Development and Application of the One-pot Julia Olefination

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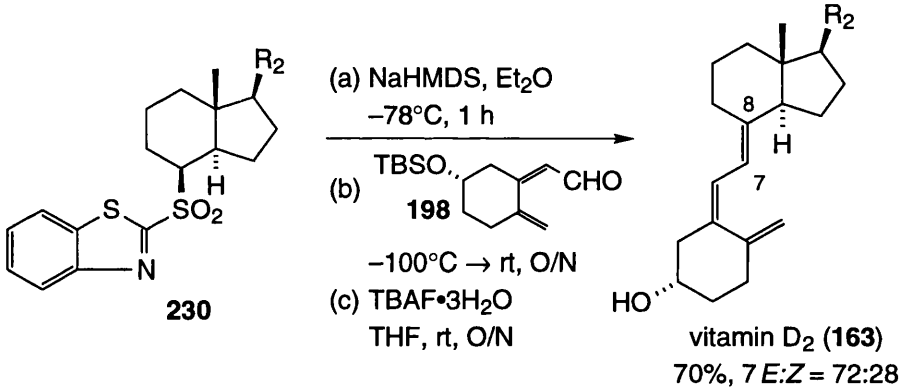
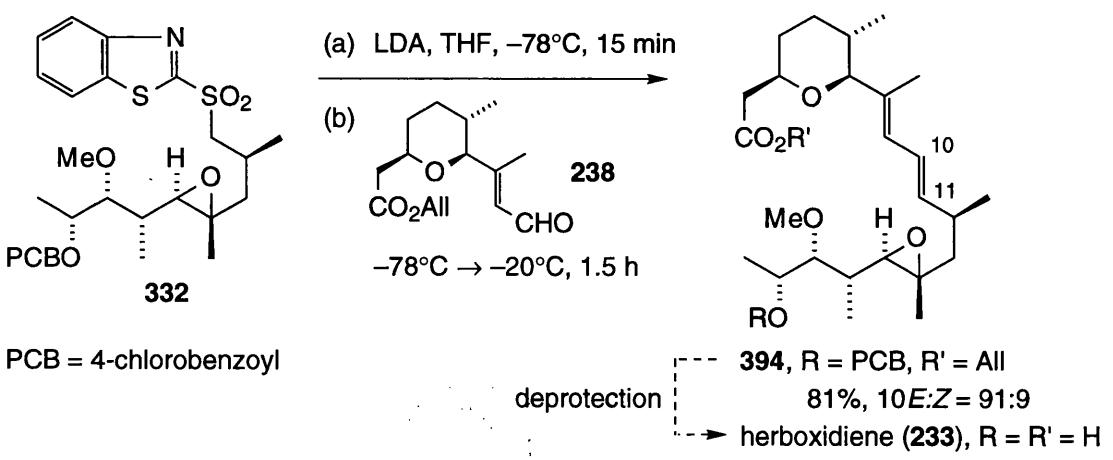
Abstract

The influence of heterocycle, base and solvent on the recently reported one-pot Julia olefination[1-3] was investigated. 1-Phenyl-1*H*-tetrazol-5-yl (PT) sulfones emerged as a promising alternative to the previously reported benzothiazol-2-yl (BT) sulfones for use in the olefin synthesis. For both BT and PT systems an increase in solvent polarity resulted in a heightened *trans* selectivity for the synthesis of simple 1,2-disubstituted monoenes. However, only for the new PT variant was the stereochemical outcome also dependent on base counter cation. Potassium derivatives of PT sulfones react with saturated aldehydes in 1,2-dimethoxyethane (DME) to produce *trans*-1,2-disubstituted alkenes with excellent selectivity[4].

A partial synthesis of vitamin D_2 was achieved employing fragments derived from a new improved degradation procedure. Condensation of the sodium derivative of BT sulfone **230** with aldehyde **198** yielded 70% of vitamin D_2 (**163**, 7*E*:*Z* = 72:28) after deprotection.



The first total synthesis of the polyketide herboxidiene (**233**) was completed in 22 linear steps from cyclohexanone[5]. Both BT and PT one-pot Julia methodologies were used at pivotal junctures in the synthesis. The new PT variant was employed to access a simple *trans*-1,2-disubstituted olefin (**327**) prior to subsequent Sharpless asymmetric dihydroxylation. The established BT technology was used to conjoin two late stage intermediates, **332** and **238**, to yield 81% of the protected herboxidiene derivative **394** with 10*E*:*Z* = 91:9.



Dedicated to the loving memory of my mother.

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Contents

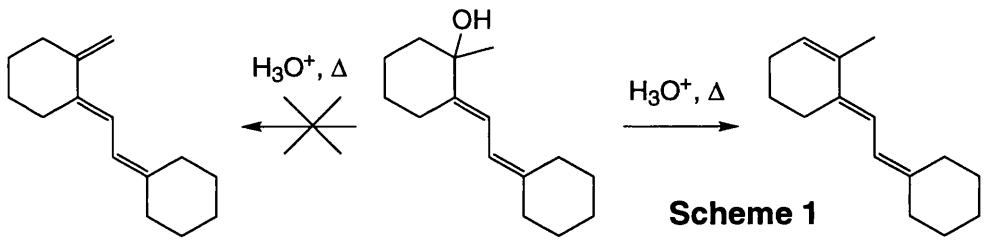
Abbreviations

Ac	-	acetyl
acac	-	acetylacetonate
All	-	allyl
Bn	-	benzyl
Boc	-	*tert*-butyloxycarbonyl
BT	-	benzothiazol-2-yl
Bz	-	benzoyl
m-CPBA	-	3-chloroperoxybenzoic acid
dba	-	dibenzylideneacetone
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	-	diethyl azodicarboxylate
DET	-	diethyl tartrate
DHP	-	3,4-dihydro-2*H*-pyran
DIAD	-	di*iso*propyl azodicarboxylate
DIBAL-H	-	di*iso*butylaluminum hydride
DMAD	-	dimethyl azodicarboxylate
DMAP	-	4-(dimethylamino)pyridine
DME	-	1,2-dimethoxyethane
DMF	-	*N,N*-dimethylformamide
DMP	-	Dess-Martin periodinane
DMPU	-	*N,N'*-dimethylpropylene urea
DMSO	-	dimethylsulfoxide
Het	-	heterocycle
HMPA	-	hexamethylphosphoramide
IM	-	1-methylimidazol-2-yl
IQ	-	*iso*quinolin-1-yl
KHMDS	-	potassium hexamethyldisilazide
LDA	-	lithium di*iso*propylamide
LiHMDS	-	lithium hexamethyldisilazide
Ms	-	methanesulfonyl
NaHMDS	-	sodium hexamethyldisilazide
NMO	-	*N*-methylmorpholine *N*-oxide
PCB	-	4-chlorobenzoyl
PCC	-	pyridinium chlorochromate
PMB	-	4-methoxybenzyl
PPTS	-	pyridinium *p*-toluenesulfonate
proton sponge®	-	1,8-bis(dimethylamino)-naphthalene
PT	-	1-phenyl-1*H*-tetrazol-5-yl
PYM	-	pyrimidin-2-yl
PYR	-	pyridin-2-yl
Red-Al®	-	sodium bis(2-methoxy-ethoxy)aluminum hydride
TBAF	-	tetra-*n*-butylammonium fluoride
TBAI	-	tetra-*n*-butylammonium iodide
TBDPS	-	*tert*-butyldiphenylsilyl
TBHP	-	*tert*-butylhydroperoxide
TBS	-	*tert*-butyldimethylsilyl
TES	-	triethylsilyl
Tf	-	trifluoromethanesulfonyl
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran
TIPS	-	tri*iso*propylsilyl
TMS	-	trimethylsilyl
Ts	-	*p*-toluenesulfonyl
TZ	-	4-methyl-1,2,4-triazol-3-yl

1. The One-pot Julia Olefination

The organic chemist now has a vast array of reactions in his/her arsenal[6], but unfortunately still relatively few procedures which are at once both mild and selective enough to effect the linkage of complex multi-functional fragments. Of those at our disposal, connective olefination processes[7,8] are amongst the most powerful, provided that chemo-, regio- and stereoselection can all be under complete control.

Until the advent of the Wittig reaction[9,10] in the early 1950's, alkenes were typically prepared *via* classical elimination methods. Under the relatively harsh conditions required for such reactions, double bond formation is frequently under thermodynamic control and thus doomed to yield Saytzeff-type products[11]. The following example provided by Inhoffen[12] exemplifies some of the problems facing chemists in the pre-Wittig era (Scheme 1). Ionic elimination of water from diene **2** not surprisingly failed to yield the desired vitamin D model triene **1**, but instead yielded the higher substituted endocyclic olefin **3**.



Scheme 1

1 **2** **3**

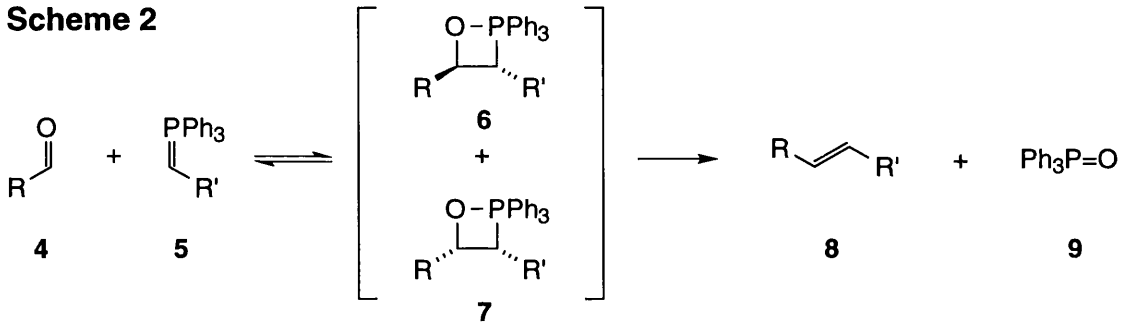
The Wittig reaction offered for the first time a mild connective olefination method which not only enabled precise positioning of the newly formed double bond but often also gave an enormous degree of stereocontrol. A large variety of the olefination methods available today employ the same basic paradigm laid down by Georg Wittig over 45 years ago: condensation of a carbanion (or ylide) stabilised by an adjacent third row heteroatom (Si, P or S) with a carbonyl group initiates a cascade of reactions ultimately leading to the formation of an alkene. Olefination procedures belonging to this general class include: the phosphorus-based Wittig[9,10], Horner-Wittig[13,14] and Horner-Wadsworth-Emmons (HWE)[15,16] reactions (all three have been comprehensively reviewed by Maryanoff and Reitz[17]); the silicon-based Peterson[18] reaction and the sulfur-based Johnson[19] and classical Julia[20] reactions. The aforementioned processes all rely on the variable valency of the key stabilising heteroatom and many are thermodynamically driven by the formation of a strong heteroatom oxygen bond. A new variant of the classical Julia reaction, the *one-pot Julia olefination*[1], is the main focus of this PhD thesis.

1.1. Phosphorus based olefination methods: the Wittig, Horner-Wittig and Horner-Wadsworth-Emmons reactions

1.1.1. The Wittig reaction

The very well known Wittig reaction involves the addition of a phosphonium ylide **5** (phosphorane) to a carbonyl compound **4**, resulting in the formation of an olefin **8** (always at the site of the original carbonyl group) and a phosphine oxide **9** (Scheme 2)[17,21]. Although zwitterionic betaines were originally thought to be intermediates in the reaction, it is now the accepted view (certainly in the case of unstabilised ylides[22]) that the reaction occurs *via* diastereomeric oxaphosphetane entities (**6** and **7**). Their formation is thought to be the result of a [2+2] cycloaddition between the ylide and carbonyl; a *syn* cycloreversion process can then either return the starting materials or yield the products irreversibly.

Scheme 2



Although regiochemistry is precisely controlled, the stereochemical outcome of the Wittig reaction depends upon several factors, being particularly sensitive to the type of ylide used. Generally, stabilised ylides yield predominately *E*-olefins whereas the contrary is true of unstabilised ylides. Indeed, in the absence of soluble lithium salts (so called 'salt-free' conditions) extremely high *Z*-selectivity can result from the use of unstabilised ylides[23].

Due to the high degree of stereochemical predictability and the large number of functional groups with which the Wittig reaction is compatible, it has found wide spread use in the field of target directed synthesis[24,25]. One of the few detractions of the process lies with the difficulty of preparation and purification of certain phosphonium salts (the precursors to phosphonium ylides). Also, being neutral species phosphoranes are poor nucleophiles and on rare occasions Wittig reactions fail because the carbonyl component is reasonably sterically hindered or of low electrophilicity.

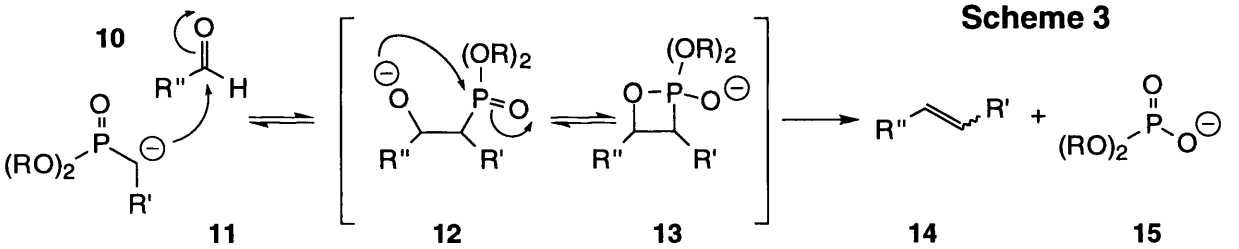
Many variants of the Wittig reaction have appeared[7] most notable being the Horner-Wadsworth-Emmons[15] and the Horner-Wittig[13,14,26] reactions. Both processes differ from the original Wittig reaction in that phosphoryl stabilised carbanions rather than phosphoranes are

employed as nucleophiles. The former are extremely potent nucleophiles when compared to neutral ylide species and have many other advantages besides.

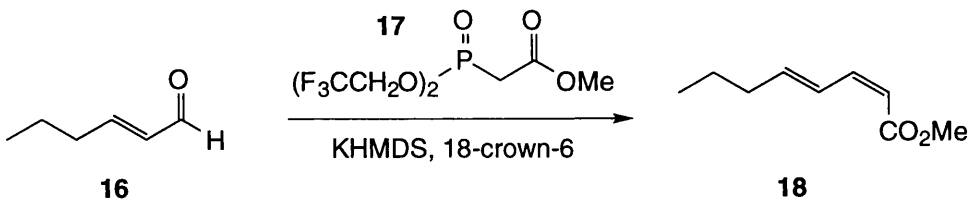
1.1.2. The Horner-Wadsworth-Emmons reaction

The Horner-Wadsworth-Emmons reaction employs carbanions derived from phosphonates. Scheme 3 outlines the basic reaction: an α-metallated phosphonate ester **11** (R' is typically a stabilising group such as carboxyl, vinyl, sulfide, amine *etc*) is condensed with an aldehyde or ketone to yield a mixture of β-alkoxyphosphonates **12**. Following intramolecular alkoxide trapping to give the heterocyclic intermediates **13**, *syn* elimination then occurs to form the alkene products **14** and a phosphate salt **15**. Overall the reaction from the alkoxyphosphonates **12** is stereospecific; the *anti* diastereomer yielding a *cis* olefin and likewise the *syn* diastereomer yielding a *trans* olefin. Thus the stereoselectivity of the HWE reaction is dependent on the initial ratio between the *syn* and *anti* β-alkoxyphosphonates **12** and their ability to equilibrate. The phosphate by-product **15** is water soluble and so easily removed during aqueous work-up, unlike the phosphine oxide remnant from the classical Wittig reaction which must be removed by chromatography. As with the Wittig reaction conditions can be subtly altered to effect the desired stereocontrol[7].

Scheme 3



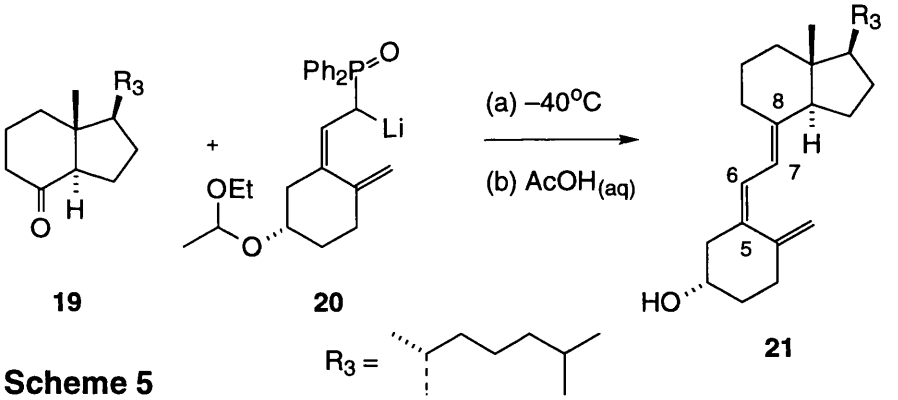
More remarkably, stereoselectivity in HWE reactions can be tuned by variation in the phosphonate ester group, R. Since this group is separate from the intrinsic make-up of the bulk of the nucleophilic partner **11**, a degree of substrate independent stereoselectivity is possible. The intermediate β-alkoxyphosphates **12** are able to equilibrate *via* retro-addition: bulky R groups (*eg iso*propyl) hinder the cyclisation step, **12** to **13**, and promote equilibration to favour the *syn* form of **12** (and so yield predominantly *E*-olefins). In contrast, small R groups (*eg* methyl) or strongly electron-withdrawing groups (R = 2,2,2-trifluoroethyl), inhibit equilibration by promoting rapid forward reaction, and favour the *anti* form of **12** (and so yield predominantly *Z*-olefins)[7]. The use of bis(trifluoroethyl)phosphonoesters (*eg* **17**) was introduced by Still and Gennari[27] and represents an important modification of the HWE providing as it does a method for synthesising *cis* α,β-unsaturated esters with good geometrical purity (see Scheme 4 overleaf). Such ideas concerning the ability of 'spectator' substituents to exert a controlling influence on double bond geometry shall be returned to much later in the discussion of our 1*H*-tetrazole based variant of the one-pot Julia olefination (*vide infra*).



Scheme 4

1.1.3. The Horner-Wittig reaction

The Horner-Wittig reaction is very similar to the Horner-Wadsworth-Emmons reaction and only differs in that a phosphine oxide rather than a phosphonate is used to stabilise the carbanion. A stabilising group α to the phosphine oxide is not required and if a lithiated phosphine oxide is employed the intermediate hydroxyphosphine oxides can be isolated[14] and the diastereoisomers separated. Further treatment of a diastereomerically pure hydroxyphosphine oxide with a sodium base can then yield the corresponding isomerically pure alkene[28]. The Horner-Wittig variant was used to great effect by Lythgoe[29] to complete the first direct total synthesis of vitamin D_3 (**21**) (Scheme 5). Indeed, the analogous Wittig reaction was tried initially for the same fragment linkage and found to be ineffectual, the low nucleophilicity of the appropriate phosphorane being the primal cause of failure. Using the Horner-Wittig procedure the coupling went in good yield, forming the required 7*E* double bond geometry and preserving the stereochemical integrity of the 5*Z* double bond.



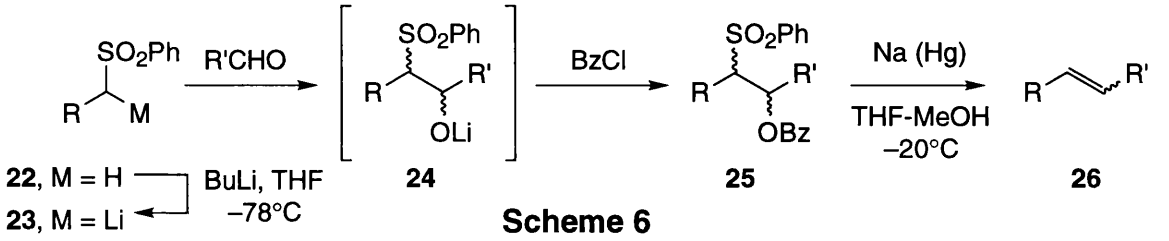
Scheme 5

1.2. Sulfur based olefination methods: the classical and the one-pot Julia olefinations

1.2.1. The classical Julia olefination

In 1973 Julia and Paris published a short paper outlining a new connective olefination procedure utilising the reductive elimination of β-hydroxysulfones[20]. Herein referred to as the *classical Julia olefination*, this mild selective method has found pivotal use in the synthesis of many natural products (for example see[30-32]). The initial proliferation of the Julia reaction was hindered by the relatively cumbersome nature of the four steps required for coupling (Scheme 6): metallation of an aryl alkyl sulfone **22**, condensation with an aldehyde to yield a β-

alkoxysulfone **24**, alkoxide acylation and finally reductive elimination with sodium amalgam to afford the alkene products (for reviews see Kelly[7], Julia[33] and Kocienski[34]). All four steps can be carried out in a single reaction vessel although in practice the overall yield of the process is found to benefit from isolation of the intermediate β-hydroxysulfone and functionalisation of the hydroxyl group in a separate step.



Scheme 6

The greatest attribute of the classical Julia olefination is the high *trans* selectivity of the reductive elimination stage. During their vitamin D synthetic studies, Kocienski and Lythgoe investigated and developed the fledgling Julia reaction before applying modified conditions to achieve the first total synthesis of vitamin D_4[30] (see Chapter 3). Kocienski discovered that increased chain branching on the coupling partners resulted in a higher *E:Z* ratio of the product alkenes[35] (Figure 1).

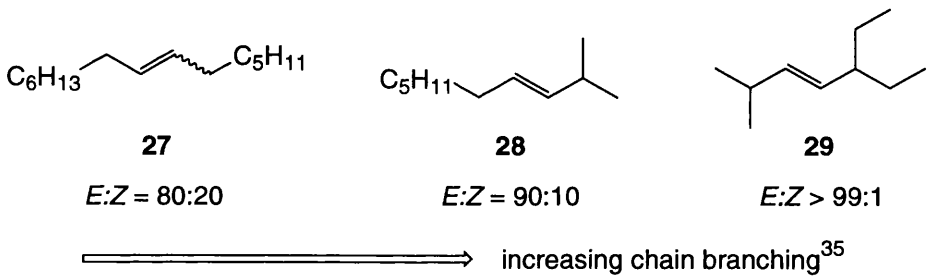
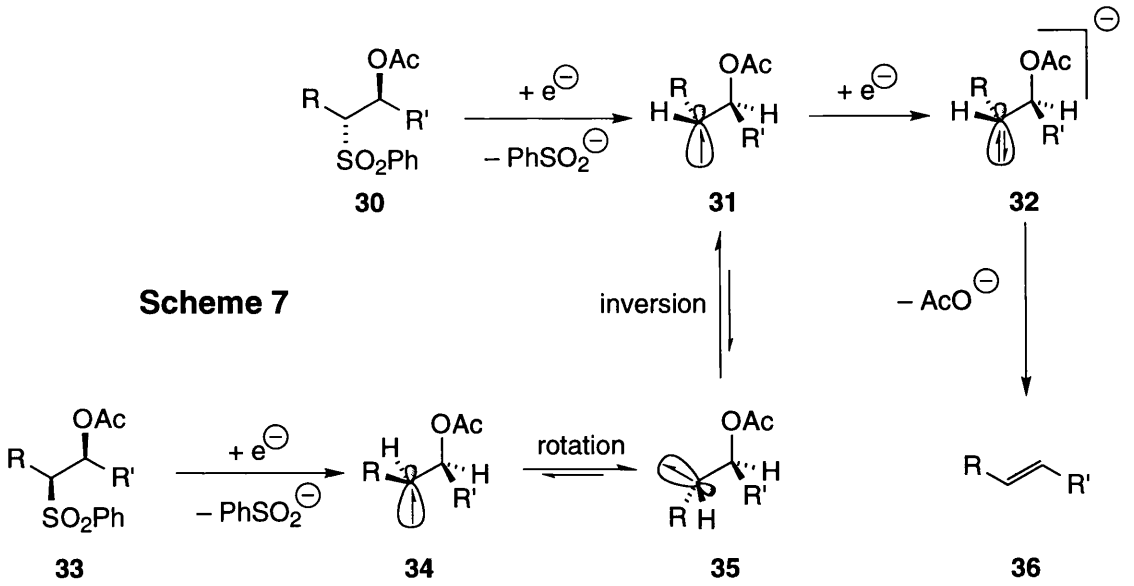


Figure 1

Furthermore, the geometry of the alkene product was completely independent of the relative stereochemistry of the β-acyloxysulfone[36,37]. Taken together these key observations suggested that reductive removal of the arylsulfonyl group led to the formation of a relatively long-lived radical or anionic intermediate (**31** or **32**) which achieves a low energy *trans* configuration before final loss of the acylate anion yields the olefin (see Scheme 7 overleaf). Of course, increased branching at the site of elimination should increase the *trans* selectivity for steric reasons.

Problems can potentially occur with any of the four steps essential for the Julia olefination[34]. Although the metallated sulfones are competent nucleophiles, their generation with *n*-butyl lithium can be inhibited if bulky α-substituents are present. Also it has been known for deprotonation to occur on the aryl ring rather than at an α site on the alkyl moiety. Such



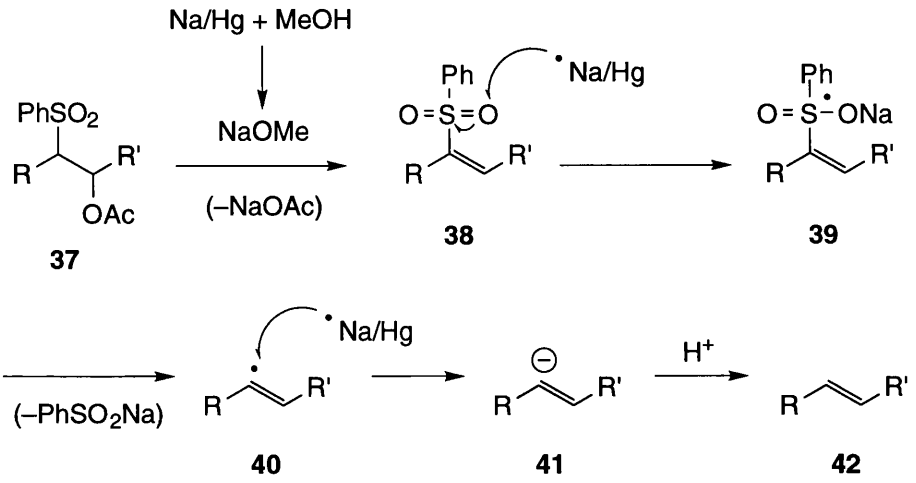
Scheme 7

problems can usually be circumvented by the use of alternative bases such as LDA, or transmetallation with $MgBr_2$ to magnesiated derivatives.

The addition of metallated sulfones to carbonyl compounds can be reversible, this is likely if either of the components is very bulky or if the sulfone carbanion is well stabilised. Such 'retroaldolisation' reactions were thought to severely limit the use of the Julia reaction for the synthesis of tri- and tetrasubstituted alkenes from ketones, although a recent report by Hart suggests otherwise[38]. Hart and co-workers advocate 1,2-dimethoxyethane (DME) rather than THF as the solvent of choice for conducting metallated sulfone-carbonyl addition reactions. Acylation of the intermediate hydroxysulfone remains an important device for inhibiting retroaldolisation during the inherently basic reductive elimination step.

More recent developments have seen the use of alternative reductants to the ever unpopular sodium amalgam. Although expensive SmI_2 seems particularly advantageous in demanding cases[39] and has also been advocated for the preparation of trisubstituted alkenes from ketones[40]. The samarium based system does, however, require the use of an additional co-solvent such as hexamethylphosphoramide (HMPA) or dimethylpropylene urea (DMPU) to promote electron transfer to phenylsulfones. Kende has demonstrated that in the case of *N*-methylimidazol-2-yl (IM) sulfones such additives are unnecessary. IM sulfones are superior one-electron acceptors to phenylsulfones and the derived β-hydroxysulfones are readily reduced by SmI_2[41]. The most convenient system discovered to date involves the reduction of β-acetoxyphenylsulfones by magnesium metal under $HgCl_2$ catalysis in ethanol[42], the general scope of this methodology is yet to be determined.

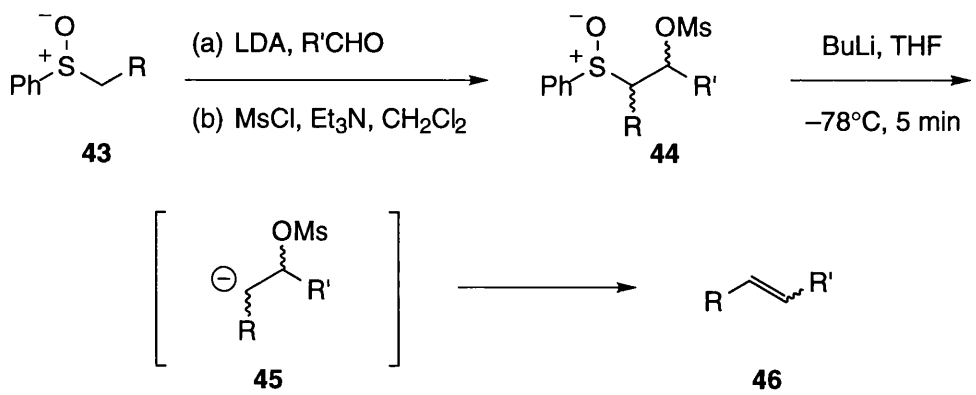
Based on deuterium labelling studies, Keck[39] has suggested an alternative mechanism for the reduction of β-acetoxyphenylsulfones by Na/Hg (Scheme 8): methoxide generated from Na/Hg



Scheme 8

and MeOH initiates the elimination of acetate to yield a vinyl sulfone **38**. Subsequent reductive removal of the sulfone moiety and a further electron transfer then yields a vinyl anion **41**; a proton quench then yields the product olefin **42**. Equilibration of the incipient vinyl radical **40** is proposed to account for the inherent *trans* selectivity. Use of MeOH-d_4 led to >90% deuterium incorporation in the product; the traditionally accepted mechanism given above (Scheme 7) does not account for any label incorporation. The analogous experiment conducted with SmI_2 gave products with no deuterium incorporation, indicating that the samarium mediated process probably proceeds solely *via* the previously accepted mechanism. The Na/Hg and SmI_2 reduction systems do not give products with identical *E:Z* ratios.

Finally, a sulfoxide version of the Julia reaction has been reported by Satoh and co-workers[43]. Following the addition of an α-sulfinyl metallate to an aldehyde subsequent trapping with mesyl chloride yields a β-mesyloxysulfoxide **44** (Scheme 9). The latter is treated with butyl lithium resulting in an exchange of sulfoxide ligands to yield the transient carbanion **45**. Before further ligand exchange can occur the highly reactive intermediate **45** eliminates mesylate to afford an alkene product. Stereoselectivity is typically poor and likely reflects meagre diastereoselective bias in the initial addition event. However, the use of aromatic aldehydes

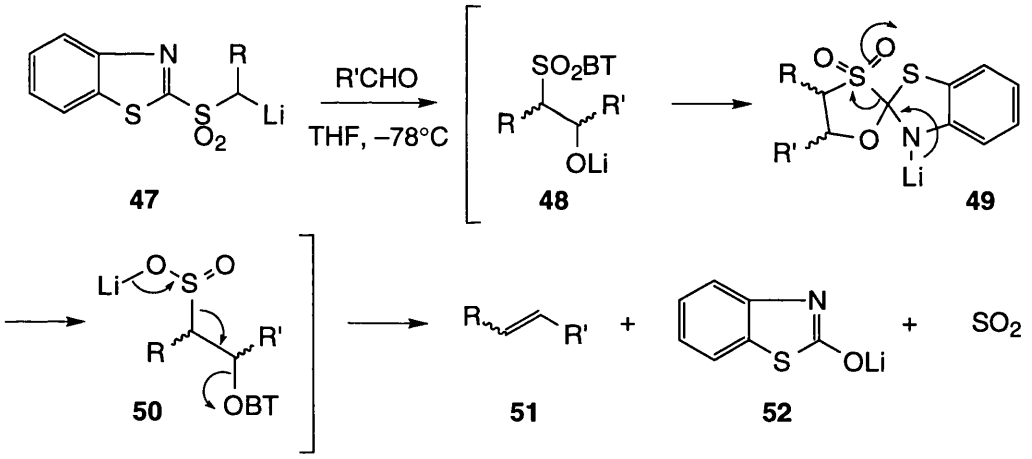


Scheme 9

yields pure *trans* olefins directly upon mesylation. The authors implicate the intermediacy of a benzylic cation to explain this phenomenon[43].

1.2.2. The one-pot Julia olefination

Eighteen years after the original disclosure of the classical Julia olefination by Marc Julia[20], Sylvestre Julia reported a significant modification of his brother's earlier discovery[1]. In common with the classical reaction, the new variant begins with the lithiation of an aryl alkyl sulfone and its subsequent condensation with a carbonyl compound. However, rather than simple phenyl sulfones, the new procedure employs benzothiazol-2-yl sulfones, hereafter denoted as BT sulfones (Scheme 10). The presence of an electrophilic site within the heterocyclic moiety allows reaction to continue beyond the β-alkoxysulfone **48**; the alkoxide intramolecularly attacks the C=N bond of the benzothiazole moiety forming the putative spirocyclic intermediate **49**. Breakdown of the spirocycle can then occur with transfer of the heterocycle from sulfur to oxygen to yield **50**; the overall process **48** to **50** is then analogous to the Smiles rearrangement[44]. Adduct **50** then loses sulfur dioxide with concomitant elimination of the lithium derivative of benzothiazolone (**52**) to form the olefin. We refer to the aforementioned procedure as the *one-pot Julia olefination* for obvious reasons.

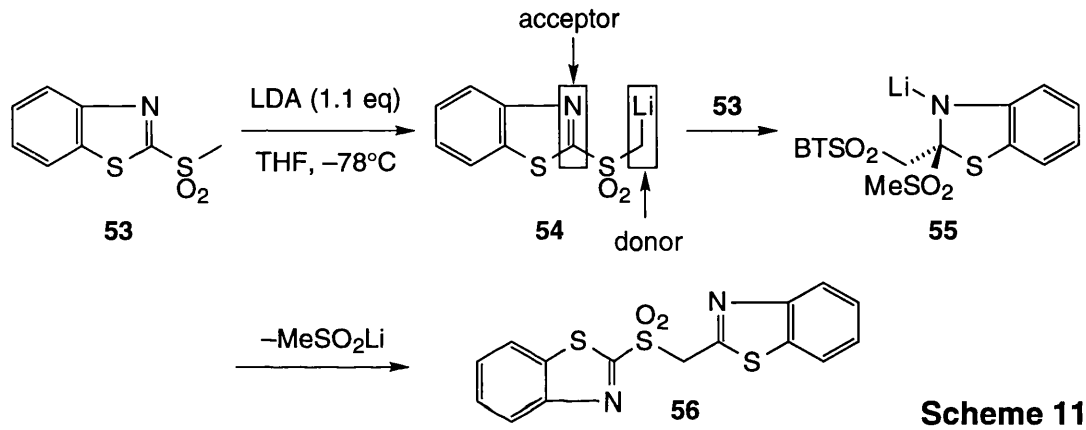


Scheme 10

In subsequent investigations Julia found that pyridine and pyrimidine heterocyclic systems could also mediate the olefination process[2,3]. Although both new heterocyclic mediators were generally inferior, work with the pyridine series provided rewarding mechanistic insight. The 2-pyridyl β-hydroxysulfone intermediates were found to be generally stable and could be isolated in many instances from the reaction mixtures. Only on rare occasions was it found possible to isolate such intermediates in the BT series. The addition of lithiated 2-pyridylsulfones to saturated or aromatic aldehydes was found to be essentially non-diastereoselective and the product *syn* β-hydroxysulfones were converted far more rapidly to alkene products than the corresponding *anti* adducts[2]. Diastereomerically pure β-hydroxysulfones (both BT and pyridyl) were next prepared *via* the base mediated opening of

stereodefined epoxides by heterocyclic thiols followed by sulfur oxidation. The data from the examples studied suggested that the final elimination step was entirely antiperiplanar only for those alkoxides bearing saturated aliphatic chains R and R'. In such cases *anti* β-hydroxysulfones yield *E*-olefins and likewise *syn* β-hydroxysulfones yield *Z*-olefins. Where 'stereochemical drift' was noted, equilibration between the hydroxysulfones (*via* retroaddition) was proposed to be the cause[2].

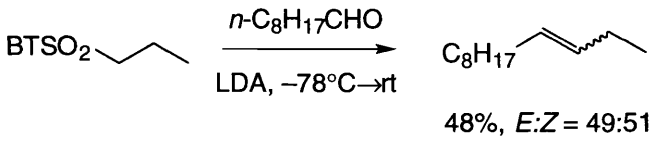
With some idea of a possible mechanism developing, Julia and co-workers embarked on an extensive study of the stereochemical outcome of over 100 representative coupling reactions encompassing a variety of different types of substrate[3]. During the investigation some basic limitations of the BT-mediated olefination process were revealed.



Scheme 11

The success of the one-pot Julia reaction hinges on the electrophilicity of the benzothiazolyl moiety; for this reason, a non-nucleophilic base must be used for the deprotonation step to prevent premature nucleophilic attack upon the heterocycle and expulsion of a sulfinic acid salt (Julia favoured the use of LDA in THF at –78°C[3]). However, if simple BT sulfones are metallated in the absence of an aldehyde, their donor-acceptor nature can lead to self-condensation (Scheme 11). 'Dimeric' species such as **56** have been isolated from Julia coupling experiments and their formation is, of course, detrimental to the olefination process. A reverse addition protocol does not prevent self-condensation; adding the sulfone to the base also results in formation of the bisheterocyclic adducts. To overcome the problem of low yields arising from self-condensation, Julia and co-workers adopted so-called 'Barbier' conditions for the vast majority of their coupling experiments. Rather than 'pre-metallate' the sulfone and then subsequently add the aldehyde (a more usual protocol for many reactions), the base was added to a *mixture* of the sulfone and aldehyde. Thus addition of the *in situ* metallated sulfone to the aldehyde competes more than adequately against a self-condensation mechanism. Employing Barbier conditions, yields were typically 10-40% higher in the case of 'simple' (*ie* small and non-sterically hindered) sulfones. Of course it is to be expected that complex multifunctional aldehyde substrates would not tolerate such conditions.

The coupling studies of Julia revealed an important relationship between substrate pairings and stereoselectivity[3]. Three distinct situations were investigated: (a) condensation of saturated BT sulfones with saturated aldehydes (simple steric effects), (b) condensation of stabilised BT sulfones with saturated aldehydes (nucleophile electronic effects), and (c) condensation of saturated BT sulfones with α,β-unsaturated aldehydes (electrophile electronic effects). Scheme 12 illustrates some actual results which crudely encompass all three variations[3].

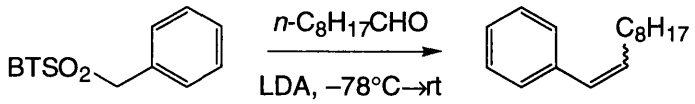


48%, *E*:*Z* = 49:51

(a)

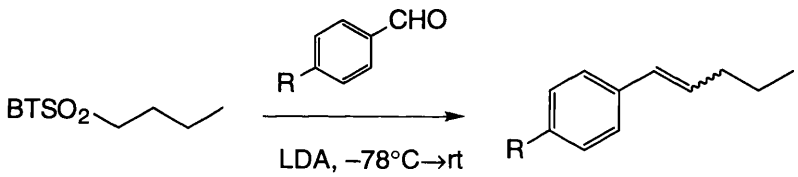
Scheme 12

	nucleophile (sulfone)	electrophile (aldehyde)
(a)	saturated	saturated
(b)	stabilised	saturated
(c)	saturated	unsaturated



80%, *E*:*Z* = 23:77

(b)



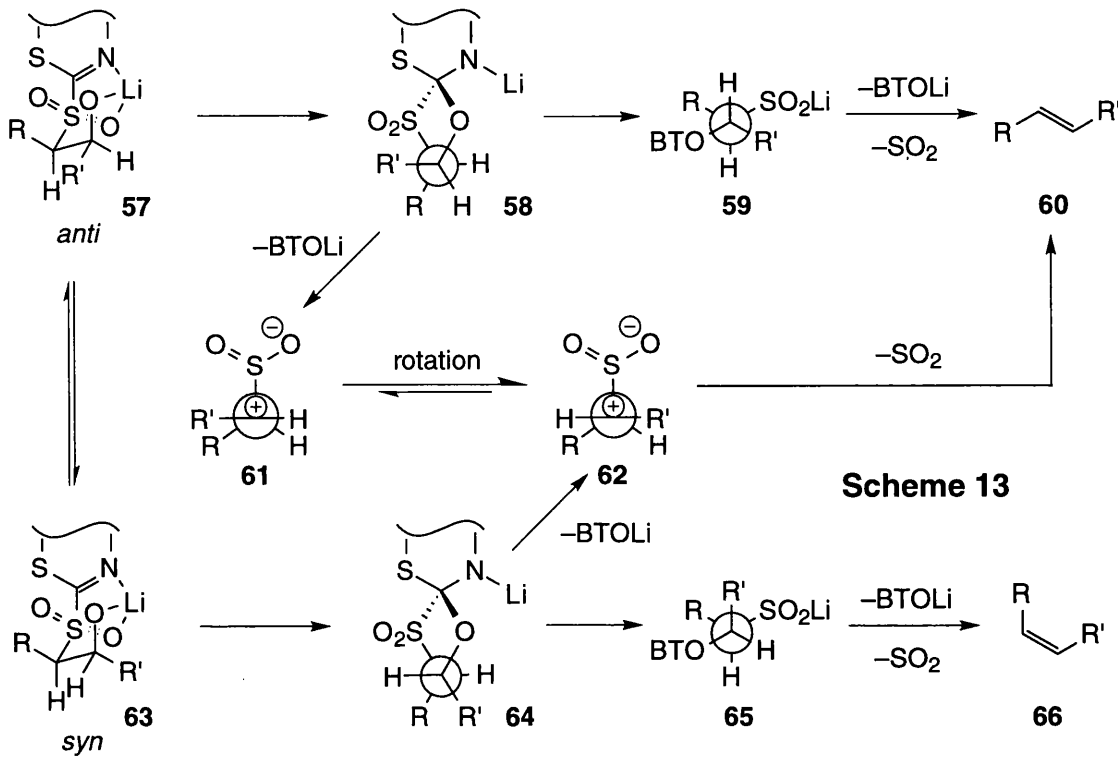
R	Yield%	*E*:*Z*
OMe	95	99:1
H	68	94:6
Cl	51	77:23

(c)

The above results display some interesting trends and the stereoselectivies shown here were echoed faithfully for other examples of the same general 'type'. Points to note are: little or no selectivity was observed for type (a) couplings; a slight *Z*-preference was generally displayed for type (b) couplings, and a significant *E*-preference noted for type (c). Notice in the type (c) example illustrated, as the benzaldehydes became more electron rich, *trans* selectivity increased.

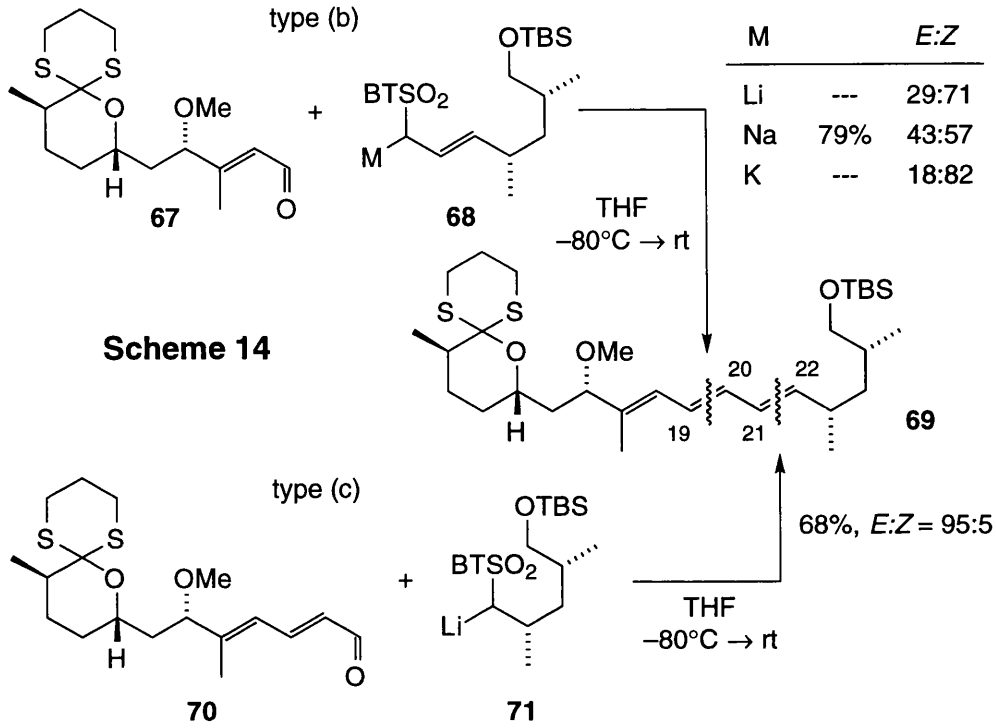
On the basis of the evidence summarised above Julia suggested the somewhat convoluted mechanism illustrated in Scheme 13. The provisional mechanism provides a very good working model for the prediction of stereoselectivity for most types of simple substrates, the ideas are ingenious and initially very attractive.

The two possible diastereoisomers of the initial β-alkoxysulfone adduct, **57** (*anti*) and **63** (*syn*), are proposed to be in equilibrium with the *syn* form being thermodynamically favoured due to the staggered nature of R and R'. Evidence from the pyridyl series already suggested the more facile reaction of *syn* β-hydroxysulfones. Equilibration is promoted if R is unsaturated



since the resultant stabilisation offered to the original α-metallated sulfone encourages reversibility of the addition step. In such cases it is often found that the product alkene is formed with high *Z*-selectivity due to initial equilibration to **63** followed by the direct route from **64** to alkene **66** (*cf* type (b) couplings). Cases where R and R' are saturated generally exhibit a complete lack of stereocontrol due to the associated inhibition of equilibration between **57** and **63** and the observed lack of addition diastereoselectivity (*cf* type (a) couplings). High *E*-selectivity is observed when R' is an electron donating group (*cf* type (c) couplings). The selectivity is proposed to arise from the possibility of both the *syn* adduct **63** and the *anti* adduct **57** being directly converted to an *E* alkene **60**. The route from **63** to **60** is postulated to proceed *via* direct loss of lithium benzothiazolone from the spirocycle **64** to yield the zwitterionic intermediate **62**. The betaine then loses sulfur dioxide from the lowest energy conformation to yield an *E*-alkene. R' electron donating groups are best able to stabilise the positive charge site of the zwitterion and so facilitate the unusual reaction pathway.

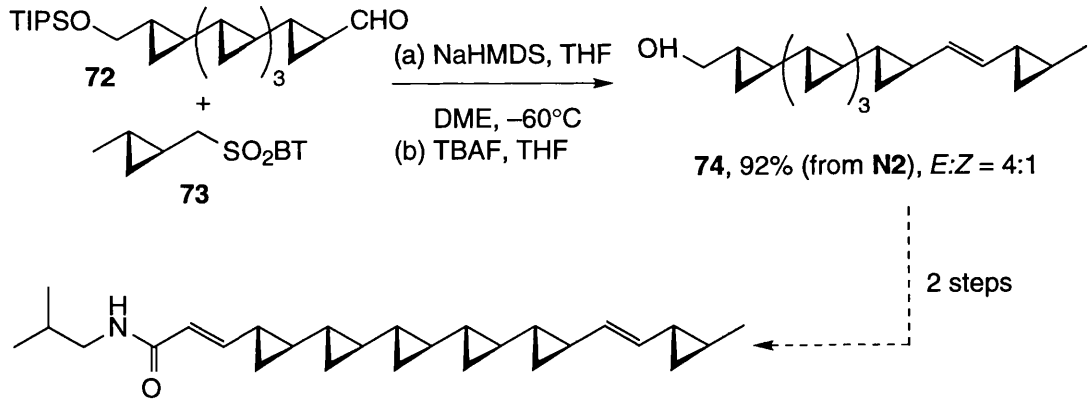
Due to its immaturity, the one-pot Julia olefination has found relatively few applications; however, the successes achieved to date suggest the reaction may become a standard tool for the synthesis of complex natural products. Several groups have discovered that the stereochemical outcome of the reaction can be subtly altered by variations in both base and solvent (*vide infra*).



Scheme 14

Kocienski's synthesis of a C10-C26 fragment of rapamycin (**69**) employed the Julia olefination to construct an all *trans* conjugated triene moiety[45]. The coupling was attempted in two different senses (Scheme 14): either unsaturated sulfone **68** was condensed with the enal **67** or the saturated sulfone **71** was condensed with the dienal **70**. As could be predicted from the above discussion, the latter strategy was far more successful in securing the all *trans* olefinic system. The reactions illustrated were initiated with hexamethyldisilazide bases and of particular interest was the dependency of stereoselectivity upon the base counter cation. Kocienski and co-workers have also used the one-pot Julia reaction to construct the diene segment of herboxidiene A[46] (see Chapter 5).

Charette's application of the one-pot Julia olefination toward the synthesis of the skipped hexakiscyclopropane natural product (+)-U-106305[47] (**75**), provides an example of an unusual type (a) coupling (Scheme 15). A number of unspecified connective olefination methods (one can only assume including common Wittig variants) were surveyed in attempts to forge the non-conjugated 1,2-disubstituted double bond of the natural product. All failed until the one-pot Julia reaction was finally tested as a last resort. To generate and then maintain a carbanion α to a cyclopropane moiety, sufficient stabilisation must be at hand to prevent ring opening: BT sulfones are apparently equal to the task. As illustrated in Scheme 15, the one-pot Julia reaction between sulfone **73** and aldehyde **72** operating under Barbier conditions, yielded after deprotection the olefin **74** in excellent yield with good stereoselectivity.



Scheme 15

The optimised reaction conditions employed by Charette were arrived at *via* an interesting model study[47] (Table 1). The coupling between the simplified aldehyde **76** and sulfone **73** was investigated in a number of solvents of differing polarity and Lewis basicity. The base counter cation had little effect on the stereochemical outcome in contrast to Kocienski's findings above (compare entries 1 and 7, 4 and 8), however, solvent had a profound effect. Non-polar solvents gave excellent *Z*-selectivities, as polarity and Lewis basicity increased the *E*-olefin was favoured (entries 1 through to 6). Of particular note is the success of the reaction in both CH_2Cl_2 and DMF, very untraditional solvents for carbanion chemistry. Ironically, the one solvent that gave the worst stereoselectivity here, THF, was the only solvent employed during Julia's extensive studies[3].

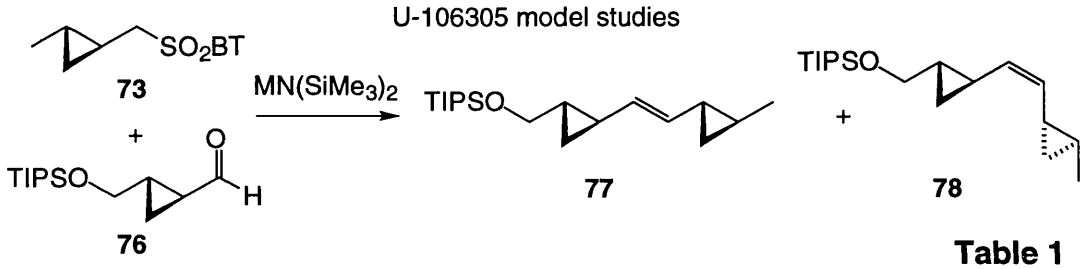


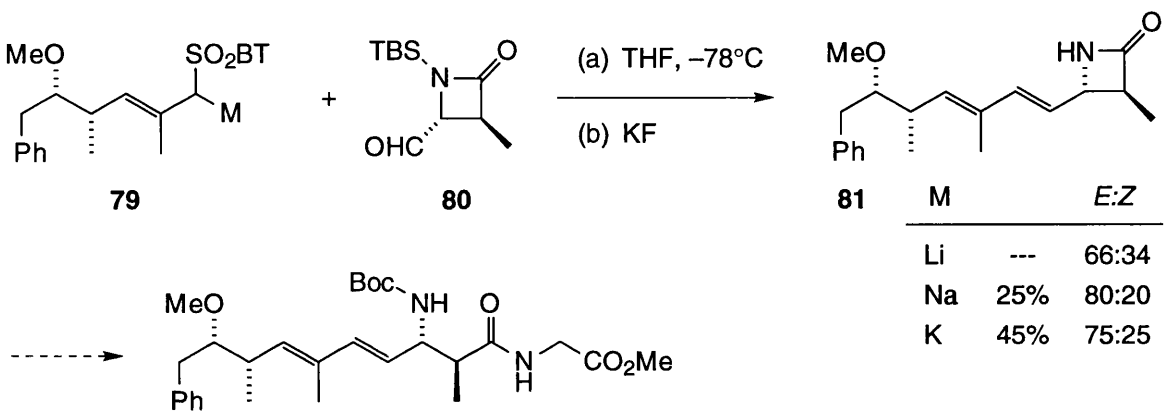
Table 1

entry	M	solvent	*E:Z* (**77**:**78**)	entry	M	solvent	*E:Z* (**77**:**78**)
1	Na	PhMe	9:91	5	Na	DME	71:29
2	Na	CH_2Cl_2	9:91	6	Na	DMF	78:22
3	Na	Et_2O	11:89	7	K	PhMe	21:79
4	Na	THF	52:48	8	K	THF	55:45

[a]All reactions conducted at –78°C except those in DMF and DME which were run at –60°C. [b]All yields >90%.

Following Kocienski's lead[45,46], the McCarthy group have also employed the one-pot Julia reaction to synthesise a conjugated olefin[48] (Scheme 16). To secure the requisite *E,E*-diene **81** rather illogically the stabilised BT sulfone metallate **79** was condensed with the carboxylactam **80**. The umpoled approach here would probably have given far superior selectivity without competing β-lactam opening ($E1_{CB}$). In any event use of potassium hexamethyldisilazide as base was found to give the optimum yield albeit with slightly compromised stereoselectivity

(*E:Z* = 75:25). The greatest selectivity was achieved with NaHMDS (*E:Z* = 80:20) although the yield was then a disappointing 25%. Perhaps more importantly the analogous coupling was also attempted using two phosphorous based olefination methods and both were found wanting. A Wittig reaction between the appropriate phosphorane and aldehyde **80** yielded only 25% of the lactam **81** with no stereochemical bias. A Horner-Wittig reaction gave solely the desired *E*-isomer but in a yield of only 15%. The lactam product of interest, **81**, is a donor of the β-amino acid ADDA and has been used to synthesise conjugates such as the protected glycine-ADDA dipeptide **82**[48].



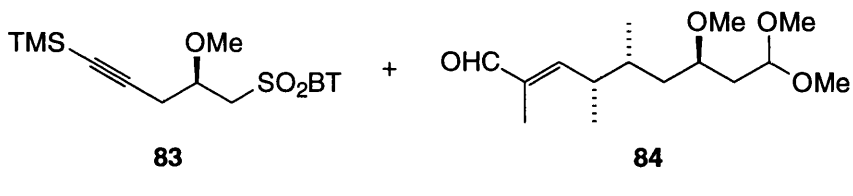
79 **80** **81**

M		*E:Z*
Li	---	66:34
Na	25%	80:20
K	45%	75:25

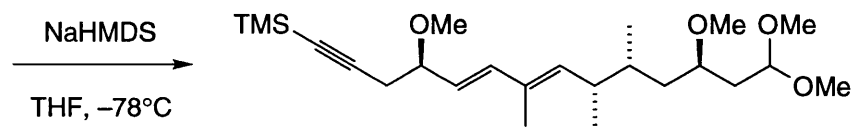
82

Scheme 16

Pattenden and co-workers have also employed the one-pot Julia olefination to construct an all *trans* conjugated diene segment[49] (Scheme 17). The diene **85** was realised most efficiently by the condensation of enal **84** and sulfone **83**. As expected for such a sensible disconnection, the *trans* selectivity of the reaction was excellent as was the yield. The diene **85** was subsequently elaborated to a C31-C46 fragment of the marine natural product phorboxazole A.



83 **84**



85, 74%, *E:Z* > 95:5

Scheme 17

Lastly, the Burke group have revealed their future intent to employ the one-pot Julia reaction by disclosing the synthesis of sulfone **87**[50] (Figure 2). The enoate encompasses the C1-C9 region of the natural product rhizoxin **86**. The C12-C26 triene **88** has also been realised[50] (the C20-

C21 double was installed *via* HWE methodology) and it shall be interesting to observe whether the completion of the total synthesis employs a standard macrolactonisation procedure or an innovative one-pot Julia macrocyclisation.

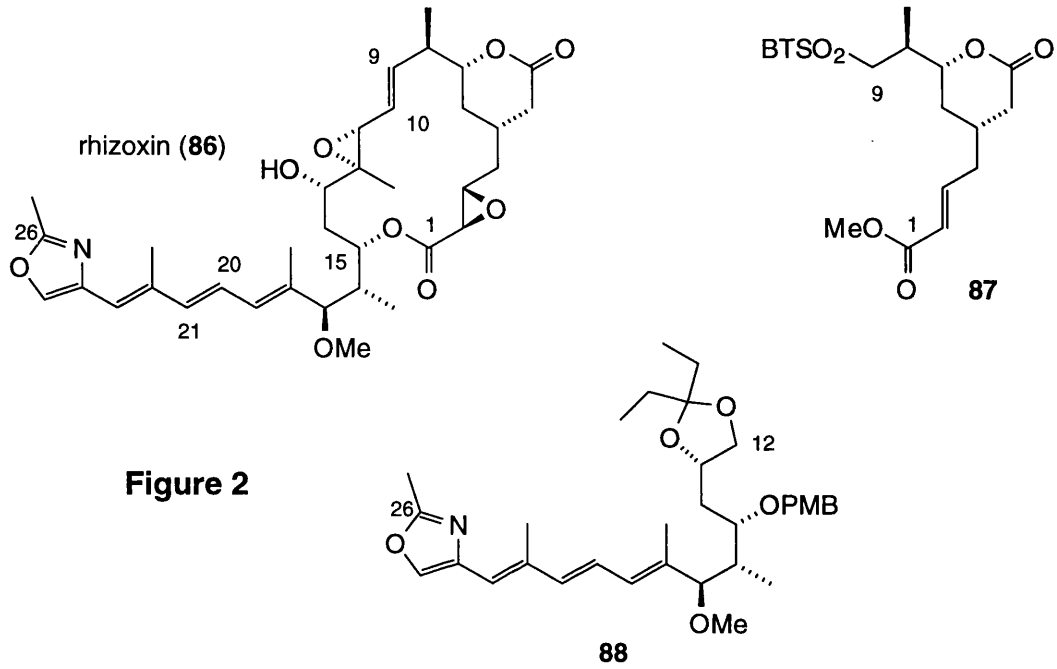


Figure 2

2. Development of the One-pot Julia Olefination

At the outset of the work described herein, our basic goal was to further develop the one-pot Julia olefination with a view to improving the applicability, operational simplicity, stereoselectivity and overall efficacy of the process. Beyond basic methodology development, our intention was to apply the olefination procedure in its various guises to some complex synthetic problems: the partial synthesis of vitamin D (see Chapters 3 and 4) and the total synthesis of herboxidiene (see Chapters 5 and 6).

To seek improvement in the existing one-pot Julia technology one must first identify its limitations. Detractions of the benzothiazole mediated process include the tendency for sterically unencumbered sulfones to self-condense under pre-metallation conditions, and general lack of stereoselectivity for the synthesis of non-conjugated 1,2-disubstituted olefins. Certainly the latter problem could be solved if it were possible to promote irreversible diastereoselective addition of a sulfone nucleophile to an aldehyde.

The key to both improved stereocontrol and increased nucleophile stability is likely to lie with the heterocyclic nucleus employed to mediate the olefination process. Our development strategy was thus to first identify a promising alternative to the benzothiazole moiety and then to optimise reaction conditions for the new system.

2.1. Screening of novel heterocyclic olefination mediators

Julia's own group had already additionally demonstrated the feasibility of pyridine (PYR) and pyrimidine (PYM) heterocycles as successful mediators for the one-pot olefination process[3]. We re-investigated the BT, PYR and PYM sulfone systems and went on to extend our screening programme to include other heterocyclic systems also in possession of appropriate electrophilic C=N bonds. Figure 3 outlines the range of surveyed heterocycles: central to the

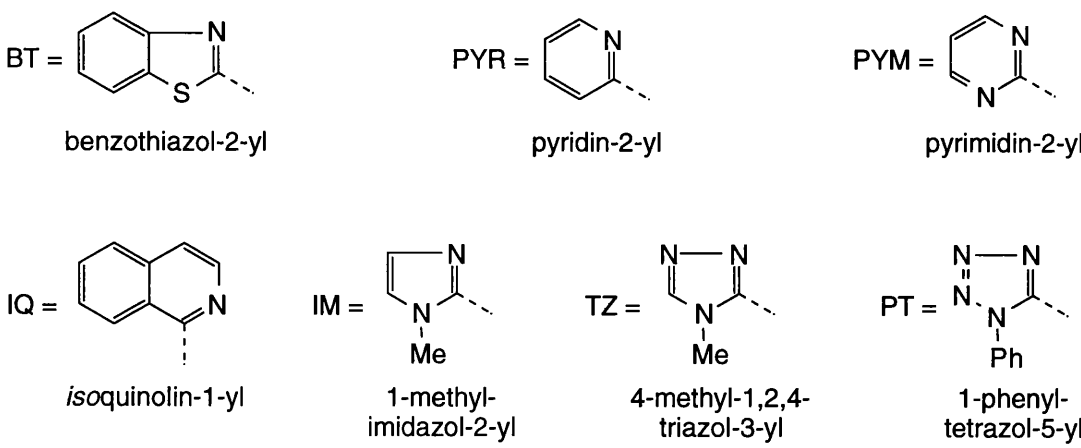


Figure 3

choice of the novel scaffolds was the ease of availability of the corresponding thiol compounds [all but *iso*thiocarbostyril[51] (IQSH) were commercially available] and the presence of a free valence site in close proximity to the electrophilic centre. The latter attribute allows for the introduction of a bulky substituent which may offer some steric shielding to the electrophilic centre and so reduce the propensity for self-condensation. Fine tuning of such substituents may also affect the diastereoselectivity of addition.

A small range of sulfones was synthesised from the chosen set of heterocyclic thiol compounds which incorporated either a simple straight aliphatic chain or a β-branched aliphatic chain (Table 2). The thiols were first elaborated *via* simple alkylation with the appropriate alkyl bromide or *via* thioetherification of an alcohol under standard Mitsunobu conditions[52]. Oxidation of the resultant sulfides to the requisite sulfones was typically effected by the action of 3-chloroperoxybenzoic acid (*m*-CPBA).

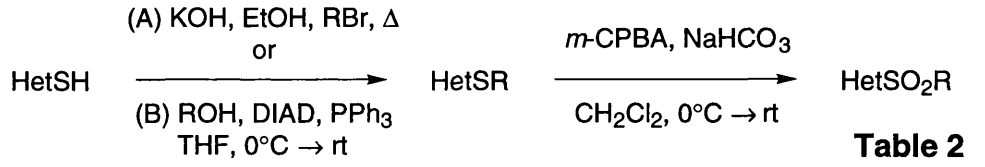
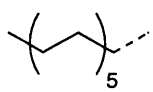
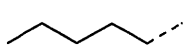
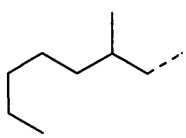
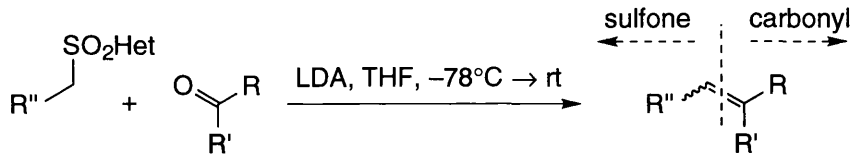


Table 2

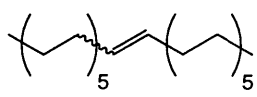
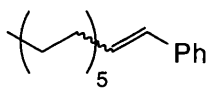
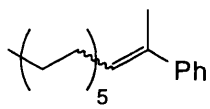
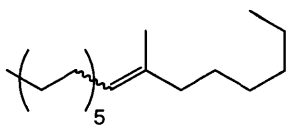
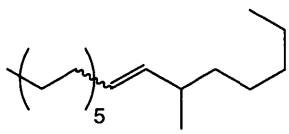
R	Het	alkylation method	sulfide	%yield	sulfone	%yield
	BT	A	**89**	81	**101**	51
	PYR	A	**90**	100	**102**	70
	PYM	A	**91**	90	**103**	68
	IM	A	**92**	89	**104**	67
	TZ	A	**93**	74	**105**	53
	IQ	A	**94**	76	**106**	77
	BT	A	**95**	71	**107**	100
	PT	A	**96**	90	**108**	65
	BT	B	**97**	89	**109**	68
	TZ	A	**98**	100	**110**	73
	IQ	B	**99**	47	**111**	65
	PT	B	**100**	89	**112**	71

In our initial studies the above sulfones (with the exception of **107** and **108**) were condensed with a selection of aldehydes and ketones (dodecanal, benzaldehyde, acetophenone, 2-octanone and its isomer 2-methylheptanal) under Julia's original Barbier conditions[3], employing LDA as base and THF as solvent. The set of coupling partners chosen allowed us to observe not only the effect of heterocyclic mediator, but also in a more limited way, the effects of chain branching and component reversal on the olefination reaction. Our primary objective here was to identify a promising heterocyclic system for further optimisation with particular regard to the synthesis of non-conjugated 1,2-disubstituted olefins. The results are outlined in Table 3: each



*isolated
†determined by GC analysis

Table 3

olefin	entry	Het	sulfone	%yield olefin*	*E:Z*†
 **113**	1	BT	**101**	47	46:54
	2	PYR	**102**	46	35:65
	3	PYM	**103**	5	55:45
	4	IM	**104**	12	3:97
	5	TZ	**105**	34	43:57
	6	IQ	**106**	54	44:56
 **114**	7	BT	**101**	30	79:21
	8	IM	**104**	<1	54:46
	9	TZ	**105**	44	38:62
	10	IQ	**106**	40	74:26
 **115**	11	BT	**101**	46	53:47
	12	IM	**104**	<1	49:51
	13	TZ	**105**	5	6:94
	14	IQ	**106**	32	6:94
 **116**	15	BT	**101**	60	34:67
	16	IM	**104**	4	31:69
	17	TZ	**105**	15	22:78
	18	IQ	**106**	56	47:53
 **117**	19	BT	**101**	58	43:57
	20	IM	**104**	17	2:98
	21	TZ	**105**	36	28:72
	22	IQ	**106**	44	55:45

(cont. overleaf)

mixture of product olefins was isolated by flash chromatography and then NMR spectroscopy used to determine which geometrical isomer predominated. GC analysis of the product mixture was then employed to accurately measure the *E:Z* ratio (see Experimental Section for full details).

Immediately from the somewhat bewildering array of results it becomes clear that, as suspected, the heterocyclic mediator can have a profound effect on the yield and stereoselectvity of olefin formation. Obvious trends to highlight from Table 3 are;

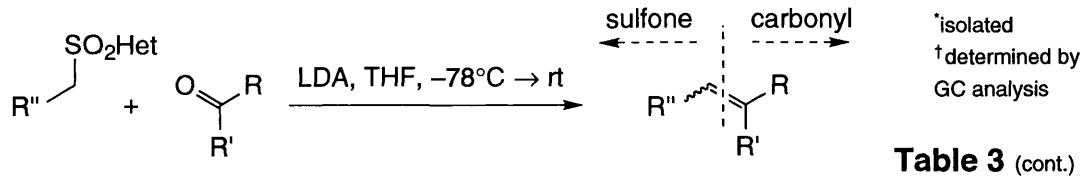
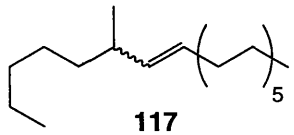
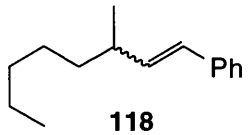
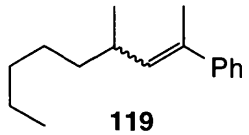
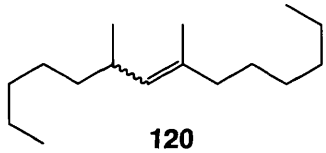
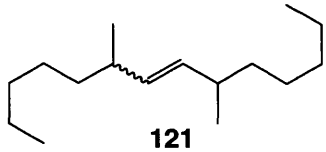


Table 3 (cont.)

olefin	entry	Het	sulfone	%yield olefin*	*E:Z*†
 **117**	23	BT	**109**	58	54:46
	24	TZ	**110**	43	47:53
	25	PT	**112**	69	65:25
 **118**	26	BT	**109**	39	>99:1
	27	TZ	**110**	39	62:38
	28	IQ	**111**	39	96:4
	29	PT	**112**	90	>99:1
 **119**	30	BT	**109**	23	14:86
	31	TZ	**110**	<1	6:94
	32	PT	**112**	11	25:75
 **120**	33	BT	**109**	33	25:75
	34	TZ	**110**	3	14:86
	35	PT	**112**	9	46:54
 **121**	36	BT	**109**	28	75:25
	37	TZ	**110**	29	6:94
	38	PT	**112**	48	39:61

(a) *Efficiency of olefination:* BT and IQ sulfones were generally the highest yielding systems, performing well when condensed with both aldehydes and ketones. PYM and IM sulfones were always low yielding and in general all of the five-membered nitrogenous heterocycles: IM, TZ and PT performed poorly with ketones. However, PT sulfones were superior when condensed with aldehydes (compare entries 26 to 28 with entry 29).

(b) *Effect of heterocycle on stereoselectivity:* All of the BT couplings concerning aldehydes typically displayed the same trends in stereoselectivity previously observed by Julia[3] [*ie* little control in the formation of non-conjugated 1,2-disubstituted olefins (see entries 1, 19, 23) and moderate to high *trans* selectivity when benzaldehyde was employed (entries 7 and 26)]. IQ sulfones gave very similar results to BT sulfones in such cases. Of greater interest was the tendency for IM sulfones (and to a lesser extent TZ sulfones) to yield *cis* 1,2-disubstituted olefins (entries 4, 16 and 20) with a high degree of control. Indeed, IM sulfone **104** was the only compound that yielded a 12-tetracosene (**113**) product with any great stereocontrol. In all

of Julia's investigations there were no examples of the use of unsymmetrical ketones and so little was known about stereoselectivity in the formation of trisubstituted double bonds. With regard to the synthesis of the trisubstituted olefins **115**, **116**, **119** and **120**, a general *Z*-preference was noted for all heterocycles tested with TZ sulfones being the most selective (entries 13, 17, 31 and 34).

(c) *Effect of chain branching on stereoselectivity:* Firstly, in the case of non-conjugated 1,2-disubstituted olefins, chain branching had little effect on stereocontrol in the BT series when present in either the sulfone or aldehyde component (compare entry 1 with entries 19 and 23). However, when present on both sides, a slight *trans* selectivity was noted (entry 36). For the TZ series branching on the sulfone had little influence (compare entries 5 and 24), although when present in the aldehyde an increased *Z*-preference was observed (entries 21 and 37). The reverse effect of increased chain branching on stereoselectivity for BT and TZ systems is noteworthy (compare entries 36 and 37). When sulfones were condensed with benzaldehyde, the presence of branching increased *trans* selectivity for BT, TZ and IQ systems [compare entries 7 and 26 (BT), 9 and 27 (TZ), 10 and 28 (IQ)]. Such behaviour is to be anticipated from Julia's explanation for general *trans* selectivity when conjugated aldehydes are utilised: the presence of branching will increase the energy difference between zwitterionic intermediates **61** and **62** (see Scheme 13, Chapter 1). In the case of acetophenone the reverse effect is noted in the BT series (*ie* the presence of branching increases *Z*-selectivity, compare entries 11 and 30) although possibly for the same reason; this time Me being more sterically demanding than Ph. However, such an argument does not explain why an increased *Z*-preference was noted when 2-octanone was employed [compare entries 15 and 33 (BT), 17 and 34 (TZ)].

Despite the interesting and complimentary behaviour of TZ sulfones when compared to their BT counterparts we did not pursue their development due to associated poor coupling yields. More promising we felt was the PT system which was eventually chosen as a candidate for further investigation. Although no great differences in stereoselectivity were yet noted between BT and PT sulfones, the latter gave by far the highest yields when condensed with aldehydes. The tetrazole nucleus is probably the most electrophilic of all the heterocycles tested above and so most suited to promoting rapid irreversible reactions. In addition, 1-phenyl-1*H*-tetrazole-5-thiol is commercially available and analogues can be easily synthesised *via* the condensation of *iso*thiocyanates with sodium azide[53].

As an aside, it is interesting to note the limited success of 1-methylimidazol-2-yl (IM) sulfones to mediate the one-pot Julia olefination. β-Hydroxy-IM-sulfones had been employed previously by Kende[41] as readily reducible substrates for the classical Julia reaction before the discovery of the one-pot Julia olefination (see Chapter 1). The possibility of a one-pot olefination reaction was over-looked at that time.

2.2. Comparison of BT and PT heterocyclic mediators: the effects of solvent and base on the one-pot Julia olefination

As already discovered by both Charette[47] and Kocienski[45] the stereochemical outcome of the one-pot Julia olefination is particularly sensitive to base and solvent effects. We conducted a systematic study of the aforementioned variables whilst concurrently providing direct comparison between the BT and PT systems. At the outset our study was limited to examine the synthesis of three classes of 'simple' 1,2-disubstituted olefins, encompassing: non-conjugated monoenes, conjugated dienes and masked allylic alcohols. We hoped the information accumulated would provide a set of optimised reaction conditions for general use in the appropriate instance.

Figure 4 illustrates the full range of variables covered; total saturation of all possible permutations leads to 192 unique experiments all of which were eventually realised. A pre-metallation protocol was adopted throughout since we felt that such an operational mode would prove more suitable to generalisation (particularly for complex aldehydes) than Julia's original Barbier conditions. Choice of base was restricted to the hexamethyldisilazide family; lithium, sodium and potassium variants are all commercially available and thus enabled the sole effect of base counter-cation to be elucidated. The four solvents chosen for the study ranged from a lipophilic non-coordinating solvent (toluene) to a Lewis basic polar solvent (1,2-dimethoxyethane). As before the effects of chain branching would also be examined.

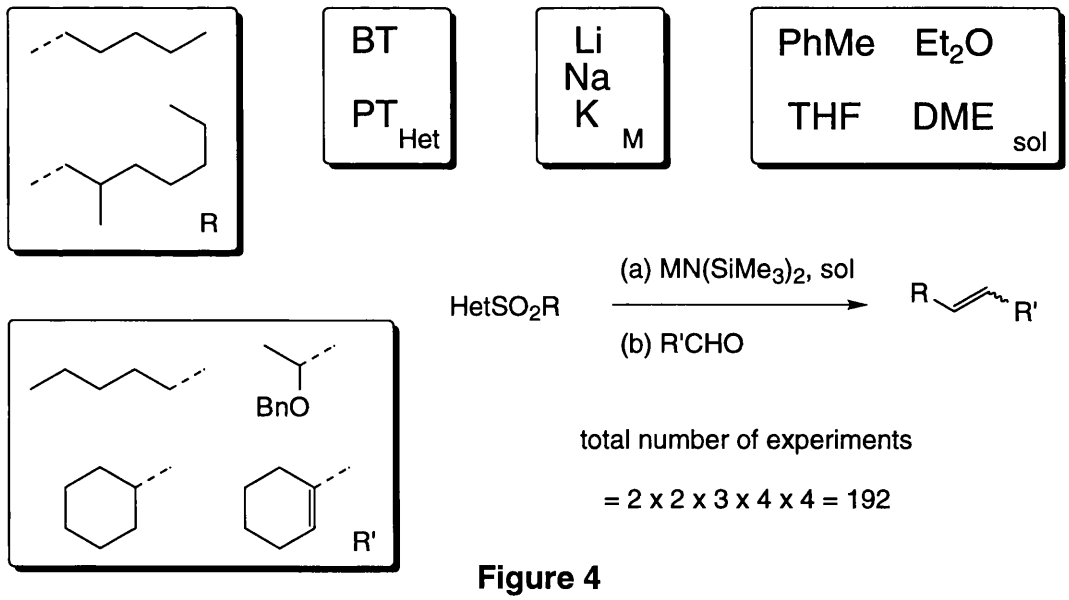


Figure 4

Due to the greater scope of the second study, GC analysis was used throughout to assess both the yield and stereoselectivity of each coupling. Such an approach obviated the need for a complex work-up/chromatography procedure after each reaction and so increased efficiency. An all GC method does, however, necessitate the independent synthesis and calibration of

standards for all possible products. The Schlosser variant of the Wiitg reaction[23] was employed to procure each targeted olefin in predominantly *cis* form suitable for GC analysis and subsequent calibration against an inert internal standard (dodecane). The Experimental Section contains full details concerning the setting-up and running of the study.

2.2.1. Synthesis of non-conjugated 1,2-disubstituted olefinic hydrocarbons

Tables 4.1 to 4.4 (pages 30 and 31) illustrate the results obtained for the first olefin class examined. Dramatic clear trends are immediately obvious;

(a) *Chain branching effects:* Coupling yields for the unbranched BT sulfone **107** (Tables 4.1 and 4.2) were typically much lower compared to those for the analogous PT sulfone **108**. The presence of branching on BT sulfone **109** (Tables 4.3 and 4.4) led to comparable yields to the PT sulfone **112** and to greatly increased yields compared to analogous couplings with **107** (Tables 4.1 and 4.2). These observations suggest that the BT sulfone **107** is unstable with regard to self-condensation; the presence of a chain branching element as exhibited by **109** increases steric bulk and thus reduces the propensity for self-condensation with the expected increase in yield. For the PT sulfones, however, the presence, or otherwise, of chain branching was of little consequence; analogous experiments for **107** (unbranched) and **112** (branched) gave very similar excellent yields. Thus PT sulfones apparently satisfy one of our early objectives and give rise to more stable metallated derivatives than their BT cousins. The effect of β-branching on stereoselectivity was very slight for the BT series, although in the analogous PT series slight increases in *trans* selectivity were noted which may be attributable to chain branching on the aldehyde component.

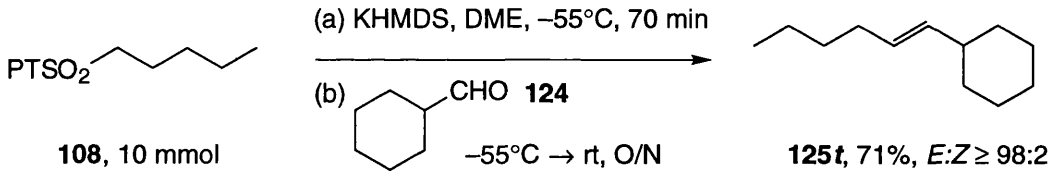
Table 4.2 best illustrates the following trends for solvent and base effects, however, they are also exhibited in Tables 4.1, 4.3 and 4.4.

(b) *Solvent effects:* For both heterocyclic systems, as the polarity/coordinating ability of the solvent was increased (PhMe $\rightarrow$ Et_2O $\rightarrow$ THF $\rightarrow$ DME) the *trans* selectivity of the reaction was heightened.

(c) *Base effects:* In the BT series a change in the base counter cation typically had very little effect on stereoselectivity and a quite unpredictable effect on yield (*nb* many of the more anomalous results presented in Tables 4 to 6 were repeated with comparable results). However, for the PT series a trend emerged: as the alkali metal series was traversed (Li $\rightarrow$ Na $\rightarrow$ K) the *trans* selectivity of the olefination process markedly increased. Regrettably, associated with the observed increase in selectivity was a decrease in yield.

The last two effects highlighted above for the new PT system act cooperatively. Thus condensation of the potassium derivative of a PT sulfone with a non-conjugated aldehyde in DME provides an efficient *trans* olefin synthesis. The reduction in yield associated with the use of a potassium base is presumably due to the increased reactivity of the metallated sulfone and so its greater ability to self-condense (see Chapter 6 for a pertinent example with a potential solution).

To demonstrate the practical value of the PT system for the preparation of simple non-conjugated *trans* olefins, (*E*)-1-cyclohexyl-1-hexene (**125*t***) was synthesised on a 10 mmol scale (Scheme 18). Under essentially identical conditions to those employed for the small scale GC experiments, the olefin **125*t*** was realised in 71% yield as a single isomer.



Scheme 18

2.2.2. Synthesis of conjugated 1,2-disubstituted olefinic hydrocarbons

Tables 5.1 and 5.2 (page 32) illustrate the results acquired for simple diene synthesis employing the α,β-unsaturated aldehyde cyclohexenecarboxaldehyde[54] (**128**). As expected from our own earlier work (Table 3) and Julia's results[3], the presence of additional unsaturation had a profound effect upon stereoselectivity.

(a) *Chain branching effects:* As before (Section 2.2.1) the presence of chain branching on the BT sulfone was essential for a respectable yield (compare any analogous results from Tables 5.1 and 5.2) and again unnecessary for the PT system. However, for the latter, the presence of chain branching on the sulfone increased *trans* selectivity when a lithium or sodium base was employed. Less of a stereochemical effect was typically observed for the BT system in this regard.

(b) *Solvent effects:* For both BT and PT sulfones the type of solvent employed had very little effect on stereoselectivity when either lithium or sodium bases were utilised. However, in the case of KHMDS, the use of DME as solvent gave a lower *trans* selectivity in the BT series and curiously a higher *trans* selectivity in the PT series. A temperature effect may be in operation here since to prevent freezing the experiments in DME were conducted at higher temperatures (*ca* +20°C) than the other examples.

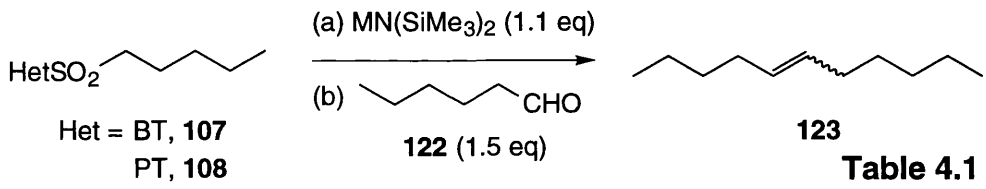
(c) *Base effects:* Again the type of base used had relatively little effect on the stereochemical outcome of the BT mediated reactions; a lithium base was found to be optimal for the expected excellent *trans* selectivity. For the PT mediated couplings a complete reversal of the trend noted in Tables 4.1 to 4.4 was observed; *ie* as the series Li → Na → K was transversed *trans* selectivity was progressively decreased. In common with the earlier results, a drop-off in yield was noted in conjunction with use of a potassium base for the PT system presumably for similar reasons.

The results given in Tables 5.1 and 5.2 reveal that the BT mediated reaction manifold remains the optimum system for the synthesis of *trans* diene systems (disconnected so as to employ an α,β-unsaturated aldehyde). Indeed the best conditions mirror those already utilised by the Kocienski group for their work towards the synthesis of rapamycin[45] (see Scheme 14, Chapter 1), *ie* use of a lithium base in THF solvent. Such conditions were subsequently used for the total synthesis of herboxidiene (see Chapter 6).

2.2.3. Synthesis of non-conjugated allylic ethers

Tables 6.1 and 6.2 (page 33) illustrate the range of results obtained for the synthesis of the last class of olefin examined. Two simple allylic ethers **132** and **133** were realised with either the BT or PT methodology. The lactate derived aldehyde **131**[55] employed enabled the effect of an additional chelating atom to be studied; the products from such couplings provide a potential source of allylic alcohols, intermediates of value to target-directed synthesis[24,25].

The allylic ether results present some peculiar anomalies but generally show the same trends previously discussed for Tables 4.1 to 4.4 (Section 2.2.1). However, the extreme *trans* selectivity noted before in the PT series was reduced to *E:Z* = 80:20 at best.



