UNIVERSITY OF SOUTHAMPTON

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS USING CYCLISATION STRATEGIES

BY

Matthew Charles Lucas

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Department of Chemistry

Faculty of Science

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

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The Total Synthesis of Natural Products Using Cyclisation Strategies

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This thesis is concerned with the total syntheses of natural products and the development of a novel diastereoselective radical cyclisation reaction. Total syntheses of marine sesquiterpenes aplysin and debromoaplysin are described. The key step involves a diastereoselective, sulfur mediated radical cyclisation that simultaneously creates the sterically demanding aplysin skeleton and establishes the relative configuration of the three contiguous stereogenic centres.

Total syntheses of aplysin, debromoaplysin, aplysinol, debromoaplysinol, isoaplysin, isolaurinterol and debromoisolaurinterol are described. Key features are a diastereoselective radical to polar crossover sequence mediated by tin, and a series of biomimetic cyclisation and oxidation reactions.

The first reported total synthesis of the linear triquinane 1-desoxyhypnophilin is described, using a ring closing metathesis, allylic oxidation and regioselective epoxidation as key transformations.

A short synthesis of the pyrrolophenanthridone alkaloid hippadine is described. The approach features the use of a low temperature Ullmann type coupling reaction to effect construction of the pentacyclic skeleton and an unusual methylene oxidation promoted by barium manganate.

A simple and direct method for converting thioamides to thioesters through the simple expedient of warming in an aqueous THF solution containing an alkylating reagent is described.

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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 1997 and October 2000. No part of this thesis has previously been submitted for a degree.

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Thanks to everyone I met at Glaxo Wellcome; particularly my supervisor Peter Howes for running all my microanalyses, for his advice and proofreading.

Thanks to mum and dad (and Rachel) for supporting me and being impressed by the letters after my name.

...and finally I would like to thank you all for your kind attention.

'Have a heart that never hardens, and a temper that never tires, and a touch that never hurts'

ABBREVIATIONS

Ac	acetyl
Ad	adamantyl
AIBN	α,α-azo*iso*butyronitrile
amu	atomic mass units
APCI	atmospheric pressure chemical ionisation
approx.	approximately
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
Calcd.	calculated
cat.	catalytic
*c*Hex	cyclohexyl
CHN	combustion analysis
CI	chemical ionisation
conc.	Concentrated
COSY	correlated spectroscopy
Cp	cyclopentadienyl
d	days
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
o-DCB	*ortho*-dichlorobenzene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsufoxide
EI	electron ionisation

ES	electrospray
eq.	Equivalents
Et	ethyl
FT	Fourier Transform
GC	gas chromatography
h	hours
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectra
IR	infra red
LDA	lithium diisopropylamide
lit.	literature
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectra
M	molar
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
min	minutes
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
n.O.e	nuclear Overhauser effect
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Py	pyridine
r.t.	room temperature
SM	starting material
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl

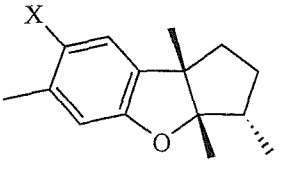
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
p-TsOH	*p*-toluenesulfonic acid
UV	ultra violet

CHAPTER 1

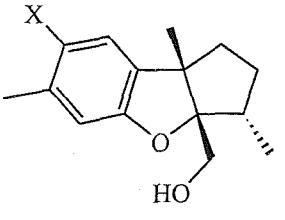
INTRODUCTION

1.1 BACKGROUND

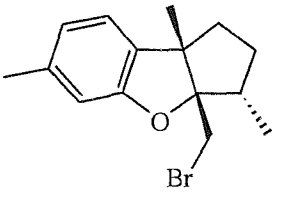
First isolated in a screen designed to obtain anti-tumour agents from natural sources, (–)–aplysin **1** was one of the first halogenated sesquiterpenes to be extracted from a marine source.[1] It is a representative of a class of natural products **1** – **5** isolated from the sea hare *Aplysia*. Sea hare inhabit tropical coastal waters throughout the world, but are prolific in the eastern Pacific Ocean and the coast of North America. The aplysins **1** – **5** are also found in the opisthobranchs of the North American coast and in the red sea alga *Laurencia*. The molluscs accumulate aplysin **1** and the related compounds **2** – **5** in their gut, where they render the harmless creatures unpalatable to predators through their antifeedant properties.[2,3] Aplysin **1** and debromoaplysin **2** have always been isolated together in all natural sources, and this has led to speculation that the compounds may also function as antioxidants to scavenge reactive halogens.[15]



X = Br, Aplysin **1**
X = H, Debromoaplysin **2**



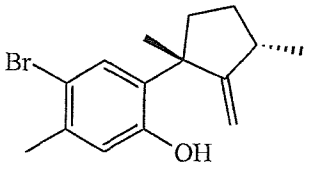
X = Br, Aplysinol **3**
X = H, Debromoaplysinol **4**



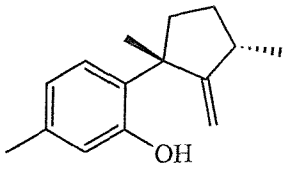
Isoaplysin **5**

The sesquiterpenes **1** – **5** in *Aplysia* originate from the red alga *Laurencia* that constitute the sea slug's main dietary component. The *Laurencia* genus is a rich source of terpenoids

including isolaurinterol **6** and debromoisolaurinterol **7**. Speculation that aplysin **1** is a metabolite derived by bioconversion of **6** and **7** is supported by the biomimetic transformations that we have performed in our total syntheses of **1** – **7** (*vide infra*).



Isolaurinterol **6**



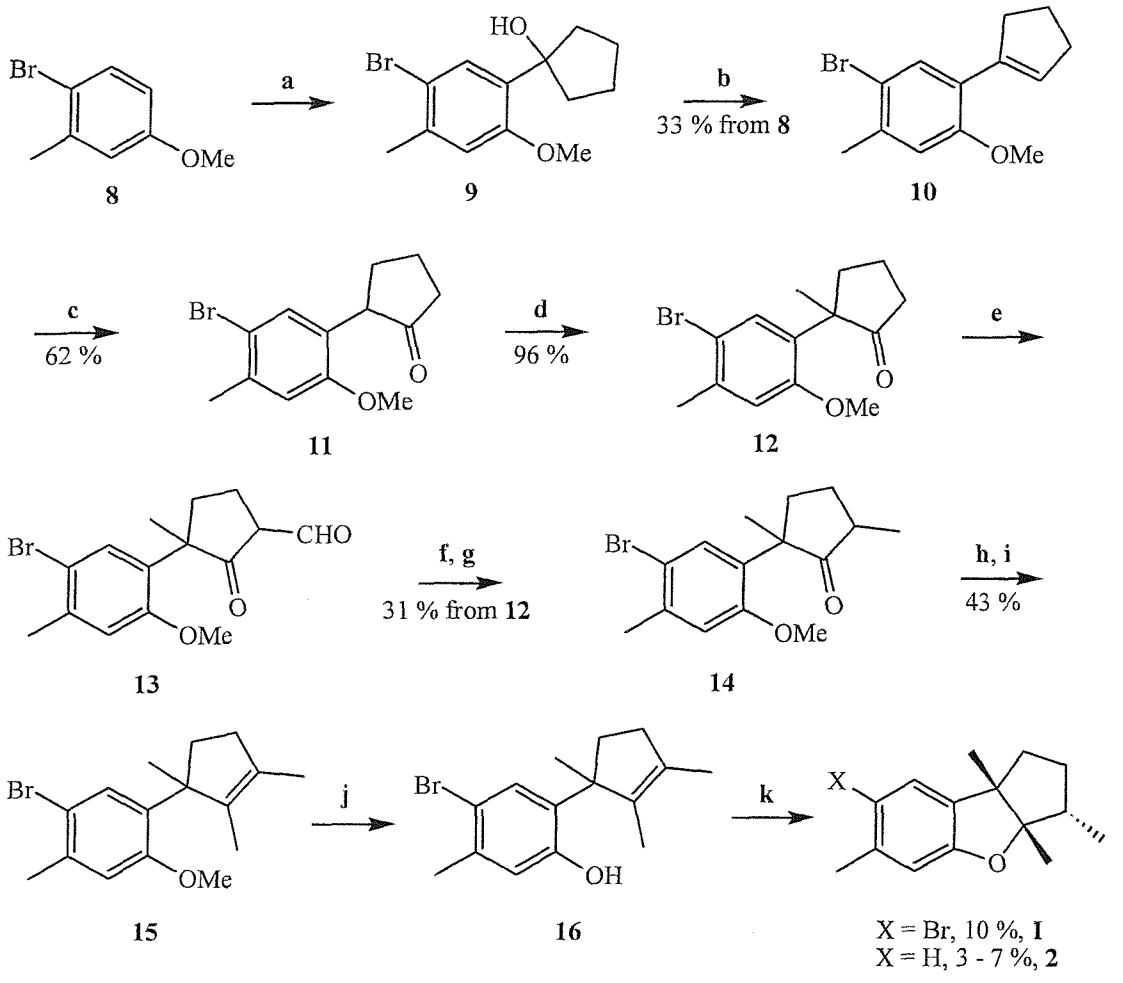
Debromoisolaurinterol 7

Aplysins **1** – **5** have aroused synthetic interest since their discovery in 1963.[1a] The sterically congested skeleton and three contiguous stereogenic centres present a significant challenge to the synthetic chemist. Both enantioselective and diastereoselective syntheses of **1** and **2** have resulted from the efforts of several groups,[3,4,6-9,12-16,18,19,21-23] as have the diastereoselective syntheses of **3** – **5**.[15] There have, however, been no reported syntheses of isolaurinterols **6** and **7**.

1.2 Previous Diastereoselective Syntheses

1.2.1 Yamada's Syntheses of Aplysin and Debromoaplysin

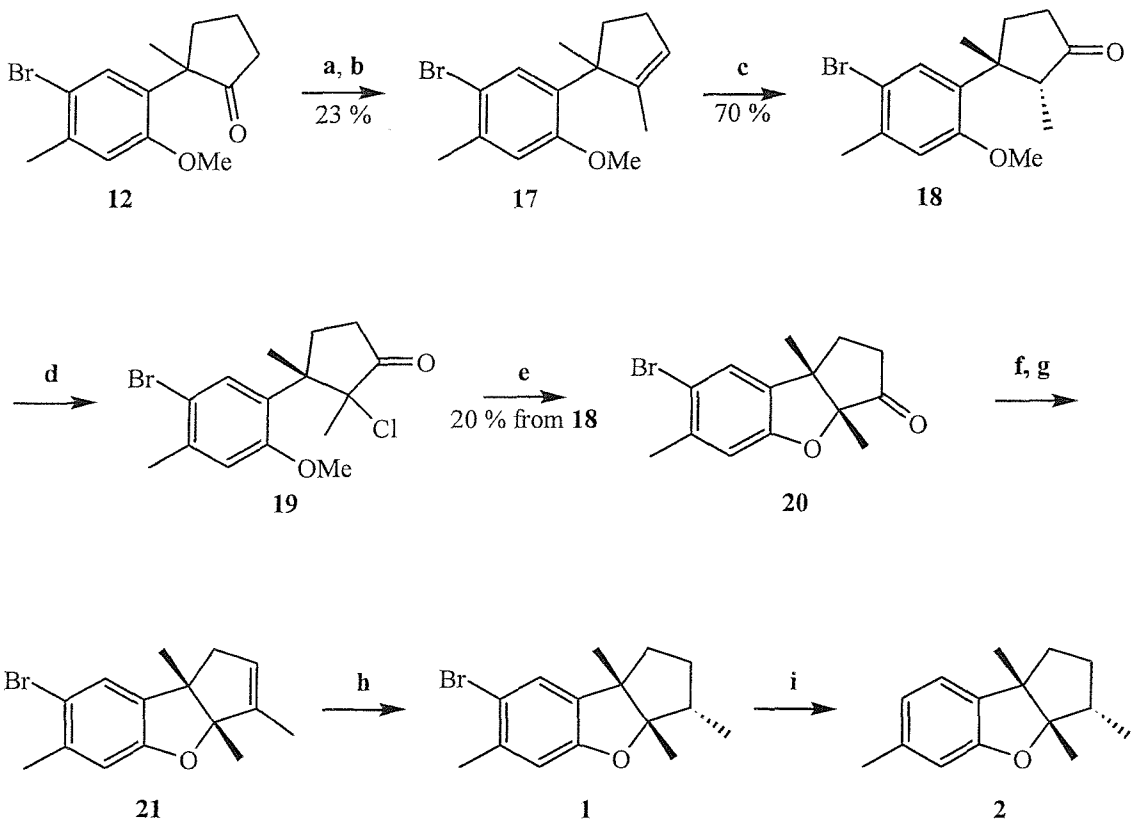
The first reported diastereoselective synthesis of (±)–aplysin **1** and (±)–debromoaplysin **2** was reported by Yamada *et al.*[4] as early as 1968 and is detailed in Scheme 1. Yamada *et al.* chose 3–methyl–4–bromoanisole **8** as the starting material for the synthesis, despite the presence of a reactive bromide in the molecule.[5] They hoped that this would avoid formation of dibromo– and tribromo–derivatives of aplysin that would arise if the aplysin skeleton was brominated at a late stage.



a. PhLi, Et_2O, Δ then cyclopentanone, 0°C; **b.** distillation at 3 mmHg; **c.** HCO_2H, H_2O_2, 40°C; **d.** NaH, DME, 70°C then MeI; **e.** NaOMe, HCO_2Et, PhH; **f.** K_2CO_3, MeI, CH_3COCH_3; **g.** KOH, EtOH; **h.** MeMgI, Et_2O, 70°C; **i.** 50 % H_2SO_4, PhH, Δ; **j.** MeMgI, 165°C, sealed tube; **k.** *p*TsOH, CH_3CO_2H.

Scheme 1

The synthesis is low yielding and fails to achieve any direct stereocontrol: the appropriate isomer of aplysin was obtained from a complex mixture of components after preparative gas chromatography. Subsequently, Yamada *et al.*[6] described an alternative synthesis that diverged at the point of the α-methyl ketone **12**. This synthesis represented a significant improvement in terms of the overall yield of aplysin **1** and debromoaplysin **2** (Scheme 2). No explanation of the diastereocontrol was provided, although it seems reasonable to suggest that hydrogenation proceeds to the most accessible *exo* face of the alkene **21**.

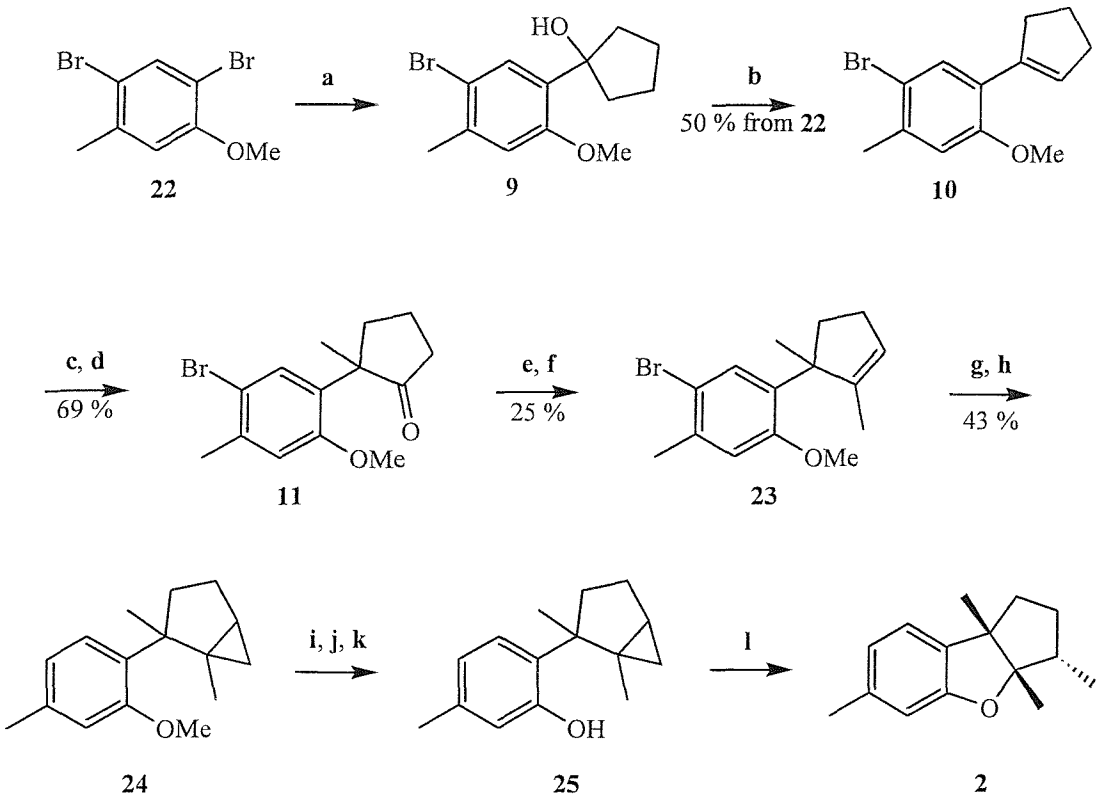


a. MeMgI, Et_2O, 70°C; **b.** 50 % H_2SO_4, PhH, Δ; **c.** HCO_2H, H_2O_2, 40°C; **d.** SO_2Cl_2; **e.** BBr_3, CH_2Cl_2; **f.** MeMgI, Et_2O; **g.** $POCl_3$, py; **h.** 10 % Pd/C, H_2, EtOH; **i.** PtO_2, H_2, EtOH.

Scheme 2

1.2.2 Feutrill's Synthesis of Debromoaplysin

Feutrill *et al.* published a total synthesis of (±)–debromoaplysin **2** in 1972.[7] Their strategy is detailed in Scheme 3 and is closely related to that of Yamada *et al.*[4,6]



22 9 10 11 23 24 25 2

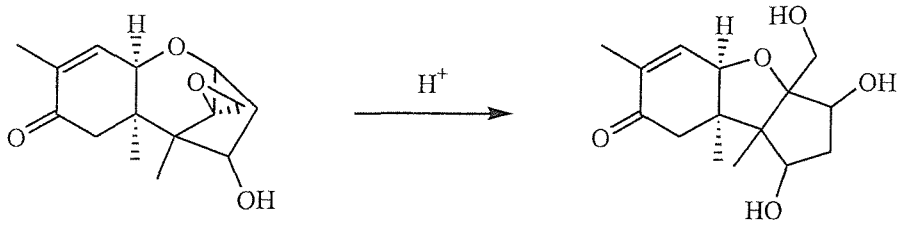
a. PhLi, Et_2O, Δ then cyclopentanone, 0°C; **b.** distillation; **c.** HCO_2H, H_2O_2, 40°C; **d.** NaH, DME, then MeI; **e.** MeMgI, Et_2O, Δ; **f.** $POCl_3$, py; **g.** Et_2Zn, CH_2I_2, PhH; **h.** $LiAlH_4$, THF, 70°C; **i.** NaSEt, DMF, 105°C; **j.** Ac_2O, py; **k.** NaOH, H_2O; **l.** *p*TsOH.

Scheme 3

Feutrill observed mixtures of compounds for several of their late reactions and precise yields were seldom quoted. It is therefore difficult to compare the efficiency of this synthesis against others.

1.2.3 Goldsmith's Synthesis of Aplysin

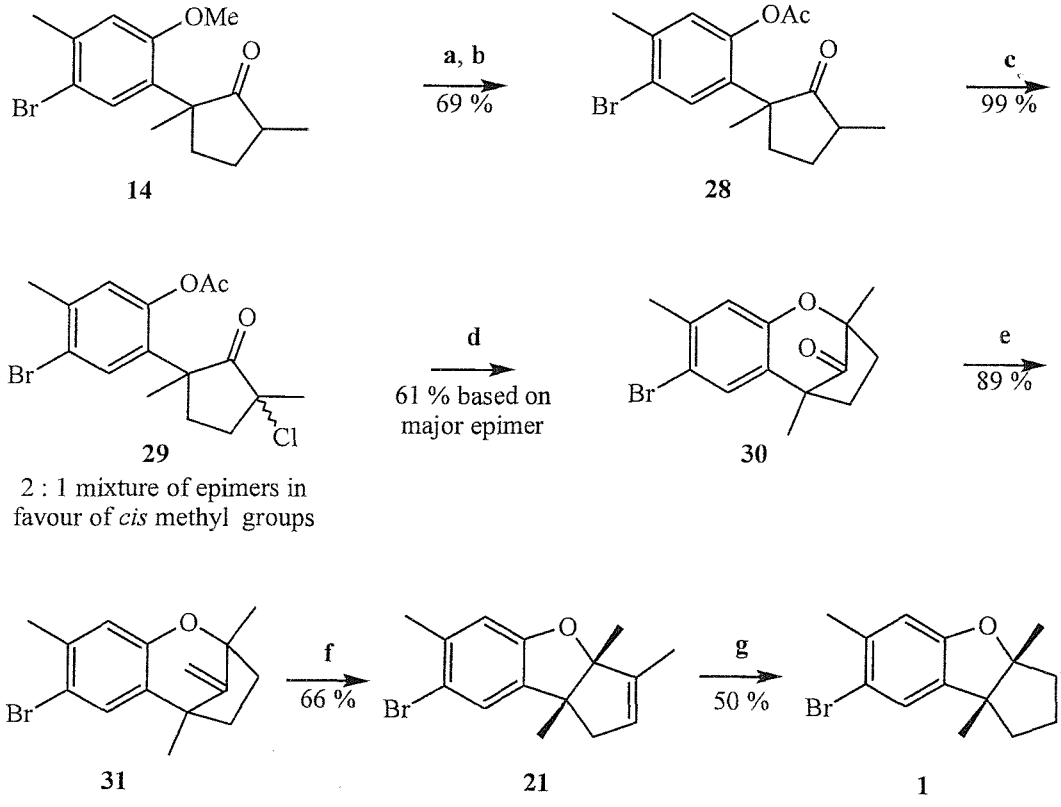
In 1980, Goldsmith *et al.*[8] subjected a trichothecane **26** to acid–catalysed rearrangement and isolated apotrichothecane triol **27** (Scheme 4).



26 **27**

Scheme 4

Goldsmith recognised the resemblance of triol **27** to the aplysin skeleton and decided to apply this rearrangement in a synthesis of **1** (Scheme 5). Notably, rearrangement of olefin **31** gave the *cis* fused aplysin skeleton exclusively. Regioselective hydrogenation then gave (±)–aplysin **1**.



14 **28**

29

2 : 1 mixture of epimers in favour of *cis* methyl groups

30

31 **21** **1**

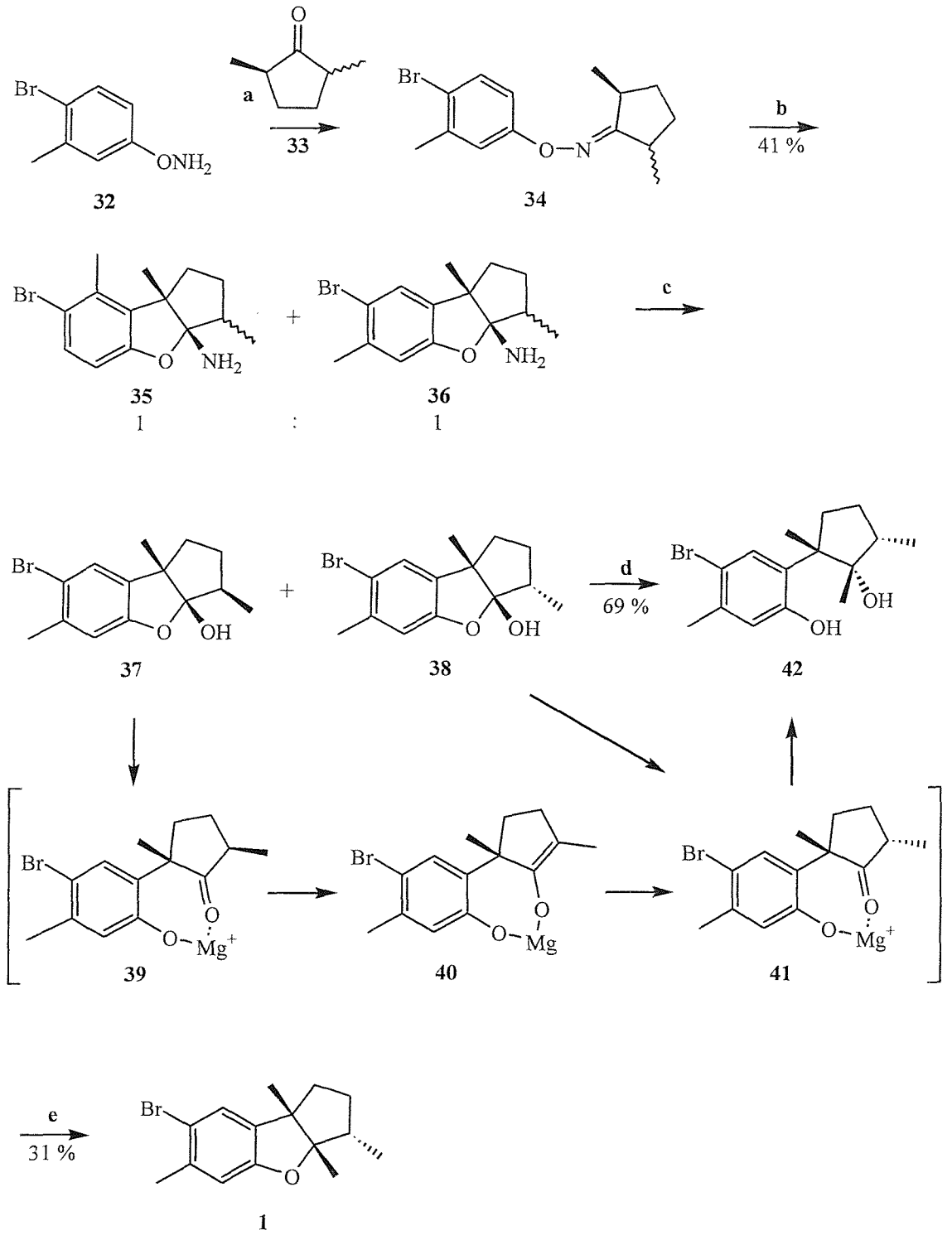
a. NaSEt, DMF, 95°C; **b.** NaH, CH_3COCl, -30°C; **c.** SO_2Cl_2, CCl_4, 0°C; **d.** DBN, PhH, 0°C; **e.** Ph_3PCH_3Br, BuLi, THF, Δ; **f.** *p*TsOH, PhH, Δ; **g.** H_2, 10 % Pd/C, EtOAc.

Scheme 5

The Goldsmith synthesis suffered from a reliance on Yamada's precursor **14**, which is prepared in 6 % yield over seven steps. The consequence is a rather lengthy synthesis that proceeds in very poor overall yield. Although the key rearrangement was elegant, there remained scope for improvement.

1.2.4 LARONZE'S SYNTHESIS OF APLYSIN AND DEBROMOAPLYSIN

In 1989, Laronze *et al.*[9] used a Sheradsky rearrangement as a key step in the synthesis of (±)–aplysin **1** (Scheme 6).[10] Their synthesis began with 5–aminoxy–2–bromotoluene **32** which in turn was prepared 'from the corresponding phenol…(whose synthesis)…was rather long.' Consequently, the yields were 'not satisfactory.'



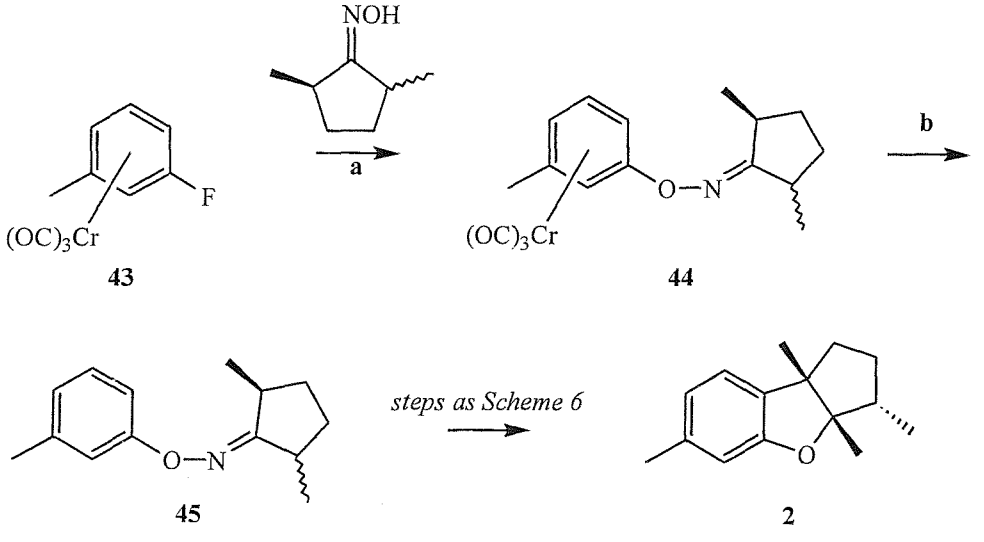
a. **33**, EtOH, cat. HCl, Δ; **b.** *p*TsOH, MeOH, Δ; **c.** AcOH, H_2O; **d.** excess MeMgI; **e.**. *p*TsOH, AcOH, Δ.

Scheme 6

The key Sheradsky rearrangement (step **b**) was completely devoid of regio– or stereo–selectivity, which flawed this strategy for the synthesis of the aplysins. Fortunately for Laronze and his co-workers the undesired regioisomers did not participate in the subsequent

hydrolysis, indicating that the intermediate oxonium ion was not formed. The oxonium cation flattens the tricyclic system and only the desired regioisomers can tolerate this intermediate. The neighbouring methyl groups in **35** are too sterically demanding to permit oxonium ion formation. Thus, the neutral lactols **37**, **38** could be separated from unreacted **35** by an acid wash. The key to Laronze's synthesis was the generation of a single diastereomer **42** upon treating the stereoisomeric mixture of lactols **37** and **38** with an excess of methyl magnesium iodide. This was achieved through an unexpected, but fortuitous, stereospecific equilibration in which the magnesium cation forms an enolate salt **40** whose geometry favours both protonation and attack of the Grignard reagent from the least hindered *exo*–face.

A significant improvement was realised after Alemagna *et al.* reported a more expedient synthesis of aryloxime **45**.[11] Laronze applied his earlier strategy to **45**, achieving the synthesis of the corresponding debromo analogues with improved yields (Scheme 7).[9b]

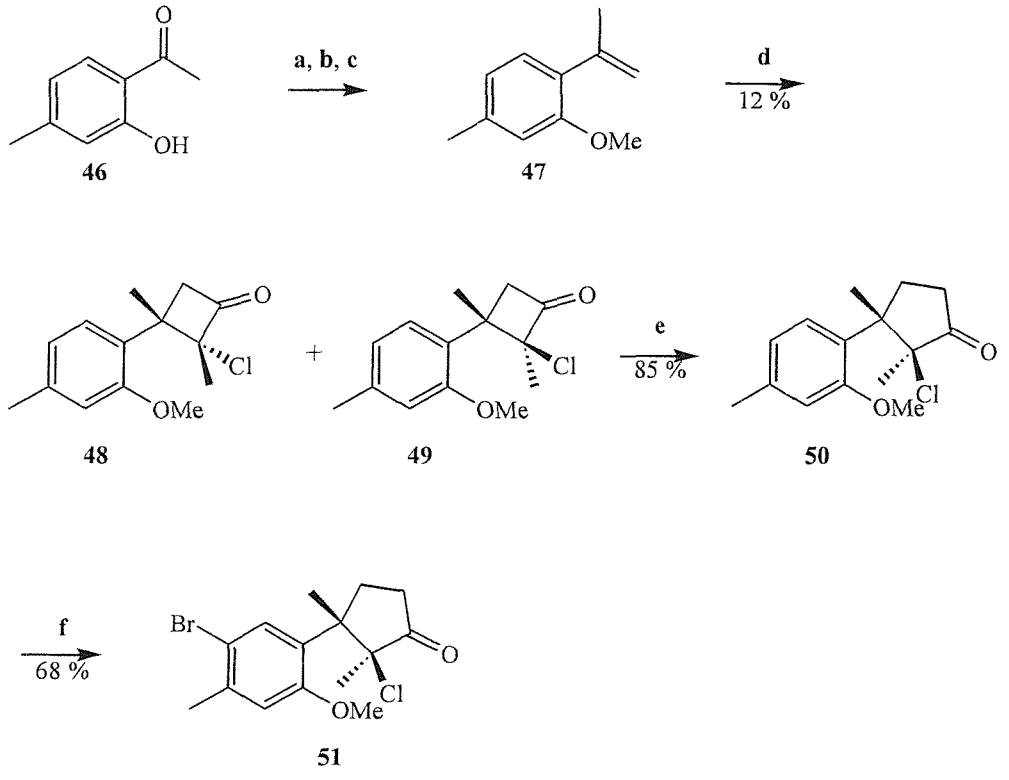


a. KOH, PhH, tetraoctylammonium bromide; **b.** I_2, Et_2O, 0°C.

Scheme 7

1.2.5 KHER'S FORMAL TOTAL SYNTHESIS OF APLYSIN

In 1990, Kher and Kulkarni published a formal total synthesis of (±)–aplysin which involved an intermolecular [2+2]-cycloaddition reaction between a ketene and an olefin as a key step.[12] Their goal, in common with Yamada,[4,6] was to construct chloroketone **51** which would then constitute a formal synthesis. Their approach to **51** is detailed below (Scheme 8).



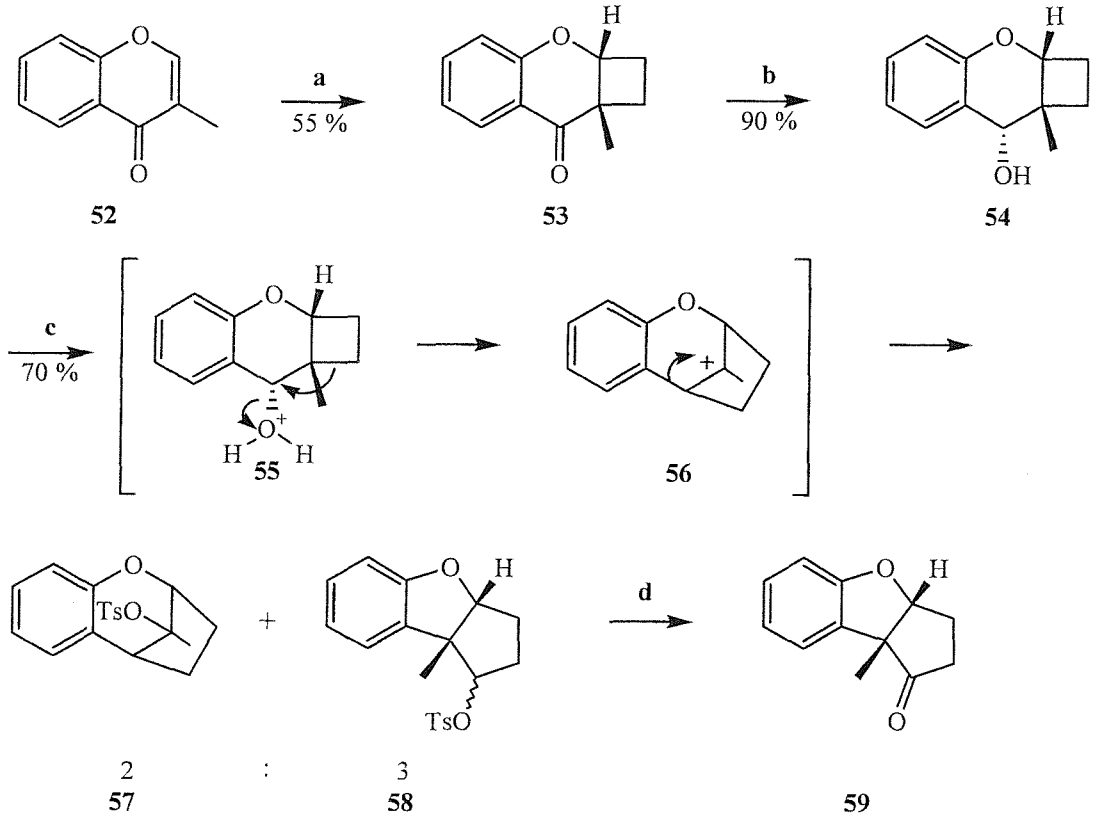
a. MeI; **b.** MeMgI; **c.** $-H_2O$; **d.** $CH_3(Cl)C{=}O$; **e.** CH_2N_2; **f.** Br_2, $CaCO_3$.

Scheme 8

Unfortunately the yield of the key step **d** was poor and much detail was missing from the experimental section. It is therefore difficult to appraise the approach fully.

1.2.6 VENKATESWARAN'S SYNTHESES OF APLYSIN, DEBROMOAPLYSIN, DEBROMOAPLYSINOL, APLYSINOL AND ISOAPLYSIN

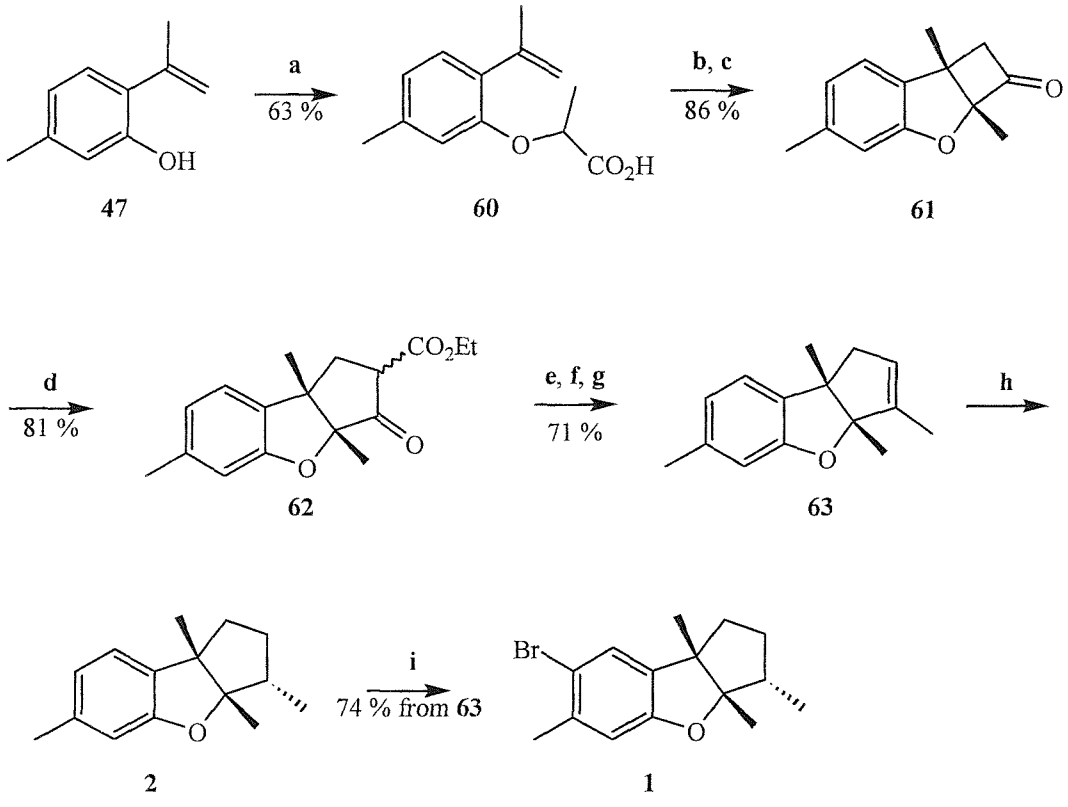
In 1992, Venkateswaran *et al.* presented an elegant, short synthesis of debromoaplysin and aplysin from chromone **70** (Scheme 12). This was the culmination of several years of investigations into synthetic approaches to the aplysins. Venkateswaran first published a facile route towards the carbocyclic skeleton of aplysin in 1986.[13] As is detailed below (Scheme 9), he approached the aplysin skeleton *via* rearrangement of an α–hydroxycyclobutane **54** to form an intermediate trichothecane–like cation **56** that closely resembles Goldsmith's strategy (Scheme 5). The *cis* cyclobutane in **53** directs hydride attack on the carbonyl moiety from the least hindered *exo* face. The resulting alcohol **54**, upon treatment with acid, then rearranges to generate **57** and **58** *via* intermediate carbocation **56**.



a. $CH_2{=}CH_2$, hν, PhH; **b.** $LiAlH_4$; **c.** *p*TsOH, PhH, Δ; **d.** DMSO, $NaHCO_3$, 150°C.

Scheme 9

Shortly after this report, Venkateswaran disclosed an alternative strategy that led to a short and stereocontrolled synthesis of racemic aplysin **1** and debromoaplysin **2** (Scheme 10).[14] This synthesis involved an *intramolecular* ketene-alkene cycloaddition to afford cyclobutanone **61**. Ring expansion then proceeded regioselectively with ethyl diazoacetate which allowed dehydrodebromoaplysin **63** to be generated. The origin of this regioselectivity is the preferential migration of the less encumbered bond. Hydrogenation of **63** with platinum oxide next gave debromoaplysin **2**, which was brominated to give aplysin **1**.

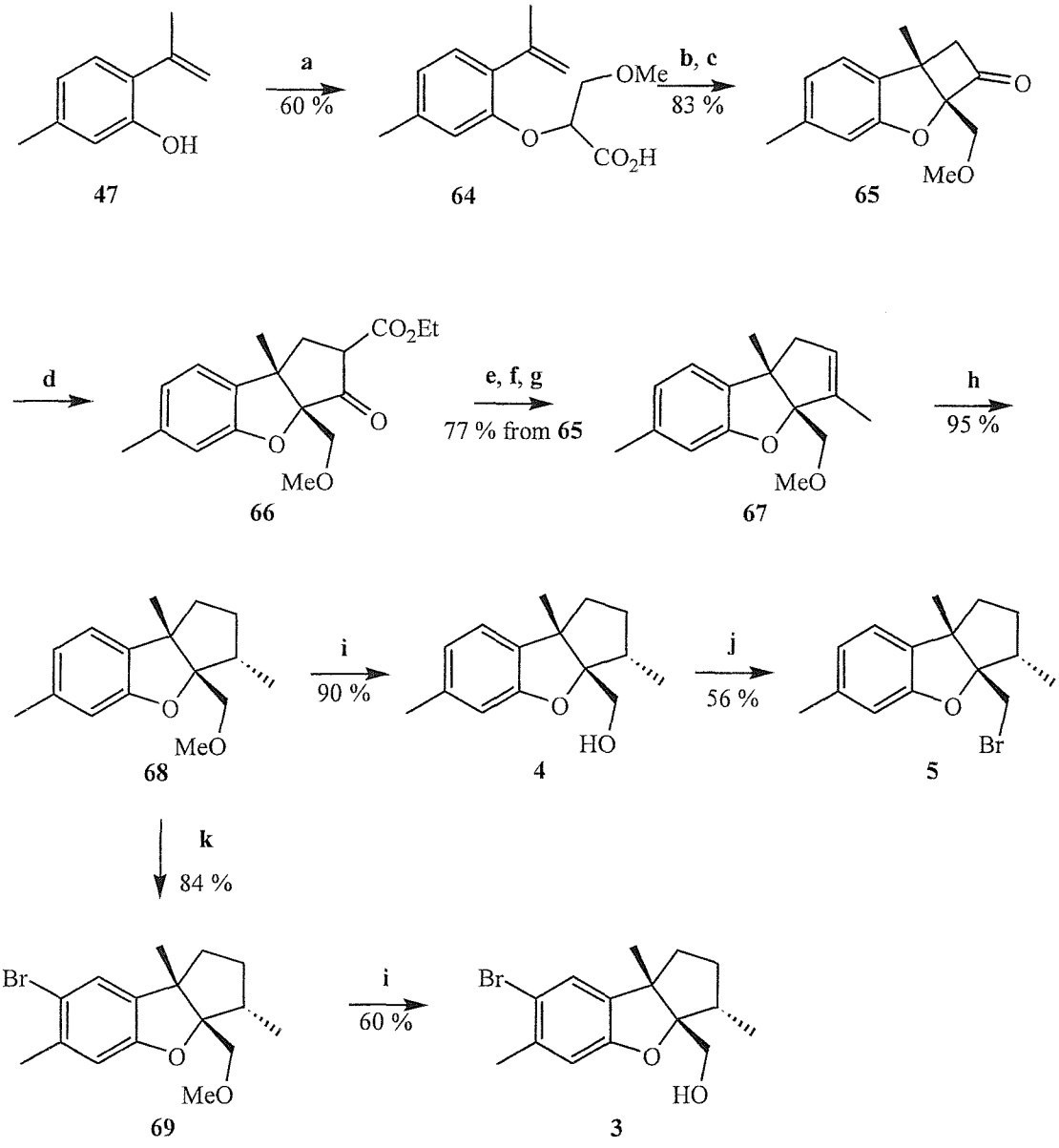


a. NaH, $MeCH(Br)CO_2H$, THF; **b.** NaOEt; **c.** $(COCl)_2$, then Et_3N, PhH, Δ; **d.** $BF_3.OEt_2$, N_2CHCO_2Et, CH_2Cl_2; **e.** LiCl, DMSO, H_2O, 160°C; **f.** MeMgI, Et_2O; **g.** $POCl_3$, py; **h.** PtO_2, H_2, EtOH; **i.** Br_2, Na_2CO_3, C_6H_{14}.

Scheme 10

This synthesis proceeds in nine steps and an overall yield of 22 % from styrenol **47**. However, the additional steps required to synthesise **47** significantly reduce the efficiency of the route. The route was subsequently extended to achieve the first published syntheses of

(±)–debromoaplysinol **4**, (±)–aplysinol **3**, and (±)–isoaplysin **5** through modification of the ketene precursor (Scheme 11).[15]

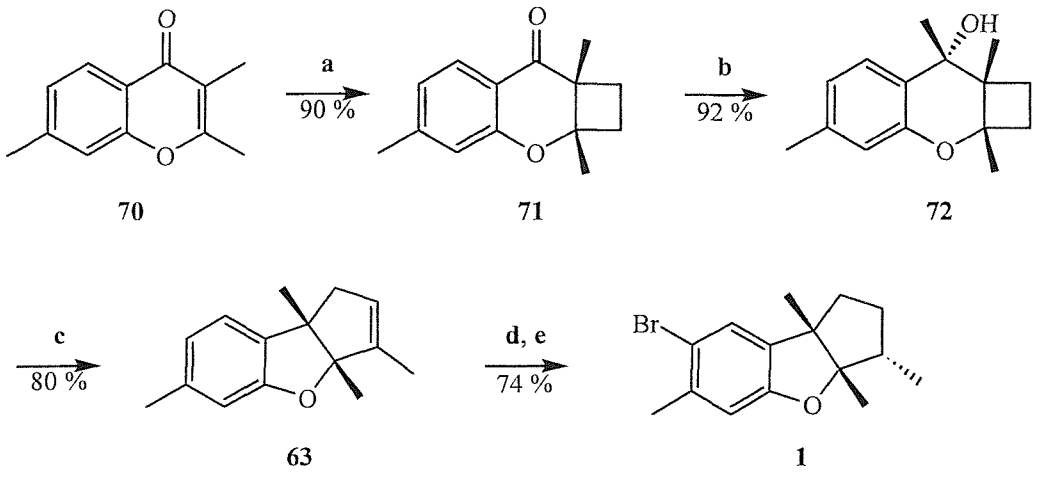


a. NaH, $MeOCH_2CH(Br)CO_2H$, THF; **b.** *p*TsCl; **c.** Et_3N, PhH, Δ; **d.** $BF_3.OEt_2$, N_2CHCO_2Et, CH_2Cl_2; **e.** LiCl, DMSO, H_2O, 160°C; **f.** MeMgI, Et_2O; **g.** $POCl_3$, py; **h.** PtO_2, H_2, EtOH; **i.** Me_3SiCl, NaI, CH_3CN; **j.** CBr_4, Ph_3P, PhH; **k.** Br_2, $NaHCO_3$, C_6H_{14}.

Scheme 11

Venkateswaran's most elegant synthesis of aplysin **1** and debromoaplysin **2** saw a return to their earlier strategy involving rearrangement of a cyclobutachromanol **54** (Scheme 9).[16] The synthesis relied upon a Wagner–Meerwein rearrangement of **72** to provide the key

intermediate **63**. The rearrangement was found to give the desired alkene regioisomer when polar solvents and low temperatures were employed. This method provided aplysin in five steps from chromone **70** in 49 % yield (Scheme 12). Chromone **70** was synthesised as described by Robertson *et al.*[17]



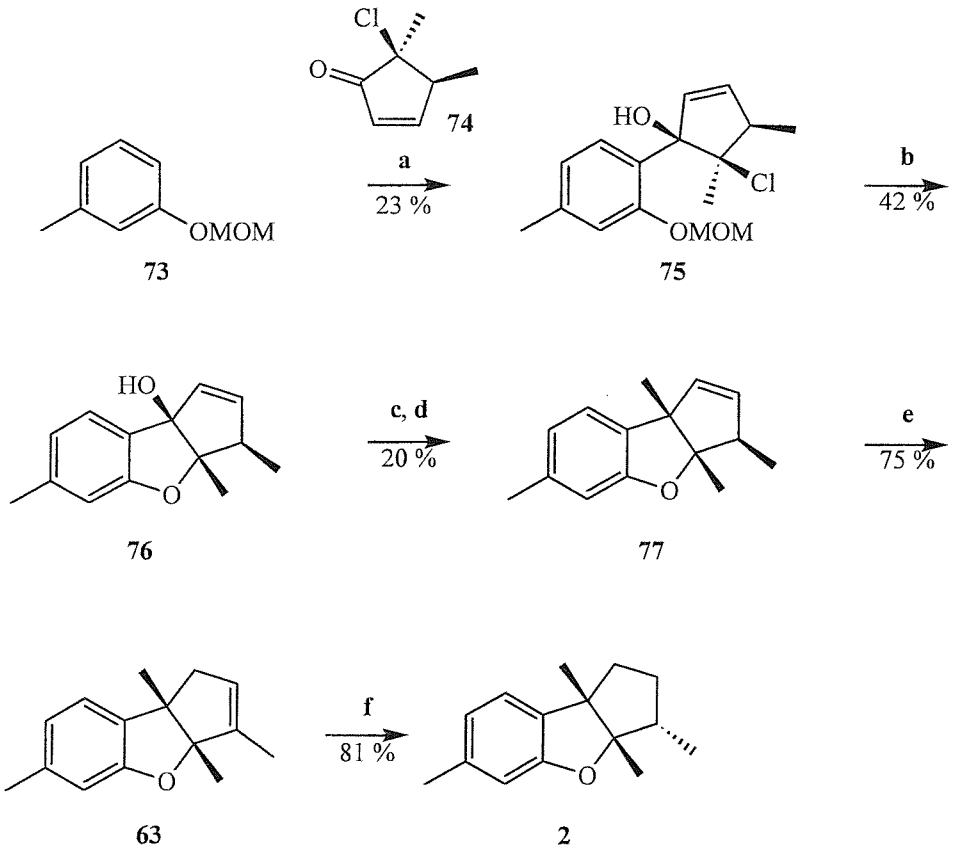
a. CH_2=CH_2, hν, PhH; **b.** MeMgI, Et_2O, 0°C; **c.** $BF_3.OEt_2$, PhH; **d.** PtO_2, H_2; **e.** Br_2, $NaHCO_3$, C_6H_{14}.

Scheme 12

1.3 Enantioselective Syntheses by Resolution

1.3.1 Ronald's Synthesis of (–)–Aplysin and (–)–Debromoaplysin

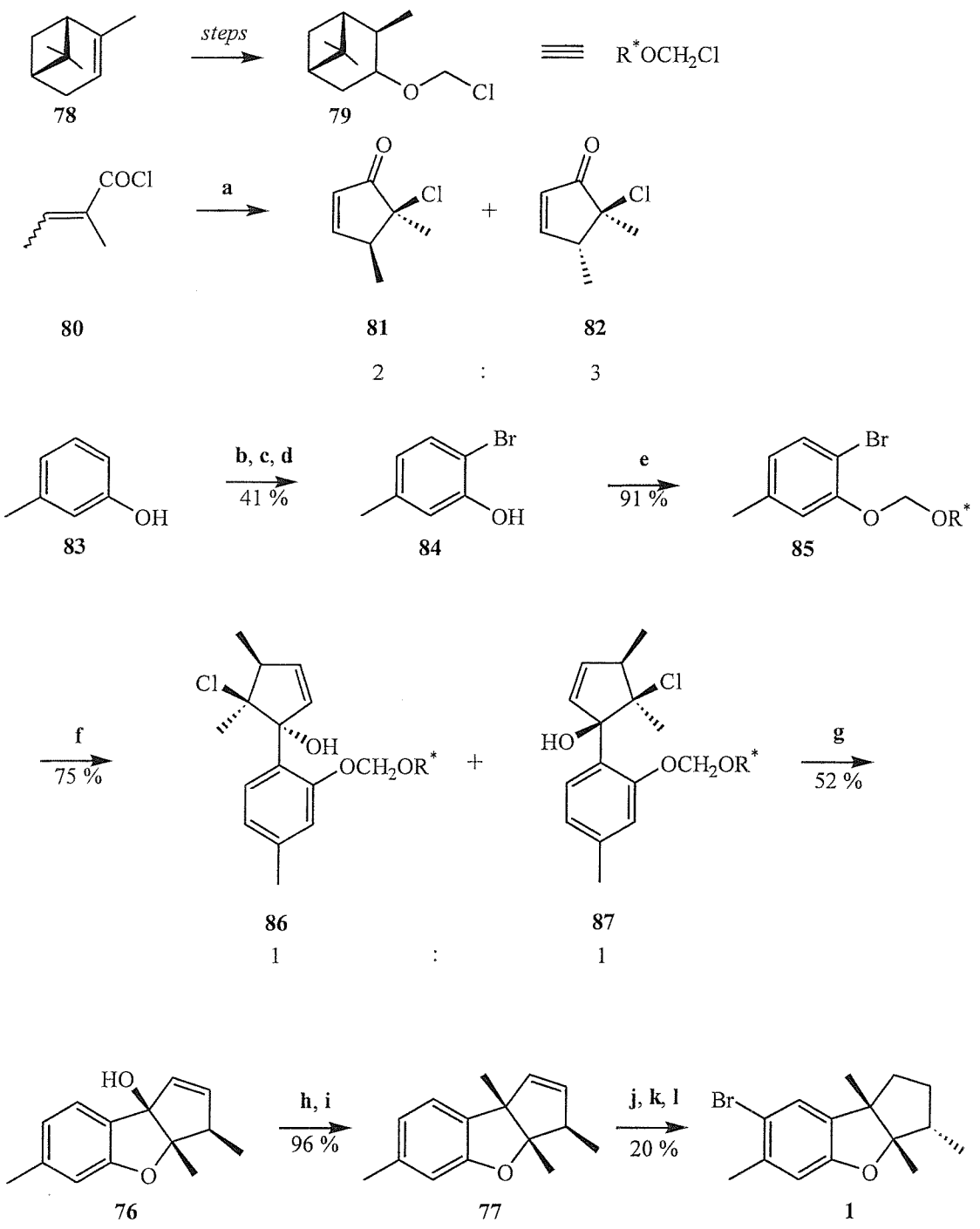
Only aplysin and debromoaplysin have thus far been synthesised in an enantioselective fashion. Ronald *et al.* presented the first reported total synthesis of (–)–aplysin **1** and (–)–debromoaplysin **2** in 1980,[18] following a preliminary synthesis of racemic **2** (Scheme 13).[19] In the racemic synthesis, a directed *ortho* metallation of **73** and union with chloroketone **74**[20] provided alcohol **75**. Cyclisation to **76** was followed by a low yielding conversion of the alcohol moiety to a methyl group. Isomerisation of the resulting alkene 77 with Wilkinson's catalyst then gave **63** which underwent hydrogenation to debromoaplysin **2**.



a. BuLi, Et_2O, 0°C then **74**; **b.** KOH, MeOH, Δ; **c.** PBr_3, Et_2O; **d.** MeMgBr, Et_2O; **e.** $(Ph_3P)_3RhCl$, PPh_3, air, $PhCH_3$, $^{i}BuOH$, Δ; **f.** H_2, PtO_2, EtOH.

Scheme 13

Ronald adapted this protocol to achieve the first reported total synthesis of (–)–aplysin **1** and (–)–debromoaplysin **2** though resolution.[18] Thus, an (isopinocampheyloxy) methyl ether was used to protect the phenol. Union with ketones **81** and **82** then produced a 1 : 1 mixture of diastereomers **86** and **87** which were separated by column chromatography. A synthesis of (–)–aplysin **1** followed (Scheme 14).



a. $AlCl_3$, C_2H_2; **b.** NaH, MOMCl; **c.** ^{t}BuLi, Pentane, 0°C then $BrCH_2CH_2Br$, THF, -78°C; **d.** HCl, H_2O; **e.** NaH, DMF, Et_2O then **79**; **f.** BuLi, Et_2O, 0°C then **81**, **82**; **g.** KOH, MeOH, Δ; **h.** PCl_3, Et_2O; **i.** MeMgBr, Et_2O; **j.** $(Ph_3P)_3RhCl$, PPh_3, air, $PhCH_3$, ^{i}BuOH, Δ; **k.** H_2, PtO_2, EtOH; **l.** Br_2, Na_2CO_3, C_6H_{12}.

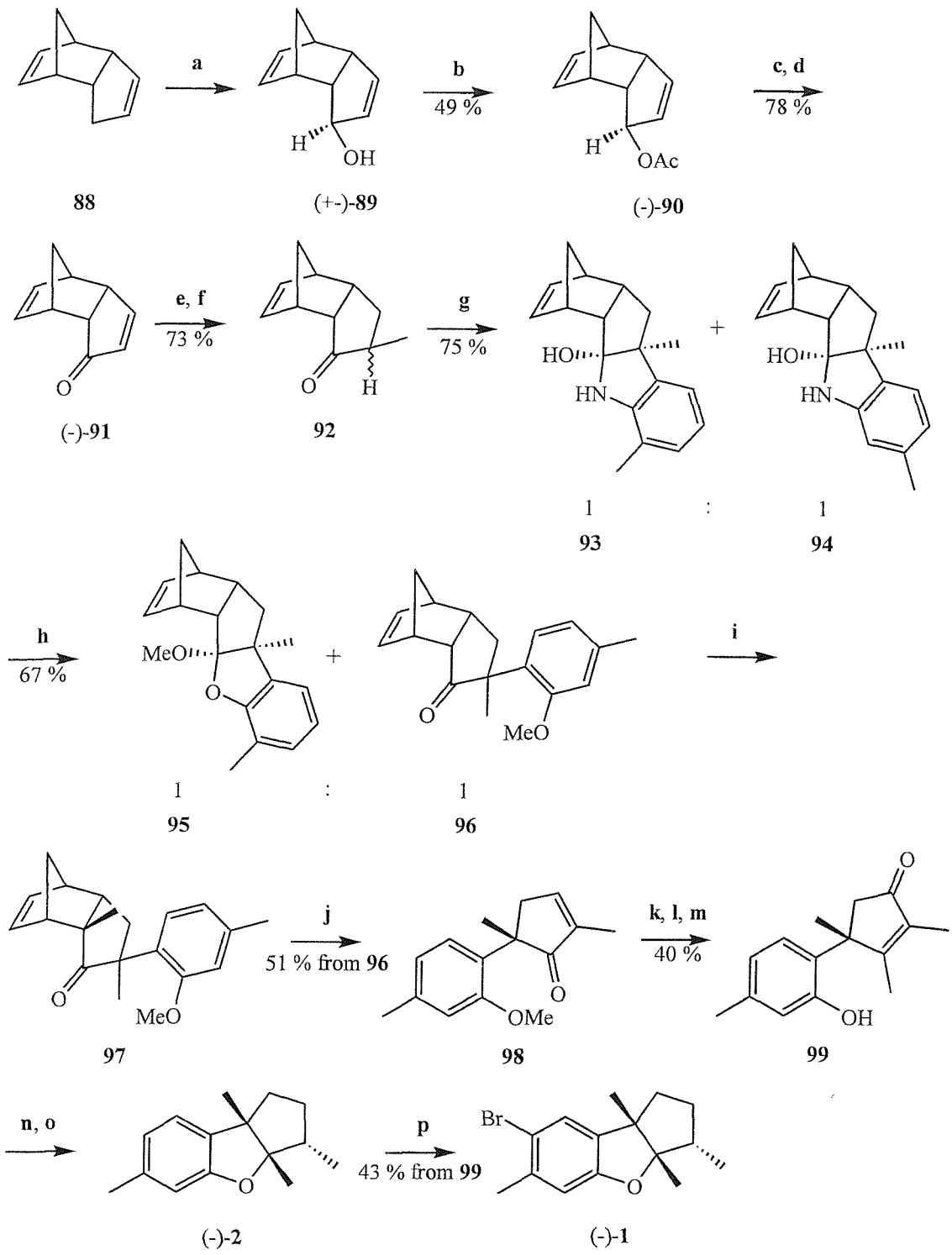
Scheme 14

As a result of using resolution this synthesis suffered from a particularly low overall yield of 1.4 %. That the synthesis also required a low yielding isomerisation at a late stage contributed to this inefficiency.

1.3.2 TAKANO'S ENANTIOCONTROLLED SYNTHESIS OF (-)-1 AND (-)-2

Following the publication of Ronald *et al.*,[18] Takano's group reported an alternative enantiocontrolled synthesis of (–)–aplysin **1** and (–)–debromoaplysin **2**.[21] The origin of their chirality was the optically active acetate **90** formed in high optical purity *via* a enzymatic resolution of alcohol **89**.[22]

The synthesis was again low yielding, in part due to the adoption of a resolution strategy. Sixteen steps were required to achieve an overall yield of 0.6 %. Key steps in the synthesis include the diastereospecific addition of *ortho*-tolylhydrazine to the convex face of **92**; a thermally induced retro-Diels-Alder reaction to furnish cyclopentenone **98**, and a DIBAL-H reduction of **99** that undergoes spontaneous cyclisation to tricyclic ether **63** (Scheme 15).



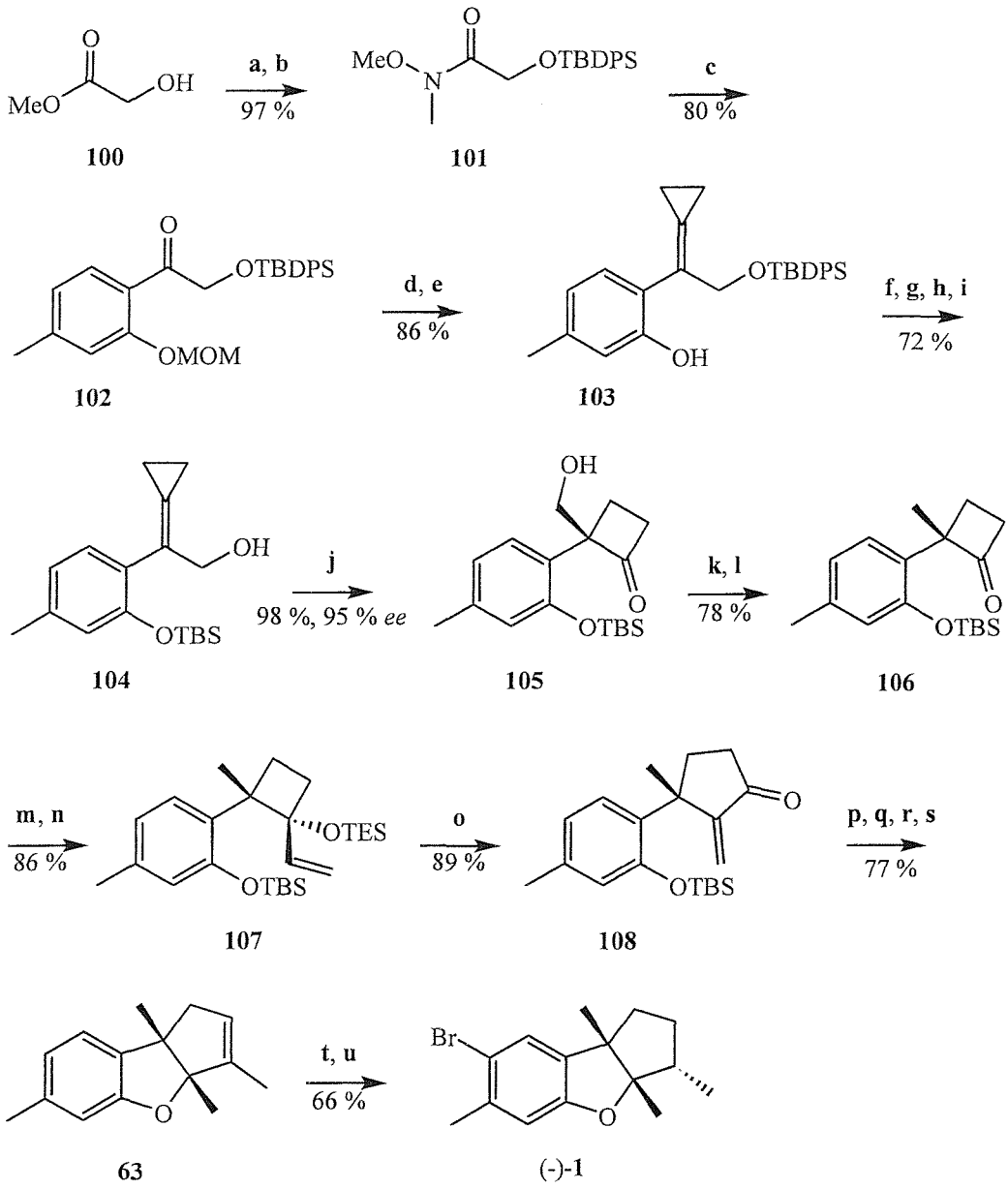
a. SeO_2; **b.** lipase, vinyl acetate; **c.** K_2CO_3, MeOH; **d.** PCC, CH_2Cl_2; **e.** Zn, AcOH, EtOH, Δ; **f.** LDA, MeI, THF; **g.** *o*-tolylhydrazine; **h.** $NaNO_2$, c. H_2SO_4, MeOH; **i.** LDA, MeI, THF; **j.** *o*-DCB, Δ; **k.** MeLi, THF; **l.** PCC, CH_2Cl_2; **m.** BBr_3, $(CH_2Cl)_2$, 80°C; **n.** DIBAL-H, CH_2Cl_2, then 10 % HCl; **o.** H_2, PtO_2, EtOH; **p.** NBS, CCl_4, Δ.

Scheme 15

1.3.3 FUKUMOTO'S ENANTIOCONTROLLED SYNTHESIS OF (–)–1 AND (–)–2

The most recent of the enantioselective syntheses of (–)–**1** and (–)–**2** was presented by Fukumoto *et al.* in 1994.[23] This extended synthesis (21 steps) rested its strategy on a substituent effect of the *tert*–butyldimethylsiloxy group. This group enabled the enantioselective tandem Katsuki–Sharpless asymmetric epoxidation and enantiospecific ring expansion of cyclopropylidene ethanol **104** to give geminally disubstituted cyclobutanone **105** (Scheme 16). The yields reported for each step are generally high. The overall yield of 13 % represents a considerable achievement in a synthesis involving 21 linear steps, though the scale of experiments varies widely in the experimental section indicating that some reactions may be capricious when scaled up.

A tandem asymmetric epoxidation and 1,2–rearrangement of the cyclopropylidene alcohol **104** provides the enantioselectivity in this synthesis. The remarkable enantioselectivity is due to a substituent effect of the sterically demanding TBS group. Other ethers, including tolyl and MOM ethers failed to provide such significant enantiomeric excesses.



a. TBDPSCl, DMAP, imidazole, DMF; **b.** $MeO(CH_3)NH.HCl$, $AlMe_3$, CH_2Cl_2, -15°C; **c.** 3-[(methoxymethyl)oxy]toluene, ^tBuLi, Et_2O, 0°C then **101**, -78°C; **d.** cyclopropyltriphenylphosphonium bromide, NaH, THF, 62°C; **e.** EtSH, $BF_3.OEt_2$, CH_2Cl_2. –78°C; **f.** $^nBu_4NF$, THF; **g.** PivCl, py; **h.** TBSCl, DMAP, imidazole, DMF, 0°C; **i.** DIBAL-H, CH_2Cl_2, -23°C; **j.** (+)-DIPT, $(^iPrO)_4Ti$, ^tBuOOH; **k.** PhSSPh, $^nBu_3P$, THF, Δ; **l.** Raney Ni, acetone; **m.** vinylMgBr, $CeCl_3$, THF, -78°C; **n.** TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; **o.** $Pd(OAc)_2$, $AsPh_3$, CH_2Cl_2; **p.** MeLi, $CeCl_3$, Et_2O, -78°C; **q.** $^nBu_4NF$, THF; **r.** $Hg(OCOCF_3)_2$, THF; **s.** NaOH, $NaBH_4$, $POCl_3$, py; **t.** H_2, PtO_2, EtOH; **u.** Br_2, $NaHCO_3$, $CHCl_3$.

Scheme 16

1.4 TOTAL SYNTHESES OF ISOLAURINTEROL AND DEBROMOISOLAURINTEROL

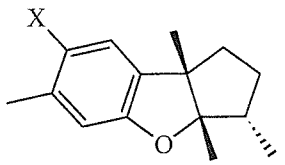
Many halogenated metabolites have been isolated from the marine red algae genus *Laurencia*. Isolaurinterol **6** and debromoisolaurinterol **7** were first isolated in 1970[24] as minor constituents of the sea weed *Laurencia intermedia* Yamada (Rhodomelaceae), and are believed to be likely biological precursors to the aplysins.[24] Isolaurinterol **6** was found by Ohta and Takagi to possess a potent antimicrobial activity against *Bacillus subtilis*.[142] There have been no reported total syntheses prior to our own.[25]

CHAPTER 2

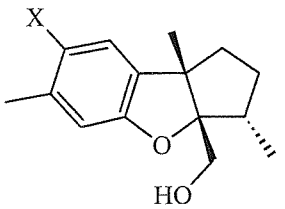
THE TOTAL SYNTHESIS OF THE APLYSINS AND ISOLAURINTEROLS

2.1 INTRODUCTION

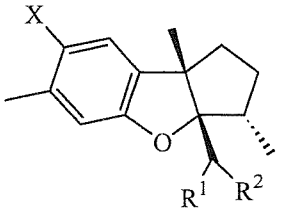
The thiyl radical mediated cyclisation of 1,6–dienes, when used in conjunction with a reductive desulfurisation, has been shown to be an effective method for generating cyclopentanes containing vicinal methyl groups (see chapter 5). The aplysin series of natural products **1** – **5**, **236** possess a skeletal structure that makes them ideal synthetic targets to which this radical cyclisation can be applied.



X = Br, Aplysin **1**
X = H, Debromoaplysin **2**



X = Br, Aplysinol **3**
X = H, Debromoaplysinol **4**

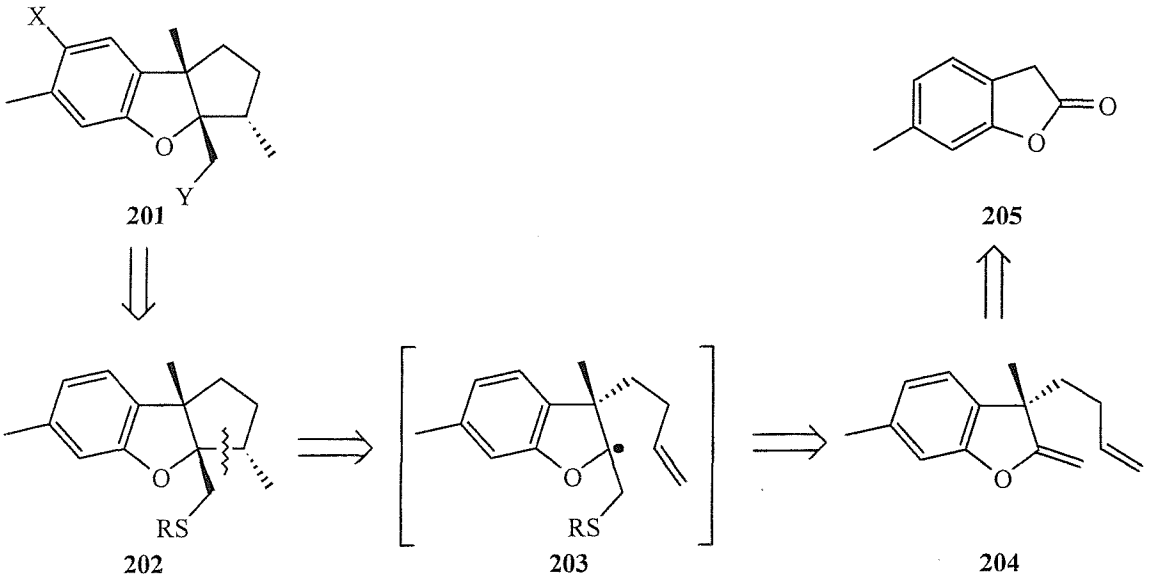


X = H, R^1 = Br, R^2 = H, Isoaplysin **5**
X = Br, R^1 = R^2 = O, Aplysinal **236**

(–)–Aplysin **1** was one of the first halogenated sesquiterpenes to be isolated from a marine organism. Its unusual structural architecture, which includes a sterically congested tricycle containing three contiguous stereogenic centres, coupled with its interesting biological activity,[2,3] prompted us to select this system as a target to demonstrate the utility of thiyl radical mediated cyclisation reactions in total synthesis.

2.2 RETROSYNTHETIC ANALYSIS

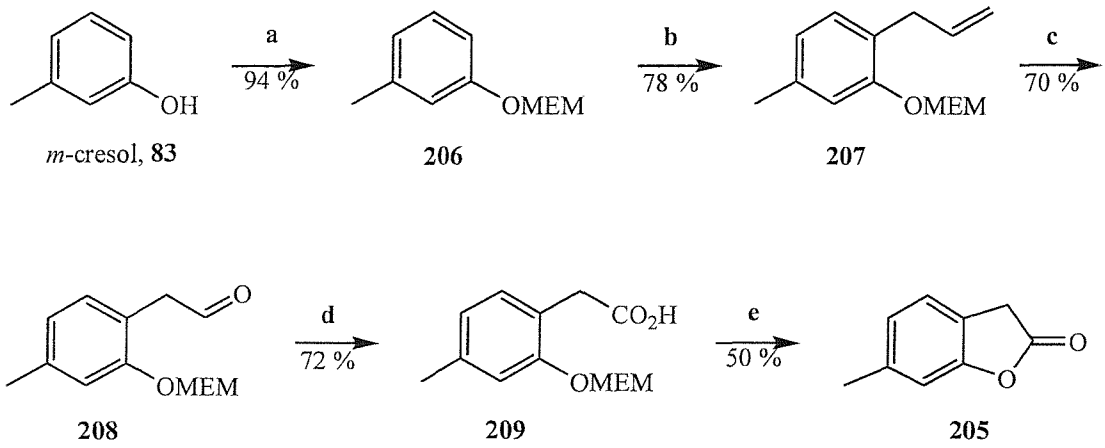
The synthetic challenge presented by the aplysins lies in the construction of the sterically demanding tricyclic skeleton and the establishment of the three contiguous stereogenic centres with appropriate relative stereochemistry. Our knowledge of the sulfur mediated radical cyclisation of 1,6–dienes led us to envisage the approach outlined in Scheme 17. We hoped that an electrophilic thiyl radical generated in the presence of diene **204** would attack the terminus of the electron rich enol ether selectively, leading to intermediate **203**. A kinetically favoured 5–*exo*–trig cyclisation would then generate the aplysin skeleton and leave the latent functionality required to address the synthesis of **1** – **5**, **236**. Reductive cleavage of the carbon to sulfur bond and, where necessary, functional group manipulation to introduce the hydroxyl and bromine moieties, was expected to elaborate all of the aplysins.



Scheme 17

2.3 Our Early Approach to Diene 204

A synthesis of lactone **205** was readily achieved using the synthetic route outlined in Scheme 18. Thus, *meta*–cresol **83** was protected as its ethoxymethylether **206** (94 %).[26] *ortho*–Lithiation of **206**, transmetallation to the corresponding organocuprate and quench with allyl bromide gave **207** in 78 % yield with complete regiocontrol.[27] Ozonolysis to aldehyde **208** (70 %),[28] Jones' oxidation to carboxylic acid **209** (72 %),[29] and deprotection of the aryl ether under conditions favouring lactonisation gave benzofuranone **205** (50 %).



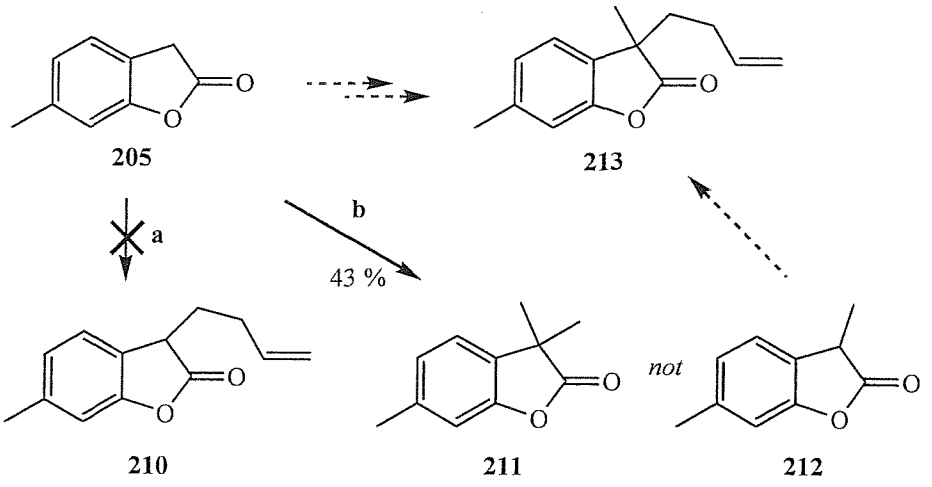
m-cresol, **83** **206** **207**

208 **209** **205**

a. NaH, MEMCl, Et_2O, DMF, r.t., 3 h; **b.** ^tBuLi, C_5H_{12}, 0°C, 7 h then CuI.$P(OEt)_3$, THF, -78°C, 30 min, then CH_2=$CHCH_2Br$, to r.t. 22 h; **c.** O_3, $CHCl_3$, -78°C, 40 min then PPh_3, r.t., 5 h; **d.** CrO_3, H_2SO_4, CH_3COCH_3, r.t., 25 min; **e.** PPTS, $PhCH_3$, Δ, 20 h.

Scheme 18

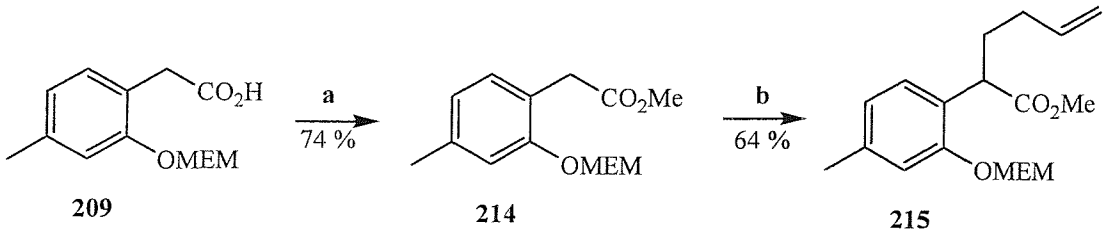
Unfortunately, attempts to effect the homoallylation of **205** using standard enolate chemistry failed to generate **210** and instead returned only starting material. In contrast, attempts to form the enolate of **205** and trap it with methyl iodide led primarily to bisalkylated lactone **211** rather than **212**. We were thus prevented from elaborating **213** *via* this route (Scheme 19).



a. *c*Hex^{i}PrNLi, CH_2=$CHCH_2CH_2Br$, HMPA, THF, –78°C; **b.** *c*Hex^{i}PrNLi, MeI, HMPA, THF, –78°C.

Scheme 19

An alternative strategy was now sought to overcome these difficulties. Ester **214** was readily synthesised from acid **209** in 74 % yield. Deprotonation of **214** followed by quenching with 4–iodo–1–butene gave the desired homoallylated precursor **215** in 64 % yield (Scheme 20).



a. DBU, MeI, r.t.; **b.** $^{i}Pr_2NLi$, THF, CH_2=$CHCH_2CH_2I$.

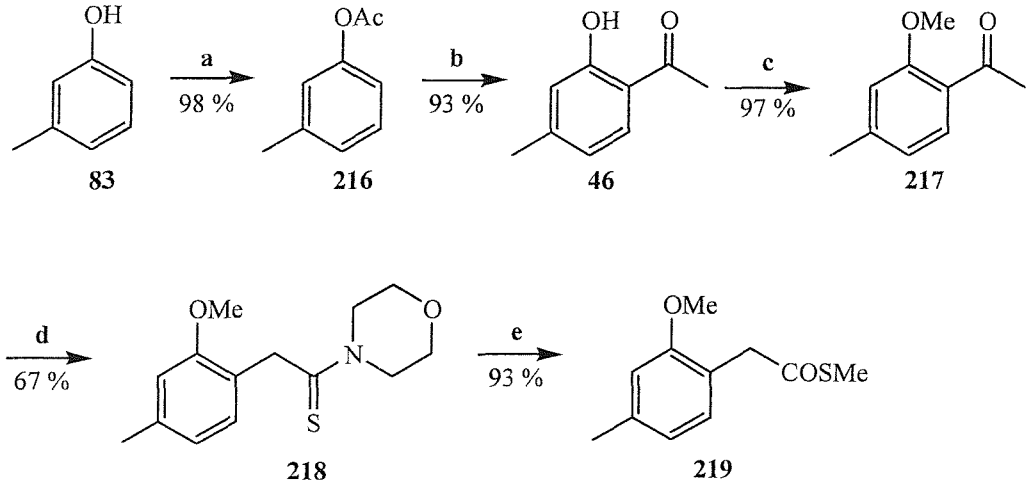
Scheme 20

Though encouraged by this result, the high number of synthetic steps and modest yields *en route* to **215**, together with the need to use *tert*–butyllithium on a large scale at an early stage in the synthesis, led us to seek an alternative route to diene **204**.

