H(8)	100.3	C(16)	C(18)	H(35)	119.2
C(16)	C(18)	H(36)	127.2	C(16)	C(18)	H(37)	104.3
H(35)	C(18)	H(36)	73.4	H(35)	C(18)	H(37)	105.6
H(36)	C(18)	H(37)	122.1	C(3)	C(19)	H(12)	111.6
C(3)	C(19)	H(13)	107.3	C(3)	C(19)	H(14)	110.2
H(12)	C(19)	H(13)	106.0	H(12)	C(19)	H(14)	101.1
H(13)	C(19)	H(14)	119.9	C(11)	C(20)	H(15)	109.6
C(11)	C(20)	H(16)	112.6	C(11)	C(20)	H(17)	112.0
H(15)	C(20)	H(16)	107.6	H(15)	C(20)	H(17)	105.3

Table 4. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
H(16)	C(20)	H(17)	109.3	C(7)	C(21)	H(18)	120.2
C(7)	C(21)	H(19)	105.6	C(7)	C(21)	H(33)	104.0
H(18)	C(21)	H(19)	109.9	H(18)	C(21)	H(33)	109.1
H(19)	C(21)	H(33)	107.2				

Table 5. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(1)	C(9)	C(8)	C(7)	-1.2(6)	O(1)	C(9)	C(8)	C(13)	178.6(4)
O(1)	C(9)	C(10)	C(11)	-179.7(4)	C(1)	C(2)	C(3)	C(4)	63.1(4)
C(1)	C(2)	C(3)	C(19)	-173.6(3)	C(1)	C(12)	C(11)	C(10)	179.5(4)
C(1)	C(12)	C(11)	C(20)	1.5(6)	C(1)	C(12)	C(13)	C(4)	-2.3(6)
C(1)	C(12)	C(13)	C(8)	179.2(4)	C(1)	C(15)	C(16)	C(17)	2.6(7)
C(1)	C(15)	C(16)	C(18)	-179.1(4)	C(2)	C(1)	C(12)	C(11)	-158.6(4)
C(2)	C(1)	C(12)	C(13)	22.6(5)	C(2)	C(1)	C(15)	C(16)	98.8(5)
C(2)	C(3)	C(4)	C(5)	-164.5(3)	C(2)	C(3)	C(4)	C(13)	-40.5(5)
C(3)	C(2)	C(1)	C(12)	-53.5(5)	C(3)	C(2)	C(1)	C(15)	69.3(4)
C(3)	C(4)	C(5)	C(6)	-174.6(4)	C(3)	C(4)	C(13)	C(8)	-170.0(4)
C(3)	C(4)	C(13)	C(12)	11.4(6)	C(4)	C(5)	C(6)	C(7)	-30.6(7)
C(4)	C(13)	C(8)	C(7)	1.2(6)	C(4)	C(13)	C(8)	C(9)	-178.6(4)
C(4)	C(13)	C(12)	C(11)	178.9(4)	C(5)	C(4)	C(3)	C(19)	72.6(5)
C(5)	C(4)	C(13)	C(8)	-44.3(5)	C(5)	C(4)	C(13)	C(12)	137.1(4)
C(5)	C(6)	C(7)	C(8)	-11.9(7)	C(5)	C(6)	C(7)	C(21)	112.7(6)
C(6)	C(5)	C(4)	C(13)	58.4(5)	C(6)	C(7)	C(8)	C(9)	-152.0(4)
C(6)	C(7)	C(8)	C(13)	28.2(6)	C(7)	C(8)	C(9)	C(10)	-178.9(4)
C(7)	C(8)	C(13)	C(12)	179.8(4)	C(8)	C(9)	O(1)	C(14)	179.0(4)
C(8)	C(9)	C(10)	C(11)	-2.0(6)	C(8)	C(13)	C(12)	C(11)	0.4(6)
C(9)	C(8)	C(7)	C(21)	81.9(6)	C(9)	C(8)	C(13)	C(12)	0.0(6)
C(9)	C(10)	C(11)	C(12)	2.5(6)	C(9)	C(10)	C(11)	C(20)	-179.4(4)
C(10)	C(9)	O(1)	C(14)	-3.3(6)	C(10)	C(9)	C(8)	C(13)	0.8(6)
C(10)	C(11)	C(12)	C(13)	-1.6(6)	C(11)	C(12)	C(1)	C(15)	78.3(5)
C(12)	C(1)	C(15)	C(16)	-138.2(4)	C(13)	C(4)	C(3)	C(19)	-163.5(4)

Table 5. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(13)	C(8)	C(7)	C(21)	-97.8(5)	C(13)	C(12)	C(1)	C(15)	-100.5(4)
C(13)	C(12)	C(11)	C(20)	-179.7(4)					

Table 6. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	H(2)	2.57	55703	O(1)	H(35)	2.75	55703
O(1)	H(8)	3.33	56703	O(1)	H(12)	3.38	45501
C(1)	H(3)	3.56	56703	C(2)	H(7)	3.17	66703
C(2)	H(4)	3.29	65501	C(2)	H(3)	3.34	56703
C(2)	H(1)	3.41	56703	C(3)	H(4)	3.21	65501
C(3)	H(5)	3.48	55703	C(4)	H(24)	3.59	55602
C(4)	H(17)	3.59	56703	C(5)	H(18)	3.22	54602
C(5)	H(5)	3.43	55703	C(5)	H(15)	3.48	55404
C(5)	H(1)	3.51	55703	C(6)	H(15)	3.22	55404
C(6)	H(27)	3.32	54602	C(6)	H(14)	3.33	54602
C(7)	H(35)	3.40	55703	C(7)	H(2)	3.45	55703
C(8)	H(17)	2.85	56703	C(9)	H(17)	3.05	56703
C(9)	H(22)	3.23	55703	C(9)	H(2)	3.26	55703
C(9)	H(29)	3.30	56703	C(10)	H(22)	2.73	55703
C(10)	H(29)	3.00	56703	C(10)	H(17)	3.19	56703
C(10)	H(25)	3.21	56703	C(11)	H(17)	3.19	56703
C(11)	H(22)	3.28	55703	C(11)	H(24)	3.41	55703
C(11)	H(29)	3.58	56703	C(12)	H(17)	2.98	56703
C(13)	H(17)	2.80	56703	C(14)	H(2)	3.07	55703
C(14)	H(26)	3.19	45501	C(14)	H(36)	3.28	45501
C(14)	H(34)	3.30	55703	C(14)	H(35)	3.31	55703
C(14)	H(12)	3.40	45501	C(14)	H(8)	3.44	56703
C(14)	H(22)	3.51	55703	C(14)	C(16)	3.572(6)	45501
C(15)	H(28)	3.22	55703	C(15)	H(4)	3.27	65501

Table 6. Non-bonded Contacts out to 3.60 Å (continued)

atom	atom	distance	ADC	atom	atom	distance	ADC
C(16)	H(4)	3.40	65501	C(16)	H(3)	3.44	65501
C(16)	H(5)	3.46	65501	C(16)	H(28)	3.52	55703
C(17)	H(26)	3.31	66703	C(17)	H(19)	3.36	65504
C(17)	H(12)	3.46	66703	C(17)	H(13)	3.47	4
C(17)	H(33)	3.51	56703	C(17)	H(37)	3.55	65702
C(17)	H(3)	3.58	65501	C(18)	H(5)	3.19	65501
C(18)	H(28)	3.22	55703	C(18)	H(6)	3.29	64702
C(18)	H(13)	3.32	65703	C(18)	H(14)	3.42	4
C(18)	H(19)	3.43	65504	C(18)	H(33)	3.45	65504
C(18)	H(12)	3.57	65703	C(19)	H(37)	3.01	55404
C(19)	H(36)	3.20	65703	C(19)	H(6)	3.29	55404
C(19)	H(35)	3.29	65703	C(19)	H(4)	3.38	65501
C(19)	H(24)	3.43	55602	C(19)	H(7)	3.45	66703
C(19)	H(16)	3.55	55404	C(20)	H(24)	3.04	55703
C(20)	H(23)	3.32	4	C(20)	H(21)	3.41	4
C(20)	H(18)	3.50	56703	C(20)	H(25)	3.58	56703
C(21)	H(21)	3.32	55602	C(21)	H(17)	3.34	56703
C(21)	H(37)	3.58	45404	C(21)	H(7)	3.59	45404
C(21)	H(36)	3.59	45404	H(1)	H(22)	2.50	55703
H(1)	H(25)	2.56	56703	H(1)	H(29)	3.05	56703
H(2)	H(28)	2.63	55703	H(2)	H(5)	3.01	55703
H(2)	H(4)	3.07	55703	H(2)	H(4)	3.24	65501
H(3)	H(8)	2.76	56703	H(3)	H(26)	2.76	45501
H(3)	H(29)	2.82	56703	H(3)	H(25)	2.97	56703

Table 6. Non-bonded Contacts out to 3.60 Å (continued)

atom	atom	distance	ADC	atom	atom	distance	ADC
H(3)	H(26)	2.98	56703	H(3)	H(7)	2.99	45501
H(3)	H(12)	3.49	45501	H(4)	H(26)	2.69	45501
H(4)	H(34)	2.71	45501	H(4)	H(12)	2.72	45501
H(4)	H(35)	2.79	55703	H(4)	H(4)	3.27	45703
H(4)	H(36)	3.28	55703	H(4)	H(36)	3.38	45501
H(4)	H(34)	3.51	55703	H(4)	H(8)	3.53	56703
H(4)	H(5)	3.56	45703	H(5)	H(34)	2.53	55703
H(5)	H(36)	2.57	45501	H(5)	H(22)	2.64	55703
H(5)	H(35)	3.42	45501	H(5)	H(7)	3.49	45501
H(5)	H(21)	3.49	55703	H(6)	H(13)	2.65	4
H(6)	H(37)	2.79	65702	H(6)	H(35)	3.12	65702
H(6)	H(33)	3.16	56703	H(6)	H(12)	3.17	4
H(6)	H(19)	3.19	65504	H(6)	H(36)	3.22	65702
H(6)	H(12)	3.41	66703	H(6)	H(14)	3.46	66703
H(6)	H(14)	3.56	4	H(6)	H(33)	3.60	65504
H(7)	H(26)	2.60	66703	H(7)	H(19)	2.68	65504
H(7)	H(25)	2.76	66703	H(7)	H(14)	2.90	66703
H(7)	H(12)	3.08	66703	H(7)	H(37)	3.53	65702
H(8)	H(33)	2.80	56703	H(8)	H(26)	2.97	66703
H(8)	H(12)	2.97	66703	H(8)	H(37)	3.56	65702
H(8)	H(14)	3.56	66703	H(12)	H(37)	2.72	55404
H(12)	H(35)	2.73	65703	H(12)	H(33)	2.98	65501
H(12)	H(36)	3.00	65703	H(13)	H(36)	2.60	65703
H(13)	H(35)	2.96	65703	H(13)	H(16)	2.97	55404

Table 6. Non-bonded Contacts out to 3.60 Å (continued)

atom	atom	distance	ADC	atom	atom	distance	ADC
H(13)	H(37)	3.19	55404	H(13)	H(18)	3.39	54602
H(13)	H(37)	3.54	65703	H(13)	H(24)	3.58	55602
H(14)	H(37)	2.58	55404	H(14)	H(24)	2.69	55602
H(14)	H(23)	2.96	55602	H(14)	H(19)	3.10	55602
H(14)	H(28)	3.27	55602	H(14)	H(16)	3.37	55404
H(15)	H(23)	2.37	4	H(15)	H(24)	2.90	55703
H(15)	H(25)	2.93	56703	H(15)	H(21)	2.94	4
H(15)	H(27)	3.25	56703	H(15)	H(22)	3.41	55703
H(15)	H(18)	3.47	56703	H(15)	H(27)	3.57	4
H(16)	H(24)	2.55	55703	H(16)	H(21)	3.17	4
H(16)	H(28)	3.51	55703	H(16)	H(18)	3.53	56703
H(17)	H(18)	2.85	56703	H(17)	H(27)	3.20	56703
H(17)	H(33)	3.27	56703	H(17)	H(21)	3.46	4
H(17)	H(23)	3.50	4	H(17)	H(25)	3.56	56703
H(18)	H(21)	2.36	55602	H(18)	H(22)	3.34	55602
H(18)	H(23)	3.37	55602	H(18)	H(36)	3.44	45404
H(18)	H(24)	3.49	55602	H(19)	H(36)	3.29	45404
H(19)	H(37)	3.34	45404	H(19)	H(25)	3.39	54602
H(19)	H(35)	3.50	55703	H(21)	H(36)	3.52	65703
H(23)	H(27)	2.69	54602	H(23)	H(25)	3.19	54602
H(24)	H(27)	2.69	54602	H(28)	H(35)	2.61	55703
H(28)	H(37)	3.19	55703	H(33)	H(37)	2.97	45404
H(33)	H(35)	3.08	55703	H(33)	H(36)	3.43	45404
H(34)	H(36)	3.10	65703	H(34)	H(35)	3.51	65703