Het = BT, **107**
PT, **108**

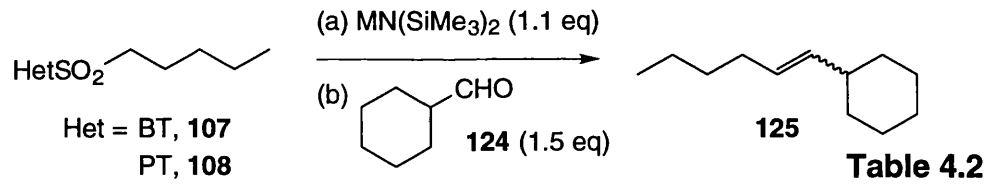
122 (1.5 eq)

123

Table 4.1

solvent*	entry	M	Het = BT %yield†	Het = BT *E:Z*†	Het = PT %yield†	Het = PT *E:Z*†
PhMe	1	Li	5	40:60	55	57:43
	2	Na	29	51:49	80	59:41
	3	K	15	47:53	13	64:36
Et_2O	4	Li	7	43:57	76	73:27
	5	Na	17	53:47	90	57:43
	6	K	68	51:49	30	72:28
THF	7	Li	42	60:40	97	75:25
	8	Na	0	---	89	76:24
	9	K	24	55:45	71	86:14
DME	10	Li	3	55:45	95	77:23
	11	Na	27	77:23	92	86:14
	12	K	6	75:25	71	94:6

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis



Het = BT, **107**
PT, **108**

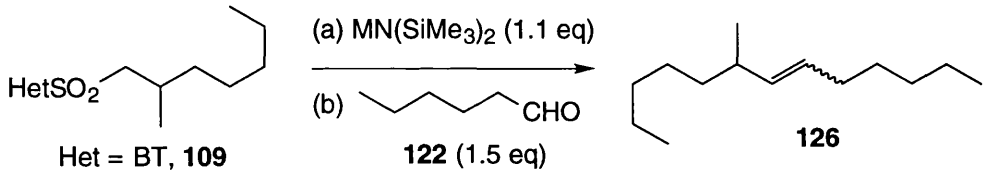
124 (1.5 eq)

125

Table 4.2

solvent*	entry	M	Het = BT %yield†	Het = BT *E:Z*†	Het = PT %yield†	Het = PT *E:Z*†
PhMe	1	Li	1	50:50	90	51:49
	2	Na	20	54:46	51	65:35
	3	K	13	54:46	22	77:23
Et_2O	4	Li	2	49:51	66	61:39
	5	Na	17	50:50	83	65:35
	6	K	57	51:49	46	89:11
THF	7	Li	6	66:34	90	69:31
	8	Na	19	62:38	92	73:27
	9	K	27	54:46	71	97:3
DME	10	Li	2	70:30	94	72:28
	11	Na	32	75:25	95	89:11
	12	K	4	76:24	81	99:1

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis



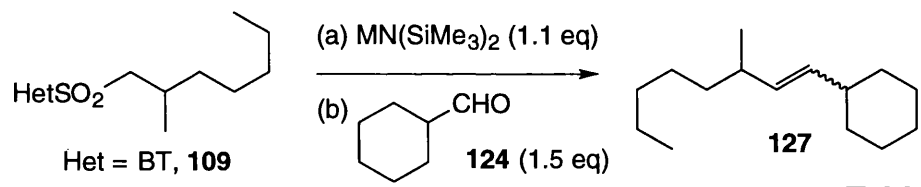
Het = BT, **109**
PT, **112**

122 (1.5 eq)

Table 4.3

solvent*	entry	M	Het = BT %yield†	Het = BT *E:Z*†	Het = PT %yield†	Het = PT *E:Z*†
PhMe	1	Li	86	54:46	96	43:57
	2	Na	78	57:43	65	38:62
	3	K	31	26:74	25	62:38
Et_2O	4	Li	74	60:40	61	48:52
	5	Na	84	58:42	98	32:68
	6	K	56	36:64	20	37:63
THF	7	Li	98	57:43	100	67:33
	8	Na	89	39:61	88	32:68
	9	K	68	25:75	23	76:24
DME	10	Li	100	44:56	100	60:40
	11	Na	87	64:36	100	78:22
	12	K	63	46:54	22	96:4

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis



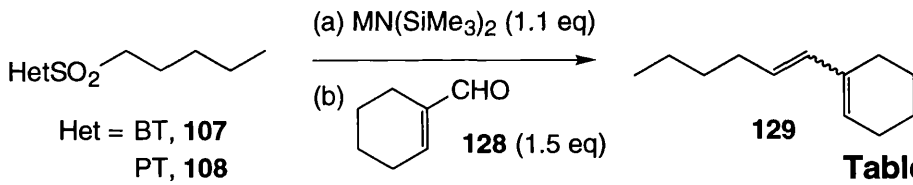
Het = BT, **109**
PT, **112**

124 (1.5 eq)

Table 4.4

solvent*	entry	M	Het = BT %yield†	Het = BT *E:Z*†	Het = PT %yield†	Het = PT *E:Z*†
PhMe	1	Li	88	70:30	85	39:61
	2	Na	66	86:14	83	67:33
	3	K	48	76:24	68	98:2
Et_2O	4	Li	70	67:33	74	41:59
	5	Na	75	87:13	98	53:47
	6	K	68	78:22	28	92:8
THF	7	Li	87	72:28	90	53:47
	8	Na	84	67:33	71	48:52
	9	K	85	40:60	58	97:3
DME	10	Li	83	58:42	100	40:60
	11	Na	96	55:45	100	84:16
	12	K	100	36:64	59	99:1

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis

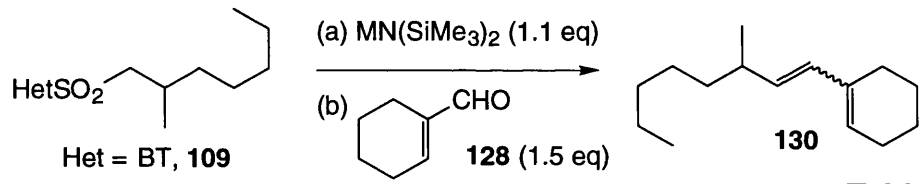


Het = BT, **107**
PT, **108**

Table 5.1

solvent*	entry	M	Het = BT		Het = PT	
			%yield†	*E:Z*†	%yield†	*E:Z*†
PhMe	1	Li	15	95:5	74	88:12
	2	Na	43	97:3	81	80:20
	3	K	17	>95:5	41	61:39
Et_2O	4	Li	24	99:1	95	89:11
	5	Na	48	97:3	82	75:25
	6	K	60	94:6	69	58:42
THF	7	Li	35	96:4	91	67:33
	8	Na	13	86:14	99	75:25
	9	K	39	79:21	93	66:34
DME	10	Li	2	---	84	84:16
	11	Na	26	77:23	100	88:12
	12	K	35	55:45	64	85:15

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis



Het = BT, **109**
PT, **112**

Table 5.2

solvent*	entry	M	Het = BT		Het = PT	
			%yield†	*E:Z*†	%yield†	*E:Z*†
PhMe	1	Li	69	98:2	71	94:6
	2	Na	98	97:3	90	82:18
	3	K	70	97:3	27	55:45
Et_2O	4	Li	16	97:3	79	95:5
	5	Na	89	97:3	85	79:21
	6	K	88	96:4	31	50:50
THF	7	Li	96	>99:1	100	98:2
	8	Na	96	94:6	78	85:15
	9	K	76	86:14	44	58:42
DME	10	Li	93	>99:1	83	99:1
	11	Na	100	91:9	48	92:8
	12	K	94	72:28	38	81:19

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis

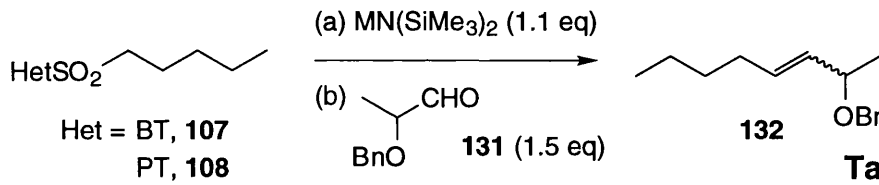


Table 6.1

solvent*	entry	M	Het = BT		Het = PT	
			%yield†	*E:Z*†	%yield†	*E:Z*†
PhMe	1	Li	2	50:50	54	31:69
	2	Na	5	52:48	100	49:51
	3	K	8	63:37	47	58:42
Et_2O	4	Li	1	55:45	31	35:65
	5	Na	5	52:48	82	44:56
	6	K	10	76:24	78	59:41
THF	7	Li	23	74:26	91	64:36
	8	Na	32	64:36	100	65:35
	9	K	44	61:39	100	72:28
DME	10	Li	<1	---	88	59:41
	11	Na	25	64:36	96	68:32
	12	K	5	58:42	94	79:21

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis

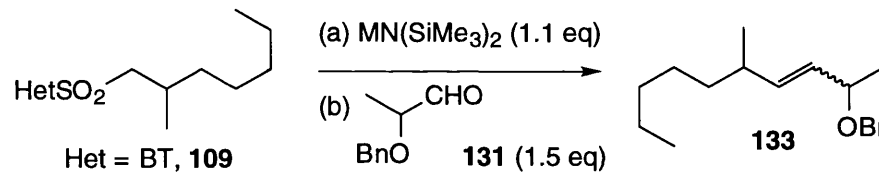


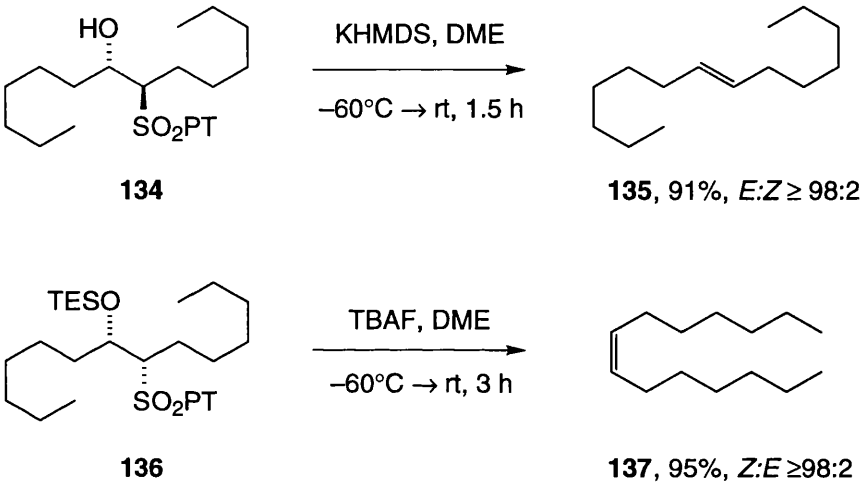
Table 6.2

solvent*	entry	M	Het = BT		Het = PT	
			%yield†	*E:Z*†	%yield†	*E:Z*†
PhMe	1	Li	100	47:53	---	43:57
	2	Na	72	61:39	79	30:70
	3	K	98	61:39	71	64:36
Et_2O	4	Li	85	48:52	100	42:58
	5	Na	34	42:58	100	28:72
	6	K	88	41:59	48	34:66
THF	7	Li	89	54:46	87	44:56
	8	Na	84	50:50	99	19:81
	9	K	95	34:66	66	45:55
DME	10	Li	55	68:32	90	45:55
	11	Na	94	57:43	93	50:50
	12	K	86	40:60	37	80:20

*all reactions run at –78°C except those in DME which were run at –60°C. †determined by GC analysis

2.3. Mechanistic studies

The base/solvent study exposed the enormous potential of PT sulfones to access non-conjugated *trans*-1,2-disubstituted olefins with excellent stereoselectivity (Tables 4.1 to 4.4). It is likely that the origin of olefin stereocontrol in this instance is a direct consequence of kinetic diastereoselectivity in the initial addition event. To prove such a postulate it is necessary and sufficient to demonstrate that under the appropriate reaction conditions β-alkoxysulfone intermediates breakdown stereospecifically and that they cannot interconvert. Julia and co-workers have already demonstrated for simple BT sulfones that the base induced breakdown of β-hydroxysulfone intermediates is stereospecific[2] (see Chapter 1). It remained to demonstrate this finding for the PT system (Scheme 19).



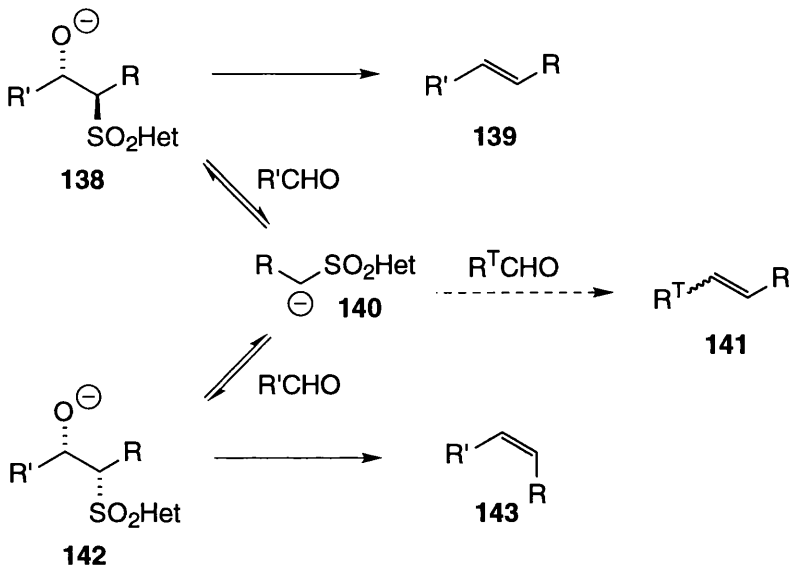
134 **135**, 91%, *E*:*Z* ≥ 98:2

136 **137**, 95%, *Z*:*E* ≥98:2

Scheme 19

Diastereomerically pure *syn* and *anti* β-hydroxy PT sulfides were synthesised *via* the opening of stereodefined epoxides by PTSH (see Experimental Section). Following sulfur oxidation, the *anti* derivative **134** was accessed without incident. Unfortunately a direct oxidation route to the *syn* analogue was not possible; upon oxidation spontaneous elimination of SO_2 and PTOH occurred to yield the olefin. The more facile elimination from such *syn* derivatives has already been noted by Julia in the BT series[2]. Protecting the carbinol as a silyl ether prior to sulfur oxidation enabled the masked *syn* β-hydroxysulfone **136** to be realised. Base treatment of the *anti* isomer **134** under the previously optimised reaction conditions for *E*-olefin synthesis (KHMDS, DME, –60°C) yielded the expected *trans* alkene **135** as a single observable isomer. Likewise fluoride induced elimination from *syn* **136** yielded the *Z*-olefin **137** as a single isomer.

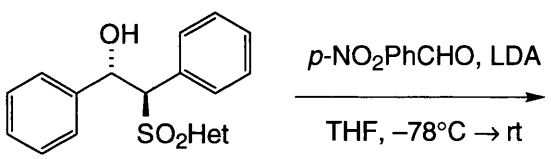
Interconversion between β-alkoxysulfone intermediates **138** and **142** is only possible *via* a retro-addition/addition mechanism (Scheme 20). The formation of the initial retro-addition product, **140**, can be indirectly detected if an additional trapping reagent is present. If the base-induced elimination of a β-hydroxysulfone is conducted in the presence of R^TCHO the

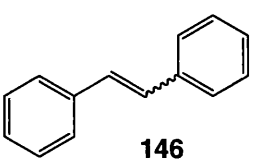


Scheme 20

formation of any of the cross-over product **141** is proof of the existence of **140** and thus the possibility of equilibration between **138** and **142**. The experiments outlined in Scheme 19 were both repeated in the presence of 4-nitrobenzaldehyde; in each case a comparable result was obtained and no cross-over adduct was found. Taken together the above observations prove that high levels of *E*-selectivity found for the one-pot Julia reaction between non-stabilised PT sulfones and saturated aliphatic aldehydes are a direct consequence of the selective formation of an *anti* β-alkoxysulfone intermediate.

To demonstrate that the 4-nitrobenzaldehyde trapping experiment was a valid method to detect β-alkoxysulfone equilibration an additional system was examined. The stilbene derivatives **144** and **145** (Scheme 21) were synthesised in an analogous manner to **134** commencing from *trans* stilbene oxide. Retro-addition from the alkoxides of such compounds would yield highly stabilised benzylic sulfone anions and so it was expected that equilibration would be a facile process. Indeed, Julia has already invoked β-alkoxysulfone equilibration to explain high *Z*-selectivities in the one-pot Julia olefination reaction of stabilised BT sulfones (see Chapter 1). Treatment of either sulfone with LDA in THF at –78°C in the presence of 4-nitrobenzaldehyde resulted in the formation of the expected stilbene **146** together with large quantities of the cross-over product 4-nitrostilbene (**147**). Thus in favourable cases





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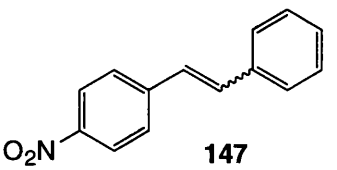


144, Het = BT
145, Het = PT

Het	%yield	*E*:*Z*
BT	40%	≥98:2
PT	35%	87:13

Het	%yield	*E*:*Z*
BT	60%	92:8
PT	60%	69:31

Scheme 21

equilibration between β-alkoxysulfones is a viable mechanistic pathway and our trapping experiments have a sound basis.

Further insight can be gleaned from a careful examination of the respective yields and selectivities found for the two products **146** and **147**. For both BT and PT systems the cross-over product **147** was formed with lower *E*-selectivity than stilbene (**146**). Two reasons may account for such an observation: (a) the initial *anti* adduct is already predisposed to yield a *trans* product if intramolecular alkoxide trapping occurs before retro-addition, and (b) due to the electronic effects suggested by Julia (see Scheme 12, Chapter 1) an electron deficient unsaturated aldehyde would be expected to yield a product with lower *trans* selectivity than an electron rich one. The PT sulfone **145** yielded stilbene products with lower *E*-selectivity than its BT counterpart **144**; the results of Tables 5.1 and 5.2 already suggested the inferiority of the PT system for the synthesis of conjugated olefins. Lastly, it is significant that both sulfones gave the same proportion of **147** to **146**, it may therefore be incorrect to assume that the tetrazole nucleus is better able than benzothiazole to trap a tethered alkoxide. The electrophilicity of both heterocyclic mediators appears equivalent in this regard.

2.4. Origin of diastereoselectivity in the heterocyclic sulfone 'aldol' reaction

The above observations taken together with those of Julia[2] establish that stereocontrol in the one-pot Julia olefin synthesis is a direct consequence of diastereoselective sulfone addition only in 'simple' cases (*ie* non-stabilised sulfones and saturated aldehydes). The results of Tables 4.1 to 4.4 thus represent a study of diastereocontrol in the sulfone analogue of the aldol reaction; the *anti:syn* ratio of the intermediate β-alkoxysulfone corresponds to the observed *E:Z* ratio of the isolated olefin. Such studies are somewhat rare in the literature in contrast to analogous sulfoxide chemistry[56]. Sulfone moieties are typically removed immediately after their activating properties have been utilised and so the isomer distribution of the intermediate β-hydroxysulfones is of little consequence and seldom determined. Where isomer ratios have been assigned and documented the selectivity is typically poor[56] ($1:1 \leq dr \leq 3:1$).

The structural nature of metallated sulfones has received much attention, however, different sources still provide varying models accompanied by their own experimental justification. *Ab initio* calculations for the hypothetical metallate HSO_2CH_2Li (**148**, R = R' = H, M = Li, Figure 5) suggest that the carbanion is intermediate between sp^2 and sp^3 hybridised and that an asymmetric chelated structure is adopted[57,58]. Theoretical studies for the anion of dimethyl sulfone also support this model[59]. However, direct probing of several stabilised sulfone metallates *via* X-ray crystallography supports a different view[60,61]. The metal cation associates with the sulfone oxygen atoms and the carbanion is sp^2 hybridised with the p-orbital lying gauche to both oxygen atoms. Gais has established with ^6Li-^1H heteronuclear nOe experiments

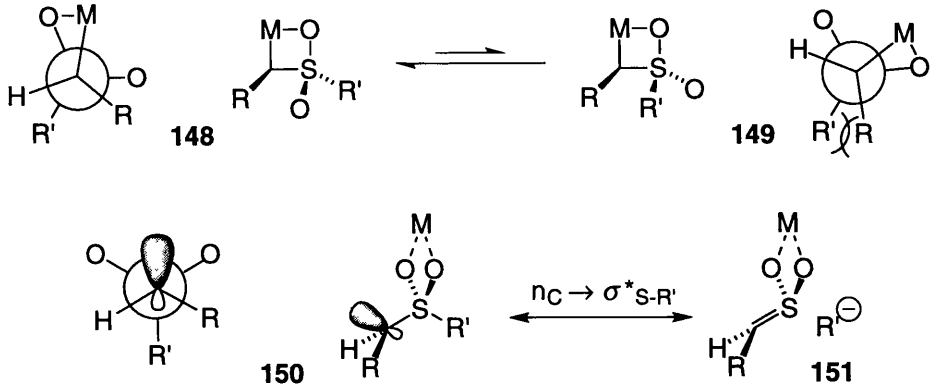


Figure 5

that it is likely such a structure is also adopted by a lithiated benzylic triflone•TMEDA complex in solution[62]. The general consensus now is that the latter model **150** (Figure 5) is the most acceptable with the α-carbon being pyramidal except in those cases where the anion receives resonance stabilisation from R[63].

Sulfones do not stabilise adjacent negative charge by resonance effects (*cf* carbonyl chemistry) but rather by a combination of induction and negative hyperconjugation ($n_C \rightarrow \sigma^*_{S\text{-}R'}$, see **151** the 'no bond' canonical form of **150**). The latter effect provides a significant energy barrier to rotation about the C_α-S bond and so enables lithiosulfones to have chiral anions even when their α-carbon atom (bearing different groups) is coordinated in a planar rather than tetrahedral fashion. Metallated sulfones are thus fundamentally different from enolates, however, in developing models for the heterocyclic sulfone aldol reaction, analogy with carbonyl enolate chemistry may yield valuable insight. Here we seek basic concepts to explain the two strong trends displayed in Tables 4.1 to 4.4, namely: (a) the rise in *anti* diastereoselectivity for both BT and PT sulfones as solvent coordinating ability increases, and (b) the dependency of *syn:anti* ratio on counter cation for the PT sulfone metallates only.

In lipophilic non-coordinating solvents polar transition states experience compression and closed systems with anionic and cationic species in close association are favoured. For sulfone-aldehyde addition reactions occurring in such media we suggest the Zimmerman-Traxler[64,65] like six-membered chair transition states **152** and **154** illustrated below (Figure 6, analogous transition states have been proposed for the addition of sulfinyl stabilised carbanions to aldehydes[66] and also for the addition of metallated phenyl sulfones to acyl silanes[67]). Upon approach of the aldehyde the metal cation (previously associated with both sulfone oxygen atoms, *cf* **150** Figure 5) exchanges one sulfone oxygen atom ligand for the carbonyl oxygen atom. Reorganisation of the resultant assembly then occurs to yield either of the chairlike forms **152** or **154**. Note that the aldehyde side-chain adopts an equatorial orientation to avoid destabilising 1,3-diaxial interactions, and that in both transition states the stereoelectronic

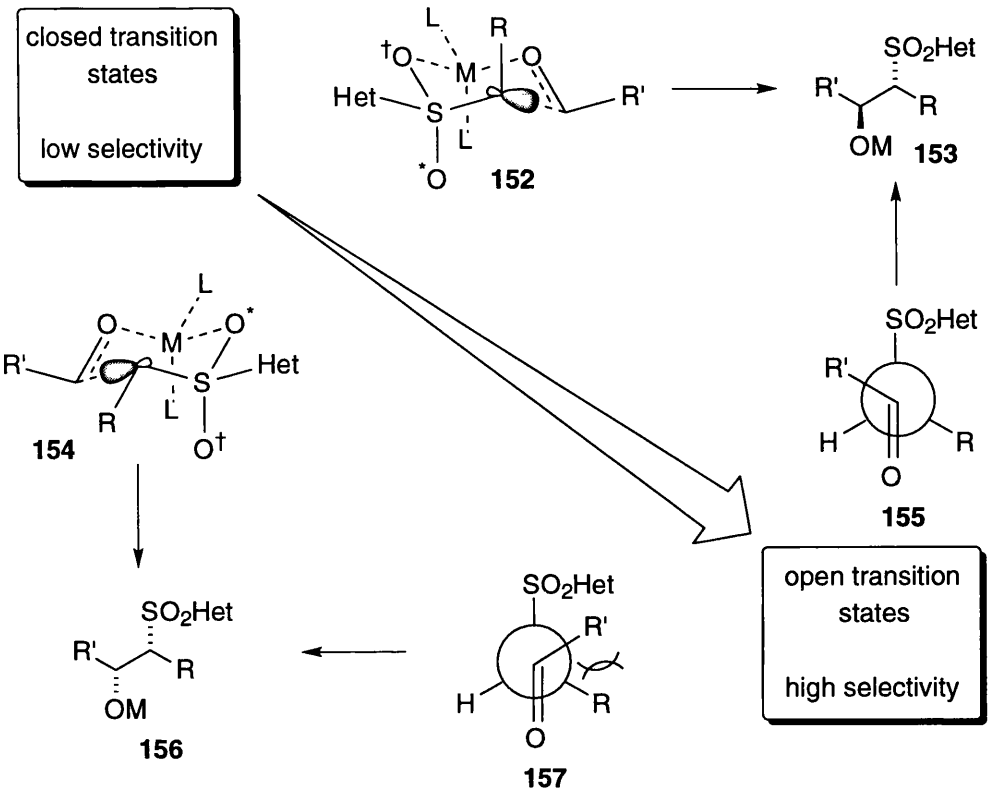
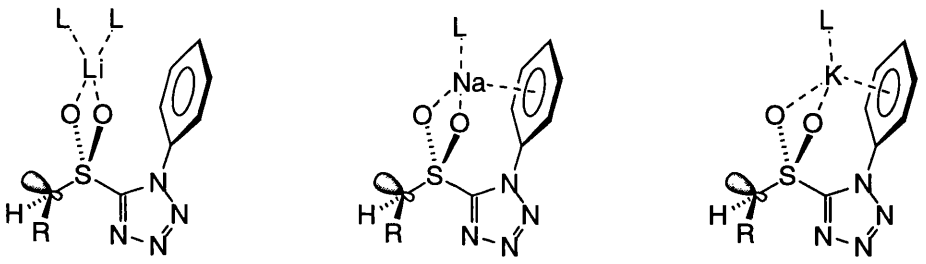


Figure 6

requirement for sulfone α-carbanion stabilisation is fulfilled. Which sulfone oxygen ligand the metal gave up (O^* or $O^\dagger$) determines whether the R group is equatorially or axially disposed; the same metallated sulfone can thus behave equally well as either an '*E*-enolate' (**154**) or a 'Z-enolate' (**152**) equivalent in the transition state. Such reactivity duality together with the lack of an obvious destabilising interaction with which to discriminate between **152** and **154** would suggest a general lack of selectivity when reaction proceeds *via* a closed transition state. Such is the case for the addition of metallated BT sulfones (Li, Na or K) and lithiated PT sulfones to aldehydes in toluene.

As the solvent is exchanged for progressively more Lewis basic media the metal cation will experience additional solvation. Under such conditions the cation will become less tightly associated with the sulfone leading to the possibility of reaction *via* a looser, or even totally open transition state. Arrays **155** and **157** represent such an extreme and are based on analogous open transition states suggested for the aldol reaction[68]. With the illustrated favoured approach of the aldehyde, transition state **155** lacks the repulsive gauche interaction present in **157** and so will be favoured. Thus in polar coordinating solvents competition from open transition states would lead to a general preference for the *anti* product. The above model accounts for the observed solvent effect, however, many other reasonable arguments (*eg* competition from closed boatlike transition states, change in aggregation state of metallate *etc*) could no doubt also be brought forward.

The dependency of diastereoselectivity on base counter-cation for the PT sulfone series and the associated independence of cation for the corresponding BT sulfones is harder to rationalise. Regarding the model presented above, we would suggest that traversing the series Li → Na → K encourages PT sulfone addition reactions to proceed *via* open transition states **155** and **157**; the solvent and cation effects are then naturally cooperative. The fact that no cation effect is observed for the BT series suggests that this phenomena is linked with the very different shapes associated with the two heterocycles. The BT moiety has no substituents with which to directly affect the choice of reaction pathway. In contrast the phenyl ring of the PT moiety is appended to the tetrazole nucleus in close proximity to the sulfone and so is likely to play an important role in transition state selection. The cation effect in the PT series may be due to the variable interaction of different alkali metals with the phenyl substituent. Alkali metals readily form intercalation compounds with graphite[69] and arene complexes of potassium cations are known[70,71]. For example, Caulton has reported the crystal structure of a cubic tetrameric complex between $KOSiMe_2Ph$ and benzene of stoichiometry $[(C_6H_6)KOSiMe_2Ph]_4$; each potassium ion within the tetramer is associated with three oxygen atoms and the coordination environment supplemented by an additional η^6-benzene ligand[71]. The η^6 coordination of potassium ions to arenes is believed to be the result of an induced dipole interaction[70].



158 **159** **160**

Figure 7

As a sulfone metallate counter-cation is varied from Li → Na → K the ionic radius of the metal increases and the sulfone O-M bond lengthens accordingly. We suggest that in the case of a PT sulfone potassium metallate **160**, the metal cation is strongly bound by both sulfone oxygen atoms and appropriately positioned to receive additional η^6 coordination from the phenyl ligand appended to the tetrazole nucleus (Figure 7). The stable 'claw-like' chelate structure immobilises the metal ion and makes a closed transition state for aldehyde addition virtually inaccessible. The reactions of PT sulfone potassium metallates with aldehydes are thus forced to proceed *via* predominantly open transition states and are typically highly stereoselective.

In contrast, lithium ions are smaller and less polarisable than potassium ions and so their susceptibility to an induced dipole is substantially reduced. The coordination of a lithium cation to an arene is thus intrinsically weak[70]. In addition the shorter sulfone O-M bond for a lithiated PT sulfone would make an analogous chelate structure to that discussed above for potassium

highly unstable. The lithium derivatives of PT sulfones **158** therefore react similarly to BT sulfone metallates and their addition reactions are typically unselective unless carried out in highly coordinating solvents. Sodium represents an intermediate case with reaction *via* an open transition state being promoted but with closed transition states still accessible and able to compete.

The absence of a cation stereochemical effect for BT sulfone reactions can then be attributed to its lack of substitution. Within the closed transition states, traversing the series Li → Na → K would obviously still result in a lengthening of the O-M bond. However, such a distortion would not lead to greater discrimination between **152** and **154**.

Our hypothesis concerning the 'claw-like' mode of PT sulfone metal chelation could of course be easily probed by varying the tetrazole substituent (*eg* to include electron rich and electron deficient phenyl rings and simple groups such as methyl, *iso*propyl, *tert*-butyl *etc*). Some initial work has been conducted involving the 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) mediator[72]; as expected the *trans* selectivity obtained by reaction of a simple TBT sulfone potassium metallate with a saturated aldehyde was less than the corresponding result with a PT sulfone (see Chapter 7). However, the selectivity of the TBT sulfone (*E:Z* = 89:11) was not reduced to the level anticipated for the analogous BT sulfone (*E:Z* ≈ 75:25).

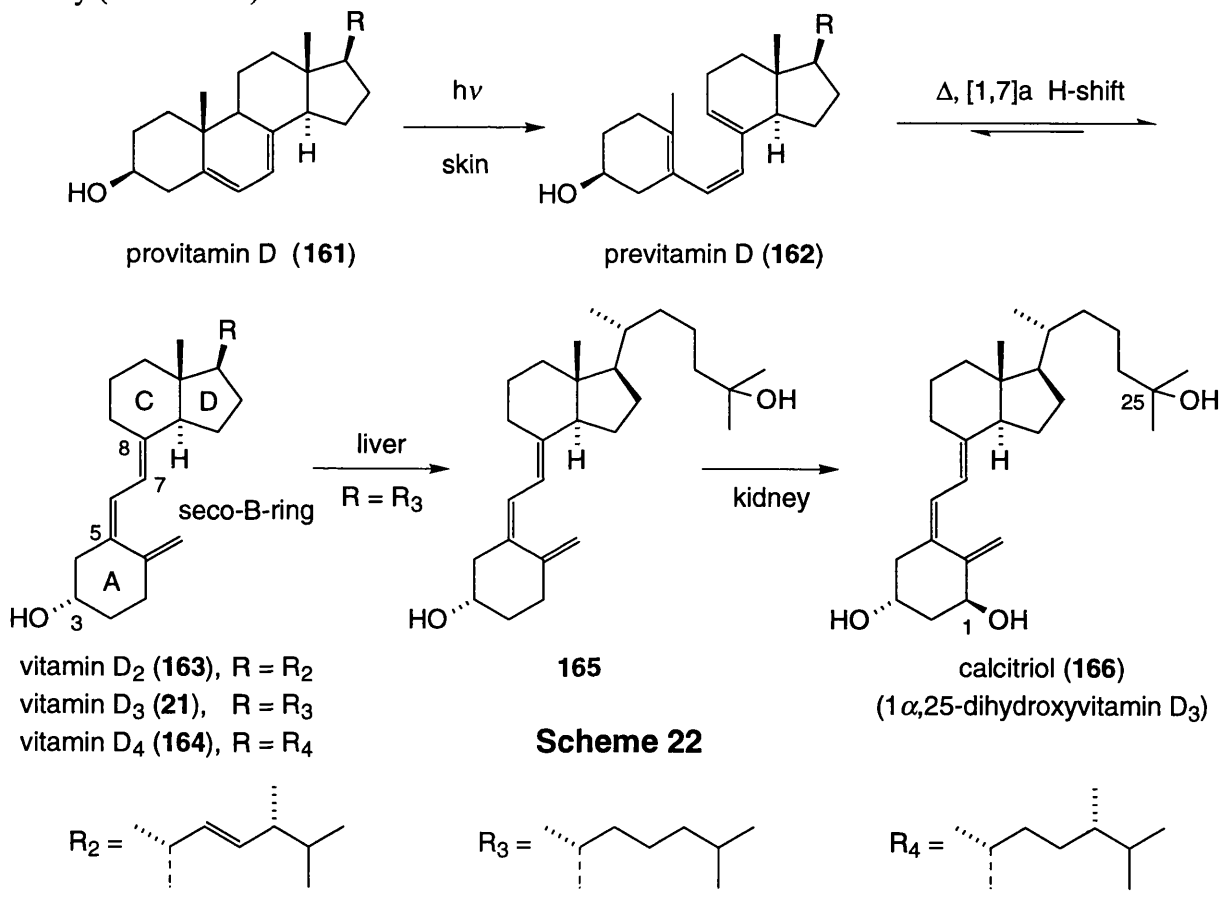
In the above discussion the influence of metal chelation to the 'imine-like' nitrogen atom of both the heterocyclic systems was neglected. Certainly in the case of lithium metallates such an effect may be important; Julia and co-workers invoked chelation to the nitrogen atom of the benzothiazole moiety in their discussion of transition state selection for the alkoxide addition step of the one-pot olefination process[2]. Of course for both PT and BT scaffolds such chelation can occur, in the PT case this would have a dramatic effect on the positioning of the phenyl substituent relative to the reactive centres. Simple models also suggest the possibility of a closed transition state in which the metal is simultaneously coordinated to the aldehyde, a sulfone oxygen atom and the heterocycle 'imine' nitrogen. Such a transition state does not, however, satisfy the stereoelectronic requirement for sulfone carbanion stabilisation.

Lastly, it would be reasonable to assume that the selectivities exhibited in Tables 6 are also a consequence of diastereocontrolled sulfone addition. The trends displayed are identical to those found in Tables 4 but stereoselectivity is reduced suggesting that the oxygenated side-chain of the aldehyde component provided an additional control element. The results of Tables 5 are not solely the effect of sulfone aldol diastereoselectivity due to additional electronic effects (see Chapter 1). It is not surprising then that the solvent and base effects are significantly perturbed, nevertheless, the reverse cation effect for the PT sulfone series is intriguing.

3. Vitamin D Fragment Linkage Strategies

The D vitamins form part of a family of compounds of steroidal origin known as *seco-steroids*; they possess the A, C and D rings common to steroids but lack ring B. There are three distinct vitamin D congeners: D_2, D_3 and D_4 (see Scheme 22). Vitamin D_3 and vitamin D_2 are derived from cholesterol and ergosterol respectively and both have recognised biological function. The biological activity of the closely related vitamin D_4 seems doubtful. Curiously vitamin D_1 is not a single compound but rather a 1:1 complex of lumisterol and vitamin D_2.

Natural vitamin D_3 (*calciferol*, **21**) is formed in the skin of man by the action of ultraviolet light on 7–dehydrocholesterol (**161**, R = R_3). The ensuing conrotatory electrocyclic ring opening yields the so-called *previtamin* (**162**) which can then undergo a thermally allowed [1,7]*a*-sigmatropic hydrogen shift to form the vitamin itself[73]. The hormonally active metabolite of the vitamin, 1α,25-dihydroxyvitamin D_3 (*calcitriol*, **166**), is then obtained by two successive enzymatic hydroxylations, the first at C25 in the liver followed by hydroxylation at C1 in the kidney (Scheme 22).



Scheme 22

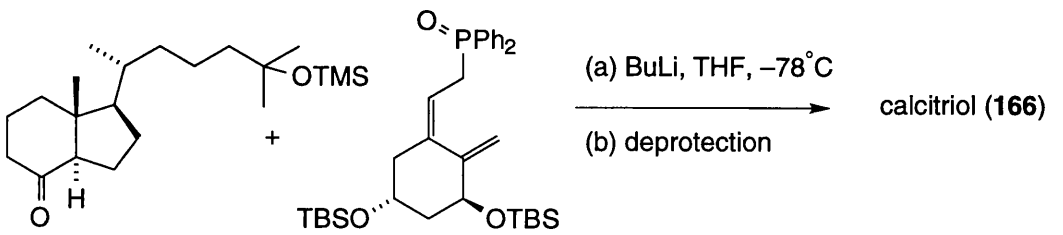
As is suggested by the above biosynthetic route to vitamin D_3, the substance is not technically a vitamin but rather belongs to a class of steroidal hormones. Long known to be essential for normal bone calcification, the hormonally active metabolite **166** regulates calcium and

phosphorus metabolism within the body. As such the vitamin D family of steroidal molecules have been extensively used in the past as curative agents for rickets and similar diseases[73]. However, it has come to light that this more classical role is supplemented by other far more significant activities. In particular, calcitriol is implicated in the promotion of cell differentiation and inhibition of cell proliferation[74]. Unfortunately, the use of 1α,25-dihydroxyvitamin D_3 (**166**) as a drug for the treatment of cancer is limited due to serious hypercalcemic side-effects at useful dose levels. The current resurgence of interest in the chemistry of vitamin D compounds is mainly due to the need to find analogues of calicitriol which retain anticancer activity but which do not affect calcium mobilisation and deposition. New efficient synthetic procedures which enable the rapid assembly of vitamin D type systems are clearly highly desirable.

The synthesis of vitamin D and related compounds has a long and well established history, beginning with the pioneering and exhaustive work of Lythgoe[75] at Leeds and Inhoffen[12] at Braunschweig. An excellent recent review article by Okamura[76] surveys the subsequent 40 years of vitamin D synthetic chemistry, and so rather than give an in-depth analysis of particular total syntheses, it is intended here to illustrate some of the more important strategies employed for final fragment linkage.

3.1. Direct coupling of A-ring and CD-ring fragments *via* connective olefination

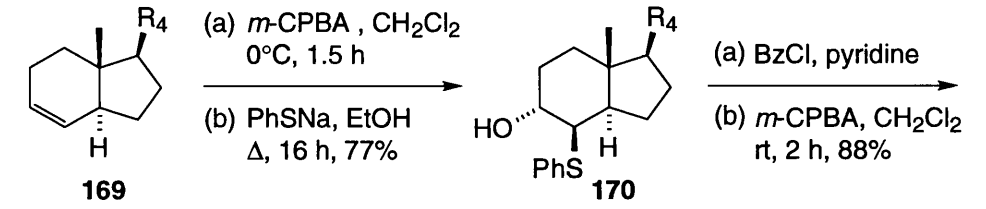
Typically vitamin D syntheses are convergent and terminate with the coupling of an A-ring fragment with a CD-ring fragment followed in some cases by a subsequent rearrangement[76]. Lythgoe was the first to successfully synthesise vitamin D_3 *via* such a direct approach in 1978, and at that time employed a Horner-Wittig[7,13] reaction to forge the C7-C8 double-bond[29] (see Scheme 5, Chapter 1). Fragment linkage *via* the connective construction of the 7*E* olefin has since become the most commonly adopted strategy for the synthesis of vitamin D type molecules. Indeed, the first total synthesis of calcitriol by a Hoffmann-La Roche group[77] utilised an analogous approach to Lythgoe for final fragment linkage (Scheme 23).



167 **168** **Scheme 23**

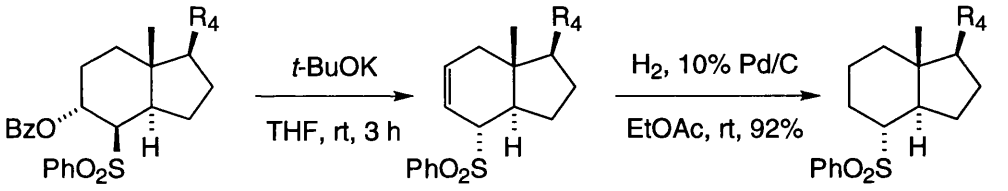
Lythgoe and co-workers were also intrigued by the notion of reversing the sense of their earlier coupling; *ie* employing an A-ring electrophile and a CD-ring nucleophile. Initial attempts to synthesise a CD-ring C8 phosphorane (with regard to later using the Wittig olefin synthesis)

were unsuccessful, highlighting the difficulty of introducing a PPh_3 group into a sterically congested environment. Instead the C8 CD-ring phenylsulfone (**173**) was realised in 6 steps from des-AB-ergost-8-ene (**169**) (Scheme 24) and the classical Julia olefination[20,34] (see Section 1.3.1) applied for the first time since its discovery to a complex synthetic problem; the synthesis of vitamin D_4[30].



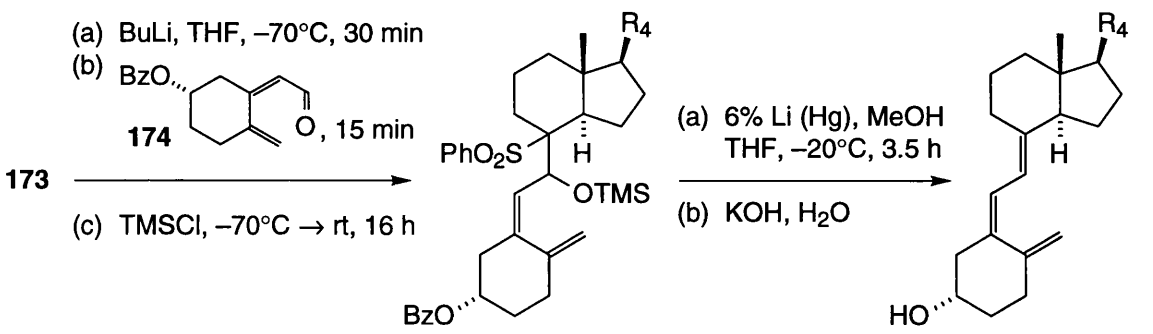
169 **170**

Scheme 24



171 **172** **173**

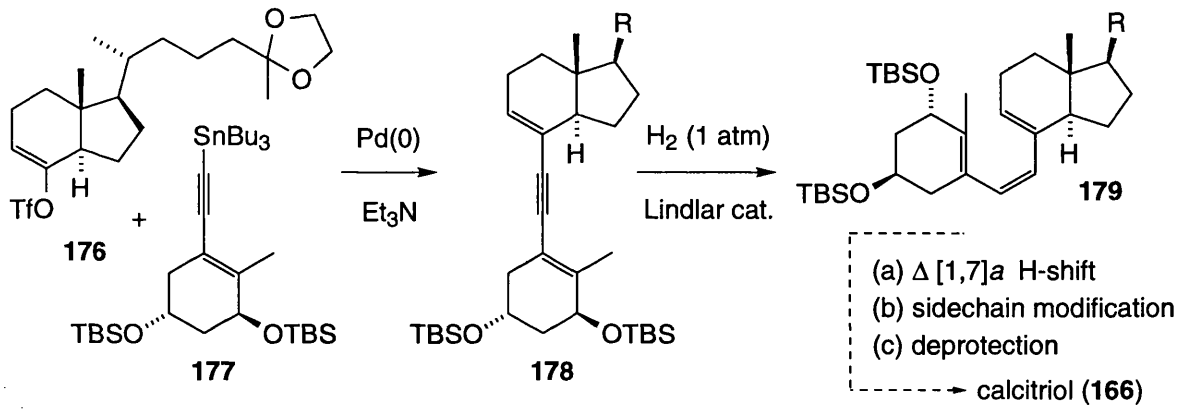
Condensation of the lithium derivative of α-sulfone **173** with the unstable dienal **174** was followed by subsequent silylation with trimethylsilylchloride to proffer the β-siloxysulfone **175** (Scheme 25). The crude compound was then treated with 6% lithium amalgam in a mixture of THF and MeOH to yield 45% of vitamin D_4 (from sulfone **173**) after saponification as a single isomer. Interestingly, reductive elimination from the β-benzoyloxysulfone analogous to **175** not only yielded vitamin D_4 (36%) but also 20% of (5*E*, 7*E*)-vitamin D_4. The *trans* selectivity of the classical Julia reaction for the vitamin D coupling is unsurpassed and others have also investigated its use. Fukumoto has described a total synthesis of the CD-ring 8α-phenylsulfone necessary for the construction of vitamin D_3 (*ie* compound **173** with R_3 sidechain). Subsequent condensation of the lithiated (LDA) sulfone with the TBS protected A-ring dienal, followed by acetylation, reductive elimination with 5% sodium amalgam and final silylether deprotection yielded 51% of vitamin D_3 as a single isomer[78].



Scheme 25 **175** vitamin D_4 (**164**)

3.2. Palladium catalysed cross-coupling approaches

Scheme 26 illustrates an interesting cross-coupling strategy towards calcitriol devised by Castedo and Mouriño which borrows a transformation from nature's biosynthetic sequence. A Stille coupling between the A-ring alkynylstannane **177** and the CD-ring fragment enol triflate **176** yielded the acetylene **178** in excellent yield[79]. Lindlar reduction of the central triple bond produced the previtamin D type triene **179**. As for previtamin D_3 itself, the system is predisposed towards a [1,7] sigmatropic H-shift and subsequently rearranged to yield the vitamin D triene system. Minor modifications of the resulting substrate then yielded 1α,25-dihydroxyvitamin D_3 (**166**).



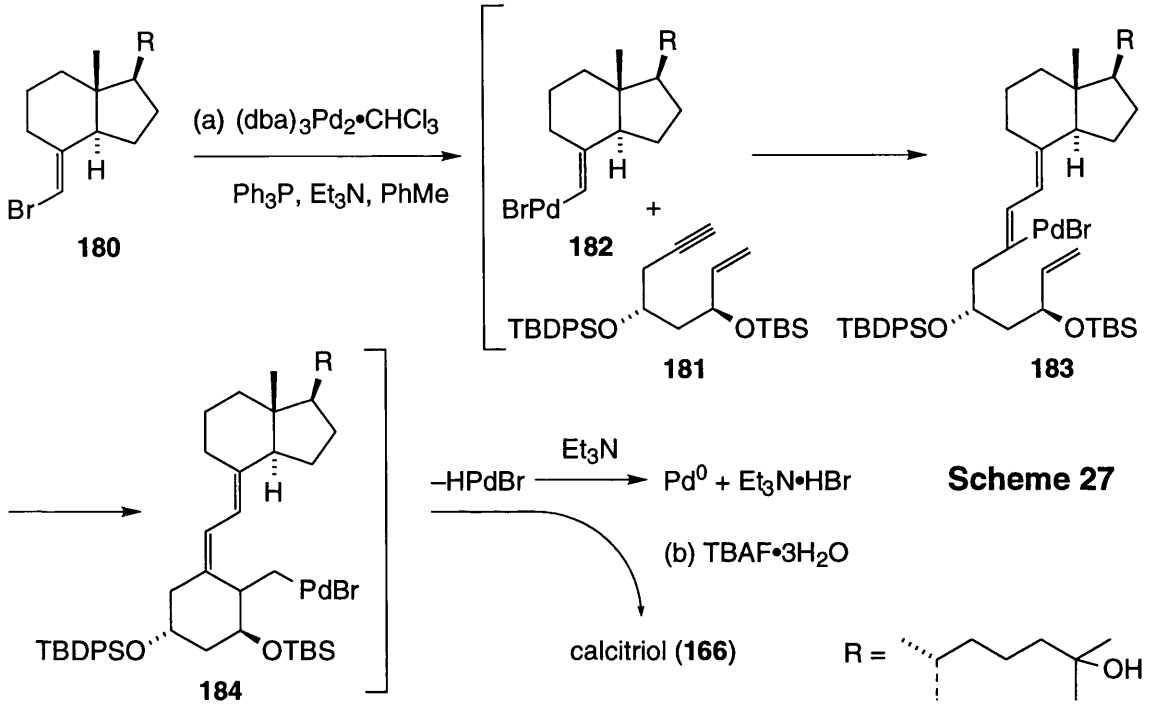
Scheme 26

The above procedure builds on earlier work also by Lythgoe[80] which predates the advent of palladium catalysed cross-coupling reactions. The original route to a previtamin structure employed the condensation of the lithium derivative of an A-ring enyne analogous to **177** with either Grundmann's ketone or its 9-chloro derivative. Elimination of the resulting alcohol or vicinal chlorohydrin respectively yielded the required dienyne intermediate.

The following approach developed by Trost differs from all other common strategies in that the A-ring is created from an acyclic unit during the coupling reaction[81]. Scheme 27 (overleaf) outlines the basic concept: after Pd(0) oxidatively inserts into the labile C-Br bond of CD-ring vinyl bromide **180**, subsequent carbopalladation across the alkyne of the acyclic seco-A-ring fragment **181** yields intermediate **183**. A further carbopalladation reaction closes the A-ring and is followed by β-elimination of HPdBr from **184** leaving the exocyclic terminal methylene moiety in place and frees the protected product. In a final step the active Pd(0) catalytic species is regenerated by reductive elimination of HBr from HPdBr assisted by triethylamine and the cycle recommences.

The vinyl bromide **180** can be realised by Wittig reaction of (bromomethylene)-triphenylphosphorane with a Grundmann's ketone derivative, unusually high *E*-selectivity is

obtained. The acyclic fragment **181** can be synthesised in homochiral form by a simple eight step sequence in 20% overall yield[81].



Scheme 27

3.3. Vinylallene rearrangement approach

Okamura has taken advantage of known vitamin D rearrangement chemistry to introduce a conceptually new synthetic approach. Upon irradiation of vitamin D_3 (**21**) two diastereomeric vinylallenes **185** are formed as minor products[82]; the result of a [1,5] hydrogen shift of the circled atom (Figure 8). Thermolysis of the vinylallenes reverses the shift to regenerate the vitamin D triene segment. Okamura has developed routes to vitamin D analogues *via* the intermediacy of such vinylallenes[83], however, under the heat-induced rearrangement protocol both allene diastereoisomers yield not only the natural 5*Z*,7*E* olefin stereochemistry but also the unnatural 5*Z*,7*Z* configuration. Unfortunately at the high temperatures required for the thermally induced reaction the 5*Z*,7*Z* isomer once formed undergoes further [1,7] H-shifts (commencing from H14 to C19) to generate a triad of equilibrating secondary and tertiary products.

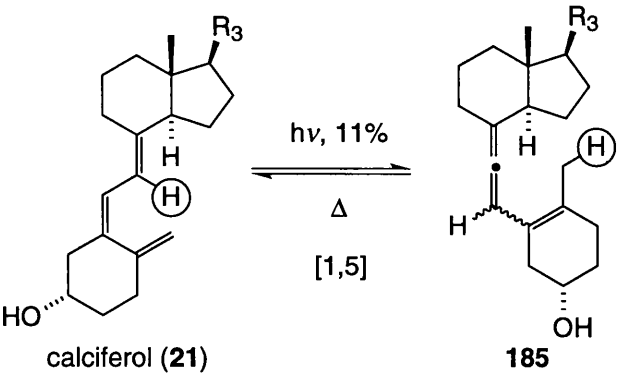
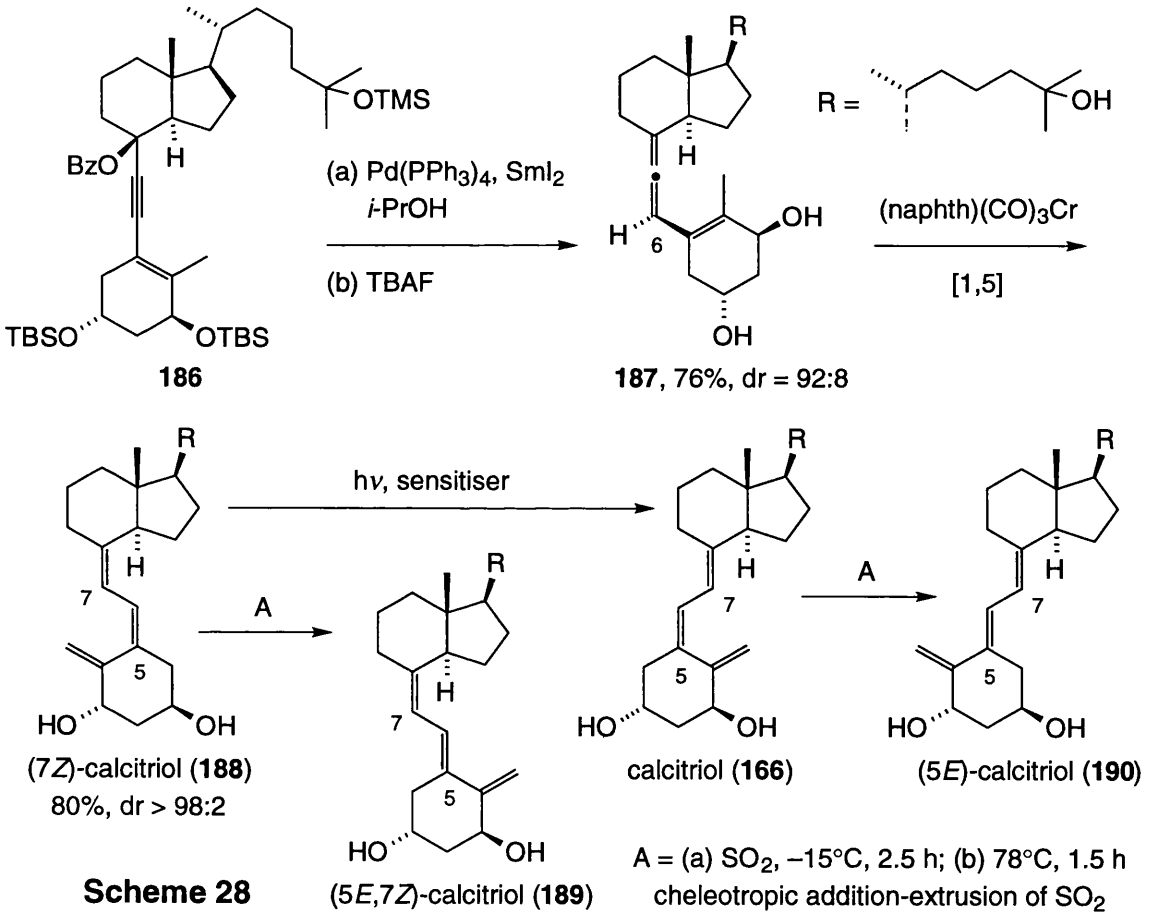


Figure 8

The aforementioned pitfall of the thermal rearrangement vinylallene route lead Okamura and co-workers to investigate and develop a practical chromium(0) mediated isomerisation route of vinylallene intermediates to calcitriol[84] (see Scheme 28). Following the addition of an A-ring

alkynyllithium to a Grundmann's ketone derivative, the benzoate **186** was easily realised. Reduction of the propargyl benzoate with a Pd(0)-Sm(II) reagent system followed by silylether deprotection, lead to the formation of the requisite vinylallene **187** with excellent stereoselectivity (the 6*S* major isomer is illustrated). Rearrangement of either vinylallene (6*S* or 6*R*) mediated by a (naphthalene)tricarbonylchromium catalyst yielded (7*Z*)-calcitriol (**188**) in excellent yield and stereoselectivity. Under the relatively mild reaction conditions further [1,7]-hydrogen shifts of the labile 5*Z*,7*Z* system were not promoted. By employing the long known $\Delta^{5,6}$ (5*Z* → 5*E*) isomerisation of vitamin D trienes *via* the cheleotropic addition-extrusion of sulfur dioxide[85,86], together with a new efficient photoisomerisation of the $\Delta^{7,8}$ bond (7*Z* → 7*E*)[84], the Okamura group were able to synthesise every double bond isomer of calcitriol from the 5*Z*,7*Z* material **188**.

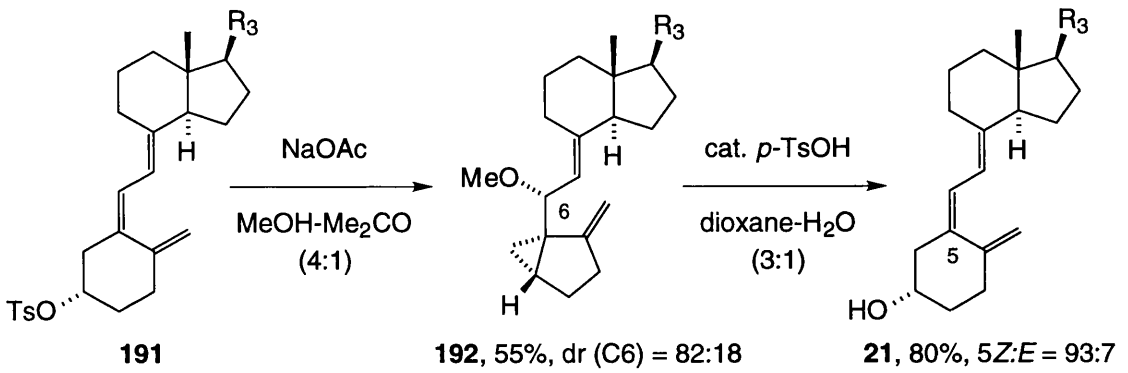


Scheme 28

3.4. Cyclovitamin D solvolysis approach

The last approach to be introduced here also exploits natural vitamin D rearrangement chemistry. In efforts to protect the delicate triene system of vitamin D_3 prior to subsequent functionalisation, Mazur discovered an intriguing interconversion between the vitamin and its *i*-steroid form, 3,5-cyclovitamin D_3[87]. Treatment of the tosylate of vitamin D_3 (**191**) with sodium acetate in methanol-acetone yielded 55% of the cyclopropane **192** and its C6 epimer (dr = 82:18) together with 10% of 3*O*-methyl vitamin D_3 (Scheme 29). Acid catalysed

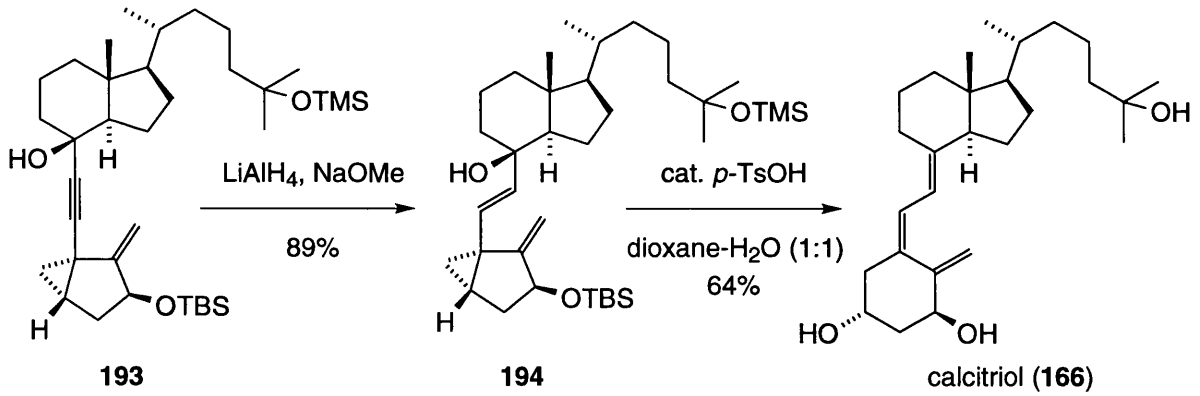
hydrolysis of the major cyclopropane epimer **192** regenerated vitamin D_3 in 80% yield with excellent selectivity (5*Z*:*E* = 93:7).



191 **192**, 55%, dr (C6) = 82:18 **21**, 80%, 5*Z*:*E* = 93:7

Scheme 29

Several groups have employed Mazur's discovery to achieve the synthesis of vitamin D systems *via* the coupling of appropriate bicyclo[3.1.0]hexane A-ring precursors to CD-ring fragments[88,89]. Wilson has devised a particularly useful vitamin D synthesis which utilises the solvolytic rearrangement of vinylogous cyclopropane **194**[90] (Scheme 30): the latter behaves similarly to Mazur's system, the solvolysis presumably involving an identical allyl cation intermediate. Condensation of a lithium derivative of a bicyclo[3.1.0]hexane A-ring alkyne with a Grundmann's ketone analogue yielded the propargylic alcohol **193**. Reduction with lithium aluminium hydride modified by sodium methoxide gave the requisite *trans* allylic carbinol **194** as a single isomer. An extremely efficient acid catalysed hydrolysis then generated the $\Delta^{5,6}$ and $\Delta^{7,8}$ double bonds with solely the natural stereochemistry and concomitantly removed the two silylether protecting groups to yield calcitriol (**166**) directly in 64% yield.



193 **194** calcitriol (**166**)

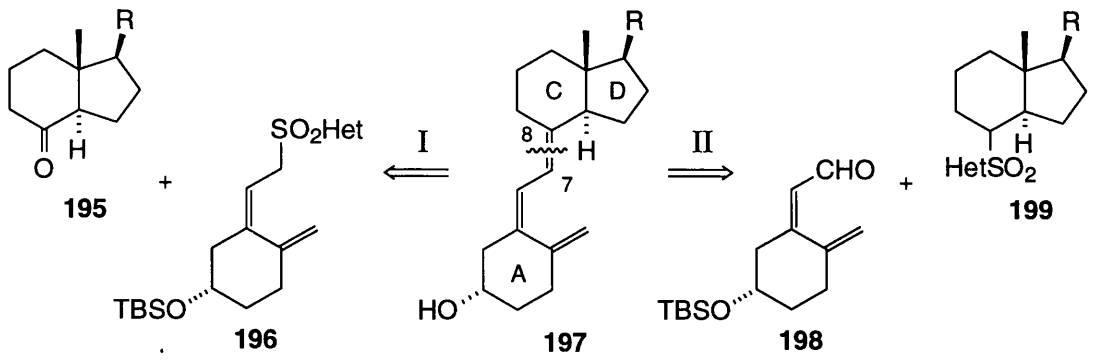
Scheme 30

4. Partial Synthesis of Vitamin D

Construction of the conjugated triene segment of vitamin D has provided major stimulus to the development of many connective olefination processes. Indeed, application of the classical Julia reaction to the synthesis of vitamin D_4 by Lythgoe and Kocienski[30] was key to its development and popularisation as a powerful synthetic tool. To draw a fitting historical parallel between classical and one-pot Julia olefination variants, we desired to apply the latter to the vitamin D problem in an analogous fashion to Lythgoe (see Scheme 25, Chapter 3). Rather than produce yet another total synthesis, we focused our studies towards formation of the crucial 7,8-olefinic bond. Not only would this work extend our knowledge of the applicability of the new Julia variant but it would also provide a further method for the synthesis of a very valuable class of natural products.

4.1. Retrosynthetic analysis

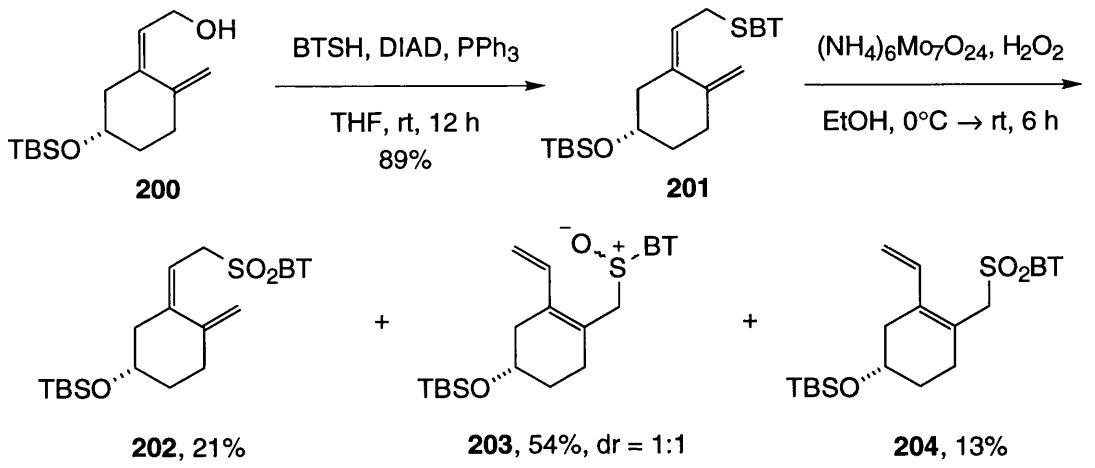
The 7,8-double bond of vitamin D (**197**, R = R_2, R_3 or R_4, see Scheme 22, Chapter 3) is potentially accessible *via* two Julia olefination strategies: (I) a metallated A-ring sulfone **196** is condensed with a CD-ring ketone **195** or, (II) a metallated CD-ring sulfone **199** is condensed with the A-ring aldehyde **198** (Scheme 31). Advanced starting materials for the speedy construction of such precursor compounds are readily available from the appropriate vitamin *via* degradation protocols (*vide infra*). *A priori* from the earlier discussions of stereocontrol in the one-pot Julia olefination (see Chapters 1 and 2) one would anticipate that the latter approach (II) employing Het = BT should be the most successful coupling protocol for securing the *trans* alkene geometry.



Scheme 31

4.2. Approach I: A-ring nucleophile, CD-ring electrophile

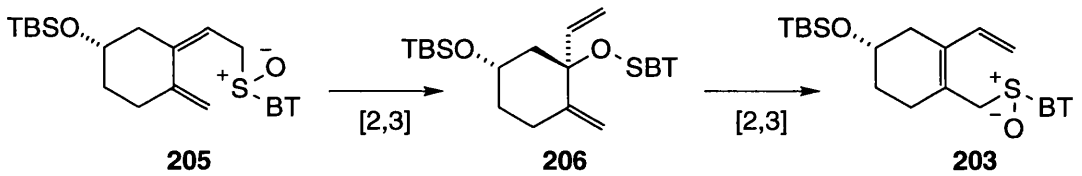
A simple degradation sequence for vitamin D_3 developed by Okamura[91] provided A-ring alcohol **200**. Mitsunobu thioetherification of **200** with 2-mercaptobenzothiazole (BTSH) under standard conditions provided the heterocyclic sulfide **201** in excellent yield (Scheme 32). Treatment of the thioether with hydrogen peroxide in the presence of an ammonium



Scheme 32

molybdate catalyst resulted in only 21% of the requisite sulfone **202** together with significant quantities of the rearranged sulfoxide **203** and corresponding sulfone **204**. Evidently the initially formed sulfoxide **205** undergoes two consecutive [2,3]-sigmatropic rearrangements resulting in the thermodynamically favoured double bond topology (see Scheme 33).

All initial coupling experiments were singularly unsuccessful: treatment of sulfone **202** with sodium hexamethyldisilazide (NaHMDS) in THF at –78°C followed by the subsequent addition of Grundmann's ketone (**19**) failed to yield any vitamin product. Rather, only decomposition of the sulfone and epimerisation of the ketone was observed[92]. Faced with such dual jeopardy, approach I was abandoned in hope of better fortune with the reversed strategy.



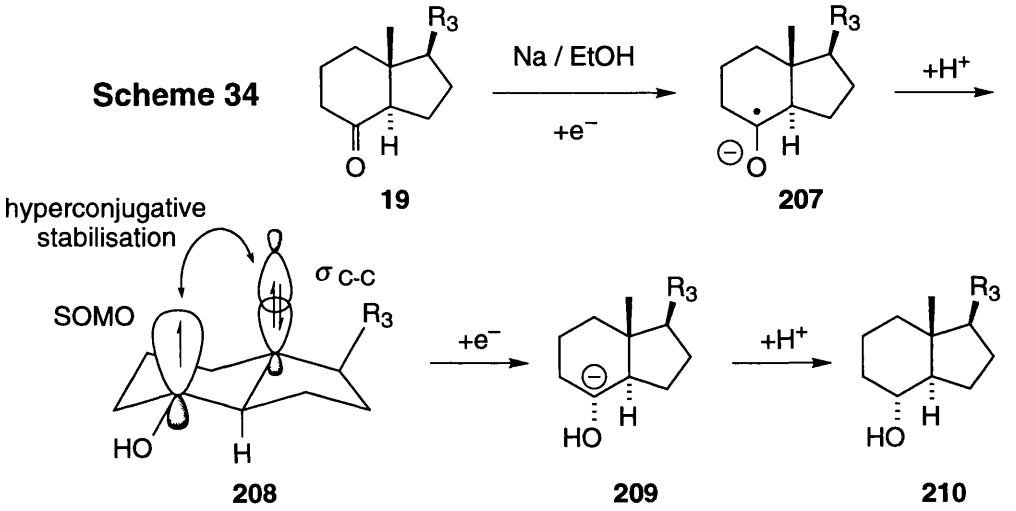
Scheme 33

4.3. Approach II: A-ring electrophile, CD-ring nucleophile

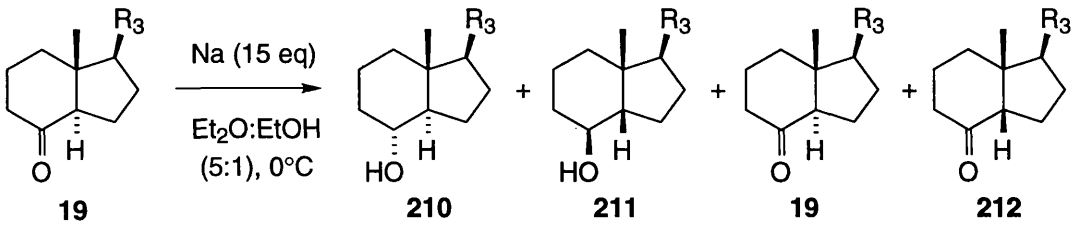
All attempts to substitute the hindered axial hydroxyl group of the CD-ring alcohol **213** (also obtained *via* Okamura's procedure[91]) with BTSH using a standard Mitsunobu reaction failed (Scheme 35). Starting material was recovered together with 18% of an elimination product. Reasoning that the less sterically encumbered α-alcohol **210** would make a better substrate for the Mitsunobu reaction, we sought an efficient means for its preparation from Grundmann's ketone (**19**) (existing routes to the seldom reported α-alcohol are circuitous[93,94]). Metal hydride type reductions of Grundmann's ketone are well known to occur from the unhindered α-face and return only the axial alcohol **213**[91,95]. However, conventional Bouveault-Blanc reduction[96] of the bicyclic carbinone should, in theory, return the desired alcohol (see Scheme 34). Initial

electron transfer to Grundmann's ketone (**19**) followed by proton abstraction would yield ketyl **208**. The expected equatorial preference for the hydroxyl group of the ketyl is reinforced by stereoelectronic effects of the surrounding carbocyclic framework. Rehybridisation of the SOMO occurs, mixing s and p orbitals appropriately so as to obtain maximum orbital stabilisation. The radical centre is thus partially pyramidalised with *orbital extension* to the β-face ensuring maximal hyperconjugative stabilisation from the adjacent axial methyl substituent. Overlap between $\sigma_{C\text{-}C}$ and the carbon radical is more effective than between the SOMO and any appropriately positioned $\sigma_{C\text{-}H}$ orbitals[96]. Subsequent electron/proton transfer to the β-face then yields the desired α-alcohol **210**.

Scheme 34

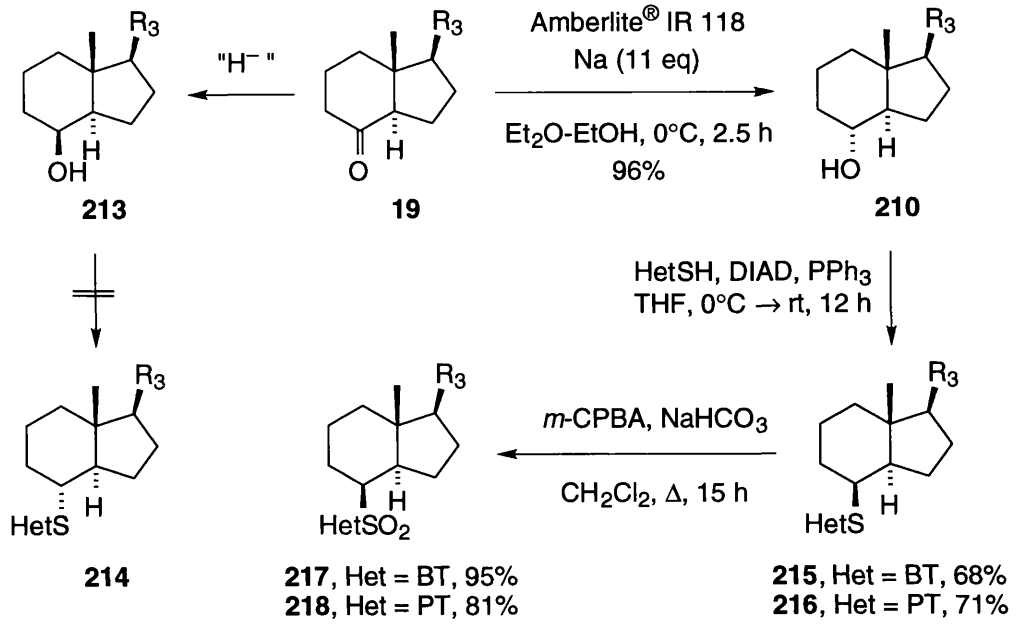


In practice significant epimerisation of the sensitive ketone occurred under the inherently basic reaction conditions. Gratifyingly, when the reduction was carried out in the presence of dried Amberlite® IR118 acidic exchange resin, the pure α-alcohol **210** was obtained in nearly quantitative yield. Table 7 illustrates the product distributions of two such Bouveault-Blanc reductions, one conducted with, and one without, the benefit of the buffering acidic resin; both were quenched at approximately their half-way stage. The effect of the resin is quite remarkable and its compatibility with metallic sodium is noteworthy. Alternative grades of acidic resin investigated proved ineffectual in preventing ketone epimerisation.



no additive	22%	16%	4%	38%
Amberlite® IR118	>38%	<1%	~ 54%	<2%

Table 7



Scheme 35

As predicted Mitsunobu reaction of the product equatorial alcohol **210** with BTSH occurred in good yield to afford the corresponding β-thioether **215** and subsequent oxidation with *m*-CPBA provided the requisite sulfone **217**. Related 1-phenyl-1*H*-tetrazol-5-yl (PT) compounds **216** and **218** were similarly prepared.

Initial attempts to link sulfone **217** and aldehyde **198** (prepared from **200** by Dess-Martin oxidation, *vide infra*) under Julia's standard Barbier conditions[3] employing a variety of bases (LDA, LiHMDS, NaHMDS, KHMDS) gave no coupling products whatsoever. Similarly, pre-metallation of the sulfone with LDA, LiHMDS or KHMDS followed by addition of the

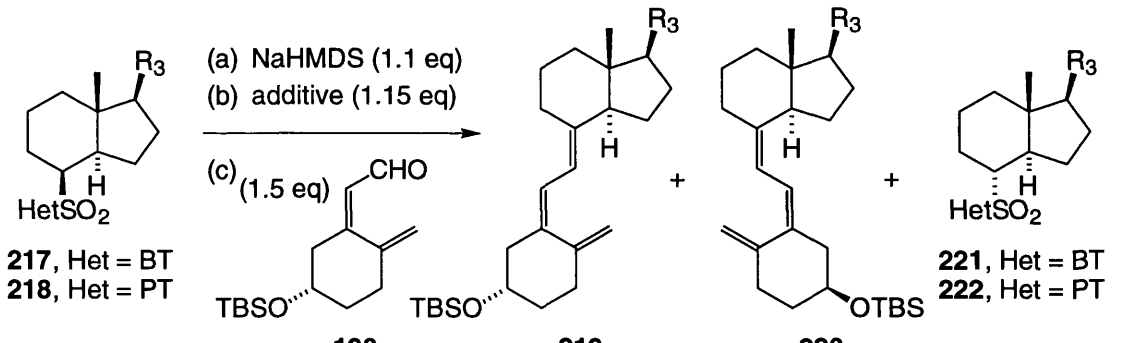


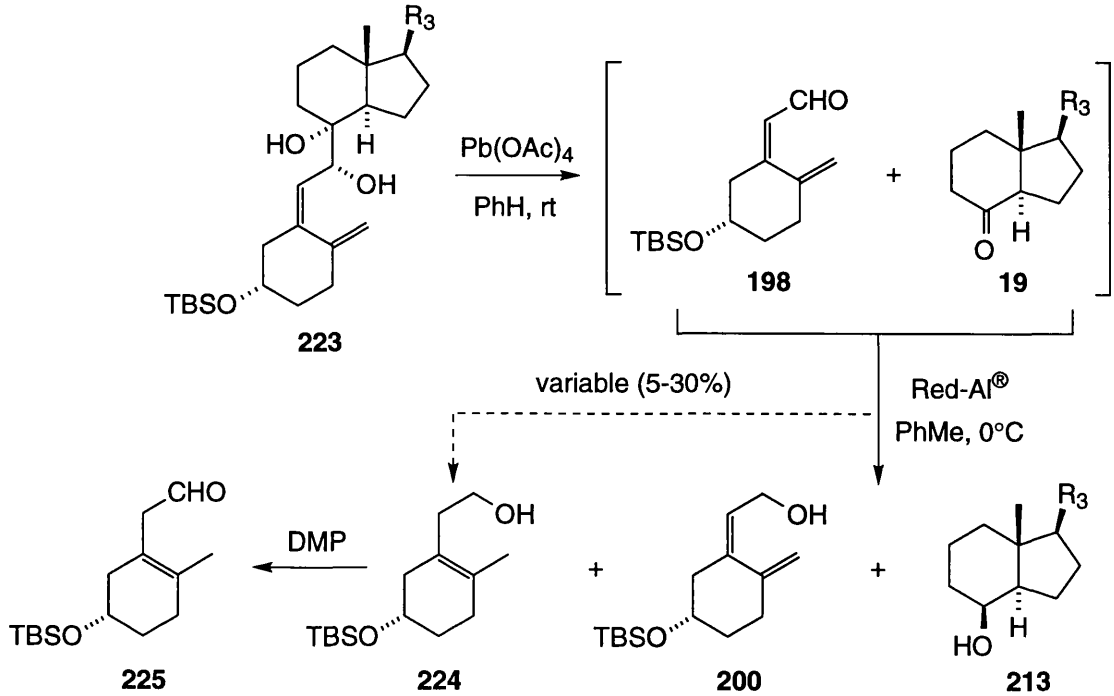
Table 8

entry	Het	solvent	temp. (°C)	additive	%yield[a] (**219+220**)	*E*:*Z*[b] (**219:220**)	%yield[a] α-sulfone
1	BT	THF	–60	none	38	67:33	42
2	BT	Et_2O	–60	none	25	83:17	54
3	BT	PhMe	–60	none	28	80:20	45
4	BT	Et_2O	–78	$MgBr_2{\bullet}OEt_2$	52	73:27	26
5	PT	Et_2O	–78	$MgBr_2{\bullet}OEt_2$	54	45:55	---[c]
6	PT	THF	–78	$MgBr_2{\bullet}OEt_2$	42	35:65	---[c]

[a] isolated yield after column chromatography. [b] determined by ^{1}H NMR analysis. [c] not determined

aldehyde failed to return any of the desired triene. However, a pre-metallation protocol using NaHMDS in THF (Table 8, entry 1) gave a 38% yield of vitamin D_3 adducts **219** and **220** (7*E*:*Z* = 2:1) together with 42% of the epimerised sulfone **221**. Varying the solvent had a beneficial effect on stereoselectivity: in Et_2O or toluene the *E*:*Z* ratio improved to 5:1 (entries 2 and 3) but at the expense of a decrease in yield. Transmetallation of the sodiated sulfone to the magnesium derivative increased the yield of the coupling adducts (entry 4). As may be predicted from our earlier methodology results (Chapter 2), use of the PT sulfone **218** was not advantageous for the synthesis of a conjugated *trans* olefin (entries 5 and 6). However, the predominance of the (5Z,7Z)-vitamin D system here is of some interest; analogues of vitamin D with such a configuration have seldom been reported in the literature nor has their biological activity been examined. The parent systems (7Z)-vitamin D_2 and (7Z)-vitamin D_3 have never been reported.

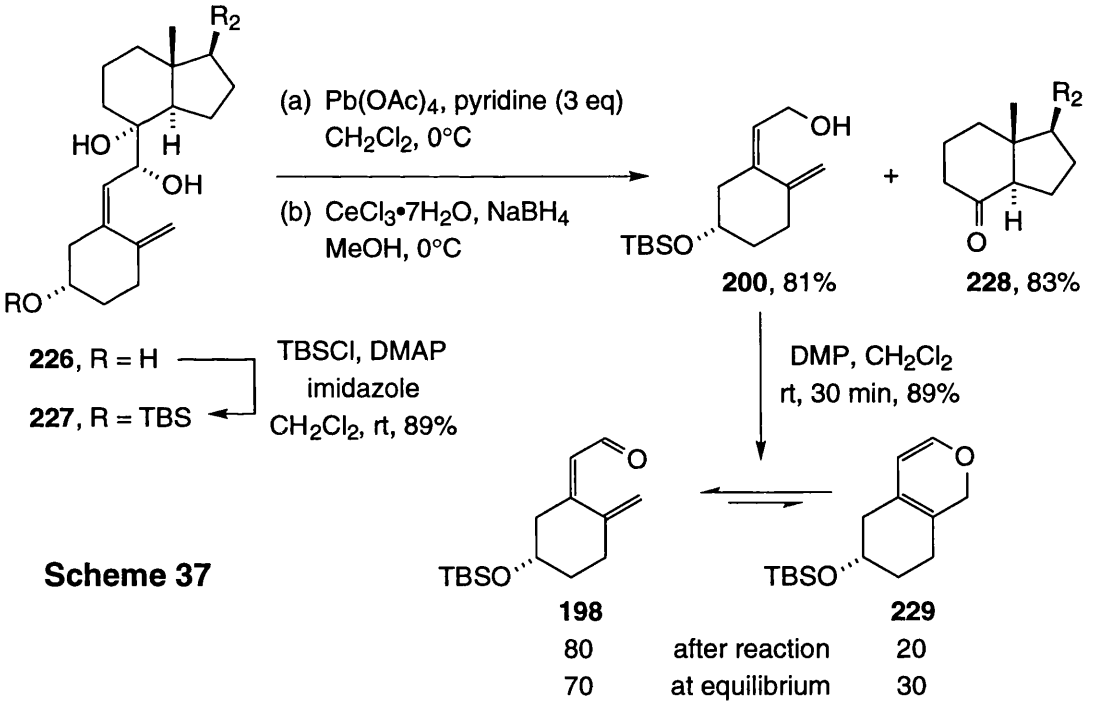
Further attempts to improve on the modest yields achieved above led us to re-investigate our protocol for the production of the unstable aldehyde **198**. Variations in the quality of the labile carbonyl compound were found ultimately to lie with Okamura's vitamin D degradation procedure[91] (Scheme 36). Following regioselective dihydroxylation of vitamin D_3 and subsequent protection of the C3 hydroxyl group, the diol **223** is oxidatively cleaved by the action of lead tetraacetate. Due to instability of the resulting dienal **198**, the mixture of the aldehyde and Grundmann's ketone (**19**) is immediately reduced *in situ* to yield the carbinol **200** and axial CD-ring alcohol **213**. However, in our hands the action of Red-Al on **198** resulted in a degree of over reduction to the enol **224**; a compound virtually inseparable from **200** by chromatography and indistinguishable from it by simple TLC analysis. In certain



Scheme 36

instances the aldehyde **198** used in our Julia coupling studies was contaminated by the enal **225** derived from concomitant oxidation of **224** and **200**. Aldehyde **225** does not appear to act as an electrophile since no coupling adducts incorporating the appropriate A-ring motif were ever observed. However, due to its presumably high enol content, it may act as a ready proton source thence reducing yields.

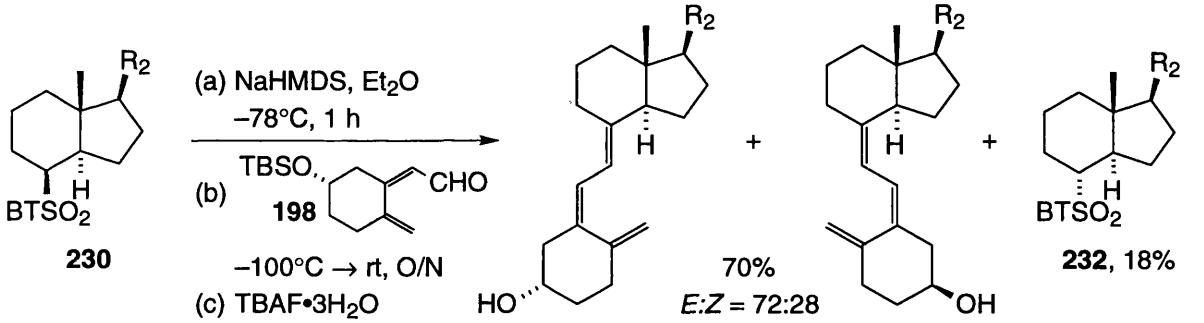
We sought an improved degradation procedure which could consistently furnish pure dienol **200** and so aid our preparation of aldehyde **198**. At this juncture we were forced to turn our attention to vitamin D_2 due to a regrettable supply problem with vitamin D_3. Degradation studies commenced from the known vitamin D_2 triol **226**[97] (Scheme 37): following silyl protection at O3, the vicinal diol was oxidatively cleaved as before by lead tetraacetate. A Luche reduction[98] then secured pure A-ring dienol **200** in excellent yield and returned the Windaus-Grundmann C19 ketone **228** relatively unscathed. No trace of the enol **224** was found and 13% of the appropriate CD-ring β-alcohol was also recovered. The new degradation sequence was ideally suited to our needs, yielding the stable A-ring dienal precursor **200** and the requisite ketone for our modified Bouveault-Blanc reduction.