2.4 TOTAL SYNTHESIS OF APLYSIN AND DEBROMOAPLYSIN

2.4.1 OUR SECOND APPROACH TO DIENE 204

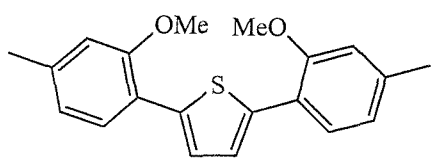
Our second approach to diene **204** also began with *meta*–cresol **83** (Scheme 21). Acetylation[30] of this material gave **216** in near quantitative yield. **216** was smoothly transformed into acetophenone **46** in 93 % yield *via* a Fries rearrangement conducted using zirconium(IV) chloride under ultrasound irradiation.[31] Protection of the phenol **46** as its methyl ether **217**,[32] followed by Willgerodt–Kindler oxidation to thioamide **218**,[33] provided access to thioester **219** through alkylation on sulfur and hydrolysis (*vide infra*).[34]



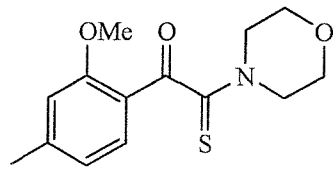
a. Ac_2O, Py, DMAP, CH_2Cl_2, r.t., 2 h; **b.** $ZrCl_4$, CH_2Cl_2, r.t.,))), 24 h; **c.** KOH, Me_2SO_4, acetone, r.t., 15 h; **d.** S_8, morpholine, 100°C, 24 h; **e.** MeI, aq. THF, Δ, 18 h.

Scheme 21

The Willgerodt–Kindler reaction furnished two major side products, thiophene **220** and thioxoketone **221**.[33] Fortunately the yield of these diminished as the scale of the reaction was increased. The structure of the thiophene was confirmed by X–ray crystallography (Figure 1).



220



221

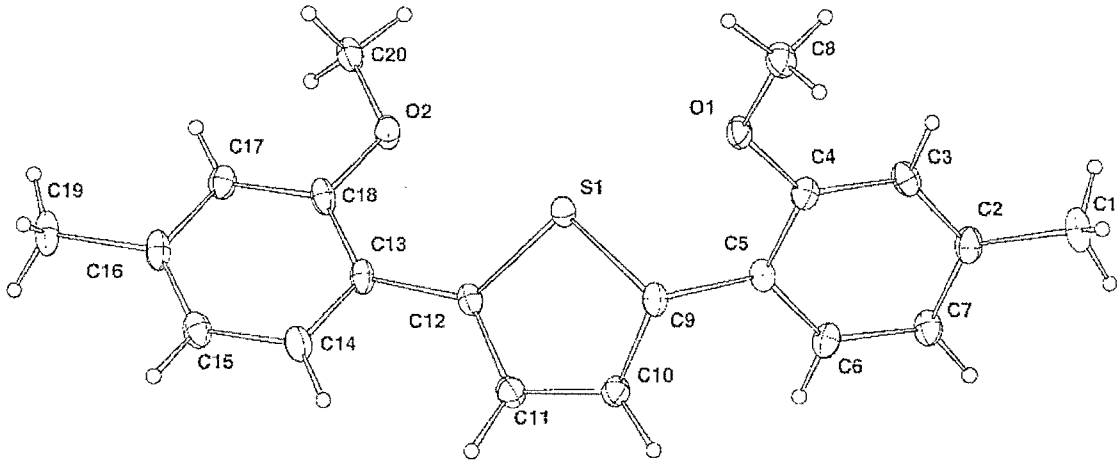
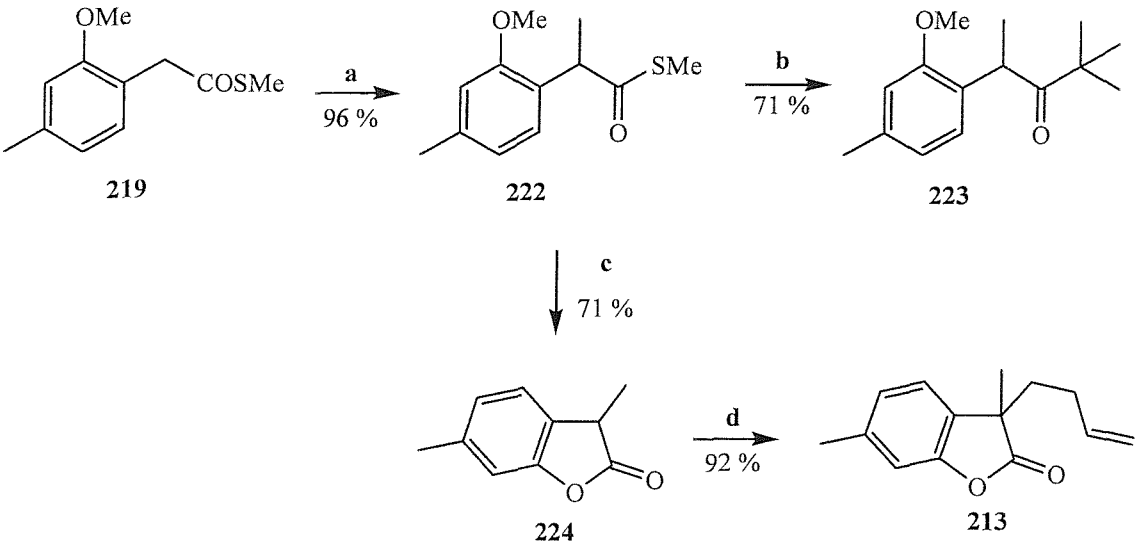


Figure 1. X-ray crystal structure of thiophene 220

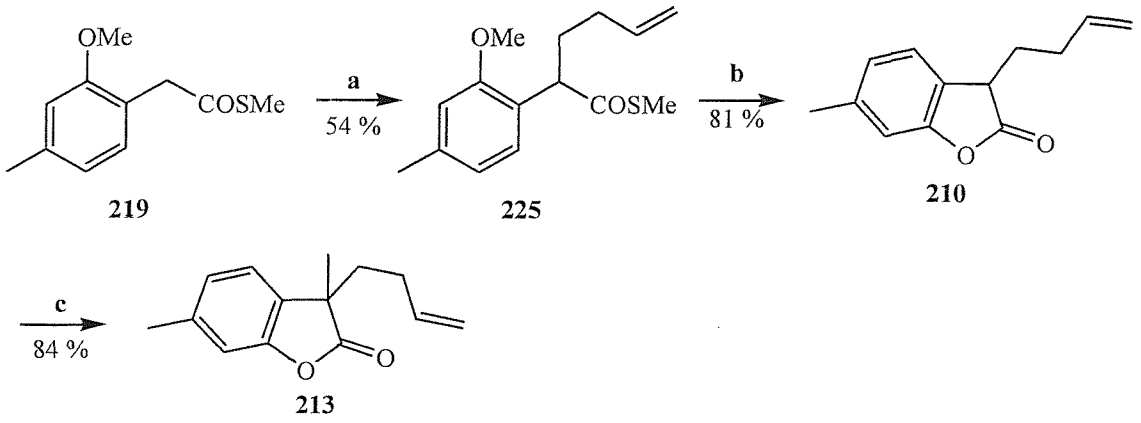
We now needed to introduce the alkyl substituents on the benzylic carbon. Pleasingly, α–methylation of **219** to **222** proceeded smoothly in 96 % yield. However, the tertiary centre generated hampered attempts to install a second alkyl group; exposure of **222** to *tert*–butyllithium giving the corresponding ketone **223** in 71 % yield. The ability of thiol esters to promote lactonisation in high yields is well documented,[35] and we were thus prompted to lactonise first and then attempt to install the second alkyl group. Thus, benzofuranone **224** was generated from **222** in 71 % yield through a synchronous boron trichloride mediated deprotection of aryl methyl ether **222** and Lewis acid catalysed lactonisation. Homoallylation proceeded smoothly to give **213** in 92 % yield (Scheme 22).



a. ^{t}BuLi, TMEDA, THF, -60°C, 10 min; CH_3I, to r.t., 2 h; **b.**. ^{t}BuLi, THF, -78°C, then CH_2=$CHCH_2CH_2Br$; **c.** BCl_3, CH_2Cl_2, 0°C, 1 h; **d.** *c*Hex(^{i}Pr)NLi, HMPA, THF, -78°C, 30 min; CH_2=$CHCH_2CH_2I$, -78°C to 0°C, 2 h.

Scheme 22

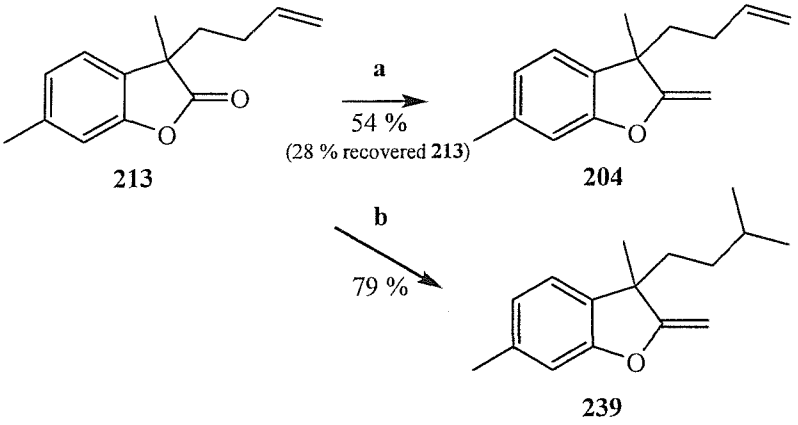
The order of the alkylation steps could be reversed. Thus **219** was homoallylated to obtain **225** which was lactonised (→ **210**) and methylated to give **213** (Scheme 23). Both routes give similar overall yields. However, 4–iodo–1–butene must be prepared prior to use from the expensive reagent 4–bromo–1–butene;[36] it is therefore more expedient to follow the route shown in Scheme 22.



a. ^{t}BuLi, TMEDA, THF, -78°C, 10 min; CH_2=$CHCH_2CH_2I$, 1h, to r.t., 8 h; **b.** BCl_3, CH_2Cl_2, 0°C to r.t., 1 h; **c.** *c*Hex(^{i}Pr)NLi, HMPA, THF, -78°C to 0°C, 15 min; CH_3I, -78°C to 0°C, 2 h.

Scheme 23

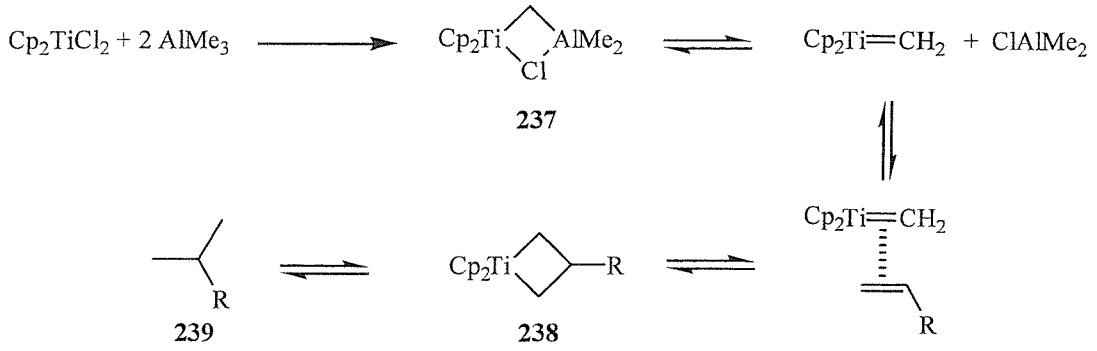
Having installed the alkyl groups on the benzylic carbon we next needed to effect methylenation of the lactone to form diene **204**. This was readily accomplished in 54 % yield using Tebbe's carbenoid chemistry[37] but unfortunately also returned 28 % unreacted starting material. Our attempts to improve the efficiency of this reaction revealed an unexpected observation. We hoped that using a large excess of Tebbe reagent would improve the yield of enol ether **204**. Instead conversion to enol ether **239** was observed (Scheme 24).



a. 2.8 eq. Cp_2TiCl_2, 7.8 eq. $AlMe_3$, $PhCH_3$, –78°C to r.t., 30 min; **b.** 6 eq. Cp_2TiCl_2, 12 eq. $AlMe_3$, $PhCH_3$, –78°C to r.t., 30 min.

Scheme 24

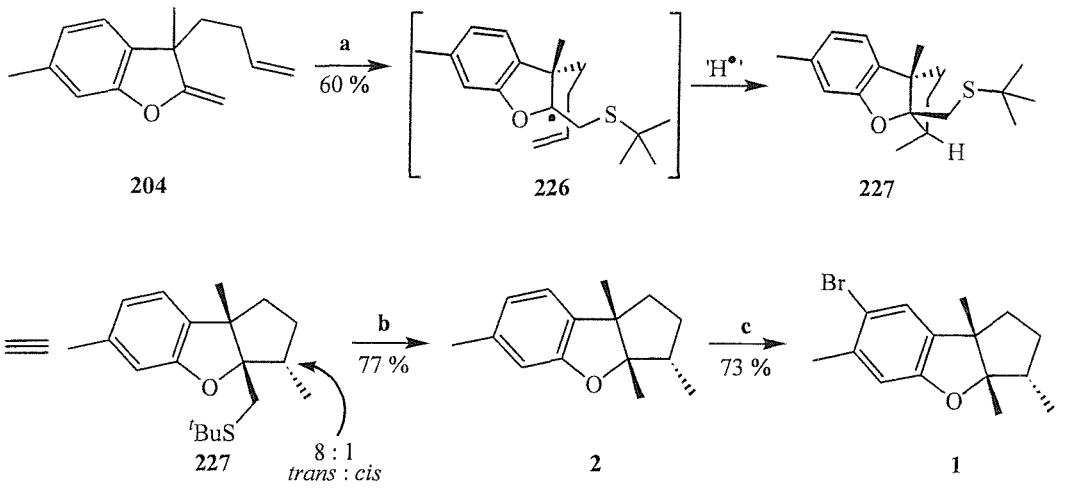
We presume that this reaction proceeds *via* metallocyclobutane **238**, which protonates on work up to give **239** (Scheme 25). As this side reaction was of no use in our synthetic program, a further study of the reaction was not embarked upon.



Scheme 25

2.4.2 Thiyl Radical Mediated Cyclisation of Diene 204. Synthesis of Debromoaplysin and Aplysin

Having accomplished the synthesis of diene **204**, we were in a position to investigate our key cyclisation. We were delighted to find that irradiation of a hexane solution of diene **204** and di–*t*–butyl disulfide gave tricycle **227** in 60 % yield, and as an 8 : 1 mixture of diastereomers. Atom transfer hydrogenolysis of the carbon to sulfur bond using Raney nickel proceeded in 77 % yield and completed the total synthesis of debromoaplysin **2**.[38] Comparison of our data for **2** with literature data confirmed the stereochemical assignment.[1] Exposure of **2** to bromine permitted the facile generation of aplysin **1** (Scheme 26).



a. (^{t}BuS)$_2$, hν, BEt_3, C_6H_{14}, r.t., 24 h; **b.** Raney Ni, EtOH, Δ, 40 h; **c.** Br_2, $NaHCO_3$, $CHCl_3$, 0°C to r.t.

Scheme 26

The observed diastereoselectivity in the thiyl radical mediated cyclisation can be rationalised in terms of the Beckwith model.[39] The electrophilic thiyl radical adds regioselectively to the terminus of the electron rich enol ether to give radical intermediate **226**. A 5–*exo*–trig cyclisation proceeds *via* a chair–like transition state in which the sterically demanding *tert*–butylsulfur moiety is aligned *anti* to the alkene. Hydrogen atom quench then provides sulfide **227**. Each of the stereogenic centres is thus installed with the desired relative stereochemistry. An X–ray crystal structure of our synthetic sample of aplysin **1** confirmed this assignment (Figure 2).

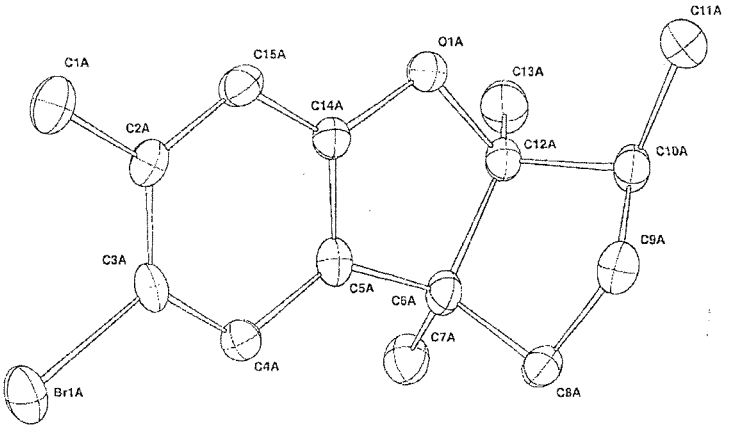
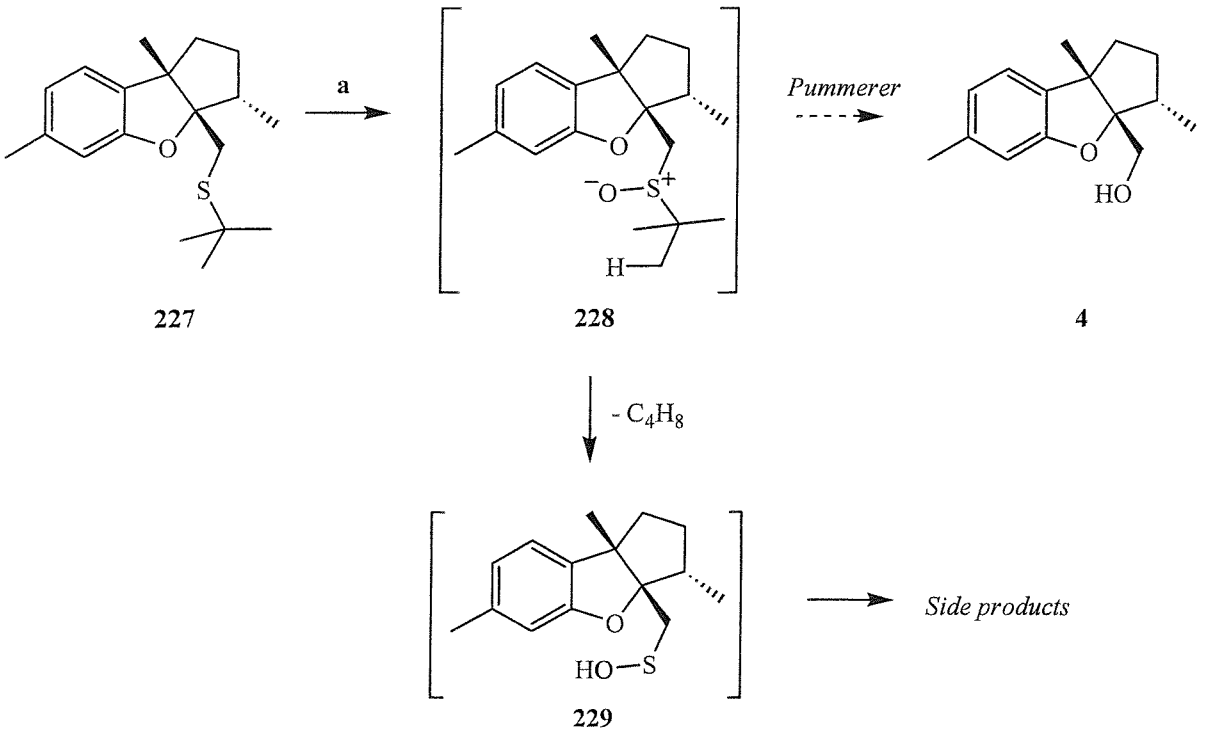


Figure 2. X-ray crystal structure of aplysin 1

2.5 FUNCTIONAL GROUP MANIPULATION OF THE SULFIDE

Having successfully completed the total syntheses of aplysin **1** and debromoaplysin **2** we sought to effect the synthesis of aplysinol **3** and isoaplysin **5**. We envisaged use of a Pummerer rearrangement[40] of sulfoxide **228** to install the alcohol functionality. Unfortunately, all attempts to generate and isolate **228** met with failure. We believe that oxidation of sulfide **227** with *meta*–chloroperbenzoic acid generated **228** which then underwent electrocyclic elimination of the *tert*–butyl group to generate an unstable sulfenic acid **229** (Scheme 27).



227 **228** **4** **229**

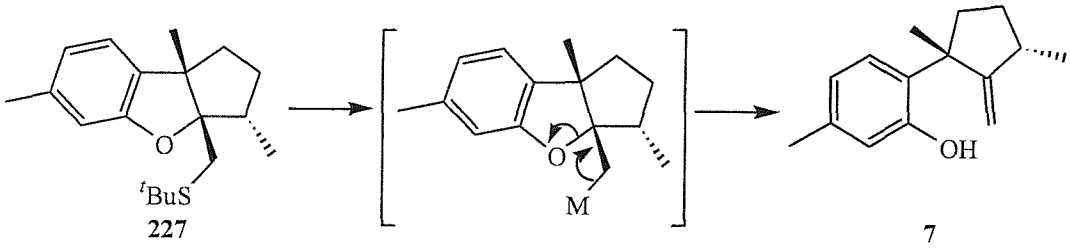
a. MCPBA, CH_2Cl_2, -78°C.

Scheme 27

Attempts to perform the radical cyclisation of **204** using diphenyl disulfide as a source of thiyl radical were unsuccessful. Oxidation of the sulfide thus formed would have generated a sulfoxide that was unable to participate in electrocyclic elimination.

2.6 Tin Mediated Cyclisations of Diene 204. Synthesis of Aplysin, Debromoaplysin and Debromoisolaurinterol

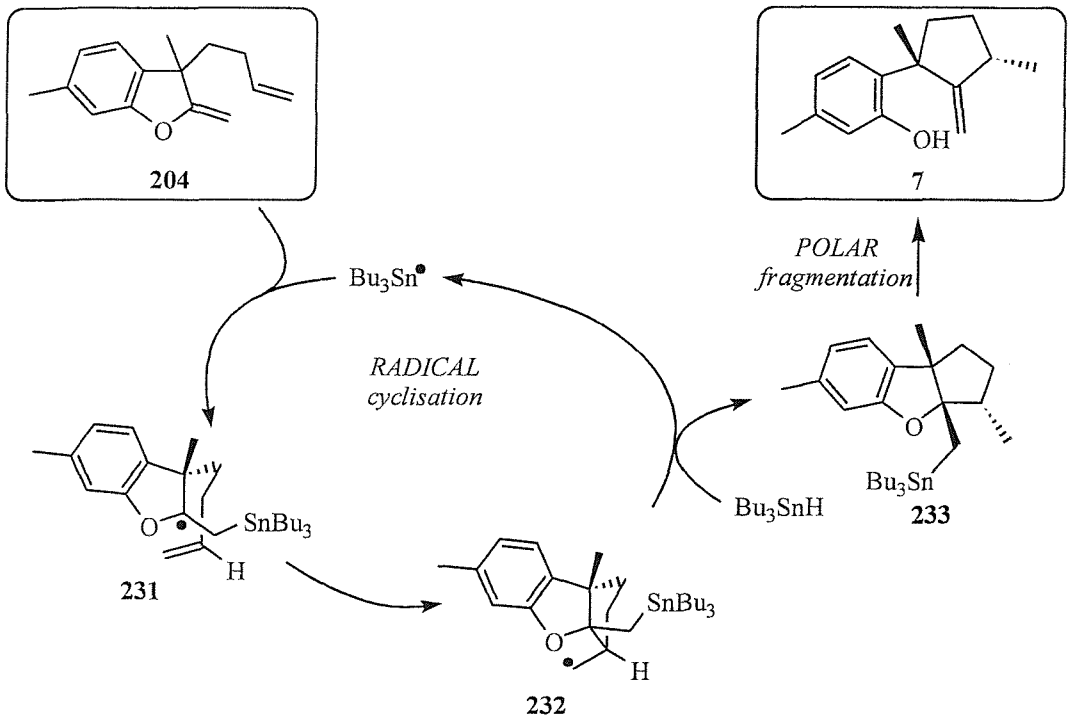
We next hoped to target debromoisolaurinterol **7** through metallation of the C–S bond (Scheme 28). From here, a series of biomimetic transformations could be envisioned to permit formation of the remaining aplysins and isolaurinterols.



Scheme 28

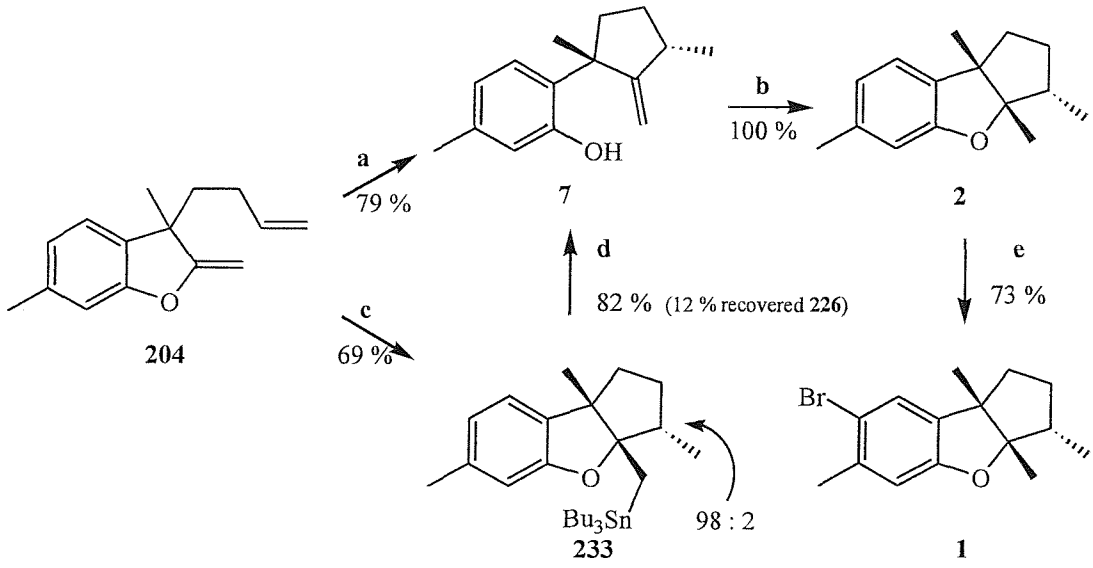
We were unable to effect sulfur metal exchange so instead chose to attempt cyclisation of diene **204** with a metal centred radical. We hoped that using a tin centred radical would offer two major advantages over sulfur. Firstly, we anticipated an enhanced diastereomeric excess as a result of its increased steric bulk. Secondly, the potential to manipulate this functionality is greater due to the inherent weakness of the carbon to tin bond.

Pleasingly, heating a toluene solution of diene **204** containing tributyltin hydride and AIBN under standard radical forming conditions furnished debromoisolaurinterol **7** and its isomer **230** in 79 % yield and as a 5 : 1 mixture of diastereomers in favour of **7** (Scheme 29). We confirmed this stereochemistry by performing the quantitative acid catalysed conversion of **7** to debromoaplysin **2**.



Scheme 29

Although delighted to have developed a new reaction to effect a vinyl group transfer from oxygen to carbon, we were less than satisfied with the observed diastereoselectivity. We suspected that the elevated temperature required to initiate collapse of AIBN was also promoting cyclisations through higher energy transition states. Indeed, diastereoselectivity was improved dramatically by conducting reactions at 10°C using ultra violet light to induce breakdown of the initiator. Under these conditions the tricyclic stannane **233** was provided as a 98 : 2 mixture of diastereomers in 69 % yield. This result was remarkable in terms of its stereoselectivity and also confirmed that fragmentation of stannane **233** was a thermal process. Thus, simply refluxing a toluene solution of **233** for 24 hours generated debromoisolaurinterol 7 as a single diastereomer in 82 % yield (Scheme 30).



a. Bu_3SnH, AIBN, $PhCH_3$, Δ, 18 h; **b.** H^+, $CDCl_3$, r.t., 16 h; **c.** Bu_3SnH, AIBN, C_6H_{14}, hν, 10°C, 24 h; **d.** $PhCH_3$, Δ, 18 h; **e.** Br_2, $NaHCO_3$, $CHCl_3$, 0°C to r.t.

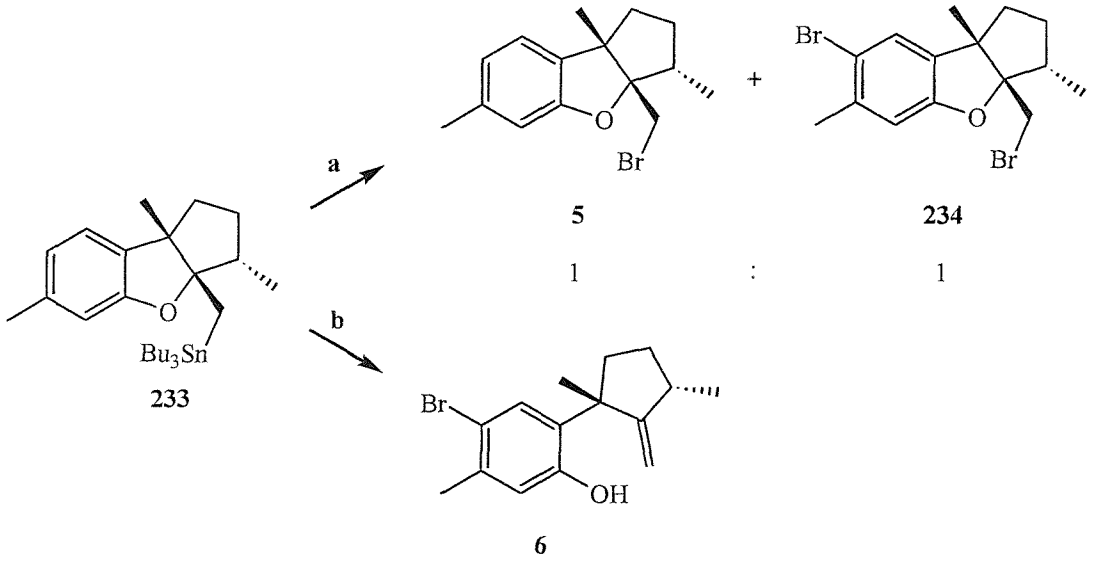
Scheme 30

Having determined how to synthesise stannane **233** and debromoisolaurinterol **7** with excellent diastereomeric excess we were able to target the remaining aplysins **3** – **5**, **236** and isolaurinterol **6**. The acid catalysed cyclisation of **7** to debromoaplysin **2** was extremely facile. Indeed, when a $CDCl_3$ solution of this compound was allowed to stand for 16 hours prior to NMR analysis a quantitative conversion was observed ($CDCl_3$ stored over anhydrous potassium carbonate failed to induce cyclisation). The ease of conversion implies that this is a biomimetic process, a suggestion first put forward by Faulkner *et al.*[2] Bromination of **2** then provided aplysin **1** in 73 % yield.

2.7 Synthesis of Isolaurinterol and Isoaplysin

Attempts to effect conversion of debromoisolaurinterol **7** into isolaurinterol **6** and isoaplysin **5** through halogenation were less rewarding, affording complex mixtures containing these materials, recovered **7** and dibromide **234**. However, exposing a cooled solution of stannane

233 to molecular bromine generated isoaplysin **5** together with dibromide **234** in a 1 : 1 ratio and 94 % total yield. These were easily separated by chromatography. We believe that this reaction proceeds by direct replacement of tin with bromine, however, it is conceivable that the system fragments first, then recyclises to generate isoaplysin. Refluxing a chloroform solution of **233** with *N*–bromosuccinimide furnished isolaurinterol **6** in 49 % yield (Scheme 31). This reaction presumably proceeds *via* a polar fragmentation followed by electrophilic bromination.



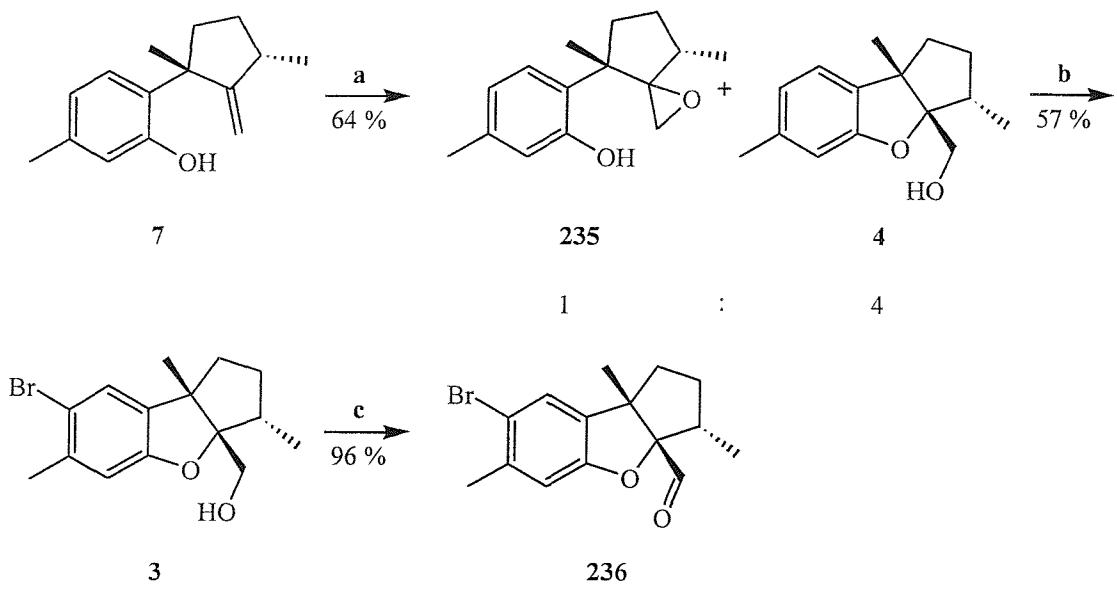
a. Br_2, $NaHCO_3$, 0°C, 5 min, 94 %; **b.** NBS, $CHCl_3$, Δ, 72 h, 49 %.

Scheme 31

2.8 SYNTHESIS OF APLYSINOL, DEBROMOAPLYSINOL AND APLYSINAL

Aplysinol **3** and debromoaplysinol **4** were next targeted. Epoxidation of debromoisolaurinterol **7** with *meta*–chloroperbenzoic acid induced spontaneous cyclisation to give debromoaplysinol **4** in 52 % yield. This reaction proceeds *via* 5–*exo*–tet cyclisation of the oxirane intermediate **235**, which was isolated as a minor product of the reaction (12 %) together with recovered **7** (10 %). Debromoaplysinol **4** was brominated to give aplysinol **3** in

57 % yield (Scheme 32). A Dess – Martin oxidation[41] then completed the synthesis of aplysinal **236**.

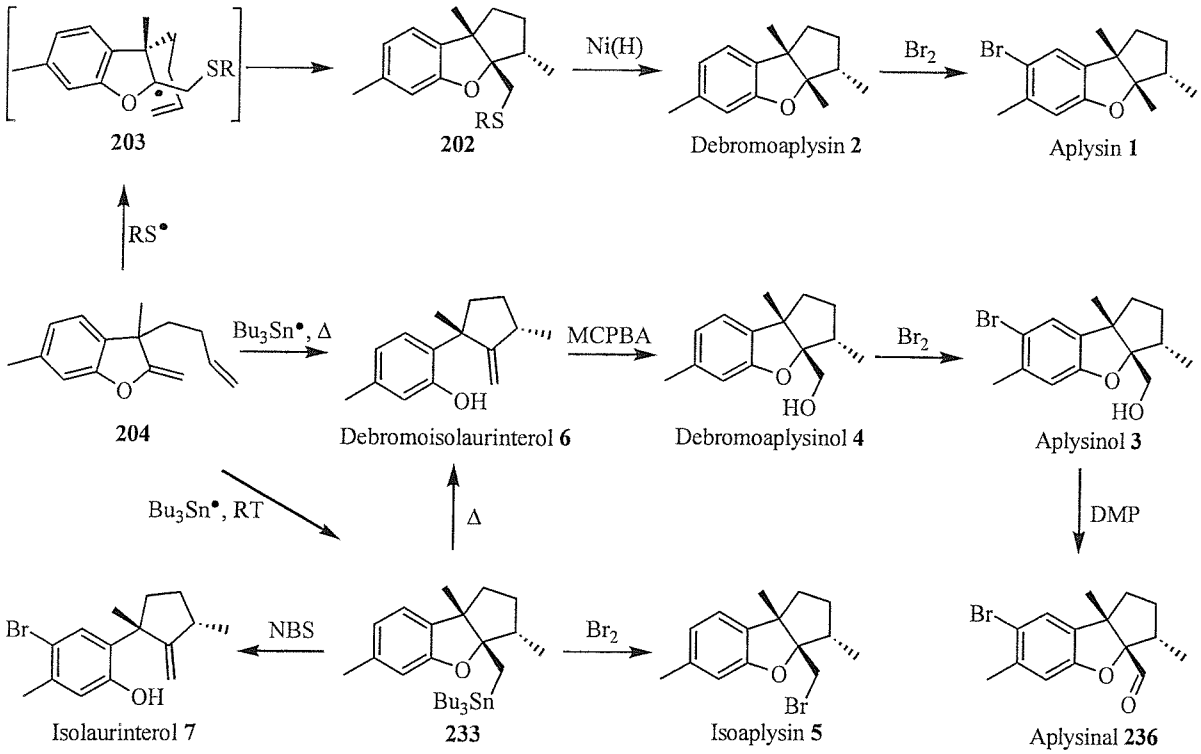


a. MCPBA, CH_2Cl_2, 0°C, 24 h; **b.** Br_2, $NaHCO_3$, 0°C, 1 h; **c.** DMP, CH_2Cl_2, r.t., 2 h.

Scheme 32

2.9 CONCLUSIONS

Thus, we completed the total synthesis of all the known aplysin and isolaurinterol natural products and provided evidence that each is derived in nature from debromoisolaurinterol **7** (Scheme 33). During our synthesis we discovered a novel halide free tin mediated radical cyclisation, a boron trichloride mediated lactonisation, and a convenient method for converting thioamides to thioesters (see Chapter 6). Our diastereoselective thiyl radical approach to aplysin and debromoaplysin has demonstrated the utility of sulfur mediated radical cyclisation reactions in synthesis. That the cyclisation used cheaper and less toxic reagents than trialkylstannane based methodologies is noteworthy.


SR
203
RS
202
Ni(H)
Debromoaplysin 2
Br2
Br
Aplysin 1
RS•
Bu3Sn•, Δ
204
OH
Debromoisolaurinterol 6
MCPBA
HO
Debromoaplysinol 4
Br2
Br
HO
Aplysinol 3
Bu3Sn•, RT
Δ
DMP
Br
OH
Isolaurinterol 7
NBS
Bu3Sn
233
Br2
Br
Isoaplysin 5
Br
O
Aplysinal 236

Scheme 33

CHAPTER 3

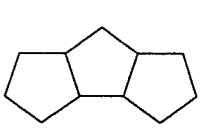
THE TOTAL SYNTHESIS OF 1–DESOXYHYPNOPHILIN

3.1 POLYQUINANES

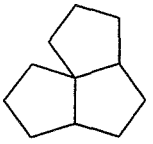
Polyquinane is a generic name given to a carbocyclic skeleton consisting of two or more fused five–membered rings. These carbocycles have stimulated interest within the synthetic community as a result of their complex architecture and often promising biological activity. Over 250 natural terpenes are members of this subgroup composed entirely of fused five membered rings. There is extensive literature concerning their synthesis, and comprehensive reviews exist.[53]

3.2 TRIQUINANES

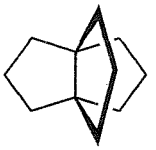
The polyquinane natural products of greatest abundance are the triquinanes. These are found widely in nature including marine, plant and microbe sources. Triquinanes are based on one of the three possible skeletal structures: linearly fused **301**, angularly fused **302** and propellane **303**.



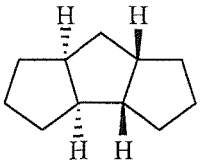
301



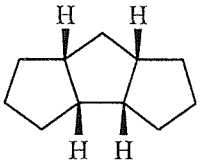
302



303

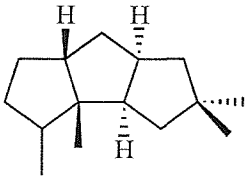


cis:anti:cis

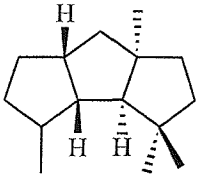


cis:syn:cis

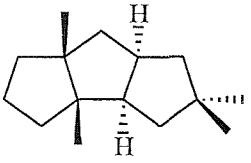
Of the two isomeric linear triquinanes, the *cis*:*anti*:*cis* isomer is most abundant in Nature. There are four different skeletal types (**304** – **307**) known among the linear triquinane natural products, representing variation in the location of the four carbon substituents and quaternary carbon centres. However, they all share a common biosynthetic origin through the humulene cyclisation cascade.[106] A review concentrating on the general methodologies for the synthesis of linear triquinanes is presented by Singh and Thomas.[54]



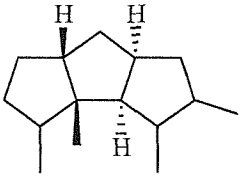
Hirsutane **304**



Capnellane **305**



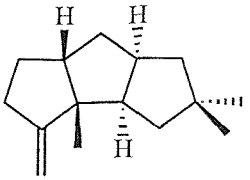
Ceratopicane **306**



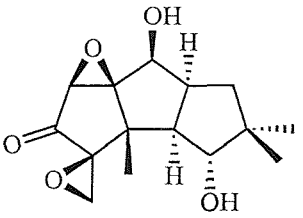
Pleurotellane **307**

3.3 The Hirsutanes

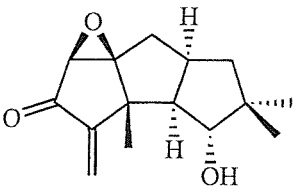
The hirsutanes are a group of fungal metabolites based on the *cis*,*anti*,*cis*–1,4,4,11–tetramethyltricyclo[6.3.0.$0^{2,6}$]undecane framework **304**. These natural products show a variety of additional functionalisation and biological activity (*e.g.* **308** – **310**) and are often the targets of synthetic chemists wishing to demonstrate cyclopentannulation protocols.



Hirsutene **308**



Coriolin **309**
anti tumour and anti bacterial

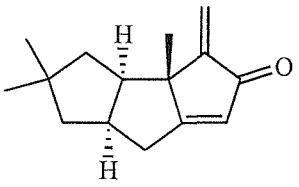


Hypnophilin **310**
growth inhibitor and anti bacterial

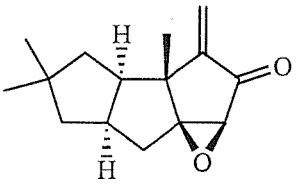
The hydrocarbon hirsutene **308**, isolated from the mould *Coriolus consors*,[55] is the simplest member of the hirsutane group and is thus the most popular target molecule.[56] The coriolins and hypnophilins constitute a group of closely related, highly functionalised triquinane sesquiterpenoids that present additional challenges to the synthetic chemist.

3.4 1–DESOXYHYPNOPHILIN

Identified in 1994 as a constituent of the East African mushroom *Lentinus crinitus*, 1–desoxyhypnophilin **312** has been shown to exhibit concentration dependent growth inhibition activity against L929 mouse fibroblasts cells and antimicrobial activity against several strains of bacteria.[57] Closely related to hypnophilin **310** and coriolin **309** (*vide supra*), these natural compounds are presumably derived from a common precursor, diene **311**. Numerous syntheses of hypnophilin and coriolin have been reported, using various cyclopentannulation strategies,[58,59] but diene **311** and 1–desoxyhypnophilin **312** have not yet been the subject of a total synthesis.



311

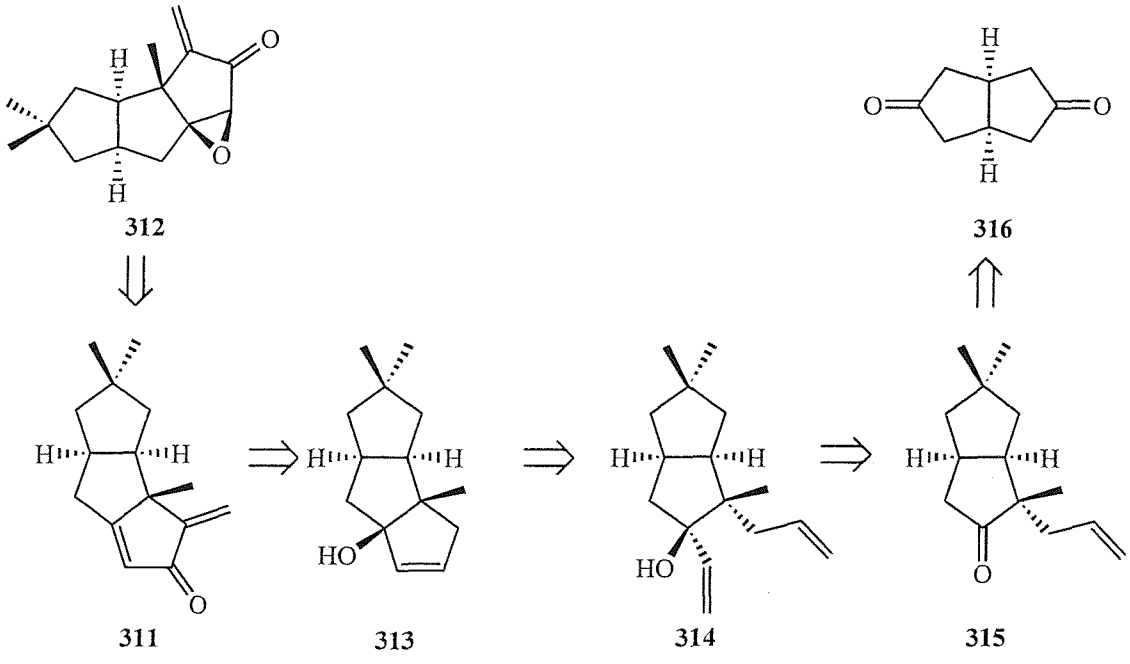


1-Desoxyhypnophilin **312**

3.5 THE SYNTHESIS OF 1–DESOXYHYPNOPHILIN

3.5.1 RETROSYNTHETIC ANALYSIS

Our retrosynthetic analysis is detailed in Scheme 34. We hoped that diene **311** would undergo regioselective epoxidation of the endocyclic alkene to release strain within the ring. **311** would be generated from allyl alcohol **313**, which in turn would be synthesised *via* a two step annulation strategy from bicyclic ketone **315**. We hoped to use standard enolate chemistry to install the alkyl substituents α to the ketone carbonyl, and envisioned commercially available symmetrical diketone **316** as our starting material. We expected that the *cis* fused bicyclic structure would exert stereochemical control on all manipulations with reactions exhibiting a strong bias toward attack of the *exo* face.

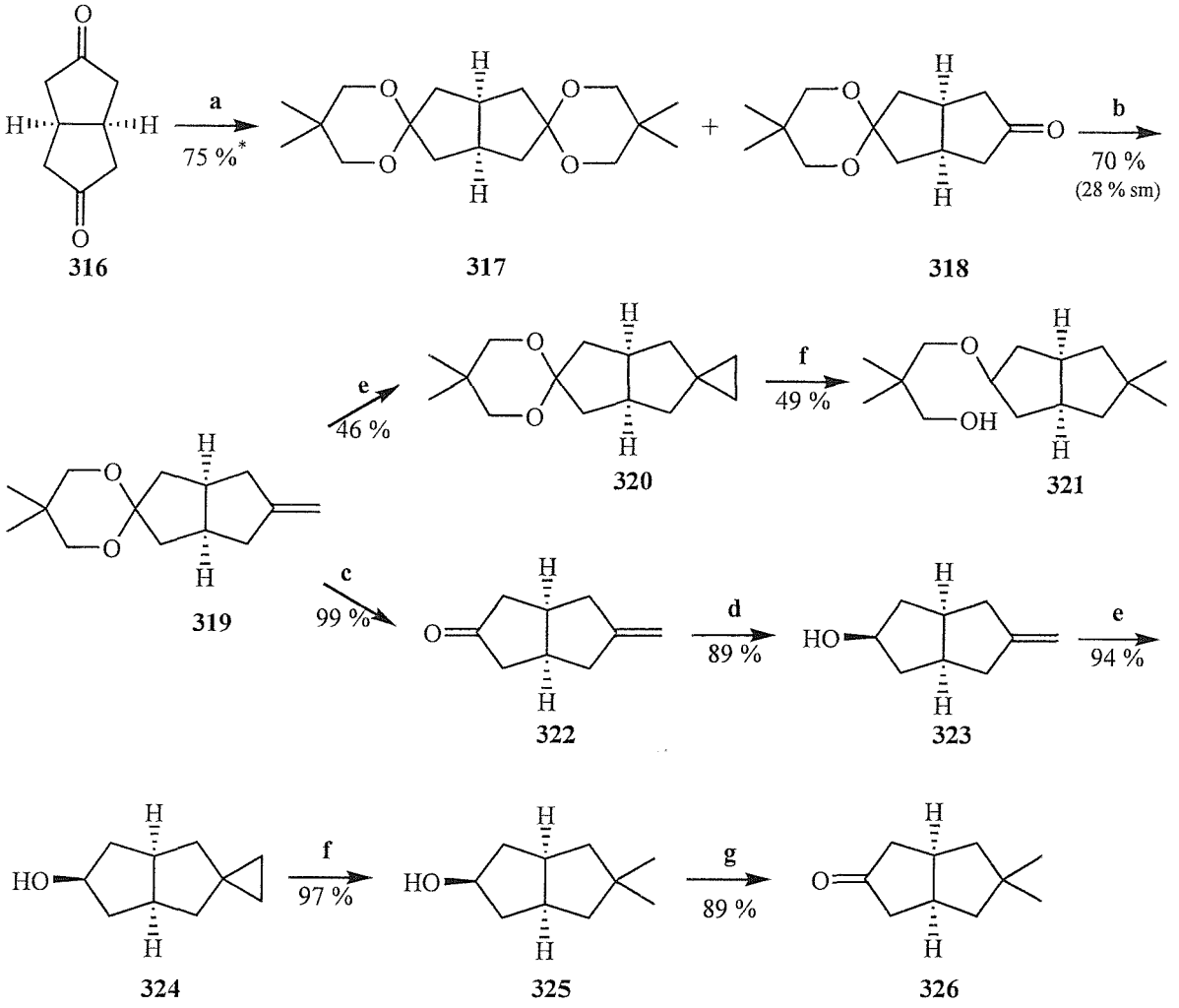


Scheme 34

3.5.2 TOTAL SYNTHESIS OF 1–DESOXYHYPNOPHILIN

cis–Bicyclo[3.3.0]octane–3,7–dione **316** is commercially available and also readily synthesised.[60] Treatment of **316** with one equivalent of 2,2–dimethyl–1,3–propanediol in refluxing toluene containing catalytic PPTS generated a statistical mixture of recovered **316**, monoacetal **318** and bisacetal **317** (ratio 1 : 2 : 1, respectively). Fortunately these materials are readily separable by chromatography, and the bisacetal **317** can be conveniently and quantitatively hydrolysed for recycling. After one recycling operation, yields approaching 75 % were generally obtained. Wittig olefination of **318** to alkene **319** proceeded in good yield (70 %). However, cyclopropanation of this material to give **320** was less satisfactory (46 % yield), and subsequent hydrogenation reduced both the cyclopropane and the acetal to give alcohol **321** (49 %).

Piers had experienced similar problems in some related work and found that cyclopropanation was more efficient when directed by an alcohol moiety.[61] We therefore hydrolysed the acetal **319** in quantitative yield and reduced the resulting ketone **322** to alcohol **323** (89 %). Cyclopropanation to **324** (94 %) and reduction to **325** (97 %) then proceeded smoothly. A Dess – Martin periodinane oxidation then gave ketone **326** (89 %).



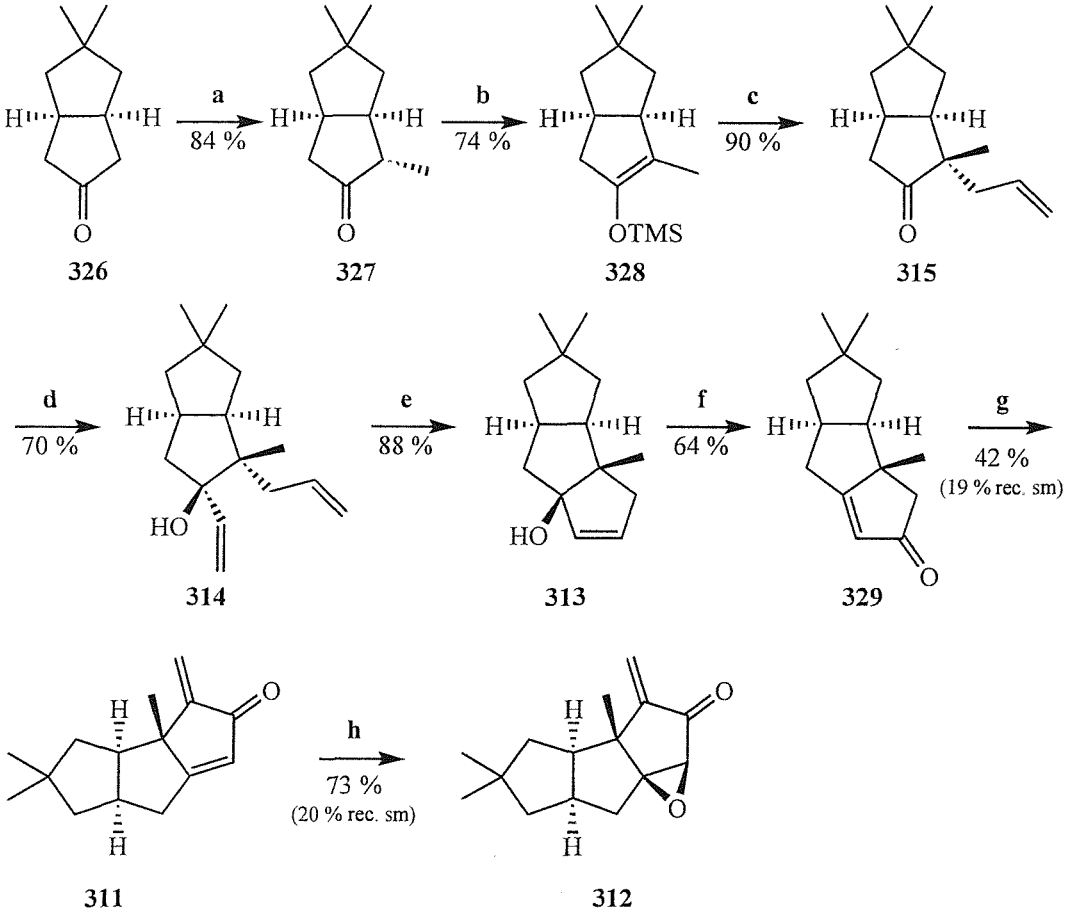
*Yield after recycling **317** and recovered **316**

a. Neopentyl glycol, PPTS, $PhCH_3$, Δ, 20 h; **b.** Ph_3PCH_3Br, BuLi, THF, r.t., 18 h; **c.** H_2SO_4, H_2O, acetone, r.t., 18 h; **d.** $LiAlH_4$, Et_2O, -78°C, 10 min; **e.** Et_2Zn, CH_2I_2, $PhCH_3$, 60°C, 4 h; **f.** H_2, PtO_2, AcOH, NaOAc, r.t., 24 h; **g.** DMP, CH_2Cl_2, r.t., 1 h.

Scheme 35

We next addressed the synthesis of 1–desoxyhypnophilin **312**. Firstly ketone **326** was enolised and methylated to give **327** in 84 % yield (Scheme 36). Conducting the reaction at –90°C was necessary to minimise bisalkylation and to ensure that only one diastereomer was produced. Trapping the thermodynamic enolate of **327** as its silyl enol ether **328**, followed by transmetallation with MeLi and allylation with allyl bromide next gave **315** in 67 % yield (from **327**). A cerium(III) chloride promoted *exo* addition of vinylmagnesium chloride to the

ketone then provided diene **314** in 70 % yield. [In the absence of cerium(III) no vinylation was observed, presumably due to steric hindrance of the ketone]. Diene **314** underwent a ring closing metathesis on exposure to Grubbs' ruthenium based catalyst to form **313** (88 %).[63] Treatment of **313** with pyridinium chlorochromate then induced allylic oxidation to enone **329**. The method of Greene *et al.* was next employed to effect methyleneation to diene **311** in a disappointing 42 % yield.[64] Finally, selective epoxidation with hydrogen peroxide (73 %) provided 1–desoxyhypnophilin **312**, our synthetic sample exhibiting spectral characteristics identical to those reported previously.[57]



a. $^{i}Pr_2NLi$, HMPA, THF, -90°C, then MeI, 5 h; **b.** Et_3N, DMF, TMSCl, Δ, 24 h; **c.** MeLi, THF, HMPA, -78°C, 15 min then AllylBr, 3h; **d.** VinylMgBr, $CeCl_3$, THF, 0°C, 15 h; **e.** $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, Δ, 3 h; **f.** PCC, CH_2Cl_2, 4 Å MS, r.t., 18 h; **g.** HCO_2Me, LiHMDS, THF, -78°C, 1 h then CH_2O, H_2O, acetone, K_2CO_3, r.t., 18 h; **h.** H_2O_2, $NaHCO_3$, THF, H_2O, 4 °C, 15 h.

Scheme 36

3.6 Conclusions and Further Work

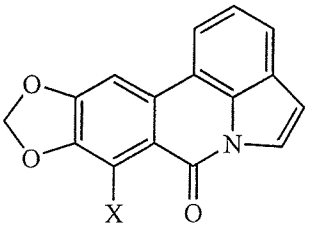
In conclusion, we have achieved a diastereoselective total synthesis of 1–desoxyhypnophilin **312** and developed a useful annulation protocol for the synthesis of cyclic enones. This procedure has enormous potential for the synthesis of other polycycles. Additionally, our method should also lend itself to enantioselective synthesis through either desymmetrisation of ketone **326** with a chiral base,[65] or through ketone **327** which is available enantioselectively using a Pauson – Khand cyclisation.[66]

CHAPTER 4

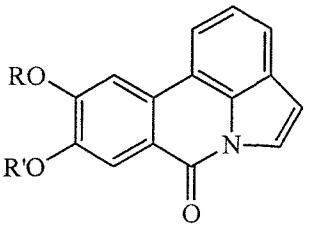
A SHORT SYNTHESIS OF HIPPADINE

4.1 BACKGROUND

The use of extracts from various Amaryllidaceae plant species in the herbal treatment of coughs, asthma, rheumatism, piles and abscesses has prompted numerous investigations into their phytochemistry.[67,68] Of the compounds identified as natural products from the *Crinum* species, (*e.g.* **401** – **404**),[67-77] the pyrrolophenanthridone alkaloids hippadine **401** and kalbretorine **402** have gained greatest prominence. Since their discovery, the alkaloids have been shown to possess significant levels of biological activity.[76-78]



X = H, Hippadine **401**
X = OH, Kalbretorine **402**



R = H, R' = Me, Pratorinine **403**
R = Me, R' = H, Pratorimine **404**

Hippadine was first isolated as a constituent of *Hippeastrum vittatum* and *Crinum Buldispermum*.[69] Its characterisation as a component of *Crinum pratense* followed in 1981.[70] Interest in this compound increased when it was found to reversibly inhibit fertility in male rats.[76] Importantly, significant reduction of both testicular weight and DNA content was observed and the mammals showed physiological changes indicative of growing hormonal

activity. These observations suggest that hippadine could act as an effective contraceptive and that it exerts its effects at a genetic level.

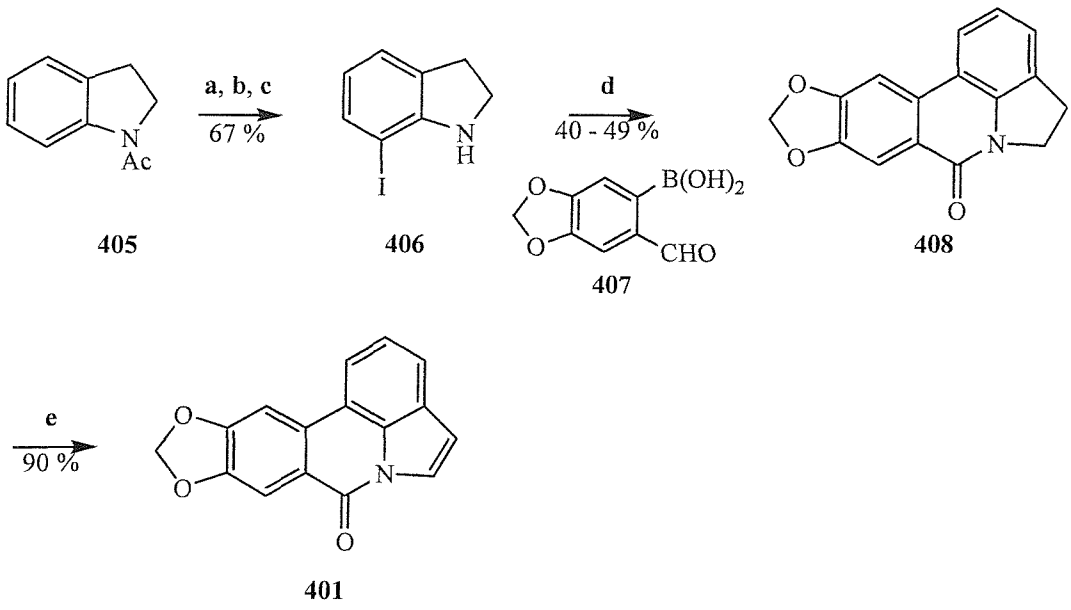
4.2 Previous Synthetic Strategies

Pyrrolophenanthridones have previously been prepared using a variety of synthetic strategies to form the key aryl to aryl bond. Palladium catalysed cross–coupling reactions have been favoured,[79,80,82,83] though other coupling methods have been successfully applied including an oxazoline–mediated process,[81] an intramolecular cycloaddition strategy,[85] and most recently *via* a radical cyclisation reaction.[84,92] With one exception, the published syntheses of hippadine have all been concise.[85]

4.2.1 Syntheses Using Intermolecular Aryl – Aryl Coupling

4.2.1.1 Suzuki Coupling

Sniekus *et al.*[79] were first to publish a synthesis of hippadine using an intermolecular aryl – aryl coupling as a key step. They used a one pot Suzuki cross–coupling – cyclisation of *o*–formyl aryl boronic acid **407** with halo–indoline **406**. A thallium mediated iodination of 1–acetylindoline **405** gave **406** after basic hydrolysis. Cross–coupling using modified Suzuki conditions afforded lactam **408** which was oxidised with DDQ to give hippadine in 24 % overall yield (Scheme 37).



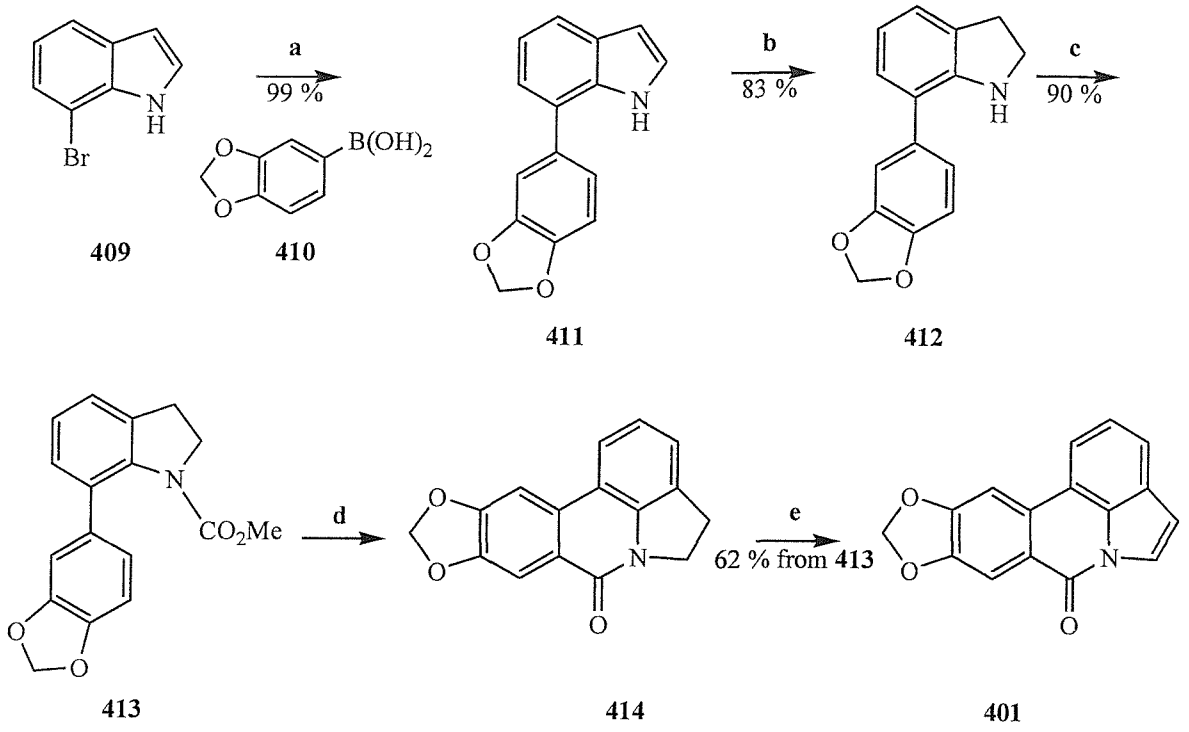
a. $Tl(OCOCF_3)_3$, TFA; **b.** KI, H_2O; **c.** NaOH, EtOH; **d.** $Pd(PPh_3)_4$, Na_2CO_3, DME, Δ; **e.** DDQ, dioxane, Δ.

Scheme 37

4.2.1.2 Suzuki Coupling and Bischler – Napieralski Cyclisation

The Bischler – Napieralski cyclisation reaction usually requires harsh reagents (*e.g.* $POCl_3$) and high temperatures, and is therefore intolerant of substrates containing sensitive functionality. Banwell *et al.*[80] sought to find a milder alternative and, having done so, applied this to the synthesis of a number of the amaryllidaceae alkaloids including hippadine **401**.

7–Bromoindole **409** was subjected to a Suzuki cross – coupling with arylboronic acid **410**. The double bond was reduced by ionic hydrogenation to obtain **412**. After converting dihydro compound **412** to carbamate **413**, the Bischler – Napieralski cyclisation was achieved by treatment with Tf_2O – DMAP at 0°C to give **414**. DDQ promoted dehydrogenation furnished hippadine **401** (Scheme 38).

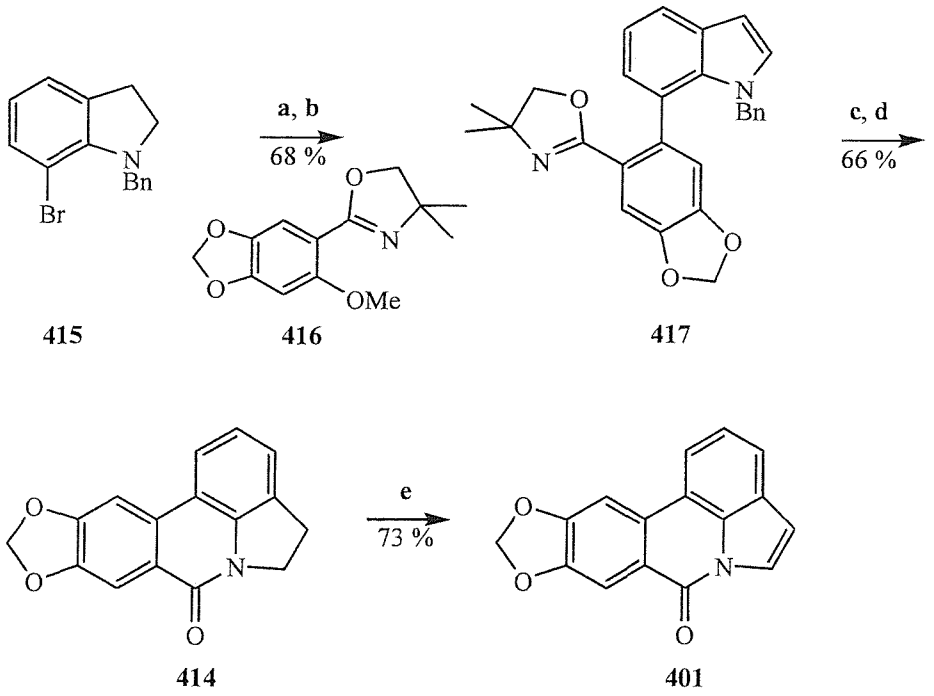


a. $Pd(PPh_3)_4$, $PhCH_3$, EtOH, Na_2CO_3, Δ, 4 d; **b.** $NaCNBH_3$, AcOH, 15°C, 2 h; **c.** NaH, $ClCO_2Me$, THF, 15°C, 16 h; **d.** Tf_2O, DMAP; **e.** DDQ, dioxane, Δ.

Scheme 38

4.2.1.3 Oxazoline – Mediated Synthesis

Meyers *et al.*[81] prepared hippadine **401** *via* coupling of aryloxazoline **416** (prepared in six steps from piperonal) with the magnesio derivative of **415** (prepared in three steps from *N*–acetylindole) to give the intermediate biaryl **417**. Hydrolysis, cyclisation, and finally oxidation with DDQ gave hippadine **401** (Scheme 39).



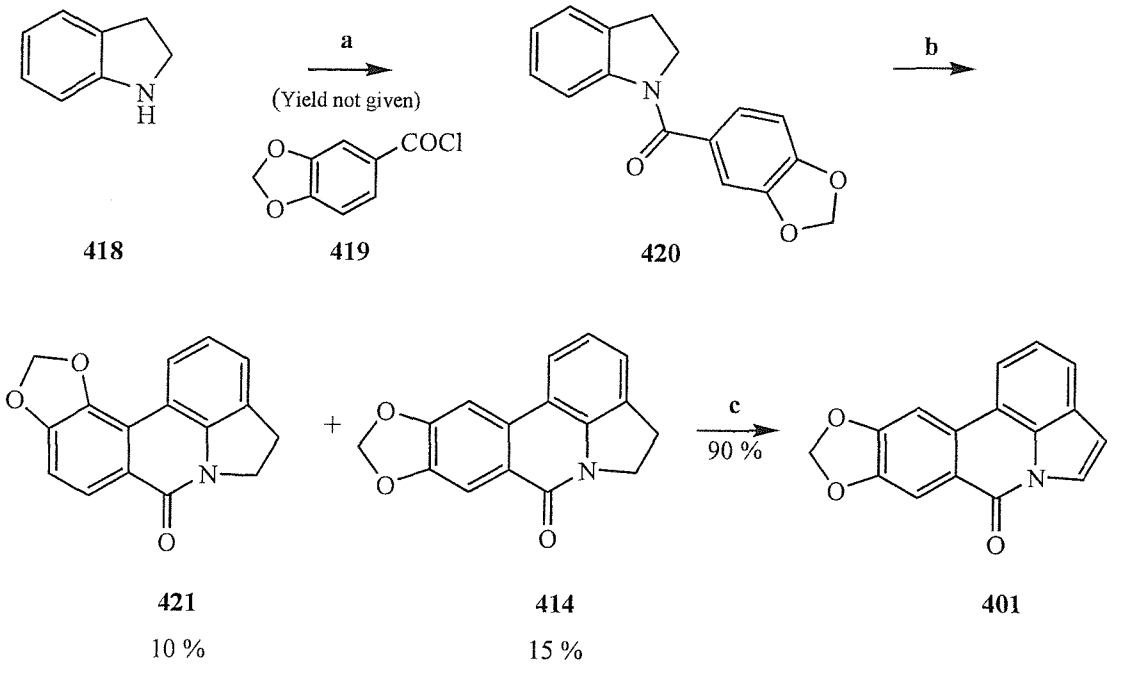
a. Mg, THF, $BrCF_2CF_2Br$; **b.** **416**; **c.** 10 % H_2SO_4, EtOH; **d.** Pd/C, H_2; **e.** DDQ.

Scheme 39

4.2.2 Syntheses Involving Intramolecular Aryl – Aryl Coupling

4.2.2.1 Palladium Couplings

Black *et al.*[82] reported a synthesis of hippadine **401** based on palladium catalysed arylation of *N*–acylindoline **420**. Indoles are not suitable substrates for this cyclisation since arylation occurs exclusively at the indole C2 position. *N*–Acylindoline **420**, derived from piperonyl chloride **419** and indoline **418**, gave a mixture of cyclised products **421** and **414** on palladium mediated cyclisation. Dehydrogenation with DDQ gave hippadine **401** (Scheme 40).

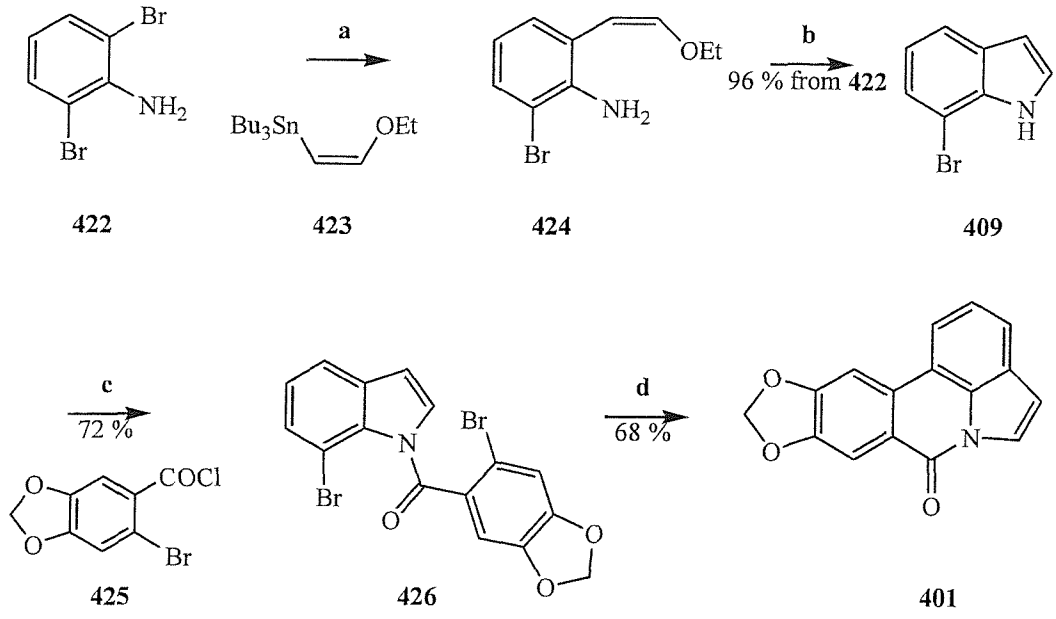


a. **419**; **b.** $Pd(OAc)_2$, AcOH, Δ, 5 h; **c.** DDQ.

Scheme 40

4.2.2.2 Stille Couplings

Yasuhara *et al.*[83] reported a concise synthesis of hippadine **401** using a palladium–catalysed cross–coupling reaction to effect union of 2,6–dibromoaniline **422** and (*Z*)–1–tributylstannyl–2–ethoxyethene **423**. Later, an intramolecular aryl to aryl coupling reaction mediated by palladium was used to effect cyclisation of **426** to hippadine **401** (Scheme 41).

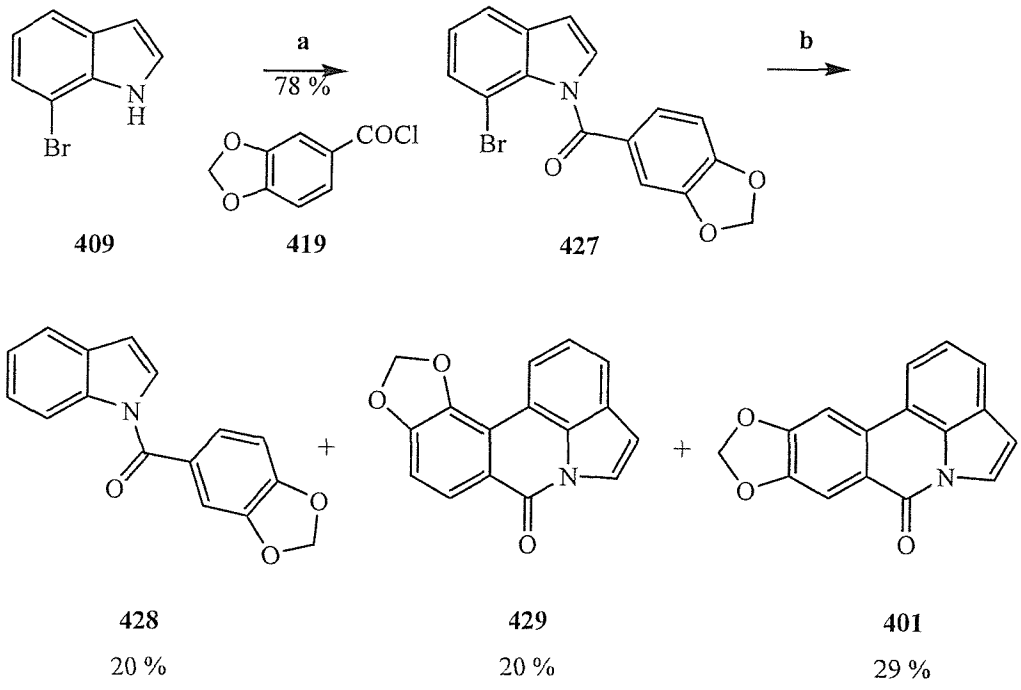


a. $Pd(PPh_3)_2Cl_2$, Et_4NCl, CH_3CN; **b.** $(COOH)_2.2H_2O$; **c.** NaH, THF; **d.** $(Bu_3Sn)_2$, Et_4NBr, Li_2CO_3, $Pd(PPh_3)Cl_2$, $PhCH_3$.

Scheme 41

4.2.2.3 Radical Cyclisation

Tsuge *et al.*[84] reported an approach to the synthesis of pyrrolophenanthridone alkaloids based on an intramolecular radical cyclisation of 1–aroyl–7–bromoindoles mediated by Bu_3SnH and AIBN. Arylindole **427** (synthesised from 7–bromoindole and piperonyl chloride) was subjected to standard radical forming conditions to induce cyclisation to give hippadine **401** along with its regioisomer **429** and reduction product **428** (Scheme 42).

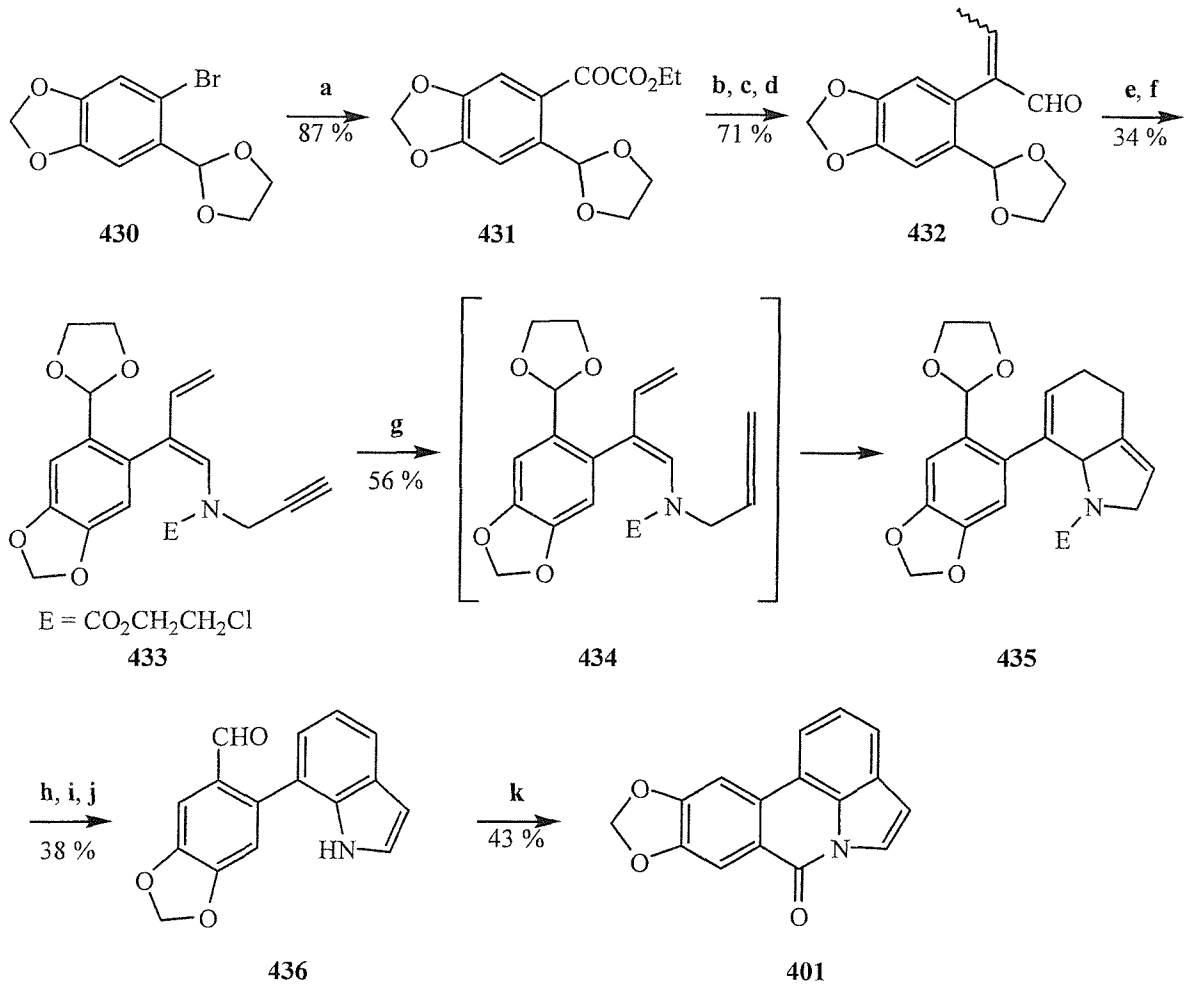


a. NaH, THF, r.t., 15 h; **b.** Bu_3SnH, AIBN, Δ, PhH.

