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THE STEREOSELECTIVE SYNTHESIS OF FUNCTIONALISED CYCLOBUTANOLS *VIA* THE SAMARIUM(II)-MEDIATED CYCLISATION OF UNSATURATED ALDEHYDES

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ABSTRACT

THE STEREOSELECTIVE SYNTHESIS OF FUNCTIONALISED CYCLOBUTANOLS *VIA* THE SAMARIUM(II)-MEDIATED CYCLISATION OF UNSATURATED ALDEHYDES

Samarium(II) iodide continues to prove an incredibly versatile reagent in organic synthesis. γ,δ-Unsaturated aldehydes having a fully substituted centre in the α- position, have been prepared from substituted γ-butyrolactones and undergo efficient 4-*exo*-trig cyclisation on treatment with samarium(II) iodide to give functionalised cyclobutanols. In all cases when the olefin has *E*-geometry, cyclisation occurs with complete diastereocontrol to give *anti*-cyclobutanol products. The importance of olefin geometry on the stereochemical outcome in the cyclisation is discussed. The stereochemistry of the products has been confirmed by NOE and X-ray crystallographic studies. In the cyclisation of substrates having a third substituent on the double bond, α- to the ester, significant control is achieved at the third newly formed stereocentre lying outside the ring. The origin of the stereoselectivity at this third centre and its marked dependence on cosolvent are discussed. The application of this novel methodology in an approach to the core of pestalotiopsin A is also discussed. Pestalotiopsin A is a structurally unique caryophyllene-type sesquiterpene which has shown immunosuppressive activity and cytotoxicity in preliminary assays. Our approach is based upon our samarium(II)-mediated 4-*exo*-trig cyclisation and a trans-lactonisation process triggered by the addition of alkylytterbium reagents to a cyclobutanone intermediate.

Dedicated to my family and the LORD.

"...when I run I feel His pleasure..."
-Eric Liddell

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr. David J. Procter in the Loudon Laboratory at the University of Glasgow between October 1998 and September 2001. Part of this thesis has been previously published:

D. Johnston, C. M. McCusker and D. J. Procter, *Tetrahedron Lett.*, 1999, **40**, 4913.

D. Johnston, C. F. McCusker, K. Muir and D. J. Procter, *J. Chem. Soc., Perkin Trans. 1*, 2000, 681

D. Johnston, N. Francon, D. J. Edmonds and D. J. Procter, *Org. Lett.*, 2001, **3**, 2001.

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Last but certainly not least, I would like to thank my family....Mum and Dad, Stuart and Catherine, and Graeme and Pamela for their solid support and nutritional donations to the cause. And finally thanks to God, who has provided me with strength and anything else I've needed over the course of this study and beyond.

Abbreviations

Å	Angstrom
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Anal.	combustion analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
n-BuLi	*n*-butyllithium
s-BuLi	*s*-butyllithium
t-BuLi	*t*-butyllithium
CAN	cerric ammonium nitrate
CSA	camphorsulfonic acid
CI	chemical ionisation
d	days
D	dextro rotary
Δ	reflux
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBM	dibenzoylmethane
DCC	N,N'-dicyclohexylcarbodiimide
de	diastereoisomeric excess
DIBALH	di*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereoisomeric ratio
EI	electron impact
eq	equivalents
er	enantiomeric ratio
Et	ethyl
FAB	fast atom bombardment

g	gram
h	hour
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
IR	infrared
KHMDS	potassium hexamethyldisilazide
L	levo rotary
LDA	lithium di*iso*-propylamide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megaHertz
min	minute
ml	millilitre
mmol	millimole
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
n	normal
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	4-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	Propyl
*p*TSA	*para*-toluene sulfonic acid
py	pyridine
rt	room temperature

SOMO	singularly occupied molecular orbital
SPS	solid phase synthesis
t	tertiary
TBDMS	*tert*-butyldimethylsilyl
TBSCN	*tert*-butyldimethylsilyl cyanide
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonate (triflate)
THF	tetrahydrofuran
TIPS	tri*iso*-propylsilyl
TMSCl	trimethylsilyl chloride
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl

Chapter 1: Samarium(II) iodide-mediated cyclisations in natural product synthesis

1.1 Introduction

Since its introduction to the synthetic community by Kagan in 1977,[1, 2] samarium(II) iodide (SmI_2) has established itself as a versatile single electron reducing agent. Part of the reagent's popularity arises from its ability to mediate both radical and anionic processes and sequences involving both.[3-11] It has been utilised in a wide range of synthetic transformations ranging from functional group interconversions to carbon-carbon bond forming reactions which include Barbier and Reformatsky reactions, pinacol and ketyl-olefin couplings. The reagent is often highly chemoselective and transformations instigated by SmI_2 tend to proceed with high degrees of stereoselectivity. Adding to its appeal, the reactivity, chemoselectivity and stereoselectivity of SmI_2 can be manipulated and fine-tuned by the addition of various salts and cosolvents to the reaction mixture.[12] This later feature of the reagent, although still poorly understood, is currently an area of considerable potential. Amongst its various roles, the lanthanide reagent is arguably most often employed for the formation of carbocycles and heterocycles of varying ring size. In this review we will examine the use of SmI_2 mediated cyclisation reactions in the synthesis of natural products.

1.2. Carbon-carbon bond forming processes mediated by SmI_2

In the following introductory section the main C-C bond forming SmI_2 mediated processes are outlined and their mechanisms discussed. The aim of this section is to provide a brief introduction to the reagent and its reactions prior to a discussion of its use in natural product synthesis.

1.2.1. The SmI_2 mediated Barbier reaction

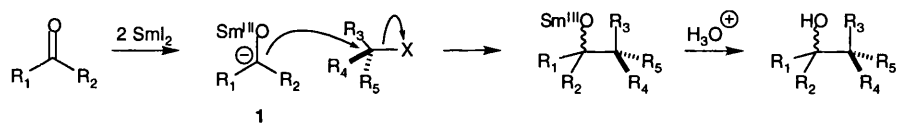
The SmI_2 mediated Barbier reaction has been well documented in the literature.[2, 8, 10, 13] Its advantage over the Mg, Li and Zn mediated Barbier reactions is that the SmI_2 reaction is homogenous and highly chemoselective. Primary, secondary, allylic and benzylic halides as well as 1-iodoalkynes can be used in the transformation, although it has its limitations in that aryl, vinyl and tertiary halides do not normally give satisfactory results. As with many SmI_2 reactions, HMPA increases the rate of the reaction.[14] Such an accelerating effect has also been observed when adding NiI_2 [15] and ferric salts, such as $FeCl_3$ [2] and $Fe(DBM)_3$,[16] to the reaction mixture.

Ambiguity still surrounds the mechanism of many SmI_2 mediated reactions. To enable the reader to appreciate the complexities of defining a mechanism for these reactions, a detailed discussion of the mechanism of the SmI_2 mediated Barbier reaction has been included. Less detailed accounts of other important SmI_2 mediated C-C bond forming reactions will then follow.

1.2.1.1. Mechanism of the SmI_2 mediated Barbier reaction

No definitive mechanism has been established for the intermolecular SmI_2 Barbier reaction, with four possible mechanisms currently being postulated.[17] Even more ambiguity surrounds the mechanism of the intramolecular Barbier reaction. Before discussing the intramolecular reaction it is important to look at the possible pathways for the intermolecular reaction.

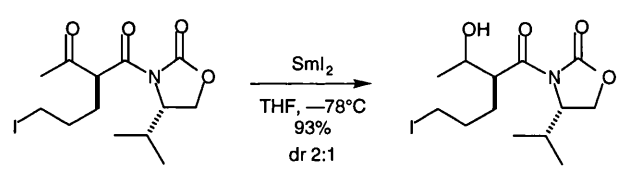
The first mechanistic possibility involves the addition of a ketone dianion **1** to the halide in an S_N2 type reaction (figure 1.1).[18]



1

figure 1.1

Little evidence for this mechanism exists, although, in the attempted intramolecular Barbier reaction of **2** conducted by Molander (scheme 1.1), reduction of the ketone carbonyl in the presence of the iodide gives some support to this postulated mechanism.[19]

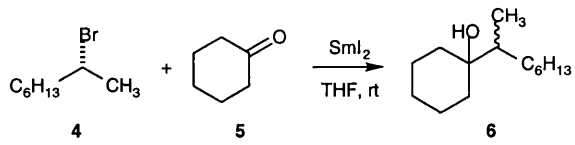


2 3

scheme 1.1

The ketone dianion mechanism, however, has generally been dismissed following experiments by Kagan.[18] A SmI_2 mediated Barbier reaction carried out between optically

active (-) 2-bromooctane **4** and cyclohexanone **5** resulted in racemic product **6** (scheme 1.2).

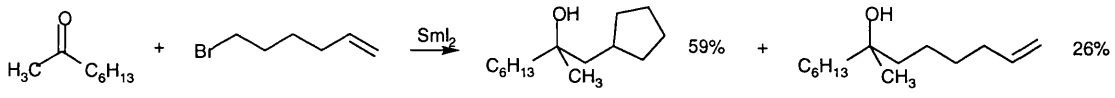


4 **5** **6**

scheme 1.2

Due to the stereospecific nature of an S_N2 mechanism, the isolation of a racemic product strongly indicates a different reaction pathway. The result also rules out a possible alternative ketyl radical S_H2 attack on the halide since again, the reaction would be expected to proceed stereoselectively.[17]

The remaining three mechanisms all involve a radical intermediate accessed *via* the halide. The reaction carried out by Kagan shown in scheme 1.3 provides evidence for the SmI_2 Barbier reaction progressing through a radical intermediate derived from the halide.[18] In this experiment the use of a hexenyl radical-clock system shows a radical intermediate is involved since the initial radical formed from 1-bromo-5-hexene **8** irreversibly cyclises to form the methylcyclopentyl radical which then proceeds to give the Barbier addition products.[20]

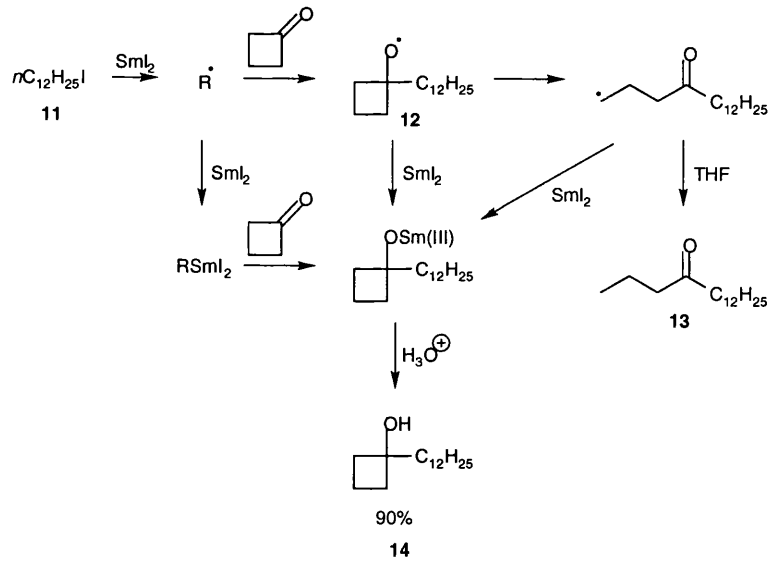


7 **8** **9** **10**

scheme 1.3

The first of the three remaining mechanisms involves the addition of a radical to the carbonyl.[9] There is precedent in the literature for such mechanisms in radical reactions involving Bu_3SnH.[21-23] However, there is little evidence to support the mechanism in SmI_2

Barbier reactions, and Curran has recently dismissed the mechanism.[17] Curran argues that radical addition to a ketone carbonyl is considerably slower than to an aldehyde yet the Barbier reaction of halides and ketones is more efficient than that of aldehydes. Curran also believes the rate of addition of radicals to carbonyls would be far slower than the lifetime expected for a radical under SmI_2 reductive conditions, *i.e.* the radical would be prone to reduction to the corresponding anion. Independent experimental observations have also led Kagan to dismiss this mechanism.[24] In a model system designed to shed light on the mechanism, *n*-dodecyl iodide was treated with SmI_2 in the presence of cyclobutanone (scheme 1.4). If the reaction proceeded by radical attack on the carbonyl then the resultant, highly strained cyclobutylalkoxy radical **12** would be expected to undergo fast β-scission to give the acyclic ketone **13**. However, cyclobutanol **14** was obtained from the reaction and none of the ketone **13**, or any other fragmentation products, were observed clearly suggesting that the reaction does not proceed by this mechanism.



scheme 1.4

Further model studies using benzyl bromide as the radical precursor with the slow addition of SmI_2 in an attempt to encourage the radical pathway, again showed the absence of fragmentation. In general then, it is possible to dismiss the addition of a radical to a ketone or aldehyde as the mechanism of the SmI_2 mediated Barbier reaction.

The remaining two possible mechanisms are much stronger possibilities. The third mechanism involves the coupling of a ketyl radical anion and a radical derived from the halide (figure 1.2), while the fourth mechanism and the most widely accepted, involves the addition of an organosamarium, or carbanion, to the carbonyl.

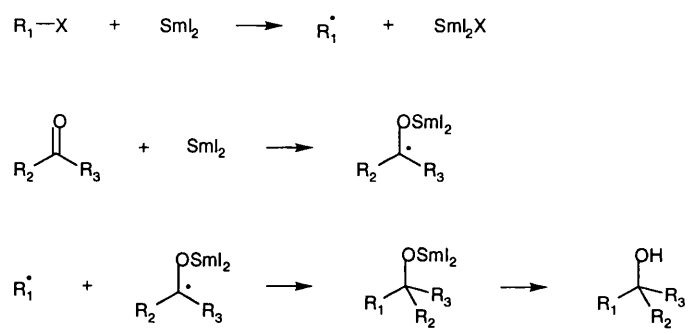
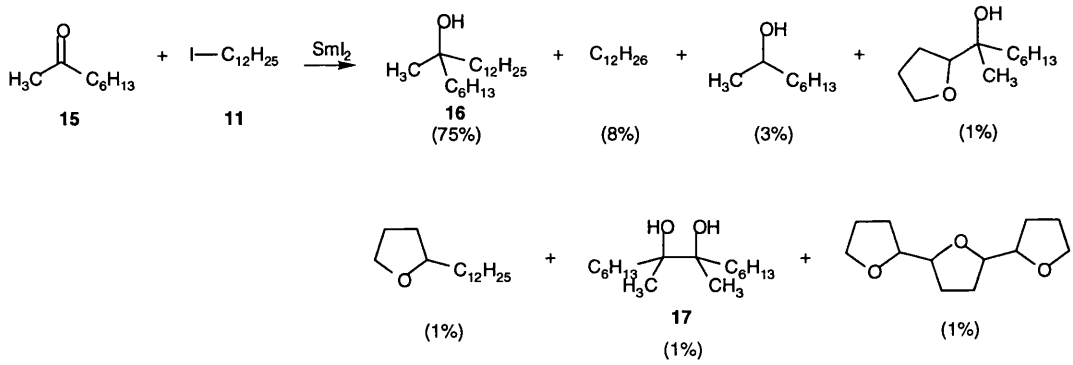


figure 1.2

Evidence supporting the ketyl radical anion-radical coupling mechanism has been gathered by Kagan (in addition to the previous reaction scheme 1.4, which could be explained by such a mechanism).[18] When halide **11** was treated with SmI_2 in the presence of ketone **15** (scheme 1.5) the product mixture was closely examined. Amongst the complex product mixture was a small quantity of pinacol coupling product **17** and various solvent adduct products. From the product mixture, it is clear that both alkyl and ketyl radicals are present in the reaction mixture. However the result is inconclusive since although it confirms the presence of both alkyl and ketyl radicals, it does not give direct

information about the mechanism of the Barbier reaction. The products detected could easily be the result of competitive side reactions.



scheme 1.5

Further observations have been noted which appear to provide evidence for the mechanism, however, on closer examination this evidence is found to be largely circumstantial. For example, the observation that in the absence of alkyl halides, ketones and aldehydes can be reduced to alcohols or undergo pinacol coupling merely shows that ketyl radicals can be formed, but does not really give any mechanistic insight into the Barbier reaction with alkyl halides.[17]

Trapping experiments with D_2O conducted by Kagan on alkyl halides reduced by SmI_2, under essentially 'Grignard' conditions, did not result in deuterated alkyl products, instead giving the unlabelled reduction product.[18] Furthermore, the reaction of alkyl halides with ketones in the presence of SmI_2, again under Grignard conditions, gave no addition products. Such results can be interpreted as being indicative of the existence of an alkyl radical (which abstracts a hydrogen atom from the solvent). There is, however, substantial evidence against the ketyl radical anion-radical coupling mechanism.

In Curran's argument against the mechanism he points out that aryl ketones are reduced more easily than dialkyl ketones yet, using "Kagan's original SmI_2 procedure", the reduction of dialkyl ketones gives far better results. If aryl ketones form ketyl radical anions more efficiently than dialkyl ketones then, if this mechanism were correct, they should undergo more efficient Barbier reactions.[17] This is not the case. Another discrepancy cited by Curran is the fact that when using tertiary halides in the reaction, the yield drops considerably and the reaction is inefficient. If the reaction proceeded by a ketyl radical anion-radical pathway such a poor result would be unexpected. Tertiary radicals are stable and easily formed and such low yields would appear to suggest the Barbier reaction does not proceed *via* such a radical.

The remaining mechanism to be discussed is the alkylsamarium addition to the carbonyl group (figure 1.3).

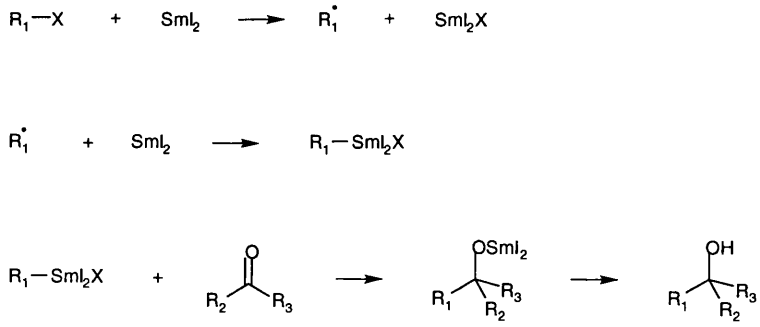
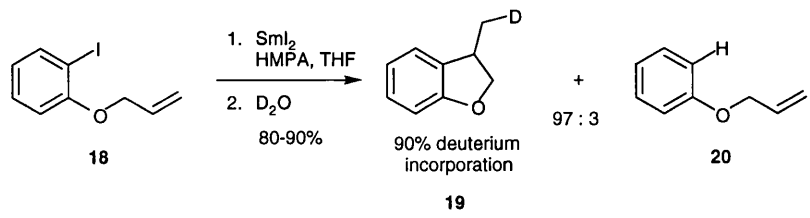


figure 1.3

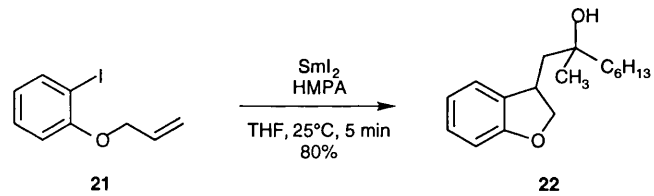
Curran has provided substantial evidence for this mechanism.[17] D_2O quenching studies on iodide **18** after treatment with SmI_2 indicated the existence of an organosamarium (scheme 1.6). It was reasoned that the aryl radical was initially formed which then underwent 5-*exo*-trig cyclisation to form a primary radical. Further reduction by SmI_2

then gave the alkylsamarium and subsequent quenching with D_2O resulted in efficient deuterium incorporation to give **19**.



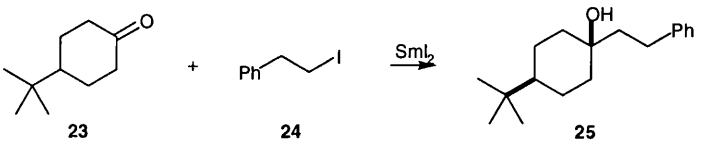
scheme 1.6

The result from this experiment would appear to contradict quenching studies carried out by Kagan, mentioned previously. Curran explains that Kagan's conditions were harsh enough and the reaction time long enough to allow for the decomposition of alkylsamarium formed. Further evidence was also obtained in studies where, again following the Grignard procedure, the iodide **21** was added to a solution of SmI_2 (scheme 1.7).[25] After loss of the blue/purple colour, 2-octanone was added. The formation of the tertiary alcohol **22** would suggest that attack on the carbonyl by an alkylsamarium had occurred. However, although these results certainly indicate the formation of an alkylsamarium, the studies were carried out under Grignard conditions, and not Barbier conditions (Grigard conditions involve the addition of the electrophile to a mixture of the halide and SmI_2. Barbier conditions differ in that SmI_2 is added to a mixture of the halide and electrophile).



scheme 1.7

Having shown that alkylsamariums participate in SmI_2 Grignard conditions, Curran designed studies that would shed some light on whether alkylsamariums also participate in Barbier reactions.[25] He proposed that if the mechanism is the same under both SmI_2 Grignard and Barbier conditions, then the degree of stereoselectivity should be similar in the reaction of iodide **24** with 4-tert-butyl cyclohexanone **23** under both sets of conditions. The results showed similar stereoselectivity in the formation of **25** and adds weight to the intermediacy of alkylsamariums in the reaction (scheme 1.8).

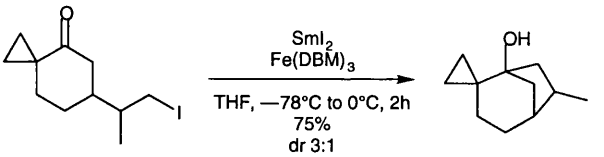


23 **24** **25**

Grignard conditions	91 : 9	88%
Barbier conditions	97 : 3	86%

scheme 1.8

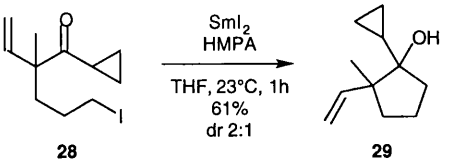
Even more ambiguity surrounds the mechanism of the intramolecular Barbier reaction with a lack of evidence supporting any of the above mechanisms for the cyclisation.[26] Studies by Molander have indicated that the intramolecular reaction probably does not proceed by a ketyl radical anion-radical coupling mechanism (scheme 1.9).[27] In the cyclisation of ketone **26**, no fragmentation from ring opening of a cyclopropyl carbinyl ketyl was observed in the formation of **27**, which suggests that a ketyl radical anion was not formed in the reaction.



26 **27**

scheme 1.9

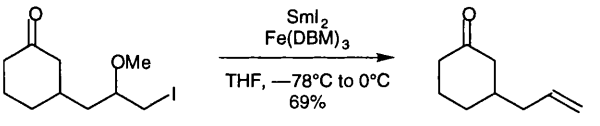
In an independent study by Curran, a similar observation was made (scheme 1.10).[26] Cyclopropyl ketone **28** undergoes smooth cyclisation to give **29** with no fragmentation observed.



28 **29**

scheme 1.10

Molander also conducted an experiment designed to show the existence of an alkylsamarium.[27] β-Elimination of the methoxy group in **30** on treatment with SmI_2 clearly suggests the formation of an alkylsamarium (scheme 1.11). This report combined with a reported deuterium trapping study in the same paper certainly provides evidence for the alkylsamarium mechanism. Curran argues however, that caution is required when drawing conclusions from the experiment, as the presence of the α-heteroatom could quite conceivably change the reduction potential of the halide, thus resulting in a less than general result.[26]

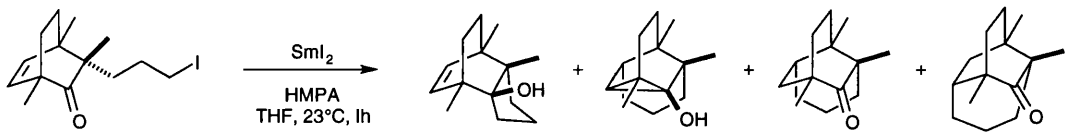


30 **31**

scheme 1.11

Work by Curran has also provided inconclusive results.[26] In an experiment designed to show the existence of an organosamarium, the cyclisation of iodide **32** was performed under a variety of SmI_2 concentrations (scheme 1.12). In the event of the formation of an alkylsamarium the ratio of **33** formed to **34** and **35** should increase with increased SmI_2 concentration, as the existence of radicals becomes shorter lived with increased

concentration therefore less radical cyclisation products should be observed. However the opposite effect occurred. Other experiments were carried out by Curran in the study which provided equally puzzling results.



32		33	34	35	36
	Concentration SmI_2 (M)				
	0.01	64%	21%	11%	4%
	0.07	20%	59%	15%	6%

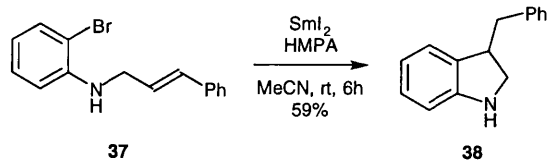
scheme 1.12

In this section we have sought to illustrate the mechanistic ambiguity of the SmI_2 Barbier reaction, an ambiguity which also surrounds many other important processes mediated by SmI_2. Whatever the mechanism, the SmI_2 mediated Barbier cyclisation has been used to great effect in many syntheses of natural products (*vide infra*).

1.2.2. Reductive Radical Reactions

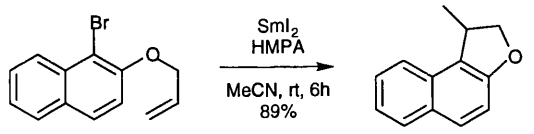
Simple SmI_2 *radical* cyclisations have also been used in natural product synthesis. Radical generation in such cyclisations is normally achieved by the reduction of halides and sulfonates, *etc.* In the majority of radical cyclisations, the radical acceptor is either an olefin or an alkyne although examples involving hydrazones have also been reported.

Few simple *intermolecular*, reductive radical reactions mediated by SmI_2 have been reported,[28-30] however reductive radical cyclisations mediated by SmI_2 have much precedent and provide an attractive alternative to Bu_3SnH mediated reactions. The reaction itself is a versatile process with halides, N-((N',N'-dialkylamino)alkenyl)benzotriazoles,[31] and cyclopropyl ketones[32] all being used as the radical precursors. The radicals formed have then been employed in cyclisations on to various functional groups including alkenes, alkynes and hydrazones.[33, 34] With the ability of SmI_2 to further reduce carbon centred radicals to carbanions, it is important that the rate of cyclisation is faster than the rate of the second reduction. In order to aid cyclisation, reactions are often performed at low concentration of reagent. Work by Bennet has demonstrated the utility of SmI_2 as an alternative to Bu_3SnH,[35] and Inanaga has reported cyclisations to form various heterocycles such as benzofurans, naphthofurans and indoles (scheme 1.13 and 1.14).[36]



37 **38**

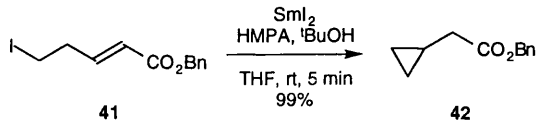
scheme 1.13



39 40

scheme 1.14

The methodology can be extended to involve conjugate addition reactions, with α,β-unsaturated esters, amides, nitriles, lactones and lactams being used as the radical acceptor.[37] Again, various heterocycles can be accessed using such reactions.[31, 38] A recent report by Guibe demonstrates that strained cyclopropane systems can also be prepared using this methodology (scheme 1.15).[39]



41 42

scheme 1.15

1.2.2.1. Reductive Radical Cyclisations – The Mechanism

In Bennett's radical cyclisation of iodide **43** to give cyclopentane **46**, it is proposed that the reaction proceeds by reduction of the halide to form the radical **44** (figure 1.4).[35] Cyclisation then occurs to form vinyl radical **45** which then abstracts a hydrogen atom from the solvent before a second SmI_2 reduction can occur. Failure to obtain any deuterium incorporated products in D_2O quenching studies adds support to this mechanism.

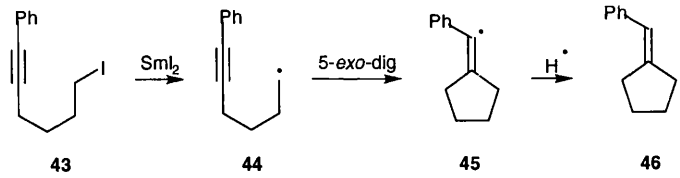
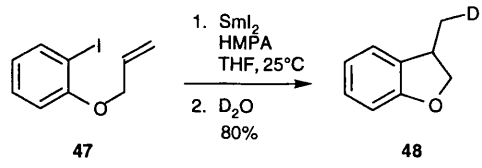


figure 1.4

It would appear probable that this is the usual mechanism for these types of reactions, however, whether hydrogen atom capture or proton capture terminates the sequence is probably dependent upon the type of radical formed after cyclisation and the specific reaction conditions. Indeed, in studies by Curran upon iodide **47**, deuterium incorporation in the formation of **48** suggests proton capture is the final step (scheme 1.16),[40] the second SmI_2 reduction occurring before hydrogen atom capture can occur.

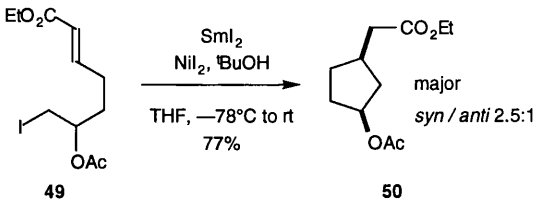


scheme 1.16

1.2.2.2. Reductive Radical Conjugate Addition - The Mechanism

Three possible mechanisms exist for radical conjugate addition cyclisations.[37] The first involves the Michael addition of a radical generated from the halide. The second involves the conjugate addition of an organosamarium. The last possibility entails the formation of a metal radical enolate species which attacks the halide in a S_H2 manner. Studies by Molander support the radical Michael addition mechanism by discrediting the other two possibilities.[37] The fact that the reactions proceed in the presence of a proton source would appear to rule out the later two mechanisms. In addition, the successful cyclisation

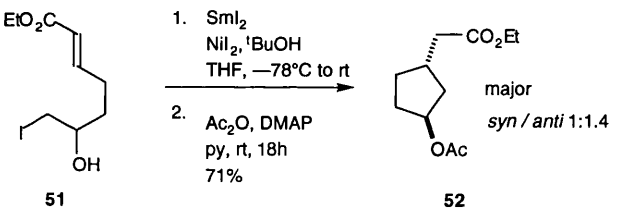
of iodide **49** proceeds with no β-elimination of the acetoxy group indicating that no organosamarium is formed in the cyclisation (scheme 1.17).



49 **50**

scheme 1.17

Molander also suggests that the successful cyclisation of iodide **51** (scheme 1.18) indicates that the formation of a metal radical enolate (figure 1.5) is unlikely. Such a high yield of the cyclic product would not be expected due to competitive intramolecular proton transfer from the unprotected hydroxyl.



51 **52**

scheme 1.18

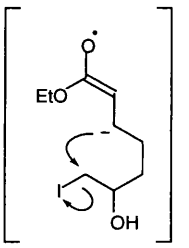
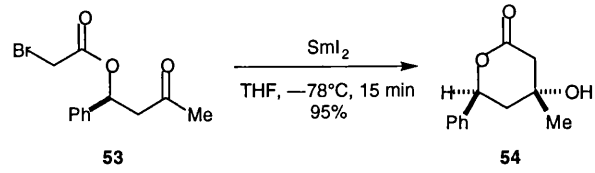


figure 1.5

1.2.3. Reformatsky and aldol-type reactions

The SmI_2 mediated Reformatsky reaction provides a useful alternative to the zinc mediated reaction with the main advantage that the reaction is homogenous. Again it is in the intramolecular sense that the SmI_2 Reformatsky reaction has been used to greatest effect with cyclisations giving high yields and proceeding with high levels of

stereocontrol. For example, treatment of α-bromo ester **53** with SmI_2 gives lactone **54** as a single diastereoisomer (scheme 1.19).[41]



53 **54**

scheme 1.19

The intermolecular reaction usually involves Barbier-type conditions where the α-halo ester, aldehyde or ketone and SmI_2 are in the same pot. When Grignard conditions are used, side reactions are observed.[42-44] Both chlorides and bromides have been used as substrates in these reactions. The intramolecular reaction has been used to access medium and large rings, carbocycles and lactones. The successful formation of such rings, Inanaga suggests, could be assisted by the large ionic radius of samarium, its flexible co-ordination number and its high oxophilicity;[45] the lanthanide centre effectively bringing the two reacting centres together through chelation.

1.2.3.1. Mechanism of Reformatsky and aldol-type reactions

It is generally believed that the intermolecular and intramolecular Reformatsky reactions progress through a samarium(III) enolate (figure 1.6).[41,45]

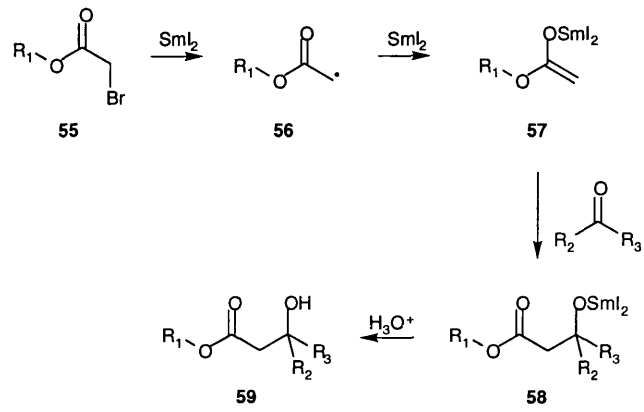
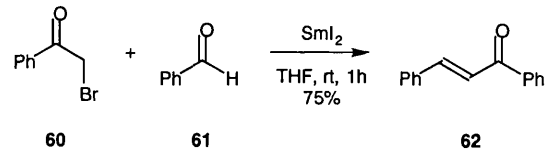


figure 1.6

It would seem likely that a similar mechanism is occurring in the SmI_2 aldol reaction, however, studies by Zhang would appear to indicate an alternative route for enolate formation (scheme 1.20).[46] [Although it should be noted that the reaction was performed under Grignard type conditions]. Zhang found that optimal conditions for the transformation involved the use of equimolar amounts of α-halo ketone **60**, aldehyde **61** and SmI_2. Strangely, when two equivalents of SmI_2 were employed, only a 5% yield of the enone **62** was observed.



scheme 1.20

Following the detection of I_2 and/or IBr in the reaction mixture, Zhang has proposed two different mechanisms for enolate formation (figure 1.7).

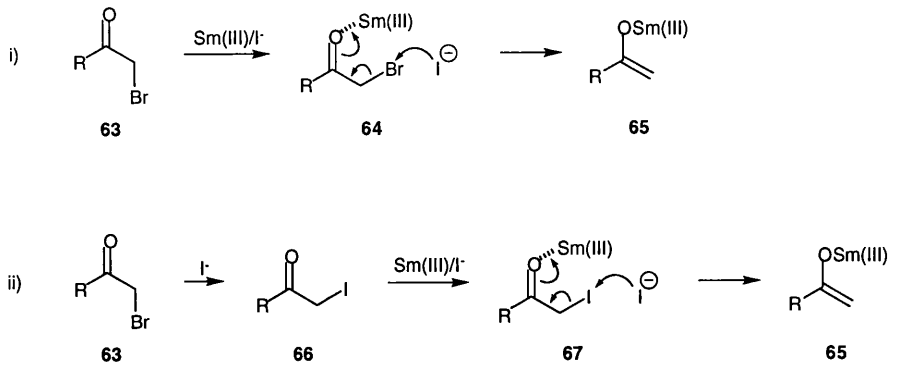
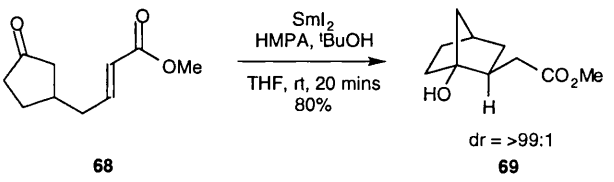


figure 1.7

1.2.4. Ketyl-olefin coupling reactions

The SmI_2 mediated ketyl-olefin reaction is a widely documented reaction with a wealth of precedent for both intermolecular and intramolecular reactions. The intramolecular reaction is particularly useful and allows a variety of cyclic alcohols of varying ring sizes to be assembled under mild conditions with normally high stereoselectivities being observed.[19, 47] The highly stereoselective nature of the reaction is demonstrated by the formation of bicyclic alcohol **69** from the cyclopentanone **68** (scheme 1.21).



68 **69**

scheme 1.21

Both aldehydes and ketones can be employed as the ketyl radical anion precursor and both activated and unactivated olefins and alkynes have been employed as radical acceptors in cyclisations.[5] In the majority of cases, the olefin geometry has been found to

have an effect upon the stereochemical outcome of the reaction. The reaction has also been used for the synthesis of a variety of heterocycles.[5, 48, 49]

1.2.4.1. Ketyl-olefin coupling mechanism

The most generally accepted mechanism for SmI_2 mediated ketyl-olefin reactions is shown in figure 1.8. Reduction of the aldehyde or ketone carbonyl with SmI_2 gives a samarium ketyl radical anion **71**. The ketyl radical anion then attacks the double bond to form a new carbon-carbon bond **72**. A second SmI_2 reduction results in the formation of an enolate **73**, which is protonated by the alcohol cosolvent or upon aqueous work up.

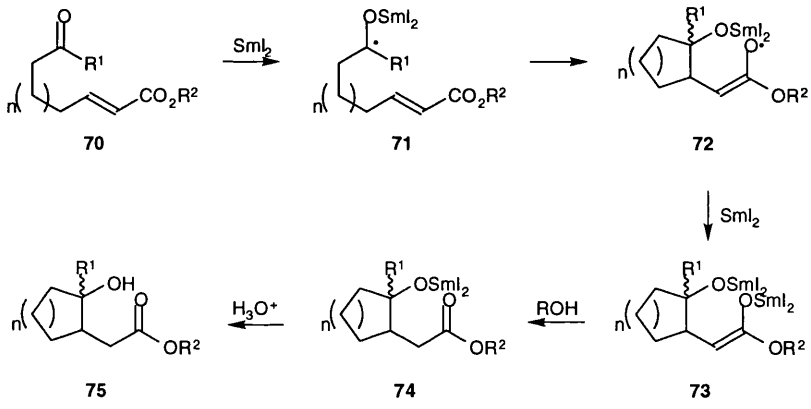
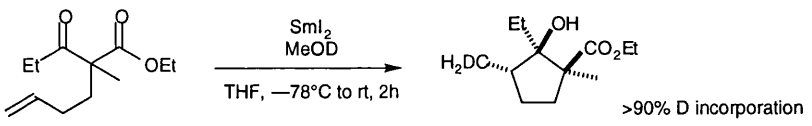


figure 1.8

Studies undertaken by Molander support this mechanism. Following the successful cyclisation of the keto-ester **76** by SmI_2 in methanol, the reaction was repeated in the presence of deuterated methanol (scheme 1.22). More than 90% deuterium incorporation in the cyclopentanol product **77** indicating the existence of the anion.[50] Additional evidence for this mechanism comes from the observation that at least two equivalents of SmI_2 are required for the reaction to progress to completion.

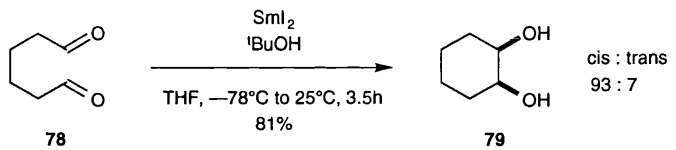


76 77

scheme 1.22

1.2.5. Pinacol couplings

SmI_2 has been used to mediate the pinacol coupling reactions of both aldehydes and ketones.[13, 51] An example of such a reaction is shown in scheme 1.23 where the dialdehyde **78** is transformed to the diol **79**.[52]

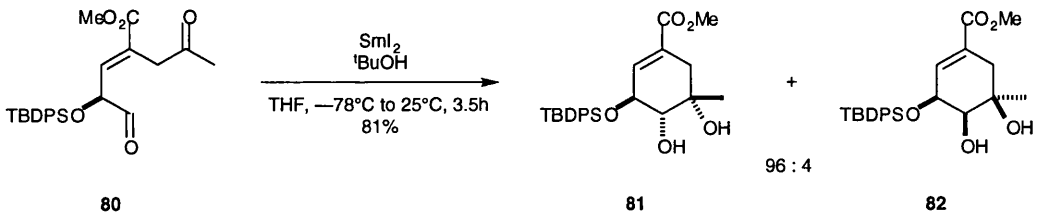


78 79

scheme 1.23

It has been observed that the reactions of aromatic aldehydes or ketones progress faster than aliphatic aldehydes and ketones. The reaction is most often carried out in the absence of a proton source, and it has been reported that the presence of TMSCl in the reaction mixture can accelerate the reaction.[53] The coupling of an aldehyde or ketone with oximes,[54, 55] hydrazones,[33, 34] imines and nitriles[50] has also been reported.

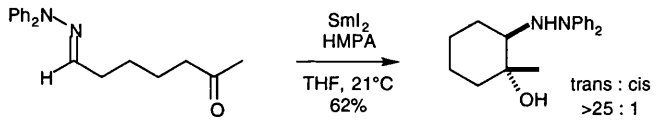
The SmI_2 mediated intramolecular pinacol coupling normally progresses with significant stereoselectivity, as demonstrated previously in scheme 1.23. The coupling of two carbonyls tends to form predominately *cis* diols. Furthermore when the carbonyl has an alkoxy group in the α position, the orientation of the hydroxyls is predominately '*anti*' relative to that substituent. The cyclisation of dicarbonyl **80** illustrates this phenomena (scheme 1.24).[52]



80 **81** **82**

scheme 1.24

Interestingly, the coupling of an aldehyde or ketone with a hydrazone tends to yield products with *trans* stereochemistry across the newly formed bond. Such stereoselectivity was observed in the cyclisation of keto-hydrazone **83** to give the corresponding hydrazine **84** (scheme 1.25).[33]

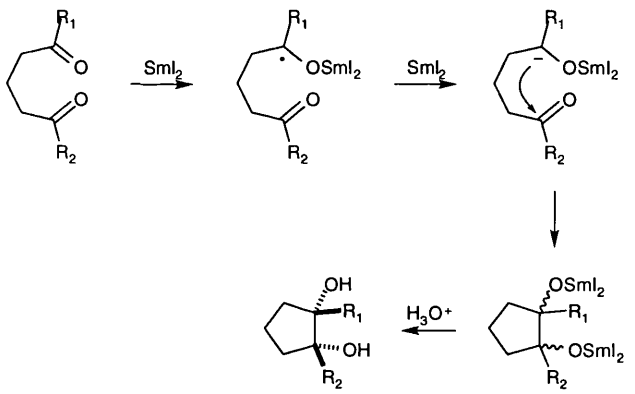


83 **84**

scheme 1.25

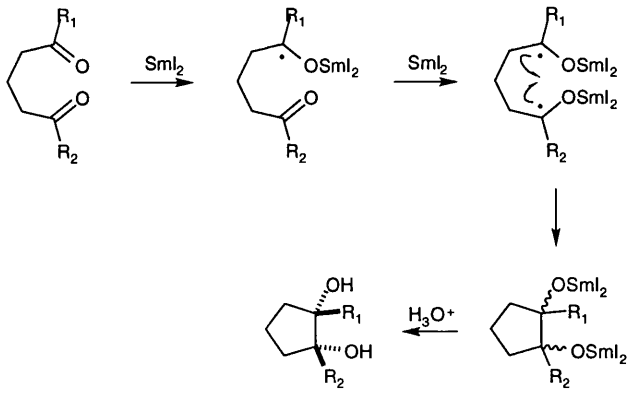
1.2.5.1. Pinacol coupling – the mechanism

There are three possible mechanisms for the SmI_2 mediated pinacol coupling reaction.[50, 56-58] The first, involves the formation of a ketyl dianion after reduction of the dicarbonyl **85** with 2 equivalents of SmI_2 (equation 1). The dianion then attacks the other carbonyl. Molander has ruled out such a mechanism by claiming that under normal pinacol coupling conditions SmI_2 is not a strong enough reducing agent to reduce a ketyl radical anion to a ketyl dianion. He also proposes that under the commonly used protic solvent conditions for the reaction, such as *tert*-BuOH and MeOH, a dianion intermediate would be rapidly protonated resulting in acyclic products.



equation 1

The second possible mechanism involves the coupling of two ketyl radical anions (equation 2). Molander has also ruled out this mechanism by rationalising the normal *cis* stereochemistry of pinacol coupling products. If the reactions progressed *via* a di-Sm(III) complexed diketyl intermediate, *trans* diol products would be expected in the product mixture due to dipolar repulsion. However, this is not the case.



equation 2

Instead Molander proposes the most likely mechanism to involve attack on a carbonyl group by a ketyl radical anion (figure 1.9). Reduction of one of the carbonyls by SmI_2 results in the formation of a ketyl radical anion. The Sm(III) centre then co-ordinates and possibly activates the second carbonyl before attack by the ketyl radical anion. A subsequent second reduction by SmI_2 then occurs before protonation upon work up, or from the cosolvent, yields the diol **86**. Co-ordination of the Sm(III) centre to the second carbonyl following the initial reduction, would explain the observed *cis* stereochemistry of the cyclisation products.

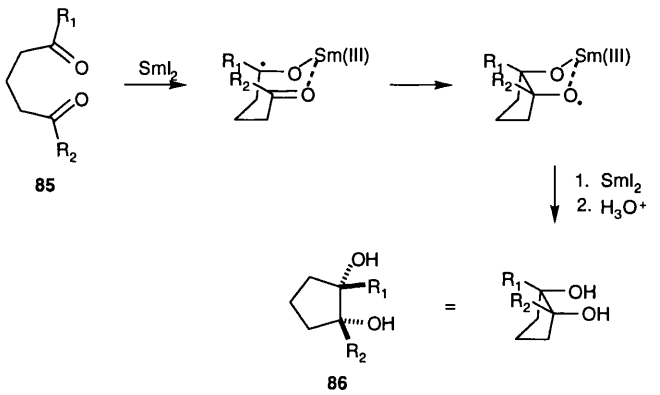


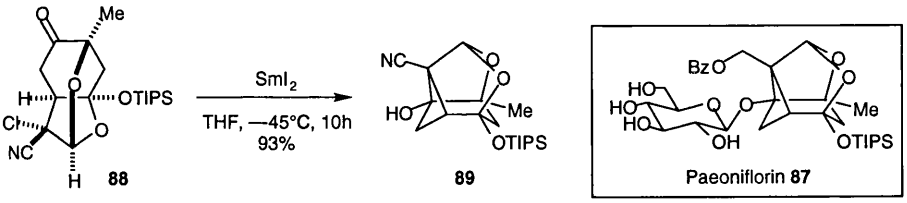
figure 1.9

1.3 SmI_2 mediated cyclisations in natural product synthesis

1.3.1 Four-membered rings

Despite the extensive literature surrounding SmI_2 transformations, prior to our studies (*vide infra*) few examples of 4-membered ring formation using the reagent have been reported.[59-61] More specifically, only a single example of the lanthanide reagent being used to mediate 4-membered ring formation in natural product synthesis had been reported in the literature prior to our work. The example in question involves the use of an intramolecular Barbier reaction.

Paeoniflorin **87** is an interesting monoterpene with a complex pinane structure extracted from the root of *Paeonia albiflora* Pallus.[62] The plant has been used in traditional Chinese and Japanese medicine and since its isolation, Paeoniflorin has been found to show sedative, anticoagulant, anti-inflammatory and neuromuscular activities. In 1993, Corey reported the first total synthesis of Paeoniflorin.[63] In Corey's approach to the natural product, paeoniflorigenin **89** was first prepared. Subsequent glycosylation then gave the natural product Paeoniflorin. The caged structure of **89** was prepared using a multistep reaction sequence, which featured a SmI_2 mediated Barbier reaction (scheme 1.26). The Barbier reaction of chloride **88** proceeded smoothly in the absence of additives at —45°C to give cyclobutanol **89** in excellent yield. An aldol-type cyclisation could not be used to effect the transformation as the cyclobutanol products were found to be extremely base sensitive. In fact, when the authors attempted to protect the tertiary alcohol formed upon cyclisation with a silyl-protecting group, the mild base used in the transformation triggered a retro-aldol reaction and opening of the cyclobutanol ring. Protection of the hydroxyl was achieved however using TMSCN under non-basic conditions.

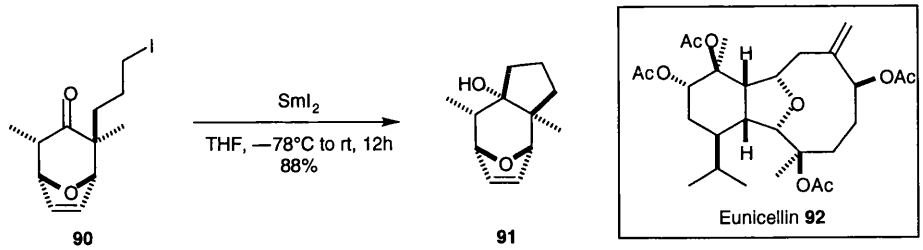


scheme 1.26

1.3.2 Five-Membered Rings

In stark contrast to SmI_2 mediated 4-membered ring formation, many examples of the formation of 5-membered rings using the reagent have been reported. In the context of natural product synthesis, a wide variety of SmI_2 mediated reaction types have been employed to form the 5-membered rings found in the targets.