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

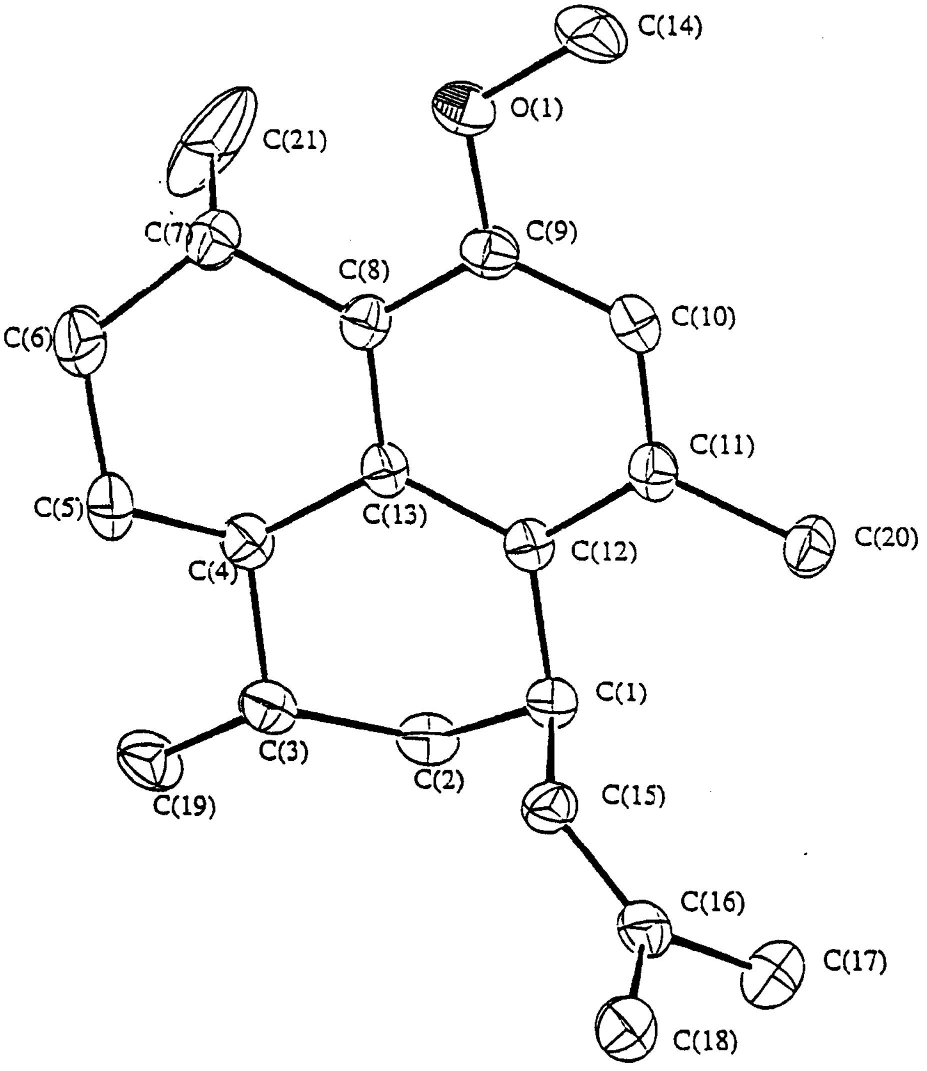
The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	1/2+Y,	1/2-Z
(3)	-X,	-Y,	-Z	(4)	X,	1/2-Y,	1/2+Z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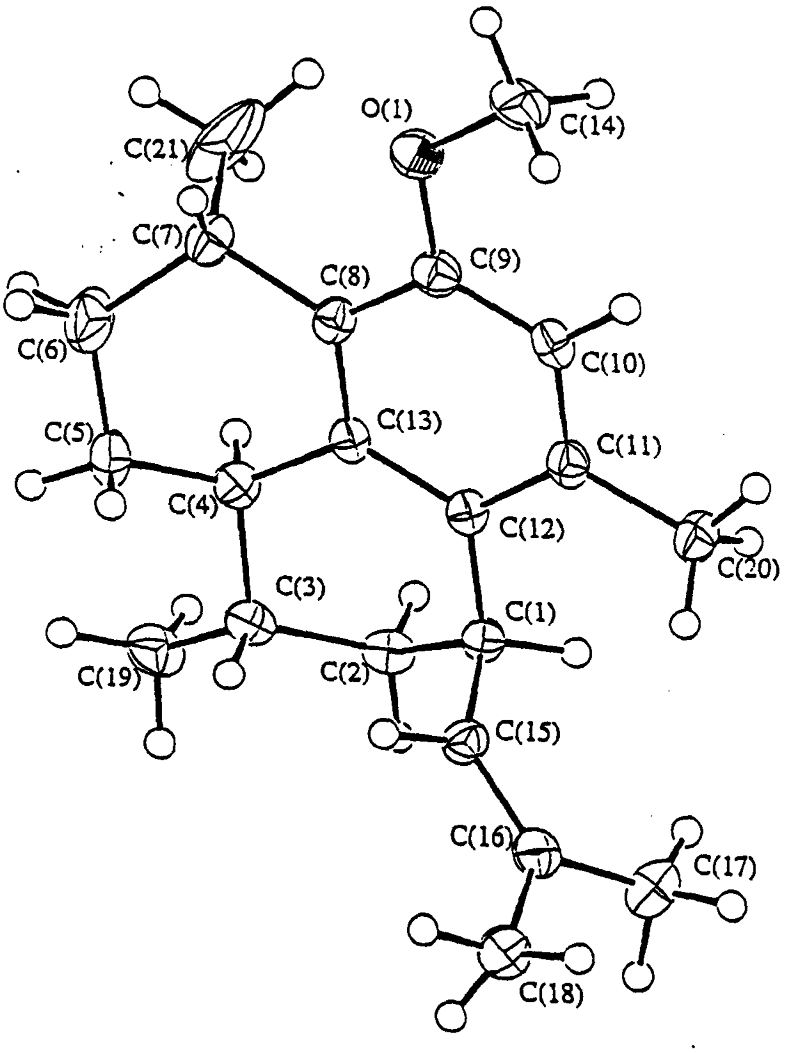
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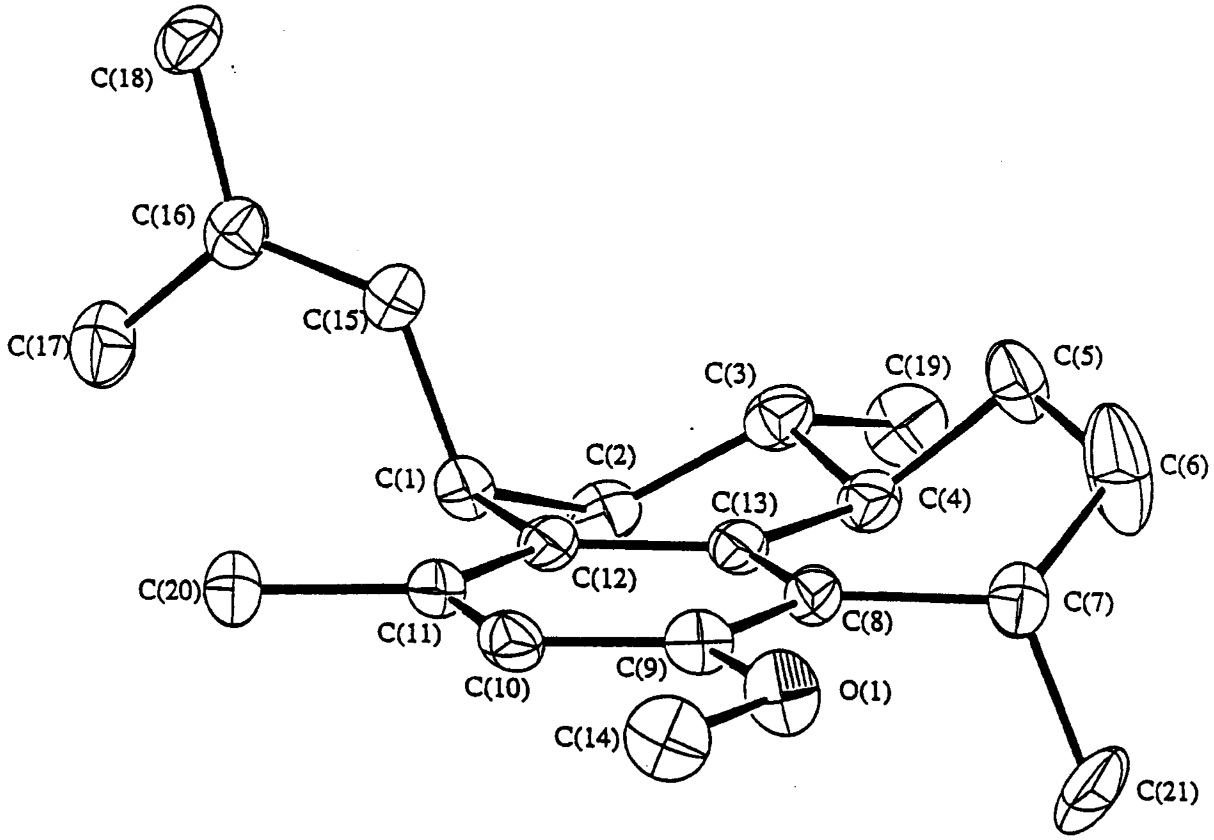
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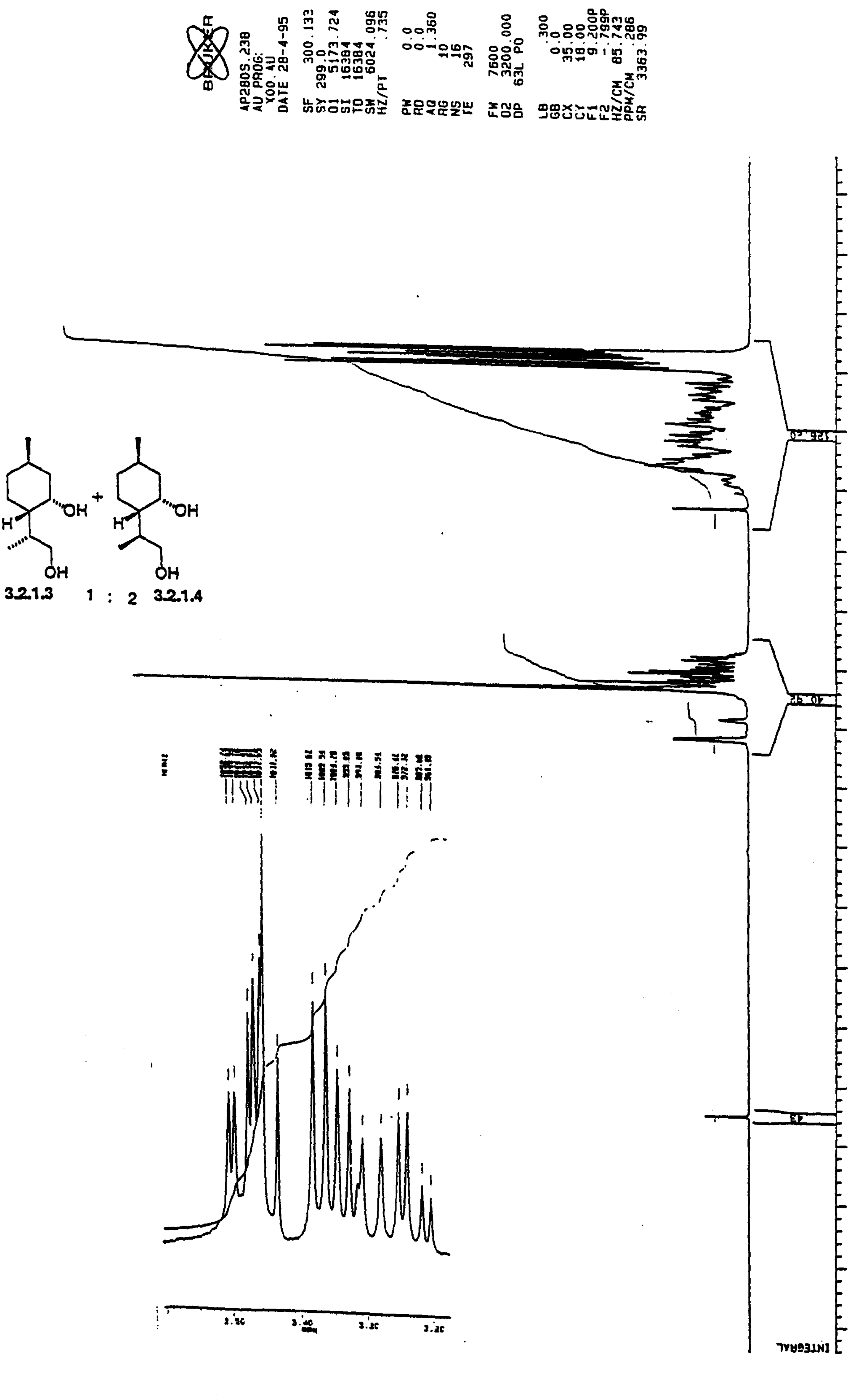
Appendix 2
Spectra of representative compounds.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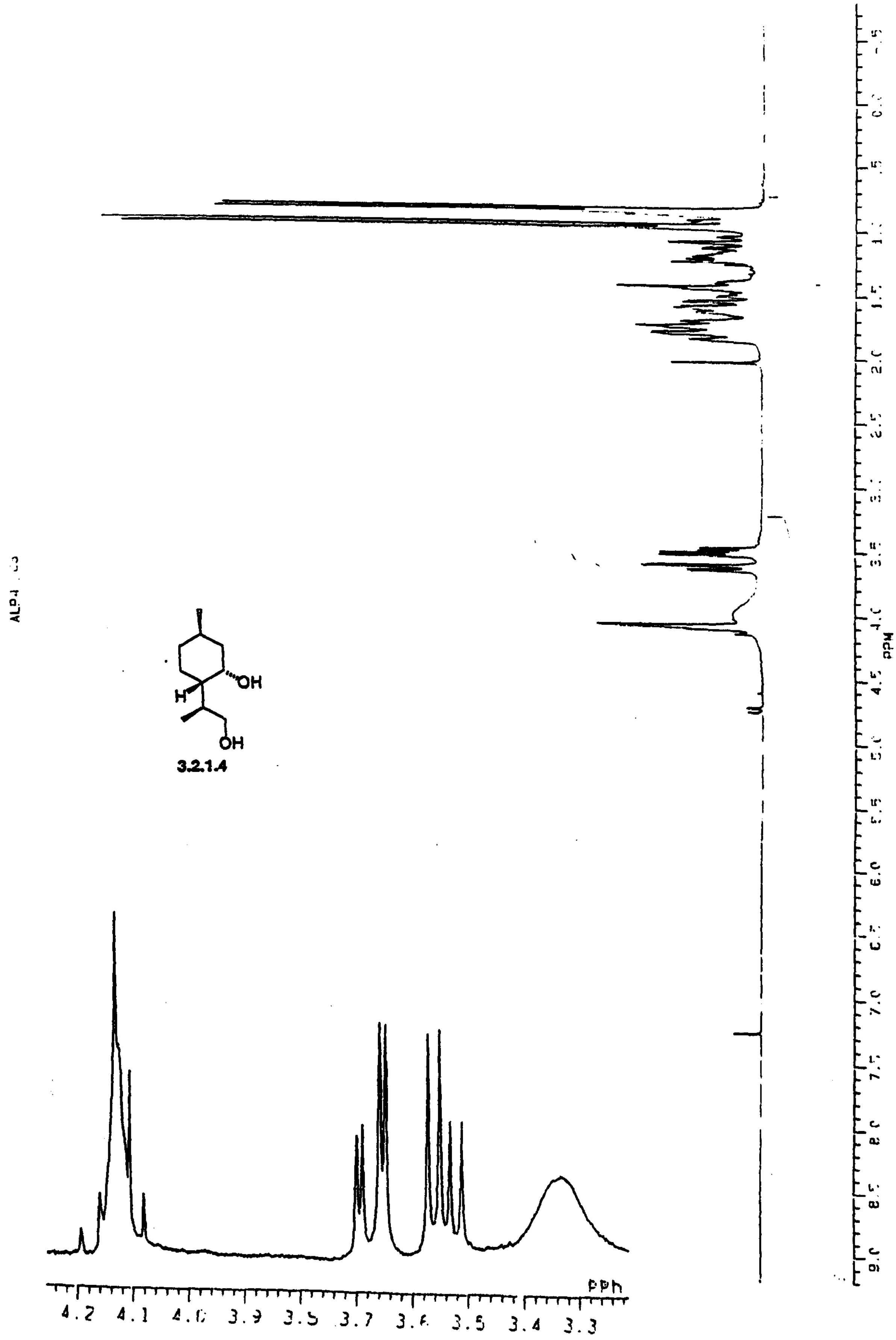
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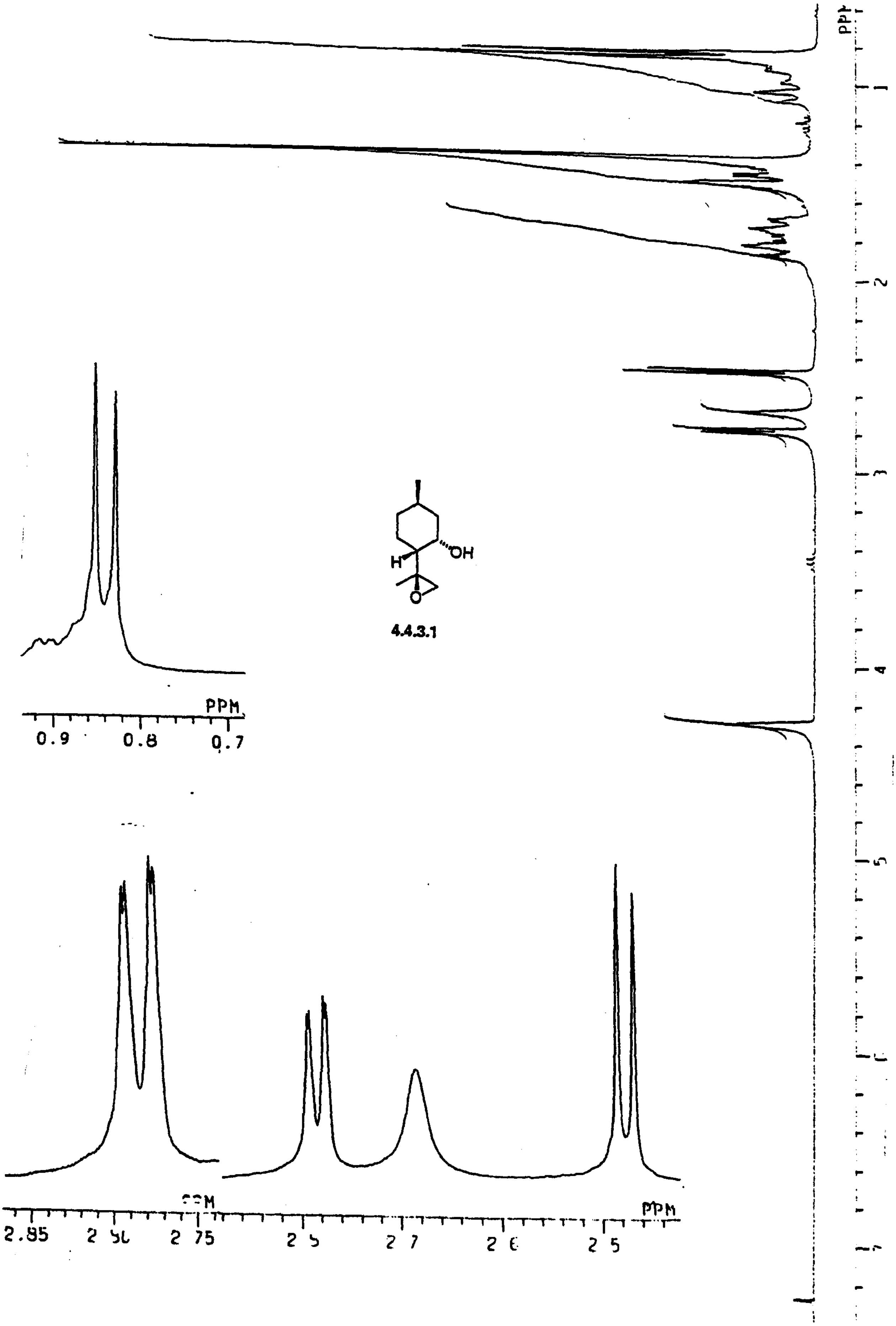

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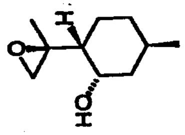

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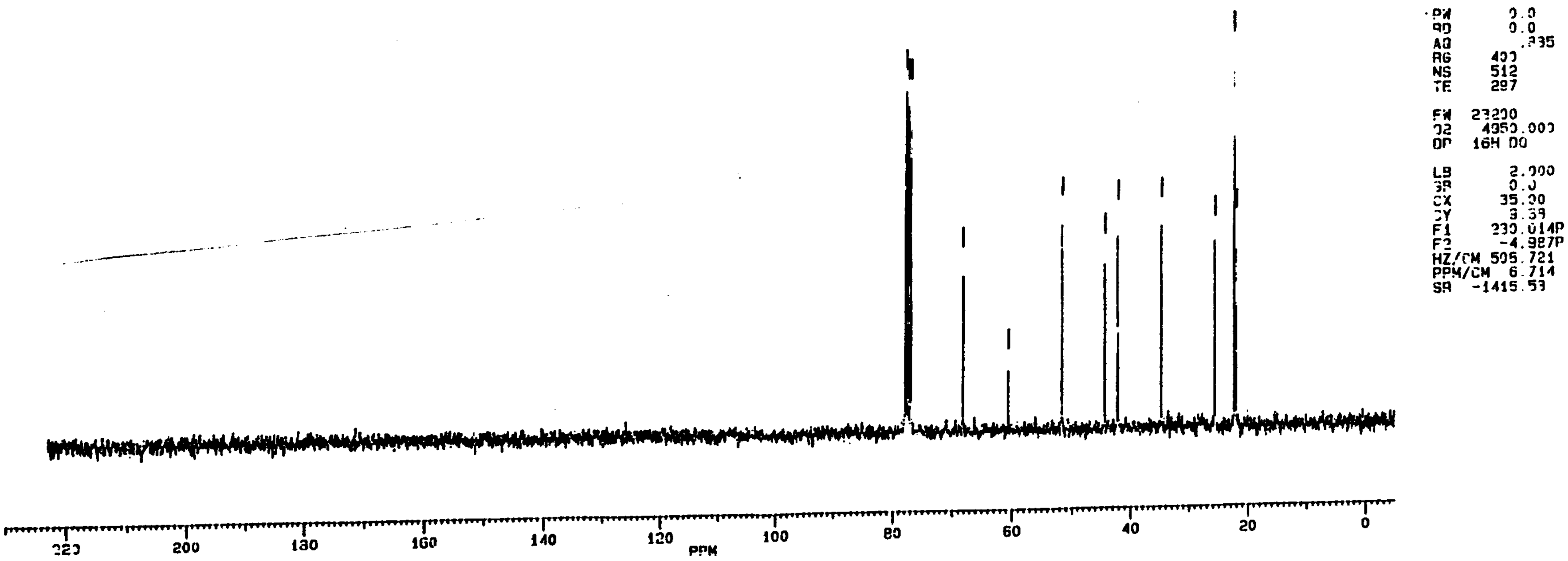

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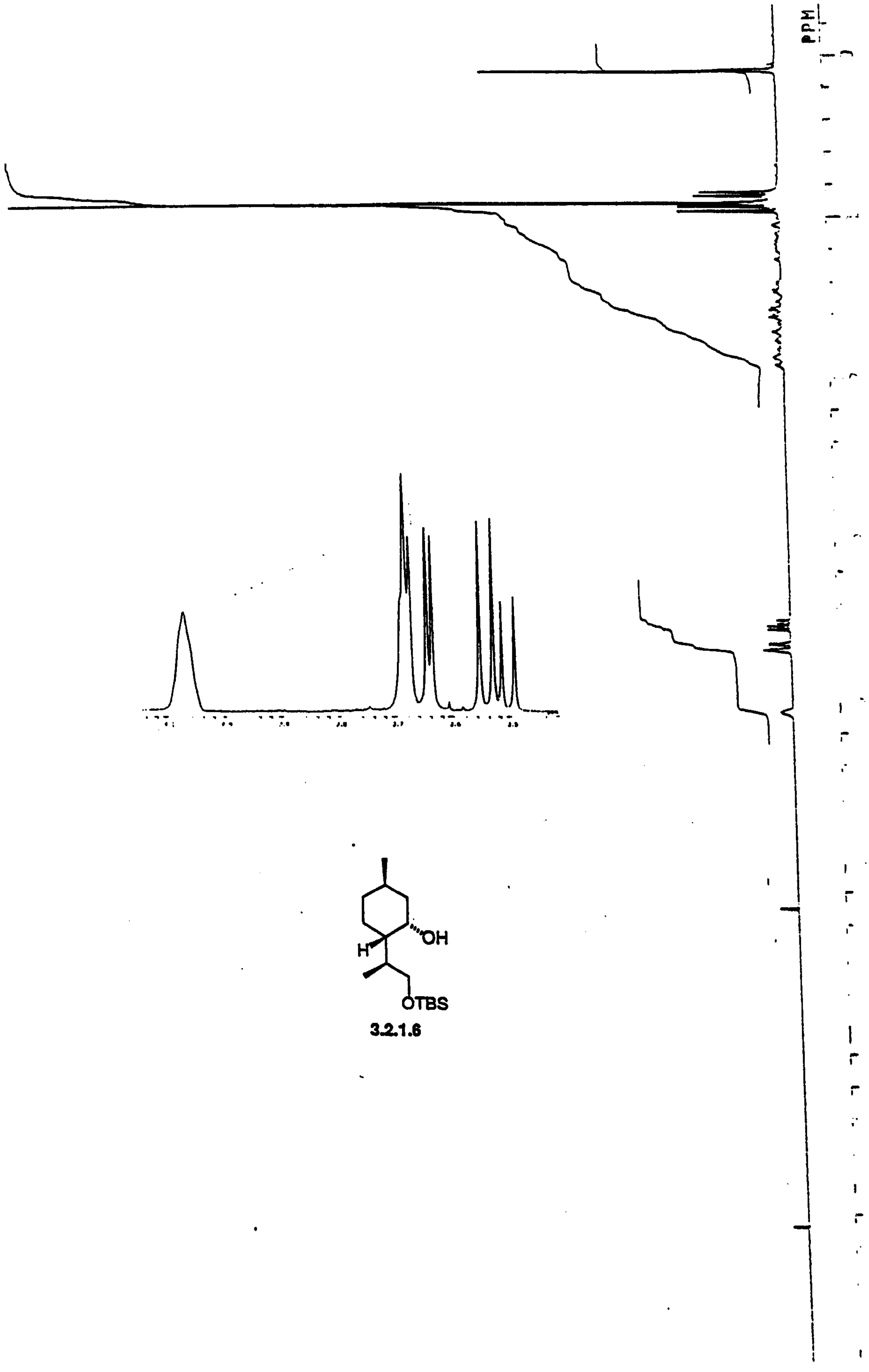