Scheme 37

The instability of aldehyde **198** necessitated its rapid preparation and dispensation, thus slow chromatographic purification was avoided. As such it was of paramount importance that the precursor **200** was of a high purity and that the oxidation method employed was both fast and clean. Oxidation by Dess-Martin periodinane[99] (DMP) suited our needs perfectly (Scheme 37). It should be noted that dienal **198** exists in dynamic equilibrium with its cyclic tautomer **229**; complete separation of these components is impossible (due to subsequent interconversion) and pointless, the 2*H*-pyran merely acts as a latent aldehyde equivalent.

Finally, the vitamin D_2 CD-ring sulfone **230** was synthesised from **228** in analogy with the corresponding vitamin D_3 fragments **217** and **218** (see Experimental Section for details). Adopting the previously optimised reaction conditions, metallation of the sulfone **230** with NaHMDS in Et_2O was followed by addition of the freshly prepared 'aldehyde' **198** (Scheme 38). Subsequent deprotection yielded 70% (2 steps) of the separable vitamin D_2 isomers, **163** (natural) and **231** (unnatural), with moderate stereoselectivity (7*E*:*Z* = 72:28). Our synthetic vitamin D_2 exhibited identical physical and spectroscopic characteristics to those previously reported[100-102]. The unnatural isomer **231** exhibited only limited stability and its stereochemistry was assigned by comparison of NMR data with that reported for other (7*Z*)-vitamin D derivatives[84,103].



Scheme 38

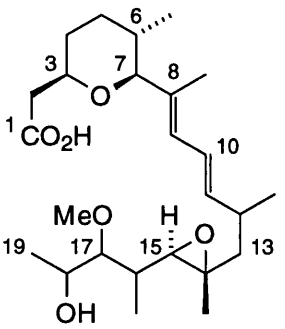
After the initial coupling event some epimeric α-sulfone **232** was recovered as before (*cf* **221**, Table 8); the isomer arose from configurational instability of the metallated β-sulfone **230**. Treatment of **230** with NaHMDS in Et_2O at –78°C followed by subsequent low temperature protonolysis (MeOH) yielded 92% of the epimeric sulfones **230** and **232** in the ratio 15:85 respectively.

Curiously, conducting the vitamin D_2 coupling experiment *via* the intermediacy of the magnesiated derivative of **230** (formed by transmetallation of the sodium metallate with $MgBr_2$•OEt_2) gave only 63% of TBS protected vitamin D_2 isomers in the ratio 7*E*:*Z* = 69:31. The higher yields associated with the use of $MgBr_2$•OEt_2 previously for the vitamin D_3 series (Table 8, entries 4 to 6) were in cases where the contaminating enal **225** was present.

5. The Herbicidal Polyketide Herboxidiene

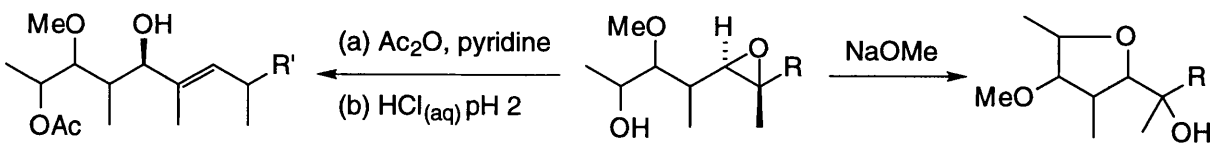
In 1992 the Monsanto company reported the isolation of a secondary metabolite produced by a fermentation broth of *Streptomyces* sp. A7847 (ATCC 49982)[104]. The agent exhibited exceptional phytotoxicity towards several broadleaf annual weed species: oilseed rape (*Brassica napus*), wild buckwheat (*Polygonum convolvulus*), morning glory (*Ipomoea* sp.) and hemp sesbania (*Sesbania exaltata*) all had their growth inhibited by >90% when treated with 35 g $acre^{-1}$ of the metabolite. Indeed, good inhibition (75%) was retained at a dosing of just 7 g $acre^{-1}$. More importantly, when the above weed species were co-planted with wheat (*Triticum aestivum*), the agent was able to selectively control growth of the pest plants whilst exhibiting no phytotoxicity toward the cash crop.

Extensive NMR studies by the Monsanto group enabled elucidation of the gross structure of the active compound. Named *herboxidiene* (**233**) to reflect its biological activity and structural features, the agent was an essentially linear polyketide possessing epoxide and tetrahydropyran ring systems linked by a conjugated diene segment[104]. At the conclusion of these studies the absolute stereochemistry and the relative configuration at C12 and C16-C18 remained ambiguous.



herboxidiene (**233**)

Some synthetic modifications of herboxidiene were undertaken to determine if the structure could be simplified whilst phytotoxic properties were retained[104]. Derivatives which decreased the polarity, such as the C1 methyl ester and the O18 acetylated adduct were slightly more active. Interestingly, if the C1 carboxyl group was reduced to a primary alcohol, activity was also retained indicating the relative unimportance of an acid group masked or otherwise. However, the presence of the epoxide moiety was essential for biological activity as was the presence of the C18 hydroxyl function at that oxidation level (the C18 ketone was completely inactive). The latter two structural features also account for the inherent instability of herboxidiene under both acidic and basic conditions (Scheme 39). Unfortunately, any significant skeletal simplifications resulted in compounds devoid of all herbicidal activity.



234 **Scheme 39** **233** **235**

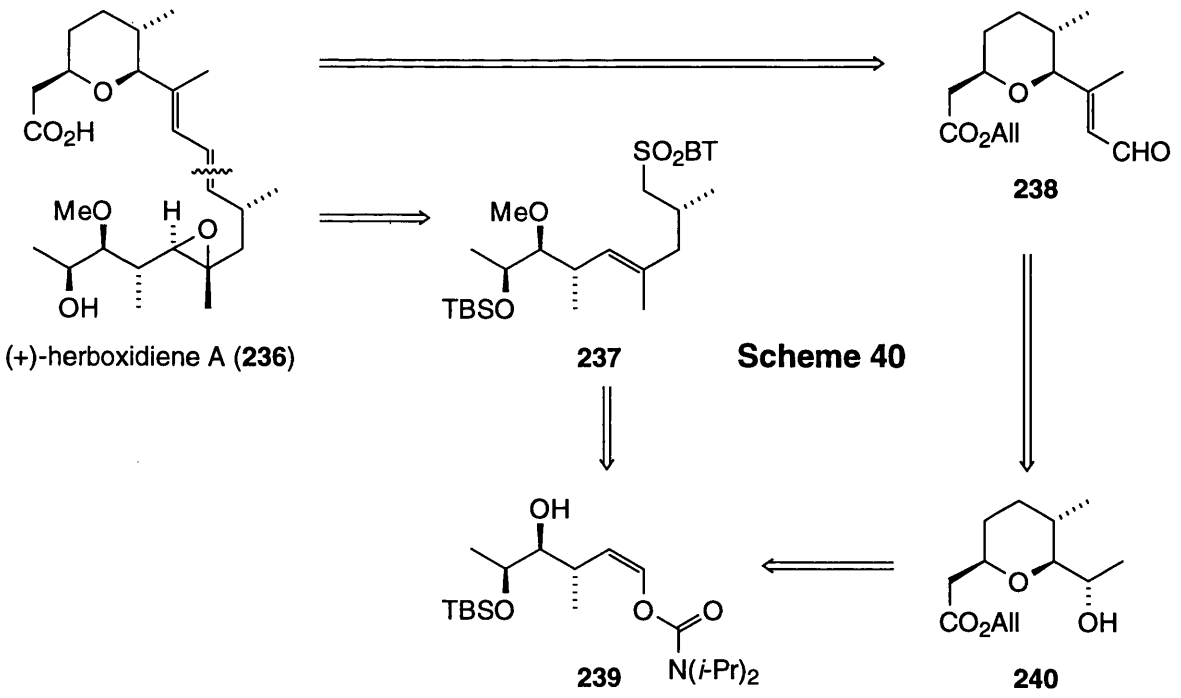
At this juncture Kocienski's Southampton group[46] and the Banwell group in Canberra[105-107] both instigated independent synthetic studies toward certain arbitrary herboxidiene

diastereoisomers. Of course with the relative configuration of four stereogenic centres and the absolute stereochemistry yet to be determined there was only a slim chance that either group would target the true structure first time around. This has subsequently been borne out, neither camp sighted compounds of the correct natural configuration (*vide infra*).

5.1. Kocienski's total synthesis of (+)-herboxidiene A

In 1996 Kocienski reported the total synthesis of (+)-herboxidiene A[46] (**236**), a notional target chosen to best demonstrate certain synthetic methodologies, among them the original BT variant of the one-pot Julia olefination[1-3] and the Hoppe homoaldol reaction[108-110]. Comparison of ^{1}H and ^{13}C NMR data for the synthetic material **236** with the previously published data for natural herboxidiene[104], revealed several discrepancies suggesting the two were diastereomeric.

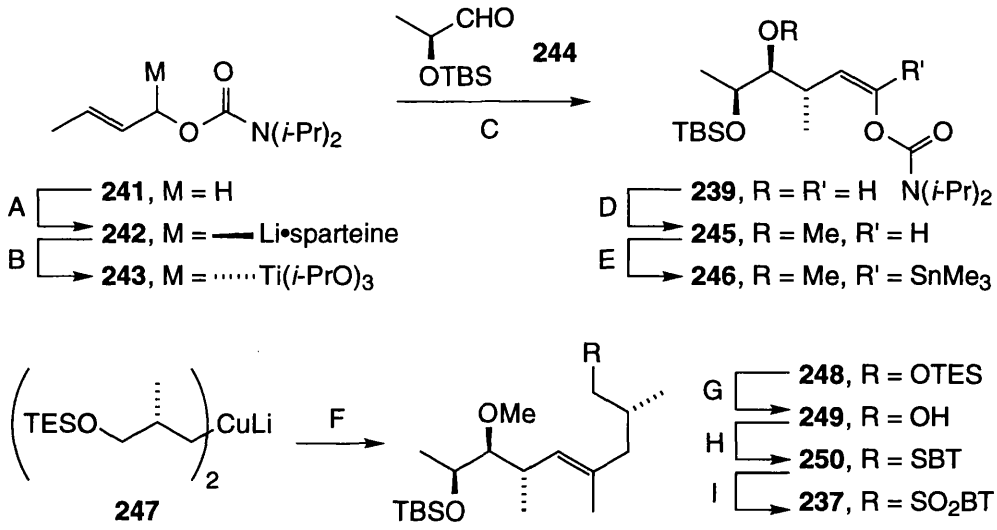
Scheme 40 outlines the original basic retrosynthetic analysis: the BT mediated Julia olefination is used to conjoin two late stage intermediates, sulfone **237** and the aldehyde **238**, forming the C10-C11 double bond stereoselectively. The validity of such an approach had been previously demonstrated both in Julia's methodology work[3] and Kocienski's rapamycin studies [45]. Each of the fragments can in turn be derived from the vinyl carbamate **239** since, by design, they share the same relative and absolute configurations.



Scheme 40

Synthesis of the pivotal intermediate **239** commenced with the *E*-crotyl carbamate **241**: metallation with butyl lithium in the presence (–)-sparteine resulted in the precipitation of a single diastereomeric complex *via* a dynamic resolution process. Transmetallation with Ti(*i*-PrO)$_4$ proceeded with inversion of configuration[110], and was followed by reaction with aldehyde **244** to yield the vinyl carbamate **239** with good stereocontrol (see Scheme 41). After

methylation of the C17 hydroxyl, elaboration toward **237** continued with stereoselective synthesis of the requisite trisubtituted olefin *via* a 1,2-metallate rearrangement sequence[111,112]. Addition of vinyl stannane **246** to a 1:1 mixture of cuprate **247** and its alkyl lithium precursor resulted in transmetallation to a putative higher-order mixed cuprate. Upon slow warming a 1,2-metallate rearrangement occurred, the resultant lower-order vinyl cuprate was then alkylated with methyl iodide to afford olefin **248** together with 12% of the terminal acetylene resulting from Fritsch Buttenburg Wiechell (FBW) rearrangement[113-115] of the lithiated enol carbamate. Standard synthetic steps then yielded the sulfone **237**.

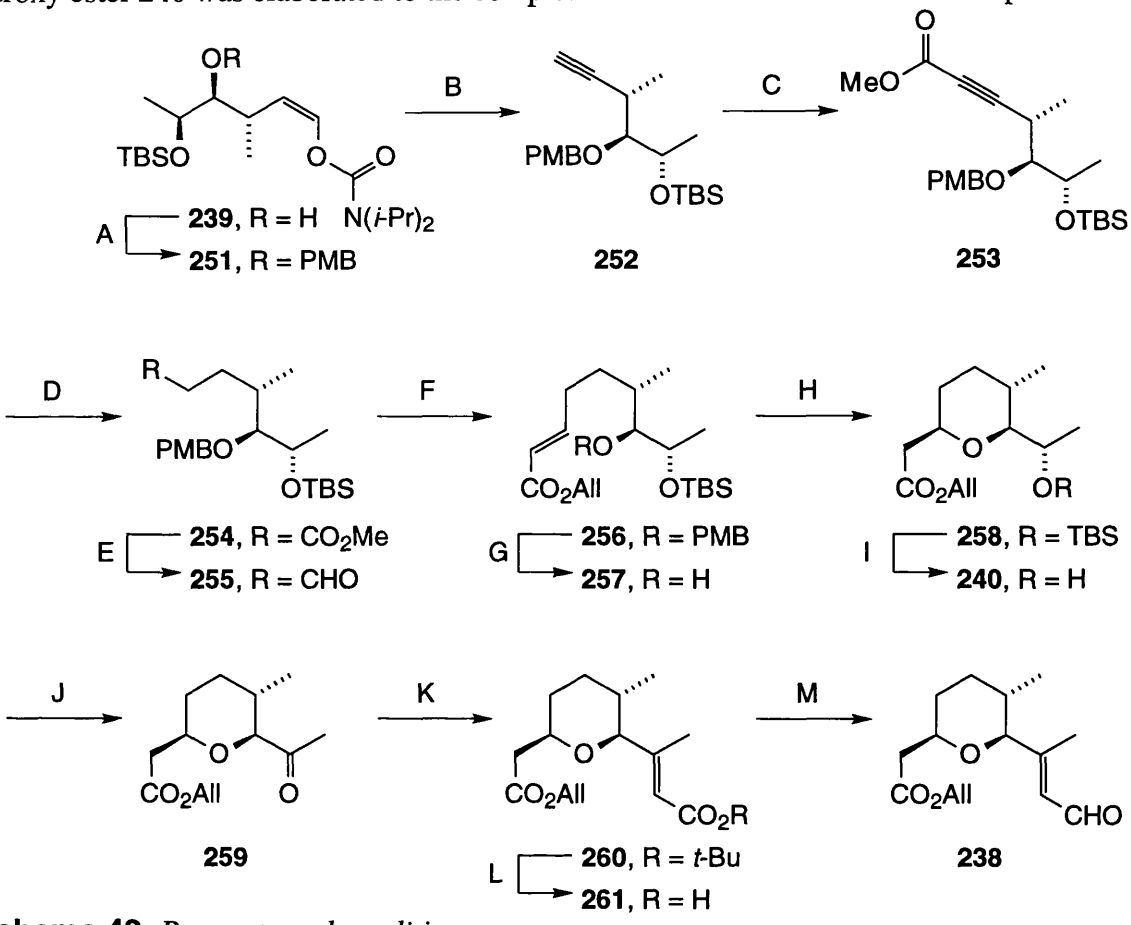


Scheme 41. *Reagents and conditions:*

A	↓	BuLi, (–)-sparteine, cyclohexane-pentane, 80°C, 3 h
B	↓	Ti(*i*-PrO)$_4$, pentane, –80°C, 20 min
C	63%	**244**, –80°C → rt, 2.5 h, dr (*anti*) = 7:1
D	70%	4-Me-2,6-di-*t*-Bu-pyridine, MeOTf, PhMe, 70°C, 10 h
E	95%	(a) *t*-BuLi, THF, –85°C, 50 min; (b) Me_3SnCl, –85°C → rt, 80 min
F	64%	(a) **246**, Et_2O-pentane, –35°C → 0°C; (b) MeI, HMPA-THF, –20°C, *E*:*Z* = 88:12
G	93%	HF•pyridine, pyridine-THF, 0°C → rt, 1 h
H	94%	BTSH, Ph_3P, DEAD, THF, rt, 30 min
I	84%	Mo(VI), H_2O_2, EtOH-H_2O, 0°C → rt, 24 h

Synthesis of the dienal fragment **238** began with PMB protection of the C7 hydroxyl of **239** followed by a synthetically useful FBW rearrangement of the derived lithiated enol carbamate to yield alkyne **252** (see Scheme 42). Homologation of the terminal acetylene with methyl chloroformate followed by hydrogenation and DIBAL-H reduction afforded the masked dihydroxy aldehyde **255**. A Horner-Wadsworth-Emmons olefination of the aldehyde followed by selective deprotection of the C7 hydroxyl yielded the *trans* δ-hydroxyenoate **257**, a suitable cyclisation precursor to the tetrahydropyran ring system. Intramolecular conjugate addition of the tethered O-nucleophile to the proximal α,β–unsaturated ester resulted in selective formation of the thermodynamically most stable *cis* oxane **258** (all substituents equatorial). The authors claim tetrahydropyran **258** is both the thermodynamic and kinetic product of the cyclisation[46].

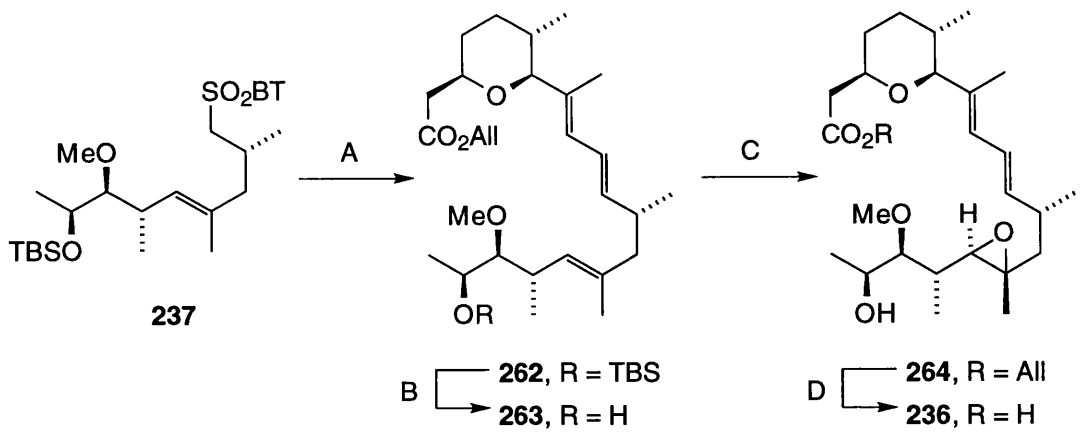
However, investigations from Banwell[116] and our own results here (*vide infra*) suggest that the *trans* oxane is actually the kinetic product. Following silyl ether deprotection the heterocyclic hydroxy ester **240** was elaborated to the completed dienal **238** in four standard steps.



Scheme 42. *Reagents and conditions:*

A	66%	PMBO-C(=NH)-CCl_3, TMSOTf, Et_2O	H	99%	*t*-BuOK, THF, –65°C
B	81%	*t*-BuLi, Et_2O, –20°C	I	84%	TBAF, 4Å MS, THF, rt
C	95%	(a) BuLi, THF, –80°C; (b) $ClCO_2Me$	J	89%	PCC, 4Å MS, CH_2Cl_2, rt
D	84%	H_2 (1 atm), Pd/C, EtOAc, rt	K	81%	$(EtO)_2P(=O)CH_2CO_2{}^tBu$, NaH, THF
E	85%	DIBAL-H, CH_2Cl_2, –80°C	L	96%	TFA, PhSMe, CH_2Cl_2
F	96%	$(EtO)_2P(=O)CH_2CO_2All$, NaH, THF	M	---	(a) $[Me_2N{=}CHCl]Cl$, THF-MeCN;
G	93%	DDQ, CH_2Cl_2-H_2O, rt		78%	(b) $LiAlH(O^tBu)_3$

The synthetic studies were completed as shown in Scheme 43. The one-pot Julia olefination performed admirably in its role, linking together the advanced intermediates **237** and **238** *via* a standard premetallation protocol; the (*E,E*)-diene **262** was obtained in 65% yield together with a further 6% of a 1:1 mixture of two isomeric dienes. Following TBS-deprotection the bishomoallyic C18 hydroxy of triene **263** served to direct the epoxidation of the C14-C15 trisubstituted olefin. Although a single diastereoisomeric epoxide was obtained and a model presented to account for the illustrated facial selectivity, no direct proof of stereochemistry was obtained. Following allyl ester deprotection, herboxidiene A (**236**) was obtained in twenty linear steps from (*S*)-ethyl lactate. As already noted, comparison of NMR data revealed that herboxidiene A was a diastereoisomer of the natural product.

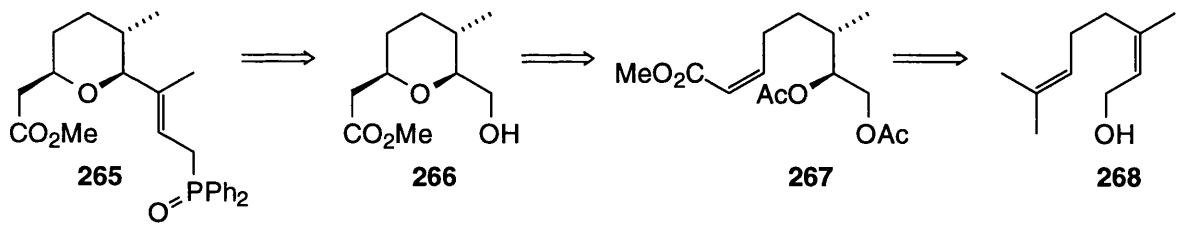


Scheme 43. *Reagents and conditions:*

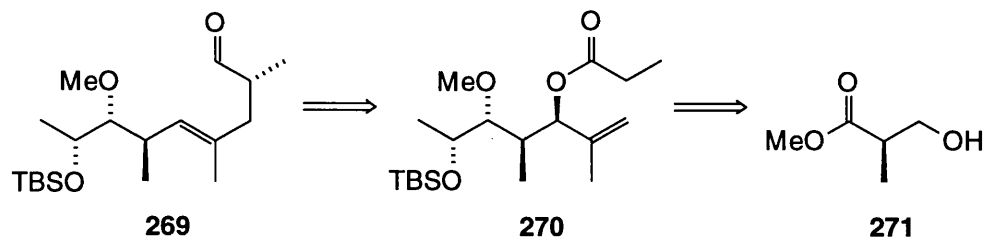
A	---	(a) LDA, THF, –80°C;	C	52%	$VO(acac)_2$, TBHP, CH_2Cl_2, 0°C
	65%	(b) aldehyde **238**, –80°C → rt	D	67%	$Pd(PPh_3)_4$, morpholine, THF, rt
B	77%	HF•pyridine, THF-pyridine, rt			

5.2. Banwell's synthetic studies towards the herboxidiene skeleton

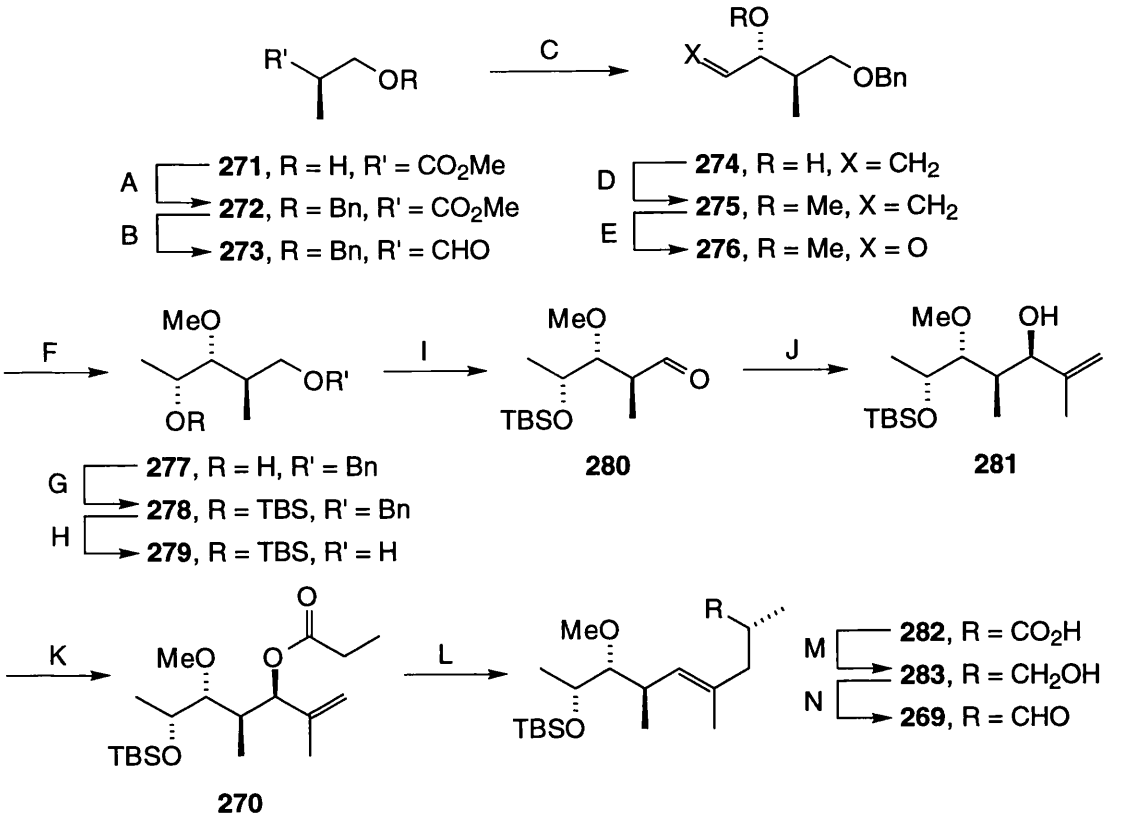
In common with Kocienski's work, Banwell chose a strategy involving late stage connective olefination of two major fragments followed by hydroxyl directed epoxidation and final deprotection. The two fragments the Canberra group have synthesised to date, phosphine oxide **265** and aldehyde **269**, are illustrated in Scheme 44. A Horner-Wittig reaction has been selected to forge the C10-C11 double bond, model studies have already illustrated the validity of such an approach.



Scheme 44



For the synthesis of the C11-C19 aldehyde fragment **269**, a rather ambitious strategy was adopted[106]. All four of the contiguous stereogenic centres in the Claisen rearrangement precursor **270** were to be derived directly from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**271**) *via* stereocontrolled nucleophilic addition to chiral aldehydes (1,2-asymmetric induction). Scheme 45 illustrates the execution of the plan; the somewhat laborious route toward **270** was not without its pitfalls. The first addition, to aldehyde **273**, was



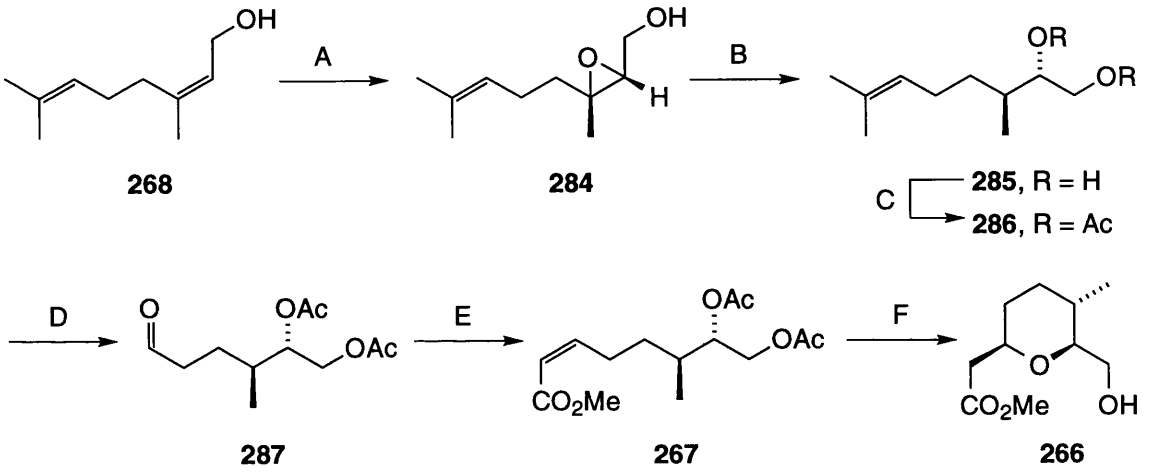
Scheme 45. *Reagents and conditions:*

A	73%	$BnOC(=NH)CCl_3$, TfOH, CH_2Cl_2, rt	I	---	(a) $(COCl)_2$, DMSO, CH_2Cl_2, –60°C;
B	---	(a) $LiAlH_4$, Et_2O, 0°C; (b) $(COCl)_2$,		98%	(b) Et_3N, –60°C
	68%	DMSO, CH_2Cl_2, –60°C; (c) Et_3N, –60°C	J	83%	$[H_2C=C(Me)]_2CuLi$, Et_2O, –78°C, dr >95:5
C	70%	$H_2C=CHMgBr$, THF, –78°C, dr = 1:1	K	82%	$(EtCO)_2O$, DMAP, pyridine, rt
D	94%	MeI, KH, THF, 0°C → rt	L	---	(a) KHMDS, HMPA-THF, –78°C;
E	92%	(a) O_3, CH_2Cl_2, –78°C; (b) Ph_3P		80%	(b) TMSCl, Et_3N; (c) 45°C, dr > 95:5
F	96%	MeMgCl, THF, –78°C, dr = 4:1	M	83%	$LiAlH_4$, Et_2O, 0°C
G	93%	TBSCl, imidazole, DMF, 60°C	N	---	(a) $(COCl)_2$, DMSO, CH_2Cl_2, –60°C;
H	77%	H_2 (1 atm), Pd/C, EtOH		94%	(b) Et_3N, –60°C

completely non-diastereoselective and yielded only 70% of the product allylic alcohols. Subsequent additions fared better: reaction of methylmagnesium chloride with aldehyde **276** yielded 96% of masked triol **277** with a 4:1 diastereoselectivity. The addition of *iso*propenyl cuprate to aldehyde **280** was most successful, yielding alcohol **281** as a single isomer in 83% yield. An X-ray structure of the derived silyl-deprotected crystalline diol confirmed relative stereochemistry at this stage. The Ireland-Claisen rearrangement[117] of the *Z*-silyl ketene acetal derived from **270** occurred without incident and furnished the *E*-trisubstituted olefin **282** and thence the aldehyde **269** by standard steps.

In contrast to the lengthy route to the C11-C19 fragment, Banwell's route to the oxane portion of herboxidiene, **265**, was succinct (Scheme 46)[105,107]. Commencing with nerol (**268**),

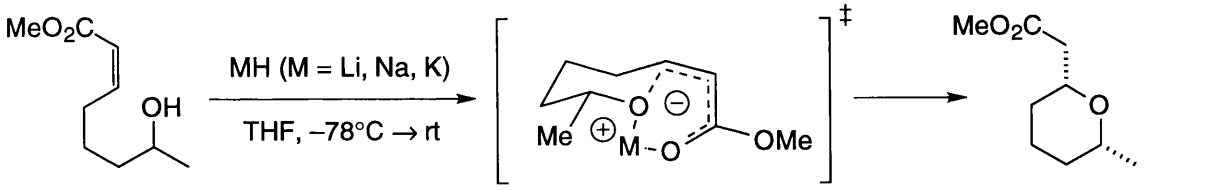
Sharpless asymmetric epoxidation[118] afforded the epoxy alcohol **284** in good yield but with poor enantioselectivity (50% ee). Regioselective reduction of the epoxide with $NaCNBH_3$ / BF_3•OEt_2 followed by acetylation yielded diacetate **286**. Ozonolytic cleavage of the olefin extremity to give aldehyde **287** was followed by a Still-Gennari[27] modified HWE reaction to yield the *Z*-enoate **267**.



Scheme 46. *Reagents and conditions:*

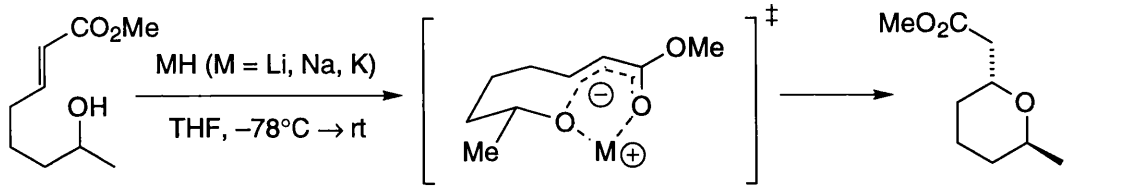
A 76% (–)-DET, Ti(*i*-PrO)$_4$, TBHP, CH_2Cl_2, –20°C, er = 75:25
B 73% $NaCNBH_3$, BF_3•OEt_2
C 96% Ac_2O, DMAP, pyridine, rt
D 97% (a) O_3, CH_2Cl_2, –60°C; (b) Ph_3P, –30°C → rt
E 78% $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, 18-crown-6•MeCN, KHMDS, THF, –78°C
F 88% (a) K_2CO_3, MeOH, rt; (b) H_2SO_4, MeOH

Model studies by Banwell and co-workers have shown that under non-equilibrating conditions the stereochemistry of tetrahydropyrans formed *via* the intramolecular Michael addition of O-nucleophiles to tethered acrylates is governed by the geometry of the enoate[116] (see Scheme 47). Thus, *Z*-enoates **288** yield *cis* oxanes **290** selectively due to the proposed intermediacy of the chair-like transition state **289** in which tight chelation of the participating metal ion to both the carbinol and ester oxygen atoms is possible. Reaction of the *E*-enoate **291** is suggested to proceed *via* the boat-like transition state **292** leading to *trans* oxanes **293** with only moderate selectivity. Metal binding in **292** may be looser than in **289** and stereochemical leakage *via* an alternative chair-like transition state is proposed to account for the poorer control. A change in the alkali metal base counter cation (Li, Na and K) had little effect on these findings. As predicted by Banwell's model, cyclisation of *Z*-enoate **267** by treatment with excess potassium carbonate in methanol afforded *cis* oxane **266** as a single detectable diastereoisomer. Saponification of all the ester groups occurred under the reaction conditions and the product carboxylic acid was immediately re-esterified.



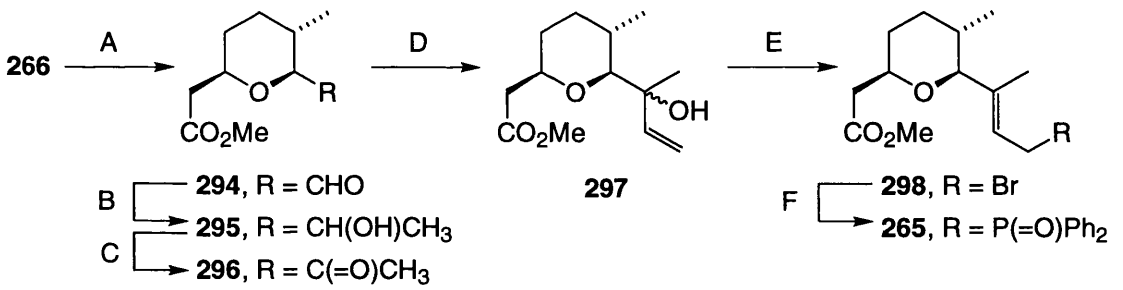
288 **289** **290**, 98%, dr = 97:3 (M = Na)

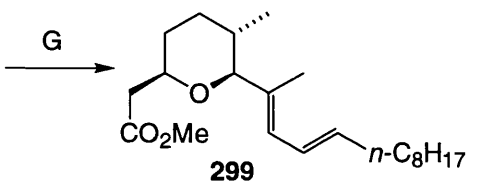
Scheme 47



291 **292** **293**, 98%, dr = 3:1 (M = Na)

Completion of the synthesis of phosphine oxide **265** and the attachment of a model side-chain are depicted in Scheme 48. Clumsy elaboration of the alcohol **266** afforded the ketoester **296**, a known degradation product of herboxidiene[104], produced *via* ozonolysis of its methyl ester. Comparison of the sign of optical rotation for the synthetic material with the degraded material[119] revealed a match thus confirming the absolute stereochemical assignment of the tetrahydropyran sub-unit of herboxidiene.





299

Scheme 48. *Reagents and conditions:*

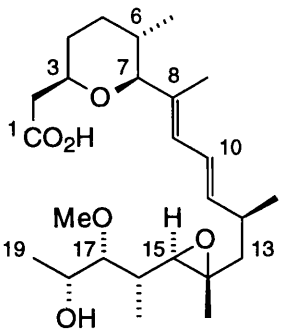
A	51%	PCC, NaOAc, CH_2Cl_2, rt
B	77%	MeMgCl, THF, –60°C → 0°C
C	51%	PCC, NaOAc, CH_2Cl_2, rt
D	37%	H_2C=CHMgBr, THF, –78°C → 0°C
E	91%	PBr_3, Et_2O, 0°C
F	84%	Ph_2POEt, THF, Δ
G	---	(a) nonanal, NaH, THF, 45°C;
	94%	(b) H_2SO_4, MeOH, rt, *E:Z* = 85:15

Addition of a vinyl Grignard reagent to ketone **296** yielded 37% of isomeric alcohols **297** together with a significant quantity of vinyl ketone adducts (31%), the result of nucleophilic addition to both the ketone and ester moieties present in **296**. Treatment of **297** with PBr_3 yielded the geometrically pure rearranged *E*-allylic bromide **298**; a standard Michaelis-Arbuzov reaction then gave the desired second fragment, phosphine oxide **265**, as a crystalline solid.

To ascertain the selectivity of the projected Horner-Wittig olefination, nonanal was selected as a simplified model for fragment **269**. Under the illustrated conditions, olefination with phosphine oxide **265** resulted in concomitant ester hydrolysis. The product mixture was re-esterified to aid purification and yielded the herboxidiene model compound **299** in 94% yield (from **265**) with *E:Z* = 85:15 about the newly formed olefin. The above summary concludes Banwell's published studies on herboxidiene to date.

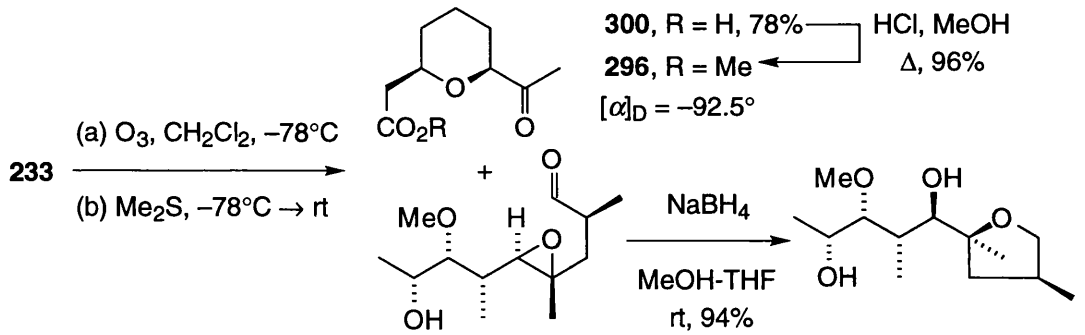
5.3. Determination of the absolute configuration of herboxidiene by degradation and synthetic studies

To aid synthetic chemistry programs towards herboxidiene, a Swiss group in collaboration with the late Professor Oppolzer, set out to elucidate the absolute configuration of the natural product *via* unambiguous independent asymmetric synthesis of certain degradation fragments[119]. Their efforts were facilitated by an X-ray analysis of crystals of herboxidiene which yielded the complete relative stereochemistry[120]. Ultimately, the Swiss study not only succeeded in determining the structure of herboxidiene as **233**, but also provided a wealth of information concerning its stability under a variety of conditions.



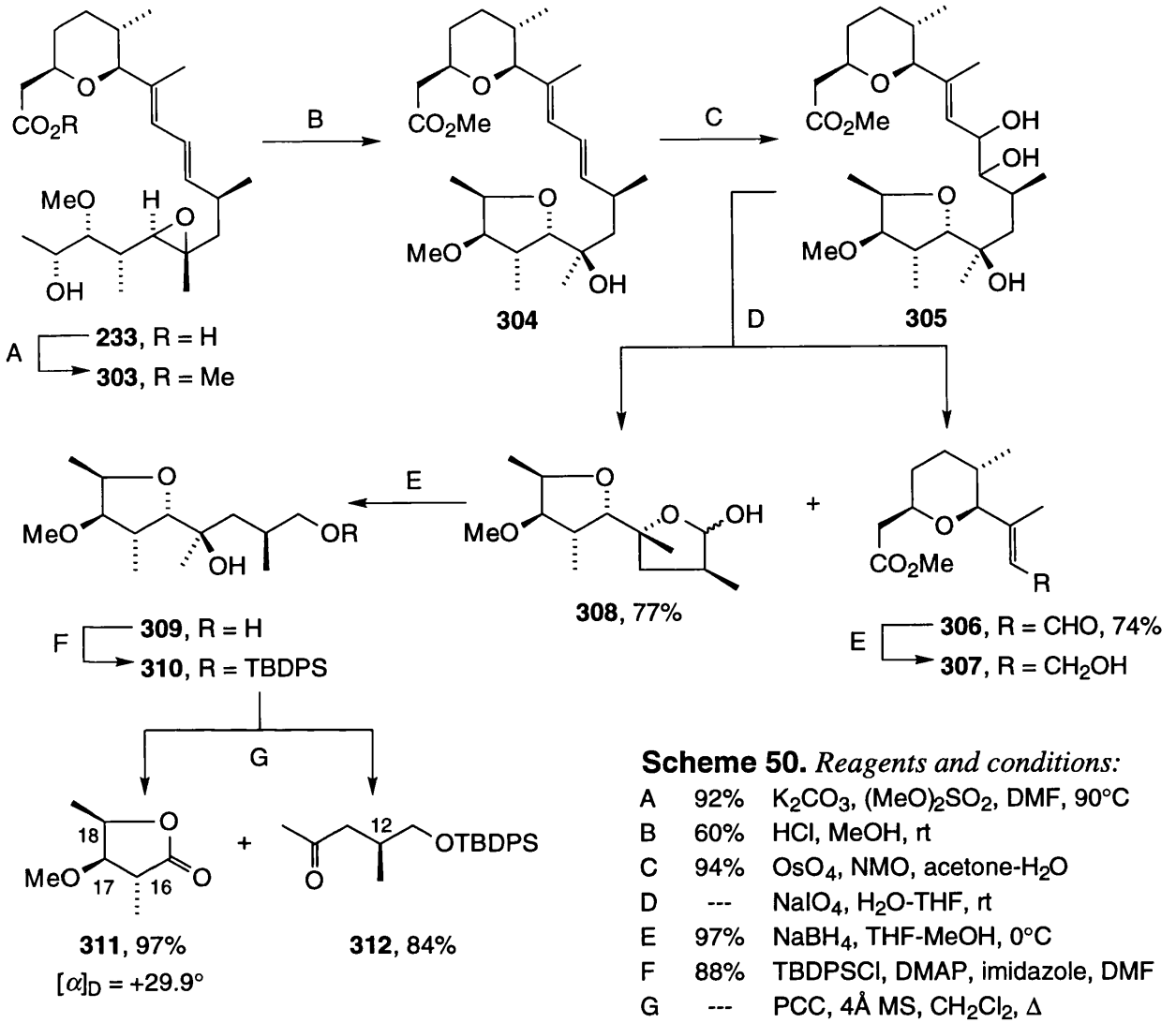
herboxidiene (**233**)

Ozonolysis of herboxidiene afforded the acid **300** (subsequently esterified to ease purification) and the unstable aldehyde **301** (Scheme 49). The latter compound was immediately reduced to yield an alcohol which spontaneously cyclised to the tetrahydrofuran **302**. Fragment **302** was regarded as useless for the preparation of semi-synthetic derivatives and so a new degradation procedure was developed (see Scheme 50).



Scheme 49

Following esterification of herboxidiene, the methyl ester **303** was treated with anhydrous HCl to yield the tetrahydrofuran adduct **304**. Issac and co-workers[104] reported the same transformation catalysed under basic conditions (*cf* Scheme 39). Osmium(VIII)-catalysed dihydroxylation of the diene selectively oxidised the less hindered C10-C11 olefin to afford diol **305** as a mixture of diastereoisomers. Standard oxidative cleavage produced bicyclic lactol

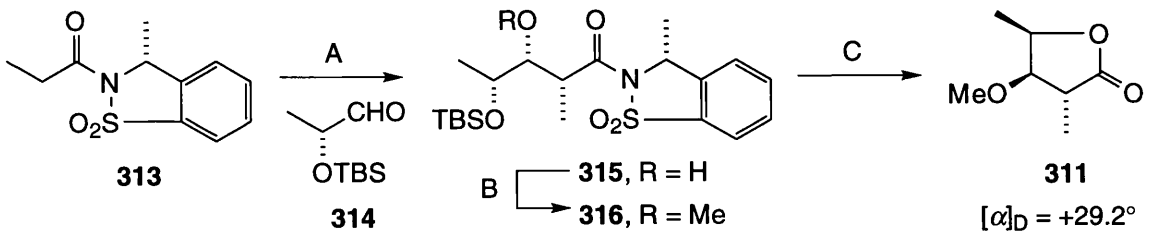


Scheme 50. *Reagents and conditions:*

A	92%	K_2CO_3, $(MeO)_2SO_2$, DMF, 90°C
B	60%	HCl, MeOH, rt
C	94%	OsO_4, NMO, acetone-H_2O
D	---	$NaIO_4$, H_2O-THF, rt
E	97%	$NaBH_4$, THF-MeOH, 0°C
F	88%	TBDPSCl, DMAP, imidazole, DMF
G	---	PCC, 4Å MS, CH_2Cl_2, Δ

308 and dienal **306**. The latter compound is very closely related to the dienal **238** used by Kocienski *et al* in their first total synthesis of the herboxidiene skeleton[46]. Both of these compounds were subsequently reduced to the corresponding alcohols. Selective mono-protection of diol **309** was followed by a further oxidative fragmentation: treatment of the hydroxy tetrahydrofuran with PCC yielded lactone **311** and ketone **312**. At this stage tetrahydropyran **296** and the γ-lactone **311** were chosen as targets for independent asymmetric synthesis.

The lactone **311** was totally synthesised stereospecifically in short order *via* the boron mediated aldol reaction between (*R*)-lactate derived aldehyde **314** and the propionyl saccharin based sultam **313**. Although the auxiliary and aldehyde comprised a mis-matched pair the all *syn* aldol adduct **315** was obtained with greater than 95% diastereoselectivity. Methylation was followed by silyl ether deprotection with 5% HF which resulted in concomitant lactonisation (Scheme 51). Spectroscopic and optical rotation data for the synthetic material matched that obtained previously for the herboxidiene degradation fragment.

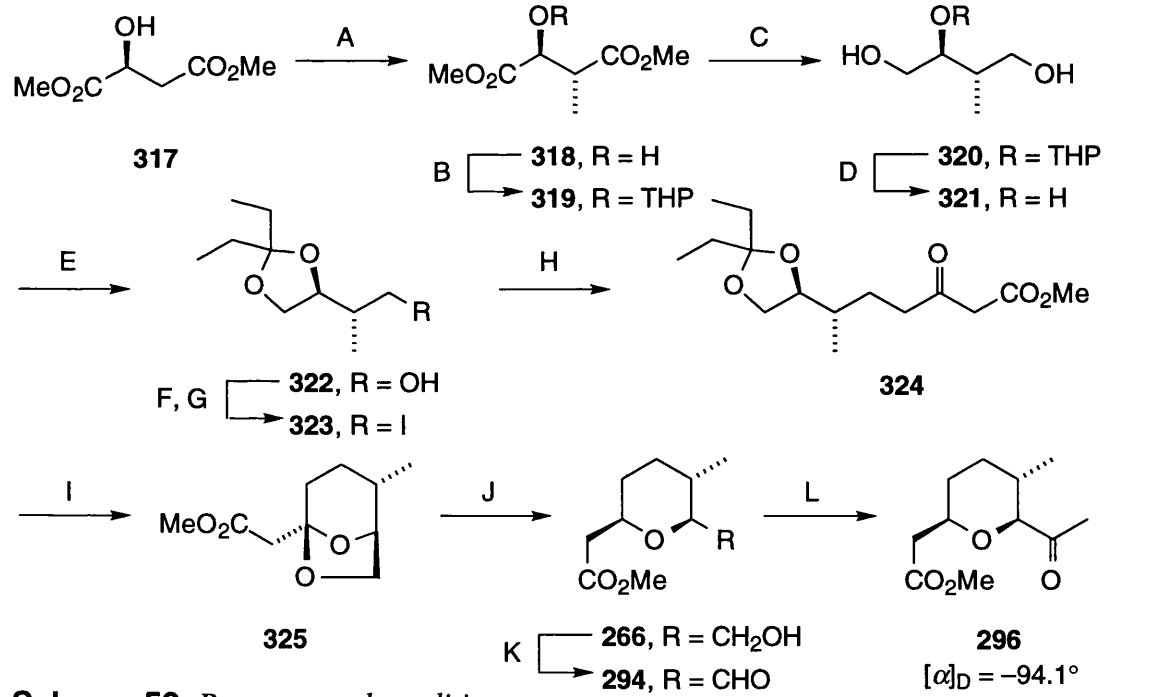


Scheme 51. *Reagents and conditions:*

A	---	(a) Et_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, –5°C;	B	98%	Me_3OBF_4, proton sponge®, CH_2Cl_2, rt
	72%	(b) aldehyde **O2**, –78°C	C	75%	5% HF, MeCN, rt

Synthesis of the oxane degradation fragment **296** was achieved *via* a very different strategy to the similar line adopted by both Kocienski and Banwell (see Schemes 42 and 46 respectively). Rather than employ a conjugate addition reaction to form the requisite heterocycle, the Swiss group utilised the stereodefined reductive ring opening of a bicyclic ketal to access the *cis* tetrahydropyran (Scheme 52).

Commencing with diastereoselective alkylation of (*S*)-dimethyl malate **317**, standard steps yielded the ketodioxolane **324**. Intramolecular transacetalisation afforded the bicyclic ketal



Scheme 52. *Reagents and conditions:*

A	---	(a) LDA, THF, –78°C;	H	74%	methyl acetoacetate, LDA,
	66%	(b) MeI, –78°C, dr = 91:9			THF-HMPA, 0°C
B	↓	TsOH, DHP, CH_2Cl_2, rt	I	87%	TsOH, CH_2Cl_2, Δ
C	↓	$LiAlH_4$, Et_2O, 0°C	J	71%	Et_3SiH, $TiCl_4$, CH_2Cl_2, –78°C → –25°C
D	↓	Amberlite IR120, MeOH, rt	K	---	(a) $(COCl)_2$, DMSO, CH_2Cl_2, –78°C;
E	56%	TsOH, Et_2CO-THF, Δ		87%	(b) Et_3N, –78°C → rt
F	87%	TsCl, pyridine, 0°C → rt	L	---	(a) MeMgBr, Et_2O, –78°C → –40°C;
G	92%	NaI, acetone, Δ		64%	(b) CrO_3, H_2SO_4, acetone, rt

325; the reduction method of Kotsuki[121] then gave the *cis* oxane **266** as a single diastereoisomer. Final transformation to the degradation fragment **296** was then achieved in three steps reminiscent of Banwell's end-game (see Scheme 48). Again it was found that the synthetic and degraded fragments had identical spectroscopic and optical rotational properties.

The studies presented above conclusively prove the absolute stereochemistry of herboxidiene as: 3*R*, 6*S*, 7*S*, 12*S*, 14*R*, 15*R*, 16*R*, 17*R*, 18*R*.

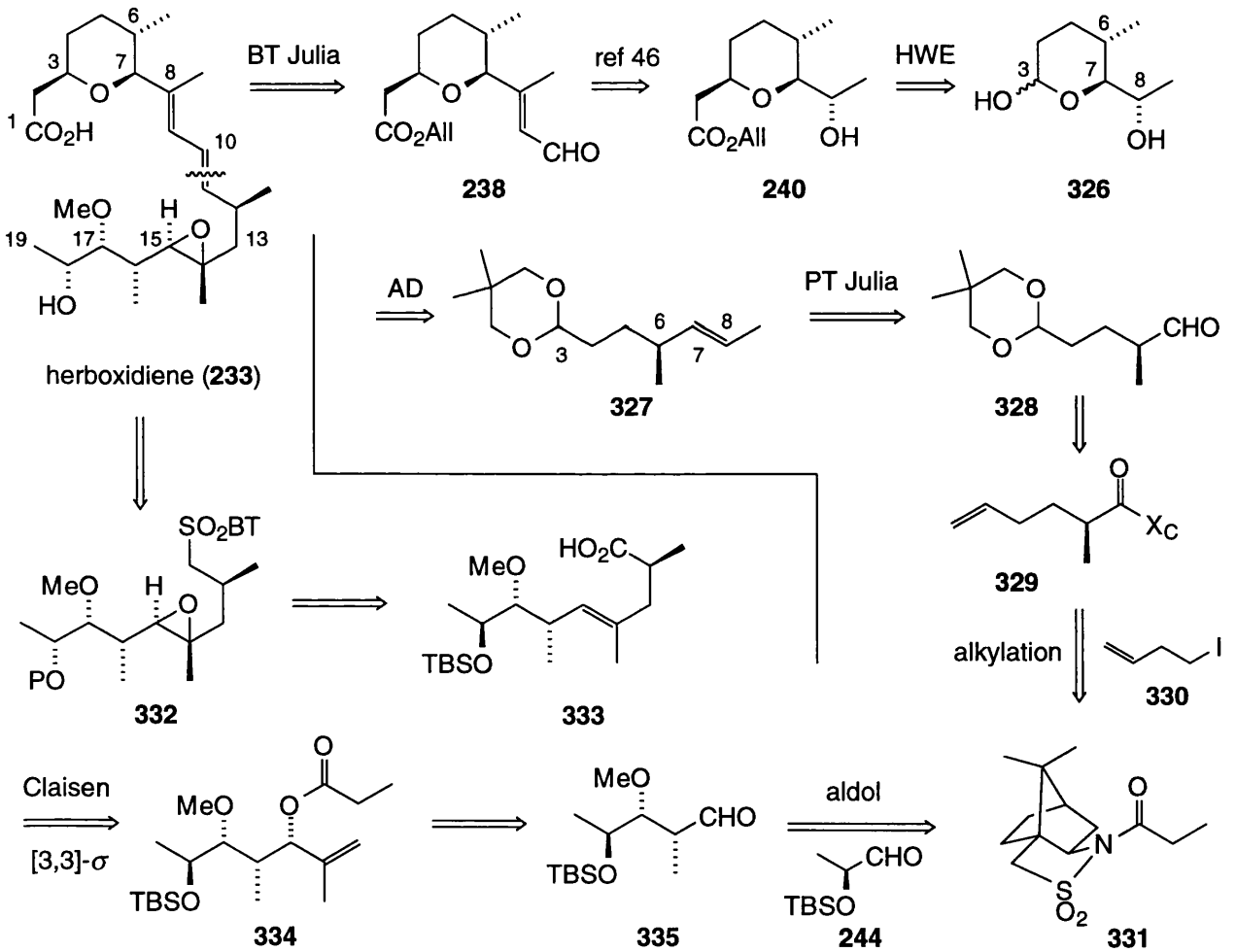
Recent reports suggest that the biology of herboxidiene is not restricted to mere herbicidal activity. The polyketide has been found to up-regulate the gene expression of low density lipoprotein receptors[122] and also block the cell-cycle at the G2 phase in human tumour cells[123]. Such findings taken together with the now definite structural assignment further validate new synthetic endeavours towards herboxidiene.

6. Total Synthesis of Herboxidiene

To fully assess the scope of any new methodology, it must be applied in ever more complex situations. Herein we present the first total synthesis of herboxidiene (**233**), a particularly valid target molecule (see Chapter 5), and an excellent vehicle for demonstrating the utility of the one-pot Julia olefination to solve demanding synthetic problems.

6.1. Retrosynthetic analysis

Our initial synthetic plan to construct herboxidiene is laid bare below (Scheme 53). A one year time constraint for the synthesis necessitated a fairly conservative approach which built in part on the previous Kocienski group synthesis of herboxidiene A[46] and also borrowed ideas from Banwell[106].



Scheme 53

In common with the synthesis of herboxidiene A by Smith and Kocienski[46] a BT mediated one-pot Julia olefination reaction was chosen as a device for advanced fragment linkage to forge the 10*E* double bond. However, here we desired to increase the scope of the coupling and to

further demonstrate its mildness by employing a sulfone fragment **332** already replete with the C14-C15 oxirane ring. Following the alkenation reaction, deprotection of the masked C1 acid and C18 hydroxyl function would then furnish herboxidiene directly. Aldehyde **238** is the same coupling partner used previously and so its competency as an electrophile for the Julia olefination was not in any doubt. The chemistry already developed to synthesise **238** from alcohol **240** was to be taken verbatim from Kocienski[46].

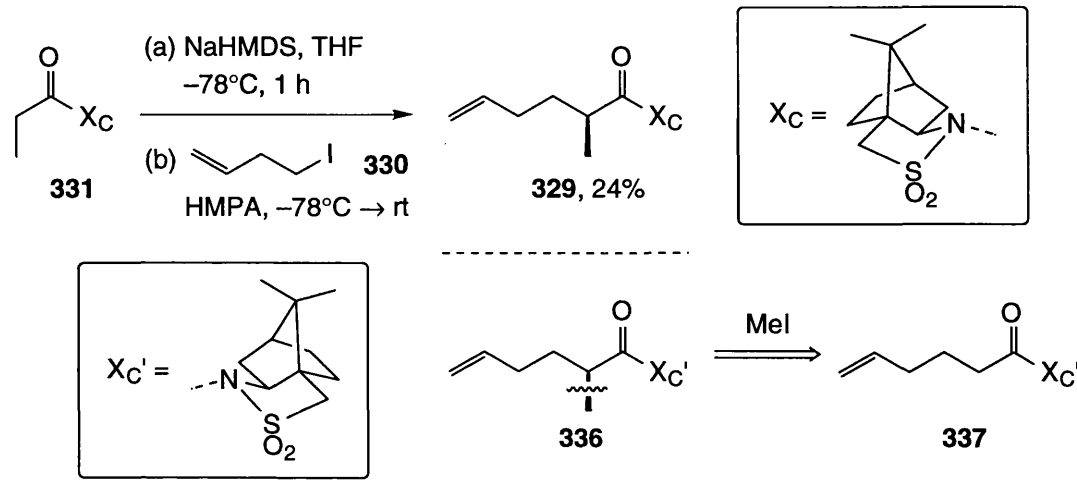
A linch-pin in the herboxidiene A synthesis was the use of vinyl carbamate **239** as a synthon for both C11-C19 sulfone **237** and dienal **238**. However, the stereochemistry inherent in **239** is not appropriate for direct elaboration to sulfone **332**, and now could only be used efficiently to make aldehyde **238** *via* the route previously described (Scheme 42). For this reason, and to add originality to our synthesis, a completely new route to **240** was devised. A tandem Horner-Wadsworth-Emmons (HWE) - conjugate addition sequence was to furnish **240** directly from hydroxylactol **326**; it was hoped that protection of the C8 hydroxyl would be superfluous. Lactol **326** could be derived in turn from the Sharpless asymmetric dihydroxylation (AD)[124] of *trans* olefin **327**. Herein lies an excellent opportunity to road-test our own PT modification of the one-pot Julia reaction; it was anticipated from earlier precedent (see Chapter 2) that condensation of the potassium metallate of $PTSO_2Et$ (**347**) with aldehyde **328** would yield alkene **327** with excellent stereoselectivity. Standard steps commencing with the asymmetric alkylation of acyl sultam **331** with homoallyl iodide (**330**) would yield **328**.

For the synthesis of sulfone **332** a fusion of chemical ideas from Kocienski[46], Banwell[106] and Oppolzer[119] were harvested. A series of oxidation level changes and standard manipulations of acid **333** (a diastereoisomer of Banwell group intermediate **282**) would yield **332**. A key step in the void **333** to **332** would be a C18 hydroxyl directed epoxidation of the trisubstituted olefin (*cf* Kocienski, Scheme 43, Chapter 5). To gain the necessary stereocontrol an unnatural configuration of the C18 hydroxyl function was implicit (*vide infra*) obviously requiring subsequent correction. Chemistry reminiscent of Banwell's herboxidiene work would be adapted to procure acid **333** from aldehyde **335**. Here it was anticipated that a [3,3] sigmatropic rearrangement of the *Z*-silyl ketene acetal derived from propionate **334** would yield **333** in a predictable manner. Finally, some Oppolzer chemistry would be employed to synthesise **335** *via* a boron-mediated aldol reaction between aldehyde **244** and sultam **331** (a common intermediate to both **332** and **238**). The aldehyde **244** is itself honed from cheap ethyl (*S*)-lactate[46] and comprises a 'matched' pair with sultam **331**, thus aldol stereoselectivity was expected to be excellent.

6.2. Synthesis of alcohol 240

Our synthesis of the tetrahydropyran **240** experienced its first problems early on. Alkylation of (2*R*)-*N*-propanoylbornane-10,2-sultam (**331**) with homoallyl iodide (**330**) under the standard

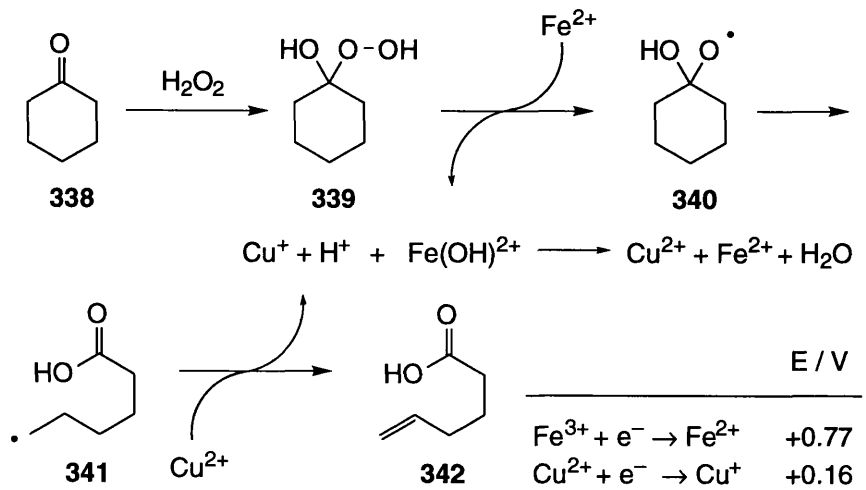
conditions developed by Oppolzer[125] proved disappointing (Scheme 54). Although diastereoselectivity appeared to be good, low yields were a constant problem and the product was difficult to separate from the highly crystalline starting material **331**. In addition, homoallyl iodide is not commercially available and had to be synthesised from the expensive chloride *via* a standard Finkelstein reaction[126].



Scheme 54

Oppolzer has disclosed that homoallyl halides do not react smoothly with acyl sultam enolates[125] despite the fact that other non-activated halides pose no problem. Rather than dwell on such a minor set-back we elected to change the sense of the alkylation; employing the antipodean auxiliary X_C'H with a 5-hexenoyl substituent (*ie* acyl sultam **337**) and the highly reactive methyl iodide as electrophile.

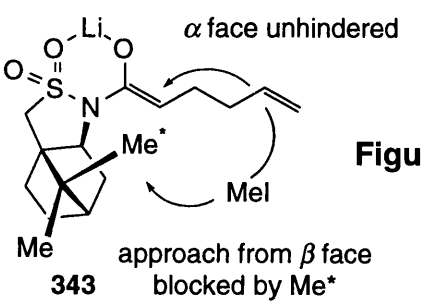
Derivatives of 5-hexenoic acid are not commercially available and so we turned to an interesting synthesis of the parent acid (**342**) developed by Rust[127] (Scheme 55). The process relies on the oxidation and reduction of free radicals by metal salts. A ketone hydroperoxide (**339**), formed by the action of hydrogen peroxide on cyclohexanone (**338**), is first reduced by an Fe(II) salt.



Scheme 55

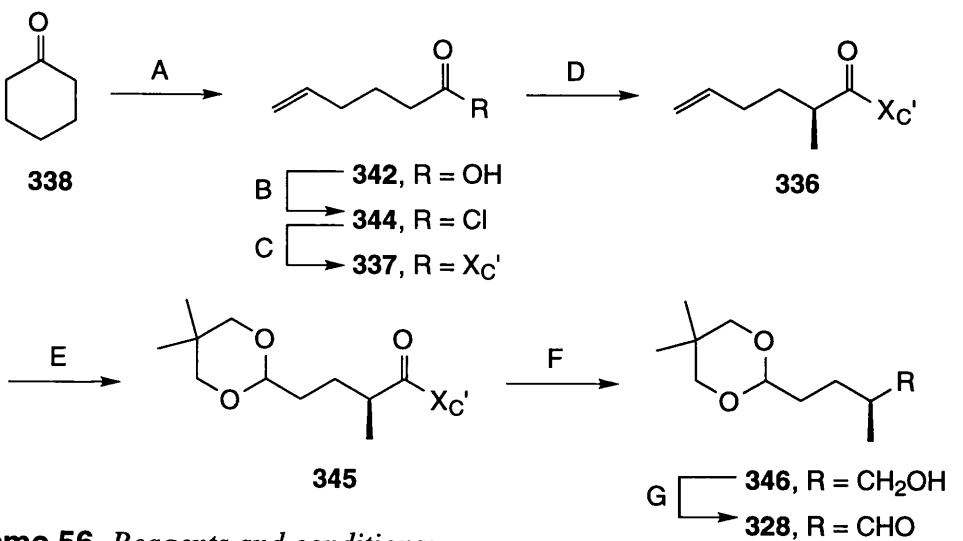
The resulting oxygen centred radical **340** rapidly ring-opens to afford carbon radical **341**. Oxidation of the latter species by Cu(II) then yields 5-hexenoic acid (**342**). The Cu(I) and Fe(III) salts formed comprise a redox pair and the Fe(II) and Cu(II) species needed to effect the overall conversion are regenerated. In practice, optimum yields of 5-hexenoic acid (**342**) are not obtainable when working with catalytic quantities of the metal salts; however, the aqueous metal ion solution can be recycled many times.

With a ready source of 5-hexenoic acid to hand good progress was made (Scheme 56). Sultam **337** was synthesised by standard methodology and alkylation of its lithium *Z*-enolate with methyl iodide suffered from none of the previously encountered set-backs. In common with a recent synthesis of Ibuprofen[128], we found dimethyl propylene urea (DMPU) a sufficiently powerful co-solvent to effect the alkylation. Slow addition of the base (BuLi) to **337** *via* syringe pump was advantageous; a fast addition lead to some deprotonation α to the sulfone of the chiral auxiliary. The stereoselectivity of the alkylation can be easily predicted *via* the standard model presented in Figure 9[125,129]. A six-membered lithium chelate between the enolate oxygen atom and an auxiliary sulfone oxygen atom locks the conformation; approach of the electrophile then occurs from the face not shielded by Me*.



343

Figure 9

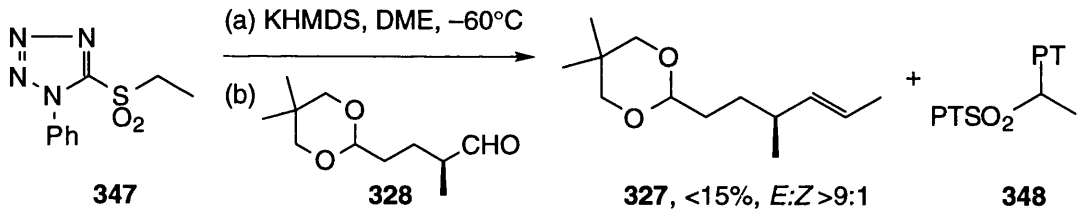


Scheme 56. *Reagents and conditions:*

A 37% (a) $H_2O_{2(aq)}$, 35°C → –5°C, 40 min; (b) $CuSO_4$, $FeSO_4$, $H_2SO_{4(aq)}$, 0°C → rt, 5 h
B 75% $SOCl_2$, 80°C, 30 min
C 94% (a) (2*S*)-bornane-10,2-sultam, NaH, PhMe, rt, 1 h; (b) acid chloride **344**, O/N
D 80% (a) BuLi, THF, –80°C, 2 h; (b) MeI, DMPU, –80°C → rt, O/N, dr > 98:2 (recrys.)
E --- (a) O_3, MeOH-CH_2Cl_2 (1:3), –78°C, 2 h; (b) Me_2S, –78°C → rt, O/N;
72% (c) 2,2-dimethylpropane-1,3-diol, pTsOH, PhMe, Δ (–H_2O), O/N (recrys.)
F 93% $LiAlH_4$, Et_2O, rt, O/N
G 96% SO_3•pyridine, Et_3N, DMSO, rt, 30 min

The crystalline alkylated product **336** was formed with excellent stereoselectivity. A simple recrystallisation yielded analytically pure material with no detectable isomeric contaminants in 80% yield. Ozonolysis of **336** in MeOH-CH_2Cl_2 (1:3) yielded a mixture of the corresponding aldehyde (minor) and dimethyl acetal (major) after reductive work-up. The mixture was immediately taken up in toluene and acetalised/transacetalised to the 1,3-dioxane **345**. The dioxane protecting acetal was chosen to lend increased weight to olefin **327**, an otherwise potentially volatile intermediate. **345** was also a solid and again only needed recrystallisation to yield pure compound in 72% overall yield from **336**. Reductive removal of the chiral auxiliary followed by oxidation of the resulting alcohol **346** yielded aldehyde **328** in excellent yield. It is worth commenting that alcohol **346** turned out to be one of the most sensitive intermediates of the entire synthesis; under mildly acidic conditions (*eg* dissolution in unbuffered $CDCl_3$) the 1,3-dioxane ring was opened by the distal hydroxyl to afford the corresponding oxane.

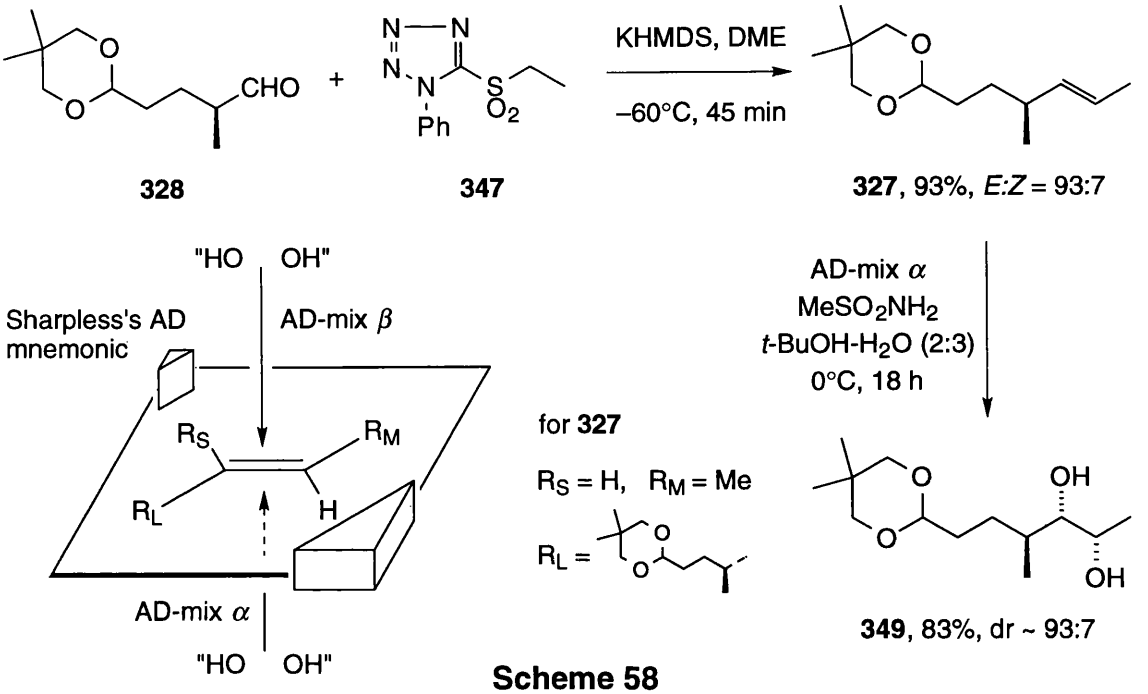
Initial attempts to condense aldehyde **328** with the potassium metallate of PT sulfone **347** proved disheartening (Scheme 57). Under the pre-metallation protocol which had previously been so successful in the PT series (see Chapter 2), at most a 15% yield of **327** was obtained albeit with excellent *E:Z* selectivity (>9:1). Unreacted aldehyde was typically recovered from these failed experiments. The low yields were rationalised as the result of self-condensation of the potassium metallate of the sterically unencumbered **347**. Although the isolation of bisheterocyclic adduct **348** (the expected product of self-condensation) was not vigorously pursued here, in a separate study it has been prepared under identical metallation conditions[72].



347 **328** **327**, <15%, *E:Z*>9:1 **348**

Scheme 57

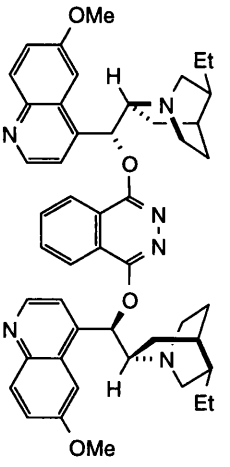
Again it is likely that an 'umpoled' approach could save the day; a metallated PT sulfone derived from alcohol **346** would be too bulky to self-condense. However, a reversal in the coupling sense adds one extra step to the linear sequence of the synthesis and would involve the use of acetaldehyde, a compound notoriously difficult to purify and dry for small scale work. An alternative was to apply Barbier conditions to the current system of **328** and **347**, although then racemisation of the aldehyde was a possibility. Such fears proved unfounded; addition of potassium hexamethyldisilazide to a mixture of **328** and **347** in DME at –60°C yielded 93% of the olefin **327** with *E:Z* = 93:7 (Scheme 58). The product was degraded back to alcohol **346** and the derived mandelate ester analysed by NMR; no detectable racemisation was found (see Experimental Section for details). Despite aldehyde **328** being thermodynamically more acidic than the PT sulfone **347**, the kinetic acidity of the latter is obviously higher.



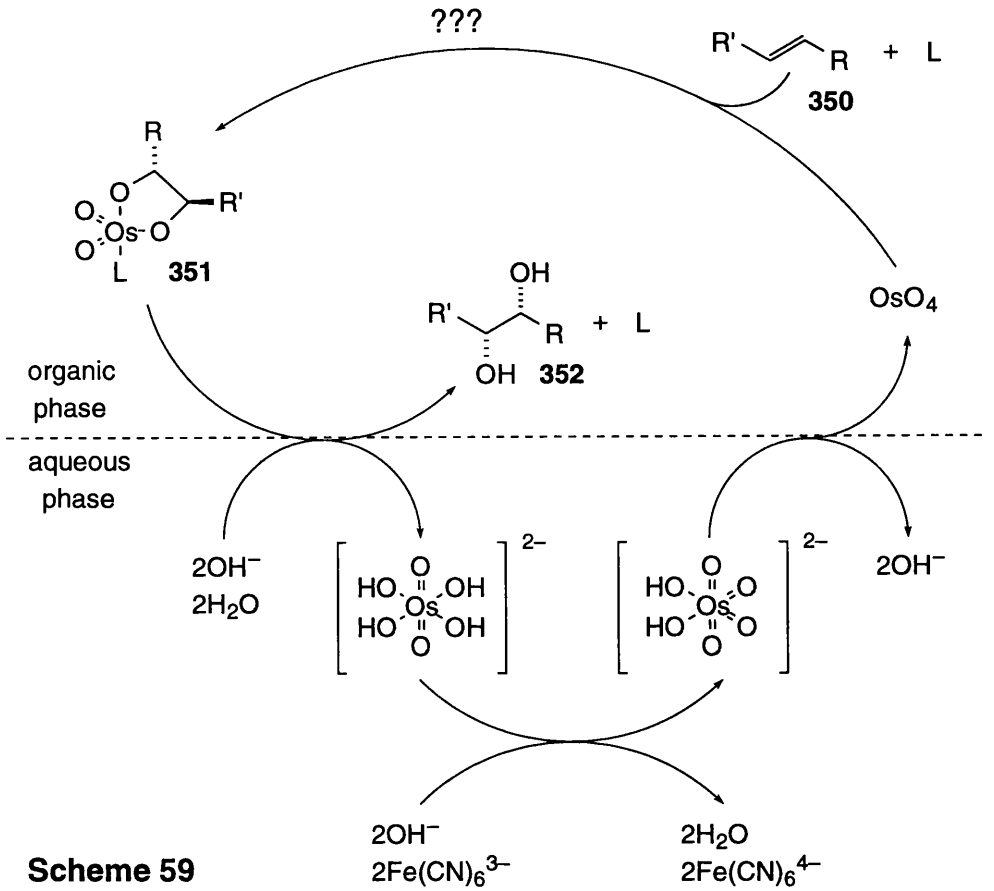
Scheme 58

trans-1,2-Disubstituted olefins comprise one of the optimum classes of substrate for the Sharpless asymmetric dihydroxylation[124] and alkene **327** proved no exception. Under the most standard reported reaction conditions[130] commercially available AD-mix α was chosen to oxidise **327** based on the illustrated mnemonic device. Two diastereoisomers of **349** were formed in 83% yield in a distribution which reflected the *E:Z* ratio of the starting material (dr ~ 93:7). A total of four isomers should be formed, the other two isomers were presumably too insignificant to be detected by simple NMR experiments.

As commented by Nicolaou, use of the pre-formulated AD-mixes has reduced the 'commonly perceived "black art" of organic synthesis to a nearly embarrassing level of simplicity'[25]. The commercially available AD-mixes contain: a catalytic quantity of an involatile source of OsO_4 ($K_2OsO_2(OH)_4$), a chiral cinchona alkaloid derived ligand (AD-mix α contains the $(DHQ)_2$-PHAL ligand), a stoichiometric oxidant ($K_3Fe(CN)_6$), and K_2CO_3 to maintain the correct pH level. The reaction is carried out in a two-phase system of *t*-BuOH and H_2O, the gross reaction manifold is illustrated below (Scheme 59). For all but terminal olefins hydrolysis of the osmate ester **351** becomes rate-limiting. In such cases the addition of an organic sulfonamide assists in the saponification, freeing the product **352** and ligand L and returning the Os(VI) by-product to the catalytic cycle. The presence of $MeSO_2NH_2$ can accelerate an AD reaction by up to 50 times.

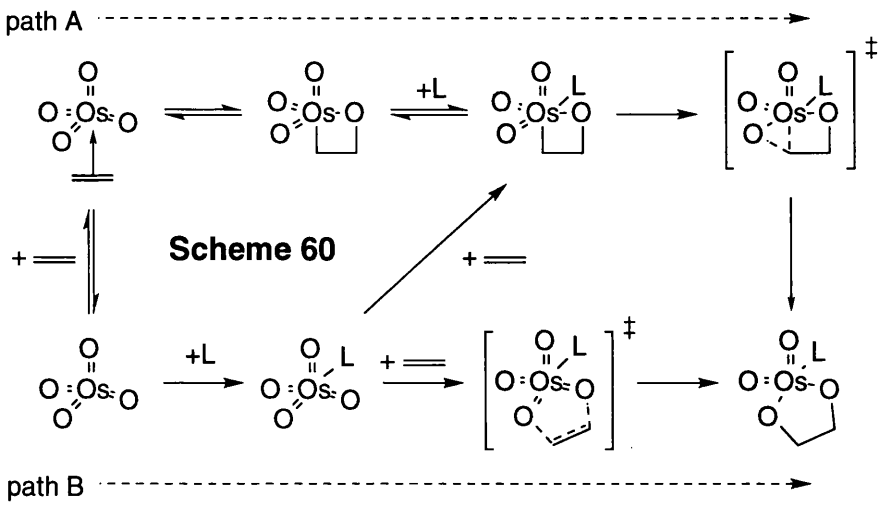


$(DHQ)_2$-PHAL



Scheme 59

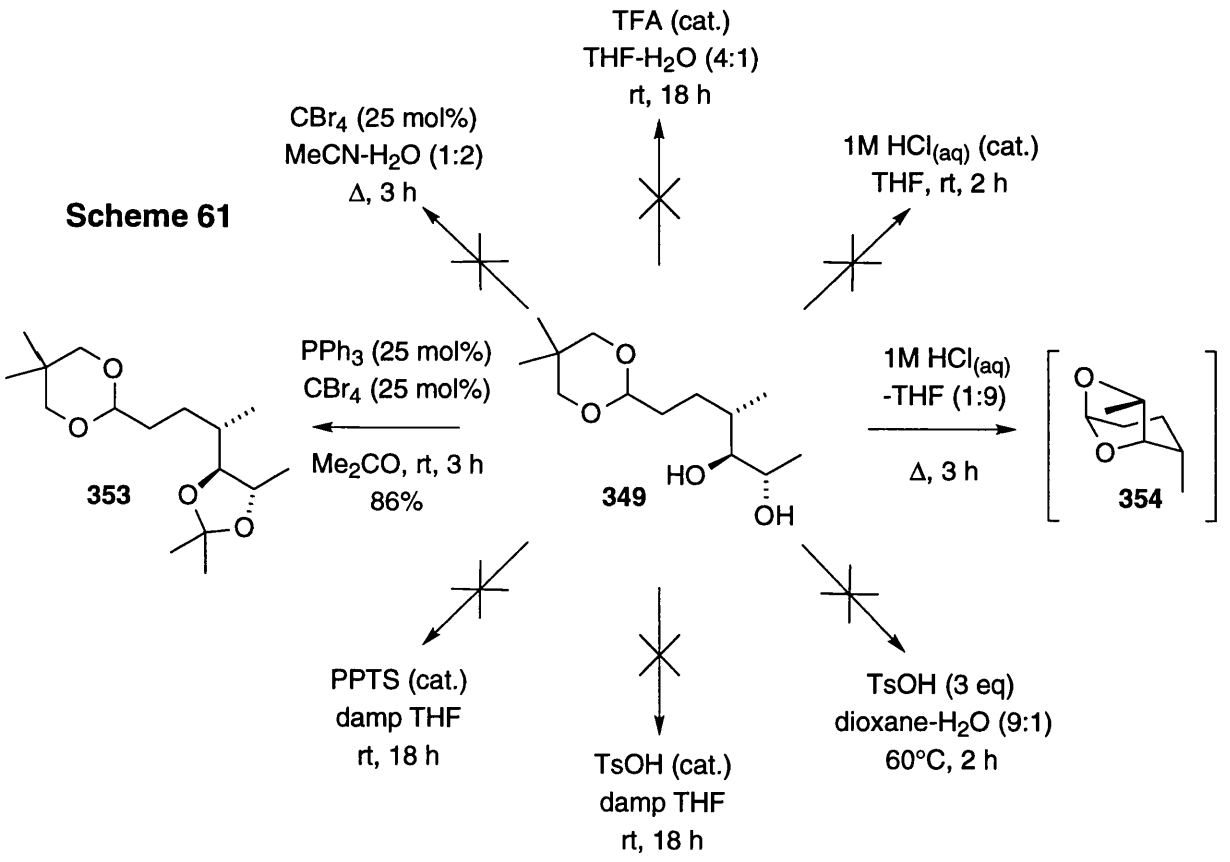
The precise mechanism for the crucial oxidation step (**350** to **351**) has been the subject of great controversy in the recent literature. For many years Sharpless held with the notion that a stepwise [2+2] mechanism involving the formation of an osmaoxetane was followed by ligand assisted ring expansion to form the osmium glycolate ligand complex **351**[124] (see Scheme 60, path A). Corey and Noe have always supported the direct [3+2] mechanism originally proposed by Criegee[131] (path B) and have produced a critical analysis of the two pathways[132]. Remarkably a recent report by Sharpless comparing experimental and theoretical kinetic isotope effects, actually supports a rate-limiting [3+2] cycloaddition[133]. At which exact stage the ligand becomes involved is still under debate.



Whatever the exact nature of the oxidation step, key to asymmetric induction is that oxidation of the olefin with OsO_4 alone is very slow compared to reaction of the olefin with a complex of OsO_4 and the chiral ligand (the principle of *ligand accelerated catalysis*[134]). Coordination of the chiral tertiary amine ligand $(DHQ)_2$-PHAL to OsO_4 greatly enhances its reactivity towards olefins. A substrate molecule is therefore within a chiral environment when oxidised, ensuring asymmetry. The mnemonic given in Scheme 58 is a crude representation of the shape of the binding pocket within an "OsO_4+L" complex: the SE quadrant is extremely sterically demanding and can normally only admit a hydrogen atom, the NW corner is moderately demanding whilst conversely the SW quadrant represents an area particularly attractive to aromatic or long aliphatic substituents[124]. There is thus an intrinsic shape incompatibility with *cis*-1,2-disubstituted olefins; the highest recorded enantioselectivities observed in such cases are only 80% ee and require a special indoline based ligand. The use of our PT sulfone mediated Julia reaction to generate **327** with high *trans* selectivity was thus of great importance and makes it a natural partner to the AD process.

