UNIVERSITY OF SOUTHAMPTON

Approaches to total synthesis of Peyssonol A and Peyssonol B

By

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A Thesis Submitted for the Degree of Doctor of Philosophy

Faculty of Science
Department of Chemistry

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

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This thesis is concerned with the total synthesis of the two natural products peyssonol A and peyssonol B, which were isolated from a Red Sea Alga, *Peyssonnelia sp.* They were shown to display inhibition of HIV Reverse Transcriptases. Syntheses of several related natural products containing the same sesquiterpene skeleton, such as avarol and ilimiquanone, are reviewed in the first chapter.

The second chapter describes our first route towards the total synthesis of peyssonol A. We intended to synthesise the decalin portion first and then couple it to the aromatic moiety. The key step in the formation of the decalin ring is a 6-*exo*-trig intramolecular radical cyclisation. Samarium (II) iodide intramolecular radical cyclisation was also investigated. Entries based on the Robinson annulation and the related Robinson-Mannich base methiodide method are also described.

An alternative route towards the total synthesis was developed, in which the key step involved a Ring Closure Metathesis reaction. A synthesis of the aromatic portion is also described. Studies on the introduction of an electrophilic group on the aromatic portion to facilitate the coupling with the decalin ring are then discussed. Finally, studies relating to a Mukayiama reaction are described as this too could provide a method of introducing the aromatic moiety.

A third route towards the total synthesis is described. It is based on work by Laube *et al.* and their total synthesis of the natural product zonarol. Lewis acid intramolecular cyclisation is involved as a key step. Studies on an alternate $Mn(OAc)_3$ intramolecular reductive cyclisation complete the discussion.

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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 1999 and October 2002. No part of this thesis has previously been submitted for a degree.

ACKNOWLEDGEMENTS

Firtsly, I would like to thank Dr D.C. Harrowven for giving me the opportunity to study a PhD in Organic Chemistry, although I am not sure I deserved it... Also, for his support, advice and huge patience during the last three years. I will remember the long drinking sessions, the Christmas dinners, as well as the gambling and the Queen brainwashing during those events…

To the Harrowven group, past and present: thank you for making me feel at home as soon as I arrived and make my life in the lab as pleasant as possible. Thanks go to Matt "SG" for his impressions of "Under the Moon of Love", and his natural ability to make people laugh (Ride baby, ride…), Pete "baby" for his awful jokes, his French lessons and his impressions of "Cypress Hill" and "Bodycount", Nikki "I'll give up again soon", Jonnhy Pops for letting me stroke his hair on demand (I know you love it dear!!!), Melpeu for being my second mother when I needed it, and for bringing me to the worst places in Southampton (Hummm…..), Michaelius Nunnus for his love of chemistry and his always accurate and right answers, Bèèèèèèèèèn Sutton for bringing a bit of the army discipline into the lab and his not so famous dance moves, Nigel, better known as "The Dwarf" for just being himself and as bad as me as football (hehehehe…), Heather, for bringing a stream of happiness and silliness in the lab, Stuart for his constant burping, singing and laughing, Nathalie for being the second french person in the lab, Tommi for giving me tennis lessons (don't be so hard next time, please…), Paul for being "stunning my son!!!", Tim for his oh so right comments when he is drunk or sober, Ian better known as "Gaylord, the Pop Idol" for not being the next Gareth Gates, and of course, last but not least Daniela for being more than a girlfriend.

Thanks to Joan Street and Neil Wells for an excellent NMR service, John Langley and Julie Herniman for their mass spectrometry expertise, and Mike Hurthouse for X-ray crystal structures.

I would also like to take the opportunity to thank all the friends I made during my time in Southampton. Thanks go to all the chemists of the third floor for making my time as enjoyable as ever, apart from when France had been slaughtered by England

at rugby, past and present housemates (don't you worry Nico and Katja, I'll do the washing up in a week or two), Julien, Sam, Fabrice...and all the remaining others that are too numerous to list, but they know who they are. A special thank goes to little miss Sheila for all the lovely meals she cooked for me and to the 2002 Southampton University Handball team for being the best of England on that year.

My appreciation also goes to those who have done invaluable proof reading, especially Stuart, Heather, Tim and Daniela.

Finally huge thanks go to my parents and all the members of my family for being proud of me....

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AIBN	α,α-azo-iso-butyronitrile
amu	atomic mass units
app.	apparent
BuI	iodobutane
^{n}BuLi	*n*-butyllithium
^{t}BuLi	tert-butyllithium
Bu_3SnH	tributyltin hydride
CAN	ammonium cerium(IV) nitrate
CBr_4	carbon tetrabromide
CCl_4	carbon tetrachloride
CHN	combustion analysis
CI	chemical ionisation
DBP	dibenzoyl peroxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DHP	3,4-dihydro-2*H*-pyran
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethylsulfoxide
EI	electron ionisation
ES	electrospray
Et_3N	triethylamine
h	hours
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
IR	infra red
KCN	potassium cyanide
KO^{t}Bu	potassium-*tert*-butoxide

LDA	lithium diisopropylamide
min	minute
Me_2CuLi	lithium dimethylcuprate
MeI	methyl iodide
MeLi	methyl lithium
MeOH	methanol
$MgBr_2.OEt_2$	magnesium bromide diethyl etherate complex
mp	melting point
Ms	mesylate
MS	mass spectrometry
MVK	methyl vinyl ketone
N	normal
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NBS	*N*-bromosuccinimide
NH_3	ammonia
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
M	molar
PCC	pyridinium chlorochromate
ppm	parts per million
PPh_3	triphenylphosphine
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluene sulfonic acid
RCM	ring closure metathesis
RT	reverse transcriptase
r.t.	room temperature
SEM	ethoxymethoxy silyl
$SnCl_4$	tin tetrachloride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
$TiCl_4$	titanium tetrachloride

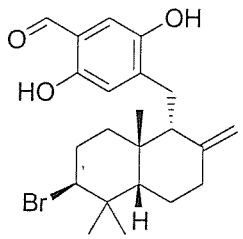
$Ti(O^{i}\text{-}Pr)_4$	titanium tetra-*iso*-propoxide
TLC	thin layer chromatography
TMS	trimethylsilyl

CHAPTER 1

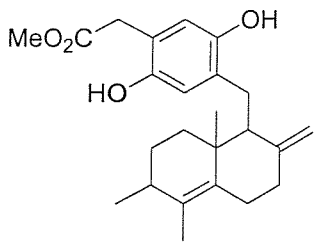
INTRODUCTION:

1.1 BACKGROUND:

Marine algae and sponges have yielded a variety of novel natural products of mixed biogenesis.[1-4] One class based on a farnesyl hydroquinone skeleton has attracted considerable attention in recent years since avarol **3** and several related compounds were shown to be active against HIV reverse transcriptases.[5-8] During a subsequent survey of marine organisms for anti HIV RTs activities, Kashman and co-workers isolated two new compounds, peyssonol A **1** and peyssonol B **2**, from the Red Sea Alga *Peyssonnelia sp.* (family Peyssonneliaceae).[9,10]

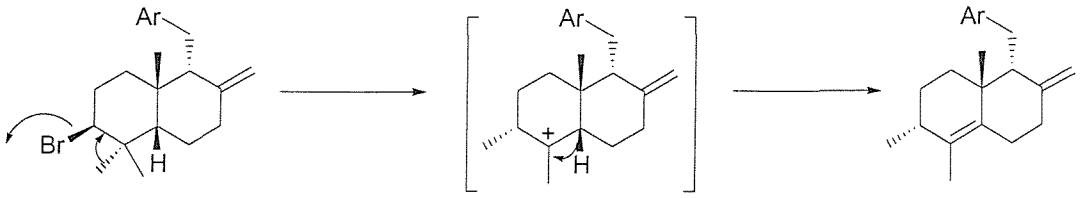


peyssonol A
1



peyssonol B
2

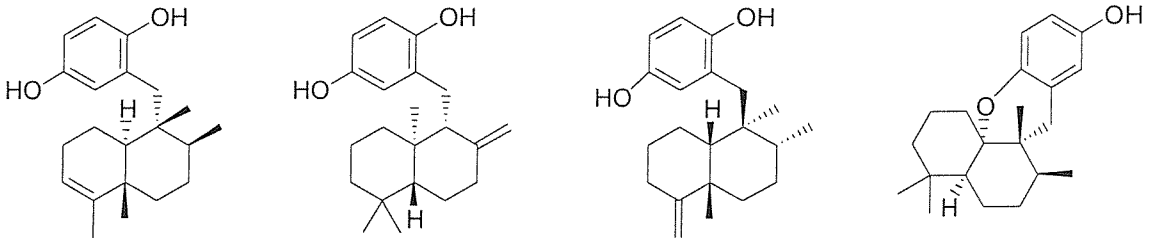
NMR studies afforded the gross structures of peyssonols A and B, and established that peyssonol A was the first bromo farnesyl hydroquinone metabolite to have been isolated from marine sources. Though insufficient material prevented an unequivocal assignment of stereogenic centres in peyssonol B, it seems reasonable to suggest that peyssonol A is a biosynthetic precursor of peyssonol B, involving the skeletal rearrangement depicted in Scheme 1.



peyssonol B

Scheme 1

Many related farnesyl hydroquinones have a longer history and also display biological activity. Zonarol **4** for example shows antifeedant and anti fungal properties [11-14] while aureol **6** displays antibacterial activity.[15,16]



Avarol **3** Zonarol **4** Arenarol **5** Aureol **6**

The limited bioavailability of peyssonols A **1** and B **2** (0.01% yield on extraction, dry weight), their HIV RTs activity and the unknown stereochemistry of peyssonol B **2** make these worthwhile targets for total synthesis. They represent a significant challenge to the synthetic chemist, in particular the *cis* fused drimane skeleton and axial bromine in peyssonol A **1**. The exocyclic double bond and the substituted hydroquinone moiety require special attention.

1.2 TOTAL SYNTHESIS OF AVAROL

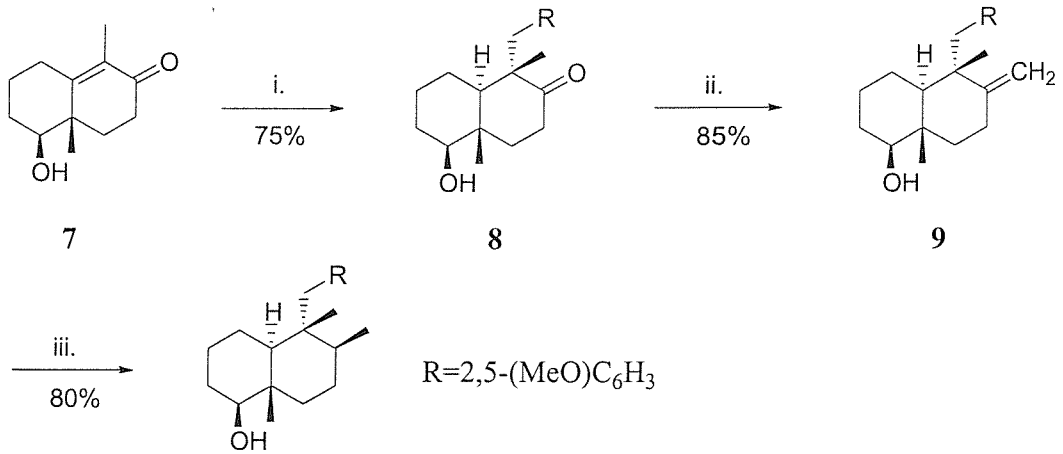
1.2.1: ISOLATION OF AVAROL

Avarol **3** was first isolated from solvent extracts of the sponge *Disidae avara* by Minale *et al.* in 1974.[17] It represented the first sesquiterpenoid with a rearranged drimane skeleton and

was shown to display inhibitory activity against $pp60^{v\text{-}src}$ PTK (proteine tyrosine kinase). Its structure was first determined thanks to spectral data and degradation reactions. Sarma's total synthesis also contributed to the confirmation of its structure.[18] In a second publication, Minale proposed a 5*S*,8*S*,9*R*,10*S* absolute stereochemistry for avarol, based on CD measurements of an enone oxidation product of avarol dimethyl ether.[19]

1.2.2: SARMA'S STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-AVAROL.

The first reported stereocontrolled total synthesis of (±)-avarol was by Sarma *et al.*[18] in 1982, and is detailed in the following schemes. They suggested that access to avarol might be achieved via a suitably functionalised bicyclo[4.4.0]decane such as **10**. Access to **10** followed a Birch reduction of enone **7** to a lithium enolate which was quenched *in situ* with a benzylbromide to give **8**. Wittig methylenation to **9** and hydrogenation of the resultant alkene then gave precursor **10.**



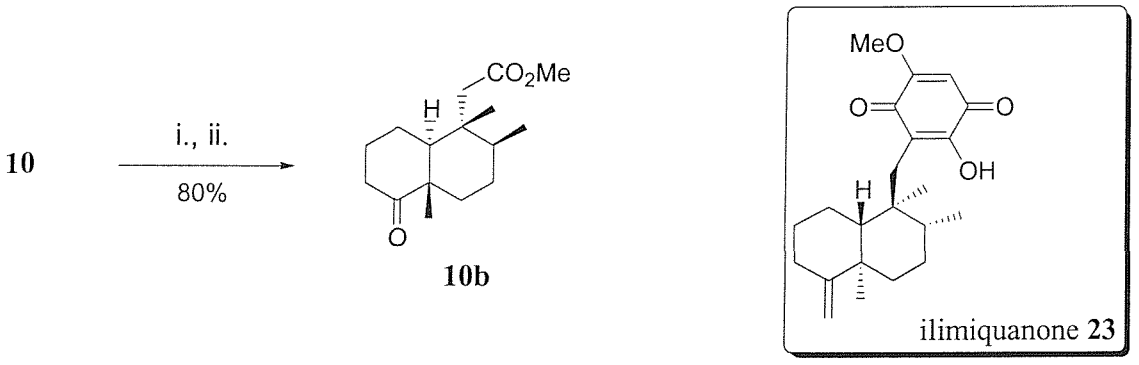
7 **8** **9** **10**

i. Li-NH_3 (l)/THF, 2,5-dimethoxy-benzylbromide; **ii.** CH_2=PPh_3/Me_2SO; **iii.** H_2, 10% Pd/C.

Scheme 2

The sequence outlined in scheme 2 had previously been reported [20], albeit in poorer yield. Catalytic hydrogenation of **9** to **10** initially proved difficult. In early experiments, an aged

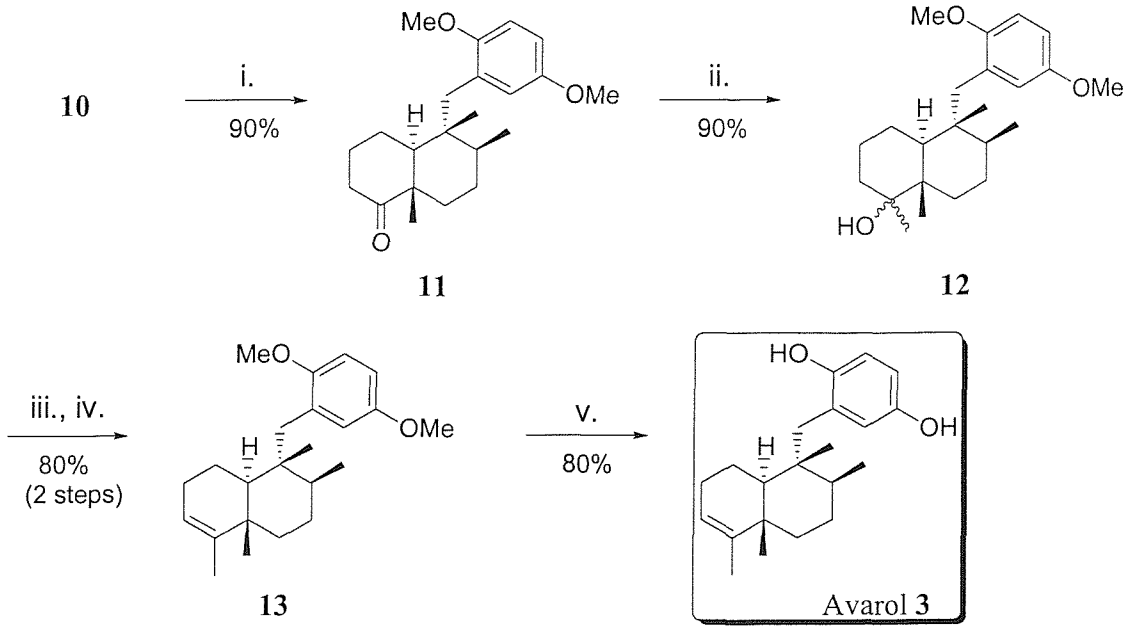
catalyst (10% Pd/C) was used, which efficiently catalysed isomerization of the exo double bond of **9** to the more hindered endocyclic position. The hydrogenation was later made successful by using a large excess of the catalyst in triethylamine containing a trace of methanol. In this way, a quantitative yield was achieved with an 85:15 diastereoisomer ratio in favour of **10**. Hydrogenation in ethanol gave rise to a 4:1 ratio, showing that the choice of solvent influenced the stereochemical course of the reaction to some extent.



i. RuO_2, $NaIO_4/CCl_4/H_2O$; **ii.** CH_2N_2/Et_2O.

Scheme 3

Considering steric factors in **9**, Sarma *et al.* suggested that the major epimer would have the secondary methyl group in the equatorial position (β), as addition of hydrogen from the β face, leading to two axial methyl groups, would be hindered to some extent by the two axial methyl groups of **9**. Yet, the exact stereochemistry of the major compound could not be resolved from the available spectral data. Indeed, its stereostructure was only clarified by conversion of **10** to the known ester **10b** and comparison of these spectral data with those previously reported (Scheme 3, **10b** had been prepared by degradation of ilimiquanone).



i. PCC/CH_2Cl_2; **ii.** $MeLi/Et_2O$; **iii.** $POCl_3/C_5H_5N$; **iv.** $RhCl_3/EtOH$; **v.** n-BuSLi/HMPA.

Scheme 4

Oxidation of alcohol **10** to ketone **11** next facilitated introduction of the final methyl group. Addition of MeLi to **11** gave an epimeric mixture of alcohols **12** (~3:1), and treatment of these carbinols with phosphorus oxychloride in pyridine afforded a 2:1 mixture of endo and exocyclic alkenes. On exposure to rhodium chloride, this mixture was isomerised to **13**. Finally, deprotection of the aryl methyl ethers afforded (±) avarol **3**.[21]

Overall, the total synthesis was achieved in eight steps and in 28% yield from **7**. It represents a useful route to avarol and related natural products containing the *trans* clerodane skeleton.

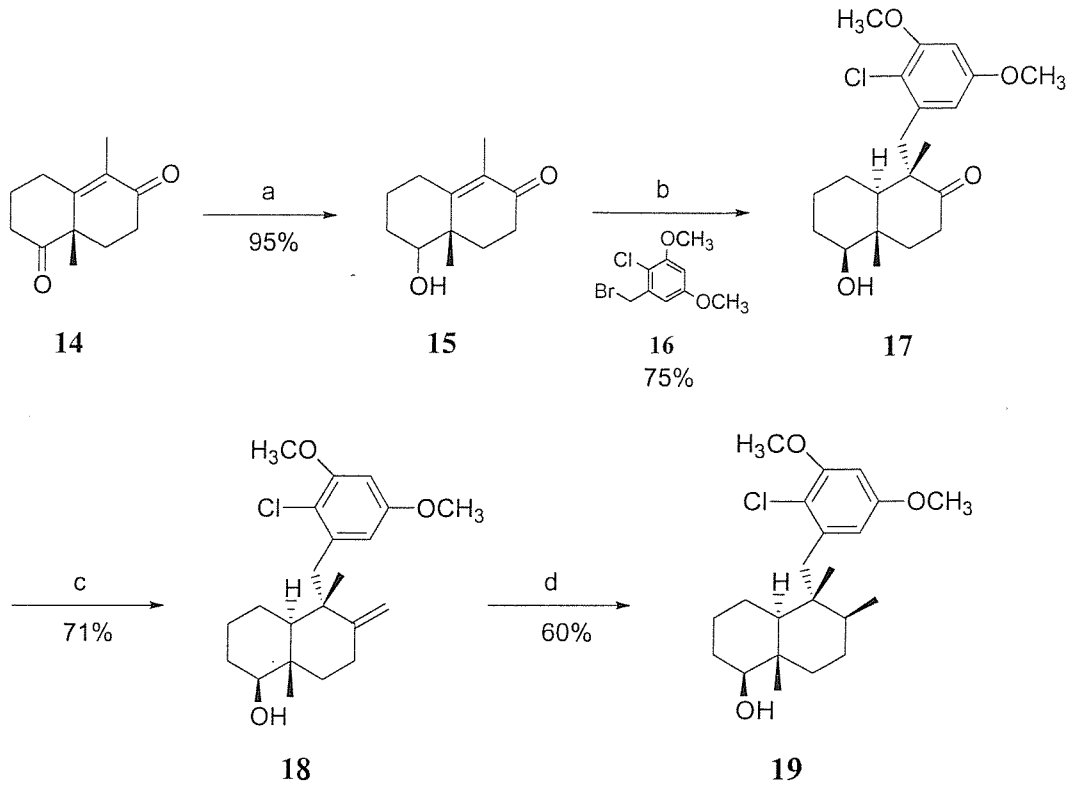
1.3: TOTAL SYNTHESIS OF (-)-ILIMIQUANONE.

1.3.1: ISOLATION OF ILIMIQUANONE.

Ilimiquanone **23** was originally isolated from the marine sponge *Hippiospongia metachromia*.[22,23] It was reported to have antimicrobial, anti HIV,[7] anti-inflammatory, antimitotic[24,25] and antisecretory activity.[26] In addition ilimiquanone was recently demonstrated to inhibit the toxicity of ricin and diphteria toxin, to reversibly disrupt the Golgi complex and to provoke the loss of the gap junction plaques and inhibition of intercellular communication in BICR-MIRk and NRK cells.[27]

1.3.2: BRUNER'S TOTAL SYNTHESIS OF (-)-ILIMIQUANONE.

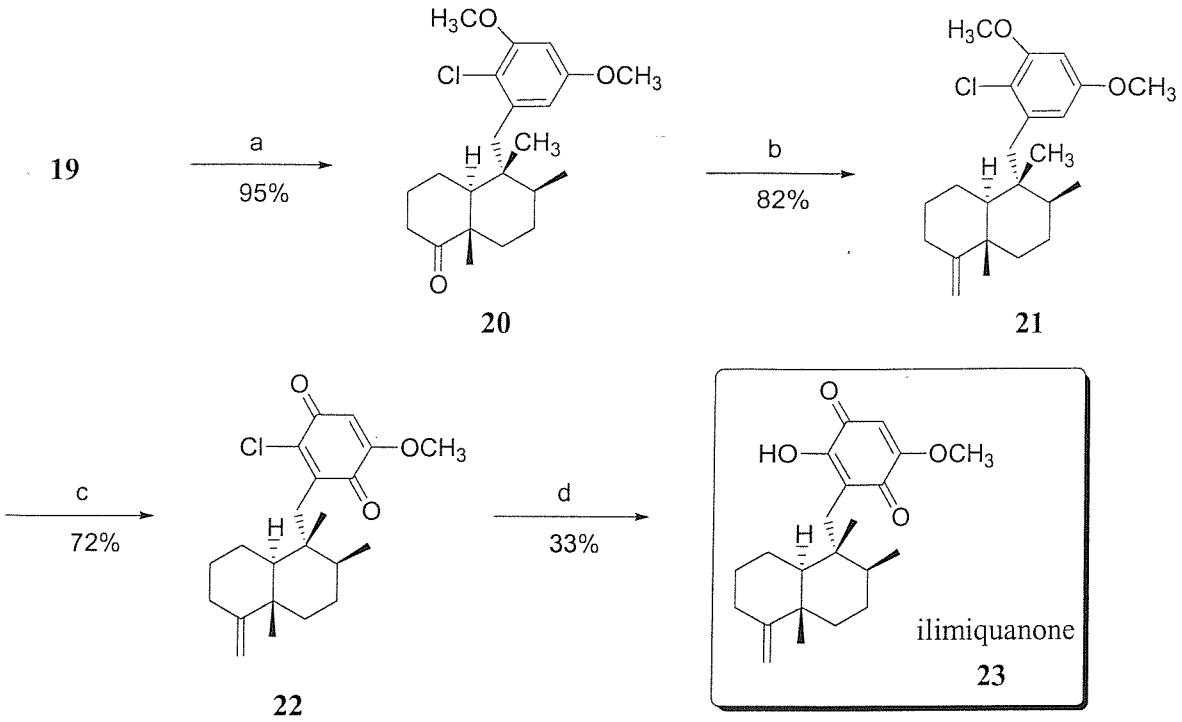
Bruner *et al.* reported the first total synthesis of (-)-ilimiquanone **23** in 1995.[28] Their synthesis was initially aimed at deciphering the mechanism of action of the natural product. It began with diketone **14,** which was readily obtained in 60% yield and 75-90% ee through an L-phenylalanine-mediated enantioselective Robinson annulation.[29,30] Recrystallisation from ether/hexanes provided material with an ee >99%. Reduction of ketone **14** with sodium borohydride gave alcohol **15**. A Birch reduction of the enone then formed an enolate, which was alkylated to afford **17** in 75% yield. This sequence established the ilimiquanone ring system and three of the four contiguous stereocentres found in the decalin ring. A Wittig olefination of **17**, followed by a platinum catalysed hydrogenation, introduced the remaining methyl group and stereocentre as a 3:1 mixture of diastereoisomers in favour of compound **19** (Scheme 5).



a. $NaBH_4$, EtOH; **b.** Li, NH_3, **16**; **c.** $Ph_3P{=}CH_2$, DMSO; **d.** H_2, PtO_2, CH_2Cl_2.

Scheme 5

PCC oxidation of alcohol **19** led to ketone **20** and a Wittig olefination afforded **21** in 78% overall yield. Further oxidation of **21** with CAN (ammonium cerium(IV) nitrate) delivered the chloromethoxyquinone **22** in 72% yield, and a palladium mediated chloride-alcohol exchange in basic aqueous THF afforded (-)-ilimiquanone **23** in 33% yield (Scheme 6).



a. PCC, CH_2Cl_2; **b.** $Ph_3P{=}CH_2$, DMSO; **c.** CAN, CH_3CN, H_2O; **d.** $Pd(Ph_3P)_4$, THF, H_2O, $NaHCO_3$.

Scheme 6

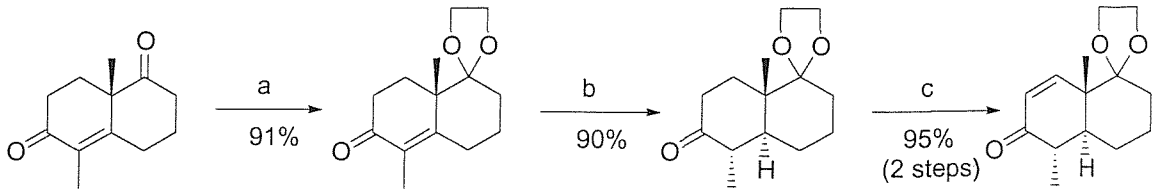
The result is a total synthesis of (-)-ilimiquanone in 10 steps and 3% overall yield, the main feature being the oxidation strategy developed to establish the natural product's sensitive quinone functionality. Besides, this synthetic route offers numerous opportunities for the preparation of analogues.

1.3.3: POIGNY *ET AL.* TOTAL SYNTHESIS OF (-)-ILIMIQUANONE.

A total synthesis of (-)-ilimiquanone was reported by Poigny *et al.* in 1998.[31] The two crucial steps are the attachment of the benzyl group to the drimane skeleton and the introduction of the appropriate substituents to the quinone moiety.

The synthesis of the target molecule started with the same material as for Bruner'synthesis, that is the amino acid mediated enantioselective product of Robinson annulation diketone **14**.[30] Conversion of diketone **14** to its monoacetal derivative **24** was followed by reduction

of the double bond to afford **25** as a single diastereoisomer. Ketone **25** was then converted to the enone **26**, via its silyl enol ether (Scheme 7).

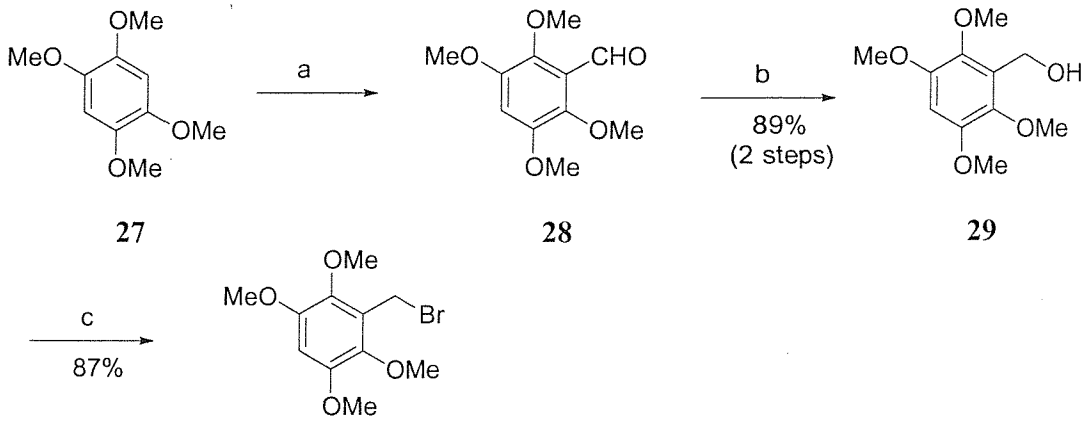


14 **24** **25** **26**

a. $HO(CH_2)_2OH$, cat. PTSA, benzene, reflux; **b.** 4 equiv. of Li, 1 equiv of H_2O, liquid NH_3, THF, -78 to 30°C; **c.** i: 1.2 equiv of LDA, 2 equiv of TMSCl, THF, -78 to 0°C, ii: 1.1 equiv of $Pd(OAc)_2$, CH_3CN, reflux.

Scheme 7

The synthesis of the aromatic moiety was undemanding. Treatment of the lithio derivative of **27** with *N*,*N*-dimethyl formamide afforded the desired aldehyde **28**, which was then reduced to the benzyl alcohol **29**. Introduction of the bromide was then accomplished in 87% yield using CBr_4 and PPh_3 (Scheme 8).



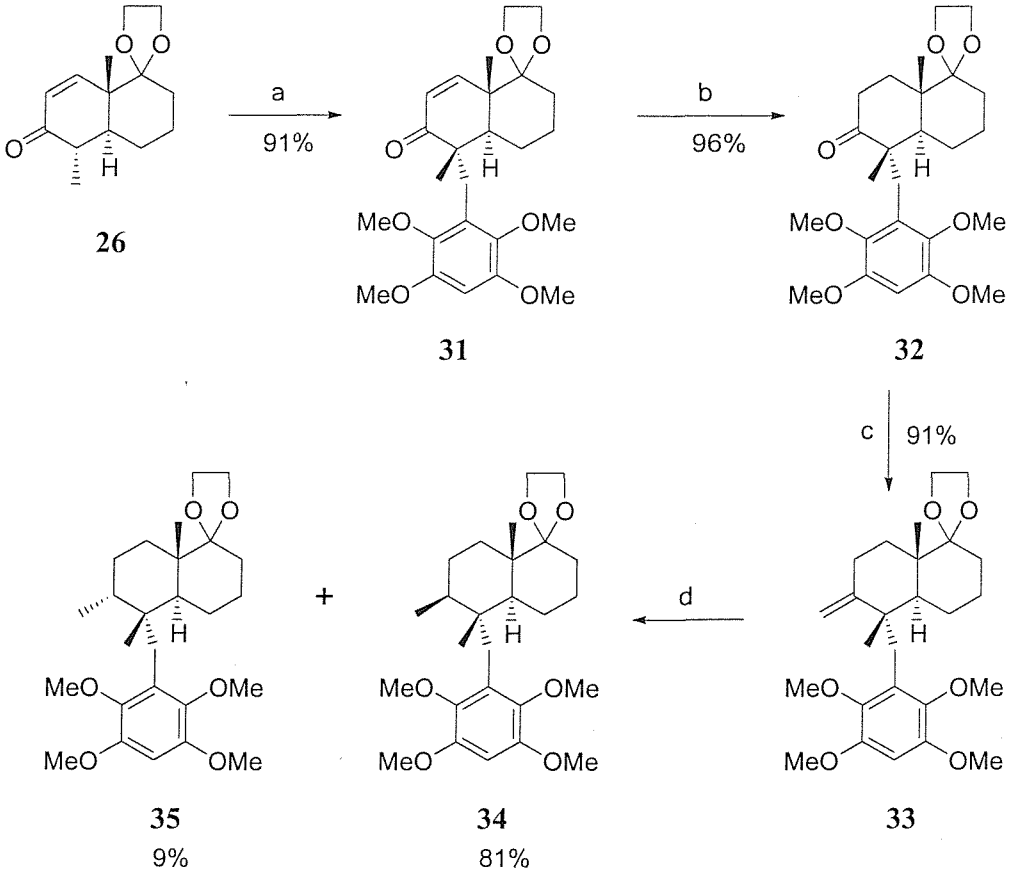
27 **28** **29**

30

a. 1.1 equiv of ^nBuLi, 5 equiv of DMF, THF, -78 to 20°C; **b.** 1 equiv of $LiAlH_4$, THF, 0°C; **c.** 1.2 equiv of CBr_4, 1.3 equiv of PPh_3, CH_2Cl_2, 0°C.

Scheme 8

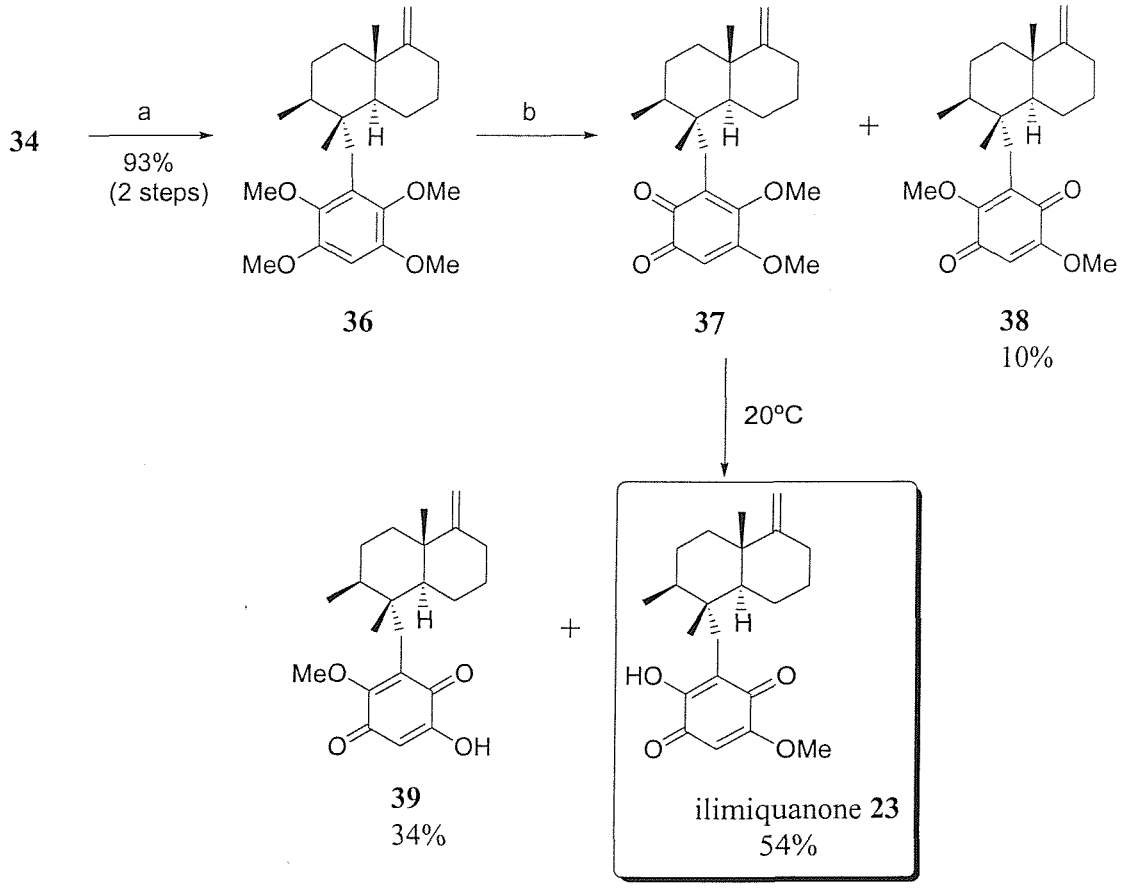
Union of **26** and **30** was effected via the lithium enolate of **26** and yielded **31** as a single diastereoisomer. Subsequent catalytic hydrogenation of **31**, followed by a Wittig olefination afforded the exo compound **33** in 87% overall yield. Further treatment of **33** with H_2 over Pd/C in Et_3N led to the formation of two diastereoisomers **34** and **35**, which were separated by column chromatography (9:1 ratio). This highly selective hydrogenation might be explained by chelation of the methoxy groups of the benzyl moiety on the palladium surface, directing the addition of hydrogen to the α face, favouring the β isomer **34** as the major product (Scheme 9).



a. 1.2 equiv of LiHMDS, **30** (1.2 equiv), THF, -78 to 50°C; **b.** H_2 (balloon), Pd/C 10%, EtOH, 20°C; **c.** 7 equiv of NaH, 9 equiv of Ph_3PCH_3I, DMSO, 80°C; **d.** H_2 (balloon), Pd/C 10%, Et_3N, 20°C.

Scheme 9

Hydrolysis of the cyclic acetal under acidic conditions afforded the corresponding ketone, which was subjected to Wittig olefination providing alkene **36** in 93% overall yield. Deprotection of the aryl methyl ether and formation of the quinone moiety was accomplished using ammonium cerium(IV) nitrate. Stirring at room temperature resulted in the demethylation of the more hindered methyl group, leading to the target molecule **23** (54%) along with its isomer **39** (34%) as shown in Scheme 10.



a. i: THF-1N HCl (4:1), 20°C; ii: 6.4 equiv of ^{n}BuLi, 7 equiv of Ph_3PCH_3Br, dioxane, 110°C; **b.** 2.5 equiv of CAN, CH_3CN-H_2O, -5 to 20°C.

Scheme 10

This total synthesis of (-)-ilimiquanone required 11 steps and proceeded in an overall 25% yield. The marked improvements were the coupling process using an equimolar amount of reagent under mild conditions in the enone **26** alkylation step, and the highly selective hydrogenation of the exo olefin. In addition, this synthesis offers a new route to the

preparation of analogues for evaluation of biological activities through enone **26** and quinone moiety **30**.

1.4: TOTAL SYNTHESIS OF ARENAROL.

1.4.1: ISOLATION OF ARENAROL.

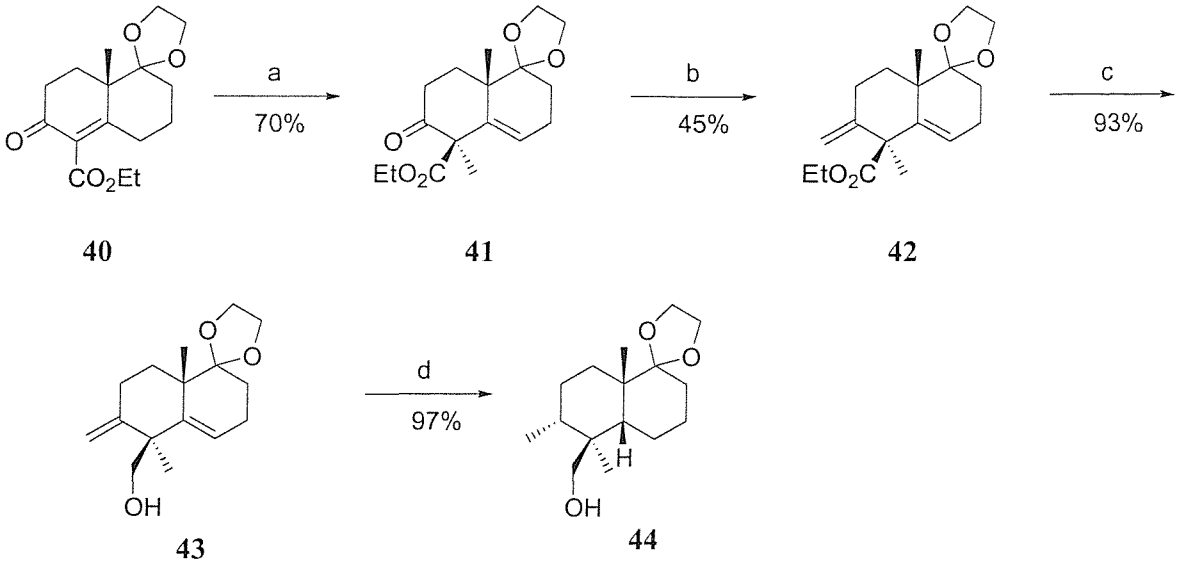
The hydroquinone arenarol **5** and its quinone arenarone **51**, were isolated from the Pacific sponge *Dysidae arenaria* by Schmitz *et al.* in 1984,[32] and found to be cytotoxic.[22] Arenarol was subsequently reported from as a constituent of *Fenestraspongia* species[33], and more recently from a *Disydea* species.[34] It is reported to show moderate cytotoxicity against the P388 murine leukaemia cell. (The ED_{50}'s-effective dose in the tissue culture causing 50% inhibition of cell growth- against P388 lymphocytic leukaemia being 17.5 and 1.7 μg/mL respectively).[35]

They share the same rearranged sesquiterpene skeleton with avarol, but differ in the stereochemistry of the decalin, as it is *cis* rather than *trans* fused. The exocyclic methylene group constitutes a further difference. The structure of arenarol, including its relative stereochemistry, was determined by X-ray diffraction analysis of the corresponding diacetate[32] and the absolute configuration was later established by extensive chemical correlation.

1.4.2: WIEMER'S TOTAL SYNTHESIS OF (±)-ARENAROL.

Wiemer *et al.* reported the first total synthesis of arenarol in 1995.[36] It was a considerable synthetic challenge as issues of stereocontrol are significant because of the *cis* fused decalin and the necessity for stereocontrol at two tertiary and two quaternary carbons.[37] The group had earlier shown that neopentyl iodides undergo efficient reduction when treated with ethylmagnesium bromide in Pd catalysed reactions.[38] They subsequently found that using

(dppf)-$NiCl_2$ leads to efficient coupling of neopentyl iodides with Grignard reagents, in the presence of $ZnCl_2$.dioxane.[39] These results prompted them to target arenarol using this methodology.



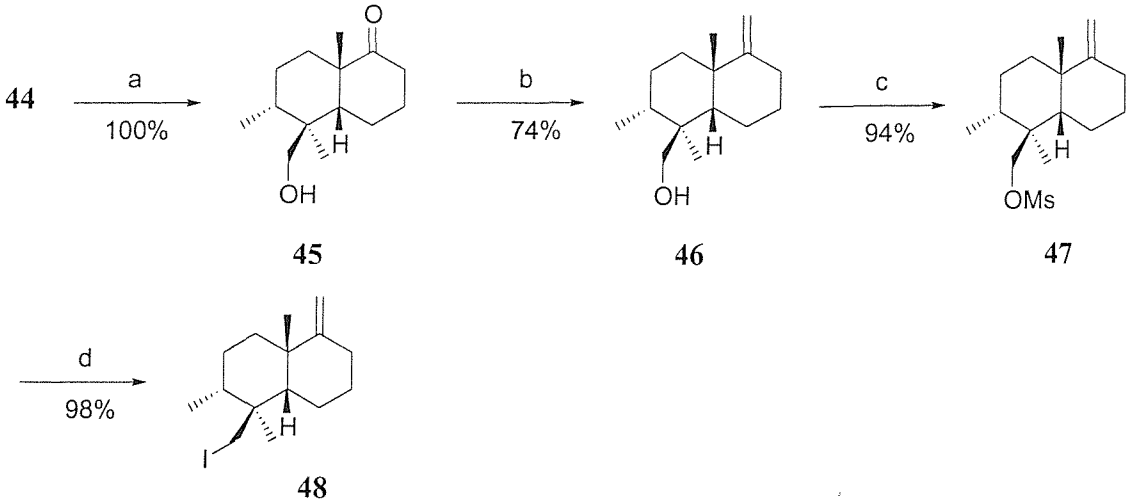
40 **41** **42**

43 **44**

a. KOtBu/MeI; **b**. $Zn(CH_2ZnBr)_2$.THF; **c**. $LiAlH_4$; **d**. H_2, 1000psi, $[Ir(cod)(Pcy_3)(py)]^+PF_6^-$, 6 days.

Scheme 11

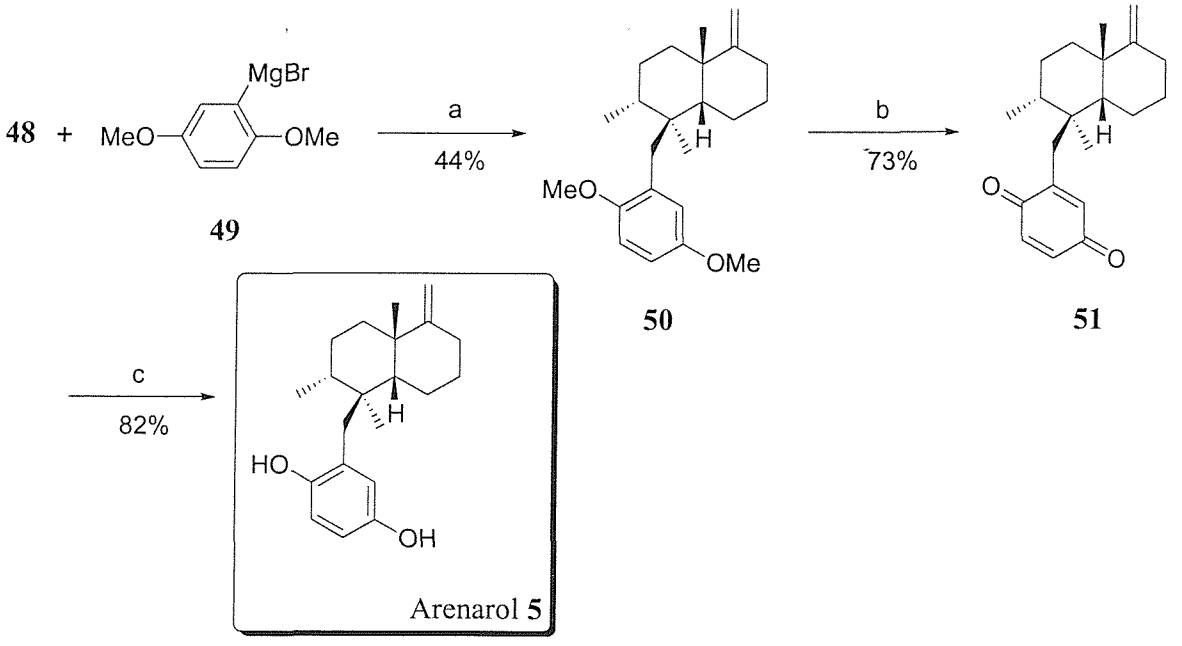
The synthesis started with the known decalin **40**, formed by reaction of 2-methyl-1,3-cyclohexanedione and Nazarov's reagent[40] (with subsequent protection of the carbonyl functionality). On treatment with MeI/KO^{t}Bu conditions, the ethyl ester **40** yielded olefin **41**, undergoing a parallel reaction to that previously reported by Pelletier *et al.*.[41] Nysted's reagent[42] in presence of $TiCl_4$ then afforded the exocyclic methylene compound **42** (35-57% yield). Several catalysts are known to participate in hydroxyl directed hydrogenations. In this case, an iridium catalyst developed by Crabtree[43] was used under harsh conditions to give **44** as a single diastereoisomer (Scheme 11).



a. H^+/H_2O; **b**. Nysted's reagent, $TiCl_4$; **c**. Et_3N, MsCl; **d**. DMPU/NaI, THF.