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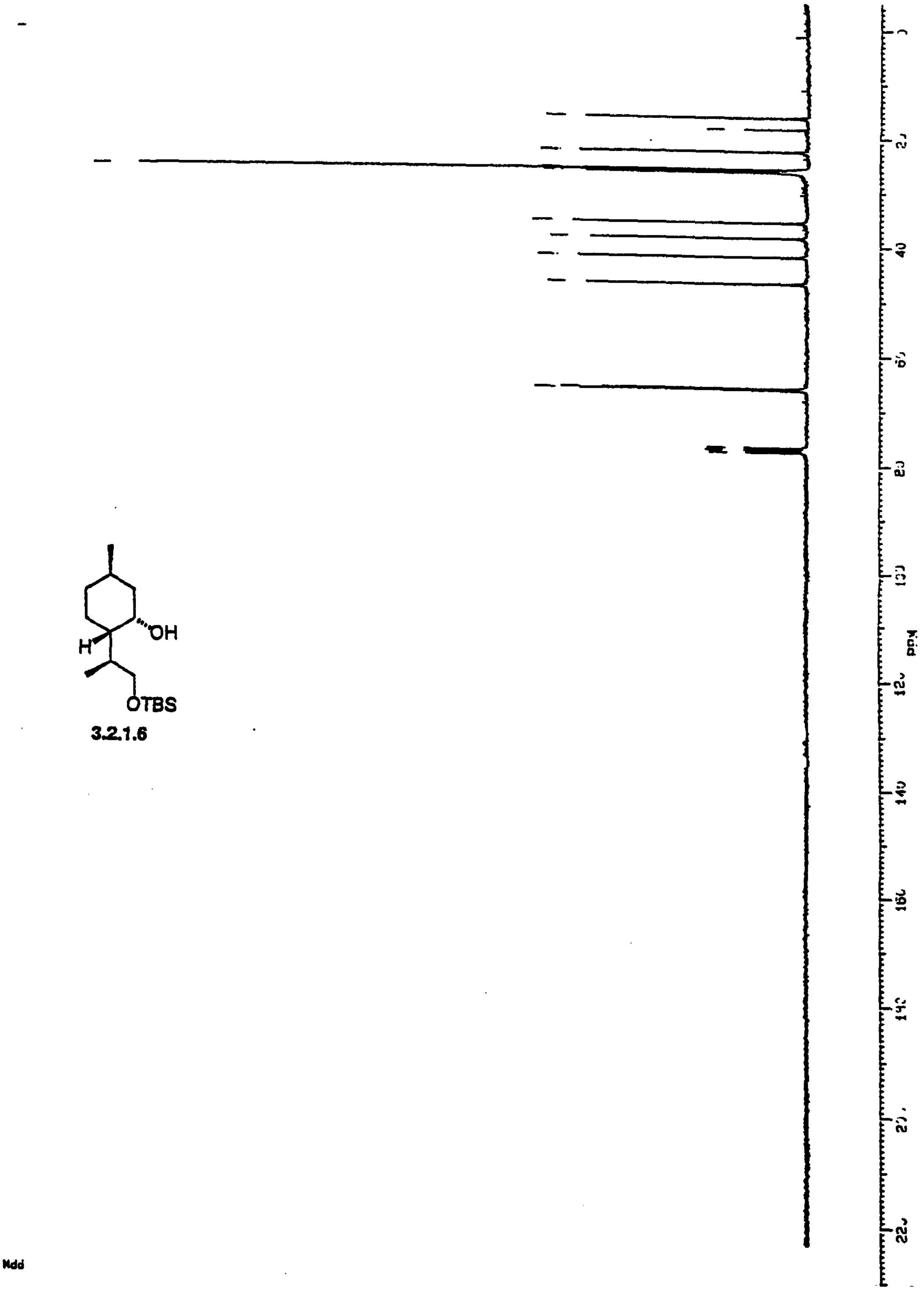

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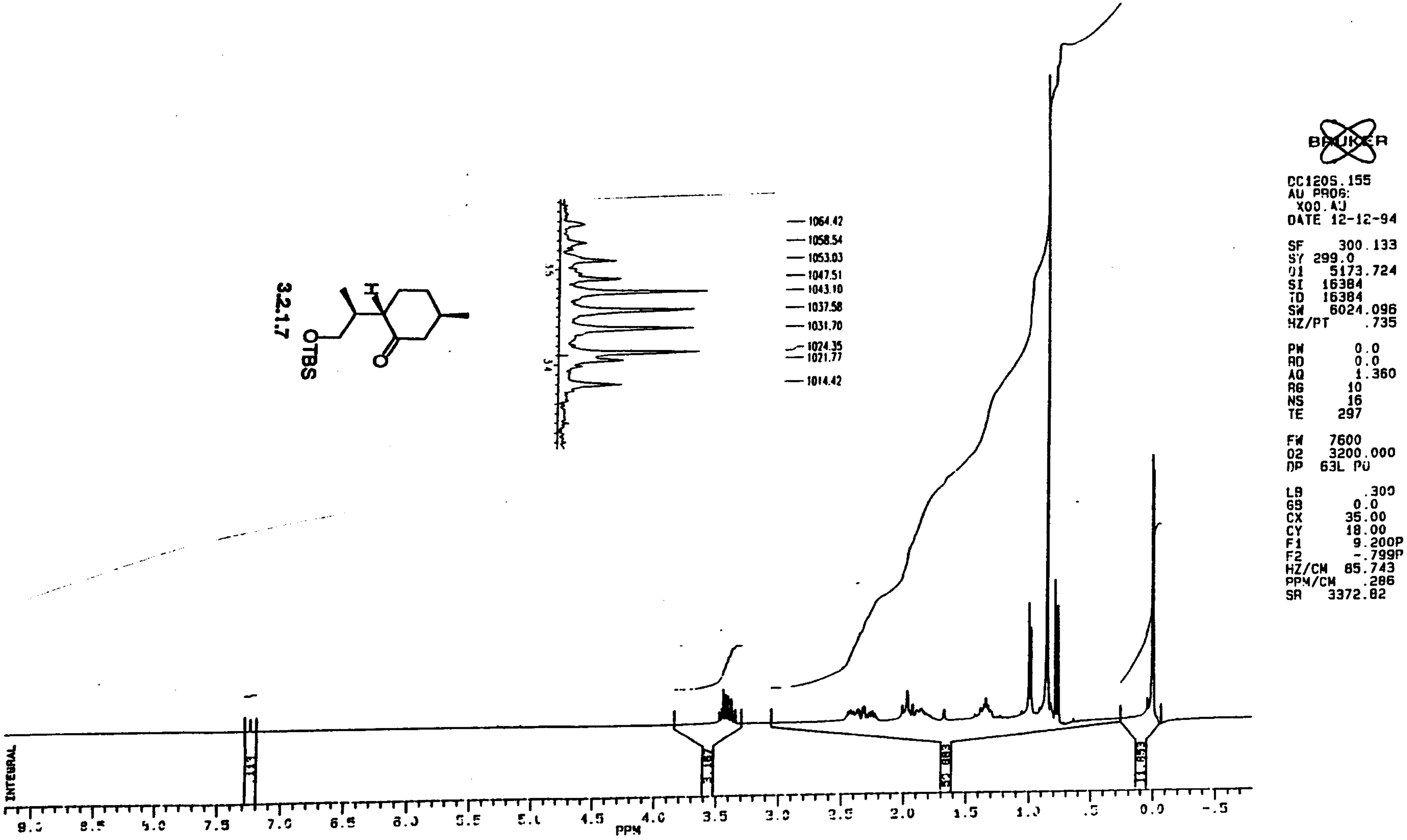
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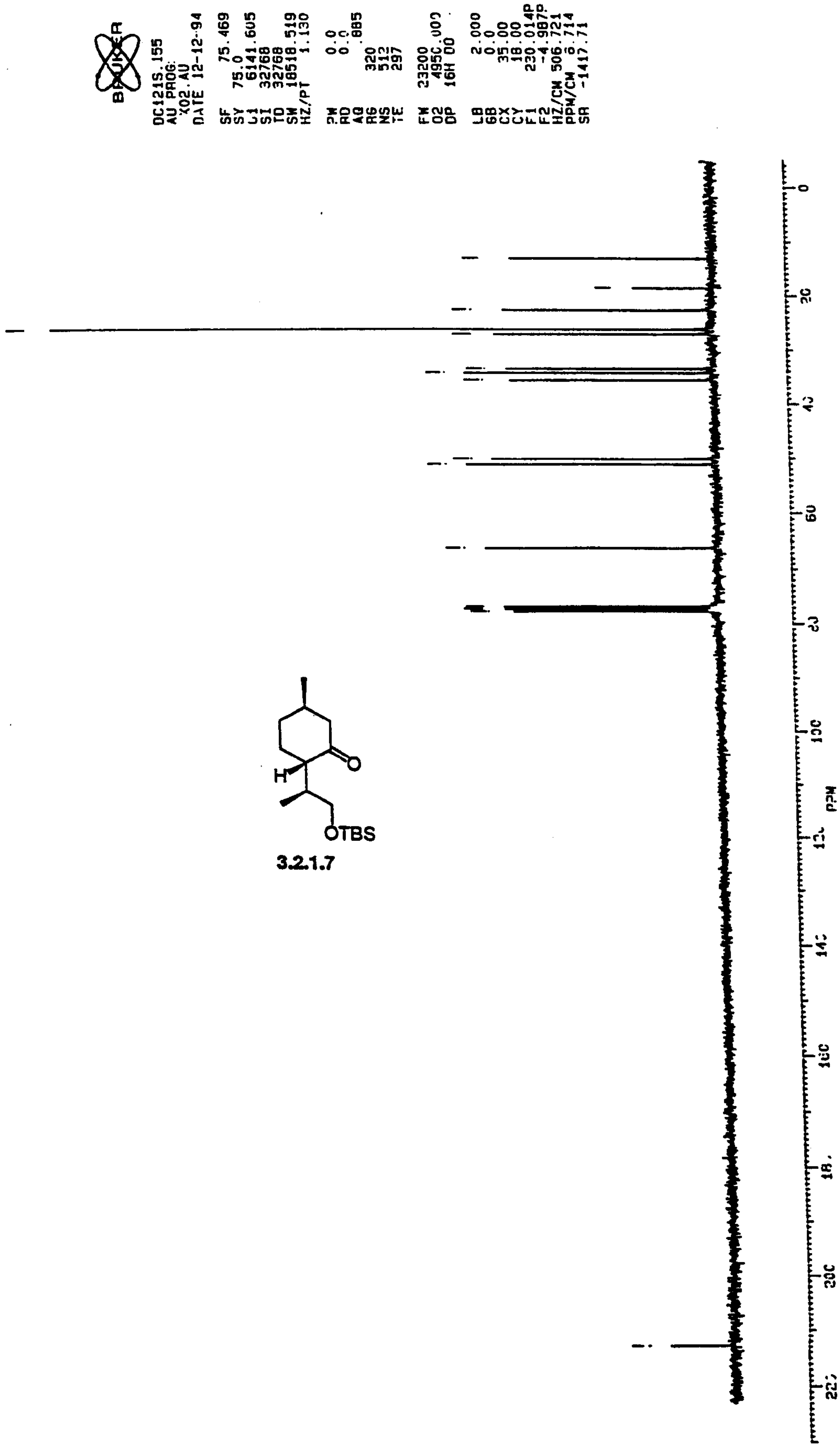
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SI 32768
TD 32768
SW 18518.519
HZ/PT 1.130
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RD 0.0
AQ .885
RG 320
NS 512
TE 297
FW 23200
O2 4950.000
DP 16H 00
LB 2.000
GB 0.0
CX 35.00
CY 18.00
F1 230.014P
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HZ/CM 506.721
PPM/CM 6.714
SR -1417.71
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160
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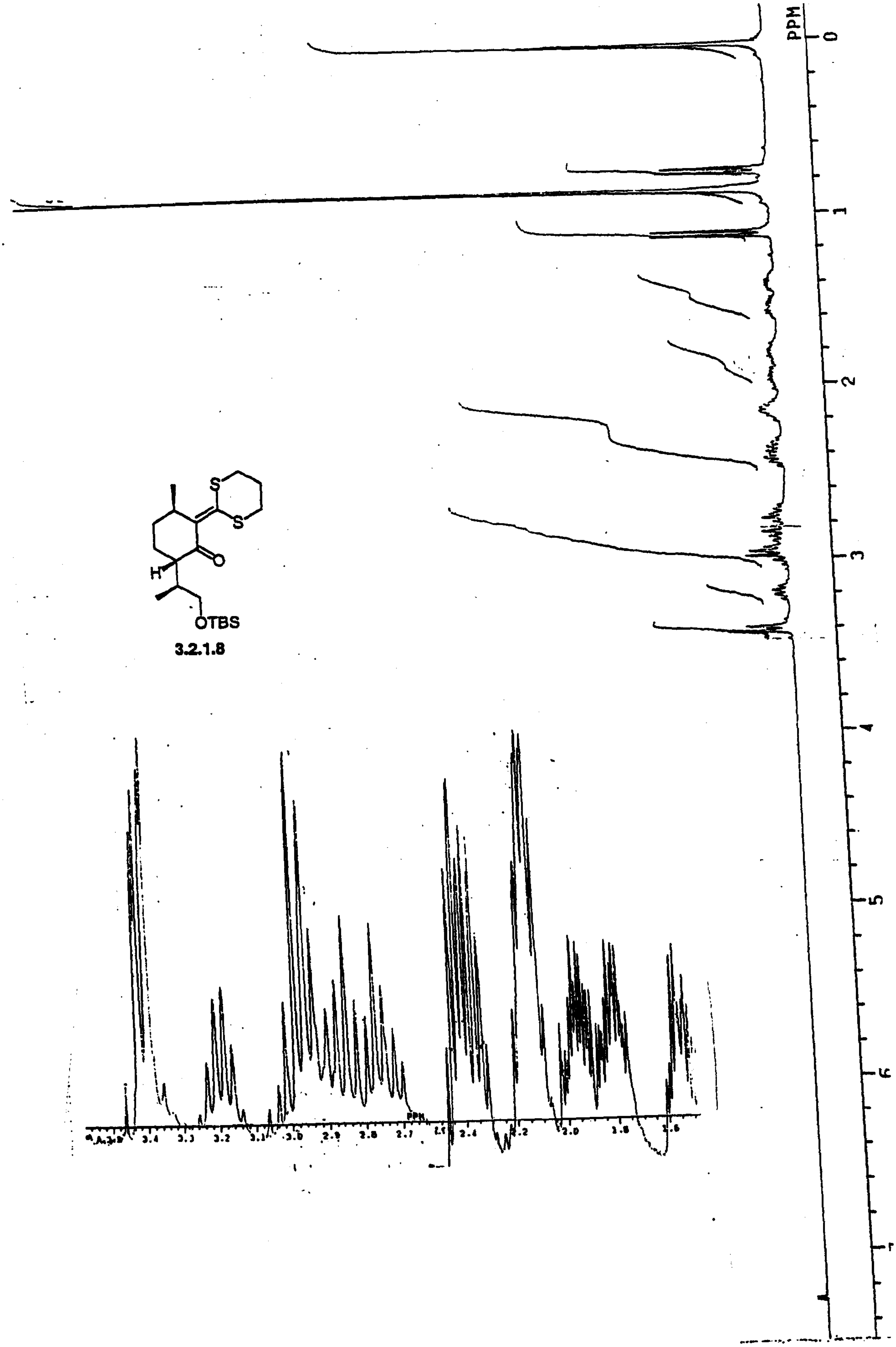
220
PPM

3.2.1.7



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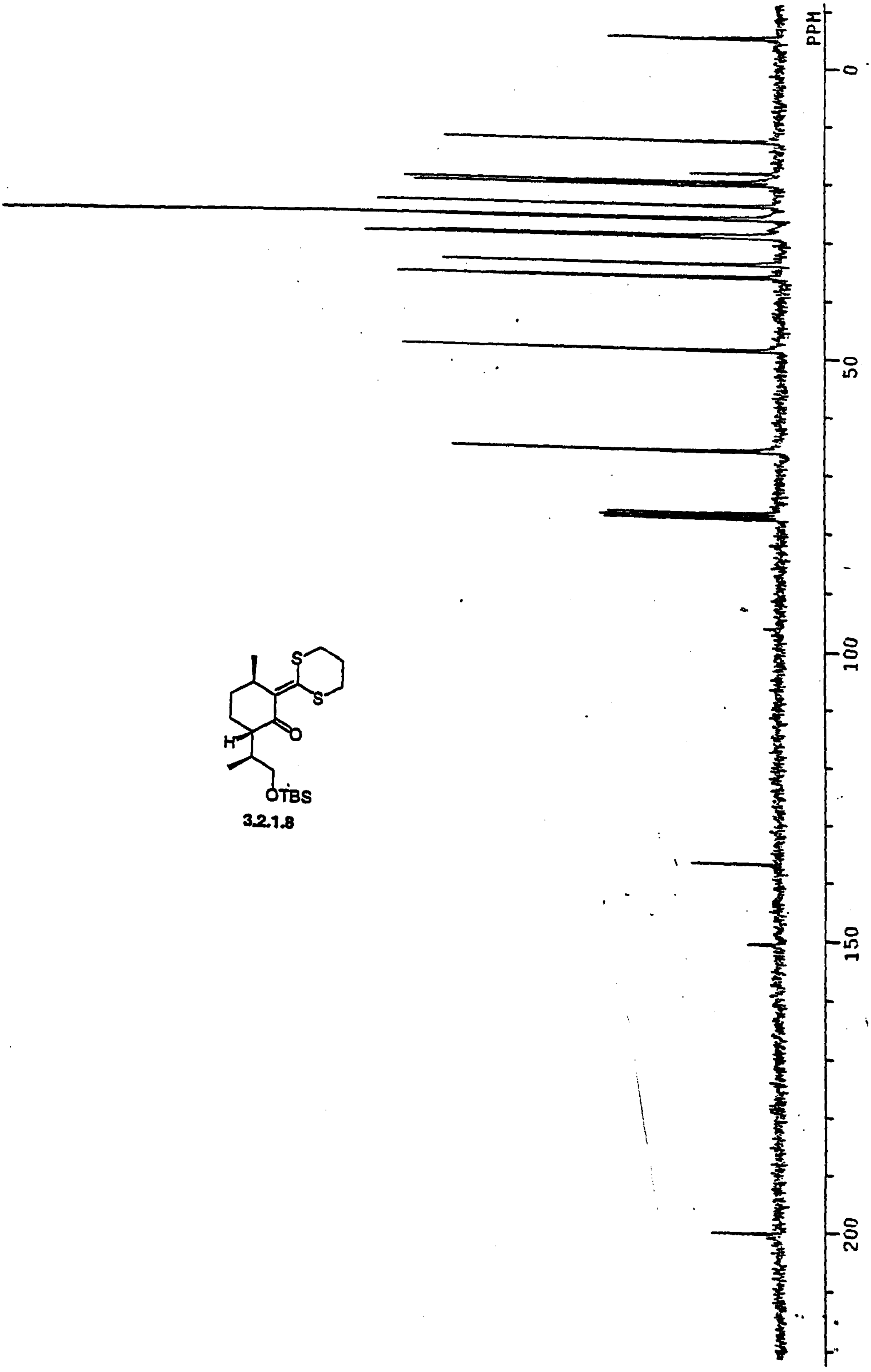
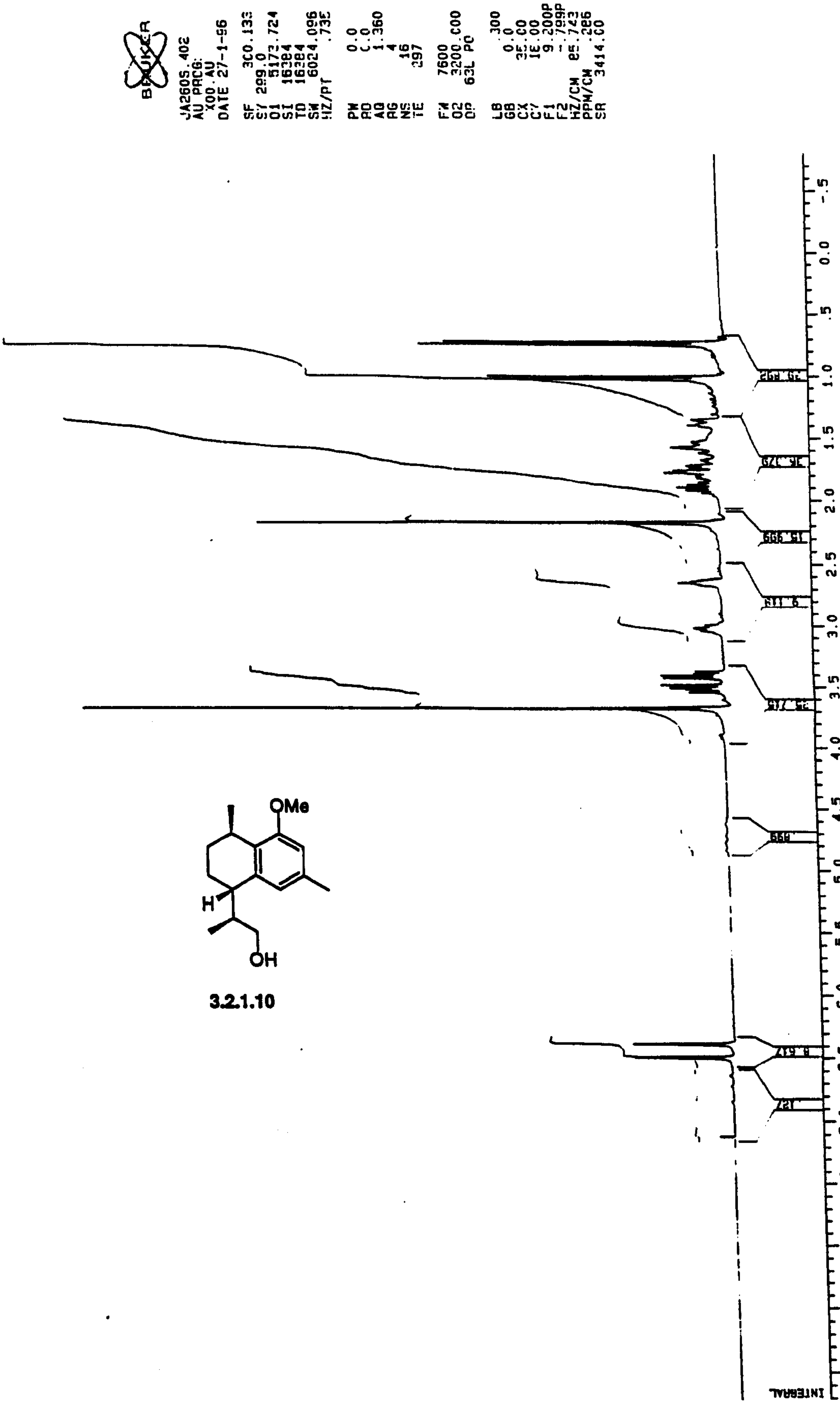


