UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

The Enantioselective Synthesis Of (-)-Luminacin D

by

Nathan Bartlett

Thesis for the degree of Doctor of Philosophy

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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Luminacin D, isolated from the fermentation broth of soil bacterium *Streptomyces* sp. Mer-VD1207, has angiogenesis inhibitory activity. *In vivo* studies have shown this activity derives from a novel mode of action, thus making luminacin D an interesting target for synthesis. Previous syntheses have not enabled the preparation of the spiro-epoxypyran moiety in a stereoselective manner, and luminacin D has been isolated as a mixture with the 6',8' – epimer as a result. This has been overcome by early, stereospecific introduction of the epoxide in our synthesis and we have constructed the natural product skeleton with the correct absolute stereochemistry, by chelation controlled diastereoselective additions. This has enabled possibly the first enantioselective and diastereoselective synthesis of this natural product to be completed. The allylation of α-heteroatom substituted aldehydes was of significance to the synthesis as the key step in the synthesis involved allylation of an α-epoxyaldehyde. These allylation reactions have been investigated by DFT calculations to unambiguously assign the Evans-Conforth and Polar Felkin-Ahn models in these additions.

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DECLARATION OF AUTHORSHIP

I, **Nathan Bartlett**

declare that the thesis entitled

'**The Enantioselective Synthesis Of (-)-Luminacin D**'

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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Preface

The research described in this thesis was carried out under the supervision of Dr. Bruno Linclau at the University of Southampton between October 2008 and September 2012. No part of this thesis has previously been submitted for a degree. All work is my own unless otherwise stated.

Acknowledgements

As many of my friends and peers can appreciate, working towards a PhD can be a life encompassing task. As my efforts towards this goal are now finishing I would like to thank a number of people who have helped and made this period of my life very enjoyable. Firstly I would like to thank Bruno, who has been incredibly supportive ever since I was an undergraduate student at Southampton. His guidance has given me my current scientific mind set and I am very grateful for all the opportunities that were made possible through his efforts.

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Lastly I would like to thank my friends and family, who have always been there to help when times have been hard in whatever way required, but also who have been good company when the sun was shining. You know who you are.

Abbreviations

6-31G*	basis set for DFT calculations
Ac	acetyl group
AMAP-1	AMY-1-binding protein 1
B3LYP	Becke, three-parameter, Lee-Yang-Parr method
BAE	bovine aortic endothelial cell line
BBN	borabicyclononane
BCA	bi-dentate chelated aldehyde
Bn	Benzyl
BOC	*tert*-butoxycarbonyl
BOP	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
CI	chemical ionisation
CSA	camphorsulfonic acic
c-src	cellular sarcoma (proto-oncogene encoding for tyrosine kinases)
d.r.	diastereomeric ratio
DBU	1,8-diazabicycloundec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
Dess-martin	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(*1H*)-one
DET	diethyl tartrate
DFT	density functional theory
DIAD	di*iso*propyl azodicarboxylate
DIBAL	di*iso*butylaluminium hydride
DIBAL-H	di*iso*butylaluminium hydride
DIC	di*iso*propyl carbodimide
DIPEA	di*iso*propylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNPH	dinitrophenylhydrazine
e.r.	entiomeric ratio
ee	entiomeric excess
EI	electron impact
ES	electrospray
Et	Ethyl
FLT1	vascular endothelial growth factor receptor 1
FTIR	fourier transform infrared spectroscopy
Grb-2	growth factor receptor bound protein 2

GST	Glutathione S-transferase
HATU	2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium
HIF-1α	hypoxia-inducible factors 1 *alpha*
HIF-1β	hypoxia-inducible factors 1 *beta*
HMBC	heteronuclear multiple bond correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HUVEC	human umbilical vascular endothelial cell line
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
Imid	Imidazole
*i*Pr	*iso*-propyl
IR	infrared spectroscopy
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
LRMS	low resolution mass spectrometry
Lum D	Luminacin D
m-CPBA	*meta*-chloroperbenzoic acid
Mer-VD1207	designated bacteria strain number
MOM	Methoxymethylene
MS	mass spectrometry
MsCl	methanesulfonyl chloride
NcK1	scaffold adapter protein also involved in receptor signalling and cell migration and adhesion
NIS	*N*-iodo succinimide
NMO	*N*-methymorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	Nucleophile
OMe	Methoxy
P4 peptide	small SH3 region mimic peptide
PECAM-1	platelet endothelial cell adhesion molecule 1
Ph	Phenyl
PLCγ	phospholipase C gamma
PLPI	proline rich protein-protein interactions
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	Propyl
PTP-α	protein-tyrosine phosphatase alpha
PyAOP	(7-azabenzotriazole-1-yloxy)tripyrrolidinophosphonium Hexafluorophosphate

PyBrOP	bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
Pyr	pyridine
ras	a family of related proteins all of which are small GTPases
RATF	rat aortic fragment
RNA	ribosenuclec acid
RSV	Rous Sarcoma virus
Sam-68	68KDa src substrate
SEM	standard error measurement
SH1	src homology 1 region
SH2	src homology 2 region
SH3	src homology 3 region
SI-4228	Luminacin designated compound number
src	sarcoma (proto-oncogene encoding for tyrosine kinases)
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydrogen peroxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	Triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TPAP	tetrapropylammonium perruthenate
TS	transition state
Tyr	tyrosine residue
UCS15A	Luminacin C2 designation
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VEGFR-1	vascular endothelial growth factor receptor 1
VHL	Von Hippel-Lindau tumour suppressor
v-src	viral sarcoma (proto-oncogene encoding for tyrosine kinases)
XRD	X-ray diffraction
ZO1	tight junction protein 1

“And I have felt
A presence that disturbs me with the joy
Of elevated thoughts; a sense sublime
Of something far more deeply interfused,
Whose dwelling is the light of setting suns,
And the round ocean and the living air,
And the blue sky, and in the mind of man;
A motion and a spirit, that impels
All thinking things, all objects of all thought,
And rolls through all things. Therefore am I still
A lover of the meadows and the woods,
And mountains; and of all that we behold
From this green earth; of all the mighty world”

Tintern Abbey,
William Wordsworth

Chapter 1 Introduction

1.1 The luminacins

1.1.1 Isolation of the luminacins

The luminacins are a group of natural products composed of peculiar structural features such as a highly substituted aromatic fragment and a spiro-epoxide ring. All the luminacins are products of soil bacteria fermentation, specifically the actinomycete streptomyces species designated Mer-VD1207.[1] Soil bacteria of this type are well known historically for their diverse and bioactive natural products.[2]

At the turn of the century all the presently known luminacin structures were described but the first discovery of a luminacin mixture can be credited to Suzuki *et al*. in the early eighties.[3] This has caused disparity in the chemical nomenclature used between natural science disciplines, and it is worth noting that luminacin C, in particular, is commonly referred to as UCS15A and SI-4228 in the biological literature.

The diversity of the luminacin structures is found on the periphery of the molecules, and permutation at 3 sites leads to all 14 members of the luminacin family. The original isolation from 200 litres of harvested broth gave the key bioactive members in the quantities stated in fig **1.1**, with luminacin C_2 (UCS15A) being the most abundant of the highly bioactive members after purification.[1]

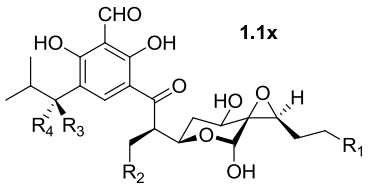


Fig 1.1 – General luminacin Structure and key members (including isolated amount)[1]

luminacin (A-H)		R_1	R_2	R_3	R_4	Isolated (mg)
1.1c$_1$	C_1	H	Et	H	OMe	60.8
1.1c$_2$	C_2	H	Et	OMe	H	256.4
1.1d	**D**	**H**	**Et**	**H**	**H**	**63.7**
1.1e$_1$	E_1	H	*i*Pr	OMe	H	16.2
1.1e$_2$	E_2	H	*i*Pr	H	OMe	125.4
1.1f	F	Me	Et	H	H	9.2
1.1g$_1$	G_1	H	*i*Pr	H	H	10.4

1.1.2 Biosynthetic considerations and polyketides

The highly decorated resorcinol fragment and the aliphatic fragment do appear chemically distinct, however, it is likely that these two parts were forged by the same cellular machinery. The luminacins' underlying skipped oxygenation pattern throughout the backbone attests to origins from a polyketide synthase. The large degree of conserved structure between luminacin members further supports this hypothesis.

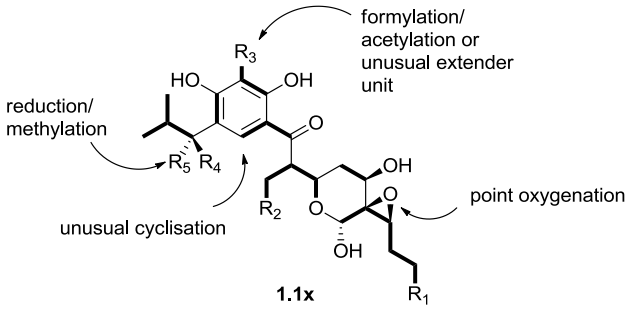


Fig 1.2 – Luminacins as polyketides, divided up into biosynthetic precursor and extender units

1.2 Biological activity & angiogenesis

1.2.1 Angiogenesis

Angiogenesis is the term used to describe the migration and organisation of new endothelial cells into blood capillaries, branching from the existing vascular network of the human body. In healthy adults, the process of angiogenesis rarely occurs.[4] The growth and development of new or existing tissue does however require the proliferation and extension of new capillary blood vessels, for example in the female reproductive system in follicle development, in the corpus luteum during ovulation and in the growth of the placenta during pregnancy.[4-5] Angiogenesis is also an integral part of the healing process in wound and fracture repair. In these normal circumstances the process is highly regulated, in localised areas and active for brief periods of time only.[5c]