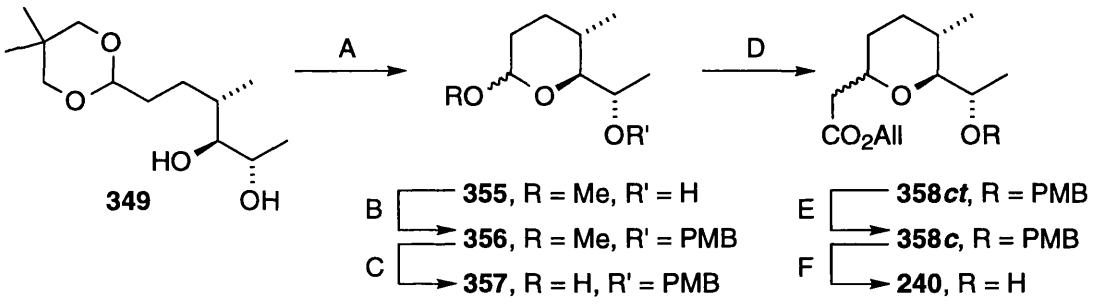
With the diol **349** in hand we attempted the seemingly trivial task of acetal hydrolysis. As outlined below (Scheme 61) a variety of conditions were screened for the hydrolysis; far from being a facile process, only the most aggressive of conditions tested (1M $HCl_{(aq)}$, THF, reflux) succeeded in freeing the substrate from the 1,3-dioxane acetal. However, rather than liberate the desired hydroxylactol **326**, a subsequent dehydration yielded the odoriferous bicyclic acetal **354**. The structure of **354** could only confirmed by LRMS due to its extreme volatility. In an attempt to remove the cyclic acetal under milder conditions, the deprotection procedure of

Scheme 61



Kerr[135] was employed unsuccessfully: upon treating dioxane **349** with PPh_3 and CBr_4 in acetone, the acetonide **353** was produced in 86% yield. In a final attempt to procure lactol **326**, dioxane **349** was transacetalised with ethylene glycol to yield the corresponding 1,3-dioxolane. Exposure of the labile dioxolane to Kerr's process also resulted in the formation of bicycle **354**. It was concluded that hydroxylactol **326** was not a viable intermediate in our synthesis, spontaneously dehydrating under particularly mild conditions.

To prevent the dehydration of lactol **326**, the C8 hydroxyl group must be provided with a suitable acid stable protecting group. Acid catalysed methanolysis of **349** provided methyl acetal **355** as a mixture of diastereoisomers in favour of the α anomer (α:β = 3:1, Scheme 62). Selective PMB protection of the free C8 carbinol was then possible in 93% yield by treatment of the potassium alkoxide with PMBCl in the presence of tetrabutylammonium iodide (TBAI). Careful hydrolysis of the resulting ether **356** with aqueous acetic acid then yielded an alternative lactol **357** suitable for our planned tandem HWE-Michael sequence. The acetal hydrolysis had to be carefully monitored, excessive reaction time lead to PMB removal and formation of bicycle **354** again became a problem. Terminating the reaction before completion enabled **357** to be isolated in 74% yield (α:β = 1.4:1) together with 18% of recovered starting material.



Scheme 62. *Reagents and conditions:*

A 73% TsOH, MeOH, rt, 3 d, α:β = 3:1
B 93% (a) KHMDS, THF, 0°C, 20 min; (b) PMBCl, TBAI, 0°C → rt, 24 h
C 74% AcOH-THF-H_2O (3:2:2), 65°C, 2 h, α:β = 1.4:1
D 82% allyl diethylphosphonoacetate, Cs_2CO_3, THF, Δ, 18 h, *cis:trans* = 4:6
E 89% *t*-BuOK, THF, –65°C, 10 min, pure *cis* isomer
F 95% DDQ, H_2O-CH_2Cl_2 (1:15), rt, 30 min

Treatment of the lactol **357** with allyl diethylphosphonoacetate in the presence of Cs_2CO_3 in refluxing THF lead to the formation of a mixture of *cis* (**358*c***, desired) and *trans* (**358*t***, undesired) oxane products (82%) in the ratio 4:6 respectively. The initial HWE reaction would yield a *trans* enoate intermediate with high stereoselectivity[136], and the subsequent *in situ* Michael addition is essentially irreversible since protracted heating of the reaction mixture led to no change in the ratio of products. The distribution of products therefore reflects the kinetic selectivity of an intramolecular conjugate addition of a δ-hydroxyl group to a tethered *E*-enoate

and is in accord with the model proposed by Banwell[116] (see Scheme 47, Chapter 5). To obtain the *cis* oxane **358*c*** selectively as the kinetic product would require an intermediate *Z*-enoate and thus an expensive Still-Gennari phosphonate[27]; this tack was employed by the Banwell group in their synthesis of herboxidiene tetrahydropyran fragment **266**[107] (see Scheme 46, Chapter 5).

It is known from Maurer's synthesis of methyl (*cis*-6-methyloxan-2-yl)acetate[137] (a derivative of civet (*Viverra civetta*) extract), and Kocienski's synthesis of herboxidiene A[46], that alkoxide bases can promote the equilibration of our tetrahydropyranyl system to the all equatorial *cis* isomer. Treatment of the mixture of oxanes **358*ct*** (*cis:trans* = 4:6) with *t*-BuOK in THF at –78°C resulted in rapid equilibration to **358*c*** which was isolated in 89% yield. Careful examination of the proton NMR spectrum of **358*c*** enabled complete assignment of the relative stereochemistry around the ring. Diagnostic axial-axial *J*-couplings were discernible for both H3 and H7 (Figure 10). The relative stereochemistry of the stereogenic centre at C8 is thus also fixed since it was derived from the same dihydroxylation event which determined the configuration at C7. Finally, oxidative removal of the PMB ether moiety from **358*c*** was effected by DDQ in aqueous CH_2Cl_2 and yielded the target alcohol **240** in 95% yield. The free alcohol was identical in all respects to that synthesised previously by Kocienski and Smith[46].

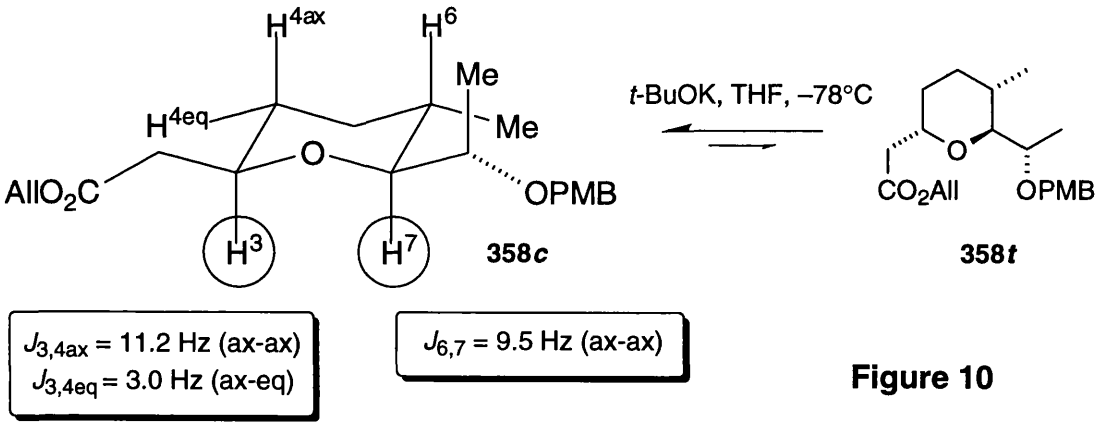


Figure 10

6.3. Synthesis of sulfone 332

Construction of sulfone **332** began simply enough with a standard boron-mediated aldol reaction between propionyl sultam **331** and aldehyde **244** (Scheme 63)[138]. Pre-complexation of sultam **331** with diethylboron triflate (generated *in situ* from triethylborane and triflic acid) facilitates a highly selective deprotonation by Hünig's base to form the (*Z*)-boron enolate[129,139]. Subsequent addition of aldehyde **244** initiates an aldol reaction which proceeds *via* the Zimmerman-Traxler[64] transition state illustrated in Figure 11. The natural Felkin preference of **244** for attack from its *re* face is matched by the intrinsic bias of the camphor sultam chiral auxiliary, here oriented to minimise dipole-dipole repulsion. The crystalline *syn* aldol **359** was thus produced with excellent diastereoselectivity and subsequent recrystallisation furnished 75% of the adduct as a single isomer.

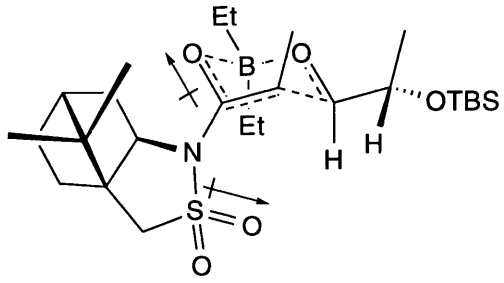
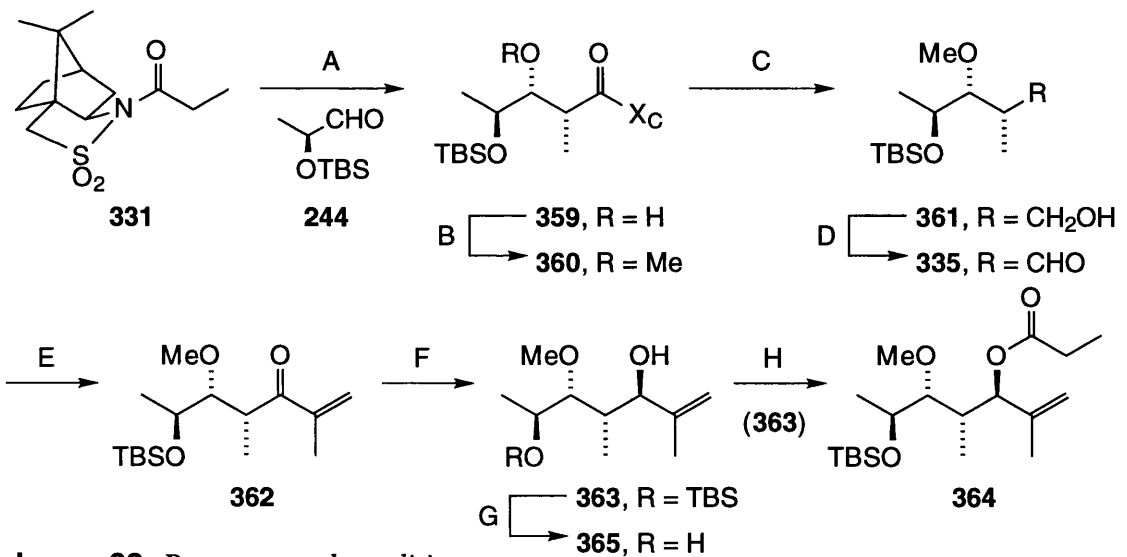


Figure 11

To effect methylation of the aldol **359** a combination of proton sponge® (1,8-bis(dimethylamino)naphthalene) and methyl triflate was employed. The conditions were derived as a cheap hybrid formulation of two other costly mild methylation procedures popularised by Evans[140]: (a) methyl triflate (inexpensive) with 1,6-di-*tert*-butyl-4-methylpyridine (DTBMP, very expensive) and, (b) trioxonium tetrafluoroborate (Meerwein's salt, expensive) with proton sponge® (inexpensive). Methyl triflate and proton sponge® proved to be compatible partners and produced the methylated adduct **360** in 90% yield with no trace of retroaldolisation. Following reductive removal of the chiral auxiliary the alcohol **361** was oxidised with Dess-Martin reagent to afford aldehyde **335** in excellent yield.

After the non-stereoselective addition of *iso*propenyl magnesium bromide to aldehyde **335**, the resulting mixture of enols (*syn:anti* = 57:43) was immediately oxidised to the corresponding enone in 80% overall yield. Methodology developed by Mori[141] for the directed reduction of β-alkoxyketones to yield masked *syn*-1,3-diols was then employed. A solution of the enone **362**



Scheme 63. *Reagents and conditions:*

A 75% (a) Et_2BOTf, CH_2Cl_2, –5°C; (b) *i*-Pr_2NEt, 30 min; (c) **244**, –78°C, 3 h, dr > 98:2 (recrys.)
B 90% MeOTf, proton sponge®, PhMe, 80°C, 24 h
C 99% $LiAlH_4$, Et_2O, 0°C, 15 min
D 91% Dess-Martin reagent (DMP), CH_2Cl_2, 0°C → rt, 2 h
E 80% (a) CH_2=C(Me)MgBr, Et_2O, 0°C, 1 h, dr (*anti*) = 43:57; (b) DMP, CH_2Cl_2, rt, 4 h
F 75% $LiAlH_4$, LiI, Et_2O, –100°C, 1 h, dr (*anti*) = 85:15, > 98:2 (recrys.)
G 72% TBAF•$3H_2O$, THF, rt, 15 min
H 97% $(EtCO)_2O$, DMAP, pyridine, rt, 16 h

in ether was treated with anhydrous lithium iodide at –30°C; after further cooling to –100°C the supposedly chelated ketone was reduced with lithium aluminum hydride to yield, rather unexpectedly, the *anti* alcohol **363** with 70% de. Unambiguous determination of the stereochemistry was provided by single crystal X-ray diffraction studies on the derived diol **365** (see appendix for details).

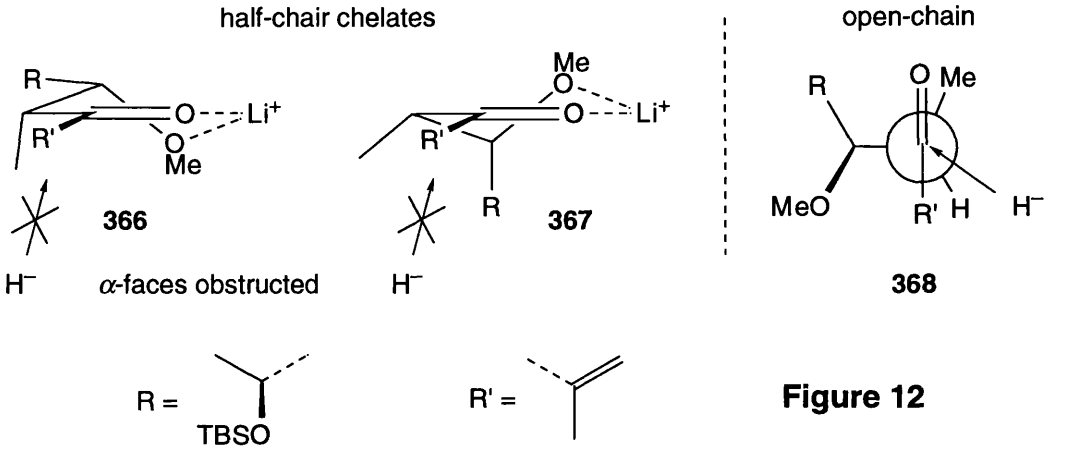
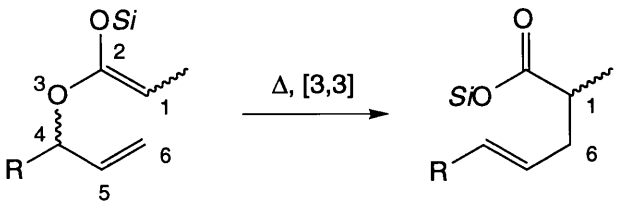


Figure 12

Hydride addition to the possible half-chair lithium chelates of **362** (see conformers **366** and **367** above, Figure 12) is unlikely to occur from the observed α-face due to severe steric hindrance. Rather the reduction appears to be under Felkin-type control[129], with an open chain model (**368**) correctly predicting the observed outcome. Why chelation control does not appear to operate here is unclear; however, all of the substrates examined by Mori lacked α-substituents and acetonide ether oxygen atoms were used to direct the reduction[141]. In any event, recrystallisation of the solid product **363** followed by careful chromatography of the resulting mother liquor residues gave a combined yield of 75% of isomerically homogeneous material. Esterification of the pure alcohol **363** under standard conditions then afforded the Ireland-Claisen precursor **364** in near quantitative yield.

For the [3,3]-sigmatropic rearrangement of a silyl ketene acetal **369** (the *Ireland-Claisen rearrangement*[117], see Table 9) to yield a product with predictable stereochemistry it is vital that three variables are determined absolutely: (a) the configuration of the stereogenic centre at C4 of the starting material (the R group will be equatorially/pseudoequatorially oriented in chairlike or boatlike transition states), (b) the geometry of the silyl ketene acetal, and (c) the transition state (chairlike C, or boatlike B) through which the rearrangement proceeds. It is clear that misassignment of any of the three factors (a) to (c) leads to a reversal in the configuration of the C1 stereogenic centre in the product **370**. The extent to which the variables are controlled affects the selectivity of the process; poor 1,4-chirality transfer in Claisen ester enolate rearrangements is typically due to associated problems with selective enolisation but can also be caused by competition between chair- and boatlike transition states.



369 **370**

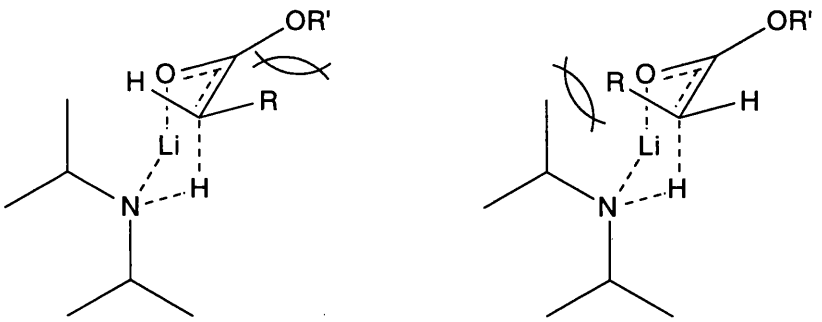
(a) C4 configuration in **369**
(b) geometry of enolate
(c) transition state type
(d) C1 configuration in **370**

Table 9

(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)
α	*Z*	C	β	β	*Z*	C	α
α	*Z*	B	α	β	*Z*	B	β
α	*E*	C	α	β	*E*	C	β
α	*E*	B	β	β	*E*	B	α

It is well precedented for simple acyclic substrates that Ireland-Claisen rearrangments occur *via* chairlike transition states[142]. We were therefore required to form an *E*-silyl ketene acetal of **364** to yield acid **333** with the natural β-configuration at the newly formed stereogenic centre (*ie* set (a) = β, (c) = C and (d) = β in the above chart).

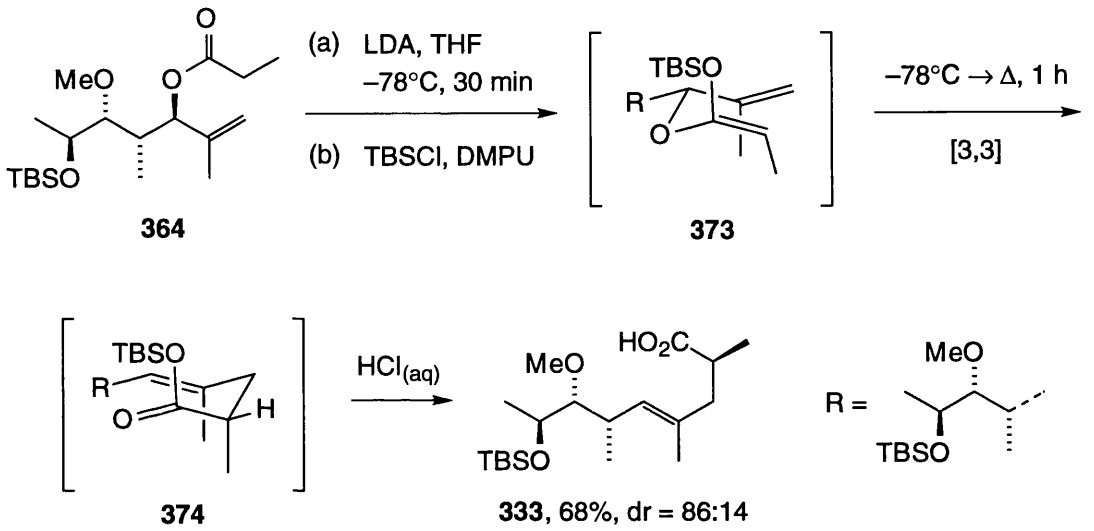
Ireland and co-workers have extensively investigated the factors controlling ester enolisation[143,144]. At low temperatures ester enolates are formed irreversibly and so the geometry of the adduct is under kinetic control. Ireland discovered that *E*-silyl ketene acetals can be formed with high stereoselectivity (*E*:*Z* = 94:6) by the treatment of esters with lithium di*iso*propylamide (LDA) in THF at –78°C followed by silylation. Conversely, in the presence of an additional dipolar co-solvent (*eg* HMPA or DMPU) under essentially the same conditions *Z*-silyl ketene acetals could be formed with even greater selectivity (*Z*:*E* ≥ 98:2)[144].



371 **Figure 13** **372**

To explain the origin of the remarkable kinetic selectivity observed, Ireland proposed that in the absence of a dipolar co-solvent, deprotonation by LDA occurs *via* a tight 6-membered transition state (Figure 13). Two conformations are stereoelectronically permitted for deprotonation, **371** and **372**. The dominant steric interaction occurs in **372** which exhibits severe 1,3-diaxial strain between the *N-iso*propyl group and the R group. Deprotonation in

THF alone thus occurs preferentially from conformer **371** and leads to the *Z*-lithium enolate (and thence to the *E*-silyl ketene acetal). In the presence of a dipolar co-solvent, the lithium cation experiences greater solvation, weakening the Li^+-carbonyl oxygen bond and leading to a looser (or even open) transition state. The repulsive interaction in **372** is thus significantly diminished whilst the destabilising interaction in **371** between R and OR' remains constant. Therefore in the presence of HMPA or DMPU deprotonation occurs preferentially from **372** and leads to the *E*-lithium enolate (and thence to the *Z*-silyl ketene acetal).

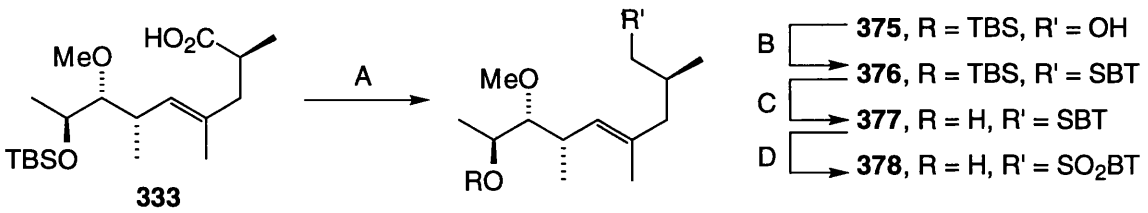


364 **373** **374** **333**, 68%, dr = 86:14

Scheme 64

Adopting standard conditions for the generation of a *Z*-lithium enolate, the propionate **364** was exposed to the action of LDA in THF at −78°C (Scheme 64). Following silylation with *tert*-butyldimethylsilyl chloride (TBSCl) in DMPU, rearrangement of the resulting *E*-silyl ketene acetal **373** to the corresponding silyl ester **374** was effected by heating. The dipolar co-solvent is required to assist silylation at low temperatures and does not affect enolate geometry when added after the enolisation event[144]. Hydrolysis of the labile silyl ester with dilute mineral acid yielded the desired carboxylic acid **333** in good yield with moderate diastereoselectivity (dr = 86:14).

Reduction of acid **333** yielded the alcohol **375** in good yield (Scheme 65), it was possible at this stage to remove the minor diastereoisomer resulting from the Ireland-Claisen reaction *via* simple flash chromatography. A standard Mitsunobu thioetherification then installed the



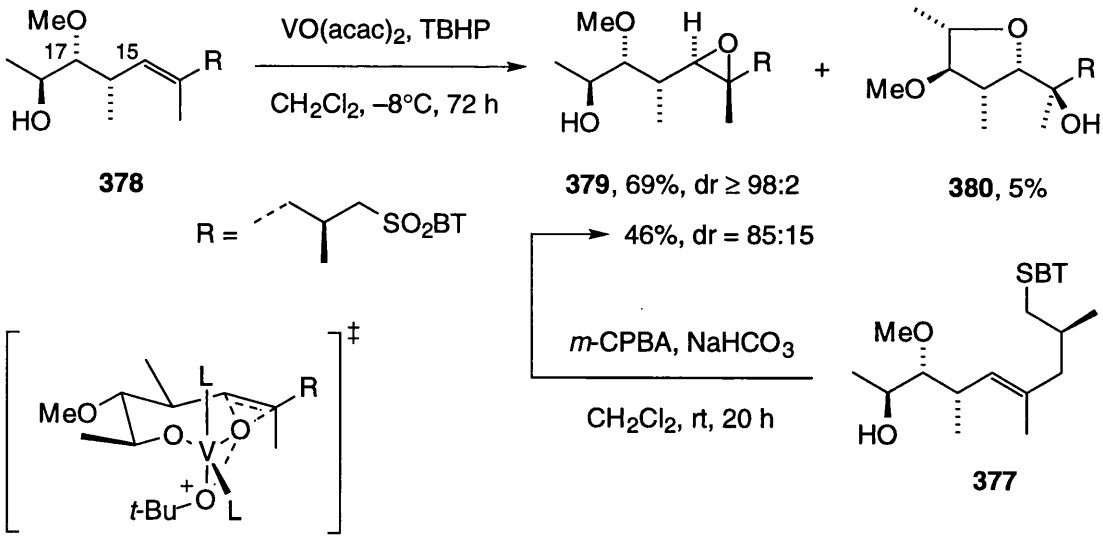
333

Scheme 65. *Reagents and conditions:*

A	90%	$LiAlH_4$, Et_2O, 0°C, 10 min	C	98%	TBAF•3H_2O, THF, rt, 32 h
B	99%	BTSH, PPh_3, DIAD, THF, 0°C → rt, 2 h	D	88%	Mo(VI), H_2O_2, H_2O-EtOH, rt, 24 h

requisite BT sulfide moiety in quantitative yield. Oxidation of the resulting thioether **376** to the corresponding sulfone by Mo(VI) catalysis proved sluggish requiring over 48 h for complete conversion. Furthermore, attempted silyl ether deprotection of the resulting sulfone with TBAF•3H_2O lead to complete decomposition; only benzothiazolone was isolated in 86% yield. Evidently the BT sulfone was not stable to the basic conditions of the deprotection protocol. Simply reversing the order of the aforementioned steps solved both problems. Deprotection of the sulfide **376** with TBAF•3H_2O occurred in excellent yield with no detectable decomposition of substrate. The sulfide moiety of the resulting alcohol **377** was then rapidly converted to the sulfone **378** *via* treatment with a Mo(VI) catalyst and $H_2O_{2(aq)}$ in EtOH. The absence of the TBS ether presumably reduced the lipophilicity of the sulfide, increasing its solubility in the reaction medium and thus facilitated oxidation.

The directed epoxidation reaction used by Kocienski for the synthesis of herboxidiene A[46] was next re-investigated for the oxidation of olefin **378** (Scheme 66). The reactivity of an olefinic alcohol towards $VO(acac)_2$ catalysed epoxidation depends on the proximity of the hydroxyl group to the alkene[145]. As a consequence the oxidation of bishomoallylic alcohol **378** was extremely slow at sub-ambient temperatures and low catalyst loadings. Unfortunately, at higher temperatures or catalyst loadings the formation of unwanted by-products became significant. Specifically, conducting the epoxidation in toluene at 60°C (3 mol% $VO(acac)_2$, 1.5 eq TBHP) resulting in sole formation of the tetrahydrofuran **380** in 63% yield; the product of intramolecular attack of the free hydroxyl on the virgin epoxide. Alternatively the reaction could be hurried at 0°C if repeated portions of catalyst (40 mol%) were added, but then acetates of the product **379** and starting material **378** were formed. The only potential source of acetate in the reaction manifold was the acetylacetonate ligand and the mechanism for acetate formation remains unclear.



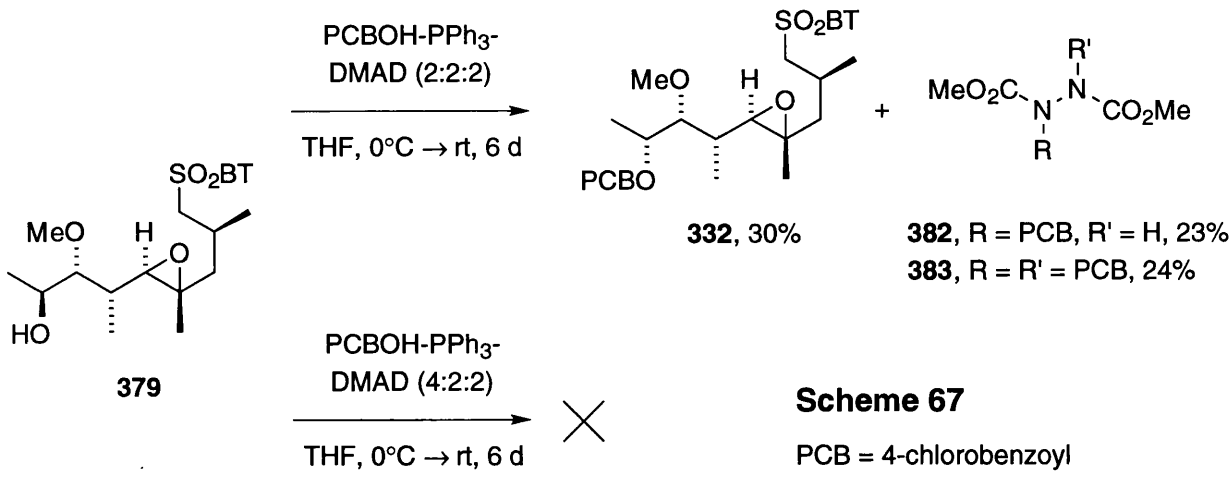
Scheme 66

After careful optimisation of the reaction, patience was found to pay dividends: at a fixed catalyst loading of just 1 mol% a cold (–8°C) solution of the olefin **378** in CH_2Cl_2 was treated with three equivalents of TBHP *via* a syringe pump delivery system over 48 h. After the complete addition, the oxidation was allowed a further 24 h of reaction time. Such a protocol yielded 69% of **379** as a *single diastereoisomer*, together with a small quantity of the THF-adduct **380** and 26% of recovered starting material **378**. The illustrated facial selectivity of the reaction was rationalised by transition state **381** in analogy with that suggested by Kocienski[46] for the epoxidation of **263** (see Scheme 43, Chapter 5). The derivation of the model was based on earlier work by Sharpless[146] and Mihelich[147] and has been discussed at great length by Smith[148]. Key points to note are: (a) the trigonal bipyrimidal co-ordination geometry of the V(V) ternary complex, (b) the pseudo-chair conformation adopted by the substrate, (c) interactions between substituents along the carbon skeleton and vanadium ligands are minimised, and (d) breakage of the peroxide bond occurs from the backside along the O-O bond axis[46]. The inherent stereochemistry found in **378** allows for the all pseudo-equatorial disposition of substituents within **381** and presumably accounts for the high level of stereocontrol observed.

Epoxidation was also achieved with *m*-CPBA commencing from the corresponding sulfide **377**. Concomitant oxidation of the sulfide and olefin occurred to yield 46% (unoptimised) of the epoxysulfone **379** directly with good diastereoselectivity (dr = 85:15).

To complete the synthesis of the nucleophilic coupling partner **332**, all that remained was to invert the stereogenic centre at C18 and to protect the resultant hydroxyl group. Reasoning that an ester function would be a sufficiently robust protecting group for the imminent Julia olefination, a Mitsunobu reaction was the logical choice for the inversion operation[149]. Initial experiments employed the most standard of Mitsunobu conditions: *viz*, a mixture of the alcohol **379**, triphenylphosphine and 4-chlorobenzoic acid (PCBOH) in THF at 0°C was treated with either diethyl azodicarboxylate (DEAD) or di*iso*propyl azodicarboxylate (DIAD) and allowed to warm[52]. Although these simple experiments afforded the product ester **332**, yields were low to moderate (23-66%) and more infuriatingly the product proved very difficult to separate from the appropriate hydrazodicarboxylate by-product. To solve the purification problem the azodicarboxylate component was changed to the rarely used dimethyl congener (DMAD[150]) which has a water soluble hydrazine derivative. The increased reactivity of DMAD produced difficulties of a different nature (Scheme 67). Under standard conditions (equal quantities of the three reagents) significant quantities of acylated hydrazine adducts (**382** and **383**) were formed and the yield of the product ester **332** was disappointing (30%).

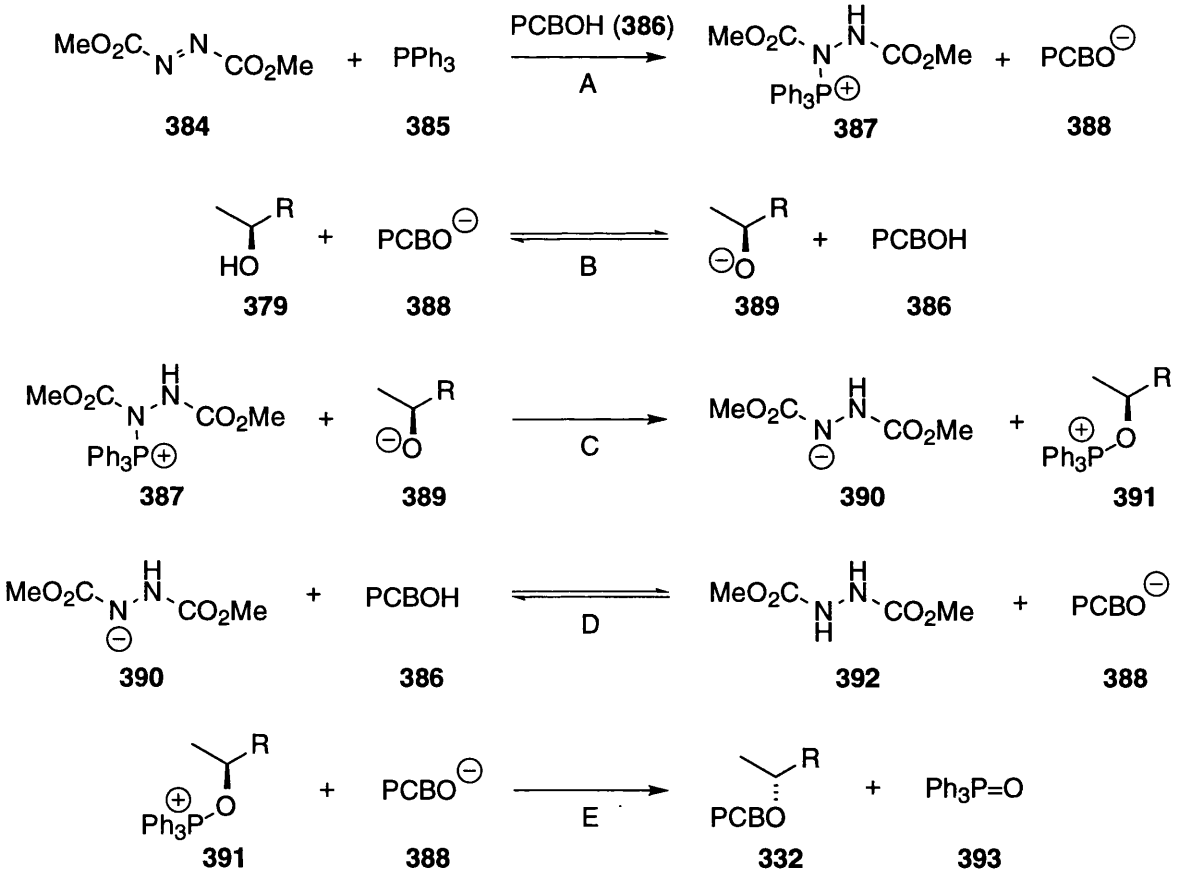
An explanation for these findings and a potential remedy can be gleaned from consideration of the mechanism for the Mitsunobu process (Scheme 68)[149]. The formation of adduct **382** is a



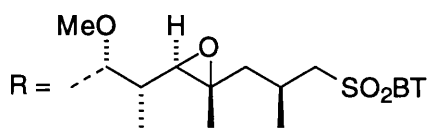
Scheme 67

PCB = 4-chlorobenzoyl

consequence of direct attack of the carboxylate **388** on the azaphosphonium adduct **387** followed by displacement of triphenyl phosphine oxide by **390**. An extension of such a reaction path can lead to the double acylated hydrazine derivative **383**. The enhanced reactivity of the DMAD adduct **387** toward weak nucleophile **388**, and the expected low rate of steps B and C (due to steric hindrance of **379**) account for competition from the undesired reaction path.

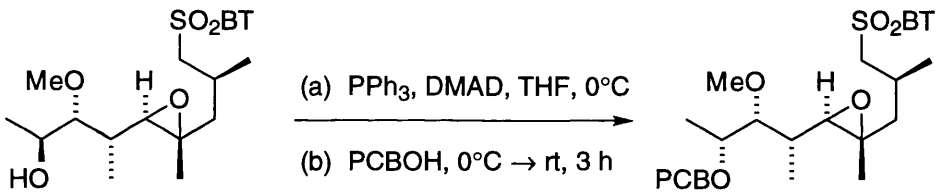


Scheme 68



A potential solution to the problem is to employ an excess of the acid component (*ie* a ratio of PCBOH:PPh_3:DMAD = 2:1:1)[149]; herein the PCBOH/$PCBO^-$ ratio is increased. The excess acid form solvates the carboxylate thus reducing its nucleophilicity and so stabilising the complex **387+388**. Such conditions were tested on our system (Scheme 67). No product formation (or **382** and **383**) occurred and the starting material was recovered in 72% yield. The problem arises because accompanying the reduction in carboxylate nucleophilicity is a reduction in its basicity; thus, step B is retarded and so too the rate of oxyphosphonium ion **391** formation.

To circumvent all of the aforementioned difficulties a different approach was adopted. Preforming the betaine adduct between triphenyl phosphine and DMAD in THF at 0°C, the alcohol **379** was added followed by the slow portionwise addition of the acid PCBOH (Scheme 69). Thus the concentration of the carboxylate **388** is kept low whilst its nucleophilicity and basicity are uncompromised. Under the new protocol ester **332** was produced rapidly in good yield (74%) and proved easy to purify. The hydrazine **392** was removed by aqueous work-up.



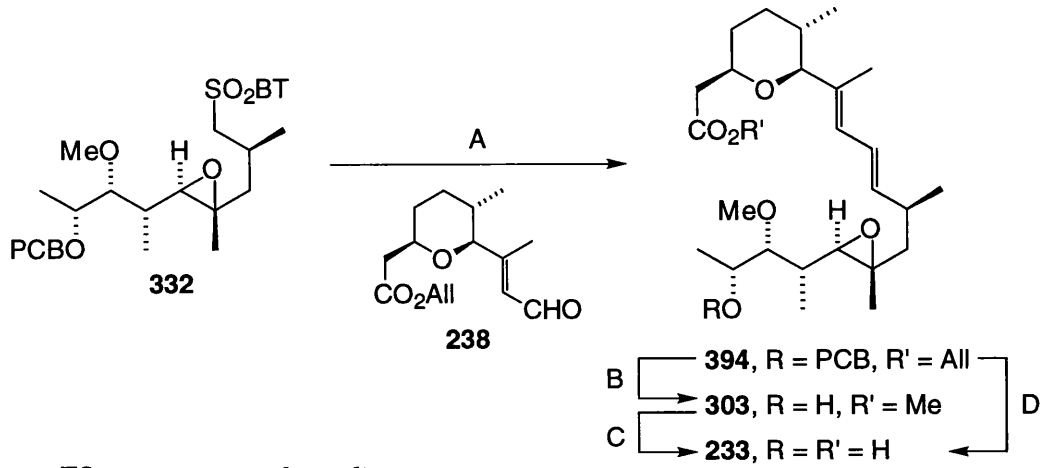
379 PCB = 4-chlorobenzoyl **332**, 74%

Scheme 69

6.4. Completion of synthesis - union of sulfone 332 and aldehyde 238

After the various problems encountered in realising alcohol **240** and sulfone **332**, the synthesis was easily completed (Scheme 70). Aldehyde **238** was prepared from **240** as previously disclosed by Kocienski[46] (see Scheme 42, Chapter 5). The one-pot Julia reaction between sulfone **332** and **238** employing standard pre-metallation conditions yielded 81% of the protected herboxidiene derivative **394** with excellent selectivity (10*E*:*Z* = 91:9). Some minor points are worth noting: (a) the presence of any excess base resulted in the enolisation of the aldehyde **238** thus inhibiting its role as electrophile, the most successful conditions employed sulfone (1.2 eq), base (1.1 eq) and aldehyde (1 eq); (b) quenching of the reaction at –78°C yielded only 60% of **394** with *E*:*Z* = 80:20. The reduced selectivity and yield were probably due to the moderate stability of an *anti* β-alkoxysulfone intermediate which required a longer reaction time and/or higher temperature than the corresponding *syn* adduct to undergo

spirocyclisation (see Chapter 1). Allowing some warming of the reaction mixture to –20°C before quenching thus raised both yield and selectivity.



Scheme 70. *Reagents and conditions:*

A	---	(a) LDA, THF, –78°C, 15 min;	C	84%	K_2CO_3, H_2O-MeOH (1:4), Δ, 1 h
	81%	(b) **238**, –78°C → –20°C, 1.5 h, *E*:*Z* = 91:9	D	93%	K_2CO_3, H_2O-MeOH (1:4), Δ, 2 h
B	72%	K_2CO_3, MeOH, Δ, 2 h			

Although direct double deprotection of **394** was possible by simple saponification (step D above), we favoured a two step deprotection protocol (B+C) *via* the previously reported methyl ester of herboxidiene **303**[104]. Separation of minor impurities and the 10*Z* isomer from **394** by chromatography proved very difficult, as was direct purification of herboxidiene **233** itself. The natural product was not separable from 4-chlorobenzoic acid or its minor 10*Z* isomer by simple flash chromatography. Gratifyingly, purification of the methyl ester **303** (produced *via* transesterification of **394**) proved relatively straightforward and our synthetic material matched that reported by Isaac[104] in all respects. Subsequent deprotection of pure ester **303** then enabled the production of a high quality sample of herboxidiene **233** in excellent yield.

Comparison of ^1H and ^{13}C NMR data for our synthetic herboxidiene (**233**) and the natural material reported by Isaac[104] revealed significant discrepancies in the C1-C3 region (see Tables 10 and 11). Variation in the geminal coupling constant between the C2 protons suggested a difference in the ionisation state for natural and synthetic samples. The sodium salt of our synthetic material (prepared by treatment with Na_2CO_3 in CD_3OD) provided ^1H and ^{13}C NMR data in complete agreement with Isaac[104]. The data reported in the literature therefore likely pertains to a carboxylate derivative rather than the free acid of herboxidiene and the integrity of our synthesis is without doubt.

^{1}H NMR data for herboxidiene (**233**) **Table 10**

	natural herboxidiene*			synthetic herboxidiene†		
position	δ	multiplicity	J (Hz)	δ	multiplicity	J (Hz)
$H2_A$	2.45	dd	14.1, 6.6	2.46	dd	15.6, 7.2
$H2_B$	2.25	dd	14.1, 7.5	2.38	dd	15.3, 5.7
H3	3.76	m	---	3.80-3.70	m	---
$H4_A$	1.86-1.68	m	---	1.90-1.82	m	---
$H4_B$	1.30	m	---	1.40-1.22	m	---
$H5_A$	1.86-1.68	m	---	1.74-1.65	m	---
$H5_B$	1.26-1.12	m	---	1.40-1.22	m	---
H6	1.55	m	---	1.60-1.43	m	---
C6-Me	0.66	d	6.6	0.68	d	6.6
H7	3.34	d	9.9	3.34	d	9.9
C8-Me	1.68	s	---	1.69	s	---
H9	5.90	d	11.1	5.92	d	10.8
H10	6.29	dd	15.0, 10.8	6.30	dd	15.0, 10.8
H11	5.45	dd	15.0, 9.0	5.47	dd	15.0, 9.1
H12	2.44	m	---	2.50-2.38	m	---
C12-Me	1.03	d	6.6	1.04	d	6.7
$H13_A$	1.91	dd	13.1, 4.3	1.92	dd	13.4, 4.3
$H13_B$	1.26-1.12	m	---	1.18	dd	13.0, 11.2
C14-Me	1.27	s	---	1.28	s	---
H15	2.65	d	9.6	2.65	d	9.4
H16	1.45	m	---	1.60-1.43	m	---
C16-Me	0.83	d	6.9	0.83	d	6.9
H17	2.96	dd	6.0, 4.5	2.97	dd	6.1, 4.3
H18	3.78	dq	6.6, 6.3	3.78	quintet	6.4
H19	1.11	d	6.6	1.10	d	6.4
OMe	3.52	s	---	3.52	s	---

*recorded from CD_3OD at 300MHz, reported by Isaac *et al*[104]. †recorded from CD_3OD at 360 MHz

^{13}C NMR data for herboxidiene (**233**) **Table 11**

	natural*	synthetic†			natural*	synthetic†	
position	δ	δ	$\Delta\delta$	position	δ	δ	$\Delta\delta$
C1	179.8	175.3	–4.5	C12	36.5	36.6	+0.1
C2	46.4	42.3	–4.1	C12-Me	22.7	22.7	0.0
C3	77.0	75.5	–1.5	C13	48.1	48.1	0.0
C4	33.1	32.8	–0.3	C14	62.6	62.6	0.0
C5	33.7	33.4	–0.3	C14-Me	16.8	16.8	0.0
C6	33.5	33.4	–0.1	C15	67.8	67.9	+0.1
C6-Me	18.2	18.1	–0.1	C16	36.4	36.4	0.0
C7	92.2	92.2	0.0	C16-Me	11.7	11.5	–0.2
C8	136.5	136.2	–0.3	C17	88.6	88.5	–0.1
C8-Me	12.1	12.1	0.0	C18	69.8	69.9	+0.1
C9	129.5	129.6	+0.1	C19	19.9	19.8	–0.1
C10	126.6	126.5	–0.1	OMe	61.9	61.9	0.0
C11	140.5	140.7	+0.2				

*recorded from CD_3OD at 75MHz, reported by Isaac *et al*[104]. †recorded from CD_3OD at 90 MHz

7. Summary of Results and Conclusion

The 1-phenyl-1*H*-tetrazol-5-yl (PT) variant of the one-pot Julia olefination reaction has emerged as a powerful synthetic tool for the synthesis of non-conjugated 1,2-disubstituted *trans* alkenes (see Chapter 2). The new variant was found to complement the existing benzothiazol-2-yl (BT) system introduced by Julia[1] which remains optimum for the construction of *trans* conjugated dienes. In contrast to the classical Julia olefination, *trans* selectivity in the PT variant of the one-pot reaction shows little dependence on the degree of chain branching about the point of connection (Figure 14). Indeed, the new system is able to access simple non-branched *E*-alkenes (*eg* **123**) with much greater selectivity than the classical Julia reaction (*eg* **27**).

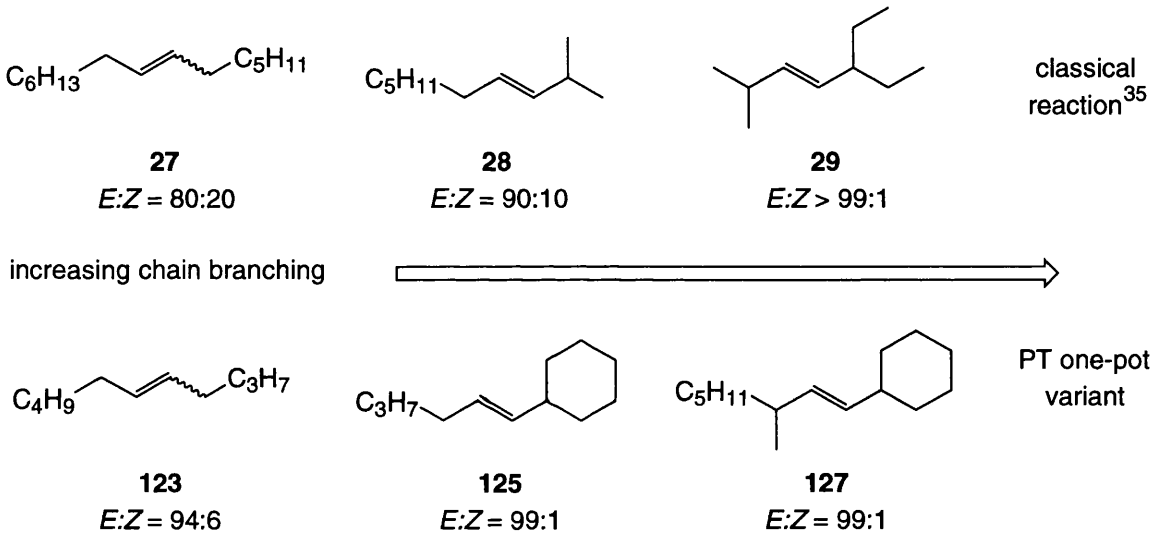
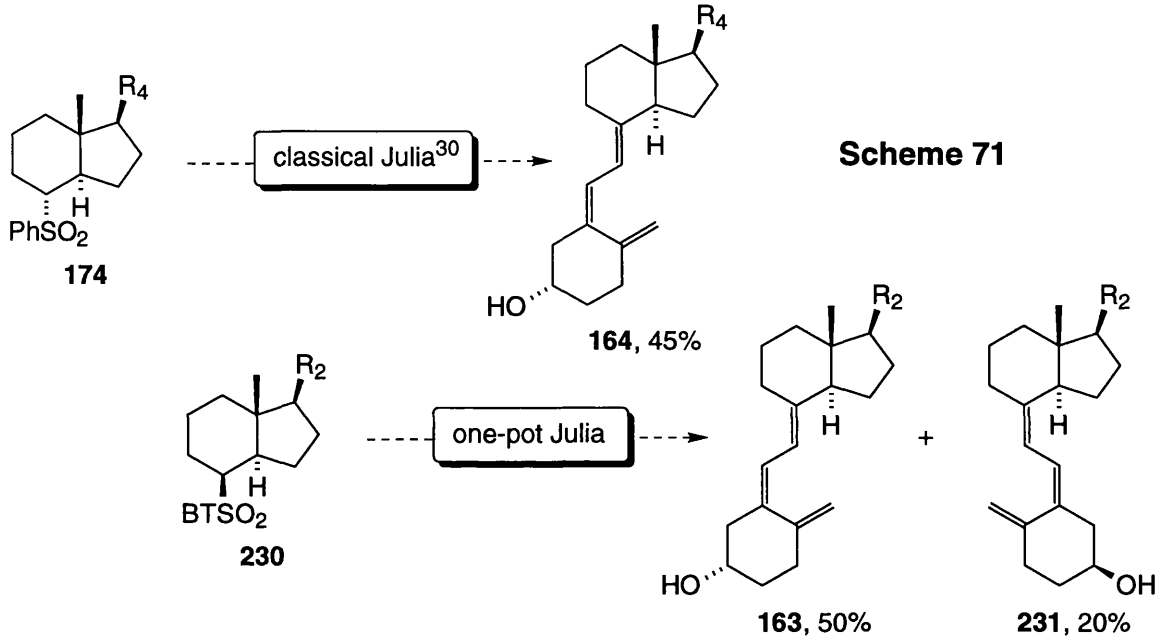


Figure 14

Further to the discovery of an alternative class of heterocyclic mediator for the one-pot Julia olefination, we also demonstrated the efficacy of both variants (BT and PT) toward target directed synthesis. Vitamin D_2 and herboxidiene were both successfully synthesised by employing one-pot Julia technology at pivotal junctures.

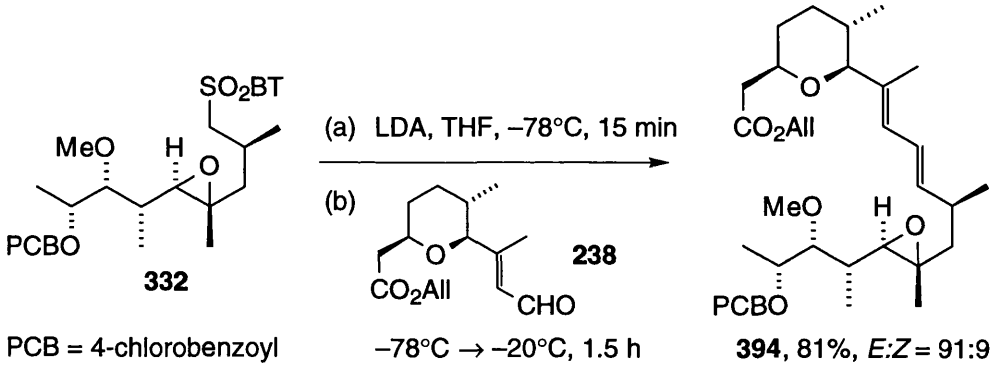
The ability to synthesise vitamin D derivatives convergently by joining complex A- and CD-ring fragments enables the rapid assembly of analogues with potentially beneficial biological properties. The BT variant of the one-pot Julia reaction proved equal to the task of forging the crucial 7,8-double bond of vitamin D from such fragments with reasonable selectivity and in good yield (see Chapter 4). Drawing a parallel with the original Julia olefination, it is important to note that, although the classical reaction is completely stereoselective for the formation of the 7*E*-double bond, yields seldom exceed 50%[30,78]. Furthermore, with the advent of new photoisomerisation protocols for the conversion of 7*Z* vitamin D trienes into the natural 7*E* state[84], the onus is now on methods to be higher yielding. The one-pot Julia olefination method

presented here is both more convenient and higher yielding than the classical reaction for the linkage of A-ring and CD-ring vitamin D fragments (Scheme 71).



Scheme 71

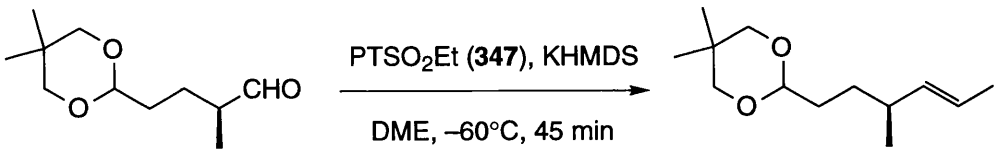
The first total synthesis of herboxidiene (**233**) was achieved in a total of 36 steps from cyclohexanone with a longest linear sequence of 22 steps (see Chapter 6). The high level of convergency achieved was in part due to the ability of the one-pot Julia olefination to conjoin two complex late stage intermediates, sulfone **332** and aldehyde **238** (Scheme 72). Of particular note was the presence of both epoxide and ester functionalities in the sulfone component. The compatibility of the one-pot Julia reaction with such groups bodes well for its wider scope and future potential in more demanding applications.



Scheme 72

Equally important was the role of our PT variant of the reaction to achieve a two carbon extension of the aldehyde **328** to access *trans* olefin **327**, an excellent substrate for a subsequent asymmetric dihydroxylation (Scheme 73). Although metallated PT sulfones were generally more resistant than their BT counterparts towards self-condensation, sulfone **347** was incompatible with a premetallation protocol. However, despite employing Barbier

conditions for the requisite coupling, no racemisation of the α-branched chiral aldehyde was observed.

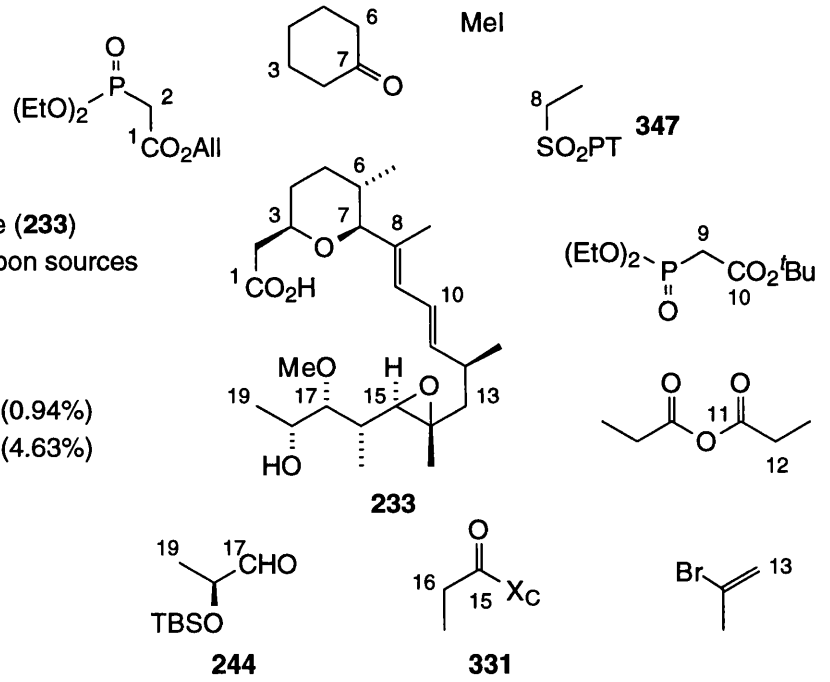


328 **327**, 93%, *E:Z* = 93:7

Scheme 73

The only chiral pool material used to construct the carbon skeleton of herboxidiene was cheap ethyl (*S*)-lactate from which the aldehyde **244** was derived[46]. All other stereogenic centres were manufactured *via* asymmetric synthesis employing both chiral auxiliary and chiral catalyst methods. The remaining achiral carbon sources were generally cheap bulk chemicals (*eg* cyclohexanone, propionic anhydride, methyl iodide *etc*) and the two phosphonate esters employed for HWE reactions were the most costly materials (Figure 15). Antipodes of Oppolzer's camphor sultam auxiliary[151] (X_C and X_C', see Scheme 54, Chapter 6) were derived from the appropriate enantiomer of camphorsulfonic acid[152] and were recycled many times during the course of the synthesis. The low material cost and the operational simplicity of the experimental procedures employed make the herboxidiene synthesis presented herein particularly efficient and amenable to scale-up.

Figure 15



total synthesis of herboxidiene (**233**)
summary information and carbon sources

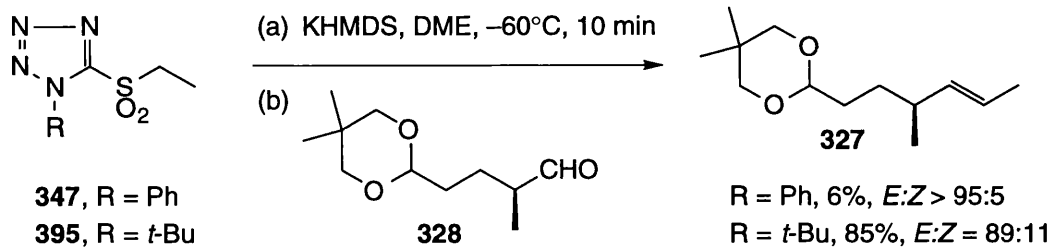
linear sequences = 2

length of sequences = 22 (0.94%)
(overall yield) 17 (4.63%)

total number of steps = 36

To conclude this thesis it would be pertinent to briefly survey an extension of the tetrazole olefination technology recently developed in the Kocienski group[72]. Replacement of the *N*-phenyl moiety in a PT sulfone with an *N-tert*-butyl substituent yields a one-pot Julia system exhibiting even greater stability toward premetallation. Such sulfones (denoted TBT; 1-*tert*-butyl-1*H*-tetrazol-5-yl) are available *via* analogous methods to the PT sulfones commencing

from the known compound 1-*tert*-butyl-1*H*-tetrazole-5-thiol[153]. An illustration of the increased stability of the TBT system over the PT variant was provided by a repeat of the two carbon extension of aldehyde **328** (Scheme 74).



347, R = Ph
395, R = *t*-Bu

328

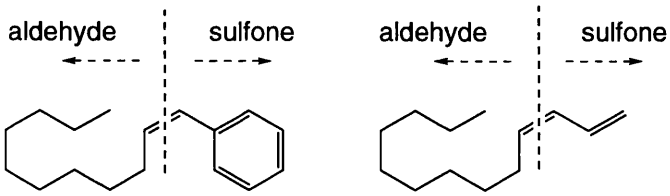
327

R = Ph, 6%, *E:Z* > 95:5
R = *t*-Bu, 85%, *E:Z* = 89:11

Scheme 74

Under a premetallation protocol the TBT sulfone **395** was condensed with aldehyde **328** to yield the olefin **327** in excellent yield (85%) albeit with a slightly reduced *trans* selectivity (*E:Z* = 89:11) when compared to the analogous result with the PT sulfone **347** (*E:Z* > 95:5)[72]. However, the low yield in the latter case is of little preparative value and was no doubt due to self-condensation of metallated sulfone **347**.

The additional steric shielding of the electrophilic centre provided by the sterically demanding *tert*-butyl group is presumably responsible for the heightened stability of TBT metallated sulfones. Of course the bulky group would also retard intramolecular nucleophilic attack upon the C=N bond and thus inhibit spirocyclisation of the initially formed β-alkoxysulfones. In the case of stabilised sulfones, such an effect would facilitate equilibration between *syn* and *anti* β-alkoxysulfones and lead to a preference for the *cis* olefin product (see Chapter 1). Indeed, reaction of benzylic or allylic TBT sulfones with saturated aldehydes yielded olefins with excellent *Z*-selectivity at a level which exceeded that of the analogous BT or PT sulfones[72] (Figure 16).



396

Het	%yield	*Z:E*
BT	80	77:23
PT	70	71:29
TBT	**95**	**99:1**

397

Het	%yield	*Z:E*
BT	78	68:32
PT	39	33:67
TBT	**60**	**96:4**

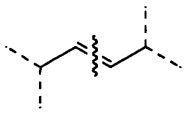
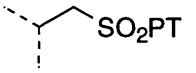
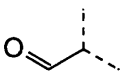
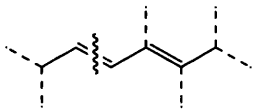
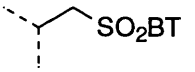
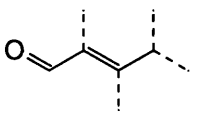
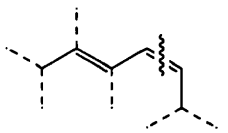
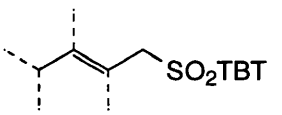
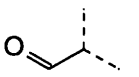
Figure 16

The ability of a substituent on the tetrazole scaffold to tune the reactivity of a metallated sulfone, and so affect product olefin geometry, provides great scope for further optimisation. It may be possible in future for the selectivity of a one-pot Julia olefination reaction to become completely independent of substrate class by use of the appropriate heterocycle substituents. In this regard the tetrazole variant of the one-pot Julia reaction in some ways mirrors the HWE

reaction (Chapter 1), in which variation in phosphonate ester groups can control equilibration between β-alkoxyphosphonates and ultimately the product olefin geometry.

Finally, Table 12 provides a guide to the currently accepted optimum choice of heterocyclic sulfone for the synthesis of a range of 1,2-disubstituted olefin systems *via* the one-pot Julia olefination.

Table 12

olefin class	sulfone	aldehyde	base	solvent
 isolated *trans*			KHMDS	DME
 conjugated *trans*			LiHMDS (LDA)	THF
 conjugated *cis*			– unoptimised –	

reactions should first be attempted employing a premetallation protocol and Barbier conditions adopted if low yields are experienced

8. Experimental Section

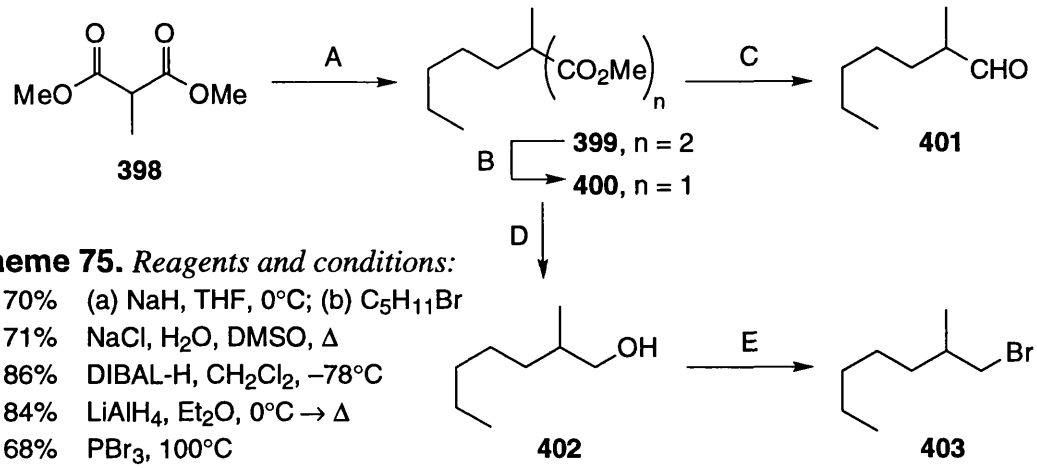
All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under a static atmosphere of nitrogen. 1,2-Dimethoxyethane (DME), tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. *N,N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 at sub-ambient pressure (*ca* 15 mmHg, water aspirator). Dichloromethane was freshly distilled from CaH_2 and toluene was distilled from molten sodium. Where required anhydrous methanol and ethanol were obtained by distillation from their respective magnesium alkoxides and stored over activated 4Å molecular sieves (MS). Preparative chromatographic separations were performed on Macherey-Nagel silica gel 60 (230-400 mesh) and reactions were followed by TLC analysis using Macherey-Nagel silica gel 60 plates with fluorescent indicator (254 nm) and visualised with UV or phosphomolybdic acid. All commercially available reagents were purchased from Aldrich and were typically used as supplied.

Melting points were recorded using open capillary tubes on a Griffin melting point apparatus and are uncorrected. Specific optical rotations ($[\alpha]_D$) were measured at ambient temperature (24±3°C) from $CHCl_3$ solutions on an Optical Activity polAAr 2000 polarimeter using a 5 mL cell with 1 dm path length. Infra-red (IR) spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer using a thin film supported between NaCl plates or KBr discs where stated. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, w = weak or br = broad. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in Fourier transform mode at the field strength specified either on a Bruker AM360 or a Jeol Gx-270 spectrometer. All spectra were obtained in $CDCl_3$ solution in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H = 7.27 ppm or δ_C = 77.2 ppm). Multiplicities in the ^1H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. Numbers in parentheses following the chemical shift in the ^{13}C NMR spectra refer to the number of attached hydrogens as revealed by the DEPT spectral editing technique employing secondary pulses at 90° and 135°. Low (LRMS) and high (HRMS) resolution mass spectra were run on a Jeol JMS700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%).

Where given, assignment of NMR spectral data is notional and based only on standard reference sources[154-156]. Any assignment of the complex NMR signals of vitamin D derivatives was made by analogy to the work of Mizhiritskii *et al*[100] and likewise NMR signal assignment of herboxidiene derivatives was made by analogy to the work of Isaac[104] and Kocienski[46].

–SECTION 2.1–

Scheme 75 outlines the synthesis of racemic 2-methylheptanal (**401**), 2-methyl-1-heptanol (**402**) and 1-bromo-2-methylheptane (**403**); commercially unavailable materials required to synthesise many of the compounds in Tables 2 and 3 (Chapter 2).



Scheme 75. *Reagents and conditions:*

A	70%	(a) NaH, THF, 0°C; (b) $C_5H_{11}Br$
B	71%	NaCl, H_2O, DMSO, Δ
C	86%	DIBAL-H, CH_2Cl_2, –78°C
D	84%	$LiAlH_4$, Et_2O, 0°C → Δ
E	68%	PBr_3, 100°C

Dimethyl methylpentylmalonate (399):

To a stirred suspension of sodium hydride (9.0 g, 60 wt.% dispersion in mineral oil subsequently washed with dry hexanes 3x10 mL, 225 mmol) in anhydrous THF (200 mL) under $N_{2(g)}$ at 0°C was added dropwise dimethyl methylmalonate (**398**, 27.3 mL, ρ =1.098, 30.0 g, 205 mmol) over 30 min (CARE! $H_{2(g)}$ evolution). After 1 h the mixture was an homogeneous yellow solution of the sodium enolate. 1-Bromopentane (28.0 mL, ρ =1.22, 34.2 g, 226 mmol) in anhydrous THF (30 mL) was then added dropwise and the mixture heated to reflux and stirred O/N (a white precipitate of NaBr was observed to form). The mixture was then allowed to cool and the solvent removed *in vacuo*. The residue was partitioned between H_2O (150 mL) and Et_2O (100 mL). The layers were then separated and the aqueous phase extracted (2x50 mL Et_2O). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 45 g of a crude yellow oil. The oil was further purified *via* distillation under reduced pressure to yield dimethyl methylpentylmalonate (**399**, 30.9 g, 143 mmol, 70%) as a clear oil: bp 116°C, 20 mmHg. (CAS No. 98061-04-2).

^1H and ^{13}C NMR in complete agreement with that previously reported[157].

(±)-Methyl 2-methylheptanoate (400):

Decarbalkoxylation was effected *via* the method of Krapcho[158]: A suspension of dimethyl methylpentylmalonate (**399**, 30.9 g, 143 mmol), sodium chloride (17.0 g, 291 mmol) and water (3 mL, 3.0 g, 167 mmol) in DMSO (150 mL) was stirred vigorously at reflux for 48 h. The mixture was then allowed to cool to rt and partitioned between H_2O (300 mL) and Et_2O

(100 mL). The layers were separated and the aqueous phase extracted (4x75 mL Et_2O). The combined organic extracts were washed successively with H_2O (4x75 mL), brine (75 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 16.9 g of a light brown oil. Further purification was effected by distillation under reduced pressure to yield (±)-methyl 2-methylheptanoate (**400**, 14.4 g, 101 mmol, 71%) as a clear oil: bp 86-88°C, 20 mmHg. (lit.[159] bp 78-80°C, 21 mmHg. CAS No. 51209-78-0).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 177.4 (0), 51.47 (3), 39.6 (1), 33.9 (2), 31.8 (2), 27.0 (2), 22.6 (2), 17.1 (3), 14.1 (3) ppm.

(±)-2-Methylheptanal (401):

A stirred solution of (±)-methyl 2-methylheptanoate (**400**, 1.03 g, 6.0 mmol) in anhydrous CH_2Cl_2 (25 mL) under $N_{2(g)}$ at –78°C was treated dropwise with di*iso*butylaluminium hydride (DIBAL-H, 4.1 mL, 1.5 M in PhMe, 6.15 mmol) over 5 min . After stirring for 2 h, sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture allowed to warm slowly to rt. The resultant jellified biphasic system was then poured into an aqueous solution of potassium sodium tartrate (5 g in 30 mL H_2O) and stirred vigorously for 30 min. Et_2O (30 mL) was then added and the layers shaken and separated. The aqueous phase was extracted (3x10 mL Et_2O) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield (±)-2-methylheptanal (**401**, 0.66 g, 5.2 mmol, 86%) as a clear oil. (CAS No. 16630-91-4).

IR (film): ν = 2931 (s), 2860 (m), 1729 (s), 1462 (m), 1378 (w), 1241 (w), 1108 (w), 926 (w) cm^{-1}.

^1H NMR in agreement with that previously reported[160].

(±)-2-Methyl-1-heptanol (402):

To a stirred suspension of lithium aluminium hydride (3.9 g, 103 mmol) in anhydrous Et_2O (150 mL) under $N_{2(g)}$ at 0°C was added dropwise (±)-methyl 2-methylheptanoate (**400**, 14.4 g, 101 mmol) in anhydrous Et_2O (75 mL) at such a rate as to maintain a gentle reflux (CARE! total addition complete after 30 min). The reaction mixture was then stirred at rt O/N before being cooled to 0°C and the excess reductant quenched by dropwise addition of EtOAc (25 mL, CARE!). Sat. $NH_4Cl_{(aq)}$ (100 mL) was then added cautiously and mixture stirred vigorously for 15 min. The resultant precipitate was then removed by filtration through a celite pad and the residue washed well with Et_2O (2x100 mL) and H_2O (100 mL). The layers of the biphasic filtrate were separated and the aqueous phase extracted (2x50 mL Et_2O). Combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and then concentrated *in vacuo* .

The residue (11.8 g) was further purified *via* distillation under reduced pressure to yield (±)-2-methyl-1-heptanol (**402**, 11.1 g, 85 mmol, 84%) as a clear oil: bp 94-100°C, 20 mmHg. (lit.[161] bp 184-185°C, 760 mmHg. CAS No. 60435-70-3).

IR (film): ν = 3336 (s, br), 2927 (s), 1466 (m), 1379 (w), 1033 (m), 987 (w) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 3.51 (1H, dd, J = 10.4, 5.8 Hz), 3.41 (1H, dd, J = 10.4, 6.6 Hz), 1.67-1.47 (1H, m), 1.47-1.17 (7H, m), 1.17-1.02 (1H, m), 0.91 (3H, d, J = 6.6 Hz), 0.89 (3H, t, J = 6.8 Hz) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 68.3 (2), 35.8 (1), 33.3 (2), 32.3 (2), 26.8 (2), 22.8 (2), 16.7 (3), 14.2 (3) ppm.

(±)-1-Bromo-2-methylheptane (403):

To stirred (±)-2-methyl-1-heptanol (**402**, 6.5 g, 50 mmol) under $N_{2(g)}$ at 0°C was added dropwise phosphorous tribromide (2.4 mL, ρ =2.85, 6.8 g, 25 mmol) and the mixture stirred at 80°C for 2 h. TLC analysis then indicated complete loss of starting material. The reaction mixture was then cooled to 0°C and ice (3 g) added (CARE! HBr evolved). After gas evolution had ceased the aftermath was partitioned between Et_2O (20 mL), H_2O (20 mL) and the layers separated. The aqueous phase was extracted (3x10 mL Et_2O) and the combined organic extracts washed with H_2O (2x10 mL), brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue (9.0 g) was distilled under reduced pressure to yield only 3.9 g of the title bromide: bp 48-49°C, 20 mmHg (lit.[162] 72°C, 11 mmHg). The residue was treated with further phosphorous tribromide (5 mL, 52 mmol) as above and then heated at 100°C for 1 h. After an identical work-up procedure the crude product was combined with the original distillate (not completely pure) and further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield (±)-1-bromo-2-methylheptane (**403**, 6.5 g, 34 mmol, 68%) as a clear oil. (CAS No. 72279-59-5).

^1H NMR (270 MHz): δ = 3.40 (1H, dd, J = 9.7, 5.0 Hz), 3.32 (1H, dd, J = 9.9, 6.0 Hz), 1.90-1.75 (1H, m), 1.55-1.15 (8H, m), 1.01 (3H, d, J = 6.6 Hz), 0.89 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 41.7 (2), 35.4 (1), 35.0 (2), 32.1 (2), 26.7 (2), 22.8 (2), 19.0 (3), 14.2 (3) ppm.

Thiol alkylation method A (Table 2):

In a typical experiment a stirred solution/suspension of the heterocyclic thiol (5 mmol) in EtOH (50 mL) under $N_{2(g)}$ was treated with finely powdered potassium hydroxide (0.3 g, 5.4 mmol) and the mixture stirred at reflux for 2 h. The neat alkyl bromide (5.7 mmol) was then added dropwise and the reaction mixture stirred at reflux O/N. After allowing the resultant suspension to cool the solvent was then removed *in vacuo*. The residue was then partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL) and the layers separated. The aqueous layer was extracted (2x20 mL CH_2Cl_2) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then purified *via* column chromatography.

Thiol alkylation method B (Table 2):

In a typical experiment a stirred solution of the heterocyclic thiol (3.8 mmol), triphenylphosphine (1.13 g, 4.3 mmol) and the alcohol (3.6 mmol) in anhydrous THF under N_2 at –5°C was treated dropwise with neat di*iso*propylazodicarboxylate (DIAD, 0.85 mL, ρ = 1.027, 0.87 g, 4.3 mmol). The mixture was stirred for 1 h then allowed to warm to rt and stirred O/N. The solvent was then removed *in vacuo* and the residue further purified *via* column chromatography.

2-(Dodecylthio)benzothiazole (89):

2-Mercaptobenzothiazole (1.70 g, 10.0 mmol) was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 2-(dodecylthio)benzothiazole (**89**, 2.71 g, 8.1 mmol, 81%) as a clear oil.

IR (film): ν = 2922 (s), 2852 (s), 1462 (s), 1428 (s), 1309 (m), 1275 (w), 1239 (m), 1125 (w), 1077 (w), 995 (s), 754 (s), 725 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.88 (1H, dm, J = 7.4 Hz), 7.75 (1H, dm, J = 8.1 Hz), 7.42 (1H, td, J = 7.7, 1.5 Hz), 7.32-7.25 (1H, m), 3.35 (2H,t, J = 7.4 Hz), 1.83 (2H, quintet, J = 7.5 Hz), 1.54-1.42 (2H, m), 1.36-1.24 (16H, m), 0.91 (3H, t, J = 7.0 Hz) ppm.

^{13}C NMR (75 MHz): δ = 167.6 (0), 153.5 (0), 135.3 (0), 126.1 (1), 124.2 (1), 121.6 (1), 121.0 (1), 33.8 (2), 32.1 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.5 (2), 29.4 (2), 29.3 (2), 29.0 (2), 22.9 (2), 14.3 (3) ppm.

LRMS (electrospray): m/z = 336 $(M+H)^+$.

2-(Dodecylthio)pyridine (90):

2-Mercaptopyridine (1.11g, 10.0 mmol) was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 2-(dodecylthio)pyridine (**90**, 2.79 g, 10.0 mmol, 100%) as a clear oil.

IR (film): ν = 2922 (s), 2853 (s), 1579 (s), 1556 (m), 1454 (m), 1414 (m), 1281 (w), 1125 (s), 1043 (w), 985 (w), 756 (m), 724 (w) cm^{-1}.

^1H NMR (300 MHz): δ = 8.42 (1H, dd, J = 5.5, 2.6 Hz), 7.45 (1H, td, J = 7.7, 2.2 Hz), 7.16 (1H, d, J = 8.1 Hz), 6.97-6.92 (1H, m), 3.16 (2H, t, J = 7.4 Hz), 1.71 (2H, quintet, J = 7.4 Hz), 1.48-1.39 (2H, m), 1.33-1.24 (16H, m), 0.88 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 159.8 (0), 149.6 (1), 135.9 (1), 122.2 (1), 119.2 (1), 32.1 (2), 30.3 (2), 29.8 (2), 29.7 (2), 29.5 (2), 29.4 (2), 29.1 (2), 28.9 (2), 22.9 (2), 14.3 (3) ppm.

LRMS (electrospray): m/z = 280 $(M+H)^+$.

2-(Dodecylthio)pyrimidine (91):

2-Mercaptopyrimidine (1.12g, 10.0 mmol) was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 2-(dodecylthio)pyrimidine (**91**, 2.52 g, 9.0 mmol, 90%) as a crystalline solid: mp 29-31°C.

IR (film): ν = 2923 (s), 2853 (s), 1566 (s), 1547 (s), 1466 (w), 1382 (s), 1205 (m), 795 (w), 774 (w), 750 (w) cm^{-1}.

^1H NMR (300 MHz): δ = 8.48 (2H, d, J = 4.4 Hz), 6.92 (1H, t, J = 4.8 Hz), 3.12 (2H, t, J = 7.4 Hz), 1.71 (2H, quintet, J = 7.4 Hz), 1.50-1.36 (2H, m), 1.35-1.10 (16H, m), 0.86 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 173.0 (0), 157.2 (1), 116.3 (1), 32.1 (2), 31.0 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.5 (2), 29.3 (2), 29.2 (2), 29.1 (2), 22.8 (2), 14.3 (3) ppm.

LRMS (electrospray): m/z = 281 $(M+H)^+$.

2-(Dodecylthio)-1-methylimidazole (92):

2-Mercapto-1-methylimidazole (1.14g, 10 mmol) was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 2-(dodecylthio)-1-methylimidazole (**92**, 2.52 g, 8.9 mmol, 89%) as a clear oil.

IR (film): ν = 2919 (s), 2851 (s), 1509 (w), 1463 (m), 1417 (w), 1376 (w), 1278 (m), 1125 (w), 1079 (w), 913 (w), 721 (m), 681 (m) cm^{-1}.

^1H NMR (300 MHz): δ = 7.01 (1H, d, J = 1.5 Hz), 6.87 (1H, d, J = 1.5 Hz), 3.57 (3H, s), 3.01 (2H, t, J = 7.4 Hz), 1.62 (2H, quintet, J = 7.4 Hz), 1.42-1.30 (2H, m), 1.28-1.18 (16H, m), 0.85 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 142.2 (0), 129.3 (1), 122.1 (1), 34.5 (2), 33.3 (3), 32.0 (2), 29.9 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.3 (2), 28.8 (2), 22.8 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 283 $(M+H)^+$.

3-(Dodecylthio)-4-methyl-1,2,4-triazole (93):
3-Mercapto-4-methyl-1,2,4-triazole (1.15g, 10.0 mmol) was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 3-(dodecylthio)-4-methyl-1,2,4-triazole (**93**, 2.09 g, 7.4 mmol, 74%) as a white solid: mp 68-69°C.

IR (film): ν = 2931 (s), 1519 (m), 1463 (m), 1417 (m), 1381 (m), 1218 (m), 1162 (w), 1058 (w), 998 (w), 958 (w), 885 (w), 754 (w), 723 (m), 693 (m), 648 (m) cm^{-1}.

^1H NMR (300 MHz): δ = 8.06 (1H, s), 3.50 (1H, s), 3.13 (2H, t, J = 8.1 Hz), 1.65 (2H, quintet, J = 7.4 Hz), 1.40-1.28 (2H, m), 1.28-1.12 (16H, m), 0.78 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 151.1 (0), 145.1 (1), 33.3 (2), 32.0 (2), 31.0 (3), 29.7 (2), 29.6 (2), 29.6 (2), 29.4 (2), 29.2 (2), 28.7 (2), 22.8 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 284 $(M+H)^+$, 306 $(M+Na)^+$, 567 $(2M+H)^+$, 872 $(3M+Na)^+$.

1-(Dodecylthio)*iso*quinoline (94):
1-Mercapto*iso*quinoline (1.61g, 10.0 mmol)[51] was alkylated with 1-bromododecane (2.5 mL, 11 mmol) *via* method A to afford 1-(dodecylthio)*iso*quinoline (**94**, 2.50 g, 7.6 mmol, 76%) as a clear oil.

IR (film): ν = 3051 (m), 2921 (s), 2852 (2), 1620 (w), 1584 (m), 1552 (s), 1494 (m), 1466 (m), 1337 (s), 1301 (s), 1261 (m), 1183 (w), 1148 (m), 990 (s), 813 (s), 743 (s), 676 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 8.32 (1H, d, J = 5.6 Hz), 8.23 (1H, dm, J = 7.7 Hz), 7.76 (1H, dm, J = 7.7 Hz), 7.66 (1H, td, J = 7.4, 1.4 Hz), 7.56 (1H, ddd, J = 7.5, 7.5, 1.4 Hz), 7.33 (1H, d, J = 5.8 Hz), 3.38 (2H, t J = 7.3 Hz), 1.80 (2H, quintet, J = 7.4 Hz), 1.54-1.46 (2H, m), 1.40-1.15 (16H, m), 0.90 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 160.0 (0), 141.9 (1), 135.4 (0), 130.2 (1), 127.2 (0), 127.1 (1), 126.9 (1), 124.7 (1), 117.0 (1), 31.9 (2), 29.8 (2), 29.7 (2), 29.6 (2), 29.6 (2), 29.4 (2), 29.3 (2), 29.2 (2), 29.1 (2), 22.7 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 330 $(M+H)^+$.

2-(Pentylthio)benzothiazole (95):

2-Mercaptobenzothiazole (5.0 g, 30 mmol) was alkylated with 1-bromopentane (4.1 mL, 33 mmol) *via* method A to afford 2-(pentylthio)benzothiazole (**95**, 5.07 g, 21 mmol, 71%) as a clear oil.

IR (film): ν = 2955 (s), 2858 (m), 1460 (s), 1428 (s), 1109 (m), 995 (s), 755 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.87 (1H, dm, J = 8.2 Hz), 7.74 (1H, dm, J = 8.0 Hz), 7.40 (1H, ddd, J = 8.4, 7.3, 1.3 Hz), 7.27 (1H, ddd, J = 8.3, 7.3, 1.2 Hz), 3.34 (2H, t, J = 7.4 Hz), 1.82 (2H, quintet, J = 7.1 Hz), 1.51-1.32 (4H, m), 0.92 (3H, t, J = 7.2 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 167.5 (0), 153.5 (0), 135.3 (0), 126.1 (1), 124.2 (1), 121.6 (1), 121.0 (1), 33.7 (2), 31.1 (2), 29.0 (2), 22.3 (2), 14.1 (3) ppm.

LRMS (EI+ mode): m/z = 237 (31%), 190 (37), 181 (17), 167 (100), 108 (16).

