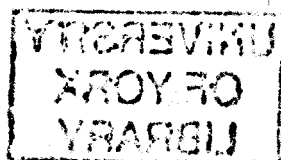


**TOWARDS THE C20-C32 FRAGMENT OF THE
PHORBOXAZOLES**

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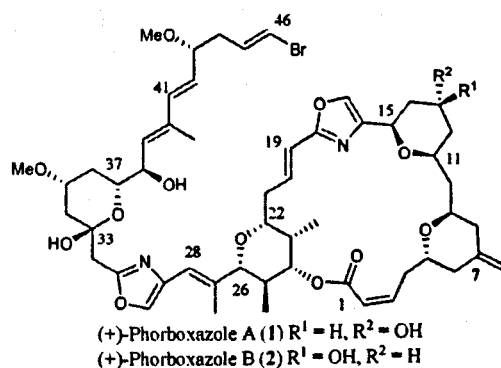


Thesis Submitted to the University of York for the Degree of Doctor of
Philosophy

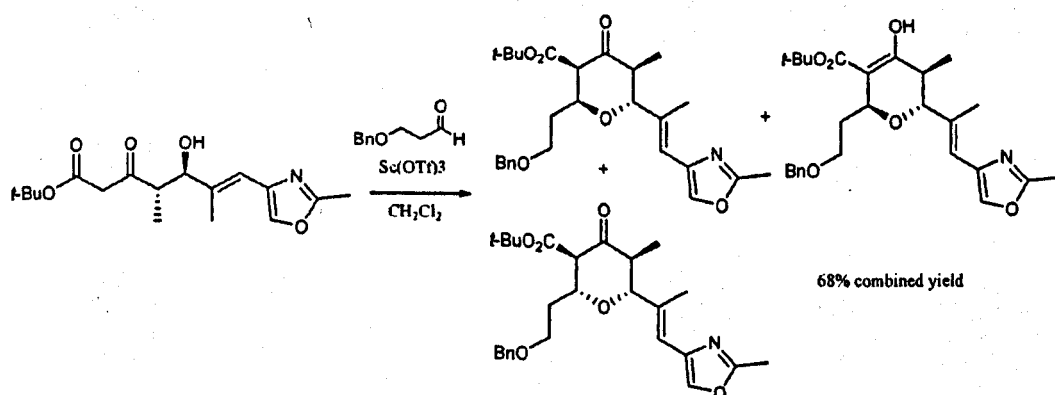
September 2009

1. Abstract

Phorboxazole A (1) and its C13 epimer phorboxazole B (2) are naturally occurring pyran-oxazole based macrolides which were isolated from the *phorbas* sponge, found in the Indian Ocean. It is an extremely exciting target for total synthesis due to its complex architecture and remarkable cytotoxic activity.



To date, there have been eight reported total syntheses of the phorboxazoles, but none of these have produced more than a few milligrams of material. Our ultimate goal was to exploit the one-pot, multi-component Maitland-Japp methodology to provide rapid access to the tetrahydropyran-4-one units present within phorboxazole A. This approach was met with success as tetrahydropyran-4-ones were formed in good yield, however optimisation of the reaction's diastereoselectivity proved to be a challenge.



2. Acknowledgements

I would first of all like to thank my parents for their undying love and support that they have given me throughout my education. I would like to acknowledge my close friends and family for their support and for the kudos that they continually attribute to my achievements. Dr. Paul Clarke has ensured that the quality of the research detailed in this thesis has been the very best that I could have produced. His enthusiasm and belief, in both me and the chemistry, has facilitated the achievement of our challenging goals. I therefore thank him for this drive, and also for recruiting the best possible set of work colleagues during my 4 years in the group. Of these colleagues, I would like to thank Will, Rich, Cridders, Mat, Nigel, Soraia and Gabriele for providing endless help and advice during the early years of my training. Soraia, Gabriele, Reeder, Nimesh, Laurence, Mudassar, Joby and Dan will always be close friends of mine, and I feel very privileged to have spent countless hours with them each day in the lab. I will also hold fond memories of the fun we had on the rare occasions we managed to escape. With that in mind, thanks go to Phil de Barnsley for putting in a sterling shift as social secretary, and for reaffirming my belief that I did in fact come from the right side of the Pennines. Particular thanks go to Dan for his extensive proof-reading of this thesis; any mistakes that remain are mine, and mine alone. I am also indebted to Reeder, Nimesh, Laurence, Elin and Paul for ensuring that I met the deadline for submission. Finally, I would like to acknowledge Rosa Maria Rodriguez Sarmiento for her continued interest in my progress, and for ensuring that I felt right at home during my 3 month industrial placement at Roche, in Basel.

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4. Abbreviations

Ac	acetyl
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAB	chiral acyloxyborane
cat	catalytic
Cbz	carboxybenzyl
COSY	correlation spectroscopy
Cy	cyclohexyl
d	day(s)
DA	Diels-Alder
dba	dibenzylidene acetone
DBU	1,8-diazobicyclo[5.4.0]undec-7ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement of polarisation transfer
DHPO	dihydropyran-4-one
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine

DMB	3,4-dimethoxybenzyl
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(<i>1H</i>)-one)
DMSO	dimethyl sulfoxide
DPPBA	2-diphenyl phosphino benzoic acid
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereoisomeric ratio
ee	enantiomeric excess
EI	electron impact
eq	equivalents
Et	ethyl
GSK	GlaxoSmithKline
h	hour(s)
HDA	hetero-Diels-Alder
hex	hexyl
HMBC	heteronuclear multiple bond coherence
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOBT	<i>N</i> -hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
ipc	diisopinocampheyl

IR	infra-red
<i>i</i>-Pr	isopropyl
J	coupling constant
LA	Lewis Acid
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamine
mCPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
Mes	mesitylene
MHz	megahertz
min	minute(s)
MOM	methoxymethyl
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MTPA	α -methoxytrifluorophenylacetic
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl

PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
quant	quantitative
ROESY	rotating-frame Overhauser effect spectroscopy
RT	room temperature
sat	saturated
sol	solution
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS/TPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butylhydrogen peroxide
TES	triethylsilyl
Tf	triflate (trifluoromethanesulfonate)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
THPO	tetrahydropyran-4-one
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	tosyl (toluenesulfonyl)
ν	vibration frequency (cm^{-1})

5. Introduction

5.1 Natural Product Synthesis Today

Throughout the course of history, man has relied upon natural products as a means of targeting disease. A recent review documents that of all anticancer drugs available between the 1940s and June 2006, 14% are natural products whereas 28% are natural product derived.¹ Furthermore, 12% of these drugs mimic the action of a natural product towards the target enzyme, while although another 11% were made entirely by total synthesis, they still contained the pharmacophore of a natural product. Despite this record of productivity, the early 1990s saw the introduction of automation, robotics and fast personal computers into drug discovery and that has resulted in a shift away from natural product synthesis in big pharma.² Instead, the development of high throughput screening led to the demand for large libraries of compounds, which are rapidly formed by the process of diversity oriented synthesis.^{3,4} This decision to move away from natural product synthesis has been described as “*disastrous*” by Prof. Samuel Danishefsky,⁵ though that was always likely to be his viewpoint as a natural product synthetic chemist. However there is evidence to support his belief. In 2004, the level of small molecule new chemical entities fell to a 24 year low to just eighteen. Danishefsky had earlier stated, with reference to combinatorial chemistry, that “*a small collection of smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled*”.⁶ It isn't necessarily too surprising that natural products have been found to be so adept at combating disease, since they themselves have evolved over time to become resistant to similar protein structures that would cause us detriment. Despite this shift away from natural product synthesis, natural products are still prevalent in the new small

molecule chemical entities that have been formed since 1981 to June 2006, a timespan which is long enough for the effect of combinatorial chemistry to have made its mark. Of these new chemical entities, 6% are natural products, 28% are natural product derived, 24% mimic the action of the natural product, while another 5% are synthetic drugs that have retained the pharmacophore.

5.2 The Phorboxazoles

5.2.1 Structure and Activity

Phorboxazole A (1) (Figure 1) and its C13 epimer phorboxazole B (2) are naturally occurring pyran-oxazole based macrolide structures which were isolated from the *phorbas* sponge, found in the Indian Ocean. The relative stereochemistry of their structures was elucidated by the groups of Searle and Molinski in 1995 *via* intensive 2D NMR spectroscopy and ROESY experiments.⁷ The phorboxazole skeleton was found to consist of fifteen stereogenic centres, seven carbon-carbon double bonds, two 2,4-disubstituted oxazoles and four tetrahydropyran (THP) units. These structural motifs are arranged into a C1-C26 macrolide, which contains an unprecedented oxazole-trisoxane fused system, and a C27-C46 tail.

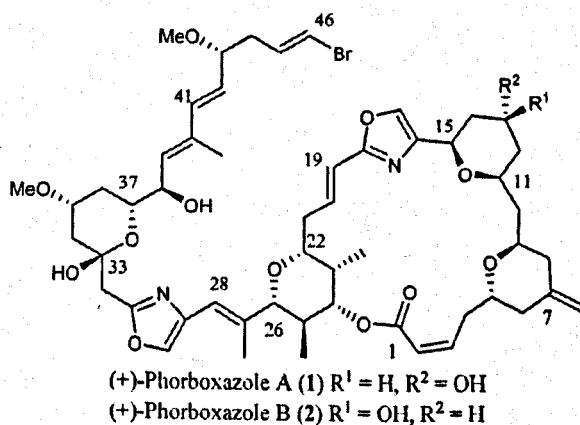


Figure 1: The structures of the phorboxazoles

The absolute configurations of the phorboxazoles were confirmed soon after by the use of MTPA ester analysis and comparison of ¹H NMR spectroscopy data with a model system.⁸ This new class of macrolide was considered to be a very important discovery due to not only the phorboxazoles' unique molecular architecture, but also their extreme potency against a variety of human solid tumour cell lines. They exhibited mean GI₅₀ values of 8×10^{-10} M against the sixty cell lines at the National Cancer Institute of the USA, and are thus among the most potent cytostatic naturally occurring species to be discovered. Although the mode of action has yet to be elucidated, phorboxazole A has been found to arrest the tumour cell cycle at the S-phase, without affecting tubulin.⁹

Following the first reported total synthesis of (+)-phorboxazole A by Craig Forsyth,¹⁰ the biological evaluation of a number of structural analogues (Figure 2) were assessed as a means ascertaining which of the structural motifs were essential for the maintenance of the molecule's potency against a sample of tumour cell lines.¹¹

Compound	NALM-6 Leukemia IC ₅₀ (nM)	BT-20 Breast cancer IC ₅₀ (nM)	U373 Brain tumour IC ₅₀ (nM)
1	1.7	3.4	6.7
3	4.8	12.6	27.4
4	5.2	11.3	29.2
5	>2000	>2000	>2000
6	>2000	>2000	>2000
7	>2000	>2000	>2000
8	>2000	>2000	>2000
9	>2000	>2000	>2000

Table 1: Effect of (+)-phorboxazole A and various structural analogues on proliferation of human cancer cells¹¹

A side-by-side comparison was undertaken of the compounds' antiproliferative activity against the human B-lineage acute lymphoblastic leukaemia cell line NALM-6, human breast cancer cell line BT-20, and human brain tumor (glioblastoma) cell

line U373 (Table 1). The data revealed that some minor structural modifications would not result in substantial loss of anticancer activity. For instance, replacement of the C46 vinyl bromide in **1** with an alkyne **3** did not have a drastic effect. Likewise for the replacement of the C33 hemi-acetal with a mixed methyl acetal **4** was similarly ineffectual.

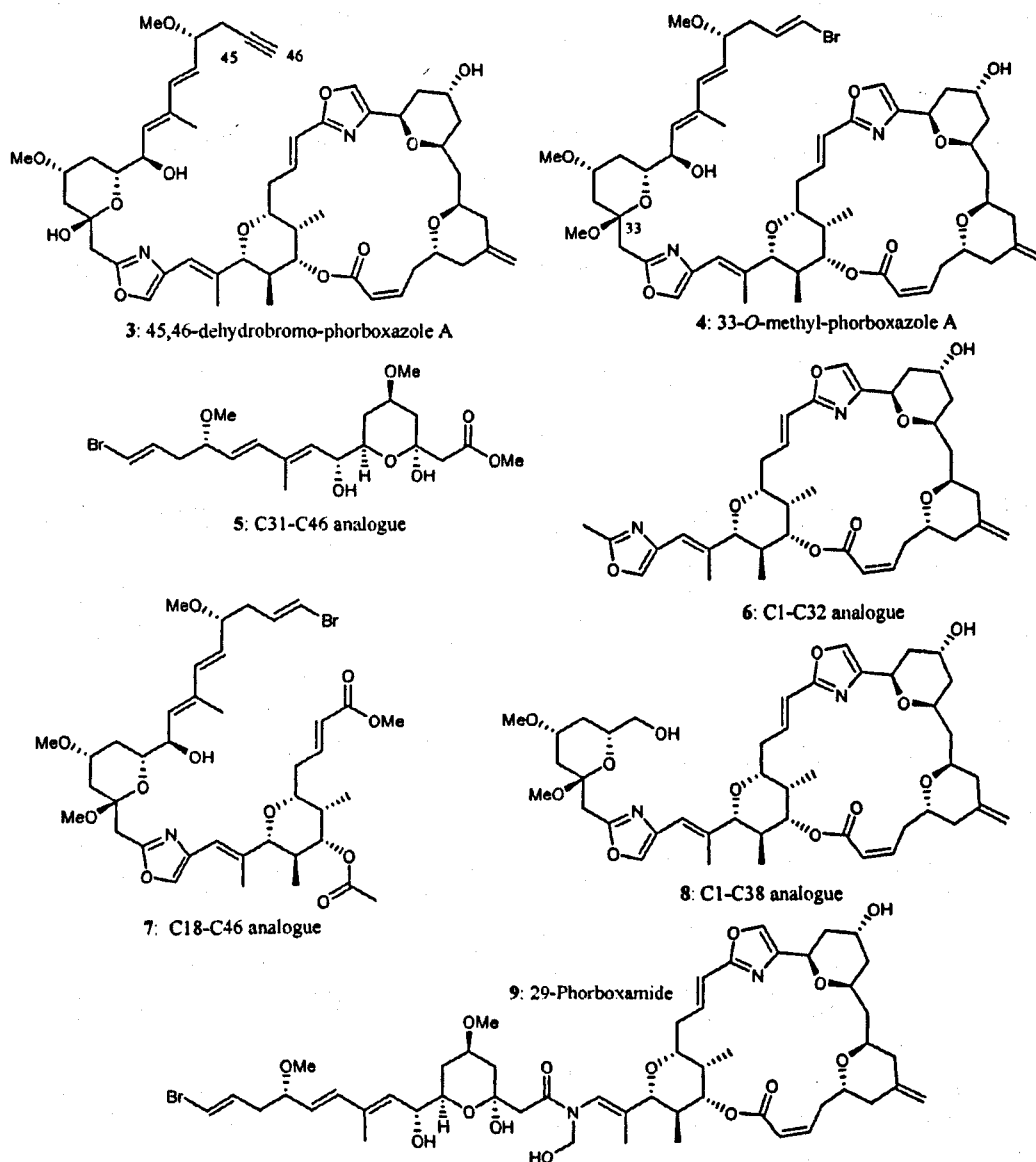


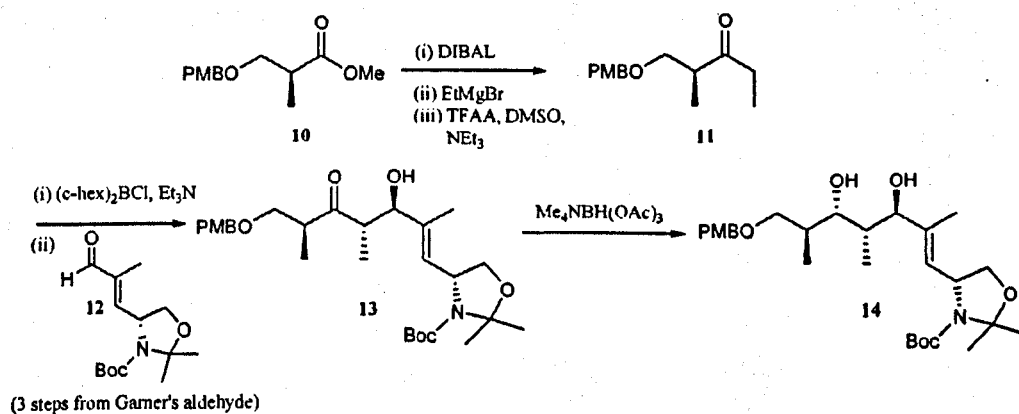
Figure 2: Forsyth's synthetic analogues of (+)-phorboxazole A

However, it was evident that key structural features were required for the maintenance of anticancer activity. Neither the C31-C46 side chain **5** nor the C1-C32 macrolide **6**

could sustain activity alone. Removal of the *bis*-pyran motif results in a severe loss in activity as displayed by 7. Likewise, activity could not be sustained upon removal of the C29 oxazole motif (9), whereas maintenance of this central oxazole but loss of the unsaturated chain (8) yielded a similar loss in activity. More recently, Forsyth has shown fluorescently labelled phorboxazole derivatives to induce association of cell-cycle dependent kinase 4 (cdk4), and perturbation of cdk4 is known to inhibit cell cycle progression at the G1/S phase.¹²

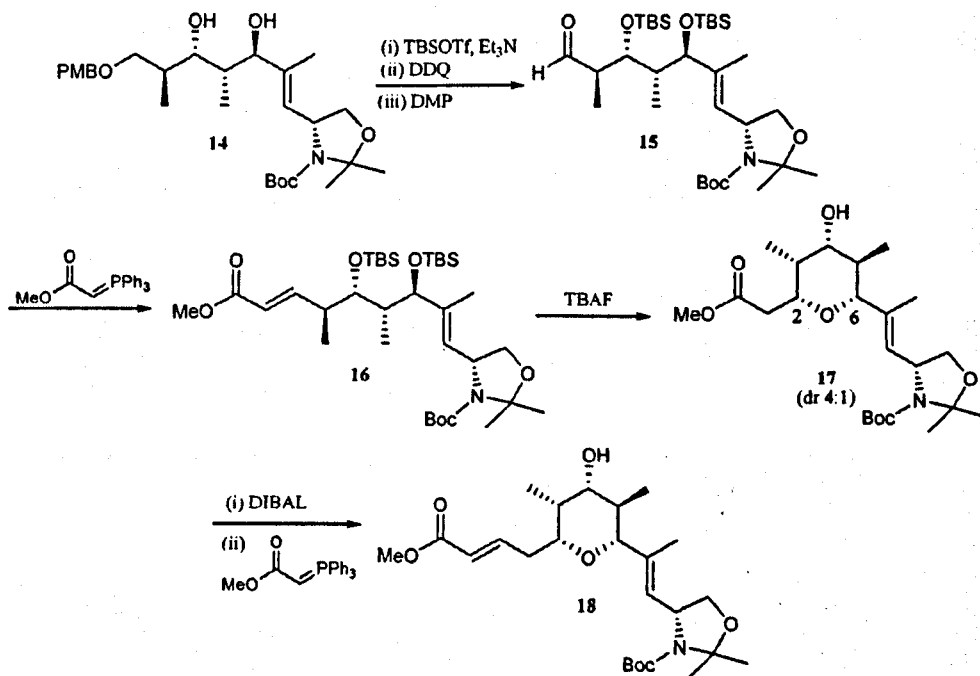
5.2.2 Previous Syntheses of the C20-C32 Fragment

To date, there have been five groups to have reported total syntheses of phorboxazole A,^{10,13-16} while three more have reported total syntheses of phorboxazole B.¹⁷⁻¹⁹ In each of these syntheses, emphasis was placed upon the asymmetric assembly of the THP functional groups. A wide range of chemistry has been encompassed in the various syntheses the C22-C26 tetrahydropyran central core, which contains five of the molecule's fifteen stereogenic centres. In six of the eight approaches, the stereochemistry around the ring was installed *via* the formation of an enantiomerically enriched acyclic precursor, prior to cyclisation.^{10,14-18}



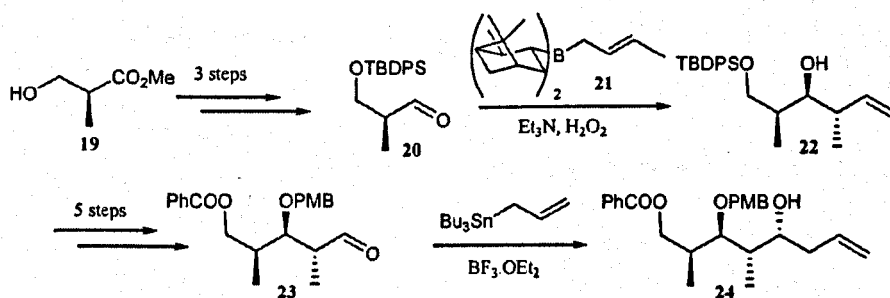
Scheme 1: Forsyth's assembly of enantiomerically enriched acyclic precursor 14

The first approach to be reported was that of Forsyth and co-workers.²⁰ At the time, the absolute configuration of the phorbaxozoles had yet to be established, so the synthesis was undertaken in an arbitrary enantiomeric series. Coincidentally, the correct enantiomeric series was chosen. An acyclic intermediate **14** was synthesised with the required relative stereochemistry in five linear steps from the commercially available (*S*)-3-(*p*-methoxybenzyl)oxy-2-methyl propionate (**10**) (Scheme 1). The installation of the acyclic stereotetrad **14** hinged on a combination of (*E*)-enol borinate aldol chemistry²¹ and Evans' β -hydroxy directed ketone reduction methodology.²² Thus the formation of the (*E*)-enol borinate from ketone **11**, followed by reaction with an α,β -unsaturated aldehyde **12** afforded the *anti-anti* β -hydroxy ketone **13** in 66% yield. β -Hydroxy directed ketone reduction using tetramethylammonium triacetoxyborohydride resulted in the formation of the 1,3-*anti* diol **7** in 89% yield, and thus completed the installation of the required stereogenic centres prior to cyclisation.



Scheme 2: Intramolecular hetero-Michael cyclisation to form 2,6 *cis* THP **19**

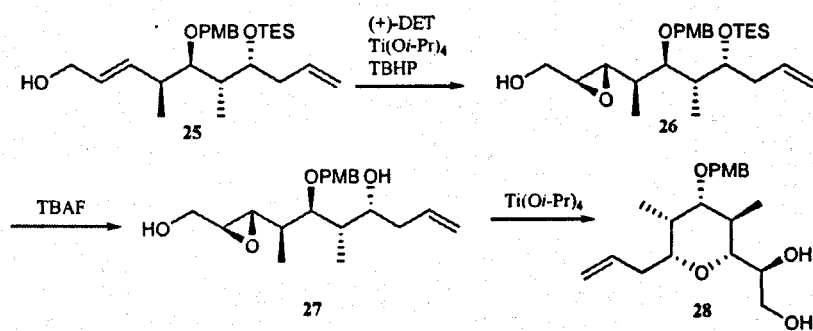
Tetrahydropyran formation proceeded upon fluoride promoted removal of the TBS protecting groups from **16** via an intramolecular 1,4-addition. The THP **17**, equatorially substituted at C2 and C6, was isolated as a 4:1 mixture of diastereoisomers, in only 46% yield. Reduction of the ester to the aldehyde and subsequent treatment with methyl (triphenylphosphoranylidene)-acetate revealed the α,β -unsaturated ester functionality in **18**. Overall, Forsyth's synthesis of this fragment was twelve linear steps in length from **10**, with most transformations proceeding in good yields; the only exception being the intramolecular hetero-Michael cyclisation. It played a key role in the first reported synthesis of (+)-phorboxazole A (**1**) in 1998,¹⁰ which was a remarkable achievement considering it was assembled so soon after the structure of **1** had been elucidated.



Scheme 3: Pattenden's synthesis of the enantiomerically enriched acyclic precursor **24**

A similar approach to this central tetrahydropyran unit of the phorboxazoles was reported by Pattenden and co-workers in a synthetic study published in 1998.²³ The chiral pool starting material **19** was subjected to a series of three transformations; protection of the alcohol, reduction of the ester to the alcohol and subsequent oxidation to the aldehyde **20** (Scheme 3). The addition of crotyl borane **21** under Brown's conditions furnished the next two stereogenic centres in one step, yielding **22** in 76% yield and excellent diastereoselectivity (96:4 dr).²⁴ A further five steps were

required to afford aldehyde **23**, including protection group manipulations, dihydroxylation of the terminal alkene, and periodate cleavage of the resulting diol. Felkin-Ahn controlled addition of allyltributyltin to **23** resulted in the formation of **24**, which contained the fourth contiguous stereogenic centre, in 94% yield and excellent diastereoselectivity (98:2 dr). Alcohol **24** was advanced to **25** in five steps (Scheme 4).

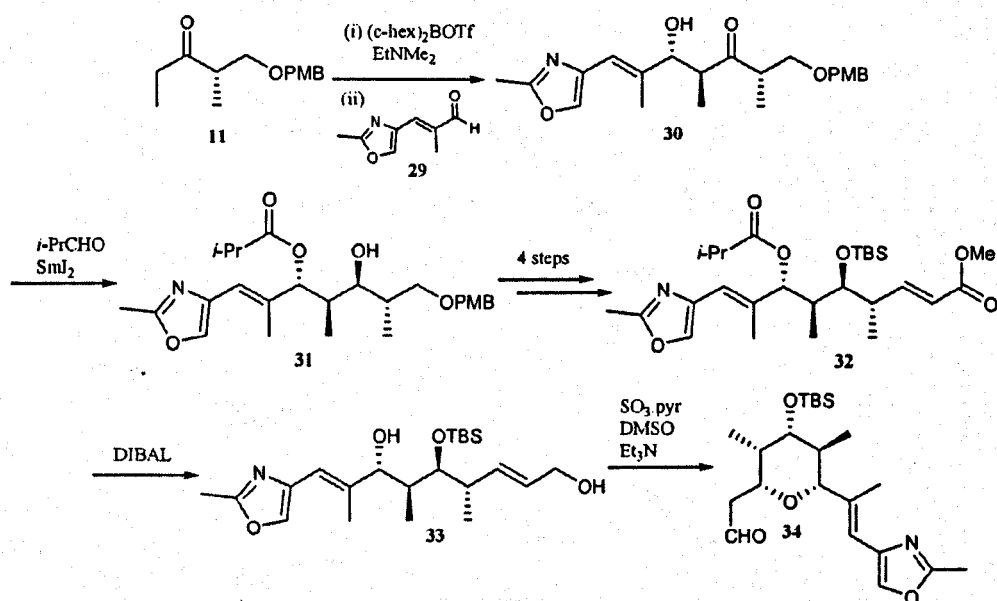


Scheme 4: Intramolecular epoxide opening

A Sharpless asymmetric epoxidation revealed **26** in 95% yield and excellent diastereoselectivity (98:2 dr), and as such furnished the final stereogenic centre prior to cyclisation.²⁵ Removal of the silyl protection with fluoride afforded the hydroxyl group required for the cyclisation. Treatment of **27** with a Lewis acid promoted intramolecular epoxide opening which resulted in the formation of the penta-substituted THP **28**. The synthesis of **28** occurred over 18 steps and in an overall yield of 6% from **20**. A total synthesis of phorboxazole A was reported by the Pattenden group in 2003.¹⁴

Although there is no reported total synthesis from Paterson and co-workers, a synthetic study on the formation of the C20–C32 fragment of the phorboxazoles was published in 1998.²⁶ The synthetic route is related to Forsyth's in that it hinges upon an initial asymmetric aldol reaction, followed by a β -hydroxy directed reduction of a ketone, and finishing with an intra-molecular hetero-Michael addition as a means of

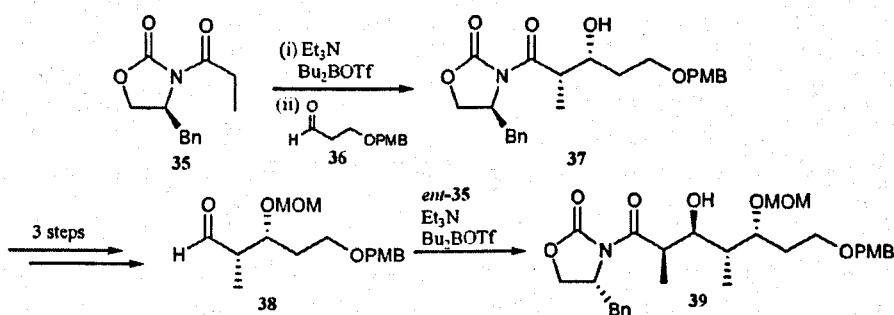
THP formation. However, Paterson's route is more concise, affording a more highly functionalised fragment **34** in eight linear steps from the common chiral ketone **11** (Scheme 5), as opposed to Forsyth's nine steps.



Scheme 5: Paterson's use of an intramolecular hetero-Michael addition

Thus, an *anti*-selective aldol addition of the *(E)*-enol borinate of **11** to the known aldehyde **29**,²¹ produced the β -hydroxy ketone **30** in 94% yield and excellent diastereoselectivity (97:3 dr). Next, a modified Evans-Tischenko reduction²⁷ of the ketone resulted in the formation of the 1,3-*anti* reduction product **31** in 86% yield and excellent diastereoselectivity (97:3 dr). A further four steps were required to introduce the α,β -unsaturated carbonyl functionality, required for the Michael addition. Silyl protection of the hydroxyl group in **31** proceeded with some observed migration of the butyrate group. The resulting regioisomers could be separated, but this migration was responsible for a decrease in yield to 70% for the silyl protection step. Nevertheless, the differential protection of the 1,3-*anti* hydroxyls would prove to be step-saving later on in the synthesis. Next, removal of the PMB protection and Swern oxidation of the free hydroxyl revealed an aldehyde which underwent a Horner-

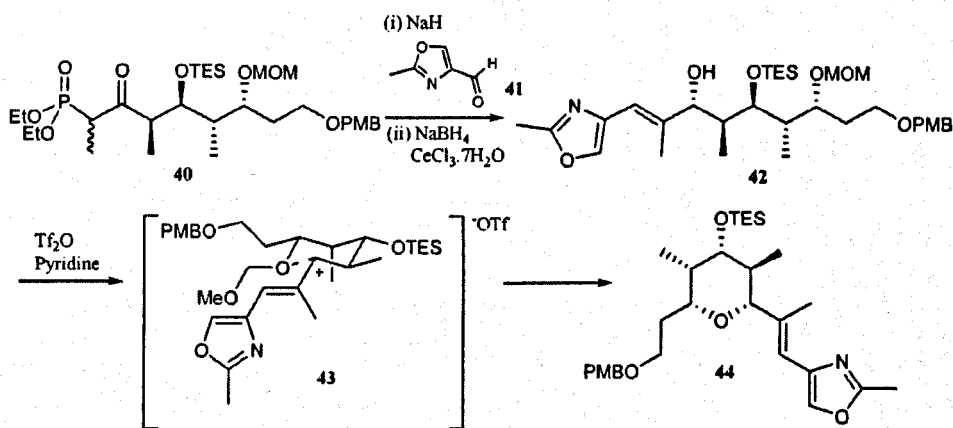
Wadsworth-Emmons olefination with trimethyl phosphonoacetate to yield the α,β -unsaturated ester **32**. Reduction of both ester groups in **32** was brought about by treatment with DIBAL to reveal the diol **33**. Finally, selective oxidation of the primary hydroxyl under Parikh-Doering conditions²⁸ induced the required intramolecular hetero-Michael cyclisation to **34**. The THP **34** was formed as a separable 4:1 mixture of diastereoisomers in 81% yield from **33**. The overall yield of the route was 30% from **11**, establishing this work as a significant contribution to the synthesis of the C20-C32 THP central core of the phorboxazoles.



Scheme 6: Williams' use of consecutive asymmetric aldols

Williams and co-workers published a synthetic study in 1999, which documented the syntheses of both the C20-C32 central core and the C1-C19 *bis*-pyran subunits.²⁹ *En route* to the central core, the use of successive asymmetric aldol reactions, using Evans' oxazolidinone auxiliaries **35** and *ent*-**35**, assembled **39** in only five steps (Scheme 6). Reaction of the (*Z*)-enolate of **35** with aldehyde **36** furnished the *syn* aldol product **37** in 96% yield. Three further steps; MOM-protection of the hydroxyl, removal of the oxazolidinone auxiliary, and Swern oxidation of the resulting alcohol accessed aldehyde **38**. Aldehyde **38** was then used in another *syn* selective aldol reaction using the auxiliary *ent*-**35** to give **39** in 83% yield. Silyl protection of the hydroxyl in **39**, followed by auxiliary removal with BnOLi revealed the benzyl ester. Claisen condensation of the benzyl ester with the carbanion of ethyl

diethylphosphonate resulted in the formation of the β -ketophosphonate **40** in good yield over the three steps. A selective (*E:Z* / 15:1) Horner-Emmons condensation with 2-methyloxazole-4-carboxaldehyde **41**³⁰ followed by diastereoselective Luche reduction³¹ (7:1 dr) revealed the cyclisation precursor **42** in good yield (Scheme 7).

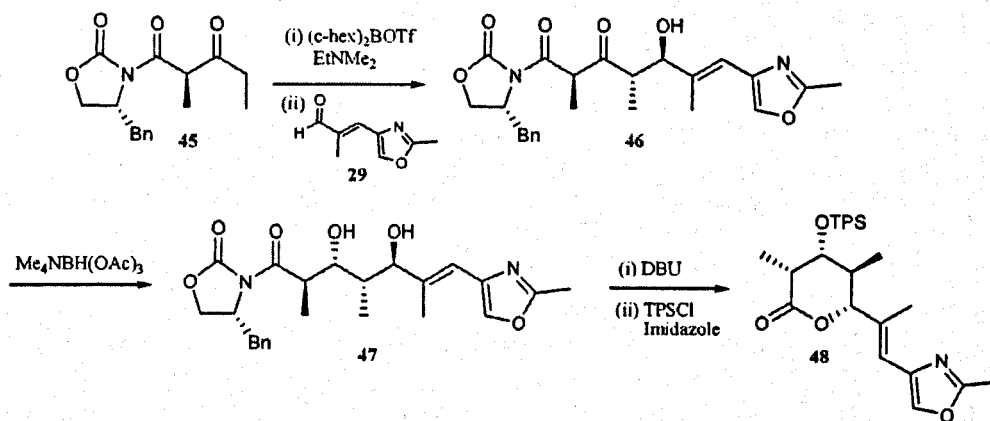


Scheme 7: Cyclisation via allyl cation formation

The formation of a single tetrahydropyran product **44** was observed upon treatment of **42** with triflic anhydride and pyridine, in only 43% yield. When the minor diastereoisomer from the Luche reduction was submitted to the same conditions, the formation of the same diastereoisomer of the tetrahydropyran product **37** was obtained. This indicated that cyclisation had occurred by means of nucleophilic attack of the methoxymethyl ether onto the allyl cation **43**, followed by elimination of the MOM ether. Overall, Williams' route to the central core bore similar success to Forsyth's since it comprised of only eleven steps, of which all were highly yielding with the exception of the cyclisation step. The synthesis afforded the THP **44** in 12% yield from **35**.

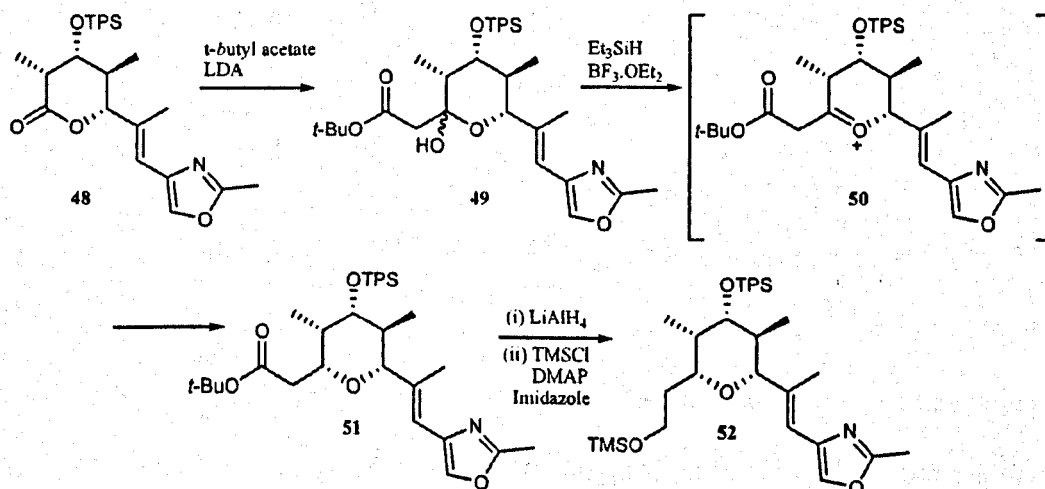
In 2000, Evans published a total synthesis of (+)-phorboxazole B which relied upon complex aldol reactions to install the required stereochemistry in the molecule.¹⁷ The synthesis of the C20-C32 fragment of the molecule commenced with an *anti*

selective aldol reaction between known aldehyde **29**³⁰ and (*E*)-boron enolate of β -ketoimide **45** (Scheme 8).



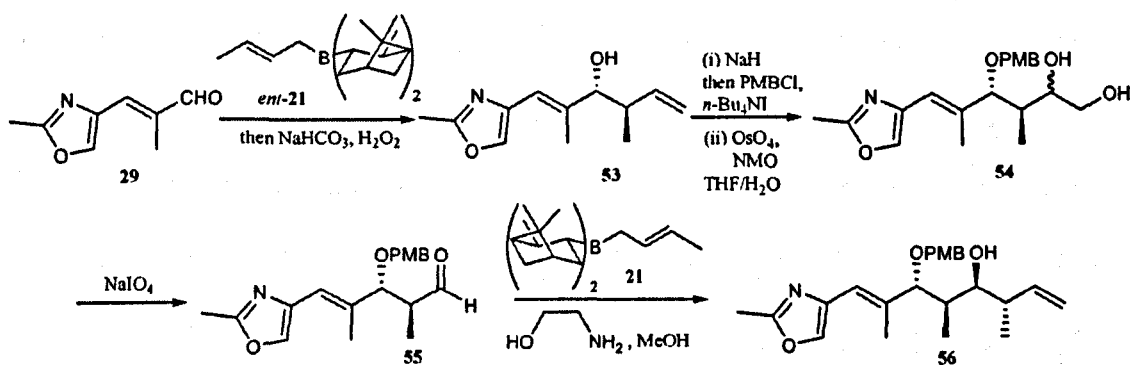
Scheme 8: Evans' route to the penta-substituted THP core *via* lactone **48**

The asymmetric synthesis of **45** had been established from previous methodology studies conducted in the same research group.³² Thus, the aldol reaction afforded **46** with the desired *anti* relationship in 97% yield and excellent diastereoselectivity (94:6 dr). A hydroxyl directed borane reduction of the ketone in **46** revealed the 1,3 *anti* diol **47** as a single diastereoisomer in 81% yield. Cyclisation to the lactone **48** was then induced under basic conditions. The displacement of the oxazolidinone in this way obviates the need for an additional step dedicated to its removal.



Scheme 9: Diastereoselective reduction of of hemi-ketal **49**

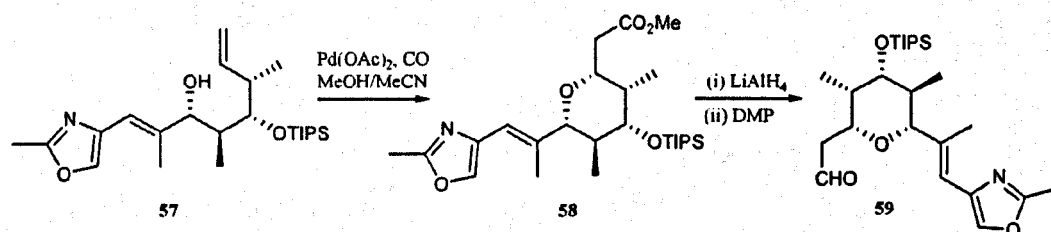
Treatment of the lactone **48** with the enolate of *tert*-butyl acetate resulted in the formation of the hemi-ketal **49** (Scheme 9). Reduction of the hemi-ketal proceeded by treatment of **49** with triethylsilane in the presence of a Lewis acid. The transformation occurs by means of the Lewis acid promoted formation of the oxocarbenium ion **50**, which was subsequently reduced *via* pseudo-axial hydride delivery from triethylsilane to afford the 2,6-*cis* THP **51** in 91% yield and excellent diastereoselectivity (95:5 dr). With installation of the correct stereochemistry complete, the *tert*-butyl ester was reduced using lithium aluminium hydride, and the resulting alcohol was silyl protected to provide the THP **52**. Evans' synthesis of the C20-C32 penta-substituted THP core of the phorboxazoles is an outstanding example of stereoselective synthetic chemistry, since **52** was synthesised in only eight steps from **45** in an overall yield of 59%.



Scheme 10: White's use of iterative asymmetric crotyl additions

A synthetic study, published in 2001 by White and co-workers,³³ detailed the use of successive asymmetric crotylations as a means of installing the required stereochemistry in the acyclic precursor **56** (Scheme 10). Treatment of aldehyde **29**²⁸ with the chiral boron reagent *ent*-**21**, derived from (*E*)-but-2-ene, *n*-butyllithium, potassium *tert*-butoxide, and (+)-*B*-methoxydiisopinocampheylborane, under Brown's conditions²⁴ furnished the *anti* addition product in 67% yield, with excellent diastereoselectivity (96:4 dr). The hydroxyl was then protected as the *para*-methoxy

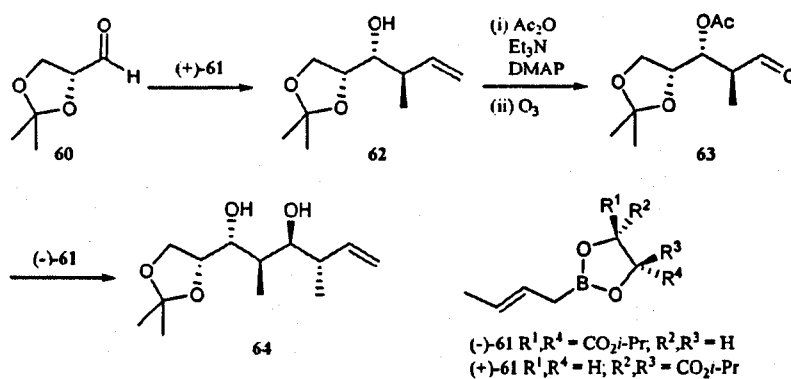
benzyl ether and the terminal alkene underwent selective dihydroxylation with osmium tetroxide to reveal the diol **54**. Oxidative cleavage of the diol with sodium periodate afforded the aldehyde **55**, which was then subjected to a further asymmetric crotylation. Treatment of aldehyde **55** with the chiral crotyl borane **21** resulted in the formation of the acyclic precursor **56** in only 53% yield, as a 6:1 mixture of separable diastereoisomers.



Scheme 11: Pd(II)-mediated cyclisation to the C20 – C32 THP

Nevertheless, silyl protection of the resulting hydroxyl groups, followed by removal of the PMB-group under the mild conditions of aluminium trichloride and ethanethiol yielded the hydroxyl alkene **57**.³⁴ Standard conditions for the PMB-removal had resulted in the observed oxidation of the allylic alcohol. Work within the White group had previously involved construction of THP units *via* an intra-molecular alkoxy carbonylation, which was mediated by a stoichiometric amount of palladium(II).³⁵ Thus, treatment of **57** with palladium(II) acetate in methanol under an atmosphere of carbon monoxide furnished THP **58** as a single diastereoisomer in 86% yield (Scheme 11). However, it was found that the necessary inclusion of a nitrile cosolvent such as acetonitrile caused a deactivation of the palladium species, and as such three equivalents of palladium(II) acetate were required to drive the reaction to completion. Nevertheless, this is the highest reported yield for an intramolecular cyclisation of an enantiomerically enriched acyclic precursor in the syntheses of the central THP of the phorboxazoles. Reduction of the methyl ester with lithium aluminium hydride,

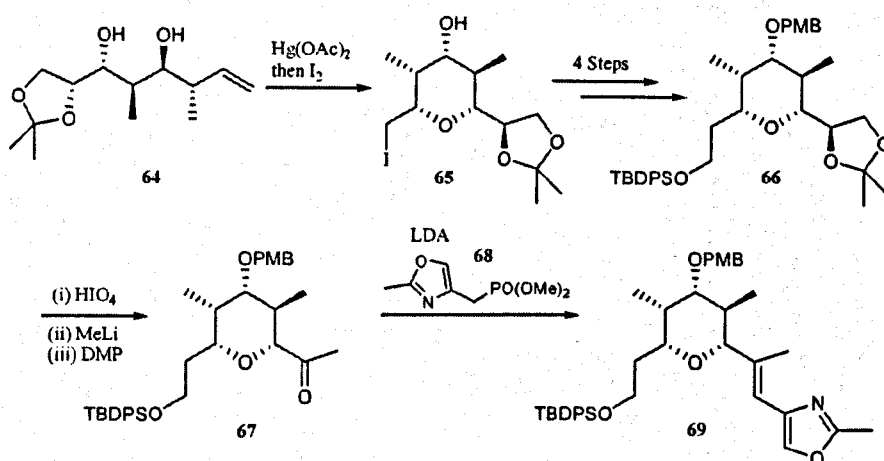
followed by oxidation with DMP revealed the aldehyde **59**, which was analogous to Paterson's C20–C32 fragment **33** of the phorboxazoles (Scheme 5). White's route is ten linear steps in length and produced THP **59** in an overall yield of 7% from aldehyde **29**. The White group published their total synthesis of (+)-phorboxazole A in 2006.¹⁶



Scheme 12: Zhou's use of iterative asymmetric crotyl additions

A very similar approach to White's was reported by Zhou, first of all in a synthetic study published in 2003,³⁶ and again in a full paper on the total synthesis of (+)-phorboxazole B in 2005.¹⁸ The similarities in the routes towards the synthesis of the C20–C32 THP central core include the use of successive asymmetric crotyl additions as the means of installing the required stereochemistry of the four contiguous stereogenic centres in the acyclic precursor **64**, and the use of an intramolecular cyclisation *via* attack of an hydroxyl onto an activated alkene. Thus aldehyde **60**, which is readily accessible from D-mannitol, underwent an asymmetric crotylation *via* addition of chiral boronate (-)-**61**, under Roush's conditions,³⁷ to reveal homoallylic alcohol **62** in 65% yield. The hydroxyl group was then protected as its acetate and the terminal alkene was converted to the aldehyde **63** *via* ozonolysis. A second asymmetric crotylation between aldehyde **63** and the chiral boronate (+)-**61** under Roush's conditions, proceeded to give a homoallylic alcohol. The work-up procedure

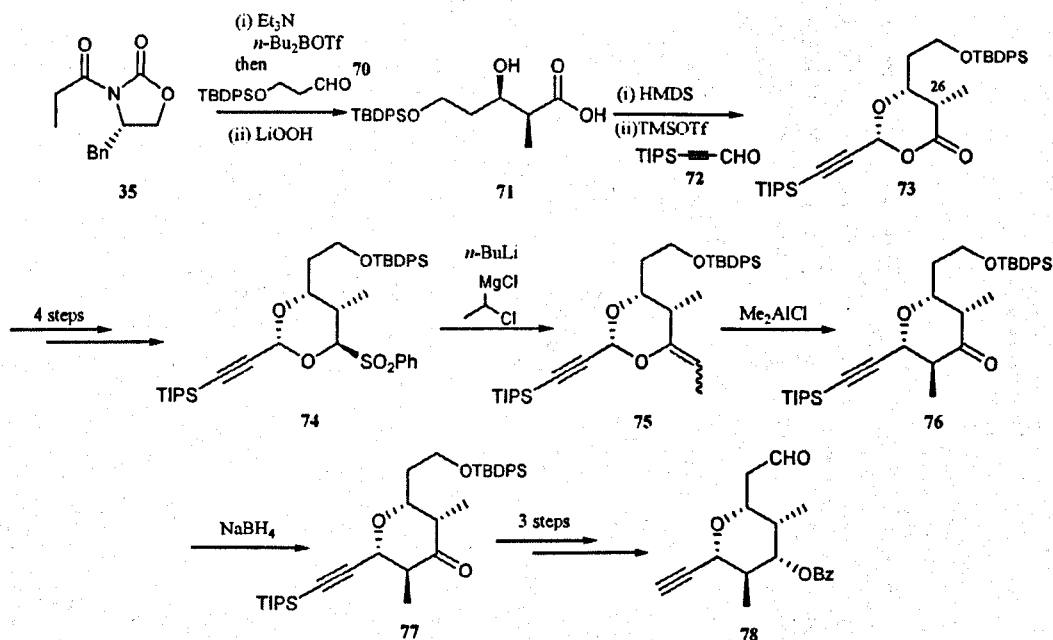
required the use of sodium hydroxide for the cleavage of the B-O bond. Treatment with sodium hydroxide resulted in concomitant hydrolysis of the ester, and as such providing access to the desired diol **64**, in 70% yield.



Scheme 13: Hg(II) promoted cyclisation to the C20 – C32 THP core.

Treatment of the diol **64** with first mercury(II) acetate and then iodine, resulted in the formation of THP **65** in 86% yield. The product existed as a 5:1 mixture of separable 2,6-*syn*:2,6-*anti* diastereoisomers. A further four steps were required to access **66**; protection of the hydroxyl as the PMB ether, S_N2 displacement of the iodide with cyanide, reduction of the nitrile to an hydroxyl group its subsequent silyl protection. Treatment of **66** with periodic acid caused both removal of the acetonide protection and oxidative cleavage of the resulting diol to afford an aldehyde. Next, treatment of the aldehyde with methyl lithium resulted in the formation of a secondary alcohol which underwent oxidation with DMP to the ketone **67**. Finally, olefination was carried out after reference to Pattenden's total synthesis, which details the use of the oxazole phosphonate ester **68** in a (*E*)-selective Wadsworth-Emmons reaction.¹⁴ Thus, treatment of ketone **67** with **68** under basic conditions revealed **69**, but in only 58% yield, which was comparable to Pattenden's. Overall, Zhou's synthesis of the C20-C32 fragment was thirteen steps in length and occurred in 3.8% yield from **60**.

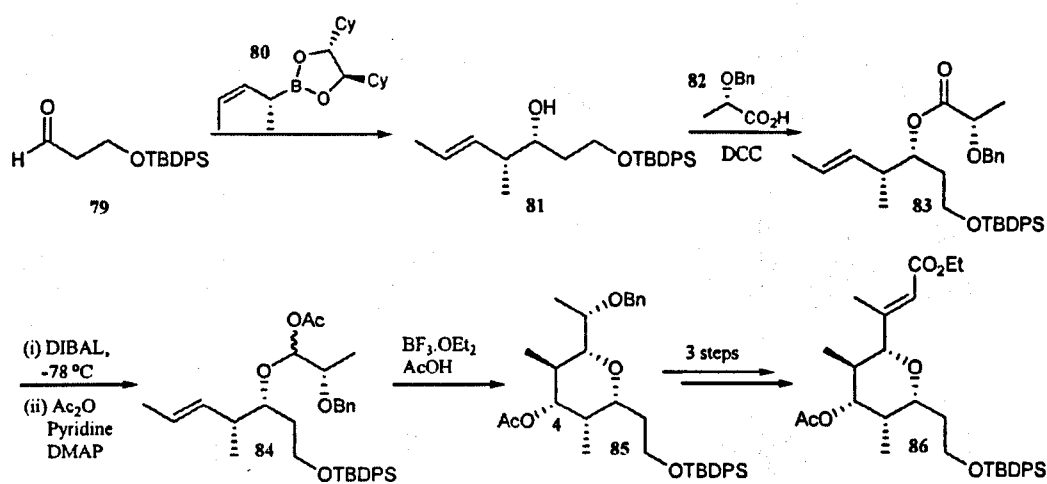
A novel synthesis of the C20-C28 THP core was reported by Smith and co-workers.³⁸ An enantiomerically pure coupling fragment containing the central THP unit of the phorbaxozoles was synthesised in thirteen linear steps.