3.2.1.8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AQ 1.360
RG 4
NS 16
TE 297
FW 7600
O2 3200.000
DP 63L PO
LB .300
GB 0.0
CX 35.00
CY 16.00
F1 9.200P
F2 -.799P
HZ/CM 85.743
PPM/CM .286
SR 3414.60
25.964
36.129
15.999
9.114
35.716
.899
8.617
.157
PPM
INTEGRAL
-.5
0.0
.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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7.0
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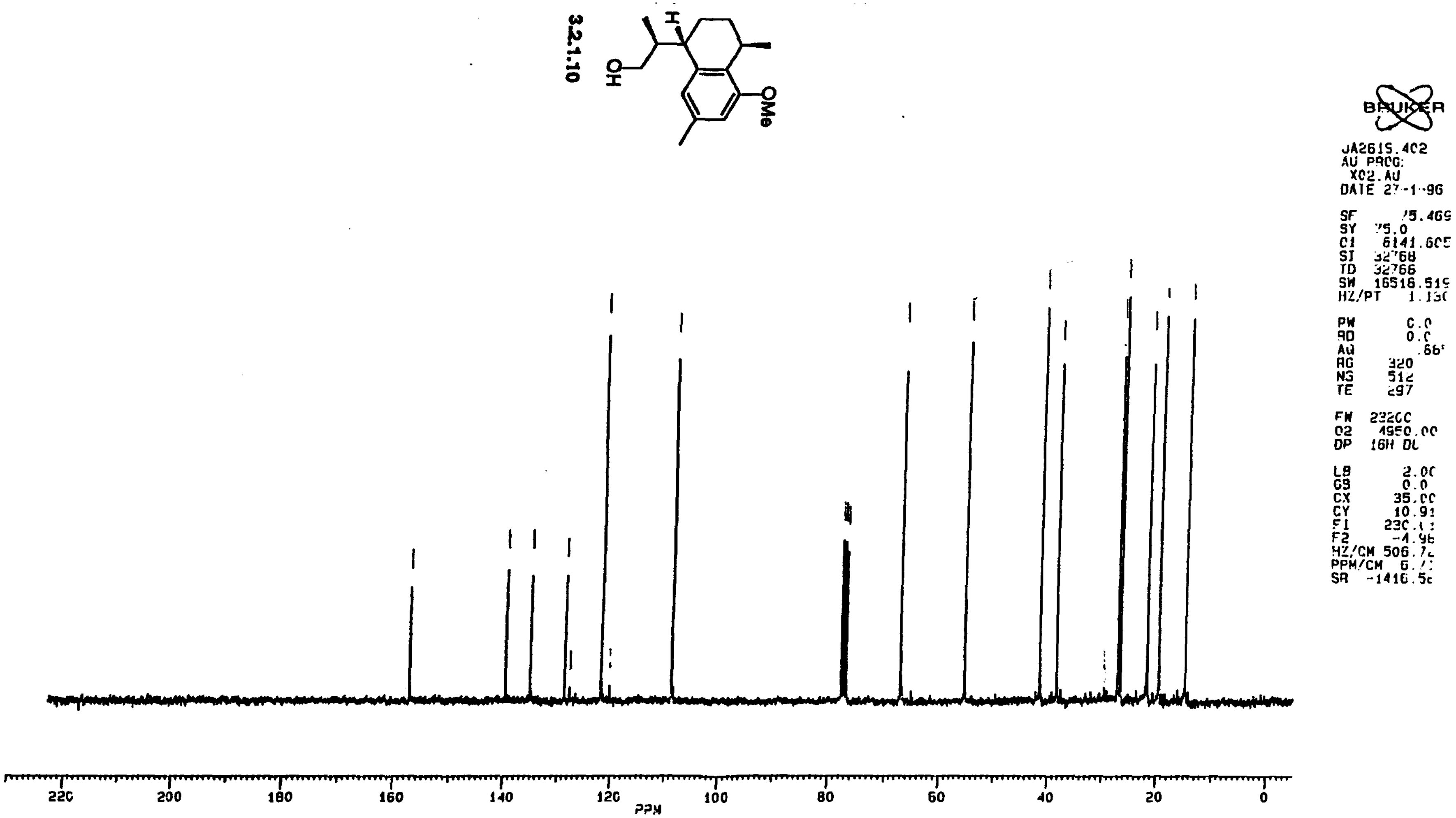
8.0
8.5
9.0
OMe
H
OH

3.2.1.10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H
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RD 0.0
AQ .66
RG 320
NS 512
TE 297
FW 23200
O2 4950.00
DP 16H DL
LB 2.00
GB 0.0
CX 35.00
CY 10.91
F1 230.
F2 -4.96
HZ/CM 506.7
PPM/CM 6.7
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180
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140
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60
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0
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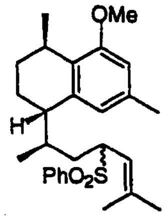
3.2.1.10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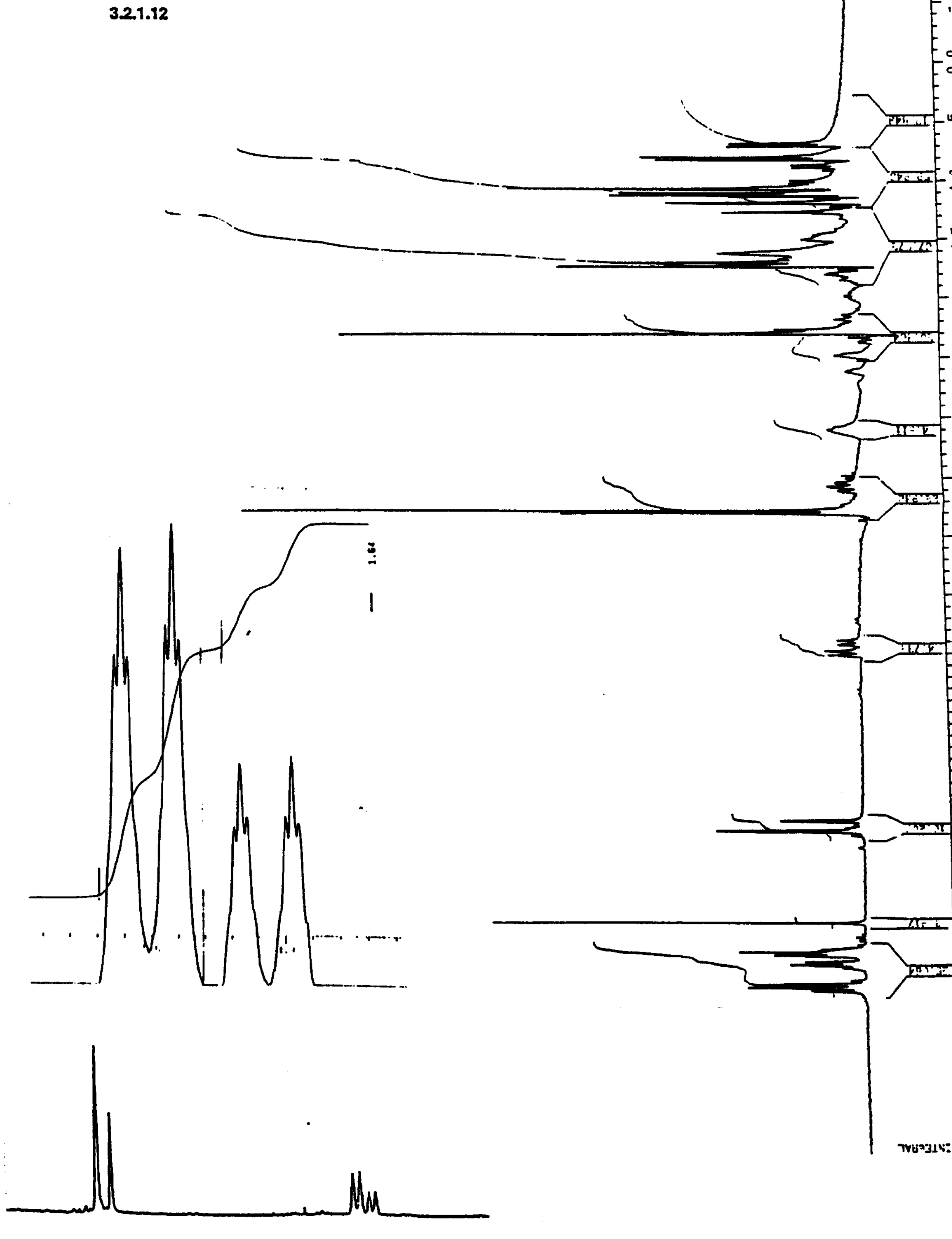
H
PhO$_2$S

3.2.1.12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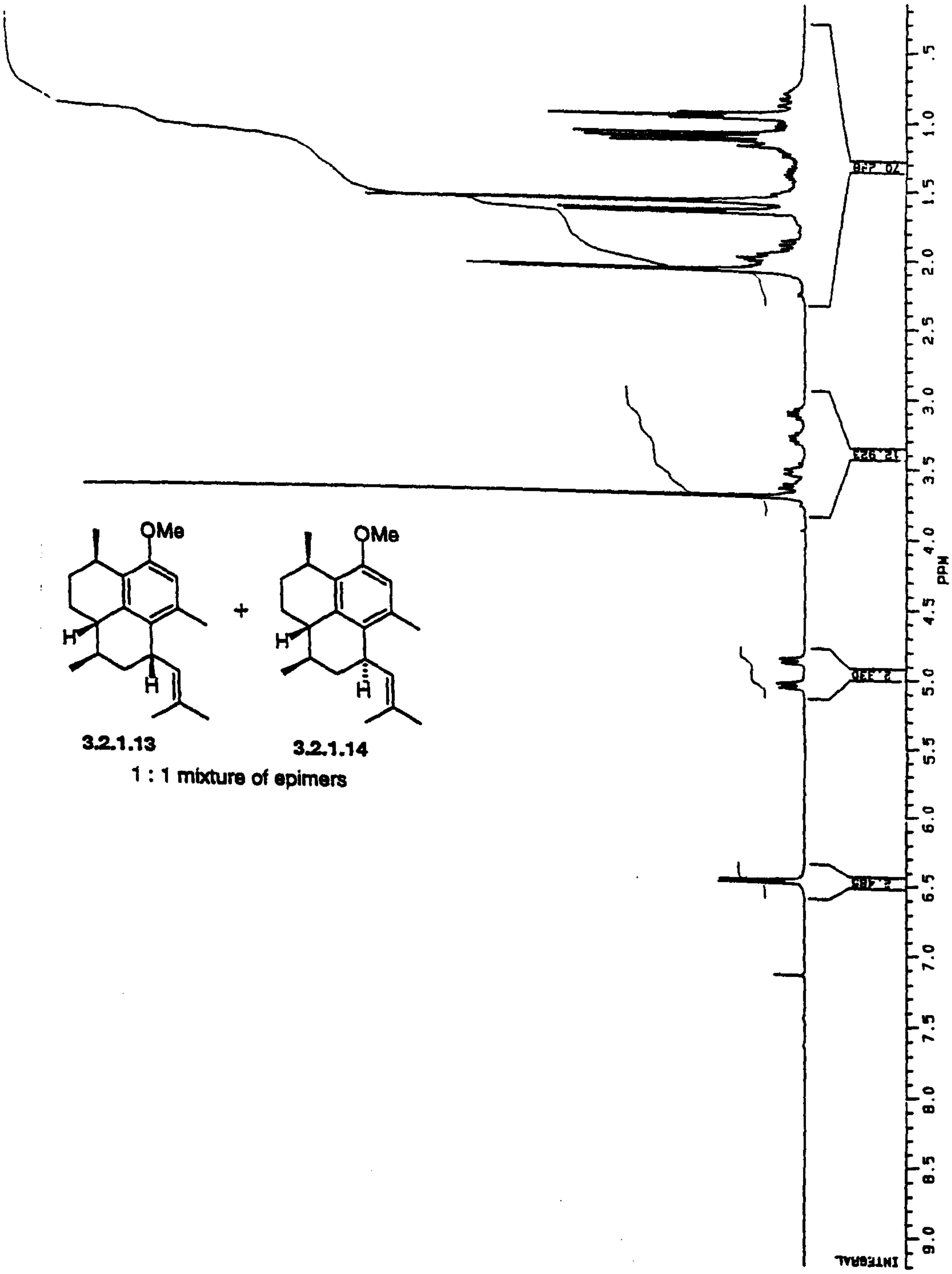
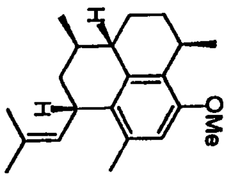
RD 0.0
AQ 1.350
RG 10
NS 15
TE 297
FW 7600.000
O2 3300.000
DP 63L PO
LB .300
HZ/CM 35.743
PPM/CM .119
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM
INTEGRAL
1.64
7
6
5