Persistent and unregulated angiogenesis forms the underlying cause of many diseases. Ocular neovascularisation can lead to twenty described eye ailments, including age-related macular degeneration and diabetic retinopathy vascularisation, all of which may lead to

blindness.[6] The processes involved in the physical formation of new capillary networks can lead to the degradation of any tissue, obstructing growth. In arthritis, new blood vessels invade the joint and destroy cartilage leading to the loss of joint function.[5a] Mutation in the chromosomal regions associated with stimulatory and inhibitory regulation of angiogenesis is a key factor in a benign neoplasm developing into a malignant and metastasizing tumour associated with all cancers. It is for this latter reason in particular, that interest in angiogenic modulators has grown rapidly.[5b]

For some identified pro- and anti-angiogenic constituents, the biochemical signalling processes of angiogenesis have been well-studied over the past few decades. The complexities of pathways have meant that in some cases little is understood about the mechanism of action involved. Studies have shown that the following cellular and extracellular components are involved in angiogenesis:

- *Hypoxia-Inducible Transcription Factor-1 (HIF-1):* A heterodimeric transcription factor composed of HIF-1α and HIF-1β under hypoxic conditions HIF-1 activates the transcription of VEGF (see below) and VEGFR-1 (VEGF tyrosine kinase receptor). When oxygen is present, HIF-1 becomes modified by oxygen dependent enzymes and is quickly inactivated by VHL (Von Hippel-Lindau protein) tumour suppressor, the binding preventing VEGF transcription.[5c]
- *VEGF:* The vascular endothelial growth factors (VEGF) A-E have pleiotropic effects on the formation of new vessels, increasing endothelial cell fenestrations and causing vessels to become "leaky". Other effects include endothelial cell migration, apoptosis, proliferation and capillary tube formation.
- *VEGFR (VEGF receptors):* VEGF isoforms bind to FLT1[1] (among other VEGFR), which phosphorylates members of the family of c-src (cellular sarcoma) tyrosine kinase receptors.[7]

[1] Vascular endothelial growth factor receptor 1 is a protein that in humans is encoded by the *FLT1* oncogene gene which belongs to src gene family.

These components are mainly associated with the sensing and signalling of hypoxic conditions, which lead to an angiogenic cellular response. There are many other molecular sensing and signalling components which are involved in angiogensis that have been omitted for clarity in this discussion.[8] The key VEGFR receptor proteins are very relevant however with relation to the luminacins' activity, and specifically their inherent relation and interactions with/as c-src family tyrosine kinase receptors.

1.2.2 Protein-protein interactions and src tyrosine kinases

The c-src gene was identified by J. Michael Bishop and Harold E. Varmus and changed the modern understanding of cancer dramatically.[9] Previously, a similar related v-src (viral sarcoma) gene had been identified in the Rous sarcoma virus (RSV) which was a causative agent of a tumour in chickens, called fibrosarcoma. This v-src gene was found to be the oncogene gene that gave retroviruses (like RSV) the ability to cause cancer. The later discovery of the c-src gene, which gives rise to tyrosine kinases, showed that a normal cellular component when mutated can lead to cancer (proto-oncogene).

The src tyrosine kinases have a number of functions and interactions and are implicated in a number of cellular functions related to growth and angiogensis. This includes cell adhesion events (via interactions with the platelet endothelial cell adhesion molecule - PECAM-1) and modifications to the actin cytoskeleton. It is known that cell surface focal points, with concentrations of cell surface proteins called integrins, can sense the extracellular matrix. The response of these focal points may lead to cell mobility and shape change, or progression through the cell cycle. Another src-associated protein in mitosis, Sam-68 (the 68 from 68KDa), which regulates the expression and processing of RNA, is phosphorylated during the cell cycle and appears to play a critical role in the timing of this cycle.[10]

Phosphorylation and dephosphorylation of c-src is closely related to the cell cycle. Dephosphorylation on key residue Tyr527 is mediated by protein-tyrosine phosphatase alpha (PTP-α), which is blocked by the binding of growth factor receptor bound protein (Grb-2) to PTP-α. The regulation is complex and dependent on specific bindings which are dependent on

the phosphorylation of specific residues of the three proteins.[11] The modulation of these phosphorylation events affects c-src conformation and hence the activity of the kinase.[12]

Src kinases have defined regions, most of which have recognition functions and not just the catalytic kinase activity that is expected from its classification. The src-homology one (SH1) region is the catalytic domain, which enables the kinase activity. There is also an SH2 and an SH3 region, separated by a thin proline rich sequence (Figure 1).[12] Both of the regions are thought to regulate the active state of the kinase through protein-protein interaction, most likely with the interacting proteins discussed (and many others poorly understood). SH3 regions are known to recognise and interact with proline rich sequences with some distinction and many of the interacting proteins also have similar regions. Grb-2, for example, has both SH2 and SH3 domains. (This poses interesting questions about the evolution of such systems but is not within the scope of discussion here.)

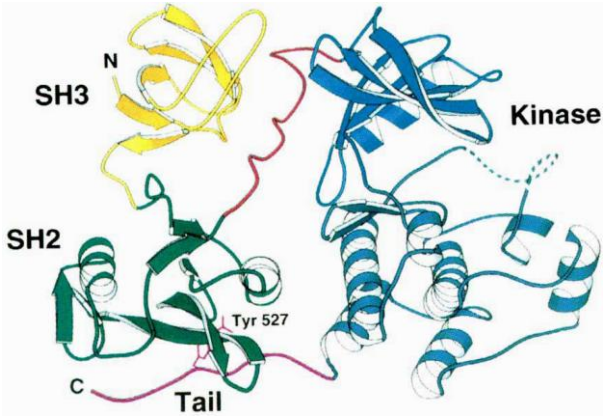


Fig 1.3 – c-src kinase - Picture published by Nature from Xu *et al*, the proline rich region has been highlighted in red.[12]

The luminacins are thought to exhibit their unique mode of action by disrupting protein-protein interactions with SH3 regions. Two very detailed studies by Sharma *et al*. elucidated a mechanism, specifically for luminacin C_2 (UCS15A) in model and *in vivo* systems.[10-11]

1.2.3 The interesting activities of luminacins[10-11]

Sharma inferred that SH3 domains which normally bind to proline rich regions on target proteins via protein-protein interactions were blocked by luminacin C_2 (UCS15A). This was achieved not just by binding to SH3 domain, but rather through interactions directly with the target proline rich regions. Importantly, as other related proteins use such SH3 domains, luminacin C_2 was also found to disrupt *in vivo* interactions of Sam 68 with Grb-2 and phospholipase Cγ (PLCγ) as well as Grb2-Sos1 and cortactin-ZO1 interactions. [2]

All these signalling pathways are implicated not just in angiogenesis but also specifically in cancers. Because of this, the possible therapeutic application of the luminacins in cancer treatment is great with minimal cytotoxicity. The angiogenesis activity profile of the luminacin family was examined, along with their structural elucidation. Minor structural changes between the members were found to perturb their activity significantly. This may indicate that for certain proline rich protein-protein interactions (PLPI), some specificity is present between the naturally occurring compounds.

This is also apparent from the differing activities between the compounds action on angiogensis and endothelial cell growth. In a study by Wakabayashi *et al*. angiogensis was modelled using rat aortic fragment cultures in collagen, which grow capillary tubes and microvascular sprouts.[13] Cultures treated with a luminacin concentration showed a decrease in tube formation. In this angiogensis model luminacin D showed the highest activity of all the tested members (IC_{50} – 0.017 μgmL^{-1}, Table **1.2**). However luminacin E_2, G_1 and C_2 showed much higher endothelial cell anti-proliferative activity.

[2] son of sevenless homolog 1 – involved in regulation of guanine nucleotide binding proteins (ras), activation of ras, which in turn is involved in the transduction of signals that control cell growth and differentiation. ZO1 - tight junction protein 1, found at tight junctions between cells in the cell membrane; cortactin – involved in rearrangement and polymerisation of the actin cytoskeleton

Table 1.2 – Members of the luminacin family with high anti-angiogenic activity

Luminacin (A-H)	Anti-angiogenesis activity[a]	Endothelial cell anti-proliferative activity[a]
C_1	0.053	0.24
C_2	0.050	0.08
D	**0.017**	**0.18**
E_1	0.047	0.21
E_2	0.067	0.06
F	0.065	0.11
G_1	0.038	0.07

[a] IC_{50} (μg/mL). (For structure see Fig **1.1**)

Table 1.3 – Inhibition of Matrigel invasion of different cancer cells by luminacin C_2, taken with modification from Hashimoto *et al*.[14]

		Luminacin C_2	
Cell line	Origin	Invasion[a]	Viability[b,c]
MDA-MB-231	Human breast cancer	12.8±0.0047	11.0±1.46
Hs578T	Human breast cancer	11.7±0.0053	18.1±2.53
MDA-MB-435s	Human breast cancer	15.4±0.0045	13.3±2.12
4T1 /luc	Mouse breast cancer	8.2±0.0021	10.4±0.61
CCF-STTG1	Human glioblastoma	10.0±0.0031	9.8±2.14
IN351	Human glioblastoma	10.6±0.0025	15.3±1.68
T98G	Human glioblastoma	11.5±0.0013	8.6±1.91
U373	Human glioblastoma	15.0±0.0019	10.9±1.36
H1299	Human lung cancer	52.4±0.0037	6.5±1.78
Lu99	Human lung cancer	18.3±0.0026	12.6±2.64

[a] IC_{50} (nM ± SEM), [b] IC_{50} (μM ± SEM), [c] Viability – Survival of cell lines

The effect of luminacin C_2 (UCS15A) on metastasis was tested in various cancer cell lines. This was measured by its inhibition of the invasion of stated cell lines into Matrigel, a good model of the complex extracellular matrix of many tissues (Table **1.3**). The effect was thought to arise primarily from the disruption of AMAP1-cortactin binding, another SH3 proline rich protein-protein interaction.[14]