Scheme 14: Smith's synthetic study towards the core THP unit

This synthesis exploits the Petasis-Ferrier union/rearrangement of a dioxanone as a means of both forming the THP unit and installing one of the stereogenic centres in a single step. The first two stereocentres were installed *via* the aldol condensation of the boron enolate derived from Evans's oxazolidinone **35**³⁹ with aldehyde **70** to form the *syn*- β -hydroxy acid **71** in 84%, upon cleavage of the auxiliary with lithium peroxide (Scheme 14). *bis*-Silylation followed by TMSOTf-promoted condensation with aldehyde **72** afforded the dioxanone **73** in 66% yield as a 3:1 mixture of diastereomers, epimeric at C26. A further four steps were required to incorporate the sulfone **74**, before an *exo*-olefin moiety was installed *via* a Julia protocol as a 1:1 mixture of (*E*):(*Z*) isomers **75**.⁴⁰ When subjected to Petasis-Ferrier conditions, however, this 1:1 mixture of isomers was found to yield only the desired

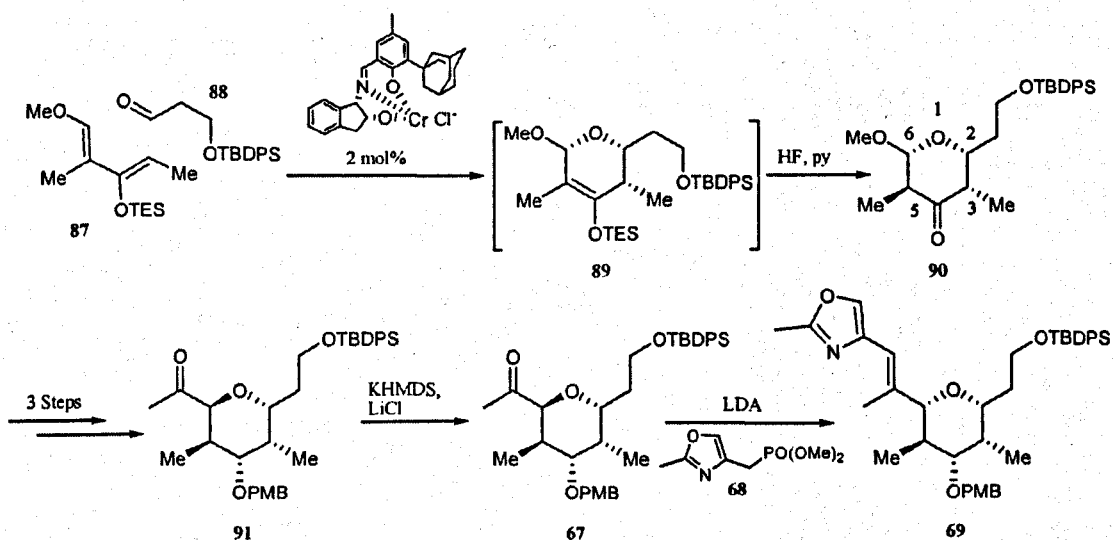
diastereoisomer of tetrahydropyranone (THPO) **76** in 91% yield. The final stereocentre was installed using a diastereoselective sodium borohydride reduction of the ketone, as part of a four step sequence to furnish the coupling fragment **77**. Smith's thirteen-step synthesis produced **77** in an overall yield of 20%. The route was reduced to ten steps in a second generation, multi-gram synthesis of (+)-phorboxazole A reported by the same group and this will be discussed in detail in the next section.⁴¹



Scheme 16: Rychnovsky's use of a Prins cyclisation

Although no total synthesis has been published by Rychnovsky and co-workers, a synthetic study, published in 2000,⁴² demonstrated the power of the Prins cyclisation methodology that had been previously established within the group.⁴³ The synthesis commenced with coupling of aldehyde **79**, available in two steps from 1,3-propanediol, with Hoffmann's chiral (*Z*)-pentenyl boronate **80** to produce *syn* adduct **81**.⁴⁴ The use of DCC-coupling with *O*-benzyl (*S*)-lactic acid (**82**) then afforded the ester **83** in 53% yield over the first two steps. Reduction of the ester to the hemiacetal with DIBAL, followed by acetylation to the α -acetoxyether proceeded to give **84** in 91% yield. Treatment of **84** with boron trifluoride diethyl etherate in the presence of excess acetic acid revealed the THP **85** in 53% yield as a single diastereoisomer. Treatment with boron trifluoride diethyl etherate alone resulted in predominantly

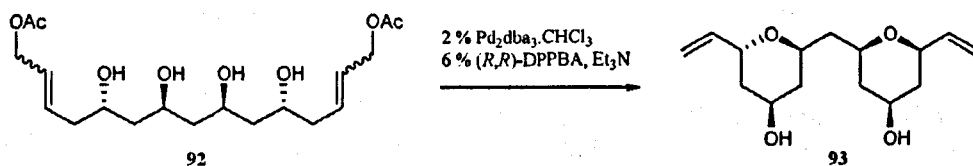
fluoride trapping at C4, which was undesirable. A further three steps were required to give **86**; benzyl group removal, oxidation of the resulting alcohol to the ketone and finally a Horner-Emmons reaction with the anion of triethyl phosphonoacetate. These three steps afforded **86** in 72% but as a 4:1 mixture of geometrical isomers. Overall, Rychnovsky's route yielded THP **86** in 14% yield, in only eight steps from aldehyde **79**, but when comparing the brevity of the synthesis with others, it must be noted that the oxazole functionality at C30 has yet to be introduced. Nevertheless, the level of stereocontrol that was employed in the cyclisation step ensures that Rychnovsky's contribution to the synthesis of the THP central core of the phorboxazoles is regarded as significant.



Scheme 17: Burke's rapid construction of the C22-C26 THP

A synthesis of the C20-C32 fragment of the phorboxazoles, which was reported in 2007 by Burke and co-workers, details a rapid access to the central THP **69** (Scheme 17).⁴⁵ The correct C2, C3 and C5 stereochemistry was installed in the asymmetric one-pot THP ring-forming hetero-Diels-Alder reaction between Danishefsky diene **87**⁴⁶ and aldehyde **88** under Jacobsen conditions⁴⁷ to afford **90** in 77% yield, *via* the silyl enol ether intermediate **89**. Diastereoselective reduction of the ketone at C4 with

sodium borohydride provided the equatorial hydroxyl group in 92% yield, which then underwent PMB-protection. Two further steps were required to introduce a ketone functionality at C6; an initial introduction of an axial nitrile group, followed by treatment with trimethylaluminium in the presence of catalytic Ni(acac)₂ revealed the THP **91**. Epimerisation at the C6 position was induced by treatment of the axial ketone with base. Upon reprotonation, the ketone was observed to adopt a more favourable equatorial position, thus furnishing **67** in 91% yield. Conversion of the equatorial methyl ketone to the trisubstituted alkene proceeded *via* the use of Zhou's endgame in his synthesis of the C20-C32 THP.³⁶ Treatment of **67** with oxazole phosphonate ester **68** proceeded in 68% yield under basic conditions to give the C20-C32 THP central core **69**. Overall, Burke's route to the fragment was only seven steps in length from readily available starting materials and it provided **69** in an overall yield of 20%.

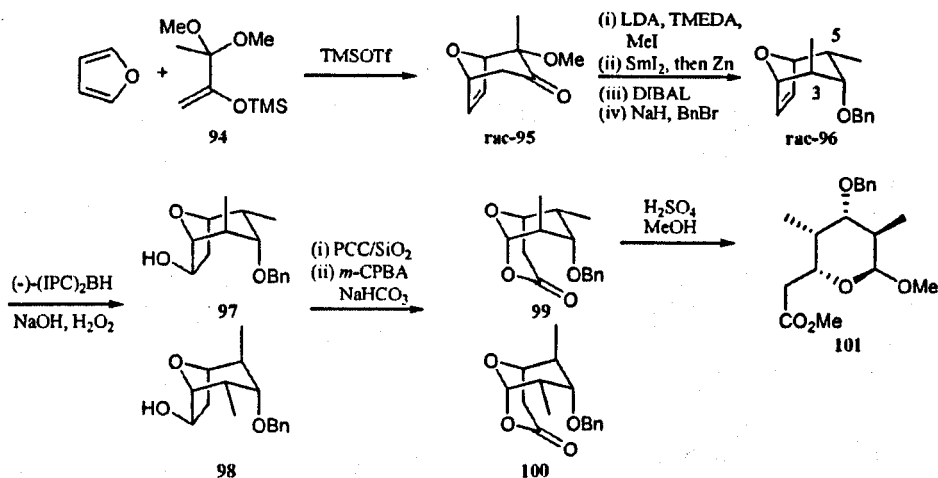


Scheme 18: Rapid assembly of *bis*-pyran sub-unit with correct C2 and C6 stereochemistry

Another noteworthy aspect of Burke's total synthesis, published in 2007,¹⁹ is the rapid construction of the *bis*-pyran moiety *via* palladium (0)-mediated desymmetrisation of *meso* tetraol **92** to yield the *bis*-pyran sub-unit **93** in 75% yield (Scheme 18).⁴⁶ Overall, this is an interesting total synthesis due to the diversity of chemistry employed in the direct assembly of these separate THP systems.

Hoffmann published a piece of THP-forming methodology in 1999, which reported the synthesis of **101** in eight steps from accessible starting materials (Scheme 19).⁴⁹ A Lewis acid promoted [4+3] cycloaddition afforded bicycle *rac*-**95** in 77%

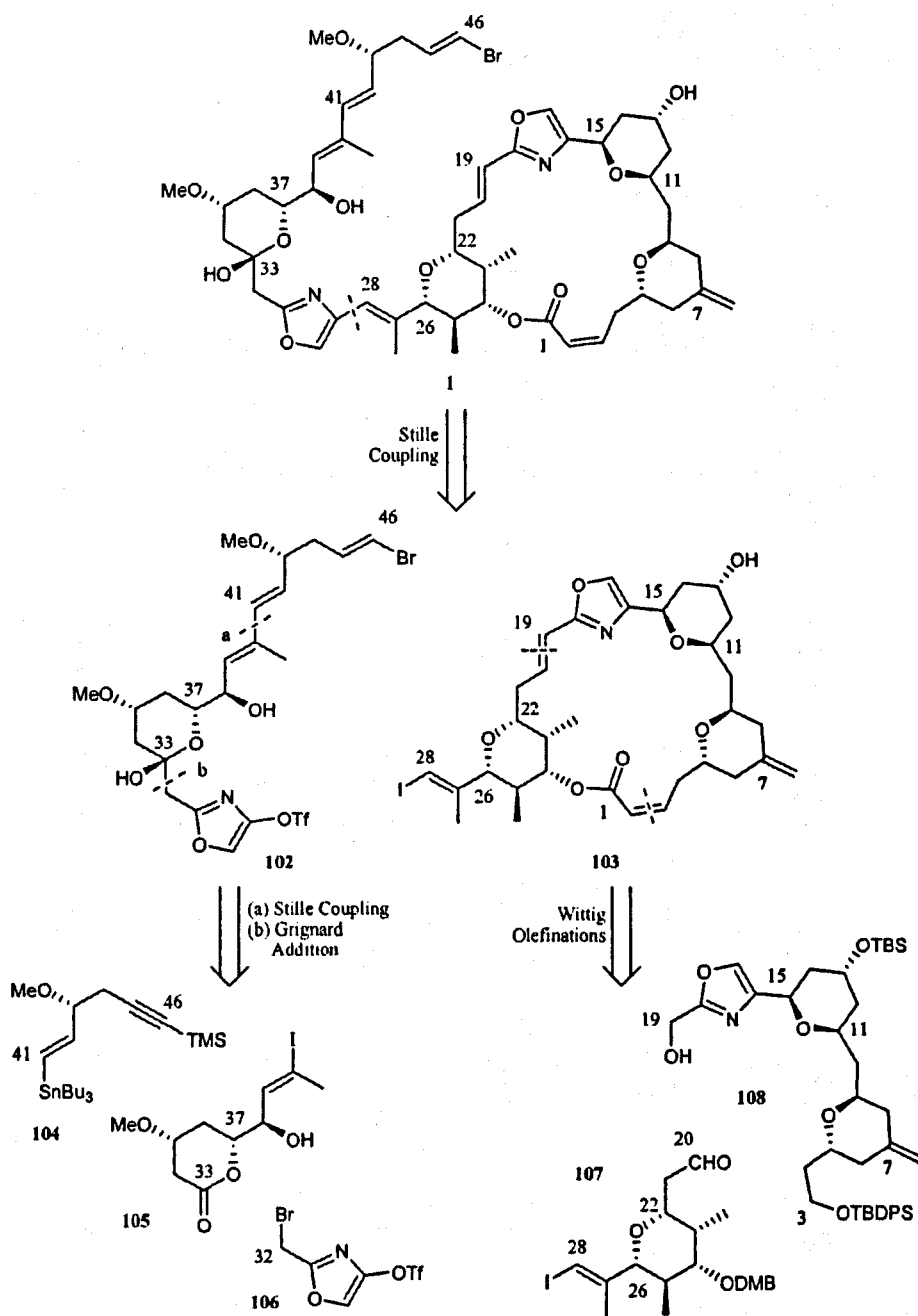
yield and good diastereoselectivity (dr 6:1 / MeO_{eq} : MeO_{ax}). Diastereoselective methylation, followed by SmI₂ reduction furnished a *bis*-methylated THP, which exhibited a 3,5-*anti* relationship.



Scheme 19: Hoffmann's [4+3] cycloaddition

Diastereoselective reduction of the ketone, and subsequent protection achieved **rac-96** in 71% yield over the four steps. Asymmetric hydroboration of the racemate **rac-96** revealed the diastereoisomeric alcohols **97** and **98** in 93% yield. Oxidation with PCC, followed by a regioselective Baeyer-Villiger reaction produced separable lactones **99** and **100** in 82% yield. Methanolysis of **99** proceeded to give **101** in 84% yield. Overall **101** was formed in eight steps and 18% yield from **94**, but it should be noted that **101** would require a lot of further functionalisation before the length of the route can be compared with other syntheses of the core. Firstly, the stereochemistry at C26 is incorrect and would need to be rectified with a S_N2 displacement, and secondly, the attachment of the oxazole unit is required.

5.2.3 Smith's Second Generation Synthesis of (+)-Phorboxazole A



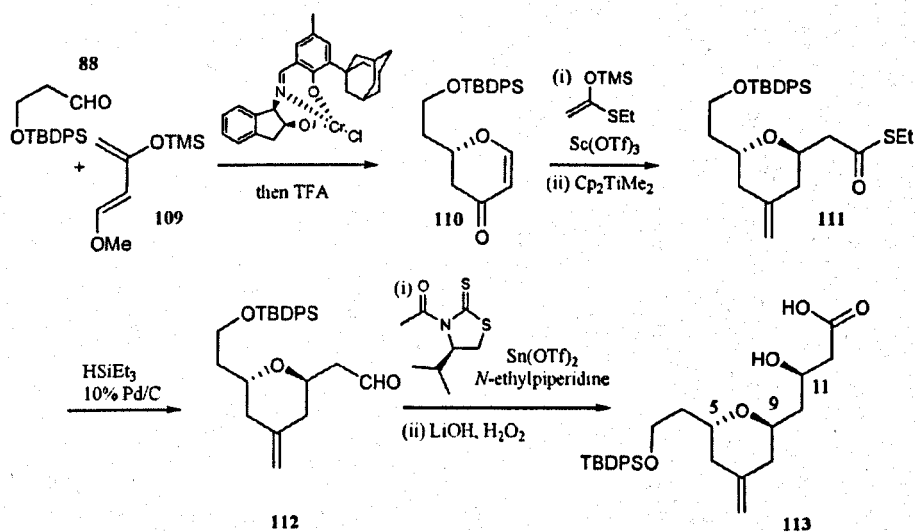
Scheme 20: Smith's retrosynthetic analysis

In 2008, Amos B. Smith III reported a highly convergent second generation synthesis of (+)-phorboxazole A, which was achieved with a longest linear sequence of only 24 steps, the shortest reported to date.⁴¹ Importantly, the high yielding nature of the

Petasis-Ferrier union/rearrangement in the assembly of the C11-C15 and C22-C26 THPs provided access to multigram quantities of the C1-C28 macrolide. Previously, only milligram quantities of the phorboxazoles had been accessible from both isolation and total synthesis. Smith's aim was to synthesise hundreds of milligrams of (+)-phorboxazole A and its analogues for the purpose of their biological evaluation. In order to achieve the highest level of convergence, the late stage coupling of two highly elaborated fragments was foreseen. Retrosynthetic scission of the C28-C29 bond would reveal the C1-C28 macrolide **103** and the C29-C46 tail **102** which could be joined by a Stille union in the forward sense (Scheme 20). The synthesis of the side chain **102** adopted an almost identical approach to Smith's first generation synthesis^{13a}. The vinyl stannane **104** would undergo a Stille union with the vinyl iodide **105** and the resulting dienyl lactone intermediate would undergo a diastereoselective attack of a Grignard derived from oxazole **106**. The overall approach to the macrocycle **103** involved retrosynthetic scission of the olefins to afford the C20-C32 penta-substituted THP **107** and the C3-C19 *bis*-pyran unit **108**. The C2-C3 (*Z*)-enoate would be installed *via* a Still-Gennari modified Horner-Emmons reaction⁵⁰ and the C19-C20 olefin *via* an (*E*)-selective Wittig reaction. It was envisaged that large amounts of the *cis*-pyrans in **107** and **108** could be accessed *via* the Petasis-Ferrier union/rearrangement.^{13a}

The synthesis of the *bis*-pyran unit **108** commenced with an asymmetric Diels Alder reaction of aldehyde **88** with Danishefsky diene **109**⁴⁷ using Jacobsen's catalyst⁴⁸ which afforded the dihydropyranone **110** after treatment with TFA in 85% yield and 95% ee on scales of up to 70 g (Scheme 21). Conjugate addition of a thioenol ether to **110** was promoted by scandium(III) triflate, and treatment of the

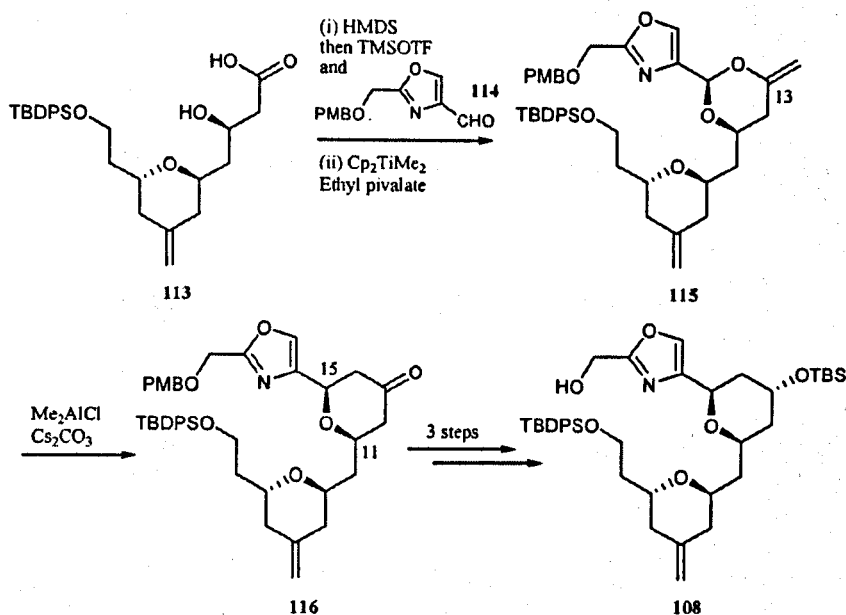
resulting ketone with the Petasis-Tebbe reagent⁵¹ provided **111** as a single diastereoisomer in 75% yield over two steps.



Scheme 21: Assembly of C5-C9 THP

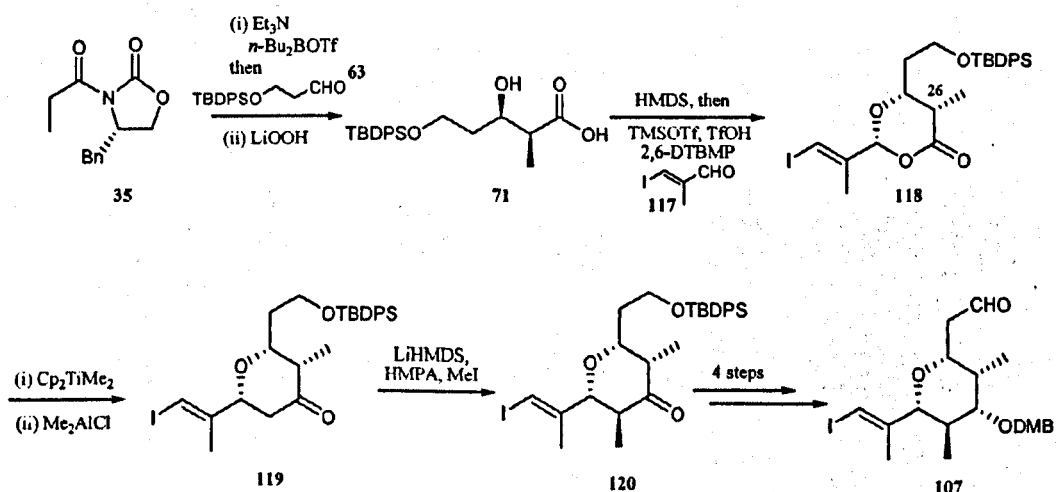
Reduction of the thioester **111** to the aldehyde **112** occurred *via* treatment with triethylsilane in 97% yield on scales of up to 55 g. A tin(II) triflate promoted Nagao⁵² acetate aldol reaction was employed as a means of installing the C11 stereochemistry, which would be responsible for directing the Petasis-Ferrier union/rearrangement. Subsequent removal of the thioimide auxiliary with lithium peroxide revealed the β -hydroxy acid **113** in 90% yield with good diastereoselectivity (10:1 dr).

Dioxanone formation proceeded *via* condensation with oxazole aldehyde **114** in 95% yield with good diastereoselectivity (10:1 dr) on scales of up to 20 g (Scheme 22). Subsequent treatment with the Petasis-Tebbe reagent afforded the *exo*-olefin at C13 in the enol acetal **113**.



Scheme 22: Construction of *bis*-pyran unit **108** via Petasis-Ferrier union/rearrangement

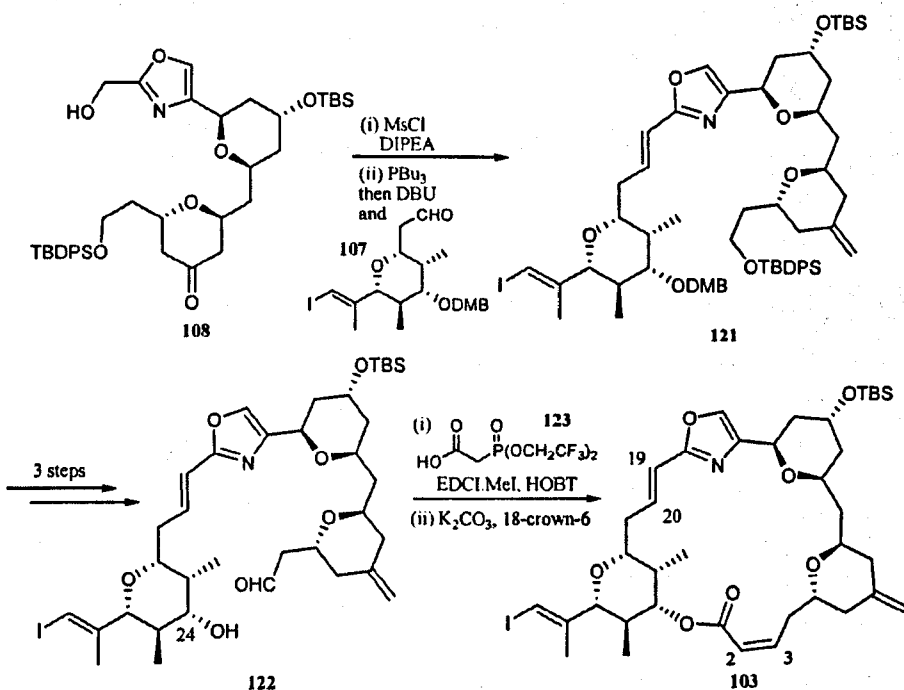
The enol acetal was found to be unstable to prolonged silica purification on scales over 1 g, so the crude enol acetal underwent immediate Petasis-Ferrier union/rearrangement to furnish the C11-C15 THPO moiety of **116** in 66% yield over the two steps. A further three steps; diastereoselective K-selectride reduction of the ketone and subsequent protection group manipulation revealed the *bis*-pyran fragment **108** in 92% yield with good diastereoselectivity (9:1 dr).



Scheme 23: Second generation synthesis of C20-C32 THP

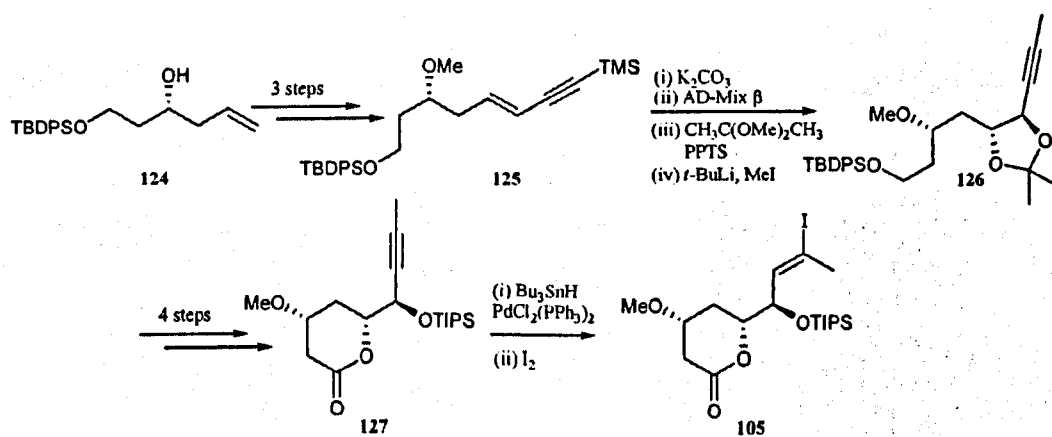
Enantiomerically pure β -hydroxy acid **71** was constructed according to the first generation synthesis (Scheme 23), and subsequently underwent condensation with vinyl iodide aldehyde **117** to produce the dioxanone **118** in 93% yield and excellent diastereoselectivity. At this stage in the first generation synthesis, the analogous dioxanone was converted to an ethylidene acetal, which served as the Petasis-Ferrier union/rearrangement precursor. However this required four steps which weren't deemed to be amenable to 10-15 g scale synthesis. A more direct approach was preferred, thus dioxanone **118** was converted to the enol acetal *via* treatment with the Petasis-Tebbe reagent. Treatment of the enol acetal with dimethylaluminium chloride promoted a Petasis-Ferrier union/rearrangement, accessing the THPO **119** in 78% yield over the two steps. Installation of an equatorial methyl group α to the carbonyl, *via* lithium enolate formation and subsequent iodomethane quench, proceeded to give **120** in 68% yield as a single diastereoisomer. The THPO **120** was converted to the THP **107** by means of a four step protocol that was established in the first generation synthesis, and included the reduction of the ketone with sodium borohydride to afford an equatorial hydroxyl with very good diastereoselectivity (15:1 dr).

The coupling of fragments **108** and **107** at C1-2 and C19-C20 was achieved in six steps (Scheme 24). The construction of the C19-C20 (*E*)-olefin was accomplished in two steps which initially involved the conversion of the alcohol **108** to its mesylate. Treatment of the mesylate with tri-*n*-butylphosphine under basic conditions revealed the phosphonium ylide which underwent condensation with aldehyde **107** to furnish the (*E*)-olefin **121**. This protocol was first developed by Evans in his synthesis of (+)-phorboxazole B,¹⁷ and produced **121** in 95% yield over the two steps with excellent control of the double bond geometry (20:1 *E:Z*), on scales of up to 2 g.



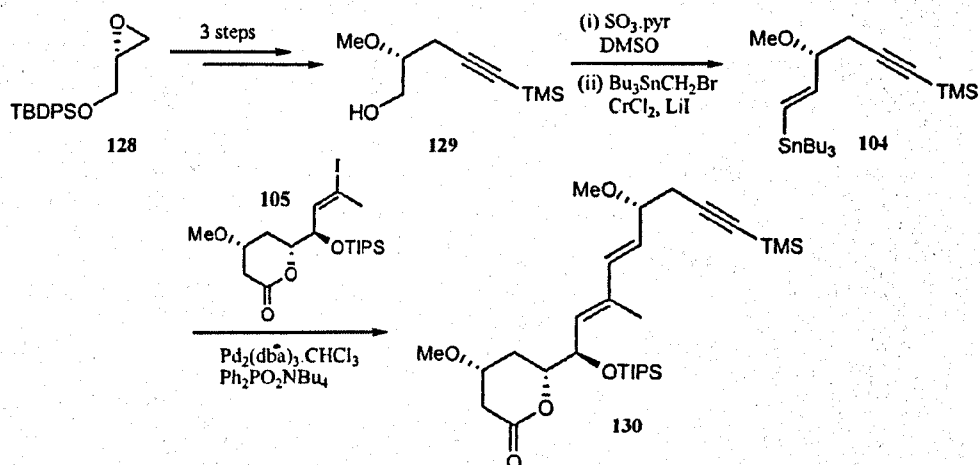
Scheme 24: Coupling of fragments 108 and 107 to form the macrocycle 103

The aldehyde **122** was formed in three steps from **121** and closure of the macrocycle proceeded *via* initial attachment of a two-carbon ester fragment derived from **123**. A subsequent Still-Gennari modified Horner-Emmons olefination,⁵⁰ which achieved **103** as a 2.5:1 mixture of *Z:E* geometrical isomers in 67% yield over the two steps. The macrocycle **95** was synthesised in an overall yield of 20%, and with a longest linear sequence of twenty steps.



Scheme 25: Asymmetric synthesis of lactone 105

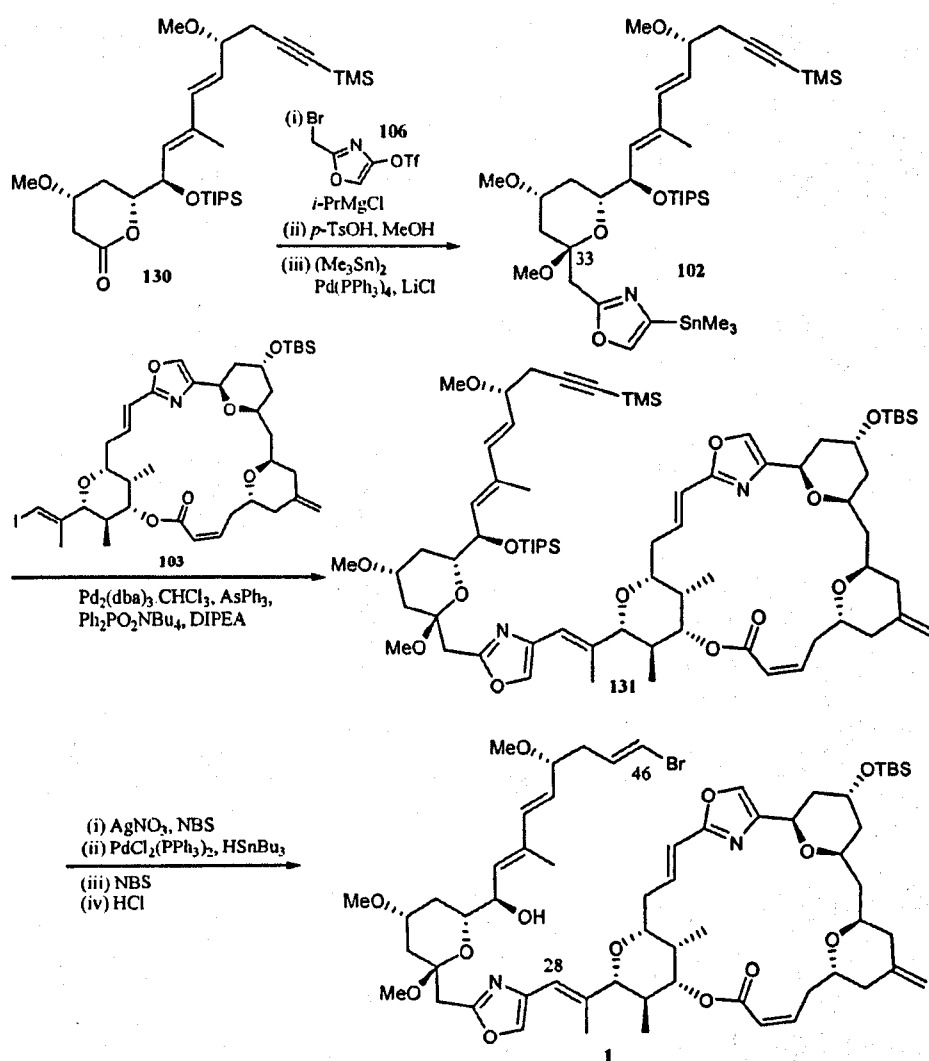
The synthesis of the coupling fragment **105** commenced from the homoallylic alcohol **124** (Scheme 25). Three steps were required for the conversion of the homoallylic alcohol to its methyl ether, and the incorporation of the silyl protected alkyne functionality present in **125**. Removal of the silyl protection, asymmetric dihydroxylation of the olefin, acetonide protection of the resulting 1,2-diol, and methylation of the terminal alkyne proceeded to give **126** in 55% yield over the four steps. A further four steps were required to achieve the assembly of the lactone **127**. Stannylation of the alkyne **127** using $\text{PdCl}_2(\text{PPh}_3)_2$ as a catalyst yielded an inseparable regioisomeric mixture of vinyl stannanes, 5:1 external to internal. However, upon exposure of this mixture to iodine, only the external stannane reacted to produce the (*E*)-vinyl iodide **105** in 76% yield over the two steps.



Scheme 26: Stille coupling of vinyl stannane **104** with vinyl iodide **105**

Elaboration of the side chain progressed with the Stille union of vinyl stannane **104** with **105**. A three step sequence of reactions was performed on the chiral epoxide **128**, which resulted in the installation of the silyl protected alkyne functionality in **129** (Scheme 26). The terminal alcohol was oxidised under Parikh-Doering conditions,²⁸ and vinyl stannylation of the resulting aldehyde was executed using a protocol

developed by Hodgson,⁵³ to furnish the vinyl stannane **104** in 71% yield over two steps. Stille coupling of vinyl stannane **104** with vinyl iodide **105** afforded **130** in 90% yield and the success of this reaction was attributed to the use of $\text{Ph}_2\text{PO}_2\text{NBu}_4$, which was reported by Liebskind to remove the Bu_3SnI by-product, thus accelerating the coupling process.⁵⁴



Scheme 27: Final steps in the synthesis of (+)-phorboxazole A (**1**)

Approaching the end of the synthesis, Smith had proposed to perform a reduction of the alkyne **130** to the (*E*)-vinyl silane, and had developed conditions to do so with a high level of control of the olefin geometry (Scheme 27). Furthermore, coupling of

the resultant vinyl silane fragment to first oxazole **106** and then to the macrocycle **103** proceeded in good yields, however bromodesilylation at C46 proved to be impossible. Instead bromination at C28 was observed. It was therefore necessary to revert to the endgame reported in the first generation synthesis. Exposure of the lactone **130** to the Grignard reagent derived from the oxazole **106** resulted in the formation of a single diastereoisomer of the C33 hemi-acetal. The hemi-acetal was converted to the mixed methyl acetal *via* treatment with tosic acid in methanol, in 73% yield over two steps. Palladium catalysed triflate-trimethylstannane exchange furnished the side chain **102** in 64% yield. Stille union of the side chain **102** with the macrocycle **103** revealed **130** in 68% yield, again exploiting the use of the Liebskind additive $\text{Ph}_2\text{PO}_2\text{NBu}_4$.⁵⁴ The synthesis of (+)-phorboxazole A was completed by first converting **131** to the bromoalkyne in 95% yield. Exposure of this bromoalkyne to $\text{PdCl}_2(\text{PPh})_2$ and Bu_3SnH yielded an inseparable 6:1 regioisomeric mixture of external and internal vinyl stannanes respectively. Bromination of this mixture with NBS did not aid separation, nor did global deprotection with HCl, therefore the use of HPLC was required to separate (+) phorboxazole A **1** from the C45 bromide. Nevertheless **1** was furnished in 35% yield over the final three steps, but there is no mention of the quantity achieved from this route.

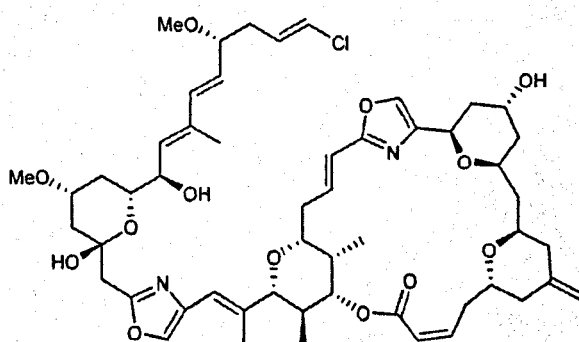


Figure 3: (+)-C46-Chlorophorboxazole A **132**

Overall, Smith's highly convergent synthesis has yielded (+)-phorboxazole A in an overall yield of 4.6%. The high yielding nature of the Petasis-Ferrier union/rearrangement for the formation on *cis*-THPs has provided access to multi-gram quantities of the C1-C28 macrolide **103**. Such quantities of this late-stage intermediate enabled Smith's group to undertake an analogue programme.⁵⁵ Variations in the C45-C46 functionality were easily introduced due to the convergent nature of the synthesis of the side chain **102**. It was found that the C45-C46 vinyl chloride analogue **132** (Figure 3) was found to exhibit GI_{50} values of picomolar magnitude *i.e.* ten orders of magnitude more potent than those exhibited by (+)-phorboxazole A. Although Evans' synthesis of (+)-phorboxazole B was more efficient overall (12.6%),¹⁵ Smith's synthetic route is arguably the best that has published to date due to the quantity of late stage material that it has afforded.

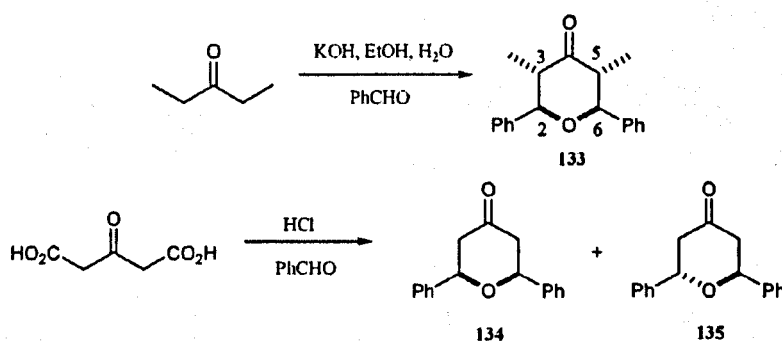
It is crucial that research of the total synthesis of the phorboxazoles is still prevalent within academia, since their mode of action is still yet to be fully elucidated. Furthermore, the biological evaluation of various late-stage intermediates or synthetic analogues can facilitate the search for the minimal pharmacophore. A multigram synthesis to rival Smith's is required, and is the ultimate goal of our research reported herein.

6 Results and Discussion

6.1 Background

6.1.1 The Maitland-Japp Reaction

In 1904, Maitland and Japp reported the formation of the fully substituted tetrahydropyranone (THPO) unit **133** via a low-yielding condensation reaction between 3-butanone and two molecules of benzaldehyde (Scheme 28).⁵⁶

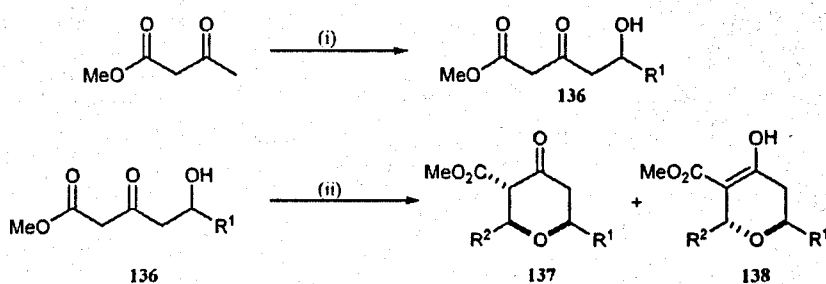


Scheme 28: Early reported THPO-forming reactions

Similarly, in the 1930s, an analogous reaction was reported by Cornubert and Robinet.⁵⁷ Acetone dicarboxylic acid was used in an acid mediated condensation reaction, which proceeded with subsequent decarboxylation to furnish the disubstituted THPO units **134** and **135** in the ratio of 250:1 respectively. It was later determined that the major products formed in the Maitland-Japp and Cornubert-Robinet reactions were all-equatorially substituted 2,6-*syn* THPOs.^{58,59}

Our group was attracted to this method of THPO formation, because THP rings are commonplace throughout the natural product arena. Although there are many established methods in place for THP assembly,⁶⁰ the one-pot, multi-component nature of the Maitland-Japp reaction hinted at the reaction's potential to be turned into a synthetically useful procedure for the formation of THP units. Initial studies within

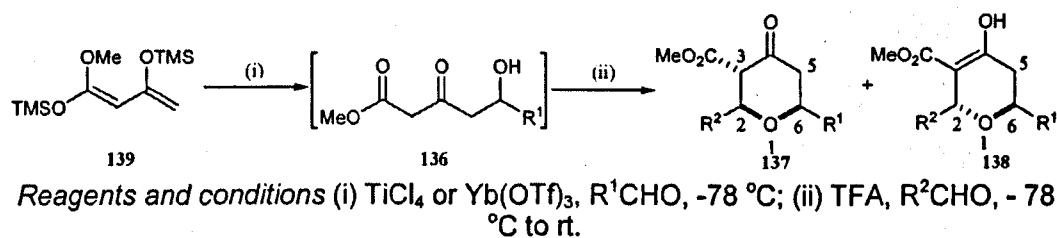
the group involved the use of a β -ketoester in place of the ketone used by Maitland and Japp in order to allow the formation of unsymmetrical THPOs. The difference in reactivities of the α and γ positions meant that the THPOs **137** and **138** could be furnished in two steps. A regioselective aldol reaction of methyl acetoacetate at the γ position with an aldehyde $R^1\text{CHO}$ using Weiler dianion chemistry revealed **136** (Scheme 29).⁶¹ A Knoevenagel condensation with a second aldehyde $R^2\text{CHO}$ at the α position, and a subsequent intramolecular oxy-Michael addition furnished THPOs **137** and **138**.



Reagents and conditions: (i) NaH, THF, 0 °C, then *n*-BuLi, $R^1\text{CHO}$, -78 °C to rt; (ii) $R^2\text{CHO}$, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , rt.

Scheme 29: Two-pot approach to THPO formation

This process yielded THPO units as mixtures of *trans* and *anti* isomers in up to 80% yield over the two steps, with observed diastereoselectivities of up to 12:1 in favour of the 2,6-*syn* keto diastereoisomer **137**. It was found that the 2,6-*anti* enol diastereoisomer **138** was formed as a minor product in two-pot reactions with the majority of substrates investigated. A one-pot protocol was later established, in which dienol ether **139** was used as the nucleophile in a Lewis acid mediated aldol reaction (Scheme 30). Upon treatment with TFA, the δ -hydroxy- β -ketoester **136** formed *in situ* from the silyl enol ether, and then proceeded to react with the second aldehyde in a Knoevenagel reaction, followed by intramolecular oxy-Michael addition.^{62,63}



Scheme 30: One-pot approach to THPO formation

The one-pot process resulted in the formation of THPO units as a mixture of 2,6-*cis* and *trans* isomers in up to 98% isolated yield and was proved to be general for a range of aldehydes. The choice of Lewis acid was found to be important in this case, since ytterbium triflate mediated reactions were seen to produce mainly the *syn* isomer **137** (up to 11:1 dr), whereas the titanium tetrachloride mediated reactions were seen to produce mainly the *trans* isomer **138** (up to 4:1 dr). The reason for this marked reversal in selectivity was attributed to the fact that the two Lewis acids interacted with the two diastereoisomeric products **137** and **138** differently, such that, in the case of TiCl_4 , it is thought that formation of a 6-membered chelate occurs from the coordination of $\text{Ti}(\text{IV})$ to the lone pairs of both the enol and ester oxygen atoms (Figure 4).

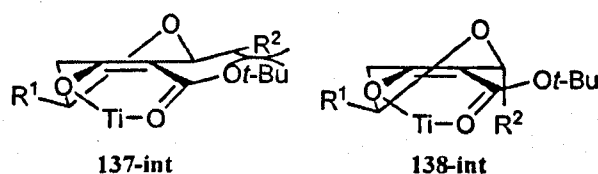


Figure 4: Steric clashes in 2,6-*cis* vs 2,6-*trans* as a consequence of ring flattening

Models of the 2,6-*cis* enol diastereoisomer show that the inherent ring-flattening induces a steric interaction between the ester and the pseudo-equatorial substituents at C2 (**137-int**). Substituents at C2 in the enol diastereoisomer prefer to adopt an axial position in order to avoid such reaction (**138-int**), hence forming the 2,6-*trans* relationship across the ring. It is proposed that the energy penalty for having an axial

C2 substituent is not substantial since the flattening of the ring will reduce any 1,3-diaxial interactions.

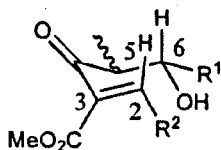


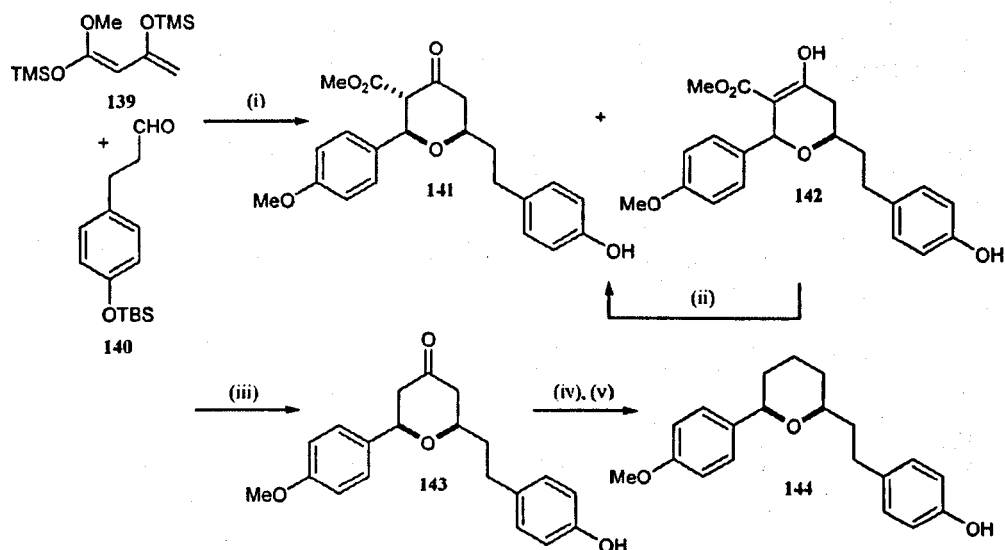
Figure 5: Non-chelated chair-like reactive conformation

In the case of Yb(OTf)₃, chelate formation is thought to be less prevalent, since Yb(OTf)₃ is only partially soluble in CH₂Cl₂, thus THPO formation proceeds *via* the more favoured chair-like reactive conformation with pseudo-equatorial substituents, resulting in a predominantly 2,6-*cis* relationship across the ring (Figure 5).

6.1.2 The Total Synthesis of (±)-Centrolobine

In order to demonstrate the methodology's synthetic utility, a total synthesis of (±)-centrolobine **144** was undertaken (Scheme 31).^{64,65} (-)-Centrolobine is a small 2,6-*cis* substituted THP-containing natural product which has been often used as a synthetic challenge for previous pyran-forming methodologies.^{66,67,68} Previous to the work undertaken in our group, it was deemed that these syntheses either contained too many steps or returned too little material. It was thought that the one-pot multi-component nature of the Maitland-Japp reaction could alleviate these problems. The synthesis started with a Mukaiyama-type aldol reaction between Chan's diene (**139**) and aldehyde **140**, which was a common precursor in the previous syntheses and can itself be synthesised in three steps from the commercially available *p*-hydroxy 3-phenylpropanoic acid. Upon formation of the aldol adduct *in situ*, the Knoevenagel/oxy-Michael reaction was induced by the addition of *p*-anisaldehyde and trifluoroacetic acid. Concomitant TBS-group removal was observed, resulting in

the formation of diastereoisomeric THPOs **141** and **142** in 92% yield in a ratio of 2:1 respectively.

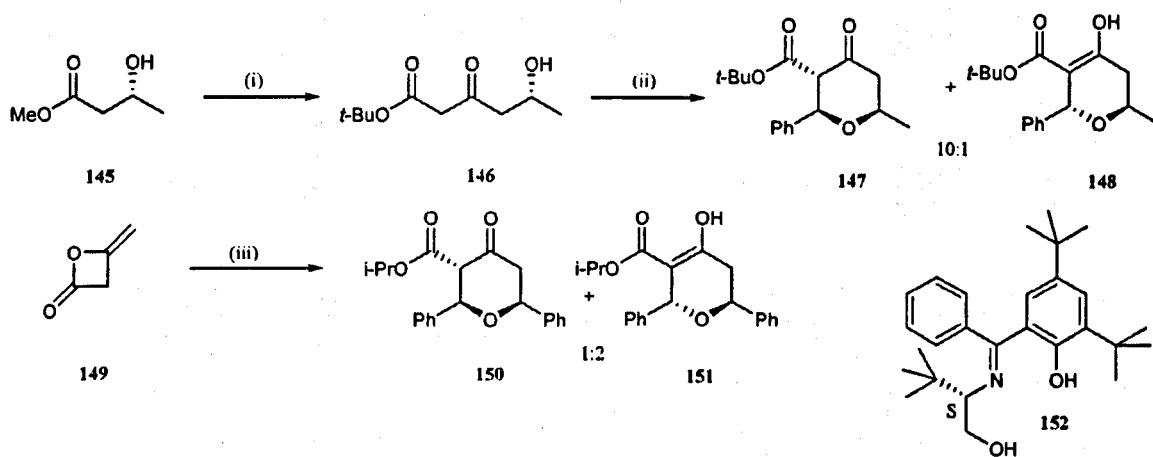


Reagents and conditions: (i) Yb(OTf)₃, -78 °C, 1 h, then TFA, *p*-anisaldehyde, -78 °C to rt, 12 h, 92%, dr 2:1 **141**:**142**; (ii) Yb(OTf)₃, -78 °C to rt, 12 h, 82% of **141** over 2 steps; (iii) H₂O₂, LiOH, THF, H₂O, room temperature, 5 h, then 70 °C, 30 min, then rt, 12 h, 60%; (iv) HSCH₂CH₂SH, BF₃·OEt₂, CH₂Cl₂, rt, 100%; (v) Raney Ni, H₂, EtOH, 30 °C, 100%.

Scheme 31: Synthesis of (±)-centrolobine

The unwanted 2,6-*trans* enol diastereoisomer could be recycled to the equilibrium mixture of 2:1 **141**:**142** by resubmission to the reaction conditions, and as such the isolated yield of the desired 2,6-*cis* keto diastereoisomer was increased to 82% overall after one recycle. Decarboxylation proceeded *via* treatment with hydrogen peroxide and lithium hydroxide in 60% yield, to furnish **143**. Finally the carbonyl group was removed by initial formation of a dithiane, which was reduced with Raney Nickel in quantitative yield over the two steps to reveal (±)-centrolobine **144** in an overall four steps and 50% yield from **139**.

6.1.3 The Asymmetric Maitland-Japp Reaction



Reagents and conditions: (i) $\text{CH}_3\text{CO}_2t\text{-Bu}$, LDA, $-78\text{ }^\circ\text{C}$ to rt, 55%; (ii) TiCl_4 , py, PhCHO, 55 %; (iii) PhCHO, $\text{Ti}(\text{O}^i\text{Pr})_4$, **152**, IPA, CH_2Cl_2 ; (iv) PhCHO, TiCl_4 , 43%, 92% ee.