Scheme 42

4.2.3 SYNTHESES *VIA* INTRAMOLECULAR CYCLOADDITION

Hawakawa *et al.*[85] offered an alternative strategy for the construction of hippadine **401**. They initially synthesised the indole *via* an intramolecular Diels–Alder reaction of 3–substituted allenic dienamide **434**. The product, **435**, was dehydrogenated with DDQ then hydrolysed to **436**. Base–catalysed ring closure of **436** followed by aerial oxidation on work up gave hippadine **401** (Scheme 43).



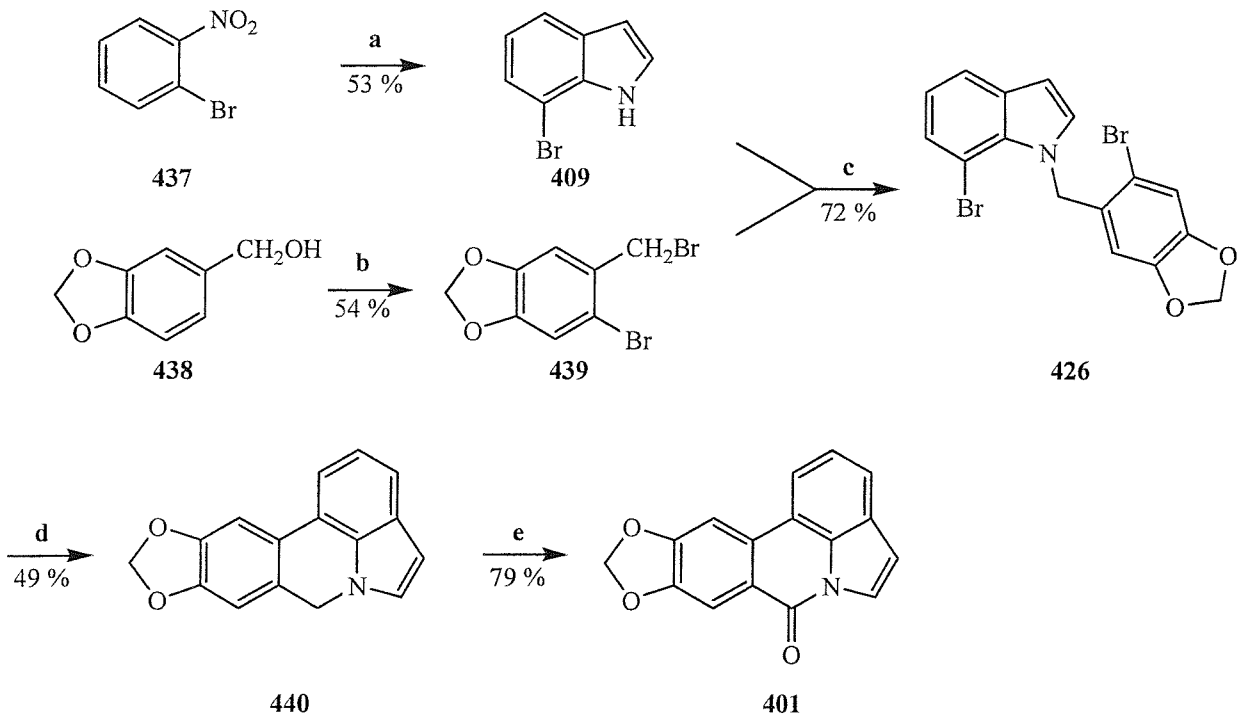
a. BuLi, Et_2O, -78°C, $(CO_2Et)_2$; **b.** $Ph_3PCH_2CH_3Br$, BuLi, Et_2O, 25°C; **c.** DIBAL-H, Et_2O, -40°C; **d.** DMSO, TFAA, CH_2Cl_2, -78°C then Et_3N; **e.** propargylamine, 4Å MS, $PhCH_3$, 25°C; **f.** 2-chloroethyl chloroformate, diethylaniline, $PhCH_3$, 25°C; **g.** CH_2O, $^iPr_2NH$, CuBr, dioxane, 100°C; **h.** DDQ, PhH, 80°C; **i.** KOH, MeOH, H_2O, 70°C; **j.** HCl, THF, H_2O, 25°C; **k.** NaH, THF, 25°C.

Scheme 43

4.3 Our Synthesis of Hippadine

Our synthesis of hippadine **401** began with the union of the known bromides **409** and **439** (each prepared in one step, from 2–bromonitrobenzene **437** and piperonyl alcohol **438**, respectively)[86,87] to give tethered dibromide **426** in 72 % yield. Sequential transmetallation of dibromide **426** with two equivalents of butyllithium, then two equivalents of copper(I)

iodide next promoted an intramolecular aryl–aryl coupling to give pentacycle **440** in 49 % yield (itself a natural product found in the bulbs of *Pancratium biflorum*).[74,75,88-90] This Ziegler modified Ullman type coupling is remarkable in that it proceeds at low temperature.[91] This pentacycle is particularly unstable, and our attempts to effect the known aerial oxidation of **440** to hippadine led to substantial decomposition with only traces of the natural product being isolated.[88] However, simply stirring a dichloromethane solution of **440** with barium manganate provided hippadine **401** in good yield (Scheme 44).



a. VinylMgCl, THF, -70°C, 3h; **b.** Br_2, AcOH. 0°C, 15 h; **c.** KOH, DMSO, 2 h; **d.** 2 eq. BuLi, THF, -78°C then 2 eq. CuI.$P(OEt)_3$, 3h to r.t, 21 h; **e.** $BaMnO_4$, CH_2Cl_2, r.t., 12 h.

Scheme 44

4.4 CONCLUSIONS

Our synthesis of hippadine was accomplished in four steps from cheap, commercially available starting materials. It compares favourably with all previously published syntheses and has demonstrated further the utility of copper(I)–promoted aryl to aryl couplings in target synthesis. In addition, we have used barium manganate to effect the oxidation of the benzylic methylene to a ketone in high yield.

CHAPTER 5

DIASTEREOSELECTIVE THIYL MEDIATED RADICAL CYCLISATIONS

5.1 BACKGROUND

For a long time, synthetic organic chemists were reluctant to use free radical chemistry to construct a target molecule. Early radical chemistry had gained a reputation for being capricious, with poor selectivity and leading to an unpredictable array of products. The work of figures such as Stork, Beckwith, Curran, Barton, and Giese has done much to dispel this view.[93,94] There is now a vast array of synthetically useful radical reactions. Radical chemistry boasts several significant advantages over the more traditional synthetic methods.[93d] Despite their high reactivity, radicals react under mild, neutral conditions without compromising chemo–, regio–, or stereo–selectivity. The high reactivity permits the generation of bonds between sterically crowded centres because of the absence of bulky counterions or solvation spheres. Finally, carbon centred radicals are inert to hydroxyl, amino and related functional groups so protection chemistry is often avoidable, and reactions do not demand dry conditions.

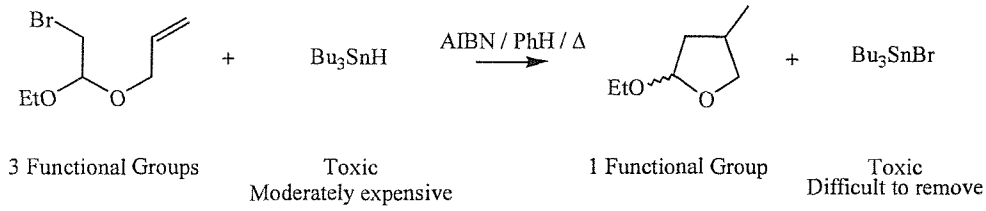
5.2 ORGANOTIN HYDRIDES

An important foundation of the modern use of radical reactions in organic chemistry was the realisation that organotin hydrides could efficiently mediate them.[93d,95] Reactions mediated by alkyl stannanes are mild and selective. Generally carbonyl groups as well as hydroxyl and amino groups need no protection. Significant collections of physical data on alkylstannane reaction kinetics mean that the technique is accessible to chemists whose area of expertise

does not lie within radical chemistry, enabling reaction products to be predicted reliably in most cases.

The chemistry of alkyl stannanes does possess disadvantages. Criticism focuses on the expense and toxicity of the reagents.[96] Stoichiometric production of toxic organotin residues, which are notoriously difficult to remove during work up, provides another deterrent to their utilisation.[97] Radical reactions are often wasteful in their use of functionality. A typical radical cyclisation, for example, expends two functional groups to generate one new carbon to carbon bond. Poor stereoselectivity in radical cyclisations from acyclic starting materials is also a disadvantage and, as most carbon–centred radicals have a negligible energy barrier to inversion, they do not normally retain their stereochemical information.

Tributyltin hydride (Bu_3SnH) is the most commonly encountered alkylstannane in the scientific literature. It is a convenient mediator of reactions involving carbon centred radicals as they have a relatively long lifetime in the presence of low concentrations of Bu_3SnH. Hence they have time to undergo fast intramolecular and intermolecular reactions prior to suffering hydrogen atom quench. Moreover, provided that the product radical has a reasonably long lifetime it will be quenched by Bu_3SnH before slow side reactions become a serious complication. Where the desired reaction is excessively slow, RH contaminants begin to appear. The influence of reagent concentration can be dramatic in such cases. Scheme 45 presents some of the problems that are associated with tributyl tin hydride propagated radical reactions.[98]



Scheme 45

Thus, stannane based methodology has largely been restricted to laboratory scale experiments where waste, toxicity and expense are manageable.[99] Some of the problems have been solved; stoichiometric use is avoided by using catalytic quantities of the stannane and a cheap reducing agent to regenerate the hydride,[100] while Chatgilialoglu's reagent, tris(trimethylsilyl)silicon hydride ($[TMS]_3SiH$), is one expensive alternative to tributyltin hydride.[101] There is, however, still scope for improvement.

5.3 Radical Cyclisation Reactions

There are a number of procedures for effecting radical cyclisation reactions. The key steps normally involve the generation of an initial carbon centred radical, then addition of that reactive centre to an unsaturated moiety to effect an intramolecular cyclisation. Finally, atom abstraction from a mediator simultaneously furnishes the product and another radical to propagate the chain.

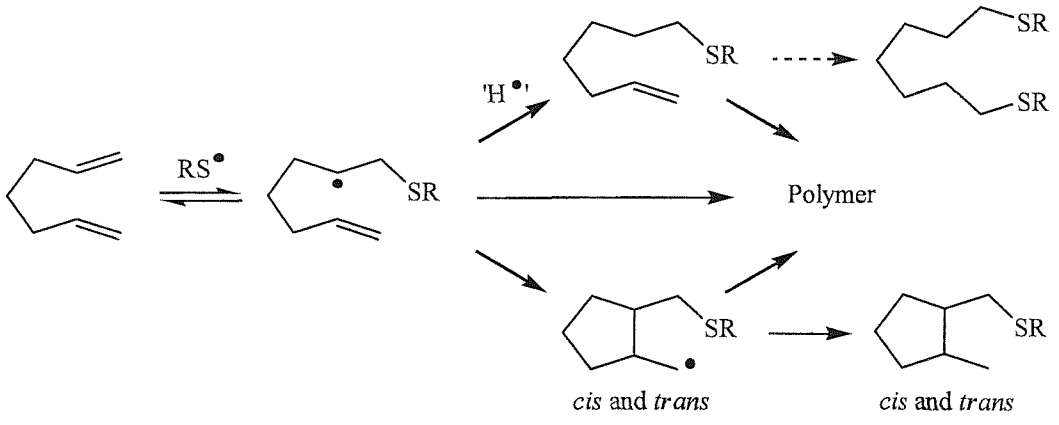
Radical cyclisation reactions are most commonly applied to the synthesis of five membered rings. These rings form at a kinetically faster rate than any other ring size (provided that the reaction centres are able to attain good orbital overlap). Where cyclisations lead to the creation of a new stereogenic centre stereoselectivity is generally modest. The stereochemical outcome can usually be predicted using the Beckwith transition state model in which the intermediate radical is assumed to adopt a pseudo chair structure.[39]

Much interest in radical cyclisation reactions stems from a desire to generate a series of fused ring structures simultaneously during the targeting of complex polycyclic systems. The tolerance of radicals to many functional groups means that the basic framework of a complex

natural product can often be achieved without disruption of inert functional groups. These groups then provide 'handles' that permit the completion and elaboration of the target structure using chemistry that is more conventional. The potential of radicals to generate carbon to carbon bonds at congested centres provides a particular advantage in natural product syntheses. These systems are common in natural compounds and are frequently difficult to form by conventional approaches.

5.4 THIYL MEDIATED RADICAL CYCLISATIONS

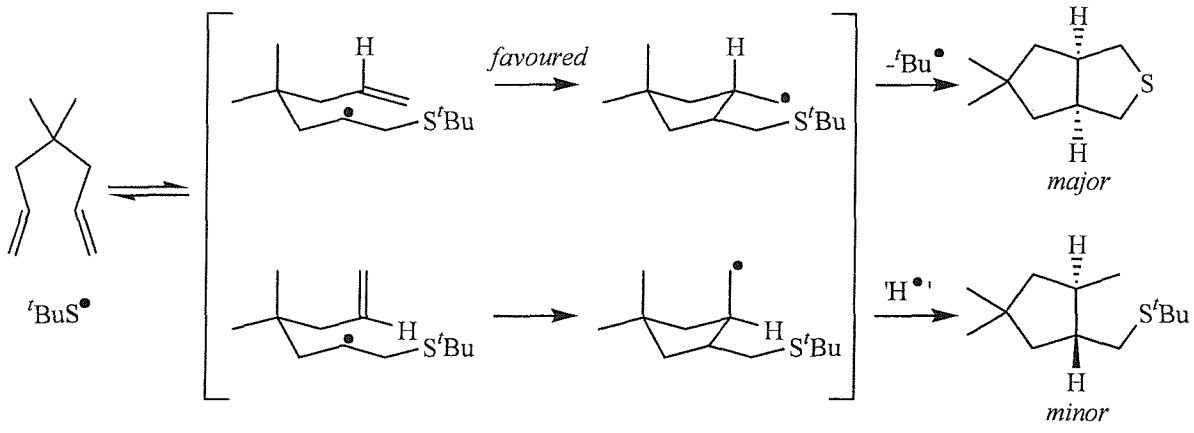
Heteroatom centred radical addition to olefins is a central reaction in organic chemistry.[102] The addition of thiyl radicals to alkenes is fast and reversible. The usual fate of the intermediate carbon centred radical is to revert back to starting materials or to suffer a fast hydrogen atom quench from a thiol (Scheme 46).[103] For 1,6–dienes there exists a third option: cyclisation. Often the consequence of this is the generation of a complex mixture of products that severely limits the use of such reactions in synthesis.



Scheme 46

The Harrowven group has been investigating methods of controlling such reactions using *tert*–butylthiyl radicals. These may be generated either thermally, using

azobisisobutyronitrile (AIBN) and *tert*–butyl disulfide in refluxing toluene, or through photolytic cleavage of *tert*–butyl disulfide. If this methodology is employed then the first cyclisation can be followed by a second *irreversible* homolytic displacement of a *tert*–butyl radical. This effects the concomitant generation of a second ring, fused to the first, to give a bicyclic ring system. The displacement can only proceed if the carbon centred radical intermediate is proximal to the sulfur atom, rendering the reaction diastereoselective, generating *cis* fused bicyclic compounds (Scheme 47). If the carbon centred radical is not proximal to the sulfur, then the compound suffers hydrogen atom quench to form a monocycle, or polymerises.



Scheme 47

Early research within the group showed that photochemical generation of thiyl radicals was superior to thermal techniques. It was also found that monocyclic side products, arising from hydrogen atom quench prior to an intramolecular S_H2 substitution at sulfur, were minimised through the selection of an appropriate thiyl radical mediator. Thus, dibenzyl disulfide is a poor mediator as it is able to participate in a 1,5–hydrogen atom transfer from the benzylic position (Figure 3). Use of *tert*–butyl disulfide was found to augment bicyclic formation but did not significantly alter monocyclic generation from the *trans* diastereomer. Presumably the hydrogen atoms of the *t*–butyl moiety are less prone to abstraction but can participate in a

slow elimination reaction leading to hydrogen atom transfer (Figure 4). *Bis*–(1–adamantyl) disulfide **504** was also investigated as a source of adamantyl thiyl radicals. Abstraction of a hydrogen atom in this case is much less favourable because of the concomitant generation of a bridgehead double bond (Figure 5).

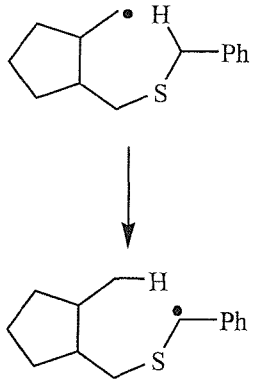


Figure 3

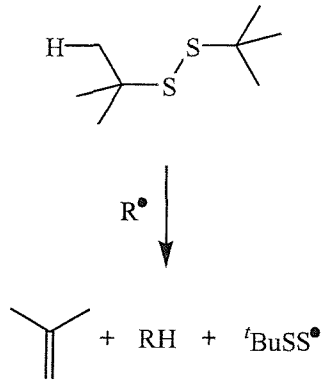


Figure 4

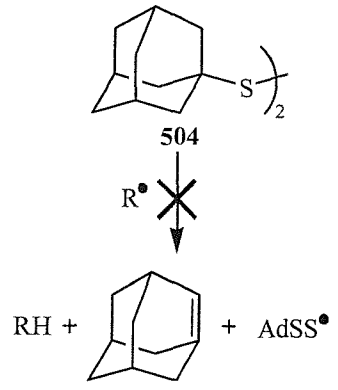
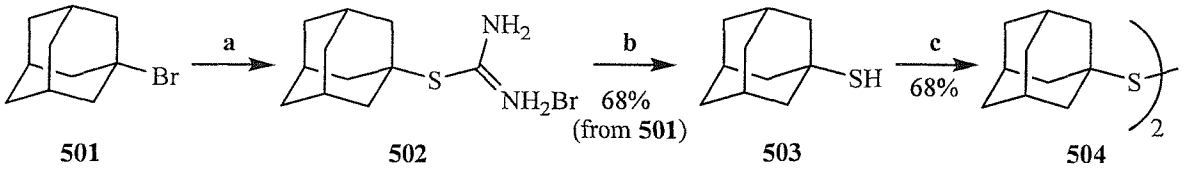


Figure 5

While use of **504** was found to minimise formation of monocycles it only gave moderate improvements to yields of bicyclic products. As it had to be synthesised prior to use [in two steps from 1–bromoadamantane **501** and an overall yield of 46 % (Scheme 48)] *tert*–butyl disulfide remains the reagent of choice because of its low cost and commercial availability.



a. H_2NCSNH_2, HBr, AcOH; **b.** NaOH then HCl; **c.** NaOH, H_2O, $K_3Fe(CN)_6$

Scheme 48

Triethylborane was also found to enhance the rate of cyclisation, although no improvements in yield were observed. The use of a quartz filter that allows more ultra violet light into the reaction mixture was found to accelerate reaction rates considerably over the same reactions

conducted in Pyrex vessels. Hexane was found to be the solvent of choice in cyclisation reactions although when a more polar solvent is required to solubilise the diene substrate, acetonitrile too gave good results. The use of acetonitrile extends reaction times but makes minimal difference to overall yield. Tetrahydrofuran was found to encourage monocyclic production through facile hydrogen atom donation.

5.5 Scope and Limitations

Several examples of the radical cyclisation were accomplished in order to investigate and extend the scope of the thiyl radical mediated cyclisation methodology. The results of this investigation are summarised in Tables 1 and 2. Details of the syntheses of the 1,6–diene substrates for the cyclisation can be found in the experimental section, 7.5.

A number of simple dienes (**505** – **509**) were first synthesised then subjected to the radical cyclisation conditions. These gave the corresponding *cis* fused carbocycles in moderate yields (Table 1). We hoped to extend the methodology further by increasing the complexity of the diene substrates in terms of steric encumbrance and functionality (Table 2). Cyclisation of the maleate derivative **515** proceeded smoothly to give a mixture of diastereomers, demonstrating that the reaction is able to proceed when one of the alkenes is severely congested. Cyclisation of dienes **515** – **518** was accomplished in reasonable yields and gave a mixture of diastereomers.

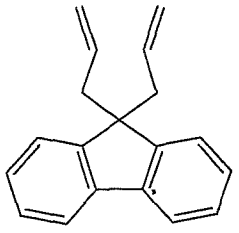
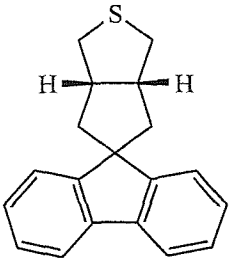
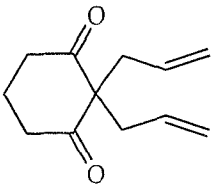
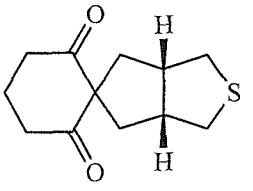
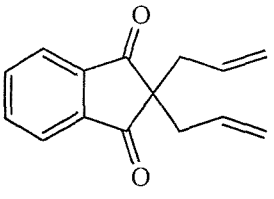
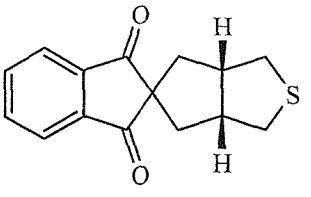
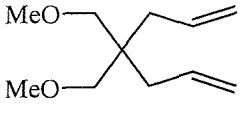
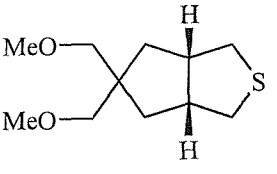
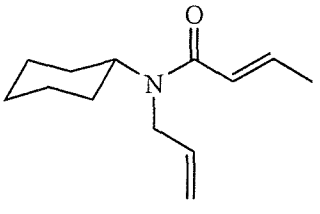
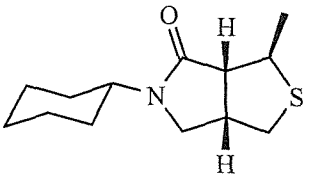
Starting Material	Product of thiyl radical mediated cyclisation
 **505**	 **510** (tBuS)$_2$, C_6H_{14}, hv, 10°C, 24 h, 50 % (45 % recovered starting material)
 **506**	 **511** (tBuS)$_2$, C_6H_{14}, hv, 10°C, 18 h, 55 % (10 % recovered starting material)
 **507**	 **512** (tBuS)$_2$, C_6H_{14}, hv, 10°C, 20 h, 10 % (74 % recovered starting material)
 **508**	 **513** (tBuS)$_2$, C_6H_{14}, hv, 10°C, 20 h, 46 %
 **509**	 **514** (tBuS)$_2$, C_6H_{14}, hv, 10°C, 20 h, 34 %

Table 1. Cyclisations forming one diastereomer

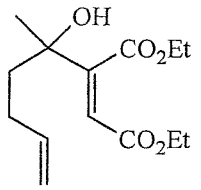
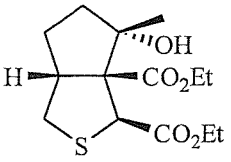
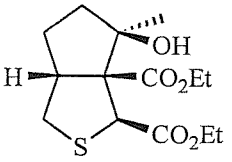
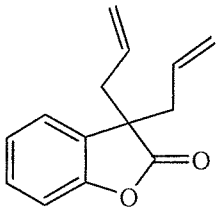
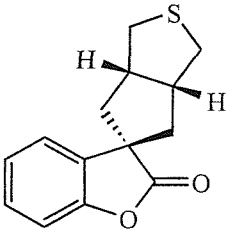
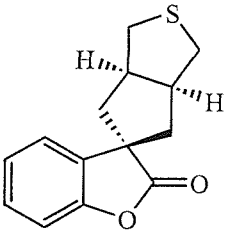
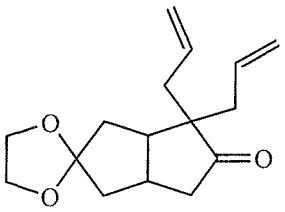
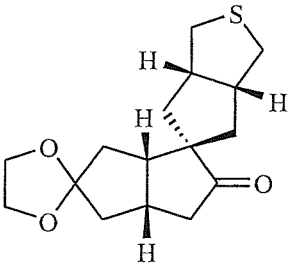
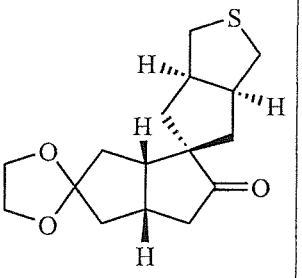
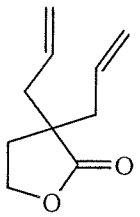
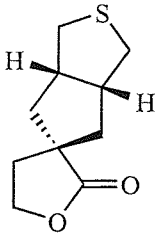
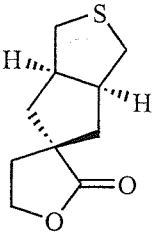
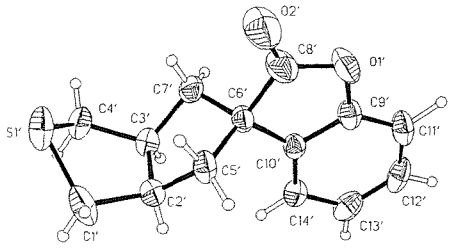
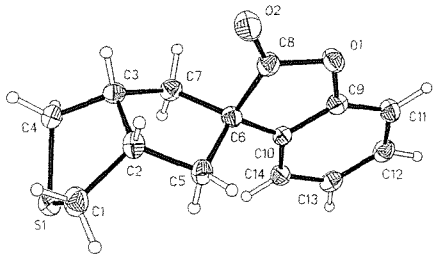
Starting Material	Product of thiyl radical mediated cyclisation
 **515**	  **519** **520** 2 : 1 (tBuS)$_2$, C_6H_{14}, hv, 10°C, 24 h, 62 %
 **516**	  **521** **522** 1 : 2 (tBuS)$_2$, C_6H_{14}, BEt_3, hv, 10°C, 30 h, 61 %
 **517**	  **523** **524** 3 : 2 (tBuS)$_2$, C_6H_{14}, BEt_3, hv, 10°C, 24 h, 50 %
 **518**	  **525** **526** 3 : 2 (tBuS)$_2$, C_6H_{14}, hv, 10°C, 20 h, 51 %

Table 2. Cyclisations generating two diastereomers

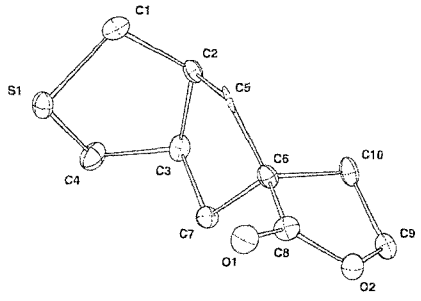
Where appropriate, X–ray crystallography was used to determine the stereochemistry of solid diastereomers (Figure 6). In the case of the oils **519** and **520** we were unable to use X–ray crystallography to distinguish the diastereomers, however, the relative stereochemistry has been assigned through both n.O.e experiments and derivatisation.



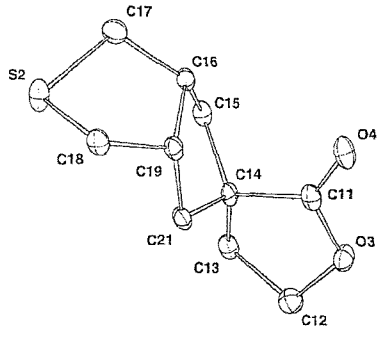
521



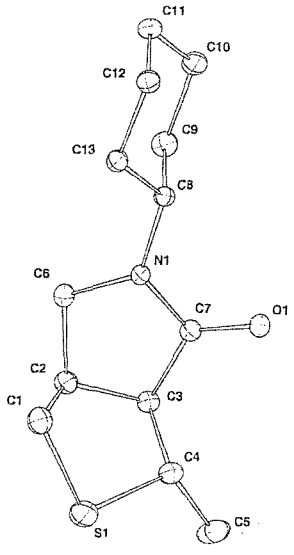
522



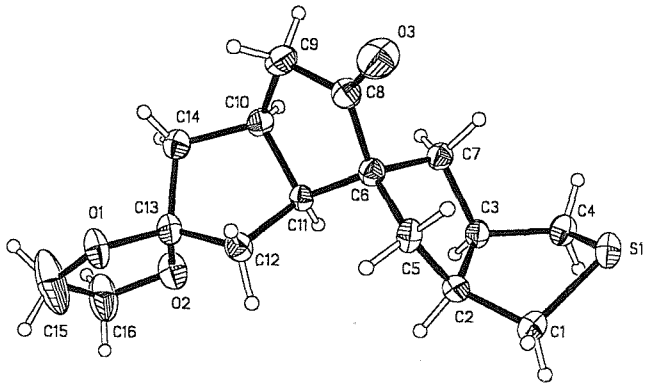
525



526



514



523

Figure 6

These cyclisation reactions show that the method is tolerant of a range of functionality including ketone, ester, lactone, amide, ether and hydroxyl functions. It appears that the Thorpe – Ingold effect may play a role in determining whether these cyclisations proceed efficiently.[105] The observations noted here complement those previously found within the group; amines and ethers were also found to undergo cyclisation (Table 3).

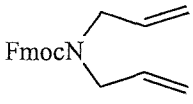
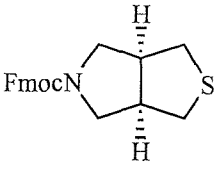
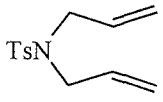
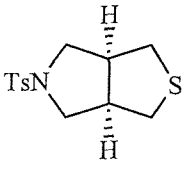
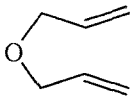
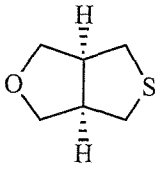
Starting Material	Product
	 (tBuS)$_2$, C_6H_{14}, BEt_3, hν, 10°C, 42 %
	 (tBuS)$_2$, C_6H_{14}, BEt_3, hν, 10°C, 33 %
	 (tBuS)$_2$, C_6H_{14}, BEt_3, hν, 10°C, 45 %

Table 3

Although we enjoyed success in cyclising a number of 1,6–dienes (*vide supra*), limitations to the methodology also emerged (Table 4). Where failure to cyclise was observed (entries **A** – **C**), starting materials were usually recovered from the reaction mixtures. The exception was in the case of styrene **532** (entry **C**) that underwent polymerisation. Other dienes found to undergo cyclisation yet give unsatisfactory results are also detailed in Table 4. Inseparable mixtures (entry **D**), low yields with poor recovery of starting materials (entry **E**), or inseparable diastereomers (entry **F**) were given in these cases.

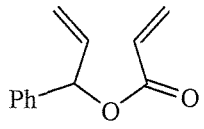
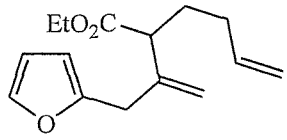
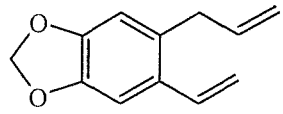
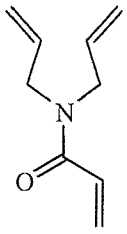
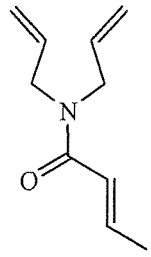
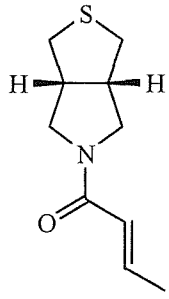
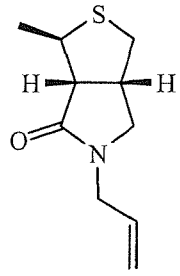
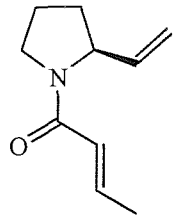
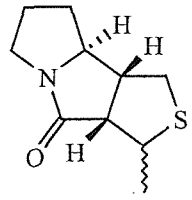
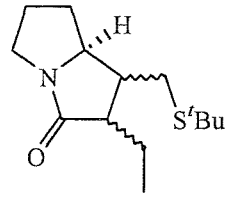
	Starting material	Products
A	 **530**	No reaction
B	 **531**	No reaction
C	 **532**	Polymer
D	 **533**	Inseparable mixture
E	 **534**	 **535** 1 :  **536** 1 (tBuS)$_2$, CH_3CN, BEt_3, hv, 10°C, 32 %
F	 **537**	 **538** 1 :  **539** 1 (tBuS)$_2$, CH_3CN, BEt_3, hv, 10°C, 40 % (15 % recovered starting material)

Table 4

5.6 CONCLUSIONS

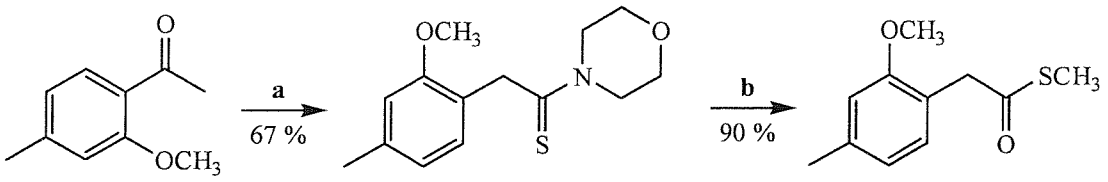
Our radical cyclisation is a diastereoselective method of forming cyclic compounds from acyclic precursors. The methodology is tolerant of a variety of functional groups and can generate sterically congested molecules. Its benefits over the use of tin include its economy and low toxicity, however, the lack of any secure guidelines for those substrates that are likely to cyclise successfully remains as a severe restriction to its widespread use.

CHAPTER 6

A CONVENIENT METHOD FOR CONVERTING THIOAMIDES INTO THIOESTERS

Thioesters are activated carboxylic acid derivatives which exhibit acylating properties similar to those of acid anhydrides.[42] As such, they have found widespread application in synthetic chemistry as precursors to aldehydes,[43] ketones,[44] acids,[45] esters,[46] lactones,[47] amides,[48] lactams and related heterocycles.[49] Most commonly prepared by the reactions of thiols or their metal salts with acid halides, anhydrides and esters,[42,43] their ability to form stable enolate anions makes them particularly versatile intermediates.[50]

We devised a convenient method for converting thioamides to thioesters in order to address a need for a reliable, multi–gram synthesis of thioester **219** (see 2.4.1). As thioamide **218** can be prepared from acetophenone **46** using a Willgerodt–Kindler reaction we used this as a starting point. On warming an aqueous THF solution of **218** with methyl iodide we found it was transformed into thioester **219** directly and in high yield (Scheme 49).



46 **218** **219**

a. S_8, morpholine, 100°C, 24 h; **b.** MeI, aq. THF, Δ, 18 h

Scheme 49

To explore the scope of the method for thioester preparation, we decided to seek some further examples (Table 5). The reaction was found to proceed efficiently with both aliphatic and aromatic thioamides. Alkyl iodides, dialkyl sulfates and activated alkyl bromides proved

suitable alkylating agents. Unactivated alkyl bromides also gave the reaction but at a much slower rate. Notably, reaction conditions are mild and tolerant of aryl ethers and acetals. When volatile halides are employed, products of ~95% purity can be obtained in near quantitative yield after a simple acid wash. (Yields given in Table 5 refer to samples purified by recrystallisation or chromatography).

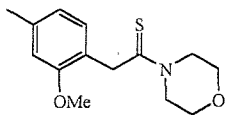
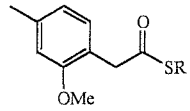
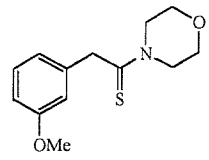
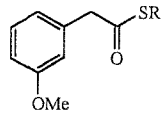
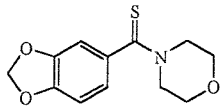
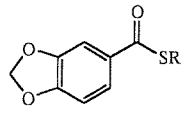
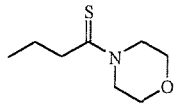
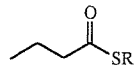
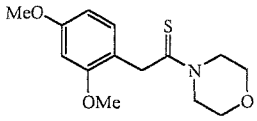
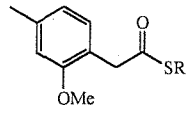
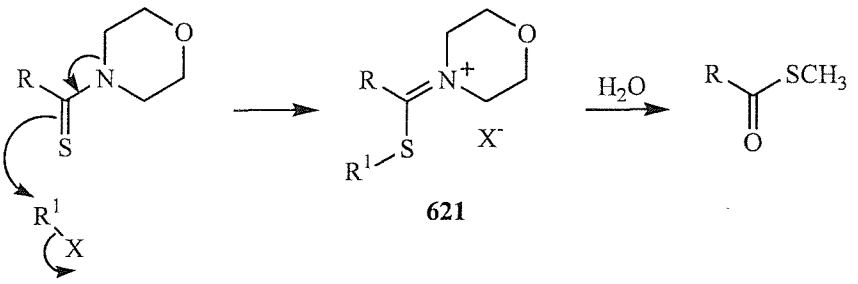
Substrate	Alkylating Agent	Reaction Time	Product	R=	No.	Yield* %
 **218**	MeI	18 h		Me	**219**	90
	Me_2SO_4	15 h		Me	**219**	73
	EtI	44 h		Et	**601**	76
	EtBr	45 h		Et	**601**	20 (75)
	AllylBr	20 h		Allyl	**602**	67
	BnBr	20 h		Bn	**603**	82
	$Ph(CH_2)_2Br$	72 h		$Ph(CH_2)_2$	**604**	35 (38)
 **605**	MeI	15 h		Me	**606**	85
	Me_2SO_4	18 h		Me	**606**	72
	EtI	48 h		Et	**607**	69
	AllylBr	24 h		Allyl	**608**	79
	BnBr	15 h		Bn	**609**	66
 **610**	MeI	18 h		Me	**611**	77
	Me_2SO_4	17 h		Me	**611**	67
	EtI	17 h		Et	**612**	96
	AllylBr	18 h		Allyl	**613**	93
	BnBr	15 h		Bn	**614**	81
 **615**	Me_2SO_4	36 h		Me	**616**	51
	EtI	72 h		Et	**617**	83
	AllylBr	48 h		Allyl	**618**	81
 **619**	MeI	4 h		Me	**620**	85

Table 5: Conversion of Thioamides to Thioesters *via* Alkylation in aqueous THF at reflux

* Figures in parentheses refer to % of recovered starting material

CONCLUSION

We have shown that thioamides may be transformed into thioesters through the simple expedient of warming them in an aqueous THF solution containing an alkylating agent. Reactions proceed in high yield *via in situ S*–alkylation to an iminium ion **621** followed by hydrolysis to form a thioester and morpholine (Scheme 50).[51] These reactions are amenable to multi–gram scales and, if volatile alkyl halides are employed, will deliver products of ~95 % purity without the need for chromatographic purification. The methodology has also been extended within the Harrowven group to include a novel solid–phase linker strategy.[52]



Scheme 50

CHAPTER 7

EXPERIMENTAL SECTION

7.1 GENERAL REMARKS

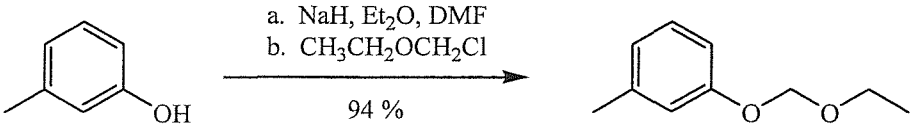
Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal Melting Point Apparatus or a Reichert heated stage apparatus and are uncorrected. Infra red spectra were recorded using a Perkin Elmer 1600 series Fourier transform infrared spectrometer, or a Bio–Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR. Maxima are reported as ν_{max} followed by the signal intensity (described using the abbreviations s, strong; m, medium; w, weak; v, very; br., broad). UV spectra were recorded on either a Pye Unicam SP800 or 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 300 MHz for ^1H and at 75 MHz for ^{13}C), a Bruker AM360 (operating at 360 MHz for ^1H and at 90 MHz for ^{13}C), or a Bruker AM400 (operating at 400 MHz for ^1H and at 100 MHz 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. 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 atmospheric pressure chemical ionisation (APCI) or electrospray (ES) were recorded on a Micromass Platform quadrupole mass analyser with an electrospray ion source. Electron ionisation (EI) or 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 either at Southampton University Mass Spectrometry Centre or at the EPSRC mass spectrometry centre, Swansea. Column chromatography was performed using MN Kieselgel 60, 0.04–0.063 mm 230–400 mesh ASTM silica, slurry packed and run under low pressure. Reactions were monitored by thin layer chromatography using precoated aluminium backed sheets coated with Sil G/UV_{254} 0.25 mm Silica gel 60. Compounds were visualised firstly by UV irradiation, then by exposure to iodine, and finally by exposure to solutions of potassium permanganate in aqueous sodium carbonate or phosphomolybdic acid in ethanol. Microanalyses were conducted at Glaxo Wellcome, Stevenage.

Tetrahydrofuran and diethyl ether were dried and degassed by distillation 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. *N*,*N*–Dimethylformamide was distilled under reduced pressure from magnesium sulfate and stored over 3Å MS. All other solvents and reagents were used directly as supplied except where stated otherwise.

7.2 EXPERIMENTAL FOR CHAPTER 2

1-(Ethoxymethoxy)-3-methylbenzene **206**[107]



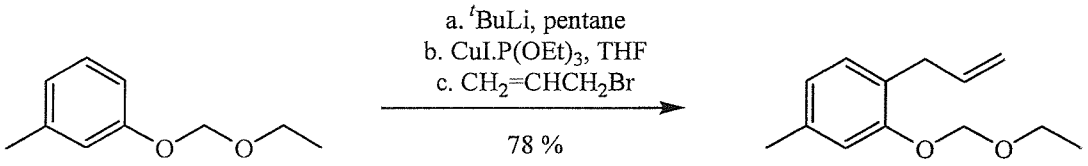
C_7H_8O
Mol. Wt.: 108

$C_{10}H_{14}O_2$
Mol. Wt.: 166

Prepared following the procedure of Ronald *et al.*[26] To a stirred suspension of sodium hydride (26.6 g, 666 mmol) in dry ether (160 mL) and DMF (40 mL) under nitrogen and with cooling to 0°C was added *meta*-cresol **83** (24.0 g, 23.2 mL, 222 mmol) over 25 min. Once effervescence had ceased (~10 min), chloromethyl ethyl ether (21.0 g, 20.6 mL, 222 mmol) was added *via* syringe over 15 min. The reaction mixture was warmed to ambient temperature and stirred for 5 h, then quenched by slow addition of water (50 mL). The mixture was extracted into ether (3 × 50 mL), then the combined organic extracts were washed with water (50 mL) and brine (40 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (43 g). Purification by chromatography (silica, petrol) gave **206** (34.8 g, 210 mmol, 94 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3038m, 2977s, 2791w, 1586s, 1491s, 1458s, 1410m, 1393s, 1252s, 1150s, 1106s, 910m.
λ_{max}/nm (ε_{max})	278 (700), 271 (750), 266 inf (600).
δ_H (300MHz, $CDCl_3$)	7.21 (1H, dd, *J* 7.9, 7.7 Hz, Ar*H*), 6.91 (1H, s, Ar*H*), 6.89 (1H, d, *J* 7.7 Hz, Ar*H*), 6.85 (1H, d, *J* 7.9 Hz, Ar*H*), 5.25 (2H, s, OCH_2O), 3.75 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 2.35 (3H, s, $ArCH_3$), 1.25 (3H, t, *J* 7.1 Hz, OCH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	157.6 (0, Ar), 139.7 (0, Ar), 129.4 (1, Ar), 122.7 (1, Ar), 117.1 (1, Ar), 113.3 (1, Ar), 93.3 (2, OCH_2O), 64.3 (2, OCH_2CH_3), 21.7 (3, $ArCH_3$), 15.3 (3, OCH_2CH_3) ppm.
LRMS (CI)	166 (M^+, 90 %), 136 ($[MH-C_2H_5]^+$, 40 %), 108 (75 %) amu.

1-Allyl-2-(ethoxymethoxy)-4-methylbenzene **207**



$C_{10}H_{14}O_2$
Mol. Wt.: 166

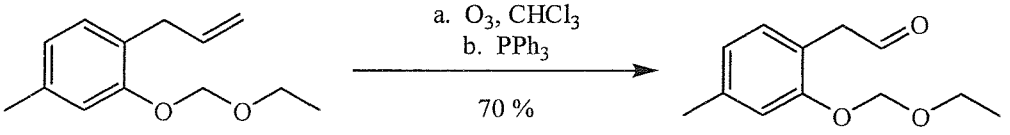
$C_{13}H_{18}O_2$
Mol. Wt.: 206

Prepared following the procedure of Ziegler *et al.*[27] Thus, a solution of *tert*-butyllithium (44.2 mL of a 1.5 M solution in pentane, 66 mmol) was transferred to a flask and maintained at 0°C under an atmosphere of nitrogen. To this was added 1-(ethoxymethoxy)-3-methylbenzene **206** (11.0 g, 66 mmol) in pentane (100 mL) *via* cannula over 3 min with vigorous stirring. After 1 h stirring was halted and the anion allowed to settle over 6 h. The bright yellow supernatant was removed *via* cannula, the anion cooled to –78°C and resuspended in dry THF (100 mL). Copper(I) iodide triethylphosphite complex (24.8 g, 70 mmol) was added in a single portion and the mixture stirred for 30 min. Allyl bromide (7.99 g, 5.71 mL, 66 mmol) was added dropwise over 5 min. After stirring for 1 h the reaction mixture was warmed to ambient temperature and stirred for 22 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed repeatedly with c.$NH_{3\,(aq)}$ (10 × 200 mL) until no more blue discolouration of the ammonia solution was observed. The combined aqueous phases were washed with dichloromethane (100 mL) then the combined organic phases were washed with water (2 × 80 mL) and brine (60 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (21.0 g). Purification by chromatography (silica, 10 % ethyl acetate in petrol) gave **207** (10.7 g, 51.8 mmol, 78 %) as a pale yellow oil.

ν_{max}/**cm^{-1} (neat)**	3077m, 2977s, 2900s, 1638s, 1613s, 1582s and 1508s, 1442br. s, 1392s, 1317s, 1248s, 1016br. s, 912s, 716w.
λ_{max}/**nm** (ε_{max}, **MeOH**)	282 (850), 274 (900).
δ_H (**300MHz, $CDCl_3$**)	7.07 (1H, d, *J* 7.5 Hz, Ar*H*), 6.97 (1H, s, Ar*H*), 6.81 (1H, d, *J* 7.4 Hz, Ar*H*), 6.02 (1H, ddt, *J* 16.7, 10.2, 6.4 Hz, C*H*=), 5.28 (2H, s, OCH_2O), 5.07 (1H, dd, *J* 16.7, 1.5 Hz, =C*H*H), 5.04 (1H, br. d, *J* 10.2 Hz, =CH*H*), 3.78 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.41 (2H, d, *J* 6.4 Hz, $ArCH_2$), 2.37 (3H, s, $ArCH_3$), 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3) ppm.

δ_C **(75.5MHz, $CDCl_3$)**	155.1 (0, Ar), 137.5 (1, *C*H=), 137.5 (0, Ar) 129.9 (1, Ar), 126.3 (0, Ar), 122.5 (1, Ar), 115.3 (2, =*C*H_2), 115.0 (1, Ar), 93.3 (2, O*C*H_2O), 64.4 (2, *C*H_2CH$_3$), 34.3 (2, Ar*C*H_2), 21.6 (3, Ar*C*H_3), 15.3 (3, CH_2*C*H_3) ppm.
LRMS (APCI)	206 (M^+, 20 %), 161 (100 %), 147 (45 %) amu.
HRMS (CI)	Found MH^+: 207.1385. $C_{13}H_{18}O_2$ requires MH^+: 207.1385.

2-[2-(Ethoxymethoxy)-4-methylphenyl]acetaldehyde **208**



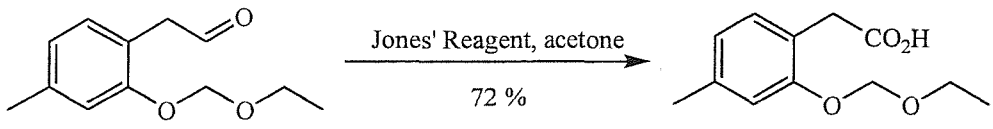
$C_{13}H_{18}O_2$
Mol. Wt.: 206

$C_{12}H_{16}O_3$
Mol. Wt.: 208

Prepared following the procedure of Knowles and Thompson.[28] Thus, a stirred solution of alkene **207** (5.00 g, 24.3 mmol) in chloroform (90 mL) was cooled to −78°C and ozone bubbled through the solution for 40 min. Oxygen was bubbled through the mixture for 15 min then triphenylphosphine (12.78 g, 48.6 mmol) was added. The mixture was warmed to ambient temperature and stirred for 5 h. The pale yellow solution was concentrated *in vacuo* to a cloudy yellow residue (20.5 g). Purification by chromatography (silica, 0 – 5 % ethyl acetate in petrol) gave **208** (3.56 g, 17.1 mmol, 70 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2977s, 2901s, 2818m, 1725s, 1614m, 1583m, 1508s, 1444m, 1391s, 1007br. s, 811m.
λ_{max}/nm (ε_{max}, MeOH)	280 (850), 274 (850).
δ_H (300MHz, $CDCl_3$)	9.60 (1H, t, *J* 2.0 Hz, C*H*O), 7.05 (1H, d, *J* 7.5 Hz, Ar*H*), 7.00 (1H, s, Ar*H*), 6.82 (1H, d, *J* 7.5 Hz, Ar*H*), 5.25 (2H, s, OCH_2O), 3.71 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 3.62 (2H, d, *J* 2.0 Hz, CH_2CHO), 2.36 (3H, s, ArCH_3), 1.24 (3H, t, *J* 7.1 Hz, CH$_2$CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	200.5 (1, *C*HO), 155.6 (0, Ar), 139.3 (0, Ar), 131.2 (1, Ar), 122.7 (1, Ar), 118.7 (0, Ar), 114.8 (1, Ar), 93.1 (2, OCH$_2$O), 64.6 (2, *C*H$_2$CH$_3$), 45.5 (2, *C*H$_2$CHO), 21.7 (3, ArCH$_3$), 15.2 (3, CH$_2$*C*H$_3$) ppm.
LRMS (APCI)	208 (M$^+$, 10 %), 163 (50 %), 133 (80 %) amu.
HRMS (CI)	Found [M+NH$_4$]$^+$: 226.1443. $C_{12}H_{16}O_3$ requires [M+NH$_4$]$^+$: 226.1443

2-[2-(Ethoxymethoxy)-4-methylphenyl]acetic acid **209**



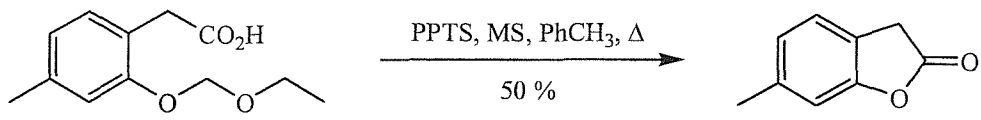
$C_{12}H_{16}O_3$
Mol. Wt.: 208

$C_{12}H_{16}O_4$
Mol. Wt.: 224

Prepared following the procedure of Jones *et al.*[29] Thus, to a stirred solution of aldehyde **208** (3.00 g, 14.4 mmol) in acetone (100 mL) was added Jones reagent (9.0 mL, 57.7 mmol) over 20 min at ambient temperature. Stirring was continued for a further 5 min after addition was complete, then to the turquoise mixture was added water (200 mL). The reaction mixture was extracted with ether (5 × 20 mL) then the organic phases were combined, washed with water (2 × 20 mL) then brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (3.58 g). Purification by chromatography (silica, 50 % ether in petroleum ether) gave **209** (2.32 g, 10.4 mmol, 72 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3300 - 2900br. s, 2978m, 1710s, 1616w, 1585w, 1510m, 1258m, 1154m, 1012s, 846w.
λ_{max}/nm (ε_{max}, MeOH)	276 (650).
δ_H (300MHz, $CDCl_3$)	10.2 (1H, br. s, CO_2H), 7.09 (1H, d, *J* 7.5 Hz, Ar*H*), 6.98 (1H, s, Ar*H*), 6.81 (1H, d, *J* 7.5 Hz, Ar*H*), 5.28 (2H, s, OCH_2O), 3.72 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 3.63 (2H, s, CH_2COOH), 2.38 (3H, s, $ArCH_3$), 1.25 (3H, t, *J* 7.2 Hz, CH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	178.5 (0, *C*O), 155.4 (0, Ar), 139.2 (0, Ar), 130.9 (1, Ar), 122.5 (1, Ar), 120.0 (0, Ar), 114.9 (1, Ar), 93.1 (2, OCH_2O), 64.5 (2, CH_2CH_3), 35.8 (2, $ArCH_2$), 21.7 (3, $ArCH_3$), 15.2 (3, CH_2CH_3) ppm.
LRMS (APCI)	224 (M^-, 80 %), 165 ($[M-C_2H_5OCH_2]^-$, 100 %) amu.
HRMS (ES)	Found MH^+: 225.1125. $C_{12}H_{16}O_4$ requires MH^+: 225.1127.

6-Methyl-2,3-dihydrobenzo[*b*]furan-2-one **205**[108]



$C_{12}H_{16}O_4$
Mol. Wt.: 224

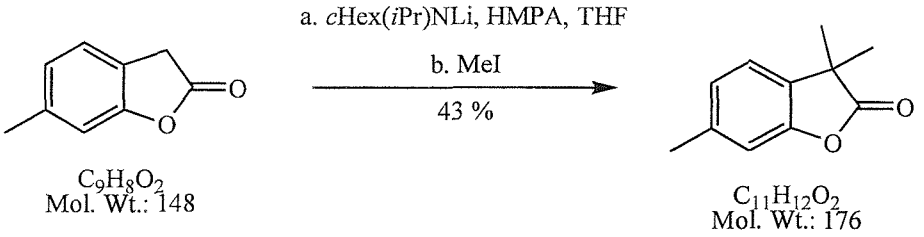
$C_9H_8O_2$
Mol. Wt.: 148

To a stirred solution of 2-[2-(ethoxymethoxy)-4-methylphenyl]acetic acid **209** (0.150 g, 0.67 mmol) in toluene (80 mL) was added pyridinium *para*-toluenesulfonate (20 mg, 0.08 mmol) and the mixture heated at reflux under a soxhlet containing 3Å molecular sieves for 20 h. The reaction was cooled to ambient temperature and the toluene removed *in vacuo* to give a brown oil (0.160 g). Purification by chromatography (silica, 10 – 20 % ether in petroleum ether) afforded **205** as a colourless oil that crystallised upon standing to a colourless solid. Recrystallisation from petrol gave lactone **205** (50 mg, 0.34 mmol, 50 %) as colourless needles.

All physical and spectroscopic data were fully consistent with literature values.[108]

MP	68 - 70°C (petrol). Lit. 73°C;[108a] lit. 66 - 69°C (hexane).[108b]
ν_{max}/cm^{-1} ($CHCl_3$)	2917w, 1796s, 1633m, 1504m, 1228m, 1203m, 1156m, 1064s, 950s, 840w.
λ_{max}/nm (ε_{max}, MeOH)	273 (600).
δ_H (300MHz, $CDCl_3$)	7.16 (1H, d, *J* 7.5 Hz, Ar*H*), 6.95 (1H, d, *J* 7.5 Hz, Ar*H*), 6.95 (1H, s, Ar*H*), 3.70 (2H, s, ArCH_2CO), 2.39 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	174.7 (0, *C*O), 154.9 (0, Ar), 139.5 (0, Ar), 124.9 (1, Ar), 124.4 (1, Ar), 120.0 (0, Ar), 111.5 (1, Ar), 33.0 (2, ArCH_2), 21.8 (3, ArCH_3) ppm.
LRMS (APCI)	149 ([MH]$^+$, 5 %), 148 (M^+, 15 %), 147 (60 %), 109 (100 %) amu.
CHN	Found: C, 72.86; H, 5.34. $C_9H_8O_2$ requires C, 72.96; H, 5.44.

3,3,6-Trimethyl-2,3-dihydrobenzo[*b*]furan-2-one **211**[109]



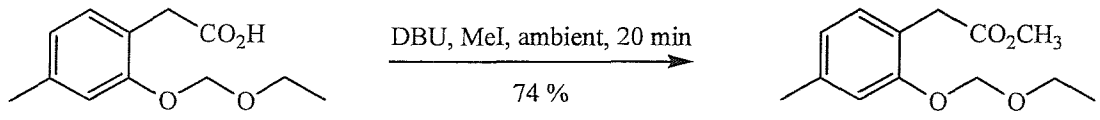
$C_9H_8O_2$
Mol. Wt.: 148

$C_{11}H_{12}O_2$
Mol. Wt.: 176

Following the procedure of Padwa *et al.*[110] Thus, to a stirred solution of *N*–isopropylcyclohexylamine (0.105 g, 0.12 mL, 0.74 mmol) and HMPA (0.24 g, 0.24 mL, 1.35 mmol) in THF (10 mL) under nitrogen and with cooling to -78°C was added *tert*–butyllithium (0.43 mL of a 1.7 M solution in hexane, 0.74 mmol) over 1 min. The mixture was stirred for 15 min, warmed to 0°C over 30 min, then recooled to -78°C. A solution of lactone **205** (0.100 g, 0.68 mmol) in THF (5 mL) was added dropwise over 1 min. After 30 min a solution of methyl iodide (0.104 g, 0.74 mmol) in THF (5 mL) was added over 2 min. After 4 h the reaction mixture was warmed to ambient temperature over 30 min then partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL) then the combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (0.57 g). Purification by chromatography (silica, 0 – 5 % ether in petroleum ether) afforded **211** (0.052 g, 0.30 mmol, 43 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2974m, 2930m, 1808s, 1630m, 1596w, 1501m, 1143m, 1110m, 1033s, 950s, 819m.
λ_{max}/nm (ε_{max}, MeOH)	273 (1500).
δ_H (300MHz, $CDCl_3$)	7.10 (1H, d, *J* 7.4 Hz, Ar*H*), 6.97 (1H, d, *J* 7.4 Hz, Ar*H*), 6.95 (1H, s, Ar*H*), 2.38 (3H, s, ArCH_3), 1.49 (6H, app. s, Ar$C(CH_3)_2$) ppm.
δ_C (75.5MHz, $CDCl_3$)	181.5 (0, *C*O), 152.4 (0, Ar), 139.1 (0, Ar), 130.8 (0, Ar), 125.0 (1, Ar), 122.5 (1, Ar), 111.6 (1, Ar), 42.9 (0, Ar*C*$(CH_3)_2$), 25.5 (3, ArC$(CH_3)_2$), 21.8 (3, ArCH_3) ppm.
LRMS (APCI)	177 ($[MH]^+$, 5 %), 176 (M^+, 100 %), 148 ($[M\text{-}CO]^+$, 40 %) amu.

Methyl 2-(2-{[(ethyloxy)methyl]oxy}-4-methylphenyl)ethanoate **214**



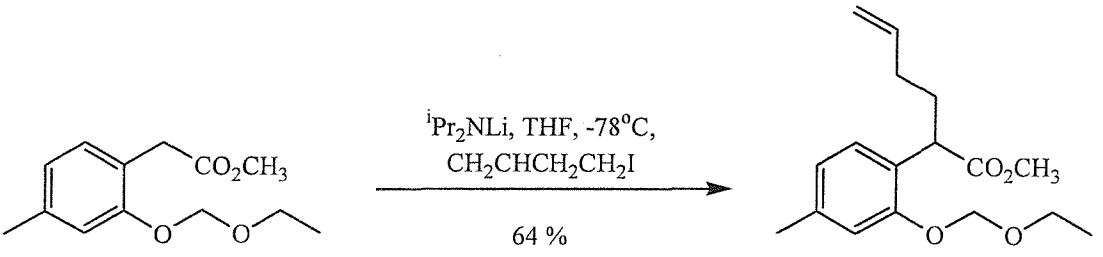
$C_{12}H_{16}O_4$
Mol. Wt.: 224

$C_{13}H_{18}O_4$
Mol. Wt.: 238

To acid **209** (0.40 g, 1.79 mmol) was added DBU (0.54 g, 0.53 mL, 3.56 mmol) followed by methyl iodide (2.54 g, 17.9 mmol). The reaction mixture was stirred at ambient temperature for 20 min then concentrated *in vacuo*. Purification by chromatography (silica, 10 – 30 % ether in petroleum ether) gave **214** (0.316 g, 1.33 mmol, 74 %) as a pale yellow oil.

ν_{max}/cm^{-1} (neat)	2977m, 1740s, 1616w, 1583w, 1511m, 1341w, 1257m, 1158s, 1011s, 801w.
λ_{max}/nm (ε_{max}, MeOH)	275 (600).
δ_H (300MHz, $CDCl_3$)	7.69 (1H, d, *J* 7.5 Hz, Ar*H*), 6.97 (1H, s, Ar*H*), 6.80 (1H, d, *J* 7.5 Hz, Ar*H*), 5.23 (2H, s, OCH_2O), 3.73 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$), 3.69 (3H, s, CO$_2$CH_3), 3.62 (2H, s, ArCH_2), 2.35 (3H, s, ArCH_3), 1.25 (3H, t, *J* 7.0 Hz, CH$_2$CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	172.5 (0, *C*O), 155.4 (0, Ar), 138.8 (0, Ar), 130.8 (1, Ar), 122.4 (1, Ar), 120.7 (0, Ar), 114.9 (1, Ar), 93.2 (2, OCH$_2$O), 64.4 (2, *C*H$_2$CH$_3$), 52.0 (3, CO$_2$*C*H$_3$), 35.8 (2, Ar*C*H$_2$), 21.7 (3, Ar*C*H$_3$), 15.3 (3, CH$_2$*C*H$_3$) ppm.
LRMS (APCI)	385 ([2M-2{EtO}]$^+$, 20 %), 239 ([MH]$^+$, 5 %), 238 (M$^+$, 30 %), 193 ([M-C_2H_5O]$^+$, 100 %) amu.
HRMS (ES)	Found MH$^+$: 239.1280. $C_{13}H_{18}O$ requires MH$^+$: 239.1283.

Methyl 2-(2-{[(ethyloxy)methyl]oxy}-4-methylphenyl)-5-hexenoate **215**



$C_{13}H_{18}O_4$
Mol. Wt.: 238.28

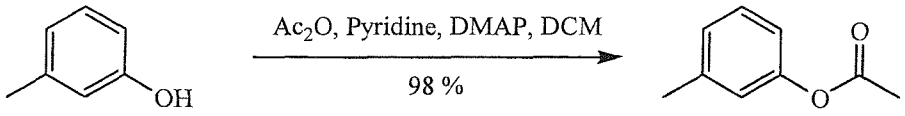
$C_{17}H_{24}O_4$
Mol. Wt.: 292.37

To a stirred solution of *N,N*-diisopropylamine (0.134 g, 0.17 mL, 1.32 mmol) in THF (20 mL) at -78°C and under nitrogen was added butyllithium (1.10 mL of a 1.21 M solution in THF, 1.32 mmol) over 30 s. The mixture was warmed to 0°C then recooled to –78°C. A solution of ester **214** (0.300 g, 1.26 mmol) in THF (5 mL) was added over 30 s. After 30 min, a solution of butenyl iodide (0.275 g, 1.51 mmol) in THF (5 mL) was added over 30 s. After 2 h the mixture was warmed to ambient temperature over 20 min. After 13 h, the yellow solution was quenched with saturated aqueous ammonium chloride (10 mL) then extracted into ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 10 % ether in petroleum ether) gave **215** (0.236 g, 0.81 mmol, 64 %) as a colourless oil.

ν_{max}/cm^{-1} (thin film)	2977m, 1738s, 1642w, 1615w, 1583w, 1510m, 1255m, 1012s, 917w, 803w
λ_{max}/nm (ε_{max}, MeOH)	276 (1230).
δ_H (300MHz, $CDCl_3$)	7.08 (1H, d, *J* 7.5 Hz, Ar*H*), 6.96 (1H, s, ArH), 6.78 (1H, d, *J* 7.5 Hz, Ar*H*), 5.78 (1H, ddt, *J* 17.1, 10.2, 6.7 Hz, CH_2CH=CH_2), 5.24 (2H, s, OCH_2O), 5.10 (1H, dd, *J* 17.1, 1.5 Hz, =C*H*H), 5.07 (1H, dd, *J* 10.2, 1.5 Hz, =CH*H*), 4.15 (1H, t, *J* 6.8 Hz, ArC*H*(CH_2R)CO), 3.73 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.65 (3H, s, CO_2CH_3), 2.34 (3H, s, $ArCH_3$), 2.20 – 2.10 (1H, m), 2.10 – 1.99 (2H, br. m), 1.90 – 1.77 (1H, m), 1.25 (3H, t, *J* 7.1 Hz, OCH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	175.0 (0, *C*O), 154.8 (0, Ar), 138.4 (0, Ar), 138.2 (1, *C*H=), 128.5 (1, Ar), 125.4 (0, Ar), 122.7 (1, Ar), 115.2 (1, Ar), 115.1

	(2, =CH_2), 93.3 (2, OCH_2O), 64.5 (2, CH_2CH_3), 52.0 (3, OCH_3), 43.7 (1, $CHCO_2$), 31.7 (2, CH_2), 31.6 (2, CH_2), 21.6 (3, ArCH_3), 15.3 (3, CH_2CH_3) ppm.
LRMS (APCI)	292 (M^+, 3 %), 202 ([M-$C_2H_5OCH_2OCH_3$]$^+$, 14 %), 160 (100 %) amu.
HRMS (CI)	Found MH^+: 293.1753. $C_{17}H_{24}O_4$ requires MH^+: 293.1753.

3-Methylphenylacetate **216**[109]



C_7H_8O
Mol. Wt.: 108

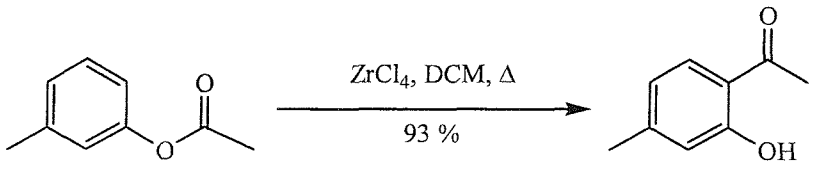
$C_9H_{10}O_2$
Mol. Wt.: 150

Prepared by the method of Cullinane and Edwards.[30] Thus, a solution of *meta*-cresol **83** (10.0 g, 9.67 mL, 92.5 mmol), acetic anhydride (21.6 g, 20.0 mL, 211.6 mmol), pyridine (14.7 g, 15.0 mL, 185.5 mmol) and *N,N*-dimethylaminopyridine (0.30 g, 2.3 mmol) in dichloromethane (160 mL) was stirred at ambient temperature for 18 h. The solution was washed successively with dilute $HCl_{(aq)}$ (2 × 50 mL), water (2 × 30 mL) and brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pale yellow oil (25.0 g). Purification by chromatography (silica, 0 – 20 % ether in petroleum ether) afforded **216** (13.7 g, 90.9 mmol, 98 %) as a colourless oil.

All physical and spectroscopic data were fully consistent with literature values.[30]

ν_{max}/cm^{-1} (neat)	3041w, 1766s, 1610w, 1589w, 1489w, 1369m, 1209s, 1143m, 1018w, 942w, 786w.
λ_{max}/nm (ε_{max}, MeOH)	261 (150).
δ_H (300MHz, $CDCl_3$)	7.27 (1H, app. t, *J* 7.7 Hz, Ar*H*), 7.06 (1H, d, *J* 7.7 Hz, Ar*H*), 6.93 (1H, s, Ar*H*), 6.91 (1H, d, *J* 7.7 Hz, Ar*H*), 2.39 (3H, s, ArCH_3), 2.32 (3H, s, $COCH_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	169.7 (0, *C*O), 150.8 (0, Ar), 139.7 (0, Ar), 129.3 (1, Ar), 126.8 (1, Ar), 122.3 (1, Ar), 118.6 (1, Ar), 21.4 (3, ArCH_3), 21.2 (3, $COCH_3$) ppm.
LRMS (APCI)	150 (M^+, 15 %), 149 ($[M-H]^+$, 75 %), 101 (100 %) amu.

(2-Hydroxy-4-methyl-acetophenone **46**[27]



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

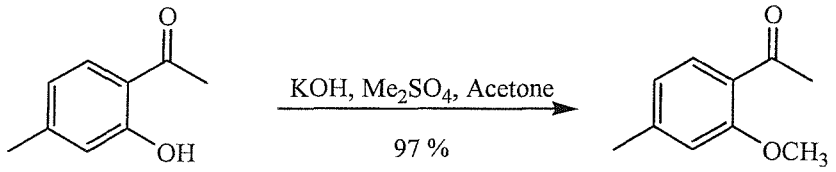
$C_9H_{10}O_2$
Mol. Wt.: 150

Following the procedure of Harrowven and Dainty.[31] Thus, to a solution of **216** (27.9 g, 186 mmol) in dichloromethane (400 mL) was added zirconium tetrachloride (86.7 g, 372 mmol). The vessel was partially immersed into the water filled bath of a Branson 1200, Bransonic® ultrasound cleaner and sonicated for 24 h. The resulting suspension was poured onto ice / water (500 mL) and extracted with dichloromethane (4 × 80 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a green oil. Purification by chromatography (silica, 0 – 5 % ether in petrol) furnished **46** (26.0 g, 173 mmol, 93 %) as a yellow oil.

Spectral and physical data were in accord with previous reports.[27, 111]

ν_{max}/cm^{-1} (neat)	3500 - 2700br. s, 1638s, 1576m, 1508m, 1324s, 1247s, 1226s, 1166m, 1150m, 978m, 933m, 795s.
λ_{max}/nm (ε_{max}, MeOH)	325 (2000), 259 (5500).
δ_H (300MHz, $CDCl_3$)	12.30 (1H, s, ArO*H*), 7.62 (1H, d, *J* 8.1 Hz, Ar*H*), 6.79 (1H, s, Ar*H*), 6.72 (1H, d, *J* 8.1 Hz, Ar*H*), 2.60 (3H, s, ArCOCH_3), 2.35 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	204.1 (0, *C*O), 162.6 (0, Ar), 148.2 (0, Ar), 130.8 (1, Ar), 120.4 (1, Ar), 118.5 (1, Ar), 117.7 (0, Ar), 26.6 (3, CO*C*H$_3$), 22.1 (3, Ar*C*H$_3$) ppm.
LRMS (APCI)	151 ([MH]$^+$, 90 %), 135 ([M-CH$_3$]$^+$, 20 %), 124 (100 %) amu.

1-[4-Methyl-2-(methyloxy)phenyl]-1-ethanone **217**[112,113]



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

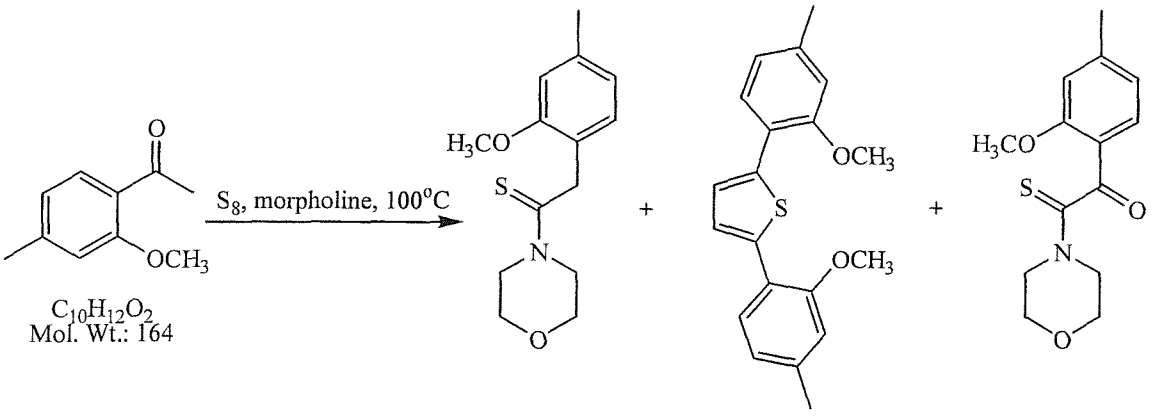
$C_{10}H_{12}O_2$
Mol. Wt.: 164

Following a modified procedure of Jurd.[32] Thus, a mixture of phenol **46** (21.2 g, 141 mmol), dimethyl sulfate (18.7 g, 14.0 mL, 0.148 mol) and powdered potassium hydroxide (9.1 g, 162 mmol) in acetone (400 mL) was stirred at ambient temperature for 15 h. The mixture was partitioned between brine (300 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a viscous oil (31.1 g). Purification by column chromatography (silica, petroleum ether) gave **217** (22.4 g, 0.137 mol, 97 %) as a pale yellow crystalline solid. A sample (1.00 g) was recrystallised from pentane to give colourless needles.

Spectral and physical characteristics were in accord with previous reports.[112,113]

MP	35–37°C (pentane). Lit. 35–37°C (no solvent reported).[112,113]
ν_{max}/cm^{-1} ($CHCl_3$)	2988w, 1657s, 1604s, 1361w, 1258s, 1172w, 1030m, 968w, 855w, 812m.
λ_{max}/nm (ε_{max}, MeOH)	307 (2500), 253 (6500).
δ_H (300MHz, $CDCl_3$)	7.68 (1H, d, *J* 7.7 Hz, Ar*H*), 6.80 (1H, d, *J* 7.7 Hz, Ar*H*), 6.77 (1H, s, Ar*H*), 3.89 (3H, s, ArOC*H*$_3$), 2.59 (3H, s, ArCOC*H*$_3$), 2.38 (3H, s, ArC*H*$_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	199.3 (0, *C*O), 159.3 (0, Ar), 145.0 (0, Ar), 130.7 (1, Ar), 125.5 (0, Ar), 121.5 (1, Ar), 112.4 (1, Ar), 55.5 (3, ArO*C*H$_3$), 32.0 (3, ArCO*C*H$_3$), 22.0 (3, Ar*C*H$_3$) ppm.
LRMS (APCI)	165 ([MH]$^+$, 100 %), 149 ([M-CH_3]$^+$, 10 %) amu.

2-[4-Methyl-2-(methyloxy)phenyl]-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanethione **218** with 3,4-di[4-methyl-2-(methyloxy)phenyl]thiophene **220** and 1-[4-methyl-2-(methyloxy)phenyl]-2-tetrahydro-2*H*-1,4-oxazin-4-yl-2-thioxo-1-ethanethione **221** as significant biproducts



$C_{10}H_{12}O_2$
Mol. Wt.: 164

218, 57%
$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

220, 22%
$C_{20}H_{20}O_2S$
Mol. Wt.: 324

221, 10%
$C_{14}H_{17}NO_3S$
Mol. Wt.: 279

Following the procedure of Carmack and Spielman.[33] Thus, a stirred mixture of acetophenone **217** (23.3 g, 142 mmol), sulfur (6.8 g, 213 g-atom) and morpholine (18.5 g, 213 mmol) was heated at 100 - 120°C for 24 h then allowed to cool to ambient temperature. The resulting red oil was purified by chromatography (silica, 10 – 50 % ether in petroleum ether) to yield firstly thiophene **220** (which was recrystallised from ether / pentane to give colourless needles: 5.01 g, 15.4 mmol, 22 %), then thiomorpholide **218** (which was recrystallised from ethyl acetate / pentane to furnish colourless crystals: 21.6 g, 81 mmol, 57 %), and finally ketothioamide **221** (which was recrystallised from ethyl acetate / pentane to give fine yellow needles: 4.00 g, 14.3 mmol, 10 %).

Data for **218**

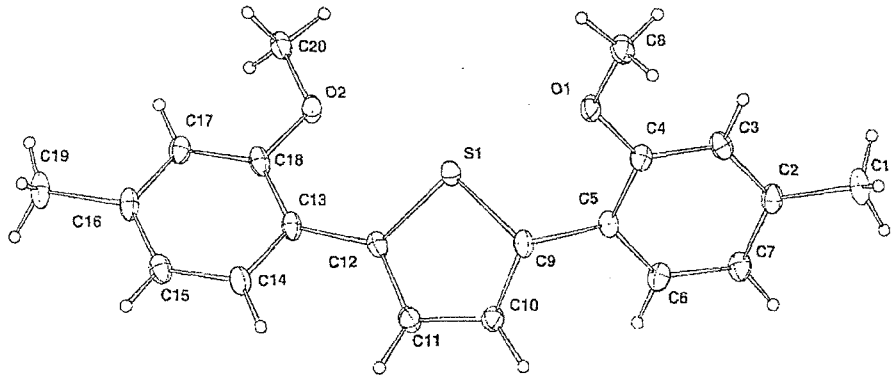
MP	62 - 64°C (ethyl acetate/pentane).
ν_{max}/cm^{-1} ($CHCl_3$)	2920m, 1612m, 1581m, 1506s, 1488s, 1463s, 1287s, 1267s, 1168w, 1032s, 963m, 816w.
λ_{max}/nm (ε_{max}, MeOH)	279 (13500).
δ_H (300MHz, $CDCl_3$)	7.29 (1H, d, *J* 7.7 Hz, Ar*H*), 6.76 (1H, d, *J* 7.7 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 4.37 (2H, app. t, *J* 4.9 Hz, 2 × OC*H*H), 4.24 (2H, s, CH_2CS), 3.83 (3H, s, ArOCH_3), 3.74 (2H, app. t, *J* 4.9 Hz, 2

	× OCH*H*), 3.61 (2H, app. t, *J* 4.7 Hz, 2 × NC*H*H), 3.42 (2H, app. t, *J* 4.7 Hz, 2 × NCH*H*), 2.36 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	201.7 (0, *C*S), 155.7 (0, Ar), 138.5 (0, Ar), 128.5 (1, Ar), 121.8 (1, Ar), 121.1 (0, Ar), 111.5 (1, Ar), 66.6 (2, OCH_2), 66.4 (2, OCH_2), 55.6 (3, ArOCH_3), 50.8 (2, NCH_2), 50.3 (2, NCH_2), 43.4 (2, CH_2CS), 21.7 (3, ArCH_3) ppm.
LRMS (APCI)	266 ($[MH]^+$, 100 %) amu.
CHN	Found: C, 63.23; H, 6.87; N, 5.14; S, 11.68. $C_{14}H_{19}NO_2S$ requires C, 63.36; H, 7.22; N, 5.28; S, 12.08.

Data for **220**

MP	84 - 86°C (ether/pentane).
ν_{max}/cm^{-1} ($CHCl_3$)	2934m, 1608m, 1570m, 1537w, 1510s, 1278s, 1258m, 1165m, 1133m, 1036s, 800s.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	343 (22000), 308inf (10000), 235 (14500).
δ_H (300MHz, $CDCl_3$)	7.58 (2H, d, *J* 7.5 Hz, 2 × Ar*H*), 7.46 (2H, s, 2 × thiophene), 6.86 (2H, d, *J* 7.5 Hz, 2 × Ar*H*), 6.83 (2H, s, 2 × Ar*H*), 3.95 (6H, s, 2 × ArOCH_3), 2.41 (6H, s, 2 × ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	155.8 (0), 139.1 (0), 138.5 (0), 128.4 (1), 125.4 (1), 121.8 (1), 121.1 (0), 112.7 (1), 55.7 (3, ArOCH_3), 21.7 (3, ArCH_3) ppm.
LRMS (APCI)	325 ($[MH]^+$, 100 %), 324 (M^+, 40 %) amu.
CHN	Found: C, 73.88; H, 6.23; S, 9.95. $C_{20}H_{20}O_2S$ requires C, 74.04; H, 6.21; S, 9.88.