5-(Pentylthio)-1-phenyl-1*H* -tetrazole (96):

1-Phenyl-1*H* -tetrazole-5-thiol (6.6 g, 37 mmol) was alkylated with 1-bromopentane (5.0 mL, 40 mmol) *via* method A to afford 5-(pentylthio)-1-phenyl-1*H* -tetrazole (**96**, 8.3 g, 33.5 mmol, 90%) as a clear oil.

IR (film): ν = 2957 (m), 2930 (m), 2859 (m), 1597 (m), 1500 (s), 1463 (m), 1411 (s), 1386 (s), 1298 (w), 1277 (m), 1242 (m), 1108 (s), 1055 (m), 1015 (m), 980 (w), 761 (s), 694 (m), 617 (w) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63-7.50 (5H, m), 3.38 (2H, t, J = 7.2 Hz), 1.81 (2H, quintet, J = 7.3 Hz), 1.52-1.23 (4H, m), 0.89 (3H, t, J = 7.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.6 (0), 133.8 (0), 130.2 (1), 129.9 (1), 123.9 (1), 33.4 (2), 30.9 (2), 28.9 (2), 22.2 (2), 14.0 (3) ppm.

LRMS (EI+ mode): v = 248 (8%), 220 (7), 163 (7), 150 (17), 135 (6), 118 (100), 91 (19), 77 (34).

(±)-2-(2-Methylheptylthio)benzothiazole (97):
2-Mercaptobenzothiazole (0.64 g, 3.8 mmol) was alkylated with (±)-2-methyl-1-heptanol (**402**, 0.47 g, 3.6 mmol) *via* the Mitsunobu conditions of method B to yield (±)-2-(2-methylheptylthio)benzothiazole (**97**, 0.90 g, 3.2 mmol, 89%) as a clear oil.

IR (film): v = 2927 (s), 2870 (s), 1461 (s), 1428 (s), 1377 (m), 1309 (m), 1239 (m), 1125 (w), 1077 (m), 995 (s), 755 (s), 726 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.87 (1H, d, J = 8.1 Hz), 7.74 (1H, d, J = 7.9 Hz), 7.41 (1H, t, J = 7.7 Hz), 7.27 (1H, t, J = 8.1 Hz), 3.41 (1H, dd, J = 13.3, 5.6 Hz), 3.20 (1H, dd, J = 14.0, 7.5 Hz), 2.05-1.80 (1H, m), 1.60-1.20 (8H, m), 1.08 (3H, d, J = 6.8 Hz), 0.91 (3H, t, J = 6.3 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 167.8 (0), 153.4 (0), 135.3 (0), 126.0 (1), 124.1 (1), 121.5 (1), 121.0 (1), 40.8 (2), 36.2 (2), 33.3 (1), 32.0 (2), 26.7 (2), 22.7 (2), 19.5 (3), 14.2 (3) ppm.

LRMS (electrospray): m/z = 280 $(M+H)^+$.

(±)-4-Methyl-3-(2-methylheptylthio)-1,2,4-triazole (98):
3-Mercapto-4-methyl-1,2,4-triazole (0.58 g, 5.0 mmol) was alkylated with (±)-1-bromo-2-methylheptane (**403**, 1.10 g, 5.7 mmol) *via* method A to afford (±)-4-methyl-3-(2-methylheptylthio)-1,2,4-triazole (**98**, 1.14 g, 5.0 mmol, 100%) as a clear oil.

IR (film): v = 3412 (br, s), 3110 (m), 2921 (s), 1514 (s), 1463 (s), 1422 (s), 1378 (m), 1199 (s), 1161 (m), 1065 (w), 954 (w), 725 (w), 690 (m) cm^{-1}.

^1H NMR (270 MHz):δ = 8.04 (1H, s), 3.50 (3H, s), 3.18 (1H, dd, J = 12.6, 5.8 Hz), 3.00 (1H, dd, J = 12.4, 7.5 Hz), 1.84-1.65 (1H, m), 1.45-1.05 (8H, m), 0.93 (3H, d, J = 6.6 Hz), 0.77 (3H, t, J = 6.8 Hz) ppm.

^{13}C NMR (270 MHz): δ = 151.3 (0), 144.9 (1), 40.4 (2), 35.8 (2), 33.1 (1), 31.9 (2), 30.8 (3), 26.4 (2), 22.5 (2), 19.0 (3), 13.9 (3) ppm.

LRMS (electrospray): *m/z* = 455 $(2M+H)^+$, 477 $(2M+Na)^+$, 493 $(2M+K)^+$.

(±)-1-(2-Methylheptylthio)*iso*quinoline (99):
1-Mercapto*iso*quinoline (0.45 g, 2.8 mmol)[51] was alkylated with (±)-2-methyl-1-heptanol (**402**, 0.36 g, 2.8 mmol) *via* the Mitsunobu conditions of method B to yield (±)-1-(2-methylheptylthio)*iso*quinoline (**99**, 0.36 g, 1.3 mmol, 47%) as a clear oil.

IR (film): ν = 2925 (s), 1620 (w), 1584 (m), 1551 (m), 1494 (m), 1456 (m), 1375 (w), 1337 (m), 1314 (m), 1261 (m), 1183 (w), 1148 (m), 990 (s), 814 (s), 743 (m), 676 (m), 648 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 8.32 (1H, d, J = 5.6 Hz), 8.28 (1H, d, J = 8.3 Hz), 7.74 (1H, d, J = 7.9 Hz), 7.65 (1H, t, J = 7.3 Hz), 7.55 (1H, t, J = 7.9 Hz), 7.32 (1H, d, J = 5.6 Hz), 3.49 (1H, dd, J = 12.6, 5.6 Hz), 3.25 (1H, dd, J = 12.7, 7.5 Hz), 2.00-1.80 (1H, m), 1.65-1.20 (8H, m), 1.11 (3H, d, J = 6.6 Hz), 0.92 (3H, t, J = 6.8 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 160.3 (0), 142.9 (1), 135.5 (0), 130.3 (1), 127.4 (0), 127.2 (1), 127.0 (1), 124.9 (1), 117.1 (1), 37.0 (2), 36.7 (2), 33.3 (1), 32.2 (2), 26.9 (2), 22.8 (2), 19.8 (3), 14.3 (3) ppm.

LRMS (electrospray): *m/z* = 274 $(M+H)^+$.

(±)-5-(2-Methylheptylthio)-1-phenyl-1H-tetrazole (100):
1-Phenyl-1H-tetrazole-5-thiol (0.68 g, 3.8 mmol) was alkylated with (±)-2-methyl-1-heptanol (**402**, 0.47 g, 3.6 mmol) *via* the Mitsunobu conditions of method B to yield (±)-5-(2-methylheptylthio)-1-phenyl-1H-tetrazole (**100**, 0.93 g, 3.2 mmol, 89%) as a clear oil.

IR (film): ν = 2926 (s), 2856 (s), 1598 (m), 1501 (s), 1462 (m), 1410 (m), 1386 (s), 1279 (w), 1241 (m), 1088 (m), 1015 (m), 761 (s), 695 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.60-7.50 (5H, m), 3.44 (1H, dd, J = 13.8, 5.8 Hz), 3.23 (1H, dd, J = 12.6, 7.3 Hz), 2.00-1.75 (1H, m), 1.60-1.15 (8H, m), 1.01 (3H, d, J = 6.6 Hz), 0.85 (3H, t, J = 6.5 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 154.8 (0), 133.9 (0), 130.1 (1), 129.8 (1), 123.9 (1), 40.6 (2), 35.9 (2), 33.0 (1), 32.0 (2), 26.5 (2), 22.6 (2), 19.2 (3), 14.1 (3) ppm.

LRMS (electrospray): *m/z* = 291 $(M+H)^+$, 581 $(2M+H)^+$.

Sulfide oxidation method (Table 2):

In a typical experiment a stirred suspension of the heterocyclic sulfide (10 mmol) and $NaHCO_{3(s)}$ (4.2 g, 50 mmol) in CH_2Cl_2 (50 mL) at 0°C was treated portionwise with 3-chloroperoxybenzoic acid (*m*-CPBA, 8.7 g, 50 wt.%, 25 mmol). The mixture was stirred for 2 h and then allowed to warm to rt and stirred O/N. After this time the mixture was poured into sat. $Na_2S_2O_3/NaHCO_{3(aq)}$ (80 mL), stirred vigorously for 30 min and then the layers separated. The aqueous phase was extracted (2x30 mL CH_2Cl_2) and the combined organic extracts washed successively with sat. $NaHCO_{3(aq)}$ (30 mL), brine (30 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography.

2-(Dodecylsulfonyl)benzothiazole (101):

2-(Dodecylthio)benzothiazole (**89**, 2.71 g, 8.1 mmol) was oxidised *via* the above procedure to yield 2-(dodecylsulfonyl)benzothiazole (**101**, 1.52 g, 4.1 mmol, 51%) as a white solid: mp 58-60°C.

IR ($CHCl_3$): ν = 2928 (s), 2856 (m), 1472 (m), 1333 (s), 1220 (s), 1147 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 8.22 (1H, dm, J = 7.3 Hz), 8.02 (1H, dm, J = 6.8 Hz), 7.64 (1H, td, J = 7.2, 1.6 Hz), 7.59 (1H, td, J = 7.1, 2.1 Hz), 3.55-3.46 (2H, m), 1.94-1.76 (2H, m), 1.46-1.38 (2H, m), 1.32-1.18 (16H, m), 0.87 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1 (0), 152.9 (0), 136.9 (0), 128.2 (1), 127.8 (1), 125.6 (1), 122.5 (1), 54.9 (2), 32.0 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.3 (2), 29.1 (2), 28.4 (2), 22.8 (2), 22.4 (2), 14.3 (3) ppm.

LRMS (electrospray): m/z = 757 $(2M+Na)^+$.

Anal. Calcd. for $C_{19}H_{29}NO_2S_2$ (M = 367): C, 62.08; H, 7.95; N, 3.81; S, 17.45. Found: C, 62.32; H, 8.26; N, 3.70; S, 16.18.

2-(Dodecylsulfonyl)pyridine (102):

2-(Dodecylthio)pyridine (**90**, 2.79 g, 10.0 mmol) was oxidised *via* the above procedure to yield 2-(dodecylsulfonyl)pyridine (**102**, 2.18 g, 7.0 mmol, 70%) as a white solid: mp 39-42°C.

IR (film): ν = 2854 (s), 1579 (m), 1455 (m), 1428 (m), 1317 (s), 1164 (s), 1114 (m), 1083 (m), 992 (m), 776 (m) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.70 (1H, ddd, J = 5.5, 1.8, 1.1 Hz), 8.04 (1H, dt, J = 7.7, 1.1 Hz), 7.93 (1H, td, J = 7.7, 1.7 Hz), 7.52 (1H, ddd, J = 7.5, 4.8, 1.4 Hz), 3.36-3.28 (2H, m), 1.73-1.60 (2H, m), 1.39-1.26 (2H, m), 1.22-1.14 (16H, m), 0.81 (3H, t, J = 6.7 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3 (0), 150.4 (1), 138.4 (1), 127.5 (1), 122.3 (1), 52.0 (2), 32.0 (2), 29.7 (2), 29.6 (2), 29.4 (2), 29.3 (2), 29.1 (2), 28.4 (2). 22.8 (2), 22.2 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 312 $(M+H)^+$, 623 $(2M+H)^+$, 645 $(2M+Na)^+$, 956 $(3M+Na)^+$.

Anal. Calcd. for $C_{17}H_{29}NO_2S$ (M = 311): C, 65.55; H, 9.38; N, 4.50; S, 10.29. Found: C, 65.80; H, 9.93; N, 4.53; S, 9.06.

2-(Dodecylsulfonyl)pyrimidine (103):

2-(Dodecylthio)pyrimidine (**91**, 2.52 g, 9.0 mmol) was oxidised *via* the above procedure to yield 2-(dodecylsulfonyl)pyrimidine (**103**, 1.90 g, 6.1 mmol, 68%) as a white solid: mp 65-68°C.

IR ($CHCl_3$): ν = 2923 (s), 2856 (s), 1566 (s), 1466 (m), 1389 (s), 1325 (s), 1235 (m), 1125 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 8.93 (2H, d, J = 4.8 Hz), 7.58 (1H, t, J = 4.7 Hz), 3.52-3.44 (2H, m), 1.87-1.73 (2H, m), 1.45-1.30 (2H, m), 1.25-1.17 (16H, m), 0.83 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz): δ = 165.9 (0), 158.9 (1), 124.1 (1), 51.5 (2), 32.0 (2), 29.7 (2), 29.6 (2), 29.4 (2), 29.3 (2), 29.1 (2), 28.5 (2), 22.8 (2), 22.1 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 313 $(M+H)^+$, 647 $(2M+Na)^+$, 959 $(3M+Na)^+$.

Anal. Calcd. for $C_{16}H_{28}N_2O_2S$ (M = 312): C, 61.50; H, 9.03; N, 8.97; S, 10.26. Found: C, 61.71; H, 9.36; N, 8.96; S, 10.15.

2-(Dodecylsulfonyl)-1-methylimidazole (104):

2-(Dodecylthio)-1-methylimidazole (**92**, 2.52 g, 8.9 mmol) was oxidised *via* the above procedure to yield 2-(dodecylsulfonyl)-1-methylimidazole (**104**, 1.88 g, 6.0 mmol, 67%) as a white solid: mp 45-48°C.

IR (film): ν = 2920 (s), 2852 (s), 1469 (s), 1320 (s), 1279 (m), 1182 (w), 1125 (s), 915 (w), 782 (m), 720 (w), 680 (w), 632 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 7.10 (1H, d, J = 1.0 Hz), 6.99 (1H, d, J = 0.8 Hz), 3.96 (3H, s), 3.45-3.36 (2H, m), 1.85-1.72 (2H, m), 1.40-1.30 (2H, m), 1.25-1.20 (16H, m), 0.85 (3H, t, J = 6.7 Hz) ppm.

^{13}C NMR (75 MHz): δ = 142.1 (0), 129.2 (1), 125.6 (1), 55.2 (2), 35.2 (3), 32.0 (2), 29.7 (2), 29.6 (2), 29.4 (2), 29.4 (2), 29.1 (2), 28.3 (2), 22.8 (2), 22.2 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 315 $(M+H)^+$, 629 $(2M+H)^+$, 651 $(2M+Na)^+$.

Anal. Calcd. for $C_{16}H_{30}N_2O_2S$ (M = 314): C, 61.11; H, 9.62; N, 8.91; S, 10.20. Found: C, 61.91; H, 10.12; N, 8.96; S, 9.56.

3-(Dodecylsulfonyl)-4-methyl-1,2,4-triazole (105):
3-(Dodecylthio)-4-methyl-1,2,4-triazole (**93**, 2.09 g, 7.4 mmol) was oxidised *via* the above procedure to yield 3-(dodecylsulfonyl)-4-methyl-1,2,4-triazole (**105**, 1.24 g, 3.9 mmol, 53%) as a white solid: mp 77-80°C.

IR ($CHCl_3$): ν = 2927 (s), 2856 (s), 1511 (m), 1467 (m), 1329 (s), 1198 (m), 1139 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 8.21 (1H, s), 3.95 (3H, s), 3.63-3.52 (2H, m), 1.95-1.80 (2H, m), 1.50-1.30 (2H, m), 1.30-1.05 (16H, m), 0.84 (3H, t, J = 6.5 Hz) ppm.

^{13}C NMR (75 MHz): δ = 151.6 (0), 146.7 (1), 55.3 (2), 33.0 (3), 32.0 (2), 29.7 (2), 29.6 (2), 29.4 (2), 29.4 (2), 29.1 (2), 28.3 (2), 22.8 (2), 22.1 (2), 14.2 (3) ppm.

LRMS (electrospray): m/z = 316 $(M+H)^+$, 631 $(2M+H)^+$, 653 $(2M+Na)^+$.

1-(Dodecylsulfonyl)*iso*quinoline (106):
1-(Dodecylthio)*iso*quinoline (**94**, 2.38 g, 7.2 mmol) was oxidised *via* the above procedure to yield 1-(dodecylsulfonyl)*iso*quinoline (**106**, 2.0 g, 5.5 mmol, 77%) as a white solid: mp 59-60°C.

IR (film): ν = 2908 (s), 1583 (w), 1467 (m), 1371 (w), 1302 (s), 1130 (s), 833 (m), 750 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 9.02 (1H, dm, J = 8.5 Hz), 8.48 (1H, d, J = 5.4 Hz), 7.91 (1H, dm, J = 7.2 Hz), 7.84 (1H, d, J = 5.6 Hz), 7.78 (1H, ddd, J = 6.8, 6.8, 1.5 Hz), 7.72 (1H, ddd, J = 6.8, 6.8, 1.4 Hz), 3.73-3.67 (2H, m), 2.03-1.87 (2H, m), 1.56-1.40 (2H, m), 1.40-1.20 (16 H, m), 0.87 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHZ): δ = 156.3 (0), 140.1 (1), 137.7 (0), 131.3 (1), 129.2 (1), 127.5 (1), 125.1 (1), 125.1 (1), 124.0 (0), 52.3 (2), 31.9 (2), 29.6 (2), 29.5 (2), 29.3 (2), 29.3 (2), 29.1 (2), 28.5 (2), 22.7 (2), 22.2 (2), 14.1 (3) ppm.

LRMS (electrospray): m/z = 362 $(M+H)^+$, 384 $(M+Na)^+$, 426, 745 $(2M+Na)^+$.

Anal. Calcd. for $C_{21}H_{31}NO_2S$ (M = 361): C, 69.76; H, 8.64; N, 3.87; S, 8.87. Found: C, 69.98; H, 8.89; N, 3.70; S, 8.32.

2-(Pentylsulfonyl)benzothiazole (107):
2-(Pentylthio)benzothiazole (**95**, 4.9 g, 21 mmol) was oxidised *via* the above procedure to yield 2-(pentylsulfonyl)benzothiazole (**107**, 5.65 g, 21 mmol, 100%) as a white solid: 48-49°C. (CAS No. 19094-29-2).

IR (film): ν = 2932 (w), 2872 (w), 1472 (m), 1458 (w), 1329 (s), 1146 (s), 1126 (w), 1108 (w), 1087 (w), 1025 (w), 853 (w), 763 (m), 628 (w), 592 (w), 424 (w), 404 (w) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.21 (1H, dm, J = 8.0 Hz), 8.02 (1H, dm, J = 7.0 Hz), 7.69-7.53 (2H, m), 3.54-3.45 (2H, m), 1.97-1.79 (2H, m), 1.50-1.22 (4H, m), 0.86 (3H, t, J = 7.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9 (0), 152.8 (0), 136.8 (0), 128.1 (1), 127.7 (1), 125.5 (1), 122.5 (1), 54.8 (2), 30.3 (2), 22.1 (2), 22.0 (2), 13.8 (3) ppm.

LRMS (EI+ mode): m/z = 269 (7%), 177 (39), 162 (62), 135 (100), 108 (12), 90 (10).

5-(Pentylsulfonyl)-1-phenyl-1*H*-tetrazole (108):
5-(Pentylthio)-1-phenyl-1*H*-tetrazole (**96**, 2.19 g, 8.8 mmol) was oxidised *via* the above procedure to yield 5-(pentylsulfonyl)-1-phenyl-1*H*-tetrazole (**108**, 1.60 g, 5.7 mmol, 65%) as a white solid: mp 38-40°C (*i*-PrOH).

IR (film): ν = 2959 (w), 2933 (w), 2874 (w), 1498 (w), 1464 (w), 1384 (w), 1340 (m), 1229 (w), 1151 (m), 1107 (s), 1048 (m), 764 (w), 618 (m), 519 (w) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75-7.54 (5H, m), 3.78-3.68 (2H, m), 2.02-1.87 (2H, m), 1.57-1.32 (4H, m), 0.92 (3H, t, J = 7.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.6 (0), 133.2 (0), 131.6 (1), 129.8 (1), 125.2 (1), 56.1 (2), 30.3 (2), 22.2 (2), 21.8 (2), 13.8 (3) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 578 (13), 561 (50), 337 (35), 298 (26), 281 (100).

Anal. Calcd. for $C_{12}H_{16}N_4O_2S$ (M = 280): C, 51.41; H, 5.75; N, 19.98. Found C, 51.44; H, 5.82; N, 20.01.

(±)-2-(2-Methylheptylsulfonyl)benzothiazole (109):
(±)-2-(2-Methylheptylthio)benzothiazole (**97**, 0.90 g, 3.2 mmol) was oxidised *via* the above procedure to yield (±)-2-(2-methylheptylsulfonyl)benzothiazole (**109**, 0.68 g, 2.2 mmol, 68%) as a clear oil.

IR (film): ν = 2929 (s), 2857 (m), 1472 (m), 1324 (s), 1147 (s), 1086 (w), 1024 (w), 853 (m), 762 (s), 730 (m), 689 (w), 631 (m) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.18 (1H, d, J = 7.5 Hz), 7.99 (1H, d, J = 7.3 Hz), 7.62 (1H, t, J = 6.4 Hz), 7.56 (1H, t, J = 7.3 Hz), 3.55 (1H, dd, J = 14.3, 4.6 Hz), 3.33 (1H, dd, J = 14.3, 7.9 Hz), 2.40-2.15 (1H, m), 1.55-1.10 (8H, m), 1.12 (3H, d, J = 6.8 Hz), 0.81 (3H, t, 6.8 Hz) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 166.8 (0), 152.7 (0), 136.8 (0), 128.1 (1), 127.7 (1), 125.4 (1), 122.4 (1), 60.8 (2), 36.6 (2), 31.6 (2), 28.6 (1), 26.0 (2), 22.5 (2), 19.9 (3), 14.0 (3) ppm.

LRMS (electrospray): *m/z* = 312 $(M+H)^+$, 623 $(2M+H)^+$, 645 $(2M+Na)^+$, 956 $(3M+Na)^+$.

HRMS (CI+ mode, NH_3): Found $(M+H)^{+\bullet}$, 312.1072. $C_{15}H_{21}NO_2S_2$+H requires 312.1092.

(±)-4-Methyl-3-(2-methylheptylsulfonyl)-1,2,4-triazole (110):
(±)-4-Methyl-3-(2-methylheptylthio)-1,2,4-triazole (**98**, 1.36 g, 6.0 mmol) was oxidised *via* the above procedure to yield (±)-4-methyl-3-(2-methylheptylsulfonyl)-1,2,4-triazole (**110**, 1.13 g, 4.4 mmol, 73%) as a white solid: mp 58-60°C.

IR (film): ν = 2926 (s), 2860 (m), 1510 (m), 1463 (m), 1415 (w), 1323 (s), 1177 (m), 1131 (s), 770 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 8.21 (1H, s), 3.95 (3H, s), 3.64 (1H, dd, J = 14.3, 4.6 Hz), 3.42 (1H, dd, J = 14.3, 7.9 Hz), 2.40-2.15 (2H, m), 1.55-1.40 (1H, m), 1.40-1.16 (7H, m), 1.11 (3H, d, J = 6.8 Hz), 0.84 (3H, t, J = 6.7 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 152.2 (0), 146.7 (1), 61.1 (2), 36.6 (2), 33.0 (1), 31.7 (2), 28.2 (3), 26.0 (2), 22.5 (2), 19.8 (3), 14.0 (3) ppm.

LRMS (electrospray): m/z = 260 $(M+H)^+$, 519 $(2M+H)^+$, 541 $(2M+Na)^+$.

Anal. Calcd. for $C_{11}H_{21}N_3O_2S$ (M = 259): C, 50.94; H, 8.16; N, 16.20; S, 12.36. Found: C, 50.95; H, 8.56; N, 16.38; S, 11.78.

(±)-1-(2-Methylheptylsulfonyl)*iso*quinoline (111):
(±)-1-(2-Methylheptylthio)*iso*quinoline (**99**, 0.36 g, 1.32 mmol) was oxidised *via* the above procedure to yield (±)-1-(2-methylheptylsulfonyl)*iso*quinoline (**111**, 0.26 g, 0.85 mmol, 65%) as a yellow oil.

IR (film): ν = 2928 (s), 1770 (w), 1583 (m), 1456 (m), 1370 (m), 1300 (s), 1216 (w), 1130 (s), 1021 (w), 843 (m), 750 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 9.04 (1H, d, J = 8.1 Hz), 8.48 (1H, d, J = 5.4 Hz), 7.91 (1H, d, J = 7.5 Hz), 7.83 (1H, d, J = 5.4 Hz), 7.77 (1H, t, J = 7.0 Hz), 7.72 (1H, t, J = 7.9 Hz), 3.77 (1H, dd, J = 14.3, 4.5 Hz), 3.51 (1H, dd, J = 14.3, 7.7 Hz), 2.45-2.20 (1H, m), 1.62-1.45 (1H, m), 1.40-1.15 (7H, m), 1.17 (3H, d, J = 6.8 Hz), 0.86 (3H, t, J = 6.8 Hz) ppm.

^{13}C NMR (67.5 MHz): δ = 156.9 (0), 140.1 (1), 137.8 (0), 131.4 (1), 129.3 (1), 127.6 (1), 125.2 (1), 124.1 (0), 58.1 (2), 37.0 (2), 31.8 (2), 28.3 (1), 26.2 (2), 22.7 (2), 20.2 (3), 14.1 (3) ppm.

LRMS (electrospray): m/z = 306 $(M+H)^+$, 611 $(2M+H)^+$, 633 $(2M+Na)^+$, 938 $(3M+Na)^+$.

(±)-5-(2-Methylheptylsulfonyl)-1-phenyl-1H-tetrazole (112):
(±)-5-(2-Methylheptylthio)-1-phenyl-1H-tetrazole (**100**, 0.93 g, 3.2 mmol) was oxidised *via* the above procedure to yield (±)-5-(2-methylheptylsulfonyl)-1-phenyl-1H-tetrazole (**112**, 0.74 g, 2.3 mmol, 71%) as a clear oil.

IR (film): ν = 2930 (s), 2859 (s), 1770 (w), 1596 (m), 1498 (s), 1463 (m), 1339 (s), 1153 (s), 1076 (w), 1044 (w), 1015 (w), 919 (w), 824 (w), 763 (s), 688 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.70-7.54 (5H, m), 3.81 (1H, dd, J = 14.5, 4.6 Hz), 3.58 (1H, dd, J = 14.5, 7.9 Hz), 2.40-2.24 (1H, m), 1.60-1.20 (8H, m), 1.15 (3H, d, J = 6.8 Hz), 0.88 (3H, t, J = 6.6 Hz) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 154.2 (0), 133.2 (0), 131.5 (1), 129.8 (1), 125.3 (1), 62.0 (2), 36.6 (2), 31.7 (2), 28.4 (1), 26.1 (2), 22.6 (2), 19.8 (3), 14.1 (3) ppm.

LRMS (electrospray): m/z = 361 $(M+K)^+$, 667 $(2M+Na)^+$.

HRMS (CI+ mode, NH_3): Found $(M+H)^{+\bullet}$, 323.1538. $C_{15}H_{22}N_4O_2S$+H requires 323.1542.

Julia olefination under Barbier conditions (Table 3):

In a typical procedure a stirred solution of the heterocyclic sulfone (0.5 mmol) and carbonyl compound (0.55 mmol) in anhydrous THF (5 mL) under $N_{2(g)}$ at –78°C was treated dropwise with LDA (1 mL, 0.6 M in THF, 0.6 mmol) over 1 min. The resultant coloured solution was stirred for 1 h and then allowed to warm to rt and stirred for a further 3 h. H_2O (5 mL), Et_2O (5 mL) and a little brine (1 mL) were added and the layers shaken and then separated. The aqueous phase was then extracted (2x5 mL Et_2O) and the combined organic extracts dried ($MgSO_4$). Silica (0.4 g) was then added to the ethereal solution and the solvent removed *in vacuo*. The silica adsorbed residue was then loaded onto a packed column (ϕ 2 cm, 3 cm depth, silica) and eluted with hexanes. The pure hydrocarbon alkene products were completely contained within the first six 5 mL fractions.

Alkenes **113** to **121** were obtained as isomeric mixtures from the above procedure when the appropriate sulfone and carbonyl compounds were coupled. Yields and stereoselectivities are listed in Table 3. The spectroscopic data which follows for individual alkene isomers was typically extracted from spectra containing a mixture of all possible isomers, as such some spectra are incomplete and none constitute characterisation data for the compounds (isomers were not separable by the simple purification procedure detailed above). The following discussion illustrates how a given stereochemistry was assigned to a particular major isomer.

Stereochemical assignment of alkenes 113 to 121: γ-gauche effects in ^{13}C NMR spectroscopy

For the majority of the alkenes given in Table 3, ^{1}H NMR spectra were ineffectual for the assignment of stereochemistry. Infact, only for the two unsymmetric disubstituted alkenes **114** and **118** were proton spectra useful, here vicinal vinyl couplings were evident (typically for the *trans* isomer J = 15-18 Hz, and for the *cis* isomer J = 10-12 Hz[154]). For the other alkenes so-called γ-gauche effects[154,155,163] in ^{13}C NMR spectroscopy were used to determine the stereochemistry of the major isomer in a mixture.

A hydrogen bearing carbon atom which is conformationally fixed γ-gauche or γ-eclipsed with respect to another such carbon atom experiences a significant upfield shift. The effect is believed to be due to the forced overlap of $\sigma_{C\text{-}H}$ bonding orbitals which results in a shift of electron density towards the carbon nuclei thus shielding them[155]. Obviously such an effect can be used to discriminate between the two isomers of an alkene within a mixture. Figure 17 illustrates the effect for olefin **115**; when presented with the ^{13}C NMR spectrum containing a mixture of both alkenes, DEPT experiments (90° and 135°) are used to identify the two allylic methyl carbon resonances. The further upfield signal can be attributed to the *E* isomer, here the allylic methyl group is sterically compressed by the adjacent chain. Providing there is a significant difference in the relative quantities of the two isomers present in the mixture, most, if not all of the peaks within the carbon spectrum can be assigned to a particular geometrical isomer.

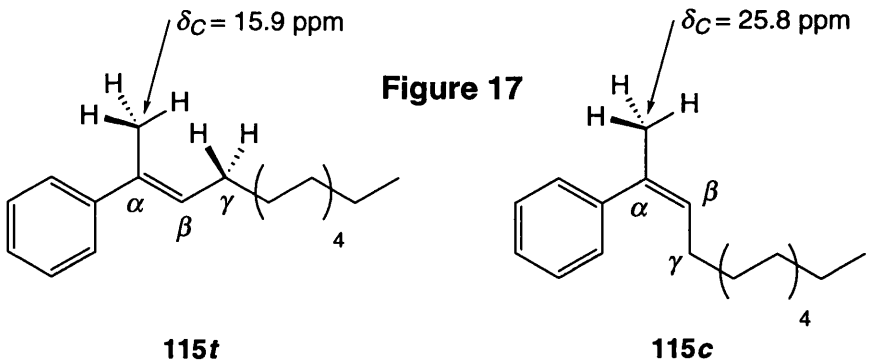


Figure 17

115*t* **115*c***

In the following NMR assignments chemical shifts in bold signify the diagnostic resonance(s) for geometrical isomer assignment.

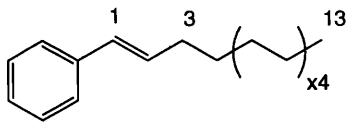
(*E*)-12-Tetracosene (113*t*):

^{13}C NMR in agreement with that previously reported[164]. (CAS No. 76665-54-8).

(*Z*)-12-Tetracosene (113*c*):

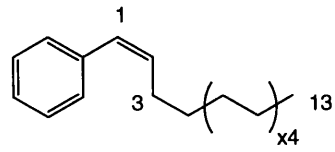
^{13}C NMR in agreement with that previously reported[164]. (CAS No. 77428-46-7).

(*E*)-1-Phenyl-1-tridecene (114*t*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.50-7.10 (5H, m, Ar), **6.40** (1H, d, J = 15.8 Hz, H1), **6.25** (1H, dt, J = 15.8, 6.7 Hz, H2), 2.23 (2H, q, J = 7.0 Hz, H3), 1.60-1.40 (2H, m, H4), 1.40-1.15 (16H, m), 0.95 (3H, t, J = 6.7 Hz, H13) ppm. (CAS No. 42036-74-8).

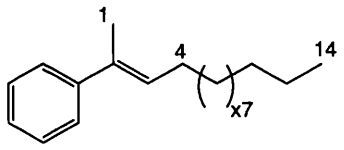
(*Z*)-1-Phenyl-1-tridecene (114*c*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.50-7.10 (5H, m, Ar), **6.43** (1H, d, J = 11.4 Hz, H1), **5.70** (1H, dt, J = 11.6, 7.3 Hz, H2), 2.35 (2H, q, J = 7.0 Hz, H3), 1.60-1.40 (2H, m, H4), 1.40-1.15 (16H, m), 0.95 (3H, t, J = 6.7 Hz, H13) ppm. (CAS No. 83897-71-6).

lit.[165] ^{1}H NMR (100 MHz, $CDCl_3$, isomer mixture): δ = 7.5-7.0 (5H, m), 6.55-6.00 ($1H_Z$ + $2H_E$, m), 5.62 ($1H_Z$, dt, J = 12, 7 Hz), 2.4-2.2 (2H, m), 1.5-1.3 (18H, m), 0.96 (3H, m) ppm.

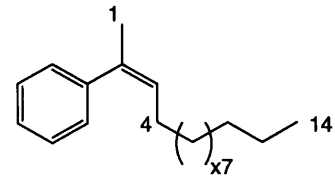
(*E*)-2-Phenyl-2-tetradecene (115*t*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.35-7.10 (5H, m, Ar), 5.74 (1H, t, J = 7.3 Hz, H3), 2.14 (2H, q, J = 7.0 Hz, H4), 1.97 (3H, s, H1), 1.45-1.10 (18H, m), 0.83 (3H, t, J = 6.6 Hz, H14) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.3 (0, C2), 134.6 (0, Ar), 129.0 (1, Ar), 128.3 (2C, 1, Ar), 126.6 (1, C3), 125.8 (2C, 1, Ar), 32.1 (2, C12), 29.8 (intense, 2), 29.6 (2), 29.6 (2), 29.0 (2), 22.9 (2, C13), **15.9** (3, C1), 14.3 (3, C14) ppm.

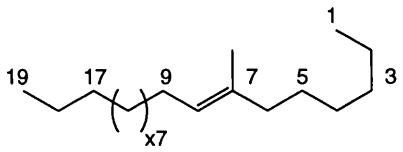
(*Z*)-2-Phenyl-2-tetradecene (115*c*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.35-7.10 (5H, m, Ar), 5.41 (1H, t, J = 7.3 Hz, H3), 1.97 (3H, s, H1), 1.91 (2H, q, J = 7.1 Hz, H4), 1.45-1.10 (18H, m), 0.83 (3H, t, J = 6.6 Hz, H14) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 142.5 (0, C2), 136.1 (0, Ar), 128.2 (intense, 1, Ar), 126.5 (1, C3), 32.1 (2, C12), 30.4 (2, C4), 29.8 (intense, 2), 29.7 (2), 29.6 (2), 29.5 (2), 29.3 (2), **25.8** (3, C1), 22.9 (2, C13), 14.3 (3, C14) ppm.

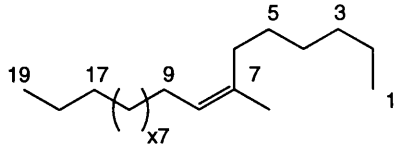
(*E*)-7-Methyl-7-nonadecene (116*t*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.13 (1H, t, J = 7.3 Hz, H8), 2.10-1.90 (4H, m, H6, H9), 1.59 (3H, s, C7-Me), 1.35-1.20 (26H, m), 0.90 (6H, m, H1, H19) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 135.3 (0, C7), 124.8 (1, C8), **40.0** (2, C6), 32.1 (2C, 2, C3, C17), 30.2 (2, C9), 29.9 (intense, 2), 29.6 (2), 29.2 (2), 28.2 (2), 28.1 (2), 22.9 (2C, 2, C2, C18), **16.1** (3, C7-Me), 14.3 (2C, 3, C1, C19) ppm.

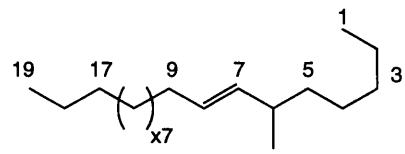
(*Z*)-7-Methyl-7-nonadecene (116*c*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.13 (1H, t, J = 7.3 Hz, H8), 2.10-1.90 (4H, m, H6, H9), 1.69 (3H, s, C7-Me), 1.35-1.20 (26H, m), 0.90 (6H, m, H1, H19) ppm.

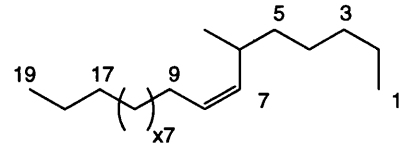
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 135.6 (0, C7), 125.5 (1, C8), 32.2 (2C, 2, C3, C17), **32.0** (2, C6), 30.4 (2, C9), 29.9 (intense, 2), 29.6 (2), 28.3 (2), 28.0 (2), **23.6** (3, C7-Me), 22.9 (2C, 2, C2, C18), 14.3 (2C, 3, C1, C19) ppm.

(*E*)-6-Methyl-7-nonadecene (117*t*):



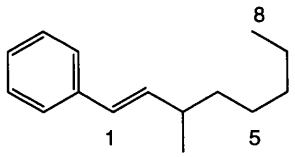
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.7 (1, C7), 128.7 (1, C8), 37.5 (2, C5), **36.9** (1, C6), 32.8 (2, C17), 29.9 (intense, 2), 29.8 (2), 29.6 (2), 29.4 (2), 27.3 (2), 22.9 (2C, 2, C2, C18), 21.2 (3, C6-Me), 14.3 (2C, 3, C1, C19) ppm.

(*Z*)-6-Methyl-7-nonadecene (117*c*):



^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.6 (1, C7), 128.6 (1, C8), 37.8 (2, C5), 32.3 (2, C3), 32.2 (2, C17), **31.9** (1, C6), 30.2 (2, C9), 29.9 (intense, 2), 29.8 (2), 29.6 (2), 27.7 (2), 27.4 (2), 22.9 (2C, 2, C2, C18), 21.6 (3, C6-Me), 14.3 (2C, 3, C1, C19) ppm.

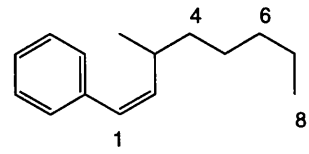
(*E*)-3-Methyl-1-phenyl-1-octene (118*t*):



^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.45-7.15 (5H, m, Ar), **6.37** (1H, d, J = 15.8 Hz, H1), **6.13** (1H, dd, J = 15.8, 7.8 Hz, H2), 2.40-2.20 (1H, m, H3), 1.45-1.20 (8H, m), 1.11 (3H, d, J = 6.8 Hz, C3-Me), 0.92 (3H, t, J = 5.5 Hz, H8) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 138.2 (0, Ar), 137.3 (1, C1), 128.6 (2C, 1, Ar), 128.1 (1, Ar), 126.9 (1, C2), 126.2 (2C, 1, Ar), **37.5** (1, C3), 37.3 (2, C4), 32.2 (2, C6), 27.3 (2, C5), 22.8 (2, C7), 20.9 (3, C3-Me), 14.3 (3, C8) ppm.

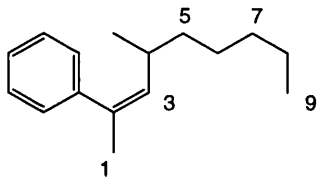
(*Z*)-3-Methyl-1-phenyl-1-octene (118*c*):



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.15 (5H, m, Ar), **6.40** (1H, d, J = 11.8 Hz, H1), **5.46** (1H, dd, J = 11.8, 10.3 Hz, H2), 2.83-2.70 (1H, m, H3), 1.45-1.20 (8H, m), 1.07 (3H, d, J = 6.6 Hz, C3-Me), 0.88 (3H, t, J = 7.4 Hz, H8) ppm.

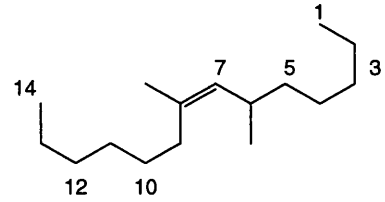
^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8 (1, C1), 128.8 (2C, 1, Ar), 128.3 (2C, 1, Ar), 127.5 (1, Ar), 126.5 (1, C2), 37.8 (2, C4), **32.3** (1, C3), 32.2 (2, C6), 27.2 (2, C5), 22.8 (2, C7), 21.2 (3, C3-Me), 14.2 (3, C8) ppm.

(*Z*)-4-Methyl-2-phenyl-2-nonene (119*c*):



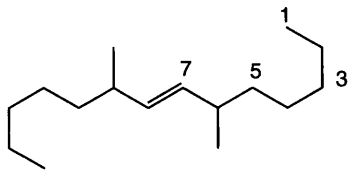
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 134.5 (1, C3), 128.2 (2C, 1, Ar), 128.1 (2C, 1, Ar), 126.4 (1, Ar), 37.8 (2, C5), 33.1 (1, C4), 32.1 (2, C7), 27.2 (2, C6), **26.0** (3, C1), 22.8 (2, C8), 21.7 (3, C4-Me), 14.3 (3, C9) ppm.

(*Z*)-6,8-Dimethyl-7-tetradecene (120*c*):



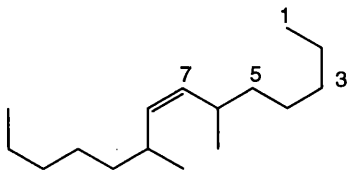
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 133.9 (0, C8), 132.3 (1, C7), 38.1 (2, C5), 32.3 (1, C6), 32.1 (2C, 2, C3, C12), 29.6 (2, C9), 28.5 (2, C11), 27.5 (2, C4), **23.6** (3, C8-Me), 22.9 (2C, 2, C2, C13), 21.8 (3, C6-Me), 14.3 (2C, 3, C1, C14) ppm.

(± & *meso*,*E*)-6,9-Dimethyl-7-tetradecene (121*t*):



^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.8 (1, C7), 134.7 (1, C7), 37.4 (both isomers, 2, C5), **37.0** (1, C6), **36.8** (1, C6), 32.2 (both isomers, 2, C3), 27.2 (2, C4), 27.1 (2, C4), 22.7 (both isomers, C2), 21.3 (3, C6-Me), 21.2 (3, C6-Me), 14.2 (both isomers, C1) ppm. (dr = 50:50)

(± &*meso*,*Z*)-6,9-Dimethyl-7-tetradecene (121*c*):



^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1 (1, C7), 134.9 (1, C7), 37.8 (2, C5), 37.7 (2, C5), 32.2 (both isomers, 2, C3), **32.2** (1, C6), **32.1** (1, C6), 27.5 (2, C4), 27.4 (2, C4), 22.7 (both isomers, 2, C2), 21.9 (3, C6-Me), 21.8 (3, C6-Me), 14.2 (both isomers, 3, C1) ppm. (dr = 50:50)

To confirm the above stereochemical assignment the phosphorane derived from the triphenylphosphonium salt of (±)-1-bromo-2-methylheptane (**403**) was oxidatively homocoupled *via* the method of Poulain[166] to yield an authentic sample of a 1:1 mixture of (±, *Z*)-6,9-dimethyl-7-tetradecene and (*meso*, *Z*)-6,9-dimethyl-7-tetradecene. ^{13}C NMR data for the mixture of *cis* olefins matches that given above.

Gas chromatography conditions for the analysis of Table 3 olefins

The following gas chromatography was carried out using a Hewlett Packard GC system fitted with a flame ionisation detector. Separations were effected using a HP5 capillary column (5% phenyl methyl silicone, dimensions 30m x 0.32 mm x 0.25 μm) at the indicated constant oven temperature with a helium carrier gas flow rate of 2 mL min^{-1}.

olefin	oven temp. (°C)	retention time (min)	
		Z	*E*
12-tetracosene (**113**)	200	17.0	17.6
1-phenyl-1-tridecene (**114**)	240	2.3	2.6
2-phenyl-2-tetradecene (**115**)	240	2.3	2.8
7-methyl-7-nonadecene (**116**)	200	4.6	4.9
6-methyl-7-nonadecene (**117**)	200	4.2	4.3
3-methyl-1-phenyl-1-octene (**118**)	150	4.7	6.6
4-methyl-2-phenyl-2-nonene (**119**)	200	1.9	2.3
6,8-dimethyl-7-tetradecene (**120**)	150	4.3	4.6
6,9-dimethyl-7-tetradecene (**121**)	130	6.9, 7.4	7.5, 7.8

–SECTION 2.2–

Synthesis of alkene standards from Tables 4 to 6

Each of the product olefins illustrated in Tables 4 to 6 were synthesised as described below in predominantly *cis* form*via* the Schlosser modification of the Wittig reaction[23] (so-called 'salt-free' conditions). For general methods for the preparation of phosphonium salts see Lawrence[136] and references therein.

Pentyltriphenylphosphonium bromide:

To a solution of triphenylphosphine (5.5 g, 21 mmol) in benzene (20 mL) at rt under $N_{2(g)}$ was added 1-bromopentane (2.50 mL, ρ = 1.22, 3.1 g, 20 mmol) and the resultant solution stirred at reflux for 24 h. A fine white precipitate of the product salt was observed to form. The mixture was then allowed to cool and filtered to yield pentyltriphenylphosphonium bromide (3.11 g, 7.5 mmol, 38%) as a white solid: mp 158-169°C.

(±)-(2-Methyl-1-heptyl)triphenylphosphonium bromide:

A stirred solution of triphenylphosphine (1.4 g, 5.3 mmol) in benzene (5 mL) at rt under $N_{2(g)}$ was treated with (±)-1-bromo-2-methylheptane (**403**, 1.0 g, 5.2 mmol) in benzene (2 mL) and the resultant mixture stirred at reflux for 42 h. No precipitate was observed to form during this time. The solvent was then removed *in vacuo*. The residue (*ca* 2.3 g) was heated to 150°C and the resultant melt stirred O/N under $N_{2(g)}$. After this time the mixture was allowed to cool and the crude oil 'triturated' with ether (to remove soluble bromide and PPh_3) to yield presumably (±)-(2-methyl-1-heptyl)triphenylphosphonium bromide (1.37 g, 3.0 mmol, 58%) as a clear oil. It proved impossible to crystallise the salt which was later used without analysis or further purification.

Wittig olefination under 'salt-free' conditions[23]:

To a stirred solution/suspension of phosphonium salt (1.0 mmol) in anhydrous THF (2 mL) at rt under $N_{2(g)}$ was added dropwise sodium hexamethyldisilazide (1.1 mL, 0.93 M in THF, 1.0 mmol) and the resultant solution of ylide stirred for 5 min. The mixture was then cooled to –78°C and treated with the neat aldehyde (2.0 mmol). After 5 min the reaction was allowed to warm to rt and stirred for a further 20 min. H_2O (5 mL) was then added followed by Et_2O (5 mL) and the layers separated. The aqueous phase was then extracted (5 mL Et_2O) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with hexanes). For branched alkenes extended reaction times were employed.

(*Z*)-Undec-5-ene (123*c*):

The title alkene was prepared *via* the above method utilising (1-pentyl)triphenylphosphonium bromide (420 mg, 1.02 mmol) and *n*-hexanal (245 μL, ρ = 0.834, 204 mg, 2.0 mmol) as

substrates. The procedure yielded (*Z*)-undec-5-ene (**123*c***, 132 mg, 0.86 mmol, 84%, *Z:E* > 95:5 by ^{13}C NMR analysis) as a clear oil. (CAS No. 764-96-5).

^{13}C NMR data in agreement with that previously reported[167].

IR (film): ν = 2958 (s), 1466 (m), 1378 (w), 1104 (w), 966 (w), 908 (w), 736 (m) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 5.44-5.29 (2H, m), 2.10-1.94 (4H, m), 1.40-1.22 (10H, m), 0.90 (3H, t, J = 6.8 Hz), 0.89 (3H, t, J = 6.6 Hz) ppm.

LRMS (EI+ mode): *m/z* = 154 (23%), 97 (17), 84 (19), 83 (24), 70 (46), 69 (68), 67 (13), 57 (24), 56 (60), 55 (100), 54 (17), 43 (27), 41 (54).

(*Z*)-1-Cyclohexyl-1-hexene (125*c*):
The title alkene was prepared *via* the above method utilising pentyltriphenylphosphonium bromide (420 mg, 1.02 mmol) and cyclohexanecarboxaldehyde (245 μL, ρ = 0.926, 227 mg, 2.0 mmol) as substrates. The procedure yielded (*Z*)-1-cyclohexyl-1-hexene (**125*c***, 141 mg, 0.85 mmol, 83%, *Z:E* = 98:2 by GC analysis) as a clear oil. (CAS No. 17301-35-8).

^1H and ^{13}C NMR data in agreement with that previously reported[168].

IR (film): ν = 2956 (s), 1448 (m), 1406 (w), 1378 (w), 944 (w), 890 (w), 728 (m) cm^{-1}.

LRMS (EI+ mode): *m/z* = 166 (43%), 109 (62), 96 (66), 81 (83), 67 (100), 55 (34), 41 (41).

(±,*Z*)-8-Methyltridec-6-ene (126*c*):
The title alkene was prepared *via* the above method utilising (±)-(2-methyl-1-heptyl)triphenylphosphonium bromide (615 mg, 1.35 mmol) and *n*-hexanal (325 μL, ρ = 0.834, 271 mg, 2.7 mmol) as substrates. The reaction was allowed 40 min for the initial ylide formation and left to stir at rt O/N before quenching. The procedure yielded (±,*Z*)-8-methyltridec-6-ene (**126*c***, 56 mg, 0.29 mmol, 21%, *Z:E* = 94:6 by GC analysis) as a clear oil.

IR (film): ν = 2928 (s), 1458 (m), 1378 (m), 1106 (w), 966 (w), 742 (m) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 5.30 (1H, dt, J = 11.0, 7.3 Hz), 5.11 (1H, dd, J = 10.8, 9.6 Hz), 2.47-2.30 (1H, m), 2.08-1.93 (2H, m), 1.40-1.14 (14H, m), 0.98-0.84 (9H, m) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 136.6 (1), 128.5 (1), 37.8 (2), 32.2 (2), 31.8 (1), 31.7 (2), 29.8 (2), 27.6 (2), 27.4 (2), 22.9 (2), 22.8 (2), 21.6 (3), 14.3 (3), 14.2 (3) ppm.

LRMS (EI+ mode): *m/z* = 196 (9%), 125 (13), 112 (10), 97 (17), 83 (43), 69 (100), 55 (76), 41 (39).

(±,*Z*)-1-Cyclohexyl-3-methyl-1-octene (127*c*):
The title alkene was prepared *via* tha above method utilising (±)-(2-methyl-1-heptyl)triphenylphosphonium bromide (520 mg, 1.14 mmol) and cyclohexanecarboxaldehyde (275 μL, ρ = 0.926, 254 mg, 2.26 mmol) as substrates. The reaction was given 40 min for the initial ylide formation and left to stir at rt O/N before quenching. The procedure yielded (±,*Z*)-1-cyclohexyl-3-methyl-1-octene (**127*c***, 74 mg, 0.36 mmol, 31%, *Z:E* = 89:11 by GC analysis) as a clear oil.

IR (film): ν = 2958 (s), 1448 (m), 1372 (w), 1270 (w), 958 (w), 890 (m), 842 (w), 746 (m) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.14 (1H, dd, *J* = 10.9, 8.9 Hz), 5.00 (1H, dd, *J* = 10.8, 9.7 Hz), 2.46-2.12 (2H, m), 1.78-1.52 (6H, m), 1.33-0.97 (12H, m), 0.93 (3H, d, *J* = 6.6 Hz), 0.89 (3H, t, *J* = 7.0 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 134.7 (1), 134.6 (1), 37.8 (2), 36.9 (1), 34.0 (2), 33.7 (2), 32.2 (2), 32.2 (1), 27.4 (2), 26.3 (2), 26.2 (2) x2, 22.9 (2), 22.0 (3), 14.3 (3) ppm.

LRMS (EI+ mode): *m/z* = 208 (20), 137 (12), 109 (47), 96 (82), 81 (100), 67 (74), 55 (89), 41 (57).

(*Z*)-1-Cyclohexenyl-1-hexene (129*c*):
The title alkene was synthesised *via* the above method utilising pentyltriphenylphosphonium bromide (413 mg, 1.0 mmol) and cyclohexenecarboxaldehyde[54] (7, 170 μL, ρ = 0.966, 164 mg, 1.5 mmol) as substrates. The procedure yielded (*Z*)-1-cyclohexenyl-1-hexene (**129*c***, 123 mg, 0.75 mmol, 75%, *Z:E* = 92:8 by GC analysis) as a clear oil. (CAS No. 85437-90-7, 137097-94-0).

^{1}H and ^{13}C NMR data in agreement with that previously reported[169].

IR (film): ν = 2928 (s), 1640 (w), 1436 (m), 1378 (w), 1340 (w), 1268 (w), 1134 (w), 1078 (w), 962 (w), 918 (m), 852 (m), 804 (w) cm^{-1}.

LRMS (EI+ mode): *m/z* = 164 (42%), 135 (31), 121 (29), 107 (31), 93 (52), 79 (100), 77 (29), 67 (45).

(±, *Z*)-1-Cyclohexenyl-3-methyl-1-octene (130*c*):

The title alkene was synthesised *via* the above method utilising (±)-(2-methyl-1-heptyl)triphenylphosphonium bromide (500 mg, 1.0 mmol) and cyclohexenecarboxaldehyde[54] (7, 170 μL, ρ = 0.966, 164 mg, 1.5 mmol) as substrates. The procedure yielded (±, *Z*)-1-cyclohexenyl-3-methyl-1-octene (**130*c***, 81 mg, 0.39 mmol, 39%, *Z:E* = 92:8 by GC analysis) as a clear oil.

IR (film): *ν* = 2848 (s), 1456 (s), 1372 (w), 1340 (w), 1268 (w), 1134 (w), 1078 (w), 964 (w), 920 (m), 854 (m), 806 (m), 762 (w), 742 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.70 (1H, d, *J* = 11.8 Hz), 5.61 (1H, m), 5.03 (1H, dd, *J* = 11.0, 11.0 Hz), 2.75-2.65 (1H, m), 2.17-2.06 (4H, m), 1.68-1.55 (4H, m), 1.36-1.18 (8H, m), 0.96 (3H, d, *J* = 6.6 Hz), 0.89 (3H, t, *J* = 6.9 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 136.5 (1), 135.8 (0), 130.4 (1), 126.8 (1), 38.1 (2), 32.7 (1), 32.2 (2), 29.2 (2), 27.4 (2), 25.8 (2), 23.1 (2), 22.9 (2), 22.4 (2), 21.9 (3), 14.3 (3) ppm.

LRMS (EI+ mode): *m/z* = 206 (48%), 163 (3), 149 (27), 135 (100), 121 (11), 107 (37), 93 (63), 79 (69).

(±, *Z*)-(1-Methylhept-2-enyloxymethyl)benzene (132*c*):

The title alkene was synthesised *via* the above method utilising pentyltriphenylphosphonium bromide (413 mg, 1.0 mmol) and 2-(benzyloxy)propanal[55] (8, 235 μL, ρ = 1.048, 246 mg, 1.5 mmol) as substrates. The procedure yielded (±, *Z*)-(1-methylhept-2-enyloxymethyl)benzene (**132*c***, 184 mg, 0.84 mmol, 84%, *Z:E* = 99:1 by GC analysis) as a clear oil.

IR (film): *ν* = 2930 (s), 1496 (w), 1454 (m), 1368 (m), 1306 (w), 1202 (w), 1094 (s), 1068 (s), 1028 (m), 910 (w) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.37-7.25 (5H, m), 5.58 (1H, dt, *J* = 5.38 (1H, dd, *J* = 10.9, 8.9 Hz), 4.59 (1H, d, *J* = 11.9 Hz), 4.37 (1H, d, *J* = 11.8 Hz), 4.31 (1H, dq, *J* = 8.8, 6.3 Hz), 2.10-1.97 (2H, m), 1.43-1.28 (4H, m), 1.27 (3H, d, *J* = 6.4 Hz), 0.91 (3H, t, *J* = 6.8 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1 (0), 132.7 (1), 132.1 (2C, 1), 128.4 (2C, 1), 127.9 (1), 127.5 (1), 70.2 (1), 69.9 (2), 32.0 (2), 27.5 (2), 22.5 (2), 21.8 (3), 14.1 (3) ppm.

LRMS (EI+ mode): *m/z* = 218 (2%), 203 (1), 160 (6), 127 (3), 112 (6), 107 (6), 91 (100), 69 (11).

(*Z*)-(1,4-Dimethylnon-2-enyloxymethyl)benzene (133*c*):
The title alkene was synthesised *via* the above method utilising (±)-(2-methyl-1-heptyl)triphenylphosphonium bromide (500 mg, 1.0 mmol) and 2-(benzyloxy)propanal[55] (8, 156 μL, ρ = 1.048, 163 mg, 1.0 mmol) as substrates. The procedure yielded a diastereomeric mixture of (*Z*)-(1,4-dimethylnon-2-enyloxymethyl)benzene (**133*c***, 111 mg, 0.43 mmol, 43%, *Z:E* = 86:14 by GC analysis) as a clear oil.

IR (film): ν = 2926 (s), 1496 (w), 1454 (m), 1370 (m), 1306 (w), 1202 (w), 1098 (s), 1070 (s), 1028 (m), 734 (s), 696 (s) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40-7.20 (5H, m), 5.40-5.22 (2H, m), 4.61 (1H, d, *J* = 11.9 Hz, major isomer), 4.37 (1H, d, *J* = 12.1 Hz, major isomer), 4.40-4.20 (1H, m), 2.45-2.26 (1H, m), 1.45-1.10 (11H, m), 1.05-0.80 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$, major isomer): δ = 139.2 (0), 130.4 (1), 128.5 (1, 2C), 127.8 (1), 127.7 (1, 2C), 127.5 (1), 70.8 (1), 70.0 (2), 37.7 (2), 32.5 (1), 32.2 (2), 27.5 (2), 22.8 (2), 22.3 (3), 21.7 (3), 14.3 (3) ppm.

LRMS (EI+ mode): *m/z* = 260 (1%), 245 (1), 202 (1), 169 (2), 152 (14), 131 (2), 112 (3), 95 (7), 91 (100), 69 (14).

Gas chromatography conditions for the analysis of olefins from Tables 4 to 6
With the exception of undec-5-ene (**123**) GC separations were effected with a Hewlett-Packard 6890 instrument equipped with a SGE HT5 capilliary column (5% phenyl equivalent polysiloxane-carborane, 12 m x 0.22 mm x 0.1 μm) and flame ionisation detector (FID) interfaced to a HP 3395 integrator. The injector was operated in split mode (75:1) and the helium carrier gas and make-up flow rates were 1.4 mL min^{-1} and 25 mL min^{-1} respectively. The injection port and detector temperatures were 255°C and 300°C respectively. [For undec-5-ene (**123**) GC separations were effected with identical hardware equipped with a DB-225 fused silica capilliary column (50% cyanopropylphenylsilicone, 30 m x 0.32 mm x 0.25 μm). The injector was operated in split mode (300:1) and the helium carrier gas and make-up flow rates were 1.5 mL min^{-1} and 25 mL min^{-1} respectively. The injection port and detector

temperatures were both set at 200°C]. All analyses were carried out by Dr W. J. Cole of the University of Glasgow. Alkene samples rich in *cis* isomer (synthesised as described above) were employed to calibrate the gas chromatographs against an internal dodecane standard [retention times are listed relative to dodecane=1; temperature programming (TP): X°C (hold time/min), Y ramp rate °C min^{-1} → Z°C (hold time/min)].

$$k_s^a = \frac{A_s n_a}{n_s A_a} \Longrightarrow n_a = \frac{k_s^a A_a n_s}{A_s}$$

k_s^a = calibration factor for standard (s), analyte (a)
n_a = amount of analyte, n_s = amount of standard
A_a = area of analyte GC peak
A_s = area of standard GC peak

olefin	TP	relative retention time		$k_{dodecane}$
		Z	*E*	
undec-5-ene (**123**)	50 (2), 3 → 90 (1)	0.80	0.78	1.090
1-cyclohexyl-1-hexene (**125**)	60 (2), 5 → 90 (1), 10 → 190 (5)	1.02	1.11	0.996
8-methyltridec-6-ene (**126**)	60 (2), 5 → 100 (1), 10→ 190 (5)	1.36	1.39	0.890
1-cyclohexyl-3-methyl-1-octene (**127**)	70 (2), 5 → 120 (1), 10 → 190 (5)	1.77	1.92	0.877
1-cyclohexenyl-1-hexene (**129**)	60 (2), 5 → 90 (1), 10 → 190 (5)	1.27	1.54	1.040
1-cyclohexenyl-3-methyl-1-octene (**130**)	70 (2), 5 → 120 (1), 10 → 190 (5)	2.20	2.68	0.942
(1-methylhept-2-enyloxy-methyl)benzene (**132**)	80 (2), 5 → 140 (1), 10 → 210 (5)	3.05	3.13	0.917
(1,4-dimethylnon-2-enyloxymethyl)benzene (**133**)	80 (2), 5 → 160 (1), 10 → 230 (5)	4.18 4.26	4.29 4.35	0.834

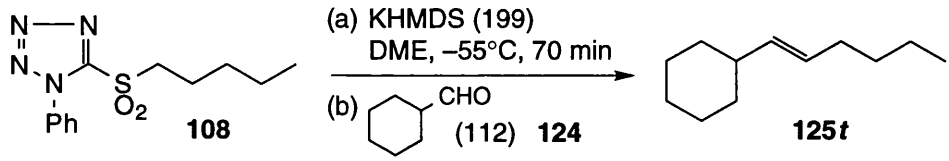
The identity of olefin peaks for each of the standard samples was verified by gas chromatography-mass spectrometry (GCMS). Analyses were carried out on a Hewlett-Packard 5971 mass selective detector interfaced to a 5890 series II gas chromatograph and computer (Vectra QS/16S). Separations were effected with a HP1 fused silica capilliary column (12.5 m x 0.2 mm x 0.33 μm). Injection and temperature programming conditions were identical to those given for GC above. Retention times from the total ion current (TIC) traces practically

matched those of the FID chromatograms. Mass spectra (70 eV) were recorded in continuous scanning mode over the range *m/z* 40 to *m/z* 600 and are given above along with other characterisation data.

Julia olefination under pre-metallation conditions (Tables 4 to 6):
To a stirred solution of the sulfone (0.2 mmol) and dodecane (23 μL, ρ = 0.749, 17 mg, 0.1 mmol, internal standard) in anhydrous reaction solvent (1 mL) at –78°C (–60°C in case of DME) under $N_{2(g)}$ was added dropwise the base (0.22 mmol of a *ca* 0.5 M solution). The mixture was then stirred for 30 min before being treated with the neat aldehyde (0.3 mmol). After stirring for a further 2 h at –78°C the reaction mixture was allowed to warm slowly to rt and stirred O/N. H_2O (1 mL) and Et_2O (2 mL) were then added and the mixture shaken well. The organic layer was then separated and dried ($MgSO_4$). An aliquot of the dry organic extract was then diluted by a factor of 5 with further Et_2O and the resultant sample subjected to GC analysis. The absolute quantity of alkene produced by the reaction (n_a) could then be assessed by using the appropriate calibration factor and setting n_s = 0.1 mmol in the above relation.

Solvent preparation: Et_2O, THF and DME were all freshly distilled from Na / benzophenone directly before use. PhMe was dried by distillation from molten sodium and stored over activated 4Å molecular sieves under an atmosphere of $N_{2(g)}$. Stock solutions of lithium hexamethyldisilazide (LiHMDS, 0.45 M in hexanes), NaHMDS (0.54 M in PhMe) and KHMDS (0.44 M in PhMe) were dispensed.

Preparation of (*E*)-1-cyclohexyl-1-hexene (125*t*):



$C_{12}H_{16}N_4O_2S$ (280.35) –55°C → rt, O/N $C_{12}H_{22}$ (166.30)

To a stirred solution of 5-(pentylsulfonyl)-1-phenyl-1*H*-tetrazole (**108**, 2.80 g, 10 mmol) in anhydrous DME (40 mL) under $N_{2(g)}$ at –55°C was added dropwise *via* cannular a similarly cooled solution of potassium hexamethyldisilazide (KHMDS, 2.74 g, 80 wt.%, 11 mmol) in anhydrous DME (20 mL) over 10 min. The initially yellow/orange solution darkened to a deep brown over the subsequent 70 min. After this time neat cyclohexanecarboxaldehyde (**124**, 1.80 mL, ρ = 0.926, 1.67 g, 15 mmol) was added dropwise over 5 min. During the following 20 min the colour dramatically lightened to a pale yellow and TLC analysis indicated complete consumption of the sulfone. The reaction mixture was then allowed to stir for 1 h at –55°C before being allowed to warm slowly to rt O/N. The resulting orange suspension was then quenched by the addition of H_2O (5 mL) and stirred for 1 h leaving a pale yellow homogeneous solution. The mixture was then diluted with Et_2O (150 mL) and H_2O (200 mL)

and the layers well shaken and then separated. The aqueous phase was then extracted (3x30 mL Et_2O) and the combined organic extracts washed successively with H_2O (3x50 mL), brine (50 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 2.74 g of a crude yellow oil. The residue was then further purified *via* column chromatography (eluting with hexanes) to yield 1.32 g of a clear non-polar oil. Subsequent kugelrohr distillation (oven temperature 180°C, 15 mmHg) yielded (*E*)-1-cyclohexyl-1-hexene (**125*t***, 1.18 g, 7.1 mmol, 71%) as a clear oil. ^{13}C NMR analysis indicated the presence of only the desired *trans* isomer.

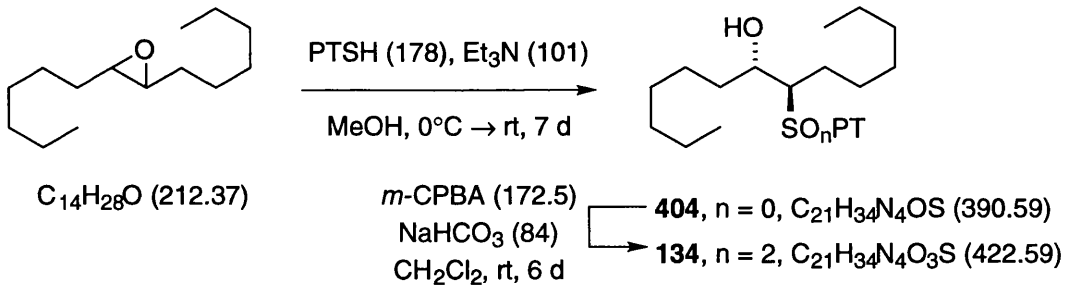
IR (film): ν = 2926 (s), 1448 (m), 1378 (w), 1258 (w), 1044 (w), 966 (s), 892 (w), 842 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.43-5.30 (2H, m), 2.03-1.94 (2H, m), 1.94-1.84 (1H, m), 1.76-1.60 (5H, m), 1.37-0.99 (9H, m), 0.90 (3H, t, J = 6.9 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 136.6 (1), 127.9 (1), 41.0 (1), 33.5 (2, 2C), 32.6 (2), 32.1 (2), 26.5 (2), 26.4 (2, 2C), 22.4 (2), 14.2 (3) ppm.

(lit.[170] IR (film): ν = 2880, 1450, 970 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 5.38 (2H, m), 2.2-0.8 (20H, m) ppm; ^{13}C NMR (15 MHz, $CDCl_3$): δ = 136.6, 127.8, 33.5, 32.5, 32.1, 26.4, 22.3, 14.0 ppm).

–SECTION 2.3–



5-[(1*R,2*S**)-1-Hexyl-2-hydroxyoctyl]thio-1-phenyl-1*H*-tetrazole (404).**
To a stirred solution of 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 4.0 g, 22.5 mmol) and (*E*)-7-tetradecene oxide[2] (1.18 g, 5.56 mmol) in MeOH (50 mL) at 0°C was added triethylamine (3.1 mL, ρ = 0.726, 2.25 g, 22.3 mmol). The resultant mixture was allowed to warm to rt and stirred for 7 d. After this time the solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (75 mL) and sat. $K_2CO_{3(aq)}$ (75 mL). The layers were well shaken and then separated. The organic phase was then washed successively with sat. $K_2CO_{3(aq)}$ (3x50 mL), 1M $HCl_{(aq)}$ (4x50 mL), brine (25 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The resulting residue was then further purified *via* column chromatography (eluting with 5-15% Et_2O in hexanes) to yield recovered oxirane (0.39 g, 1.84 mmol, 33%) and the sulfide **404** (1.26 g, 3.23 mmol, 58%) as a clear oil.

IR (film): ν = 3416 (s, br), 2926 (s), 1598 (w), 1500 (m), 1464 (m), 1386 (m), 1316 (w), 1280 (w), 1240 (w), 1074 (w), 1016 (w), 912 (w), 760 (m), 734 (m), 694 (m) 554 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.62-7.52 (5H, m), 4.10-4.04 (2H, m), 3.10-2.78 (1H, broad s), 1.83-1.73 (1H, m), 1.67-1.47 (5H, m), 1.43-1.20 (14H, m), 0.87 (3H, t, J = 6.6 Hz), 0.85 (3H, t, J = 7.1 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 154.8 (0), 133.8 (0), 130.3 (1), 129.9 (2C, 1), 124.2 (2C, 1), 74.2 (1), 56.9 (1), 33.6 (2), 31.9 (2), 31.7 (2), 29.4 (2C, 2), 29.1 (2), 27.7 (2), 26.2 (2), 22.7 (2), 22.7 (2), 14.2 (3), 14.2 (3) ppm.

LRMS (CI+ mode, NH_3): m/z = 391 (100%), 230 (9), 164 (8), 136 (16).

5-[(1*R,2*S**)-1-Hexyl-2-hydroxyoctyl]sulfonyl-1-phenyl-1*H*-tetrazole (134):** A stirred suspension of the sulfide **404** (900 mg, 2.30 mmol) and sodium hydrogencarbonate (1.0 g, 11.9 mmol) in CH_2Cl_2 (40 mL) at rt was treated with 3-chloroperoxybenzoic acid (*m*-CPBA, 4.4 g, 50 wt.%, 12.8 mmol) and stirred vigorously for 6 d. After this time the resultant gel was poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (50 mL) and stirred vigorously for 3 h. The layers were separated and the aqueous phase extracted (3x10 mL CH_2Cl_2). The combined organic extracts were then washed with sat. $NaHCO_{3(aq)}$ (2x10 mL), brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 15-20% Et_2O in hexanes) to yield the sulfone **134** (486 mg, 1.15 mmol, 50%) as a white solid: mp 68-69°C (cyclohexane).

IR (film): ν = 3458 (br, m), 2930 (s), 2856 (s), 1594 (w), 1500 (m), 1460 (w), 1332 (s), 1154 (s), 1068 (m), 770 (m), 692 (m), 620 (m), 572 (w), 540 (w) cm^{-1}.

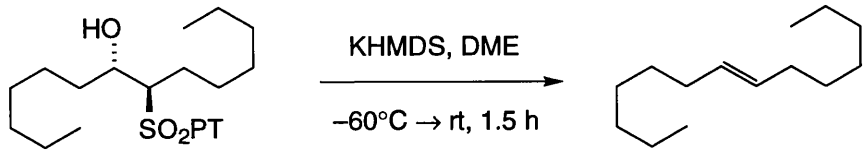
^1H NMR (360 MHz, $CDCl_3$): δ = 7.70-7.57 (5H, m), 4.34 (1H, dd, J = 8.8, 3.4 Hz), 3.76 (1H, t, J = 5.6 Hz), 2.93 (1H, br s), 2.01-1.92 (2H, m), 1.75-1.65 (1H, m), 1.64-1.42 (4H, m), 1.37-1.23 (13H, m), 0.90 (3H, t, J = 6.4 Hz), 0.88 (3H, t, J = 6.9 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 153.4 (0), 133.2 (0), 131.7 (1), 129.8 (2C, 1), 125.6 (2C, 1), 70.8 (1), 69.0 (1), 34.8 (2), 31.8 (2), 31.5 (2), 29.2 (2), 29.1 (2), 28.8 (2), 26.1 (2), 22.7 (2), 22.7 (2), 22.4 (2), 14.2 (3), 14.2 (3) ppm.

LRMS (CI+ mode, *iso*butane): m/z = 423 (20%), 230 (28), 147 (100).

Anal. Calcd. for $C_{21}H_{34}N_4O_3S$ (M = 422): C, 59.69; H, 8.11; N, 13.26. Found C, 59.77; H, 8.16; N, 13.27.

Base induced elimination of *anti*-β-hydroxysulfone 134 (Scheme 19):



134
$C_{21}H_{34}N_4O_3S$ (422.59)

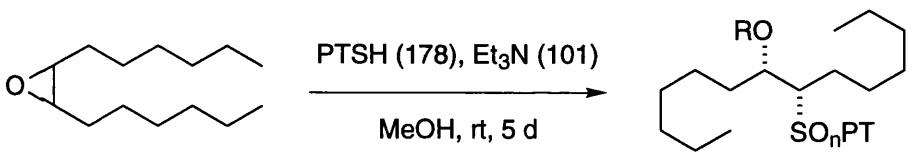
135
$C_{14}H_{28}$ (196.37)

To a stirred solution of the β-hydroxysulfone **134** (100 mg, 0.24 mmol) in anhydrous DME (2 mL) at –60°C under $N_{2(g)}$ was added dropwise potassium hexamethyldisilazide (0.69 mL, 0.45 M in DME, 0.31 mmol). The resultant mixture was stirred for 30 min and then allowed to warm slowly to rt over 1 h. The reaction was then diluted with Et_2O (10 mL) and H_2O (5 mL) and the layers shaken then separated. The aqueous phase was extracted (2x5 mL Et_2O) and the combined organic extracts washed with H_2O (2x5 mL), brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with hexanes) to afford (*E*)-7-tetradecene (**135**, 43 mg, 0.22 mmol, 91%) as a clear oil (CAS No. 41446-60-0). A single isomer was observable by ^{13}C NMR analysis.

^1H and ^{13}C NMR data was in complete agreement with that previously reported[164].

IR (film): ν = 2958 (s), 1466 (m), 1378 (w), 966 (m), 724 (w) cm^{-1}.

LRMS (EI+ mode): *m/z* = 196 (43%), 111 (27), 97 (50), 83 (72), 55 (100).



$C_{14}H_{28}O$
(212.37)

TESCl (150.7), imidazole (68)
DMAP (122), CH_2Cl_2, rt, 4 h
m-CPBA (172.5), $NaHCO_3$ (84)
CH_2Cl_2, rt, 6 d

405, R = H, n = 0, $C_{21}H_{34}N_4OS$ (390.59)

406, R = TES, n = 0, $C_{27}H_{48}N_4OSSi$ (504.85)

136, R = TES, n = 2, $C_{27}H_{48}N_4O_3SSi$ (536.85)

5-[(1*R,2*R**)-1-Hexyl-2-hydroxyoctyl]thio-1-phenyl-1*H*-tetrazole (405):**

To a stirred solution of 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 4.94 g, 27.8 mmol) and (*Z*)-7-tetradecene oxide[2] (1.47 g, 6.92 mmol) in MeOH (50 mL) at rt was added triethylamine (3.9 mL, ρ = 0.726, 2.83 g, 28.0 mmol) and the resultant mixture stirred for 5 d. After this time the

solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (75 mL). The organic phase was then washed successively with sat. $K_2CO_{3(aq)}$ (4x20 mL), 1M $HCl_{(aq)}$ (20 mL), brine (20 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to afford the sulfide **405** (1.83 g, 4.69 mmol, 68%) as a clear oil.

IR (film): ν = 3430 (s, br), 2858 (s), 1598 (w), 1500 (s), 1464 (m), 1386 (m), 1280 (w), 1240 (w), 1074 (w), 1018 (w), 912 (w), 760 (s), 730 (w), 694 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.62-7.50 (5H, m), 4.01 (1H, ddd, J = 8.9, 5.6, 3.3 Hz), 3.93 (1H, ddd, J = 7.9, 4.4, 4.4 Hz), 3.12 (1H, s br), 1.97-1.88 (1H, m), 1.80-1.68 (1H, m), 1.65-1.55 (2H, m), 1.53-1.40 (3H, m), 1.32-1.19 (13H, m), 0.85 (3H, t, J = 7.1 Hz), 0.84 (3H, t, J = 6.9 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 154.8 (0), 133.8 (0), 130.2 (1), 130.2 (2C, 1), 124.1 (2C, 1), 73.2 (1), 56.6 (1), 34.9 (2), 32.3 (2), 31.8 (2), 31.7 (2), 29.3 (2), 29.1 (2) 27.4 (2), 26.0 (2), 22.7 (2), 22.6 (2), 14.2 (3), 14.1 (3) ppm.

LRMS (CI+ mode, NH_3): m/z = 391 (100%), 230 (8), 164 (7), 136 (11).

5-[(1*R,2*R**)-1-Hexyl-2-[(triethylsilyl)oxy]octyl]sulfonyl-1-phenyl-1*H*-tetrazole (136):**

A stirred solution of the hydroxysulfide **405** (730 mg, 1.87 mmol), imidazole (380 mg, 5.59 mmol) and 4-(dimethylamino)pyridine (DMAP, 20 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (10 mL) at rt under $N_{2(g)}$ was treated with triethylsilylchloride (TESCl, 0.47 mL, ρ = 0.898, 422 mg, 2.80 mmol). After 4 h the mixture was diluted with Et_2O (20 mL) and H_2O (20 mL) and the layers shaken then separated. The aqueous phase was then extracted (2x10 mL Et_2O) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to yield 5-[(1*R**,2*R**)-1-hexyl-2-[(triethylsilyl)oxy]octyl]thio-1-phenyl-1*H*-tetrazole (**406**, *ca* 920 mg, 90 wt.% contaminated by TESOH, 1.64 mmol, 88%). A suspension of the silyl ether **406** (*ca* 920 mg, 90 wt.%, 1.64 mmol) and sodium hydrogencarbonate (800 mg, 9.5 mmol) in CH_2Cl_2 (20 mL) at rt was treated with 3-chloroperoxybenzoic acid (*m*-CPBA, 3.20 g, 50 wt.%, 9.3 mmol) and stirred for 2 d. After this time the mixture was worked-up as for sulfone **134** above and further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfone **136** [407 mg, 0.76 mmol, 41% from **405** (2 steps)] as a clear oil.

IR (film): ν = 2929 (s), 2875 (s), 1498 (m), 1462 (m), 1414 (w), 1341 (s), 1238 (w), 1153 (s), 1127 (w), 1073 (m), 1005 (m), 729 (m), 688 (m) 636 (w) cm^{-1}.

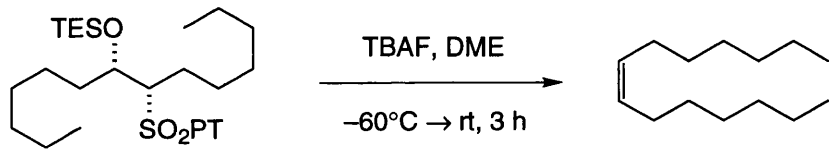
^1H NMR (360 MHz, $CDCl_3$): δ = 7.67-7.56 (5H, m), 4.38 (1H, dt, J = 7.6, 4.0 Hz), 4.05 (1H, td, J = 6.1, 4.0 Hz), 2.04-1.80 (2H, m), 1.71-1.50 (2H, m), 1.48-1.15 (16H, m), 0.94 (9H, t, J = 8.1 Hz), 0.88 (3H, t, J = 7.1 Hz), 0.88 (3H, t, J = 7.0 Hz), 0.61-0.53 (6H, m) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 154.6 (0), 133.4 (0), 131.5 (1), 129.7 (2C, 1), 125.7 (2C, 1), 70.2 (1), 69.4 (1), 34.0 (2), 31.9 (2), 31.5 (2), 29.4 (2), 29.4 (2), 27.5 (2), 25.4 (2), 25.0 (2), 22.7 (2), 22.7 (2), 14.2 (3), 14.2 (3), 7.0 (3C, 3), 5.0 (3C, 2) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 593 (19%), 537 (100), 507 (10).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 537.3297. $C_{27}H_{49}N_4O_3SSi$ requires 537.3295.

Fluoride induced elimination of *syn*-β-siloxysulfone 136 (Scheme 19):

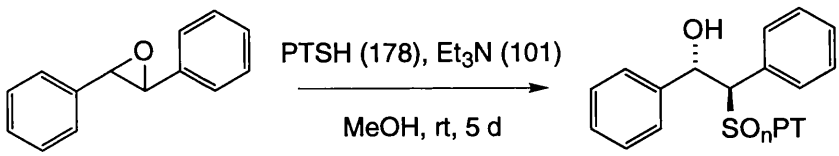


136
$C_{27}H_{48}N_4O_3SSi$ (536.85)

137
$C_{14}H_{28}$ (196.37)

To a stirred solution of the β-siloxysulfone **136** (100 mg, 0.19 mmol) in anhydrous DME (2 mL) at –60°C under $N_{2(g)}$ was added dropwise anhydrous tetra-*n*-butylammonium fluoride (TBAF, 1.9 mL, 1.0 M in DME, solvated water removed by activated 4Å MS). The resulting solution was then allowd to warm slowly to rt over 3 h. After this time the mixture was diluted with Et_2O (5 mL) and H_2O (5 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2x5 mL Et_2O) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with hexanes) to yield (*Z*)-7-tetradecene (**137**, 42 mg, 84 wt.% contaminated by TESF, 0.18 mmol, 95%) as a clear oil (CAS No. 41446-63-3). A single isomer was observable by ^{13}C NMR analysis.

^1H and ^{13}C NMR data was in complete agreement with that previously reported[164].



$C_{14}H_{12}O$ (196.24)

m-CPBA (172.5), CH_2Cl_2, rt, 8 d

407, n = 0, $C_{21}H_{18}N_4OS$ (374.46)

145, n = 2, $C_{21}H_{18}N_4O_3S$ (406.46)

5-[(1*R,2*S**)-2-Hydroxy-1,2-diphenylethyl]thio-1-phenyl-1*H*-tetrazole (407).** A solution of *trans*-stilbene oxide (1.50 g, 7.65 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 4.60 g, 25.8 mmol) in MeOH (50 mL) at rt under $N_{2(g)}$ was treated with triethylamine (4.30 mL, ρ = 0.726, 3.12 g, 30.9 mmol) and stirred for 5 d. After this time the solvent was removed *in vacuo* and the resulting residue partitioned between sat. $K_2CO_{3(aq)}$ (40 mL) and CH_2Cl_2 (50 mL). The layers were well shaken and separated. The organic phase was then washed successively with sat. $K_2CO_{3(aq)}$ (3x40 mL), 2M $HCl_{(aq)}$ (3x40 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The resulting crude solid was then recrystallised from EtOAc (30 mL) to yield the sulfide **407** (1.02 g, 2.73 mmol, 36%) as a buff solid: mp 163-165°C.

IR (KBr): ν = 3510 (br m), 1595 (w), 1499 (s), 1450 (m), 1419 (m), 1390 (s), 1295 (w), 1174 (w), 1094 (w), 1054 (m), 1015 (w), 857 (w), 764 (s), 700 (s), 686 (m), 606 (w), 557 (w), 520 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.62-7.53 (5H, m), 7.32-7.24 (10H, m), 5.53 (1H, t, J = 4.2 Hz), 5.43 (1H, d, J = 4.7 Hz), 2.86 (1H, d, J = 3.8 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 153.7 (0), 140.1 (0), 135.7 (0), 133.6 (0), 130.3 (1), 129.9 (1), 129.4 (1), 128.4 (1), 128.4 (1), 126.7 (1), 124.2 (1), 76.2 (1), 59.3 (1) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 375 (100%), 357 (9), 268 (14), 197 (30), 181 (18), 167 (5), 119 (21), 107 (10).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 375.1277. $C_{21}H_{19}N_4OS$ requires 375.1280.

Anal. Calcd. for $C_{21}H_{18}N_4OS$ (M = 374): C, 67.36; H, 4.85; N, 14.96. Found C, 67.37; H, 4.81; N, 14.86.

5-[(1*R,2*S**)-2-Hydroxy-1,2-diphenylethyl]sulfonyl-1-phenyl-1*H*-tetrazole (145):**

A stirred solution of the sulfide **407** (978 mg, 2.61 mmol) in CH_2Cl_2 (50 mL) was treated with 3-chloroperoxybenzoic acid (*m*-CPBA, 2.25 g, 50 wt.%, 6.52 mmol) and stirred at rt for

8 d. After this time the mixture was poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (100 mL) and stirred vigorously for 1 h. The layers were then separated and the aqueous phase extracted (2x25 mL CH_2Cl_2). The combined organic extracts were washed with sat. $NaHCO_{3(aq)}$ (2x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 40% EtOAc in hexanes) to yield the sulfone **145** (809 mg, 1.99 mmol, 76%) as a white solid: mp 138-140°C (50% EtOAc-hexanes).

IR (KBr): ν = 3444 (br m), 1591 (w), 1494 (m), 1453 (m), 1342 (s), 1238 (w), 1153 (s), 1061 (m), 1014 (w), 919 (w), 867 (w), 766 (s), 703 (s), 640 (s), 610 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.64 (1H, tt, J = 7.5, 1.2 Hz), 7.58-7.51 (2H, m), 7.41 (1H, tt, J = 7.2, 1.4 Hz), 7.37-7.19 (11H, m), 6.10, (1H, t, J = 3.4 Hz), 5.19 (1H, d, J = 3.1 Hz), 3.11 (1H, d, J = 3.6 Hz) ppm.