Scheme 12

Quantitative removal of the dioxolane group, under acidic conditions, led to ketone **45**. Reacting **45** with Nysted's reagent furnished the desired alkene **46**. The hydroxyl function in **46** was then converted to the corresponding iodide **48** via the mesylate **47** in good yield. The neopentyl iodide **48** was then obtained from the known decalin **40** in 7 steps (21-34% yield).



a. $(dppf)NiCl_2$, THF, 0°C; **b**. $(NH_4)_2Ce(NO_2)_6$; **c**. $Na_2S_2O_4$.

Scheme 13

The coupling of the two precursors **48** and **49** initially occurred with the formation of several isomeric by-products in variable amounts. This was due to acid/Lewis acid induced rearrangement of the desired product **50**. When the $ZnCl_2$.dioxane complex was omitted from the reaction mixture, to minimize the potential for Lewis acid catalysed rearrangement, and the coupling reaction was quenched with aqueous $NaHCO_3$, the coupling reaction proceeded less efficiently. However, it was easier to isolate the desired compound, and a yield of 45% was readily attained.

Arenarone **51** was obtained by treatment of **50** with CAN.[44] The reaction was conducted in presence of $NaHCO_3$ and CH_3CN to avoid the acid-catalysed rearrangement. A mild reduction of the quinone **51** with sodium sulfite afforded the desired compound (±)-arenarol **5**.

Thus, the first total synthesis of (±)-arenarol was completed through a short, efficient and stereocontrolled sequence.

1.4.3: KAWANO'S ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-ARENAROL.

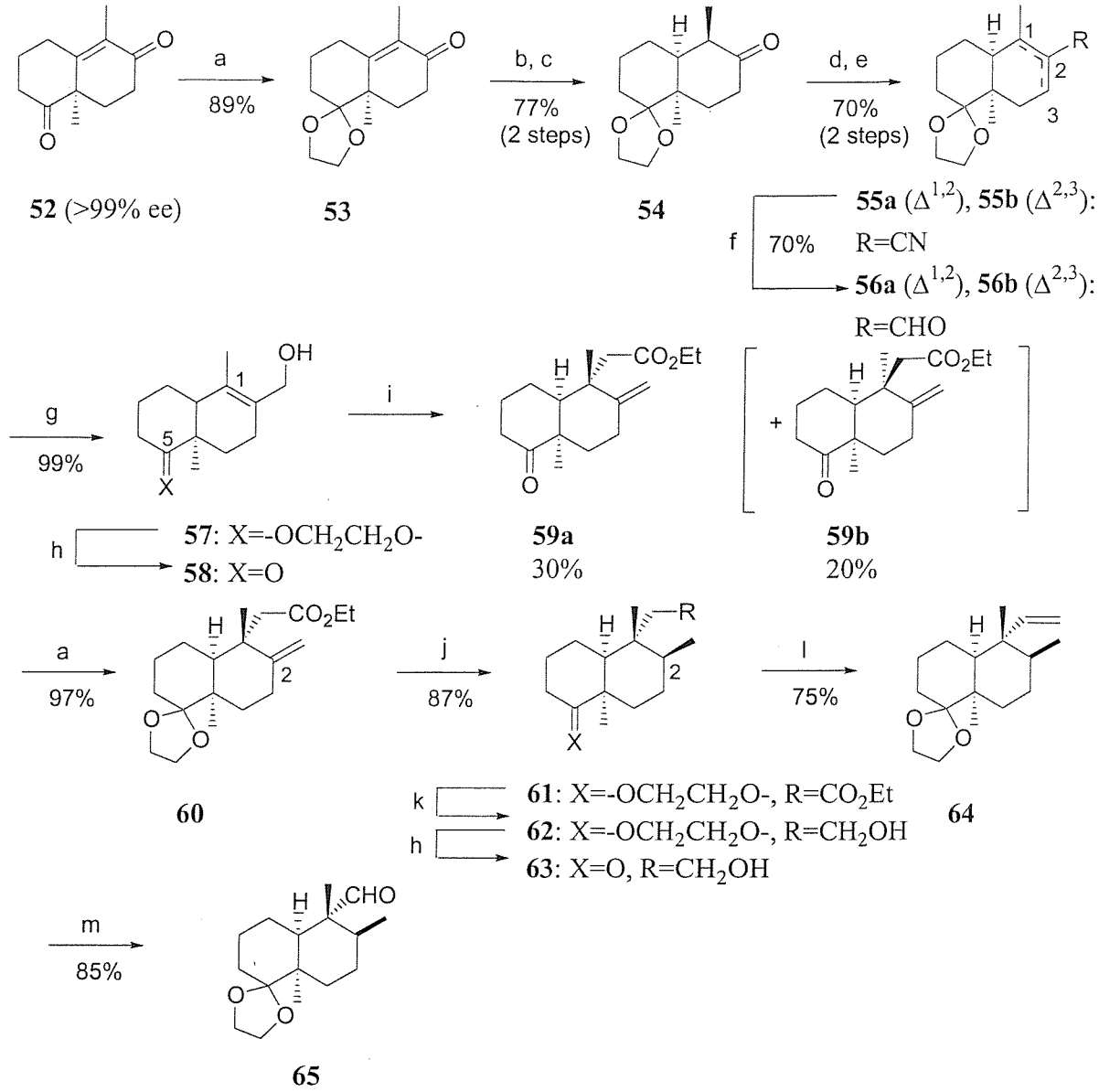
In 1997, Kawano *et al.* reported the first enantioselective total synthesis of (+)-arenarol **5**.[45] Their starting material, a Wieland-Miescher ketone derivative **52**, was prepared in an enantiomerically pure form (>99% ee), using a reported procedure.[30] Chemoselective protection of **52** followed by stereocontrolled hydrogenation of the acetal **53** exclusively afforded the desired *cis*-fused decalin derivative as a mixture of C-1 epimers. Although this mixture was difficult to separate, it was readily equilibrated to the thermodynamically more stable diastereoisomer **54**.

Nitriles **55a** and **55b** were obtained, as a mixture of the two possible regioisomers, on treatment of **54** with KCN in presence of acetic acid followed by dehydration induced by

thionyl chloride. The mixture was then reduced with DIBAL-H to afford the aldehydes **56a** and **56b** (20:1), which were separated by recrystallisation to afford the desired $\Delta^{1,2}$ aldehyde **56a** (70%). Further reduction to alcohol **57** with $NaBH_4$ followed by removal of the acetal moiety afforded hydroxy ketone **58**.

The crucial ortho ester Claisen rearrangement was conducted in *o*-dichlorobenzene at 180°C, in presence of hydroquinone and triethyl orthoacetate. It resulted in a mixture of two stereoisomers **59a** and **59b** (3:2) in 50% combined yield. When the acetal **57** was employed as the substrate, the stereochemical course of reaction was reversed; this difference presumably arises from conformational changes resulting from the change in hybridization at C-5.

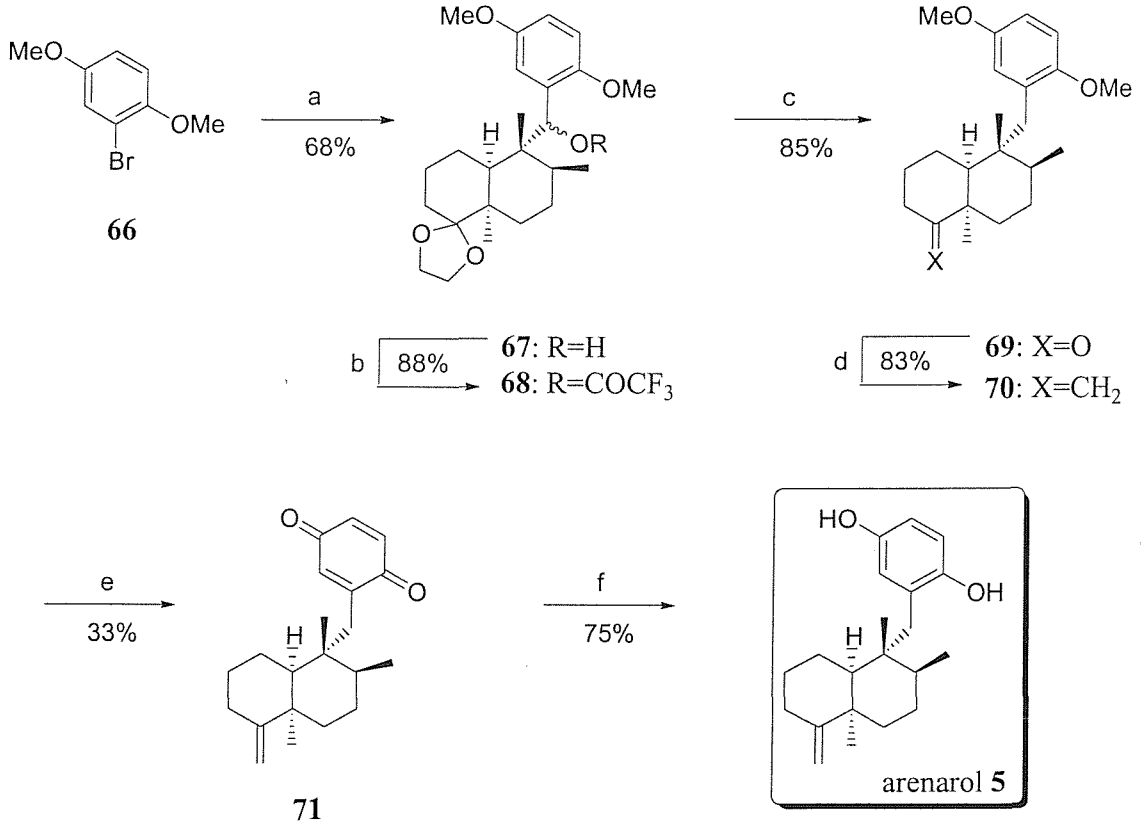
After separation, **59a** was protected as its acetal **60**, and the critical hydrogenation was achieved using the Crabtree catalyst, as in Wiemer's synthesis, to afford **61**, as a single diastereoisomer. When the hydrogenation was conducted using a conventional palladium-carbon catalyst, a 3:1 mixture of the stereoisomers was produced, favouring the undesired C-2 epimer. Deprotection of **62** to ketone **63**, methylenation to olefin **64** and ozonolysis to **65** completed the first stage of the total synthesis (Scheme 14).



a. ethylene glycol, *p*-TsOH, benzene, reflux; **b**. H_2 (10atm), 10% Pd/C, piperidine, rt; **c**. MeONa, MeOH, reflux; **d**. KCN, AcOH, EtOH, 15°C; **e**. $SOCl_2$, pyridine, CH_2Cl_2, 0°C, (**55a**:**55b**=20:1); **f**. DIBAL-H, toluene, -78°C; **g**. $NaBH_4$, THF-H_2O, 0°C; **h**. 4M HCl, MeOH, rt, 99% for **58**, 97% for **63**; **i**. $CH_3C(OEt)_3$, hydroquinone, *o*-dichlorobenzene, 180°C; **j**. H_2 (1atm), $[Ir(cod)(Pcy_3)py]PF_3$, CH_2Cl_2, rt; **k**. $LiAlH_4$, THF, 0°C, 98%; **l**. *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt, 30% H_2O_2, 0°C; **m**. O_3, CH_2Cl_2, -78°C then PPh_3, -78→0°C.

Scheme 14

The coupling reaction of the *cis*-fused decalin segment with the aryllithium, generated *in situ* from the commercially available aryl bromide **66** proceeded easily leading to a mixture of diastereoisomers **67** in 68% yield. Synthesis of ketone **69** was achieved in an overall 72% yield by initial formation of the trifluoroacetate **68** and subsequent hydrogenolysis. Methylenation of the carbonyl group was then accomplished using Oshima's procedure, a combination of dibromoethane, zinc powder and titanium tetrachloride[46,47], affording **70**. As (±)-**70** is an intermediate in Wiemer's synthesis, the two final steps were conducted using his procedure (Scheme 15).



a. *n*-BuLi, Et_2O, -78°C, **65** in Et_2O, -78°C; **b**. $(CF_3CO)_2O$, pyridine, 0°C; **c**. H_2 (5atm), 10% Pd/C, MeOH, rt; **d**. CH_2Br_2, Zn, $TiCl_4$, THF, rt; **e**. $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, rt; **f**. $Na_2S_2O_4$, THF-H_2O, rt.

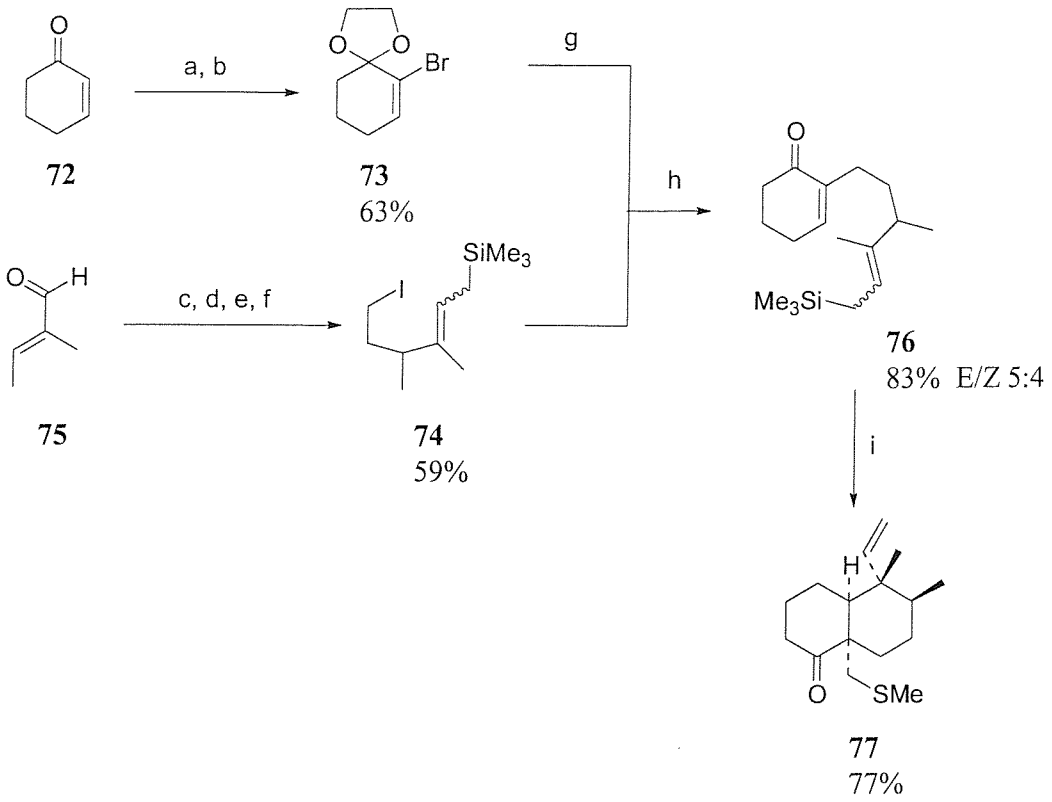
Scheme 15

Overall, Kawano *et al.* have developed a facile, if long, synthetic pathway to the optically active *cis* fused decalin fragment **65**. In addition, they produced the first enantioselective total synthesis of (+)-arenarol **5** using this key fragment.

1.4.4: PEARSON'S TOTAL SYNTHESIS OF (±)-ARENAROL.

Pearson *et al.* reported their total synthesis of (±)-arenarol **5** in 1998.[48] They decided to broadly follow the procedure of Tokoroyama to address the diastereoselective formation of the *cis*-decalin,[49] to which they added some modifications of their own. Thus cyclohexenone **72** was brominated in presence of Et_3N and the resulting enone protected as its cyclic acetal **73**. Lithium-halogen exchange led to a vinyllithium, which was quenched with iodide **74**. Treatment of the coupled product with aqueous acid afforded ketone **76**, as a mixture of isomers. A subsequent intramolecular Hosomi Sakurai cyclisation stereoselectively provided the cis decalin **77**.[49]

Alkyl halide **74** had been formed by treatment of tiglic aldehyde **75** with a Peterson Grignard reagent. The resulting allyl alcohol was subjected to a Claisen rearrangement and the subsequent aldehyde was reduced to the corresponding alcohol, which in turn was transformed into iodide **74** followed by the conversion of the alcohol to the corresponding iodide to yield **75**. The use of a one-pot iodination under the shown conditions proved more successful than the two steps procedure reported in the literature (mesylation then displacement with the iodide).[49] (Scheme 16)

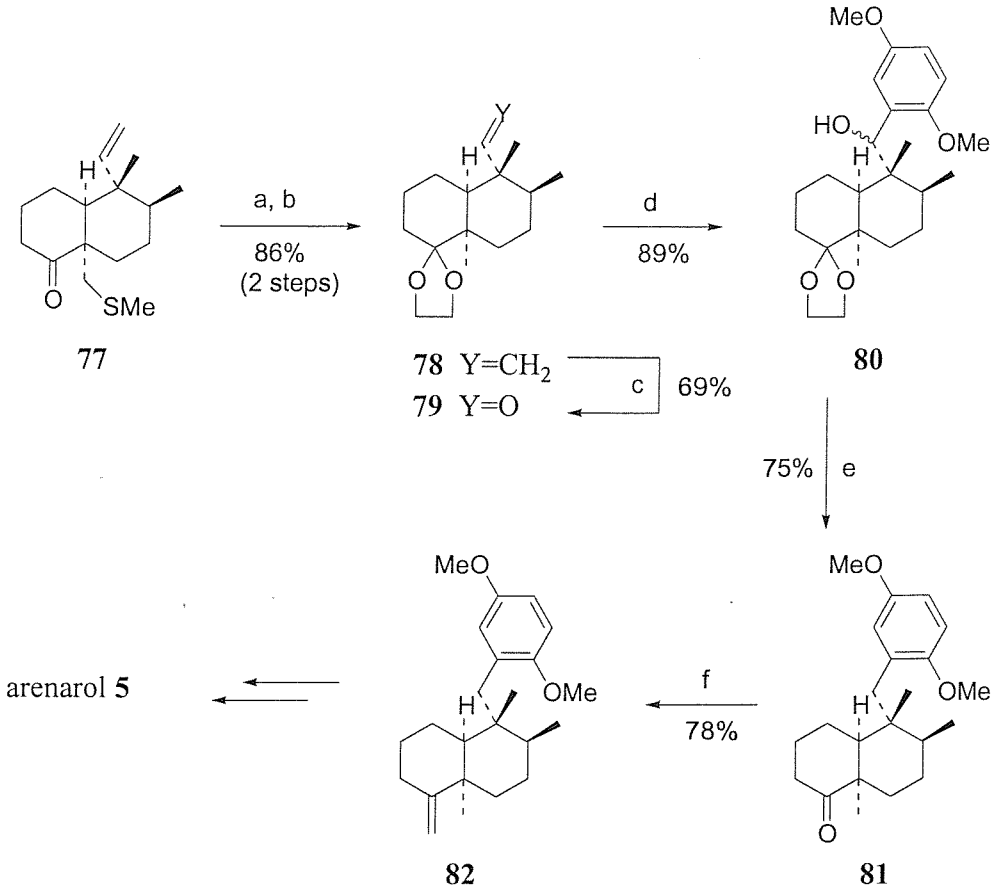


a. Br_2, Et_3N, $CHCl_3$, 0°C, 55 min; **b.** $HOCH_2CH_2OH$, CSA, PhH, 80°C, 14 h; **c.** Me_3SiCH_2MgCl, Et_2O, 0°C, 30 min; **d.** $Hg(OAc)_2$, $CH_2CHOCH_2CH_3$, 33°C, 48 h then PhMe, 110°C, 2 h; **e.** $NaBH_4$, EtOH, rt, 1 h; **f.** imidazole, Ph_3P, I_2, MeCN, rt, 3.5 h; **g.** ^{s}BuLi, THF-HMPA (~10:1), **75**, -78°C, 20 h; **h.** HCl (aq), THF, rt, 4.5h; **i.** $TiCl_4$, $ClCH_2SMe$, 0°C, 1 h.

Scheme 16

After initial studies and publication of Wiemer's total synthesis, Pearson *et al.* came to the conclusion that the coupling of the two fragments might be best performed *via* addition of a suitable aromatic nucleophile to an aldehyde, with a subsequent reduction of the benzylic alcohol. Thus, the *cis* decalin system **77** was transformed into the requisite aldehyde, coupled with **66** and the sulfide reduced with freshly prepared Raney nickel in presence of acetone to prevent over reduction of the ketone moiety.[50] Acetal protection afforded **78**, and ozonolysis of the terminal alkene followed by reduction of the ozonide provided aldehyde **79**. Treatment of **79** with ortholithiated-1,4-dimethoxybenzene next gave the benzylic

alcohol **80** in 89% yield, as an inseparable mixture of diastereoisomers. Standard hydrogenation in ethyl acetate afforded ketone **81**, the generation of acetic acid *in situ* presumably facilitating acetal hydrolysis. The final exocyclic alkene **82** was obtained on treatment with Nysted's reagent in presence of $TiCl_4$. Spectroscopic data for intermediate **82** were identical to that reported by Wiemer, and the two final steps of the synthesis were conducted using his procedure. (Scheme 17)



a. Raney Ni, THF, 67°C, 2 h; **b.** $HOCH_2CH_2OH$, CSA, PhH, 80°C, 14 h; **c.** O_3, DCM-MeOH (3:1), -78°C; **d.** 2,5-dimethylphenyllithium, TMEDA, THF, 0°C, 30 min; **e.** H_2 (1atm), $Pd(OH)_2/C$ cat., EtOAc, 72 h; **f.** $Zn(CH_2ZnBr)_2.THF$, $TiCl_4$, CH_2Cl_2, rt, 20 h.

Scheme 17

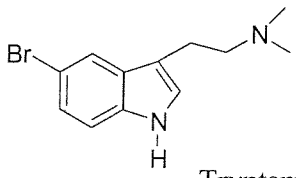
The problems associated with the introduction of the hindered aromatic portion were addressed and the result was an efficient protocol for the formal synthesis of (±)-arenarol.

1.5: TOTAL SYNTHESES OF AUREOL.

1.5.1: ISOLATION OF AUREOL.

Aureol **6** was isolated, along with 5-bromo-*N*,*N*-dimethyltryptamine, from the Caribbean sponge *Smenospongia aurea*, by Faulkner *et al* in 1979. It possesses an unusual sesquiterpene hydroquinone skeleton and was found to be an antimicrobial metabolite.[15]

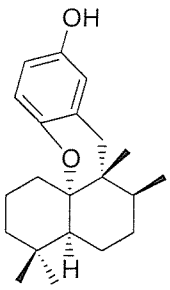
Its structure was determined by X-ray diffraction analysis of the corresponding brominated acetate prepared by treatment of aureol with bromine in CCl_4 followed by acetylation of the bromophenol.



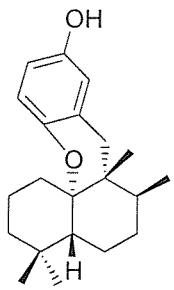
Tryptamine

1.5.2: BIOSYNTHESIS OF AUREOL.

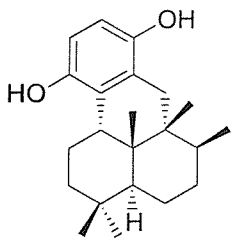
There is no reported total synthesis of Aureol so far, though a biomimetic synthesis has been accomplished via an acid catalysed rearrangement of sesquiterpenes such as avarol and arenarol.[51] Previously, the acid catalysed rearrangement had been used to determine the absolute stereochemistry of sesquiterpene quinones. It then seemed credible to use the same approach to chemically interrelate sesquiterpenes/hydroquinones. Although sesquiterpene hydroquinones reacted well to the acidic conditions of AcOH/HCl/MeOH (1:1:1), they returned better yields when treated with *p*-TsOH in benzene. Treatment of avarol **3** with *p*-TsOH in dry benzene at reflux for 30 min generated a three-component mixture (**6**, **88**, **89**), from which aureol was separated by semipreparative HPLC.



6

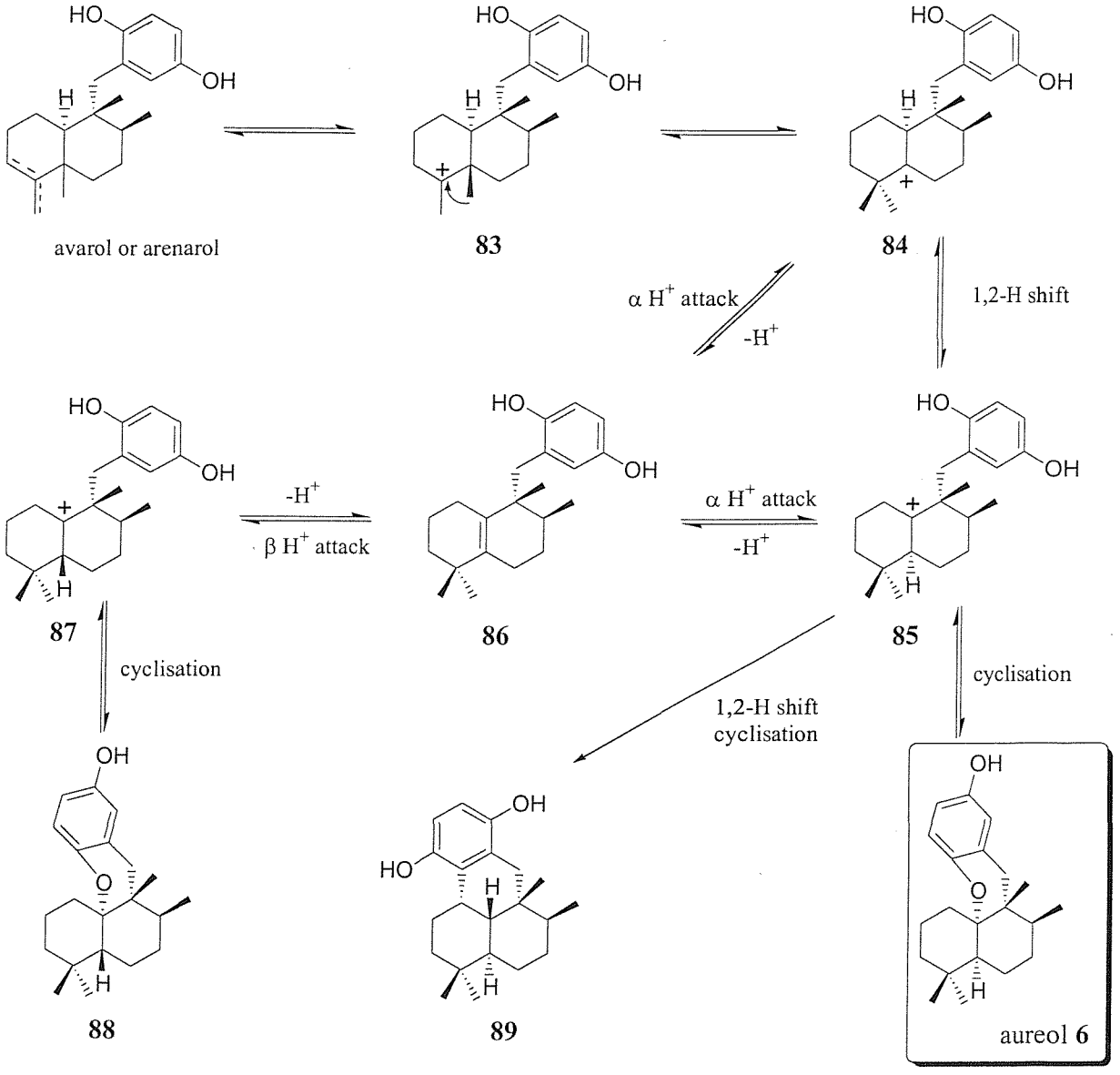


89



88

The mechanism of conversion of avarol/and arenarol/to aureol **6** is outlined in scheme 18. Formation of carbocation **83**, by protonation of the double bond, is followed by a 1,2-methyl shift to give intermediate **84**. **84** can then undergo a 1,2-H shift leading to **85** which on cyclisation produces aureol **6**, or by a subsequent 1,2-H shift cyclisation gives **89**. **84** and **85** can also undergo an α-H^+ attack, with loss of a proton, leading to **86**, which after an β-H^+ attack and loss of a proton cyclises to yield **88**.



Scheme 18

CHAPTER 2

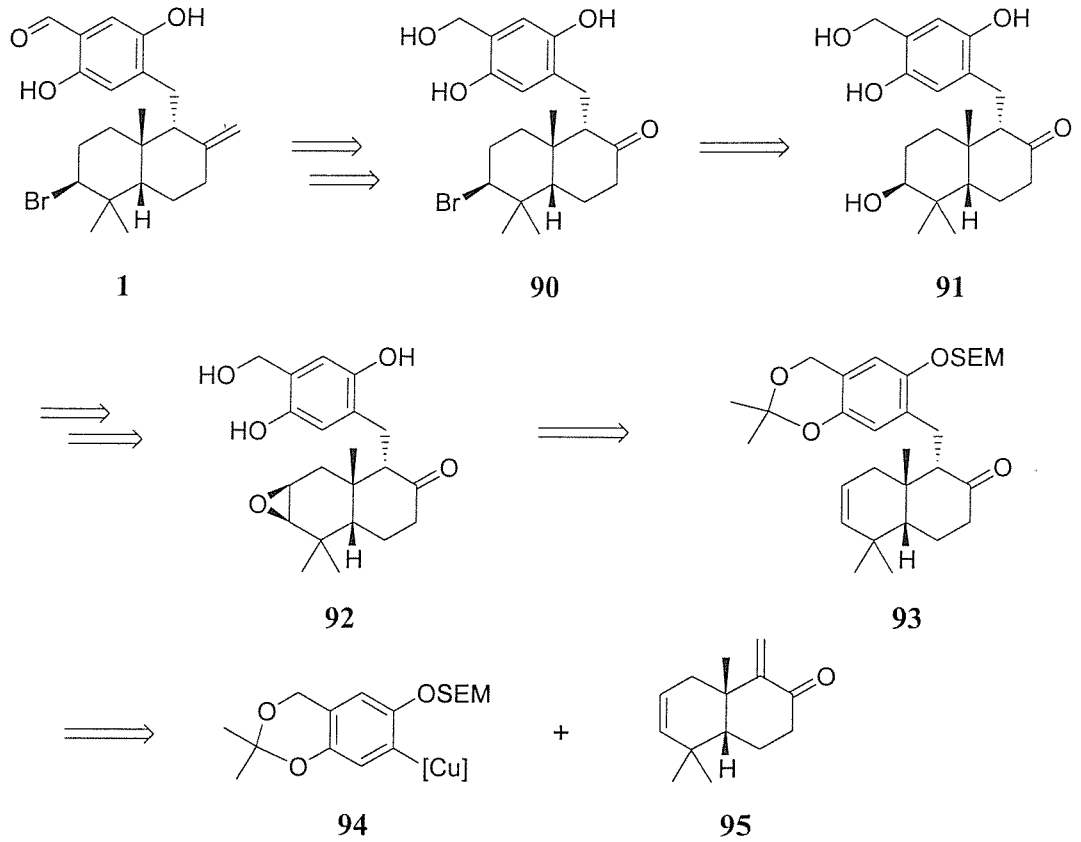
OUR FIRST APPROACH TO PEYSSONOL A

2.1: BACKGROUND

No total synthesis of peyssonol A **1** has been reported in the literature to date. The synthetic challenge presented by peyssonol A lies in the construction of the *cis* fused drimane skeleton and axial bromine. The *exo*-cyclic double bond and the substituted hydroquinone moiety also require special attention.

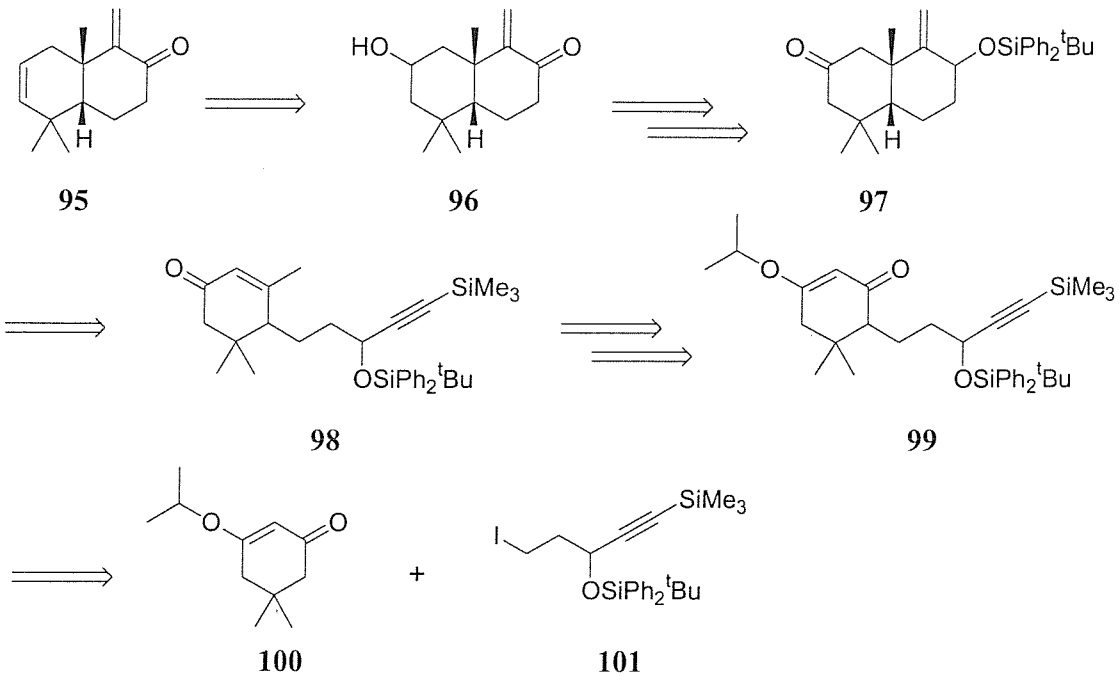
2.2: RETROSYNTHETIC ANALYSIS.

Our retrosynthetic analysis is depicted in the following schemes.



Scheme 19

We hoped to synthesise the decalin **97** from **98**, *via* a 6-*exo*-trig radical reaction. The radical precursor would in turn be synthesised *via* a coupling of the two fragments **100** and **101** (Scheme 20). Introduction of the aromatic portion was to be achieved *via* a Michael addition reaction of the copper derivative **94** to the decalin **95**. Further functional group manipulation and finally bromination, were expected to elaborate peyssonol A.



95 **96** **97**

98 **99**

100 **101**

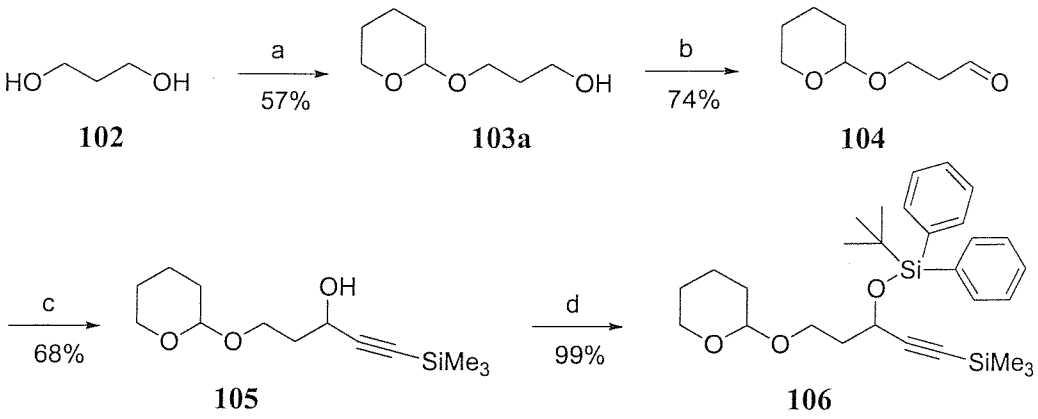
Scheme 20

2.3 SYNTHESIS OF THE RADICAL PRECURSOR 98

2.3.1 SYNTHESIS OF ALKYNYL IODIDE 101

1,3-Propandiol **102**, cheap and commercially available, was chosen as the starting point for a synthesis of the iodide **101**. Thus, treatment of **102** with DHP in DCM afforded the desired monoprotected alcohol **103a**, in a moderate yield of 57%, as formation of the diprotected alcohol also occurred.[52] A subsequent Swern oxidation afforded aldehyde **104** (74%).[53] Formation of the lithium anion of trimethylsilylacetylene with ^{n}BuLi, followed by

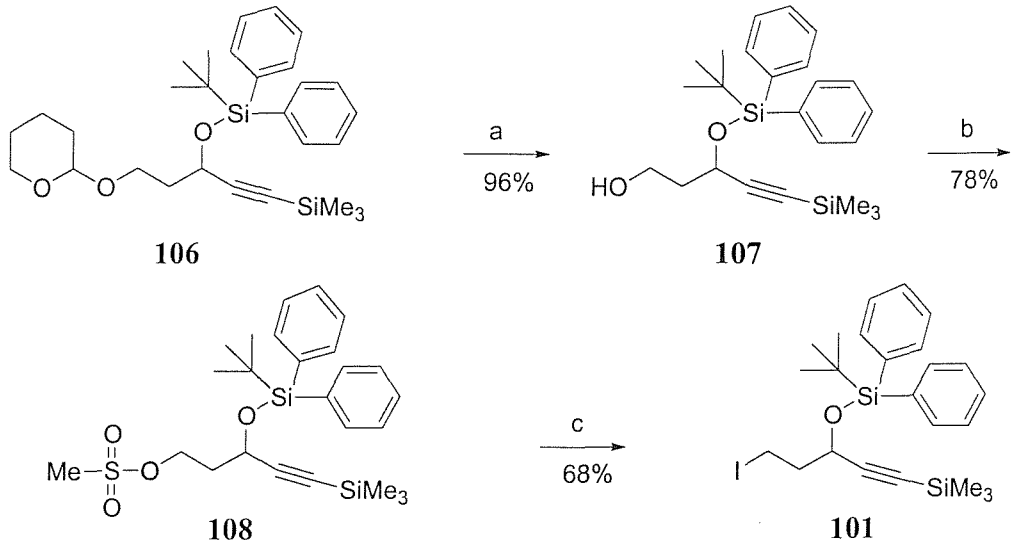
quenching with aldehyde **104** afforded **105** in 67% yield, therefore introducing the desired alkyne functionality.[54,55] This was followed by the quantitative (99%) protection of the hydroxyl function as its silyl ether **106**.[56] Among all the available protecting groups for the hydroxy group, TBDPS was chosen, as it is more stable towards acidic hydrolysis than TBDMS and is less prone to migration under basic conditions (Scheme 21).[57]



a. DHP, DCM, PPTS, rt; **b.** $(COCl)_2$, DMSO, Et_3N, DCM, -78°C; **c. i.** ^{n}BuLi and trimethylsilaneacetylene, THF, 0°C; **ii.** Aldehyde **104**, -45°C; **d.** $^{t}BuPh_2SiCl$, imidazole, DMF, 55°C.

Scheme 21

Cleavage of the THP group was carried out using $MgBr_2$ OEt_2 complex, leading to alcohol **107** in quantitative yield.[58,59] Treatment of **107** with mesyl chloride in DCM afforded the corresponding mesylate **108** (78%)[60] which was converted to the desired iodide **101** under conditions analogous to the Filkenstein reaction (Scheme 22).[61]

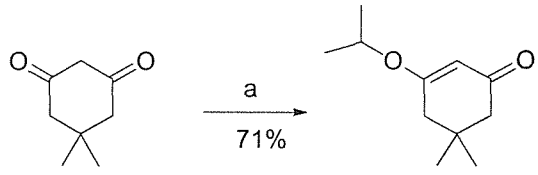


a. $MgBr_2.OEt_2$, Et_2O; **b.** MsCl, Et_3N, DCM, 0°C; **c.** NaI, acetone, reflux.

Scheme 22

2.3.2 SYNTHESIS OF FRAGMENT 100

Dimedone **109**, a cheap and readily available starting material was chosen to address the synthesis of **100**. This was straight forward as it simply involved a monoprotection of the ketone functionality, leading to **100** in good yield (Scheme 23).[62]



a. ^{i}PrOH, PTSA, toluene, reflux.

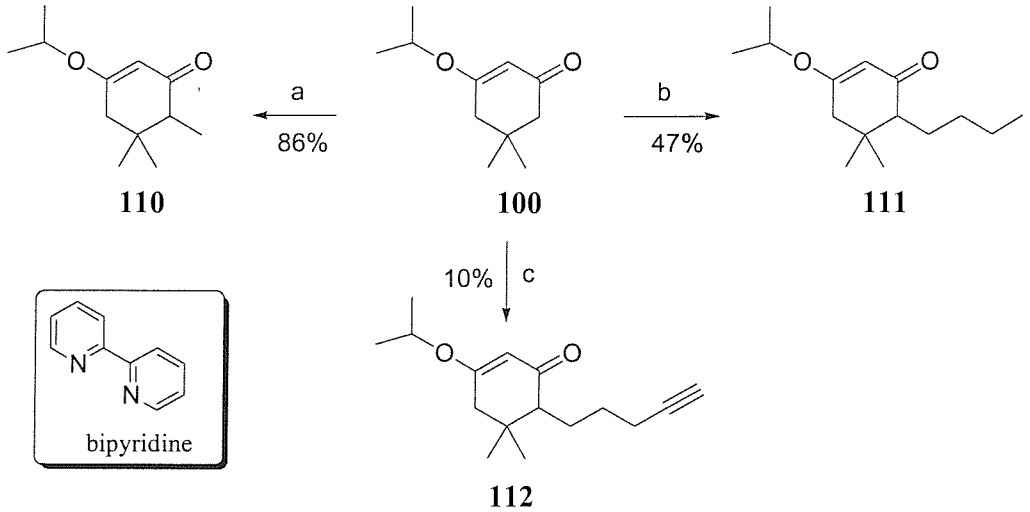
Scheme 23

With our two fragments in hand, we now had to investigate the coupling process.

2.4 COUPLING OF THE TWO FRAGMENTS

Initial studies were performed in order to establish the optimum conditions for the coupling process. Thus, treatment of **100** with LDA generated the enolate anion, which was quenched with MeI to afford the *C*-alkylated product **110**, in low yield (24%) with a significant amount of recovered starting material.[63] We found that addition of 2-bipyridine to the reaction mixture resulted in an increased yield (86%). This suggests that complexation between the lithium atom and bpy (two nitrogen lone pairs) leads to an enhancement in the nucleophilicity of the enolate anion.

We then decided to repeat the procedure, but this time using the more encumbered material BuI. Alkylation was markedly less efficient as **111** was only obtained in 47% yield. A further drop in yield was observed when introducing a pentynyl substituent. Indeed, using iodopentyne as quenching material produced **112** in 10% yield (Scheme 24). (Iodopentyne had been synthesised by a Filkenstein reaction on chloropentyne).



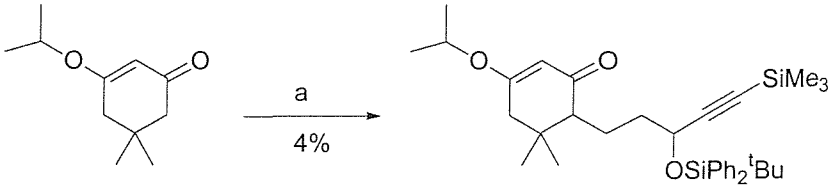
110 **100** **111**

112

a. i. LDA, bpy, THF, 0°C; **ii.** MeI, -78°C; **b. i.** LDA, bpy, THF, 0°C; **ii.** BuI, -78°C; **c. i.** LDA, bpy, THF, -78°C; **ii.** Iodopentyne.

Scheme 24

The real system was then investigated. Alas, the coupling reaction proceeded in a very disappointing yield, as only 4% of the desired product **99** was generated. Steric effects have surely played a major role (Scheme 25).

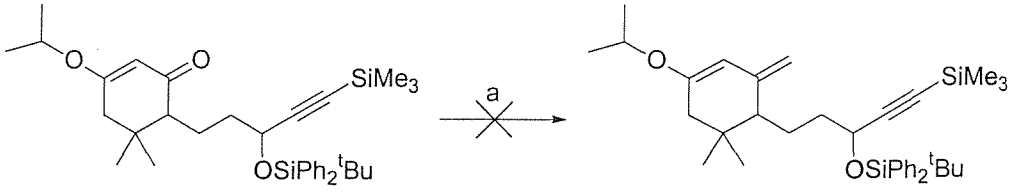


100 **99**

a. i. LDA, bpy, THF, -78°C, **ii.** compound **101**.

Scheme 25

Although the overall yield of the sequence to the radical precursor **99** was poor, we nonetheless decided to investigate the intramolecular radical cyclisation. To do so, our precursor **99** required another transformation, the olefination of the carbonyl functionality. Alas, when triphenylphosphinemethylene bromide was treated sequentially with ^{n}BuLi and **99,** none of the desired *exo* alkene **113** was produced. Indeed, starting material was recovered even when the reaction mixture was heated at reflux (Scheme 26).