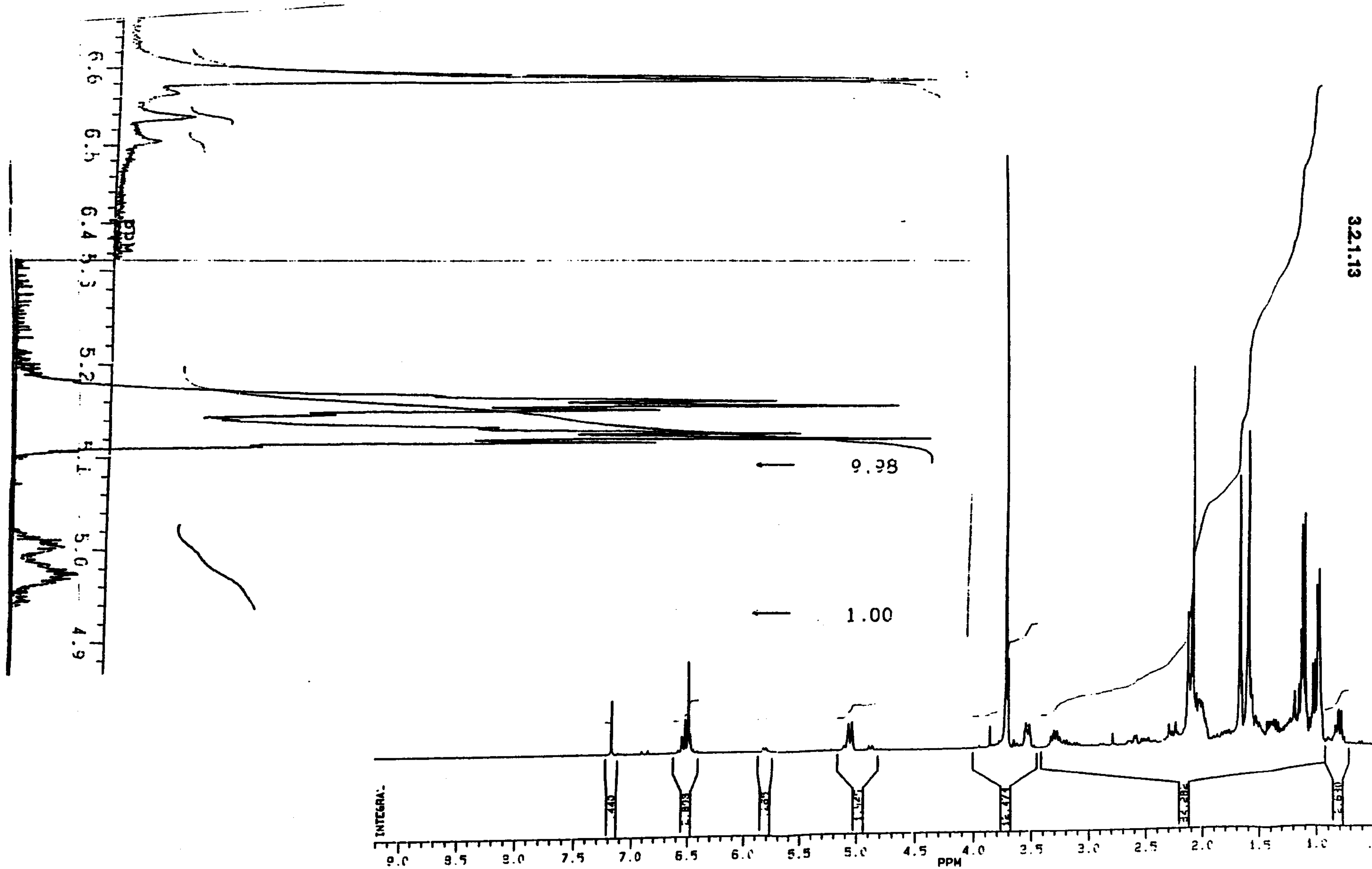


3.2.1.13 **3.2.1.14**

1 : 1 mixture of epimers


OMe
H
H

3.2.1.13


6.6
6.5
6.4
PPM
5.2
5.1
5.0
4.9
9.98
1.00
INTEGRAL
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
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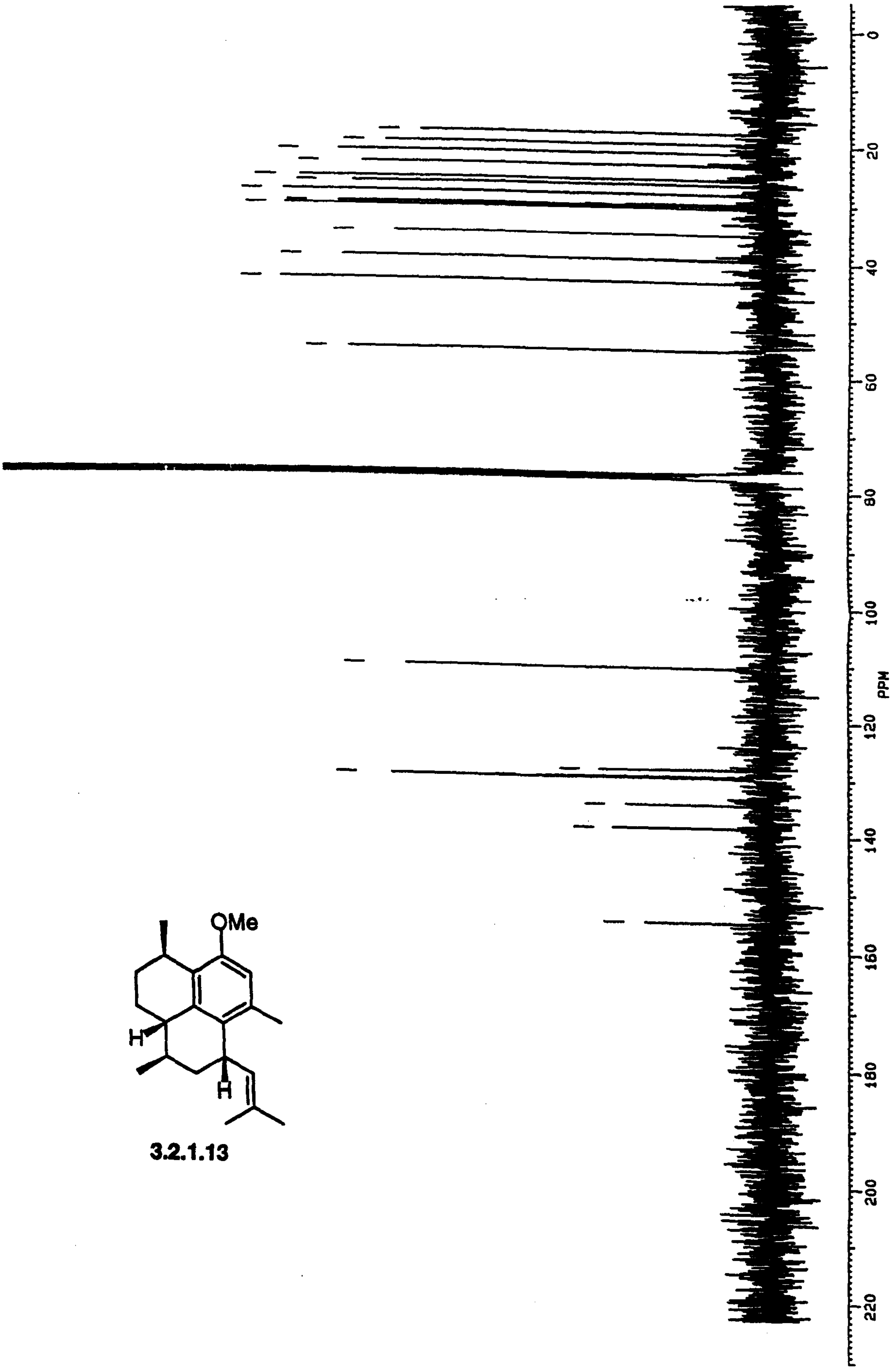
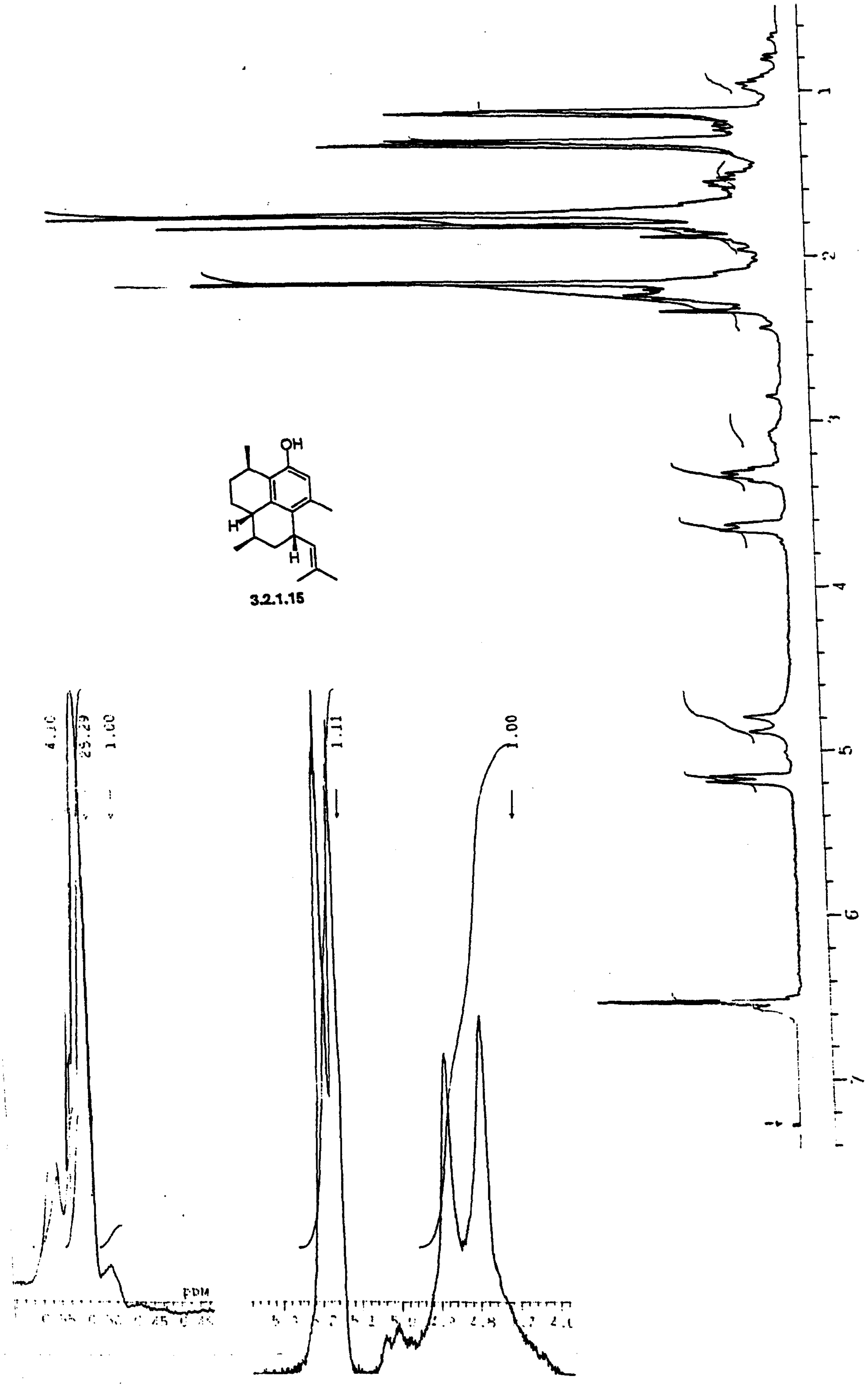
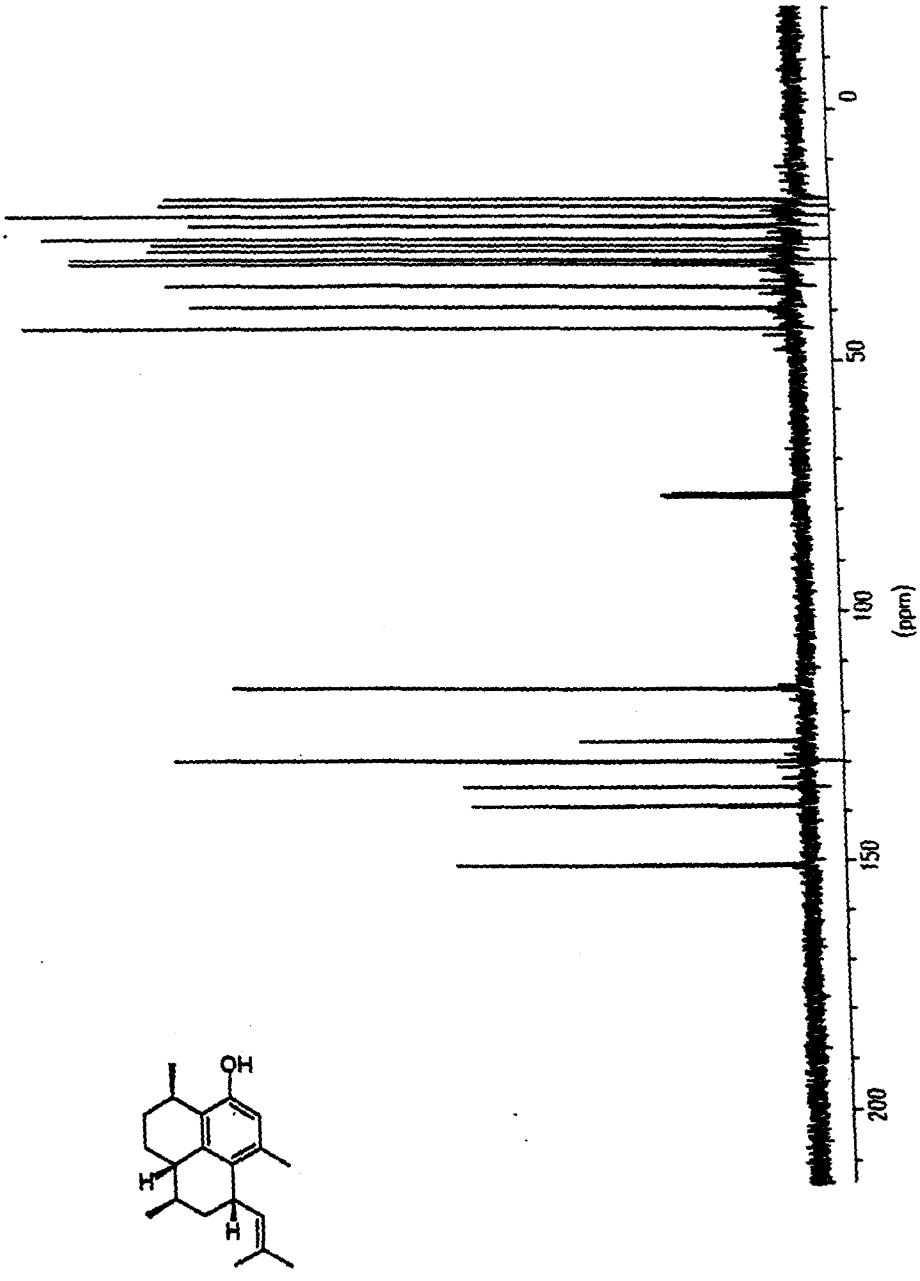
2.5
2.0
1.5
1.0
.5
PPM



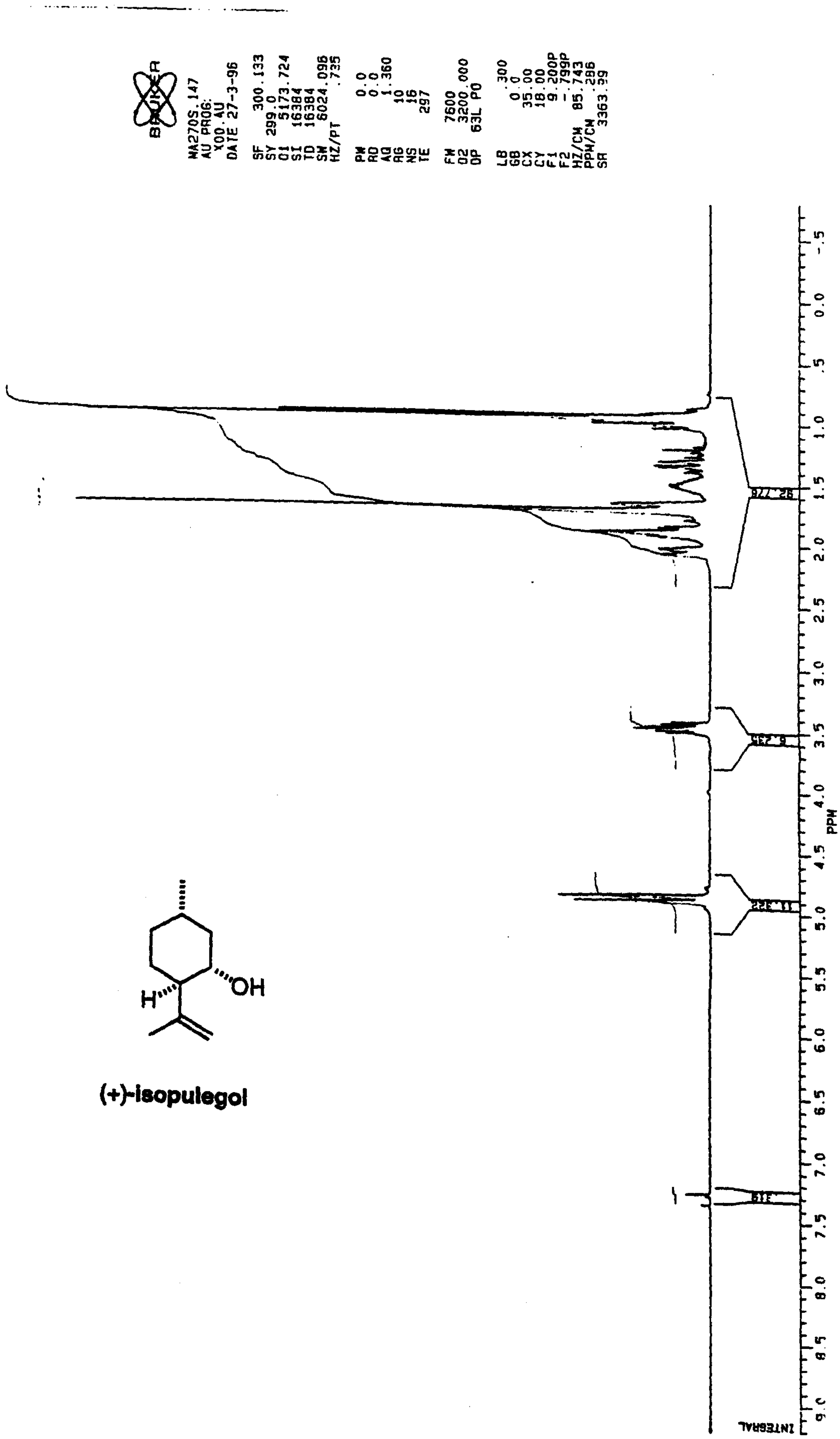
3.2.1.13



3.2.1.15



3.2.1.15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TD 16384
SW 6024.096
HZ/PT .735
PW 0.0
RD 0.0
AQ 1.360
RG 10
NS 16
TE 297
FW 7600
O2 3200.000
DP 63L PO
LB .300
GB 0.0
CX 35.00
CY 18.00
F1 9.200P
F2 -.799P
HZ/CM 85.743
PPM/CM .286
SR 3363.99
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6.235
11.325
.318
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PPM
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
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1.5
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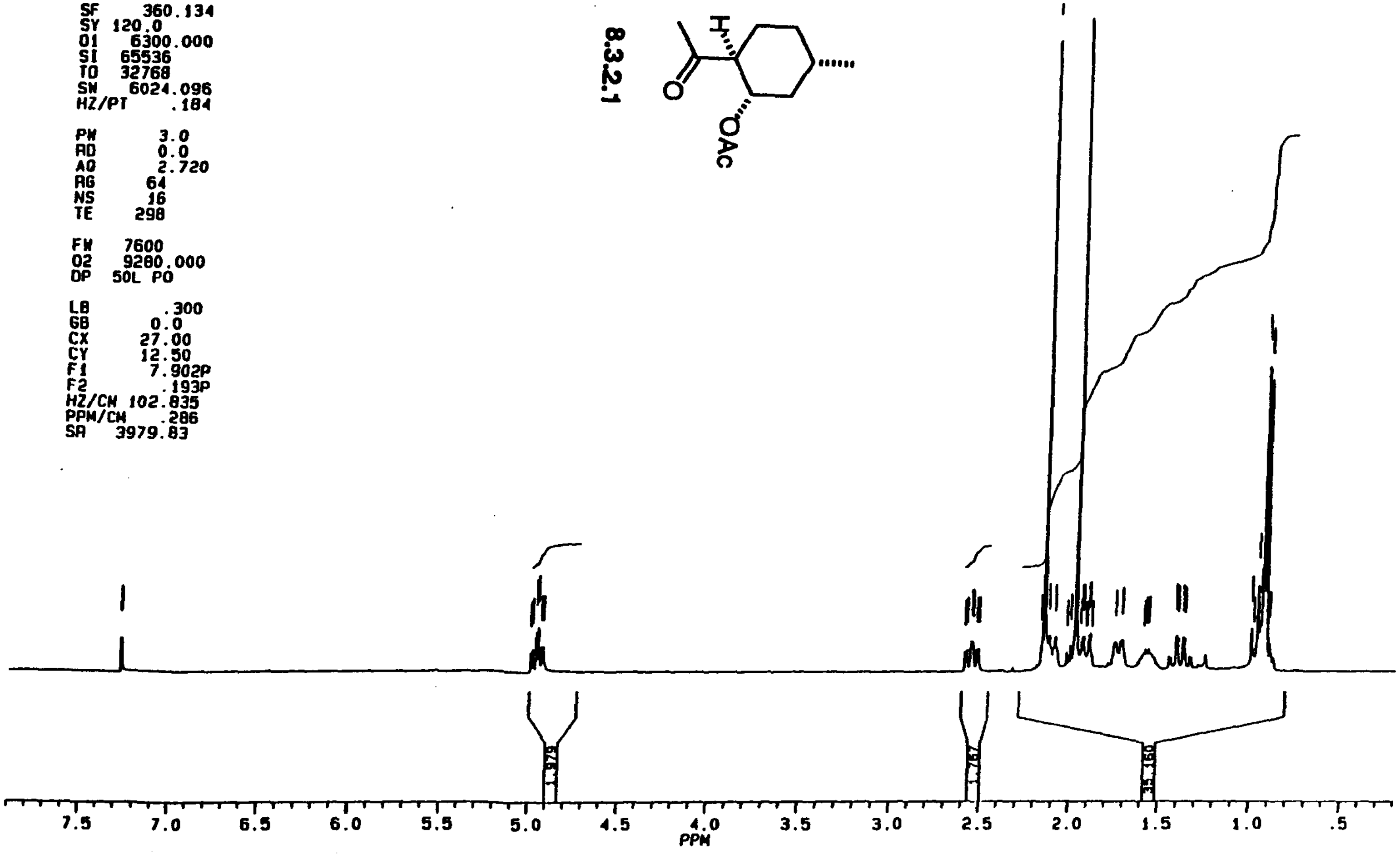
.5
0.0
-.5
H
OH
(+)-isopulegol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O1 6300.000
SI 65536
TD 32768
SW 6024.096
HZ/PT .184
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RD 0.0
AQ 2.720
RG 64
NS 16
TE 298
FW 7600
O2 9280.000
DP 50L PO
LB .300
GB 0.0
CX 27.00
CY 12.50
F1 7.902P
F2 .193P
HZ/CM 102.835
PPM/CM .286
SR 3979.83
H
OAc
O
1.979
1.767
35.160
7.5
7.0
6.5
6.0
5.5
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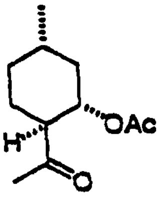
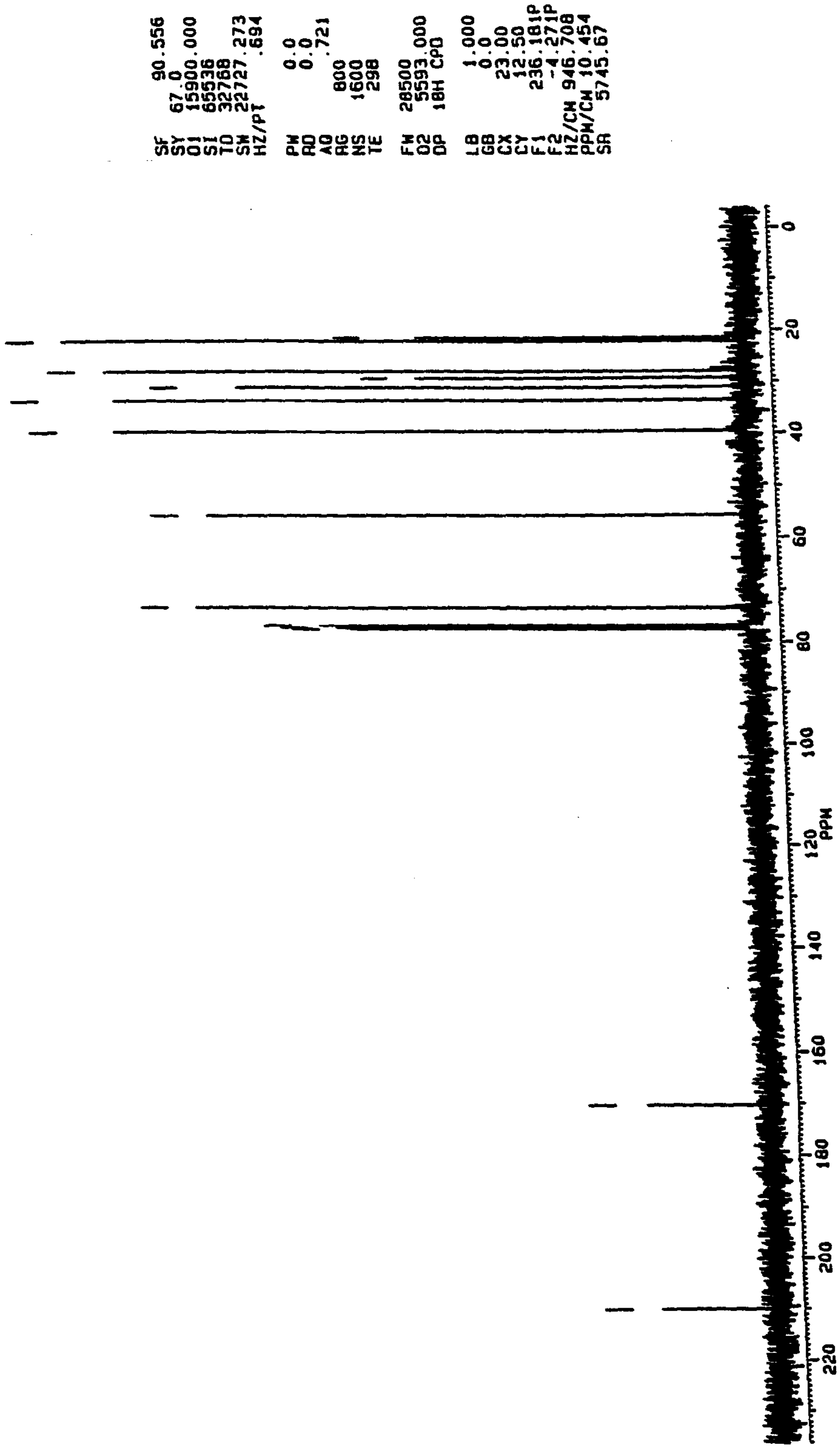
3.0
2.5
2.0
1.5
1.0
.5
PPM

