UNIVERSITY OF SOUTHAMPTON

The Total Synthesis of Colombiasin A *tert*-butyl ether

by

Heather Opal Bourne

A Thesis Submitted for the Degree of Doctor of Philosophy

Department of Chemistry

Faculty of Engineering, Science and Mathematics

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

The total synthesis of colombiasin A t-butyl ether

by Heather Opal Bourne

This thesis is concerned with the synthesis of (-)-colombiasin A, a natural product with reported anti-tubercular activity, recently isolated from the Carribean sea whip *Pseudopterogorgia elisabethae*. This thesis describes a new approach to (+)- and (-)-colombiasin A *tert*-butyl ether from (+)- and (-)-dihydrocarvone respectively. Key features are a one-pot Shapiro reaction; an asymmetric hydroboration-oxidation reaction and an elaborate "reagent free" cascade sequence. The latter involves sequential thermal rearrangement of a cyclobutenone to a hydroquinone, aerial oxidation to a quinone and an intramolecular Diels-Alder cycloaddition.

Since its isolation, two syntheses of (-)-colombiasin A and two further approaches have been reported, all of which are reviewed in detail in Chapter I. Model studies on the Shapiro reaction and the thermal rearrangement of the resulting cyclobutenones are described in detail in Chapter II.

Studies leading to the elaboration of a diene side-chain on (+)-dihydrocarvone are featured in Chapter III. Key reactions are an asymmetric hydroboration step, which proceeds with good diastereoselectivity and an extremely efficient Kocieński-Julia coupling which provides an appealing alternative to a Wittig reaction.

In Chapter IV, routes to (+)- and (-)-colombiasin A *tert*-butyl ether are described. These sequences implement the findings of our preliminary studies together with an intramolecular Diels-Alder cycloaddition to complete the syntheses.

Experimental procedures are outlined in Chapter V.

Table of Contents

Preface

The research described in this thesis was carried out under the supervision of Dr. D. C. Harrowven at the University of Southampton between October 2000 and October 2003. No part of this thesis has previously been submitted for a degree.

Acknowledgements

My first BIG thank you has to go to David Harrowven for giving me the opportunity to join his group. Thanks for the immense patience you have shown during the past 3 years, for always having a positive comment and for the support in times of near desperation. Thanks for the laughs, the drinks, the proof-reading and the columns/recrysts!! Thank you thank you thank you thank you.....

My second BIG thank you has to go to all those who were there, day in, day out, sharing the joys and pains of the lab. You all know who you are! In particular, I'd like to thank Pete for his advice which I (regrettably?) never took; Melly for making me laugh and giving me the opportunity to exert my tongue muscle; Mike, for all the advice and patience; Matpeu, for great parties and sharing good musical taste; Stu for the tomatoes and cream and introducing me to the delights of "Heat"; Tim for always being up for going through the alphabet, any day of the week, for his appreciation of Margaritas and for his friendship; Hian for the air guitar duets and Geoff for his white russians and for being a good friend. You've made it all worth it!!
Colleen, Lucy and Tim thanks for giving me a place to stay in the last few months. My appreciation also goes to Daniela and Dave P. for sharing the delights of this project. Good luck!!

Thirdly, a few special people deserve a mention. Bine, you've been a great listener and "cheerer-up" on top of being a great Fencheltee maker. Thanks for everything. Dr. Nellie, thanks for the laughs over the past 8 years. We can now both happily say that "we've made it!!!!!". A telepathic huge thank you has to go to Louis for being "there" despite the thousands of miles between us and for sharing an understanding of the Soul of the World. Sibel, Nat, Virginie and Kylie thanks for all the moral support and for still being great friends after 15 odd years.

My appreciation goes to Neil Wells and Joan Street for the NMR service provided; to John Langley and Julie Herniman for MS; to all in the X-ray suite; to Dr. Martin Grossel for his advice and to Dr. Jeremy Hinks for being a great pedagogue. A

special thank you goes to Jill Queen and Sue Pipe for always having a smile and good words of comfort. Tim, Geoff, Hian and Dave, thanks for the proofreading and Neil thanks for your help in piecing this work of art together!

Finally, words could never convey the love and appreciation I have for my family. I'll try anyway... Papa, thank you for all the words of wisdom throughout the years; Mamita, thank you for the never-ending encouragement; Juju, thanks for the comforting and Debsipoos, thanks for always putting a smile on my face. Grogro, Tonton Pierre and Marie thank you for your financial help and for being there in your own special way. To all of you, I have to say thank you for believing in me and always being there for me. I could never have done this without you.

List of abbreviations

Ac	acetate
AIBN	α,α-azo-*iso*-butyronitrile
amu	atomic mass units
app.	apparent
approx.	approximately
aq.	aqueous
Ar	aryl
atm.	atmospheres
BINAP	2, 2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1, 1'-bi-2,2'-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	ammonium cerium(IV) nitrate
cat.	catalytic
CHN	combustion analysis
CI	chemical ionisation
conc.	concentrated
COSY	correlated spectroscopy
Cp	cyclopentadienyl
d	days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereoisomeric excess
DIBAL-H	di-*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane

DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
ee	enantiomeric excess
EI	electron impact
eq.	equivalents
ES	electrospray
Et	ethyl
ether	diethyl ether
EtOH	ethanol
FT	fourier transform
GC	gas chromatography
h	hours
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
Im	imidazole
Ipc	isopinocamphyl
IR	infrared
LDA	lithium di-*iso*-propylamide
Lgf	longifolyl
lit.	literature
LRMS	low resolution mass spectroscopy
M	molar
m-CPBA	*meta*-choloroperoxybenzoic acid
Me	methyl
min	minutes
MP	melting point
NMR	nuclear magnetic resonance spectroscopy
obsc.	obscured

PCC	pyridinium chlorochromate
Pd	palladium
Ph	phenyl
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
i-Pr	*iso*propyl
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
quant.	quantitative
RSM	recovered starting material
RT	room temperature
sat.	saturated
SM	starting material
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluyl
Tris	tri-*iso*-propylsulfonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
Δ	heat

"Every search begins with beginner's luck and ends with the victor being severely tested."

The Alchemist, Paulo Coelho

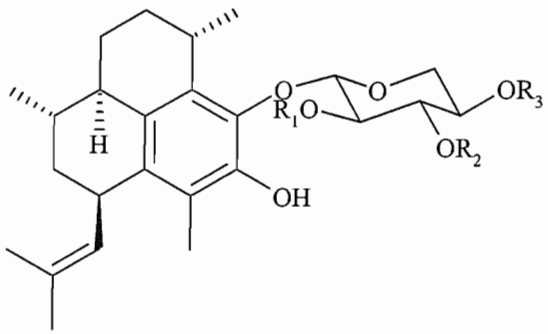
CHAPTER I – INTRODUCTION

I.1 - *Pseudopterogorgia Elisabethae* – a source of biologically active metabolites

Since the 1970s, *Pseudopterogorgia elisabethae*, a gorgonian octocoral found in the Caribbean Sea, has attracted increasing interest from natural product chemists. This coral has indeed proved to be a rich source of biologically active secondary metabolites, many having intriguing structural features.[1-5]

i. The Pseudopterosins

Amongst these natural products, a predominant class of diterpenes, namely the pseudopterosins, have been the subject of a number of creative total syntheses,[6] due to their strong anti-inflammatory and analgesic properties.[7] Pseudopterosin C, in particular, has found commercial application as the active component of a topical skin cream, "Resilience®".[8]



Pseudopterosins

(Pseudopterosin C, R_1=R_3=H, R_2=Ac)

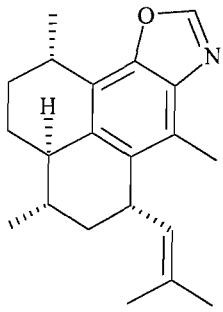
ii. Anti-tubercular metabolites

In the last 5 years, ongoing investigation on the marine organism has led to the isolation of a plethora of previously undescribed compounds with activities ranging from anti-inflammatory,[9] anti-tumour,[10-12] to anti-malarial activity.[13]

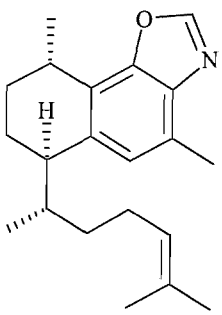
Most significantly however, the antimycobacterial activity observed during the screening of hexane extracts from *Pseudopterogorgia elisabethae* for growth inhibition of *Mycobacterium tuberculosis* $H_{37}Rv$, the agent that causes tuberculosis, has led to the isolation and characterisation of a number of potential antitubercular leads.

a) Benzoxazole alkaloids

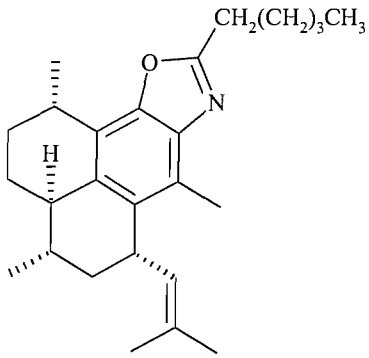
Amongst these, the isolation of benzoxazole alkaloids is noteworthy due to the extreme rarity of such structures in marine biota. Pseudopteroxazole **1.1** and *seco*-pseudopteroxazole **1.2** were isolated in 1999 and exhibited potent inhibitory activity (97% and 66% respectively) against *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of 12.5 $\mu g.mL^{-1}$.[14] Isolated more recently, homopseudopteroxazole **1.3** was found to possess similar antitubercular activity.[15]



1.1



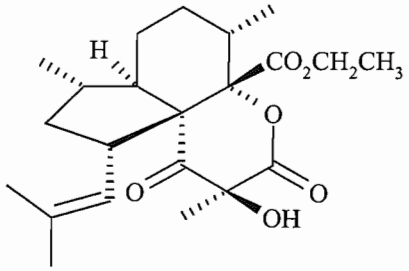
1.2



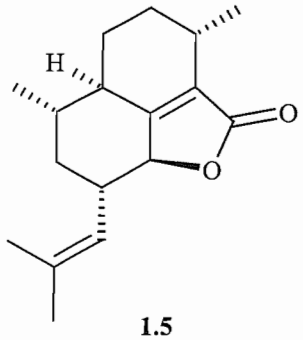
1.3

b) Novel lactones

A number of active diterpenes with intricate carbocyclic skeletons were also identified. For instance, lactones elisabetholide **1.4** and amphilectolide **1.5** are the first examples of such structural classes.[16] Amphilectolide **1.5** induced 42% growth inhibition at a concentration of 6.25 $\mu g.mL^{-1}$.



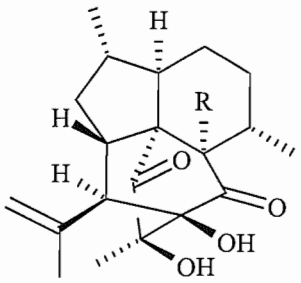
1.4



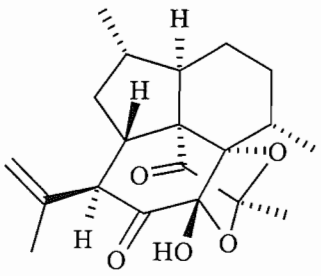
1.5

c) Cumbiasins

The cumbiasins (**1.6 A, 1.6 B,** and **1.6 C**), although moderately active (17% growth inhibition), possess an unusual architecture which probably results from a series of rearrangements on a serrulatane diterpene precursor.[12]



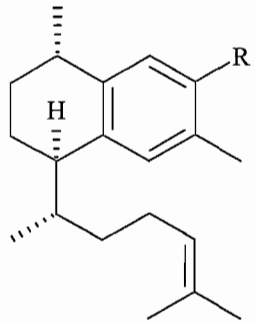
Cumbiasin A **1.6 A** (R = H)
Cumbiasin B **1.6 B** (R = OH)



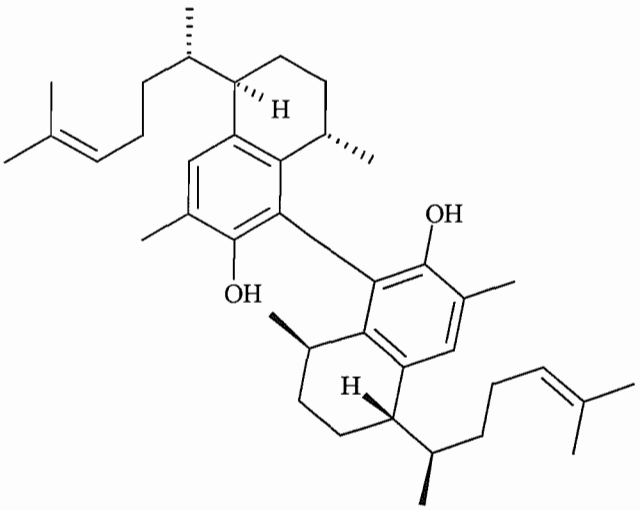
Cumbiasin C **1.6 C**

d) Other diterpenes

Two serrulatane-based diterpenes, erogorgiaene **1.7** and 7-hydroxyerogorgiaene **1.8** and a novel bis-diterpene, bis-hydroxyerogorgiaene **1.9**, were also identified as strong inhibitors of *Mycobacterium tuberculosis* $H_{37}Rv$.[17]



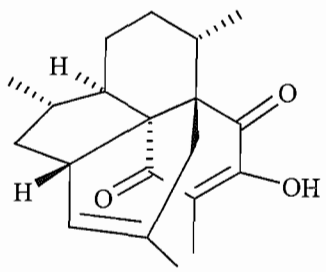
erogorgiaene (R = H) **1.7**
7-hydroxyerogorgiaene (R = OH) **1.8**



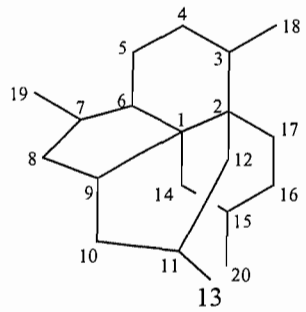
bis-7-hydroxyerogorgiaene **1.9**

e) Colombiasin A

As synthetic chemists, we were particularly interested in an active secondary metabolite, (-)-colombiasin A **1.10**, which after extensive structure elucidation was found to belong to a previously undescribed class of C_{20} rearranged diterpenes.[18] Indeed, (-)-colombiasin A **1.10** is a complex tetracycle consisting of a 'propellane' arrangement of three six-membered rings to which is further fused a cyclopentane ring. This natural product also contains six stereogenic centres, two of which are quarternary and one of which is common to all four rings, adding to the synthetic challenge posed by this molecule.



(-)-Colombiasin A
1.10

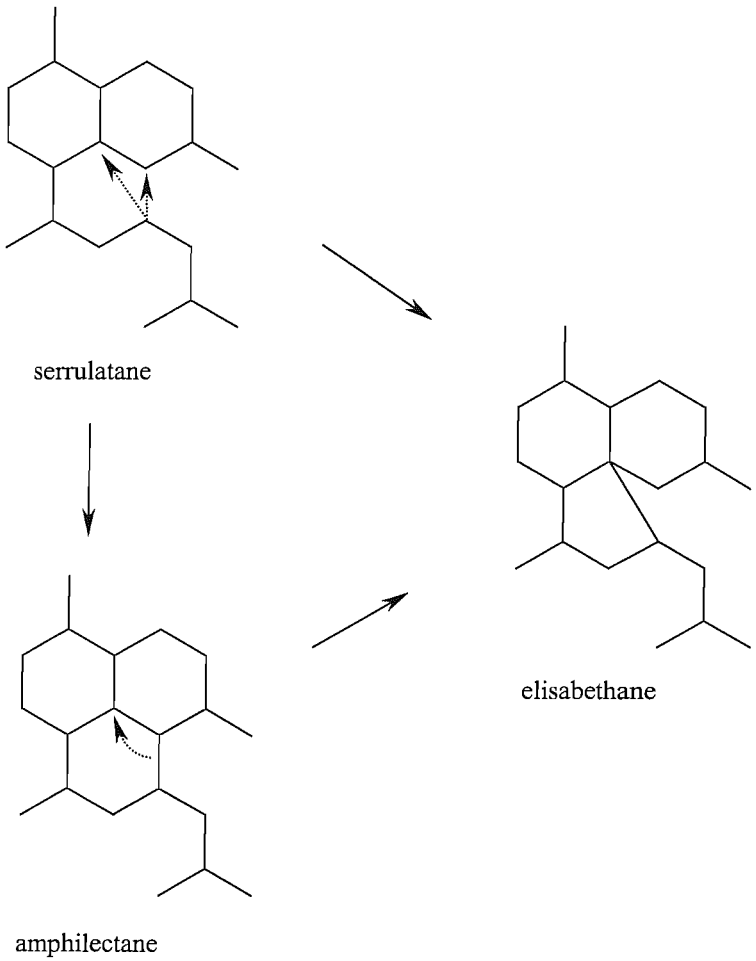


colombiane skeleton

The absolute configuration of colombiasin A was not assigned until Nicolaou *et al.* compared data of the synthetic material with the natural sample.[19] It was established to be 1*S*,2*S*,3*S*,6*R*,7*S*,9*S*.

I.2 Proposed biosynthesis

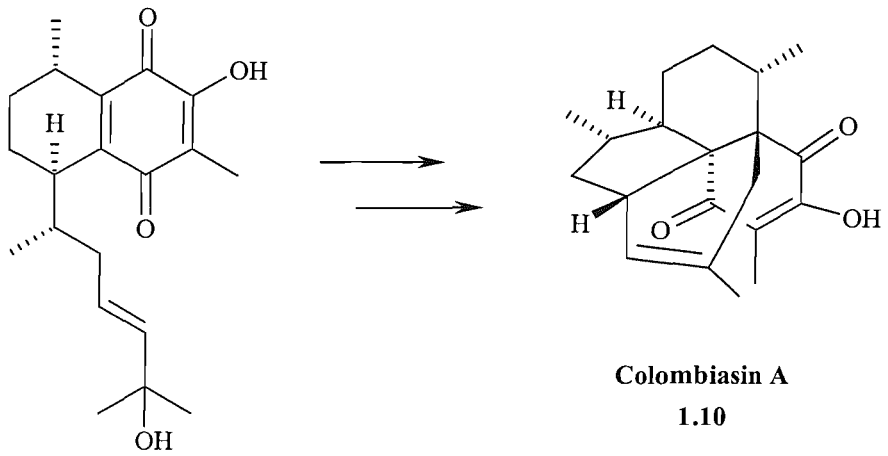
It can be noted that all the metabolites described above belong to structurally similar classes of diterpenes. Their concomitance in *Pseusopterogorgia Elisabethae* strongly suggests that, *in vivo*, a serrulatane diterpene is the biosynthetic precursor to many of these structurally novel diterpenes (Scheme 1.1).[20]



Scheme 1.1

i. *p*-Benzoquinone **1.11** as a biosynthetic precursor

Similarly, the colombiane skeleton could result from a series of rearrangements on a serrulatane precursor. For instance, elimination of the C15 hydroxy group of the serrulatane diterpene *p*-benzoquinone **1.11**,[4] followed by an intramolecular cyclisation would yield colombiasin A (Scheme 1.2).



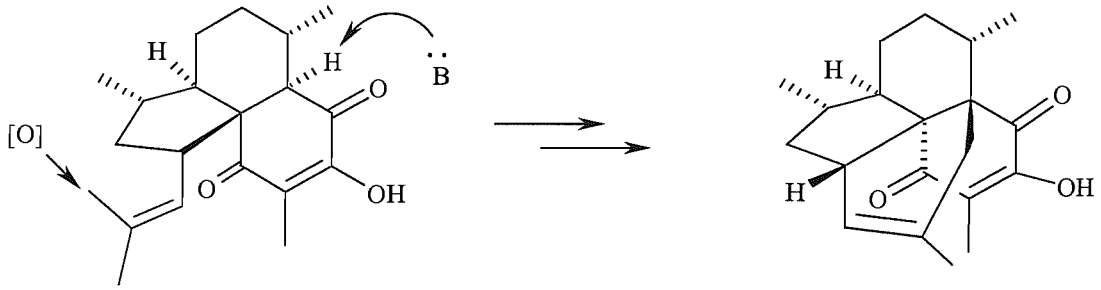
***p*-benzoquinone**
1.11

Colombiasin A
1.10

Scheme 1.2

ii. Elisabethin A **1.12** as a biosynthetic precursor

Alternatively, hydroxylation of elisabethin A **1.12**, a metabolite also isolated from *Pseudopterogorgia elisabethae*,[20] at the C12 position followed by phosphorylation or protonation of the new oxygen, base-catalysed removal of the proton at C2 and intramolecular alkylation of the resulting enolate could furnish colombiasin A **1.10** (Scheme 1.3).[18]



Elisabethin A

1.12

Colombiasin A

1.10

Scheme 1.3

From a synthetic point of view, the biosynthetic pathway involving a serrulatane diterpene precursor (Scheme 1.2), has provided inspiration for all reported synthetic strategies towards this natural product. These are discussed in detail below.

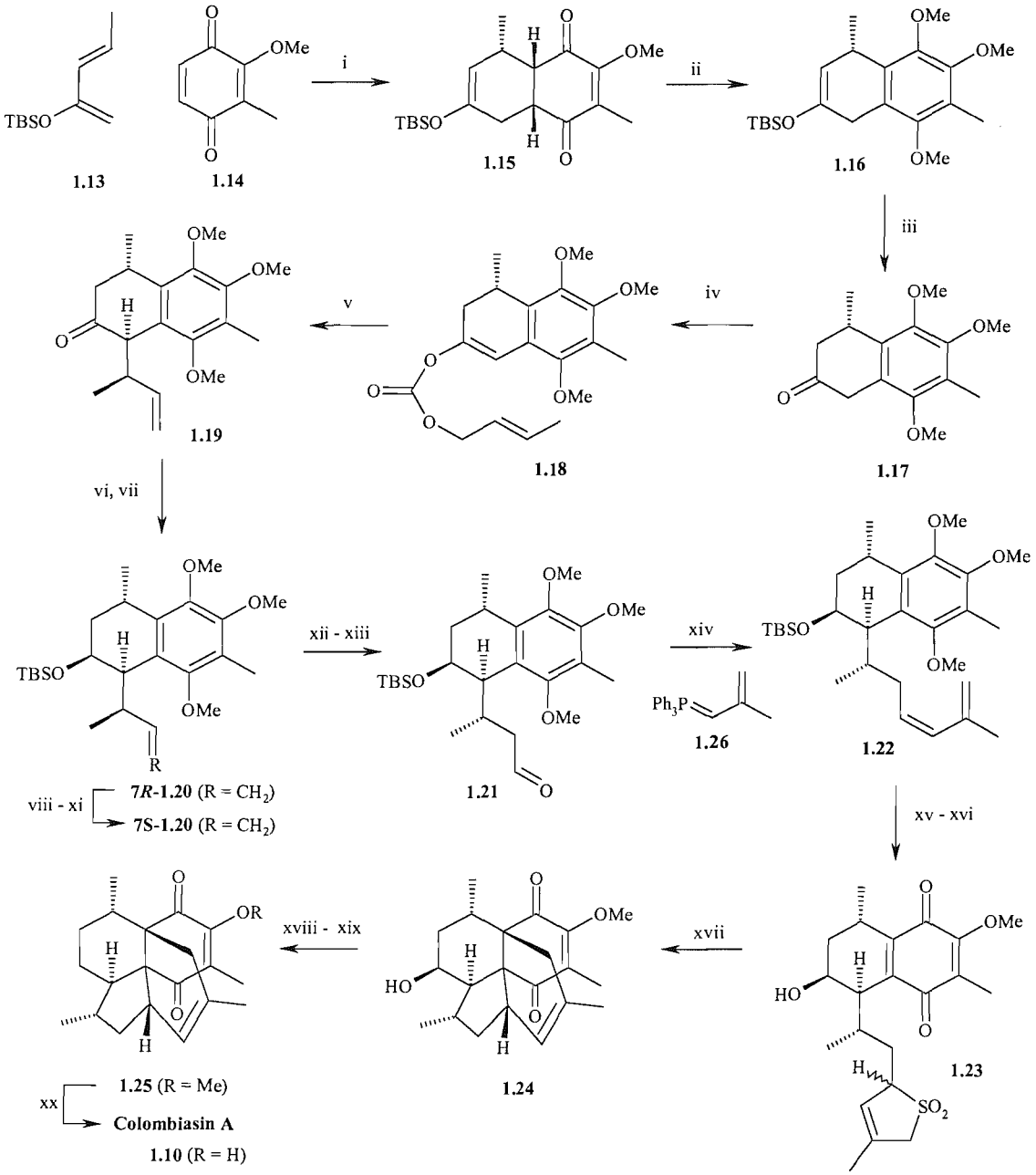
I.3 Previous syntheses

i. The Nicolaou total synthesis of (-)-colombiasin A

In 2001, Nicolaou *et al.*[19] published the first total synthesis of colombiasin A. Two key Diels-Alder reactions are the main features of the synthesis. Firstly, formation of the bicyclic precursor **1.15** is achieved by a cycloaddition reaction between diene **1.13** and quinone **1.14**. More interestingly however a key intramolecular Diels-Alder reaction in the latter stages of the synthesis effects closure of the colombiane skeleton (Scheme 1.4).

In the early stages, diene **1.13** was fused to quinone **1.14** (obtained by *ortho*-methylation of 1,2,4-trimethoxybenzene followed by oxidative demethylation using AgO and HNO_3) at ambient temperature in ethanol to give the *endo*-cycloadduct **1.15**. Conversion of the silyl enol ether **1.15** to the corresponding ketone **1.17** using TFA required prior aromatisation of **1.15** to **1.16** with K_2CO_3 and MeOH. Alkylation of the bicyclic ketone **1.17** failed to proceed by "standard methods" and

instead, a Pd catalysed sigmatropic rearrangement of carbamate **1.18** successfully installed the side-chain at the C6 position. The stereochemistry of the C7 methyl group however was opposite to that required. Inversion of the C7 centre was achieved by ozonolysis of alkene **(7*R*)-1.20** followed by epimerisation of the resulting aldehyde with NaOMe in MeOH. A Wittig reaction converted the aldehyde to alkene **(7*S*)-1.20**. Hydroboration-oxidation of alkene **(7*S*)-1.20**, oxidation of the resulting alcohol to aldehyde **1.21** and olefination using phosphonium ylid **1.26** yielded the key diene intermediate **1.22**. Protection of the diene moiety as the cyclic sulfone and subsequent oxidative demethylation furnished quinone **1.23**. Heating quinone **1.23** to 180 °C resulted in SO_2 extrusion and the key intramolecular [4+2] cycloaddition of the diene to the quinone proceeded exclusively *via* an *endo* transition state to give the colombiane skeleton **1.24** in 89% yield. Shielding from light was necessary for this key step to proceed successfully as a competing [2+2] cycloaddition was observed. Dehydroxylation at the C5 centre was achieved by formation of the xanthate followed by reductive cleavage of the C-O bond with tributyltin hydride. Attempts at deprotecting the resulting quinone **1.25** with BBr_3 partially resulted in partial isomerisation of the C10-C11 double bond to the C11-C12 position. Nevertheless, the deprotected product was observed in 30% yield and this step concluded the first racemic total synthesis of colombiasin A. In the asymmetric series, the use of a chiral catalyst [(*S*)-BINOLTiCl_2] in the first Diels-Alder cycloaddition reaction resulted in asymmetric induction (94% *ee*) and the chemistry elaborated in the racemic series was then applied to give (-)-colombiasin A **1.10** in an overall 0.8 % yield.



Reagents/Conditions: i) EtOH, 25 °C, 2h, 83%; ii) K_2CO_3 (5 eq.), MeI (20 eq.), acetone, reflux, 48h, 83%; iii) 2% TFA in CH_2Cl_2, 25 °C, 2h, 91%; iv) LiHDMS (1.2 eq.), THF, -78 °C, 1h, then crotyl chloroformate (1.4 eq.), 25 °C, 30 min, 94%; v) $[Pd(PPh_3)_4]$ (0.04 eq.), THF, 25 °C, 15 min, 58%; vi) $NaBH_4$ (3 eq.), MeOH, 25 °C, 30 min, 96%; vii) Et_3N (2 eq.), TBSOTf (1.2 eq.), CH_2Cl_2, -78 °C, 1h, 95%; viii) OsO_4 (0.05 eq.), NMO (2 eq.), acetone/H_2O (10/1), 25 °C, 5h, 89%; ix) $NaIO_4$ on silica gel, CH_2Cl_2, 25 °C, 30 min, 82%; x) NaOMe (4 eq.), MeOH/THF (2/1), 25 °C, 12h, 30%; xi) methyltriphenylphosphonium bromide (1.2 eq.), KO^{t}Bu (1.4 eq.), THF, 25 °C, 1h then **7*S*-1.20** (R = O), 25 °C, 30 min, 97%; xii) BH_3.THF (3 eq.), THF, 25 °C, 1h then NaOH (3M) and H_2O_2 (30%), 25 °C, 1h, 87%; xiii) PCC (1.5 eq.), CH_2Cl_2, 25 °C, 1h, 95%; xiv) phosphorane **1.26** (1.5 eq.), THF, 70 °C, 8h, 89%; xv) SO_2, sealed tube, 25 °C, 30 min, 97%; xvi) dioxane/6M HNO_3 (10/1), 25 °C, 2h then AgO (6.0 eq.), 25 °C, 1h, 85%; xvii) toluene (sealed tube), 180 °C, 20 min, 89%; xviii) NaH (5 eq.), THF/CS_2/MeI (4/1/1), 50 °C, 3h, 91%; xix) AIBN (cat.), $n$$Bu_3SnH$ (5 eq.), toluene, 110 °C, 30 min, 88%; xx) BBr_3 (10 eq.), CH_2Cl_2, -78 °C, 30 min, 30%.

Scheme 1.4

Although lengthy, this first route to (-)-colombiasin A has allowed the determination of the natural product's absolute configuration, as well as the construction of a variety of chemical analogues for possible biological studies. However, installation of the correct configuration at the C7 centre proved cumbersome, and the problems encountered in the last deprotection step suggest that there is still room for improvement.

ii. The Harrowven approach

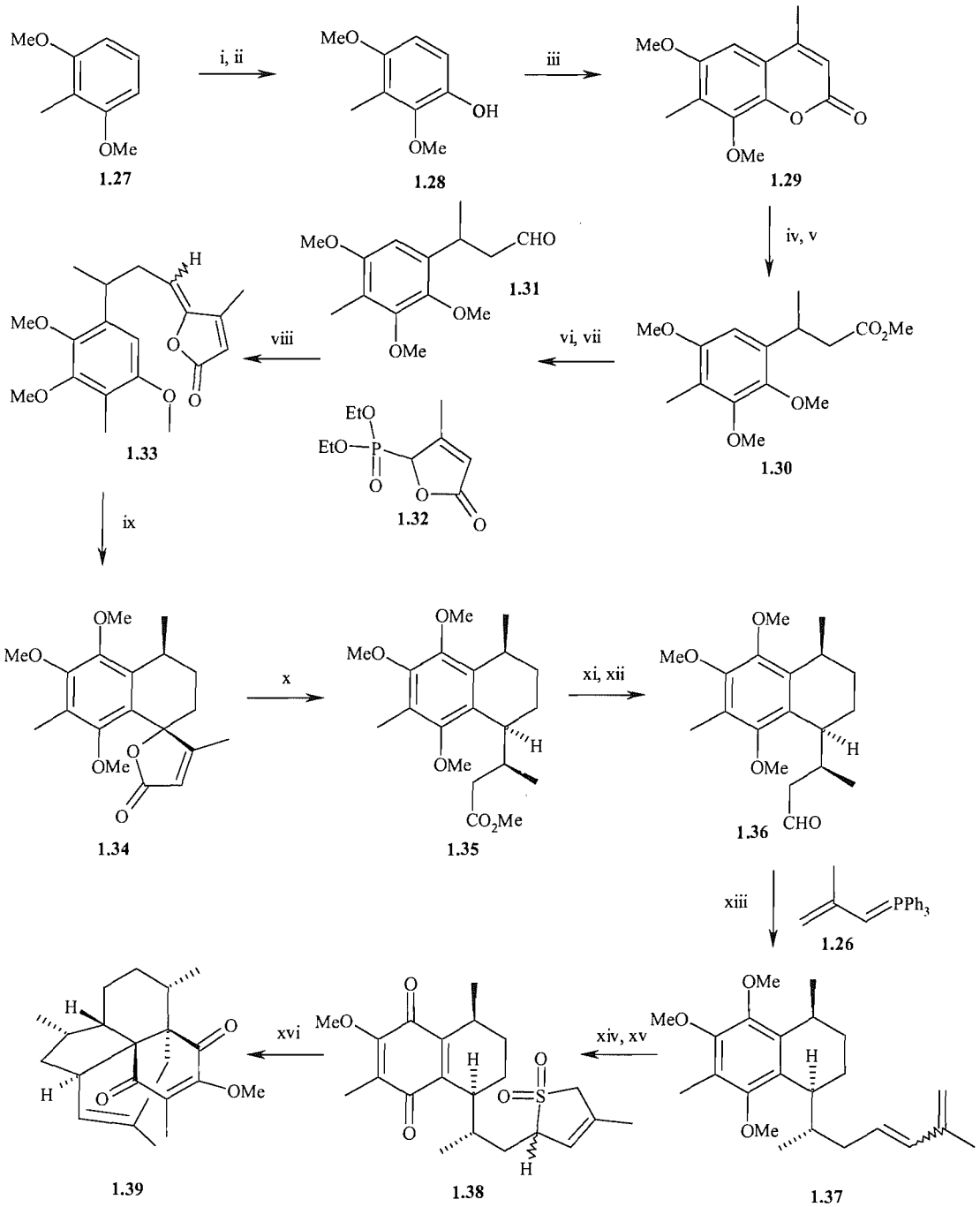
Shortly after publication of the work of Nicolaou, Harrowven *et al.*[21] reported an approach to *epi*-colombiasin A methyl ether **1.39** (Scheme 1.5). Similarly, a key intramolecular cycloaddition on **1.38** effects closure of the colombiane framework. However, construction of the bicyclic framework relies on a new arene alkylation method.

The starting point of the synthetic sequence was the synthesis of phenol **1.28** from 2,6-dimethoxytoluene **1.27**. A Vilsmeier reaction on **1.27** followed by treatment with *m*CPBA furnished phenol **1.28** in good yield after basic cleavage. A Pechman condensation with ethyl acetoacetate then gave coumarin **1.29**. Hydrogenation of alkene **1.29** and saponification of the lactone led to ester **1.30**. Conversion to the corresponding aldehyde **1.31** and treatment with phosphonate **1.32** yielded alkene **1.33**. On treatment with triflic acid, **1.33** underwent an aromatic alkylation to give spirolactone **1.34**, thus furnishing the bicyclic core. Unfortunately, opening of the spirolactone using catalytic hydrogenolysis installed the inverse stereochemistry at the C6 centre.

Elaboration of the side-chain was achieved by converting ester **1.35** to aldehyde **1.36**. A Wittig reaction then gave diene **1.37** which was protected as the cyclic sulfone in order to achieve oxidative demethylation of the arene. Heating quinone **1.38** in the dark yielded *epi*-colombiasin A methyl ether **1.39** in 0.6% overall yield.

The inverse stereochemistry at the C6 centre has yet to be addressed. Nonetheless, this route represents an improvement in terms of length and features some interesting chemical transformations. The sequence of arene-alkylation and opening of the spirocycle by tandem hydrogenation-hydrogenolysis is particularly

noteworthy as it unveils the bicyclic core and installs the side-chain in just a few steps.



Reagents/Conditions: i) $POCl_3$, DMF, 2h, 105 °C, 68%; ii) *m*CPBA, DCM, reflux then KOH, MeOH, 1h, RT, 96%; iii) ethyl acetoacetate, TfOH, 3h, 70 °C, 60%; iv) H_2, Pd-C, EtOAc, 96h, RT, 98%; v) Me_2SO_4, KOH, acetone, 16h, 89%; vi) $LiAlH_4$, THF, 40 min, -78 °C to 0 °C, 99%; vii) DMP, DCM, 30 min, 0 °C, 96%; viii) KO^{t}Bu, THF, 24h, 0 °C to RT, 62%; ix) TfOH, PhMe, 72h, 80 °C, 59%; x) H_2, Pd-C, PtO_2, AcCl, MeOH, 48h, RT, 85%; xi) $LiAlH_4$, THF, 20 min, -78 °C to 0 °C, 99%; xii) DMP, DCM, 30 min, 0 °C, 99%; xiii) phosphorane **1.26**, THF, 40 min, 0 °C to RT, 60%; xiv) liquified SO_2, 4h, -78 °C to RT, 71%; xv) AgO, HNO_3, dioxane, 5 min, RT, 25%; xvi) toluene, sealed tube, dark, 7h,180 °C, 64%.

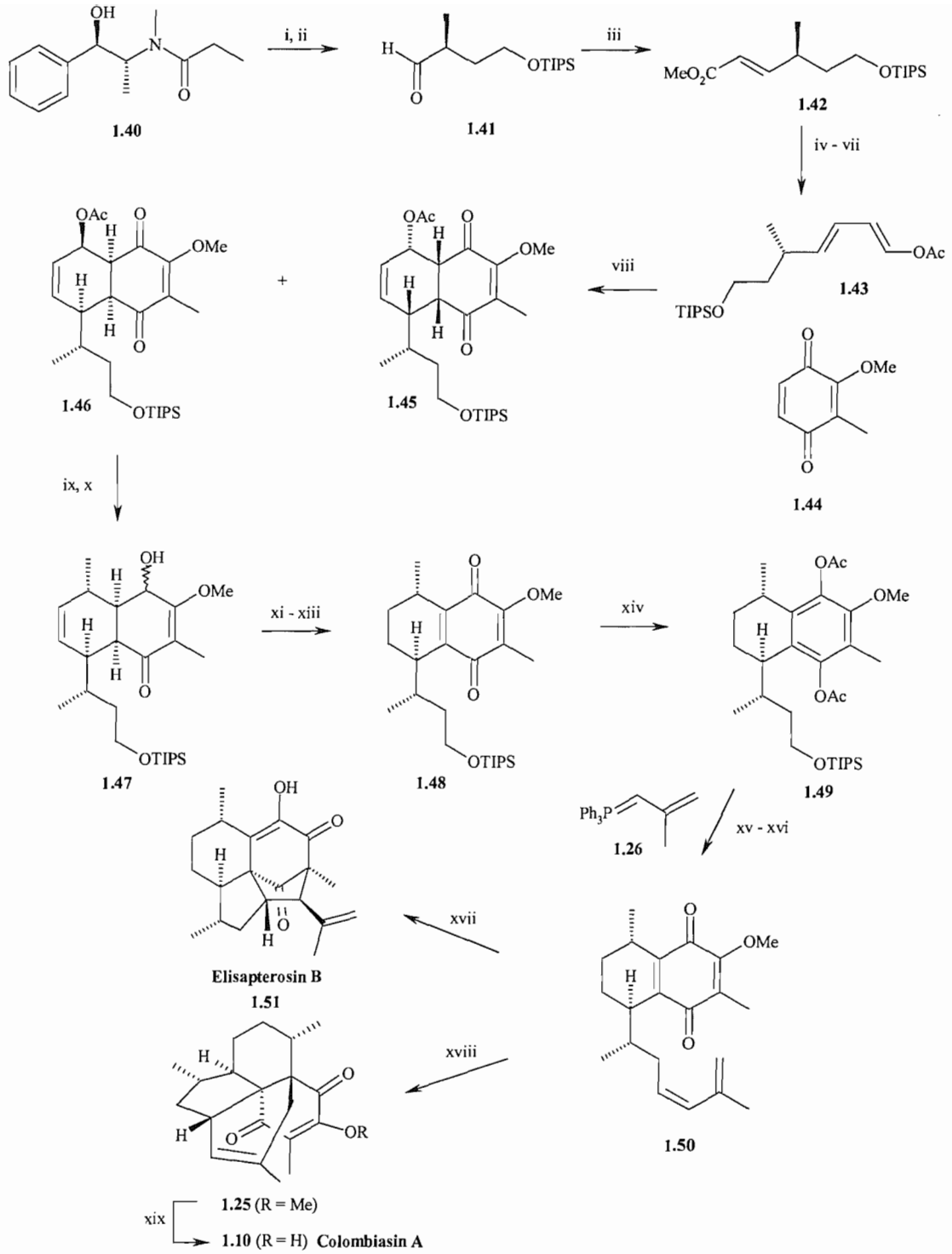
Scheme 1.5

iii. The Rychnovsky synthesis of (-)-colombiasin A

More recently, Rychnovsky *et al.*[22] published work on the synthesis of elisapterosin B **1.51** and colombiasin A **1.10** using, in both cases, the same serrulatane diterpene precursor **1.50**. In fact, a [5+2] intramolecular cycloaddition of **1.50** leads to the elisapterosin skeleton **1.51**, whereas a [4+2] cycloaddition yields the colombiane skeleton **1.10**.

Starting with Myers' pseudoephedrine chiral auxiliary **1.40**,[23] enantiomerically pure aldehyde **1.41** was obtained by a sequence of alkylation, reduction and hydrolysis. Wittig olefination next furnished ester **1.42**. Elaboration of ester **1.42** into diene **1.43** was achieved by homologation to the lithium ynolate using bromomethylenelithium followed by butyllithium. Treatment with lithium hydride and subsequent acetylation yielded diene **1.43** in 79% yield. Union of diene **1.43** with quinone **1.44** by a lithium perchlorate promoted Diels-Alder reaction yielded decalin **1.46** as the major product. Reduction of enedione **1.46** with $NaBH_4$ prevented aromatisation and the acetate group could then be easily substituted with a methyl group using lithium dimethylcuprate. Reduction of the C4-C5 alkene of **1.47** with hydrogen, oxidation and treatment with DBU furnished quinone **1.48** which was protected as the acetylated arene **1.49**. Elaboration of the side-chain was then achieved by TIPS deprotection, oxidation and olefination using phosphonium ylid **1.26** to furnish the serrulatane diterpene **1.50**. $BF_3.OEt_2$ (25 fold excess) was found to induce the [5+2] cycloaddition whereas thermal conditions in the absence of light gave the [4+2] cycloaddition product i.e. (-)-colombiasin A methyl ether **1.25** (R = Me). Deprotection with $AlCl_3$ completed the synthesis of (-)-colombiasin A **1.10** (R = H) in 17 steps and a 3.9% overall yield (Scheme 1.6).

Rychnovsky's ingenious use of a Diels-Alder cycloaddition to construct the key intermediate **1.46** in an asymmetric fashion lends all merit to this sequence. Also, elaboration of quinone **1.48** into an intermediate that can provide both natural products by fine-tuning of reaction conditions is remarkable. However, the stereocontrol observed in the synthesis of **1.46** is quite poor (1.7:1) and this is carried out through the synthesis yielding both natural products as an inseparable mixture of diastereomers.

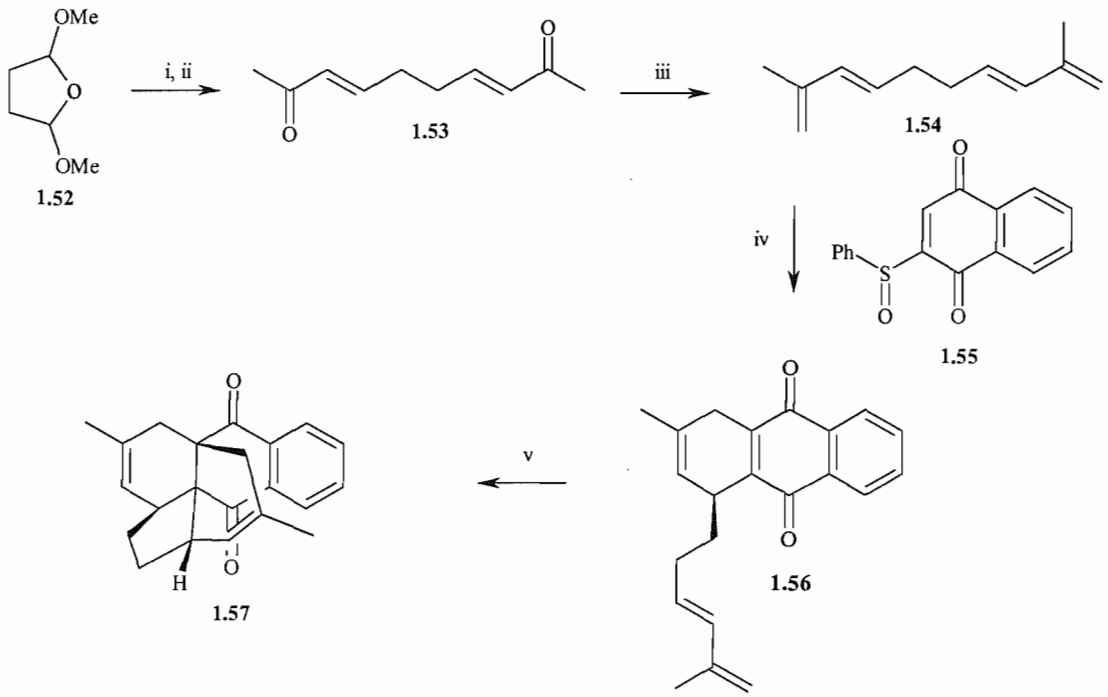


Reagents/Conditions: i) LDA, LiCl, ICH_2CH_2OTIPS, 94%, > 97% *de*; ii) $LiAlH(OEt_3)$, then H^+, 77%; iii) $Ph_3P{=}CHCO_2Me$, CH_3CN, reflux, 85%; iv) $LiCH_2Br$, THF, -78 °C; v) *n*BuLi, -78 °C to 23 °C; vi) LiH, reflux; vii) Ac_2O, 79%; viii) 5 M $LiClO_4$, Et_2O, 24h, 75%; ix) $NaBH_4$, $CeCl_3$, MeOH, 93%; x) $LiCuMe_2$, Et_2O, 0 °C to 23°C, 83%; xi) H_2, Pd/C, EtOH, 95%; xii) Dess-Martin periodinane, CH_2Cl_2, 92%; xiii) DBU, CH_2Cl_2, air, 70%; xiv) Zn, Ac_2O, NaOAc, then Ac_2O, pyridine, 96%; xv) HF-pyridine, THF, 94%; xvi) Dess-Martin periodinane, CH_2Cl_2, 99%; xv) phosphorane **1.26**, THF, 78%, 3:1 *E/Z*; xvi) K_2CO_3, MeOH, air, 79%; xvii) $BF_3.OEt_2$ (25 eq.), CH_2Cl_2, -78 °C, 41%; xviii) 180 °C, toluene, 83%; xix) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0 °C to 23 °C, 73%.

Scheme 1.6

iv. The Flynn approach

Most recently, Flynn *et al.*[24] have demonstrated that the tetracyclic core of colombiasin A could be accessed by a tandem Diels-Alder-elimination-intramolecular Diels-Alder (DA-E-IMDA) sequence. The method relies on the synthesis of a tetraene **1.54**, which can be fused to a sulfoxide dienophile **1.55** by a Diels-Alder reaction. Sulfoxide elimination ensues and a subsequent intramolecular Diels-Alder reaction on **1.56** effects the cyclisation to the colombiane skeleton **1.57** (Scheme 1.7).

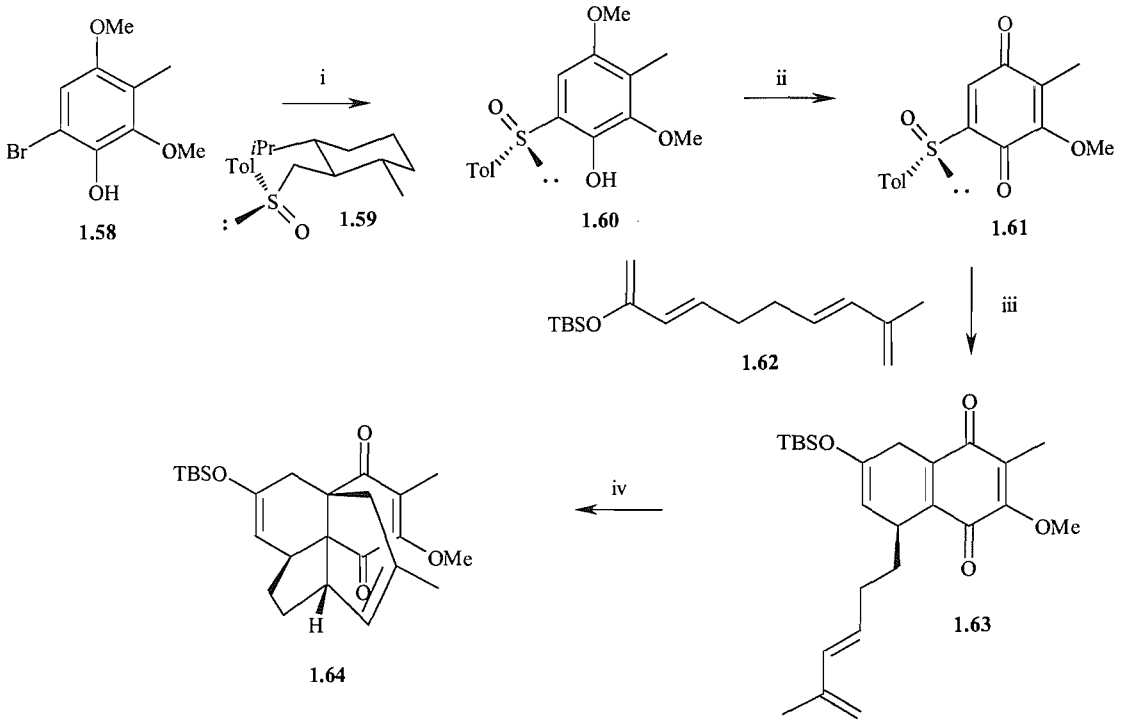


Reagents/Conditions: i) HCl (aq.); ii) $Ph_3P{=}CHC(O)CH_3$; iii) $Ph_3P{=}CH_2$ (2 eq.); iv) CH_2Cl_2, -15 °C to 18 °C; v) toluene, 160 °C.

Scheme 1.7

Flynn also demonstrated the viability of this method as an asymmetric route to the colombiasin A core by using unichiral sulfinylquinone **1.61** as the dienophile. Bromophenol **1.58** (accessed from 2,6 dimethoxytoluene) can be lithiated and reaction with (*S*,*S*)-menthyl *p*-toluenesulfinate **1.59** yields, upon subsequent CAN oxidation, chiral sulfinylquinone **1.61**. Sulfinylquinone **1.61** undergoes a cycloaddition with tetraene **1.62** which, after elimination gives diene **1.63** with

excellent enantioselectivity (*ee* 94:6). Quinone **1.63** can then undergo an intramolecular cycloaddition to give the *endo*-adduct **1.64** (Scheme 1.8).



Reagents/Conditions: i) *n*BuLi (2 eq.), THF, -78 °C then **1.59**; ii) ammonium cerium(IV) nitrate, CH_3CN, 18 °C; iii) CH_2Cl_2, -15 °C to 18 °C; iv) toluene, 160 °C.

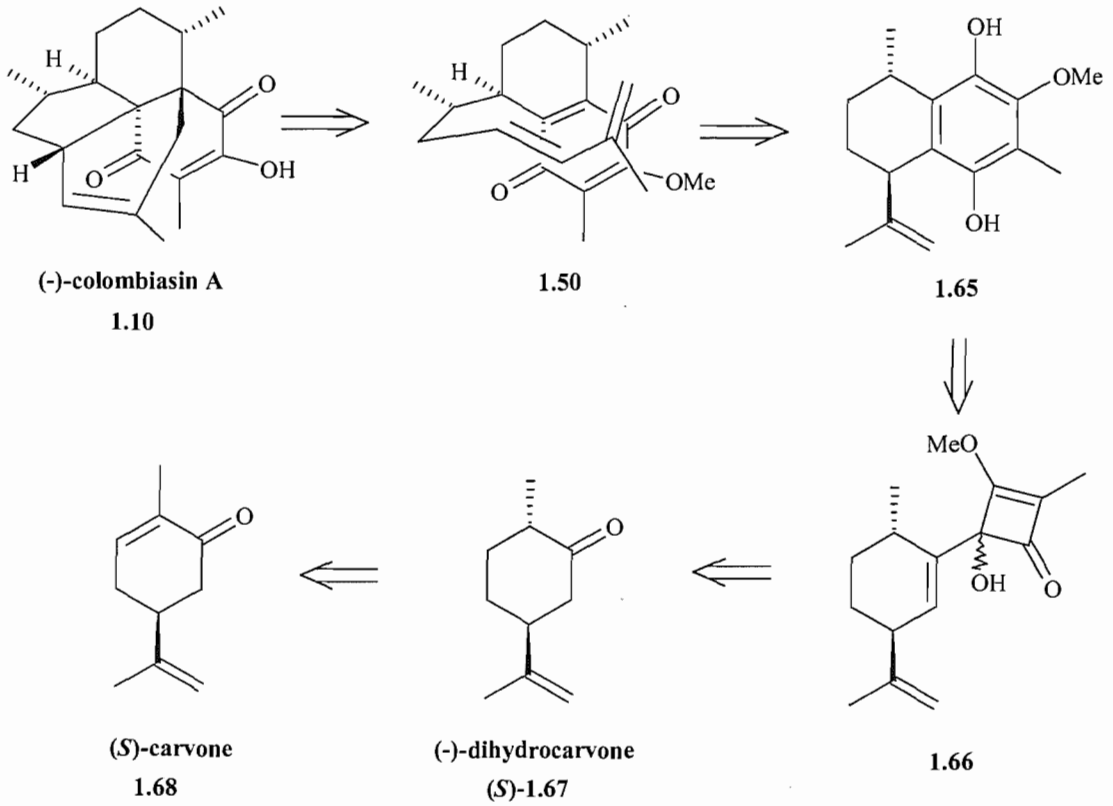
Scheme 1.8

Although access to the natural product has yet to be achieved, the Flynn approach provides a rapid, asymmetric route to the colombiane skeleton.