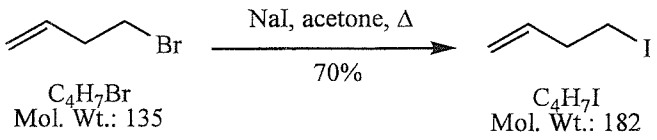
X-ray crystal structure:



Data for **221**

MP	108 - 110°C (ethyl acetate/pentane).
ν_{max}/cm^{-1} ($CHCl_3$)	2857w, 1645s, 1605s, 1572w, 1509s, 1297m, 1276s, 1113s, 1064w, 954m, 806w.
λ_{max}/nm (ε_{max}, MeOH)	380 (900), 319 (7000), 266 (21000).
δ_H (300MHz, $CDCl_3$)	7.87 (1H, d, *J* 7.9 Hz, Ar*H*), 6.89 (1H, d, *J* 7.9 Hz, Ar*H*), 6.78 (1H, s, Ar*H*), 4.24 (2H, app. t, *J* 5.0 Hz, 2 × OC*H*H), 3.88 (2H, app. t, *J* 5.0 Hz, 2 × OCH*H*), 3.85 (3H, s, ArOCH_3), 3.74 (2H, app. t, *J* 4.8 Hz, 2 × NC*H*H), 3.64 (2H, app. t, *J* 4.8 Hz, 2 × NCH*H*), 2.39 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	198.6 (0, *C*S), 186.7 (0, *C*O), 159.4 (0, Ar), 147.4 (0, Ar), 131.9 (1, Ar), 122.7 (1, Ar), 121.7 (0, Ar), 113.3 (1, Ar), 66.4 (2, OCH_2), 66.1 (2, OCH_2), 56.2 (3, ArOCH_3), 51.8 (2, NCH_2), 47.0 (2, NCH_2), 22.3 (3, ArCH_3) ppm.
LRMS (APCI)	280 ($[MH]^+$, 50 %), 165 (25 %), 111 (100 %) amu.
CHN	Found: C, 60.16; H, 5.85; N, 5.08; S, 11.44. $C_{14}H_{17}NO_3S$ requires C, 60.19; H, 6.13; N, 5.01; S, 11.48.

4-Iodo-1-butene[114]



C_4H_7Br
Mol. Wt.: 135

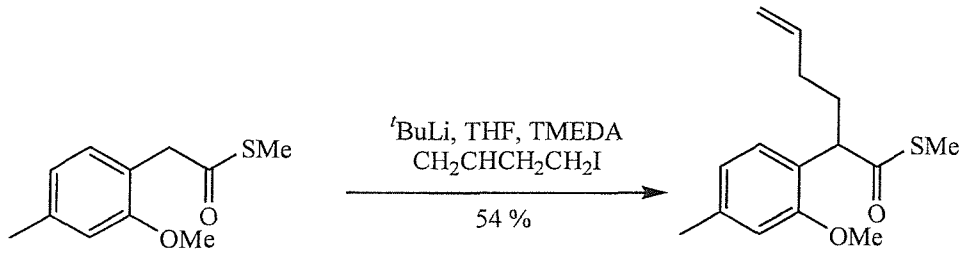
C_4H_7I
Mol. Wt.: 182

Prepared following the procedure as described by Fry and Hoarau.[115] Thus, a solution of 4–bromo–1–butene (1.50 g, 1.13 mL, 11.1 mmol) and sodium iodide (3.30 g, 22.2 mmol) in dry acetone (80 mL) was refluxed for 20 h. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was distilled to leave a brown oil containing a yellow solid. Water (20 mL) was added then the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and distilled at atmospheric pressure to remove ether and leave butenyl iodide (1.42 g, 7.8 mmol, 70 %) as a brown oil.

Data was consistent with literature values.[114, 115]

δ_H (300MHz, $CDCl_3$)	5.76 (1H, ddt, *J* 18.2, 9.2, 6.6 Hz, C*H*=), 5.17 - 5.08 (2H, m, =CH_2), 3.19 (2H, t, *J* 7.2 Hz, CH_2I), 2.63 (2H, app. q, J 7.0 Hz, CH_2CH_2I) ppm.
δ_C (75.5MHz, $CDCl_3$)	137.0 (1, CH_2=*C*H), 117.2 (2, *C*H_2=CH), 37.8 (2, *C*H_2CH_2I), 4.9 (2, *C*H_2I) ppm.
LRMS	183 ($[MH]^+$, 15 %), 178 (30 %), 124 (100 %) amu.

Methyl 2-[4-methyl-2-(methyloxy)phenyl]-5-hexenethioate **225**



$C_{11}H_{14}O_2S$
Mol. Wt.: 210

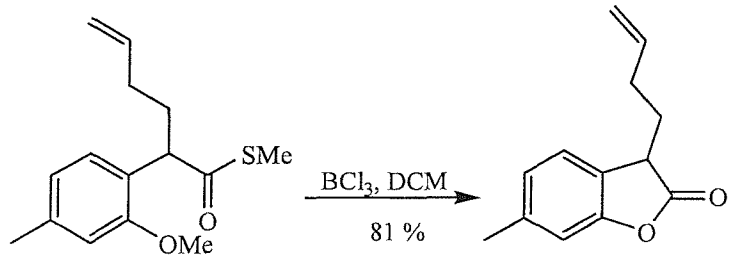
$C_{15}H_{20}O_2S$
Mol. Wt.: 264

To a stirred solution of the thioester **219** (2.10 g, 10.0 mmol) in THF (10 mL) cooled to -78°C and under nitrogen was added *tert*-butyllithium (7.70 mL of a 1.3 M solution in pentane, 10.0 mmol) *via* syringe over 90 s. The reaction mixture was stirred for 10 min then 4–iodo–1–butene (2.60 g, 14.2 mmol) in THF (5 mL) was added dropwise *via* syringe over 90 s. After 1 h the reaction mixture was warmed to ambient temperature and stirred for a further 8 h. Water (20 mL) and ether (20 mL) were added then the aqueous phase extracted with ether (3 × 20 mL). The combined organic extracts were washed with saturated sodium thiosulfate (20 mL) then brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (3.10 g). Purification by column chromatography (silica, 0 – 3 % ether in petrol) gave **225** (1.42 g, 5.40 mmol, 54 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3075w, 2929m, 2863w, 1688s, 1640w, 1612w, 1582w, 1506m, 1266m, 1040m, 795w.
λ_{max}/nm (ε_{max}, MeOH)	280 (2600).
δ_H (300MHz, $CDCl_3$)	7.16 (1H, d, *J* 7.7 Hz, Ar*H*), 6.78 (1H, br. d, *J* 7.7 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 5.80 (1H, ddt, *J* 16.8, 10.3, 6.4 Hz, C*H*=), 5.02 (1H, dd, *J* 16.8, 1.7 Hz, =CH*H*), 4.97 (1H, br. d, *J* 10.3 Hz, =C*H*H), 4.25 (1H, t, *J* 7.4 Hz, ArC*H*), 3.83 (3H, s, OCH_3), 2.36 (3H, s, ArCH_3), 2.23 (3H, s, SCH_3), 2.27 - 2.14 (1H, m, C*H*HCH$_2$CH=), 2.02 (2H, app. q, *J* 7.0 Hz, CH_2CH=), 1.94 - 1.80 (1H, m, CH*H*CH$_2$CH=) ppm.
δ_C (75.5MHz, $CDCl_3$)	201.8 (0, *C*O), 157.3 (0, Ar), 138.8 (0, Ar), 138.1 (1, *C*H=), 128.6 (1, Ar), 124.0 (0, Ar), 121.6 (1, Ar), 115.2 (2, =CH_2), 112.0 (1, Ar), 55.7 (3, OCH_3), 51.5 (1, ArCH), 31.6 (2), 31.4 (2), 21.8 (3, ArCH_3), 11.9 (3, SCH_3) ppm.

LRMS (APCI)	265 ($[MH]^+$, 20 %), 189 ($[M\text{-}CH_3SCO]^+$, 20 %), 101 (100 %) amu.
HRMS (EI)	Found M^+: 264.1182. $C_{15}H_{20}O_2S$ requires M^+: 264.1184.

3-(3-Butenyl)-6-methyl-2,3-dihydrobenzo[*b*]furan-2-one **210**



$C_{15}H_{20}O_2S$
Mol. Wt.: 264.38

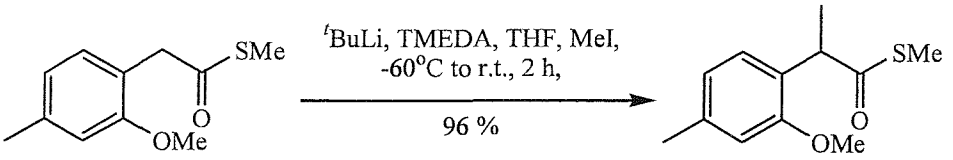
$C_{13}H_{14}O_2$
Mol. Wt.: 202.25

To a stirred solution of thioester **225** (0.34 g, 1.29 mmol) in dry, distilled dichloromethane (10 mL) cooled to 0°C and under nitrogen was added boron trichloride (1.55 mL of a 1 M solution, 1.55 mmol) *via* syringe over 30 s. The reaction mixture was stirred for 1 h then warmed to ambient temperature and stirred for 2 h. Water (5 mL) was added then the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were washed with dilute HCl (10 mL), NaOH (2 M, 10 mL), water (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (0.35 g). Purification by chromatography (silica, 0 – 5 % ether in petrol) gave **210** (0.21 g, 1.04 mmol, 81 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3078w, 2978w, 2925w, 1802s, 1630m, 1594w, 1500m, 1260m, 1065s, 947m.
λ_{max}/nm (ε_{max}, MeOH)	272 (2000).
δ_H (300MHz, $CDCl_3$)	7.15 (1H, d, *J* 7.5 Hz, Ar*H*), 6.96 (1H, d, *J* 7.5 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 5.79 (1H, ddt, *J* 17.1, 10.1, 6.6 Hz, C*H*=), 5.04 (1H, dd, *J* 17.1, 1.5 Hz, =CH*H*), 5.01 (1H, br. d, *J* 9.4 Hz, =C*H*H), 3.70 (1H, app. t, *J* 6.5 Hz, ArC*H*), 2.38 (3H, s, ArCH_3), 2.26 - 2.14 (2H, m, CH_2CH_2), 2.14 - 1.98 (2H, m, CH_2CH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	177.7 (0, *C*O), 154.0 (0, Ar), 139.4 (0, Ar), 136.9 (1, Ar) 136.9 (1, *C*H=), 124.9 (1, Ar), 124.3 (0, Ar), 124.0 (1, Ar), 116.3 (2, =*C*H_2), 42.6 (1, ArCH), 30.5 (2), 30.1 (2), 21.8 (3, ArCH_3) ppm.
LRMS (APCI)	243 ($[M+CH_3CN]^+$, 20 %), 203 ($[MH]^+$, 50 %), 202 (M^+, 40 %), 101 (100 %) amu.

HRMS (EI) Found M^+: 202.0986. $C_{13}H_{14}O_2$ requires M^+: 202.0994.

Methyl 2–(2–methoxy–4–methylphenyl)propanethioate **222**



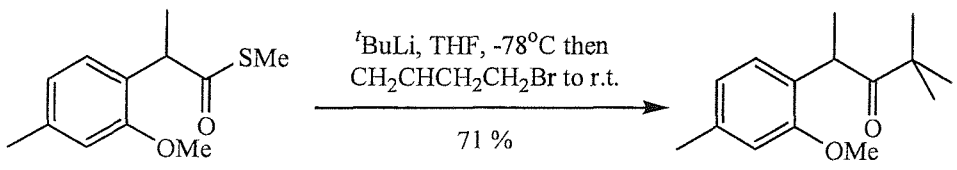
$C_{11}H_{14}O_2S$
Mol. Wt.: 210

$C_{12}H_{16}O_2S$
Mol. Wt.: 224

To a stirred solution of thioester **219** (13.72 g, 65.0 mmol) in THF (150 mL) and TMEDA (14.8 mL, 98.0 mmol) at -70°C and under nitrogen was added *tert*–butyllithium (43.0 mL of a 1.50 M solution in pentane, 65.0 mmol) over 30 min. After 5 min a solution of methyl iodide (13.9 g, 6.1 mL, 98.0 mmol) in THF (15 mL) was added over 15 min. After 2 h the reaction mixture was warmed to ambient temperature. After 16 h, water (75 mL) was added and the aqueous phase extracted with ether (3 × 50 mL). The organic extracts were combined and washed with saturated aqueous sodium thiosulfate (60 mL) and brine (60 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (17.1 g). Purification by chromatography (silica, 5 % ether in petroleum ether) gave **222** (14.0 g, 62.5 mmol, 96 %) as a colourless oil.

ν_{max}/**cm^{-1} (neat)**	2974w, 1684s, 1612m, 1581w, 1505m, 1265m, 1040m, 940m, 814w.
λ_{max}/**nm** (ε_{max}, **MeOH**)	280 (2500).
δ_H **(300MHz, $CDCl_3$)**	7.17 (1H, d, *J* 7.7 Hz, Ar*H*), 6.80 (1H, d, *J* 7.7 Hz, Ar*H*), 6.73 (1H, s, Ar*H*), 4.28 (1H, q, *J* 7.0 Hz, ArC*H*), 3.84 (3H, s, OCH_3), 2.37 (3H, s, ArCH_3), 2.24 (3H, s, SCH_3), 1.50 (3H, d, *J* 7.0 Hz, CH_3) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	202.8 (0, *C*O), 157.1 (0, Ar), 139.9 (0, Ar), 128.3 (1, Ar), 125.6 (0, Ar), 121.5 (1, Ar), 111.9 (1, Ar), 55.6 (3, OCH_3), 46.9 (1, Ar*C*H), 21.8 (3, ArCH_3), 17.4 (3, *C*H_3), 11.9 (3, SCH_3) ppm.
LRMS (APCI)	150 ([M-CH_3SCO+H]$^+$, 10 %), 149 ([M-CH_3SCO]$^+$, 100 %) amu.
HRMS (ES)	Found [M+NH_4]$^+$: 242.1213. $C_{12}H_{16}O_2S$ requires [M+NH_4]$^+$: 242.1215.

2,2-Dimethyl-4-[4-methyl-2-(methyloxy)phenyl]-3-pentanone **223**



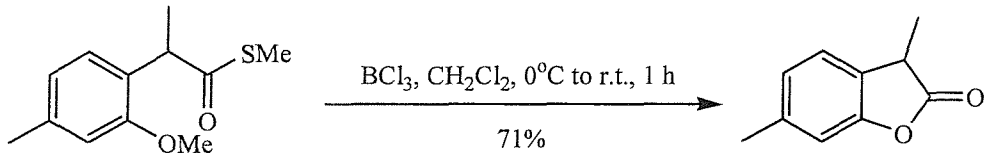
$C_{12}H_{16}O_2S$
Mol. Wt.: 224

$C_{15}H_{22}O_2$
Mol. Wt.: 234

To a stirred solution of the thioester (0.150 g, 0.67 mmol) in THF (5 mL) cooled to –78°C and under nitrogen was added *tert*-butyllithium (0.39 mL of a 1.7 M solution in pentane, 0.67 mmol) over 1 min. After 15 min, 4-bromo-1-butene (0.095 g, 0.070 mL, 0.70 mmol) was added over 1 min. After 2 h, the mixture was warmed to ambient temperature over 2 h. After 14 h, water (5 mL) was added and the mixture extracted with ether (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (0.45 g). Purification by chromatography (silica, 0 to 10 % ether in petroleum ether) gave **223** (0.112 g, 0.48 mmol, 71 %) as a colourless oil.

ν_{max}/em^{-1} (neat)	2869m, 1702s, 1612m, 1581m, 1506s, 1263s, 1191m, 1042s, 926w, 816m.
λ_{max}/nm (ε_{max}, MeOH)	279 (3500).
δ_H (300MHz, $CDCl_3$)	7.09 (1H, d, *J* 7.4 Hz, Ar*H*), 6.73 (1H, d, *J* 7.4 Hz, Ar*H*), 6.68 (1H, s, Ar*H*), 4.72 (1H, q, *J* 6.9 Hz, ArC*H*), 3.86 (3H, s, OCH_3), 2.34 (3H, s, $ArCH_3$), 1.28 (3H, d, *J* 6.9 Hz, $CHCH_3$), 1.05 (9H, app. s, $C(CH_3)_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	217.4 (0, *C*O), 155.8 (0, Ar), 137.8 (0, Ar), 127.8 (1, Ar), 126.8 (0, Ar), 121.5 (1, Ar), 111.6 (1, Ar), 55.5 (3, OCH_3), 44.9 (0, $C(CH_3)_3$, 37.9 (1, ArCH), 26.8 (3, $C(CH_3)_3$), 21.6 (3, $ArCH_3$), 19.6 (3, $CHCH_3$) ppm.
LRMS (CI)	235 ($[MH]^+$, 6 %), 149 ($[M-C_4H_9CO]^+$, 100 %) amu.
HRMS (CI)	Found $[M+NH_4]^+$: 252.1963. $C_{15}H_{22}O_2$ requires $[M+NH_4]^+$: 252.1964.

3,6–Dimethyl–2,3–dihydrobenzo[*b*]furan–2–one **224**



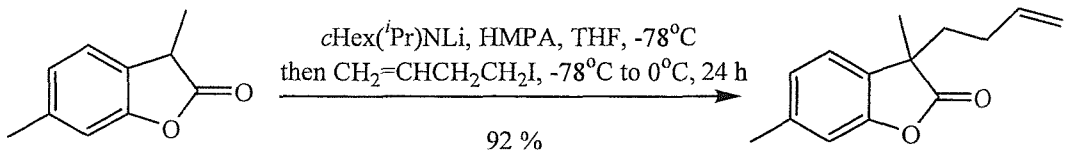
$C_{12}H_{16}O_2S$
Mol. Wt.: 224

$C_{10}H_{10}O_2$
Mol. Wt.: 162

To a stirred solution of thioester **222** (14.5 g, 64.7 mmol) in dichloromethane (250 mL) at 0°C and under nitrogen was added boron trichloride (77.6 mL of a 1.0 M solution in heptane, 77.6 mmol) dropwise over 5 min. After 30 min at 0°C the reaction mixture was warmed to ambient temperature and water (100 mL) added. The phases were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed with 1M HCl (2 × 30 mL), 1M NaOH (50 mL), water (50 mL) and brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil (9.80 g). Purification by chromatography (silica, 0 to 5 % ether in petrol) gave **224** (7.37 g, 45.5 mmol, 71 %) as a colourless oil which crystallised on standing to a colourless solid. Recrystallisation from petroleum ether gave large cubic crystals.

MP	35 - 37°C (petrol).
ν_{max}/cm^{-1} (neat)	2978w, 2932w, 1804vs, 1630m, 1594w, 1499w, 1452w, 1425m, 1258m, 1095s, 1027s, 941s.
λ_{max}/nm (ε_{max}, MeOH)	274 (1800).
δ_H (300MHz, $CDCl_3$)	7.13 (1H, d, *J* 7.5 Hz, Ar*H*), 6.96 (1H, d, *J* 7.5 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 3.69 (1H, q, *J* 7.5 Hz, ArC*H*), 2.39 (3H, s, ArCH_3), 1.56 (3H, d, *J* 7.5 Hz, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	178.6 (0, *C*O), 153.7 (0, Ar), 139.4 (0, Ar), 125.9 (0, Ar), 124.9 (1, Ar), 123.6 (1, Ar), 111.5 (1, Ar), 38.4 (1, ArCH), 21.8 (3, ArCH$_3$), 16.2 (3, *C*H$_3$) ppm.
LRMS (APCI)	180 ([M+NH$_4$]$^+$, 100 %), 162 (M$^+$, 24 %), 134 (20 %) amu.
CHN	Found: C, 74.33; H, 6.19. $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21.

3–(3–Butenyl)–3,6–dimethyl–2,3–dihydrobenzo[*b*]furan–2–one **213**



$C_{10}H_{10}O_2$
Mol. Wt.: 162

$C_{14}H_{16}O_2$
Mol. Wt.: 216

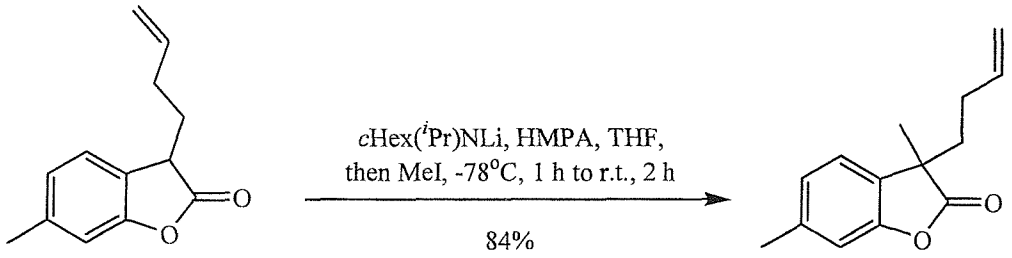
Prepared following the procedure of Padwa *et al.*[110] Thus, to a stirred solution of *N*–isopropylcyclohexylamine (3.40 mL, 15.8 mmol) in THF (30 mL) and HMPA (4.9 mL, 28.3 mmol) at –78°C and under nitrogen was added *sec*–butyllithium (13.9 mL of a 1.14 M solution in cyclohexane, 15.8 mmol) over 30 s. After 10 min the mixture was warmed to 0°C then recooled to –78°C. Lactone **224** (1.83 g, 11.3 mmol) in THF (10 mL) was added *via* syringe over 30 s. After 10 min a solution of the 1–iodo–3–butene (4.10 g, 22.5 mmol) in THF (10 mL) was added over 30 s. After 12 h the reaction mixture was warmed to ambient temperature and stirred for 12 h. Water (15 mL) and ether (15 mL) was added and the phases separated. The aqueous phase was extracted with ether (3 × 15 mL) then the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, petrol then 5 % ether in petrol) gave **213** (2.25 g, 10.4 mmol, 92 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3079w, 2929m, 1806vs, 1633m, 1596w, 1500m, 1453m, 1259m, 1029s, 948s, 815m.
λ_{max}/nm (ε_{max}, MeOH)	274 (1450).
δ_H (300MHz, $CDCl_3$)	7.07 (1H, d, *J* 7.6 Hz, Ar*H*), 6.98 (1H, br. d, *J* 7.6 Hz, Ar*H*), 6.94 (1H, s, Ar*H*), 5.63 (1H, ddt, *J* 17.3, 9.6, 6.6 Hz, C*H*=), 4.94 - 4.84 (2H, m, =CH_2), 2.39 (3H, s, ArCH_3), 2.05 (1H, app. dd, *J* 10.7, 7.2 Hz, C*H*HCH=), 1.93 - 1.72 (3H, m, CH*H*CH= & CH_2), 1.48 (3H, s, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	180.9 (0, *C*O), 153.0 (0, Ar), 139.2 (0, Ar), 137.0 (1, *C*H=), 128.7 (0, Ar), 125.1 (1, Ar), 122.8 (1, Ar), 115.5 (2, =*C*H_2), 111.5 (1, Ar), 47.2 (0, Ar*C*), 38.2 (2), 29.3 (2), 24.8 (3, *C*H_3), 21.8 (3, Ar*C*H_3) ppm.

LRMS (APCI) 258 ($[MH+CH_3CN]^+$, 20 %), 217 ($[MH]^+$, 100 %), 216 (M^+, 40 %), 111 (20 %), 101 (75 %) amu.

HRMS (EI) Found: M^+, 216.1151. $C_{14}H_{16}O_2$ requires 216.1150.

Alternatively:

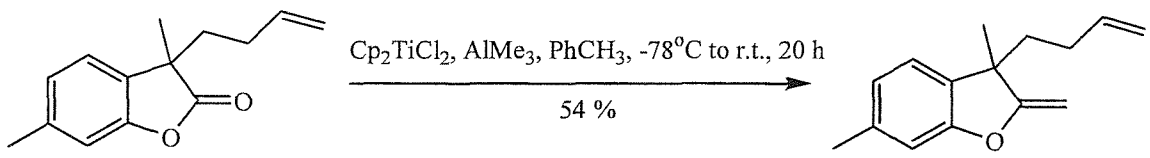


$C_{13}H_{14}O_2$
Mol. Wt.: 202

$C_{14}H_{16}O_2$
Mol. Wt.: 216

To a stirred solution of *N*–isopropylcyclohexylamine (0.70 mL, 4.27 mmol) in THF (15 mL) and HMPA (1.29 mL, 7.42 mmol) at –78°C and under nitrogen was added *sec*–butyllithium (3.0 mL of a 1.4M solution in cyclohexane, 4.26 mmol). After 10 min the mixture was warmed to 0°C then recooled to –78°C. Lactone **210** (0.75 g, 3.71 mmol) in THF (10 mL) was added *via* syringe over 4 min. After 15 min a solution of methyl iodide (0.79 g, 0.35 mL, 5.57 mmol) in THF (5 mL) was added over 2 min. After ½ h the reaction mixture was warmed to ambient temperature and stirred for 1 h. Water (10 mL) and ether (10 mL) was added and the phases separated. The aqueous phase was extracted with ether (3 × 15 mL) then the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (1.9 g). Purification by chromatography (silica, 0 to 2 % ether in petrol) gave **213** (0.67 g, 3.10 mmol, 84 %) as a colourless oil.

3-(3-Butenyl)-3,6-dimethyl-2-methylene-2,3-dihydrobenzo[*b*]furan **204**



$C_{14}H_{16}O_2$
Mol. Wt.: 216

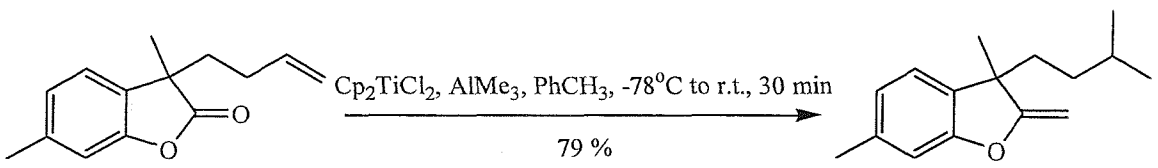
$C_{15}H_{18}O$
Mol. Wt.: 214

Prepared following the procedure of Cannizzo *et al.*[37b] Thus, trimethylaluminium (14.4 mL of a 2 M solution in heptane, 28.8 mmol) was added *via* syringe to titanocene dichloride (2.56 g, 10.28 mmol) and the mixture stirred at ambient temperature for 24 h. The mixture was cooled to −78°C then THF (10 mL) added followed by a solution of lactone **213** (0.80 g, 3.70 mmol) in THF (10 mL) dropwise over 5 min. After ½ h the mixture was warmed to ambient temperature and stirred for a further 20 h. THF (10 mL) was added and the mixture cooled to 0°C. Sodium hydroxide (1.15 g, 28.8 mmol) in water (3 mL) was added dropwise then the reaction mixture was filtered through a pad of celite. The celite was washed with ether (3 × 20 mL) and the combined filtrates dried ($MgSO_4$), filtered and concentrated *in vacuo* to a cloudy yellow oil (1.05 g). Purification by chromatography (silica, 0 to 1 % ether in petrol) firstly gave diene **204** (0.43 g, 2.01 mmol, 54 %) as a colourless oil then **213** (0.22 g, 1.02 mmol, 28 %).

ν_{max}/cm^{-1} (neat)	3072w, 2864m, 1685s, 1640m, 1618s, 1595m, 1140s, 960s, 911w, 809m.
λ_{max}/nm (ε_{max}, MeOH)	283 (3050), 235 (10100).
δ_H (300MHz, C_6D_6)	6.75 - 6.68 (2H, m, 2 × Ar*H*), 6.64 (1H, d, *J* 7.7 Hz, Ar*H*), 5.64 (1H, ddt, *J* 16.5, 10.7, 6.1 Hz, C*H*=), 4.94 - 4.84 (2H, m, CH=CH_2), 4.82 (1H, d, *J* 2.4 Hz, =C*H*H), 4.04 (1H, d, *J* 2.4 Hz, =CH*H*), 2.05 (3H, s, ArCH_3), 1.78 - 1.50 (3H, m), 1.40 - 1.25 (1H, m), 1.23 (3H, s, CH_3) ppm.
δ_C (75.5MHz, C_6D_6)	170.8 (0, *C*=), 157.4 (0, Ar), 138.4 (0, Ar), 138.3 (1, *C*H=), 130.7 (0, Ar), 122.9 (1, Ar), 122.5 (1, Ar), 114.3 (2, CH=*C*H_2), 110.2 (1, Ar), 82.9 (2, =*C*H_2), 47.5 (0, Ar*C*), 42.5 (2, *C*H_2CH=), 29.6 (2, *C*H_2), 29.2 (3, *C*H_3), 21.3 (3, Ar*C*H_3) ppm.

LRMS (APCI)	230 ($[M+H_2O]^+$, 10 %), 215 ($[MH]^+$, 50 %), 214 (M^+, 100 %), 152 (5 %), 126 (10 %), 111 (25 %), 85 (15 %) amu.
HRMS (EI)	Found: M^+, 214.1347. $C_{15}H_{18}O$ requires 214.1358.

3-Isopentyl-3,6-dimethyl-2-methylene-2,3-dihydrobenzo[*b*] furan **239**



$C_{14}H_{16}O_2$
Mol. Wt.: 216

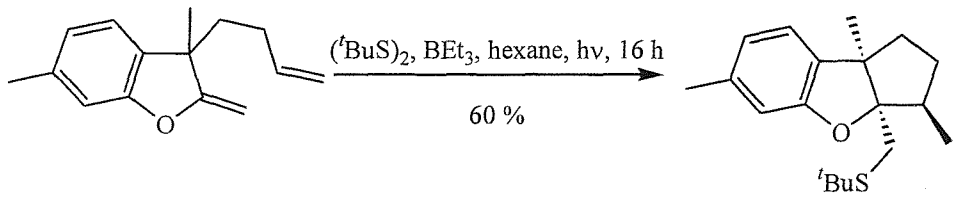
$C_{16}H_{22}O$
Mol. Wt.: 230

Prepared following a modified procedure of Cannizzo *et al.*[37b] Thus, trimethylaluminium (27.8 mL of a 2 M solution in heptane, 55.5 mmol) was added *via* syringe to titanocene dichloride (6.92 g, 27.8 mmol) and toluene (10 mL) under argon and at ambient temperature. After 24 h the mixture was cooled to –78°C and to it was added a solution of lactone **213** (1.20 g, 5.56 mmol) in THF (10 mL) over 5 min. After 30 min the mixture was warmed to ambient temperature. After 24 h the mixture was cooled to 0°C and sodium hydroxide (2.2 g, 55.5 mmol) in water (5 mL) was carefully added. The mixture was dried ($MgSO_4$) then filtered through a pad of celite. The cake was washed thoroughly with ether (3 × 50 mL) then the filtrate was concentrated *in vacuo* to a red residue. Purification by chromatography (silica, petroleum ether) gave **214** (1.00 g, 4.39 mmol, 79 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2956m, 2925m, 2868w, 1684m, 1618m, 1595m, 1498m, 1325w, 1141s, 958s, 806s.
λ_{max}/nm (ε_{max}, MeOH)	283 (2650).
δ_H (400MHz, $CDCl_3$)	7.08 (1H, d, *J* 7.5 Hz, Ar*H*), 6.91 (1H, d, *J* 7.5 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 4.79 (1H, d, *J* 2.6 Hz, =C*H*H), 4.26 (1H, d, *J* 2.6 Hz, =CH*H*), 2.47 (3H, s, ArCH_3), 1.86 (1H, app. td, *J* 12.8, 4.4 Hz, C*H*HCH$_2$), 1.71 (1H, app. td, *J* 12.8, 4.4 Hz, CH*H*CH$_2$), 1.55 - 1.50 (1H, m, C*H*(CH$_3$)$_2$), 1.52 (3H, s, CH_3), 1.21 (1H, tdd, *J* 12.8, 6.8, 4.4 Hz, C*H*HCH(CH$_3$)$_2$), 0.93 (3H, d, *J* 7.1 Hz, CH(CH_3)$_2$), 0.91 (3H, d, *J* 6.8 Hz, CH(CH_3)$_2$), 0.86 (1H, tdd, *J* 12.8, 6.8, 4.4 Hz, CH*H*CH(CH$_3$)$_2$) ppm.
δ_C (75.5MHz, $CDCl_3$)	171.0 (0, *C*=), 156.9 (0, Ar), 138.3 (0, Ar), 131.0 (0, Ar), 122.7 (1, Ar), 122.5 (1, Ar), 110.0 (1, Ar), 82.6 (2, =*C*H$_2$), 47.6 (0, Ar*C*), 41.1 (2, *C*H$_2$), 33.8 (2, *C*H$_2$), 29.7 (3, *C*H$_3$), 28.3 (1,

	$CH(CH_3)_2$), 22.7 (3, $CH(CH_3)$), 22.6 (3, $CH(CH_3)$), 21.7 (3, $ArCH_3$) ppm.
LRMS (APCI)	231 ($[MH]^+$, 70 %), 230 (M^+, 90 %), 165 (50 %), 111 (100 %) amu.
HRMS (EI)	Found MH^+: 231.1754. $C_{16}H_{22}O$ requires MH^+: 231.1749.

rel-(3*R*,3a*R*,8b*R*)-(3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl)methyl (*tert*–butyl) sulfide **227**



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

$C_{19}H_{28}OS$
Mol. Wt.: 304

A stirred solution of diene **204** (0.40 g, 1.87 mmol) and di-*tert*-butyl disulfide (1.67 g, 1.81 mL, 9.35 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter). Triethylborane (1.0 mL of a 1M solution in hexanes, 1 mmol) was added *via* syringe. After 16 h, saturated ammonium chloride (20 mL) was added and the phases separated. The aqueous phase was extracted with ether (3 × 15 mL) then the organic phases were combined and washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to an orange oil (2.15 g). Purification by chromatography (silica, 0 to 2 % ether in petrol) gave **227** (0.34 g, 1.12 mmol, 60 %) as a yellow oil which was determined by NMR to be a 8 : 1 mixture of diastereomers. Further purification (silica, 5 to 10 % dichloromethane in petrol) gave firstly a mixture of *cis* and *trans* isomers **227a** and **227b** then pure **227b** as a colourless oil.

Data for *trans* isomer **227b**

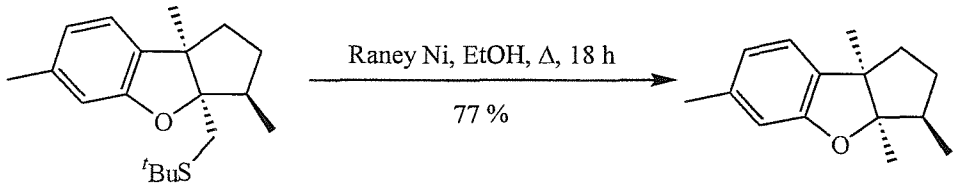
ν_{max}/cm^{-1} (neat)	2955s, 2862m, 1620w, 1593s, 1499s, 1320w, 1280s, 1160m, 948s, 852w.
λ_{max}/nm (ε_{max}, MeOH)	284 (4000).
δ_H (300MHz, $CDCl_3$)	6.91 (1H, d, *J* 7.4 Hz, Ar*H*), 6.67 (1H, d, *J* 7.4 Hz, Ar*H*), 6.58 (1H, s, Ar*H*), 2.99 (1H, d, *J* 12.2 Hz, S*H*H), 2.87 (1H, d, *J* 12.2 Hz, SH*H*), 2.30 (3H, s, ArCH_3), 2.17 (1H, m, C*H*CH$_3$), 1.87 (1H, app. dd, *J* 11.2, 7.1 Hz), 1.72 - 1.58 (3H, m), 1.51 (3H, s, CH_3), 1.34 (9H, app. s, C(CH_3)$_3$), 1.14 (3H, d, *J* 6.8 Hz, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	159.0 (0, Ar), 137.9 (0, Ar), 133.4 (0, Ar), 122.2 (1, Ar), 121.0 (1, Ar), 109.2 (1, Ar), 99.2 (0, OC), 55.4 (0, ArC), 43.8 (1,

	*C*HCH$_3$), 42.4 (2, S*C*H$_2$), 42.2 (0, *C*(CH$_3$)$_3$), 32.8 (2), 31.5 (2), 30.7 (3, (*C*H$_3$)$_3$), 23.6 (3, C*C*H$_3$), 21.5 (3, Ar*C*H$_3$), 13.8 (3, CH*C*H$_3$) ppm.
LRMS (APCI)	305 ([MH]$^+$, 60 %), 304 (M$^+$, 40 %), 249 ([M-C$_4$H$_7$]$^+$, 70 %), 83 (100 %) amu.
HRMS (EI)	Found: M$^+$, 304.1858. C$_{19}$H$_{28}$OS requires 304.1861.

A pure sample of the *cis* isomer could not be obtained. Spectral peaks in a ^{1}H NMR spectra of an enriched sample that were attributed to **227a** follow:

δ_H (300MHz, CDCl$_3$)	6.91 (1H, d, *J* 7.4 Hz, Ar*H*), 6.68 (1H, d, *J* 7.4 Hz, Ar*H*), 6.57 (1H, s, Ar*H*), 3.34 (1H, d, *J* 13.2 Hz, S*H*H), 3.19 (1H, d, *J* 13.2 Hz, SH*H*), 2.29 (3H, s, ArC*H*$_3$), 2.13 (1H, app. dq, *J* 13.2, 6.6 Hz, C*H*CH$_3$), 1.87 (1H, app. dd, *J* 11.4, 6.1 Hz), 1.71 - 1.58 (3H, m), 1.49 (3H, s, C*H*$_3$), 1.35 (9H, app. s, C(C*H*$_3$)$_3$), 1.16 (3H, d, *J* 6.8 Hz, CHC*H*$_3$) ppm.

rel-(3*R*,3a*R*,8b*R*)-3,3a,6,8b-Tetramethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-Debromoaplysin) **2**[1]



$C_{19}H_{28}OS$
Mol. Wt.: 304

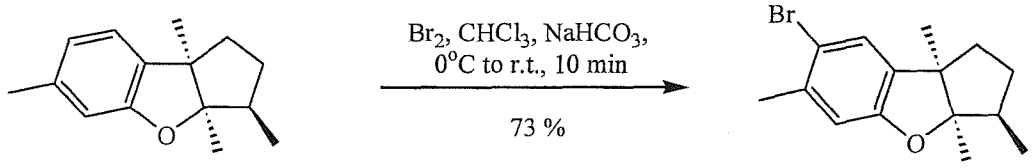
$C_{15}H_{20}O$
Mol. Wt.: 216

Prepared following the procedure of Pettit *et al.*[116] Thus, to a suspension of Raney nickel (*c.a.* 1 g, 17 mmol) in ethanol (4 mL) was added a solution of sulfide **227b** (42 mg, 0.14 mmol) in ethanol (2 mL) and the mixture heated at reflux. After 40 h the mixture was cooled and filtered through a pad of celite. The celite was extracted with chloroform (80 mL) using a Soxhlet apparatus. The combined organic phases were concentrated *in vacuo* to a colourless oil (29 mg). Purification by chromatography (silica, 5 to 10 % dichloromethane in petrol) gave debromoaplysin **2** (23 mg, 0.11 mmol, 77 %) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[1]

ν_{max}/cm^{-1} (neat)	2954s, 2866m, 1619w, 1593m, 1499s, 1280s, 1123m, 1009m, 948m, 801m.
λ_{max}/nm (ε_{max}, MeOH)	285 (2400).
δ_H (300MHz, $CDCl_3$)	6.93 (1H, d, *J* 7.4 Hz, Ar*H*), 6.66 (1H, d, *J* 7.4 Hz, Ar*H*), 6.54 (1H, s, Ar*H*), 2.29 (3H, s, ArCH_3), 1.90 – 1.70 (2H, m), 1.66 - 1.53 (2H, m), 1.33 (3H, s), 1.29 (3H, s), 1.25 - 1.15 (1H, m), 1.12 (3H, d, *J* 6.6 Hz, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	159.0 (0, Ar), 138.0 (0, Ar), 133.8 (0, Ar), 122.7 (1, Ar), 120.9 (1, Ar), 109.5 (1, Ar), 99.0 (0, O*C*), 55.2 (0, *C*CH_3), 46.3 (1), 42.8 (2), 31.4 (2), 23.7 (3, OCCH_3), 21.6 (3, ArCH_3), 20.2 (3, *C*CH_3), 13.3 (3, CHCH_3) ppm.
LRMS (APCI)	217 ([MH]$^+$, 10 %), 216 (M$^+$, 20 %), 100 (100 %) amu.
HRMS (EI)	Found: M$^+$, 216.1507. $C_{15}H_{20}O$ requires 216.1514.

rel-(3*R*,3a*R*,8b*R*)-7-Bromo-3,3a,6,8b-tetramethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-aplysin) **1**[1]



$C_{15}H_{20}O$
Mol. Wt.: 216

$C_{15}H_{19}BrO$
Mol. Wt.: 295

Prepared following the procedure of Nemoto *et al.*[23] Thus, to a stirred solution of debromoaplysin **2** (14 mg, 0.065 mmol) and sodium hydrogen carbonate (8.7 mg, 0.140 mmol) in chloroform (5 mL) at 0°C was added a solution of bromine (0.97 mL of a 0.1 M solution in chloroform, 0.097 mmol). After stirring at ambient temperature for 10 min, concentration *in vacuo* gave a pale brown residue (40 mg). Purification by chromatography (silica, 5 to 10 % dichloromethane in petrol) gave aplysin **1** (14 mg, 0.047 mmol, 73 %) as a white crystalline solid which was recrystallised from methanol to give a white powder.

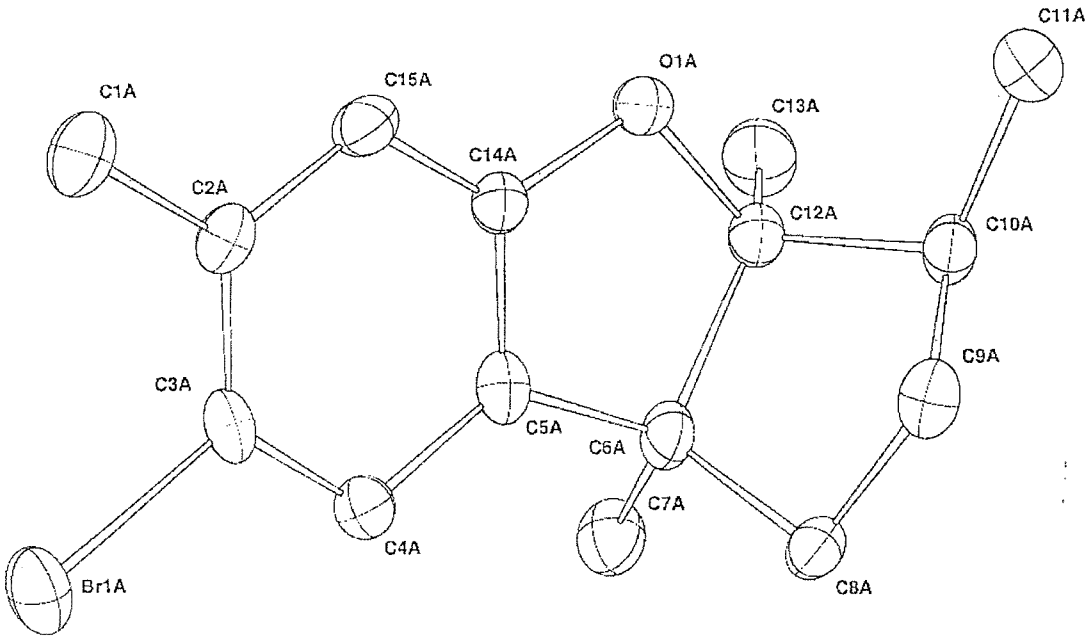
Spectral and physical characteristics were consistent with literature values.[1,9,15]

MP	96 - 98°C (methanol). Lit. 96°C (no solvent reported);[9] lit. 98 - 100°C (methanol).[15]
ν_{max}/cm^{-1} ($CDCl_3$)	2956s, 2849m, 1479m, 1460s, 1391m, 1308w, 1192w, 1006m, 904w, 846w.
λ_{max}/nm (ε_{max}, MeOH)	296 (2950), 234 (5500).
δ_H (300MHz, $CDCl_3$)	7.15 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 2.31 (3H, s, ArCH_3), 1.90 - 1.50 (4H, m), 1.32 (3H, s), 1.29 (3H, s), 1.20 - 1.05 (1H, obscured m), 1.11 (3H, d, *J* 6.8 Hz, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	158.3 (0, Ar), 137.1 (0, Ar), 136.4 (0, Ar), 126.7 (1, Ar), 114.1 (0, Ar), 111.0 (1, Ar), 100.0 (0, O*C*), 54.5 (0, Ar*C*), 46.2 (1), 42.7 (2), 31.3 (2), 23.5 (3), 23.3 (3), 20.1 (3, CCH_3), 13.2 (3, CHCH_3) ppm.

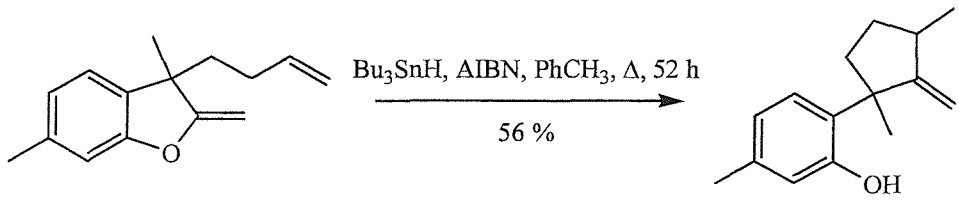
LRMS (APCI) 296 ([M(^{81}Br)]$^+$, 70 %), 294 ([M(^{79}Br)]$^+$, 100 %), 100 (50 %) amu.

HRMS (EI) Found: M^+, 294.0616. $C_{15}H_{19}BrO$ requires 294.0619.

X-ray structure



2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol ((±)-debromoisolaurinterol) **7**[24] and epidebromoisolaurinterol **230**



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

$C_{15}H_{20}O$
Mol. Wt.: 216

A solution of diene **204** (60 mg, 0.28 mmol) in toluene (3 mL) was heated at reflux then tributyltin hydride (163 mg, 0.15 mL, 0.56 mmol) and AIBN (23 mg, 0.14 mmol) were added under a stream of nitrogen. After 52 h, the mixture was cooled to ambient temperature and saturated aqueous potassium fluoride (10 mL) was added. After 30 min the phases were separated and the aqueous phase extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, petroleum ether) gave firstly recovered **204** (15 mg, 0.07 mmol, 25 %) R_f 0.8; secondly **7** (17 mg, 0.079 mmol, 28 %) R_f 0.33 as a colourless oil; and finally a mixture of **7** and **230** (17 mg, 0.078 mmol, 28 %) R_f 0.32.

Spectral and physical characteristics were consistent with literature values.[24]

Data for **7**:

ν_{max}/cm^{-1} (neat)	3453br. s, 3069w, 3026w, 2978m, 2958s, 2870m, 1641w, 1622w, 1570w, 1503m, 1372m, 1291m, 1137m, 805s.
λ_{max}/nm (ε_{max}, MeOH)	270 (10100).
δ_H (300MHz, $CDCl_3$)	7.22 (1H, d, *J* 8.4 Hz, Ar*H*), 6.74 (1H, dd, *J* 8.4, 1.2 Hz, Ar*H*), 6.68 (1H, d, *J* 1.2 Hz, Ar*H*), 5.59 (1H, s, ArO*H*), 5.11 (1H, d, *J* 2.0 Hz, =C*H*H), 4.97 (1H, d, *J* 2.0 Hz, =CH*H*), 2.86 (1H, dtt, *J* 9.1, 7.0, 2.2 Hz, C*H*CH_3), 2.30 (3H, s, ArCH_3), 2.25 (1H, ddd, *J* 12.9, 8.0, 6.6 Hz, C*H*HCH_2CH), 2.06 (1H, dddd, *J* 12.9, 8.8, 7.3, 6.6 Hz, C*H*HCH), 1.60 (1H, dt, *J* 12.9, 7.1 Hz,

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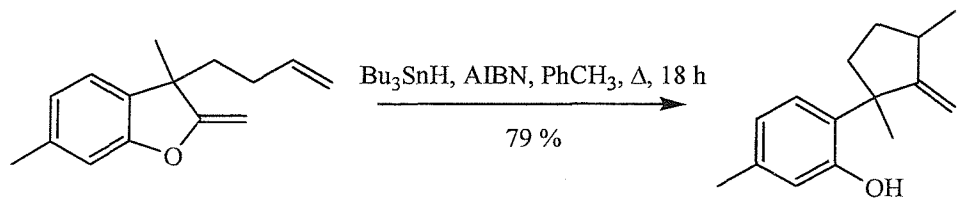
	CH*H*CH_2CH), 1.48 (3H, s, CH_3), 1.40 - 1.30 (1H, m), 1.22 (3H, d, *J* 7.0 Hz, CHCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	165.8 (0, =*C*), 153.9 (0, Ar), 138.0 (0, Ar), 130.2 (0, Ar), 127.9 (1, Ar), 121.6 (1, Ar), 119.0 (1, Ar), 106.8 (2, =*C*H_2), 50.1 (0, Ar*C*), 39.5 (2, *C*H_2), 38.0 (1, *C*HCH_3), 31.5 (2, *C*H_2), 28.1 (3, *C*H_3C), 21.3 (3, Ar*C*H_3), 20.9 (3, CH*C*H_3) ppm.
LRMS (APCI)	217 ($[MH]^+$, 15 %), 216 (M^+, 30 %), 163 (15 %), 146 (40 %), 105 (100 %) amu.
HRMS (EI)	Found M^+: 216.1504. $C_{15}H_{20}O$ requires M^+: 216.1514.

230 has not been isolated in pure form but shows NMR signals in the mixture at:

δ_H (300MHz, $CDCl_3$)	7.29 (1H, obsc. d, Ar*H*), 5.65 (1H, s, ArO*H*), 5.12 (1H, d, *J* 2.0 Hz, =C*H*H), 5.02 (1H, d, *J* 2.0 Hz, =CH*H*), 1.46 (3H, s, CH_3), 1.23 (3H, d, *J* 7.0 Hz, CHCH_3). All remaining signals obscured by **7**.
δ_C (75.5MHz, $CDCl_3$)	165.5 (0), 131.0 (0), 127.4 (1, Ar), 118.8 (1, Ar), 106.2 (2, =*C*H_2), 49.7 (0, Ar*C*), 39.7 (2, *C*H_2), 38.7 (1, *C*HCH_3), 32.3 (2, *C*H_2), 27.4 (3, *C*H_3), 20.0 (3, CH*C*H_3). All remaining signals obscured by **7**.

2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol ((±)-debromoisolaurinterol) 7[24] and epidebromoisolaurinterol **230**

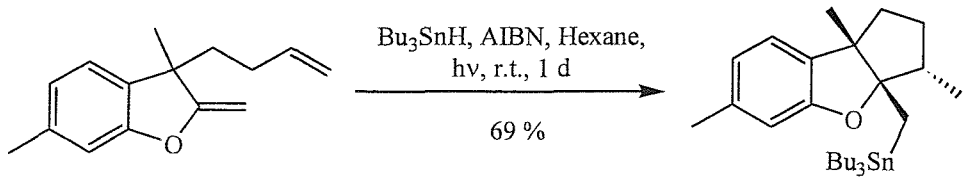


$C_{15}H_{18}O$
Mol. Wt.: 214

$C_{15}H_{20}O$
Mol. Wt.: 216

To a stirred solution of diene **224** (0.100 g, 0.47 mmol) and tri-*n*-butyltin hydride (0.270 g, 0.25 mL, 0.93 mmol) in toluene (10 mL) at reflux under nitrogen was added AIBN (38 mg, 0.23 mmol). After 18 h, the mixture was cooled to ambient temperature then concentrated *in vacuo* to a colourless oil. Purification by chromatography (silica, 5 % ether in petroleum ether) gave debromoisolaurinterol **7** and **230** (0.080 g, 0.37 mmol, 79 %) as a 5 : 1 mixture of diastereoisomers.

rel-(3*S*,3a*S*,8b*S*)-[(3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl)methyl] (tributyl)stannane **233**



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

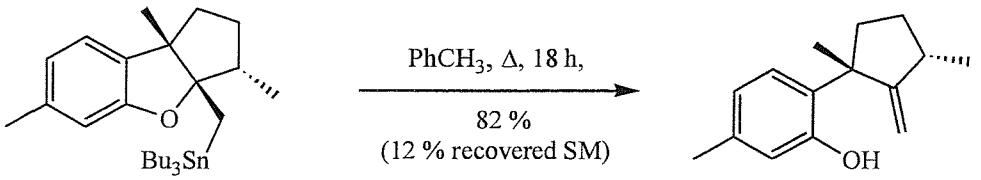
$C_{27}H_{46}OSn$
Mol. Wt.: 505

A mixture of diene **204** (0.50 g, 2.34 mmol), tri-*n*-butyltin hydride (1.36 g, 1.24 mL, 4.67 mmol) and AIBN (0.19 g, 1.17 mmol) in degassed hexane (110 mL) was irradiated with UV (Quartz filter) at 10°C and under nitrogen. After 24 h the solvents were removed *in vacuo* and the residue purified by chromatography (silica, petroleum ether) to give **233** (0.815 g, 1.61 mmol, 69 %) as a colourless oil.

ν_{max}/**cm^{-1} (neat)**	2953s, 2924s, 2866m, 1619w, 1592m, 1499s, 1456s, 1269s, 1125s, 1068s, 945s, 801s.
λ_{max}/**nm** (ε_{max}, **MeOH**)	286 (3800).
δ_H **(300MHz, $CDCl_3$)**	6.88 (1H, d, *J* 7.5 Hz, Ar*H*), 6.62 (1H, d, *J* 7.5 Hz, Ar*H*), 6.45 (1H, s, Ar*H*), 2.28 (3H, s, ArCH_3), 1.90 - 1.75 (2H, m), 1.70 - 1.55 (2H, m), 1.50 - 1.18 (15H, m), 1.32 (3H, s, CH_3), 1.11 (3H, d, *J* 6.6 Hz, CHCH_3), 0.88 (9H, app. t, *J* 7.2 Hz, 3 × CH_3), 0.73 (6H, m, 3 × SnCH_2) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	159.1 (0, Ar), 137.8 (0, Ar), 133.7 (0, Ar), 122.6 (1, Ar), 120.6 (1, Ar), 109.4 (1, Ar), 102.4 (0, O*C*), 54.9 (0, Ar*C*), 49.0 (1, *C*HCH$_3$), 43.0 (2), 31.4 (2), 29.3 (2, 3 × SnCH$_2$CH$_2$CH$_2$, [residual $J_{^{117/119}Sn-^{13}C}$ 20 Hz]), 27.6 (2, 3 × SnCH$_2$CH$_2$CH_2 [residual $J_{^{117/119}Sn-^{13}C}$ 58 Hz]), 24.1 (3, CCH$_3$), 21.6 (3, ArCH$_3$), 17.4 (2, SnCH$_2$C), 13.9 (3, CHCH$_3$), 13.8 (3, 3 × SnCH$_2$CH$_2$CH$_2$CH$_3$), 10.6 (2, 3 × SnCH$_2$, [residual $J_{^{119}Sn-^{13}C}$ 325 Hz, residual $J_{^{117}Sn-^{13}C}$ 311 Hz]) ppm.

LRMS (APCI)	449 ([M-C_4H_9]$^+$, 100 %), 447 (90 %), 445 (40 %), 341 ([M–(C_4H_9)$_3$]$^+$, 5 %), 276 (40 %), 274 (35 %), 272 (15 %), 220 ([M–Sn(C_4H_9)$_3$]$^+$, 35 %), 218 (35 %), 216 (25 %) amu.
HRMS (EI)	For M_r = 506.2571. Found MH^+: 507.2642. $C_{27}H_{46}OSn$ requires MH^+: 507.2649.

2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol (Debromoisolaurinterol) **7**[24]



$C_{27}H_{46}OSn$
Mol. Wt.: 505

$C_{15}H_{20}O$
Mol. Wt.: 216

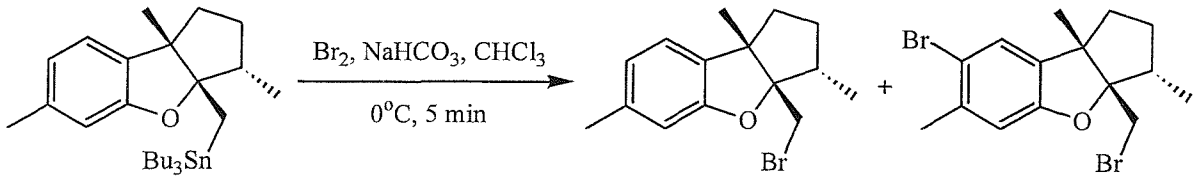
A mixture of stannane **233** (0.100 g, 0.198 mmol) in toluene (5 mL) was heated at reflux under nitrogen. After 18 h the mixture was concentrated *in vacuo* then purified by chromatography (silica, petroleum ether then 5 % ether in petroleum ether) to give firstly recovered **233** (12 mg, 0.002 mmol, 12 %) as a colourless oil then debromisolaurinterol **7** (35 mg, 0.163 mmol, 82 %) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[24]

ν_{max}/cm^{-1} (neat)	3453br. s, 3069w, 3026w, 2978m, 2958s, 2870m, 1641w, 1622w, 1570w, 1503m, 1372m, 1291m, 1137m, 805s.
λ_{max}/nm (ε_{max}, MeOH)	270 (10100).
δ_H (300MHz, $CDCl_3$)	7.22 (1H, d, *J* 8.4 Hz, Ar*H*), 6.74 (1H, dd, *J* 8.4, 1.2 Hz, Ar*H*), 6.68 (1H, d, *J* 1.2 Hz, Ar*H*), 5.59 (1H, s, ArO*H*), 5.11 (1H, d, *J* 2.0 Hz, =C*H*H), 4.97 (1H, d, *J* 2.0 Hz, =CH*H*), 2.86 (1H, dtt, *J* 9.1, 7.0, 2.2 Hz, C*H*CH_3), 2.30 (3H, s, ArCH_3), 2.25 (1H, ddd, *J* 12.9, 8.0, 6.6 Hz, C*H*HCH_2), 2.06 (1H, dddd, *J* 12.9, 8.8, 7.3, 6.6 Hz, C*H*HCH), 1.60 (1H, dt, *J* 12.9, 7.1 Hz, CH*H*CH_2CH), 1.48 (3H, s, CH_3), 1.40 - 1.30 (1H, m), 1.22 (3H, d, *J* 7.0 Hz, CHCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	165.8 (0, =*C*), 153.9 (0, Ar), 138.0 (0, Ar), 130.2 (0, Ar), 127.9 (1, Ar), 121.6 (1, Ar), 119.0 (1, Ar), 106.8 (2, =CH_2), 50.1 (0, Ar*C*), 39.5 (2, CH_2), 38.0 (1, $CHCH_3$), 31.5 (2, CH_2), 28.1 (3, CH_3C), 21.3 (3, ArCH_3), 20.9 (3, $CHCH_3$) ppm.
LRMS (APCI)	217 ([MH]$^+$, 15 %), 216 (M$^+$, 30 %), 163 (15 %), 146 (40 %), 105 (100 %) amu.

HRMS (EI) Found M^+: 216.1504. $C_{15}H_{20}O$ requires M^+: 216.1514.

rel-(3*S*,3a*S*,8b*S*)-3a-(Bromomethyl)-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan ((±)-Isoaplysin) **5**[15] and rel-(3*S*,3a*S*,8b*S*)-7-bromo-3a-(bromomethyl)-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan **234**



$C_{27}H_{46}OSn$
Mol. Wt.: 505

$C_{15}H_{19}BrO$
Mol. Wt.: 295

47 %

$C_{15}H_{18}Br_2O$
Mol. Wt.: 374

47 %

Prepared following a modified procedure of Nemoto *et al.*[23] To a stirred solution of the stannane (0.15 g, 0.30 mmol) and sodium hydrogen carbonate (43 mg, 0.59 mmol) in chloroform (10 mL) at 0°C and under nitrogen was added a solution of bromine (3 mL of a 0.1 M solution in chloroform, 0.30 mmol) over 2 min. After 5 min the mixture was concentrated *in vacuo* to a brown residue. Purification by chromatography (silica, petroleum ether then 2 ½ % ether in petroleum ether) gave firstly dibromide **234** (53 mg, 0.14 mmol, 47 %) as a white solid then isoaplysin **5** (42 mg, 0.14 mmol, 47 %) as a colourless oil.

Data for isoaplysin **5**:

Spectral and physical characteristics were consistent with literature values.[15]

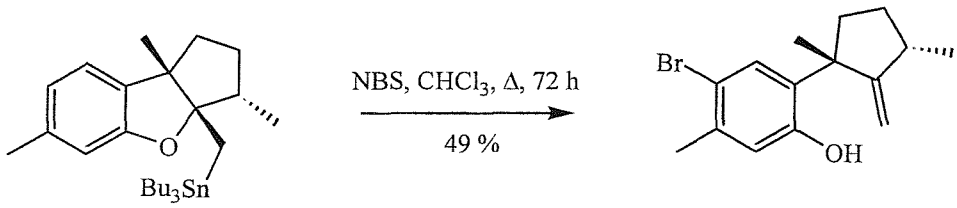
ν_{max}/cm^{-1} (neat)	2953s, 2931s, 2867m, 1622m, 1593s, 1499s, 1456s, 1424s, 1378m, 1271s, 1137m, 947s.
λ_{max}/nm (ε_{max}, MeOH)	284 (3750).
δ_H (300MHz, $CDCl_3$)	6.92 (1H, d, *J* 7.4 Hz, Ar*H*), 6.70 (1H, br. d, *J* 7.6 Hz with fine splitting, Ar*H*), 6.61 (1H, br. d, *J* 0.5 Hz, Ar*H*), 3.70 (1H, d, *J* 11.2 Hz, C*H*HBr), 3.59 (1H, d, *J* 11.2 Hz, CH*H*Br), 2.31 (3H, s, ArC*H*$_3$), 2.20 (1H, app. dq, *J* 13.4, 6.7 Hz, C*H*CH$_3$), 1.90 (1H, dd, *J* 12.0, 6.7 Hz, CCH$_3$C*H*H), 1.75 - 1.65 (2H, m), 1.53 (3H, s, C*H*$_3$), 1.30 - 1.12 (1H, obsc. m), 1.13 (3H, d, *J* 6.7 Hz, CHC*H*$_3$) ppm.

δ_C (75.5MHz, $CDCl_3$)	158.9 (0, Ar), 138.4 (0, Ar), 133.2 (0, Ar), 122.3 (1, Ar), 121.6 (1, Ar), 109.5 (1, Ar), 97.4 (0, O*C*), 55.7 (0, Ar*C*), 43.9 (1, *C*HCH_3), 42.8 (2), 34.8 (2, *C*H_2Br), 31.7 (2), 23.1 (3, *C*H_3), 21.7 (3, Ar*C*H_3), 14.0 (3, CH*C*H_3) ppm.
LRMS (APCI)	297 ($[MH]^+$, 90 %), 296 (M^+, 80 %), 295 ($[MH]^+$, 100 %), 294 (M^+, 65 %), 165 (30 %), 111 (35 %), 100 (65 %) amu.
HRMS (CI)	Found MH^+: 294.0620. $C_{15}H_{19}BrO$ requires MH^+: 294.0619.

Data for bromoisoaplysin **234**:

MP	126 - 128°C (methanol).
ν_{max}/cm^{-1} (solid)	2954m, 2931m, 2868w, 1581m, 1484s, 1394s, 1378s, 1267s, 1230m, 1140m, 1105w, 911s.
λ_{max}/nm (ε_{max}, MeOH)	292 (2470).
δ_H (400MHz, $CDCl_3$)	7.14 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 3.70 (1H, d, *J* 11.3 Hz, C*H*HBr), 3.56 (1H, d, *J* 11.3 Hz, CH*H*Br), 2.34 (3H, s, ArC*H*$_3$), 2.16 (1H, app. dq, *J* 12.7, 6.6 Hz, C*H*CH_3), 1.94 – 1.85 (1H, m), 1.77 – 1.58 (2H, m), 1.52 (3H, s, C*H*$_3$), 1.33 – 1.11 (1H, obsc. m), 1.13 (3H, d, *J* 6.7 Hz, CHC*H*$_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	158.2 (0, Ar), 137.5 (0, Ar), 135.9 (0, Ar), 126.3 (1, Ar), 115.0 (1, Ar), 111.0 (1, Ar), 98.1 (0, O*C*), 55.8 (0, Ar*C*), 43.9 (1, *C*HCH_3), 42.9 (2, *C*H_2C), 34.5 (2, *C*H_2Br), 31.6 (2, CH_2CH_2CH), 23.4 (3, *C*H_3), 22.9 (3, Ar*C*H_3), 13.8 (3, CH*C*H_3) ppm.
LRMS (APCI)	391 ($[M+NH_4]^+$, 5 %), 376 (M^+, 50 %), 374 (M^+, 100 %), 372 (M^+, 45 %), 296 ($[M-Br]^+$, 25 %), 294 ($[M-Br]^+$, 23 %) amu.
HRMS (CI)	Found M^+: 371.9726. $C_{15}H_{18}Br_2O$ requires M^+: 371.9724.

2-[rel-(1*R*,3*S*)-1,3-Dimethyl-2-methylenecyclopentyl]-5-methylphenol ((±)-Isolaurinterol) **6**[23]



$C_{27}H_{46}OSn$
Mol. Wt.: 505

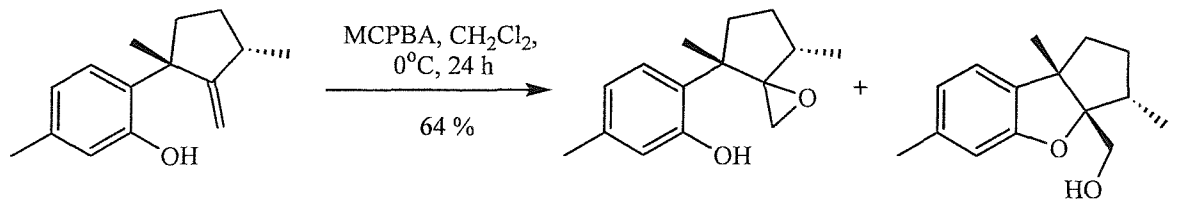
$C_{15}H_{19}BrO$
Mol. Wt.: 295

A solution of stannane **233** (0.150 g, 0.30 mmol) and *N*-bromosuccinimide (51 mg, 0.29 mmol) in chloroform (5 mL) was stirred at 0°C under argon for 18 h. The mixture was then heated at reflux. After 72 h the mixture was concentrated and purified by chromatography (silica, petroleum ether then 2 % ether in petroleum ether) to give firstly recovered **233** (28 mg, 0.05 mmol, 18 %) as a colourless oil then isolaurinterol **6** (43 mg, 0.146 mmol, 49 %) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[23]

ν_{max}/cm^{-1} (CH_2Cl_2)	3442m, 2958s, 2870m, 1644w, 1612w, 1390s, 1242m, 1165s, 903m, 669m.
λ_{max}/nm (ε_{max}, MeOH)	285 (2005).
δ_H (400MHz, $CDCl_3$)	7.45 (1H, s, Ar*H*), 6.74 (1H, s, Ar*H*), 5.55 (1H, s, ArO*H*), 5.10 (1H, d, *J* 2.0 Hz, =C*H*H), 4.94 (1H, d, *J* 2.0 Hz, =CH*H*), 2.85 (1H, m, C*H*CH_3), 2.31 (3H, s, ArCH_3), 2.20 (1H, ddd, *J* 13.0, 7.8, 6.8 Hz, C*H*HCH_2), 2.06 (1H, app. ddt, *J* 12.8, 8.8, 7.3 Hz, C*H*HCHCH_3), 1.60 (1H, dt, *J* 12.8, 7.1 Hz, CH*H*CH_2CH), 1.45 (3H, s, CH_3), 1.46 - 1.35 (1H, m), 1.21 (3H, d, *J* 7.1 Hz, CHCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	165.4 (0, =*C*), 153.4 (0, Ar), 137.6 (0, Ar), 133.2 (0, Ar), 131.7 (1, Ar), 120.9 (1, Ar), 116.0 (0, Ar), 107.4 (2, =CH_2), 50.3 (0, Ar*C*), 39.6 (2, CH_2), 38.1 (1, *C*HCH_3), 31.7 (2, CH_2), 28.2 (3, CH_3), 22.7 (3, ArCH_3), 21.5 (3, CHCH_3) ppm.
LRMS (APCI)	297 ([MH]$^+$, 35 %), 296 (M$^+$, 100 %), 294 (M$^+$, 90 %) amu.
HRMS (CI)	Found M$^+$: 294.0615. $C_{15}H_{19}BrO$ requires M$^+$: 294.0619.

[rel-(3*S*,3a*S*,8b*S*)-3,6,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methanol ((±)-Debromoaplysinol) **4**[15] and 2-[rel-(4*S*,7*S*)-4,7-dimethyl-1-oxaspiro[2.4]hept-4-yl]-5-methylphenol **235**



$C_{15}H_{20}O$
Mol. Wt.: 216

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

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

To a stirred solution of debromoisolaurinterol **7** (110 mg, 0.51 mmol) in dichloromethane (4 mL) at 0°C and under argon was added MCPBA (105 mg, 0.61 mmol). After 24 h, the solution was diluted with dichloromethane (20 mL), washed with sodium thiosulfate (20 mL) and sodium hydrogen carbonate (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow gum (90 mg). Purification by chromatography (silica, petrol then 5 % ether in petrol) gave firstly recovered **7** (11 mg, 0.05 mmol, 10 %) as a colourless oil, secondly oxirane **235** (14 mg, 0.06 mmol, 12 %) as a colourless oil and finally debromoaplysinol **4** (57 mg, 0.26 mmol, 52 %) as a faintly yellow solid. Recrystallisation from hexane furnished **4** as a white powder.

Data for debromoaplysinol **4**:

Spectral and physical characteristics were consistent with literature values.[15]

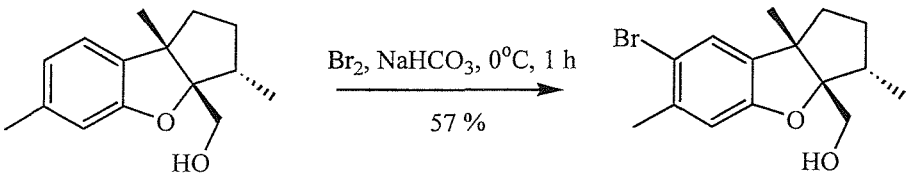
MP	103 - 105°C (hexane). Lit. 79 - 80°C (petrol).[15]
ν_{max}/cm^{-1} (solid)	3427m, 2947s, 2867m, 1620w, 1593s, 1500s, 1455s, 1268s, 1044m, 999s, 854m.
λ_{max}/nm (ε_{max}, MeOH)	284 (2600).
δ_H (300MHz, $CDCl_3$)	6.93 (1H, d, *J* 7.5 Hz, Ar*H*), 6.70 (1H, br. d, *J* 7.5 Hz, Ar*H*), 6.60 (1H, br. s, Ar*H*), 3.87 (1H, dd, *J* 12.1, 4.3 Hz, C*H*HOH), 3.74 (1H, dd, *J* 12.0, 8.6 Hz, CH*H*OH), 2.31 (3H, s, ArCH_3), 1.94 - 1.80 (2H, m), 1.76 (1H, dd, *J* 8.6, 4.3 Hz, CH_2OH), 1.71 - 1.60 (2H, m), 1.50 (3H, s, CH_3), 1.23 - 1.11 (1H, m), 1.11 (3H, d, *J* 6.8 Hz, CH_3) ppm.

δ_C (75.5MHz, $CDCl_3$)	159.3 (0, Ar), 138.2 (0, Ar), 133.7 (0, Ar), 122.6 (1, Ar), 121.6 (1, Ar), 109.4 (1, Ar), 99.6 (0, O*C*), 64.4 (2, *C*H_2OH), 54.6 (0, Ar*C*), 42.8 (1, *C*HCH$_3$), 42.7 (2, *C*H_2C), 32.0 (2, *C*H_2CH), 23.2 (3, *C*H_3C), 21.6 (3, Ar*C*H_3), 14.1 (3, CH*C*H_3) ppm.
LRMS (APCI)	233 ($[MH]^+$, 100 %), 232 (M^+, 30 %), 215 ($[M\text{-}OH]^+$, 30 %), 111 (20 %), 105 (15 %) amu.
HRMS (CI)	Found MH^+: 233.1536. $C_{15}H_{20}O_2$ requires MH^+: 233.1542.
CHN	Calculated: C, 77.55; H, 8.68. Found: C, 77.58; H, 8.63.

Data for oxirane **235**:

ν_{max}/cm^{-1} (neat)	3417s, 3268s, 2964s, 1730m, 1621m, 1503s, 1290s, 1121w, 933m, 803s.
δ_H (400MHz, $CDCl_3$)	7.71 (1H, s, ArO*H*), 7.08 (1H, d, *J* 7.8 Hz, Ar*H*), 6.72 (1H, br. s, Ar*H*), 6.67 (1H, br. d, *J* 7.8 Hz, Ar*H*), 2.93 (1H, d, *J* 4.3 Hz, OC*H*H), 2.73 (1H, d, *J* 4.3 Hz, OCH*H*), 2.61 (1H, m), 2.34 (1H, m, C*H*CH$_3$), 2.23 (3H, s, ArC*H*$_3$), 2.09 (1H, m), 1.63 (1H, m), 1.31 (3H, s, C*H*$_3$), 0.85 (1H, m), 0.74 (3H, d, *J* 7.0 Hz, CHC*H*$_3$) ppm.
δ_C (100MHz, $CDCl_3$)	158.8 (0, Ar), 138.4 (0, Ar), 127.1 (0, Ar), 127.0 (1, Ar), 121.4 (1, Ar), 120.5 (1, Ar), 106.8 (2, =*C*H_2), 73.6 (0, *C*O), 51.5 (2, *C*H_2O), 46.1 (0, Ar*C*), 36.3 (2, *C*H_2), 35.2 (1, *C*HCH$_3$), 30.0 (2, *C*H_2), 24.8 (3, *C*H$_3$), 20.7 (3, Ar*C*H$_3$), 15.8 (3, CH*C*H$_3$) ppm.
LRMS (APCI)	232 (M^+, 90 %), 201 (58 %), 159 (100 %) amu.
HRMS (CI)	Found $[M+NH_4]^+$: 250.1806. $C_{15}H_{20}O_2$ requires $[M+NH_4]^+$: 250.1807.

[rel-(3*S*,3a*S*,8b*S*)-7-Bromo-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3-yl]methanol ((±)-Aplysinol) **3**[1a]



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

$C_{15}H_{19}BrO_2$
Mol. Wt.: 311

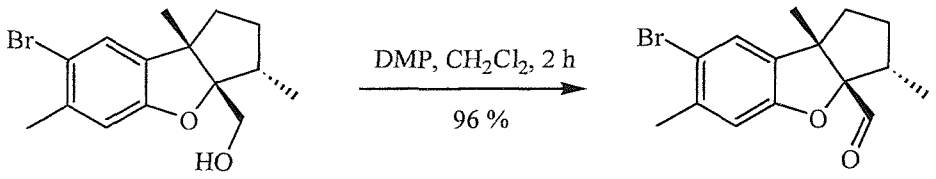
Following a modified procedure of Nemoto *et al.*[23] Thus, to a stirred solution of debromoaplysinol **4** (25 mg, 0.107 mmol) and sodium hydrogen carbonate (16 mg, 0.216 mmol) in chloroform (3 mL) at 0°C was added bromine (0.86 mL of a 0.125 M solution in chloroform, 0.107 mmol) dropwise over 2 min. After 1 h the mixture was concentrated *in vacuo* and purified by chromatography (silica, 10 % ether in petrol) to give firstly recovered **4** (6 mg, 0.26 mmol, 24 %) then aplysinol **3** (19 mg, 0.06 mmol, 57 %) as a white solid. Recrystallisation from carbon tetrachloride gave white needles.

Spectral and physical characteristics were consistent with literature values.[1,15]

MP	154 - 156°C (CCl_4). Lit. 158 - 160°C (CCl_4);[1a] lit. 151 – 153°C CCl_4).[15]
ν_{max}/cm^{-1} (solid)	3186m, 2957m, 2933m, 2871m, 1579m, 1375s, 1234s, 1156s, 1100s, 841s, 790m.
λ_{max}/nm (ε_{max}, MeOH)	292 (1680).
δ_H (400MHz, $CDCl_3$)	7.16 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), 3.85 (1H, dd, *J* 12.2, 2.5 Hz, C*H*HOH), 3.71 (1H, dd, *J* 12.2, 8.1 Hz, CH*H*OH), 2.33 (3H, s, ArCH_3), 1.92 - 1.78 (2H, m), 1.75 - 1.58 (3H, m), 1.47 (3H, s, CH_3), 1.20 - 1.10 (1H, m), 1.09 (3H, d, *J* 7.0 Hz, CHCH_3) ppm.
δ_C (100MHz, $CDCl_3$)	174.2 (0, Ar), 137.1 (0, Ar), 136.3 (0, Ar), 126.4 (1, Ar), 114.8 (0, Ar), 110.8 (1, Ar), 100.3 (0, *C*O), 64.0 (2, *C*H_2O), 54.7 (0, *C*), 42.5 (2), 42.4 (1, *C*HCH$_3$), 31.7 (2), 23.2 (3, Ar*C*H$_3$), 22.9 (3, *C*H$_3$), 13.9 (3, CH*C*H$_3$) ppm.

LRMS (APCI)	313 ($[MH]^+$, 40 %), 312 (M^+, 100 %, 310 (M^+, 98 %), 295 ($[M-OH]^+$, 55 %), 293 ($[M-OH]^+$, 50 %), 233 ($[MH-Br]^+$, 20 %) amu.
HRMS (CI)	Found M^+: 310.0569. $C_{15}H_{19}BrO_2$ requires M^+: 310.0568.

rel-(3*S*,3a*S*,8b*S*)-7-Bromo-3,6,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3a-carbaldehyde ((±)-Aplysinal) **236**[142]



$C_{15}H_{19}BrO_2$
Mol. Wt.: 311

$C_{15}H_{17}BrO_2$
Mol. Wt.: 309

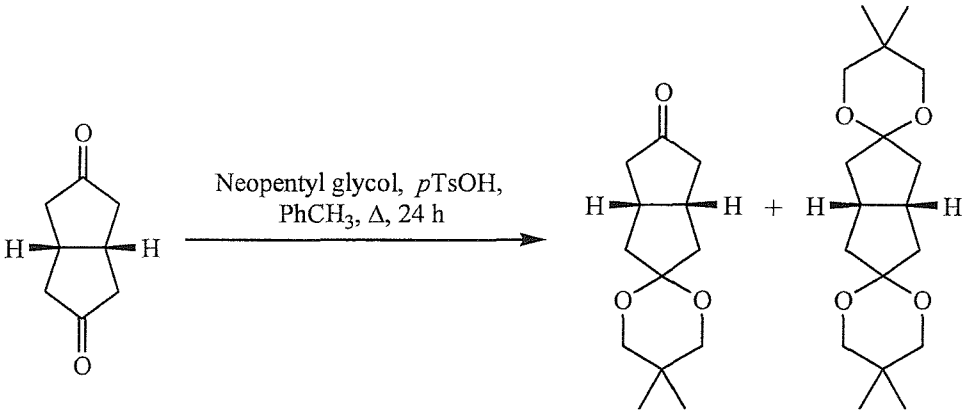
To a stirred solution of aplysinol **3** (4.0 mg, 0.013 mmol) in dichloromethane (1 mL) under argon and at ambient temperature was added Dess – Martin periodinane (10.9 mg, 0.026 mmol). After 2 h, the mixture was purified by chromatography (silica, 20 % ether in petroleum ether) to give **236** (3.8 mg, 0.0123 mmol, 96 %) as a colourless solid.

Spectral and physical characteristics were consistent with literature values.[142]

MP	87 - 89°C.
ν_{max}/cm^{-1} (solid)	2958m, 2930m, 1731vs, 1580w, 1483s, 1377s, 1264m, 1150s, 1099m, 941w.
δ_H (400MHz, $CDCl_3$)	9.69 (1H, s, C*H*O), 7.09 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*), 2.55 – 2.45 (1H, m, C*H*CH_3), 2.29 (3H, s, ArCH_3), 1.85 (1H, dd, *J* 11.5, 5.6 Hz), 1.73 - 1.63 (2H, m), 1.24 (3H, s, CH_3), 1.24 - 1.15 (1H, m), 0.95 (3H, d, *J* 6.8 Hz, $CHCH_3$) ppm.
δ_C (100MHz, $CDCl_3$)	204.4 (1, *C*HO), 160.2 (0, Ar), 139.5 (0, Ar), 135.8 (0, Ar), 127.9 (1, Ar), 117.1 (0, Ar), 113.1 (1, Ar), 105.5 (0, *C*CHO), 60.3 (0, *C*CH_3), 44.5 (2), 44.0 (1, *C*HCH_3), 33.2 (2), 25.6 (3, ArCH_3), 24.8 (3, *C*H_3C), 14.6 (3, CHCH_3)
LRMS (APCI)	310 ($[MH]^+$, 60 %), 281 ($[M\text{-}CHO]^+$, 70 %), 239 (100 %) amu.
HRMS (CI)	Found $[M+NH_4]^+$: 326.0747. $C_{15}H_{17}BrO_2$ requires $[M+NH_4]^+$: 326.0756.

7.3 EXPERIMENTAL FOR CHAPTER 3

5,5,5'',5''-Tetramethyl-dispiro[dioxane-2,5'-bicyclo[3.3.0]octane-2,2''-dioxane] **317** and rel-(3a*R*,6a*S*)-5',5'-dimethyl-5-oxo-spiro[bicyclo[3.3.0]octane-2,2'-dioxane] **318**



$C_8H_{10}O_2$
Mol. Wt.: 138

$C_{13}H_{20}O_3$
Mol. Wt.: 224

$C_{18}H_{30}O_4$
Mol. Wt.: 310

Prepared following the procedure of Piers *et al.*[61] Thus, a solution of dione **316** (12.4 g, 89.9 mmol), neopentyl glycol (9.36 g, 90.0 mmol) and *para*-toluene sulfonic acid (0.20 g, 1.05 mmol) in toluene (250 mL) was heated under azeotropic removal of water for 24 h. The resultant mixture was concentrated *in vacuo* then purified by chromatography to give firstly bisacetal **317** (6.50 g, 21.0 mmol, 23 %) as a flocculent white solid which was recrystallised from hexane to give colourless needles; secondly acetal **318** (8.65 g, 38.6 mmol, 43 %) as a colourless solid which was recrystallised from hexane to give shiny flakes, and finally recovered **316** (3.34 g, 24.2 mmol, 27 %) as a white solid.