The Eunicellins are polycyclic diterpenes isolated from soft corals and gorgonians octocorals. They are of particular interest due to their range of biological activity, which includes cytotoxicity, antiproliferative and anti-inflammatory properties. They possess an interesting α,α'-bridged nine-membered ring ether, a framework which Hoffmann has attempted to construct in model studies using a cerium(IV) ammonium nitrate (CAN) oxidative fragmentation process.[64] In the preparation of the tricyclic substrate for CAN-mediated fragmentation, Hoffmann employs a SmI_2 mediated Barbier reaction to form the tertiary cyclopentanol **91** necessary for the oxidative fragmentation step (scheme 1.27). The cyclisation of **90** proceeds very efficiently under mild conditions in the absence of additives to give **91** as a single diastereomer. The authors have yet to prepare eunicellin **92** or any of the eunicellin based natural products using this methodology.



scheme 1.27

The isomeric sesquiterpenes (±)-isocaryophyllene **93** and (±)-caryophyllene **94** isolated from clove oil contain 9-membered rings fused to cyclobutane rings (figure 1.10). In a similar strategy to the one discussed in the previous example, Suginome has utilised a Hg(II) oxide mediated oxidative fragmentation to access the nine membered ring in his approach to caryophyllene.[65]

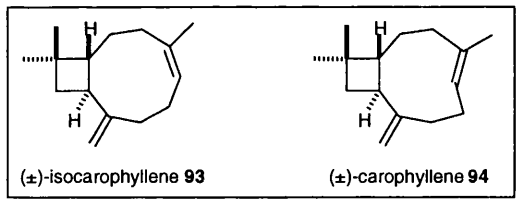
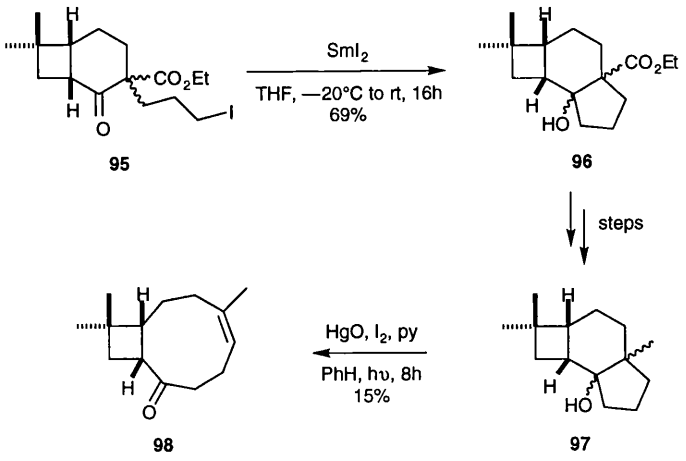


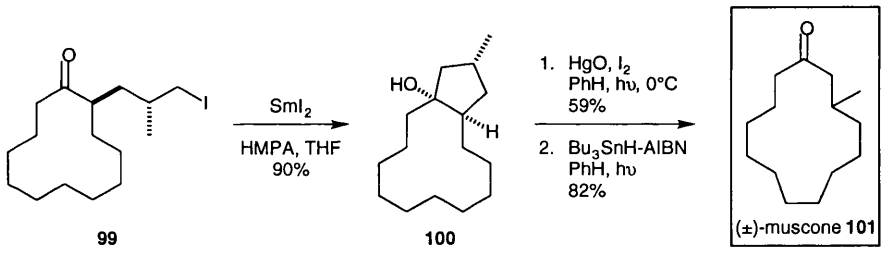
figure 1.10

Substrate **97**, for oxidative fragmentation, was again prepared using a SmI_2 mediated intramolecular Barbier reaction (scheme 1.28). The transformation was achieved under mild conditions in the absence of additives to give the tertiary alcohol **96** in good yield. In this particular transformation, the stereochemistry of the tertiary alcohol and the quaternary centre bearing the ethyl ester in **96** is unimportant as the stereochemistry at both centres is lost later in the synthesis.



scheme 1.28

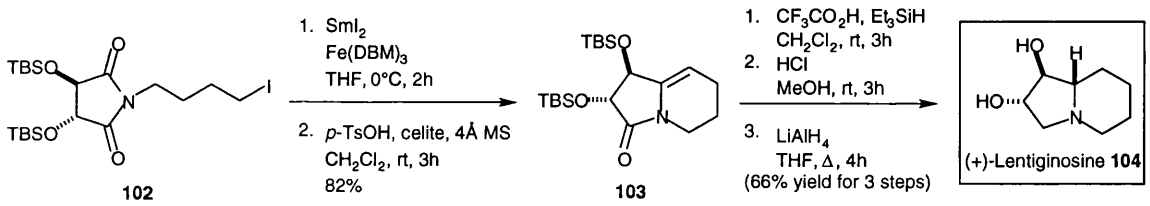
In an earlier paper, Suginome again used a SmI_2 mediated Barbier reaction to form the intermediate cyclopentanol **100** (scheme 1.29), followed by a similar Hg(II) oxide β-scission of an alkoxy radical, in an approach to (±)-muscone **101**.[66] In this example of an intramolecular Barbier reaction, HMPA was employed as a cosolvent.



scheme 1.29

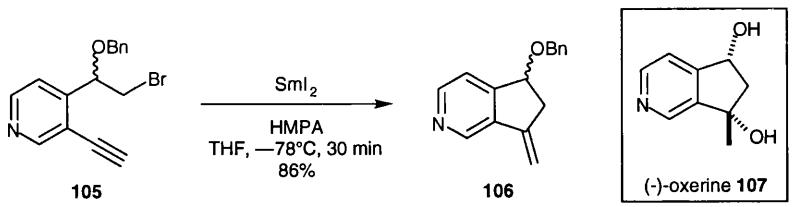
SmI_2 mediated Barbier reaction methodology has also been extended to additions to imide carbonyls, and applied in the synthesis of (+)-Lentiginosine **104**. Indolizidine heterocycles have attracted much attention in recent years due to their broad range of potent biological activity. (+)-Lentiginosine is a dihydroxylated indolizidine alkaloid that has shown itself to be a selective inhibitor of amyloglucosidase. In a paper, which describes the synthesis of the natural product starting from L-malic acid, Ha and co-workers use SmI_2 in the key step to mediate the Barbier cyclisation of an *N*-(iodobutyl)-

succinimide **102** (scheme 1.30).[67] The cyclisation proceeded efficiently in the presence of a catalytic amount of $Fe(DBM)_3$ and after subsequent dehydration, indolizidine **103** was obtained in good yield. The mechanism of the cyclisation is ambiguous with an earlier publication suggesting the possibility of a similar reaction progressing through a ketyl radical intermediate. Subsequent reduction of the olefin in **103**, removal of the silyl protecting groups and reduction of the amide using $LiAlH_4$, gave (+)-Lentiginosine. The paper also describes the application of this SmI_2 reaction to the formation of pyrrolizidine and quinolizidine heterocycles, systems that are found extensively in biologically important molecules.



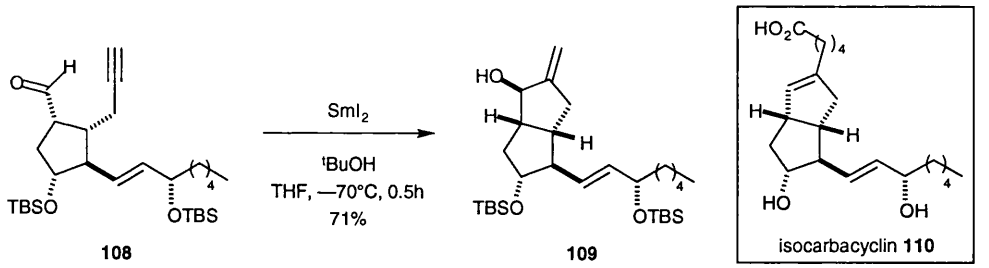
scheme 1.30

Simple SmI_2 mediated *radical* cyclisations have also been used in natural product synthesis to generate five-membered rings. In Ohta's racemic total synthesis of oxerine **107**, a monoterpene alkaloid isolated from the ariel parts of the tree *Oxera morieri*, a SmI_2 mediated 5-*exo*-dig cyclisation was used to form the cyclopentane ring.[68] The natural product is of interest since many monoterpene alkaloids have been found to display interesting biological activity. The primary radical was generated from bromide **105**, which attacked the triple bond to close the five-membered ring and form the exocyclic double bond of **106** (scheme 1.31). As would be expected, none of the 6-*endo*-dig cyclisation product was detected and furthermore, no products from the elimination of the *O*-benzyloxy group were observed - a common problem when the carbon radical has a heteroatom in the α position. Ozonolysis, Grignard addition, and finally deprotection, furnished racemic oxerine.



scheme 1.31

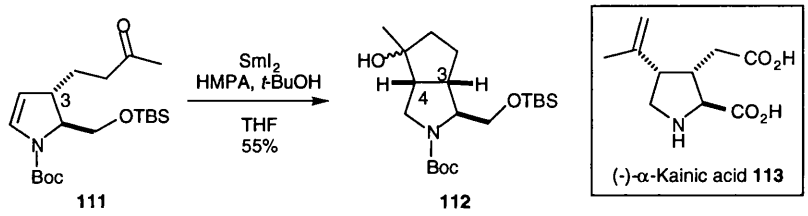
Another example of a SmI_2 mediated 5-*exo*-dig cyclisation appears in Kurozumi's approach to Isocarbacyclin **110**.[69] Isocarbacyclin is of interest as, being a stable analogue of prostacyclin (PGI2), it has potential as a therapeutic agent for cardiovascular diseases. In 1990, Kurozumi *et. al.* described two similar strategies towards isocarbacyclin that both employ the reductive cyclisation of γ-ethynyl aldehyde **108** to form the second 5-membered ring in the bicyclo[3.3.0] octane system present in the target molecule (scheme 1.32). Several reagents for the transformation were examined, however SmI_2 showed itself to be the reagent of choice giving the highest yield and rate of cyclisation. The 5-*exo*-dig aldehyde-alkyne coupling gave a 9:1 ratio of diastereomers, **109** being the major product. The intermolecular pinacol coupling product and the acyclic alcohol reduction product, probably arising from competitive reduction of the ketyl radical intermediate, were both formed as by-products in the reaction.



scheme 1.32

(-)-α-Kainic acid **113** was first isolated in 1953 and is found in the algae *Digenea simplex* and *Centrocerus clavulatum*. The potent neuroexcitatory activity of the natural product

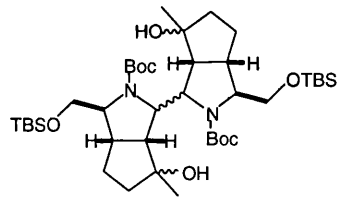
aswell as the synthetic challenge of installing three contiguous stereocentres on the pyrrolidine ring has attracted the attention of many groups. In Cossy's approach to (-)-α-Kainic acid, which began from L-pyroglutamic acid, a SmI_2 mediated intramolecular coupling of a ketone and an enamine was used as a key step.[70] The ketyl radical anion derived from **111** attacked the olefin from the bottom face as shown in scheme 1.33, due to the stereochemistry at C3. The cyclisation, therefore, established the *cis* stereochemical relationship at C3 and C4 in the natural product.



111 **112**

scheme 1.33

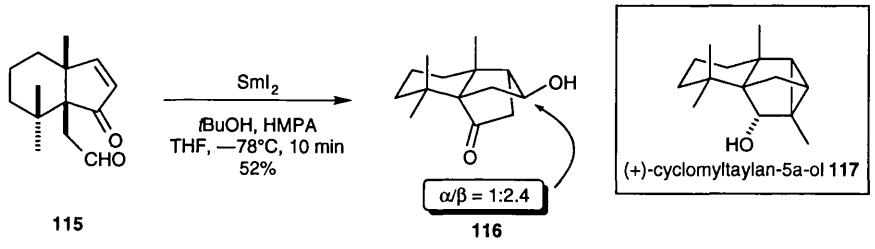
A 55% yield of the bicyclic pyrrolidine **112** was obtained from the cyclisation although, interestingly, significant amounts of the bis by-product **114** was also obtained (figure 1.11). The formation of **114** is probably due to competitive dimerisation of the radical formed upon cyclisation. The stereochemistry of the newly generated tertiary alcohol is not discussed and is largely unimportant as the stereochemistry was lost during the formation of the propenyl group of the target.



114

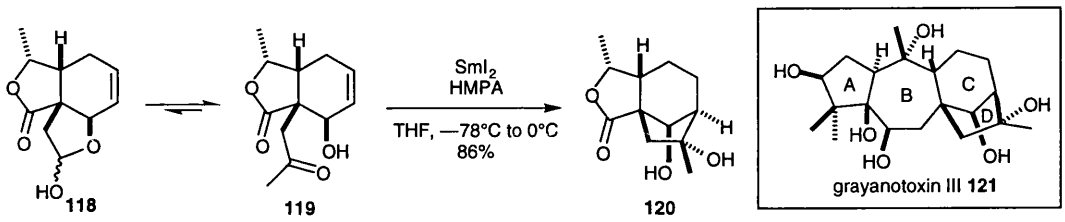
figure 1.11

(+)-Cyclomyltaylan-5-a-ol **117** is a tetracyclic sesquiterpenoid isolated from a Taiwanese thallus liverwort, *Reboulia hemisphaerica.* In Hagiwara's enantioselective total synthesis of the natural product, a SmI_2 mediated reductive cyclisation was used to form a tricyclic intermediate.[71] The reaction involved the coupling of an aldehyde with a cyclic enone in the presence of HMPA to give cyclopentanol **116** in moderate yield and with moderate diastereocontrol (scheme 1.34). The authors rationalised the observed stereochemistry by invoking a vinylogous pinacol coupling mechanism, the β-stereoisomer predominating due to the steric repulsion of the two samarium alkoxides. They argue that if the reaction proceeded by conjugate addition of the ketyl radical to the enone then the α-stereoisomer would be favoured due to a 7-membered chelate intermediate. Furthermore, the additional observation that a poor yield was obtained when only 1 equivalent of SmI_2 was used serves to support the vinylogous pinacol coupling theory. However, the alternative ketyl-olefin coupling mechanism should not be discarded. It is widely known that ketyl-olefin cyclisations to form 5-membered rings proceed with predominately *anti* stereochemistry across the new carbon-carbon bond, a scenario that is observed in this particular case. Two equivalents of SmI_2 are also required in ketyl-olefin cyclisations. [Furthermore, if the reaction was proceeding *via* a ketyl-olefin coupling pathway and if chelation was possible thus favouring formation of the α-stereoisomer, carrying out the reaction in HMPA, which is a highly co-ordinating solvent for SmI_2, could break down such chelation. Electronic factors would then result in predominately the β-stereoisomer forming]. A further six steps were needed to convert **116** into the target compound.



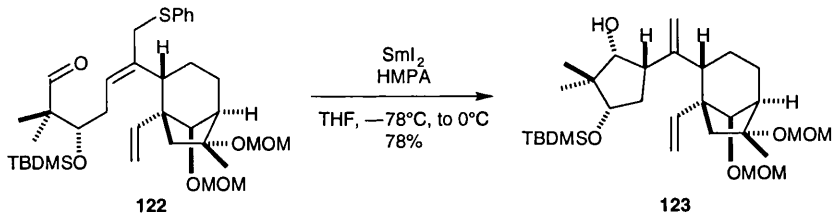
scheme 1.34

In their approach to Grayanotoxin III **121**, Matsuda and co-workers used SmI_2 for the three key carbocycle forming steps.[72] Two of these carbocycles are five membered rings. In the first SmI_2 mediated step to form the CD rings of the natural product, the hemi-ketal **118**, which is in equilibrium with the hydroxy ketone **119**, was treated with SmI_2 in the presence of HMPA (scheme 1.35). Cyclisation of the ketyl-radical anion onto the unactivated olefin proceeded well to give **120** in high yield.



scheme 1.35

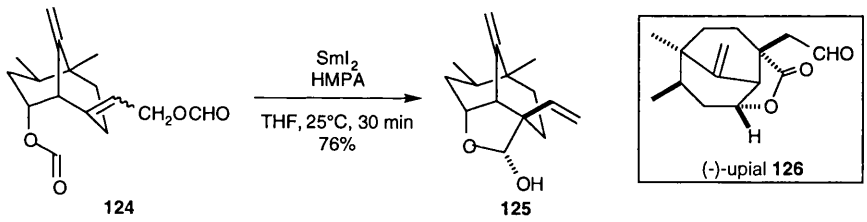
In the second SmI_2 mediated cyclisation in Matsuda's approach, an allylic sulfide was used as a radical acceptor in a cyclisation to form the A ring of the natural product (scheme 1.36). The cyclisation of **122** resulted in elimination of the sulfide to generate a new double bond which was then epoxidised and reduced to form the tertiary alcohol found in the B ring of the target. The cyclisation proceeded to form exclusively the *syn* cyclopentanol **123** in good yield. Interestingly, in model studies, related cyclisation substrates without gem disubstitution on the aldehyde gave exclusively *anti* cyclopentanol products.[73] No reason for the observed stereoselectivity is given by the authors. Also, noteworthy is the fact that the stereochemistry and yield of the cyclisation are independent of the initial olefin geometry. The third SmI_2 mediated cyclisation in Matsuda's approach will be discussed in a later section.



122 123

scheme 1.36

The monoisoprenoid sesquiterpene (-)-upial **126** was isolated from the marine sponge *Dysidea fragilis* at Kaneohe Bay, Oahu, and provides an interesting target for synthetic chemists with its five stereocentres and unusual bicyclo[3.3.1]nonane framework. In his approach to the natural product, Yamada used an interesting 5-*exo*-trig cyclisation to generate tricyclic lactol **125** (scheme 1.37).[74] The reaction, which progressed in the presence of HMPA, involved the use of **124** as a 2:1 mixture of double bond isomers and as **125** was obtained as a single diastereoisomer, it is clear the olefin geometry has no bearing on the stereochemical outcome of the reaction in this particular system. A single lactol isomer was obtained from the cyclisation, however stereochemistry at the lactol carbon is unimportant as oxidation at a later stage in the route resulted in the loss of stereochemistry at that centre.



124 125

scheme 1.37

At first glance, the reaction appears to be analogous to Matsuda's second SmI_2 cyclisation in his approach to Grayanotoxin III **121** (see scheme 1.36), *i.e.* ketyl-olefin addition followed by β-elimination, however, the mechanism here is quite different (figure 1.12).

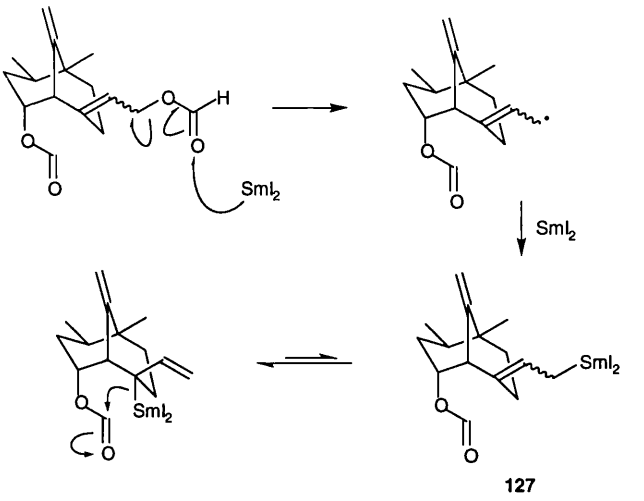
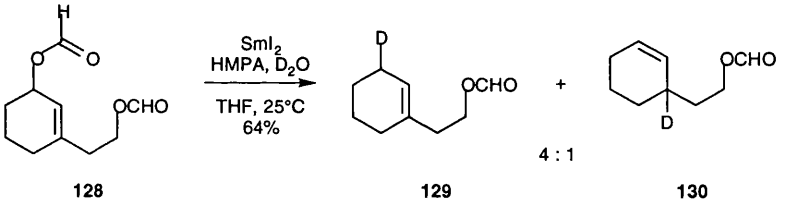


figure 1.12

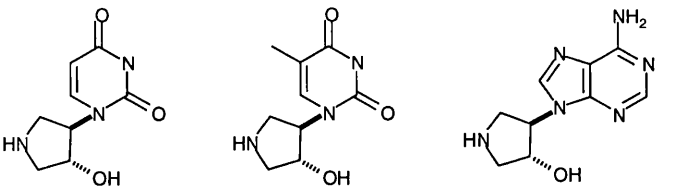
In model studies the authors showed the reaction proceeds by an allylic organosamarium **127**.[75] By carrying out the cyclisation of simple substrate **128** in the presence of D_2O, the formation of products **129** and **130** in which deuterium was incorporated in the allylic positions were observed (scheme 1.38).



scheme 1.38

The SmI_2 coupling of aldehydes and ketones with oximes has also been employed to access five-membered rings in approaches to natural products. Naito *et. al.* used an aldehyde-oxime coupling reaction to form the functionalised pyrrolidine ring in their approach to 4-pyrimidinyl and 4-purinylpyrrolidin-3-ol nucleoside analogues.[74] Recently nucleoside analogues have attracted the attention of synthetic chemists as the range of their biological activities and potential as anti-cancer and anti-viral therapeutic agents has

become known. Naito has reported the synthesis of uridine **131**, thymidine **132** and adenosine **133** analogues (figure 1.13).



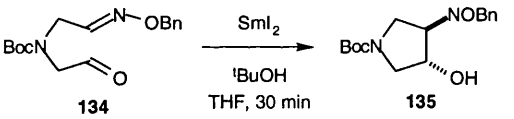
131
uridine analogue

132
thymidine analogue

133
adenosine analogue

figure 1.13

The aldehyde-oxime coupling of **134** proceeded efficiently in the presence of *tert*-BuOH to afford the cyclic product in 70% yield with good stereoselectivity, giving a 9:1 mixture of diastereoisomers in favour of the *anti* product **135** (scheme 1.39). This is far superior to the analogous Bu_3SnH mediated cyclisation that proceeded to give the product in 66% yield but as only a 3:1 ratio of diastereoisomers.



134

SmI_2
^{t}BuOH
THF, 30 min

135
25°C; 33%, 3:2
—78°C; 70%, 9:1

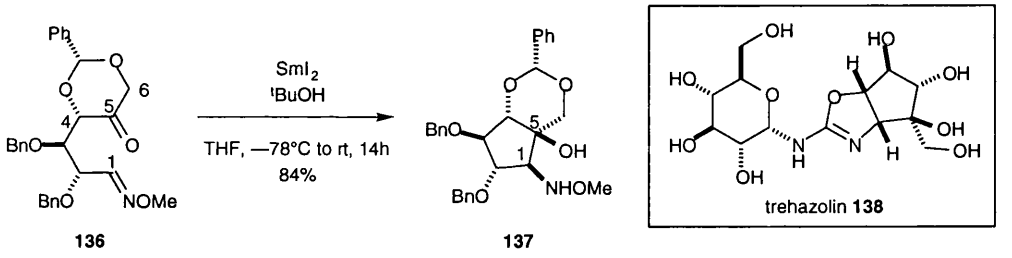
scheme 1.39

The origin of the stereoselectivity can be seen in the transition structures A and B (figure 1.14). The *syn* transition structure B is disfavoured over the *anti* A due to electronic repulsion between the Sm-alkoxide and the developing partial negative charge of the nitrogen radical. Both the stereoselectivity and overall yield of the cyclisation were found to be dependent upon the reaction temperature, and furthermore the reaction was found not to proceed in the absence of *tert*-BuOH.

transition structure A transition structure B

figure 1.14

Trehazolin **138** has been isolated from the culture broth of a Micromonospora strain. It is of particular interest as it has shown itself to be a potential insecticide due to its potent and specific inhibition of trehalase, an enzyme which plays an important role in the metabolism of insects and fungi. In Giese's synthesis of the natural product, a SmI_2 mediated ketone-oxime reductive coupling similar to the previous example was used to form the trehazolamine structure **137** as a single diastereoisomer (scheme 1.40).[76]



136 **137**

scheme 1.40

The substrate **136**, which was derived from D-glucose, has three stereocentres already established. The authors found it necessary to protect the hydroxyls at C6 and C4 as a benzylidene acetal to obtain the desired stereochemistry from the cyclisation. When these hydroxyls were protected as benzyl ethers, the product formed on cyclisation had the wrong stereochemistry at C5. The authors propose that this is due to a normal preference (when P_1 and P_2 = $-CH_2Ph$) for the chair-like transition structure A over B (figure 1.15). The use of a cyclic acetal rules out conformation A and the cyclisation proceeds through conformation B resulting in the product having the correct stereochemistry at C5 in the product. The stereochemistry at C1 was inverted in a subsequent step.

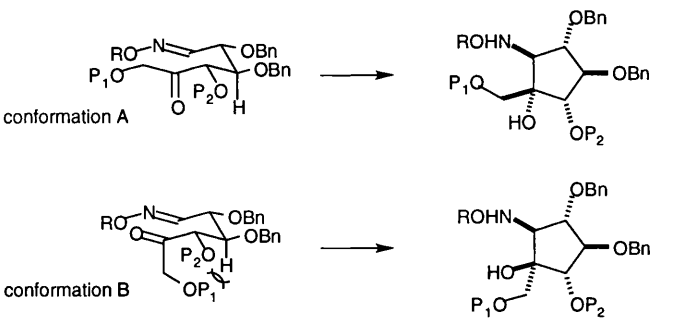
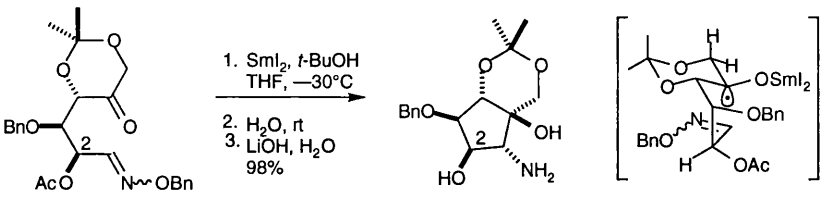


figure 1.15

Chiara has also used a ketone-oxime reductive cyclisation in an approach to trehazolin.[77, 78] The substrate **139** for the cyclisation was obtained from D-mannose in 9 steps and resulted in C2 possessing the wrong configuration for the natural product. This stereocentre, however, behaves as an element of stereocontrol in the cyclisation and was elegantly inverted later in the synthesis *via* an intramolecular S_N2 cyclisation. An excess of SmI_2 was used in the cyclisation of **139** and after the cyclisation a large excess of H_2O was added (scheme 1.41). This had the effect of converting the initially formed benzyloxyamine to the amine. *In situ* treatment with aqueous LiOH removed the acetate protecting group, giving trehazolamine **140** in almost quantitative yield. Amazingly, in contrast to Giese's exclusively *syn* relationship across the newly generated C-C bond, Chiara obtains exclusively the *anti* product. Scheme 1.41 also shows a transition structure for the cyclisation which was proposed by the authors.

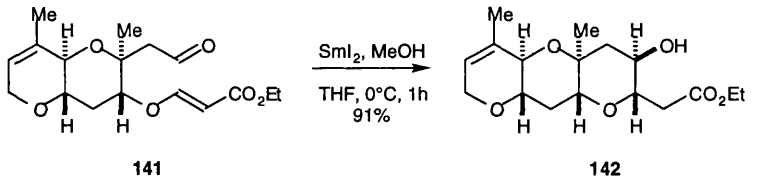


139 **140**

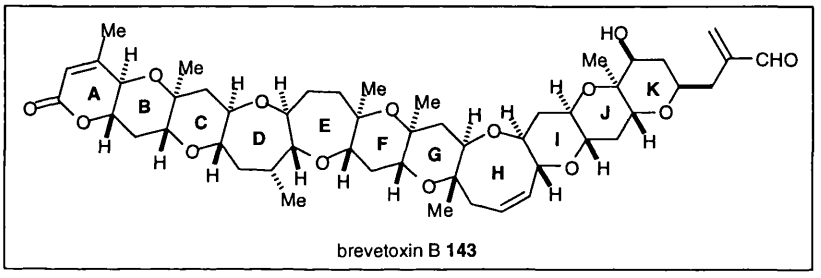
scheme 1.41

1.3.3 Six-membered rings

SmI_2 has been employed in a variety of ways to access 6-membered rings, with the most popular method involving 6-*exo* ketyl-olefin cyclisations. Nakata has used a SmI_2 mediated 6-*exo*-trig ketyl-olefin cyclisation to form the ABC trans-fused tricyclic furan ring system of the neurotoxin brevetoxin B **143** (scheme 1.42).[79, 80] The reductive cyclisation of **141** occurred very efficiently under mild conditions to form the tetrahydropyran C ring of **143** and followed the usual stereochemical course of such cyclisations to give *anti* stereochemistry across the newly formed C-C bond.



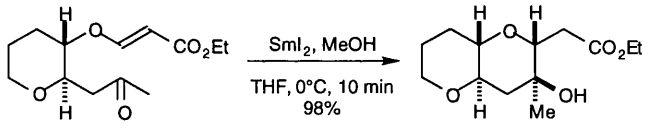
141 **142**



brevetoxin B **143**

scheme 1.42

Interestingly, similar *anti* stereochemistry was observed in the analogous cyclisation of **144** which constructed the D ring system of maitotoxin, despite the fact that the ketyl radical was generated from the methyl ketone instead of the aldehyde (scheme 1.43).[81]



144 **145**

scheme 1.43

(-)-Anastrephin **146** and (-)-epianastrephin **147** are insect pheromones produced by the Caribbean fruit flies which are pests of citrus crops in Mexico (figure 1.16). In his approach to the natural products, Tadano used a SmI_2 mediated 6-*exo*-trig ketyl-olefin cyclisation in conjunction with a glucose derived "chiral auxiliary" to generate the 6-membered ring stereoselectively.[82]

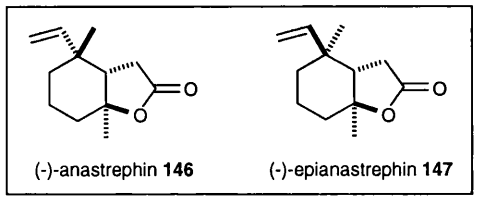
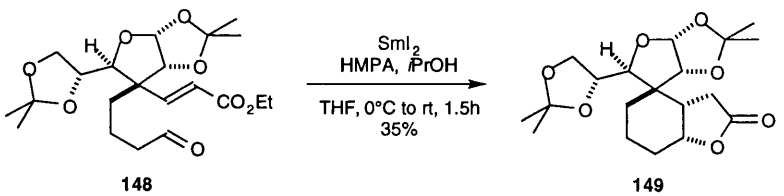


figure 1.16

Following the cyclisation of aldehyde **148** on treatment with SmI_2, *in situ* lactonisation occurred spontaneously to give the bicyclic lactone as a mixture of three stereoisomers, the major stereoisomer **149** having *cis* stereochemistry across the new carbon-carbon bond (scheme 1.44). As we have previously stated, SmI_2 mediated ketyl-olefin couplings involving aldehydes, typically give products possessing *anti* stereochemistry. Hence, the stereochemical outcome of the cyclisation of **148** is unusual.

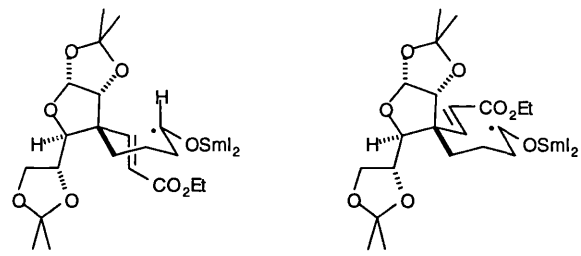


148 **149**

scheme 1.44

The authors tentatively propose that the observed stereochemistry arises from a chair-like transition state for the cyclisation (figure 1.17). Interactions between the cyclic acetal and the ester group result in the olefin assuming an axial orientation and transition structure A is favoured. Furthermore, the samarium(III) alkoxide adopts an equatorial orientation due

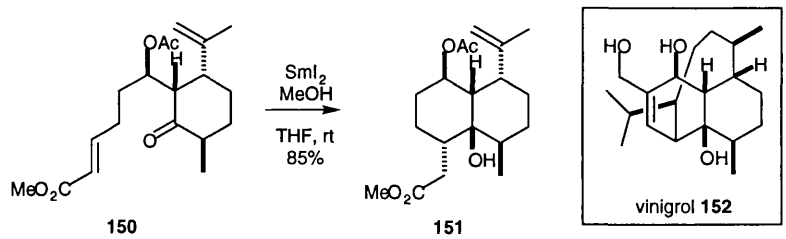
to unfavourable 1,3-diaxial interactions when in an axial position. The role of HMPA in the cyclisation was of great importance. When the cyclisation was attempted in its absence, significant over-reduction of the ketyl-radical occurred to give the acyclic alcohol. The authors also report differing stereochemical outcomes from related cyclisations involving a Z-olefin substrate and a methyl ketone. The glucose derived fragment of the product was dismantled in a series of transformations *en route* to the final product.



transition structure A transition structure B

figure 1.17

Matsuda utilised a SmI_2 mediated 6-*exo*-trig ketyl-olefin cyclisation to form the *cis*-decalin skeleton of the diterpene vinigrol **152** in an 8 step approach from (+)-dihydrocarvone (scheme 1.45).[83] The reaction proceeded with *anti* selectivity across the new C-C bond.

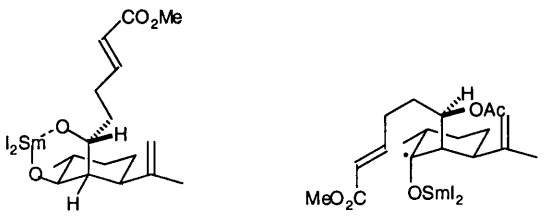


150 **151** vinigrol **152**

scheme 1.45

Crucially, in this approach the β-hydroxyl was protected as the acetate. When the substrate had a free β-hydroxyl, chelation of the samarium(III) ketyl radical anion and the

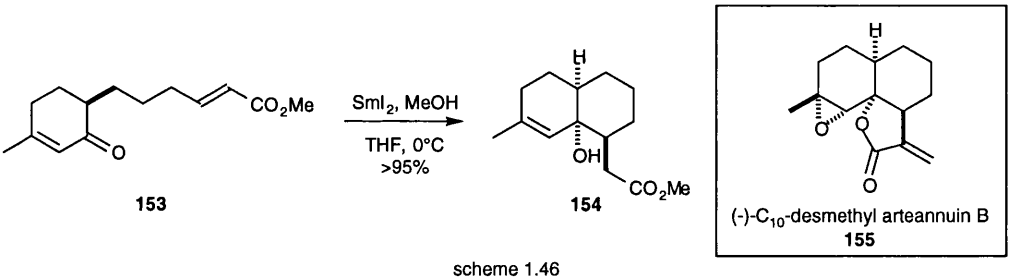
β-hydroxyl led to transition structure A (figure 1.18), where the ketyl radical anion and olefin are held some distance apart. The use of acetate protection in **150** prevented such chelation and allowed the ketyl-radical and olefin to come into closer proximity, as seen in transition structure B, thus permitting cyclisation to the desired product **151**.



transition structure A transition structure B

figure 1.18

Little also used a similar reaction as the key step in his approach to the synthesis of (-)-C10-desmethyl arteannuin B **155**.[84] The molecule is of importance as it can be used to prepare an anti-malarial analogue of artemisinin, and the route is general enough for the potential preparation of other active analogues of the natural product. The cyclisation of **153** proceeded in excellent yield using similar conditions to those employed in Nakata's 6-*exo*-trig cyclisation (scheme 1.46). The authors reason that the observed stereochemical outcome can be explained by an eleven-membered ring chelate transition state (figure 1.19). The target molecule is made in 6 steps from the cyclisation product **154**.



153 **154** (-)-C_{10}-desmethyl arteannuin B **155**

scheme 1.46

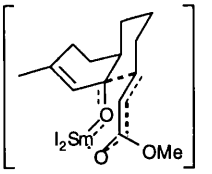
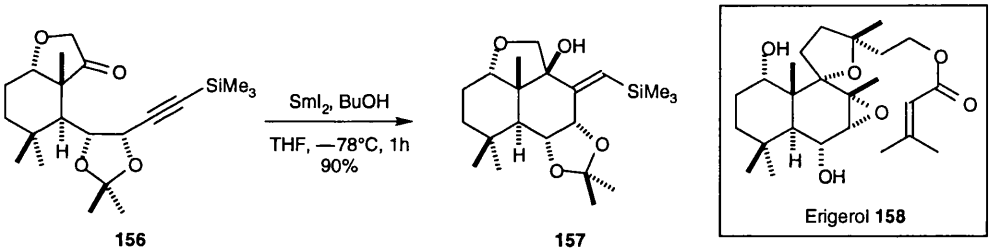


figure 1.19

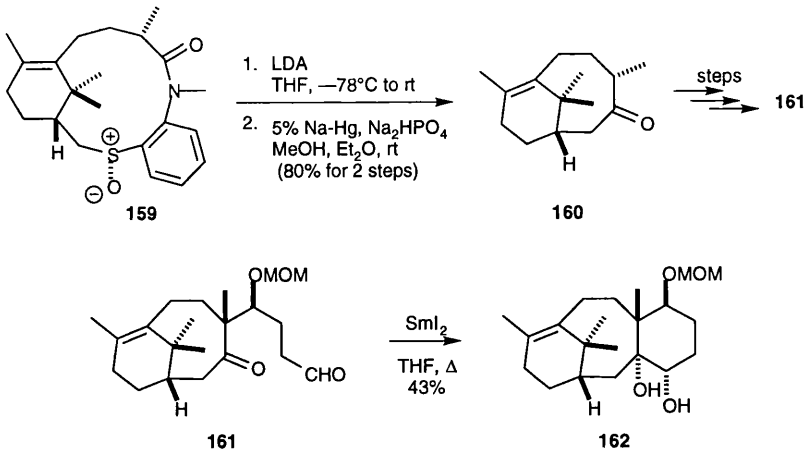
A SmI_2 mediated 6-*exo*-dig ketyl-olefin cyclisation has been used to form the *trans* decalin skeleton of (±)-Erigerol **158** (scheme 1.47), a labdane type diterpene isolated from the plant *Erigeron philadelphicus*.[85] The natural product has similarities in structure to the adenylate cyclase activator Forskoline. The cyclisation of **156** proceeded in the absence of HMPA to give **157** as a single diastereomer, in excellent yield.



156 **157**

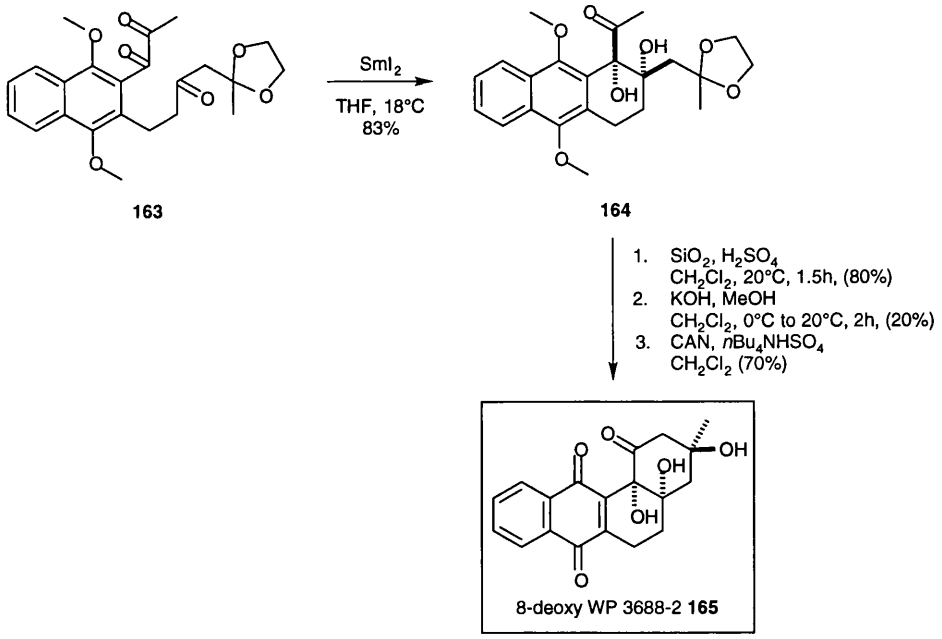
scheme 1.47

SmI_2 mediated pinacol coupling reactions have also been used to generate 6-membered rings. Such a reaction was used by Kajiwara as a key step in his preparation of the taxane ABC rings skeleton.[86] Having previously established the AB ring system of substrate **161** using a lactam-sulfoxide ring contraction (scheme 1.48), the authors then explored the use of SmI_2 to set up the C ring. The cyclisation of aldehyde **161** was carried out in refluxing THF in the absence of any additives. The *syn* diol was obtained in 43% yield with the necessary *trans* stereochemistry at the BC ring junction.



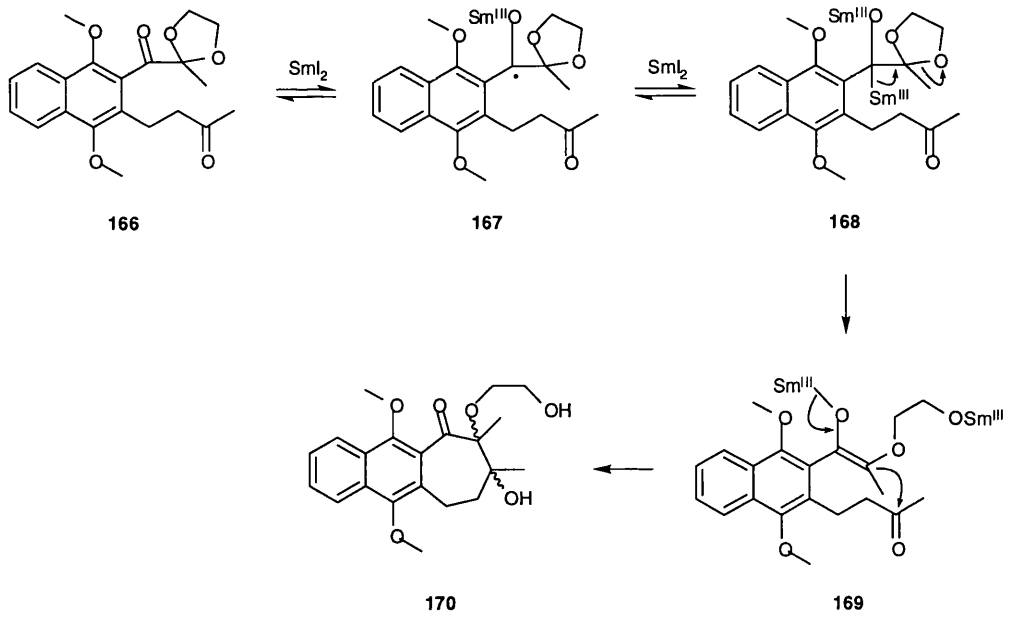
scheme 1.48

The angucycline antibiotics are a large group of secondary metabolites isolated from microbes. WP 3688-2 is such an antibiotic isolated from *Streptomyces phaeochromogenes* and has a *cis* 1,2-diol unit between the A and B rings. In Krohn's synthesis of the aquayamycin, 8-deoxy WP 3688-2 **165**, SmI_2 is used to form the six-membered B ring *via* an intramolecular 'pinacol-type' coupling reaction.[87] The cyclisation of **163** progressed under mild conditions to afford the diol **164** in good yield and as a 9:1 ratio of diastereoisomers, the desired *cis* diol being the major product (scheme 1.49).



scheme 1.49

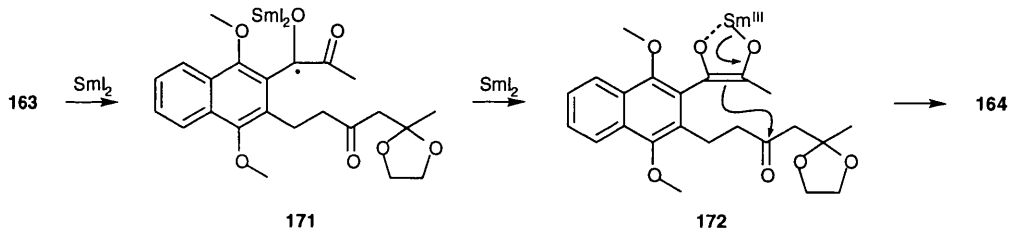
Interestingly, the authors found that problems occurred when the carbonyl of the methyl ketone was protected as an acetal, as in **166** (figure 1.20). Instead of the desired cyclisation, elimination to form the enolate followed by an intramolecular aldol to form a seven-membered ring occurred.



166 167 168 169 170

figure 1.20

Cyclisation of diketone **163**, with no leaving group in the α position, was therefore studied (scheme 1.49). The mechanism proposed for the formation of **164** is outlined in figure 1.21, and also involves an intramolecular aldol of a Sm(III) enolate. The authors observed a dependence of diastereoselectivity on reaction temperature. When the reaction was cooled to —100°C the formation of the *trans* diol was the major product. The diol **164** was converted to 8-deoxy WP 3688-2 in three steps.

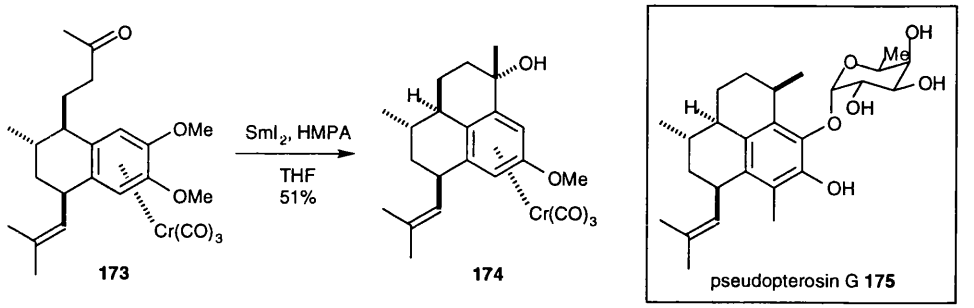


171 172

figure 1.21

Schmalz *et. al.* have carried out extensive studies on chiral tetralin-$Cr(CO)_3$ complexes and have reported the first examples of radical additions to arene $Cr(CO)_3$ complexes.[88, 89] In the cyclisation of **173**, the bulky $Cr(CO)_3$ group serves not only to control the

stereoselectivity of the cyclisation but the electron withdrawing nature of the group activates the aromatic ring to ketyl radical addition in a system that would otherwise be deactivated by the electron-donating methoxy substituents (scheme 1.50). The ketyl radical anion was generated by SmI_2 and was found to add to the top face of the complexed aryl ring. Following a second electron reduction by SmI_2, regioselective elimination of a methoxyl group gave **174**, the skeleton of pseudopterosin G **175** and helioporin E (not shown), in moderate yield (scheme 1.50).



173 **174** pseudopterosin G **175**

scheme 1.50

A proposed mechanism for the cyclisation is shown in figure 1.22.

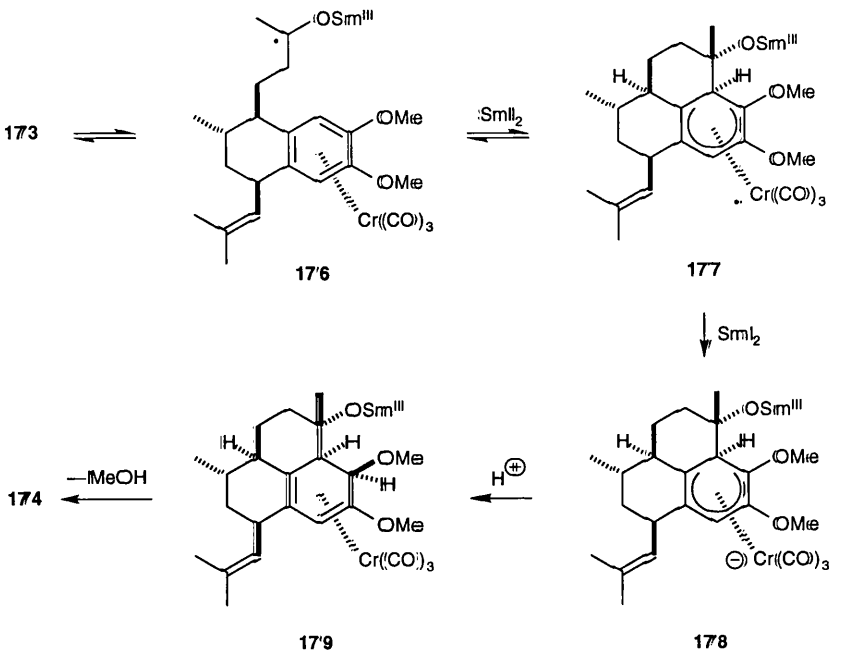
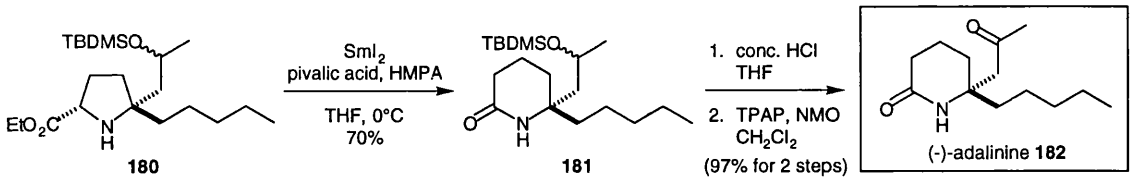


figure 1.22

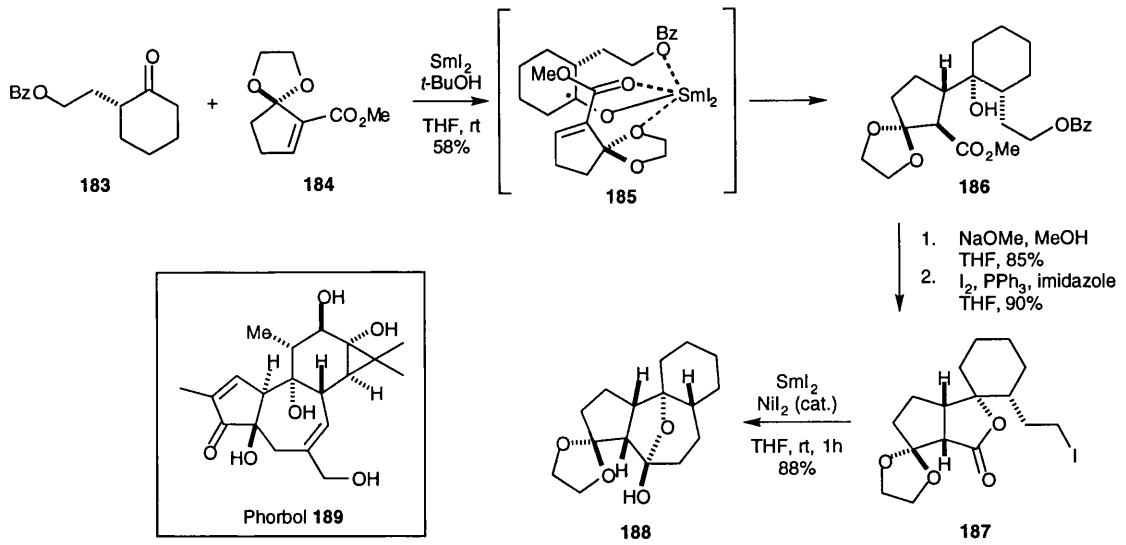
(-)-Adalinine **182** is a piperidine alkaloid isolated from the ladybird beetles *Adalia bipunctata* and *Adalia decempunctata*. In his approach to the natural product, Honda used a SmI_2 mediated ring expansion reaction as the key step in a synthesis which began from (S)-(-)-pyroglutamic acid.[90] Upon treatment of the amino acid derivative **180** with SmI_2, a regioselective carbon-nitrogen bond cleavage occurred to give an acyclic amino ester intermediate which then underwent lactamisation to form the δ-lactam **181** in good yield (scheme 1.51). The reaction was carried out in the presence of 5 equivalents of HMPA. Using less additive, or in its absence, the reaction was considerably slower and gave lower yields of the desired product. The authors also used pivalic acid as a proton source in the transformation. Removal of the silyl protecting group in δ-lactam **181** and TPAP oxidation, gave the target alkaloid **182** in good yield.



scheme 1.51

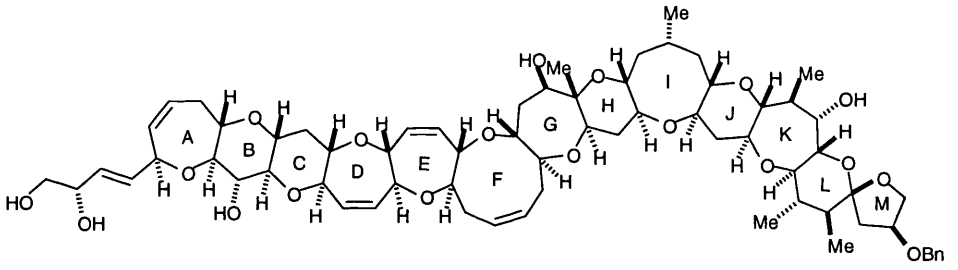
1.3.4 Seven-membered rings

Phorbol **189** is a tigliane diterpene isolated from the seeds of *Croton tiglium L.* The esters of this tetracyclic natural product have attracted much attention due to their potent biological activity which includes the promotion of tumour growth as well as antitumour and anti-HIV activity. In a preliminary disclosure, describing the preparation of the carbon framework of the natural product, Little used SmI_2 in two key carbon-carbon bond forming transformations (scheme 1.52).[91] The first involved a chelation controlled intermolecular ketyl-olefin coupling which formed the tricyclic structure **186**. The authors propose that the reaction progressed through the Sm(III) chelate intermediate **185** to give the observed stereochemistry in the product. After epimerisation, which triggered lactonisation, and transformation of the hydroxyl to the iodide, tricyclic **187** was ready for the second SmI_2 transformation. The lanthanide reagent was used in an intramolecular Barbier reaction to construct the seven-membered ring of the target. Although at first the reaction was sluggish with mediocre yields, the addition of a catalytic amount of nickel(II) iodide, a known promoter of SmI_2 halide-carbonyl couplings, resulted in a more efficient reaction giving **188** as a single isomer in good yield.[15]



scheme 1.52

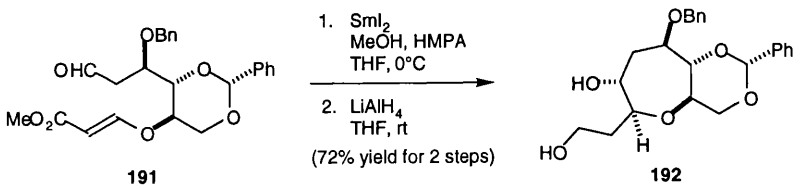
Ciguatoxin **190** is a complex polycyclic ether believed to be the cause of many reported cases of ciguatera (sea food poisoning) (figure 1.23).[92] The complex molecule is found in the flesh of coral reef fish and originates from the epiphytic dinoflagelate *Gambierdiscus toxicus*. The potent neurotoxicity combined with the extremely complex structure makes ciguatoxin an interesting challenge for the synthetic community.



ciguatoxin **190**

figure 1.23

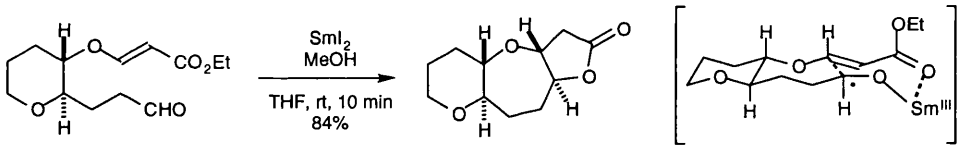
In the preparation of the GHIJKLM fragment, Sasaki has used a SmI_2 mediated 7-*exo*-trig ketyl-olefin cyclisation to generate the seven membered oxacyclic G ring.[93] The cyclisation of **191** proceeded selectively to give the *anti* cycloheptanol product. The crude product was reduced directly with $LiAlH_4$ to give diol **192** (scheme 1.53).