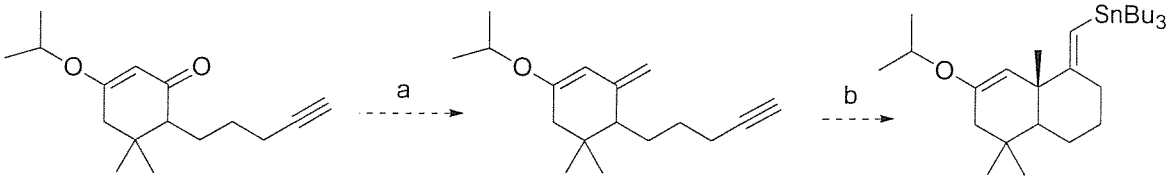
99 **113**

a. PPh_3CH_2Br, ^{n}BuLi, THF, 0°C or reflux.

Scheme 26

2.5 RADICAL CYCLISATION MODEL STUDY

Since we had alkyne **112** available from the model study, we decided to embark on another model study. Again, olefination of the carbonyl functionality was first needed to furnish the desired precursor **114**. Unfortunately, reacting enone **112** with the Wittig reagent failed to produce **114**, and consequently the radical cyclisation of **114** to the bicyclic product **115** could not be examined. This failure is presumably due to the reduced reactivity of vinylogous ester **112** towards nucleophiles; steric hindrance may have also played a role (Scheme 27).

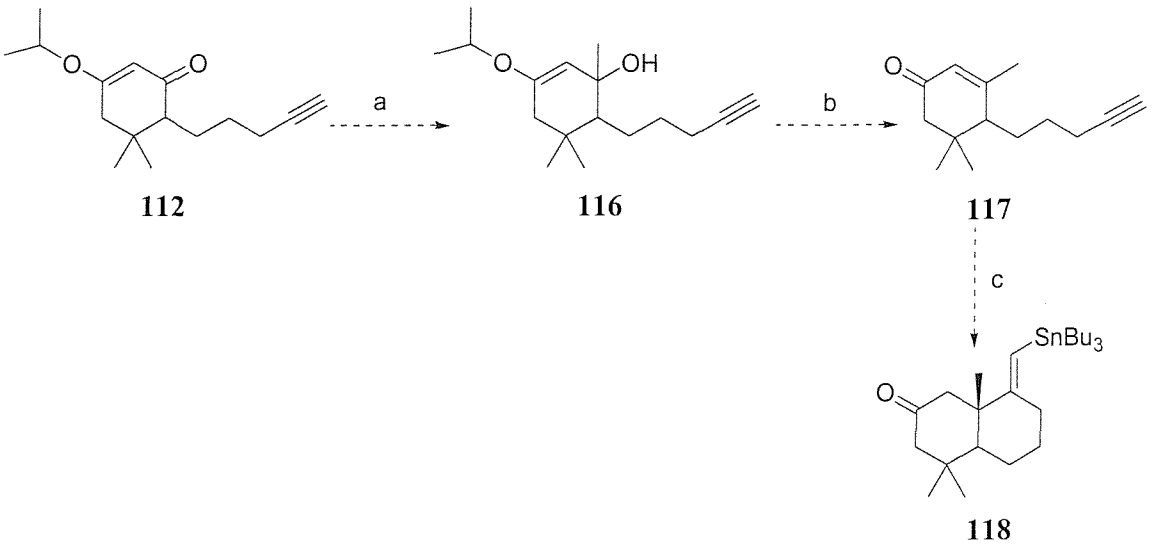


112 **114** **115**

a. PPh_3CH_2Br, THF, 0°C; **b.** AIBN, Bu_3SnH, toluene, reflux.

Scheme 27

Other methods to introduce the crucial *exo*-cyclic double bond were then examined. Treatment of **112** with methylmagnesium bromide should furnish the alcohol **116**, which can then be dehydrated under acidic conditions to yield the unsaturated ketone **117**. Reacting **117** with Bu_3SnH, in presence of AIBN, would then produce the bicyclic product **118**. Alas, alcohol **116** was obtained only in a trace amount and therefore the synthesis of **118** could not be realised (Scheme 28).



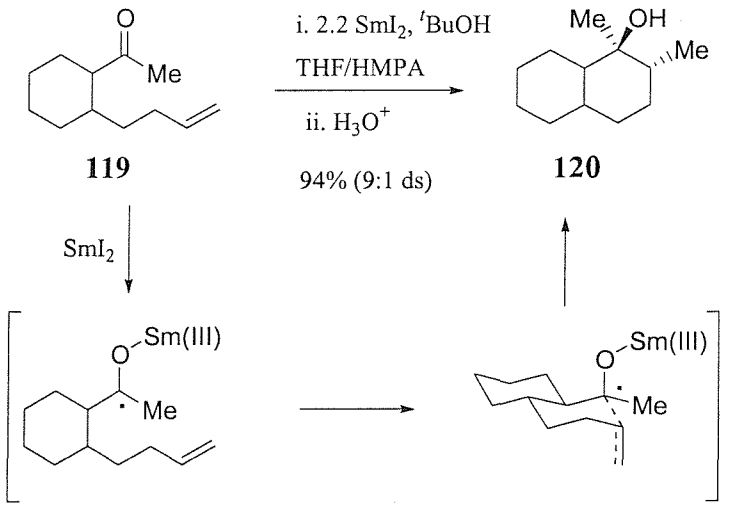
112 **116** **117** **118**

a. MeMgBr, THF, 0°C; **b.** H^+/H_2O, reflux; **c.** AIBN, Bu_3SnH, toluene.

Scheme 28

2.6 SAMARIUM(II) IODIDE RADICAL CYCLISATION

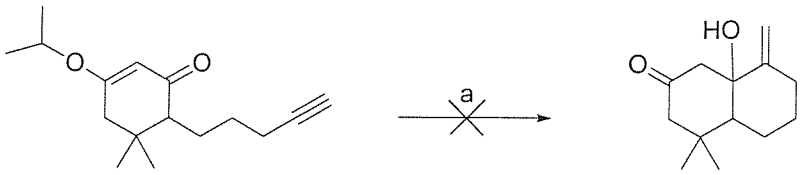
During the past two decades, SmI_2 has become a powerful and widely used reagent for a number of reactions.[64] Among its numerous applications, reductive intramolecular radical cyclisation was of interest to us. Molander, for example, reported the cyclisation of substituted unsaturated ketones leading to decalin ring systems,[65] as depicted in scheme 29, and Curran *et al.* has used this method successfully in the synthesis of natural products.[66]



119 **120**

Scheme 29

The difference between our system and those of Molander lies in the fact that we have a terminal alkyne group instead of an olefin, but we felt this should not be too significant as alkynes are typically more reactive than alkenes in radical cyclisation reactions. The combination of THF/HMPA was used as the solvent as it is thought to increase the reductive potential of SmI_2.[67]

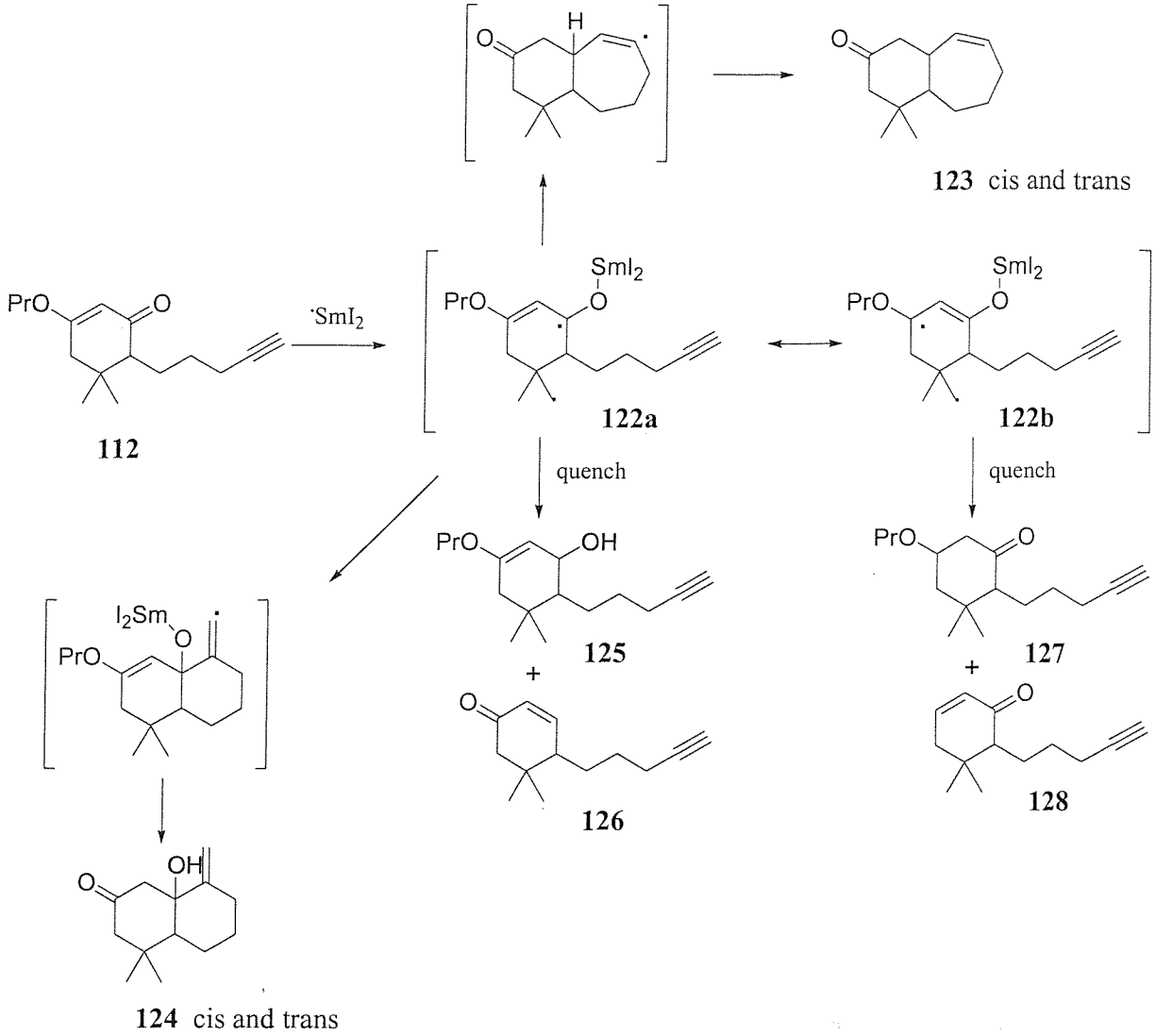


112 **121**

a. i. SmI_2, ^tBuOH, HMPA/THF, 0°C; **ii.** H_3O^+.

Scheme 30

Alas, on treatment of **112** with SmI_2, none of the desired compound **121** was observed. Rather, a complex mixture of inseparable polar compounds was obtained. Possible outcomes are depicted in scheme 31.



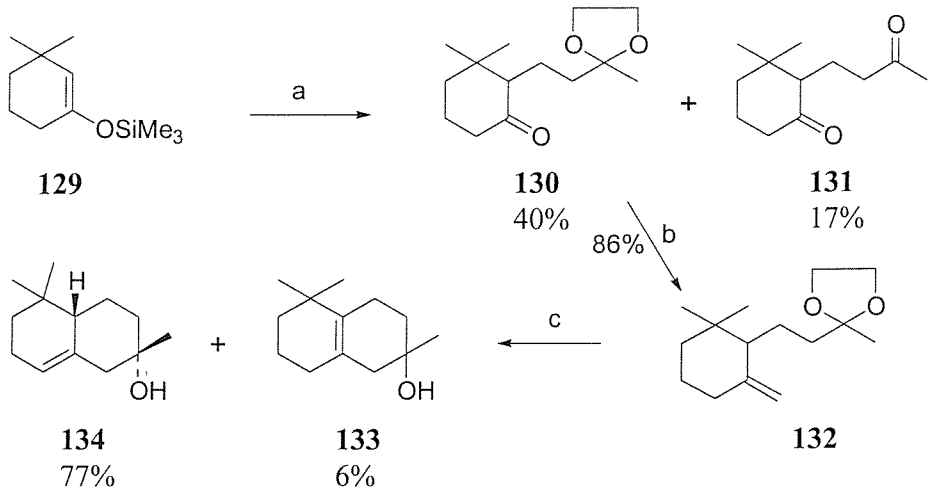
Scheme 31

There are several possible products. Two cyclisation modes, 6-*exo*-dig and 7-*endo*-dig doubtless compete and each can lead to either a *cis* or a *trans*-ring fusion. As the initial radical **122** is highly stabilised, it may also be quenched leading to **125**, **126**, **127** and/or **128**. Intermolecular couplings, reduction and elimination reactions could also occur leading to the observed complex product mixture.

2.7 AN ALTERNATIVE APPROACH TO DECALIN 95

2.7.1 ROBINSON ANNULATION

In 1976, Mukayiama *et al.* reported the Michael addition reaction of silyl enol ethers with different α,β-unsaturated ketones and acetals.[68] They found that such reactions conducted in the presence of $TiCl_4$ led to 1,5-dicarbonyl compounds instead of the aldol products. In addition, they noticed that for $TiCl_4$ sensitive substrates, the use of $TiCl_4$ and $Ti(O^i\text{-}Pr)_4$ in conjunction elevated yields to a useful level. Soon afterwards, the reliability of the process was demonstrated when Takazawa *et al.* achieved a short and high yielding synthesis of the potent perfume (±)-α-ambrinol **134** (Scheme 32).[69]



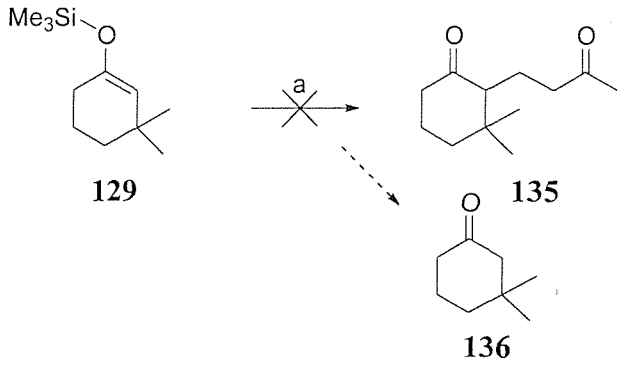
a. methyl vinyl ketone ethylene acetal, $TiCl_4$, $Ti(O^i\text{-}Pr)_4$, DCM, -78°C; **b.** $MePPh_3Br$, BuLi, THF, rt; **c.** 2N HCl, THF, H_2O.

Scheme 32

Thus, treating silyl enol ether **129** with methyl vinyl ketone ethylene acetal in the presence of $TiCl_4$ and $Ti(O^i\text{-}Pr)_4$ afforded **130** together with its deacetalized derivative **131**. **130** was then subjected to an *exo*-methylenation leading to **132** in 86% yield. A subsequent acidic treatment resulted in cyclisation to afford α-ambrinol **134** in 77% yield along with β-ambrinol **133** (6%).

The method appealed to us as it could provide a good method to synthesise a derivative of our decalin portion **95** very rapidly. Our aim was to use MVK itself to selectively produce

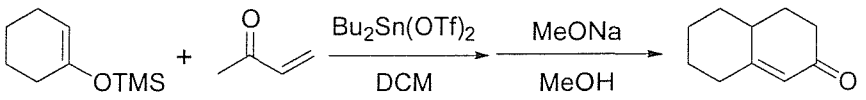
the second adduct **131**. Alas, treating silyl enol ether **129** did not furnish the desired Michael product **135**. Serious side reactions occurred and only the ketone **136** could be identified from the complex product mixture given (Scheme 33).



a. $TiCl_4/Ti(^iPrO)_4$, MVK, DCM, -78°C.

Scheme 33

The Robinson annulation has been a subject of study for a long time and in 1990 Sato *et al.* reported a new catalyst for the Mukayiama-type Michael reaction. They found that $Bu_2Sn(OTf)_2$ catalyses the addition reaction of silyl enol ethers with MVK and returns much better yields than with conventional Lewis acids.[70] Of even more importance was the one-pot synthesis of $\Delta^{1,9}$-octalone-2 **138** from the silyl enol ether **137** and MVK. The big advantage of this process is that no isomers of **138** were obtained, which is typical with the more conventional methods (Scheme 34).

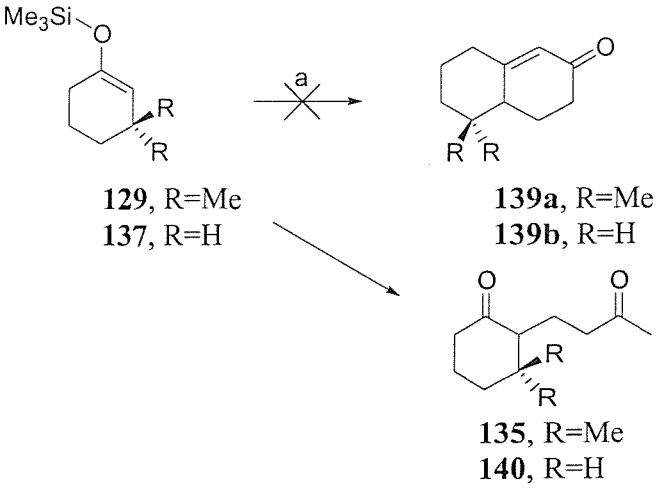


137 **MVK** **138**

Scheme 34

We accordingly decided to apply this procedure to our system. $Bu_2Sn(OTf)_2$ was first synthesised, following the procedure of Schmeisser.[71] However, reacting silyl enol ether

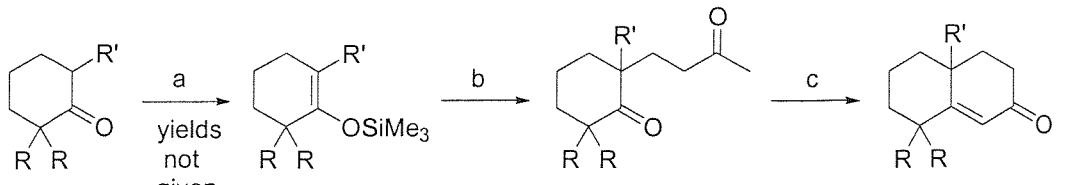
137 and MVK failed to afford the desired products **139b**. The Michael adduct **140** could nonetheless be separated from the complex mixture of products. Applying the reaction to the more hindered silyl enol ether **129** resulted in a failure, as none of the Michael adduct **135** or decalin **139a** was observed (Scheme 35).



a. i. $Bu_2Sn(OTf)_2$, MVK, DCM, -78°C, **ii.** MeOH, MeONa

Scheme 35

Interestingly, Duhamel *et al.* later reported a new annulation method in which Michael addition of trialkylsilyl enol ethers to MVK was catalysed with boron trifluoride in presence of an alcohol.[72] The major advantages of this process are its high regioselectivity and stereoselectivity, which are major drawbacks in the "classical" Robinson annulation. This procedure was also reported to be highly efficient with silyl enol ethers derived from sterically hindered ketones (Scheme 36).



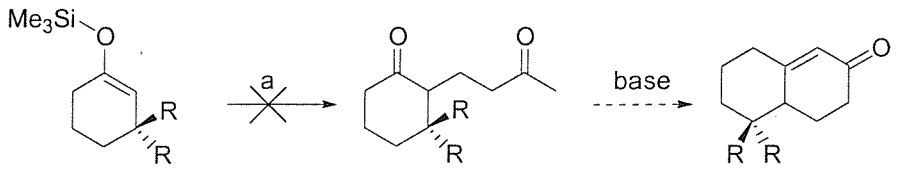
141a-b **142a-b** **143a** 100% **143b** 80% **144a** 86% **144b** 73%

a: R=Me, R'=H **b**:R=R'=Me

a. base, TMSCl; **b.** MVK, PhCH(OH)Me, BF_3 Et_2O; **c.** base.

Scheme 36

Encouraged by those results, we decided to apply this procedure to our system, as it is similarly encumbered by two methyl groups. Alas, under the same reaction conditions, silyl enol ethers **129** and **137** failed to furnish the desired Michael adducts **135** and **140**, and therefore none of the decalin **139a** or **139b** were obtained. Starting material and menthol were the only identified compounds in the product mixture (Scheme 37).



129, R=Me
137, R=H

135, R=Me
140, R=H

139a, R=Me
139b, R=H

a. MVK, menthol, CH_3NO_2, $BF_3.Et_2O$, -20°C.

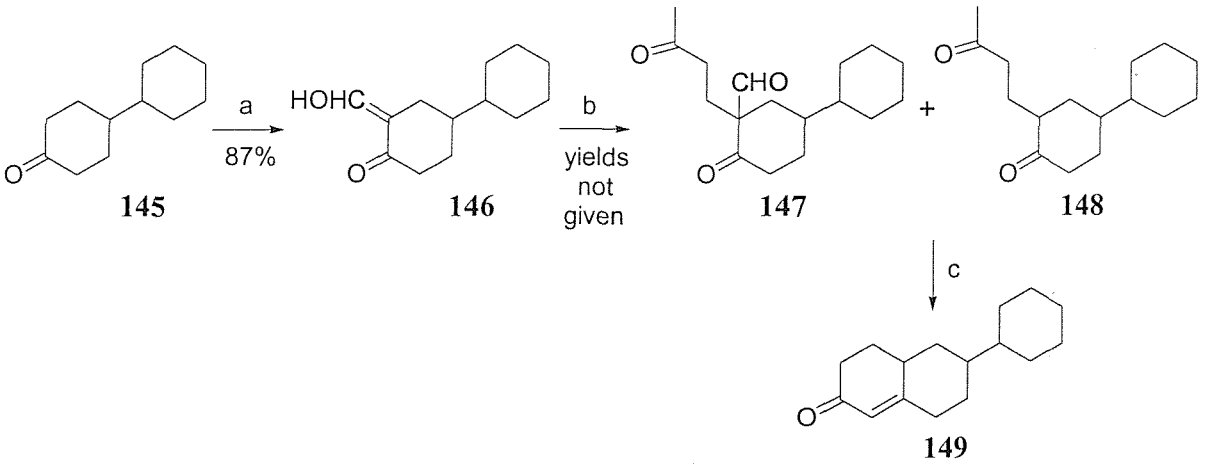
Scheme 37

Those consecutive failures led us to abandon the Robinson annulation methodology.

2.7.2 ROBINSON-MANNICH BASE METHIODIDE METHOD

In 1940's, Robinson and co-workers developed a method to synthesise decalin rings from cyclic ketones.[73] It consisted in treating the keto-enolate with a methiodide derived from a Mannich base such as 1-diethyl-aminobutan-3-one, the latter compound acting as a MVK

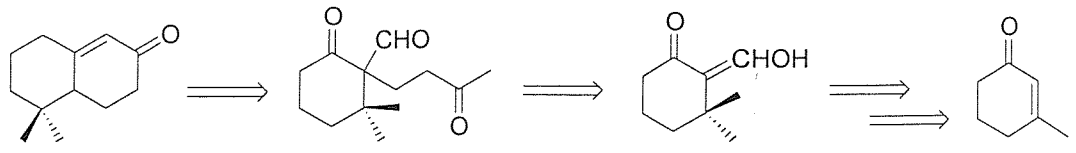
equivalent. Once coupled, an intramolecular cyclisation provided the decalin ring system. In the same decade, this method was successfully applied to the construction of numerous chrysene derivatives.[74,75] Poor yields in a program directed towards the synthesis of steroid analogs lacking ring C led Shunk *et al.* to investigate this process further.[76] A hydroxymethylene ketone derivative **146** was their new starting point for the synthesis (Scheme 38).



a. ethyl formate, NaOMe, benzene; **b.** 1-diethylaminobutan-3-one methiodide; **c.** acid or dilute methanolic alkali, r.t.

Scheme 38

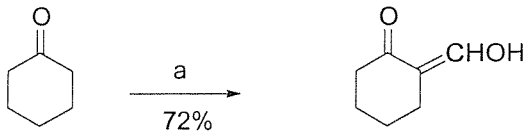
Thus, treating ketone **145** with an excess of ethyl formate and sodium methoxide led to the hydroxymethylene derivative **146** in 87% yield. This was followed by introduction of the γ-ketobutyl group in excellent yield by reaction with the Mannich base derived methiodide. The ratio of the two products **147** and **148** was shown to depend on the reaction conditions. The cyclisation was then performed in acidic medium at room temperature, to afford enone **149** in 60-65% overall yield. We therefore decided to base our new cyclisation route on those results, hoping to form the desired decalin system **139a**. Our retrosynthetic analysis is depicted in scheme 39.



139a **150** **151** **152**

Scheme 39

To validate the process, we first decided to investigate a model system. Thus, treating cyclohexanone **153** with ethyl formate and sodium methoxide furnished the desired hydroxymethylene derivative **154** in good yield (Scheme 40).[77]

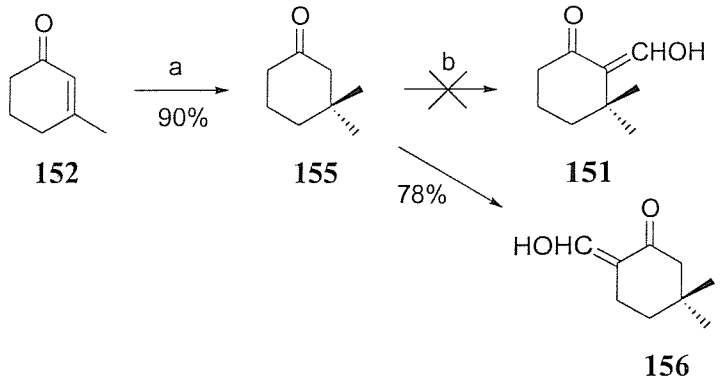


153 **154**

a. NaOMe, ethylformate, benzene, r.t.

Scheme 40

Reacting **152** with Me_2CuLi in presence of boron trifluoride etherate complex furnished **155** in good yield.[78] Alas, on treatment with sodium methoxide and ethylformate, **155** failed to furnish the desired product **151**, providing the regioisomer **156** instead.[77] Again, steric encumbrance from the methyl groups was the factor causing the reaction to follow the undesired course (Scheme 41).



152 **155** **151** **156**

a. Me_2CuLi, $BF_3.Et_2O$, THF, -78°C; **b.** NaOMe, ethylformate, benzene, r.t.

Scheme 41

2.8 CONCLUSIONS

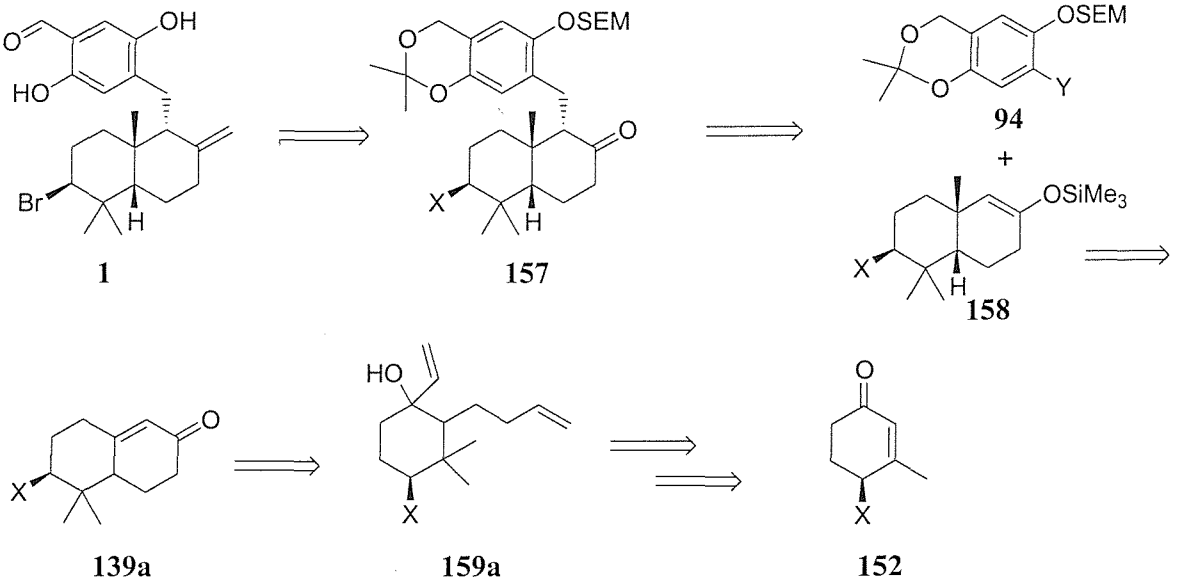
Although time consuming and lengthy in terms of the number of steps, the synthesis of iodide **101** proved to be undemanding. Problems occurred when we sought to couple this to the cyclohexane **100**. Model studies were conducted in an attempt to overcome our difficulties, but these showed little success in terms of elevating the yield. Further studies were carried out, but their failure led us to abandon the route. SmI_2 seemed to provide us with a good alternative but in the event our substrate did not prove to be suitable. Final attempts to employ the Robinson annulation and the related Robinson-Manich methiodide method, showed little promise. In each case, failure can be attributed, in part, to steric encubrance induced by the two methyl substituents present in the cyclohexane moiety.

CHAPTER 3:

OUR SECOND APPROACH TO PEYSSONOL A

3.1 RETROSYNTHETIC ANALYSIS

At this juncture, we decided to plan a new approach to peyssonol A. Our retrosynthetic analysis features a Ring Closure Metathesis using Grubbs' catalyst as a key step, *via* **159a** to **139a**. We expected to obtain *cis* stereochemistry at the ring junction through a subsequent Michael addition reaction. Then introduction of the aromatic moiety would be accomplished via methyleneation of silyl enol ether **158** and conjugate addition of an organo cuprate **94** (Y=Cu). Subsequent functional group manipulations would then lead to our target molecule **1** (Scheme 42).

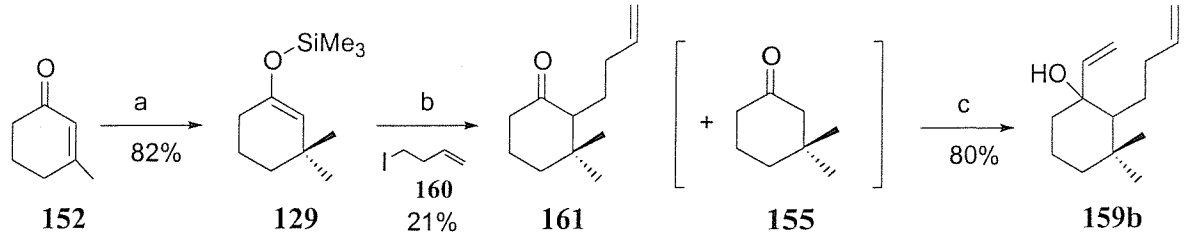


Scheme 42

3.2 STUDIES TOWARDS THE RING CLOSING METATHESIS PRECURSOR

Our model study started with 3-methyl-2-cyclohexen-1-one **152** (X=H). Thus, methylation with Me_2CuLi (formed *in situ* by reaction of methyllithium with copper iodide) followed by

trapping of the enolate as its silyl enol ether afforded **129** in good yield.[78,79] Transmetallation to the lithium enolate with methyllithium and addition of iodobutene **160** (synthesised by a Filkenstein reaction on bromobutene) led to homolallylation in poor yield (21%), cyclohexanone **155** accounting for much of the mass balance of the reaction.[80] Its formation indicates that the enolate abstracts a proton from the reaction medium, presumably via dehydroiodination of **160**. The low yield for homoallylation may also be due to severe steric encumbrance at the reacting enolate centre. This did not unduly affect the subsequent addition of vinylmagnesium bromide to enone **161**, which gave diene **159b** in 80% yield, as a single isomer with unresolved stereochemistry (Scheme 43).[81]



a. Me_2CuLi, HMPA, Et_3N, TMSCl, ether; **b. i.** MeLi, HMPA, THF, -10°C, **ii.** iodide **160**; **c.** vinylmagnesium bromide, THF, r.t.

Scheme 43

3.3 RING CLOSURE METATHESIS

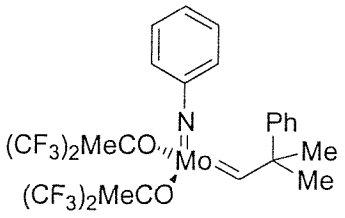
3.3.1 BACKGROUND

Olefin metathesis involves a carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexe. In the last few years, the development of new selective and stable catalysts has brought the reaction to prominance in main-stream organic synthesis. Indeed, it has become a very efficient tool for constructing a wide range of carbon-to-carbon bonds. As a consequence, the number of application has considerably increased.[82] The synthesis of small, medium and large size

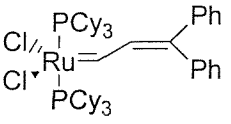
rings via RCM has been of intensively studied, and it has been found that many of the newer Ru and Mo based metathesis catalysts are tolerant of many functional groups.[82]

3.3.2 WELL-DEFINED CATALYST SYSTEMS

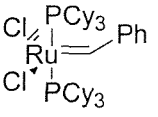
There are a vast number of catalyst systems suitable for initiating olefin metathesis. Titanium and tungsten catalysts were developed first, but were soon left behind with the expansion of well-defined molybdenum complex **162** and ruthenium systems **163** and **164**. The latter are now widely used as they are highly active, easy to handle and use and do not require Lewis acidic co-catalysts or promoters (Scheme 44).[82]



162



163



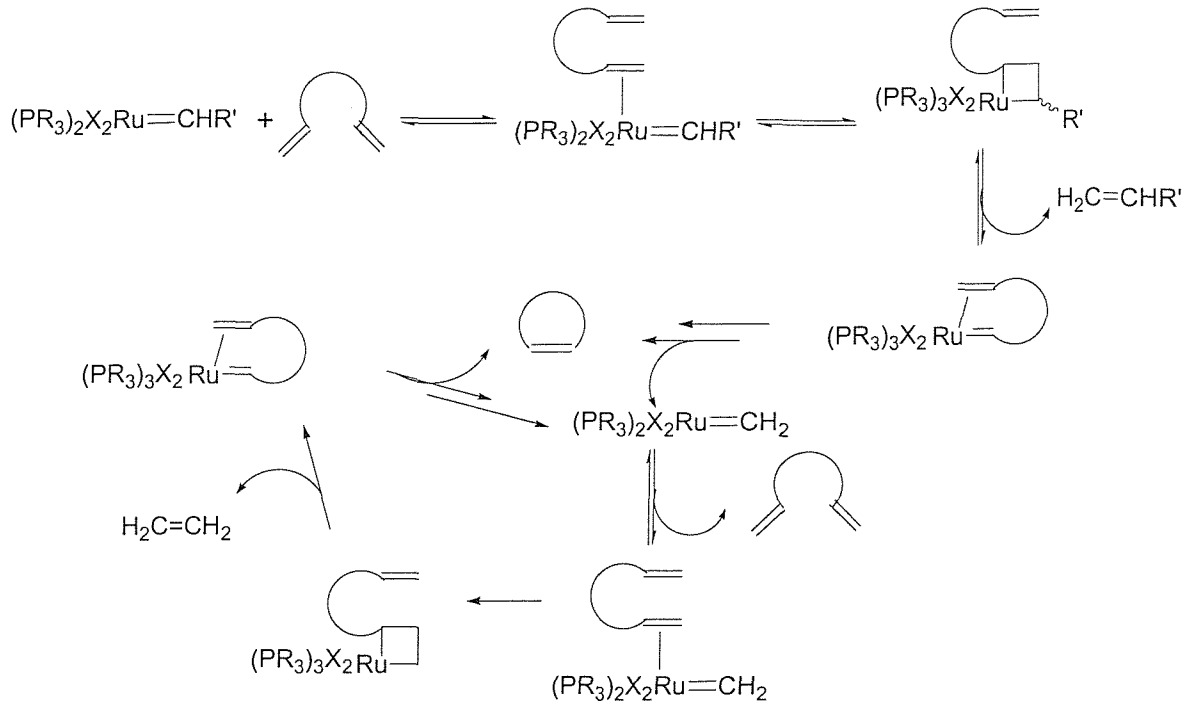
164

Scheme 44

162 was developed by Shrock and co-workers, while ruthenium systems **163** and **164** were by Grubbs and co-workers. More recently, Grubbs has developed a further ruthenium-based catalyst, known as Grubbs' 2nd generation catalyst, which is more stable to air and moisture and is more reactive than **163** and **164**. The availability and ease of use of these Ru-based complexes has made them the best choice of catalyst for all but the most difficult substrates.

3.3.3 MECHANISM OF RING CLOSURE METATHESIS

It has been established that the course of such reactions proceed via a series of metallacyclobutane and carbene complexes.[83] Catalyst composition and alkene substitutions are the main factors affecting the relative stability of metallocarbenes and metallacyclobutanes, yet, the mechanism of reaction seems to be similar for all catalysts (Scheme 45).



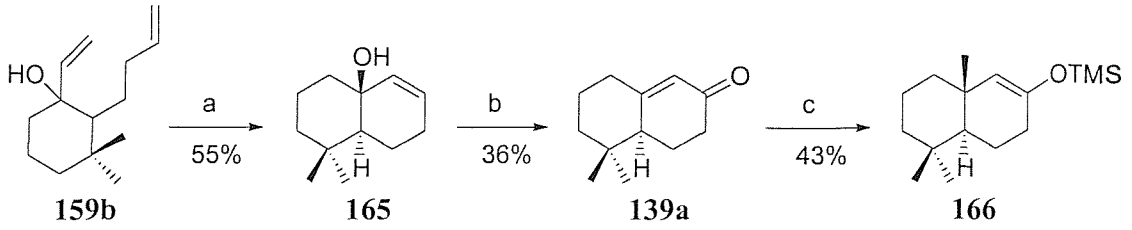
Scheme 45

Thus, the alkene binds to the ruthenium catalyst, forming the 18-electron olefin complex. This is rapidly followed by metathesis, releasing the desired cyclic product. Formation of a cycloalkene is frequently observed as the outcome of the reaction is determined by thermodynamic rather than kinetic factors. In addition, it has been found that DCM is the best choice of solvent, as ring-closure is approximately three times quicker than in benzene. Catalyst decomposition is generally slow but can be an issue for slow transformations requiring long reaction times.

3.3.4 SYNTHESIS OF SILYL ENOL ETHER 166

Thus, treatment of diene **159b** with Grubbs catalyst in refluxing DCM led to decalin **165** in moderate yield (55%).[82] The next step of the sequence involved an allylic oxidation and was performed using PCC on alumina.[84] The two proved to be low yielding (36%). Introduction of the final methyl group was then achieved by addition of dimethylcopper lithium to **139a**

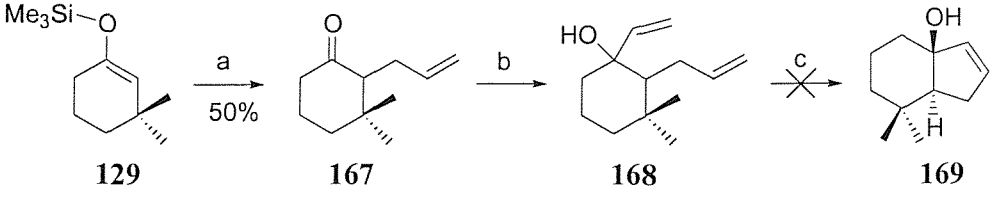
and trapping of the resulting enolate with TMSCl to give the corresponding silyl enol ether **166** in 43% yield (Scheme 46).[79]



a. Grubbs cat. (0.5%mol), DCM, reflux; **b.** PCC/alumina, DCM, rt; **c.** Me_2CuLi, HMPA, TMSCl, Et_3N, ether.

Scheme 46

We now had our key decalin portion **166** in hand. Its synthesis presented many problems, with a number of steps being low yielding. In particular, the homoallylation step at the start of the sequence, **129** to **161**, and the cost of the reagents involved (4-bromobut-1-ene is very expensive) meant that scale up would be prohibitively expensive. As a consequence, we initiated a model study of the alkylation reaction with the aim of introducing a propenyl group rather than a butenyl side chain (Scheme 47).

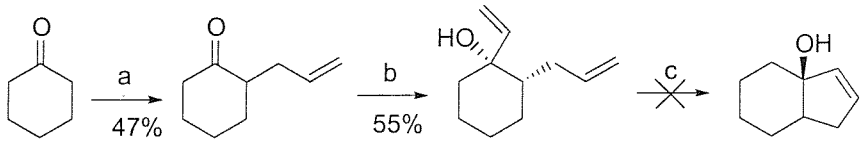


a. MeLi, HMPA, THF, allyl bromide; **b.** vinylmagnesium bromide, THF, rt; **c.** Grubbs cat., DCM, reflux.

Scheme 47

Treatment of **129** with MeLi and then allyl bromide afforded **167** in 50% yield.[80] A Grignard reaction with vinylmagnesium bromide furnished **168**, as an inseparable mixture with the starting ketone. Formation of **169** was not observed under RCM conditions,[82] presumably due to ring strain. To check that this was indeed the case, the same procedure

was applied to diene **171**. Once again, none of the desired bicycle **172** was observed (Scheme 48).[82]



153 **170** **171** **172**

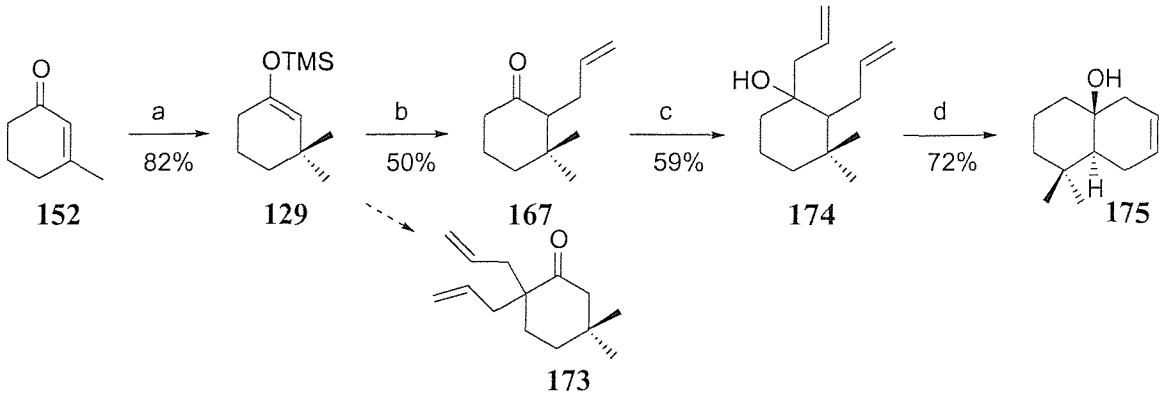
a. LDA, allyl bromide, THF; **b.** vinylmagnesium bromide, THF, rt; **c.** Grubbs cat., DCM, reflux.

Scheme 48

Although those model studies were blessed with only limited success, they prompted us to consider another approach to the synthesis of the target molecule.

3.4 SECOND SYNTHESIS OF THE SILYL ENOL ETHER 166

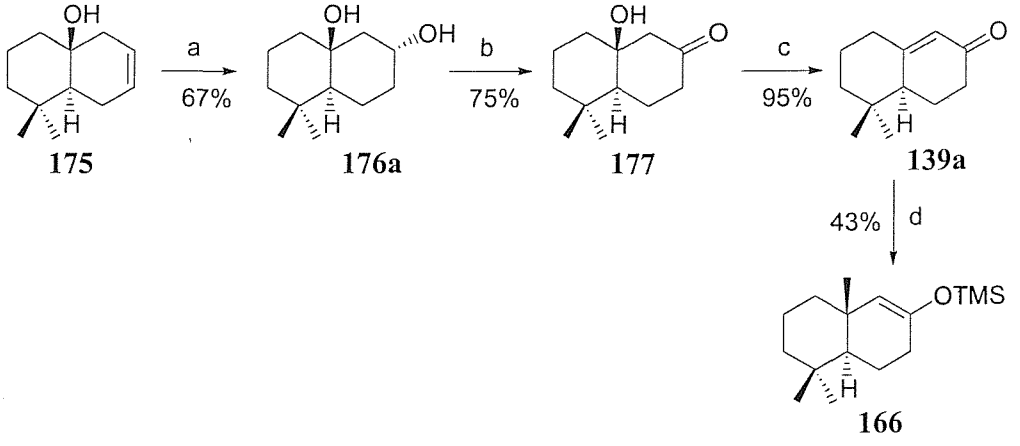
We started the sequence with the same material, 3-methyl-2-cyclohexenone **152**. Thus, methylation was accomplished using the same reaction conditions as before to give silyl enol ether **129** in good yield (80-90%). Allylation on a large scale again led to enone **167** in 50% yield.[80] Two minor component of the reaction were also noted, cyclohexanone **155** and the diallylated ketone **173**. Addition of allylmagnesium bromide to enone **167** next gave diene **174** with the requisite number of carbon atoms for 6-membered ring by ring closure metathesis. The RCM was carried out in refluxing DCM and pleasingly led to decalin **175** in 72% yield (Scheme 49).[82]



a. Me_2CuLi, HMPA, TMSCl, Et_3N, ether; **b.** i. MeLi, HMPA, THF, -10°C, ii. allyl bromide, r.t; **c.** allylmagnesium bromide, THF, 0°C; **d.** Grubbs catalyst (0.5% mol), DCM, reflux.

Scheme 49

Clearly, allylic oxidation was not possible in this case so our route to the desired unsaturated ketone **139a** had to be modified. The alternative plan we followed is outlined in the following scheme (Scheme 50).



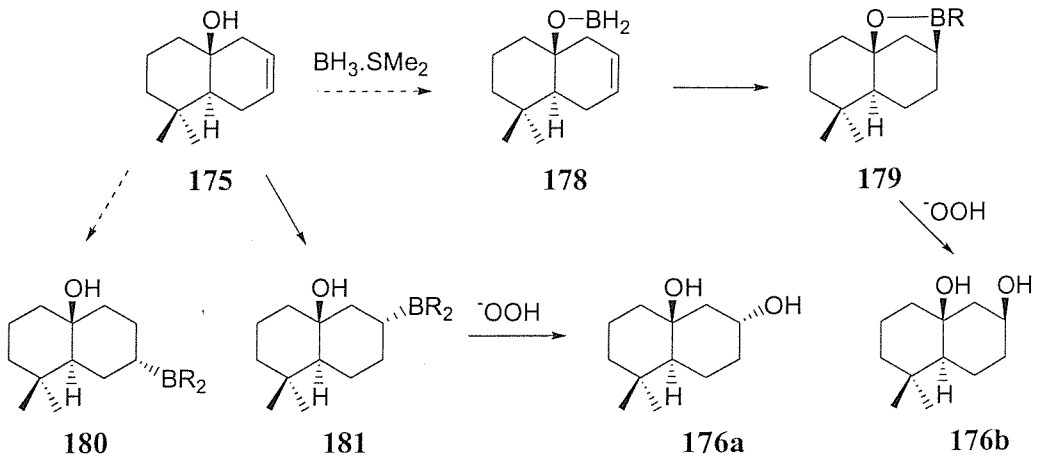
a. i. $BH_3.SMe_2$, THF, 5°C, ii. NaOH, H_2O_2, 50°C; **b.** PCC/alumina, DCM, rt; **c.** PTSA, benzene, reflux; **d.** Me_2CuLi, HMPA, THF, TMSCl, Et_3N, ether.