Studies by Hashimoto *et al*. using a commercially available human SH3 domain array demonstrated the ability of luminacin C_2 to block the binding of a biotinylated small proline rich region mimic, P4 peptide (Fig **1.5**). The binding of the SH3 domain of Nck1 (NCK-D2) to P4 was less than that of the '100%' reference cortactin. Intriguingly however, this affinity was interrupted significantly by luminacin C_2 (UCS15A). Nck is a scaffold adapter protein also involved in receptor signalling and cell migration and adhesion. This array clearly demonstrates the selectivity of the luminacin C_2, but also demonstrates the potential to affect other SH3 bindings.[14]

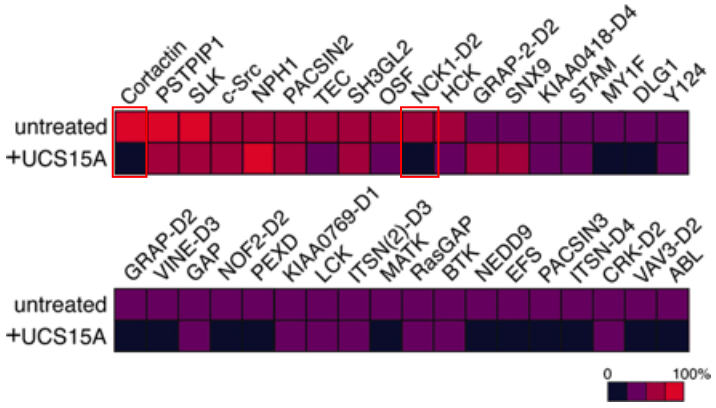


Fig 1.5 – "Human SH3 domains with the potential to bind to P4 peptide and their blockage by UCS15A." Taken without modification from Hashimoto *et al*.[14]

1.2.4 The activities of luminacin analogues

The successful demonstration of luminacin C_2 and other luminacins as potential drug candidates has led to investigations of the activity of related analogues. An early patent (2003) was filed to cover analogues, based around an unselective synthesis of luminacin D (see below). Biological activities in the document are not described with any specificity and hence only mentioned here for completeness.[15]

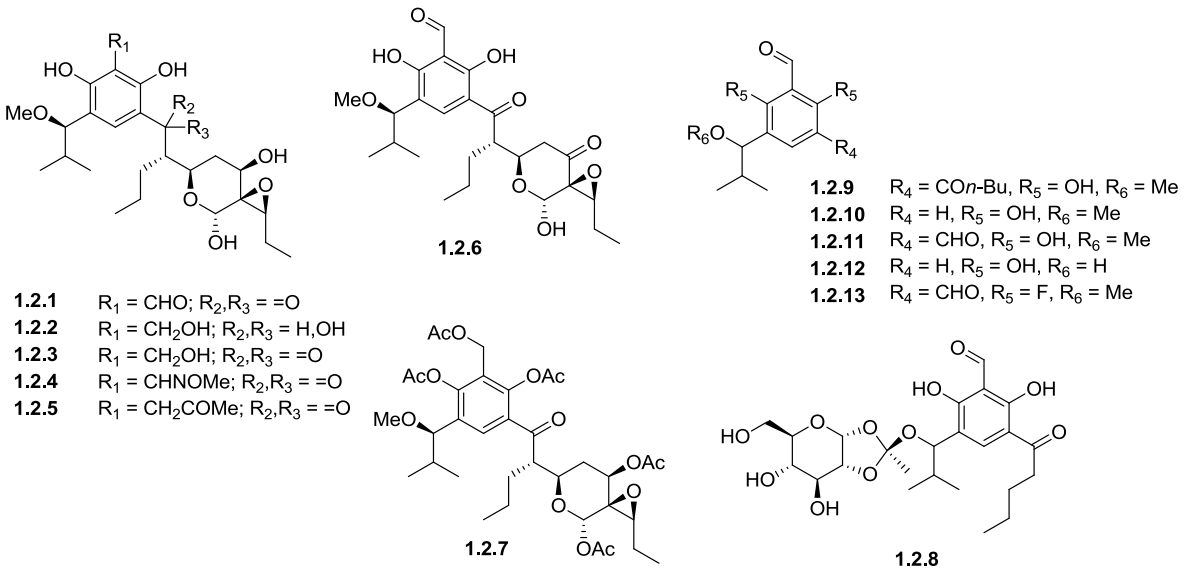
Of relevance, again, is the work by Sharma *et al.*, who screened a number of related aromatic compounds and luminacin C_2 derivatives for their inhibitory activity of the SH3 mediated, proline rich protein-protein interactions (PLPI) of Sam68 with the SH3 domain of Fyn (a proto-oncogene protein-tyrosine kinase - implicated in the control of cell growth through the

regulation of ras) *in vitro* (structures **1.2.9** – **1.2.13**, Fig **1.6**).[16] What is clear is that the penta-substituted aromatic system of the luminacins is important for biological activity, as active analogues completely devoid of the aliphatic fragment can be made.

However the selectivity and very high activity of the luminacins has not been matched by any such analogues and a complex aliphatic structure is perhaps required for selectivity. As part of studies by Hashimoto *et al*. it was observed that only 3 μM luminacin C_2 was sufficient to completely block binding of GST-cortactin and AMAP1 *in vitro*. Whereas, >300 μM was required of the resorcinol derivative **1.2.10**.[14] The SH3 mediated bindings of GST-cortactin and dynamin2; as well as paxillin and GST-AMAP1 (SH3) were unaffected by luminacin C_2 at similar concentrations, however analogue **1.2.10** again showed activity at higher concentrations (>300 μM).

Such detailed biological studies involving luminacin C_2 are a result of its greater availability through fermentation of Streptomyces Mer-VD1207. The need for a reliable synthetic route to the more active luminacin D becomes ever clearer in the light of these studies. A synthetic route with the ability to easily diverge to new analogues would be of great utility in the biological understanding of luminacin selectivity, in SH3 proline rich PLPIs.

Other reported analogues include an isosteric/isoelectronic difluoro analogue **1.2.13** which was devoid of the aliphatic fragment (Fig **1.6**). The effect on c-src activity of the analogue, in HCT 116 wtSrc23 human colorectal carcinoma cells, was an increase in c-src Tyr 418 phosphorylation.[17] No investigation on its effect on the various PLPI was documented in this study by Freeman *et al.* Since kinase activity is not necessarily expected to be decreased by luminacin like analogues according to the work of Sharma *et al*., this result is perhaps unsurprising.



1.2.1 R_1 = CHO; R_2,R_3 = =O
1.2.2 R_1 = CH_2OH; R_2,R_3 = H,OH
1.2.3 R_1 = CH_2OH; R_2,R_3 = =O
1.2.4 R_1 = CHNOMe; R_2,R_3 = =O
1.2.5 R_1 = CH_2COMe; R_2,R_3 = =O

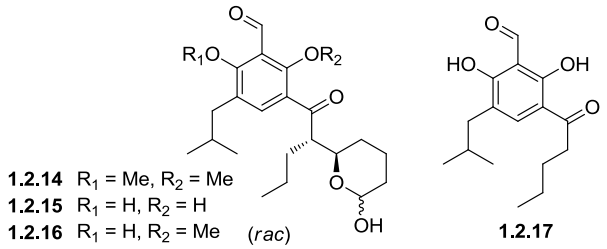
1.2.9 R_4 = CO*n*-Bu, R_5 = OH, R_6 = Me
1.2.10 R_4 = H, R_5 = OH, R_6 = Me
1.2.11 R_4 = CHO, R_5 = OH, R_6 = Me
1.2.12 R_4 = H, R_5 = OH, R_6 = H
1.2.13 R_4 = CHO, R_5 = F, R_6 = Me

Fig 1.6 – luminacin C2 analogues

Analogues devoid of the full functionalization of the luminacin aliphatic portion have also been prepared. In this study Shipman *et al*. demonstrated inhibition of the analogues on VEGF-induced angiogenesis in human umbilical vein endothelial cells (HUVEC) using an established fibrin matrix assay (Fig **1.7**).[18] The analogue **1.2.14** which was methylated at the phenolic positions was the most potent analogue, completely inhibiting VEGF-induced angiogenesis (50 μM, 98% ±2). The more luminacin 'like' phenols **1.2.15** and **1.2.16**, were found to be less effective at the same concentration (28% ± 26% and 28% ± 31% respectively). An analogue devoid of the simplified aliphatic system **1.2.17** did not inhibit angiogenesis at the same concentration (50 μM).

Table 1.4 – Inhibitory activity of luminacin C_2 analogs on PLPI in vitro (Fig **1.6**)

Luminacin C_2 analog	Inhibitory Activity (%) 20μM	100μM	300μM
(Lum C_2) **1.2.1**	8	39	100
1.2.2		85	100
1.2.3		95	100
1.2.7	15	100	100
1.2.4		0	0
1.2.5		80	100
1.2.6		39	100
1.2.9	45	100	100
1.2.10		0	0
1.2.11	72	100	100
1.2.12		32	100
1.2.8		13	35



1.2.14 R_1 = Me, R_2 = Me
1.2.15 R_1 = H, R_2 = H
1.2.16 R_1 = H, R_2 = Me (*rac*)

1.2.17

Fig 1.7 – Analogues of luminacin D in order of decreasing inhibitory activity against VEGF-induced angiogesis in HUVEC

Other analogues with the phenol alcohols protected with other groups, made during previous attempted syntheses of luminacin D also showed good activities against angiogenesis. In a diastereoselective synthesis of luminacin D from Crews *et al*., a protected (Bn) late stage phenolic intermediate showed equivalent anti-proliferative profiles to luminacin D in bovine aortic endothelial (BAE) cells. The inhibition was determined by the degree of incorporation of [^{3}H]-thymidine into cellular DNA.[19] This information may be crucial in the design of more potent analogues of the luminacins.

1.2.5 The anti-angiogenesis activity of luminacin D

As well as its activity described in the RATF model, luminacin D showed very high activity in the HUVEC model at concentrations as low as 0.1 μg/mL, with more dramatic morphological changes occurring around 1 μg/mL.[13] The number of cells was conserved over 4 days, even at concentrations as high as 3 μg/mL, indicating that luminacin D selectively inhibits the processes in tube formation, but was not cytotoxic. This shows that its mechanism of action has some specificity to angiogenesis signalling processes, and is probably not just generally blocking all PLPI interactions, mediated by the many SH3 domain containing proteins.[13] Luminacin D was found to have reasonable anti-proliferative activities in a number of caner cell lines however (Table **1.5**).