8.3.2.1


OAc
H
O

8.3.2.1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SI 65536
TD 32768
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HZ/PT .694
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RD 0.0
AQ .721
RG 800
NS 1600
TE 298
FW 28500
O2 5593.000
DP 18H CPD
LB 1.000
GB 0.0
CX 23.00
CY 12.50
F1 236.181P
F2 -4.271P
HZ/CM 946.708
PPM/CM 10.454
SR 5745.67
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60
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100
120
PPM
140
160
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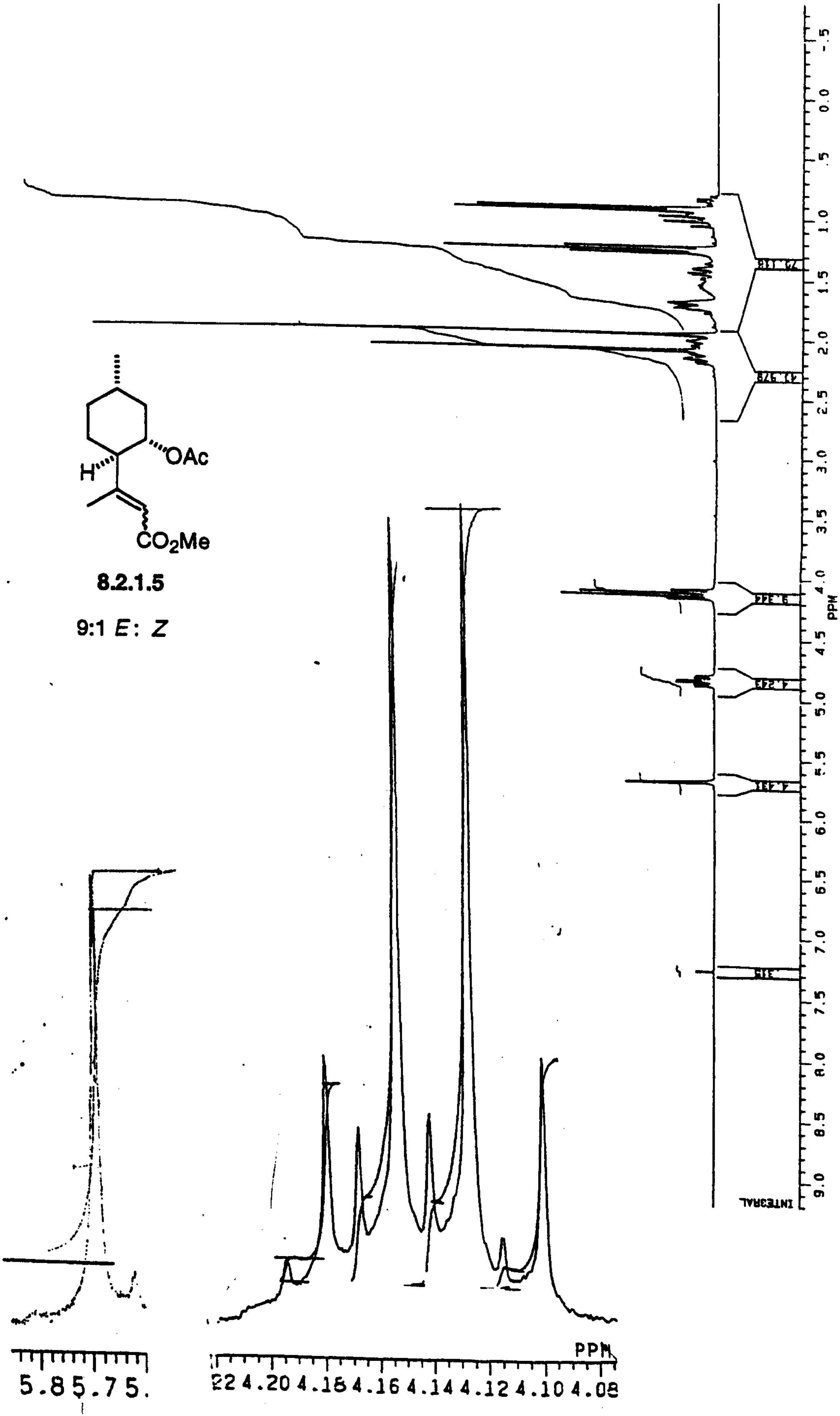
200
220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H
CO2Me
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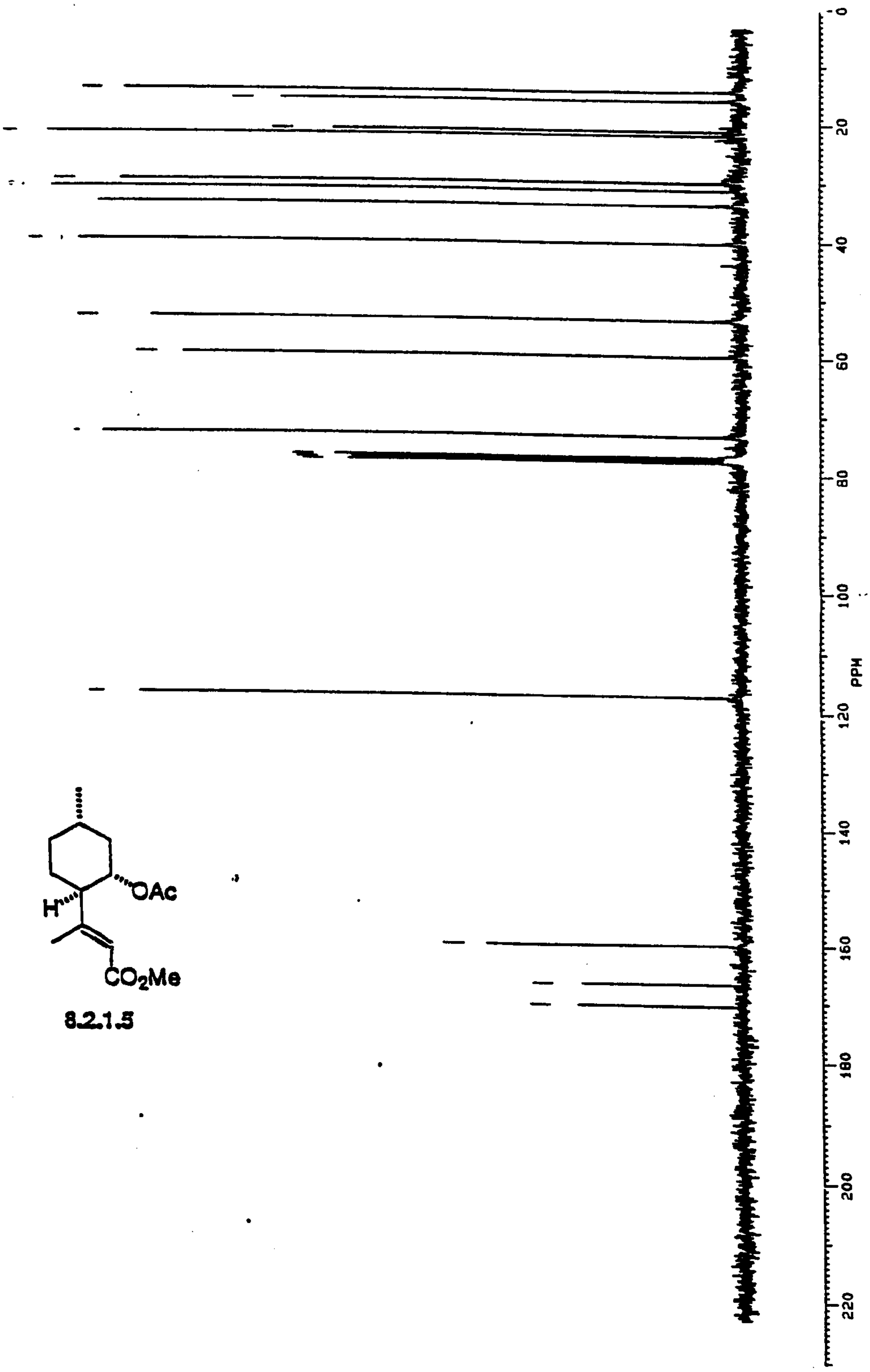
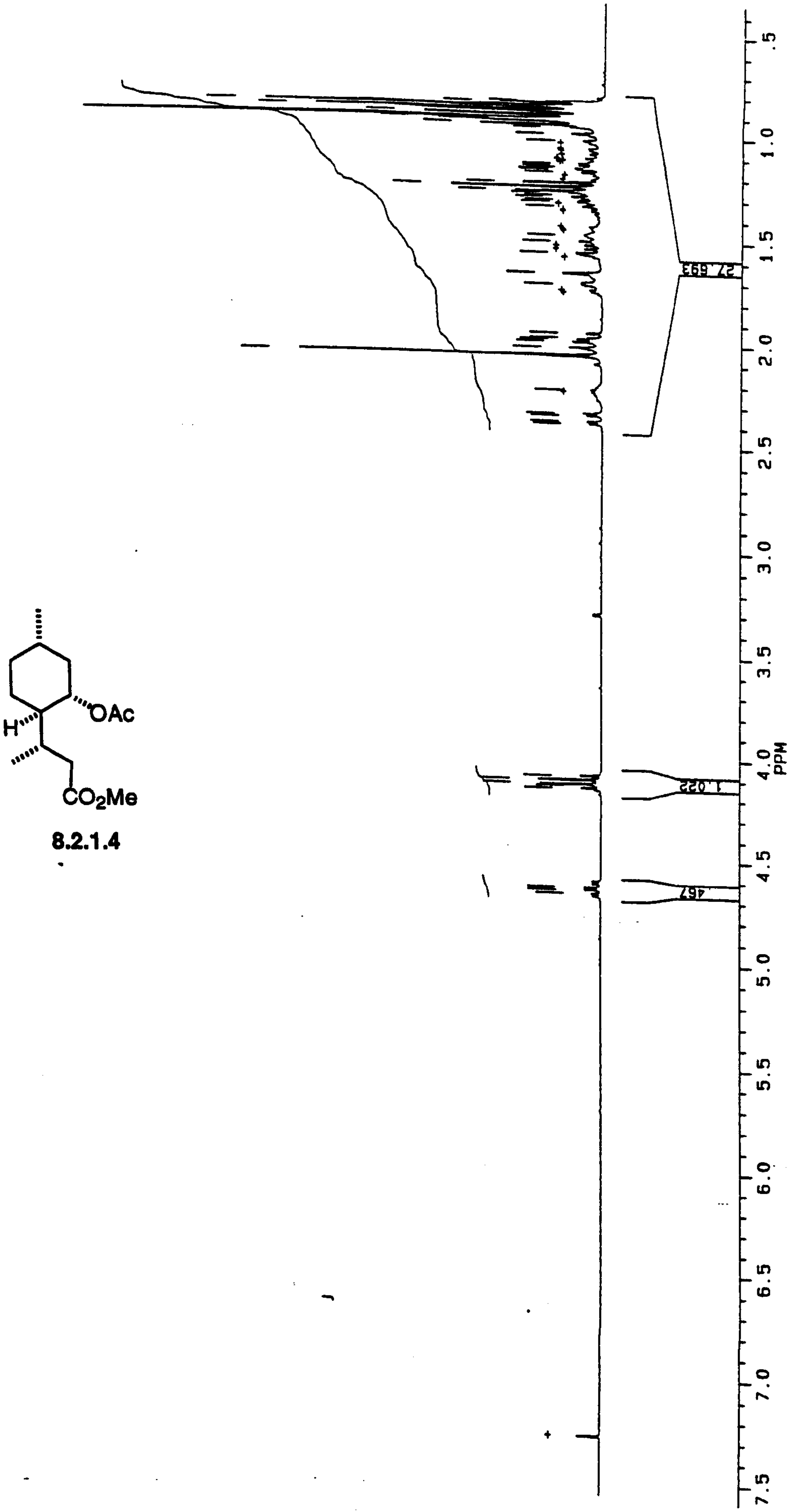
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
PPM
INTEGRAL
75.118
41.978
9.344
4.243
4.431
.313
5.8
5.75
22
4.20
4.18
4.16
4.14
4.12
4.10
4.08
PPM

8.2.1.5

9:1 *E*: *Z*



8.2.1.5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H
CO2Me
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1.0
1.5
2.0
2.5
3.0
3.5
4.0
PPM
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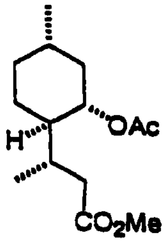
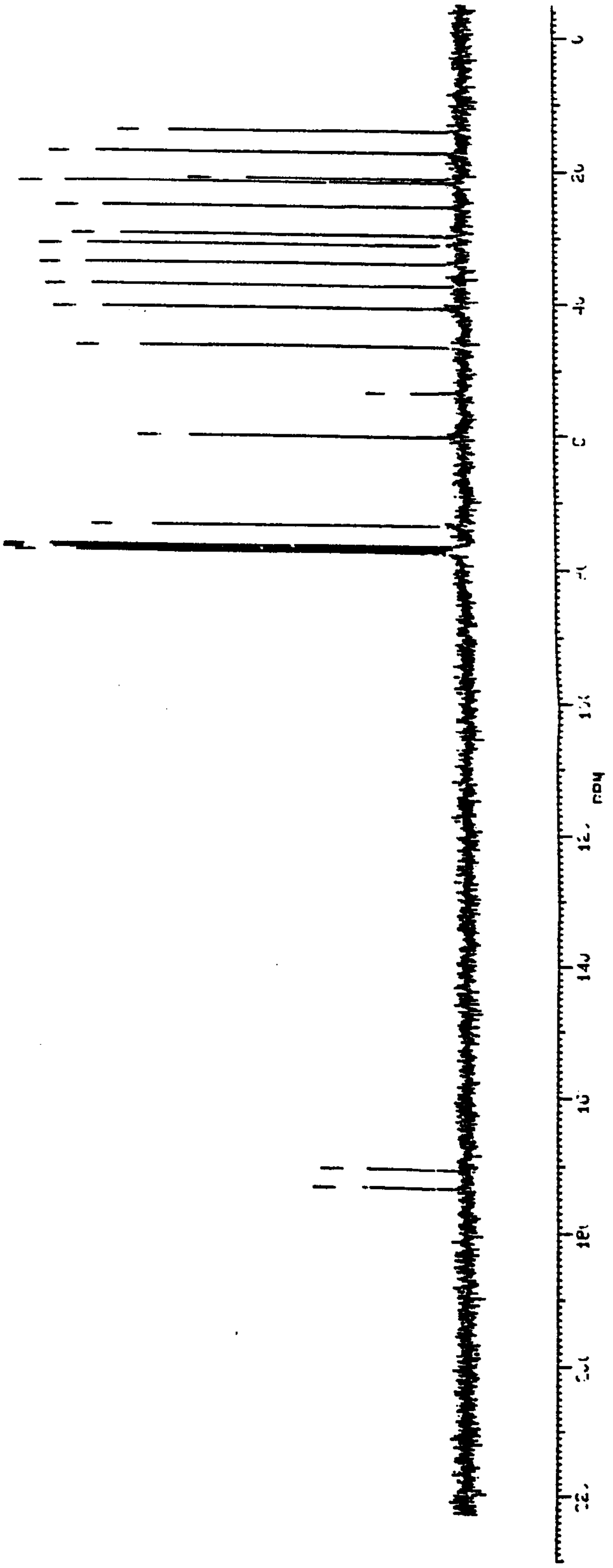
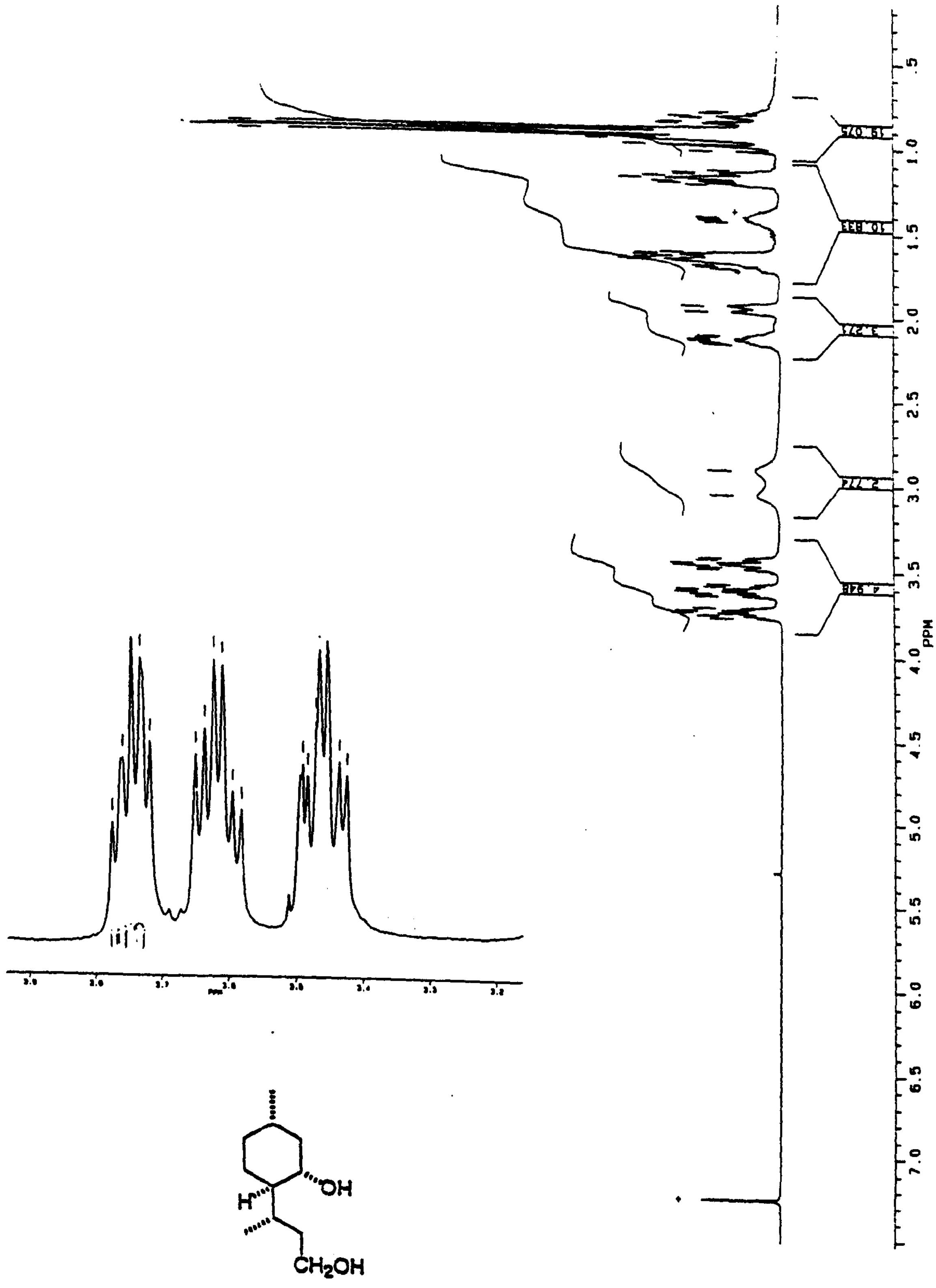
5.5
6.0
6.5
7.0
7.5
27.693
1.022
.467