Scheme 50

Thus, treatment of **175** with borane dimethylsulfide complex, followed by oxidation with basic hydrogen peroxide afforded diol **176a** in 67%.[85] Oxidation of the secondary alcohol with PCC on alumina proceeded smoothly, and subsequent treatment with *p*-TsOH in

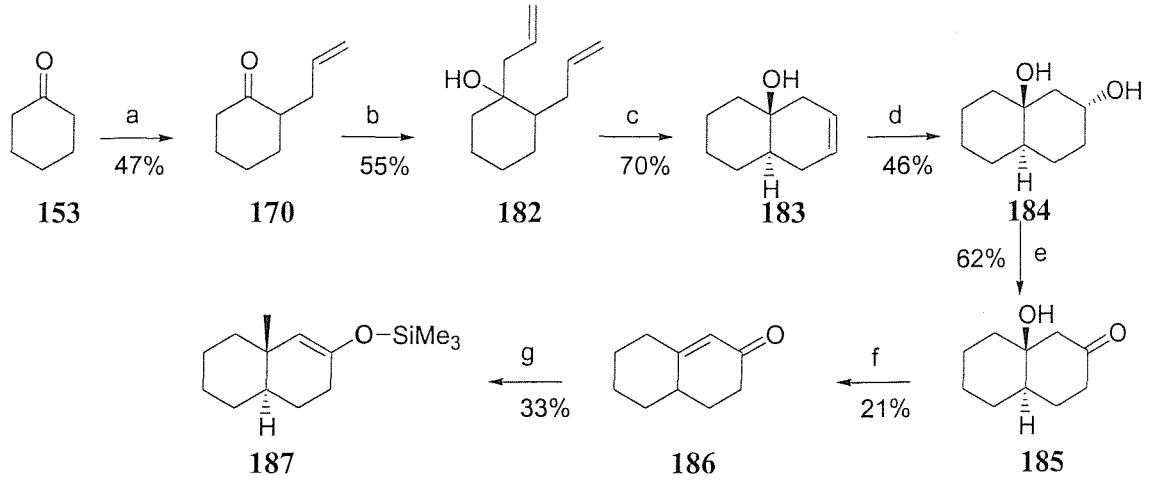
refluxing benzene resulted in the dehydration to enone **139a** in good yield. As before, the extra methyl group was introduced using copper chemistry leading to the formation of the silyl enol ether **166**.

It is interesting to note that the hydroboration step displayed good regioselectivity and diastereoselectivity. In principle, hydroboration can occur to both faces of the alkene (ie **179** or **181**), with two possible regiochemical outcomes (ie **180/181**). We believed that the diastereoselectivity would be driven by the hydroxy function, as depicted in scheme 51, but it turned out that the outcome of the reaction followed a different course as only the *trans*-diol **176b** was obtained.



Scheme 51

The high selectivity observed in this transformation led us to examine further example in order to explore the generality of the protocol as a means of preparing such 1,3-diols. Thus, allylation of cyclohexanone **153** was performed leading to **170** in 47% yield.[86] Subsequent treatment with allymagnesium bromide afforded the corresponding alcohol **182**. RCM next gave decalin **183** in good yield.[82] As before, hydroboration of **183**, followed by oxidation with basic hydrogen peroxide, gave *cis*-1,3-diol **184** as the major product in an isolated yield of 46% (Scheme 52).[85]



a. LDA, allyl bromide, THF; **b.** allylmagnesium bromide, THF, 0°C; **c.** Grubbs cat., DCM, reflux; **d. i.** $BH_3.SMe_2$, THF, 5°C, **ii.** NaOH, H_2O_2, 50°C; **e.** PCC on alumina, DCM, rt; **f.** PTSA, benzene, reflux; g. Me_2CuLi, TMSCl, Et_3N, HMPA, ether.

Scheme 52

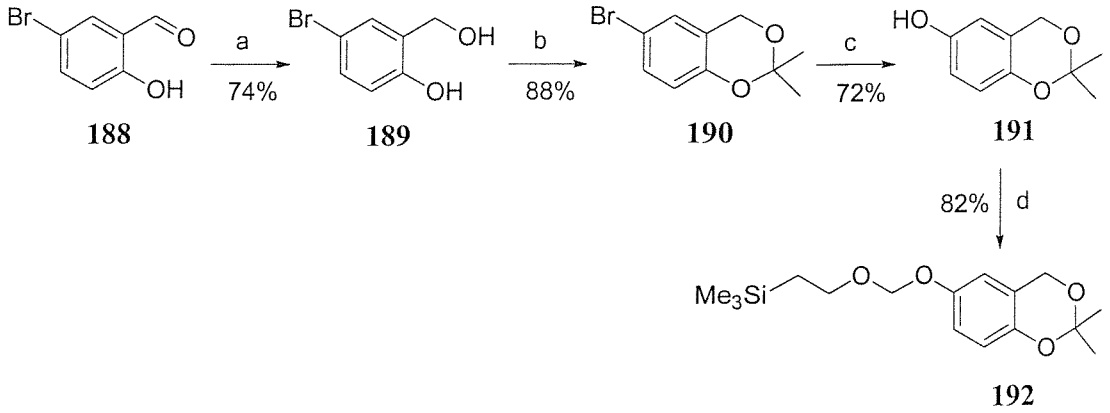
Oxidation of diol **184** to enone **185** with PCC on alumina proceeded smoothly. However, in this case dehydration to enone **186** was low yielding giving enone **186** in a disappointing 21% yield. Treatment of **186** with Me_2CuLi followed by trapping of the enolate as its silyl enol ether gave *trans*-decalin **187** in 33% yield.

The stereochemistry of the decalin **185** was assigned as *trans* by comparison of our data with those reported in the literature.[87] It seems reasonable to suggest that when reacting **174** under the same conditions, the same stereochemical course is followed. For this reason, we assigned the *trans* stereochemistry to decalin **166**.

3.5 SYNTHESIS OF THE AROMATIC PORTION 192

Starting from the cheap and readily available 5-bromosalicaldehyde **188**, our projected synthesis of the aromatic moiety proved to be extremely facile. A reduction was performed with sodium borohydride in good yield. The resulting diol **189** was then protected as its acetal under acidic conditions.[88] Halogen-metal exchange with butyllithium,

transmetallation with $B(OMe)_3$ and oxidation with basic hydrogen peroxide then gave phenol **191**.[85] This was protected as its (trimethylsilyl)ethoxymethoxy ether **192** in order to facilitate ortho-metallation of the arene (Scheme 53).[89]



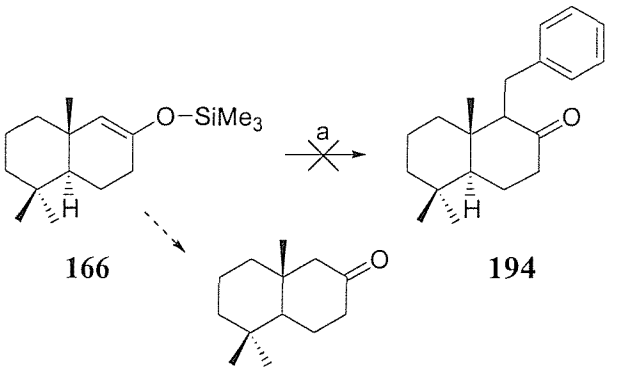
a. $NaBH_4$, ethanol, 0°C; **b.** PTSA, acetone, rt; **c.** i. ^{t}BuLi, $B(OMe)_3$, -78°C, ii. NaOAc, H_2O_2, THF; **d.** NaH, SEMCl, THF, 0°C.

Scheme 53

We decided to introduce the OSEM moiety in the molecule because of its ease of preparation and deprotection[90] and because it is known to be an excellent oxygen-based DMG (Directed Metalation Group) for aryl and pyridyl systems.[91] Ortholithiation provides us with a convenient method of introducing electrophilic substituents, which in turn would facilitate coupling with the decalin portion **166**.

3.6 COUPLING OF THE TWO FRAGMENTS

With this in mind, we first attempted to introduce a benzyl group to the decalin **166**. Alas, treating silyl enol ether **166** with MeLi and adding benzylbromide to the resulting lithium enolate, did not achieve the desired coupling reaction. Indeed, rather than furnishing **194**, the product of protonation **193** seemed to be obtained together with some recovered benzylbromide (Scheme 54).

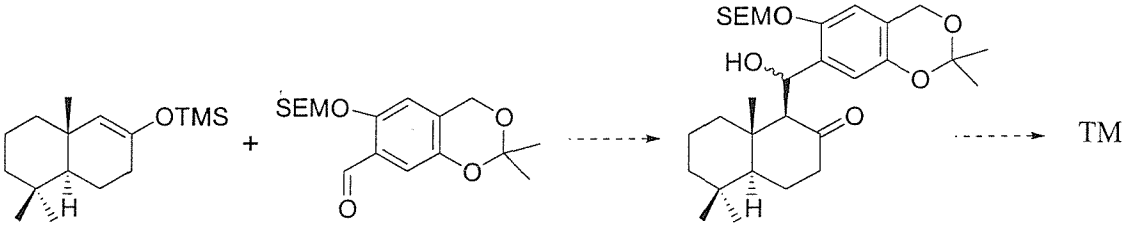


166 193 194

a. MeLi, THF, 0°C then benzylbromide.

Scheme 54

A Mukayiama reaction between silyl enol ether **166** and aldehyde **195** seemed to provide us with a good alternative to couple the two fragments. We hoped that treating silyl enol ether **166** with aldehyde **195** would generate β-hydroxy ketone **196**, which after a series of functional group manipulations would lead to our target molecule. (Scheme 55)



166 195 196

Scheme 55

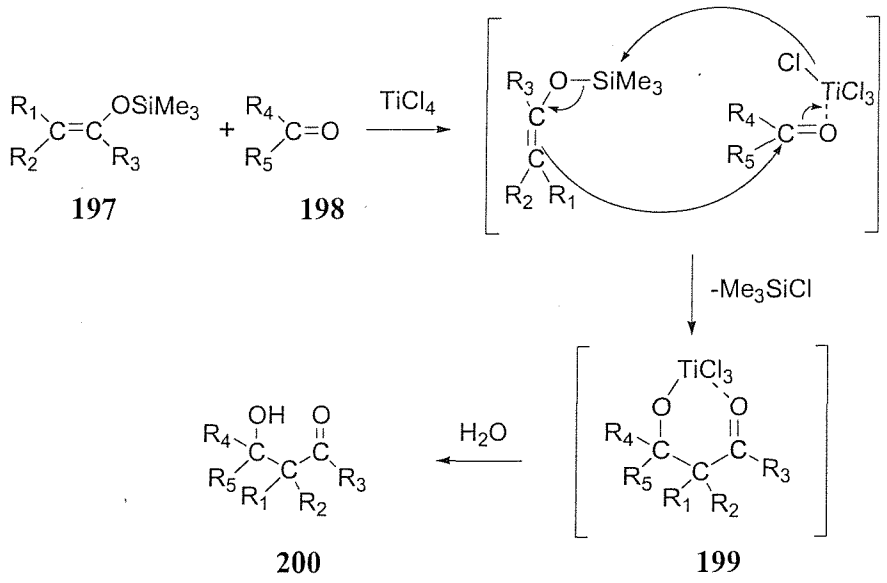
3.7 THE MUKAIYAMA REACTION

3.7.1 BACKGROUND

The aldol condensation is well-known for its flexibility. Early examples were however of limited in use as they led to product mixtures containing di-, poly- and self-condensation products which were difficult to separate and compromised chemical yields. To overcome that problem, Wittig and Hesse developed a valuable procedure using lithio derivatives of imines in 1970.[92] House and co-workers also reported the use of lithium enolates and metal

salts in aldol condensations. Mukaiyama *et al.* reported a method of preparing aldol adducts from silyl enol ethers and carbonyl compounds or acetals in presence of $TiCl_4$; processes that are now known as Mukaiyama reactions.[68,93]

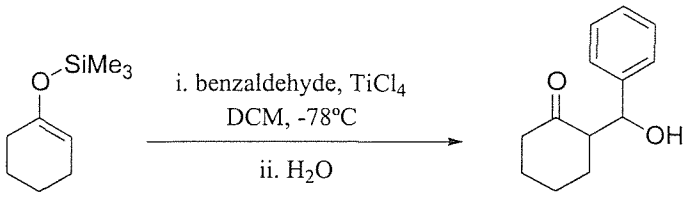
Mukaiyama found that titanium tetrachloride was a powerful activator of ketones and aldehydes towards nucleophilic addition reactions. They then assumed that a silyl enol ether **197** could attack the activated carbonyl compound **198**, to form trimethylsilyl chloride and chelate **199**. Hydrolysis would then occur leading to **200**, as outlined in scheme 56.



197 **198** **200** **199**

Scheme 56

Their assumptions were soon demonstrated as treating silyl enol ether **137** with benzaldehyde in presence of titanium tetrachloride led to the formation of **201** in 92% yield (Scheme 57)

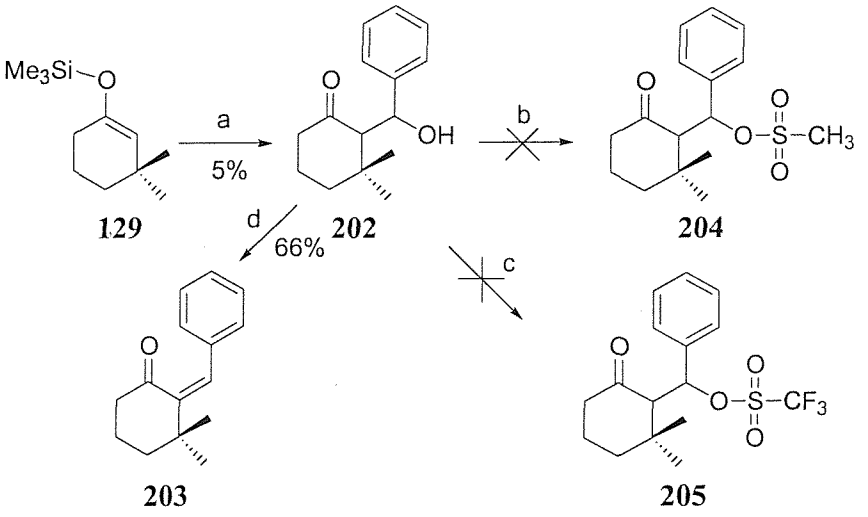


137 **201**

Scheme 57

3.7.2 EXPERIMENTATION

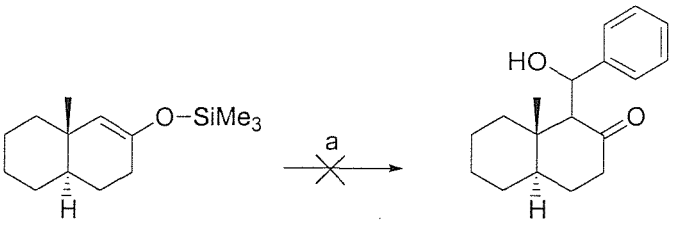
Before embarking on the coupling of our precious silyl enol ether **166** with aldehyde **195**, we initiated a model study to establish optimal reaction conditions. Thus, treatment of silyl enol ether **129** with benzaldehyde in DCM in presence of $TiCl_4$ afforded alcohol **202**, but only in 5% yield. Steric hindrance engendered by the methyl groups might explain this disappointing result. The dehydration of **202**, which we thought would be straightforward, did not prove facile. We were hoping that formation of mesylate **204** or triflate **205** would lead to the α,β-unsaturated ketone **203** directly. Unfortunately, their synthesis could not be realised under standard reaction conditions. Dehydration was eventually achieved by stirring **202** in hydrobromic acid at room temperature leading to enone **203** in 66% yield (Scheme 58).



a. $TiCl_4$, benzaldehyde, DCM, -78°C; **b.** Et_3N, MsCl, DCM, -78°C; **c.** Et_3N, $(CF_3SO_2C)_2O$, DCM, 0°C; **d.** aqueous HBr, rt.

Scheme 58

The same procedure was next applied to a more elaborate model, decalin **187**, which is a closer mimic of the real system. Alas, none of desired aldol adduct **206** was observed in the product mixture (Scheme 59).

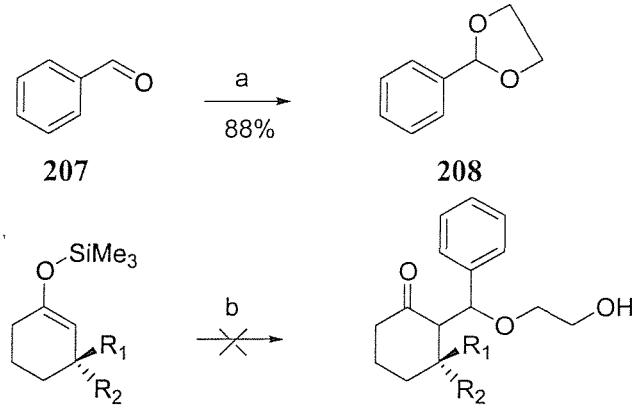


187 **206**

a. $TiCl_4$, benzaldehyde, DCM, -78°C

Scheme 59

We then tried to improve the yield of the Mukaiyama reaction by using the dioxolane of benzaldehyde. Thus, treatment of benzaldehyde **207** with *p*-TsOH in refluxing toluene gave **208** in good yield. Unfortunately, reacting **129** and **137** under the same reaction conditions failed to afford ethers **209** or **210** respectively (Scheme 60).



207 **208**

129 R=Me
137 R=H

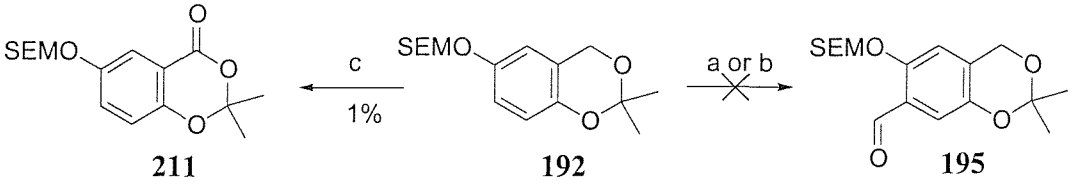
209 R=Me
210 R=H

a. PTSA, ethanediol, toluene, reflux; **b.** $TiCl_4$, **nb**, DCM, -78°C.

Scheme 60

We nonetheless decided to apply this procedure to the real system. First we had to prepare aryl aldehyde **195**. Following treatment of SEM ether **192** with ^{n}BuLi at –78°C and quenching the resulting organo-lithium with DMF, none of the desired aldehyde **195** was observed.[94] Instead, starting material was recovered. The same result was observed when carrying out the metallation reaction at 0°C. Using ^{t}BuLi as a lithiating agent at –78°C

resulted in the deprotonation at the benzylic position, which on quenching with DMF afforded **211** and starting material. Finally, using a mixture of ^{t}BuLi and ^{t}BuOK at –95°C also proved unsuccessful (Scheme 61).[94]

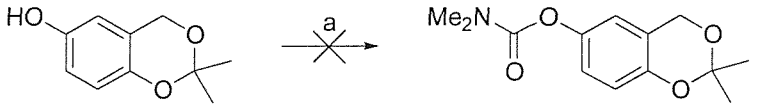


211 **192** **195**

a. ^{n}BuLi, DMF, ether, -78°C or 0°C; **b.** ^{t}BuLi + ^{t}BuOK, DMF, THF, -95°C; **c.** ^{t}BuLi, DMF, ether, -78°C.

Scheme 61

Among the oxygen-based DMGs reported, $OCONMe_2$ is known to be highly versatile and as a consequence it was the most logical choice to effect the introduction of the aldehyde function. However, treatment of **191** with sodium hydride in presence of dimethylcarbamyl chloride[95] failed to afford **212**, preventing us from taking this approach further (Scheme 62).



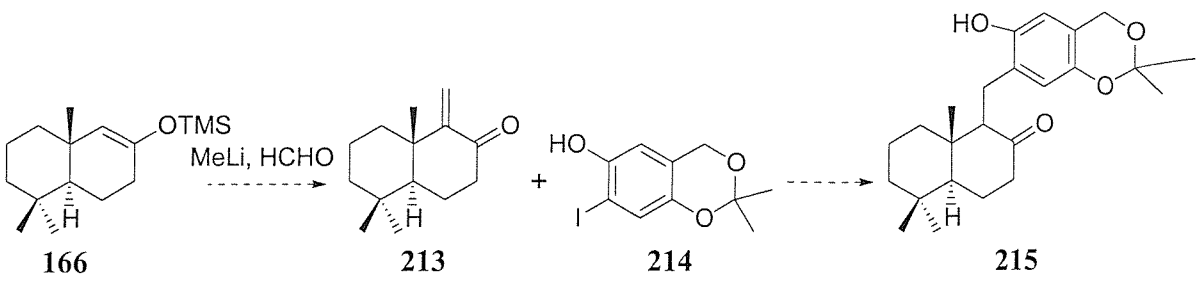
191 **212**

a. NaH, dimethylcarbamyl chloride, DMF/ether, rt.

Scheme 62

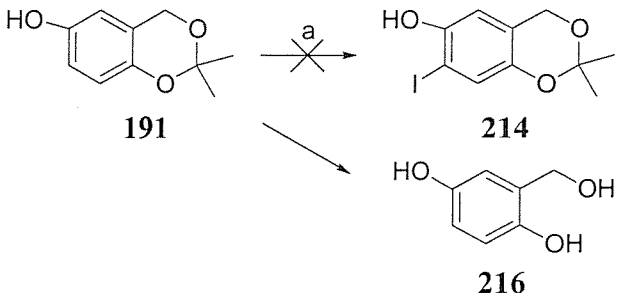
3.8 FURTHER ATTEMPTS

To affect coupling of the two fragments, we might also employ some Michael type addition reactions of an organocuprate to an enone. To that end, we needed to prepare enone **213** and a suitable arene, such as iodide **214** (Scheme 63).



Scheme 63

Treatment of silyl enol ether **166** with MeLi and then formaldehyde should afford the desired enone **213** after dehydration. Likewise, access to iodide **214** requires halogenation ortho to the phenol, a process that is usually undemanding. Alas, reacting **191** with $AgOCOCF_3$ in presence of iodine[96] resulted in the cleavage of the acetal protecting group rather than halogenation of the arene, leading to **216** (Scheme 64).

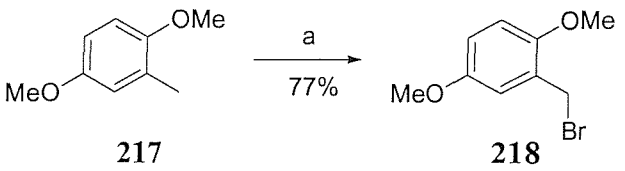


a. $AgOCOCF_3$, I_2, $CHCl_3$, -5°C

Scheme 64

We then decided to look for some more robust protecting groups, and the benzyl group seemed to be a good alternative. However, difficulties were also encountered in the iodination of such arenes, so we decided to abandon this approach to synthesis of the aromatic portion. Rather, 2,5-dimethoxytoluene **217** became our new starting point, with our intention being to introduce other functional groups at a later stage. The first

transformation involves an allylic bromination with NBS in presence of DBP, it led to **218** in 77% yield. (Scheme 65)[97]



217 **218**

a. NBS, DBP, CCl_4, reflux.

Scheme 65

3.9 CONCLUSIONS

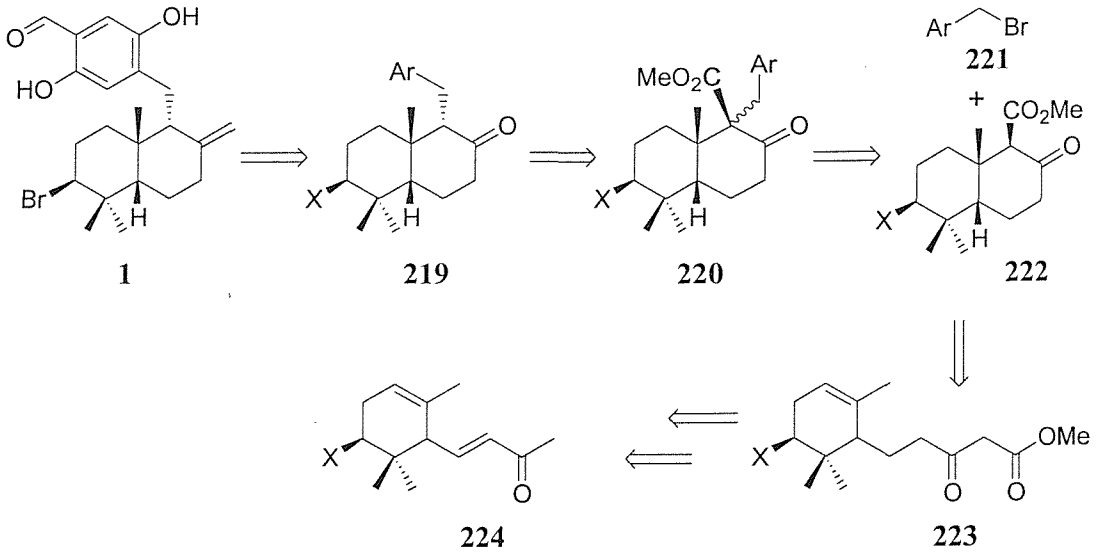
We have achieved the synthesis of the decalin ring, but the wrong stereochemistry at the ring junction was observed, as it is *trans* rather than *cis*. The synthesis of the aromatic portion was undemanding, but difficulties were encountered when trying to couple the two fragments together. Indeed, the methods we used were all unsuccessful and therefore this route to total synthesis to the target molecule **1** was abandoned.

CHAPTER 4

OUR THIRD APPROACH TO PEYSSONOL A

4.1 RETROSYNTHETIC ANALYSIS

Our new retrosynthetic analysis is depicted in scheme 66. We hoped that treatment of **223** with a Lewis acid would induce cyclisation, leading to the decalin portion **222** with the required *cis* stereochemistry. Then formation of the enolate anion of **222** would induce attack on benzylbromide **221**, thus introducing our aromatic portion. Decarboxylation and further functional group manipulation would then be necessary to reach our target molecule.

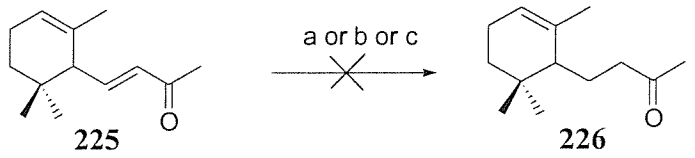


Scheme 66

4.2 OUR FIRST APPROACH TO DECALIN 222

We started this new synthesis with α-ionone (X=H) **225**, a readily available and cheap material. The strategy was to selectively reduce the enone whilst leaving the other double bond in the ring. Alas, treating a toluene solution of α-ionone **225** with aqueous sodium

carbonate and sodium dithionite, in presence of the phase transfer catalyst adogen 464, failed to afford the desired reduced α-ionone **226**.[98] Modifying the reaction conditions did not lead to the desired molecule either. For example, reacting **225** with hydrogen in presence of Raney nickel was no more successful.[99,100] Likewise, attempts to induce reduction, using tributyltin hydride with AIBN also failed (Scheme 67).[101]

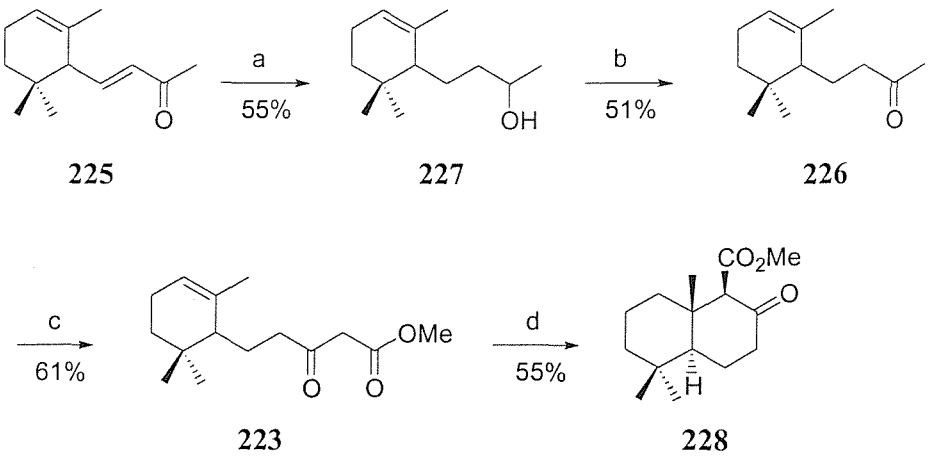


225 **226**

a. adogen 464, $NaHCO_3$, $Na_2S_2O_4$, toluene/H_2O, 90°C or benzene/H_2O, reflux; **b.** H_2, Raney nickel, EtOH; **c.** Bu_3SnH, AIBN, 80°C.

Scheme 67

The alternative plan was to reduce the unsaturated ketone **225** to the corresponding saturated alcohol **227**, which could afterwards be oxidised to the desired ketone **226**. Thus, treatment of α-ionone with sodium borohydride in pyridine afforded the desired alcohol **227** in moderate yield (55%). Reacting alcohol **227** with Jones reagent led to decomposition rather than ketone **226**. The oxidation was however achieved using pyridinium chlorochromate on alumina, in 51% yield. A Claisen condensation with dimethyl carbonate afforded β-keto-ester **227**[102] and a subsequent tin tetrachloride mediated cyclisation led to **228**.[103] We had now developed a short route to the decalin ring system, but the stereochemistry still had to be dealt with, as once again the *trans* stereochemistry was observed (Scheme 68).



a. $NaBH_4$, pyridine, rt; **b.** PCC on alumina, DCM, rt; **c.** NaH, dimethyl carbonate, toluene, reflux; **d.** $SnCl_4$, DCM, -78°C to rt.

Scheme 68

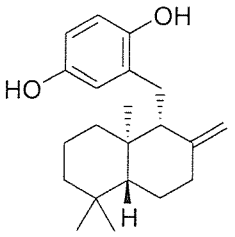
4.3 TOTAL SYNTHESIS OF ZONAROL: A MODEL FOR US?

In 2002, Laube *et al.* reported the total synthesis of zonarol **4** and some related compounds.[104] Their synthesis was achieved via (+)-albicanic acid **229**, a sesquiterpene of the drimane type. Coupling of the appropriate drimane-synthon with lithiated hydroquinone ethers led to sesquiterpenes arenes, which were then modified to the target molecules. The aim of this synthesis was to promote a convenient synthetic pathway to sesquiterpenes arenes containing a drimane skeleton. Thus, our route will be based on those results.

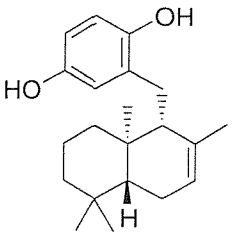
4.3.1 ISOLATION OF ZONAROL

Zonarol **4** and its isomer isozonarol **230** are two sesquiterpene hydroquinones that were reported by Fenical *et al.* in 1973.[11] They were obtained from separate methanol extracts of *Dictyopteris zonarioides* collected in the Pacific Ocean and in the Gulf of California. Their structural assignments were based upon spectral data and by degradation to dihydrotauranic acid and comparison with an authentic sample. Both are moderately fungitoxic toward

Phytophtora cinnamomi, *Rhizoctonia solani*, *Sclerotinia sclerotorium* and *Sclerotium rolfsii*.



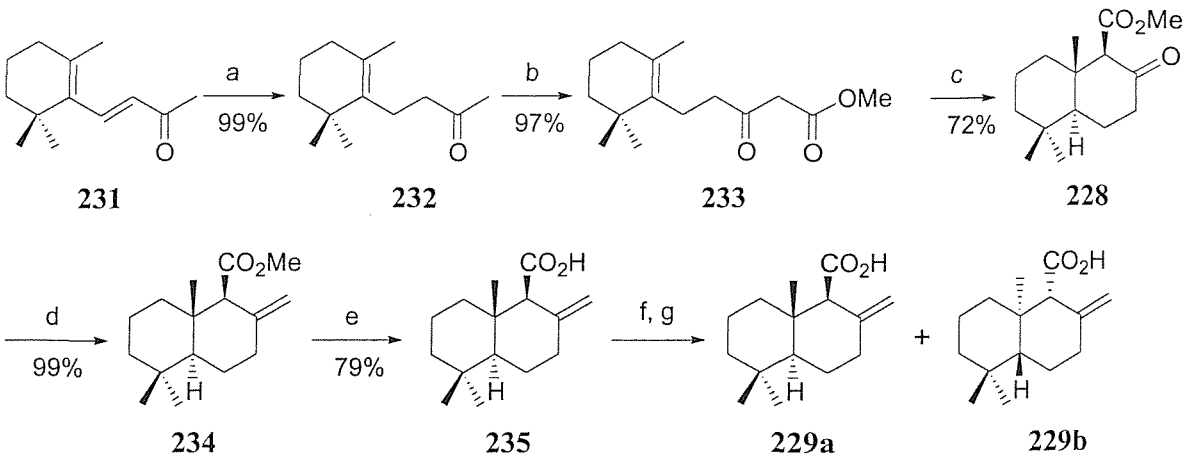
Zonarol **4**



Isozonarol **230**

4.3.2 LAUBE *ET AL.* TOTAL SYNTHESIS OF ZONAROL

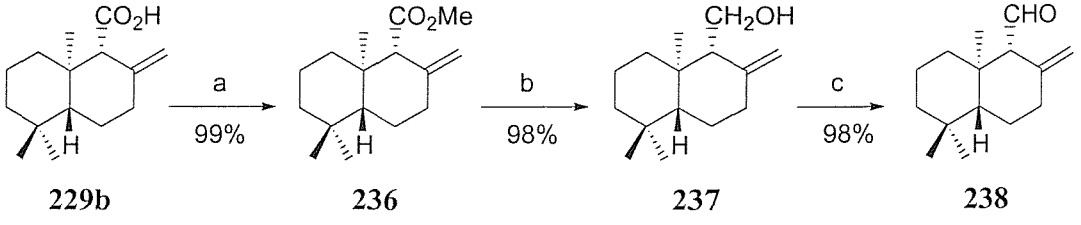
This route began with a regioselective hydrogenation of β-ionone **231** (following Ojima and Kogure procedure).[105] Subsequent Claisen condensation with dimethyl carbonate afforded β-keto ester **233** quantitatively, and the cyclised product **228** was obtained on treatment with $SnCl_4$ in good yield. A Wittig reaction provided the exo methylene double bond but solvolysis of the methyl ester **235** proved troublesome. The desired albicanic acid **229** was obtained in 55% yield using DMF/LiI.[106] On exposure of **234** to NaSEt/DMF, the time of reaction was shortened considerably and the yield of the desired product was elevated to 79% after purification. Resolution of the racemic mixture was carried out following the procedure described by Ragoussis *et al.* (Scheme 69).[106]



a. i. $EtMe_2SiH$ or Et_3SiH, $(Ph_3P)RhCl$ (0.5%), 50-55°C; **ii.** MeOH, K_2CO_3; **b.** dimethyl carbonate, NaH, toluene, 100°C; **c.** 1.62 equivalent $SnCl_4$, CH_2Cl_2; **d.** methylenetriphenylphosphorane, toluene; **e.** NaSEt, DMF, 150°C; **f.** and **g.** separation of the racemate using (+) and (-)-α-phenylethylamine as chiral auxiliary.

Scheme 69

Quantitative esterification of **229b** was carried out by formation of the tetra-ethylammonium salt of acid **229b** and its treatment with an excess of dimethyl sulfate. Reduction of **236** was performed in presence of diisobutylaluminium hydride to give alcohol **237**, and subsequent oxidation with pyridinium chlorochromate in DCM afforded the desired aldehyde **238** quantitatively (Scheme 70).

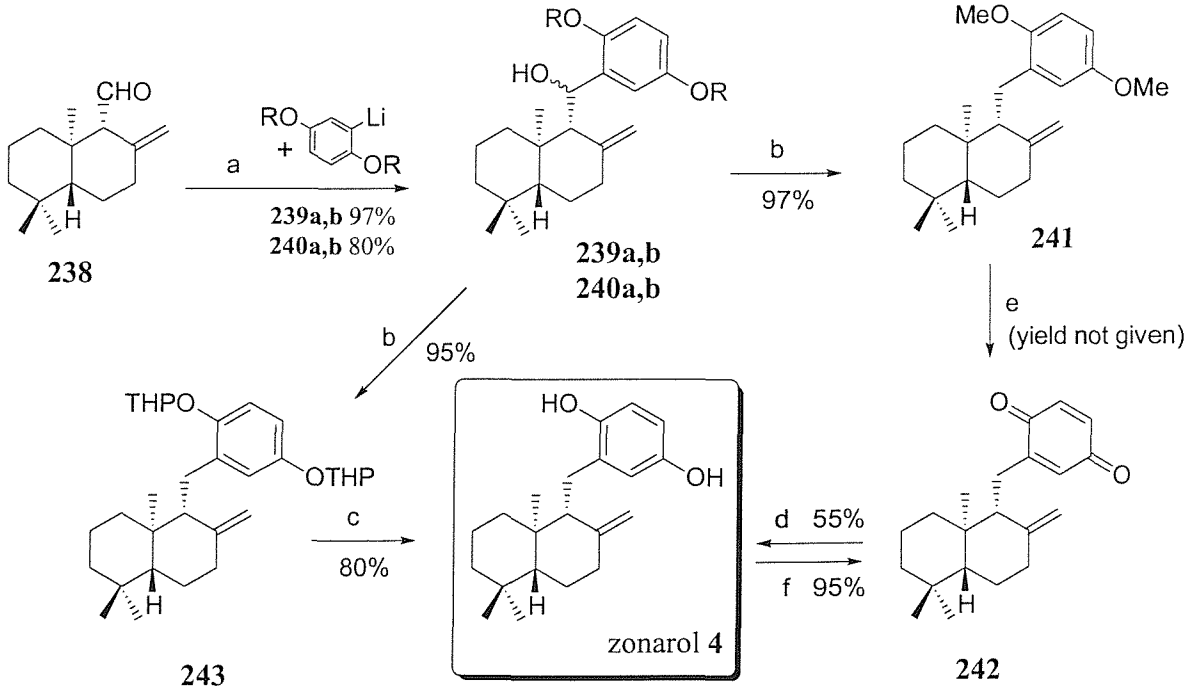


a. i. $[Et_4N]^+OH^-$, MeOH; **ii.** dimethyl sulfate, THF; **b.** DIBAH, CH_2Cl_2, 0°C; **c.** PCC, CH_2Cl_2, rt.

Scheme 70

(+)-Albicanal **238** was coupled with 2-lithiohydroquinone dimethyl ether or 2-lithiodihydroquinone di-THP ether to obtain the benzyl alcohols **239a,b** and **240a,b**.

Reduction of these compounds with lithium in liquid NH_3/THF, followed by treatment with excess NH_4Cl,[107] resulted in their benzylic desoxygenation. The deprotection of the di-THP-ether **240a,b** was conducted following the procedure of Prelog *et al.* in 80%.[108] Mixtures or decomposition was observed when employing stronger acids. Using the methyl protecting group was advantageous for characterisation as the mixtures of diastereoisomers obtained with the THP moiety could be avoided. The deprotection of (±)-zonarol dimethyl ether **239a,b** proved to be challenging though. Finally, a one-pot-two-steps procedure was performed: an oxidative demethylation of **241** with CAN/pyridine-2,6-dicarboxylic acid *N*-oxide yielded (±)-zonarone **242**, which was reduced with sodium dithionite to give (±)-zonarol **4**, in 55% over two steps. Zonarol can also easily be oxidised to its quinone derivative on treatment with CAN in H_2O/MeCN. (Scheme 71)

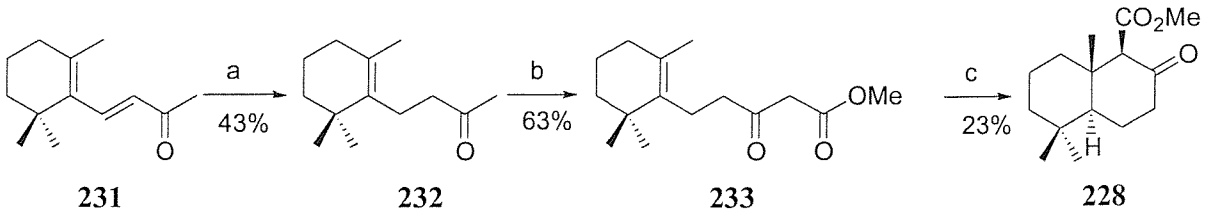


a. R=Me: Et_2O, 0°C, (**239a,b**), R=THP: THF, 0°C, (**240a,b**); **b.** 5.3 equivalent Li liq.NH_3, THF, NH_4Cl, -78°C; **c.** oxalic acid, H_2O, MeOH, ethyl acetate; **d.** THF/H_2O, (3:2), $Na_2S_2O_4$, reflux; **e.** 12.3 equivalent CAN, DMF/MeCN/H_2O (1:1:1), pyridine-2,6-dicarboxylic acid *N*-oxide; **f.** 3.0 equivalent CAN, MeCN/H_2O.

Scheme 71

4.4 OUR SECOND APPROACH TO DECALIN 222

We followed the procedure described by Laube *et al.*.[104] Thus, treatment of β-ionone **231** with Wilkinson's catalyst in presence of triethylsilane, and then solvolysis with basic methanol afforded **232** in a poor yield (43%). Further attempts to effect the reduction of the resulting silyl enol ether were performed so that the yield obtained by Laube *et al.* could be matched, but were unsuccessful. Isolating the silyl enol ether and then carry out the solvolysis also failed to improve the yield of conversion. Subsequent Claisen condensation with dimethyl carbonate afforded keto-ester **233**. Treatment of **233** with tin tetrachloride in DCM afforded **228** in 23% yield. Again the yield reported by Laube *et al.* could not be matched as considerable starting material was recovered (46%) (Scheme 72).



231 **232** **233** **228**

a. i. Et_3SiH, $(Ph_3P)RhCl$, 55°C, **ii.** $MeOH/K_2CO_3$; b. NaH, dimethyl carbonate, toluene, reflux; **c.** $SnCl_4$, DCM, -78°C to rt.

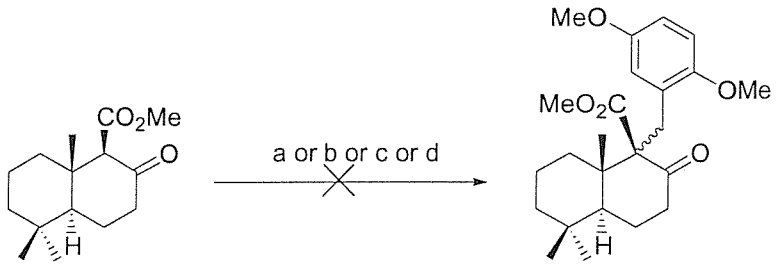
Scheme 72

4.5 SYNTHESIS OF THE MAIN SKELETON

4.5.1 INTRODUCTION OF THE AROMATIC MOIETY 218

With our key decalin intermediate **228** in hand, we now had to investigate the introduction of the aromatic moiety. Our strategy was to deprotonate **228** and then quench the enolate anion with benzylbromide **218**. Treating **228** with DBU in DCM followed by quenching did not lead to the desired product **244**, returning only starting material. Reacting **228** with sodium hydride in THF at 0°C with quenching at room temperature, or at reflux, was also

unsuccessful. The same results were observed when using dimethylaminopyridine as a base (Scheme 73).

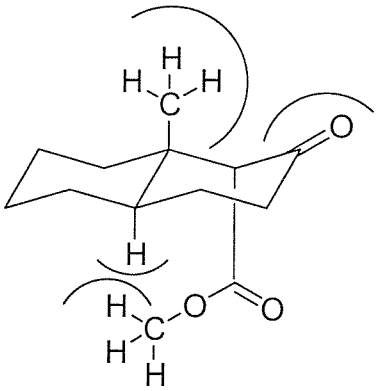


228 **244**

a. DBU, DCM, rt; then **218**; **b.** NaH, THF, **218**, 0°C to rt; **c.** NaH, THF, 0°C, **218**, then reflux; **d.** DMAP, $CHCl_3$, **218**, reflux.

Scheme 73

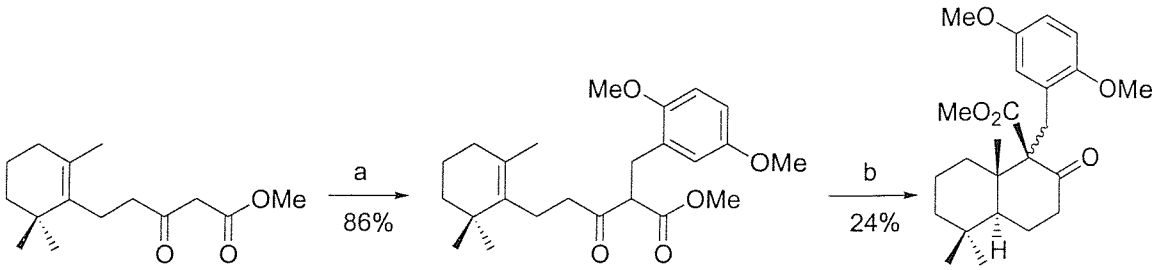
The high steric hindrance of the molecule might well be the cause of our problem, as the formation of the enolate is made more difficult. Indeed, the top face is blocked by the axial methyl group, and the bottom face blocked by the axial carboxylate (Scheme 74).



Scheme 74

We were thus prompted to introduce the aromatic portion prior to cyclisation. The coupling of **231** and **218** was achieved in 86% yield, by treating **231** with sodium hydride followed by quenching with the benzylbromide **218** at reflux. The Lewis acid mediated cyclisation afforded **244**, as a mixture of diastereoisomers, again in a poor yield (24%). Again, steric

hindrance for the cyclisation is considerable and may play a part in the low yield observed (Scheme 75).



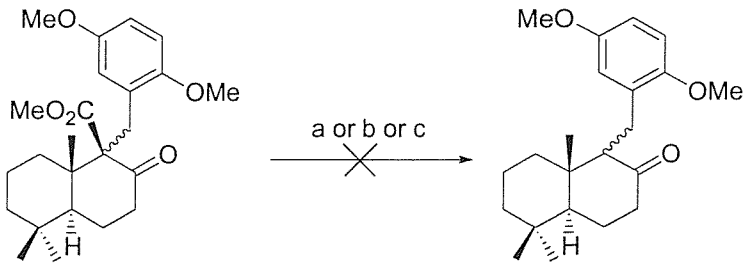
231 245 244

a. NaH, compound **218**, THF, reflux; **b.** $SnCl_4$, DCM, -78°C to r.t.