Table 1.5 – Anti-proliferative activity of luminacin D on various cell lines[13]

Cell line	Origin	IC_{50} (μg/mL)
SD6	rat smooth muscle	17.4
WI 38	human fibroblast	3.9
WiDr	human colon cancer	4.8
H-520	human lung cancer	8.0
MDA-MB-435	human breast cancer	8.0
MDA-MB-231	human breast cancer	5.6

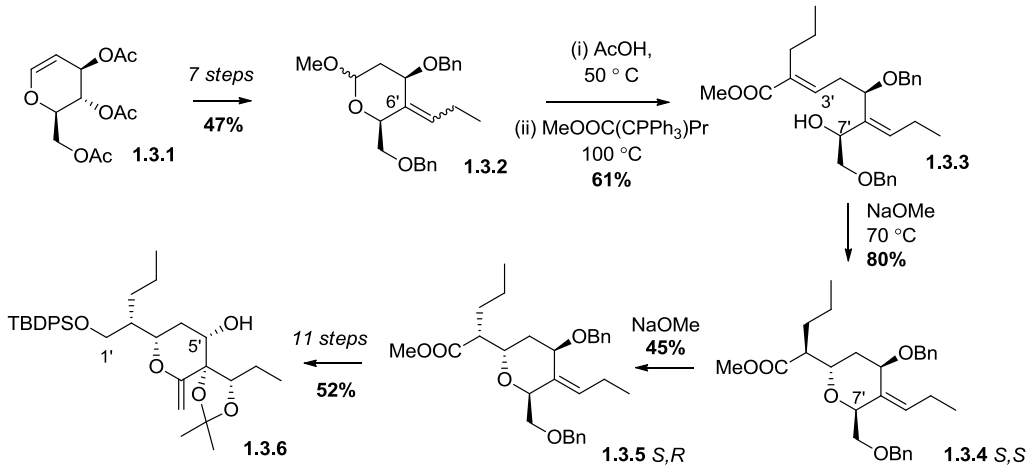
For this reason luminacin D is perhaps the most interesting of the luminacins currently studied and an investigation of its precise biological mechanism would be of great value in designing better analogues for the inhibition of angiogensis. To enable such investigations a substantial quantity of the pure luminacin D would be required and given the small quantities isolated from fermentation of Mer-VD1207 streptomyces, an enantioselective route to this natural product is important. The need for Luminacin D through synthesis becomes a greater priority for biological study, due to the fact that fermented luminacin D is nolonger available as notified by Wakabayashi. The isolation of luminacin D as a single enantiomer free of other isomers, from a highly selective synthetic route, has yet to be achieved despite numerous efforts towards this goal.

1.3 Previous syntheses

1.3.1 The unnatural enantiomers, luminacin C1 & C2 (Tatsuta 2001)[20]

Shortly after the publication of the Wakabashi's paper, the first attempted synthesis of luminacin C_1 and C_2 was published by the group of Tatsuta.[20] Although the route was long (36 linear steps, 43 total steps) and low yielding (0.35% - (+)-luminacin C_1), the unnatural enantiomers of luminacin C_1 and C_2 were isolated as pure compounds. The syntheses were important in confirming the absolute stereochemistry of the luminacins and the relative configuration of the pendent methoxy group, of the C1" of luminacin C_1 and C_2.

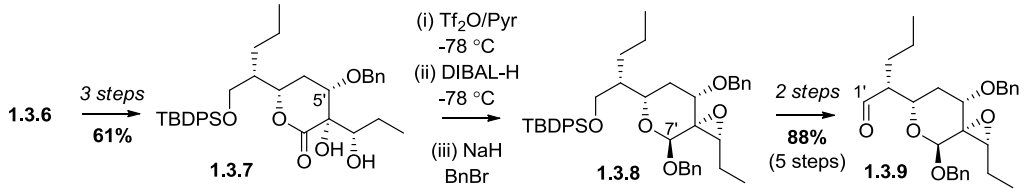
Scheme 1.1 – Aliphatic synthesis (*part 1*)



The synthesis starts from D-glucal derivative **1.3.1** and after a deprotection/protection strategy oxidation at C6' gave a handle for Wittig reaction to give the alkene **1.3.2** (Scheme **1.1**). Another Wittig reaction, on the deprotected hemiacetal of the C3' position installs all the carbons of the aliphatic portion **1.3.3**. From here, intramolecular Michael addition involving the C7' hydroxyl gave the undesired *S,S*-configuration in **1.3.4**, which could only be epimerised to a mixture of the *S,S* **1.3.4** and *S,R* **1.3.5** compounds (*1* : *1*), giving a low yield of the desired *S,R*-configuration **1.3.5** (45%). From here, dihydroxylation of C6' - C8' olefin followed by some functional group interconversions and protection steps, led to the enol ether. Through a number of transformations the alcohol was inverted at the C5' position, whilst reduction and protection of the C1' as the TBDPS ether was achieved, to give the interemediate **1.3.6**.

Benzylation at the C5' hydroxyl, followed by ozonolysis and acetal cleavage, gave the diol **1.3.7** which was readily converted to the epoxide (Scheme **1.2**). The lactone at the C7' position was then converted to a lactol, which was protected as the benzyl ether **1.3.8**. Deprotection and oxidation at the C1' position then gave the protected aliphatic fragment as the aldehyde **1.3.9**.

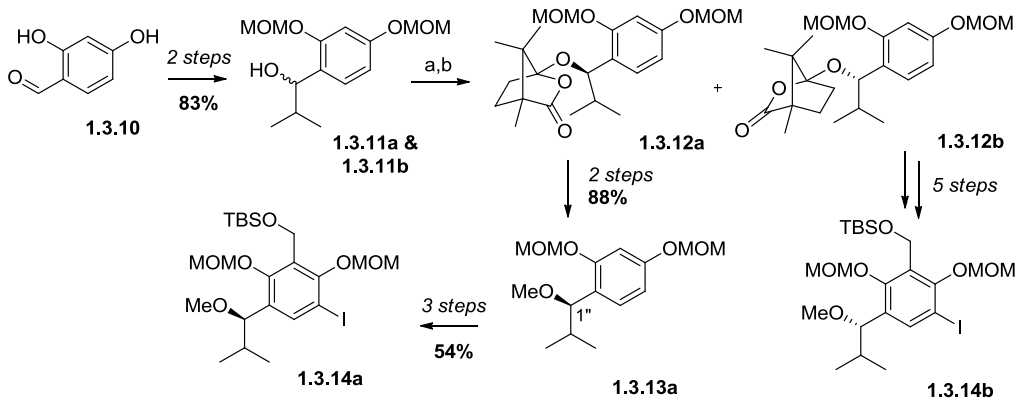
Scheme 1.2 – Aliphatic synthesis (*part 2*)



The aromatic fragment was constructed from 4-formylresorcinol **1.3.10** first by protection, then addition of *i*-propylmagnesium bromide. The racemate **1.3.11** was then resolved by a 2-step kinetic derivatisation with (-)-camphanic chloride for *R*-**1.3.11** and (+)-camphanic chloride for the remaining *S*-**1.3.11**. Each of the separated compounds were then hydrolysed and methylated to give the correct pendent methoxy group, at the C1" position. The intermediates **1.3.13a** and **1.3.13b** were then subjected to hydroxymethylation conditions, TBS protection, and finally iodination to give the aromatic fragments **1.3.14a** and **1.3.14b** (respectively).

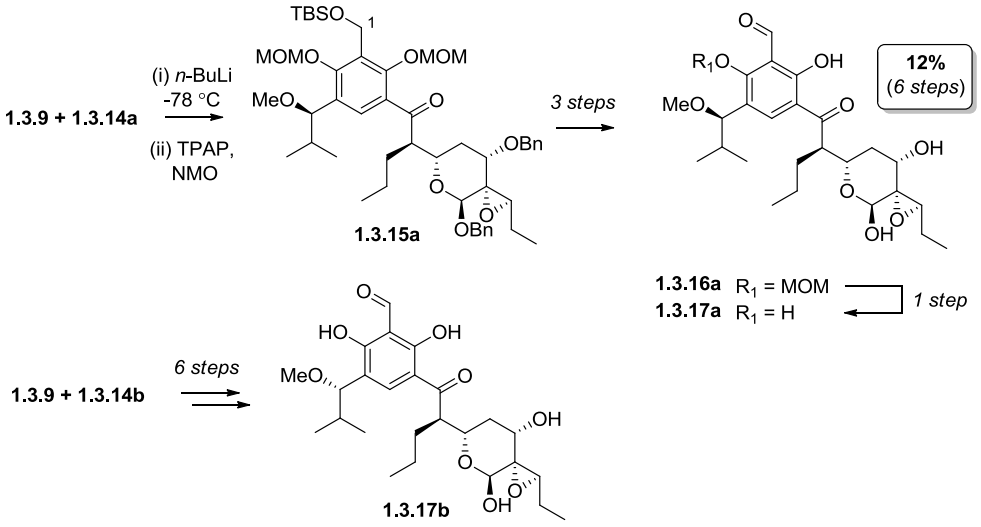
Using this iodide **1.3.14a**, the aryllithium could be prepared and coupled with the aliphatic aldehyde **1.3.9** to give, after oxidation, the protected intermediate **1.3.15a** (Scheme 1.4). Stepwise deprotection, to reveal the benzylic alcohol at the C1 position, allowed this position to be oxidised to the protected luminacin derivative **1.3.16a**. Final deprotection gave (+)-luminacin C_1 **1.3.17a**. Repetition of these final steps for the other aromatic intermediate **1.3.14b** gave (-)-luminacin C_2 **1.3.17b**.