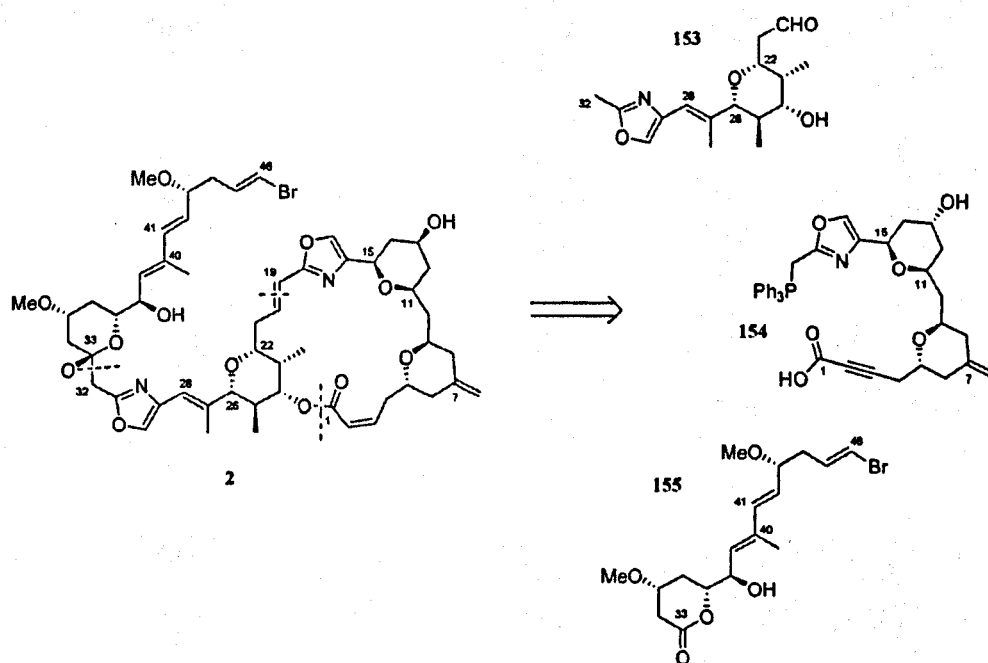
Scheme 32: Original two-pot asymmetric THPO formation, and a more recent one-pot example

Work within the group has focused on asymmetric one-pot syntheses of THPO units, building upon the reported asymmetric two-pot reaction, in which δ -hydroxy- β -ketoesters, formed from enantiomerically pure alcohols, were shown to undergo cyclisation under Knoevenagel/oxy-Michael conditions with the transfer of chiral information (Scheme 32). Claisen condensation of enantiomerically pure **145** with *tert*-butyl acetate afforded the cyclisation precursor **146**.⁶³ Subsequent cyclisation resulted in the formation of THPOs **147** and **148** as a 10:1 mixture of diastereoisomers with no erosion of enantiomeric excess. More recently, a successful one-pot approach to the asymmetric Maitland-Japp reaction has been established. An aldol reaction between diketene **149** and an aldehyde was promoted by a chiral Ti(IV) complex, which was formed *in situ* from the reaction of titanium isopropoxide with chiral Schiff's base ligand **152**. Once the aldol addition was deemed to be complete, addition of a second aldehyde and titanium tetrachloride promoted the

Knoevenagel/oxy-Michael cyclisation which furnished compounds **150** and **151** in a 1:2 ratio respectively in 43% yield and 92% ee.⁶⁹

6.1.4 Application of the Maitland-Japp reaction to the Total Synthesis of (+)-Phorboxazole B

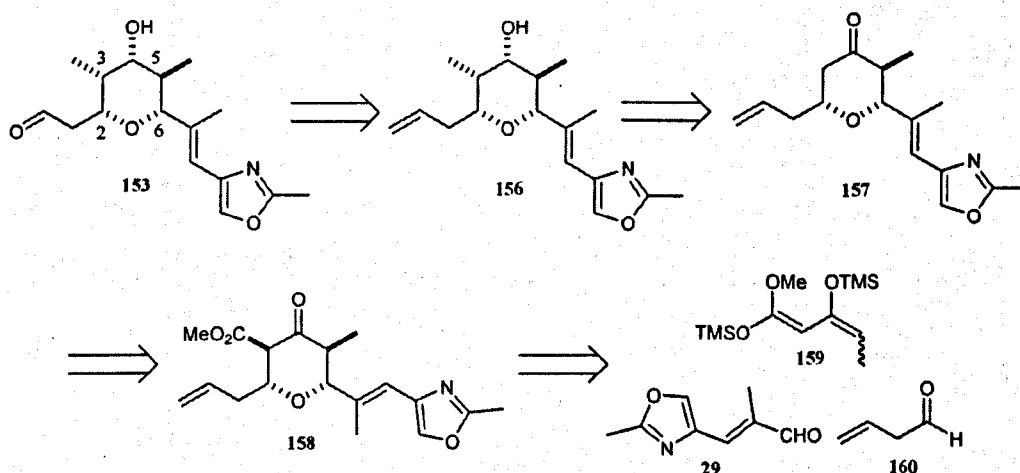
After experiencing the use of the Maitland-Japp reaction as a powerful tool for the assembly of a THP containing natural product in the synthesis (±)-centrolobine (**144**), a decision was made to tackle the architecturally challenging (+)-phorboxazole B (**2**), which contains four THP sub-units (Scheme 33). Furthermore, the aim would be to use the asymmetric methodology developed within the group to synthesise the molecule as a single enantiomer.



Scheme 33: Retrosynthetic analysis

Retrosynthetic scissions across C19/C20, C32/C33, and C1-O bonds reveal three equally complex fragments **153**, **154**, and **155**. In the forward sense, coupling of

fragments **153** and **154** was envisaged by means of a stereoselective Wittig reaction, and lactonisation at C1. The resultant macrolactone species could then be coupled to fragment **155** *via* diastereoselective addition on to the δ -lactone carbonyl, yielding the C32-C33 bond.¹⁷



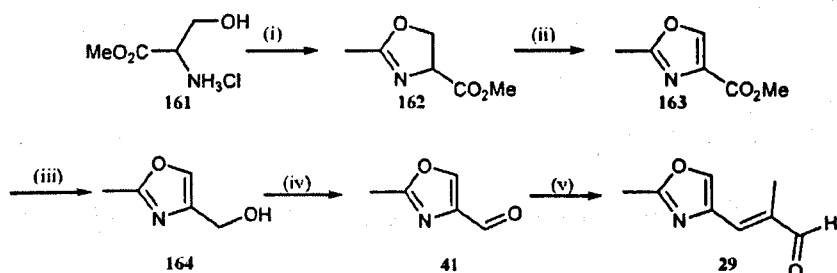
Scheme 34: Retrosynthetic analysis of central THP **153**

The central core of the phorboxazoles, fragment **153**, is a penta-substituted THP which contains a stereogenic centre at each of the five carbon atoms on the ring. The racemic synthesis of **153** was initially considered. It was envisaged that the aldehyde **153** could be formed from selective oxidative cleavage of alkene **156** as demonstrated by White.³³ It was proposed that the alcohol **156** could be formed from a diastereoselective reduction of a ketone, and that the installation of an axial methyl group at C5 could arise from treatment of the lithium enolate of **157** with iodomethane, under kinetic control (Scheme 34). The THPO **157** would result from the decarboxylation of **158**, which in turn would be constructed by application of the Clarke group's Maitland-Japp protocol to the reaction of known aldehydes **29**⁷⁰ and **160**⁷¹ with *bis*-silyl enol ether **159**.⁷²

6.2 Tetrahydropyran-4-one Synthesis

6.2.1 Synthesis of tri-Substituted THPOs

In order to assess the feasibility of the Maitland-Japp methodology in the efficient synthesis of the C19-C32 tetra-substituted THP core of the phorboxazoles, it was first necessary to apply the known protocol to the aldehydes **29** and **160**. Aldehydes **29** and **160**, together with Chan's diene (**139**) were synthesised according to literature procedures.^{70, 71, 73}

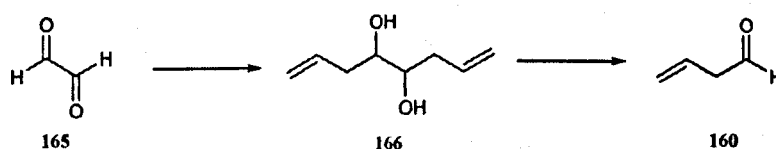


Reagents and conditions: (i) Ethyl acetimidate hydrochloride, Et₃N, CH₂Cl₂, 21 °C, 12 h, 83%; (ii) BrCCl₃, DBU, CH₂Cl₂, 0 °C, 12 h, 76%; (iii) DIBAL-H, Et₂O, 0 °C, 12 h, 74 %; (iv) Swern, 84%; (v) 2-(triphenylphosphoranylidene)-propionaldehyde, PhH, 25 °C, 82%.

Scheme 35: Synthesis of aldehyde **29**

Oxazoline **162** was synthesised in 83% yield from DL-serine methyl ester hydrochloride **161** and ethyl acetimidate hydrochloride under basic conditions (Scheme 35).⁷⁰ Oxazoline **162** was oxidised by use of 1,8 diazabicyclo[5.4.0]undec-7-ene and bromotrichloromethane which performed an initial bromination at the C-4 position of the oxazole and subsequent elimination of HBr. This generated oxazole **163** in 76% yield. Lithium aluminium hydride reduction of ester **163** to alcohol **164** proceeded in 75% yield.⁷⁰ However, when this was carried out on gram-scale, the yield decreased to a disappointing 57%. This reduction in yield could have been associated with the increased difficulty of the work-up procedure, due to the formation of large amounts of aluminium salts, from which it was difficult to extract

the alcohol **164**. The use of an alternative reducing agent, diisobutylaluminium hydride, resulted in the formation of **164** in 74% yield on both large and small scales. Alcohol **164** was oxidised with manganese dioxide to give aldehyde **41**, in 74% yield. Disappointingly, this yield was seen to decrease to 50% upon scale-up, which after further experience of dealing with the product could be attributed to its volatility. However, the use of modified Swern conditions (*i.e.* 1.5 eq (COCl)₂, 3 eq DMSO, and 5 eq Et₃N) was seen to give aldehyde **41** 84% yield on the gram scale. It should be noted at this point that Dr. John Carey from GlaxoSmithKline, Tonbridge, has very kindly donated to the group in excess of fifty grams of **29** after a conversation in 2007 unveiled that GSK make **29** on the hundred gram scale. Previous to the donation, the desired homologated aldehyde **29** was obtained in 82% yield as a single geometrical isomer *via* Wittig olefination in a reaction of aldehyde **41** with 2-(triphenylphosphoranylidene)-propionaldehyde.⁷⁰

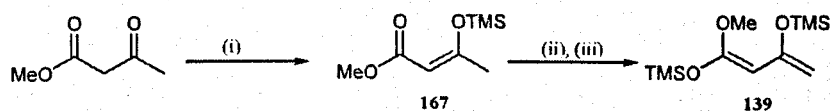


Reagents and conditions: (i) allyl bromide, Sn (powder), 1:1 THF/H₂O, rt, hv, 3 h, 69%; (ii) NaIO₄, pH4 buffer, CH₂Cl₂, 21 °C, 3 h, 48%.

Scheme 36: Synthesis of aldehyde **160**

Octadiene **166** was synthesised *via* a Barbier reaction of glyoxal **165** conducted under sonication conditions using tin powder and allyl bromide, in 69% yield (Scheme 36).⁷¹ Progression from the octadiene **166** to the aldehyde **160** proceeded in a disappointing 48% yield. The low yield arose from the fact that aldehyde **160** is volatile, and thus needed to be used as the CH₂Cl₂ reaction solution which was washed 10% aqueous sodium thiosulfate and brine. The concentration of aldehyde in the CH₂Cl₂ extract was determined by comparison of the integrals in the ¹H NMR

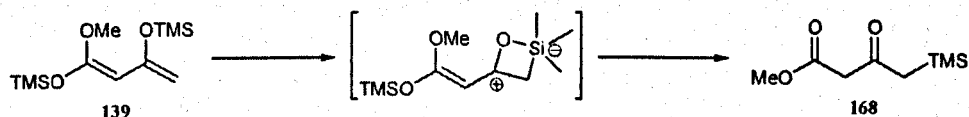
spectrum with a known standard, a 1.0 M solution of tetramethylsilane in chloroform-
d.



Reagents and conditions: (i) Et₃N, TMSCl, pet. ether (dry), 21 °C, 14 h, quant.; (ii) LDA, -78 °C, 30 minutes (iii) TMSCl, -78 °C to 0 °C, 1 hr, 64%.

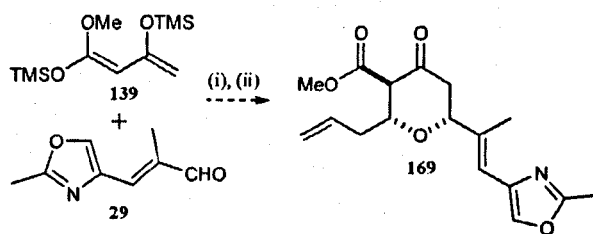
Scheme 37: Synthesis of Chan's diene (**139**)

The diene **139** was synthesised in a double silylation process from methyl acetoacetate in 64% yield over two steps (Scheme 37).⁷² Although it may appear so, the synthesis of the diene **139** was not trivial during initial attempts as it was observed that using only a necessarily small excess of LDA in the second deprotonation step would not always result in the completion of the reaction. The reaction could not be monitored by thin layer chromatography (TLC), as the TMS groups were labile in the presence of silica. The distillates of the crude reaction mixture were often found to contain small amounts of the mono-TMS species **167**, which had to be taken into account when using the diene **139** in subsequent reactions.



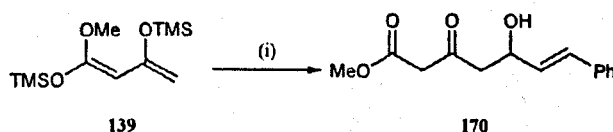
Scheme 38: Retro-Brook rearrangement of **139**

Furthermore the retro-Brook rearrangement product of **139** (Scheme 38), which was generated upon heating during the distillation process to form **168**, was also thought to have an adverse effect on the aforementioned subsequent reactions. The best results for the synthesis of the diene **139** were obtained after a greater amount of experience had been gained, thus initial cyclisation attempts were carried out using diene which exhibited a certain level of contamination.



Reagents and conditions: (i) LA, CH₂Cl₂, -78 °C, 2 h; (ii) TFA, 160, CH₂Cl₂, rt, 2 h.
Scheme 39: Initial cyclisation conditions

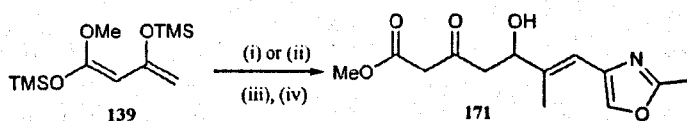
Initial attempts at cyclisation using the standard Clarke group protocol for either ytterbium triflate or titanium tetrachloride mediated one-pot THPO formation proved to be fruitless (Scheme 39). Observations by TLC of the aldol step, *i.e.* reaction between the diene 139 and aldehyde 29, suggested that the reaction hadn't gone to completion, despite the addition of further equivalents of 139. This observation highlighted a couple of possible problems associated with the reaction: (i) impurities in the diene could impede the reaction; (ii) or the incompatibility of the component aldehydes 29 and 160 to the known protocol. For instance the use of α,β -unsaturated aldehydes in Maitland-Japp reactions had thus far been unprecedented. In order to investigate the matter more closely, *trans*-cinnamaldehyde was used in a model study of the aldol step of the Maitland-Japp reaction, using the diene 139. Disappointingly, completion of the aldol step was again not observed, and subsequently no pyran formation was seen when using butanal in the Knoevenagel/Michael step to mimic the alkyl chain of aldehyde 160.



Reagents and conditions: (i) *trans*-cinnamaldehyde, Yb(OTf)₃, CH₂Cl₂, -78 °C, 2 h, 38%.

Scheme 40: Yb(OTf)₃-promoted Mukaiyama-type aldol reaction using *trans*-cinnamaldehyde

It was then decided to revert to a two-pot approach whereby each step would be investigated separately. A ytterbium triflate mediated Mukaiyama aldol reaction between Chan's diene (**139**) and *trans*-cinnamaldehyde went to completion, but the aldol adduct **170** was only isolated in 38% yield (Scheme 40). Although the reaction was low yielding, the result was encouraging since it showed that aldol products derived from diene **139** and α,β -unsaturated aldehydes were isolatable. Encouraged by this result, it was decided to repeat the reaction with aldehyde **29**, using both titanium tetrachloride and ytterbium triflate as the Lewis acids (Scheme 41).

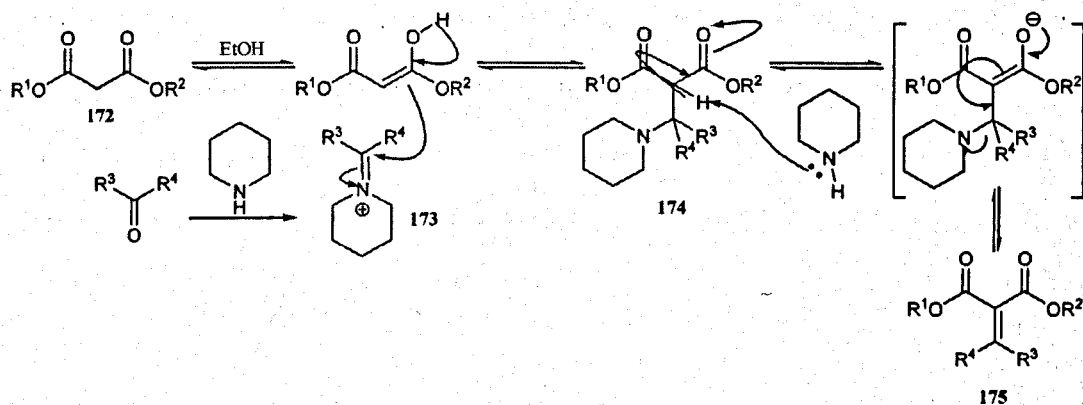


Reagents and conditions: (i) **29**, TiCl_4 , $-78\text{ }^\circ\text{C}$, 2 h; (iii) $-20\text{ }^\circ\text{C}$, 18 h; (iv) TFA, $-78\text{ }^\circ\text{C}$, 5 mins, 37%; (ii) **29**, $\text{Yb}(\text{OTf})_3$, $-78\text{ }^\circ\text{C}$, 2 h; (iii) $-20\text{ }^\circ\text{C}$, 18 h; (iv) TFA, $-78\text{ }^\circ\text{C}$, 5 mins, 63%.

Scheme 41: Mukaiyama-type aldol reaction on oxazole functionalised aldehyde.

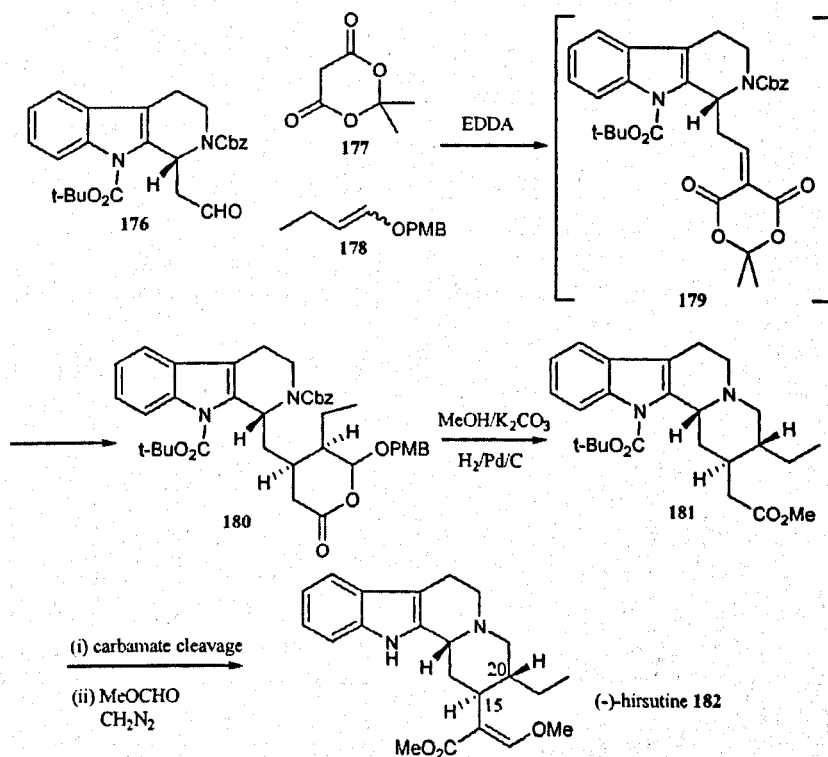
Observation by TLC showed that the reactions had gone nowhere near completion after two hours at $-78\text{ }^\circ\text{C}$ and it was therefore decided to raise the temperature of both Lewis acid mediated reactions to $-20\text{ }^\circ\text{C}$. After eighteen hours, some starting aldehyde was still observed by TLC. Addition of trifluoroacetic acid at $-78\text{ }^\circ\text{C}$ was seen to drive the reaction to completion and aldol adduct **171** was isolated in 37% and 63% yield for the TiCl_4 and $\text{Yb}(\text{OTf})_3$ promoted reactions respectively. Further to this success, a Knoevenagel condensation of **171** with *n*-butanal was attempted.

The Knoevenagel condensation is the reaction between a carbonyl compound and an activated methylene group **172** to form an alkene (Scheme 42), eliminating water in the process. The reaction is commonly found to be catalysed by a weak base such as piperidine, and proceeds *via* initial formation of an iminium species **173**.



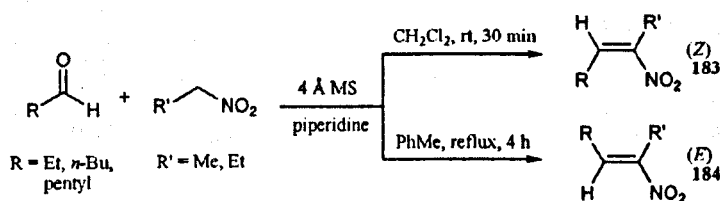
Scheme 42: The Knoevenagel condensation

Attack on this iminium **173** with the enol tautomer of **172**, followed by E1_{cb} elimination of the free amine affords α,β -unsaturated carbonyl compounds **175**. The reaction is fastest with aldehydes, but a comprehensive list of complementary substrates has been published in a review by Jones.⁷⁴



Scheme 43: Use of Knoevenagel condensation in the total synthesis of (-)-hirsutine

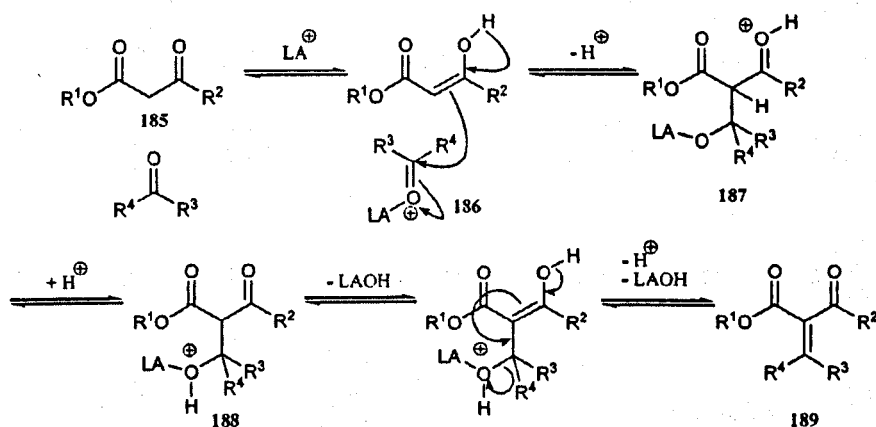
One particularly elegant use of the Knoevenagel condensation has been documented by Tietze and co-workers in their synthesis of hirsutine (Scheme 43).⁷⁵ The initial Knoevenagel condensation of **176** with Meldrum's acid **177** set up the α,β -unsaturated carbonyl compound **179** *in situ*, which underwent a facially selective hetero-Diels-Alder reaction with the alkene **178**, which exists as a 1:1 mixture of *E:Z* geometrical isomers. The reaction proceeded with concomitant decarboxylation and the stereogenic centres and C15 and C20 were installed with a diastereoselectivity of greater than 20:1. Methanolysis of **180** followed by removal of the carboxybenzyl protection *via* hydrogenolysis set up the tetracycle **181**. Subsequent carbamate cleavage and Knoevenagel condensation with methyl formate, followed by treatment with diazomethane revealed enantiomerically pure (-)-hirsutine **182**.



Scheme 44: Knoevenagel condensation to form (*E*) and (*Z*)-nitroalkenes

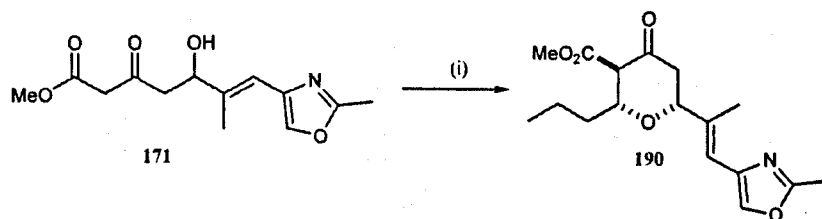
More recently in the literature, the Knoevenagel condensation has been used to synthesise (*E*)- and (*Z*)-nitroalkenes (Scheme 44).⁷⁶ Methylene activation in nitroalkane arises from the electron-withdrawing nature of the nitro group, thus facilitating a reaction with an electrophile such as an aldehyde, under basic conditions. Nitroalkenes are powerful electrophiles and as such readily undergo Diels-Alder cyclisations and Michael reactions, which makes them useful tools for the synthetic chemist. Previously, nitroalkenes have been formed by use of the Henry reaction followed by dehydration, but the dehydration step requires harsh reaction

conditions and culminates in the synthesis of predominantly the (*E*) isomer. This report by Pellacani and co-workers details the synthesis of both geometrical isomers of the nitroalkene in high yield; variation of the Knoevenagel condensation conditions results in the formation of (*Z*)-nitroalkenes **183** in yields of greater than 90% at room temperature, and the formation of (*E*)-nitroalkenes **184** in yields of greater than 80% at reflux in toluene. One major drawback of this methodology, however, is the high substrate specificity of the aldehyde. No nitroalkene formation is observed at room temperature when the aldehyde has α -branched R-substituents, thus only straight-chain aliphatic (*Z*)-nitroalkene formation is observed. In both of the above examples from the literature, the Knoevenagel condensations have been catalysed by a weak base, however the Maitland-Japp reaction conditions are Lewis acidic and as such Knoevenagel condensations may also be promoted by Lewis acids (Scheme 45).



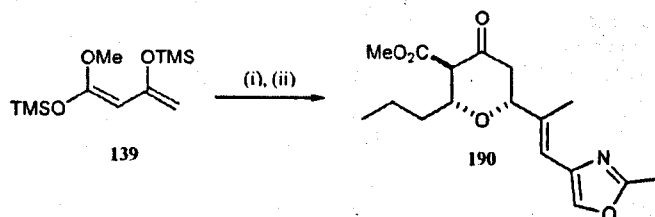
Scheme 45: Lewis acid promoted Knoevenagel condensation

The enol tautomer of the malonate **185** initially attacks the Lewis acid activated aldehyde **186**, and subsequent Lewis acid promoted dehydration of the enol tautomer of **188** would then occur to produce the α,β -unsaturated β -keto ester **189**.



Reagents and conditions: (i) Butanal, Yb(OTf)₃, TFA, CH₂Cl₂, RT, 16 h, 5%.
 Scheme 46: Cyclisation step to form THPO 190

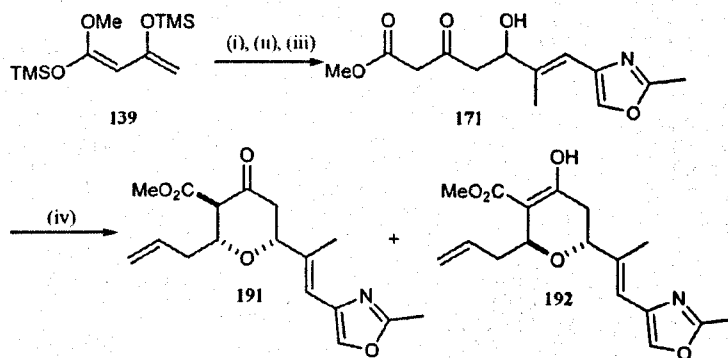
Cyclisation of **171** was therefore attempted *via* an initial Yb(OTf)₃ promoted Knoevenagel condensation with butanal, followed by an intramolecular oxy-Michael reaction (Scheme 46). Boron trifluoride diethyl etherate, titanium tetrachloride, and Yb(OTf)₃ were used as Lewis acids in separate reactions. It was found that the Yb(OTf)₃ promoted reaction produced the best result, although pitiful in itself, with a yield of 5%. The boron trifluoride diethyl etherate promoted reaction resulted in a small amount of THPO formation, visible in the ¹H NMR spectrum of the crude reaction mixture, however, it was clear that the reaction mixture contained a vast amount of other material. The titanium tetrachloride promoted reaction was completely unsuccessful, yielding only starting material and methyl acetoacetate. Although the process was disappointingly low yielding, the two-pot approach was a worthwhile venture as it resulted in the formation a pure sample of THPO **190**, and thus gave us information about the appearance of the molecule by TLC and ¹H NMR spectroscopy, thus aiding our future attempts at synthesising the compound.



Reagents and conditions: (i) **29**, Yb(OTf)₃, CH₂Cl₂, -78 °C, 2 h; (ii) TFA, butanal, CH₂Cl₂, rt, 2 h; 72%.

Scheme 47: One-pot formation of **190**

A one-pot Maitland-Japp reaction was the next logical step in the investigations towards the synthesis of **190** (Scheme 47). The ytterbium triflate promoted one-pot process was reasonably successful, yielding THPO **190** as a 9:1 mixture of 2,6-*cis* keto : 2,6-*trans* enol diastereoisomers in 72% yield.

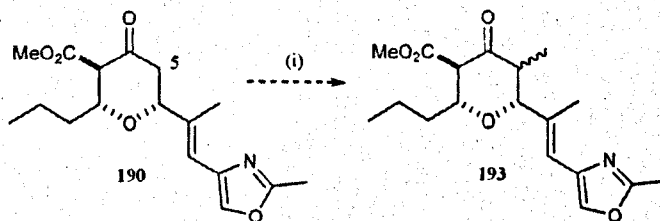


Scheme 48: Reagents and conditions: (i) **29**, Yb(OTf)₃, CH₂Cl₂, -78 °C, 2 h; (ii) -20 °C, 18 hr; (iii) TFA, -78 °C, 5 mins, 63% (iv) **160**, Yb(OTf)₃, TFA, CH₂Cl₂, rt, 15 h; 43% (4:1 / **191**:**192**).

Scheme 48: Two-pot formation of THPOs **191** and **192**

Tetrahydropyranone diastereoisomers **191** and **192**, analogous to **190**, were formed using but-3-enal **160** in an ytterbium triflate promoted two-pot Maitland-Japp cyclisation, albeit in a modest 27% overall yield (Scheme 49). Although the reaction remains unoptimised, this was a very promising result since it confirmed that our desired aldehydes **29** and **160** could be used as the first and second aldehydes respectively in the Maitland-Japp reaction.

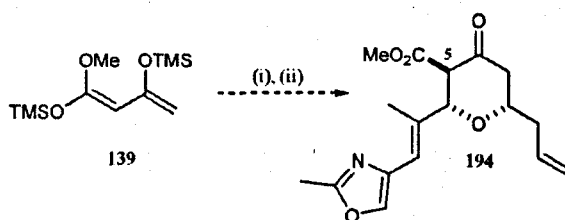
6.2.2 Synthesis of tetra-Substituted THPOs



Reagents and conditions: (i) NaH, THF, 0 °C, 20 min; (ii) *n*-BuLi, 0 °C to rt, 30 min; (iii) MeI, -78 °C to rt, 4 h, no reaction.

Scheme 49: Attempted methylation of **190**

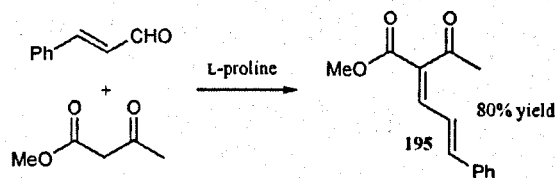
Building upon the successful formation of the model THPO units **190** and **191/192**, functionalisation at the C5 of **190** was attempted using a literature procedure for the methylation of β -ketoesters at the γ -position (Scheme 49).⁷⁷ However, on no occasion was the crude reaction mixture seen to exhibit a ^1H NMR spectrum resembling the desired methylated product.



Reagents and conditions: (i) **160**, Yb(OTf)₃, CH₂Cl₂, -78 °C, 1 h; (ii) TFA, **29**, CH₂Cl₂, rt, 12 h.

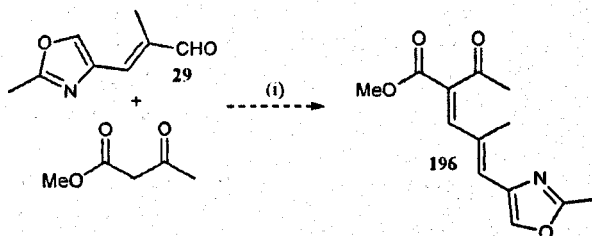
Scheme 50: Proposed formation of THPO **194** via opposite addition of aldehydes

It was thought that the problem arising from our unsuccessful attempts to methylate could be overcome by carrying out a Maitland-Japp reaction with opposite addition of aldehydes *i.e.* using but-3-enal **160** in the aldol reaction, and **29** in the Knoevenagel/Michael step (Scheme 50). Successful cyclisation would furnish THPO **194**, which can be seen to possess methyl ester functionality at C5 which upon reduction to a methyl group would sit in the correct orientation for the central core of the phorboxazoles (Scheme 34). Observations by TLC indicated that the aldol step had proceeded as expected with complete consumption of but-3-enal **160** after one hour. However, twelve hours after the addition of aldehyde **29**, the reaction was observed to have proceeded no further, and indeed aldehyde **29** was abundant in the ^1H NMR of the crude reaction mixture. This result is in accordance with the fact that there are very few examples of Knoevenagel condensations using α,β -unsaturated aldehydes.



Scheme 51: Reported Knoevenagel condensation with an α,β -unsaturated aldehyde

We were therefore attracted by a very recent publication which detailed the successful Knoevenagel condensation of *trans*-cinnamaldehyde with a wide range of β -keto esters and diketones to form (*E*)-selective conjugated enones, such as **195** in over 80% yield in most cases (Scheme 51).⁷⁸ The optimum reaction conditions described in the article with regards to the best (*E*)-selectivity were achieved when the reaction was conducted without solvent, using a pestle and mortar. However, in the range of experiments to determine the optimum solvent for this type of reaction, it was found that the use of CH_2Cl_2 as a solvent afforded the conjugated enones in the highest yield, albeit in 65:35 *E/Z* selectivity.

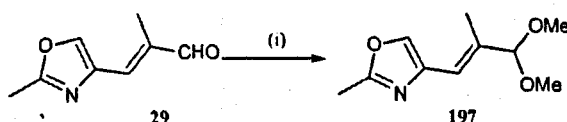


Reagents and conditions: (i) L-proline, CH_2Cl_2 , rt, 6 h, no reaction.

Scheme 52: Failed Knoevenagel condensation with α,β -unsaturated aldehyde **29**

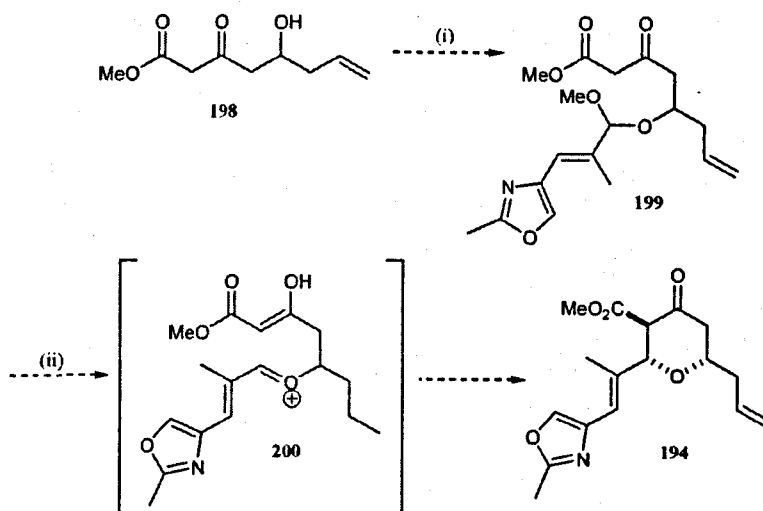
It would be interesting to investigate whether the reported result could be replicated using aldehyde **29**, instead of *trans*-cinnamaldehyde in a reaction with methyl acetoacetate, in the presence of L-proline, to form conjugated enone **196** (Scheme 52). Since *E/Z* selectivity was at this stage considered to be less important than the yield, the conditions that include the use of dichloromethane as solvent were the first attempted. Furthermore, aldehyde **29** is a solid which makes solventless conditions

impractical. After 6 hours of stirring, only starting material was returned, which was deemed to be a disappointing result. Solventless conditions were then tried, in which a large excess of methyl acetoacetate (10 equivalents) was used in order to get sufficient mixing. Only starting material was returned after 40 minutes of grinding in the mortar. In order to ascertain whether the aldehyde **29** was compatible with the reaction conditions or whether this chemistry did not work in our hands, an example from the paper was replicated (Scheme 51). After 30 minutes of grinding together methyl acetoacetate, *trans*-cinnamaldehyde and L-proline, only starting material was returned. The paper reports that these particular reaction conditions should yield conjugated enone **195** in 80% yield after only 15 minutes. The failure to repeat the results reported enforced the conclusion that a Knoevenagel condensation using an α,β -unsaturated aldehyde was unachievable in our hands.



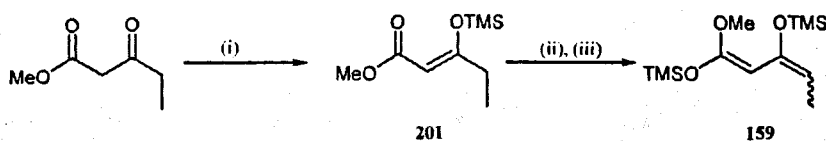
Reagents and conditions: (i) *p*-TsOH, HC(OMe)₃, MeOH, reflux, 8 h, quant.
 Scheme 53: Formation of acetal **197**

It was thought that this problem could be circumvented by using the acetal **197** in the second step of the Maitland-Japp reaction, as it has been shown that cyclisation can be effected using an acetal *via* an oxocarbenium ion **200** (Scheme 54).⁶³ Acetal **197** was formed in quantitative yield from aldehyde **29** using a literature procedure (Scheme 53).⁷⁹ Addition of acetal **197** to the reaction mixture, however, resulted in the immediate formation of a spot observed by TLC that corresponded to the formation of aldehyde **29**, which suggested that the acetal was unstable to the reaction conditions.



Reagents and conditions: (i) **197**, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $-22\text{ }^\circ\text{C}$, 14 h; (ii) TiCl_4 , TFA
 Scheme 54: Proposed cyclisation through oxocarbenium ion.

The ^1H NMR spectrum of the crude reaction mixture showed that the major product was aldehyde **29**, and thus no further reaction occurred. These failures forced us to turn to the Maitland Japp reaction using diene **159**, as this was considered to be the only viable route to a THPO with methyl functionality at C5. The diene itself was synthesised as a 6:1 mixture of double bond isomers in an overall 61% yield from methyl propionyl acetate (Scheme 55).⁷³

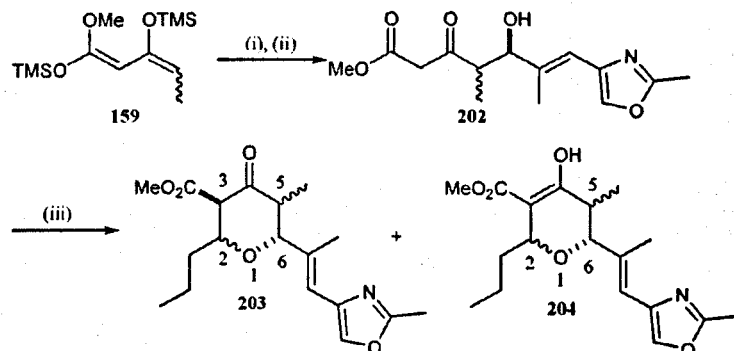


Reagents and conditions: (i) Et_3N , TMSCl , pet. ether (dry), $21\text{ }^\circ\text{C}$, 14 hr, 95% (ii) LDA , $-78\text{ }^\circ\text{C}$, 30 minutes (iii) TMSCl , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 1 hr, 63% (6:1 mixture of isomers).

Scheme 55: Formation of diene **159**

There had been only one reported example of a Maitland-Japp cyclisation using diene **159** previously in the research group, which resulted in the formation of multiple diastereoisomers, of which the desired all equatorially substituted THPO was formed in only 16% yield.⁸⁰ Initial attempts at achieving a one-pot cyclisation when using

diene **159** proved to be fruitless. This lack of success made it necessary to separate the Mukaiyama aldol and Knoevenagel/Michael steps into two pots in order to understand the source of the problem.



Reagents and conditions: (i) **29**, TiCl_4 , CH_2Cl_2 , -78°C , 30 min; (ii) TFA, 20 min, -78°C to 0°C , 98%; (iii) butanal, $\text{Yb}(\text{OTf})_3$, TFA, CH_2Cl_2 , rt, 16 h, 53%, dr 3:1:1:1:1:1.

Scheme 56: Maitland-Japp reactions using diene **159**

Investigations into the Mukaiyama aldol reaction were carried out using ytterbium triflate and titanium tetrachloride as Lewis acids (Scheme 56). The ytterbium triflate promoted reaction was observed to be far from complete even after twelve hours stirring at room temperature. The titanium tetrachloride promoted reaction, on the other hand, was observed to be complete in half an hour at -78°C . The ^1H NMR spectrum of the crude reaction mixture of the titanium tetrachloride promoted aldol reaction exhibited the exclusive presence of the aldol adduct **202**, which was formed in 98% yield. Investigations were then undertaken into the Knoevenagel/Michael cyclisation step, initially using commercially available *n*-butanal as a model for but-3-enal **160**. Again, both ytterbium triflate and titanium tetrachloride were initially used in order to determine the optimum Lewis acid for the cyclisation. From observation by TLC it was seen that, in this case, only ytterbium triflate promoted successful cyclisation, producing THPOs **203** and **204** in 54% yield. However, the product of this cyclisation existed as an inseparable mixture of six diastereoisomers in the ratio

of 3:1:1:1:1 (Figure 7, overleaf), of which three of the diastereoisomers existed as enols in a ratio of 1:1:1. This conclusion was drawn from the three peaks in the ratio of 1:1:1 in the ^1H NMR of the crude reaction mixture in the region of 12 ppm, which are characteristic of the hydrogen-bonded enol proton for each of the three diastereoisomers.

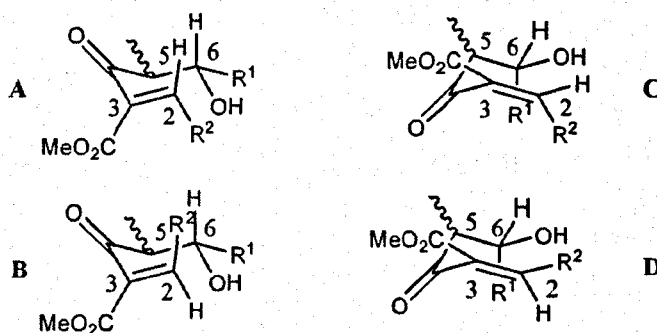


Figure 6: Chair-like reactive conformations of the cyclisation

When attempting to assign the diastereoisomers that have been generated in complex mixtures such as these, from here on in, it has been assumed that the C6 substituent will always adopt an equatorial position. When considering the possible transition states for the cyclisation (Figure 6),⁶³ Reactive conformations A and B, which will yield 2,6-*cis* and *trans* diastereoisomers respectively, are considered to be lower in energy than reactive conformations C and D due to the fact that R¹ adopts an unfavourable pseudo-axial position in C and D. This effect will be even more pronounced when R¹ represents a large substituent such as the oxazole-containing chain attached to C6 in 203 and 204. A less confident assumption when assigning such diastereoisomers is that the ester group will also always adopt an equatorial position in order to avoid destabilising 1,3 diaxial interactions. Therefore, the first piece of evidence that needs to be addressed from the ^1H NMR spectrum (Figure 7) of this crude reaction mixture is the fact that there are three enol species in this mixture. This contradicts the previously established theory for the tri-substituted THPOs; that

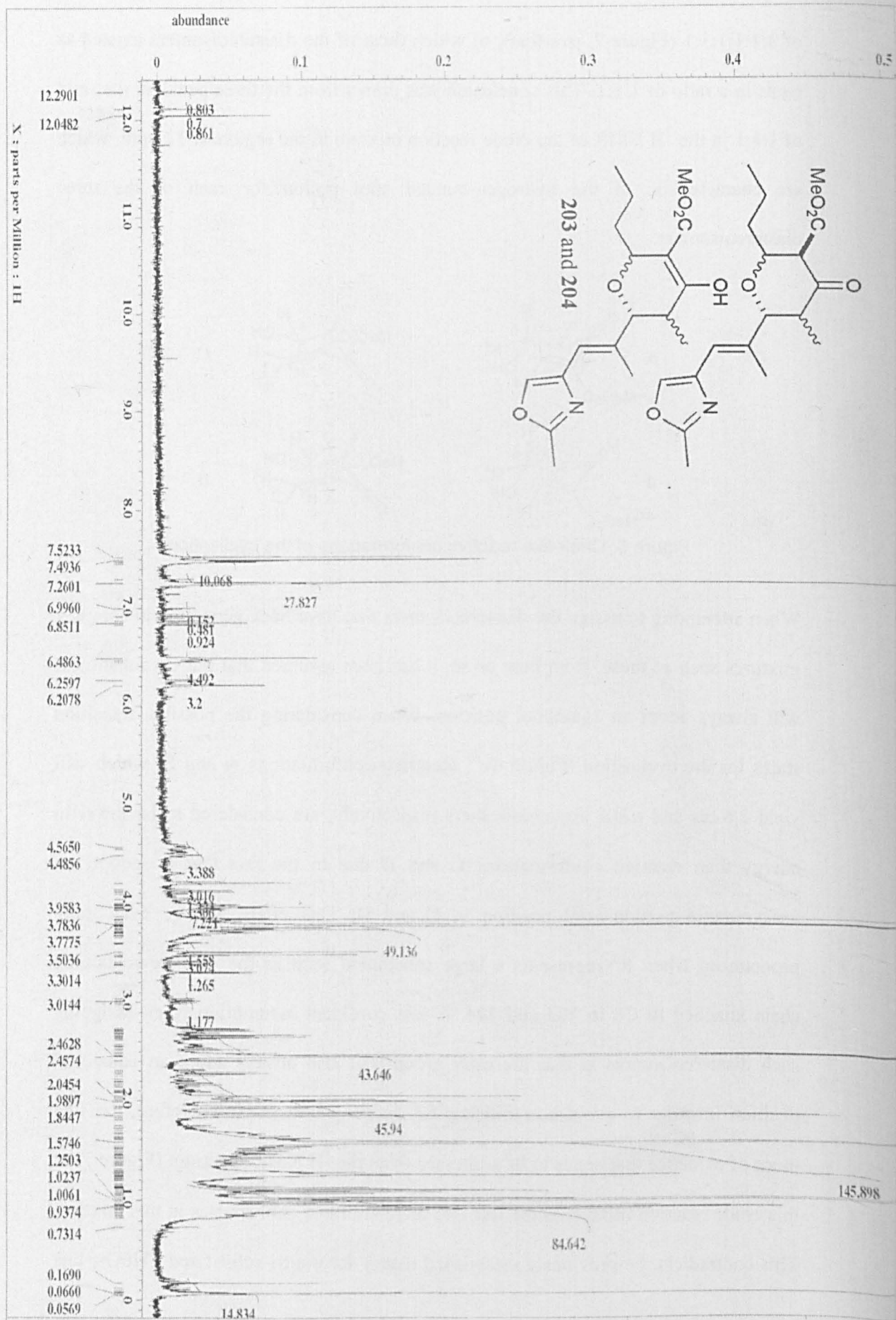


Figure 7: ¹H NMR spectrum of THPO diastereoisomeric mixture

the enols all exhibit a 2,6-*trans* relationship, because at least one of the four possible enol species 209-212 (Figure 8) must exhibit a 2,6-*cis* relationship, 209 or 210. Likewise, it contradicts the theory that all keto species exhibit a 2,6-*cis* relationship, since at least one of the remaining possible keto species 205-208 must exhibit a 2,6-*trans* relationship.

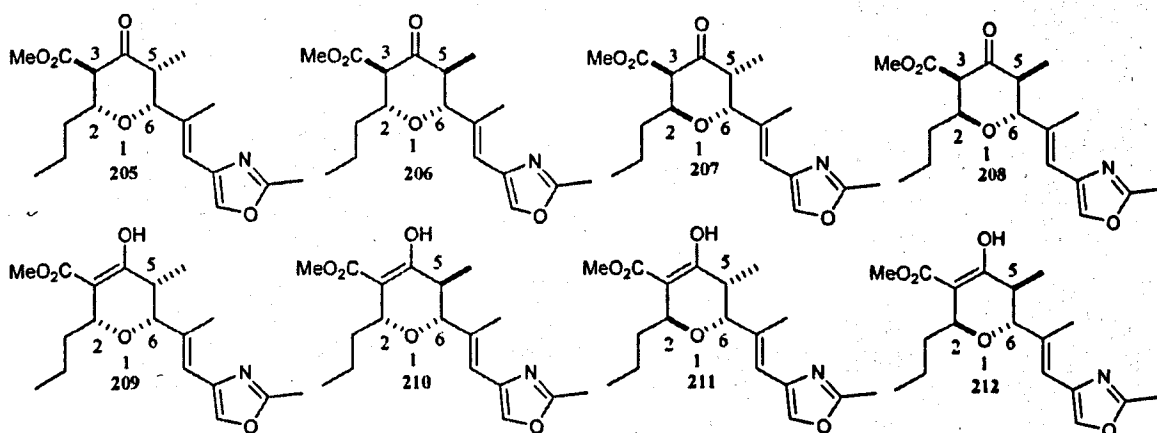


Figure 8: Possible diastereoisomers from $\text{Yb}(\text{OTf})_3$ promoted cyclisation

The desired diastereoisomer 206 was soon isolated and characterised from the use of different reaction conditions (Scheme 58), and retrospective analysis of the ^1H NMR spectrum of the crude reaction mixture for the $\text{Yb}(\text{OTf})_3$ promoted reaction (Scheme 57) indicates there to be an amount of 206 present in the mixture of magnitude 1 relative to 3:1:1:1:1 ratio of diastereoisomers. The ^1H NMR spectrum of clean 206 will be discussed in detail in the next section, but the characteristic peaks are visible in this spectrum. The multiplet between 3.90 and 4.00 ppm (Figure 9), in which can be seen a ddd with coupling constants of 9.7, 7.3 and 2.4 Hz, which can be assigned as H2. The proton assigned as H2 therefore exhibits a *trans*-diaxial coupling with H3 (9.7 Hz) indicating that the C2 and C3 substituents are both in equatorial positions; and the dd at 3.40 ppm with coupling constants of 9.7 and 1.1 Hz, which integrates to 1H and can be assigned as H3. The proton assigned as H3 exhibits a *trans*-diaxial

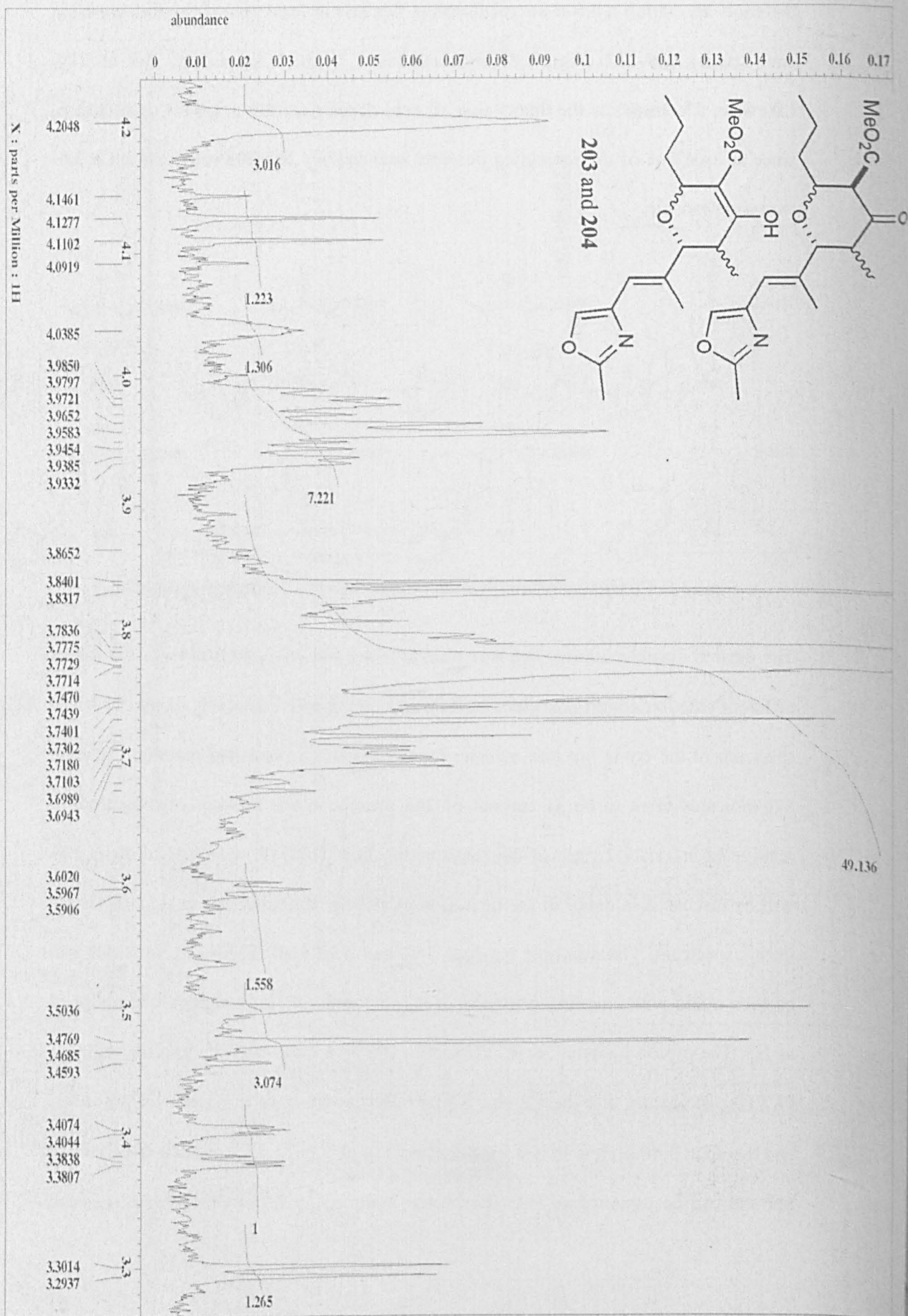
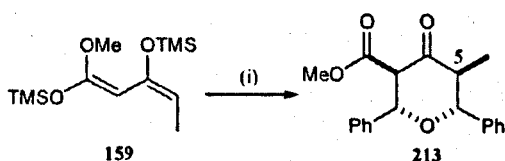


Figure 9: Expansion of 3.4 ppm region

coupling with H2 (9.7 Hz) and a J^A -coupling (1.1 Hz) with H5, which in turn indicates that the substitution at C5 is also equatorial.