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

Data for bisacetal **317**

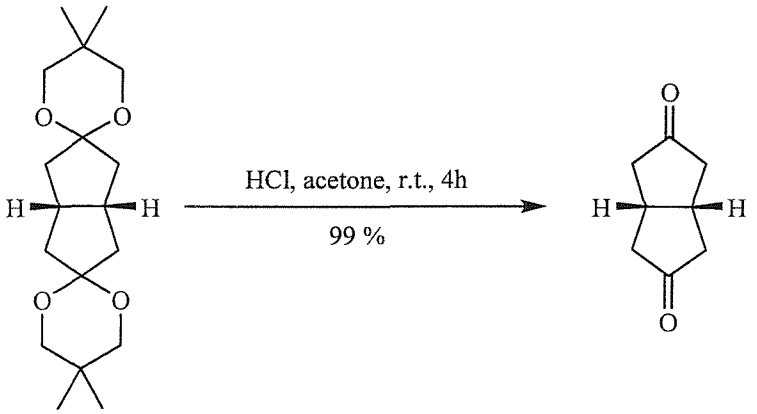
MP	138 - 140 °C (hexane). Lit. 140 - 142 °C (ethanol).[61]
ν_{max}/cm^{-1} (solid)	2947s, 2866m, 1468m, 1447m, 1303s, 1220m, 1098s, 1017s, 871s, 719m.
δ_H (300MHz, $CDCl_3$)	3.43 (4H, s, 2 × OC*H*$_2$), 3.42 (4H, s, 2 × OC*H*$_2$), 3.10 - 2.95 (2H, m, 2 × C*H*), 2.55 (4H, dd, *J* 19.5, 8.8 Hz, 4 × CH*H*), 2.12

	(4H, dd, *J* 19.5, 5.1 Hz, 4 × C*H*H), 0.95 (12H, app. s, 4 × C*H*$_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	110.1 (0, 2 × O*C*O), 72.6 (2, 2 × O*C*H$_2$), 71.8 (2, 2 × O*C*H$_2$), 40.0 (2, 4 × *C*H$_2$), 37.1 (1, 2 × *C*H), 30.2 (0, 2 × *C*(CH$_3$)$_2$), 22.7 (3, 4 × *C*H$_3$) ppm.
LRMS (CI)	311 ([MH]$^+$, 100 %), 267 (20 %), 225 (55 %) amu.

Data for monoacetal **318**

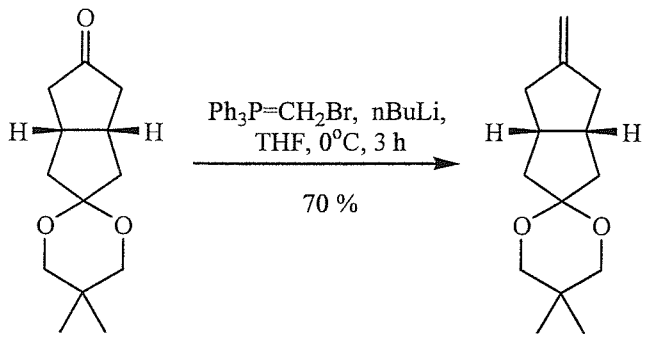
MP	46 - 48 °C (hexane). Lit. 48 °C (heptane).[61]
ν_{max}/cm^{-1} (solid)	2951m, 2864m, 1743s, 1467m, 1391m, 1326m, 1314m, 1113s, 1072m, 906m.
δ_H (300MHz, $CDCl_3$)	3.48 (4H, app. d, *J* 11.4 Hz, 2 × OC*H*$_2$), 2.90 – 2.79 (2H, m), 2.49 (2H, br. dd, *J* 19.2, 9.6 Hz), 2.30 (2H, dd, *J* 13.7, 8.6 Hz), 2.18 (2H, dd, *J* 19.2, 4.6 Hz), 1.83 (2H, dd, *J* 13.7, 5.2 Hz), 0.97 (6H, app. s, C(C*H*$_3$)$_2$) ppm.
δ_C (75.5MHz, $CDCl_3$)	220.2 (0, *C*=O), 109.6 (0, *C*(O)), 72.2 (2, 2 × O*C*H$_2$), 44.6 (2, 2 × *C*H$_2$), 41.2 (2, 2 × *C*H$_2$), 36.8 (1, 2 × *C*H), 30.2 (0, *C*(CH$_3$)$_2$), 22.5 (3, 2 × *C*H$_3$) ppm.
LRMS (CI)	225 ([MH]$^+$, 100 %) amu.

1,5-Oxabicyclo[3.3.0]octanedione **316**[60]



Bisacetal **317** (28.5 g, 91.9 mmol) was stirred at ambient temperature with dilute $HCl_{(aq)}$ (400 mL) and acetone for 4 h. Dichloromethane (100 mL) was added and the phases separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **316** (12.3 g, 89.1 mmol, 99 %) as a brown solid. This material was not purified any further and was recycled directly in the acetal protection.

rel-(3a*R*,6a*S*)-5',5'-Dimethyl-5-methylidene-spiro[perhydro-2-pentalene-2,2'-dioxane] **319**[61]



$C_{13}H_{20}O_3$
Mol. Wt.: 224

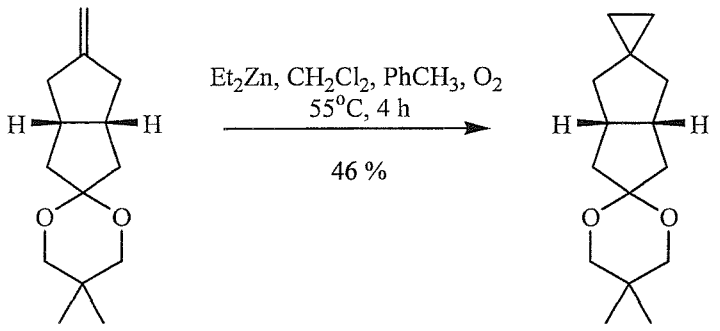
$C_{14}H_{22}O_2$
Mol. Wt.: 222

Prepared following the procedure of Piers *et al.*[61] Thus, to a stirred solution of methyltriphenylphosphonium bromide (2.53 g, 7.08 mmol) in THF (30 mL) at 0°C and under nitrogen was added butyllithium (6.4 mL of a 1.1 M solution in hexanes, 7.04 mmol) over 1 min. After 10 min a solution of ketone **318** (1.00 g, 4.46 mmol) in THF (20 mL) was added over 2 min. After 3 h, water (5 mL) was added then the mixture extracted with ether (3 × 10 mL). The combined organic phases were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by chromatography (silica, 10 % ether in petroleum ether) gave **319** (0.691 g, 3.11 mmol, 70 %) as a colourless oil.

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

ν_{max}/**cm^{-1} (neat)**	3073w, 2947s, 2853m, 1658w, 1470w, 1432w, 1432w, 1393w, 1329m, 1314w, 1112s, 1037m.
δ_H **(300MHz, $CDCl_3$)**	4.84 – 4.80 (2H, br. m, =CH_2), 3.50 (4H, app. d, *J* 12.7 Hz, 2 × OCH_2), 2.60 – 2.40 (4H, m), 2.31 (2H, br. dd, *J* 13.0, 7.9 Hz), 2.06 (2H, br. d, *J* 13.6 Hz), 1.50 (2H, br. dd, *J* 13.3, 6.8 Hz), 0.97 (6H, app. s, C(CH_3)$_2$) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	152.4 (0, =*C*), 109.8 (0, *C*(O)), 106.4 (2, =CH_2), 72.9 (2, OCH_2), 71.6 (2, OCH_2), 40.6 (2, 2 × CH_2), 39.8 (1, 2 × CH), 39.7 (2, 2 × CH_2), 30.2 (0, *C*(CH_3)$_2$), 22.7 (3, 2 × CH_3) ppm.
LRMS (CI)	223 ([MH]$^+$, 100 %), 136 (15 %) amu.

5'',5''-Dimethyl-dispiro[cyclopropane-1,5'-perhydro-2-pentalene-2',2''-dioxane] **320**



$C_{14}H_{22}O_2$
Mol. Wt.: 222

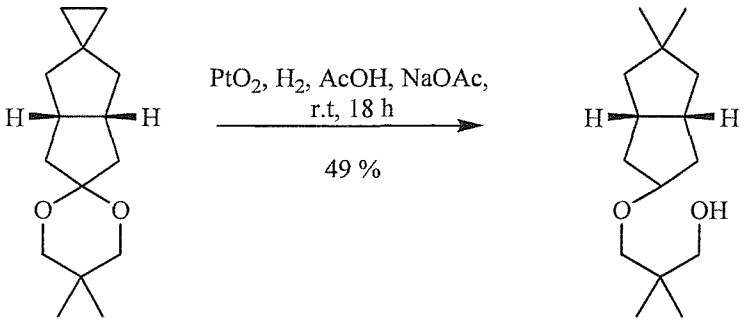
$C_{15}H_{24}O_2$
Mol. Wt.: 236

Prepared following the procedure of Piers *et al.*[61] To a well stirred solution of the alkene **319** (3.00 g, 13.5 mmol) in toluene (20 mL) at 60°C and under nitrogen was added solution of diethylzinc (18.4 mL of a 1.1 M solution in toluene, 20.2 mmol) followed by diiodomethane (5.42 g, 1.63 mL, 20.2 mmol). Through the cloudy suspension was bubbled dry air for 1 h. The mixture was then cooled over 1 h and poured onto 2M hydrochloric acid (50 mL). The phases were separated and the aqueous phase extracted with ether (3 × 20 mL). The combined organic phases were washed with sodium hydrogen carbonate (20 mL), water (20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 5 % ether in petroleum ether) gave **320** (1.48 g, 6.27 mmol, 46 %) as a colourless oil that crystallised on standing to a colourless solid. Recrystallisation from ethanol furnished colourless needles.

MP	53 - 55 °C (ethanol).
ν_{max}/cm^{-1} (solid)	2952m, 2851w, 1442w, 1395w, 1329w, 1113vs, 1096m, 1010m, 987m, 947w.
δ_H (400MHz, $CDCl_3$)	3.41 (4H, app. d, *J* 8.8 Hz, 2 × OC*H*$_2$), 2.56 – 2.48 (2H, m, 2 × C*H*), 2.30 – 2.23 (2H, m), 1.71 (2H, app. dd, *J* 12.8, 8.3 Hz), 1.55 (2H, app. dd, *J* 12.8, 7.7 Hz), 1.19 (2H, app. dd, *J* 12.8, 3.2 Hz), 0.89 (6H, app. s, 2 × C*H*$_3$), 0.44 – 0.40 (2H, m, cyclopropyl), 0.25 – 0.20 (2H, m, cyclopropyl) ppm.
δ_C (100MHz, $CDCl_3$)	109.3 (0, *O*CO), 71.8 (2, O*C*H$_2$), 70.4 (2, O*C*H$_2$), 41.1 (2, 2 × *C*H$_2$), 39.5 (2, 2 × *C*H$_2$), 39.4 (1, 2 × *C*H), 29.1 (0, *C*), 22.0 (0,

	cyclopropyl), 21.7 (3, *C*H$_3$), 21.5 (3, *C*H$_3$), 11.6 (2, cyclopropyl), 6.7 (2, cyclopropyl) ppm.
LRMS (CI)	237 ([MH]$^+$, 100 %) amu.
CHN	Found: C, 76.09; H, 10.32. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23.

rel-(3a*R*,6a*S*)-3-[(5,5-Dimethylperhydro-2-pentalenyl)oxy]-2,2-dimethyl-1-propanol **321**



$C_{15}H_{24}O_2$
Mol. Wt.: 236

$C_{15}H_{28}O_2$
Mol. Wt.: 240

Prepared following the procedure of Cossy *et al.*[123] Thus, to a stirred solution of the cyclopropane **320** (0.240 g, 1.02 mmol) and sodium acetate (89 mg, 1.06 mmol) in acetic acid (5 mL) at ambient temperature was added platinum oxide (23 mg, 0.102 mmol). The mixture was stirred under an atmosphere of hydrogen for 18 h. Water (10 mL) and ether (10 mL) were added, then sodium hydrogen carbonate was added portionwise until effervescence ceased. The mixture was filtered through celite, the phases separated, then the aqueous phase extracted with ether (3 × 10 mL). The combined organic phases were washed with water (2 × 5 mL), saturated aqueous sodium hydrogen carbonate (5 mL) then brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish **321** (120 mg, 0.50 mmol, 49 %) as a colourless oil.

ν_{max}/cm^{-1} (solid) 3500 – 3000br. m, 2949s, 2864m, 1465m, 1364m, 1278w, 1119s, 1090vs, 1047s, 906w.

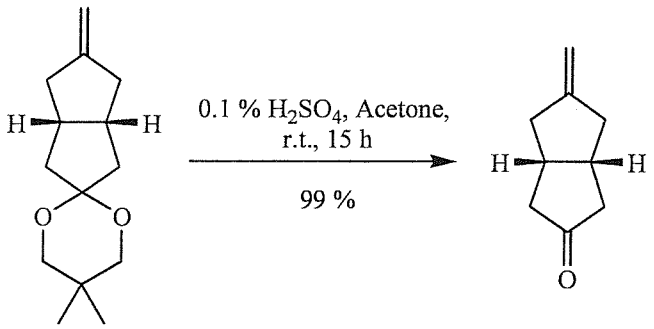
δ_H (400MHz, $CDCl_3$) 3.88 (1H, app. quintet, *J* 5.0 Hz, C*H*OCH_2), 3.46 (2H, s, CH_2OH), 3.27 (2H, s, OCH_2), 2.84 – 2.79 (1H, br. s, O*H*), 2.63 – 2.54 (2H, m), 1.95 – 1.85 (2H, m), 1.67 (2H, app. br. dd, *J* 12.3, 8.3 Hz), 1.55 (2H, app. dt, *J* 13.3, 4.5 Hz), 1.32 (2H, br. dd, *J* 12.0, 8.3 Hz), 1.06 (3H, s, CH_3CCH_2OH), 0.94 (6H, app. s, 2 × CH_3), 0.92 (3H, s, CH_3CCH_2OH) ppm.

δ_C (100MHz, $CDCl_3$) 84.2 (1, *C*HOCH_2), 78.3 (2, *C*H_2O), 71.8 (2, *C*H_2OH), 48.2 (2, *C*H_2), 48.1 (2, *C*H_2), 41.6 (0), 40.6 (3, *C*H_3CCH_2O), 40.4 (3, *C*H_3CCH_2O), 37.6 (2), 37.3 (2), 35.1 (0), 28.9 (1), 26.2 (1), 21.2 (3, 2 × CH_3) ppm.

LRMS (CI) 241 ($[MH]^+$, 22 %), 153 ($[M-C_5H_{11}O]^+$, 30 %), 137 ($[M-C_5H_{11}O_2]^+$, 80 %), 95 (68 %), 81 (100 %) amu.

HRMS (CI) Found MH^+: 241.2170. $C_{15}H_{28}O_2$ requires MH^+: 241.2168.

rel-(3a*R*,6a*S*)-5-Methyleneperhydro-2-pentalenone **322**[61]



$C_{14}H_{22}O_2$
Mol. Wt.: 222

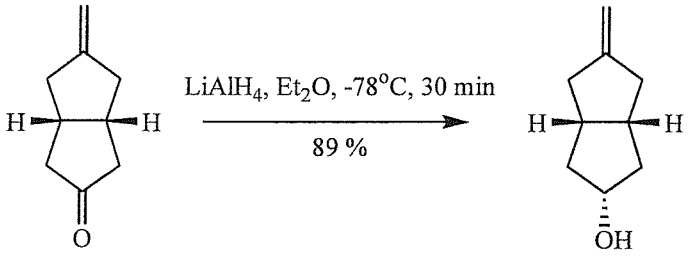
$C_9H_{12}O$
Mol. Wt.: 136

Prepared following the procedure of Piers *et al.*[61] Thus, a solution of the acetal **319** (5.90 g, 26.6 mmol) in acetone (70 mL) and 0.1 % sulfuric acid (70 mL) was stirred at ambient temperature for 15 h. Saturated aqueous sodium bicarbonate (30 mL) was added then the mixture was extracted with ether (3 × 75 mL). The combined organic phases were washed with brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by chromatography (silica, 20 % ether in petroleum ether) gave **322** (3.58 g, 26.3 mmol, 99 %) as a colourless oil.

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

ν_{max}/**cm^{-1} (neat)**	3071w, 2941m, 2835w, 1736vs, 1658w, 1434w, 1404m, 1168m, 1143m, 878s.
δ_H **(300MHz, $CDCl_3$)**	4.91 (2H, app. quintet, *J* 2.2 Hz, =C*H*$_2$), 2.85 - 2.73 (2H, m), 2.71 - 2.60 (2H, m), 2.42 (2H, dd, *J* 19.3, 8.6 Hz), 2.15 (2H, bd, *J* 16.6 Hz), 2.05 (2H, dd, *J* 19.3, 4.8 Hz) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	220.7 (0, *C*O), 151.3 (0, =*C*), 107.7 (2, =*C*H$_2$), 44.0 (2, 2 × *C*H$_2$), 40.1 (1, 2 × *C*H), 38.9 (2, 2 × *C*H$_2$) ppm.
LRMS (CI)	154 ([M+NH_4]$^+$, 42 %), 136 (M$^+$, 75 %), 93 (100 %) amu.

rel-(3a*R*,6a*S*)-5-Methyleneperhydro-2-pentalenol **323**[61]



$C_9H_{12}O$
Mol. Wt.: 136

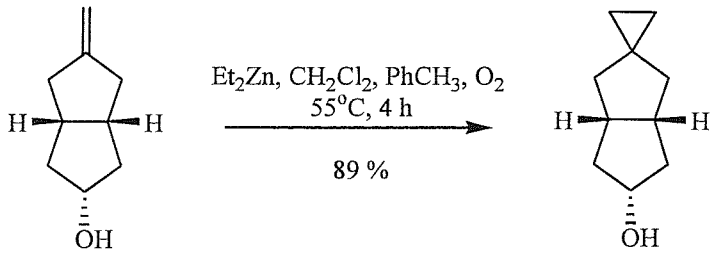
$C_9H_{14}O$
Mol. Wt.: 138

Prepared following the procedure of Piers *et al.*[61] Thus, to a stirred solution of lithium aluminium hydride (0.49 g, 12.9 mmol) in dry ether (80 mL) at –78°C and under nitrogen was added a solution of keto-alkene **322** (3.50 g, 25.7 mmol) in ether (40 mL) over 5 min. After 30 min, saturated aqueous ammonium chloride (10 mL) was added then the mixture warmed to ambient temperature. The mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by chromatography (silica, 10 – 50 % ether in petroleum ether) gave **323** (3.14 g, 22.8 mmol, 89 %) as a colourless oil.

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

ν_{max}/cm^{-1} (neat)	3350bs, 3071w, 2940s, 2856m, 1656m, 1431m, 1350m, 1086s, 1061s, 1026m, 877s.
δ_H (300MHz, $CDCl_3$)	4.85 (2H, s, =C*H*$_2$), 4.13 (1H, app. quintet, *J* 7.0 Hz, C*H*OH), 2.55 - 2.42 (4H, br. m), 2.20 - 2.00 (4H, m), 1.68 (1H, s, O*H*), 1.34 - 1.21 (2H, m) ppm.
δ_C (75.5MHz, $CDCl_3$)	152.6 (0, =*C*), 106.6 (2, =*C*H$_2$), 74.3 (1, *C*HOH), 42.8 (2, 2 × *C*H$_2$), 40.6 (2, 2 × *C*H$_2$), 40.3 (1, 2 × *C*H) ppm.
LRMS (CI)	138 (M^+, 16 %), 137 ($[M-H]^+$, 100 %), 119 (30 %) amu.

Spiro[cyclopropane-1,5'-perhydro-2-pentalenol] **324**[61]



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

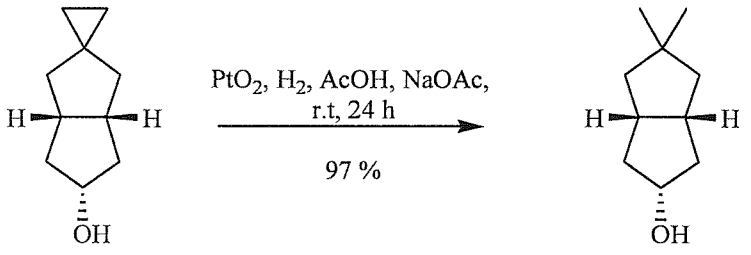
$C_{10}H_{16}O$
Mol. Wt.: 152

Prepared following the procedure of Piers *et al.*[61] Thus, to a well stirred solution of the alkene-alcohol **323** (3.00 g, 21.7 mmol) in toluene (25 mL) at 55°C and under argon was added solution of diethylzinc (29.6 mL of a 1.1 M solution in toluene, 32.6 mmol) followed by diiodomethane (8.73 g, 2.63 mL, 32.6 mmol). Through the cloudy suspension was bubbled dry air for 4 h. The mixture was then cooled and quenched with 2M hydrochloric acid (40 mL). The phases were separated and the aqueous phase extracted with ether (4 × 20 mL). The combined organic phases were washed with 2M hydrochloric acid (2 × 25 mL) and brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a green oil. Purification by chromatography (silica, 25 % ether in petroleum ether) gave **324** (2.69 g, 17.7 mmol, 82 %) as a faintly yellow oil.

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

ν_{max}/cm^{-1} (neat)	3306br. s, 3068w, 2931s, 2852m, 1460m, 1441m, 1349s, 1200w, 1091s, 880s.
δ_H (300MHz, $CDCl_3$)	4.12 (1H, app. tt, *J* 9.2, 6.1 Hz, C*H*OH), 2.50 - 2.40 (2H, m), 2.24 (1H, s, O*H*), 2.20 - 2.10 (2H, m), 1.78 (2H, app. dd, *J* 12.9, 8.3 Hz), 1.39 (2H, app. dt, *J* 12.3, 8.7 Hz), 1.25 (2H, app. dd, *J* 12.9, 3.1 Hz), 0.50 (2H, m, cyclopropane), 0.29 (2H, m, cyclopropane) ppm.
δ_C (75.5MHz, $CDCl_3$)	74.7 (1, *C*HOH), 42.8 (2, 2 × CH_2), 42.7 (2, 2 × CH_2), 40.9 (1, 2 × *C*H), 22.9 (0, *C*), 13.1 (2, cyclopropane), 7.3 (2, cyclopropane) ppm.
LRMS (CI)	153 ($[MH]^+$, 15 %), 135 ($[M\text{-}OH]^+$, 100 %), 91 (60 %) amu.

rel-(3a*R*,6a*S*)-5,5-Dimethylperhydro-2-pentalenol **325**



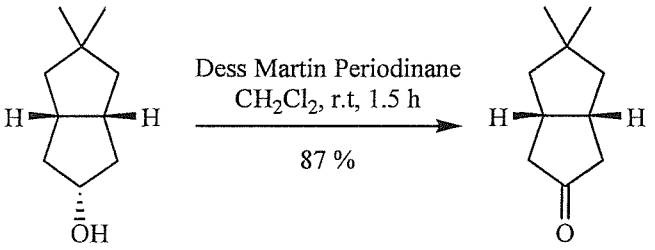
$C_{10}H_{16}O$
Mol. Wt.: 152

$C_{10}H_{18}O$
Mol. Wt.: 154

Prepared following the procedure of Cossy *et al.*[123] Thus, to a stirred solution of the cyclopropane **324** (2.40 g, 15.8 mmol) and sodium acetate (1.30 g, 15.8 mmol) in acetic acid (30 mL) at ambient temperature was added platinum oxide (269 mg, 1.19 mmol). The mixture was stirred under an atmosphere of hydrogen for 24 h. Water (50 mL) and ether (30 mL) were added, then sodium hydrogen carbonate was added portionwise until effervescence ceased. The mixture was filtered through celite then the phases were separated and the aqueous phase extracted with ether (4 × 25 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (2 × 30 mL) then brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish **325** (2.35 g, 15.3 mmol, 97 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3350br. s, 2948s, 2931s, 2858m, 1464m, 1364m, 1268w, 1110s, 1076m, 1023w.
δ_H (300MHz, $CDCl_3$)	4.26 (1H, app. tt, *J* 7.2, 5.7 Hz, C*H*OH), 2.60 - 2.49 (2H, m), 2.15 - 2.02 (2H, m), 1.74 - 1.65 (1H, br. dd), 1.54 (1H, s, O*H*), 1.40 - 1.25 (5H, m), 1.05 (3H, s, CH_3), 0.89 (3H, s, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	76.8 (1, *C*HOH), 49.5 (2, 2 × CH_2), 43.1 (0, *C*), 42.7 (2, 2 × CH_2), 41.1 (1, 2 × *C*H), 29.2 (3, CH_3), 27.3 (3, CH_3) ppm.
LRMS (CI)	136 ([M-H_2O]$^+$, 60 %), 121 ([M-H_2O-CH_3]$^+$, 40 %), 95 (100 %) amu.
HRMS (ES)	Found [MH-H_2O]$^+$: 137.1331. $C_{10}H_{18}O$ requires [MH-H_2O]$^+$: 137.1330.

rel-(3a*R*,6a*S*)-5,5-Dimethylperhydro-2-pentalenone **326**[137]



$C_{10}H_{18}O$
Mol. Wt.: 154

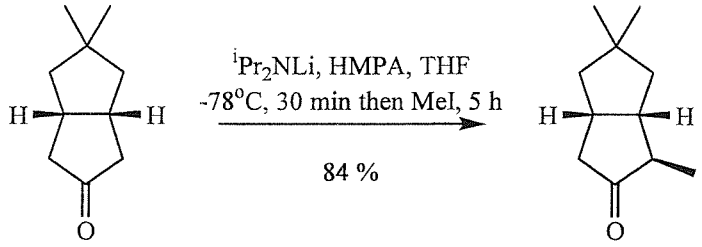
$C_{10}H_{16}O$
Mol. Wt.: 152

To a stirred suspension of Dess – Martin periodinane (1.70 g, 4.00 mmol) in dichloromethane (10 mL) at ambient temperature and under nitrogen was added a solution of alcohol **325** (0.522 g, 3.39 mmol) in dichloromethane (5 mL). After 1½ h, sodium hydrogen carbonate (2 g) was added. After 5 min the mixture was filtered through celite and the filtrate concentrated *in vacuo* to a white solid. Purification by chromatography (silica, 10 % ether in petroleum ether) gave **326** (0.441 g, 2.90 mmol, 87 %) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[137]

ν_{max}/cm^{-1} (neat)	2951s, 2935s, 2865w, 1736vs, 1462w, 1404w, 1366w, 1160m.
δ_H (300MHz, $CDCl_3$)	2.90 - 2.78 (2H, m), 2.56 - 2.44 (2H, m), 2.05 (2H, dd, *J* 19.1, 4.1 Hz), 1.84 (2H, dd, *J* 13.2, 7.7 Hz), 1.23 (2H, dd, *J* 12.9, 7.7 Hz), 1.08 (3H, s, CH_3), 0.98 (3H, s, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	221.8 (0, *C*O), 49.1 (2, 2 × CH_2), 45.0 (2, 2 × CH_2), 41.0 (0, *C*), 38.8 (1, 2 × *C*H), 29.9 (3, CH_3), 28.5 (3, CH_3) ppm.
LRMS (CI)	170 ($[M+H_2O]^+$, 60 %), 152 (M^+, 100 %), 137 ($[M-CH_3]^+$, 20 %), 109 (68 %) amu.
HRMS (ES)	Found $[MH]^+$: 153.1277. $C_{10}H_{16}O$ requires $[MH]^+$: 153.1279.

rel-(1*R*,3a*S*,6a*S*)-1,5,5-Trimethylperhydro-2-pentalenone **327**[138]



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

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

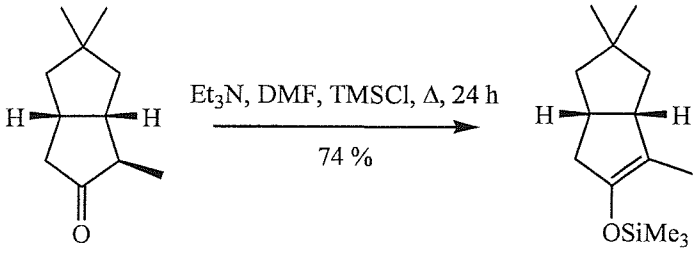
To a stirred solution of *N*,*N*-diisopropylamine (0.82 g, 1.06 mL, 8.15 mmol) in tetrahydrofuran (15 mL) at –78°C and under argon was added butyllithium (5.66 mL of a 1.44 M solution in THF, 8.15 mmol). After 2 min, HMPA (2 mL) was added. The mixture was warmed to –10°C then recooled to –88°C. A solution of ketone **326** (1.18 g, 7.76 mmol) in THF (20 mL) was added over 5 min. After 30 min, a solution of methyl iodide (1.32 g, 0.58 mL, 9.32 mmol) in THF (20 mL) was added over 2 min. After 6 h, the reaction was warmed to ambient temperature over 15 h then quenched by addition of saturated aqueous ammonium chloride (20 mL). The phases were separated and the aqueous phase extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 2 ½ % ether in petroleum ether) gave **327** (1.08 g, 6.51 mmol, 84 %) as a colourless oil.

Spectral and physical characteristics were consistent with literature values.[66,138]

ν_{max}/cm^{-1} (neat)	2952m, 2931m, 2866w, 1738vs, 1456m, 1408w, 1367m, 1168m, 913w, 734w.
δ_H (300MHz, $CDCl_3$)	2.83 - 2.68 (1H, m), 2.46 (1H, dd, *J* 19.1, 9.4 Hz), 2.28 (1H, qd, *J* 8.4, 6.3 Hz), 2.15 (1H, ddd, *J* 19.1, 4.4, 1.5 Hz), 2.04 - 1.93 (1H, m), 1.90 (1H, ddd, *J* 13.2, 8.1, 1.5 Hz), 1.81 (1H, ddd, *J* 12.5, 7.5, 1.5 Hz), 1.34 (1H, dd, *J* 13.2, 6.3 Hz), 1.26 (1H, dd, *J* 12.5, 10.8 Hz), 1.09 (3H, s, C*H*$_3$), 1.05 (3H, d, *J* 7.2 Hz, CHC*H*$_3$), 0.99 (3H, s, C*H*$_3$) ppm.

δ_C **(75.5MHz, $CDCl_3$)**	222.4 (0, *C*O), 50.6 (1, *C*HCH_3), 49.0 (2, *C*H_2CO), 48.0 (1), 47.9 (2), 43.2 (2), 41.4 (0), 36.9 (1), 30.3 (3, *C*H_3), 29.2 (3, *C*H_3), 14.5 (3, CH*C*H_3) ppm.
LRMS (CI)	184 ($[M+NH_4]^+$, 100 %), 166 (M^+, 98 %) amu.
HRMS (ES)	Found $[MH]^+$: 167.1436. $C_{11}H_{18}O$ requires $[MH]^+$: 167.1436.

rel-(3a*S*,6a*S*)-3,5,5-Trimethyl-1,3a,4,5,6,6a-hexahydro-2-pentalenyl-(1,1,1-trimethylsilyl)ether **328**[124]



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

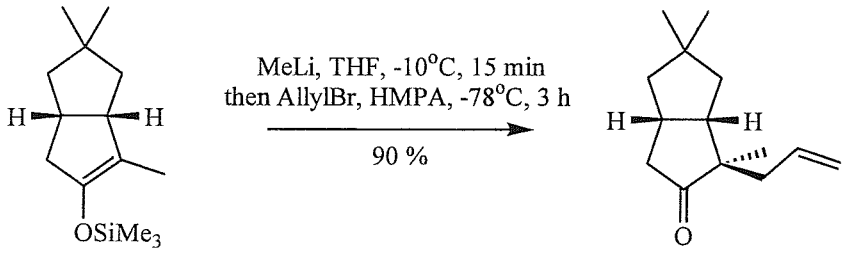
$C_{14}H_{26}OSi$
Mol. Wt.: 238

To a stirred solution of the ketone **327** (0.350 g, 2.11 mmol) in dry DMF (4 mL) was added triethylamine (1.28 g, 1.76 mL, 12.7 mmol) and trimethylsilyl chloride (0.64 g, 0.74 mL, 5.91 mmol) under argon. The solution was stirred at reflux for 24 h then cooled and filtered. The crystals were washed with ether (20 mL), then the combined organic phases were washed successively with saturated aqueous sodium hydrogen carbonate (10 mL), 5 % hydrochloric acid (4 mL), saturated aqueous sodium hydrogen carbonate (10 mL) and brine (10 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 20 % ether in petroleum ether) gave **328** (0.374 g, 1.57 mmol, 74 %) as a yellow oil.

Spectroscopic and physical characteristics were in accordance with literature values.[124]

ν_{max}/cm^{-1} (neat)	2956m, 2926m, 2871w, 2851w, 1689m, 1253m, 1208m, 843w.
δ_H (300MHz, $CDCl_3$)	2.63 - 2.50 (2H, m), 2.05 - 1.90 (1H, m), 1.75 - 1.55 (2H, m), 1.47 (3H, s, =CCH_3), 1.10 - 0.80 (3H, m), 1.00 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.18 (9H, s, Si(CH_3)$_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	142.5, 116.5, 49.2, 49.0, 45.7, 39.7, 39.5, 35.8, 28.4, 26.7, 10.0, 0.0 (3 × Si(CH_3)$_3$) ppm.
LRMS (CI)	239 ([MH]$^+$, 100 %), 181 (60 %), 165 ([M-SiMe$_3$]$^+$, 25 %), 90 (34 %), 73 (80 %) amu.

rel-(1*R*,3a*S*,6a*S*)-1-Allyl-1,5,5-trimethylperhydro-2-pentalenone **315**[125]



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

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

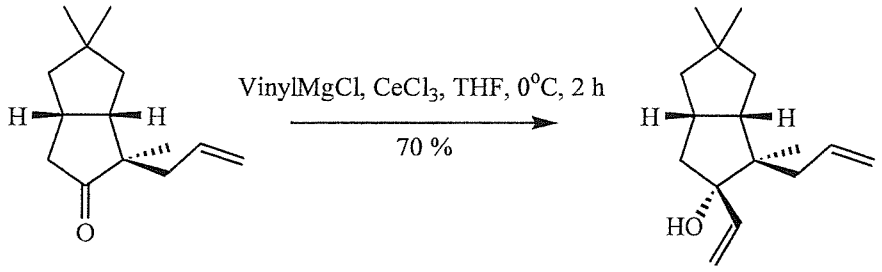
To a stirred solution of silyl enol ether **328** (0.350 g, 1.47 mmol) in THF (10 mL) at -10°C and under argon was added methyllithium (0.97 mL of a 1.6 M solution in THF, 1.55 mmol). After 15 min, HMPA (1 mL) was added, the mixture cooled to -78°C, then allyl bromide (0.186 g, 0.13 mL, 1.54 mmol) added over 30 s. After 3 h, the mixture was warmed to ambient temperature over 1 h then quenched with saturated aqueous ammonium chloride (10 mL). The phases were separated and the aqueous phase extracted with ether (2 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 2 % ether in petroleum ether) gave **315** (0.273 g, 1.33 mmol, 90 %) as a colourless oil.

Spectroscopic and physical characteristics were in accordance with literature values.[125]

ν_{max}/cm^{-1} (neat)	2932s, 2865m, 1733vs, 1639w, 1459m, 1409m, 1374m, 1366w, 994m, 913s.
δ_H (300MHz, $CDCl_3$)	5.70 (1H, ddt, *J* 17.3, 9.9, 7.4 Hz, C*H*=), 5.10 - 4.99 (2H, m, =CH_2), 2.80 - 2.55 (3H, m), 2.11 (2H, br. m), 1.95 - 1.85 (2H, br. m), 1.44 (1H, ddd, *J* 12.5, 6.8, 1.5 Hz), 1.20 (1H, dd, *J* 13.2, 4.6 Hz), 1.11 (1H, t, *J* 12.5 Hz), 1.06 (3H, s, CH_3), 0.97 (3H, s, CH_3), 0.95 (3H, s, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	222.8 (0, *C*O), 133.6 (1, *C*H=), 118.4 (2, =*C*H_2), 52.7 (0), 50.2 (1), 49.1 (2, *C*H_2CH=), 44.7 (2), 43.8 (2), 43.7 (2), 40.4 (0), 34.3 (1), 30.2 (3, C(*C*H_3)$_2$), 28.7 (3, C(*C*H_3)$_2$), 17.5 (3, *C*H_3) ppm.
LRMS (CI)	207 ([MH]$^+$, 100 %), 206 (M$^+$, 70 %), 149 (50 %), 123 (100 %) amu.

HRMS (ES) Found $[MH]^+$: 207.1747. $C_{14}H_{22}O$ requires $[MH]^+$: 207.1749.

rel-(1*R*,2*S*,3a*S*,6a*S*)-1-Allyl-1,5,5-trimethyl-2-vinylperhydro-2-pentalenol **314**



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

$C_{16}H_{26}O$
Mol. Wt.: 234

Cerium trichloride heptahydrate (3.36 g, 9.56 mmol) was warmed to 140°C under high vacuum with stirring for 2½ h. The white powder was cooled under argon, suspended in THF (20 mL), and sonicated for 30 min. After cooling to 0°C a solution of ketone **315** (0.197 g, 0.956 mmol) in THF (5 mL) was added followed by vinylmagnesium chloride (5.56 mL of a 1.72 M solution in THF, 9.56 mmol). After 2 h the mixture was warmed to ambient temperature over 30 min. After 16 h the mixture was poured onto 2 M HCl (50 mL) then extracted with ether (3 × 15 mL). The combined organic phases were washed with brine (25 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 4 % ether in petroleum ether) gave **314** (0.157 g, 0.671 mmol, 70 %) as a colourless oil.

^{1}H NMR showed the presence of ~5 % of an isomeric product.

ν_{max}/cm^{-1} (neat) 3600 – 3400br. w, 2950m, 2864w, 1637w, 1463w, 1376w, 997m, 913s.

δ_H (300MHz, $CDCl_3$) 6.03 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=), 5.80 (1H, ddt, *J* 17.7, 10.3, 7.4 Hz, CH_2CH=), 5.25 (1H, dd, *J* 17.4, 1.6 Hz, =C*H*H), 5.11 (1H, dd, *J* 10.8, 1.6 Hz, =CH*H*), 5.05 - 4.93 (2H, m, CH_2CH=CH_2), 2.62 - 2.50 (2H, m), 2.11 (1H, app. dd, *J* 13.4, 9.3 Hz), 2.00 – 1.85 (2H, m), 1.74 – 1.62 (2H, m), 1.53 (1H, dd, *J* 13.4, 3.8 Hz), 1.39 – 1.25 (3H, m), 1.05 (3H, s, CH_3), 0.90 (6H, app. s, C(CH_3)$_2$) ppm.

δ_C (100MHz, $CDCl_3$) 144.0 (1, *C*H=), 138.3 (1, *C*H=), 119.0 (2, =CH_2), 114.8 (2, =CH_2), 89.7 (0, *C*OH), 52.8 (1, *C*H), 51.7 (2, *C*H_2CH=), 51.5

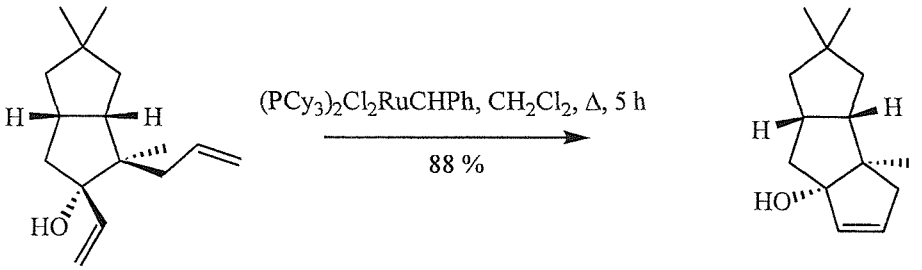
(0, *C*), 46.6 (2), 45.8 (2), 45.4 (2), 44.1 (0), 41.1 (1, *C*H), 31.1 (3, C(*C*H$_3$)$_2$), 29.0 (3, C(*C*H$_3$)$_2$), 18.0 (3, *C*H$_3$) ppm.

LRMS (CI) 235 ([MH]$^+$, 10 %), 217 ([MH-H$_2$O]$^+$, 76 %), 177 (100 %) amu.

HRMS (ES) Found [M+Na]$^+$: 257.1879. $C_{16}H_{26}O$ requires [M+Na]$^+$: 257.1881.

Found [M+H-H$_2$O]$^+$: 217.1955. $C_{16}H_{26}O$ requires [M+H-H$_2$O]$^+$: 217.1956.

rel-(3a*S*,3b*R*,6a*S*,7a*S*)-2,2,3b-Trimethyl-2,3,3a,3b,4,6a,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalen-6a-ol **313**



$C_{16}H_{26}O$
Mol. Wt.: 234

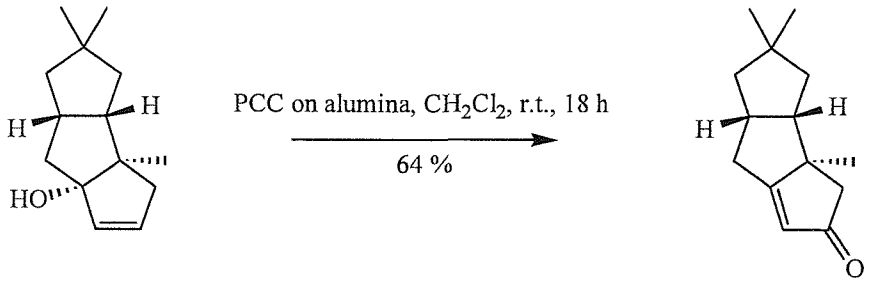
$C_{14}H_{22}O$
Mol. Wt.: 206

A solution of diene **314** (0.160 g, 0.684 mmol) in dichloromethane (10 mL) was heated at 40°C with Grubbs' catalyst (31.6 mg, 0.038 mmol) under argon for 5 h. The mixture was concentrated *in vacuo* and purified by chromatography (silica, 5 – 20 % ether in petroleum ether) to give **313** (0.116 g, 0.604 mmol, 88 %) as a faintly grey oil.

^{1}H NMR showed this material contained ~5 % of an unknown isomer.

ν_{max}/cm^{-1} (neat)	3500 – 3300 br. m, 2933m, 2863w, 1463w, 1363m, 1277w, 1077s, 1009vs, 770m, 732s.
δ_H (300MHz, $CDCl_3$)	5.79 (1H, app. dt, *J* 5.6, 2.4 Hz, CH=C*H*CH_2), 5.58 (1H, app. dt, *J* 5.6, 2.1 Hz, C*H*=$CHCH_2$), 2.29 (2H, app. t, *J* 2.2 Hz, C*H*$_2$CH=), 2.32 – 2.12 (3H, m), 1.65 – 1.50 (2H, m), 1.50 – 1.32 (3H, m), 1.19 (1H, dd, *J* 12.8, 4.6 Hz), 1.08 (3H, s, C(C*H*$_3$)$_2$), 0.99 (3H, s, C(C*H*$_3$)$_2$), 0.90 (3H, s, C*H*$_3$) ppm.
δ_C (75.5MHz, $CDCl_3$)	136.6 (1, *C*H=), 132.8 (1, =*C*H), 95.1 (0, *C*OH), 56.6 (1, *C*H), 50.2 (2), 50.1 (0), 47.3 (2), 45.6 (2), 42.9 (2), 41.4 (0), 40.2 (1), 30.8 (3, C(*C*H$_3$)$_2$), 29.1 (3, C(*C*H$_3$)$_2$), 19.5 (3, *C*H$_3$) ppm.
LRMS (CI)	206 (M^+, 22 %), 189 ($[MH-H_2O]^+$, 12 %), 96 (100 %) amu.
HRMS (CI)	Found $[M+NH_4-H_2O]^+$: 206.1914. $C_{14}H_{22}O$ requires $[M+NH_4-H_2O]^+$: 206.1909.

rel-(3a*S*,3b*R*,7a*S*)-2,2,3b-Trimethyl-2,3,3a,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalen-5-one **329**



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

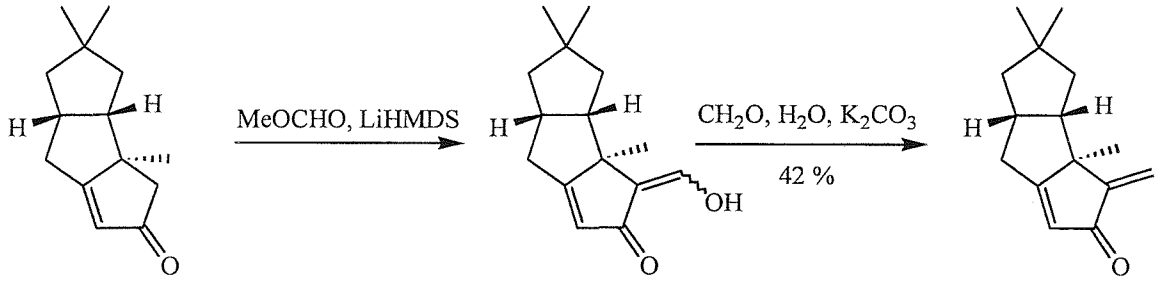
$C_{14}H_{20}O$
Mol. Wt.: 204

Thus, to a solution of the allyl alcohol **313** (49 mg, 0.238 mmol) in dichloromethane (5 mL) was added PCC on alumina (0.55 g of ca. 20 % wt on alumina, 0.510 mmol) at ambient temperature under argon. After 24 h the mixture was purified by chromatography (silica, 20 – 50 % ether in petroleum ether) to give **329** (31 mg, 0.152 mmol, 64 %) as a colourless oil.

^{1}H NMR showed this material contained ~5 % of an unknown isomer inseparable by GC-MS.

ν_{max}/cm^{-1} (neat)	2951w, 2866w, 1708vs, 1633m, 1465w, 1366w, 1223w, 1151w, 909w, 843w.
δ_H (300MHz, $CDCl_3$)	5.68 (1H, d, *J* 2.1 Hz, C*H*=), 2.85 – 2.74 (2H, m), 2.44 – 2.20 (2H, m), 2.26 (2H, app. d, *J* 2.1 Hz, CH_2CO), 1.79 (1H, ddd, *J* 12.2, 7.2, 1.6 Hz, C*H*), 1.56 – 1.40 (2H, m), 1.25 – 1.15 (1H, m), 1.10 (3H, s, C(CH_3)$_2$), 1.08 (3H, s, C(CH_3)$_2$), 0.95 (3H, s, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	211.1 (0, *C*O), 196.0 (0, *C*=), 122.2 (1, =*C*H), 52.9 (2, *C*H$_2$CO), 50.7 (1, *C*H), 49.7 (2), 49.5 (0), 44.6 (1), 44.0 (0), 40.5 (2), 33.1 (2), 29.2 (3, C(*C*H$_3$)$_2$), 27.6 (3, C(*C*H$_3$)$_2$), 24.8 (3, *C*H$_3$) ppm.
LRMS (CI)	205 ([MH]$^+$, 100 %) amu.
HRMS (ES)	Found [MH]$^+$: 205.1590. $C_{14}H_{20}O$ requires [MH]$^+$: 205.1592.

rel-(3a*S*,3b*R*,7a*S*)-2,2,3b-Trimethyl-4-methylene-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalen-5-one **311**



$C_{14}H_{20}O$
Mol. Wt.: 204

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

$C_{15}H_{20}O$
Mol. Wt.: 216

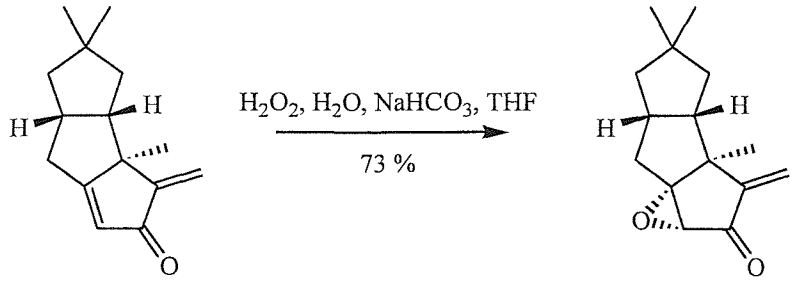
Prepared using the procedure of Greene *et al.*[64] Thus, enone **329** (29 mg, 0.142 mmol) in THF (2 mL) at –78°C and under argon was treated with LiHMDS (0.284 mL of a 1 M solution in THF, 0.284 mmol). The reaction was warmed to –35°C over 1 h, then methyl formate (34 mg, 0.035 mL, 0.568 mmol) was added. The mixture was warmed to ambient temperature over 45 min then cooled to –78°C and treated with a second portion of LiHMDS (0.66 mL of a 1 M solution in THF, 0.66 mmol). After warming to –35°C over 1 h, methyl formate (0.345 g, 0.354 mL, 5.76 mmol) was added and the mixture warmed to ambient temperature. 10 % aqueous HCl (5 mL) was added and the mixture extracted into dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. This crude oil was treated to the same set of conditions for a second time, then the resultant oil was stirred in acetone (5 mL) with potassium carbonate (0.119 g, 0.86 mmol) and aqueous formaldehyde (0.30 mL of a 37 % wt solution in water, 3.21 mmol). After 14 h, aqueous 2M HCl (5 mL) was added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 10 – 20 % ether in petroleum ether) gave firstly dienone **311** (13 mg, 0.060 mmol, 42 %) then recovered **329** (5.6 mg, 0.027 mmol, 19 %) each as colourless oils.

^{1}H NMR showed **311** contained ~ 10 % unknown impurity, inseparable by GC-MS.

ν_{max}/cm^{-1} (neat) 2951m, 1702vs, 1623s, 1464w, 1368w, 1255w, 1153w, 932w, 859m, 782w.

δ_H (400MHz, $CDCl_3$)	5.82 (1H, br. d, *J* 1.8 Hz, =C*H*), 5.80 (1H, s, =C*H*H), 5.07 (1H, s, =CH*H*), 2.77 – 2.65 (2H, m), 2.34 (1H, dt, *J* 10.8, 8.8 Hz, C*H*), 2.28 – 2.17 (1H, m), 1.74 (1H, ddd, *J* 12.3, 7.5, 1.3 Hz), 1.55 – 1.45 (2H, m), 1.18 (1H, t, *J* 11.8 Hz), 1.09 (3H, s, C(C*H*$_3$)$_2$), 1.06 (3H, s, C(C*H*$_3$)$_2$), 0.88 (3H, s, C*H*$_3$) ppm.
δ_C (100MHz, $CDCl_3$)	198.3 (0, *C*O), 190.3 (0, *C*=), 154.6 (0, *C*=), 123.6 (1, =*C*H), 113.3 (2, =*C*H$_2$), 52.2 (0, *C*), 50.1 (2), 48.6 (1, *C*H), 45.3 (1, *C*H), 44.5 (0, *C*), 40.6 (2), 33.1 (2), 29.4 (3, C(*C*H$_3$)$_2$), 27.8 (3, C(*C*H$_3$)$_2$), 23.9 (3, *C*H$_3$) ppm.
LRMS (CI)	217 ([MH]$^+$, 26 %), 95 (100 %) amu.
HRMS (CI)	Found MH$^+$: 217.1591. $C_{15}H_{20}O$ requires MH$^+$: 217.1592.

rel-(1*R*,3a*S*,3b*S*,6a*S*,7a*S*)-3a,5,5-Trimethyl-3-ethyleneperhydrocyclopenta[4,5]pentaleno[1,6a-*b*]oxiren-2-one (Desoxyhypnophilin) **312**[57]



$C_{15}H_{20}O$
Mol. Wt.: 216

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

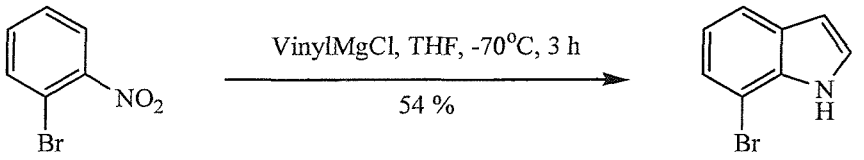
Prepared following the procedure of Van Hijfte *et al.*[126] Thus, a solution of **311** (8.0 mg, 0.037 mmol) in THF (1 mL) and water (1 mL), with sodium hydrogen carbonate (50 mg) and 30 % H_2O_2 (0.1 mL) was stirred at 4°C for 15 h. Ether (20 mL) was added then the phases separated. The organic phase was dried ($MgSO_4$), filtered and concentrated to a colourless oil. Purification by chromatography (silica, 10 % ether in petroleum ether) gave firstly **312** (6.2 mg, 0.027 mmol, 73 %) then recovered **311** (1.6 mg, 0.0074 mmol, 20 %) each as colourless oils.

ν_{max}/cm^{-1} (neat)	2951m, 2866w, 1728vs, 1642w, 1465w, 1417w, 1258w, 941w, 906m, 862w, 730s.
δ_H (400MHz, $CDCl_3$)	6.06 (1H, s, =C*H*H), 5.27 (1H, s, =CH*H*), 3.44 (1H, s, C*H*CO), 2.74 (1H, dtd, *J* 16.3, 11.04, 8.53 Hz), 2.40 (1H, dt, *J* 11.3, 9.3 Hz, C*H*), 2.00 (2H, d, *J* 8.5 Hz), 1.81 (1H, ddd, *J* 12.3, 7.5, 1.5 Hz), 1.55 (1H, dd, *J* 12.8, 8.6 Hz), 1.49 (1H, ddd, *J* 12.8, 8.8, 1.5 Hz), 1.26 – 1.16 (1H, m), 1.17 (3H, s, C(C*H*$_3$)$_2$), 1.13 (3H, s, C(C*H*$_3$)$_2$), 0.93 (3H, s, C*H*$_3$) ppm.
δ_C (100MHz, $CDCl_3$)	198.3 (0, *C*O), 153.4 (0, *C*=), 120.1 (2, =*C*H$_2$), 76.7 (0, obscured by $CHCl_3$), 61.2 (1, *C*HCO), 50.2 (1), 49.9 (2), 46.6 (0), 42.6 (0), 40.5 (2), 39.5 (1), 30.5 (2), 29.3 (3, C(*C*H$_3$)$_2$), 27.6 (3, C(*C*H$_3$)$_2$), 17.9 (3, *C*H$_3$) ppm.
LRMS (CI)	233 ([MH]$^+$, 1 %), 217 (32 %), 95 (100 %).

HRMS (CI) Found $[M+NH_4]^+$: 250.1810. $C_{15}H_{20}O_2$ requires $[M+NH_4]^+$: 250.1807.

7.4 EXPERIMENTAL FOR CHAPTER 4

7-Bromoindole **409**[127]



$C_6H_4BrNO_2$
Mol. Wt.: 202

C_8H_6BrN
Mol. Wt.: 196

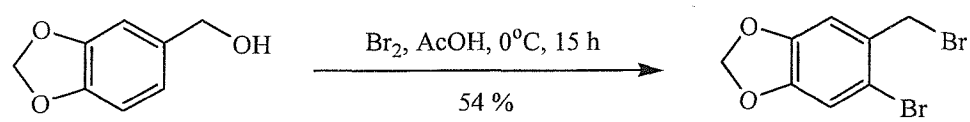
Prepared following the procedure of Bartoli *et al.*[128] Thus, to a stirred solution of 2–bromonitrobenzene **437** (10.0 g, 49.5 mmol) in THF (150 mL) cooled to –70°C and under nitrogen was added vinylmagnesium chloride (86.3 mL of a 1.72 M solution in THF, 148.5 mmol) over 30 min. After 3 h the mixture was warmed to ambient temperature and poured onto saturated aqueous ammonium chloride (300 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with brine (200 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil (13.9 g). Purification by chromatography (silica, petroleum ether) gave a yellow solid (5.4 g) which was recrystallised from pentane to give **409** (5.10 g, 26.0 mmol, 53 %) as colourless crystals.

Spectral and physical characteristics were consistent with literature values.[127]

MP	42 - 44°C (pentane). Lit. 42 - 43°C (no solvent given);[127] lit. 43–44°C.[128]
ν_{max}/cm^{-1} (solid)	3398s, 1671w, 1560m, 1533w, 1426m, 1329s, 1189s, 1133s, 1094s, 919s.
λ_{max}/nm (ε_{max}, MeOH)	273 (4400).
δ_H (300MHz, $CDCl_3$)	8.34 (1H, br. s, N*H*), 7.62 (1H, d, *J* 7.9 Hz, Ar*H*), 7.39 (1H, d, *J* 7.6 Hz, Ar*H*), 7.27 (1H, app. t, *J* 2.8 Hz, NC*H*), 7.05 (1H, app. t, *J* 7.8 Hz, Ar*H*), 6.66 (1H, dd, *J* 2.8, 2.0 Hz, NCHC*H*) ppm.
δ_C (75.5MHz, $CDCl_3$)	134.7 (0), 129.2 (0), 124.9 (1), 124.5 (1), 121.2 (1), 120.1 (1), 104.8 (0), 104.0 (1) ppm.

LRMS (APCI) 198 ([M{^{81}Br}H]$^{+}$, 20 %), 197 ([M{^{81}Br}]$^{+}$, 100 %), 195 ([M{^{79}Br}]$^{+}$, 80 %) amu.

5-Bromo-6-(bromomethyl)-1,3-benzodioxole **439**[129]



$C_8H_8O_3$
Mol. Wt.: 152

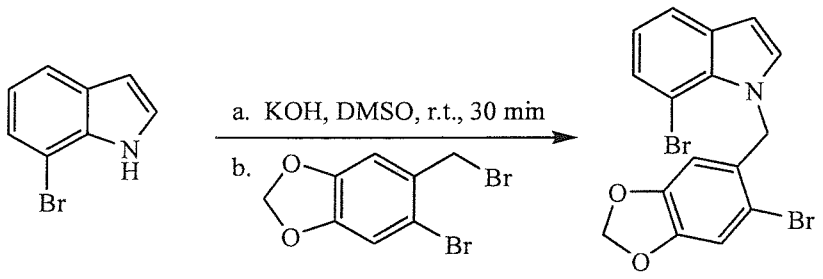
$C_8H_6Br_2O_2$
Mol. Wt.: 294

Prepared following the procedure of Barthel *et al.*[130] Thus, to a stirred solution of piperonyl alcohol **438** (14.1 g, 92.8 mmol) in acetic acid (40 mL) at 0°C was added bromine (23.1 g, 7.41 mL, 144.4 mmol) in acetic acid (40 mL) dropwise over 1 h. After 15 h the mixture was filtered to isolate the precipitate and the solid washed with water (3 × 50 mL). The filtrate was extracted with dichloromethane (3 × 50 mL) then the organic extracts were combined and washed with brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown solid. The combined solids (16.0 g) were recrystallised from petroleum ether/ether to give **439** (14.7 g, 50.1 mmol, 54 %) as white needles.

Spectral and physical characteristics were consistent with literature values.[129,130]

MP	91 - 93°C (petroleum ether/ether). Lit. 94°C (petroleum ether);[129] lit. 92–93°C (methanol).[130]
ν_{max}/cm^{-1} (solid)	3044w, 2897w, 1618w, 1534w, 1500s, 1480s, 1434m, 1211s, 1034s, 929s.
λ_{max}/nm (ε_{max}, MeOH)	299 (4730), 262 (5550).
δ_H (300MHz, $CDCl_3$)	7.01 (1H, s, Ar*H*), 6.92 (1H, s, Ar*H*), 6.00 (2H, s, OCH_2O), 4.56 (2H, s, CH_2Br) ppm.
δ_C (75.5MHz, $CDCl_3$)	148.9 (0, Ar), 147.8 (0, Ar), 130.1 (0, Ar), 115.8 (0, Ar), 113.3 (1, Ar), 110.7 (1, Ar), 102.3 (2, OCH_2O), 34.3 (2, CH_2Br) ppm.
LRMS (APCI)	294 ([M{^{81}Br, ^{79}Br}H]$^+$, 5 %), 215 ([M-{^{79}Br}]$^+$, 100 %), 213 ([M-{^{81}Br}]$^+$, 98 %) amu.

1-(5-Bromobenzo[1,3]dioxol-6-yl)-methyl-7-bromo-1*H*-indole **426**



C_8H_6BrN
Mol. Wt.: 196

72 %

$C_{16}H_{11}Br_2NO_2$
Mol. Wt.: 409

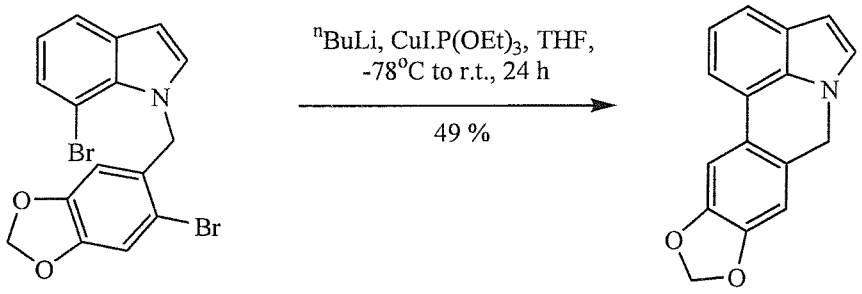
The general procedure for *N*–alkylation of indoles described by Heaney *et al.* was followed.[131] Thus, to a stirred solution of powdered KOH (2.29 g, 40.9 mmol) in DMSO (20 mL) under nitrogen and at ambient temperature was added **409** (2.00 g, 10.2 mmol). After 30 min the dibromide **439** (6.00 g, 20.4 mmol) was added in a single portion. After a further 2 h, water (25 mL) was added and the resultant mixture extracted with ether (3 × 30 mL). The organic phases were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow solid (7.09g). Purification by chromatography (silica, 5 to 10 % ether in petroleum ether) and recrystallisation from ether/petroleum ether gave **426** (2.97 g, 7.26 mmol, 72 %) as a pale brown solid.

MP	138 - 140°C (petroleum ether/ether).
ν_{max}/cm^{-1} (solid)	3104w, 2904w, 1557w, 1515w, 1479s, 1392m, 1318s, 1235s, 1033s, 927s.
λ_{max}/nm (ε_{max}, MeOH)	289 (7600), 272 (9400).
δ_H (300MHz, DMSO-d_6)	7.64 (1H, d, *J* 7.9 Hz, Ar*H*), 7.50 (1H, d, *J* 3.1 Hz, NC*H*), 7.36 (1H, d, *J* 7.5 Hz, Ar*H*), 7.29 (1H, s, Ar*H*), 6.98 (1H, app. t, *J* 7.7 Hz, Ar*H*), 6.65 (1H, d, *J* 3.1 Hz, NCHC*H*), 5.96 (2H, s, OCH_2O), 5.68 (2H, s, NCH_2), 5.43 (1H, s, Ar*H*) ppm.
δ_C (75.5MHz, DMSO-d_6)	147.6 (0, Ar), 147.4 (0, Ar), 132.6 (0, Ar), 131.9 (0, Ar), 131.7 (0, Ar), 126.7 (1, Ar), 121.2 (1, Ar), 120.8 (1, Ar), 112.7 (1, Ar), 110.6 (0, Ar), 106.2 (1, Ar), 103.1 (0, Ar), 102.4 (1, Ar), 102.1 (2, OCH_2O), 52.3 (2, NCH_2) ppm.
LRMS (APCI)	412 ([M{^{81}Br, ^{81}Br}H]$^+$, 40 %), 411 ([M{^{81}Br, ^{81}Br}]$^+$, 60 %), 409 ([M{^{81}Br, ^{79}Br}]$^+$, 90 %), 407 ([M{^{79}Br, ^{79}Br}]$^+$, 30 %),

328 ([M-^{81}Br]$^+$, 10 %), 215 ([M-C_8H_5{^{79}Br}N]$^+$, 90 %), 213 ([M-C_8H_5{^{81}Br}N]$^+$, 100 %) amu.

CHN Found: C, 47.14; H, 2.61; Br, 39.10; N, 3.42. $C_{16}H_{11}Br_2NO_2$ requires C, 46.98; H, 2.71; Br, 39.07; N, 3.42.

7*H*-1,3-Dioxolo-4,5-*j*-pyrrolo-3,2,1-*de*-phenanthridine **440**[88]



$C_{16}H_{11}Br_2NO_2$
Mol. Wt.: 409

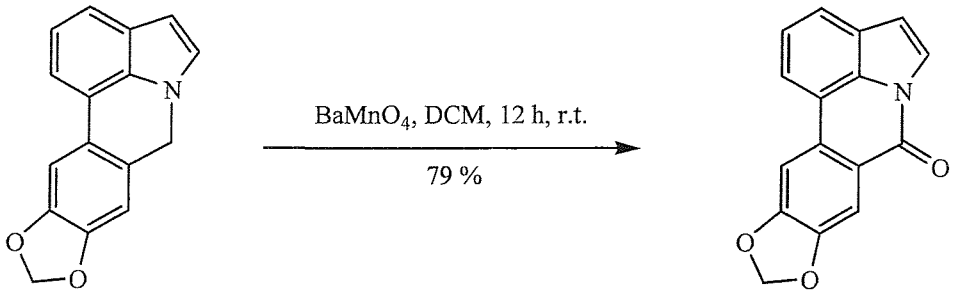
$C_{16}H_{11}NO_2$
Mol. Wt.: 249

Prepared following a modified procedure of Ziegler *et al.*[27b] Thus, to a stirred solution of **426** (0.60 g, 1.47 mmol) in THF (10 mL) at –78°C and under nitrogen was added *n*-butyllithium (2.65 mL of a 1.3 M solution in hexane, 3.45 mmol) over 30 s. After 20 min copper(I) iodide triethylphosphite complex (1.57 g, 4.40 mmol) was added in a single portion. The mixture was allowed to warm to ambient temperature over 3 h then stirred for 21 h. The mixture was diluted with ether (40 mL) then washed repeatedly with concentrated ammonia solution (10 × 40 mL), water (50 mL) and brine (30 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pink solid (0.79 g). Purification by chromatography (silica, 0 to 4 % ether in petroleum ether) gave **440** (0.179 g, 0.72 mmol, 49 %) as a white solid.

MP	Partial sublimation at 151°C, melting at 158 - 161°C. Lit. 159–161°C (methanol);[88] lit. 154 - 156°C.[75]
ν_{max}/cm^{-1} (solid)	3097w, 2897w, 1496m, 1483m, 1335s, 1236s, 1038s, 938w, 790s.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	355 (11300), 344 (12250).
δ_H (300MHz, DMSO-d_6)	7.59 (1H, s, Ar*H*), 7.44 (1H, d, *J* 7.2 Hz, Ar*H*), 7.40 - 7.30 (2H, m, NC*H* + Ar*H*), 6.96 (1H, app. t, *J* 7.6 Hz, Ar*H*), 6.88 (1H, s, Ar*H*), 6.46 (1H, d, *J* 2.9 Hz, NCHC*H*), 6.07 (2H, s, OCH_2O), 5.48 (2H, s, NCH_2) ppm.
δ_C (75.5MHz, DMSO-d_6)	147.4 (0, Ar), 147.3 (0, Ar), 132.5 (0, Ar), 127.0 (1, Ar), 125.3 (0, Ar), 124.3 (0, Ar), 123.3 (0, Ar), 120.2 (1, Ar), 119.7 (1, Ar), 118.4 (0, Ar), 113.0 (1, Ar), 107.5 (1, Ar), 102.9 (1, Ar), 101.9 (1, Ar), 101.4 (2, OCH_2O), 47.4 (2, NCH_2) ppm.

LRMS (APCI)	250 ($[MH]^+$, 100 %), 249 (M^+, 40 %), 111 (30 %), 101 (20 %) amu.
HRMS (EI)	Found M^+ 249.0768. $C_{16}H_{11}NO_2$ requires M^+ 249.0789.

1,3-dioxolo-4,5-*j*-pyrrolo-3,2,1-*de*-phenanthridin-7-one (Hippadine) **401**[88]



$C_{16}H_{11}NO_2$
Mol. Wt.: 249

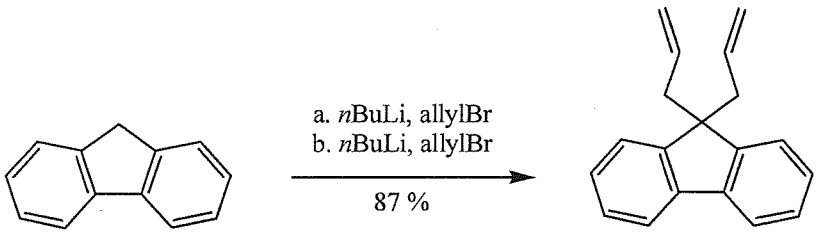
$C_{16}H_9NO_3$
Mol. Wt.: 263

A solution of **440** (0.091 g, 0.36 mmol) in dichloromethane (10 mL) was stirred with barium manganate (0.93 g, 3.6 mmol) for 12 h at ambient temperature. The mixture was filtered through a pad of Celite and the cake washed with dichloromethane (50 mL). The solvent was removed *in vacuo* to give a white solid (0.101 g). Recrystallisation from acetone/petroleum ether furnished hippadine **401** (0.075 g, 0.29 mmol, 79 %) as a white powder.

MP	216 - 218°C (acetone/petrol). Lit. 217 - 218°C (methanol);[88] lit. 207 - 209°C.[75]
ν_{max}/cm^{-1} (solid)	3020w, 2920w, 1658m, 1602m, 1490m, 1440m, 1359w, 1253s, 1091m, 1037m.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	360inf (6050), 350 (7900), 300 (17100).
δ_H (400MHz, DMSO-d_6)	8.18 (1H, d, *J* 8.0 Hz, Ar*H*), 8.10 (1H, d, *J* 3.6 Hz, NC*H*), 7.96 (1H, s, Ar*H*), 7.89 (1H, s, Ar*H*), 7.87 (1H, d, *J* 7.7 Hz, Ar*H*), 7.56 (1H, app. t, *J* 7.7 Hz, Ar*H*), 7.06 (1H, d, *J* 3.6 Hz, NCHC*H*), 6.29 (2H, s, OCH_2O) ppm.
δ_C (100.6MHz, DMSO-d_6)	155.8 (0, Ar), 151.2 (0, Ar), 147.0 (0, Ar), 129.9 (0, Ar), 129.1 (0, Ar), 126.5 (0, Ar), 122.4 (1, Ar), 121.6 (1, Ar), 121.1 (1, Ar), 120.4 (0, Ar), 117.4 (1, Ar), 114.9 (0, Ar), 109.3 (1, Ar), 105.5 (1, Ar), 101.0 (2, OCH_2O), 100.7 (1, Ar) ppm.
LRMS (APCI)	264 ([MH]$^+$, 15 %), 146 (5 %), 127 (70 %), 125 (100 %) amu.
CHN	Found: C, 72.80; H, 3.29; N, 5.04. $C_{16}H_9NO_3$ requires: C, 73.00; H, 3.45; N, 5.32.

7.5 EXPERIMENTAL FOR CHAPTER 5

9,9-Di(prop-2-enyl)-(9*H*)-fluorene **505**[133]



$C_{13}H_{10}$
Mol. Wt.: 166

$C_{19}H_{18}$
Mol. Wt.: 246

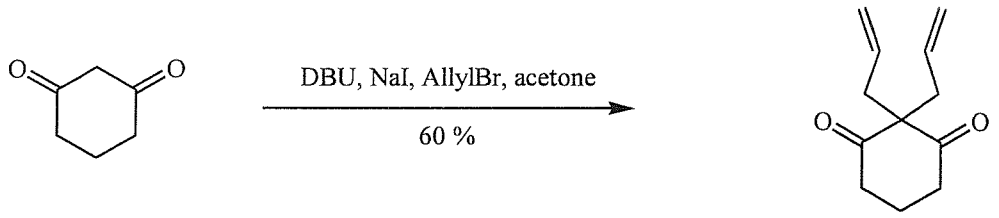
A solution of fluorene (1.67 g, 10 mmol) in dry THF (25 mL) was cooled to –78°C under nitrogen then butyllithium (7.6 mL of a 1.31 M solution in hexane, 10 mmol) added dropwise. The mixture was warmed to ambient temperature, stirred for 1 h, recooled to -78°C, then allyl bromide (1.21 g, 0.87 mL, 10 mmol) added. The mixture was warmed to ambient temperature, stirred for 1½ h, recooled to –78°C and a second portion of butyllithium (7.6 mL of a 1.31 M solution in hexane, 10 mmol) added. The mixture was warmed to ambient temperature, stirred for 1 h, then recooled to –78°C and allyl bromide (1.21 g, 0.87 mL, 10 mmol) added. After warming to ambient temperature the mixture was stirred for 18 h then partitioned between water (20 mL) and ether (20 mL). The aqueous phase was extracted with ether (3 × 10 mL) then the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, petrol) gave **505** (2.15 g, 8.7 mmol, 87 %) as a colourless oil.

All spectral and physical data were consistent with literature values.[133]

ν_{max}/cm^{-1} (neat)	3071w, 2977w, 2908w, 1640m, 1477m, 1448s, 1414w, 1155w, 994m, 914vs.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	298 (5500), 267 (14700).
δ_H (300MHz, $CDCl_3$)	7.74 (2H, br. dd, *J* 7.2, 1.8 Hz, 2 × Ar*H*), 7.48 - 7.30 (6H, m, 6 × Ar*H*), 5.30 (2H, ddt, *J* 17.1, 10.1, 7.2 Hz, 2 × =C*H*), 4.83 (2H,

	br. d, *J* 17.1 Hz, 2 × =C*H*H), 4.77 (2H, br. d, *J* 10.1 Hz, 2 × =CH*H*), 2.75 (4H, d, *J* 7.2 Hz, 2 × CH_2CH=) ppm.
δ_C **(75MHz, $CDCl_3$)**	149.5 (0, 2 × Ar), 140.9 (0, 2 × Ar), 133.9 (1, 2 × *C*H=), 127.3 (1, 2 × Ar), 127.1 (1, 2 × Ar), 123.8 (1, 2 × Ar), 119.9 (1, 2 × Ar), 117.7 (2, 2 × =*C*H_2), 54.3 (0, *C*), 43.7 (2, 2 × *C*H_2) ppm.
LRMS (CI)	264 ($[M+NH_4]^+$, 26 %), 246 (M^+, 6 %), 205 ($[M-CH_2CH=CH_2]^+$, 100 %) amu.

2,2-Diallyl-1,3-cyclohexanedione **506**[132]



$C_6H_8O_2$
Mol. Wt.: 112

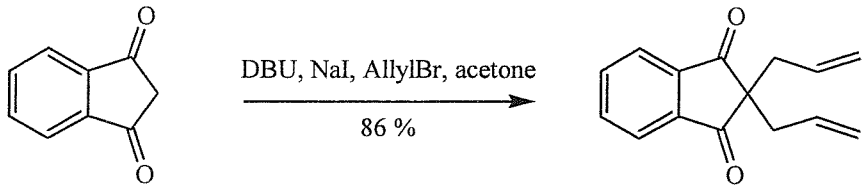
$C_{12}H_{16}O_2$
Mol. Wt.: 192

To a stirred solution of sodium iodide (5.36 g, 35.7 mmol) and allyl bromide (4.32 g, 3.09 mL, 35.7 mmol) in acetone (50 mL) under nitrogen and at ambient temperature was added DBU (5.44 g, 5.34 mL, 35.7 mmol) and 1,3-cyclohexanedione (1.00 g, 8.93 mmol). After 16 h the mixture was concentrated *in vacuo* to a brown solid. The residue was partitioned between water (50 mL) and ether (50 mL) then the aqueous phase was extracted with ether (2 × 30 mL). The combined organic extracts were washed with brine (30 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil (1.6 g). Purification by chromatography (silica, 60 % ether in petroleum ether) gave **506** (1.03 g, 5.36 mmol, 60 %) as a colourless oil.

All spectroscopic data were consistent with literature values.[132]

ν_{max}/cm^{-1} (solid)	3078w, 2961w, 2921w, 1723m, 1693vs, 1639m, 1415m, 1322m, 1210m, 992m, 919s.
δ_H (300MHz, $CDCl_3$)	5.54 (2H, ddt, *J* 17.1, 9.6, 7.5 Hz, 2 × =C*H*), 5.05 - 4.97 (4H, m, 2 × =CH_2), 2.58 – 2.44 (8H, m, 2 × COCH_2 & 2 × CH_2CH=), 1.91 (2H, quintet, *J* 7.2 Hz, $CH_2CH_2CH_2$) ppm.
δ_C (75MHz, $CDCl_3$)	210.6 (0, 2 × *C*O), 132.6 (1, 2 × *C*H=), 119.5 (2, 2 × =CH_2), 68.4 (0, *C*), 41.1 (2, 2 × *C*H_2), 40.1 (2, 2 × *C*H_2), 16.6 (2, $CH_2CH_2CH_2$) ppm.
LRMS (CI)	193 ([MH]$^+$, 100 %), 137 (10 %) amu.

2,2-Di(prop-2-enyl)-indane-1,3-dione **507**[134]



$C_9H_6O_2$
Mol. Wt.: 146

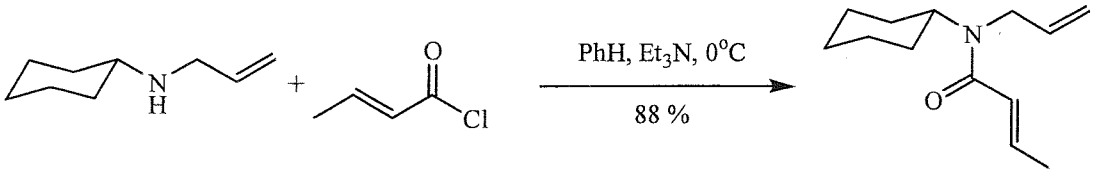
$C_{15}H_{14}O_2$
Mol. Wt.: 226

A solution of sodium iodide (6.16 g, 41.1 mmol) and allyl bromide (4.97 g, 3.55 mL, 41.1 mmol) in acetone (80 mL) under nitrogen and at ambient temperature was stirred for 15 min then DBU (3.12 g, 3.07 mL, 20.5 mmol) and indane-1,3-dione (1.50 g, 10.3 mmol) were added. After 10 min the mixture was concentrated *in vacuo* to a red solid. The residue was partitioned between water (20 mL) and ether (20 mL) then the aqueous phase extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a red oil. Purification by chromatography (silica, 10 % ether in petroleum ether) gave **507** (2.00 g, 8.85 mmol, 86 %) as a yellow solid which was recrystallised from petroleum ether to give yellow crystals.

All spectral and physical data were consistent with literature values.[134]

MP	35 - 37°C (petrol).
ν_{max}/cm^{-1} (neat)	3086w, 2093w, 1739m, 1704s, 1639w, 1592s, 1428m, 1351m, 1276s, 923s, 750vs.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	294inf (1200), 247 (10650).
δ_H (300MHz, $CDCl_3$)	7.94 (2H, app. dd, *J* 5.5, 3.1 Hz, 2 × Ar*H*), 7.82 (2H, app. dd, *J* 5.7, 2.9 Hz, 2 × Ar*H*), 5.45 (2H, ddt, *J* 16.9, 10.1, 7.5 Hz, 2 × =C*H*), 5.02 (2H, br. d, *J* 16.9 Hz, 2 × =C*H*H), 4.88 (2H, br. d, *J* 10.1 Hz, 2 × =CH*H*), 2.54 (4H, d, *J* 7.5 Hz, 2 × CH_2CH=) ppm.
δ_C (75.5MHz, $CDCl_3$)	203.5 (0, 2 × *C*O), 142.4 (0, 2 × Ar), 135.9 (1, 2 × Ar), 131.6 (1, 2 × *C*H=), 123.2 (1, 2 × Ar), 119.7 (2, 2 × =CH_2), 58.4 (0, *C*), 39.0 (1, 2 × CH_2CH=) ppm.
LRMS (CI)	227 ([MH]$^+$, 100 %), 185 (14 %), 157 (20 %) amu.

(*E*)-*N*-Allyl-*N*-cyclohexyl-2-butenamide **509**[104a]



$C_{13}H_{21}NO$
Mol. Wt.: 207

Prepared following the procedure of Naito *et al.*[104a] To a stirred solution of allylcyclohexylamine (2.0 g, 2.08 mL, 0.014 mol) and triethylamine (1.6 g, 2.2 mL, 16 mmol) in toluene (30 mL) at 0°C and under nitrogen was added crotonyl chloride (1.50 g, 1.38 mL, 0.014 mol) in toluene (10 mL) *via* syringe over 2 min. After stirring for 30 min the reaction mixture was warmed to ambient temperature and the triethylamine hydrochloride precipitate filtered off. The filtrate was concentrated *in vacuo* to a brown oil (3.2 g). Chromatography (silica, 10 % ethyl acetate in petrol) gave **509** (2.6 g, 0.013 mol, 88 %) as a colourless oil.

Note: NMR shows that at 25°C this compound exists as a mixture of rotamers (3 : 1).