It can be noted that in all the reported syntheses of colombiasin A, a similar strategy is being used. In the primary stages, a bicyclic core is constructed, in most cases by means of a Diels-Alder reaction. Elaboration of a diene side-chain ensues and the resulting "serrulatane-type" structure is subjected to heat to induce an intramolecular cycloaddition. Optical purity is achieved by the use of chiral auxiliaries in the early stages of the syntheses.

I.4 Retrosynthesis

Our retrosynthesis relies on the previously described intramolecular Diels-Alder reaction to effect closure of the tetracycle. We envisioned that key intermediate **1.50** could however be accessed in fewer steps from a commercially available and cheap chiral starting material (*S*)-carvone **1.68**. A Shapiro reaction on ketone **1.67**, followed by coupling with a squarate species can then yield the bis-allylic alcohol **1.66**. A thermal rearrangement reaction developed by Moore *et al.*[25] would then furnish hydroquinone **1.65**, which can readily oxidise to the corresponding quinone. We anticipated that diene **1.50** could be obtained by a Suzuki coupling of alkene **1.65** with a vinyl stannane thus giving the key intermediate **1.50**. A Diels-Alder cycloaddition reaction, followed by aromatic deprotection would complete a total synthesis of (-)-colombiasin A **1.10** in 7 steps (Scheme 1.9).

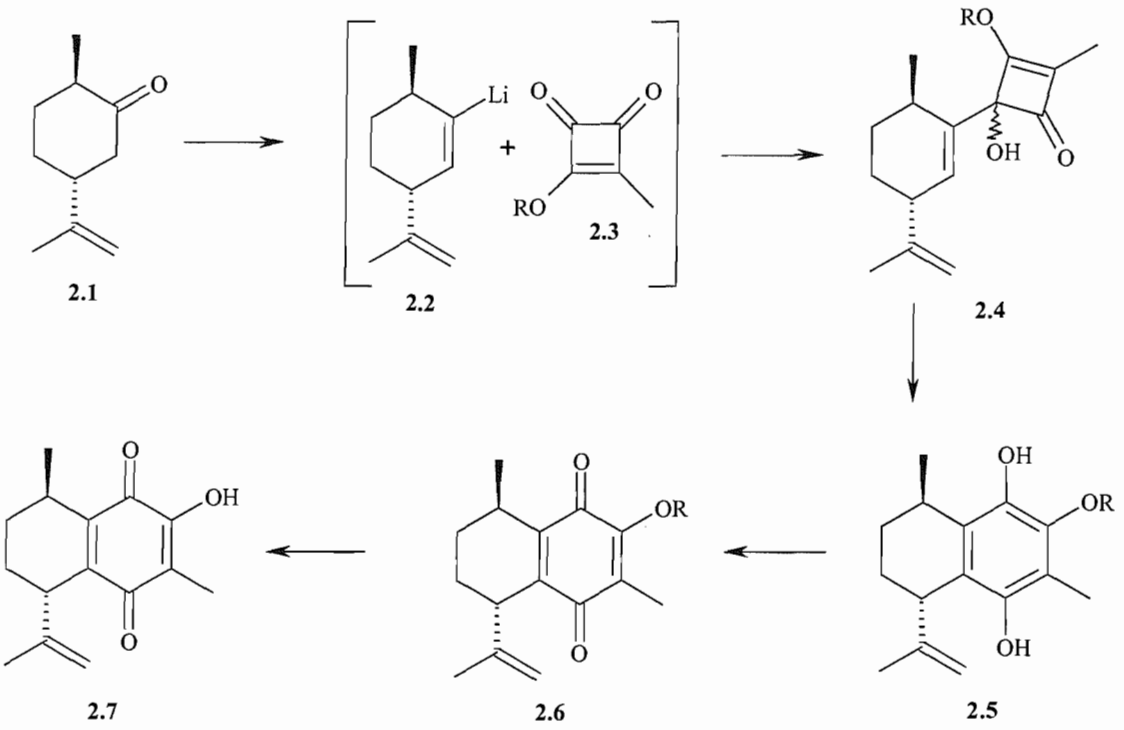


Scheme 1.9

In order to verify the viability of our proposed route, model studies were carried out. Firstly, synthesis of hydroquinone **1.65** was attempted. Secondly, appendage of the diene side-chain was tried. These model studies are described in detail in the following chapters.

CHAPTER II - MODEL STUDIES: SYNTHESIS OF QUINONE 2.7

Our model studies were carried out on (+)-dihydrocarvone **2.1** as it is an inexpensive and readily available chiral starting material. The first goal was to establish the validity of the cyclobutenone ring expansion strategy. This required the synthesis of tertiary alcohol **2.4** which in turn was to be prepared by coupling of vinyllithium **2.2** and a squarate compound **2.3**. Various approaches to vinyllithium **2.2** are discussed as indeed is the nature of the squarate **2.3**. Finally, the thermal rearrangement of **2.4** to hydroquinone **2.5**, oxidation to quinone **2.6** and the final deprotection step are described (Scheme 2.1).



Scheme 2.1

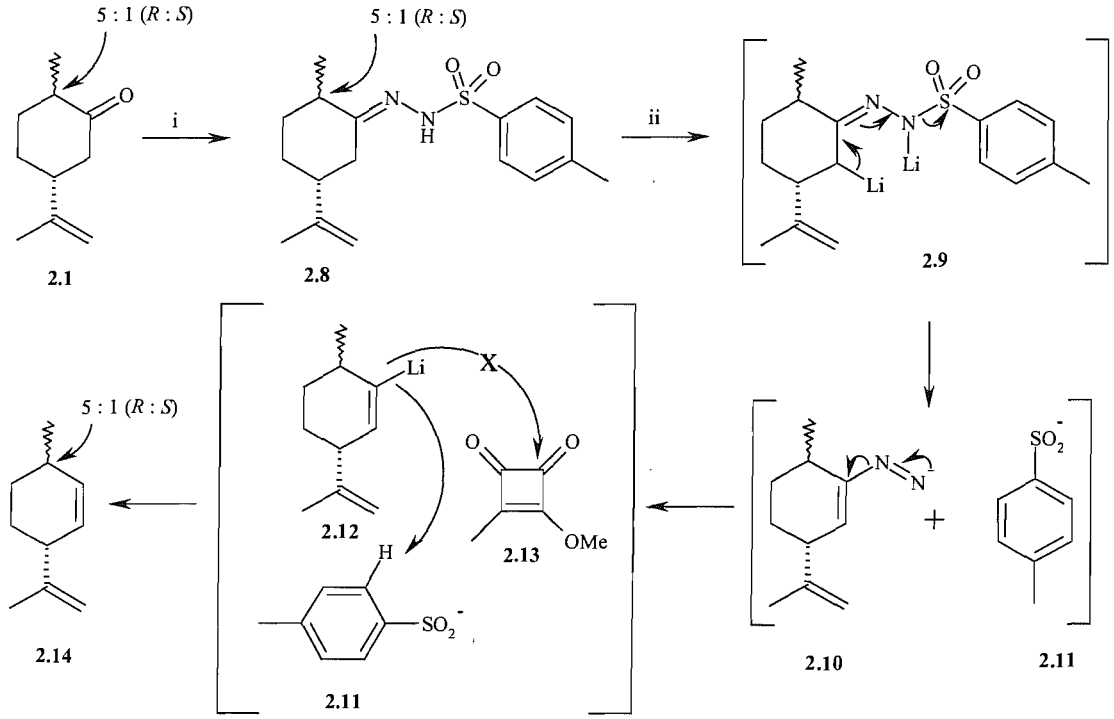
II.1-Vinyllithium

i. *via* the Shapiro reaction

The Shapiro reaction provides a means to create a new C-C bond between the carbon centres of two ketones, simultaneously introducing a vinylic moiety into the product. In order to carry out the Shapiro reaction, formation of an aromatic hydrazone is necessary. Treatment with an alkyllithium base then converts the hydrazone into a dianionic species, which, upon warming to -20 °C, decomposes directly to the vinyllithium (*viz.* **2.9** → **2.12**, Scheme 2.2). For our purpose, the formation of an aromatic hydrazone from dihydrocarvone **2.1** was primordial.

a) Tosyl hydrazone

Tosyl hydrazone **2.8** was readily obtained in high yield by stirring dihydrocarvone **2.1** with tosyl hydrazine in acetic acid. However, when subjecting it to Shapiro conditions (i.e. adding 2 equivalents of butyllithium), the vinyllithium intermediate **2.12** was readily quenched by a proton source to give limonene **2.14**. It is likely that the proton is abstracted from the 'tosyl' group as SO_2 is a powerful "ortho-lithiating" directing group (Scheme 2.2).



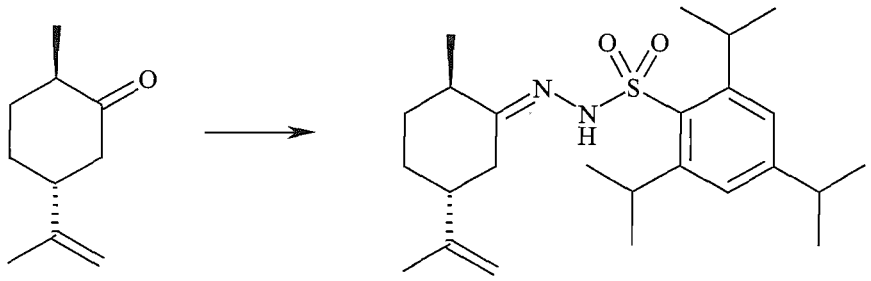
Reagents/Conditions: i) tosylhydrazine, AcOH, RT, 16h, 84%; ii) *n*BuLi (2 eq.), THF, -78 °C to -20 °C, then squarate **2.13**, THF, -78 °C, 68%.

Scheme 2.2

In order to favour quenching of the vinyllithium by the squarate electrophile **2.13**, the next obvious choice was to transfer to an "ortho-protected" hydrazone and thus suppress formation of limonene **2.14**.

b) Trisyl hydrazone

Formation of the trisylhydrazone of dihydrocarvone **2.15** proved to be more difficult than the tosyl hydrazone case. A number of methods have been reported for the formation of trisyl hydrazones, and a summary of the methods tried is given in Table 2.1.



2.1 **2.15**

Solvent	Trisylhydrazide	Acid	Product
MeOH	3.9 eq.	0.1 eq. (*c*HCl)	x
MeOH	1.0 eq.	0.1 eq. (*c*HCl)	55-89%
Et_2O	1.0 eq.	0 eq.	x
CH_3CN	1.1 eq.	1.1 eq. (*c*HCl)	x
EtOH	1.0 eq.	0.06 eq. (*p*TsOH.H_2O)	x
AcOH	1.0 eq.	0 eq.	x

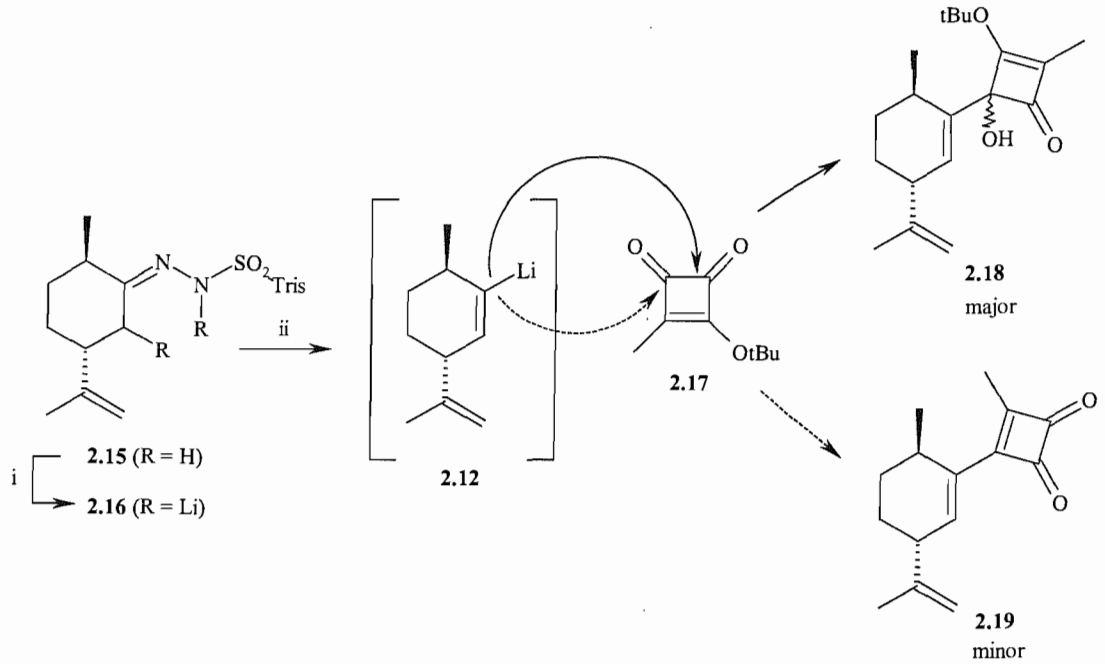
Table 2.1

Although in most cases TLC monitoring showed that a reaction had occurred, isolation of hydrazone **2.15** proved problematic with decomposition observed on both silica and alumina. On occasions when **2.15** could be isolated by filtration, yields varied between 55% and 89%.

Since formation of the trisylhydrazone of cyclohexanone **2.47** was facile in our hands, it seems that the hindrance engendered by the proximal methyl group in **2.1** was responsible for its acute acid sensitivity.

Notwithstanding these difficulties, isolation of hydrazone **2.15** allowed us to test the Shapiro reaction with an "ortho-protected" aromatic hydrazone. Thus, when **2.15** was treated with *t*-butyllithium, formation of limonene **2.14** was reduced considerably and accounted for just 15% of the total mass-balance. The result suggests that proton quench primarily originates from the arene but that there is a secondary source, presumably the solvent or possibly one of the by-products other than the aromatic

portion. It was also found that, by reducing the length of time the reaction mixture was stirred at higher temperatures (-20 °C), this side-reaction was *quasi* eliminated. Thus, a fine balance needed to be struck so as to achieve complete decomposition of dianion **2.16** to vinyllithium **2.12** while simultaneously avoiding protonation of that intermediate. An important by-product of the Shapiro reaction was the result of an attack of vinyl anion **2.12** at the "ester-like" carbonyl to yield, after loss of *tert*-butanol, diketone **2.19**. Despite this side reaction, we were pleased to isolate the desired alcohol **2.18** as the major product of the reaction (38%). Alcohol **2.18** results from the attack of intermediate vinyllithium **2.12** at the more electrophilic carbonyl of squarate **2.17** (Scheme 2.3).

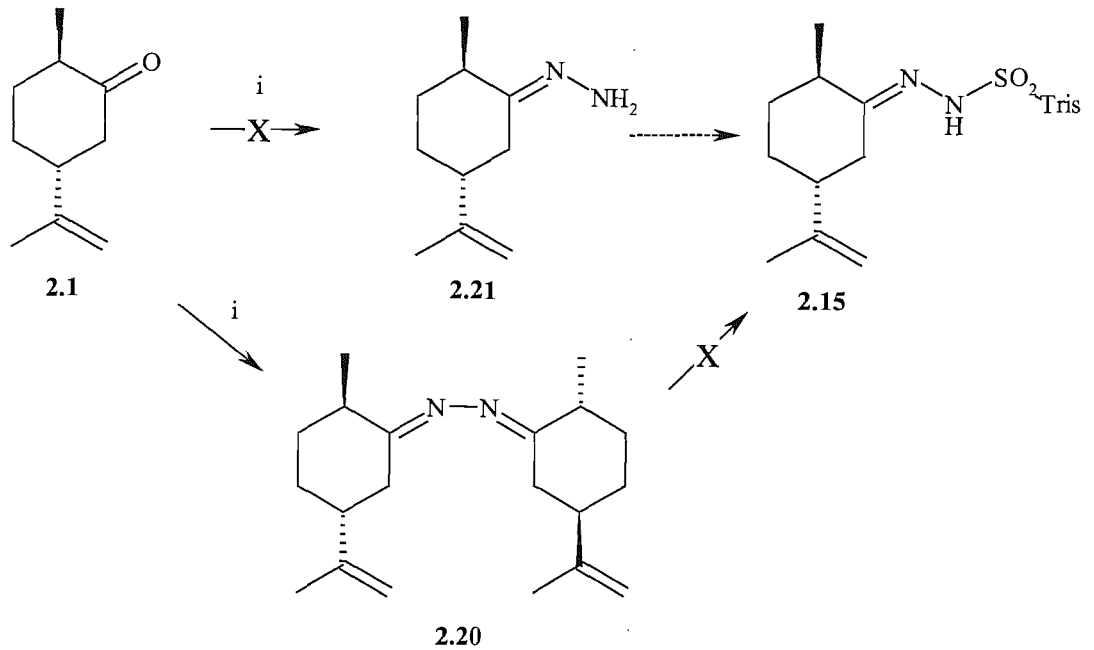


Reagents/Conditions: i) *t*BuLi (3 eq.), THF, -78 °C, 2h; ii) -78 °C to -20 °C, 1 min. then **2.17**, THF, -78 °C, 30 min.

Scheme 2.3

Although hydrazone formation allowed us to try out the Shapiro reaction, the reaction proved so temperamental that alternative ways to access hydrazones were sought. An alternative route to trisylhydrazones is the prior reaction of ketones with hydrazine. The resulting hydrazone, when treated with trisyl chloride, should yield the sulfonated

product. However, our hopes of effecting the two-step synthesis of trisylhydrazone **2.15** were quickly dashed when treatment of dihydrocarvone **2.1** with hydrazine yielded the dimer **2.20** (Scheme 2.4).



Reagents/Conditions: i) $N_2H_4.H_2O$, Et_3N, EtOH, 100 °C, 60h, 40%.

Scheme 2.4

c) One-pot Shapiro

The problems encountered with the isolation of hydrazone **2.15** led us to investigate a one-pot Shapiro reaction, whereby isolation of the hydrazone would be eliminated. Monitoring the hydrazone formation by ^{1}H and ^{13}C NMR showed that, when stirring dihydrocarvone **2.1** with trisylhydrazine in $CDCl_3$ in the absence of acid, formation of the hydrazone **2.15** had occurred after 15 minutes. Longer reaction times led to decomposition as shown in Figure 2.1.

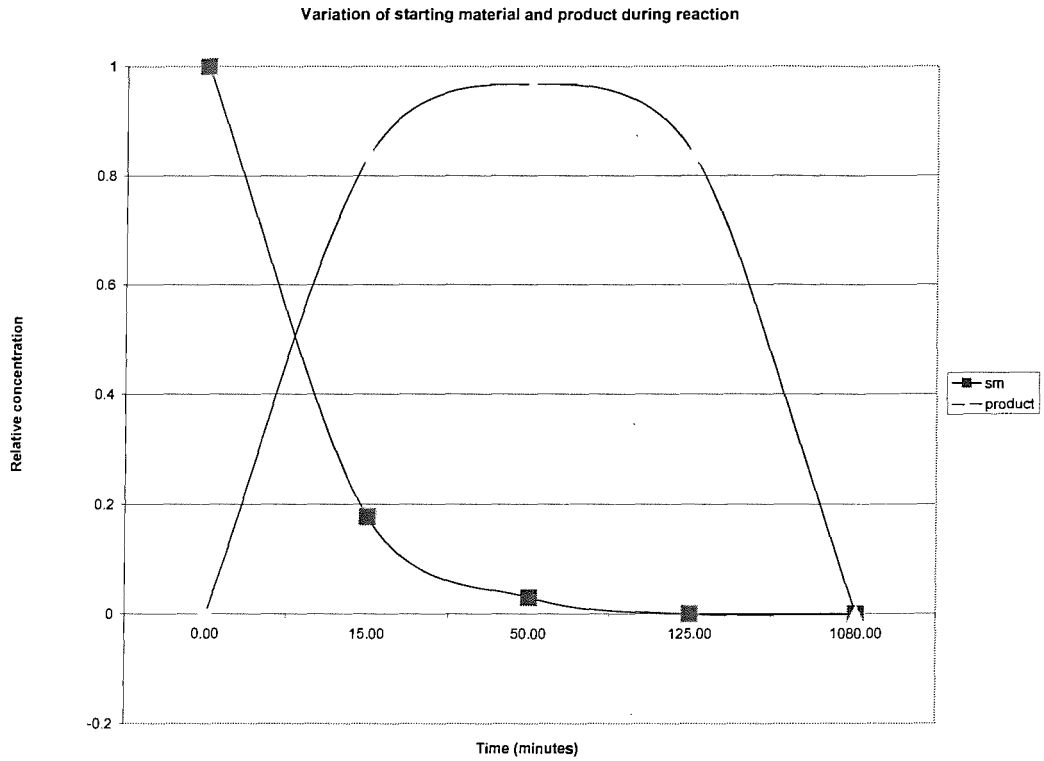


Figure 2.1

This spectroscopic evidence suggested that the solution could subsequently be subjected to the Shapiro conditions and quenched with squarate **2.17** in order to obtain the desired bis-allylic alcohol **2.18**. Thus, assuming a change of solvent ($CDCl_3$ to THF) would be of no consequence, a solution of trisylhydrazine and dihydrocarvone **2.1** in THF was stirred at ambient temperature for 2 hours, after which it was treated with 4 equivalents of *tert*-butyllithium at -78 °C. The characteristic observations were noted, i.e. colour change and nitrogen evolution upon warming to -30 °C. Cooling down to -78 °C and quenching with squarate **2.17** indeed gave the desired product in a 38% yield.

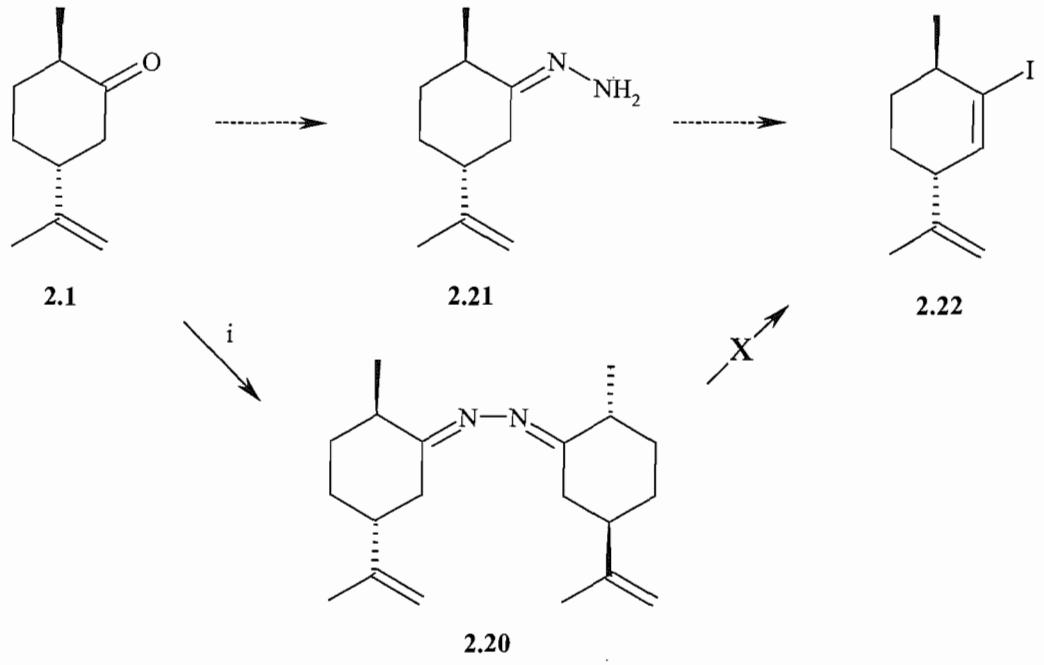
Although encouraging results were obtained, the yields of alcohol **2.18** were still unsatisfactory. Therefore, we contemplated other ways in which the vinyllithium species could be accessed *in situ*.

ii. *via* vinyl iodides

Vinyllithiums can easily be accessed from vinyl iodides by a halogen-metal exchange reaction. Therefore, investigation into the formation of vinyl iodides was carried out.

a) Hydrazones

Several ways to access vinyl iodides from ketones have been reported. For instance, converting ketone **2.1** to the corresponding hydrazone **2.21**, could open up many ways into the corresponding vinyl iodides **2.22**.[26-28] Again, however, we were quickly stopped in our attempts since treatment of dihydrocarvone **2.1** with hydrazine yielded the hydrazone dimer **2.20** (Scheme 2.5).



2.1 **2.21** **2.22**

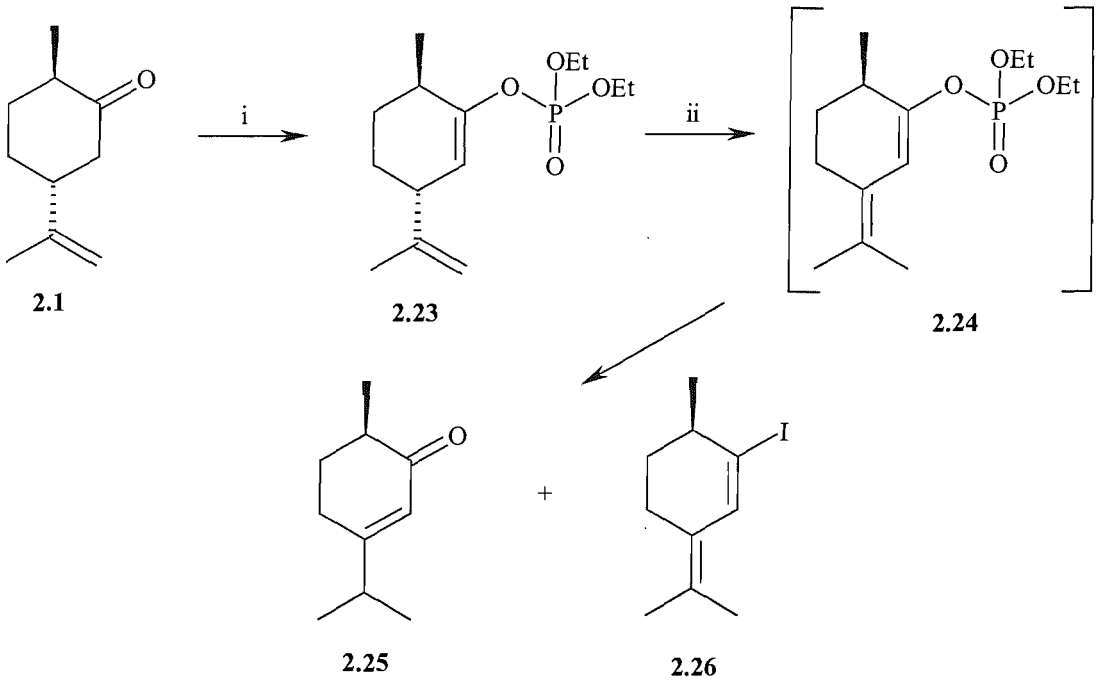
2.20

Reagents/Conditions: i) $N_2H_4.H_2O$, Et_3N, EtOH, 100 °C, 60h, 40%.

Scheme 2.5

b) Vinyl phosphonates

Vinyl phosphonates upon treatment with TMSI have been reported to undergo transformation to the corresponding vinyl iodides.[29] Thus, phosphonate **2.23** was synthesised by treatment of ketone **2.1** with LDA, followed by quenching with diethyl chlorophosphate. Upon treatment of **2.23** with TMSI (generated *in situ*), our observations revealed a migration of the terminal double bond and that the α,β-unsaturated ketone **2.25** and conjugated vinyl iodide **2.26** had been formed in a 2:1 ratio.



Reagents/Conditions: i) preformed LDA, THF, -78 °C, 3h, then diethylchlorophosphate, -78 °C to RT, 16h, 52%; ii) NaI, TMSCl, MeCN, 15min, 98%.

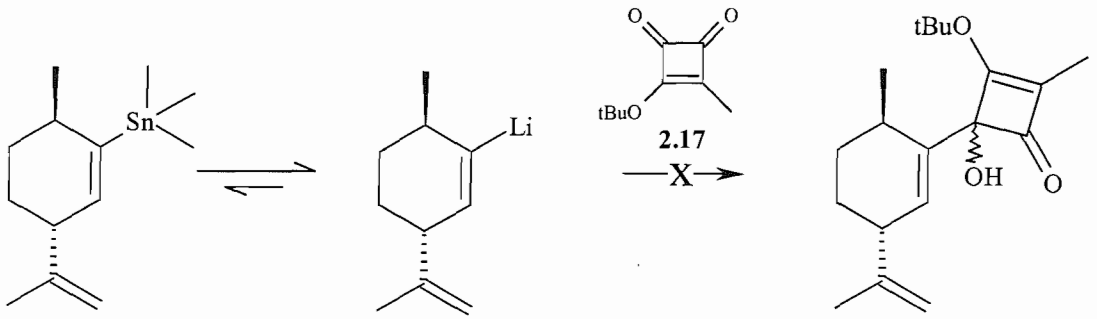
Scheme 2.6

These observations could be rationalised by the formation of intermediate **2.24**. TMSI being a powerful Lewis acid, migration of the double bond to the more favourable isomer **2.24** occurred. "De-phosphorylation" or iodination could then ensue, leading to the formation of ketone **2.25** and iodide **2.26** respectively.

c) Vinyl stannanes

Following a string of disappointing results, our attention turned to vinyl stannanes as precursors to vinyl iodides. Thus, dihydrocarvone **2.1** was converted to the corresponding thermodynamic vinyl triflate **2.27 A**. A palladium-catalysed cross-coupling reaction between triflate **2.27 A** and hexamethylditin furnished stannane **2.28** in good yield (Scheme 2.8).

We were surprised to find that direct lithiation of the vinylstannane **2.28** using methyl lithium, *n*-butyllithium or even *t*-butyllithium failed to give the characteristic colour change and that only unreacted starting material was recovered. As the reaction ought to be thermodynamically favourable, we presume that it is too slow to be practicable for our purposes (Scheme 2.7).

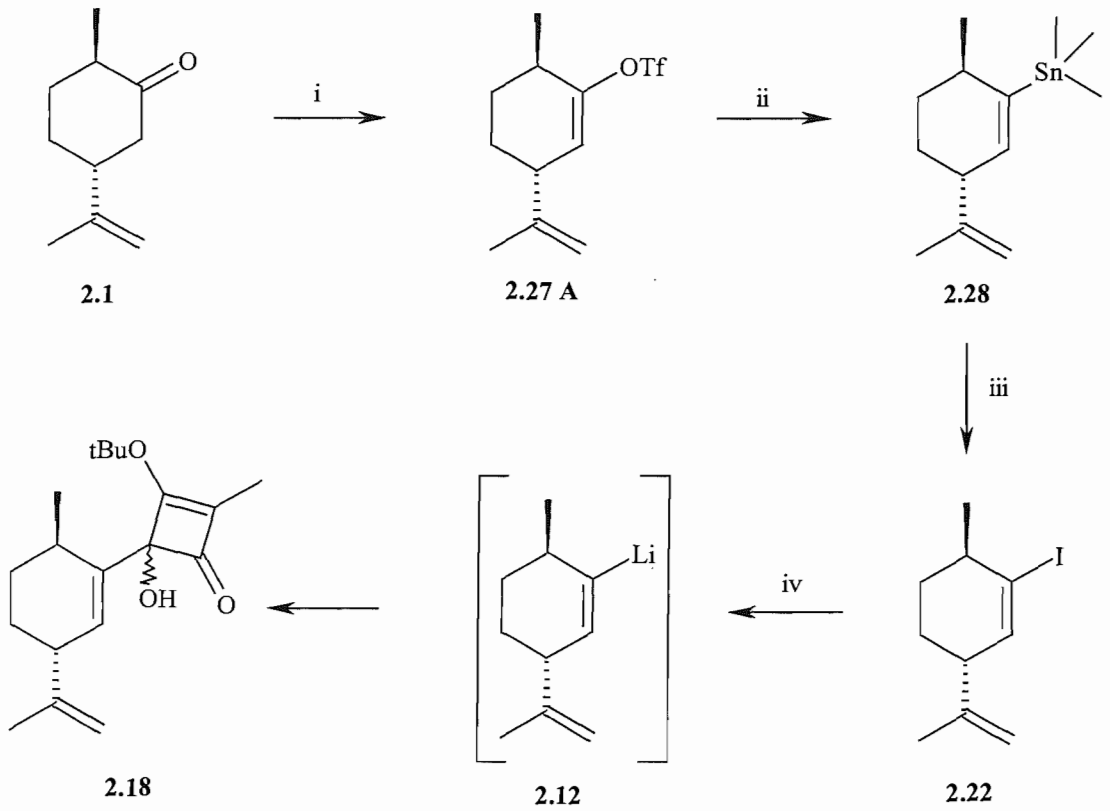


2.28 + RLi ⇌ **2.12** + $RSnMe_3$

2.12 + **2.17** → **2.18**

Scheme 2.7

In the hope of generating alcohol **2.18**, direct treatment of vinyl stannane **2.28** with $BF_3.OEt_2$ and the electrophile **2.17** in DCM was attempted. However, this method also failed to give us the desired allylic alcohol **2.18**. Eventually, it was found that iodination of **2.28** followed by lithium-halogen exchange did indeed yield the vinyllithium **2.12** *in situ*. Quenching with squarate **2.17** finally provided the bis-allylic alcohol **2.18** in good yields (Scheme 2.8).



Reagents/Conditions: i) preformed LDA, THF, -78 °C, 1.5h then N-phenyltrifluoromethanesulfonimide **2.51**, -78 °C to RT, 16h, 61%; ii) Sn_2Me_6, $Pd(PPh_3)_4$, LiCl, THF, reflux, 16h, 71% (+16% RSM); iii) I_2, DCM, RT, 1h, 99%; iv) *t*-BuLi, THF, -78 °C, 1.5h then squarate **2.17**, THF, -78 °C to RT, 30 min., 69%.

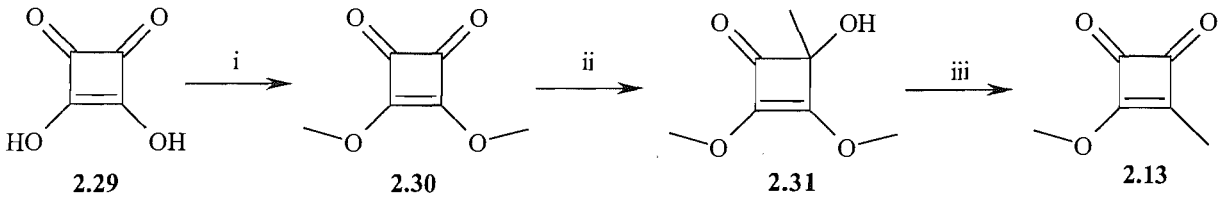
Scheme 2.8

Although the sequence to alcohol **2.18** was lengthened, the reliability of the chemistries combined with an improvement in the yields represented a great advantage over the Shapiro reaction.

II.2 - Squarate

i. Methyl squarate

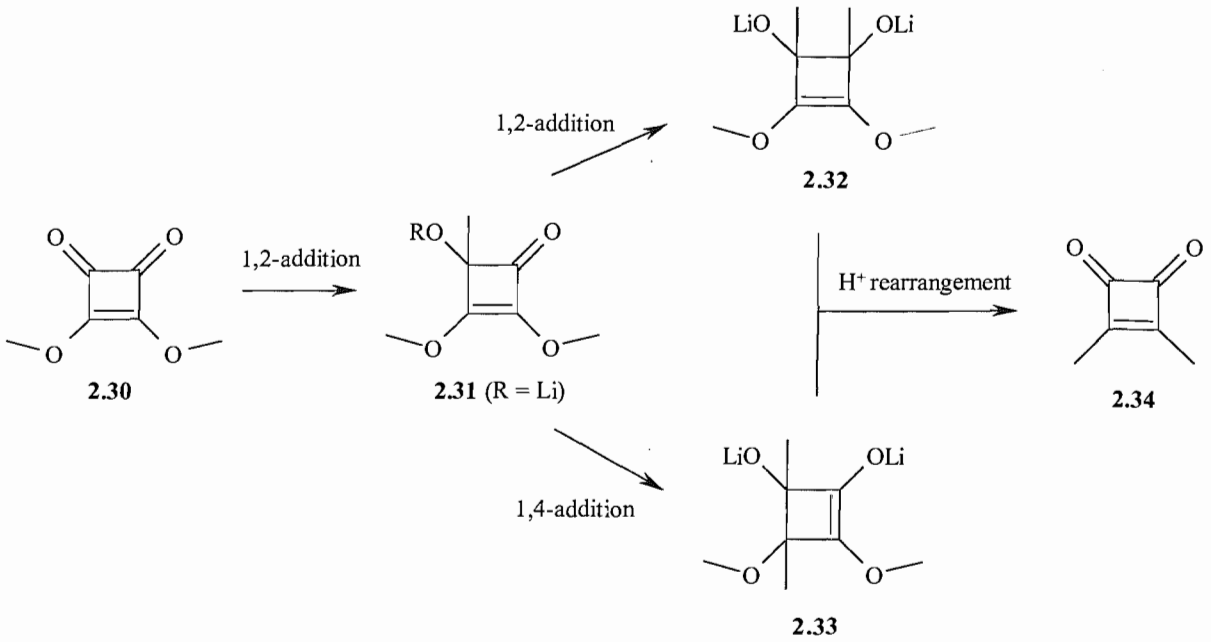
Our initial approach was to use squarate **2.13** as the electrophile for the Shapiro reaction. Dimethyl squarate **2.30** was synthesised in moderate yield (50%) by refluxing squaric acid **2.29** in methanol and toluene under azeotropic removal of water. The yield could be optimised by repetitive removal of the azeotrope, thus pushing the equilibrium in favour of the desired diester **2.30**. Treatment of **2.30** with methyllithium yielded alcohol **2.31** (32%) and the acid catalysed rearrangement gave product **2.13** in an overall 17% yield (Scheme 2.9).



Reagents/Conditions: i) MeOH, toluene, reflux, 16h, 49%; ii) MeLi, THF, -78 °C, 1h, 32%; iii) cHCl, DCM, RT, 1h, 53%.

Scheme 2.9

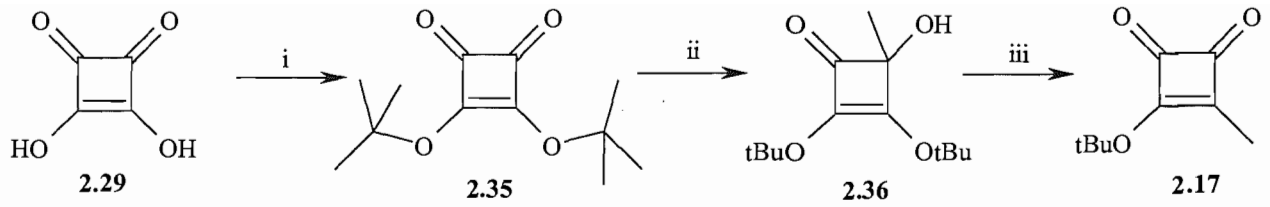
The low yields observed in this sequence could be attributed to two factors. Firstly, the high volatility of these compounds lowered the isolation yields. Also, although strictly one equivalent of the organolithium reagent was used, on several occasions, double 1,2-addition as well as 1,4-addition to diketone **2.30** was observed. The resulting products were not easily separable by column chromatography and on treatment with acid, the unexpected rearrangement product **2.34** was obtained. This could be rationalised by the sequence shown in Scheme 2.10.



Scheme 2.10

ii. *tert*-Butyl squarate

Liebeskind and co-workers encountered similar difficulties and overcame the problem of 1,4-addition by the introduction of bulkier groups.[30] Therefore, our efforts turned to the synthesis of di-*tert*-butyl squarate **2.35** from which diketone **2.17** can be derived. Squarate **2.35** was obtained by refluxing squaric acid **2.29** in *tert*-butanol in the presence of methyl orthoformate. The problem of 1,4-addition of methyllithium on **2.35** was indeed suppressed and after acid-catalysed rearrangement, diketone **2.17** was obtained in 47% overall yield from squaric acid.



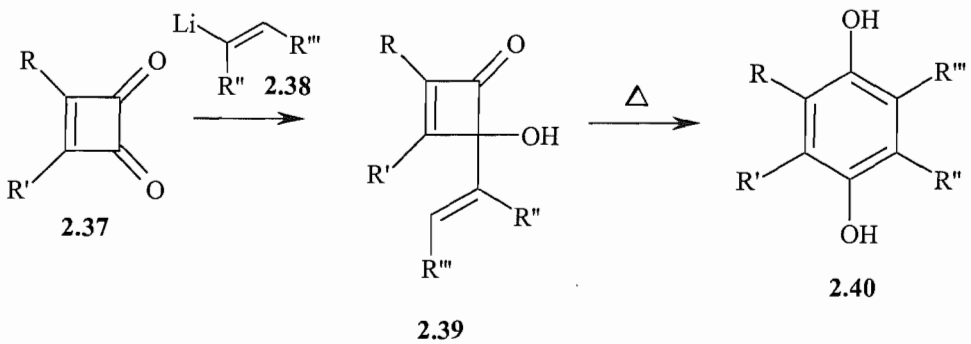
Reagents/Conditions: i) methyl orthoformate, *t*BuOH, reflux, 1h, 70%; ii) MeLi, THF, -78 °C, 1h, 97%; iii) cHCl, DCM, RT, 1h, 69%.

Scheme 2.11

The synthesis of electrophile **2.17** proved extremely facile and represented a clear advantage over that of methyl squarate **2.13**. With foresight, deprotection of a *tert*-butyl ether requires milder conditions than the corresponding deprotection of a methyl ether. The use of *t*-butyl squarate **2.17** may therefore offer a further advantage by greatly facilitating the deprotection step in the late stages of our synthesis of colombiasin A.

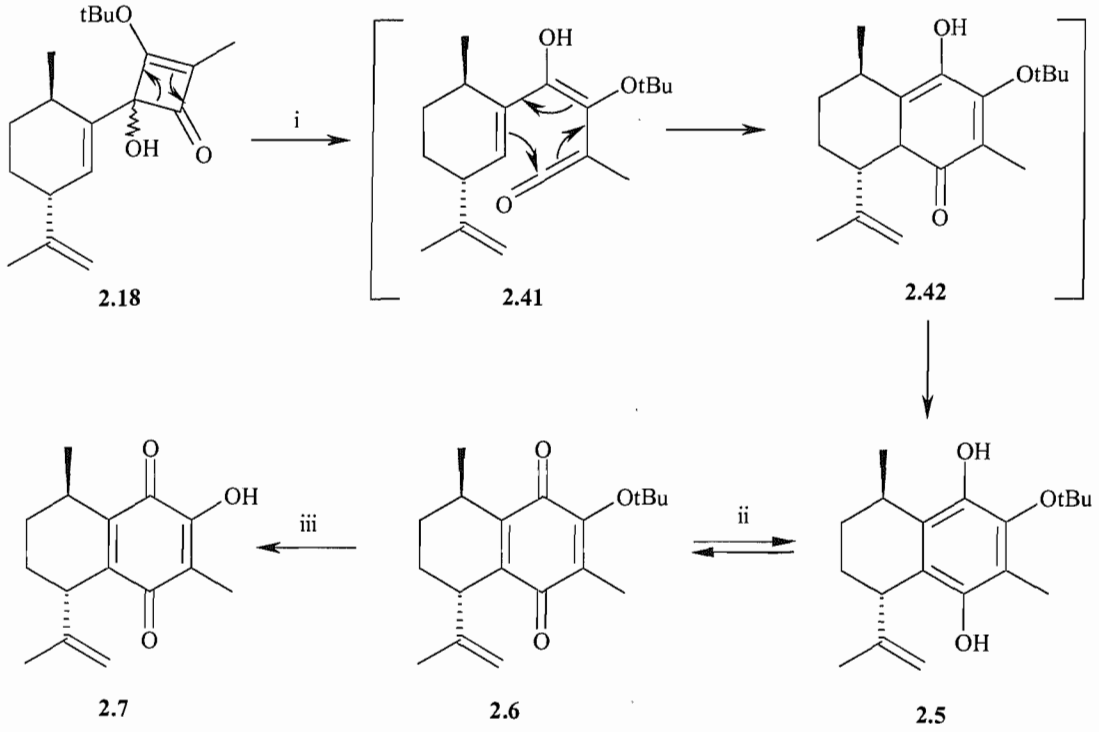
II.3 - Rearrangement and oxidation

In the 1980s, substantial advances in the chemistry of cyclobutenediones and their usefulness in the synthesis of quinones were made by the groups of Liebeskind ,[31-41] and Moore.[42,43] Interestingly, it was shown that addition of alkenyl or aryllithium reagents **2.38** to cyclobutenediones **2.37**, followed by thermolysis, provided a range of highly substituted hydroquinones **2.40** in excellent yields (Scheme 2.12).[25,40]



Scheme 2.12

Having established a route to alcohol **2.18**, we were able to apply the thermal rearrangement reaction, by heating a solution of **2.18** in xylene, or THF (sealed tube) to 130 °C. The reaction proceeded smoothly and in excellent yields (85%), presumably *via* a ketene intermediate **2.41**. It should be noted that although hydroquinone **2.5** was isolated, it was rapidly oxidised to the corresponding quinone **2.6** on standing in air. Indeed, after 24 hours, conversion to quinone **2.6** was complete. Deprotection of **2.6** with titanium tetrachloride concluded our model studies towards the synthesis of hydroxyquinone **2.7** (Scheme 2.13).



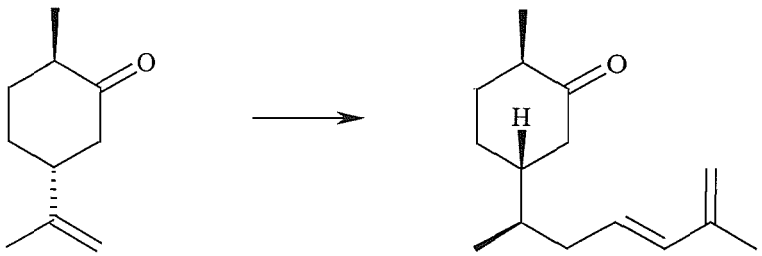
Reagents/Conditions: i) xylene or THF (sealed tube), 130 °C, 25 min, 85%; ii) air, 24h, 100%; iii) $TiCl_4$, DCM, 0 °C, 1 min., 54%.

Scheme 2.13

In summary, although encouraging results were obtained with the Shapiro reaction, we were pleased to have developed a more reliable route to alcohol **2.18** *via* a vinyl iodide intermediate. The thermal rearrangement-oxidation sequence proceeded smoothly and the final Lewis-acid catalysed deprotection concluded our model studies.

CHAPTER III - MODEL STUDIES: SYNTHESIS OF DIENE 3.1

In this chapter, various means to elaborate diene **3.1** from dihydrocarvone **2.1** are described. Explorations of some facets of boron chemistry are discussed, as well as the use of metal-catalysed approaches for C-C bond formation. Finally, the discussion focuses on means by which the new asymmetric centre was introduced in the dienone **3.1** with control of the absolute configuration.



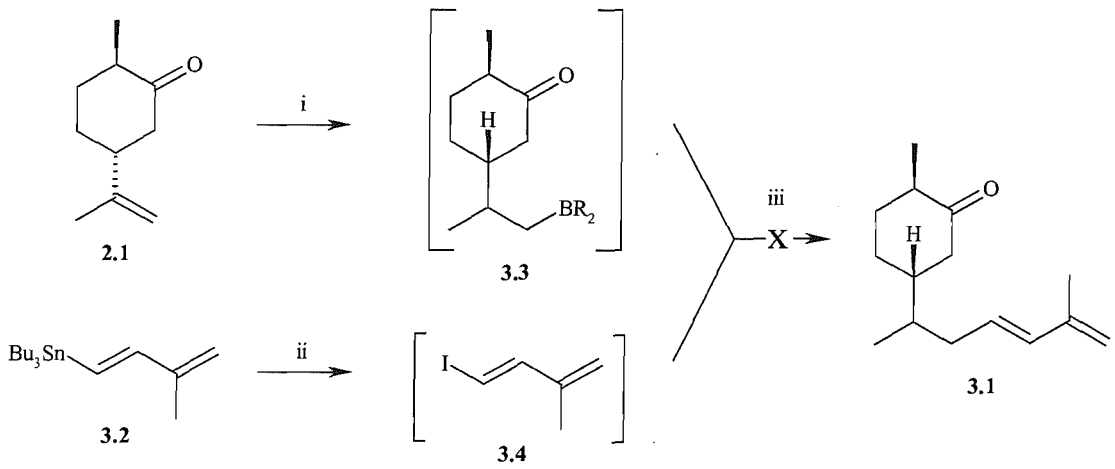
2.1 **3.1**

Scheme 3.1

III.1 - Boron chemistry

i. Suzuki coupling

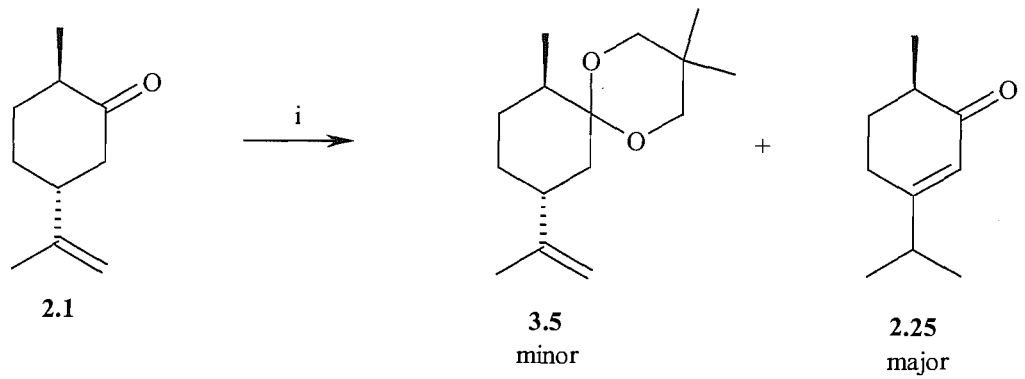
Initial attempts to append the diene moiety in one step by a Suzuki coupling between iodide **3.4** and the hydroborated alkene **3.3** failed to produce the desired product (Scheme 3.2). At first, it was thought that the reaction was undermined by the hydroboration step. Spectroscopic evidence suggested that the ketone moiety instead of the alkene had been reduced. However, even when dihydrocarvone **2.1** was protected as its acetal **3.5** the reaction failed. Also, it was found that vinyl iodide **3.4** was difficult to isolate in a pure state and bypassing its purification gave no success. At this stage, failure could be attributed to a number of parameters including temperature, choice of catalyst, base, solvent, reaction times, etc. We therefore decided to seek a more robust synthesis of diene **3.1** involving more classical transformations.



Reagents/Conditions: i) 9-BBN, THF; ii) I_2, THF; iii) Pd catalyst, base, heat.

Scheme 3.2

It should be noted that, contrary to our expectations, protection of ketone **2.1** as the corresponding acetal **3.5** failed to go in quantitative yields. Indeed, the presence of acid caused migration of the double bond to give the α,β-unsaturated ketone **2.25** majorly (Scheme 3.3).

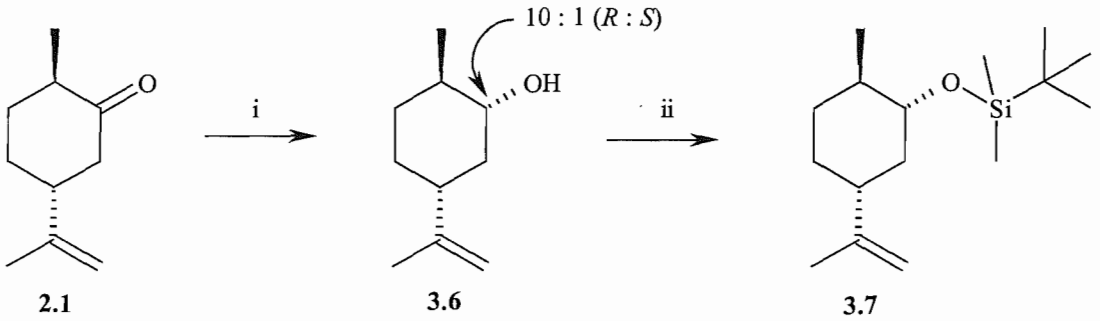


Reagents/Conditions: i) neopentyl glycol, *p*TsOH, toluene, reflux, 16h or neopentyl glycol, TMSCl, toluene, RT, 16h.

Scheme 3.3

This result suggested that ketone **2.1** should be protected as the silyl ether **3.7** to ensure better efficiency in the protection/deprotection step. Reduction of (+)-dihydrocarvone

2.1 with $LiAlH_4$ resulted in a separable mixture of alcohols **(*R*)-3.6** and **(*S*)-3.6** with the product of axial attack **(*R*)-3.6** obtained predominantly (10:1). Protection of **(*R*)-3.6** with tert-butyldimethylsilyl chloride proceeded smoothly and in excellent yields (Scheme 3.4).