The diastereoisomer of magnitude 3 can be confidently assigned as **205**. The very broad singlet which integrates for 3H at 4.20 ppm is characteristic of H6 in a 5,6-*cis* relationship; the doublet at 3.49 ppm with a coupling constant of 10.7 Hz which integrates for 3H could be assigned as H3, which is exhibiting a *trans*-diaxial coupling with H2, but no J^A -coupling with H5. The qd at 2.72 ppm with coupling constants of 7.2 and 2.6 Hz which integrates to 3H can be assigned as H5 which is exhibiting a *cis* coupling (2.6 Hz) with H6.

The remaining four diastereoisomers cannot be confidently assigned from the ^1H NMR spectrum alone, however evidence for the 2,6-*trans* keto species **208** or **209** comes from the doublet at 3.30 ppm with a coupling constant of 3.3 Hz which integrates for 1H and can be assigned as H3. This coupling indicates a 2,3-*cis* relationship, and as substituents at C-3 are assumed to be in equatorial positions it would imply that the C2 substituent is sitting axially.

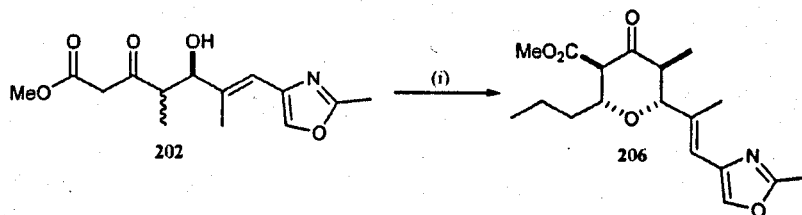


Reagents and conditions: (i) PhCHO, TiCl_4 , CH_2Cl_2 , -78°C , 1 hr, then TFA, PhCHO, -78°C to rt, 2 hr, 16%.

Scheme 57: Previous work on tetra-substituted THPOs within the group

There has been a very limited amount of work within the group on Maitland-Japp reactions to form penta-substituted systems. The reaction of diene **159** with two equivalents of benzaldehyde has been investigated and the 2,6-*cis*; 5,6-*cis* keto THPO **213** was isolated in 16% yield (Scheme 57).⁸⁰ However, a further 48% of THPO material was also isolated and assigned as "other diastereoisomers". Therefore,

perhaps it isn't uncommon to observe the formation of multiple diastereoisomers in these types of reactions without prior stereocontrol of the C5 position.



Reagents and conditions: (i) TMSI, *n*-butanal, CH₂Cl₂, rt, 26 h, 35%.
Scheme 58: TMSI-promoted cyclisation

This complex mixture of diastereoisomers was hardly desirable, so it was a very pleasing result when, at the start of a Lewis acid screen, when a single diastereoisomer 206 was produced in 35% yield when using iodotrimethylsilane as the Lewis acid in the Knoevenagel/Michael step (Scheme 58). Our attention was drawn to iodotrimethylsilane by a publication detailing iodotrimethylsilane mediated Prins-type cyclisations as a means of THP formation.⁸¹ The ¹H NMR spectrum of the isolated THPO enables conclusive assignment of the relative stereochemistry of 206 (Figure 10, overleaf). The ddd at 4.06 ppm with coupling constants of 9.7, 7.3 and 2.4 Hz (Figure 11) which integrates for 1H can be assigned as H2. H2 therefore exhibits a *trans*-diaxial coupling with H3 (9.7 Hz) indicating that the C2 and C3 substituents are both in equatorial positions. The dd at 3.40 ppm with coupling constants of 9.7 and 1.1 Hz, which integrates to 1H and can be assigned as H3.

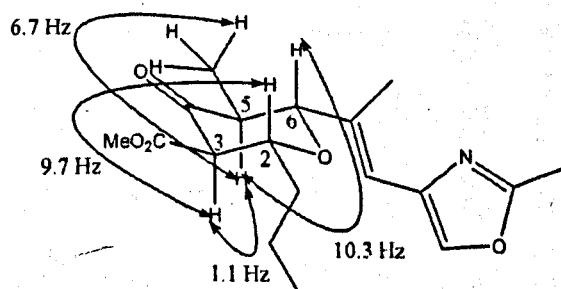


Figure 11: Assignment of relative stereochemistry of 206 from ¹H NMR coupling constants

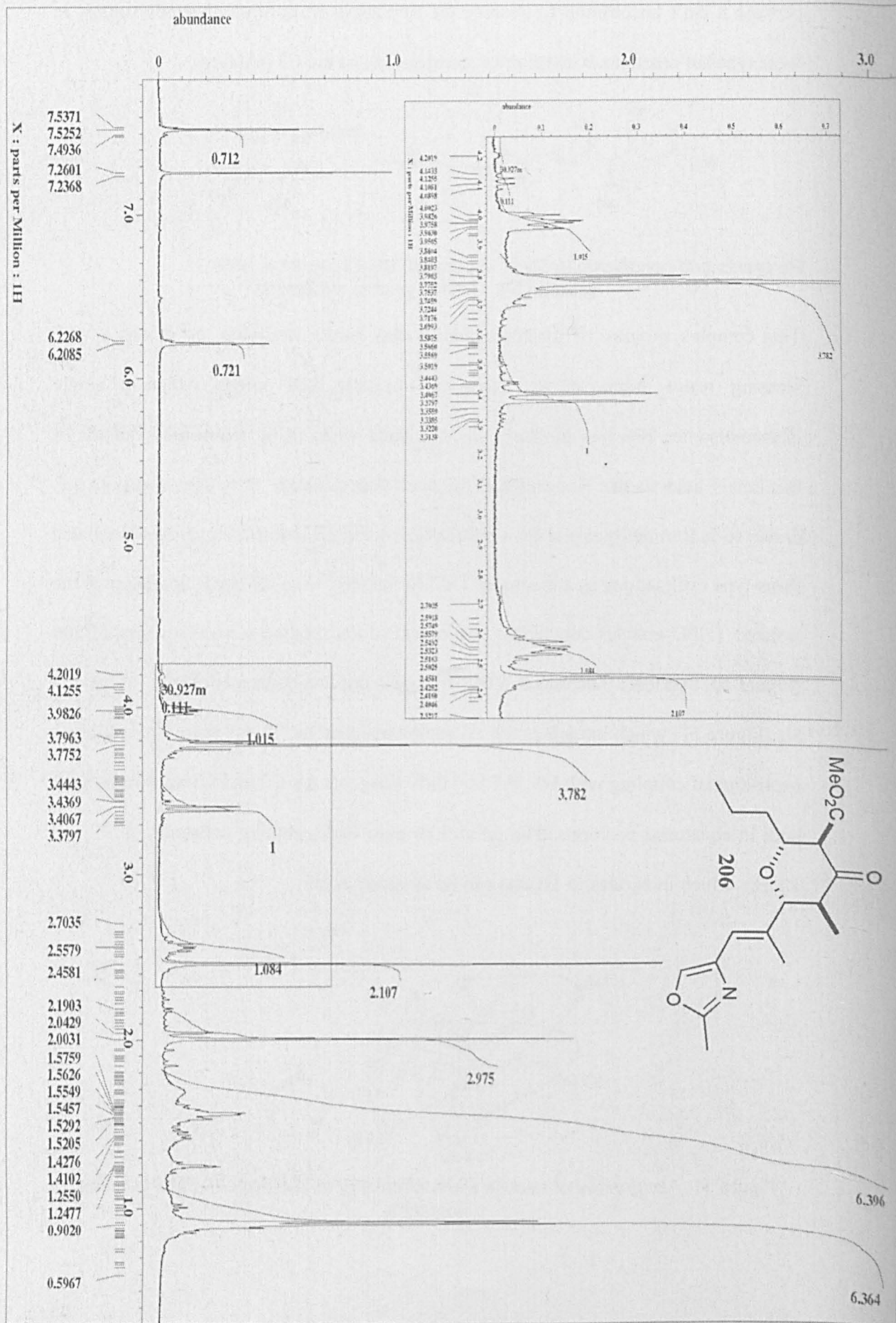
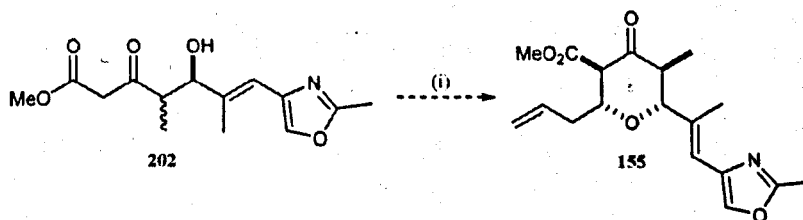


Figure 10: ¹H NMR spectrum of clean 206

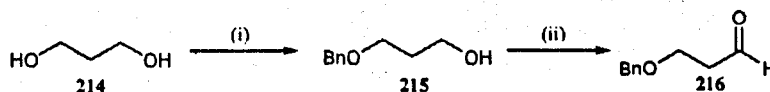
The proton assigned as H3 exhibits a *trans*-diaxial coupling with H-2 (9.7 Hz) and a J^A -coupling with H5 (1.1 Hz), which in turn indicated that the substituent at C5 is also equatorial. The dqd at 2.54 ppm with coupling constants of 10.3, 6.7, and 1.1 Hz which integrates to 1H can be assigned as H5. The proton assigned as H5 therefore exhibits a *trans*-diaxial coupling with H6 (10.3 Hz), a coupling to the adjacent methyl (6.7 Hz), and a J^A -coupling with H3 (1.1 Hz). The *trans*-diaxial coupling indicates the 5,6-*trans* relationship and confirms that the substituent at C-6 is also equatorial. The ^1H - ^1H COSY spectrum indicates that the peak for H6 is under the 3H singlet at 3.74. Re-running of the spectra in benzene- d_6 resulted in the separation of these two peaks, and a doublet at 3.42 ppm with a coupling constant of 10.4 Hz (to H-5 from ^1H - ^1H COSY) could be assigned as H6, enhancing the proof of the 5,6-*trans* relationship of equatorial substituents.



Reagents and conditions: (i) LA, buten-3-al 160, CH_2Cl_2 , rt, 26 h, no reaction.
Scheme 59: Failed cyclisation with buten-3-al

In an attempt to build upon this successful cyclisation, buten-3-al 160 was instead used as the second aldehyde under the same reaction conditions (Scheme 59). No reaction was seen to occur however, which was initially surprising as it had been previously shown that an analogous cyclisation using aldol adduct 170 and but-3-enal had proceeded in 43% yield to give THPOs 191 and 192 (Scheme 48). Extensive effort was invested in the Knoevenagel/Michael cyclisation of aldol adduct 202 with buten-3-al, but no reaction occurred when screening a range of Lewis acid reaction

conditions: $\text{Yb}(\text{OTf})_3$, TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, neat TMSI, or TMSI formed *in situ* from NaI and TMSCl. A possible reason for this could be that the rate of isomerisation of 3-butenal to the crotonaldehyde under the reaction conditions is faster than the rate of cyclisation. The rate of cyclisation of such γ -methylated aldol adducts as **202** are slower than that of aldol adducts such as **170**, due to steric hindrance in the transition state of the cyclisation. This effect will be even more prominent in *syn* aldol adducts since one of the two *syn* substituents must adopt an axial position in the transition state. In the synthesis of buten-3-al **160**, it has been noted that if the reaction mixture is left stirring at room temperature for longer than 4 hours, the buten-3-al starts to undergo bond migration to form crotonaldehyde. It is therefore feasible that in the Lewis acid cyclisation conditions at room temperature, bond migration is faster than the Knoevenagel/Michael reaction.

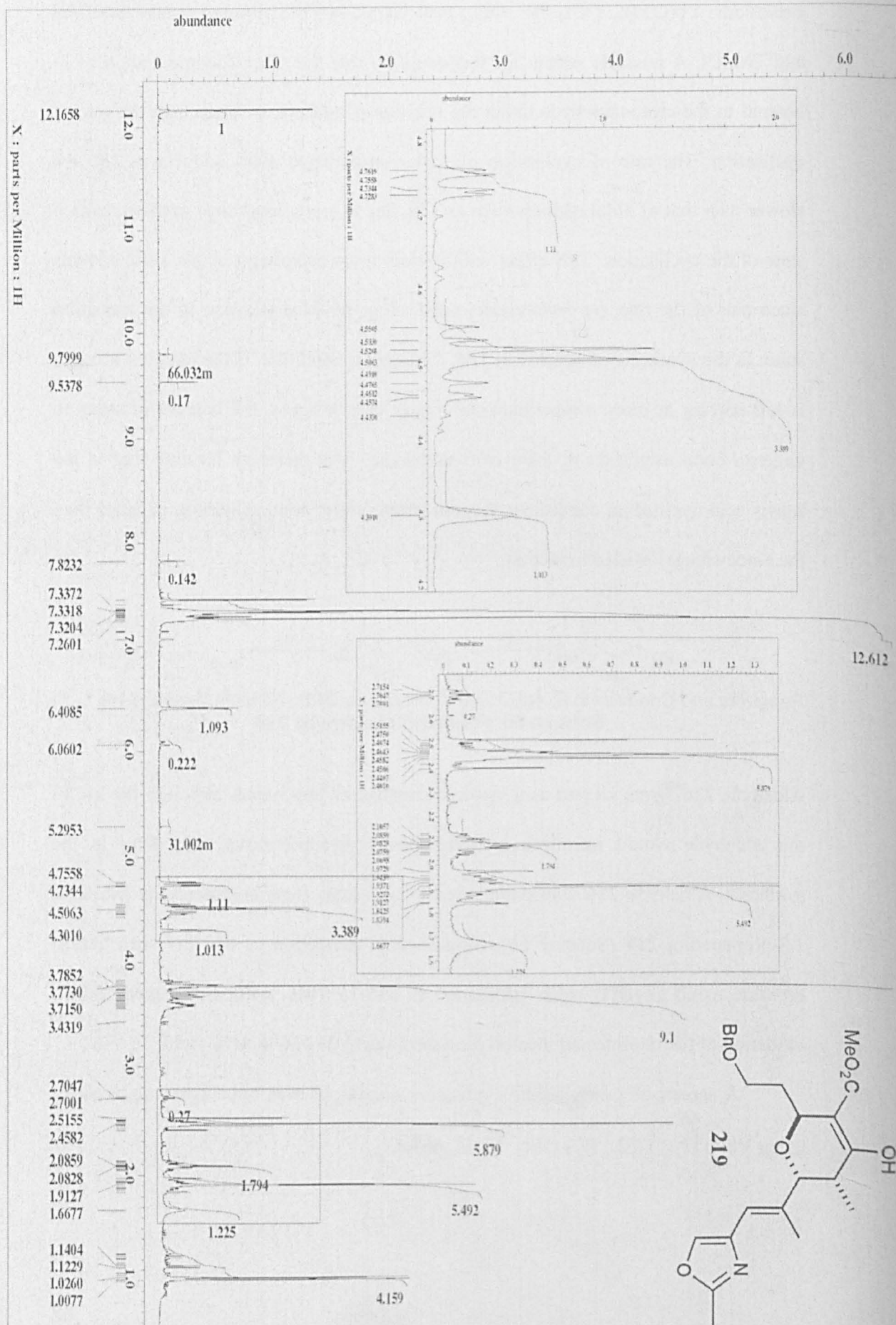


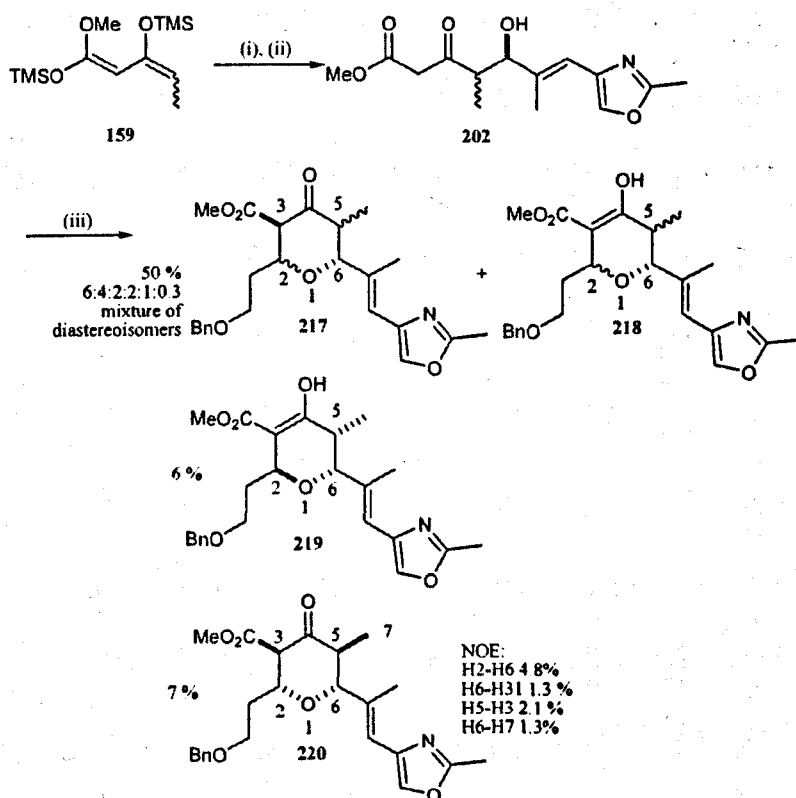
Reagents and Conditions: (i) Ag_2O , BnBr , CH_2Cl_2 , rt, 24 h, 70%; (ii) Swern, 81%.
 Scheme 60: Formation of aldehyde **216**

Aldehyde **216**⁸² was viewed as a viable alternative to but-3-enal, although the use of this aldehyde would introduce an extra benzyl group-removal step later in the synthesis. Aldehyde **216** was synthesised in two steps from commercially available 1,3-propanediol **214** (Scheme 60). Mono-benzyl protection of the diol with benzyl bromide using silver(I) oxide proceeded to **215** in 70% yield. Subsequent Swern oxidation of the unprotected alcohol furnished aldehyde **216** in 81% yield.

A screen of Lewis acidic cyclisation conditions was once again undertaken, using $\text{Yb}(\text{OTf})_3$, TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, TMSI, or InCl_3 .

Figure 12: ¹H NMR spectrum of clean 219





Reagents and conditions: (i) 29, TiCl_4 , CH_2Cl_2 , -78°C , 2 h; (ii) TFA; (iii) 216, $\text{Yb}(\text{OTf})_3$, TFA, CH_2Cl_2 , rt, 15 h, 63% over two steps.

Scheme 61: Cyclisation with aldehyde 216

The result of this screen showed the $\text{Yb}(\text{OTf})_3$ promoted cyclisation to be the only reliable conditions to furnish THPO products as a mixture of diastereoisomers (Scheme 61). Only the 5,6-*cis*-2,6-*trans* enol THPO 219 (6% yield from diene 158) and the 5,6-*trans*-2,6-*cis* keto THPO 220 (7% yield from diene 159) were isolatable by flash column chromatography, as these species run on silica at either end of an observed “diastereoisomeric streak”. The ^1H NMR data for 219 (Figure 12) enables the confident assignment of its structure. The 1H singlet at 12.16 ppm is characteristic of the hydrogen-bonded hydroxyl proton. The dd at 4.75 ppm with coupling constants of 11.0 and 2.8 Hz can be assigned as H2 from the ^1H - ^1H COSY correlation with the 2H multiplet at 1.86-1.96 ppm. Although not conclusive, the large coupling constant (11.0 Hz) is characteristic of H2 of enol THPOs with an axial non-branched chain

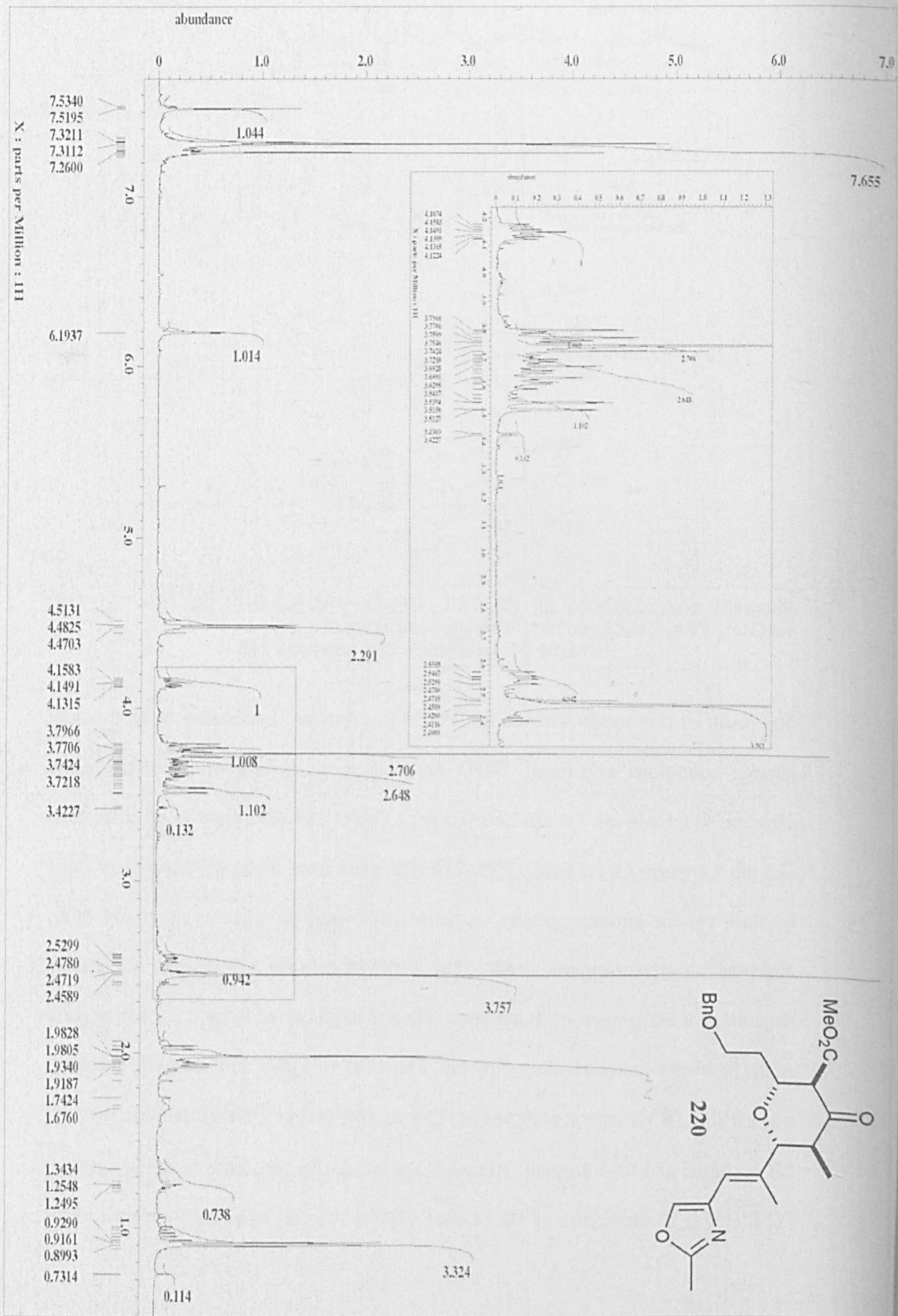


Figure 13: ^1H NMR spectrum of clean 220

substituent at C2. The broad singlet at 4.30 ppm can be assigned as H6 and is characteristic of a 5,6-*cis* relationship. The multiplet at 2.44-2.48 ppm can be assigned as H5 from the ^1H - ^1H COSY correlations with H-6 and the 3H doublet at 1.02 ppm. Since the peak for H5 is under a 3H singlet, the exact coupling constants between H5 and H6 could not be determined, however it can be inferred with a high level of confidence that there is no *trans*-diaxial interaction between H5 and H6, due to the broad singlet nature of the H6 peak.

The ^1H NMR data for 220 (Figure 13) provides conclusive evidence for its structural assignment. The 1H ddd at 4.15 ppm with coupling constants of 10.6, 7.0 and 3.5 Hz can be assigned as H2. The proton assigned as H2 therefore exhibits a *trans*-diaxial coupling with H3 (10.6 Hz) indicating that the C-2 and C-3 substituents are both in equatorial positions. The 1H dd at 3.53 ppm with coupling constants of 10.6 and 0.9 Hz, and can be assigned as H3. The proton assigned as H3 exhibits a *trans*-diaxial coupling with H2 (10.6 Hz) and a J^4 -coupling with H5 (0.9 Hz), which in turn indicates that the substitution C5 is also equatorial. The 1H dqd at 2.55 ppm with coupling constants of 10.6, 6.8, and 0.9 Hz can be assigned as H5. The proton assigned as H5 therefore exhibits a *trans*-diaxial coupling with H6 (10.6 Hz), a coupling to the adjacent methyl (6.8 Hz), and a J^4 -coupling with H3 (0.9 Hz). The *trans*-diaxial coupling indicates the 5,6-*trans* relationship and confirms that the substitution at C6 is also equatorial. The 1H doublet at 3.78 ppm with a coupling constant of 10.6 Hz can be assigned as H6, and reconfirms its *trans*-diaxial relationship with H-5. Furthermore, an NOE correlation of 4.8% from H2 to H6 confirm the 2,6-*cis* relationship, and an NOE correlation of 2.1% from H5 to H3 likewise confirms the 3,5-*cis* relationship.

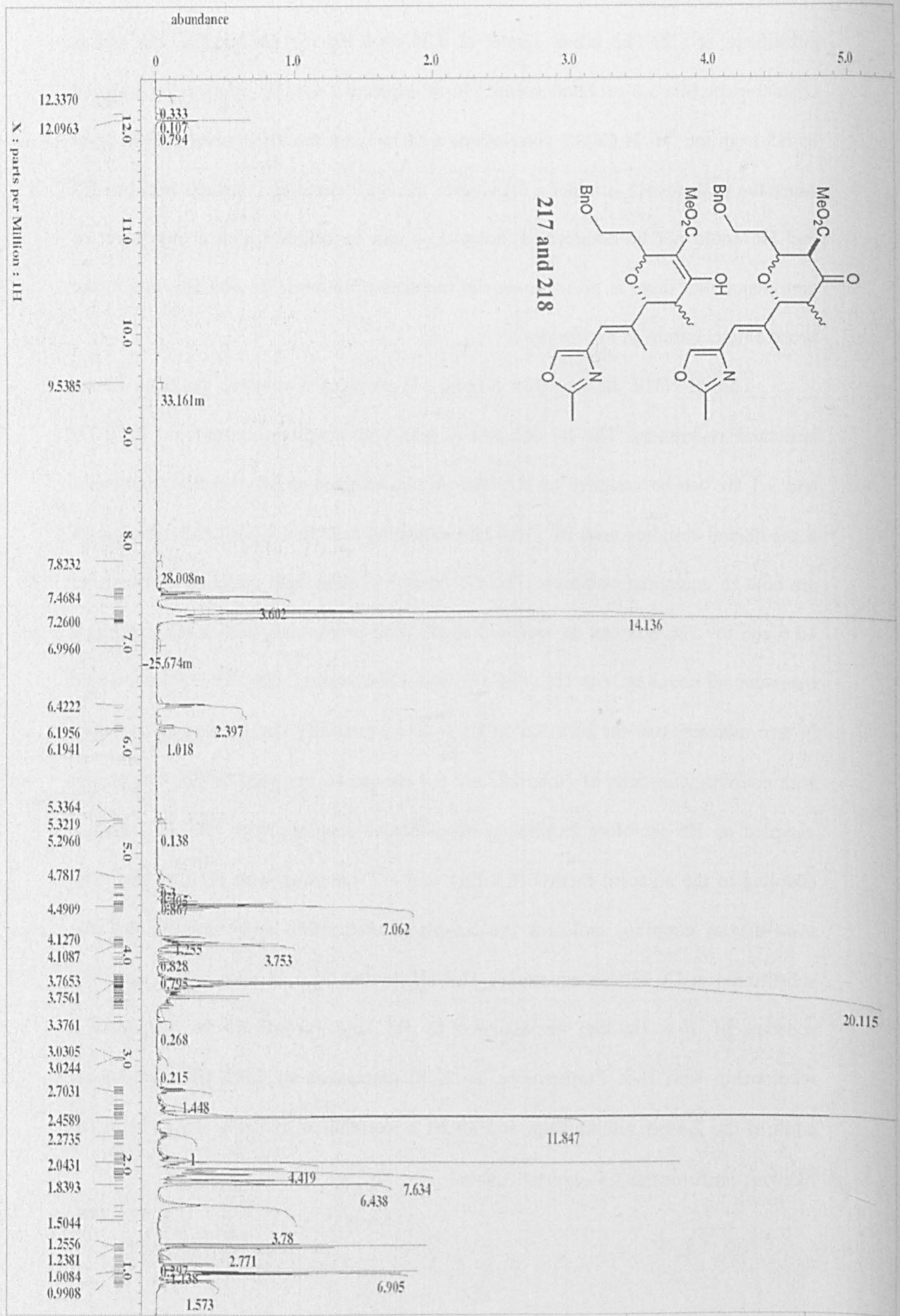


Figure 14: ^1H NMR spectrum of the diastereomeric mixture

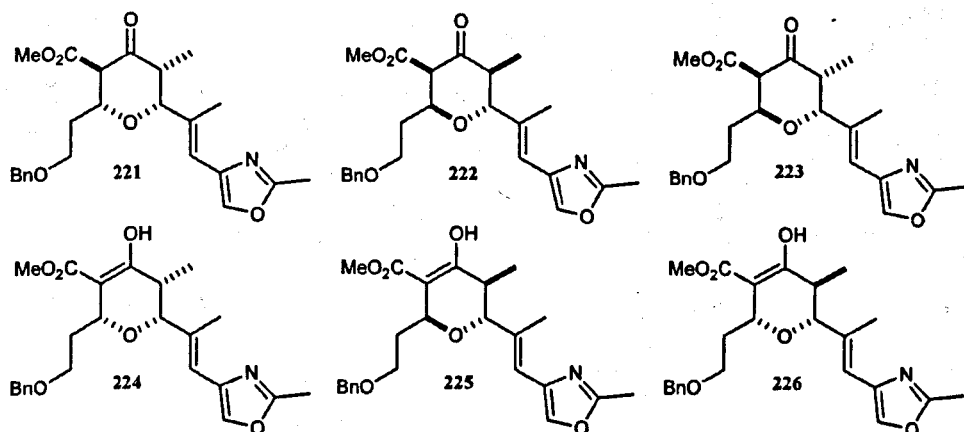


Figure 15: Possible diastereoisomers from $\text{Yb}(\text{OTf})_3$ promoted cyclisation

The majority of the product (50% yield from diene 158) existed as a mixture of six diastereoisomers 217 and 218. From the ^1H NMR spectrum of this mixture (Figure 14), it was clear that 219 and 220 were present, with 219 comprising 0.3 and 220 2 of the 6:4:2:2:1:0.3 diastereoisomeric distribution. However, the other remaining four diastereoisomers could be any of six (Figure 15). It was clear that two of the diastereoisomers were enol THPOs in the ratio of 4:2 from examination of the peaks in the 12 ppm region (Figure 16).

Therefore, from analysis of all the peaks that integrate for 4, it would be possible to tentatively assign the structure of this species representative of these peaks. The 1H broad singlet at 4.04 ppm is characteristic of H6 in a 5,6-*cis* relationship. Furthermore the 1H qd at 2.30 ppm with coupling constants of 7.3 and 2.6 ppm is characteristic of H5 in a 5,6-*cis* relationship. That would leave the 1H ddd at 4.60 ppm with coupling constants of 7.4, 2.3, and 1.2 Hz as H2. It would be expected for H2 of an enol of this THPO to be represented by a dd. However, since the 5,6-*cis*-2,6-*trans* enol has already been assigned, then the only other possibility is that this diastereoisomer is the 5,6-*cis*-2,6-*cis* enol 224 and that the extra coupling is due to a long range allylic-type coupling between the axial H2 and the hydroxyl proton. Having had no previous experience of 2,6-*cis* enol THPOs, this should be

considered as conjecture at this time. The species comprising 4 of the 6:4:2:2:1:0.3 diastereoisomeric distribution can be tentatively assigned as **224**.

From the analysis of all the peaks that integrate for 2 and do not represent 205 it would be possible to tentatively assign the structure of the final enol species. The 1H dd at 4.69 ppm with coupling constants of 10.4 and 2.7 Hz is characteristic of H-2, when the C-2 substitution is axial. Although as discussed earlier, this is not conclusive. The 1H doublet at 3.94 ppm with a coupling constant of 9.5 Hz is characteristic of H-6 in a *trans* diaxial relationship with H-5. Therefore the enol species comprising 2 of the 6:4:2:2:1:0.3 diastereoisomeric distribution can be tentatively assigned as **225**.

From analysis of the peaks that integrate for 6, it would be possible to tentatively assign the structure of this species representative of these peaks, since it is now known that this species exists as a keto THPO. The 1H broad singlet at 4.19 ppm is characteristic of H6 in a 5,6-*cis* relationship. Furthermore the 1H qd at 2.55 ppm with coupling constants of 7.2 and 2.6 ppm is characteristic of H5 in a 5,6-*cis* relationship. The 1H doublet at 3.62 ppm with a coupling constant of 10.8 Hz is characteristic of H-3 in a *trans*-diaxial relationship with H2, but which exhibits no J^A -coupling with an equatorial H5. From this analysis, the species comprising 6 of the 6:4:2:2:1:0.3 diastereoisomeric distribution can be assigned as **221**.

Finally, from analysis of all the peaks that integrate for 1, it should now be possible to tentatively assign the structure of the remaining THPO structure present in the diastereoisomeric mixture. The 1H ddd at 4.77 ppm with coupling constants of 8.5, 4.7, and 3.8 Hz is characteristic of H2 in a 2,3-*cis* relationship. The 1H doublet at 3.38 ppm with a coupling constant of 3.8 Hz is characteristic of H3 in a 2,3-*cis* relationship. The 1H doublet at 3.99 Hz with a coupling constant 9.0 Hz is

characteristic of H6 in a *trans*-diaxial relationship. Furthermore the ¹H dq at 3.03 ppm with coupling constants of 9.0 and 6.6 Hz is characteristic of H5 in a *trans*-diaxial relationship. This evidence indicates that the diastereoisomer comprising 1 in the 6:4:2:2:1:0.3 ratio is **222**. Thus the diastereoisomeric mixture can be tentatively confirmed to exist as a 6:4:2:2:1:0.3 ratio of **221** : **224** : **220** : **225** : **222** : **219**.

The required THPO diastereoisomer **220** for the synthesis of the phorboxazoles, could only be isolated in a disappointing 7% yield. The equivalent of another 6.4% of **220** had been produced by the reaction in the **217/218** mixture, but unless a suitable method could be found to alter these diastereoisomeric ratios, the formation of **220** as the major diastereoisomer would become ever-so more reliant upon the initial 5,6-*anti* stereochemistry of the cyclisation precursor **20**.

Lewis Acid	Starting ratio 221:224:220:225:222:219 / %	Reaction time / h	Ratio after stirring 221:224:220:225:222:219 / %
a BF ₃ .OEt ₂	39:26:13:13:6:2	12	26:42:11:15:4:2
b Yb(OTf) ₃	39:26:13:13:6:2	24	48:14:18:9:8:4
c TiCl ₄	43:0:12:16:13:16	20	85:0:0:0:0:15

Table 2: Lewis acid promoted re-equilibration of diastereoisomeric THPOs

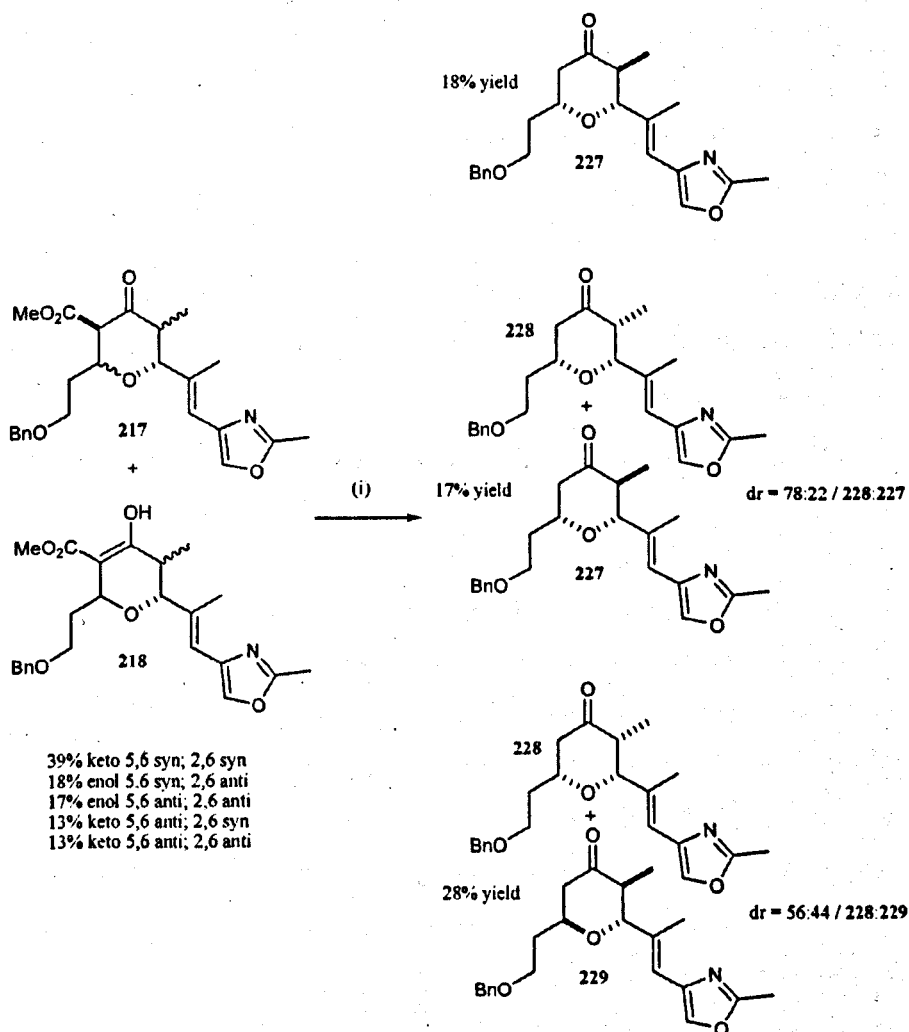
It was thought that stirring the diastereoisomeric mixture in the presence of a Lewis acid for a prolonged period of time could perturb the ratio of the mixture, by induction of a series of retro-Michael/Michael reactions. Previous work in the group has achieved the desired re-equilibration with some success, most notably in the synthesis of (±)-centrolobine (Scheme 31).^{64,65} The magnitude of the effect on the diastereoisomeric ratio was dependent upon the choice of Lewis acid (Table 2). Stirring in the presence of titanium tetrachloride resulted in the decomposition of THPO material, and therefore skewed the result of the re-equilibration as only diastereoisomers **221** and **219** were present in the product mixture (entry c). This

result is in accordance with the fact that cyclisation reactions with titanium tetrachloride at room temperature resulted in decomposition of the starting material. Stirring in the presence of boron trifluoride diethyl etherate did not seem to alter the ratio significantly (entry a); apart from initiating an apparent tautomerisation from **221** to **224**. The desired diastereoisomer **220** was seen to be slightly less abundant in the product distribution than in the starting distribution. Stirring in the presence of ytterbium triflate resulted in an increase in the abundance of the desired diastereoisomer **220** from 13% to 18% however this result was unlikely to be highly impacting upon the synthetic strategy as it was such a negligible increase (entry b). This result was likely to be due to the fact that some **220** had been separated from the mixture and isolated, so stirring with $\text{Yb}(\text{OTf})_3$ readdressed the diastereoisomeric equilibrium of the reaction and thus the increase in **220** compensated for its deficit due to separation. One key point to note from these two re-equilibration experiments is that the Lewis acids had seemingly no effect on the *5,6-trans* : *5,6-cis* ratios. Attempts to make the reaction diastereoselective, such as running the reactions at high and low temperatures, in a bid to target the thermodynamic and kinetic products respectively, proved fruitless. The low temperature conditions resulted in no reaction, and the high temperatures in the decomposition of starting material.

6.2.3 Decarboxylation

It was thought that maybe the diastereoisomeric ratio would equilibrate to the favourable all-equatorially substituted THPO species after decarboxylation. A number of decarboxylation techniques were employed to no avail. The conditions investigated involved initial saponification of the ester: LiOH in THF/H₂O,⁸⁰ Ba(OH)₂ in MeOH/H₂O,⁸³ and 5% H₂SO₄ in THF/H₂O. None of these methods achieved the

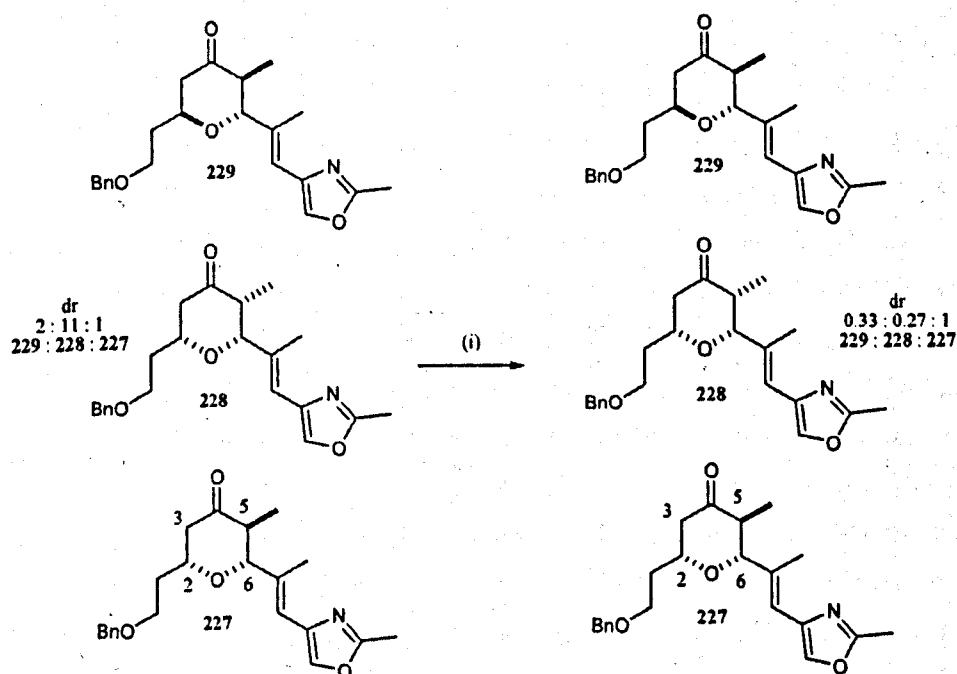
desired saponification, and observations by TLC were consistent throughout: the diastereoisomeric mixture remained unchanged until the reaction was heated or left in excess of 3 days, resulting in the decomposition of starting material.



Reagents and conditions: (i) H₂O, DMF, microwave, 120 °C, 250 W, 20 min, 63%.
 Scheme 62: Microwave-promoted decarboxylation

A Kraptcho decarboxylation was attempted by heating the THPO diastereoisomeric mixture in DMSO, H₂O, and NaCl.⁸⁴ After two hours, the starting material was still present by TLC analysis, however it looked as if the diastereoisomeric mixture was converging to a more single spot on the TLC plate. Continued heating again caused decomposition of the product. A subsequent reaction was stopped after two hours, and

although it had not gone to completion, there was some sign of decarboxylated THPO material in the ^1H NMR spectrum of the crude material. It was then decided to carry out essentially the same reaction (heating in DMF/ H_2O) using the microwave as the source of heating (Scheme 62). Pleasingly, complete decarboxylation was seen to occur after 20 minutes at 250 W. The reaction proceeded in an overall 63% yield and the 2,6 and 5,6 stereochemical information was seemingly retained. It was thought that desired isomer **227** could be produced from the epimerisation of **228** under thermodynamic conditions since **227** should be the most thermodynamically stable isomer, as all substituents on the ring adopt an equatorial position.



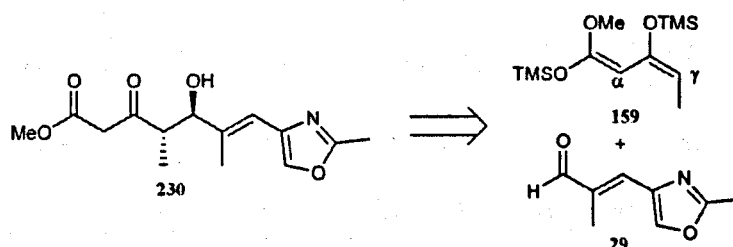
Reagents and conditions: (i) LDA, 0.95 eq, THF, rt, 16 h; (ii) 10 M AcOH (aq), rt, 64%
Scheme 63: Epimerisation of **228**

Treatment of the diastereoisomeric mixture comprising of **229:228:227** (dr 2:11:1) with 0.95 equivalents of LDA at room temperature resulted in a change in the diastereoisomeric composition to **229:228:227** (dr 0.33:0.27:1) (Scheme 63). This was an encouraging result as it showed that the 5,6 stereochemistry could be manipulated

to the desired *trans* configuration, and so the initial *syn* or *anti* orientation of the cyclisation precursor was at this stage deemed unimportant, unless however it were to have an effect on the 2,6 *trans:cis* ratio in the cyclisation step.

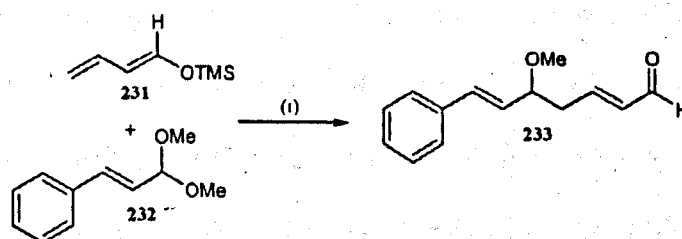
6.3 Catalytic, Asymmetric, Vinylogous Aldol Studies

6.3.1 Background



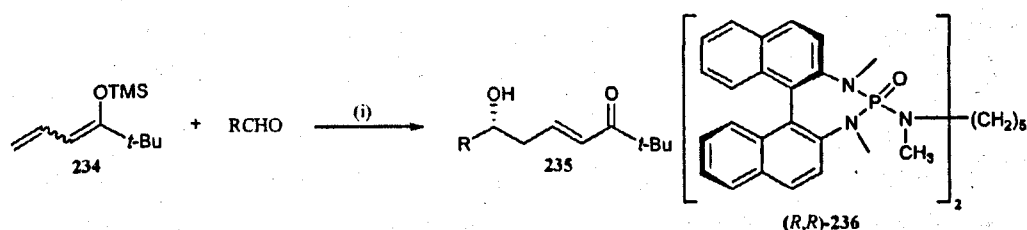
Scheme 64: Retrosynthetic analysis of chiral cyclisation precursor **230**

It was envisaged that the δ -hydroxy- β -ketoester species **230** (Scheme 64) would be synthesised as a single enantiomer by means of an asymmetric vinylogous aldol reaction between the dienol ether **159** and aldehyde **29**. Progress in the development of enantioselective vinylogous aldol reactions has been substantially slower than that of the classic enantioselective aldol reaction due to the additional problem of α,γ -site selectivity of the addition. However since the mid 1990s, a number of examples have been published which document vinylogous aldol reactions with high levels of regio-, diastereo- and enantiocontrol.⁸⁵



Reagents and conditions: (i) TiCl_4 , THF, $-78\text{ }^\circ\text{C}$, 88%, >99:1 $\gamma:\alpha$
Scheme 65: Mukaiyama vinylogous alkylation

Early research found that metallodienolates, formed from the deprotonation of α,β -unsaturated esters with LDA/HMPA were trapped with iodomethane to form the α -methylated esters exclusively.⁸⁶ However, Mukaiyama later reported the exclusive formation of the γ -addition product from the reaction of dienol ether **231** with the dimethyl acetal **232** under Lewis acid conditions (Scheme 65).⁸⁷ The steric crowding of the α -position relative to the γ -position, due to the presence of the neighbouring silyl group, was cited as a reason for the observed selectivity. Mukaiyama's findings provided a base from which to start in the quest for an enantioselective vinylogous reaction.



Reagents and conditions: (i) 5-10 mol% (*R,R*)-**236**, SiCl_4 , 20 mol% DIPEA, CH_2Cl_2 , -50 °C.

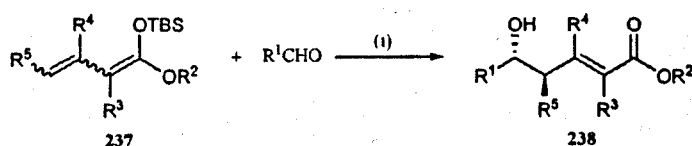
Scheme 66: Denmark's vinylogous aldol reaction of the ketone-derived dienol ether

R	Product no.	Yield / %	er / R:S
	235a	94	99.5 : 0.5
	235b	82	99.5 : 0.5
	235c	90	96 : 4
	235d	40	84 : 16

Table 3: Results of vinylogous aldol reaction of ketone-derived enol ether **234**⁸⁸

Research in the Denmark group has focused on asymmetric variants of a Mukaiyama-type aldol reaction, and has progressed to encompass the enantioselective additions of dienol ethers derived from acetoacetate species, α,β -unsaturated esters, and the more seldom explored α,β -unsaturated ketones.^{88,89} A catalytic amount of chiral

bisphosphoramidate (*R,R*)-**236** and silicon tetrachloride promoted the aldol addition of ketone-derived enol ether **234** with aldehydes to access δ -hydroxy-(*E*)-enones exclusively (Scheme 66). The vinylogous aldol additions proceeded in good yield and with excellent enantioselectivity for reactions with aromatic, heteroaromatic and olefinic aldehydes, while addition to acetylenic aldehydes proceeded in modest yield with good enantioselectivity. A drawback of this methodology is its failure to accommodate aliphatic aldehydes (Table 3).



Reagents and conditions: (i) 1-5 mol% (*R,R*)-**236**, SiCl₄, 20 mol% DIPEA, CH₂Cl₂, 3-24 h, -78 °C.

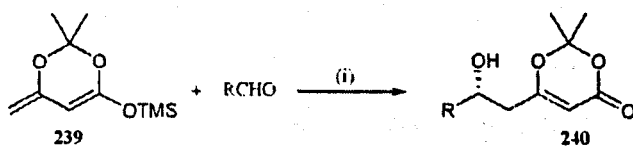
Scheme 67: Denmark's vinylogous aldol reaction of the dienol ethers of simple esters **237**

R ¹	Dienol ether	R ²	R ³	R ⁴	R ⁵	Product no.	Yield / %	dr / <i>syn:anti</i>	er / <i>R:S</i>
Ph	237a	Et	H	H	H	238a	89		99:1
PhCH=CH	237a	Et	H	H	H	238b	84		98:2
PhCH ₂ CH ₂	237a	Et	H	H	H	238c	68		95:5
Ph	237b	Me	Me	H	H	238d	93		99.5:0.5
PhCH=CH	237b	Me	Me	H	H	238e	88		99.5:0.5
PhCH ₂ CH ₂	237b	Me	Me	H	H	238f	0		
Ph	237c	Et	H	Me	H	238g	91		96:4
PhCH=CH	237c	Et	H	Me	H	238h	97		94:6
PhCH ₂ CH ₂	237c	Et	H	Me	H	238i	73		97.5:2.5
Ph	237d	<i>t</i> -Bu	H	H	Me	238j	92	99:1	94.5:5.5
PhCH=CH	237d	<i>t</i> -Bu	H	H	Me	238k	99	99:1	91:9
PhCH ₂ CH ₂	237d	<i>t</i> -Bu	H	H	Me	238l	0		

Table 4: Results of vinylogous aldol reaction of ester-derived enol ethers **237**⁸⁹

Application of the methodology to the addition of ester-derived dienol ethers has afforded an expedient route to the formation of δ -hydroxy-(*E*)-enones with substitution at either the α,β - or γ -positions (Scheme 67). Dienol ether **237** derived from ethyl but-2-enoate underwent an aldol addition with all three of the sample aldehydes, which were aromatic, olefinic, and aliphatic in nature, at the γ site

exclusively (Table 4). The reactions proceeded in good yield and with excellent diastereoselectivity. Addition to the aliphatic aldehyde was considered to be an especially exciting result since such additions had previously proved problematic under these conditions. Dienol ethers which exhibited methyl substitution at the α - or β -positions, **237b** and **237c**, were also found to undergo aldol additions in good yield and with excellent enantioselectivity. However, addition of the methyl tiglate derivative **237b** to the aliphatic aldehyde proved to be unsuccessful. The use of dienol ether **237d**, which exhibited a terminal methyl group, in an aldol reaction resulted in the formation of contiguous stereocentres and as such would give an indication of the level of diastereoselectivity of the reaction. The reaction of less bulky esters, such as the derivative of ethyl pent-2-enoate resulted in reduced α,γ -site selectivity. Addition of **237d** to benzaldehyde and *trans*-cinnamaldehyde furnished *anti* aldol adducts **238j** and **238k** exclusively, in good yield and with excellent enantioselectivity. However, addition of **237d** to the aliphatic aldehyde was again unsuccessful. Nevertheless, the extension of this methodology to a range of dienol ethers and aldehydes is testament to its versatility.