ν_{max}/cm^{-1} (neat)	3082w, 2931s, 2855m, 1662s, 1615s, 1449s, 1413s, 1374w, 1220m, 827w.
λ_{max}/nm (ε_{max}, MeOH)	256 (1350).
δ_H (300MHz, $CDCl_3$)	Major rotamer: 6.89 (1H, dq, *J* 14.9, 6.6 Hz, =C*H*CH_3), 6.11 (1H, d, *J* 14.9 Hz, C*H*=$CHCH_3$), 5.91 – 5.73 (1H, m, C*H*=CH_2), 5.23 - 5.00 (2H, m, NCH_2CH=CH_2), 4.55 - 4.40 (1H, m, NC*H*), 3.90 - 3.80 (2H, m, NCH_2), 1.95 - 1.00 (10H, m, $(CH_2)_5$), 1.85 (3H, d, *J* 6.8 Hz, CH_3) ppm. Minor rotamer: 6.89 (1H, obscured, =C*H*CH_3), 6.28 (1H, d, J 14.9 Hz, C*H*=$CHCH_3$), 5.82 (1H, obscured, C*H*=CH_2), 5.23 - 5.20 (2H, obscured, CH=CH_2), 4.00 - 3.90 (2H, m, NCH_2), 3.78 - 3.62 (1H, m, NC*H*), 2.0 - 1.9 (13H, obscured, $(CH_2)_2$ & CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	Major rotamer: 166.9 (0, *C*O), 141.5 (1, CH_3*C*H=CH), 135.8 (1, *C*H=CH_2), 123.3 (1, CH_3CH=*C*H), 116.3 (2, CH=*C*H_2), 53.4 (1,

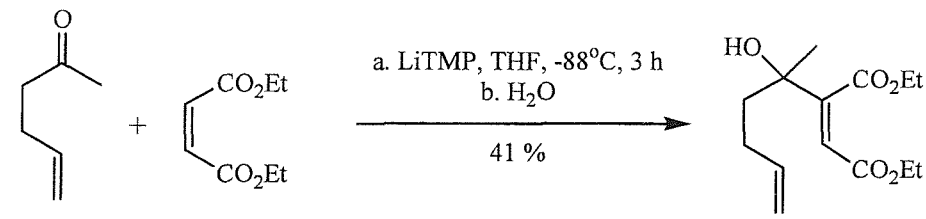
NCH), 45.3 (2, NCH_2), 30.8 (2, 2 × CH_2), 26.0 (2, 2 × CH_2), 25.9 (2, CH_2), 18.3 (3, CH_3) ppm.

Minor rotamer: 166.3 (0, *C*O), 141.3 (1, CH_3CH=CH), 135.8 (1, *C*H=CH_2), 122.3 (1, CH_3CH=*C*H), 115.6 (2, NCH_2CH=CH_2), 57.4 (1, NCH), 44.4 (2, NCH_2), 32.2 (2, 2 × CH_2), 26.0 (2, 2 × CH_2), 25.4 (2, CH_2), 18.3 (3, CH_3) ppm.

LRMS (APCI) 208 ($[MH]^+$, 100 %), 207 (M^+, 10 %) amu.

HRMS (CI) Found: MH^+ 208.1701. $C_{13}H_{22}NO$ requires MH^+ 208.1701.

Diethyl (*Z*)-2-(1-hydroxy-1-methyl-4-pentenyl)-2-butenedioate **515**



$C_6H_{10}O$ Mol. Wt.: 98 $C_8H_{12}O_4$ Mol. Wt.: 172 $C_{14}H_{22}O_5$ Mol. Wt.: 270

Prepared following the procedure of Harrowven *et al.*[135] 2,2,6,6-Tetramethylpiperidine (1.98 g, 14 mmol) in THF (20 mL) was cooled to –78°C and butyllithium (12.6 mL of a 1.32 M solution in THF, 16.6 mmol) added dropwise. The reaction mixture was warmed to ambient temperature, stirred for 1 h, then cooled to –88°C. A solution of 5-hexen-2-one (0.98 g, 10 mmol) and diethyl maleate (1.72 g, 10 mmol) in THF (10 mL) was added over 10 min such that the temperature was maintained below –70°C. After 2½ h water (15 mL) was added and the mixture warmed to ambient temperature. The mixture was extracted with ether (3 × 20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a red oil (6.0 g). Purification by chromatography (silica, 0 – 10 % ether in petroleum ether) gave **515** (1.11 g, 4.11 mmol, 41 %) as a colourless oil.

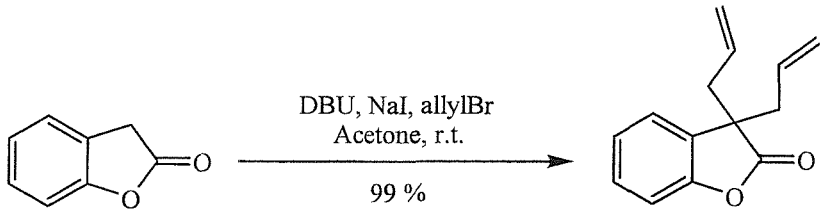
ν_{max}/cm^{-1} (neat) 3495br. s, 3078w, 2981m, 1717vs, 1642m, 1371m, 1248s, 1160s, 1032s, 910m.

δ_H (300MHz, $CDCl_3$) 6.08 (1H, s, =C*H*), 5.82 (1H, ddt, *J* 16.9, 10.1, 6.6 Hz, C*H*=CH_2), 5.05 (1H, br. dd, *J* 17.1, 1.7 Hz, CH=C*H*H), 4.96 (1H, br. d, *J* 10.1 Hz, CH=CH*H*), 4.29 (2H, q, *J* 7.2 Hz, OCH_2), 4.18 (2H, q, *J* 7.2 Hz, OCH_2), 2.24 (1H, br. s, O*H*), 2.15 (2H, app. q, *J* 7.2 Hz, CH_2CH_2CH=), 1.86 - 1.68 (2H, m, CH_2), 1.44 (3H, s, CH_3), 1.33 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3) ppm.

δ_C (75MHz, $CDCl_3$) 168.0 (0, *C*O), 165.1 (0, *C*O), 156.6 (0, *C*=), 138.2 (1, *C*H=CHCO), 118.4 (1, *C*H=CH_2), 115.2 (2, CH=*C*H_2), 74.5 (0, *C*OH), 61.7 (2, OCH_2), 61.0 (2, OCH_2), 40.1 (2, *C*H_2CH=), 28.2 (2, *C*H_2C(OH)), 28.1 (3, *C*H_3C(OH)), 14.3 (3, CH_2CH_3), 14.1 (3, CH_2CH_3) ppm.

LRMS (CI)	271 ($[MH]^+$, 28 %), 252 ($[M-H_2O]^+$, 38 %), 209 ($[MH-EtOH]^+$, 100 %) amu.
HRMS (EI)	Found MH^+: 271.1541. $C_{14}H_{22}O_5$ requires MH^+: 271.1545.

3,3-Diallyl-2,3-dihydrobenzo[*b*]furan-2-one **516**



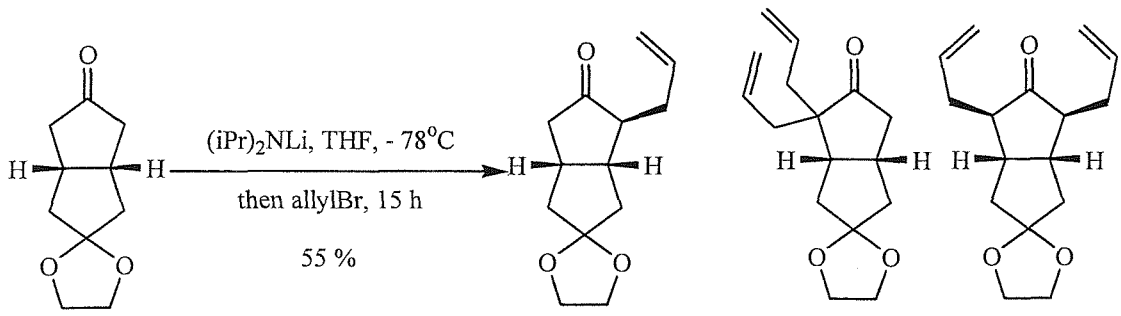
$C_8H_6O_2$
Mol. Wt.: 134

$C_{14}H_{14}O_2$
Mol. Wt.: 214

A solution of sodium iodide (2.24 g, 14.9 mmol) and allyl bromide (1.81 g, 1.29 mL, 14.9 mmol) were stirred in acetone (50 mL) for 1 h under nitrogen and at ambient temperature then DBU (1.14 g, 1.12 mL, 7.46 mmol) and 2-coumaranone (0.50 g, 3.73 mmol) were added. After 3 h the mixture was concentrated *in vacuo* to a brown solid. Water (50 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 5 % ether in petroleum ether) gave **516** (0.79 g, 3.69 mmol, 99 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3081w, 2981w, 2911w, 1799vs, 1641w, 1619w, 1599w, 1035s, 922s, 751s.
λ_{max}/nm (ε_{max}, MeOH)	271 (1270).
δ_H (300MHz, $CDCl_3$)	7.30 (1H, ddd, *J* 7.9, 7.2, 1.8 Hz, Ar*H*), 7.24 - 7.14 (2H, m, 2 × Ar*H*), 7.09 (1H, br. dt, *J* 7.9, 0.7 Hz, Ar*H*), 5.47 (2H, ddt, *J* 17.1, 9.9, 7.0 Hz, 2 × C*H*=), 5.10 - 4.99 (4H, m, 2 × =CH_2), 2.68 (4H, m, 2 × CH_2CH=) ppm.
δ_C (75MHz, $CDCl_3$)	178.6 (0, *C*O), 153.0 (0, Ar), 131.2 (1, 2 × *C*H=), 129.4 (0, Ar), 128.8 (1, Ar), 124.1 (1, Ar), 123.7 (1, Ar), 120.1 (2, 2 × =CH_2), 110.1 (1, Ar), 52.4 (0), 41.7 (2, 2 × *C*H_2) ppm.
LRMS (EI)	214 (M^+, 20 %), 173 ([M-C_3H_5]$^+$, 55 %), 128 (100 %) amu.
HRMS (EI)	Found M^+: 214.0996. $C_{14}H_{14}O_2$ requires M^+: 214.0994.

rel-(3'*R*,3a'*S*,6a'*S*)-3'-Propen-1-yl-spiro[perhydro-2-pentalene-5',2-dioxolane **527**, rel-(3a'*S*,6a'*S*)-3',3'-(dipropen-1-yl)-spiro[perhydro-2-pentalene-5',2-dioxolane **517**, and rel-(1'*S*,3'*R*,3a'*S*,6a'*R*)-1',3'-(dipropen-1-yl)-spiro[perhydro-2-pentalene-5',2-dioxolane **528**



$C_{10}H_{14}O_3$
Mol. Wt.: 182

$C_{13}H_{18}O_3$
Mol. Wt.: 222
527

$C_{16}H_{22}O_3$
Mol. Wt.: 262
517

$C_{16}H_{22}O_3$
Mol. Wt.: 262
528

To a stirred solution of diisopropylamine (0.37 g, 0.47 mL, 3.63 mmol) in THF (15 mL) at -78°C and under nitrogen was added *tert*-butyllithium (3.63 mL of a 1M solution in pentane, 3.63 mmol). After 15 min a solution of ketone **529**[139] (0.60 g, 3.30 mmol) in THF (5 mL) was added dropwise. After 15 min, allyl bromide (0.80 g, 0.57 mL, 6.60 mmol) was added dropwise. After 15 min the mixture was warmed to ambient temperature. After 15 h saturated aqueous ammonium chloride (10 mL) was added and the mixture extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 0 to 15 % ether in petroleum ether) gave firstly **528** (0.11 g, 0.42 mmol, 13 %) as a colourless oil then **517** (0.163 g, 0.62 mmol, 19 %) as a colourless oil and finally **527** (0.170 g, 0.77 mmol, 23 %) also as a colourless oil.

Data for **527** (monoallyl)

This material contained ~20 % unknown impurities. Data given is for major component.

ν_{max}/**cm**$^{-1}$ **(neat)**	2969m, 2936m, 2884m, 1733vs, 1640m, 1434m, 1324m, 1113s, 1017s, 913s.
δ_H **(300MHz, $CDCl_3$)**	5.73 (1H, ddd, *J* 17.1, 10.1, 7.2 Hz, C*H*=CH_2), 5.12 - 4.96 (2H, m, =CH_2), 3.90 - 3.88 (4H, m, OCH_2CH_2O), 2.82 - 2.70 (1H, ddd, *J* 13.4, 8.4, 4.6 Hz), 2.55 - 2.40 (3H, m), 2.33 – 1.95 (5H,

	m), 1.82 (1H, dd, *J* 14.9, 5.6 Hz), 1.66 (1H, dd, *J* 12.7, 8.6 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	220.6 (0, *C*O), 135.6 (1, *C*H=), 118.5 (0, *C*), 117.1 (2, =CH_2), 64.7 (2, OCH_2), 64.3 (2, OCH_2), 53.9 (1, *C*HCO), 44.0 (2, CH_2CO), 43.0 (1, *C*HCHCO), 42.7 (2, CH_2C), 42.4 (2, CH_2C), 35.0 (1, *C*H), 34.7 (2, CH_2CH=) ppm.
LRMS (CI)	223 ($[MH]^+$, 100 %) amu.

Data for **517** (asymmetric diallyl)

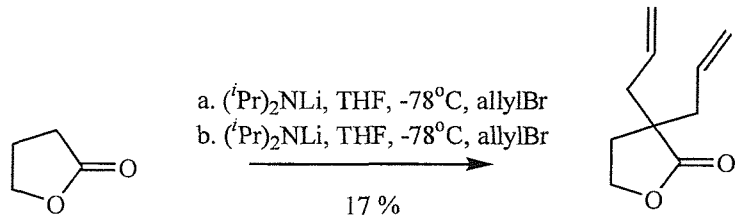
ν_{max}/cm^{-1} (neat)	3074w, 2974m, 2936m, 1731vs, 1638m, 1435m, 1325s, 1114vs, 1016s, 912s.
λ_{max}/nm (ε_{max}, MeOH)	300inf (130).
δ_H (300MHz, $CDCl_3$)	5.77 (1H, dddd, *J* 17.6, 9.6, 8.1, 6.6 Hz, C*H*=CH_2), 5.65 (1H, ddt, *J* 17.6, 10.3, 7.4 Hz, C*H*=CH_2), 5.14 – 4.97 (4H, m, 2 × =CH_2), 3.92 - 3.86 (4H, m, OCH_2CH_2O), 2.86 - 2.64 (2H, m), 2.56 (1H, dt, *J* 12.0, 7.5 Hz), 2.42 (1H, br. dd, *J* 14.7, 8.1 Hz), 2.28 - 2.18 (1H, m), 2.21 (2H, br. d, *J* 7.4 Hz), 2.14 - 1.90 (3H, m), 1.78 (1H, dd, *J* 14.3, 2.9 Hz), 1.59 (1H, app. t, *J* 12.7 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	220.5 (0, *C*O), 133.8 (1, *C*H=), 133.0 (1, *C*H=), 118.6 (2, =CH_2), 118.5 (2, =CH_2), 117.9 (0, *C*), 64.9 (2, OCH_2), 64.2 (2, OCH_2), 56.2 (0, *C*CO), 48.4 (1, *C*H), 43.8 (2), 43.0 (2), 39.6 (2), 37.7 (2), 35.2 (2), 32.6 (1) ppm.
LRMS (EI)	262 (M^+, 18 %), 221 ($[M\text{-}CH_2{=}CHCH_2]^+$, 37 %), 112 (100 %) amu.
HRMS (EI)	Found M^+: 182.0943. $C_{16}H_{22}O_3$ requires M^+: 182.0937.

Data for **528**

This material contained ~10 % unknown impurity. Data given is for major component.

ν_{max}/cm^{-1} (neat)	2929w, 1734s, 1640w, 1435w, 1327w, 1223w, 1113m, 1019s, 947w, 914s.
δ_H (300MHz, $CDCl_3$)	5.73 (2H, ddt, *J* 16.9, 10.1, 6.8 Hz, 2 × C*H*=), 5.15 – 5.00 (4H, m, 2 × =CH_2), 3.92 (4H, app. s, 2 × OCH_2), 2.55 - 2.30 (5H, m), 2.25 – 2.20 (5H, m), 1.77 (2H, dd, *J* 13.8, 4.3 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	220.1 (0, *C*O), 135.9 (1, 2 × *C*H=), 118.0 (0, *C*), 117.0 (2, 2 × =*C*H_2), 64.7 (2, O*C*H_2), 64.3 (2, O*C*H_2), 53.6 (1, 2 × *C*H), 42.5 (2, 2 × *C*H_2), 40.8 (1, 2 × *C*H), 34.4 (2, 2 × *C*H_2) ppm.
LRMS (CI)	263 ([MH]$^+$, 34 %), 221 ([M-CH_2=$CHCH_2$]$^+$, 52 %), 86 (100 %) amu.
HRMS (CI)	Found [M+NH_4]$^+$: 280.1907. $C_{16}H_{22}O_3$ requires [M+NH_4]$^+$: 280.1913.

3,3-Diallyldihydro-2-furanone **518**[136]



$C_4H_6O_2$
Mol. Wt.: 86

$C_{10}H_{14}O_2$
Mol. Wt.: 166

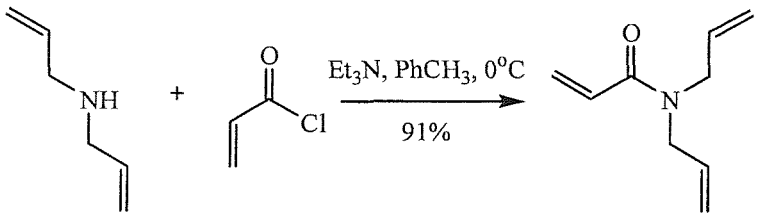
To a stirred solution of *N,N*-diisopropylamine (2.02 g, 2.60 mL, 20 mmol) in THF (20 mL) at –78°C and under nitrogen was added butyllithium (11.3 mL of a 1.77 M solution in hexanes, 20 mmol) over 1 min. The mixture was warmed to ambient temperature over 30 min then recooled to –78°C. γ-butyrolactone (1.72 g, 1.54 mL, 20 mmol) in THF (10 mL) was added dropwise over 3 min, maintaining a temperature below –70°C. After 10 min, allyl bromide (2.42 g, 1.73 mL, 20 mmol) was added. The mixture was warmed to 0°C over 30 min then recooled to –78°C. After 30 min a solution of lithium diisopropylamide (20 mmol) in THF (20 mL) was added. After 10 min, allyl bromide (1.73 mL, 20 mmol) was added, the mixture stirred for 30 min, then warmed to ambient temperature. After 15 h the mixture was diluted with ether (20 mL) and water (20 mL) then extracted into ether (3 × 20 mL). The combined organic extracts were washed with brine (30 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 20 % ether in petrol) gave **518** (0.57 g, 3.43 mmol, 17 %) as a pale yellow oil.

ν_{max}/**cm^{-1} (neat)**	3078w, 2981w, 2914w, 1761vs, 1640m, 1486m, 1438m, 1376m, 1179s, 1026s, 917s.
δ_H **(300MHz, $CDCl_3$)**	5.79 – 5.63 (2H, m, 2 × C*H*=CH_2), 5.16 - 5.08 (4H, m, 2 × =CH_2), 4.17 (2H, t, *J* 7.5Hz, OCH_2), 2.35 (2H, app. ddt, *J* 13.8, 6.8, 1.3 Hz, 2 × *CH*HCH=), 2.25 (2H, app. br. ddt, *J* 13.8, 7.9, 0.7 Hz, 2 × CH*H*CH=), 2.13 (2H, t, *J* 7.5Hz, CH_2CH_2O) ppm.
δ_C **(75MHz, $CDCl_3$)**	180.6 (0, *C*O), 132.7 (1, 2 × *C*H=), 119.8 (2, 2 × =CH_2), 65.5 (2, OCH_2), 46.2 (0, *C*), 41.0 (2, 2 × CH_2CH=), 30.6 (2, OCH_2CH_2) ppm.

LRMS (CI) 184 ($[M+ H_2O]^+$, 88 %), 167 ($[MH]^+$, 100 %), 124 (60 %) amu.

HRMS (ES) Found MH^+: 167.1074. $C_{10}H_{14}O_2$ requires MH^+: 167.1072.

N,N-Diallylacrylamide **533**[143]



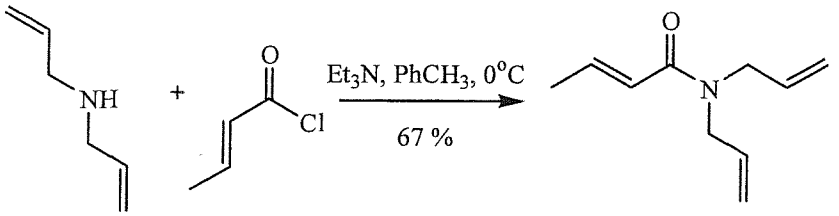
$C_9H_{13}NO$
Mol. Wt.: 151

Prepared following the procedure of Naito *et al.*[104a] Thus, to a stirred solution of diallylamine (1.50 g, 1.9 mL, 15 mmol) and triethylamine (1.72 g, 2.4 mL, 17 mmol) in toluene (35 mL) at 0°C was added a solution of acryloyl chloride (1.40 g, 1.25 mL, 15 mmol) in toluene (10 mL) over 5 min. After 30 min the mixture was filtered then the filtrate concentrated *in vacuo* to an orange oil (3.50 g). Purification by chromatography (silica, 20 % ethyl acetate in petrol) gave **533** (2.06 g, 13.6 mmol, 91 %) as a colourless oil.

All spectral and physical characteristics were consistent with literature values.[143]

ν_{max}/cm^{-1} (neat)	3080m, 2920m, 1653bs, 1615s, 1360m, 1223s, 1138m, 980s, 925s, 795s.
λ_{max}/nm (ε_{max}, MeOH)	248 (2700).
δ_H (300MHz, $CDCl_3$)	6.47 (1H, dd, *J* 16.5, 10.3 Hz, =C*H*CO), 6.32 (1H, dd, *J* 16.5, 2.2 Hz, CH*H*=CHCO), 5.88 – 5.60 (2H, m, 2 × CH_2CH), 5.65 (1H, dd, *J* 10.3, 2.2 Hz, C*H*H=CHCO), 5.25 – 5.00 (4H, m, 2 × $CH_2CH=CH_2$), 4.02 (2H, d, *J* 5.9 Hz, NCH_2), 3.98 – 3.83 (2H, m, NCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	166.5 (0, *C*O), 133.2 (1, =*C*HCH$_2$N), 133.0 (1, =*C*HCH$_2$N), 128.4 (2, *C*H$_2$=CHCON), 127.8 (1, =*C*HCON), 117.6 (2, NCH$_2$CH=*C*H$_2$), 116.9 (2, NCH$_2$CH=*C*H$_2$), 49.2 (2, N*C*H$_2$), 48.5 (2, N*C*H$_2$) ppm.
LRMS (APCI)	152 ($[MH]^+$, 100 %) amu.

(*E*)-*N*,*N*-Diallyl-2-butenamide **534**[143]



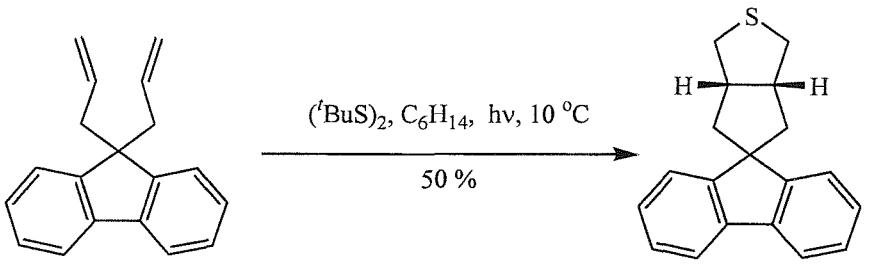
$C_{10}H_{15}NO$
Mol. Wt.: 165

Prepared following the procedure of Naito *et al.*[104a] Thus, to a stirred solution of diallylamine (1.21 g, 1.54 mL, 12.5 mmol) and triethylamine (1.39 g, 1.92 mL, 13.8 mmol) in toluene (30 mL) at 0°C was added a solution of crotonyl chloride (1.31 g, 1.2 mL, 12.5 mmol) in toluene (20 mL) *via* syringe over 5 min. After 30 min the reaction mixture was warmed to ambient temperature, filtered to remove the triethylamine hydrochloride salt and concentrated *in vacuo* to an orange oil (2.4 g). Purification by chromatography (silica, 30 % ethyl acetate in petroleum ether) gave **534** (1.37 g, 8.3 mmol, 67 %) as a colourless oil.

All spectral and physical characteristics were consistent with literature values.[143]

ν_{max}/cm^{-1} (neat)	3082w, 2982w, 2915w, 1663s, 1621s, 1464s, 1284m, 1104w, 994m, 962s.
λ_{max}/nm (ε_{max})	247 (3200).
δ_H (300MHz, $CDCl_3$)	6.94 (1H, dq, *J* 14.7, 7.0 Hz, CH_3CH=CH), 6.17 (1H, dd, *J* 14.7, 1.4 Hz, CH=C*H*CO), 5.79 (2H, ddt, *J* 15.4, 10.3, 5.5 Hz, CH_2CH=CH_2), 5.26 – 5.07 (4H, m, 2 × CH_2CH=CH_2), 4.02 (2H, d, *J* 5.5 Hz, NCH_2), 3.93 (2H, br s, NCH_2), 1.87 (3H, dd, *J* 7.0, 1.5 Hz, CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	166.9 (0, *C*O), 142.3 (1, CH_3CH=CH), 133.5 (1, CH_2=*C*H), 133.2 (1, CH_2=*C*H), 121.9 (1, =*C*HCO), 117.3 (2, =*C*H_2), 116.7 (2, =*C*H_2), 49.2 (2, N*C*H_2), 48.4 (2, N*C*H_2), 18.3 (3, *C*H_3) ppm.
LRMS (APCI)	166 ([MH]$^+$, 100 %) amu.

rel-(3a'*S*,6a'*R*)-Spiro[(9*H*)-fluorene-9,5'-2'-thiabicyclo[3.3.0]octane] **510**



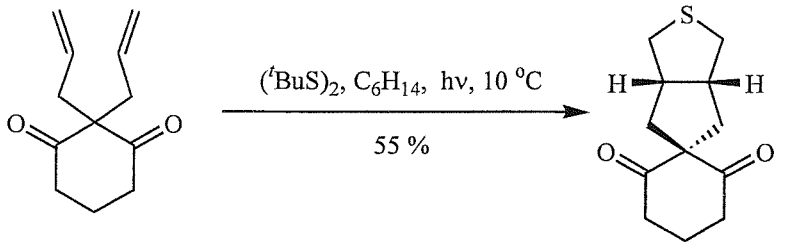
$C_{19}H_{18}$
Mol. Wt.: 246

$C_{19}H_{18}S$
Mol. Wt.: 278

A stirred solution of **505** (0.500 g, 2.19 mmol) and *tert*-butyldisulfide (1.96 g, 2.12 mL, 11.0 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen and at 10°C. After 24 h the mixture was concentrated *in vacuo* then purified by chromatography (silica, petroleum ether) to give firstly recovered **505** (0.224 g, 0.91 mmol, 45 %) as a colourless oil, then **510** (0.280 g, 1.01 mmol, 50 %) as a colourless solid.

MP	202 - 204°C dec. (ether).
ν_{max}/cm^{-1} (solid)	3056w, 2908m, 2843w, 1476w, 1440s, 1307m, 1223w, 1102w, 1029w, 734vs.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	300 (6100), 267 (15850).
δ_H (300MHz, $CDCl_3$)	7.78 - 7.70 (2H, m, 2 × Ar), 7.62 - 7.56 (2H, m, 2 × Ar), 7.40 - 7.26 (4H, m, 4 × Ar), 3.52 - 3.40 (2H, m), 3.06 (2H, dd, *J* 11.9, 6.3 Hz), 2.70 (2H, d, *J* 11.9 Hz), 2.22 (2H, dd, *J* 12.9, 9.0 Hz), 2.05 (2H, dd, *J* 12.9, 8.1 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	153.4 (0, Ar), 150.2 (0, Ar), 139.7 (0, Ar), 139.5 (0, Ar), 127.6 (1, Ar), 127.3 (1, Ar), 127.1 (1, Ar), 127.0 (1, Ar), 123.4 (1, Ar), 122.8 (1, Ar), 120.0 (1, Ar), 119.7 (1, Ar), 59.6 (0, *C*), 48.2 (1, 2 × *C*H), 45.4 (2, 2 × *C*H_2), 40.0 (2, 2 × *C*H_2) ppm.
LRMS (CI)	279 ([MH]$^+$, 100 %), 179 (34 %) amu.
CHN	Found: C, 82.13; H, 6.48; S, 11.53. $C_{19}H_{18}S$ requires C, 81.97; H, 6.52; S, 11.52.

rel-(3a'*S*,6a'*R*)-Spiro[cyclohexane-1,3-dione-2,5'-2'-thiabicyclo[3.3.0]octane] **511**



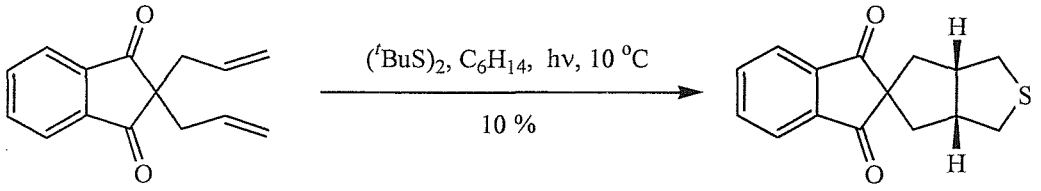
$C_{12}H_{16}O_2$
Mol. Wt.: 192

$C_{12}H_{16}O_2S$
Mol. Wt.: 224

A stirred solution of **506** (0.250 g, 1.30 mmol) and *tert*-butyldisulfide (1.16 g, 1.26 mL, 6.51 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen and at 10°C. After 18 h the mixture was concentrated *in vacuo* to a yellow oil (1.40 g). Purification by chromatography (silica, 20 - 40 % ether in petroleum ether) gave firstly recovered **506** (24 mg, 0.125 mmol, 10 %) as a colourless oil, then **511** (0.160 g, 0.714 mmol, 55 %) as a colourless solid which was recrystallised from ethanol to give colourless flakes.

MP	82 - 84°C (ethanol).
ν_{max}/cm^{-1} (solid)	2966w, 2932m, 2874w, 1718m, 1688vs, 1446w, 1319s, 1228m, 965m, 890m.
δ_H (300MHz, $CDCl_3$)	2.95 - 2.80 (4H, m), 2.71 (2H, t, *J* 6.8 Hz), 2.68 - 2.54 (4H, m), 2.31 (2H, br. dd, *J* 12.5, 5.7 Hz), 2.05 - 1.90 (4H, m) ppm.
δ_C (75MHz, $CDCl_3$)	208.6 (0, *C*O), 207.6 (0, *C*O), 74.5 (0, *C*), 47.7 (1, 2 × *C*H), 38.7 (2), 38.1 (2, 2 × *C*H_2C), 37.5 (2, 2 × S*C*H_2), 37.4 (2), 18.0 (2, $CH_2CH_2CH_2$) ppm.
LRMS (CI)	225 ([MH]$^+$, 100 %) amu.
CHN	Found: C, 64.50; H, 6.78; S, 14.37. $C_{12}H_{16}O_2S$ requires: C, 64.25; H, 7.19; S 14.29.

rel-(3a'*S*,6a'*R*)-Spiro[indane-1,3-dione-2,5'-2'-thiabicyclo[3.3.0]octane] **512**



$C_{15}H_{14}O_2$
Mol. Wt.: 226

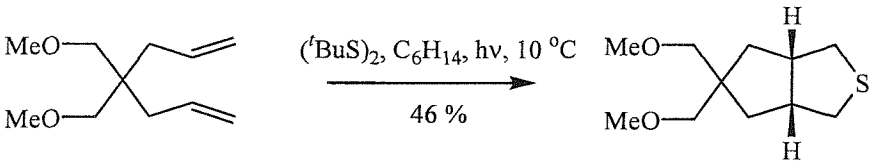
$C_{15}H_{14}O_2S$
Mol. Wt.: 258

A stirred solution of **36** (0.500 g, 2.21 mmol) and *tert*-butyldisulfide (1.97 g, 2.13 mL, 11.1 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen and at 10°C. After 20 h the mixture was concentrated *in vacuo* then purified by chromatography (silica, 20 - 40 % ether in petroleum ether) to give firstly recovered **36** (0.368 g, 1.63 mmol, 74 %) as a colourless oil, then **37** (0.055 g, 0.21 mmol, 10 %) as a waxy yellow solid.

Data was consistent with a previously prepared sample.[141]

MP	123 - 125°C.
ν_{max}/cm^{-1} (solid)	3006w, 2960w, 2916w, 1731m, 1696s, 1589m, 1439w, 1276vs, 1231s, 749vs.
λ_{max}/nm (ε_{max}, MeOH)	248 (8800), 232 (8500).
δ_H (300MHz, $CDCl_3$)	8.02 – 7.94 (2H, m, 2 × Ar*H*), 7.89 – 7.82 (2H, m, 2 × Ar*H*), 3.30 - 3.20 (2H, m), 3.10 - 2.92 (2H, br. m), 2.84 - 2.72 (2H, br. m), 2.10 (2H, app. dd, *J* 13.4, 7.7 Hz, 2 × C*H*HCH), 2.05 (2H, app. dd, *J* 13.3, 7.7 Hz, 2 × CH*H*CH) ppm.
δ_C (75MHz, $CDCl_3$)	204.6 (0, *C*O), 202.8 (0, *C*O), 141.7 (0, Ar), 141.0 (0, Ar), 135.93 (1, Ar), 135.90 (1, Ar), 123.7 (1, Ar), 123.6 (1, Ar), 61.6 (0, *C*), 49.1 (1, 2 × *C*H), 39.6 (2, 2 × S*C*H$_2$), 37.2 (2, 2 × *C*H$_2$) ppm.
LRMS (CI)	259 ([MH]$^+$, 100 %) amu.
HRMS (EI)	Found: M$^+$ 258.0715. $C_{15}H_{14}O_2S$ requires M$^+$ 258.0715.

rel-(3a*R*,6a*S*)-5,5-Di(methoxymethyl)perhydrocyclopent[*c*]thiophene **513**



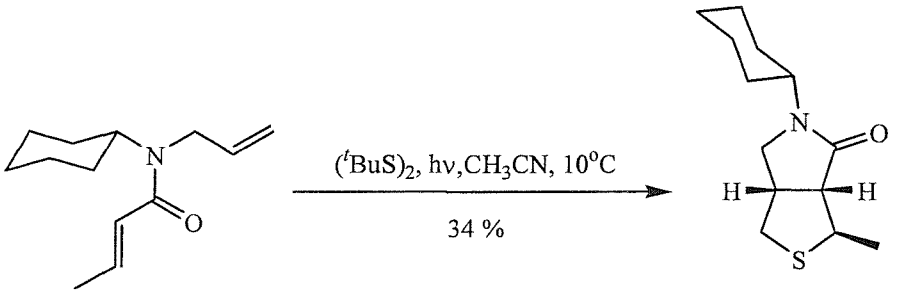
$C_{11}H_{20}O_2$
Mol. Wt.: 184

$C_{11}H_{20}O_2S$
Mol. Wt.: 216

A solution of diene **508** (0.50 g, 2.72 mmol) and *tert*-butyldisulfide (2.37 g, 2.57 mL, 13.6 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen and at 10°C. After 20 h the mixture was concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 2 % ether in petroleum ether) gave **513** (0.270 g, 1.25 mmol, 46 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2920s, 2871s, 2807m, 1476m, 1447s, 1254w, 1197m, 1103vs, 961m, 712w.
δ_H (300MHz, $CDCl_3$)	3.34 (3H, s, OC*H*$_3$), 3.33 (3H, s, OC*H*$_3$), 3.28 (2H, s, OC*H*$_2$), 3.20 (2H, s, OC*H*$_2$), 2.92 - 2.80 (3H, m), 2.56 (2H, d, *J* 9.2 Hz), 1.82 (2H, dd, *J* 13.6, 7.7 Hz), 1.36 - 1.28 (3H, m) ppm.
δ_C (75.5MHz, $CDCl_3$)	78.1 (2, O*C*H$_2$), 75.6 (2, O*C*H$_2$), 59.5 (3, O*C*H$_3$), 59.4 (3, O*C*H$_3$), 49.7 (0), 47.3 (1, 2 × *C*H), 38.7 (2, 2 × *C*H$_2$), 30.1 (2, 2 × *C*H$_2$) ppm.
LRMS (CI)	217 ([MH]$^+$, 42 %), 185 ([M-CH_3O]$^+$, 58 %) amu.
HRMS (ES)	Found: MH$^+$ 217.1262. $C_{11}H_{21}O_2S$ requires MH$^+$ 217.1262.

rel-(3*R*,3a*S*,6a*S*)-5-Cyclohexyl-3-methylperhydrothieno[3,4-c]pyrrol-4-one **514**



$C_{13}H_{21}NO$
Mol. Wt.: 207

$C_{13}H_{21}NOS$
Mol. Wt.: 239

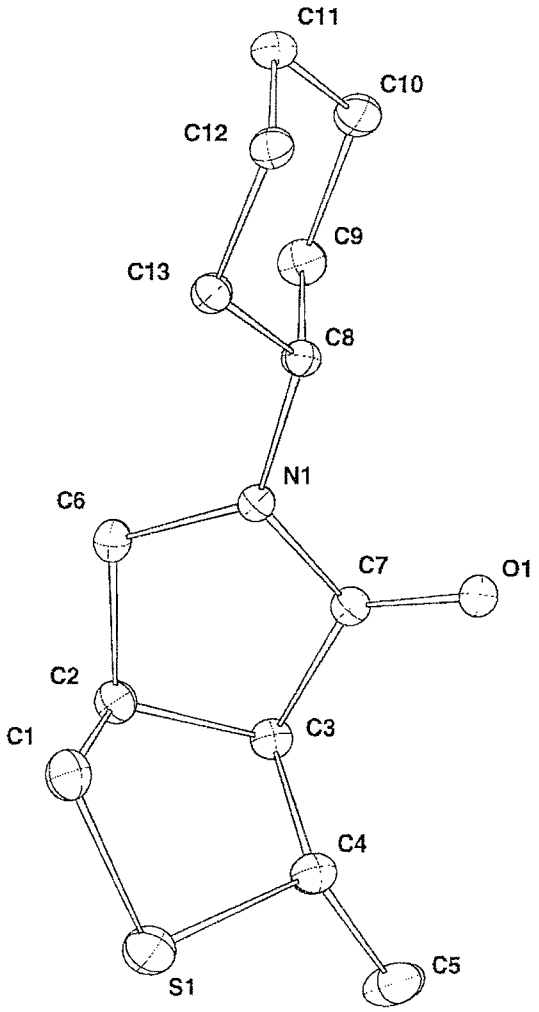
A stirred solution of **509** (0.41 g, 2.0 mmol) and *tert*-butyldisulfide (3.57 g, 3.8 mL, 20.0 mmol) in degassed acetonitrile (100 mL) under nitrogen was irradiated with UV light (Pyrex filter) for 22 h at 10°C. The organic liquors were concentrated *in vacuo* to a yellow oil (3.4 g). Purification by chromatography (silica, 10 % acetone in toluene) afforded **513** (0.161 g, 0.67 mmol, 34 %) as a yellow solid which was recrystallised from pentane to give shiny cream crystals (0.094 g).

MP	67 - 68°C (pentane).
ν_{max}/cm^{-1} ($CHCl_3$)	2930s, 2854m, 1662s, 1487w, 1448m, 1374w, 1329w, 1288m, 1256m, 893w.
δ_H (300MHz, $CDCl_3$)	3.90 (1H, m, NC*H*R$_2$), 3.75 (1H, qd, *J* 7.0, 2.6 Hz, SC*H*(CH$_3$)), 3.52 (1H, dd, *J* 9.5, 7.3 Hz, SC*H*H), 3.22 (1H, dd, *J* 11.5, 7.0 Hz, NCH*H*), 3.20 – 3.00 (1H, m, NCH$_2$C*H*), 3.08 (1H, m, SC*H*), 2.84 (1H, dd, *J* 8.1, 2.6 Hz, NCOC*H*), 2.62 (1H, dd, *J* 11.5, 4.0 Hz, NC*H*H), 1.76 (2H, m, cyclohexyl), 1.66 (3H, m, cyclohexyl), 1.41 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.33 (4H, m, cyclohexyl), 1.08 (1H, m, cyclohexyl) ppm.
δ_C (75.5MHz, $CDCl_3$)	173.3 (0, NCO), 59.5 (1, cyclohexyl), 50.8 (1, SCH), 48.1 (2, NCH$_2$), 46.6 (1, CHCH), 39.8 (1, CHCH), 38.6 (2, SCH$_2$), 30.3 (2, cyclohexyl), 30.2 (2, cyclohexyl), 25.6 (2, cyclohexyl), 25.5 (2, cyclohexyl), 23.6 (3, CH$_3$) ppm.
LRMS (APCI)	480 ([2M+H]$^+$, 70 %), 281 ([MH+CH$_3$CN]$^+$, 5 %), 240 ([MH]$^+$, 100 %) amu.

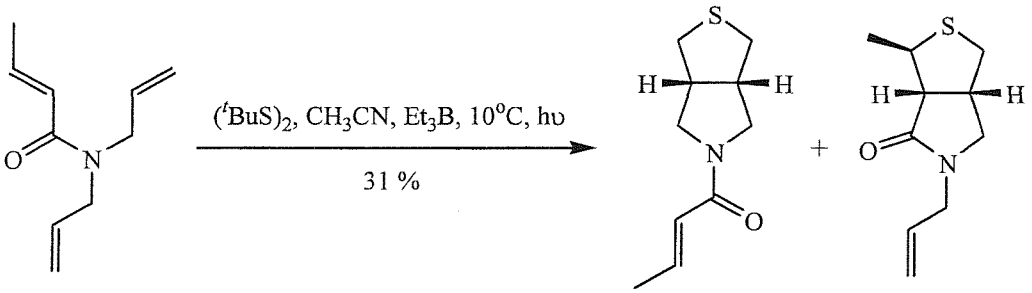
HRMS Found: M^+, 239.1325; $C_{13}H_{21}NOS$ requires M^+ 239.1344.

CHN Found: C, 65.45; H, 8.68; N, 5.93; S, 13.13. $C_{13}H_{21}NOS$ requires: C, 65.23; H, 8.84; N, 5.85; S, 13.40.

X-ray crystal structure:



rel–(2*E*,3'a*R*,6'a*S*)–(Perhydrothieno[3,4–c]pyrrol–5'–yl)–2–buten–1–one **535** and rel–(3*R*,3a*S*,6a*S*)–5–allyl–3–methylperhydrothieno[3,4–c]pyrrol–4–one **536**



$C_{10}H_{15}NO$
Mol. Wt.: 165

$C_{10}H_{15}NOS$
Mol. Wt.: 197

$C_{10}H_{15}NOS$
Mol. Wt.: 197

535 : **536**

1 : 1

To a stirred mixture of **534** (0.33 g, 2.0 mmol) and *tert*-butyldisulfide (3.57 g, 3.8 mL, 20.0 mmol) in degassed acetonitrile (100 mL) under nitrogen was added triethylborane (1.0 mL of a 1M solution in hexane, 1.0 mmol) then the mixture irradiated with UV light (Quartz filter). After 15 h, the mixture was quenched with saturated ammonium chloride solution (30 mL), stirred for 20 min then extracted into ether (3 × 15 mL). The combined organic extracts were washed with water (25 mL) then brine (30 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo* to a yellow oil (3.51 g). Purification by chromatography (silica, 20 % acetone in toluene) afforded firstly **536** (0.061 g, 0.310 mmol, 15 %) as a colourless oil then **535** (0.062 g, 0.315 mmol, 16 %) as a cream solid which was recrystallised from ethyl acetate/petrol to give flocculent white crystals (0.025 g).

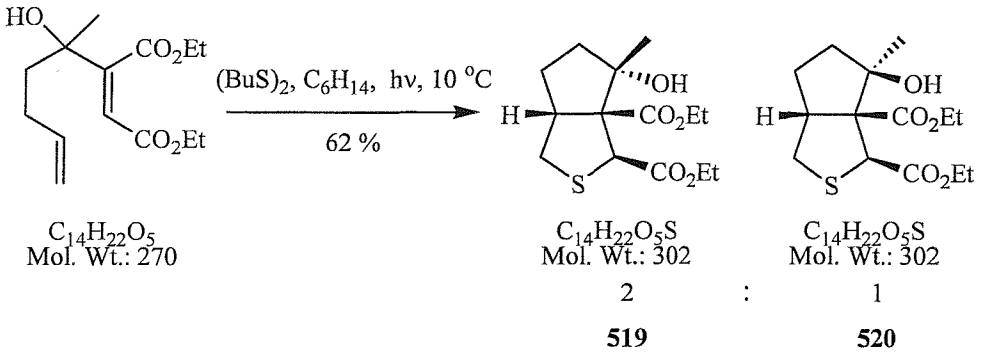
Data for **535**

M.p.	74 - 76°C (ethyl acetate/petrol).
ν_{max}/cm^{-1} ($CHCl_3$)	2932m, 2866m,1663m, 1610s, 1450m, 1423m, 976w.
λ_{max}/nm (ε_{max}, MeOH)	254 (2500).
δ_H (300MHz, $CDCl_3$)	6.93 (1H, dq, *J* 14.9, 6.8 Hz, =C*H*CH_3), 6.10 (1H, dd, *J* 15.1, 1.5 Hz, C*H*=$CHCH_3$), 3.80 (1H, d, *J* 7.2 Hz, NC*H*H), 3.76 (1H, br. d, *J* 7.0 Hz, NCH*H*), 3.51 (1H, dd, *J* 12.7, 4.8 Hz, NC*H*H), 3.46 (1H, dd, *J* 10.5, 5.5 Hz, NCH*H*), 3.20 – 3.00 (3H, m,

	*CH*HSC*H*HC*H*), 3.05 – 2.90 (1H, m, C*H*CH), 2.82 – 2.68 (2H, m, 2 × SCH*H*), 1.88 (3H, dd, *J* 6.8, 1.5 Hz, C*H*$_3$) ppm. Assigned with the aid of a ^{1}H-^{1}H COSY experiment.
δ_C (75.5MHz, $CDCl_3$)	165.2 (0, *C*O), 141.6 (1, CH_3CH=), 122.8 (1, =*C*H), 50.3 (2, N*C*H$_2$), 49.9 (2, N*C*H$_2$), 48.0 (1, *C*HCH), 46.2 (1, CH*C*H), 35.3 (2, S*C*H$_2$), 35.2 (2, S*C*H$_2$), 18.2 (3, *C*H$_3$) ppm.
LRMS (ES)	395 ($[2M+H]^+$, 30 %), 198 ($[MH]^+$, 100 %) amu.
HRMS (CI)	Found M^+, 197.0874. $C_{10}H_{15}NOS$ requires M^+ 197.0874
Data for **536**	
ν_{max}/em^{-1} (neat)	2960w, 2872w, 1682s, 1490w, 1450m, 1420m, 1325w, 1265m, 994w, 925m.
λ_{max}/nm (ε_{max}, MeOH)	247inf (1050).
δ_H (300MHz, $CDCl_3$)	5.80 – 5.60 (1H, m, C*H*=), 5.17 (1H, d, *J* 16.7 Hz, =C*H*H), 5.16 (1H, d, *J* 10.3 Hz, =CH*H*), 3.92 (1H, dd, *J* 15.2, 5.7 Hz, CH*H*CH=), 3.88 – 3.72 (2H, m, NC*H*HCH=CH$_2$ & SC*H*CH$_3$), 3.52 (1H, dd, *J* 9.8, 7.7 Hz, NCH$_\alpha$*H*$_\beta$C), 3.23 (1H, dd, *J* 11.6, 7.2 Hz, SC*H*$_\alpha$H$_\beta$), 3.23 – 3.12 (1H, m, SCH$_2$C*H*), 3.10 (1H, dd, *J* 9.9, 2.9 Hz, NC*H*$_\alpha$H$_\beta$), 2.90 (1H, dd, *J* 8.3, 2.4 Hz, NCOC*H*), 2.68 (1H, dd, *J* 11.4, 3.3 Hz, SCH$_\alpha$*H*$_\beta$), 1.39 (3H, d, *J* 7.0 Hz, C*H*$_3$) ppm. Solved with the aid of ^{1}H-^{1}H COSY NMR and nOe experiments.
δ_C (75.5MHz, $CDCl_3$)	173.7 (0, N*C*O), 131.9 (1, *C*H=), 118.0 (2, =*C*H$_2$), 58.9 (1, S*C*H), 51.9 (2, N*C*H$_2$CH=), 46.7 (1, NCO*C*H), 45.3 (2, N*C*H$_2$CH), 39.3 (1, NCH$_2$*C*H), 38.5 (2, S*C*H$_2$), 18.1 (3, *C*H$_3$) ppm.
LRMS (APCI)	239 ($[MH+CH_3CN]^+$, 7 %), 198 ($[MH]^+$, 100 %) amu.

rel-(1*S*,3a*S*,6*S*,6a*R*)-Diethyl 6-hydroxy-6-methylperhydrocyclopenta[*c*]thiophene-1,6a-dicarboxylate **519** &

rel-(1*S*,3a*S*,6*R*,6a*R*)-diethyl 6-hydroxy-6-methylperhydrocyclopenta[*c*]thiophene-1,6a-dicarboxylate **520**



$C_{14}H_{22}O_5$
Mol. Wt.: 270

$C_{14}H_{22}O_5S$
Mol. Wt.: 302

2 : 1

519 **520**

A stirred solution of **515** (0.662 g, 2.45 mmol) and *tert*-butyldisulfide (2.19 g, 2.37 mL, 12.3 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under argon and at 10°C. After 24 h the mixture was concentrated *in vacuo* then purified by chromatography (silica, 10 - 30 % ether in petroleum ether) to give firstly **519** (0.317 g, 1.05 mmol, 43 %) as a colourless oil, then **520** (0.133 g, 0.44 mmol, 19 %) as a colourless oil.

Data for **519**

ν_{max}/cm^{-1} (neat) 3467br. m, 2979m, 2939m, 1729vs, 1368m, 1276s, 1191s, 1027m, 750s.

δ_H (300MHz, $CDCl_3$) 4.14 (2H, qd, *J* 7.2, 1.3 Hz, OC*H*$_2$), 4.11 (1H, s, SC*H*), 4.08 (2H, q, *J* 7.2 Hz, OC*H*$_2$), 3.72 (1H, app. q, *J* 7.7 Hz), 3.58 (1H, br. s, O*H*), 3.44 (1H, dd, *J* 11.6, 6.8 Hz), 2.53 (1H, br. d, *J* 11.6 Hz), 2.18 (1H, dddd, *J* 13.1, 8.8, 5.9, 4.4 Hz, SCH_2CHCH_2), 1.85 - 1.78 (2H, m), 1.56 - 1.44 (1H, m), 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.24 (3H, s, CH_3), 1.23 (3H, t, *J* 7.2 Hz, CH_2CH_3) ppm.

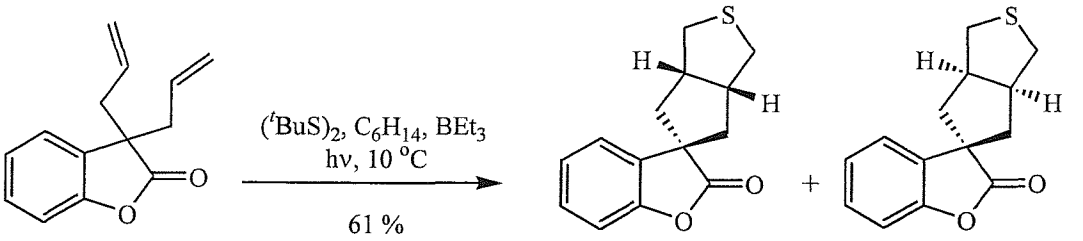
δ_C (75MHz, $CDCl_3$) 173.2 (0, *C*O), 171.9 (0, *C*O), 83.7 (0, *C*OH), 73.5 (0, *C*CO_2Et), 61.3 (2, 2 × O*C*H_2), 52.2 (1), 51.5 (1), 41.0 (2), 39.1 (2), 31.1 (2), 24.9 (3, CH_3C(OH)), 14.2 (3, CH_2CH_3), 14.0 (3, CH_2CH_3) ppm.

LRMS (CI)	302 (M^+, 10 %), 228 (26 %), 210 (38 %), 139 (100 %) amu.
HRMS (CI)	Found $[M+NH_4]^+$: 320.1528. $C_{14}H_{22}O_5S$ requires $[M+NH_4]^+$: 320.1532.

Data for **520**

ν_{max}/cm^{-1} (neat)	3511br. m, 2981m, 2939w, 1731s, 1368w, 1276s, 1260s, 1194m, 1025w, 750s.
δ_H (300MHz, $CDCl_3$)	4.15 (4H, br. q, *J* 7.0 Hz, 2 × OC*H*$_2$), 3.95 (1H, s, SC*H*), 3.76 - 3.68 (1H, m), 3.51 (1H, dd, *J* 11.4, 7.3 Hz), 2.59 (1H, dd, *J* 11.4, 1.3 Hz), 2.32 - 2.18 (1H, m), 2.00 (1H, ddd, *J* 13.1, 11.0, 7.7 Hz), 1.83 (1H, ddd, *J* 13.1, 7.5, 3.0 Hz), 1.70 - 1.60 (1H, m), 1.53 (3H, s, C*H*$_3$), 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.26 (3H, t, *J* 7.0 Hz, CH_2CH_3) ppm.
δ_C (75MHz, $CDCl_3$)	172.4 (0, *C*O), 171.6 (0, *C*O), 84.3 (0, *C*OH), 74.4 (0, *C*CO_2Et), 61.5 (2, O*C*H_2), 61.2 (2, O*C*H_2), 54.3 (1), 51.5 (1), 41.2 (2), 39.9 (2), 31.2 (2), 23.6 (3, *C*H_3C(OH)), 14.2 (3, 2 × CH_2CH_3) ppm.
LRMS (CI)	303 ($[MH]^+$, 30 %), 274 ($[MH-OH]^+$, 22 %), 230 ($[MH-CO_2Et]^+$, 22 %), 181 (40 %), 109 (38 %) amu.
HRMS (CI)	Found MH^+: 303.1274. $C_{14}H_{22}O_5S$ requires MH^+: 303.1266.

rel-(3a'*R*,6a'*S*)-Spiro[2,3-dihydrobenzo[*b*]furan-2-one-3,5'-2'-thiabicyclo[3.3.0]octane] **521** & rel-(3a'*S*,6a'*R*)-spiro[2,3-dihydrobenzo[*b*]furan-2-one-3,5'-2'-thiabicyclo[3.3.0]octane] **522**



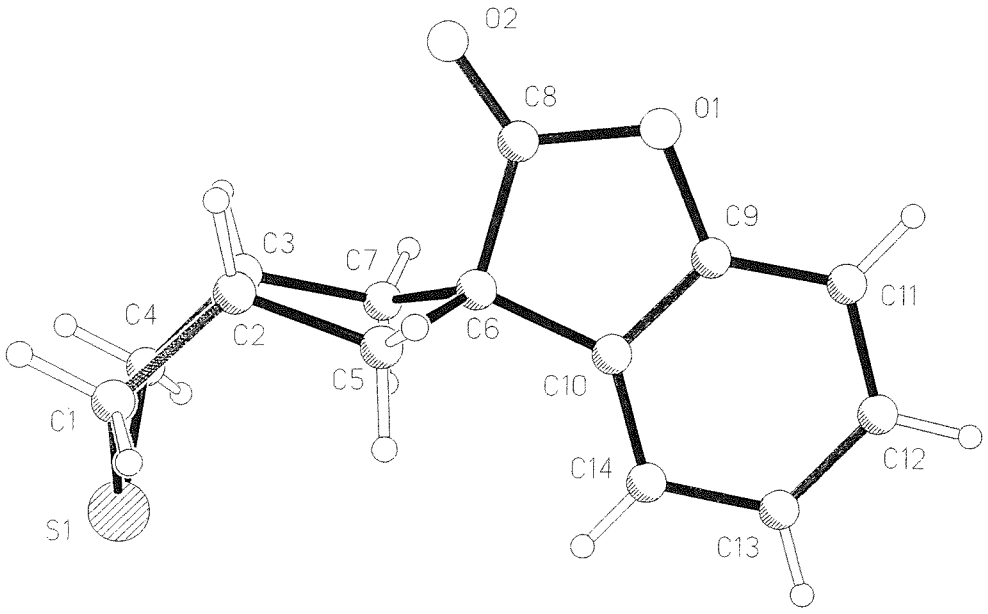
A solution of **516** (0.40 g, 1.87 mmol), *tert*-butyldisulfide (1.67 g, 1.81 mL, 9.35 mmol) and triethylborane (1 mL of a 1 M solution in hexanes, 1 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen and at 10°C. After 30 h the mixture was washed with water (30 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 1 - 10 % ether in petroleum ether) gave firstly **522** (0.187 g, 0.76 mmol, 41 %) as a colourless solid which was recrystallised from hexane to give colourless prisms, then **521** (0.089 g, 0.36 mmol, 20 %) as a colourless solid which was recrystallised from hexane to give large opaque prisms.

Data for **522**

MP	99 - 101°C (hexane).
ν_{max}/cm^{-1} ($CHCl_3$)	2956m, 2926m, 1797vs, 1614w, 1599w, 1461m, 1232m, 1047m, 971m, 751vs.
λ_{max}/nm (ε_{max}, CH_2Cl_2)	271 (1350).
δ_H (300MHz, $CDCl_3$)	7.35 - 7.26 (2H, m, 2 × Ar*H*), 7.18 - 7.11 (2H, m, 2 × Ar*H*), 3.35 - 3.21 (2H, m), 3.10 - 2.90 (2H, br. s), 2.80 - 2.65 (2H, br. m), 2.28 - 2.10 (4H, m) ppm.
δ_C (75MHz, $CDCl_3$)	179.7 (0, *C*O), 152.3 (0, Ar), 133.6 (0, Ar), 128.8 (1, Ar), 124.4 (1, Ar), 123.0 (1, Ar), 111.0 (1, Ar), 54.0 (0, C), 48.0 (1, 2 × *C*H), 44.4 (2, 2 × *C*H$_2$), 38.3 (2, 2 × *C*H$_2$) ppm.
LRMS (EI)	246 (M^+, 59 %), 171 (100 %), 85 (40 %) amu.

CHN Found: C, 68.41; H, 5.88; S, 12.98. $C_{14}H_{14}O_2S$ requires C, 68.26; H, 5.73; S 13.02.

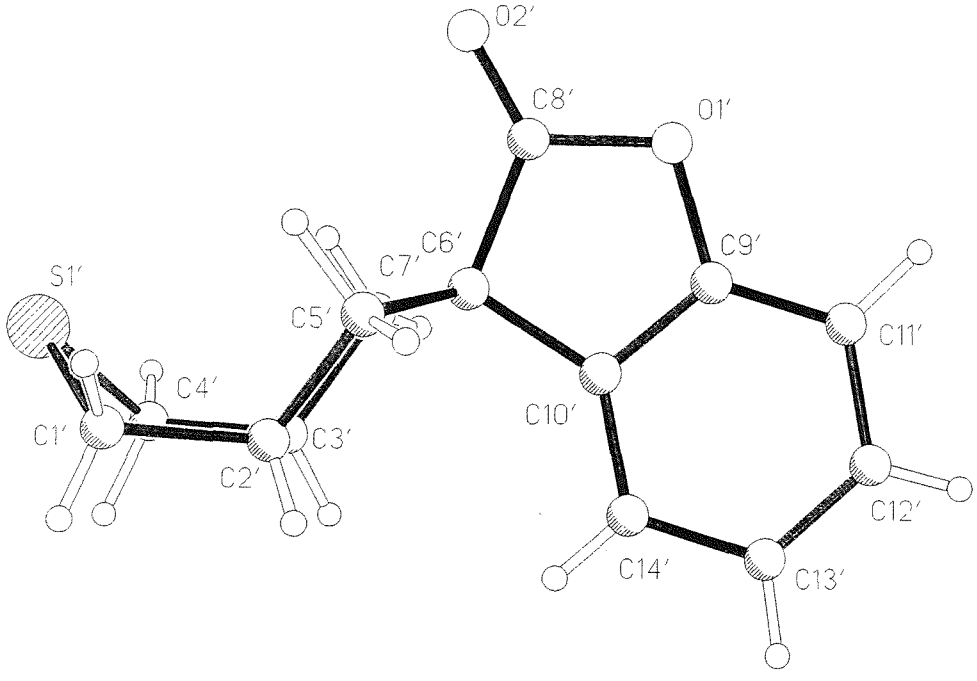
X-ray crystal structure:



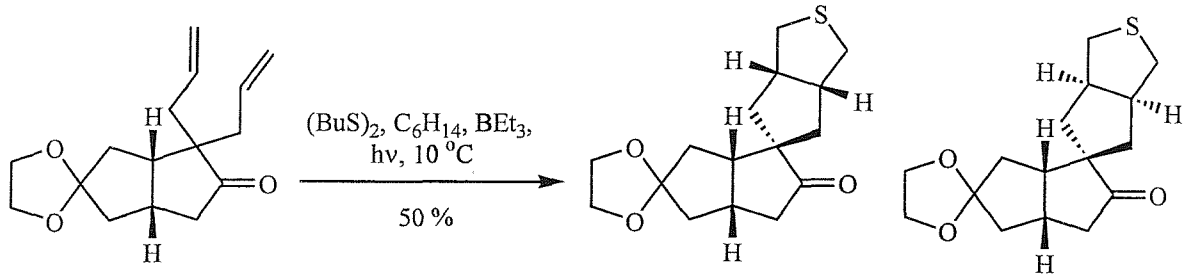
Data for **521**

MP	148 - 150°C (hexane).
ν_{max}/cm^{-1} ($CHCl_3$)	3066w, 2931w, 2841w, 1797vs, 1619w, 1599w, 1297w, 1047m, 1004m, 905m, 760m.
λ_{max}/nm (ε_{max}, MeOH)	272 (1250).
δ_H (300MHz, $CDCl_3$)	7.32 - 7.26 (2H, m, 2 × Ar*H*), 7.20 - 7.14 (1H, m, Ar*H*), 7.11 - 7.07 (1H, m, ArH), 3.46 - 3.34 (2H, m), 2.95 (2H, dd, *J* 12.0, 6.0 Hz), 2.60 (2H, app. d, *J* 11.8 Hz), 2.35 (2H, br. ddd, *J* 13.6, 8.1, 1.3 Hz), 1.93 (2H, br. dd, *J* 13.4, 9.0 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	180.8 (0, *C*O), 152.9 (0, Ar), 130.3 (0, Ar), 128.9 (1, Ar), 124.5 (1, Ar), 122.8 (1, Ar), 110.7 (1, Ar), 54.0 (0, C), 46.8 (1, 2 × *C*H), 44.0 (2, 2 × *C*H_2), 39.0 (2, 2 × *C*H_2) ppm.
LRMS (EI)	246 (M^+, 62 %), 171 (100 %) amu.
CHN	Found: C, 68.22; H, 5.79; S, 12.92. $C_{14}H_{14}O_2S$ requires C, 68.26; H, 5.73; S 13.02.

X-ray crystal structure:



rel-(3a*R*,3a'*S*,6a*S*,6a'*R*)-Dispiro[perhydrocyclopenta[*c*]thiophene-5,3'-oxabicyclo[3.3.0]octane-5',2''-dioxolane **523** and rel-(3a*S*,3a'*S*,6a*R*,6a'*R*)-dispiro[perhydrocyclopenta[*c*]thiophene-5,3'-oxabicyclo[3.3.0]octane-5',2''-dioxolane **524**



$C_{16}H_{22}O_3$
Mol. Wt.: 262

$C_{16}H_{22}O_3S$
Mol. Wt.: 294

3 : 2

523 **524**

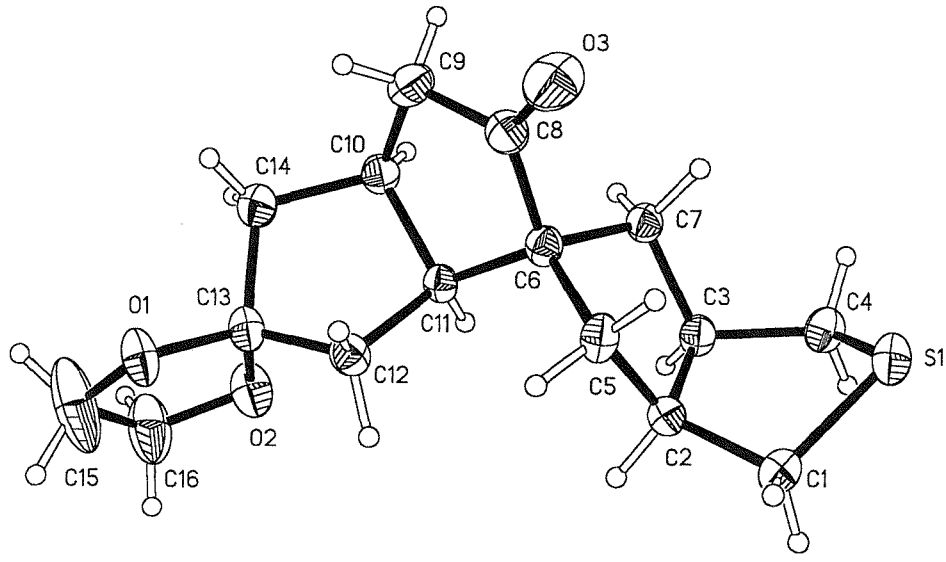
A solution of **517** (0.11 g, 0.42 mmol), *tert*-butyldisulfide (0.37 g, 0.41 mL, 2.10 mmol) and triethylborane (1 mL of a 1 M solution in heptane, 1 mmol) in degassed hexane (100 mL) was irradiated with UV light (Quartz filter) under nitrogen at 10°C. After 24 h the mixture was concentrated *in vacuo* then purified by chromatography (silica, 10 to 50 % ether in petroleum ether) to give firstly recovered **517** (22 mg, 0.082 mmol, 20 %) as a colourless oil, then **524** (22 mg, 0.075 mmol, 18 %) as a colourless oil and finally **523** (40 mg, 0.136 mmol, 32 %) as a colourless solid which was recrystallised from hexane to give colourless needles.

Data for **523**

MP	129 - 131°C (hexane).
ν_{max}/cm^{-1} (solid)	2950m, 2911m, 1723vs, 1431m, 1322s, 1200m, 1118vs, 1007s, 946m, 885s.
δ_H (400MHz, $CDCl_3$)	4.00 - 3.90 (4H, m, OCH_2CH_2O), 3.00 - 2.60 (9H, m), 2.31 (1H, ddd, *J* 14.4, 8.0, 1.5 Hz), 2.13 (1H, dd, *J* 18.4, 7.4 Hz), 1.97 (2H, dd, *J* 13.3, 9.0 Hz), 1.95 - 1.88 (2H, m), 1.70 (1H, ddd, *J* 13.2, 7.4, 2.0 Hz), 1.53 (1H, app. t, *J* 12.2 Hz), 1.49 (1H, dd, *J* 12.2, 9.0 Hz) ppm.

δ_C (75MHz, $CDCl_3$)	220.7 (0, *C*O), 118.1 (0, *C*), 64.9 (2, O*C*H_2), 64.2 (2, O*C*H_2), 62.6 (0, *C*CO), 48.5 (1), 47.4 (1), 47.3 (1), 43.9 (2), 43.5 (2), 43.2 (2), 38.7 (2), 38.4 (2), 38.1 (2), 37.4 (2), 33.3 (1) ppm.
LRMS (CI)	295 ($[MH]^+$, 100 %), 88 (14 %) amu.
HRMS (EI)	Found MH^+: 295.1367. $C_{16}H_{22}O_3S$ requires MH^+: 295.1368.

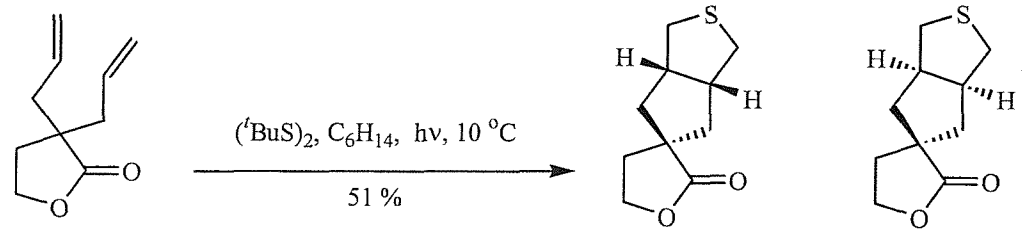
X-ray structure:



Data for **524**

ν_{max}/cm^{-1} (neat)	2932s, 1730vs, 1435w, 1407w, 1325m, 1208w, 1116s, 1018s, 909w, 846w.
δ_H (300MHz, $CDCl_3$)	3.95 - 3.84 (4H, m, OC*H*$_2$C*H*$_2$O), 3.21 – 3.08 (1H, m), 2.95 - 2.45 (7H, m), 2.22 (1H, br. dd, *J* 14.2, 6.7 Hz), 2.12 - 1.92 (4H, m), 1.83 (1H, dd, *J* 14.2, 2.0 Hz), 1.56 - 1.30 (4H, m) ppm.
δ_C (75MHz, $CDCl_3$)	221.8 (0, *C*O), 118.1 (0, *C*), 64.8 (2, O*C*H_2), 64.2 (2, O*C*H_2), 62.4 (0, *C*CO), 50.7 (1), 47.5 (1), 46.7 (1), 43.4 (2), 43.2 (2), 42.4 (2), 39.1 (2), 39.0 (2), 38.4 (2), 37.4 (2), 33.7 (1) ppm.
LRMS (CI)	295 ($[MH]^+$, 100 %) amu.
HRMS (CI)	Found $[M+NH_4]^+$: 312.1635. $C_{16}H_{22}O_3S$ requires $[M+NH_4]^+$: 312.1633.

rel-(3a'*R*,6a'*S*)-Spiro[dihydro-2-furanone-3,5'-2'-thiabicyclo[3.3.0]octane] **525** and rel-(3a'*S*,6a'*R*)-spiro[dihydro-2-furanone-3,5'-2'-thiabicyclo[3.3.0]octane] **526**



$C_{10}H_{14}O_2$
Mol. Wt.: 166

525
$C_{10}H_{14}O_2S$
Mol. Wt.: 198

526
$C_{10}H_{14}O_2S$
Mol. Wt.: 198

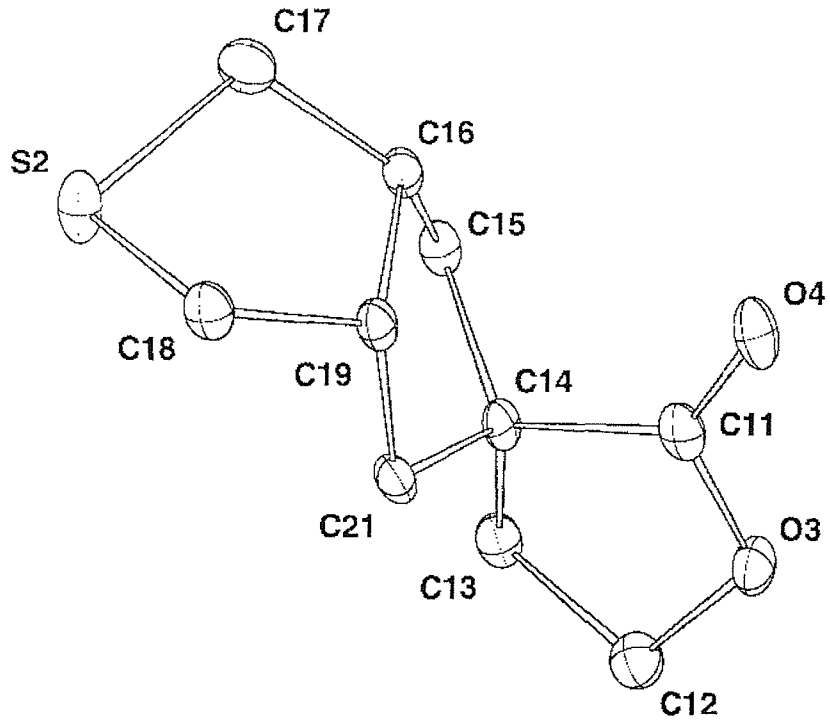
A solution of diene **518** (0.40 g, 2.41 mmol) and *tert*-butyldisulfide (2.15 g, 2.33 mL, 12.0 mmol) in hexane (100 mL) was irradiated with UV (Quartz filter) under nitrogen and at 10°C. After 20 h, the reaction mixture was concentrated *in vacuo* to give a pale yellow oil. Purification by chromatography (silica, 40 % ether in petrol) gave firstly recovered **518** (0.148 g, 0.89 mmol, 37 %), then **525** (0.097 g, 0.49 mmol, 20 %) as a colourless solid that was recrystallised from hexane to give colourless needles, and finally **526** (0.418 g, 0.75 mmol, 31 %) as a colourless solid which was recrystallised from hexane to give colourless needles.

Data for **525**

MP	62 - 64°C (hexane).
ν_{max}/cm^{-1} (solid)	2939m, 1763vs, 1445w, 1372m, 1279w, 1179w, 1129s, 1024s, 913w, 748w.
δ_H (300MHz, $CDCl_3$)	4.26 (2H, t, *J* 7.0 Hz, OC*H*$_2$), 3.17 (2H, m), 2.91 (2H, app. dd, *J* 11.5, 5.6 Hz), 2.52 (2H, app. d, *J* 11.6 Hz), 2.29 (2H, obsc. app. dd, *J* 13.4, 8.1 Hz), 2.28 (2H, t, *J* 7.0 Hz, C*H*$_2$CH$_2$O), 1.56 (2H, app. dd, *J* 13.4, 7.9 Hz) ppm.
δ_C (75MHz, $CDCl_3$)	182.0 (0, *C*O), 66.1 (2, O*C*H$_2$), 50.1 (0), 47.0 (1, 2 × *C*H), 41.8 (2, 2 × *C*H$_2$), 38.8 (2, 2 × *C*H$_2$), 35.7 (2, OCH$_2$*C*H$_2$) ppm.
LRMS (CI)	216 ([M+NH$_4$]$^+$, 100 %), 199 ([MH]$^+$, 6 %) amu.

CHN	Found: C, 60.50; H, 7.05; S, 16.01. $C_{10}H_{14}O_2S$ requires C, 60.57; H, 7.12; S, 16.17.

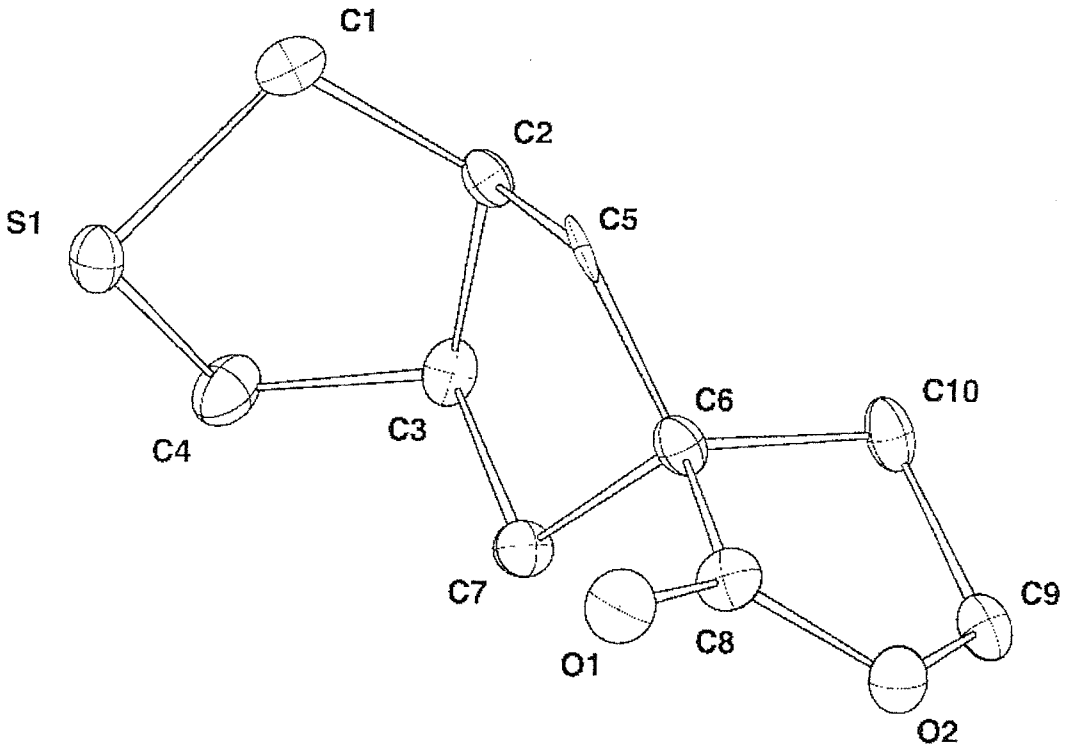
X-ray crystal structure:



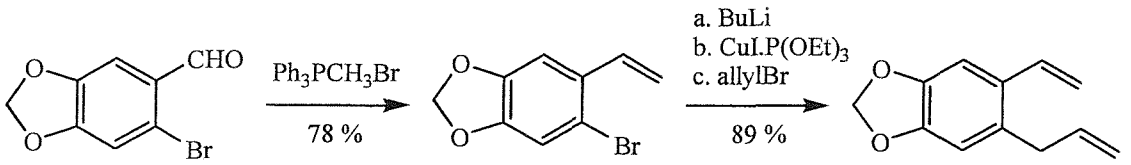
Data for **526**

MP	91 - 93°C (hexane).
ν_{max}/cm^{-1} (solid)	2928w, 1754vs, 1446w, 1375w, 1295w, 1204m, 1175s, 1067w, 1019s, 746m.
δ_H (300MHz, $CDCl_3$)	4.26 (2H, t, *J* 6.9 Hz, OCH_2), 2.84 (4H, br. app. d, *J* 7.7 Hz), 2.62 (2H, br. d, *J* 10.1 Hz), 2.12 (2H, t, *J* 6.9 Hz, CH_2CH_2O), 1.91 (4H, m) ppm.
δ_C (75MHz, $CDCl_3$)	180.9 (0, *C*O), 65.4 (2, OCH_2), 50.1 (0), 47.2 (1, 2 × *C*H), 41.9 (2, 2 × CH_2), 38.2 (2, 2 × CH_2), 35.5 (2, OCH_2CH_2) ppm.
LRMS (CI)	199 ($[MH]^+$, 100 %) amu.
CHN	Found: C, 60.25; H, 7.26; S, 16.08. $C_{10}H_{14}O_2S$ requires C, 60.57; H, 7.12; S, 16.17.

X-ray crystal structure:



Preparation of **532**



$C_8H_5BrO_3$
Mol. Wt.: 229
540

$C_9H_7BrO_2$
Mol. Wt.: 227
541

$C_{12}H_{12}O_2$
Mol. Wt.: 188
532

Piperonyl bromide **540** was prepared following the procedure of Orr *et al.*[144] 5-Bromo-6-vinyl-1,3-benzodioxole **541** was prepared following the procedure of Clark *et al.*[145]

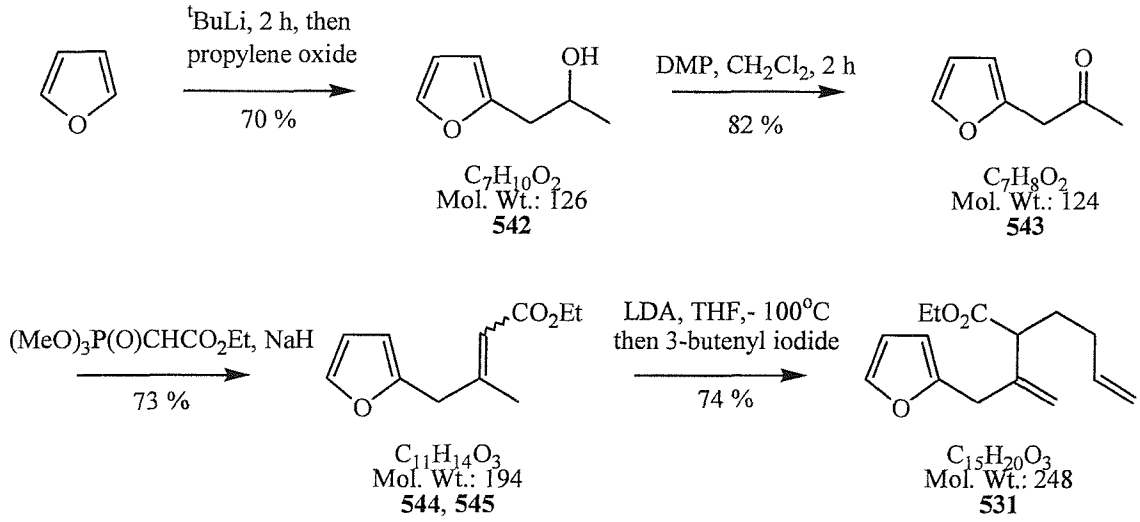
5-Allyl-6-vinyl-1,3-benzodioxole **532**

To a stirred solution of **541** (3.50 g, 15 mmol) in THF (100 mL) at -78°C and under nitrogen was added butyllithium (23.6 mL of a 0.75 M solution in hexane, 18 mmol) *via* syringe over 10 min. After 15min, CuI.P(OEt)$_3$ (6.50 g, 18 mmol) was added in a single portion. After a further 30 min, allyl bromide (1.87 g, 1.33 mL, 15 mmol) was added over 30 s then the reaction mixture warmed to ambient temperature over 30 min. After 30 min, dichloromethane (100 mL) and aqueous ammonia solution (60 mL, 33 % in water) were poured onto the mixture, giving a royal blue aqueous layer. The organic layer was washed repeatedly with ammonia solution until no more blue colour appeared (10 × 100 mL), then washed with water (100 mL) and brine (100mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil (5.17 g). Purification by chromatography (silica, 5 % ether in petroleum ether) gave **532** (2.5 g, 13 mmol, 89 %) as a pale yellow oil.