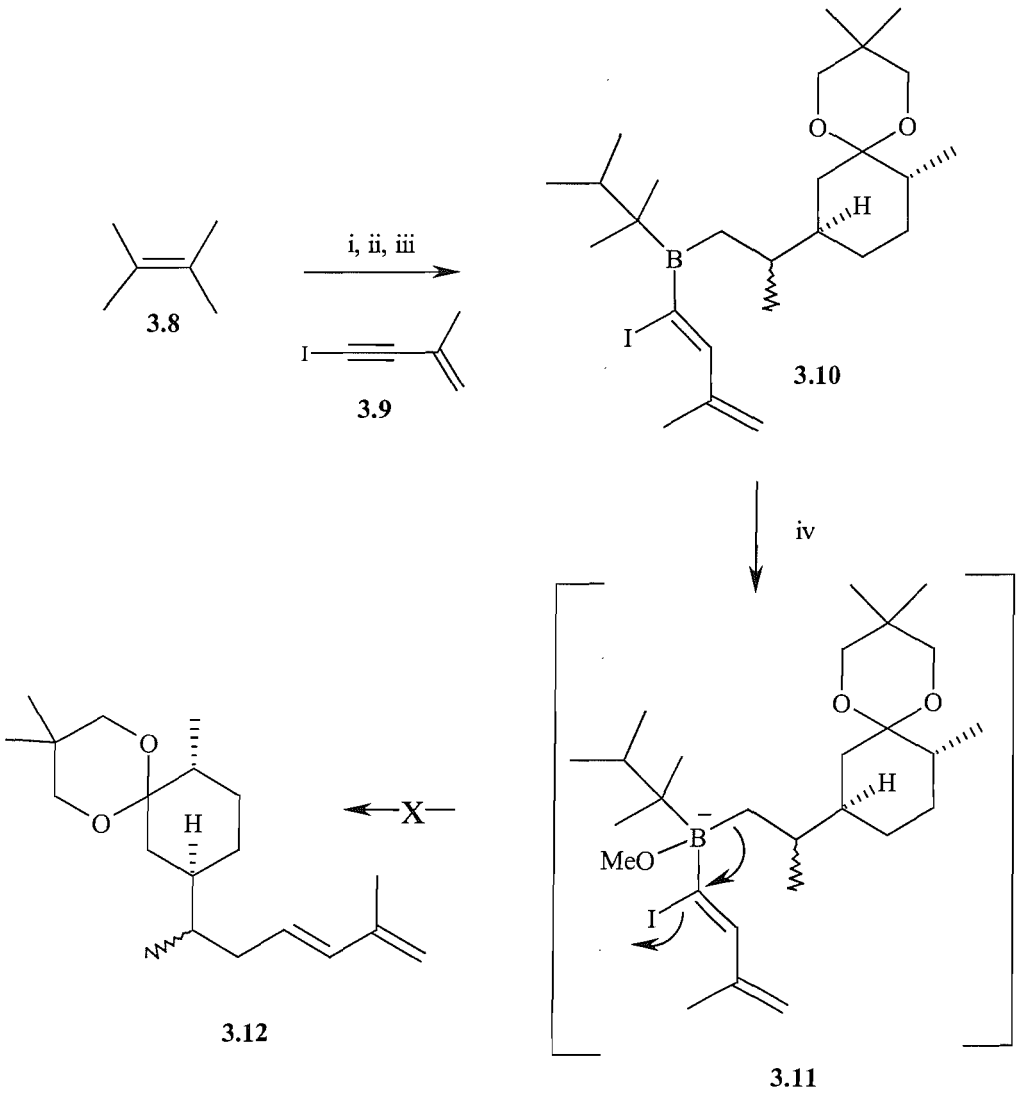
2.1 **3.6** **3.7**

Reagents/Conditions: i) $LiAlH_4$, Et_2O, -78 °C to RT, 30 min., 96%; ii) TBSCl, DMAP, imidazole, DCM, RT, 96h, 99%.

Scheme 3.4

ii. Nucleophilic displacement

Despite low yields, a sufficient amount of acetal **3.5** was synthesised to allow us to attempt the introduction of the diene moiety by other means. Although the Suzuki coupling reaction had failed, further exploitation of boron chemistry developed by Brown *et al.*[44] was attempted on our system. This consisted in sequential hydroboration of halo-alkyne **3.9** and alkene **3.5** with thexylborane in an attempt to bring about their union. It was hoped that activation of the borane **3.10** with sodium methoxide would cause migration of the primary alkyl residue with displacement of the halogen, thus yielding the desired diene **3.12** (Scheme 3.5). However, in our case, the products of the reaction remained unidentified and the approach was ultimately abandoned.



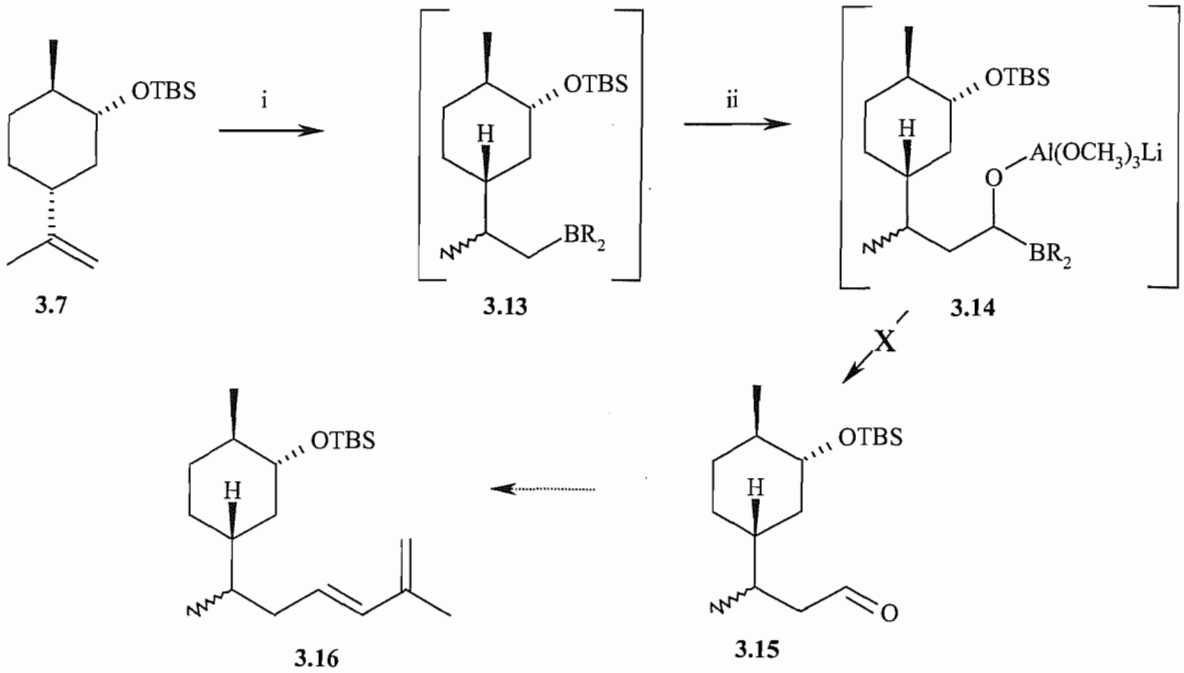
Reagents/Conditions: i) BH_3, THF, 0 °C; ii) **3.5**, THF, -30 °C; iii) preformed **3.9**; iv) NaOMe, -30 °C.

Scheme 3.5

iii. Hydroformylation

At this stage, we considered the use of hydroformylation as a means of introducing an extra carbon unit and the new stereogenic centre. The resulting aldehyde **3.15** could then undergo a Wittig olefination to yield diene **3.16**. A boron-based approach

developed by Brown *et al.*,[45] whereby carbon monoxide inserts in an activated carbon-boron bond only yielded unidentified products (Scheme 3.6).



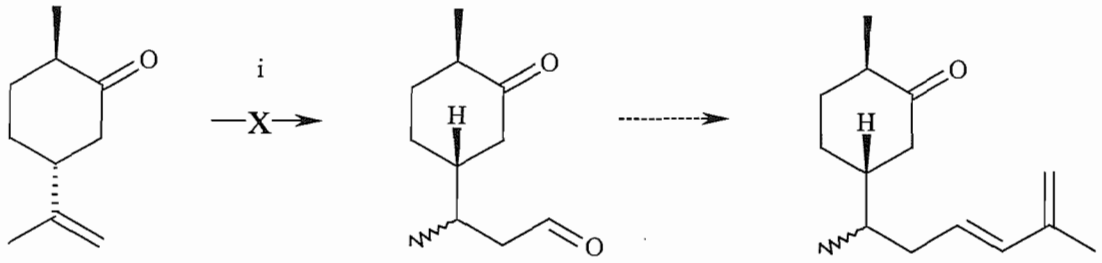
Reagents/Conditions: i) 9-BBN, THF, 0 °C, 1.5h; ii) preformed $LiAlH(OCH_3)_3$, THF, 0 °C; iii) CO, 15 min.

Scheme 3.6

III.2 – Metal-catalysed approaches

i. Hydroformylation

A rhodium-catalysed approach developed by Alper *et al.*[46] for the hydroformylation of alkenes could also provide us with aldehyde **3.17**. However, the method requires relatively high pressures (8 atm) and it was with little surprise that the reaction did not yield the desired aldehyde **3.17** when conducted using an *in situ* method for carbon monoxide generation (Scheme 3.7).



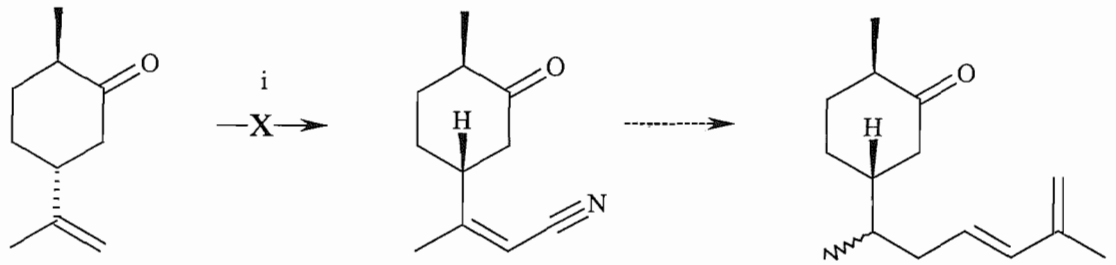
2.1 **3.17** **3.18**

Reagents/Conditions: i) Rh/C (5%), dppp, formic acid, DME, 100 °C, 20h.

Scheme 3.7

ii. Cross-metathesis

A cross-metathesis reaction between (+)-dihydrocarvone **2.1** and acrylonitrile was attempted using Grubb's catalyst but no reaction was observed (Scheme 3.8). Variants on Grubb's catalyst have been reported to catalyse cross-metathesis reactions,[47,48] but the cost of these, as well as the scarcity of reported applications, led us to seek an alternative methodology.



2.1 **3.19** **3.18**

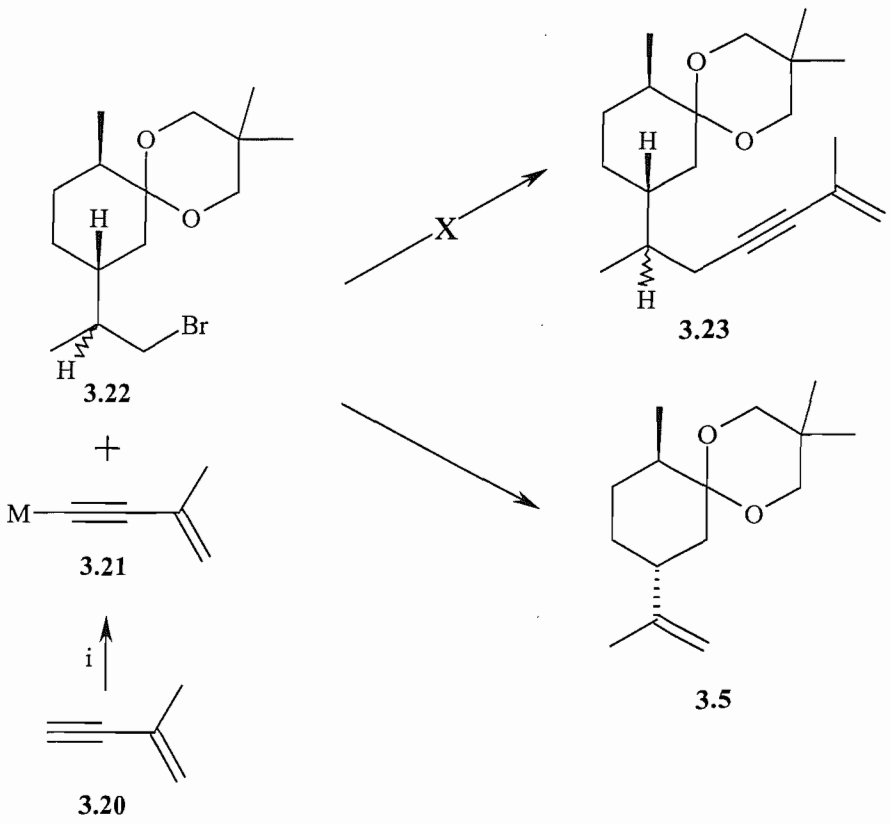
Reagents/Conditions: i) tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (5%), acrylonitrile (5 eq.), RT, 16 hours or Grubb's II, 40 °C, 48h.

Scheme 3.8

III.3 – Nucleophilic displacement

i. Bromide

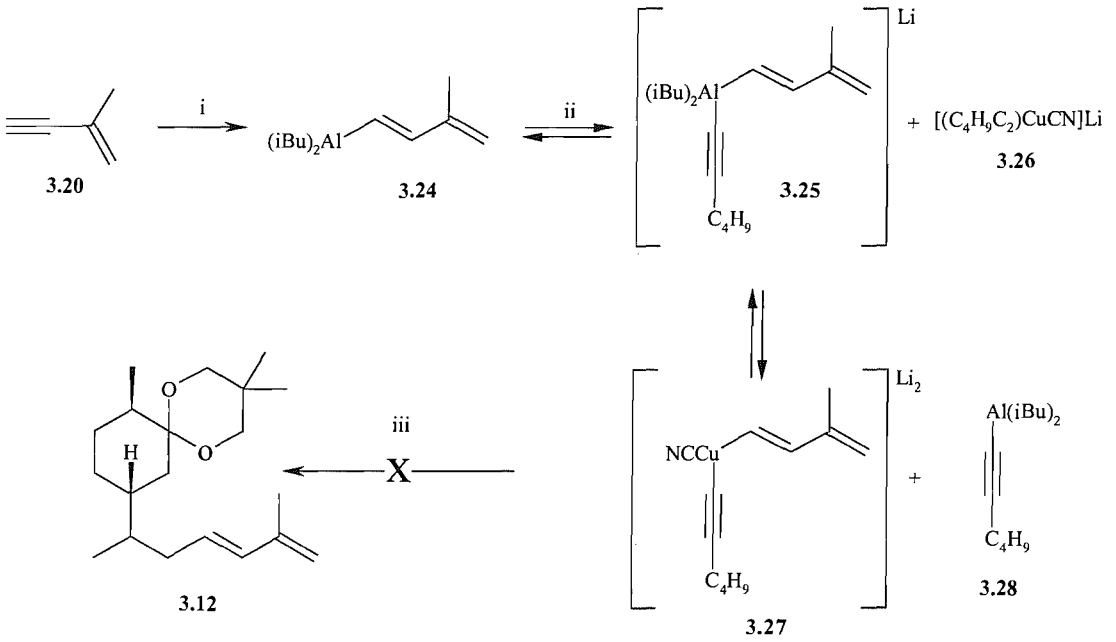
The approach adopted at this stage was to convert alkene **3.5** to the corresponding primary alkyl bromide **3.22** which could then undergo a nucleophilic displacement. Anti-Markovnikov addition of HBr across alkene **3.5** was achieved *via* a two-step process. Hydroboration followed by treatment with bromine and sodium methoxide yielded alkyl bromide **3.22** in 35% yield as an inseparable mixture of diastereomers. The alkyne anion **3.21** generated by treatment of **3.20** with either butyllithium or a Grignard reagent failed to displace the bromide and, under extended reaction times resulted in elimination to yield alkene **3.5** (Scheme 3.9).



Reagents/Conditions: i) *n*BuLi or *t*BuLi or EtMgBr then **3.22**. (M = Li or MgBr)

Scheme 3.9

In order to "soften" the alkyne anion, a method developed by Wipf *et al.*[49] was attempted. Hydroalumination of alkyne **3.20** followed by transmetallation to the corresponding copper(I) salt **3.27** and treatment with alkyl bromide **3.22**, should yield diene **3.12** (Scheme 3.10). Again, however, the reaction did not yield the desired product. These results suggested that the alkyl bromide was unreactive towards nucleophilic attack and conversion to a better leaving group was then sought.



Reagents/Conditions: i) DIBAL-H, hexane, 0 °C then 60 °C, 2h; ii) preformed $[(C_4H_9C_2)_2CuCN]Li_2$, -25 °C; iii) **3.22**, THF, -25 °C.

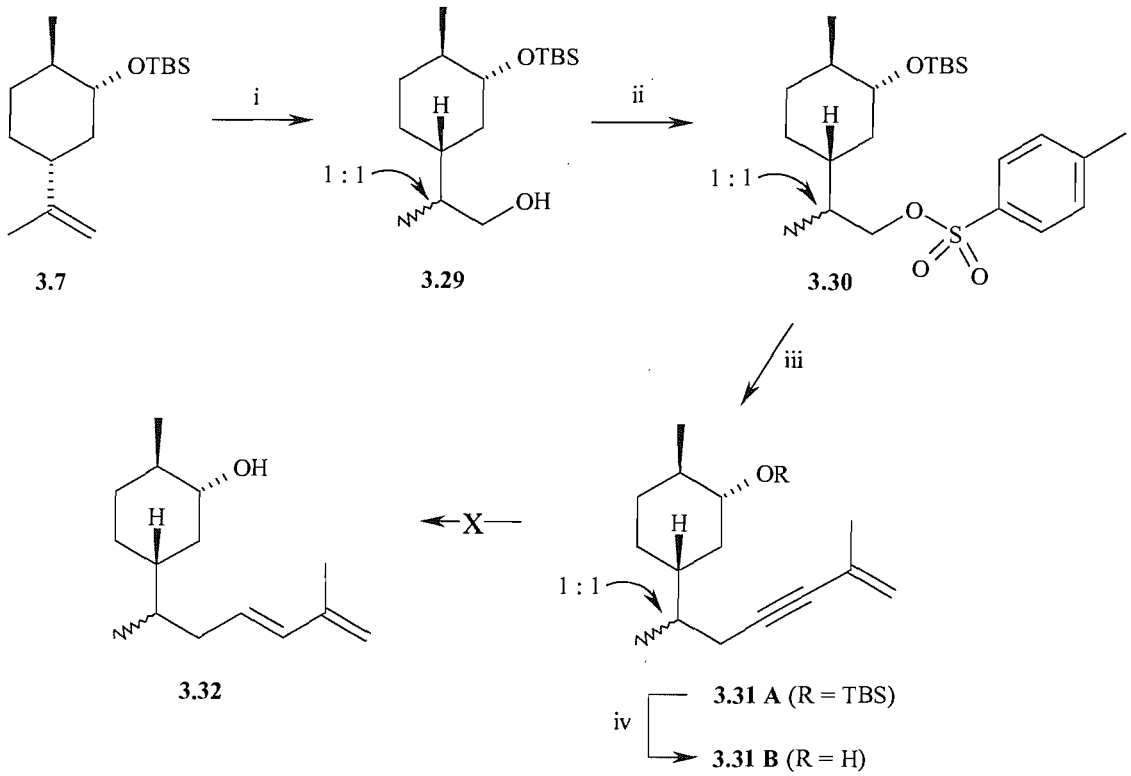
Scheme 3.10

ii. Tosylate

Having protected (+)-dihydrocarvone **2.1** as the corresponding silyl ether **3.7** (Scheme 3.4), hydroboration of alkene **3.7**, followed by oxidation, yielded primary alcohol **3.29** in excellent yield as a 1:1 inseparable mixture of diastereoisomers. Conversion to the corresponding tosylate **3.30**, proceeded smoothly and it was found that addition of alkyne anion **3.21** in DMSO, yielded enyne **3.31 A** in good yield (60% + RSM,

Scheme 3.11). Interestingly, when switching to THF as the solvent, the reaction failed, returning only unreacted starting material.

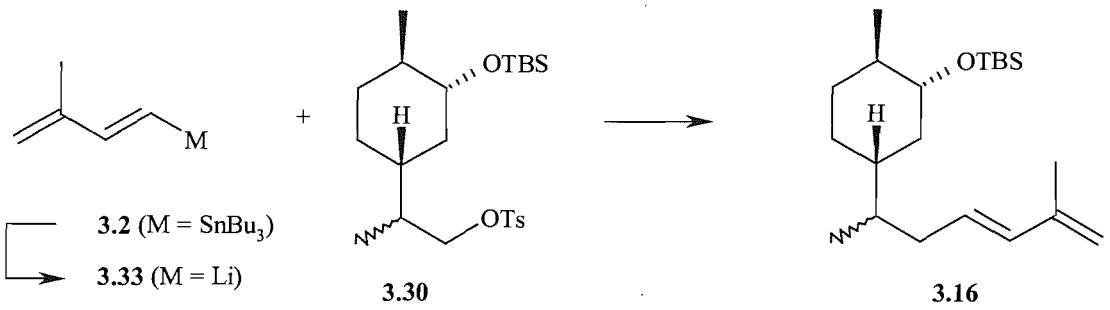
Having appended the 5-carbon extension needed, reduction of the alkyne moiety remained to be performed. Reports of reduction of alkynes to alkenes using a hydride source led us to treat protected alcohol **3.31 A** and alcohol **3.31 B** with $LiAlH_4$ and DIBAL-H.[50,51] However, even under extended reaction times, and elevated temperatures the alkyne remained untouched. Reduction using H_2 and a poisoned palladium catalyst (Lindlar's catalyst) led to a myriad of overreduced products. These were copolar and could not be isolated in a pure state.



Reagents/Conditions: i) BH_3.DMS, THF, 0 °C, 2h, then NaOH, H_2O_2, 0 °C to RT, 16h, 88%; ii) TsCl, Et_3N, DCM, RT, 48h, 75%; iii) preformed **3.21**, DMSO, RT, 1h, 60% (+RSM); iv) TBAF, THF, RT, 72h, 95%.

Scheme 3.11

Encouraged by the S_N2 reaction observed on **3.30**, we hoped to effect the nucleophilic displacement using vinyl anion **3.33**, thus leading to diene **3.16** (Scheme 3.12). With vinyl stannane **3.2** in hand, we were able to attempt the displacement using various reaction conditions (Table 3.1).



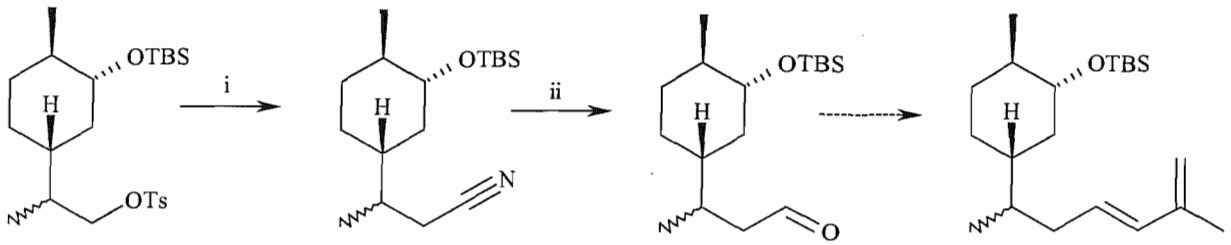
Scheme 3.12

Again, however, only unreacted starting material was recovered, accompanied in some cases with alcohol **3.29**. Although the use of DMSO as a solvent had given positive results in the case of the alkyne anion **3.21**, it was readily deprotonated by the vinyl anion **3.33**. Switching to THF as the solvent left the tosylate **3.30** unaffected, even when anion **3.33** was pre-treated with copper cyanide (Table 3.1).

Reaction conditions	Product
i) **3.2**, *n*BuLi, THF, -78 °C ii) **3.30** in DMSO	RSM
i) **3.2**, *n*BuLi, THF, -78 °C ii) **3.30** in THF	RSM + alcohol **3.29**
i) **3.2**, *n*BuLi, THF, -78 °C ii) CuCN iii) **3.30** in THF	RSM + unidentified product

Table 3.1

Disheartened by our slow progress we decided to focus on a more classical way of introducing the side-chain. With tosylate **3.30** in hand, we were able to effect a cyanide displacement to yield nitrile **3.34**. Reduction with DIBAL-H next furnished aldehyde **3.15** which could be coupled to a 4-carbon unit by means of a Wittig reaction or a Julia coupling to give diene **3.16** (Scheme 3.13).



3.30 **3.34** **3.15** **3.16**

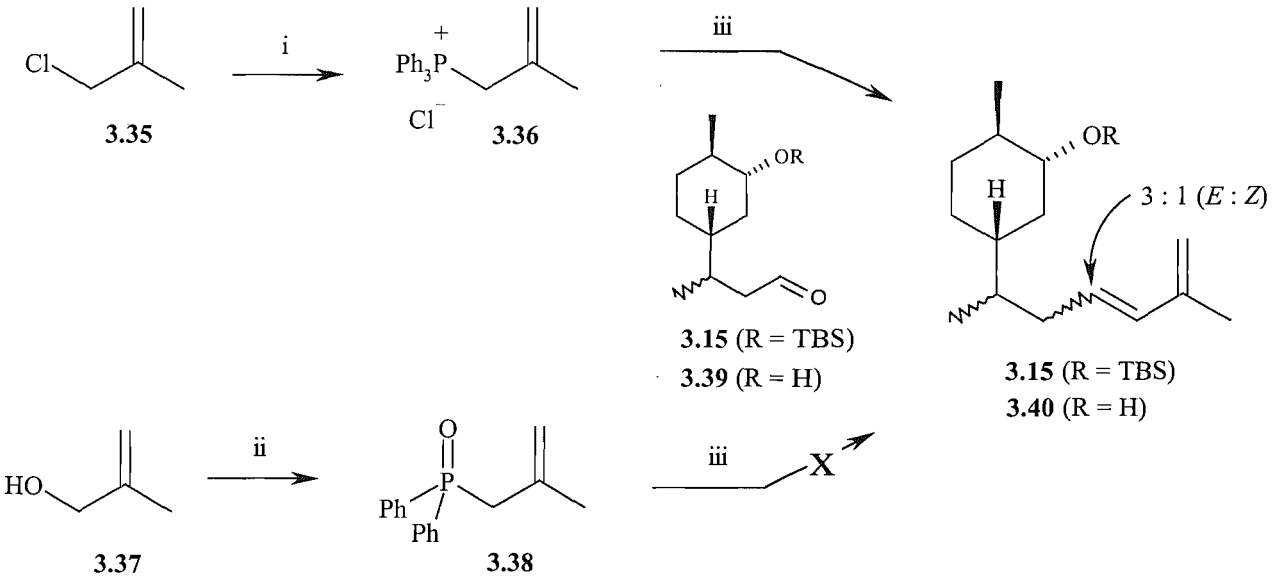
Reagents/Conditions: i) NaCN, DMSO, 90 °C, 1h, 99%; ii) DIBAL-H, toluene, 0 °C then HCl, RT, 1h, 75%.

Scheme 3.13

a) Wittig olefination

Phosphonium salt **3.36** has been used extensively as a building block in natural product synthesis. It is easily prepared by treatment of methallyl chloride **3.35** with triphenylphosphine. In our case, formation of the corresponding ylid using *n*BuLi or *t*BuOK, followed by addition of aldehyde **3.15** yielded diene **3.16** in modest yield (45%) as a 3:1 mixture of (*E*)- and (*Z*)-isomers. The yields were considerably reduced when the reaction was performed on the free alcohol **3.39**.

In an attempt to improve both the yields and *E*:*Z* selectivity, we looked at a Horner-Wadsworth-Emmons variant using phosphine oxide **3.38** (Scheme 3.14). Unfortunately, in our case, no significant improvement was observed. This could be due to side-reactions that can occur when hydroxy-aldehyde **3.39** is treated with a base (*e.g.* aldol and Cannizzarro reactions). Protection of the alcohol may have improved the outcome of the reaction. However, a more appealing alternative was contemplated at this juncture.

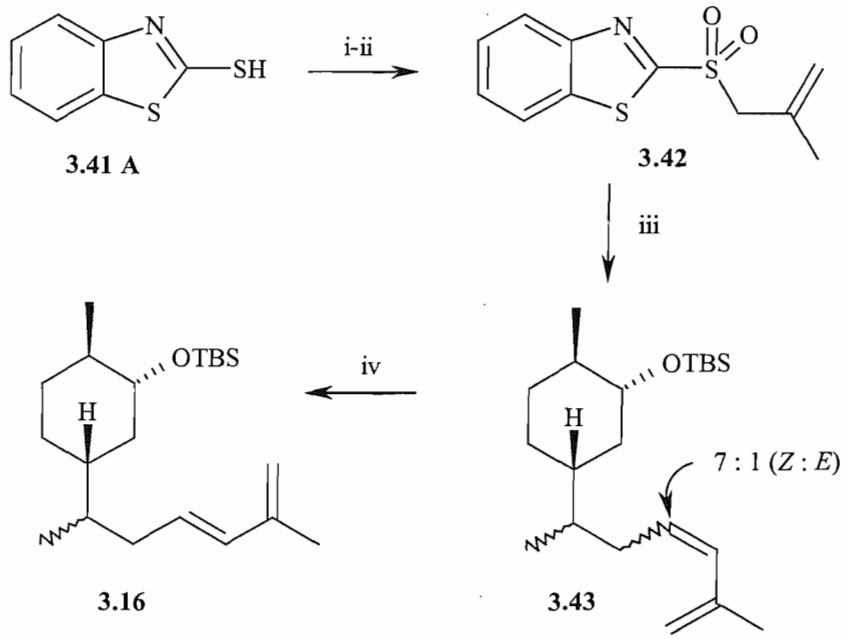


Reagents/Conditions: i) PPh_3, toluene, reflux, 16h, 73%; ii) chlorodiphenylphosphine, pyridine, ether, RT, 1h, 48%; iii) *n*BuLi or *t*BuOK, THF, then **3.39**, THF.

Scheme 3.14

b) Kocieński-Julia coupling

The Kocieński-Julia olefination process provides a useful alternative to phosphine-based olefination reactions and makes use of benzothiazole sulfones.[52] Sulfone **3.42** was easily accessible from mercaptothiazole **3.41 A** in two steps. Generation of the corresponding carbanion with NaHMDS and exposure to aldehyde **3.15** furnished diene **3.43** in good yields (70-90%) and selectivity (7:1, *Z*:*E*). Notably, the selectivity was the reverse of that obtained using the Wittig protocol, the *cis* isomer being formed as the major product. For the purpose of our synthesis, iodine-catalysed isomerisation was used to convert this material into the *trans* isomer **3.16** (Scheme 3.15).

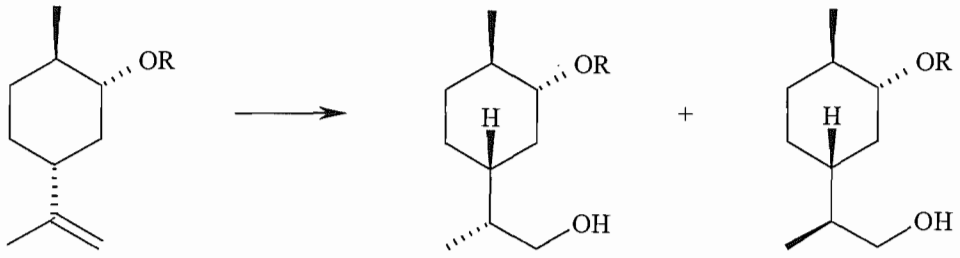


Reagents/Conditions: i) NaOMe, methallyl chloride, MeOH, RT, 4h, 91%; ii) $(NH_4)_6Mo_7O_{24}.4H_2O$, H_2O_2 (30% aq.), EtOH, 0 °C, 20h, 69%; iii) NaHMDS, DME, -50 °C, 1.5h then **3.15**, DME, -50 °C to RT, 14h, 96%; iv) I_2 (1%), $CHCl_3$, RT, 1.5h, 75%.

Scheme 3.15

III.4 – Asymmetric induction

Having established a reliable route to diene **3.16**, we focussed our attention on installing the correct stereochemistry at the C7 centre. The first step in the sequence employed a hydroboration-oxidation reaction to give diols **3.45** and **3.46**. We hoped that the use of a homochiral hydroborating agent would allow us to induce some selectivity in the formation of the new stereogenic centre (Scheme 3.16).



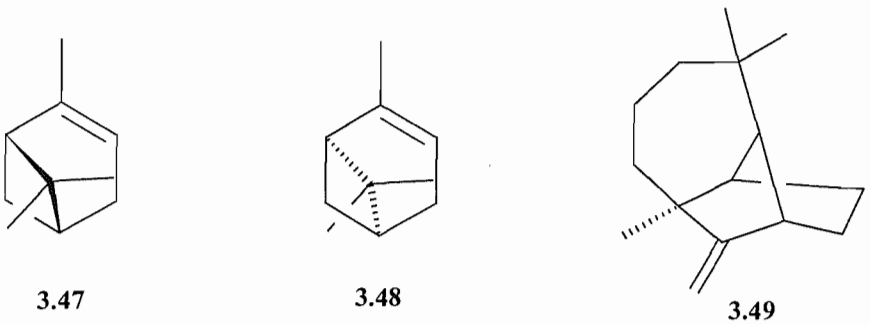
3.7 (R = TBS)
***(R)*-3.6** (R = H)

3.45

3.46

Scheme 3.16

Using both isomers of α-pinene **3.47** and **3.48**, and (+)-longifolene **3.49**, we were able to prepare the corresponding hydroborating agents, i.e. (+)-Ipc_2BH, (-)-Ipc_2BH and (+)-$(Lgf)_2BH$ respectively. Trials on various substrates showed that the use of (+)-$(Ipc)_2BH$ on ***(R)*-3.6** led to a 2.3:1 mixture of desired and undesired diastereoisomers **3.46** and **3.45** respectively (Table 3.2)



3.47

(+)-alpha-pinene

3.48

(-)-alpha-pinene

3.49

(+)-longifolene

Hydroborating agent	R group	Ratio 3.45 : 3.46
BH_3.DMS	TBS	1:1
BH_3.DMS	H	1:1
$(Lgf)_2BH$	TBS	1:1
$(Lgf)_2BH$	H	poor reaction
(+)-$(Ipc)_2BH$	TBS	1:2 (inseparable)
(+)-$(Ipc)_2BH$	H	1:2.3 (separable)
(-)-$(Ipc)_2BH$	TBS	1:1
(-)-$(Ipc)_2BH$	H	1:1

Table 3.2

The advantage of carrying out the reaction on ***(R)*-3.6** is that the diastereoisomers could be separated by repetitive careful chromatography. Being crystalline products, we were able to identify by X-ray crystallography the relative stereochemistry of diastereoisomers **3.45** and **3.46**. Pleasingly, we found that the major isomer **3.46** (R = H) had the correct relative configuration for the synthesis of (+)-colombiasin A (Figures 3.1 and 3.2).

Although the mechanism of asymmetric induction was not fully understood, we established that it was both substrate and reagent dependent. Indeed, treatment of alcohol ***(S)*-3.6** with (+)-Ipc_2BH did not yield the corresponding diols selectively, nor did (-)-isopinocampheylborane exhibit an equal and opposite effect.

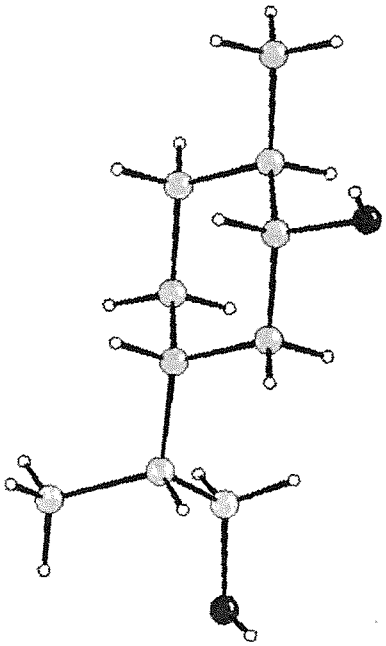


Figure 3.1

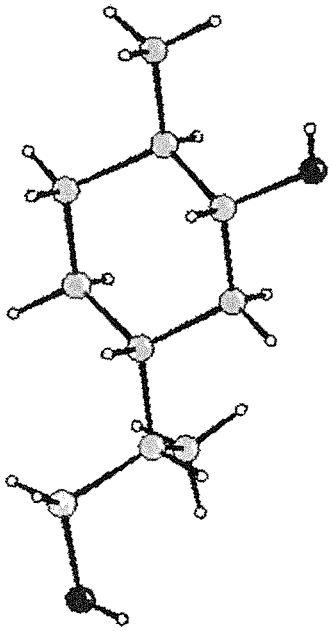
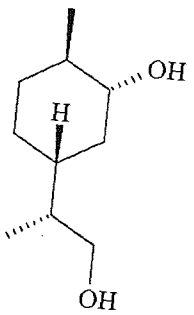
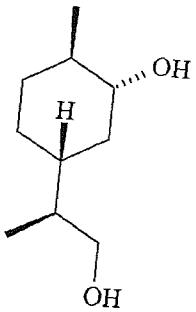


Figure 3.2



3.45

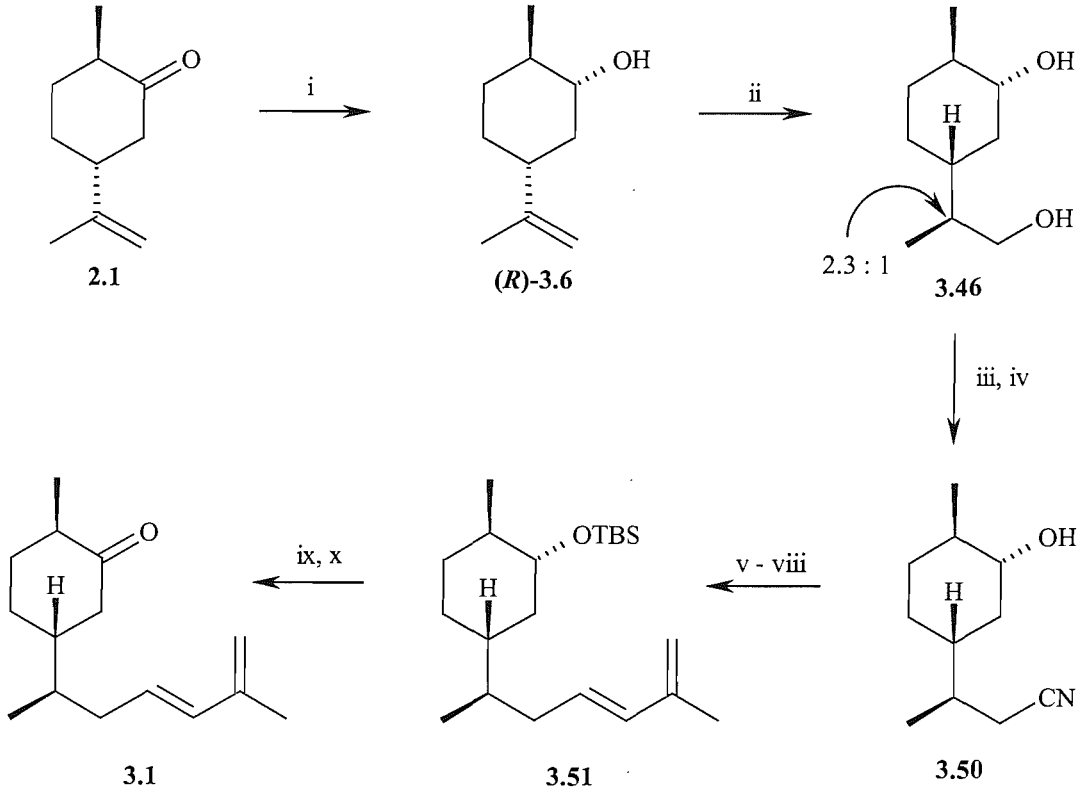
minor



3.46

major

In summary, we have developed an asymmetric route to diene **3.1** from (+)-dihydrocarvone **2.1**. A small sacrifice in terms of length has been compensated by the reliability and high yields in all steps (Scheme 3.16).



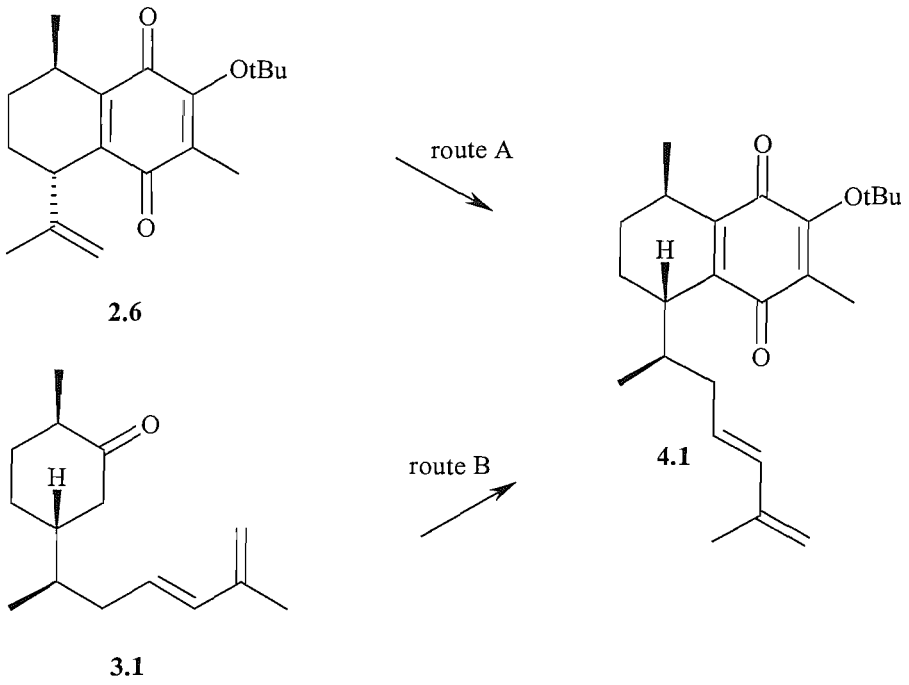
Reagents/Conditions: i) lithium aluminium hydride, Et_2O, -78 °C to 0 °C, 80%; ii) preformed (+)-$(Ipc)_2BH$, RT, 2h, then NaOH, H_2O_2, 0 °C to RT, 16h, 93%; iii) TsCl, NEt_3, DCM, RT, 96h, 85%; iv) NaCN, DMSO, 90 °C, 99%; v) TBSCl, imidazole, DMAP, DCM, RT, 96h, 99%; vi) DIBAL-H, toluene, 0 °C, 1h, then HCl (2M aq.), $CHCl_3$, RT, 1h, 75%; vii) **3.42**, NaHMDS, DME, -50 °C, 1.5h, then **3.15**, DME, -50 °C to RT, 14h, 96%; viii) I_2 (1%), $CHCl_3$, 1.5h, 75%; ix) TBAF (5 eq.), THF, RT, 48h, 99%; x) DMP, DCM, 0 °C to RT, 1h, 80%.

Scheme 3.16

CHAPTER IV – COLOMBIASIN A: THE LAST STEPS

IV.1 - Synthesis of quinone 4.1

Having successfully completed our model studies, we needed to establish the best route to quinone **4.1**. With foresight, elaborating the diene side-chain onto quinone **2.6** would require some preliminary protection due to the nucleophilicity of the reagents used in the sequence (route A, Scheme 4.1). Similarly, formation of quinone **4.1** from dienone **3.1** (route B, Scheme 4.1), requires careful planning due to the sensitivity of the diene functionality.

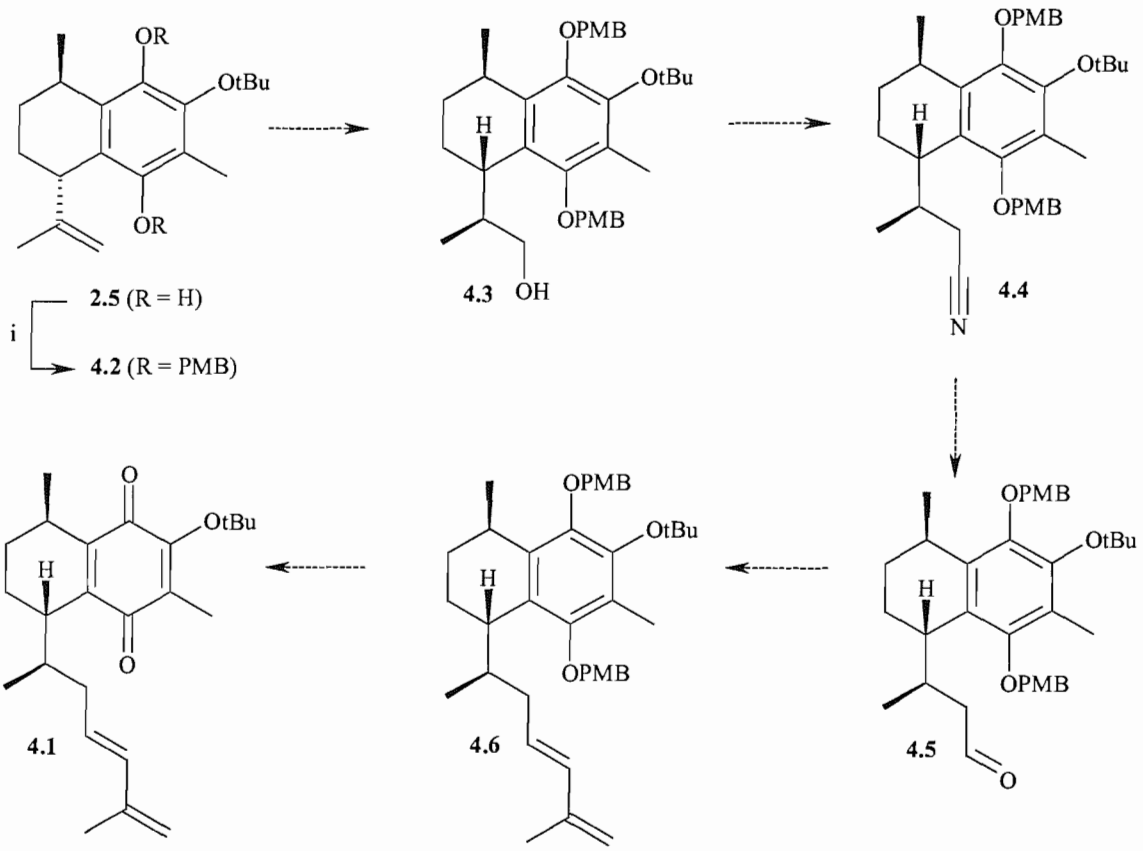


Scheme 4.1

i. Route A

With quinone **2.6** in hand, we envisaged applying the sequence depicted in Scheme 4.2 for the appendage of the side-chain. However, we anticipated that complications would arise right from the initial hydroboration step, since ketones are prone to react with

hydroborating agents. Further in the sequence, the use of sodium cyanide could also create unwanted side-reactions (*e.g.* cyanohydrin formation), not to mention the complications that could arise from the Julia olefination process. It was therefore thought that protection of quinone **2.6**, or its precursor - hydroquinone **2.5**, would be a necessary preliminary step for the successful installation of the diene side-chain (Scheme 4.2).



Reagents/Conditions: i) NaH, PMBBr, TBAI, -10 °C to RT, 20h, 90% (+10% RSM).

Scheme 4.2

The advantage of using *para*-methoxybenzyl (PMB) protecting groups is their easy removal by DDQ, which, after side-chain elaboration, would simultaneously oxidise the resulting hydroquinone to the corresponding quinone **4.1**. As shown in Table 4.1, protection of hydroquinone **2.5** proceeded smoothly and in excellent yield. However, synthesis of *para*-methoxybenzyl bromide by reaction of the corresponding alcohol

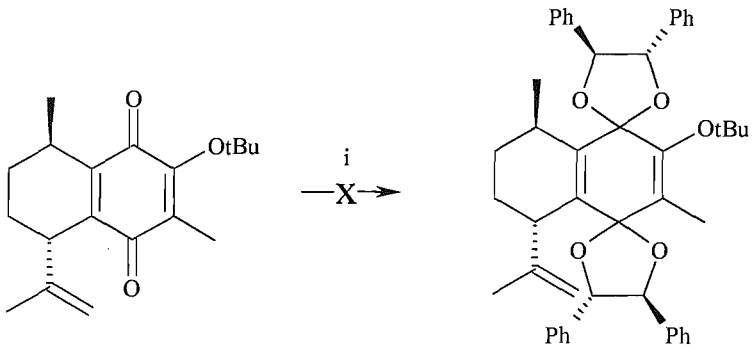
with phosphorus tribromide was compromised by its rapid decomposition at ambient temperature. Attempting the protection with *para*-methoxybenzyl chloride, hydroquinone **2.5** readily oxidised to the corresponding quinone **2.6**. This could be attributed to the lower reactivity of *p*-methoxybenzyl chloride, thus allowing the oxidative process to compete with the protection step. In an attempt to overcome this problem, the hydroquinone-quinone mixture was subjected to hydride reduction ($LiAlH_4$) in the presence of *p*-methoxybenzyl chloride. However, although oxidation of hydroquinone **2.5** was prevented, protection was not observed.

Another approach was to effect the thermal rearrangement of alcohol **2.18** in the presence of PMBCl and sodium hydride. This way, the intermediate hydroquinone **2.5** could be trapped as the corresponding PMB ether **4.2**. Disappointingly however, the thermal rearrangement only yielded unprotected hydroquinone **2.5** (Table 4.1).

Starting material	**Reaction conditions**	**Outcome (Yield)**
hydroquinone **2.5** (R = H)	NaH, PMBBr, TBAI	**4.2** (R = PMB) (90%)
hydroquinone **2.5** (R = H)	NaH, PMBCl, TBAI	**2.6** (100%)
quinone **2.6**	$LiAlH_4$, PMBCl	no reaction
alcohol **2.18**	heat, TBAI, PMBCl, NaH	**2.5** (R = H) (85%)

Table 4.1

As an alternative solution, protection of quinone **2.6** as the bis-acetal **4.7** was attempted. The reaction, however, did not meet with the success we had wished (Scheme 4.3).



2.6 **4.7**

Reagents/Conditions: i) diphenylethylene glycol, $BF_3.OEt_2$, DME.