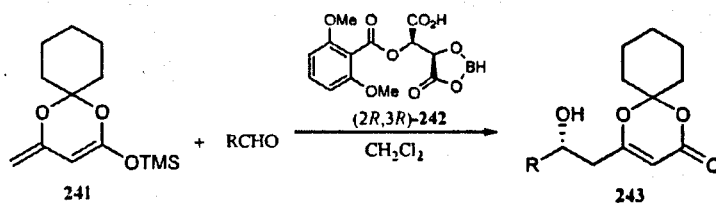
Reagents and conditions: (i) 1-5 mol% (*R,R*)-**236**, SiCl_4 , 20 mol% DIPEA, CH_2Cl_2 , 3-24 h, -78°C .

Scheme 68: Denmark's vinylogous aldol reaction of the dioxanone-derived dienol ether **239**

R	Product no.	Yield / %	er / <i>R:S</i>
Ph	240a	92	87 : 13
PhCH=CH	240b	88	89 : 11
PhCH ₂ CH ₂	240c	83	94.5 : 5.5

Table 5: Results of vinylogous aldol reaction of dioxanone-derived enol ether **239**⁸⁸

Further extension of the methodology entailed an aldol addition of the dioxanone-derived enol ether **239** to the same three sample aldehydes (Scheme 68). Quick functional group interconversion of the aldol adduct **240**, upon successful completion of the addition, would reveal a β -ketoester, which is the desired functionality for our synthetic strategy. The discussion will therefore now focus upon dienol ethers derived from acetoacetate/acetopropanoate species. Denmark's chiral Si-complex catalytic system promoted the vinylogous aldol addition of the dioxanone-derived dienol ether to all three aldehydes in very good yields and with good to excellent enantioselectivities (Table 5).



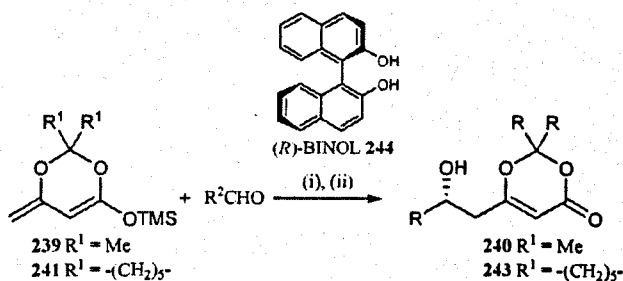
Scheme 69: Sato's vinylogous aldol reaction of the dioxanone-derived dienol ether **241** using a CAB catalytic system

R	Product no.	Conc. Of 242 / mol%	Temp. / °C	Yield / %	er / R:S
Ph	243a	50	-78	69	83.5 : 16.5
Ph	243a	100	-98	91	86.5 : 13.5
PhCH=CH	243b	50	-78	56	86.5 : 13.5
PhCH=CH	243b	100	-98	93	88 : 12
<i>n</i> -Bu	243c	50	-78	52	15 : 85
<i>n</i> -Bu	243c	100	-98	39	18 : 82

Table 6: Results of vinylogous aldol reaction of dioxanone-derived enol ether **241** in CAB catalyst system⁹⁰

The first enantioselective vinylogous aldol addition of a dioxanone-derived dienol ether **241** to aldehydes was reported by Sato in 1994, who documented the use of the chiral acyloxyborane (CAB) complex (2*R*,3*R*)-**242** (Scheme 69).⁹⁰ Successful aldol reactions of **241** with aromatic, olefinic, and aliphatic aldehydes were observed (Table 6). The reactions yielded the masked β -ketoester aldol adducts in moderate yields and

enantioselectivities. The use of high catalyst loadings was necessary due to the notorious competitive achiral addition associated with the CAB catalytic system.



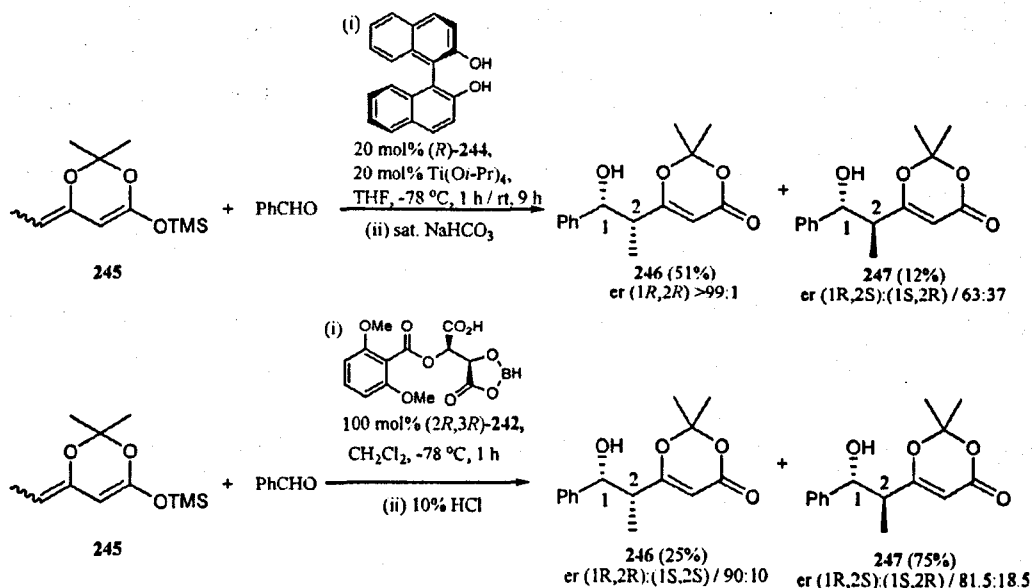
Reagents and conditions: (i) 20 mol% (R)-244, 20 mol% Ti(O*i*-Pr)₄, 4 Å MS, THF, -78 °C to rt, 16 h; (ii) TFA, -78 °C.

Scheme 70: Sato's use of Ti(IV)-BINOL complex for the activation of aldehydes in vinylogous aldol reactions

R ²	R ¹	Product	Yield / %	er / R:S
Ph	Me	240a	38	94 : 6
	Me	240b	32	66.5 : 33.5
<i>n</i> -C ₉ H ₁₉	Me	240d	55	6 : 94
Ph	-(CH ₂) ₅ -	243a	93	96 : 4
	-(CH ₂) ₅ -	243b	58	89.5 : 10.5
<i>n</i> -C ₉ H ₁₉	-(CH ₂) ₅ -	243d	37	12 : 88

Table 7: Results of Ti(IV)-BINOL complex activated vinylogous aldol reactions⁹⁰

In a bid to improve the selectivity of the addition, the use of a chiral Ti(IV)-BINOL complex was also employed, as it was a commonly used Lewis acid catalyst system in aldol reactions of silyl ketene acetals (Scheme 70).⁹⁰ The use of a different dioxanone-derived dienol ether **239** was also investigated as a comparison to the dienol ether **241**. The use of the Ti(IV)-BINOL catalytic system tolerated lower levels of catalyst loading and resulted in an increase in the enantioselectivity of the addition in most cases (Table 7). However, this increase in selectivity was generally accompanied by an observed drop in yield, compared to the reactions promoted by the CAB-catalytic system. This catalytic system was optimum for the aromatic and aliphatic aldehydes whereas the CAB-system was better for the olefinic aldehyde.

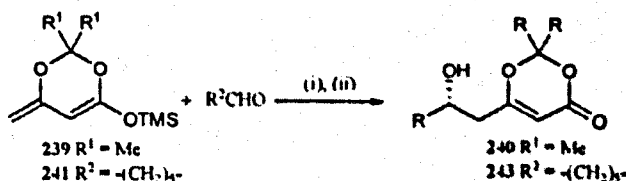


Scheme 71: Sato's use of dioxanone-derived dienol ether **245**

Extension of the methodology to incorporate the acetopropanoate-derived dienol ether **245** was investigated by using both Ti(IV)-BINOL and CAB catalytic systems to promote addition to benzaldehyde (Scheme 71).⁹⁰ This was of particular interest, as this dienol ether **245** would provide quick access to the desired δ -hydroxy- γ -methyl- β -ketoester upon addition to an aldehyde. Sato reports the use of chiral Ti(IV)-BINOL system to promote the addition, furnishing the aldol adduct in 63% yield, as a 4:1 mixture of *syn:anti* diastereoisomers, **246** and **247** respectively. The formation of the two adducts proceeded with differing levels of enantioselectivity; excellent for the *syn* adduct, but poor for the *anti* adduct. The CAB-promoted reaction, on the other hand, exhibited a reversal of this diastereoselectivity, furnishing a 1:3 mixture of *syn:anti* diastereoisomers in quantitative yield. Both diastereoisomers were formed with moderate enantioselectivity.

A report by Scettri and Soriente details that a slight modification of the reaction conditions for Sato's chiral Ti(IV)-BINOL promoted vinylogous aldol reactions of the dioxanone-derived dienol ethers **239** and **241** has led to an increase in

both yield and enantioselectivity for their addition to benzaldehyde, *trans*-cinnamaldehyde and *n*-decanal (Scheme 72, Table 8).⁹¹



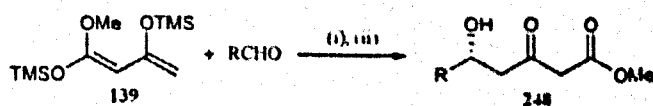
Reagents and conditions: (i) 8 mol% (*R*)-244, 8 mol% Ti(O*i*-Pr)₄, 4 Å MS, THF, -78 °C to rt, 16 h; (ii) TFA, -78 °C.

Scheme 72: Scettri/Soriente use of Ti(IV)-BINOL complex for the activation of aldehydes in vinylogous aldol reactions using dioxanone-derived enol ethers

R ¹	R ²	Product	Yield / %	er / R:S
Ph	Me	240a	84	99.5 : 0.5
	Me	240b	92	94.5 : 5.5
<i>n</i> -C ₉ H ₁₉	Me	240d	79	94.5 : 5.5
Ph	-(CH ₂) ₅ -	243a	81	98 : 2
	-(CH ₂) ₅ -	243b	82	92 : 8
<i>n</i> -C ₉ H ₁₉	-(CH ₂) ₅ -	243d	60	99.5 : 0.5

Table 8: Results of vinylogous aldol reactions promoted by Ti(IV)-BINOL complex using dioxanone-derived enol ethers 239 and 241⁹¹

The use of TFA is cited as the reason for the increase in the observed enantioselectivity, since cleavage of the silyl group before work-up prevents racemization of the newly created stereocentre.



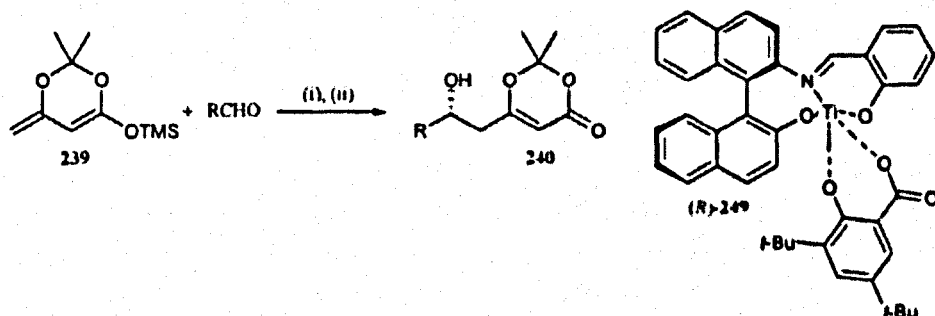
Reagents and conditions: (i) 8 mol% (*R*)-244, 8 mol% Ti(O*i*-Pr)₄, 4 Å MS, THF, -78 °C to rt, 16 h; (ii) TFA, -78 °C.

Scheme 73: Scettri/Soriente use of Ti(IV)-BINOL complex for the activation of aldehydes in vinylogous aldol reactions using Chan's diene 139

R ¹	Product	Yield / %	er / R:S
Ph	248a	94	96 : 4
	248b	84	99.5 : 0.5
	248c	82	99.5 : 0.5
<i>n</i> -C ₉ H ₁₉	248d	70	99 : 1

Table 9: Results of vinylogous aldol reactions promoted by Ti(IV)-BINOL complex using Chan's diene 139⁹¹

Scettri and Soriente also demonstrated the application of their methodology to the addition of Chan's diene **139** to a range of aldehydes (Scheme 73, Table 8).⁹¹ Aldol addition promoted by Ti(IV)-BINOL furnished adducts in reproducibly high yields and with excellent enantioselectivity. The use of Chan's diene was also of particular interest to us, since it provides access to the direct assembly of chiral δ -hydroxy- β -ketoester. Moreover, if the protocol was applicable to the dienol ether **159**, it would provide an ideal platform from which to begin our studies into the asymmetric vinylogous aldol reaction.



Reagents and conditions: (i) (*R*)-**249** (1-3 mol%), Et₂O, 0 °C; (ii) TFA, THF.

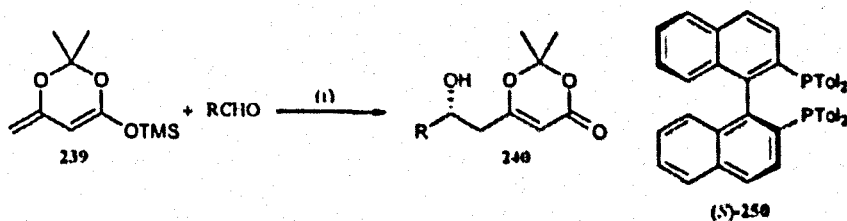
Scheme 74: Carreira's use of chiral Ti(IV) activation of aldehydes in vinylogous aldol reactions with dioxanone-derived dienol ether **239**

R	Product no.	Yield / %	cr / <i>R</i> : <i>S</i>
	240e	86	95.5 : 4.5
	240f	97	97 : 3
	240b	88	96 : 4
	240g	95	96 : 4
	240a	83	92 : 8
	240h	97	90 : 10
	240i	79	96 : 4

Table 10: Results of catalytic asymmetric addition of dienol ether **239** to a range of chiral Ti(IV) activated aldehydes⁹²

Previous to Soriente and Scettri's findings, Carreira had reported some very robust methodology for the asymmetric vinylogous aldol reaction of the dioxanone-derived dienol ether with a range of aldehydes, also promoted by activation with a chiral

Ti(IV) species, (*R*)-**249** (Scheme 74). Vinylogous aldol addition of dioxanone-derived dienol ether **239**, promoted by (*R*)-**249**, furnished adducts **240** in high yields upon reaction with aldehydes that were aliphatic, olefinic, acetylenic and aromatic in nature (Table 9). Additions to olefinic and acetylenic aldehydes proceeded with excellent diastereoselectivity, whereas a slight decrease in enantioselectivity was observed for additions to the aliphatic and aromatic aldehydes. Carreira documents the facile unmasking of the acetoacetate derivative from reactions of **240** with: $\text{LiAl}(\text{NHBn})_4$ to access amides; BuOH to access β -ketoesters; and ZnNO_3 under basic conditions to access lactones. This methodology was utilised in Carreira's total synthesis of macrolactin A.⁹³



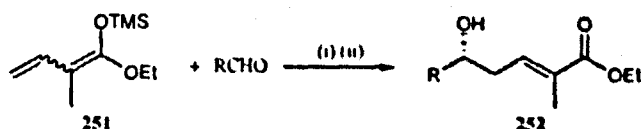
Reagents and conditions: (i) 2.2 mol% (*S*)-**250**, 2 mol% $\text{Cu}(\text{OTf})_2$, 4 mol% $(\text{Bu}_4\text{N})\text{Ph}_3\text{SiF}_2$, THF, $-78\text{ }^\circ\text{C}$.

Scheme 75: Carreira's use of chiral Cu(II) dienolate of **239** formation in vinylogous aldol reactions

R	Product	Yield / %	er / R:S
Ph	240a	92	97 : 3
	240j	86	96.5 : 3.5
	240k	98	97.5 : 2.5
	240l	91	97 : 3
<i>p</i> -MeOC ₆ H ₄	240m	93	97 : 3
	240b	83	92.5 : 7.5
	240n	82	95 : 5
	240o	48	95.5 : 4.5

Table 11: Results of catalytic asymmetric addition of chiral Cu(II) dienolates to a range of aldehydes⁹⁴

In contrast to all of the examples of enantioselective vinylogous aldol reactions discussed thus far which have involved the use of chiral Lewis acids to activate aldehydes, Carreira developed a catalytic system based on the formation of a chiral Cu(II) dienolate (Scheme 75).⁹⁴ It is proposed that the mixing of (*S*)-Tol-BINAP, Cu(OTf)₂ and (Bu₄N)Ph₃SiF₂ assembles the Cu(II) fluoride complex (*S*)-Tol-BINAP.CuF₂, which effects desilylation of the dienol ether with concomitant Cu(II) enolate formation. Enantioselective addition of the chiral Cu(II) dienolate derivative of **239** to a number of aromatic, heteroaromatic and olefinic aldehydes proved to be general (Table 10). Addition to aliphatic aldehydes was also observed, but the reactions were poor yielding.



Reagents and conditions: (i) 11 mol% (*S*)-**250**, 10 mol% Cu(OTf)₂, 20 mol% (Bu₄N)Ph₃SiF₂, THF, -78 °C, 0.5-8 h; (ii) TFA, THF, -78 -78 °C to rt.

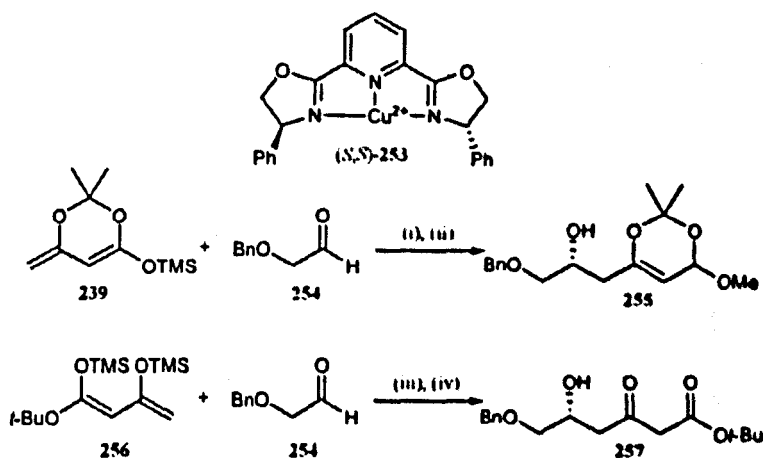
Scheme 76: Bluet and Campagne's application of chiral Cu(II) methodology to the vinylogous aldol reactions of ester-derived dienol ether **251**

R	Product no.	Yield / %	er / R:S
Ph	252a	80	85 : 15
	252b	35	78 : 22
<i>i</i> -Pr	252c	70	74 : 26
	252d	68	88.5 : 11.5

Table 12: Results of chiral Cu (II) dienolate methodology applied to the vinylogous aldol reactions of ester-derived enol ether **251**⁹⁵

Bluet and Campagne applied Carreira's chiral Cu(II) dienolate methodology to the enantioselective vinylogous aldol addition of the ester-derived enol ether **251** to aromatic, olefinic and aliphatic aldehydes (Scheme 76, Table 11).⁹⁵ Their examples were the first reported of their kind and furnished δ -hydroxy enones with moderate

enantioselectivity. The addition to aliphatic and aromatic aldehydes proceeded in good yield, however the addition to *trans*-cinnamaldehyde was low yielding.

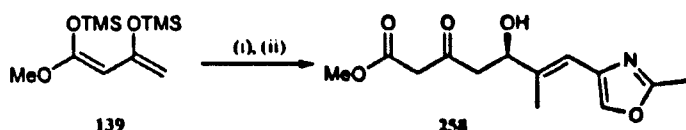


Reagents and conditions: (i) 5 mol% (S,S)-253, CH₂Cl₂, -78 °C; (ii) 1 N HCl, THF, 94%, er 96:4/S:R; (iii) 2 mol% (S,S)-253, CH₂Cl₂, -98 °C to -78 °C; (iv) PPTS, MeOH, 85%, er 99.5:0.5/S:R.

Scheme 77: Evans use of Cu(II)-pybox catalytic system

Evans has demonstrated the use of a Cu(II)-*bis*-oxazoline complex (S,S)-253 to promote enantioselective vinylogous aldol reactions of the dioxanone-derived enol ether **239** and *bis*-silyl enol ether **256** with aldehydes that possess α -heteroatom substitution (Scheme 77).⁹⁶ The substrate specificity of the methodology is a drawback, and arises from the need for potential chelation to achieve high selectivity. Nevertheless, the vinylogous aldol additions of **239** and **256** to benzyloxyacetaldehyde afford adducts **255** and **257** in excellent yield and with excellent enantioselectivity. The power of this methodology was exemplified in its application to the asymmetric assembly of the C33-C37 lactone in Evans' total synthesis of (+)-phorboxazole B **2**.¹⁷

6.3.2 Application of Asymmetric Vinylogous Aldol Reaction to the Synthesis of (+)-Phorboxazole B



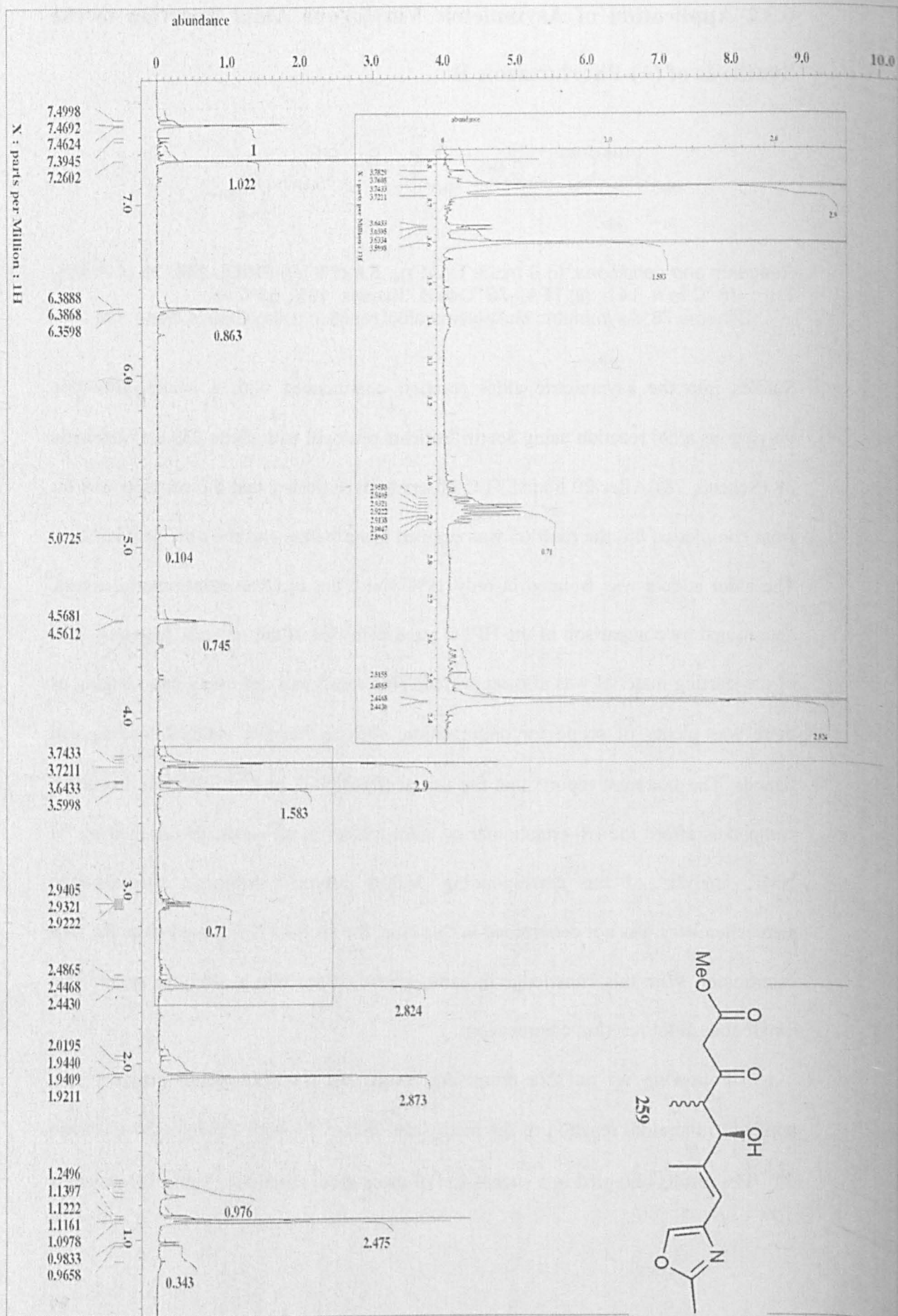
Reagents and conditions: (i) 8 mol% $\text{Ti}(\text{O}^i\text{Pr})_4$, 8 mol% (*R*)-BINOL-244, 29, 4 Å MS, THF, $-78\text{ }^\circ\text{C}$ to rt, 14 h; (ii) TFA, $-78\text{ }^\circ\text{C}$ to rt, 30 mins, 19%, 68% ee.

Scheme 78: Asymmetric Mukaiyama aldol reaction using Chan's diene 139

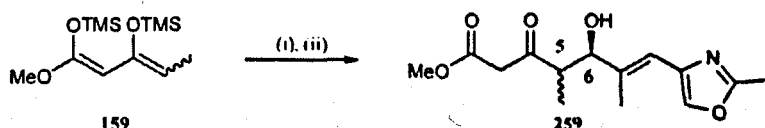
Studies into the asymmetric aldol reaction commenced with a Mukaiyama-type vinylogous aldol reaction using Scettri/Soriente protocol with diene 139 and aldehyde 29 (Scheme 78). After 20 hours, TLC observation indicated that the reaction was far from completion but the reaction was stopped nevertheless and the new spot isolated. The aldol adduct was isolated in only 19% yield, but in 68% enantiomeric excess, determined by comparison of the HPLC trace with that of the racemic material; 75% of the starting material was also recovered. This result was definitely encouraging as there was plenty of scope for optimisation, such as varying catalyst loading and ligands. The literature reports that the use of (*R*)-BINOL and (*R*)-BINOL derivative complexes afford the (*R*)-enantiomer of aldol adduct in all cases, determined by ^1H NMR analysis of the corresponding MTPA esters.⁹¹ Although the absolute stereochemistry was not determined in this case, the product is assumed to be the (*R*)-enantiomer. With this knowledge in hand, investigations into a catalytic asymmetric vinylogous aldol reaction commenced.

Following up on this promising result, the Scettri/Soriente protocol was applied to the aldol reaction of the methylated diene 159 with aldehyde 29 (Scheme 79). The results obtained in a succession of these aldol reactions (Table 13) revealed

Figure 17: ¹H NMR spectrum of the diastereoisomeric mixture



that the reproduction of the reported high yields and selectivities was impossible on our substrate.⁹¹



Reagents and conditions: (i) $\text{Ti}(\text{O}^i\text{Pr})_4$, (*R*)-BINOL-244, 4 Å MS, **29**, THF, $-78\text{ }^\circ\text{C}$ to rt.
(ii) TFA, $-78\text{ }^\circ\text{C}$ to rt, 30 mins.

Scheme 79: Asymmetric Mukaiyama aldol reaction using diene **159**

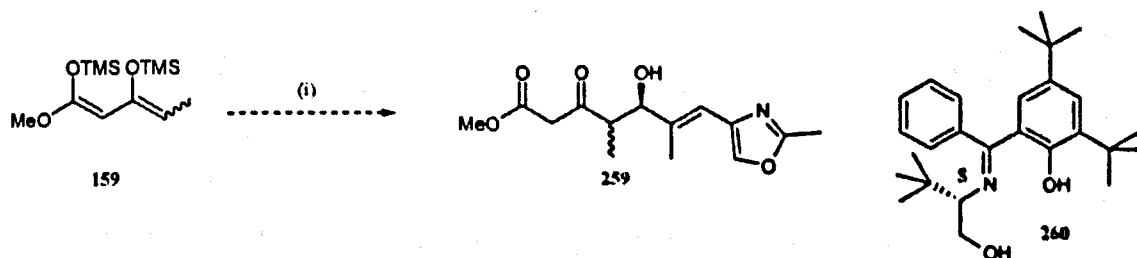
	Catalyst loading / mol%	Conc. of catalyst in reaction mixture/ M	Reaction time / h	<i>Syn:Anti</i> ratio	Yield / %	ee / %
a	8	0.016	14.5	97:3	18	57
b	8	0.016	19	97:3	15	81
c	8	0.016	14.5	94:6	13	58
d	25	0.016	14.5	97:3	13	82
e	25	0.016	21	95:5	15	58
f	25	0.016	36	97:3	16	67
g	25	0.053	36	88:12	34	68
h	25	0.016	17.5	95:5	25	58
i	25	0.016	17.5	94:6	26	57
j	100	0.016	35	-	0	-

Table 13: Summary of results obtained in asymmetric Mukaiyama aldol reaction using Soriente protocol

Variations were made in: level of catalyst loading, concentration of catalyst in the reaction mixture, and reaction time. However, there was no obvious trend associated with any of these variations. The major diastereoisomer was tentatively assigned as the *syn* adduct, since the coupling constant between H5 and H6 was seen to be 3.3 Hz (Figure 17) which is characteristic of *syn* aldol adducts of this type. The *syn:anti* diastereoisomeric excess (*de*) remained virtually constant throughout at 88-94 except in the case of increased reaction concentration (entry g) where a decrease in *de* to 74% was observed. The highest yield obtained for this reaction was a modest 34%, again when using an increased reaction concentration, however, the reproducible yield was only 13-18%. Surprisingly, no aldol product was isolated when the catalyst

mixture was used in stoichiometric quantities. Likewise, the highest value for the enantiomeric excess (*ee*) obtained was 82% (entry d), but on only one other occasion did the reaction furnish a product with a comparable *ee*, although in both cases the yields were seen to be pitiful.

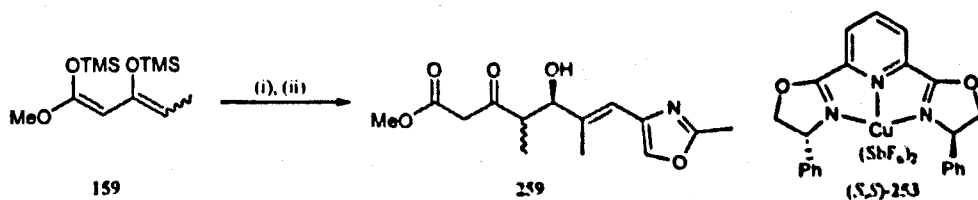
Therefore, due to the lack of reproducibility associated with obtaining aldol adducts that exhibited high *ee* coupled with the generally low reaction yields, the Scettri/Soriente protocol was deemed synthetically impractical when applied to our system. Despite the number of examples of reactions involving Ti/BINOL complexes in the literature, the structures and exact mechanisms remain unclear and it appears that most reactions operate efficiently within a narrow concentration range of catalyst utilised and are highly solvent dependent. Thus without monitoring the structure of the catalyst formed in these reactions, correct catalyst formation is far from certain. Indeed, Scettri and Soriente later published their investigations into the catalyst structure, and they report the observance of a strong, positive non-linear effect which was not concentration dependent. This is indicative of a ML_2 catalytic system, suggesting that the active catalytic species may comprise two-BINOL units.⁹⁷ The authors' investigations also indicate that the reaction of **217** with benzaldehyde exhibited autoinductive effects *i.e.* the use of enantiomerically enriched aldol products as additives resulted in increased enantioselectivities. It is argued by Denmark that the protocol is not suitable for synthetic planning, due to the poorly defined catalyst structure and the fact that the observed autoamplification is unlikely to be general for all substrates.⁸⁵



Reagents and conditions: (i) 29, $\text{Ti}(\text{OPr})_4$, 260, THF, $-78\text{ }^\circ\text{C}$ to rt, 7 days, no reaction.

Scheme 80: Schiff base type catalyst promoted aldol reaction

Previous research within the group has shown Schiff-base type ligands such as 260 can provide vinylogous aldol products with high enantioselectivity.⁶⁹ These aldol reactions used diketene as the nucleophile however, and when applied to Mukaiyama aldol conditions with diene 159, no formation of aldol product was observed when using catalyst loadings of 8 and 25 mol% (Scheme 80).



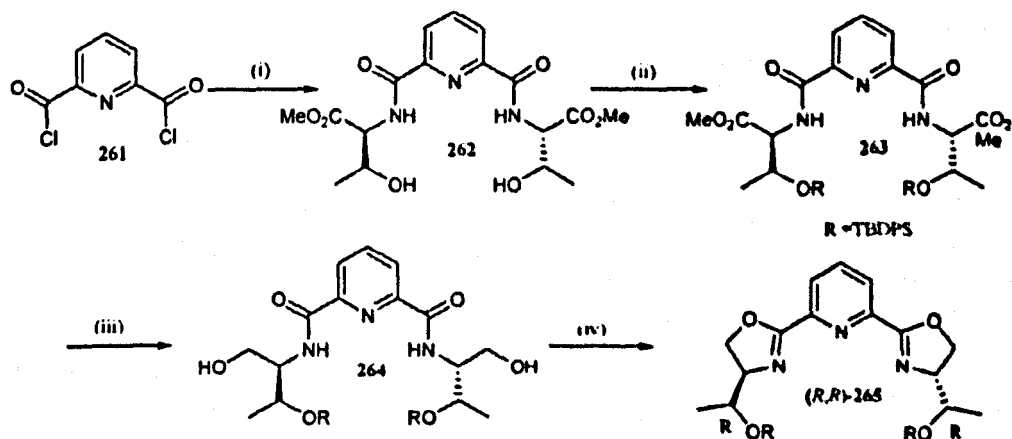
Reagents and conditions: (i) 29, (a) (S,S) -253, 4 mol% or (b) (S,S) -253, 20 mol%, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 12 h; (ii) 1 N HCl, THF, rt, 15 min; (a) 31%, 4:1 *syn:anti*, 4% ee; (b) 21%, 4:1 *syn:anti*, racemic.

Scheme 81: Evans aldol reaction

Aldol reactions using enantiomerically pure copper(II) PyBox catalysts such as (S,S) -253 have been documented by Evans et al.⁹⁶ Although literature precedent states that these catalyst systems are only highly enantioselective when using benzyloxyacetaldehyde since the oxygen participates in a six-membered chelate to $\text{Cu}(\text{II})$ (Scheme 77), it was considered to be a worthwhile venture, since some selectivity could maybe arise from coordination to the heteroatoms of the oxazole. However, when conducted the reaction (Scheme 81) was found to yield essentially racemic aldol adducts 259 as a mixture of 4:1 *syn:anti* diastereoisomers when using

between 4 and 20 mol% catalyst. The yields for these reactions were 31% and 21% respectively, and the enantiomeric excesses of the respective products were 4% and 0%.

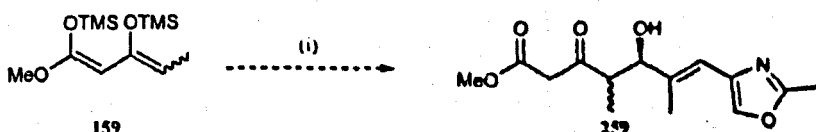
This point in time coincided with the arrival in the group of a summer placement student Florie Lavigne, funded through the ERASMUS Scheme. Florie was put under my supervision and together we set about investigating catalytic asymmetric aldol reactions, with emphasis attributed to high diastereoselectivity.



Reagents and conditions: (i) L-threonine methyl ester hydrochloride, NEt_3 , CHCl_3 , rt, 12 h, 96%; (ii) TPDPSCI, imidazole, CH_2Cl_2 , rt, 18 h, 75%; (iii) LiBH_4 , THF, 0°C to rt, 18 h, 54%; (iv) PPh_3 , CCl_4 , CH_2Cl_2 , rt, 18 h, 74%.

Scheme 82: Synthesis of ligand (*R,R*)-265

We were attracted to an article which reports highly diastereoselective and enantioselective high-yielding Mukaiyama aldol reactions.⁹⁸ Again, these reactions used a PyBox catalyst system, and the ligand (*R,R*)-265 was required to be synthesised following a literature procedure (Scheme 82).⁹⁹

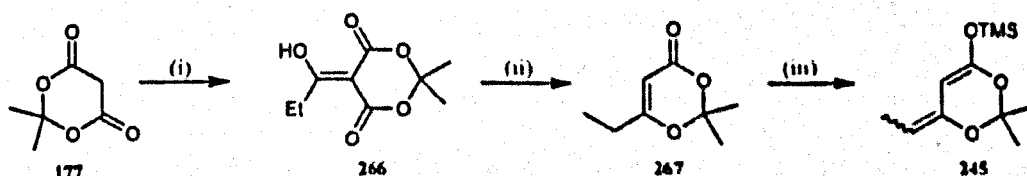


Reagents and conditions: (i) 29, $\text{Zn}(\text{OTf})_2$ and (*R,R*)-265 (10 mol%), 9:1/EtOH:H₂O, 19 h, -22°C , no reaction.

Scheme 83: Unsuccessful asymmetric Zn-PyBox Mukaiyama aldol reaction

The subsequent aldol reaction did not result in the formation of any product (Scheme 83), which was a great disappointment considering the time and effort invested in synthesising the ligand. This may be explained by the fact that the silyl enol ether described in the article is (*Z*)-trimethylsilylated propiophenone, and as such the catalytic system may be substrate specific and thus incompatible with our diene 159.

The lack of success achieved thus far with regards to yield and diastereoselectivity enforced a change of approach to the asymmetric Mukaiyama aldol reaction. Primarily, the low yields obtained from these reactions were the major hindrance to the synthesis in the asymmetric series and thus a more highly yielding catalyst system was sought. It has been shown that the problem regarding diastereoselectivity could be circumvented to some extent by epimerisation at C5, using LDA. However, the existence of the epimerisation step is not ideal, and thus formation of the required 5,6-*anti* stereochemistry via an *anti*-diastereoselective aldol reaction looked to be a more attractive prospect. To this end, a succession of reactions were carried out using the diene 245 as this molecule has some literature precedence for use in *anti*-diastereoselective Mukaiyama aldol reactions.⁹⁰

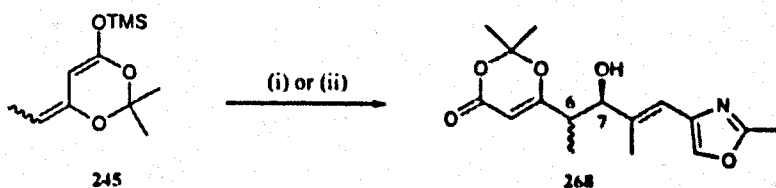


Reagents and conditions: (i) EtCOCl, py, CH₂Cl₂, 0 °C, 1 h, rt, 1 h, 95%; (ii) Me₂CO, PhMe, reflux 1 h, 62%; (iii) LDA, -78 °C, 45 min, then TMSCl, -78 °C to rt, 3h, 51%.

Scheme 84: Synthesis of diene 245

The diene 245 was synthesised in 3 steps from commercially available Meldrum's acid (Scheme 84). Acylation of Meldrum's acid 177 with propionyl chloride and pyridine afforded the acyl Meldrum's acid 266 in 95% yield.¹⁰⁰ The reaction of acyl

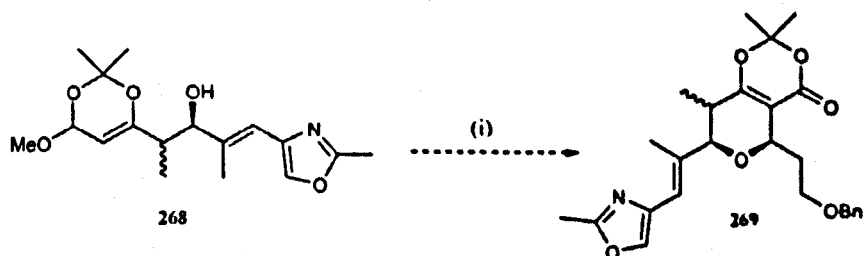
Meldrum's acid with acetone resulted in the formation of the decarboxylative rearrangement product, 6-ethyl-2,2-dimethyldioxinone **267** in 62% yield,¹⁰¹ and subsequent silylation gave 6-ethylidenedioxine **245** as a mixture of *E* and *Z* isomers (*E*:*Z* = 3:5) in 51% yield.



Reagents and conditions: (i) **29**, Ti(OⁱPr)₄ (20 mol%), (*R*)-BINOL-**244** (20 mol%), 4 Å MS, THF, -78 °C, 1 h, then rt, 12 h, 17%, dr 2:1, 93% *ee* (d1), 64% *ee* (d2); (ii) **29**, Ti(OⁱPr)₄ (50 mol%), (*R*)-BINOL-**244** (50 mol%), 4 Å MS, THF, -78 °C, 1 h, then rt, 12 h, 11%, dr 2:1, 80% *ee* (d1), 52% *ee* (d2); (iii) TFA, -78 °C to rt, 30 mins.

Scheme 85: Aldol reaction under Keck conditions using diene **245**

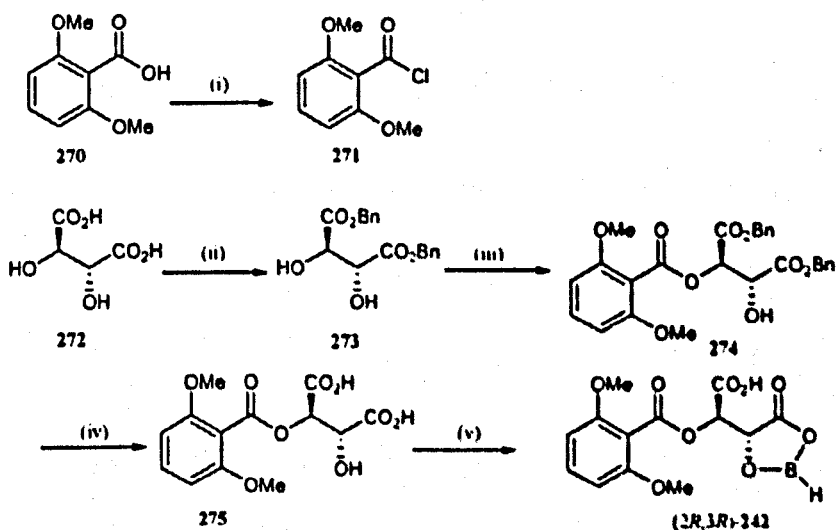
An asymmetric vinylogous aldol reaction was conducted with the diene **245** using the standard Keck conditions in order to gain some comparison of **245** with the diene **158** in reactions of this type (Scheme 85).¹⁰² The reaction was seen to proceed with similarly poor yields as when using diene **158**, at both 20 mol% and 50 mol% of catalyst loadings. However, the reproducible enantioselectivity of the reaction appears to be markedly increased, especially for the major diastereoisomer at 80% *ee*. The reaction produced a 2:1 mixture of diastereoisomers, but it wasn't possible to conclusively assign whether the *syn* or *anti* was the more abundant. However, analysis of the coupling between H6 and H7 reveals the major diastereoisomer to exhibit a coupling of 6.0 Hz which is characteristic of a 6,7-*syn* relationship, whereas the minor diastereoisomer exhibits a coupling of 9.3 Hz, which is characteristic of a 6,7-*anti* relationship. The diastereoselectivity of the reaction can thus be tentatively assigned as being 2:1 *syn:anti*.



Reagents and Conditions: (i) 216, $\text{Sc}(\text{OTf})_3$, CaSO_4 (10 mol%), CH_2Cl_2 , -10°C , 4h, then rt, 16 h, no reaction.

Scheme 86: Unsuccessful attempted cyclisation of aldol adduct 268

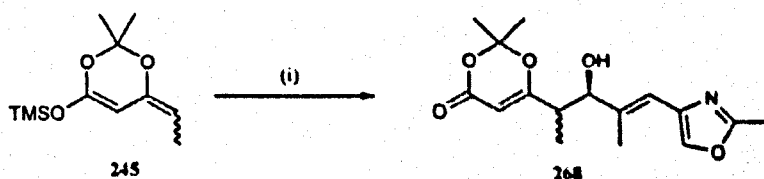
Cyclisation of 269 was attempted using a literature procedure for the reaction of similar aldol adducts with aldehydes (Scheme 86).¹⁰³ However, no reaction was seen to occur, and so conclusive assignment of the diastereoisomers of 268 was not achieved. The limited amount of material resulting from this aldol reaction restricted the extent of investigations into this cyclisation. Furthermore, the information gained from the aldol reaction so far was sufficient to confirm that this was not the way to furnish the cyclisation precursor in the synthesis of the central core TIIP of the phorboxazoles.



Reagents and Conditions: (i) $(\text{COCl})_2$, DMF, CH_2Cl_2 , rt, 3h, 98%; (ii) DBU, BnBr, DMF, 0°C to rt, 16 h, 63%; (iii) 271, Et_3N , DMAP (cat.), CH_2Cl_2 , 0°C to rt, 18 h, 86%; (iv) EtOAc , 10% Pd-C, H_2 , EtOAc , rt, 1 h, 60%; (v) $\text{BH}_3\text{-THF}$, CH_2Cl_2 , 0°C , 1 h, formed *in situ*.

Scheme 87: Synthesis of chiral borane catalyst (2R,3R)-242

A catalyst system was reported by Sato to deliver predominantly *anti* aldol adducts from the reaction of diene **245** with aldehydes (Scheme 71).⁹⁰ The catalyst system was formed *in situ* from the reaction of borane-tetrahydrofuran complex with ligand (2*R*,3*R*)-**242** (Scheme 87). The mono-acylated tartaric acid ligand **275** was synthesised in three steps from L-tartaric acid **272**.¹⁰⁴ Dibenylation of tartaric acid proceeded to give dibenzyl tartrate **273** in 63% yield from reaction with benzyl bromide, in the presence of DBU. Coupling of dibenzyl tartrate with 2,6-dimethoxy benzoyl chloride **271**, which was in turn formed from 2,6-dimethoxy benzoic acid **270**, in the presence of triethylamine and DMAP catalyst produced the mono-acylated dibenzyl tartrate **274** in 86% yield. Removal of the benzyl groups using 10% palladium(0) on carbon proceeded without event to furnish **275** in 60% yield.



Reagents and conditions: (i) **275**, $\text{BH}_3 \cdot \text{THF}$, **29**, THF, -78°C , 3 h.
Scheme 88: Chiral borane-promoted aldol

With the ligand **275** in hand, the target aldol reaction was carried out (Scheme 88), by first forming the chiral borane (2*R*,3*R*)-**242** *in situ* in a bid to improve the yield of the reaction. Variations were made in catalyst loading and the amount of diene **245** used (Table 14). The highest yield was obtained when using two equivalents of diene **245** and 50 mol% of chiral borane catalyst, which was consistent with Sato's findings. These conditions afforded aldol adduct **268** with the highest enantioselectivity and diastereoselectivity.

Entry	mol% of 242 used	No. of equivalents of diene 245 used	Yield / %	<i>ee</i> (<i>anti</i>) / %	<i>ee</i> (<i>syn</i>) / %	dr (<i>anti:syn</i>)
a	50	2	28	85	52	(1.5:1)
b	50	4	23	81	38	(1:1.2)
c	100	2	12	79	39	(1:1.3)

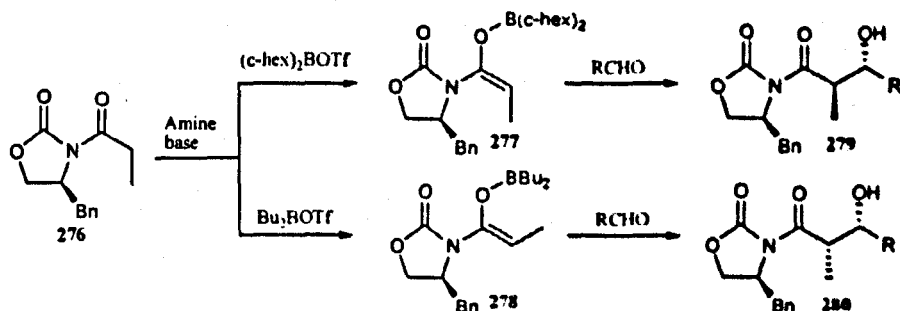
Table 14: Summary of results using chiral borane catalyst 242

Arguably, these conditions (entry a) have proved to be the best of all asymmetric aldol conditions that have thus far been investigated, yielding the most amount of aldol adduct material with a workable enantiomeric excess.

Overall, the consistently low yields associated with these Mukaiyama aldol reactions rendered the strategy unfeasible and so attention was turned to more robust methods of executing aldol reactions with high diastereoselectivity and enantioselectivity. However, any modification of the route would unavoidably add extra steps to the synthesis, since the asymmetric Mukaiyama aldol was deemed the only possible route of achieving an enantiomerically enriched δ -hydroxy β -keto ester in a single step. Nevertheless, given the above results an alternative method of incorporating asymmetry into the aldol reaction had to be sought.

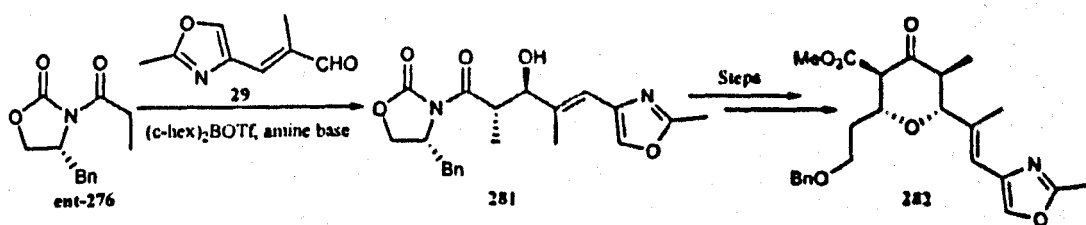
6.4 Aldol Reactions using Chiral Auxiliaries

Chiral auxiliaries have been used to successfully furnish diastereoselective asymmetric aldol adducts for some time now. The diastereoselectivity of the reaction between an aldehyde and the enolate of a propionyl species is governed by the enolate geometry when a cyclic transition state is employed; (*Z*)-enolates afford *syn* adducts whereas (*E*)-enolates afford *anti* adducts.



Scheme 89: Formation of Evans *syn* and *anti* aldol adducts

The pioneering work by Evans on the boron enolates of *N*-acyl oxazolidinone **276** is still the most commonly utilised methodology for reactions of this type (Scheme 89).¹⁰⁵ The facile generation of either the (*E*)- or (*Z*)-boron enolate **277** and **278**, determined by the steric bulk of the ligands attached to boron, allows for the diastereoselective synthesis of *anti* or *syn* aldol adducts **279** and **280**. Small linear ligands such as *n*-butyl lead to the formation of the (*Z*)-enolate, whereas large bulky ligands such as cyclohexyl lead to the formation of the (*E*)-enolate. One drawback of this methodology is the access to only one enantiomeric series. To access the other enantiomeric series to that shown, the auxiliary derived from the unnatural enantiomer of **276** would be required. For the synthesis of the aldol adduct **281** towards the synthesis of the C19 to C32 fragment of the phorbotoxazoles, the enantiomer of **276** would be required (Scheme 90).



Scheme 90: The proposed synthesis of the "non-Evans" *anti* aldol adduct

6.4.1 *Syn*-selective Aldol Reaction using the Nagao auxiliary

Crimmins and co-workers have reported aldol methodology which circumvents the need for the synthesis of *ent*-276, due to the fact that their methodology can produce either the “Evans *syn*” or “non-Evans *syn*” aldol adducts *via* slight changes in the reaction conditions.¹⁰⁶ Upon successful completion, the aldol reaction would furnish the C25-C26 contiguous stereogenic centres of the phorbaxazoles. In the natural products, these exhibit an *anti* relationship, whereas the Crimmins methodology affords *syn* aldol adducts. However, facile epimerisation of the C25 methyl substituent had been previously demonstrated in our studies in the racemic series (Scheme 63). It was therefore decided to apply this methodology to our system since there is also a great amount of experience within the group of these *syn*-selective aldol reactions, and a plentiful supply of the required oxazolidinethione auxiliary **283** (Figure 18), the use of which was first reported by Nagao.⁵²

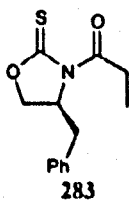
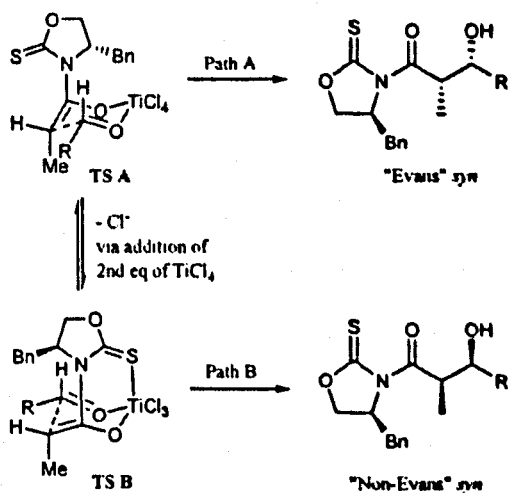


Figure 18: Oxazolidinethione auxiliary

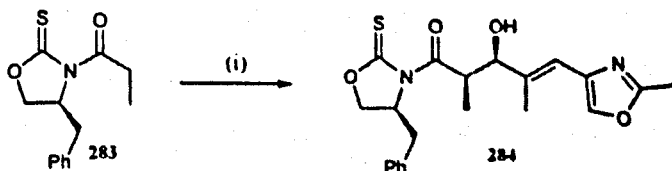
The observed selectivity hinges upon the use of this thione auxiliary. It was proposed by Crimmins that the enantiomeric pathway undertaken is dependent upon the existence of coordination between titanium and the sulfur of oxazolidinethione **283**, which can be visualised as competing Zimmerman-Traxler transition states (Scheme 91). The reaction is *syn*-selective since the steric bulk of the oxazolidinethione forces the enolate to adopt a *Z*-configuration. In the case of the nonchelated transition state **TS A**, there is a minimisation of the dipoles arising from the two carbonyl groups and

this results in the formation of “Evans” *syn* products (path A). The reaction conditions that favour TS A include an excess of bidentate base, such as (-)-sparteine, with respect to titanium tetrachloride as it is thought that the base competes with the sulfur for coordination to titanium. Conversely if an excess of titanium tetrachloride is used, a pathway for Cl⁻ abstraction is established, and thus the titanium(IV) enolate is now able to coordinate to the sulfur of the oxazolidinethione auxiliary.