Scheme 1.3 – Aromatic Synthesis



(a) (-)-camphanic chloride, Py/THF, -78 ºC, (b) (+)-camphanic chloride, Py/THF, -78 ºC, 45%.

Scheme 1.4 – Finishing Syntheses



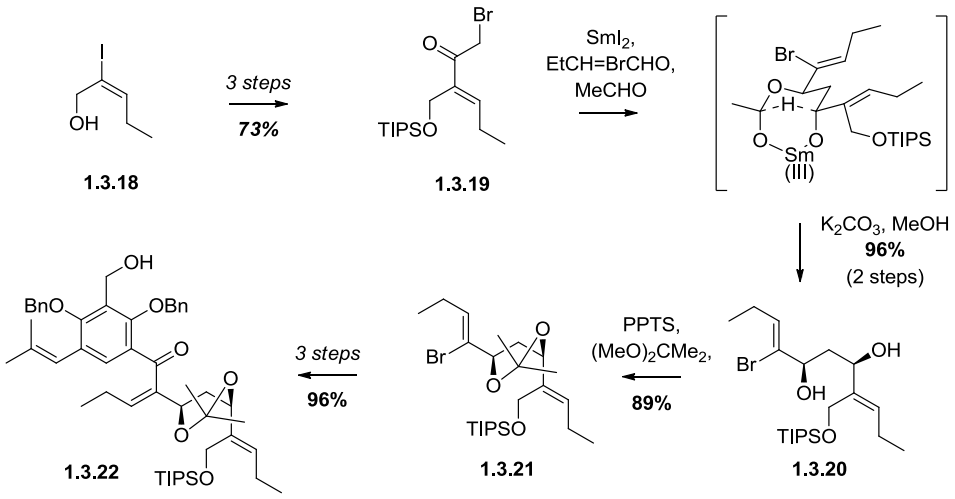
The strategy, although successful in confirming the stereochemistries of natural luminacins C_1 and C_2, was hindered significantly by the need to correct stereocenters at the C5' and C2' positions, significantly lowering the overall efficiency of the synthesis. The complicated protection strategy utilised also lowered the overall efficiency of the synthesis.

1.3.2 Synthesis of (±)-luminacin D with its 2' epimer (Wood 2002)[19]

Shortly afterwards, Wood and Crews *et al.* devised a diastereoselective synthesis of luminacin D.[19] The synthesis was concise (13 linear steps, 19 steps total), with a much increased overall yield in comparison to Tatsuta route (5.3% overall),[20] however this route only led to the racemate of luminacin D **1.3.31** (Schemes **1.5** – **1.7**).

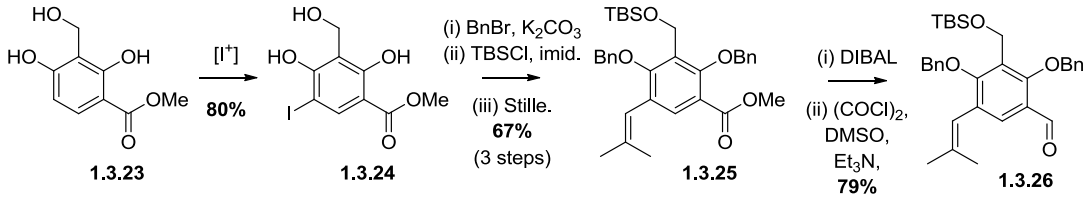
Using known vinyl iodide **1.3.18** (available in a two stage process from ethyl pent-2-ynoate), the synthesis begins with the protection of the allylic alcohol as the TIPS ether. This is followed by Heck coupling and bromination to yield the α'-bromo-enone **1.3.19**. The key step, a samarium(II) mediated tandem aldol-Evans-Tishchenko-type addition then occurs, constructing the C3',C5' *anti* hydroxyl relationship with complete diastereoselectivity. Protection of the diol **1.3.20** then gave the bromide **1.3.21**, which after lithiation was coupled to the aromatic fragment **1.3.26** leading to **1.3.22**.

Scheme 1.5 – Aliphatic synthesis



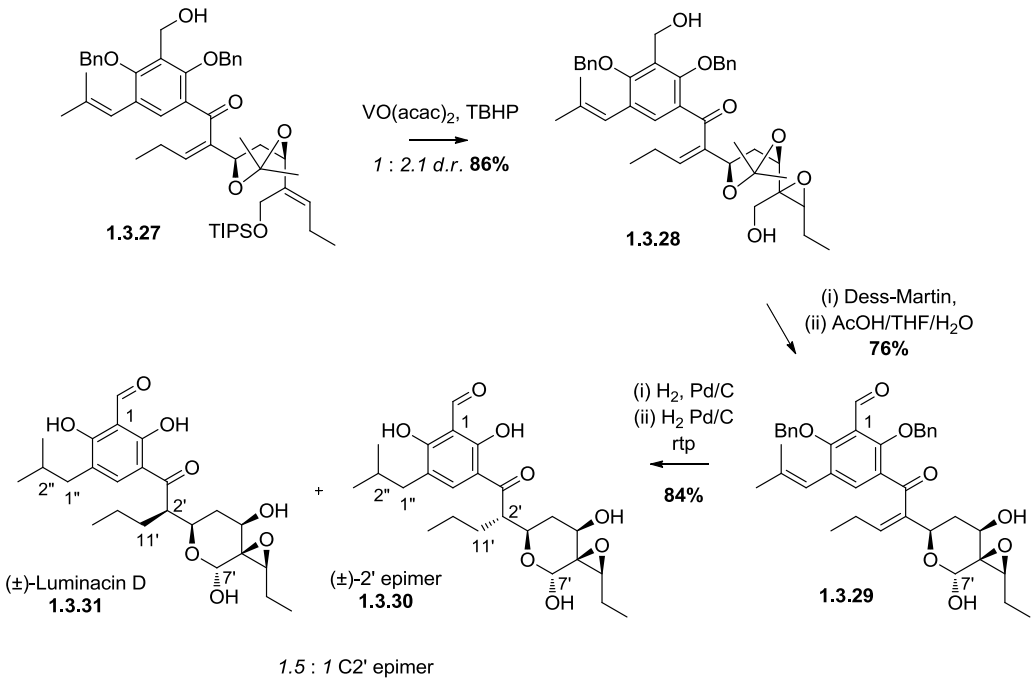
The aromatic fragment **1.3.26** was constructed from known triol **1.3.23** (1 step from commercially available starting material) initially by iodination at the C5 position. This iodide **1.3.24** was then sequentially protected, before subjecting to Stille coupling conditions, to give the alkene **1.3.25**. A reduction/oxidation sequence then gave the desired aromatic fragment **1.3.26**.

Scheme 1.6 – Aromatic synthesis



After oxidation and desilylation of the joined intermediate **1.3.27**, a poorly selective epoxidation gave a mixture of (regio-[C2', C11' & C6', C8'] and diasteromeric) epoxides (**1.3.28**). These were however separable, and oxidation of the terminal alcohols at the C1 and C7' position gave the hemiacetal **1.3.29** on acetonide hydrolysis. Sequential removal of the protecting benzyls and hydrogenation of the pendent alkenes at the C1", C2" and C2', C11' positions, yielded (±)-luminacin D **1.3.31** as a (*1.5* : *1*) mixture with the (±)-2' epimer **1.3.30**. The yield of the synthesis was thus compromised by the unselective epoxide introduction and reduction of the enone **1.3.29** at C2', C11' position, favouring luminacin D only marginally (*ca. 1.5* : *1*) to the C2' epimer for the latter process. Despite this, the initial stages of the synthesis gave good yields and it is arguably the most successful synthesis to date, though it does not produce enantio-enriched luminacin D.

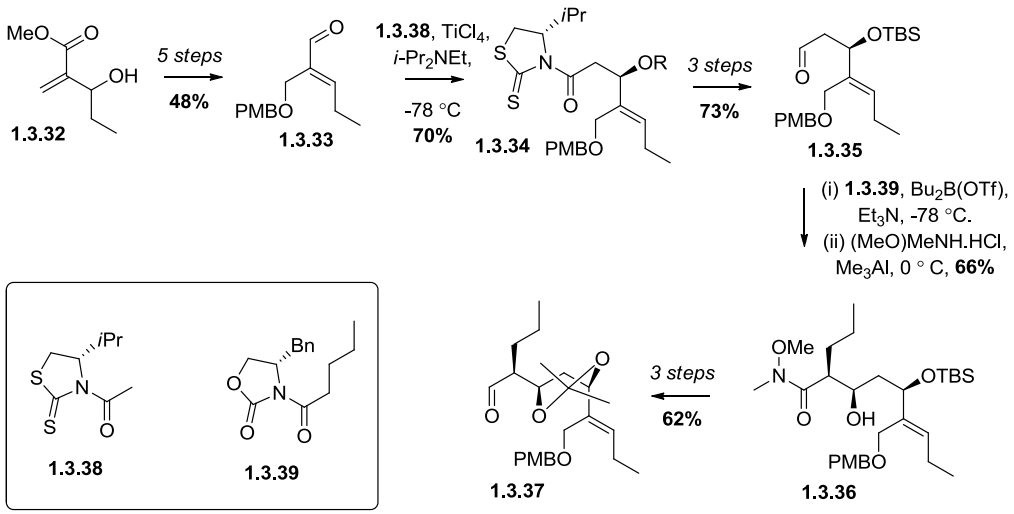
Scheme 1.7 – Finishing synthesis



1.3.3 The synthesis of luminacin D with its 6',8' epimer (Maier 2006)[21]

The first attempted enantioselective synthesis of luminacin D was the synthesis of Maier and Jogireddy. The strategy here was construction of the aliphatic portion through successive aldol reactions. Starting from the known Bayliss-Hillman adduct **1.3.32**, bond migration under Mitsunobu conditions gave the more substituted alkene. After hydrolysis and protection, the ester was reduced to an alcohol and this was then easily oxidised to the aldehyde **1.3.33**. Aldol reaction on this substrate then gave the non-Evans adduct **1.3.34**, which was protected and converted to the aldehyde **1.3.35**. Evans aldol, followed directly by transamination, gave the Weinreb amide **1.3.36**. After exchanging protecting groups for the acetal, the aliphatic aldehyde **1.3.37** was then afforded with DIBAL.