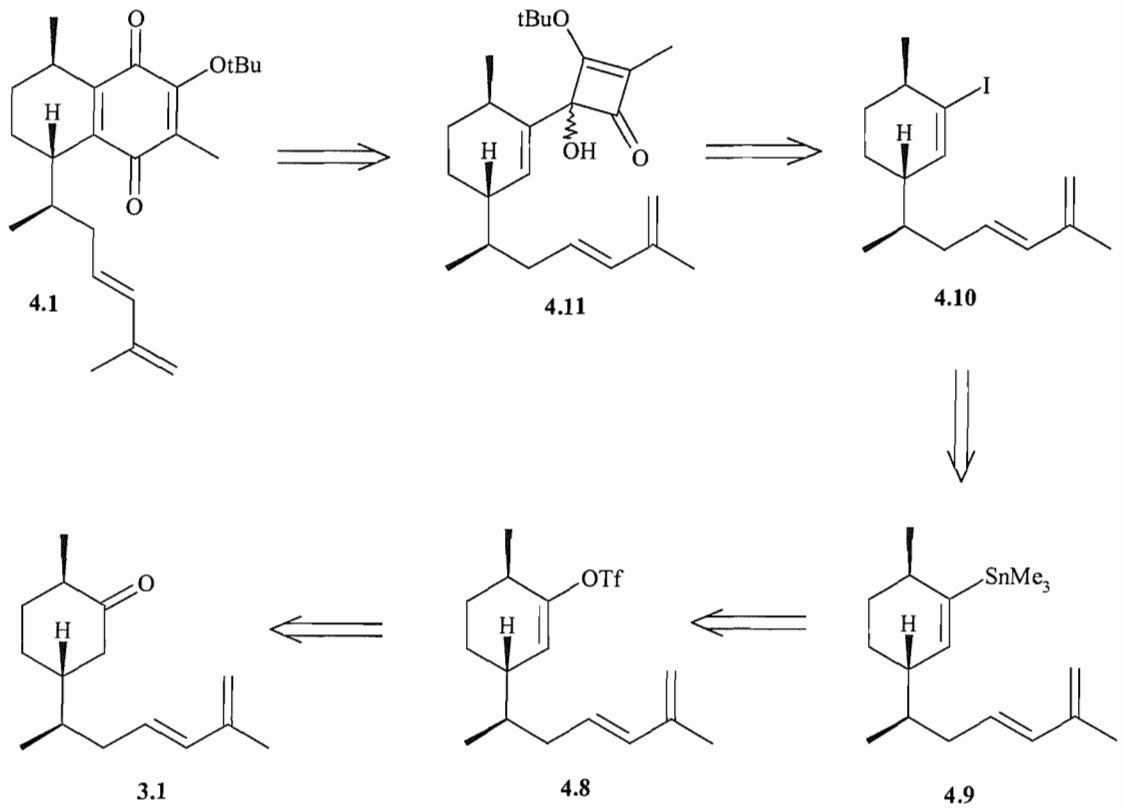
Scheme 4.3

The difficulties encountered in our attempt to effect the protection of hydroquinone **2.5** and quinone **2.6** prevented the route described in Scheme 4.2 from being amenable to large-scale synthesis. These findings emphasised the need to introduce the quinone moiety in the latter stages of the synthesis.

ii. Route B

Thus, we turned our attention to using dienone **3.1** as a building block onto which the cyclobutenedione moiety could be appended. This would consist in transforming ketone **3.1** into the corresponding vinyl triflate **4.8**. A palladium catalysed transformation with hexamethylditin would then convert triflate **4.8** to stannane **4.9**. Treatment with iodine should furnish vinyl iodide **4.10** which, after treatment with *t*BuLi, could be coupled to the squarate moiety. Thermal rearrangement of **4.11** should provide us with quinone **4.1** (Scheme 4.4). This approach however, also caused us concerns. The very presence of a diene functionality prohibits the use of palladium

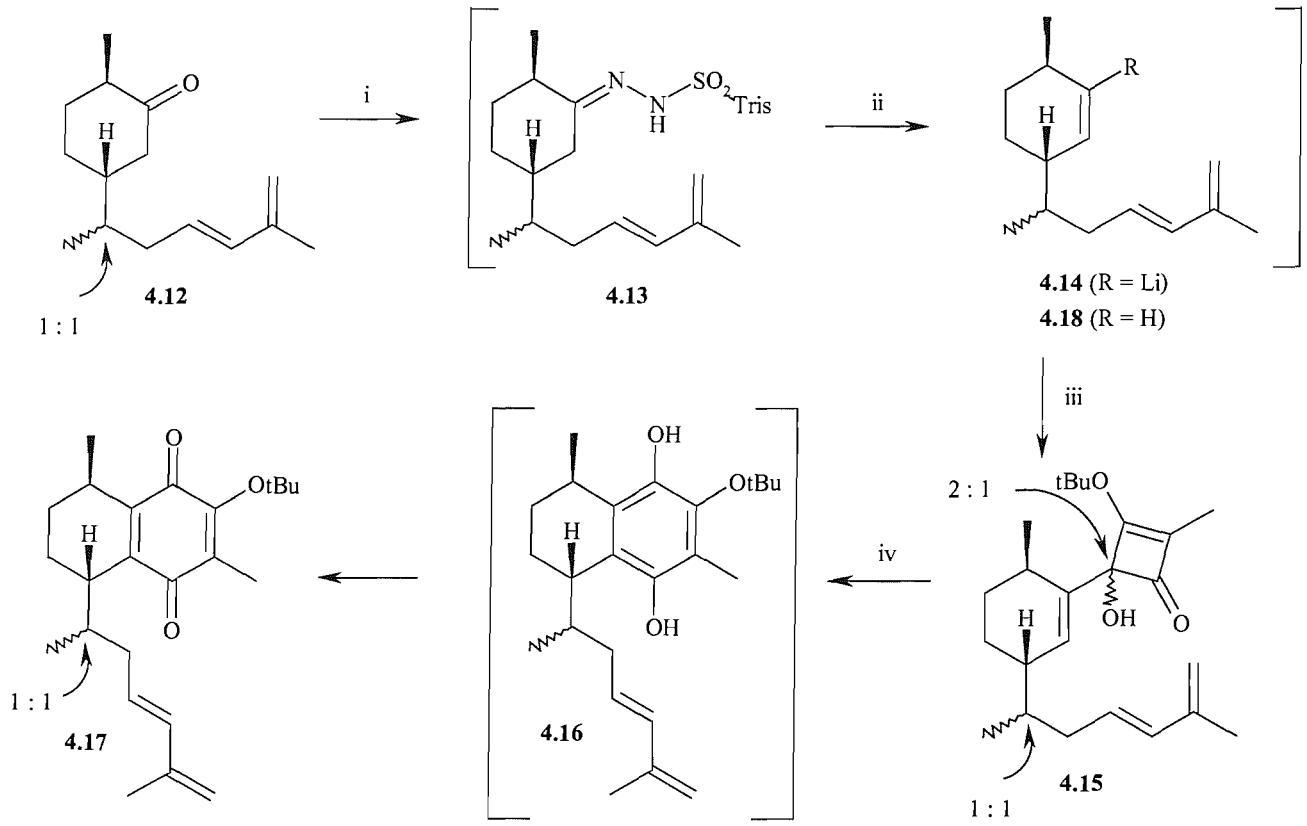
catalysts, which had been used in our model studies for the transformation of vinyl triflate **2.27 A** into vinyl stannane **2.28** (Scheme 2.8).



Scheme 4.4

Therefore, although our model studies had appeared to provide us with a useful alternative to the Shapiro reaction, we would be constrained to applying it as a means of obtaining quinone **4.1** (Scheme 4.5). Starting with ketone **4.12** (where the C7 stereocentre had not been defined), we attempted the formation of the corresponding trisylhydrazone **4.13** by treatment with trisylhydrazine in acidic methanol. As with our model studies, however, isolation and purification of hydrazone **4.13** proved difficult, presumably due to the acid sensitivity of the substrate. Therefore, the one-pot Shapiro protocol we had developed was applied once more. Thus, stirring ketone **4.12** with trisylhydrazine in THF for two hours and subjecting the solution to treatment with 3-4 equivalents of *tert*-butyllithium yielded alcohol **4.15** in poor yield (Scheme 4.5). The

low yields for this reaction were concordant with those obtained in our model studies. A number of side reactions were observed, notably quenching of the generated vinyllithium **4.14** to provide us with triene **4.18** (R = H). Numerous attempts to favour quenching of the vinyllithium **4.14** by squarate **2.17** using temperature control or using a large excess of the squarate **2.17** led to an optimised yield of 24%. Notwithstanding these difficulties, heating alcohol **4.15** in xylene or THF provided us with hydroquinone **4.16** in good yields. The advantage of using THF to effect the thermal rearrangement is that subsequent oxidation to quinone **4.17** occurred readily by stirring the resulting solution in air.

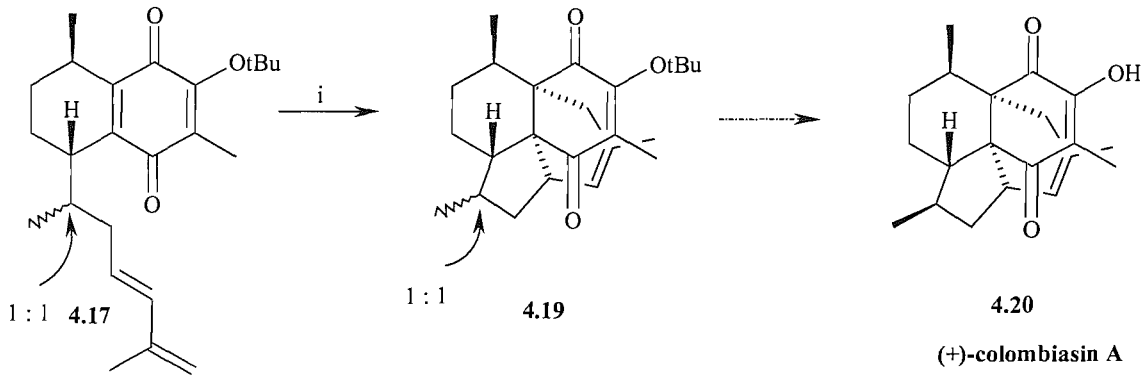


Reagents/Conditions: i) trisylhydrazine, THF, RT, 2h; ii) *t*BuLi (4eq.), THF, -78 °C, 2h, then -25 °C, 2 min.; iii) squarate **2.17** (6 eq.), THF, -78 °C, 30 min., 24%; iv) 130 °C, sealed tube, THF, 30 min., then RT, open vessel, 24h, 80%.

Scheme 4.5

IV.2 – (+)-Colombiasin A *t*-butyl ether

With quinone **4.17** in hand, all that remained was to effect the cyclisation to yield (+)-colombiasin A *t*-butyl ether **4.19**. Heating **4.17** for 6 hours in the dark promoted the intramolecular Diels-Alder cycloaddition, and (+)-colombiasin A *t*-butyl ether **4.19** was obtained in 60% yield as a 1:1 mixture of diastereoisomers (Scheme 4.6).



Reagents/Conditions: i) toluene, 180 °C, sealed tube, dark, 6h, 60% (+20% RSM).

Scheme 4.6

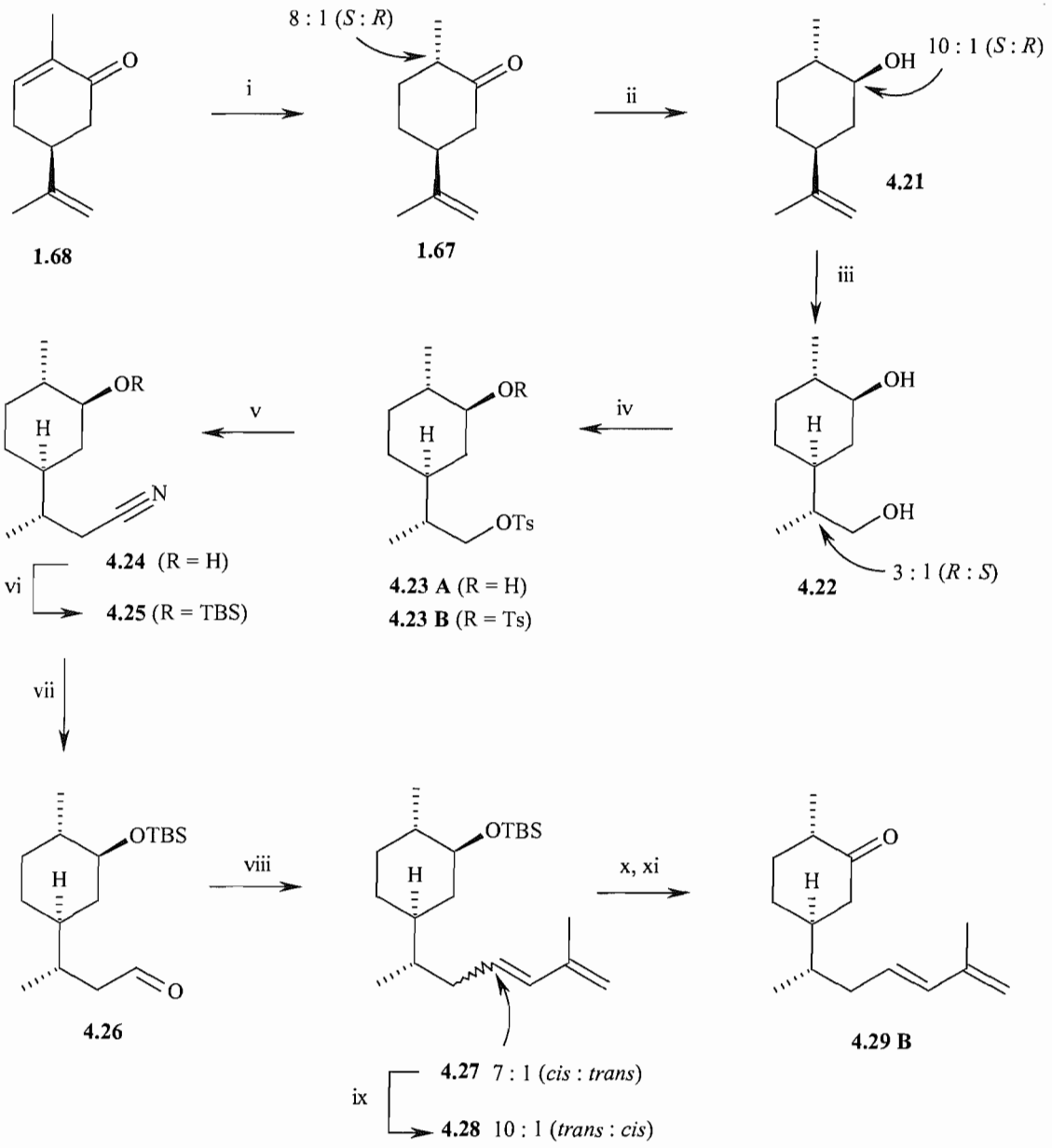
According to our model studies, deprotection of the *t*-butyl enol ether with $TiCl_4$ followed by HPLC separation of the diastereoisomers should complete the synthesis of (+)-colombiasin A **4.20**. However, at this juncture, our attention turned to the synthesis of the naturally occurring diasteroisomer, (-)-colombiasin A.

IV.3 – Towards (-)-colombiasin A

Having finally established an effective route to quinone **4.17**, and completed the synthesis of (+)-colombiasin A *t*-butyl ether **4.19**, we were in a position to carry out the sequence on (-)-dihydrocarvone **1.67** in an asymmetric fashion to yield the natural diastereoisomer of colombiasin A.

(-)-Dihydrocarvone **1.67** needed to be synthesised from (*S*)-carvone **1.68** by reduction with L-selectride. Reduction of the enone **1.68** occurred preferentially from the top face, yielding **(*S*)-1.67** and **(*R*)-1.67** as a separable 8:1 mixture of diastereoisomers in 83% yield. The major diastereoisomer **(*S*)-1.67** was taken through the same sequence described in the model studies with (+)-dihydrocarvone **2.1**. Thus, reduction of **(*S*)-1.67** with $LiAlH_4$ yielded a 10:1 mixture of diastereomeric alcohol **(*S*)-4.21** and **(*R*)-4.21**. Hydroboration of **(*S*)-4.21** was effected using (-)-$(Ipc)_2BH$ to produce diol **4.22** as an enriched 3:1 mixture of diastereoisomers. Repetitive column chromatography allowed **(*R*)-4.22** and **(*S*)-4.22** to be separated and identified by analogy to their respective enantiomers **3.46** and **3.45** obtained in the model studies.

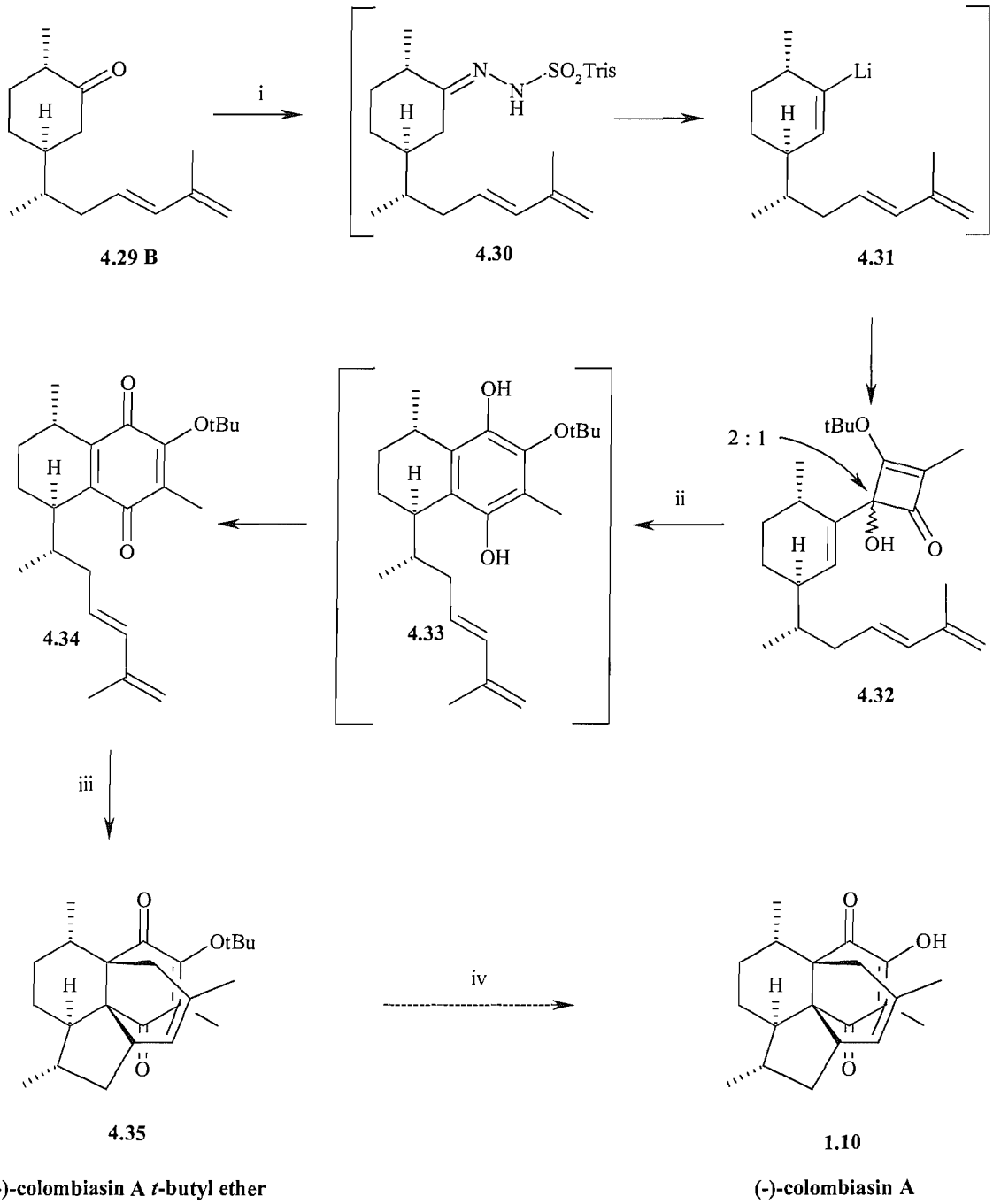
Conversion of diol **(*R*)-4.22** to the tosylate **4.23 A** required strictly one equivalent of tosyl chloride in order to prevent formation of bis-tosylate **4.23 B**. Formation of nitrile **4.24**, protection of the secondary alcohol with TBSCl and subsequent reduction to aldehyde **4.26** were facile and high yielding processes. The Kocieński-Julia olefination protocol was extremely efficient in yielding diene **4.27**. However, *cis* selectivity (7:1) was observed and iodine catalysed isomerisation was required to convert the mixture to the *trans* adduct exclusively. Deprotection with TBAF followed by oxidation with DMP yielded ketone **4.29 B** in moderate yield. The oxidation step was slightly undermined (75% yield) by the sensitivity of the diene moiety towards oxidising agents. Nevertheless, ketone **4.29 B** was obtained as a single diastereoisomer in reasonable overall yield and the last crucial sequence could be tested (Scheme 4.7).



Reagents/Conditions: i) lithium tri-*sec*-butylborohydride, THF, -78 °C to 0 °C, 1.5h, then NaOH, H_2O_2, 0 °C, 1h, 83%; ii) lithium aluminium hydride, Et_2O, -78 °C to 0 °C, 96%; iii) preformed (-)-$(Ipc)_2BH$, RT, 2h, then NaOH, H_2O_2, 0 °C to RT, 16h, 93%; iv) TsCl, NEt_3, DCM, RT, 96h, 85%; v) NaCN, DMSO, 90 °C, 99%; vi) TBSCl, imidazole, DMAP, DCM, RT, 96h, 99%; vii) DIBAL-H, toluene, 0 °C, 1h, then HCl (2M aq.), $CHCl_3$, RT, 1h, 75%; viii) **3.42**, NaHMDS, DME, -55 °C, 1.5h then **4.26**, DME, -55 °C to RT, 16h, 96%; ix) I_2 (1%), $CHCl_3$, 1.5h, 75%; x) TBAF (5 eq.), THF, RT, 48h, 99%; xi) DMP, DCM, 0 °C to RT, 1h, 75%.

Scheme 4.7

The one-pot Shapiro reaction on ketone **4.29 B** yielded alcohol **4.32** in 24% yield. Heating alcohol **4.32** in THF to 130 °C in a sealed tube for 30 minutes and allowing the resulting solution to stir for 48 hours in air meant that isolation of hydroquinone **4.33** was bypassed and quinone **4.34** was obtained in high yields. Heating quinone **4.34** to 180 °C in the dark for 12 hours yielded (-)-colombiasin A *tert*-butyl ether **4.35** in reasonable yield. **4.35** was then subjected to deprotection with $TiCl_4$ (Scheme 4.8). Unfortunately, the scale on which the reaction was performed did not allow for conclusive characterisation of the product.



Reagents/Conditions: i) $TrisNHNH_2$, THF, RT, 2h, then *t*-butyllithium (4 eq.), -78 °C, 2h, -20 °C, 5 min, then **2.17** in THF, -78 °C, 0.5h, 24%; ii) 130 °C, 20 min, sealed tube, THF, then RT, THF, 48h, 85%; iii) 180 °C, dark, toluene, 12h, 60%; iv) $TiCl_4$, DCM, 0 °C, 1 min.

Scheme 4.8

IV.4 - Conclusion and further work

In summary, we have secured an asymmetric route to (-)-colombiasin A *t*-butyl ether. Particularly noteworthy is the cyclobutenone thermal rearrangement-aerial oxidation-intramolecular Diels-Alder cycloaddition sequence used to construct the colombiane skeleton.

However, it should be noted that two main factors have undermined our synthesis of colombiasin A and these remain to be addressed. Firstly, although diol **(*R*)-4.22** was prepared stereoselectively, its separation from diol **(*S*)-4.22** by careful chromatography was extremely time-consuming. To overcome this problem, fractional recrystallisation of these diols could be attempted. Alternatively, an in-depth investigation of our initial idea, i.e. an asymmetric Suzuki coupling of **3.3** with **3.4**, would greatly facilitate the synthesis of (-)-colombiasin A.

Secondly, although the Shapiro reaction has provided us with a means to obtain key intermediate **4.32**, the low yields observed at such a late stage in our sequence have prevented us from obtaining enough material to conclude the synthesis of the natural product. This problematic step could be addressed by a change in the electrophile used to quench vinyllithium **4.31**. For instance, formation of a vinyl stannane intermediate could perhaps improve the yields of the Shapiro reaction as well as provide a way to access alcohol **4.32**. Alternatively, the route depicted in Scheme 4.4 where vinyl triflate **4.8** is converted to vinyl stannane **4.9** by a palladium catalysed reaction, could prove more successful than anticipated, despite the presence of a diene moiety. These issues are currently being addressed and we are hopeful that they will be resolved shortly.

CHAPTER V – EXPERIMENTAL

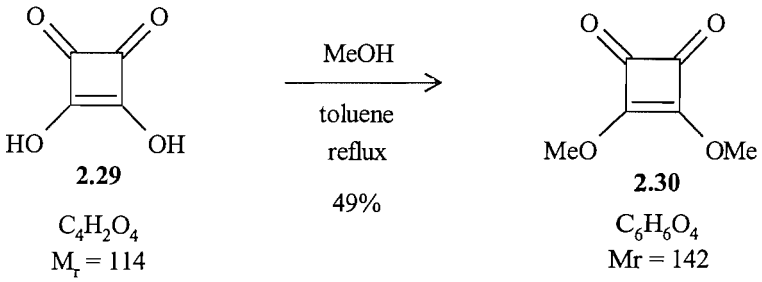
V.1 - General remarks

All air and/or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried glassware. Reactions were monitored by TLC using glass-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with, most commonly, 20 % phosphomolybdic acid in ethanol or 10% aqueous $KMnO_4$. Where flash chromatography was undertaken, Apollo silica gel (0.040-0.063 mm, 230-400 mesh) was used, slurry packed and run at low pressure. HPLC was performed using a Kontron Instruments pump with a 10 mm × 250 mm Biosyl D 90/10 column eluting at 3 mL/min. Infrared (IR) spectroscopy was performed using a Bio-Rad FT-IR Goldengate spectrometer or Thermo Mattson Satellite FT-IR spectrometer. Positions of absorption maxima are quoted in cm^{-1}. Letters after give an indication of the relative strength of the peak (w = weak, m = moderate, s = strong, br. = broad, v = very). ^{1}H, ^{13}C, ^{19}B and ^{31}P spectroscopy was performed on a Bruker AC/AM300 or DPX400 spectrometer at operating frequencies indicated in the text. Chemical shifts are quoted as δ-values in ppm and multiplicities are reported using the following notation: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, app. = apparent, br. = broad, obsc. = obscured. Chemical ionisation (CI) and electron ionisation (EI) mass spectroscopy was performed on a Thermoquest Trace GCMS spectrometer. Electrospray (ES) mass spectroscopy was performed on a Micromass Platform (MP) spectrometer. High resolution EIMS was performed on a VG Analytical 70-250-SE spectrometer and high resolution ESMS was performed on a Bruker Apex III spectrometer. Combustion analysis was performed by Medac Ltd. Melting points were carried out using a Griffin melting point apparatus and are uncorrected. Optical rotations were measured on a PolAAr 2001 polarimeter operating at a wavelength of 589 nm and an external temperature of 24 °C. Benzene, toluene, 1,4-dioxane, ether and THF were distilled from sodium immediately before use. Except in the case of toluene,

benzophenone was used as an internal indicator of water content. Chloroform and dichloromethane were distilled from calcium hydride immediately prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[53] Methallylphosphonium chloride was prepared by the method of Baird *et al.*[54] Stannane **3.2** was prepared following the procedure of Aksela *et al.*[55]

V.2 – Synthetic procedures

3,4-Dimethoxycyclobut-3-ene-1,2-dione **2.30**

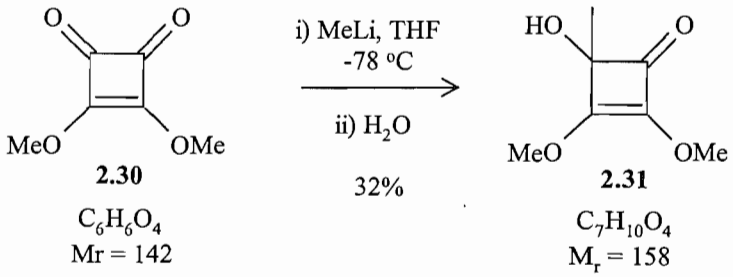


Prepared following the procedure of Liebeskind *et al.*[30] Thus, a stirred suspension of squaric acid **2.29** (10.67 g, 94.00 mmol) in methanol (150 mL) and toluene (150 mL) was heated to reflux under azeotropic removal of water. After 16 hours, the solvents were removed *in vacuo*. The residual oily solid was once again suspended in methanol : toluene (1 : 1, 300 mL) and the reaction mixture was heated to reflux with azeotropic removal of water for 16 hours. The solvents were removed *in vacuo*. The residual oil was taken up in ether (200 mL) and washed with a saturated sodium bicarbonate solution (2 × 150 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to a white solid **2.30** (6.56 g, 46.20 mmol, 49%) which was recrystallised from ether/petroleum ether. Spectroscopic and physical data (except for melting point data) were in accordance with literature values.[56]

MP	41 - 43°C (ether/petroleum ether) (lit.[56] 55 °C).
ν_{max}/cm^{-1} (neat)	1834 (w), 1724 (m), 1603 (s), 1484 (s), 1427 (w), 1366 (s).
δ_H (300 MHz, $CDCl_3$)	4.38 (6H, s, 2 × -OC*H*$_3$) ppm.

δ_C (75.5 MHz, $CDCl_3$)	189.3 (s, 2 × -*C*=O), 184.6 (s, (MeO)*C*=*C*(OMe)), 61.2 (q, 2 × -O*C*H_3) ppm.
LRMS (CI)	160 ($[M + (NH_4)]^+$, 82%), 143 ($[MH]^+$, 100%), 114 (24%), 86 (50%) amu.

4-Hydroxy-2,3-dimethoxy-4-methylcyclobut-2-en-1-one **2.31**



2.30
$C_6H_6O_4$
Mr = 142

2.31
$C_7H_{10}O_4$
M_r = 158

Prepared following the procedure of Liebeskind *et al.*[30] Thus, to a cooled (-78 °C) solution of dimethyl squarate **2.30** (1.23 g, 8.66 mmol) in THF (40 mL) under nitrogen was added methyllithium (5.5 mL, 1.6 M in ether, 8.75 mmol) dropwise over 10 minutes. The reaction mixture was maintained at -78 °C for 1 hour. Water (10 mL) was added and the reaction mixture allowed to warm to ambient temperature. Ether (20 mL) was added and the phases separated. The aqueous phase was extracted with ether (2 × 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to a pale yellow oil **2.31** (0.44 g, 2.79 mmol, 32%).

Spectroscopic and physical data were in accordance with literature values.[30]

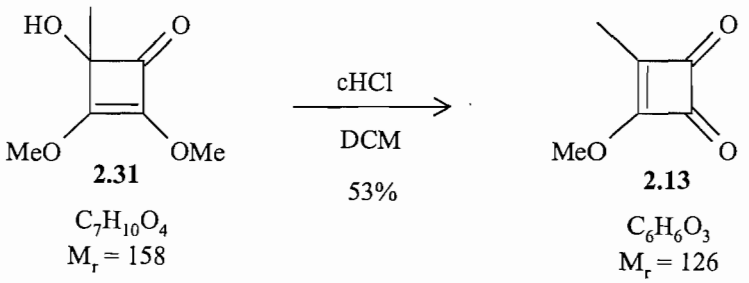
ν_{max}/cm^{-1} (neat) 3413 (br. m), 1758 (s), 1431 (m), 1124 (br. s).

δ_H (400 MHz, $CDCl_3$) 4.18 (3H, s, -OC*H*$_3$), 3.97 (3H, s, -OC*H*$_3$), 3.27 (1H, br. s, -O*H*), 1.57 (3H, s, -C*H*$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 188.0 (s, *C*=O), 169.4 (s, -C(O)-*C*-OMe), 133.2 (s, -C(OH)-*C*-OMe), 83.9 (s, -*C*(OH)-), 60.4 (q, -O*C*H$_3$), 58.8 (q, -O*C*H$_3$), 19.7 (q, -C-*C*H$_3$) ppm.

LRMS (CI) 159 ([MH]$^+$, 68%), 141 ([MH – (H_2O)]$^+$, 100%) amu.

3-Methoxy-4-methylcyclobut-3-ene-1,2-dione **2.13**



2.31
$C_7H_{10}O_4$
$M_r = 158$

2.13
$C_6H_6O_3$
$M_r = 126$

Prepared following the procedure of Liebeskind *et al.*[30] Thus, to a stirred solution of **2.31** (0.40 g, 2.53 mmol) in DCM (25 mL) was added HCl (12 N, 3 drops). After 1 hour, the reaction mixture was diluted with DCM (30 mL), dried over K_2CO_3, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 0% - 100% ether in petroleum ether) gave diketone **2.13** (0.17 g, 1.35 mmol, 53%) as a pale yellow oil.

Spectroscopic and physical data were in accordance with literature values.[30]

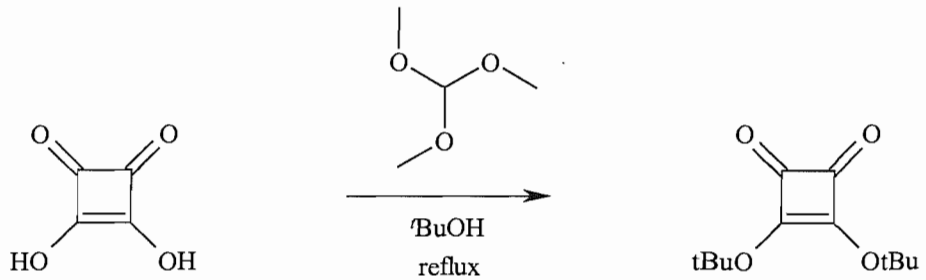
ν_{max}/cm^{-1} (in $CDCl_3$) 1807 (s), 1788 (s), 1755 (vs), 1599 (vs), 1458 (m), 1385 (s), 1347 (s).

δ_H (300 MHz, $CDCl_3$) 4.42 (3H, s, -OC*H*$_3$), 2.21 (3H, s, -C*H*$_3$) ppm.

δ_C (75.5 MHz, $CDCl_3$) 199.2 (s, -*C*=O), 195.1 (s, -*C*=O), 194.0 (s, (MeO)*C*=), 180.5 (s, (CH_3)*C*=), 61.1 (q, -O*C*H$_3$), 9.8 (q, -*C*H$_3$) ppm.

LRMS (CI) 144 ([M + (NH_4)]$^+$, 26%), 127 ([MH]$^+$, 62%), 98 (90%), 83 (100%) amu.

3,4-Di-*tert*-butoxy-cyclobut-3-ene-1,2-dione **2.35**



2.29

$C_4H_2O_4$

$M_r = 114$

2.35

$C_{12}H_{18}O_4$

$M_r = 226$

Prepared following the procedure of Moore *et al.*[57] Thus, to a stirred suspension of squaric acid **2.29** (6.89 g, 60.44 mmol) in *tert*-butanol (240 mL) at reflux was added trimethyl orthoformate (66 mL, 64.00 g, 0.60 mol) was added dropwise over 1 hour. Simultaneously, the distillate was collected *via* short path distillation. The solvent was removed *in vacuo* and the residual crude oil was purified by column chromatography (SiO_2, 10 – 25% ethyl acetate in petrol) to give the title compound **2.35** as a white solid (9.60 g, 42.48 mmol, 70%).

Spectroscopic and physical data were in accordance with literature values.[58]

MP 103 – 104 °C (lit.[58] 104 – 105 °C).

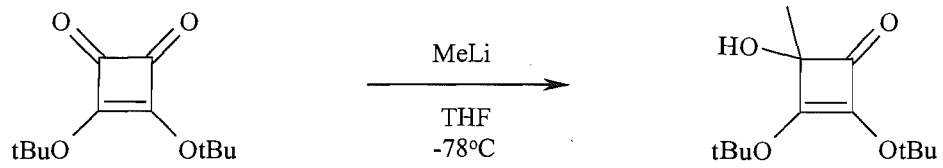
ν_{max}/cm^{-1} (in $CDCl_3$) 2985 (w), 1805 (m), 1721 (m), 1574 (s), 1476 (w), 1386 (vs), 1145 (m).

δ_H (300 MHz, $CDCl_3$) 1.63 (18H, s, 2 × -C(C*H*$_3$)$_3$) ppm.

δ_C (75.5 MHz, $CDCl_3$) 188.6 (s, 2 × -*C*=O), 186.3 (s, 2 × -*C*(O*t*Bu)), 87.1 (s, 2 × -O*C*(CH$_3$)$_3$), 28.7 (q, 2 × -C(*C*H$_3$)$_3$) ppm.

LRMS (EI) 171 (2%), 56 ([*t*Bu-H]$^+$, 38%) amu. Parent ion not observed.

2,3-Di-*tert*-butoxy-4-hydroxy-4-methyl-cyclobut-2-enone **2.36**



2.35
$C_{12}H_{18}O_4$
$M_r = 226$

2.36
$C_{13}H_{22}O_4$
$M_r = 242$

To a stirred solution of di-*tert*-butyl squarate **2.35** (9.59 g, 42.43 mmol) in THF (60 mL) at -78 °C under nitrogen was added methyllithium (26.5 mL, 1.6 M in THF) dropwise over 10 minutes. After 2 hours, the reaction was quenched with water (35 mL), warmed to room temperature and the phases were separated. The aqueous phase was extracted with ether (3 × 25 mL). The combined organic phases were washed with brine (35 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **2.36** (10.00 g, 41.32 mmol, 97%) as colourless crystals which were not further purified.

MP 73 – 74 °C

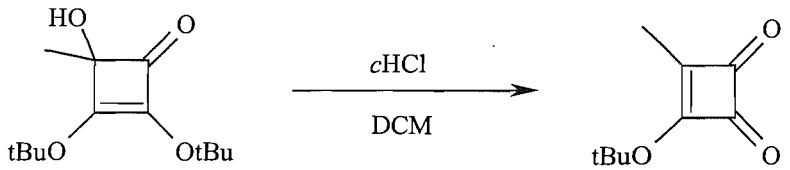
ν_{max}/cm^{-1} (in $CDCl_3$) 3388 (br. m), 2978 (s), 2936 (m), 1799 (m), 1755 (s), 1594 (vs), 1475 (w), 1396 (s), 1370 (vs), 1265 (m), 1154 (vs).

δ_H (400 MHz, $CDCl_3$) 2.49 (1H, br. s, -C-O*H*), 1.66 (3H, s, -C-C*H*$_3$), 1.57 (9H, s, -O-C(C*H*$_3$)$_3$), 1.51 (9H, s, -O-C(C*H*$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 187.6 (s, *C*=O), 168.5 (s, =*C*-C=O), 129.2 (s, =*C*-O*t*Bu), 83.9 (s, -*C*-O), 82.4 (s, -*C*-O), 80.6 (s, -*C*-O), 29.2 (q, -C(*C*H$_3$)$_3$), 28.7 (q, -C(*C*H$_3$)$_3$), 19.3 (q, -*C*H$_3$) ppm.

LRMS (CI)	243 ($[MH]^+$, 2%), 169 ($[M - (-OtBu)]^+$, 6%), 130 (100%) amu.

3-*tert*-Butoxy-4-methyl-cyclobut-3-ene-1,2-dione **2.17**



2.36

$C_{13}H_{22}O_4$
$M_r = 242$

2.17

$C_9H_{12}O_3$
$M_r = 168$

To a stirred solution of alcohol **2.36** (9.75 g, 40.29 mmol) in DCM (100 mL) was added concentrated hydrochloric acid (1 mL) dropwise over 2 minutes. The reaction mixture was stirred at room temperature for one hour after which another aliquot of concentrated hydrochloric acid (1 mL) was added. After 30 minutes, water (20 mL) was added and the phases were separated. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a yellow solid, which was recrystallised from ether/petrol to give the title diketone **2.17** (4.7 g, 28.00 mmol, 69%) as a colourless flaky solid.

Spectroscopic and physical data were in accordance with literature values.[59]

MP 63 – 65 °C (ether/petroleum ether) (lit.[59] 72 – 73 °C).

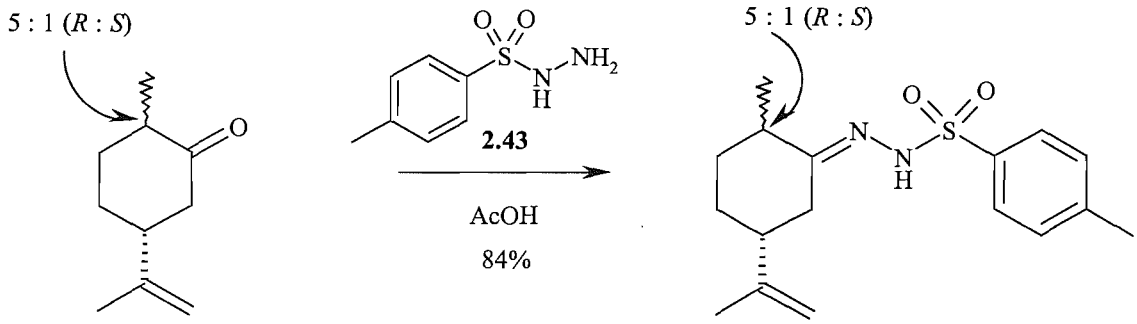
ν_{max}/cm^{-1} (in $CDCl_3$) 2987 (m), 2940 (w), 2255 (m), 1799 (s), 1747 (s), 1583 (vs), 1399 (s), 1350 (s), 1153 (s).

δ_H (300 MHz, $CDCl_3$) 2.13 (3H, s, =C-C*H*$_3$), 1.55 (9H, s, -C(C*H*$_3$)$_3$) ppm.

δ_C (75.5 MHz, $CDCl_3$) 200.0 (s, -*C*(O)-C(O*t*Bu)-), 196.1 (s, -*C*=O), 192.9 (s, -*C*(O*t*Bu)-), 182.9 (s, Me-*C*=), 87.6 (s, -*C*(CH$_3$)$_3$), 28.8 (q, -C(*C*H$_3$)$_3$), 9.5 (q, -*C*H$_3$) ppm.

LRMS (CI) 169 ([MH]$^+$, 10 %), 130 (44%), 83 (42%), 57 (100%) amu.

Dihydrocarvone *p*-toluenesulfonylhydrazone **2.8**



2.1
$C_{10}H_{16}O$
$M_r = 152$

2.8
$C_{17}H_{24}N_2O_2S$
$M_r = 320$

To a stirred solution of *p*-toluenesulfonylhydrazine **2.43** (1.86 g, 10.00 mmol) in acetic acid (30 mL) was added dihydrocarvone **2.1** (1.6 mL, 10.00 mmol) and the reaction mixture was stirred at ambient temperature for 16 hours. Water (20 mL) was added and the reaction mixture was extracted with DCM (2 × 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (3 × 20 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 100% DCM – 100% ether) gave hydrazone **2.8** (2.70 g, 8.44 mmol, 84%) as a white solid which was recrystallised from ether/petroleum ether.

MP 112 – 114 °C (ether/petroleum ether)

ν_{max}/cm^{-1} (in $CDCl_3$) 3220 (w), 2926 (w), 1711 (w), 1697 (w), 1640 (w), 1451 (w), 1336 (m), 1167 (s).

δ_H (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.1 Hz, 2 × aryl-C*H*-, major isomer), 7.84 (2H, obsc. d, *J* 8.1 Hz, 2 × aryl-C*H*-, minor isomer) 7.51 (1H, br. s, -N*H*-, major isomer), 7.48 (1H, br. s, -N*H*-, minor isomer), 7.31 (2H, d, *J* 8.1 Hz, 2 × aryl-C*H*-, major isomer), 7.29 (2H, d, *J* 8.1 Hz, 2 × aryl-C*H*-, minor isomer), 4.76 (1H, app. t, *J* 1.5 Hz, -C=C*H*H, minor isomer), 4.73 (1H, app. t, *J*

1.3 Hz, -C=C*H*H, major isomer), 4.68 (1H, br. s, -C=CH*H*, major isomer), 4.63 (1H, br. s, -C=CH*H*, minor isomer), 2.72 (2H, ddd, *J* 13.6, 3.3, 1.8 Hz, 2 × -C*H*H-C=N-), 2.47 – 2.28 (2H, obsc. m, 2 × -CH*H*-C=N), 2.43 (6H, s, 2 × -aryl-CH_3), 2.19 – 1.79 (8H, m), 1.74 (3H, s, CH_3-C=CH_2, minor isomer), 1.69 (3H, s, CH_3-C=CH_2, major isomer), 1.42 – 1.16 (4H, m), 1.04 (3H, d, *J* 6.3 Hz, CH_3-CH-, major isomer), 1.03 (3H, d, *J* 6.6 Hz, CH_3-CH-, minor isomer) ppm.

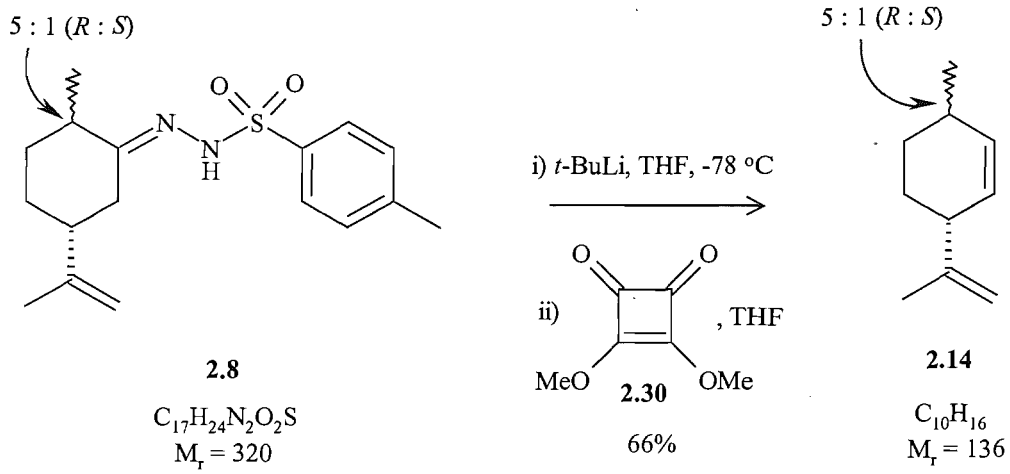
δ_C (75.5 MHz, $CDCl_3$)

148.1 (s, -*C*=CH_2, major isomer), 148.0 (s, -*C*=CH_2, minor isomer), 144.0 (s, 2 × aryl -*C*-), 135.3 (s, 2 × -*C*=N), 129.6 (d, 2 × aryl -*C*H-, minor isomer), 129.4 (d, 2 × aryl -*C*H-, major isomer), 128.5 (d, 4 × aryl -*C*H-), 128.3 (s, aryl -*C*-, major isomer), 128.2 (s, aryl -*C*-, minor isomer), 109.9 (t, -C=*C*H_2, major isomer), 109.8 (t, -C=*C*H_2, minor isomer), 45.3 (q, aryl-*C*H_3, major isomer), 44.9 (q, aryl-*C*H_3, minor isomer), 39.4 (d, 2 × -*C*H-C=N), 35.3 (t, -*C*H_2-C=N, major isomer), 35.1 (t, -*C*H_2-C=N, minor isomer), 32.0 (t, 2 × -*C*H_2-CH-C=N), 31.0 (t, -*C*H_2-CH-C=CH_2, major isomer), 30.9 (t, -*C*H_2-CH-C=CH_2, minor isomer), 21.8 (d, 2 × -*C*H-C=CH_2), 20.7 (q, 2 × *C*H_3-C=CH_2), 16.5 (q, *C*H_3-CH-C=N-, major isomer), 14.5 (q, *C*H_3-CH-C=N-, minor isomer) ppm.

LRMS (CI)

165 ($[M\text{-}SO_2Tol]^+$, 30%), 149 ($[M\text{-}NH_2SO_2Tol]^+$, 6%), 123 (100%) amu. Parent ion was not observed.

Limonene **2.14**



2.8

$C_{17}H_{24}N_2O_2S$

$M_r = 320$

2.30

66%

2.14

$C_{10}H_{16}$

$M_r = 136$

To a stirred solution of *tert*-butyllithium (2.15 mL, 0.93 M in pentane, 2.00 mmol) in THF (10 mL) at -60 °C under nitrogen was added hydrazone **2.8** (0.16 g, 0.50 mmol) in THF (3 mL) dropwise over 2 minutes causing the reaction to turn bright orange in colour. The reaction mixture was stirred at -60 °C for 1 hour, warmed to ambient temperature and stirred for a further 2 hours. The dark red solution was cooled to 0 °C and dimethyl squarate **2.30** (0.28 g, 2.00 mmol) in THF (2 mL) was added dropwise. The reaction was allowed to warm to room temperature. After 2 hours, water (10 mL) was added and the reaction mixture stirred for a further 16 hours then extracted with *n*-pentane (2 × 15 mL). The combined organic extracts were washed with water (2 × 15 mL), saturated copper sulfate solution (2 × 15 mL) and brine (3 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0% - 5% ether in petroleum ether) gave limonene **2.14** (0.045 g, 0.33 mmol, 66%) as a colourless oil.

Spectroscopic and physical data were in accordance with literature values.[60]

ν_{max}/cm^{-1} (in $CDCl_3$) 2956 (s), 2928 (s), 2856 (m), 1640 (m), 1455 (m), 1111 (br. m).

δ_H (300 MHz, $CDCl_3$) 5.69 – 5.55 (2H, obsc. m, -C*H*=C*H*-, minor isomer), 5.60 (1H, br. d, *J* 10.2 Hz, -C*H*=CH-, major isomer), 5.52 (1H, br. d, *J* 9.9 Hz, -CH=C*H*-, major isomer),

4.81 (1H, br. s, =C*H*H, minor isomer), 4.74 (2H, s, =CH_2, major isomer), 4.70 (1H, br. s, =CH*H*, minor isomer), 2.80 – 2.65 (2H, br. m, 2 × CH_2=C-C*H*-CH=), 2.22 – 2.10 (2H, br. m, 2 × CH_3-C*H*-CH=), 1.85 (2H, m), 1.80 (3H, s, CH_3-C-, minor isomer), 1.72 (3H, s, CH_3-C-, major isomer), 1.50 – 1.12 (4H, m), 0.99 (6H, d, *J* 7.2 Hz, 2 × CH_3-CH-), 0.95 – 0.84 (2H, m, minor isomer) ppm.

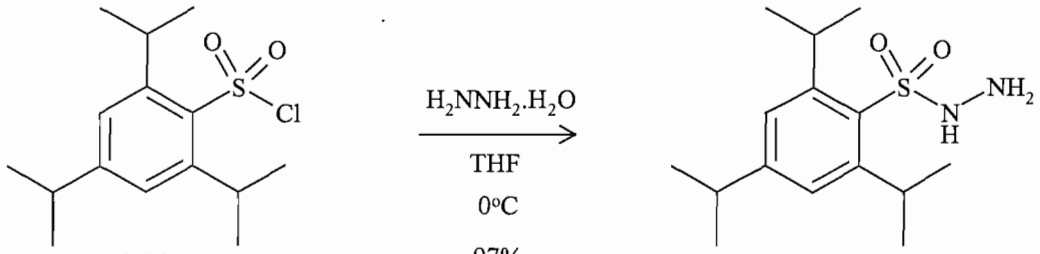
δ_C (75.5 MHz, $CDCl_3$)

149.6 (s, 2 × -*C*=CH_2), 134.3 (d, 2 × =*C*H-CH-C=), 129.4 (d, =C*H*-CH-CH_3, major isomer), 129.0 (d, =C*H*-CH-CH_3, minor isomer), 110.2 (t, -C=*C*H_2, minor isomer), 109.9 (t, -C=*C*H_2, major isomer), 43.7 (d, CH_2=C-*C*H-CH=, major isomer), 42.5 (d, CH_2=C-*C*H-CH=, minor isomer), 31.3 (t, 2 × -*C*H_2-), 30.5 (d, -*C*H-CH=, major isomer), 30.0 (d, -*C*H-CH=, minor isomer), 28.3 (t, -*C*H_2-, major isomer), 28.1 (t, -*C*H_2-, minor isomer), 25.5 (q, *C*H_3-C=, minor isomer), 22.3 (q, *C*H_3-CH-, minor isomer), 21.9 (q, *C*H_3-C=, major isomer), 20.7 (q, *C*H_3-CH-, major isomer) ppm.

LRMS (CI)

137 ($[MH]^+$, 95%), 136 ($[M]^+$, 100%), 107 (86%), 93 (56%) amu.

2,4,6-Triisopropylbenzenesulfonohydrazide **2.45**



2.44

$C_{15}H_{23}ClO_2S$
$M_r = 303$

2.45

$C_{15}H_{26}N_2O_2S$
$M_r = 298$

To a stirred solution of 2,4,6-triisopropylsulfonyl chloride **2.44** (3.28 g, 10.83 mmol) in THF (15 mL) at 0 °C was added hydrazine monohydrate (1.46 mL, 30.00 mmol) dropwise over 5 minutes. The cloudy white reaction mixture was stirred at 0 °C for 16 hours. Water (20 mL) was then added and the phases were separated. The aqueous phase was extracted with ether (3 × 20 mL), the combined organic phases were washed with cold brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a white solid **2.45** (3.13g, 10.50 mmol, 97%) which was not further purified.

Spectroscopic and physical data were in accordance with literature values.[61]

MP 121–123 °C (lit.[61] 118-120 °C).

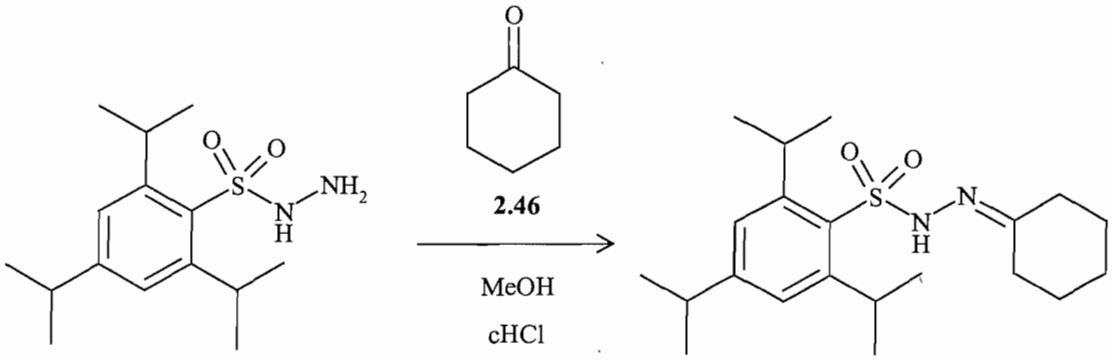
ν_{max}/cm^{-1} (neat) 3053 (w), 2985 (w), 1421 (br. w), 1265 (s), 895 (w).

δ_H (300 MHz, $CDCl_3$) 7.21 (2H, s, 2 × aryl –C*H*-), 5.50 (1H, br. s, -N*H*-), 4.16 (2H, septet, *J* 6.8 Hz, 2 × -C*H*(CH_3)$_2$), 3.34 (2H, br. s, -N*H*$_2$), 2.92 (1H, septet, *J* 6.9 Hz, -C*H*(CH_3)$_2$), 1.28 (12H, d, *J* 7.0 Hz, 2 × -CH(C*H*$_3$)$_2$), 1.27 (6H, d, *J* 7.0 Hz, -CH(C*H*$_3$)$_2$) ppm.