Scheme 75

4.5.2 DECARBOXYMETHYLATION

Decarboxymethylation is a well-known process and several procedures are described in the literature. Unfortunately, all three of the procedures we followed were unsuccessful and returned only starting material. Thus treating **244** with calcium chloride in presence of dimethyl sulfoxide,[109] reacting **244** with sodium hydroxide in aqueous methanol at reflux[110] and heating **244** in presence of lithium chloride in dimethyl formamide[111] all failed to give **246** (Scheme 76).



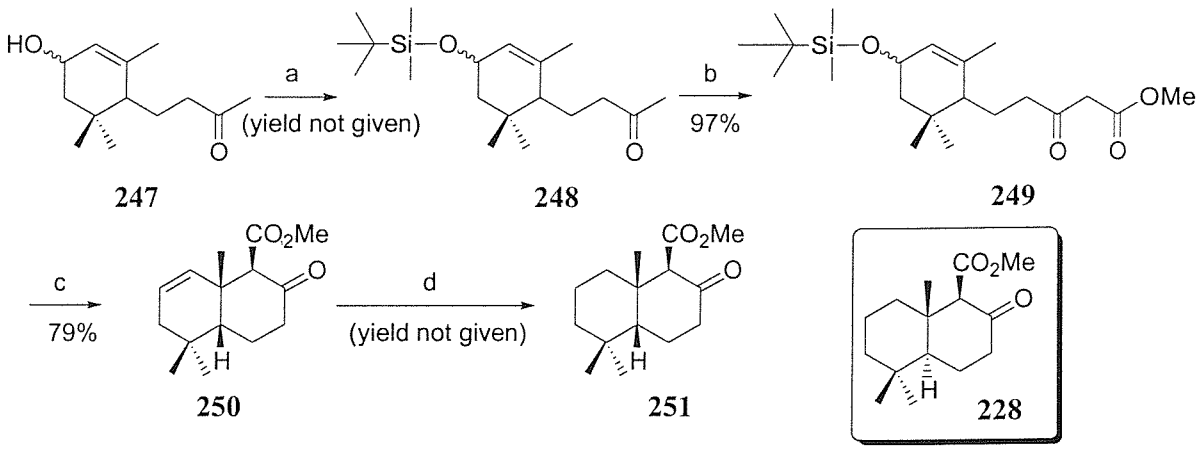
244 246

a. $CaCl_2.2H_2O$, DMSO, reflux; **b.** NaOH, aqueous MeOH, reflux; **c.** LiCl, DMF, 145°C.

Scheme 76

4.6 AN INTERESTING FEATURE

In 1987, Zhiyu *et al.* reported an efficient synthesis of 7,8-dehydrogenated decalone derivative via allylic cation promoted cyclisation.[112] It was of interest to us as the reaction gave the required *cis* stereochemistry at the ring junction. Thus, treatment of **247** with *tert*-butyldimethylsilane in presence of imidazole afforded the corresponding protected alcohol **248**. Then, a Claisen condensation with dimethyl carbonate led to **249** quantitatively and direct treatment of **249** with $SnCl_4$ in DCM afforded **250**. To confirm its stereochemistry, hydrogenation in presence of Pd/C gave **251,** which has similar MS and IR features to the known *trans*-analogue **228**, but gave different NMR data. This supported the fact that **251** had the *cis* ring junction stereochemistry (Scheme 77).

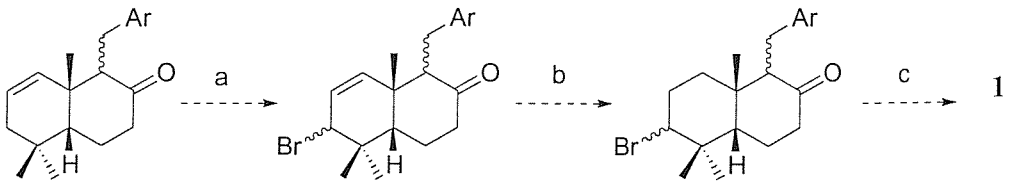


a. *tert*-butyl-dimethylsilylchloride, imidazole, DMF; **b.** NaH (excess), dimethyl carbonate; **c.** $SnCl_4$, DCM, -78°C; **d.** H_2, Pd/C.

Scheme 77

Besides leading to the desired *cis* ring junction, this cyclisation process also provides an extra double bond, which will be very useful to us towards the end of the synthesis. Indeed, treating **252** with *N*-bromosuccinimide in presence of a radical precursor should induce an

allylic bromination, thus introducing the bromine atom in the desired position for peyssonol A. A subsequent hydrogenation of the double bond and a Wittig reaction would then provide the target molecule (Scheme 78).

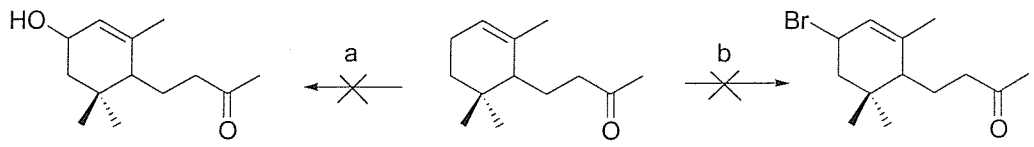


252 **253** **254**

a. NBS, DBP, CCl_4, reflux; **b.** H_2, Pd/C; **c.** Wittig or Tebbe.

Scheme 78

Alas, introduction of functionality at the allylic position of dihydro-α-ionone **226** proved difficult. Treatment of **226** with selenium dioxide in refluxing dioxane did not afford the desired allylic alcohol **255**. Reacting **226** with *N*-bromosuccinimide in presence of dibenzoyl peroxide did not provide the corresponding bromo compound **256** either (Scheme 79).



255 **226** **256**

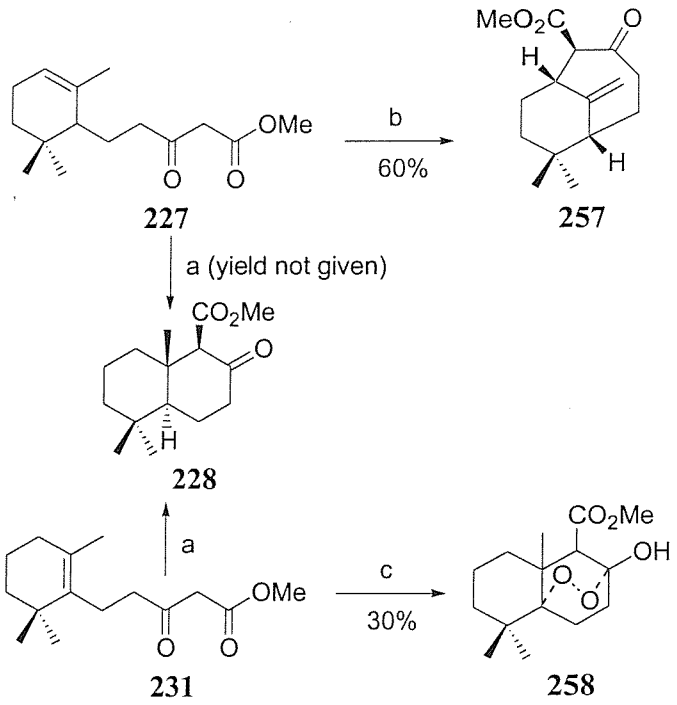
a. SeO_2, dioxane; **b.** NBS, AIBN, CCl_4, reflux.

Scheme 79

4.7 AN ALTERNATIVE ROUTE TO DECALIN 222

4.7.1 BACKGROUND

Lewis acids and photochemically mediated cyclisations have been used to construct a great number of substituted decalin intermediates.[112] More recently, free radical cyclisations of haloalkanes have also been developed, but their reductive nature renders the products somewhat less versatile. The alternative Mn(III) mediated oxidative cyclisation of β-keto esters seems to offer an interesting option to overcome those limitations.[113-116] In 1990 Ruveda *et al.* described the regiochemical and stereochemical outcome of such Mn(III) cyclisations of α-ionone derivative **227** and β-ionone derivative **231** and compared these with the corresponding Lewis acid mediated cyclisations. Results are shown in scheme 80.[117]

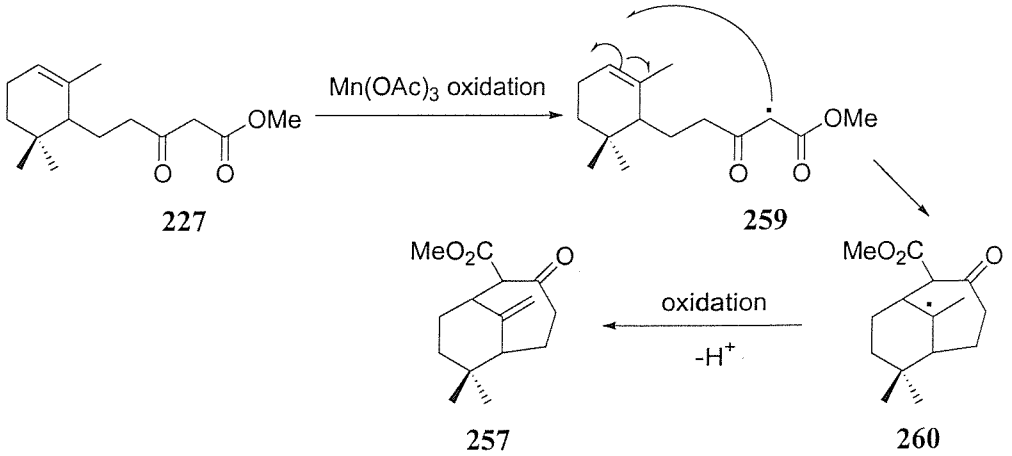


a. $SnCl_4$, DCM; **b.** $Mn(OAc)_3$, CH_3CO_2H, 58°C; **c.** $Mn(OAc)_3$, CH_3CO_2H, rt

Scheme 80

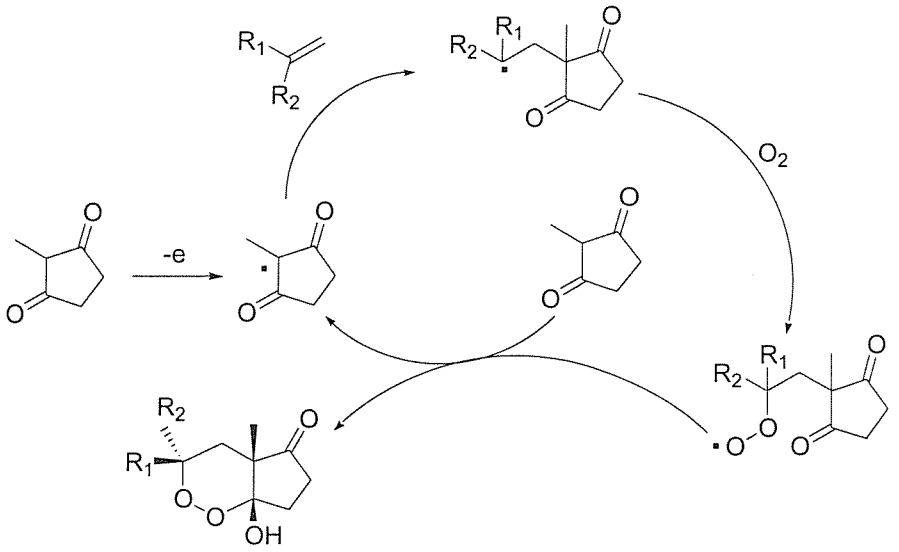
Thus, reacting **227** with 2 equivalents of manganese triacetate in acetic acid at 58°C produced compound **257** as a major product. In contrast, treatment of **231** with 2 equivalents of manganese triacetate at room temperature afforded **258** as major product.

The formation of a seven membered ring may be explained as follows: the carbon centred radical in **259** adds to the less substituted carbon of the double bond,[118] and so forms a tertiary radical. The tertiary radical is rapidly oxidised to a cation leading to alkene **257** (Scheme 81).



Scheme 81

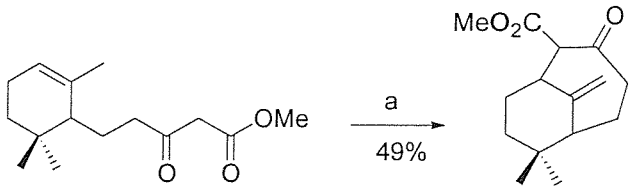
The formation of the endoperoxide **258** suggests that the radical attack of the β-keto ester is followed by trapping of molecular oxygen, which then generates the cyclic peroxide, in a similar way as that described in scheme 82.[119]



Scheme 82

4.7.2 OUR NEW APPROACH TO DECALIN 222

We decided to follow the Ruveda procedure, with addition of copper(II) acetate to the reaction mixture hoping that this might promote the 6-*exo*-trig pathway leading to a decalin **228**. Alas reacting **227** with Mn(III) in presence of Cu(II) produced compound **257** in 49% yield, as described previously (Scheme 83).



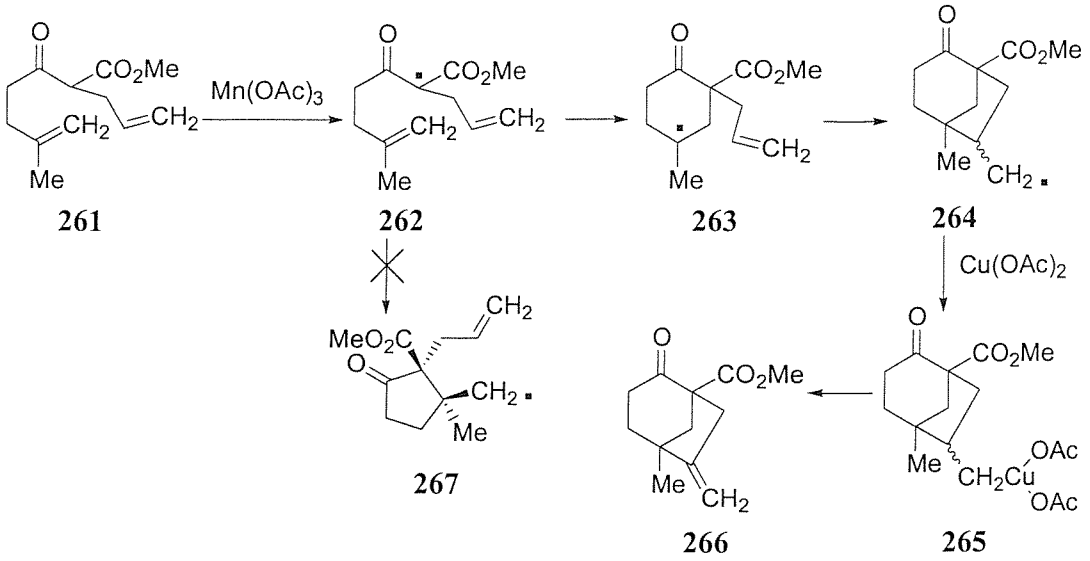
227 **257**

a. $Mn(OAc)_3$, $Cu(OAc)_2$, CH_3CO_2H, 55°C.

Scheme 83

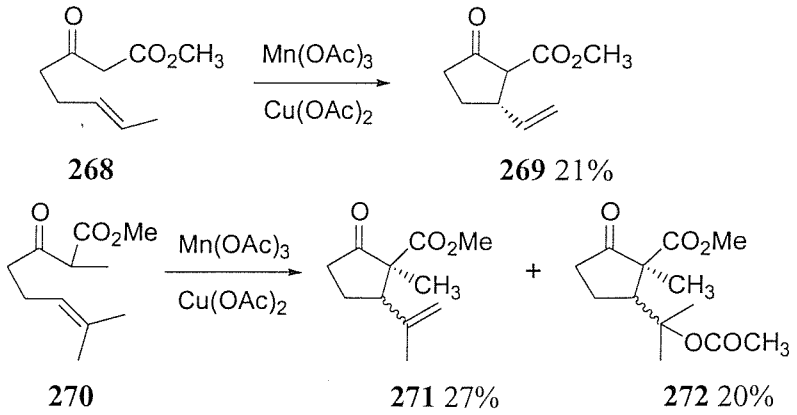
Snider *et al.* have intensely studied manganese(III) based oxidative free radical cyclisations.[120,121] They reported numerous procedures to prepare five-, six-, seven- and eight-membered rings. Some of their results are shown in the following schemes.

Thus, treatment of **261** with Mn(III) and Cu(II) at room temperature for 26 h produced **266** in 86% yield. Cyclisation totally proceeds via the tertiary cyclohexyl radical **263**; the primary cyclopentylmethyl radical **267** is not formed. Cyclopentylmethyl radical **264** then reacts with copper acetate to undergo β-hydride elimination and provide the alkene **266** (Scheme 84).



Scheme 84

On the other hand, 5-membered rings only were obtained from different substrates under the same reaction conditions (Scheme 85).[122]

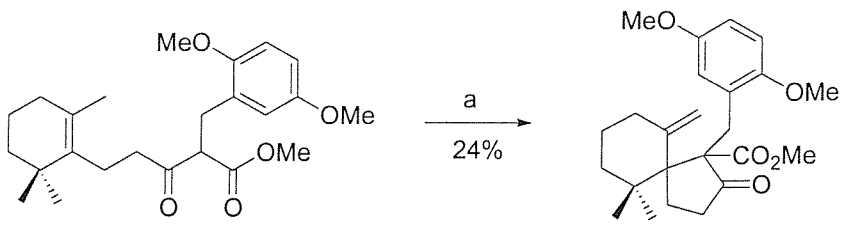


Scheme 85

In each case, the radical preferentially attacks on the less sterically encumbered part of the molecule, *ie* the less substituted end of the alkene as described earlier.

From those results, we decided to perform the same experiment on compound **245** under the same conditions, hoping to obtain the desired 6-membered ring, or as a mixture with the 5-membered ring. Reacting **245** with Mn(III) in presence of Cu(II) afforded a complex

mixture of very polar compounds from which **273** was the only product isolated, as a mixture of diastereoisomers (Scheme 86).



245 **273**

a. $Mn(OAc)_3$, $Cu(OAc)_2$, CH_3CO_2H, 55°C.

Scheme 86

We have never encountered formation of the 6-membered ring, although the decalin product might be present in the mixture of polar products. Thus, it seems that when both end of the alkene are disubstituted, 5-*exo*-trig cyclisation is faster than 6-*endo*-trig cyclisation even when this is to the more sterically encumbered carbon. In this example, formation of the spiro cycle leads to 3 successive quaternary centres!

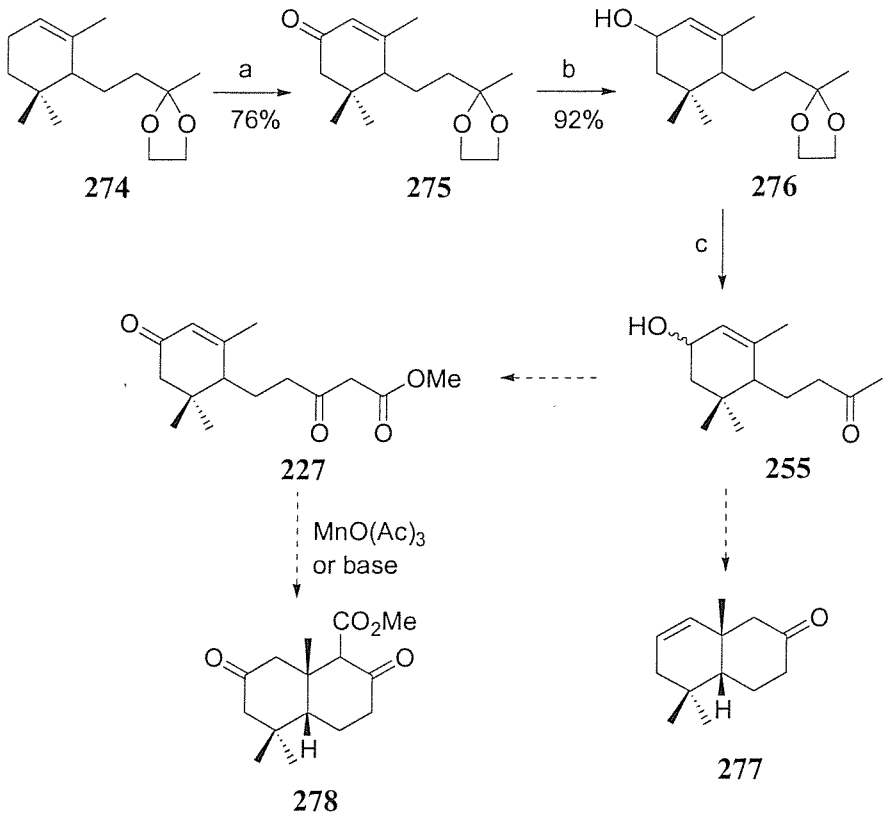
The presence of many polar products suggests that some peroxide formation may have occurred. Addition of Cu(II) salts to the reaction mixture should help to prevent this, as Cu(II) oxidation of 3°-alkyl radical intermediates is a very fast process. β-hydride elimination then occurs to produce the end alkene.

4.8 CONCLUSIONS AND FURTHER WORK

We have achieved the formation of the main skeleton of the target molecule. Once again, the undesired *trans*-stereochemistry at the ring junction was observed. Controlling the stereochemical course of the reaction, as well as the effect, the subsequent decarboxymethylation present us with a considerable challenge. If these can be overcome,

the route well provides a useful entry to the peyssonol A skeleton, being superior in terms of the number of steps and the overall yield to the other routes we have investigated.

As far as future work is concerned, it seems reasonable to base further synthetic work on the functionalisation of α-ionone so as to promote 6-ring closure in both Lewis acid and radical cyclisation reactions. The presence of an allylic alcohol during the Lewis acid mediated cyclisation step will promote ring closure to give the *cis* stereochemistry at the ring junction. Oxidation of **255** to the ketone **227** also promotes radical ring closure via the 6-*exo* trig pathway or a Michael type addition leading to **278** (Scheme 87).



274 275 276 227 255 277 278

Scheme 87

CHAPTER 5

EXPERIMENTAL SECTION

5.1. GENERAL REMARKS

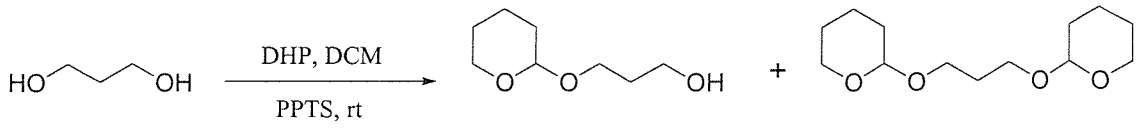
Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infra red spectra were recorded using a Nicolet Impact 400 FT-IR spectrometer. Maxima are reported as ν_{max} followed by the signal intensity (described using the abbreviations s: strong, m: medium, w: weak, br: broad). UV spectra were recorded on a Pye Unicam SP8-400 Ultraviolet spectrophotometer. Maxima are reported as λ_{max} followed in parentheses by the extinction coefficient ε_{max} ($dm^3mol^{-1}cm^{-1}$). NMR spectra were recorded on a Bruker AM300 or AC300 (operating at 300MHz for ^1H and at 75MHz for ^{13}C), or a Bruker AM400 (operating at 400MHz for ^1H and at 100MHz for ^{13}C). Chemical shifts (δ) are reported as values in parts per million relative to residual $CHCl_3$ (δ_H 7.27, δ_C 77.2) unless otherwise stated. Multiplicities in ^1H NMR spectra are described using the abbreviations s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, app.: apparent. Coupling constants are measured in Hertz. Multiplicities in ^{13}C NMR spectra refer to the signals in the off-resonance spectra, as determined by DEPT 135° and DEPT 90° experiments. Low-resolution mass spectra using electrospray (ES) were recorded on a Micromass Platform quadrupole mass analyser with an electrospray ion source. Chemical ionisation (CI) spectra were recorded on a Thermoquest Trace GC-MS with a 15 metre Rtx-5MS column, 0.25mm ID, 0.25 micron. The MS source is a combined EI/CI source with a quadrupole analyser. Signals are reported as values in atomic mass units and are followed in parentheses by the peak intensity relative to the base peak (100%). High-resolution mass spectra were recorded on a variety of instruments at Southampton University. Column chromatographies were performed using 230-400 Mesh 60H silica gel (Merck), slurry packed and run under low pressure. Reactions were monitored by thin layer chromatography using precoated

aluminium backed sheets coated with Merck silica gel 60 F254, thickness 0.25mm. Compounds were visualised under UV irradiation, followed by $KMnO_4$. Microanalyses were conducted at Medac Ltd.

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus (or dried with a heat gun), under a positive atmosphere of N_2. Dry solvents were prepared using the standard procedures (Tetrahydrofuran and diethyl ether were dried and degassed from sodium-benzophenone ketyl; dichloromethane and chloroform were distilled from calcium hydride; toluene was distilled from sodium; petroleum ether refers to the fraction boiling at 40-60°C). All other solvents and reagents were used directly as supplied except where stated otherwise.

5.2 SYNTHETIC PROCEDURES

Synthesis of 3-(tetrahydro-2H-2-pyranyloxy)-1-propanol **103**[52]



$C_3H_8O_2$	$C_8H_{16}O_3$	$C_{13}H_{24}O_4$
MWt: 76	MWt: 160	MWt: 244
102	**103a**	**103b**
	57%	29%

To 1,3-propandiol **102** (10.00 g, 131.57 mmol) in DCM (40 mL) was added PPTS (0.5 eq, 16.56 g, 66.00 mmol) and DHP (16.55 g, 145.17 mmol). The mixture was stirred at room temperature for 18h. An additional portion of PPTS (8.00 g, 31.87 mmol) was added and the solution stirred for a further 4 h. The reaction mixture was washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded **103a** (12.00 g, 75.00 mmol, 57%) as a colourless oil, and the diprotected alcohol **103b** (9.31 g, 38.15 mmol, 29%) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[123]

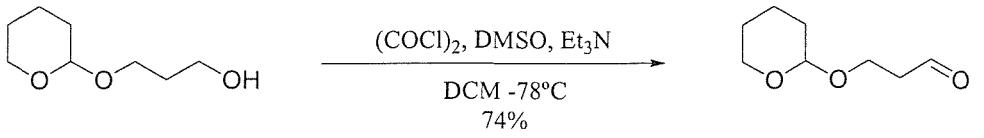
Data for the title compound **103a**:

ν_{max}/cm^{-1} (neat):	3511br. m, 2941s, 2870s, 1441m, 1123s, 1077s, 990s.
δ_H (400MHz, $CDCl_3$):	4.60 (1H, t, *J* 4.2Hz, O-C*H*-O), 3.90-3.65 (4H, m, 2 x OCH_2), 3.60-3.40 (2H, m, OCH_2), 2.75 (1H, app. s, O*H*), 1.90-1.40 (8H, CH_2) ppm.
δ_C (100MHz, $CDCl_3$):	99.2 (1, O-*C*H-O), 66.4 (2, *C*H_2OH), 62.6 (2, OCH_2), 61.7 (2, OCH_2), 32.0 (2), 30.7 (2), 25.7 (2), 19.7 (2) ppm.
LRMS (CI):	161 ([M+H]$^+$, 7%), 102 (22%), 85 (100%) amu.

Data for the minor compound **103b**:

ν_{max}/cm^{-1} (neat):	2940s, 2869m, 1440w, 1122s, 1076s, 1034s.
δ_H (300MHz, $CDCl_3$):	4.60 (2H, t, *J* 3.3Hz, 2 x O-C*H*-O), 3.90-3.70 (4H, m, 2 x OCH_2), 3.50-3.40 (4H, m, 2 x OCH_2), 1.95-1.45 (14H, m, 7 x CH_2) ppm.
δ_C (75MHz, $CDCl_3$):	100.0 (1, 2 x O-*C*H-O), 64.8 (2, *C*H_2O), 64.5 (2, *C*H_2O), 62.4 (2, 2 x OCH_2), 30.8 (2, 2 x *C*H_2), 30.2 (2, CH_2), 25.6 (2, 2 x *C*H_2), 19.7 (2, 2 x CH_2) ppm.
LRMS (CI):	178 ($[M+NH_4]^+$, 4%), 161 (28%), 102 (48%), 85 (100%) amu.

Synthesis of 3-(tetrahydro-2H-2-pyranyloxy)-1-propanal **104**[53]



$C_8H_{16}O_3$
MWt: 160
103a

$C_8H_{14}O_3$
MWt: 158
104

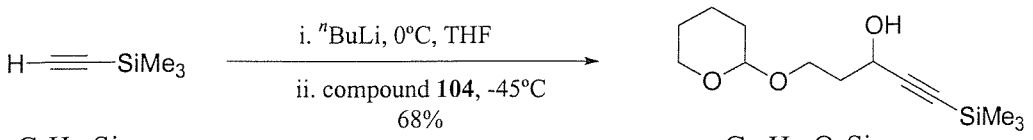
DMSO was distilled prior to use.

To a solution of oxalyl chloride (17.00 mL, 34.00 mmol) in DCM (40 mL) at –78°C and under N_2 was added DMSO (4.85 mL, 68.00 mmol) in DCM (15 mL). The mixture was stirred at –78°C for 20 min before adding alcohol **103a** (5.00 g, 31.00 mmol) in DCM (25 mL). The resulting cloudy mixture was stirred at –78°C for 1.5 h followed by addition of Et_3N (20.80 mL, 149.00 mmol). The mixture was then warmed to room temperature over 1 h and partitioned over water (80 mL). The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 1:1 Petroleum Ether:EtOAc) afforded **104** (3.62 g, 22.90 mmol, 74%) as a pale yellow oil.

Data is consistent with literature values.[124]

ν_{max}/cm^{-1} (neat):	2945m, 2873w, 1727s, 1195w, 1123s, 1072s, 1030s.
δ_H (300MHz, $CDCl_3$):	9.80 (1H, t, *J* 1.8Hz, C*H*O), 4.60 (1H, t, *J* 3.3Hz, O-C*H*-O), 4.10-4.00 (1H, m, C*H*HO), 3.85-3.70 (2H, m, CH_2O), 3.54-3.44 (1H, m, CH*H*O), 2.66 (2H, td, *J* 6.3, 1.8Hz, CH_2CO), 1.70-1.50 (6H, m, 3 x CH_2 from THP) ppm.
δ_C (75MHz, $CDCl_3$):	201.4 (0, *C*=O), 99.1 (1, O-*C*H-O), 62.6 (2, CH_2O), 60.2 (2, CH_2O), 43.9 (2, CH_2O), 30.6 (2), 25.5 (2), 19.6 (2) ppm.
LRMS (CI):	159 ($[MH]^+$, 7%), 84 (67%), 55 (100%) amu.

Synthesis of 5-(tetrahydro-2H-2-pyranyloxy)-1-trimethylsilyl-1-pentyn-3-ol **105**[54,55]



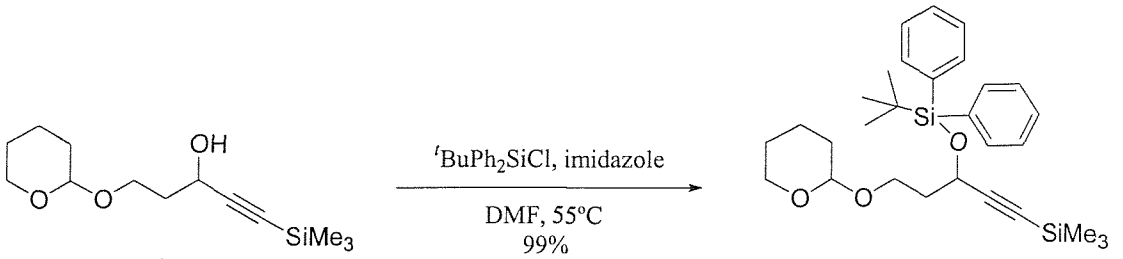
$C_5H_{10}Si$
MWt: 98

$C_{13}H_{24}O_3Si$
MWt: 256
105

To a stirred solution of trimethylsilylacetylene (3.00 mL, 21.30 mmol) in THF (12 mL) was added ^{n}BuLi (1.6 M, 11.30 mL, 18.05 mmol) at 0°C and under N_2. The mixture was stirred at 0°C for 45 min then cooled to –45°C before addition of aldehyde **104** (2.50 g, 15.80 mmol). The mixture was stirred for 45 min and warmed to room temperature. Ice-cold aqueous saturated NH_4Cl (20 mL), ether (25 mL) and water (15 mL) were successively added and the phases were separated. The aqueous phase was extracted with ether (2 x 15 mL) and the combined organic layers were washed with water (2 x 30 mL), brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded **105** (2.77 g, 10.80 mmol, 68%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3432br. m, 2946m, 2164w, 1521m, 1070m.
δ_H (300MHz, $CDCl_3$):	4.63-4.50 (2H, m, O-C*H*-O + C*H*-OH), 4.07-3.98 (1H, m, C*H*HO), 3.92-3.75 (2H, m, OCH_2-CH_2) 3.68-3.60 (1H, m, CH*H*O), 2.10-1.82 (2H, m, CH_2-CH-OH), 1.70-1.50 (7H, m, 3 x CH_2 from THP + 1 O*H*), 0.14 (9H, s, TMS) ppm.
δ_C (75MHz, $CDCl_3$):	106.5 (0, C≡*C*), 98.9 (1, O-*C*H-O), 89.2 (0, *C*≡C), 65.9 (2, *C*H_2O), 64.5 (2, *C*H_2O), 61.2 (1, *C*H-OH), 37.0 (2), 30.6 (2), 25.4 (2), 19.3 (2), 0.0 (TMS) ppm.
LRMS (CI):	239 ([M-OH]$^+$, 8%), 183 (14%), 85 (100%), 73 (25%) amu.
HRMS (ES):	Found [M+Na]$^+$: 279.1387. $C_{13}H_{24}O_3SiNa$ requires 279.1385.

Synthesis of [3-{*tert*-butyldiphenylsilyloxy}-5-(tetrahydro-2H-2-pyranyloxy)-1-pentinyl]trimethylsilane **106**[56]



$C_{13}H_{24}O_3Si$
MWt: 256
105

$C_{29}H_{42}O_3Si_2$
MWt: 494
106

To alcohol **105** (2.35 g, 9.18 mmol) in DMF (30 mL) was added imidazole (1.57 g, 23.06 mmol) followed by tert-butyldiphenylsilane chloride (2.94 mL, 11.30 mmol). The mixture was heated at 55°C for 21 h, cooled to room temperature and poured into water (40 mL). Ether (40 mL) was added to the white solution and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL) and the combined organic phases were washed with 10% aqueous sodium chloride solution (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded **106** (4.49 g, 9.09 mmol, 99%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3030w, 2857m, 2164m, 1473m, 1110s.

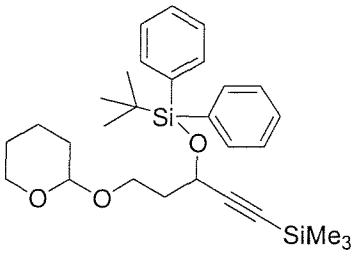
δ_H (400MHz, $CDCl_3$): 7.75-7.65 (4H, m, Ar*H*), 7.40-7.29 (6H, m, Ar*H*), 4.58-4.49 (1H, m, O-C*H*-O), 4.39 (1H, t, *J* 4.5Hz, -C*H*-OTBDPS), 3.89-3.70 (2H, m, CH_2), 3.54-3.37 (2H, m, CH_2), 2.09-1.92 (2H, m, CH_2), 1.85-1.35 (6H, m, 3 CH_2), 1.02 (9H, s, -C(CH_3)$_3$), 0.0 (9H, s, TMS) ppm.

δ_C (100MHz, $CDCl_3$): 136.4 (1, 2 x Ar), 136.2 (1, 2 x Ar), 134.0 (0, Ar), 133.8 (0, Ar), 129.8 (1, Ar), 129.7 (1, Ar), 127.8 (1, 2 x Ar), 127.6 (1, 2 x Ar), 106.2 (0, *C*≡C), 98.5 (1, O-*C*H-O), 89.8 (0, C≡*C*), 64.0 (2, *C*H_2O), 63.5 (2, *C*H_2O), 61.9 (1, -*C*H-OTBDPS), 38.8 (2), 30.8 (2), 27.3 (3, 3 x *C*H_3), 25.8 (2), 19.6 (2), 19.4 (0), -0.1 (TMS) ppm.

LRMS (CI): 411 ([M-THP group]$^+$, 32%), 339 (12%), 274 (8%), 216 (12%), 196 (24%), 155 (24%), 85 (100%) amu.

HRMS (ES): Found $[M+Na]^+$: 517.2565. $C_{29}H_{42}O_3Si_2Na$ requires 517.2560.

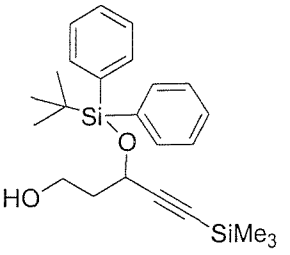
Synthesis of 3-tert-butyldiphenylsilyloxy-5-trimethylsilyl-4-pentyn-1-ol **107**[59]



$C_{29}H_{42}O_3Si_2$
MWt: 494
106

$MgBr_2.OEt_2$, Et_2O

96%



$C_{24}H_{34}O_2Si_2$
MWt: 410
107

To Magnesium turnings (0.17 g, 6.99 g-atom) in ether (2 mL) under N_2 was slowly added 1,2-dibromoethane (0.55 mL, 6.40 mmol) in ether (2 mL). The mixture was gently heated to reflux for 5 min and cooled to room temperature. The liquid phase was decanted from the residual solids and the solvent was removed by evaporation using N_2 flow to give a white/grey solid. Ether (5 mL) was added and the resulting solution was slowly added to a solution of **106** (0.688 g, 1.40 mmol) in ether (10 mL). The mixture was stirred at room temperature for 3 h and partitioned over water (15 mL). The aqueous phase was extracted with ether (3 x 20 mL). The organic layers were combined and washed with water (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **107** (0.55 g, 1.34 mmol, 96%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3451br. m, 3072w, 2976m, 2860m, 2170w, 1250m, 1112s, 909s.

δ_H (300MHz, $CDCl_3$): 7.80-7.74 (2H, m, 2 x Ar*H*), 7.74-7.68 (2H, m, 2 x Ar*H*), 7.47-7.35 (6H, m, 6 x Ar*H*), 4.57 (1H, t, *J* 5.1Hz, CH_2-C*H*-OTBDPS), 4.01-3.90 (1H, m, C*H*H-OH), 3.87-3.77 (1H, m, CH*H*-OH), 2.09-1.85 (3H, m, CH_2 + O*H*), 1.09 (9H, s, -C(CH_3)$_3$), 0.00 (9H, s, TMS) ppm.

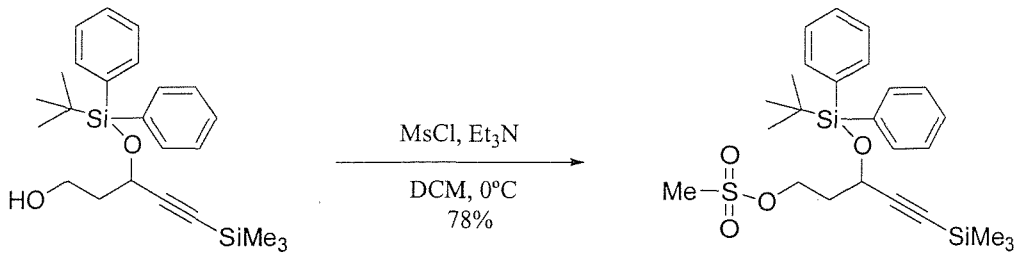
δ_C (75MHz, $CDCl_3$): 136.2 (1, 2 x Ar), 136.0 (1, 2 x Ar), 133.3 (0, Ar), 133.1 (0, Ar), 130.1 (1, Ar), 129.9 (1, Ar), 127.8 (1, 2 x Ar), 127.6 (1, 2 x Ar), 106.1 (0, *C*≡C-TMS), 90.7 (0, C≡*C*-TMS), 63.3 (1, -

*C*H-OTBDPS), 59.9 (2, *C*H_2-OH), 40.0 (2), 27.0 (3, C-(*C*H_3)$_3$), 19.4 (0), -0.2 (TMS) ppm.

LRMS (CI): 411 ([M+H]$^+$, 70%), 339 (52%), 274 (23%), 216 (44%), 196 (100%), 155 (82%), 90 (94%) amu.

HRMS (ES): Found: [M+Na]$^+$ 433.1993. $C_{24}H_{34}O_2SiNa$ requires 433.1989.

Synthesis of 3-tert-butyldiphenylsilyloxy-5-trimethylsilyl-4-pentyn-1-ylmethanesulfinate **108**[60]



$C_{24}H_{34}O_2Si_2$
MWt: 410
107

$C_{25}H_{36}O_4Si_2S$
MWt: 488
108

To alcohol **107** (0.185 g, 0.45 mmol) in DCM (5 mL) was added MsCl (0.04 mL, 0.49 mmol) and Et_3N (0.10 mL, 0.72 mmol) at 0°C. The solution was stirred at 0°C for 45 min then poured into ice-water (10 mL). The aqueous phase was extracted with DCM (3 x 15 mL), the organic phases combined and washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:Ether) afforded **108** (0.171 g, 0.35 mmol, 78%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3068w, 3045w, 2958m, 2931m, 2173w, 1472m, 1363s, 1250s, 1176s, 1112s.

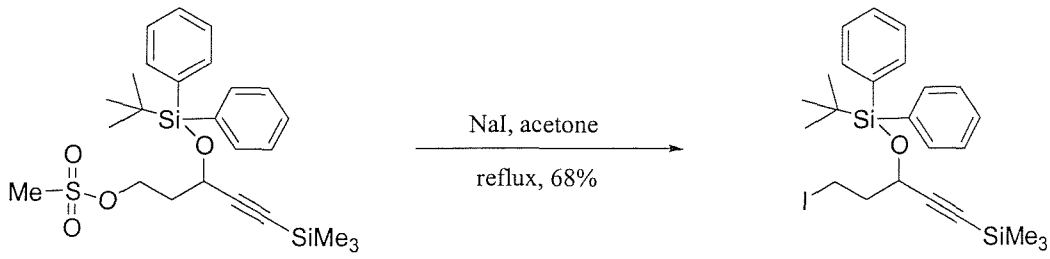
δ_H (300MHz, $CDCl_3$): 7.77-7.66 (4H, m, 4 x Ar*H*), 7.47-7.28 (6H, m, 6 x Ar*H*), 4.45 (1H, t, *J* 6.0Hz, -C*H*-OTBDPS), 4.35 (2H, t, *J* 6.4Hz, O-CH_2-CH_2), 2.85 (3H, s, SCH_3), 2.08 (2H, dt, *J* 6.4, 1.9Hz, CH_2-CH_2-CH), 1.02 (9H, s, C(CH_3)$_3$), 0.10 (9H, s, TMS) ppm.

δ_C (75MHz, $CDCl_3$): 136.2 (1, Ar), 136.0 (1, Ar), 134.9 (1, Ar), 133.4 (0, Ar), 133.2 (0, Ar), 130.1 (1, Ar), 129.9 (1, Ar), 129.8 (1, Ar), 127.9 (1, 2 x Ar), 127.6 (1, 2 x Ar), 105.1 (0, *C*≡C), 91.0 (0, C≡*C*), 66.6 (2, *C*H_2-OMs), 61.0 (1, *C*H-OTBDPS), 37.6 (2, *C*H_2), 27.0 (3, 3 x *C*H_3), 26.7 (3, *C*H_3-S), 19.4 (0, *C*(CH_3)$_3$), -0.2 (9, TMS) ppm.

LRMS (CI): 506 ($[M+NH_4]^+$, 15%), 393 (24%), 335 (15%), 296 (42%), 268 (39%), 196 (30%), 154 (35%), 139 (48%), 90 (100%) amu.

HRMS (ES): Found $[M+Na]^+$ 511.1776. $C_{25}H_{36}O_4Si_2SNa$ requires 511.1765.

Synthesis of (3-*tert*-butyldiphenylsilyloxy-5-iodo-1-butynyl)trimethylsilane **101**[61]



$C_{25}H_{36}O_4Si_2S$
MWt: 488
108

$C_{24}H_{33}IOSi_2$
MWt: 521
101

To mesylate **108** (1.07 g, 2.19 mmol) in acetone (20 mL) under N_2 was added NaI (1.31 g, 8.73 mmol). The mixture was heated at reflux for 12 h. Ether (25 mL) and water (20 mL) were added and the phases were separated. The aqueous phase was extracted with ether (2 x 15 mL) and the combined organic layers were washed with water (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **101** (0.77 g, 1.48 mmol, 68%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3070s, 3049s, 2958s, 2175m, 1470s, 1422s, 1250s, 1110s.

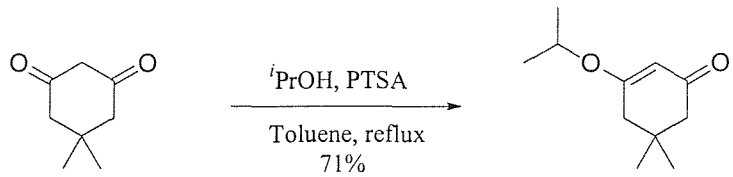
δ_H (300MHz, $CDCl_3$): 7.80-7.62 (4H, m, 4 x Ar-*H*), 7.45-7.30 (6H, m, 6 x Ar-*H*), 4.42 (1H, t, *J* 5.9Hz, -C*H*-OTBDPS), 3.35-3.25 (2H, m, -CH_2I), 2.28-2.18 (2H, m, CH_2CH_2I), 0.98 (9H, s, -C(CH_3)$_3$), -0.20 (9H, s, TMS) ppm.

δ_C (75MHz, $CDCl_3$): 136.0 (1, Ar), 135.9 (1, Ar), 135.1 (1, Ar), 134.8 (1, Ar), 133.4 (0, Ar), 133.1 (0, Ar), 129.8 (1, Ar), 129.6 (1, 2 x Ar), 127.9 (1, Ar), 127.5 (1, Ar), 127.3 (1, Ar), 105.1 (0, *C*≡C-TMS), 90.5 (C≡*C*-TMS), 64.6 (1, -*C*H-OTBDPS), 42.2 (2, *C*H_2), 27.1 (3, 2 x *C*H_3), 26.7 (3, *C*H_3), 19.3 (0, *C*(CH_3)$_3$), 0.9 (2, *C*H_2I), -0.2 (TMS) ppm.

LRMS (CI): 393 ([M-I]$^+$, 20%), 335 (82%), 296 (88%), 279 (100%), 251 (38%), 199 (48%), 154 (44%), 139 (48%), 90 (50%) amu.

HRMS (EI): Found [M]$^+$ 520.1095. $C_{24}H_{33}IOSi_2$ requires 520.1115.