ν_{max}/cm^{-1} (neat)	3083m, 3009m, 2773w, 1638s, 1626s, 1607w, 1502s.
λ_{max}/nm (ε_{max}, MeOH)	310 (9400), 264 (15000).
δ_H (300MHz, $CDCl_3$)	7.03 (1H, s, Ar*H*), 6.88 (1H, dd, *J* 17.0, 11.0 Hz, ArC*H*=), 6.70 (1H, s, Ar*H*), 5.95 (2H, s, CH_2), 6.04 – 5.82 (1H, m, CH_2CH=) 5.54 (1H, d, *J* 17.0 Hz, ArCH=C*H*H), 5.21 (1H, d, *J* 11.0 Hz, ArCH=CH*H*)), 5.08 (1H, d, *J* 9.1 Hz, CH_2CH=C*H*H), 4.99 (1H, d, *J* 17.0 Hz, CH_2CH=CH*H*), 3.38 (2H, br. d, *J* 7.2 Hz, ArCH_2) ppm.

δ_C **(75.5MHz, $CDCl_3$)**	147.5 (0, Ar), 146.6 (0, Ar), 137.0 (1), 134.2 (1), 131.3 (0), 130.3 (0), 115.9 (2), 113.8 (2), 109.8 (1), 105.5 (1), 101.1 (2, O-CH_2-O), 37.4 (2, ArCH_2) ppm.
LRMS (APCI)	189 ($[MH]^+$, 100 %) amu.

Preparation of **531**



1-(2-Furyl)-2-propanol **542** was prepared following the procedure of Fogagnolo *et al.*[146] All data was consistent with literature values.

1-(2-Furyl)acetone **543**[146]

To a stirred suspension of Dess Martin periodinane (7.54 g, 17.9 mmol) in dichloromethane (30 mL) at ambient temperature and under nitrogen was added a solution of alcohol **542** (1.88 g, 14.9 mmol) in dichloromethane (15 mL). After 12 h, sodium hydrogen carbonate (5 g) was added. After 5 min, the mixture was filtered through celite and the filtrate concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 20 % ether in petroleum ether) gave **543** (1.51 g, 12.2 mmol, 82 %) as a pale yellow oil.

All data was consistent with literature values.[146]

Ethyl (*Z*)-4-(2-furyl)-3-methyl-2-butenoate **544** & Ethyl (*E*)-4-(2-furyl)-3-methyl-2-butenoate **545**

To a suspension of sodium hydride (0.70 g, 17.5 mmol) in tetrahydrofuran (20 mL) at ambient temperature and under nitrogen was added ethyl dimethylphosphonoacetate (3.43 g, 3.07 mL, 17.5 mmol) in tetrahydrofuran over 5 min. To the suspension was added a solution of ketone **543** (1.55 g, 12.5 mmol) in tetrahydrofuran (10 mL) over 2 min. After 2 h, the mixture was partitioned between water (20 mL) and ether (20 mL) and the layers separated. The aqueous phase was extracted with ether (2 × 20 mL) then the combined organic phases were washed with water (10 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by chromatography (silica, 2 % ether in petroleum ether) gave firstly **544** (0.42 g, 2.16 mmol, 17 %) as a colourless oil, then mixed fractions of **544** and **545** (1.10 g, 5.67 mmol, 45 %) as a colourless oil, and finally **545** (0.39 g, 2.00 mmol, 16 %) as a colourless oil.

Data for **545**

ν_{max}/cm^{-1} (neat)	2981w, 2908w, 1712s, 1653m, 1595w, 1504w, 1276w, 1212vs, 1141vs, 730s.
δ_H (300MHz, $CDCl_3$)	7.35 (1H, dd, *J* 1.8, 0.8 Hz, furan-*H*), 6.33 (1H, dd, *J* 3.1, 1.8 Hz, furan-*H*), 6.11 (1H, dd, *J* 3.1, 0.8 Hz, furan-*H*), 5.70 (1H, q, *J* 1.2 Hz, =C*H*), 4.15 (2H, q, *J* 7.2 Hz, OCH_2), 3.45 (2H, s, CH_2), 2.17 (3H, d, *J* 1.2 Hz, CH_3), 1.28 (3H, t, *J* 7.2 Hz, OCH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	166.7 (0, CO), 155.5 (0, *C*=), 151.6 (0, furan), 142.0 (1, furan-H), 117.6 (1, =*C*H), 110.5 (1, furan-H), 107.5 (1, furan-H), 59.8 (2, OCH_2), 39.3 (2, *C*H_2), 18.7 (3, *C*H_3), 14.4 (3, OCH_2CH_3) ppm.
LRMS (CI)	212 ($[M+H_2O]^+$, 10 %), 195 ($[MH]^+$, 100 %), 148 ($[M-EtOH]^+$, 26 %) amu.

Data for **544**

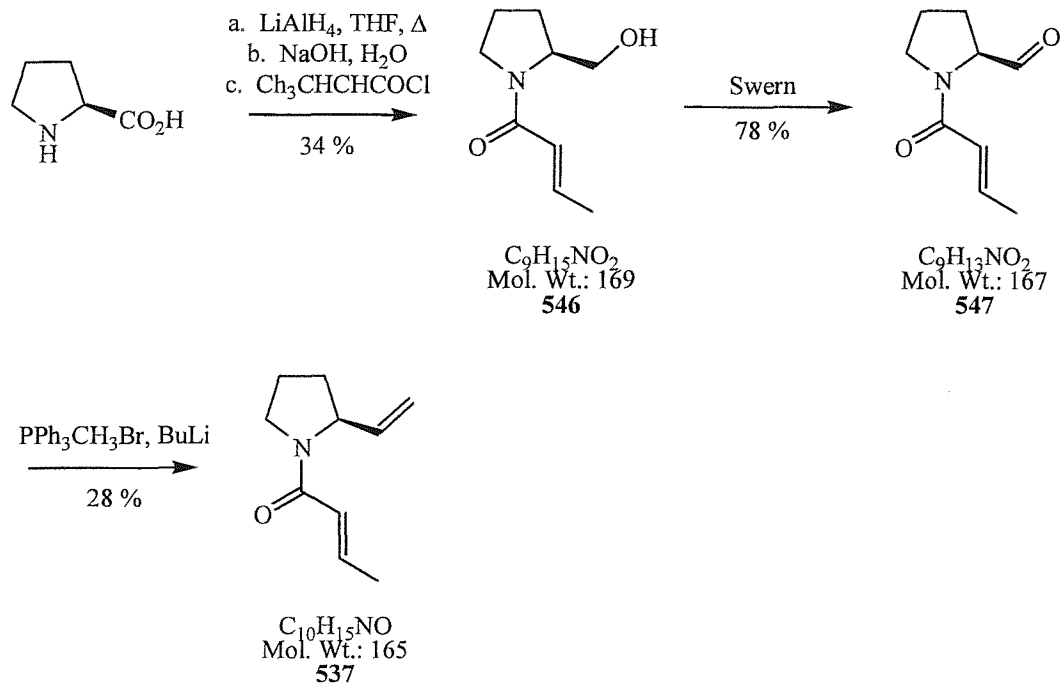
ν_{max}/cm^{-1} **(neat)**	2981w, 2912w, 1711vs, 1650m, 1594w, 1504w, 1442m, 1267w, 1145vs, 728s
δ_H **(300MHz, $CDCl_3$)**	7.32 (1H, dd, *J* 1.8, 0.8 Hz, furan-*H*), 6.30 (1H, dd, *J* 3.1, 1.8 Hz, furan-*H*), 6.10 (1H, dd, *J* 3.1, 0.8 Hz, furan-*H*), 5.78 (1H, q, *J* 1.3 Hz, =C*H*), 4.18 (2H, q, *J* 7.2 Hz, OCH_2), 4.07 (2H, s, CH_2), 1.89 (3H, d, *J* 1.3 Hz, CH_3), 1.30 (3H, t, *J* 7.2 Hz, OCH_2CH_3) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	166.3 (0, CO), 155.2 (0, *C*=), 152.6 (0, furan), 141.5 (1, furan-H), 117.7 (1, =*C*H), 110.5 (1, furan-H), 106.7 (1, furan-H), 59.9 (2, O*C*H_2), 31.7 (2, *C*H_2), 24.9 (3, *C*H_3), 14.4 (3, OCH_2CH_3) ppm.
LRMS (CI)	195 ($[MH]^+$, 100 %), 148 ($[MH\text{-}EtO]^+$, 30 %) amu.
HRMS (ES)	Found $[MH]^+$ 195.1023. $C_{11}H_{14}O_3$ requires $[MH]^+$ 195.1021.

Ethyl 2-[1-(2-furylmethyl)vinyl-5-hexenoate **531**

To a stirred solution of *N,N*-diisopropylamine (0.45 g, 0.62 mL, 4.44 mmol) in tetrahydrofuran (15 mL) at –100°C and under nitrogen was added butyllithium (3.17 mL of a 1.4 M solution in hexanes, 4.44 mmol). The mixture was warmed to 0°C then recooled to -100°C. A solution of the esters **544**, **545** (0.82 g, 4.23 mmol) in tetrahydrofuran (25 mL) was added over 5 min. After 30 min, a solution of 3-butenyl iodide (1.16 g, 6.35 mmol) in tetrahydrofuran (20 mL) was added over 5 min. After 3 h at -100°C the mixture was warmed to ambient temperature over 2 h. After 15 h, saturated aqueous ammonium chloride (10 mL) was added and the phases separated. The aqueous phase was extracted with ether (3 × 20 mL) then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil. Purification by chromatography (silica, 3 % ether in petroleum ether) gave **531** (0.78 g, 3.15 mmol, 74 %) as a colourless oil.

ν_{max}/cm^{-1} **(neat)**	2988s, 2869s, 1736s, 1448w, 1365m, 1217m, 1142vs, 911w.
δ_H **(300MHz, $CDCl_3$)**	7.34 (1H, dd, *J* 1.8, 0.9 Hz, furan-*H*), 6.30 (1H, dd, *J* 3.1, 1.8 Hz, furan-*H*), 6.08 (1H, br. dd, *J* 3.1, 0.9 Hz, furan-*H*), 5.74 (1H, ddt, *J* 17.1, 10.3, 6.8 Hz, C*H*=), 5.08 (1H, br. s, =C*H*H), 5.04 – 4.92 (3H, m, =CH*H* & CH=CH_2), 4.11 (2H, q, *J* 7.2 Hz, OCH_2), 3.42 (2H, s, furan-CH_2), 3.05 (1H, t, *J* 6.8 Hz, C*H*CO_2), 2.05 – 1.85 (4H, m), 1.66 (1H, dd, *J* 13.1, 7.5 Hz), 1.25 (3H, t, *J* 7.2 Hz, OCH_2CH_3) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	173.6 (0, CO), 152.9 (0, furan), 143.3 (0, *C*=), 141.6 (1, furan-H), 137.8 (1, *C*H=), 115.4 (2, =*C*H_2), 114.9 (2, =*C*H_2), 110.4 (1, furan-H), 107.2 (1, furan-H), 60.8 (2, O*C*H_2), 50.6 (1, *C*H), 34.1 (2), 31.6 (2, furan-*C*H_2), 30.0 (2), 14.4 (3, OCH_2CH_3) ppm.
LRMS (CI)	249 ([MH]$^+$, 100 %) amu.

Formation of **537**



$C_9H_{15}NO_2$
Mol. Wt.: 169
546

$C_9H_{13}NO_2$
Mol. Wt.: 167
547

$C_{10}H_{15}NO$
Mol. Wt.: 165
537

(2*E*,2'*S*)-1-[2'-(Hydroxymethyl)tetrahydro-1*H*-pyrrol-1-yl]-2-buten-1-one **546** was prepared following the procedure of Greene *et al.*[148] All spectral and physical characteristics were consistent with literature values.

(2*S*,2'*E*)-1-[2'-Butenoyl]tetrahydro-1*H*-pyrrole-2-carboxaldehyde **547**

Prepared following the procedure of Swern *et al.*[148] Thus, to a stirred solution of oxalyl chloride (2.53 mL of a 2M solution in dichloromethane, 5.0 mmol) in dichloromethane (5 mL) at -78°C and under nitrogen was added a solution of DMSO (8.9 mL of a 1.0 M solution in DCM, 8.9 mmol) over 2 min. After 45 min, a solution of **546** (0.50 g, 2.96 mmol) in dichloromethane (10 mL) was added *via* cannula over 2 min. The reaction mixture was stirred for a further 2 h then triethylamine (1.20 g, 1.65 mL, 11.8 mmol) was added and the reaction mixture warmed to -20°C over 30 min. The mixture was poured onto 0.5 M sodium bisulfate (30 mL) and the aqueous phase extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with saturated sodium bicarbonate (25 mL) then brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pale yellow oil (0.65 g). Purification by chromatography (silica, 30 % ethyl acetate in dichloromethane) gave **547** (0.38 g, 2.28 mmol, 78 %) as a colourless oil.

Note: NMR showed that at 25°C this compound exists as a mixture of rotamers (~1 : 5 ratio).

ν_{max}/cm^{-1} **(neat)**	2973m, 2881m, 1732s, 1662s, 1606s, 1450s, 1424s, 1307w, 1046w, 966m, 828w.
δ_H **(300MHz, $CDCl_3$)**	Major rotamer: 9.53 (1H, d, *J* 1.8 Hz, C*H*O), 6.97 (1H, dq, *J* 15.1, 7.0 Hz, =C*H*CH_3), 6.18 (1H, app. dd, *J* 15.1, 1.7 Hz, C*H*=$CHCH_3$), 4.53 – 4.41 (1H, m, NC*H*), 3.75 – 3.54 (2H, m, NCH_2), 2.15 – 1.80 (4H, m, $NCH_2CH_2CH_2$), 1.90 (3H, dd, *J* 6.8, 1.5 Hz, CH_3) ppm. Minor rotamer: 5.84 (1H, app dd, *J* 14.9, 1.5 Hz, C*H*=$CHCH_3$), 4.4. – 4.30 (1H, m, NC*H*), 1.83 (3H, br. dd, *J* 6.8, 1.3 Hz, CH_3) ppm. All remaining signals obscured by major rotamer.
δ_C **(75.5MHz, $CDCl_3$)**	Major rotamer: 199.7 (1, *C*HO), 165.5 (0, N*C*O), 143.0 (1, *C*H=$CHCH_3$), 122.2 (1, CH=*C*HCH_3), 65.0 (1, N*C*H), 47.2 (2, NCH_2), 26.2 (2, $NCH_2CH_2CH_2$), 25.2 (2, NCH_2CH_2), 18.3 (3, CH_3) ppm. Minor rotamer: 199.4 (1, *C*HO), 143.2 (1, *C*H=$CHCH_3$), 122.4 (1, =*C*HCH_3), 65.4 (1, N*C*H), 47.0 (2, NCH_2), 28.4 (2, $NCH_2CH_2CH_2$), 22.9 (2, NCH_2CH_2) ppm. Other signals obscured by major rotamer.
LRMS (ES)	335 ($[2M+H]^+$, 10 %), 168 ($[MH]^+$, 100 %) amu.
CHN	Found C, 60.16; H, 8.15; N, 8.04; M.0.75H_2O requires C, 59.8; H, 8.03; N, 7.76.

(2*E*,2'*S*)-1-[2'-Vinyltetrahydro-1'*H*-pyrrol-1-yl]-2-buten-1-one **537**

Prepared following the procedure of Wittig.[149] Thus, to a stirred solution of methyltriphenylphosphonium bromide (0.64 g, 1.8 mmol) in THF (10 mL) under nitrogen and at –78°C was added butyllithium (1.71 mL of a 1.05M solution in hexane, 1.8 mmol) over 1 min. After 1 h the mixture was warmed to ambient temperature over 10 min. After 15 min at room temperature, the mixture was recooled to –78°C and to it was added a solution of aldehyde **547** (0.30 g, 1.8 mmol) in THF (5 mL) over 1 min. After 14 h the mixture was warmed to ambient temperature, filtered and concentrated *in vacuo* to a yellow residue (0.66 g). Purification by chromatography (silica, 50 % ethyl acetate in petrol) gave **537** (0.082 g, 0.50 mmol, 28 %) as a colourless oil.

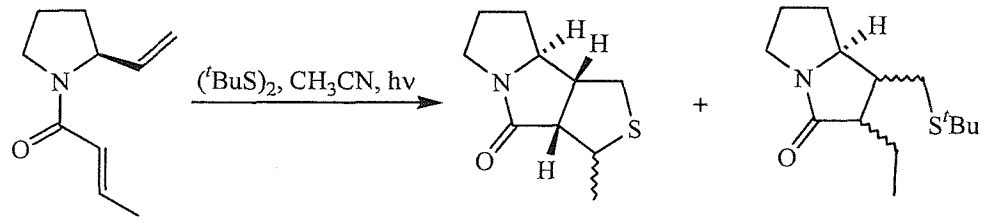
Note: NMR showed that at 25°C this compound exists as a mixture of rotamers (~1 : 2 ratio).

ν_{max}/**cm^{-1} (neat)**	3082w, 2971m, 2878w, 1665s, 1614s, 1449s, 1417s, 1347w, 1305w, 965m, 909m, 827w.
λ_{max}/**nm** (ε_{max}, **MeOH**)	235 (950).
δ_H (**300MHz, $CDCl_3$**)	Major rotamer: 6.88 (1H, dq, *J* 15.2, 6.9 Hz, =C*H*CH_3), 6.02 (1H, app. dd, *J* 15.2, 1.4 Hz, C*H*=$CHCH_3$), 5.76 (1H, ddd, *J* 17.0, 10.2, 4.6 Hz, C*H*=CH_2), 5.13 (1H, d, *J* 10.2 Hz, CH=C*H*H), 5.03 (1H, d, *J* 17.0 Hz, CH=CH*H*), 4.42 (1H, t, *J* 6.1 Hz, NC*H*), 3.65 – 3.40 (2H, m, NCH_2), 2.20 – 1.70 (4H, m, $NCH_2CH_2CH_2$), 1.81 (3H, dd, *J* 6.9, 1.4 Hz, CH_3) ppm. Minor rotamer: 6.13 (1H, app. dd, *J* 15.1, 1.5 Hz, C*H*=$CHCH_3$), 4.75 – 4.63 (1H, br. m, *J* 6.1 Hz, NC*H*) ppm. All remaining signals obscured by major rotamer.
δ_C (**75.5MHz, $CDCl_3$**)	Major rotamer: 165.6 (0, *C*O), 140.7 (1, *C*H=$CHCH_3$), 138.6 (1, *C*H=CH_2), 123.5 (1, =*C*HCH_3), 115.3 (2, CH=*C*H_2), 59.3 (1, N*C*H), 46.3 (2, NCH_2), 32.6 (2, $NCH_2CH_2CH_2$), 21.7 (2, NCH_2CH_2), 18.2 (3, *C*H_3) ppm. Minor rotamer: 164.8 (0, *C*O), 141.4 (1, *C*H=$CHCH_3$), 137.5 (1, *C*H=CH_2), 123.2 (1, =*C*HCH_3), 114.2 (2, CH=*C*H_2), 58.6 (1,

	NCH), 46.9 (2, NCH_2), 30.4 (2, $NCH_2CH_2CH_2$), 23.8 (2, NCH_2CH_2), 18.2 (3, CH_3) ppm.
LRMS (ES)	353 ($[2M+Na]^+$, 15 %), 331 ($[2M+H]^+$, 60 %), 166 ($[MH]^+$, 100 %) amu.
HRMS (EI)	Found M^+, 165.1145. $C_{10}H_{15}NO$ requires M^+, 165.1154.

(3*RS*,3a*R*,7a*S*,7b*R*)–3–Methylperhydrothieno[3,4–a]pyrrolizin–4–one **538** and

(7a*S*)–1–{[(1,1–dimethylethyl)thio]methyl}–2–ethylperhydro–3–pyrrolizinone **539**



$C_{10}H_{15}NO$
Mol. Wt.: 165

$C_{10}H_{15}NOS$
Mol. Wt.: 197

538
22 %

$C_{14}H_{25}NOS$
Mol. Wt.: 255

539
18 %

(15 % recovered starting material)

To a stirred solution of **537** (0.75 g, 4.6 mmol) and *tert*-butyldisulfide (4.1 g, 4.4 mL, 22.7 mmol) in degassed acetonitrile (10 mL) was added triethylborane (1.0 mL of a 1M solution in hexane, 1.0 mmol). The reaction mixture was irradiated (Quartz filter) at reflux for 30 h then cooled to ambient temperature and concentrated *in vacuo*. The oily residue was purified by chromatography (silica, ether) to give firstly **539** (0.21g, 0.81 mmol, 18 %) as a brown oil then recovered **537** (0.11 g, 0.67 mmol, 15 %) as a brown oil and finally **538** (0.20 g, 1.01 mmol, 22 %) as a brown oil.

Data for **538** (isolated as an inseparable mixture of diastereomers in ~5 : 4 ratio).

ν_{max}/cm^{-1} (neat)	2962m, 2927m, 2884m, 1687s, 1422m, 1376w, 1330w, 1285w, 1216w.
δ_H (300MHz, $CDCl_3$)	4.05 – 3.92 (1H m), 3.90 – 3.79 (1H, app. q, *J* 7.0 Hz), 3.70 – 3.60 (2H, m), 3.60 – 3.40 (3H, m), 3.22 – 3.10 (3H, m), 3.09 – 2.95 (3H, m), 2.95 – 2.80 (2H, m), 2.79 – 2.65 (2H, m), 2.30 – 1.70 (8H, m), 1.70 – 1.53 (1H, m), 1.45 – 1.15 (8H, m) ppm.
δ_C (75.5MHz, $CDCl_3$)	Major isomer: 174.7 (0, *C*O), 67.6 (1), 63.4 (1), 47.3 (1), 44.0 (1), 41.4 (2), 37.0 (2), 31.5 (2), 26.0 (2), 23.3 (3, *C*H_3) ppm. Minor isomer: 174.7 (0, *C*O), 67.6 (1), 61.9 (1), 48.9 (1), 44.2 (1), 41.1 (2), 32.8 (2), 26.7 (2), 25.6 (2), 23.3 (3, *C*H_3) ppm.
LRMS (APCI)	239 ($[MH+CH_3CN]^+$, 90 %), 198 ($[MH]^+$, 100 %) amu.

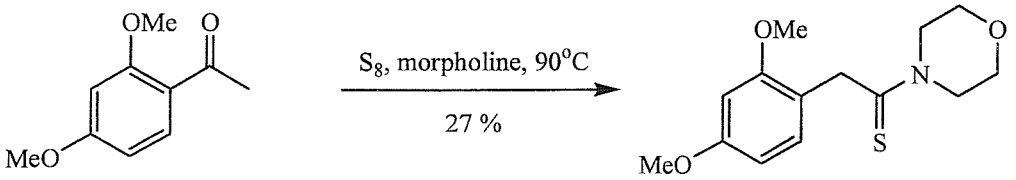
HRMS (EI)	Found M^+, 197.0870. $C_{10}H_{15}NOS$ requires M^+, 197.0874.

Data for **539** (isolated as an inseparable mixture of diastereomers in ~8 : 1 ratio).

ν_{max}/cm^{-1} (neat)	2961m, 2872w, 1695s, 1455w, 1412w, 1331w, 1279w, 1208w, 1164w.
δ_H (300MHz, $CDCl_3$)	Major component: 3.56 – 3.42 (2H, m, NC*H*$_2$), 3.10 – 2.96 (1H, m), 2.82 (1H, dd, *J* 11.4, 4.0 Hz), 2.60 – 2.42 (2H, m), 2.20 – 2.10 (2H, m), 2.10 – 1.90 (3H, m), 1.80 – 1.65 (1H, m), 1.65 – 1.50 (1H, m), 1.30 (9H, br. s, C(C*H*$_3$)$_3$), 0.97 (3H, t, *J* 7.5 Hz, CH_2CH_3) ppm. Minor component: all signals obscured by major component.
δ_C (75.5MHz, $CDCl_3$)	Major component: 174.9 (0, *C*O), 65.5 (1), 53.0 (1), 47.1 (1), 42.4 (0, *C*(CH$_3$)$_3$), 41.1 (2, NCH$_2$), 32.7 (2), 31.7 (2), 31.0 (3, C(*C*H$_3$)$_3$), 26.8 (2), 22.4 (2, *C*H$_2$CH$_3$), 11.4 (3, CH$_2$*C*H$_3$) ppm. Minor component: 65.2 (1), 52.4 (1), 46.7 (1), 32.5 (2), 30.1(3), 26.0 (2) ppm. All other signals obscured by major component.
LRMS (APCI)	297 ([MH+CH$_3$CN]$^+$, 10 %), 288 (10 %), 256 ([MH]$^+$, 100 %) amu.
HRMS (EI)	Found M^+, 255.1658. $C_{14}H_{25}NOS$ requires M^+, 255.1657.

7.6 EXPERIMENTAL FOR CHAPTER 6

2-(2,4-Dimethoxyphenyl)-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanethione **619**[140]



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

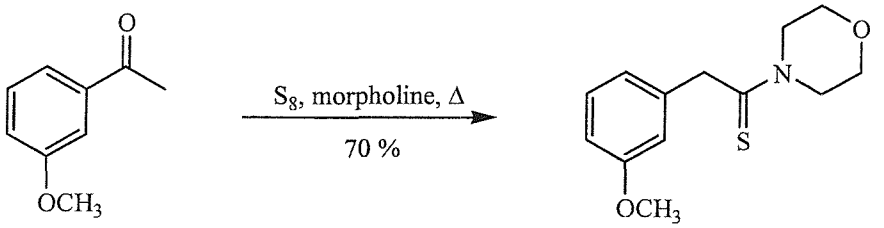
$C_{14}H_{19}NO_3S$
Mol. Wt.: 281

Following the procedure of Carmack and Spielman.[33] Thus, a mixture of 2,4-dimethoxyacetophenone (12.0 g, 66.7 mmol), sulfur (3.20 g, 100 g atom), and morpholine (8.72 g, 100 mmol) was stirred at 90°C for 18 h. The mixture was cooled and purified by chromatography (silica, 50 to 100 % ether in petroleum ether) to give firstly recovered starting material (6.60 g, 36.6 mmol, 55 %) then **619** (5.04 g, 17.9 mmol, 27 %) as a yellow solid that was recrystallised from ethanol to give **619** as colourless crystals.

MP	76 - 78°C (ethanol). Lit. 80°C (ether).[140]
ν_{max}/cm^{-1} (neat)	2941w, 2856w, 1606m, 1587m, 1501s, 1435s, 1297s, 1260m, 1206s, 1025s.
λ_{max}/nm (ε_{max}, MeOH)	280 (14600).
δ_H (300MHz, $CDCl_3$)	7.31 (1H, d, *J* 8.3 Hz, Ar*H*), 6.47 (1H, dd, *J* 8.3, 2.4 Hz, Ar*H*), 6.44 (1H, d, *J* 2.4 Hz, Ar*H*), 4.35 (2H, m, 2 × OC*H*H), 4.19 (2H, s, ArCH_2), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.73 (2H, m, 2 × OCH*H*), 3.61 (2H, m, 2 × NC*H*H), 3.42 (2H, m, 2 × NCH*H*) ppm.
δ_C (75.5MHz, $CDCl_3$)	201.7 (0, *C*S), 160.1 (0, Ar), 156.8 (0, Ar), 129.3 (1, Ar), 116.6 (0, Ar), 104.7 (1, Ar), 98.6 (1, Ar), 66.6 (2, OCH_2), 66.5 (2, OCH_2), 55.6 (3, OCH_3), 55.5 (3, OCH_3), 50.8 (2, NCH_2), 50.3 (2, NCH_2), 43.0 (2, ArCH_2) ppm.
LRMS (APCI)	282 ([MH]$^+$, 40 %), 252 ([MH-C_2H_6]$^+$, 20 %), 195 ([M-$C_4H_6N_2O_2$]$^+$, 88 %) amu.

CHN Found: C, 59.56; H, 6.59; N, 4.83; S, 11.45. $C_{14}H_{19}NO_3S$ requires C, 59.76; H, 6.81; N, 4.98; S, 11.39.

2-[3-(Methyloxy)phenyl]-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanethione **605**[117]



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

$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

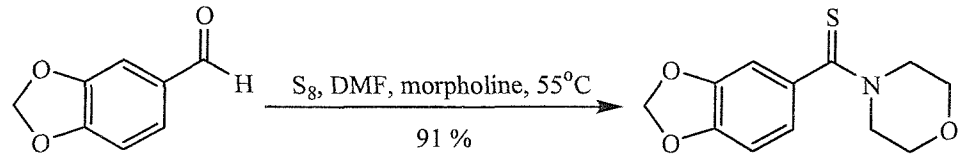
Prepared as described by Schwenk and Bloch (with slight modification).[117] Thus, a mixture of 3–methoxyacetophenone (9.4 g, 8.6 mL, 62.6 mmol), sulfur (3.0 g, 94.0 g atom), and morpholine (8.17 g, 8.2 mL, 94.0 mmol) were stirred with heating to 90°C for 12h. The resulting red oil was purified by chromatography (silica, 20 - 50 % ether in petroleum ether) to afford a yellow solid (15.0 g) which was recrystallised from ether to give thiomorpholide **605** (11.0 g, 44 mmol, 70 %) as colourless, cubic crystals.

Spectral and physical characteristics were consistent with literature values.[81,117]

MP	81 - 83°C (ether). Lit. 82 - 84°C (solvent not reported).[81]
ν_{max}/cm^{-1} (neat)	2957w, 2851w, 1600m, 1256m, 1146w, 1110s, 1034m, 958w, 869w.
λ_{max}/nm (ε_{max}, MeOH)	280 (12800).
δ_H (300MHz, $CDCl_3$)	7.24 (1H, app. t, *J* 7.8 Hz, Ar*H*), 6.90 (1H, s, Ar*H*), 6.88 (1H, d, *J* 7.8 Hz, Ar*H*), 6.79 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 4.35 (2H, app. t, *J* 4.8 Hz, OCH_2), 4.32 (2H, s, ArCH_2), 3.80 (3H, s, ArOCH_3), 3.74 (2H, app. t, *J* 4.8 Hz, OCH_2), 3.64 (2H, app. t, *J* 5.1 Hz, NCH_2), 3.42 (2H, app. t, *J* 5.0 Hz, OCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	199.9 (0, *C*S), 160.1 (0, Ar), 137.4 (0, Ar), 130.1 (1, Ar), 120.1 (1, Ar), 113.6 (1, Ar), 112.6 (1, Ar), 66.5 (2, OCH_2), 66.3 (2, OCH_2), 55.4 (3, $ArOCH_3$), 51.0 (2, NCH_2), 50.8 (2, NCH_2), 50.3 (2, Ar*C*H_2) ppm.
LRMS (APCI)	252 ([MH]$^+$, 100 %), 130 (10 %) amu.

CHN	Found: C, 62.16; H, 6.72; N, 5.56; S, 12.75. $C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57; S, 12.76.

1,3-Benzodioxol-5-yl(tetrahydro-2*H*-1,4-oxazin-4-yl)methanethione **610**



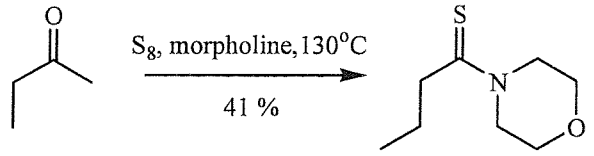
$C_8H_6O_3$
Mol. Wt.: 150

$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

Prepared following the procedure of Carayon-Gentil.[118] Thus, to a stirred mixture of piperonal (2.50 g, 16.7 mmol) in dry DMF (5 mL) and under nitrogen was added sulfur (0.80 g, 25.0 g atom) and morpholine (1.59 g, 1.60 mL, 18.3 mmol). The reaction mixture was heated at 55°C for 6 h then cooled. Water (50 mL) was added causing a yellow solid to precipitate. The solid was filtered, washed with petroleum ether and recrystallised from ethanol to give **610** (3.81 g, 15.2 mmol, 91 %) as pale yellow crystals.

MP	164 - 166°C (ethanol).
ν_{max}/cm^{-1} (neat)	2966w, 2855w, 1604w, 1342w, 1291m, 1251s, 1112m, 1033s, 856w.
λ_{max}/nm (ε_{max}, MeOH)	287 (13500).
δ_H (300MHz, $CDCl_3$)	6.83 (1H, s, Ar*H*), 6.80 (2H, app. s, 2 × Ar*H*), 5.98 (2H, s, OCH_2O), 4.40 (2H, br. s, OCH_2), 3.87 (2H, br. s, OCH_2), 3.66 (4H, br. s, 2 × NCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	200.7 (0, *C*S), 148.5 (0, Ar), 147.8 (0, Ar), 136.4 (0, Ar), 120.2 (1, Ar), 108.3 (1, Ar), 107.7 (1, Ar), 101.7 (2, OCH_2O), 66.9 (2, OCH_2), 66.7 (2, OCH_2), 52.9 (2, NCH_2), 50.1 (2, NCH_2) ppm.
LRMS (APCI)	252 ([MH]$^+$, 100 %), 165 ([M-N(C_2H_4)$_2$O]$^+$, 10 %) amu.
CHN	Found: C, 56.97; H, 4.98; N, 5.39; S, 12.64. $C_{12}H_{13}NO_3S$ requires C, 57.35; H, 5.21; N, 5.57; S, 12.76.

1-Tetrahydro-2*H*-1,4-oxazinyl-1-butanethione **615**[118]



C_4H_8O
Mol. Wt.: 72

$C_8H_{15}NOS$
Mol. Wt.: 173

Prepared following the procedure of Viehe *et al.*[119] Thus, methyl ethyl ketone (5.0 g, 6.2 mL, 69 mmol), morpholine (12.0 g, 12.1 mL, 140 mmol) and sulfur (3.3 g, 110 g atom) were heated at 130°C for 2½ h. The resultant black oil was cooled to ambient temperature then purified by chromatography (silica, 20 - 50 % ether in petrol) to give **615** (4.91 g, 28 mmol, 41 %) as a brown solid. Recrystallisation from ethanol gave a cream solid (1.03 g, 5.9 mmol, 9 %).

Spectral and physical properties were consistent with literature.[118,119]

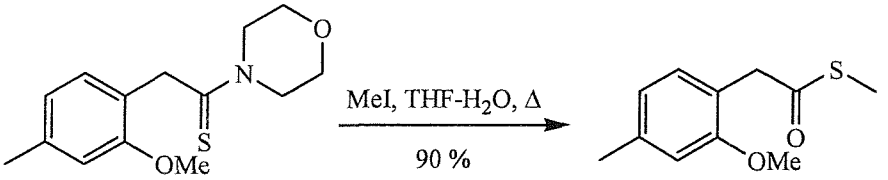
MP	41 - 43°C (ethanol). Lit. 40 - 42°C (ethanol);[119] lit. 46°C (water).[118]
ν_{max}/**cm**$^{-1}$ **($CHCl_3$)**	2961s, 2860m, 1470s, 1445m, 1304m, 1208m, 1114s, 1023s, 878w, 743w.
λ_{max}/**nm** (ε_{max}, **MeOH**)	279 (14500).
δ_H **(300MHz, $CDCl_3$)**	4.34 (2H, app. t, *J* 5.0 Hz, OCH_2), 3.80 - 3.70 (6H, m, 2×NCH_2 & OCH_2), 2.84 (2H, m, CH_2CS), 1.72 (2H, m, $CH_2CH_2CH_3$), 1.01 (3H, t, *J* 7.4 Hz, CH_2CH_3) ppm.
δ_C **(75.5MHz, $CDCl_3$)**	203.9 (0, *C*S), 66.7 (2, 2 × OCH_2), 50.3 (2, NCH_2), 50.1 (2, NCH_2), 45.6 (2, CH_2CS), 22.8 (2, CH_2CH_3), 14.0 (3, CH_3) ppm.
LRMS (APCI)	174 ($[MH]^+$, 100 %), 140 (5 %), 124 (30 %) amu.

GENERAL PROCEDURE FOR EFFECTING THE CONVERSION OF THIOAMIDES INTO THIOESTERS

A stirred solution of thiomorpholide (1.89 mmol) and alkyl halide (4.47 mmol) in THF (10 mL) and water (1 mL) was refluxed for 18 h. The reaction mixture was then cooled to ambient temperature and partitioned between water (5 mL) and ether (5 mL). The aqueous layer was extracted into ether (3 × 5 mL), the combined organic phases were washed with saturated aqueous sodium thiosulfate (10 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography and / or recrystallisation afforded the thioester.

COMPOUNDS PREPARED USING THE ABOVE PROCEDURE

Methyl 2-[4-methyl-2-(methyloxy)phenylethanethioate **219**

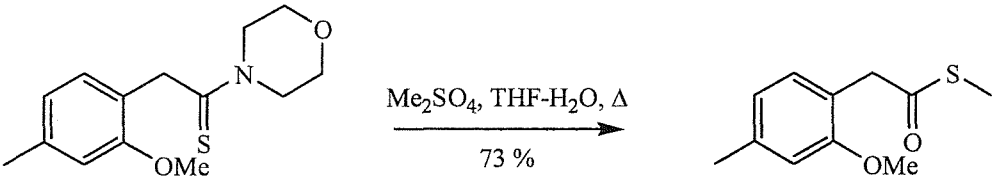


$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{11}H_{14}O_2S$
Mol. Wt.: 210

218 (20.0 g, 75.4 mmol), MeI (26.8 g, 11.8 mL, 189 mmol), THF (180 mL), water (20 mL), 18 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **219** (14.2 g, 67.5 mmol, 90 %) as a yellow oil.

Alternatively:



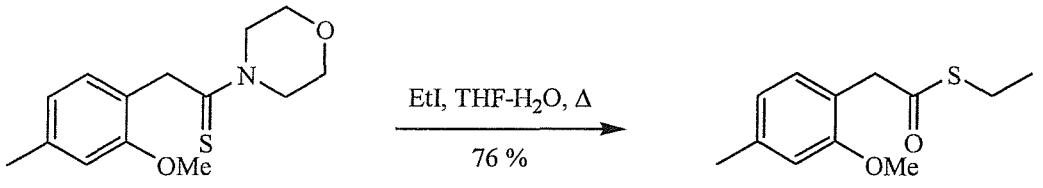
$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{11}H_{14}O_2S$
Mol. Wt.: 210

218 (0.50 g, 1.88 mmol), Me_2SO_4 (0.60 g, 4.75 mmol), THF (9 mL), water (1 mL), 15 h gave thioester **219** (0.29 g, 1.38 mmol, 73 %) after purification by column chromatography (silica, 0 – 5 % ether in petrol) as a yellow oil.

ν_{max}/cm^{-1} (neat)	3002w, 1688s, 1613w, 1583w, 1509m, 1318w, 1270m, 1039m, 933w, 799w.
λ_{max}/nm (ε_{max}, MeOH)	278 (3000).
δ_H (300MHz, $CDCl_3$)	7.10 (1H, d, *J* 7.4 Hz, Ar*H*), 6.77 (1H, d, *J* 7.4 Hz, Ar*H*), 6.73 (1H, s, Ar*H*), 3.83 (5H, s, ArCH_2COS & ArOCH_3), 2.37 (3H, s, ArCH_3), 2.27 (3H, s, SCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	199.1 (0, *C*O), 157.8 (0, Ar), 139.4 (0, Ar), 131.4 (1, Ar), 121.3 (1, Ar), 119.5 (0, Ar), 111.8 (1, Ar), 55.6 (3, ArOCH_3), 44.7 (2, ArCH_2CO), 21.8 (3, ArCH_3), 11.9 (3, SCH_3) ppm.
LRMS (APCI)	211 ($[MH]^+$, 80 %), 210 (M^+, 60 %), 135 ($[M-CH_3SCO]^+$, 100 %) amu.
HRMS (EI)	Found: M^+, 210.0724. $C_{11}H_{14}O_2S$ requires M^+, 210.0715.

Ethyl 2-[4-methyl-2-(methyloxy)phenyl]ethanethioate **601**

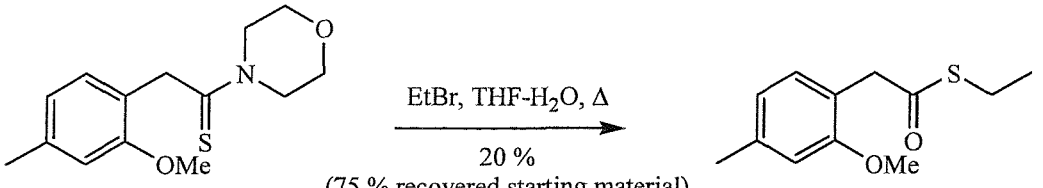


$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{12}H_{16}O_2S$
Mol. Wt.: 224

218 (0.50 g, 1.89 mmol), EtI (0.67 g, 4.72 mmol), THF (10 mL), water (1 mL), 44 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **601** (0.32 g, 1.43 mmol, 76 %) as a colourless oil.

Alternatively:



$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

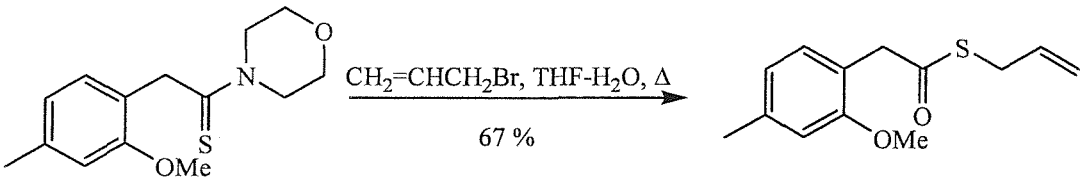
$C_{12}H_{16}O_2S$
Mol. Wt.: 224

218 (0.50 g, 1.88 mmol), EtBr (0.51 g, 4.68 mmol), THF (9 mL), water (1 mL), 45 h gave thioester **601** (0.86 g, 0.38 mmol, 20 %) after purification by column chromatography (silica, 0 – 50 % ether in petrol) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2966m, 2872w, 1682s, 1614m, 1584m, 1509s, 1270s, 1040s, 933m, 717w.
λ_{max}/nm (ε_{max}, MeOH)	278 (2500).
δ_H (300MHz, $CDCl_3$)	7.09 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 3.83 (3H, s, ArOC*H*$_3$), 3.80 (2H, s, ArC*H*$_2$), 2.85 (2H, q, *J* 7.5 Hz, SC*H*$_2$), 2.37 (3H, s, ArC*H*$_3$), 1.23 (3H, t, *J* 7.5 Hz, CH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	198.8 (0, *C*O), 157.7 (0, Ar), 139.3 (0, Ar), 131.3 (1, Ar), 121.3 (1, Ar), 119.6 (0, Ar), 111.8 (1, Ar), 55.6 (3, ArO*C*H$_3$), 44.9 (2,

	Ar*C*H_2CO), 23.6 (2, S*C*H_2), 21.8 (3, Ar*C*H_3), 14.8 (3, CH_2*C*H_3) ppm.
LRMS (APCI)	225 ($[MH]^+$, 75 %), 224 (M^+, 60 %), 135 ($[M\text{-}CH_3CH_2SCO]^+$, 55 %), 101 (100 %) amu.
HRMS (EI)	Found: M^+, 224.0869. $C_{12}H_{16}O_2S$ requires M^+, 224.0871.

2-Propenyl 2-[4-methyl-2-(methyloxy)phenyl]ethanethioate **602**



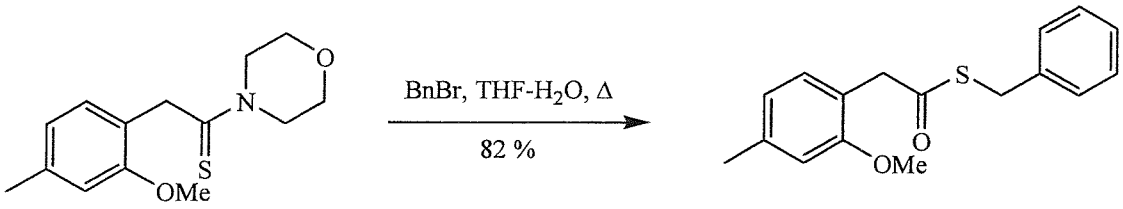
$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{13}H_{16}O_2S$
Mol. Wt.: 236

218 (0.50 g, 1.88 mmol), Allyl-Br (0.57 g, 4.7 mmol), THF (10 mL), water (1 mL), 20 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **602** (0.30 g, 1.27 mmol, 67 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3007w, 1687s, 1639w, 1613w, 1582w, 1508m, 1269s, 1184m, 1040s, 923m, 798w.
λ_{max}/nm (ε_{max}, MeOH)	277 (2500).
δ_H (300MHz, $CDCl_3$)	7.10 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 5.80 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=), 5.22 (1H, dd, J 16.9, 1.1 Hz, =C*H*H), 5.09 (1H, d, *J* 9.9 Hz, =CH*H*), 3.83 (3H, s, OCH_3), 3.80 (2H, s, ArCH_2), 3.52 (2H, d, *J* 7.0 Hz, SCH_2), 2.38 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	198.0 (0, *C*O), 157.8 (0, Ar), 139.4 (0, Ar), 133.4 (1, *C*H=CH_2), 131.4 (1, Ar), 121.3 (1, Ar), 119.4 (0, Ar), 117.8 (2, CH=*C*H_2), 111.8 (1, Ar), 55.6 (3, ArO*C*H_3), 44.8 (2, Ar*C*H_2), 32.1 (2, S*C*H_2), 21.9 (3, Ar*C*H_3) ppm.
LRMS (APCI)	237 ([MH]$^+$, 80 %), 236 (M^+, 50 %), 135 ([M-C_3H_5SCO]$^+$, 100 %) amu.
HRMS (EI)	Found: M^+, 236.0871. $C_{13}H_{16}O_2S$ requires M^+, 236.0871.

Phenylmethyl 2-[4-methyl-2-(methyloxy)phenyl]ethanethioate **603**



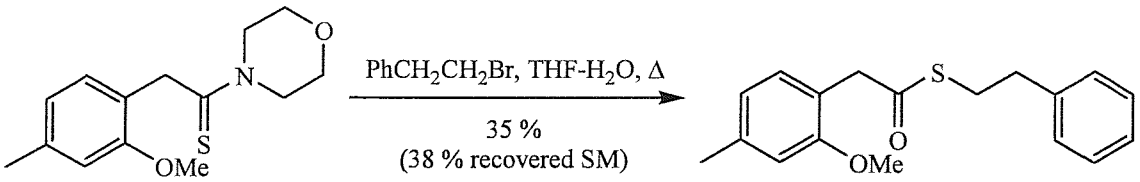
$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{17}H_{18}O_2S$
Mol. Wt.: 286

218 (0.50 g, 1.88 mmol), $PhCH_2Br$ (0.81 g, 4.7 mmol), THF (10 mL), water (1 mL), 20 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) and recrystallisation from pentane gave thioester **603** (0.44 g, 1.54 mmol, 82 %) as colourless crystals.

MP	52 - 54°C (pentane).
ν_{max}/cm^{-1} ($CHCl_3$)	3028w, 1687s, 1612w, 1582w, 1508m, 1320w, 1270m, 1124m, 1040m, 933w, 703m.
λ_{max}/nm (ε_{max}, MeOH)	277 (3500).
δ_H (300MHz, $CDCl_3$)	7.35 - 7.20 (5H, m, 5 × Ar*H*), 7.10 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 4.11 (2H, s, PhCH_2), 3.83 (2H, s, ArCH_2), 3.79 (3H, s, OCH_3), 2.38 (3H, s, ArCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	198.1 (0, *C*O), 157.8 (0, Ar), 139.4 (0, Ar), 138.0 (0, Ar), 131.4 (1, Ar), 129.1 (1, 2 × Ar), 128.7 (1, 2 × Ar), 127.3 (1, Ar), 121.3 (1, Ar), 119.4 (0, Ar), 111.8 (1, Ar), 55.5 (3, OCH_3), 44.8 (2, $ArCH_2$), 33.5 (2, SCH_2), 21.9 (3, $ArCH_3$) ppm.
LRMS (APCI)	287 ($[MH]^+$, 25 %), 193 ($[C_6H_5CH_2SCO+CH_3CN+H]^+$, 100 %), 152 ($[C_6H_5CH_2SCO+H]^+$, 12 %), 135 ($[M-C_6H_5CH_2SCO]^+$, 20 %) amu.
CHN	Found: C, 71.20; H, 6.34; S, 11.04. $C_{17}H_{18}O_2S$ requires C, 71.30; H, 6.34; S, 11.20.

2-Phenylmethyl 2-[4-methyl-2-(methyloxy)phenylethanethioate **604**



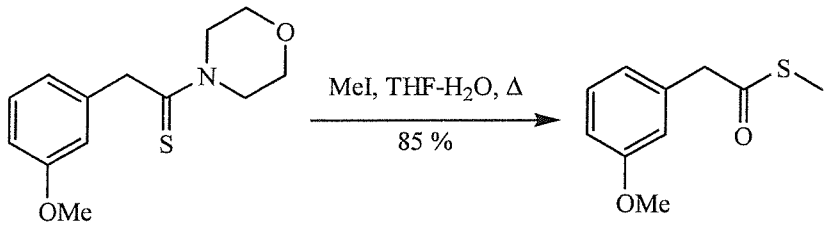
$C_{14}H_{19}NO_2S$
Mol. Wt.: 265

$C_{18}H_{20}O_2S$
Mol. Wt.: 300

218 (0.50 g, 1.88 mmol), $PhCH_2CH_2Br$ (0.87 g, 4.7 mmol), THF (10 mL), water (1 mL), 72 h. Purification by column chromatography (silica, 0 – 50 % ether in petrol) gave thioester **604** (0.20 g, 0.66 mmol, 35 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3027w, 1686s, 1614m, 1584m, 1509s, 1320w, 1271m, 1125m, 1040m, 933w, 698m.
λ_{max}/nm (ε_{max}, MeOH)	279 (2800).
δ_H (300MHz, $CDCl_3$)	7.35 - 7.16 (5H, m, 5 × Ar*H*), 7.09 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.71 (1H, s, Ar*H*), 3.83 (5H, app. s, ArCH_2 & ArOCH_3), 3.08 (2H, app. dd, *J* 9.2, 5.9 Hz, SCH_2), 2.85 (2H, app. dd, *J* 9.2, 5.9 Hz, PhCH_2), 2.38 (3H, s, ArCH_3)
δ_C (75.5MHz, $CDCl_3$)	198.6 (0, *C*O), 157.7 (0, Ar), 140.4 (0, Ar), 139.3 (0, Ar), 131.3 (1, Ar), 128.8 (1, 2 × Ar), 128.6 (1, 2 × Ar), 126.6 (1, Ar), 121.3 (1, Ar), 119.6 (0, Ar), 111.8 (1, Ar), 55.6 (3, OCH_3), 45.0 (2, ArCH_2), 36.1 (2, PhCH_2), 30.6 (2, SCH_2), 21.9 (3, ArCH_3) ppm.
LRMS (APCI)	301 ($[MH]^+$, 60 %), 300 (M^+, 10 %), 196 ($[MH\text{-}Ph(CH_2)_2]^{+\cdot}$, 40 %), 135 ($[M\text{-}Ph(CH_2)_2SCO]^{+\cdot}$, 100 %) amu.
HRMS (CI)	Found: M^+, 300.1180. $C_{18}H_{20}O_2S$ requires M^+, 300.1184.

Methyl 2-[3-(methyloxy)phenyl]ethanethioate **606**[120]

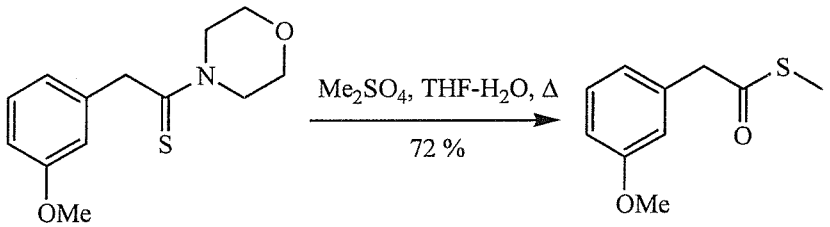


$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

$C_{10}H_{12}O_2S$
Mol. Wt.: 196

605 (0.50 g, 1.99 mmol), MeI (0.71 g, 5.0 mmol), THF (10 mL), water (1 mL), 15 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **606** (0.33 g, 1.68 mmol, 85 %) as a colourless oil.

Alternatively:



$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

$C_{10}H_{12}O_2S$
Mol. Wt.: 196

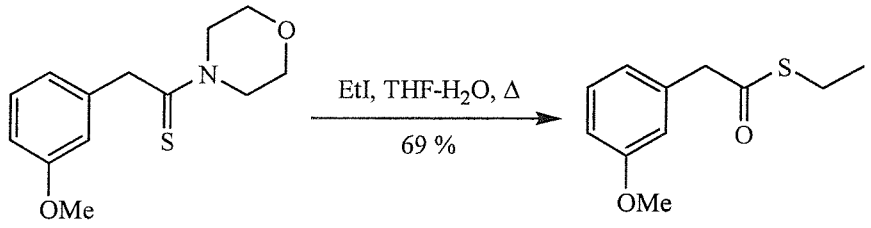
605 (0.50 g, 1.99 mmol), Me_2SO_4 (0.63 g, 5.0 mmol), THF (10 mL), water (1 mL), 18 h gave thioester **606** (0.28 g, 1.43 mmol, 72 %) after purification by column chromatography.

This data was in broad agreement with that reported previously.[120]

ν_{max}/cm^{-1} (neat)	3002w, 2835w, 1686s, 1600s, 1585s, 1258s, 1150m, 1051s, 758m.
λ_{max}/nm (ε_{max}, MeOH)	276 (1800).
δ_H (300MHz, $CDCl_3$)	7.27 (1H, m, Ar*H*), 6.89 (1H, d, *J* 7.5 Hz, Ar*H*), 6.87 - 6.82 (2H, m, 2 × Ar*H*), 3.82 (3H, s, OCH_3), 3.81 (2H, s, ArCH_2), 2.29 (3H, s, SCH_3) ppm.

δ_C **(75.5MHz, $CDCl_3$)**	197.8 (0, *C*O), 159.9 (0, Ar), 135.2 (0, Ar), 129.8 (1, Ar), 122.0 (1, Ar), 115.3 (1, Ar), 113.1 (1, Ar), 55.4 (3, O*C*H_3), 50.5 (2, Ar*C*H_2), 12.1 (3, S*C*H_3) ppm.
LRMS (APCI)	196 (M^+, 5 %), 121 ([M-CH_3SCO]$^+$, 100 %) amu.
HRMS (EI)	Found: M^+, 196.0548. $C_{10}H_{12}O_2S$ requires M^+, 196.0558.

Ethyl 2-[3-(methyloxy)phenyl]ethanethioate **607**



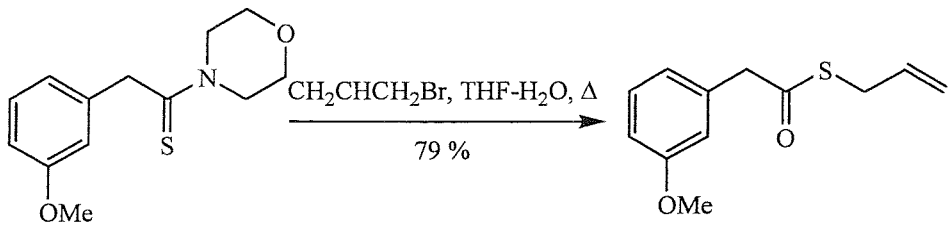
$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

$C_{11}H_{14}O_2S$
Mol. Wt.: 210

605 (0.50 g, 1.99 mmol), EtI (0.78 g, 5.0 mmol), THF (10 mL), water (1 mL), 48 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **236** (0.29 g, 1.38 mmol, 69 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2966w, 2835w, 1688s, 1600m, 1585m, 1259s, 1150m, 1051m, 759m, 690w.
λ_{max}/nm (ε_{max}, MeOH)	276 (2000).
δ_H (300MHz, $CDCl_3$)	7.26 (1H, dd, *J* 8.6, 7.7 Hz, Ar*H*), 6.92 - 6.81 (3H, m, 3×Ar*H*), 3.82 (3H, s, OC*H*$_3$), 3.79 (2H, s, ArC*H*$_2$), 2.88 (2H, q, *J* 7.5 Hz, SC*H*$_2$), 1.24 (3H, t, *J* 7.5 Hz, CH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	197.6 (0, *C*O), 159.9 (0, Ar), 135.3 (0, Ar), 129.8 (1, Ar), 122.1 (1, Ar), 115.3 (1, Ar), 113.1 (1, Ar), 55.4 (3, OCH_3), 50.7 (2, ArCH_2), 23.8 (2, SCH_2), 14.7 (3, CH_2CH_3) ppm.
LRMS (APCI)	211 ([MH]$^+$, 20 %), 210 (M^+, 60 %), 162 ([M–C_2H_5SCO+ CH_3CN]$^+$, 100 %) amu.
HRMS (EI)	Found: M^+, 210.0706. $C_{11}H_{14}O_2S$ requires M^+, 210.0715.

2-Propenyl 2-[3-(methyloxy)phenyl]ethanethioate **608**



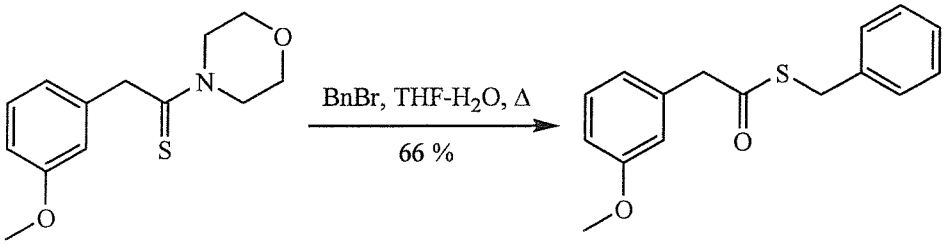
$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

$C_{12}H_{14}O_2S$
Mol. Wt.: 222

605 (0.50 g, 1.99 mmol), allyl-Br (0.60 g, 5.0 mmol), THF (10 mL), water (1 mL), 24 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **608** (0.35 g, 1.57 mmol, 79 %) as a yellow oil.

ν_{max}/cm^{-1} (neat)	3084w, 2835w, 1690s, 1637m, 1600s, 1585s, 1259s, 1151m, 924m, 759m.
λ_{max}/nm (ε_{max}, MeOH)	276 (2400).
δ_H (300MHz, $CDCl_3$)	7.27 (1H, m, Ar*H*), 6.89 (1H, d, *J* 7.8 Hz, Ar*H*), 6.86 (1H, d, *J* 6.3 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 5.80 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=CH_2), 5.23 (1H, dd, *J* 16.9, 1.1 Hz, CH=C*H*H), 5.10 (1H, br. d, *J* 9.9 Hz, CH=CH*H*), 3.82 (3H, s, OCH_3), 3.81 (2H, s, $ArCH_2$), 3.54 (2H, d, *J* 7.0 Hz, SCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	196.8 (0, *C*O), 159.9 (0, Ar), 135.0 (0, Ar), 133.0 (1, *C*H=CH_2), 129.8 (1, Ar), 122.1 (1, Ar), 118.2 (2, CH=CH_2), 115.3 (1, Ar), 113.1 (1, Ar), 55.4 (3, ArOCH_3), 50.6 (2, $ArCH_2CO$), 32.3 (2, SCH_2) ppm.
LRMS (APCI)	222 (M^+, 10 %), 129 (30 %), 112 (50 %), 111 (M^{2+}, 20 %), 100 (100 %) amu.
HRMS (EI)	Found: M^+, 222.0718. $C_{12}H_{14}O_2S$ requires M^+, 222.0715.

Phenylmethyl 2-[3-(methyloxy)phenyl]ethanethioate **609**



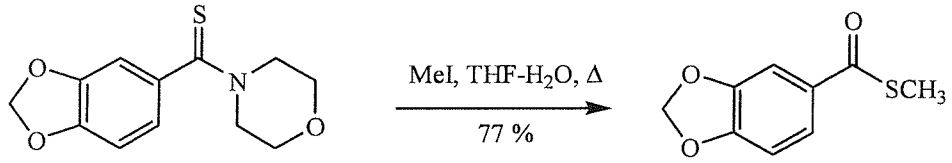
$C_{13}H_{17}NO_2S$
Mol. Wt.: 251

$C_{16}H_{16}O_2S$
Mol. Wt.: 272

605 (0.50 g, 1.99 mmol), $PhCH_2Br$ (0.85 g, 5.0 mmol), THF (10 mL), water (1 mL), 15 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **609** (0.36 g, 1.32 mmol, 66 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3060w, 2834w, 1686s, 1600s, 1584s, 1314w, 1151s, 875w, 758m, 700s.
λ_{max}/nm (ε_{max}, MeOH)	277 (2400).
δ_H (300MHz, $CDCl_3$)	7.32 - 7.23 (6H, m, 5 × Ph*H* + Ar*H*), 6.89 (1H, d, *J* 7.7 Hz Ar*H*), 6.86 (1H, d, *J* 7.7 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 4.13 (2H, s, ArCH_2), 3.84 (2H, s, SCH_2), 3.82 (3H, s, OCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	196.8 (0, *C*O), 159.9 (0, Ar), 137.4 (0, Ph), 135.0 (0, Ar), 129.8 (1, Ar), 129.0 (1, 2 × Ph), 128.8 (1, 2 × Ph), 127.5 (1, Ph), 122.1 (1, Ar), 115.3 (1, Ar), 113.2 (1, Ar), 55.4 (3, OCH_3), 50.4 (2, ArCH_2), 33.8 (2, SCH_2) ppm.
LRMS (APCI)	273 ([MH]$^+$, 30 %), 272 (M^+, 50 %), 162 (100 %) amu.
HRMS (EI)	Found: M^+, 272.0873. $C_{16}H_{16}O_2S$ requires M^+, 272.0871.

Methyl 1,3-benzodioxole-5-carbothioate **611**

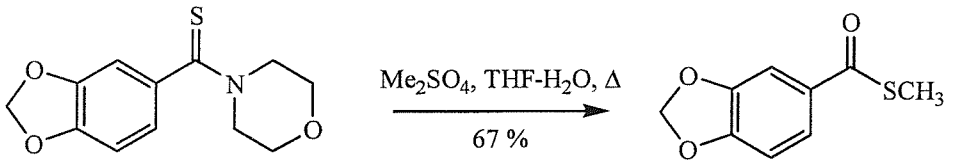


$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

$C_9H_8O_3S$
Mol. Wt.: 196

610 (0.40 g, 1.59 mmol), MeI (0.56 g, 4.0 mmol), THF (10 mL), water (1 mL), 18 h gave crude thioester (0.31 g, 1.59 mmol, 100 %). Purification by recrystallisation from ethanol gave thioester **611** (0.24 g, 1.22 mmol, 77 %) as colourless needles.

Alternatively:



$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

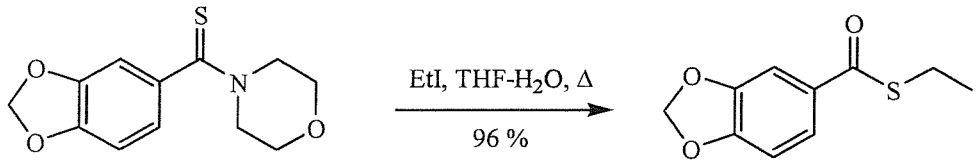
$C_9H_8O_3S$
Mol. Wt.: 196

610 (0.40 g, 1.59 mmol), Me_2SO_4 (0.50 g, 4.0 mmol), THF (10 mL), water (1 mL), 17 h gave thioester **611** (0.21 g, 1.07 mmol, 67 %) after purification.

MP	68 - 70°C (ethanol).
ν_{max}/cm^{-1} ($CHCl_3$)	3037w, 2930w, 1654s, 1611w, 1503m, 1311w, 1270m, 1092s, 927s, 862s.
λ_{max}/nm (ε_{max}, MeOH)	310 (16000), 279 (11500).
δ_H (300MHz, $CDCl_3$)	7.61 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.43 (1H, d, *J* 1.6 Hz, Ar*H*), 6.84 (1H, d, *J* 8.2 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 2.45 (3H, s, SCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	190.9 (0, *C*O), 152.1 (0, Ar), 148.2 (0, Ar), 131.8 (0, Ar), 123.3 (1, Ar), 108.2 (1, Ar), 107.3 (1, Ar), 102.1 (2, OCH_2O), 12.0 (3, SCH_3) ppm.
LRMS (APCI)	197 ($[MH]^+$, 30 %), 111 (100 %) amu.

CHN	Found: C, 55.10; H, 4.06; S, 16.50. $C_9H_8O_3S$ requires C, 55.09; H, 4.11; S, 16.34.

Ethyl 1,3-benzodioxole-5-carbothioate **612**



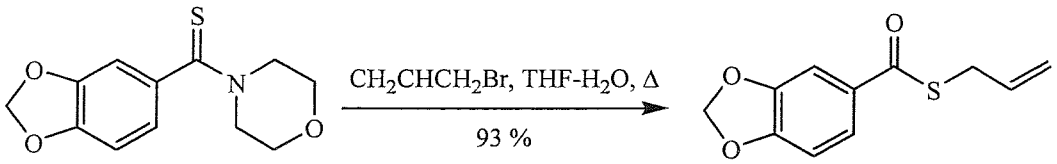
$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

$C_{10}H_{10}O_3S$
Mol. Wt.: 210

610 (0.40 g, 1.59 mmol), EtI (0.62 g, 3.97 mmol), THF (10 mL), water (1 mL), 17 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **612** (0.32 g, 1.52 mmol, 96 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2969w, 2930w, 1659s, 1612m, 1503m, 1355m, 1254s, 1092m, 1039s, 851m.
λ_{max}/nm (ε_{max}, MeOH)	309 (9500), 281 (7500).
δ_H (300MHz, $CDCl_3$)	7.61 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.43 (1H, d, *J* 1.6 Hz, Ar*H*), 6.84 (1H, d, *J* 8.2 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 3.05 (2H, q, *J* 7.4 Hz, SCH_2CH_3), 1.33 (3H, t, *J* 7.4 Hz, CH_2CH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	190.5 (0, *C*O), 152.0 (0, Ar), 148.1 (0, Ar), 131.9 (0, Ar), 123.3 (1, Ar), 108.1 (1, Ar), 107.3 (1, Ar), 102.1 (2, OCH_2O), 23.7 (2, SCH_2), 15.0 (3, CH_2CH_3) ppm.
LRMS (APCI)	211 ($[MH]^+$, 100 %), 142 (25 %), 111 (40 %), 101 (40 %) amu.
HRMS (EI)	Found: M^+, 210.0342. $C_{10}H_{10}O_3S$ requires M^+, 210.0351.

2-Propenyl 1,3-benzodioxole-5-carbothioate **613**



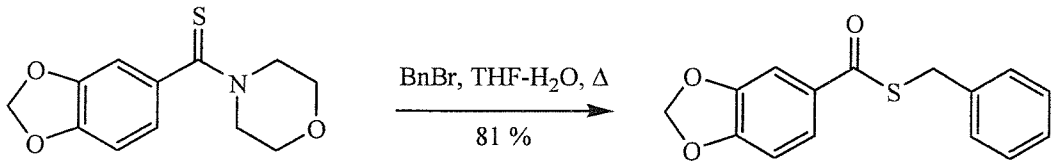
$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

$C_{11}H_{10}O_3S$
Mol. Wt.: 222

610 (0.40 g, 1.59 mmol), allyl-Br (0.48 g, 3.97 mmol), THF (10 mL), water (1 mL), 18 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **613** (0.33 g, 1.49 mmol, 93 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3081w, 2904m, 1661s, 1613s, 1503s, 1355s, 1256m, 1098s, 850s, 729m.
λ_{max}/nm (ε_{max}, MeOH)	310 (10000), 280 (7000).
δ_H (300MHz, $CDCl_3$)	7.61 (1H, dd, *J* 8.3, 1.6 Hz, Ar*H*), 7.42 (1H, d, *J* 1.6 Hz, Ar*H*), 6.85 (1H, d, *J* 8.3 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 5.90 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=CH_2), 5.32 (1H, dd, *J* 16.9, 1.2 Hz, CH=C*H*H), 5.15 (1H, br. d, *J* 9.9 Hz, CH=C*H*H), 3.72 (2H, d, *J* 7.0 Hz, SCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	189.7 (0, *C*O), 152.0 (0, Ar), 148.2 (0, Ar), 133.4 (1, *C*H=CH_2), 131.6 (0, Ar), 123.5 (1, Ar), 118.2 (2, CH=*C*H_2), 108.2 (1, Ar), 107.4 (1, Ar), 102.1 (2, O*C*H_2O), 32.1 (2, S*C*H_2) ppm.
LRMS (APCI)	223 ([MH]$^+$, 100 %), 149 ([M-SAllyl]$^+$, 10 %), 101 (90 %) amu.
HRMS (EI)	Found: M$^+$, 222.0342. $C_{11}H_{10}O_3S$ requires M$^+$, 222.0351.

Phenylmethyl 1,3-benzodioxole-5-carbothioate **614**



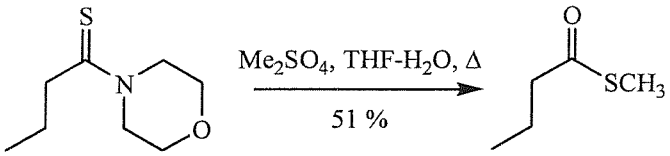
$C_{12}H_{13}NO_3S$
Mol. Wt.: 251

$C_{15}H_{12}O_3S$
Mol. Wt.: 272

610 (0.40 g, 1.59 mmol), $PhCH_2Br$ (0.68 g, 3.98 mmol), THF (10 mL), water (1 mL), 15 h gave crude thioester (0.45 g, 1.65 mmol, 105 %). Purification by recrystallisation from ethanol gave thioester **614** (0.35 g, 1.29 mmol, 81 %) as colourless flakes.

MP	86 - 88°C (ethanol).
ν_{max}/cm^{-1} ($CHCl_3$)	2910w, 1656s, 1600w, 1502m, 1265s, 1040m, 970m, 806m, 707m.
λ_{max}/nm (ε_{max}, MeOH)	311 (12000), 280 (8500).
δ_H (300MHz, $CDCl_3$)	7.62 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.44 (1H, d, *J* 1.6 Hz, Ar*H*), 7.42 - 7.24 (5H, m, 5×Ar), 6.84 (1H, d, J 8.2 Hz, Ar*H*), 6.06 (2H, s, OCH_2O), 4.31 (2H, s, SCH_2) ppm.
δ_C (75.5MHz, $CDCl_3$)	189.7 (0, *C*O), 152.2 (0, Ar), 148.2 (0, Ar), 137.7 (0, Ar), 131.5 (0, Ph), 129.1 (1, 2 × Ph), 128.8 (1, 2 × Ph), 127.5 (1, Ar), 123.6 (1, Ar), 108.2 (1, Ar), 107.4 (1, Ar), 102.1 (2, OCH_2O), 33.6 (2, SCH_2) ppm.
LRMS (APCI)	273 ($[MH]^+$, 20 %), 149 ($[M\text{-}PhCH_2S]^+$, 10 %), 111 (100 %) amu.
CHN	Found: C, 66.15; H, 4.48; S, 11.57. $C_{15}H_{12}O_3S$ requires C, 66.16; H, 4.44; S, 11.78.

Methyl butanethioate **616**[121]



$C_8H_{15}NOS$
Mol. Wt.: 173

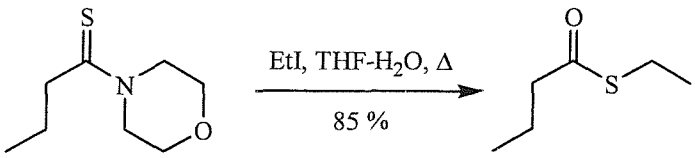
$C_5H_{10}OS$
Mol. Wt.: 118

615 (0.40 g, 2.31 mmol), Me_2SO_4 (0.33 g, 3.47 mmol), THF (10 mL), water (1 mL), 36 h. Purification by column chromatography (silica, 0 – 5 % ether in petrol) gave thioester **616** (0.14 g, 1.19 mmol, 51 %) as a colourless liquid.

Spectral data was in accord with that of a commercial sample.

δ_H **(300MHz, $CDCl_3$)** 2.55 (2H, t, *J* 7.4 Hz, CH_2CO), 2.29 (3H, s, SCH_3), 1.71 (2H, sextet, *J* 7.4 Hz, CH_3CH_2), 0.95 (3H, t, *J* 7.4 Hz, CH_2CH_3) ppm.

Ethyl butanethioate **617**[122]



$C_8H_{15}NOS$
Mol. Wt.: 173

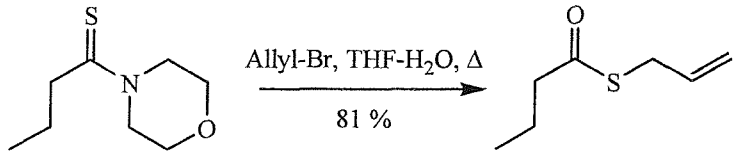
$C_6H_{12}OS$
Mol. Wt.: 132

615 (0.40 g, 2.31 mmol), EtI (0.49 g, 3.47 mmol), THF (10 mL), water (1 mL), 72 h. Purification by column chromatography (silica, 0 – 4 % ether in petrol) gave thioester **617** (0.26 g, 1.97 mmol, 85 %) as a colourless oil.

Data was consistent with literature values.[122]

ν_{max}/**cm^{-1} ($CHCl_3$)**	2967s, 2876m, 1690s, 1456m, 1417w, 1370w, 1266w, 1115m, 990m, 757s.
λ_{max}/**nm** (ε_{max}, **MeOH**)	232 (2000).
δ_H (**300MHz, $CDCl_3$**)	2.87 (2H, q, *J* 7.4 Hz, SCH_2), 2.57 (2H, t, *J* 7.4 Hz, CH_2CO), 1.69 (2H, sextet, *J* 7.4 Hz, $CH_3CH_2CH_2$), 1.25 (3H, t, *J* 7.4 Hz, SCH_2CH_3), 0.95 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$) ppm.
δ_C (**75.5MHz, $CDCl_3$**)	199.8 (0, *C*O), 46.1 (2, SCH_2), 23.2 (2, CH_2CO), 19.3 (2, $CH_3CH_2CH_2$), 14.9 (3, SCH_2CH_3), 13.6 (3, $CH_2CH_2CH_3$) ppm.
LRMS (APCI)	133 ($[MH]^+$, 100 %), 124 (40 %) amu.

2-Propenyl butanethioate **618**



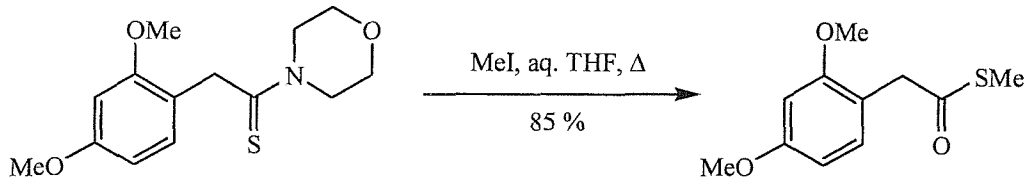
$C_8H_{15}NOS$
Mol. Wt.: 173

$C_7H_{12}OS$
Mol. Wt.: 144

615 (0.40 g, 2.31 mmol), allyl-Br (0.42 g, 3.47 mmol), THF (10 mL), water (1 mL), 48 h. Purification by column chromatography (silica, 0 – 10 % ether in petrol) gave thioester **618** (0.27 g, 1.88 mmol, 81 %) as a colourless oil.

ν_{max}/**cm^{-1} ($CHCl_3$)**	2966m, 2876w, 1694s, 1638w, 1459w, 1421w, 1232w, 1114m, 989m, 921m.
λ_{max}/**nm** (ε_{max}, **MeOH**)	231 (3800).
δ_H (**300MHz, $CDCl_3$**)	5.81 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=), 5.23 (1H, dd, *J* 16.9, 1.3 Hz, =C*H*H), 5.11 (1H, br. d, *J* 9.9Hz, =CH*H*), 3.54 (2H, d, *J* 7.0 Hz, SCH_2), 2.54 (2H, t, *J* 7.4 Hz, CH_2CO), 1.71 (2H, sextet, *J* 7.4 Hz, $CH_3CH_2CH_2$), 0.97 (3H, t, *J* 7.4 Hz, CH_2CH_3) ppm.
δ_C (**75.5MHz, $CDCl_3$**)	199.0 (0, *C*O), 133.4 (1, *C*H=), 117.9 (2, =CH_2), 46.0 (2, SCH_2), 31.8 (2, CH_2CO), 19.3 (2, CH_3CH_2), 13.6 (3, CH_3) ppm.
LRMS (APCI)	145 ([MH]$^+$, 30 %), 143 (30 %), 124 (100 %) amu.

Methyl 2-(2,4-dimethoxyphenyl)ethanethioate **620**



$C_{14}H_{19}NO_3S$
Mol. Wt.: 281

$C_{11}H_{14}O_3S$
Mol. Wt.: 226

619 (1.50 g, 5.34 mmol), MeI (1.89 g, 0.83 mL, 13.4 mmol), THF (40 mL), water (4 mL), 4 h. Purification by column chromatography (silica, 0 – 20 % ether in petrol) gave thioester **620** (1.02 g, 4.51 mmol, 85 %) as a colourless oil.

ν_{max}/cm^{-1} ($CHCl_3$)	2931w, 2835w, 1680s, 1612s, 1587s, 1507s, 1457m, 1330w, 1290s, 1206s.
λ_{max}/nm (ε_{max}, MeOH)	280 (2700).
δ_H (300MHz, $CDCl_3$)	7.12 (1H, d, *J* 9.0 Hz, Ar*H*), 6.48 (1H, dd, *J* 9.0, 2.2 Hz, Ar*H*), 6.47 (1H, d, *J* 2.2 Hz, Ar*H*), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.77 (2H, s, ArCH_2), 2.23 (3H, s, SCH_3) ppm.
δ_C (75.5MHz, $CDCl_3$)	199.4 (0, *C*O), 160.8 (0, Ar), 158.9 (0, Ar), 132.0 (1, Ar), 114.9 (0, Ar), 104.3 (1, Ar), 98.8 (1, Ar), 55.6 (3, O*C*H$_3$), 55.5 (3, O*C*H$_3$), 44.3 (2, Ar*C*H$_2$), 11.9 (3, S*C*H$_3$) ppm.
LRMS (APCI)	227 ([MH]$^+$, 90 %), 153 (100 %) amu.
HRMS (CI)	Found [M+NH$_4$]$^+$: 244.1008. $C_{11}H_{14}O_3S$ requires [M+NH$_4$]$^+$: 244.1007.

CHAPTER 8

APPENDICES

8.1

X-RAY DATA FOR 523

Table 1. Crystal data and structure refinement.