191 192

scheme 1.53

An explanation for the high diastereoselectivity of the cyclisation, was not postulated by the authors, however, in a report by Nakata, in which he describes the similar SmI_2 mediated 7-*exo*-trig ketyl-olefin cyclisation of aldehyde **193** to give the *anti* product **194** (scheme 1.54), a 12-membered chelate transition state was used to explain the complete diastereocontrol in the reaction (figure 1.24).[94] Whether such chelation was responsible for the diastereoselectivity in Sasaki's cyclisation is debatable particularly as the cyclisation was carried out in the presence of HMPA, a cosolvent which might be expected to disrupt chelation.

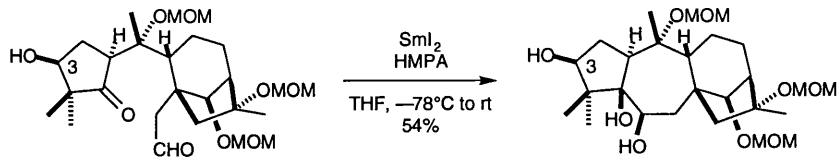


193 194 figure 1.24

scheme 1.54

Several other SmI_2 cyclisation reactions have been used to construct 7-membered rings. Previously we have discussed two SmI_2 cyclisations to form 5-membered rings developed by Matsuda in his approach to Grayanotoxin III **121** (scheme 1.35). The final SmI_2 mediated cyclisation in the synthesis involved the construction of the 7-membered B ring of Grayanotoxin *via* a pinacol coupling reaction.[72] Initially, Matsuda *et. al.* examined the use of a titanium mediated intramolecular pinacol coupling to form the 7-membered carbocycle, however, undesired side-reactions were observed. Instead, the cyclisation of dicarbonyl **195** was attempted with SmI_2 in the presence of HMPA (scheme 1.55).

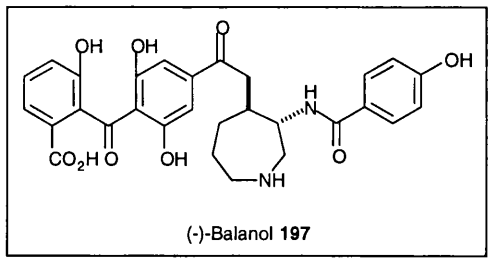
Cyclisation occurred smoothly to give the diol **196** in good yield, with no other stereoisomers of **196** being detected. Interestingly the hydroxyl at C3 of **195** appears to play an important role in the cyclisation as when the reaction was attempted with the hydroxyl protected as the MOM ether, no cyclisation took place. No explanation is given by the authors for this observation.



195 **196**

scheme 1.55

Balanol **197** is a novel metabolite that was first isolated from the fungus *Verticillium balanoides* in North Carolina in 1993 (figure 1.25). The natural product is of particular interest as it has been shown to be a potent inhibitor of Protein Kinase C (PKC) enzymes. PKC's are important enzymes playing a major role in cell growth and function. In addition, the enzymes have been associated with a range of diseases which include asthma, cancer, cardiovascular ailments, central nervous system problems, diabetes and HIV. Therefore PKC inhibitors such as Balanol are lead compounds for potential therapeutic agents to alleviate these widespread health problems. The therapeutic possibilities combined with the interesting structure of the natural product has prompted widespread interest from synthetic chemists.



(-)-Balanol **197**

figure 1.25

In Naito's asymmetric approach to the molecule, SmI_2 methodology was used to form the hexahydroazepine ring *via* the ketyl-oxime cyclisation of **198**.[95, 96] Initially, attempts to carry out the cyclisation using Bu_3SnH led to moderate yields of the hexahydroazepine ring with mediocre diastereocontrol, approximately a 3:1 ratio favouring the *anti* cyclisation product **200**. The authors then examined the use of SmI_2 and found that in the presence of HMPA, they obtained an improved yield with a marked increase in diastereoselectivity, again favouring the *anti* product **200** but now by nearly 7:1 (scheme 1.56). Such stereoselectivity was explained by invoking an 11-membered Sm(III) chelate intermediate (figure 1.26).

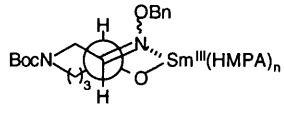
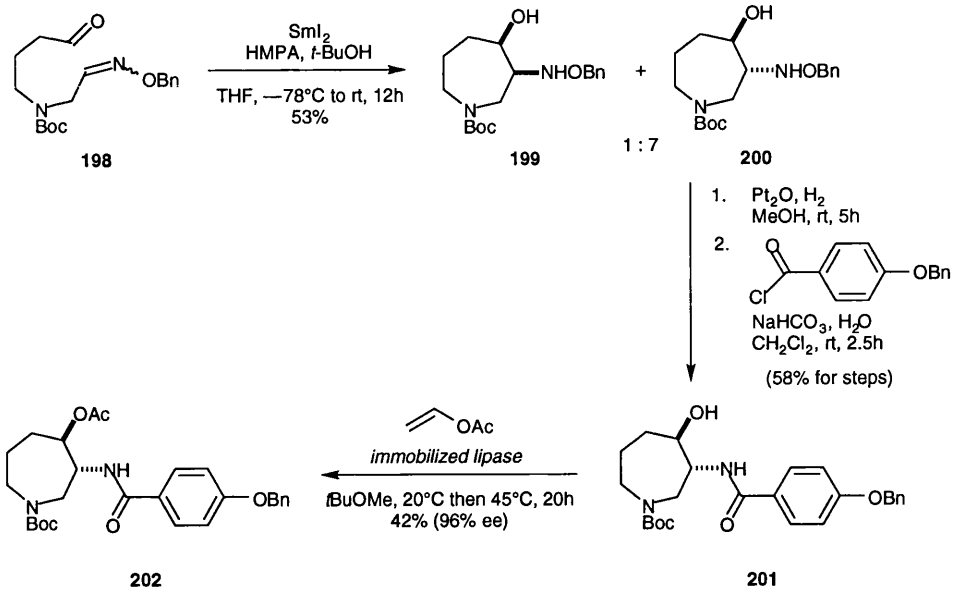


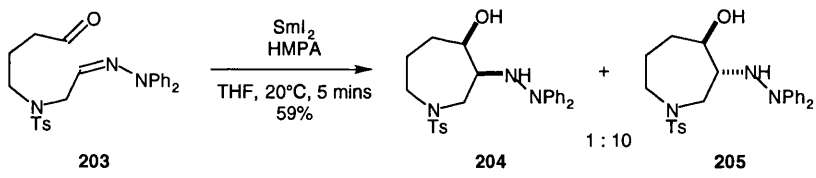
figure 1.26

The important role of HMPA in the cyclisation was highlighted when in its absence, treatment of **198** with SmI_2 failed to give any of the desired product. Further studies by Naito also revealed that the initial geometry of the oxime had no influence on the yield or stereoselectivity of the cyclisation. The racemic hexahydroazepine fragment of Balanol was resolved using an enzymatic approach. Following the isolation of the *anti* diastereoisomer by column chromatography, reduction then gave the amine which was acylated with *p*-(benzyloxy)benzoyl chloride to give **201**. Enzymatic acetylation of **201** using the lipase from *Pseudomonas* sp. resulted in the formation of **202** in good yield and excellent enantiopurity.



scheme 1.56

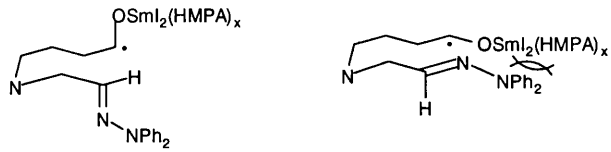
Work by Skrydstrup on the synthesis of Balanol also employs a radical cyclisation to form the hexahydroazepine ring.[97] SmI_2 was used to mediate the intramolecular ketyl-hydrazone coupling of **203** to form the seven-membered ring of the target (scheme 1.57). The hexahydroazepine ring was formed in good yield and with greater diastereoselectivity than for the cyclisation reported by Naito. Skrydstrup proposed that HMPA is playing a key role in promoting the cyclisation simply by discouraging competitive reactions such as intermolecular pinacol coupling reactions.



scheme 1.57

Unlike Naito, Skrydstrup does not invoke an 11-membered chelate intermediate to explain the observed stereoselectivities. Instead he ascribes the *anti* stereoselectivity to steric repulsions between the complexed Sm(III)-ketyl and the bulky diphenylhydrazone

group in the intermediate transition structure, with the substituents taking up pseudoaxial positions (figure 1.27).

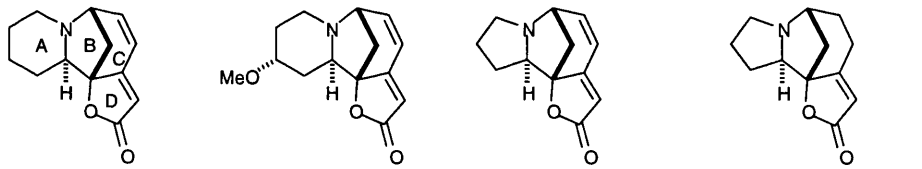


conformation A **favoured**

conformation B **unfavoured**

figure 1.27

The Securinega group of alkaloids are tetracyclic compounds isolated from plants of the Securinega and the Phyllanthus genera of the Euphorbiaceae family. Securinine **206** is the most abundant alkaloid from the family and has a wide range of biological activity which includes antibacterial and antimalarial properties (figure 1.28). Recently, it has been found to induce apoptosis in human leukaemia cells. In addition, Securinine has been shown to be a specific antagonist of the GABA receptor and has significant central nervous system activity.



206 securinine

207 phyllanthine

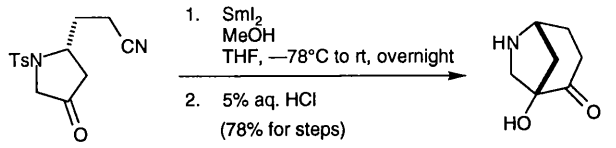
208 (-)-norsecurinine

209 (+)-14,15-dihydronorsecurinine

figure 1.28

In Weinreb's total synthesis of three securinine alkaloids, he used a synthetic strategy in which a key bicyclic intermediate **211** was prepared containing the B and C rings from which phyllanthine **207**, (-)-norsecurinine **208** and (+)-14,15-dihydronorsecurinine **209** were subsequently accessed (figure 1.28).[98] Enantiopure bicyclic **211** was obtained from trans-4-hydroxy-L-proline in 9 steps with the key reaction being a SmI_2 mediated

intramolecular ketone-nitrile coupling of **210** (scheme 1.58). The cyclisation occurred under mild conditions in the presence of MeOH, giving the imine, which was subsequently hydrolysed during an acidic work-up to give **211** in good yield.

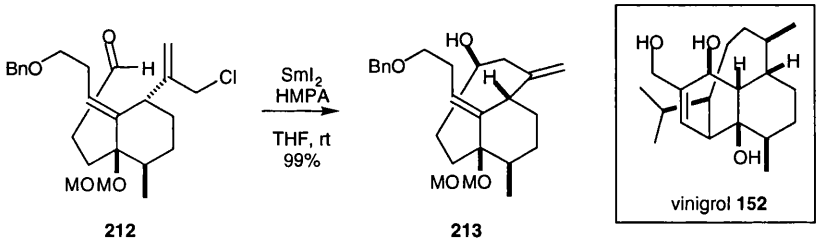


210 **211**

scheme 1.58

1.3.5 Eight-membered rings

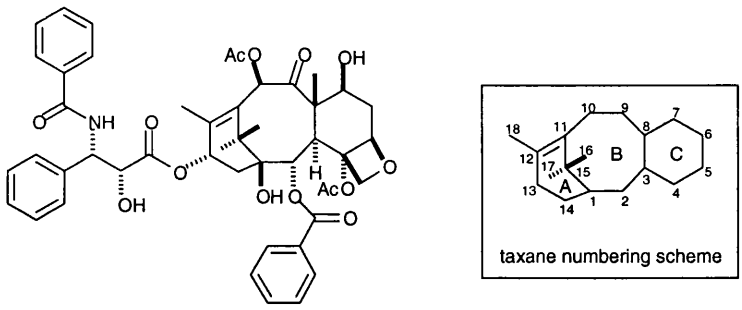
Samarium(II) iodide has been used in a variety of ways and to great effect in the formation of 8-membered rings. In an alternative approach to that previously discussed to vinigrol **152**, Matsuda has shown the SmI_2 mediated intramolecular Barbier coupling of an aldehyde and an allylic chloride to be a viable method for generating the 8-membered ring of the diterpene (scheme 1.59).[99] Remarkably high yields were obtained for the formation of cyclooctanol **213** under non-high dilution conditions in the presence of HMPA.



212 **213**

scheme **1.59**

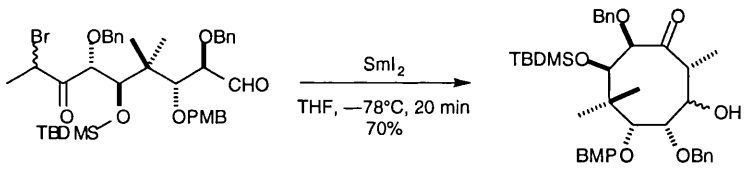
Taxol **214** is a biologically important natural product which has provided arguably the greatest challenge to synthetic chemists of recent years (figure 1.29).



taxol© (paclitaxel) **214**

figure 1.29

In Mukaiyama's approach to the complex molecule, SmI_2 was used to instigate an intramolecular Reformatsky reaction which formed the 8-membered B ring across the C3-C8 bond with the four previously installed stereocentres in the substrate **215** remaining intact (scheme 1.60).[100, 101] **216** was obtained as an 83:17 ratio of stereoisomers at the stereocentre corresponding to C3 of the natural product (see taxane numbering scheme in figure 1.29), however, the stereochemistry at this centre and the second newly generated stereocentre C8, is irrelevant as in subsequent steps the stereochemistry was lost and regenerated in the formation of the C ring. In their most recent paper,[101] Mukaiyama shows that α-chloro ketones can also be employed in analogous cyclisation reactions.

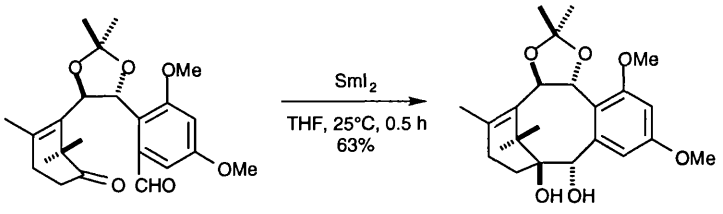


215 **216**

scheme 1.60

In a different approach to the B ring of the taxane skeleton, Swindell has shown how **217** underwent SmI_2 mediated pinacol coupling to close the ring between C1 and C2.[102] In a previous study SmI_2 showed itself to be a superior reagent to a $TiCl_4$-Zn reagent system

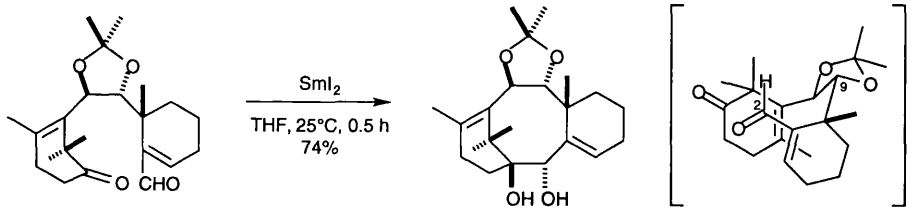
for a similar transformation. Initial attempts to carry out the pinacol coupling when the C ring was saturated failed, however the use of an aromatic C ring which could be transformed later, possibly by Birch reduction, resulted in an efficient pinacol cyclisation (scheme 1.61).



217 **218**

scheme 1.61

Swindell later showed that the presence of an aromatic C-ring was not essential as αβ-unsaturated aldehyde **219** cyclised in good yield on treatment with SmI_2 (scheme 1.62).[102] Employing aldehyde **219** meant that the methyl group at C8 could be present prior to the cyclisation. Swindell suggests that the formation of the *anti* diol product **220** can be rationalised by invoking an *endo* boat-chair transition structure **221** (scheme 1.62).

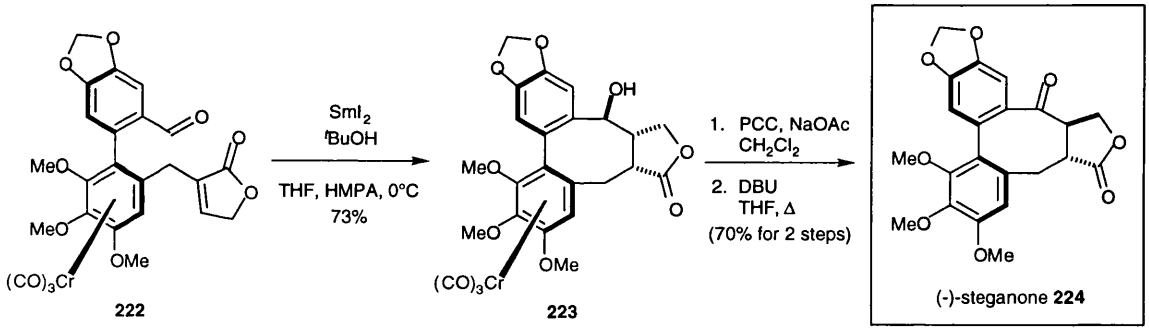


219 **220** **221**

scheme 1.62

Eight membered rings can also be constructed using other SmI_2 methodology. An 8-*endo*-trig ketyl-olefin cyclisation has been utilised in the formation of the 8-membered ring system of (-)-Steganone **224** (scheme 1.63).[103] Formation of the large carbocycle was enhanced by the biaryl system which held four of the carbon atoms in a suitable arrangement for cyclisation. Furthermore, the presence of the electron donating

methylene dioxy group on the same aromatic ring as the aldehyde was beneficial as it served to raise the SOMO of the ketyl-radical and so encourage cyclisation of **222**. The main feature of this approach, however, was the use of a chromium tricarbonyl complex to control the stereochemistry of the cyclisation. In what would normally be a labile biaryl system, the chromium tricarbonyl group forces the formyl group to occupy a distal position. This holds the cyclic precursor in a conformation that gives rise to the desired stereochemistry at the stereocentre α to the lactone carbonyl (figure 1.30). The synthesis was finished in two steps from cyclooctanol **223**. Oxidation of the alcohol using PCC also removed the chromium complex, and epimerisation of the stereocentre α to the newly formed ketone carbonyl group gave the enantiopure natural product **224** (scheme 1.63).



scheme 1.63

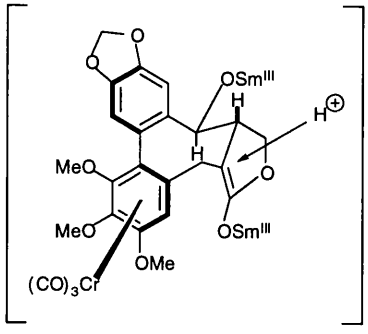
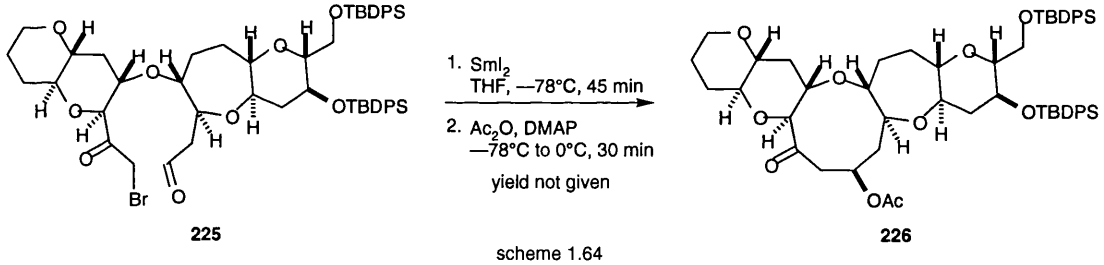


figure 1.30

1.3.6 Nine-membered rings

We have seen how the SmI_2 mediated intramolecular Reformatsky reaction has been employed in approaches to the 8-membered B-ring of Taxol, but the reaction has also been used to form larger rings. Tachibana used the reaction to good effect in forming the 9-membered oxonone F ring of ciguatoxin **190** (see figure 1.23).[104] In earlier model studies, slow addition of bromide **225** to a solution of SmI_2 in THF at 0°C led to over reduction of the desired product *via* reductive cleavage of the C-O bond α to the ketone.[105] The problem of over reduction was solved when bromide **225** was added at a faster rate to the SmI_2 in THF at —78°C (scheme 1.64). Although no yield for the cyclisation, followed by *in situ* acetylation, is reported, the reaction was sufficiently efficient enough to allow the crude product **226** to be used in the next step without further purification (no yield is given for the cyclisation but it was part of a five step reaction sequence which proceeded in 66% overall yield).[104]



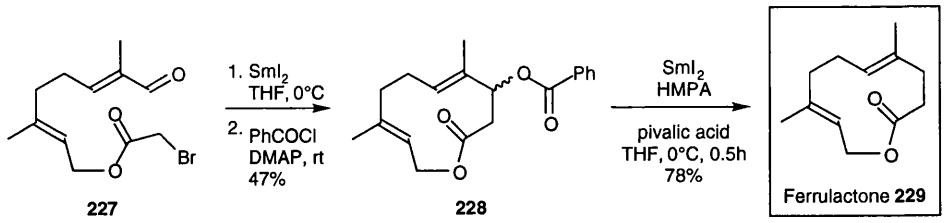
225 **226**

scheme 1.64

1.3.7 Eleven-membered rings

Using their previously developed conditions, Inanaga and co-workers have utilised the SmI_2 promoted Reformatsky reaction to generate the 11-membered ring of Ferrulactone **229**.[106] Cyclisation of bromide **227** onto an α,β-unsaturated aldehyde formed an unstable

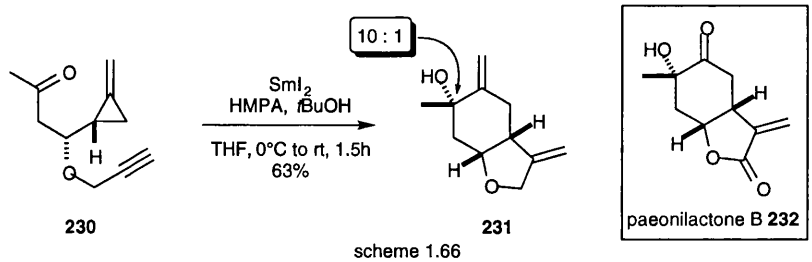
β-hydroxydecadienolide which was isolated as the corresponding benzoate **228** (scheme 1.65). The next and final step involved the SmI_2 reduction of the allylic benzoate.



scheme 1.65

1.3.8 Tandem reactions

SmI_2 has been used to great effect in mediating cascade reactions where complex polycyclic systems are constructed in one synthetic operation. Kilburn has used a SmI_2 mediated radical cascade cyclisation of a methylenecyclopropyl ketone in the preparation of paeonilactone B **232**.[107, 108] The paeonilactones are monoterpenoids isolated from the roots of *Paeonia albiflora* Pallas, a plant whose roots have been used extensively in Chinese folk medicine. In Kilburn's synthesis of the natural product, the 6-membered and 5-membered rings are generated in one stereoselective transformation. SmI_2 is used in the presence of HMPA and *tert*-BuOH to transform methylenecyclopropyl ketone **230** to the bicyclic lactone **231**, which is obtained as a 10:1 mixture of diastereoisomers (scheme 1.66).



scheme 1.66

The reaction mechanism has been postulated to involve the cyclisation of ketyl-radical anion **233** onto the methylenecyclopropane moiety in a 5-*exo*-trig manner (figure 1.31). Ring opening of cyclopropane intermediate **234** gives rise to the cyclohexane radical **235** which then cyclises in a 5-*exo*-dig fashion to form the second ring.

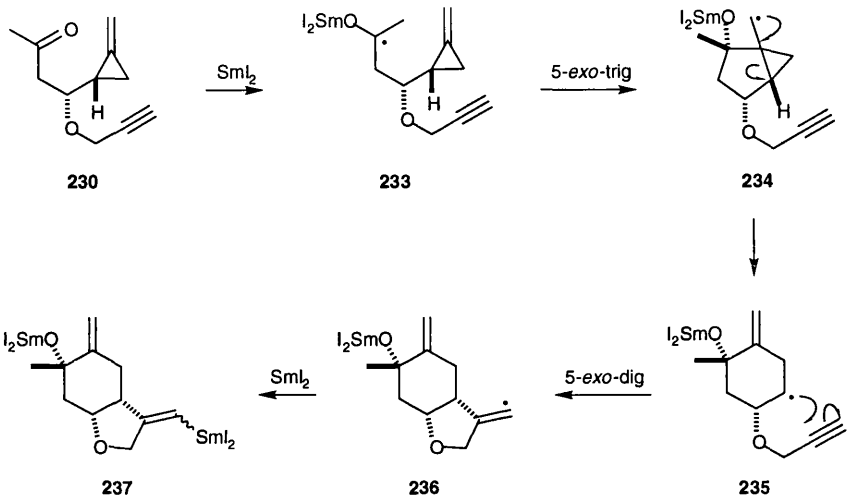
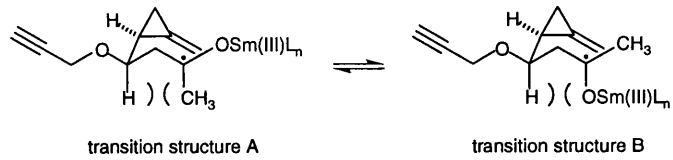


figure 1.31

The presence of HMPA was found to have a dramatic effect on the diastereoselectivity of the reaction. When HMPA was replaced with the lesser coordinating solvent DMPU, the yield and diastereoselectivity decreased. In the absence of any coordinating solvent, the yield decreased further and in addition, a switch in diastereoselectivity was observed. The authors explain the diastereoselectivity by invoking the transition structures shown in figure 1.32. In the presence of a strongly coordinating solvent such as HMPA, the effective steric bulk of the samarium alkoxide results in it taking up a more favourable pseudo-equatorial position as it seeks to minimise 1,3-diaxial interactions (transition structure A in figure 1.32). In a poorer coordinating solvent such as DMPU, or in the absence of any coordinating solvent, the effective steric bulk of the samarium alkoxide is less and the methyl group adopts an equatorial position as it is the bulkier group

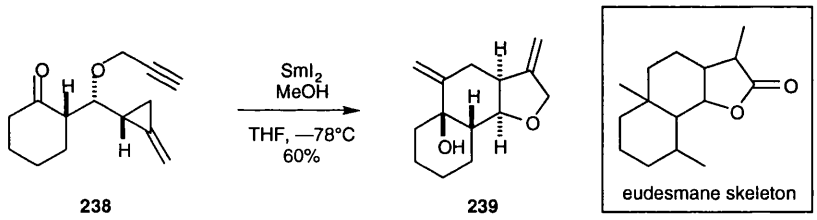
(transition structure B in figure 1.32). The natural product was obtained in seven steps from the cyclisation product **231**.



transition structure A transition structure B

figure 1.32

A related radical cascade cyclisation has also been used by Kilburn to access the tricyclic ether skeleton of the eudemanes.[109] Many sesquiterpenoid lactones containing the eudesmane carbon framework have been isolated from plants of the Artemesia genra. The conditions employed in the sequential process were examined and it was found that a THF-MeOH (4:1) solvent system improved the efficiency of the transformation of **238** to give tricyclic **239** (scheme 1.67). Interestingly, in the same disclosure, the formation of an analogous tricyclic structure is reported where a change in the solvent system could bring about a change in the stereochemistry of one of the newly generated stereocentres.



238 **239**

scheme 1.67

Curran has also used a SmI_2 mediated cascade process in his total synthesis of (±)-Hypnophilin **240** and the formal synthesis of (±)-Coriolin **241** (figure 1.33).[110] Due to his inability to prepare substrates from **242** suitable for tin hydride cyclisation and the failure of **242** to cyclise to give the desired products on treatment with Zn/TMSCl or hυ, Curran chose to examine the reaction of SmI_2 with aldehyde **242** (scheme 1.68).

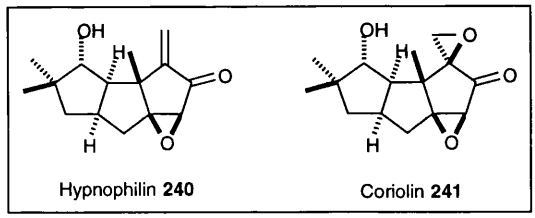
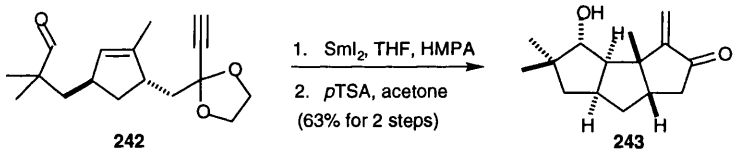


figure 1.33

Treatment of **242** with SmI_2 in the presence of HMPA at 0°C gave **243** (scheme 1.68). The reaction proceeded with complete diastereocontrol generating three new stereocentres in the sequence, and giving the *cis*, *trans*, *cis* stereochemistry of the tricyclic product. Interestingly, when DMPU was used as cosolvent, the stereoselectivity of the reaction decreased and a 10:1 ratio of diastereoisomers of the tricyclic product was obtained. When using either HMPA or DMPU, a small amount of the uncyclised, reduced aldehyde was also isolated.



scheme 1.68

It would appear that the mechanism of the reaction involves the generation of a ketyl-radical anion which cyclises in a 5-*exo*-trig manner to form a tertiary cyclopentyl radical **245** which adds to the alkyne in a 5-*exo*-dig cyclisation to form the final 5-membered ring. Hydrogen atom capture terminates the sequence (figure 1.34).

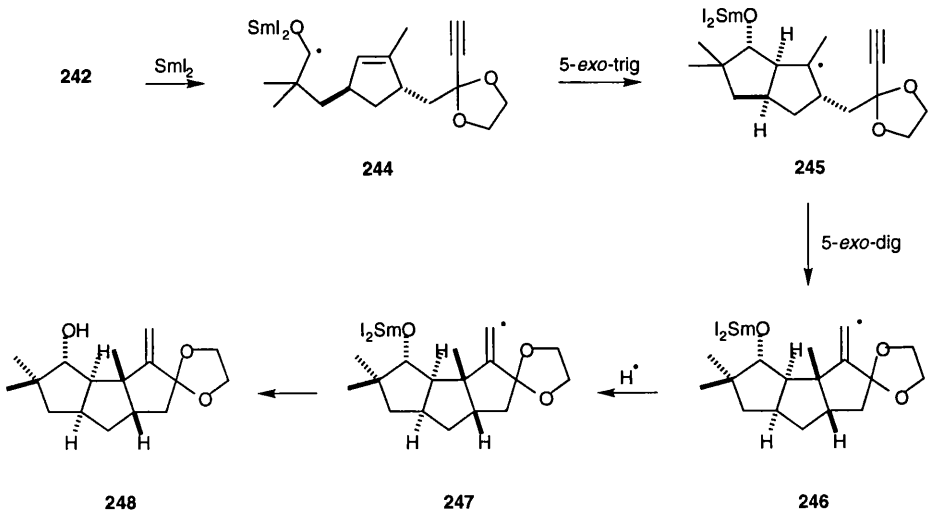


figure 1.34

The authors explain that less than two equivalents of SmI_2 are necessary for the cascade reaction. Furthermore, when the reaction was quenched with D_2O, no deuterium incorporation was observed, the authors concluded that the final radical species **247** undergoes hydrogen atom capture from the solvent before a second SmI_2 reduction can generate the organosamarium.

1.4 Conclusion

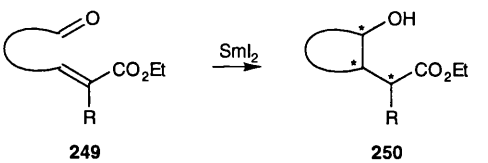
Quite clearly, SmI_2 is an incredibly useful reagent, which can mediate a number of C-C bond forming transformations. Although only a recent addition to the tools of the synthetic chemist, there is no shortage of examples of its use in natural product synthesis. The versatility of the reagent has been highlighted by its use in the preparation of a variety of highly complex molecules which often bear sensitive structural features and functionality. High yields and stereoselectivities are also a feature of reactions mediated by the lanthanide reducing agent. Perhaps the most exciting application of SmI_2, is in mediating sequential reactions where molecular complexity can be assembled rapidly in a single synthetic operation. When such tandem processes are applied to complex natural products, the results are often staggering with whole carbon skeletons being assembled in one step with high levels of stereocontrol. It seems certain that SmI_2 will enjoy continued application as chemists pursue more and more challenging structures from the natural world.

Chapter 2: Results and discussion

The two principle aims of this investigation were the development of a samarium(II) mediated 4-*exo*-trig ketyl olefin cyclisation and the application of this reaction to the synthesis of the biologically active natural product pestalotiopsin A.[111, 112] The following chapter is an account of our investigations.

2.1 Stereoselective synthesis of functionalised cyclobutanols *via* the samarium(II)-mediated 4-*exo*-trig cyclisation of unsaturated aldehydes

The samarium(II) mediated reductive cyclisation of unsaturated aldehydes or ketones is a particularly powerful cyclisation protocol which allows a variety of cyclic alcohols of varying ring size to be assembled under mild conditions with moderate to good diastereocontrol. The reaction is atom efficient with functionality present in the starting material being retained in the product, albeit in a different oxidation state. In generating the new ring junction two new stereocentres are formed and a third stereocentre is established when the olefin bears an additional substituent α to the electron withdrawing group. Thus highly functionalised products with multiple stereocentres can be accessed in a mild and atom-efficient manner (figure 2.1).

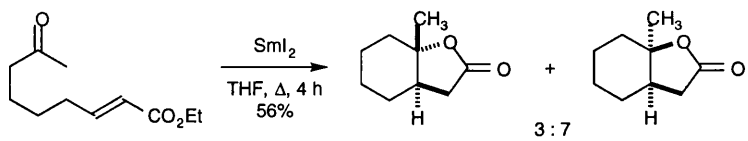


249 **250**

figure 2.1

The versatility of the reaction has been further highlighted by its use in the preparation of heterocycles. When the electron withdrawing group is an ester, the SmI_2 cyclisation is

often followed by spontaneous lactonisation, allowing convenient access to bicyclic lactones. For example, the cyclisation of ketone **251**, shown in scheme 2.1, gives lactones **252** in moderate yield.[113, 114]



251 **252**-*trans* **252**-*cis*

scheme 2.1

Our initial objective was to see if reductive cyclisations of this type could be used to form small ring systems, in particular, cyclobutanols.

2.1.1 Introduction

Radical cyclisations to form cyclobutane rings are reversible and hence few efficient reactions employing such processes have been reported.[115-118] At the outset of the project, we believed that the ability of samarium(II) iodide to not only generate carbon-centred radicals but to further reduce such radicals to the corresponding carbanions might provide a way of trapping the cyclic product and hence prevent the facile ring-opening process (figure 2.2).[39] We proposed that this proposed 'trapping' mechanism might provide a general approach to functionalised cyclobutanols. Following the initial SmI_2 reduction, the uncyclised ketyl radical anion **254** is in equilibrium with the cyclobutinyl radical **255**. However, reduction of **255** to the carbanion **256** prevents ring-opening and 'traps out' the cyclic product, which in effect moves the equilibrium to the right, driving the reaction forward.

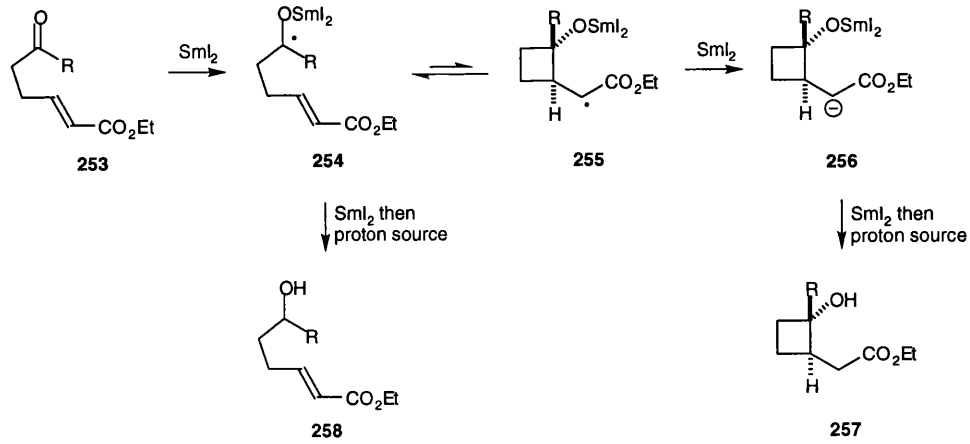
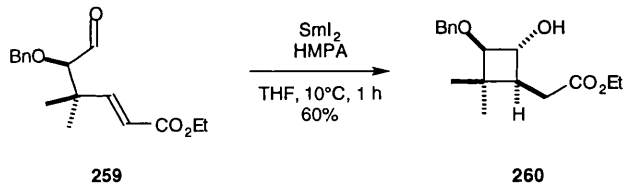


figure 2.2

Prior to our investigation there was only one previous example of a samarium(II) mediated 4-*exo*-trig ketyl-olefin cyclisation, which was reported by Weinges,[59] and this disclosure contained only a single example employing substrate **259** and using relatively harsh conditions (scheme 2.2).

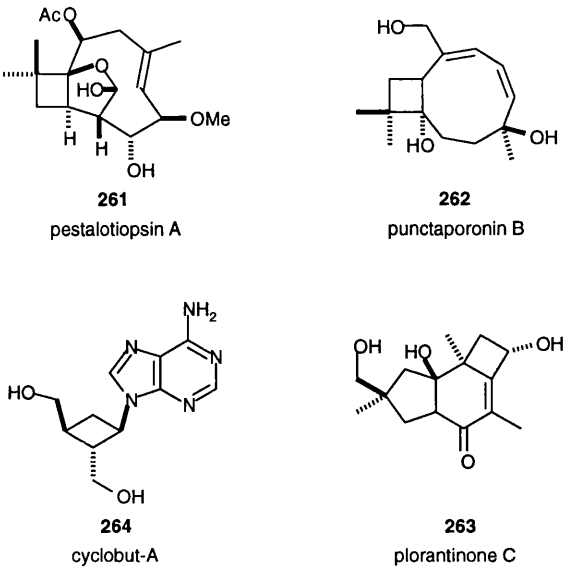


scheme 2.2

Despite the limited precedent, we believed the reaction might have considerable potential as a general route to cyclobutanols and that the nature of the reaction would result in a highly diastereoselective process.

Cyclobutane and cyclobutanol derivatives are important building blocks in organic synthesis and constitute a structural motif that is found extensively in natural products. For example, pestalotiopsin A **261**,[112] punctaporonin B **262**,[119] and plorantinone C **263**,[120-

[122] and non-natural, biologically important molecules, such as the anti-viral, cyclobut-A **264** (figure 2.3).[123-125]



261
pestalotiopsin A

262
punctaporonin B

264
cyclobut-A

263
plorantinone C

figure 2.3

Cyclobutanes are most often prepared using photochemical [2+2] cycloaddition processes.[126-130] [The preparation of functionalised cyclobutanols using SmI_2 mediated nucleophilic acyl substitutions has recently been reported].[60, 131] Although these reactions are useful in synthesis, alternative processes, which would allow more substituted cyclobutanes, and in particular cyclobutanols, to be prepared stereoselectively, would be very useful.

We felt that a samarium(II)-mediated approach to cyclobutanols would follow a well-defined stereochemical course, very different to those involved in conventional cyclobutane ring-forming reactions. The origin of the expected stereoselectivity can be seen in the Beckwith-Houk type transition structures in figure 2.4.[132, 133] Following the formation of the ketyl-radical anion, repulsion between the lone pairs of electrons on the oxygen and the developing methylene radical should result in the *anti* transition structure

being favoured. Thus we expected the cyclisation, if successful, to yield *anti*-cyclobutanols as the major products.

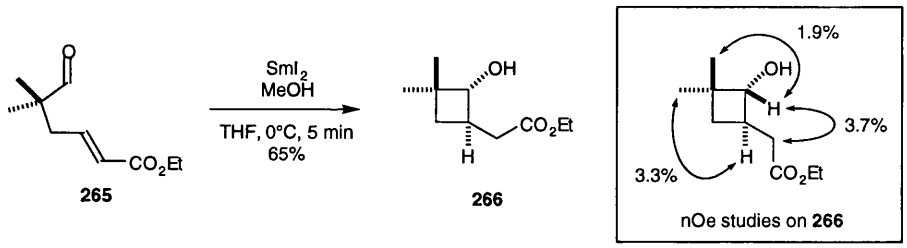
syn-transition structure

anti-transition structure
favoured

figure 2.4

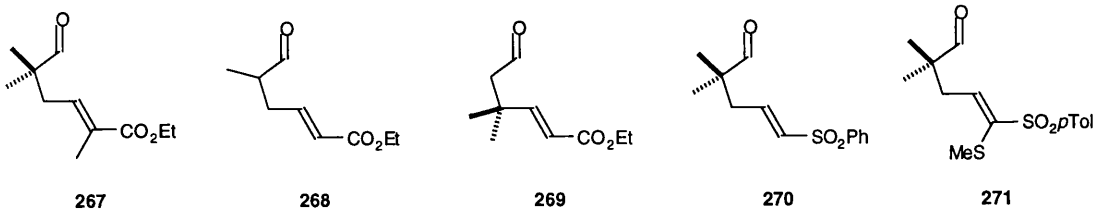
2.1.2 Selection of cyclisation substrates

My early work involved building upon a previous example of a SmI_2 mediated 4-*exo*-trig ketyl-olefin cyclisation carried out within the group. Aldehyde **265** had been prepared from γ-butyrolactone in 6 steps. On treatment with SmI_2 **265** underwent cyclisation to give the corresponding cyclobutanol **266** in 65% yield. Furthermore, only a single diastereoisomer was observed, with nOe studies revealing that the cyclobutanol product had *anti* stereochemistry across the newly formed C-C bond.



scheme 2.3

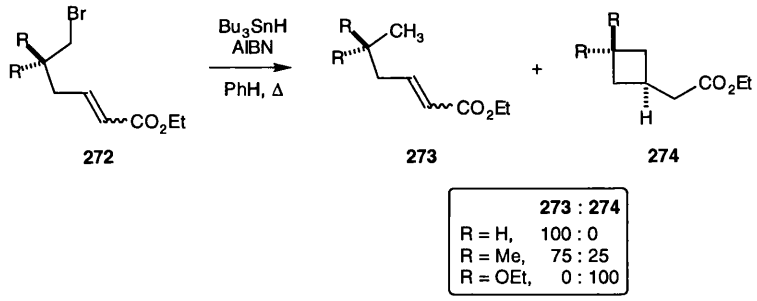
Building upon this sole example we decided to prepare five other cyclisation substrates in order to develop optimum conditions for the cyclisation and, importantly, to examine the scope and generality of the reaction. The cyclisation substrates we selected are shown in figure 2.5.



267 **268** **269** **270** **271**

figure 2.5

Substrate **267** was selected as a suitable aldehyde that would enable us to study cyclisations which would form 3 contiguous stereocentres in a single step. For example, would any stereocontrol be observed at the third stereocentre α- to the ester group? Preparation of aldehyde **268** would allow us to examine whether the presence of the *gem* dimethyl group was a precondition for cyclisation. The importance of *gem* disubstitution in certain examples of small ring system formation has previously been observed and discussed,[115, 116, 134-137] although there are other cases where *gem* disubstitution is not required (such as the example reported by Guibe previously discussed in section **1.2.2**[39] and the example discussed in the later section **2.1.4**.[117] Scheme 2.4 illustrates results obtained by Jung in a study examining the effects of various *gem*-substituents in a tributyltin hydride 4-*exo*-trig cyclisation.[134] With the unsubstituted bromide **272** (R=H) only the acyclic reduction product **273** (R=H) was detected. However, when *gem*-dimethyl groups were introduced, bromide **272** (R=Me) cyclised to give the cyclobutane **274** (R=Me) in low yield. Interestingly, with bromide **272** (R=OEt), cyclisation was highly efficient and gave the cyclobutane **274** (R=OEt) exclusively.



scheme 2.4

The importance of the *position* of the *gem* dimethyl group was of interest to us and so aldehyde substrate **269** was targeted. In order to assess the feasibility of using other radical acceptors in the cyclisation, vinyl sulfone substrate **270** was designed. Finally, the α-thio methyl substituted vinyl sulfone **271** was also targeted. We envisaged the presence of the thio methyl group α to the sulfone in **271** might facilitate cyclisation by formation of a more stable cyclised radical intermediate. This effect is known as the Captodative effect and will be discussed in greater detail in section **2.1.4**.[138]

2.1.3 Preparation of cyclisation substrates

Retrosynthetic analysis of the cyclisation substrates revealed that **267**, **268**, **270** and **271** could be accessed using a general route starting from γ-butyrolactone **278** (figure 2.6).

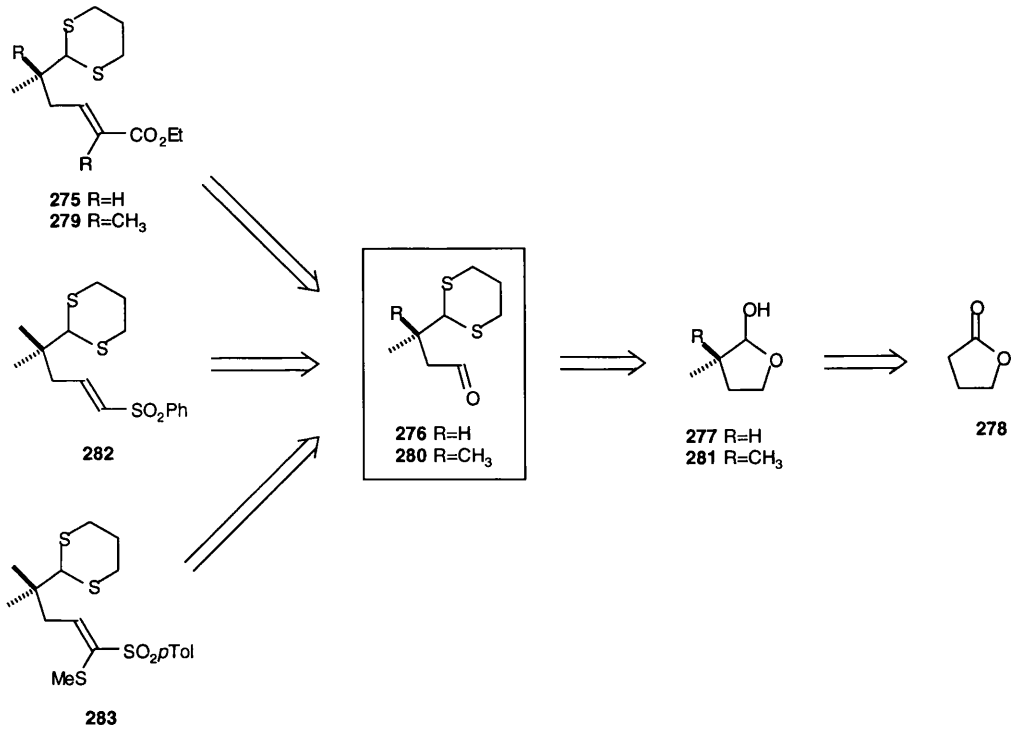


figure 2.6

Retrosynthetic analysis of aldehyde substrate **269** also revealed that it could also be prepared from γ-butyrolactone using similar transformations (figure 2.7).

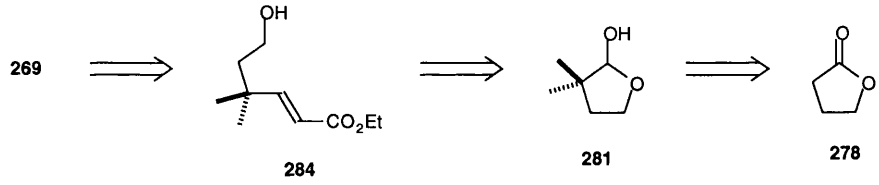
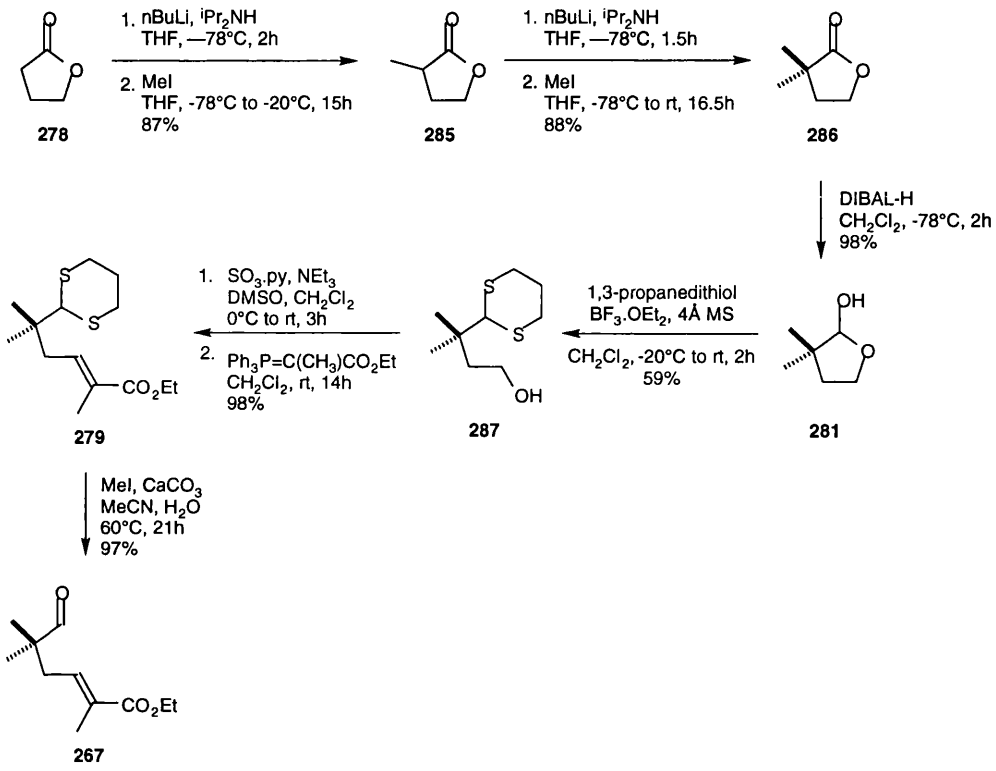


figure 2.7

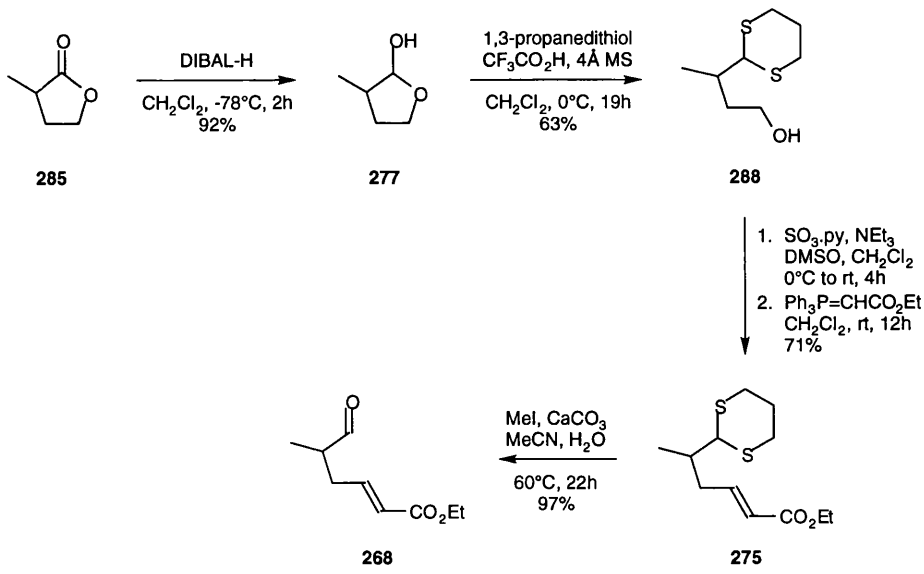
Aldehyde substrate **267** was first prepared. γ-Butyrolactone **278** was alkylated twice using LDA and MeI to give **286** in good yield. Lactone **286** was then converted to lactol **281** by DIBALH reduction.[139] Ring opening of the lactol with 1,3-propanedithiol to give alcohol **287** was first attempted in the presence of triflic acid,[140] however the yields for the reaction were not reproducible and were often unsatisfactory. When the protic acid was replaced with the Lewis acid, $BF_3.OEt_2$, the reaction was greatly improved giving the

alcohol **287** in good yield. Subjecting alcohol **287** to a one pot Parikh-Doering oxidation[141]-Wittig reaction sequence, gave the unsaturated ester **279** in excellent yield. The expected *E*-stereoisomer was formed exclusively. Removal of the thioacetal protecting group to unmask the aldehyde group was achieved by refluxing **279** in the presence of MeI and $CaCO_3$ in a 4:1 mixture of MeCN and H_2O.[142] Aldehyde **267** was obtained in almost quantitative yield and required no further purification (scheme 2.5).