Scheme 91: Comparison of enantiomeric pathways in Crimmins aldol

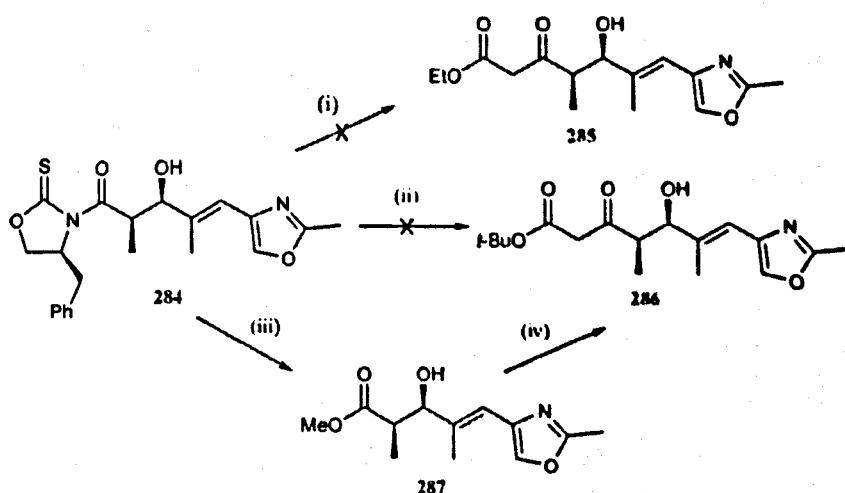
The strength of the sulfur-titanium bond is sufficient to compensate for the energy penalty incurred from the opposing dipoles in TS B. Path B therefore leads to “non-Evans” *syn* products, and the fact that both enantiomeric series are accessible from one enantiomer of the auxiliary is of great benefit since a synthesis of the auxiliary originating from the expensive unnatural amino acid, is not required.



Reagents and conditions: (i) TiCl₄ (2 eq), CH₂Cl₂, 0 °C, 10 min; then (-)-sparteine, 0 °C, 20 min; then 29, -78 °C, 90 min, quant, dr>99:1

Scheme 92: Crimmins aldol to form “non-Evans” *syn* product

The “non-Evans” aldol adduct was required to ultimately furnish the cyclisation precursor with the correct stereochemistry at the carbon atom bearing the hydroxyl group. Therefore, the aldol reaction was carried out with an excess of titanium tetrachloride, as reported by Crimmins (Scheme 92). Pleasingly, the reaction was seen to proceed in quantitative yield on the gram-scale, producing only one diastereoisomer by analysis of the ^1H NMR spectrum of the crude reaction mixture. Crimmins reports the facile conversion of the auxiliary portion to a number of functional groups such as alcohols, esters, and amides.¹⁰⁶

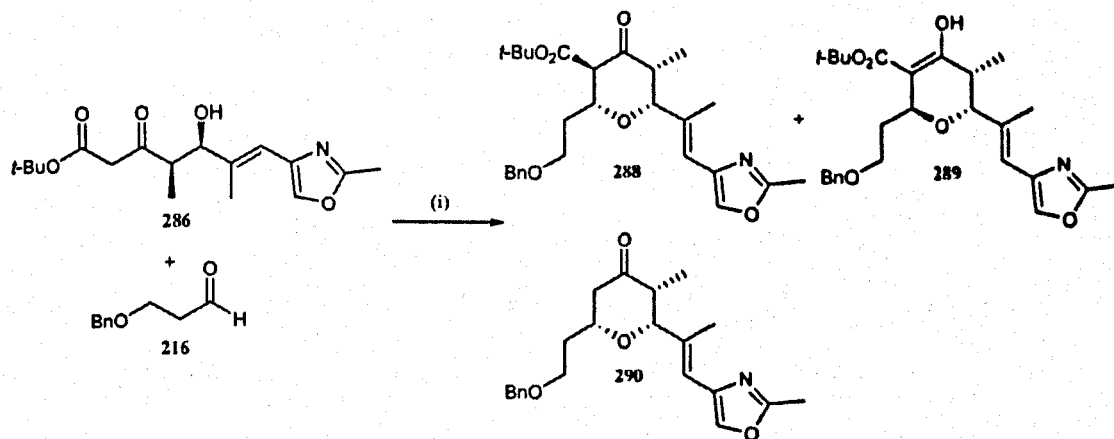


Reagents and conditions: (i) 2-bromoethyl acetate, Zn, THF, reflux, 7h; (ii) *t*-butyl acetate and LDA or NaHMDS, $-78\text{ }^\circ\text{C}$, 2 h; (iii) NaOMe, MeOH, $0\text{ }^\circ\text{C}$ to rt, 3 days, 79%; (iv) *t*-butyl acetate and LDA, $-30\text{ }^\circ\text{C}$, 4 h, 61%

Scheme 93: Attempts to cleave the oxazolidinethione auxiliary of 284

Initial attempts were made to convert the auxiliary of 284 directly to a β-keto ester such as 285 or 286, which would serve as the cyclisation precursors (Scheme 93). We initially attempted the conversion of the oxazolidinone to a β-ketoester via a Reformatsky reaction.¹⁰⁷ The Reformatsky reaction is the nucleophilic addition of a zinc enolate derivative of an ester, in this case ethyl acetate, to a carbonyl such as the amide 284. If successful, the reaction would reveal the β-keto ethyl ester 285 which would serve as a cyclisation precursor. However, when the reported reaction

conditions were applied to our substrate **284**, no reaction was seen to occur until decomposition of the starting material, after a prolonged period of time heating at reflux. Similarly, treatment of **284** with the enolate of *t*-butyl acetate simply returned starting material. Ultimately, the transformation had to be executed over two steps. Methanolysis of **284** by treatment with a methanolic solution of sodium methoxide revealed the methyl ester **287** in 79% yield. Subsequent Claisen condensation of **287** with the enolate of *t*-butyl acetate proceeded in 63% yield to produce **286** with no erosion of diastereoselectivity. Rigorous optimisation was required to achieve this 63% yield, since it was necessary to address a balance between the slow rate of reaction at colder reaction temperatures, and the observed decomposition of **286** via retro-aldol at higher temperatures (above -15 °C) under these conditions. Furthermore, the amount of enolate required to force the reaction to approach completion was found to be ten equivalents. It was anticipated that the reaction would require more than two equivalents due to the acidity of the hydroxyl proton, however the fact that four equivalents saw the reaction proceed to only 27% completion was somewhat surprising. A possible reason for this observation is that the methyl protons on the oxazole could be also deprotonated by the enolate since the values of pK_a of these protons and *t*-butyl acetate are of similar magnitude. With **286** in hand, Knoevenagel/oxy-Michael cyclisation was attempted using the conditions developed from the investigations on the racemic series material *i.e.* stirring with aldehyde **216** in the presence of ytterbium triflate and trifluoroacetic acid (Scheme 94). However, whereas cyclisation of the racemic series material was seen to yield THIP material in 63% yield, the cyclisation of **286** proceeded to yield only 4% of an inseparable mixture of diastereoisomeric THPOs **288** and **289**, 2:1 keto-2,6 *cis* : enol-2,6 *trans*.



Reagents and conditions: (i) Yb(OTf)₃, TFA, CH₂Cl₂, rt, 17 h, 4%, dr 2:1/288:289, 9% 290.

Scheme 94: Yb(OTf)₃-promoted cyclisation

A further 9% yield was achieved in the isolation of the decarboxylated THP 290, which in hindsight was a result of the *t*-butyl ester's sensitivity to trifluoroacetic acid. It was thought that if there was evidence for the *t*-butyl ester group being removed after cyclisation, then maybe it was also being removed prior to cyclisation from 286, and consequently allowing the reaction to proceed no further.

	Lewis Acid	Temperature	Reaction time / h	288:289 ratio	Yield of THP material / %
a	Yb(OTf) ₃	-78 °C to rt	17	n/a	0 (no reaction)
b	TiCl ₄	rt	3	n/a	0 (decomposition)
c	TiCl ₄	-22 to -30 °C	17	1 : 0.8	24
d	Sc(OTf) ₃	-78 °C to rt	48	1 : 0.8	17

Table 15: Results of Lewis acid screen in cyclisation

In order to distinguish whether or not the presence of trifluoroacetic acid was detrimental to the cyclisation, a small Lewis acid screen was undertaken which explored reaction in the absence of trifluoroacetic acid. It was found that promotion *via* ytterbium triflate alone simply returned starting material after a prolonged period of stirring at room temperature (Table 15, entry a). Furthermore, a room temperature titanium tetrachloride-promoted reaction resulted in the decomposition of 286, thus

proving to be too harsh conditions (entry b). As such, a temperature-monitored titanium tetrachloride-promoted cyclisation was initiated, whereby the reaction was monitored by TLC as the reaction temperature was gradually increased from $-78\text{ }^{\circ}\text{C}$. Observations by TLC indicated the first sign of cyclisation had occurred when the temperature had been warmed to $-30\text{ }^{\circ}\text{C}$ (entry c). The reaction was then kept between $-30\text{ }^{\circ}\text{C}$ and $-20\text{ }^{\circ}\text{C}$ for a further 17 hours, after which time THP material was isolated in 24% yield as 1.8:1 mixture of keto 2,6-*cis* : enol 2,6-*trans* diastereoisomers. These two diastereoisomers were inseparable by column chromatography in all the solvent systems that were investigated. A similar temperature-controlled reaction using scandium triflate as the promoter (entry d) yielded the same ratio of diastereoisomers but in a lower overall yield and over a longer period of time. In this case, TLC observations indicated that cyclisation did not begin to occur until the reaction temperature had warmed to room temperature.

Overall, the low yields associated with the Knoevenagel/oxy-Michael reaction of **286** with aldehyde **216** are a clear indication that this route is not a feasible way of synthesising the central THP of the phorboxazoles. The lack of success achieved in this cyclisation was surprising when considering the structural similarity of the cyclisation precursors **202** and **216**. It was found that the reaction conditions that promoted Knoevenagel/oxy-Michael cyclisation of **202** with aldehyde **216** *i.e.* stirring in the presence of a Lewis acid at room temperature were not transferrable to the same cyclisation with **286**. This observation can be attributed to the fact that **286** is more prone to both decarboxylation and retro-aldol at room temperature than **202**. This in turn required that the cyclisations to be conducted at a lower temperature. Cyclisations of *syn* aldol adducts in this manner are likely to be slow due to the 1,3-diaxial interactions of the methyl group in the transition state.

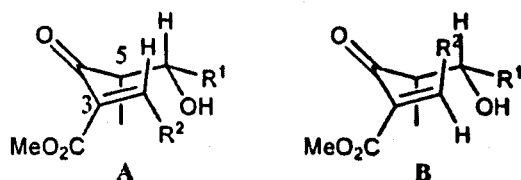
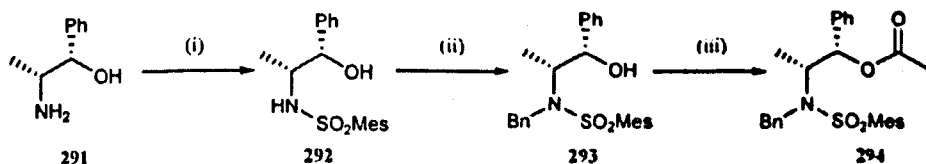


Figure 19: Predicted chair-like reactive conformations for cyclisation of 286

The reactive conformations for the formation of the 2,6-*cis* species and the 2,6-*trans* species are depicted by A and B respectively (Figure 19). Furthermore, the late-stage formation of the 2,6-*cis*; 5,6-*cis* THP 288 will encounter a 1,3 diaxial interaction between the methyl group at C-5 and H-3. It is therefore feasible that cyclisation is slow with respect to retro-aldol and decarboxylation in some cases. It was therefore envisaged that the cyclisation of *anti* aldol adducts may prove more fruitful.

6.4.2 *Anti*-Selective Aldol Reaction using the Masamune-Abiko Auxiliary

Investigations were immediately undertaken into an *anti*-selective aldol reaction in order to ascertain what effect, if any, the initial stereochemistry of the aldol adduct cyclisation precursor were to have on the Knoevenagel/oxy-Michael step of the reaction. Furthermore, upon successful cyclisation to the desired 2,6-*cis* THP, the stereochemistry and positions C2, C5, and C6 of the THP formed would be correct for the synthesis of the central THP of the phorbaxazoles. From a survey of the literature, it was found that the most commonly used auxiliary for such aldol reactions was the Masamune-Abiko ester 294 derived from (-)-norephedrine 291 in three steps (Scheme 95).¹⁰⁸



Reagents and conditions: (i) Et₃N, MesSO₂Cl, CH₂Cl₂, 12 h, 98%; (ii) Cs₂CO₃, BnBr, MeCN, reflux, 90 min, 93%; (iii) py, propionyl chloride, CH₂Cl₂, 0 °C, 4 h, 96%.

Scheme 95: Synthesis of Masamune-Abiko auxiliary 294

The nitrogen of norephedrine **291** was protected with two bulky groups by first reaction with mesitylene sulfonyl chloride under basic conditions to furnish **294** in 98% yield, and then reaction with benzyl bromide under basic conditions produced **293** in 93% yield. Finally, propionylation revealed the auxiliary **294** in 96% yield.

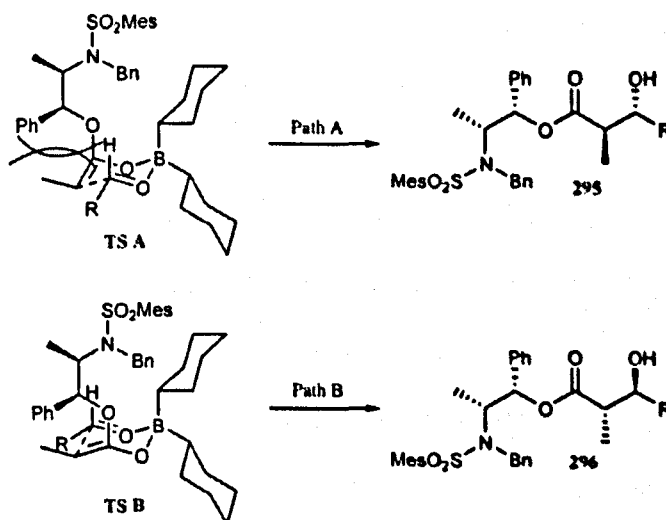
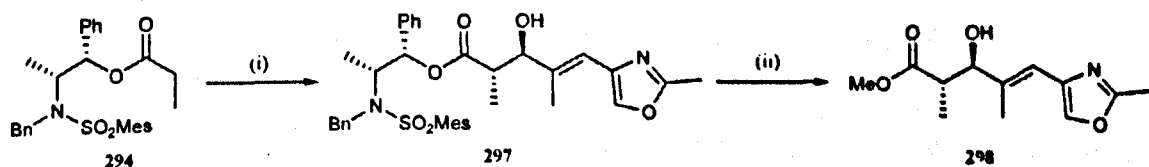


Figure 20: Enantiomeric pathways when using Masamune-Abiko auxiliary

The aldol reactions reported by Masamune and Abiko all furnish *anti* aldol adducts with excellent diastereoselectivity and in high yields. The reaction proceeds *via* a dicyclohexylboron enolate, and the steric crowding of the cyclohexyl groups forces the enolate to adopt an *E*-configuration. It has been noted that the cyclohexyl ligands alone are not sufficient to impose the *E*-enolate geometry; a bulky ester group is also a necessity.¹⁰⁸ The absolute stereochemistry of the aldol adducts were not determined by Masamune and Abiko, instead the auxiliary was cleaved and the data compared

with corresponding methyl esters or diols that had been esters.¹⁰⁹ Upon reaction with an aldehyde, the *E*-enolate will yield *anti*-selective aldol adducts. From analysis of the Zimmerman-Traxler transition states (Figure 20), it can be seen that the substituents of the auxiliary must adopt a conformation to avoid a steric clash with the cyclohexyl groups. From comparison of the two transition states, TS A and TS B, it is clear that TS A will be unfavoured due to the steric clash between the phenyl group of the auxiliary and the methyl group of the enolate and the *pseudo*-axial aldehyde proton. Pathway B exhibits no such interaction, and will be therefore favoured over pathway A; reaction with this auxiliary would lead to an aldol adduct with the stereochemistry required for the synthesis of the natural product.

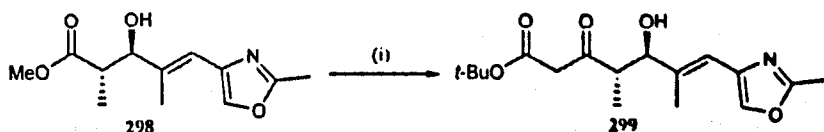


Reagents and conditions: (i) Et₃N, (c-hex)₂BOTf, CH₂Cl₂, -78 °C, 3 h, then 29, -78 °C, 1 h, 0 °C to rt, 1 h, 91%, dr 14:1; (ii) NaOMe, MeOH, 0 °C, 3 days, 83%.

Scheme 96: *Anti*-selective aldol reaction and subsequent cleavage

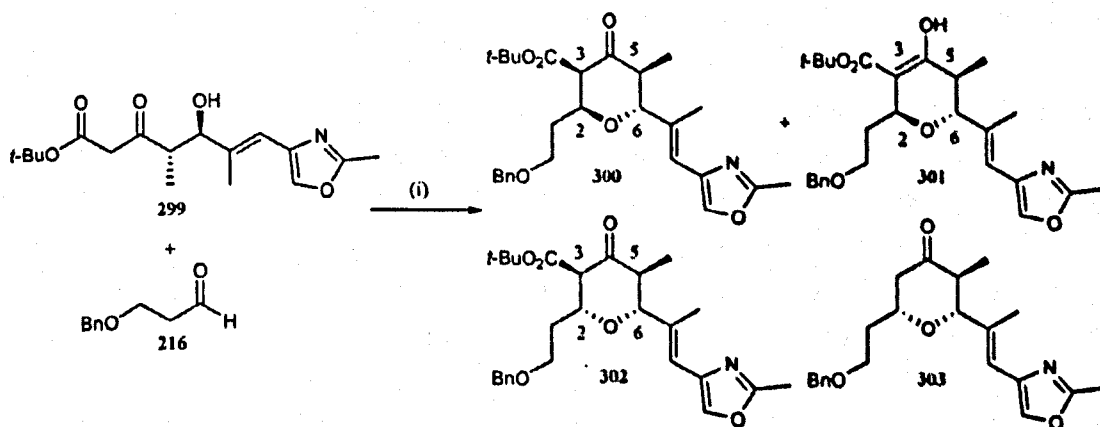
Application of the Masamune-Abiko protocol to our system furnished the *anti*-selective aldol adduct 297 in 91% yield and as a 14:1 mixture of diastereoisomers, which was a very pleasing result. The auxiliary is notoriously difficult to remove *via* nucleophilic attack, with Masamune and Abiko citing lithium aluminium hydride as the reagent of choice. Reduction of the ester in this way would be an inelegant route to the cyclisation precursor, since it would require a protection/deprotection of the free hydroxyl, together with oxidation and diazo-insertion steps. The problem of the auxiliary being difficult to remove has been addressed by Alison Hulme's group, who report the synthesis of a thiol ester auxiliary which is much more susceptible to nucleophilic attack.¹¹⁰ However, this auxiliary requires a laborious seven step

synthesis compared to the three steps required to make the Masamune-Abiko auxiliary, and so although the route would cut down the number of linear steps, the overall workload would be the same. It was therefore very pleasing to discover that the conditions which were used for the cleavage of the Crimmins oxazolidinethione auxiliary could be applied to the aldol adduct **297** with great success. Thus, treatment of **297** with a methanolic solution of sodium methoxide revealed the methyl ester **298** 83% yield, however it did take three days for the reaction to go to completion.



Reagents and conditions: (i) *t*-butyl acetate and LDA, THF, -30 °C, 75%.
Scheme 97: Claisen condensation to furnish cyclisation precursor **299**

Claisen condensation of **298** with the enolate of *t*-butyl acetate proceeded to produce the β -keto ester cyclisation precursor **299** in 75% yield (Scheme 97). Experience of the Claisen condensation in the *syn*-series quickly established the fact that ten equivalents of enolate were required to drive the reaction towards completion.



Reagents and conditions: (i) Yb(OTf)₃, TFA, CH₂Cl₂, rt, 17 h, 11%, dr 1:1/300:301, 5% **302**, 7% **303**.

Scheme 98: Cyclisation of *anti* aldol adduct **299**

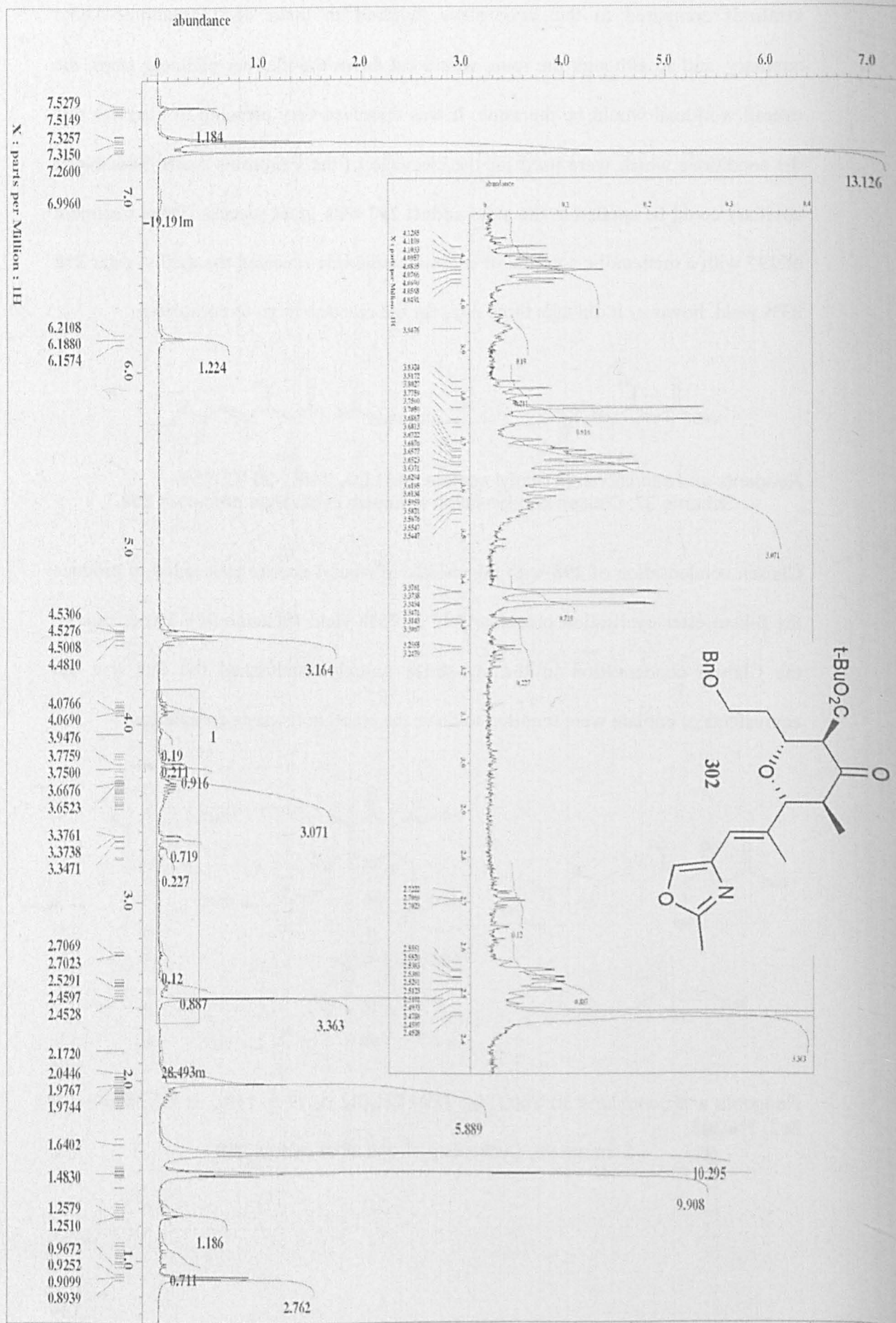
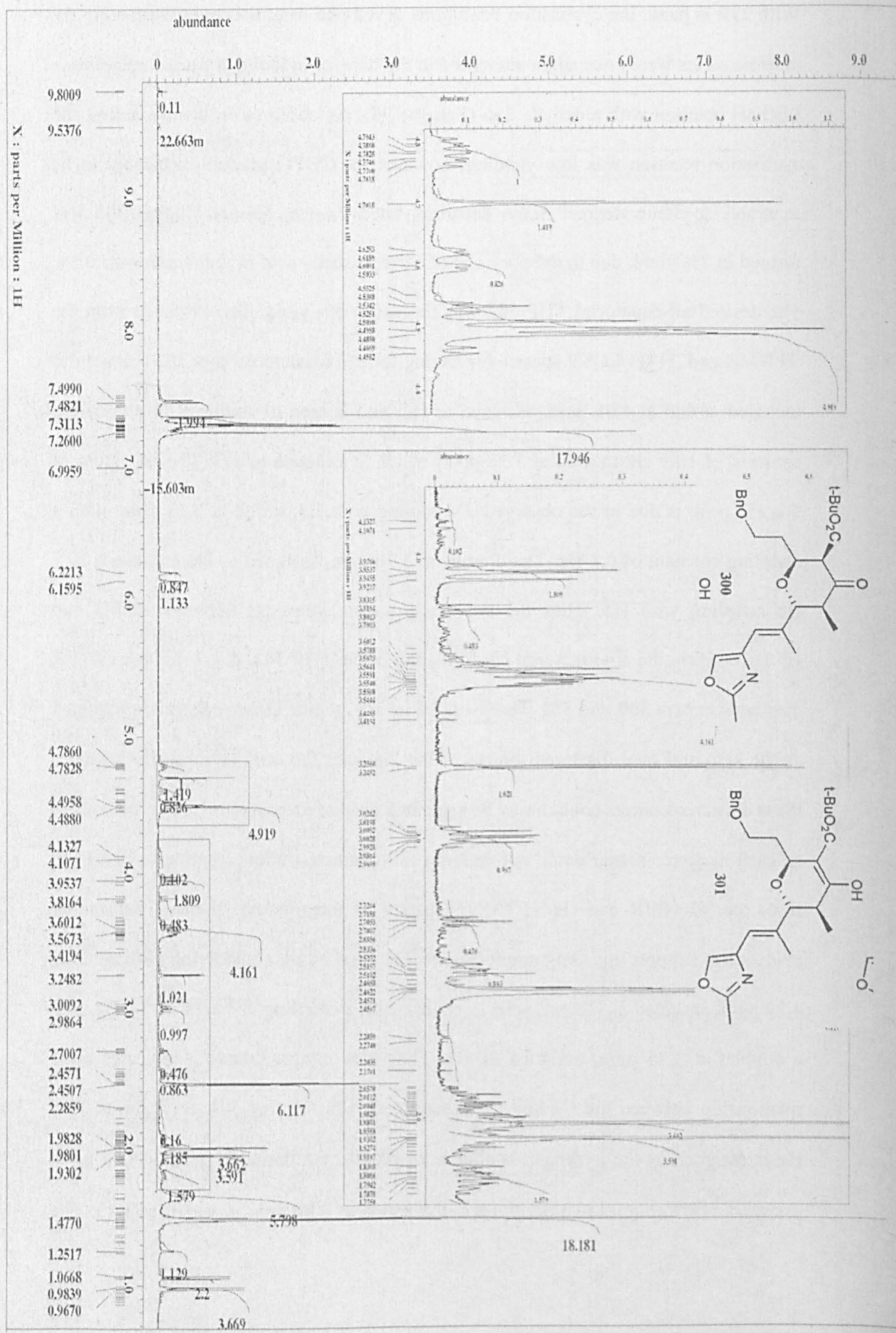
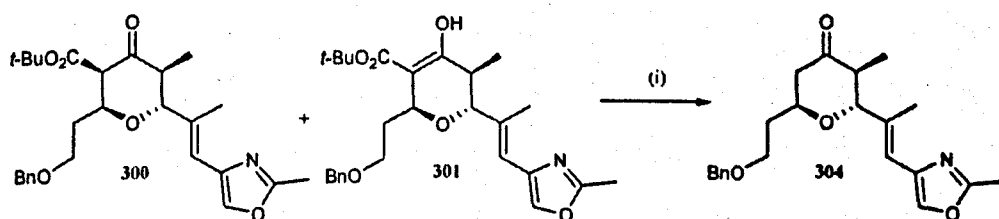


Figure 21: ¹H NMR spectrum of clean 302

With 299 in hand, the cyclisation conditions developed from the investigations in the racemic series were once again attempted in the hope of inducing a Knoevenagel/oxy-Michael reaction with aldehyde 216 (Scheme 98). As observed in the *syn* series, the cyclisation reaction was low yielding; however the THPO products appeared to be separable to some degree. Some decarboxylated 2,6-*cis*; 5,6-*anti* THPO 303 was formed in 7% yield, due to the presence of trifluoroacetic acid in the reaction mixture. The desired all-equatorial THP 302 was formed in 5% yield. The evidence from the ^1H NMR and ^1H - ^1H COSY spectra for having formed diastereoisomer 302 (Figure 21) included: a ddd at 4.08 ppm, assigned as H2, and is seen to couple with a coupling constant of 10.7 Hz to a dd at 3.36 ppm, which is assigned as H3. The dd nature of this H3 peak is due to the observed J^4 -coupling with H5, a dqd at 2.53 ppm, with a coupling constant of 0.8 Hz. The doublet at 3.76 ppm, assigned as H6 exhibits a 10.7 Hz coupling with H5. Thus the two trans-diaxial couplings between H2/H3 and H5/H6 confirm the all-equatorial conformation of the THP 302. A 1:1 mixture of THP diastereoisomers 300 and 301 were isolated in 11% yield. This mixture was assigned as the keto and enol diastereoisomers of the 2,6 *anti*; 5,6 *anti* THPs. Unfortunately, these diastereoisomers could never be separated despite extensive efforts to do so, and so each diastereoisomer could not undergo full characterisation separately. However, from the ^1H NMR and ^1H - ^1H COSY spectra of the mixture, there is substantial evidence to support this assignment (Figure 22). First of all, considering 300: a ddd at 4.79 ppm, assigned as H2 was seen to couple with a coupling constant of 3.2 Hz with a doublet at 3.25 ppm, assigned as H3. The value of this coupling indicates a *cis* relationship between the C2 and C3 substituents. Considering 301: a singlet at 12.1 Hz is assigned as the hydrogen-bonded enol proton. Furthermore, a dd at 4.61 ppm, assigned as H2 couples to a multiplet in the region of 2.00 ppm, assigned as H13. The

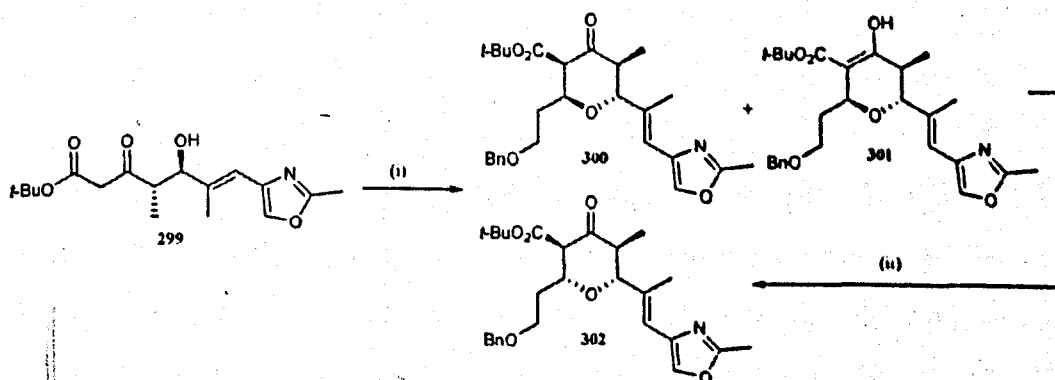


values of the coupling constant, 9.9 and 2.6 Hz are characteristic of the H2 coupling constants for tetra-substituted enol THPOs. There are two doublets at 3.96 and 3.93 ppm, which are assigned as H6 in **300** and **301**. These couple with coupling constants of 9.2 and 9.6 Hz with dq at 3.01 and 2.53 ppm respectively. These trans-diaxial relationships prove the fact that there are two species with H5/H6 substituents in a *trans* orientation.



Reagents and conditions: (i) H₂O, DMF, microwave, 160 °C, 83%.
Scheme 99: Decarboxylation of mixture **300** and **301**

A piece of experimental evidence to support the claim that **300** and **301** are tautomers of the 2,6-*trans*; 5,6-*trans* THPOs was exhibited by the removal of the *t*-butyl ester functionality by heating a 1:1 mixture of **300** and **301** in wet DMF to 160 °C in the microwave (Scheme 99). The sole product of the reaction was the 2,6-*trans*; 5,6-*trans* THPO **304**, indicating that this stereochemistry was present in both **300** and **301**. This is the first evidence of the formation of a 2,6-*trans* keto-THP.



Reagents and conditions: (i) LA, CH₂Cl₂ (Table 16); (ii) LA, CH₂Cl₂ (Table 17).
Scheme 100: Cyclisation to 5,6-*trans* THPs

The low yielding nature of the initial cyclisation forced us to undertake a Lewis acid screen in order to determine the optimum conditions for the reaction (Scheme 100, Table 16). In most cases, the formation of all three THPO diastereoisomers **300**, **301**, and **302** was seen.

	Lewis Acid	Temperature	Reaction time / h	300:301:302:29 ratio	Yield of THP material / %
A	Yb(OTf) ₃	RT	21	1 : 1 : 0.5 : 0.5	38
b	TiCl ₄ /py	RT	20	1 : 1 : 0.2 : 0.7	60
c ^a	TiCl ₄	-22 to -30 °C	21	1 : 0 : 0 : 0	47
d	BF ₃ .OEt ₂	RT	21	0 : 0 : 0 : 1	0
e	Ti(O ⁱ Pr) ₄	RT	21	0 : 0 : 0 : 1	0
f	InCl ₃	RT	21	1 : 1.2 : 0.4 : 0	32
g	Sc(OTf) ₃	-78 °C to RT	23	1 : 1 : 2 : 0.8	68
h	Sc(OTf) ₃ /CaSO ₄	-78 °C to RT	22	1 : 1 : 1.4 : 0	68
i	Sc(OTf) ₃ /K ₂ CO ₃	-78 °C to RT	21	1 : 1 : 0.7 : 0	26
j	Yb(OTf) ₃ /CaSO ₄	-78 °C to RT	21	1 : 1.2 : 0.7 : 1.4	54
k	FeCl ₃	-78 °C to RT	21	1 : 1 : 0.5 : 0	45

a After column chromatography, ratio changed to 5:5:1/300:301:302

Table 16: Results from Lewis acid-promoted cyclisation

Furthermore, most cases saw evidence of a retro-aldol reaction having occurred, through the existence of aldehyde **29** in the ¹H NMR spectrum of the crude reaction mixture. It was possible to isolate cleanly up to half of the desired THPO **302** present in these mixtures as it ran on silica ever-so slightly slower than the 2,6-*trans* THPOs **300** and **301**, providing just enough material to take the synthesis forward. It was shown that the unwanted 2,6 *trans* THPs could be recycled back to the desired **302** via treatment with a number of Lewis acids (Table 17) which promoted retro-Michael/Michael reactions until the thermodynamic equilibrium was reached. In most cases, the 2,6 *trans* THPs **300** and **301** were found to be most abundant in the product distribution mixture. This was somewhat surprising as it would be easy to assume that the all-equatorial THP **302** would be the most stable configuration of the ring.

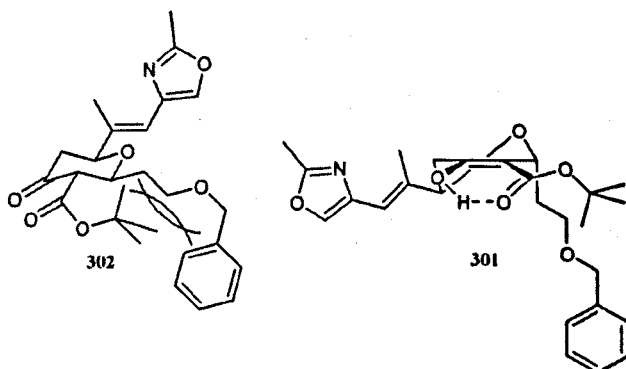


Figure 23: Comparison of steric clash between **302** and **301**

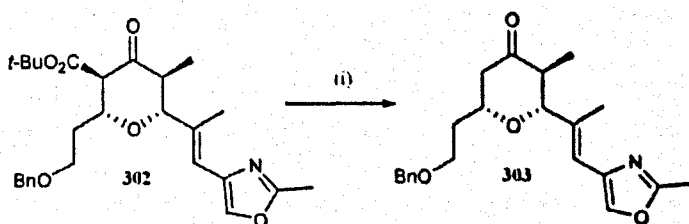
However, when viewing models of the three different diastereoisomers in three dimensions it is clear that in **302**, there is a steric clash between the phenyl group of the C-2 substituent and C-3 substituents as they occupy the same space. Whereas in the 2,6 *trans* THPs **300** and **301**, because the C-2 substituent sits in an axial orientation, there is far more free rotation of the substituents thus lowering the overall energy of the molecules with respect to **302**. From the results, it is clear that scandium triflate was the best promoter of the Knoevenagel/oxy-Michael cyclisation since it was both the highest yielding and the most **302**-selective.

	Lewis Acid	Starting ratio 300:301:302 / %	Reaction temp/ °C	Reaction time / h	Ratio after stirring 300:301:302 / %
a	Sc(OTf) ₃	50:50:0	Rt	72	32:35:32
b	Yb(OTf) ₃	40:40:20	rt	10	30:45:24
c	TiCl ₄	50:50:0	rt	24	n/a (decomposed)
d	SiO ₂	50:50:0	rt	30	43:43:14
e	Sc(OTf) ₃	50:50:0	65	3	n/a (decomposed)
f	Amberlyst	50:50:0	rt	24	n/a (decomposed)
g	Al ₂ O ₃	50:50:0	rt	24	50:50:0

Table 17: Re-equilibration of diastereoisomers

The highest yield of pure **302** achieved was 21%, using scandium triflate as the Lewis acid. However, when these optimum conditions were applied to the cyclisation on the gram scale, the yield of **302** dropped to 9%, which was a result of a more difficult work-up and more difficult separation of the diastereoisomers *via* flash column

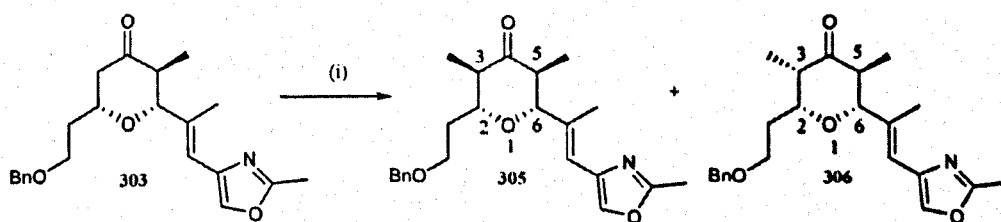
chromatography. This made pushing material through the cyclisation step to the frontier very laborious, affording limited fruits for that labour in the process. Stirring of the THP species which exhibited predominantly 2,6-*trans*; 5,6-*cis* in the presence of various Lewis acids was investigated (Table 17). Both stirring of the mixture in the presence ytterbium triflate and SiO₂ were found to cause a slight increase in the abundance of the desired diastereoisomer 302 in the diastereoisomeric mixture. The best results were obtained from stirring a 1:1 mixture of 301:302 in the presence of scandium triflate at room temperature for a prolonged period of time, resulting in the formation a 1:1.1:1 diastereoisomeric mixture of 300:301:302. The best yield for the recovery of 302 is 10% with respect to the amount of 2,6-*trans*; 5,6-*cis* THP material in the starting material. Heating a 1:1 mixture of 300:301 in refluxing THF in the presence of scandium triflate resulted in decomposition of the starting material, as did stirring at room temperature in the presence of titanium tetrachloride or Amberlyst resin. Stirring in the presence of neutral alumina afforded no change in the diastereoisomeric composition.



Reagents and conditions: (i) H₂O, DMF, microwave, 160 °C, 250W, 83%.

Scheme 101: Decarboxylation of 302

With pure 302 in hand, albeit in modest amounts, attempts to remove the *t*-butyl ester group were undertaken, and thankfully the conditions developed on the racemic series material were found to be successful (Scheme 101). Thus, heating in wet dimethylformamide to 160 °C with 250 W power in the microwave was found to reveal THPO 303 in 83% yield.



Reagents and conditions: (i) LiHMDS, $-78\text{ }^{\circ}\text{C}$, 1 h, $-20\text{ }^{\circ}\text{C}$, 1 h, then HMPA and MeI, $-20\text{ }^{\circ}\text{C}$, 5 h, 41% conversion, dr 2:1 305:306.

Scheme 102: C3 Methylation

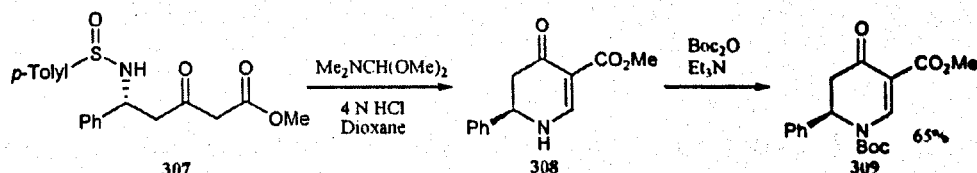
After surveying the literature, few examples were found on methylation α - to a ketone in a six-membered ring. Furthermore, the reported methylations displayed very little stereocontrol. However, we were confident that methylation was possible because Smith had used such a reaction for the installation of an equatorial methyl group in his synthesis of (+)-phorboxazole A (Scheme 23, Introduction).⁴¹ Investigations began into the installation of a methyl group at C3 of 303, under kinetic control since the desired THP 305 is seen to exhibit an axially-substituted methyl group at this position (Scheme 102). Thus, enolate formation at $-78\text{ }^{\circ}\text{C}$ was attempted with a variety of organolithium bases such as LDA, LiHMDS, and LiTMP. However, trapping at $-78\text{ }^{\circ}\text{C}$ with iodomethane, resulted in no product formation. Furthermore, attempts to increase the reactivity of the enolate by using HMPA as an additive proved fruitless. The HMPA has an affinity for the lithium cation and as such reduces its affinity for the enolate, thus increasing the enolate's reactivity. At this stage, it was unclear as to where the problem with the methylation lay. The fact that these reactions were consistently carried out on such small scale (20 mg) due to the low yielding nature of the cyclisation was far from ideal since any moisture in the reaction vessel would have a comparatively large detrimental effect. We were also mindful of the earlier Claisen condensation (Scheme 97) where it had required ten equivalents of enolate for the reaction to approach completion due to the acidity of the methyl protons of the oxazole. However, increasing

the amount of base to five equivalents made no difference, and at no point was methylation of the oxazole methyl observed. To this end, deuterium-labelling was attempted *via* quenching the enolate at $-78\text{ }^{\circ}\text{C}$ with ten equivalents of a 10 M solution of AcOD in THF. However, from analysis of the ^1H NMR spectrum, incorporation of deuterium was neither observed α to the ketone, nor at the oxazole methyl. This suggested that deprotonation under these conditions was non-existent.

The failure of the methylation slowed progress drastically, because although the starting material **303** remained untouched in the reaction, it wasn't very stable to column chromatography which hindered the efficiency of its recovery. In order to ascertain whether the problem lay with the cold reaction conditions or the substrate itself, Smith's conditions for the methylation were replicated.⁴¹ Thus enolization was effected by treatment of **303** with lithium hexamethyldisilazide at first $-78\text{ }^{\circ}\text{C}$ before being warmed to $-20\text{ }^{\circ}\text{C}$. Trapping with iodomethane and HMPA was seen to afford some methylated product, though lots of starting material was seen to remain by TLC. Analysis by ^1H NMR spectroscopy indicated that the reaction had gone to 41% completion and had afforded the C-3 methylated THPs **305** and **306** in a ratio of 2:1 respectively. The diastereoisomers were assigned as such from analysis of the ^1H NMR analysis of a 3:1 mixture of **305**:**306** which was separated from the starting material by column chromatography. Unfortunately, vanishingly small amounts of these diastereoisomers (ca. 3 mg) were so closely running by TLC that neither could be isolated cleanly in any of the solvent systems investigated by neither flash column chromatography nor preparative TLC. The 1H dq with J-values of 10.3 and 6.7 Hz at 2.71 ppm and the 1H dqd with J-values of 10.4, 6.6, and 1.2 Hz at 2.55 ppm can be assigned as H-5 in **305** and **306** respectively from the ^1H - ^1H COSY data. The J' -coupling (1.2 Hz) exhibited by the peak at 2.55 ppm, which integrates for 3 times the

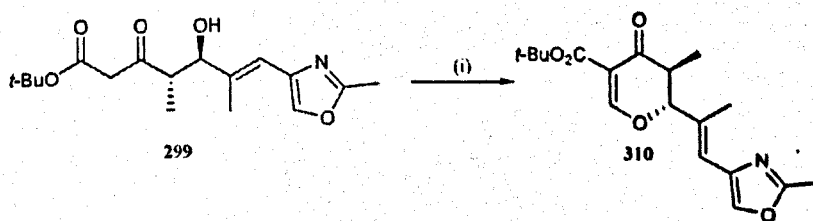
peak at 2.71 ppm resulted in the tentative assignment of this as a diastereoisomeric mixture of 3:1 **305:306**. Attempts to improve the conversion from 41% proved fruitless, but included increasing the amount of base from two equivalents up to five and using 12-crown-4-ether as an alternative lithium-sequestering agent.

Unfortunately, the low yielding nature of the cyclisation step, mainly due to poor 2,6-*cis* selectivity, had hampered the synthesis greatly because it had limited the amount of material required to fully investigate the stereoselective methylation of **303**. We were therefore attracted to an alternative approach which would furnish a 2,6-*cis* selective THP in higher yield.



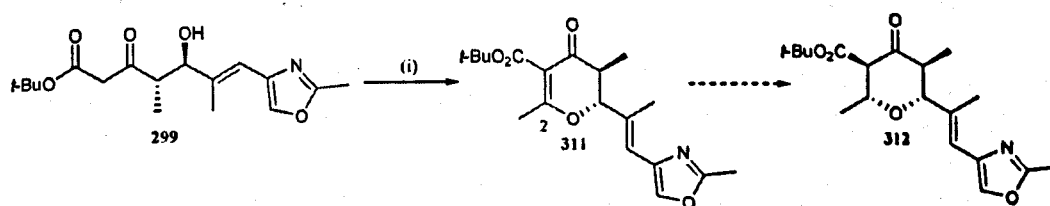
Scheme 103: Dihydropiperidine formation

Our attention was drawn to a piece of methodology which uses sulfinimine-derived δ -amino β -ketoesters in condensation with the dimethyl acetal of dimethylformamide to form 2,4,5-trisubstituted dihydropiperidines (Scheme 103).¹¹¹ The cyclisation from **307** to **308** occurs *via* a Knoevenagel/Michael cyclisation, followed by a retro-Michael-type elimination.



Reagents and conditions: (i) $\text{Me}_2\text{NCH}(\text{OMe})_2$, PhMe, rt, 24 h, 65%.
Scheme 104: Formation of dihydropyran **310**

It would be interesting to see if this methodology could be transferred to our δ -hydroxy β -ketoesters for the formation of dihydropyranones (DHPOs), and furthermore whether the reaction could provide dihydropyrans with substitution at C2 from reaction with the dimethyl acetals of more complex amides. Pleasingly, δ -hydroxy β -ketoester **299** was seen to undergo cyclisation with the dimethyl acetal of dimethyl formamide to reveal the dihydropyran **310** in 65% yield (Scheme 104).



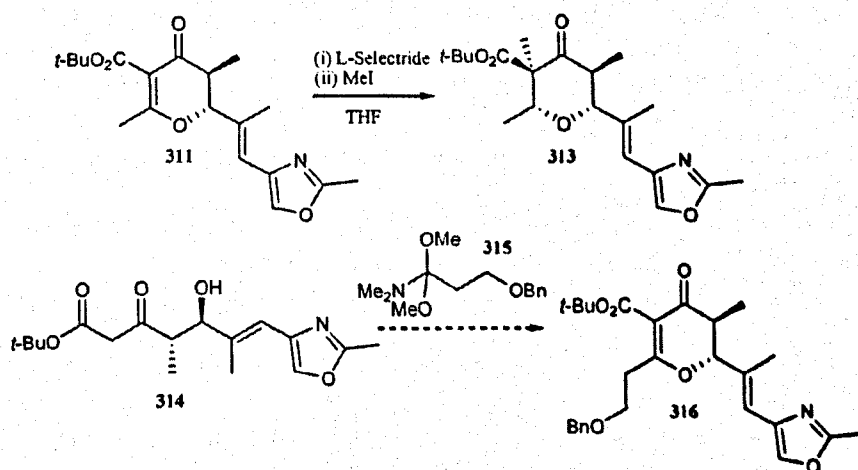
Reagents and conditions: (i) $\text{Me}_2\text{NCMe}(\text{OMe})_2$, PhMe , rt, 24 h, 71%.
Scheme 105: Formation of DHPO **311**

Furthermore, reaction with the dimethyl acetal of dimethylacetimidate furnished the DHPO **311** with methyl substitution at C2 (Scheme 105). This was a very exciting result, because subsequent diastereoselective conjugate reduction of the enone **311** would provide access to the 2,6-*cis* THPO **312**. To this end, reduction of **311** was attempted with a number of known conditions; Stryker's reagent,¹¹² Et_3SiH with a number of Lewis acids, and $\text{BH}_3\cdot\text{THF}$ complex. Unfortunately, these conditions only returned starting material. As this work was carried out towards the end of my time in the lab, it was passed on to a postdoctoral research assistant in the group, Dan Woollaston, who has since managed to achieve the conjugate reduction of **311** with *L*-selectride to furnish a single diastereoisomer of **312** in 70% yield.

6.5 Conclusions and Future Work

Investigations, based on the Maitland-Japp reaction, into the cyclisations to form tetra-substituted tetrahydropyranones have been undertaken with a view to synthesising the

C19 to C32 central core THP of (+)-phorboxazole B. In order to conduct an asymmetric synthesis, enantioselective aldol reactions have been studied which have culminated in the formation of the *syn* and *anti* cyclisation precursors **286** and **299** in good yield. The cyclisation of these precursors to tetra-substituted THPOs proceeded in moderate yields. However, this step has proved to be troublesome to the synthesis due to the poor 2,6-*cis* selectivity exhibited by the reactions, resulting in the formation of **302** to be achieved in very poor yield. As such, it was not possible to achieve sufficient material of **303** to fully investigate the selective methylation at C3. An alternative route to the formation 2,6-*cis* THPOs was sought and included the formation of the dihydropyranone **311**, which has since been converted to **313** in good yield and excellent selectivity (Scheme 106).



Scheme 106: Future work

Current work within the group involves removal of the *t*-butyl ester group in **313** whilst retaining the stereochemistry around the ring. Upon successful removal of this ester, the focus would then shift to the synthesis of dimethyl acetal **315** in order for it to be used in the synthesis of the dihydropyran **316**.

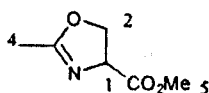
7. Experimental

General

Melting points were determined using a Stuart SMP3 apparatus. Infrared spectra were recorded on a ThermoNicolet Avatar 370 FT-IR spectrometer using NaCl plates or as a solution in CHCl_3 . Nuclear magnetic resonance spectra were recorded on a Jeol EX-270, a Jeol ECX-400, or a Bruker DRX 500 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm; benzene-d₆, 7.16 ppm for ^1H NMR data; chloroform-d, 77.0 ppm, benzene-d₆ 126.06 ppm for ^{13}C NMR data. Coupling constants (J) are quoted in Hertz. ^{13}C NMR spectra were assigned using DEPT and HMQC experiments. Mass spectrometry was performed by the University of York mass spectrometry service EI or ES ionisation techniques. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F₂₅₄. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich, unless stated otherwise. CH_2Cl_2 was distilled from calcium hydride; THF and Et_2O were distilled from sodium-benzophenone ketyl; PhMe was dried over sodium wire; hexanes was distilled prior to use. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not conform to IUPAC rules. However, the compound names are standardised and correspond to IUPAC rules.