Synthesis of 3-ispropoxy-5,5-dimethylcyclohex-2-en-1-one **100**[62]



$C_8H_{12}O_2$
MWt: 140
109

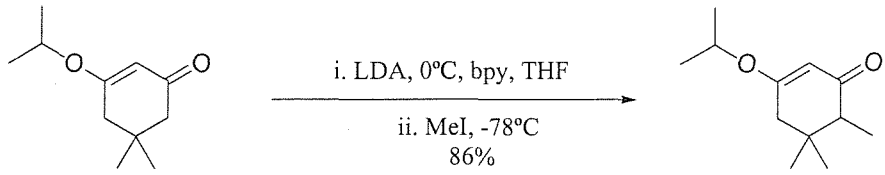
$C_{11}H_{18}O_2$
MWt: 182
100

To dimedone **109** (5.00 g, 35.71 mmol) in toluene (35 mL) was added PTSA (0.59 g, 3.12 mmol) and ^{i}PrOH (21 mL) in toluene (10 mL). The mixture was heated at reflux for 15 h. The product was extracted with ether (2 x 25 mL), then the organic layer was washed with 5% aqueous $NaHCO_3$ solution (2 x 15 mL), water (25 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded the desired product **100** (4.61 g, 25.30 mmol, 71%) as a pale yellow solid. Recrystallisation from petroleum ether afforded a white solid.

Spectral and physical characteristics are consistent with literature.[62]

MP:	38-39°C (pet. ether), lit: 42°C (pet.ether)[62]
ν_{max}/cm^{-1} (neat):	3054m, 2959m, 1709w, 1643s, 1600s, 1380s, 1265s, 1223s, 1143m.
δ_H (300MHz, $CDCl_3$):	5.35 (1H, s, -C=C*H*), 4.45 (1H, sept., *J* 5.9Hz, O-C*H*$(CH_3)_2$), 2.25 (2H, s, CH_2-CO), 2.22 (2H, s, CH_2), 1.29 (6H, d, *J* 6.0Hz, -CH(CH_3)$_2$), 1.04 (6H, s, -C(CH_3)$_2$) ppm.
δ_C (75MHz, $CDCl_3$):	199.9 (0, *C*=O), 175.4 (0, *C*=CH), 101.9 (1, C=*C*H), 71.1 (1, O-*C*H$(CH_3)_2$), 50.8 (2, *C*H_2-CO), 43.5 (2, *C*H_2), 32.6 (0), 28.4 (3, 2 x *C*H_3), 21.6 (3, 2 x *C*H_3) ppm.
LRMS (CI):	183 ([M+H]$^+$, 100%), 142 (8%), 125 (17%), 58 (8%) amu.

Synthesis of 3-isopropoxy-5,5,6-trimethyl-2-cyclohex-2-ene **110**[63]



$C_{11}H_{18}O_2$
MWt: 182
100

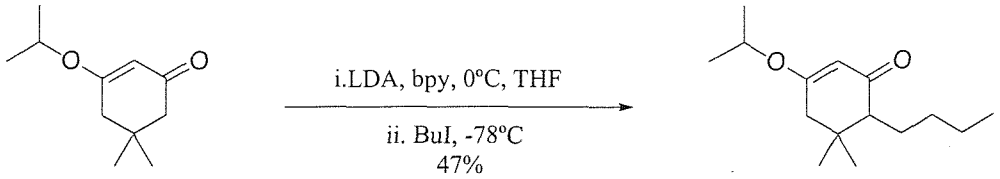
$C_{12}H_{20}O_2$
MWt: 196
110

MeI was distilled and diisopropylamine was distilled over $CaCl_2$ prior to use.

To a solution of diisopropylamine (0.27 mL, 1.92 mmol) and bipyridyl (2.0 mg, 0.012 mmol) in THF (5 mL) at 0°C and under N_2 was added ^{n}BuLi (1.44 M, 1.13 mL, 1.63 mmol). After the resulting red solution had been stirred for 15 min at 0°C, compound **100** (0.25 g, 1.37 mmol) in THF (5 mL) was added. A further 30 min stirring at 0°C was followed by rapid addition of MeI (2.02 g, 14.25 mmol); the solution turned yellow. The reaction mixture was warmed to room temperature and a white precipitate formed. After 40 min, the mixture was poured into saturated aqueous $NaHCO_3$ solution (30 mL) and the product was extracted with petroleum ether (3 x 15 mL). The organic layers were combined and washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded **110** (0.23 g, 1.17 mmol, 86%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	2975m, 1656s, 1611s, 1465m, 1377m, 1156m.
λ_{max}/nm (ε_{max}, MeOH):	310 (2000).
δ_H (300MHz, $CDCl_3$):	5.23 (1H, s, C=C*H*), 4.40 (1H, sept, *J* 6.4Hz, OC*H*$(CH_3)_2$), 2.30-2.20 (2H, m, CH_2), 2.15 (1H, q, *J* 7.0Hz, C*H*-CH_3), 1.27 (3H, d, *J* 6.1Hz, CH_3-CH-C*H*$_3$), 1.26 (3H, d, *J* 6.1Hz, C*H*$_3$-CH-CH_3), 1.06 (3H, d, *J* 7.2Hz, CH-C*H*$_3$), 1.05 (3H, s, C-C*H*$_3$), 0.90 (3H, s, C-C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	202.6 (0, *C*=O), 173.7 (0, *C*=CH), 101.3 (1, C=*C*H), 70.9 (1, O*C*H$(CH_3)_2$), 51.1 (1, CO-*C*H-CH_3), 43.3 (2, CH_2), 35.3 (0), 28.9 (3, 2 x CH_3), 21.7 (3), 21.6 (3), 10.3 (3) ppm.
LRMS (CI):	197 ([M+H]$^+$, 100%), 156 (8%), 139 (22%), 58 (10%) amu.
HRMS (EI):	Found [M]$^+$: 196.1461. $C_{12}H_{20}O_2$ requires 196.1463.

Synthesis of 6-butyl-3-isopropoxy-5,5-dimethyl-2-cyclohex-2-enone **111**[63]



$C_{11}H_{18}O_2$
MWt: 182
100

$C_{15}H_{26}O_2$
MWt: 238
111

Diisopropylamine was dried over $CaCl_2$ prior to use.

To a solution of diisopropylamine (0.16 mL, 1.15 mmol) and bipyridyl (2.0 mg, 0.012 mmol) in THF (5 mL) at 0°C and under N_2, ^{n}BuLi (1.44 M, 0.67 mL, 0.97 mmol) was added dropwise. After the red solution had been stirred at 0°C for 15 min, compound **100** (0.15 g, 0.82 mmol) in THF (5 mL) was added dropwise. After 30 min stirring at 0°C, the solution was cooled to –78°C and BuI (0.97 mL, 8.53 mmol) was added. The solution was then warmed to room temperature. After 14 h stirring at room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and the product was extracted with petroleum ether (3 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel 2:1 Petroleum Ether:EtOAc) afforded compound **111** (0.09 g, 0.38 mmol, 47%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 2956m, 2871m, 1654s, 1607s, 1466m, 1376s, 1220s, 1109m.

λ_{max}/nm (ε_{max}, MeOH): 309 (2452).

δ_H (300MHz, $CDCl_3$): 5.21 (1H, s, C=C*H*), 4.40 (1H, sept, *J* 6.1Hz, O-C*H*$(CH_3)_2$), 2.30 (1H, d, *J* 17.5Hz, C*H*H), 2.05 (1H, d, *J* 17.6Hz, CH*H*), 1.85 (1H, t, *J* 6.3Hz, C*H*$(CH_2)_3$), 1.50-1.20 (6H, m, 3 x CH_2), 1.25 (6H, d, *J* 6.1Hz, -CH(CH_3)$_2$), 1.04 (3H, s, CH_3), 0.98 (3H, s, CH_3), 0.85 (3H, t, *J* 6.6Hz, $(CH_2)_3$-CH_3) ppm.

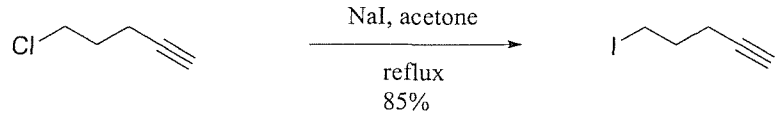
δ_C (75MHz, $CDCl_3$): 203.1 (0, *C*=O), 173.2 (0, *C*=CH), 100.9 (1, C=*C*H), 70.7 (1, O-*C*H$(CH_3)_2$), 57.2 (1, -*C*H-CO), 41.9 (2), 35.0 (0), 31.1 (2),

28.7 (3), 26.3 (2), 25.1 (3), 23.1 (2), 21.6 (2 x CH_3), 14.1 (3) ppm.

LRMS (CI): 239 ($[M+H]^+$, 100%), 181 (20%), 125 (7%), 58 (20%) amu.

HRMS (EI): Found $[M]^+$: 238.1930. $C_{15}H_{26}O_2$ requires 238.1930.

Synthesis of 5-iodopentyn-1-yl **279**



C_5H_7Cl
Mol Wt: 102.56

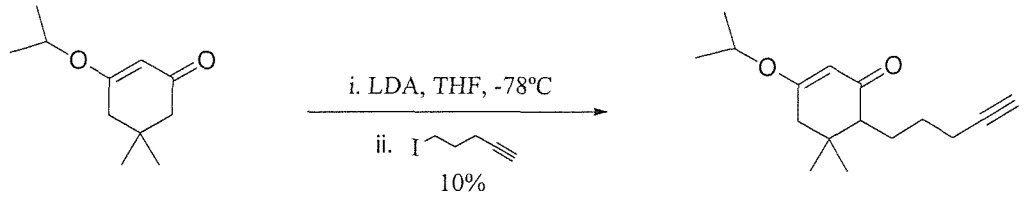
C_5H_7I
Mol Wt: 194
279

Chloropentynyl (1.00 g, 9.75 mmol) and sodium iodide (2.92 g, 19.50 mmol) were placed in acetone (30 mL), and the resulting mixture was heated at reflux overnight. Acetone was then removed *in vacuo* and water (30 mL) was added. The solution was extracted with petroleum ether (2 x 20 mL); the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 40% ether in petroleum ether) afforded compound **279** (1.608 g, 8.27 mmol, 85%) as a colourless oil.

Spectral and physical characteristics are consistent with literature.[125]

ν_{max}/cm^{-1} (neat):	3295s, 2940m, 2909m, 2118m, 1427m, 1256w, 1221m.
δ_H (300MHz, $CDCl_3$):	3.32 (2H, t, *J* 6.6Hz, C*H*$_2$-I), 2.31 (2H, td, *J* 6.6, 2.6Hz, ICH$_2$-C*H*$_2$-CH$_2$-), 2.00 (3H, m, C*H*$_2$ + C≡*H*) ppm.
δ_C (75MHz, $CDCl_3$):	82.2 (0), 69.6 (1), 31.9 (2), 19.6 (2), 5.3 (2) ppm.
LRMS (CI):	194 ([M]$^+$, 43%), 155 (7%), 127 (18%), 67 (100%) amu.

Synthesis of 6-pentyn-1-yl-3-isopropoxy-5,5-dimethyl-2-cyclohexen-2-one **112**[63]



$C_{11}H_{18}O_2$
Mol Wt: 182
100

$C_{16}H_{24}O_2$
Mol Wt: 248
112

Diisopropylamine was distilled prior to use.

To a solution of diisopropylamine (0.27 mL, 1.92 mmol) in THF (2 mL) at –78°C and under N_2 was added ^{n}BuLi (2.30 M, 0.71 mL, 1.64 mmol). The mixture was stirred at –78°C for 20 min, and the ketone **100** (0.250 g, 1.37 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 20 min at –78°C, and the iodopentynyl **279** was added neat (0.292 g, 1.51 mmol). The mixture was allowed to reach room temperature and left to stir overnight. The solution was then poured into saturated aqueous solution of $NaHCO_3$ (10 mL) and product was extracted with ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:Ether) afforded compound **112** (0.034 g, 0.14 mmol, 10%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3295.5w, 2961.0m, 2115.5w, 1651.4s, 1606.5s, 1379.2s, 1219.0s, 1108.5m.

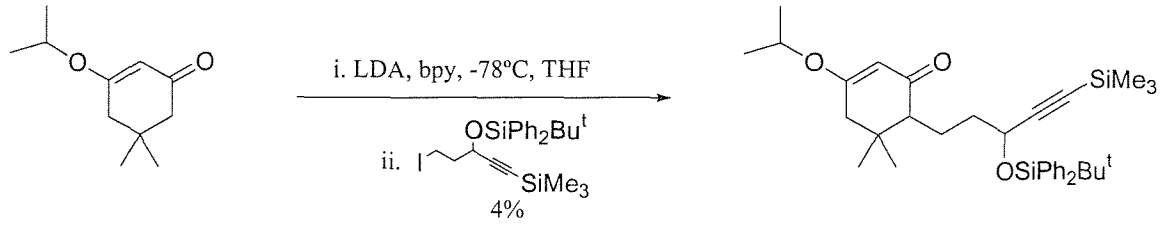
δ_H (300MHz, $CDCl_3$): 5.20 (1H, s, C=C*H*), 4.40 (1H, sept, *J* 5.8Hz, $(CH_3)_2$-C*H*-O), 2.39-2.10 (4H, m, 2 x CH_2), 1.94-1.88 (1H, m, -C*H*-$(CH_2)_3$), 1.80-1.45 (5H, m, 2 x CH_2 + C≡C*H*), 1.28 (3H, d, *J* 5.8Hz, $CH(CH_3)_2$), 1.27 (3H, d, *J* 5.8Hz, $CH(CH_3)_2$), 1.05 (3H, s, CH_3), 0.97 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 202.6 (0, *C*=O), 173.4 (0, *C*=CH), 100.9 (1, C=*C*H), 84.5 (0, -*C*≡CH), 70.9 (1, $(CH_3)_2$-*C*H-O), 68.5 (1, -C≡*C*H), 56.5 (1, *C*H-CO), 42.2 (2), 35.2 (0), 28.7 (3), 27.5 (2), 25.3 (2), 24.7 (3), 21.6 (2 x CH_3), 18.5 (2) ppm.

LRMS (CI): 249 ($[M+H]^+$, 100%), 182 (22%), 167 (12%), 125 (10%) amu.

HRMS (ES) Found $[M+Na]^+$: 271.1666. $C_{16}H_{24}O_2Na$ requires 271.1668.

Synthesis of 6-[3(*tert*-butyl-diphenyl-silanyloxy)-5-trimethylsilanyl-pent-4-ynyl]-3-isopropoxy-5,5-dimethyl-cyclohex-2-enone **99**[63]



$C_{11}H_{18}O_2$
Mol Wt: 182
100

$C_{35}H_{50}O_3Si_2$
Mol Wt: 574
99

Diisopropylamine was distilled prior to use.

To a solution of diisopropylamine (0.27 mL, 1.92 mmol) and bipyridyl (2.0 mg, 0.012 mmol) in THF (2 mL) at –78°C and under N_2 was added ^{n}BuLi (2.30 M, 0.71 mL, 1.64 mmol). After the red solution had been stirred for 20 min, the ketone **100** (0.250 g, 1.37 mmol) in THF (5 mL) was added. The mixture was stirred at –78°C for 0.5 h, and the iodo compound **101** (0.712 g, 1.37 mmol) in THF (3 mL) was added. The mixture was then allowed to reach room temperature and left overnight. It was then poured into a saturated aqueous $NaHCO_3$ solution (10 mL) and ether was added (10 mL). The phases were separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 5% ether in petroleum ether) afforded compound **99** (0.030 g, 0.05 mmol, 4%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3072w, 2959s, 2931s, 2173w, 1653s, 1607s, 1472m, 1220s, 1110s

δ_H (300MHz, $CDCl_3$): 7.77 (2H, d, with fine splitting, *J* 7.6Hz, 2 x Ar*H*), 7.68 (2H, d, *J* 6.6Hz, 2 x Ar*H*), 7.44-7.34 (6H, m, 6 x Ar*H*), 5.21 (1H, s, C=C*H*), 4.40 (1H, sept, *J* 6.3Hz, O-C*H*$(CH_3)_2$), 4.30 (1H, t, *J* 5.9Hz, C*H*-OTBDPS), 2.35-2.22 (1H, m, C*H*H-C=C), 2.13-2.02 (1H, m, CH*H*-C=C), 1.90-1.75 (2H, m, CH_2), 1.75-1.40 (3H, m, C*H* + CH_2), 1.30 (3H, d, *J* 5.9Hz, CH$(CH_3)_2$), 1.28

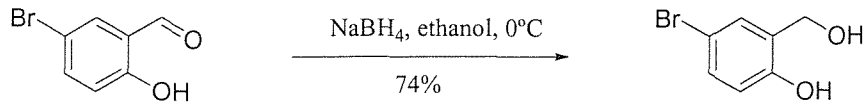
(3H, d, *J* 5.9Hz, CH(CH_3)$_2$), 1.08 (12H, s, Si-C(CH_3)$_3$ + C-CH_3), 0.92 (3H, s, CH_3), 0.2 (9H, s, TMS) ppm.

δ_C (75MHz, $CDCl_3$): 202.9 (0, *C*=O), 173.4 (0, *C*=CH), 136.4 (1, 2 x Ar), 136.2 (1, 2 x Ar), 134.1 (0, Ar), 133.9 (0, Ar), 129.9 (1, Ar), 129.7 (1, Ar), 127.8 (1, 2 x Ar), 127.6 (1, 2 x Ar), 107.2 (0, *C*≡C-TMS), 100.9 (1, C=*C*H), 89.5 (0, C≡*C*-TMS), 70.9 (1, O-*C*H(CH_3)$_2$), 64.5 (1, -*C*H-OTBDPS), 57.0 (1, *C*H-CO), 42.0 (2), 37.4 (2), 35.3 (0), 28.8 (3), 27.2 (3, 3 x CH_3), 25.1 (3, 2 x CH_3), 22.2 (2), 21.8 (3), 19.6 (0), 0.0 (TMS) ppm.

LRMS (ES): 575.5 ([M+H]+, 5%), 208 (5%), 168 (9%), 153 (7%), 127 (100%) amu.

HRMS (ES) Found $[M+Na]^+$: 597.3206. $C_{35}H_{50}O_3Si_2Na$ requires 597.3191.

Synthesis of 4-bromo-2-hydroxymethylphenol **189**



$C_7H_5BrO_2$
Mol Wt: 201
188

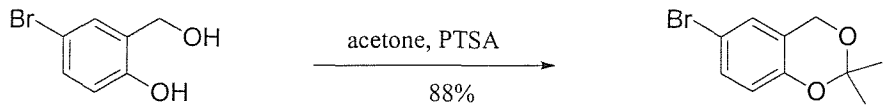
$C_7H_7BrO_2$
Mol Wt: 203
189

To the bromosalicaldehyde **188** (10.00 g, 49.80 mmol) in ethanol (26 mL) at 0°C was slowly added $NaBH_4$ (0.94 g, 24.86 mmol) in water (5 mL plus some drops of ethanol). After the resulting yellow solution had been stirred for 30 min at 0°C, acetone (30 mL) was added and the mixture was stirred at room temperature for 15 min. The solvent was removed *in vacuo* and the residue was diluted with ether (50 mL) and aqueous HCl (1 M, 72 mL) was added. The product was extracted with ether (50 mL), the organic layer was washed with water (25 mL) dried over $MgSO_4$, filtered and concentrated to afford compound **189** (7.45 g, 36.69 mmol, 74%) as a colourless oil. No further purification was needed.

Spectral and physical characteristics are consistent with literature.[126]

Mp:	106-108°C (pet/ether); literature: 105-107°C.
ν_{max}/cm^{-1} (neat):	3147br. s, 2975m, 1637w, 1403m, 1301m, 704m.
λ_{max}/nm (ε_{max}, MeOH):	282 (12810), 226 (31950).
δ_H (300MHz, $CDCl_3$):	9.70 (1H, br. s, O*H*), 7.41 (1H, d, *J* 2.2Hz, Ar-*H*), 7.19 (1H, dd, *J* 2.6, 2.2Hz, Ar-*H*), 6.71 (1H, d, *J* 8.5Hz, Ar-*H*), 5.15 (1H, br. s, CH_2-O*H*), 4.45 (2H, s, C*H*$_2$-OH) ppm.
δ_C (75MHz, $CDCl_3$):	153.3 (0, *C*-OH), 131.6 (0, *C*-Br), 129.7 (1, ArH), 129.4 (1, ArH), 116.6 (1, ArH), 110.1 (0, *C*-CH_2OH), 57.7 (2, *C*H_2OH) ppm.
LRMS (CI):	202 ([M-H]$^+$, 6%), 186 (60%), 107 (94%), 77 (100%) amu.

Synthesis of 6-bromo-2,2-dimethyl-4H-1,3-benzodioxin **190**[88]



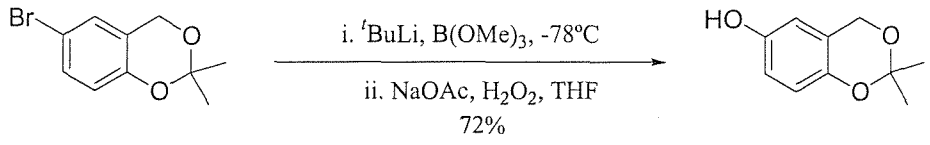
$C_7H_7BrO_2$
Mol Wt: 203
189

$C_{10}H_{11}BrO_2$
Mol Wt: 243
190

To diol **189** (1.41 g, 6.95 mmol) in acetone (50 mL) was added PTSA (0.67 g, 3.67 mmol) and molecular sieves (4 Å). The resulting solution was then stirred at room temperature for 36 h. Solid $NaHCO_3$ was added, the solvent was removed *in vacuo* and ether was added (50 mL). The solid residue was filtered off and the filtrate was concentrated. Purification by column chromatography (silica gel, DCM) afforded compound **190** (1.49 g, 6.13 mmol, 88%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	2994s, 2942m, 1605w, 1581s, 1484s, 1384s, 1148s.
λ_{max}/nm (ε_{max}, MeOH):	284 (10620), 225 (32320).
δ_H (300MHz, $CDCl_3$):	7.25 (1H, dd, *J* 8.1, 2.2Hz, Ar-*H*), 7.11 (1H, d, *J* 2.4Hz, Ar-*H*), 6.70 (1H, d, *J* 8.8Hz, Ar-*H*), 4.81 (2H, s, -CH_2-), 1.53 (6H, s, 2 x CH_3) ppm.
δ_C (75MHz, $CDCl_3$):	150.5 (0, Ar *C*-O), 131.2 (1, ArH), 127.5 (1, ArH), 121.5 (0, *C*-Br), 119.1 (1, ArH), 112.6 (0, Ar *C*-CH_2O), 99.9 (0, O_2-*C*-$(CH_3)_2$), 60.5 (2, CH_2-O-), 24.8 (3, 2 x CH_3) ppm.
LRMS (CI):	244 ($[M+H]^+$, 60%), 202 (84%), 186 (100%), 158 (46%), 122 (94%), 77 (70%) amu.
HRMS (EI):	Found $[M]^+$: 241.9944. $C_{10}H_{11}O_2{}^{79}Br$ requires: 241.9942

Synthesis of 2,2-dimethyl-4H-1,3-benzodioxin-6-ol **191**



$C_{10}H_{11}BrO_2$
Mol Wt: 243
190

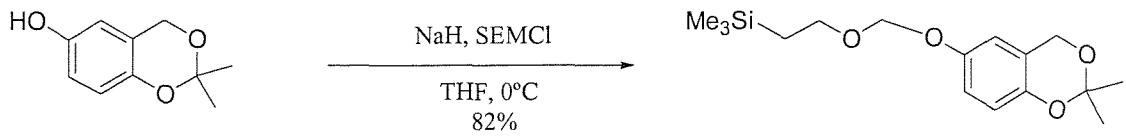
$C_{10}H_{12}O_3$
Mol Wt: 180
191

^{t}BuLi (1.12 M, 4.70 mL, 5.26 mmol) was added to the bromoacetal **190** (0.640 g, 2.63 mmol) in THF (7 mL) under N_2 and at –78°C. The resulting yellow mixture was stirred at –78°C for 0.5 h, then $B(OMe)_3$ (26.30 mmol, 2.99 mL) was added neat and the solution was allowed to reach room temperature and stirred overnight. NaOAc (3 M, 4 mL) and H_2O_2 (30% aqueous, 4 mL) were added. The mixture was then stirred at room temperature for 2 h, and heated at 50°C for 1 h. NaCl was added in excess, then DCM (30 mL) and water (30 mL). Phases were separated and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:Ether) afforded compound **191** (0.340 g, 1.89 mmol, 72%) as a pale yellow oil.

Data is consistent with literature values.[127]

ν_{max}/cm^{-1} (neat):	3395br. s, 2992w, 1499s, 1375m, 1283s, 1139s, 873s
δ_H (300MHz, $CDCl_3$):	6.71-6.63 (2H, m, Ar-*H*), 6.44 (1H, d, *J* 2.2Hz, Ar-*H*), 5.40 (1H, br. s, Ar-O*H*), 4.72 (2H, s, CH_2), 1.53 (6H, s, 2 x CH_3) ppm.
δ_C (75MHz, $CDCl_3$):	149.4 (0, *C*-OH), 145.0 (0, *C*-O-), 120.3 (0, *C*-CH_2O), 118.0 (1, ArH), 115.5 (1, ArH), 111.0 (1, ArH), 99.5 (0, O_2-*C*-$(CH_3)_2$), 61.0 (2, CH_2O), 24.7 (3, 2 x CH_3) ppm.
LRMS (CI):	180 ([M]$^+$, 14%), 140 (100%), 123 (46%), 94(18%) amu.

Synthesis of (2-{[2,2-dimethyl-4H-1,2-benzodioxin-6-yloxy]methoxy}-ethyl)(trimethyl)silane **192**[89]



$C_{10}H_{12}O_3$
Mol Wt: 180
191

$C_{16}H_{26}O_4Si$
Mol Wt: 310
192

NaH was preliminary washed with petroleum ether.

NaH (0.160 g, 4.01 mmol) was suspended in THF (5 mL) at 0°C and under N_2. The phenol **191** (0.601 g, 3.34 mmol) in THF (20 mL) was added and the resulting mixture was stirred at 0°C for 0.5 h. SEMCl (0.77 mL, 4.34 mmol) was then added neat and the mixture was stirred at 0°C for 1 h. Water (7 mL) was added to quench the reaction, the phases were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 5:1 Petroleum Ether:Ether) afforded compound **192** (0.853 g, 2.75 mmol, 82%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 2993s, 2952s, 1618w, 1497s, 1384s, 1266s, 1142s, 1010s.

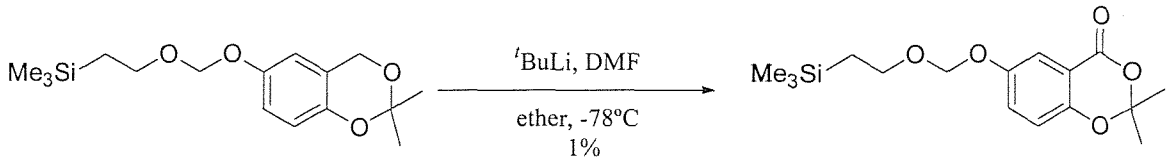
δ_H (300MHz, $CDCl_3$): 6.85-6.65 (3H, m, Ar-*H*), 5.12 (2H, s, O-C*H*$_2$-O), 4.81 (2H, s, =C-C*H*$_2$-O), 3.75 (2H, t, *J* 5.3Hz, CH_2-C*H*$_2$-O), 1.51 (6H, s, 2 x C*H*$_3$), 1.00-0.89 (2H, m, TMS-C*H*$_2$), 0.10 (9H, s, TMS) ppm.

δ_C (75MHz, $CDCl_3$): 151.3 (0, *C*-OSEM), 146.0 (0, *C*-O), 120.0 (0, *C*-CH_2O), 117.9 (1, ArH), 117.0 (1, ArH), 112.2 (1, ArH), 99.4 (0, O_2-*C*-$(CH_3)_2$), 93.8 (2, O-*C*H_2-O), 65.1 (2, *C*H_2O), 61.1 (2, *C*H_2O), 24.8 (3, 2 x *C*H_3), 18.3 (2, *C*H_2-TMS), -1.2 (TMS) ppm.

LRMS (CI): 310 ([M]+, 2%), 270 (100), 253 (44%), 211 (12%), 194 (44%), 131 (10%), 90 (86%) amu.

HRMS (EI): Found $[M]^+$: 310.1602. $C_{16}H_{26}O_4Si$ requires 310.1600.

Synthesis of 2,2-dimethyl-6-(2-trimethylsilanyl-ethoxymethoxy)-benzo[1,3]dioxin-4-one **211**



$C_{16}H_{26}O_4Si$
Mol Wt: 310
192

$C_{16}H_{24}O_5Si$
Mol Wt: 324
211

To compound **192** (0.500 g, 1.61 mmol) in ether (25 mL) at –78°C and under N_2 was added ^{t}BuLi (1.12 M, 1.58 mL, 1.77 mmol). The solution was stirred at –78°C for 2 h and DMF (0.15 mL, 1.93 mmol) was added. The mixture was warmed to room temperature and left overnight. It was then washed with water (2 x 15 mL), brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 5% ether in petroleum ether) gave compound **211** (0.022 g, 0.07 mmol, 1%), while starting material was recovered.

ν_{max}/cm^{-1} (neat): 3054m, 2986w, 1736w, 1607w, 1422m, 1237s, 896m, 742s.

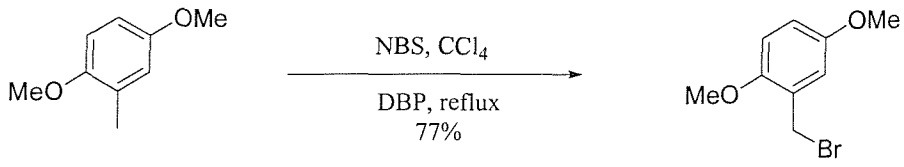
δ_H (300MHz, $CDCl_3$): 7.56 (1H, d, *J* 2.3Hz, Ar-*H*), 7.29-7.19 (1H, m, Ar-*H*), 6.90 (1H, d, *J* 8.9Hz, Ar-*H*), 5.18 (2H, s, O-C*H*$_2$-O), 3.75 (2H, t, *J* 5.6Hz, CH_2-C*H*$_2$-O), 1.71 (6H, s, 2 x C*H*$_3$), 0.95 (2H, t, *J* 5.7Hz, C*H*$_2$-TMS), 0.0 (9H, s, TMS) ppm.

δ_C (75MHz, $CDCl_3$): 161.2 (0, O-*C*=O), 152.7 (0, *C*-OSEM), 150.9 (0, *C*-O-C=O), 125.8 (1, ArH), 118.3 (1, ArH), 115.7 (1, ArH), 114.0 (0, C=C-*C*-O), 106.5 (0, O_2-*C*$(CH_3)_2$), 93.5 (2, O-*C*H_2-O), 66.6 (2, *C*H_2O), 25.9 (3, 2 x *C*H_3), 18.2 (2, TMS-*C*H_2), -1.4 (TMS) ppm.

LRMS (CI): 342 ([M+NH_4]$^+$, 10%), 325 ([M+H]$^+$, 100%), 267 (36%), 225 (64%), 208 (74%), 90 (47%), 73 (78%) amu.

HRMS (ES): Found [M+Na]$^+$: 347.1283. $C_{16}H_{24}O_5SiNa$ requires 347.1285.

Synthesis of 2-(bromomethyl)-1,4-dimethoxybenzene **218**[97]



$C_9H_{12}O_2$
Mol Wt:152
217

$C_9H_{11}O_2Br$
Mol Wt: 231
218

NBS was recrystallised from water prior to use.

Dimethoxytoluene **217** (2.00 g, 13.14 mmol), NBS (3.51 g, 19.71 mmol) and dibenzoylperoxide (0.159 g) were placed in CCl_4 (40 mL). The resulting solution was heated at reflux for 3 h. The succinimide was filtered off and the filtrate was concentrated *in vacuo*. Petroleum ether was added and a precipitate formed. Recrystallisation from petroleum ether gave the desired product **218** (2.33 g, 10.12 mmol, 77%) as a white solid.

Spectral and physical characteristics are consistent with literature.[128]

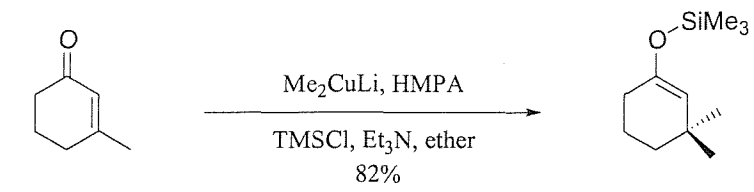
ν_{max}/cm^{-1} (neat): 1612w, 1493s, 1280m, 1224s, 1044s.

δ_H (300MHz, $CDCl_3$): 6.92 (1H, app, s, Ar-*H*), 6.85-6.82 (2H, m, Ar-*H*), 4.55 (2H, s, CH_2-Br), 3.87 (3H, s, O-CH_3), 3.78 (3H, s, O-CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 153.5 (0, *C*-OMe), 151.8 (0, *C*-OMe), 127.0 (0, *C*-CH_2Br), 116.5 (1, ArH), 115.2 (1, ArH), 112.3 (1, ArH), 56.3 (3, O-CH_3), 55.9 (3, O-CH_3), 29.1 (2, CH_2-Br) ppm.

LRMS (CI): 302 (72%), 230 ($[M]^+$, 12%), 165 (42%), 151 ($[M-Br]^+$, 100%), 121 (60%) amu.

Synthesis of 3,3-dimethyl-1-cyclohexenyl-(1,1,1-trimethylsilyl)ether **129**[78,79]



$C_7H_{10}O$
Mol Wt: 110
152

$C_{11}H_{22}OSi$
Mol Wt: 198
129

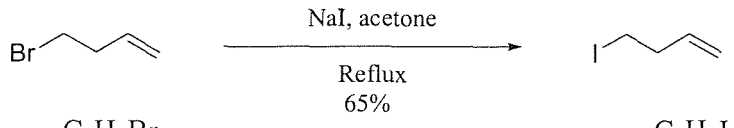
Triethylamine was dried over CaH_2 prior to use.

To a slurry of copper iodide (7.600 g, 40.00 mmol) in ether (40 mL) at 0°C and under N_2 was added MeLi (1.6 M, 45 mL, 72.00 mmol). After complete addition, 3-methyl-2-cyclohexen-1-one **152** (2.20 g, 20.00 mmol) was added. After the resulting solution had been stirred for 15 min at 0°C, TMSCl (6.1 mL), Et_3N (7.6 mL) and HMPA (3.8 mL) were added. The yellow solution was then stirred at room temperature for 1 h. Petroleum ether was added (120 mL), the mixture was washed with 5% aqueous HCl solution (2 x 50 mL), 5% aqueous $NaHCO_3$ solution (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc), gave the desired compound **129** (3.23 g, 16.31 mmol, 82%) as a colourless oil.

Spectral and physical characteristics are consistent with literature.[129]

ν_{max}/cm^{-1} (neat):	2955s, 1668s, 1356.s, 1247s, 1209s, 1138s.
δ_H (300MHz, $CDCl_3$):	4.62 (1H, s, C=C*H*), 1.95 (2H, t, *J* 6.2Hz, CO-CH_2), 1.72-1.62 (2H, m, CO-CH_2-CH_2), 1.38-1.30 (2H, m, -CH_2-C$(CH_3)_2$), 0.96 (6H, s, 2 x CH_3), 0.2 (9H, s, TMS) ppm.
δ_C (75MHz, $CDCl_3$):	148.9 (0, *C*=CH), 116.0 (1. C=*C*H), 37.1 (2, CO-*C*H_2), 31.9 (0), 30.7 (3, 2 x *C*H_3), 30.0 (2, *C*H_2), 20.0 (2, *C*H_2), 0.4 (TMS) ppm.
LRMS (CI):	199 ($[M+H]^+$, 100%), 183 (78%), 90 (32%), 73 (25%) amu.

Synthesis of 4-iodo-1-butene **160**



C_4H_7Br
Mol Wt: 135

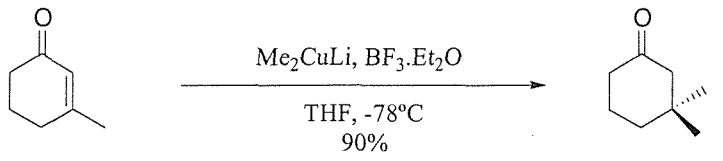
C_4H_7I
Mol Wt: 182
160

Prepared following the procedure as desribed by Fry and Hoarau.[130] Thus, a solution of 4-bromo-1-butene (2.00 g, 14.81 mmol) and sodium iodide (4.44 g, 29.63 mmol) in dry acetone (50 mL) was refluxed for 20 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was distilled and the residual yellow oily solid was taken up in water (25 mL). The aqueous solution was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and distilled at atmospheric pressure to remove ether and leave the desired product **160** (1.75 g, 9.63 mmol, 65%) as a brown oil.

Data was consistent with literature values.[131]

ν_{max}/cm^{-1} (neat):	3079m, 2977m, 1639m, 1426m, 1248s, 1179m, 920s.
δ_H (300MHz, $CDCl_3$):	5.85-5.69 (1H, m, C=C*H*), 5.17-5.08 (2H, m, =CH_2), 3.20 (2H, t, *J* 7.3Hz, CH_2I), 2.63 (2H, app.q, *J* 7.4Hz, CH_2CH_2I) ppm.
δ_C (75MHz, $CDCl_3$):	137.0 (1, CH_2=*C*H), 117.2 (2, *C*H_2=CH), 37.8 (2, CH_2*C*H_2I), 4.9 (2, *C*H_2CH_2I) ppm.
LRMS (EI):	182 ([M]$^+$, 6%), 127 (7%), 84 (20%), 55 (100%) amu.

Synthesis of 3,3-dimethylcyclohexane **155**[78]



$C_7H_{10}O$
Mol Wt: 110
152

$C_8H_{14}O$
Mol Wt: 126
155

$BF_3.Et_2O$ was distilled prior to use.

To a slurry of CuI (2.59 g, 13.62 mmol) in THF (30 mL) at –78°C and under N_2 was added MeLi (1.6 M, 17.02 mL, 27.24 mmol). The mixture was allowed to warm to room temperature until homogeneous (colourless) and was cooled again to –78°C. $BF_3.Et_2O$ (3.45 mL, 27.24 mmol) was then added. Ketone **152** (1.50 g, 13.62 mmol) was added neat and the reaction mixture was stirred for 1.5 h. It was then quenched with aqueous NH_4OH/ aqueous saturated NH_4Cl solution (10:90, 15 mL). The phases were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 40% ether in petroleum ether) afforded compound **155** (1.54 g, 12.26 mmol, 90%) as a colourless oil.

Data is consistent with literature values.[129]

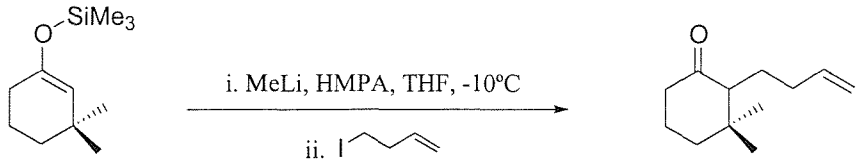
ν_{max}/cm^{-1} (neat): 2936w, 2860w, 1711s, 1446w, 1124w.

δ_H (300MHz, $CDCl_3$): 2.21 (2H, t, *J* 6.6Hz, CH_2-CO), 2.08 (2H, s, CH_2), 1.85 (2H, app.quin, *J* 6.4Hz, CH_2-CH_2-CH_2), 1.55 (2H, t, *J* 6.4Hz, CH_2), 0.95 (6H, s, 2 CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 212.2 (0, *C*=O), 55.1 (2, CH_2CO), 40.9 (2, CH_2CO), 38.0 (2), 36.2 (0), 28.6 (3, 2 x CH_3), 22.6 (2) ppm.

LRMS (CI): 144 ($[M+NH_4]^+$, 51%), 126 ($[M]^+$, 43%), 111 (14%), 83 (100%) amu.

Synthesis of 2-(3-butenyl)-3,3-dimethyl-1-cyclohexanone **161**[80]



$C_{11}H_{22}OSi$
Mol Wt: 198
129

$C_{12}H_{20}O$
Mol Wt: 180
161

To a solution of silyl enol ether **129** (1.00 g, 5.05 mmol) in THF (20 mL) at –10°C and under N_2 was added MeLi (1.0 M, 6.06 mL, 6.06 mmol). The mixture was then stirred at –10°C for 15 min and HMPA (1.5 mL) was added, followed by rapid addition of the iodo compound (0.92 g, 5.05 mmol). The reaction mixture was allowed to reach room temperature and stirred for 16h. It was then diluted with ether (15 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **161** (0.194 g, 1.07 mmol, 21%) as a colourless oil.

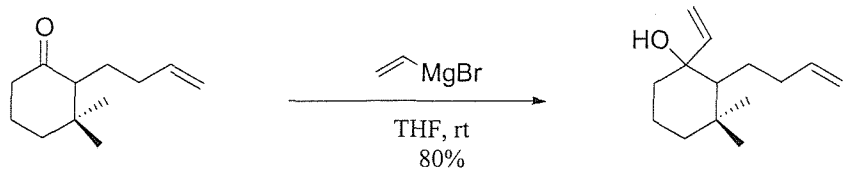
ν_{max}/cm^{-1} (neat): 3077w, 2953m, 1701s, 1640w, 1456m.

δ_H (300MHz, $CDCl_3$): 5.75 (1H, ddt, *J* 17.1, 9.9, 6.6Hz, -C*H*=CH_2), 5.05-4.90 (2H, m, -CH=CH_2), 2.30-1.20 (11H, m, 5 x CH_2 + C*H*), 1.05 (3H, s, CH_3), 0.92 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 138.6 (1, *C*H=CH_2), 114.7 (2, CH=*C*H_2), 54.9 (2, *C*H_2-CO), 48.6 (1, *C*H-CO), 37.9 (2), 37.1 (0), 31.3 (2), 31.2 (3), 29.4 (2), 28.2 (2), 25.7 (3) ppm. Ketone not observed.

LRMS (CI): 198 ([M+NH_4]$^+$, 12%), 181 ([M+H]$^+$, 100%), 163 (5%), 126 (8%), 55 (9%) amu.

Synthesis of 2-(3-butenyl)-3,3-dimethyl-1-vinyl-1-cyclohexanol **159b**[81]



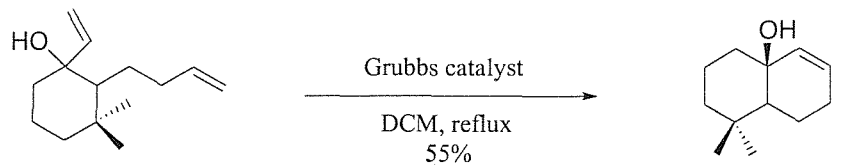
$C_{12}H_{20}O$
Mol Wt: 180
161

$C_{14}H_{24}O$
Mol Wt: 208
159b

To ketone **161** (0.063 g, 0.35 mmol) in THF (10 mL) at 0°C and under N_2 was added vinylmagnesiumchloride (0.83 mL, 1.40 mmol, 15% w/w in THF). The solution was warmed to room temperature and stirred for 2 h. Saturated aqueous NH_4Cl solution (15 mL) was then added and the phases were separated. The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded compound **159b** (0.058 g, 0.28 mmol, 80%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3503br. m, 3023w, 2976s, 1652w, 1456m, 1123s.
δ_H (300MHz, $CDCl_3$):	5.85-5.70 (2H, m, 2 x C*H*=CH_2), 5.30-4.80 (4H, m, 2 x CH=C*H*$_2$), 2.25-2.10 (1H, m, C*H*H), 2.04-1.89 (1H, m, CH*H*), 1.62-1.54 (1H, m, C*H*), 1.55-1.38 (4H, m, 2 x C*H*$_2$), 1.35 (2H, app. s, C*H*$_2$), 1.27-1.15 (2H, m, C*H*$_2$), 1.14 (1H, s, O*H*), 1.10 (3H, s, C*H*$_3$), 0.89 (3H, s, C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	147.3 (1, *C*H=CH_2), 139.2 (1, *C*H=CH_2), 114.6 (2, CH=*C*H$_2$), 111.8 (2, CH=*C*H$_2$), 76.2 (0, *C*-OH), 50.8 (2), 43.6 (1), 39.5 (2), 34.3 (3), 31.9 (2), 30.5 (0), 28.5 (2), 26.7 (3), 23.4 (2) ppm.
LRMS (CI):	209 ([M+H]$^+$, 6%), 191 ([MH-H_2O]$^+$, 100%), 135 (18%), 95 (23%), 55 (94%) amu.
HRMS (EI):	Found [M]$^+$: 208.1831. $C_{14}H_{24}O$ requires 208.1827.

Synthesis of 1,1-dimethyl-1,2,3,4,4a,7,8,8a-octahydro-4a-naphtalenol **165**[82]



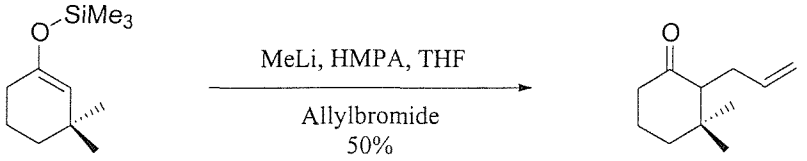
$C_{14}H_{24}O$
Mol Wt: 208
159b

$C_{12}H_{20}O$
Mol Wt: 180
165

To alcohol **159b** (0.050 g, 0.24 mmol) in DCM (7 mL) was added Grubbs catalyst (0.99 mg, 1.2 x 10^{-3} mmol). The resulting solution was heated at reflux under N_2 for 20 h then concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **165** (0.024 g, 0.13 mmol, 55%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3546br. w, 3022w, 2925s, 1637w, 1452s,
δ_H (300MHz, $CDCl_3$):	5.65 (2H, app. s, C*H*=C*H*), 2.13-2.06 (2H, m, CH_2), 1.72-1.44 (6H, m, 3 x CH_2), 1.36-1.17 (4H, m, CH_2 + O*H* + C*H*), 1.12 (3H, s, CH_3), 0.98 (3H, s, CH_3) ppm.
δ_C (75MHz, $CDCl_3$):	135.2 (1, =*C*H), 128.7 (1, =*C*H), 69.1 (0, *C*-OH), 49.5 (2), 43.0 (1), 40.3 (2), 34.5 (3), 31.6 (0), 27.7 (3), 26.2 (2), 25.0 (2), 21.1 (2) ppm.
LRMS (CI):	180 ($[M]^+$, 100%), 163 ($[MH-H_2O]^+$, 88%), 147 (34%), 123 (20%), 109 (90%), 91 (50%), 81 (34%), 55 (50%) amu.
HRMS (EI):	Found $[M]^+$: 180.1518. $C_{12}H_{20}O$ requires 180.1514.