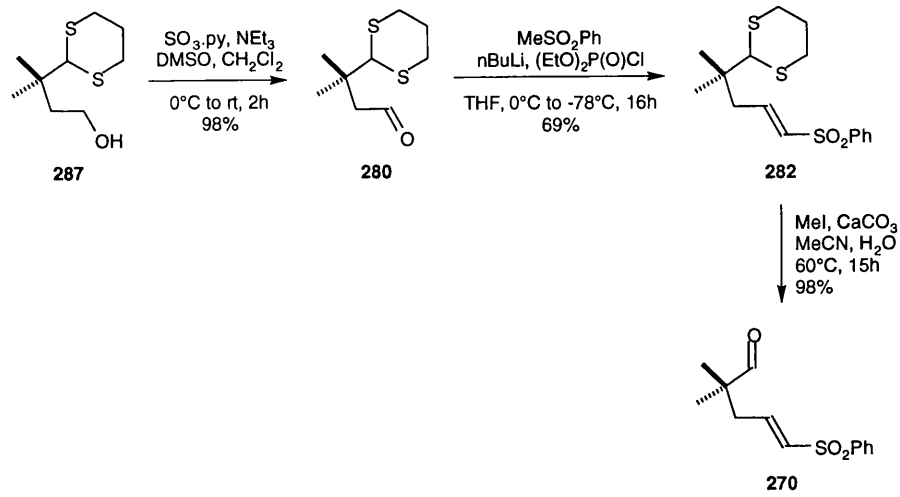
scheme 2.5

Aldehyde substrate **268** was prepared in a similar fashion with the exception that the lactone was only mono-methylated and a different Wittig reagent was used in the oxidation-olefination sequence (scheme 2.6).



scheme 2.6

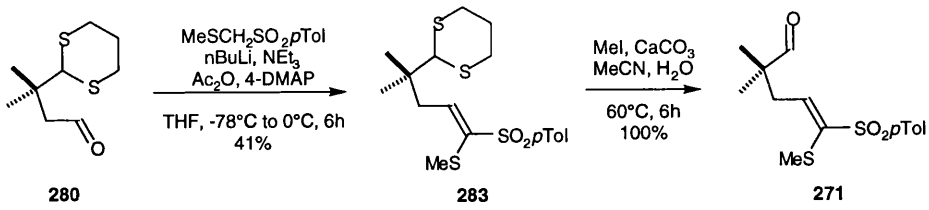
The preparation of the vinyl sulfone substrate **270** was next examined. Our approach utilised a stereoselective Horner-Wadsworth-Emmons reaction as the key transformation (scheme 2.7). Alcohol **287** was prepared using the route discussed earlier (scheme 2.5). Parikh-Doering oxidation of the alcohol gave the aldehyde **280**, which was isolated in good yield. Using conditions developed by Lee and Oh,[143] aldehyde **280** was treated with α-phosphorylated-α-lithio methyl phenyl sulfone, prepared *in situ* by the reaction of the dianion of methyl phenyl sulfone and diethylchlorophosphate. The reaction proceeded stereoselectively, giving exclusively the *E*-vinyl sulfone **282** in good yield, the *E*-geometry being assigned by analysis of the ^{1}H NMR coupling constants. Deprotection of the aldehyde was achieved using the same conditions as discussed previously and aldehyde **270** was obtained in almost quantitative yield, again, with no need for further purification.



scheme 2.7

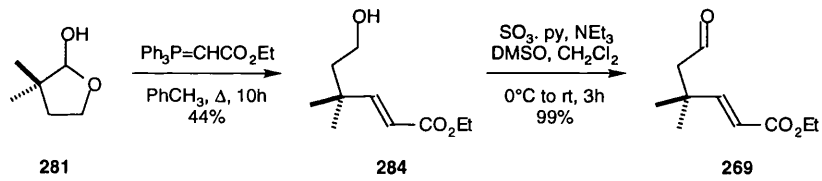
Aldehyde substrate **271** was prepared using an olefination reaction developed by Jackson and co-workers.[144] Aldehyde **280** was added to the stabilised anion formed from deprotonation of methylthio methyl *p*-tolyl sulfone with *n*BuLi (scheme 2.8). *In situ* acetylation and subsequent elimination gave a single double bond isomer, which we assumed to be the *E*-isomer from Jackson's precedent (Jackson assigned the *E*-geometry of his compounds by the chemical shift of the vinylic proton). The mediocre yield was disappointing but no attempts were made to optimise the reaction. It is possible the problem lay with the acetylation and elimination steps.

The subsequent deprotection step to give the aldehyde **271** was a concern due to the perceived similarity of the substituted vinyl sulfone and the thioacetal moieties. However, treatment of vinyl sulfone **283** under the usual conditions afforded the aldehyde **271** in quantitative yield with no chemoselectivity problems.



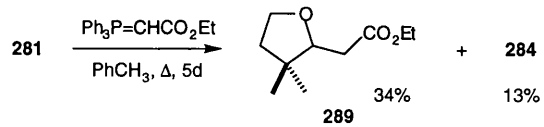
scheme 2.8

Finally, the preparation of aldehyde **269** was investigated. A Wittig reaction on the lactol **281**, which is in equilibrium with the hydroxy aldehyde, was expected to give the alcohol **284**. However, the transformation provided some interesting results. When the transformation was carried out in THF at room temperature, only starting material was recovered from the reaction mixture. The reaction was also attempted in refluxing CH_2Cl_2, however, again no reaction was observed. It is possible the *gem* dimethyl groups were hindering the Wittig reaction. The reaction was then attempted in refluxing toluene. After 10 h olefination occurred giving a low yield of the unsaturated alcohol **284** (scheme 2.9).



scheme 2.9

When the reaction was left refluxing for longer periods, the substituted tetrahydrofuran **289** was the major product arising from **284** by an intramolecular Michael addition (scheme 2.10).



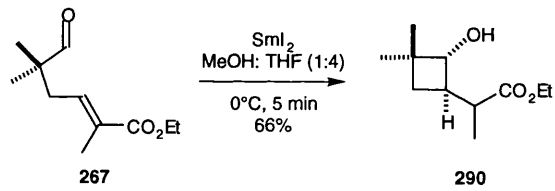
scheme 2.10

Fortunately, Patrikh-Doering oxidation of the unsaturated alcohol **284** was straight forward giving the aldehyde substrate **269** in excellent yield.

2.1.4 SmI_2 mediated 4-*exo*-trig cyclisations of substrates 267, 268, 269, 270 and 271

The SmI_2 solutions used in this study were prepared using a modification of Imamoto's method.[145] Samarium metal was dissolved in THF and iodine added. The solution was then heated at 60°C for 18h after which time a deep, dark blue solution of SmI_2 was obtained. We found these solutions could be stored for up to 3 days under Argon.

We first attempted the cyclisation of aldehyde **267**. After extensive studies, optimal conditions for the cyclisation were found to involve the addition of the substrate to a solution of SmI_2 (inverse addition) in THF, in the presence of excess MeOH (ratio of THF to MeOH, 4:1) as cosolvent (scheme 2.11). [146, 147]



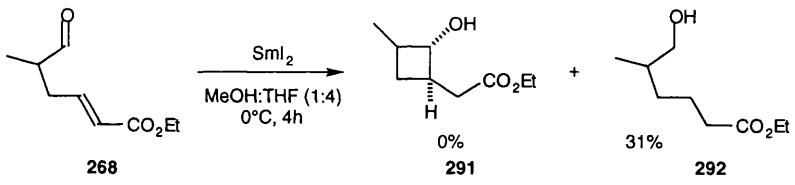
267 **290**

scheme 2.11

The MeOH serves not only as a proton source but also appears to promote cyclisation by increasing the reduction potential of samarium(II) iodide, a phenomenon which has been suggested by Curran,[148] but has since received little attention. Cyclisations carried out using EtOH or *tert*-BuOH as cosolvent were found to be considerably slower, and were only successful using the inverse mode of addition. The reaction followed a well defined stereochemical course to give exclusively the *anti* cyclobutanol **290** with no trace of the

corresponding *syn* product being detected. Significant stereochemical control at the third newly generated stereocentre was observed but will be discussed later in the chapter (section **2.1.5.1**).

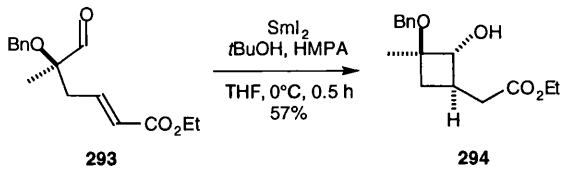
The cyclisation of the mono-methyl substituted aldehyde **268** was next examined. When treated with SmI_2 under the optimal conditions no cyclisation occurred. Instead, straight reduction of the aldehyde and carbon-carbon double bond took place to give the acyclic saturated alcohol **292** as the major product (scheme 2.12). Similarly, no cyclobutanol **291** was formed when the cyclisation was attempted in the presence of LiCl, an additive known to increase the reduction potential of SmI_2.[149] From this result we were able to conclude that the quaternary centre was an important factor for the success of the cyclisation.



268 **291** (0%) **292** (31%)

scheme 2.12

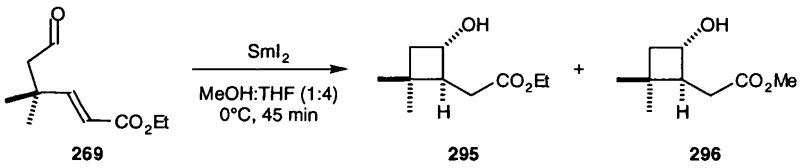
During this investigation, work carried out by another member of the group provided some interesting observations concerning the apparent need for *gem*-disubstitution (scheme 2.13). The aldehyde **293**, where a methyl group from **265** has been replaced by a benzyloxy group, was also treated with SmI_2. Cyclisation occurred in reasonable yield to give cyclobutanol **294** as a 5:1 ratio of diastereoisomers (scheme 2.13). The result is of interest as it reveals that *gem*-dialkyl substitution is not necessary for cyclisation. Work is currently underway in the group to develop new strategies for facilitating the cyclisation.



293 294

scheme 2.13

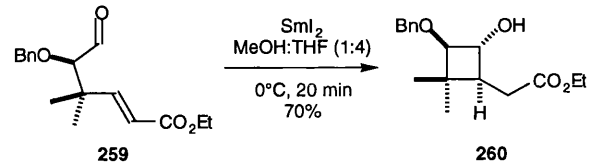
Having established the importance of the quaternary centre it appeared sensible to investigate the effect of the position of the quaternary centre. When aldehyde substrate **269** was treated with SmI_2 under the optimal conditions, a complex product mixture was obtained (scheme 2.14). Suprisingly, the major product isolated from the mixture was the methyl ester cyclobutanol **296**. It appears that trans-esterification occurred in the reaction either before or after the cyclisation. Interestingly, trans-esterification was rarely a problem in the cyclisation of other substrates. No further study of the reaction was undertaken, however, further work on the cyclisation is ongoing within the group.



269 295 296

scheme 2.14

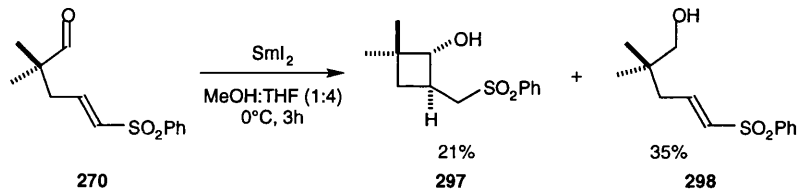
Scheme 2.15 again illustrates a reaction carried out by another member of the group but which is of interest here. In the aldehyde **259**, the *gem*-dimethyl group is in the β-position. When treated with SmI_2 under our optimum conditions, cyclisation occurred to give the corresponding cyclobutanol **260** in good yield (c.f. scheme 2.2).[59, 147] The result suggests that cyclisation occurs regardless of whether the *gem*-dimethyl group is in the α- or β- position of the substrate.



259 260

scheme 2.15

Following our studies on the effect of the quaternary centre, we began to investigate the feasibility of using different radical acceptors in the cyclisation. The vinyl sulfone **270** was treated with SmI_2 under our optimal conditions (scheme 2.16).



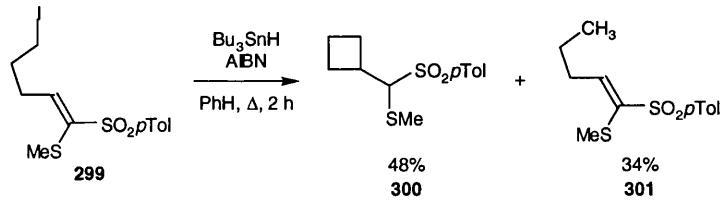
270 21% 297 35% 298

scheme 2.16

Cyclisation occurred to give the corresponding cyclobutanol **297**, however the reaction was considerably less efficient than the analogous cyclisations of α,β-unsaturated esters **265** and **267**. As expected, the reaction proceeded stereoselectively to give only the *anti* cyclobutanol product. Various cyclisation conditions were examined to improve the yield including the use of HMPA and HMPA/*tert*-BuOH cosolvent systems as well as different modes of addition, however, the alterations only increased the quantity of unsaturated alcohol **298** obtained. It was concluded that vinyl sulfones are generally less efficient than α,β-unsaturated esters as radical acceptors in the cyclisation.

We felt that the efficiency of vinyl sulfones as radical acceptors might be improved if an electron donating group were introduced α to the sulfone in the cyclisation substrates. A study by Ogura *et. al.* has demonstrated that the presence of a methylsulfanyl substituent α to the sulfone group resulted in a more efficient radical acceptor in a tin hydride mediated 4-*exo*-trig cyclisation of iodide **299** (scheme 2.17).[117] The efficiency of Ogura's

cyclisation was attributed to the formation of a cyclised radical stabilised by the captodative effect.[138]



scheme 2.17

We decided to prepare aldehyde **271** to see if such a strategy would be helpful in our SmI_2 mediated 4-*exo*-trig ketyl-olefin cyclisation. According to the captodative effectt (see Appendix 1) radicals positioned between an electron donating group and an electron withdrawing group, *i.e.* **303**, are more stable than the analogous radicals lacking one or other these substituents, *i.e.* **302** (figure 2.8). The reaction is reversible, therefore the greater stability of the cyclic radical should result in more of this ring closed radical existing at equilibrium, and hence more cyclobutanol product should be formed.

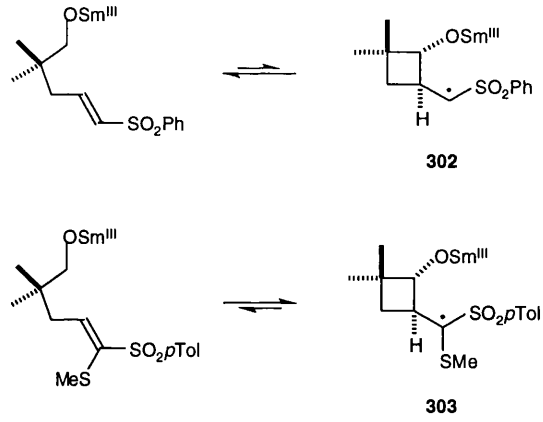
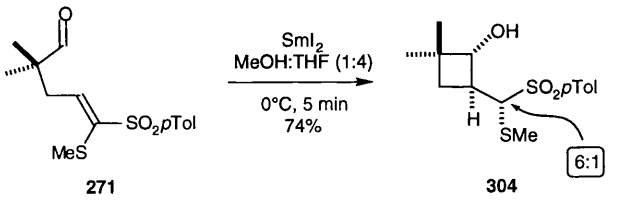


figure 2.8

When aldehyde **271** was treated with SmI_2 under our standard conditions, cyclisation occurred to give cyclobutanol **304** in high yield (scheme 2.18).



scheme 2.18

The reaction proceeded with good stereocontrol. Again, giving exclusively *anti* stereochemistry was obtained across the new C-C bond. Furthermore, good selectivity was observed at the 3rd new stereocentre, α- to the sulfone, with a 6:1 ratio of diastereoisomers being obtained.

The stereochemistry of the major diastereoisomer from the cyclisation was determined by X-ray crystallography (figure 2.9).

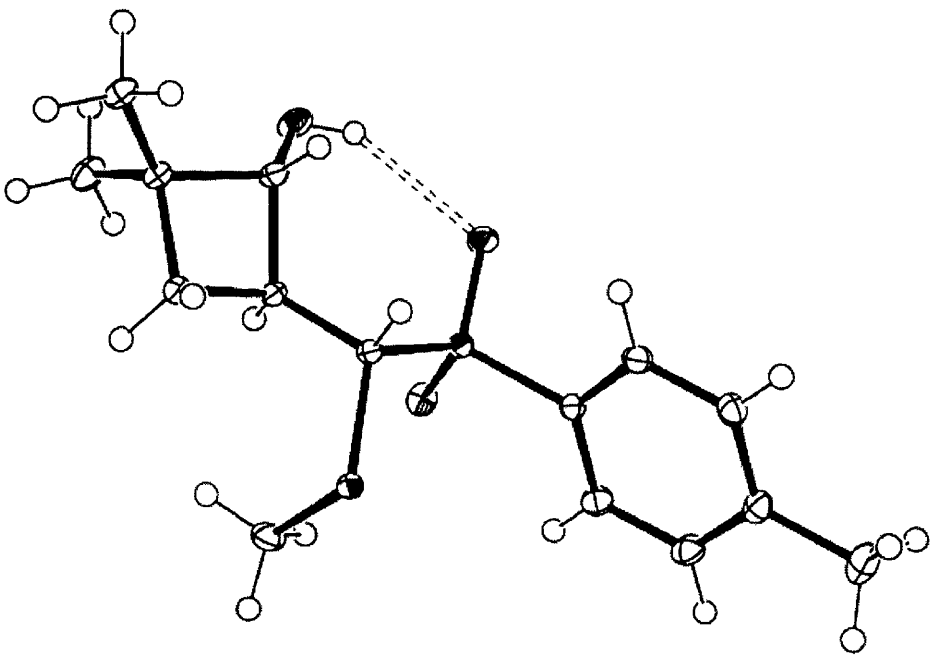


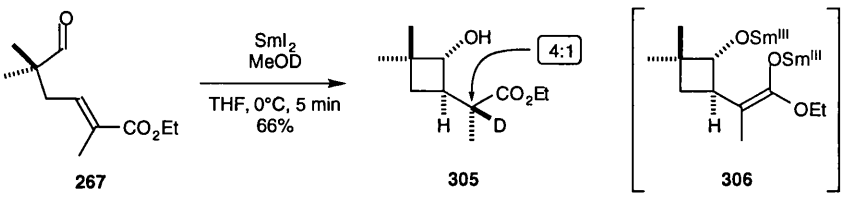
figure 2.9

Clearly, the cyclisation of the substituted vinyl sulfone **271** is far more efficient than the cyclisation of the unsubstituted vinyl sulfone **270**.

2.1.5 Investigation into the mechanism and diastereoselectivity of the cyclisation

2.1.5.1 Examination of the role of the cosolvent

When the cyclisation of **267** was carried out in MeOD, complete deuterium incorporation was observed α to the ester in the cyclobutanol product **305** (scheme 2.19). This clearly illustrates that protonation rather than hydrogen atom capture terminates the reaction. This agrees with the accepted two step two electron mechanism for ketyl-olefin cyclisation reactions with SmI_2,[50] although it does not rule out an anionic mechanism. [A mechanistically ambiguous, magnesium-mediated reductive cyclisation of ketones tethered to olefins bearing ester and nitrile groups has been reported].[150] In the cyclisation of **267**, protonation of the intermediate samarium(III) enolate **306** generates a third chiral centre. With MeOH as the cosolvent, we found that selectivities at this centre range from 4.5-3:1.

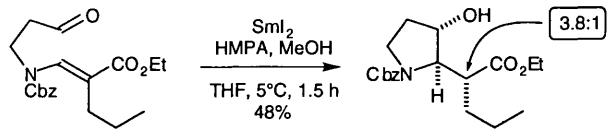


267 **305** **306**

scheme 2.19

Little is known about the stereochemistry of processes in which prochiral enolates, generated by radical addition to an olefin, followed by further reduction, react with

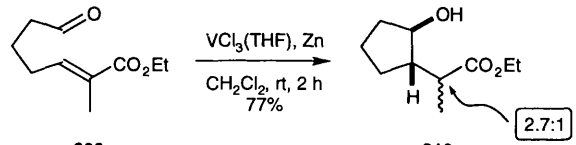
electrophiles. Recently, an analogous stereochemical issue involving a 5-*exo*-trig ketyl-olefin cyclisation of **307** mediated by samarium(II) iodide was discussed and selectivities slightly lower than our own were observed (scheme 2.20).[151]



307 **308**

scheme 2.20

In the vanadium(II) mediated ketyl-olefin cyclisation of aldehyde **309** by Torii *et. al.*, similar selectivities were again observed but not discussed (scheme 2.21).[152]



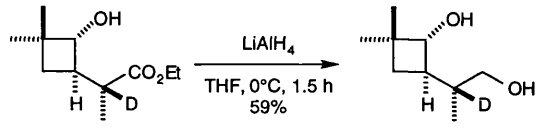
309 **310**

scheme 2.21

The intermolecular addition of alkyl radicals to α-substituted-α,β-unsaturated esters followed by reduction to enolates, mediated by zinc metal or cobalt complexes has also been studied.[153] This study concluded that the 1,2-asymmetric induction in enolate protonation was comparable to that observed for hydrogen atom capture in the same system. It was also observed that the stereoselectivity of protonation could be influenced to a small degree by the addition of amines.[153]

In investigating the cyclisation of **267**, we observed that the stereochemistry at the centre α- to the ester in the product cyclobutanols was highly dependent on the alcohol employed as the cosolvent in the cyclisation. As previously mentioned, cyclisation of **267** in MeOH led to a diastereoisomeric ratio of 4:1. Remarkably, however, when the reaction

was repeated using the same conditions but employing *tert*-BuOH as the cosolvent, the diastereoselectivity was reversed, favouring the other diastereoisomer by 2:1. In order to rationalise the observed diastereoselectivity, we sought to determine the stereochemistry of the major diastereoisomer from the cyclisation of **267** in MeOH. The major cyclobutanol was obtained by column chromatography and a crystalline derivative pursued. Unfortunately, both the 4-nitrobenzoate, and the 3,5-dinitrobenzoate esters of **305** were non-crystalline. However, reduction of **305** gave diol **311**, and subsequent sublimation of the low-melting solid gave crystals suitable for low temperature X-ray crystallographic analysis (scheme 2.22).



305 **311**

scheme 2.22

The X-ray structure clearly shows the *anti* stereochemistry across the new C-C bond and the stereochemistry at the position that was α- to the ester in the major cyclobutanol **305** (figure 2.10).

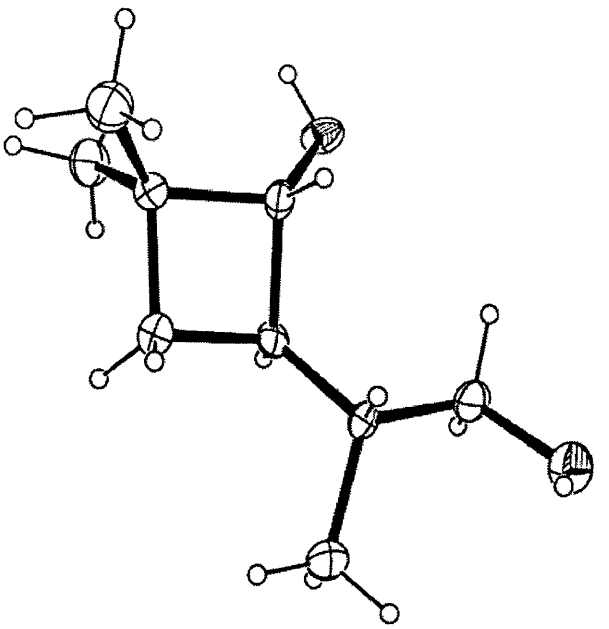
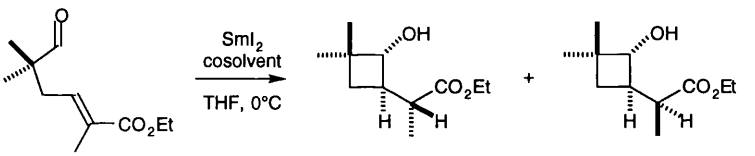


figure 2.10

With the relative stereochemistry of the major cyclobutanol from the cyclisation of **267** in MeOH established, the cyclisation of **267** using a variety of cosolvents under otherwise identical conditions was then carried out and the diastereomeric ratio α- to the ester determined (Table 1).



267 **290a** **290b**

cosolvent	additive	time[a]	ratio of **290a**:**290b**[b]	isolated yield of **290** (%)
H_2O		< 1 min	5:1	44 %
MeOH		5 min	4:1	66 %
MeOH	HMPA[c]	5 sec	4:1	35 %
EtOH		1 hr 25 min	1:1	84 %
tert-BuOH		9 hr	1: 2	53 %

table 1: *Reaction conditions*: **267** in THF (0.25 M) was added to a solution of SmI_2 (0.1 M in THF, 2 eq and cosolvent (123 eq) (+ additive) at 0°C. [a] Time taken for SmI_2 to decolourise. [b] From crude ^1H NMR. [c] 12 eq added.

The use of water as an additive gave the highest selectivities under these specific conditions, and the fastest reaction, as indicated by the time taken for the samarium(II) iodide solution to decolourise. Unfortunately, additional products arising from over-reduction prior to cyclisation were formed. The use of EtOH gave a slower reaction and a 1:1 mixture of diastereoisomers **290a** and **290b** was formed. As previously mentioned, when *tert*-BuOH was employed as a cosolvent, the reaction was extremely slow and showed a switch in selectivity in favour of cyclobutanol **290b**.

A possible explanation for the cosolvent dependency of the stereochemistry, lies in the degree of solvation about the samarium(III) centres in the key samarium(III) enolate intermediate. In figure 2.11 two possible conformations, A and B, of the intermediate samarium(III) enolate are shown.

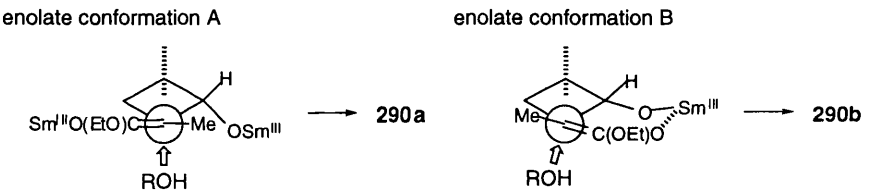


figure 2.11

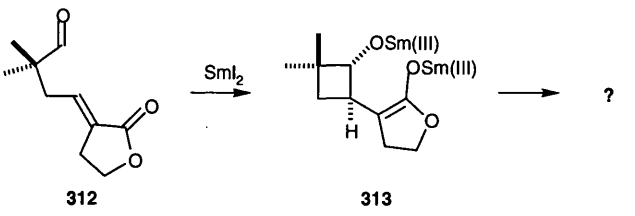
In the absence of strongly co-ordinating solvents, chelation of the lanthanide centre to both the alkoxide on the cyclobutane ring and the enolate would be expected to lock the system in conformation B. Protonation of the intermediate whilst in conformation B would lead to cyclobutanol **290b**. In highly co-ordinating solvents, such as water and methanol, however, this chelation will be disrupted and conformation A will predominate, due to electronic and steric factors.[154] Protonation of the intermediate whilst in conformation A will lead to cyclobutanol **290a**. Hence, the reactions in EtOH and *tert*-BuOH show a gradual swing towards enolate conformation B as chelation becomes more

important. This is only one of several possible explanations and further studies are needed to explore this issue further.

An additional observation that the cyclisation of **267** in the presence of only 4 equivalents of MeOH gave a low yield of cyclobutanol **290** as a 1:1 ratio, not only supports these ideas but also shows the importance of excess alcohol for activation of SmI_2 and thus, efficient reaction.

2.1.5.2 Does the geometry of the intermediate samarium(III) enolate influence the diastereoselectivity of cyclisation?

We were concerned that the cosolvent driven switch in diastereoselectivity observed in the cyclisation of **267** might be the result of a switch in enolate geometry in the intermediate samarium(III) enolate. We therefore felt it was important to investigate the role of the samarium(III) enolate geometry in the process. The cyclisation substrate **312** was devised where the geometry of the enolate intermediate **313** would be locked (figure 2.12). If the cyclisation of **312** in MeOH and *tert*-BuOH showed a similar switch in diastereoselectivity, then any role ascribed to the geometry of the samarium(III) enolate could be discounted.

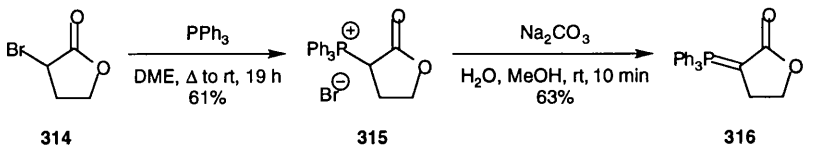


312 **313**

figure 2.12

For the preparation of the aldehyde **312**, it was necessary to prepare the literature phosphonium ylide **316** which could then be used in a Wittig reaction on our key

aldehyde **280** (scheme 2.23).[155] Treatment of α-bromo-γ-butyrolactone **314** with triphenylphosphine in refluxing DME gave, after recrystallisation, the phosphonium bromide salt **315**. Subsequent treatment of **315** with Na_2CO_3 gave the ylide **316** in good yield.



314 **315** **316**

scheme 2.23

One pot Parikh-Doering oxidation and Wittig reaction, using **316**, on alcohol **287** gave the corresponding unsaturated thioacetal **317** as a 4:1 ratio of stereoisomers, which were separated by column chromatography (scheme 2.24). To help establish the stereochemistry of the major product, nOe studies were undertaken and confirmed the major product to possess *E*-double bond stereochemistry (figure 2.13). Removal of the thioacetal protection was achieved using the deprotection conditions described previously and gave the cyclisation substrate **312** in excellent yield.

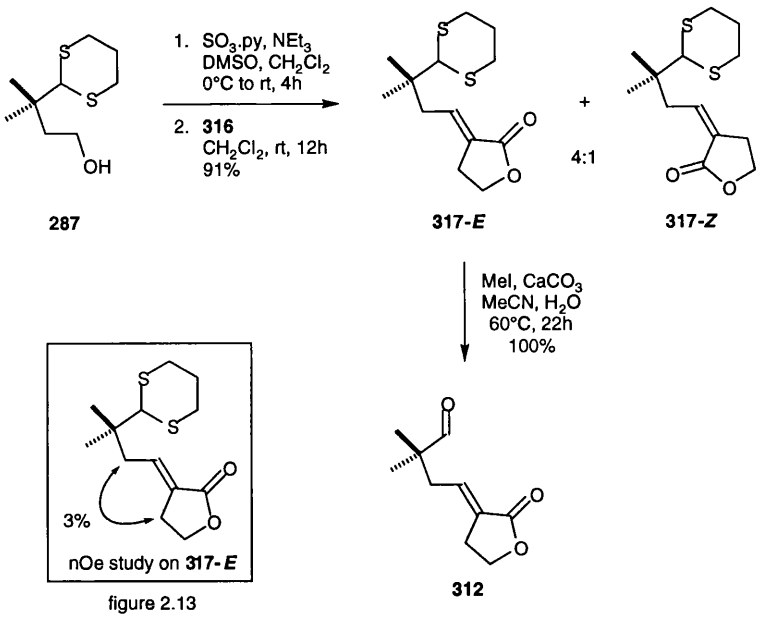
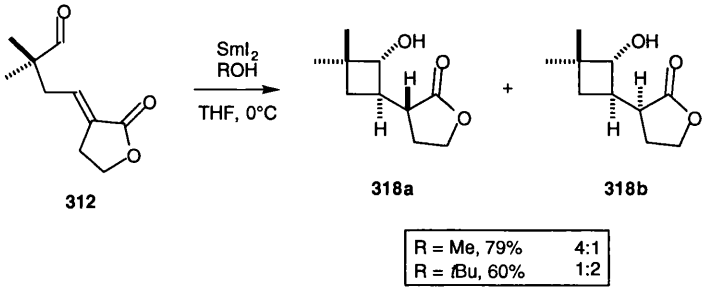


figure 2.13

scheme 2.24

When aldehyde **312** was treated with SmI_2 in the presence of MeOH, cyclisation occurred to give *anti* cyclobutanol **318** in good yield (scheme 2.25). As with the cyclisation of aldehyde **267**, a 4:1 ratio of diastereoisomers in favour of cyclobutanol **318a** was obtained. Significantly, when the cosolvent was changed to *tert*-BuOH and the cyclisation repeated, a switch in stereoselectivity in favour of cyclobutanol **318b** was observed.



scheme 2.25

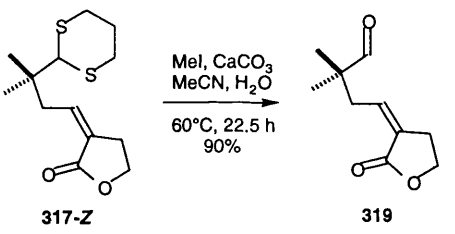
As previously noted, in this cyclisation the intermediate samarium(III) enolate geometry is locked. Since a similar cosolvent dependency is observed in this cyclisation when

compared to that of **267**, it appears that enolate geometry is not an important factor in the variation of product stereochemistry with solvent.

2.1.5.3 Does double bond stereochemistry influence the diastereoselectivity of the cyclisation?

In order to assess the effect of the initial double bond geometry on the stereochemistry of the cyclisation, we next examined the cyclisation of **319** (Scheme 2.26).

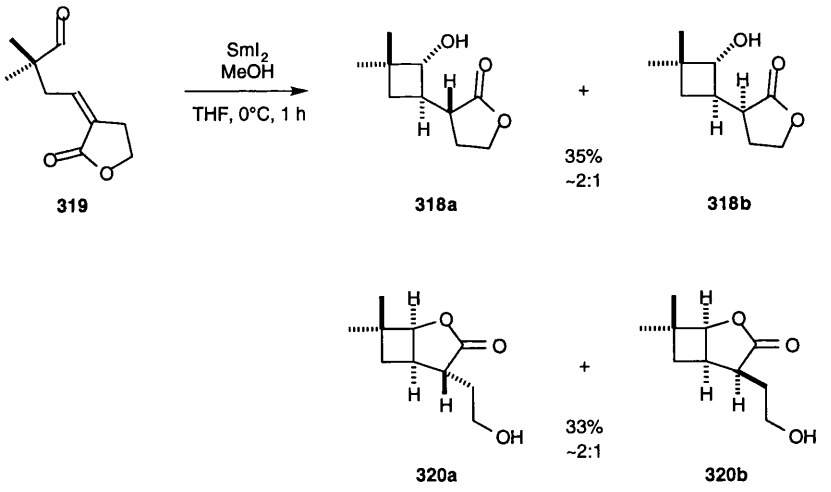
Thioacetal **317-Z** was obtained as the minor stereoisomer from the Wittig reaction in the synthesis of aldehyde **312** (see scheme 2.24). Removal of the aldehyde protecting group as before gave the cyclisation substrate **319** in good yield.



317-Z **319**

scheme 2.26

Interestingly, cyclisation of **319** gave a complex mixture of products (scheme 2.27). In stark contrast to the complete *anti*-selectivity observed in the cyclisation of **312**, a 1:1 mixture of *syn* and *anti*-cyclisation products was obtained, the *syn* products undergoing spontaneous trans-lactonisation to give bicyclic lactones **320**. In addition, approximately 2:1 mixtures at the centre α to the lactone carbonyl group were also obtained.



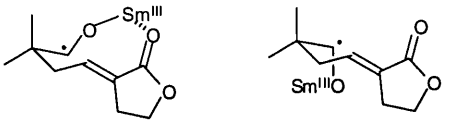
319 318a 318b 320a 320b

scheme 2.27

It is therefore clear that the initial double bond stereochemistry has a profound effect on the relative stereochemistry across the newly formed ring junction but has a less dramatic effect on the stereochemistry α to the lactone carbonyl group. Enholm first observed a marked dependence of diastereoselectivity on the olefin-geometry in samarium(II)-mediated reductive cyclisations to form 5-membered carbocycles.[156-158] Identification of the products from the cyclisation was facilitated by the preparation of both bicyclic lactones **320a** and **320b** independently (see section **2.2.6**).

The observed stereochemical outcome from the cyclisation of **319** can be explained by considering pre-association of the Sm(III) of the ketyl-radical anion with the ester carbonyl. On treatment of **312** with SmI_2, the *anti* transition structure **321** is favoured over the *syn* transition structure **322** for two reasons (figure 2.14). Firstly, the structure is favoured due to electronic repulsion between the lone pairs of electrons on the oxygen and the developing methylene radical, as previously discussed in section **2.1.1**. Secondly, it appears likely that a 9-membered ring chelate is formed prior to cyclisation: Sm(III) of the ketyl-radical anion coordinating to the carbonyl of the lactone. Such chelation is only possible in the *anti* arrangement **321**. It is plausible that this chelation to the Lewis acidic

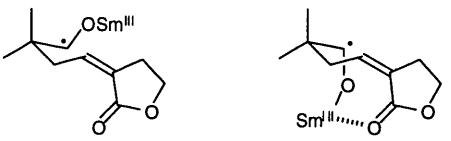
samarium(III) centre also activates the enoate to radical addition, thus enhancing the preference for structure **321** over the *syn* structure **322**. Thereby, only *anti* cyclobutanol products are obtained from the reaction of the *E*-substrate **312**.



anti **321** *syn* **322**

figure 2.14

However, in the cyclisation of **319**, there is no clear preference for either transition state. In the *anti* transition structure **323**, although the electronic arguments are satisfied, chelation between the Sm(III) of the ketyl-radical anion and the ester carbonyl cannot easily occur (figure 2.15). The *syn* transition structure **324**, on the other hand, does not satisfy the electronic arguments but can form a 9-membered chelate with samarium(III). The overall result is a mixture of *anti* and *syn* cyclobutanol products as no transition state is significantly favoured over the other.



anti **323** *syn* **324**

figure 2.15

2.1.6 Conclusions

The SmI_2 mediated 4-exo-trig cyclisation of unsaturated aldehydes has been shown to be an efficient and mild method for the preparation of functionalised cyclobutanols. The methanol cosolvent has an important role in the cyclisations and appears to activate SmI_2, hence removing the need for the highly carcinogenic additive HMPA. In all cases, where the olefin has *E*-geometry, the reaction has been shown to proceed with complete *anti* selectivity across the newly formed C-C bond. However, the cyclisation of the *Z*-olefin substrate **319** proceeded to give a mixture of *syn* and *anti* cyclobutanols, clearly showing the importance of olefin geometry in the cyclisation.

The importance of *gem*-disubstitution in the reaction was demonstrated by the failure of substrate **268** to undergo cyclisation. Furthermore the position of the *gem*-disubstitution has been shown to be of importance by the inefficient cyclisation of **269**. However, the successful cyclisation of **259** highlights that disubstitution need not be *dialkyl* substitution. Work is currently underway in the group to find other strategies for facilitating the cyclisation.

α,β-Unsaturated esters were shown to be more efficient radical acceptors in the cyclisation than the corresponding vinyl sulfones. Furthermore, the cyclisation of aldehyde **271** has illustrated how the captodative effect can be exploited to increase the efficiency of the 4-*exo*-trig cyclisation.

Mechanistic studies on the cyclisation of **267** have shown that the reaction progresses *via* a samarium(III) enolate intermediate. Furthermore, in the cyclisation of substrates **267**, **271** and **312** we have observed significant stereocontrol with respect to the third newly generated stereocentre. Further studies on the cyclisation of **267** have illustrated the

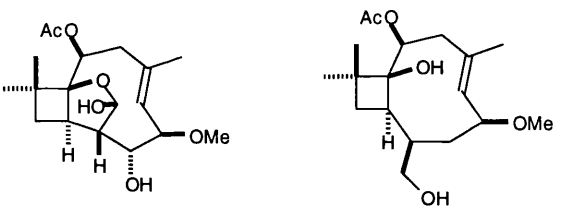
importance of the cosolvent in controlling the stereochemical outcome at this centre, and an attempt to rationalise the observed cosolvent dependency of stereochemistry has been made.

Finally, in the cyclisation of **312** we have clearly shown that the stereochemical dependency on cosolvent does not originate from a change in the stereochemistry of the intermediate Sm(III) enolate.

2.2 A stereocontrolled approach to the core of pestalotiopsin A

2.2.1 Introduction to pestalotiopsin A

The pestalotiopsins are caryophyllene-type sesquiterpenes isolated from an endophytic fungus of *Taxus brevifolia*, the Pacific yew tree.[111, 112] They were first isolated as a result of an intensive screening programme examining secondary metabolites of the tree and associated microorganisms, triggered by the discovery of the potent anti-cancer agent Taxol®. Pestalotiopsin A **261** is of particular interest as it possesses an oxatricylic structure unique amongst natural products and has a high density of functionality around the ring system (figure 2.16). [Kende has reported a synthetic intermediate with a related structure].[159] In addition, the compound has six stereocentres on six contiguous centres all combining to make the structure a challenging target for total synthesis. In preliminary assays the natural product has been shown to possess immunosuppressive activity and cytotoxicity.[112] It would appear possible that the activity of this compound originates from the 2-oxabicyclo[3.2.0]heptan-3-ol core, as pestalotiopsin B **325**, which lacks this structural feature, has no reported activity (figure 2.16).



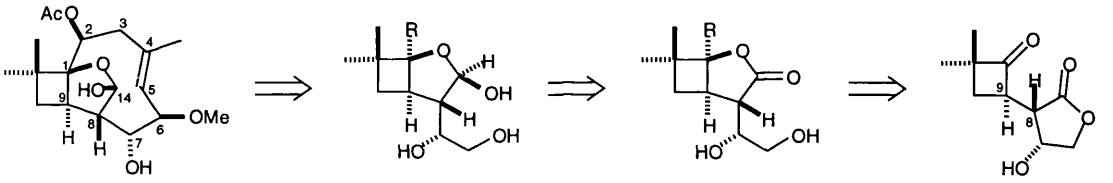
pestalotiopsin A **261**

pestalotiopsin B **325**

figure 2.16

2.2.2 Retrosynthetic analysis of the natural product

Retrosynthetic analysis of pestalotiopsin A (figure 2.17) reveals possible disconnections of the 9-membered ring at several points between C1 and C6 (pestalotiopsin A numbering scheme). Disconnections between C3 and C4, or across the C4-C5 double-bond appear particularly attractive and approaches to the final ring will be discussed later. Bicyclic lactones **327**, therefore, are key intermediates in our approach to pestalotiopsin A. Importantly, flexibility in the nature of the 'R' group is crucial for the examination of several future approaches to the final, 9-membered ring.



261 **326** **327** **328**

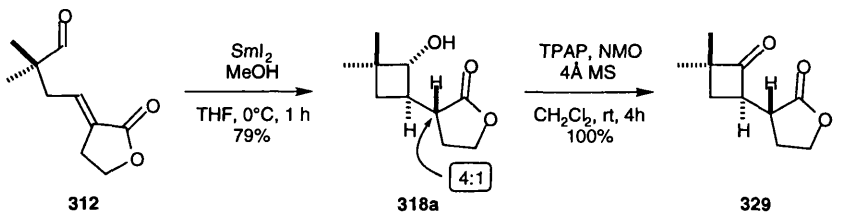
figure 2.17

We envisaged that the addition of alkylmetal reagents to cyclobutanone **328** would proceed selectively from the opposite face to the lactone substituent,[159, 160] triggering trans-lactonisation and releasing the hydroxyethyl side chain necessary for the construction of the final ring. We felt that cyclobutanones such as **328**, would be accessible using our previously described samarium(II) cyclisation chemistry. A feature of our strategy is that stereocentres at C8 and C9 can be established directly in the samarium(II)-cyclisation step and carried intact through the addition / trans-lactonisation sequence.

In this chapter I will describe studies which illustrate the feasibility of our approach and represent the first synthetic approach to the core of pestalotiopsin A[161].

2.2.3 Model studies in our approach to pestalotiopsin A

As previously mentioned in section **2.1.5.2** (scheme 2.25) the SmI_2 mediated cyclisation of aldehyde **312** proceeded in good yield and gave *anti* cyclobutanol **318** as a 4:1 mixture at the centre α- to the lactone carbonyl. In this reaction three contiguous stereocentres are established in a single step with significant control. We felt cyclobutanone **329** would be an excellent model compound for our studies since it lacked only the hydroxy functionality at C7 (compare with **328** in figure 2.17). The major cyclobutanol diastereoisomer was isolated by column chromatography and subsequent oxidation of **318a** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) gave cyclobutanone **329** in quantitative yield (scheme 2.28).



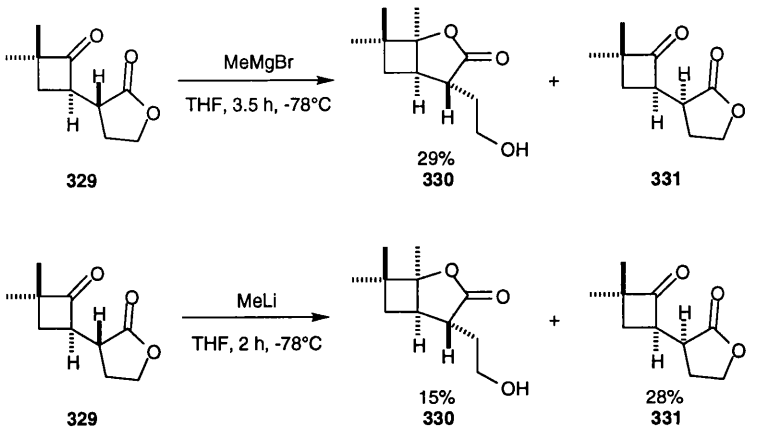
scheme 2.28

2.2.4 Alkylmetal additions to cyclobutanone 329

We next turned our attention to the sequential nucleophilic addition / trans-lactonisation step. We began by examining the addition of simple alkylmetal reagents to cyclobutanone **329**.

Initial attempts to add MeMgBr and MeLi to **329** led to substantial epimerisation of the starting material, giving cyclobutanone **331**, although pleasingly, the desired bicyclic

lactone **330** was also obtained in low yield (29% and 15%, respectively; see scheme 2.29 and table 2).



329 **330** **331**

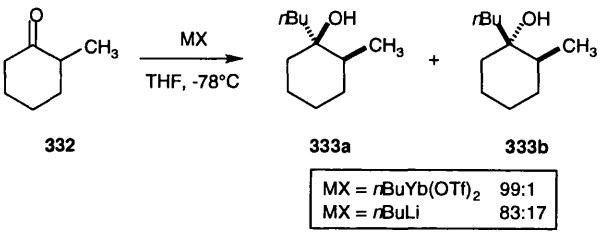
scheme 2.29

Organocerium reagents are renowned for their low basicity and hence were next investigated.[162] **329** was added to the methyl cerium reagent generated from the addition of MeLi to $CeCl_3$. A poor yield of the desired bicyclic lactone **330** was obtained, although crucially, epimer **331** was not detected. Since a large percentage of unreacted cyclobutanone was recovered from the organocerium reaction, the addition was repeated using 2 equivalents of methylcerium reagent. A slightly lower yield of the desired bicyclic lactone **330** was recovered along with unreacted starting material. A quantity of unknown by-product was also detected. The use of an even larger excess of methylcerium reagent gave even lower yields of desired product **330**.

It should be noted that the organocerium reactions were conducted by inverse addition following literature procedures.[163] Cyclobutanone **329** was therefore initially exposed to a large excess of the organocerium reagent. It is possible that after the desired addition reaction has taken place, the bicyclic lactone **330** is then reacting further with the excess methylcerium reagent. We believed that the reaction should be performed by *normal*

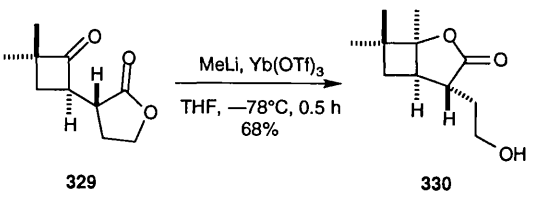
addition of the organocerium to the substrate. This was attempted, however, the heterogeneous nature of the organocerium made such a procedure problematic and the results were often irreproducible. We therefore sought alternative conditions for the transformation.

Molander has reported that organoytterbium reagents, prepared by the addition of alkyl lithium or Grignard reagents to ytterbium(III) triflate exist as brightly coloured, homogeneous solutions in THF and are attractive alternatives to organocerium reagents.[164-166] Such reagents have also been shown to give enhanced diastereoselectivities, when compared to the parent organolithium and magnesium reagents in additions to simple carbonyl compounds (scheme 2.30).



scheme 2.30

Using Molander's approach, the methylytterbium reagent derived from MeLi and $Yb(OTf)_3$ added smoothly to cyclobutanone **329** to give **330** in good yield and with no trace of epimerised by-product (scheme 2.31 and table 2). It was essential that the $Yb(OTf)_3$ used in the reaction (commercially available "anhydrous" $Yb(OTf)_3$) was dried thoroughly by heating at 140°C under vacuum for 20 h.



scheme 2.31

Organometallic reagent	Number of equivalents	reaction time (h)	yield of **330**
MeMgBr	1.2[a]	3.5	29%
MeLi	1.2	2	15%[b]
"$MeCeCl_2$"	1.3	2	53%[c]
"$MeCeCl_2$"	2	3	49%[c]
$MeYbOTf_2$	2	0.5	68%

table 2: (a) a further 1.2 equivalents of MeMgBr were added after 2 h. (b) 28% of epimerised starting material recovered. (c) isolated yields based on recovered starting material.

To confirm the stereochemistry of the bicyclic lactone products, nOe studies were initially conducted on **330** (figure 2.18).

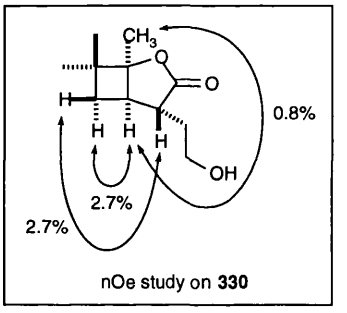
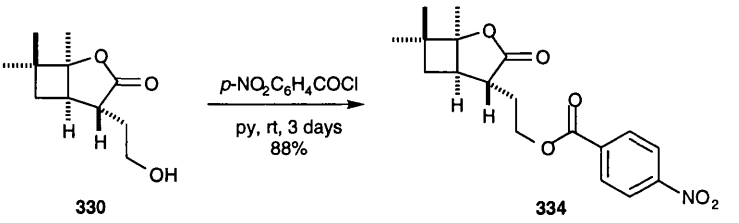


figure 2.18

Further confirmation of the stereochemistry of **330** was obtained by the conversion of **330** into the corresponding *p*-nitrobenzoate **334** and structure determination by X-ray crystallography (scheme 2.32).



scheme 2.32

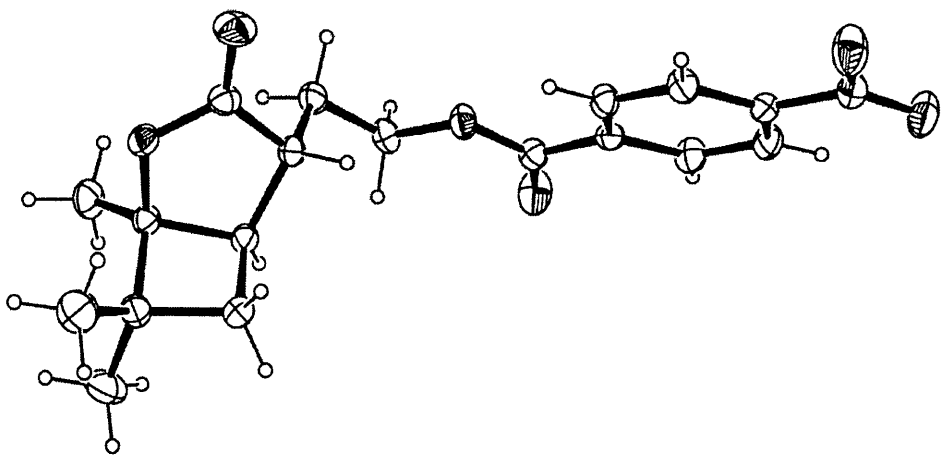
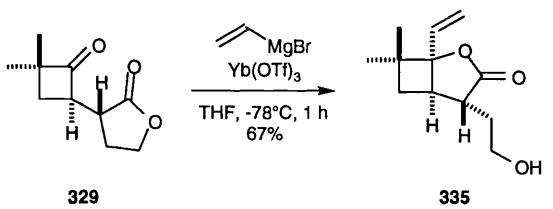


figure 2.19

Building on the successful addition of the methylytterbium reagent, the addition of more structurally and functionally diverse organoytterbiums was examined. Orange-red vinylytterbium, generated from vinylmagnesium bromide and $Yb(OTf)_3$ was added to the cyclobutanone **329**. Addition and *in situ* trans-lactonisation occurred to give bicyclic lactone **335** in good yield.