δ_C (75.5 MHz, $CDCl_3$) 154.0 (s, aryl -*C*-), 151.2 (s, 2 × aryl -*C*-), 128.7 (s, aryl -*C*-), 124.2 (d, 2 × aryl -*C*H-), 34.4 (d, -

	$CH(CH_3)_2$), 30.0 (q, -CH(CH_3)$_2$), 25.1 (q, 2 × -CH(CH_3)$_2$), 23.7 (d, 2 × -$CH(CH_3)_2$) ppm.
LRMS (EI)	204 (90%), 189 ([M – (SO_2NHNH_2)]$^+$, 100%) amu. Parent ion not observed.

Cyclohexanone 2,4,6-triisopropylbenzenesulfonylhydrazone **2.47**



2.45

$C_{15}H_{26}N_2O_2S$
$M_r = 298$

2.47

$C_{21}H_{34}N_2O_2S$
$M_r = 378$

To a stirred suspension of finely ground trisylhydrazide **2.45** (2.90 g, 9.73 mmol) in methanol (10 mL) was added freshly distilled cyclohexanone **2.46** (1 mL, 9.73 mmol) which caused the suspension to clear. Concentrated HCl (12 N, 4 drops) was added to the solution, and after 1 minute, a white precipitate became apparent. The reaction mixture was stirred for 15 minutes and was then placed in a freezer at -20 °C for 20 hours. The white precipitate was filtered, washed with cold methanol (20 mL) and dried *in vacuo* for 3 hours. The resulting powdery white solid **2.47** (3.03g, 8.02 mmol, 82%) was not further purified.

Spectroscopic and physical data were in accordance with literature values.[61]

MP 143-145 °C (lit.[61] 142 – 144 °C).

ν_{max}/cm^{-1} (in DCM) 3054 (m), 2962 (br. m), 2869 (w), 1599 (vw), 1424 (m), 1265 (s) 1166 (m), 896 (w).

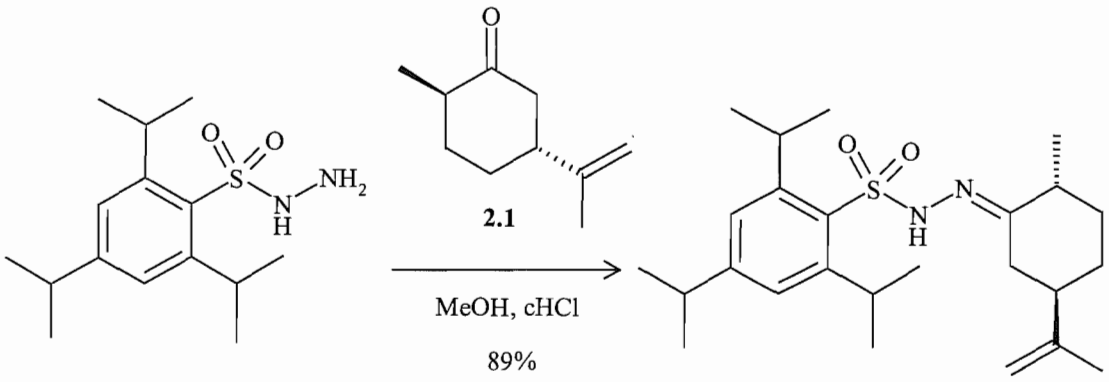
δ_H (300 MHz, $CDCl_3$) 7.43 (1H, br. s, -N*H*-), 7.17 (2H, s, 2 × aryl -C*H*-), 4.25 (2H, septet, *J* 6.8 Hz, 2 × -C*H*$(CH_3)_2$), 2.91 (1H, septet, *J* 6.9 Hz, -C*H*$(CH_3)_2$), 2.22 – 2.19 (4H, m, 2 × -C*H*$_2$-C=N), 1.69 – 1.55 (6H, m, 3 × -C*H*$_2$-), 1.27

(12H, d, *J* 6.7 Hz, 2 × -CH(C*H*$_3$)$_2$), 1.26 (6H, d, *J* 7.0 Hz, -CH(C*H*$_3$)$_2$) ppm.

δ_C (75.5 MHz, $CDCl_3$) 160.8 (s, aryl -*C*-), 153.1 (s, aryl -*C*-), 151.4 (s, 2 × aryl -*C*-), 131.6 (s, *C*=N), 123.9 (d, 2 × aryl -*C*H-), 35.4 (t, -*C*H$_2$-C=N), 34.3 (d, -*C*H(CH$_3$)$_2$), 30.1 (q, -CH(*C*H$_3$)$_2$), 26.8 (t, -*C*H$_2$-), 26.6 (t, -*C*H$_2$-), 25.7 (t, -*C*H$_2$-), 25.6 (t, -*C*H$_2$-), 25.0 (q, 2 × -CH(*C*H$_3$)$_2$), 23.7 (d, 2 × -*C*H(CH$_3$)$_2$) ppm.

LRMS (ES^+) 1157 ($[3M + Na]^+$, 100%), 757 ($[2M + H]^+$, 70%), 379 ($[M + H]^+$, 20%) amu.

(*R*, *R*)-Dihydrocarvone 2,4,6-triisopropylbenzenesulfonylhydrazone **2.15**



2.45
$C_{15}H_{26}N_2O_2S$
$M_r = 298$

2.15
$C_{25}H_{40}N_2O_2S$
$M_r = 432$

To a stirred suspension of finely ground trisylhydrazide **2.45** (3.64 g, 12.22 mmol) in methanol (5 mL) was added (+)-dihydrocarvone **2.1** (2.00 mL, 1.86 g, 12.24 mmol) which caused the suspension to clear. Concentrated HCl (12 N, 3 drops) was added to the solution. After 1 minute, a white precipitate became apparent. The reaction mixture was stirred for 15 minutes and was then placed in a freezer at -20 °C for 20 hours. The white precipitate was filtered, washed with cold methanol (20 mL) and dried *in vacuo* for 3 hours. The resulting powdery white solid **2.15** (4.73 g, 10.88 mmol, 89%) was not further purified.

MP 97 – 98 °C

ν_{max}/cm^{-1} (in $CDCl_3$) 3054 (s), 2987 (m), 2686 (w), 2306 (w), 1600 (vw), 1422 (s), 1265 (vs), 1166 (w), 896 (m).

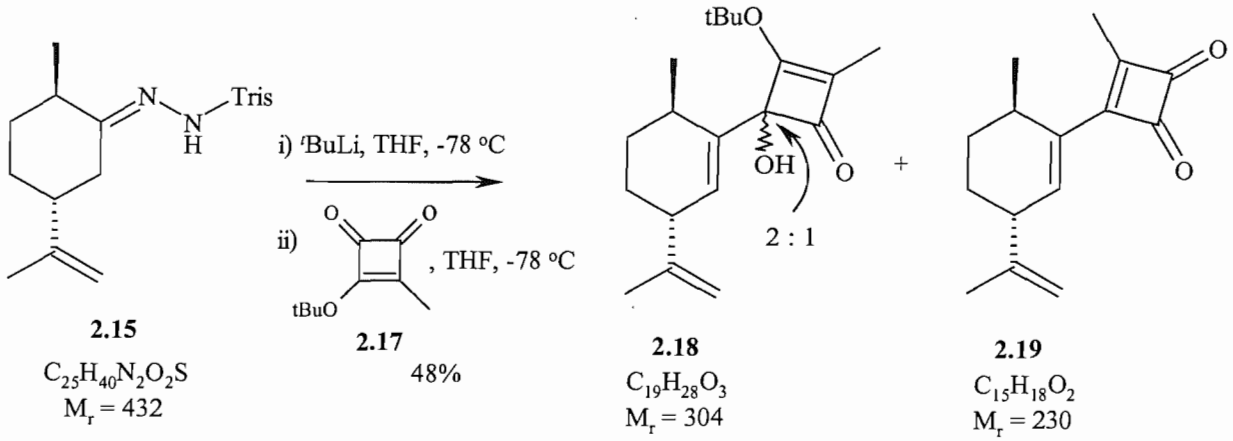
δ_H (400 MHz, $CDCl_3$) 7.32 (1H, s, aryl –C*H*-), 7.22 (1H, s, aryl –C*H*-), 4.82 (1H, s, =C*H*H), 4.77 (1H, s, =CH*H*), 4.26 (2H, septet, *J* 6.7 Hz, 2 × -C*H*$(CH_3)_2$), 2.96 (1H, septet, *J* 6.9 Hz, -C*H*$(CH_3)_2$), 2.70 (1H, ddd, *J* 13.6, 3.5, 1.5 Hz, -C*H*H-C=N), 2.23 – 1.84 (4H, m), 1.78 (3H, s, C*H*$_3$-C=CH_2), 1.32 (6H, d, *J* 6.8 Hz, -CH(C*H*$_3$)$_2$), 1.31

(12H, d, *J* 7.0 Hz, 2 × -CH(C*H*$_3$)$_2$), 1.26 – 1.05 (4H, m), 1.00 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH-C=N) ppm.

δ_C (100 MHz, $CDCl_3$) 161.5 (s, aryl-*C*-SO_2-), 153.5 (s, aryl-*C*-), 151.6 (s, 2 × aryl-*C*-), 148.4 (s, -*C*=N), 124.4 (s, -*C*=CH_2), 124.0 (d, 2 × aryl-*C*H-), 110.3 (t, -C=*C*H_2), 45.7 (d, -*C*H-C=N), 39.6 (t, -*C*H_2-C=N), 35.7 (d, *C*H_3-C-CH_2), 34.6 (d, -*C*H-C=CH_2), 31.8 (d, -*C*H(CH_3)$_2$), 31.3 (q, *C*H_3-CH-C=N), 30.3 (d, 2 × -*C*H(CH_3)$_2$), 25.3 (q, -CH(*C*H_3)$_2$), 25.2 (q, -CH(*C*H_3)$_2$), 24.0 (q, -CH(*C*H_3)$_2$), 20.9 (t, -*C*H_2-), 16.7 (t, -*C*H_2-) ppm.

LRMS (ES^+) 1319 ($[3M + Na]^+$, 100%), 865 ($[2M + H]^+$, 60%), 433 ($[MH]^+$, 52%) amu.

3-*tert*-Butoxy-4-hydroxy-4-[(3*R*,6*R*)-3-isopropenyl-6-methyl-cyclohex-1-enyl)-2-methyl-cyclobut-2-enone **2.18** and 3-[(3*R*,6*R*)-3-isopropenyl-6-methyl-1-cyclohexenyl]-4-methyl-3-cyclobutene-1,2-dione **2.19**



2.15
$C_{25}H_{40}N_2O_2S$
$M_r = 432$

2.17
48%

2.18
$C_{19}H_{28}O_3$
$M_r = 304$

2.19
$C_{15}H_{18}O_2$
$M_r = 230$

1.5 : 1

To a solution of trisylhydrazone **2.15** (0.98 g, 2.27 mmol) in THF (20 mL) at -78 °C under argon was added *tert*-butyllithium (3.1 mL of a 1.5 M solution in pentane, 4.65 mmol) dropwise over 3 minutes causing the solution to become a bright orange colour. The reaction mixture was stirred for 75 minutes at -78 °C and was then gradually warmed to -20 °C where it was kept until gas evolution had ceased (5 minutes). It was then cooled to -78 °C and a preformed solution of diketone **2.17** (0.46 g, 2.74 mmol) in THF (5 mL) was added dropwise over 5 minutes causing the mixture to turn pale yellow in colour. After stirring at -78 °C for 30 minutes, an ammonium chloride solution (20 mL) was added and the reaction mixture was allowed to warm to ambient temperature. The aqueous phase was separated and extracted with ether (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 10 – 80% ether in petroleum ether) gave firstly **2.19** (0.100 g, 0.43 mmol, 19%) as a yellow oil, then the desired product **2.18** (0.200 g, 0.66 mmol, 29%, 2:1 mixture of inseparable diastereoisomers) as a pale yellow oily solid.

Data for diketone **2.19**

ν_{max}/cm^{-1} (in $CDCl_3$)	2964 (m), 2931 (m), 1783 (s), 1763 (s), 1607 (m), 1570 (br. m), 1465 (br. m), 1376 (m), 1216 (m).
δ_H (400 MHz, $CDCl_3$)	7.08 (1H, d, *J* 3.8 Hz, =C*H*-), 4.80 (1H, br. t, *J* 1.3 Hz, =C*H*H), 4.53 (1H, br. s, =CH*H*), 2.90 (1H, br. d, *J* 3.8 Hz, -C*H*-CH=), 2.68 – 2.62 (1H, m, CH_3-C*H*-), 2.40 (3H, s, C*H*$_3$-C(CO)=C-), 1.86 – 1.82 (2H, m, 2 × -C*H*H-), 1.73 (3H, s, C*H*$_3$-C=CH_2), 1.55 – 1.49 (1H, m, -C*H*H-CH-C=), 1.42 – 1.35 (1H, m, -C*H*H-CH-CH_3), 1.03 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH-) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.
δ_C (100 MHz, $CDCl_3$)	197.2 (s, -*C*=O), 196.2 (s, -*C*=O), 191.2 (s, -*C*=C-), 189.6 (s, -C=*C*-), 144.7 (s, -*C*=CH_2), 142.1 (d, =*C*H-), 134.0 (s, -*C*=CH-), 111.1 (t, =*C*H_2), 41.4 (d, =CH-*C*H-), 27.5 (d, CH_3-*C*H-), 25.2 (t, -*C*H_2-), 20.8 (t, -*C*H_2-), 20.4 (q, *C*H_3-C=CH_2), 18.9 (q, *C*H_3-CH-), 10.8 (q, *C*H_3-C=) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
LRMS (EI)	230 ([M]$^+$, 96%), 215 ([M – CH_3]$^+$, 12%), 202 (20%), 174 ([MH – ^{t}Bu]$^+$, 100%), 159 (96%) amu.
HRMS (EI)	$C_{15}H_{18}O_2$ (M^+) requires 230.1307; found 230.1310.
$[\alpha]_D$	+309.2 (c = 0.76, $CHCl_3$)

Data for alcohol **2.18** was recorded on the mixture.

ν_{max}/cm^{-1} (in $CDCl_3$) 3370 (br.m), 2983 (m), 2937 (m), 2870 (w), 2252 (m), 1752 (s), 1599 (vs), 1388 (s), 1342 (s), 1161 (s).

δ_H (400 MHz, $CDCl_3$)

major isomer

5.59 (1H, d, *J* 3.3 Hz, =C*H*-), 4.71 (1H, br. s, =C*H*H), 4.60 (1H, br. s, =CH*H*), 2.77 (1H, br. s, -O*H*), 2.69 – 2.63 (1H, m, =C-C*H*-C=), 2.37 – 2.28 (1H, m, -C*H*-CH_3), 1.75 (3H, s, isopropenyl –CH_3), 1.67 (3H, s, =C-CH_3), 1.45 (9H, s, -C(CH_3)$_3$), 1.41 – 1.31 (2H, m, -CH_2-), 1.27 – 1.20 (2H, m, -CH_2-), 1.09 (3H, d, *J* 6.8 Hz, -CH-CH_3) ppm.

minor isomer

5.84 (1H, d, *J* 3.8 Hz, =C*H*-), 4.65 (1H, br. s, =C*H*H), 4.54 (1H, br. s, =CH*H*), 2.62 – 2.58 (1H, m, =C-C*H*-C=), 2.20 – 2.13 (1H, m, -C*H*-CH_3), 1.72 (3H, s, isopropenyl –CH_3), 1.63 (3H, s, =C-CH_3), 1.44 (9H, s, -C(CH_3)$_3$), 1.02 (3H, d, *J* 6.8 Hz, -CH-CH_3) ppm.
(-CH_2- peaks obscured by major isomer)

δ_C (100 MHz, $CDCl_3$)

major isomer

192.6 (s, -*C*=O), 178.9 (s, -*C*-O^{t}Bu), 148.7 (s, -*C*=CH_2), 139.7 (s, -*C*=CH-), 127.9 (d, -C=*C*H-), 122.2 (s, Me-*C*=), 111.5 (t, -C=*C*H_2), 94.8 (s, -*C*-OH), 83.6 (s, -*C*(CH_3)$_3$), 42.5 (d, -*C*H-), 29.2 (d, -*C*H-), 29.1 (q, -C(*C*H_3)$_3$), 28.9 (t, -*C*H_2-), 23.8 (t, -*C*H_2-), 22.0 (q, -CH-*C*H_3), 20.5 (q, *C*H_3-C=CH_2), 9.8 (q, *C*H_3-C=) ppm.

minor isomer

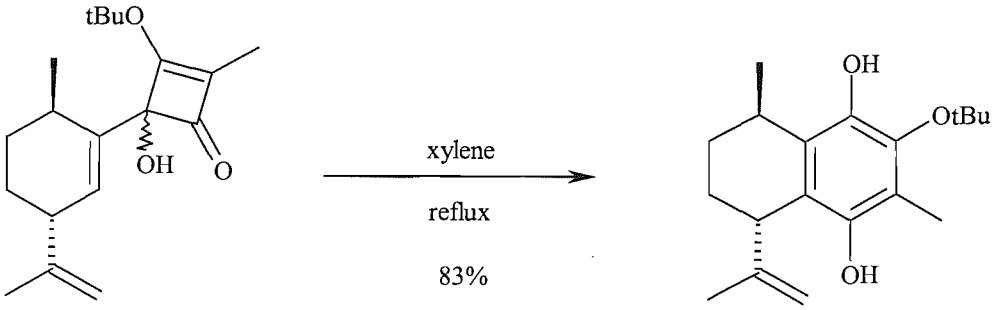
193.6 (s, -*C*=O), 180.5 (s, -*C*-O^{t}Bu), 148.8 (s, -*C*=CH_2), 140.0 (-*C*=CH-), 128.2 (d, -C=*C*H-), 123.1

(s, Me-*C*=), 111.6 (t, -C=*C*H_2), 94.5 (s, -*C*-OH), 84.0 (s, -*C*$(CH_3)_3$), 41.9 (d, -*C*H-), 29.9 (d, -*C*H-), 29.1 (q, -C(*C*$H_3)_3$), 28.3 (t, -*C*H_2-), 22.7 (t, -*C*H_2-), 22.2 (q, -CH-*C*H_3), 20.9 (q, *C*H_3-C=CH_2), 9.2 (q, *C*H_3-C=) ppm.

LRMS (CI) 305 ($[MH]^+$, 10%), 249 ($[MH - (^tBu)]^+$, 100%), 233 ($[MH - (O^tBu)]^+$, 14%) amu.

HRMS (ES^+) $C_{19}H_{28}O_3Na$ ($[M + Na]^+$) requires 327.1931; found 327.1938.

(5*S*,8*R*)-2-(*tert*-butoxy)-5-isopropenyl-3,8-dimethyl-5,6,7,8-tetrahydro-1,4-naphthalenediol **2.5**



2.18
$C_{19}H_{28}O_3$
$M_r = 304$

2.5
$C_{19}H_{28}O_3$
$M_r = 304$

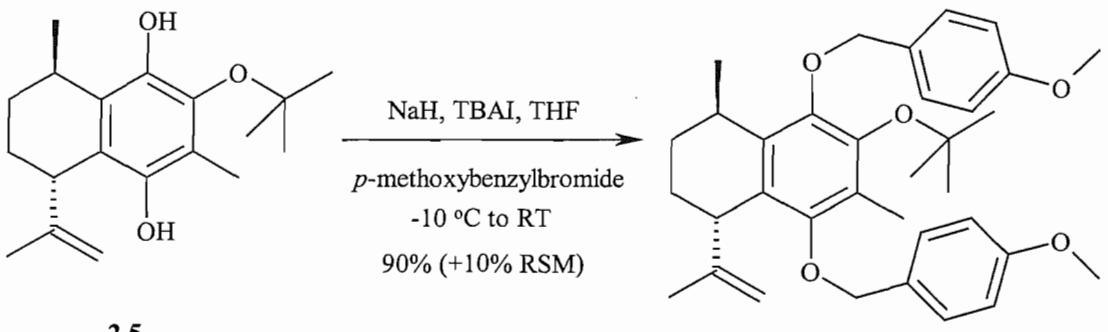
A stirred solution of alcohol **2.18** (0.18 g, 0.59 mmol) in dry xylene (40 mL) was heated to reflux under argon for 30 minutes. The solvent was removed *in vacuo* and the residual oil was purified by column chromatography (SiO_2, 5% ether in petroleum ether) to give hydroquinone **2.5** (0.15 g, 0.49 mmol, 83%) as a yellow oil.

ν_{max}/cm^{-1} (in $CDCl_3$) 3539 (br.w), 3019 (s), 2978 (m), 2941 (m), 1650 (m), 1609 (w), 1457 (m), 1217 (vs).

δ_H (400 MHz, $CDCl_3$) 5.21 (1H, s, aromatic –O*H*), 4.84 (1H, s, aromatic –O*H*), 4.37 (1H, s, =C*H*H), 4.34 (1H, s, =CH*H*), 3.30 (1H, app. d, *J* 6.3 Hz, -C*H*-C=CH_2), 3.04 (1H, app. quint., *J* 6.3 Hz, -C*H*-CH_3), 2.06 (3H, s, aromatic -CH_3), 1.97 – 1.88 (1H, m, -C*H*H-), 1.81 (3H, s, =C-CH_3), 1.75 – 1.63 (2H, m, -CH_2-), 1.43 – 1.36 (1H, m, -CH*H*-), 1.31 (9H, s, -C(CH_3)$_3$), 1.14 (3H, d, *J* 6.8 Hz, -CH-CH_3) ppm.

δ_C (100 MHz, $CDCl_3$)	147.8 (s, -*C*=CH_2), 145.0 (s, aromatic =*C*-O), 142.4 (s, aromatic =*C*-O), 139.7 (s, aromatic =*C*-O), 126.6 (s, aromatic =*C*-Me), 120.5 (s, aromatic -*C*-), 117.9 (s, aromatic -*C*-), 113.4 (t, =CH_2), 81.9 (s, -O-*C*$(CH_3)_3$), 41.0 (d, -*C*H-), 29.4 (q, -C(*C*$H_3)_3$), 27.0 (d, -*C*H-), 24.8 (t, -*C*H_2-), 22.4 (q, -*C*H_3), 20.7 (t, -*C*H_2-), 20.2 (q, aromatic -*C*H_3), 11.9 (q, CH-*C*H_3) ppm.
LRMS (CI)	304 ($[M]^+$, 56%), 248 ($[MH - (^tBu)]^+$, 100%), 231 (40%) amu.
HRMS (EI)	$C_{19}H_{28}O_3$ (M^+) requires 304.2038; found 304.2045.

(1*S*,4*R*)-6-(*tert*-butoxy)-1-isopropenyl-5,8-di(4-methoxybenzyloxy)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene **4.2**



2.5
$C_{19}H_{28}O_3$
$M_r = 304$

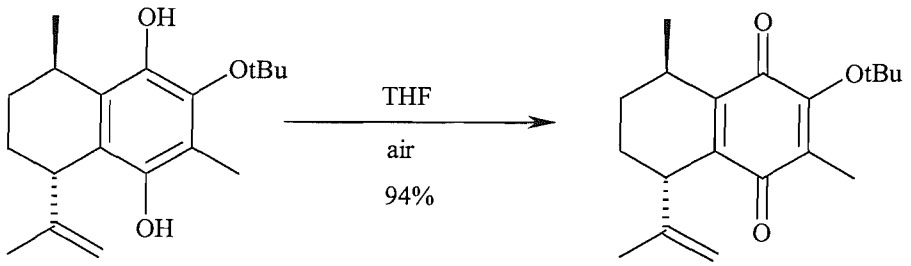
4.2
$C_{35}H_{44}O_5$
$M_r = 544$

Prepared following the procedure of Jin *et al.*[62] Thus, to a stirred suspension of sodium hydride (46 mg, 1.15 mmol) in THF (5 mL) was added hydroquinone **2.5** (0.18 g, 0.59 mmol), *p*-methoxybenzyl bromide (0.23 g, 1.15 mmol), and tetrabutylammonium iodide (21 mg, 0.06 mmol) at -10 °C under nitrogen. The reaction mixture was allowed to warm to ambient temperature and after 16 hours, another aliquot of sodium hydride (46 mg, 1.15 mmol), *p*-methoxybenzyl bromide (0.23 g, 1.15 mmol) and tetrabutylammonium iodide (21 mg, 0.06 mmol) were added. After stirring for 36 hours at room temperature, ammonium chloride (20 mL) was added. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 5% - 30% ether in petroleum ether) gave firstly recovered hydroquinone **2.5** (18 mg, 0.06 mmol, 10%) followed by alkene **4.2** (0.28 g, 0.52 mmol, 90%) as a yellow oil.

ν_{max}/cm^{-1} (neat) 2933 (s), 2864 (m), 1612 (m), 1583 (w), 1514 (vs), 1463 (s), 1416 (m), 1365 (m), 1247 (vs), 1172 (s), 1038 (s), 821 (m).

δ_H (400 MHz, $CDCl_3$)	7.26 (2H, d, *J* 8.5 Hz, 2 × -C*H*- (aryl)), 7.23 (2H, d, *J* 8.5 Hz, 2 × -C*H*- (aryl)), 6.83 (2H, d, *J* 8.5 Hz, 2 × -C*H*- (aryl)), 6.79 (2H, d, *J* 8.5 Hz, 2 × -C*H*- (aryl)), 5.00 (1H, app. d, *J* 10.8 Hz, -O-C*H*H-aryl), 4.82 (1H, obsc. d, -O-CH*H*-aryl), 4.74 (1H, d, *J* 11.0 Hz, -O-C*H*H-aryl), 4.67 (2H, br. s, =CH_2), 4.57 (1H, d, *J* 10.8 Hz, -O-CH*H*-aryl), 3.75 (3H, s, -OCH_3), 3.72 (3H, s, -OCH_3), 3.35 (1H, app. br. d., *J* 3.3 Hz, -C*H*-C=), 2.86 (1H, app. br. s, -C*H*-CH_3), 2.16 (3H, s, aryl-CH_3), 1.75 –1.65 (2H, obsc. m, -CH_2-), 1.68 (3H, s, CH_3-C=), 1.30 (9H, s, -C(CH_3)$_3$), 1.26 –1.17 (2H, m, -CH_2-), 1.09 (3H, d, *J* 7.0 Hz, CH_3-CH-) ppm.
δ_C (100 MHz, $CDCl_3$)	159.7 (s, -*C*-O (aryl)), 159.5 (s, -*C*-O (aryl)), 151.8 (s, -*C*-O (aryl)), 148.3 (s, -*C*-O (aryl)), 147.7 (s, -*C*=CH_2), 147.3 (-*C*-O (aryl)), 135.2 (s, -*C*- (aryl)), 131.0 (s, -*C*- (aryl)), 130.7 (s, -*C*- (aryl)), 129.8 (d, 2 × -*C*H- (aryl)), 129.6 (d, 2 × -*C*H- (aryl)), 128.3 (s, -*C*- (aryl)), 125.6 (s, -*C*- (aryl)), 114.2 (d, 2 × -*C*H- (aryl)), 114.0 (d, 2 × -*C*H- (aryl)), 112.4 (t, =*C*H_2), 82.1 (s, -O-*C*(CH_3)$_3$), 74.5 (t, -O*C*H_2-), 73.5 (t, -O*C*H_2-), 55.7 (q, -O*C*H_3), 55.6 (q, -O*C*H_3), 40.5 (d, -*C*H-), 29.8 (q, -C(*C*H_3)$_3$), 27.8 (d, -*C*H-), 24.8 (t, -*C*H_2-), 23.4 (q, *C*H_3-C=), 22.7 (q, *C*H_3- (aryl)), 20.9 (t, -*C*H_2-), 12.6 (q, *C*H_3-CH-) ppm.
LRMS (CI)	305 ([MH – (2 × PMB)]$^+$, 20%), 247 (100%), 231 (30%) amu. Parent ion not observed by GC-CI/EI or ES$^+$.
$[\alpha]_D$	+61.4 (c = 0.24, $CHCl_3$)

(5*S*,8*R*)-2-(*tert*-butoxy)-5-isopropenyl-3,8-dimethyl-1,4,5,6,7,8-hexahydro-1,4-naphthalenedione **2.6**



2.5
$C_{19}H_{28}O_3$
$M_r = 304$

2.6
$C_{19}H_{26}O_3$
$M_r = 302$

A solution of hydroquinone **2.5** (15 mg, 0.040 mmol) in THF (2 mL) was stirred in an open vessel at ambient temperature for 24 hours. The solvent was removed *in vacuo* and the resulting bright orange oil **2.6** (14 mg, 0.038 mmol, 94%) was not further purified.

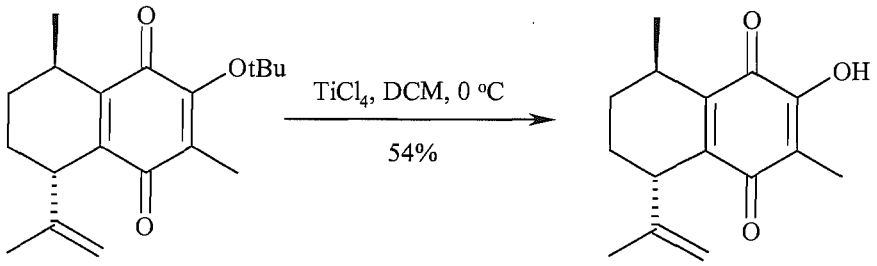
ν_{max}/cm^{-1} (neat) 3295 (w), 3263 (w), 3075 (m), 2975 (vs), 2938 (vs), 2868 (vs), 1771 (m), 1651 (br. vs), 1609 (vs), 1453 (s), 1391 (s), 1370 (s), 1144 (s).

δ_H (400 MHz, $CDCl_3$) 4.73 (1H, t, *J* 1.4 Hz, =C*H*H), 4.16 (1H, br. s, =CH*H*), 3.30 (1H, br. d, *J* 4.8 Hz, -C*H*-C=CH_2), 2.92 – 2.85 (1H, m, -C*H*-CH_3), 1.87 (3H, s, aromatic -C*H*$_3$), 1.84 (3H, s, =C-C*H*$_3$), 1.72 – 1.66 (2H, m), 1.65 – 1.61 (1H, m), 1.49 – 1.40 (1H, obsc. m), 1.32 (9H, s, -C(C*H*$_3$)$_3$), 1.03 (3H, d, *J* 7.0 Hz, -CH-C*H*$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 187.3 (s, -*C*=O), 184.2 (s, -*C*=O), 153.5 (s, -*C*=C-), 146.3 (s, -*C*=CH_2), 144.8 (s, -*C*=C-), 141.6 (s, -*C*=C-), 133.1 (s, -*C*=C-), 110.7 (t, =*C*H$_2$), 82.9 (s, -O-*C*(CH$_3$)$_3$), 37.5 (d, -*C*H-), 28.5 (q, -C(*C*H$_3$)$_3$), 25.1 (d,

	-*C*H-), 22.8 (t, -*C*H_2-), 22.1 (q, -*C*H_3), 19.3 (q, -*C*H_3), 19.2 (t, -*C*H_2-), 9.5 (q, -CH-*C*H_3) ppm.
LRMS (EI)	302 ($[M]^+$, 1%), 246 ($[MH - (^tBu)]^+$, 30%), 231 (64%) amu.
HRMS (EI)	$C_{19}H_{26}O_3$ (M^+) requires 302.1882; found 302.1886.
$[\alpha]_D$	-39.6 (c = 0.37, $CHCl_3$)

(5*S*,8*R*)-2-hydroxy-5-isopropenyl-3,8-dimethyl-1,4,5,6,7,8-hexahydro-1,4-naphthalenedione **2.7**



2.6
$C_{19}H_{26}O_3$
Mr = 302

2.7
$C_{15}H_{18}O_3$
Mr = 246

To a stirred solution of quinone **2.6** (32 mg, 0.106 mmol) in DCM (1 mL) at 0 °C under nitrogen was added titanium tetrachloride (0.015 mL, 0.15 mmol) causing the reaction mixture to turn brown. After 1 minute, water (2 mL) was added and the phases separated. The aqueous phase was extracted with DCM (2 × 5 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a brown oil. Purification by column chromatography (SiO_2, 5% ether in petroleum ether) gave the title compound **2.7** (14 mg, 0.057 mmol, 54%) as a bright yellow oil.

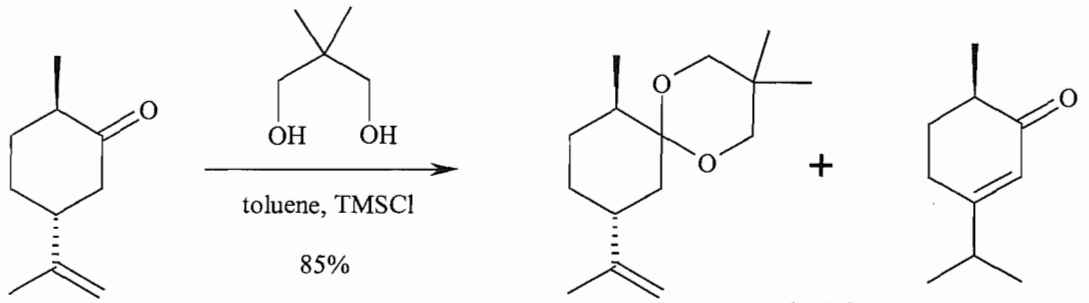
ν_{max}/cm^{-1} (neat) 3395 (br. m), 2938 (m), 2855 (w), 1641 (vs), 1619 (m), 1451 (w), 1395 (m), 1375 (m), 1337 (s), 1320 (s), 1155 (m).

δ_H (300 MHz, $CDCl_3$) 6.99 (1H, s, -O*H*), 4.84 (1H, br. s, =C*H*H), 4.27 (1H, s, =CH*H*), 3.41 (1H, d, *J* 4.5 Hz, -C*H*-C=), 2.97 – 2.91 (1H, m, -C*H*-CH_3), 1.93 (6H, s, C*H*$_3$-C= & aromatic -C*H*$_3$), 1.81 – 1.57 (3H, m), 1.49 – 1.39 (1H, m), 1.16 (3H, d, *J* 7.1 Hz, C*H*$_3$-CH-) ppm.

δ_C (75.5 MHz, $CDCl_3$) 187.3 (s, -*C*=O), 183.4 (s, -*C*=O), 151.0 (s, -C=*C*-), 147.7 (s, -*C*=CH_2), 145.8 (s, -*C*=C-), 142.7 (s, -C=*C*),

	117.1 (s, -*C*=C-), 112.2 (t, =*C*H_2), 38.8 (d, -*C*H-C=), 26.2 (d, -*C*H-C=), 23.8 (t, -*C*H_2-), 23.4 (q, -*C*H_3), 20.5 (q, -*C*H_3), 20.2 (t, -*C*H_2-), 8.2 (q, *C*H_3-CH-) ppm.
LRMS (EI)	246 ($[M]^+$, 40%), 231 ($[M - CH_3]^+$, 100%), 218 (22%), 185 (14%), 83 (38%) amu.
HRMS (EI)	$C_{15}H_{18}O_3$ (M^+) requires 246.1256; found 246.1254.
$[\alpha]_D$	-221.3 (c = 0.03, $CHCl_3$)

(7*R*,10*R*)-10-isopropenyl-3,3,7-trimethyl-1,5-dioxaspiro[5.5]undecane **3.5** and (6*R*)-3-isopropyl-6-methyl-2-cyclohexen-1-one **2.25**



2.1
$C_{10}H_{16}O$
$M_r = 152$

3.5
$C_{15}H_{26}O_2$
$M_r = 238$

1 : 2.5

2.25
$C_{10}H_{16}O$
$M_r = 152$

To a solution of (+)-dihydrocarvone **2.1** (2.72 g, 17.90 mmol) in toluene (30 mL) was added neopentyl glycol (2.79 g, 26.83 mmol) followed by chlorotrimethylsilane (4.5 mL, 3.88 g, 35.70 mmol) and the suspension was stirred at ambient temperature for 16 hours. The solvent was removed *in vacuo* and the residual oil was purified by column chromatography (SiO_2, 0 – 2% ether in petroleum ether) to give firstly acetal **3.5** (1.09 g, 4.60 mmol, 26%) as a colourless oil then ketone **2.25** (1.65 g, 10.86 mmol, 61%) as a colourless oil.

Data for acetal **3.5**

ν_{max}/cm^{-1} (in $CDCl_3$) 3073 (w), 2935 (s), 2860 (s), 1640 (m), 1465 (s), 1451 (s), 1103 (s).

δ_H (300 MHz, $CDCl_3$) 4.72 (2H, s, =C*H*$_2$), 3.82 (1H, d, *J* 11.0 Hz, -OCH*H*-), 3.63 (1H, d, *J* 11.4 Hz, -O-CH*H*-), 3.32 (2H, app. d, *J* 11.4 Hz, 2 × -O-C*H*H-), 2.78 (1H, br. d, *J* 13.2 Hz, -C*H*-CH$_3$), 2.02 (1H, tt, *J* 12.3, 2.8 Hz, -CH$_2$-C*H*-CH$_2$), 1.74 (3H, s, =C-C*H*$_3$), 1.62 – 1.51 (2H, m), 1.41 (1H, dd, *J* 12.9, 3.7 Hz, -CH*H*-CO-), 1.25 (1H, dd, *J* 12.5, 3.3 Hz, -C*H*H-CO-), 1.20 (3H, s, -C-C*H*$_3$),

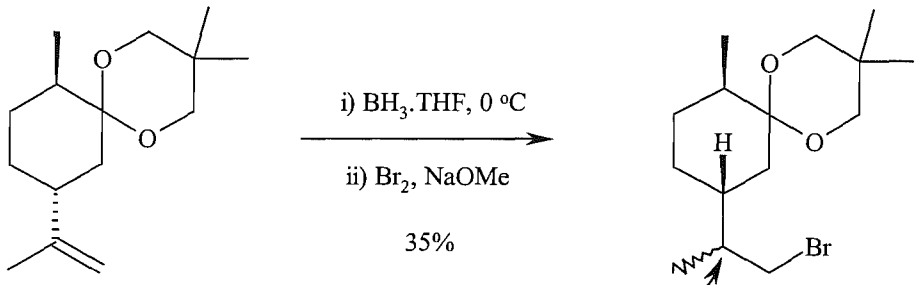
	1.05 (3H, d, *J* 6.6 Hz, -CH-C*H*$_3$), 0.99 – 0.89 (2H, m), 0.73 (3H, s, -C-C*H*$_3$) ppm.
δ_C (75.5 MHz, $CDCl_3$)	150.1 (s, -*C*=CH_2), 108.7 (t, =*C*H_2), 98.9 (s, acetal -*C*O-), 69.9 (t, -O*C*H_2-), 69.7 (t, -O*C*H_2-), 41.5 (d, -*C*H-CH_3), 41.4 (d, -CH_2-C*H*-CH_2-), 32.2 (t, -*C*H_2-), 31.5 (t, -*C*H_2-), 31.0 (t, -*C*H_2-), 30.2 (s, -*C*$(CH_3)_2$), 23.4 (q, =C-*C*H_3), 22.4 (q, -C-*C*H_3), 21.0 (q, -CH-*C*H_3), 13.8 (q, -C-*C*H_3) ppm.
LRMS (CI)	239 ($[MH]^+$, 100%), 181 (16%), 155 (48%) amu.
HRMS (EI)	$C_{15}H_{26}O_2$ (M^+) requires 238.1933; found 238.1931.
$[\alpha]_D$	-11.3 (c = 0.69, $CHCl_3$)

Data for ketone **2.25** was in accordance with literature values.[63]

ν_{max}/cm^{-1} (neat)	2958 (vs), 2932 (vs), 2869 (vs), 1673 (m), 1466 (s), 1363 (s), 1108 (vs).
δ_H (300 MHz, $CDCl_3$)	5.85 (1H, br. s, =C*H*-), 2.45 – 2.23 (4H, m), 2.07 (1H, dtd, *J* 13.1, 4.6, 4.5 Hz, -C*H*H-), 1.72 – 1.61 (1H, m, -CH*H*-), 1.13 (3H, d, *J* 6.8 Hz, C*H*$_3$-), 1.10 (3H, d, *J* 6.8 Hz, C*H*$_3$-), 1.09 (3H, d, *J* 6.8 Hz, C*H*$_3$-) ppm.
δ_C (75.5 MHz, $CDCl_3$)	203.0 (s, -*C*=O), 171.0 (s, -*C*=CH-), 123.2 (d, =*C*H-), 42.0 (d, -*C*H-C=O), 35.7 (d, -C*H*$(CH_3)_2$), 31.2 (t, -*C*H_2-), 27.5 (t, -*C*H_2-), 21.0 (q, *C*H_3-CH-CH_3), 20.7 (CH_3-CH-*C*H_3), 15.3 (q, *C*H_3-CH-) ppm.
LRMS (CI)	153 ($[MH]^+$, 100%), 110 (16%), 95 (10%) amu.

$[\alpha]_D$	+1.2 (c = 0.35, $CHCl_3$).

(2'*RS*,7*R*,10*R*)-10-(1'-Bromoprop-2'-yl)-3,3,7-trimethyl-1,5-dioxa-spiro[5.5]undecane **3.22**



3.5
$C_{15}H_{26}O_2$
$M_r = 238$

3.22
$C_{15}H_{27}BrO_2$
$M_r = 319$

Prepared following the procedure of Brown *et al.*[64] Thus, alkene **3.5** (1.50 g, 6.30 mmol) in THF (20 mL) was treated with borane-THF complex (2.10 mL, 2.10 mmol) at 0 °C under nitrogen. The solution was allowed to warm to ambient temperature and stirred for one hour. A freshly prepared solution of sodium methoxide (0.16 g, 6.93 mmol in 6.93 mL methanol) and bromine (0.32 mL, 6.30 mmol) was added simultaneously over 15 minutes. The orange solution was stirred for 20 minutes after which potassium carbonate (10 mL, saturated aqueous solution) and water (10 mL) were added until all excess bromine had been destroyed. The resulting clear solution was extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 0 – 1% ether in petroleum ether) yielded **3.22** (0.71 g, 2.23 mmol, 35%) as a clear oil and as an inseparable 1:1 mixture of diastereoisomers.

ν_{max}/cm^{-1} (neat) 2933 (vs), 2859 (s), 1711 (w), 1468 (s), 1450 (s), 1394 (m), 1152 (m), 1104 (vs).

δ_H (400 MHz, $CDCl_3$) 3.68 (1H, d, *J* 11.3 Hz, -O-C*H*H-, one isomer), 3.66 (1H, d, *J* 11.5 Hz, -O-C*H*H-, other isomer), 3.55 (1H,

d, *J* 11.3 Hz, -O-C*H*H-, one isomer), 3.47 (1H, d, *J* 11.6 Hz, -O-C*H*H-, other isomer), 3.36 – 3.29 (2H, m, 2 × -C*H*H-Br), 3.25 (1H, d, *J* 9.8 Hz, -CH*H*-Br, one isomer), 3.23 (1H, d, *J* 9.8 Hz, -CH*H*-Br, other isomer), 3.18 (4H, br. d, *J* 11.3 Hz, 4 × -O-CH*H*-), 2.64 (1H, app. dt, *J* 13.8, 2.0 Hz, -CH_2-C*H*-CH_2-, one isomer), 2.60 (1H, app. dt, *J* 13.8, 2.3 Hz, -CH_2-C*H*-CH_2-, other isomer), 1.63 – 1.20 (14H, m), 1.05 (6H, s, 2 × -C-CH_3), 0.89 (12H, d, *J* 6.3 Hz, 4 × -CH-CH_3), 0.68 – 0.55 (2H, obsc. m), 0.60 (6H, s, 2 × -C-CH_3) ppm.

δ_C (100 MHz, $CDCl_3$)

99.1 (s, -*C*-O), 99.0 (s, -*C*-O), 70.2 (t, 2 × -O-*C*H_2-), 70.1 (t, -O-*C*H_2-), 70.0 (t, -O-*C*H_2-), 41.8 (d, 2 × CH_3-*C*H-C-O), 40.4 (t, -*C*H_2-Br), 40.3 (d, -*C*H-), 40.1 (d, -*C*H-), 39.9 (t, -*C*H_2-Br), 37.4 (d, -*C*H-), 37.3 (d, -*C*H-), 31.5 (t, -*C*H_2-), 31.0 (t, -*C*H_2-), 30.9 (t, -*C*H_2-), 30.4 (t, -*C*H_2-), 30.3 (q, 2 × -*C*$(CH_3)_2$), 29.4 (t, -*C*H_2-), 28.5 (t, -*C*H_2-), 23.6 (q, 2 × -C-*C*H_3), 22.7 (q, 2 × -C-*C*H_3), 16.3 (q, -CH-*C*H_3), 16.2 (q, -CH-*C*H_3), 14.0 (q, 2 × -CH-*C*H_3) ppm.

LRMS (CI)

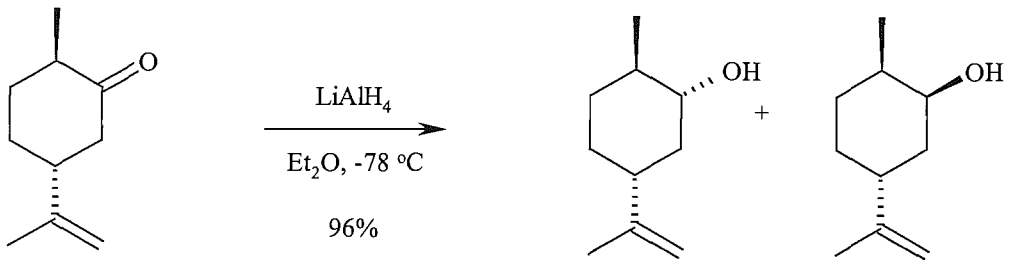
321 ($[MH]^+$, (^{81}Br), 20%), 319 ($[MH]^+$, (^{79}Br), 20%), 239 ($[MH - (HBr)]^+$, 100%), 197 (10%), 155 (34%) amu.

HRMS (EI)

$C_{15}H_{27}O_2{}^{79}Br$ (M^+) requires 318.1194; found 318.1179.

$C_{15}H_{26}O_2{}^{79}Br$ ($[M - H]^+$) requires 317.1116; found 317.1120.

(1*R*,2*R*,5*R*)-5-isopropenyl-2-methylcyclohexan-1-ol **(*R*)-3.6** and (1*S*,2*R*,5*R*)-5-isopropenyl-2-methylcyclohexan-1-ol **(*S*)-3.6**



2.1
(+)-dihydrocarvone
$C_{10}H_{16}O$
$M_r = 152$

(*R*)-3.6
$C_{10}H_{18}O$
$M_r = 154$

(*S*)-3.6
$C_{10}H_{18}O$
$M_r = 154$

11 : 1

To a stirred suspension of lithium aluminium hydride (0.76 g, 20.00 mmol) in ether (30 mL) at -78 °C under nitrogen was added a solution of (+)-dihydrocarvone **2.1** (6.1 g, 40.00 mmol) in ether (30 mL) dropwise over 10 minutes. The reaction was stirred for 5 minutes then quenched with ammonium chloride (30 mL). After warming to ambient temperature, the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (SiO_2, 10 – 25% ether in petroleum ether) gave firstly alcohol **(*S*)-3.6** (0.49 g, 3.18 mmol, 8%) then alcohol **(*R*)-3.6** (5.42 g, 35.19 mmol, 88%) both as clear oils. Physical and spectroscopic data were in accordance with literature values.[65]

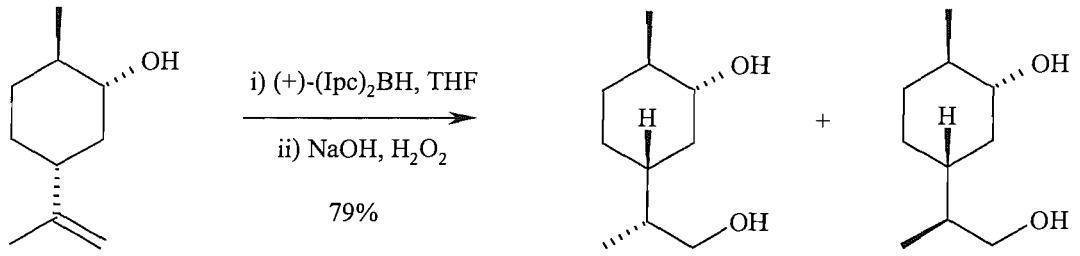
Data for **(*R*)-3.6**

ν_{max}/cm^{-1} (neat) 3348 (br. s), 3078 (w), 2926 (vs), 2870 (s), 1645 (m), 1452 (s), 1374 (w), 1050 (s), 887 (s).

δ_H (400 MHz, $CDCl_3$) 4.73 (2H, s, =C*H*$_2$), 3.23 (1H, td, *J* 10.3, 3.9 Hz, C*H*OH), 2.09 – 1.99 (2H, m), 1.83 – 1.72 (2H, obsc. m), 1.77 (3H, s, =C-C*H*$_3$), 1.59 (1H, br. s, O*H*), 1.31 – 1.11 (4H, m), 1.07 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH-) ppm.