Scheme 1.8 – Enantioselective aliphatic synthesis

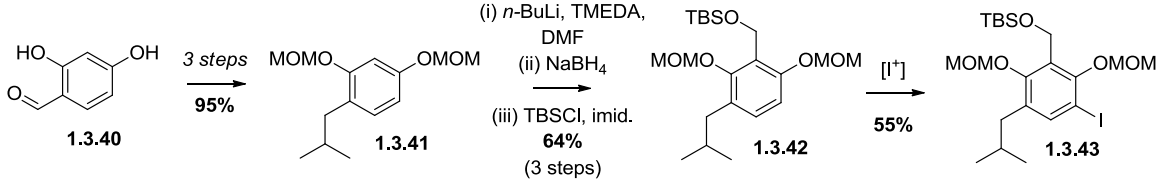


In the synthesis of the aromatic fragment, the 4-formylresorcinol **1.3.40** is protected as the *bis*-MOM ether, before Wittig reaction and hydrogenation yielded the protected 4-*i*-propylresorcinol **1.3.41**. Formylation of this substrate was followed by reduction and protection as the TBS ether **1.3.42**. *Ortho*-lithiation is followed by iodination to give the iodide **1.3.43**, ready for arylation of the aliphatic fragment **1.3.37**.

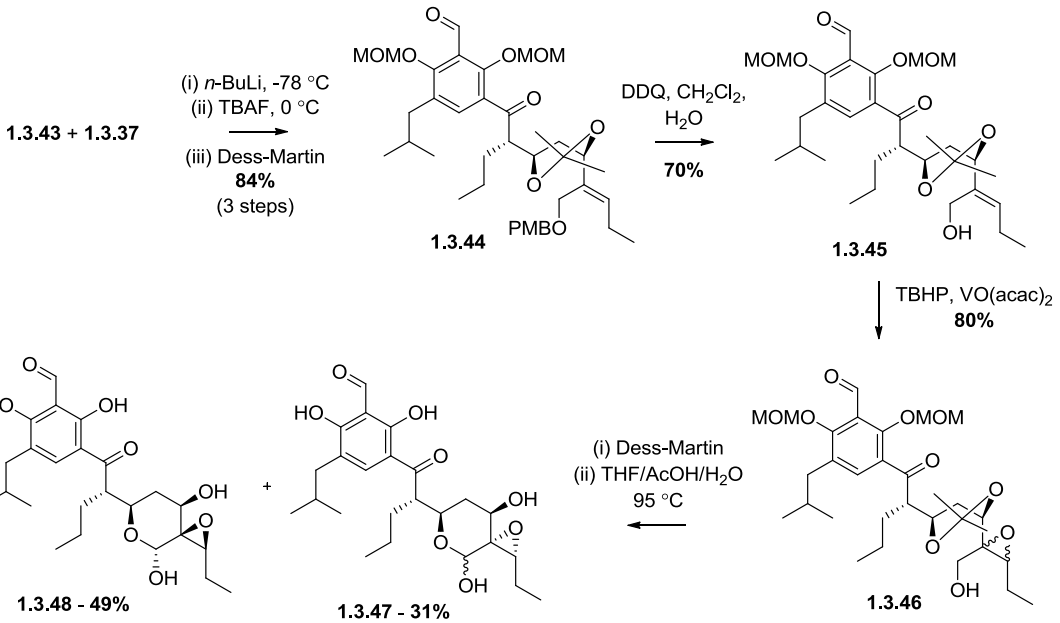
The last stages of the Jogireddy and Maier synthesis (Scheme **1.10**), involves subjecting the aliphatic aldehyde **1.3.37** to the lithiated iodide **1.3.43**. The product is desilylated, enabling

oxidation of the revealed benzylic alcohols, to aldehyde/ketone containing compound **1.3.44**. The PMB protection was then removed with DDQ, to give the alcohol **1.3.45**. Epoxidation then yields a mixture of the desired and undesired 6',8'-epimer, which is then carried through a Dess-Martin mediated oxidation to give the epimeric α-oxiranyl aldehyde mixture. After acetal hydrolysis, luminacin D **1.3.48** and the 6',8'-epimer **1.3.47** are obtained as a mixture (*3* : *2* respective ratio of isolated compounds). The 6',8'-epimer was isolated as a mixture of anomers.

Scheme 1.9 – Aromatic Synthesis



Scheme 1.10 – Final Stages – *Reagents & Conditions*



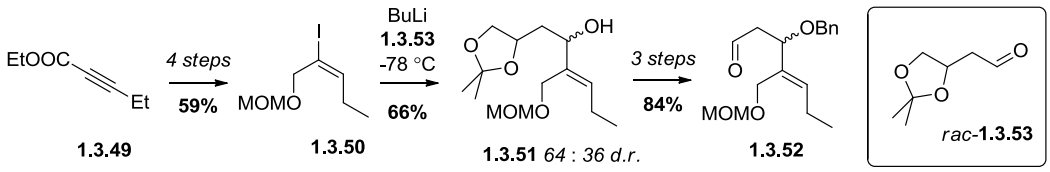
Although this enantioselective synthesis affords a 'luminacin D' like compound after chromatography, the ^{1}H and ^{13}C NMR does differ significantly from the data reported for the isolated natural material. No explanation is given by the authors for this discrepancy. In

general, the synthesis also suffers from major selectivity drawbacks, including, again, an unselective epoxidation reaction.

1.3.4 The synthesis of (±)-luminacin D with its 6',8' epimer (Shipman 2007)[22]

In 2007 Shipman *et al*. published a synthesis of *racemic* luminacin D and the 6',8'-epimer. It starts by a four step synthesis of the iodide **1.3.50** from ethyl 2-pentynoate **1.3.49** with a stannylation as the key step (Scheme **1.11**). Lithiation and reaction with aldehyde **1.3.53** gave an inseparable diastereomeric mixture of allylic alcohols **1.3.51**. The mixture was then benzylated, before the acetal was hydrolysed and the aldehyde **1.3.52** revealed by oxidation. In effect the poor diastereoselectivity is inconsequential as the synthesis is racemic.

Scheme 1.11 – Aliphatic synthesis

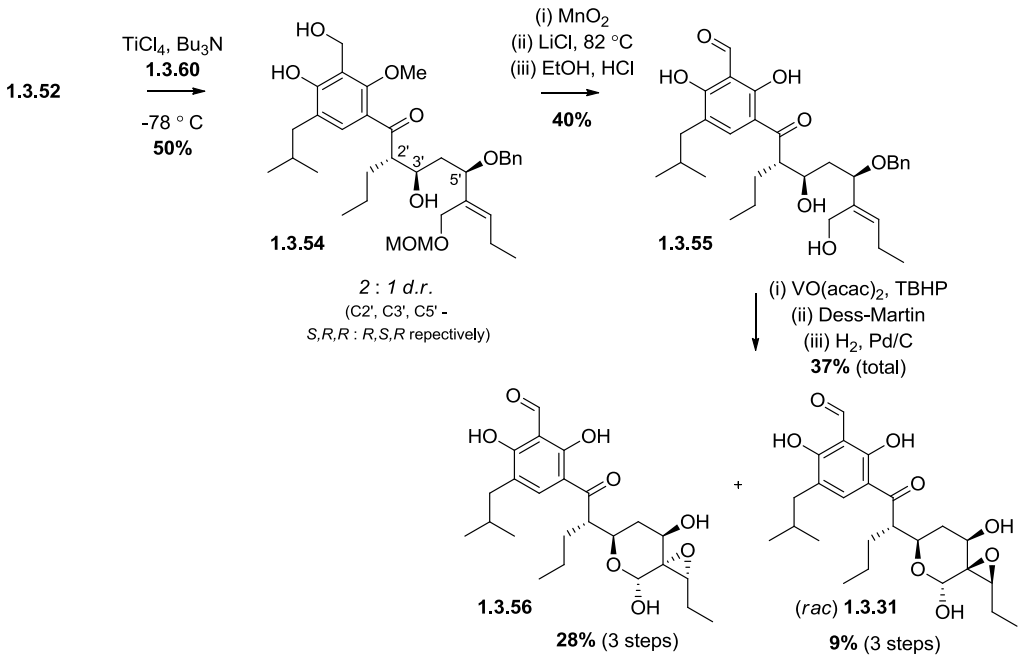


The addition of the aromatic fragment **1.3.60** to the aldehyde **1.3.52** is achieved through a *syn*-selective aldol condensation (Scheme **1.12**). A low selectivity is achieved for the desired 2',3'-*syn*-3',5'-*anti* **1.3.54** configuration, and the undesired stereochemistry is formed as the minor isomer. Oxidation of the benzylic alcohol is then followed by demethylation of the phenolic position and hydrolysis of the MOM ether to give the alcohol **1.3.55**. The allylic alcohol was then subjected to epoxidation conditions producing an inseparable mixture of epimers with the desired epimer as the minor compound (*3 : 1 d.r.*). However, diastereomeric separation was possible after oxidation of the primary C7' alcohol. Debenzylation of each epimer gave (±)-luminacin D **1.3.31** and (±)-6',8'-epimer **1.3.56**. In this paper, Shipman *et al*. describe the difficulty experienced in finding effective and selective conditions for the late stage epoxidation in the synthesis.