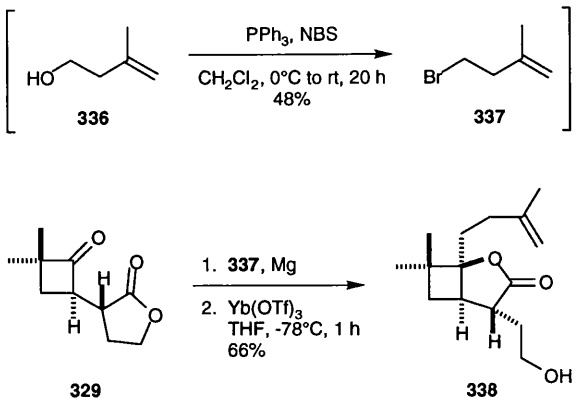


329 **335**

scheme 2.33

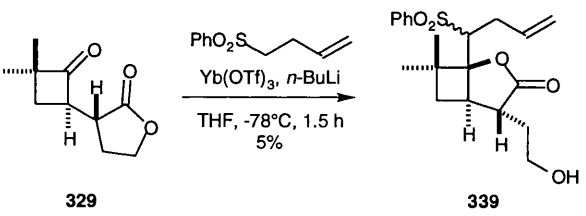
Next we attempted to use the organoytterbium, generated from 3-methyl-3-butenylmagnesium bromide. The bromide **337** was conveniently prepared from the corresponding commercially available alcohol **336**.[167] Treatment of the bromide with magnesium metal formed the Grignard which was then added to $Yb(OTf)_3$. After the *inverse* addition of the cyclobutanone, bicyclic lactone **338** was isolated in good yield

(scheme 2.34). It is thought that the reaction did not go to completion due to the incomplete formation of the Grignard from the bromide precursor. Work is ongoing within the group to improve the yield of the reaction.



scheme 2.34

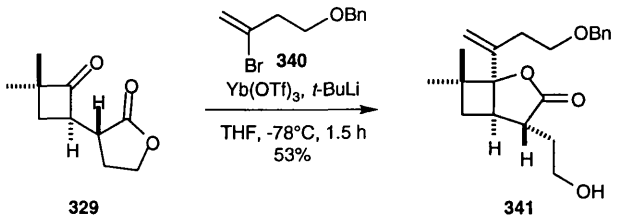
The possibility of using an alkylytterbium generated from an α-lithiated sulfone in the addition trans-lactonisation sequence was also examined. 3-Butenyl phenyl sulfone was deprotonated with *n*-butyllithium and then added to $Yb(OTf)_3$, generating an orange coloured solution. On addition to cyclobutanone **329** the desired bicyclic lactone **339** was formed as a mixture of diastereoisomers in very low yield amongst a complex product mixture (scheme 2.35).



scheme 2.35

To further increase the number of possible strategies with regard to the closure of the final 9-membered ring, an organoytterbium incorporating a protected hydroxyl group was required. Lithium-halogen exchange on treatment of vinyl bromide **340** with *tert*-BuLi,

followed by addition of $Yb(OTf)_3$ gave an intense red/brown solution of the corresponding organoytterbium which underwent addition to cyclobutanone **329** to afford **341** in moderate yield (scheme 2.36).[168]



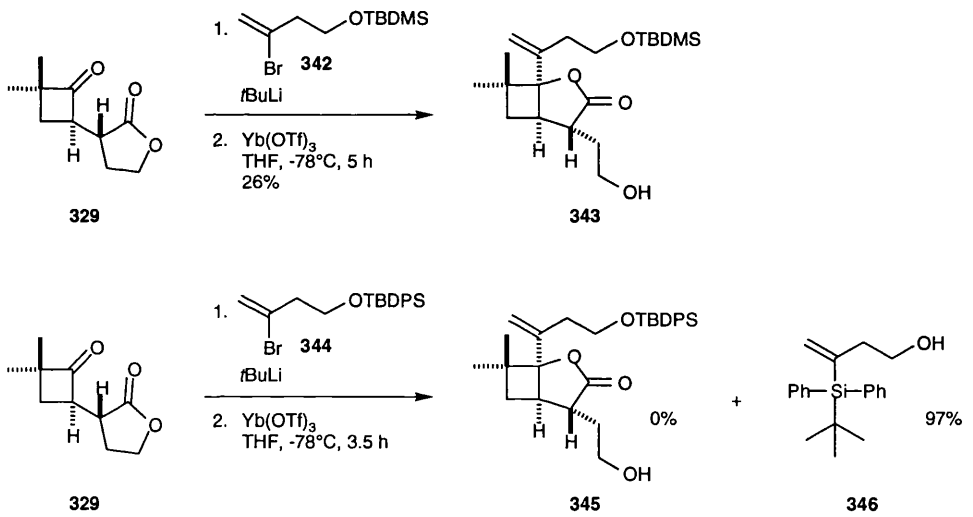
329 **341**

scheme 2.36

Clearly, by varying the alkylmetal reagent employed in our addition / trans-lactonisation procedure, a wide range of substrates accommodating a variety of approaches to the final 9-membered ring can be accessed.

2.2.5 The retro-Brook rearrangement

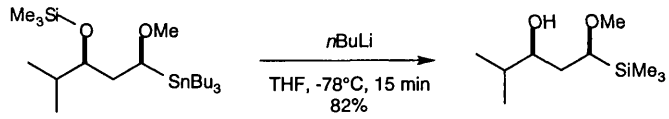
In the course of studying the reaction shown in scheme 2.36 we made some interesting observations. Originally we employed bromide **342** where the hydroxyl group was protected by the *tert*-butyldimethylsilyl protecting group. When the organoytterbium was formed and added to **329** a complex mixture of products was obtained from which bicyclic lactone **343** was obtained in low yield (scheme 2.37). The reaction was repeated using bromide **344** containing bulkier and more robust *tert*-butyldiphenylsilyl protection. Suprisingly none of the expected bicyclic lactone **345** was detected and the cyclobutanone **329** was recovered in good yield. Interestingly, a product from the reaction, derived from bromide **344**, was found not to correspond to the quenched organometallic and was isolated and identified as the vinyl silane **346** (scheme 2.37).



scheme 2.37

It appears facile migration of the silyl group from oxygen to carbon is occurring. Such an anionic 1,4-O to C silyl migration has been previously documented and is known as the retro-Brook rearrangement.[169] The retro-Brook rearrangement was first reported by West

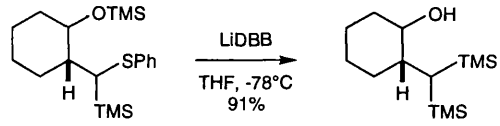
in 1968 and involves the migration of a silyl group from oxygen to a carbon.[170, 171] Examples of [1,2],[172] [1,3],[170, 171] and [1,4][169, 173, 174] migrations have all been reported in the literature and, as the example in scheme 2.38 illustrates, the migration occurs stereoselectively with retention of stereochemistry at the carbanion.[175]



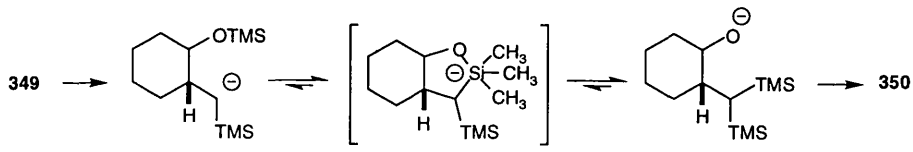
347 **348**

scheme 2.38

It is believed the 1,4-O to C migration proceeds through a 5-membered ring silicate. In a paper by Rücker which discusses the 1,4-O to C migration, he proposes the intermediacy of the pentacoordinate silicon species **351** in the retro-Brook rearrangement of **349** (scheme 2.39).[169]



349 **350**

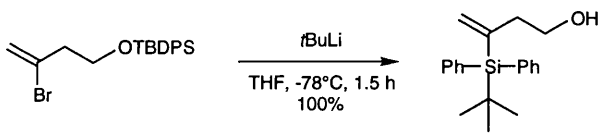


351

scheme 2.40

Lithium-halogen exchange on the tertiarybutyldimethylsilyl protected alcohol **342** has been previously reported, with no mention of the retro-Brook rearrangement which we had observed. We initially felt, therefore, that transmetallation to 'Yb' might play a significant role in the process, and so decided to investigate further. However, when

bromide **344** was subjected to lithium-halogen exchange with *tert*-butyllithium, after a short period of time and in the absence of $Yb(OTf)_3$, the retro-Brook rearrangement product was obtained in almost quantitative yield (scheme 2.41). Thus it is clear transmetallation to ytterbium plays no significant role in the retro-Brook rearrangement. It is not clear why rearrangement products were not observed in previous work using the vinyllithium derived from **342**.

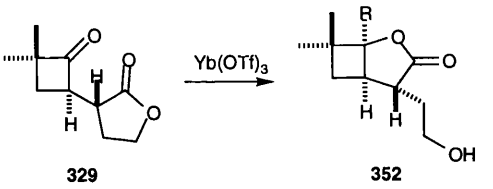


344 **346**

scheme 2.41

2.2.6 A summary

To summarise then, table 3 shows the successful alkylytterbium additions to cyclobutanone **329** and illustrates the versatility of our route to bicyclic lactones of generic structure **352**.

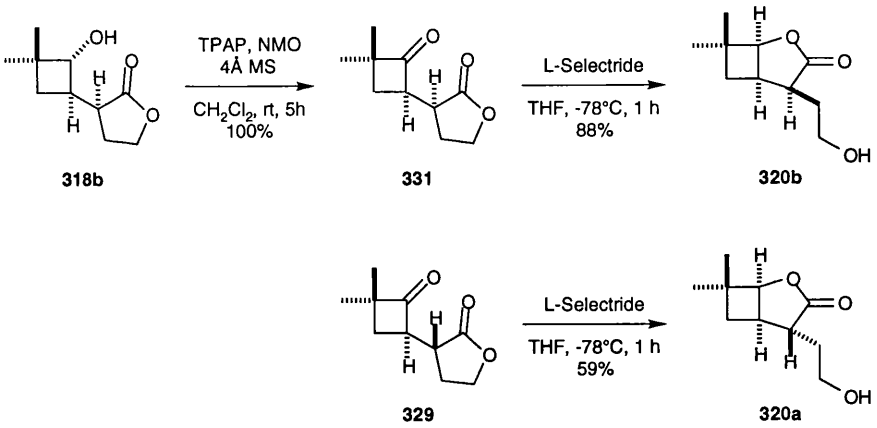


329 352

alkyl metal	product	yield
MeLi	**330** R = Me	68%
BrMg	**335** R =	67%
MgBr	**338** R =	66%
PhO_2S Li	**339** R = PhO_2S	5%
OBn Li	**341** R = OBn	53%

table 3: a summary of alkylytterbium additions to cyclobutanone **329**

A similar addition/trans-lactonisation procedure was also observed when reducing cyclobutanone **329** with L-Selectride (scheme 2.42). Reduction of cyclobutanone **329** and its diastereoisomer **331** with L-Selectride at —78°C was found to give bicyclic lactones **320a** and **320b** respectively. Cyclobutanone **331** was obtained from the TPAP oxidation of the cyclobutanol **318b**.



318b 331 320b

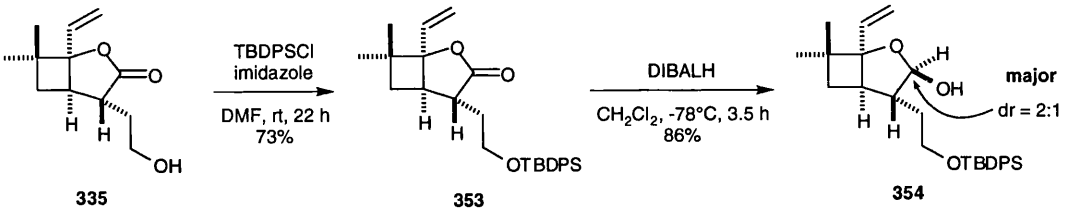
329 320a

scheme 2.42

The successful formation of bicyclic lactones **320a** and **320b** confirmed our assignment of the products from the SmI_2 mediated cyclisation of aldehyde **319**, discussed previously in section **2.1.5.3** (scheme 2.27).

2.2.7 Reduction of the lactone carbonyl group

To complete our approach to models of the pestalotiopsin A core, the primary hydroxyl group of **335** was protected, and the lactone **353** reduced to the lactol **354**. Treatment of the lactone with DIBAL-H gave a 2:1 mixture of lactols (scheme 2.43). We envisaged that the major product would arise from reduction from the 'outside' of the bicyclic system. NOE studies on the lactols did indeed reveal that **354** was the major product from the reduction (figure 2.20). The retention of the desired stereochemistry at C4 was clear from the lack of coupling between H4 and H5, the dihedral angle between the two protons being virtually 90° in the correct C4 epimer (the numbering system referred to here is the numbering used for the bicyclic lactones and not pestalotiopsin A; see figure 2.20 for numbering).



scheme 2.43

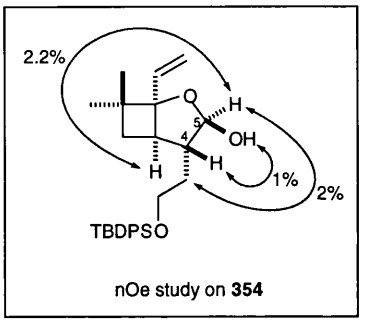


figure 2.20

In the above section we have described the first approach to the core of pestalotiopsin A utilising our samarium(II) iodide mediated 4-*exo*-trig cyclisation methodology. In our approach, the four contiguous stereocentres of the core have been established using a flexible approach which will allow several routes to the target to be pursued.

2.2.8 Conclusions

A route to the bicyclic system found in pestalotiopsin A has been developed. Organoytterbiums generated from various alkylmetals have been shown to react with cyclobutanone **329** in an efficient addition/trans-lactonisation sequence to form the bicyclic lactone moiety. Flexibility in the nature of the organoytterbiums employed will allow for a range of different strategies for closure of the final 9-membered ring to be examined.

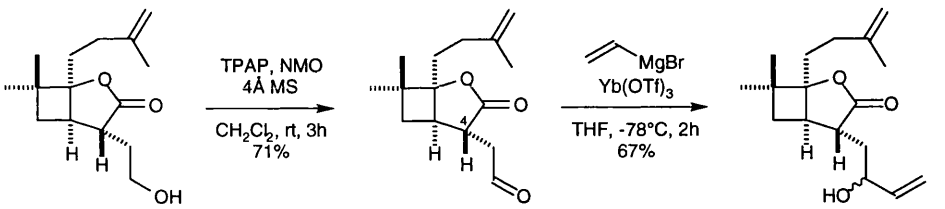
Chapter 3: Future work

The results discussed in the previous chapter have laid the foundations for further studies. The development of the SmI_2 mediated 4-*exo*-trig cyclisation and its application an approach to pestalotiopsin A have been discussed. The final ring of the natural product has yet to be constructed and also the fully functionalised core (possessing the C7-OH) of the natural product has to be prepared. Work to address these issues is currently ongoing within the group. This chapter contains a brief account of future approaches to the final 9-membered ring of pestalotiopsin A, and includes preliminary results obtained towards the end of my studies.

Also discussed in this section are my preliminary studies into a 4-*exo*-trig cyclisation on solid phase and future ideas for the development of catalytic Sm(II) ketyl-olefin cyclisations.

3.1 Possible approaches to the final ring of pestalotiopsin A

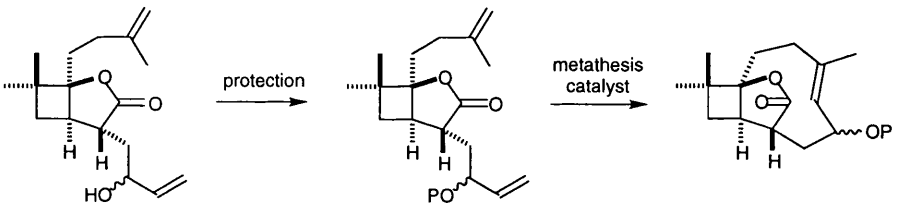
As previously mentioned, our approach to pestalotiopsin A is sufficiently versatile to allow disconnections at a number of positions around the final 9-membered ring. We decided to initially focus on a ring closing metathesis approach to the pestalotiopsin A skeleton. The primary hydroxyl of bicyclic lactone **338** was oxidised to give the aldehyde **355** in good yield (scheme 3.1). In the preparation of allylic alcohol **356,** we chose to use a non-basic vinylytterbium reagent again since the substrate contained an acidic proton at the C4 stereocentre. Treatment of **355** with the vinylytterbium, derived as before from vinylmagnesium bromide and $Yb(OTf)_3$, resulted in smooth addition to give allylic alcohol **356** in good yield as an approximately 1:1 ratio of diastereoisomers (scheme 3.1).



338 355 356

scheme 3.1

Alcohol **356**, or protected derivatives such as **357**, are suitable model substrates on which to attempt ring closing metathesis to form the 9-membered ring (scheme 3.2). Olefin metathesis is currently an area of great interest to the synthetic community.[176-178] However, as a recent review on the subject highlights, little is known about the formation of medium-sized rings using the reaction and much work needs to be done in this area.[179] Only one example of the preparation of a 9-membered carbocycle using ring closing metathesis has been reported,[180] hence a study of such a process should be of widespread interest. We expect our studies will also provide important information with regards to the stereochemistry of the process and also the influence, if any, of potentially directing hydroxyl group. Unfortunately, time did not allow for the reaction to be investigated. Work is now ongoing within the group to examine whether RCM is a viable method for forming the 9-membered ring of the target.

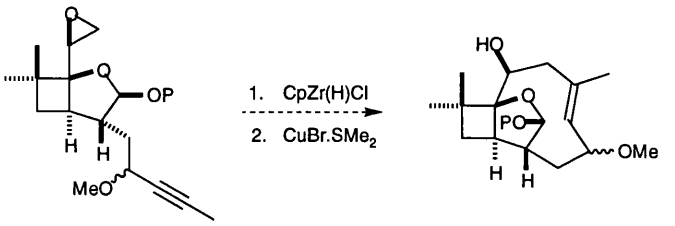


356 357 358

scheme 3.2

Another possible approach to the 9-membered ring involves the use of novel zirconium chemistry. Alkenyl zirconium species, upon transmetallation to the corresponding

cuprates, have been shown to undergo smooth intermolecular addition to epoxides.[181] We believe stereo- and regioselective hydrozirconation of epoxyacetylene **359** with *in situ* trans-metallation to copper will result in intramolecular epoxide opening to yield the 9-membered ring product **360** (scheme 3.3). Work is ongoing within the group to examine this interesting route to pestalotiopsin A.



359 **360**

scheme 3.3

The above two methods for preparing the final ring (schemes 3.2 and 3.3) are just two of many possible approaches. Importantly, the flexibility available in the later stages of our approach stems from the convergent nature of earlier steps, in particular the organoytterbium mediated addition / trans-lactonisation sequence. Work towards the completed carbon skeleton of pestalotiopsin A and towards the fully functionalised natural product, is currently underway.

3.2 SmI_2-mediated cyclisations on solid support

In the later stages of my studies, we began to examine the possibility of applying our recently developed SmI_2 cyclisation methodology to solid supported aldehydes. At present no examples of solid supported SmI_2 mediated ketyl-olefin couplings exist in the literature, hence the study of this potentially useful solid phase cyclisation protocol is of great interest. The nature of the SmI_2 mediated solid phase cyclisation may also provide opportunities for devising a system that is catalytic with respect to the lanthanide reagent.

3.2.1 Why the need for a Sm(II) catalytic system?

Despite the popularity and versatility of SmI_2, as highlighted in the Chapter **1**, practical limitations on its use remain. Stoichiometric amounts of SmI_2 are required for transformations such as ketyl-olefin cyclisations. Therefore relatively large scale reactions are problematic not only due to the expense but also due to the fact that SmI_2 is used as a 0.1M solution in THF[182] resulting in large volumes of the reagent being required. The development of a catalytic Sm(II) process would alleviate this problem. A less expensive stoichiometric reductant could be employed to reduce the by-product of the reaction, Sm(III), back to Sm(II) *in situ*, thus allowing sub-stoichiometric quantities of SmI_2 to be used (figure 3.1). Such technology would be appealing to both industry and academia due to its convenient, inexpensive and environmentally friendly nature.

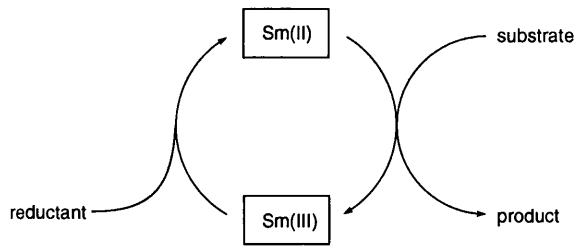


figure 3.1: general representation of a Sm(II) catalytic cycle

3.2.2 Previous catalytic Sm(II) systems

The need for a catalytic Sm(II) system has not gone unnoticed, although currently, only three examples have been reported. Endo's group has produced a SmI_2 catalysed pinacol coupling (figure 3.2).[183] Activated magnesium was used as the reductant for SmI_2 which enabled the reaction to proceed smoothly with only 0.05 equivalents of SmI_2 for every equivalent of the aldehyde substrate. The yield for the coupling reaction was comparable to the uncatalysed version of the reaction. An additional feature of the system was the inclusion of TMSCl which was required to liberate Sm(III) from the Sm(III) pinacolate, enabling a more efficient reduction back to Sm(II). Although an excellent effort, the synthetic value of this catalytic cycle is limited as pinacol coupling of carbonyl compounds can be conveniently carried out using existing inexpensive catalytic reagent systems.[184]

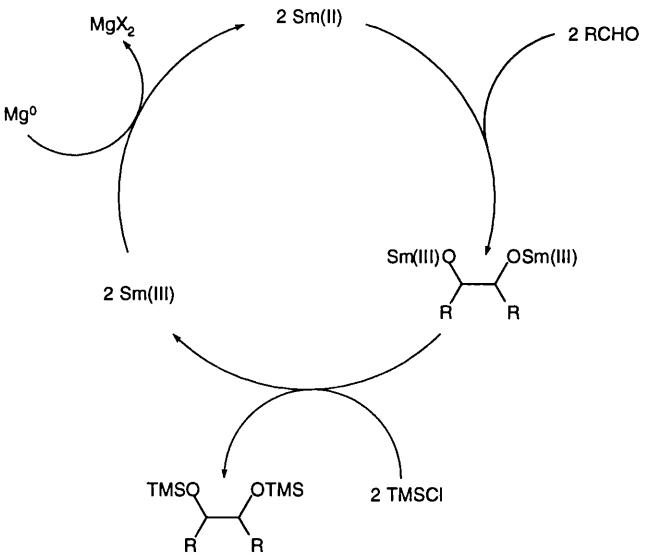


figure 3.2

A second catalytic Sm(II) system has been derived by Corey for use in SmI_2 mediated intermolecular addition reactions.[185] The system developed, however, is not general or convenient as the paper reports the use of just a single olefin substrate. In addition, a zinc-mercury amalgam is employed as the stoichiometric reductant (prepared from zinc powder and the highly toxic mercury dichloride).

More recently a report by Namy advocates the use of *mischmetall* as a co-reductant for SmI_2 in Barbier type reactions, simple dehalogenations, pinacol couplings and the coupling of acid chlorides.[186] The inexpensive alloy of the early lanthanides has proved to be a more attractive proposition than magnesium and zinc/mercury amalgam reductants. However, even this report has short comings, such as the failure to discuss the reactions of more functionally diverse substrates. Also the lack of the ability of *mischmetall* to reduce Sm(III) to Sm(II) in the presence of HMPA is a problem since many Sm(II) mediated reactions depend upon the cosolvent.

3.2.3 Devising a Sm(II) catalytic system using solid supported substrates

We believe there is potential for SmI_2 mediated ketyl-olefin cyclisations on solid supported substrates to be made catalytic in SmI_2. The major problem with SmI_2 catalytic systems is the background reaction between the stoichiometric reductant and the substrate. This leads to undesired side reactions. However, if the reaction substrates are resin bound and if, for example, a heterogeneous stoichiometric reductant, is used then minimal background reactions should occur. The solution phase Sm(II) species will therefore effectively act as a 'shuttle' between the two solid phase reactants (figure 3.3). Figure 3.3 illustrates this idea for a solid-phase Sm(II)-mediated 4-*exo*-trig cyclisation of an immobilised unsaturated aldehyde.

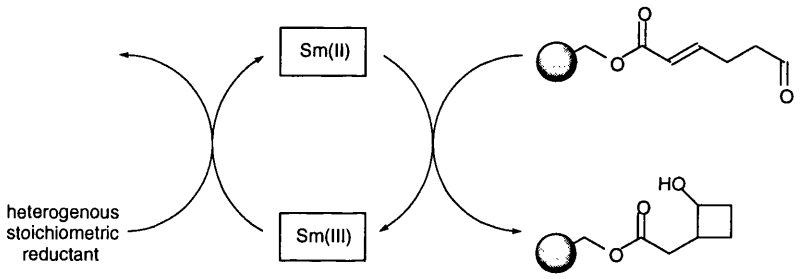
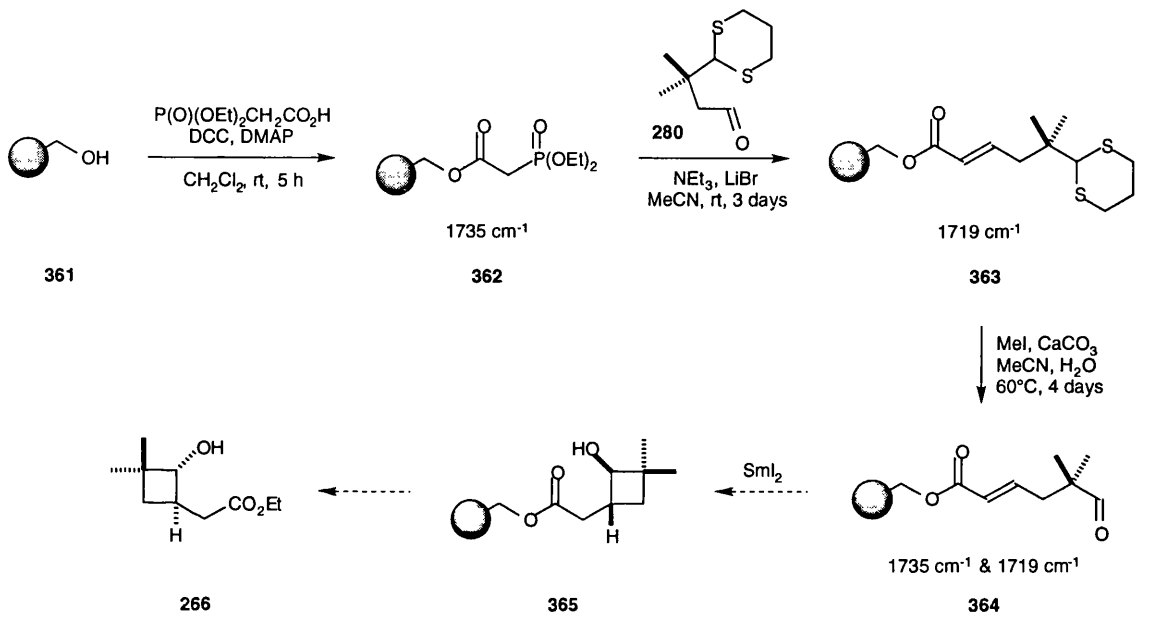


figure 3.3

3.2.4 Preparation of solid supported cyclisation substrates

Building upon our earlier work in developing the SmI_2 mediated 4-*exo*-trig cyclisation, it was decided to attempt the 4-*exo*-trig cyclisation of a suitably designed solid phase substrate. Conveniently, the substrate could be attached to the resin through the ester functionality. Hydroxy methyl polystyrene resin **361** was used to prepare the solid supported Horner-Wadsworth-Emmons reagent **362** with characteristic IR absorption at 1735 cm^{-1} (scheme 3.4). Treatment of **362** with aldehyde **280** gave the unsaturated

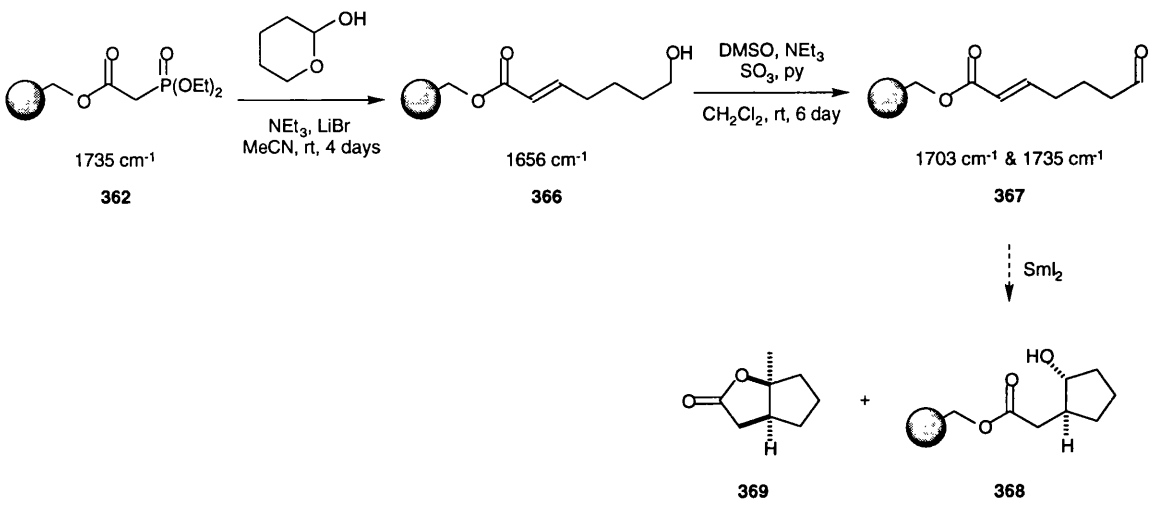
thioacetal **363**.[187] Removal of the thioacetal to give the unsaturated aldehyde **364** was carried out using standard conditions. Unfortunately, time did not allow us to study the cyclisation of **364** to be carried out. This work is currently being carried out by others in the group. It is hoped that treatment of the solid supported substrate with samarium(II) iodide using our standard conditions will yield cyclobutanol **365** which will be cleaved from the resin with sodium ethoxide to give cyclobutanol **266**.



scheme 3.4

Studies into the analogous 5-*exo*-trig cyclisation of unsaturated aldehydes were also initiated. Treatment of the Horner-Wadsworth-Emmons reagent **362** with δ-valerolactol yielded the unsaturated alcohol **366** (scheme 3.5). Swern oxidation of the alcohol gave the aldehyde **367**.[188] Previously, similar solution phase cyclisations have yielded a mixture of both *syn* and *anti* cyclopentanol products, the *syn* under going spontaneous lactonisation.[113] One of the proposed benefits of the cyclisation on solid support is that separation of the two isomers will occur *in situ*. While the *anti* cyclopentanol remains

attached to the polystyrene support **368**, spontaneous lactonisation of the *syn* isomer **369** results in cleavage from the resin.



scheme 3.5

Initial studies into the samarium(II) iodide mediated cyclisation of **367** have proved interesting. No bicyclic lactone **369** was detected in the solution phase, yet IR of the resin showed the absence of both the aldehyde absorption at 1703 cm^{-1} and the olefin absorption at 1651 cm^{-1}. Cleavage of the solid supported material was then attempted using sodium methoxide, however a complex product mixture was obtained. Studies are ongoing within the group to further develop this solid-phase chemistry.

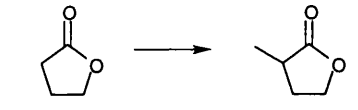
Chapter 4: Experimental

General considerations

All reactions were performed under argon or nitrogen atmospheres with anhydrous solvents unless otherwise stated. THF was distilled from sodium and benzophenone. CH_2Cl_2 was distilled from CaH_2. Toluene was distilled from sodium wire. MeOH, EtOH and *tert*-BuOH were distilled from the corresponding magnesium alkoxide and stored under argon. HMPA was dried by refluxing with CaH_2 followed by fractional distillation under reduced pressure. SmI_2 was prepared by the method of Imamoto and Ono with the modification that the samarium-iodine-THF solution was heated at 60°C rather than at reflux.

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on Bruker AM 360 or DPX 400 spectrometers with chemical shift values being reported in ppm relative to residual chloroform (δ_H = 7.27 or δ_C = 77.2) as internal standard unless otherwise stated. All coupling constants (*J*) are reported in hertz (Hz). Infrared spectra were recorded using JASCO FT/IR 410 and Impact 400 spectrometers and mass spectra were obtained using a JEOL JMS-700 spectrometer. Microanalyses were carried out at the University of Glasgow using an Elemental Analyser MOD 1106.

Column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by UV or staining with iodine or alkali $KMnO_4$.



278
$C_4H_6O_2$
Mol. Wt.: 86.09

285
$C_5H_8O_2$
Mol. Wt.: 100.12

α-methyl-γ-butyrolactone **285**[189]

A solution of LDA was prepared by the dropwise addition of *n*-butyllithium (1.42 M in hexane, 48.6 ml, 66.3 mmol, 1.2 eq) to a stirred solution of diisopropylamine (9.60 ml, 66.3 mmol, 1.2 eq) in THF (70 ml) at -78°C. After 40 min, γ-butyrolactone (4.20 ml, 55.2 mmol, 1 eq) in THF (50 ml) was addded dropwise and the mixture left for 2 h before the addition of MeI (17.9 ml, 276 mmol, 5 eq). The reaction was then allowed to warm to —20°C and stirred for 15 h before quenching with aqueous saturated NH_4Cl (4 ml). The aqueous layer was then separated and extracted with EtOAc (3 x 40 ml), dried ($NaSO_4$), and concentrated *in vacuo*. Filtration through a short column of silica gel (eluting with 50% EtOAc in hexane) gave **285** (4.81 g, 48.0 mmol, 87%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 4.36 (1H, td, *J* 2.6, 8.8, 1H from CH_2O), 4.23-4.17 (1H, m, 1H from CH_2O), 2.67-2.57 (1H, m, 1H from CH_2CH), 2.49-2.41 (1H, m, 1H from CH_2CH), 1.99-1.89 (1H, m, CH), and 1.30 (3H, d, *J* 7.1, CH_3).

285
$C_5H_8O_2$
Mol. Wt.: 100.12

286
$C_6H_{10}O_2$
Mol. Wt.: 114.14

α,α-dimethyl-γ-butyrolactone **286**[190, 191]

A solution of LDA was prepared by the dropwise addition of *n*-butyllithium (1.34 M in hexane, 88.9 ml, 119 mmol, 1.3 eq) to a stirred solution of diisopropylamine (16.7 ml,

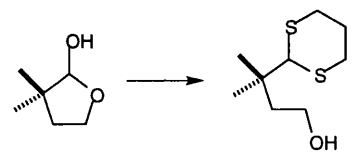
119 mmol, 1.3 eq) in THF (150 ml) at —78°C. After 30 min, a solution of α-methyl-γ-butyrolactone **285** (9.17 ml, 91.6 mmol, 1 eq) in THF (100 ml) was addded dropwise and the mixture left for 1.5 h before the addition of MeI (22.8 ml, 366 mmol, 4 eq). The reaction was then allowed to warm to rt and stirred for 16.5 h before quenching with aqueous saturated NH_4Cl (4 ml). The aqueous layer was then separated and extracted with Et_2O (5 x 50 ml), dried ($NaSO_4$), and concentrated *in vacuo* to give **286** (9.18 g, 80.4 mmol, 88%) as an orange oil which was used without further purification: δ_H (400 MHz, $CDCl_3$) 4.27 (2H, t, *J* 7.0, CH_2O), 2.11 (2H, t, *J* 7.0, CH_2CH_2O), and 1.27 (6H, s, 2 x CH_3).

286
$C_6H_{10}O_2$
Mol. Wt.: 114.14

281
$C_6H_{12}O_2$
Mol. Wt.: 116.16

α,α-dimethyl-γ-butyrolactol **281**[190, 191]

To a stirred solution of α,α-dimethyl-γ-butyrolactone **286** (9.34 g, 81.8 mmol, 1 eq) in CH_2Cl_2 (207 ml) at —78 °C was added dropwise DIBAL-H (1.5 M in toluene, 54.5 ml, 81.8 mmol, 1 eq) and the reaction stirred for 2 h at that temperature. The mixture was then added dropwise to a stirred solution of K/Na tartrate (69.3 g, 94.3 mmol, 3 eq) in H_2O (16.5 ml) and CH_2Cl_2 (207 ml). The aqueous layer was separated and extracted with CH_2Cl_2 (5 x 150 ml), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give lactol **281** (9.32 g, 80.2 mmol, 98%) as a pale yellow oil which was used without further purification: δ_H (400 MHz, $CDCl_3$) 4.90 (1H, d, *J* 3.4, C*H*OH), 4.09 (1H, td, *J* 8.4, 3.4, 1H from CH_2O), 3.92 (1H, apparent q, *J* 8.4, 1H from CH_2O), 2.58 (1H, d, *J* 3.4, OH), 1.99-1.92 (1H, m, 1H from CH_2CH_2O), 1.68-1.62 (1H, m, 1H from CH_2CH_2O), 1.13 (3H, s, CH_3), and 1.03 (3H, s, CH_3).

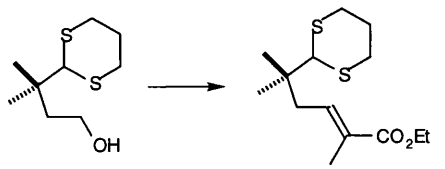


281 $C_6H_{10}O_2$ Mol. Wt.: 114.14

287 $C_9H_{18}OS_2$ Mol. Wt.: 206.37

3-(1,3-Dithian-2-yl)-3-methyl-butan-1-ol 287

To a stirred solution of lactol **281** (1.45 g, 12.5 mmol, 1 eq) in CH_2Cl_2 (24 ml) at —20 °C was added activated 4Å molecular sieves and 1,3-propanedithiol (1.50 ml, 15.0 mmol, 1.2 eq) before the dropwise addition of BF_3•OEt_2 (1.58 ml, 12.5 mmol, 1 eq). The reaction was left for 2 h and then aqueous saturated $NaHCO_3$ (5 ml) was added. The aqueous layer was then separated and extracted with CH_2Cl_2 (4 x 50 ml). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (eluting with 30% EtOAc in hexane) yielded **287** (1.51 g, 7.32 mmol, 59%) as a clear pale yellow oil: υ_{max} (neat)/cm^{-1} 3369s (O-H), 2961s, 2930s, 2899s, 1465m, 1388m, 1367m, 1277m, 1055m, and 1026m; δ_H (400 MHz, $CDCl_3$) 4.13 (1H, s, SCHS), 3.77 (2H, apparent q, *J* 6.9, C*H*$_2$OH), 2.91-2.89 (4H, m, 2 x SCH_2), 2.09 (1H, d quintets, *J* 14.0, 3.3, 1H from CH_2), 1.88-1.76 (1H, m, 1H from CH_2), 1.81 (2H, t, *J* 6.9, C*H*$_2$$CH_2$OH) and 1.15 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 60.9 (SCHS), 59.6 (CH_2OH), 43.0 (*C*$H_2$$CH_2$OH), 38.0 (C), 31.5 (2 x SCH_2), 26.2 (CH_2), and 26.1 (2 x CH_3); *m/z* (EI mode) 206 (82%), 119 (100), 99 (19), 85 (14), 69 (14), and 55 (17) (Found M^+, 206.0797. $C_9H_{18}OS_2$ requires *M*, 206.0799) (Found: C, 52.11; H, 8.77. $C_9H_{18}OS_2$ requires, C, 52.38; H, 8.79%).

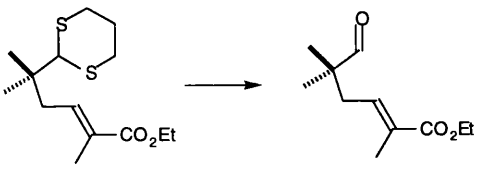


287
$C_9H_{18}OS_2$
Mol. Wt.: 206.37

279
$C_{14}H_{24}O_2S_2$
Mol. Wt.: 288.47

Ethyl (*E*)-2,5-dimethyl-5-[1,3-dithian-2-yl]-hex-2-enoate 279

To a solution of **287** (500 mg, 2.42 mmol, 1 eq) in CH_2Cl_2 (25 ml) at 0°C was added DMSO (1.72 ml, 24.2 mmol, 10 eq) and then triethylamine (1.65 ml, 16.0 mmol, 6.6 eq). After 5 min, pyridine-sulfur trioxide complex (1.47 g, 9.21 mmol, 3.8 eq) was added and the reaction stirred for a further 45 min before being allowed to slowly warm to rt and left for 2 h. To the golden coloured solution was then added (1-ethoxycarbonylethylidene)triphenylphosphorane (2.63 g, 7.26 mmol, 3 eq) and the reaction mixture stirred for 13 h. The reaction mixture was then poured onto a short column of silica gel and eluted with 40% EtOAc in hexane. Concentration *in vacuo* gave crude **279** as a brown solid. The residue was purified by column chromatography (eluting with 10% EtOAc in hexane) which yielded **279** (684 mg, 2.37 mmol, 98%) as a clear colourless oil: υ_{max} (neat)/cm^1 2964s, 2900s, 2828m, 1712s (C=O), 1647s (C=C), 1465s, 1422m, 1388s, 1367s, 1261s, 1177m, and 1101m; δ_H (400 MHz, $CDCl_3$) 6.84 (1H, t, *J* 7.8, CH_2CH=), 4.21 (2H, q, *J* 7.1, CH_2CH_3), 4.03 (1H, s, SCHS), 2.91-2.88 (4H, m, 2 x SCH_2), 2.38 (2H, d, *J* 7.8, CH_2CH=), 2.09 (1H, m, 1H from CH_2), 1.87 (3H, s, =CCH_3), 1.87-1.76 (1H, m, 1H from CH_2), 1.31 (3H, t, *J* 7.1, CH_2CH_3), and 1.13 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 168.3 (C=O), 138.0 (CH=), 130.3 (=CCH_3), 60.8 (SCHS), 60.7 (CH_2CH_3), 39.7 (C), 39.1 (CH_2CH=), 31.5 (2 x SCH_2), 26.2 (CH_2), 25.5 (2 x CH_3), 14.5 (CCH_3), and 12.9 (CH_2CH_3); *m/z* (EI mode) 288 (26%), 243 (8), 162 (17), 123 (12), 119 (100), 99 (5), and 55(5) (Found M^+, 288.1220. $C_{14}H_{24}O_2S_2$ requires *M*, 288.1218).



279
$C_{14}H_{24}O_2S_2$
Mol. Wt.: 288.47

267
$C_{11}H_{18}O_3$
Mol. Wt.: 198.26

Ethyl (*E*)-2,5,5-trimethyl-6-oxo-hex-2-enoate 267

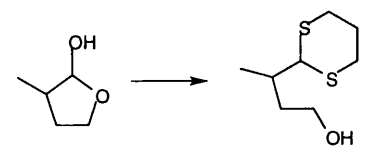
To a stirred solution of **279** (692 mg, 2.40 mmol, 1 eq) in acetonitrile (9 ml) and distilled water (2.3 ml) was added $CaCO_3$ (721 mg, 7.20 mmol, 3 eq) and iodomethane (2.99 ml, 48.0 mmol, 20 eq). The mixture was then refluxed for 21 h at 60°C with more iodomethane (1.49 ml, 24.0 mmol, 10 eq) being added after 6 h. The reaction mixture was then allowed to cool before being poured onto a short column of silica gel and eluted with 20% EtOAc in hexane. Concentration *in vacuo* yielded **267** (461 mg, 2.33 mmol, 97%) as a clear colourless oil which was stored at —20°C under nitrogen, and used without further purification: ν_{max}(neat)/cm^{-1} 2976s, 2935s, 2809m, 2705m, 1716s (C=O), 1650s (C=C), 1390s, 1367s, 1255s, 1109s, and 1082s; δ_H (400 MHz, $CDCl_3$) 9.51 (1H, s, CHO), 6.70 (1H, t, *J* 7.8, CH_2CH=), 4.19 (2H, q, *J* 7.1, CH_2CH_3), 2.35 (2H, d, *J* 7.8, CH_2CH=), 1.85 (3H, s, CH_3C=), 1.29 (3H, t, *J* 7.1, CH_2CH_3), and 1.11 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 205.3 (C=O), 167.9 (CO_2Et), 136.3 (CH=), 130.7 (C=), 60.8 (CH_2CH_3), 46.5 (C), 35.7 (CH_2), 21.6 (2 x CH_3), 14.4 (CH_2CH_3), and 12.8 (=CCH_3); *m/z* (CI mode, NH_3) 216 (100%), 199 (8), 134 (7), 96 (6), and 79 (4) (Found (M + H)$^+$, 199.1332. $C_{11}H_{19}O_3$ requires *M*, 199.1329).

285
$C_5H_8O_2$
Mol. Wt.: 100.12

277
$C_5H_{10}O_2$
Mol. Wt.: 102.13

α-methyl-γ-butyrolactol **277**[189]

To a stirred solution of α-methyl-γ-butyrolactone **285** (2.99 g, 29.9 mmol, 1 eq) in CH_2Cl_2 (80 ml) at -78 °C was added DIBAL-H (1.5 M in toluene, 23.9 ml, 35.9 mmol, 1.2 eq) and the reaction left for 1 h. The mixture was then added dropwise to a stirred solution of K/Na tartrate (25.8 g, 89.7 mmol, 3 eq) in H_2O (8 ml) and CH_2Cl_2 (80 ml). The aqueous layer was then separated and extracted with CH_2Cl_2 (3 x 20 ml) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* gave lactol **277** (2.82 g, 27.6 mmol, 92%) as a pale yellow oil (2:1 mixture of *cis:trans* diastereoisomers) which was used without further: δ_H (400 MHz, $CDCl_3$) 5.29 (1H, t, *J* 3.6, C*H*OH of *cis* isomer), 5.13 (1H, dd, *J* 3.3, 1.3, C*H*OH of *trans* isomer), 4.14-4.04 (2H, m, 1H from CH_2O of *cis* isomer and 1H from CH_2O of *trans* isomer), 4.01-3.95 (1H, m, 1H from CH_2O of *trans* isomer), 3.87-3.81 (1H, m, 1H from CH_2O of *cis* isomer), 2.83 (1H, d, *J* 3.3, OH of *trans* isomer), 2.64 (1H, d, *J* 3.6, OH of *cis* isomer), 2.29-2.22 (2H, m, 1H from CH_2 of *cis* isomer and 1H from CH_2 of *trans* isomer), 2.18-2.12 (1H, m, 1H from CH_2 of *cis* isomer) and 2.05-1.97 (1H, m, 1H from CH_2 of *trans* isomer), 1.81-1.71 (1H, m, C*H*CH_3 of *cis* isomer), 1.58-1.52 (1H, m, C*H*CH_3 of *trans* isomer), 1.12 (3H, d, *J* 6.8, CH_3 of *cis* isomer), and 1.05 (3H, d, *J* 7.1, CH_3 of *trans* isomer).

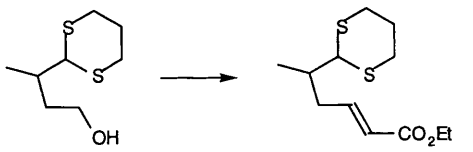


277
$C_5H_{10}O_2$
Mol. Wt.: 102.13

288
$C_8H_{16}OS_2$
Mol. Wt.: 192.34

3-(1,3-Dithian-2-yl)butan-1-ol 288

To a stirred solution of lactol **277** (2.82 g, 27.6 mmol, 1 eq) in CH_2Cl_2 (3 ml) at 0 °C was added 1,3-propanedithiol (3.30 ml, 33.1 mmol, 1.2 eq) and 4Å molecular sieves. Trifluoromethanesulfonic acid (0.98 ml, 11.0 mmol, 0.4 eq) was then added and the reaction mixture allowed to warm to room temperature and stirred for 19 h. Aqueous saturated $NaHCO_3$ (1 ml) was added and the aqueous layer separated and extracted with EtOAc (4 x 20 ml). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 20% EtOAc in hexane) to give alcohol **288** (3.32 g, 17.3 mmol, 63%) as a pale yellow oil: υ_{max}(neat)/cm^{-1} 3397br s (O-H), 2930s, 1276s, 1185s, 1053s, 1011s, and 907s; δ_H (400 MHz, $CDCl_3$) 4.17 (1H, d, *J* 4.1, SCHS), 3.77-3.67 (2H, m, C*H*$_2$OH), 2.95-2.82 (4H, m, 2 x SCH_2), 2.14-2.06 (2H, m, 1H from CH_2 and 1 H from C*H*CH_3), 1.95-1.80 (2H, m, 1H from C*H*$_2$CH and 1H from CH_2), 1.64-1.56 (1H, m, 1H from CHC*H*$_2$), 1.34 (1H, s, OH), and 1.12 (3H, d, *J* 6.9, C*H*$_3$CH); δ_C (100 MHz, $CDCl_3$) 60.8 (CH_2OH), 55.3 (SCHS), 36.9 (CH*C*H$_2$), 35.3 (*C*HCH$_3$), 31.0 (SCH_2), 30.8 (SCH_2), 26.3 (CH_2), and 17.1 (CH_3); *m/z* (EI mode) 192 (26%), 119 (100), 106 (4), 86 (10), 75 (6), and 74 (4) (Found M^+, 192.0643. $C_8H_{16}OS_2$ requires *M*, 192.0639).

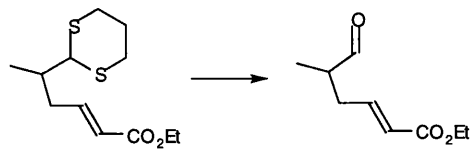


288
$C_8H_{16}OS_2$
Mol. Wt.: 192.34

275
$C_{12}H_{20}O_2S_2$
Mol. Wt.: 260.42

Ethyl (*E*)-5-(1,3-dithian-2-yl)hex-2-enoate 275

To a solution of **288** (500 mg, 2.60 mmol, 1 eq) in CH_2Cl_2 (25 ml) at 0°C was added DMSO (1.84 ml, 26.0 mmol, 10 eq) and then triethylamine (1.77 ml, 17.2 mmol, 6.6 eq). After 5 min pyridine-sulfur trioxide complex (1.57 g, 9.88 mmol, 3.8 eq) was added and the reaction stirred for 30 min before being allowed to slowly warm to rt and left for 4 h. To the golden coloured solution was then added (carbethoxymethylene)triphenylphosphorane (1.81 g, 5.20 mmol, 2 eq) and the reaction mixture left for a further 11 h. The reaction mixture was then poured onto a short column of silica gel and eluted with 40% EtOAc in hexane. Concentration *in vacuo* then gave crude **275** as a red oil. The residue was purified by column chromatography (eluting with 10% EtOAc in hexane) to give α,β-unsaturated ester **275** (482 mg, 1.85 mmol, 71%) as a clear yellow oil: υ_{max}(neat)/cm^{-1} 2978m, 2930m, 2898m, 1717s (C=O), 1653s (C=C), 1367m, 1175s, 1042s, and 983s; δ_H (400 MHz, $CDCl_3$) 6.90 (1H, dt, *J* 15.5, 7.5, C*H*=CHCO$_2$Et), 5.87 (1H, d, *J* 15.5, CH=C*H*CO$_2$Et), 4.19 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 4.09 (1H, d, *J* 4.6, SCHS), 2.94-2.82 (4H, m, 2 x SCH$_2$), 2.55 (1H, dt, *J* 14.4, 7.5, 1H from C*H*$_2$CH=), 2.27-2.19 (1H, dt, *J* 14.4, 7.5, 1H from C*H*$_2$CH=), 2.15-2.02 (2H, m, 1H from CH$_2$ and 1H from C*H*CH$_3$), 1.86-1.80 (1H, m, 1H from CH$_2$), 1.29 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), and 1.10 (3H, d, *J* 6.9, C*H*$_3$CH); δ_C (100 MHz, $CDCl_3$) 166.6 (C=O), 146.8 (*C*H=CHCO$_2$Et), 123.5 (CH=*C*HCO$_2$Et), 60.4 (*C*H$_2$CH$_3$), 54.5 (SCHS), 38.1 (*C*HCH$_3$), 36.8 (*C*H$_2$CH=), 31.1 (SCH$_2$), 30.8 (SCH$_2$), 26.4 (CH$_2$), 17.2 (CH*C*H$_3$), and 14.4 (CH$_2$*C*H$_3$); *m/z* (EI mode) 260 (14%), 215 (7), 147 (36), 119 (100), 114 (12), and 73 (10) (Found M$^+$, 260.0905. $C_{12}H_{20}S_2O_2$ requires *M*, 260.0900).