Synthesis of 2-allyl-3,3-dimethyl-1-cyclohexanone **167**[80]



$C_{11}H_{22}OSi$
Mol Wt: 198
129

$C_{11}H_{18}O$
Mol Wt: 166
167

To a solution of silyl enol ether **129** (1.75 g, 8.84 mmol) in THF (50 mL) at -10°C and under N_2 was added MeLi (1.6 M, 6.63 mL, 10.61 mmol). The mixture was then stirred at -10°C for 15 min. HMPA (2.5 mL) and 3-bromo-1-propene (0.76 mL, 8.84 mmol) were then added. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken up in ether (20 mL), the organic layer was washed with water (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **167** (0.74 g, 4.40 mmol, 50%) as a colourless oil.

Data is consistent with literature values.[132]

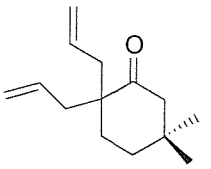
ν_{max}/cm^{-1} (neat): 3075w, 2956m, 1708s, 1639w, 1458m.

δ_H (300MHz, $CDCl_3$): 5.85-5.65 (1H, m, *CH*=CH_2), 5.10-4.96 (2H, m, CH=*CH_2*), 2.55-1.45 (9H, m, 4 x *CH_2* + *CH*), 1.02 (3H, s, *CH_3*), 0.85 (3H, s, *CH_3*) ppm.

δ_C (75MHz, $CDCl_3$): 212.4 (0, *C*=O), 136.6 (1, *C*H=CH_2), 116.4 (2, CH=*CH_2*), 55.1 (2, *CH_2*-CO), 49.3 (1, *C*H-CO), 38.1 (2), 37.1 (0), 33.7 (2), 31.6 (3), 29.1 (2), 25.7 (3) ppm.

LRMS (CI): 184 ($[M+NH_4]^+$, 6%), 167 ($[M+H]^+$,100%), 151 (14%), 137 (10%), 122 (48%), 109 (34%), 95 (12%), 83 (22%), 55 (19%) amu.

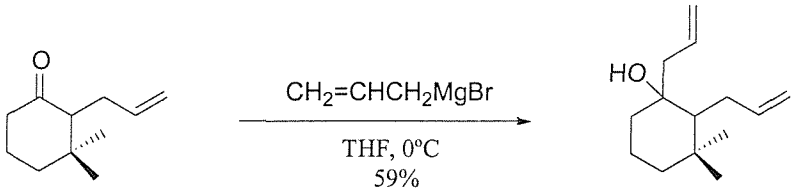
Possible by-product: 2,2-diallyl-5,5-dimethylcyclohexanone **173**



$C_{14}H_{22}O$
Mol Wt: 206
173

ν_{max}/cm^{-1} (neat):	3055s, 2986m, 1701s, 1639w, 1422m,1265s.
δ_H (300MHz, $CDCl_3$):	5.76-5.60 (2H, m, 2 x C*H*=CH_2), 5.10-5.00 (4H, m, 2 x CH=C*H*$_2$), 2.39-2.22 (6H, m, 3 x C*H*$_3$), 1.75-1.68 (2H, m, C*H*$_2$), 1.65-1.59 (2H, m, C*H*$_2$), 0.95 (6H, s, 2 x C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	214.3 (0, *C*=O), 133.8 (1, 2 x *C*H=CH_2), 118.3 (2, 2 x CH=*C*H_2), 52.4 (2, *C*H_2-CO), 50.3 (0, *C*-CO), 39.4 (2, 2 x *C*H_2), 36.3 (0, *C*$(CH_3)_2$), 34.2 (2), 31.8 (2), 28.8 (3, 2 x *C*H_3) ppm.
LRMS (EI):	206 ($[M]^+$, 12%), 191 (27%), 165 (61%), 150 (65%), 121 (29%), 91 (52%), 67 (77%), 55 (55%) amu.
HRMS (EI):	Found $[M]^+$: 206.1674. $C_{14}H_{22}O$ requires 206.1671.

Synthesis of 1,2-diallyl-3,3-dimethyl-1-cyclohexanol **174**



$C_{11}H_{18}O$
Mol Wt: 166
167

$C_{14}H_{24}O$
Mol Wt: 208
174

Mg powder was preliminary activated by stirring under N_2.

To Mg powder (1.68 g, 69.00 mmol) in ether (25 mL) at 0°C and under N_2 was added allylbromide (2.49 mL, 28.75 mmol) dropwise so that the internal temperature did not exceed 10°C. After complete addition, the resultant grey mixture was stirred at room temperature for 0.5 h. It was then cooled to 0°C, and a solution of ketone **167** (0.955 g, 5.75 mmol) in ether (20 mL) was added dropwise. The resultant solution was stirred at room temperature for 2 h. It was filtered through glass wool into saturated aqueous NH_4Cl solution (50 mL) and the remaining magnesium powder was washed with ether (2 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **174** (0.412 g, 1.98 mmol, 34%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3570br. s, 3076m, 2947s, 2865s,1639m, 1454m, 1364m, 1177w.

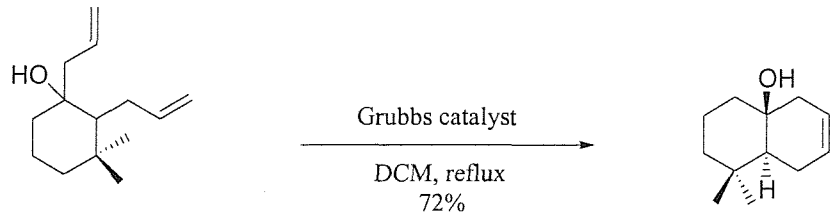
δ_H (300MHz, $CDCl_3$): 5.90-5.75 (2H, m, 2 x -C*H*=CH_2), 5.15-4.96 (4H, m, 2 x CH=C*H*$_2$), 2.46-2.36 (1H, m, C*H*H), 2.35-2.17 (2H, m, C*H*$_2$), 2.00-1.85 (1H, m, CH*H*), 1.58-1.20 (6H, m, 3 x C*H*$_2$), 1.15 (1H, dd, *J* 5.9, 4.8Hz, C*H*), 1.09 (3H, s, C*H*$_3$), 0.90 (1H, s, -O*H*), 0.88 (3H, s, C*H*$_3$) ppm.

δ_C (75MHz, $CDCl_3$): 138.4 (1, *C*H=CH_2), 134.3 (1, *C*H=CH_2), 118.6 (2, CH=*C*H$_2$), 115.9 (2, CH=*C*H$_2$), 75.1 (0, *C*-OH), 49.3 (2), 46.7 (2), 43.6 (1), 39.3 (2), 34.3 (3), 33.8 (2), 30.8 (0), 26.9 (3), 23.9 (2) ppm.

LRMS (CI): 191 ([MH-H_2O]$^+$, 10%), 167 (100%), 149 (18%), 109 (15%), 83 (18%), 69 (36%), 55 (29%) amu.

HRMS (EI): Found [M]$^+$: 208.1864. $C_{14}H_{24}O$ requires 208.1827.

Synthesis of 1,1-dimethyl-1,3,4,5,8,8a-hexahydro-*2H*-naphtalen-4a-ol **175**[82]



$C_{14}H_{24}O$
Mol Wt: 208
174

$C_{12}H_{20}O$
Mol Wt: 180
175

Grubbs catalyst (0.374 g, 0.45 mmol) was added to the alcohol **174** (1.89 g, 9.08 mmol) in DCM (40 mL). The resulting solution was heated at reflux under N_2 for 18 h then concentrated. Purification by column chromatography (silica gel, 10:1 Petroleum Ether:EtOAc) afforded compound **175** (1.18 g, 6.55 mmol, 72%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3585br. w, 3024w, 2947s, 2902s, 1651w, 1434m, 1274m.

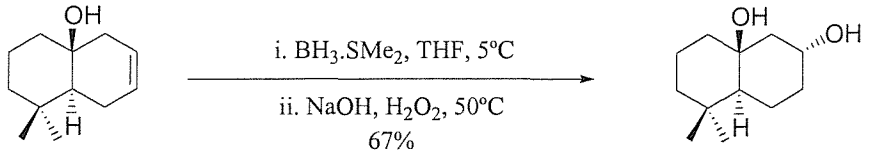
δ_H (300MHz, $CDCl_3$): 5.83-5.71 (1H, m, C*H*=CH), 5.60-5.51 (1H, m, CH=C*H*), 2.10-1.18 (12H, m, 5 x CH_2 + O*H* + C*H*), 1.12 (3H, s, CH_3), 0.88 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 127.4 (1, *C*H=CH), 124.3 (1, CH=*C*H), 70 (0, *C*-OH), 50.5 (2), 41.9 (2), 39.6 (1), 39.5 (2), 34.6 (3), 31.2 (0, $C(CH_3)_2$), 29.0 (2), 26.6 (3), 25.5 (2) ppm.

LRMS (CI): 198 ($[M+NH_4]^+$, 5%), 180 ($[M]^+$, 17%), 163 ($[MH-H_2O]^+$, 100%), 143 (8%), 126 (20%) amu.

HRMS (EI): Found $[M+NH_4]^+$: 198.1865. $C_{12}H_{24}NO$ requires 198.1858.

Synthesis of 5,5-dimethylperhydro-2,8a-naphtalenediol **176a**[85]



$C_{12}H_{20}O$
Mol Wt: 180
175

$C_{12}H_{22}O_2$
Mol Wt: 198
176a

To alcohol **175** (0.901 g, 5.00 mmol) in THF (20 mL), under N_2 and at 5°C was slowly added $BH_3.SMe_2$ (10 M, 0.5 mL, 5.00 mmol). After complete addition, the resulting solution was stirred at room temperature for 30 min. Water was added carefully (2 mL), and after total H_2 evolution (10 min), NaOH (1.5 mL) was added. Then H_2O_2 (30% aqueous, 1 mL) was added dropwise so that the temperature did not exceed 40°C. After addition, the solution was heated at 50°C for 1 h. After cooling, ether was added (25 mL), and the organic layer was washed with water (2 x 10 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc), afforded compound **176a** (660 mg, 3.3 mmol, 67%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3424br. m, 2935m, 1450m.

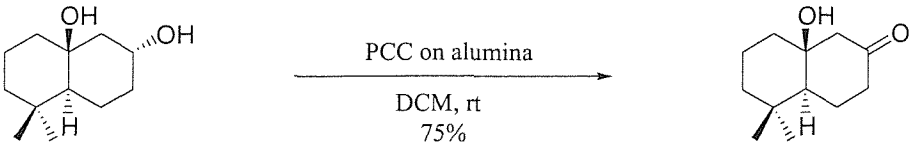
δ_H (300MHz, $CDCl_3$): 3.98 (1H, tt, *J* 11.0, 4.5Hz, CH-O*H*), 2.06-1.98 (1H, m, CH*H*), 1.92 (1H, ddd, *J* 12.5, 4.5, 2.5Hz, C*H*H-CMe_2), 1.70-0.80 (13H, m), 1.09 (3H, s, CH_3), 0.89 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 73.3 (0, *C*-OH), 67.8 (1, *C*H-OH), 52.5 (2), 50.1 (2), 44.2 (1), 40.1 (2), 36.3 (2), 35.2 (3), 31.1 (0, $C(CH_3)_2$), 27.7 (3), 26.9 (2), 25.0 (2) ppm.

LRMS (CI): 198 ($[M]^+$, 96%), 180 ($[MH-H_2O]^+$, 48%), 163 (100), 140 (12) amu.

HRMS (EI): Found $[M]^+$: 198.1627. $C_{12}H_{22}O_2$ requires 198.1620.

Synthesis of 8a-hydroxy-5,5-dimethyl-perhydro-2-naphtalenone **177**



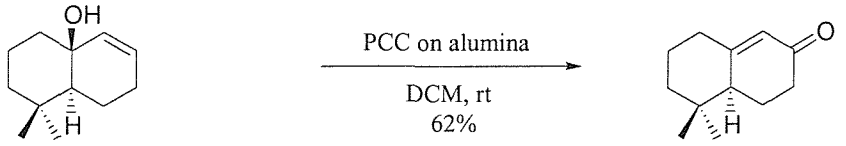
$C_{12}H_{22}O_2$
Mol Wt: 198
176a

$C_{12}H_{20}O_2$
Mol Wt: 196
177

PCC on alumina (2.76 g, 2.57 mmol, 20% w/w) was added to alcohol **176a** (204 mg, 1.03 mmol) in DCM (20 mL). The resulting mixture was placed under N_2 and stirred at room temperature for 2 h. Ether was then added (20 mL) and the mixture was stirred for a further 20 min. The mixture was then filtered through a florisil pad, which was eluted with ether (50 mL) and then ethyl acetate (50 mL). The combined eluates were concentrated *in vacuo*. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **177** (151 mg, 0.70 mmol, 75%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3483br. m, 2946m, 1703s, 1453m.
δ_H (300MHz, $CDCl_3$):	2.81-2.64 (2H, m, C*H*$_2$), 2.60-2.48 (1H, m, C*H*H), 2.35-2.07 (2H, m, C*H*$_2$), 1.92-1.81 (1H, m, CH*H*), 1.77-1.42 (5H, m, 2 x C*H*$_2$ + C*H*), 1.37-1.24 (2H, m, C*H*$_2$), 1.21 (1H, s, O*H*), 1.16 (3H, s, C*H*$_3$), 0.92 (3H, s, C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	212.2 (0, *C*=O), 70.2 (0, *C*-OH), 51.2 (2, *C*H$_2$CO), 44.1 (1), 43.6 (2, *C*H$_2$CO), 40.6 (2), 38.8 (2), 37.3 (2), 34.4 (3), 31.2 (0, *C*(CH$_3$)$_2$), 27.2 (3), 25.6 (2) ppm.
LRMS (CI):	214 ([M+NH$_4$]$^+$, 100), 196 ([M]$^+$, 78%), 179 ([MH-H$_2$O]$^+$, 64%), 139 (10%) amu.
HRMS (EI):	Found [M]$^+$: 196.1469. $C_{12}H_{20}O_2$ requires 196.1463.

Synthesis of 5,5-dimethyl-2,3,4,4a,5,6,7,8-octahydro-2-naphtalenone **139a**[84]



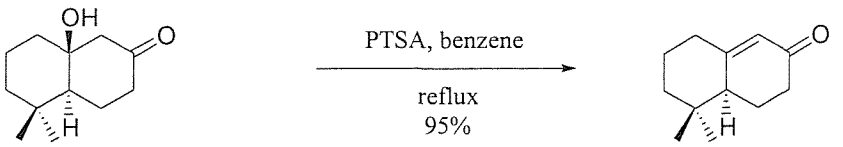
$C_{12}H_{20}O$
Mol Wt: 180
165

$C_{12}H_{18}O$
Mol Wt: 178
139a

PCC on alumina (5.02 g, 4.67 mmol, 20% w/w) was added to alcohol **165** (0.337 g, 1.87 mmol) in DCM (30 mL). The resulting solution was then stirred at room temperature for 3.5 h. Ether was added (25 mL) and the mixture was stirred for another hour. It was filtered through a florisil pad, which was eluted with ether (50 mL) and ethyl acetate (50 mL). The combined extracts were concentrated *in vacuo*. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded compound **139a** (206 mg, 1.16 mmol, 62%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	2924m, 1671s, 1620w, 1456w, 1251m.
λ_{max}/nm (ε_{max}, MeOH)	313 (17082).
δ_H (400MHz, $CDCl_3$):	5.72 (1H, s, C=C*H*), 2.35 (1H, t, *J* 4.5Hz, C*H*H), 2.31 (1H, t, *J* 4.5Hz, CH*H*), 2.27-1.10 (9H, m, 4 x CH_2 + C*H*), 0.92 (3H, s, CH_3), 0.78 (3H, s, CH_3) ppm.
δ_C (100MHz, $CDCl_3$):	200.3 (0, *C*=O), 166.6 (0, *C*=CH), 126.1 (1, C=*C*H), 49.4 (2, CH_2-CO), 38.8 (2), 37.6 (1), 37.0 (2), 32.5 (3), 30.7 (2), 30.1 (0, $C(CH_3)_2$), 29.3 (2) 24.9 (3) ppm.
LRMS (CI):	178 ([M]$^+$, 100%), 163 (71%), 150 (42%), 110 (45%), 91 (45%), 55 (22%) amu.
HRMS (EI):	Found [M]$^+$: 178.1357. $C_{12}H_{18}O$ requires 178.1358.

Alternatively:



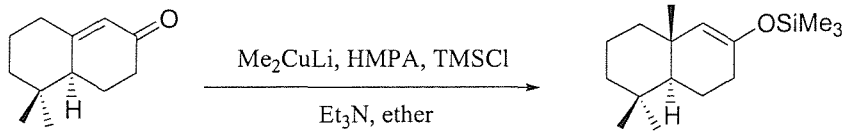
$C_{12}H_{20}O_2$
Mol Wt: 196
177

$C_{12}H_{18}O$
Mol Wt: 178
139a

To ketone **177** (0.258 g, 1.31 mmol) in benzene (15 mL) was added *p*-TsOH (0.012 g, 0.065 mmol). The resulting mixture was heated at reflux for 1.5 day in a flask fitted with a condenser and a dean stark. It was then washed with saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:Ether) afforded compound **139a** (0.187 g, 1.05 mmol, 95%) as a colourless oil.

Spectral data was identical to those found previously.

Synthesis of [(5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphtalenyl)oxy](trimethyl)silane **166**[79]



$C_{12}H_{18}O$
Mol Wt: 178
139a

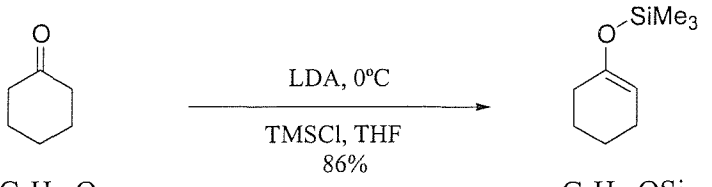
$C_{16}H_{30}OSi$
Mol Wt: 266
166

Triethylamine was dried over CaH_2 prior to use.

To a slurry of copper iodide (0.083 g, 0.44 mmol) in ether (10 mL), at 0°C and under N_2 was added MeLi (1.6 M, 0.49 mL, 0.79 mmol). After complete addition, compound **139a** was added. After the resulting mixture had been stirred at 0°C for 20 min, TMSCl (0.15 mL), Et_3N (0.25 mL) and HMPA (0.1 mL) were added. The yellow solution was allowed to reach room temperature and stirred for 1.5 h. Petroleum ether was added (15 mL), the mixture was washed with 5% aqueous HCl solution (10 mL), 5% aqueous $NaHCO_3$ solution (15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded compound **166** (0.025 g, 0.09 mmol, 41%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	2948m, 1664m, 1454m, 1365m, 1251s, 1134.s.
δ_H (400MHz, $CDCl_3$):	4.62 (1H, s, C=C*H*), 2.20-1.10 (11H, m, 5 x CH_2 + C*H*), 0.97 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.84 (3H, s, CH_3), 0.17 (9H, s, TMS) ppm.
δ_C (100MHz, $CDCl_3$):	115.4 (1, C=*C*H), 53.0 (2), 39.7 (3), 39.3 (2), 34.1 (3), 33.4 (3), 31.4 (1), 25.9 (2), 24.6 (2), 24.3 (2), -0.7 (3, Si(*C*H$_3$)$_3$) ppm. Quaternary C not observed.
LRMS (CI):	212 (56%), 195 (100%), 179 (31%), 136 (62%), 121 (20%) amu. Parent ion not observed.

Synthesis of (1-cyclohexenyloxy)(trimethylsilane) **137**



$C_9H_{10}O$
Mol Wt: 98
153

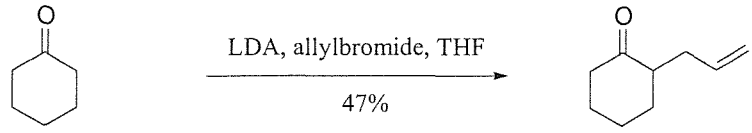
$C_9H_{18}OSi$
Mol Wt: 170
137

LDA was prepared by adding ^{n}BuLi (2.2 M, 5.56 mL, 12.24 mmol) to a solution of freshly distilled diisopropylamine (2.00 mL, 14.24 mmol) in THF (20 mL) under N_2 and at 0°C. The mixture was then stirred at 0°C for 20 min and cyclohexanone **153** (1.00 g, 10.20 mmol) was added. After complete addition, TMSCl (1.94 mL, 15.30 mmol) was added and the mixture was stirred for 0.5 h. It was then washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **137** (1.51 g, 8.90 mmol, 86%) as a colourless oil.

Data is consistent with literature values.[133]

ν_{max}/cm^{-1} (neat):	2933m, 1669m, 1448w, 1251s, 1188s.
δ_H (300MHz, $CDCl_3$):	4.85 (1H, t, *J* 3.7Hz, C=C*H*), 2.05-1.95 (4H, m, 2 x CH_2), 1.71-1.63 (2H, m, CH_2), 1.55-1.47 (2H, m, CH_2), 0.12 (9H, s, TMS) ppm.
δ_C (75MHz, $CDCl_3$):	150.3 (0, *C*=CH), 104.3 (1, C=*C*H), 29.9 (2), 23.9 (2), 23.3 (2), 22.5 (2), 0.5 (3, Si(CH_3)$_3$) ppm.
LRMS (CI):	171 ([M+H]$^+$, 100%), 155 (11%), 127 (9%), 90 (80%) amu.

Synthesis of 2-allyl-1-cyclohexanone **170**[86]



$C_6H_{10}O$
Mol Wt: 98
153

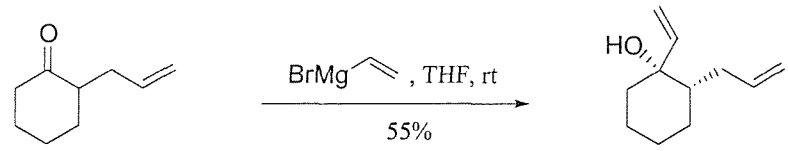
$C_9H_{14}O$
Mol Wt: 138
170

LDA was prepared by adding ^{n}BuLi (1.36 M, 18.00 mL, 24.48 mmol) to a solution of preliminary distilled diisopropylamine (4.00 mL, 28.56 mmol) in THF (25 mL) under N_2 and at 0°C. The mixture was then stirred at 0°C for 20 min and cyclohexanone **153** (2.00 g, 20.40 mmol) in THF (20 mL) was added. After stirring at 0°C for 30 min, allylbromide (1.76 mL, 20.40 mmol) was added. The mixture was then warmed to room temperature, stirred for 2 h, then poured into saturated aqueous Na_2CO_3 solution (100 mL). The product was extracted with petroleum ether (3 x 15 mL), the organic layer washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **170** (1.31 g, 6.61 mmol, 47%) as a colourless oil.

Data is consistent with literature values.[134]

ν_{max}/cm^{-1} (neat):	3012w, 2933m, 2861m, 1711s, 1448m.
δ_H (300MHz, $CDCl_3$):	5.75 (1H ddt, *J* 17.1, 10.6, 6.3Hz, C*H*=CH_2), 5.02-4.87 (2H, m, CH=CH_2), 2.52 (1H, dt, *J* 7.2, 6.3Hz, CO-C*H*), 2.40-2.20 (3H, m, CH_2 + CH*H*), 2.15-1.55 (6H, m, 3 x CH_2), 1.40-1.20 (1H, m, C*H*H) ppm.
δ_C (75MHz, $CDCl_3$):	212.6 (0, *C*=O), 136.6 (1, *C*H=CH_2), 116.3 (2, CH=*C*H_2), 50.4 (1, *C*H-CO), 42.2 (2), 33.9 (2), 33.5 (2), 28.1 (2), 25.1 (2) ppm.
LRMS (CI):	156 ([M+NH_4]$^+$, 27%), 138 ([M+H]$^+$, 100%), 123 (7%), 109 (13%), 94 (20%) amu.

Synthesis of 2-allyl-1-vinylcyclohexanol **171**



$C_9H_{14}O$
Mol Wt: 138
170

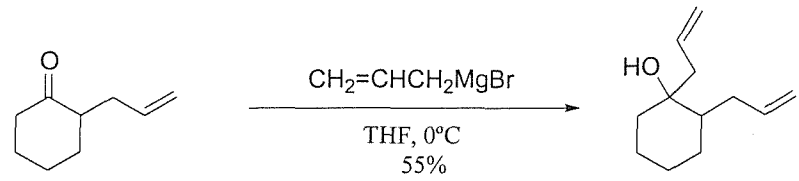
$C_{11}H_{18}O$
Mol Wt: 166
171

To a solution of vinylmagnesiumbromide (1.0 M, 4.71 mL, 4.71 mmol) in THF (20 mL) and under N_2 was added drop wise compound **170** (0.50 g, 3.62 mmol). The mixture was stirred at room temperature for 2 h, then cooled to 0°C and quenched by drop wise addition of water (7 mL). The reaction mixture was concentrated to c.a. 10 mL, partitioned between water (10 mL) and ether (15 mL). The organic layer was washed with 0.2M aqueous HCl solution (15 mL) and brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **171** (0.331 g, 1.99 mmol, 55%) as a colourless oil.

Data is consistent with literature values.[81]

ν_{max}/cm^{-1} (neat):	3375br. s, 2931m, 1638m, 1444w.
δ_H (300MHz, $CDCl_3$):	5.90-5.68 (2H, m, 2 x C*H*=CH_2), 5.25-4.90 (4H, m, 2 x CH=C*H*$_2$), 2.24-2.10 (1H, m, C*H*), 1.89-1.00 (11H, m, 5 C*H*$_2$ + O*H*) ppm.
δ_C (75MHz, $CDCl_3$):	146.2 (1, *C*H=CH_2 next to OH), 138.1 (1, *C*H=CH_2), 115.9 (2, CH=*C*H$_2$ next to OH), 111.9 (2, CH=*C*H$_2$), 74.8 (0), 44.1 (1), 39.2 (2), 34.8 (2), 26.5 (2), 26.0 (2), 21.5 (2) ppm.
LRMS (CI):	166 ([M]$^+$, 21%), 149 ([M-OH]$^+$, 100%), 109 (15%), 91 (10%), 55 (14%) amu.

Synthesis of 1,2-diallyl-1-cyclohexanol **182**[81]



$C_9H_{14}O$
Mol Wt: 138
170

$C_{12}H_{20}O$
Mol Wt: 180
182

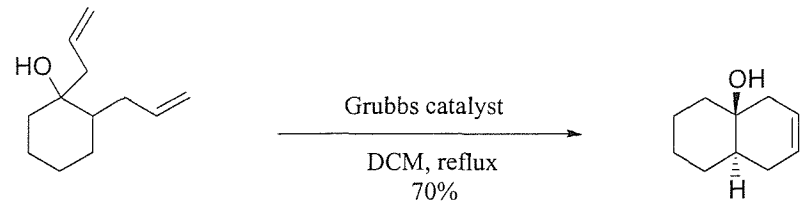
Mg powder was preliminary activated by stirring under N_2 for 0.5 h.

To Mg coarse powder (1.39 g, 57.24 mmol) in ether (20 mL) at 0°C and under N_2 was added allylbromide (2.06 mL, 23.85 mol). First, 10 drops were added and once a temperature change was observed, the reminder at such a rate so that the temperature does not exceed 10°C. After complete addition, the resultant grey mixture was stirred at room temperature for 0.5 h. The mixture was then cooled to 0°C and the ketone **170** (0.659 g, 4.77 mL) in ether (10 mL) was added following the same procedure as for allylbromide. The resultant mixture was then stirred at room temperature for 1.5 h. It was filtered and poured into a saturated aqueous NH_4Cl solution (25 mL) and the remaining magnesium was washed with ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 20:1 Petroleum Ether:EtOAc) afforded compound **182** (0.475 g, 2.64 mmol, 55%) as a colourless oil.

Data is consistent with literature.[135]

ν_{max}/cm^{-1} (neat):	3469br. w, 3075w, 2933m, 2862w, 1639m, 1447m.
δ_H (300MHz, $CDCl_3$):	6.00-5.70 (2H, m, 2 x C*H*=CH_2), 5.23-4.95 (4H, m, 2 x CH=C*H*$_2$), 2.50-1.10 (14H, m) ppm.
δ_C (75MHz, $CDCl_3$):	138.1 (1, *C*H=CH_2), 133.9 (1, *C*H=CH_2), 118.3 (2, CH=*C*H$_2$), 115.8 (2, CH=*C*H$_2$), 73.3 (0), 45.3 (2), 43.0 (1), 36.7 (2), 33.8 (2), 26.8 (2), 25.2 (2), 21.7 (2) ppm.
LRMS (CI):	180 ($[M]^+$, 6%), 163 ($[M\text{-}OH]^+$, 100%), 139 (88%), 121 (37%), 81 (13%) amu

Synthesis of 1,2,3,4,4a,5,8,8a-octahydro-4a-naphtalenol **183**[82]



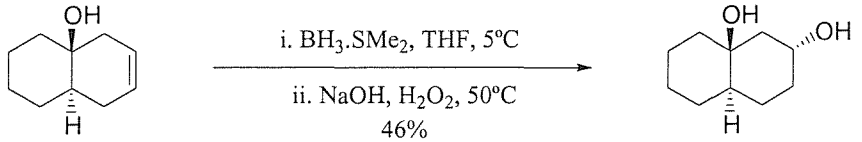
$C_{12}H_{20}O$
Mol Wt: 180
182

$C_{10}H_{16}O$
Mol Wt: 152
183

Grubbs catalyst (111 mg, 0.13 mmol) was added to the alcohol **182** (0.488 g, 2.71 mmol) in DCM (25 mL). The resulting mixture was heated at reflux for 16 h under N_2 then concentrated. Purification by column chromatography (silica gel, 10:1 Petroleum Ether:EtOAc) afforded compound **183** (0.289 mg, 1.90 mmol, 70%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3491br. w, 3023w, 2927s, 2852m, 1653w, 1446m.
δ_H (300MHz, $CDCl_3$):	5.75-5.69 (1H, m, C*H*=CH), 5.58-5.52 (1H, m, CH=C*H*), 2.15-1.20 (14H, m) ppm.
δ_C (75MHz, $CDCl_3$):	127.1 (1, *C*H=CH), 124.3 (1, CH=*C*H), 68.9 (0), 40.7 (2), 39.2 (1), 38.8 (2), 29.3 (2), 28.8 (2), 26.2 (2), 21.9 (2) ppm.
LRMS (CI):	170 ($[M+NH_4]^+$, 10%), 152 ($[M]^+$, 22%), 135 ($[M-OH]^+$, 100%), 98 (33%) amu.
HRMS (EI):	Found: 152.1199. $C_{10}H_{16}O$ requires 152.1201.

Synthesis of perhydro-2,8a-naphtalenediol **184**[85]



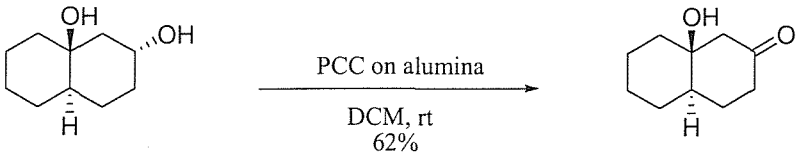
$C_{10}H_{16}O$
Mol Wt: 152
183

$C_{10}H_{18}O_2$
Mol Wt: 170
184

To alcohol **183** (0.173 g, 1.14 mmol) in THF (25 mL) under N_2 and at 5°C was added $BH_3.SMe_2$ (10 M, 0.11 mL, 1.14 mmol). The resulting mixture was then stirred at room temperature for 0.5 h. Water was added (1.5 mL), and after no more gas evolved (5 min) NaOH (3 M, 0.9 mL) was added. Then H_2O_2 (30% aqueous, 0.6 mL) was added drop-wise so that the temperature did not exceed 40°C. The solution was then heated at 50°C for 1 h. Ether was added (10 mL) and the organic layer was washed with water (2 x 10 mL), then brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 8:1 Petroleum Ether:EtOAc) afforded diol **184** (0.088 g, 0.52 mmol, 46%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3356br. s, 2928s, 2850s, 1448m, 1260m.
δ_H (300MHz, $CDCl_3$):	4.15-4.03 (1H, m, C*H*-OH), 3.40 (1H, br, O*H*), 3.10 (1H, br, O*H*), 2.20-1.00 (15H, m, 7 CH_2 + C*H*) ppm.
δ_C (75MHz, $CDCl_3$):	72.1 (0), 68.2 (1, *C*H-OH), 44.2 (1), 43.6 (2), 39.6 (2), 33.3 (2), 28.5 (2), 26.2 (2), 22.9 (2), 21.1 (2) ppm.
LRMS (CI):	170 ($[M]^+$, 44%), 152 ($[M-H_2O]^+$, 56%), 135 (100%), 98 (21%) amu.

Synthesis of 8a-hydroxyperhydro-2-naphtalenone **185**



$C_{10}H_{18}O_2$
Mol Wt: 170
184

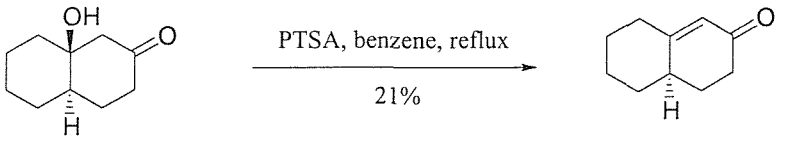
$C_{10}H_{16}O_2$
Mol Wt: 168
185

To diol **184** (0.088 g, 0.52 mmol) in DCM (10 mL) was added PCC on alumina (1.31 g, 1.22 mmol, 20% w/w). The resulting suspension was stirred at room temperature for 2 h. Ether was added (10 mL) and the solution was stirred for further 20 min. It was then filtered through a florisil pad, which was eluted with ether and ethyl acetate. The combined organic eluates were concentrated *in vacuo*. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **185** (0.064 g, 0.37 mmol, 62%) as a colourless oil.

Data is consistent with literature values.[87]

ν_{max}/cm^{-1} (neat):	3358.0br. m, 2927.5m, 2854.8m, 1697.8s, 1446.9m, 1256.8m.
δ_H (300MHz, $CDCl_3$):	2.76 (1H, dt, *J* 14.3, 6.6Hz, CH*H*-CO), 2.50-2.20 (3H, m, C*H*H-CO + CH_2-CO), 2.12-2.04 (1H, m, C*H*), 1.93-1.85 (1H, m, O*H*), 1.82-1.47 (6H, m, 3 x CH_2), 1.45-1.10 (4H, m, 2 x CH_2) ppm.
δ_C (75MHz, $CDCl_3$):	212.0 (0, C=O), 74.1 (0), 55.5 (2), 43.8 (1), 41.6 (2), 39.7 (2), 28.8 (2), 27.8 (2), 25.9 (2), 20.8 (2) ppm.
LRMS (CI):	186 ($[M+NH_4]^+$, 100%), 169 ($[M+H]^+$, 37%), 151 ($[M-OH]^+$, 37%) amu.

Synthesis of 2,3,4,4a,5,6,7,8-octahydro-2-naphtalenone **186**



$C_{10}H_{16}O_2$
Mol Wt: 168
185

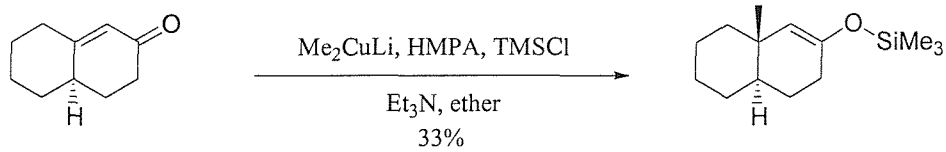
$C_{10}H_{14}O$
Mol Wt: 150
186

The ketone **185** (0.747 g, 4.45 mmol) and *p*-TsOH (0.085 g, 0.45 mmol) in benzene (50 mL) were heated at reflux for 18 h in a flask fitted with a soxlet and condenser. The mixture was then washed with saturated aqueous $NaHCO_3$ solution (40 mL), water (40 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15:1 Petroleum Ether:EtOAc) afforded compound **186** (0.138 g, 0.92 mmol, 21%) as a colourless oil.

Data is consistent with literature values.[136]

ν_{max}/cm^{-1} (neat):	2929m, 2859m, 1673s, 1620m, 1449m.
δ_H (300MHz, $CDCl_3$):	5.79 (1H, s, C=C*H*), 2.50-1.00 (13H, m, 6 x CH_2 + C*H*) ppm.
δ_C (75MHz, $CDCl_3$):	200.3 (0, *C*=O), 167.5 (0, *C*=CH), 124.4 (1, C=*C*H), 38.0 (1), 36.7 (2), 35.7 (2), 34.6 (2), 29.3 (2), 27.0 (2), 25.7 (2) ppm.
LRMS (CI):	168 ($[M+NH_4]^+$, 9%), 151 ($[M+H]^+$, 100%), 122 (5%) amu.

Synthesis of trimethyl-(8a-methyl-3,4,4a,5,6,7,8,8a-octahydro-naphtalen-2-yloxy)-silane **187**



$C_{10}H_{14}O$
Mol Wt:150
186

$C_{14}H_{26}OSi$
Mol Wt: 238
187

Triethylamine was distilled over CaH_2 prior to use.

To a slurry of copper iodide (1.26 g, 6.60 mmol) in ether (25 mL), at 0°C and under N_2 was added MeLi (1.6 M, 7.42 mL, 11.88 mmol). After complete addition, compound **186** was added (0.475 g, 3.30 mmol) in ether (15 mL). After the resulting mixture had been stirred at 0°C for 20 min, TMSCl (1.5 mL), Et_3N (2.5 mL) and HMPA (1 mL) were added. The yellow solution was allowed to reach room temperature and stirred for 1.5 h. Petroleum ether was added (30 mL) then the mixture was washed with 5% aqueous HCl solution (2 x 20 mL) and 5% aqueous $NaHCO_3$ solution (2 x 20 mL). It was then dried over $MgSO_4$ filtered and concentrated. Purification by column chromatography (silica gel, 2:1 Petroleum Ether:EtOAc) afforded compound **187** (0.260 g, 1.09 mmol, 33%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 2948m, 1663m, 1446w, 1124m.

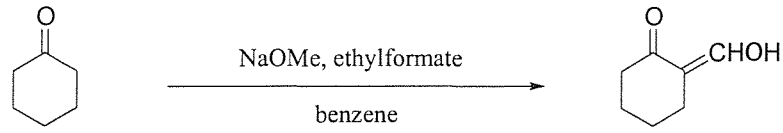
δ_H (300MHz, $CDCl_3$): 4.32 (1H, s, C=C*H*), 1.92-1.49 (6H, m, 3 x CH_2), 1.45-0.90 (7H, m, 3 x CH_2 + C*H*), 0.82 (3H, s, CH_3), 0.00 (9H, s, $Si(CH_3)_3$) ppm.

δ_C (75MHz, $CDCl_3$): 148.8 (0, *C*=CH), 115.1 (1, C=*C*H), 40.3 (1), 38.8 (0), 28.4 (3), 28.2 (2), 27.4 (2), 27.1 (2), 24.7 (2), 23.2 (2), 22.1 (2), 0.5 ($SiC(CH_3)_3$ ppm.

LRMS (CI): 239 ([M+H]+, 65%), 223 (100%), 195 (54%), 182 (17%), 73 (50%) amu.

HRMS (EI): Found: 238.1753. $C_{14}H_{26}OSi$ requires 238.4411.

Synthesis of 2-[1-hydroxymethylidene]-1-cyclohexanone **154**[77]



$C_6H_{10}O$
Mol Wt: 98
153

$C_7H_{10}O_2$
Mol Wt: 126
154

Ethylformate was distilled over K_2CO_3 prior to use.

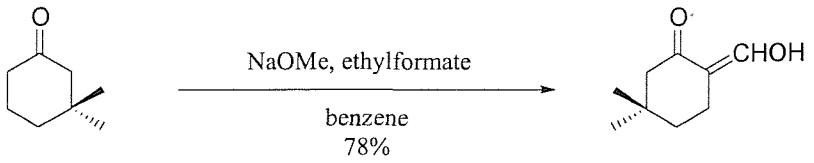
NaOMe was prepared from sodium (0.68 g, 29.59 g-atom) and methanol (10 mL). It was freed of solvent, cooled in N_2 and suspended in dry benzene (10 mL) under N_2. To the vigorously stirred solution was added ethylformate (5.00 mL), at room temperature. The mixture was stirred at room temperature for 0.5 h and then cooled on ice. Cyclohexanone **153** (1.00 g, 1.02 mmol) in benzene (10 mL) was added dropwise, more benzene was added (10 mL) and the mixture was stirred at room temperature overnight. The yellow gelatinous mixture was then diluted with benzene (10 mL) and ice-dilute aqueous H_2SO_4 (3 mL). The phases were separated and the aqueous layer extracted with ether (10 mL) and benzene (10 mL). The combined organic extracts were shaken with excess ice cold 2% aqueous KOH solution. The alkaline layer was washed with ether (10 mL), acidified with dilute aqueous HCl and well extracted with benzene/ether solution (50/50, 2 x 15 mL). The organic extracts were then washed with water (10 mL) dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 8% ether in petroleum ether) afforded compound **154** (0.930 g, 7.38 mmol, 72%) as a yellow oil.

Data is consistent with literature values.[137]

ν_{max}/cm^{-1} (neat):	3432br. s, 2940s, 2863m, 1715s, 1621s, 1446m, 1162s.
δ_H (300MHz, $CDCl_3$):	14.42 (1H, s, O=C-*H*), 8.65 (1H, s, C=C*H*OH), 2.39-2.31 (4H, m, 2 x CH_2), 1.75-1.63 (4H, m, 2 x CH_2) ppm.
δ_C (75MHz, $CDCl_3$):	187.9 (1, *C*HO), 185.0 (0), 109.0 (0, *C*=CHOH), 31.3 (2), 23.3 (2), 22.7 (2), 21.4 (2) ppm

LRMS (CI): 144 ($[M+NH_4]^+$, 4%), 127 $(M+H]^+$, 100%), 98 (8%), 55 (7%) amu.

Synthesis of 2-[1-hydroxymethylidene]-5,5-dimethyl-1-cyclohexanone **156**[77]



$C_8H_{14}O$
Mol Wt: 126
155

$C_9H_{14}O_2$
Mol Wt: 154
156

Ethylformate was distilled over K_2CO_3 prior to use.

NaOMe was prepared from sodium (0.32 g, 13.91 g-atom) and methanol (4 mL). It was freed of solvent, cooled in N_2 and suspended in dry benzene (5 mL) under N_2. To the vigorously stirred solution was added ethylformate (1.1 mL), at room temperature. The mixture was stirred at room temperature for 0.5 h and then cooled on ice. Compound **155** (0.250 g, 1.99 mmol) in benzene (5 mL) was added dropwise, more benzene was added (10 mL) and the mixture was stirred at room temperature overnight. The yellow gelatinous mixture was then diluted with benzene (10 mL) and ice-cold dilute aqueous H_2SO_4 (3 mL). The phases were separated and the aqueous layer was extracted with ether (10 mL) and benzene (10 mL). The combined organic extracts were shaken with excess ice cold 2% aqueous KOH solution. The alkaline layer was washed with ether (10 mL), acidified with dilute aqueous HCl and extracted with benzene/ether solution (50/50, 2 x 15 mL). The organic extracts were washed with water (10 mL) dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 8% ether in petroleum ether) afforded compound **156** (0.239 g, 1.55 mmol, 78%) as a yellow oil.

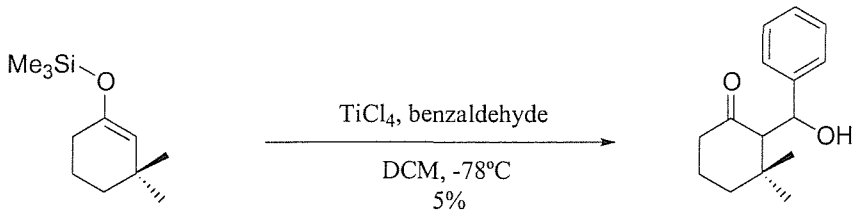
ν_{max}/cm^{-1} (neat): 3402br. s, 2940s, 2863s, 1714s, 1633s, 1448m.

δ_H (300MHz, $CDCl_3$): 14.40 (1H, s, O=C*H*), 8.72 (1H, s, C=C*H*OH), 2.38 (2H, t, *J* 6.6Hz, CH_2), 2.12 (2H, s, CO-CH_2), 1.45 (2H, t, *J* 6.6Hz, CH_2), 0.97 (6H, s, 2 CH_2) ppm.

δ_C (75MHz, $CDCl_3$): 189.3 (1, *C*HO), 183.2 (0), 107.2 (0, *C*=CHOH), 44.5 (2), 35.2 (2), 29.4 (0), 28.0 (3, 2 x *C*H_3), 20.3 (2) ppm.

LRMS (CI): 154 ([M]$^+$, 2%), 84 (70%), 49 (100%) amu.

Synthesis of 2-[hydroxy(phenyl)methyl]-3,3-dimethyl-1-cyclohexanol **202**



$C_{11}H_{22}OSi$
Mol Wt: 198
129

$C_{15}H_{20}O_2$
Mol Wt: 232
202

To benzaldehyde (0.11 mL, 1.66 mmol) and $TiCl_4$ (0.33 mL, 3.03 mmol) in DCM (15 mL) under N_2 and at –78°C was added compound **129** (0.30 g, 1.51 mmol) in DCM (5 mL). The resulting mixture was then warmed to room temperature and stirred for 1 h. After hydrolysis, the resulting organic layer was extracted with ether (2 x 5 mL), and the extract was washed with water (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 25:1 Petroleum Ether:Ether) afforded the desired compound **202** (0.016 g, 0.07 mmol, 5%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3360br, 3032w, 2961s, 1712s, 1613s, 1426s

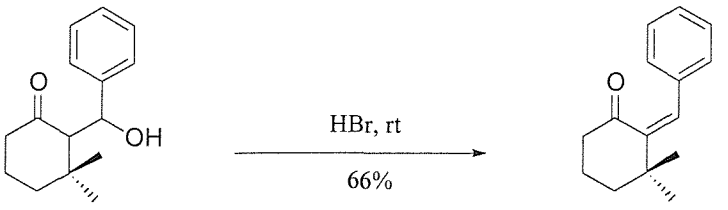
δ_H (300MHz, $CDCl_3$): 7.44-7.30 (5H, m, Ar-*H*), 5.25 (1H, d, *J* 10.1Hz, C*H*-OH), 3.10 (1H, d, *J* 10.1Hz, C*H*-CO), 2.61 (1H, dt, *J* 12.7, 3.7Hz, C*H*HCO), 2.42 (1H, dt, *J* 12.8, 6.1Hz, CH*H*CO), 1.90 (2H, app. quintet, *J* 6.0Hz, CH_2), 1.72 (1H, dt, *J* 13.8, 6.8Hz, C*H*H), 1.61 (1H, s, -O*H*), 1.51 (1H, dt, *J* 14.0, 5.7Hz, CH*H*), 0.70 (3H, s, CH_3), 0.65 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 210.4 (0, *C*=O), 141.6 (0, Ar), 128.8 (1, 2 x Ar), 128.7 (1, Ar), 128.1 (1, 2 x Ar), 67.6 (1, *C*H-CO), 60.9 (1, *C*H-OH), 40.7 (2), 40.5 (0), 37.7 (2), 29.4 (3), 25.8 (3), 23.1 (2) ppm.