8.2.1.4



8.2.1.4

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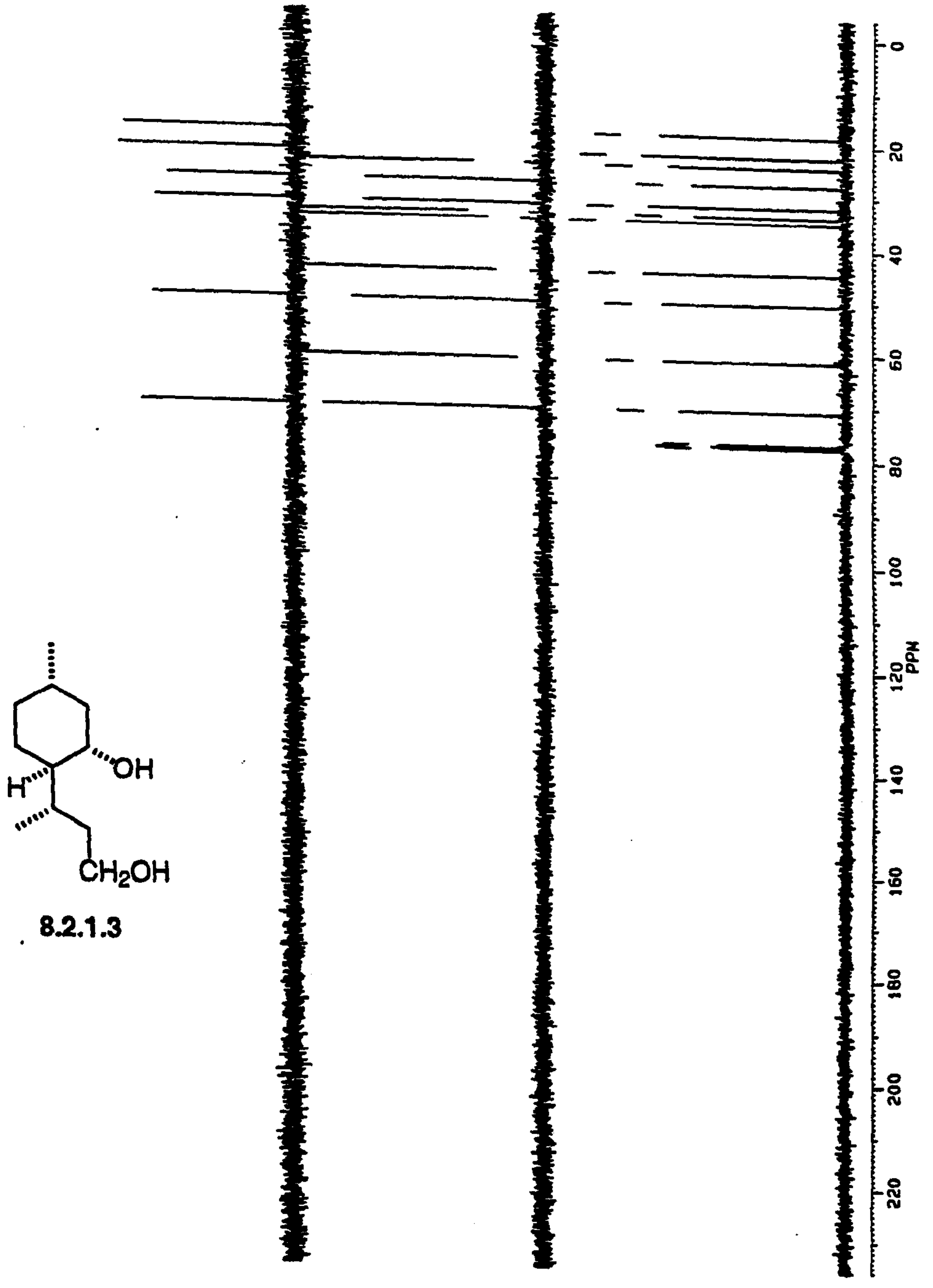
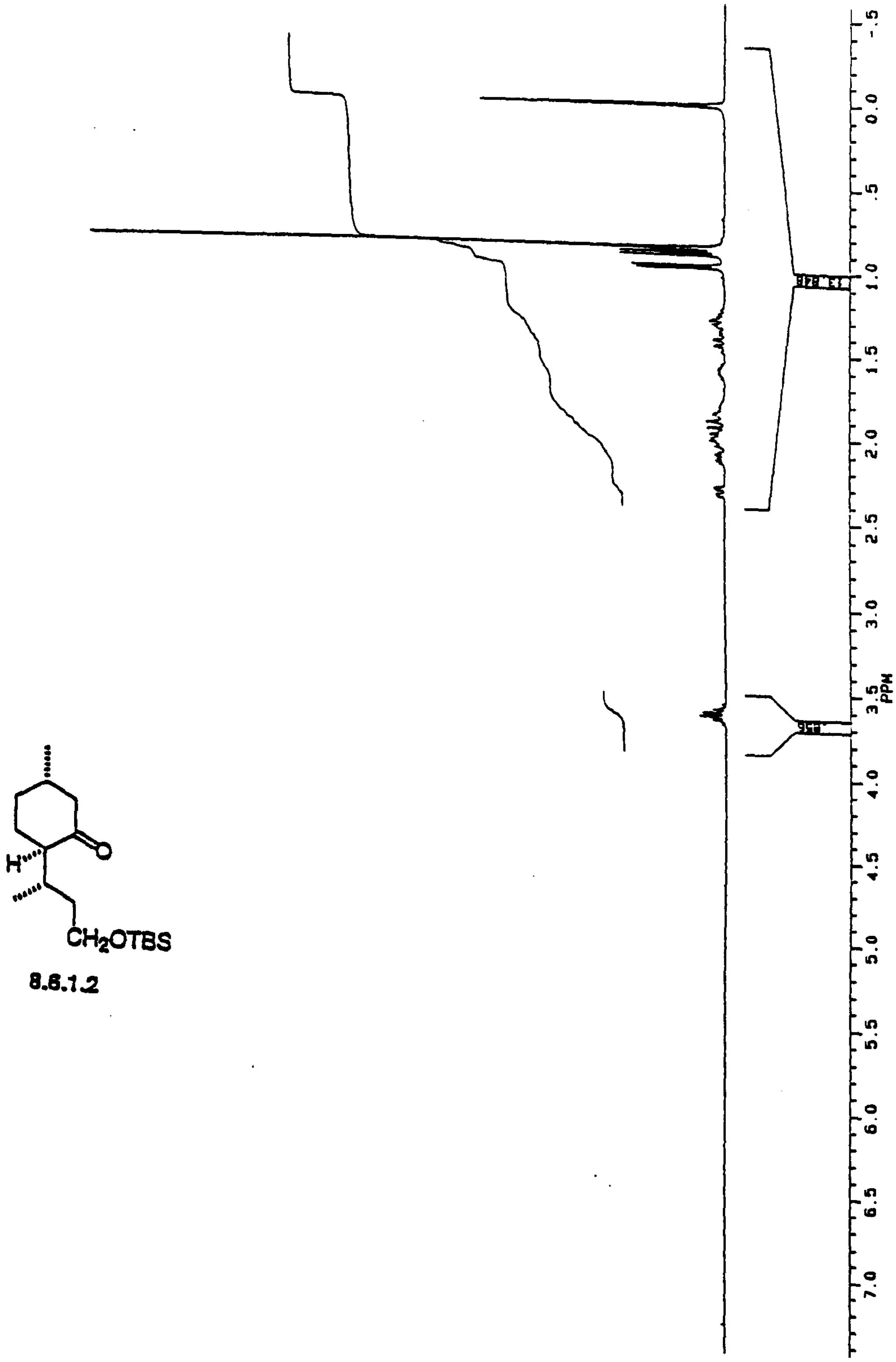
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
15.075
10.833
3.275
2.774
4.948
OH
H
CH₂OH

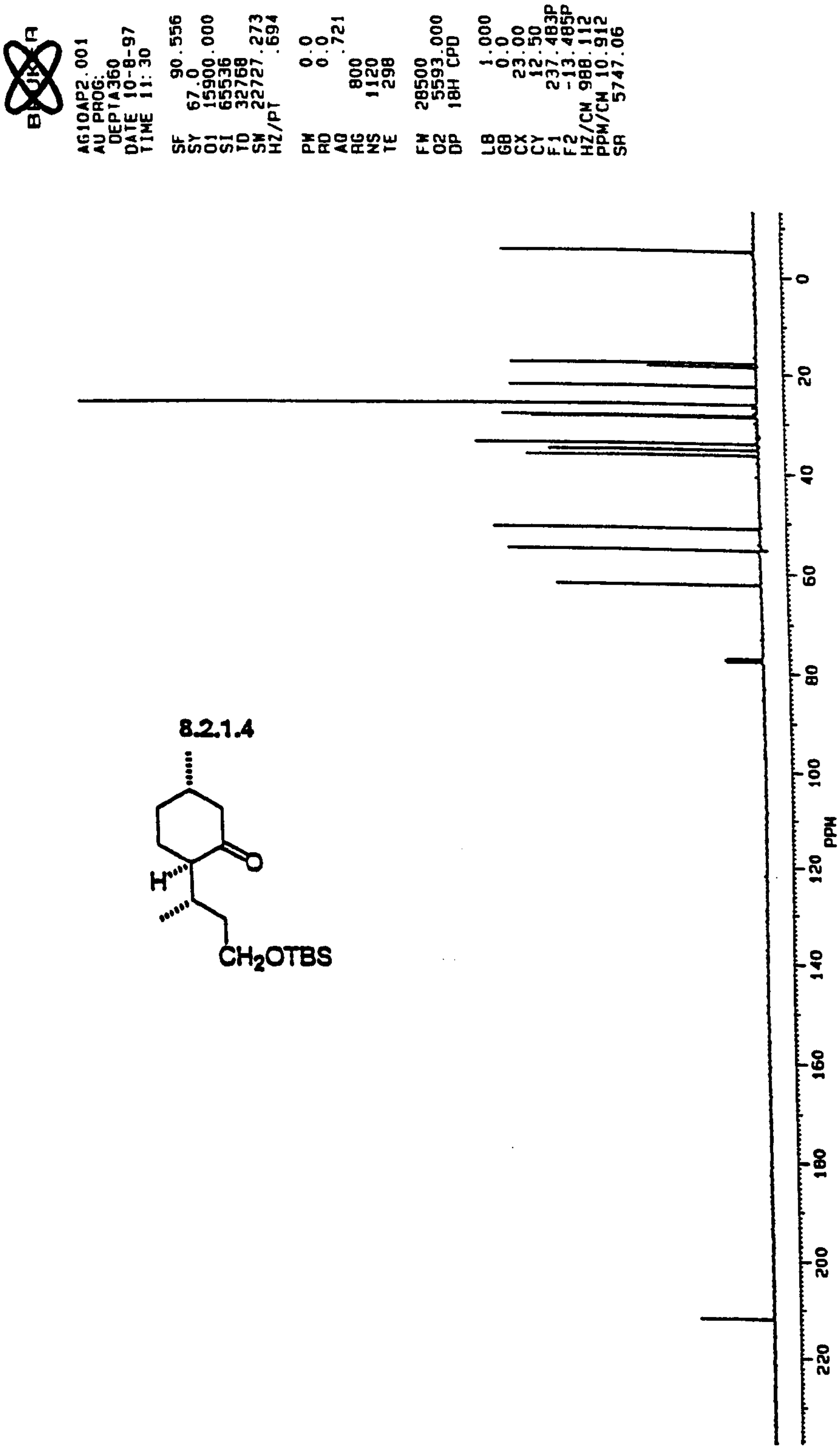
8.2.1.3



8.2.1.3



8.6.1.2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AQ .721
RG 800
NS 1120
TE 298
FW 28500
O2 5593.000
DP 18H CPD
LB 1.000
GB 0.0
CX 23.00
CY 12.50
F1 237.483P
F2 -13.485P
HZ/CM 988.112
PPM/CM 10.912
SR 5747.06
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60
80
100
120
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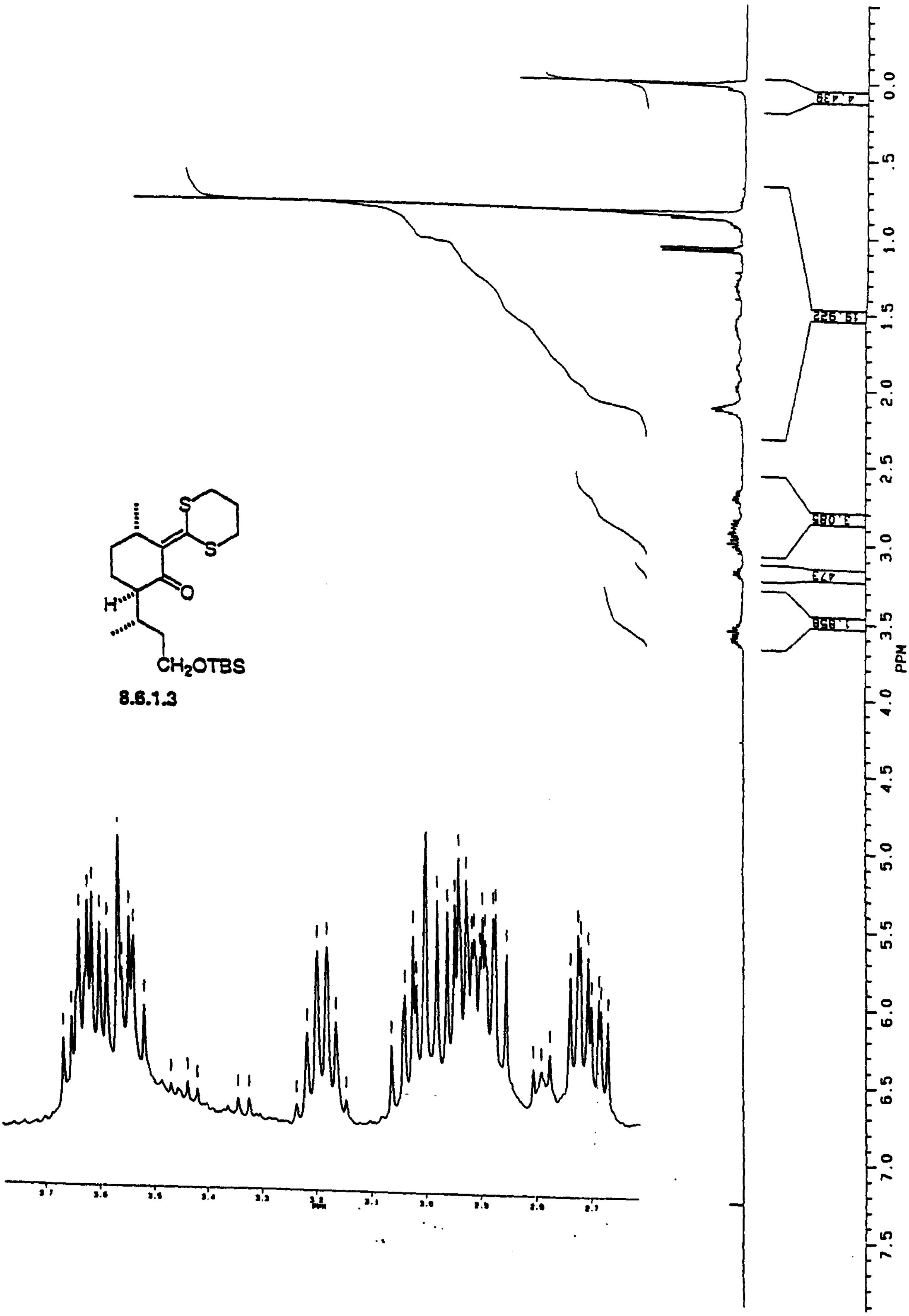
200
220
PPM
8.2.1.4
H
CH2OTBS


CH2OTBS
H
O
S
S
PPM
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1.5
2.0
2.5
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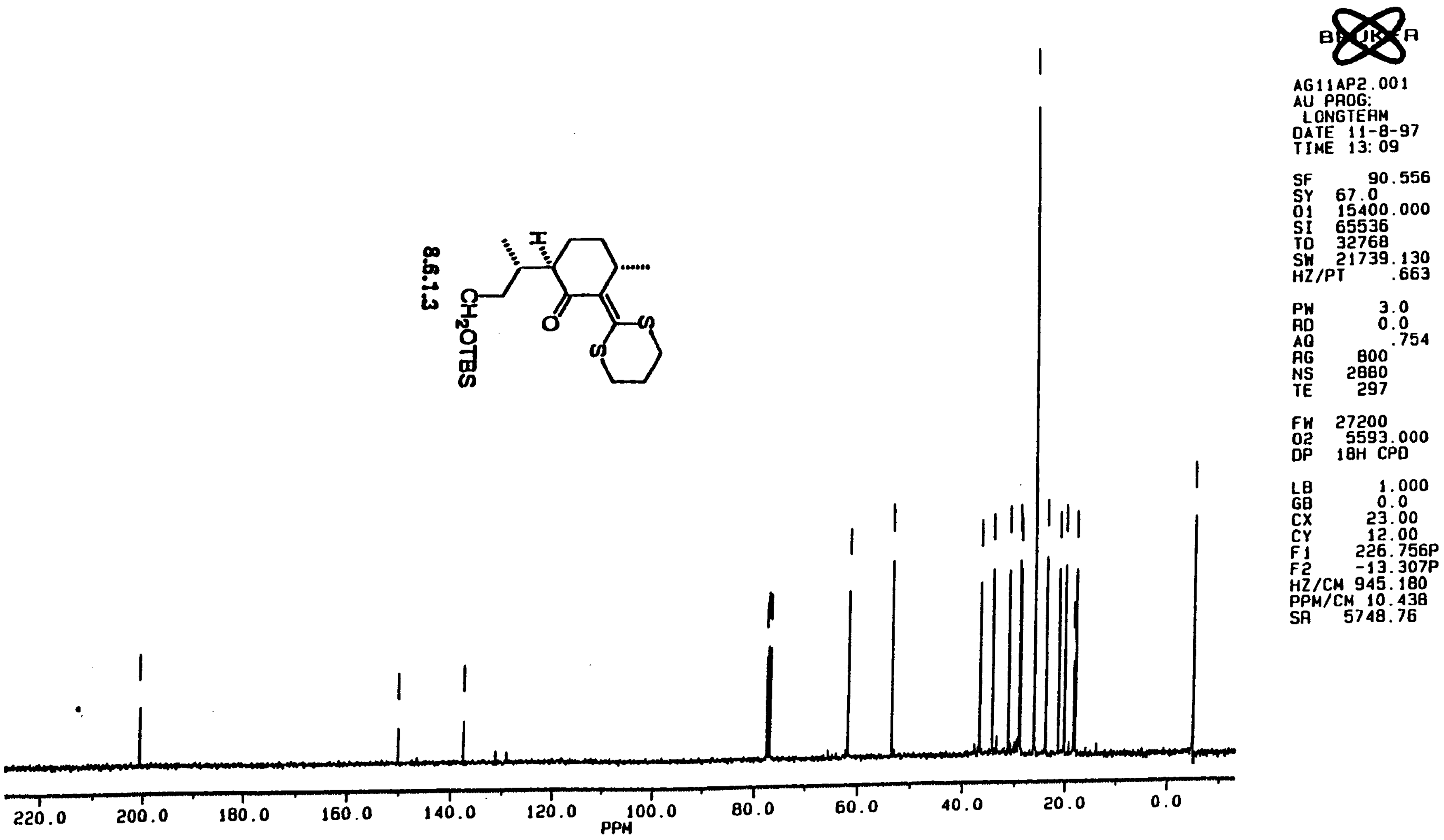
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
4.439
19.922
3.085
.473
1.858
3.7
3.6
3.5
3.4
3.3
3.2
PPM
3.1
3.0
2.9
2.8
2.7

8.6.1.3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TIME 13:09
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RD 0.0
AQ .754
RG 800
NS 2880
TE 297
FW 27200
O2 5593.000
DP 18H CPD
LB 1.000
GB 0.0
CX 23.00
CY 12.00
F1 226.756P
F2 -13.307P
HZ/CM 945.180
PPM/CM 10.438
SR 5748.76
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200.0
180.0
160.0
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120.0
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40.0
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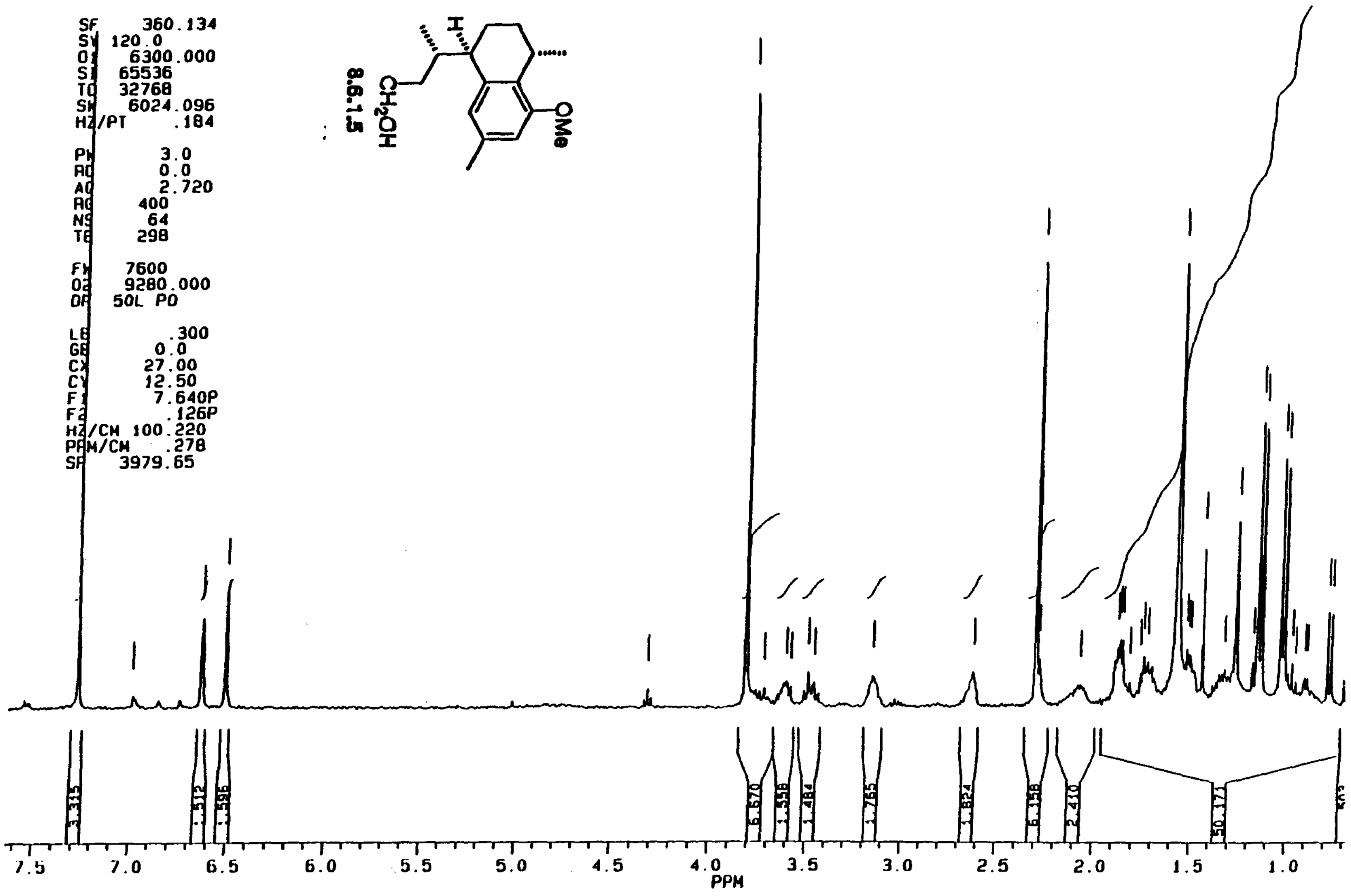
H
O
S
S
CH₂OTBS