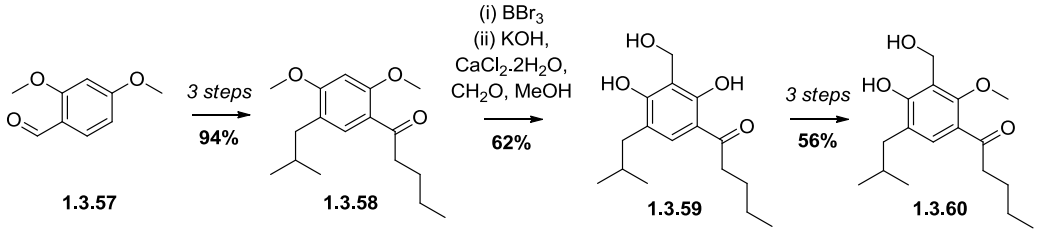
In Shipman's synthesis the aromatic ketone is generated in a similar manner to the method of Maier *et al*. From the methylated 4-formylresorcinol **1.3.57**, a Wittig reaction and then

subsequent hydrogenation, gave the 4-*i*-butylresorcinol (Scheme **1.13**). This substrate is then subjected to Friedel-Crafts conditions which gave the phenone **1.3.58**. Removal of the phenolic methyl groups then allows hydroxymethylation, to give triol **1.3.59**. To enable the single methylation at C2 hydroxyl, the acetonide was formed bridging the C1 and C6 hydroxyls and allowing selective methylation at the C2 position, hydrolysing the acetal under acidic conditions then gave the required aromatic fragement **1.3.60**.

Scheme 1.12 – Final Stages



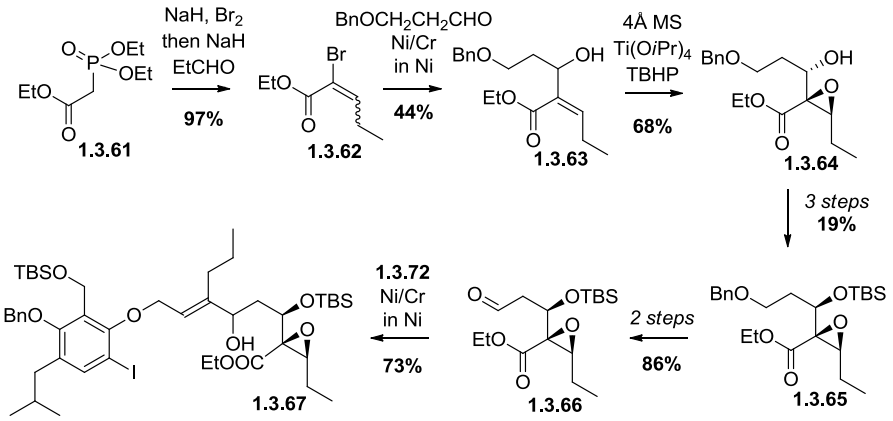
Scheme 1.13 – Aromatic synthesis



1.3.5 The most recent synthesis of (±)-luminacin D (Fang 2010)[15]

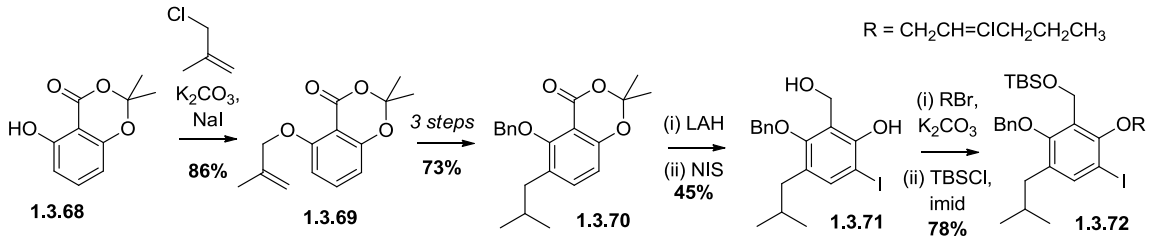
In early 2010, a patent was filed by Fang *et al*. with the title 'luminacin analogs and the uses thereof'. It contains a description of a route to (±)-luminacin D and analogs. The route starts from the phosphonate **1.3.61** and after bromination and Horner-Wadsworth-Emmons reaction, a mixture of alkene isomers **1.3.62** is obtained (Scheme **1.14**). This mixture is then added to the 3-benzyloxypropionaldehyde, to give the alcohol **1.3.63** (via an organonickel intermediate). The alcohol is then subjected to epoxidation conditions, to give the undesired epoxide diastereomer **1.3.64**. Mitsunobu inversion, hydrolysis and TBS protection then gave the desired protected epoxide diastereomer **1.3.65**, which after debenzylation and oxidation gives the aldehyde **1.3.66**. This fragment **1.3.66** is then coupled to the aromatic fragment **1.3.72** via Ni/Cr chemistry, to give the intermediate **1.3.67**.

Scheme 1.14 – Aliphatic synthesis (*racemic*)



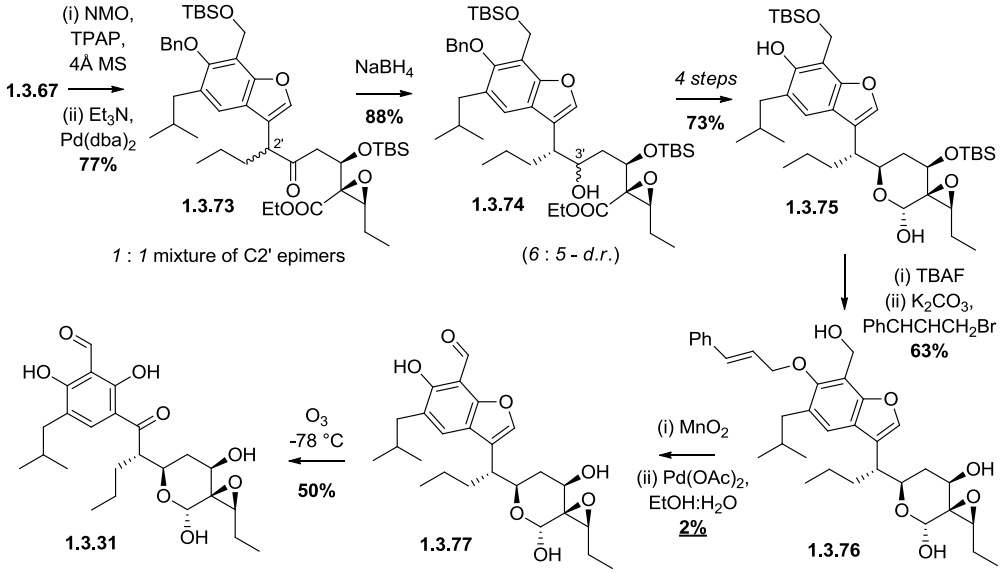
The aromatic fragment **1.3.72** is made from 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,4-dioxin **1.3.68** (Scheme **1.15**). From this commercially available material, the allylether **1.3.69** is made which is then thermally rearranged to the substituted intermediate. This is then easily reduced and benzylated to give protected compound **1.3.70**. Reduction and iodination on this intermediate, then gives the diol **1.3.71**. The aliphatic vinyl iodide is then added by forming a phenolic ether linkage with diol **1.3.71**, leaving the remaining primary alcohol which was then protected as the TBS ether to give pre-coupling aromatic intermediate **1.3.72**.

Scheme 1.15 – Aromatic synthesis



After a coupling of the aromatic **1.3.72** and aliphatic **1.3.66** fragments, oxidation and intramolecular Heck reaction, yields a (*1* : *1*) mixture of C2' epimers **1.3.73** (Scheme **1.16**) which were separated by chromatographic methods. The desired C2' epimer was then reduced to give a mixture of C3', hydroxyl epimers **1.3.74**, which were separated and the desired epimer carried through. This epimer was then hydrolysed, cyclised and the resultant lactone reduced to the lactol, giving the phenol **1.3.75** on benzyl deprotection. After TBS deprotection, a cinnamyl group was introduced at the phenolic position to give the intermediate **1.3.76**. The primary benzylic alcohol was then oxidised to the aldehyde and the isolated material was deprotected to give **1.3.77** in a very low yield over these two steps (2%). Ozonolysis revealed luminacin D **1.3.31**. The overall efficiency of this synthesis is very low, however early epoxide introduction did alleviate selectivity problems at this centre.

Scheme 1.16 – Finishing synthesis



1.3.6 Summary of past synthetic efforts

With the exception of the patent report, the epoxidation has always been realised at the final stages of previous syntheses. The result of this choice of strategy has been an unselective reaction which has been difficult to rationalise and hence optimise. Even given the many different approaches taken to this target, an effective route to enantioenriched luminacin D still seems elusive and this is perhaps indicative of the many challenges faced when synthesising such a densely functionalised molecule.

It also appears that a late stage introduction of C2' stereochemistry may be difficult to control (via diastereoselection). Both reduction tactics of Crews *et al*. and Heck introduction of Fang *et al*. struggled to control the stereochemistry at this position. Perhaps the most controlled synthesis to date was that of Tatsuta *et al.* to give the unnatural enantiomers of luminacin C_1 and C_2. However, the approach was long and the cost on the overall yield of the final product was great. A summary of the current strategies has been included for easy comparison (see Table **1.6**).

Table 1.6 – Summary of past synthetic efforts

Author *et al*. (Year)	Synthetic steps		Racemate or Enantiomer	Yield /(%)	Poor selectivity postions
	Linear	Total			
Tatsuta (2001)[20]	36	43	un-natural - Lum C	0.35	(C3') C2'
Crews (2002)[19]	13	19	racemate	5.3	C2', C6', C8'
Maier (2006)[21]	**20**	**27**	**Natural** (diastereomer?)	**2.1**	**C6', C8'**
Shipman (2007)[22]	15	22	racemate	0.64	C5', C6', C8'
Fang (2010)[15]	21	28	racemate	0.003	C2', C3'

The route of Maier *et al*. was also very promising and previous efforts within the Linclau group (not discussed here) used a similar approach to that used in the Maier synthesis.[21, 23] Again, the problem here was selectivity and a final specialised purification is required to separate the natural enantiomer from its C6',C8'-epimer. It is important to highlight that the

NMR spectral data of the isolated luminacin D from this route differed significantly from the obtained data of natural compound, isolated by Wakabayashi *et al*.[1]

Hence, the selective and concise synthesis of this target with incredibly interesting biological potential, is still a goal yet to be achieved. Such a synthesis must be also amenable to future diversification, if the possible pharmacological potential of luminacin analogues as selective SH3 proline rich protein-protein interaction disruptors is to be investigated fully.