δ_C (100 MHz, $CDCl_3$)	149.8 (s, -*C*=CH_2), 108.8 (t, =*C*H_2), 76.8 (d, -*C*HOH), 44.6 (d, -*C*H-CHOH), 41.0 (t, -*C*H_2-CHOH), 40.4 (d, -CH_2-*C*H-CH_2-), 33.7 (t, -*C*H_2-), 31.5 (t, -*C*H_2-), 21.3 (q, *C*H_3-C=), 18.7 (q, *C*H_3-CH-) ppm.
LRMS (CI)	172 ($[M + NH_4]^+$, 36%), 155 ($[MH]^+$, 50%), 137 ($[MH - H_2O]^+$, 100%) amu.
$[\alpha]_D$	-19.7 (c = 0.59, $CHCl_3$)
Data for **(*S*)-3.6**	
ν_{max}/cm^{-1} (neat)	3406 (br. s), 3083 (w), 2925 (vs), 2871 (s), 1643 (m), 1451 (s), 1376 (m), 995 (s), 886 (s).
δ_H (400 MHz, $CDCl_3$)	4.73 (2H, s, =C*H*$_2$), 3.93 (1H, br. s, -C*H*OH), 2.32 (1H, tt, *J* 12.3, 3.3 Hz, -CH_2-C*H*-CH_2-), 1.96 (1H, app. dq, *J* 13.6, 3.1 Hz, -C*H*H-CHOH), 1.81 (1H, app. dquint., *J* 12.8, 3.1 Hz, -C*H*H-CH-CHH), 1.76 (3H, s, C*H*$_3$-C), 1.60 – 1.41 (5H, m), 1.24 (1H, qd, *J* 12.3, 4.7 Hz, -CH*H*-CH-CHH-), 1.01 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-) ppm.
δ_C (100 MHz, $CDCl_3$)	152.5 (s, *C*=CH_2), 110.6 (t, C=*C*H_2), 73.2 (d, *C*HOH), 40.9 (t, *C*H_2-CHOH), 40.0 (d, CH_3-*C*H), 38.3 (q, *C*H_3-C=), 33.7 (t, *C*H_2), 30.4 (t, *C*H_2), 23.2 (d, *C*H-C=CH_2), 20.6 (q, *C*H_3-CH) ppm.
LRMS (CI)	172 ($[M + NH_4]^+$, 8%), 155 ($[MH]^+$, 16%), 137 ($[MH - H_2O]^+$, 100%) amu.
$[\alpha]_D$	+21.5 (c = 0.94, $CHCl_3$)

(1*R*,2*R*,5*R*)-5-((2*S*)-1-Hydroxyprop-2-yl)-2-methyl-cyclohexanol **3.45** and (1*R*,2*R*,5*R*)-5-((2*R*)-1-hydroxyprop-2-yl)-2-methyl-cyclohexanol **3.46**



(*R*)-3.6
$C_{10}H_{18}O$
$M_r = 154$

3.45
$C_{10}H_{20}O_2$
$M_r = 172$

3.46
$C_{10}H_{20}O_2$
$M_r = 172$

1 : 2.3

An ice-cold solution of (+)-alpha-pinene (0.64 mL, 4.0 mmol) in THF (10 mL) was treated with borane.dimethylsulfide (0.19 mL, 2.0 mmol) for 30 minutes. Alcohol **(*R*)-3.6** (0.34 g, 2.2 mmol) as a solution in THF (10 mL) was then added dropwise over 5 minutes. The reaction mixture was stirred at ambient temperature for 75 minutes and then treated with sodium hydroxide (0.73 mL, 2.2 mmol) followed by hydrogen peroxide (30% w/w aqueous solution, 0.66 g, 6.4 mmol). After 16 hours, water (50 mL) was added and the reaction mixture extracted with chloroform (3 × 30 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 55 % ethyl acetate in petroleum ether) gave firstly diol **3.45** (0.090 g, 0.52 mmol, 24%) as a white solid which was recrystallised from ether/petrol, then diol **3.46** (0.209g, 1.22 mmol, 55%) as clear crystals. X-ray data was obtained on both compounds (see Chapter VI). Spectroscopic data were in accordance with literature data (reported on the mixture of diastereoisomers).[66]

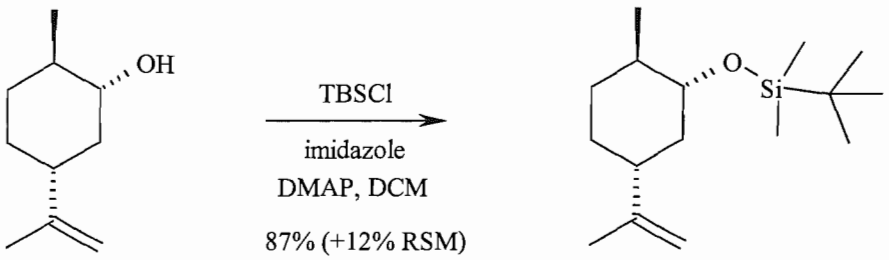
Data for **3.45**

MP 83-85 °C (ether/petrol)

ν_{max}/cm^{-1} (neat)	3335 (br. s), 2921 (vs), 2872 (s), 1453 (m), 1372 (w), 1337 (w), 1035 (s).
δ_H (400 MHz, $CDCl_3$)	3.61 (1H, dd, *J* 10.3, 5.8 Hz, -C*H*H-OH), 3.49 (1H, dd, *J* 10.7, 6.4 Hz, -CH*H*-OH), 3.14 (1H, td, *J* 10.1, 4.4 Hz, -C*H*OH), 1.92 (1H, br. d, *J* 11.8 Hz, -C*H*H-CHOH), 1.76 – 1.70 (1H, m, -C*H*-CHOH), 1.62 – 1.44 (5H, m), 1.30 – 1.19 (2H, m), 1.15 – 0.95 (2H, obsc. m), 1.01 (3H, d, *J* 6.3 Hz, C*H*$_3$-), 0.91 (3H, d, *J* 7.0 Hz, C*H*$_3$-) ppm.
δ_C (100 MHz, $CDCl_3$)	77.1 (d, -*C*HOH), 66.6 (t, -*C*H_2OH), 40.7 (d, -*C*H-CHOH), 40.6 (d, -*C*H-CH_2OH), 38.5 (d, -CH_2-*C*H-CH_2), 38.1 (t, -*C*H_2-CHOH), 33.6 (t, -*C*H_2-), 30.5 (t, -*C*H_2-), 18.7 (q, *C*H_3-CH-), 13.7 (q, *C*H_3-CH-) ppm.
LRMS (EI)	172 ($[M]^+$, 1%), 154 ($[M - (H_2O)]^+$, 8%), 136 ($[M - 2(H_2O)]^+$, 38%), 107 (48%), 93 (90%), 79 (100%) amu.
HRMS (EI)	$C_{10}H_{20}O_2$ (M^+) requires 172.1463; found 172.1462.
$[\alpha]_D$	-11.0 (c = 0.83, $CHCl_3$)
Data for **3.46**	
MP	59-61 °C
ν_{max}/cm^{-1} (neat)	3334 (br. s), 2922 (vs), 2872 (s), 1453 (m), 1372 (w), 1043 (s), 1020 (s).
δ_H (400 MHz, $CDCl_3$)	3.60 (1H, dd, *J* 10.5, 5.5 Hz, -C*H*H-OH), 3.49 (1H, dd, *J* 10.5, 6.5 Hz, -CH*H*-OH), 3.15 (1H, td, *J* 10.3, 4.3 Hz, -C*H*OH), 1.94 – 1.89 (1H, m, -C*H*H-CHOH), 1.76 - 1.70 (1H, m), 1.82 – 1.45 (5H, obsc. m), 1.29 –

	1.20 (1H, m, -C*H*-CH_3), 1.11 (1H, app. q, *J* 11.7 Hz, -CH*H*-CHOH), 1.05 – 0.97 (1H, obsc. m), 1.01 (3H, d, *J* 6.3 Hz, C*H*$_3$-), 0.94 – 0.83 (1H, obsc. m), 0.90 (3H, d, *J* 6.8 Hz, C*H*$_3$-) ppm.
δ_C (100 MHz, $CDCl_3$)	77.0 (d, -*C*HOH), 66.5 (t, -*C*H_2OH), 40.7 (d, -*C*H-CH_2OH), 40.6 (d, -*C*H-CHOH), 40.3 (t, -*C*H_2-CHOH), 38.6 (d, -CH_2-*C*H-CH_2-), 33.6 (t, -*C*H_2-), 28.3 (t, -*C*H_2-), 18.7 (q, *C*H_3-CH-), 13.8 (q, *C*H_3-CH) ppm.
LRMS (EI)	172 ($[M]^+$, 1%), 154 ($[M - (H_2O)]^+$, 24%), 136 ($[M - 2(H_2O)]^+$, 62%), 113 (100%), 95 (100%), 55 (98%) amu.
HRMS (EI)	$C_{10}H_{20}O_2$ (M^+) requires 172.1463; found 172.1461.
$[\alpha]_D$	-15.2 (c = 0.39, $CHCl_3$)

tert-butyl-[(1*R*,2*R*,5*R*)-5-isopropenyl-2-methylcyclohexyloxy]dimethylsilane **3.7**



(*R*)-3.6
$C_{10}H_{18}O$
$M_r = 154$

3.7
$C_{16}H_{32}OSi$
$M_r = 268$

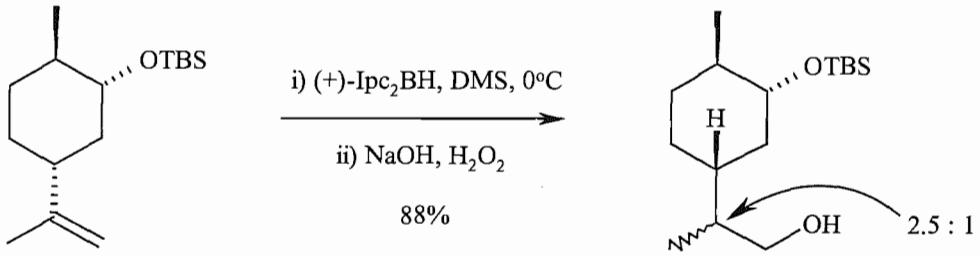
To alcohol **(*R*)-3.6** (12.0 g, 78.0 mmol) in DCM (100 mL) was added imidazole (13.3 g, 0.196 mol), 4-dimethylaminopyridine (0.19 g, 1.57 mmol) and *tert*-butyldimethylsilyl chloride (12.9 g, 86.1 mmol). The reaction mixture was stirred at ambient temperature for 16 hours then ammonium chloride (50 mL, saturated aqueous solution) was added and the phases were separated. The aqueous phase was extracted with ether (3 × 35 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 100 % petroleum ether) gave firstly silyl ether **3.7** (18.2 g, 67.9 mmol, 87%) as a colourless oil then recovered starting material **(*R*)-3.6** (1.4 g, 9.4 mmol, 12%) as a clear oil.

ν_{max}/cm^{-1} (neat) 3620 (w), 2928 (m), 2858 (m), 1643 (w), 1454 (s), 1377 (s), 1216 (m).

δ_H (400 MHz, $CDCl_3$) 4.62 (2H, s, =C*H*$_2$), 3.10 (1H, td, *J* 10.0, 4.2 Hz, -C*H*-O), 1.89 (1H, tt, *J* 12.2, 3.1 Hz, -CH$_2$-C*H*-CH$_2$-), 1.84 – 1.78 (1H, m, -C*H*H-CH-O), 1.71 – 1.56 (2H, obsc. m, 2 × -CH*H*-), 1.65 (3H, s, =C-C*H*$_3$), 1.21 (1H, br. q., *J* 11.9 Hz, -C*H*-CH-O-), 1.11 (1H, qd, *J* 12.5, 3.3 Hz, -C*H*H-), 1.02 – 0.85 (1H, obsc. m, -C*H*H-), 0.89

	(3H, d, *J* 6.3 Hz, -CH-CH_3), 0.84 (9H, s, -Si-C(CH_3)$_3$), 0.00 (6H, s, -Si(CH_3)$_2$-) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
δ_C (100 MHz, $CDCl_3$)	150.2 (s, -*C*=CH_2), 108.9 (t, -C=*C*H_2), 77.6 (d, -*C*H-O), 44.8 (d, -CH_2-*C*H-CH_2-), 41.6 (t, -*C*H_2-CH-O), 40.6 (d, -C*H*-CH-O-), 33.7 (t, -*C*H_2-), 31.6 (t, -*C*H_2-), 26.3 (q, -C(*C*H_3)$_3$), 21.1 (q, *C*H_3-C=), 19.5 (q, *C*H_3-CH), 18.5 (s, -Si-*C*(CH$_3$)$_3$), -3.6 (q, -Si-(*C*H_3)), -4.2 (q, -Si-(*C*H_3)) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
LRMS (CI)	269 ([MH]$^+$, 2%), 211 (10%), 154 (10%), 137 (100%) amu.
HRMS	$C_{16}H_{31}OSi$ ([M – H]$^+$) requires 267.2144; found 267.2138.
$[\alpha]_D$	-40.8 (c = 0.63, $CHCl_3$)

(2'*RS*)-2'-{[(1*R*,3*R*,4*R*)-3-*tert*-butyldimethylsilyloxy]-4-methylcyclohexyl)}-1'-propanol **3.29**



3.7
$C_{16}H_{32}OSi$
$M_r = 268$

3.29
$C_{16}H_{34}O_2Si$
$M_r = 286$

To an ice-cold solution of (+)-alpha-pinene **3.47** (0.86 mL, 5.4 mmol) in THF (10 mL) was added borane-DMS (0.26 mL, 2.7 mmol) and the reaction mixture was stirred at room temperature for 2.5 hours. Silyl ether **3.7** (0.54 g, 2.0 mmol) was then added dropwise as a solution in THF (10 mL) and the resulting reaction mixture was stirred at ambient temperature for 2 hours. Sodium hydroxide (3M, 0.9 mL, 2.7 mmol) was then added, followed by hydrogen peroxide (30% w/w solution in water, 0.92 g, 8.1 mmol). The resulting solution was stirred at room temperature for 16 hours. Water (50 mL) was added and the reaction mixture was extracted into chloroform (3 × 30 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. Column chromatography (SiO_2, 5% – 15 % ether in petroleum ether) gave the desired alcohol **3.29** (5.05 g, 17.6 mmol, 88%) as a pale yellow oil as an inseparable mixture of diastereomers in a 2.5:1 ratio. Data were recorded on the mixture.

ν_{max}/cm^{-1} (neat) 3348 (br. m), 2953 (s), 2928 (vs), 2857 (s), 1472 (m), 1463 (m), 1361 (w), 1255 (s), 1082 (vs), 834 (vs).

δ_H (300 MHz, $CDCl_3$) 3.62 (1H, obsc. dd, *J* 10.3, 5.6 Hz, -C*H*H-OH, minor isomer), 3.61 (1H, dd, *J* 10.3, 6.5 Hz, -C*H*H-OH,

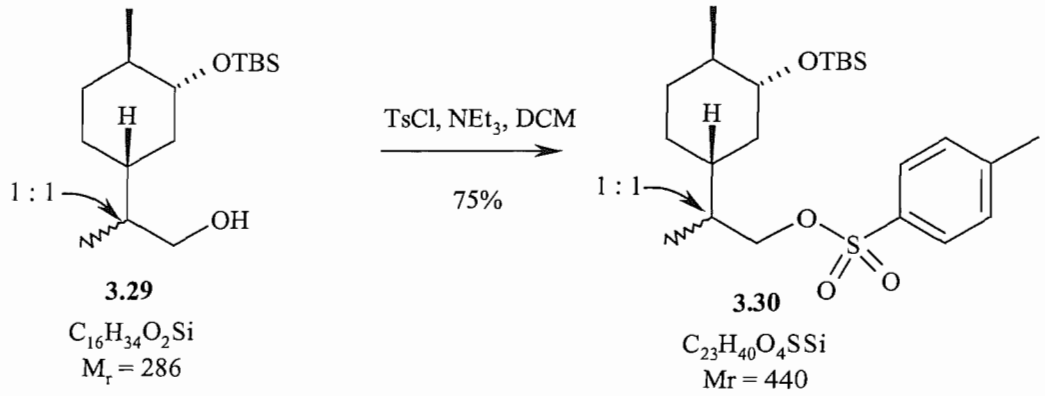
major isomer), 3.48 (2H, dd, *J* 10.5, 6.7 Hz, -CH*H*-OH), 3.18 – 3.08 (1H, obsc. m, -C*H*-OTBS, minor isomer), 3.14 (1H, td, *J* 9.9, 4.3 Hz, -C*H*-OTBS), 1.82 – 1.65 (4H, m), 1.59 – 1.40 (6H, m), 1.29 – 1.02 (6H, m), 1.00 – 0.81 (10H, obsc. m), 0.99 (6H, d, *J* 7.0 Hz, 2 × C*H*$_3$-CH), 0.84 (18H, s, 2 × Si-C(C*H*$_3$)$_3$), 0.03 (12H, s, 2 × Si-(C*H*$_3$)$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 77.8 (d, -*C*H-OTBS, minor isomer), 77.7 (d, -*C*H-OTBS, major isomer), 66.7 (t, -*C*H$_2$OH, major isomer), 66.6 (t, -*C*H$_2$OH, minor isomer), 40.9 (t, -*C*H$_2$-CH-OTBS, major isomer), 40.8 (d, -*C*H-CH-OTBS, major isomer), 40.8 (d, -*C*H-CH-OTBS, minor isomer), 40.7 (d, 2 × -*C*H-CH$_2$OH), 39.5 (t, -*C*H$_2$-CH-OTBS, minor isomer), 38.8 (d, -CH$_2$-*C*H-CH$_2$-, minor isomer), 38.4 (d, -CH$_2$-*C*H-CH$_2$-, major isomer), 33.8 (t, -*C*H$_2$-, minor isomer), 33.7 (t, -*C*H$_2$-, major isomer), 30.4 (t, -*C*H$_2$-, minor isomer), 28.1 (t, -*C*H$_2$-, major isomer), 26.3 (q, 2 × -C(*C*H$_3$)$_3$), 19.5 (d, 2 × *C*H$_3$-CH-), 18.5 (s, 2 × -*C*(CH$_3$)$_3$), 14.0 (q, *C*H$_3$-CH-, minor isomer), 13.5 (q, *C*H$_3$-CH-, major isomer), -3.6 (q, 2 × -Si-(*C*H$_3$)), -4.2 (q, 2 × -Si-(*C*H$_3$)) ppm.

LRMS (CI) 287 ([MH]$^+$, 26%), 172 ([MH – (TBS)]$^+$, 10%), 155 ([M – (OTBS)]$^+$, 64%), 137 ([M – (OTBS) – (H$_2$O)]$^+$, 100%) amu.

HRMS (EI) $C_{16}H_{33}O_2Si$ ([M – H]$^+$) requires 285.2250; found 285.2245.

2-((1*R*,3*R*,4*R*)-3-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-4-methylcyclohexyl)propyl 4-methyl-1-benzenesulfonate **3.30**



3.29
$C_{16}H_{34}O_2Si$
$M_r = 286$

3.30
$C_{23}H_{40}O_4SSi$
Mr = 440

To a stirred solution of alcohol **3.29** (1.78 g, 6.23 mmol) in DCM (30 mL) was added triethylamine (2.17 mL, 15.6 mmol) followed by *p*-toluenesulfonyl chloride (2.37 g, 12.45 mmol) and the reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a brown oil. Purification by column chromatography (SiO_2, 10% - 20% ether in petroleum ether) gave tosylate **3.30** (2.06 g, 4.7 mmol, 75%) as a colourless oil as an inseparable mixture of diastereoisomers.

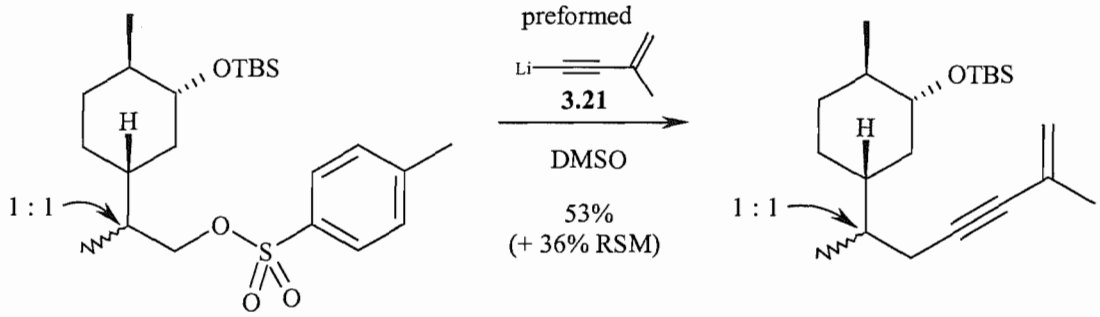
Data were recorded on the mixture.

ν_{max}/cm^{-1} (neat) 2951 (s), 2927 (s), 2856 (s), 1599 (w), 1463 (m), 1362 (s), 1256 (s), 1189 (s), 1177 (vs), 1081 (s), 967 (m), 834 (s).

δ_H (400 MHz, $CDCl_3$) 7.77 (4H, d, *J* 8.3 Hz, 4 × -C*H*-(aryl)), 7.33 (4H, d, *J* 7.8 Hz, 4 × -C*H*-(aryl)), 3.94 (2H, dd, *J* 9.3, 5.8 Hz, 2 × -C*H*H-OTs), 3.89 – 3.81 (2H, m, 2 × -CH*H*-OTs), 3.12 – 3.02 (2H, m, 2 × -C*H*-OTBS), 2.43 (6H, s, 2 × -C*H*$_3$ (aryl)), 1.75 – 1.62 (6H, m), 1.45 – 1.20 (8H,

	m), 1.15 – 0.95 (4H, m), 0.91 (6H, d, *J* 6.6 Hz, 2 × C*H*$_3$-CH-), 0.89 (18H, s, 2 × -C(C*H*$_3$)$_3$), 0.84 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH-), 0.81 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH), 0.02 (3H, s, -Si-(C*H*$_3$)), 0.02 (3H, s, -Si-(C*H*$_3$)), 0.01 (3H, s, -Si(C*H*$_3$)), 0.00 (3H, s, -Si-(C*H*$_3$)) ppm.
δ_C (100 MHz, $CDCl_3$)	145.1 (s, 2 × -*C*-(aryl)), 133.6 (s, 2 × -*C*-(aryl)), 130.2 (d, 4 × -*C*H-(aryl)), 128.3 (d, 4 × -*C*H-(aryl)), 77.4 (d, -*C*HOTBS), 77.3 (d, -*C*HOTBS), 73.8 (t, -*C*H$_2$OTs), 73.7 (t, -*C*H$_2$OTs), 40.7 (d, -CH$_2$-*C*H-CH$_2$-), 40.6 (d, -CH$_2$-*C*H-CH$_2$-), 40.4 (t, -*C*H$_2$-CHOTBS), 38.7 (t, -*C*H$_2$-CHOTBS), 38.3 (d, CH$_3$-*C*H-), 37.9 (d, CH$_3$-*C*H-), 37.7 (d, 2 × CH$_3$-*C*H-), 33.4 (t, -*C*H$_2$-), 33.3 (t, -*C*H$_2$-), 30.0 (t, -*C*H$_2$-), 27.5 (t, -*C*H$_2$-), 26.3 (q, 2 × -C(*C*H$_3$)$_3$), 22.0 (q, 2 × *C*H$_3$-aryl), 19.4 (q, 2 × *C*H$_3$-CH-), 18.5 (s, 2 × -*C*(CH$_3$)$_3$), 14.0 (q, *C*H$_3$-CH-), 13.3 (q, *C*H$_3$-CH-), -3.6 (q, 2 × -Si(*C*H$_3$)), -4.2 (q, 2 × -Si(*C*H$_3$)) ppm.
LRMS (CI)	441 ([MH]$^+$, 2%), 326 ([MH – TBS]$^+$, 2%), 269 ([M – OTs]$^+$, 2%), 211 ([M – (TsOH) – ^{t}Bu]$^+$, 22%), 137 ([M – (TsOH) – OTBS]$^+$, 100%) amu.
HRMS	$C_{23}H_{40}O_4SSiNa$ ([M + Na]$^+$) requires 463.2314; found 463.2314.

tert-Butyl[(1*R*,2*R*,5*R*)-5-(1,5-dimethyl-5-hexen-3-ynyl)-2-methylcyclohexyl]oxydimethylsilane **3.31 A**



3.30
$C_{23}H_{40}O_4SSi$
Mr = 440

3.31 A
$C_{21}H_{38}OSi$
M_r = 334

A solution of 2-methyl-1-butene-3-yne **3.20** (0.16 mL, 1.7 mmol) in THF (5 mL) was treated with *n*-butyllithium (0.59 mL of a 2.49M solution in hexanes, 1.48 mmol) at -45 °C under nitrogen. After 50 minutes, the preformed lithium anion solution was added to a solution of tosylate **3.30** (0.5 g, 1.14 mmol) in DMSO (40 mL) at room temperature. The clear reaction mixture gradually turned dark red in colour. After 30 minutes, water (50 mL) was added. The phases were separated and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic fractions were washed with water (5 × 20 mL) and brine (2 × 25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% ether in petroleum ether) yielded alkyne **3.31 A** (0.20 g, 0.60 mmol, 53%, 1:1 mixture of diasteroisomers) as a clear oil, followed by recovered tosylate **3.30** (0.18 g, 0.40 mmol, 36%).

Data was recorded on the mixture.

ν_{max}/cm^{-1} (neat) 2952 (s), 2927 (s), 2856 (s), 2354 (w), 1612 (w), 1471 (m), 1463 (m), 1455 (m), 1360 (w), 1255 (s), 1081 (vs).

δ_H (400 MHz, $CDCl_3$) 5.13 (2H, br. s, 2 × =C*H*H), 5.07 (2H, app. t, *J* 1.6 Hz, 2 × =CH*H*), 3.08 (1H, td, *J* 10.0, 4.3 Hz, -C*H*-OTBS), 3.06 (1H, td, *J* 10.0, 4.3 Hz, -C*H*-OTBS), 2.26 (1H, dd, *J* 16.8, 5.5 Hz, -C*H*H-CH-O), 2.25 (1H, dd, *J* 16.8, 5.3 Hz -C*H*H-CH-O), 2.14 (2H, br. dd, *J* 16.8, 8.0 Hz, 2 × -CH*H*-CH-O), 1.81 (6H, s, 2 × C*H*$_3$-C=), 1.81 – 1.72 (2H, obsc. m), 1.68 – 1.63 (2H, m), 1.58 – 1.47 (4H, m), 1.38 – 1.18 (6H, m), 0.91 (6H, d, *J* 6.8 Hz, 2 × C*H*$_3$-CH-), 0.91 (4H, d, *J* 6.8 Hz, 2 × -C*H*$_2$-C≡C-), 0.87 (6H, d, *J* 6.5 Hz, 2 × C*H*$_3$-CH-), 0.84 (18H, s, 2 × -C(C*H*$_3$)$_3$), - 0.12 (12H, s, 2 × -Si(C*H*$_3$)$_2$-) ppm.

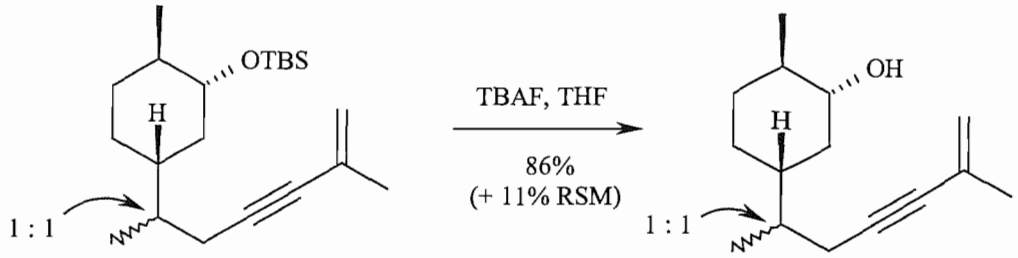
δ_C (100 MHz, $CDCl_3$) 127.8 (s, 2 × -*C*=CH$_2$), 120.5 (t, 2 × =*C*H$_2$), 88.8 (s, 2 × -*C*≡C-), 83.3 (s, 2 × -C≡*C*-), 77.8 (d, -*C*H-OTBS), 77.7 (d, -*C*H-OTBS), 41.2 (d, -CH$_2$-*C*H-CH$_2$-), 41.1 (d, -CH$_2$-*C*H-CH$_2$-), 40.8 (d, 2 × -*C*H-CH-O-), 40.6 (t, -*C*H$_2$-C-O), 38.9 (t, -*C*H$_2$-C-O), 37.8 (d, CH$_3$-*C*H), 37.7 (d, CH$_3$-*C*H-), 33.7 (t, -*C*H$_2$-), 33.6 (t, -*C*H$_2$-), 30.0 (t, -*C*H$_2$-), 28.5 (t, -CH$_2$-), 26.3 (q, 2 × -C(*C*H$_3$)$_3$), 24.8 (t, -*C*H$_2$-C≡), 24.7 (t, -*C*H$_2$-C≡), 24.3 (q, 2 × *C*H$_3$-C=), 19.5 (q, 2 × *C*H$_3$-CH), 18.5 (s, 2 × -*C*(CH$_3$)$_3$), 16.9 (q, 2 × *C*H$_3$-CH), -3.6 (q, 2 × -Si(*C*H$_3$)), -4.3 (q, 2 × -Si(*C*H$_3$)) ppm.

LRMS (EI) 334 ([M]$^+$, 2%), 277 ([M- ^{t}Bu]$^+$, 10%), 201 (14%), 121 (12%), 75 (100%) amu.

HRMS (EI) $C_{21}H_{38}OSi$ (M^+) requires 334.2692; found 334.2704.

(1*R*,2*R*,2'*RS*,5*R*)-5-(2'-Methyl-hept-1'-en-3'-yn-6'-yl)-2-methylcyclohexan-1-ol

3.31 B



3.31 A
$C_{21}H_{38}OSi$
$M_r = 334$

3.31 B
$C_{15}H_{24}O$
$M_r = 220$

To a solution of alkyne **3.31 A** (0.2 g, 0.6 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.2 mL of a 1M solution in THF, 1.2 mmol) and the reaction mixture was stirred at room temperature. After 18 hours, a further aliquot of tetrabutylammonium fluoride hydrate (1.2 mL, 1.2 mmol) was added. After 4 days, the solvent was removed *in vacuo*. The resulting pink oil was purified by column chromatography (SiO_2, 0% - 35% ether in petroleum ether) to give firstly recovered starting material **3.31 A** (22 mg, 0.07 mmol, 11%, 1:1 mixture of diastereoisomers) then alcohol **3.31 B** (0.113 g, 0.51 mmol, 86%, 1:1 mixture of diastereoisomers) as a yellow oil.

Data were recorded on the mixture.

ν_{max}/cm^{-1} (neat) 3362 (br. m), 2969 (s), 2921 (vs), 2872 (s), 2222 (w), 1614 (m), 1452 (s), 1372 (s), 1292 (w), 1228 (m), 1217 (m), 1039 (s), 1021 (s).

δ_H (400 MHz, $CDCl_3$) 5.09 (2H, s, 2 × =C*H*H), 5.03 (2H, app. t, *J* 1.6 Hz, 2 × =CH*H*), 3.05 (2H, app. br. t, *J* 9.5 Hz, 2 × -C*H*OH), 2.23 (2H, dd, *J* 16.8, 5.5 Hz, 2 × -C*H*H-CHOH), 2.12 (2H, dd, *J* 16.8, 7.5 Hz, 2 × -CH*H*-CHOH), 1.85 (2H, br. d, *J* 12.0 Hz, 2 × -C*H*-CHOH), 1.77 (6H, s, 2 × C*H*$_3$-C=), 1.67 – 1.61 (2H, m), 1.56 – 1.45 (6H, m),

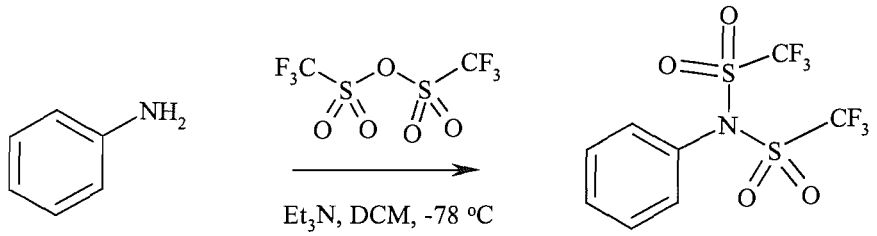
1.38 – 1.31 (4H, m), 1.17 – 1.09 (4H, m), 0.95 – 0.85 (2H, obsc. m), 0.91 (6H, d, *J* 6.5 Hz, 2 × C*H*$_3$-CH), 0.88 (6H, d, *J* 6.8 Hz, 2 × C*H*$_3$-CH) ppm.

δ_C (100 MHz, $CDCl_3$) 129.5 (s, 2 × -*C*=CH_2), 122.4 (t, 2 × =*C*H_2), 90.5 (s, 2 × -*C*≡C-), 85.1 (s, 2 × -C≡*C*-), 77.0 (d, -*C*HOH), 76.9 (d, -*C*HOH), 42.8 (d, -CH_2-*C*H-CH_2-), 42.4 (d, -CH_2-*C*H-CH_2-), 41.8 (t, -*C*H_2-CHOH), 40.1 (t, -*C*H_2-CHOH), 39.6 (d, 2 × -*C*H-CHOH), 35.4 (t, -*C*H_2-), 35.3 (t, -*C*H_2-), 32.1 (t, -*C*H_2-), 30.2 (t, -*C*H_2-), 26.6 (t, -*C*H_2-C≡), 26.5 (t, -*C*H_2-C≡), 26.0 (d, 2 × CH_3-*C*H-), 20.5 (q, 2 × *C*H_3-CH- & 2 × *C*H_3-C=), 18.7 (q, *C*H_3-CH-), 18.6 (q, *C*H_3-CH-) ppm.

LRMS (EI) 220 ($[M]^+$, 2%), 202 ($[M - H_2O]^+$, 6%), 187 (36%), 145 (66%), 91 (100%) amu.

HRMS (EI) $C_{15}H_{24}O$ (M^+) requires 220.1827; found 220.1829.

N-Phenyltrifluoromethane sulfonimide **2.51**



2.50
aniline

C_6H_7N
$M_r = 93$

75%

2.51

$C_8H_5F_6NO_4S_2$
$M_r = 357$

Prepared following the procedure of Hendrickson *et al.*[67] Thus, a solution of aniline **2.50** (4.5 mL, 49 mmol) and triethylamine (13.7 mL, 98 mmol) in DCM (100 mL) was cooled to -78 °C. Trifluoromethanesulfonic anhydride (16.5 mL, 98 mmol) was added dropwise to the solution and the reaction mixture was stirred for 2 hours. Hydrochloric acid (50 mL, 2M aqueous solution) was added and the reaction mixture was warmed to room temperature. The organic phase was washed with aq. HCl (2M, 30 mL), water (2 × 30 mL), brine (2 × 30 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* yielded a light brown solid. Recrystallisation from DCM/hexane gave two crops of **2.51** (13.20 g, 37 mmol, 75%) as white needles.

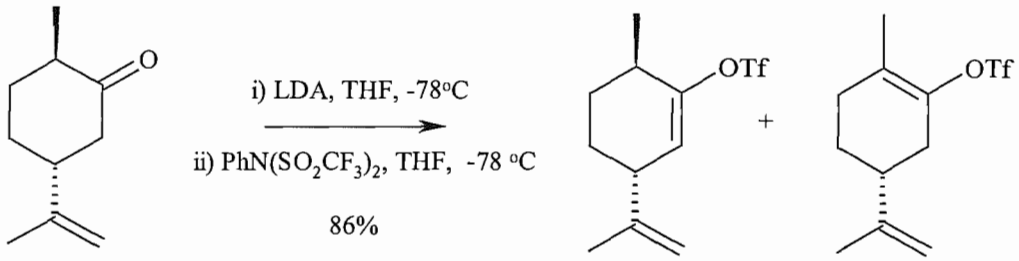
MP 86-88 °C (DCM/hexane) (lit.[67] 93-94 °C).

ν_{max}/cm^{-1} (neat) 3019 (w), 1492 (m), 1443 (s), 1420 (m), 1376 (w), 1217 (vs), 1128 (s), 1029 (vw).

δ_H (400 MHz, $CDCl_3$) 7.85 (1H, tt, *J* 7.4, 1.5 Hz, -C*H*- (aryl)), 7.79 (2H, br. t, *J* 7.5 Hz, 2 × -C*H*- (aryl)), 7.68 (2H, br. d, *J* 8.0 Hz, 2 × -C*H*- (aryl)) ppm.

δ_C (100 MHz, $CDCl_3$)	132.4 (d, -*C*H- (aryl)), 131.4 (d, 2 × -*C*H- (aryl)), 130.4 (d, 2 × -*C*H- (aryl)), 124.2 (s, -*C*-N-), 119.8 (q, 2 × -*C*F_3) ppm.
LRMS (EI)	357 ($[M]^+$, 12%), 224 ($[M - (SO_2CF_3)]^+$, 8%), 91 ($[M - 2 \times (SO_2CF_3)]^+$, 100%) amu.

(3*R*,6*R*)-3-Isopropenyl-6-methyl-1-cyclohexenyl trifluoromethanesulfonate **2.27 A** and (5*R*)-5-isopropenyl-2-methyl-1-cyclohexenyl trifluoromethanesulfonate **2.27 B**



2.1
(+)-dihydrocarvone
$C_{10}H_{16}O$
$M_r = 152$

2.27 A
$C_{11}H_{15}F_3O_3S$
$M_r = 284$

2.27 B
$C_{11}H_{15}F_3O_3S$
$M_r = 284$

2.4 : 1

Prepared following the procedure of Hendrickson *et al.*[67] Thus, a cooled solution (-78 °C) of *N*,*N*-diisopropylamine (1.67 mL, 11.90 mmol) in THF (5 mL) was treated with *n*-butyllithium (5.4 mL of a 2.2 M solution in hexanes, 11.88 mmol) and the solution was allowed to stir for 30 minutes. (+)-Dihydrocarvone **2.1** (1.64 g, 10.79 mmol) in THF (10 mL) was then added and the resulting solution was stirred for 1.5 hour. *N*-phenyltrifluoromethanesulfonimide **2.51** (4.24 g, 11.88 mmol) in THF (10 mL) was then added dropwise over 10 minutes and the reaction mixture was stirred at -78 °C for 6 hours and allowed to warm to room temperature over 10 hours. Hydrochloric acid (20 mL of a 2 M aqueous solution) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic phases were washed with HCl (15 mL), water (20 mL) and brine (20 mL) then dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 100% petroleum ether) gave firstly **2.27 A** (1.05 g, 3.69 mmol, 34%), followed by a mixture of **2.27 A** and **2.27 B** (1.23 g, 4.33 mmol, 40%) and finally **2.27 B** (0.38 g, 1.34 mmol, 12%) all as clear oils.

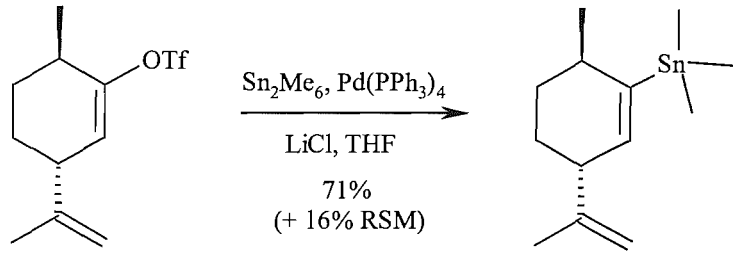
Data for **2.27 A**

ν_{max}/cm^{-1} (neat) 2969 (m), 2941 (m), 2863 (m), 1676 (w), 1646 (w), 1456 (m), 1415 (s), 1246 (s), 1215 (vs), 1143 (s).

δ_H (400 MHz, $CDCl_3$)	5.70 (1H, dd, *J* 3.0, 1.5 Hz, -C*H*=C-OTf), 4.88 (1H, app. t, *J* 1.5 Hz, =C*H*H), 4.81 (1H, br. s, =CH*H*), 3.01 – 2.96 (1H, m, CH_3-C*H*-), 2.64 – 2.56 (1H, m, =CH-C*H*-), 2.08 – 2.02 (1H, m, -C*H*H-), 1.91 – 1.84 (1H, m, -CH*H*-), 1.79 (3H, s, C*H*$_3$-C=), 1.57 – 1.39 (2H, m, 2 × -C*H*H-), 1.20 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-) ppm.
δ_C (100 MHz, $CDCl_3$)	151.8 (s, =*C*-O), 144.6 (s, -*C*=CH_2), 119.4 (d, -*C*H=), 116.7 (q, -*C*F_3), 110.1 (t, =*C*H_2), 41.1 (d, =C-*C*H-CH=), 30.7 (d, CH_3-*C*H-), 28.4 (t, -*C*H_2-), 23.6 (t, -*C*H_2-), 18.9 (q, *C*H_3-C=), 15.8 (q, *C*H_3-CH-) ppm.
LRMS (EI)	284 ($[M]^+$, 8%), 151 ($[M - (SO_2CF_3)]^+$, 34%), 123 (30%), 81 (100%) amu.
HRMS (EI)	$C_{11}H_{15}F_3O_3S$ (M^+) requires 284.0694; found 284.0698.
$[\alpha]_D$	+99.4 (c = 0.53, $CHCl_3$).
Data for **2.27 B**	
ν_{max}/cm^{-1} (neat)	2926 (m), 2869 (m), 1645 (w), 1414 (s), 1246 (s), 1208 (vs), 1143 (vs), 1042 (m).
δ_H (400 MHz, $CDCl_3$)	4.84 (1H, app. t, *J* 1.4 Hz, =C*H*H), 4.80 (1H, br. s, =CH*H*), 2.43 – 2.31 (3H, m), 2.28 – 2.17 (2H, m), 1.87 – 1.82 (1H, obsc. m), 1.81 (3H, s, C*H*$_3$-), 1.79 (3H, s, C*H*$_3$-), 1.60 – 1.50 (1H, m) ppm.
δ_C (100 MHz, $CDCl_3$)	147.7 (s, =*C*-O), 142.8 (s, -*C*=CH_2), 126.5 (s, CH_3-*C*=), 118.8 (q, -*C*F_3), 110.4 (t, =*C*H_2), 42.3 (d, -CH_2-

	*C*H-CH_2-), 33.1 (t, -*C*H_2-), 30.8 (t, -*C*H_2-), 27.1 (t, -*C*H_2-), 21.0 (q, *C*H_3-C=), 16.9 (q, *C*H_3-C=) ppm.
LRMS (EI)	284 ($[M]^+$, 2%), 241 (14%), 151 ($[M - (SO_2CF_3)]^+$, 20%), 123 (22%), 107 (60%), 81 (84%), 55 (100%) amu.
HRMS (EI)	$C_{11}H_{15}F_3O_3S$ (M^+) requires 284.0694; found 284.0685.
$[\alpha]_D$	+50.9 (c = 0.44, $CHCl_3$).

(3*R*,6*R*)-3-Isopropenyl-6-methyl-1-cyclohexenyl trimethylstannane **2.28**



2.27 A
$C_{11}H_{15}F_3O_3S$
$M_r = 284$

2.28
$C_{13}H_{24}Sn$
$M_r = 299$

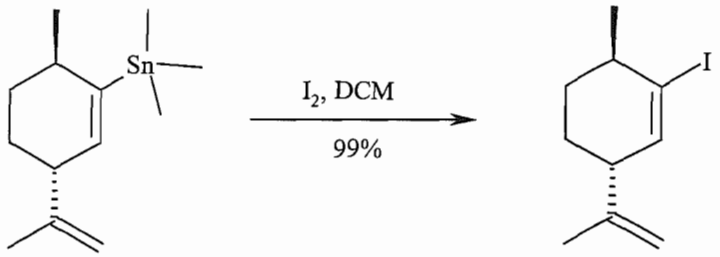
Prepared following the procedure of Wulff *et al.*[68] Thus, a stirred solution of triflate **2.27 A** (1.10 g, 3.87 mmol), hexamethylditin (1.14 g, 3.49 mmol), lithium chloride (1.04 g, 24.53 mmol) and $Pd(PPh_3)_4$ (75 mg, 0.065 mmol) in THF (10 mL) was thoroughly deoxygenated by the freeze-thaw method and heated to 60 °C under argon for 60 hours. After cooling to room temperature, the reaction mixture was filtered through celite and the resulting filtrate was concentrated *in vacuo*. Purification by column chromatography (3% Et_3N doped SiO_2, 100% petroleum ether) gave firstly vinyl stannane **2.28** (0.82 g, 2.74 mmol, 71%) as a clear oil then recovered starting material **2.27 A** (0.18 g, 0.64 mmol, 16%).

ν_{max}/cm^{-1} (neat) 3075 (w), 2953 (s), 2922 (vs), 2848 (m), 1644 (m), 1597 (w), 1452 (m), 1373 (m), 1280 (w), 1188 (m).

δ_H (400 MHz, $CDCl_3$) 5.54 (1H, app. t, *J* 2.3 Hz, =C*H*-), 4.63 (1H, br. s, =C*H*H), 4.60 (1H, br. s, =CH*H*), 2.65 – 2.60 (1H, m), 2.21 – 2.14 (1H, m), 1.71 (2H, br. dd, *J* 9.9, 4.4 Hz, -CH_2-), 1.42 (3H, s, CH_3-C=), 1.32 (1H, app. q, *J* 10.3 Hz, -C*H*H-), 1.13 (1H, app. q, *J* 10.3 Hz, -CH*H*-), 0.90 (3H, d, *J* 7.0 Hz, CH_3-CH-), -0.16 (9H, s, -Sn(CH_3)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$)	150.0 (s, =*C*-Sn-), 148.3 (s, -*C*=CH_2), 139.7 (d, -*C*H=), 110.3 (t, =*C*H_2), 45.6 (d, -*C*H-C=CH_2), 35.5 (d, CH_3-*C*H-), 31.9 (t, -*C*H_2-), 27.7 (t, -*C*H_2-), 23.5 (q, *C*H_3-C=), 21.1 (q, *C*H_3-CH-), -10.0 (q, 3 × *C*H_3-Sn) ppm.
LRMS (EI)	299 ($[M]^+$, 4%), 285 ($[MH - (CH_3)]^+$, 90%), 165 ($[SnMe_3]^+$, 90%), 135 ($[MH - Sn(CH_3)_3]^+$, 94%), 93 (100%) amu.
HRMS (EI)	$C_{13}H_{24}{}^{120}Sn$ (M^+) requires 300.0900; found 300.0890.
$[\alpha]_D$	+83.9 (c = 0.10, $CHCl_3$).

(3*R*,6*R*)-1-Iodo-3-isopropenyl-6-methyl-1-cyclohexene **2.22**



2.28
$C_{13}H_{24}Sn$
$M_r = 299$

2.22
$C_{10}H_{15}I$
$M_r = 262$

To a stirring solution of vinyl stannane **2.28** (0.20 g, 0.67 mmol) in DCM (5 mL) was added a solution of iodine (0.17 g, 0.67 mmol) in DCM (15 mL) dropwise. The reaction mixture was stirred at room temperature under nitrogen for 1 hour. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, 100% petroleum ether) to give vinyl iodide **2.22** (0.17 g, 0.66 mmol, 99%) as a clear oil.

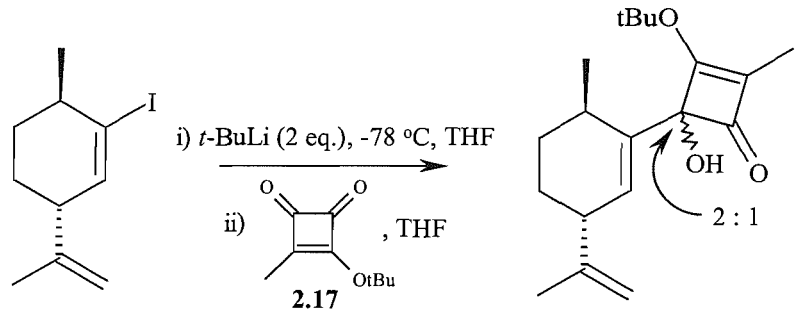
ν_{max}/cm^{-1} (neat) 2958 (vs), 2922 (s), 2867 (s), 1599 (w), 1552 (w), 1488 (m), 1454 (m), 1377 (m), 1216 (m), 1028 (m), 817 (m).

δ_H (400 MHz, $CDCl_3$) 6.17 (1H, dd, *J* 3.3, 1.8 Hz, =C*H*-), 4.69 (1H, app. t, *J* 1.5 Hz, =C*H*H), 4.61 (1H, br. s, =CH*H*), 2.66 – 2.61 (1H, m, -CH_2-C*H*-CH_2-), 2.30 (1H, dt, *J* 6.9, 1.9 Hz, -C*H*-C=), 1.89 – 1.81 (1H, m, -C*H*H-), 1.77 – 1.69 (1H, m, -CH*H*-), 1.61 (3H, s, C*H*$_3$-C=), 1.43 (1H, dddd, *J* 12.6, 9.5, 7.0, 2.6 Hz, -C*H*H-), 1.33 (1H, dddd, *J* 12.4, 9.4, 6.7, 2.5 Hz, -CH*H*-), 1.03 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH-) ppm.

δ_C (100 MHz, $CDCl_3$) 145.7 (s, -*C*=CH_2), 139.3 (d, =*C*H-), 110.1 (t, =*C*H_2), 107.0 (s, =*C*-I), 45.6 (d, -*C*H-C=CH_2), 38.6 (d, CH_3-

	*C*H-), 28.6 (t, -*C*H_2-), 23.4 (t, -*C*H_2-), 20.1 (q, *C*H_3-CH-), 19.4 (q, *C*H_3-C=) ppm.
LRMS (EI)	262 ($[M]^+$, 6%), 135 ($[M - I]^+$, 100%), 107 (60%), 93 (84%), 79 (60%) amu.
$[\alpha]_D$	+7.2 (c = 0.15, $CHCl_3$).

(4*RS*)-3-*tert*-Butoxy-4-hydroxy-4-[(3*R*,6*R*)-3-isopropenyl-6-methyl-1-cyclohexenyl]-2-methyl-2-cyclobuten-1-one **2.18**



2.22
$C_{10}H_{15}I$
$M_r = 262$

2.17

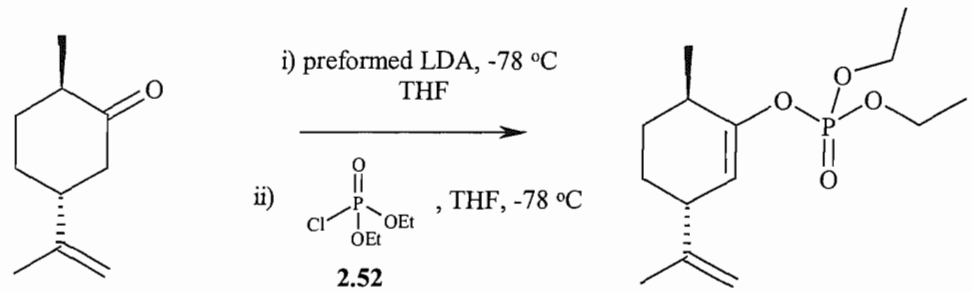
69%

2.18
$C_{19}H_{28}O_3$
$M_r = 304$

Prepared following the procedure of Corey *et al.*[69] Thus, a cooled solution (-78 °C) of vinyl iodide **2.22** (0.56 g, 2.14 mmol) in THF (15 mL) under argon was treated with *tert*-butyllithium (3.1 mL of a 1.5M solution in pentane, 4.65 mmol) dropwise over 5 minutes. After stirring for 1.5 hours, a solution of squarate **2.17** (0.79 g, 4.70 mmol) in THF (10 mL) was added. After 30 minutes, the reaction mixture was quenched with water (20 mL) and extracted with ether (3 × 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% - 60% ether in petroleum ether) gave an inseparable 2:1 mixture of diastereoisomeric alcohol **2.18** (0.45 g, 1.48 mmol, 69%) as a pale yellow oily solid.

Data were in accordance with that described previously.

Diethyl-[(3*R*,6*R*)-3-isopropenyl-6-methyl-1-cyclohexenyl]-phosphate **2.23**



2.1

(+)-dihydrocarvone

$C_{10}H_{16}O$

$M_r = 152$

2.52

19% (+33% RSM)

2.23

$C_{14}H_{25}O_4P$

$M_r = 288$

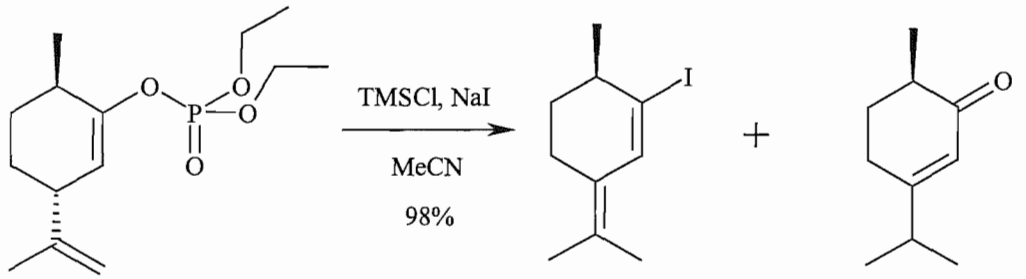
To a stirred solution of *N,N*-diisopropylamine (0.52 mL, 3.69 mmol) in THF (5 mL) at -78 °C was added *n*-butyllithium (1.48 mL, 3.69 mmol) dropwise over 5 minutes. After 1.5 hours, (+)-dihydrocarvone **2.1** (0.51 g, 3.36 mmol) in THF (5 mL) was added and after 3 hours, diethylchlorophosphate **2.52** (0.5 mL, 3.69 mmol) was added dropwise over 5 minutes. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. Water (10 mL) was then added and the reaction mixture was extracted with ether (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% - 100% ether in petroleum ether) gave firstly recovered starting material **2.1** (0.17 g, 1.12 mmol, 33%) then phosphate **2.23** (0.18 g, 0.62 mmol, 19%) as a yellow oil.

ν_{max}/cm^{-1} (neat) 2981 (m), 2935 (m), 2862 (w), 1672 (m), 1644 (m), 1452 (m), 1377 (m), 1272 (s), 1143 (s), 1034 (vs), 963 (s).

δ_H (300 MHz, $CDCl_3$) 5.41 (1H, br. s, =C*H*-), 4.78 (1H, br. s, =C*H*H), 4.77 (1H, br. s, =CH*H*), 4.19 (2H, q, *J* 7.3 Hz, -O-CH_2-), 4.17 (2H, q, *J* 7.3 Hz, -O-CH_2-), 2.90 – 2.82 (1H, m, -C*H*-CH=), 2.46 – 2.37 (1H, m, CH_3-C*H*-), 2.00 –

	1.71 (2H, obsc. m, 2 × -CH*H*-), 1.84 (3H, s, C*H*$_3$-C=), 1.48 – 1.35 (2H, obsc. m, 2 × -C*H*H-), 1.37 (6H, t, *J* 7.0 Hz, 2 × C*H*$_3$-CH$_2$-O-), 1.12 (3H, d, *J* 6.9 Hz, C*H*$_3$-CH-) ppm.
δ_C (100 MHz, $CDCl_3$)	152.3 (s, =*C*-O), 148.4 (s, -*C*=CH$_2$), 113.6 (d, =*C*H-), 111.4 (t, =*C*H$_2$), 64.5 (t, -O-*C*H$_2$-), 64.4 (t, -O-*C*H$_2$-), 42.9 (d, =C-*C*H-CH=), 32.7 (d, CH$_3$-*C*H-), 30.2 (t, -*C*H$_2$-), 26.0 (t, -*C*H$_2$-), 21.3 (q, *C*H$_3$-C=), 18.5 (q, *C*H$_3$-CH-), 16.6 (q, *C*H$_3$-CH$_2$-), 16.5 (q, *C*H$_3$-CH$_2$-) ppm.
LRMS (CI)	289 ([MH]$^+$, 100%), 259 (4%), 155 (12%), 134 (26%) amu.
HRMS (ES$^+$)	$C_{14}H_{25}O_4NaP$ ([M + Na]$^+$) requires 311.1382; found 311.1385.
$[\alpha]_D$	+60.7 (c = 0.15, $CHCl_3$).

(6*R*)-1-Iodo-6-methyl-3-(1-methylethylidene)-1-cyclohexene **2.26** and (6*R*)-3-isopropyl-6-methyl-2-cyclohexen-1-one **2.25**



2.23
$C_{14}H_{25}O_4P$
$M_r = 288$

2.26
$C_{10}H_{15}I$
$M_r = 262$

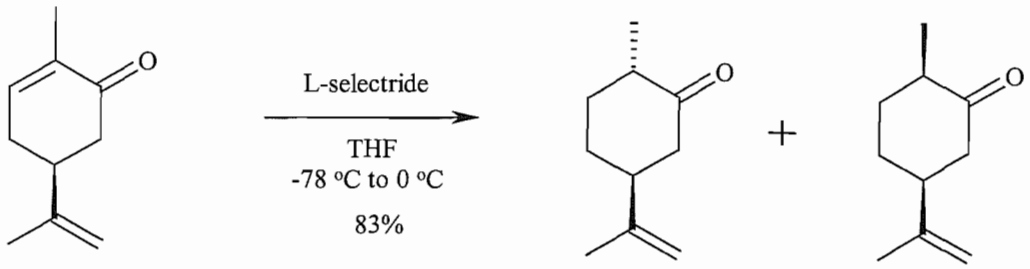
2.25
$C_{10}H_{16}O$
$M_r = 152$

Prepared following the procedure of Lee *et al.*[29] Thus, to a stirred solution of vinyl phosphate **2.23** (0.16 g, 0.56 mmol) and sodium iodide (0.25 g, 1.67 mmol) in acetonitrile (2 mL) was added TMSCl (0.21 mL, 1.67 mmol) dropwise over 5 minutes causing a precipitate to form and the reaction mixture to turn gradually brown in colour. After 10 minutes, the precipitate was filtered off and the solution concentrated *in vacuo*. The residual oil was taken up in DCM (5 mL), washed with sodium bicarbonate (sat. aq. solution, 2 × 15 mL), sodium sulfite (sat. aq. solution, 2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 5% ether in petroleum ether) gave firstly a fraction tentatively assigned as vinyl iodide **2.26** (48 mg, 0.18 mmol, 33%) then ketone **2.25** (55 mg, 0.36 mmol, 65%) both as clear oils. Data for ketone **2.25** were in accordance with literature values and with that reported previously.[63]

Only ^{1}H NMR data for iodide **2.26** were obtained due to the high instability of this compound.