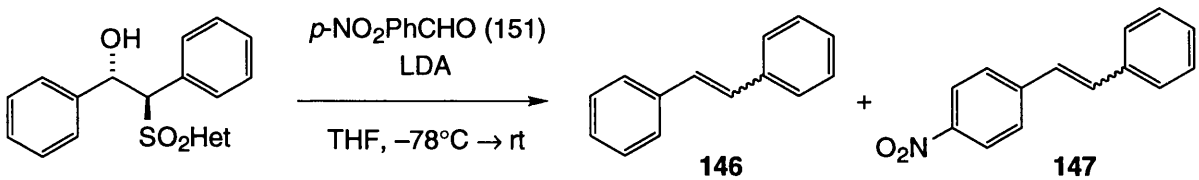
^{13}C NMR (90 MHz, $CDCl_3$): δ = 153.1 (0), 138.8 (0), 132.8 (0), 132.1 (1), 131.5 (1), 129.9 (1), 129.4 (1), 128.7 (1), 128.5 (1), 126.4 (1), 126.2 (0), 125.7 (0) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 301 (59%, $PTSO_2Bn$+H), 181 (7), 147 (16), 119 (21), 107 (100%, PhCHO).

Anal. Calcd. for $C_{21}H_{18}N_4O_3S$ (M = 406): C, 62.05; H, 4.46; N, 13.78. Found C, 62.11; H, 4.56; N, 13.83.

Cross-over experiment (Scheme 21):

The following precedure employing 5-[(1*R**,2*S**)-2-hydroxy-1,2-diphenylethyl]sulfonyl-1-phenyl-1*H*-tetrazole (**145**) is representative; an analogous experiment with the benzothiazole derivative **144** (prepared as previously described[2]) was conducted in a like manner.



144, Het = BT, $C_{21}H_{17}NO_3S_2$ (395.50)
145, Het = PT, $C_{21}H_{18}N_4O_3S$ (406.46)

146
$C_{14}H_{12}$ (180.25)

147
$C_{14}H_{11}NO_2$ (225.24)

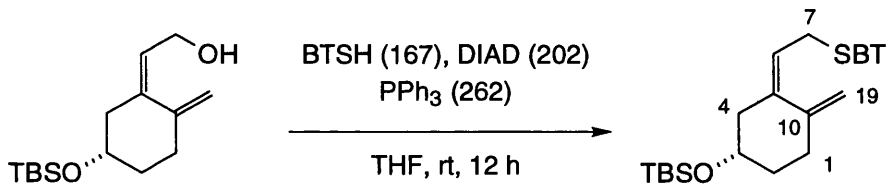
A stirred solution of 5-[(1*R**,2*S**)-2-hydroxy-1,2-diphenylethyl]sulfonyl-1-phenyl-1*H*-tetrazole (**145**, 150 mg, 0.37 mmol) and 4-nitrobenzaldehyde (61 mg, 0.40 mmol) in anhydrous THF (5 mL) at –78°C under $N_{2(g)}$ was treated dropwise with freshly prepared lithium di*iso*propylamide (LDA, 0.5 mL, 0.82 M in THF, 0.41 mmol). The resulting deep purple mixture was stirred for 30 min and then allowed to warm to rt. After a further 15 min

the reaction mixture was quenched with H_2O (5 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted (2x5 mL Et_2O). The combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 3% Et_2O in hexanes) to yield in order of elution: stilbene isomers (**146**, 23 mg, 0.13 mmol, 35%, *E:Z* = 87:13) and 4-nitrostilbene isomers (**147**, 52 mg, 96 wt.% (contaminated by benzaldehyde), 0.22 mmol, 60%, *E:Z* = 69:31) both as off-white powders. The analogous results for the BT system are given in Scheme 21.

Geometrical selectivities were determined by ^1H NMR (360 MHz, $CDCl_3$) analysis as follows. For stilbene isomers (**146**), integration of the olefinic proton resonances: δ_E = 7.15 (2H, s), δ_Z = 6.64 (2H, s) ppm. For 4-nitrostilbene isomers (**147**), integration of ortho nitro proton resonances: δ_E = 8.29 (2H, d, *J* = 8.8 Hz), δ_Z = 8.14 (2H, d, *J* = 8.8 Hz) ppm. ^1H NMR data was consistent with that previously reported for *trans*-stilbene[171] (CAS No. 103-30-0), *cis*-stilbene[172] (CAS No. 645-49-8), *trans*-4-nitrostilbene[173] (CAS No. 1694-20-8) and *cis*-4-nitrostilbene[174] (CAS No. 6624-53-9).

– SECTION 4.2 –

(*Z,S*)-2-[2-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]ethylthio]benzothiazole (201):



200
$C_{15}H_{28}O_2Si$ (268.47)

201
$C_{22}H_{31}NOS_2Si$ (417.71)

To a stirred solution of the A-ring dienol **200**[91] (540 mg, 2.0 mmol), triphenylphosphine (630 mg, 2.4 mmol) and 2-mercaptobenzothiazole (BTSH, 550 mg, 3.3 mmol) in anhydrous THF (10 mL) at rt under $N_{2(g)}$ was added dropwise neat di*iso*propyl azodicarboxylate (DIAD, 0.48 g, 2.4 mmol). The resultant solution was stirred for 12 h and then concentrated *in vacuo*. The crude residue was further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfide **201** (747 mg, 1.79 mmol, 89%) as a clear oil.

$[\alpha]_D$ = +36.9 (*c* = 1.04, $CHCl_3$).

IR (film): ν = 2934 (s), 2855 (s), 1460 (s), 1428 (s), 1252 (m), 1092 (s), 997 (s), 902 (m), 869 (m), 836 (s), 774 (s), 755 (s), 726 (m) cm^{-1}.

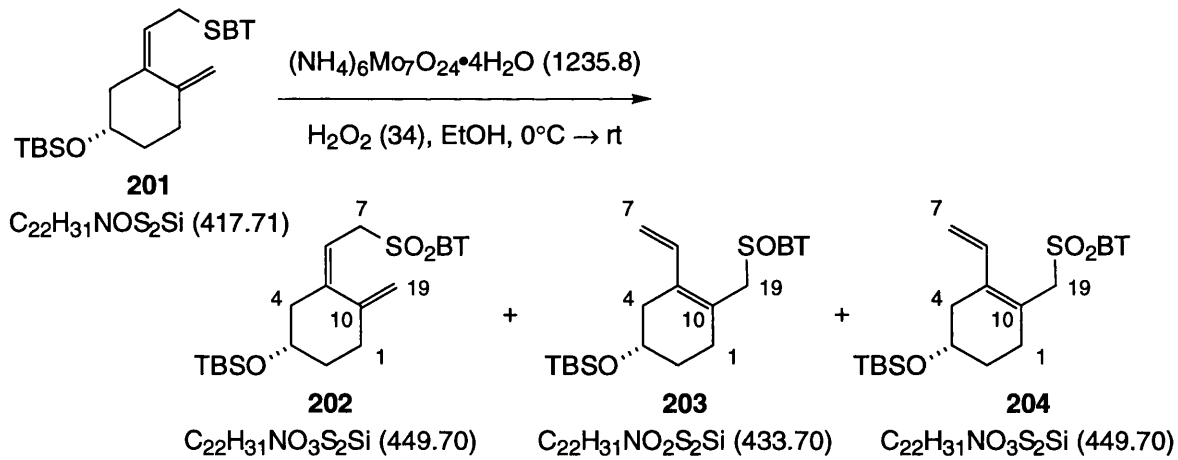
^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.88 (1H, dm, J = 8.2 Hz, BT), 7.76 (1H, dm, J = 8.0 Hz, BT), 7.42 (1H, ddd, J = 8.4, 7.3, 1.2 Hz, BT), 7.30 (1H, ddd, J = 8.1, 7.0, 1.2 Hz, BT), 5.51 (1H, tm, J = 7.8 Hz, H6), 5.06 (1H, br s, $H19_E$), 4.87 (1H, br s, $H19_Z$), 4.19 (1H, dd, J = 12.8, 7.9 Hz, $H7_A$), 4.11 (1H, ddd, J = 12.8, 7.6, 1.1 Hz, $H7_B$), 3.83 (1H, tt, J = 8.2, 3.7 Hz, H3), 2.50-2.38 (2H, m, H4), 2.22 (1H, dd, J = 12.9, 8.1 Hz, $H1_A$), 2.11 (1H, dddm, J = 14.4, 8.4, 4.4 Hz, $H1_B$), 1.90-1.82 (1H, m, $H2_A$), 1.62 (1H, dddd, J = 12.9, 9.8, 8.2, 4.6 Hz, $H2_B$), 0.87 (9H, s, CMe_3), 0.04 (6H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 167.1 (0, BT), 153.5 (0, BT), 145.1 (0, C10), 142.9 (0, C5), 135.5 (0, BT), 126.2 (1, BT), 124.3 (1, BT), 121.7 (1, BT), 121.1 (1, BT), 119.0 (1, C6), 112.1 (2, C19), 70.1 (1, C3), 46.3 (2, C4), 36.2 (2, C2), 32.6 (2, C7), 32.5 (2, C1), 26.0 (3C, 3, $C\underline{Me}_3$), 18.3 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.5 (3, $SiMe_2$) ppm.

LRMS (EI+ mode): m/z = 417 (37%), 370 (25), 285 (17), 252 (17), 224 (26), 193 (17), 149 (18), 119 (100), 91 (52), 73 (64).

HRMS (EI+ mode): Found $M^{+\bullet}$, 417.1619. $C_{22}H_{31}NOS_2Si$ requires 417.1616.

(*Z*,*S*)-2-[2-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]ethylthio]benzothiazole (202):



A stirred solution of the sulfide **201** (200 mg, 0.48 mmol) in EtOH (5 mL) at 0°C was treated with ammonium heptamolybdate tetrahydrate (150 mg, 0.12 mmol) in 30% $H_2O_{2(aq)}$ (230 mg, 2.0 mmol). The resulting yellow suspension was allowed to stir for 2 h at 0°C and then for a further 4 h at rt. The mixture was then diluted with H_2O (10 mL) and extracted (4x10 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 10-25% Et_2O in hexanes) to yield in order of elution: the sulfone **202** (44 mg, 0.10 mmol, 21%), the

isomeric sulfone **204** (28 mg, 0.06 mmol, 13%) and its parent sulfoxides **203** (113 mg, 0.26 mmol, 54%, dr = 1:1) all as clear oils.

(*Z,S*)-2-[2-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]-ethylthio]benzothiazole (**202**).

$[\alpha]_D$ = +9.2 (*c* = 0.48, $CHCl_3$).

IR (film): ν = 2930 (s), 2856 (s), 1472 (m), 1332 (s), 1252 (m), 1149 (s), 1091 (s), 868 (m), 837 (m), 763 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.23 (1H, dm, *J* = 7.6 Hz, BT), 8.02 (1H, dm, *J* = 7.6 Hz, BT), 7.65 (1H, ddd, *J* = 7.2, 7.2, 1.4 Hz, BT), 7.60 (1H, ddd, *J* = 7.3, 7.3, 1.3 Hz, BT), 5.35 (1H, t, *J* = 7.6 Hz, H6), 4.99 (1H, br s, $H19_E$), 4.83 (1H, m, $H19_Z$), 4.57 (1H, dd, *J* = 14.2, 8.9 Hz, $H7_A$), 4.28 (1H, ddd, *J* = 13.0, 6.2, 1.2 Hz, $H7_B$), 3.55 (1H, tt, *J* = 8.8, 3.8 Hz, H3), 2.42 (1H, dd, *J* = 12.9, 3.9 Hz, $H4_A$), 2.25 (1H, dt, *J* = 12.1, 4.4 Hz, $H4_B$), 2.23-2.16 (1H, m, $H1_A$), 1.77-1.67 (2H, m, $H1_B$, $H2_A$), 1.55-1.46 (1H, m, $H2_B$), 0.84 (9H, s, CMe_3), 0.00 (3H, s, $SiMe_2$), –0.01 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.0 (0, BT), 152.9 (0, BT), 149.0 (0, C10), 144.5 (0, C5), 137.0 (0, BT), 128.2 (1, BT), 127.8 (1, BT), 125.6 (1, BT), 122.5 (1, BT), 112.8 (2, C19), 108.9 (1, C6), 70.3 (1, C3), 55.4 (2, C7), 46.8 (2, C4), 36.1 (2, C2), 32.3 (2, C1), 26.0 (3C, 3, $C\underline{Me}_3$), 18.3 (0, $\underline{C}Me_3$), –4.6 (3, $SiMe_2$), –4.6 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 450 (100%), 136 (26).

HRMS (CI+ mode): Found $(M+H)^+$, 450.1595. $C_{22}H_{32}NO_3S_2Si$ requires 450.1593.

(*S*)-4-[(Benzothiazol-2-yl)sulfoxy]methyl-1-[(1,1-dimethylethyl)dimethylsilyl]oxy-3-vinylcyclohex-3-ene (**203**).

IR (film): ν = 2928 (s), 2856 (s), 1472 (m), 1427 (w), 1252 (s), 1007 (s), 1004 (m), 881 (m), 836 (s), 774 (m), 760 (m), 729 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, isomeric mixture - * denotes a resolved signal arising from a single isomer): δ = 8.06 (1H, dm, *J* = 8.2 Hz, BT), 7.99 (1H, dm, *J* = 8.1 Hz, BT), 7.56 (1H, ddd, *J* = 8.4, 7.3, 1.3 Hz, BT), 7.51-7.45 (1H, m, BT), 6.65 (1H, dd, *J* = 17.1, 11.0 Hz, H6), 5.15 (1H, d, *J* = 17.1 Hz, $H7_Z$), 4.96 (1H, d, *J* = 11.0 Hz, $H7_E$), 4.17 ($1H^*$, d, *J* = 13.1 Hz, $H19_A$), 4.09 ($1H^*$, d, *J* = 13.0 Hz, $H19_A$), 4.03 ($1H^*$, d, *J* = 13.1 Hz, $H19_B$),

3.96 (1H*, d, J = 12.8 Hz, $H19_B$), 3.99-3.90 (1H, m, H3), 2.52-2.20 (3H, m, $H4_A$, $H4_B$, $H1_A$), 2.19-2.08 (1H, m, $H1_B$), 1.85-1.74 (1H, m, $H2_A$), 1.68-1.56 (1H, m, $H2_B$), 0.89 (9H*, s, CMe_3), 0.88 (9H*, s, CMe_3), 0.07 (3H, s, $SiMe_2$), 0.07 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$, isomeric mixture - † denotes signals common to both isomers): δ = 177.6† (0, BT), 153.9† (0, BT), 136.1 (0, BT), 136.0 (0, BT), 135.4 (0, C5), 135.4 (0, C5), 133.4 (1, BT), 133.3 (1, BT), 127.0† (1, BT), 126.3† (1, BT), 124.5 (0, C10), 124.3 (0, C10), 124.1 (1, C6), 124.0 (1, C6), 122.4 (1, BT), 122.4 (1, BT), 114.4 (2, C7), 114.3 (2, C7), 67.4 (1, C3), 67.2 (1, C3), 61.9 (2, C19), 61.8 (2, C19), 35.1† (2, C4), 31.6 (2, C2), 31.4 (2, C2), 31.0 (2, C1), 30.6 (2, C1), 26.0† (3C, 3, $C\underline{Me}_3$), 18.3† (0, $\underline{C}Me_3$), –4.5† (3, $SiMe_2$), –4.5† (3, $SiMe_2$) ppm.

LRMS (CI+ mode, *iso*butane): m/z = 434 (100%), 251 (20), 184 (20), 119 (39).

(*S*)-4-[(Benzothiazol-2-yl)sulfonyl]methyl-1-[(1,1-dimethylethyl)-dimethylsilyl]oxy-3-vinylcyclohex-3-ene (**204**).

IR (film): ν = 2929 (s), 2856 (s), 1472 (s), 1334 (s), 1252 (s), 1152 (s), 1097 (s), 1006 (m), 882 (m), 837 (s), 763 (s), 729 (m) cm^{-1}.

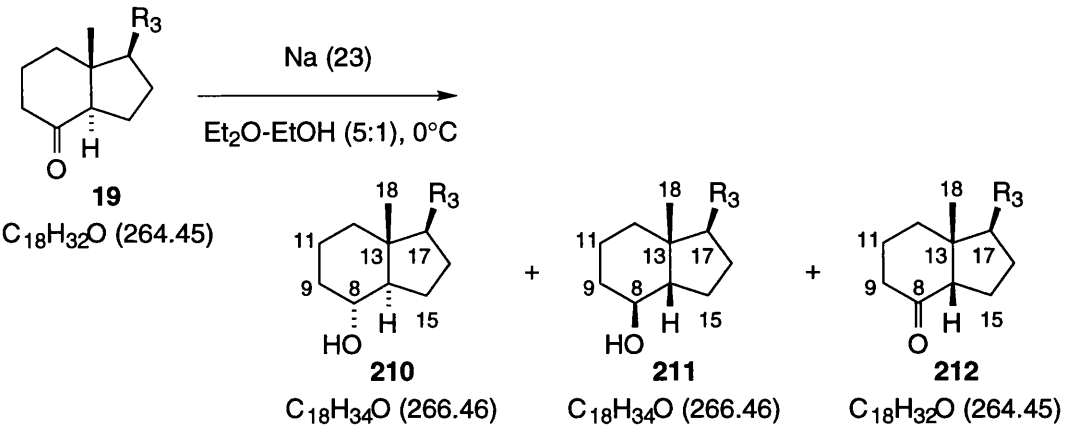
^1H NMR (360 MHz, $CDCl_3$): δ = 8.23 (1H, dm, J = 7.9 Hz, BT), 7.99 (1H, dm, J = 8.4 Hz, BT), 7.64 (1H, ddd, J = 8.2, 7.2, 1.4 Hz, BT), 7.59 (1H, ddd, J = 8.1, 7.2, 1.3 Hz, BT), 6.50 (1H, dd, J = 17.1, 10.9 Hz, H6), 5.01 (1H, d, J = 16.4 Hz, $H7_Z$), 4.79 (1H, d, J = 11.1 Hz, $H7_E$), 4.42 (1H, d, J = 14.2 Hz, $H19_A$), 4.33 (1H, d, J = 14.0 Hz, $H19_B$), 3.97-3.90 (1H, m, H3), 2.59-2.34 (3H, m, $H4_A$, $H4_B$, $H1_A$), 2.07 (1H, ddm, J = 17.2, 7.0 Hz, $H1_B$), 1.84-1.75 (1H, m, $H2_A$), 1.68-1.58 (1H, m, $H2_B$), 0.89 (9H, s, CMe_3), 0.07 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 165.4 (0, BT), 153.0 (0, BT), 137.7 (0, BT), 136.7 (0, C5), 133.1 (1, C6), 128.1 (1, BT), 127.8 (1, BT), 125.6 (1, BT), 122.3 (1, BT), 121.9 (0, C10), 114.8 (2, C7), 67.1 (1, C3), 58.8 (2, C19), 35.3 (2, C4), 31.5 (2, C2), 30.1 (2, C1), 26.0 (3C, 3, $C\underline{Me}_3$), 18.3 (0, $\underline{C}Me_3$), –4.4 (3, $SiMe_2$), –4.5 (3, $SiMe_2$) ppm.

LRMS (CI mode, *iso*butane): m/z = 450 (100%), 136 (16).

– SECTION 4.3 –

Partial reduction of Grundmann's ketone (19) with and without Amberlite® IR118 resin additive (Table 7).



Two reductions were performed in parallel, one reaction devoid of the buffering acidic resin and the other provided with 1.2 g of dried Amberlite® IR118 resin. Both adhered to the following protocol: a stirred solution of Grundmann's ketone (**19**, 100 mg, 0.38 mmol) in Et_2O-EtOH (5 mL:1 mL) at 0°C under $N_{2(g)}$ was treated portionwise with sodium metal (100 mg, 4.3 mmol, *ca* 10 portions). H_2O (5 mL) and Et_2O (5 mL) were then added and mixture filtered if need be to remove resin beads. The layers of the filtrate were separated and the aqueous phase extracted (2x5 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The resultant crude residue was further purified *via* column chromatography (eluting with 10-40% Et_2O in hexanes) to afford in order of elution a mixture of ketone epimers (**19** and **212**) and a separate mixture of alcohol diastereoisomers (**210** and **211**) both as clear oils.

The reaction without resin yielded 38 mg of alcohol isomers (0.14 mmol, 38%, **210**:**211**= 59:41 by GC analysis) and 42 mg of ketone epimers (0.16 mmol, 42%, **19**:**212**= 10:90 by ^{13}C NMR analysis). In contrast the reaction buffered by the resin yielded 39 mg of alcohol isomers (0.15 mmol, 38%, **210**:**211**> 99:1 by GC analysis) and 54 mg of ketone epimers (0.20 mmol, 54%, predominantly **19** by TLC analysis). Ketone epimers could not be effectively analysed by GC due to the interconversion of **19** to **212** upon volatilisation.

(1*R*,3a*R*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-one (Grundmann's ketone, **19**, CAS No. 66251-18-1).

^1H and ^{13}C NMR data was in complete agreement with that previously reported[100].

(1*R*,3a*R*,4*R*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-ol (**210**).
^1H NMR (360 MHz, $CDCl_3$, selected): δ = 3.58 (1H, td, J = 10.4, 4.6 Hz, H8) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$, selected): δ = 12.2 (3, C18) ppm.

Full characterisation data together with optimised preparation method for **210** are given below.

(1*R*,3a*S*,4*S*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-ol (**211**).

^{1}H NMR (360 MHz, $CDCl_3$, selected): δ = 3.34 (1H, ddd, J = 11.2, 9.8, 4.5 Hz, H8) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 71.9 (1, C8), 58.1 (1, C17), 46.1 (1, C14), 45.8 (0, C13), 39.6 (2), 36.6 (2), 35.5 (1, C20), 35.4 (2), 35.3 (2), 28.2 (1, C25), 28.0 (2), 24.4 (2), 24.1 (2), 24.0 (3, C18), 23.0 (3, C27), 22.7 (3, C26), 20.1 (2), 19.4 (3, C21) ppm.

(1*R*,3a*S*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-one (**212**).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 213.9 (0, C8), 61.6 (1, C14), 50.6 (1, C17), 48.9 (0, C13), 40.3 (2), 39.6 (2), 36.6 (2), 35.9 (2), 34.5 (1, C20), 28.1 (1, C25), 27.9 (2), 24.3 (2), 23.2 (3, C18), 23.0 (3, C27), 22.7 (3, C26), 21.4 (2), 21.0 (2), 19.3 (3, C21) ppm.

(lit.[175] ^{13}C NMR ($CDCl_3$, selected): δ = 213.3 (0, C8), 19.0 (3, C21) ppm).

(1*R*,3a*R*,4*R*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyloctahydro-1*H*-inden-4-ol (210):

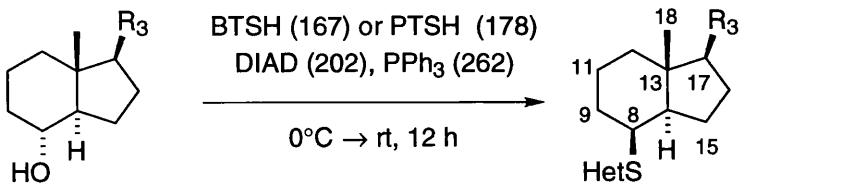
To a stirred suspension of Grundmann's ketone (**19**, 1.64 g, 6.2 mmol), dried Amberlite® IR118 acidic ion-exchange resin (10.0 g, commercially supplied grade (Aldrich) dried at 0.1 mmHg, 50°C, 5 h) and anhydrous EtOH (15 mL) in Et_2O (60 mL) at 0°C under $N_{2(g)}$ was added portionwise sodium metal (2.3 g, 100 mmol, *ca* 20 portions) over 2.5 h. After this time H_2O (15 mL) was added and the biphasic mixture filtered to remove the resin beads. The resin beads were then washed well (3x10 mL Et_2O) into the filtrate and the layers separated. The aqueous phase was then extracted (2x10 mL Et_2O) and the combined organic extracts washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 25% Et_2O in hexanes) to yield the vitamin D_3 CD-ring α-alcohol **210** (1.59 g, 6.0 mmol, 96%) as a white solid: mp 53-60°C (hexanes). (BR No. 6799217).

$[\alpha]_D$ = +17 (c = 0.45, $CHCl_3$).

IR (film): ν = 3343 (m), 2952 (s), 2931 (s), 1467 (w), 1376 (w), 1090 (s), 799 (w), 465 (m) cm^{-1}.

LRMS (EI+ mode): *m/z* = 266 (12%), 251 (7), 249 (5), 163 (7), 152 (17), 135 (20), 125 (20), 111 (100), 97 (25), 81 (25).

^1H and ^{13}C NMR data was in complete agreement with that previously reported[94].



210
$C_{18}H_{34}O$ (266.46)

215, Het = BT, $C_{25}H_{37}NS_2$ (415.70)
216, Het = PT, $C_{25}H_{38}N_4S$ (426.66)

(1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyl-4-(1-phenyl-1*H*-tetrazol-5-yl)thiooctahydro-1*H*-indene (216):

To a stirred solution of the vitamin D_3 CD-ring α-alcohol **210** (500 mg, 1.88 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 400 mg, 2.3 mmol) and triphenylphosphine (690 mg, 2.6 mmol) in anhydrous THF (10 mL) under $N_{2(g)}$ at 0°C was added dropwise di*iso*propyl azodicarboxylate (DIAD, 460 mg, 2.3 mmol) in anhydrous THF (3 mL). After 1 h the reaction was allowed to warm to rt and stirred for a further 24 h. The solvent was then removed *in vacuo* and the crude residue further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to yield the β-sulfide **216** (570 mg, 1.34 mmol, 71%) as a white solid: mp 132-134°C (hexanes).

$[\alpha]_D$ = +114 (*c* = 0.50, $CHCl_3$).

IR (film): ν = 2950 (s), 1597 (w), 1500 (m), 1464 (w), 1382 (m), 1273 (w), 1233 (w), 1086 (w), 1015 (w), 759 (s) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.70-7.50 (5H, m, PT), 4.78-4.56 (1H, m, H8), 2.25-1.00 (20H, m), 0.89 (3H, d, *J* = 6.6 Hz, H21), 0.87 (3H, d, *J* = 6.6 Hz, H27), 0.86 (3H, d, *J* = 6.6 Hz, H26), 0.80 (3H, s, H18) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 155.5 (0, PT), 134.0 (0, PT), 130.1 (1, PT), 129.9 (2C, 1, PT), 124.2 (2C, 1, PT), 56.5 (1, C17), 52.0 (1, C14), 49.3 (1, C8), 42.7 (0, C13), 40.0 (2), 39.6 (2), 36.0 (2), 35.6 (1, C20), 33.2 (2), 28.1 (1, C25), 27.2 (2), 24.4 (2), 23.8 (2), 23.0 (3, C27), 22.7 (3, C26), 18.7 (3, C21), 18.4 (2), 13.6 (3, C18) ppm.

LRMS (electrospray): *m/z* = 427 $(M+H)^+$.

Anal. Calcd. for $C_{25}H_{38}N_4S$ (M = 426): C, 70.38; H, 8.98; N, 13.13. Found C, 70.37; H, 8.97; N, 12.92.

(1*R*,3a*R*,4*S*,7a*R*)-4-(Benzothiazol-2-yl)thio-1-[(1*R*)-1,5-dimethylhexyl]-7a-methyloctahydro-1*H*-indene (215):

The vitamin D_3 CD-ring α-alcohol **210** (600 mg, 2.26 mmol) was reacted with 2-mercaptobenzothiazole (BTSH, 450 mg, 2.69 mmol) under the Mitsunobu conditions described above, to yield the β-sulfide **215** (639 mg, 1.54 mmol, 68%) as a white solid: mp = 72-73°C (hexanes).

$[\alpha]_D$ = +80.9 (c = 0.53, $CHCl_3$).

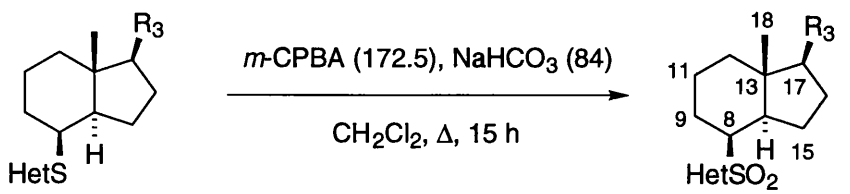
IR (KBr): ν = 2948 (s), 2864 (s), 1460 (s), 1427 (s), 1369 (w), 1238 (m), 1077 (m), 992 (s), 757 (m), 726 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.85 (1H, d, J = 8.1 Hz, BT), 7.74 (1H, d, J = 8.3 Hz, BT), 7.40 (1H, tm, J = 7.7 Hz, BT), 7.27 (1H, tm, J = 7.6 Hz, BT), 4.57-4.53 (1H, m, H8), 2.19 (1H, dm, J = 9.0), 2.02 (1H, dm, J = 12.6 Hz), 1.95-1.76 (4H, m), 1.73-1.47 (5H, m), 1.45-0.96 (10H, m), 0.92 (3H, d, J = 6.5 Hz, H21), 0.90-0.85 (6H, m, H26, H27), 0.89 (3H, s, H18) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.7 (0, BT), 153.4 (0, BT), 135.2 (0, BT), 126.0 (1, BT), 124.2 (1, BT), 121.5 (1, BT), 121.0 (1, BT), 56.7 (1, C17), 52.4 (1, C14), 48.5 (1, C8), 42.9 (0, C13), 40.3 (2), 39.7 (2), 36.1 (2), 35.7 (1, C20), 33.5 (2), 28.2 (1, C25), 27.3 (2), 24.5 (2), 24.0 (2), 23.0 (3, C27), 22.7 (3, C26), 18.7 (3, C21), 13.6 (3, C18) ppm.

LRMS (EI mode): m/z = 415 (47%), 382 (100), 248 (12), 233 (19), 168 (72), 135 (60).

Anal. Calcd. for $C_{25}H_{37}NS_2$ (M = 415): C, 72.23; H, 8.97; N, 3.37. Found C, 72.25; H, 8.91; N, 3.47.



215, Het = BT, $C_{25}H_{37}NS_2$ (415.70)
216, Het = PT, $C_{25}H_{38}N_4S$ (426.66)
217, Het = BT, $C_{25}H_{37}NO_2S_2$ (447.70)
218, Het = PT, $C_{25}H_{38}N_4O_2S$ (458.66)

(1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*)-1,5-Dimethylhexyl]-7a-methyl-4-(1-phenyl-1*H*-tetrazol-5-yl)sulfonyloctahydro-1*H*-indene (218):

To a stirred suspension of the sulfide **216** (445 mg, 1.04 mmol) and $NaHCO_{3(s)}$ (0.42 g, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was added 3-choroperoxybenzoic acid (*m*-CPBA, 0.90 g, 50 wt.%, 2.61 mmol) and the mixture stirred for 1 h followed by 5 h at reflux. TLC analysis then indicated incomplete oxidation and only showed the presence of sulfoxide. Further *m*-CPBA (0.45 g, 50 wt.%, 1.30 mmol) was then added and the reaction heated to reflux and stirred O/N. The reaction mixture was then poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (20 mL) and stirred vigorously for 1 h. The layers were then separated and the aqueous phase extracted (2x5 mL CH_2Cl_2). The combined organic extracts were then washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfone **218** (384 mg, 0.84 mmol, 81%) as a white solid: mp 98-100°C (hexanes).

$[\alpha]_D$ = +61 (*c* = 0.64, $CHCl_3$).

IR (film): ν = 2952 (s), 1595 (w), 1497 (m), 1463 (w), 1338 (s), 1158 (m), 1136 (w), 1015 (w), 762 (m), 692 (m) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.75-7.54 (5H, m, PT), 4.67 (1H, tm, *J* = 5.7 Hz, H8), 2.28-2.16 (1H, m), 2.14-1.04 (19H, m), 0.94 (3H, s, H18), 0.92 (3H, d, *J* = 6.6 Hz, H21), 0.87 (3H, d, *J* = 6.6 Hz, H27), 0.86 (3H, d, *J* = 6.6 Hz, H26) ppm.

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 154.9 (0, PT), 133.5 (0, PT), 131.5 (1, PT), 129.7 (2C, 1, PT), 125.6 (2C, 1, PT), 62.5 (1, C8), 56.0 (1, C17), 52.0 (1, C14), 41.2 (0, C13), 40.0 (2), 39.6 (2), 36.0 (1, C20), 36.0 (2), 28.2 (1, C25), 27.6 (2), 27.0 (2), 23.9 (2), 23.5 (2), 23.0 (3, C27), 22.7 (3, C26), 18.8 (3, C21), 18.4 (2), 12.7 (3, C18) ppm.

LRMS (electrospray): *m/z* = 459 $(M+H)^+$, 934 $(2M+NH_4)^+$, 939 $(2M+Na)^+$, 1397 $(3M+Na)^+$.

Anal. Calcd. for $C_{25}H_{38}N_4O_2S$ (M = 458): C, 65.47; H, 8.35; N, 12.22. Found C, 65.24; H, 8.45; N, 11.97.

(1*R*,3a*R*,4*S*,7a*R*)-4-(Benzothiazol-2-yl)sulfonyl-1-[(1*R*)-1,5-dimethylhexyl]-7a-methyloctahydro-1*H*-indene (217):

The sulfide **215** (560 mg, 1.35 mmol) was oxidised with *m*-CPBA according to the above procedure to yield the corresponding sulfone **217** (576 mg, 1.29 mmol, 95%) as a white solid: mp 138-139°C.

$[\alpha]_D$ = +31.1 (*c* = 0.28, $CHCl_3$).

IR (KBr): ν = 3432 (m), 2954 (s), 1470 (m), 1379 (s), 1321 (m), 1087 (s), 763 (m), 466 (m) cm^{-1}.

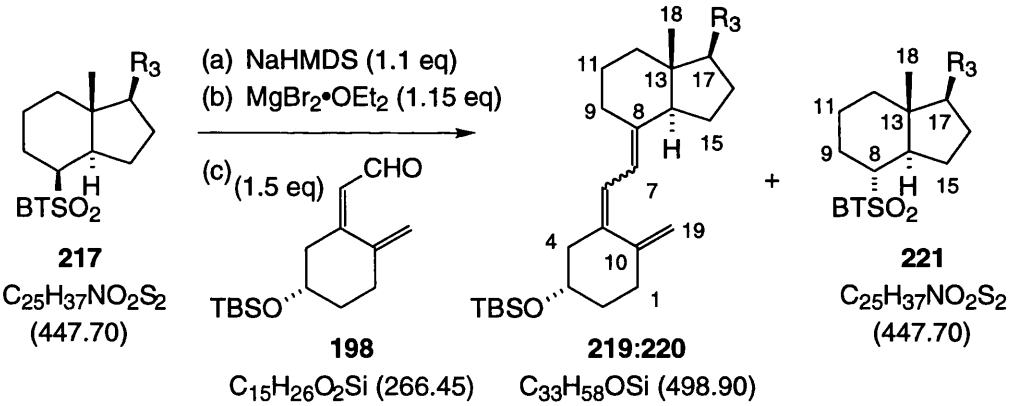
^1H NMR (360 MHz, $CDCl_3$): δ = 8.19 (1H, dm, J = 7.7 Hz, BT), 8.00 (1H, dm, J = 7.6 Hz, BT), 7.62 (1H, td, J = 7.3, 1.4 Hz, BT), 7.57 (1H, td, J = 7.2, 1.3 Hz, BT), 4.25 (1H, tm, J = 5.6 Hz, H8), 2.36 (1H, dq, J = 18.1, 6.0 Hz), 2.22-2.06 (3H, m), 1.97-1.75 (3H, m), 1.60-1.25 (7H, m), 1.24-0.99 (6H, m), 1.12 (3H, s, H18), 0.94 (3H, d, J = 6.5 Hz, H21), 0.88 (3H, d, J = 6.6 Hz, H27), 0.87 (3H, d, J = 6.6 Hz, H26) ppm.

^{13}C NMR (90MHz, $CDCl_3$): δ = 168.6 (0, BT), 152.9 (0, BT), 137.0 (0, BT), 127.9 (1, BT), 127.6 (1, BT), 125.4 (1, BT), 122.4 (1, BT), 61.2 (1, C8), 56.2 (1, C17), 52.0 (1, C14), 41.4 (0, C13), 40.3 (2), 39.6 (2), 36.0 (1, C20), 28.2 (1, C25), 27.1 (2), 27.0 (2), 23.9 (2), 23.9 (2), 23.0 (3, C27), 22.7 (3, C26), 18.8 (3, C21), 18.5 (2), 12.9 (3, C18) ppm.

LRMS (EI mode): m/z = 448 (2%), 432 (2), 383 (90), 249 (44), 136 (72), 109 (100), 83 (86).

Anal. Calcd. for $C_{25}H_{37}NO_2S_2$ (M = 447): C, 67.07; H, 8.33; N, 3.13. Found C, 67.01; H, 8.16; N, 3.16.

Unoptimsed vitamin D_3 Julia coupling studies (Table 8):



The following experiment (entry 4) is representative: To a stirred solution of sulfone **217** (100 mg, 0.22 mmol) in anhydrous Et_2O (2.5 mL) at –78°C under $N_{2(g)}$ was added dropwise sodium hexamethyldisilazide (NaHMDS, 0.26 mL, 0.93 M in THF, 0.24 mmol). The resultant yellow/orange solution was stirred for 50 min before a solution of freshly prepared magnesium bromide diethyl etherate (1.4 mL, 0.18 M in Et_2O, 0.25 mmol) was added dropwise. An immediate colour change to deep orange together with the appearance of a fine white precipitate was observed. The magnesiated sulfone was then stirred for 1 h at –78°C. A solution of freshly prepared dienal **198** (90 mg, 0.34 mmol) in anhydrous Et_2O (1 mL) was then added dropwise.

After only 3 min the colour of the reaction had lightened to yellow and TLC analysis indicated a very strong product spot. The reaction was allowed an additional 3 h before being quenched by the addition of MeOH (0.5 mL) and then allowed to warm to rt. The reaction mixture was then diluted with Et_2O (5 mL), H_2O (5 mL) added and the layers shaken and then separated. The aqueous phase was extracted with Et_2O (5 mL) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 1-10% Et_2O in hexanes) to yield 68 mg of inseparable non-polar material and the α-sulfone **221** (26 mg, 0.058 mmol, 26%) as a clear oil. ^{1}H NMR ($CDCl_3$, 200MHz) analysis of the non-polar material revealed the presence of 57 mg of *O-tert*-butyldimethylsilylvitamin D_3 isomers (**219**:**220** = 73:27, 0.114 mmol, 52%) and 11 mg of the 2*H*-pyran **229**.

O-[(1,1-Dimethylethyl)dimethylsilyl]vitamin D_3 (**219**).

^{1}H NMR (360 MHz, $CDCl_3$, selected): δ = 6.18 (1H, d, J = 11.3 Hz, H6), 6.03 (1H, d, J = 11.2 Hz, H7), 5.02 (1H, br s, $H19_E$), 4.80 (1H, br s, $H19_Z$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 145.6 (0, C10), 141.7 (0, C8), 136.4 (0, C5), 121.6 (1, C6), 118.0 (1, C7), 112.3 (2, C19), 70.8 (1, C3), 56.8 (1, C17), 56.5 (1, C14), 47.1 (2), 46.0 (0, C13), 40.8 (2), 39.7 (2), 36.6 (2), 36.4 (1, C20), 36.4 (2), 33.0 (2), 29.1 (2), 28.2 (1, C25), 27.9 (2), 26.1 (3C, 3, $C\underline{Me}_3$), 24.1 (2), 23.7 (2), 23.0 (3, C27), 22.8 (3, C26), 22.4 (2), 19.0 (3, C21), 18.4 (0, $\underline{C}Me_3$), 12.3 (3, C18), –4.4 (2C, 3, $SiMe_2$) ppm.

(7*Z*)-*O*-[(1,1-Dimethylethyl)dimethylsilyl]vitamin D_3 (**220**).

^{1}H NMR (360 MHz, $CDCl_3$, selected): δ = 6.31 (1H, d, J = 11.5 Hz, H6), 6.23 (1H, d, J = 11.6 Hz, H7), 5.06 (1H, br s, $H19_E$), 4.83 (1H, br s, $H19_Z$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$, selected): δ = 145.0 (0, C10), 141.2 (0, C8), 137.3 (0, C5), 122.8 (1, C6), 122.1 (1, C7), 112.9 (2, C19), 71.1 (1, C3), 56.3 (1, C17), 55.2 (1, C14), 47.3 (2), 46.9 (0, C13), 41.0 (2), 39.2 (2), 36.5 (2), 33.1 (2), 28.7 (2), 26.5 (2), 26.1 (3C, 3, $C\underline{Me}_3$), 24.3 (2), 24.1 (2), 19.3 (3, C21), 12.7 (3, C18), –4.4 (2C, 3, $SiMe_2$) ppm + other signals obscured by **219**.

The stereochemistry of the olefinic linkage in **220** was assigned *via* analogy with other 7*Z* derivatives of vitamin D_3 previously reported in the literature. Okamura *et al*[84] have reported NMR data for all four of the possible double bond isomers of calcitriol (**166**): ^{1}H NMR data for the (5*Z*,7*Z*)-isomer most closely matched **220**. Similarly data reported by Mouriño[103] for (5*Z*,7*Z*,9*R*)-3*O*-[(1,1-dimethylethyl)dimethylsilyl]-9-hydroxyvitamin D_3 closely matched that

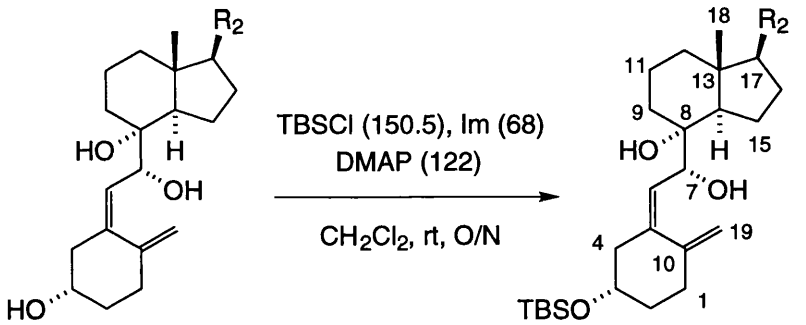
of **220** in the vinylic region, *viz*: ^{1}H NMR (250 MHz, $CDCl_3$, selected): δ = 6.42 (1H, d, J = 12 Hz, H6), 6.27 (1H, d, J = 12 Hz, H7), 5.05 (1H, s, $H19_E$), 4.78 (1H, s, $H19_Z$) ppm.

(1*R*,3a*R*,4*R*,7a*R*)-4-(Benzothiazol-2-yl)sulfonyl-1-[(1*R*)-1,5-dimethylhexyl]-7a-methyloctahydro-1*H*-indene (**221**).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.24 (1H, dm, J = 7.7 Hz, BT), 8.01 (1H, dm, J = 7.6 Hz, BT), 7.64 (1H, td, J = 7.2, 1.4 Hz, BT), 7.58 (1H, td, J = 7.3, 1.3 Hz, BT), 3.65 (1H, td, J = 11.7, 3.5 Hz, H8), 2.01-1.00 (20H, m), 0.91 (3H, d, J = 6.5 Hz, H21), 0.86 (3H, d, J = 6.6 Hz, H27), 0.85 (3H, d, J = 6.6 Hz, H26), 0.74 (3H, s, H18) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.4 (0, BT), 153.0 (0, BT), 137.0 (0, BT), 128.0 (1, BT), 127.6 (1, BT), 125.6 (1, BT), 122.4 (1, BT), 63.9 (1, C8), 55.3 (1, C17), 48.1 (1, C14), 45.0 (0, C13), 39.5 (2), 38.9 (2), 36.2 (2), 35.7 (1, C20), 28.1 (1, C25), 28.0 (2), 26.6 (2), 25.1 (2), 23.9 (2), 22.9 (3, C27), 22.7 (3, C26), 21.2 (2), 18.9 (3, C21), 12.0 (3, C18) ppm.

(3β,5*Z*,7*R*,8α,22*E*)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy-9,10-seco-ergosta-5,10(19),22-triene-7,8-diol (227):



226
$C_{28}H_{46}O_3$ (430.66)

227
$C_{34}H_{60}O_3Si$ (544.92)

To a stirred suspension of (3β,5*Z*,7*R*,8α,22*E*)-9,10-secoergosta-5,10(19),22-triene-3,7,8-triol (**226**, 5.0 g, 11.6 mmol)[91,97], imidazole (Im, 2.4 g, 35.3 mmol) and 4-(dimethylamino)pyridine (DMAP, 20 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (50 mL) at rt under $N_{2(g)}$ was added dropwise over 30 min *tert*-butylchlorodimethylsilane (TBSCl, 1.83 g, 12.2 mmol) in anhydrous CH_2Cl_2 (50 mL) and the resultant mixture stirred O/N. After this time the organic phase was washed successively with H_2O (2x50 mL), brine (50 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) to yield the monosilylated product **227** (5.60 g, 10.3 mmol, 89%) as a white powder: mp 128-129°C (hexanes).

$[\alpha]_D$ = +76.6 (*c* = 0.50, $CHCl_3$).

IR (KBr): ν = 3421 (br), 2956 (s), 2860 (s), 1461 (m), 1371 (m), 1254 (m), 1096 (s), 1005 (m), 870 (m), 837 (m), 775 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.52 (1H, dm, *J* = 9.8 Hz, H6), 5.21 (1H, dd, *J* = 15.2, 7.1 Hz, H22), 5.14 (1H, dd, *J* = 15.2, 7.4 Hz, H23), 4.98 (1H, br s, $H19_E$), 4.92 (1H, d, *J* = 9.8 Hz, H7), 4.88 (1H, br s, $H19_Z$), 3.72 (1H, tt, *J* = 9.7, 4.2 Hz, H8), 2.48-2.37 (2H, m), 2.19 (1H, ddd, *J* = 11.9, 10.0, 1.7 Hz), 2.05-1.90 (3H, m), 1.89-1.40 (10H, m), 1.30-1.08 (5H, m), 0.98 (3H, d, *J* = 6.6 Hz, H28), 0.91 (3H, d, *J* = 6.8 Hz, H21), 0.88 (9H, s, CMe_3), 0.86-0.80 (9H, m, H18, H26, H27), 0.07 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$) ppm.

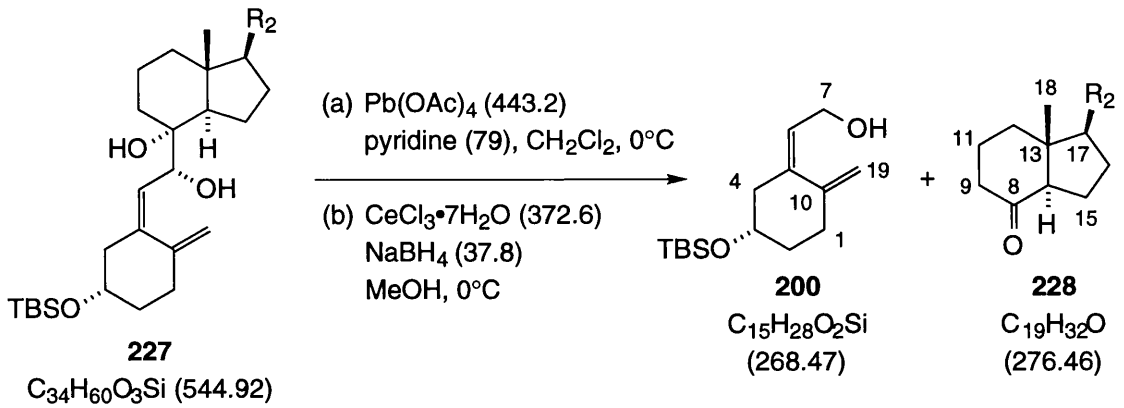
^{13}C NMR (90 MHz, $CDCl_3$): δ = 145.9 (0, C10), 141.8 (0, C5), 135.6 (1, C22), 132.2 (1, C23), 124.8 (1, C6), 111.1 (2, C19), 75.0 (0, C8), 71.4 (1, C7), 70.9 (1, C3), 59.8 (1, C17), 57.5 (1, C14), 47.2 (2), 44.2 (0, C13), 43.0 (1, C24), 40.2 (1, C20), 40.2 (2), 37.6 (2), 36.8 (2), 33.5 (2), 33.3 (1, C25), 27.9 (2), 26.0 (3C, 3, $C\underline{Me}_3$), 22.0 (2), 20.8 (3, C28), 20.6 (2), 20.2 (3, C27), 19.8 (3, C26), 18.3 (0, $\underline{C}Me_3$), 17.9 (3, C21), 13.2 (3, C18), –4.4 (3, $SiMe_2$), –4.5 (3, $SiMe_2$) ppm.

LRMS (CI mode, NH_3): *m/z* = 562 (15%), 527 (30), 509 (72), 377 (13), 294 (100), 267 (57), 249 (51).

Anal. Calcd. for $C_{34}H_{60}O_3Si$ (M = 544): C, 74.94; H, 11.10. Found C, 74.99; H, 10.9.

(*Z*,*S*)-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]-ethanol (200) and (1*R*,3a*R*,7a*R*)-7a-methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-inden-4-one (228):

To a stirred solution of the diol **227** (3.0 g, 5.5 mmol) and pyridine (1.34 mL, ρ = 0.978, 1.31 g, 16.6 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0°C under $N_{2(g)}$ was added portionwise lead(IV) acetate (2.93 g, 6.6 mmol) and the resultant suspension stirred vigorously for 10 min. The mixture was then filtered through a celite pad and the residue washed well (3x5 mL CH_2Cl_2). The filtrate and combined washings were then concentrated *in vacuo* and subsequently dissolved in a solution of cerium(III) chloride heptahydrate (4.11 g, 11.0 mmol) in MeOH (30 mL). The mixture was then cooled to 0°C, treated with sodium borohydride (0.26 g, 6.8 mmol) and stirred for 15 min. H_2O (30 mL) and Et_2O (30 mL) were then added and the layers shaken well and then separated. The aqueous phase was then further extracted (3x10 mL Et_2O) and the combined organic extracts washed with brine (15 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* column



227
$C_{34}H_{60}O_3Si$ (544.92)

200
$C_{15}H_{28}O_2Si$
(268.47)

228
$C_{19}H_{32}O$
(276.46)

chromatography (eluting with 10-15% Et_2O in hexanes) to yield in order of elution: the Windaus-Grundmann C19 ketone (**228**, 1.26 g, 4.6 mmol, 83%)[176], the corresponding over-reduced β-alcohol product (0.20 g, 0.72 mmol, 13%)[95] and the A-ring dienol **200** (1.20 g, 4.5 mmol, 81%)[91] all as clear oils.

(*Z*,*S*)-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]ethanol (**200**).

$[\alpha]_D$ = +44.0 (*c* = 0.43, $CHCl_3$).

IR (film): ν = 3340 (m, br), 2986 (s), 1472 (w), 1254 (m), 1094 (s), 1006 (m), 836 (m), 774 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.45 (1H, tm, *J* = 7.0 Hz, H6), 4.97 (1H, br s, $H19_E$), 4.63 (1H, br s, $H19_Z$), 4.27 (1H, dd, *J* = 12.5, 7.3 Hz, $H7_A$), 4.19 (1H, ddd, *J* = 12.4, 6.2, 1.8 Hz, $H7_B$), 3.85 (1H, tt, *J* = 8.6, 4.0 Hz, H3), 2.45-2.35 (2H, m), 2.25-2.17 (1H, m), 2.13-2.03 (1H, m), 1.92-1.84 (1H, m), 1.65-1.54 (1H, m), 0.89 (9H, s, CMe_3), 0.07 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 145.1 (0, C10), 140.7 (0, C5), 125.1 (1, C6), 112.1 (2, C19), 70.3 (1, C5), 60.0 (2, C7), 46.2 (2, C4), 36.2 (2, C2), 32.5 (2, C1), 26.0 (3C, 3, $C\underline{Me}_3$), 18.3 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.5 (3, $SiMe_2$) ppm.
LRMS (CI mode, NH_3): *m/z* = 286 (100%), 268 (37), 251 (16), 119 (16).

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-inden-4-one (**228**).

$[\alpha]_D$ = –19.1 (*c* = 1.00, $CHCl_3$).

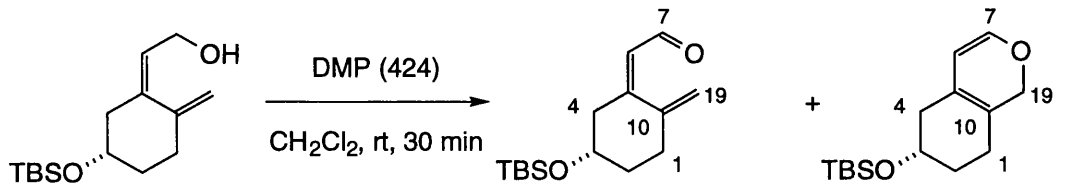
IR (film): ν = 2958 (s), 1716 (s), 1460 (m), 1372 (m), 1306 (w), 1232 (w), 1056 (w), 972 (m), 836 (w), 564 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.25 (1H, dd, J = 15.3, 7.2 Hz, H22), 5.17 (1H, dd, J = 15.3, 7.9 Hz, H23), 2.46 (1H, ddm, J = 11.0, 7.7 Hz), 2.33-2.17 (2H, m), 2.11-1.42 (14H, m), 1.35-1.30 (1H, m), 1.05 (3H, d, J = 6.7 Hz, H28), 0.92 (3H, d, J = 6.8 Hz, H21), 0.85 (3H, d, J = 6.6 Hz, H27), 0.83 (3H, d, J = 6.7 Hz, H26), 0.66 (3H, s, H18) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.3 (0, C8), 135.1 (1, C22), 132.7 (1, C23), 62.3 (1, C14), 56.8 (1, C17), 50.0 (0, C13), 43.0 (1, C24), 41.2 (2), 40.1 (1, C20), 39.1 (2), 33.2 (1, C25), 27.9 (2), 24.3 (2), 21.2 (3, C28), 20.1 (3, C27), 19.8 (3, C26), 19.3 (2), 17.8 (3, C21), 12.9 (3, C18) ppm.

LRMS (EI+ mode): m/z = 276 (100%), 261 (6), 233 (32), 215 (41), 192 (13), 178 (34), 151 (55), 133 (49), 109 (44).

(*Z,S*)-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene] ethanal (198):



200 $C_{15}H_{28}O_2Si$ (268.47)

198 $C_{15}H_{26}O_2Si$ (266.45)

229 $C_{15}H_{26}O_2Si$ (266.45)

To a stirred solution of the A-ring dienol **200** (175 mg, 0.65 mmol) in anhydrous CH_2Cl_2 (2 mL) at rt under $N_{2(g)}$ was added Dess-Martin periodinane[99,177] (DMP, 305 mg, 0.72 mmol). The resultant mixture was then stirred for 30 min and subsequently diluted with Et_2O (10 mL), poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (15 mL) and stirred vigorously for a further 10 min. The layers were then separated and the aqueous phase extracted (2x5 mL Et_2O). The combined organic extracts were then washed with sat. $NaHCO_{3(aq)}$ (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then filtered through a short (4 cm) silica pad (eluting with 7% Et_2O in hexanes) to yield a pure mixture of the aldehyde **198**[78] and its tautomeric cyclic enol ether **229** (154 mg, **198**:**229** = 4:1, 0.58 mmol, 89%) as a clear oil. A dynamic equilibrium exists between the two isomers: chloroform solutions of the separated components both exhibit **198**:**229** = 7:3 after 36 h at rt.

(*Z,S*)-[5-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methylenecyclohexylidene]ethanal (**198**).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.81 (1H, d, J = 8.0 Hz, H7), 5.89 (1H, dm, J = 8.0 Hz, H6), 5.21 (1H, m, $H19_E$), 5.00 (1H, m, $H19_Z$), 4.06 (1H, tt, J = 6.8, 3.4 Hz, H3), 2.60-2.54 (2H, m), 2.42 (1H, dd, J = 13.3, 6.9 Hz), 2.25 (1H, ddd, J = 12.4, 7.7, 4.6 Hz), 1.95-1.86 (1H, m), 1.80-1.70 (1H, m), 0.87 (9H, s, CMe_3), 0.07 (6H, s, $SiMe_2$) ppm.

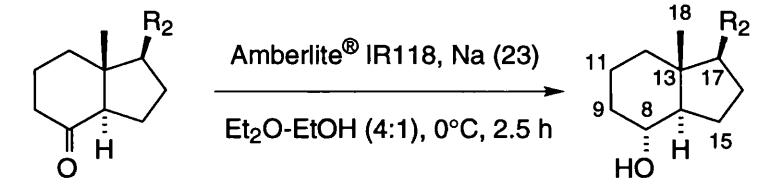
^{13}C NMR (90 MHz, $CDCl_3$): δ = 192.8 (0, C7), 163.2 (0, C5), 144.0 (0, C10), 128.5 (1, C6), 116.8 (2, C19), 69.5 (1, C3), 46.3 (2, C4), 35.4 (2, C2), 31.5 (2, C1), 25.9 (3C, 3, $C\underline{Me}_3$), 18.2 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$) ppm.

(*S*)-6-[(1,1-Dimethylethyl)dimethylsilyl]oxy-5,6,7,8-tetrahydro*iso*chroman (**229**).

^{1}H NMR (360 MHz, $CDCl_3$, selected): δ = 6.36 (1H, d, J = 5.5 Hz, H7), 5.02 (1H, d, J = 5.7 Hz, H6), 4.43 (2H, m, H19), 3.91 (1H, dddd, J = 11.2, 8.1, 5.1, 3.4 Hz, H3) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 143.2 (1, C7), 123.0 (0, C5), 119.4 (0, C10), 105.9 (1, C6), 68.3 (2, C19), 68.1 (1, C3), 36.8 (2, C4), 31.6 (2, C2), 26.1 (3C, 3, $C\underline{Me}_3$), 25.3 (2, C1), 18.4 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$) ppm.

(1*R*,3a*R*,4*R*,7a*R*)-7a-methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-inden-4-ol (408):



228
$C_{19}H_{32}O$ (276.46)

408
$C_{19}H_{34}O$ (278.47)

The Windaus-Grundmann C19 ketone (**228**, 1.0 g, 3.62 mmol) was reduced *via* buffered Bouveault-Blanc reaction, in an analogous manner to Grundmann's ketone above, to yield the previously unreported vitamin D_2 CD-ring α-alcohol **408** (812 mg, 2.92 mmol, 81%) as a crystalline solid: mp 81-83°C (hexanes).

$[\alpha]_D$ = –24.4 (c = 0.95, $CHCl_3$).

IR (KBr): ν = 3325 (br s), 2958 (s), 1459 (s), 1383 (w), 1368 (m), 1093 (m), 1068 (m), 1031 (m), 1007 (m), 970 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.22 (1H, dd, J = 15.2, 7.1 Hz, H22), 5.16 (1H, dd, J = 15.3, 7.6 Hz, H23), 3.58 (1H, ddd, J = 10.4, 10.4, 4.3 Hz, H8), 2.07-1.94 (2H, m), 1.90-

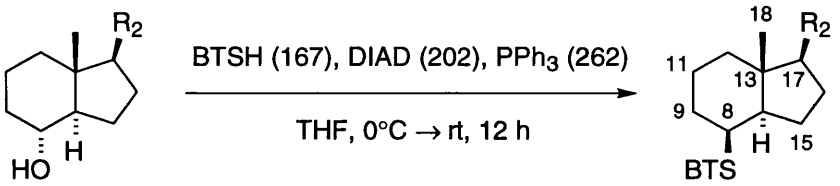
1.05 (14H, m), 1.01 (3H, d, J = 6.6 Hz, H28), 0.92 (3H, d, J = 6.8 Hz, H21), 0.84 (3H, d, J = 6.7 Hz, H27), 0.82 (3H, d, J = 6.7 Hz, H26), 0.69 (3H, s, H18) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 135.8 (1, C22), 132.1 (1, C23), 71.3 (1, C8), 57.5 (1, C14), 56.6 (1, C17), 44.8 (0, C13), 43.0 (1, C24), 40.0 (1, C20), 39.3 (2), 36.1 (2), 33.3 (1, C25), 28.4 (2), 23.6 (2), 22.0 (2), 21.1 (3, C28), 20.1 (3, C27), 19.8 (3, C26), 17.8 (3, C21), 12.4 (3, C18) ppm.

LRMS (EI+ mode): m/z = 278 (22%), 260 (8), 217 (36), 180 (29), 151 (20), 135 (100), 109 (31), 93 (35).

Anal. Calcd. for $C_{19}H_{34}O$ (M = 278): C, 81.95; H, 12.31. Found C, 81.82; H, 12.22.

(1*R*,3a*R*,4*S*,7a*R*)-4-(Benzothiazol-2-yl)thio-7a-methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-indene (409):



408
$C_{19}H_{34}O$ (278.47)

409
$C_{26}H_{37}NS_2$ (427.71)

The vitamin D_2 CD-ring α-alcohol **408** (512 mg, 1.84 mmol) was reacted with 2-mercaptobenzothiazole (BTSH, 460 mg, 2.75 mmol) according to the Mitsunobu conditions given above for the preparation of **215** and **216**, to yield the β-sulfide **409** (562 mg, 1.32 mmol, 72%) as a colourless solid: mp 68-70°C (hexanes).

$[\alpha]_D$ = +36.1 (c = 0.40, $CHCl_3$).

IR (film): ν = 2954 (s), 1456 (s), 1428 (m), 1366 (w), 1308 (w), 1272 (w), 1238 (w), 992 (s), 754 (s), 726 (m) cm^{-1}.

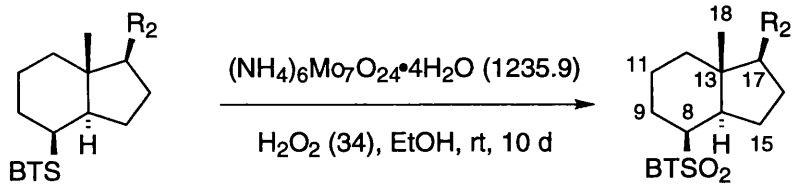
^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.85 (1H, dm, J = 8.1 Hz, BT), 7.74 (1H, dm, J = 7.9 Hz, BT), 7.34 (1H, ddd, J = 8.5, 7.3, 1.3 Hz, BT), 7.30-7.25 (1H, m, BT), 5.24 (1H, dd, J = 15.3, 7.2 Hz, H22), 5.16 (1H, dd, J = 15.3, 8.0 Hz, H23), 4.56 (1H, br s, H8), 2.20 (1H, dm, J = 10.5 Hz), 2.05-1.95 (2H, m), 1.93-1.12 (12H, m), 1.02 (3H, d, J = 6.6 Hz, H28), 0.93 (3H, d, J = 6.9 Hz, H21), 0.91 (3H, s, H18), 0.85 (3H, d, J = 6.7 Hz, H27), 0.84 (3H, d, J = 6.8 Hz, H26) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.7 (0, BT), 153.4 (0, BT), 135.6 (1, C22), 135.2 (0, BT), 132.3 (1, C23), 126.1 (1, BT), 124.2 (1, BT), 121.5 (1, BT), 121.0 (1, BT), 56.5 (1, C17), 52.5 (1, C14), 48.5 (1, C8), 43.0 (1, C24), 42.8 (0, C13), 40.2 (2), 40.2 (1, C20), 33.5 (2), 33.3 (1, C25), 27.8 (2), 24.5 (2), 21.0 (3, C28), 20.1 (3, C27), 19.8 (3, C26), 18.7 (2), 17.8 (3, C21), 13.8 (3, C18) ppm.

LRMS (EI+ mode): *m/z* = 427 (45%), 394 (66), 384 (25), 260 (11), 168 (58), 125 (40).

Anal. Calcd. for $C_{26}H_{37}NS_2$ (M = 427): C, 73.01; H, 8.72; N, 3.27. Found C, 72.97; H, 8.73; N, 3.26.

(1*R*,3a*R*,4*S*,7a*R*)-4-(Benzothiazol-2-yl)sulfonyl-7a-methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-indene (230):



409
$C_{26}H_{37}NS_2$ (427.71)

230
$C_{26}H_{37}NO_2S_2$ (459.71)

A stirred solution of the sulfide **409** (523 mg, 1.22 mmol) in EtOH (15 mL) at 0°C was treated with ammonium heptamolybdate tetrahydrate (150 mg, 0.12 mmol) in 30% $H_2O_{2(aq)}$ (680 mg, 6.0 mmol) and the resultant suspension allowed to warm to rt over 1 h. After subsequent stirring at rt for 2 d, TLC analysis indicated complete consumption of the sulfide and showed the formation of two diastereomeric sulfoxides. Further Mo catalyst (150 mg, 0.12 mmol) in 30% $H_2O_{2(aq)}$ (680 mg, 6.0 mmol) was then added and the mixture stirred at rt for a further 6 d. Due to the sluggishness of oxidation of the sulfoxides to the sulfone, a further two portions of Mo/H_2O_2 (as before) were added over the next 2 d during which time the reaction was continously sonicated. After this protracted reaction time the mixture was diluted with Et_2O (50 mL) and H_2O (30 mL) and the layers shaken and then separated. The aqueous layer was then extracted (4x15 mL Et_2O) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the sulfone **230** (410 mg, 0.89 mmol, 73%) as fine white needles: mp 135-137°C (EtOH).

$[\alpha]_D$ = –10.4 (*c* = 0.52, $CHCl_3$).

IR (KBr): ν = 2953 (s), 1470 (m), 1369 (w), 1321 (s), 1302 (s), 1258 (w), 1151 (m), 1128 (s), 1081 (w), 968 (w), 762 (s), 730 (m), 704 (w), 690 (w), 671 (m), 618 (w), 601 (m), 553 (w), 527 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.20 (1H, dm, J = 8.1 Hz, BT), 8.01 (1H, dm, J = 7.8 Hz, BT), 7.63 (1H, tm, J = 7.2 Hz, BT), 7.58 (1H, tm, J = 7.2 Hz, BT), 5.26 (1H, dd, J = 15.3, 7.4 Hz, H22), 5.16 (1H, dd, J = 15.3, 8.3 Hz, H23), 4.26 (1H, br t, J = 5.4 Hz, H8), 2.34 (1H, qd, J = 12.7, 6.0 Hz), 2.24-2.00 (4H, m), 1.96-1.62 (4H, m), 1.60-1.43 (4H, m), 1.38-1.26 (1H, m), 1.20-1.14 (1H, m), 1.14 (3H, s, H18), 1.04 (3H, d, J = 6.6 Hz, H28), 0.93 (3H, d, J = 6.8 Hz, H21), 0.85 (3H, d, J = 6.5 Hz, H27), 0.83 (3H, d, J = 6.6 Hz, H26) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.5 (0, BT), 152.9 (0, BT), 137.0 (0, BT), 135.3 (1, C22), 132.5 (1, C23), 127.9 (1, BT), 127.7 (1, BT), 125.5 (1, BT), 122.5 (1, BT), 61.2 (1, C8), 56.1 (1, C17), 52.1 (1, C14), 43.0 (1, C24), 41.3 (0, C13), 40.5 (1, C20), 40.2 (2), 33.2 (1, C25), 27.5 (2), 27.1 (2), 23.9 (2), 21.1 (3, C28), 20.2 (3, C27), 19.8 (3, C26), 18.5 (2), 17.8 (3, C21), 13.1 (3, C18) ppm.

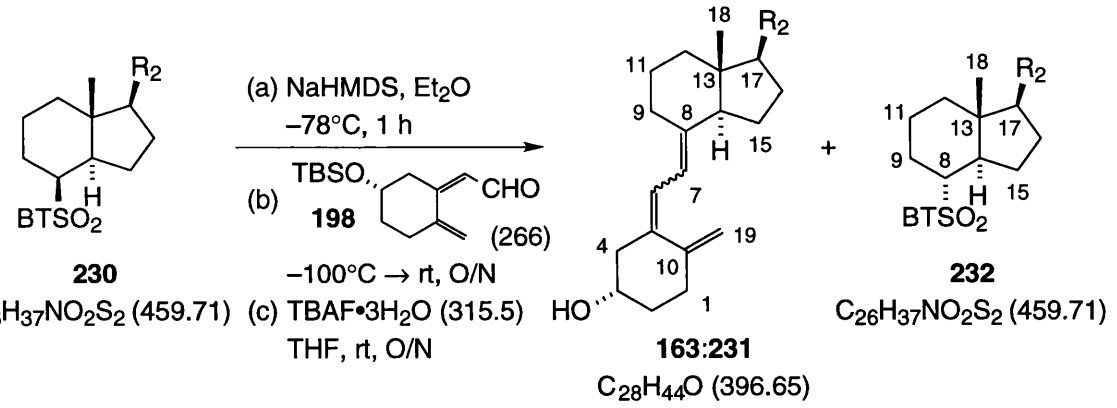
LRMS (EI+ mode): m/z = 459 (3%), 416 (11), 395 (35), 352 (30), 334 (30), 261 (57), 200 (58), 136 (100).

HRMS (EI+ mode): Found $M^{+\bullet}$, 459.2269. $C_{26}H_{37}NO_2S_2$ requires 459.2266.

Anal. Calcd. for $C_{26}H_{37}NO_2S_2$ (M = 459): C, 67.93; H, 8.11; N, 3.05. Found C, 67.98; H, 8.12; N, 3.05.

Vitamin D_2 (163):

To a stirred solution of the β-sulfone **230** (50 mg, 0.11 mmol) in anhydrous Et_2O (4 mL) at –78°C under $N_{2(g)}$ was added dropwise a solution of sodium hexamethyldisilazide (NaHMDS, 65 μL, 2.0 M in THF, 0.13 mmol) and the resultant yellow solution stirred for 1 h. After this time the mixture was cooled to –100°C and a solution of the freshly prepared aldehyde-pyran mixture (**198**:**229** = 4:1, 80 mg, 0.31 mmol) in anhydrous Et_2O (2 mL) added dropwise. The reaction was then allowed to warm steadily to rt over the next 1.5 h and then stirred O/N. After this time the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2x5 mL Et_2O) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 111 mg of a crude oil. The residue was then further purified *via* column chromatography (eluting with 1-10% Et_2O in hexanes) to yield: 57 mg of non-polar material (containing vitamin



D_2 TBS ethers and pyran **229**), recovered aldehyde (**198**, 13 mg, 0.05 mmol, 16%) and epimeric α-sulfone **232** (9 mg, 0.02 mmol, 18%). A solution of the non-polar material in anhydrous THF (2 mL) at rt under $N_{2(g)}$ was then treated with tetrabutylammonium fluoride trihydrate (TBAF•$3H_2O$, 135 mg, 0.43 mmol) and stirred O/N. After this time the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2x5 mL Et_2O) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) to yield a pure mixture of natural vitamin D_2 (**163**) and (7*Z*)-vitamin D_2 (**231**) as a clear oil [30 mg, 0.076 mmol, 70% (2 steps), **163**:**231** = 72:28]. The vitamin D_2 isomers could be successfully separated by careful chromatography (eluting with 10-15% Et_2O in hexanes); the previously unreported unnatural isomer **231** exhibited only limited stability in $CDCl_3$.

(1*R*,3a*R*,4*R*,7a*R*)-4-(Benzothiazol-2-yl)sulfonyl-7a-methyl-1-[(*E*,1*R*,4*R*)-1,4,5-trimethyl-2-hexenyl]octahydro-1*H*-indene (**232**).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.24 (1H, dm, J = 7.7 Hz, BT), 8.02 (1H, dm, J = 7.1 Hz, BT), 7.65 (1H, td, J = 7.2, 1.4 Hz, BT), 7.60 (1H, td, J = 1.3 Hz, BT), 5.21 (1H, dd, J = 15.2, 7.1 Hz, H22), 5.14 (1H, dd, J = 15.2, 7.7 Hz, H23), 3.67 (1H, td, J = 11.7, 3.4 Hz, H8), 2.07-1.89 (3H, m), 1.84 (1H, hextet, J = 6.7 Hz), 1.76-1.65 (3H, m), 1.62-1.52 (3H, m), 1.50-1.13 (5H, m), 1.01 (3H, d, J = 6.6 Hz, H28), 0.90 (3H, d, J = 6.8 Hz, H21), 0.83 (3H, d, J = 6.5 Hz, H27), 0.81 (3H, d, J = 6.5 Hz, H26), 0.75 (3H, s, H18) ppm.

Vitamin D_2 (**163**).

mp 109-110°C (MeOH-H_2O). (lit.[101] 116°C).

^{1}H and ^{13}C NMR data was in complete agreement with that previously reported[100,102].

(7Z)-Vitamin D_2 (**231**).

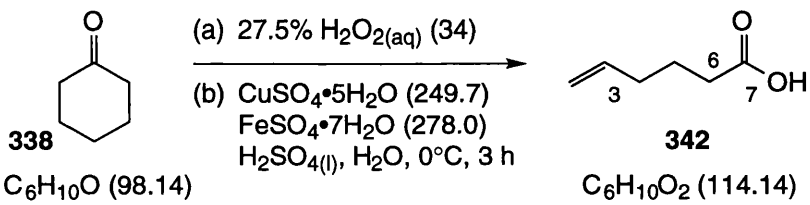
^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.36 (1H, d, J = 11.6 Hz, H6), 6.23 (1H, d, J = 11.6 Hz, H7), 5.28-5.15 (2H, m, H22, H23), 5.09 (1H, m, $H19_E$), 4.85 (1H, m, $H19_Z$), 3.82 (1H, tt, J = 9.1, 4.1 Hz, H3), 2.52 (1H, dd, J = 12.3, 3.2 Hz), 2.38 (1H, dt, J = 13.9, 5.0 Hz), 2.30-1.20 (20H, m), 1.03 (3H, d, J = 6.6 Hz, H28), 0.93 (3H, d, J = 6.5 Hz, H21), 0.85 (3H, d, J = 6.4 Hz, H27), 0.83 (3H, d, J = 6.1 Hz, H26), 0.66 (3H, s, H18) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 144.4 (0, C10), 141.7 (0, C8), 136.0 (0, C5), 135.8 (1, C22), 132.2 (1, C23), 123.5 (1, C6), 121.8 (1, C7), 113.3 (2, C19), 70.2 (1, C3), 56.3 (1, C17), 55.1 (1, C14), 46.7 (0, C13), 46.6 (2), 43.0 (1, C24), 40.8 (2), 40.5 (1, C20), 39.1 (2), 35.9 (2), 33.3 (1, C25), 32.7 (2), 28.5 (2), 26.5 (2), 24.3 (2), 21.6 (3, C28), 20.2 (3, C27), 19.8 (3, C26), 17.8 (3, C21), 13.1 (3, C18) ppm.

The stereochemistry of the olefin linkage in **231** was assigned as for **220** by comparison of ^{1}H NMR data with the results of Okamura[84] and Mouriño[103].

–SECTION 6.2–

Hex-5-enoic acid (342):



338 $C_6H_{10}O$ (98.14)

342 $C_6H_{10}O_2$ (114.14)

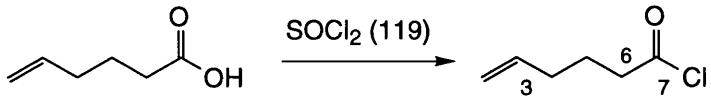
Prepared by the method of Rust[127]. To mechanically stirred cyclohexanone (**338**, 40 mL, ρ = 0.947, 37.9 g, 0.39 mol) was added in one portion aqueous hydrogen peroxide (22 mL, ρ = 1.11, 24.4 g, 27.5 wt.%, 0.20 mol). A slight exotherm was noted and the internal temperature rose to 35°C. The mixture was allowed to stir for 40 min, placed under an atmosphere of $N_{2(g)}$ and then cooled to –5°C resulting in the formation of a thick paste (ketone hydroperoxide). A solution of copper (II) sulfate pentahydrate (100 g, 0.40 mol) and iron (II) sulfate heptahydrate (111 g, 0.40 mol) in $H_2SO_{4(aq)}$ (22 mL in 400 mL H_2O) was then added at such a rate that the reaction temperature did not rise above 0°C. The mixture was then stirred for 3 h at 0°C before being allowed to warm to rt and stirred until the complete disappearance of the solid ketone hydroperoxide (2 h). The reaction was then extracted with CH_2Cl_2 (5x75 mL) and the combined organic extracts dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* distillation to yield hex-5-enoic acid (**342**, 8.42 g, 74 mmol, 37%) as a clear liquid: bp 120-123°C, 18 mmHg. (lit.[178] bp 95°C, 7 mmHg; CAS No. 1577-22-6).

IR (film): ν = 2939 (br s), 1708 (s), 1642 (w), 1415 (s), 1245 (s), 993 (w), 914 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.78 (1H, ddt, J = 17.1, 10.3, 6.7 Hz, H3), 5.07-4.96 (2H, m, CH=C$\underline{H}_2$), 2.37 (2H, t, J = 7.5 Hz, H6), 2.14-2.06 (2H, m, H4), 1.74 (2H, quintet, J = 7.4 Hz, H5) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 180.5 (0, C7), 137.6 (1, C3), 115.7 (2, CH=$\underline{C}H_2$), 33.5 (2, C6), 33.1 (2, C4), 23.9 (2, C5) ppm.

Hex-5-enoyl chloride (344):



342 $C_6H_{10}O_2$ (114.14) **344** C_6H_9ClO (132.59)

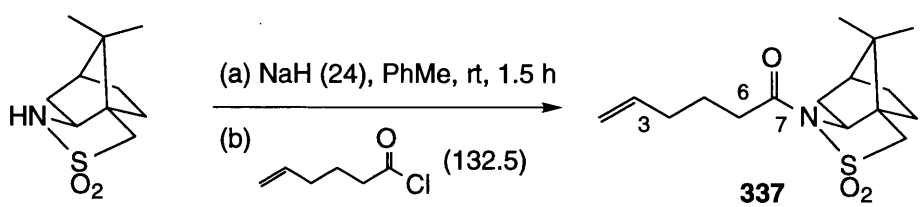
Prepared by the method of Heck[179]. To stirred hex-5-enoic acid (**342**, 16.7 g, 146 mmol) at rt under $N_{2(g)}$ was added dropwise freshly distilled thionyl chloride (35 mL, ρ = 1.63, 57.1 g, 431 mmol). Once the spontaneous emission of gas had ceased the mixture was heated to 80°C and stirred for 30 min. The reaction mixture was then allowed to cool and distilled at reduced pressure to yield hex-5-enoyl chloride (**344**, 14.5 g, 109 mmol, 75%) as a clear liquid: bp 52-54°C, 22 mmHg. (lit.[179] bp 53-54°C, 21.5 mmHg; CAS No. 36394-07-7).

IR (film): ν = 2980 (m), 2942 (m), 1801 (s), 1642 (m), 1405 (m), 1054 (w), 995 (s), 963 (s), 919 (s), 787 (w), 728 (m), 684 (m), 634 (w), 582 (m) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.75 (1H, ddt, J = 17.0, 10.3, 6.7 Hz, H3), 5.10-5.00 (2H, m, CH=C$\underline{H}_2$), 2.91 (2H, t, J = 7.3 Hz, H6), 2.17-2.08 (2H, m, H4), 1.82 (2H, quintet, J = 7.2 Hz, H5) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 173.9 (0, C7), 136.8 (1, C3), 116.4 (2, CH=$\underline{C}H_2$), 46.4 (2, C6), 32.4 (2, C4), 24.2 (2, C5) ppm.

(2*S*)-*N*-(Hex-5-enoyl)bornane-10,2-sultam (337):



$C_{10}H_{17}NO_2S$ (215.31) **344** **337** $C_{16}H_{25}NO_3S$ (311.44)

To a mechanically stirred suspension of sodium hydride (6.0 g, 60 wt.%, 150 mmol) in PhMe (125 mL) at rt under $N_{2(g)}$ was added dropwise a solution of (2*S*)-bornane-10,2-sultam[152] (25 g, 116 mmol) in PhMe (250 mL) over 30 min. The mixture was stirred for a further 1 h before being treated dropwise with hex-5-enoyl chloride (**344**, 17.4 g, 131 mmol) in PhMe (125 mL) over 30 min and then allowed to stir O/N. The reaction mixture was then quenched by the addition of sat. $NH_4Cl_{(aq)}$ (100 mL) and the layers shaken and then separated. The aqueous phase was extracted (2x50 mL Et_2O) and the combined organic extracts washed successively with 1M $NaOH_{(aq)}$ (2x20 mL), brine (40 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 30% Et_2O in hexanes) to yield the desired product contaminated by hex-5-enoic acid (**342**). The impurity was subsequently removed by dissolving the material in Et_2O (250 mL), washing with sat. $NaHCO_{3(aq)}$ (4x75 mL), drying ($MgSO_4$) and then concentrating *in vacuo* to yield the pure unsaturated acyl sultam **337** (34.0 g, 109 mmol, 94%) as a clear oil: bp (kugelrohr oven) 250°C, 0.2 mmHg.

$[\alpha]_D$ = +91.8 (*c* = 1.02, $CHCl_3$).

IR (film): ν = 2962 (s), 1701 (s), 1640 (w), 1482 (w), 1457 (m), 1414 (m), 1385 (m), 1335 (s), 1269 (s), 1238 (s), 1212 (s), 1112 (m), 1083 (m), 1057 (m), 1039 (m), 989 (m), 912 (m), 808 (w), 771 (m) 540 (s) cm^{-1}.

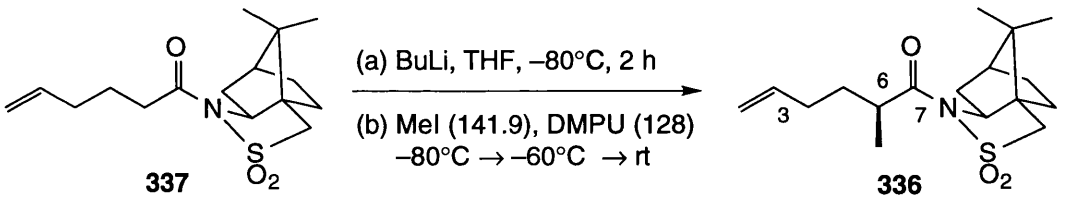
^1H NMR (360 MHz, $CDCl_3$): δ = 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, H3), 5.02 (1H, dq, *J* = 17.1, 1.7 Hz, CH=C$\underline{H_Z}H_E$), 4.96 (1H, ddt, *J* = 10.2, 1.9, 1.1 Hz, CH=C$H_Z\underline{H_E}$), 3.85 (1H, dd, *J* = 7.3, 5.3 Hz, CHN), 3.49 (1H, d, *J* = 13.8 Hz, C$\underline{H_A}H_BSO_2$), 3.42 (1H, d, *J* = 13.8 Hz, C$H_A\underline{H_B}SO_2$), 2.78-2.63 (2H, m), 2.15-2.03 (4H, m), 1.95-1.83 (3H, m), 1.77 (2H, quintet, *J* = 7.5 Hz), 1.44-1.30 (2H, m), 1.14 (3H, s, $\underline{Me}$C(CH)Me), 0.96 (3H, s, MeC(CH)$\underline{Me}$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 171.9 (0, C7), 137.8 (1, C3), 115.5 (2, CH=$\underline{C}H_2$), 65.3 (1, CHN), 53.1 (2, CH_2SO_2), 48.5 (0, $\underline{C}CH_2SO_2$), 47.9 (0, Me$\underline{C}$(CH)Me), 44.8 (1, MeC($\underline{C}$H)Me), 38.6 (2), 34.9 (2), 33.0 (2), 32.9 (2), 26.6 (2), 23.7 (2), 21.0 (3, $\underline{Me}$C(CH)Me), 20.0 (3, MeC(CH)$\underline{Me}$) ppm.

LRMS (EI+ mode): *m/z* = 311 (92%), 257 (31), 135 (100), 97 (47), 69 (69).

Anal. Calcd. for $C_{16}H_{25}NO_3S$ (M = 311): C, 61.70; H, 8.09; N, 4.50. Found C, 61.62; H, 8.05; N, 4.51.

(2*S*)-*N*-[(*S*)-2-Methylhex-5-enoyl]bornane-10,2-sultam (336):



337 $C_{16}H_{25}NO_3S$ (311.44)

336 $C_{17}H_{27}NO_3S$ (325.47)

To a stirred solution of the acyl sultam **337** (15.6 g, 50.2 mmol) in anhydrous THF (250 mL) at –80°C (internal temperature) under $N_{2(g)}$ was added *n*-butyl lithium (21.7 mL, 2.31 M in hexanes, 50.1 mmol) smoothly *via* syringe-pump over 1 h. After the complete addition the reaction was stirred at –80°C for a further 1 h before being treated dropwise with a solution of methyl iodide (9.4 mL, ρ = 2.28, 21.4 g, 151 mmol) in anhydrous dimethylpropylene urea (DMPU, 18.2 mL, ρ = 1.06, 19.3 g, 151 mmol) over 25 min. The reaction mixture was then allowed to warm slowly to –60°C, stirred for 1 h and then allowed to warm to rt O/N. After this time the mixture was diluted with H_2O (200 mL) and Et_2O (200 mL) and the layers shaken and then separated. The aqueous phase was then extracted (3x50 mL Et_2O) and the combined organic extracts washed successively with H_2O (3x50 mL), brine (50 mL), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 16.0 g of a crude white solid. The solid was further purified *via* recrystallisation (50 mL cyclohexane) to yield the methylated adduct **336** (13.0 g, 40.0 mmol, 80%) as a white solid: mp 95-97°C.