8.6.1.3


8.6.1.5
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PW 3.0
RD 0.0
AQ 2.720
RG 400
NS 64
TE 298
FW 7600
O2 9280.000
DP 50L PO
LB .300
GB 0.0
CX 27.00
CY 12.50
F1 7.640P
F2 .126P
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PPM/CM .278
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H
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1.765
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6.158
2.410
50.171
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
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3.0
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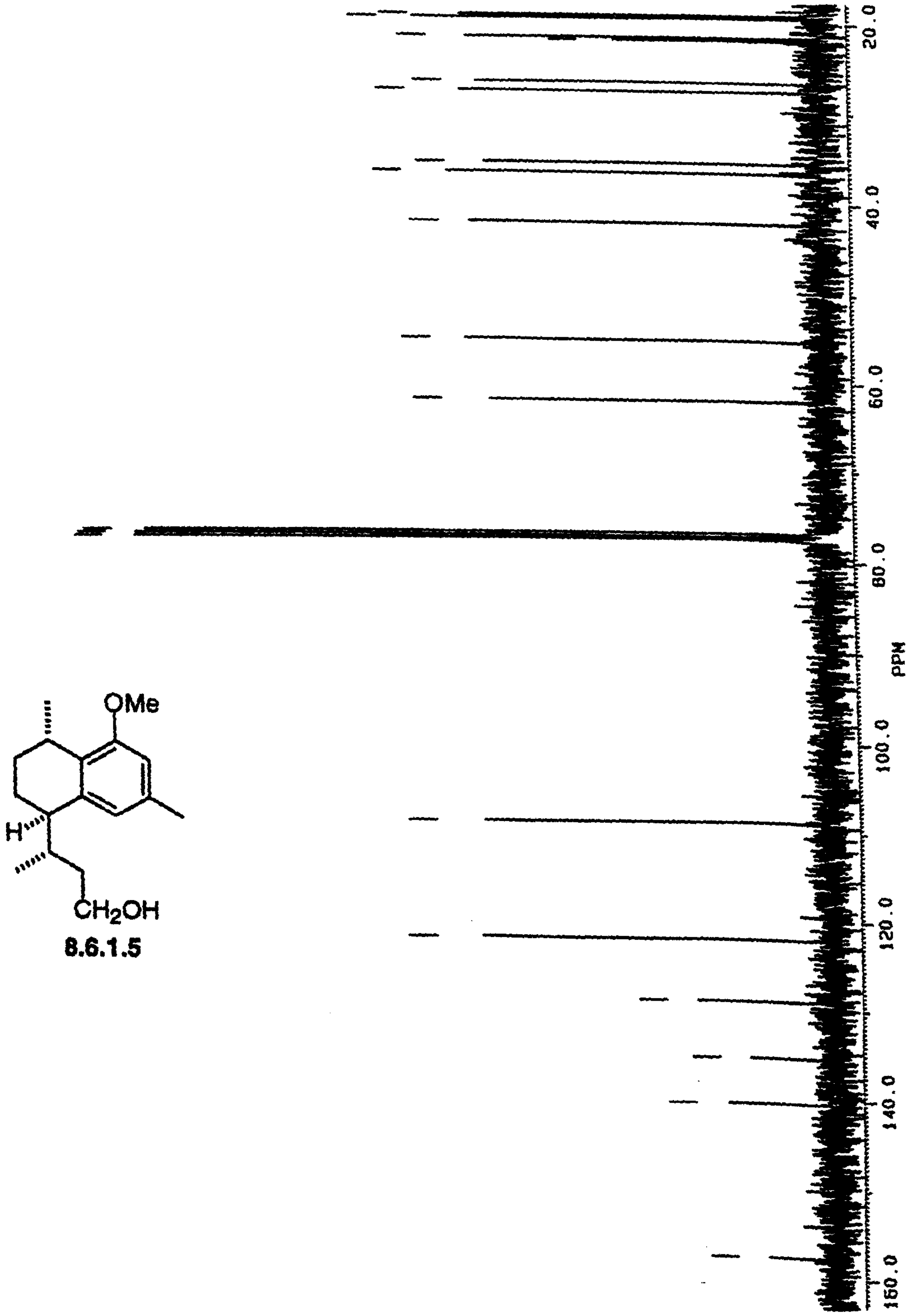
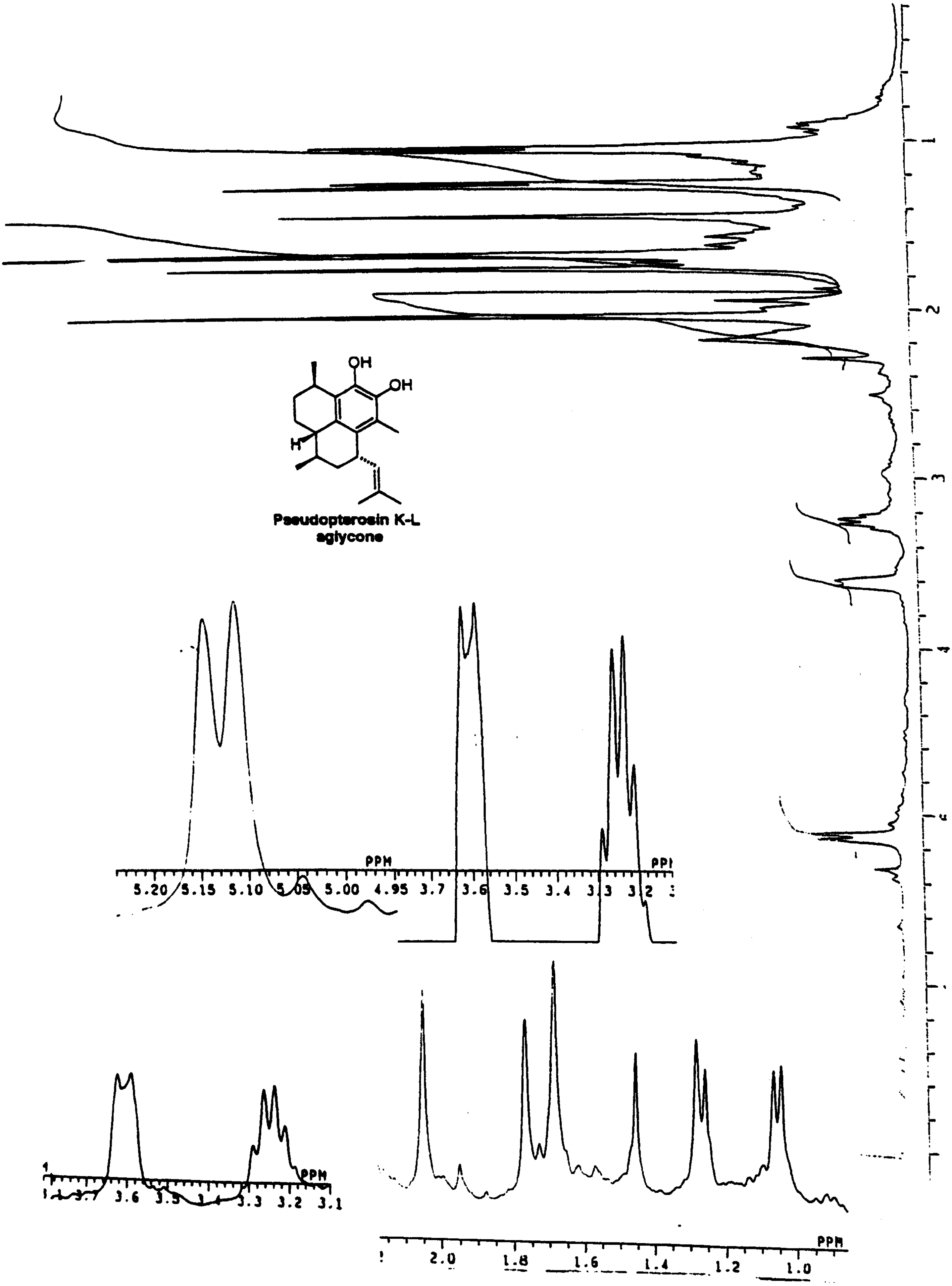
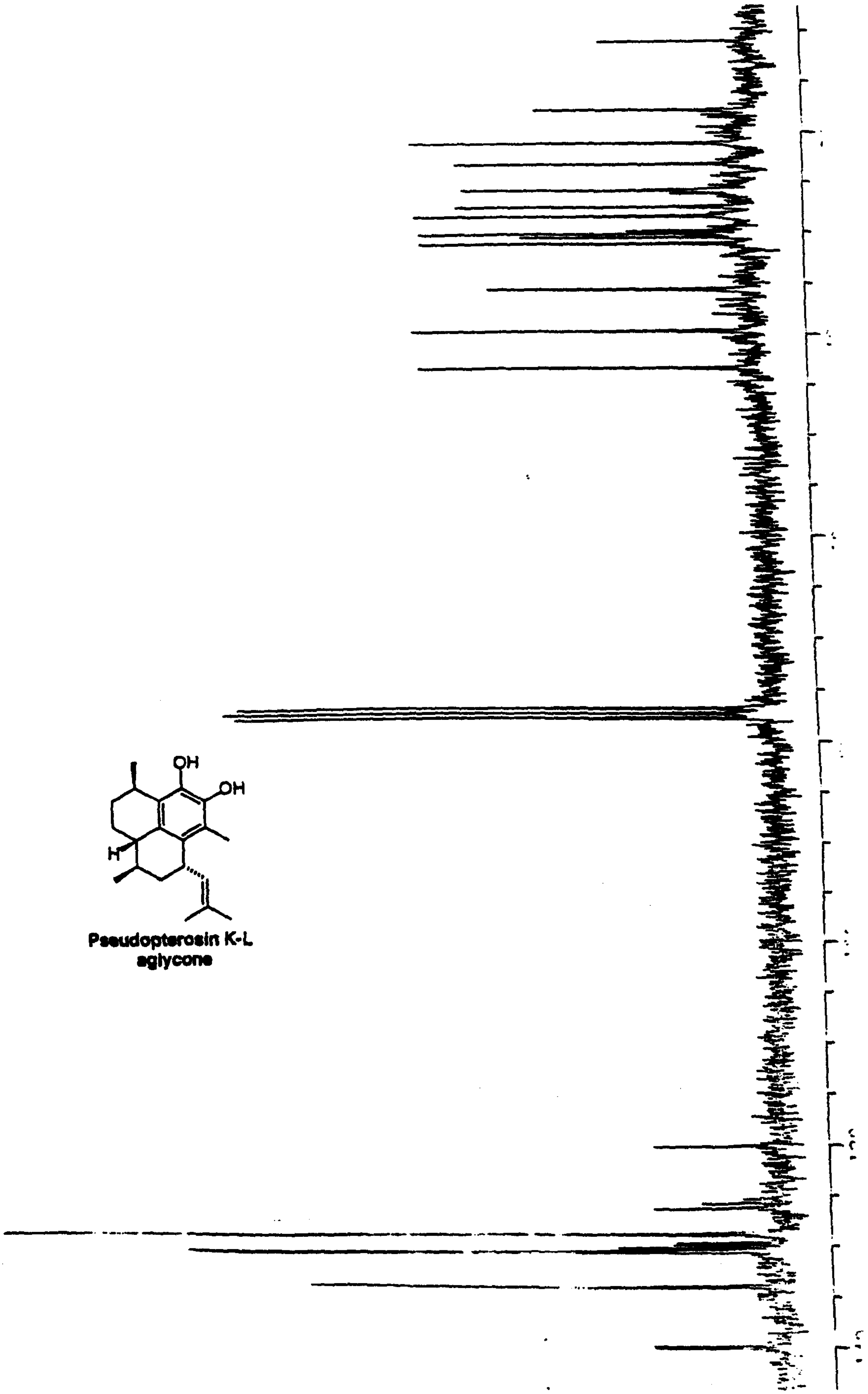
1.5
1.0

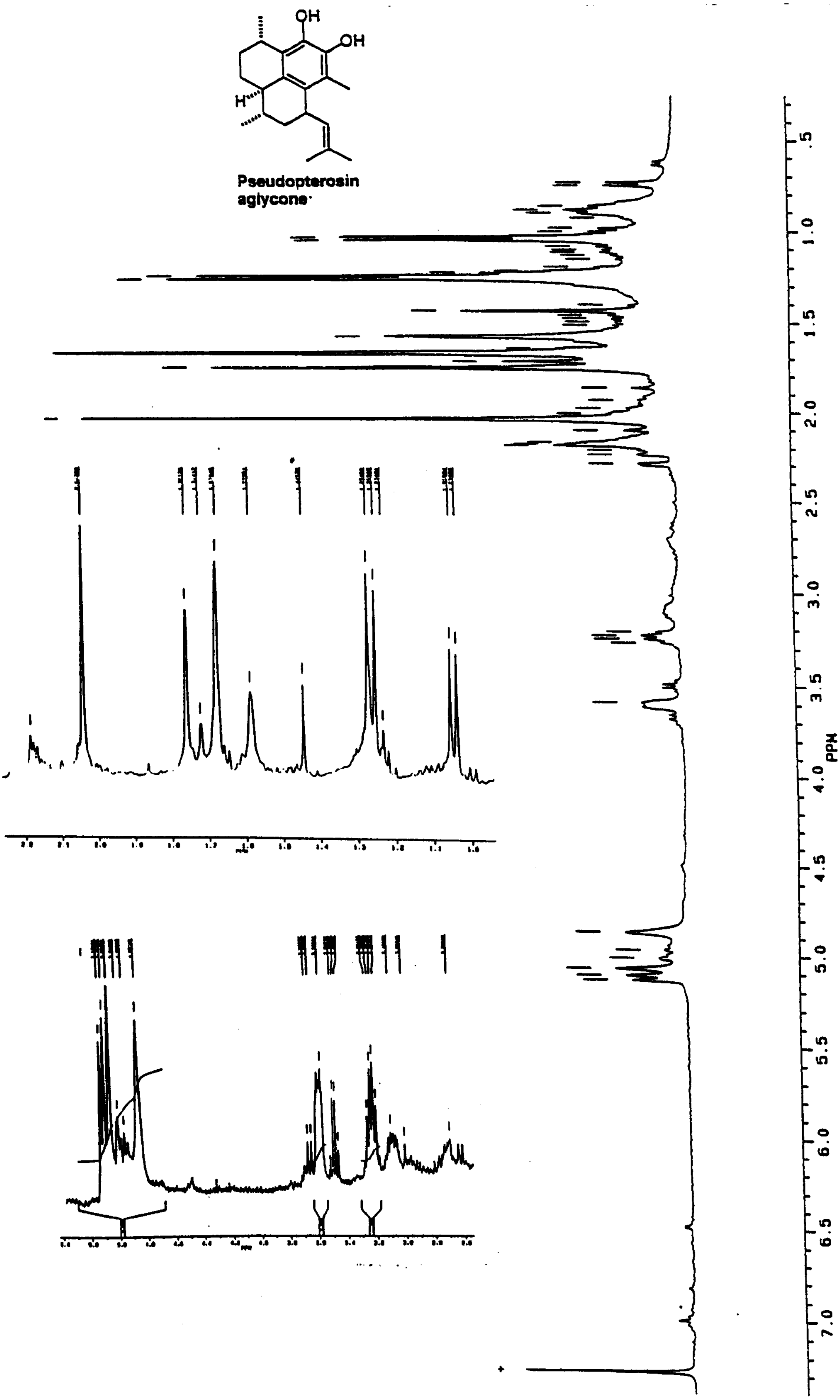


8.6.1.5

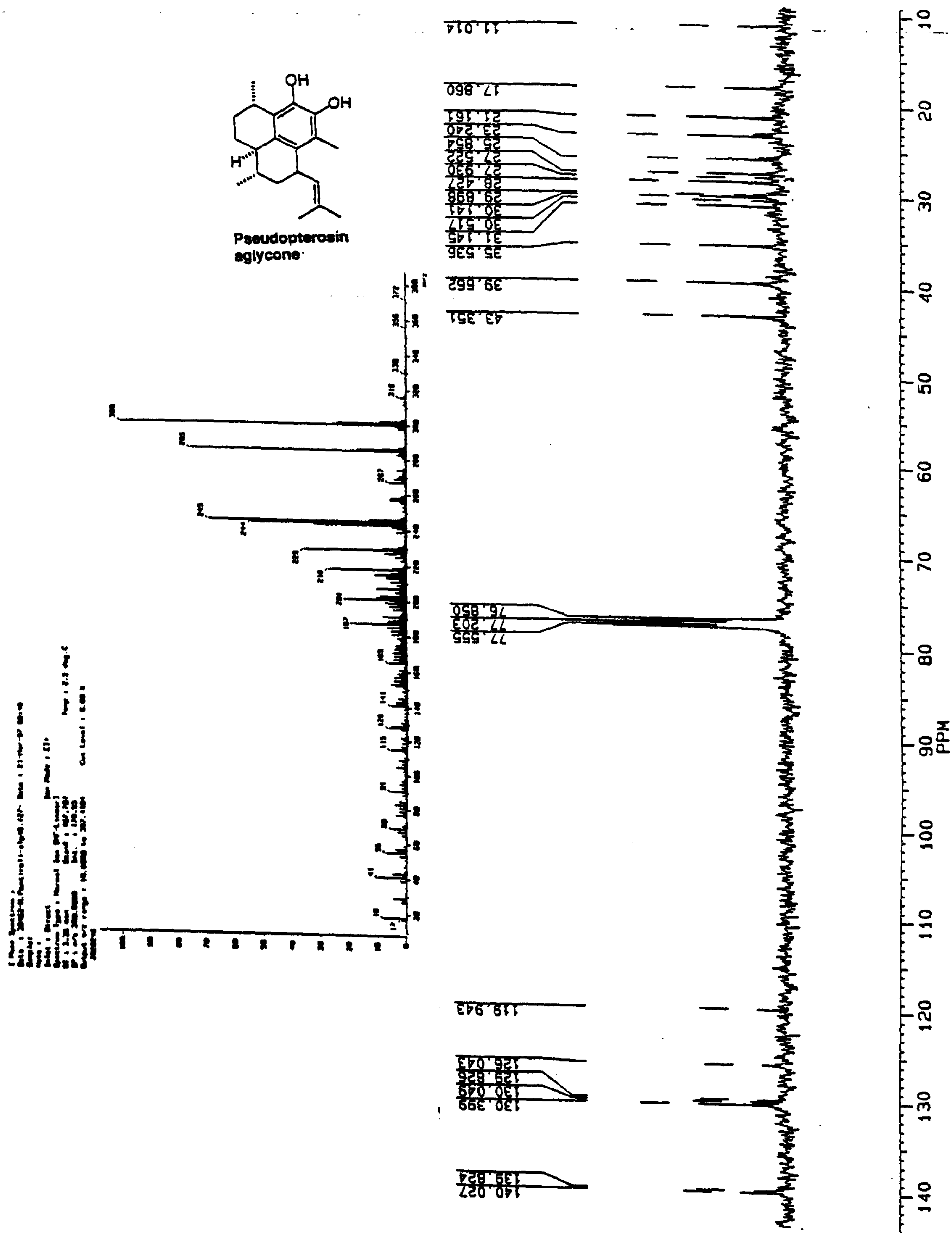


Pseudopterosin K-L aglycone


OH
OH
H
Pseudopterosin K-L aglycone



Pseudopterosin aglycone


Pseudopterosin aglycone
OH
OH
H
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27.930
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29.898
30.141
30.517
31.145
35.536
39.662
43.351
76.850
77.203
77.555
119.943
126.043
129.826
130.049
130.399
139.824
140.027
10
20
30
40
50
60
70
80
90
100
110
120
130
140
PPM

References.

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