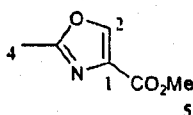
Racemic Series

2-Methyl-4-carboxy methyl ester oxazoline (162)⁷⁰



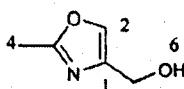
This compound was synthesised as a colourless oil (10.4 g, 83%) in accordance with a literature procedure. The ¹H NMR data were not found to be in agreement with that reported, however I believe the data quoted in the literature to be misassigned.⁷⁰ ¹H NMR (CDCl₃, 400 MHz): δ 4.72 (1 H, ddq, J = 10.6, 7.9, 1.3 Hz, H-1), 4.48 (1H, dd, J = 8.7, 7.9 Hz, H-2), 4.40 (1H, dd, J = 10.6, 8.7 Hz, H-2), 3.78 (3 H, s, H-5), 2.02 (3 H, d, J = 1.5 Hz, H-4) ppm.

2-Methyl-4-carboxy methyl ester oxazole (163)⁷⁰



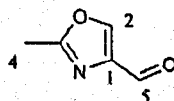
Bromotrichloromethane (6.90 mL, 69.9 mmol) and 1,8 diazabicyclo[5.4.0]undec-7-ene (10.5 mL, 69.9 mmol) were added to a solution of 2-methyl-4-carboxy methyl ester oxazoline 162 (5.00 g, 35.5 mmol) in CH₂Cl₂ (250 mL) at 0 °C, under an atmosphere of N₂. After 2 hours of stirring, the reaction mixture was reduced to ca. 50 mL *in vacuo*, and was then partitioned between EtOAc (150 mL) and 2 M HCl (50 mL). The aqueous layer was further extracted with EtOAc (150 mL), and the combined organic extracts were washed with a saturated aqueous solution of NaHCO₃ (50 mL) and brine (50 mL). The organic layer was the dried (MgSO₄), filtered, and concentrated *in vacuo*, to yield a dark brown residue (5.97 g). Flash column chromatography (1:2 / petroleum ether : EtOAc) gave 163 as a white solid (3.79 g, 76%). The ¹H NMR data were found to be in agreement with the literature.⁷⁰ ¹H NMR (CDCl₃, 62.5 MHz): δ 8.12 (1 H, s, H-1), 3.88 (3 H, s, H-3) 2.49 (3 H, s, H-2) ppm.

(2'-Methyl-oxazol-4'-yl) methanol (164)⁷⁰



A 1.0 M solution of DIBAL-H in PhMe (44.7 mL, 44.7 mmol) was added to a solution of 2-methyl-4-carboxy methyl ester oxazole **163** (3.00 g, 21.3 mmol) in Et₂O (200 mL) at 0 °C, under an atmosphere of N₂. The reaction mixture was stirred for 1 hour at 0 °C, after which time the reaction was quenched with an addition of H₂O (1.8 mL) over 5 min at 0 °C. An aqueous solution of 15% NaOH (1.8 mL) was added followed by a further portion of H₂O (4.5 mL) before the mixture was warmed to room temperature and stirred for 15 min. The reaction was dried by the addition of MgSO₄ (7.67 g), and the mixture was stirred for a further 15 min before the solids were removed by filtration. The filtrate was concentrated *in vacuo* to yield **164** as a pale yellow solid (1.79 g, 74%), which required no further purification. The ¹H NMR data was found to be in agreement with the literature.⁷⁰ ¹H NMR (CDCl₃, 400 MHz): δ 7.45 (1 H, s, H-2), 4.61 (1H, s, H-6), 4.51 (2 H, s, H-5), 2.42 (3 H, s, H-4) ppm.

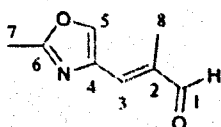
(2'-Methyl-oxazol-4'-yl) formaldehyde (41)⁷⁰



Dimethyl sulfoxide (2.54 mL, 35.8 mmol) was added to a solution of oxalyl chloride (1.56 mL, 17.9 mmol) in CH₂Cl₂ (50 mL) at -60 °C, under an atmosphere of N₂. The reaction mixture was stirred for 2 min before the addition of a solution of (2'-methyl-oxazol-4'-yl) methanol (**163**) (1.32 g, 11.9 mmol) in CH₂Cl₂ (17 mL) over a period of 10 min at -60 °C. After 20 min of stirring at -60 °C, triethylamine (8.33 mL, 59.7

mmol) was added, and the reaction mixture was stirred for a further 10 min at -60 °C. The reaction mixture was then warmed to room temperature and stirred for 30 min. The reaction was quenched with H₂O (50 mL), and the mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried (MgSO₄), and concentrated *in vacuo* to give an off-white solid (1.55 g). Flash column chromatography (1:1 / petroleum ether : EtOAc) yielded **41** as a pale yellow solid (1.26 g, 74%). The ¹H NMR data were found to be in agreement with the literature.⁷⁰ ¹H NMR (CDCl₃, 400 MHz): δ 9.90 (1 H, s, H-5), 8.17 (1 H, s, H-2), 2.53 (3 H, s, H-4) ppm.

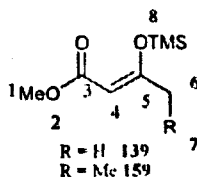
(E)-2-methyl-3-(2'-methyl-oxazol-4'-yl)-propenal (29)⁷⁰



2-(Triphenylphosphoranylidene)-propionaldehyde (3.39 g, 10.6 mmol) was added to a solution of (2'-methyl-oxazol-4'-yl)-formaldehyde (**41**) (944 mg, 8.50 mmol) in PhII (80 mL) at room temperature, under an atmosphere of N₂. After 2 days of stirring, the reaction mixture was filtered, and washed successively with pentane, resulting in precipitate formation in the filtrate. This precipitate was removed by filtration and washed with pentane. The filtrate was dried (MgSO₄), filtered, and concentrated *in vacuo* to yield an off-white solid. The solid was successively extracted with pentane, and the combined organic extracts were dried (MgSO₄) filtered, and concentrated *in vacuo* to yield a pale yellow solid (183 mg). Flash column chromatography (1:1 / petroleum ether : EtOAc) gave **29** as a pale yellow solid (1.06 g, 82%), mp 84-88 °C. The ¹H NMR data were found to be in agreement with the literature.⁷⁰ IR (film): ν_{\max}

3149, 2931, 2833, 2764, 2716, 1688, 1640, 1445 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ 9.55 (1 H, s, H-1), 7.83 (1 H, q, $J = 1.2$ Hz, H-5), 7.07 (1 H, s, H-3), 2.51 (3 H, s, H-8), 2.08 (3 H, d, $J = 1.2$ Hz, H-7) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 194.4 (C=O, C-1), 162.0 (C, C-2/4/6), 139.8 (CH, C-5), 138.5 (C, C-2/4/6), 138.0 (CH, C-3), 137.4 (C, C-2/4/6), 13.8 (CH_3 , C-8), 11.1 (CH_3 , C-7) ppm. MS (EI): m/z 151 (M^+), 136 ($\text{M}^+ - \text{CH}_3$), 123 ($\text{M}^+ - \text{CO}$), 109 ($\text{M}^+ - \text{CH}_2 - \text{CO}$), 94 ($\text{M}^+ - \text{CH}_2 - \text{CH}_3 - \text{CO}$), 81 ($\text{M}^+ - \text{HCOC}(\text{CH}_3)\text{CH} - \text{H}$).

Trimethylsilyl enol ethers 139 and 159^{72,73}



General preparation:

Triethylamine (1.2 eq) was added to a mixture of β -ketoester (1.0 eq) in dry hexanes (0.5 M reaction solution) at room temperature, under an atmosphere of N_2 . Chlorotrimethylsilane (1.1 eq) was then added over a period of 30 min, resulting in the formation of a thick white precipitate. The reaction mixture was stirred vigorously overnight, after which time the salts were filtered and washed successively with hexanes. The filtrate was concentrated *in vacuo* to a pale yellow oil, which was used without further purification.

Methyl 3-(trimethylsilyloxy)but-2-enoate (167)

The title compound was isolated as a 9:1 mixture of isomers isolated in 84% yield. ^1H NMR (major isomer) (CDCl_3 , 270 MHz): δ 5.13 (d, $J = 0.6$ Hz) and 5.11 (d, $J = 0.6$

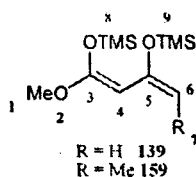
Hz) (1 H total, H-4), 3.67 (s) and 3.65 (s) (3 H total, H-1), 2.27 (d, J = 0.6 Hz) and 1.90 (d, J = 0.6 Hz) (1 H total, H-6), 0.28 (s) and 0.27 (s) (9 H total, H-8) ppm.

Methyl 3-(trimethylsiloxy)pent-2-enoate 1 (201)

The title compound was isolated as a 2:1 mixture of isomers isolated in 87% yield.

¹H NMR (CDCl₃, 270 MHz): 5.13 (s) and 5.05 (s) (1 H total, H-4), 3.65 (3 H, s, H-1), 2.71 (q, J = 7.4 Hz) and 2.13 (q, J = 7.4 Hz) (2 H total, H-6), 1.09 (t, J = 7.4 Hz) and 1.07 (t, J = 7.4 Hz) (3 H total, H-7), 0.27 (s) and 0.26 (s) (9 H total, H-8) ppm.

Bis(Trimethylsilyl) enol ethers 139 and 159⁷³



The trimethylsilyl enol ether (1.0 eq) was added to a freshly prepared solution of LDA (1.1 eq) in THF (0.5 M reaction solution). at -78 °C, under an atmosphere of N₂. The reaction mixture was stirred for 30 minutes, after which time chlorotrimethylsilane (1.2 eq) was added over a period of 10 min, and the reaction mixture was warmed to 0 °C. The reaction mixture was then stirred at 0 °C for 1 hour, after which time the volatiles were removed *in vacuo* and the salts were suspended in dry hexanes. The mixture was filtered and concentrated *in vacuo* to yield a yellow oil, which was purified by Kügelrohr distillation.

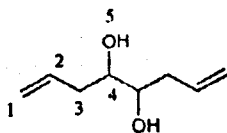
1,3-Bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene (139)

Isolated in 49% yield, bp 51-59 °C (0.2 mbar). ¹H NMR (CDCl₃, 270 MHz): δ 4.49 (1 H, s, H-6), 4.15 (1 H, s, H-4), 3.56 (3 H, s, H-1), 0.26 (9 H, s, H-9), 0.22 (9 H, s, H-8) ppm.

1,3-Bis-(trimethylsiloxy)-1-methoxypenta-1,3-diene (159)

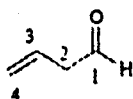
Isolated in 64% yield, bp 75-79 °C (0.2 mbar). ¹H NMR (CDCl₃, 270 MHz): δ 4.92 (1 H, q, J = 6.7 Hz, H-6), 3.90 (1 H, s, H-4), 3.52 (3 H, s, H-1), 1.58, (3 H, d, J = 6.7 Hz, H-7), 0.22 (9 H, s, H-9), 0.18 (9H, s, H-8) ppm.

4,5-Dihydroxy-octa-1,7-diene (166)⁷¹



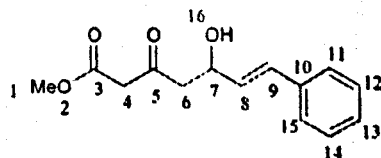
This compound was synthesised as a colourless oil (2.46 g, 69%) in accordance with a literature procedure.⁷¹ The ¹H NMR data was found to be in agreement with those reported.⁷¹ ¹H NMR (major diastereomer) (CDCl₃, 270 MHz): δ 5.86 (2 H, dddd, J = 16.8, 10.1, 7.3, 6.7 Hz, H-2), 5.08-5.26 (4 H, m, H-1), 3.56 (2 H, dq, J = 9.2, 4.6 Hz, H-4), 2.02-2.48 (6 H, m, H-3, H-5) ppm.

But-3-en-1-al (160)⁷¹



This compound was synthesised as a solution in CH_2Cl_2 (3.8 ml, 0.39 M, 42%) in accordance with a literature procedure.⁷¹ The ^1H NMR data were found to be in agreement with that reported.⁷¹ ^1H NMR (CDCl_3 , 270 MHz): δ 9.70 (1 H, t, $J = 1.8$ Hz, H-1), 5.92 (1 H, ddd, $J = 17.2, 10.3, 6.9$ Hz, H-3), 5.29 (1 H, ddd, $J = 10.3, 1.4, 1.4$ Hz, H-4), 5.22 (1 H, ddd, $J = 17.2, 1.4, 1.4$ Hz, H-4), 3.20 (2 H, ddd, $J = 6.9, 1.8, 1.4$ Hz, H-2) ppm. μ

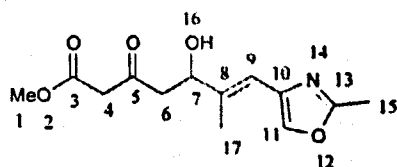
Methyl-5-hydroxy-3-oxo-7-phenyl-hept-6-enoate (170)



Trans-cinnamaldehyde (46 μL , 0.37 mmol) was added to a suspension of ytterbium triflate (228 mg, 0.37 mmol) in CH_2Cl_2 at -78 $^\circ\text{C}$, under an atmosphere of N_2 . After 10 minutes of stirring, Chan's diene (139) was added at -78 $^\circ\text{C}$. The reaction mixture was stirred at -78 $^\circ\text{C}$ for 2 hours, after which time, the reaction was quenched with H_2O (2 mL), and diluted with EtOAc (40 mL). The organic layer was then successively washed with 5% aqueous solution of NaHCO_3 (3 x 15 mL) and brine (2 x 15 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to a bright yellow oil (230 mg). The crude material was purified by flash column chromatography (10:1 / petroleum ether : EtOAc) to yield 170 as a yellow oil. (35 mg, 38%). IR (film): ν_{max} 3444 (br), 3027, 2954, 1743, 1710, 1437, 1431, 1324 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz): δ 7.23-7.41 (5 H, m, Ph), 6.66 (1 H, dd, $J = 15.9, 1.1$ Hz, H-9), 6.21 (1 H, dd, $J = 15.9, 6.1$ Hz, H-8), 4.81 (1 H, dddd, $J = 8.2, 6.1, 4.5, 1.1$ Hz, H-7), 3.76 (3 H, s, H-1), 3.54 (2 H, s, H-4), 3.15 (1 H, d, $J = 7.3$ Hz, H-16), 2.89 (1 H, dd, $J = 15.2, 6.1$ Hz, H-6), 2.67

(1 H, dd, $J = 15.2, 4.5$ Hz, H-6) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 202.6 (C, C-5) 167.3 (C, C-3), 136.3 (C, C-10), 130.7 (CH, C-9), 129.7 (CH, C-8), 128.6 (CH, C11/12/13/14/15), 127.8 (CH, C11/12/13/14/15), 126.5 (CH, C11/12/13/14/15), 68.4 (CH, C-7), 52.5 (CH_3 , C-1), 49.7 (CH_2 , C-4), 49.5 (CH_2 , C-6) ppm. MS (EI): m/z 248 (10%) (2%, M^+), 230 (12%, $\text{M}^+ - \text{H}_2\text{O}$), 171 (10%, $\text{M}^+ - \text{Ph}$), 157 (25%, $\text{M}^+ - \text{CH}_3\text{OCOCH}_2$), 131 (70%, $\text{M}^+ - \text{CH}_3\text{OCOCH}_2\text{COCH}_3 - \text{H}$), 104 (100%, $\text{M}^+ - \text{CH}_3\text{OCOCH}_2\text{COCH}_2\text{CHO}$).

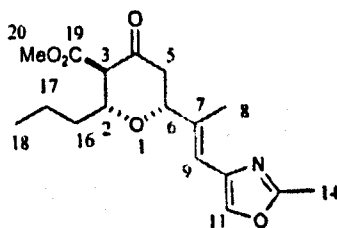
Methyl-5-hydroxy-6-methyl-7-(2'-methyl-oxazol-4'-yl)-3-oxo-hept-6-enoate (171)



A solution of enal **29** (76 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added to a suspension of ytterbium triflate (310 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) at -78 °C, under an atmosphere of N_2 . After 10 minutes of stirring, Chan's diene **139** (456 μL , 1.0 mmol) was added at -78 °C, over a period of 3 minutes. The reaction mixture was stirred at -78 °C for 2 hours, after which time, the reaction was quenched with trifluoroacetic acid (154 μL , 2.0 mmol). The reaction mixture was then diluted with EtOAc (40 mL) and successively washed with 5% aqueous solution of NaHCO_3 (2 x 20 mL), 5% aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 20 mL), and brine (2 x 15 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to a yellow oil (175 mg). Purification by flash column chromatography (1:2 / petroleum ether : EtOAc) afforded **171** as a 9:1 mixture of keto : enol tautomers, as a yellow oil (82 mg, 61%). IR (film): ν_{max} 3385 (br), 2956, 2926, 2855, 1744, 1715, 1439, 1321, 1108 cm^{-1} . ^1H NMR (keto-tautomer)

(CDCl₃, 400 MHz): δ 7.47 (1 H, s, H-11), 6.34 (1 H, d, $J = 0.9$ Hz, H-9), 4.63 (1 H, dt, $J = 8.7, 3.4$ Hz, H-7), 3.74 (3 H, s, H-1), 3.54 (2 H, s, H-4), 3.24 (1 H, d, $J = 3.1$ Hz, H-16), 2.83 (1 H, dd, $J = 16.8, 8.7$ Hz, H-6), 2.77 (1 H, dd, $J = 16.8, 3.4$ Hz, H-6), 2.44 (3 H, s, H-15), 1.93 (3 H, d, $J = 0.9$ Hz, H-17) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 202.7 (C, C-5), 167.3 (C, C-3), 139.7 (C, C-8/10/13), 137.7 (C, C-8/10/13), 135.7 (CH, C-11), 128.3 (C, C-8/10/13), 115.3 (CH, C-9), 72.5 (CH, C-7), 52.5 (CH₃, C-1), 49.8 (CH₂, C-4), 48.2 (CH₂, C-6), 14.9 (CH₃, C-17), 13.8 (CH₃, C-15) ppm. MS (EI): m/z 267 (3%, M⁺), 249 (4%, M⁺ - H₂O), 235 (3%, M⁺ - CH₃OH), 217 (3%, M⁺ - CH₃OH - H₂O), 148 (80%, M⁺ - H₂O - CH₃OCOCH₂CO), 124 (80%, M⁺ - CH₃OCOCH₂COCH₂CO), 43 (100%). On a subsequent occasion, this procedure yielded the TMS-enol ether, from which the HRMS data were taken: HRMS: found (M⁺+TMS) 340.1577 C₁₆H₂₆NO₅Si requires (M⁺+TMS) 340.1581.

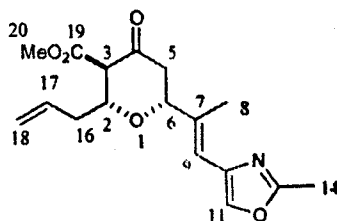
6-[1-Methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4-oxo-2-propyl-tetrahydro-pyran-3-carboxylic acid methyl ester (190)



A solution of (*E*)-2-methyl-3-(2'-methyl-oxazol-4'-yl)-propenal **171** (38 mg, 0.25 mmol) in CH₂Cl₂ (2.5 mL) was added to a suspension of ytterbium triflate in CH₂Cl₂ (0.5 mL) at -78 °C, under an atmosphere of N₂. After 10 minutes of stirring, Chan's diene **139** (228 μ L, 0.50 mmol) was added at -78 °C. The reaction mixture was stirred at -78 °C for 2 hours, after which time trifluoroacetic acid (77 μ l, 1.00 mmol) was

added, followed by butanal (27 μ L, 0.30 mmol) and the reaction mixture was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was diluted with EtOAc (40 mL) and the organic layer was washed successively with 5% aqueous solution of NaHCO_3 (3 x 20 mL), 5% aqueous solution of $\text{Na}_2\text{S}_2\text{O}_5$ (3 x 20 mL), and brine (2 x 20 mL), dried (MgSO_4), and concentrated *in vacuo* to a yellow oil (115 mg). Flash column chromatography (5:1 / petroleum ether : EtOAc) gave 190 in a 9:1 mixture of keto : enol tautomers, as a yellow oil (57 mg, 72%). IR (film): ν_{max} 2959, 2933, 2873, 1746, 1716, 1438, 1129, 1110 cm^{-1} . ^1H NMR (keto-tautomer) (CDCl_3 , 400 MHz): δ 7.51 (1 H, s, H-11), 6.35 (1 H, s, H-9), 4.17 (1 H, d (br), $J = 11.0$ Hz, H-6), 3.99 (1 H, ddd, $J = 10.4, 8.2, 2.8$ Hz, H-2), 3.79 (3 H, s, H-20), 3.32 (1 H, d, $J = 10.4$ Hz, H-3), 2.63 (1 H, dd, $J = 14.3, 2.4$ Hz, H-5eq), 2.46 (3 H, s, H-14), 2.46 (1 H, dd, $J = 14.3, 11.0$ Hz, H-5ax), 1.98 (3 H, s, H-8), 1.40-1.69 (4 H, m, H-16 & H-17), 0.94 (3 H, t, $J = 7.0$ Hz, H-18) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 202.2 (C, C-4), 168.6 (C, C-20), 160.9 (C, C-7/10/13), 137.6 (C, C-7/10/13), 137.3 (C, C-7/10/13), 135.8 (CH, C-11), 115.7 (CH, C-9), 80.6 (CH, C-6), 78.1 (CH, C-2), 63.0 (CH, C-3), 52.2 (CH_3 , C-20), 45.9 (CH_2 , C-5), 37.1 (CH_2 , C16/17), 18.5 (CH_3 , C16/17), 15.2 (CH_3 , C-8), 13.8 (CH_3 , C-18), 13.8 (CH_3 , C-14) ppm. MS (EI): m/z 321 (M^+), 306 ($\text{M}^+ - \text{CH}_3$), 278 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{CH}_3$), 246 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{CH}_3 - \text{MeOH}$), 124 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{CH}_3 - \text{C}(\text{CH}_3)\text{CHC}(\text{C}_3\text{H}_4\text{NO}) - \text{CH}_3\text{O}$). HRMS: found ($\text{M}^+ + \text{H}$) 322.1654 $\text{C}_{14}\text{H}_{20}\text{NO}_5\text{Na}$ requires ($\text{M}^+ + \text{H}$) 322.1649

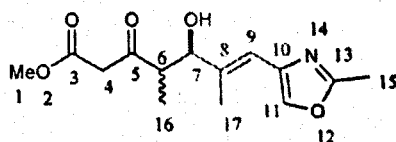
2-Allyl-6-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (191)



A solution of methyl-5-hydroxy-6-methyl-7-(2'-methyl-oxazol-4'-yl)-3-oxo-hept-6-enoate (171) (32 mg, 0.12 mmol) in CH₂Cl₂ (1 mL) was added to a stirred slurry of ytterbium triflate (74 mg, 0.12 mmol) in CH₂Cl₂ (1 mL) at room temperature, under an atmosphere of N₂. The reaction mixture was stirred for 5 min, after which time a 0.44 M solution of but-1-enal (160) in CH₂Cl₂ (408 μL, 0.18 mmol) was added, followed by trifluoroacetic acid (18 μL, 0.24 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 hours. After this time, the reaction mixture was diluted with EtOAc (50 mL) and the organic layer was washed successively with 5% aqueous solution of Na₂S₂O₅ (2 x 30 mL) and brine (2 x 30 mL). The organic extract was then dried (MgSO₄) and concentrated *in vacuo* to a yellow oil (46.7 mg), which was purified by flash column chromatography (5:1 / petroleum ether:EtOAc) to give 191 and 192 in a 4:1 mixture of keto:enol tautomers as a yellow film (17mg, 43%). IR (film): ν_{\max} 2954, 2926, 2856, 1746, 1716, 1661 1642, 1621, 1586, 1442, 1362, 1335 1110 cm⁻¹; ¹H NMR (keto-tautomer) (CDCl₃, 400 MHz): δ 7.51 (1 H, s, H-11), 6.35 (1 H, d, J = 0.8 Hz, H-9), 5.92 (1 H, dddd, J = 17.1, 10.4, 7.5, 6.7 Hz, H-17), 4.99-5.20 (2 H, m, H-18), 4.19 (1 H, d(br), J = 11.3 Hz, H-6), 4.11 (1 H, ddd, J = 10.6, 6.1, 4.0 Hz, H-2), 3.78 (3 H, s, H-20), 3.39 (1 H, d, J = 10.6 Hz, H-3), 2.61 (1 H, dd, J = 14.0, 2.0 Hz, H-5eq), 2.40-2.56 (2 H, m, H-5ax + H-16), 2.46 (3 H, s, H-14), 2.31-2.40 (1 H, m, H-16), 1.99 (3 H, d, J = 0.8 Hz, H-8) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 220.1 (C, C-4), 168.3 (C, C-19), 160.9 (C, C-13),

137.5 (C, C-10), 137.1 (C, C-7), 135.9 (CH, C-11), 132.7 (CH, C-17), 118.7 (CH₂, C-18), 115.9 (CH, C-9), 80.7 (CH, C-6), 77.5 (CH, C-2), 61.8 (CH, C-3), 52.2 (CH₃, C-20), 45.8 (CH₂, H-5), 38.9 (CH₂, C-16), 15.0 (CH₃, C-8), 13.8 (CH₃, C-14) ppm. LCMS) (ES⁺): m/z 304 (M⁺ + Na), 279 (M⁺ - 2H), 251 (M⁺ - MeOH), 149 (M⁺ - MeO₂CCH₂COCH₂CH₃). HRMS: found (M⁺ + H) 322.1654 C₁₇H₂₄NO₅ requires (M⁺ + H) 322.1649.

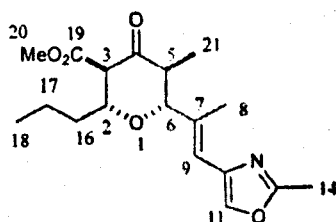
5-Hydroxy-4,6-dimethyl-7-(2-methyl-oxazol-4-yl)-3-oxo-hept-6-enoic acid methyl ester (202)



A 3 M solution of titanium tetrachloride in CH₂Cl₂ (153 μl, 0.46 mmol) was added to a solution of aldehyde 29 (69 mg, 0.46 mmol) in CH₂Cl₂ (4.5 mL) at -78 °C, under an atmosphere of N₂. After 10 minutes of stirring, diene 139 (279 μL, 0.92 mmol) was added at -78 °C. The reaction mixture was stirred for 30 minutes, after which time trifluoroacetic acid (106 μL, 1.37 mmol) was added and the reaction was warmed to room temperature. The reaction mixture was then diluted with EtOAc (40 mL) and the organic layer was washed successively with 5% aqueous solution of NaHCO₃ (2 x 30 mL) and brine (2 x 30 mL), dried (MgSO₄) and concentrated *in vacuo* to give 202 in a 9:1 ratio of *syn:anti* diastereomers as a yellow oil (127 mg, 98%) which was used without further purification. IR (film): ν_{max} 3365, 2971, 2954, 1747, 1712, 1584, 1438, 1317, 1235, 1107 cm⁻¹; ¹H NMR (data for *syn* aldol adduct) (CDCl₃, 400 MHz): δ 7.46 (1 H, s, H-11), 6.38 (1 H, s (br), H-9), 4.58 (1 H, d (br), J = 3.7 Hz, H-7), 3.73 (3 H, s, H-1), 3.60 (2 H, s, H-4), 2.91 (1 H, dq, J = 7.3, 3.7 Hz, H-6), 2.43 (3 H, s, H-15), 1.90 (3 H, s (br), H-17), 1.10 (3 H, d, J = 7.3 Hz, H-16) ppm. ¹³C NMR (CDCl₃,

100 MHz): δ 206.5 (C, C-5), 167.7 (C, C-13), 160.9 (C, C-3), 138.2 (C, C-10), 137.8 (C, C-8), 135.5 (CH, C-11), 115.3 (CH, C-9), 74.9 (CH, C-6), 52.4 (CH₃, C-1), 49.1 (CH, C-7), 47.8 (CH₂, C-4), 16.0 (CH₃, C-18), 13.8 (CH₃, C-14), 9.3 (CH₃, C-16) ppm. MS (LCMS) (ES⁺): m/z 304 (M⁺+Na), 279 (M⁺-2H), 251 (M⁺-MeOH), 149 (M⁺-MeO₂CCH₂COCH₂CH₃). HRMS: found (M⁺+Na) 304.1155 C₁₇H₂₄NO₃ requires (M⁺+Na) 304.1161.

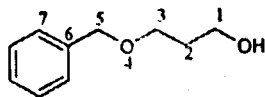
5-Methyl-6-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4-oxo-2-propyl-tetrahydropyran-3-carboxylic acid methyl ester (204)



A 3 M solution of butanal in CH₂Cl₂ (88 μ L, 0.26 mmol) was added to a solution of aldol adduct 202 (62 mg, 0.22 mmol) in CH₂Cl₂ (2 mL) at room temperature, under an atmosphere of N₂. After 5 minutes of stirring, iodotrimethylsilane (32 μ L, 0.22 mmol) was added and the reaction mixture was left to stir at room temperature for 16 hours. After this time, the reaction mixture was diluted with EtOAc (50 mL) and the organic extract was washed successively with 10% aqueous solution of Na₂S₂O₃ (2 x 20 mL), 5% aqueous solution of Na₂S₂O₅ (2 x 20 mL) and brine (2 x 20 mL). The organic extract was then dried (MgSO₄) and concentrated *in vacuo* to give a dark brown residue (66 mg), which was purified by flash column chromatography (4:1 / petroleum ether : EtOAc) to yield 204 as a yellow film (12 mg, 35%). IR (film): ν_{max} 2959, 2924, 2873, 1746, 1713, 1587, 1452, 1340, 1130, 1102 cm⁻¹; ¹H NMR (data for keto-tautomer) (C₆D₆, 400 MHz): δ 7.01 (1H, s, H-11), 6.04 (1H, s (br), H-9), 4.06 (1H, ddd, J = 10.6, 7.3, 3.0 Hz, H-2), 3.47 (3H, s, H-20), 3.42 (1H, d, J = 10.4 Hz, H-

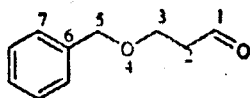
6), 3.27 (1H, dd, $J = 10.6, 0.6$ Hz, H-3), 1.99-2.06 (1H, m, H-5), 2.03 (3H, d, $J = 0.9$ Hz, H-8), 1.96 (3H, s, H-14), 1.20-1.63 (4H, m, H-16/17), 0.83 (3H, d, $J = 6.7$ Hz, H-21), 0.72-0.90 (3H, m, H-18) ppm; ^{13}C NMR (C_6D_6 , 100 MHz): δ 203.1 (C, C-4), 168.7 (C, C-19), 160.8 (C, C-13), 138.6 (C, C-7), 136.4 (C, C-10), 136.3 (CH, C-11), 119.1 (CH, C-9), 89.1 (CH, C-6), 78.4 (CH, C-2), 63.3 (CH, C-3), 51.7 (CH_3 , C-20), 47.4 (CH, C-5), 37.5 (CH_2 , C-16/17), 18.8 (CH_2 , C-16/17), 14.1 (CH_3 , C-18), 13.4 (CH_3 , C-14), 13.4 (CH_3 , C-8), 9.6 (CH_3 , C-21); MS (ESI): m/z 336 ($\text{M}^+\text{+H}$). HRMS: found ($\text{M}^+\text{+H}$) 336.1805 $\text{C}_{22}\text{H}_{28}\text{NO}_4$ requires ($\text{M}^+\text{+H}$) 336.1811.

3-Benzyloxy-1-propanol (215)⁸³



This compound was synthesised as a colourless oil (21.1 g, 70%) in accordance with a literature procedure. The ^1H NMR data were found to be in agreement with that reported,⁸² bp 62-65 °C at 0.05 mbar (lit. 118-120 °C 0.15 mbar). ^1H NMR (270 MHz, CDCl_3): δ 7.26-7.40 (5H, m, Ph), 4.50 (2H, s, H-5), 3.79 (2H, dd, $J = 5.9, 5.9$ Hz, H-3 or H-1), 3.67 (2H, dd, $J = 5.9, 5.6$ Hz, H-1 or H-3), 1.87 (2H, dddd, $J = 5.9, 5.9, 5.6, 5.6$ Hz, H-2) ppm.

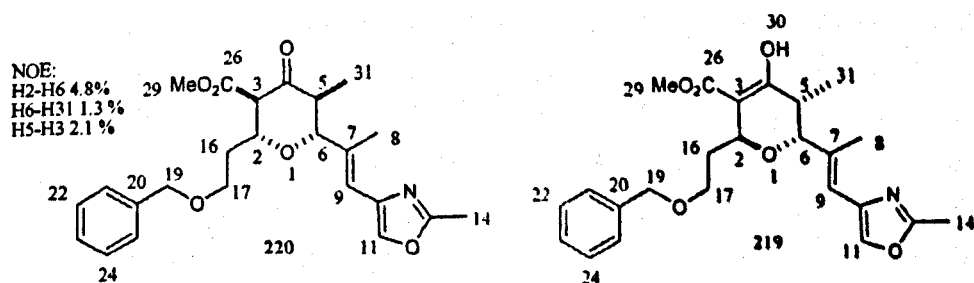
3-Benzyloxy-1-propanal (216)⁸²



A solution of dimethyl sulfoxide (2.00 mL, 28.2 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of oxalyl chloride (1.17 mL, 14.1 mmol) in CH_2Cl_2 (35 mL) at -78 °C. After 30 minutes, alcohol 215 (4.16 g, 25.0 mmol) was added to the reaction mixture at -60 °C over a period of 3 minutes, and 20 minutes after the addition

triethylamine (6.55 mL, 47.0 mmol) was added over a period of 5 minutes. After a further 17 min, the reaction mixture was warmed to room temperature and quenched with H₂O (60 mL). The mixture was extracted with CH₂Cl₂ (2 x 60 mL) and the combined organics were washed successively with a saturated aqueous solution of NH₄Cl (2 x 60 mL), a saturated aqueous solution of NaHCO₃ (2 x 60 mL), and brine (60 mL), dried (MgSO₄) and then concentrated *in vacuo*. The resulting yellow oil was distilled under reduced pressure affording the desired aldehyde **216** (2.47 g, 60%), bp 77-80 °C at 0.07 mbar (lit. 68-70 °C at 0.05 mbar). The ¹H NMR data were found to be in agreement with the literature.⁸² ¹H NMR (400 MHz; CDCl₃): δ 9.80 (1H, t, J = 1.8 Hz, H-1), 7.27-7.38 (5H, m, Ph), 4.54 (2H, s, H-5), 3.82 (1H, t, J = 6.1 Hz, H-3), 2.70 (1H, ddd, J = 6.1, 6.1, 1.8 Hz, H-2).

2-(2-Benzyloxy-ethyl)-5-methyl-6-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4-oxo-tetrahydro-pyran-3-methylcarboxylate (220) and **2-(2-Benzyloxy-ethyl)-4-hydroxy-5-methyl-6-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-5,6-dihydro-2H-pyran-3-methylcarboxylate (219)**



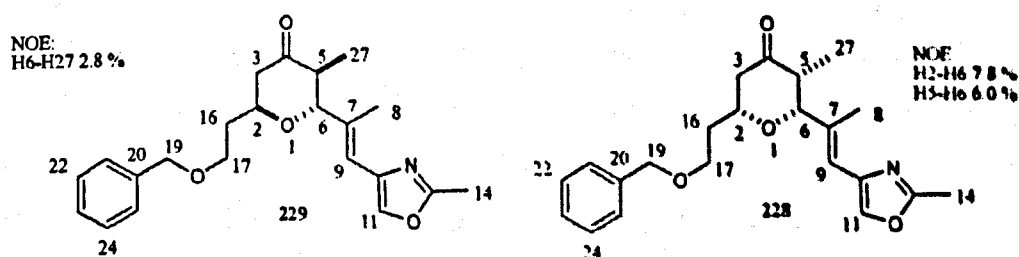
A solution of aldol adduct **202** (320 mg, 1.14 mmol) in CH₂Cl₂ (3 mL) was added to a stirred suspension of ytterbium triflate (705 mg, 1.14 mmol) in CH₂Cl₂ (8 mL) at room temperature, under an atmosphere of N₂. Aldehyde **29** (171 μL, 0.91 mmol) and trifluoroacetic acid (175 μL, 2.28 mmol) were added successively at room temperature. After 16 hours of stirring, the reaction was quenched with a 5% aqueous

solution of NaHCO₃ (5 mL). The reaction mixture was then diluted with EtOAc (40 mL) and the organics were successively washed with a 5% aqueous solution of Na₂S₂O₅ (2 x 20 mL), a 5% aqueous solution of NaHCO₃ (2 x 20 mL) and brine (20 mL). The organics were then dried (MgSO₄) and concentrated to an orange oil (342.5 mg), which was purified *via* flash column chromatography (10:1 to 2:1 to 1:1 / petroleum ether : EtOAc) to yield **220** (27 mg, 7%) as a yellow oil, **219** (23 mg, 6%) as a yellow oil, and an inseparable mixture of diastereoisomers keto *5,6-cis*; *2,6-cis* : enol *5,6-trans*; *2,6-cis* : enol : *5,6-trans*; *2,6-trans* : keto *5,6-trans*; *2,6-trans* : keto *5,6-trans*; *2,6-cis* : enol *5,6-cis*; *2,6-trans* (3 : 1 : 1 : 1 : 1 : 0.3 respectively). (185 mg, 50%) as a yellow oil.

Compound **220**: IR (film): ν_{\max} 2962, 2933, 2862, 1744, 1715, 1455, 1437, 1365, 1340, 1219, 1108 cm⁻¹; ¹H NMR (CDCl₃, 400MHz): δ 7.52 (1H, s, H-11), 7.23-7.37 (5H, m, H-21, H-22, H-23, H-24, H-25), 6.19 (1H, s (br), H-9), 4.50 (1H, d, J = 11.9 Hz, H-19), 4.45 (1H, d, J = 11.9 Hz, H-19), 4.15 (1H, ddd, J = 10.6, 7.0, 3.5 Hz, H-2), 3.55 – 3.82 (2H, m, H-17), 3.78 (1H, d, J = 10.6 Hz, H-6), 3.74 (3H, s, H-29), 3.53 (1H, dd, J = 10.6, 0.9 Hz, H-3), 2.55 (1H, dqd, J = 10.6, 6.8, 0.9 Hz, H-5), 2.49 (3H, s, H-14), 1.87-2.07 (2H, m, H-16), 1.98 (3H, d, J = 1.1 Hz, H-8), 0.91 (3H, d, J = 6.8 Hz, H-31) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 203.9 (C, C-4), 168.4 (C, C-26), 160.9 (C, C-13), 138.3 (C, C-20), 137.4 (C, C-10), 136.1 (CH, C-11), 135.9 (C, C-7), 128.3 (CH, C-21/22/23/24/25), 127.6 (CH, C-21/22/23/24/25), 127.6 (CH, C-21/22/23/24/25), 127.5 (CH, C-21/22/23/24/25), 119.4 (CH, C-9), 88.8 (CH, C-6), 75.8 (CH, C-2), 72.8 (CH₂, C-19), 65.9 (CH₂, C-17), 62.8 (CH, C-3) 52.1 (CH₃, C-26), 47.5 (CH, C-5), 34.7 (CH₂, C-16), 13.8 (CH₃, C-14), 13.4 (CH₃, C-8), 9.3 (CH₃, C-31) ppm; MS (ESI): m/z 428 (M⁺+H); HRMS: found (M⁺+H) 428.2068. C₂₄H₂₉NO₆ requires (M⁺+H) 428.2073.

Compound **219**: IR (film): ν_{\max} 3384 (br). 3030, 2934, 2871, 1653, 1618, 1454, 1368, 1269, 1081 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 12.16 (1H, s, H-30), 7.45 (1H, s, H-11), 7.23-7.37 (5H, m, H-21/22/23/24/25), 6.41 (1H, s (br), H-9), 4.75 (1H, dd, $J = 11.0, 2.8$ Hz, H-2), 4.54 (1H, d, $J = 11.9$ Hz, H-19), 4.30 (1H, s(br), H-6), 3.78 (3H, s, H-29), 3.67 (1H, t (br), $J = 7.6$ Hz, H-17), 3.59 (1H, ddd, $J = 9.4, 7.6, 4.3$ Hz, H-17), 2.44-2.48 (1H, m, H-5), 2.46 (3H, s, H-14), 2.04-2.13 (1H, m, H-16), 1.86-1.96 (1H, m, H-16), 1.91 (3H, s, H-8), 1.91 (3H, s, H-8), 1.02 (3H, d, $J = 7.0$ Hz, H-31) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 174.8 (C, C-4), 171.2 (C, C-26), 160.7 (C, C-13), 138.6 (C, C-20), 138.3 (C, C-10), 135.7 (CH, C-11) 135.4 (C, C-7), 128.3 (CH, C-21/22/23/24/25), 127.6 (CH, C-21/22/23/24/25), 127.5 (CH, C-21/22/23/24/25), 127.4 (CH, C-21/22/23/24/25) 114.1 (CH, C-9), 73.0 (CH_2 , C-19), 71.6 (CH, C-6), 68.8 (CH, C-2), 67.7 (CH_2 , C-17), 51.6 (CH_3 , C-26), 35.6 (CH, C-5), 32.6 (CH_2 , C-16), 16.0 (CH_3 , C-8), 13.9 (CH_3 , C-14), 12.3 (CH_3 , C-31) ppm; MS (ESI): m/z 428 ($\text{M}^+\text{+H}$); HRMS: found ($\text{M}^+\text{+H}$) 428.2068. $\text{C}_{24}\text{H}_{29}\text{NO}_6$ requires ($\text{M}^+\text{+H}$) 428.2073.

6-(2-Benzyloxy-ethyl)-3-methyl-2-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-Tetrahydro-pyran-4-ones (229) and (228)



A solution of a mixture of THP diastereoisomers (295 mg, 0.69 mmol) in DMF (5 mL) was heated in the microwave in the presence of H_2O (50 μL) under the following parameters: temp. 160 $^\circ\text{C}$, pressure 100 psi, power 250 W, ramp time 20 min, hold time 20 min. Actual parameters from observation of reaction progression: temp. 120 $^\circ\text{C}$, pressure 31 psi, power 250 W, a consequence of the cooling system present within

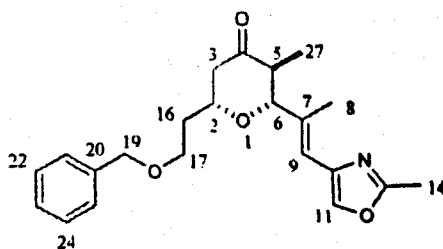
the microwave. After this time, the reaction mixture was diluted with EtOAc (40 mL) and washed with H₂O (4 x 20 mL) and brine (20 mL). The organics were then dried (MgSO₄) and concentrated to a dark brown oil (233 mg), which was purified by flash column chromatography (gradient 9:1 to 3:2 / petroleum ether : EtOAc) to yield **227** as a yellow oil (47 mg, 18%), a 1.0:3.5 diastereomeric mixture of **227:228** (44 mg, 17%) as a yellow oil, and a 1.0:1.3 diastereomeric mixture of **228:229** (72.6 mg, 28%) as a yellow oil.

Compound **229**: IR (film): ν_{\max} 2949, 2934, 2857, 1716, 1586, 1454, 1365, 1313, 1106 cm⁻¹; ¹H NMR (CDCl₃, 400MHz): δ 7.48 (1H, s, H-11) 7.23-7.37 (5H, m, H-21/22/23/24/25), 6.16 (1H, s(br), H-9), 4.44-4.54 (1H, m, H-2) 4.50 (1H, d, J = 11.9 Hz, H-19), 4.46 (1H, d, J = 11.9 Hz, H-19), 4.02 (1H, d, J = 8.8 Hz, H-6), 3.49-3.61 (2H, m, H-17), 2.71 (1H, dq⁵⁷, J = 8.8, 6.8 Hz, H-5), 2.70 (1H, dd⁵⁷, J = 14.5, 5.7 Hz, H-3), 2.45 (3H, s, H-14), 2.37 (1H, dd, J = 14.5, 4.8 Hz, H-3), 2.00 (3H, d, J = 1.1 Hz, H-8), 1.93 (1H, dddd, J = 14.4, 9.5, 5.5, 5.5 Hz, H-16), 1.76 (1H, dddd, J = 14.4, 8.4, 6.2, 4.9 Hz, H-16), 0.98 (3H, d, J = 6.8 Hz, H-27) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 209.2 (C, C-4), 160.8 (C, C-13), 138.2 (C, C-20), 137.4 (C, C-10), 136.8 (C, C-7), 136.1 (C, C-11), 128.3 (CH, C-21/25), 127.6 (CH, C-22/24), 127.6 (CH, C-23), 119.1 (CH, C-9), 83.2 (CH, C-6), 73.0 (CH₂, C-19), 70.7 (CH, C-2), 66.2 (CH₂, C-17), 46.9 (CH, C-5), 45.7 (CH₂, C-3), 33.3 (CH₂, C-16), 14.1 (CH₃, C-8), 13.8 (CH₃, C-14), 11.2 (CH₃, C-27) ppm; MS (ESI): m/z 370 (M⁺+H) HRMS: found (M⁺+H) 370.2013. C₂₂H₂₈NO₄ requires (M⁺+H) 370.2018.

Compound **228**: IR (film): ν_{\max} 2927, 2856, 1717, 1685, 1438, 1378, 1119 cm⁻¹; ¹H NMR (CDCl₃, 400MHz): δ 7.47 (1H, s, H-11), 7.23-7.47 (5H, m, H-21/22/23/24/25), 6.45 (1H, s(br), H-9), 4.51 (1H, d, J = 12.0 Hz, H-19), 4.48 (1H, d, J = 12.0 Hz, H-19), 4.10 (1H, s(br), H-6), 3.85 (1H, dddd, J = 11.8, 7.2, 3.6, 2.8, H-2), 3.61-3.79 (2H,

m, H-17), 2.61 (1H, dq, $J = 6.5, 2.2$ Hz, H-5), 2.52 (1H, dd, $J = 14.5, 11.8$ Hz, H-3ax), 2.46 (3H, s, H-14), 2.28 (1H, d(br), $J = 14.5$ Hz, H-3eq), 1.86-2.12 (2H, m, H-16), 1.85 (3H, s, H-9), 0.98 (3H, d, $J = 6.5$ Hz, H-27) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 221.3 (C, C-4), 160.8 (C, C-13), 138.3 (C, C-20), 138.1 (C-10), 135.3 (CH, C-11), 135.0 (C, C-7), 128.4 (CH, C-22/24), 127.6 (CH, C21/25), 127.6 (CH, C-23), 115.1 (CH, C-9), 81.3 (CH, C-6), 74.0 (CH, C-2), 73.1 (CH_2 , C-19), 66.3 (CH, C-17), 47.5 (CH, C-5), 44.0 (CH_2 , C-3), 36.5 (CH_2 , C-16), 15.8 (CH_3 , C-8), 13.8 (CH_3 , C-14), 11.2 (CH_3 , C-27) ppm; MS (ESI): m/z 370 ($\text{M}^+\text{+H}$) HRMS: found ($\text{M}^+\text{+H}$) 370.2014. $\text{C}_{22}\text{H}_{28}\text{NO}_4$ requires ($\text{M}^+\text{+H}$) 370.2018.

6-(2-Benzyloxy-ethyl)-3-methyl-2-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-tetrahydro-pyran-4-one (227)



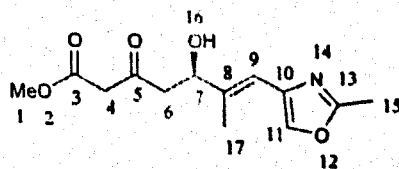
A 1.67 M solution of *n*-butyllithium in hexanes (74 μl , 0.13 mmol) was added to a solution of diisopropylamine (18 μl , 0.13 mmol) in THF (1 mL) at 0 °C, under an atmosphere of N_2 . To this freshly prepared solution of LDA was added a 2:1:1 diastereomeric mixture of 227, 228 and 229 respectively. The reaction mixture was then allowed to warm to room temperature and stirred under N_2 for 17 hours. After this time, the reaction mixture was quenched with 10 M solution of AcOH in THF (500 μl). The resultant mixture was then extracted with EtOAc (40 mL), and the organic phase was washed successively with H_2O (2 x 20 mL) and brine (20 mL). The combined organics were then dried (MgSO_4) and concentrated *in vacuo* to a yellow

oil (31.1 mg, 64%), which was seen to comprise a 0.33:0.27:1 diastereoisomeric mixture of **227**, **228** and **229**.

Compound **229**: IR (film): ν_{\max} 3016, 2925, 2858, 1716, 1455, 1366, 1217, 1106 cm^{-1}
 ^1H NMR (CDCl_3 , 400MHz): δ 7.52 (1H, s, H-11), 7.23-7.37 (5H, m, H-21/22/23/24/25), 6.20 (1H, s(br), H-9), 4.51 (1H, d, $J = 11.2$ Hz, H-19), 4.48 (1H, d, $J = 11.2$ Hz, H-19), 3.85 (1H, dddd, $J = 11.8, 7.2, 3.6, 2.8$, H-2), 3.71 (1H, d, $J = 10.5$ Hz, H-6), 3.52-3.63 (2H, m, H-17), 2.50 (1H, dq, $J = 10.5, 6.8$ Hz, H-5), 2.46 (3H, s, H-14), 2.43 (1H, dd, $J = 14.7, 2.8$ Hz, H-3eq), 2.40 (1H, ddd, $J = 14.7, 10.4, 0.9$ Hz, H-3ax), 1.80-2.02 (2H, m, H-16), 1.99 (3H, d, $J = 1.1$ Hz, H-9), 0.89 (3H, d, $J = 6.8$ Hz, H-27); ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.7 (C, C-4), 162.4 (C, C-13), 138.4 (C, C-20), 137.7 (C-10), 136.7 (C, C-7), 136.1 (CH, C-11), 128.5 (CH, C-22/24), 127.8 (CH, C21/25), 127.7 (CH, C-23), 119.3 (CH, C-9), 89.3 (CH, C-6), 74.7 (CH, C-2), 73.2 (CH_2 , C-19), 66.3 (CH, C-17), 48.3 (CH_2 , C-3), 48.1 (CH, C-5), 36.6 (CH_2 , C-16), 14.0 (CH_3 , C-8), 13.8 (CH_3 , C-14), 9.5 (CH_3 , C-27) ppm. MS (ESI): m/z 370 ($\text{M}^+\text{+H}$) HRMS: found ($\text{M}^+\text{+H}$) 370.2010. $\text{C}_{22}\text{H}_{28}\text{NO}_4$ requires ($\text{M}^+\text{+H}$) 370.2018.