$[\alpha]_D$ = +98.0 (*c* = 1.09, $CHCl_3$).

IR (KBr): ν = 2935 (m), 1685 (s), 1457 (w), 1392 (w), 1327 (s), 1272 (m), 1220 (m), 1134 (m), 1057 (m), 977 (w), 914 (w), 770 (w), 534 (m) cm^{-1}.

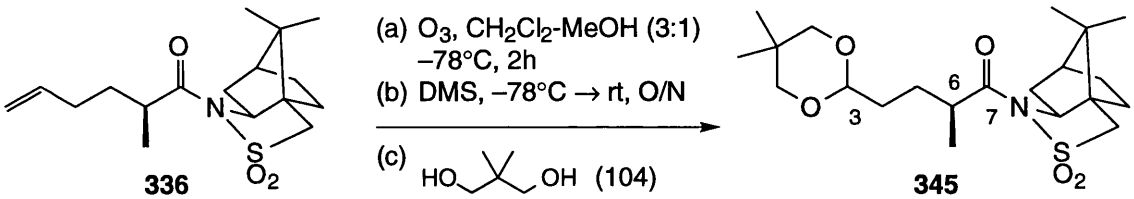
^1H NMR (360 MHz, $CDCl_3$): δ = 5.81 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, H3), 5.02 (1H, dq, *J* = 17.2, 1.8 Hz, CH=C$\underline{H}_Z$H$_E$), 4.95 (1H, dm, *J* = 10.2 Hz, CH=CH$_Z\underline{H}_E$), 3.90 (1H, t, *J* = 6.3 Hz, CHN), 3.51 (1H, d, *J* = 13.8 Hz, C$\underline{H}_A$H$_B$SO$_2$), 3.44 (1H, d, *J* = 13.8 Hz, CH$_A\underline{H}_B$SO$_2$), 3.09 (1H, sextet, *J* = 6.8 Hz, H6), 2.13-2.02 (4H, m), 1.97-1.84 (4H, m), 1.50-1.32 (3H, m), 1.22 (3H, d, *J* = 6.9 Hz, C6-Me), 1.16 (3H, s, $\underline{Me}$C(CH)Me), 0.98 (3H, s, MeC(CH)$\underline{Me}$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 176.1 (0, C7), 138.2 (1, C3), 114.8 (2, CH=$\underline{C}$H$_2$), 65.1 (1, CHN), 53.2 (2, CH$_2$SO$_2$), 48.4 (0, $\underline{C}$CH$_2$SO$_2$), 47.8 (0, Me$\underline{C}$(CH)Me), 44.7 (1, MeC($\underline{C}$H)Me), 39.9 (1, C6), 38.5 (2), 32.9 (2), 32.0 (2, C5), 31.5 (2, C4), 26.5 (2), 20.9 (3, $\underline{Me}$C(CH)Me), 19.9 (3, MeC(CH)$\underline{Me}$), 19.0 (3, C6-$\underline{Me}$) ppm.

LRMS (EI+ mode): *m/z* = 325 (46%), 271 (100), 214 (17), 191 (22), 135 (88), 111 (50), 93 (23), 83 (99), 67 (18), 55 (78), 41 (52).

Anal. Calcd. for $C_{17}H_{27}NO_3S$ (M = 325): C, 62.74; H, 8.36; N, 4.30. Found C, 62.76; H, 8.41; N, 4.27.

(2*S*)-*N*-[(*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutanoyl]bornane-10,2-sultam (345):



336 $C_{17}H_{27}NO_3S$ (325.47)

345 $C_{21}H_{35}NO_5S$ (413.57)

Ozone was bubbled through a stirred solution of the olefin **336** (5.64 g, 17.4 mmol) in CH_2Cl_2-MeOH (100 mL: 30 mL) at –78°C for 2 h. After this time the ozone flow was stopped and N_2(g) bubbled through the cold solution for 10 min to remove excess dissolved ozone. Dimethyl sulfide (30 mL) was then added and the mixture allowed to warm slowly to rt O/N. All solvent was then removed *in vacuo* to yield 8.33 g of an oily residue which was subsequently dissolved in PhMe (100 mL). Following a negative starch-iodide paper test, the solution was treated with 2,2-dimethylpropane-1,3-diol (1.90 g, 18.3 mmol) and a catalytic quantity of toslic acid (*ca* 10 mg). The mixture was then stirred at reflux with azeotropic H_2O removal (Dean-Stark apparatus) O/N. After this time the reaction was allowed to cool, diluted with Et_2O (100 mL) and washed succesively with sat. $NaHCO_{3(aq)}$ (50 mL), H_2O (4x30 mL) and brine (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield 7.25 g of a crude solid. The solid was then further purified *via* recrystallisation (30 mL cyclohexane) to yield the pure dioxane product **345** (5.20 g, 12.6 mmol, 72%) as a white solid: mp 124-126°C.

$[\alpha]_D$ = +75.0 (*c* = 1.11, $CHCl_3$).

IR (KBr): ν = 2956 (s), 1692 (s), 1470 (w), 1392 (w), 1328 (s), 1272 (w), 1219 (w), 1199 (w), 1133 (m), 1113 (m), 973 (w), 876 (w), 777 (w), 547 (m), 536 (m) cm^{-1}.

^1H NMR (MHz, $CDCl_3$): δ = 4.43 (1H, t, *J* = 4.9 Hz, H3), 3.89 (1H, t, *J* = 6.3 Hz, CHN), 3.58 (2H, d, *J* = 11.0 Hz, $C\underline{H}_AH_BO$), 3.49 (1H, d, *J* = 13.7 Hz, $C\underline{H}_AH_BSO_2$), 3.43 (1H, d, *J* = 13.8 Hz, $CH_A\underline{H}_BSO_2$), 3.41 (2H, d, *J* = 11.3 Hz, $CH_A\underline{H}_BO$), 3.08 (1H, sextet of m, 6.8 Hz, H6), 2.08-2.03 (2H, m), 1.97-1.82 (4H, m), 1.75-1.48 (3H, m), 1.44-1.30 (2H, m),

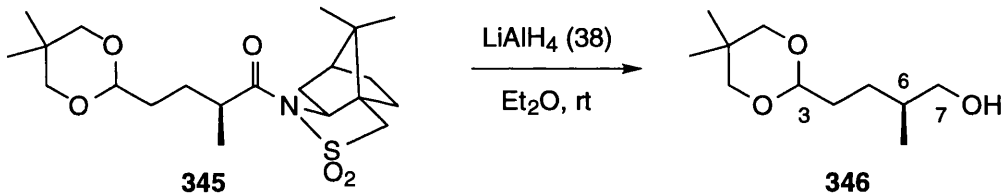
1.22 (3H, d, J = 6.9 Hz, C6-Me), 1.17 (3H, s, MeC($CH_2O)_2$Me), 1.15 (3H, s, MeC(CH)Me), 0.97 (3H, s, MeC(CH)Me), 0.70 (3H, s, MeC($CH_2O)_2$Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 176.0 (0, C7), 101.8 (1, C3), 77.2 (2, CH_2O), 77.2 (2, CH_2O), 65.1 (1, CHN), 53.2 (2, CH_2SO_2), 48.4 (0, CCH_2SO_2), 47.8 (0, MeC(CH)Me), 44.7 (1, MeC(CH)Me), 39.9 (1, C6), 38.5 (2), 32.9 (2), 32.3 (2, C5), 30.2 (0, MeC($CH_2O)_2$Me), 26.9 (2, C4), 26.5 (2), 23.1 (3, MeC($CH_2O)_2$Me), 22.0 (3, MeC($CH_2O)_2$Me), 20.9 (3, MeC(CH)Me), 20.0 (3, MeC(CH)Me), 19.1 (3, C6-Me) ppm.

LRMS (CI+ mode, NH_3): m/z = 431 (100%), 414 (26), 350 (16), 250 (14), 233 (49).

Anal. Calcd. for $C_{21}H_{35}NO_5S$ (M = 413): C, 60.99; H, 8.53; N, 3.39. Found C, 60.84; H, 8.49; N, 3.28.

(*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutan-1-ol (346):



345 $C_{21}H_{35}NO_5S$ (413.57)

346 $C_{11}H_{22}O_3$ (202.29)

To a stirred suspension of lithium aluminium hydride (0.81 g, 21.3 mmol) in anhydrous Et_2O (50 mL) at rt under $N_{2(g)}$ was added dropwise a solution of the acyl sultam **345** (3.50 g, 8.47 mmol) in anhydrous Et_2O-THF (30 mL: 10 mL) over 10 min. The resultant mixture was then allowed to stir at rt O/N. After this time the reaction was quenched by the dropwise addition of 20% $KOH_{(aq)}$ (50 mL, CARE! initial reaction very vigorous) and then stirred vigorously for 1 h. The biphasic mixture was then filtered through a pad of celite and the residue washed well (3x10 mL Et_2O). The layers of the filtrate and combined washings were then separated and the organic phase washed successively with 20% $KOH_{(aq)}$ (5x20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield essentially pure alcohol **346** (1.59 g, 7.87 mmol, 93%) as a clear oil: bp (kugelrohr oven) 170°C, 0.3 mmHg. The alcohol is unstable under mildly acidic conditions; appreciable decomposition was noted after just 30 min in $CDCl_3$.

$[\alpha]_D$ = –7.3 (c = 1.05, $CHCl_3$).

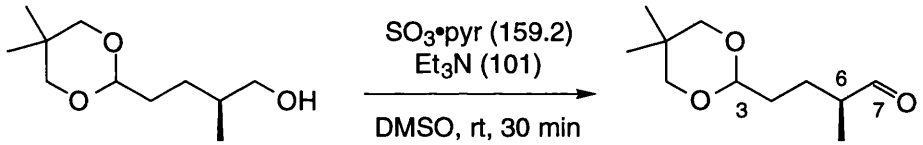
IR (film): ν = 3424 (s, br), 2954 (s), 2870 (s), 1472 (m), 1394 (m), 1312 (w), 1236 (w), 1116 (s), 1078 (m), 1042 (m), 1018 (s), 922 (w), 872 (w), 792 (w) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.43 (1H, t, J = 4.9 Hz, H3), 3.61 (2H, d, J = 11.2 Hz, $Me_2CC\underline{H}_AH_BO$), 3.52 (1H, dd, J = 10.6, 5.9 Hz, $H7_A$), 3.45 (1H, dd, J = 10.6, 6.2 Hz, $H7_B$), 3.43 (2H, d, J = 11.4 Hz, $Me_2CCH_A\underline{H}_BO$), 1.78-1.49 (4H, m), 1.27 (1H, dddd, J = 12.8, 10.3, 7.3, 5.1 Hz), 1.20 (3H, s, Me<u>Me</u>CMe), 0.93 (3H, d, J = 6.7 Hz, C6-Me), 0.73 (3H, s, MeC<u>Me</u>) ppm.

^{13}C NMR (90 MHz, C_6D_6): δ = 103.3 (1, C3), 77.6 (2C, 2, $Me_2C\underline{C}H_2O$), 68.1 (2, C7), 36.4 (1, C6), 33.2 (2, C4), 30.5 (0, Me<u>C</u>Me), 28.1 (2, C5), 23.6 (3, <u>Me</u>CMe), 22.1 (3, MeC<u>Me</u>), 17.4 (3, C6-<u>Me</u>) ppm.

LRMS (CI+ mode, NH_3): m/z = 220 (100%), 203 (3), 133 (17), 122 (64), 116 (44).

(*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutanal (328):



346 $C_{11}H_{22}O_3$ (202.29)

328 $C_{11}H_{20}O_3$ (200.27)

A biphasic mixture of the alcohol **346** (860 mg, 4.26 mmol) and triethylamine (3.55 mL, ρ = 0.726, 2.58 g, 25.5 mmol) in anhydrous dimethyl sulfoxide (DMSO, 20 mL) at rt under $N_{2(g)}$ was treated portionwise with sulfur trioxide pyridine complex (2.03 g, 12.8 mmol) and stirred vigorously for 30 min. The mixture was then poured into 10% $NaHSO_{4(aq)}$ (200 mL), stirred for 10 min and then extracted with CH_2Cl_2 (4x50 mL). The combined organic extracts were then washed successively with H_2O (2x50 mL) and brine (50 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) to yield the aldehyde **328** (816 mg, 4.08 mmol, 96%) as a clear oil: bp (kugelrohr oven) 140°C, 0.3 mmHg.

$[\alpha]_D$ = +12.8 (c = 1.07, $CHCl_3$).

IR (film): ν = 2956 (s), 2848 (s), 1726 (s), 1472 (m), 1394 (m), 1312 (w), 1236 (w), 1120 (s), 1018 (m), 984 (m), 910 (w), 872 (w), 792 (w) cm^{-1}.

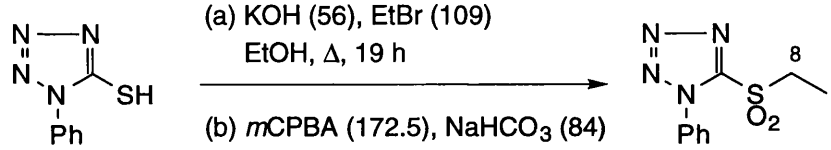
^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.62 (1H, d, J = 1.8 Hz, H7), 4.43 (1H, t, J = 4.8 Hz, H3), 3.59 (2H, d, J = 11.1 Hz, $C\underline{H}_AH_BO$), 3.41 (2H, d, J = 11.1 Hz, $CH_A\underline{H}_BO$), 2.36 (1H, sextet of d, J = 6.9, 1.7 Hz, H6), 1.92-1.82 (1H, m), 1.75-1.60 (2H, m), 1.55-1.44 (1H, m), 1.18 (3H, s, <u>Me</u>CMe), 1.10 (3H, d, J = 7.0 Hz, C6-Me), 0.72 (3H, s, MeC<u>Me</u>) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 204.9 (1, C7), 101.7 (1, C3), 77.2 (2C, 2, CH_2O), 46.1 (1, C6), 32.2 (2, C4), 30.2 (0, MeCMe), 24.7 (2, C5), 23.1 (3, MeCMe), 21.9 (3, MeCMe), 13.4 (3, C6-Me) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 218 (100%), 201 (10).

Anal. Calcd. for $C_{11}H_{20}O_3$ (M = 200): C, 65.97; H, 10.07. Found C, 65.81; H, 9.99.

5-Ethanesulfonyl-1-phenyl-1*H*-tetrazole (347):



$C_7H_6N_4S$ (178.22)

347

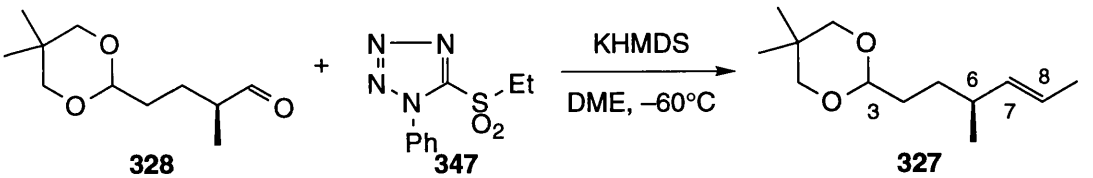
$C_9H_{10}N_4O_2S$ (238.27)

To a suspension of powdered potassium hydroxide (3.3 g, 58.9 mmol) in EtOH (100 mL) was added 1-phenyl-1*H*-tetrazole-5-thiol (10 g, 56.2 mmol) and the resulting mixture stirred at reflux for 1 h. After this time ethyl bromide (4.4 mL, ρ = 1.46, 6.42 g, 58.9 mmol) was added dropwise and the reaction stirred at reflux for a further 18 h. The solvent was then removed *in vacuo* and the residue partitioned between H_2O (100 mL) and Et_2O (100 mL). The layers were then separated and the organic phase washed successively with sat. $NaHCO_{3(aq)}$ (2x75 mL) and brine (75 mL). After drying ($MgSO_4$) the solvent was removed *in vacuo* to yield essentially pure 5-ethanethio-1-phenyl-1*H*-tetrazole (9.86 g, 47.9 mmol, 86%) as a brown oil. A mechanically stirred suspension of the sulfide (9.86 g, 47.9 mmol) and sodium hydrogencarbonate (20 g, 238 mmol) in CH_2Cl_2 (200 mL) was treated portionwise with 3-chloroperoxybenzoic acid (*m*-CPBA, 41.0 g, 50 wt.%, 119 mmol) and stirred vigorously for 18 h. After this time the reaction mixture was poured into sat. $NaHCO_3$-$Na_2S_2O_{3(aq)}$ (200 mL) and stirred vigorously for 3 h. The layers were then separated and the aqueous phase extracted (2x50 mL CH_2Cl_2). The combined organic extracts were then washed with sat. $NaHCO_{3(aq)}$ (3x75 mL), brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 40-55% Et_2O in hexanes) to yield 5-ethanesulfonyl-1-phenyl-1*H*-tetrazole (**347**, 8.33 g, 35.0 mmol, 73%) as a white solid: mp 70-71°C (10% EtOAc-hexanes). (lit.[180] mp 73-74°C; CAS No. 3206-46-0).

^1H NMR (360 MHz, $CDCl_3$): δ = 7.71-7.65 (2H, m, PT), 7.64-7.55 (3H, m, PT), 3.75 (2H, q, *J* = 7.4 Hz, H8), 1.52 (3H, t, *J* = 7.4 Hz, C8-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 153.2 (0, PT), 133.1 (0, PT), 131.6 (1, PT), 129.8 (2C, 1, PT), 125.2 (2C, 1, PT), 50.9 (2, C8), 7.0 (3, C8-Me) ppm.

5,5-Dimethyl-2-[(*E*,*S*)-3-methylhex-4-enyl]-1,3-dioxane (327):



328 $C_{11}H_{20}O_3$ (200.27) **347** $C_9H_{10}N_4O_2S$ (238.27) **327** $C_{13}H_{24}O_2$ (212.33)

To a stirred solution of the aldehyde **328** (3.82 g, 19.1 mmol) and sulfone **347** (5.95 g, 25.0 mmol) in anhydrous 1,2-dimethoxyethane (DME, 80 mL) at –60°C (bath temperature) under $N_{2(g)}$ was added dropwise *via* cannula a solution of potassium hexamethyldisilazide (KHMDS, 7.0 g, 80 wt.%, 28.1 mmol) in anhydrous DME (40 mL) over 45 min. After this time H_2O (10 mL) was added and the mixture stirred vigorously whilst warming to rt. The mixture was then diluted with Et_2O (150 mL) and H_2O (80 ml) and the layers shaken and then separated. The aqueous phase was then extracted (3x50 mL Et_2O) and the combined organic extracts washed successively with H_2O (3x50 mL) and brine (50 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 0-10% Et_2O in hexanes) to yield the olefin **327** (3.76 mg, 17.7 mmol, 93%, *E*:*Z* = 93:7) as a clear oil.

$[\alpha]_D$ = +7.2 (*c* = 1.01, $CHCl_3$).

IR (film): ν = 2956 (s), 1454 (m), 1394 (m), 1310 (w), 1122 (s), 1044 (m), 1020 (s), 966 (s), 910 (w), 878 (w), 792 (w) cm^{-1}.

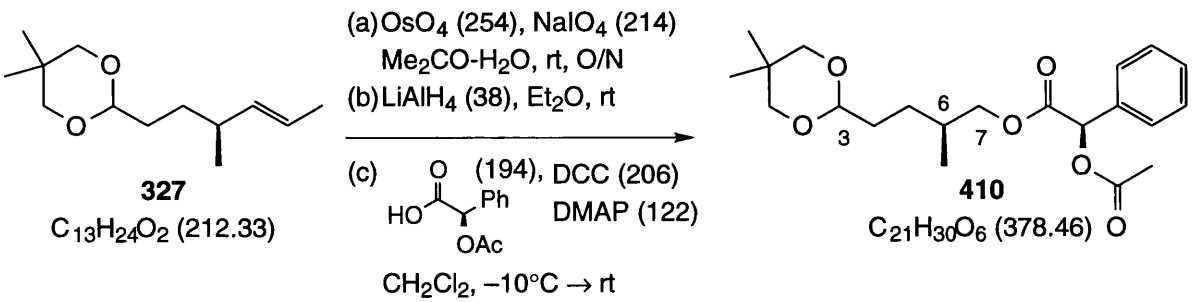
^1H NMR (360 MHz, $CDCl_3$): δ = 5.40 (1H, dqd, *J* = 15.2, 6.2, 0.7 Hz, H8), 5.26 (1H, ddq, *J* = 15.2, 7.6, 1.3 Hz, H7), 4.39 (1H, t, *J* = 5.1 Hz, H3), 3.60 (2H, d, *J* = 9.9 Hz, CH_AH_BO), 3.42 (2H, d, *J* = 10.6 Hz, CH_AH_BO), 2.04 (1H, heptet, *J* = 7.0 Hz, H6), 1.63 (3H, dm, *J* = 6.3 Hz, C8-Me), 1.70-1.52 (2H, m), 1.44-1.27 (2H, m), 1.19 (3H, s, MeCMe), 0.96 (3H, d, *J* = 6.7 Hz, C6-Me), 0.72 (3H, s, MeCMe) ppm..

^{13}C NMR (90 MHz, $CDCl_3$): δ = 137.1 (1, C7), 123.5 (1, C8), 102.6 (1, C3), 77.4 (2C, 2, CH_2O), 36.9 (1, C6), 33.0 (2, C4), 31.3 (2, C5), 30.3 (0, MeCMe), 23.1 (3, MeCMe), 22.0 (3, MeCMe), 21.0 (3, C8-Me), 18.1 (3, C6-Me) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 230 (100%), 213 (25), 126 (36), 96 (86), 79 (26).

Anal. Calcd. for $C_{13}H_{24}O_2$ (M = 212): C, 73.54; H, 11.39. Found C, 73.36; H, 11.13.

Degradation of 5,5-dimethyl-2-[(*E*,*S*)-3-methylhex-4-enyl]-1,3-dioxane (327) to (*S*)-4-(5,5-dimethyl-1,3-dioxan-2-yl)-2-methylbutan-1-ol (346) and its conversion to a mandelic ester derivative (410):

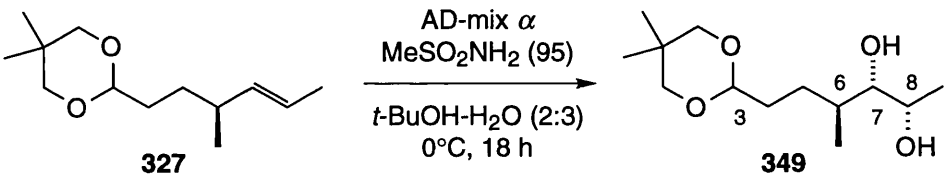


Oxidative Cleavage: To a stirred solution of the olefin **327** (51 mg, 0.24 mmol) and sodium periodate (216 mg, 1.0 mmol) in acetone-H_2O (2 mL: 2 mL) at rt was added $OsO_{4(aq)}$ (8 drops, 0.08 M in H_2O) and the resultant mixture stirred O/N. After this time the mixture was diluted with Et_2O (10 mL) and H_2O (5 mL) and the layers shaken and then separated. The aqueous phase was then extracted (3x5 mL Et_2O) and the combined organic extracts washed successively with sat. $Na_2S_2O_{3(aq)}$ (2x10 mL) and brine (10 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexaness) to yield the aldehyde **328** (23 mg, 0.12 mmol, 48%) as a clear oil. **Reduction:** To a stirred solution of the aldehyde **328** (23 mg, 0.12 mmol) in anhydrous Et_2O (2 mL) at rt under $N_{2(g)}$ was added lithium aluminium hydride (10 mg, 0.26 mmol) and the suspension stirred for 10 min. After this time 20% $KOH_{(aq)}$ (2 mL) was added dropwise (CARE!) and the mixture diluted with Et_2O (2 mL). The layers were separated and the aqueous phase extracted (2x2 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield the alcohol **346** (21 mg, 0.10 mmol, 90%) as a clear oil. **Esterification:** To a stirred solution of the alcohol **346** (21 mg, 0.10 mmol) and (2*R*)-acetyl mandelic acid (20 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (2 mL) at −10°C under $N_{2(g)}$ was added dicyclohexylcarbodiimide (DCC, 42 mg, 0.20 mmol) followed by 4-(dimethylamino)pyridine (DMAP, 5 mg, catalytic). The resultant mixture was then stirred O/N whilst being allowed to warm slowly to rt. After this time the reaction was filtered and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 25% Et_2O in hexanes) to yield the ester **410** (*ca* 39 mg, 0.10 mmol, 100%) as a clear oil. Comparison of ^1H and ^{13}C NMR spectra with a sample of ester prepared in an analogous way from partially racemised olefin suggest that dr ≥ 94:6 (HPLC studies were ineffectual in resolving diastereomeric components).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.52-7.45 (2H, m, Ar), 7.44-7.34 (3H, m, Ar), 5.93 (1H, s, C<u>H</u>OAc), 4.34 (1H, t, J = 4.9 Hz, H3), 4.01 (1H, dd, J = 10.7, 6.0 Hz, $H7_A$), 3.93 (1H, dd, J = 10.7, 6.6 Hz, $H7_B$), 3.59 (2H, d, J = 11.1 Hz, $Me_2CC\underline{H}_AH_BO$), 3.40 (2H, d, J = 11.0 Hz, $Me_2CCH_A\underline{H}_BO$), 2.20 (3H, s, MeCO), 1.80-1.37 (5H, m, H4-H6), 1.18 (3H, s, <u>Me</u>CMe), 0.82 (3H, d, J = 6.8 Hz, C6-<u>Me</u>), 0.72 (3H, s, MeC<u>Me</u>) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 170.5 (0, PhCH<u>C</u>=O), 169.0 (0, Me<u>C</u>=O), 134.1 (0, Ar), 129.3 (1, Ar), 128.9 (2C, 1, Ar), 127.7 (2C, 1, Ar), 102.3 (1, C3), 77.4 (2C, 2, $Me_2C\underline{C}H_2O$), 74.7 (1, Ph<u>C</u>HCO), 70.4 (2, C7), 32.6 (1, C6), 32.3 (2, C4), 30.3 (0, Me<u>C</u>Me), 27.4 (2, C5), 23.2 (3, <u>Me</u>CMe), 22.0 (3, MeC<u>Me</u>), 20.9 (3, <u>Me</u>C=O), 16.6 (3, C6-<u>Me</u>) ppm.

(2*S*,3*S*,4*S*)-6-(5,5-Dimethyl-1,3-dioxan-2-yl)-4-methylhexan-2,3-diol (349):



327
$C_{13}H_{24}O_2$ (212.33)

349
$C_{13}H_{26}O_4$ (246.34)

To a mechanically stirred solution of AD-mix α[130](25.0 g) in *t*-BuOH (70 mL) and H_2O (80 mL) was added methane sulfonamide (1.70 g, 17.9 mmol). The mixture was then cooled to 0°C and a solution of the olefin **327** (3.76 g, 17.7 mmol, *E:Z* = 93:7) in *t*-BuOH (10 mL) added. The reaction was then stirred vigorously at 0°C for 24 h. $Na_2SO_{3(s)}$ (26 g) was added and the mixture allowed to stir for 1 h whilst being allowed to warm to rt. The biphasic system was then extracted (4x50 mL CH_2Cl_2) and the combined organic extracts washed successively with 2M $KOH_{(aq)}$ (60 mL) and brine (50 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with Et_2O) to yield the diol **349** (3.62 g, 14.7 mmol, 83%, dr ~ 93:7) as a clear oil.

$[\alpha]_D$ = –13.5 (c = 0.48, $CHCl_3$).

IR (film): ν = 3424 (s, br), 2954 (s), 1472 (s), 1334 (s), 1236 (w), 1120 (s), 1042 (m), 1018 (m), 984 (m), 910 (w), 880 (w) cm^{-1}.

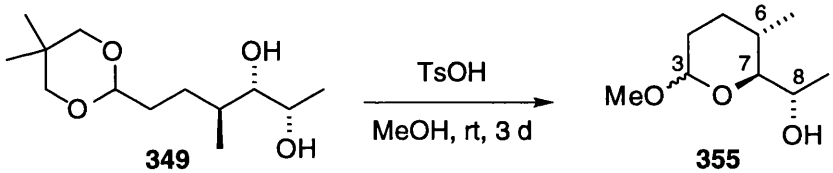
^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.41 (1H, t, J = 7.6 Hz, H3), 3.85 (1H, quintet, J = 6.0 Hz, H8), 3.60 (2H, d, J = 11.1 Hz, $C\underline{H}_AH_BO$), 3.42 (2H, d, J = 11.0 Hz, $CH_A\underline{H}_BO$), 3.13 (1H, t, J = 5.2 Hz, H7), 2.40-2.15 (2H, m, OH), 1.80-1.52 (4H, m), 1.37-1.28 (1H, m), 1.20 (3H, d, J = 6.3 Hz, C8-Me), 1.18 (3H, s, <u>Me</u>CMe), 0.96 (3H, d, J = 6.8 Hz, C6-Me), 0.72 (3H, s, MeC<u>Me</u>) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 102.6 (1, C3), 79.9 (1, C7), 77.3 (2C, 2, CH_2O), 67.9 (1, C8), 35.0 (1, C6), 32.2 (2, C4), 30.3 (0, MeCMe), 25.1 (2, C5), 23.1 (3, MeCMe), 21.9 (3, MeCMe), 20.2 (3, C8-Me), 16.7 (3, C6-Me) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 264 (36%), 247 (71), 160 (11), 143 (21), 122 (100), 105 (22).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^{+\bullet}$, 247.1911. $C_{13}H_{27}O_4$ requires 247.1909.

(*S*)-1-[(2*S*,3*S*,6*S*)-6-Methoxy-3-methyloxan-2-yl]ethanol (355α) and (*S*)-1-[(2*S*,3*S*, 6*R*)-6-methoxy-3-methyloxan-2-yl]ethanol (355β):



349 $C_{13}H_{26}O_4$ (246.34)

355 $C_9H_{18}O_3$ (174.24)

A solution of the diol **349** (3.62 g, 14.7 mmol) and toslic acid (40 mg) in MeOH (60 mL) was stirred at rt for 3 d. After this time the mixture was diluted with Et_2O (100 mL) and shaken with sat. $NaHCO_{3(aq)}$ (100 mL). The layers were then separated and the aqueous phase extracted (4x20 mL Et_2O). The combined organic extracts were then washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 40% Et_2O in hexanes) to yield the methyl acetal **355** (1.88 g, 10.8 mmol, 73%, α:β = 3:1) as a white solid: mp = 36-40°C; bp (kugelrohr oven) 100°C, 0.3 mmHg.

$[\alpha]_D$ = +101.8 (*c* = 0.50, $CHCl_3$).

IR (film): ν = 3474 (s, br), 2930 (s), 1458 (m), 1374 (m), 1350 (w), 1233 (m), 1211 (m), 1183 (w), 1158 (m), 1129 (m), 1047 (m), 1026 (m), 997 (m), 964 (m), 908 (m), 815 (w) cm^{-1}.

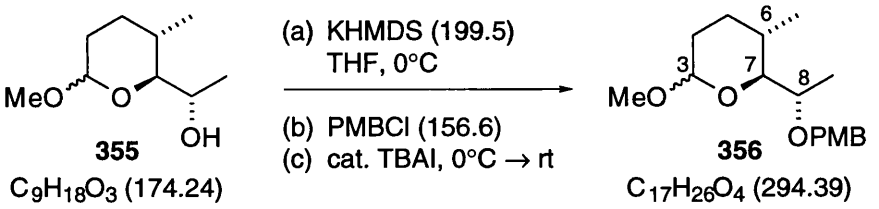
^1H NMR (360 MHz, $CDCl_3$): δ = 4.77 (1Hα, t, *J* = 2.4 Hz, H3), 4.33 (1Hβ, dd, *J* = 9.7, 2.1 Hz, H3), 4.00-3.90 (1H, m, H8), 3.50 (3Hβ, s, OMe), 3.34 (3Hα, s, OMe), 3.17 (1Hα, dd, *J* = 9.4, 0.8 Hz, H7), 2.86 (1Hβ, dd, *J* = 9.8, 1.5 Hz, H7), 2.00-1.39 (5H, m), 1.29 (3Hβ, d, *J* = 6.6 Hz, C8-Me), 1.27 (3Hα, d, *J* = 6.5 Hz, C8-Me), 0.88 (3Hα, d, *J* = 6.5 Hz, C6-Me), 0.87 (3Hβ, d, *J* = 6.5 Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): α δ = 98.5 (1, C3), 77.2 (1, C7), 66.3 (1, C8), 54.5 (3, OMe), 30.7 (1, C6), 30.1 (2, C5), 26.9 (2, C4), 20.8 (3, C8-Me), 17.7 (3, C6-Me) ppm; β δ = 103.7 (1, C3), 84.2 (1, C7), 66.5 (1, C8), 56.2 (3, OMe), 31.6 (2, C5), 31.4 (2, C4), 30.5 (1, C6), 20.8 (3, C8-Me), 16.9 (3, C6-Me) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 192 (75%), 160 (100), 143 (75), 96 (22), 79 (40).

Anal. Calcd. for $C_9H_{18}O_3$ (M = 174): C, 62.04; H, 10.41. Found C, 62.04; H, 10.22.

4-Methoxybenzyl (*S*)-1-[(2*S*,3*S*,6*S*)-6-methoxy-3-methyloxan-2-yl]ethyl ether (356α) and 4-methoxybenzyl (*S*)-1-[(2*S*,3*S*,6*R*)-6-methoxy-3-methyloxan-2-yl]ethyl ether (356β):



$C_9H_{18}O_3$ (174.24) $C_{17}H_{26}O_4$ (294.39)

A stirred solution of potassium hexamethyldisilazide (KHMDS, 1.88 g, 80 wt.%, 7.54 mmol) in anhydrous THF (45 mL) under $N_{2(g)}$ at 0°C was treated dropwise with a solution of the alcohol **355** (1.01 g, 5.80 mmol, α:β = 3:1) in anhydrous THF (15 mL). After complete addition the mixture was stirred for 20 min; neat 4-methoxybenzyl chloride (PMBCl, 1.02 mL, ρ = 1.16, 1.18 g, 7.56 mmol) was then added dropwise. A small portion of tetrabutylammonium iodide (TBAI, 60 mg) was then added and the mixture allowed to warm to rt and stirred for 24 h. The reaction mixture was then partitioned between Et_2O (40 mL) and brine (50 mL). The layers were then shaken and separated and the aqueous layer extracted (3x10 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 20-50% Et_2O in hexanes) to yield the ether **356** (1.58 g, 5.37 mmol, 93%, α:β = 3:1) as a clear oil.

$[\alpha]_D$ = +103.1 (*c* = 0.52, $CHCl_3$).

IR (film): ν = 2932 (s), 1613 (m), 1586 (w), 1514 (s), 1458 (m), 1373 (m), 1348 (w), 1302 (m), 1248 (s), 1210 (w), 1172 (m), 1128 (s), 1057 (s), 1035 (s), 998 (m), 974 (w), 964 (w), 906 (m), 821 (m) 754 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.27 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 4.78 (1Hα, d, *J* = 3.1 Hz, H3), 4.64 (1H, d, *J* = 11.8 Hz, C$\underline{H_A}H_B$Ar), 4.34 (1Hβ, *J* =

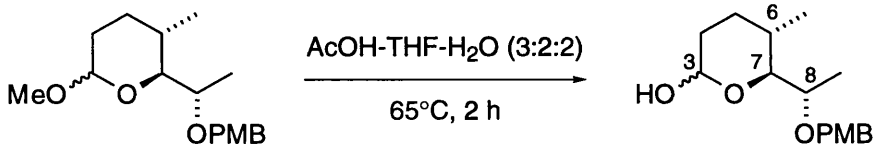
11.9 Hz, $CH_A\underline{H}_BAr$), 4.33 (1Hα, d, J = 11.8 Hz, $CH_A\underline{H}_BAr$), 4.21 (1Hβ, dd, J = 9.6, 2.0 Hz, H3), 3.78 (3H, s, MeOAr), 3.65 (1H, qd, J = 6.3, 1.6 Hz, H8), 3.47 (3Hβ, s, OMe), 3.32 (3Hα, s, OMe), 3.19 (1Hα, dd, J = 10.1, 1.6 Hz, H7), 2.87 (1Hβ, dd, J = 9.6, 2.1 Hz, H7), 1.93-1.61 (3H, m), 1.55-1.36 (2H, m), 1.27 (3Hβ, d, J = 6.4 Hz, C8-Me), 1.27 (3Hα, d, J = 6.4 Hz, C8-Me), 0.64 (3H, d, J = 6.6 Hz, C6-Me) ppm.

^{13}C NMR (MHz, $CDCl_3$): α δ = 159.2 (0, Ar), 130.9 (0, Ar), 129.8 (2C, 1, Ar), 113.7 (2C, 1, Ar), 98.6 (1, C3), 77.1 (1, C7), 71.8 (1, C8), 70.4 (2, $\underline{C}H_2Ar$), 55.3 (3, $\underline{Me}OAr$), 54.5 (3, OMe), 30.4 (1, C6), 29.9 (2, C5), 27.2 (2, C4), 17.4 (3, C8-$\underline{Me}$), 15.5 (3, C6-$\underline{Me}$) ppm; β δ = 159.2 (0, Ar), 131.0 (0, Ar), 129.7 (2C, 1, Ar), 113.7 (2C, 1, Ar), 104.0 (1, C3), 83.9 (1, C7), 72.4 (1, C8), 70.1 (2, $\underline{C}H_2Ar$), 56.0 (3, OMe), 55.3 (3, $\underline{Me}OAr$), 31.7 (2, C5), 31.5 (2, C4), 30.2 (1, C6), 16.6 (3, C8-$\underline{Me}$), 15.3 (3, C6-$\underline{Me}$) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 312 (100%), 280 (14), 155 (37), 138 (55), 121 (36).

Anal. Calcd. for $C_{17}H_{26}O_4$ (M = 294): C, 69.36; H, 8.90. Found C, 69.22; H, 8.98.

(2*S*,3*S*,6*S*)-2-[(*S*)-1-[(4-Methoxybenzyl)oxy]ethyl]-3-methyloxan-6-ol (357α) and (2*S*,3*S*,6*R*)-2-[(*S*)-1-[(4-methoxybenzyl)oxy]ethyl]-3-methyl-oxan-6-ol (357β):



356
$C_{17}H_{26}O_4$ (294.39)

357
$C_{16}H_{24}O_4$ (280.36)

A solution of the methyl glycoside **356** (1.73 g, 5.88 mmol, α:β = 3:1) in AcOH-THF-H_2O (3:2:2, 30 mL) was stirred at 65°C for 2 h. After this time the mixture was allowed to cool and diluted with Et_2O (40 mL) and H_2O (20 mL). The layers were then shaken and separated and the aqueous phase extracted (3x15 mL Et_2O). The combined organic extracts were then successively washed with H_2O (4x15 mL), sat. $NaHCO_{3(aq)}$ (3x15 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 40% Et_2O in hexanes) to afford some recovered starting material (311 mg, 1.06 mmol, 18%) and the lactol **357** (1.22 g, 4.36 mmol, 74%, α:β = 1.4:1) as a clear oil.

$[\alpha]_D$ = +73.1 (c = 0.54, $CHCl_3$).

IR (film): ν = 3405 (br m), 2930 (s), 2855 (s), 1612 (m), 1586 (w), 1514 (s), 1459 (m), 1376 (m), 1302 (w), 1247 (s), 1173 (m), 1112 (m), 1035 (s), 1001 (s), 931 (w), 910 (w), 821 (m) cm^{-1}.

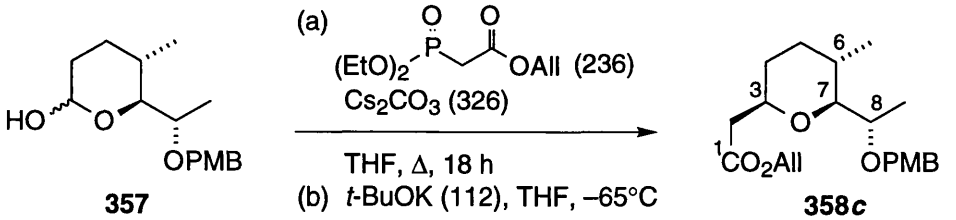
^1H NMR (360 MHz, $CDCl_3$): δ = 7.28 (2Hβ, d, J = 8.6 Hz, Ar), 7.27 (2Hα, d, J = 8.6 Hz, Ar), 6.87 (2H, d, J = 8.7 Hz, Ar), 5.40 (1Hα, m, H3), 4.64 (1Hβ, d, J = 11.8 Hz, CH_AH_BAr), 4.64 (1Hα, d, J = 11.8 Hz, CH_AH_BAr), 4.67-4.60 (1Hβ, signal obscured, H3), 4.36 (1Hβ, d, J = 11.8 Hz, CH_AH_BAr), 4.35 (1Hα, d, J = 11.8 Hz, CH_AH_BAr), 3.81 (3H, s, OMe), 3.70-3.60 (1H, m, H8), 3.46 (1Hα, dd, J = 10.3, 2.0 Hz, H7), 2.97 (1Hβ, dd, J = 9.4, 2.0 Hz, H7), 2.80-2.65 (1Hβ, br s, OH), 2.32-2.23 (1Hα, br s, OH), 1.92-1.65 (3H, m), 1.60-1.33 (2H, m), 1.28 (3Hβ, d, J = 6.4 Hz, C8-Me), 1.23 (3Hα, d, J = 6.4 Hz, C8-Me), 0.68 (3Hα, d, J = 6.4 Hz, C6-Me), 0.66 (3Hβ, d, J = 6.4 Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): α δ = 159.3 (0, Ar), 130.9 (0, Ar), 129.8 (2C, 1, Ar), 113.7 (2C, 1, Ar), 91.9 (1, C3), 77.2 (1, C7), 72.0 (1, C8), 70.4 (2, $\underline{C}H_2Ar$), 55.4 (3, OMe), 30.7 (1, C6), 30.1 (2, C5), 26.5 (2, C4), 17.6 (3, C8-$\underline{Me}$), 15.7 (3, C6-$\underline{Me}$) ppm; β δ = 159.3 (0, Ar), 130.9 (0, Ar), 129.8 (2C, 1, Ar), 113.8 (2C, 1, Ar), 97.2 (1, C3), 84.3 (1, C7), 72.3 (1, C8), 70.3 (2, $\underline{C}H_2Ar$), 55.4 (3, OMe), 33.8 (2, C5), 31.6 (2, C4), 30.0 (1, C6), 16.7 (3, C8-$\underline{Me}$), 15.5 (3, C6-$\underline{Me}$) ppm.

LRMS (CI+ mode, NH_3): m/z = 298 (100%), 280 (19), 155 (27), 138 (44), 121 (34).

HRMS (CI+ mode): Found $(M+NH_4)^{+\bullet}$, 298.2013. $C_{16}H_{24}O_4+NH_4$ requires 298.2018.

Prop-2-enyl [(2*S*,3*S*,6*R*)-2-[(*S*)-1-[(4-methoxybenzyl)oxy]ethyl]-3-methyl-oxan-6-yl]ethanoate (358*c*):



357
$C_{16}H_{24}O_4$ (280.36)

358*c*
$C_{21}H_{30}O_5$ (362.46)

A stirred suspension of the lactol **357** (1.22 g, 4.36 mmol, α:β = 1.4:1) and cesium carbonate (2.90 g, 8.90 mmol) in anhydrous THF (20 mL) under $N_{2(g)}$ was treated with allyl diethylphosphonoacetate (1.85 mL, ρ = 1.12, 2.07 g, 8.77 mmol) and heated at reflux O/N. After this time the reaction mixture was allowed to cool and partitioned between Et_2O (40 mL) and H_2O (20 mL). The layers were shaken and separated and the aqueous phase extracted (3x10 mL Et_2O). The combined organic extracts were then washed with brine (20 mL), dried

($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 40% Et_2O in hexanes) to afford 1.30 g of tetrahydropyran isomers **358*ct*** (*cis:trans* = 4:6, 82%). A solution of the isomers (1.30 g, 3.59 mmol) in anhydrous THF (30 mL) at –65°C under $N_{2(g)}$ was then treated dropwise with a solution of potassium *tert*-butoxide (485 mg, 4.33 mmol) in anhydrous THF (10 mL). After stirring for 10 min sat. $NH_4Cl_{(aq)}$ (2 mL) was added and the mixture allowed to warm to rt. The reaction mixture was then partitioned between Et_2O (40 mL) and H_2O (20 mL) and the layers shaken and separated. The aqueous phase was extracted (3x10 mL Et_2O) and the combined organic extracts washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) to yield the diastereomerically pure *cis* tetrahydropyran **358*c*** (1.15 g, 3.18 mmol, 73% overall) as a clear oil.

Prop-2-enyl [(2*S*,3*S*,6*R*)-2-[(*S*)-1-[(4-methoxybenzyl)oxy]ethyl]-3-methyloxan-6-yl] ethanoate (**358*c***).

$[\alpha]_D$ = +29.8 (*c* = 0.60, $CHCl_3$).

IR (film): ν = 2928 (s), 1738 (2), 1613 (m), 1514 (s), 1456 (m), 1372 (m), 1339 (w), 1302 (m), 1276 (m), 1248 (s), 1194 (m), 1170 (m), 1084 (m), 1036 (m), 930 (w), 822 (w), 755 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.27 (2H, d, *J* = 8.6 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 5.92 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, $CH_2C\underline{H}=CH_2$), 5.31 (1H, dq, *J* = 17.2, 1.5 Hz, $CH_2CH=C\underline{H}_ZH_E$), 5.22 (1H, dq, *J* = 10.4, 1.3 Hz, $CH_2CH=CH_Z\underline{H}_E$), 4.63 (1H, d, *J* = 11.9 Hz, $C\underline{H}_AH_BAr$), 4.58 (2H, dt, *J* = 5.7, 1.3 Hz, $C\underline{H}_2CH=CH_2$), 4.33 (1H, d, *J* = 11.9 Hz, $CH_A\underline{H}_BAr$), 3.80 (3H, s, OMe), 3.70 (1H, dddd, *J* = 11.2, 8.5, 5.6, 3.0 Hz, H3), 3.61 (1H, qd, *J* = 6.4, 2.1 Hz, H8), 2.84 (1H, dd, *J* = 9.5, 3.1 Hz, H7), 2.68 (1H, dd, *J* = 15.3, 8.1 Hz, $H2_A$), 2.43 (1H, dd, *J* = 15.3, 5.3 Hz, $H2_B$), 1.85-1.75 (2H, m), 1.62 (1H, ddt, *J* = 12.9, 4.2, 2.1 Hz), 1.39 (1H, tdd, *J* = 12.9, 11.1, 3.7 Hz, $H4_{ax}$), 1.28-1.15 (1H, signal obscured), 1.20 (3H, d, *J* = 6.4 Hz, C8-Me), 0.63 (3H, d, *J* = 6.3 Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 171.5 (0, C1), 159.3 (0, Ar), 132.4 (1, $CH_2\underline{C}H=CH_2$), 131.1 (0, Ar), 129.8 (2C, 1, Ar), 118.2 (2, $CH=\underline{C}H_2$), 113.8 (2C, 1, Ar), 86.5 (1, C7), 75.3 (1, C3), 72.2 (1, C8), 70.2 (2, $\underline{C}H_2Ar$), 65.2 (2, $\underline{C}H_2CH=CH_2$), 55.4 (3, OMe), 41.4 (2, C2), 33.0 (2, C5), 31.7 (2, C4), 30.4 (1, C6), 17.2 (3, C8-Me), 15.3 (3, C6-Me) ppm.

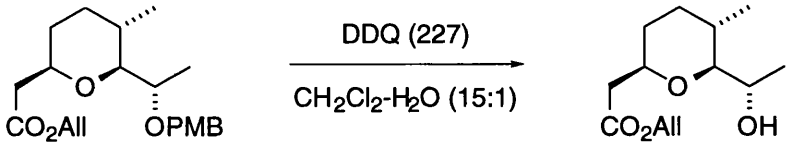
LRMS (CI+ mode, NH_3): *m/z* = 380 (100%), 121 (36).

HRMS (EI+ mode): Found $M^{+\bullet}$, 362.2095. $C_{21}H_{30}O_5$ requires 362.2093.

Prop-2-enyl [(2*S*,3*S*,6*S*)-2-[(*S*)-1-[(4-methoxybenzyl)oxy]ethyl]-3-methyloxan-6-yl] ethanoate (**358*t***).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.27 (2H, d, *J* = 8.6 Hz, Ar), 6.86 (2H, d, *J* = 8.6 Hz, Ar), 5.92 (1H, ddt, *J* = 17.2, 10.5, 5.8 Hz, $CH_2C\underline{H}=CH_2$), 5.32 (1H, dm, *J* = 17.2 Hz, $CH_2CH=C\underline{H}_ZH_E$), 5.23 (1H, dm, *J* = 10.4 Hz, $CH_2CH=CH_Z\underline{H}_E$), 4.65-4.50 (4H, m, $C\underline{H}_2CH=CH_2$, $C\underline{H}_AH_BAr$, H3), 4.32 (1H, d, *J* = 11.9 Hz, $CH_A\underline{H}_BAr$), 3.81 (3H, s, OMe), 3.62 (1H, qd, *J* = 6.4, 2.1 Hz, H8), 3.11 (1H, dd, *J* = 9.3, 2.2 Hz, H7), 2.88 (1H, dd, *J* = 14.1, 9.6 Hz, $H2_A$), 2.40 (1H, dd, *J* = 14.1, 5.6 Hz, $H2_B$), 1.97-1.77 (2H, m), 1.69-1.58 (1H, m), 1.50-1.43 (1H, m), 1.35-1.26 (1H, m), 1.16 (3H, d, *J* = 6.4 Hz, C8-Me), 0.69 (3H, d, *J* = 6.6 Hz, C6-Me) ppm.

Prop-2-enyl [(2*S*,3*S*,6*R*)-2-[(*S*)-1-hydroxyethyl]-3-methyloxan-6-yl] ethanoate (240):



358*c*
$C_{21}H_{30}O_5$ (362.46)

240
$C_{13}H_{22}O_4$ (242.31)

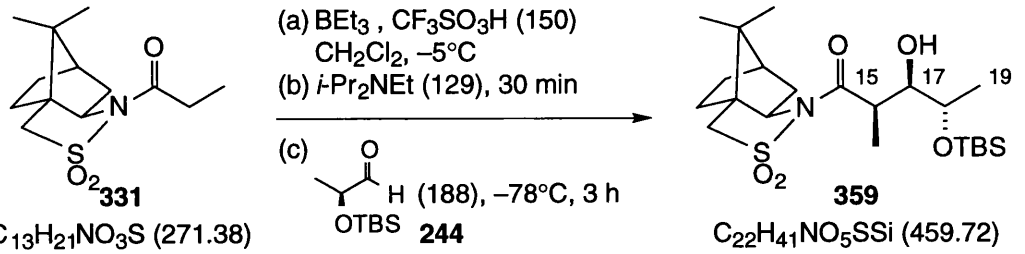
A vigorously stirred solution of the PMB ether **358*c*** (508 mg, 1.40 mmol) in CH_2Cl_2-H_2O (30 mL: 2 mL) at rt was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 470 mg, 2.07 mmol) and the resulting brown mixture stirred for 30 min. Anhydrous $MgSO_{4(s)}$ (*ca* 20 g) was then added and the mixture stirred for a further 10 min. The thick suspension was then filtered and the filtrate concentrated *in vacuo*. The resulting residue was then further purified *via* column chromatography (eluting with 30% Et_2O in hexanes) to yield the alcohol **240** (321 mg, 1.33 mmol, 95%) as a clear oil.

$[\alpha]_D$ = +7.8 (*c* = 0.97, $CHCl_3$). [lit.[46] $[\alpha]_D$ = +5.7 (*c* = 0.7, $CHCl_3$)].

^{1}H and ^{13}C NMR in complete agreement with that previously reported[46].

–SECTION 6.3–

(2*R*)-*N*-[(2*R*,3*R*,4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-hydroxy-2-methylpentanoyl]bornane-10,2-sultam (359):



331 $C_{13}H_{21}NO_3S$ (271.38)

244

359 $C_{22}H_{41}NO_5SSi$ (459.72)

Prepared by the method of Oppolzer[138]. To a stirred solution of triethyl borane (32.0 mL, 1.0 M in hexanes, 32.0 mmol) at rt under $N_{2(g)}$ was added dropwise triflic acid (2.83 mL, ρ = 1.70, 4.80 g, 32.0 mmol). Evolution of ethane was noted and the temperature of the reaction mixture rose to 38°C. The mixture was then stirred for 15 min before being cooled to –10°C and treated dropwise with (2*R*)-*N*-propanoylbornane-10,2-sultam[138] (**331**, 4.34 g, 16.0 mmol) in anhydrous CH_2Cl_2 (60 mL) at such a rate that the internal temperature did not rise above –5°C. After 5 min di*iso*propylethylamine (Hunig's base, 5.90 mL, ρ = 0.742, 4.40 g, 33.9 mmol) was added dropwise and the reaction stirred for 30 min at –5°C before cooling to –78°C. The neat aldehyde **244**[46] (9.14 g, 48.6 mmol) was then added dropwise and stirring continued for 3 h. The reaction mixture was then quenched by the addition of sat. $NH_4Cl_{(aq)}$ (50 mL), allowed to warm to rt and diluted with Et_2O (100 mL). The layers were then well shaken and separated. The aqueous phase was then further extracted (3x30 mL Et_2O) and the combined organic extracts dried ($MgSO_4$) and then concentrated *in vacuo* to yield 15.2 g of a crude oil. The residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) followed by recrystallisation (hexanes) to yield the aldol **359** (5.50 g, 12.0 mmol, 75%) as a white solid: mp = 92-95°C.

$[\alpha]_D$ = –65.8 (*c* = 1.20, $CHCl_3$).

IR (KBr): ν = 3517 (br), 2967 (s), 1680 (m), 1335 (s), 1139 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (1H, dd, *J* = 5.9, 5.9 Hz, CHN), 3.80-3.71 (2H, m, H17, H18), 3.47 (1H, d, *J* = 13.8 Hz, $C\underline{H}_AH_BSO_2$), 3.40 (1H, d, *J* = 13.8 Hz, $CH_A\underline{H}_BSO_2$), 3.36 (1H, qd, *J* = 7.1, 4.2 Hz, H16), 2.04-1.99 (2H, m), 1.91-1.82 (3H, m), 1.42-1.36 (1H, m), 1.35-1.29 (1H, m), 1.27 (3H, d, *J* = 7.1 Hz, H19), 1.17 (3H, d, *J* = 5.9 Hz, C16-Me), 1.15 (3H, s, $\underline{Me}C(CH)Me$), 0.96 (3H, s, $MeC(CH)\underline{Me}$), 0.90 (9H, s, CMe_3), 0.09 (3H, s, $SiMe_2$), 0.08 (3H, s, $SiMe_2$) ppm.

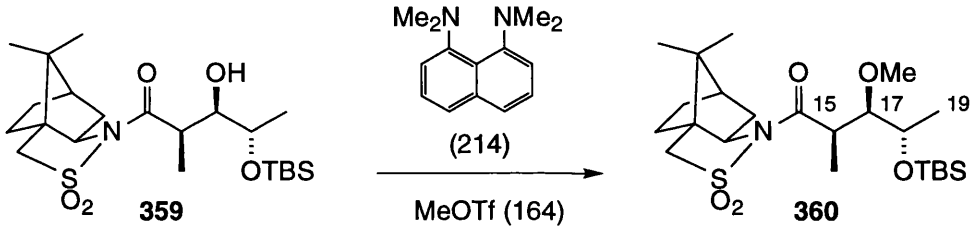
^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7 (0, C15), 75.0 (1, C17), 68.1 (1, C18), 64.7 (1, CHN), 53.0 (2, CH_2SO_2), 48.3 (0, $\underline{C}CHN$), 47.7 (0, $Me\underline{C}(CH)Me$), 44.5 (1, $MeC(\underline{C}H)Me$),

40.4 (1, C16), 38.2 (2), 32.8 (2), 26.4 (2), 25.8 (3, 3C, $C\underline{Me}_3$), 20.7 (3, $\underline{Me}C(CH)Me$), 19.8 (3, $MeC(CH)\underline{Me}$), 19.1 (3, C19), 17.9 (0, $\underline{C}Me_3$), 12.9 (3, C16-$\underline{Me}$), –4.2 (3, $SiMe_2$), –5.0 (3, $SiMe_2$) ppm.

LRMS (CI+ mode): *m/z* = 460 (12%), 442 (4), 328 (100), 289 (3), 272 (3), 245 (5).

Anal. Calcd. for $C_{22}H_{41}NO_5SSi$ (M = 459): C, 57.48; H, 8.99; N, 3.05. Found C, 57.51; H, 8.98; N, 2.97.

(2*R*)-*N*-[(2*R*,3*R*,4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-methoxy-2-methylpentanoyl]bornane-10,2-sultam (360):



To a stirred solution of the aldol **359** (12.1 g, 26.4 mmol) and 1,8-bis(dimethylamino)naphthalene (proton sponge®, 17.0 g, 79.4 mmol) in anhydrous PhMe (100 mL) at rt under $N_{2(g)}$ was added methyl triflate (9.0 mL, ρ = 1.45, 13.1 g, 79.6 mmol). The resulting mixture was then heated to 80°C and stirred for 24 h. After this time the suspension was allowed to cool to rt, treated with conc. $NH_4OH_{(aq)}$ (15 mL) and then stirred for 30 min. The biphasic mixture was then further diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL) and the layers shaken well and then separated. The aqueous phase was then extracted (2x30 mL CH_2Cl_2) and the combined organic extracts washed successively with 2M $HCl_{(aq)}$ (4x50 mL) and brine (50 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude residue was then further purified *via* column chromatography (eluting with 20% Et_2O in hexanes) to yield the methyl ether **360** (11.3 g, 23.9 mmol, 90%) as a white solid: mp 106-108°C (hexanes).

$[\alpha]_D$ = –74.9 (*c* = 0.39, $CHCl_3$).

IR (KBr): ν = 2971 (m), 1691 (m), 1466 (w), 1388 (w), 1342 (s), 1269 (w), 1142 (m), 1107 (s), 1065 (w), 847 (w), 776 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (1H, dd, *J* = 7.5, 5.1 Hz, CHN), 3.79 (1H, qd, *J* = 6.4, 2.6 Hz, H18), 3.52 (3H, s, OMe), 3.46 (1H, dd, *J* = 8.4, 2.6 Hz, H17), 3.45 (1H, d, *J* = 13.6 Hz, $C\underline{H}_AH_BSO_2$), 3.39 (1H, d, *J* = 14.0 Hz, $CH_A\underline{H}_BSO_2$), 3.07 (1H, dq, *J* = 8.3,

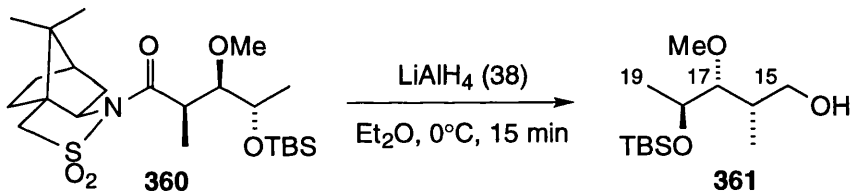
7.0 Hz, H16), 2.04 (1H, dd, J = 13.7, 7.8 Hz), 1.98 (1H, dm, J = 14.0 Hz), 1.93-1.81 (3H, m), 1.42-1.36 (1H, m), 1.35-1.29 (1H, m), 1.27 (3H, d, J = 7.0 Hz, H19), 1.12 (3H, s, MeC(CH)Me), 1.11 (3H, d, J = 6.1 Hz, C16-Me), 0.94 (3H, s, MeC(CH)Me), 0.87 (9H, s, CMe_3), 0.06 (3H, s, $SiMe_2$), 0.02 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (0, C15), 85.5 (1, C17), 70.1 (1, C18), 64.9 (1, CHN), 61.2 (3, OMe), 53.1 (2, CH_2SO_2), 48.3 (0, CCHN), 47.7 (0, MeC(CH)Me), 44.6 (1, MeC(CH)Me), 42.4 (1, C16), 38.3 (2), 32.7 (2), 26.4 (2), 25.8 (3, 3C, CMe_3), 20.8 (3, MeC(CH)Me), 19.9 (3, MeC(CH)Me), 17.9 (0, CMe_3), 17.3 (3, C19), 15.7 (3, C16-Me), –4.7 (3, 2C, $SiMe_2$) ppm.

LRMS (CI+ mode): m/z = 474 (4%), 342 (100), 310 (1), 278 (2).

Anal. Calcd. for $C_{23}H_{43}NO_5SSi$ (M = 473): C, 58.31; H, 9.15; N, 2.96. Found C, 58.34; H, 9.12; N, 2.92.

(2*S*,3*R*,4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-methoxy-2-methyl-pentan-1-ol (361):



360 $C_{23}H_{43}NO_5SSi$ (473.74)

361 $C_{13}H_{30}O_3Si$ (262.46)

A solution of the acyl sultam **360** (2.03 g, 4.3 mmol) in anhydrous Et_2O (20 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.50 g, 13.2 mmol) in Et_2O (10 mL) at 0°C under $N_{2(g)}$. After 15 min the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (10 mL, CARE!) and stirred vigorously for 10 min. The biphasic mixture was then filtered through a celite pad and the residue washed well (3x5 mL Et_2O). The layers of the filtrate and combined washings were then separated and the aqueous layer extracted (2x10 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 40% Et_2O in hexanes) to yield (2*R*)-bornane-10,2-sultam[138,152] (0.87 g, 4.05 mmol, 94%) as a white solid and the alcohol **361** (1.11 g, 4.24 mmol, 99%) as a clear oil.

$[\alpha]_D$ = +25.5 (c = 1.07, $CHCl_3$).

IR (film): ν = 3410 (br), 2941 (s), 1476 (m), 1385 (m), 1265 (m), 1110 (s), 1065 (m), 836 (s), 776 (s) cm^{-1}.

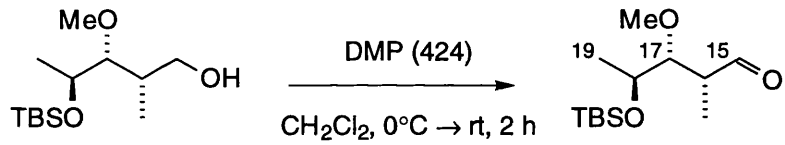
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (1H, dq, J = 6.1, 6.1 Hz, H18), 3.62-3.54 (2H, m, H15), 3.47 (3H, s, OMe), 3.07 (1H, dd, J = 6.0, 3.5 Hz, H17), 1.99 (1H, qddd, J = 6.8, 6.8, 5.6, 3.4 Hz, H16), 1.19 (3H, d, J = 6.1 Hz, H19), 0.89 (3H, d, J = 7.1 Hz, C16-Me), 0.85 (9H, s, CMe_3), 0.05 (3H, s, $SiMe_2$), 0.03 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 87.2 (1, C17), 69.0 (1, C18), 66.3 (2, C15), 60.3 (3, OMe), 36.8 (1, C16), 25.8 (3, 3C, CMe_3), 20.4 (3, C19), 18.0 (0, CMe_3), 11.3 (3, C16-Me), –4.2 (3, $SiMe_2$), –4.8 (3, $SiMe_2$) ppm.

LRMS (CI+ mode): m/z = 606 (31%), 492 (100), 263 (48), 131 (19), 117 (21).

Anal. Calcd. for $C_{13}H_{30}O_3Si$ (M = 262): C, 59.49; H, 11.52. Found C, 59.57; H, 11.41.

(2*S*,3*R*,4*S*)-4-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-methoxy-2-methylpentanal (335):



361
$C_{13}H_{30}O_3Si$ (262.46)

335
$C_{13}H_{28}O_3Si$ (260.45)

A stirred solution of the alcohol **361** (6.80 g, 26.0 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0°C under $N_{2(g)}$ was treated in one portion with Dess-Martin reagent[99,177] (DMP, 13.4 g, 31.6 mmol). The resulting solution was allowed to warm to rt and stirred for 2 h. After this time the reaction mixture was poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (200 mL) and stirred vigorously for 30 min. The biphasic system was then further diluted with Et_2O (100 mL) and the layers shaken and then separated. The aqueous phase was then extracted (2x20 mL Et_2O) and the combined organic extracts washed with sat. $NaHCO_{3(aq)}$ (4x30 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to yield the aldehyde **335** (6.15 g, 23.7 mmol, 91%) as a clear oil.

$[\alpha]_D$ = –7.5 (c = 1.0, $CHCl_3$).

IR (film): ν = 2932 (s), 1728 (s), 1472 (m), 1372 (w), 1334 (w), 1308 (w), 1258 (m), 1200 (w), 1114 (s), 1004 (m), 940 (m), 836 (s), 812 (m), 776 (m) cm^{-1}.

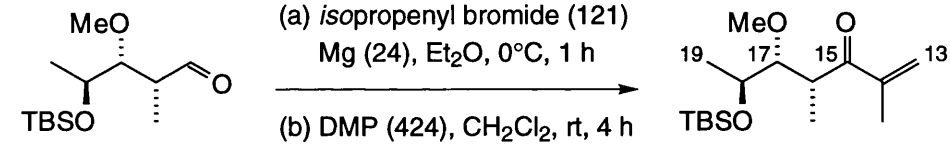
^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.81 (1H, s, H15), 3.76 (1H, quintet, J = 6.3 Hz, H18), 3.47 (1H, dd, J = 7.1, 3.0 Hz, H17), 3.34 (3H, s, OMe), 2.78 (1H, qd, J = 7.2, 3.0 Hz,

H16), 1.25 (3H, d, J = 6.0 Hz, H19), 1.04 (3H, d, J = 7.0 Hz, C16-Me), 0.88 (9H, s, CMe_3), 0.08 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 204.8 (1, C15), 84.9 (1, C17), 68.7 (1, C18), 59.7 (3, OMe), 48.3 (1, C16), 25.9 (3, 3C, $C\underline{Me}_3$), 20.9 (3, C19), 18.0 (0, $\underline{C}Me_3$), 7.6 (3, C16-$\underline{Me}$), –3.9 (3, $SiMe_2$), –4.8 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, NH_3): m/z = 278 (100%), 261 (48), 249 (16).

(4*R*,5*R*,6*S*)-2,4-Dimethyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy-5-methoxyhept-1-en-3-one (362):



335
$C_{13}H_{28}O_3Si$ (260.45)

362
$C_{16}H_{32}O_3Si$ (300.51)

A stirred suspension of activated magnesium (2.7 g, 113 mmol) in anhydrous Et_2O (130 mL) at rt under $N_{2(g)}$ was provided with 1 crystal of re-sublimed iodine. The brown mixture was then treated with one quarter of a solution of *iso*propenylbromide (10 g, 82.6 mmol) in anhydrous Et_2O (20 mL). The resultant suspension was heated to reflux until the brown colour had dissipated and Grignard formation had initiated. The remainder of the solution of bromide was then added at such a rate as to maintain a gentle reflux (*ca* 30 min). After the complete addition the cloudy solution of *iso*propenyl magnesium bromide was heated at reflux for an additional 2.5 h before being cooled to 0°C. A solution of the freshly prepared aldehyde **335** (6.15 g, 23.7 mmol) in anhydrous Et_2O (50 mL) was then added dropwise over 10 min and the reaction mixture stirred at 0°C for 1 h. H_2O (50 mL) was then added cautiously followed by 1M $HCl_{(aq)}$ (50 mL) and the biphasic mixture stirred for 10 min. The layers were then separated and the aqueous phase extracted (3x30 mL Et_2O). The combined organic extracts were then washed with sat. $NaHCO_{3(aq)}$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to afford **363** (6.51 g, 21.6 mmol, 91%) as a mixture of diastereoisomers (dr (C15) = 43:57 in favour of the *syn* isomer). The alcohols **363** (6.37 g, 21.1 mmol) were then dissolved in anhydrous CH_2Cl_2 (100 mL) and the resulting solution treated with Dess-Martin reagent[99,177] (DMP, 11.0 g, 25.9 mmol) and stirred at rt under $N_{2(g)}$ for 4 h. After this time the mixture was poured into sat. $Na_2S_2O_3$-$NaHCO_{3(aq)}$ (100 mL) and stirred vigorously for 1 h. The biphasic mixture was then diluted with Et_2O (100 mL) and the layers separated. The aqueous phase was extracted (3x30 mL Et_2O) and the combined organic extracts washed with brine (30 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude ketone was then

further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield pure **362** (5.58 g, 18.6 mmol, 88%, 80% from **335**) as a clear inviscid oil.

$[\alpha]_D = -35.2$ (c = 1.02, $CHCl_3$).

IR (film): ν = 2956 (s), 2931 (s), 2858 (s), 1676 (s), 1462 (m), 1380 (m), 1257 (s), 1115 (s), 1058 (m), 1028 (w), 981 (w), 932 (s), 835 (s), 776 (s) cm^{-1}.

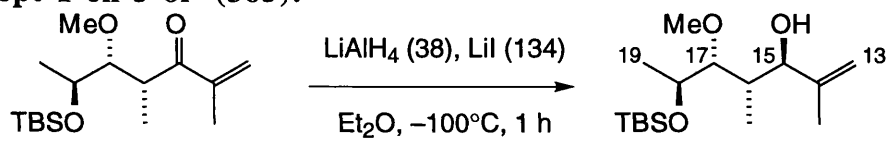
^1H NMR (360 MHz, $CDCl_3$): δ = 5.97 (1H, m, $H13_E$), 5.80 (1H, m, $H13_Z$), 3.66 (1H, quintet, J = 6.0 Hz, H18), 3.52 (1H, qd, J = 6.9, 5.1 Hz, H16), 3.37-3.34 (1H, signal obscured, H17), 3.35 (3H, s, OMe), 1.88 (3H, m, C14-Me), 1.13 (3H, d, J = 6.1 Hz, H19), 1.09 (3H, d, J = 6.8 Hz, C16-Me), 0.88 (9H, s, CMe_3), 0.06 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 205.3 (0, C15), 143.8 (0, C14), 124.9 (2, C13), 87.6 (1, C17), 69.4 (1, C18), 60.6 (3, OMe), 41.4 (1, C16), 26.0 (3C, 3, $C\underline{Me}_3$), 19.8 (3, C19), 18.3 (3, C14-$\underline{Me}$), 18.1 (0, $\underline{C}Me_3$), 11.8 (3, C16-$\underline{Me}$), –4.2 (3, $SiMe_2$), –4.7 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, *iso*butane): m/z = 301 (100%), 285 (3), 269 (5), 243 (16), 169 (63).

Anal. Calcd. for $C_{16}H_{32}O_3Si$ (M = 300): C, 63.95; H, 10.73. Found C, 63.73; H, 10.53.

(3*R*,4*R*,5*R*,6*S*)-2,4-Dimethyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy-5-methoxyhept-1-en-3-ol (363):



362 $C_{16}H_{32}O_3Si$ (300.51)

363 $C_{16}H_{34}O_3Si$ (302.52)

To a stirred solution of anhydrous lithium iodide (25.0 g, 187 mmol) in anhydrous Et_2O (200 mL) at –30°C under $N_{2(g)}$ was added the enone **362** (5.58 g, 18.6 mmol) in anhydrous Et_2O (20 mL). The resulting mixture was stirred vigorously for 20 min and then further cooled to –95°C (internal temperature). A solution of lithium aluminium hydride (20 mL, 1.0 M in Et_2O, 20 mmol) was then added dropwise *via* syringe pump over 30 min. The reaction mixture was then quenched by the careful addition of MeOH (20 mL) followed by H_2O (50 mL) and then allowed to warm to rt. The biphasic system was then filtered through a celite pad and the residue washed well (3x50 mL Et_2O). The layers of the filtrate and combined washings were then separated and the aqueous phase extracted (2x20 mL Et_2O). The combined organic extracts were then washed successively with H_2O (2x50 mL), brine (50 mL), dried ($MgSO_4$)

and then concentrated *in vacuo*. The resulting crude solid product (5.22 g, *ca* 93%, dr (C15) = 85:15) was then further purified *via* recrystallisation (5% H_2O-EtOH 30 mL) to afford 3.46 g of the title compound **363** as a white crystalline solid: mp 63-65°C. The mother liquor was concentrated *in vacuo* and the residue (1.65 g) further purified *via* column chromatography (eluting with 7% Et_2O in hexanes) to yield an additional 0.76 g of pure product as a white solid (desired isomer is the less polar component). The above procedure yielded in total 4.22 g of diastereomerically pure **363** (14.0 mmol, 75%).

$[\alpha]_D$ = +9.2 (*c* = 1.07, $CHCl_3$).

IR (KBr): ν = 3444 (br s), 2953 (s), 2858 (s), 1655 (m), 1507 (w), 1473 (w), 1446 (w), 1373 (m), 1334 (w), 1295 (w), 1257 (m), 1115 (s), 1086 (m), 1061 (w), 1043 (m), 993 (m), 974 (w), 934 (s), 899 (m), 835 (s), 810 (m), 772 (s), 745 (w) cm^{-1}.

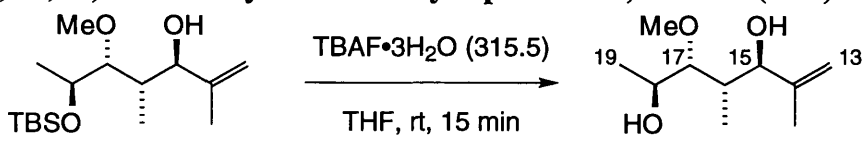
^1H NMR (360 MHz, $CDCl_3$): δ = 5.06 (1H, m, $H13_E$), 4.92 (1H, m, $H13_Z$), 3.95 (1H, d, *J* = 7.4 Hz, H15), 3.81 (1H, quintet, *J* = 6.2 Hz, H18), 3.46 (3H, s, OMe), 3.30 (1H, dd, *J* = 6.9, 2.0 Hz, H17), 2.66-2.59 (1H, m, OH), 2.08 (1H, dqd, *J* = 7.2, 7.1, 1.9 Hz, H16), 1.68 (3H, s, C14-Me), 1.22 (3H, d, *J* = 6.1 Hz, H19), 0.88 (3H, d, *J* = 7.1 Hz, C16-Me), 0.87 (9H, s, CMe_3), 0.07 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 146.7 (0, C14), 112.8 (2, C13), 85.4 (1, C17), 79.3 (1, C15), 68.9 (1, C18), 59.9 (3, OMe), 35.7 (1, C16), 26.0 (3C, 3, $\underline{C}Me_3$), 21.1 (3, C19), 18.1 (0, $\underline{C}Me_3$), 17.5 (3, C14-$\underline{Me}$), 11.3 (3, C16-$\underline{Me}$), –3.9 (3, $SiMe_2$), –4.7 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 303 (100%), 285 (13), 253 (8), 132 (7), 96 (28).

Anal. Calcd. for $C_{16}H_{34}O_3Si$ (M = 302): C, 63.52; H, 11.33. Found C, 63.48; H, 11.26.

(3*R*,4*R*,5*R*,6*S*)-2,4-Dimethyl-5-methoxyhept-1-en-3,6-diol (365):



363
$C_{16}H_{34}O_3Si$ (302.52)

365
$C_{10}H_{20}O_3$ (188.26)

A stirred solution of the silyl ether **363** (100 mg, 0.33 mmol) in anhydrous THF (5 mL) at rt under $N_{2(g)}$ was treated with tetra-*n*-butylammonium fluoride trihydrate (TBAF•$3H_2O$, 520 mg, 1.65 mmol). After stirring for 15 min the mixture was partitioned between EtOAc (20 mL) and H_2O (20 mL) and the layers shaken and then separated. The aqueous phase was then

extracted (3x10 mL EtOAc) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 50% EtOAc in hexanes) to yield the diol **365** (45 mg, 0.24 mmol, 72%) as a white solid: mp 128-130°C (EtOAc). Slow recrystallisation from EtOAc enabled the growth of fine needles appropriate for single X-ray diffraction studies (see the appendix for crystal structure details).

$[\alpha]_D = +3$ ($c = 0.34$, $CHCl_3$).

IR (KBr): ν = 3328 (m), 2926 (m), 1460 (m), 1375 (w), 1310 (w), 1133 (w), 1097 (s), 1051 (w), 1018 (s), 961 (w), 902 (m), 881 (w), 733 (m) cm^{-1}.

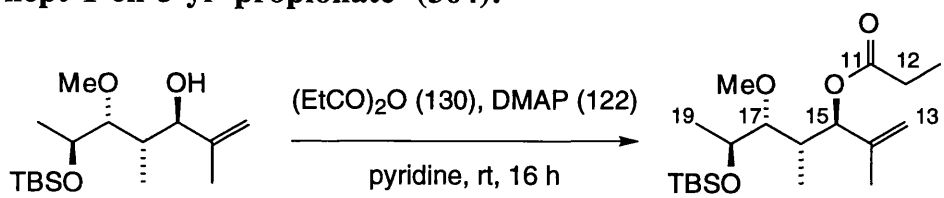
^1H NMR (360 MHz, $CDCl_3$): δ = 5.07 (1H, m, $H13_E$), 4.94 (1H, m, $H13_Z$), 4.03 (1H, quintet, J = 6.2 Hz, H18), 3.99 (1H, d, J = 7.0 Hz, H15), 3.47 (3H, s, OMe), 3.36 (1H, dd, J = 5.8, 2.1 Hz, H17), 2.67-2.60 (1H, m, OH), 2.05 (1H, quintet of d, J = 7.1, 2.0 Hz, H16), 1.98-1.90 (1H, m, OH), 1.70 (3H, s, C14-Me), 1.25 (3H, d, J = 6.4 Hz, H19), 0.98 (3H, d, J = 7.1 Hz, C16-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 146.6 (0, C14), 113.0 (2, C13), 84.0 (1, C17), 79.4 (1, C15), 67.2 (1, C18), 58.9 (3, OMe), 35.5 (1, C16), 19.6 (3, C19), 17.7 (3, C14-Me), 11.9 (3, C16-Me) ppm.

LRMS (CI+ mode, NH_3): m/z = 206 (59%), 188 (21), 171 (100), 139 (18).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 189.1490. $C_{10}H_{21}O_3$ requires 189.1491.

(3*R*,4*R*,5*R*,6*S*)-2,4-Dimethyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy-5-methoxyhept-1-en-3-yl propionate (364):



363
$C_{16}H_{34}O_3Si$ (302.52)

364
$C_{19}H_{38}O_4Si$ (358.59)

A stirred solution of the alcohol **363** (4.0 g, 13.2 mmol) in anhydrous pyridine (30 mL) at rt under $N_{2(g)}$ was treated with propionic anhydride (3.4 mL, ρ = 1.015, 3.45 g, 26.5 mmol) followed by 4-(dimethylamino)pyridine (30 mg, 0.25 mmol) and then stirred for 16 h. The mixture was then diluted with Et_2O (250 mL) and the organic phase washed successively with

2M $HCl_{(aq)}$ (5x50 mL) and sat. $NaHCO_{3(aq)}$ (2x50 mL). The ethereal liquor was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the ester **364** (4.60 g, 12.8 mmol, 97%) as a clear oil which later crystallised upon standing: mp 46-47°C; bp (kugelrohr oven) 160°C, 0.8 mmHg.

$[\alpha]_D = -5.1$ (c = 0.60, $CHCl_3$).

IR (film): ν = 2932 (s), 2858 (m), 1740 (s), 1463 (m), 1361 (m), 1257 (m), 1185 (s), 1108 (s), 1003 (m), 958 (m), 926 (m), 835 (s), 775 (m) cm^{-1}.

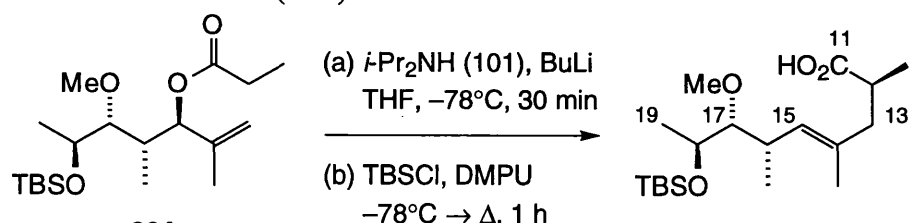
^1H NMR (360 MHz, $CDCl_3$): δ = 5.11 (1H, d, J = 10.0 Hz, H15), 5.04 (1H, m, $H13_E$), 4.96 (1H, quintet, J = 1.7 Hz, $H13_Z$), 3.74 (1H, dq, J = 7.7, 6.0 Hz, H18), 3.38 (3H, s, OMe), 2.99 (1H, dd, J = 7.8, 1.5 Hz, H17), 2.36 (2H, qd, J = 7.7, 1.4 Hz, H12), 2.23 (1H, dqd, J = 10.0, 7.1, 1.5 Hz, H16), 1.66 (3H, br s, C14-Me), 1.22 (3H, d, J = 6.1 Hz, H19), 1.16 (3H, t, J = 7.5 Hz, C12-Me), 0.89 (9H, s, CMe_3), 0.75 (3H, d, J = 7.1 Hz, C16-Me), 0.07 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 173.8 (0, C11), 142.1 (0, C14), 115.8 (2, C13), 84.7 (1, C17), 79.5 (1, C15), 69.0 (1, C18), 60.9 (3, OMe), 34.9 (1, C16), 28.2 (2, C12), 25.9 (3C, 3, $C\underline{Me}_3$), 21.2 (3, C19), 18.1 (0, $\underline{C}Me_3$), 17.3 (3, C14-$\underline{Me}$), 9.5 (3, C16-Me), 9.4 (3, C12-$\underline{Me}$), –3.7 (3, $SiMe_2$), –4.8 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, NH_3): m/z = 376 (100%), 359 (15), 285 (70), 277 (25), 253 (15) 188 (10), 132 (10), 96 (30).

Anal. Calcd. for $C_{19}H_{38}O_4Si$ (M = 358): C, 63.64; H, 10.68. Found C, 63.72; H, 10.61.

(*E*,2*S*,6*S*,7*R*,8*S*)-8-[(1,1-Dimethylethyl)dimethylsilyl]oxy-7-methoxy-2,4-6-trimethylnon-4-enoic acid (333):



364
$C_{19}H_{38}O_4Si$ (358.59)

333
$C_{19}H_{38}O_4Si$ (358.59)

To a stirred solution of di*iso*propylamine (0.65 mL, ρ = 0.722, 0.47 g, 4.6 mmol) in anhydrous THF (10 mL) at 0°C under $N_{2(g)}$ was added dropwise *n*-butyl lithium (1.85 mL,

2.27 M in hexanes, 4.2 mmol). The resulting solution of lithium di*iso*propylamide was stirred for 5 min and then further cooled to –78°C. A solution of the ester **364** (1.0 g, 2.79 mmol) in anhydrous THF (5 mL) was then added continously down the cold flask side-wall over 5 min whilst the base solution was vigorously stirred. The clear reaction mixture was stirred for 30 min and then treated dropwise with *tert*-butyldimethylsilyl chloride (TBSCl, 3.0 mL, 1.03 M in hexanes, 3.1 mmol) followed by anhydrous dimethylpropylene urea (DMPU, 4 mL). After stirring for 5 min the solution was allowed to warm rt (cold bath removed) and then heated at reflux for 1 h. The colourless mixture was then allowed to cool to rt, treated with 2M $HCl_{(aq)}$ (10 mL) and stirred vigorously for 30 min. The layers were then separated and the aqueous phase extracted (5x10 mL CH_2Cl_2). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 25-50% Et_2O in hexanes) to yield the acid **333** [835 mg, 82 wt.% (contaminated by TBSOH), 1.91 mmol, 68%, dr (C12) ≈ 6:1 determined by integration of OMe resonances in the ^1H NMR (360 MHz, $CDCl_3$): δ_{OMe} = 3.52 (major), δ_{OMe} = 3.50 (minor)] as a clear oil. An analytical sample of the acid free from TBSOH was obtained by repeated chromatography, diastereoisomers were not separated.

$[\alpha]_D$ = –0.8 (*c* = 0.51, $CHCl_3$).

IR (film): ν = 2957 (s), 2930 (s), 2857 (s), 1709 (s), 1462 (m), 1382 (w), 1255 (m), 1104 (m), 1048 (w), 932 (w), 835 (m), 775 (m) cm^{-1}.

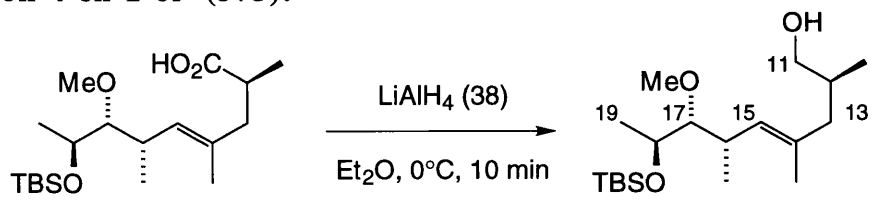
^1H NMR (360 MHz, $CDCl_3$): δ = 5.06 (1H, dm, *J* = 9.2 Hz, H15), 3.83 (1H, qd, *J* = 6.2, 3.5 Hz, H18), 3.52 (3H, s, OMe), 2.86 (1H, dd, *J* = 7.8, 3.6 Hz, H17), 2.70-2.59 (1H, m, H12), 2.50-2.38 (2H, m, H16, $H13_B$), 2.05 (1H, dd, *J* = 13.5, 8.4 Hz, $H13_A$), 1.60 (3H, d, *J* = 1.2 Hz, C14-Me), 1.12 (3H, d, *J* = 6.9 Hz, C12-Me), 1.09 (3H, d, *J* = 6.2 Hz, H19), 0.95 (3H, d, *J* = 6.6 Hz, C16-Me), 0.89 (9H, s, CMe_3), 0.04 (6H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 182.8 (0, C11), 131.2 (1, C15), 131.2 (0, C14), 90.3 (1, C17), 70.4 (1, C18), 61.5 (3, OMe), 44.0 (2, C13), 37.9 (1, C12), 35.2 (1, C16), 26.0 (3C, 3, $C\underline{Me}_3$), 18.2 (0, $\underline{C}Me_3$), 17.8 (3, C19), 17.0 (3, C16-<u>Me</u>), 16.4 (3, C12-<u>Me</u>), 15.8 (3, C14-<u>Me</u>), –4.3 (3, $SiMe_2$), –4.7 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, NH_3): *m/z* = 375 (31%), 358 (34), 327 (9), 227 (100), 212 (18), 195 (15), 172 (10).