Identification code	**00sot085**	
Empirical formula	$C_{16}H_{22}O_3S$	
Formula weight	294.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*Cc*	
Unit cell dimensions	$a = 12.1872(5)$ Å	$\alpha = 90°$
	$b = 15.2741(10)$ Å	$\beta = 125.930(3)°$
	$c = 9.5776(4)$ Å	$\gamma = 90°$
Volume	1443.64(13) Å^3	
Z	4	
Density (calculated)	1.355 Mg / m^3	
Absorption coefficient	0.229 mm^{-1}	
F(000)	632	
Crystal	Colourless plate	
Crystal size	0.10 × 0.07 × 0.05 mm^3	
θ range for data collection	3.74 – 25.50°	
Index ranges	$-14 \le h \le 14, -15 \le k \le 18, -10 \le l \le 11$	
Reflections collected	4432	
Independent reflections	2301 [$R_{int} = 0.0461$]	
Completeness to $\theta = 25.50°$	98.9 %	
Max. and min. transmission	0.9886 and 0.9774	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2301 / 2 / 200	
Goodness-of-fit on F^2	1.044	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0438, *wR2* = 0.0904	
R indices (all data)	*R1* = 0.0549, *wR2* = 0.0947	
Absolute structure parameter	−0.05(10)	
Extinction coefficient	0.0072(11)	
Largest diff. peak and hole	0.234 and −0.243 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	2413(1)	479(1)	5392(1)	44(1)	1
O1	−4733(2)	2627(2)	4078(3)	41(1)	1
O2	−3831(2)	1431(2)	5808(3)	45(1)	1
O3	−2390(3)	1343(2)	527(3)	57(1)	1
C1	2123(3)	1278(3)	6538(5)	44(1)	1
C2	689(3)	1110(2)	5976(4)	34(1)	1
C3	365(3)	115(2)	5602(4)	32(1)	1
C4	1577(3)	−344(2)	5814(4)	40(1)	1
C5	−405(3)	1567(2)	4283(4)	32(1)	1
C6	−1637(3)	966(2)	3421(4)	28(1)	1
C7	−940(3)	59(2)	3772(4)	29(1)	1
C8	−2654(3)	1093(2)	1499(4)	33(1)	1
C9	−4036(3)	848(3)	965(4)	40(1)	1
C10	−3940(3)	669(2)	2591(4)	31(1)	1
C11	−2497(3)	1008(2)	4108(4)	25(1)	1
C12	−2761(3)	1916(2)	4502(4)	32(1)	1
C13	−4073(3)	1817(2)	4310(4)	33(1)	1
C14	−4931(3)	1199(3)	2767(5)	44(1)	1
C15	−5245(7)	2597(4)	5062(9)	90(2)	1
C16	−4612(5)	1870(3)	6216(6)	67(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C4	1.808(4)
S1–C1	1.811(4)
O1–C15	1.404(4)
O1–C13	1.420(4)
O2–C16	1.394(4)
O2–C13	1.413(4)
O3–C8	1.211(4)
C1–C2	1.518(5)
C1–H1A	0.9900
C1–H1B	0.9900
C2–C5	1.535(5)
C2–C3	1.558(5)
C2–H2	1.0000
C3–C7	1.529(4)
C3–C4	1.537(5)
C3–H3	1.0000
C4–H4A	0.9900
C4–H4B	0.9900
C5–C6	1.525(4)
C5–H5A	0.9900
C5–H5B	0.9900
C6–C8	1.511(4)
C6–C11	1.531(4)
C6–C7	1.555(5)
C7–H7A	0.9900
C7–H7B	0.9900
C8–C9	1.492(5)
C9–C10	1.517(5)
C9–H9A	0.9900
C9–H9B	0.9900
C10–C14	1.543(5)
C10–C11	1.573(4)
C10–H10	1.0000
C11–C12	1.520(4)
C11–H11	1.0000
C12–C13	1.507(4)
C12–H12A	0.9900
C12–H12B	0.9900
C13–C14	1.534(5)
C14–H14A	0.9900

C14–H14B	0.9900
C15–C16	1.431(6)
C15–H15A	0.9900
C15–H15B	0.9900
C16–H16A	0.9900
C16–H16B	0.9900
C4–S1–C1	89.81(18)
C15–O1–C13	107.4(3)
C16–O2–C13	108.3(3)
C2–C1–S1	105.3(2)
C2–C1–H1A	110.7
S1–C1–H1A	110.7
C2–C1–H1B	110.7
S1–C1–H1B	110.7
H1A–C1–H1B	108.8
C1–C2–C5	113.8(3)
C1–C2–C3	109.3(3)
C5–C2–C3	104.8(3)
C1–C2–H2	109.6
C5–C2–H2	109.6
C3–C2–H2	109.6
C7–C3–C4	113.5(3)
C7–C3–C2	105.7(3)
C4–C3–C2	108.7(3)
C7–C3–H3	109.6
C4–C3–H3	109.6
C2–C3–H3	109.6
C3–C4–S1	106.1(2)
C3–C4–H4A	110.5
S1–C4–H4A	110.5
C3–C4–H4B	110.5
S1–C4–H4B	110.5
H4A–C4–H4B	108.7
C6–C5–C2	105.5(3)
C6–C5–H5A	110.6
C2–C5–H5A	110.6
C6–C5–H5B	110.6
C2–C5–H5B	110.6
H5A–C5–H5B	108.8
C8–C6–C5	115.2(3)
C8–C6–C11	103.9(2)
C5–C6–C11	116.5(3)
C8–C6–C7	109.3(3)
C5–C6–C7	100.4(2)
C11–C6–C7	111.7(3)
C3–C7–C6	105.5(3)
C3–C7–H7A	110.6
C6–C7–H7A	110.6
C3–C7–H7B	110.6
C6–C7–H7B	110.6
H7A–C7–H7B	108.8
O3–C8–C9	124.8(3)
O3–C8–C6	125.4(3)
C9–C8–C6	109.8(3)
C8–C9–C10	107.5(3)
C8–C9–H9A	110.2
C10–C9–H9A	110.2
C8–C9–H9B	110.2
C10–C9–H9B	110.2
H9A–C9–H9B	108.5
C9–C10–C14	115.1(3)
C9–C10–C11	105.1(3)
C14–C10–C11	104.4(3)
C9–C10–H10	110.6
C14–C10–H10	110.6
C11–C10–H10	110.6
C12–C11–C6	116.3(3)
C12–C11–C10	104.2(2)
C6–C11–C10	105.4(2)
C12–C11–H11	110.2

C6–C11–H11	110.2
C10–C11–H11	110.2
C13–C12–C11	104.0(3)
C13–C12–H12A	111.0
C11–C12–H12A	111.0
C13–C12–H12B	111.0
C11–C12–H12B	111.0
H12A–C12–H12B	109.0
O2–C13–O1	106.5(2)
O2–C13–C12	110.1(3)
O1–C13–C12	113.2(3)
O2–C13–C14	109.9(3)
O1–C13–C14	112.5(3)
C12–C13–C14	104.7(3)
C13–C14–C10	107.1(3)
C13–C14–H14A	110.3
C10–C14–H14A	110.3
C13–C14–H14B	110.3
C10–C14–H14B	110.3
H14A–C14–H14B	108.6
O1–C15–C16	107.1(3)
O1–C15–H15A	110.3
C16–C15–H15A	110.3
O1–C15–H15B	110.3
C16–C15–H15B	110.3
H15A–C15–H15B	108.6
O2–C16–C15	107.7(3)
O2–C16–H16A	110.2
C15–C16–H16A	110.2
O2–C16–H16B	110.2
C15–C16–H16B	110.2
H16A–C16–H16B	108.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	32(1)	53(1)	52(1)	−6(1)	27(1)	1(1)
O1	52(2)	32(2)	56(2)	12(1)	41(1)	16(1)
O2	56(2)	42(2)	52(2)	15(1)	40(1)	15(1)
O3	51(2)	81(2)	41(2)	15(2)	29(1)	0(2)
C1	27(2)	52(3)	44(2)	−12(2)	16(2)	−2(2)
C2	28(2)	42(2)	32(2)	−8(2)	18(2)	−2(2)
C3	28(2)	39(2)	31(2)	1(1)	17(2)	5(2)
C4	32(2)	43(3)	38(2)	1(2)	17(2)	8(2)
C5	27(2)	28(2)	43(2)	3(2)	21(2)	3(1)
C6	28(2)	24(2)	31(2)	1(1)	17(1)	1(1)
C7	28(2)	29(2)	31(2)	−1(1)	17(1)	−1(1)
C8	36(2)	32(2)	31(2)	4(2)	20(2)	5(2)
C9	31(2)	48(3)	34(2)	−2(2)	15(2)	−1(2)
C10	27(2)	27(2)	37(2)	−6(1)	19(2)	−5(1)
C11	25(2)	20(2)	30(2)	0(1)	17(1)	0(1)
C12	34(2)	30(2)	38(2)	−4(2)	24(2)	−3(2)
C13	34(2)	32(2)	38(2)	4(2)	24(2)	7(2)
C14	29(2)	54(3)	46(2)	−13(2)	20(2)	0(2)
C15	147(5)	67(4)	142(5)	49(3)	132(4)	54(3)
C16	79(3)	79(4)	75(3)	27(3)	64(3)	34(3)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	2781	1202	7800	27(8)	1
H1B	2209	1881	6231	41(10)	1
H2	605	1294	6911	22(7)	1
H3	209	−139	6434	55(11)	1
H4A	1264	−835	4987	43(10)	1
H4B	2203	−578	6999	59(12)	1
H5A	−624	2149	4516	41(10)	1
H5B	−95	1645	3540	16(7)	1
H7A	−1532	−414	3688	55(11)	1
H7B	−734	−59	2932	34(9)	1
H9A	−4360	320	226	108(19)	1
H9B	−4681	1332	303	72(14)	1
H10	−4029	29	2718	44(11)	1
H11	−2103	620	5138	21(8)	1
H12A	−2019	2099	5687	35(9)	1
H12B	−2851	2353	3676	38(10)	1
H14A	−5561	1539	1703	61(12)	1
H14B	−5469	801	2964	69(13)	1
H15A	−6240	2519	4302	109	1
H15B	−5034	3148	5718	109	1
H16A	−4031	2079	7424	80	1

8.2

X-RAY DATA FOR 522

Table 1. Crystal data and structure refinement.

Identification code	**99sot051**	
Empirical formula	$C_{14}H_{14}O_2S$	
Formula weight	246.31	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 7.5463(4)$ Å	$\alpha = 90°$
	$b = 21.4819(14)$ Å	$\beta = 99.548(3)°$
	$c = 7.445(4)$ Å	$\gamma = 90°$
Volume	1190.1(6) $Å^3$	
Z	4	
Density (calculated)	1.375 Mg / m^3	
Absorption coefficient	0.258 mm^{-1}	
$F(000)$	520	
Crystal	Prism; colourless	
Crystal size	0.12 × 0.06 × 0.06 mm^3	
θ range for data collection	1.90 – 25.75°	
Index ranges	$-9 \le h \le 9$, $-26 \le k \le 26$, $-9 \le l \le 9$	
Reflections collected	16408	
Independent reflections	2260 [$R_{int} = 0.1033$]	
Completeness to $\theta = 25.75°$	99.8 %	
Max. and min. transmission	0.9847 and 0.9697	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2260 / 0 / 210	
Goodness-of-fit on F^2	0.977	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0482$, $wR2 = 0.0998$	
R indices (all data)	$R1 = 0.0858$, $wR2 = 0.1089$	
Largest diff. peak and hole	0.317 and −0.254 e $Å^{-3}$	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	4778(1)	3003(1)	8163(1)	36(1)	1
O1	243(2)	4707(1)	13017(2)	33(1)	1
O2	2216(2)	5116(1)	11422(2)	44(1)	1
C1	3550(4)	3665(1)	7104(3)	38(1)	1
C2	3154(3)	4069(1)	8688(3)	30(1)	1
C3	4726(3)	4001(1)	10300(3)	27(1)	1
C4	6056(3)	3519(1)	9800(3)	30(1)	1
C5	1476(3)	3856(1)	9424(3)	28(1)	1
C6	1857(3)	3978(1)	11487(3)	25(1)	1
C7	3868(3)	3811(1)	11944(3)	28(1)	1
C8	1531(3)	4658(1)	11902(3)	30(1)	1
C9	−250(3)	4104(1)	13429(3)	28(1)	1
C10	643(3)	3660(1)	12596(3)	24(1)	1
C11	−1469(3)	3968(1)	14566(3)	32(1)	1
C12	−1785(3)	3343(1)	14846(3)	33(1)	1
C13	−907(3)	2889(1)	14024(3)	31(1)	1
C14	329(3)	3037(1)	12901(3)	27(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C4	1.805(3)
S1–C1	1.806(3)
O1–C8	1.383(3)
O1–C9	1.395(3)
O2–C8	1.194(3)
C1–C2	1.533(3)
C1–H1A	0.96(2)
C1–H1B	0.98(3)
C2–C5	1.531(3)
C2–C3	1.548(3)
C2–H2	0.99(2)
C3–C4	1.530(3)
C3–C7	1.531(3)
C3–H3	0.90(2)
C4–H4A	0.97(3)
C4–H4B	0.94(2)
C5–C6	1.537(3)
C5–H5A	0.93(2)
C5–H5B	0.96(2)
C6–C10	1.497(3)
C6–C8	1.521(3)
C6–C7	1.541(3)
C7–H7A	0.97(2)
C7–H7B	0.92(2)
C9–C10	1.373(3)
C9–C11	1.381(3)
C10–C14	1.384(3)
C11–C12	1.386(3)
C11–H11	0.93(2)
C12–C13	1.379(3)
C12–H12	0.98(2)
C13–C14	1.389(3)
C13–H13	0.94(2)
C14–H14	0.92(2)
C4–S1–C1	89.34(13)
C8–O1–C9	107.54(17)
C2–C1–S1	105.14(17)
C2–C1–H1A	110.6(14)
S1–C1–H1A	110.6(15)
C2–C1–H1B	112.3(14)
S1–C1–H1B	107.9(14)
H1A–C1–H1B	110(2)
C5–C2–C1	112.6(2)
C5–C2–C3	105.52(18)
C1–C2–C3	108.75(19)

C5–C2–H2	108.6(13)
C1–C2–H2	110.1(13)
C3–C2–H2	111.1(14)
C4–C3–C7	113.3(2)
C4–C3–C2	108.94(19)
C7–C3–C2	105.88(18)
C4–C3–H3	108.0(13)
C7–C3–H3	109.3(13)
C2–C3–H3	111.4(13)
C3–C4–S1	106.33(16)
C3–C4–H4A	110.7(14)
S1–C4–H4A	109.7(14)
C3–C4–H4B	111.5(13)
S1–C4–H4B	111.4(12)
H4A–C4–H4B	107.2(19)
C2–C5–C6	106.14(19)
C2–C5–H5A	115.1(13)
C6–C5–H5A	113.5(13)
C2–C5–H5B	110.5(13)
C6–C5–H5B	106.6(12)
H5A–C5–H5B	104.7(18)
C10–C6–C8	101.09(17)
C10–C6–C5	116.30(18)
C8–C6–C5	110.87(19)
C10–C6–C7	116.28(18)
C8–C6–C7	111.39(19)
C5–C6–C7	101.25(18)
C3–C7–C6	107.05(19)
C3–C7–H7A	113.3(11)
C6–C7–H7A	114.3(11)
C3–C7–H7B	108.8(13)
C6–C7–H7B	107.9(13)
H7A–C7–H7B	105.2(18)
O2–C8–O1	120.0(2)
O2–C8–C6	129.7(2)
O1–C8–C6	110.34(19)
C10–C9–C11	123.8(2)
C10–C9–O1	112.14(18)
C11–C9–O1	124.0(2)
C9–C10–C14	119.2(2)
C9–C10–C6	108.82(19)
C14–C10–C6	132.0(2)
C9–C11–C12	116.4(2)
C9–C11–H11	121.6(14)
C12–C11–H11	122.0(14)
C13–C12–C11	120.8(2)
C13–C12–H12	120.0(14)
C11–C12–H12	119.2(14)
C12–C13–C14	121.7(2)
C12–C13–H13	120.0(13)
C14–C13–H13	118.3(13)
C10–C14–C13	118.0(2)
C10–C14–H14	120.7(14)
C13–C14–H14	121.3(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	34(1)	35(1)	41(1)	−9(1)	10(1)	0(1)
O1	37(1)	24(1)	40(1)	−4(1)	15(1)	1(1)
O2	52(1)	25(1)	62(1)	1(1)	28(1)	−4(1)
C1	36(2)	53(2)	27(1)	3(1)	10(1)	−1(1)
C2	31(1)	30(1)	31(1)	5(1)	9(1)	3(1)
C3	28(1)	22(1)	32(1)	−1(1)	6(1)	−2(1)
C4	26(1)	33(2)	33(1)	0(1)	7(1)	−1(1)
C5	24(1)	31(2)	30(1)	2(1)	5(1)	5(1)
C6	27(1)	20(1)	27(1)	1(1)	6(1)	0(1)
C7	26(1)	30(2)	26(1)	2(1)	2(1)	−1(1)
C8	30(1)	28(1)	33(1)	0(1)	9(1)	−1(1)
C9	26(1)	27(1)	29(1)	0(1)	4(1)	−1(1)
C10	20(1)	27(1)	24(1)	−2(1)	2(1)	0(1)
C11	30(1)	38(2)	29(1)	−4(1)	9(1)	2(1)
C12	27(1)	45(2)	26(1)	2(1)	6(1)	−3(1)
C13	29(1)	32(2)	32(1)	5(1)	2(1)	−6(1)
C14	25(1)	29(1)	27(1)	0(1)	2(1)	3(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	4260(30)	3890(11)	6370(30)	39(7)	1
H1B	2450(40)	3510(11)	6350(30)	40(7)	1
H2	2990(30)	4507(11)	8300(30)	35(7)	1
H3	5320(30)	4363(10)	10540(30)	21(6)	1
H4A	6590(30)	3285(12)	10870(30)	39(7)	1
H4B	7000(30)	3711(10)	9320(30)	19(6)	1
H5A	400(30)	4030(10)	8840(30)	23(6)	1
H5B	1310(30)	3414(12)	9270(30)	28(6)	1
H7A	4480(30)	3985(10)	13090(30)	18(5)	1
H7B	3960(30)	3388(11)	12080(30)	21(6)	1
H11	−2030(30)	4281(11)	15130(30)	32(6)	1
H12	−2640(30)	3226(11)	15640(30)	37(6)	1
H13	−1150(30)	2465(11)	14210(30)	26(6)	1
H14	910(30)	2730(11)	12350(30)	29(6)	1

8.3

X-RAY DATA FOR 521

Table 1. Crystal data and structure refinement.

Identification code	**99sot052**	
Empirical formula	$C_{14}H_{14}O_2S$	
Formula weight	246.31	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	$a = 23.128(5)$ Å	$\alpha = 90°$
	$b = 9.312(2)$ Å	$\beta = 90°$
	$c = 11.434(2)$ Å	$\gamma = 90°$
Volume	2462.4(9) Å^3	
Z	8	
Density (calculated)	1.329 Mg / m^3	
Absorption coefficient	0.249 mm^{-1}	
F(000)	1040	
Crystal	Prism; colourless	
Crystal size	0.30 × 0.15 × 0.15 mm^3	
θ range for data collection	1.76 – 26.00°	
Index ranges	$-28 \le h \le 28$, $-11 \le k \le 11$, $-14 \le l \le 14$	
Reflections collected	17072	
Independent reflections	4719 [$R_{int} = 0.0556$]	
Completeness to $\theta = 26.00°$	99.9 %	
Max. and min. transmission	0.9636 and 0.9290	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4719 / 1 / 420	
Goodness-of-fit on F^2	0.912	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0404$, $wR2 = 0.0858$	
R indices (all data)	$R1 = 0.0795$, $wR2 = 0.0959$	
Absolute structure parameter	0.57(7)	
Extinction coefficient	0.0028(10)	
Largest diff. peak and hole	0.192 and −0.167 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:
Structure contains two independent molecules in the asymmetric unit

Analysis of Bond Distance and Angle Values - Identification of Chiral Center(s) and Their (R/S)-Configuration (Cahn-Ingold-Prelog):
C2 **R** C3 **S** C6 **R**
C2' **S** C3'**R** C6' **S**

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	2585(1)	4891(1)	694(1)	82(1)	1
O1	2313(1)	4421(2)	−4760(2)	73(1)	1
O2	1746(1)	4995(2)	−3264(2)	88(1)	1
C1	2825(2)	3115(4)	271(3)	82(1)	1
C2	3053(1)	3267(3)	−966(3)	62(1)	1
C3	3291(1)	4811(2)	−1142(3)	55(1)	1
C4	3209(2)	5648(4)	−15(3)	67(1)	1
C5	2953(1)	5442(3)	−2161(3)	57(1)	1
C6	2732(1)	4138(3)	−2875(3)	51(1)	1
C7	2582(2)	3082(3)	−1886(3)	60(1)	1
C8	2204(1)	4573(3)	−3587(3)	64(1)	1
C9	2866(1)	3821(3)	−4871(3)	61(1)	1
C10	3125(1)	3610(2)	−3813(2)	52(1)	1
C11	3104(2)	3474(4)	−5937(4)	81(1)	1
C12	3644(2)	2847(4)	−5899(4)	87(1)	1
C13	3917(2)	2613(3)	−4854(4)	80(1)	1
C14	3671(2)	2993(3)	−3809(3)	68(1)	1
S1'	5270(1)	2741(1)	−2981(1)	92(1)	1
O1'	4878(1)	3314(3)	2453(2)	83(1)	1
O2'	4373(1)	3877(4)	857(2)	122(1)	1
C1'	5328(2)	994(4)	−2356(3)	87(1)	1
C2'	5541(1)	1218(3)	−1097(3)	59(1)	1
C3'	5907(1)	2607(3)	−1054(2)	54(1)	1
C4'	5936(1)	3240(4)	−2292(3)	70(1)	1
C5'	5059(1)	1426(4)	−212(3)	59(1)	1
C6'	5280(1)	2560(2)	637(2)	49(1)	1
C7'	5601(2)	3574(3)	−191(3)	59(1)	1
C8'	4789(2)	3333(4)	1266(3)	79(1)	1
C9'	5374(1)	2518(3)	2666(3)	59(1)	1
C10'	5624(1)	2024(2)	1653(2)	47(1)	1
C11'	5567(2)	2204(4)	3766(3)	73(1)	1
C12'	6040(2)	1326(4)	3832(3)	76(1)	1
C14'	6105(1)	1153(3)	1753(3)	57(1)	1
C13'	6306(2)	805(4)	2857(3)	72(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C4	1.800(3)
S1–C1	1.811(4)
O1–C8	1.373(4)
O1–C9	1.400(3)
O2–C8	1.189(4)
C1–C2	1.517(5)
C1–H1A	0.88(4)
C1–H1B	0.98(4)
C2–C7	1.525(4)
C2–C3	1.552(4)
C2–H3	0.91(3)
C3–C4	1.518(4)
C3–C5	1.521(4)
C3–H2	0.92(3)
C4–H4A	0.93(3)
C4–H4B	0.93(3)
C5–C6	1.550(4)
C5–H5A	1.02(3)
C5–H5B	0.97(3)
C6–C10	1.489(4)
C6–C8	1.524(4)
C6–C7	1.538(4)
C7–H7A	0.97(3)
C7–H7B	0.97(3)
C9–C10	1.364(4)
C9–C11	1.376(5)
C10–C14	1.388(4)

C11–C12	1.380(6)
C11–H11	0.87(4)
C12–C13	1.369(6)
C12–H12	0.92(4)
C13–C14	1.370(5)
C13–H13	1.02(4)
C14–H14	0.98(4)
S1'–C1'	1.782(4)
S1'–C4'	1.791(3)
O1'–C8'	1.374(4)
O1'–C9'	1.387(4)
O2'–C8'	1.183(4)
C1'–C2'	1.536(5)
C1'–H1'1	0.95(4)
C1'–H1'2	0.91(3)
C2'–C5'	1.516(4)
C2'–C3'	1.546(4)
C2'–H2'	0.85(3)
C3'–C7'	1.511(4)
C3'–C4'	1.535(4)
C3'–H3'	0.99(3)
C4'–H4'1	1.05(3)
C4'–H4'2	0.92(3)
C5'–C6'	1.523(4)
C5'–H5'1	0.94(3)
C5'–H5'2	1.03(3)
C6'–C10'	1.494(4)
C6'–C8'	1.523(4)
C6'–C7'	1.530(4)
C7'–H7'1	0.90(3)
C7'–H7'2	0.90(3)
C9'–C11'	1.365(4)
C9'–C10'	1.374(4)
C10'–C14'	1.380(4)
C11'–C12'	1.369(5)
C11'–H11'	1.00(3)
C12'–C13'	1.363(6)
C12'–H12'	0.89(4)
C14'–C13'	1.383(4)
C14'–H14'	0.91(3)
C13'–H13'	0.92(3)

C4–S1–C1	89.52(18)
C8–O1–C9	107.3(2)
C2–C1–S1	105.7(2)
C2–C1–H1A	105(2)
S1–C1–H1A	107(2)
C2–C1–H1B	119(2)
S1–C1–H1B	106.8(19)
H1A–C1–H1B	112(3)
C1–C2–C7	112.6(3)
C1–C2–C3	109.3(3)
C7–C2–C3	105.6(2)
C1–C2–H3	108(2)
C7–C2–H3	112.2(19)
C3–C2–H3	109.0(17)
C4–C3–C5	112.8(2)
C4–C3–C2	108.8(3)
C5–C3–C2	105.9(2)
C4–C3–H2	109.8(15)
C5–C3–H2	107.2(15)
C2–C3–H2	112.3(13)
C3–C4–S1	106.3(2)
C3–C4–H4A	116.5(19)
S1–C4–H4A	104.0(17)
C3–C4–H4B	103.4(19)
S1–C4–H4B	112.2(18)
H4A–C4–H4B	114(2)
C3–C5–C6	105.7(2)
C3–C5–H5A	115.3(14)

C6–C5–H5A	111.7(14)
C3–C5–H5B	105.5(17)
C6–C5–H5B	110.9(16)
H5A–C5–H5B	108(2)
C10–C6–C8	101.1(2)
C10–C6–C7	117.1(2)
C8–C6–C7	112.4(2)
C10–C6–C5	116.0(2)
C8–C6–C5	109.7(2)
C7–C6–C5	100.8(2)
C2–C7–C6	105.9(2)
C2–C7–H7A	111(2)
C6–C7–H7A	105.2(19)
C2–C7–H7B	112.0(16)
C6–C7–H7B	112.7(17)
H7A–C7–H7B	110(2)
O2–C8–O1	120.1(3)
O2–C8–C6	129.6(3)
O1–C8–C6	110.3(3)
C10–C9–C11	125.1(3)
C10–C9–O1	112.3(2)
C11–C9–O1	122.6(3)
C9–C10–C14	117.6(3)
C9–C10–C6	108.8(2)
C14–C10–C6	133.6(3)
C9–C11–C12	115.7(4)
C9–C11–H11	119(3)
C12–C11–H11	125(3)
C13–C12–C11	120.9(4)
C13–C12–H12	119(2)
C11–C12–H12	120(2)
C12–C13–C14	121.9(4)
C12–C13–H13	115(2)
C14–C13–H13	123(2)
C13–C14–C10	118.8(4)
C13–C14–H14	122(2)
C10–C14–H14	119(2)
C1'–S1'–C4'	89.77(19)
C8'–O1'–C9'	107.7(2)
C2'–C1'–S1'	106.0(2)
C2'–C1'–H1'1	109(2)
S1'–C1'–H1'1	104(2)
C2'–C1'–H1'2	109(2)
S1'–C1'–H1'2	108(2)
H1'1–C1'–H1'2	120(3)
C5'–C2'–C1'	114.0(3)
C5'–C2'–C3'	105.9(2)
C1'–C2'–C3'	108.6(3)
C5'–C2'–H2'	112.7(18)
C1'–C2'–H2'	105.6(19)
C3'–C2'–H2'	110.0(17)
C7'–C3'–C4'	113.2(3)
C7'–C3'–C2'	105.3(2)
C4'–C3'–C2'	108.4(3)
C7'–C3'–H3'	109.8(15)
C4'–C3'–H3'	108.0(15)
C2'–C3'–H3'	112.3(14)
C3'–C4'–S1'	105.6(2)
C3'–C4'–H4'1	110.8(18)
S1'–C4'–H4'1	106.2(17)
C3'–C4'–H4'2	114.6(17)
S1'–C4'–H4'2	104.4(16)
H4'1–C4'–H4'2	114(2)
C2'–C5'–C6'	105.6(2)
C2'–C5'–H5'1	108.6(16)
C6'–C5'–H5'1	115.4(16)
C2'–C5'–H5'2	106.4(17)
C6'–C5'–H5'2	109.3(17)
H5'1–C5'–H5'2	111(2)
C10'–C6'–C5'	116.3(2)

C10'–C6'–C8'	100.8(2)
C5'–C6'–C8'	112.3(2)
C10'–C6'–C7'	115.4(2)
C5'–C6'–C7'	101.3(2)
C8'–C6'–C7'	111.2(2)
C3'–C7'–C6'	105.3(2)
C3'–C7'–H7'1	110.4(18)
C6'–C7'–H7'1	106.3(18)
C3'–C7'–H7'2	110.5(18)
C6'–C7'–H7'2	114.8(19)
H7'1–C7'–H7'2	109(3)
O2'–C8'–O1'	121.2(3)
O2'–C8'–C6'	128.4(3)
O1'–C8'–C6'	110.4(3)
C11'–C9'–C10'	124.6(3)
C11'–C9'–O1'	123.0(3)
C10'–C9'–O1'	112.3(3)
C9'–C10'–C14'	117.7(3)
C9'–C10'–C6'	108.6(2)
C14'–C10'–C6'	133.6(2)
C9'–C11'–C12'	116.1(3)
C9'–C11'–H11'	120.0(17)
C12'–C11'–H11'	123.9(17)
C13'–C12'–C11'	121.8(3)
C13'–C12'–H12'	124(2)
C11'–C12'–H12'	114(2)
C10'–C14'–C13'	118.9(3)
C10'–C14'–H14'	119.5(15)
C13'–C14'–H14'	121.5(15)
C12'–C13'–C14'	120.8(4)
C12'–C13'–H13'	124(2)
C14'–C13'–H13'	115(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	97(1)	86(1)	63(1)	−7(1)	17(1)	4(1)
O1	78(2)	80(1)	63(2)	1(1)	−15(1)	−8(1)
O2	58(1)	111(2)	95(2)	2(1)	−4(1)	11(1)
C1	104(3)	78(2)	65(2)	14(2)	−8(2)	−8(2)
C2	68(2)	55(2)	62(2)	−1(1)	−1(2)	10(2)
C3	49(2)	55(2)	59(2)	−7(1)	0(2)	0(1)
C4	71(2)	68(2)	61(2)	−12(2)	−9(2)	3(2)
C5	60(2)	48(2)	61(2)	−3(1)	1(2)	−3(1)
C6	52(2)	51(1)	51(2)	−2(1)	−2(1)	−5(1)
C7	67(2)	49(2)	62(2)	−2(1)	1(2)	−8(1)
C8	57(2)	65(2)	69(2)	3(2)	−3(2)	−6(1)
C9	64(2)	60(2)	59(2)	−7(1)	0(2)	−13(1)
C10	59(2)	45(1)	54(2)	−5(1)	−1(1)	−12(1)
C11	105(3)	81(2)	57(2)	−9(2)	−3(2)	−28(2)
C12	102(3)	78(2)	82(3)	−27(2)	31(3)	−24(2)
C13	74(2)	78(2)	88(3)	−18(2)	19(2)	−6(2)
C14	68(2)	65(2)	70(2)	−11(2)	2(2)	0(2)
S1'	98(1)	133(1)	44(1)	7(1)	−14(1)	−14(1)
O1'	78(2)	118(2)	52(1)	−21(1)	8(1)	26(1)
O2'	98(2)	181(3)	86(2)	−15(2)	−9(2)	78(2)
C1'	95(3)	112(3)	55(2)	−34(2)	10(2)	−28(2)
C2'	73(2)	56(2)	48(2)	−3(1)	0(2)	−1(2)
C3'	49(2)	65(2)	47(2)	8(1)	−1(1)	−4(1)
C4'	79(2)	82(2)	49(2)	13(2)	2(2)	−6(2)
C5'	63(2)	73(2)	41(2)	−4(1)	1(2)	−17(2)
C6'	53(2)	58(1)	37(2)	−2(1)	−1(1)	5(1)
C7'	75(2)	56(2)	46(2)	1(1)	−14(2)	−4(2)
C8'	66(2)	100(2)	69(2)	−12(2)	2(2)	28(2)

C9'	64(2)	72(2)	40(2)	−5(1)	−3(1)	−7(2)
C10'	51(2)	47(1)	41(2)	0(1)	2(1)	−10(1)
C11'	83(2)	97(2)	39(2)	−8(2)	3(2)	−19(2)
C12'	86(3)	95(2)	46(2)	23(2)	−20(2)	−32(2)
C14'	58(2)	63(2)	49(2)	4(1)	−2(2)	−1(1)
C13'	64(2)	73(2)	78(3)	20(2)	−20(2)	−4(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	3128(16)	2900(30)	700(30)	80(11)	1
H1B	2500(17)	2460(30)	420(30)	90(10)	1
H2	3674(11)	4810(20)	−1350(20)	42(6)	1
H3	3347(13)	2630(30)	−1060(30)	64(8)	1
H4A	3119(11)	6620(30)	−90(30)	63(8)	1
H4B	3548(13)	5470(30)	400(30)	77(10)	1
H5A	3178(11)	6150(30)	−2670(20)	58(7)	1
H5B	2632(12)	5960(30)	−1810(30)	58(8)	1
H7A	2209(15)	3400(30)	−1590(30)	77(10)	1
H7B	2554(11)	2100(30)	−2160(30)	64(8)	1
H11	2913(15)	3680(40)	−6570(40)	83(12)	1
H12	3829(15)	2590(30)	−6580(40)	87(11)	1
H13	4325(17)	2210(30)	−4930(30)	98(12)	1
H14	3854(15)	2780(30)	−3060(40)	93(11)	1
H1'1	4941(17)	660(30)	−2340(30)	93(11)	1
H1'2	5600(14)	500(30)	−2760(30)	83(10)	1
H2'	5751(11)	500(30)	−940(20)	50(8)	1
H3'	6306(12)	2430(20)	−790(20)	51(7)	1
H4'1	6267(14)	2750(30)	−2780(30)	81(9)	1
H4'2	5938(10)	4220(30)	−2320(20)	54(8)	1
H5'1	4970(11)	530(30)	120(20)	56(7)	1
H5'2	4711(13)	1830(30)	−670(30)	75(9)	1
H7'1	5327(13)	4100(30)	−560(30)	62(9)	1
H7'2	5853(12)	4160(30)	160(30)	64(8)	1
H11'	5369(12)	2620(30)	4460(30)	65(8)	1
H12'	6158(14)	1140(30)	4560(30)	81(10)	1
H14'	6271(11)	790(20)	1100(20)	45(7)	1
H13'	6628(13)	220(30)	2870(30)	66(9)	1

8.4

X-RAY DATA FOR 220

Table 1. Crystal data and structure refinement.

Identification code	**00SOT073**	
Empirical formula	$C_{20}H_{20}O_2S$	
Formula weight	324.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*Cc*	
Unit cell dimensions	$a = 6.3567(5)$ Å	
	$b = 16.3900(12)$ Å	$\beta = 93.092(5)°$
	$c = 15.9156(13)$ Å	
Volume	1655.8(2) Å^3	
Z	4	
Density (calculated)	1.301 Mg / m^3	
Absorption coefficient	0.203 mm^{-1}	
F(000)	688	
Crystal	Colourless needle	
Crystal size	0.40 × 0.10 × 0.07 mm^3	
θ range for data collection	3.57 – 25.02°	
Index ranges	$-7 \le h \le 7, -19 \le k \le 19, -18 \le l \le 18$	
Reflections collected	2699	
Independent reflections	1766 [$R_{int} = 0.0627$]	
Completeness to $\theta = 25.02°$	92.0 %	
Max. and min. transmission	0.9859 and 0.9233	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1766 / 2 / 209	
Goodness-of-fit on F^2	1.044	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0572, *wR2* = 0.1420	
R indices (all data)	*R1* = 0.0593, *wR2* = 0.1449	
Absolute structure parameter	0.59(12)	
Extinction coefficient	0.012(4)	
Largest diff. peak and hole	0.600 and −0.486 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1927(2)	2843(1)	159(1)	28(1)	1
O2	3475(6)	3844(2)	−1177(2)	30(1)	1
O1	3768(6)	1829(2)	1551(2)	32(1)	1
C9	85(8)	2173(2)	528(2)	24(1)	1
C4	2432(8)	1186(2)	1395(2)	26(1)	1
C11	−1923(9)	3255(2)	−6(3)	28(1)	1
C2	1338(8)	−208(2)	1574(2)	29(1)	1
C20	5082(8)	3947(2)	−1746(3)	30(1)	1
C16	998(9)	5876(2)	−1313(3)	31(1)	1
C7	−502(9)	−48(2)	1064(3)	30(1)	1
C18	2132(8)	4482(2)	−1070(2)	27(1)	1
C14	−923(9)	4989(2)	−424(3)	29(1)	1
C13	464(8)	4341(2)	−556(2)	26(1)	1
C17	2405(8)	5239(2)	−1446(2)	28(1)	1
C12	17(8)	3533(2)	−182(2)	24(1)	1
C6	−801(8)	723(2)	725(2)	29(1)	1
C3	2770(8)	415(2)	1723(2)	29(1)	1
C10	−1881(8)	2477(2)	389(3)	26(1)	1
C19	1358(11)	6703(3)	−1695(3)	42(1)	1
C1	1697(10)	−1045(2)	1949(3)	38(1)	1
C15	−642(9)	5750(2)	−797(3)	31(1)	1
C5	618(8)	1352(2)	880(2)	25(1)	1
C8	5400(10)	1720(3)	2188(3)	38(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C12	1.725(4)	C2–C7	1.412(7)
S1–C9	1.731(4)	C2–C1	1.507(5)
O2–C18	1.367(5)	C16–C15	1.377(8)
O2–C20	1.412(6)	C16–C17	1.398(7)
O1–C4	1.369(5)	C16–C19	1.509(5)
O1–C8	1.422(6)	C7–C6	1.384(6)
C9–C10	1.352(7)	C18–C13	1.392(7)
C9–C5	1.490(5)	C18–C17	1.393(5)
C4–C3	1.379(6)	C14–C15	1.396(6)
C4–C5	1.404(7)	C14–C13	1.404(6)
C11–C12	1.358(7)	C13–C12	1.486(5)
C11–C10	1.421(5)	C6–C5	1.383(6)
C2–C3	1.381(6)		

C12–S1–C9	92.6(2)
C18–O2–C20	117.8(3)
C4–O1–C8	117.0(3)
C10–C9–C5	125.7(4)
C10–C9–S1	110.3(3)
C5–C9–S1	123.8(4)
O1–C4–C3	123.7(4)
O1–C4–C5	116.0(3)
C3–C4–C5	120.3(4)
C12–C11–C10	113.4(4)
C3–C2–C7	118.6(4)
C3–C2–C1	121.4(4)
C7–C2–C1	120.0(4)
C15–C16–C17	119.3(4)
C15–C16–C19	120.8(5)
C17–C16–C19	119.8(5)
C6–C7–C2	119.1(4)
O2–C18–C13	116.5(3)
O2–C18–C17	122.4(4)
C13–C18–C17	121.2(4)
C15–C14–C13	121.1(4)
C18–C13–C14	117.8(3)
C18–C13–C12	123.5(4)
C14–C13–C12	118.6(4)
C18–C17–C16	120.3(5)
C11–C12–C13	125.2(4)
C11–C12–S1	110.3(3)
C13–C12–S1	124.3(4)
C7–C6–C5	122.5(4)
C4–C3–C2	121.7(4)
C9–C10–C11	113.4(4)
C16–C15–C14	120.4(4)
C6–C5–C4	117.8(4)
C6–C5–C9	118.2(4)
C4–C5–C9	123.9(4)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	29(1)	21(1)	33(1)	6(1)	−2(1)	1(1)
O2	36(2)	21(1)	33(1)	5(1)	4(1)	2(1)
O1	32(2)	27(1)	36(2)	11(1)	−11(1)	−4(1)
C9	36(3)	19(2)	18(2)	0(2)	0(2)	−1(2)
C4	32(3)	25(2)	20(2)	1(2)	−1(2)	−2(2)
C11	30(3)	25(2)	30(2)	1(2)	2(2)	4(2)
C2	43(3)	20(2)	25(2)	−1(2)	7(2)	2(2)
C20	36(3)	24(2)	30(2)	4(2)	−6(2)	3(2)
C16	51(3)	16(2)	25(2)	1(2)	−8(2)	−3(2)
C7	39(3)	22(2)	29(2)	−2(2)	−7(2)	−4(2)
C18	40(3)	19(2)	21(2)	−1(2)	−10(2)	3(2)
C14	39(3)	22(2)	25(2)	−1(2)	−1(2)	3(2)
C13	38(3)	20(2)	19(2)	1(2)	−7(2)	−1(2)
C17	35(3)	26(2)	23(2)	3(2)	−1(2)	−2(2)
C12	31(3)	19(2)	23(2)	−1(2)	−6(2)	1(2)
C6	36(3)	26(2)	25(2)	1(2)	−1(2)	−5(2)
C3	37(3)	29(2)	20(2)	4(2)	−2(2)	7(2)
C10	27(3)	25(2)	27(2)	2(2)	−2(2)	−2(2)
C19	64(4)	24(2)	38(2)	11(2)	−5(2)	−1(2)
C1	62(4)	22(2)	30(2)	6(2)	−4(2)	5(2)
C15	39(3)	22(2)	31(2)	−2(2)	−6(2)	1(2)
C5	32(3)	20(2)	23(2)	1(2)	0(2)	2(2)
C8	38(3)	33(2)	42(2)	9(2)	−15(2)	−4(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	*S.o.f.*
H11	−3183	3551	−134	34	1
H20A	5915	3445	−1768	45	1
H20B	5998	4400	−1558	45	1
H20C	4449	4067	−2308	45	1
H7	−1520	−465	955	36	1
H14	−2071	4909	−75	34	1
H17	3552	5324	−1795	33	1
H6	−2027	825	373	35	1
H3	4019	311	2061	34	1
H10	−3114	2198	541	32	1
H19A	2583	6679	−2043	63	1
H19B	1615	7106	−1246	63	1
H19C	110	6863	−2046	63	1
H1A	521	−1403	1771	57	1
H1B	1791	−1004	2564	57	1
H1C	3013	−1271	1755	57	1
H15	−1588	6183	−694	37	1
H8A	6252	2217	2240	57	1
H8B	6294	1261	2037	57	1
H8C	4777	1605	2725	57	1

8.5

X-RAY DATA FOR 526

Table 1. Crystal data and structure refinement.

Identification code	**00SOT074**	
Empirical formula	$C_{10}H_{14}O_2S$	
Formula weight	198.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 15.1069(9)$ Å	
	$b = 6.2985(3)$ Å	$\beta = 92.175(3)°$
	$c = 20.0215(18)$ Å	
Volume	1903.7(2) Å^3	
Z	8	
Density (calculated)	1.384 Mg / m^3	
Absorption coefficient	0.303 mm^{-1}	
F(000)	848	
Crystal	Colourless needle	
Crystal size	0.20 × 0.08 × 0.08 mm^3	
θ range for data collection	3.32 – 25.02°	
Index ranges	$-17 \le h \le 17, -7 \le k \le 7, -20 \le l \le 23$	
Reflections collected	10111	
Independent reflections	3296 [$R_{int} = 0.1479$]	
Completeness to $\theta = 25.02°$	97.9 %	
Max. and min. transmission	0.9776 and 0.9419	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3296 / 0 / 236	
Goodness-of-fit on F^2	0.909	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0545$, $wR2 = 0.0901$	
R indices (all data)	$R1 = 0.1538$, $wR2 = 0.1143$	
Extinction coefficient	0.0037(6)	
Largest diff. peak and hole	0.297 and –0.311 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

C6 = R, C9 = S, C16 = R, C19 = S

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	1410(1)	6068(2)	4425(1)	32(1)	1
S2	2757(1)	11673(2)	5142(1)	38(1)	1
O9	−2109(2)	3326(4)	2742(1)	35(1)	1
O2	−1326(2)	6158(4)	2466(2)	40(1)	1
O4	5583(2)	12204(4)	3410(2)	37(1)	1
O3	4860(2)	12095(4)	2414(2)	33(1)	1
C1	−1471(3)	4801(6)	2872(2)	27(1)	1
C2	−2147(3)	1868(6)	3301(2)	32(1)	1
C4	−1039(2)	4459(6)	3555(2)	22(1)	1
C13	3467(3)	13344(6)	2713(2)	28(1)	1
C16	4237(3)	12871(5)	4555(2)	24(1)	1
C6	89(2)	7264(5)	3589(2)	24(1)	1
C3	−1721(2)	3061(6)	3889(2)	28(1)	1
C14	3966(2)	12651(5)	3341(2)	22(1)	1
C5	−775(2)	6531(5)	3901(2)	27(1)	1
C18	3445(3)	9517(6)	4874(2)	30(1)	1
C10	−128(2)	3420(6)	3481(2)	26(1)	1
C9	504(2)	5209(5)	3294(2)	24(1)	1
C19	4055(2)	10513(6)	4364(2)	25(1)	1
C15	3957(2)	14163(5)	3937(2)	25(1)	1
C7	758(3)	8249(5)	4091(2)	33(1)	1
C11	4895(3)	12307(6)	3084(2)	29(1)	1
C21	3648(2)	10557(6)	3656(2)	26(1)	1
C12	3955(3)	12253(6)	2162(2)	34(1)	1
C8	1434(2)	4941(5)	3600(2)	27(1)	1
C17	3713(3)	13404(6)	5174(2)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C8	1.799(4)
S1–C7	1.804(4)
S2–C18	1.805(4)
S2–C17	1.808(4)
O9–C1	1.356(4)
O9–C2	1.450(4)
O2–C1	1.205(4)
O4–C11	1.208(4)
O3–C11	1.346(5)
O3–C12	1.444(4)
C1–C4	1.509(6)
C2–C3	1.519(5)
C4–C5	1.524(5)
C4–C3	1.528(5)
C4–C10	1.536(5)
C13–C14	1.507(5)
C13–C12	1.515(5)
C16–C15	1.528(5)
C16–C17	1.534(5)
C16–C19	1.555(5)
C6–C7	1.529(5)
C6–C5	1.538(5)
C6–C9	1.565(5)
C14–C11	1.529(5)
C14–C15	1.526(5)
C14–C21	1.546(5)
C18–C19	1.535(5)
C10–C9	1.534(5)
C9–C8	1.520(5)
C19–C21	1.525(5)
C8–S1–C7	89.41(18)
C18–S2–C17	89.77(18)
C1–O9–C2	109.5(3)
C11–O3–C12	110.0(3)
O2–C1–O9	120.1(4)
O2–C1–C4	129.0(4)
O9–C1–C4	110.8(3)
O9–C2–C3	104.9(3)
C1–C4–C5	112.8(3)
C1–C4–C3	101.7(3)
C5–C4–C3	117.7(3)
C1–C4–C10	109.4(3)
C5–C4–C10	100.8(3)
C3–C4–C10	114.7(3)
C14–C13–C12	103.6(3)
C15–C16–C17	113.7(3)
C15–C16–C19	105.6(3)
C17–C16–C19	108.4(3)
C7–C6–C5	113.8(3)
C7–C6–C9	108.6(3)
C5–C6–C9	105.3(3)
C2–C3–C4	102.6(3)
C13–C14–C11	101.3(3)
C13–C14–C15	116.9(3)
C11–C14–C15	112.8(3)
C13–C14–C21	115.7(3)
C11–C14–C21	108.7(3)
C15–C14–C21	101.7(3)
C4–C5–C6	106.5(3)
C19–C18–S2	104.9(2)
C9–C10–C4	106.2(3)
C8–C9–C10	113.2(3)
C8–C9–C6	108.5(3)
C10–C9–C6	104.6(3)
C21–C19–C18	113.3(3)
C21–C19–C16	105.8(3)
C18–C19–C16	109.4(3)
C14–C15–C16	106.8(3)

C6–C7–S1	105.9(2)
O4–C11–O3	122.2(4)
O4–C11–C14	127.5(4)
O3–C11–C14	110.4(4)
C19–C21–C14	105.9(3)
O3–C12–C13	104.9(3)
C9–C8–S1	106.1(3)
C16–C17–S2	106.0(3)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	29(1)	34(1)	31(1)	−3(1)	−1(1)	−3(1)
S2	29(1)	34(1)	51(1)	6(1)	15(1)	3(1)
O9	29(2)	40(2)	35(2)	4(2)	−2(2)	−3(2)
O2	32(2)	51(2)	38(2)	19(2)	3(2)	2(2)
O4	18(2)	41(2)	54(2)	6(2)	6(2)	6(1)
O3	25(2)	37(2)	39(2)	−4(2)	11(2)	3(1)
C1	13(2)	30(2)	39(3)	−2(2)	4(2)	7(2)
C2	30(3)	32(2)	33(3)	1(2)	−3(2)	−4(2)
C4	16(2)	24(2)	25(3)	3(2)	3(2)	1(2)
C13	22(2)	25(2)	36(3)	0(2)	4(2)	−1(2)
C16	18(2)	22(2)	33(3)	−4(2)	6(2)	−2(2)
C6	24(3)	21(2)	29(3)	1(2)	0(2)	1(2)
C3	25(3)	30(2)	27(3)	0(2)	4(2)	−2(2)
C14	13(2)	20(2)	32(3)	0(2)	4(2)	5(2)
C5	26(3)	19(2)	37(3)	−3(2)	7(2)	5(2)
C18	29(3)	22(2)	41(3)	2(2)	5(2)	−1(2)
C10	26(3)	27(2)	26(3)	−3(2)	0(2)	1(2)
C9	20(2)	32(2)	22(3)	−1(2)	1(2)	5(2)
C19	18(2)	22(2)	34(3)	−2(2)	5(2)	1(2)
C15	20(2)	22(2)	35(3)	2(2)	5(2)	0(2)
C7	39(3)	24(2)	37(3)	−3(2)	6(2)	0(2)
C11	26(3)	17(2)	44(4)	2(2)	7(3)	−2(2)
C21	18(2)	23(2)	38(3)	−4(2)	4(2)	−5(2)
C12	32(3)	35(2)	34(3)	1(2)	1(2)	0(2)
C8	17(2)	29(2)	36(3)	−3(2)	0(2)	−1(2)
C17	39(3)	23(2)	43(3)	−4(2)	5(2)	−6(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	−1815	550	3210	38	1
H2B	−2768	1494	3390	38	1
H13A	3485	14907	2662	33	1
H13B	2841	12879	2715	33	1
H16	4884	13077	4657	29	1
H6	−51	8298	3221	29	1
H3A	−1432	2073	4214	33	1
H3B	−2162	3929	4120	33	1
H5A	−679	6303	4388	33	1
H5B	−1244	7612	3829	33	1
H18A	3796	8917	5257	36	1
H18B	3080	8375	4665	36	1
H10A	75	2746	3907	32	1
H10B	−158	2321	3128	32	1
H9	527	5327	2796	29	1
H19	4628	9717	4367	30	1
H15A	3356	14756	3985	31	1
H15B	4374	15352	3874	31	1
H7A	449	8983	4452	40	1
H7B	1139	9286	3867	40	1
H21A	2993	10524	3664	31	1
H21B	3850	9321	3397	31	1
H12A	3703	10827	2069	41	1
H12B	3918	13102	1745	41	1
H8A	1871	5691	3330	33	1
H8B	1596	3419	3625	33	1
H17A	3526	14911	5165	42	1
H17B	4078	13148	5587	42	1

8.6

X-RAY DATA FOR 514

Table 1. Crystal data and structure refinement.

Identification code	**00SOT080**
Empirical formula	$C_{13}H_{21}NOS$
Formula weight	957.47
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	$a = 9.6070(2)$ Å
	$b = 12.0747(2)$ Å $\beta = 98.6970(8)°$
	$c = 22.0662(5)$ Å
Volume	2530.28(9) Å^3
Z	8
Density (calculated)	1.257 Mg / m^3
Absorption coefficient	0.236 mm^{-1}
F(000)	1040
Crystal	Colourless block
Crystal size	0.20 × 0.20 × 0.10 mm^3
θ range for data collection	2.99 – 25.02°
Index ranges	$-11 \le h \le 11, -14 \le k \le 14, -23 \le l \le 24$
Reflections collected	12862
Independent reflections	3863 [$R_{int} = 0.0336$]
Completeness to $\theta = 25.02°$	86.6 %
Max. and min. transmission	0.9768 and 0.9543
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3863 / 0 / 290
Goodness-of-fit on F^2	1.048
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0381$, $wR2 = 0.0954$
R indices (all data)	$R1 = 0.0480$, $wR2 = 0.1030$
Extinction coefficient	0.0054(10)
Largest diff. peak and hole	0.407 and –0.401 e Å^{-3}

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

C2 = S, C3 = R, C4 = R, C15 = R, C16 = S, C17 = S

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C18	9201(2)	3462(2)	1786(1)	38(1)	1
C5	1978(3)	3431(2)	−2129(1)	45(1)	1
S2	7492(1)	2271(1)	885(1)	35(1)	1
S1	1100(1)	1270(1)	−2239(1)	48(1)	1
O1	3880(1)	2795(1)	−549(1)	27(1)	1
O2	10121(1)	3458(1)	−77(1)	31(1)	1
N1	2466(2)	1429(1)	−252(1)	23(1)	1
N2	7919(2)	4187(1)	−369(1)	22(1)	1
C7	2794(2)	2243(2)	−625(1)	21(1)	1
C22	7296(2)	5015(2)	−1399(1)	27(1)	1
C8	3350(2)	1185(2)	335(1)	22(1)	1
C21	7837(2)	4000(2)	−1025(1)	22(1)	1
C3	1607(2)	2354(2)	−1162(1)	24(1)	1
C16	8727(2)	4149(2)	683(1)	22(1)	1
C20	9031(2)	3885(2)	42(1)	22(1)	1
C2	635(2)	1375(2)	−1089(1)	29(1)	1
C12	4558(2)	−254(2)	1033(1)	28(1)	1
C13	3529(2)	−54(2)	447(1)	24(1)	1
C17	9016(2)	3155(2)	1110(1)	27(1)	1
C4	2130(2)	2336(2)	−1792(1)	28(1)	1
C11	4041(2)	293(2)	1578(1)	32(1)	1
C26	6942(2)	2982(2)	−1224(1)	26(1)	1
C23	7248(2)	4789(2)	−2081(1)	31(1)	1
C15	7143(2)	4446(2)	589(1)	22(1)	1
C6	1045(2)	997(2)	−420(1)	29(1)	1
C24	6346(2)	3782(2)	−2283(1)	31(1)	1
C9	2804(2)	1744(2)	872(1)	31(1)	1
C10	3805(2)	1528(2)	1469(1)	33(1)	1
C1	915(3)	500(2)	−1553(1)	41(1)	1
C19	6776(2)	4689(2)	−99(1)	27(1)	1
C25	6882(2)	2765(2)	−1911(1)	30(1)	1
C14	6332(2)	3461(2)	803(1)	34(1)	1

Table 3. Bond lengths [Å] and angles [°].

C18–C17	1.520(3)
C5–C4	1.514(3)
S2–C14	1.810(2)
S2–C17	1.819(2)
S1–C1	1.809(2)
S1–C4	1.822(2)
O1–C7	1.227(2)
O2–C20	1.230(2)
N1–C7	1.350(2)
N1–C6	1.456(2)
N1–C8	1.466(2)
N2–C20	1.343(2)
N2–C21	1.455(2)
N2–C19	1.458(2)
C7–C3	1.520(3)
C22–C23	1.523(3)
C22–C21	1.524(3)
C8–C13	1.521(2)
C8–C9	1.525(3)
C21–C26	1.526(3)
C3–C2	1.530(3)
C3–C4	1.548(3)
C16–C20	1.519(3)
C16–C17	1.526(3)
C16–C15	1.546(2)
C2–C1	1.524(3)
C2–C6	1.537(3)
C12–C11	1.519(3)
C12–C13	1.525(3)

C11–C10	1.522(3)
C26–C25	1.531(3)
C23–C24	1.520(3)
C15–C19	1.534(3)
C15–C14	1.535(3)
C24–C25	1.523(3)
C9–C10	1.531(3)
C14–S2–C17	91.13(9)
C1–S1–C4	91.33(9)
C7–N1–C6	113.66(15)
C7–N1–C8	121.85(15)
C6–N1–C8	123.26(15)
C20–N2–C21	123.24(15)
C20–N2–C19	114.06(15)
C21–N2–C19	122.67(15)
O1–C7–N1	125.67(17)
O1–C7–C3	125.52(16)
N1–C7–C3	108.81(15)
C23–C22–C21	110.35(16)
N1–C8–C13	112.17(15)
N1–C8–C9	112.10(15)
C13–C8–C9	110.64(16)
N2–C21–C22	112.13(15)
N2–C21–C26	110.74(15)
C22–C21–C26	111.17(15)
C7–C3–C2	104.38(15)
C7–C3–C4	113.03(15)
C2–C3–C4	111.70(16)
C20–C16–C17	111.57(16)
C20–C16–C15	104.34(14)
C17–C16–C15	110.36(15)
O2–C20–N2	125.82(17)
O2–C20–C16	125.11(16)
N2–C20–C16	109.06(15)
C1–C2–C3	107.00(16)
C1–C2–C6	113.12(17)
C3–C2–C6	104.96(15)
C11–C12–C13	110.80(16)
C8–C13–C12	109.67(15)
C18–C17–C16	113.45(17)
C18–C17–S2	112.37(14)
C16–C17–S2	103.26(12)
C5–C4–C3	114.22(17)
C5–C4–S1	110.26(15)
C3–C4–S1	105.89(13)
C12–C11–C10	111.07(16)
C21–C26–C25	110.97(16)
C24–C23–C22	111.31(16)
C19–C15–C14	113.69(16)
C19–C15–C16	104.55(15)
C14–C15–C16	108.33(15)
N1–C6–C2	103.47(15)
C23–C24–C25	110.84(16)
C8–C9–C10	110.43(16)
C11–C10–C9	111.19(17)
C2–C1–S1	104.82(15)
N2–C19–C15	104.48(14)
C24–C25–C26	110.75(16)
C15–C14–S2	108.19(13)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C18	36(1)	51(1)	25(1)	8(1)	0(1)	−7(1)
C5	68(2)	38(1)	29(1)	6(1)	12(1)	0(1)
S2	42(1)	22(1)	39(1)	2(1)	2(1)	−4(1)
S1	68(1)	48(1)	28(1)	−8(1)	6(1)	−18(1)
O1	28(1)	27(1)	27(1)	1(1)	3(1)	−6(1)
O2	23(1)	44(1)	28(1)	1(1)	6(1)	7(1)
N1	22(1)	24(1)	21(1)	3(1)	2(1)	−3(1)
N2	21(1)	27(1)	18(1)	−2(1)	3(1)	2(1)
C7	24(1)	19(1)	22(1)	−3(1)	6(1)	2(1)
C22	30(1)	25(1)	26(1)	1(1)	6(1)	0(1)
C8	25(1)	23(1)	19(1)	0(1)	2(1)	−1(1)
C21	22(1)	26(1)	18(1)	−2(1)	4(1)	0(1)
C3	23(1)	24(1)	24(1)	1(1)	4(1)	3(1)
C16	22(1)	24(1)	21(1)	−1(1)	2(1)	−3(1)
C20	21(1)	22(1)	24(1)	1(1)	4(1)	−3(1)
C2	24(1)	34(1)	28(1)	3(1)	1(1)	−2(1)
C12	29(1)	27(1)	28(1)	4(1)	2(1)	1(1)
C13	27(1)	23(1)	23(1)	−1(1)	5(1)	−1(1)
C17	25(1)	30(1)	27(1)	3(1)	4(1)	3(1)
C4	29(1)	31(1)	24(1)	2(1)	6(1)	2(1)
C11	39(1)	37(1)	21(1)	2(1)	4(1)	−6(1)
C26	29(1)	25(1)	24(1)	1(1)	1(1)	1(1)
C23	37(1)	32(1)	23(1)	5(1)	5(1)	1(1)
C15	23(1)	22(1)	22(1)	0(1)	4(1)	2(1)
C6	25(1)	32(1)	29(1)	5(1)	2(1)	−7(1)
C24	32(1)	39(1)	20(1)	2(1)	1(1)	0(1)
C9	38(1)	25(1)	30(1)	−3(1)	7(1)	3(1)
C10	45(1)	35(1)	21(1)	−7(1)	9(1)	−7(1)
C1	51(1)	34(1)	36(1)	−4(1)	4(1)	−12(1)
C19	28(1)	31(1)	22(1)	−1(1)	6(1)	7(1)
C25	37(1)	29(1)	23(1)	−3(1)	−2(1)	−1(1)
C14	25(1)	38(1)	37(1)	10(1)	1(1)	−2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H18A	9380	2790	2035	56	1
H18B	8343	3822	1877	56	1
H18C	9999	3970	1880	56	1
H5A	2334	3356	−2521	67	1
H5B	2520	4001	−1880	67	1
H5C	983	3645	−2206	67	1
H22A	6340	5205	−1316	32	1
H22B	7922	5654	−1277	32	1
H8	4306	1496	313	27	1
H21	8813	3847	−1109	26	1
H3	1089	3061	−1120	28	1
H16	9302	4798	854	27	1
H2	−373	1614	−1166	34	1
H12A	4663	−1060	1108	34	1
H12B	5493	49	986	34	1
H13A	3889	−405	96	29	1
H13B	2606	−391	484	29	1
H17	9881	2765	1022	33	1
H4	3144	2113	−1729	33	1
H11A	4743	179	1950	39	1
H11B	3147	−59	1648	39	1
H26A	5976	3097	−1131	31	1
H26B	7347	2329	−990	31	1
H23A	6860	5444	−2318	37	1
H23B	8216	4664	−2168	37	1
H15	6986	5121	831	27	1
H6A	399	1311	−156	35	1
H6B	1033	179	−389	35	1
H24A	6364	3639	−2723	37	1
H24B	5359	3931	−2228	37	1
H9A	1857	1453	909	37	1
H9B	2722	2551	797	37	1
H10A	4720	1893	1449	40	1
H10B	3404	1853	1817	40	1
H1A	120	−29	−1631	49	1
H1B	1788	84	−1403	49	1
H19A	5860	4354	−270	32	1
H19B	6731	5497	−176	32	1
H25A	7833	2571	−1997	36	1
H25B	6250	2130	−2034	36	1
H14A	5488	3302	499	40	1
H14B		6022			

8.7

X-RAY DATA FOR 525

Table 1. Crystal data and structure refinement.

Identification code	**00SOT081**	
Empirical formula	$(C_{10}H_{14}O_2S)_2$	
Formula weight	396.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 6.2971(5) Å	α = 88.396(3)°
	b = 7.3727(6) Å	β = 75.340(3)°
	c = 10.8864(11) Å	γ = 89.422(6)°
Volume	488.77(7) Å^3	
Z	1	
Density (calculated)	1.347 Mg / m^3	
Absorption coefficient	0.295 mm^{-1}	
F(000)	212	
Crystal	Colourless Block	
Crystal size	0.20 × 0.15 × 0.10 mm^3	
θ range for data collection	3.33 – 23.26°	
Index ranges	$-6 \le h \le 6$, $-7 \le k \le 8$, $-11 \le l \le 12$	
Reflections collected	2458	
Independent reflections	2168 [R_{int} = 0.0522]	
Completeness to θ = 23.26°	94.6 %	
Max. and min. transmission	0.9711 and 0.9434	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2168 / 3 / 236	
Goodness-of-fit on F^2	1.374	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.1309, $wR2$ = 0.3064	
R indices (all data)	$R1$ = 0.1337, $wR2$ = 0.3134	
Absolute structure parameter	–0.3(2)	
Extinction coefficient	0.30(8)	
Largest diff. peak and hole	1.037 and –0.756 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

C2 = S, C3 = R, C12 = R, C13 = S

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	7714(4)	9060(3)	5108(3)	41(1)	1
O1	8354(14)	3765(10)	8176(8)	44(2)	1
O2	11702(13)	2589(10)	7746(7)	39(2)	1
C8	10312(18)	3900(14)	7655(10)	38(3)	1
C1	9609(19)	10058(13)	5904(10)	38(3)	1
C9	13901(19)	3092(15)	6917(11)	41(3)	1
C5	10511(16)	7323(14)	7210(10)	30(2)	1
C6	11329(17)	5459(13)	6818(10)	34(2)	1
C4	9980(20)	7905(16)	4053(12)	52(3)	1
C10	13759(18)	5065(15)	6773(11)	39(3)	1
C2	11205(17)	8546(13)	6037(10)	33(2)	1
C3	11505(19)	7275(14)	4866(10)	33(2)	1
C7	10863(19)	5337(13)	5492(10)	35(2)	1
S2	2799(4)	7386(3)	321(3)	43(1)	1
O4	6796(15)	13445(12)	3137(8)	53(2)	1
O3	3539(17)	12198(17)	3440(12)	80(4)	1
C14	4210(19)	9087(15)	−814(11)	36(2)	1
C17	5170(20)	11441(15)	641(12)	43(3)	1
C18	5380(20)	12288(17)	2840(11)	42(3)	1
C13	5950(20)	9870(14)	−231(11)	39(3)	1
C12	6730(20)	8391(16)	581(13)	48(3)	1
C11	5390(20)	6677(15)	616(10)	43(3)	1
C16	6453(17)	11230(16)	1680(9)	36(3)	1
C15	6370(20)	9223(17)	1914(13)	46(3)	1
C20	8740(20)	12030(20)	1297(15)	68(4)	1
C19	8890(30)	13180(30)	2342(16)	85(6)	1

Table 3. Bond lengths [Å] and angles [°].

S1–C4	1.810(12)	S2–C14	1.808(11)
S1–C1	1.814(12)	S2–C11	1.808(13)
O1–C8	1.224(14)	O4–C18	1.343(16)
O2–C8	1.316(14)	O4–C19	1.40(2)
O2–C9	1.493(15)	O3–C18	1.179(15)
C8–C6	1.491(15)	C14–C13	1.522(16)
C1–C2	1.522(14)	C17–C13	1.516(16)
C9–C10	1.463(17)	C17–C16	1.553(17)
C5–C6	1.498(15)	C18–C16	1.507(14)
C5–C2	1.515(15)	C13–C12	1.538(18)
C6–C10	1.544(15)	C12–C11	1.522(19)
C6–C7	1.549(15)	C12–C15	1.553(17)
C4–C3	1.525(17)	C16–C15	1.494(18)
C2–C3	1.575(15)	C16–C20	1.514(17)
C3–C7	1.577(14)	C20–C19	1.46(2)

C4–S1–C1	90.0(6)
C8–O2–C9	108.2(8)
O1–C8–O2	121.3(9)
O1–C8–C6	124.7(10)
O2–C8–C6	113.9(9)
C2–C1–S1	105.5(7)
C10–C9–O2	103.4(9)
C6–C5–C2	106.5(9)
C8–C6–C5	117.5(9)
C8–C6–C10	98.8(9)
C5–C6–C10	116.1(9)
C8–C6–C7	110.5(8)
C5–C6–C7	102.3(8)
C10–C6–C7	112.0(9)
C3–C4–S1	106.2(8)
C9–C10–C6	105.1(9)
C5–C2–C1	116.0(9)
C5–C2–C3	106.1(8)
C1–C2–C3	108.4(9)
C4–C3–C2	109.4(9)
C4–C3–C7	111.9(10)
C2–C3–C7	103.7(8)
C6–C7–C3	103.7(8)
C14–S2–C11	89.9(5)
C18–O4–C19	109.5(9)
C13–C14–S2	105.4(8)
C13–C17–C16	104.6(9)
O3–C18–O4	121.3(10)
O3–C18–C16	127.3(11)
O4–C18–C16	111.4(9)
C17–C13–C14	114.7(10)
C17–C13–C12	106.1(9)
C14–C13–C12	109.5(9)
C11–C12–C13	109.5(11)
C11–C12–C15	112.3(11)
C13–C12–C15	104.8(9)
C12–C11–S2	106.6(8)
C15–C16–C18	113.4(10)
C15–C16–C20	115.0(11)
C18–C16–C20	102.4(9)
C15–C16–C17	101.3(9)
C18–C16–C17	111.4(9)
C20–C16–C17	113.8(10)
C16–C15–C12	105.3(11)
C19–C20–C16	105.4(13)
O4–C19–C20	109.7(16)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	27(2)	49(2)	46(2)	3(1)	−9(1)	1(1)
O1	34(5)	53(5)	33(4)	11(3)	10(4)	−7(4)
O2	33(5)	44(4)	38(5)	10(3)	−6(4)	−4(3)
C8	30(8)	42(5)	33(6)	−3(4)	7(5)	1(5)
C1	46(8)	32(5)	27(6)	5(4)	5(5)	0(4)
C9	31(7)	52(6)	41(6)	−2(5)	−13(6)	−1(5)
C5	16(5)	58(6)	21(5)	0(4)	−16(4)	−3(4)
C6	26(6)	42(5)	34(6)	3(4)	−8(5)	−8(4)
C4	68(10)	48(7)	40(7)	0(5)	−14(7)	15(6)
C10	25(7)	60(7)	33(6)	13(5)	−9(5)	−8(5)
C2	18(6)	42(6)	39(6)	0(4)	−6(5)	−8(4)
C3	29(6)	42(5)	22(5)	10(4)	2(4)	1(4)
C7	47(7)	35(5)	25(5)	2(4)	−11(5)	−2(4)
S2	32(2)	51(2)	45(2)	2(1)	−5(1)	−11(1)
O4	51(6)	66(5)	41(5)	−24(4)	−8(4)	−3(4)
O3	29(6)	113(8)	84(8)	−55(7)	15(6)	−10(5)
C14	27(7)	49(6)	33(6)	−1(4)	−10(5)	−1(4)
C17	43(7)	43(6)	44(7)	9(5)	−16(6)	−5(5)
C18	26(7)	68(7)	23(6)	−6(5)	12(5)	5(5)
C13	37(7)	47(6)	35(6)	5(5)	−11(5)	−12(5)
C12	48(9)	48(7)	49(7)	−13(5)	−14(6)	8(5)
C11	57(8)	46(6)	22(5)	−2(4)	−6(5)	6(5)
C16	8(5)	71(7)	20(5)	−5(5)	11(4)	−6(5)
C15	35(7)	62(7)	50(7)	−17(5)	−24(6)	14(5)
C20	41(9)	105(11)	60(9)	−30(8)	−15(7)	−27(7)
C19	91(14)	100(12)	54(10)	−38(9)	2(9)	−26(10)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	10398	11091	5393	45	1
H1B	8815	10496	6748	45	1
H9A	15087	2742	7325	49	1
H9B	14169	2506	6084	49	1
H5A	11159	7745	7890	36	1
H5B	8892	7323	7530	36	1
H4A	9439	6855	3673	62	1
H4B	10753	8740	3360	62	1
H10A	14727	5495	5954	46	1
H10B	14191	5672	7473	46	1
H2	12656	9097	6022	40	1
H3	13066	7284	4353	40	1
H7A	9295	5076	5569	42	1
H7B	11773	4380	4988	42	1
H14A	4901	8534	−1638	43	1
H14B	3176	10045	−952	43	1
H17A	3566	11370	1021	51	1
H17B	5507	12616	172	51	1
H13	7225	10278	−930	47	1
H12	8322	8128	219	57	1
H11A	5140	6050	1456	51	1
H11B	6161	5837	−44	51	1
H15A	4935	8854	2471	56	1
H15B	7545	8823	2320	56	1
H20A	9864	11061	1175	81	1
H20B	8950	12760	498	81	1
H19A	9846	12590	2831	102	1
H19B	9540	14360	2003	102	1

8.8

X-RAY DATA FOR 1

Table 1. Crystal data and structure refinement.

Identification code	**99SOT050**	
Empirical formula	$C_{15}H_{19}BrO$	
Formula weight	295.21	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 14.826(3)$ Å	
	$b = 6.7530(10)$ Å	$\beta = 102.80(3)°$
	$c = 28.009(6)$ Å	
Volume	2734.6(9) Å^3	
Z	8	
Density (calculated)	1.434 Mg / m^3	
Absorption coefficient	2.989 mm^{-1}	
F(000)	1216	
Crystal	Colourless plate	
Crystal size	0.30 × 0.20 × 0.005 mm^3	
θ range for data collection	2.98 – 21.97°	
Index ranges	$-15 \le h \le 15$, $-6 \le k \le 6$, $-28 \le l \le 29$	
Reflections collected	8349	
Independent reflections	3140 [$R_{int} = 0.1219$]	
Completeness to $\theta = 21.97°$	94.4 %	
Absorption correction	Empirical, SORTAV	
Max. and min. transmission	0.9940 and 0.4675	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3140 / 0 / 315	
Goodness-of-fit on F^2	0.902	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0504$, $wR2 = 0.0820$	
R indices (all data)	$R1 = 0.1373$, $wR2 = 0.1052$	
Largest diff. peak and hole	0.264 and –0.271 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Special details: All hydrogens were placed in calculated positions and refined using a riding model. There are two chemically identical, crystallographically independent, molecules in the asymmetric unit.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1B	2279(1)	3900(1)	322(1)	78(1)	1
Br1A	3135(1)	5586(1)	1628(1)	82(1)	1
O1A	4740(4)	11187(6)	3253(2)	60(2)	1
O1B	3818(4)	−1393(7)	−1015(2)	62(2)	1
C14B	3423(6)	−297(13)	−705(2)	49(2)	1
C4B	3390(6)	2849(11)	−334(3)	55(2)	1
C2A	3212(6)	9297(13)	2127(2)	55(2)	1
C14A	4312(6)	10018(12)	2865(3)	53(2)	1
C4A	4340(6)	6822(11)	2507(3)	55(2)	1
C3A	3598(6)	7449(13)	2141(2)	51(2)	1
C15A	3582(6)	10613(11)	2502(3)	56(2)	1
C6A	5477(6)	7928(11)	3323(2)	52(2)	1
C5B	3753(6)	1618(12)	−642(2)	48(2)	1
C2B	2397(6)	205(12)	−162(2)	51(2)	1
C1B	1679(6)	−565(11)	93(3)	73(3)	1
C5A	4695(6)	8188(13)	2878(2)	53(2)	1
C12B	4542(6)	−165(12)	−1160(2)	56(2)	1
C3B	2721(7)	2138(13)	−107(2)	57(2)	1
C12A	5498(6)	10039(10)	3564(2)	52(2)	1
C15B	2761(6)	−1027(11)	−476(2)	53(2)	1
C6B	4479(6)	1917(12)	−936(3)	58(2)	1
C1A	2389(6)	9947(11)	1733(2)	76(3)	1
C8A	5192(6)	6525(10)	3705(2)	55(2)	1
C7A	6374(6)	7237(12)	3192(2)	67(3)	1
C10B	4268(7)	113(11)	−1719(2)	68(3)	1
C10A	5254(6)	9694(11)	4066(2)	57(2)	1
C9A	4675(6)	7856(12)	3997(2)	64(2)	1
C9B	3608(7)	1841(12)	−1777(2)	78(3)	1
C13A	6364(6)	11251(11)	3591(2)	74(3)	1
C11A	4824(6)	11489(11)	4267(2)	76(3)	1
C8B	4107(6)	3275(11)	−1383(3)	74(3)	1
C11B	3913(7)	−1739(12)	−2013(3)	96(3)	1
C7B	5365(6)	2771(13)	−612(3)	94(3)	1
C13B	5453(6)	−1261(13)	−985(3)	100(3)	1

Table 3. Bond lengths [Å] and angles [°].

Br1B–C3B	1.908(8)
Br1A–C3A	1.920(7)
O1A–C14A	1.379(7)
O1A–C12A	1.479(8)
O1B–C14B	1.369(9)
O1B–C12B	1.483(9)
C14B–C15B	1.377(10)
C14B–C5B	1.380(9)
C4B–C3B	1.377(10)
C4B–C5B	1.388(10)
C2A–C3A	1.370(10)
C2A–C15A	1.393(9)
C2A–C1A	1.517(9)
C14A–C5A	1.358(9)
C14A–C15A	1.371(9)
C4A–C3A	1.392(9)
C4A–C5A	1.402(9)
C6A–C5A	1.514(9)
C6A–C7A	1.529(10)
C6A–C8A	1.554(9)
C6A–C12A	1.574(9)
C5B–C6B	1.507(11)
C2B–C3B	1.388(10)
C2B–C15B	1.403(10)
C2B–C1B	1.500(11)
C12B–C13B	1.524(11)
C12B–C10B	1.538(8)
C12B–C6B	1.552(10)
C12A–C13A	1.511(10)
C12A–C10A	1.547(9)
C6B–C7B	1.533(10)
C6B–C8B	1.552(9)
C8A–C9A	1.530(9)
C10B–C9B	1.508(10)
C10B–C11B	1.526(9)
C10A–C9A	1.497(9)
C10A–C11A	1.534(9)
C9B–C8B	1.529(9)
C14A–O1A–C12A	108.7(6)
C14B–O1B–C12B	108.0(6)
O1B–C14B–C15B	123.5(8)
O1B–C14B–C5B	113.5(8)
C15B–C14B–C5B	123.0(8)
C3B–C4B–C5B	119.7(7)
C3A–C2A–C15A	117.8(7)
C3A–C2A–C1A	123.3(7)
C15A–C2A–C1A	118.9(8)
C5A–C14A–C15A	122.9(7)
C5A–C14A–O1A	112.6(7)
C15A–C14A–O1A	124.5(8)
C3A–C4A–C5A	116.8(7)
C2A–C3A–C4A	123.8(6)
C2A–C3A–Br1A	119.8(6)
C4A–C3A–Br1A	116.4(6)
C14A–C15A–C2A	119.2(7)
C5A–C6A–C7A	112.6(6)
C5A–C6A–C8A	111.2(7)
C7A–C6A–C8A	111.3(6)
C5A–C6A–C12A	100.7(6)
C7A–C6A–C12A	116.3(7)
C8A–C6A–C12A	103.9(6)
C14B–C5B–C4B	117.8(8)
C14B–C5B–C6B	109.3(7)
C4B–C5B–C6B	132.9(8)
C3B–C2B–C15B	117.1(8)
C3B–C2B–C1B	122.6(8)
C15B–C2B–C1B	120.3(7)
C14A–C5A–C4A	119.6(7)

C14A–C5A–C6A	111.5(7)
C4A–C5A–C6A	128.9(8)
O1B–C12B–C13B	106.5(6)
O1B–C12B–C10B	107.6(6)
C13B–C12B–C10B	113.8(7)
O1B–C12B–C6B	106.5(6)
C13B–C12B–C6B	116.0(7)
C10B–C12B–C6B	106.0(6)
C4B–C3B–C2B	122.9(8)
C4B–C3B–Br1B	117.2(7)
C2B–C3B–Br1B	119.8(7)
O1A–C12A–C13A	105.8(6)
O1A–C12A–C10A	108.3(7)
C13A–C12A–C10A	113.8(6)
O1A–C12A–C6A	106.5(5)
C13A–C12A–C6A	116.6(7)
C10A–C12A–C6A	105.4(6)
C14B–C15B–C2B	119.5(7)
C5B–C6B–C7B	110.5(6)
C5B–C6B–C12B	102.4(6)
C7B–C6B–C12B	117.4(7)
C5B–C6B–C8B	110.6(7)
C7B–C6B–C8B	111.1(7)
C12B–C6B–C8B	104.5(6)
C9A–C8A–C6A	104.7(6)
C9B–C10B–C11B	116.0(8)
C9B–C10B–C12B	102.9(6)
C11B–C10B–C12B	115.6(6)
C9A–C10A–C11A	115.5(7)
C9A–C10A–C12A	104.5(6)
C11A–C10A–C12A	114.6(6)
C10A–C9A–C8A	102.5(7)
C10B–C9B–C8B	102.3(7)
C9B–C8B–C6B	103.7(6)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1B	92(1)	78(1)	66(1)	−15(1)	24(1)	4(1)
Br1A	88(1)	95(1)	57(1)	−20(1)	4(1)	−14(1)
O1A	77(4)	48(3)	46(3)	−2(2)	−4(3)	7(3)
O1B	75(5)	63(4)	52(3)	−5(3)	23(3)	−3(4)
C14B	54(7)	63(6)	28(4)	−2(4)	7(4)	−1(5)
C4B	61(7)	50(5)	48(5)	1(4)	−4(5)	−6(5)
C2A	52(6)	64(6)	45(5)	10(4)	3(4)	2(5)
C14A	69(7)	46(6)	40(5)	0(4)	5(5)	−5(5)
C4A	65(7)	55(5)	48(5)	0(4)	17(5)	7(5)
C3A	49(6)	68(6)	35(5)	−12(4)	6(4)	−6(5)
C15A	59(7)	49(5)	56(5)	9(4)	4(5)	7(5)
C6A	52(7)	62(6)	37(5)	3(4)	1(4)	11(5)
C5B	49(6)	55(6)	37(5)	−7(4)	2(4)	−4(5)
C2B	55(7)	61(6)	35(5)	5(4)	8(4)	−4(5)
C1B	88(8)	68(6)	67(5)	−9(4)	28(5)	−17(6)
C5A	52(6)	68(7)	37(5)	−2(4)	5(4)	−1(5)
C12B	50(7)	67(6)	53(5)	1(4)	18(5)	−5(5)
C3B	77(8)	58(6)	35(5)	0(4)	11(5)	−3(5)
C12A	62(7)	51(5)	39(5)	1(4)	5(4)	−4(5)
C15B	63(7)	59(6)	35(4)	0(4)	10(5)	3(5)
C6B	46(6)	70(6)	56(5)	−3(5)	10(5)	−14(5)
C1A	68(7)	95(7)	58(5)	12(4)	−3(5)	5(5)
C8A	66(7)	49(5)	46(5)	9(4)	2(4)	0(5)
C7A	60(7)	80(6)	60(5)	3(4)	10(5)	11(5)
C10B	86(8)	69(6)	56(6)	8(4)	31(5)	3(6)
C10A	64(7)	67(6)	38(5)	3(4)	9(4)	8(5)
C9A	62(7)	77(6)	52(5)	8(4)	11(5)	−4(6)
C9B	95(8)	95(7)	38(5)	14(5)	2(5)	0(7)
C13A	82(8)	71(6)	69(6)	−3(4)	17(5)	−20(6)
C11A	94(8)	72(6)	64(5)	−6(4)	19(5)	9(6)
C8B	97(8)	62(6)	69(6)	22(5)	29(5)	10(6)
C11B	135(10)	88(7)	64(6)	−9(5)	17(6)	−25(7)
C7B	86(9)	115(8)	82(6)	−3(5)	19(6)	−26(7)
C13B	63(8)	119(8)	113(7)	17(5)	11(6)	20(7)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	$S.o.f.$
H4B	3597	4147	−282	66	1
H4A	4587	5558	2505	66	1
H15A	3337	11878	2507	68	1
H1B1	1948	−723	436	109	1
H1B2	1456	−1821	−45	109	1
H1B3	1175	357	52	109	1
H15B	2557	−2327	−529	63	1
H1A1	1916	8952	1692	114	1
H1A2	2579	10127	1430	114	1
H1A3	2152	11173	1828	114	1
H8A1	4794	5473	3543	66	1
H8A2	5733	5941	3917	66	1
H7A1	6292	5924	3058	101	1
H7A2	6864	7231	3481	101	1
H7A3	6531	8122	2955	101	1
H10B	4821	556	−1825	81	1
H10A	5831	9380	4301	68	1
H9A1	4051	8129	3815	77	1
H9A2	4650	7261	4309	77	1
H9B1	3013	1449	−1718	94	1
H9B2	3519	2419	−2101	94	1
H13A	6441	11522	3266	111	1
H13B	6890	10526	3768	111	1
H13C	6312	12477	3757	111	1
H11A	4241	11802	4053	115	1
H11B	5233	12603	4288	115	1
H11C	4729	11185	4587	115	1
H8B1	3683	4259	−1307	89	1
H8B2	4610	3943	−1488	89	1
H11D	3334	−2133	−1943	144	1
H11E	4355	−2790	−1925	144	1
H11F	3827	−1460	−2356	144	1
H7B1	5244	4080	−508	141	1
H7B2	5840	2828	−795	141	1
H7B3	5564	1939	−331	141	1
H13D	5606	−1295	−634	150	1
H13E	5934	−590	−1101	150	1
H13F	5394	−2590	−1110	150	1

CHAPTER 9

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