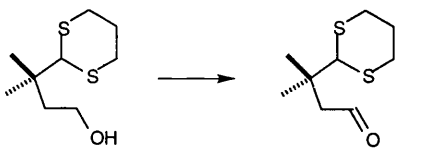


275
$C_{12}H_{20}O_2S_2$
Mol. Wt.: 260.42

268
$C_9H_{14}O_3$
Mol. Wt.: 170.21

Ethyl (*E*)-5-methyl-6-oxohex-2-enoate 268

To a stirred solution of **275** (458 mg, 1.76 mmol, 1 eq) in acetonitrile (6.5 ml) and distilled water (1.6 ml) was added $CaCO_3$ (556 mg, 5.55 mmol, 3 eq) and iodomethane (1.15 ml, 18.5 mmol, 10 eq). The mixture was refluxed for 22 h before being allowed to cool to rt. The mixture was then poured onto a short column of silica gel and eluted with 20% EtOAc in hexane. Concentration *in vacuo* gave the aldehyde **268** (289 mg, 1.70 mmol, 97%) as an oil which was stored at —20°C under nitrogen, and used without further purification: υ_{max}(neat)/cm^{-1} 2980s, 2936s, 2816m, 2719m, 1716s (C=O), 1655s (C=C), 1270s, 1179s, and 1044s; δ_H (400 MHz, $CDCl_3$) 9.67 (1H, d, *J* 1.2, CHO), 6.90 (1H, dt, *J* 15.6, 7.0, C*H*=CHCO$_2$Et), 5.89 (1H, dt, *J* 15.6, 1.5, CH=C*H*CO$_2$Et), 4.20 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 2.73-2.59 (1H, m, 1H from C*H*$_2$CH=), 2.59-2.50 (1H, m, CH$_3$C*H*), 2.30-2.22 (1H, m, 1H from C*H*$_2$CH=), 1.30 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), and 1.17 (3H, d, *J* 7.2, C*H*$_3$CH); δ_C (100 MHz, $CDCl_3$) 203.4 (CHO), 166.3 (C=O), 145.2 (CH$_2$*C*H=), 123.9 (=*C*HCO$_2$Et), 60.6 (*C*H$_2$CH$_3$), 45.4 (CH$_3$*C*H), 33.0 (CH$_2$), 14.4 (CH$_2$*C*H$_3$), and 13.4 (*C*H$_3$CH): *m/z* (CI mode, isobutane) 171 (100%), 169 (4), 125 (22), 111 (4), 95 (6), and 85 (19) (Found: (M + H)$^+$, 171.1021. $C_9H_{15}O_3$ requires *M*, 171.1017).



287

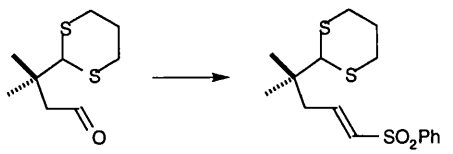
$C_9H_{18}OS_2$
Mol. Wt.: 206.37

280

$C_9H_{16}OS_2$
Mol. Wt.: 204.35

3-(1,3-Dithian-2-yl)-3-methylbutan-1-al 280

To a solution of 3-(1,3-dithian-2-yl)-3-methylbutan-1-ol **287** (127 mg, 0.62 mmol, 1 eq) in CH_2Cl_2 (6.5 ml) at 0°C was added DMSO (0.44 ml, 6.17 mmol, 10 eq) and triethylamine (0.42 ml, 4.07 mmol, 6.6 eq). After 5 min, pyridine-sulfur trioxide complex (373 mg, 2.34 mmol, 3.8 eq) was added and the reaction mixture stirred for 1 h before being allowed to warm to rt and stirred for a further 45 min. The reaction mixtue was then poured onto a short column of silica gel and eluted with 40% EtOAc in hexane. Concentration *in vacuo* gave **280** (123 mg, 0.60 mmol, 98%) as a pale yellow oil which was stored at —20°C under nitrogen, and used without further purification: υ_{max} (neat)/cm^{-1} 2963s, 2931s, 2900s, 2829m, 2734m, 1718s (C=O), 1389m, 1369m, 1046m, and 907m; δ_H (400 MHz, $CDCl_3$) 9.86 (1H, d, *J* 2.0, CHO), 4.24 (1H, s, SCHS), 2.94-2.89 (4H, m, 2 x SCH_2), 2.60 (2H, d, *J* 2.0, CH_2CHO), 2.13-2.08 (1H, m, 1H from SCH_2CH_2), 1.88-1.76 (1H, m, 1H from SCH_2CH_2), and 1.27 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 201.9 (CHO), 60.1 (SCHS), 53.1 (CH_2CHO), 38.7 (CH_3), 31.5 (2 x SCH_2), 26.1 (CH_2), and 26.0 (2 x CH_3); *m/z* (EI mode) 204 (11%), 160 (89), 145 (8), 119 (100), 85 (12), 59 (8), and 41 (23) (Found M^+, 204.0643. $C_9H_{16}OS_2$ requires *M*, 204.0639).



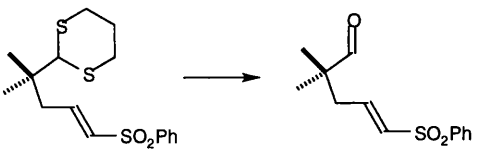
280
$C_9H_{16}OS_2$
Mol. Wt.: 204.35

282
$C_{16}H_{22}O_2S_3$
Mol. Wt.: 342.54

2-[(*E*)-(1,1-Dimethyl-4-phenylsulfonylbut-3-enyl)]-1,3-dithiane 282

To a stirred solution of $MeSO_2Ph$ (321 mg, 2.05 mmol, 2 eq) in THF (16 ml) at 0°C was added *n*-butyllithium (1.55 M in hexane, 2.92 ml, 4.52 mmol, 4.4 eq) and the mixture left for 30 min before the dropwise addition of a solution of diethylchlorophosphate (0.30 ml, 2.05 mmol, 2 eq) in THF (4 ml). The reaction was stirred for a further 30 min before being cooled to —78°C and a solution of 3-[1,3-dithian-2-yl]-3-methyl-butan-1-al **280** (210 mg, 1.03 mmol, 1 eq) in THF (4 ml) was added. After a further 1h, the reaction mixture was allowed to warm to rt and stirred for 12 h. Aqueous saturated $NaHCO_3$ (1 ml) was added and the aqueous layer separated and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 20% EtOAc in hexane) to give vinyl sulfone **282** (244 mg, 0.71 mmol, 69%) as a pale yellow oil: υ_{max}(neat)/cm^{-1} 3023s, 2968m, 2903m, 1631m (C=C), 1526m, 1451m, 1426m, 1321s (SO_2), 1226s, 1201s, 1146s (SO_2), and 1086s; δ_H (400 MHz, $CDCl_3$) 7.91 (2H, apparent d, *J* 7.7, 2 x ArH), 7.64-7.54 (3H, m, 3 x ArH), 7.00 (1H, dt, *J* 14.9, 8.0, C*H*=CHSO$_2$Ph), 6.45 (1H, d, *J* 14.9, =C*H*SO$_2$Ph), 3.85 (1H, s, SCHS), 2.87-2.72 (4H, m, 2 x SCH_2), 2.40 (2H, d, *J* 8.0, CH_2CH=), 2.07-2.01 (1H, m, 1H from CH_2), 1.81-1.71 (1H, m, 1H from CH_2), and 1.13 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 143.0 (*C*H=CHSO$_2$Ph), 141.1 (ArC), 133.6 (CH=*C*HSO$_2$Ph), 133.5 (ArCH), 129.5 (2 x ArCH), 127.8 (2 x ArCH), 60.1 (SCHS), 42.1 (*C*H$_2$CH=), 39.4 (C), 31.4 (2 x SCH_2), 26.0 (CH_2), and 25.7 (2 x CH_3); *m/z* (CI mode,

isobutane) 343 (100%), 271 (9), 237 (15), 201 (12), and 119 (5) (Found $(M + H)^+$, 343.0860. $C_{16}H_{23}O_2S_3$ requires *M*, 343.0855).

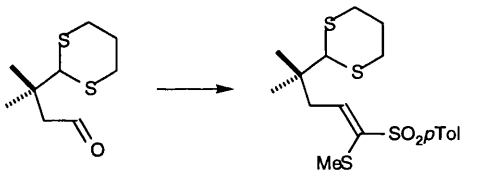


282
$C_{16}H_{22}O_2S_3$
Mol. Wt.: 342.54

270
$C_{13}H_{16}O_3S$
Mol. Wt.: 252.33

(*E*)-2,2-Dimethyl-5-phenylsulfonylpent-4-enal 270

To a stirred solution of **282** (244 mg, 0.71 mmol, 1 eq) in acetonitrile (4 ml) and distilled water (1 ml) was added $CaCO_3$ (214 mg, 2.13 mmol, 3 eq) and iodomethane (0.89 ml, 14.2 mmol, 20 eq). The mixture was refluxed at 60°C for 15 h and then allowed to cool before being poured onto a short column of silica gel and eluted with 20% EtOAc in hexane. Concentration *in vacuo* gave the aldehyde **270** (181 mg, 0.72 mmol, 100%) as a clear, pale yellow oil which was used without further purification: υ_{max} (neat)/cm^{-1} 3049w, 2968m, 2932m, 2873m, 2813w, 2713w, 1725s (C=O), 1632m (C=C), 1379w, 1368w, 1317s (SO_2), 1147s (SO_2), 1086s, and 750s; δ_H (400 MHz, $CDCl_3$) 9.46 (1H, s, CHO), 7.88 (2H, apparent d, *J* 7.9, 2 x ArH), 7.65-7.62 (1H, m, ArH), 7.58-7.54 (2H, m, 2 x ArH), 6.91 (1H, dt, *J* 15.0, 7.8, CH_2CH=), 6.39 (1H, d, *J* 15.0, =$CHSO_2Ph$), 2.39 (2H, d, *J* 7.8, CH_2CH=), and 1.11 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 204.0 (CHO), 142.1 (CH_2CH=), 140.5 (ArC), 133.8 (=$CHSO_2Ph$), 133.6 (ArCH), 129.5 (2 x ArCH), 127.8 (2 x ArCH), 46.0 (C), 38.4 (CH_2), and 21.7 (2 x CH_3). *m/z* (CI mode, isobutane) 253 (100%), 183 (6), 111 (4), 81 (3), and 69 (3) (Found $(M + H)^+$, 253.0898. $C_{13}H_{17}SO_3$ requires *M*, 253.0894).



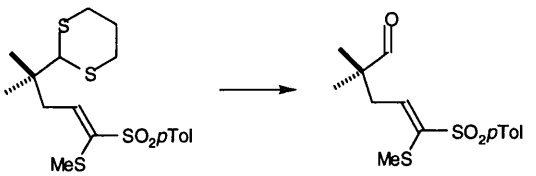
280
$C_9H_{16}OS_2$
Mol. Wt.: 204.35

283
$C_{18}H_{26}O_2S_4$
Mol. Wt.: 402.66

2-[1,1-dimethyl-4-methylsulfanyl-4-(toluene-4-sulfonyl)-but-3-enyl]-[1,3]dithiane 283

To a stirred solution of methylthiomethyl-*p*-tolylsulfone (153 mg, 0.71 mmol, 1.2 eq) in THF (3.0 ml) at -78°C was added *n*-butyllithium (1.2M in hexane, 0.57 ml, 0.71 mmol, 1.2 eq) and the reaction stirred for 15 min before warming to 0°C for 30 min. The reaction mixture was then cooled to -78°C and a solution of aldehyde **280** (120 mg, 0.59 mmol, 1 eq) in THF (1.5 ml) added *via* cannula. The reaction was stirred for 30 min before Ac_2O (0.08 ml, 0.82 mmol, 1.4 eq) was added. After a further 10 min triethylamine (0.12 ml, 1.65 mmol, 2.8 eq) and 4-dimethylaminopyridine (14 mg, 0.12 mmol, 0.2 eq) were added. After 4 h the reaction was quenched with aqueous saturated $NaHCO_3$ (2 ml) and the aqueous layer separated and extracted with CH_2Cl_2 (4 x 15 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **283** as a yellow sticky oil. Purification of the residue by column chromatography (eluting with 15% EtOAc in pet. ether (40-60)°C) gave **283** (98 mg, 0.24 mmol, 41%) as a clear yellow oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3154s, 2975s (C-H), 2902s (C-H), 2870m (C-H), 2833m (C-H), 1819s, 1793s, 1646m (C=C), 1598s (Ar-H), 1561m (Ar-H), 1467s, 1383s (SO_2) and 1152s (SO_2); δ_H (400 MHz, $CDCl_3$) 7.82 (2H, apparent d, *J* 8.2, 2 x ArH), 7.60 (1H, t, *J* 7.6, CH_2CH=), 7.33 (2H, apparent d, *J* 8.2, 2 x ArH), 4.03 (1H, s, SCHS), 2.91-2.88 (4H, m, 2 x SCH_2), 2.72 (2H, d, *J* 7.6, CH_2CH=), 2.45 (3H, s, $PhCH_3$), 2.29 (3H, s, SCH_3), 2.13-2.06 (1H, m, 1H from SCH_2CH_2), and 1.16 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 148.9 (CH_2CH=), 144.5 (ArC), 140.6 (CH=*C*), 136.2 (ArC), 129.7

(2 x ArCH), 128.9 (2 x ArCH), 60.4 (SCHS), 40.5 (CH_2CH=), 39.6 ($C(CH_3)_2$), 31.5 (2 x SCH_2), 26.1 (SCH_2CH_2), 25.8 (2 x CH_3), 21.8 ($PhCH_3$), and 19.5 (SCH_3); *m/z* (CI+ mode, isobutane) 403 (100%), 247 (25), 241 (4), 189 (8), 187 (3), and 119 (7) (Found (M + H)$^+$, 403.0894. $C_{18}H_{27}O_2S_4$ requires *M*, 403.0888).



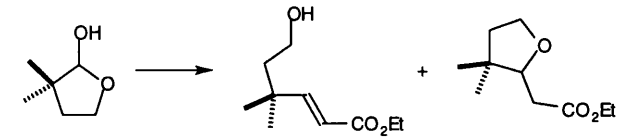
283
$C_{18}H_{26}O_2S_4$
Mol. Wt.: 402.66

271
$C_{15}H_{20}O_3S_2$
Mol. Wt.: 312.45

2,2-Dimethyl-5-methylsulfanyl-5-(toluene-4-sulfonyl)-pent-4-enal 271

To a stirred solution of **283** (34 mg, 0.08 mmol, 1 eq) in acetonitrile (1 ml) and distilled water (0.25 ml) was added $CaCO_3$ (25 mg, 0.25 mmol, 3 eq) and iodomethane (0.11 ml, 1.69 mmol, 20 eq). The mixture was refluxed for 30 h with a further quantity of MeI (0.06 ml, 1.69 mmol, 10 eq) being added after 23 h. The reaction mixture was then allowed to cool and filtrated through a short column of silica gel (eluting with 20% EtOAc in hexane). Concentration *in vacuo* gave the aldehyde **271** (25 mg, 0.08 mmol, 100%) as a clear yellow oil which was stored at —20°C under nitrogen: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3154s, 2975s (C-H), 2896m (C-H), 2870w (C-H), 2712m (CHO), 1819m, 1793s, 1730s (C=O), 1646m (C=C), 1598s (Ar-H), 1561m (Ar-H), 1383s (SO_2) and 1146s (SO_2); δ_H (400 MHz, $CDCl_3$) 9.49 (1H, s, CHO), 7.80 (2H, apparent d, *J* 8.3, 2 x ArH), 7.47 (1H, t, *J* 7.6, CH_2CH=), 7.34 (2H, apparent d, *J* 8.3, 2 x ArH), 2.69 (2H, d, *J* 7.6, CH_2CH=), 2.45 (3H, s, $PhCH_3$), 2.28 (3H, s, SCH_3), and 1.14 (6H, s, $C(CH_3)_2$; δ_C (100 MHz, $CDCl_3$) 204.2 (CHO), 147.5 (CH_2CH=), 144.7 (ArC), 141.4 (CH=*C*), 135.9 (ArC), 129.8 (2 x ArCH), 128.9 (2 x ArCH), 46.4 ($C(CH_3)_2$), 36.8 (CH_2CH=), 21.8

($PhCH_3$), 21.8 ($C(CH_3)_2$) and 19.4 (SCH_3); *m/z* (CI+ mode, isobutane) 313 (100%), 203 (12), 187 (61), 157 (68), 139 (26), 127 (8) and 81 (7) (Found M^+, 312.0855. $C_{15}H_{20}O_3S_2$ requires *M*, 312.0849).



281 $C_6H_{12}O_2$ Mol. Wt.: 116.16

284 $C_{10}H_{18}O_3$ Mol. Wt.: 186.25

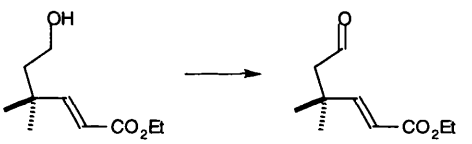
289 $C_{10}H_{18}O_3$ Mol. Wt.: 186.25

6-Hydroxy-4,4-dimethyl-hex-2-enoic acid ethyl ester 284

To a stirred solution of α,α-dimethyl-γ-butyrolactol **281** (108 mg, 0.93 mmol, 1 eq) in toluene (9 ml) was added (carbethoxymethylene)triphenylphosphorane (650 mg, 1.86 mmol, 2 eq) and the reaction mixture refluxed for 4 days. The mixture was then allowed to cool to rt and aqueous saturated $NaHCO_3$ (3 ml) added. The aqueous layer was separated and extracted with CH_2Cl_2 (4 x 10 ml), the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give a clear orange/yellow oil. Purification of the residue by column chromatography (eluting with 40% EtOAc in Pet. Ether (40-60°C)) gave **284** as a clear yellow oil (77 mg, 0.41 mmol, 44%): υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3627s (O-H), 3154s (O-H), 2965s (C-H), 2933m (C-H), 2896m (C-H), 1703s (C=O), 1646s (C=C), 1467s, 1378s, 1309s, and 1178s; δ_H (400 MHz, $CDCl_3$) 6.98 (1H, d, *J* 15.9, CH=), 5.75 (1H, d, *J* 15.9, =CHCO), 4.20 (2H, q, *J* 7.1, CH_2CH_3), 3.65 (2H, t, *J* 7.4, CH_2OH), 1.71 (2H, t, *J* 7.4, CH_2CH_2OH), 1.30 (3H, t, *J* 7.1, CH_2CH_3) and 1.11 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 167.2 (C=O), 157.6 (*C*H=), 118.2 (=*C*HCO), 60.5 (CH_2CH_3), 59.9 (CH_2OH), 44.8 (CH_2CH_2OH), 36.0 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$) and 14.5 (CH_2CH_3); *m/z* (CI+ mode, isobutane) 187 (27%), 181 (8), 169 (4), 141 (100), 127 (7),

117 (7), 95 (12), 83 (14) and 70 (13) (Found $(M + H)^+$, 187.1330. $C_{10}H_{19}O_3$ requires *M*, 187.1329).

Further elution then gave **(3,3-Dimethyl-tetrahydro-furan-2-yl)-acetic acid ethyl ester 289** (65 mg, 0.35 mmol, 38%) as a clear colourless oil: υ_{max} (film)/cm^{-1} 2959s (C-H), 2874s (C-H), 2678s (C-H), 1740s (C=O), 1389s, 1369s, 1309s, 1185s, 1157s, 1033s and 907s; δ_H (400 MHz, $CDCl_3$) 4.18 (2H, q, *J* 7.1, CH_2CH_3), 3.92-3.81 (3H, m, 2H from CH_2CH_2O and 1H from CH), 2.39-2.37 (2H, m, CH_2CO), 1.85-1.71 (2H, m, CH_2CH_2O), 1.28 (3H, t, *J* 7.1, CH_2CH_3), 1.07 (3H, s, CH_3) and 0.93 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 172.2 (C=O), 83.2 (CH), 65.9 (CH_2CH_2O), 60.8 (CH_2CH_3), 41.0 (CH_2CH_2O), 40.6 ($C(CH_3)_2$), 36.1 (CH_2CO), 25.4 (CH_3), 21.9 (CH_3) and 14.4 (CH_2CH_3); *m/z* (CI+ mode, isobutane) 187 (100%), 169 (6), 158 (8), 141 (3), 99 (10) and 70 (3) (Found $(M + H)^+$, 187.1334. $C_{10}H_{19}O_3$ requires *M*, 187.1329).



284
$C_{10}H_{18}O_3$
Mol. Wt.: 186.25

269
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

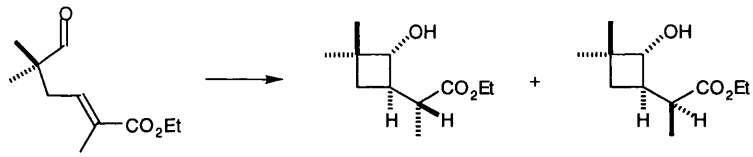
4,4-Dimethyl-6-oxo-hex-2-enoic acid ethyl ester 269

To a stirred solution of alcohol **284** (123 mg, 0.66 mmol, 1 eq) in CH_2Cl_2 (7 ml) at 0°C was added DMSO (0.47 ml, 6.61 mmol, 10 eq) and triethylamine (0.45 ml, 4.37 mmol, 6.6 eq). After 5 min pyridine-sulfur trioxide complex (400 mg, 2.51 mmol, 3.8 eq) was added and the reaction stirred at 0°C for 45 min before being allowed to warm to rt and stirred for a further 6 h. The reaction mixture was then passed through a short column of silica gel (eluting with 40% EtOAc in Pet Ether (40-60°C)). Concentration *in vacuo* gave the aldehyde **269** (121 mg, 0.66 mmol, 99%) as a clear colourless oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 2972s (C-H), 2902s (C-H), 2831m (CHO), 2737m (CHO), 1792s (CHO),

1716s (C=O), 1651s (C=C), 1469s, 1381s, 1310s and 1093s; δ_H (400 MHz, $CDCl_3$) 9.71 (1H, t, *J* 2.8, CHO), 7.02 (1H, d, *J* 15.9, CH=), 5.80 (1H, d, *J* 15.9, =CHCO), 4.20 (2H, q, *J* 7.1, CH_2CH_3), 2.45 (2H, d, *J* 2.8, CH_2CHO), 1.30 (3H, t, *J* 7.1, CH_2CH_3) and 1.22 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 201.6 (CHO), 166.8 (C=O), 155.4 (*C*H=), 119.1 (=*C*HCO), 60.7 (CH_2CH_3), 54.4 (CH_2CHO), 36.0 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$) and 14.4 (CH_2CH_3); *m/z* (CI+ mode, isobutane) 185 (72%), 171 (8), 155 (16), 139 (100), 125 (6), 113 (7), 95 (5), 85 (10) and 69 (18) (Found $(M + H)^+$, 185.1178. $C_{10}H_{17}O_3$ requires *M*, 185.1173).

Preparation of SmI_2[145]

To a stirred suspension of samarium (1.00g, 6.65 mmol, 1.2 eq) in THF (55 ml) inside a brown bottle wrapped in foil was added iodine (1.41g, 5.54 mmol, 1 eq). The reaction mixture was heated to 60°C and stirred for 23 h before being cooled to room temperature. The resultant deep blue 0.1M SmI_2 solution was then stored under Argon.



267 $C_{11}H_{18}O_3$ Mol. Wt.: 198.26

290a $C_{11}H_{20}O_3$ Mol. Wt.: 200.27

290b $C_{11}H_{20}O_3$ Mol. Wt.: 200.27

Ethyl *rel*-(2*R*)-{*rel*-(1*R*, 2*R*)-2-hydroxy-3,3-dimethyl-cyclobutyl}-propionate 290a and **ethyl *rel*-(2*S*)-{*rel*-(1*R*, 2*R*)-2-hydroxy-3,3-dimethyl-cyclobutyl}-propionate 290b**

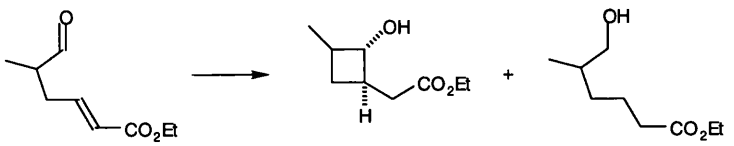
To a stirred solution of SmI_2 (0.1M in THF, 10.1 ml, 1.01 mmol) in MeOH (2.70 ml, 66.4 mmol) at 0°C was added dropwise a solution of aldehyde **267** (100 mg, 0.50 mmol) in THF (2 ml). After 2.5 h the reaction mixture was added to a stirred solution of aqueous

saturated NaCl (2 ml) before adding citric acid (128 mg, 0.61 mmol). The aqueous layer was separated and extracted with EtOAc (3 x 25 ml) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* gave crude **290** as an orange oil. The residue was purified by column chromatography (eluting with 30% EtOAc in hexane) to give cyclobutanol **290** (67 mg, 0.33 mmol, 66%) as a clear, colourless oil: υ_{max} (neat)/cm^{-1} 3448s (O-H), 2957s, 2867s, 1731s (C=O), 1461m, 1368m, 1272m, 1132m, 1096m, and 1025m; (major diastereoisomer **290a**) δ_H (400 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 3.60 (1H, dd, *J* 7.6, 3.5, C*H*OH), 2.49 (1H, d, *J* 3.5, OH), 2.42-2.34 (1H, m, C*H*CH$_3$), 2.18-2.08 (1H, m, CH), 1.71 (1H, apparent t, *J* 10.1, 1H from CH_2), 1.28 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), 1.10 (3H, d, *J* 7.0, CHC*H*$_3$), 1.08 (3H, s, CH_3), 1.07 (3H, s, CH_3), and 1.00 (1H, apparent t, *J* 10.1, 1H from CH_2); δ_C (100 MHz, $CDCl_3$) 176.6 (*C*O$_2$Et), 78.4 (CHOH), 60.8 (*C*H$_2$CH$_3$), 44.2 (*C*HCH$_3$), 43.8 (CH), 37.6 (C), 32.9 (CH_2), 28.8 (CH_3), 21.1 (CH*C*H$_3$), 14.8 (CH_3), and 14.4 (CH$_2$*C*H$_3$).

(minor diastereoisomer **290b**) mp 57-60 °C (hexane); δ_H (400 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 3.57 (1H, t, *J* 7.3, C*H*OH), 2.49-2.41 (1H, m, C*H*CH$_3$), 2.24-2.15 (1H, m, CH), 1.80 (1H, d, *J* 7.3, OH), 1.64 (1H, apparent t, *J* 10.2, 1H from CH_2), 1.26 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), 1.21 (3H, d, *J* 7.0, CHC*H*$_3$), 1.13 (1H, apparent t, *J* 10.2, 1H from CH_2), 1.07 (3H, s, Me), and 1.06 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 176.1 (CO), 78.0 (CHOH), 60.4 (*C*H$_2$CH$_3$), 44.4 (CH), 43.9 (*C*HCH$_3$), 38.3 (C), 32.3 (CH_2), 28.5 (Me), 20.9 (Me), 15.0 (CH*C*H$_3$), and 14.5 (CH$_2$*C*H$_3$).

For deuterated **305a**: δ_H (400 MHz, $CDCl_3$) as for **290a** except 2.42-2.34 (1H, m, C*H*CH$_3$) missing; δ_C (100 MHz, $CDCl_3$) as for **290a** except 44.2 (*C*HCH$_3$) missing; *m/z* (CI mode, NH_3) 219 (100%), 184 (56), 96 (79), and 79 (34) (Found $(M+H)^{+\cdot}$ 202.1553. $C_{11}H_{20}O_3D$ requires *M*, 202.1548).

For deuterated **305b**: δ_H (400 MHz, $CDCl_3$) as for **290b** except 2.49-2.41 (1H, m, C*H*CH_3) missing; δ_C (100 MHz, $CDCl_3$) as for **290b** except 43.9 (*C*HCH_3) missing (Found: C, 65.67; H, 9.61. $C_{11}H_{19}O_3D$ requires, C, 65.64; H, 9.51%).

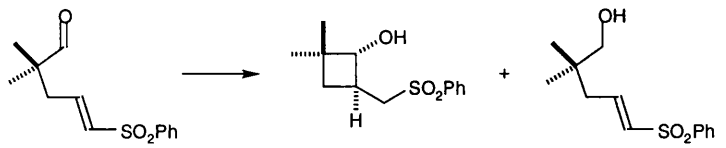


268 $C_9H_{14}O_3$ Mol. Wt.: 170.21 | **291** $C_9H_{16}O_3$ Mol. Wt.: 172.22 | **292** $C_9H_{18}O_3$ Mol. Wt.: 174.24

Attempted cyclisation of **268 - ethyl 6-hydroxy-5-methyl-hexanoate 292**

To a stirred solution of **268** (20 mg, 0.12 mmol, 1 eq) in methanol (0.60 ml, 29.6 mmol) at 0°C was added SmI_2 (0.1 M in THF, 2.35 ml, 0.24 mmol, 2 eq) dropwise over 1 min. A third equivalent of SmI_2 (1.13 ml, 0.12 mmol, 1 eq) was added after 20 min and a fourth equivalent of SmI_2 (1.13 ml, 0.12 mmol, 1 eq) after a further 30 min. The reaction mixture was then stirred for 1 h before quenching with aqueous saturated $NaHCO_3$ (1 ml), followed by the addition of citric acid (29.6 mg, 0.14 mmol, 1.2 eq). The aqueous layer was separated and extracted with EtOAc (3 x 30 ml) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give an orange solid. The residue was then purified by column chromatography (eluting with 30% EtOAc in hexane) to give the alcohol **292** (11 mg, 0.07 mmol, 31%) as a clear, colourless oil: υ_{max}(soln. in $CHCl_3$)/cm^{-1} 3154m (O-H), 3012s, 2983w, 1731m (C=O), 1467m, and 1217s; δ_H (400 MHz, $CDCl_3$) 4.13 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 3.53-3.43 (2H, m, C*H*$_2$OH), 2.32 (2H, m, C*H*$_2$CO$_2$Et), 1.73-1.57 (3H, m, 2H from CH_2 and 1H from CH_3C*H*), 1.49-1.40 (1H, m, 1H from CH_2), 1.26 (3H, t, *J* 7.1, CH_2C*H*$_3$), 1.21-1.09 (1H, m, 1H from CH_2), and 0.93 (3H, d, *J* 6.7, C*H*$_3$CH); δ_C (100 MHz, $CDCl_3$) 174.1 (C=O), 68.2 (CH_2OH), 60.5 (*C*H_2CH$_3$), 35.7 (CH), 34.7 (*C*H_2CO$_2$Et), 32.7 (CH_2), 22.4 (CH_2), 16.6 (*C*H_3CH), and 14.4 (CH_2*C*H_3);

m/z (CI mode, NH_3) 192 (100%), 175 (18), 146 (10), and 52 (8) (Found $(M + H)^+$, 175.1334. $C_9H_{19}O_3$ requires *M*, 175.1329).



270 $C_{13}H_{16}O_3S$ Mol. Wt.: 252.33

297 $C_{13}H_{18}O_3S$ Mol. Wt.: 254.35

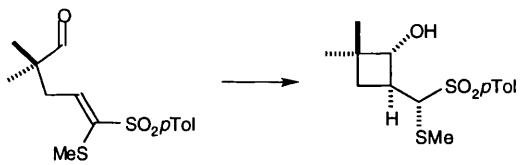
298 $C_{13}H_{18}O_3S$ Mol. Wt.: 254.35

***rel*-(1*R*, 4*S*)-2,2-Dimethyl-4-(phenylsulfonylmethyl)-cyclobutan-1-ol 297** and **(*E*)-2,2-dimethyl-5-phenylsulfonyl-pent-4-en-1-ol 298**

To a stirred solution of SmI_2 (0.1 M in THF, 1.59 ml, 0.16 mmol, 2 eq) in methanol (0.43 ml, 10.6 mmol) at 0°C was added a solution of aldehyde **270** (20 mg, 0.08 mmol, 1 eq) in THF (0.5 ml) *via* cannula. After 2 h, a further quantity of SmI_2 (0.80 ml, 0.08 mmol, 1 eq) was added before quenching the reaction with aqueous saturated NaCl (1 ml). Citric acid (20 mg, 0.10 mmol, 1.2 eq) was then added before the aqueous layer was separated and extracted with EtOAc (3 x 15 ml) and dried ($MgSO_4$). Concentration *in vacuo* gave a dark red oil. The residue was then purified by column chromatography (eluting with 30% EtOAc in hexane), which gave **297** (4 mg, 0.02 mmol, 21%) as a clear, colourless oil: ν_{max} (soln. in $CDCl_3$)/cm^{-1} 3606m, 3159m, 3070m, 3033m, 2970s, 2928m, 2865m, 1709s, 1598s, 1451s, 1309s (SO_2), and 1152s (SO_2); δ_H (400 MHz, $CDCl_3$) 7.94 (2H, apparent d, *J* 7.2, 2 x ArH), 7.71-7.67 (1H, m, ArH), 7.62-7.58 (2H, m, 2 x ArH), 3.71 (1H, d, *J* 7.7, C*H*OH), 3.26 (2H, apparent d, *J* 7.4, C$H_2$$SO_2$Ph), 2.69 (1H, br s, CHO*H*), 2.50-2.40 (1H, m, C*H*CH_2), 1.72 (1H, apparent t, *J* 10.1, 1H from CH_2), 1.11 (6H, s, 2 x CH_3), and 1.07 (1H, obscured 1H from CH_2); δ_C (100 MHz, $CDCl_3$) 139.4 (ArC), 134.0 (ArCH), 129.6 (2 x ArCH), 128.3 (2 x ArCH), 79.0 (CHOH), 60.8 (*C*$H_2$$SO_2$Ph), 39.6

(C), 35.1 (CH), 33.7 (CH_2), 28.7 (CH_3), and 20.8 (CH_3); *m/z* (CI mode, NH_3) 272 (100%), 254 (10), 237 (5), and 95 (2) (Found $(M + NH_4)^+$, 272.1320. $C_{13}H_{22}NO_3S$ requires *M*, 272.1315).

Further elution then gave **298** (7 mg, 0.03 mmol, 35%) as a colourless oil: ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3627m, 3017s, 2965s, 2928m, 2875m, 1630m, 1519m, 1446m, 1320s (SO_2), 1309s, 1215s, and 1146s (SO_2); δ_H (400 MHz, $CDCl_3$) 7.89 (2H, apparent d, *J* 8.6, 2 x ArH), 7.64-7.60 (1H, m, ArH), 7.57-7.53 (2H, m, 2 x ArH), 7.03 (1H, dt, *J* 14.9, 8.0, CH_2CH=), 6.36 (1H, d, *J* 14.9, =$CHSO_2Ph$), 3.34 (2H, s, CH_2OH), 2.22 (2H, d, *J* 8.0, CH_2CH=) and 0.93 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 144.5 (CH_2CH=), 140.9 (ArC), 133.5 (ArCH), 132.6 (=$CHSO_2Ph$), 129.4 (2 x ArCH), 127.7 (2 x ArCH), 71.3 (CH_2OH), 40.7 (CH_2CH=), 36.5 (C), 24.1 (2 x CH_3); *m/z* (CI mode, isobutane) 255 (100%), 237 (73), 198 (2), 154 (2), 143 (2), 125 (3), 113 (4), 95 (14), and 81 (12) (Found $(M + H)^+$, 255.1055. $C_{13}H_{19}O_3S$ requires *M*, 255.1050).



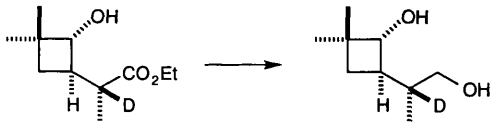
271
$C_{15}H_{20}O_3S_2$
Mol. Wt.: 312.45

304
$C_{15}H_{22}O_3S_2$
Mol. Wt.: 314.47

***rel*-(1*R*, 2*S*)-2,2-Dimethyl-4-[*rel*-(*S*)-methylsulfanyl-(toluene-4-sulfonyl)-methyl]-cyclobutan-1-ol 304**

To a stirred solution of SmI_2 (0.1M in THF, 3.53 ml, 0.35 mmol, 2 eq) in CH_3OH (0.88 ml, 22.7 mmol) at 0°C, was added a solution of aldehyde **271** (55 mg, 0.18 mmol, 1 eq) in THF (1 ml) *via* cannula. After 0.5 h another quantity of SmI_2 (1.77 ml, 0.18 mmol, 1 eq) was added and the reaction left for a further 0.5 h before aqueous saturated NaCl (1.5 ml) and citric acid (111 mg, 0.53 mmol, 3 eq) were added. The aqueous layer was then

separated and extracted with 80% EtOAc in Pet. Ether (40-60°C) (4 x 25 ml) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* then gave crude **304** as a 6:1 ratio of diastereoisomers. The residue was then purified by column chromatography (eluting with 25% EtOAc in Pet. Ether (40-60°C)) to give the major diastereomer **304** (33 mg, 0.11 mmol, 60%) as a white crystalline solid mp 140-141°C ($CHCl_3$ / hexane): υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3690m (O-H), 3154s, 2975s (C-H), 2928s (C-H), 2896s (C-H), 2865m (C-H), 1814s, 1793s, 1598s, (Ar-H), 1383s (SO_2) and 1141s (SO_2); δ_H (400 MHz, $CDCl_3$) 7.88 (2H, apparent d, *J* 8.1, 2 x ArCH), 7.38 (2H, apparent d, *J* 8.1, 2 x ArCH), 3.94 (1H, dd, *J* 7.3, 2.9, C*H*OH), 3.75 (1H, d, *J* 10.8, C*H*SCH_3), 3.31 (1H, d, *J* 2.9, OH), 2.51-2.42 (1H, partially hidden multiplet, CCH_2CH), 2.48 (3H, s, $PhCH_3$), 2.17 (3H, s, SCH_3), 1.78-1.73 (1H, dd, *J* 10.5, 9.2, 1H from CCH_2CH), 1.29-1.23 (1H, dd, *J* 10.5, 1H from CCH_2CH), 1.15 (3H, s, CH_3) and 1.13 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 145.4 (ArC), 132.9 (ArC), 130.4 (2 x ArCH), 129.6 (2 x ArCH), 79.0 (CHOH), 73.9 ($CHSCH_3$), 39.5 (CCH_2CH), 37.4 ($C(CH_3)_2$), 33.7 (CCH_2CH), 28.8 (CH_3), 21.9 ($PhCH_3$), 21.0 (CH_3) and 14.7 (SCH_3); *m/z* (CI+ mode, isobutane) 315 (2%), 297 (20), 267 (3), 229 (2), 199 (9), 197 (9), 159 (100), 157 (37), 131 (20) and 87 (27) (Found $(M + H)^+$, 315.1089. $C_{15}H_{23}O_3S_2$ requires *M*, 315.1083).



305a

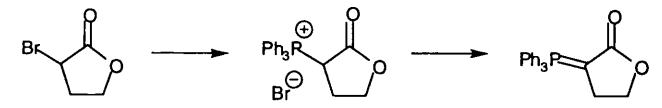
$C_{11}H_{19}DO_3$
Mol. Wt.: 201.28

311

$C_9H_{17}DO_2$
Mol. Wt.: 159.24

***rel*-(1*R*, 4*R*)-4-(2-Hydroxy-(1*R*)-1-deutero-methyl-ethyl)-2,2-dimethyl cyclobutanol 311**

To a stirred solution of deuterated cyclobutanol **305a** (30 mg, 0.15 mmol, 1 eq) in THF (1 ml), at 0 °C was added $LiAlH_4$ (11 mg, 0.30 mmol, 2 eq). After 1.5 h the reaction mixture was transferred to a solution of K/Na tartrate (421 mg, 1.49 mmol, 10 eq) in H_2O (1 ml) and the resulting mixture stirred for 10 min. The aqueous layer was then separated and extracted with EtOAc (4 x 5 ml) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* gave crude **311** as a clear colourless oil. The residue was then purified by sublimation which gave **311** as a white crystalline solid (14 mg, 0.09 mmol, 59%), mp 61-63°C: υ_{max}(neat)/cm^{-1} 3685m (O-H), 3601w, 3017s, 2954s, 2933m, 1604w, 1525m, 1477m, 1420m, 1078m, and 1020m; δ_H (400 MHz, $CDCl_3$) 3.65 (1H, dd, *J* 11.0, 8.3, 1H from C*H*$_2$OH), 3.58 (1H, dd, *J* 7.6, 5.8, C*H*OH), 3.37 (1H, dd, *J* 11.0, 4.0, 1H from C*H*$_2$OH), 2.60 (1H, dd, *J* 8.3, 4.0, CH$_2$O*H*), 2.37 (1H, d, *J* 5.8, CHO*H*), 1.79-1.69 (1H, m, CH), 1.67 (1H, apparent t, *J* 9.9, 1H from CH_2), 1.09 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.01 (1H, apparent t, *J* 9.9, 1H from CH_2), and 0.73 (3H, s, $CDCH_3$); δ_C (100 MHz, $CDCl_3$) 79.3 (CHOH), 68.9 (CH_2OH), 46.3 (CH), 37.7 (C), 32.1 (CH_2), 28.6 (CH_3), 20.8 (CH_3), and 14.1 ($CDCH_3$) ['CD' signal not observed]; *m/z* (CI mode, NH_3) 177 (16%), 159 (10), 142 (4), 124 (1), 88 (1), and 77 (1) (Found (M + NH_4)$^+$, 177.1713. $C_9H_{21}DNO_2$ requires *M*, 177.1708).



314
$C_4H_5BrO_2$
Mol. Wt.: 164.99

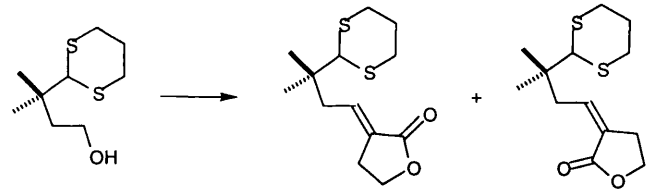
315
$C_{22}H_{20}BrO_2P$
Mol. Wt.: 427.27

316
$C_{22}H_{19}O_2P$
Mol. Wt.: 346.36

1-butyrolactonylidene triphenylphosphorane **316**[155]

To a stirred solution of α-bromo-γ-butyrolactone **314** (10.0 g, 60.6 mmol, 1 eq) in DME (24 ml) at rt, was added triphenylphosphine (15.9 g, 60.6 mmol, 1 eq). The reaction

mixture was then heated at reflux for 4 h before being allowed to cool to rt and stirred for a further 15 h. The brown crusty reaction mixture was dissolved in ethanol (10 ml) and a small quantity of EtOAc (0.5 ml) added. The mixture was cooled to —20°C for 3 days during which a pinky-brown crystalline solid formed. Phosphonium bromide salt **315** (15.9 g, 37.2 mmol, 61%) was then collected by filtration. A quantity of phosphonium bromide salt (2.00 g, 4.68 mmol) was then dissolved in H_2O (30 ml) and methanol (8ml) and the mixture stirred for 10 min, during which time gentle warming of the mixture was required to dissolve the salt. After that time aqueous saturated Na_2CO_3 (6 ml) was added, resulting in the instantaneous formation of a white precipitate which was collected by filtration, washed with H_2O (3 x 10 ml) and dried to give a white chalky solid. Recrystallisation from DMF gave **316** as a pale yellow crystalline solid (1.02 g, 2.95 mmol, 63%): δ_H (400 MHz, $CDCl_3$) 7.69-7.49 (15H, m, 15 x aromatic CH), 4.34 (2H, t, *J* 7.8, CH_2O) and 2.67 (2H, t, *J* 7.8, CH_2CH_2O).



287
$C_9H_{18}OS_2$
Mol. Wt.: 206.37

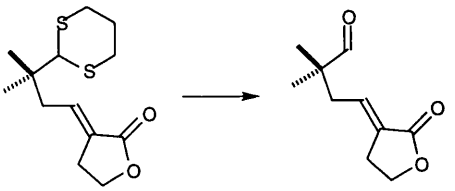
317-*E*
$C_{13}H_{20}O_2S_2$
Mol. Wt.: 272.43

317-*Z*
$C_{13}H_{20}O_2S_2$
Mol. Wt.: 272.43

2-[(*E*)-1,1-Dimethyl-3-(2-oxodihydrofuran-3-ylidene) propyl]-1,3-dithiane 317-*E* and **2-[(*Z*)-1,1-Dimethyl-3-(2-oxodihydrofuran-3-ylidene) propyl]-1,3-dithiane 317-*Z***

To a solution of **287** (1.02 g, 4.94 mmol, 1 eq) in CH_2Cl_2 (50 ml) at 0°C was added DMSO (3.51 ml, 49.4 mmol, 10 eq) and triethylamine (3.37 ml, 32.6 mmol, 6.6 eq). After 5 min, pyridine-sulfur trioxide complex (2.99 g, 18.8 mmol, 3.8 eq) was added and the reaction stirred for a further 30 min before being allowed to slowly warm to rt and left for a further 30 min. 1-Butyrolactonylidene triphenylphosphorane **316** (3.08 g, 8.89

mmol, 1.8 eq) was then added and the reaction mixture stirred for 13 h before the addition of aqueous saturated $NaHCO_3$ (5 ml). The aqueous layer was then separated and extracted with CH_2Cl_2 (5 x 50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (eluting with 30% EtOAc in hexane) gave **317** (1.23 g, 4.51 mmol, 91%) as a 4:1 mixture of (*E*) and (*Z*) isomers: ν_{max} (neat)/cm^{-1} 2965s, 2929s, 2828m, 1755s (C=O), 1679s, 1483m, 1465s, 1422s, 1387s, 1368s, 1216s, and 1034s; *m/z* (EI mode) 272 (10%), 161 (35), 119 (100), 112 (5), 83 (5), and 41 (5) (Found M^+, 272.0905. $C_{13}H_{20}S_2O_2$ requires *M*, 272.0900). The two isomers were isolated by further chromatography (eluting with CH_2Cl_2): (*E*) isomer **317-*E***; δ_H (400 MHz, $CDCl_3$) 6.82 (1H, tt, *J* 7.8, 2.9, CH_2CH=), 4.38 (2H, t, *J* 7.4, CH_2CH_2O), 4.03 (1H, s, SCHS), 2.96-2.88 (6H, m, 2H from CH_2CH_2O and 4H from 2 x SCH_2), 2.39 (2H, d, *J* 7.8, CH_2CH=), 2.13-2.06 (1H, m, 1H from SCH_2CH_2), 1.86-1.77 (1H, m, 1H from SCH_2CH_2), and 1.17 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 171.3 (C=O), 136.8 (CH_2CH=), 127.9 (CH=*C*), 65.7 (CH_2CH_2O), 60.2 (SCHS), 41.1 (CH_2CH=), 39.7 (C), 31.5 (2 x SCH_2), 26.1 (SCH_2CH_2), 25.7 (CH_2CH_2O), and 25.7 (2 x CH_3): (*Z*) isomer **317-*Z***; δ_H (400 MHz, $CDCl_3$) 6.38-6.33 (1H, m, CH_2CH=), 4.32 (2H, t, *J* 7.4, CH_2O), 4.06 (1H, s, SCHS), 2.99-2.94 (4H, m, 2H from CH_2CH_2O and 2H from CH_2CH=), 2.91-2.88 (4H, m, 2 x SCH_2), 2.13-2.06 (1H, m, 1H from SCH_2CH_2), 1.88-1.77 (1H, m, 1H from SCH_2CH_2), and 1.13 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 170.0 (C=O), 140.0 (CH_2CH=), 125.9 (CH=*C*), 65.4 (CH_2O), 60.7 (SCHS), 39.6 (C), 37.4 (CH_2CH=), 31.6 (2 x SCH_2), 29.7 (CH_2CH_2O), 26.2 (SCH_2CH_2), and 25.3 (2 x CH_3).

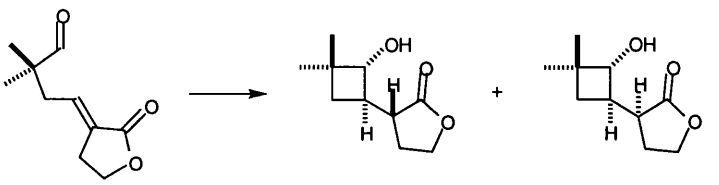


317-*E*
$C_{13}H_{20}O_2S_2$
Mol. Wt.: 272.43

312
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

(*E*)-2,2-Dimethyl-4-(2-oxo-dihydro-furan-3-ylidene)-butyraldehyde 312

To a stirred solution of **317-*E*** (117 mg, 0.43 mmol, 1 eq) in acetonitrile (4 ml) and distilled water (1 ml), was added $CaCO_3$ (129 mg, 1.28 mmol, 3 eq) and iodomethane (0.53 ml, 8.56 mmol, 20 eq). The mixture was refluxed for 20 h and then allowed to cool before filtration through a short column of silica gel (eluting with 50% EtOAc in hexane). Concentration *in vacuo* gave aldehyde **312** (80 mg, 0.43 mmol, 100%) as a clear yellow oil which was stored at —20°C under nitrogen, and used without further purification: ν_{max} (neat)/cm^{-1} 2969s, 2930s, 2873s, 2816m, 2712m, 1752s, 1725s, 1681s, 1366m, 1354m, 1214s, and 1034s; δ_H (400 MHz, $CDCl_3$) 9.49 (1H, s, CHO), 6.71 (1H, tt, *J* 7.9, 3.0, CH_2CH=), 4.39 (2H, t, *J* 7.4, CH_2CH_2O), 2.92-2.87 (2H, m, CH_2CH_2O), 2.35 (2H, d, *J* 7.9, CH_2CH=), and 1.15 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 204.6 (CHO), 170.9 (C=O), 135.4 (CH_2CH=), 128.3 (CH=*C*), 65.6 (CH_2CH_2O), 46.5 (C), 37.2 (CH_2CH=), 25.4 (CH_2CH_2O) and 21.7 (2 x CH_3); *m/z* (CI mode, isobutane) 183 (100%), 169 (3), 165 (2), 154 (2), 121 (1), and 99 (1) (Found $(M + H)^+$, 183.1019. $C_{10}H_{15}O_3$ requires *M*, 183.1017).