HRMS (EI+ mode): Found $M^{+\bullet}$, 358.2538. $C_{19}H_{38}O_4Si$ requires 358.2539.

(*E*,2*S*,6*S*,7*R*,8*S*)-8-[(1,1-Dimethylethyl)dimethylsilyl]oxy-7-methoxy-2,4,6-trimethylnon-4-en-1-ol (375):



333
$C_{19}H_{38}O_4Si$ (358.59)

375
$C_{19}H_{40}O_3Si$ (344.60)

A stirred suspension of lithium aluminium hydride (0.35 g, 9.2 mmol) in anhydrous Et_2O (15 mL) at 0°C under $N_{2(g)}$ was treated dropwise with a solution of the acid **333** (1.64 g, 82 wt.%, 3.76 mmol, dr (C12) ≈ 6:1) in anhydrous Et_2O (5 mL). A vigorous reaction ensued and after stirring for 10 min the reaction mixture was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (10 mL). The biphasic system was then filtered through a celite pad and the residue washed well (4x10 mL Et_2O). The layers of the combined washings and filtrate were then separated and the aqueous phase extracted (10 mL Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 30% Et_2O in hexanes) to yield the alcohol **375** (1.17 g, 3.40 mmol, 90%, dr (C12) ≈ 6:1) as a clear oil.

The two diastereoisomers (at C12) can be separated as follows: 1.0 g of **375** (dr (C12) ≥ 4:1) was loaded onto a silica column (Ø 7 cm, depth 12 cm) and eluted with 15% Et_2O in hexanes taking a pre-fraction of 2.2 L followed by 20 mL fractions to yield in order of elution, 303 mg of mixed material (dr ≈ 3:1) followed by 590 mg of pure material (dr ≥ 95:5).

(*E*,2*S*,6*S*,7*R*,8*S*)-8-[(1,1-Dimethylethyl)dimethylsilyl]oxy-7-methoxy-2,4,6-trimethylnon-4-en-1-ol (**375**).

$[\alpha]_D$ = +1.5 (*c* = 0.62, $CHCl_3$).

IR (film): ν = 3365 (br m), 2956 (s), 2929 (s), 2857 (s), 1461 (m), 1382 (w), 1256 (m), 1103 (m), 1047 (m), 1005 (w), 932 (w), 836 (m), 775 (m), 735 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.00 (1H, dm, *J* = 10.0 Hz, H15), 3.85 (1H, qd, *J* = 6.2, 3.4 Hz, H18), 3.52 (3H, s, OMe), 3.48 (1H, dd, *J* = 10.5, 5.8 Hz, $H11_A$), 3.41 (1H, dd, *J* = 10.6, 5.9 Hz, $H11_B$), 2.86 (1H, dd, *J* = 7.7, 3.4 Hz, H17), 2.42 (1H, ddq, *J* = 9.9, 8.0, 6.7 Hz, H16), 2.11 (1H, dd, *J* = 12.2, 5.1 Hz, $H13_A$), 1.88-1.79 (1H, m, H12), 1.79-1.70 (2H, m, $H13_B$, OH), 1.58 (3H, d, *J* = 1.3 Hz, C14-Me), 1.08 (3H, d, *J* = 6.2 Hz, H19), 0.95

(3H, d, J = 6.6 Hz, C16-Me), 0.87 (9H, s, CMe_3), 0.84 (3H, d, J = 6.5 Hz, C12-Me), 0.03 (6H, s, $SiMe_2$) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 133.0 (0, C14), 130.0 (1, C15), 90.4 (1, C17), 70.4 (1, C18), 68.6 (2, C11), 61.5 (3, OMe), 44.5 (2, C13), 35.3 (1, C16), 33.8 (1, C12), 26.0 (3C, 3, CMe_3), 18.1 (0, CMe_3), 17.6 (3, C19), 17.2 (3, C16-Me), 16.7 (3, C12-Me), 16.0 (3, C14-Me), –4.3 (3, $SiMe_2$), –4.7 (3, $SiMe_2$) ppm.

LRMS (CI+ mode, *iso*butane): *m/z* = 345 (100%), 313 (45), 213 (82), 181 (34).

Anal. Calcd. for $C_{19}H_{40}O_3Si$ (M = 344): C, 66.22; H, 11.70. Found C, 66.07; H, 11.61.

(*E*,2*R*,6*S*,7*R*,8*S*)-8-[(1,1-Dimethylethyl)dimethylsilyl]oxy-7-methoxy-2,4,6-trimethylnon-4-en-1-ol (12-epi-**375**):

$[\alpha]_D$ = +6.9 (*c* = 0.58, $CHCl_3$).

IR (film): ν = 3373 (br m), 2955 (s), 2928 (s), 2857 (s), 1462 (m), 1382 (m), 1256 (m), 1102 (s), 1047 (s), 1005 (w), 932 (m), 835 (m), 809 (w), 775 (m) cm^{-1}.

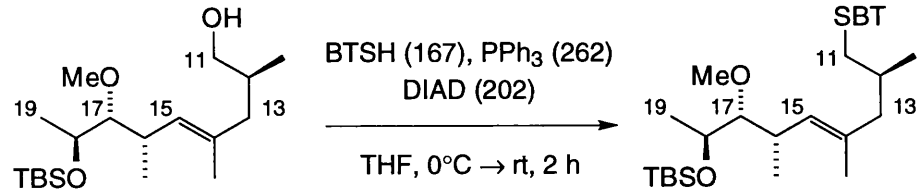
^1H NMR (360 MHz, $CDCl_3$): δ = 5.02 (1H, d, J = 9.9 Hz), 3.84 (1H, qd, J = 6.0, 3.5 Hz), 3.53 (3H, s), 3.50 (1H, dd, J = 10.5, 5.6 Hz), 3.41 (1H, dd, J = 10.5, 6.0 Hz), 2.87 (1H, dd, J = 7.7, 3.5 Hz), 2.47 (1H, ddq, J = 9.6, 7.3, 7.3 Hz), 2.10 (1H, dd, J = 12.1, 5.1 Hz), 1.90-1.74 (2H, m), 1.60 (3H, m), 1.51 (1H, br s), 1.11 (3H, d, J = 6.2 Hz), 0.97 (3H, d, J = 6.6 Hz), 0.92 (9H, s), 0.90-0.87 (3H, m), 0.05 (6H, s) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 132.8 (0), 130.1 (1), 90.4 (1), 70.3 (1), 68.5 (2), 61.4 (3), 44.3 (2), 35.2 (1), 33.9 (1), 26.0 (3C, 3), 18.2 (0), 17.9 (3), 17.1 (3), 16.7 (3), 16.3 (3), –4.2 (3), –4.7 (3) ppm.

LRMS (EI+ mode): *m/z* = 344 (3%), 287 (4), 255 (12), 229 (3), 203 (100), 181 (34), 159 (40), 123 (39), 89 (43), 73 (96), 69 (41).

HRMS (EI+ mode): Found $M^{+\bullet}$, 344.2744. $C_{19}H_{40}O_3Si$ requires 344.2747.

2-{[(*E*,2*S*,6*S*,7*R*,8*S*)-8-[(1,1-Dimethylethyl)dimethylsilyl]oxy-7-methoxy-2,4,6-trimethylnon-4-enyl]thio}benzothiazole (376):



375
$C_{19}H_{40}O_3Si$ (344.60)

376
$C_{26}H_{43}NO_2S_2Si$ (493.84)

To a stirred solution of the alcohol **375** (1.47 g, 4.27 mmol) in anhydrous THF (25 mL) at rt under $N_{2(g)}$ was added 2-mercaptobenzothiazole (BTSH, 0.86 g, 5.15 mmol) and triphenylphosphine (1.34 g, 5.11 mmol). The resulting solution was cooled to 0°C and di*iso*propyl azodicarboxylate (DIAD, 1.10 mL, ρ = 1.027, 1.13 g, 5.59 mmol) added dropwise. The cooling bath was then removed and the mixture allowed to stir for 2 h. After this time the solvent was removed *in vacuo* and the residue further purified *via* column chromatography (eluting with 3% EtOAc in hexanes) to yield the sulfide **376** (2.08 g, 4.21 mmol, 99%) as a clear oil.

$[\alpha]_D$ = +0.3 (*c* = 0.65, $CHCl_3$).

IR (film): ν = 2956 (s), 2928 (s), 2894 (s), 2856 (s), 1461 (s), 1428 (s), 1380 (w), 1255 (m), 1103 (m), 1048 (w), 995 (m), 932 (w), 836 (m), 775 (m), 755 (m), 726 (w), 670 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.86 (1H, dm, *J* = 8.1 Hz, BT), 7.75 (1H, dm, *J* = 8.0 Hz, BT), 7.41 (1H, ddd, *J* = 8.5, 7.3, 1.3 Hz, BT), 7.29 (1H, ddd, *J* = 8.1, 7.4, 1.2 Hz, BT), 5.06 (1H, dm, *J* = 9.9 Hz, H15), 3.87 (1H, qd, *J* = 6.2, 3.4 Hz, H18), 3.54 (3H, s, OMe), 3.45 (1H, dd, *J* = 12.9, 5.3 Hz, $H11_A$), 3.12 (1H, dd, *J* = 12.9, 7.5 Hz, $H11_B$), 2.88 (1H, dd, *J* = 7.9, 3.4 Hz, H17), 2.47 (1H, ddq, *J* = 9.9, 7.8, 6.7 Hz, H16), 2.27-2.10 (2H, m, H12, $H13_A$), 1.93 (1H, dd, *J* = 12.8, 8.0 Hz, $H13_B$), 1.62 (3H, d, *J* = 1.2 Hz, C14-Me), 1.11 (3H, d, *J* = 6.2 Hz, H19), 1.03 (3H, d, *J* = 6.5 Hz, C12-Me), 1.00 (3H, d, *J* = 6.6 Hz, C16-Me), 0.90 (9H, s, CMe_3), 0.05 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$) ppm.

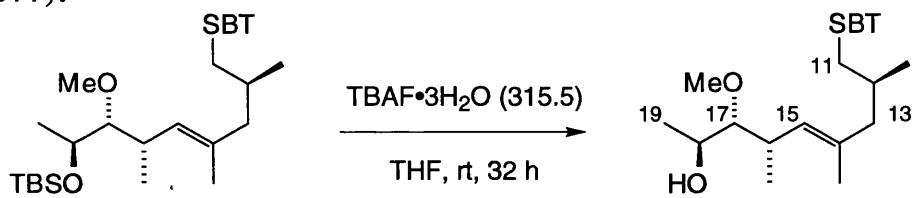
^{13}C NMR (90 MHz, $CDCl_3$): δ = 167.6 (0, BT), 153.4 (0, BT), 135.3 (0, BT), 132.2 (0, C14), 130.7 (1, C15), 126.1 (1, BT), 124.2 (1, BT), 121.5 (1, BT), 121.0 (1, BT), 90.3 (1, C17), 70.4 (1, C18), 61.5 (3, OMe), 47.2 (2, C13), 40.4 (2, C11), 35.3 (1, C16), 31.5 (1, C12), 26.0 (3C, 3, CMe_3), 19.4 (3, C12-Me), 18.2 (0, CMe_3), 17.7 (3, C19), 17.2 (3, C16-Me), 16.1 (3, C14-Me), –4.3 (3, $SiMe_2$), –4.7 (3, $SiMe_2$) ppm.

LRMS (EI+ mode): *m/z* = 493 (10%), 446 (6), 436 (4), 330 (47), 203 (97), 159 (33), 123 (63), 73 (100).

HRMS (EI+ mode): Found $M^{+\bullet}$, 493.2508. $C_{26}H_{43}NO_2S_2Si$ requires 493.2505.

Anal. Calcd. for $C_{26}H_{43}NO_2S_2Si$ (M = 493): C, 63.23; H, 8.78; N, 2.84. Found C, 63.36; H, 8.84; N, 2.82.

(*E*,2*S*,6*S*,7*R*,8*S*)-1-(Benzothiazol-2-ylthio)-7-methoxy-2,4,6-trimethylnon-4-en-8-ol (377):



376
$C_{26}H_{43}NO_2S_2Si$ (493.84)

377
$C_{20}H_{29}NO_2S_2$ (379.58)

A stirred solution of the silyl ether **376** (631 mg, 1.28 mmol) in anhydrous THF (15 mL) at rt under $N_{2(g)}$ was treated with tetra-*n*-butylammonium fluoride trihydrate (TBAF•3H_2O, 2.0 g, 6.3 mmol) and the resulting clear mixture stirred for 28 h. After this time TLC analysis indicated incomplete consumption of the silyl ether; additional TBAF•3H_2O (0.5 g, 1.6 mmol) was then added and the reaction stirred for a further 4 h. The solution was then partitioned between Et_2O (30 mL) and H_2O (30 mL) and the layers shaken well and then separated. The aqueous phase was extracted (3x15 mL Et_2O) and the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 30% EtOAc in hexanes) to yield the alcohol **377** (475 mg, 1.25 mmol, 98%) as a clear oil.

$[\alpha]_D$ = –22.1 (*c* = 1.00, $CHCl_3$).

IR (film): ν = 3441 (br s), 2979 (s), 2829 (s), 1458 (s), 1427 (s), 1239 (m), 1126 (m), 1096 (s), 1033 (w), 1048 (w), 994 (s), 904 (m), 756 (s), 727 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.85 (1H, dm, *J* = 8.1 Hz, BT), 7.75 (1H, dm, *J* = 8.0 Hz, BT), 7.40 (1H, ddd, *J* = 8.2, 7.3, 1.3 Hz, BT), 7.28 (1H, ddd, *J* = 8.0, 7.4, 1.2 Hz, BT), 5.07 (1H, dm, *J* = 9.9 Hz, H15), 3.84 (1H, m, H18), 3.53 (3H, s, OMe), 3.44 (1H, dd, *J* = 12.9, 5.1 Hz, $H11_A$), 3.09 (1H, dd, *J* = 12.9, 7.4 Hz, $H11_B$), 2.96 (1H, dd, *J* = 8.2, 3.8 Hz, H17), 2.51 (1H, ddq, *J* = 9.8, 8.2, 6.7 Hz, H16), 2.23-2.09 (2H, m, H12, $H13_A$),

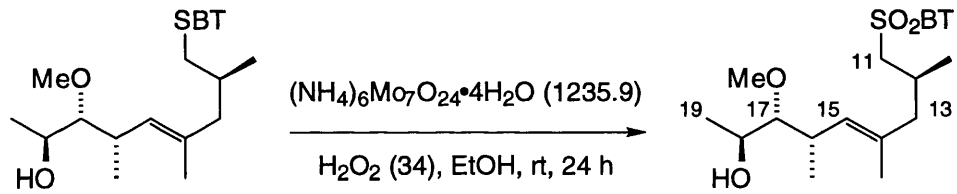
1.98-1.89 (2H, m, $H13_B$, OH), 1.63 (3H, d, J = 1.3 Hz, C14-Me), 1.14 (3H, d, J = 6.4 Hz, H19), 1.05 (3H, d, J = 6.7 Hz, C12-Me), 1.01 (3H, d, J = 6.5 Hz, C16-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 167.6 (0, BT), 153.4 (0, BT), 135.3 (0, BT), 132.6 (0, C14), 130.1 (1, C15), 126.1 (1, BT), 124.2 (1, BT), 121.5 (1, BT), 121.0 (1, BT), 89.6 (1, C17), 69.4 (1, C18), 61.6 (3, OMe), 47.0 (2, C13), 40.3 (2, C11), 35.7 (1, C16), 31.5 (1, C12), 19.4 (3, C12-Me), 17.7 (3, C19), 17.5 (3, C16-Me), 16.2 (3, C14-Me) ppm.

LRMS (EI+ mode): m/z = 379 (3%), 332 (14), 290 (18), 248 (7), 223 (6), 208 (10), 167 (73), 123 (100%), 89 (41), 81 (37).

Anal. Calcd. for $C_{20}H_{29}NO_2S_2$ (M = 379): C, 63.28; H, 7.70; N, 3.69. Found C, 63.13; H, 7.62; N, 3.61.

(*E*,2*S*,6*S*,7*R*,8*S*)-1-(Benzothiazol-2-ylsulfonyl)-7-methoxy-2,4,6-trimethylnon-4-en-8-ol (378):



377
$C_{20}H_{29}NO_2S_2$ (379.58)

378
$C_{20}H_{29}NO_4S_2$ (411.58)

To a stirred solution of the sulfide **377** (870 mg, 2.30 mmol) in EtOH (20 mL) at rt was added dropwise a yellow solution of ammonium heptamolybdate tetrahydrate (280 mg, 0.23 mmol) in aqueous hydrogen peroxide (2.6 g, 30 wt.%, 22.9 mmol). The resultant mixture was stirred vigorously for 24 h and then partitioned between Et_2O (30 mL) and H_2O (20 mL). The layers were shaken and then separated and the aqueous phase extracted (3x10 mL Et_2O). The combined organic extracts were washed with H_2O (2x20 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 40% EtOAc in hexanes) to yield the sulfone **378** (835 mg, 2.03 mmol, 88%) as a clear oil.

$[\alpha]_D$ = –24.0 (c = 1.09, $CHCl_3$).

IR (film): ν = 3447 (br s), 2962 (s), 2929 (s), 1472 (m), 1458 (m), 1318 (m), 1146 (m), 1097 (m), 1026 (w), 906 (w), 854 (w), 763 (m), 731 (m), 632 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.19 (1H, dm, J = 7.8 Hz, BT), 8.01 (1H, dm, J = 8.1 Hz, BT), 7.63 (1H, ddd, J = 8.1, 7.2, 1.4 Hz, BT), 7.58 (1H, ddd, J = 7.9, 7.2, 1.4 Hz, BT), 5.02 (1H, dm, J = 9.9 Hz, H15), 3.79 (1H, qd, J = 6.4, 3.8 Hz, H18), 3.58 (1H, dd, J = 14.4, 3.7 Hz, $H11_A$), 3.50 (3H, s, OMe), 3.23 (1H, dd, J = 14.4, 8.7 Hz, $H11_B$), 2.92 (1H, dd, J = 8.0, 3.8 Hz, H17), 2.50-2.39 (2H, m, H16, H12), 2.07 (1H, ddd, J = 13.4, 7.9, 1.1 Hz, $H13_A$), 1.98 (1H, dd, J = 13.6, 6.8 Hz, $H13_B$), 2.0-1.80 (1H, br, OH), 1.49 (3H, d, J = 1.3 Hz, C14-Me), 1.10 (6H, d, J = 6.4 Hz, C12-Me, H19), 1.01 (3H, d, J = 6.7 Hz, C16-Me) ppm.

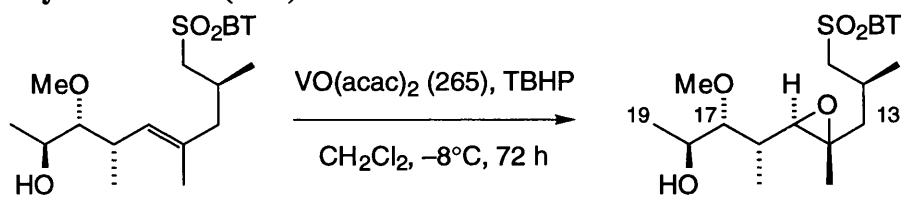
^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.7 (0, BT), 152.8 (0, BT), 136.8 (0, BT), 131.6 (0, C14), 131.3 (1, C15), 128.2 (1, BT), 127.8 (1, BT), 125.5 (1, BT), 122.5 (1, BT), 89.4 (1, C17), 69.2 (1, C18), 61.4 (3, OMe), 60.0 (2, C11), 47.4 (2, C13), 35.5 (1, C16), 26.6 (1, C12), 20.2 (3, C12-Me), 17.6 (3, C19), 17.5 (3, C16-Me), 15.9 (3, C14-Me) ppm.

LRMS (CI+ mode, *iso*butane): m/z = 412 (100%), 380 (26), 362 (42), 322 (54).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 412.1614. $C_{20}H_{30}NO_4S_2$ requires 412.1616.

Anal. Calcd. for $C_{20}H_{29}NO_4S_2$ (M = 411): C, 58.36; H, 7.10; N, 3.40. Found C, 58.17; H, 7.15; N, 3.42.

(2*S*,4*R*,5*R*,6*S*,7*R*,8*S*)-1-(Benzothiazol-2-ylsulfonyl)-4,5-epoxy-7-methoxy-2,4,6-trimethylnon-8-ol (379):



378
$C_{20}H_{29}NO_4S_2$ (411.58)

379
$C_{20}H_{29}NO_4S_2$ (427.58)

A stirred solution of the hydroxy olefin **378** (519 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (10 mL) at –8°C under $N_{2(g)}$ was treated with vandyl bis(acetylacetonate) (3.4 mg, 13 μmol) followed by the slow addition of a solution of *tert*-butyl hydroperoxide (TBHP, 0.71 mL, 5.32 M in *iso*octane, 3.8 mmol) in anhydrous CH_2Cl_2 (9 mL) *via* syringe pump over 48 h. After the complete addition of the stoichiometric oxidant the colourless solution was allowed to stir for a further 24 h at –8°C. After this time the mixture was diluted with Et_2O (20 mL) and H_2O (20 mL) and the layers shaken well and then separated. The aqueous phase was then extracted (2x10 mL) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography

(eluting with 35-60% EtOAc in hexanes) to afford in order of elution: the tetrahydrofuran by-product **380** (25 mg, 0.06 mmol, 5%), recovered starting material **378** (136 mg, 0.33 mmol, 26%) and the epoxide **379** (373 mg, 0.87 mmol, 69%) all as clear oils. ^{1}H and ^{13}C NMR analysis revealed the latter compound to be a single diastereoisomer.

(2*S*,4*R*,5*R*,6*S*,7*R*,8*S*)-1-(Benzothiazol-2-ylsulfonyl)-4,5-epoxy-7-methoxy-2,4,6-trimethyl-non-8-ol (**379**).

$[\alpha]_D = -4.0$ (c = 1.98, $CHCl_3$).

IR (film): ν = 3452 (br s), 2966 (s), 2932 (s), 1471 (m), 1318 (s), 1148 (s), 1097 (s), 910 (w), 763 (m), 730 (w) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.18 (1H, dm, J = 7.6 Hz, BT), 8.01 (1H, dm, J = 7.5 Hz, BT), 7.66-7.56 (2H, m, BT), 3.94 (1H, quintet, J = 5.8 Hz, H18), 3.61 (1H, dd, J = 14.2, 4.7 Hz, H11$_A$), 3.48 (3H, s, OMe), 3.34 (1H, dd, J = 14.3, 7.9 Hz, H11$_B$), 3.06 (1H, t, J = 5.0 Hz, H17), 2.61 (1H, d, J = 9.5 Hz, H15), 2.62-2.50 (1H, m), 2.08-2.00 (1H, m), 1.80 (1H, dd, J = 14.2, 7.3 Hz, H13$_A$), 1.67-1.55 (1H, m), 1.59 (1H, dd, J = 14.2, 7.4 Hz, H13$_B$), 1.27 (3H, s, C14-Me), 1.22 (3H, d, J = 6.8 Hz, H19), 1.20 (3H, d, J = 6.5 Hz, C12-Me), 1.01 (3H, d, J = 6.9 Hz, C16-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.6 (0, BT), 152.7 (0, BT), 136.8 (0, BT), 128.2 (1, BT), 127.9 (1, BT), 125.5 (1, BT), 122.5 (1, BT), 86.6 (1, C17), 68.1 (1, C18), 64.9 (1, C15), 60.5 (3, OMe), 60.3 (2, C11), 60.2 (0, C14), 45.4 (2, C13), 34.7 (1, C16), 26.1 (1, C12), 20.9 (3, C12-Me), 19.1 (3, C19), 16.4 (3, C14-Me), 11.8 (3, C16-Me) ppm.

LRMS (CI+ mode, *iso*butane): m/z = 428 (11%), 410 (15), 378 (100), 322 (14), 298 (12), 213 (14), 136 (27).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 428.1561. $C_{20}H_{30}NO_5S_2$ requires 428.1565.

Anal. Calcd. for $C_{20}H_{29}NO_5S_2$ (M = 427): C, 56.18; H, 6.84; N, 3.28. Found C, 56.19; H, 6.84; N, 3.23.

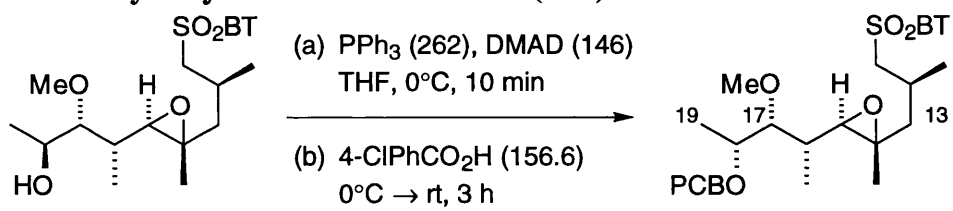
(2*S*,3*S*,4*R*,5*S*)-3,5-Dimethyl-2-[(1*R*,3*S*)-4-(benzothiazol-2-ylsulfonyl)-1,3-dimethyl-1-hydroxybutyl]-4-methoxyoxolane (**380**).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.22 (1H, dm, J = 7.5 Hz), 8.03 (1H, dm, J = 7.9 Hz), 7.68-7.55 (2H, m), 3.80 (1H, qd, J = 6.7, 2.6 Hz), 3.57 (1H, dd, J = 14.3, 6.7 Hz), 3.57

(1H, d, J = 4.6 Hz), 3.48 (1H, dd, J = 14.3, 6.0 Hz), 3.29 (3H, s), 3.08 (1H, d, J = 2.5 Hz), 2.73-2.60 (1H, m), 2.20-2.10 (2H, m), 1.77 (1H, dd, J = 14.1, 3.4 Hz), 1.65 (1H, dd, J = 14.2, 8.8 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.28 (3H, d, J = 6.8 Hz), 1.27 (3H, s), 1.03 (3H, d, J = 7.4 Hz) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.9 (0), 152.8 (0), 136.8 (0), 128.2 (1), 127.8 (1), 125.6 (1), 122.5 (1), 95.1 (1), 85.6 (1), 79.8 (1), 73.3 (0), 62.1 (2), 56.9 (3), 42.9 (2), 40.2 (1), 26.2 (3), 25.3 (1), 22.3 (3), 20.7 (3), 15.0 (3) ppm.

(1*R*,2*R*,3*R*,4*R*,5*R*,7*S*)-8-(Benzothiazol-2-ylsulfonyl)-4,5-epoxy-2-methoxy-1,3,5,7-tetramethyloctyl 4-chlorobenzoate (332):



379 **332**

$C_{20}H_{29}NO_4S_2$ (427.58) PCB = 4-chlorobenzoyl $C_{27}H_{32}ClNO_6S_2$ (566.13)

A solution of triphenylphosphine (393 mg, 1.50 mmol) in anhydrous THF (3 mL) at 0°C under $N_{2(g)}$ was treated with neat dimethyl azodicarboxylate[150] (DMAD, 170 μL, ρ = 1.22, 207 mg, 1.42 mmol) and the resultant colourless suspension stirred for 5 min. A solution of the alcohol **379** (304 mg, 0.71 mmol) in anhydrous THF (3 mL) was then added dropwise and the mixture stirred for a further 5 min. One third of a solution of 4-chlorobenzoic acid (138 mg, 0.88 mmol) in anhydrous THF (1.8 mL) was then added dropwise and the cooling bath removed. After 1 h a further one third of the acid solution was added, followed by the remainder after a subsequent hour. The reaction was then stirred for a final 1 h period after complete addition of the acid component and then worked-up as follows: the mixture was diluted with EtOAc (20 mL) and washed successively with sat. $NaHCO_{3(aq)}$ (15 ml), H_2O (4x10 mL) and brine (10 mL). The resulting organic phase was dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% EtOAc in hexanes) to afford the benzoate **332** (297 mg, 0.52 mmol, 74%) as a white foam.

$[\alpha]_D$ = –17.3 (c = 1.60, $CHCl_3$).

IR (film): ν = 2964 (s), 2933 (s), 1712 (s), 1594 (m), 1472 (m), 1459 (m), 1321 (s), 1273 (s), 1148 (s), 1090 (s), 1015 (m), 910 (w), 852 (w), 760 (m), 730 (m), 632 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.19 (1H, dm, J = 7.2 Hz, BT), 8.02 (1H, dm, J = 7.6 Hz, BT), 7.99 (2H, d, J = 8.7 Hz, Ar), 7.65 (1H, ddd, J = 7.3, 7.3, 1.4 Hz, BT), 7.60 (1H, ddd, J = 7.3, 7.3, 1.4 Hz, BT), 7.40 (2H, d, J = 8.7 Hz, Ar), 5.29 (1H, quintet, J = 6.6 Hz, H18), 3.61 (1H, dd, J = 14.2, 4.7 Hz, $H11_A$), 3.51 (3H, s, OMe), 3.37 (1H, dd, J = 6.8, 4.2 Hz, H17), 3.34 (1H, dd, J = 14.2, 7.9 Hz, $H11_B$), 2.65 (1H, d, J = 9.3 Hz, H15), 2.64-2.51 (1H, m, H16), 1.80 (1H, dd, J = 14.1, 7.3 Hz, $H13_A$), 1.62 (1H, dd, J = 14.1, 7.5 Hz, $H13_B$), 1.63-1.52 (1H, m, H12), 1.30 (3H, d, J = 6.5 Hz, H19), 1.27 (3H, s, C14-Me), 1.24 (3H, d, J = 6.7 Hz, C12-Me), 1.02 (3H, d, J = 6.9 Hz, C16-Me) ppm.

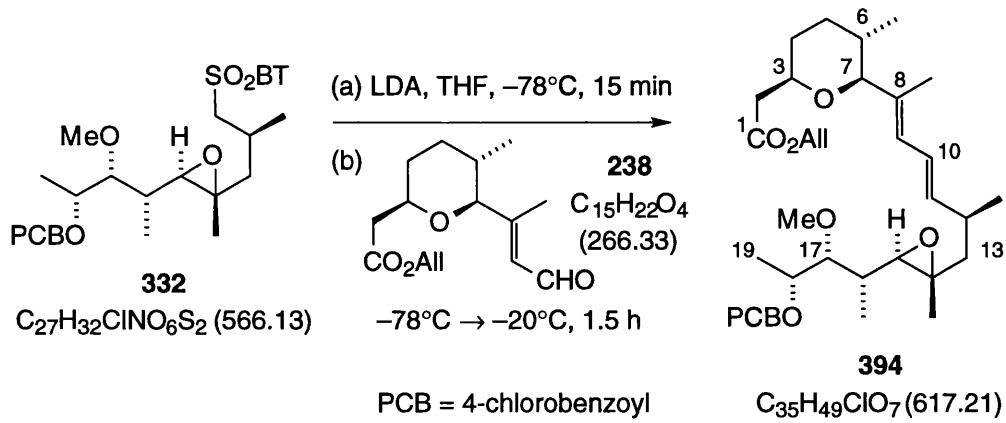
^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.6 (0, BT), 165.2 (0, ArC=O), 152.7 (0, BT), 139.4 (0, Ar), 136.8 (0, BT), 131.1 (2C, 1, Ar), 129.2 (0, Ar), 128.8 (2C, 1, Ar), 128.3 (1, BT), 127.9 (1, BT), 125.5 (1, BT), 122.5 (1, BT), 84.5 (1, C17), 73.1 (1, C18), 64.6 (1, C15), 61.5 (3, OMe), 60.3 (2, C11), 59.9 (0, C14), 45.5 (2, C13), 35.0 (1, C16), 26.1 (1, C12), 20.9 (3, C12-Me), 16.8 (3, C19), 16.4 (3, C14-Me), 10.8 (3, C16-Me) ppm.

LRMS (CI+ mode, NH_3): m/z = 583 (8%), 548 (23), 378 (67), 213 (92), 136 (100).

HRMS (CI+ mode, *iso*butane): Found $(M+H)^+$, 566.1433. $C_{27}H_{33}ClNO_6S_2$ requires 566.1438.

–SECTION 6.4–

18*O*-(4-Chlorobenzoyl)herboxidiene allyl ester (394):



PCB = 4-chlorobenzoyl

To a stirred solution of the sulfone **332** (331 mg, 0.58 mmol) in anhydrous THF (6 mL) at –78°C under $N_{2(g)}$ was added dropwise a solution of freshly prepared lithium di*iso*propylamide (LDA, 1.3 mL, 0.41 M in THF, 0.53 mmol) and the resulting deep yellow solution stirred for 15 min. A solution of the enal **238** (131 mg, 0.49 mmol, prepared in 4 steps from **240** as previously described[46]) in anhydrous THF (2 mL) was then added dropwise. The colour of the reaction mixture lightened. The mixture was stirred for 30 min at –78°C and then allowed to warm slowly to –20°C over 1 h. The resulting colourless solution was then quenched by the

addition sat. $NH_4Cl_{(aq)}$ (2 mL) and allowed to warm to rt with vigorous stirring. After further dilution with EtOAc (15 mL) and H_2O (15 mL) the layers were well shaken and separated. The aqueous phase was then extracted (3x5 mL EtOAc) and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 15% EtOAc in hexanes) to yield the diene **394** (246 mg, *ca* 0.40 mmol, 81%) as a clear oil. ^1H NMR analysis indicated the presence of a small quantity of the associated 10*Z* isomer together with other minor impurities (<5%). Conversion to the methyl ester **303** as outlined below facilitated purification and enabled accurate measurement of the *E:Z* ratio for the olefination step as 91:9 in favour of the natural 10*E* geometry. Repeated chromatography (eluting with 20% Et_2O in hexanes) provided a good purity sample of **394** for characterisation purposes.

$[\alpha]_D = -25$ ($c = 0.4$, $CHCl_3$).

IR (film): $\nu = 2927$ (m), 1720 (s), 1594 (w), 1456 (w), 1191 (w), 1159 (w), 1091 (m), 1015 (w) cm^{-1}.

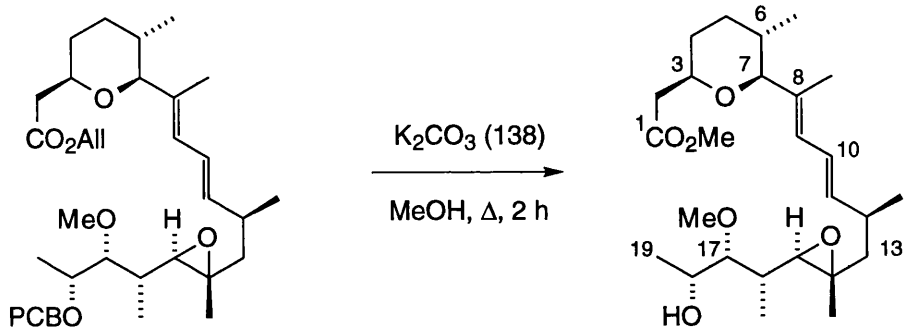
^1H NMR (360 MHz, $CDCl_3$): $\delta = 8.00$ (2H, d, $J = 8.7$ Hz, Ar), 7.41 (2H, d, $J = 8.7$ Hz, Ar), 6.22 (1H, dd, $J = 15.0$, 10.9 Hz, H10), 5.94-5.82 (1H, m, $CH_2C\underline{H}=CH_2$), 5.88 (1H, dm, $J = 10.4$ Hz, H9), 5.42 (1H, dd, $J = 15.0$, 8.9 Hz, H11), 5.30 (1H, dm, $J = 17.9$ Hz, $CH_2CH=C\underline{H}_ZH_E$), 5.27 (1H, quintet, $J = 6.9$ Hz, H18), 5.20 (1H, dm, $J = 10.5$ Hz, $CH_2CH=CH_Z\underline{H}_E$), 4.58 (2H, d, $J = 5.5$ Hz, $C\underline{H}_2CH=CH_2$), 3.83-3.74 (1H, m, H3), 3.52 (3H, s, OMe), 3.37 (1H, dd, $J = 6.9$, 3.9 Hz, H17), 3.31 (1H, d, $J = 9.9$ Hz, H7), 2.62 (1H, d, $J = 9.7$ Hz, H15), 2.61 (1H, dd, $J = 15.1$, 6.5 Hz, $H2_A$), 2.43 (1H, dd, $J = 15.2$, 6.5 Hz, $H2_B$), 2.47-2.34 (1H, m, H12), 1.91 (1H, dd, $J = 13.5$, 4.6 Hz, $H13_A$), 1.88-1.80 (1H, m, $H5_A$), 1.72-1.65 (1H, m, $H4_A$), 1.69 (3H, s, C8-Me), 1.57-1.46 (2H, m, H6, H16), 1.40-1.15 (3H, m, $H4_B$, $H5_B$, $H13_B$), 1.29 (3H, d, $J = 6.5$ Hz, H19), 1.24 (3H, s, C14-Me), 1.03 (3H, d, $J = 6.6$ Hz, C12-Me), 0.88 (3H, d, $J = 6.9$ Hz, C16-Me), 0.64 (3H, d, $J = 6.6$ Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 171.2$ (0, C1), 165.3 (0, Ar$\underline{C}$=O), 139.4 (1, C11), 139.4 (0, Ar), 135.3 (0, C8), 132.3 (1, $CH_2\underline{C}H=CH_2$), 131.2 (2C, 1, Ar), 129.3 (0, Ar), 128.8 (2C, 1, Ar), 128.3 (1, C9), 125.3 (1, C10), 118.0 (2, $CH=\underline{C}H_2$), 90.8 (1, C7), 84.7 (1, C17), 74.0 (1, C3), 73.3 (1, C18), 66.0 (1, C15), 65.1 (2, $\underline{C}H_2CH=CH_2$), 61.5 (3, OMe), 60.9 (0, C14), 47.1 (2, C13), 41.6 (2, C2), 35.4 (1, C12), 35.2 (1, C16), 32.4 (2, C5), 32.2 (1, C6), 31.8 (2, C4), 22.3 (3, C12-$\underline{Me}$), 17.7 (3, C6-$\underline{Me}$), 16.8 (3, C19), 16.8 (3, C14-$\underline{Me}$), 12.0 (3, C8-$\underline{Me}$), 10.8 (3, C16-$\underline{Me}$) ppm.

LRMS (EI+ mode): *m/z* = 616 (0.6%), 460 (2), 361 (4), 304 (16), 290 (24), 227 (46), 183 (15), 139 (100), 95 (41).

HRMS (EI+ mode): Found $M^{+\bullet}$, 616.3169. $C_{35}H_{49}ClO_7$ requires 616.3167.

Herboxidiene methyl ester (303):



394
$C_{35}H_{49}ClO_7$ (617.21)

PCB = 4-chlorobenzoyl

303
$C_{26}H_{44}O_6$ (452.62)

A stirred suspension of the benzoate **394** (223 mg, 0.36 mmol) and potassium carbonate (100 mg, 0.72 mmol) in anhydrous MeOH (5 mL) was heated at reflux for 2 h. After this time the mixture was allowed to cool to rt and subsequently diluted with EtOAc (20 mL) and H_2O (10 mL). The layers were then shaken and separated and the aqueous phase extracted (3x5 mL EtOAc). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 35% EtOAc in hexanes) to yield the pure methyl ester **303** (117 mg, 0.26 mmol, 72%) as a clear oil. The 10*E:Z* ratio of this material reflected that of the starting material [*E:Z* = 91:9, determined by integration of the H11 resonance in the ^1H NMR; δ_{H11} (10*E*) = 5.44 (1H, dd, *J* = 15.0, 8.7 Hz), δ_{H11} (10*Z*) = 5.21 (1H, t, *J* = 10.0 Hz)]. The pure natural isomer could be isolated if desired by subsequent careful column chromatography (eluting with 20% EtOAc in hexanes, the 10*E* isomer is the less polar component). ^1H and ^{13}C NMR data was in complete agreement with that previously reported by Isaac *et al*[104] (DEPT data and proton resonance coupling constants were not reported by Isaac and so are listed here).

$[\alpha]_D$ = +0.9 (*c* = 0.66, $CHCl_3$).

IR (film): *v* = 3501 (br m), 2954 (s), 2925 (s), 2849 (m), 1740 (s), 1455 (m), 1382 (w), 1198 (w), 1090 (w), 1067 (m), 1019 (w), 966 (w), 731 (w) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.24 (1H, dd, *J* = 15.0, 10.8 Hz, H10), 5.90 (1H, d, *J* = 11.0 Hz, H9), 5.45 (1H, dd, *J* = 14.9, 8.8 Hz, H11), 3.90-3.83 (1H, m, H18), 3.82-3.73 (1H, m, H3), 3.67 (3H, s, CO_2Me), 3.55 (3H, s, OMe), 3.33 (1H, d, *J* = 9.8 Hz, H7), 2.98

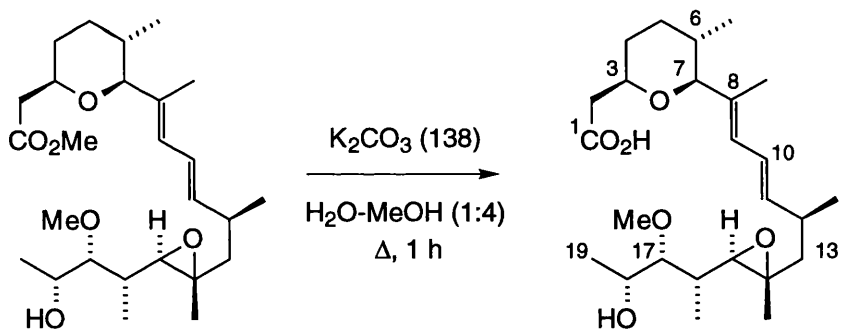
(1H, t, J = 5.3 Hz, H17), 2.60 (1H, dd, J = 15.2, 6.2 Hz, $H2_A$), 2.60-2.53 (1H, m, OH), 2.56 (1H, d, J = 9.7 Hz, H15), 2.45-2.37 (1H, m, H12), 2.41 (1H, dd, J = 15.2, 6.7 Hz, $H2_B$), 1.90 (1H, dd, J = 13.6, 4.7 Hz, $H13_A$), 1.88-1.81 (1H, m, $H5_A$), 1.71 (3H, s, C8-Me), 1.70-1.50 (3H, m, $H4_A$, H6, H16), 1.40-1.20 (3H, m, $H4_B$, $H5_B$, $H13_B$), 1.29 (3H, s, C14-Me), 1.19 (3H, d, J = 6.4 Hz, H19), 1.05 (3H, d, J = 6.7 Hz, C12-Me), 0.88 (3H, d, J = 6.9 Hz, C16-Me), 0.67 (3H, d, J = 6.6 Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 172.0 (0, C1), 139.4 (1, C11), 135.4 (0, C8), 128.3 (1, C9), 125.4 (1, C10), 90.8 (1, C7), 87.8 (1, C17), 74.0 (1, C3), 68.4 (1, C18), 66.2 (1, C15), 61.5 (0, C14), 61.5 (3, OMe), 51.7 (3, CO_2Me), 47.1 (2, C13), 41.5 (2, C2), 35.5 (1, C12), 35.3 (1, C16), 32.4 (2, C5), 32.3 (1, C6), 31.8 (2, C4), 22.2 (3, C12-Me), 19.2 (3, C19), 17.8 (3, C6-Me), 16.7 (3, C14-Me), 12.1 (3, C8-Me), 12.0 (3, C16-Me) ppm.

LRMS (EI+ mode): m/z = 452 (28%), 434 (9), 351 (12), 305 (10), 278 (22), 265 (19), 237 (12), 211 (11), 197 (15), 173 (44), 157 (42), 129 (100), 123 (55), 95 (56), 69 (50).

HRMS (EI+ mode): Found $M^{+\bullet}$, 452.3136. $C_{26}H_{44}O_6$ requires 452.3138.

Herboxidiene (233):



303
$C_{26}H_{44}O_6$ (452.62)

233
$C_{25}H_{42}O_6$ (438.60)

A solution of the methyl ester **303** (16 mg, 35 μmol) in MeOH (2 mL) was treated with an aqueous solution of potassium carbonate (24 mg, 174 μmol in 0.5 mL H_2O) and the resultant mixture stirred at reflux for 1 h. After this time the reaction was allowed to cool and diluted with EtOAc (10 mL) and H_2O (5 mL). The aqueous layer was then acidified to pH 2 by the careful addition of 2M $HCl_{(aq)}$ (*ca* 0.5 mL) and the layers shaken well and then separated. The aqueous phase was extracted (4x5 mL EtOAc) and the combined organic extracts washed with brine (5 mL), dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 7% MeOH in CH_2Cl_2) to yield herboxidiene (**233**, 13 mg, 30 μmol, 84%) as a clear oil. ^1H and ^{13}C NMR data recorded in CD_3OD are listed in Tables 10 and 11 respectively.

$[\alpha]_D = -30$ (c = 0.2, $CHCl_3$, T = 293K).

IR (film): ν = 3470 (br w), 2962 (s), 2919 (s), 2849 (m), 1731 (m), 1456 (m), 1382 (w), 1276 (w), 1198 (w), 1154 (w), 1068 (m), 1018 (w), 967 (w), 798 (w) cm^{-1}.

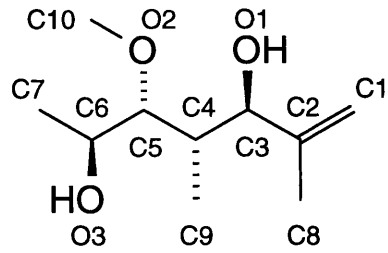
^1H NMR (360 MHz, $CDCl_3$): δ = 6.24 (1H, dd, J = 15.0, 10.8 Hz, H10), 5.95 (1H, d, J = 10.7 Hz, H9), 5.50 (1H, dd, J = 15.1, 8.9 Hz, H11), 3.87 (1H, quintet, J = 6.2 Hz, H18), 3.84-3.74 (1H, m, H3), 3.55 (3H, s, OMe), 3.43 (1H, d, J = 10.0 Hz, H7), 3.01 (1H, t, J = 5.3 Hz, H17), 2.58-2.54 (3H, m, $H2_A$, $H2_B$, H15), 2.50-2.38 (1H, m, H12), 1.95-1.85 (1H, m, $H5_A$), 1.93 (1H, dd, J = 13.5, 4.6 Hz, $H13_A$), 1.73 (3H, s, C8-Me), 1.63 (1H, m, $H4_A$), 1.54 (1H, m, H6), 1.43 (1H, qm, J = 12.7 Hz, H16), 1.32-1.17 (3H, m, $H4_B$, $H5_B$, $H13_B$), 1.29 (3H, s, C14-Me), 1.19 (3H, d, J = 6.4 Hz, H19), 1.07 (3H, d, J = 6.7 Hz, C12-Me), 0.87 (3H, d, J = 6.9 Hz, C16-Me), 0.72 (3H, d, J = 6.6 Hz, C6-Me) ppm.

^{13}C NMR (90 MHz, $CDCl_3$): δ = 172.2 (0, C1), 140.5 (1, C11), 133.9 (0, C8), 129.4 (1, C9), 125.0 (1, C10), 91.2 (1, C7), 87.7 (1, C17), 74.0 (1, C3), 68.5 (1, C18), 66.2 (1, C15), 61.4 (0, C14), 61.4 (3, OMe), 47.1 (2, C13), 40.9 (2, C2), 35.5 (1, C12), 35.3 (1, C16), 32.6 (1, C6), 32.0 (2, C5), 31.6 (2, C4), 22.1 (3, C12-Me), 19.2 (3, C19), 17.6 (3, C6-Me), 16.7 (3, C14-Me), 12.4 (3, C8-Me), 11.9 (3, C16-Me) ppm.

LRMS (EI+ mode): m/z = 438 (10%), 420 (4), 337 (7), 293 (7), 251 (58), 183 (18), 173 (34), 129 (85), 95 (100), 69 (82).

HRMS (EI+ mode): Found $M^{+\bullet}$, 438.2980. $C_{25}H_{42}O_6$ requires 438.2981.

9. Appendix - Crystal Structure of Diol 365



365

The following study was conducted by Dr K. W. Muir of the University of Glasgow. The structure will be deposited in the Cambridge Structural Database.

9.1. Crystal and molecular structure of $C_{10}H_{20}O_3$ (365)

The asymmetric unit contains two independent molecules which have nearly indistinguishable structures (Figure 19, Tables 13 to 16): a change of 6° in the C4-C5-C6-O3 torsion angle is their most obvious difference. They are approximately related by the operation 1/2+x, –y, 0.815–z which defines the action of a non-crystallographic 2_1 screw axis parallel to a at y = 0, z = 0.4075. Bond lengths in both agree with standard values[181] to within 0.026Å. Based on the known stereochemistry of C4 (*S*), C5 (*R*), and C6 (*S*) the absolute configuration at C3 is *R*.

Each molecule adopts a conformation in which the C2-C3-C4-C5-C6-C7 chain defines nearly a planar zigzag and the C2-C8 bond is staggered with respect to C3-C4 and C3-O1. In consequence the two hydroxyl groups lie above the same face of the zigzag. This facilitates formation of a cooperative O-H...O hydrogen bond network which links O1 in each independent molecule to O3 in the corresponding molecule at 1+x, y, z. Two parallel chains of molecules running parallel to the a-axis are thereby generated. They are interlinked by O3-H...O1 bonds (Figure 18) so that the unit O11-H...O31^{i}-H...O12-H...O32^{i}-H...O11^{i} repeats continually along the a-axis. The uni-directional nature of the hydrogen bonding is reflected in the morphology of the crystals which are fine needles elongated in the a-direction.

9.2. Crystal structure analysis of $C_{10}H_{20}O_3$ (365)

Measurements were made at 20°C on an Enraf-Nonius CAD4 diffractometer with graphite-monochromatised Mo $K\alpha$ radiation, λ = 0.71073 Å. The crystals were long, extremely fine needles which invariably shattered on cutting. Data were therefore collected using an uncut crystal of dimensions 3.0 x 0.15 x 0.02 mm and a beam diameter of 0.80 mm.

Crystal data:- $C_{10}H_{20}O_3$, M = 188.26, monoclinic, space group $P2_1$, a = 7.3028(10), b = 19.019(3), c = 8.1976(12) Å, β = 90.816(12) °, V = 1138.5(3) Å^3, Z = 4, D_c = 1.098 g cm^{-3}, μ(Mo Kα) = 0.079 mm^{-1}.

Cell dimensions are based on the setting angles of 25 reflections with $7.5 < \theta(\text{Mo K}\alpha) < 16.2°$. The intensities of 3957 reflections with $2 < \theta(\text{Mo K}\alpha) < 23°$, $-8 \leq h \leq 1$, $-20 \leq k \leq 20$ and $-9 \leq l \leq 9$ were estimated from ω scans and corrected for Lp effects, 25% crystal decomposition and for variations in the irradiated volume (correction factors 1.000-0.921)[182]. Averaging gave 3115 unique reflections (Rint = 0.049); of these 1620 were deemed observed [$I > 2\sigma(I)$]. The structure was solved by direct methods[183] and refined to convergence ($\Delta/\sigma < 0.001$ for 245 parameters) using all 3115 F^2 values, with $w = [\sigma^2(F^2) + (0.069P)^2]^{-1}$ where $P = (F_{obs}^2 + 2F_{calc}^2)/3$. Final agreement indices were $R[I<2\sigma(I)] = 0.054$ and wR_2(all data) = 0.14 and in the final difference map $|\Delta\rho| < 0.24$ eÅ^3. Anisotropic U^{ij} were refined for all non-hydrogen atoms. H atoms rode on parent C atoms and an orientation parameter was successfully refined for each CH_3 and OH group except for those bonded to C101 and O11 whose positions were determined from stereochemical considerations. Although the data contained 1495 Friedel pairs the absolute configuration of the model could not be reliably determined; it was therefore chosen to accord with the known absolute stereochemistry of atoms C4n, C5n and C6n (n = 1, 2). Scattering factors and dispersion corrections were those incorporated in the least-squares refinement program SHELXL-97 and the WINGX package was used for other calculations[184,185].

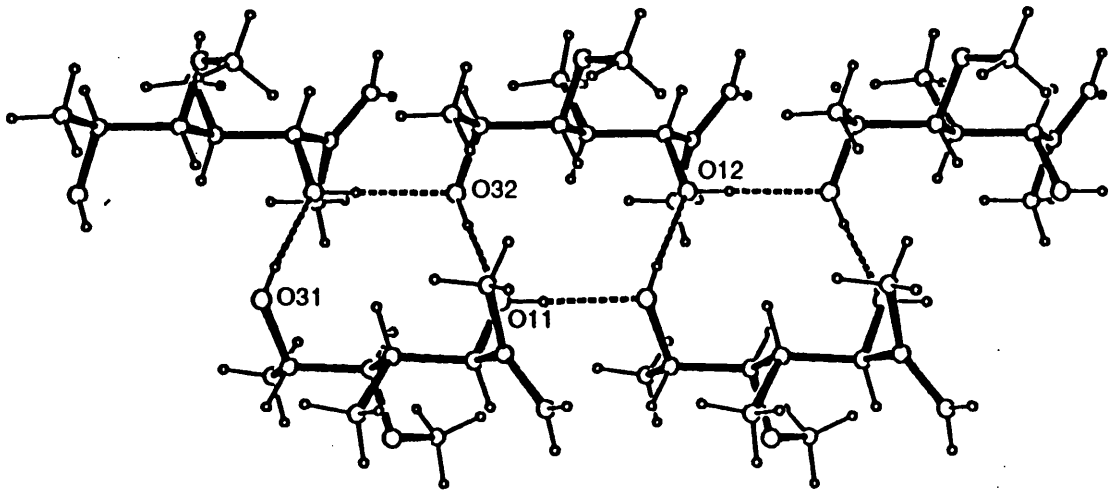


Figure 18. The cooperative hydrogen bonding network in **365**. The direction of view is approximately down c and the a-axis runs horizontally left to right. Only the molecules of the asymmetric unit and those derived from them by translation along the a-axis are shown. Labels are shown for the hydroxyl oxygen atoms in the reference asymmetric unit.

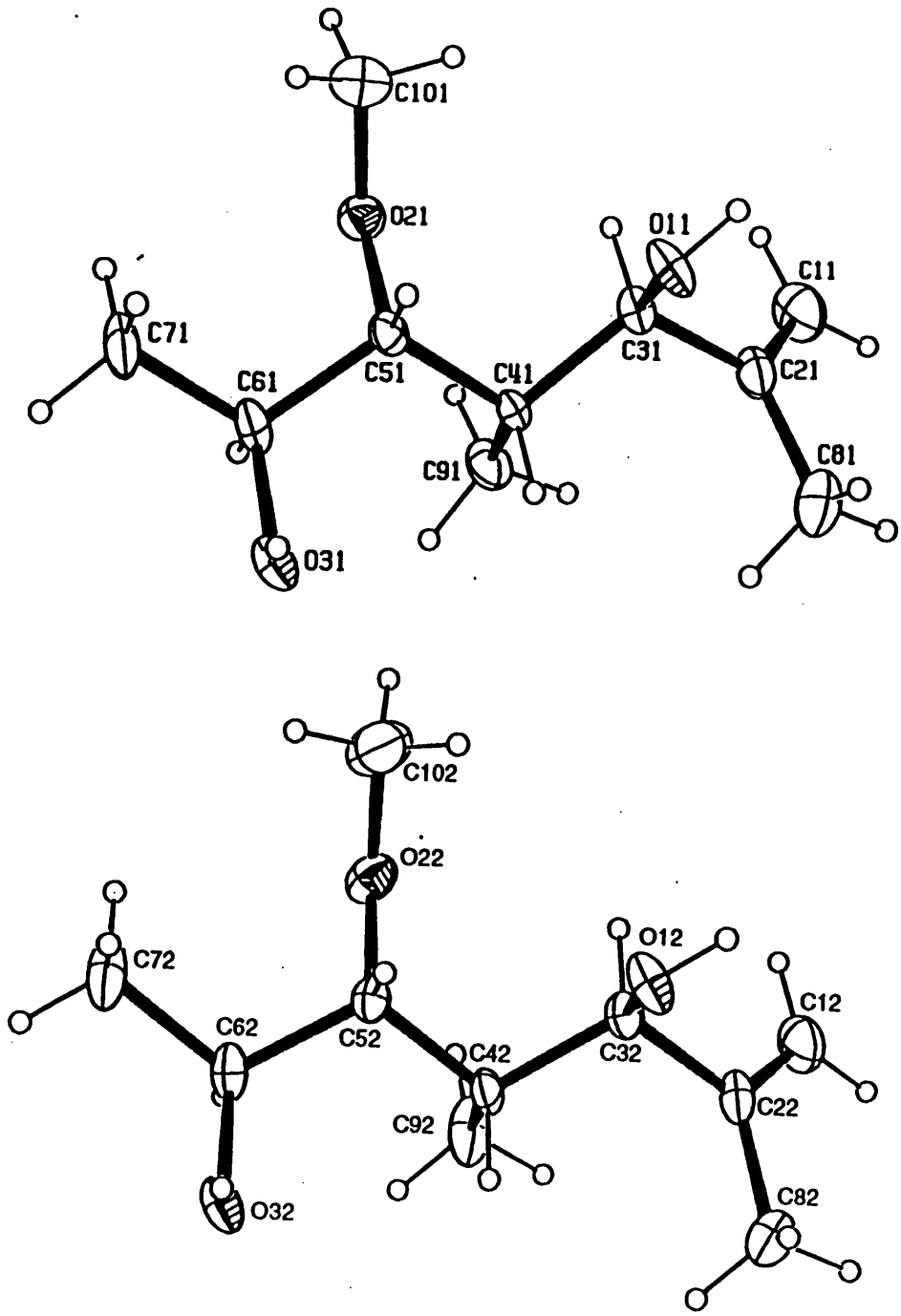


Figure 19. Views of the two independent molecules of **365** in the same orientation showing 20% probability ellipsoids. Hydrogen atoms are shown as spheres of arbitrary size. The final digit of the atom number n is either 1 or 2 to distinguish corresponding atoms in the two independent molecules (see Tables 13 to 16).

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **365**. U_{eq} is defined as one third of the trace of the orthogonalised U^{ij} tensor. **Table 13**

atom	x	y	z	U_{eq}
O11	2364(5)	530(2)	2952(4)	56(1)
O21	–486(5)	1888(2)	4140(4)	52(1)
O31	–3833(5)	509(2)	3210(4)	51(1)
C11	3558(10)	1496(4)	–344(8)	80(2)
C21	2509(8)	994(3)	232(7)	52(2)
C31	1718(7)	1083(3)	1891(6)	40(1)
C41	–391(7)	1049(3)	1928(6)	40(1)
C51	–1047(7)	1197(3)	3639(6)	39(1)
C61	–3164(7)	1173(3)	3814(6)	48(2)
C71	–3756(8)	1296(4)	5552(7)	74(2)
C81	2108(10)	346(4)	–699(9)	93(2)
C91	–1214(8)	1566(3)	678(7)	62(2)
C101	642(10)	1909(4)	5563(8)	85(2)
O12	7355(5)	–538(2)	5305(5)	56(1)
O22	4518(6)	–1847(2)	3844(5)	61(1)
O32	1159(5)	–524(2)	5017(5)	55(1)
C12	8674(9)	–1581(4)	8479(8)	79(2)
C22	7582(7)	–1074(3)	7959(7)	50(2)
C32	6769(6)	–1122(3)	6268(6)	39(1)
C42	4638(6)	–1124(3)	6236(6)	42(1)
C52	3907(7)	–1195(3)	4496(6)	40(1)
C62	1797(7)	–1186(3)	4375(7)	50(2)
C72	1109(8)	–1286(4)	2625(7)	77(2)
C82	7152(9)	–452(4)	8977(8)	79(2)
C92	3929(9)	–1700(4)	7363(7)	75(2)
C102	5508(11)	–1801(4)	2392(9)	96(3)

Hydrogen bonds [Å and °] for **365**. **Table 14**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O11-H11...O31^{i}	0.82	1.96	2.782(5)	176.3
O31-H31...O12^{ii}	0.82	1.94	2.762(5)	175.7
O12-H12...O32^{i}	0.82	1.97	2.791(5)	176.2
O32-H32...O11	0.82	1.96	2.776(5)	176.9

symmetry transformations used to generate equivalent atoms: (i) x+1, y, z; (ii) x–1, y, z.

Bond lengths [Å] and angles [°] in the two independent **365** molecules. **Table 15**

bond	molecule 1	molecule 2	bond	molecule 1	molecule 2
O1-C3	1.440(5)	1.433(6)	C2-C3	1.495(7)	1.503(7)
O2-C10	1.420(7)	1.405(8)	C3-C4	1.542(6)	1.556(7)
O2-C5	1.434(6)	1.425(6)	C4-C5	1.514(6)	1.522(6)
O3-C6	1.438(6)	1.444(7)	C4-C9	1.536(7)	1.529(7)
C1-C2	1.315(8)	1.319(8)	C5-C6	1.556(7)	1.543(7)
C2-C8	1.477(8)	1.484(8)	C6-C7	1.512(7)	1.526(7)
angle			angle		
C10-O2-C5	114.9(4)	115.5(5)	C5-C4-C3	109.9(4)	110.7(4)
C1-C2-C8	122.2(6)	122.3(6)	C9-C4-C3	109.9(4)	109.8(5)
C1-C2-C3	118.6(6)	118.8(6)	O2-C5-C4	110.1(4)	108.7(4)
C8-C2-C3	119.2(6)	118.9(6)	O2-C5-C6	106.3(4)	107.6(4)
O1-C3-C2	109.8(4)	110.1(4)	C4-C5-C6	114.1(4)	113.3(4)
O1-C3-C4	106.0(4)	107.4(4)	O3-C6-C7	111.1(4)	110.3(5)
C2-C3-C4	114.3(4)	113.4(4)	O3-C6-C5	109.1(4)	108.2(4)
C5-C4-C9	111.9(4)	112.7(4)	C7-C6-C5	112.4(4)	112.0(5)

Torsion angles [°] in the two independent **365** molecules. **Table 16**

angle	mol. 1	mol. 2	angle	mol. 1	mol. 2
C1-C2-C3-O1	–118.7(6)	118.8(6)	C10-O2-C5-C6	115.3(5)	113.3(6)
C8-C2-C3-O1	60.6(7)	60.2(6)	C9-C4-C5-O2	–61.6(5)	–62.0(6)
C1-C2-C3-C4	122.3(6)	120.9(6)	C3-C4-C5-O2	60.8(5)	61.4(5)
C8-C2-C3-C4	–58.4(7)	–60.1(7)	C9-C4-C5-C6	57.8(6)	57.7(7)
O1-C3-C4-C5	62.9(5)	59.7(6)	C3-C4-C5-C6	–179.8(4)	–178.9(5)
C2-C3-C4-C5	–176.0(5)	–178.4(5)	O2-C5-C6-O3	175.6(4)	–179.4(4)
O1-C3-C4-C9	–173.5(4)	–175.2(5)	C4-C5-C6-O3	54.1(6)	60.3(6)
C2-C3-C4-C9	–52.4(6)	–53.4(7)	O2-C5-C6-C7	–60.7(6)	–57.6(6)
C10-O2-C5-C4	–120.6(5)	–123.6(5)	C4-C5-C6-C7	177.8(5)	–177.8(5)

10. References

1. J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel *Tetrahedron Lett.* **1991**, *32*, 1175.
2. J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel *Bull. Soc. Chim. Fr.* **1993**, *130*, 336.
3. J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne, O. Ruel *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.
4. P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley *SynLett* **1998**, 26.
5. P. R. Blakemore, P. J. Kocienski, A. Morley, K. W. Muir *J. Chem. Soc., Perkin Trans. I* **1999**, in press.
6. *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991.
7. S. E. Kelly In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 1; pp 729.
8. J. M. J. Williams *Preparation of Alkenes: A Practical Approach;* 1st ed.; Oxford University Press: Oxford, 1996.
9. G. Wittig, G. Geissler *Liebigs Ann. Chem.* **1953**, *580*, 44.
10. G. Wittig, U. Schöllkopf *Chem. Ber.* **1954**, *87*, 1318.
11. J. March *Advanced Organic Chemistry: Reactions Mechanisms, and Structure;* 4th ed.; John Wiley & Sons: New York, 1992.
12. H. H. Inhoffen, K. Brückner, R. Gründel *Chem. Ber.* **1954**, *87*, 1.
13. L. Horner, H. Hoffmann, H. G. Wippel *Chem. Ber.* **1958**, *91*, 61.
14. L. Horner, H. Hoffmann, H. G. Wippel, G. Klahre *Chem. Ber.* **1959**, *92*, 2499.
15. W. S. Wadsworth, W. D. Emmons *J. Am. Chem. Soc.* **1961**, *83*, 1733.
16. W. S. Wadsworth *Org. React.* **1977**, *73*, 25.
17. B. E. Maryanoff, A. B. Reitz *Chem. Rev.* **1989**, *89*, 863.
18. D. J. Peterson *J. Org. Chem.* **1968**, *33*, 780.
19. C. R. Johnson, J. R. Shanklin, R. A. Kirchhoff *J. Am. Chem. Soc.* **1973**, *95*, 6462.
20. M. Julia, J.-M. Paris *Tetrahedron Lett.* **1973**, *49*, 4833.
21. E. Vedejs, M. J. Peterson *Top. Stereochem.* **1994**, *21*, 1.
22. E. Vedejs, K. A. J. Snoble *J. Am. Chem. Soc.* **1973**, *95*, 5778.
23. M. Schlosser, B. Schaub, J. de Oliveira-Neto, S. Jeganathan *Chimia* **1986**, *40*, 244.
24. E. J. Corey, X.-M. Cheng *The Logic of Chemical Synthesis;* 1st ed.; John Wiley & Sons: New York, 1989.
25. K. C. Nicolaou, E. J. Sorensen *Classics in Total Synthesis: Targets, Strategies, Methods;* 1st ed.; VCH: Weinheim, 1996.
26. L. Horner, W. Klink, H. Hoffmann *Chem. Ber.* **1963**, *96*, 3133.
27. W. C. Still, C. Gennari *Tetrahedon Lett.* **1983**, *24*, 4405.

28. A. D. Buss, W. B. Cruse, O. Kennard, S. Warren *J. Chem. Soc., Perkin Trans. 1* **1984**, 243.
29. B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, J. Tideswell, P. W. Wright *J. Chem. Soc. Perkin I* **1978**, 590.
30. P. J. Kocienski, B. Lythgoe, S. Ruston *J. Chem. Soc. Perkin I* **1979**, 1290.
31. S. Hanessian, A. Ugolini, D. Dubé, P. J. Hodges, C. André *J. Am. Chem. Soc.* **1986**, *108*, 2776.
32. S. J. Danishefsky, A. Villalobos *J. Org. Chem.* **1989**, *54*, 12.
33. M. Julia *Pure & Appl. Chem.* **1985**, *57*, 763.
34. P. J. Kocienski In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 6; pp 975.
35. P. Kocienski, B. Lythgoe, I. Waterhouse *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.
36. P. Kocienski, B. Lythgoe, S. Ruston *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.
37. P. Kocienski, B. Lythgoe, D. A. Roberts *J. Chem. Soc., Perkin Trans. 1* **1978**, 834.
38. D. J. Hart, W.-L. Wu *Tetrahedron Lett.* **1996**, *37*, 5283.
39. G. E. Keck, K. A. Savin, M. A. Weglarz *J. Org. Chem.* **1995**, *60*, 3194.
40. I. E. Markó, F. Murphy, S. Dolan *Tetrahedron Lett.* **1996**, *37*, 2089.
41. A. S. Kende, J. S. Mendoza *Tetrahedron Lett.* **1990**, *31*, 7105.
42. G. H. Lee, H. K. Lee, E. B. Choi, B. T. Kim, C. S. Pak *Tetrahedron Lett.* **1995**, *31*, 5607.
43. T. Satoh, N. Yamada, T. Asano *Tetrahedron Lett.* **1998**, *39*, 6935.
44. W. E. Truce, E. M. Kreider, W. W. Brand *Org. React.* **1971**, *18*, 99.
45. R. Bellingham, K. Jarowicki, P. Kocienski, V. Martin *Synthesis* **1996**, 285.
46. N. D. Smith, P. J. Kocienski, S. D. A. Street *Synthesis* **1996**, 652.
47. A. B. Charette, H. Lebel *J. Am. Chem. Soc.* **1996**, *118*, 10327.
48. D. J. Cundy, A. C. Donohue, T. D. McCarthy *Tetrahedron Lett.* **1998**, *39*, 5125.
49. G. Pattenden, A. T. Plowright, J. A. Tornos, T. Ye *Tetrahedron Lett.* **1998**, *39*, 6099.
50. S. D. Burke, J. Hong, J. R. Lennox, A. P. Mongin *J. Org. Chem.* **1998**, *63*, 6952.
51. A. Albert, G. B. Barlin *J. Chem. Soc.* **1959**, 2384.
52. O. Mitsunobu *Synthesis* **1981**, 1.
53. D. H. R. Barton, G. Fontana, Y. Yang *Tetrahedron* **1996**, *52*, 2705.
54. J. Rodriguez, P. Brun, B. Waegell *J. Organomet. Chem.* **1989**, *359*, 343.
55. R. S. Coleman, A. J. Carpenter *J. Org. Chem.* **1993**, *58*, 4452.
56. K. Ogura In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 1; pp 505.
57. S. Wolfe, L. A. LaJohn, D. F. Weaver *Tetrahedron Lett.* **1984**, *25*, 2863.
58. S. Wolfe, A. Rauk, I. G. Csizmadia *J. Am. Chem. Soc.* **1969**, *91*, 1567.

59. D. A. Bors, A. Streitwieser *J. Am. Chem. Soc.* **1986**, *108*, 1397.
60. G. Boche, M. Marsch, K. Harms, G. M. Sheldrick *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 573.
61. H.-J. Gais, J. Vollhardt, H. J. Lindner *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 939.
62. H.-J. Gais, G. Hellman, H. Günther, F. Lopez, H. J. Lindner, S. Braun *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1025.
63. G. H. Whitham *Organosulfur Chemistry*; Oxford University Press: Oxford, 1995; Vol. 33.
64. H. E. Zimmerman, M. D. Traxler *J. Am. Chem. Soc.* **1957**, *79*, 1920.
65. C. H. Heathcock In *Asymmetric Synthesis*; J. D. Morrison, Ed.; Academic Press: New York, 1984; Vol. 3; pp 111.
66. S. G. Pyne, G. Boche *J. Org. Chem.* **1989**, *54*, 2663.
67. H. J. Reich, R. C. Holtan, C. Bolm *J. Am. Chem. Soc.* **1990**, *112*, 5609.
68. M. A. Walker, C. H. Heathcock *J. Org. Chem.* **1991**, *56*, 5747.
69. J. O. Besenhard, H. P. Fritz *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 950.
70. C. J. Schaverien, J. B. vanMechelen *Organometallics* **1991**, *10*, 1704.
71. G. R. Fuentes, P. S. Coan, W. E. Streib, K. G. Caulton *Polyhedron* **1991**, *10*, 2371.
72. A. G. Bell "Investigations on a New Fragment Linkage Reaction Based on Heterocyclic Sulfones," University of Glasgow, 1998.
73. A. W. Norman *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979.
74. L. Cancela, G. Theofan, A. W. Norman In *Hormones and Their Actions*; B. A. Cooke, R. J. B. King and H. J. Vander Moler, Ed.; Elsevier: New York, 1988.
75. I. T. Harrison, B. Lythgoe, S. Trippett *J. Chem. Soc. (C)* **1955**, 4016.
76. W. H. Okamura, G. D. Zhu *Chem. Rev.* **1995**, *95*, 1877.
77. E. G. Baggiolini, J. A. Iacobelli, B. M. Hennessy, A. D. Batcho, J. F. Sereno, M. R. Uskokovic *J. Org. Chem.* **1986**, *51*, 3098.
78. H. Nemoto, H. Kurobe, K. Fukumoto, T. Kametani *J. Org. Chem.* **1986**, *51*, 5311.
79. L. Castedo, A. Mouriño, L. A. Sarandeses *Tetrahedron Lett.* **1986**, *27*, 1523.
80. T. M. Dawson, J. Dixon, P. S. Littlewood, B. Lythgoe, A. K. Saksena *J. Chem. Soc. (C)* **1971**, 2960.
81. B. M. Trost, J. Dumas *J. Am. Chem. Soc.* **1992**, *114*, 1924.
82. S. A. Bakker, J. Lugtenburg, E. Havinga *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459.
83. W. H. Okamura, J. M. Aurrecoechea, R. A. Gibbs, A. W. Norman *J. Org. Chem.* **1989**, *54*, 4072.
84. E. M. VanAlstyne, A. W. Norman, W. H. Okamura *J. Am. Chem. Soc.* **1994**, *116*, 6207.
85. S. Yamada, H. Takayama *Chem. Lett.* **1979**,

86. W. Reischl, E. Zbiral *Helv. Chim. Acta.* **1979**, *62*, 1763.
87. M. Sheves, Y. Mazur *J. Am. Chem. Soc.* **1975**, *97*, 6249.
88. H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto *Tetrahedron Lett.* **1984**, *25*, 3095.
89. S. R. Wilson, M. S. Haque *Tetrahedron Lett.* **1984**, *25*, 3147.
90. S. R. Wilson, A. M. Venkatesan, C. E. Augelli-Szafran, A. Yasmin *Tetrahedron Lett.* **1991**, *32*, 2339.
91. H. T. Toh, W. H. Okamura *J. Org. Chem.* **1983**, *48*, 1414.
92. Personal communication from Prof. J. Wicha and Dr S. Marzcek.
93. W. G. Dauben, R. R. Ollmann, S. C. Wu *Tetrahedron Lett.* **1994**, *35*, 2149.
94. C. A. Hoeger, A. D. Johnston, W. H. Okamura *J. Am. Chem. Soc.* **1987**, *109*, 4690.
95. A. G. M. Barrett, D. H. R. Barton, R. A. Russell, D. A. Widdowson *J. Chem. Soc., Chem. Comm.* **1975**, 102.
96. S. K. Pradhan *Tetrahedron* **1986**, *42*, 6351.
97. Y. Wang, H.-S. Ting, J.-J. Huang, Y.-C. Chow, Y.-T. Huang *Acta Chim. Sin.* **1958**, *24*, 126.
98. J.-L. Luche, L. Rodriguez-Hahn, P. Crabbé *J. Chem. Soc., Chem. Comm.* **1978**, 601.
99. D. B. Dess, J. C. Martin *J. Am. Chem. Soc.* **1991**, *113*, 7277.
100. M. D. Mizhiritskii, L. E. Konstantinovskii, R. Vishkautsan *Tetrahedron Letters* **1996**, *52*, 1239.
101. A. Windaus, K. Dithmar, E. Fernholz *Justus Liebigs Ann. Chem.* **1932**, *493*, 259.
102. C. Mahé, H. Patin, M.-T. VanHulle, D. H. R. Barton *J. Chem. Soc., Perkin Trans. I* **1981**, 2504.
103. M. A. Maestro, F. J. Sardina, L. Castedo, A. Mouriño *J. Org. Chem.* **1991**, *56*, 3582.
104. B. G. Isaac, S. W. Ayer, R. Elliott, R. J. Stonard *J. Org. Chem.* **1992**, *57*, 7220.
105. M. G. Banwell, C. T. Bui, G. W. Simpson, K. G. Watson *Chem. Commun.* **1996**, 723.
106. M. G. Banwell, C. T. Bui, D. C. R. Hockless, G. W. Simpson *J. Chem. Soc., Perkin Trans. 1* **1997**, 1261.
107. M. G. Banwell, C. T. Bui, G. W. Simpson *J. Chem. Soc., Perkin Trans. 1* **1998**, 791.
108. D. Hoppe *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932.
109. D. Hoppe, T. Krämer, J.-R. Schwark, O. Zschage *Pure & Appl. Chem.* **1990**, *62*, 1999.
110. D. Hoppe, O. Zschage *Tetrahedron* **1992**, *48*, 5657.
111. P. Kocienski, N. J. Dixon *Synlett* **1989**, 52.

112. P. J. Kocienski, C. Barber *Pure Appl. Chem.* **1990**, *62*, 1933.
113. W. P. Buttenberg *Liebigs Ann Chem.* **1894**, *279*, 324.
114. P. Fritsch *Liebigs Ann Chem.* **1894**, *279*, 319.
115. H. Wiechell *Liebigs Ann Chem.* **1894**, *279*, 337.
116. M. G. Banwell, C. T. Bui, H. T. T. Pham, G. W. Simpson *J. Chem. Soc., Perkin Trans. 1* **1996**, 967.
117. P. Wipf In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon Press: Oxford, 1991; Vol. 5; pp 827.
118. T. Katsuki, K. B. Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5974.
119. A. J. F. Edmunds, W. Trueb, W. Oppolzer, P. Cowley *Tetrahedron* **1997**, *53*, 2785.
120. N. Le-Van, H. P. Weber, W. Trueb, J. J. Sanglier *J. Antibiotics*, in preparation.
121. H. Kotsuki, Y. Ushio, I. Kadota, M. Ochi *Chem. Lett.* **1988**, 927.
122. Y. Koguchi, M. Nishio, J. Kotera, K. Omori, T. Ohnuki, S. Komatsubara *J. Antibiotics* **1997**, *50*, 970.
123. T. Horiguchi, M. Shirasuki, S. Tanida *Takeda Kenkyushoho* **1996**, *55*, 149.
124. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless *Chem. Rev.* **1994**, *94*, 2483.
125. W. Oppolzer, R. Moretti, S. Thomi *Tetrahedron Lett.* **1989**, *30*, 5603.
126. A. J. Fry, R. D. Little, J. Leonetti *J. Org. Chem.* **1994**, *59*, 5017.
127. H. E. D. L. Mare, J. K. Kochi, F. F. Rust *J. Am. Chem. Soc.* **1963**, *85*, 1437.
128. W. Oppolzer, S. Rosset, J. DeBrabander *Tetrahedron Lett.* **1997**, *38*, 1539.
129. G. Procter *Asymmetric Synthesis;* 1st ed.; Oxford University Press: Oxford, 1996.
130. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang *J. Org. Chem.* **1992**, *57*, 2768.
131. R. Criegee *Justus Liebigs Ann. Chem.* **1936**, *522*, 75.
132. E. J. Corey, M. C. Noe *J. Am. Chem. Soc.* **1996**, *118*, 11038.
133. A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner, A. A. Thomas *J. Am. Chem. Soc.* **1997**, *119*, 9907.
134. E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schröder, K. B. Sharpless *J. Am. Chem. Soc.* **1988**, *110*,
135. C. Johnstone, W. J. Kerr, J. S. Scott *Chem. Commun.* **1996**, 341.
136. N. J. Lawrence In *Preparation of Alkenes*; 1st ed.; J. M. J. Williams, Ed.; Oxford University Press: Oxford, 1996; pp 19.
137. B. Maurer, A. Grieder, W. Thommen *Helv. Chim. Acta* **1979**, *62*, 44.
138. W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther *J. Am. Chem. Soc.* **1990**, *112*, 2767.
139. B. M. Kim, S. F. Williams, S. Masamune In *Comprehensive Organic Synthesis*; B. M. Trost and I. Fleming, Ed.; Pergamon: Oxford, 1991; Vol. 2; pp 239.

140. D. A. Evans, A. M. Ratz, B. E. Hopf, G. S. Sheppard *Tetrahedron Lett.* **1995**, *35*, 7171.
141. Y. Mori, M. Kuhara, A. Takeuchi, M. Suzuki *Tetrahedron Lett.* **1988**, *29*, 5419.
142. R. E. Ireland, P. Wipf, J.-N. Xiang *J. Org. Chem.* **1991**, *56*, 3572.
143. R. E. Ireland, R. H. Mueller, A. K. Willard *J. Am. Chem. Soc.* **1976**, *98*, 2868.
144. R. E. Ireland, P. Wipf, J. D. Armstrong *J. Org. Chem.* **1991**, *56*, 650.
145. D. A. Evans, A. H. Hoveyda, G. C. Fu *Chem. Rev.* **1993**, *93*, 1307.
146. B. E. Rossiter, T. R. Verhoeven, K. B. Sharpless *Tetrahedron Lett.* **1979**, *20*, 4733.
147. E. D. Mihelich, K. Daniels, D. J. Eickhoff *J. Am. Chem. Soc.* **1981**, *103*, 7690.
148. N. D. Smith Thesis, Southampton University, 1996.
149. D. L. Hughes *Org. React.* **1992**, *42*, 335.
150. J. C. Kauer *Org. Synth.* **1963**, *Coll. Vol. 4*, 411.
151. W. Oppolzer *Tetrahedron* **1987**, *43*, 1969.
152. F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal, P. J. Carroll *J. Am. Chem. Soc.* **1988**, *110*, 8477.
153. H. Quast, L. Bieber *Chem. Ber.* **1981**, *114*, 3253.
154. T. Clerc, E. Pretsch, J. Seibl, W. Simon *Tables of Spectral Data for Structure Determination of Organic Compounds;* 2 ed.; Springer-Verlag: Berlin, 1989.
155. J. B. Stothers *Carbon-13 NMR Spectroscopy;* 1st ed.; Academic Press: London, 1972; Vol. 24.
156. D. H. Williams, I. Fleming *Spectroscopic Methods in Organic Chemistry;* 5 ed.; McGraw-Hill: London, 1995.
157. F. Bjoerkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szmulik *Tetrahedron* **1985**, *41*, 1347.
158. A. P. Krapcho *Synthesis* **1982**, 805.
159. F. H. Owens, W. L. Myers, F. E. Zimmerman *J. Org. Chem.* **1961**, *26*, 2288.
160. Y. Odic, M. Peregre *J. Organomet. Chem.* **1973**, *55*, 273.
161. B. Rickborn, S. E. Wood *J. Am. Chem. Soc.* **1971**, *93*, 3940.
162. B. Dobner, B. Elsner, P. Nuhn *Pharmazie* **1989**, *44*, 758.
163. J. K. Whitesell, M. A. Minton *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy;* 1st ed.; Chapman and Hall: London, 1987.
164. L. R. Collazo, F. S. Guziec *J. Org. Chem.* **1993**, *58*, 43.
165. M. Bernard, W. T. Ford *J. Org. Chem.* **1983**, *48*, 326.
166. S. Poulain, N. Noiret, H. Patin *Tetrahedron Lett.* **1996**, *37*, 7703.
167. B. B. Snider, T. Kwon *J. Org. Chem.* **1990**, *55*, 1965.
168. T. Harada, T. Katsuhira, D. Hara, Y. Kotani, K. Maejima *J. Org. Chem.* **1993**, *58*, 4897.
169. K. K. Wang, K.-H. Chu, Y. Lin, J.-H. Chen *Tetrahedron* **1989**, *45*, 1105.
170. J. B. Campbell, G. A. Molander *J. Organometallic Chem.* **1978**, *156*, 71.

171. C. S. Chao, C. H. Cheng, C. T. Chang *J. Org. Chem.* **1983**, *48*, 4904.
172. B.-M. Kwon, C. S. Foote, S. I. Khan *J. Org. Chem.* **1989**, *54*, 3378.
173. P. Wan, M. J. Davis, M. A. Teo *J. Org. Chem.* **1989**, *54*, 1354.
174. S. Gueste, M. Salzwedel *Tetrahedron* **1967**, *23*, 187.
175. P. E. Peterson, R. L. Breedlove, B. L. Jensen *J. Org. Chem.* **1986**, *51*, 1948.
176. A. Windaus, W. Grundmann *Annalen* **1936**, *524*, 295.
177. R. E. Ireland, L. Liu *J. Org. Chem.* **1993**, *58*, 2899.
178. M. Ansell, S. Brown *J. Chem. Soc.* **1957**, 1788.
179. R. F. Heck *J. Am. Chem. Soc.* **1963**, *85*, 3116.
180. V. L. Nirenburg, I. Y. Postovskii, E. I. Chertkova *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol* **1965**, *8*, 258.
181. *International Tables for Crystallography*; Vol. C, International Union of Crystallography, Kluwer Academic Publishers, Dordrecht, 1992, pp. 714-778.
182. B. A. Coyle, L. W. Schroeder *Acta Cryst.* **1971**, *A27*, 291; ibid., 1972, **A28**, 231. K. W. Muir. ABCYL. *A program for correcting for variations in irradiation volumne*, University of Glasgow, UK, 1995.
183. G. M. Sheldrick. SHELXS97. *A program for the solution of crystal structures*, University of Göttingen, Germany, 1997.
184. G. W. Sheldrick. SHELXL97. *A program for the refinement of crystal structures*, University of Göttingen, Germany, 1997.
185. L. J. Farrugia. WINGX. *A program system for X-ray analysis*, University of Glasgow, UK, 1996.