δ_H (300 MHz, $CDCl_3$) 5.87 (1H, br. s, =C*H*-), 2.67 (1H, ddd, *J* 13.3, 3.5, 2.5 Hz, -C*H*H-), 2.46 – 2.11 (2H, m), 2.02 (3H, s, CH_3-C=), 1.95 (3H, s, CH_3-C=), 1.72 – 1.51 (1H, m), 1.14 (1H, dd, *J* 12.2, 6.9 Hz, -C*H*H-), 1.06 (3H, d, *J* 6.4 Hz, CH_3-CH-) ppm.

(2*S*,5*S*)-5-Isopropenyl-2-methylcyclohexan-1-one **(*S*)-1.67**



1.68
$C_{10}H_{14}O$
$M_r = 150$

(*S*)-1.67
$C_{10}H_{16}O$
$M_r = 152$

(*R*)-1.67
$C_{10}H_{16}O$
$M_r = 152$

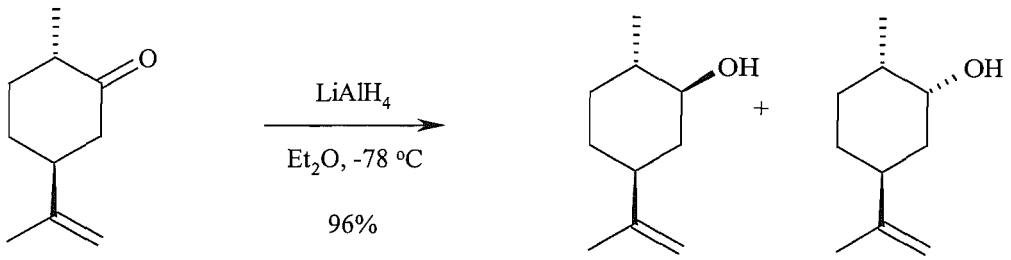
Prepared following the procedure of Baudouy *et al.*[70] Thus, to a cooled (-78 °C) solution of (*S*)-carvone **1.68** (14.90 mL, 95.00 mmol) in THF (95 mL) was added lithium tri-*sec*-butylborohydride (100 mL, 0.10 mol) dropwise over 1.5 hour. After complete addition, the reaction mixture was warmed to 0 °C, stirred for 1 hour and treated with sodium hydroxide (10% aq., 120 mL) followed by hydrogen peroxide (30% aq., 80 mL). After stirring for 1 hour, water (50 mL) was added and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (50 mL), sodium bisulfite (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a clear oil. Purification by column chromatography (SiO_2, 0.5% ether in petroleum ether) gave (-)-dihydrocarvone **(*S*)-1.67** (10.68 g, 70.26 mmol, 74%) and **(*R*)-1.67** (1.30 g, 8.55 mmol, 9%) both as a clear oil. Physical and spectroscopic data were in accordance with literature.[70] Only data for **(*S*)-1.67** are reported.

ν_{max}/cm^{-1} (neat) 2968 (m), 2932 (s), 2858 (m), 1713 (vs), 1645 (w), 1449 (m), 1376 (w), 891 (s).

δ_H (400 MHz, $CDCl_3$) 4.76 (1H, br. s, =C*H*H), 4.73 (1H, br. s, =CH*H*), 2.48 - 2.23 (4H, m), 2.13 (1H, ddt, *J* 13.3, 5.8, 3.3 Hz, -C*H*H-), 1.98 – 1.92 (1H, m, -CH*H*-), 1.74 (3H, s, =C-C*H*$_3$), 1.70 – 1.58 (1H, m, -CH*H*-), 1.37 (1H, app. qd, *J* 13.1, 3.5 Hz, -C*H*H-), 1.04 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH-) ppm.

δ_C (100 MHz, $CDCl_3$)	213.0 (s, -*C*=O), 148.0 (s, -*C*=CH_2), 110.0 (t, =*C*H_2), 47.4 (t, -*C*H_2-C=O), 47.3 (d, -*C*H-C=O), 45.2 (d, -*C*H-C=CH_2), 35.3 (t, -*C*H_2-), 31.2 (t, -*C*H_2-), 20.9 (q, *C*H_3-C=), 14.7 (q, *C*H_3-CH-) ppm.
LRMS (EI)	152 ($[M]^+$, 20%), 109 (30%), 95 (68%), 67 (84%) amu.
$[\alpha]_D$	-13.5 (c = 1.43, $CHCl_3$).

(1*S*,2*S*,5*S*)-5-Isopropenyl-2-methylcyclohexan-1-ol (***S***)-**4.21** and (1*R*,2*S*,5*S*)-5-isopropenyl-2-methylcyclohexan-1-ol (***R***)-**4.21**



(*S*)-1.67
(-)-dihydrocarvone
$C_{10}H_{16}O$
$M_r = 152$

(*S*)-4.21
$C_{10}H_{18}O$
$M_r = 154$

(*R*)-4.21
$C_{10}H_{18}O$
$M_r = 154$

11 : 1

To a stirred suspension of lithium aluminium hydride (0.76 g, 20.00 mmol) in ether (30 mL) at -78 °C under nitrogen was added a solution of (-)-dihydrocarvone (***S*)-1.67** (6.10 g, 40.00 mmol) in ether (30 mL) dropwise over 10 minutes. The reaction was stirred for 5 minutes and quenched with sat. aq. ammonium chloride (30 mL). After warming to ambient temperature, the reaction mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (SiO_2, 10 – 25% ether in petroleum ether) gave firstly alcohol (***R*)-4.21** (0.49 g, 3.18 mmol, 8%) then alcohol (***S*)-4.21** (5.42 g, 35.20 mmol, 88%) both as clear oils. Physical and spectroscopic data were in accordance with literature values and, except for optical rotation, with that described above for enantiomers (***R*)-3.6** and (***S*)-3.6**.[71]

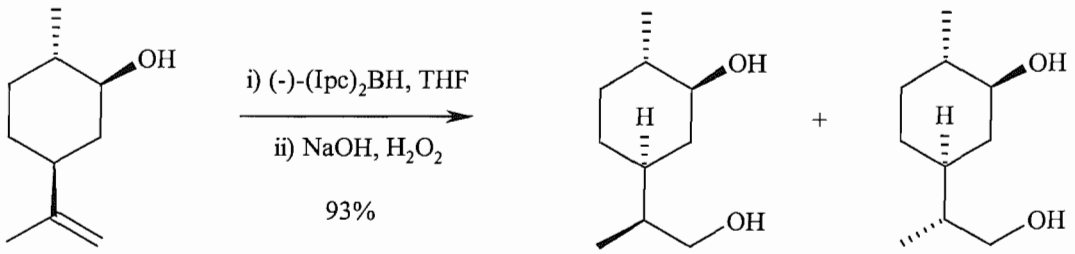
Optical rotation for (***S*)-4.21**

$[\alpha]_D$ +17.5 (c = 0.47, $CHCl_3$).

Optical rotation for (***R*)-4.21**

$[\alpha]_D$ -20.2 (c = 0.85, $CHCl_3$).

(1*S*,2*S*,5*S*)-5-[(1*R*)-2-Hydroxy-1-methylethyl]-2-methylcyclohexan-1-ol **(*R*)-4.22** and (1*S*,2*S*,5*S*)-5-[(1*S*)-2-hydroxy-1-methylethyl]-2-methylcyclohexan-1-ol **(*S*)-4.22**



(*S*)-4.21
$C_{10}H_{18}O$
$M_r = 154$

(*S*)-4.22
$C_{10}H_{20}O_2$
$M_r = 172$

1 : 3

(*R*)-4.22
$C_{10}H_{20}O_2$
$M_r = 172$

The experimental procedure used and, except for optical rotation, the spectral data attained were identical to those of the corresponding enantiomers **3.45** and **3.46**.

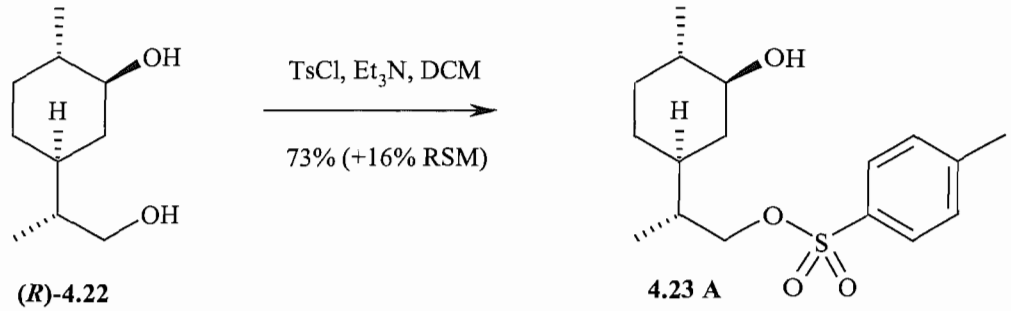
Optical rotation for **(*R*)-4.22**

$[\alpha_D]$ +19.5 (c = 0.52, $CHCl_3$).

Optical rotation for **(*S*)-4.22**

$[\alpha]_D$ +13.1 (c = 0.91, $CHCl_3$).

(2*R*)-2-[(1*S*,3*S*,4*S*)-3-Hydroxy-4-methylcyclohexyl]propyl 4-methylbenzenesulfonate **4.23 A**



(*R*)-4.22
$C_{10}H_{20}O_2$
$M_r = 172$

4.23 A
$C_{17}H_{26}O_4S$
$M_r = 326$

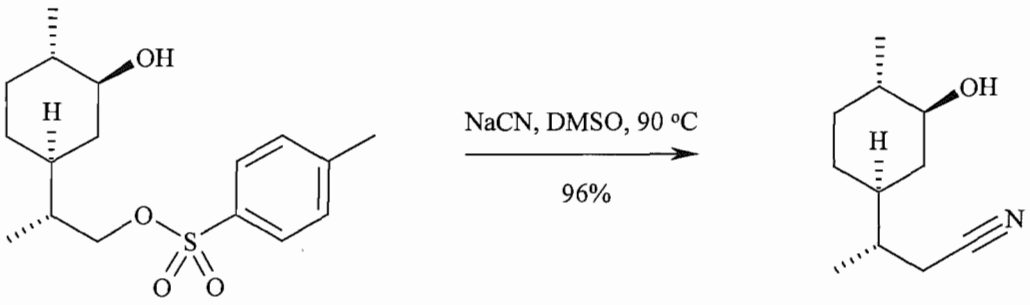
To a stirred solution of alcohol **(*R*)-4.22** (0.57 g, 3.31 mmol) in DCM (30 mL) was added triethylamine (0.46 mL, 3.30 mmol) followed by *p*-toluenesulfonyl chloride (0.63 g, 3.30 mmol) and the reaction mixture was stirred at room temperature for 72 hours. The reaction mixture was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a brown oil. Purification by column chromatography (SiO_2, 10% - 60% ether in petroleum ether) gave firstly tosylate **4.23 A** (0.78 g, 2.39 mmol, 73%) as a colourless oil then recovered diol **(*R*)-4.22** (92 mg, 0.53 mmol, 16%).

ν_{max}/cm^{-1} (neat) 3547 (br. w), 3414 (br. w), 2925 (m), 2870 (m), 1598 (m), 1458 (br. m), 1356 (s), 1176 (vs), 1097 (m), 1042 (m), 1020 (m).

δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.35 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 3.94 (1H, ddd, *J* 9.5, 6.0, 3.3 Hz, -C*H*H-OTs), 3.87 (1H, ddd, *J* 9.5, 6.3, 1.1 Hz, -CH*H*-OTs), 3.08 (1H, app. qd, *J* 10.2, 4.2 Hz, -C*H*OH), 2.45 (3H, s, Ar-CH_3), 1.80 – 1.75 (1H, br. d, *J* 11.9 Hz, -C*H*-CHOH), 1.71 – 1.65 (2H, m, -C*H*-CH_2OTs & -C*H*H-CHOH), 1.48 - 1.39 (2H, m, -CH_2-C*H*-CH_2- & -O*H*), 1.22 – 1.18 (1H, m, -CH*H*-CHOH), 1.04 –

	0.84 (4H, obsc. m, 2 × -C*H*$_2$-), 0.99 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH-CHOH), 0.86 (3H, d, *J* 6.9 Hz, C*H*$_3$-CH-CH$_2$OTs) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.
δ_C (100 MHz, $CDCl_3$)	145.1 (s, -SO$_2$-*C*-(Ar)), 133.5 (s, CH$_3$-*C*-(Ar)), 130.2 (d, 2 × -*C*H-(Ar)), 128.3 (d, 2 × -*C*H-(Ar)), 76.6 (d, -*C*HOH), 73.7 (t, -*C*H$_2$OTs), 40.5 (d, -CH$_2$-*C*H-CH$_2$-), 39.8 (t, -*C*H$_2$-CHOH), 38.2 (d, -*C*H-CH$_2$OTs), 37.7 (d, -*C*H-CHOH), 33.3 (t, -*C*H$_2$-), 28.0 (t, -*C*H$_2$-), 22.0 (q, *C*H$_3$-Ar), 18.6 (q, *C*H$_3$-CH-CHOH-), 13.7 (q, *C*H$_3$-CH-CH$_2$OTs) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
LRMS (EI)	154 ([M – TsOH]$^+$, 14%), 136 (28%), 121 (34%), 97 (100%) amu. Parent ion was not observed.
HRMS (ES)	$C_{17}H_{26}O_4SNa$ ([M + Na]$^+$) requires 349.1444; found 349.1450.
$[\alpha]_D$	+4.1 (c = 0.41, $CHCl_3$).

(2*S*)-2-[(1*S*,3*S*,4*S*)-3-Hydroxy-4-methylcyclohexyl]propyl cyanide **4.24**



4.23 A
$C_{17}H_{26}O_4S$
$M_r = 326$

4.24
$C_{11}H_{19}NO$
$M_r = 181$

A solution of tosylate **4.23 A** (6.16 g, 18.90 mmol) in DMSO (100 mL) was treated with sodium cyanide (1.02 g, 20.82 mmol) and heated to 90 °C for 1 hour. After cooling, water (50 mL) was added. The aqueous phase was further extracted with ether (3 × 30 mL). The combined organic extracts were thoroughly washed with water (6 × 25 mL) and brine (3 × 25 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield nitrile **4.24** (3.28 g, 18.12 mmol, 96%) as a clear oil.

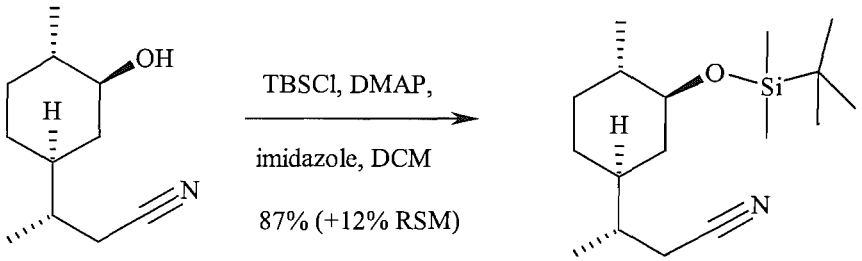
ν_{max}/cm^{-1} (neat) 3405 (br. s), 2925 (vs), 2871 (vs), 2247 (m), 1458 (s). 1428 (m), 1384 (m), 1344 (m), 1041 (vs), 1024 (s).

δ_H (400 MHz, $CDCl_3$) 3.15 (1H, td, *J* 10.3, 4.3 Hz, -C*H*OH), 2.37 (1H, dd, *J* 16.8, 5.8 Hz, -C*H*H-CN), 2.28 (1H, dd, *J* 16.7, 7.4 Hz, -CH*H*-CN), 1.99 – 1.92 (1H, m, -C*H*-CHOH), 1.89 (1H, br. s, -O*H*), 1.79 – 1.72 (2H, m, CH_3-C*H*-CH_2CN & -CH_2-C*H*-CH_2-), 1.65 – 1.61 (1H, m, -C*H*H-CH-CH_3), 1.49 – 1.40 (1H, m, -CH*H*-CH-CH_3), 1.29 – 1.20 (1H, m, -C*H*H-CHOH), 1.07 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH-CH_2-CN), 1.06 – 0.97 (3H, m), 1.02 (3H, d, *J* 6.3 Hz, C*H*$_3$-CH-CHOH) ppm. These

assignments were confirmed by a $^{1}H - {}^{1}H$ COSY experiment.

δ_C (100 MHz, $CDCl_3$)	118.7 (s, -*C*≡N), 75.6 (d, -*C*HOH), 40.1 (d, -*C*H-CHOH), 39.5 (d, -CH_2-*C*H-CH_2-), 38.2 (t, -*C*H_2-CHOH), 35.5 (d, -*C*H-CH_2CN), 33.2 (t, -*C*H_2-CH-CH_3), 29.1 (t, -*C*H_2-), 22.8 (t, -*C*H_2-CN), 17.8 (q, *C*H_3-CH-CH_2CN), 16.2 (q, *C*H_3-CH-CHOH) ppm. These assignments were confirmed by a $^{1}H - {}^{13}C$ HMQC experiment.
LRMS (EI)	180 ($[M - H]^+$, 4%), 164 ($[M - OH]^+$, 14%), 136 (14%), 113 (100%), 95 (98%), 57 (80%) amu.
HRMS (EI)	$C_{11}H_{19}NO$ (M^+) requires 181.1467; found 181.1465.
$[\alpha]_D$	+6.9 (c = 0.38, $CHCl_3$).

(2*S*)-2-((1*S*,3*S*,4*S*)-3-[*tert*-Butyl-dimethylsilyloxy-4-methylcyclohexyl)propyl cyanide **4.25**



4.24
$C_{11}H_{19}NO$
$M_r = 181$

4.25
$C_{17}H_{33}NOSi$
Mr = 295

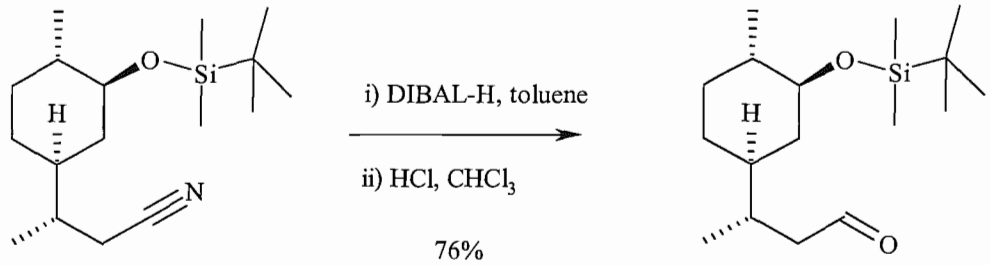
To alcohol **4.24** (2.54 g, 14.03 mmol) in DCM (50 mL) was added imidazole (2.39 g, 35.11 mmol), 4-dimethylaminopyridine (34 mg, 0.28 mmol) and *tert*-butyldimethylsilyl chloride (3.18 g, 21.10 mmol). The reaction mixture was stirred at ambient temperature for 72 hours. Sat. aq. ammonium chloride solution (50 mL) was added and the phases were separated. The aqueous phase was further extracted with ether (3 × 35 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 100 % petroleum ether) gave firstly silyl ether **4.25** (3.60 g, 12.20 mmol, 87%) as a colourless oil then recovered starting material **4.24** (0.30 g, 1.66 mmol, 12%) as a clear oil.

ν_{max}/cm^{-1} (neat) 2952 (vs), 2927 (vs), 2856 (vs), 2250 (w), 1463 (m), 1361 (w), 1256 (s), 1082 (vs), 875 (s).

δ_H (400 MHz, $CDCl_3$) 3.07 (1H, td, *J* 10.0, 4.3 Hz, -C*H*-OTBS), 2.28 (1H, dd, *J* 16.8, 6.0 Hz, -C*H*H-CN), 2.20 (1H, dd, *J* 16.7, 7.4 Hz, -CH*H*-CN), 1.75 – 1.65 (3H, m, CH_3-C*H*-CHOTBS, -C*H*H-CHOTBS & -C*H*-CH_2CN), 1.55 – 1.49 (1H, m, -CH_2-C*H*-CH_2-), 1.40 – 1.31 (1H, m, -

	C*H*H-), 1.25 – 1.19 (1H, m, -CH*H*-CHOTBS), 0.99 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-CHOTBS), 1.00 – 0.80 (3H, obsc. m, -C*H*$_2$- & -CH*H*-), 0.87 (3H, d, *J* 6.3 Hz, C*H*$_3$-CH-CH$_2$CN), 0.84 (9H, s, C(C*H*$_3$)$_3$), 0.00 (6H, s, -Si(C*H*$_3$)$_2$) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.
δ_C (100 MHz, $CDCl_3$)	119.5 (s, -*C*≡N), 77.2 (d, -*C*H-OTBS), 40.9 (d, *C*H-CH-OTBS), 40.7 (d, -CH$_2$-*C*H-CH$_2$-), 40.3 (t, -*C*H$_2$-CN), 35.5 (d, -*C*H-CH$_2$CN), 33.2 (t, -*C*H$_2$-CHOTBS), 28.2 (t, -*C*H$_2$-), 26.3 (q, -C(*C*H$_3$)$_3$), 22.8 (t, -*C*H$_2$-), 19.3 (q, *C*H$_3$-CH-CHOTBS), 18.5 (s, -*C*(CH$_3$)$_3$), 16.8 (q, *C*H$_3$-CH-), -3.6 (q, Si(*C*H$_3$)), -4.2 (q, Si(*C*H$_3$)) ppm.
LRMS (CI)	313 ([M + $(NH_4)^+$]$^+$, 4%), 296 ([MH]$^+$, 26%), 278 (74%), 238 ([M – ^{t}Bu]$^+$, 100%), 181 ([MH – TBS]$^+$, 20%), 164 ([M – OTBS]$^+$, 38%) amu.
HRMS (EI)	$C_{17}H_{33}NOSi$ (M^+) requires 295.2331; found 295.2333.
$[\alpha]_D$	+28.0 (c = 0.96, $CHCl_3$).

(3*S*)-3-((1*S*,3*S*,4*S*)-3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4-methylcyclohexyl)butanal **4.26**



4.25
$C_{17}H_{33}NOSi$
$M_r = 295$

4.26
$C_{17}H_{34}O_2Si$
$M_r = 298$

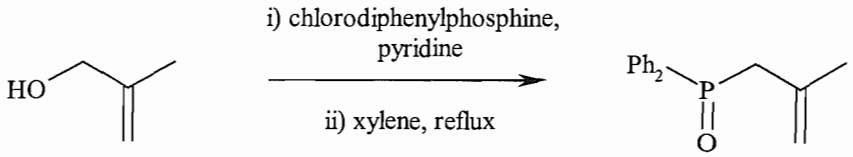
Prepared following the procedure of Wen *et al.*[72] Thus, a stirred solution of nitrile **4.25** (0.47 g, 1.59 mmol) in toluene (20 mL) was treated with DIBAL-H (1.0 M solution in hexanes, 1.75 mL, 1.75 mmol) at 0 °C under nitrogen. After 1 hour, chloroform (20 mL) and hydrochloric acid (2M, 10 mL) were added and the reaction mixture was stirred for 1 hour. The phases were then separated and the aqueous phase was extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with water (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a pale yellow oil. Purification by column chromatography (SiO_2, 5% ether in petroleum ether) yielded aldehyde **4.26** (0.36 g, 1.21 mmol, 76%) as a colourless oil.

ν_{max}/cm^{-1} (neat) 2952 (vs), 2928 (vs), 2857 (vs), 1709 (vs), 1463 (m), 1256 (m), 1082 (s), 875 (s).

δ_H (400 MHz, $CDCl_3$) 9.70 (1H, app. dd, *J* 2.6, 1.9 Hz, -C*H*O), 3.05 (1H, td, *J* 10.0, 4.3 Hz, -C*H*-OTBS), 2.39 (1H, ddd, *J* 16.1, 4.8, 1.8 Hz, -C*H*H-CHO), 2.17 (1H, ddd, *J* 16.1, 8.8, 2.8 Hz, -CH*H*-CHO), 1.97 – 1.93 (1H, m, -C*H*-CH_2-CHO), 1.75 – 1.64 (2H, m, -C*H*-CHOTBS & -CH*H*-

	CHOTBS), 1.54 – 1.46 (1H, m), 1.28 – 1.18 (1H, m), 1.08 – 0.82 (4H, obsc. m), 0.87 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH), 0.86 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH), 0.84 (9H, s, -C(C*H*$_3$)$_3$), 0.00 (6H, s, -Si(C*H*$_3$)$_2$) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.
δ_C (100 MHz, $CDCl_3$)	203.3 (d, -*C*HO), 77.5 (d, *C*H-OTBS), 49.0 (t, -*C*H$_2$-CHO), 42.0 (d, -*C*H-CHOTBS), 40.8 (d, -CH$_2$-*C*H-CH$_2$-), 40.2 (t, -*C*H$_2$-CHOTBS), 33.4 (t, -*C*H$_2$-), 32.9 (d, -*C*H-CH$_2$CHO), 28.4 (t, -*C*H$_2$-), 26.3 (q, -C(*C*H$_3$)$_3$), 19.3 (q, *C*H$_3$-CH-), 18.5 (s, -*C*(CH$_3$)$_3$), 17.2 (q, *C*H$_3$-CH-), -3.6 (q, Si-(*C*H$_3$)), -4.2 (q, Si-(*C*H$_3$)) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
LRMS (CI)	299 ([MH]$^+$, 22%), 241 ([M – ^{t}Bu]$^+$, 14%), 167 ([M – OTBS]$^+$, 54%), 149 ([M – OTBS – H$_2$O]$^+$, 100%) amu.
HRMS (EI)	$C_{16}H_{31}O_2Si$ ([M – (CH$_3$)]$^+$) requires 283.2093; found 283.2088.
$[\alpha]_D$	+35.6 (c = 1.35, $CHCl_3$).

2-Methyl-3-diphenylphosphinoyl-prop-1-ene **3.38**



3.37

C_4H_8O
$M_r = 72$

48% (+40% RSM)

3.38

$C_{16}H_{17}PO$
$M_r = 256$

Prepared following the procedure of Yamamoto *et al.*[73] Thus, a stirred solution of methallyl alcohol **3.37** (0.17 mL, 2.00 mmol) in ether (1.5 mL) was treated with chlorodiphenylphosphine (0.36 mL, 2.00 mmol) followed by pyridine (0.32 mL, 4.00 mmol) causing the clear reaction to turn milky white in colour. The reaction mixture was stirred for 1 hour before addition of potassium hydrogen sulfate (0.54 g, 4.00 mmol). After 5 minutes, the precipitate was filtered off, washed with ether (10 mL) and the filtrate was concentrated *in vacuo*. The residual oil was taken up in xylene (4 mL) and heated to reflux for 25 hours. After cooling, the reaction mixture was concentrated *in vacuo* and the resulting oil was purified by column chromatography (SiO_2, 50 – 75% ether in petroleum ether) to give the title compound **3.38** (0.24 g, 0.93 mmol, 48%) as a yellow oil and recovered starting material (56 mg, 0.78 mmol, 40%).

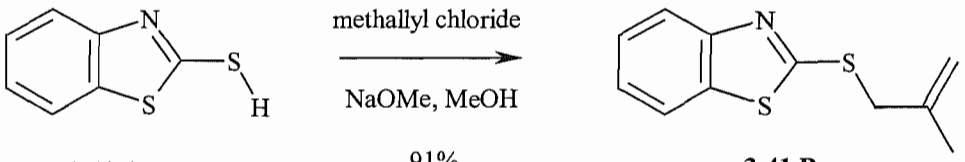
ν_{max}/cm^{-1} (neat) 3057 (m), 1659 (m), 1593 (m), 1439 (vs), 1228 (vs), 1130 (vs), 1113 (s), 1045 (s), 995 (s), 730 (vs), 696 (vs).

δ_H (400 MHz, $CDCl_3$) 7.87 – 7.79 (4H, m, 4 × -C*H*- (aryl)), 7.55 – 7.42 (6H, m, 6 × -C*H*- (aryl)), 5.06 (1H, br. s, =C*H*H), 4.94 (1H, br. s, =CH*H*), 4.43 (2H, d, *J* 6.5 Hz, -CH_2-), 1.78 (3H, s, -CH_3) ppm.

δ_C (100 MHz, $CDCl_3$) 140.2 (ds, $J_{C\text{-}P}$ 27.0 Hz, 2 × -*C*- (aryl)), 132.0 (d, 2 × -*C*H- (aryl)), 131.5 (d, 2 × -*C*H- (aryl)), 131.4 (d, 2 × -

	*C*H- (aryl)), 130.6 (s, -*C*=CH_2), 128.4 (d, 2 × -*C*H- (aryl)), 128.3 (d, 2 × -*C*H- (aryl)), 112.8 (t, =*C*H_2), 67.7 (dt, $J_{C\text{-}P}$ 23.2 Hz, -P-*C*H_2-), 19.0 (q, *C*H_3-C-) ppm.
LRMS (EI)	272 (60%), 257 ($[M + H]^+$, 2%), 201 ($[M - C_4H_7]^+$, 100%), 77 ($[C_6H_5]^+$, 84%) amu.

2-(2-Methyl-allylsulfanyl)-benzothiazole **3.41 B**



3.41 A
$C_7H_5NS_2$
$M_r = 167$

3.41 B
$C_{11}H_{11}NS_2$
$M_r = 221$

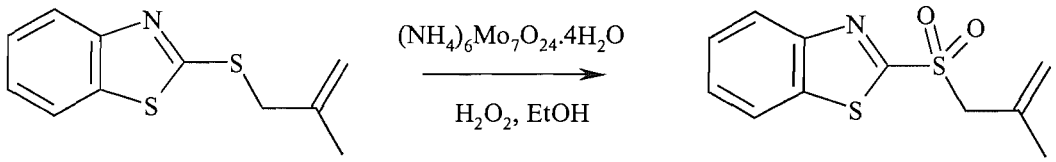
Prepared following the procedure of Phillips *et al.*[74] Thus, 2-mercaptobenzothiazole **3.41 A** (1.68 g, 10.06 mmol) was added to a freshly prepared solution of sodium methoxide formed by careful addition of sodium (0.23 g, 10.00 mmol) to methanol (12 mL). To the bright yellow solution was added methallyl chloride **3.35** (1 mL, 10.10 mmol) over 10 minutes. After stirring at room temperature for 3 hours, the reaction mixture was heated to reflux for 15 minutes. The reaction mixture was then taken up in toluene (30 mL) and water (50 mL) was added. The aqueous phase was extracted with toluene (2 × 30 mL) and the combined organic phases were washed with sodium hydroxide (2M aq. sol., 50 mL), hydrochloric acid (1M, 50 mL) and brine (50 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 1% ether in petroleum ether) gave benzothiazole **3.41 B** (2.01 g, 9.10 mmol, 91%) as a clear oil. Spectroscopic and physical data were in accordance with the literature.[74]

ν_{max}/cm^{-1} (neat) 3082 (w), 3059 (w), 2978 (w), 1649 (w), 1456 (s), 1427 (vs), 1304 (w), 1238 (m).

δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 8.3 Hz, Ar*H*), 7.74 (1H, d, *J* 8.0 Hz, Ar*H*), 7.40 (1H, td, *J* 7.7, 1.3 Hz, Ar*H*), 7.28 (1H, td, *J* 7.7, 1.0 Hz, Ar*H*), 5.11 (1H, br. s, =C*H*H), 4.95 (1H, br. t, *J* 1.3 Hz, =CH*H*), 4.04 (2H, s, -CH_2-S-), 1.93 (3H, s, CH_3-C=) ppm.

δ_C (100 MHz, $CDCl_3$)	167.1 (s, -*C*=N), 153.6 (s, -*C*-(Ar)), 140.2 (s, -*C*-(Ar)), 135.8 (s, -*C*=CH_2), 126.4 (d, -*C*H-(Ar)), 124.7 (d, -*C*H-(Ar)), 122.0 (d, -*C*H-(Ar)), 121.4 (d, -*C*H-(Ar)), 115.8 (t, =*C*H_2), 41.0 (t, -S-*C*H_2-), 21.7 (q, -*C*H_3) ppm.
LRMS (EI)	221 ($[M]^+$, 42%), 206 ($[M - CH_3]^+$, 100%), 188 (70%), 166 (40%), 108 (64%) amu.

2-(2-Methyl-prop-2-ene-1-sulfonyl)-benzothiazole **3.42**



3.41 B
$C_{11}H_{11}NS_2$
$M_r = 221$

69%

3.42
$C_{11}H_{11}NO_2S_2$
$M_r = 253$

Prepared following the procedure of Phillips *et al.*[74] A cooled (0 °C) solution of benzothiazole **3.41 B** (2.00 g, 9.05 mmol) in ethanol (35 mL) under nitrogen was treated dropwise with a solution of ammonium molybdate tetrahydrate (0.44 g, 0.36 mmol) in hydrogen peroxide (30% aq., 3.60 g, 31.77 mmol). The reaction mixture was stirred at 0 °C for 3.5 hours and was then placed in the freezer for 16 hours. Evaporation of the solvent *in vacuo* gave a yellow solid which was taken up in DCM (20 mL) and washed with sulfuric acid (2M, 50 mL). The aqueous phase was extracted with DCM (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow solid. Recrystallisation from DCM/EtOH gave sulfone **3.42** as off-white crystals (1.58 g, 6.24 mmol, 69%). Physical and spectroscopic data were in accordance with the literature.[74]

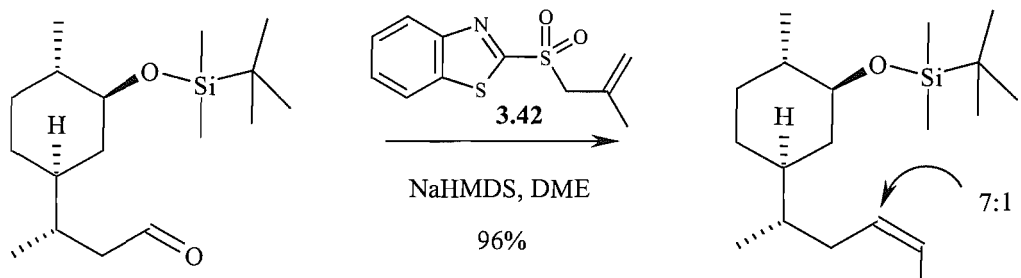
MP 89-91 °C (DCM/EtOH) (lit.[74] 96-97 °C).

ν_{max}/cm^{-1} (neat) 1640 (vw), 1555 (vw), 1471 (m), 1330 (vs), 1233 (w), 1151 (s), 1132 (s), 1020 (m).

δ_H (300 MHz, $CDCl_3$) 8.24 (1H, dd, *J* 7.4, 1.5 Hz, Ar*H*), 8.02 (1H, dd, *J* 7.4, 1.8 Hz, Ar*H*), 7.66 (1H, td, *J* 7.5, 1.5 Hz, Ar*H*), 7.60 (1H, td, *J* 7.9, 1.7 Hz, Ar*H*), 5.12 (1H, t, *J* 1.5Hz, =C*H*H), 4.92 (1H, br. s, =CH*H*), 4.22 (2H, s, -SO_2-CH_2-), 1.97 (3H, s, CH_3-) ppm.

δ_C (75 MHz, $CDCl_3$)	165.6 (s, -*C*=N), 152.8 (s, -*C*-(Ar)), 137.0 (s, -*C*-(Ar)), 132.2 (s, -*C*=CH_2), 128.2 (d, -*C*H-(Ar)), 127.8 (d, -*C*H-(Ar)), 125.6 (d, -*C*H-(Ar)), 122.5 (d, -*C*H-(Ar)), 122.3 (t, =*C*H_2), 62.7 (t, -SO_2-*C*H_2-), 23.0 (q, -*C*H_3) ppm.
LRMS (EI)	254 ($[M + H]^+$, 2%), 188 (100%), 174 (92%), 149 (90%), 134 (48%), 108 (36%), 55 (76%) amu.

tert-Butyl((1*S*,2*S*,5*S*)-5-[(3*Z*,6*S*)-2-methyl-1,3-heptadien-6-yl]-2-methylcyclohexyloxy)dimethylsilane **4.27**



4.26

$C_{17}H_{34}O_2Si$

$M_r = 298$

4.27

$C_{21}H_{40}OSi$

Mr = 336

Prepared following the procedure of Kocieński *et al.*[75] Thus, a stirred solution of sulfone **3.42** (0.84 g, 3.32 mmol) in DME (10 mL) at -55 °C under argon was treated dropwise with sodium hexamethyldisilazide (1M solution in THF, 3.32 mL, 3.32 mmol) causing the solution to turn deep red. After stirring at -55 °C for 70 minutes, a solution of aldehyde **4.26** (0.92 g, 3.08 mmol) in DME (5 mL) was added. The reaction mixture was allowed to gradually warm to room temperature and stirred for 16 hours. Water (10 mL) was added and the reaction mixture stirred for a further hour. Following extraction with ether (3 × 20 mL) the combined organic extracts were washed with water (20 mL) and brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100% petroleum ether) gave diene **4.27** (1.00 g, 3.00 mmol, 96%) as a clear oil and as an inseparable 7:1 mixture of *cis* : *trans* diastereoisomers.

Only data for the *cis* isomer are reported.

ν_{max}/cm^{-1} (neat) 3385 (br. m), 2955 (vs), 2925 (vs), 2855 (vs), 1635 (w), 1462 (s), 1380 (m), 1356 (m), 1255 (s), 1081 (vs), 876 (s).

δ_H (400 MHz, $CDCl_3$) 5.82 (1H, d, *J* 12.1 Hz, =C*H*-), 5.35 (1H, dtd, 11.5, 7.5, 2.3 Hz, -CH_2-C*H*=CH-), 4.89 (1H, br. s, =C*H*H),

4.78 (1H, br. s, =CH*H*), 3.09 – 3.01 (1H, m, -C*H*-OTBS), 2.30 – 2.21 (1H, m, -C*H*H-CH=), 2.10 – 2.01 (1H, m, -CH*H*-CH=), 1.82 (3H, s, CH_3-C=), 1.75 – 1.68 (1H, m, -C*H*-CH-OTBS), 1.67 – 1.62 (1H, m), 1.50 – 1.43 (1H, m), 1.39 – 1.17 (3H, m), 1.15 – 0.92 (3H, m), 0.87 (3H, d, *J* 6.5 Hz, CH_3-CH-), 0.84 (9H, s, -C(CH_3)$_3$), 0.80 (3H, d, *J* 7.0 Hz, CH_3-CH-), 0.00 (6H, s, -Si-(CH_3)$_2$) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.

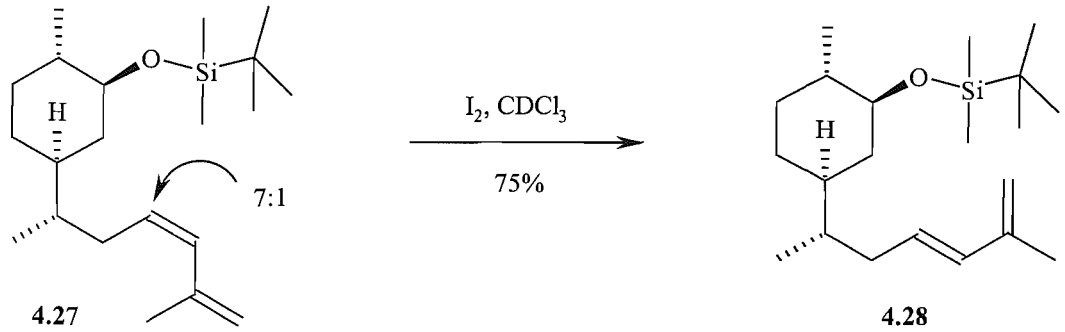
δ_C (100 MHz, $CDCl_3$)

142.3 (s, -*C*=CH$_2$), 131.8 (d, -*C*H=CH-), 131.3 (d, -CH=*C*H-), 115.5 (t, =*C*H$_2$), 78.0 (d, -*C*H-OTBS), 41.6 (d, -*C*H-CHOTBS), 40.9 (d, -CH$_2$-*C*H-CH$_2$), 39.0 (d, CH$_3$-*C*H-), 38.4 (t, -*C*H$_2$-), 33.8 (t, -*C*H$_2$-), 33.7 (t, -*C*H$_2$-), 28.0 (t, -*C*H$_2$-), 26.4 (q, -C(*C*H$_3$)$_3$), 23.9 (q, *C*H$_3$-C=), 19.5 (q, *C*H$_3$-CH), 18.5 (s, -*C*(CH$_3$)$_3$), 16.6 (q, *C*H$_3$-CH), -4.2 (q, -Si-(*C*H$_3$)$_2$) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.

LRMS (EI)

336 ([M]$^+$, 1%), 279 ([M – ^{t}Bu]$^+$, 24%), 204 ([M – ^{t}BuSi(Me)$_2$OH]$^+$, 26%), 183 (38%), 75 (100%) amu.

tert-Butyl((1*S*,2*S*,5*S*)-5-[(3*E*,6*S*)-2-methyl-1,3-heptadien-6-yl]-2-methylcyclohexyloxy)dimethylsilane **4.28**



4.27
$C_{21}H_{40}OSi$
Mr = 336

4.28
$C_{21}H_{40}OSi$
Mr = 336

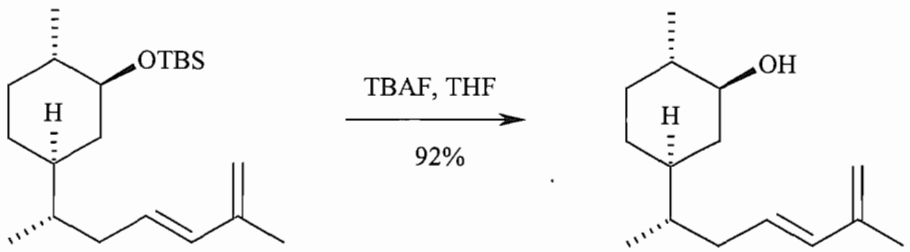
A stirred solution of diene **4.27** (0.02 g, 0.06 mmol) in $CDCl_3$ (0.5 mL) was treated with a solution of iodine (0.015 mg, 0.006 mmol) in $CDCl_3$ (0.5 mL). After 1 hour, complete conversion was observed and the reaction mixture was washed with aqueous sodium thiosulfate (2 × 3 mL). The aqueous phase was extracted with chloroform (2 × 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **4.28** (0.015 g, 0.045 mmol, 75%) as a pale yellow oil.

ν_{max}/cm^{-1} (neat) 3081 (w), 2953 (vs), 2927 (vs), 2857 (vs), 1609 (w), 1462 (m), 1378 (w), 1256 (m), 1081 (s), 876 (m).

δ_H (400 MHz, $CDCl_3$) 6.07 (1H, d, *J* 15.6 Hz, =C*H*-C=), 5.57 (1H, dt, *J* 15.6, 7.5 Hz, -C*H*=CH-), 4.80 (2H, br. s, =CH_2), 3.05 (1H, td, *J* 10.0, 4.3 Hz, -C*H*OTBS), 2.19 (1H, dt, *J* 14.1, 5.2 Hz, -CH*H*-CH-O), 1.96 (1H, dt, *J* 14.1, 7.9 Hz, -C*H*H-CH-O), 1.85 (3H, s, CH_3-C=), 1.87 – 1.74 (1H, obsc. m), 1.72 – 1.69 (1H, m), 1.58 – 1.54 (1H, m), 1.45 – 1.41 (1H, m), 1.34 – 1.21 (2H, m), 1.11 (1H, app. q, *J* 11.8 Hz), 0.99 – 0.88 (2H, obsc. m), 0.94 (3H, d, *J* 6.3 Hz, CH_3-CH-), 0.91 (9H, s, -

	C(CH_3)$_3$), 0.85 (3H, d, *J* 6.8 Hz, CH_3-CH-), 0.07 (6H, s, -Si(CH_3)$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	142.6 (s, -*C*=CH_2), 134.3 (d, -*C*H=CH-), 130.2 (d, -CH=*C*H-), 114.5 (t, =*C*H_2), 77.7 (d, -*C*H-OTBS), 41.7 (d, -*C*H-CH-O-), 40.9 (d, -CH_2-*C*H-CH_2-), 40.7 (t, -*C*H_2-CH-O-), 38.4 (d, -*C*H-CH_3), 38.1 (t, -*C*H_2-CH=), 33.7 (t, -*C*H_2-), 28.3 (t, -*C*H_2-), 26.4 (q, -C(*C*H_3)$_3$), 19.5 (q, *C*H_3-CH-), 19.1 (q, *C*H_3-C=), 16.6 (q, *C*H_3-CH-), -3.6 (q, -Si(*C*H_3)), -4.2 (q, -Si(*C*H_3)) ppm.
LRMS (CI)	336 ([M]$^+$, 2%), 279 ([M – (^{t}Bu)]$^+$, 18%), 204 ([MH – (OTBS)]$^+$, 40%), 183 (46%), 117 (50%), 75 (100%) amu.
HRMS (EI)	$C_{21}H_{40}OSi$ (M^+) requires 336.2848; found 336.2837.
$[\alpha]_D$	+21.4 (c = 0.45, $CHCl_3$).

(1*S*,2*S*,5*S*)-5-[(3*E*,6*S*)-2-Methyl-1,3-heptadien-6-yl]-2-methylcyclohexan-1-ol **4.29 A**



4.28
$C_{21}H_{40}OSi$
Mr = 336

4.29 A
$C_{15}H_{26}O$
Mr = 222

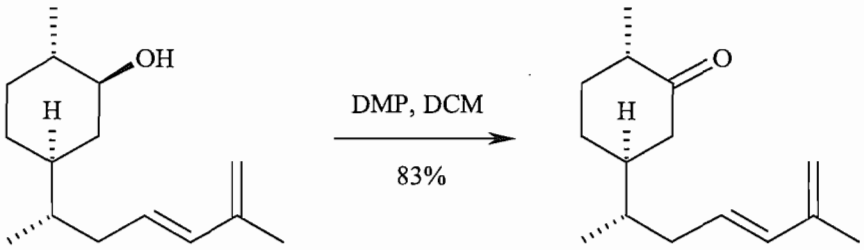
To a solution of diene **4.28** (2.38 g, 7.08 mmol) in THF (50 mL) was added tetrabutylammonium fluoride hydrate (2.77 g, 10.59 mmol) and the reaction mixture was stirred at room temperature. After 18 hours, another aliquot of tetrabutylammonium fluoride hydrate (1.40 g, 5.35 mmol) was added. After 4 days, another aliquot of tetrabutylammonium fluoride hydrate (1.40 g, 5.35 mmol) was added. After a further 2 days, the solvent was removed *in vacuo*. The resulting pink oil was purified by column chromatography (SiO_2, 60% ether in petroleum ether) to yield alcohol **4.29 A** (1.43 g, 6.45 mmol, 92%) as a colourless oil.

ν_{max}/cm^{-1} (neat) 3354 (br. s), 2917 (vs), 2860 (vs), 1645 (w), 1607 (m), 1451 (s), 1370 (s), 1044 (s), 965 (s), 874 (s).

δ_H (400 MHz, $CDCl_3$) 6.03 (1H, d, *J* 15.6 Hz, -CH=C*H*-), 5.51 (1H, dt, *J* 15.6, 7.5 Hz, -CH_2-C*H*=), 4.76 (2H, s, =CH_2), 3.04 (1H, td, *J* 10.2, 4.2 Hz, -C*H*-OTBS), 2.10 (1H, br. dt, *J* 13.8, 6.4 Hz, -C*H*H-CH=), 1.87 – 1.80 (2H, m, -CH*H*-CH= & -C*H*-CHOH), 1.74 (3H, s, CH_3-C=), 1.64 – 1.60 (1H, m), 1.50 (1H, br. s, -O*H*), 1.50 – 1.47 (1H, obsc. m), 1.38 – 1.30 (1H, m), 1.27 – 1.12 (2H, m), 1.05 – 0.80 (3H, obsc. m), 0.91 (3H, d, *J* 6.3

	Hz, C*H*$_3$-CH-), 0.76 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-) ppm. These assignments were confirmed by a ^{1}H – ^{1}H COSY experiment.
δ_C (100 MHz, $CDCl_3$)	142.5 (s, -*C*=CH$_2$), 134.4 (d, -*C*H=CH-), 130.1 (d, -CH=*C*H-), 114.6 (t, =*C*H$_2$), 77.1 (d, -*C*H-OH), 41.6 (d, -*C*H-CHOH), 40.7 (d, -CH$_2$-*C*H-CH$_2$), 38.4 (d, CH$_3$-*C*H-), 38.1 (t, -*C*H$_2$-CHOH), 37.9 (t, -*C*H$_2$-CH=), 33.7 (t, -*C*H$_2$-), 28.3 (t, -*C*H$_2$-), 19.1 (q, *C*H$_3$-C=), 18.8 (q, *C*H$_3$-CH-), 16.6 (q, *C*H$_3$-CH-) ppm. These assignments were confirmed by a ^{1}H – ^{13}C HMQC experiment.
LRMS (EI)	222 ([M]$^+$, 10%), 204 ([M – (H$_2$O)]$^+$, 18%), 189 (20%), 109 (60%), 93 (68%), 81 (100%) amu.
HRMS (EI)	$C_{15}H_{26}O$ (M^+) requires 222.1984; found 222.1980.
$[\alpha]_D$	+1.3 (c = 0.39, $CHCl_3$).

(2*S*,5*S*)-5-[(3*E*,6*S*)-2-Methyl-1,3-heptadien-6-yl]-2-methylcyclohexan-1-one **4.29 B**



4.29 A
$C_{15}H_{26}O$
Mr = 222

4.29 B
$C_{15}H_{24}O$
Mr = 220

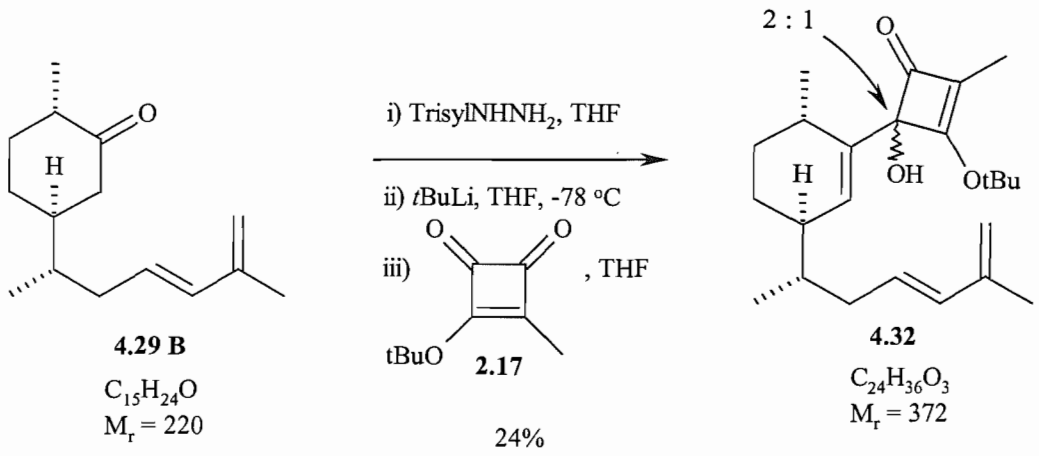
A solution of alcohol **4.29 A** (0.055 g, 0.25 mmol) in DCM (4 mL) was treated with Dess-Martin periodinane (0.12 g, 0.27 mmol) at 0 °C under nitrogen. After 30 minutes, ether (5 mL) was added followed by sodium hydroxide (3M, 5 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic extracts were washed with sodium hydroxide (3M, 2 × 5 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 0% - 10% ether in petroleum ether) gave the desired ketone **4.29 B** (0.045 g, 0.21 mmol, 83%) as a clear oil.

ν_{max}/cm^{-1} (neat) 2968 (s), 2933 (s), 2873 (m), 1708 (vs), 1456 (m), 1375 (m), 1228 (w), 968 (m).

δ_H (400 MHz, $CDCl_3$) 6.06 (1H, d, *J* 15.6 Hz, -C*H*=CH-), 5.51 (1H, dt, *J* 15.3, 7.4 Hz, -CH=C*H*-), 4.79 (2H, s, =C*H*$_2$), 2.32 – 2.21 (2H, m), 2.18 – 2.00 (3H, m), 1.88 (1H, dt, *J* 14.1, 7.4 Hz), 1.80 – 1.71 (1H, obsc. m), 1.75 (3H, s, C*H*$_3$-C=), 1.69 – 1.60 (1H, m), 1.48 – 1.33 (2H, m), 1.22 (1H, qd, *J* 12.9, 3.5 Hz, -C*H*H-), 0.94 (3H, d, *J* 6.5 Hz, C*H*$_3$-CH-), 0.82 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-) ppm.