Catalytic Enantioselective Aldol Series

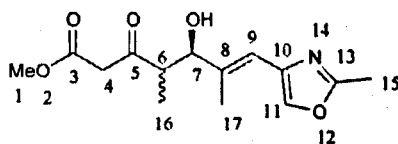
(*R*)-Methyl-5-hydroxy-6-methyl-7-(2'-methyl-oxazol-4'-yl)-3-oxo-hept-6-enoate
(**258**)⁹¹



Molecular sieves (4 Å, 150 mg) were heated under to 140 °C at 0.2 mbar for 12 hours using Kugelrohr apparatus, and then cooled to room temperature under a stream of

N₂. A solution of (*R*)-1,1'-bi-2-naphthol (0.12g, 0.40 mmol) and titanium isopropoxide (0.12 mL, 0.40 mmol) in THF (5 mL) was stirred at room temperature for 10 minutes. A portion of this solution (440 μ l) was added to the cooled sieves and the reaction mixture was stirred for 1 hour. The reaction mixture was then cooled to -78 $^{\circ}$ C, diluted with THF (1 mL) and a solution of diene **139** (229 mg, 0.88mmol) in THF (1 mL) was added. After 2 hours of stirring, a solution of aldehyde **29** (66 mg, 0.44 mmol) in THF (1 mL) was added at -78 $^{\circ}$ C and the reaction mixture was stirred at -78 $^{\circ}$ C for 2 hours before being warmed to room temperature and stirred for 14 hours. After this time, the reaction mixture was cooled to -78 $^{\circ}$ C and trifluoroacetic acid (246 μ l, 3.20 mmol) was added. After 30 minutes stirring, the reaction mixture was warmed to room temperature and a saturated aqueous solution of NaHCO₃ (1.5 mL) was added over a period of 30 minutes. After this time, the reaction mixture was diluted with EtOAc (10 mL) and an excess of MgSO₄ was added. The mixture was then filtered through a thin pad of Celite[®] with the aid of EtOAc. The filtrate was washed with brine (2 x 20 mL), dried (MgSO₄), and concentrated *in vacuo* to yield a dark brown residue (224 mg). Flash column chromatography (2:3 / petroleum ether : EtOAc) yielded **258** as a yellow oil (22.5 mg, 19%). ¹H NMR (CDCl₃, 400 MHz): δ 7.47 (1 H, s, H-11), 6.34 (1 H, d, J = 0.9 Hz, H-9), 4.63 (1 H, app. dt, J = 8.7, 3.4 Hz, H-7), 3.74 (3 H, s, H-1), 3.54 (2 H, s, H-4), 3.24 (1 H, d, J = 3.4 Hz, H-16), 2.83 (1 H, dd, J = 16.8, 8.7 Hz, H-6), 2.77 (1 H, dd, J = 16.8, 3.4 Hz, H-6), 2.44 (3 H, s, H-15), 1.93 (3 H, d, J = 0.9 Hz, H-17) ppm. ¹H NMR consistent with **171**. The enantiomeric excess was determined to be 68% by HPLC using a chiral column (CHIRACEL OD-H, hexanes / ¹PrOH = 75:25, flow rate = 0.25 ml/min): t_R(minor) = 97.1 min, t_R(major) = 111.8 min. IR (film)

(*R,E*)-methyl 5-hydroxy-4,6-dimethyl-7-(2-methyl-oxazol-4-yl)-3-oxo-hept-6-enoate (259)



Soriente reaction.⁹¹

Molecular sieves (4 Å, 113 mg) were heated under a stream of N₂ at 140 °C for 16 hours and then cooled to room temperature. A solution of (*R*)-1,1'-bi-2-naphthol (0.12g, 0.40 mmol) and titanium isopropoxide (0.12 mL, 0.40 mmol) in THF (5 mL) was stirred at room temperature for 10 minutes. A portion of this solution (0.33 mL) was added to the cooled sieves and the reaction mixture was stirred for 1 hour. The reaction mixture was then cooled to -78 °C, diluted with THF (1.32 mL) and diene **159** (181 mg, 0.66 mmol) was added. After stirring for 1 hour at -78°C, a solution of aldehyde **29** (66 mg, 0.44 mmol) in THF (0.6 mL) was added at -78 °C and the reaction mixture was stirred at -78 °C for 2 hours before being warmed to room temperature and stirred for 14.5 hours. After this time, the reaction mixture was cooled to -78 °C and trifluoroacetic acid (185 µl, 3.20 mmol) was added. After 30 minutes stirring, the reaction mixture was warmed to room temperature and a saturated aqueous solution of NaHCO₃ (1 mL) was added over a period of 30 minutes. After this time, the reaction mixture was diluted with EtOAc (20 mL) and an excess of MgSO₄ was added. The mixture was then filtered through a thin pad of Celite[®] with the aid of EtOAc. The filtrate was washed with brine (2 x 20 mL), dried (MgSO₄), and concentrated *in vacuo* to yield a dark orange oil (163 mg). Flash column chromatography (1:1 / petroleum ether : EtOAc) yielded **259** as a yellow oil in a mixture of 97:3 *syn:anti* diastereomers (13.8 mg, 15%). ¹H NMR (*syn*) (CDCl₃, 400 MHz): δ 7.46 (1 H, s, H-11), 6.38 (1 H, s (br), H-9), 4.58 (1 H, d (br), J = 3.7 Hz,

H-7), 3.73 (3 H, s, H-1), 3.60 (2 H, s, H-4), 2.91 (1 H, dq, $J = 7.3, 3.7$ Hz, H-6), 2.43 (3 H, s, H-15), 1.90 (3 H, s (br), H-17), 1.10 (3 H, d, $J = 7.3$ Hz, H-16) ppm. ^1H NMR consistent with **202**. The enantiomeric excess was determined to be 81% (*syn*) by HPLC using a chiral column (CHIRACEL OD-H, hexanes / $^i\text{PrOH} = 75:25$, flow rate = 0.25 ml/min): $t_{\text{R}}(\text{minor } anti) = 38.7$ min, $t_{\text{R}}(\text{minor } syn) = 51.7$ min, $t_{\text{R}}(\text{major } anti) = 67.1$ min, $t_{\text{R}}(\text{major } syn) = 85.1$ min.

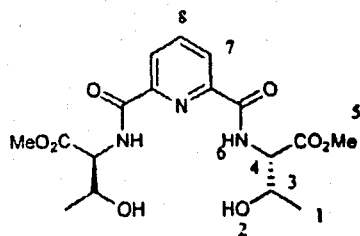
Evans aldol reaction:⁹⁶

Copper (II) chloride (13 mg, 0.10 mmol) and *bis*-(4,5-dihydro-4-phenyl-2-oxazolyl) pyridine (37 mg, 0.10 mmol) were weighed into a foil-covered round-bottom flask (5 mL) in a N_2 glove box environment. The flask was then charged with CH_2Cl_2 (2 mL) at room temperature and stirred for 1 hour, after which time a green colouration was observed. Silver (I) antimonite (66 mg, 0.20 mmol) was weighed into a separate 5 mL round-bottom flask in a N_2 glove box environment. This second flask was then charged with CH_2Cl_2 (1.8 mL) at room temperature and the resultant solution was added to the green Cu-PyBox solution at room temperature. After 2 hours of stirring, the reaction mixture was filtered through a pre-dried cotton wool-packed pipette to yield a clear blue solution of **253**.

Diene **159** (0.2 mL, 0.66 mmol) was added to a solution of aldehyde **29** (50 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) at -78 °C, under an atmosphere of N_2 . After 15 minutes of stirring, the 0.13 M solution of **159** in CH_2Cl_2 (0.1 mL, 0.013 mmol) was added at -78 °C, under an atmosphere of N_2 . The reaction mixture was stirred at -78 °C for 1 hour, after which time the reaction was warmed to room temperature and stirred for a further 10 hours. The reaction mixture was then filtered through a small plug of silica with the aid of Et_2O (100 mL). The filtrate was concentrated to a yellow oil, which was then dissolved in THF (50 mL) and 1 N HCl (5 mL) was added to the resultant

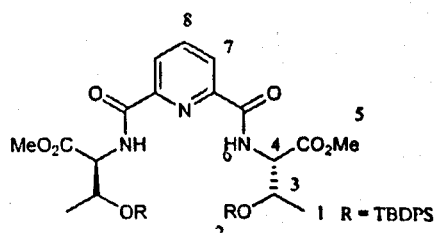
solution. After 15 minutes standing at room temperature, the reaction mixture was diluted with Et₂O (50 mL), the aqueous layer discarded, and the combined organics washed successively with a saturated aqueous solution of NaHCO₃ (25 mL) and brine (25 mL), dried (MgSO₄) and concentrated to a yellow oil (221 mg), which was purified by flash column chromatography (1:1 / petroleum ether : EtOAc) to yield **259** in a 8.3:1.0 mixture of *syn:anti* diastereoisomers as a yellow film (29 mg, 31%). The ¹H NMR spectrum was found to be consistent with that of **202**. The enantiomeric excess was determined to be 2% by HPLC using a chiral column (CHIRACEL OD-II, hexanes / ¹PrOH = 75:25, flow rate = 0.25 ml/min): t_R(minor *anti*) = 38.9 min, t_R(minor *syn*) = 52.1 min, t_R(major *anti*) = 67.9 min, t_R(major *syn*) = 88.2 min.

2,6-O-bis[(1'-*S*)-Carbomethoxy-2'-(*R*)-hydroxy]propyl carbamoyl] pyridine (262)⁹⁹



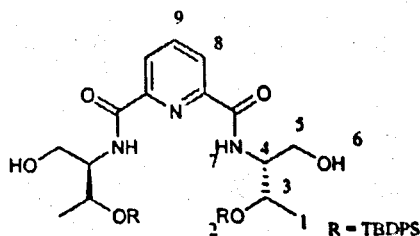
This compound was synthesised as a yellow oil (1.13 g, 96%) in accordance with a literature procedure. The ¹H NMR data were found to be in agreement with that reported.⁹⁹ ¹H NMR (270 MHz, CDCl₃): δ 8.76 (2 H, d, J = 9.1 Hz, H-6), 8.31 (2 H, d, J = 7.7 Hz, H-7), 8.01 (1 H, d, J = 7.7 Hz, H-8), 4.76 (2 H, dd, J = 9.1, 2.5 Hz, H-4), 4.50 (2 H, ddq, J = 6.4, 6.2, 2.5 Hz, H-3), 3.80 (6 H, s, H-5), 3.17 (2 H, s (br), H-2), 1.31 (6 H, d, J = 6.4 Hz, H-1) ppm.

***O*-bis-*tert*-butyldiphenylsilyl-2,6-bis[(1'-*S*)-carbomethoxy-2'-(*R*)-hydroxy)propyl carbamoyl]pyridine (263)⁹⁹**



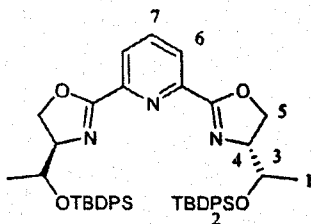
This compound was synthesised as a colourless oil (0.37 g, 75%) in accordance with a literature procedure. The ¹H NMR data was found to be in agreement with that reported.⁹⁹ ¹H NMR (270 MHz, CDCl₃): δ 8.42 (2 H, d, J = 8.2 Hz, H-6), 8.35 (2 H, d, J = 7.6 Hz, H-7), 8.06 (1 H, dd, J = 8.4, 7.6 Hz, H-8), 7.61-7.68 (8 H, m, H_{AR}), 7.31-7.37 (12 H, m, H_{AR}), 4.86 (2 H, dd, J = 8.2, 3.4 Hz, H-4), 4.49-4.51 (2 H, m, H-3), 3.63 (6 H, s, H-5), 1.06 (6 H, d, J = 6.1 Hz, H-1), 1.03 (18, s, 6 x Me(TPS)) ppm.

***O*-bis-*tert*-butyldiphenylsilyl-*N*2,*N*6-bis((2*R*,3*R*)-1,3-dihydroxybutan-2-yl)pyridine-2,6-dicarboxamide (264)⁹⁹**



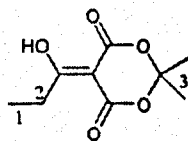
This compound was synthesised as a white solid (0.21 g, 54%) in accordance with a literature procedure. The ¹H NMR data was found to be in agreement with that reported.⁹⁹ ¹H NMR (270 MHz, CDCl₃): δ 8.36 (2 H, d, J = 7.8 Hz, H-7), 8.11 (2 H, dd, J = 8.1, 7.8 Hz, H-8), 8.02 (1 H, d, J = 8.5 Hz, H-9), 7.51-7.71 (8 H, m, H_{AR}), 7.29-7.41 (12 H, m, H_{AR}), 4.17-4.32 (2 H, m, H-3), 4.00-4.15 (2 H, m, H-4), 3.78-3.84 (4 H, m, H-5), 2.41 (2 H, s (br), H-6), 1.08 (6 H, d, J = 6.1 Hz, H-1), 1.04 (18 H, s, 6 x Me(TPS)) ppm.

***O*-bis-*tert*-Butyldiphenylsilyl-hydroxyethyl-pybox (TPS-he-pybox) (265)⁹⁹**



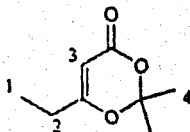
This compound was synthesised as a yellow oil (0.24 g, 74%) in accordance with a literature procedure. The ¹H NMR data was found to be in agreement with that reported.⁹⁹ ¹H NMR (270 MHz, CDCl₃): δ 8.10 (2 H, d, J = 7.8 Hz, H-6), 7.80 (1 H, dd, J = 7.8, 8.1 Hz, H-7), 7.51-7.71 (8 H, m, H_{AR}), 7.52-7.57 (4 H, m, H_{AR}), 7.27-7.43 (8 H, m, H_{AR}), 4.55-4.61 (2 H, m, H-4), 4.46-4.52 (4 H, m, H-5), 4.19-2.27 (2 H, m, H-3), 1.05 (18 H, s, 6 x Me(TPS)), 1.02 (6 H, d, J = 6.3 Hz, H-1) ppm.

5-(1-Hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (266)¹⁰⁰



This compound was synthesised as a brown solid (13.10 g, 95%) in accordance with a literature procedure. The ¹H NMR data was found to be in agreement with that reported.¹⁰⁰ ¹H NMR (270 MHz, CDCl₃): δ 3.11 (2 H, q, J = 7.3 Hz, H-2), 1.73 (6 H, s, H-3), 1.26 (3 H, t, J = 7.6 Hz, H-1) ppm.

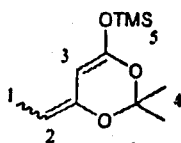
6-Ethyl-2,2'-dimethyldioxinone (267)¹⁰⁰



This compound was synthesised as a yellow oil (6.10 g, 62%) in accordance with a literature procedure. The ¹H NMR data was found to be in agreement with that

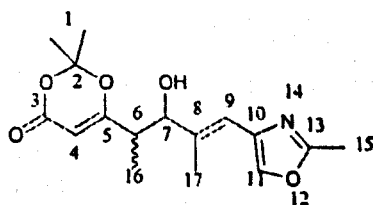
reported.¹⁰⁰ Bp 64-68 °C at 0.07 mbar. ¹H NMR (270 MHz, CDCl₃): δ 5.23 (1 H, s, H-3), 2.24 (2 H, q, J = 7.6 Hz, H-2), 1.68 (6 H, s, H-4), 1.12 (3 H, t, J = 7.6 Hz, H-1) ppm.

6-Ethylidenedioxine (245)¹⁰⁰



This compound was synthesised as a yellow oil (1.48 g, 51%) in accordance with a literature procedure. The product existed as a 5:3 mixture of inseparable *Z* and *E* geometrical isomers. The ¹H NMR data were found to be in agreement with that reported.¹⁰⁰ Bp 53-57 °C at 0.07 mbar. ¹H NMR (270 MHz, CDCl₃): δ 4.75 (1 H, s, H-3, *E* isomer), 4.58 (1 H, q, J = 7.1 Hz, H-2, *Z* isomer), 4.54 (1 H, s, H-3, *E* isomer), 4.30 (1 H, q, J = 7.1 Hz, H-2, *E* isomer), 1.61 (3 H, d, J = 7.1 Hz, H-1, *E* isomer), 1.56 (3 H, d, J = 7.1 Hz, H-1, *Z* isomer), 1.54 (6 H, s, H-4, *E* isomer), 1.50 (6 H, s, H-4, *Z* isomer), 0.27 (18 H, s, H-5, *E* and *Z* isomers) ppm.

6-(3-Hydroxy-4-methyl-5-(2-methyl-oxazol-4-yl)pent-4-en-2-yl)-2,2-dimethyl-1,3-dioxin-4-one (268)



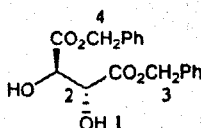
Keck protocol:¹⁰¹

Molecular sieves (4 Å, 300 mg) were heated at 140 °C under a stream of N₂ for 15 hours and then cooled to room temperature. A solution of (*R*)-1,1'-bi-2-naphthol (0.14 g, 0.50 mmol) and titanium isopropoxide (0.14 mL, 0.50 mmol) in THF (5 mL) was stirred at room temperature for 10 minutes. A portion of this solution (0.66 mL) was

added to the cooled sieves and the reaction mixture was stirred for 1 hour. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and both aldehyde **29** (0.05 g, 0.33 mmol) in THF (1.0 mL) and diene **245** (0.09 g, 0.39 mmol) were added simultaneously over a 10 minute period. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour, warmed to room temperature and stirred for 18 hours. The mixture was poured into saturated aqueous NaHCO_3 solution (2 mL), stirred for 30 minutes and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine (10 mL), dried (MgSO_4) and concentrated *in vacuo* to an orange oil (143 mg). Flash column chromatography (1:1 to 1:2 / petroleum ether : EtOAc) yielded as a yellow oil (16 mg, 17%) comprising 1:2 *dl:d2* diastereoisomers. IR (film): ν_{max} 3419, 2998, 1718, 1629, 1276 cm^{-1} . ^1H NMR (270 MHz, CDCl_3): δ 7.50 (1 H, s, H-11, *dl*), 7.47 (1 H, s, H-11, *d2*), 6.31 (1 H, s, H-9, *d2*), 6.26 (1 H, s, H-9, *dl*), 5.36 (1 H, s, H-4, *dl*), 5.30 (1 H, s, H-4, *d2*), 4.30 (1 H, d, $J = 6.0\text{ Hz}$, H-7, *d2*), 4.11 (1 H, d, $J = 9.3\text{ Hz}$, H-7, *dl*), 2.58 (1 H, qd, $J = 5.9, 7.1\text{ Hz}$, H-6, *d2*), 2.55 (1 H, dq, $J = 9.3, 7.1\text{ Hz}$, H-6, *dl*), 2.45 (3 H, s, H-15, *dl*), 2.44 (3 H, s, H-15, *d2*), 1.93 (3 H, s, H-17, *dl*), 1.90 (3 H, s, H-17, *d2*), 1.70 (6 H, app. s, H-1, *dl*) 1.65 (3 H, m, H-1, *d2*), 1.63 (3 H, m, H-1, *d2*), 1.18 (3 H, d, $J = 7.1\text{ Hz}$, H-16, *d2*), 1.01 (3 H, d, $J = 7.1\text{ Hz}$, H-16, *dl*) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 173.2 + 173.1 (C, C-5, *dl* + *d2*), 161.4 + 161.4 (C, C-3/13, *dl* + *d2*), 160.9 + 160.9 (C, C-3/13, *dl* + *d2*), 139.1 + 139.1 (C, C-8/10, *dl* + *d2*), 137.5 + 137.5 (C, C-8/10, *dl* + *d2*), 135.8 (CH, C-11, *dl*), 135.6 (CH, C-11, *d2*), 118.5 (CH, C-9, *dl*), 116.9 (CH, C-9, *d2*), 106.5 (C, C-2, *dl*), 106.4 (C, C-2, *d2*), 94.2 (CH, C-4, *dl*), 93.4 (CH, C-4, *d2*), 79.2 (CH, C-7, *dl*), 79.1 (CH, C-7, *d2*), 42.4 (CH, C-6, *dl*), 41.7 (CH, C-6, *d2*), 25.3 (CH_3 , C-1, *d2*), 24.7 (CH_3 , C-1, *dl*), 16.5+16.5 (CH_3 , C-17, *dl* + *d2*), 14.9 (CH_3 , C-15, *d2*), 14.7 (CH_3 , C-15, *dl*), 13.7 (CH_3 , C-16, *dl*), 11.8 (CH_3 , C-16, *d2*) ppm; MS (ESI): m/z 308 ($\text{M}^+ + \text{H}$), 250

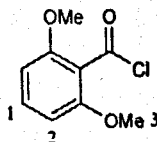
($M^+ + H - C_3H_6O$); HRMS: found: ($M^+ + H$) 308.1492. $C_{16}H_{22}NO_5$ requires ($M^+ + H$) 308.1498. The enantiomeric excesses for the diastereoisomers were determined to be 93% (*d2*) and 64% (*d1*) by HPLC using a chiral column (CHIRACEL OD-H, hexanes / i -PrOH = 75:25, flow rate = 0.25 ml/min): t_R (minor *d2*) = 37.1 min, t_R (minor *d1*) = 48.8 min, t_R (major *d2*) = 68.8 min, t_R (major *d1*) = 82.6 min.

Dibenzyl tartrate (272)¹⁰⁴



This compound was synthesised as a white solid (1.39 g, 63%) in accordance with a literature procedure. The 1H NMR data were found to be in agreement with those reported.¹⁰⁴ 1H NMR (270 MHz, $CDCl_3$): δ 7.38-7.40 (10 H, m, H-Ar), 5.28 (2 H, J = 12 Hz, H-4), 5.24 (2 H, J = 12 Hz, H-3), 4.61 (2 H, d, J = 7.3 Hz, H-2), 3.19 (2 H, d, J = 7.32 Hz, H-1) ppm.

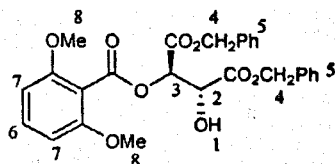
2,6-Dimethoxybenzoyl chloride (271)¹⁰⁴



Oxalyl chloride (2.9 mL, 32.94 mmol) was added over a 3 minute period to a solution of 2,6-dimethoxybenzoic acid (2.00 g, 10.98 mmol) in CH_2Cl_2 (60 mL) at room temperature, under an atmosphere of N_2 . DMF (50 μ L) was added to the solution. The reaction mixture was stirred for 3 hours at room temperature and progress was monitored by 1H NMR. The mixture was concentrated *in vacuo* to an orange solid. The solid was purified by Kugelrohr distillation to give 271 as a white solid (2.18 g, 98 %). Bp 162 $^\circ C$ at 0.07 mbar. The 1H NMR data were found to be in accordance

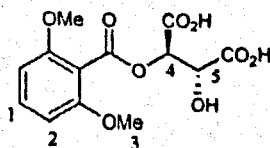
with the literature.¹⁰⁴ ¹H NMR (270 MHz, CDCl₃): δ 7.41 (1 H, t, J = 8.5 Hz, H-1), 6.54 (2 H, d, J = 8.5 Hz, H-2), 3.73 (6 H, s, H-3) ppm.

Benzyl (2*R*,3*R*)-3-Hydroxy-2-[(2,6-dimethoxybenzoyl)-oxy]butane-dioate (274)¹⁰⁴



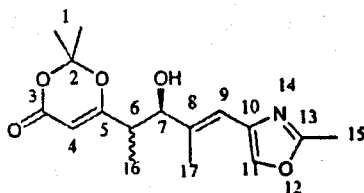
Triethylamine (0.88 mL, 6.37 mmol) and DMAP (97 mg, 0.79 mmol) were added to a solution of dibenzyl tartrate **273** (1.34 g, 4.06 mmol) in CH₂Cl₂ (22 mL) at room temperature, under an atmosphere of N₂. The reaction mixture was cooled to 0 °C and 2,6-dimethoxybenzoyl chloride **271** (796 mg, 3.98 mmol) was added to the solution. The reaction mixture was then warmed to room temperature and heated to reflux for 24 hours. The mixture was allowed to cool to room temperature and poured onto 5 mL of water. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organics were dried (MgSO₄) and concentrated to a white solid. Flash column chromatography (3:1:5 / hexanes : Et₂O : CH₂Cl₂) to give **274** as a white solid (1.49 g, 76%). The ¹H NMR data were found to be in agreement with that reported.¹⁰⁴ ¹H NMR (270 MHz, CDCl₃): δ 7.34-7.40 (11 H, m, H-5/H-8), 6.53 (1 H, d, J = 8.5 Hz, H-6), 5.99 (1 H, d, J = 1.8 Hz, H-3), 5.30 (4H, m, H-4), 4.88 (1 H, dd, J = 1.8, 8.5 Hz, H-2), 3.72 (6 H, s, H-8), 3.19 (1 H, d, J = 8.5 Hz, H-1) ppm.

(2*R*,3*R*)-3-Hydroxy-2-[(2,6-dimethoxybenzoyl)-oxy]butanedioic acid (275)¹⁰⁴



This compound was synthesised as a white solid (842 mg, 98%) in accordance with a literature procedure. The ^1H NMR data were found to be in agreement with that reported.¹⁰⁴ ^1H NMR (270 MHz, CDCl_3): δ 7.33 (1 H, t, $J = 7.3$ Hz, H-1), 6.64 (2 H, d, $J = 7.3$ Hz, H-2), 5.66 (1 H, d, $J = 2.1$ Hz, H-5), 4.74 (1 H, d, $J = 2.1$ Hz, H-4), 3.78 (6 H, s, H-3) ppm.

6-(3-Hydroxy-4-methyl-5-(2-methyl-oxazol-4-yl)pent-4-en-2-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one (268)



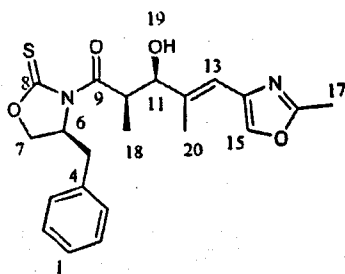
Prepared using the CAB catalyst system:

A 1.0 M solution of borane-tetrahydrofuran complex in THF (1.65 μL , 0.16 mmol) was added to a stirred suspension of monoacylated tartaric acid **xx** (52 mg, 0.16 mmol) in CH_2Cl_2 (3.3 mL) at 0 $^\circ\text{C}$ under an atmosphere of N_2 . The reaction mixture was stirred for 1 hour at 0 $^\circ\text{C}$, during which period the evolution of gas was observed, before being cooled to -78°C . Aldehyde **29** (0.05 g, 0.33 mmol) was added to the reaction mixture at -78°C . After 20 minutes of stirring at -78°C , diene **245** (0.15 g, 0.66 mmol) was added over a 3 minute period. Stirring continued for 3 hours at -78°C , after which time the reaction was quenched with 1M HCl (2 mL), and the reaction warmed to room temperature. After vigorous stirring for 1 hour at room temperature, the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried (MgSO_4) and concentrated *in vacuo* to an orange oil (199 mg). Flash column chromatography (1:1 to 1:2 / petroleum ether : EtOAc) yielded **268** as a yellow oil (28 mg, 28%) which comprised of a 1:1.5 mixture of *syn:anti* diastereoisomers. IR (film):

ν_{\max} 3419, 2998, 1718, 1629, 1276 cm^{-1} . The ^1H NMR data was found to be consistent with its previous synthesis. The enantiomeric excesses for the diastereoisomers were determined to be 85% (*anti*) and 52% (*syn*) by HPLC using a chiral column (CHIRACEL OD-H, hexanes / $^i\text{PrOH}$ = 75:25, flow rate = 0.25 ml/min): t_{R} (minor *anti*) = 36.7 min, t_{R} (minor *syn*) = 47.2 min, t_{R} (major *anti*) = 68.6 min, t_{R} (major *syn*) = 80.1 min.

Auxiliary Approach to Asymmetric Aldol

(*E,2R,3R*)-1-((*S*)-4-Benzyl-2-thioxooxazolidin-3-yl)-3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-en-1-one (284)

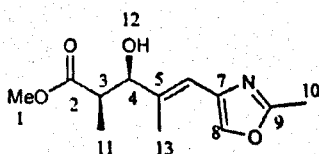


Titanium tetrachloride (5.47 mL, 50 mmol) was added over a period of 2 minutes to a solution of 1-((*S*)-4-benzyl-2-thioxooxazolidin-3-yl)propan-1-one (283) (6.21 g, 24.9 mmol) in CH_2Cl_2 (100 ml) at 0 $^\circ\text{C}$, under an atmosphere of N_2 . After 10 minutes, (-)-sparteine (6.28 mL, 27.4 mmol) was added at 0 $^\circ\text{C}$ and once the solid mass had completely dissolved, the reaction was stirred at this temperature for a further 20 minutes. After this time, the reaction was cooled to -78 $^\circ\text{C}$, and a solution of aldehyde 29 (4.14 g, 27.4 mmol) in CH_2Cl_2 (10 mL) was added over 5 minutes. Further CH_2Cl_2 (20 mL) was required to ensure the complete dissolution of the observed red solid. After stirring for 4 hours at -78 $^\circ\text{C}$, the reaction was warmed to 0 $^\circ\text{C}$ and quenched with a half-saturated aqueous solution of NH_4Cl (100 mL). The phases were separated, and the organics were dried (MgSO_4) and concentrated *in vacuo* to a thick

orange residue, which was purified by flash column chromatography (5:1 / petroleum ether : EtOAc) to yield **284** as a thick yellow residue (9.92 g, 99%).

$[\alpha]_D^{24} +58.7$ ($c = 0.175$, CHCl_3); IR (film): ν_{max} 3338, 3021, 2979, 2931, 1700, 1583, 1453, 1369, 1194 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.49 (1H, s, H-15), 7.18 – 7.37 (5H, m, Ar), 6.47 (1H, app. d, $J = 0.7$ Hz, H-13), 5.13 (1H, dq, $J = 7.0, 3.6$ Hz, H-18), 4.97 (1H, app. dddd, $J = 10.7, 7.1, 3.5, 3.5$ Hz, H-6), 4.69 (1H, app. s(br), H-11), 4.27 – 4.36 (2H, m, H-7), 3.30 (1H, dd, $J = 13.5, 3.5$ Hz, H-5), 2.91 (1H, d, $J = 3.0$ Hz, H-19), 2.72 (1H, dd, $J = 13.5, 10.7$ Hz, H-5), 2.44 (3H, s, H-17), 2.02 (3H, app. s, H-20), 1.17 (3H, d, $J = 7.0$ Hz, H-18) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 185.1 (C, C-8/9), 177.9 (C, C-8/9), 160.7 (C, C-16), 138.0 (C, C-4/12/14), 135.6 (CH, C-15), 135.1 (C, C-4/12/14), 129.3 (CH, Ar), 129.0 (CH, Ar), 127.4 (CH, Ar), 115.6 (CH, C-13), 75.0 (CH, C-11), 70.3 (CH_2 , C-7), 60.0 (CH, C-6), 40.4 (CH, C-10), 37.7 (CH_2 , H-5), 16.0 (CH_3 , C-20), 13.8 (CH_3 , C-17), 10.5 (CH_3 , C-18) ppm; MS (ESI): m/z 401 ($\text{M}^+ + \text{H}$), 383 ($\text{M}^+ - \text{OH}$); HRMS: found: ($\text{M}^+ + \text{H}$) 401.1538 $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$ requires ($\text{M}^+ + \text{H}$) 401.1530.

(*E,2R,3R*)-Methyl 3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-enoate (287)

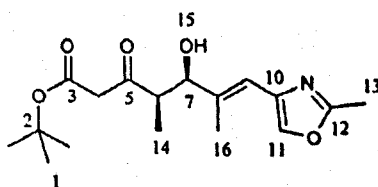


A 1.0 M solution of sodium methoxide in methanol (90 μl , 0.09 mmol) was added to a solution of (*E,2R,3R*)-1-((*S*)-4-benzyl-2-thioxooxazolidin-3-yl)-3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-en-1-one (**284**) (12.1 mg, 0.03 mmol) in methanol (1 mL) at 0 $^{\circ}\text{C}$, under an atmosphere of N_2 . The reaction was allowed to warm to room temperature and stirring continued for 22 hours. After this time, the

reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL) and the methanol was evaporated *in vacuo*. The remaining aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organics were concentrated *in vacuo* to a dark orange residue, which was purified by flash column chromatography (4:1 to 1:2 / petroleum ether : EtOAc) to 287 as a yellow oil (5.7 mg, 79%).

$[\alpha]_D^{24} +21.5$ ($c = 4.37$, CHCl_3); IR (film): ν_{max} 3389, 2982, 2950, 1730, 1585, 1454, 1107 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.45 (1H, s, H-8), 6.37 (1H, app d, $J = 0.8$ Hz, H-6), 4.48 (1H, app d, $J = 4.5$ Hz, H-4), 3.68 (3H, s, H-1), 2.75 (1H, qd, $J = 7.3$, 4.5 Hz, H-3), 2.43 (3H, s, H-10), 1.89 (3H, d, $J = 0.8$ Hz, H-13), 1.14 (3H, d, $J = 7.3$ Hz, H-11) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 175.9 (C, C-2), 160.7 (C, C-9), 138.5 (C, C-7/9), 137.9 (C, C-7/9), 135.5 (CH, C-8), 115.5 (CH, C-6), 76.1 (CH, C-4), 51.9 (CH_3 , C-1), 42.7 (CH, C-3), 15.5 (CH_3 , C-13), 13.8 (CH_3 , C-10), 9.9 (CH_3 , C-11) ppm; MS (ESI): m/z 262 ($\text{M}^+ + \text{Na}$); HRMS: found: ($\text{M}^+ + \text{H}$) 262.1043. $\text{C}_{12}\text{H}_{18}\text{NO}_5$ requires ($\text{M}^+ + \text{H}$) 262.1050.

(*E,4R,5R*)-*tert*-Butyl 5-hydroxy-4,6-dimethyl-7-(2-methyloxazol-4-yl)-3-oxohept-6-enoate 286

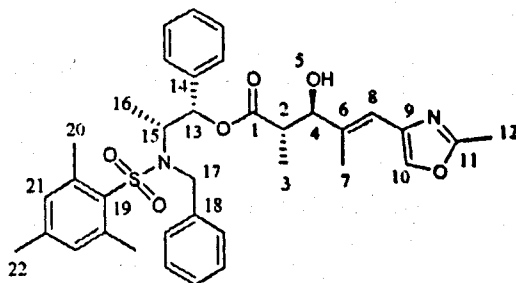


A 2.53 M solution of *n*-butyllithium in hexanes (4.35 mL, 11.0 mmol) was added to a solution of diisopropylamine (1.66 mL, 11.7 mmol) in THF (20 mL) at 0 °C, under an atmosphere of N_2 , and the reaction was stirred for 15 minutes before being cooled to -78 °C. *tert*-Butyl acetate (1.48 mL, 11.0 mmol) was added and after stirring for 1 hour, the reaction mixture was added *via* cannula to a pre-cooled (-30 °C) solution of (*E,2R,3R*)-methyl 3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-enoate

(287) (438 mg, 1.83 mmol) in THF (10 mL). The reaction was then warmed to -22 °C and left without stirring for 12 hours, after which time the reaction was quenched with a saturated aqueous solution of NH₄Cl (30 mL) and the mixture was warmed to room temperature. The THF was evaporated *in vacuo* and the remaining aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organics were dried (MgSO₄) and concentrated *in vacuo* to a dark orange residue, which was purified *via* flash column chromatography (3:1 / petroleum ether : EtOAc) to yield 286 as a yellow oil (476 mg, 77%).

[α]_D²⁴ +25.5 (c = 4.92, CHCl₃); IR (film): ν_{\max} 3396, 2980, 2936, 1730, 1711, 1584, 1455, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.41 (1H, s, H-11), 6.36 (1H, app s, H-9), 4.49 (1H, app d(br), J = 3.3 Hz H-7), 3.45 (2H, app s, H-4), 2.86 (1H, qd, J = 7.1, 3.3 Hz, H-6), 2.39 (3H, s, H-13), 1.83 (3H, s (br), H-16), 1.42 (9H, s, H-1), 1.04 (3H, d, J = 7.2 Hz, H-14) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 206.9 (C, C-5), 166.5 (C, C-3), 160.8 (C, C-12), 138.7 (C, C-8/10), 137.7 (C, C-8/10), 135.3 (CH, C-11), 115.1 (CH, C-9), 81.9 (C, C-2), 74.9 (CH, C-7), 49.2 (CH₂, C-4), 49.0 (CH, C-6), 27.8 (CH₃, C-1), 15.9 (CH₃, C-16), 13.9 (CH₃, C-13), 9.3 (CH₃, C-14) ppm; MS (ESI): m/z 346 (M⁺ + Na), 324 (M⁺ + H), 306 (M⁺ - OH), 250 (M⁺ - t-BuO); HRMS: found: (M⁺ + H) 324.1801. C₁₇H₂₆NO₅ requires (M⁺ + H) 324.1805.

2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl 3'-hydroxy-2',4'-dimethyl-5'-(2-methyloxazol-4-yl)pent-4'-enoate (297)

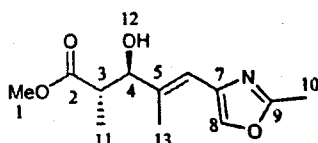


Triethylamine was added to a solution of 2-(*N*-Benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate **294** (1.50 g, 3.13 mmol) in CH₂Cl₂ (31 mL) at room temperature, under an atmosphere of N₂. The reaction mixture was cooled to -78 °C, and a pre-cooled 1.0 M solution of dicyclohexylboron triflate in hexanes (9.42 mL, 9.42 mmol) in CH₂Cl₂ (10 mL) was added to the reaction mixture *via* cannula. After stirring for 3 hours at -78 °C, aldehyde **29** (569 mg, 3.76 mmol) was added as a solution in CH₂Cl₂ (5 mL). After stirring for 2 hours at -78 °C, the reaction was warmed to room temperature and quenched with an aqueous solution of pH 7 buffer (20 mL), followed by methanol (50 mL) and hydrogen peroxide (30% w/v in H₂O) (10 mL). The phases were separated and the aqueous was further extracted with CH₂Cl₂ (4 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na₂SO₄), and concentrated *in vacuo* to a yellow oil, which was purified by flash column chromatography (2:1 / heptane : EtOAc) to yield **297** as an off-white solid (1.91 g, 91%).

$[\alpha]_D^{24}$ -40.3 (c = 0.785, CHCl₃); Melting point 70-72 °C; IR (solution, CHCl₃): ν_{\max} 2979, 2939, 1738, 1604, 1585, 1496, 1150 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.49 (1H, s, H-10), 7.14-7.37 (8H, m, Ar), 6.89 (2H, s, H-21), 6.80-8.87 (2H, m, Ar), 6.23 (1H, m, H-8), 5.82 (1H, d, J = 3.9 Hz, H-13), 4.81 (1H, d, J = 16.6 Hz, H-17), 4.60 (1H, d, J = 16.6 Hz, H-17), 4.23 (1H, d (br), J = 9.7 Hz, H-4), 4.07 (1H, dq, J = 7.0, 3.9 Hz, H-15), 2.56-2.76 (2H, m, H-2 + H-5), 2.50 (6H, s, H-20), 2.44 (3H, s, H-12), 2.29 (3H, s, H-22), 1.95 (3H, d, J = 0.8 Hz, H-7), 1.15 (3H, d, J = 7.0 Hz, H-16), 0.98 (3H, d, J = 7.2 Hz, H-3) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 174.5 (C, C-1); 160.9 (C, C-11), 142.5, 138.8, 138.2, 138.1, 137.4 (all C) 135.8 (CH, C-10), 133.4 (C), 132.1 (CH, C-21), 128.4, 128.3, 127.8, 127.6, 127.0, 125.7, (all CH, Ar), 118.5 (CH, C-8), 79.9 (CH, C-4), 78.3 (CH, C-13), 56.8 (CH, C-15), 48.2 (CH₂, C-17), 43.5 (CH,

C-2), 22.9 (CH₃, C-20), 20.8 (CH₃, C-22), 14.2 (CH₃, C-3), 13.7 (CH₃, C-12), 13.3 (CH₃, C-7) 13.3 (CH₃, C-16) ppm; MS (ESI): m/z 631 (M⁺); HRMS: found: (M⁺) 631.2851. C₃₆H₄₃N₂O₆S requires (M⁺) 631.2836.

(E,2*S*,3*R*)-methyl 3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-enoate (298)

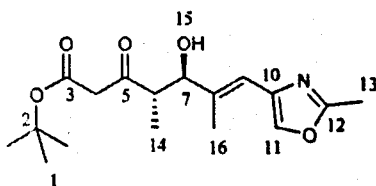


A 1.0 M solution of sodium methoxide in methanol (7.34 mL, 7.34 mmol) was added to a solution of 2-(*N*-Benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl 3'-hydroxy-2',4'-dimethyl-5'-(2-methyloxazol-4-yl)pent-4'-enoate (**297**) (1.56 g, 2.45 mmol) in methanol (85 mL) at 0 °C, under an atmosphere of N₂. The reaction was allowed to warm to room temperature and stirring continued for 2 days. After this time, the reaction was quenched with a saturated aqueous solution of NH₄Cl (85 mL) and the methanol was evaporated *in vacuo*. The remaining aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organics were concentrated *in vacuo* to a dark orange residue, which was purified by flash column chromatography (4:1 to 1:2 / petroleum ether : EtOAc) to **298** as a yellow oil (476 mg, 81%).

$[\alpha]_D^{24}$ -7.5 (c = 0.33, CHCl₃); IR (film): ν_{\max} 3369, 2979, 2951, 1733, 1584, 1456, 1436, 1108 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50 (1H, s, H-8), 6.27 (1H, m, H-6), 4.25 (1H, dd, J = 8.8, 4.0 Hz, H-4), 3.73 (3H, s, H-1), 2.73 (1H, dq, J = 8.8, 7.2 Hz, H-3), 2.72 (1H, d, J = 4.0 Hz, H-12), 2.45 (3H, s, H-10), 1.92 (3H, d, J = 1.2 Hz, H-13), 1.08 (3H, d, J = 7.2 Hz, H-11) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 176.2 (C, C-2), 160.9 (C, C-9), 138.5 (C, C-7/9), 137.5 (C, C-7/9), 135.7 (CH, C-8), 118.2 (CH, C-6), 79.8 (CH, C-4), 51.9 (CH₃, C-1), 43.4 (CH, C-3), 14.4 (CH₃, C-11), 13.7 (CH₃,

C-10), 13.5 (CH₃, C-13) ppm; MS (ESI): m/z 262 (M⁺ + Na), 240 (M⁺ + H), 222 (M⁺ - OH), 190 (M⁺ - H₂O - MeO); HRMS: found: (M⁺ + Na) 262.1047. C₁₂H₁₇NO₅Na requires (M⁺ + Na) 262.1050.

(*E,4S,5R*)-*tert*-Butyl 5-hydroxy-4,6-dimethyl-7-(2-methyloxazol-4-yl)-3-oxohept-6-enoate (299)

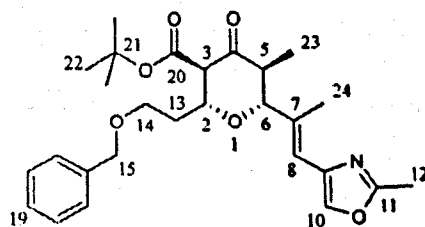


A 2.53 M solution of *n*-butyllithium in hexanes (7.56 mL, 19.1 mmol) was added to a solution of diisopropylamine (2.84 mL, 20.1 mmol) in THF (20 mL) at 0 °C, under an atmosphere of N₂, and the reaction was stirred for 15 minutes before being cooled to -78 °C. *tert*-Butyl acetate (2.84 mL, 20.1 mmol) was added and after stirring for 1 hour, the reaction mixture was added *via* cannula to a pre-cooled (-78 °C) solution of (*E,2S,3R*)-methyl 3-hydroxy-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-enoate (298) (457 mg, 1.91 mmol) in THF (10 mL). The reaction was then warmed to -30 °C and stirred at this temperature for 2 hours, after which time the reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL) and the mixture was warmed to room temperature. The THF was evaporated *in vacuo* and the remaining aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organics were dried (MgSO₄) and concentrated *in vacuo* to a dark orange residue, which was purified *via* flash column chromatography (4:1 / petroleum ether : EtOAc) to yield 299 as a yellow oil (410 mg, 69%).

[α]_D²⁴ +6.3 (c = 0.33, CHCl₃); IR (film): ν_{\max} 3361, 2978, 2933, 1734, 1713, 1652, 1635, 1585, 1457, 1394, 1150 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50 (1H, s, H-11), 6.23 (1H, dq, J = 1.2, 0.6 Hz, H-9), 4.24 (1H, d(br), J = 9.0 Hz, H-7), 3.54 (1H, d,

J = 15.4 Hz, H-4), 3.47 (1H, d, J = 15.4 Hz, H-4), 2.99 (1H, dq, J = 9.0, 7.1 Hz, H-6), 2.43-2.47 (4H, m, H-13 + H-15), 1.94 (3H, d, J = 1.2 Hz, H-16), 1.47 (9H, s, H-1), 0.98 (3H, d, J = 7.1 Hz, H-14) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 207.4 (C, C-5), 166.6 (C, C-3), 160.9 (C, C-12), 138.8 (C, C-8/10), 137.3 (C, C-8/10), 135.7 (CH, C-11), 118.3 (CH, C-9), 81.9 (C, C-2), 80.4 (CH, C-7), 51.5 (CH_2 , C-4), 49.1 (CH, C-6), 27.9 (CH_3 , C-1), 13.7 (CH_3 , C-13), 13.7 (CH_3 , C-16) 13.2 (CH_3 , C-14) ppm; MS (ESI): m/z 346 ($\text{M}^+ + \text{Na}$), 324 ($\text{M}^+ + \text{H}$), 306 ($\text{M}^+ - \text{OH}$), 268 ($\text{M}^+ + \text{H}_2 - \text{t-Bu}$), 250 ($\text{M}^+ - \text{t-BuO}$); HRMS: found: ($\text{M}^+ + \text{H}$) 324.1798. $\text{C}_{17}\text{H}_{26}\text{NO}_5$ requires ($\text{M}^+ + \text{H}$) 324.1805.

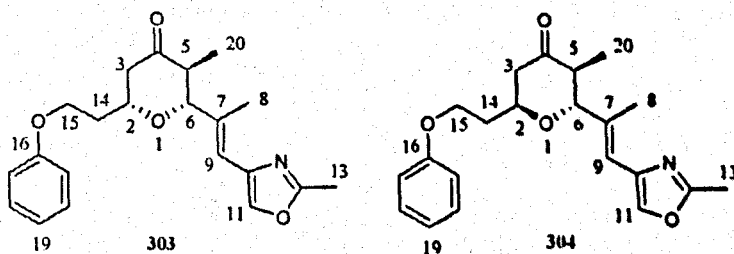
(2*R*,3*R*,5*S*,6*R*)-tert-Butyl 2-(2-(benzyloxy)ethyl)-tetrahydro-5-methyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-oxo-2H-pyran-3-carboxylate (302)



A solution of aldehyde **29** (76 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) was added to a stirred suspension of scandium triflate (190 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at -78°C , under an atmosphere of N_2 . After 3 minutes of stirring, a solution of (*E*,4*S*,5*R*)-tert-butyl 5-hydroxy-4,6-dimethyl-7-(2-methyloxazol-4-yl)-3-oxohept-6-enoate **299** (125 mg, 0.38 mmol) in CH_2Cl_2 (5 mL). The reaction was allowed to warm to room temperature gradually and then stirred for 12 hours. After this time, the reaction mixture was filtered through a thin pad of silica, which was washed with EtOAc (3 x 20 ml). The filtrate was concentrated to a yellow residue which was seen to contain the THPs **300**, **301**, and **302** in a ratio of 1.1:1.0:1.0. Flash column chromatography (9:1 / petroleum ether : EtOAc) yielded **302** (20 mg, 12%) as a yellow residue.

$[\alpha]_D^{24} +14.1$ ($c = 0.16$, CHCl_3); IR (film): ν_{max} 2976, 2932, 2863, 1734, 1712, 1586, 1455, 1367, 1109 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.52 (1H, s, H-10), 7.23-7.35 (5H, m, Ar), 6.19 (1H, app. s, H-8), 4.52 (1H, d, $J = 12.0$ Hz, H-15), 4.46 (1H, d, $J = 12.0$ Hz, H-15), 4.08 (1H, ddd, $J = 10.7, 7.7, 2.9$ Hz, H-2), 3.76 (1H, d, $J = 10.3$ Hz, H-6) 3.55 – 3.72 (2H, m, H-14), 3.36 (1H, dd, $J = 10.7, 0.8$ Hz, H-3), 2.53 (1H, dqd, $J = 10.3, 6.6, 0.8$ Hz, H-5), 2.46 (3H, s, H-12), 1.98 (3H, d, $J = 0.9$ Hz, H-21), 1.85-2.10 (2H, m, H-13), 1.48 (9H, s, H-22), 0.90 (3H, d, $J = 6.6$ Hz, H-23); ^{13}C NMR (100 MHz, CDCl_3): δ 204.5 (C, C-4), 167.2 (C, C-20), 160.9 (C, C-11), 138.4 (C, C-6), 137.5 (C, C-9), 137.4 (C, C-7), 136.1 (CH, C-10), 128.3 (CH, Ph), 127.5 (CH, Ph), 127.5 (CH, Ph), 119.3 (CH, C-8), 88.8 (CH, C-6), 81.9 (C, C-21), 75.9 (CH, C-2), 72.8 (CH_2 , C-15), 66.1 (CH_2 , C-14), 63.7 (CH, C-3), 47.5 (CH, C-5), 34.7 (CH_2 , C-13), 28.1 (CH_3 , C-22), 13.8 (CH_3 , C-12), 13.5 (CH_3 , C-24), 9.3 (CH_3 , C-20). MS (ESI): m/z 492 ($\text{M}^+ + \text{Na}$); HRMS: found: ($\text{M}^+ + \text{Na}$) 492.2362 $\text{C}_{27}\text{H}_{35}\text{NO}_5\text{Na}$ requires ($\text{M}^+ + \text{Na}$) 492.2357.

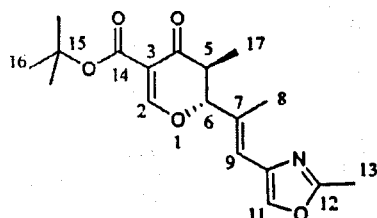
(2*R*,3*S*,6*R*)-Tetrahydro-3-methyl-2-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-6-(2-phenoxyethyl)pyran-4-one (303) and (2*R*,3*S*,6*S*)-tetrahydro-3-methyl-2-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-6-(2-phenoxyethyl)pyran-4-one (304)



A solution of a THP mixture comprising 8:1:1 302 : 300 : 301 (142 mg, 0.30 mmol) in DMF (3 mL) was heated in the presence of H_2O (30 μl) under microwave conditions: temp. 160 $^\circ\text{C}$, pressure, 0 psi, power 300 W, ramp time 20 min, hold time 20 min. The DMF was removed *in vacuo* and the resulting dark brown residue was

purified by flash column chromatography to yield **303** (77 mg, 70%) and **304** (15 mg, 13%) as yellow residues.

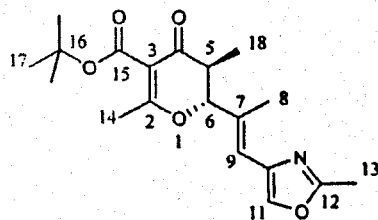
(5*S*,6*R*)-tert-Butyl 5,6-dihydro-5-methyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-oxo-4H-pyran-3-carboxylate (310)



N,N-Dimethylformamide dimethyl acetal (290 μ l, 2.1 mmol) was added to a solution of *tert*-butyl 5-hydroxy-4,6-dimethyl-7-(2-methyloxazol-4-yl)-3-oxohept-6-enoate (**299**) (69 mg, 0.21 mmol) in PhMe (3 mL) at room temperature, under an atmosphere of N_2 . After 16 hours of stirring, the solvents were removed *in vacuo* and the resulting dark brown residue was purified by flash column chromatography (5:2 / petroleum ether : EtOAc) to yield **310** (43 mg, 61%) as a yellow residue.

$[\alpha]_D^{24}$ -26.8 ($c = 0.52$, $CHCl_3$); IR (film): ν_{max} 2978, 2934, 1732, 1698, 1589, 1455, 1384, 1308, 1140, 1107 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 8.24 (1H, app d, $J = 0.7$ Hz, H-2), 7.56 (1H, s, H-11), 6.31 (1H, m, H-9), 4.57 (1H, d, $J = 13.5$ Hz, H-6), 2.74 (1H, dq, $J = 13.5, 6.9$ Hz, H-5), 2.46 (3H, s, H-13), 2.04 (3H, app s, H-8), 1.51 (9H, s, H-16), 1.01 (3H, d, $J = 6.9$ Hz, H-17) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8 (C, C-4), 169.8 (CH, C-2), 162.5 (C, C-12/14), 161.2 (C, C-12/14), 137.1 (C, C-7/10), 136.8 (CH, C-11), 133.0 (C, C-7/10), 121.7 (CH, C-9), 111.2 (C, C-3), 91.5 (CH, C-6), 81.2 (C, C-15), 41.5 (CH, C-5), 28.2 (CH_3 , C-16), 13.8 (CH_3 , C-13), 13.2 (CH_3 , C-8), 9.6 (CH_3 , C-17) ppm. MS (ESI): m/z 356 ($M^+ + Na$), HRMS: found: ($M^+ + Na$) 356.1577 $C_{27}H_{35}NO_5Na$ requires ($M^+ + Na$) 356.1576.

(5*S*,6*R*)-tert-Butyl 5,6-dihydro-2,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-oxo-4H-pyran-3-carboxylate (311)



N,N-Dimethylacetamide dimethyl acetal (270 μ l, 2.1 mmol) was added to a solution of tert-butyl 5-hydroxy-4,6-dimethyl-7-(2-methyloxazol-4-yl)-3-oxohept-6-enoate **299** (59 mg, 0.18 mmol) in PhMe (3 mL) at room temperature, under an atmosphere of N_2 . After 16 hours of stirring, the solvents were removed *in vacuo* and the resulting dark brown residue was purified by flash column chromatography (5:2 / petroleum ether : EtOAc) to yield **311** (42 mg, 66%) as a yellow residue.

$[\alpha]_D^{24}$ -31.4 ($c = 0.44$, $CHCl_3$); IR (film): ν_{max} 2979, 2934, 1722, 1674, 1590, 1392, 1365, 1164 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, s, H-11), 6.30 (1H, app s, H-9), 4.49 (1H, d, $J = 13.6$ Hz, H-6), 2.66 (1H, dq, $J = 13.6, 6.9$ Hz, H-5), 2.46 (3H, s, H-13), 2.16 (3H, s, H-14), 2.03 (3H, app s, H-8), 1.53 (9H, s, H-17), 0.98 (3H, d, $J = 6.9$ Hz, H-18) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5 (C, C-4), 174.3 (C, C-2), 165.1 (C, C-12/15), 161.1 (C, C-12/15), 137.1 (C, C-7/10), 136.6 (CH, C-11), 133.7 (C, C-7/10), 121.5 (CH, C-9), 113.6 (C, C-3), 98.2 (CH, C-6), 81.7 (C, C-16), 40.3 (CH, C-5), 28.1 (CH_3 , C-17), 19.9 (CH_3 , C-14), 13.8 (CH_3 , C-13), 13.3 (CH_3 , C-8), 9.5 (CH_3 , C-17) ppm. MS (ESI): m/z 370 ($M^+ + Na$), 314 ($M^+ + Na - t-Bu$); HRMS: found: ($M^+ + Na$) 370.1620 $C_{27}H_{35}NO_5Na$ requires ($M^+ + Na$) 370.1625.

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