312
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

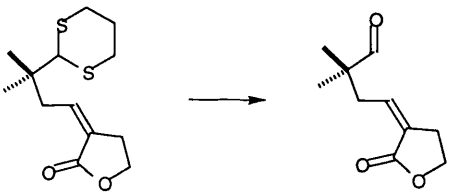
318a
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

318b
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

***rel*-(3*R*)-(*rel*-(1*R*, 2*R*)-2-Hydroxy-3,3-dimethyl-cyclobutyl)-dihydro-furan-2-one 318a** and ***rel*-(3*S*)-(*rel*-(1*R*, 2*R*)-2-Hydroxy-3,3-dimethyl-cyclobutyl)-dihydro-furan-2-one 318b**

To a stirred solution of SmI_2 (0.1M in THF, 11.8 ml, 1.18 mmol, 2 eq) in CH_3OH (2.94 ml) at 0°C was added dropwise a solution of aldehyde **312** (108 mg, 0.59 mmol, 1 eq) in THF (1.5 ml). After 0.5 h, another quantity of SmI_2 (0.1 M in THF, 2.96 ml, 0.30 mmol, 0.5 eq) was added and the reaction stirred for a further 1 h. To the reaction mixture was then added aqueous saturated NaCl (5 ml) and citric acid (310 mg, 1.48 mmol, 2.5 eq). The aqueous layer was separated and extracted with 80% EtOAc in hexane (4 x 30 ml) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* gave crude **318** as a red oil. Purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave 3(*R/S*)-(*rel*-(1*R*, 2*R*)-2-hydroxy-3,3-dimethyl-cyclobutyl)-dihydro-furan-2-one (86 mg, 0.47 mmol, 79%) as a 4:1 mixture of diastereoisomers; ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3548m, 3025s, 2961s, 2925s, 2867s, 1762s (C=O), 1375s, 1216s, 1105s, and 1028s; *m/z* (CI mode, isobutane) 185 (41%), 167 (100), 149 (1), 128 (3), and 113 (2) (Found $(M + H)^+$, 185.1178. $C_{10}H_{17}O_3$ requires *M*, 185.1173). The epimers were separated by further chromatography (eluting with 50% EtOAc in hexane): major cyclobutanol **318a**; δ_H (400 MHz, $CDCl_3$) 4.40 (1H, td, *J* 8.8, 2.6, 1H from CH_2CH_2O), 4.27-4.20 (1H, m, 1H from CH_2CH_2O), 3.76 (1H, d, *J* 7.7, *CH*OH), 2.81 (1H, br s,

CHO*H*), 2.60 (1H, q, *J* 9.6, CHC(O)O), 2.38-2.30 (1H, m, 1H from C*H*$_2$CH$_2$O), 2.23-2.14 (1H, m, CH), 1.99-1.88 (1H, m, 1H from C*H*$_2$CH$_2$O), 1.71 (1H, apparent t, *J* 9.9, 1H from CH$_2$), 1.16 (1H, obscured, 1H from CH$_2$), 1.13 (3H, s, CH$_3$), and 1.12 (3H, s, CH$_3$); δ_C (100 MHz, $CDCl_3$) 180.0 (C=O), 78.1 (CHOH), 67.6 (CH$_2$*C*H$_2$O), 44.0 (*C*HCO$_2$), 41.6 (CH), 38.8 (C), 32.4 (CH$_2$), 28.8 (CH$_3$), 27.7 (*C*H$_2$CH$_2$O), 21.0 (CH$_3$); minor cyclobutanol **318b**; δ_H (400 MHz, $CDCl_3$) 4.33 (1H, dt, *J* 8.7, 4.2, 1H from CH$_2$C*H*$_2$O), 4.26-4.19 (1H, m, 1H from CH$_2$C*H*$_2$O), 3.78 (1H, d, *J* 8.0, C*H*OH), 2.66 (1H, apparent q, *J* 8.5, CHC(O)O), 2.43-2.28 (2H, m, 1H from *C*H$_2$CH$_2$O and 1H from CCH$_2$C*H*), 2.17-2.05 (1H, m, 1H from C*H*$_2$CH$_2$O), 1.82 (1H, apparent t, *J* 10.3, 1H from CC*H*$_2$CH), 1.20 (1H, app. t, *J* 10.3, 1H from CC*H*$_2$CH) and 1.09 (6H, s, C(CH$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 178.7 (C=O), 77.0 (CHOH), 66.9 (CH$_2$*C*H$_2$O), 42.2 (*C*HC(O)O), 41.5 (CCH$_2$*C*H), 39.2 (*C*(CH$_3$)$_2$), 32.1 (C*C*H$_2$CH), 28.3 (CH$_3$), 27.2 (*C*H$_2$CH$_2$O) and 20.7 (CH$_3$).



317-*Z*

$C_{13}H_{20}O_2S_2$
Mol. Wt.: 272.43

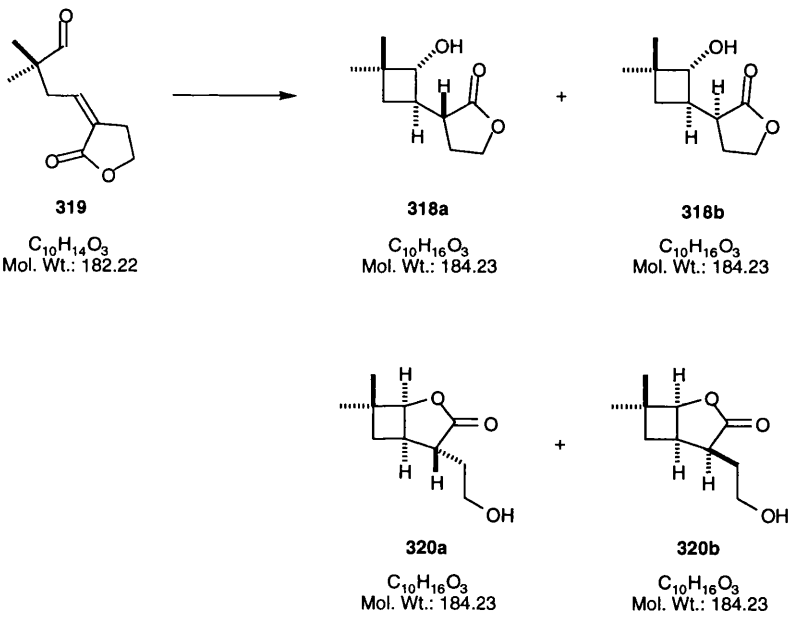
319

$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

(*Z*)-2,2-Dimethyl-4-(2-oxo-dihydro-furan-3-ylidene)-butyraldehyde 319

To a stirred solution of **317-*Z*** (246 mg, 0.90 mmol, 1 eq) in acetonitrile (5.6 ml) and distilled water (1.4 ml) was added $CaCO_3$ (271 mg, 2.71 mmol, 3 eq) and iodomethane (1.13 ml, 18.1 mmol, 20 eq). The mixture was then heated at reflux for 19 h before a further quantity of iodomethane (0.28 ml, 4.52 mmol, 5 eq) was added. The reaction was left for another 5 h and then allowed to cool to room temerature before being poured onto a short column of silica gel and eluted with 50% EtOAc in hexane. Concentration *in*

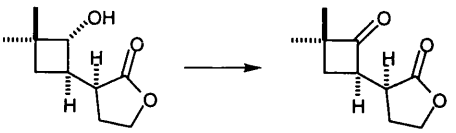
vacuo gave the aldehyde **319** (147 mg, 0.81 mmol, 90%) as a clear pale yellow oil which was used without further purification: υ_{max} (neat)/cm^{-1} 2969s (C-H), 2930s (C-H), 2873s, 2816m (CHO), 2712m (CHO), 1752s (lactone C=O), 1725s (aldehyde C=O), 1681s (C=C), 1366m ($C(CH_3)_2$), 1354m ($C(CH_3)_2$), 1214s, 1034s; δ_H (400 MHz, $CDCl_3$) 9.48 (1H, s, CHO), 6.17 (1H, t, *J* 7.9, CH_2CH=), 4.33 (2H, t, *J* 7.3, CH_2O), 2.97-2.92 (4H, m, 2H from CH_2CH_2O and 2H from CH_2CH=) and 1.13 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 205.5 (CHO), 170.1 (C=O), 138.4 (*C*H=C), 126.5 (CH=*C*), 65.5 (CH_2O), 46.8 ($C(CH_3)_2$), 34.1 (CH_2CH=), 29.3 (CH_2CH_2O) and 21.5 ($C(CH_3)_2$); *m/z* (CI+ mode, isobutane) 183 (100%), 165 (6), 153 (7), 101 (3), 81 (6) and 69 (12) (Found $(M + H)^+$, 183.1021. $C_{10}H_{15}O_3$ requires *M*, 183.1017).



Cyclisation of **(*Z*)-2,2-Dimethyl-4-(2-oxo-dihydro-furan-3-ylidene)-butyraldehyde 319**

To a stirred solution of SmI_2 (0.1M in THF, 4.70 ml, 0.47 mmol, 2 eq) in CH_3OH (1.17 ml) at 0°C was added dropwise a solution of aldehyde **319** (43 mg, 0.23 mmol, 1 eq) in THF (0.6 ml). After 10 min, another quantity of SmI_2 (0.1 M in THF, 2.30 ml, 0.23

mmol, 1 eq) was added and the reaction stirred for a further 1 h. To the reaction mixture was then added aqueous saturated NaCl (2 ml) and citric acid (148 mg, 0.70 mmol, 3 eq). The aqueous layer was separated and extracted with 80% EtOAc in hexane (4 x 15 ml) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* gave the crude product mixture as a red oil. Purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave an approximately 2:1:2:1 mixture of compounds **318a**:**318b**:**320a**:**320b** (29 mg, 0.16 mmol, 68% (combined yield)). Elucidation of the product mixture was achieved by the preparation of bicyclic lactones **320a** and **320b** by an independent method (*vide infra*).



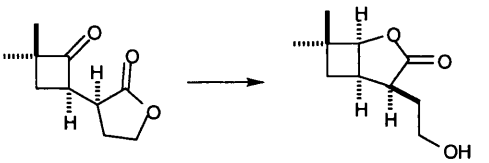
318b
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

331
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

***rel*-(3*S*)-(*rel*-(1*R*)-3,3-Dimethyl-2-oxo-cyclobutyl)-dihydrofuran-2(3*H*)-one 331**

To a stirred solution of cyclobutanol **318b** (70 mg, 0.38 mmol, 1 eq) in CH_2Cl_2 (3.8 ml) at room temperature was added 4Å molecular sieves, NMO (177 mg, 1.51 mmol, 4 eq), and TPAP (7 mg, 0.02 mmol, 0.05 eq). After 5 h, the reaction mixture was poured onto a short column of silica gel and eluted with 50% EtOAc in Pet. Ether (40-60°C). Concentration *in vacuo* gave the cyclobutanone **331** (67 mg, 0.37 mmol, 97%) as a clear colourless oil: υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3028s (C-H), 2949s (C-H), 2875s (C-H), 1756s (lactone C=O), 1709s (ketone C=O), 1656m, 1530m, 1467m, and 1367m; δ_H (400 MHz, $CDCl_3$) 4.37 (1H, td, *J* 8.8, 2.9, 1H from CH_2O), 4.21 (1H, dt, *J* 9.3, 6.7, 1H from CH_2O), 3.66-3.60 (1H, m, CCH_2CH), 2.89-2.82 (1H, m, $CHC(O)O$), 2.49-2.41 (1H, m, 1H from CH_2CH_2O), 2.18 (1H, apparent t, *J* 11.2, 1H CCH_2CH), 2.15-2.04 (1H, m, 1H from

C*H*$_2$CH$_2$O), 1.78 (1H, dd, *J* 11.2, 8.4, 1H from CC*H*$_2$CH), 1.27 (3H, s, CH_3) and 1.19 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.4 (C=O, ketone), 177.2 (C=O, ester), 67.0 (CH_2O), 58.5 (*C*(CH_3)$_2$), 54.2 (CCH_2*C*H), 39.6 (*C*HC(O)O), 31.5 (C*C*H$_2$CH), 27.3 (*C*H$_2$CH$_2$O), 24.1 (CH_3) and 21.9 (CH_3); *m/z* (CI+ mode, isobutane) 182 (22%), 154 (9), 126 (27), 111 (12), 83 (36), 70 (100) and 41 (21) (Found M^+, 182.0943. $C_{10}H_{14}O_3$ requires *M*, 182.0939).



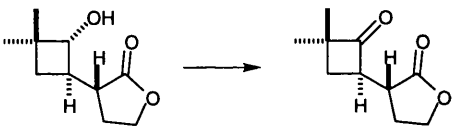
331
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

320b
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

***rel*-(1*S*, 4*S*, 5*R*)-4-(2-Hydroxy-ethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 320b**

To a stirred solution of cyclobutanone **331** (22 mg, 0.12 mmol, 1 eq) in THF (0.5 ml) at —78°C was added L-Selectride (1.0 M in THF, 0.13 ml, 0.13 mmol, 1.1 eq) dropwise. After 1 h, aqueous saturated $NaHCO_3$ (1 ml) was added and the aqueous layer separated and extracted with EtOAc (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude as a clear colourless oil. Purification by column chromatography (eluting with 60% EtOAc in Pet. Ether (40-60°C)) gave bicyclic lactone **320b** (20 mg, 0.11 mmol, 88%) as a clear colourless oil: υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3681s (O-H), 3020s (C-H), 2959s (C-H), 2869s (C-H), 1761s (C=O), 1520s, 1425s, 1021s and 932s; δ_H (400 MHz, $CDCl_3$) 4.44 (1H, dd, *J* 5.2, 3.0, HCOC(O)), 3.83-3.77 (1H, m, 1H from C*H*$_2$OH), 3.70-3.64 (1H, m, 1H from C*H*$_2$OH), 3.24-3.17 (1H, m, CCH$_2$C*H*), 2.85-2.79 (1H, apparent q, *J* 8.0, C*H*C(O)O), 2.11-2.01 (1H, m, 1H from C*H*$_2$CH$_2$OH), 1.87-1.76 (1H, m, 1H from CC*H*$_2$CH), 1.73-1.65 (2H, m, 1H from C*H*$_2$CH$_2$OH and 1H from CC*H*$_2$CH), 1.23 (3H, s, CH_3) and 1.13 (3H, s, CH_3); δ_C (100

MHz, $CDCl_3$) 199.1 (C=O), 85.1 (*C*HOC(O)), 61.4 (CH_2OH), 41.1 (*C*HCO), 38.3 ($C(CH_3)_2$), 33.3 (CCH_2CH), 33.2 (CCH_2CH), 29.0 (CH_2CH_2OH), 26.4 (CH_3) and 22.4 (CH_3); *m/z* (CI+ mode, isobutane) 185 (100%), 167 (8), 128 (2) and 111 (2) (Found $(M + H)^+$, 185.1176. $C_{10}H_{17}O_3$ requires M, 185.1173).



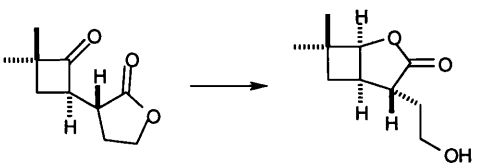
318a
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

***rel*-(3*R*)-(*rel*-(1*R*)-3,3-Dimethyl-2-oxo-cyclobutyl)-dihydrofuran-2(3*H*)-one 329**

To a stirred solution of **318a** (101 mg, 0.55 mmol, 1 eq) in CH_2Cl_2 (5.5 ml) at room temperature was added 4Å molecular sieves (10 mg), NMO (256 mg, 2.19 mmol, 4 eq), and TPAP (16 mg, 0.05 mmol, 0.09 eq). After 4 h the reaction mixture was filtered through a short column of silica gel (eluting with 50% EtOAc in Pet. Ether (40-60°C)). Concentration *in vacuo* gave cyclobutanone **329** (100 mg, 0.55 mmol, 100%) as a clear colourless oil: υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3028s (C-H), 2949s (C-H), 2875s (C-H), 1756s (lactone C=O), 1709s (ketone C=O), 1656m, 1530m, 1467m, and 1367m; δ_H (400 MHz, $CDCl_3$) 4.41 (1H, td, *J* 8.9, 1.9, 1H from CH_2O), 4.24-4.18 (1H, m, 1H from CH_2O), 3.98-3.92 (1H, m, CCH_2CH), 3.00-2.94 (1H, m, *CH*C(O)), 2.39-2.32 (1H, m, 1H from CH_2CH_2O), 2.19-2.08 (1H, m, 1H from CH_2CH_2O), 2.05 (1H, t, *J* 11.0, 1H from CCH_2CH), 1.91-1.86 (1H, m, 1H from CCH_2CH), 1.30 (3H, s, 3H from $C(CH_3)_2$), and 1.16 (3H, s, 3H from $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 214.8 (C=O of ketone), 177.5 (C=O of lactone), 66.8 (CH_2O), 58.1 ($C(CH_3)_2$), 53.7 (CCH_2CH), 37.7 (*C*HC(O)), 28.7 (CCH_2CH), 26.1 (CH_2CH_2O), 24.0 (CH_3), and 21.2 (CH_3); *m/z* (EI+ mode) 182 (26%),

154 (11), 126 (35), 111 (12), 82 (35), 70 (100), and 41 (27) (Found M^+, 182.0943. $C_{10}H_{14}O_3$ requires *M*, 182.0939).

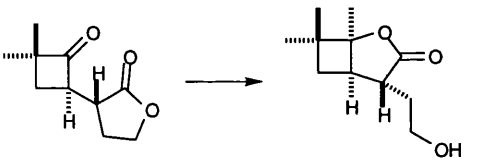


329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

320a
$C_{10}H_{16}O_3$
Mol. Wt.: 184.23

***rel*-(1*S*, 4*R*, 5*R*)-4-(2-Hydroxy-ethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 320a**

To a stirred solution of cyclobutanone **329** (22 mg, 0.12 mmol, 1 eq) in THF (0.5 ml) at —78°C was added L-Selectride (1.0 M in THF, 0.14 ml, 0.14 mmol, 1.1 eq) dropwise. After 1 h, aqueous saturated $NaHCO_3$ (0.5 ml) was added and the aqueous layer separated and extracted with EtOAc (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless cloudy oil. Purification by column chromatography (eluting with 60% EtOAc in Pet. Ether (40-60°C)) gave bicyclic lactone **320a** (13 mg, 0.07 mmol, 59%) as a clear colourless oil: υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3619s (O-H), 3149s, 2959s (C-H), 2931s (C-H), 2863s (C-H), 1755s (C=O), 1637m, 1559m, 1464s, 1380s, 1167s and 1094s; δ_H (400 MHz, $CDCl_3$) 4.50-4.48 (1H, dd, *J* 5.8, 2.6, HCOC(O)), 3.84-3.71 (2H, m, C*H*$_2$OH), 2.85-2.79 (1H, m, CCH_2CH), 2.65 (1H, dt, *J* 7.4, 1.4, C*H*C(O)O), 2.10-2.04 (1H, m, 1H from C*H*$_2$CH), 1.92-1.74 (2H, m, C*H*$_2$CH$_2$OH), 1.63-1.58 (1H, dd, *J* 12.2, 6.8, 1H from C*H*$_2$CH), 1.20 (3H, s, CH_3) and 1.15 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 181.8 (C=O), 85.6 (*C*HOC(O)), 60.5 (CH_2OH), 44.9 (*C*HCO), 39.0 (*C*$(CH_3)_2$), 38.7 (C*C*H$_2$CH), 34.6 (CCH_2CH), 34.5 (*C*H$_2$CH$_2$OH), 27.0 (CH_3) and 22.6 (CH_3); *m/z* (CI+ mode, isobutane) 185 (100%), 167 (21), 149 (2), 139 (1), 128 (4), 110 (2), 95 (1) and 83 (1) (Found $(M + H)^+$, 185.1178. $C_{10}H_{17}O_3$ requires M, 185.1173).



329

$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

330

$C_{11}H_{18}O_3$
Mol. Wt.: 198.26

***rel*-(1*S*, 4*R*, 5*R*)-4-(2-Hydroxyethyl)-1,7,7-trimethyl-2-oxa-bicyclo[3.2.0]heptane-3-one 330**

Method A-using MeMgBr.

To a stirred solution of cyclobutanone **329** (18 mg, 0.10 mmol, 1 eq), in THF (0.5 ml) at —78°C was added MeMgBr (3.0 M in Et_2O, 0.04 ml, 0.12 mmol, 1.2 eq) dropwise. The reaction mixture was allowed to stir at this temperature for 2 h before a further quantity of MeMgBr (3.0 M in Et_2O, 0.04 ml, 0.12 mmol, 1.2 eq) was added. After another 1 h, aqueous saturated NH_4Cl (1 ml) was added and the aqueous layer separated and extracted with EtOAc (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **330** as a clear colourless oil. Purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave the pure bicyclic lactone **330** (6 mg, 0.03 mmol, 29%) as a clear colourless oil.

Method B-using MeLi

To a stirred solution of cyclobutanone **329** (27 mg, 0.15 mmol, 1 eq), in THF (0.8 ml) at —78°C was added MeLi.LiBr (1.26 M in Et_2O, 0.14 ml, 0.18 mmol, 1.2 eq) dropwise. The reaction mixture was allowed to stir at this temperature for 2 h before aqueous saturated NH_4Cl (1 ml) was added and the aqueous layer separated and extracted with EtOAc (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy colourless oil. Purification of the residue by column

chromatography (eluting with 50% EtOAc in hexane) gave the pure bicyclic lactone **330** (0.5 mg, 0.003 mmol, 2%) as a clear colourless oil and cyclobutanone **329** (6.3 mg, 0.03 mmol, 28%).

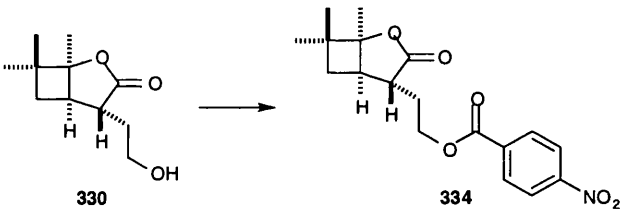
Method C-using 'MeLi-$CeCl_3$'

$CeCl_3.7H_2O$ (49 mg, 0.13 mmol, 1.3 eq) was dried at 140°C, 0.1 mmHg for 2 h. The resultant white powder was then allowed to cool, THF (0.5 ml) added, and the resulting solution stirred for 30 min before being cooled to —78°C. MeLi.LiBr (1.26 M in Et_2O, 0.1 ml, 0.13 mmol, 1.3 eq) was then added dropwise and the reaction mixture left for a further 45 min. A solution of cyclobutanone **329** (18 mg, 0.10 mmol, 1 eq) in THF (0.2 ml) was then added *via* cannula and the reaction mixture left to stir at that temperature for 2 h. Aqueous saturated NH_4Cl (1 ml) was then added and the aqueous layer separated and extracted with $CHCl_3$ (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave the pure fused lactone **330** (7 mg, 0.04 mmol, 53%). [Yield based on recovered starting material].

Method D-using "MeLi-$Yb(OTf)_3$"

To a stirred solution of dried $Yb(OTf)_3$ (185 mg, 0.30 mmol, 2 eq) in THF (7.2 ml) at —78°C was added MeLi.LiBr (1.26 M in THF, 0.24 ml, 0.30 mmol, 2 eq) and the mixture left for 40 min. The intensely coloured burgandy solution was then added dropwise *via* cannula to a stirred solution of cyclobutanone **329** (27 mg, 0.15 mmol, 1 eq) in THF (0.4 ml) also at —78°C. After 35 min, aqueous saturated $NaHCO_3$ (1 ml) was added and the aqueous layer separated and extracted with $CHCl_3$ (4 x 15 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a clear, colourless oil. Purification by column chromatography (eluting with 50% EtOAc in Pet. Ether (40-60°C)) gave the pure bicyclic lactone **330** as a clear colourless oil (20 mg, 0.10 mmol, 68%): υ_{max} ($CHCl_3$ soln.)/cm^{-1}

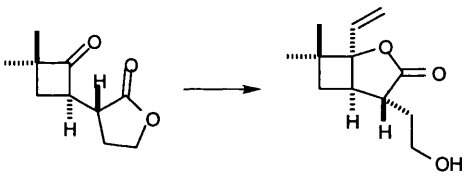
3685s (O-H), 3028s, (C-H), 2959s (C-H), 2933s (C-H), 2870m (C-H), 1750s (C=O), 1519s, 1477s and 1425s; δ_H (400 MHz, $CDCl_3$) 3.86-3.74 (2H, m, CH_2OH), 2.66 (1H, t, *J* 7.7, CHCO), 2.55 (1H, td, *J* 8.0, 1.0, CCH_2CH), 2.02 (1H, dd, *J* 12.2, 8.0, 1H from CCH_2CH), 1.93-1.85 (1H, m, 1H from CH_2CH_2OH), 1.83-1.74 (1H, m, 1H from CH_2CH_2OH), 1.54 (1H, dd, *J* 12.2, 8.0, 1H from CCH_2CH), 1.36 (3H, s, CH_3C), 1.15 (3H, s, 3H from $C(CH_3)_2$), and 1.04 (3H, s, 3H from $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 181.0 (C=O), 92.3 ($COC(O)$), 77.4 ($C(CH_3)_2$), 60.8 (CH_2OH), 46.3 ($CHCO$), 40.9 (CCH_2CH), 38.1 (CCH_2CH), 35.4 (CH_2CH_2OH), 25.8 (CH_3), 22.4 (CH_3), and 19.7 (CH_3C); *m/z* (CI+ mode, isobutane) 199 (100%), 181 (18), 155 (4), 142 (5), 115 (15), and 69 (3) (Found $(M + H)^+$, 199.1334. $C_{11}H_{19}O_3$ requires *M*, 199.1329).



p-Nitro benzoic acid-2-(*rel*-(1*S*, 4*R* , 5*R*)-1,7,7-trimethyl-2-oxa-3-oxo-bicyclo[3.2.0]hept-4-yl)ethyl ester 334

To a stirred solution of bicyclic lactone **330** (15 mg, 0.08 mmol, 1 eq) in pyridine (0.5 ml) at room temperature was added *p*-nitrobenzyl chloride (21 mg, 0.12 mmol, 1.5 eq) and the reaction mixture stirred at that temperature for 3.5 days. Aqueous saturated $NaHCO_3$ (1 ml) was then added and the aqueous layer separated and extracted with $CHCl_3$ (4 x 10 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **334** as a yellow solid (23 mg, 0.07 mmol, 88%). Recrystallisation from EtOH gave white crystals suitable for crystallographic analysis (mp 146-147°C): υ_{max} ($CDCl_3$

soln.)/cm^{-1} 3154s, 2980s (C-H), 2933s (C-H), 2902s (C-H), 2870m (C-H), 1756s (C=O, lactone), 1724s (C=O, ester), 1646m, 1614m, 1567m (NO_2), 1530s (NO_2) and 1383s (NO_2); δ_H (400 MHz, $CDCl_3$) 8.31-8.29 (2H, apparent d, *J* 8.8, 2 x ArH), 8.22-8.20 (2H, apparent d, *J* 8.8, 2 x ArH), 4.56-4.46 (2H, m, CH_2O), 2.66-2.58 (2H, m, 1H from COCH and 1H from CCH_2CH), 2.24-2.16 (1H, m, 1H from CH_2CH_2OH), 2.08-1.96 (2H, m, 1H from CCH_2CH and 1H from CH_2CH_2OH), 1.55 (1H, dd, *J* 12.2, 7.0, 1H from CCH_2CH), 1.37 (3H, s, $CH_3COC(O)$), 1.16 (3H, s, 3H from $C(CH_3)_2$), and 1.06 (3H, s, 3H from $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 179.5 (C=O, lactone), 164.5 (C=O, ester), 150.6 (ArC), 135.4 (ArC), 131.0 (2 x ArCH), 123.8 (2 x ArCH), 91.8 (CCH_3), 63.4 (CH_2CH_2O), 46.0 (*C*HCO), 41.0 ($C(CH_3)_2$), 40.2 (CCH_2CH), 38.1 (CCH_2CH), 31.4 (CH_2CH_2O), 25.8 (CCH_3), 22.5 ($C(CH_3)_2$) and 19.8 ($C(CH_3)_2$); *m/z* (CI+ mode, isobutane) 348 (100%), 318 (6), 291 (2), 181 (5), 163 (2) and 150 (2) (Found $(M + H)^+$, 348.1450. $C_{18}H_{22}O_6N$ requires *M*, 348.1441) (Found: C, 62.29; H, 6.10; N, 3.91. $C_{18}H_{21}O_6N$ requires, C, 62.24; H, 6.09; N, 4.03%).



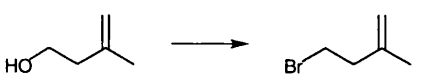
329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

335
$C_{12}H_{18}O_3$
Mol. Wt.: 210.27

rel-(1*S*, 4*R*, 5*R*)-4-(2-Hydroxyethyl)-7,7-dimethyl-1-vinyl-2-oxa-bicyclo[3.2.0]heptan-3-one 335

To a stirred solution of $Yb(OTf)_3$ (359 mg, 0.58 mmol, 3.2 eq) in THF (14 ml) at —78°C was added vinylmagnesium bromide (1.0 M in THF, 0.58 ml, 0.58 mmol, 3.2 eq) and the mixture left for 15 min. Half of the orange coloured solution (7ml, 0.29 mmol, 1.6 eq) was then added dropwise *via* cannula to a stirred solution of cyclobutanone **329** (33 mg,

0.18 mmol, 1 eq) in THF (0.4 ml) also at —78°C. After 20 min, the remaining vinylytterbium (7 ml, 0.29 mmol, 1.6 eq) was added to the reaction mixture and the reaction left for another 20 min. Aqueous saturated $NaHCO_3$ (2 ml) was then added followed by citric acid (122 mg, 0.58 mmol, 3.2 eq). The aqueous layer was separated and extracted with EtOAc (4 x 20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (eluting with 20% EtOAc in CH_2Cl_2) to give the bicyclic lactone **335** (26 mg, 0.12 mmol, 67%) as a clear colourless oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3685s (O-H), 3022s (C-H), 2959s (C-H), 2933m (C-H), 2870m (C-H), 1756s (C=O), 1604m (C=C), 1519s, 1425s and 1335m; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, dd, *J* 17.3, 11.0, C*H*=CH_2), 5.34 (1H, d, *J* 17.3, *trans* 1H from CH=C*H*$_2$), 5.23 (1H, d, *J* 11.0, *cis* 1H from CH=C*H*$_2$), 3.80-3.72 (2H, m, C*H*$_2$OH), 2.83 (1H, apparent t, *J* 8.2, CCH_2CH), 2.67 (1H, t, *J* 7.8, CHCO), 2.01 (1H, dd, *J* 12.0, 8.8, 1H from CC*H*$_2$CH), 1.86-1.68 (2H, m, C*H*$_2$CH$_2$OH), 1.57 (1H, dd, *J* 12.0, 7.6, 1H from CC*H*$_2$CH), 1.15 (3H, s, CH_3) and 1.06 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.6 (C=O), 134.4 (*C*H=CH_2), 116.5 (CH=*C*H$_2$), 93.2 (*C*OC(O)), 60.7 (CH_2OH), 45.5 (*C*HCO), 42.3 (*C*(CH_3)$_2$), 39.3 (CCH_2CH), 37.4 (C*C*H$_2$CH), 34.5 (*C*H$_2$CH$_2$OH), 26.1 (CH_3) and 22.3 (CH_3); *m/z* (CI+ mode, isobutane) 211 (100%), 193 (17), 167 (5), 154 (7), 136 (3), 115 (9), 107 (2) and 79 (2) (Found $(M + H)^+$, 211.1334. $C_{12}H_{19}O_3$ requires *M*, 211.1329).



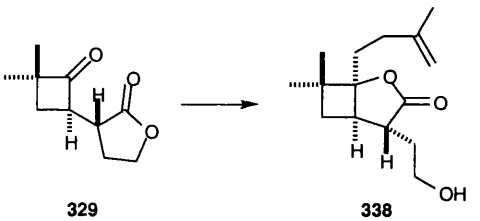
336
$C_5H_{10}O$
Mol. Wt.: 86.13

337
C_5H_9Br
Mol. Wt.: 149.03

4-Bromo-2-methyl-1-butene **337**[167]

To a stirred solution of 4-hydroxy-2-methyl-but-1-ene **336** (5.05 ml, 50.0 mmol, 1 eq) and triphenylphosphine (14.4 g, 55.0 mmol, 1.1 eq) in CH_2Cl_2 (15 ml) at 0°C, was added

N-bromosuccinimide (9.79 g, 55.0 mmol, 1.1 eq) slowly over 10 min. After 1 h the purple coloured reaction mixture was allowed to warm to room temperature and left to stir at that temperature for a further 15 h. The mixture was then diluted with pentane (30 ml) and passed through a short column of silica gel, eluting with pentane. After concentration *in vacuo*, the resultant oil was distilled under reduced pressure (29°C/water pump pressure) to give the title compound **337** (3.60g, 24.2 mmol, 48%) as a clear colourless oil: δ_H (400 MHz, $CDCl_3$) 4.87 (1H, apparent s, 1H from $=CH_2$), 4.79 (1H, apparent s, 1H from $=CH_2$), 3.49 (2H, t, *J* 7.4, CH_2Br), 2.59 (2H, t, *J* 7.4, CH_2CH_2Br) and 1.76 (3H, s, CH_3).



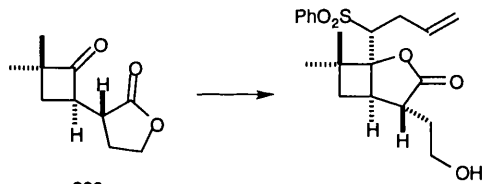
329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

338
$C_{15}H_{24}O_3$
Mol. Wt.: 252.35

***rel*-(1*S*, 4*R*, 5*R*)-4-(2-Hydroxyethyl)-1-[3-methyl-but-3-enyl]-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 338**

To a stirred solution of $Yb(OTf)_3$ (170 mg, 0.27 mmol, 2 eq) in THF (6 ml) at —78°C was added 3-methyl-3-butenylmagnesium bromide (1.0 M in THF, 0.41 ml, 0.41 mmol, 3 eq) dropwise and the mixture left for 15 min. After that time a solution of cyclobutanone **329** (25 mg, 0.14 mmol, 1 eq) in THF (2.5 ml) also at —78°C was added to the lilac coloured mixture. The reaction mixture was left at that temperature for 3 h before aqueous saturated $NaHCO_3$ (1 ml) was added followed by citric acid (58 mg, 0.27 mmol, 3.2 eq). The aqueous layer was then separated and extracted with Et_2O (4 x 15 ml) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy, colourless oil. Purification by column chromatography (eluting with 40% EtOAc in Pet.

Ether (40-60°C) gave bicyclic lactone **338** (23 mg, 0.09 mmol, 66%) as a clear colourless oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3616m (O-H), 3154 (O-H), 2965s (C-H), 2933s (C-H), 2902s, 2865s, 1751s (C=O), 1651m (C=C), 1467s, 1383s and 1099s; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, s, 1H from $C=CH_2$), 4.69 (1H, s, 1H from $C=CH_2$), 3.83-3.74 (2H, m, CH_2OH), 2.66 (1H, t, *J* 7.9, CHCO), 2.53 (1H, apparent t, *J* 7.9, CCH_2CH), 2.19-2.12 (1H, m, 1H from CH_2^A), 2.06-1.88 (4H, m, 1H from CCH_2CH, 1H from CH_2CH_2O, 1H from CH_2^A and 1H from CH_2^B), 1.81-1.64 (2H, m, 1H from CH_2CH_2O and 1H from CH_2^B), 1.74 (3H, s, $=CCH_3$), 1.51 (1H, dd, *J* 12.2, 6.9, 1H from CCH_2CH), 1.22 (3H, s, CH_3) and 1.11 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 181.3 (C=O), 145.3 ($C=CH_2$), 110.1 ($C=CH_2$), 93.9 (COC(O)), 61.0 (CH_2O), 46.4 (CHCO), 41.3 ($C(CH_3)_2$), 39.8 (CCH_2CH), 38.3 (CCH_2CH), 35.2 (CH_2CH_2O), 33.2 (CH_2^B), 31.7 (CH_2^A), 25.5 (CH_3), 23.7 (CH_3) and 22.8 ($=CCH_3$); *m/z* (CI+ mode, isobutane) 253 (100%), 235 (22), 196 (30), 179 (19), 149 (14), 127 (10), 115 (15), 109 (4), 95 (4) and 81 (2) (Found $(M + H)^+$, 253.1800. $C_{15}H_{25}O_3$ requires *M*, 253.1797).



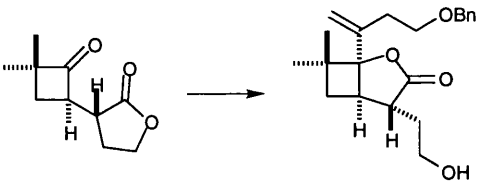
329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

339
$C_{20}H_{26}O_5S$
Mol. Wt.: 378.48

rel-(1_R_, 4_R_, 5_R_)-1-(1-Benzenesulfonyl-but-3-enyl)-4-(2-hydroxy-ethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 339

To a stirred solution of 3-butenyl phenyl sulfone (95 mg, 0.48 mmol, 3 eq) in THF (0.5 ml) at —78°C was added *n*-butyllithium (2.5 M in hexanes, 0.19 ml, 0.48 mmol, 3 eq). After 25 min the golden coloured mixture was added *via* cannula to a stirred solution of $Yb(OTf)_3$ (300 mg, 0.48 mmol, 3 eq) in THF (11.7 ml) also at —78°C. After a further 25

min a portion of the orange organoytterbium (5.9 ml, 0.24 mmol, 1.5 eq) was added to a stirred solution of cyclobutanone **329** (29 mg, 0.16 mmol, 1 eq) in THF (0.36 ml) at the same temperature. After a further 35 min, another portion of the organoytterbium (5.9 ml, 0.24 mmol, 1.5 eq) was added to the reaction mixture. After 20 min aqueous saturated $NaHCO_3$ (2 ml) was added followed by citric acid (102 mg, 0.48 mmol, 3 eq). The aqueous layer was separated and extracted with Et_2O (4 x 20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (eluting with 40% EtOAc in Pet. Ether (40-60°C), gradually increased to 70% EtOAc in Pet. Ether (40-60°C)) which yielded bicyclic lactone **339** (3 mg, 0.01 mmol, 5%) as a clear, colourless oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3695m (O-H), 3154s (O-H), 2984s (C-H), 2937m (C-H), 2902s (C-H), 1792s, 1786s (C=O), 1639m (C=C), 1557m (aryl-H), 1469s, 1381s (SO_2), 1304s, 1222s and 1093s (SO_2); δ_H (400 MHz, $CDCl_3$) 8.00-7.97 (2H, m, 2 x ArCH), 7.69-7.63 (1H, m, ArCH), 7.61-7.53 (2H, m, 2 x ArCH), 5.79 (1H, ddt, *J* 17.1, 10.2, 6.4, C*H*=CH_2), 5.09 (1H, dd, *J* 10.2, 1.2, *cis* 1H from CH=CH_2), 4.72 (1H, dd, *J* 17.1, 1.2, *trans* 1H from CH=CH_2), 3.85-3.71 (3H, m, 2H from CH_2OH and 1H from C*H*SO_2Ph), 2.94-2.90 (1H, m, CCH_2CH), 2.71 (1H, td, *J* 7.7, 2.2, CHCO), 2.44-2.38 (1H, m, 1H from CH_2CH=CH_2), 2.29-2.23 (1H, m, 1H from CH_2CH=CH_2), 2.15 (1H, dd, *J* 12.5, 9.7, 1H from CCH_2CH), 1.97-1.91 (1H, m, 1H from CH_2CH_2OH), 1.76-1.72 (1H, m, 1H from CH_2CH_2OH), 1.51-1.47 (1H, partially obscured, 1H from CCH_2CH), 1.47 (3H, s, CH_3) and 1.30 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.1 (C=O), 139.1 (ArCH), 134.3 (*C*H=CH_2), 134.0 (ArCH), 130.0 (2 x ArCH), 128.9 (2 x ArCH), 118.1 (CH=*C*H_2), 91.9 (*C*OC(O)), 67.9 (*C*HSO_2Ph), 61.2 (CH_2OH), 47.0 (*C*HCO), 43.4 (*C*(CH_3)$_2$), 40.0 (C*C*H_2CH), 38.7 (CCH_2*C*H), 34.5 (*C*H_2CH_2OH), 30.4 (*C*H_2CH=CH_2), 27.2 (CH_3) and 23.9 (CH_3); *m/z* (CI+ mode, isobutane) 379 (83%), 361 (60), 277 (7), 266 (8), 219 (100), 180 (48), 155 (8), 125 (18), 109 (9) and 81 (8) (Found $(M + H)^+$, 379.1575. $C_{20}H_{27}O_5S$ requires *M*, 379.1572).



329

$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

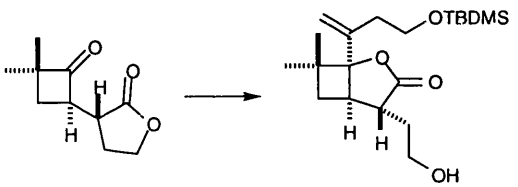
341

$C_{21}H_{28}O_4$
Mol. Wt.: 344.44

***rel*-(1*R*, 4*R*, 5*R*)-4-(2-Hydroxyethyl)-1-[1-(2-benzyloxyethyl)vinyl]-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 341**

To a stirred solution of 1-benzyloxy-3-bromo-but-3-ene **340** (102 mg, 0.42 mmol, 2.8 eq) in THF (1.4 ml) at —78°C was added *tert*-butyllithium (1.48 M in pentane, 0.57 ml, 0.84 mmol, 5.5 eq) slowly over 2 min. After 30 min the orange/brown solution was added dropwise to a stirred solution of $Yb(OTf)_3$ (285 mg, 0.46 mmol, 3 eq) in THF (10 ml) also at —78°C. After a further 10 min, a solution of cyclobutanone **329** (28 mg, 0.15 mmol, 1 eq) in THF (3.3 ml) at —78°C was added. After 1 h at —78°C, aqueous saturated $NaHCO_3$ (1 ml) was added followed by citric acid (97 mg, 0.46 mmol, 3 eq). The aqueous layer was separated and extracted with Et_2O (4 x 15 ml) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (eluting with 50% EtOAc in Pet. Ether (40-60°C) yielded bicyclic lactone **341** (28 mg, 0.08 mmol, 53%) as a clear colourless oil: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3617m (O-H), 3154s (Ar C-H), 2981s (C-H), 2963s (C-H), 2901s (C-H), 1758s (C=O), 1641m (C=C), 1604m, 1468s and 1382s; δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, 5 x ArCH), 5.15 (1H, s, 1H from $C=CH_2$), 5.02 (1H, s, 1H from $C=CH_2$), 4.55 (AB system, 1H, d, *J* 11.9, 1H from $PhCH_2$), 4.51 (AB system, 1H, d, *J* 11.9, 1H from $PhCH_2$), 3.83-3.71 (2H, m, CH_2CH_2OH), 3.70-3.59 (2H, m, CCH_2CH_2O), 3.02 (1H, apparent t, *J* 8.2, CCH_2CH), 2.67 (1H, apparent t, *J* 7.9, CHCO), 2.51-2.44 (1H, m, 1H from CCH_2CH_2), 2.36-2.28 (1H, m, 1H from CCH_2CH_2), 1.94 (1H, dd, *J* 12.0, 8.2, 1H

from CCH_2CH), 1.87-1.66 (2H, m, CH_2CH_2OH), 1.51 (1H, dd, *J* 12.0, 8.2, 1H from CCH_2CH), 1.15 (3H, s, CH_3) and 1.02 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.2 (C=O), 143.4 (C=CH_2), 138.5 (ArC), 128.6 (2 x ArCH), 127.9 (2 x ArCH), 127.8 (ArCH), 113.8 (C=CH_2), 96.8 ($COC(O)$), 73.1 (CH_2Ph), 69.0 (CCH_2CH_2O), 60.7 (CH_2CH_2OH), 45.8 ($CHCO$), 41.5 ($C(CH_3)_2$), 37.1 (CCH_2CH), 36.8 (CCH_2CH), 34.3 (CH_2CH_2OH), 31.8 (CCH_2CH_2), 25.5 (CH_3) and 23.1 (CH_3); *m/z* (CI+ mode, isobutane) 345 (13%), 327 (13), 270 (11), 253 (20), 235 (49), 223 (19), 197 (22), 167 (11), 149 (11), 138 (16), 109 (11) and 91 (100) (Found M^+, 344.1989. $C_{21}H_{28}O_4$ requires *M*, 344.1980).



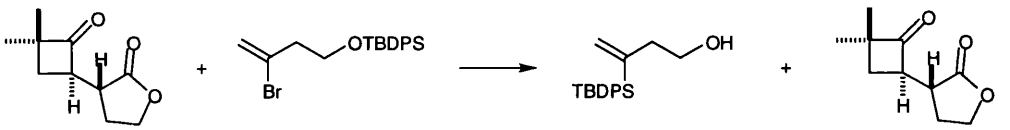
329
$C_{10}H_{14}O_3$
Mol. Wt.: 182.22

343
$C_{20}H_{36}O_4Si$
Mol. Wt.: 368.58

***rel*-(1*R*, 4*R*, 5*R*)-1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-1-methylene-propyl]-4-(2-hydroxy-ethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 343**

As for the preparation of **341**, except 1-*tert*-butyldimethylsiloxy-3-bromo-but-3-ene **342** was used. Purification of the crude product mixture by column chromatography (eluting with 15% EtOAc in CH_2Cl_2) gave **343** as a white crystalline solid (20 mg, 0.05 mmol, 26%): υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3154s (O-H), 2954s (C-H), 2928s (C-H), 2902s (C-H), 1761s (C=O), 1640s (C=C), 1604m, 1467s and 1383s; δ_H (400 MHz, $CDCl_3$) 5.13 (1H, s, 1H from C=CH_2), 5.01 (1H, s, 1H from C=CH_2), 3.84-3.69 (4H, m, 2H from CH_2OH and 2H from CH_2OSi), 3.01 (1H, apparent t, *J* 8.2, CCH_2CH), 2.66 (1H, apparent t, *J* 7.9, CHCO), 2.37-2.30 (AB system, 1H, m, 1H from CH_2CH_2OSi), 2.26-2.18 (AB system, 1H, m, 1H from CH_2CH_2OSi), 1.93 (1H, dd, *J* 12.0, 8.2, 1H from CCH_2CH), 1.87-1.70 (2H, m, CH_2CH_2OH), 1.50 (1H, dd, *J* 12.0, 8.2, 1H from CCH_2CH), 1.16 (3H, s,

$C(CH_3)_2$), 1.02 (3H, s, $C(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$) and 0.06 (6H, s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 180.2 (C=O), 143.3 (C=CH_2), 113.9 (C=CH_2), 96.9 (COC(O)), 61.8 (CH_2O), 60.7 (CH_2O), 45.9 (CHCO), 41.5 ($C(CH_3)_2$), 37.1 (CCH_2CH), 36.8 (CCH_2CH), 35.1 (CH_2CH_2OSi), 34.3 (CH_2CH_2OH), 26.1 (C(CH_3)$_3$), 25.5 (C(CH_3)$_2$), 23.1 (C(CH_3)$_2$), 18.4 ($C(CH_3)_3$) and —5.1 ($Si(CH_3)_2$); *m/z* (CI+ mode, isobutane) 369 (16%), 351 (16), 311 (58), 283 (60), 255 (54), 227 (100), 219 (42), 183 (27), 145 (38), 133 (50), 109 (46) and 75 (71) (Found $(M + H)^+$, 369.2458. $C_{20}H_{37}OSi$ requires *M*, 369.2451).



329 $C_{10}H_{14}O_3$ Mol. Wt.: 182.22 | **344** $C_{20}H_{25}BrOSi$ Mol. Wt.: 389.40 | **346** $C_{20}H_{26}OSi$ Mol. Wt.: 310.51 | **329** $C_{10}H_{14}O_3$ Mol. Wt.: 182.22

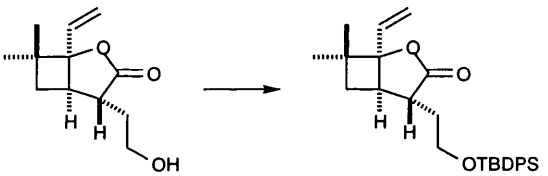
3-(*tert*-Butyl-diphenyl-silanyl)-but-3-en-1-ol 346

As for the preparation of **341** except the vinyllithium was formed from 1-*tert*-butyl diphenylsiloxy-3-bromo-but-3-ene **344**. Purification of the crude product mixture by column chromatography (eluting with 20% EtOAc in Pet. Ether (40-60°C)) gave cyclobutanone starting material **329** (31mg, 0.17 mmol, 100%) and vinyl silane **346** (152 mg, 0.49 mmol, 97%) as a white crystalline solid: υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3616m (O-H), 3022s (C-H), 2965s (C-H), 2949s (C-H), 2933s (C-H), 1604m (C=C), 1525s, 1472s, 1367m ($C(CH_3)_2$) and 1335m ($C(CH_3)_2$); δ_H (400 MHz, $CDCl_3$) 7.63-7.61 (4H, m, 4 x *o*ArCH), 7.44-7.35 (6H, m, 4 x *m*ArCH and 2 x *p*ArCH), 6.06 (1H, d, *J* 2.6, 1H from C=CH_2), 5.78 (1H, d, *J* 2.6, 1H from C=CH_2), 3.55 (2H, t, *J* 6.7, CH_2OH), 2.47 (2H, t, *J* 6.7, CH_2CH_2OH), 1.32 (1H, bs, OH) and 1.17 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 143.4 (C=CH_2), 136.4 (4 x *o*ArCH), 134.5 (2 x ArC), 131.9 (C=CH_2), 129.4 (2 x *p*ArCH), 127.9 (4 x *m*ArCH), 61.6 (CH_2OH), 40.4 (CH_2CH_2O), 28.8 (C(CH_3)$_3$) and 18.7

($C(CH_3)_3$); *m/z* (FAB+ mode, sodium) 333 (28%), 253 (73), 199 (100), 175 (33), 135 (52) and 105 (15) (Found $(M + Na)^+$, 333.1647. $C_{20}H_{26}OSiNa$ requires *M*, 333.1644) (Found: C, 77.26; H 8.43. $C_{20}H_{26}OSi$ requires C, 77.36; H, 8.44%).

Preparation of vinyl silane **346** in a test reaction

To a stirred solution of bromide **344** (117 mg, 0.30 mmol, 1 eq) in THF (9.4 ml) at —78°C was added *tert*-butyllithium (1.32 M in pentane, 0.46 ml, 0.60 mmol, 2 eq). After 1.5 h aqueous saturated $NaHCO_3$ (1 ml) was added at —78°C and the aqueous layer separated and extracted with Et_2O (4 x 10 ml). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude vinyl silane **346** as a cloudy colourless oil. No further purification was carried out.



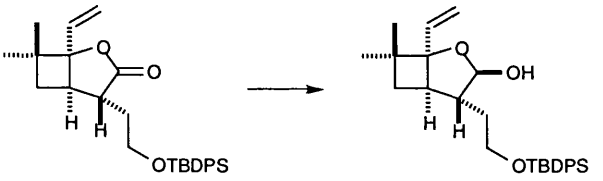
335 $C_{12}H_{18}O_3$ Mol. Wt.: 210.27

353 $C_{28}H_{36}O_3Si$ Mol. Wt.: 448.67

***rel*-(1*S*, 4*R*, 5*R*)-4-(2-*tert*-butyldiphenylsilyloxyethyl)-7,7-dimethyl-1-vinyl-2-oxa-bicyclo[3.2.0]heptan-3-one 353**

To a stirred solution of bicyclic lactone **335** (9 mg, 0.04 mmol, 1 eq) in DMF (0.2 ml) at rt was added imidazole (9 mg, 0.13 mmol, 3 eq) and TBDPSCl (0.017 ml, 0.07 mmol, 1.5 eq). After 4 days, a further quantity of imidazole (4 mg, 0.06 mmol, 1.5 eq) and TBDPSCl (0.008 ml, 0.03 mmol, 0.75 eq) was added. The reaction mixture was stirred for a further 12 h before aqueous saturated $NaHCO_3$ (0.5 ml) was added and the aqueous layer extracted with 50% EtOAc in Pet. Ether (40-60°C). The combined organic extracts

were dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy oil. Purification of the residue by column chromatography (eluting with 5% EtOAc in Pet. Ether 40-60°C) gave the bicyclic lactone **353** oil (14 mg, 0.03 mmol, 73%) as a clear colourless: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3154s (C-H), 3072w (Ph-H), 2990s (C-H), 2961s (C-H), 2931s (C-H), 2902s, 2861m, 1815s, 1792s, 1762s (C=O), 1645s (C=C), 1610m, 1563s, 1475s, 1387s ($C(CH_3)_3$), 1216s, 1169s and 1099s (Si-O); δ_H (400 MHz, $CDCl_3$) 7.67-7.63 (4H, m, 4 x ArCH), 7.47-7.37 (6H, m, 6 x ArCH), 5.95 (1H, dd, *J* 17.3, 11.0, C*H*=CH_2), 5.27 (1H, dd, *J* 17.3, 1.3, *trans* 1H from CH=CH_2), 5.16 (1H, dd, *J* 11.0, 1.3, *cis* 1H from CH=CH_2), 3.80-3.74 (1H, m, 1H from CH_2OH), 3.71-3.66 (1H, m, 1H from CH_2OH), 2.84 (1H, t, *J* 8.2, CCH_2CH), 2.68 (1H, dd, *J* 10.3, 4.9, CHCO), 2.00-1.91 (2H, m, 1H from CH_2CH_2OH and 1H from CCH_2CH), 1.60-1.52 (2H, m, 1H from CH_2CH_2OH and 1H from CCH_2CH), 1.11 (3H, s, CH_3), 1.06 (9H, s, $C(CH_3)_3$) and 1.05 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.5 (C=O), 135.7 (4 x ArCH), 134.5 ($CH=CH_2$), 133.6 (2 x ArC), 129.9 (2 x ArCH), 127.9 (4 x ArCH), 116.3 ($CH=CH_2$), 92.7 (*C*OC(O)), 61.9 (CH_2O), 45.4 (*C*HCO), 42.1 ($C(CH_3)_2$), 38.3 (CCH_2CH), 37.4 (CCH_2CH), 34.2 (CH_2CH_2OH), 27.0 ($C(CH_3)_3$), 26.1 (CH_3), 22.3 (CH_3) and 19.4 ($C(CH_3)_3$); *m/z* (CI+ mode, isobutane) 449 (27%), 391 (30), 371 (100), 335 (7), 293 (4), 199 (6) and 107 (3) (Found $(M + H)^+$, 449.2513. $C_{28}H_{37}O_3Si$ requires *M*, 449.2502).