LRMS (CI): 215 ($[M-OH]^+$, 100%), 199 (8%), 91 (10%) amu.

HRMS (EI): Found $[M]^+$: 232.2139. $C_{15}H_{20}O_2$ requires 232.3181.

Synthesis of 3,3-dimethyl-2-[1-phenylmethylidene]-1-cyclohexanone **203**



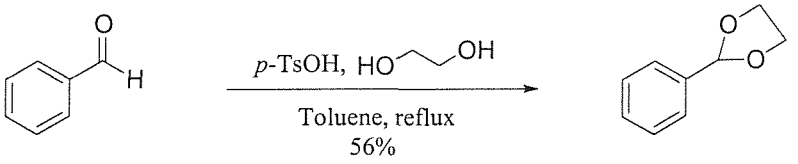
$C_{15}H_{20}O_2$
Mol Wt: 232
202

$C_{15}H_{18}O$
Mol Wt: 214
203

The alcohol **202** (7 mg, 0.03 mmol) was placed in HBr (48% aqueous, 0.5 mL) and stirred at room temperature for 2 h. The mixture was then extracted with DCM (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 4:1 Petroleum Ether:EtOAc) afforded compound **203** (5 mg, 0.02 mmol, 66%) as a colourless oil.

ν_{max}/cm^{-1} (neat):	3026w, 2959s, 1753s, 1653w, 1446m, 1260m.
λ_{max}/nm (ε_{max}, MeOH):	311 (2184).
δ_H (400MHz, $CDCl_3$):	7.35-7.15 (5H, m, Ar-*H*), 6.30 (1H, s, C=C*H*), 2.62 (2H, t, *J* 6.7Hz, CO-CH_2), 2.01 (2H, app. quintet, *J* 6.1Hz, $CH_2CH_2CH_2$), 1.81 (2H, t, *J* 6.4Hz, CH_2CH_2-C$(CH_3)_2$), 1.20 (6H, s, 2 x CH_3) ppm.
δ_C (75MHz, $CDCl_3$):	127.5 (1, 2 x Ar), 127.1 (1, Ar), 126.3 (1, 2 x Ar), 124.1 (1, C=*C*H), 43.4 (2), 39.4 (2), 26.0 (3, 2 x *C*H_3), 21.2 (2) ppm. Quaternary C not observed.
LRMS (CI):	232 ($[M+NH_4]^+$, 14%), 215 ($[M+H]^+$, 100%) amu.
HRMS (EI):	Found $[M]^+$: 214.1349. $C_{15}H_{18}O$ requires 214.1358.

Synthesis of 2-phenyl-1,3-dioxolane **208**



C_7H_6O
Mol Wt: 106
207

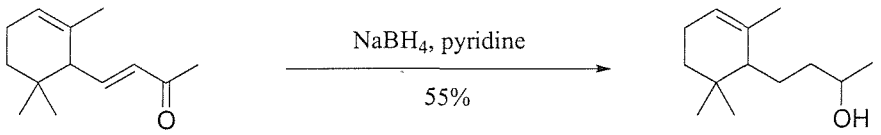
$C_9H_{10}O_2$
Mol Wt: 150
208

To benzaldehyde **207** (2.00 g, 18.86 mmol) in DCM (40 mL) was added *p*-TsOH (0.036 g, 0.19 mmol) and ethanediol (2.33 g, 37.53 mmol). The resulting mixture was heated at reflux in a flask fitted with a condenser and soxlet for 18 h. It was then washed with saturated aqueous $NaHCO_3$ solution (30 mL), water (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, petroleum ether) afforded compound **208** (1.55 g, 10.34 mmol, 56%) as a colourless oil.

Data is consistent with literature values.[138]

ν_{max}/cm^{-1} (neat):	3086m, 3026s, 2976m, 1604m, 1495s, 1119m.
δ_H (300MHz, $CDCl_3$):	7.55-7.39 (5H, m, Ar-*H*), 5.73 (1H, s, C=C-C*H*-O_2), 4.20-4.12 (2H, m, CH_2), 4.11-4.02 (2H, m, CH_2) ppm.
δ_C (75MHz, $CDCl_3$):	138.0 (0, Ar), 129.4 (1, Ar), 128.5 (1, 2 x Ar), 126.6 (1, 2 x Ar), 103.9 (1, C=C-*C*H-O_2), 65.5 (2, 2 x *C*H_2) ppm.
LRMS (CI):	151 ([M+H]$^+$, 100%), 105 (20%), 73 (22%) amu.

Synthesis of 4-(2,6,6,-trimethyl-2-cyclohexenyl)-2-butanol **227**



$C_{13}H_{20}O$
Mol Wt: 192
225

$C_{13}H_{24}O$
Mol Wt: 196
227

$NaBH_4$ (4.95 g, 130.26 mmol) was placed in pyridine (30 mL) and the mixture was stirred at room temperature for 15 min. It was then cooled at 0°C and α-ionone **225** (10.00 g, 52.08 mmol) in pyridine (70 mL) was added over 30 min. The resulting solution was stirred at room temperature for 12 h. It was then poured into cold aqueous KIO_3 solution (11.00 g, 150 mL of water) and stirred at room temperature for 2 h. The phases were separated and the aqueous layer was extracted with petrol (2 x 30 mL). The aqueous layer was then acidified to pH 2 with conc. HCl and was extracted with petrol (2 x 30 mL), The combined organic layers were washed with 2N HCl (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 15% ether in petroleum ether) afforded the desired compound **227** (5.61 g, 28.52 mmol, 55%) as a colourless oil.

Data is consistent with literature values.[139]

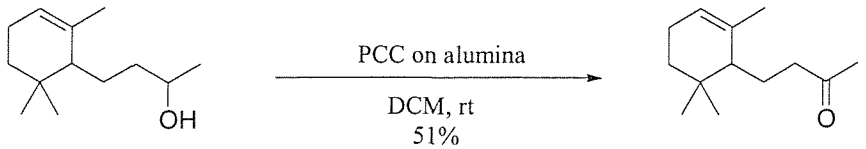
ν_{max}/cm^{-1} (neat): 3339br. s, 2963s, 1659m, 1454s.

δ_H (300MHz, $CDCl_3$): 5.30 (1H, s, C=C*H*), 3.79-3.66 (1H, m, C*H*-OH), 1.65 (3H, s, CH_3), 2.01-1.20 (9H, m, 4 x CH_2 + C*H*), 1.21 (3H, d, *J* 5.7Hz, CHOHCH_3), 0.91 (3H, s, CH_3), 0.85 (3H, s, CH_3) ppm. OH not observed.

δ_C (75MHz, $CDCl_3$): 136.5 (0, *C*=CH), 120.3 (1, C=*C*H), 68.9 (1, *C*HOH), 54.4 (0), 49.3 (1), 39.9 (2), 32.7 (2), 31.6 (2), 28.7 (2), 27.1 (3), 23.6 (3), 23.5 (3), 23.1 (3) ppm.

LRMS (CI): 214 ($[M+NH_4]^+$, 11%), 197 ($[M+H]^+$, 100%), 177 ($[M-OH]^+$, 61%), 163 (29%), 136 (54%), 123 (92%), 109 (36%), 93 (56%) amu.

Synthesis of 4-(2,6,6-trimethyl-2-cyclohexenyl)-2-butanone **226**



$C_{13}H_{24}O$
Mol Wt: 196
227

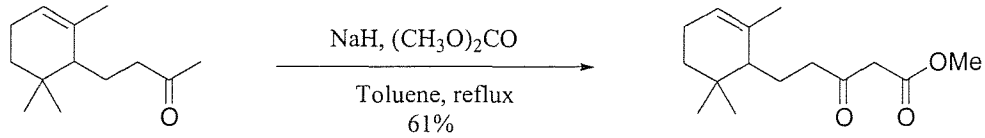
$C_{13}H_{22}O$
Mol Wt: 194
226

To a solution of alcohol **227** (2.68 g, 13.67 mmo) in DCM (150mL) was added PCC on alumina (36.73 g, 34.17 mmol, 20% w/w). The resulting suspension was then stirred at room temperature for 2 h. EtOAc was added (40 mL), and the reaction mixture was stirred for 0.5 h. It was then filtered through a florisil pad, which was eluted with ether and ethyl acetate. The combined eluates were concentrated *in vacuo*. Purification by column chromatography (silica gel, 40% ether in petroleum ether) afforded **226** (1.34 g, 6.93 mmol, 51%) as a colourless oil.

Data is consistent with literature values.[100]

ν_{max}/cm^{-1} (neat):	2955s, 2867s, 1716s, 1611w, 1449m, 1363s.
δ_H (300MHz, $CDCl_3$):	5.32 (1H, app. s, C=C*H*), 2.45-2.40 (2H, m, CH_2CO), 2.12 (3H, s, CO-CH_3), 2.20-1.00 (7H, m, 3 x CH_2 + C*H*), 1.67 (3H, s, CH_3), 0.90 (3H, s, CH_3), 0.85 (3H, s, CH_3) ppm.
δ_C (75MHz, $CDCl_3$):	209.5 (0, *C*=O), 135.7 (0, *C*=CH), 121.2 (1, C=*C*H), 48.4 (1), 43.7 (2, *C*H$_2$CO), 32.7 (0), 31.6 (2), 29.9 (3), 27.6 (3, 2 x CH_3), 24.3 (2), 23.5 (3), 22.9 (2) ppm.
LRMS (CI):	212 ([M+NH$_4$]$^+$, 4%), 195 ([M+H]$^+$, 52%), 177 ([M-OH]$^+$, 74%), 136 (100%), 121 (47%), 95 (44%), 81 (21%) amu.

Synthesis of 3-oxo-5-(2,6,6-trimethyl-cyclohex-2-enyl)-pentanoic acid methyl ester **223**[102]



$C_{13}H_{22}O$
Mol Wt: 194
226

$C_{15}H_{24}O_3$
Mol Wt: 252
223

Sodium hydride was preliminary washed with petroleum ether.

To a suspension of NaH (0.410 g, 10.26 mmol) in toluene (5 mL) was added dimethylcarbonate (0.62 mL, 7.32 mmol). The mixture was heated at reflux and ketone **226** (711 mg, 3.66 mmol) in toluene (10 mL) was slowly added. After complete addition, the solution was left heated at reflux until no gas evolved. Ice was added (5 g), and the mixture was acidified to pH 5 with 2N HCl solution. The phases were separated and the aqueous layer was further acidified to pH 3, and extracted with ether (2 x 25 mL). The combined organic extracts were washed with aqueous saturated Na_2CO_3 solution (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 5% ether in petroleum ether) afforded compound **223** (0.562 g, 2.23 mmol, 61 %) as a colourless oil.

Data is consistent with literature value.[140]

ν_{max}/cm^{-1} (neat): 3073w, 2977s, 2869s, 1750m, 1772m, 1437w, 1117m.

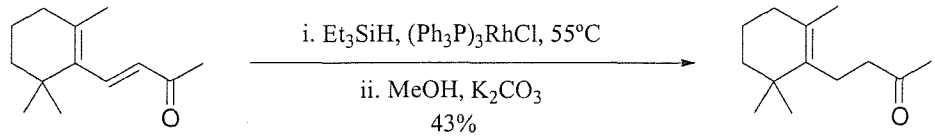
δ_H (300MHz, $CDCl_3$): 5.35 (1H, app. s, C=C*H*), 3.72 (3H, s, OCH_3), 3.43 (2H, s, CO-CH_2CO), 2.62-2.53 (2H, m, -CH_2CO), 2.00-1.90 (2H, app. br. s, CH_2), 1.80-1.72 (1H, m, CH*H*), 1.66 (3H, s, C=C-CH_3), 1.60-1.55 (1H, m, C*H*H), 1.48 (1H, t, *J* 6.7Hz, C*H*), 1.42-1.36 (1H, m, CH*H*), 1.13 (1H, dt, *J* 13.4, 4.8Hz, C*H*H), 0.89 (3H, s, CH_3), 0.85 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 202.9 (0, *C*=O), 167.8 (0, O-*C*=O), 135.5 (0, *C*=CH), 121.3 (1, C=*C*H), 52.5 (3, O*C*H_3), 49.2 (2, CO*C*H_2CO), 48.4 (3),

43.1 (2, CH_2CO), 32.7 (0), 31.6 (2), 27.8 (3, 2 x CH_3), 24.1 (2), 23.6 (1), 23.0 (2) ppm.

LRMS (CI): 195 (56%), 177 (80%), 136 (100%), 121 (51%), 95 (42%) amu.

Synthesis of 4-(2,6,6-trimethyl-cyclohex-1-enyl)-butan-2-one **232**



$C_{13}H_{20}O$
Mol Wt: 192
231

$C_{13}H_{22}O$
Mol Wt: 194
232

To β-ionone **231** (10.00 g, 52.00 mmol) in THF (150 mL) were added Wilkinson's catalyst (240 mg, 0.26 mmol) and Et_3SiH (16.61 mL, 104.00 mmol). The resulting solution was then heated at 55°C for 2 h. After cooling to room temperature, 0.1% K_2CO_3 solution (in 40 mL of methanol) was added and the mixture was stirred for 3 h. It was then concentrated *in vacuo*. Purification by column chromatography (silica gel, 5% ether in petroleum ether) afforded compound **232** (4.332 g, 22.32 mmol, 43%) as a pale yellow oil.

Data is consistent with literature values.[104]

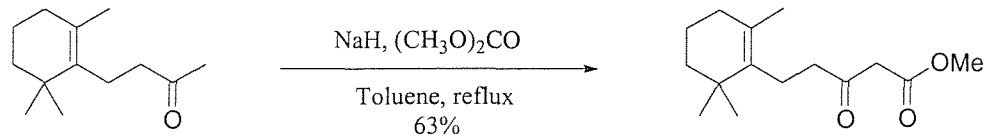
ν_{max}/cm^{-1} (neat): 2956s, 2868s, 1716s, 1674m, 1449m, 1363s, 1252m.

δ_H (300MHz, $CDCl_3$): 2.55-2.45 (2H, m, CH_2-CO), 2.29-2.21 (2H, m, CH_2), 2.14 (3H, s, C=C-CH_3), 1.89 (2H, t, *J* 6.1Hz, -C=C-CH_2CH_2), 1.55 (3H, s, -CO-CH_3), 1.58-1.50 (2H, m, CH_2), 1.43-1.36 (2H, m, CH_2), 0.96 (6H, s, 2 x CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 209.3 (0, *C*=O), 136.1 (0, *C*=C), 127.9 (0, C=*C*), 44.5 (2, CH_2-CO), 39.7 (2), 35.2 (0), 32.7 (2), 29.8 (3), 28.4 (3, 2 x CH_3), 22.2 (2), 19.7 (3), 19.4 (2) ppm.

LRMS (CI): 212 ($[M+NH_4]^+$, 10%), 177 (100%), 161 (5%), 136 (80%), 121 (44%), 95 (45%), 81 (19%) amu.

Synthesis of 3-oxo-5-(2,6,6-trimethyl-cyclohex-1-enyl)-pentanoic acid methyl ester **233**



$C_{13}H_{22}O$
Mol Wt: 194
232

$C_{15}H_{24}O_3$
Mol Wt: 252
233

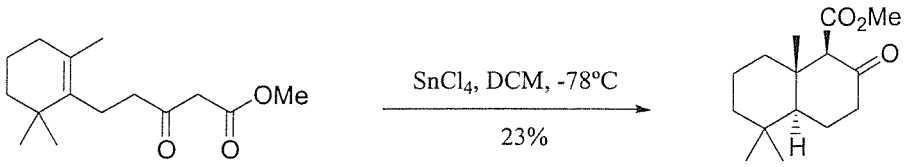
Sodium hydride was preliminary washed with petrol.

To a suspension of NaH (2.50 g, 62.52 mmol) in toluene (35 mL) was added dimethylcarbonate (3.76 mL, 44.66 mmol). The mixture was heated at reflux and ketone **232** (4.332 g, 22.33 mmol) in toluene (35 mL) was slowly added. After complete addition, the solution was left heated at reflux until no gas evolved anymore. Ice was added (20 g), and the mixture was acidified to pH 5 with 2N HCl solution. The phases were separated and the aqueous layer was further acidified to pH 3, and extracted with ether (2 x 40 mL). The combined organic extracts were washed with aqueous saturated Na_2CO_3 solution (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 5% ether in petroleum ether) afforded compound **233** (3.544 g, 14.06 mmol, 63 %) as a colourless oil.

Data is consistent with literature values.[104]

ν_{max}/cm^{-1} (neat):	2955s, 2869m, 1749s, 1719s, 1641w, 1438m, 1241m
δ_H (300MHz, $CDCl_3$):	3.72 (3H, s, O-C*H*$_3$), 3.45 (2H, s, CO-C*H*$_2$-CO), 2.65-2.57 (2H, m, -COC*H*$_2$), 2.34-2.25 (2H, m, C*H*$_2$), 1.89 (2H, t, *J* 5.9Hz, C=C-C*H*$_2$CH$_2$), 1.55 (3H, s, -CO-C*H*$_3$), 1.64-1.50 (2H, m, C*H*$_2$), 1.44-1.36 (2H, m, C*H*$_2$), 0.96 (6H, s, 2 x C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	202.9 (0, *C*=O), 167.8 (0, O-*C*=O), 135.6 (0, *C*=C), 128.3 (0, C=*C*), 52.5 (3, O*C*H$_3$), 49.1 (2, CO-*C*H$_2$-CO), 43.9 (2, CO-*C*H$_2$), 39.8 (2), 35.1 (0), 32.8 (2), 28.5 (3, 2 x *C*H$_3$), 22.1 (2), 19.8 (3), 19.5 (2) ppm.
LRMS (CI):	195 (100%), 177 (67%), 161 (17%), 121 (22%) amu.

Synthesis of 5,5,8a-trimethyl-2-oxo-decahydro-naphtalene-1-carboxylic acid methyl ester **228**

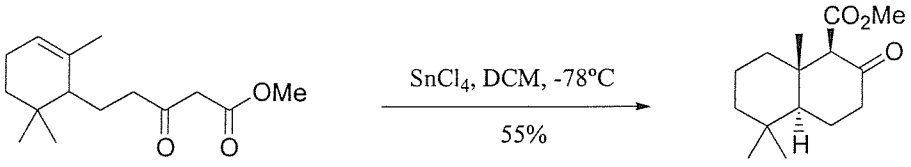


$C_{15}H_{24}O_3$
Mol Wt: 252
233

$C_{15}H_{24}O_3$
Mol Wt: 252
228

To keto-ester **233** (2.00 g, 7.94 mmol) in DCM (35mL) under N_2 and at –78°C was added $SnCl_4$ (1.86 mL, 15.88 mmol). The solution was allowed to reach room temperature and stirred for 18h. It was then diluted with EtOAc (15 mL), washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded compound **228** (0.467 g, 1.85 mmol, 23%) as a white solid. Recrystallisation from petroleum ether afforded colourless needles. Some starting material was also recovered (924 mg, 3.67 mmol).

Or alternatively:



$C_{15}H_{24}O_3$
Mol Wt: 252
223

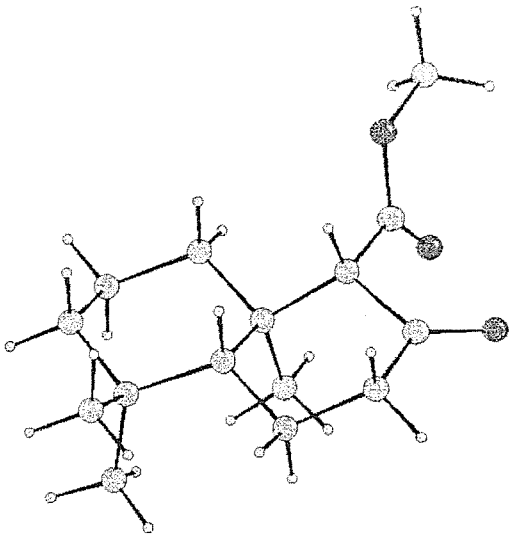
$C_{15}H_{24}O_3$
Mol Wt: 252
228

To keto-ester **223** (0.300 g, 1.19 mmol) in DCM (15 mL) under N_2 and at –78°C was added $SnCl_4$ (0.28 mL, 2.38 mmol). The solution was allowed to reach room temperature and stirred for 18h. It was then washed with 10% aqueous HCl solution (10 mL), saturated aqueous $KHCO_3$ solution (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and

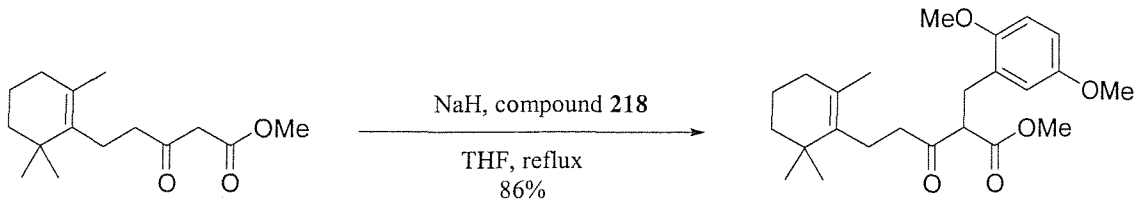
concentrated. Recrystallisation from petroleum ether afforded compound **228** (165 mg, 0.65 mmol, 55%) as colourless needles.

Mp:	84-85°C (petroleum ether/ether). Lit: 85-86°C.[104]
ν_{max}/cm^{-1} (neat):	2951s, 1750s, 1715s, 1434m, 1196s, 1167s.
δ_H (300MHz, $CDCl_3$):	3.69 (3H, s, O-C*H*$_3$), 3.23 (1H, s, -CO-C*H*-CO), 2.55-2.45 (1H, m, CH*H*), 2.40-2.27 (1H, m, C*H*H), 2.10-2.00 (1H, m, C*H*H), 1.80-1.70 (1H, m, CH*H*), 1.70-1.10 (7H, m, 3 x C*H*$_2$ + C*H*), 1.11 (3H, s, C*H*$_3$), 0.95 (3H, s, C*H*$_3$), 0.87 (3H, s, C*H*$_3$) ppm.
δ_C (75MHz, $CDCl_3$):	205.8 (0, *C*=O), 168.9 (0, O-*C*=O), 70.1 (1, *C*H-CO_2Me), 53.3 (3, O*C*H$_3$), 51.6 (1), 42.2 (0), 42.0 (2, *C*H$_2$CO), 41.4 (2), 39.3 (2), 33.7 (0), 33.6 (3), 23.2 (2), 21.9 (3), 18.7 (2), 14.9 (3) ppm.
LRMS (CI):	212 (100%), 195 (90%), 176 (17%), 161 (7%), 109 (10%), 81 (13%), 55 (23%) amu.
CHN:	Found C: 71.15; H: 9.77. $C_{15}H_{24}O_3$ requires C: 71.39; H: 9.59.

X-RAY STRUCTURE:



Synthesis of 2-(2,5-dimethyl-benzyl)-3-oxo-5-(2,6,6-trimethyl-cyclohex-1-enyl)-pentanoic acid methyl ester **245**



$C_{15}H_{24}O_3$
Mol Wt: 252
231

$C_{24}H_{34}O_5$
Mol Wt: 402
245

Sodium hydride was preliminary washed with petrol.

NaH (0.105 g, 2.62 mmol, 60% w/w) was suspended in THF (7 mL) under N_2 and cooled to 0°C. Keto-ester **231** (0.599 g, 2.38 mmol) in THF (15 mL) was added and the solution was stirred at 0°C for 30 min. The aromatic compound **218** (605 mg, 2.62 mmol) in THF (10 mL) was then added and the resulting mixture was heated at reflux for 18h. Water (10 mL) and ether (10 mL) were added, the phases were separated and the aqueous layer was washed with ether (10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded compound **245** (0.820 g, 2.04 mmol, 86%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 2954s, 2867s, 1747s, 1716s, 1647w, 1611m, 1464s, 1225s, 1178s, 804m.

δ_H (300MHz, $CDCl_3$): 6.78-6.69 (3H, m, Ar-*H*), 3.95 (1H, t, *J* 7.3Hz, CO-C*H*-CO), 3.76 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.11 (2H, d, *J* 7.3Hz, Ar-CH_2-), 2.65-2.50 (1H, m, C*H*H), 2.44-2.31 (1H, m, CH*H*), 2.17 (2H, dt, *J* 11.0, 5.5Hz, CH_2-CH_2-CH_2), 1.87 (2H, t, *J* 5.9Hz, CH_2-CH_2-CH_2), 1.57-1.50 (2H, m, CH_2), 1.47 (3H, s, -C=C-CH_3), 1.37-1.30 (2H, m, CH_2-CH_2-CH_2), 0.96 (3H, s, -CH_3), 0.89 (3H, s, -CH_3) ppm.

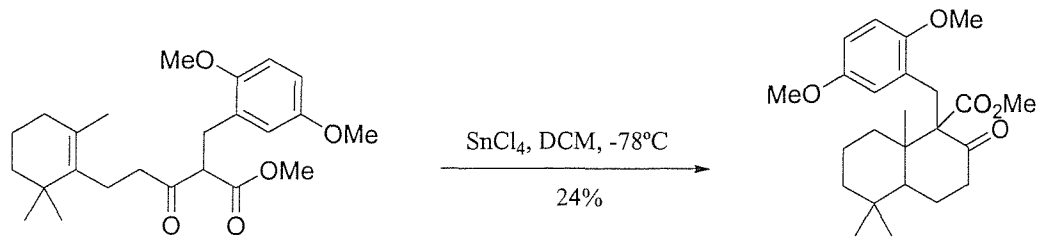
δ_C (75MHz, $CDCl_3$): 205.7 (0, *C*=O), 170.1 (0, O-*C*=O), 153.5 (0, Ar next to OMe), 151.7 (0, Ar next to OMe), 135.8 (0, Ar next to CH_2),

128.1 (0, *C*=C), 127.4 (0, C=*C*), 117.2 (1, Ar), 112.5 (1, Ar), 111.8 (1, Ar), 57.8 (3, O*C*H$_3$), 55.9 (1, CO-*C*H-CO), 55.8 (3, O*C*H$_3$), 52.4 (3, O*C*H$_3$), 44.0 (2, *C*H$_2$CO), 39.8 (2), 35.1 (0), 32.8 (2), 30.1 (2), 28.4 (3, 2 x *C*H$_3$), 22.1 (2), 19.7 (3), 19.5 (2) ppm.

LRMS (CI): 345 ([M-CO_2Me]$^+$, 100%), 327 (11%), 209 (34%), 195 (10%), 165 (20%), 151 (24%), 137 (87%), 123 (14%) amu.

HRMS (ES): Found [2M+Na]$^+$: 827.4685. $(C_{24}H_{34}O_5)_2$,Na requires 827.4705.

Synthesis of 1-(2,5-dimethoxy-benzyl)-5,5,8a-trimethyl-2-oxo-decahydro-naphatlene-1-carboxylic acid methyl ester **244**



$C_{24}H_{34}O_5$
Mol Wt: 402
245

$C_{24}H_{34}O_5$
Mol Wt: 402
244

To keto-ester **245** (250 mg, 0.62 mmol) in DCM (15 mL) at –78°C and under N_2 was added $SnCl_4$ (0.15 mL, 1.24 mmol). The solution was warmed to room temperature and stirred for 18h. It was then washed with 10% aqueous HCl solution (10 mL), saturated aqueous $KHCO_3$ solution (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded the desired compound **244** (60 mg, 0.15 mmol, 24%) as colourless oil and a mixture of diastereoisomers.

ν_{max}/cm^{-1} (neat): 2953s, 1747s, 1716s, 1647.5w, 1611w, 1464s, 1178s, 1049s.

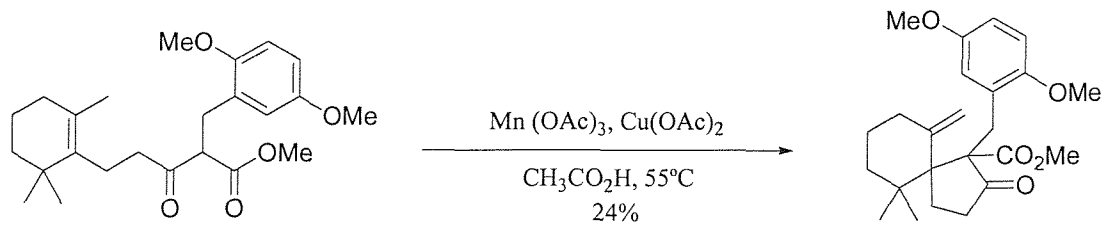
δ_H (300MHz, $CDCl_3$): 6.69-6.53 (3H, m, 3 x Ar*H*), 3.72 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.22-2.99 (4H, m, 2 x CH_2), 2.10-1.96 (2H, m, CH_2), 1.93-1.62 (2H, m, CH_2), 1.45-1.15 (4H, m, 2 x CH_2), 1.05 (1H, t, *J* 6.3Hz, C*H*), 0.84 (6H, s, 2 x CH_3), 0.72 (3H, s, CH_3) ppm.

δ_C (75MHz, $CDCl_3$): 174.0 (0, O-*C*=O), 154.0 (0, Ar next to OMe), 152.5 (0, Ar next to OMe), 131.8 (0, Ar next to CH_2), 115.2 (1, Ar), 111.5 (1, Ar), 110.7 (1, Ar), 97.5 (0, CO-*C*-CO_2Me), 57.5 (3, OCH_3), 56.6 (3, OCH_3), 56.1 (3, OCH_3), 51.2 (1, *C*H), 39.2 (0), 38.4 (2), 36.7 (2), 35.4 (0), 33.4 (3), 32.8 (2), 27.8 (2), 26.2 (2), 21.6 (3), 23.2 (2), 16.1 (3) ppm. Ketone not observed.

LRMS (CI): 403 ($[M+H]^+$, 100%), 371 (10%) amu.

HRMS (ES): Found $[2M+Na]^+$: 827.4688. $(C_{24}H_{34}O_5)_2Na$ requires 827.4705.

Synthesis of 1-(2,5-dimethoxy-benzyl)-6,6-dimethyl-10-methylene-2-oxo-spiro[4.5]decane-2-carboxylic acid methyl ester **273**



$C_{24}H_{34}O_5$
Mol Wt: 402
245

$C_{24}H_{32}O_5$
Mol Wt: 400
273

Manganese triacetate (333 mg, 1.24 mmol) and copper diacetate (225 mg, 1.24 mmol) were suspended in glacial acetic acid (10 mL) and heated at 55°C. The keto-ester **245** (250 mg, 0.62 mmol) in acetic acid (5 mL) was added at once and the solution was stirred at 55°C for 20 min whereby the original brown solution slurry turned to a blue turquoise suspension. It was allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned over water (10 mL) and ethyl acetate (10 mL), and the particulate was filtered off through celite. The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (2 x 15 mL), 10% aqueous $NaHCO_3$ solution (2 x 15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel 10% ether in petroleum ether) afforded compound **273** (0.060 g, 0.15 mmol, 24%) as a colourless oil and a mixture of diastereoisomers.

ν_{max}/cm^{-1} (neat): 3027m, 2976m, 1751m, 1716m, 1604m, 1496s.

δ_H (300MHz, $CDCl_3$): 6.78-6.62 (3H, m, 3 x Ar*H*), 4.72 (1H, app. s, -C=C*H*H), 4.62 (1H, app. s, -C=CH*H*), 3.78 (3H, s, -OC*H*$_3$), 3.72 (3H, s, -OC*H*$_3$), 3.64 (3H, s, -OC*H*$_3$), 3.42-3.00 (2H, m, C*H*$_2$), 2.46-1.90 (4H, m, 2 C*H*$_2$), 1.55-1.47 (5H, m, 2 x C*H*$_2$ + CH*H*), 0.85 (7H, m, 2 x C*H*$_3$ + C*H*H) ppm.

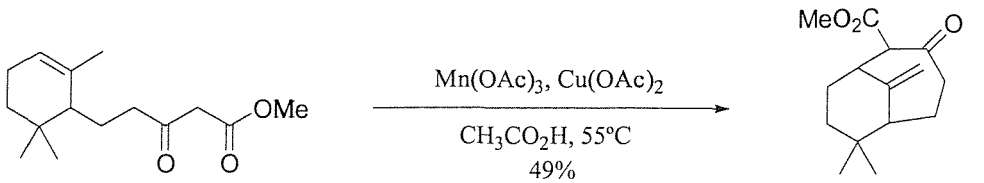
δ_C (75MHz, $CDCl_3$): 173.9 (0, O-*C*=O), 153.5 (0, Ar next to OMe), 151.9 (0, Ar next to OMe), 147.8 (0, -*C*=CH$_2$), 136.4 (0, Ar next to CH$_2$), 123.8 (1, Ar), 114.9 (1, Ar), 111.1 (1, Ar), 107.9 (2, -C=*C*H$_2$),

99.3 (0), 56.3 (3, O*C*H$_3$), 55.8 (3, O*C*H$_3$), 51.0 (3, O*C*H$_3$), 38.9 (0), 38.0 (2), 37.3 (0), 33.3 (2), 31.6 (2), 28.2 (2), 25.9 (2), 23.9 (3), 22.7 (2), 21.9 (3) ppm. Ketone not observed.

LRMS (CI): 400 ([M]$^+$, 40%), 369 (12%), 264 (22%), 232 (100%), 191 (32%), 176 (18%), 151 (54%), 135 (16%), 121 (74%), 107 (38%), 91 (58%), 79 (37%), 55 (28%) amu.

HRMS (EI): Found [M+Na]$^+$: 423.2153. $C_{24}H_{32}O_5Na$ requires 423.2142.

Synthesis of 7,7-dimethyl-10-methylene-3-oxo-bicyclo[4.3.1]decane-2-carboxylic acid methyl ester **257**



$C_{15}H_{24}O_3$
Mol Wt: 252
227

$C_{15}H_{22}O_3$
Mol Wt: 250
257

Manganese triacetate (1.302 g, 4.86 mmol) and copper diacetate (883 mg, 4.86 mmol) were suspended in glacial acetic acid (20 mL) and heated at 70°C. The keto-ester **227** (612 mg, 2.43 mmol) in acetic acid (10 mL) was added at once and the solution was stirred at 70°C for 20 min whereby the original brown solution slurry turned to a blue turquoise suspension. It was allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned over water (25 mL) and ethyl acetate (25 mL), and the particulate was filtered off through celite. The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (2 x 20 mL), 10% aqueous $NaHCO_3$ solution (2 x 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded compound **257** (0.299 g, 1.20 mmol, 49%) as a colourless oil.

ν_{max}/cm^{-1} (neat): 3073w, 2977s, 2869s, 1750m, 1713m, 1647w, 1437w, 1117m.

δ_H (300MHz, $CDCl_3$): 4.86 (1H, d, *J* 2.0Hz, C=C*H*H), 4.69 (1H, d, *J* 2.0Hz, C=CH*H*), 4.00 (1H, d, 8.5Hz, Me_2OC-C*H*-CO), 3.61 (3H, s, OC*H*$_3$), 3.07 (1H, d, *J* 8.0Hz, CO-CH-C*H*), 2.35 (1H, dt, *J* 15.5, 3.5Hz, CO-CH*H*), 2.27-2.14 (1H, m, CO-C*H*H), 2.03 (1H, t, *J* 9.5Hz, $_2$HC=C-C*H*), 1.87-1.68 (4H, m, CO-CH_2-C*H*$_2$ + C*H*H-C*H*H), 1.37 (1H, m, CH*H*), 1.23 (1H, m, C*H*H), 0.89 (3H, s, -C*H*$_3$), 0.87 (3H, s, -C*H*$_3$) ppm.

δ_C (75MHz, $CDCl_3$): 206.7 (0, *C*=O), 170.5 (0, O-*C*=O), 147.3 (0, *C*=CH_2), 114.5 (2, C=*C*H$_2$), 59.0 (3, O*C*H$_3$), 52.5 (1,CO_2Me-*C*H-CO), 51.2

(1, CH_2-*C*H-CO_2Me), 40.3 (1), 40.1 (2, *C*H_2-CO), 34.8 (0), 28.9 (2), 27.7 (3), 27.3 (2), 27.1 (3), 22.2 (2) ppm.

LRMS (CI): 210 (12%), 193 (100%), 175 (22%), 136 (31%), 107 (16%), 91 (30%), 79 (21%) amu.

HRMS (EI): Found $[M]^+$: 250.1573. $C_{15}H_{22}O_3$ requires 250.1569.

CHAPTER 6

APPENDICES

X-ray data for compound **228**

Scale	Du(iso)	Ou(iso)	Polarity	Flack	Extinction
1.696(15)	0.050	0.050	1.000	0.000	0.000

10301001 Compound X 02-30-10
Formula C15 H24 O3

Crystal Class	Triclinic	Space Group P	-1
a	6.3408(2)	alpha	80.6034(11)
b	9.8288(3)	beta	82.7956(12)
c	11.1929(4)	gamma	88.590(2)
Volume	682.77(4)	Z	2
Radiation type	Mo K\a	Wavelength	0.710730
Dx	1.23	Mr	252.35
Mu	0.083	Temperature (K)	120
Size	0.20x 0.20x 0.50		
Colour	colourless	Shape	plate
Cell from	2722 Reflections	Theta Range	3 to 27
Standard Interval	0	Standard Count	0
Diffractometer type	KAPPACCD	Scan type	OMEGA
Absorption type	multi-scan	Transmissionrange	0.98 0.98
Reflections measured	5596	Independent reflections	3042
Rint	0.0002	Theta max	27.48
Hmin, Hmax	-8 8		
Kmin, Kmax	-12 12		
Lmin, Lmax	-14 14		

Refinement on Fsqd

R-factor	0.042	Weighted R-factor	0.119
		Max shift/su	0.0003
Delta Rho min	-0.25	Delta Rho max	0.33
Reflections used	2529	sigma(I) limit	3.00
Number of parameters	163	Goodness of fit	0.958

O(1)	- C(6)	1.3437(16)	
O(1)	- C(15)	1.4488(16)	
O(2)	- C(11)	1.2145(16)	
O(3)	- C(6)	1.2086(17)	
C(4)	- C(5)	1.5572(17)	
C(4)	- C(12)	1.5349(17)	
C(4)	- C(17)	1.5618(17)	
C(5)	- C(9)	1.5424(17)	
C(5)	- C(10)	1.5685(17)	
C(5)	- C(13)	1.5388(18)	
C(6)	- C(10)	1.5172(17)	
C(7)	- C(14)	1.5243(19)	
C(7)	- C(17)	1.5363(18)	
C(8)	- C(11)	1.5064(19)	
C(8)	- C(12)	1.5373(19)	
C(9)	- C(14)	1.5278(18)	
C(10)	- C(11)	1.5262(17)	
C(16)	- C(17)	1.540(2)	
C(17)	- C(18)	1.5351(19)	
C(6)	- O(1) - C(15)	115.06(11)	
C(5)	- C(4) - C(12)	110.8(1)	
C(5)	- C(4) - C(17)	116.2(1)	
C(12)	- C(4) - C(17)	113.5(1)	
C(4)	- C(5) - C(9)	109.4(1)	
C(4)	- C(5) - C(10)	105.7(1)	
C(9)	- C(5) - C(10)	107.5(1)	
C(4)	- C(5) - C(13)	114.03(11)	
C(9)	- C(5) - C(13)	110.34(11)	
C(10)	- C(5) - C(13)	109.5(1)	
O(1)	- C(6) - O(3)	123.25(12)	
O(1)	- C(6) - C(10)	110.68(11)	
O(3)	- C(6) - C(10)	126.07(12)	
C(14)	- C(7) - C(17)	114.09(11)	
C(11)	- C(8) - C(12)	114.39(11)	
C(5)	- C(9) - C(14)	112.83(11)	
C(5)	- C(10) - C(6)	113.4(1)	
C(5)	- C(10) - C(11)	112.2(1)	
C(6)	- C(10) - C(11)	111.2(1)	
O(2)	- C(11) - C(8)	122.51(12)	
O(2)	- C(11) - C(10)	122.26(12)	
C(8)	- C(11) - C(10)	115.00(11)	
C(4)	- C(12) - C(8)	112.56(11)	
C(7)	- C(14) - C(9)	110.50(11)	
C(4)	- C(17) - C(7)	108.7(1)	
C(4)	- C(17) - C(16)	108.92(11)	
C(7)	- C(17) - C(16)	107.18(11)	
C(4)	- C(17) - C(18)	114.70(11)	
C(7)	- C(17) - C(18)	109.72(11)	
C(16)	- C(17) - C(18)	107.33(12)	

Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
	U(iso)	Size	D/100	A/100		
O(1)	0.0175(5)	0.0146(5)	0.0260(5)	0.0002(4)	-0.0010(4)	-0.0037(4)
O(2)	0.0266(5)	0.0154(5)	0.0257(6)	-0.0062(4)	-0.0005(4)	0.0021(4)
O(3)	0.0266(5)	0.0175(5)	0.0272(6)	0.0031(4)	-0.0059(4)	-0.0006(4)
C(4)	0.0160(6)	0.0121(6)	0.0152(6)	-0.0026(5)	-0.0012(5)	-0.0009(5)
C(5)	0.0149(6)	0.0118(6)	0.0139(6)	-0.0025(5)	-0.0015(5)	-0.0006(4)
C(6)	0.0188(6)	0.0134(6)	0.0162(6)	-0.0048(5)	-0.0001(5)	-0.0008(5)
C(7)	0.0186(6)	0.0148(6)	0.0235(7)	-0.0071(5)	-0.0026(5)	0.0011(5)
C(8)	0.0238(7)	0.0169(6)	0.0176(7)	-0.0040(5)	0.0044(5)	-0.0015(5)
C(9)	0.0169(6)	0.0152(6)	0.0169(6)	-0.0031(5)	0.0007(5)	-0.0009(5)
C(10)	0.0162(6)	0.0112(6)	0.0151(6)	-0.0016(5)	-0.0017(5)	-0.0006(5)
C(11)	0.0187(6)	0.0163(6)	0.0154(6)	-0.0038(5)	-0.0037(5)	0.0008(5)
C(12)	0.0197(7)	0.0160(6)	0.0218(7)	-0.0042(5)	0.0041(5)	-0.0036(5)
C(13)	0.0203(6)	0.0172(6)	0.0199(7)	-0.0031(5)	-0.0063(5)	0.0020(5)
C(14)	0.0211(7)	0.0187(7)	0.0187(7)	-0.0066(5)	0.0008(5)	-0.0001(5)
C(15)	0.0220(7)	0.0187(7)	0.0375(9)	0.0032(6)	0.0005(6)	-0.0070(5)
C(16)	0.0359(8)	0.0136(7)	0.0302(8)	-0.0028(6)	0.0036(6)	-0.0030(6)
C(17)	0.0172(6)	0.0120(6)	0.0220(7)	-0.0040(5)	-0.0014(5)	-0.0013(5)
C(18)	0.0192(7)	0.0235(7)	0.0380(9)	-0.0142(6)	-0.0067(6)	-0.0012(6)

Atom	x/a	y/b	z/c	U(iso)	Occ
O(1)	0.15472(15)	0.44159(9)	0.74179(9)	0.0198	
O(2)	0.69961(16)	0.4287(1)	0.58424(9)	0.0225	
O(3)	0.44439(16)	0.3562(1)	0.8251(1)	0.0243	
C(4)	0.5991(2)	0.81410(13)	0.68610(12)	0.0144	
C(5)	0.5197(2)	0.68085(13)	0.77404(11)	0.0135	
C(6)	0.3596(2)	0.44597(13)	0.76027(12)	0.0160	
C(7)	0.4031(2)	0.96384(14)	0.82608(13)	0.0185	
C(8)	0.7721(2)	0.66984(14)	0.52970(13)	0.0199	
C(9)	0.3124(2)	0.71293(13)	0.85249(12)	0.0165	
C(10)	0.4638(2)	0.57733(13)	0.68999(12)	0.0143	
C(11)	0.6551(2)	0.54535(14)	0.60170(12)	0.0165	
C(12)	0.8022(2)	0.78486(14)	0.60401(13)	0.0195	
C(13)	0.6843(2)	0.61454(14)	0.85603(13)	0.0188	
C(14)	0.3335(2)	0.83587(14)	0.91785(13)	0.0194	
C(15)	0.0402(2)	0.31995(15)	0.80544(15)	0.0272	
C(16)	0.6387(3)	1.07299(15)	0.64426(15)	0.0273	
C(17)	0.6135(2)	0.94609(13)	0.74565(13)	0.0170	
C(18)	0.7999(2)	0.94667(15)	0.82088(15)	0.0256	

Atom	x/a	y/b	z/c	U(iso)	Occ
H(41)	0.4833	0.8391	0.6326	0.0168	
H(71)	0.4187	1.0419	0.8721	0.0216	
H(72)	0.2890	0.9882	0.7716	0.0216	
H(81)	0.9156	0.6393	0.4943	0.0223	
H(82)	0.6896	0.7089	0.4606	0.0223	
H(91)	0.2708	0.6298	0.9143	0.0194	
H(92)	0.1979	0.7341	0.7974	0.0194	
H(101)	0.3552	0.6262	0.6403	0.0157	
H(121)	0.9187	0.7564	0.6562	0.0222	
H(122)	0.8474	0.8715	0.5460	0.0222	
H(131)	0.6230	0.5298	0.9102	0.0225	
H(132)	0.7240	0.6817	0.9076	0.0225	
H(133)	0.8143	0.5885	0.8040	0.0225	
H(141)	0.4430	0.8137	0.9755	0.0223	
H(142)	0.1940	0.8541	0.9645	0.0223	
H(151)	-0.1110	0.3251	0.7866	0.0314	
H(152)	0.0398	0.3147	0.8958	0.0314	
H(153)	0.1090	0.2352	0.7796	0.0314	
H(161)	0.6490	1.1591	0.6797	0.0313	
H(162)	0.7713	1.0631	0.5863	0.0313	
H(163)	0.5132	1.0805	0.5967	0.0313	
H(181)	0.8001	1.0338	0.8555	0.0341	
H(182)	0.7886	0.8659	0.8882	0.0341	
H(183)	0.9382	0.9393	0.7665	0.0341	

CHAPTER 7

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