δ_C (100 MHz, $CDCl_3$)	213.6 (s, *C*=O), 142.3 (s, *C*=CH_2), 134.8 (d, *C*H=CH), 129.3 (d, CH=*C*H), 114.9 (t, =*C*H_2), 46.6 (t, -*C*H_2-C=O), 45.4 (d, -*C*H-C=O), 44.9 (d, CH_3-*C*H), 38.4 (d, -CH_2-*C*H-CH_2), 37.7 (t, -*C*H_2-CH=), 35.4 (t, -*C*H_2-), 28.0 (t, -*C*H_2-), 19.1 (q, *C*H_3-C=), 16.2 (q, *C*H_3-CH-), 14.8 (q, *C*H_3-CH-) ppm. These assignments were confirmed by a ^1H – ^{13}C HMQC experiment.
LRMS (EI)	220 ($[M]^+$, 10%), 109 (100%) amu.
HRMS (EI)	$C_{15}H_{24}O$ (M^+) requires 220.1827; found 220.1835.
$[\alpha]_D$	-25.1 (c = 0.36, $CHCl_3$).

3-(*tert*-Butoxy)-4-(3*S*,6*S*)-3-[(1*S*,3*E*)-1,5-dimethyl-3,5-hexadienyl]-6-methyl-1-cyclohexenyl-4-hydroxy-2-methyl-2-cyclobuten-1-one **4.32**



4.29 B
$C_{15}H_{24}O$
$M_r = 220$

4.32
$C_{24}H_{36}O_3$
$M_r = 372$

A stirred solution of trisylhydrazide **2.45** (81 mg, 0.27 mmol) in THF (5 mL) was treated with a solution of ketone **4.29 B** (60 mg, 0.27 mmol) in THF (2 mL) and the resulting clear solution was stirred at ambient temperature under argon for 3 hours. The solution was then cooled to -78 °C and treated with *t*-butyllithium (0.84 mL, 1.09 mmol). The resulting orange solution was stirred at -78 °C for 2 hours, then gradually warmed to -25 °C and cooled again to -78 °C at which point it was treated with a solution of squarate **2.17** (0.27 g, 1.63 mmol) in THF (5 mL). The resulting reaction mixture was stirred for a further 30 minutes, quenched with water (15 mL), and allowed to warm to ambient temperature. The phases were then separated. The aqueous phase was further extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (15 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 5% - 55% ether in petroleum ether) gave the title alcohol **4.32** (24 mg, 0.065 mmol, 24%) as a 2:1 mixture of inseparable diastereoisomers and as a pale yellow oil. Data were recorded on the mixture.

ν_{max}/cm^{-1} (neat) 3369 (br. m), 2958 (s), 2930 (s), 2871 (m), 1748 (s), 1597 (vs), 1456 (m), 1386 (s), 1372 (s), 1339 (s), 1260 (w), 1160 (s).

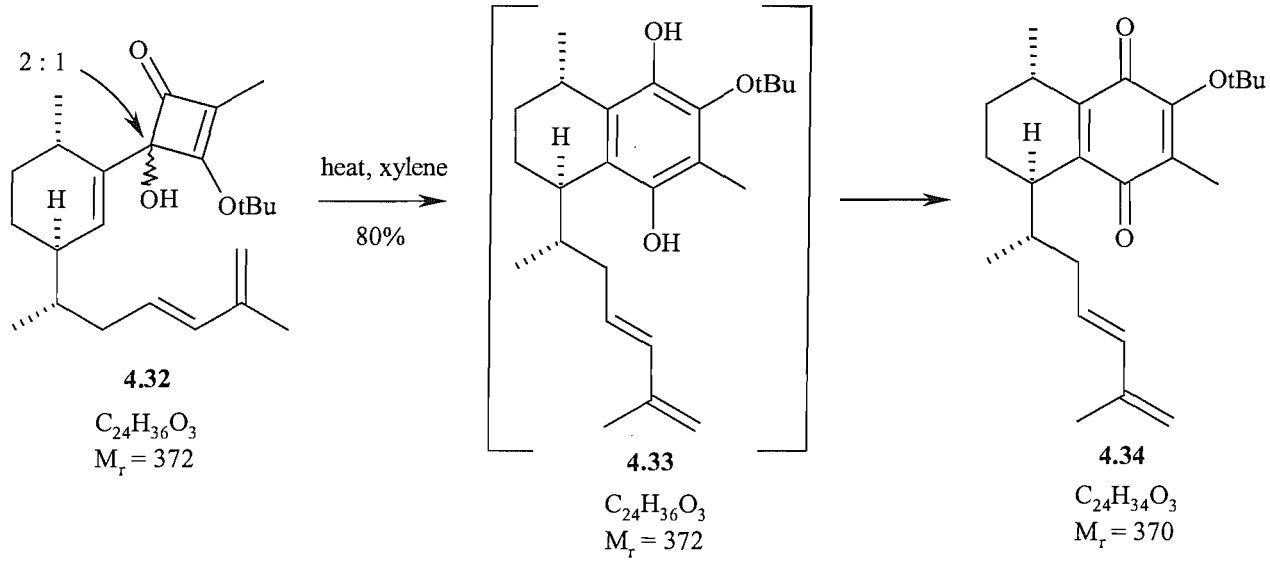
δ_H (400 MHz, $CDCl_3$) 6.06 (2H, d, *J* 15.6 Hz, 2 × -CH=C*H*-C-, major & minor isomers), 5.88 (1H, d, *J* 2.8 Hz, =C*H*-CH-, minor isomer), 5.61 (1H, br. s, =C*H*-CH-, major isomer), 5.55 (2H, dt, *J* 15.6, 7.5 Hz, 2 × -CH_2-C*H*=CH-, major & minor isomers), 4.79 (2H, s, =CH_2, major isomer), 4.78 (2H, s, =CH_2, minor isomer), 2.35 (1H, br. s, -O*H*, minor isomer), 2.28 (1H, br. s, -O*H*, major isomer), 2.18 – 1.82 (6H, m), 1.76 (3H, s, CH_3-C=, major isomer), 1.72 (3H, s, CH_3-C=, minor isomer), 1.70 – 1.50 (8H, m), 1.46 (9H, s, -C(CH_3)$_3$, major isomer), 1.45 (3H, s, CH_3-C=, major isomer), 1.45 (9H, s, -C(CH_3)$_3$, minor isomer), 1.45 (3H, s, CH_3-C=, minor isomer), 1.39 – 1.33 (4H, m), 1.10 (3H, d, *J* 7.0 Hz, CH_3-CH-, major isomer), 1.04 (3H, d, *J* 6.8 Hz, CH_3-CH-, minor isomer), 0.77 (3H, d, *J* 6.8 Hz, CH_3-CH-, major isomer), 0.80 – 0.72 (3H, obsc. m, , CH_3-CH-, minor isomer) ppm.

δ_C (100 MHz, $CDCl_3$) 187.6 (s, 2 × -*C*=O), 177.9 (s, 2 × =*C*-O-), 153.9 (s, 2 × -C(O)-*C*(Me)=), 140.5 (s, 2 × -*C*=CH_2), 132.4 (d, 2 × -*C*H=CH-), 128.4 (s, 2 × =*C*-C(OH)-), 128.0 (d, 2 × -CH=*C*H-), 126.9 (d, -C=*C*H-), 126.8 (d, -C=*C*H-), 112.6 (t, 2 × =*C*H_2), 90.3 (s, -*C*-OH), 86.8 (s, -*C*-OH), 82.5 (s, $(CH_3)_3$-*C*-), 82.0 (s, $(CH_3)_3$-*C*-), 38.0 (d, -*C*H-C=), 37.6 (d, -*C*H-C=), 36.4 (d, CH_3-*C*H-), 35.9 (d, CH_3-*C*H-), 34.3 (t, 2 × -*C*H_2-), 29.8 (t, -*C*H_2-), 29.4 (t, -*C*H_2-), 28.7 (d, CH_3-*C*H-), 28.1 (d, CH_3-*C*H-), 27.1 (q, -C(*C*H_3)$_3$), 27.0 (q, -C(*C*H_3)$_3$), 21.9 (t, 2 × -CH_2-), 19.0 (q, *C*H_3-C=), 18.9 (q, *C*H_3-C=), 17.1 (q, 2 × *C*H_3-C=), 15.1 (q, *C*H_3-CH-), 14.6 (q, *C*H_3-CH-), 7.4 (q, 2 × *C*H_3-CH-) ppm.

LRMS (EI) 204 ([M – squarate]$^+$, 10%), 189 (24%), 151 (26%), 81 (36%), 55 (52%), 41 (100%) amu. Parent ion was not observed.

HRMS (EI) $C_{24}H_{36}O_3$ (M^+) requires 372.2665; found 372.2663.

(5*R*,8*S*)-2-(*tert*-Butoxy)-5-[(3*E*)-1,5-dimethyl-3,5-hexadienyl]-3,8-dimethyl-5,6,7,8-tetrahydro-1,4-naphthalenedione **4.34**



4.32
$C_{24}H_{36}O_3$
$M_r = 372$

4.33
$C_{24}H_{36}O_3$
$M_r = 372$

4.34
$C_{24}H_{34}O_3$
$M_r = 370$

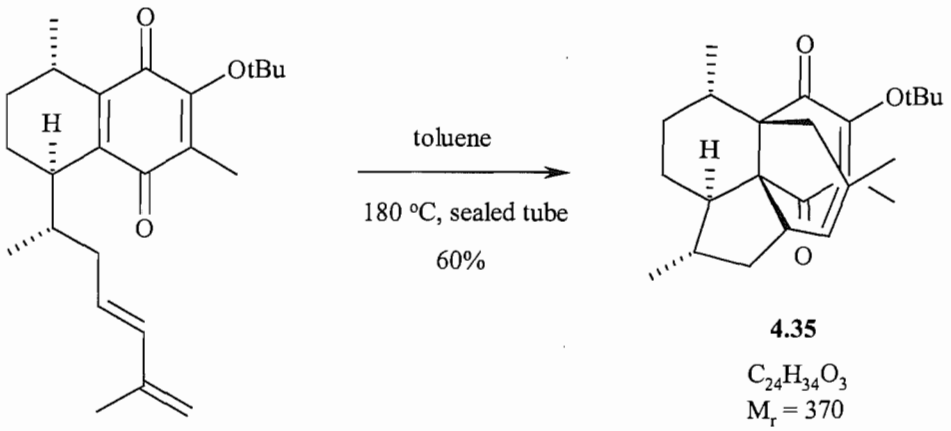
A solution of alcohol **4.32** (0.025 g, 0.067 mmol) in THF (2 mL) was heated to 120 °C in a sealed tube. After 25 minutes, the sealed tube was opened up to the atmosphere and the solution was stirred at ambient temperature for a further 24 hours. The bright yellow solution was concentrated *in vacuo* and purified by column chromatography (SiO_2, 5% ether in petroleum ether) to give quinone **4.34** (0.020 g, 0.054 mmol, 80%) as a bright yellow oil.

ν_{max}/cm^{-1} (neat) 2962 (s), 2932 (s), 2871 (m), 1660 (vs), 1646 (vs), 1606 (s), 1455 (br. m), 1368 (s), 1145 (vs), 965 (m).

δ_H (400 MHz, $CDCl_3$) 6.05 (1H, d, *J* 15.3 Hz, -CH=C*H*-), 5.57 (1H, dt, *J* 15.5, 7.2 Hz, -C*H*=CH-), 4.79 (2H, br. s, =CH_2), 2.94 – 2.87 (1H, m, -C*H*-C-C=O), 2.79 – 2.72 (1H, m, -C*H*-C-C=O), 2.24 – 1.95 (2H, m), 1.90 (3H, s, CH_3-C=), 1.82 – 1.63 (1H, obsc. m), 1.74 (3H, s, CH_3-CH=), 1.62 –1.50 (2H, m), 1.32 (9H, s, -C(CH_3)$_3$),

	1.00 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-), 0.80 – 0.71 (2H, obsc. m), 0.79 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-) ppm.
δ_C (100 MHz, $CDCl_3$)	189.7 (s, -*C*=O), 185.4 (s, -*C*=O), 154.7 (s, =*C*-O-), 146.5 (s, -*C*=C-), 145.2 (s, -C=*C*-), 142.5 (s, -*C*=CH_2), 134.7 (d, -*C*H=CH-), 132.0 (s, =*C*-CH_3), 129.8 (d, -CH=*C*H-), 114.9 (t, =*C*H_2), 84.3 (s, -O-*C*$(CH_3)_3$), 38.8 (t, -*C*H_2-CH=), 38.0 (d, -*C*H-C-C=O), 35.9 (d, -*C*H-C-C=O), 33.9 (t, -*C*H_2-), 30.7 (d, CH_3-*C*H-), 29.9 (q, -OC(*C*$H_3)_3$), 26.8 (q, *C*H_3-), 25.8 (t, -*C*H_2-), 21.3 (q, *C*H_3-), 19.2 (q, *C*H_3-), 11.1 (q, *C*H_3-) ppm.
LRMS (EI)	314 ([M – ^{t}Bu + H]$^+$, 12%), 206 (24%), 91 (31%), 56 (48%) amu. Parent ion not observed.
$[\alpha]_D$	+52.5 (c = 0.02, $CHCl_3$).

(-)-Colombiasin A *tert*-butyl ether **4.35**



4.34
$C_{24}H_{34}O_3$
$M_r = 370$

4.35
$C_{24}H_{34}O_3$
$M_r = 370$

A stirred solution of quinone **4.34** (5 mg, 0.014 mmol) in toluene (1 mL) was shielded from light and heated to 180 °C in a sealed tube for 12 hours. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 1% - 4% ether in petroleum ether) yielded (-)-colombiasin A *tert*-butyl ether **4.35** (3 mg, 0.008 mmol, 60%) as a colourless film.

ν_{max}/cm^{-1} (neat) 2923 (s), 2851 (m), 1731 (m), 1649 (vw), 1463 (m), 1378 (w), 1260 (m), 1214 (m), 1078 (m), 1006 (m).

δ_H (400 MHz, $CDCl_3$) 5.66 (1H, br. s, =C*H*-), 3.09 – 2.99 (1H, m), 2.40 (1H, br. d, *J* 18.8 Hz, -C*H*H-C=), 2.15 – 2.05 (1H, m), 1.98 – 1.82 (5H, obsc. m), 1.91 (3H, s, C*H*$_3$-C=), 1.69 –1.66 (1H, m), 1.57 (3H, br. s, C*H*$_3$-C=), 1.40 (9H, s, -C(C*H*$_3$)$_3$), 1.38 – 1.30 (3H, obsc. m), 1.33 (3H, d, *J* 6.8 Hz, C*H*$_3$-CH-), 0.82 (3H, d, *J* 7.0 Hz, C*H*$_3$-CH-) ppm.

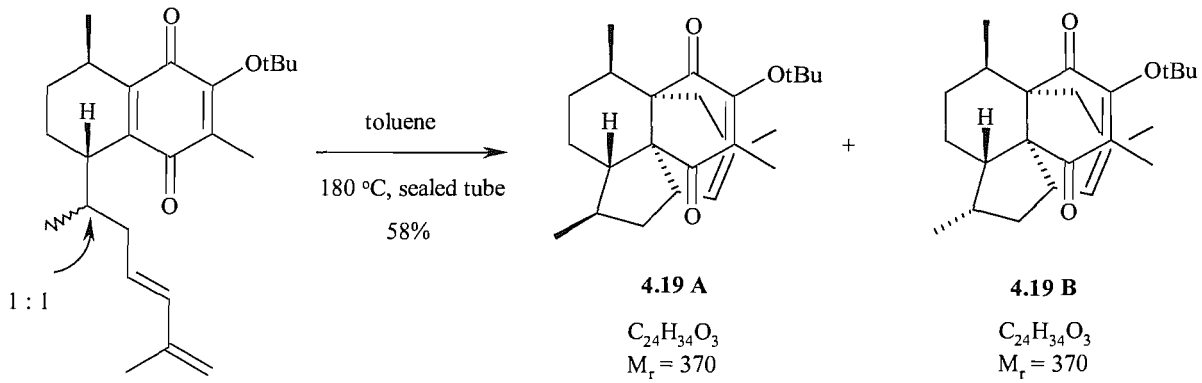
δ_C (100 MHz, $CDCl_3$) 203.3 (s, -*C*=O), 200.0 (s, -*C*=O), 155.6 (s, =*C*-O-), 137.3 (s, =*C*-), 129.3 (s, =*C*-), 123.1 (d, =*C*H-), 83.1

(s, -O*C*(CH_3)$_3$), 63.3 (s, -*C*-C=O), 51.3 (s, -*C*-C=O), 48.1 (d, -*C*H-CH=), 39.4 (d, -*C*H-), 38.8 (d, -*C*H-), 36.3 (t, -*C*H_2-), 33.4 (t, -*C*H_2-), 33.4 (d, -*C*H-), 31.8 (t, -*C*H_2-), 31.2 (t, -*C*H_2-), 29.7 (q, -C(*C*H_3)$_3$), 22.9 (q, *C*H_3-C=), 22.3 (q, *C*H_3-CH-), 17.9 (q, *C*H_3-CH-), 12.2 (q, *C*H_3-C=) ppm.

LRMS (EI) 370 ($[M]^+$, 1%), 314 ($[M - {}^tBu + H]^+$, 36%), 286 (24%), 271 (28%), 243 (25%), 206 (100%), 145 (56%), 91 (88%), 83 (84%) amu.

$[\alpha]_D$ -7.5 (c = 0.03, $CHCl_3$).

(+)-Colombiasin A *tert*-butyl ether **4.19 A** and 7-*epi*-colombiasin A *tert*-butyl ether **4.19 B**



4.17
$C_{24}H_{34}O_3$
$M_r = 370$

4.19 A
$C_{24}H_{34}O_3$
$M_r = 370$

4.19 B
$C_{24}H_{34}O_3$
$M_r = 370$

A stirred solution of quinone **4.17** (12 mg, 0.03 mmol) in toluene (2 mL) was shielded from light and heated to 180 °C in a sealed tube for 5 hours. The solvent was removed *in vacuo* and purification by column chromatography (SiO_2, 1% - 4% ether in petroleum ether) yielded an inseparable 1:1 mixture of (+)-colombiasin A *tert*-butyl ether **4.19 A** and 7-*epi*-colombiasin A *tert*-butyl ether **4.19 B** (7 mg, 0.02 mmol, 58%) as a colourless film. Data was recorded on the mixture. IR and MS data were concordant with those obtained for (-)-colombiasin A *tert*-butyl ether **4.35**.

Only data for **4.19 B** is reported.

δ_H (400 MHz, $CDCl_3$) 5.66 (1H, br. s, =C*H*-), 3.20 – 3.13 (1H, m), 2.38 (1H, br. d, *J* 19.1 Hz, -C*H*H-C=), 2.30 – 2.22 (1H, m), 1.98 – 1.82 (5H, obsc. m), 1.94 (3H, s, CH_3-C=), 1.89 –1.80 (1H, m), 1.56 (3H, br. s, CH_3-C=), 1.41 (9H, s, -C(CH_3)$_3$), 1.38 – 1.30 (3H, obsc. m), 1.35 (3H, d, *J* 6.8 Hz, CH_3-CH-), 0.92 (3H, d, *J* 7.3 Hz, CH_3-CH-) ppm.

Additional signals corresponding to **4.19 A** were in accordance with those reported for (-)-colombiasin A *tert*-butyl ether **4.35**.

δ_C (100 MHz, $CDCl_3$) 203.8 (s, -*C*=O), 200.4 (s, -*C*=O), 153.7 (s, =*C*-O-), 136.0 (s, =*C*-), 129.5 (s, =*C*-), 125.0 (d, =*C*H-), 83.6 (s, -O*C*(CH_3)$_3$), 66.7 (s, -*C*-C=O), 51.8 (s, -*C*-C=O), 44.2 (d, -*C*H-CH=), 37.1 (d, -*C*H-), 37.0 (d, -*C*H-), 34.6 (t, -*C*H_2-), 33.8 (t, -*C*H_2-), 33.5 (d, -*C*H-), 31.3 (t, -*C*H_2-), 30.7 (t, -*C*H_2-), 30.1 (q, -C(*C*H_3)$_3$), 24.6 (q, *C*H_3-C=), 17.9 (q, *C*H_3-CH-), 16.2 (q, *C*H_3-CH-), 12.3 (q, *C*H_3-C=) ppm.

Additional signals corresponding to **4.19 A** were in accordance with those reported for (-)-colombiasin A *tert*-butyl ether **4.35**.

CHAPTER VI - APPENDICES

VI.1 X-ray data for compound (*S*)-4.22

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 6.1. Crystal data and structure refinement

Identification code	**03sot073**	
Empirical formula	$C_{10}H_{20}O_2$	
Formula weight	172.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.0026(9) Å	α = 90°
	b = 8.9106(13) Å	β = 90°
	c = 19.201(2) Å	γ = 90°
Volume	1027.0(2) Å^3	
Z	4	
Density (calculated)	1.114 Mg / m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	384	
Crystal	Slab; Colourless	
Crystal size	0.12 × 0.05 × 0.03 mm^3	
θ range for data collection	3.12 – 27.48°	
Index ranges	$-6 \le h \le 7$, $-11 \le k \le 11$, $-23 \le l \le 24$	
Reflections collected	7214	
Independent reflections	2197 [R_{int} = 0.0855]	
Completeness to θ = 27.48°	96.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9978 and 0.9911	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2197 / 0 / 114	
Goodness-of-fit on F^2	1.103	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0800, $wR2$ = 0.1272	
R indices (all data)	$R1$ = 0.1179, $wR2$ = 0.1399	
Absolute structure parameter	0(3)	

Extinction coefficient	0.032(6)
Largest diff. peak and hole	0.206 and –0.222 e $Å^{-3}$

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.
It was not possible to accurately determine the absolute configuration, just the relative conformations.

Table 6.2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2387(5)	−134(4)	9107(2)	31(1)	1
C2	4839(5)	−238(4)	8893(2)	31(1)	1
C3	5104(6)	−1334(4)	8289(2)	35(1)	1
C4	4071(5)	−2867(4)	8436(2)	33(1)	1
C5	1592(5)	−2706(4)	8620(2)	28(1)	1
C6	1373(5)	−1659(4)	9245(2)	29(1)	1
C7	5841(6)	1293(4)	8729(2)	42(1)	1
C8	385(5)	−4205(4)	8723(1)	32(1)	1
C9	1706(5)	−5308(4)	9174(2)	34(1)	1
C10	−254(6)	−4938(4)	8028(2)	44(1)	1
O1	2131(4)	771(2)	9722(1)	34(1)	1
O2	379(4)	−6580(2)	9366(1)	38(1)	1

Table 6.3. Bond lengths [Å] and angles [°].

C1–O1	1.438(3)	C6–H6A	0.9900
C1–C6	1.512(4)	C6–H6B	0.9900
C1–C2	1.531(4)	C7–H7A	0.9800
C1–H1	1.0000	C7–H7B	0.9800
C2–C7	1.524(4)	C7–H7C	0.9800
C2–C3	1.525(4)	C8–C9	1.531(4)
C2–H2	1.0000	C8–C10	1.535(4)
C3–C4	1.527(4)	C8–H8	1.0000
C3–H3A	0.9900	C9–O2	1.434(4)
C3–H3B	0.9900	C9–H9A	0.9900
C4–C5	1.536(4)	C9–H9B	0.9900
C4–H4A	0.9900	C10–H10A	0.9800
C4–H4B	0.9900	C10–H10B	0.9800
C5–C6	1.525(4)	C10–H10C	0.9800
C5–C8	1.532(4)	O1–H1A	0.8400
C5–H5	1.0000	O2–H2A	0.8400
O1–C1–C6	108.5(2)	C6–C5–C4	108.7(2)
O1–C1–C2	110.9(2)	C8–C5–C4	114.0(3)
C6–C1–C2	112.3(3)	C6–C5–H5	106.9
O1–C1–H1	108.3	C8–C5–H5	106.9
C6–C1–H1	108.3	C4–C5–H5	106.9
C2–C1–H1	108.3	C1–C6–C5	112.2(2)
C7–C2–C3	112.0(2)	C1–C6–H6A	109.2
C7–C2–C1	112.4(3)	C5–C6–H6A	109.2
C3–C2–C1	110.1(3)	C1–C6–H6B	109.2
C7–C2–H2	107.4	C5–C6–H6B	109.2
C3–C2–H2	107.4	H6A–C6–H6B	107.9
C1–C2–H2	107.4	C2–C7–H7A	109.5
C2–C3–C4	112.9(2)	C2–C7–H7B	109.5
C2–C3–H3A	109.0	H7A–C7–H7B	109.5
C4–C3–H3A	109.0	C2–C7–H7C	109.5
C2–C3–H3B	109.0	H7A–C7–H7C	109.5
C4–C3–H3B	109.0	H7B–C7–H7C	109.5
H3A–C3–H3B	107.8	C9–C8–C5	112.8(2)
C3–C4–C5	110.7(3)	C9–C8–C10	110.4(3)
C3–C4–H4A	109.5	C5–C8–C10	112.1(2)
C5–C4–H4A	109.5	C9–C8–H8	107.1
C3–C4–H4B	109.5	C5–C8–H8	107.1
C5–C4–H4B	109.5	C10–C8–H8	107.1
H4A–C4–H4B	108.1	O2–C9–C8	111.4(3)
C6–C5–C8	113.0(2)	O2–C9–H9A	109.3

C8–C9–H9A	109.3
O2–C9–H9B	109.3
C8–C9–H9B	109.3
H9A–C9–H9B	108.0
C8–C10–H10A	109.5
C8–C10–H10B	109.5
H10A–C10–H10B	109.5
C8–C10–H10C	109.5
H10A–C10–H10C	109.5
H10B–C10–H10C	109.5
C1–O1–H1A	109.5
C9–O2–H2A	109.5

Table 6.4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	34(2)	27(2)	31(2)	−2(1)	−3(1)	0(2)
C2	27(2)	29(2)	37(2)	1(1)	−2(1)	1(2)
C3	28(2)	38(2)	38(2)	2(1)	5(1)	1(2)
C4	39(2)	30(2)	31(2)	−2(2)	3(1)	3(2)
C5	28(2)	25(2)	31(2)	0(1)	0(1)	2(1)
C6	25(2)	32(2)	30(2)	2(1)	0(1)	4(2)
C7	42(2)	39(2)	44(2)	1(2)	9(2)	−5(2)
C8	29(2)	35(2)	31(2)	−4(1)	2(1)	3(2)
C9	31(2)	32(2)	40(2)	0(2)	1(1)	4(2)
C10	48(2)	40(2)	42(2)	−3(2)	−2(2)	−4(2)
O1	40(1)	27(1)	36(1)	−2(1)	−1(1)	2(1)
O2	40(1)	27(1)	46(1)	2(1)	7(1)	0(1)

Table 6.5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	$S.o.f.$
H1	1541	352	8719	37	1
H2	5679	−660	9298	37	1
H3A	6710	−1466	8188	42	1
H3B	4397	−901	7868	42	1
H4A	4867	−3350	8828	40	1
H4B	4231	−3516	8021	40	1
H5	860	−2193	8217	33	1
H6A	−223	−1535	9360	35	1
H6B	2120	−2120	9652	35	1
H7A	5030	1750	8340	62	1
H7B	7412	1173	8601	62	1
H7C	5727	1942	9139	62	1
H8	−1034	−3983	8976	38	1
H9A	3034	−5653	8913	41	1
H9B	2225	−4790	9600	41	1
H10A	1096	−5141	7757	65	1
H10B	−1226	−4259	7765	65	1
H10C	−1042	−5882	8117	65	1
H1A	1552	1597	9614	51	1
H2A	−690	−6297	9616	57	1

Table 6.6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1A···O2^{i}	0.84	1.83	2.673(3)	178.0
O2–H2A···O1^{ii}	0.84	1.88	2.719(3)	172.3

Symmetry transformations used to generate equivalent atoms:
(i) x,y+1,z (ii) x–1/2,–y–1/2,–z+2

VI.2 X-ray data for compound (*R*)-4.22

University of Southampton · School of Chemistry

EPSRC National Crystallography Service

Table 6.7. Crystal data and structure refinement.

Identification code	**03sot115**	
Empirical formula	$C_{10}H_{20}O_2$	
Formula weight	172.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.3118(5) Å	α = 90°
	b = 16.7092(11) Å	β = 102.778(4)°
	c = 10.2218(8) Å	γ = 90°
Volume	1551.05(18) Å^3	
Z	6	
Density (calculated)	1.107 Mg / m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	576	
Crystal	Slab; Colourless	
Crystal size	0.30 × 0.16 × 0.05 mm^3	
θ range for data collection	2.94 – 27.48°	
Index ranges	$-12 \le h \le 12$, $-20 \le k \le 21$, $-13 \le l \le 11$	
Reflections collected	17930	
Independent reflections	6866 [R_{int} = 0.0755]	
Completeness to θ = 27.48°	99.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9963 and 0.9780	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6866 / 1 / 338	
Goodness-of-fit on F^2	1.013	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0642, *wR2* = 0.1395	
R indices (all data)	*R1* = 0.1126, *wR2* = 0.1598	
Absolute structure parameter	1.8(13)	
Extinction coefficient	0.004(4)	

Largest diff. peak and hole	0.698 and −0.221 e $Å^{-3}$

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.
It was not possible to accurately determine the absolute structure.
The relative stereochemistry is *R, R, R, S* (C1, C3, C6, C8) and all three molecules are the same.

Table 6.8. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4067(3)	1133(2)	7173(3)	34(1)	1
C2	5388(3)	969(2)	6569(3)	35(1)	1
C3	6791(3)	1346(2)	7402(3)	34(1)	1
C4	7060(3)	1030(2)	8837(3)	34(1)	1
C5	5702(3)	1168(2)	9434(3)	38(1)	1
C6	4305(3)	791(2)	8591(3)	34(1)	1
C7	2980(3)	923(2)	9216(3)	42(1)	1
C8	8097(3)	1249(2)	6697(3)	41(1)	1
C9	9336(3)	1812(2)	7266(4)	44(1)	1
C10	8658(4)	392(2)	6689(4)	46(1)	1
O1	2800(2)	781(2)	6304(2)	49(1)	1
O2	10433(2)	1833(2)	6478(2)	48(1)	1
C11	9707(3)	2574(2)	3045(3)	35(1)	1
C12	11311(3)	2431(2)	3653(3)	35(1)	1
C13	12297(3)	2538(2)	2661(3)	33(1)	1
C14	12059(3)	3362(2)	2018(4)	44(1)	1
C15	10427(4)	3509(2)	1416(4)	46(1)	1
C16	9474(3)	3421(2)	2450(3)	41(1)	1
C17	7871(4)	3599(2)	1856(4)	55(1)	1
C18	13912(3)	2330(2)	3313(3)	36(1)	1
C19	14834(3)	2279(2)	2279(3)	39(1)	1
C20	14627(4)	2888(2)	4453(4)	51(1)	1
O11	8905(2)	2466(1)	4085(2)	41(1)	1
O12	16212(2)	1894(1)	2791(2)	43(1)	1
C21	6398(3)	−297(2)	2962(3)	32(1)	1
C22	7867(3)	103(2)	2992(3)	32(1)	1
C23	9117(3)	−498(2)	3128(3)	33(1)	1
C24	8749(3)	−1101(2)	1997(4)	41(1)	1
C25	7260(3)	−1504(2)	1942(4)	42(1)	1
C26	6003(3)	−896(2)	1810(3)	34(1)	1
C27	4528(3)	−1295(2)	1747(4)	45(1)	1
C28	10616(3)	−75(2)	3278(3)	36(1)	1
C29	11884(3)	−622(2)	3869(4)	44(1)	1
C30	10838(3)	306(2)	1964(3)	43(1)	1
O21	5307(2)	316(1)	2854(2)	40(1)	1
O22	13246(2)	−196(1)	4249(2)	46(1)	1

Table 6.9. Bond lengths [Å] and angles [°].

C1–O1	1.435(4)	C13–H13	1.0000
C1–C2	1.518(4)	C14–C15	1.528(4)
C1–C6	1.528(4)	C14–H14A	0.9900
C1–H1	1.0000	C14–H14B	0.9900
C2–C3	1.529(4)	C15–C16	1.530(4)
C2–H2A	0.9900	C15–H15A	0.9900
C2–H2B	0.9900	C15–H15B	0.9900
C3–C4	1.526(4)	C16–C17	1.512(5)
C3–C8	1.553(4)	C16–H16	1.0000
C3–H3	1.0000	C17–H17A	0.9800
C4–C5	1.538(4)	C17–H17B	0.9800
C4–H4A	0.9900	C17–H17C	0.9800
C4–H4B	0.9900	C18–C19	1.504(4)
C5–C6	1.529(4)	C18–C20	1.527(5)
C5–H5A	0.9900	C18–H18	1.0000
C5–H5B	0.9900	C19–O12	1.428(4)
C6–C7	1.526(4)	C19–H19A	0.9900
C6–H6	1.0000	C19–H19B	0.9900
C7–H7A	0.9800	C20–H20A	0.9800
C7–H7B	0.9800	C20–H20B	0.9800
C7–H7C	0.9800	C20–H20C	0.9800
C8–C9	1.502(5)	O11–H11A	0.8400
C8–C10	1.525(5)	O12–H12	0.8400
C8–H8	1.0000	C21–O21	1.431(3)
C9–O2	1.434(4)	C21–C22	1.518(4)
C9–H9A	0.9900	C21–C26	1.526(4)
C9–H9B	0.9900	C21–H21	1.0000
C10–H10A	0.9800	C22–C23	1.521(4)
C10–H10B	0.9800	C22–H22A	0.9900
C10–H10C	0.9800	C22–H22B	0.9900
O1–H1A	0.8400	C23–C24	1.514(5)
O2–H2	0.8400	C23–C28	1.542(4)
C11–O11	1.439(3)	C23–H23	1.0000
C11–C12	1.505(4)	C24–C25	1.531(4)
C11–C16	1.536(4)	C24–H24A	0.9900
C11–H11	1.0000	C24–H24B	0.9900
C12–C13	1.522(4)	C25–C26	1.534(4)
C12–H12A	0.9900	C25–H25A	0.9900
C12–H12B	0.9900	C25–H25B	0.9900
C13–C14	1.520(4)	C26–C27	1.515(4)
C13–C18	1.544(4)	C26–H26	1.0000

C27–H27A	0.9800	C29–H29A	0.9900
C27–H27B	0.9800	C29–H29B	0.9900
C27–H27C	0.9800	C30–H30A	0.9800
C28–C29	1.509(4)	C30–H30B	0.9800
C28–C30	1.541(4)	C30–H30C	0.9800
C28–H28	1.0000	O21–H21A	0.8400
C29–O22	1.431(4)	O22–H22	0.8400

O1–C1–C2	107.7(2)	C6–C7–H7A	109.5
O1–C1–C6	111.1(2)	C6–C7–H7B	109.5
C2–C1–C6	110.9(2)	H7A–C7–H7B	109.5
O1–C1–H1	109.0	C6–C7–H7C	109.5
C2–C1–H1	109.0	H7A–C7–H7C	109.5
C6–C1–H1	109.0	H7B–C7–H7C	109.5
C1–C2–C3	111.7(2)	C9–C8–C10	110.8(3)
C1–C2–H2A	109.3	C9–C8–C3	111.6(3)
C3–C2–H2A	109.3	C10–C8–C3	113.9(2)
C1–C2–H2B	109.3	C9–C8–H8	106.7
C3–C2–H2B	109.3	C10–C8–H8	106.7
H2A–C2–H2B	107.9	C3–C8–H8	106.7
C4–C3–C2	109.3(2)	O2–C9–C8	112.3(3)
C4–C3–C8	115.5(2)	O2–C9–H9A	109.1
C2–C3–C8	111.0(3)	C8–C9–H9A	109.1
C4–C3–H3	106.8	O2–C9–H9B	109.1
C2–C3–H3	106.8	C8–C9–H9B	109.1
C8–C3–H3	106.8	H9A–C9–H9B	107.9
C3–C4–C5	110.8(2)	C8–C10–H10A	109.5
C3–C4–H4A	109.5	C8–C10–H10B	109.5
C5–C4–H4A	109.5	H10A–C10–H10B	109.5
C3–C4–H4B	109.5	C8–C10–H10C	109.5
C5–C4–H4B	109.5	H10A–C10–H10C	109.5
H4A–C4–H4B	108.1	H10B–C10–H10C	109.5
C6–C5–C4	112.7(2)	C1–O1–H1A	109.5
C6–C5–H5A	109.0	C9–O2–H2	109.5
C4–C5–H5A	109.0	O11–C11–C12	107.7(2)
C6–C5–H5B	109.0	O11–C11–C16	111.0(2)
C4–C5–H5B	109.0	C12–C11–C16	110.5(2)
H5A–C5–H5B	107.8	O11–C11–H11	109.2
C7–C6–C1	112.5(2)	C12–C11–H11	109.2
C7–C6–C5	111.8(3)	C16–C11–H11	109.2
C1–C6–C5	107.9(2)	C11–C12–C13	113.4(3)
C7–C6–H6	108.2	C11–C12–H12A	108.9
C1–C6–H6	108.2	C13–C12–H12A	108.9
C5–C6–H6	108.2	C11–C12–H12B	108.9

C13–C12–H12B	108.9	C18–C20–H20A	109.5
H12A–C12–H12B	107.7	C18–C20–H20B	109.5
C14–C13–C12	110.0(2)	H20A–C20–H20B	109.5
C14–C13–C18	115.2(2)	C18–C20–H20C	109.5
C12–C13–C18	111.1(2)	H20A–C20–H20C	109.5
C14–C13–H13	106.7	H20B–C20–H20C	109.5
C12–C13–H13	106.7	C11–O11–H11A	109.5
C18–C13–H13	106.7	C19–O12–H12	109.5
C13–C14–C15	110.9(3)	O21–C21–C22	107.9(2)
C13–C14–H14A	109.5	O21–C21–C26	111.4(2)
C15–C14–H14A	109.5	C22–C21–C26	111.5(2)
C13–C14–H14B	109.5	O21–C21–H21	108.7
C15–C14–H14B	109.5	C22–C21–H21	108.7
H14A–C14–H14B	108.0	C26–C21–H21	108.7
C14–C15–C16	112.6(3)	C21–C22–C23	112.2(2)
C14–C15–H15A	109.1	C21–C22–H22A	109.2
C16–C15–H15A	109.1	C23–C22–H22A	109.2
C14–C15–H15B	109.1	C21–C22–H22B	109.2
C16–C15–H15B	109.1	C23–C22–H22B	109.2
H15A–C15–H15B	107.8	H22A–C22–H22B	107.9
C17–C16–C15	112.1(3)	C24–C23–C22	109.3(2)
C17–C16–C11	112.4(3)	C24–C23–C28	115.3(2)
C15–C16–C11	108.0(2)	C22–C23–C28	111.3(2)
C17–C16–H16	108.1	C24–C23–H23	106.8
C15–C16–H16	108.1	C22–C23–H23	106.8
C11–C16–H16	108.1	C28–C23–H23	106.8
C16–C17–H17A	109.5	C23–C24–C25	111.8(3)
C16–C17–H17B	109.5	C23–C24–H24A	109.3
H17A–C17–H17B	109.5	C25–C24–H24A	109.3
C16–C17–H17C	109.5	C23–C24–H24B	109.3
H17A–C17–H17C	109.5	C25–C24–H24B	109.3
H17B–C17–H17C	109.5	H24A–C24–H24B	107.9
C19–C18–C20	110.6(3)	C24–C25–C26	112.3(3)
C19–C18–C13	111.2(3)	C24–C25–H25A	109.1
C20–C18–C13	114.2(3)	C26–C25–H25A	109.1
C19–C18–H18	106.8	C24–C25–H25B	109.1
C20–C18–H18	106.8	C26–C25–H25B	109.1
C13–C18–H18	106.8	H25A–C25–H25B	107.9
O12–C19–C18	112.0(3)	C27–C26–C21	112.6(3)
O12–C19–H19A	109.2	C27–C26–C25	112.2(3)
C18–C19–H19A	109.2	C21–C26–C25	108.5(2)
O12–C19–H19B	109.2	C27–C26–H26	107.8
C18–C19–H19B	109.2	C21–C26–H26	107.8
H19A–C19–H19B	107.9	C25–C26–H26	107.8

C26–C27–H27A	109.5	O22–C29–H29A	109.2
C26–C27–H27B	109.5	C28–C29–H29A	109.2
H27A–C27–H27B	109.5	O22–C29–H29B	109.2
C26–C27–H27C	109.5	C28–C29–H29B	109.2
H27A–C27–H27C	109.5	H29A–C29–H29B	107.9
H27B–C27–H27C	109.5	C28–C30–H30A	109.5
C29–C28–C30	110.8(2)	C28–C30–H30B	109.5
C29–C28–C23	111.9(2)	H30A–C30–H30B	109.5
C30–C28–C23	113.3(3)	C28–C30–H30C	109.5
C29–C28–H28	106.8	H30A–C30–H30C	109.5
C30–C28–H28	106.8	H30B–C30–H30C	109.5
C23–C28–H28	106.8	C21–O21–H21A	109.5
O22–C29–C28	112.1(3)	C29–O22–H22	109.5

Symmetry transformations used to generate equivalent atoms:

Table 6.10. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	23(1)	47(2)	31(2)	1(1)	5(1)	−1(1)
C2	29(2)	48(2)	28(2)	4(1)	7(1)	2(1)
C3	26(1)	37(2)	41(2)	9(1)	9(1)	3(1)
C4	26(2)	46(2)	30(2)	2(1)	4(1)	0(1)
C5	36(2)	51(2)	27(2)	−1(1)	8(1)	4(1)
C6	30(2)	41(2)	31(2)	1(1)	8(1)	2(1)
C7	33(2)	59(2)	36(2)	6(2)	12(1)	−2(2)
C8	32(2)	57(2)	36(2)	11(2)	10(1)	−4(1)
C9	37(2)	48(2)	49(2)	5(2)	14(2)	−1(2)
C10	37(2)	56(2)	48(2)	3(2)	17(2)	10(2)
O1	26(1)	84(2)	36(1)	−7(1)	5(1)	2(1)
O2	34(1)	63(2)	47(2)	6(1)	13(1)	−3(1)
C11	32(2)	44(2)	33(2)	−1(1)	12(1)	1(1)
C12	31(2)	42(2)	34(2)	−3(1)	10(1)	0(1)
C13	27(1)	39(2)	35(2)	−4(1)	8(1)	0(1)
C14	40(2)	49(2)	46(2)	7(2)	18(2)	2(2)
C15	46(2)	50(2)	45(2)	8(2)	15(2)	5(2)
C16	36(2)	47(2)	43(2)	0(2)	13(1)	3(2)
C17	41(2)	62(2)	59(3)	17(2)	7(2)	10(2)
C18	31(2)	47(2)	32(2)	−3(1)	8(1)	1(1)
C19	37(2)	42(2)	39(2)	−3(2)	11(1)	1(1)
C20	39(2)	68(2)	44(2)	−16(2)	7(2)	6(2)
O11	26(1)	58(1)	39(1)	6(1)	9(1)	−1(1)
O12	31(1)	42(1)	52(2)	−5(1)	6(1)	3(1)
C21	26(1)	38(2)	35(2)	−4(1)	10(1)	−3(1)
C22	28(1)	37(2)	31(2)	−2(1)	8(1)	−2(1)
C23	29(2)	37(2)	36(2)	6(1)	10(1)	0(1)
C24	35(2)	37(2)	56(2)	−2(2)	20(2)	4(1)
C25	39(2)	34(2)	52(2)	−4(2)	12(2)	0(1)
C26	33(2)	36(2)	32(2)	−2(1)	4(1)	−2(1)
C27	38(2)	45(2)	49(2)	−1(2)	3(2)	−6(1)
C28	29(2)	39(2)	42(2)	1(1)	13(1)	−1(1)
C29	26(2)	53(2)	51(2)	5(2)	9(1)	−4(1)
C30	37(2)	51(2)	45(2)	5(2)	17(2)	−6(2)
O21	29(1)	42(1)	52(1)	−2(1)	17(1)	−1(1)
O22	29(1)	58(1)	54(2)	−6(1)	15(1)	−7(1)

Table 6.11. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	3917	1724	7210	40	1
H2A	5197	1187	5646	42	1
H2B	5529	384	6515	42	1
H3	6599	1933	7446	41	1
H4A	7922	1306	9396	41	1
H4B	7283	451	8842	41	1
H5A	5893	939	10350	45	1
H5B	5545	1751	9508	45	1
H6	4472	202	8541	40	1
H7A	2778	1497	9247	64	1
H7B	3193	705	10129	64	1
H7C	2118	651	8674	64	1
H8	7722	1406	5739	49	1
H9A	8934	2357	7311	53	1
H9B	9801	1643	8191	53	1
H10A	9451	372	6200	69	1
H10B	7850	42	6249	69	1
H10C	9034	211	7614	69	1
H1A	2034	940	6529	73	1
H2	10034	1947	5680	71	1
H11	9359	2173	2318	43	1
H12A	11433	1880	4018	42	1
H12B	11634	2806	4411	42	1
H13	11961	2139	1927	40	1
H14A	12622	3404	1304	53	1
H14B	12432	3776	2701	53	1
H15A	10084	3125	676	55	1
H15B	10303	4056	1033	55	1
H16	9833	3813	3189	50	1
H17A	7474	3195	1177	82	1
H17B	7782	4130	1437	82	1
H17C	7316	3588	2566	82	1
H18	13907	1783	3710	44	1
H19A	14286	1978	1491	47	1
H19B	15014	2826	1978	47	1
H20A	15646	2720	4813	76	1
H20B	14076	2867	5166	76	1
H20C	14618	3437	4114	76	1
H11A	8048	2308	3743	61	1
H12	16070	1465	3172	64	1

H21	6462	−589	3827	39	1
H22A	8090	482	3755	38	1
H22B	7799	415	2156	38	1
H23	9152	−799	3980	40	1
H24A	9528	−1515	2122	50	1
H24B	8727	−828	1133	50	1
H25A	7317	−1823	2768	50	1
H25B	7043	−1875	1168	50	1
H26	5938	−596	953	41	1
H27A	4346	−1691	1021	67	1
H27B	3747	−891	1576	67	1
H27C	4538	−1563	2602	67	1
H28	10633	372	3932	43	1
H29A	11675	−893	4668	52	1
H29B	11977	−1038	3204	52	1
H30A	11742	626	2148	65	1
H30B	9996	651	1589	65	1
H30C	10917	−117	1318	65	1
H21A	4564	134	3093	60	1
H22	13177	151	4827	69	1

Table 6.12. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1A···O2^{i}	0.84	2.10	2.855(3)	149.1
O2–H2···O11	0.84	1.94	2.754(3)	163.6
O11–H11A···O12^{i}	0.84	1.90	2.735(3)	172.6
O12–H12···O21^{ii}	0.84	2.05	2.772(3)	144.2
O21–H21A···O22^{i}	0.84	1.96	2.767(3)	160.4
O22–H22···O1^{ii}	0.84	1.94	2.764(3)	168.3

Symmetry transformations used to generate equivalent atoms:
(i) x−1,y,z (ii) x+1,y,z

CHAPTER VII - REFERENCES

(1) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571 - 4618.

(2) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I. *J. Nat. Prod.* **1999**, *62*, 997 - 999.

(3) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I. *Tetrahedron Lett.* **1999**, *40*, 7627 - 7631.

(4) Rodríguez, A. D.; Shi, Y.-P. *Tetrahedron* **2000**, *56*, 9015 - 9023.

(5) Rodríguez, A. D.; Rodríguez, I. I. *Tetrahedron Lett.* **2002**, *43*, 5601 - 5604.

(6) For an overview of previous syntheses, see Tyte, M. J., *PhD Thesis*; University of Southampton, 2002.

(7) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sciences* **1998**, *62*, PL 401 - 407.

(8) Bongiorni, L.; Pietra, F. *Chem. & Ind.* **1996**, 54 - 58.

(9) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215 - 4222.

(10) Rodríguez, A. D.; González, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083 - 7091.

(11) Ata, A.; Kerr, R. G. *Tetrahedron Lett.* **2000**, *41*, 5821 - 5825.

(12) Rodríguez, A. D.; Ramírez, C.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 6682 - 6687.

(13) Shi, Y.-P.; Rodríguez, I. I.; Rodríguez, A. D. *Tetrahedron Lett.* **2003**, *44*, 3249 - 3253.

(14) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527 - 530.

(15) Rodríguez, I. I.; Rodríguez, A. D. *J. Nat. Prod.* **2003**, *66*, 855 - 857.

(16) Rodríguez, A. D.; Ramírez, C.; Medina, V.; Shi, Y.-P. *Tetrahedron Lett.* **2000**, *41*, 5177 - 5180.

(17) Rodríguez, A. D.; Ramírez, C. *J. Nat. Prod.* **2001**, *64*, 100 - 102.

(18) Rodríguez, A. D.; Ramírez, C. *Org. Lett.* **2000**, *2*, 507 - 510.

(19) Nicolaou, K. C.; Vassilikogiannakis, G.; Maegerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359 - 5371.

(20) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390 - 1398.

(21) Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2001**, *42*, 8709 - 8711.

(22) Rychnovsky, S. D.; Kim, A. I. *Angew. Chem. Int. Ed.* **2003**, *42*, 1267 - 1270.

(23) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496 - 6511.

(24) Flynn, B. D.; Chaplin, J. H.; Edwards, A. J. *Org. Biomol. Chem.* **2003**, *1*, 1842 - 1844.

(25) Moore, H. W.; Heerding, J. M. *J. Org. Chem.* **1991**, *56*, 4048 - 4050.

(26) Pazos, Y.; Iglesias, B.; R. de Lera, A. *J. Org. Chem.* **2001**, *66*, 8483 - 8489.

(27) Barton, D. H. R.; Bashiardes, G.; Fourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605 - 1608.

(28) Groszek, G.; Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron* **1989**, *45*, 2223 - 2236.

(29) Lee, K.; Wiener, D. F. *Tetrahedron Lett.* **1993**, *34*, 2433 - 2436.

(30) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482 - 2488.

(31) Liebeskind, L. S.; Baydon, S. L.; South, M. S.; Blount, J. F. *J. Organomet. Chem.* **1980**, *202*, C73 - C76.

(32) Liebeskind, L. S.; Baydon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397 - 7398.

(33) Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771 - 775.

(34) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815 - 3821.

(35) South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181 - 4185.

(36) Liebeskind, L. S.; Leeds, J. P.; Baysdon, S. L.; Iyer, S. *J. Am. Chem. Soc.* **1984**, *106*, 6451 - 6453.

(37) Liebeskind, L. S.; Baysdon, S. L. *Tetrahedron Lett.* **1984**, *25*, 1747 - 1750.

(38) Liebeskind, L. S.; Jewell, C. F., Jr. *J. Organomet. Chem.* **1985**, *285*, 305 - 319.

(39) Jewell, C. F., Jr.; Liebeskind, L. S.; Williamson, M. *J. Am. Chem. Soc.* **1985**, *107*, 6715 - 6716.

(40) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065 - 3067.

(41) Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759 - 2770.

(42) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392 - 3393.

(43) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174 - 1175.

(44) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J.-J. *J. Org. Chem.* **1986**, *51*, 5270 - 5276.

(45) Brown, H. C.; Knights, E. F.; Coleman, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 2144 - 2146.

(46) Alper, H.; Somasunderam, A. *J. Mol. Catalysis* **1994**, *92*, 35 - 40.

(47) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973 - 9976.

(48) Grela, K.; Bienik, M. *Tetrahedron Lett.* **2001**, *42*, 6425 - 6428.

(49) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178 - 3186.

(50) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684 - 3686.

(51) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595 - 4597.

(52) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175 - 1178.

(53) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Butterworth-Heinemann Ltd: Oxford, 1994.

(54) Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775 - 2779.

(55) Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163 - 1176.

(56) Miles, D. H.; Payne, M. *Tetrahedron* **2001**, *57*, 5769 - 5772.

(57) Moore, H. W.; Liu, H.; Tomooka, C. S. *Synthetic Commun.* **1997**, *27*, 2177 - 2180.

(58) Dehmlow, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*, 1 - 8.

(59) Ehnsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177 - 1185.

(60) Crockett, R.; Roduner, E. *J. Chem. Soc., Perkin Trans. 2* **1994**, *2*, 347 - 350.

(61) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157 - 2162.

(62) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773 - 5784.

(63) Barieux, J.-J.; Gore, J. *Bull. Soc. Chim. Fr.* **1971**, *11*, 3978 - 3985.

(64) Brown, H. C.; Lane, C. F. *Tetrahedron* **1988**, *44*, 2763 - 2772.

(65) Hirata, T.; Hamada, H.; Aoki, T.; Suga, T. *Phytochemistry* **1982**, *21*, 2209 - 2212.

(66) Asawaka, Y.; Takahashi, H.; Toyota, M.; Noma, Y. *Phytochemistry* **1991**, *30*, 3981 - 3987.

(67) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *14*, 4607 - 4610.

(68) Wulff, W. D.; Peterson, G. A.; Banta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem* **1986**, *51*, 277 - 279.

(69) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc* **1985**, *107*, 257 - 259.

(70) Baudouy, R.; Maliverney, C. *Tetrahedron* **1988**, *44*, 471 - 480.

(71) Hua, D. H.; Venkataraman, S. *J. Org. Chem* **1988**, *53*, 1095 - 1097.

(72) Wen, L.; Li, M. *J. Am. Chem. Soc* **1997**, *119*, 7726 - 7733.

(73) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029 - 4032.

(74) Phillips, E. D.; Warren, E. S.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 307 - 320.

(75) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1*, 26 - 28.