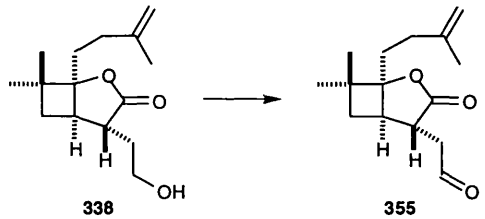
353
$C_{28}H_{36}O_3Si$
Mol. Wt.: 448.67

354
$C_{28}H_{38}O_3Si$
Mol. Wt.: 450.69

***rel*-(1*S*, 4*R*, 5*R*)-4-(2-*tert*-butyldiphenylsilyloxyethyl)-7,7-dimethyl-1-vinyl-2-oxa-bicyclo[3.2.0]heptan-3-ol 354**

To a stirred solution of lactone **353** (39 mg, 0.09 mmol, 1 eq) in CH_2Cl_2 (0.45 ml) at —78°C was added DIBAL-H (1.5 M in $PhCH_3$, 0.076 ml, 0.11 mmol, 1.3 eq) dropwise. After 3.5 h aqueous saturated $NaHCO_3$ (1 ml) was added and the aqueous layer separated and extracted with CH_2Cl_2 (3 x 10 ml) and dried ($MgSO_4$). Concentration *in vacuo* gave the clear colourless oil lactol **354** (34mg, 0.08 mmol, 86%) as a 2:1 mixture of diastereoisomers: υ_{max} ($CDCl_3$ soln.)/cm^{-1} 3602s (O-H), 3155s, 3071m, 2959s (C-H), 2925s (C-H), 2903s (C-H), 2858s, 1816m, 1794s, 1643s (C=C), 1559s, 1464s, 1425m, 1380s ($C(CH_3)_3$), 1212m, 1167m and 1094s (Si-O); δ_H (400 MHz, $CDCl_3$) 7.69-7.65 (8H, m, 4H from 4 x ArCH of major, 4H from 4 x ArCH of minor), 7.46-7.38 (12H, m, 6H from 6 x ArCH of major, 6H from 6 x ArCH of minor), 6.10 (1H, dd, *J* 17.3, 10.8, C*H*=CH_2 of minor), 5.97 (1H, dd, *J* 17.2, 10.8, C*H*=CH_2 of major), 5.69 (1H, dd, *J* 6.6, 5.0, C*H*OH of minor), 5.50 (1H, dd, *J* 3.7, 1.2, C*H*OH of major), 5.26 (1H, dd, *J* 17.3, 1.9, *trans* 1H from CH=CH_2 of minor), 5.18 (1H, dd, *J* 17.2, 2.0, *trans* 1H from CH=CH_2 of major), 5.10 (1H, dd, *J* 10.8, 1.9, *cis* 1H from CH=CH_2 of minor), 5.03 (1H, dd, *J* 10.8, 2.0, *cis* 1H from CH=CH_2 of major), 3.74-3.65 (4H, m, 2H from CH_2O of major, 2H from CH_2O of minor), 3.08 (1H, d, *J* 6.6, OH of minor), 2.93 (1H, d, *J* 3.7, OH of major), 2.58-2.51 (2H, m, 1H from CCH_2CH of major, 1H from CCH_2CH of minor), 2.37-2.25 (1H, m, 1H from C*H*CHOH of minor), 2.20 (1H, t, *J* 7.7, C*H*CHOH of major), 2.03 (1H, dd, *J* 11.4, 7.6, 1H from CCH_2CH of major), 1.87-1.79 (2H, m, 1H from CH_2CH_2OH, 1H from CCH_2CH both minor), 1.72 (1H, dd, *J* 11.4, 9.0, 1H from CCH_2CH of major), 1.68-1.59 (1H, m, 1H from CH_2CH_2OH of major), 1.52-1.41 (3H, m, 1H from CH_2CH_2OH of major, 1H from CH_2CH_2OH of minor, 1H from CCH_2CH of minor), 1.06 (18H, s, 9H from $C(CH_3)_3$ of major, 9H from $C(CH_3)_3$ of minor), 1.07-1.05 (9H, obscured singlets, 6H from $C(CH_3)_2$ of major, 3H from $C(CH_3)_2$ from minor) and 1.01 (3H, s, 3H from $C(CH_3)_2$ of minor); δ_C (100 MHz, $CDCl_3$) 138.8 (CH= from minor), 137.8 (CH= from major), 135.6 (8 x ArCH, 4C from major and 4C from minor), 133.8 (2 x ArC from major), 133.5 (2 x ArC from minor), 129.7 (2 x ArCH from minor), 129.6 (2

x ArCH from major), 127.7 (4 x ArCH from minor), 127.6 (4 x ArCH from major), 113.4 (=CH_2 from major), 113.3(=CH_2 from minor), 107.7 (CHOH from major), 102.1 (CHOH from minor), 94.7 (*C*OCH(OH) from major), 90.3 (*C*OCH(OH) from minor), 62.9 (CH_2O from minor), 62.5 (CH_2O from major), 49.5 (*C*HCH(OH) from major), 48.6 (*C*HCH(OH) from minor), 42.3 (CCH_2CH from major), 41.5 (CCH_2CH from minor), 40.4 ($C(CH_3)_2$ from minor), 39.3 ($C(CH_3)_2$ from major), 37.1 (CCH_2CH from minor), 36.4 (CCH_2CH from major), 35.2 (CH_2CH_2O from major), 31.6 (CH_2CH_2O from minor), 28.7 (CH_3 from major), 26.9 ($C(CH_3)_3$ from major), 26.8 ($C(CH_3)_3$ from minor and CH_3 from minor), 23.4 (CH_3 from minor), 22.5 (CH_3 from major) and 19.2 (2 x $C(CH_3)_3$ 1C from major and 1C from minor); *m/z* (FAB+ mode, sodium) 473 (43%), 433 (64), 393 (13), 375 (7), 319 (40), 259 (7), 239 (8), 199 (93), 177 (71), 135 (100), 107 (47), 94 (23) and 76 (17) (Found $(M + Na)^+$, 473.2490. $C_{28}H_{38}O_3SiNa$ requires *M*, 473.2488).

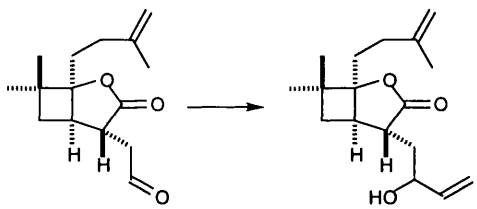


338 $C_{15}H_{24}O_3$ Mol. Wt.: 252.35 **355** $C_{15}H_{22}O_3$ Mol. Wt.: 250.33

***rel*-(1*S*, 4*R* , 5*R*)-[7,7-Dimethyl-1-(3-methyl-but-3-enyl)-3-oxo-2-oxa-bicyclo[3.2.0]hept-4-yl]-acetaldehyde 355**

To a stirred solution of alcohol **338** (23 mg, 0.09 mmol, 1 eq) in CH_2Cl_2 (1 ml) at 0°C was added 4Å molecular sieves (5 mg), NMO (43 mg, 0.36 mmol, 4 eq), and TPAP (4 mg, 0.01 mmol, 0.1 eq). After 2 h, the reaction mixture was allowed to warm to room temperature for 30 min before being filtered through a short column of silica gel (eluting with 40% EtOAc in Pet. Ether (40-60°C)). Concentration *in vacuo* gave aldehyde **355** (16

mg, 0.06 mmol, 71%) as a colourless oil; υ_{max} ($CHCl_3$ soln.)/cm^{-1} 3031s (C-H), 3015s (C-H), 2964m (C-H), 2863w (CHO), 1755s (C=O, lactone), 1733s (C=O, aldehyde), 1649w (C=C), 1593w, 1419m and 1369m; δ_H (400 MHz, $CDCl_3$) 9.79 (1H, s, CHO), 4.73 (1H, apparent s, 1H from $C=CH_2$), 4.68 (1H, apparent s, 1H from $C=CH_2$), 3.03-2.97 (2H, m, 1H from CH_2CHO and 1H from $CHCHCO$), 2.62 (1H, dd, *J* 11.2, 18.9, 1H from CH_2CHO), 2.44-2.40 (1H, m, CCH_2CH), 2.17-1.96 (4H, m, 2H from CH_2^B, 1H from CH_2^A and 1H from CCH_2CH), 1.73 (3H, s, $CH_3C=$), 1.73-1.61 (1H, m, 1H from CH_2^A), 1.58 (1H, dd, *J* 6.5, 12.3, 1H from CCH_2CH), 1.19 (3H, s, CH_3) and 1.10 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.7 (CHO), 179.9 (C=O, lactone), 145.1 ($C=CH_2$), 110.3 ($C=CH_2$), 93.5 ($COC(O)$), 46.0 (CH_2CHO), 43.1 ($CHCO$), 41.2 ($C(CH_3)_2$), 39.6 (CCH_2CH), 38.4 (CCH_2CH), 33.0 (CH_2^A), 31.7 (CH_2^B), 25.5 (CH_3), 23.9 (CH_3) and 22.8 ($CH_3C=$); *m/z* (CI+ mode, isobutane) 251 (17%), 233 (26), 205 (13), 194 (62), 166 (38), 152 (37), 139 (100), 111 (25), 83 (52) and 69 (30) (Found M^+, 250.1564. $C_{15}H_{22}O_3$ requires *M*, 250.1563).



355
$C_{15}H_{22}O_3$
Mol. Wt.: 250.33

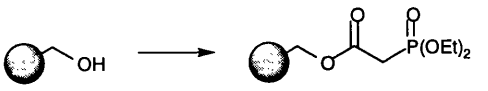
356
$C_{17}H_{26}O_3$
Mol. Wt.: 278.39

***rel*-(1*S*, 4*R* , 5*R*)-4-(2-Hydroxy-but-3-enyl)-7,7-dimethyl-1-(3-methyl-but-3-enyl)-2-oxa-bicyclo[3.2.0]heptan-3-one 356**

To a stirred solution of $Yb(OTf)_3$ (87 mg, 0.14 mmol, 3.2 eq) in THF (4 ml) at —78°C was added vinylmagnesium bromide (1.0 M in THF, 0.14 ml, 0.14 mmol, 3.2 eq) and the mixture left for 15 min. Half of the orange coloured solution (2 ml, 0.07 mmol, 1.6 eq) was then added dropwise to a stirred solution of aldehyde **355** (11 mg, 0.04 mmol, 1 eq)

in THF (0.2 ml) also at —78°C. After 20 min the remaining vinylytterbium solution (2 ml, 0.07 mmol, 1.6 eq) was added to the reaction mixture and the reaction then left stirring at that temperature for 1 h. Aqueous saturated $NaHCO_3$ (1 ml) was then added before the addition of citric acid (30 mg, 0.14 mmol, 3.2 eq). The aqueous layer was separated and extracted with Et_2O (4 x 15 ml). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude **356** as a 1:1 mixture of diastereoisomers. The residue was purified by column chromatography (eluting with 5% EtOAc in CH_2Cl_2) to give one diastereoisomer of the allylic alcohol **356** (2 mg, 0.01 mmol, 16%) as a clear oil; δ_H (400 MHz, $CDCl_3$) 5.91-5.83 (1H, m, C*H*=CH_2), 5.30 (1H, apparent d, *J* 17.1, *trans* 1H from CH=CH_2), 5.17 (1H, apparent d, *J* 10.4, *cis* 1H from CH=CH_2), 4.73 (1H, apparent s, 1H from C=CH_2), 4.69 (1H, apparent s, 1H from C=CH_2), 4.38 (1H, m, C*H*OH), 2.72 (1H, t, *J* 7.7, CHCO), 2.55 (1H, t, *J* 7.5, CCH_2CH), 2.19 (1H, d, *J* 4.8, CHO*H*), 2.15-2.12 (1H, m, 1H from CH_2^A), 2.06-1.97 (3H, m, 2H from CH_2^B and 1H from CCH_2CH), 1.93-1.83 (1H, m, 1H from CH_2CHOH), 1.74 (3H, s, =CCH_3), 1.72-1.61 (2H, m, 1H from CH_2^A and 1H from CH_2CHOH), 1.50 (1H, dd, *J* 12.2, 7.5, 1H from CCH_2CH), 1.21 (3H, s, CH_3) and 1.10 (3H, s, CH_3); *m/z* (CI+ mode, NH_3) 279 (100%), 261 (3), 222 (3), 204 (2), 176 (2), 140 (2), 96 (10) and 79 (13) (Found M^+, 278.1878. $C_{17}H_{26}O_3$ requires *M*, 278.1875). ^{13}C NMR not obtained.

Further elution then gave the other diastereoisomer of allylic alcohol **356** as a clear oil (2 mg, 0.01 mmols, 18%); δ_H (400 MHz, $CDCl_3$) 5.93 (1H, m, C*H*=CH_2), 5.32 (1H, apparent d, *J* 17.2, *trans* 1H from CH=CH_2), 5.18 (1H, apparent d, *J* 10.4, *cis* 1H from CH=CH_2), 4.73 (1H, apparent s, 1H from C=CH_2), 4.69 (1H, apparent s, 1H from C=CH_2), 4.31-4.28 (1H, m, C*H*OH), 2.71 (1H, t, *J* 7.0, CHCO), 2.55 (1H, t, *J* 7.4, CCH_2CH), 2.23 (1H, d, *J* 4.2, CHO*H*), 2.14-2.10 (1H, m, 1H from CH_2^A), 2.06-1.90 (4H, m, 2H from CH_2^B, 1H from CCH_2CH, 1H from CH_2CHOH), 1.74 (3H, s, =CCH_3), 1.72-1.62 (2H, m, 1H from CH_2CHOH and 1H from CH_2^A), 1.50 (1H, dd, *J* 12.2, 7.4, 1H from CCH_2CH), 1.21 (3H, s, CH_3) and 1.10 (3H, s, CH_3). ^{13}C NMR not obtained.



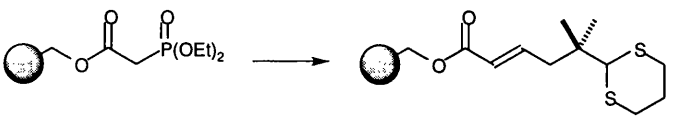
361 362

Solid supported Horner-Wadsworth-Emmons reagent **362**

Diethylphosphonoacetic acid (0.21 ml, 1.31 mmol, 5 eq) was added to a suspension of hydroxymethylpolystyrene **361** (0.87 mmol/g, 300 mg, 0.26 mmol, 1 eq), pre-swollen in THF (5 ml) in a SPS cartridge. N,N'-dicyclohexylcarbodiimide (269 mg, 1.31 mmol, 5 eq) and DMAP (96 mg, 0.78 mmol, 3 eq) were then added and the reaction mixture 'rotated' at room temperature for 5 h. The resin was then drained and washed using a general washing procedure described below.

General washing and drying procedure

The resin was washed once with THF (20 ml), then THF:H_2O (1:1) (3 x 20 ml), then THF:H_2O (1:2) (3 x 20 ml), then THF:H_2O (2:1) (3 x 20 ml), then H_2O (20 ml), then DMF (2 x 20 ml). The resin was then washed with CH_2Cl_2 (3 x 20 ml) and MeOH (3 x 20 ml), alternating between the two solvents. The resin was then left to dry for 10 min under water pump pressure before being dried for 6 h under high vacuum which gave resin **362**; υ_{max} KBr/cm^{-1} 1735s (C=O).

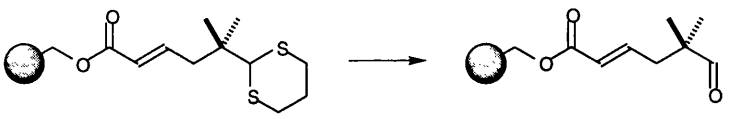


362 363

Solid supported thioacetal **363**

A solution of aldehyde **280** (44 mg, 0.22 mmol, 5 eq) in MeCN (1.5 ml) was added to a solution of resin **362** (<0.87 mmol/g, 50 mg, 0.04 mmol, 1 eq) in MeCN (1 ml). LiBr (38

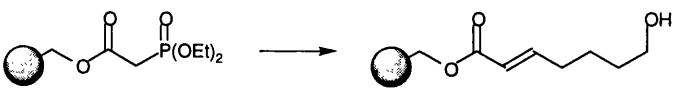
mg, 0.43 mmol, 10 eq) and triethylamine (45 µl, 0.43 mmol, 10 eq) were then added and the reaction mixture stirred slowly at room temperature for 3 d. The resin was then washed and dried according to the general washing procedure to give resin **363**; υ_{max} KBr/cm^{-1} 1719s (C=O), 1651s (C=C).



363 **364**

Solid supported aldehyde **364**

To a slowly stirred solution of resin **363** (<0.87 mmol/g, 41 mg, 0.04 mmol, 1 eq) in MeCN (1 ml) and H_2O (0.25 ml) were added $CaCO_3$ (32 mg, 0.32 mmol, 9 eq) and MeI (0.13 ml, 2.14 mmol, 60 eq). The mixture was then heated at 60°C for 3 d before a further quantity of MeI (0.13 ml, 2.14 mmol, 60 eq) was added. After a further 24 h the reaction mixture was allowed to cool to room temperature before being drained, washed and dried according to the general washing procedure to give resin **364**; υ_{max} KBr/cm^{-1} 1735s (C=O), 1719s (C=O), 1651s (C=C).



362 **366**

Solid supported alcohol **366**

A solution of lactol (697 mg, 6.83 mmol, 5 eq) in MeCN (15 ml) was added to a solution of resin **362** (<0.87 mmol/g, 1.57 g, 1.37 mmol, 1 eq) in MeCN (10 ml). LiBr (1.19 g, 13.7 mmol, 10 eq) and triethylamine (1.41 ml, 13.7 mmol, 10 eq) were then added and

the reaction mixture stirred slowly at room temperature for 4 d. The resin was then washed and dried according to the general washing procedure to give resin **366**; υ_{max} KBr/cm^{-1} 1735s (C=O), 1656s (C=C).

366 **367**

Solid supported aldehyde **367**

DMSO (2.75 ml, 38.8 mmol, 30 eq) and triethylamine (2.65 ml, 25.6 mmol, 19.8 eq) were added to a suspension of resin **366** (<0.87 mmol/g, 1.49 g, 1.29 mmol, 1 eq), pre-swollen in CH_2Cl_2 (30 ml) in a SPS cartridge. After 5 min, pyridine-sulfur trioxide complex (2.35 g, 14.7 mmol, 11.4 eq) was added and the reaction mixture 'rotated' at room temperature for 6 d. The resin was then washed and dried according to the general washing procedure to give resin **367**; υ_{max} KBr/cm^{-1} 1735s (C=O), 1703s (CHO), 1651s (C=C).

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Appendix 1

The Captodative Effect

The captodative effect[138]

The captodative effect is the combined action of an electron withdrawing group and an electron-donating group to stabilise a radical. Below is a simplified molecular orbital explanation of the captodative effect. First the separate stabilising effect of both the acceptor group and the donor group will be discussed.

The stabilising effect of the acceptor group

An acceptor group has the effect of lowering the SOMO of the hybridised ACH_2 orbital in comparison to the SOMO of the CH_3 radical (figure 5.1). It therefore has a stabilising influence on the radical since the SOMO has a lower energy than the SOMO of the CH_3 radical.

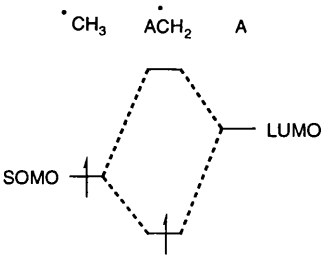

figure 5.1

The stabilising effect of the donor group

A donor group has the effect of stabilising the radical through a three electron interaction, whereby the radical is stabilised overall but the SOMO becomes higher in energy than the analogous CH_3 radical (figure 5.2).

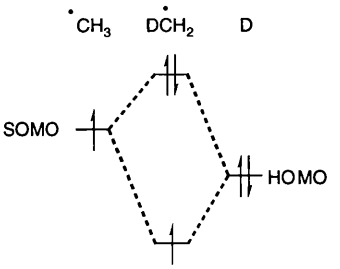

figure 5.2

The combined stabilising effect of the donor and acceptor groups

As the frontier orbitals of the radical and donor or acceptor become closer in energy the degree of stabilisation increases. Therefore, in a ACHD system, if the radical is stabilised by the donor group, the hybrid SOMO orbital, being of higher energy than the analogous CH_3 radical group, becomes closer in energy to the LUMO of the acceptor. The resultant effect is a greater degree of stabilisation exerted by the acceptor group. Similarly, the ACHD radical being stabilised by the acceptor group means the hybrid SOMO orbital is lower in energy than the analogous CH_3 radical, thus becoming closer in energy to the HOMO of the donor group. The resultant effect is a greater degree of stabilisation exerted by the donor group.

Appendix 2

Crystal structure data for *rel*-(1*R*, 2*S*)-2,2-Dimethyl-4-[*rel*-(*S*)-methylsulfanyl-(toluene-4-sulfonyl)-methyl]-cyclobutan-1-ol 304

Table 1. Crystal data and structure refinement for km2600.

Identification code	DJ3-22-1	
Empirical formula	$C_{15}H_{22}O_3S_2$	
Formula weight	314.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.4696(2) Å	α= 108.3780(12)°.
	b = 9.8584(2) Å	β= 99.2964(13)°.
	c = 12.0585(3) Å	γ= 107.2420(13)°.
Volume	772.30(3) Å^3	
Z	2	
Density (calculated)	1.352 Mg/m^3	
Absorption coefficient	0.349 mm^{-1}	
F(000)	336	
Crystal size	0.40 x 0.30 x 0.18 mm^3	
Theta range for data collection	3.51 to 29.96°.	
Index ranges	$-7 \le h \le 10$, $-13 \le k \le 12$, $-15 \le l \le 16$	
Reflections collected	6088	
Independent reflections	4403 [R(int) = 0.0182]	
Completeness to theta = 29.96°	98.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4403 / 0 / 186	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.0301, wR2 = 0.0862	
R indices (all data)	R1 = 0.0335, wR2 = 0.0890	
Largest diff. peak and hole	0.36 and -0.49 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for km2600. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-1245(1)	-1605(1)	933(1)	13(1)
S(2)	2737(1)	-1743(1)	1566(1)	13(1)
O(1)	3676(1)	-3002(1)	-1449(1)	20(1)
O(2)	4539(1)	-1394(1)	1218(1)	19(1)
O(3)	1919(1)	-3227(1)	1637(1)	18(1)
C(1)	559(2)	-3065(1)	-2672(1)	13(1)
C(2)	2217(2)	-2356(1)	-1465(1)	13(1)
C(3)	661(2)	-2730(1)	-785(1)	12(1)
C(4)	-845(2)	-2802(1)	-1870(1)	14(1)
C(5)	950(2)	-1558(1)	473(1)	12(1)
C(6)	3091(2)	-295(1)	2980(1)	13(1)
C(7)	4111(2)	1235(1)	3186(1)	16(1)
C(8)	4399(2)	2373(1)	4310(1)	17(1)
C(9)	3690(2)	1997(1)	5219(1)	17(1)
C(10)	2670(2)	454(1)	4986(1)	19(1)
C(11)	2354(2)	-700(1)	3870(1)	17(1)
C(12)	747(2)	-2211(1)	-3526(1)	17(1)
C(13)	106(2)	-4781(1)	-3351(1)	20(1)
C(14)	-2557(2)	-3627(1)	542(1)	20(1)
C(15)	4014(2)	3233(2)	6435(1)	25(1)

In the reference molecule C(2), C(3) and C(5) have respectively R, S and S absolute configurations.

Table 3. Bond lengths [Å] and angles [°] for km2600.

S(1)-C(14)	1.8054(12)	C(2)-C(3)	1.5506(14)
S(1)-C(5)	1.8064(10)	C(3)-C(5)	1.5239(14)
S(2)-O(3)	1.4446(8)	C(3)-C(4)	1.5499(14)
S(2)-O(2)	1.4518(8)	C(6)-C(7)	1.3921(15)
S(2)-C(6)	1.7635(11)	C(6)-C(11)	1.3946(15)
S(2)-C(5)	1.8111(10)	C(7)-C(8)	1.3949(16)
O(1)-C(2)	1.4162(13)	C(8)-C(9)	1.3955(16)
C(1)-C(12)	1.5206(15)	C(9)-C(10)	1.3954(17)
C(1)-C(13)	1.5309(15)	C(9)-C(15)	1.5095(16)
C(1)-C(2)	1.5500(15)	C(10)-C(11)	1.3909(16)
C(1)-C(4)	1.5592(15)		

C(14)-S(1)-C(5)	103.47(5)	C(5)-C(3)-C(2)	118.33(9)
O(3)-S(2)-O(2)	117.84(5)	C(4)-C(3)-C(2)	87.16(8)
O(3)-S(2)-C(6)	108.71(5)	C(3)-C(4)-C(1)	88.99(8)
O(2)-S(2)-C(6)	108.55(5)	C(3)-C(5)-S(1)	115.86(7)
O(3)-S(2)-C(5)	108.61(5)	C(3)-C(5)-S(2)	108.25(7)
O(2)-S(2)-C(5)	106.66(5)	S(1)-C(5)-S(2)	112.24(5)
C(6)-S(2)-C(5)	105.83(5)	C(7)-C(6)-C(11)	121.26(10)
C(12)-C(1)-C(13)	111.21(9)	C(7)-C(6)-S(2)	119.12(8)
C(12)-C(1)-C(2)	116.73(9)	C(11)-C(6)-S(2)	119.62(8)
C(13)-C(1)-C(2)	112.37(9)	C(6)-C(7)-C(8)	118.83(10)
C(12)-C(1)-C(4)	116.07(9)	C(7)-C(8)-C(9)	121.03(11)
C(13)-C(1)-C(4)	111.60(9)	C(10)-C(9)-C(8)	118.88(10)
C(2)-C(1)-C(4)	86.85(8)	C(10)-C(9)-C(15)	120.31(11)
O(1)-C(2)-C(1)	116.15(9)	C(8)-C(9)-C(15)	120.81(11)
O(1)-C(2)-C(3)	119.75(9)	C(11)-C(10)-C(9)	121.13(10)
C(1)-C(2)-C(3)	89.30(8)	C(10)-C(11)-C(6)	118.86(10)
C(5)-C(3)-C(4)	117.41(8)		

Note: intramolecular hydrogen bond:

O(1)-H(1)...O(2) O-H = 0.84 Å, O...H = 2.26 Å, O(1)...O(2) = 2.9628(12) Å, ∠O-H...O = 140.77°.

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for km2600. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	12(1)	14(1)	13(1)	4(1)	5(1)	5(1)
S(2)	12(1)	15(1)	12(1)	5(1)	4(1)	6(1)
O(1)	20(1)	32(1)	16(1)	11(1)	8(1)	17(1)
O(2)	13(1)	28(1)	17(1)	7(1)	6(1)	9(1)
O(3)	23(1)	16(1)	18(1)	8(1)	5(1)	9(1)
C(1)	16(1)	15(1)	11(1)	6(1)	5(1)	7(1)
C(2)	14(1)	17(1)	13(1)	7(1)	6(1)	8(1)
C(3)	14(1)	12(1)	10(1)	4(1)	5(1)	5(1)
C(4)	14(1)	17(1)	11(1)	5(1)	4(1)	5(1)
C(5)	12(1)	13(1)	11(1)	5(1)	4(1)	5(1)
C(6)	12(1)	16(1)	11(1)	5(1)	3(1)	5(1)
C(7)	13(1)	19(1)	15(1)	8(1)	4(1)	5(1)
C(8)	15(1)	18(1)	17(1)	6(1)	2(1)	5(1)
C(9)	16(1)	22(1)	13(1)	5(1)	2(1)	10(1)
C(10)	22(1)	24(1)	15(1)	10(1)	7(1)	9(1)
C(11)	19(1)	19(1)	16(1)	9(1)	6(1)	6(1)
C(12)	21(1)	21(1)	14(1)	9(1)	7(1)	11(1)
C(13)	28(1)	16(1)	15(1)	5(1)	8(1)	9(1)
C(14)	17(1)	16(1)	24(1)	6(1)	9(1)	3(1)
C(15)	29(1)	27(1)	15(1)	3(1)	3(1)	13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for km2600.

	x	y	z	U(eq)
H(1)	4430	-2624	-741	30
H(2)	2833	-1217	-1220	16
H(3)	400	-3777	-767	14
H(4A)	-1057	-1826	-1741	17
H(4B)	-2102	-3682	-2146	17
H(5)	1551	-517	453	14
H(7)	4603	1499	2573	19
H(8)	5088	3421	4458	21
H(10)	2184	188	5600	23
H(11)	1648	-1747	3716	21
H(12A)	1799	-2330	-3893	25
H(12B)	1050	-1117	-3066	25
H(12C)	-486	-2637	-4169	25
H(13A)	-1129	-5232	-3996	29
H(13B)	-4	-5301	-2780	29
H(13C)	1160	-4908	-3712	29
H(14A)	-2760	-4197	-325	30
H(14B)	-3825	-3776	713	30
H(14C)	-1797	-4007	1028	30
H(15A)	5234	3397	6997	37
H(15B)	2922	2912	6769	37
H(15C)	4097	4194	6330	37

All hydrogen atoms were observed in difference maps. All rode on their parent C-atoms. Orientation parameters were refined for the four methyl groups and for H(1).

Table 6. Torsion angles [°] for km2600.

C(12)-C(1)-C(2)-O(1)	-98.39(11)	O(2)-S(2)-C(5)-C(3)	61.61(8)
C(13)-C(1)-C(2)-O(1)	31.79(13)	C(6)-S(2)-C(5)-C(3)	177.07(7)
C(4)-C(1)-C(2)-O(1)	143.89(9)	O(3)-S(2)-C(5)-S(1)	62.77(7)
C(12)-C(1)-C(2)-C(3)	138.46(9)	O(2)-S(2)-C(5)-S(1)	-169.27(5)
C(13)-C(1)-C(2)-C(3)	-91.35(9)	C(6)-S(2)-C(5)-S(1)	-53.80(7)
C(4)-C(1)-C(2)-C(3)	20.74(8)	O(3)-S(2)-C(6)-C(7)	171.31(8)
O(1)-C(2)-C(3)-C(5)	99.29(11)	O(2)-S(2)-C(6)-C(7)	41.99(10)
C(1)-C(2)-C(3)-C(5)	-140.66(9)	C(5)-S(2)-C(6)-C(7)	-72.18(9)
O(1)-C(2)-C(3)-C(4)	-140.91(10)	O(3)-S(2)-C(6)-C(11)	-8.45(11)
C(1)-C(2)-C(3)-C(4)	-20.87(8)	O(2)-S(2)-C(6)-C(11)	-137.78(9)
C(5)-C(3)-C(4)-C(1)	141.37(9)	C(5)-S(2)-C(6)-C(11)	108.05(9)
C(2)-C(3)-C(4)-C(1)	20.74(8)	C(11)-C(6)-C(7)-C(8)	0.23(16)
C(12)-C(1)-C(4)-C(3)	-139.09(9)	S(2)-C(6)-C(7)-C(8)	-179.53(8)
C(13)-C(1)-C(4)-C(3)	92.09(9)	C(6)-C(7)-C(8)-C(9)	0.28(17)
C(2)-C(1)-C(4)-C(3)	-20.75(8)	C(7)-C(8)-C(9)-C(10)	-0.34(17)
C(4)-C(3)-C(5)-S(1)	51.87(11)	C(7)-C(8)-C(9)-C(15)	179.69(11)
C(2)-C(3)-C(5)-S(1)	154.36(8)	C(8)-C(9)-C(10)-C(11)	-0.09(17)
C(4)-C(3)-C(5)-S(2)	178.94(7)	C(15)-C(9)-C(10)-C(11)	179.88(11)
C(2)-C(3)-C(5)-S(2)	-78.58(10)	C(9)-C(10)-C(11)-C(6)	0.58(17)
C(14)-S(1)-C(5)-C(3)	46.25(9)	C(7)-C(6)-C(11)-C(10)	-0.65(17)
C(14)-S(1)-C(5)-S(2)	-78.79(7)	S(2)-C(6)-C(11)-C(10)	179.11(9)
O(3)-S(2)-C(5)-C(3)	-66.35(8)		

Appendix 3

Crystal structure data for *rel*-(1*R*, 4*R*)-4-(2-Hydroxy-(1*R*)-1-deutero-methyl-ethyl)-2,2-dimethyl cyclobutanol 311

Table 1. Crystal data and structure refinement for km0299.

Identification code	km0299
Empirical formula	C9 H18 O2
Formula weight	158.23
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbna (No 60)
Unit cell dimensions	a = 8.2540(16) A b = 11.2290(15) A c = 20.088(2) A
Volume	1861.8(5) A^3
Z, Calculated density	8, 1.129 Mg/m^3
Absorption coefficient	0.077 mm^-1
F(000)	704
Crystal size	0.20 x 0.15 x 0.15 mm
Theta range for data collection	2.67 to 23.95 deg.
Index ranges	-1<=h<=9, -12<=k<=1, -22<=l<=2
Reflections collected / unique	2044 / 1454 [R(int) = 0.0562]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1454 / 0 / 111
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1181 [933 data]
R indices (all data)	R1 = 0.0977, wR2 = 0.1405
Largest diff. peak and hole	0.19 and -0.27 e.A^-3
Weight	1/[sigma^2(Fo^2) + (0.0760 * P)^2]

where P = (Max (Fo^2, 0) + 2 * Fc^2) / 3

Table 2. Atomic coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for km0299.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor for non-hydrogen atoms and is the isotropic displacement parameter for hydrogen atoms.

	x	y	z	U(eq)
O(1)	5184(2)	7239(2)	2956(1)	24(1)
O(2)	2086(2)	3556(2)	2728(1)	19(1)
C(1)	2954(3)	4686(2)	3774(1)	17(1)
C(2)	1636(3)	4266(2)	3286(1)	16(1)
C(3)	668(3)	3688(2)	3865(1)	17(1)
C(4)	1732(3)	4435(2)	4344(1)	21(1)
C(5)	4629(3)	6050(2)	3077(1)	18(1)
C(6)	3617(3)	5943(2)	3705(1)	16(1)
C(7)	4580(4)	6299(2)	4323(1)	26(1)
C(8)	-1146(3)	3955(2)	3878(1)	22(1)
C(9)	981(3)	2361(2)	3920(1)	24(1)
H(1)	4400(42)	7660(28)	2743(16)	39(9)
H(2)	2870(44)	3070(28)	2866(16)	43(10)
H(1A)	3863	4097	3788	20
H(2A)	1026	4978	3123	19
H(4A)	2198	3965	4715	25
H(4B)	1187	5159	4513	25
H(5A)	5579	5516	3114	22
H(5B)	3976	5781	2692	22
H(6)	2676	6499	3663	19
H(7A)	3882	6245	4716	38
H(7B)	4969	7119	4273	38
H(7C)	5508	5763	4376	38
H(8A)	-1316	4818	3869	32
H(8B)	-1621	3625	4286	32
H(8C)	-1666	3591	3490	32
H(9A)	521	2062	4337	36
H(9B)	2151	2213	3914	36
H(9C)	473	1950	3543	36

Note 1 O-bonded H(1) and H(2) were freely refined. An orientation parameter was refined for each of the three methyl groups. Otherwise H atoms rode on their parent C atoms.

Note 2 These coordinates define a molecule in which atoms C(1), C(2) & C(6) each have absolute configuration R.

Table 3. Bond lengths [A] and angles [deg] for km0299.

O(1)-C(5)	1.432(3)
O(2)-C(2)	1.425(3)
C(1)-C(6)	1.520(3)
C(1)-C(2)	1.538(4)
C(1)-C(4)	1.552(4)
C(2)-C(3)	1.552(4)
C(3)-C(9)	1.516(4)
C(3)-C(8)	1.527(4)
C(3)-C(4)	1.550(4)
C(5)-C(6)	1.517(4)
C(6)-C(7)	1.528(4)
C(6)-C(1)-C(2)	118.8(2)
C(6)-C(1)-C(4)	118.0(2)
C(2)-C(1)-C(4)	87.40(19)
O(2)-C(2)-C(1)	119.2(2)
O(2)-C(2)-C(3)	119.3(2)
C(1)-C(2)-C(3)	90.91(19)
C(9)-C(3)-C(8)	111.0(2)
C(9)-C(3)-C(4)	112.9(2)
C(8)-C(3)-C(4)	116.0(2)
C(9)-C(3)-C(2)	112.2(2)
C(8)-C(3)-C(2)	115.9(2)
C(4)-C(3)-C(2)	86.98(18)
C(3)-C(4)-C(1)	90.44(19)
O(1)-C(5)-C(6)	113.1(2)
C(5)-C(6)-C(1)	110.4(2)
C(5)-C(6)-C(7)	111.6(2)
C(1)-C(6)-C(7)	110.9(2)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for km0299.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	18(1)	24(1)	32(1)	11(1)	-4(1)	-5(1)
O(2)	17(1)	22(1)	18(1)	-3(1)	-2(1)	3(1)
C(1)	15(1)	17(1)	18(1)	0(1)	-2(1)	1(1)
C(2)	15(1)	16(1)	16(1)	-4(1)	-1(1)	4(1)
C(3)	16(1)	19(1)	16(1)	0(1)	0(1)	-2(1)
C(4)	23(2)	23(2)	17(1)	2(1)	-1(1)	-4(1)
C(5)	16(1)	17(1)	22(1)	1(1)	0(1)	-4(1)
C(6)	14(1)	16(1)	19(1)	0(1)	-1(1)	-1(1)
C(7)	28(2)	25(2)	23(2)	-3(1)	1(1)	-11(1)
C(8)	19(2)	22(1)	24(1)	-1(1)	2(1)	-2(1)
C(9)	20(1)	22(1)	30(2)	4(1)	-2(1)	-3(1)

Table 5. Torsion angles [deg] for km0299.

C(6)-C(1)-C(2)-O(2)	99.0(3)
C(4)-C(1)-C(2)-O(2)	-140.3(2)
C(6)-C(1)-C(2)-C(3)	-136.3(2)
C(4)-C(1)-C(2)-C(3)	-15.57(19)
O(2)-C(2)-C(3)-C(9)	26.7(3)
C(1)-C(2)-C(3)-C(9)	-98.0(2)
O(2)-C(2)-C(3)-C(8)	-102.2(3)
C(1)-C(2)-C(3)-C(8)	133.2(2)
O(2)-C(2)-C(3)-C(4)	140.2(2)
C(1)-C(2)-C(3)-C(4)	15.6(2)
C(9)-C(3)-C(4)-C(1)	97.4(2)
C(8)-C(3)-C(4)-C(1)	-132.9(2)
C(2)-C(3)-C(4)-C(1)	-15.45(19)
C(6)-C(1)-C(4)-C(3)	137.0(2)
C(2)-C(1)-C(4)-C(3)	15.59(19)
O(1)-C(5)-C(6)-C(1)	175.4(2)
O(1)-C(5)-C(6)-C(7)	-60.9(3)
C(2)-C(1)-C(6)-C(5)	-69.9(3)
C(4)-C(1)-C(6)-C(5)	-173.4(2)
C(2)-C(1)-C(6)-C(7)	165.9(2)
C(4)-C(1)-C(6)-C(7)	62.4(3)

Table 6. Hydrogen-bonds for km0299 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)#1	0.91(4)	1.84(4)	2.754(3)	176(3)
O(2)-H(2)...O(1)#2	0.89(4)	1.87(4)	2.734(3)	164(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y+1/2,-z+1/2 #2 -x+1,y-1/2,z

Appendix 4

Crystal structure data for *p*-Nitro benzoic acid-2-(*rel*-(1*S*, 4*R*, 5*R*)-1,7,7-trimethyl-2-oxa-3-oxo-bicyclo[3.2.0]hept-4-yl)ethyl ester 334

Table 1. Crystal data and structure refinement for km0500.

Identification code	km0500	
Empirical formula	$C_{18}H_{21}NO_6$	
Formula weight	347.36	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.5693(6) Å	α= 85.814(11)°.
	b = 7.6665(10) Å	β= 81.746(10)°.
	c = 19.936(2) Å	γ = 62.170(12)°.
Volume	878.70(18) $Å^3$	
Z	2	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
Absorption correction	None	
F(000)	368	
Crystal size	0.40 x 0.35 x 0.18 mm^3	
θ range for data collection	3.0 to 30.0°.	
Index ranges	$-9 \le h \le 8, -10 \le k \le 1, -27 \le l \le 27$	
Reflections collected	6176	
Independent reflections	5116 [R(int) = 0.0435]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5116 / 0 / 229	
Goodness-of-fit on F^2	0.996	
R indices [2504 $I>2\sigma(I)$]	R1 = 0.0506, wR2 = 0.1252	
R indices (all data)	R1 = 0.1339, wR2 = 0.1550	
Largest diff. peak and hole	0.19 and -0.23 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for km0500. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5080(2)	9549(2)	1202(1)	56(1)
O(2)	7678(2)	7916(2)	1908(1)	81(1)
O(3)	2562(2)	6949(2)	3542(1)	59(1)
O(4)	-638(3)	7011(3)	4117(1)	85(1)
O(5)	6150(3)	8268(3)	6402(1)	90(1)
O(6)	3325(3)	8072(3)	7017(1)	86(1)
N(1)	4396(3)	8082(2)	6471(1)	60(1)
C(1)	1395(3)	12622(3)	1183(1)	53(1)
C(2)	2594(3)	10346(3)	1174(1)	46(1)
C(3)	1605(3)	10330(3)	1920(1)	46(1)
C(4)	1068(4)	12501(3)	1965(1)	62(1)
C(5)	5684(3)	8684(3)	1802(1)	54(1)
C(6)	3602(3)	8813(3)	2271(1)	48(1)
C(7)	3652(3)	6796(3)	2355(1)	57(1)
C(8)	1856(3)	6748(3)	2905(1)	58(1)
C(9)	1163(3)	7070(3)	4104(1)	51(1)
C(10)	2064(3)	7307(2)	4715(1)	46(1)
C(11)	3947(3)	7670(3)	4663(1)	52(1)
C(12)	4705(3)	7921(3)	5240(1)	55(1)
C(13)	3566(3)	7808(2)	5859(1)	47(1)
C(14)	1714(3)	7420(3)	5927(1)	60(1)
C(15)	972(3)	7172(3)	5349(1)	59(1)
C(16)	2777(4)	13650(4)	868(1)	87(1)
C(17)	-933(4)	13491(4)	908(1)	87(1)
C(18)	2305(4)	9242(3)	632(1)	72(1)

Table 3. Bond lengths [Å] and angles [°] for km0500.

O(1)-C(5)	1.344(2)	C(2)-C(3)	1.537(2)
O(1)-C(2)	1.4602(19)	C(3)-C(6)	1.511(2)
O(2)-C(5)	1.203(2)	C(3)-C(4)	1.538(3)
O(3)-C(9)	1.3232(19)	C(5)-C(6)	1.508(2)
O(3)-C(8)	1.455(2)	C(6)-C(7)	1.528(2)
O(4)-C(9)	1.201(2)	C(7)-C(8)	1.503(3)
O(5)-N(1)	1.214(2)	C(9)-C(10)	1.485(2)
O(6)-N(1)	1.2097(18)	C(10)-C(11)	1.378(2)
N(1)-C(13)	1.472(2)	C(10)-C(15)	1.383(2)
C(1)-C(16)	1.507(3)	C(11)-C(12)	1.375(2)
C(1)-C(17)	1.523(3)	C(12)-C(13)	1.369(2)
C(1)-C(2)	1.544(2)	C(13)-C(14)	1.368(2)
C(1)-C(4)	1.544(2)	C(14)-C(15)	1.372(3)
C(2)-C(18)	1.505(2)		
C(5)-O(1)-C(2)	111.78(13)	O(2)-C(5)-O(1)	120.59(17)
C(9)-O(3)-C(8)	117.66(14)	O(2)-C(5)-C(6)	128.20(17)
O(6)-N(1)-O(5)	123.38(17)	O(1)-C(5)-C(6)	111.21(14)
O(6)-N(1)-C(13)	118.54(17)	C(5)-C(6)-C(3)	102.42(13)
O(5)-N(1)-C(13)	118.06(15)	C(5)-C(6)-C(7)	110.73(14)
C(16)-C(1)-C(17)	110.28(18)	C(3)-C(6)-C(7)	113.91(14)
C(16)-C(1)-C(2)	117.99(16)	C(8)-C(7)-C(6)	113.26(15)
C(17)-C(1)-C(2)	111.31(16)	O(3)-C(8)-C(7)	106.26(14)
C(16)-C(1)-C(4)	116.81(17)	O(4)-C(9)-O(3)	123.70(17)
C(17)-C(1)-C(4)	110.76(16)	O(4)-C(9)-C(10)	124.08(16)
C(2)-C(1)-C(4)	88.01(12)	O(3)-C(9)-C(10)	112.22(14)
O(1)-C(2)-C(18)	107.32(14)	C(11)-C(10)-C(15)	119.48(16)
O(1)-C(2)-C(3)	103.37(12)	C(11)-C(10)-C(9)	121.52(14)
C(18)-C(2)-C(3)	122.64(15)	C(15)-C(10)-C(9)	119.00(15)
O(1)-C(2)-C(1)	110.57(13)	C(12)-C(11)-C(10)	119.95(15)
C(18)-C(2)-C(1)	121.33(15)	C(13)-C(12)-C(11)	119.17(16)
C(3)-C(2)-C(1)	89.67(12)	C(14)-C(13)-C(12)	122.23(17)
C(6)-C(3)-C(2)	105.84(13)	C(14)-C(13)-N(1)	119.20(15)
C(6)-C(3)-C(4)	117.33(15)	C(12)-C(13)-N(1)	118.56(16)
C(2)-C(3)-C(4)	88.44(12)	C(13)-C(14)-C(15)	118.09(16)
C(3)-C(4)-C(1)	89.64(13)	C(14)-C(15)-C(10)	121.07(16)

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for km0500. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	42(1)	69(1)	51(1)	-2(1)	1(1)	-22(1)
O(2)	48(1)	93(1)	98(1)	-1(1)	-25(1)	-24(1)
O(3)	56(1)	81(1)	44(1)	3(1)	-9(1)	-36(1)
O(4)	78(1)	138(2)	70(1)	-4(1)	-4(1)	-77(1)
O(5)	86(1)	148(2)	62(1)	-9(1)	-10(1)	-72(1)
O(6)	93(1)	119(1)	46(1)	-14(1)	7(1)	-52(1)
N(1)	62(1)	67(1)	46(1)	-5(1)	-3(1)	-26(1)
C(1)	57(1)	54(1)	49(1)	3(1)	-9(1)	-26(1)
C(2)	45(1)	54(1)	41(1)	-4(1)	-7(1)	-23(1)
C(3)	42(1)	53(1)	42(1)	-1(1)	-3(1)	-21(1)
C(4)	66(1)	53(1)	51(1)	-9(1)	-2(1)	-15(1)
C(5)	47(1)	55(1)	58(1)	-6(1)	-12(1)	-20(1)
C(6)	52(1)	51(1)	38(1)	-5(1)	-9(1)	-20(1)
C(7)	68(1)	53(1)	46(1)	-2(1)	-11(1)	-23(1)
C(8)	70(1)	64(1)	49(1)	6(1)	-18(1)	-36(1)
C(9)	52(1)	55(1)	51(1)	4(1)	-4(1)	-29(1)
C(10)	42(1)	41(1)	50(1)	2(1)	-3(1)	-17(1)
C(11)	50(1)	66(1)	43(1)	6(1)	-1(1)	-31(1)
C(12)	50(1)	68(1)	53(1)	7(1)	-4(1)	-33(1)
C(13)	46(1)	46(1)	43(1)	0(1)	-2(1)	-17(1)
C(14)	54(1)	76(1)	47(1)	0(1)	7(1)	-32(1)
C(15)	51(1)	79(1)	55(1)	2(1)	2(1)	-39(1)
C(16)	99(2)	72(2)	95(2)	7(1)	-1(1)	-47(1)
C(17)	74(1)	76(2)	96(2)	10(1)	-37(1)	-16(1)
C(18)	92(2)	79(2)	51(1)	-7(1)	-19(1)	-42(1)

Table 5. Torsion angles [°] for km0500.

C(5)-O(1)-C(2)-C(18)	-116.48(16)	C(2)-C(3)-C(6)-C(5)	21.81(17)
C(5)-O(1)-C(2)-C(3)	14.43(17)	C(4)-C(3)-C(6)-C(5)	-74.78(17)
C(5)-O(1)-C(2)-C(1)	109.18(16)	C(2)-C(3)-C(6)-C(7)	-97.79(16)
C(16)-C(1)-C(2)-O(1)	30.8(2)	C(4)-C(3)-C(6)-C(7)	165.62(14)
C(17)-C(1)-C(2)-O(1)	159.77(16)	C(5)-C(6)-C(7)-C(8)	170.15(14)
C(4)-C(1)-C(2)-O(1)	-88.69(14)	C(3)-C(6)-C(7)-C(8)	-75.06(18)
C(16)-C(1)-C(2)-C(18)	-96.1(2)	C(9)-O(3)-C(8)-C(7)	175.93(14)
C(17)-C(1)-C(2)-C(18)	32.8(2)	C(6)-C(7)-C(8)-O(3)	-68.68(19)
C(4)-C(1)-C(2)-C(18)	144.38(17)	C(8)-O(3)-C(9)-O(4)	0.4(3)
C(16)-C(1)-C(2)-C(3)	134.98(18)	C(8)-O(3)-C(9)-C(10)	-178.97(14)
C(17)-C(1)-C(2)-C(3)	-96.06(17)	O(4)-C(9)-C(10)-C(11)	-169.81(18)
C(4)-C(1)-C(2)-C(3)	15.48(13)	O(3)-C(9)-C(10)-C(11)	9.6(2)
O(1)-C(2)-C(3)-C(6)	-22.45(16)	O(4)-C(9)-C(10)-C(15)	9.7(3)
C(18)-C(2)-C(3)-C(6)	98.59(19)	O(3)-C(9)-C(10)-C(15)	-170.87(15)
C(1)-C(2)-C(3)-C(6)	-133.54(13)	C(15)-C(10)-C(11)-C(12)	-0.9(3)
O(1)-C(2)-C(3)-C(4)	95.56(14)	C(9)-C(10)-C(11)-C(12)	178.67(16)
C(18)-C(2)-C(3)-C(4)	-143.40(17)	C(10)-C(11)-C(12)-C(13)	-0.1(3)
C(1)-C(2)-C(3)-C(4)	-15.53(13)	C(11)-C(12)-C(13)-C(14)	1.1(3)
C(6)-C(3)-C(4)-C(1)	122.58(15)	C(11)-C(12)-C(13)-N(1)	-179.94(15)
C(2)-C(3)-C(4)-C(1)	15.53(13)	O(6)-N(1)-C(13)-C(14)	-4.3(3)
C(16)-C(1)-C(4)-C(3)	-136.03(18)	0(5)-N(1)-C(13)-C(14)	174.27(17)
C(17)-C(1)-C(4)-C(3)	96.61(17)	O(6)-N(1)-C(13)-C(12)	176.63(16)
C(2)-C(1)-C(4)-C(3)	-15.46(13)	0(5)-N(1)-C(13)-C(12)	-4.7(3)
C(2)-O(1)-C(5)-O(2)	178.62(16)	C(12)-C(13)-C(14)-C(15)	-1.1(3)
C(2)-O(1)-C(5)-C(6)	-0.51(19)	N(1)-C(13)-C(14)-C(15)	179.97(17)
O(2)-C(5)-C(6)-C(3)	167.12(19)	C(13)-C(14)-C(15)-C(10)	0.1(3)
O(1)-C(5)-C(6)-C(3)	-13.84(18)	C(11)-C(10)-C(15)-C(14)	0.9(3)
O(2)-C(5)-C(6)-C(7)	-71.1(2)	C(9)-C(10)-C(15)-C(14)	-178.67(17)
O(1)-C(5)-C(6)-C(7)	107.96(16)		