1.4 General disconnection philosophy of the luminacin skeleton

The obvious disconnection of the aliphatic and aromatic fragment was to be one of the last transformations in our synthesis (Figure **1.8**). The aromatic and aliphatic moieties could then be assembled separately, conserving the number of linear steps. This is common to all current luminacin D syntheses.

In recognition of the unselective epoxidation conditions, a synthetic route was desired from an epoxide containing intermediate. In addition, the epoxide would then be used as a chiral handle for diastereoselective introduction of the next stereocentre. This is a unique feature compared to the previous luminacin D syntheses. This epoxide fragment **1.4.1** contains the proto-acetal, as an ester, and the pendent ethyl group (C9' – C10'). All chirality in the synthesis could then be constructed ultimately from the epoxide of this early fragment, itself obtained from the chiral pool via the sulfoxide stereochemistry.

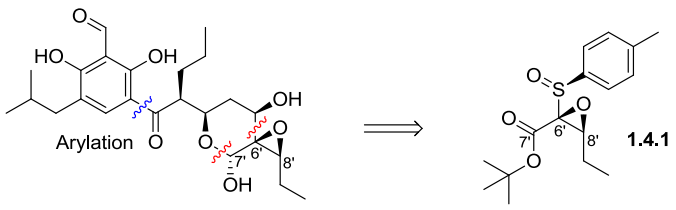


Fig 1.8 – Crucial disconnections in our synthesis of luminacin D

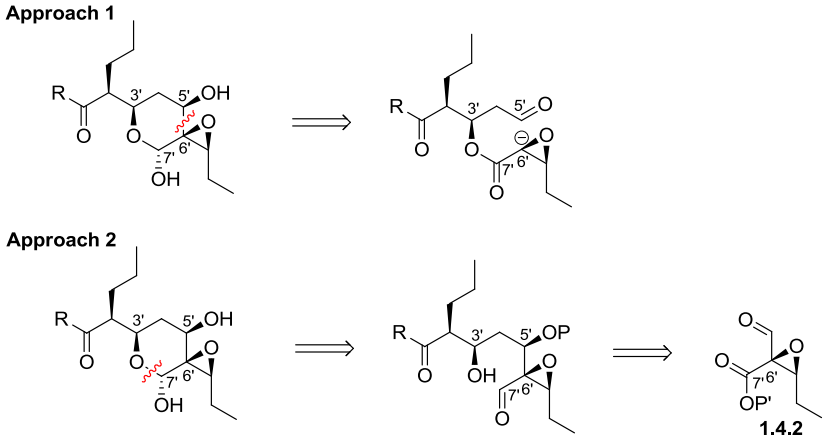


Fig 1.9 – The differences in the two major approaches investigated

Two very different approaches to the aliphatic fragment were then envisaged (Figure **1.9**). The first and ultimately unsuccessful approach (discussed in Chapter 3), involved formation of the proto-acetal (C7'-O-C3') bond after which the aliphatic fragment ring would then be formed through oxiranyl anionic cyclisation. The second approach was to involve formation of this C-O bond much later in the synthesis and instead create the C5'-C6' bond soon after epoxidation. It was proposed that from this chiral epoxide, in the form of key aldehyde **1.4.2**, the aliphatic fragment would be built diastereoselectively. The finer details of the synthetic route evolved much over the course of the synthesis, and for clarity, the changes which occurred in the choice of disconnection will be discussed, where relevant.

Chapter 2 Enantioselective preparation of the epoxide

2.1 Currently available epoxidation methods

To ensure an efficient synthesis, the epoxidation procedure selected for this functional group introduction would need to occur with good yield and high selectivity. There are a number of selective epoxidation reactions known, each requiring specific substrates and each having intrinsic advantages and disadvantages.

2.1.1 Epoxidation through additions to carbonyls

One strategy to epoxide formation is via addition of an ylide or carbenoid (Darzens reaction) moiety to a ketone or aldehyde, where the carbonyl oxygen atom becomes the associated oxiranyl oxygen (Fig **2.1**). The enantioselectivity in all these cases can be controlled by the reagent or substrate. When using ylides, *i.e.* sulfonium ylides, the reaction is often referred to as the Corey-Chaykovsky reaction. Many variations are known (where L/L* sufoxide ligands can be chiral or a chiral ring or bridgehead structure which can induce enantioselectivity – Fig **2.1**), although often the selectivity is low.[24] Most examples of these reactions require the reacting substituent (CH_2R") of the ylide to be aromatic or methyl (R" = H) and this helps stabilise the formed ylide. For this reason, the reaction is inappropriate for our purposes. The Darzens reaction enables an ester/amide with α-halo or α-leaving group substituent to be condensed with an aldehyde.[25] The selectivity of classical variants of this reaction depends entirely on substrate control however modern examples where the leaving group is a directing chiral sulfonium ylide are known.[26]

2.1.2 Epoxidations of alkenes - undirected

Perhaps the most successful strategy to prepare epoxides is through the oxidation of alkenes. For nucleophilic alkenes, reagents with electrophilic oxygen, like *m*-CPBA in the Prilezhaev reaction, are the most appropriate.[27] The Shi epoxidation is another example of electrophilic oxygen in an epoxidation. In this case the dioxirane of a modified fructose skeleton allows reagent control of the reaction selectivity.[28] Unfortunately however, both these reaction types have limited substrate range. The Shi epoxidation works best for

trisubstitued alkenes devoid of polar substituents like oxygen (however primary alkenes have been epoxidised with a modified catalyst). Both reactions would be ineffective on the α,β-unsaturated ester required for our route to luminacin D. Another example of this type of reagent controlled epoxidation is that of the Jacobsen-Katsuki epoxidation which uses a Mn(III) catalyst complex and bleach as the co-oxidant.[29] The original reaction worked best with *cis* alkenes but was later extended to trisubstituted alkenes.[30] The range of substrates accepted is somewhat broader compared to the Prilezhaev or Shi epoxidations, however the reaction still does not tolerate unprotected hetereoatoms or polarised/electron deficient alkenes.

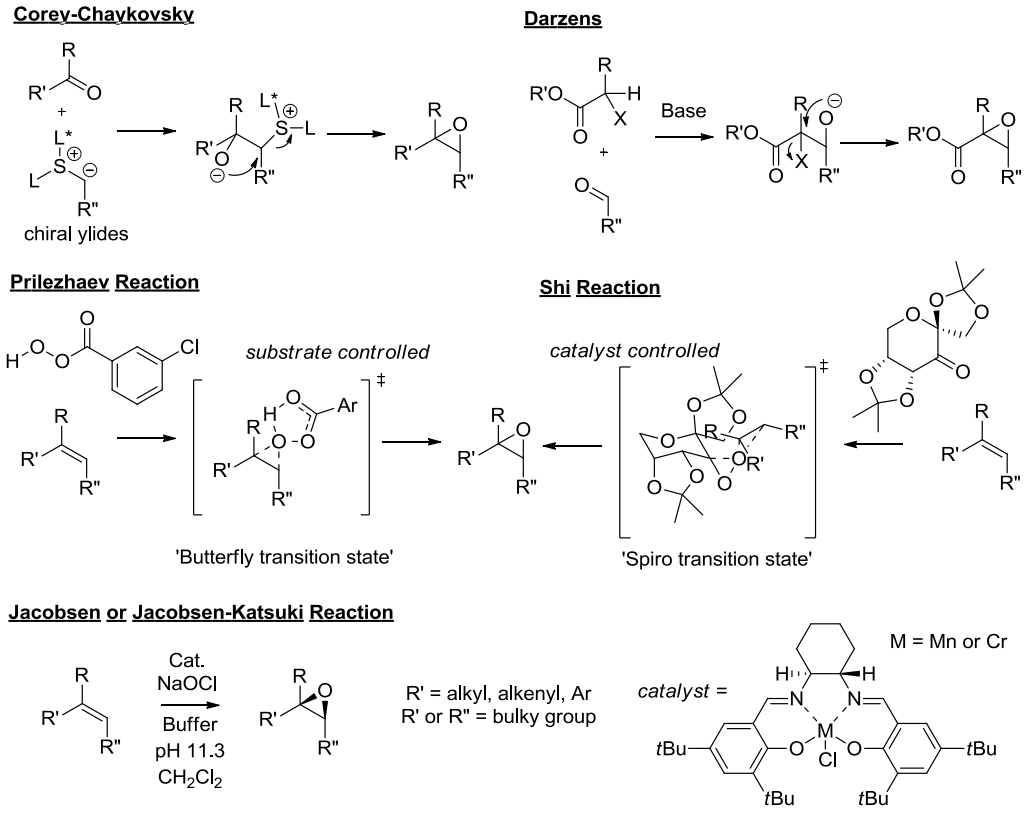


Fig 2.1 – Undirected epoxidation reactions

2.1.3 Epoxidation of alkenes – directed

When a polar substituent, such as a hydroxyl group, is present on the substrate a directed epoxidation can be carried out. There are many examples of these, involving transition metal catalysts which datively bond to the substrate. In the previous syntheses of luminacin D, the late stage epoxidation was mediated through such an epoxidation using a vanadium catalyst directed by the present allylic alcohol in the substrate (Fig **2.2**).[19, 22] (Directed epoxidations via hetereoatoms 3 or 4 bonds from the alkene are also known but bare little relevance here.[31])

One of the most popular of these directed reactions is the Sharpless epoxidation, (using $Ti(OiPr)_4$ and DET ligand). Although very effective, reaction times can be long and reaction mixtures complicated (Fig **2.2**).[32] We were however drawn to the work of De La Pradilla *et al*. who have shown that a chiral sulfoxide directing group on the substrate can direct the epoxidation of electron deficient alkenes with lithium *t*-butylperoxide with good diastereoselectivity.[33] The sulfoxide can then be further transformed in the synthesis. Importantly, the diastereomeric products would enable straightforward determination of epoxidation selectivity and can be prepared from a chiral pool material in enantiomerically pure form.

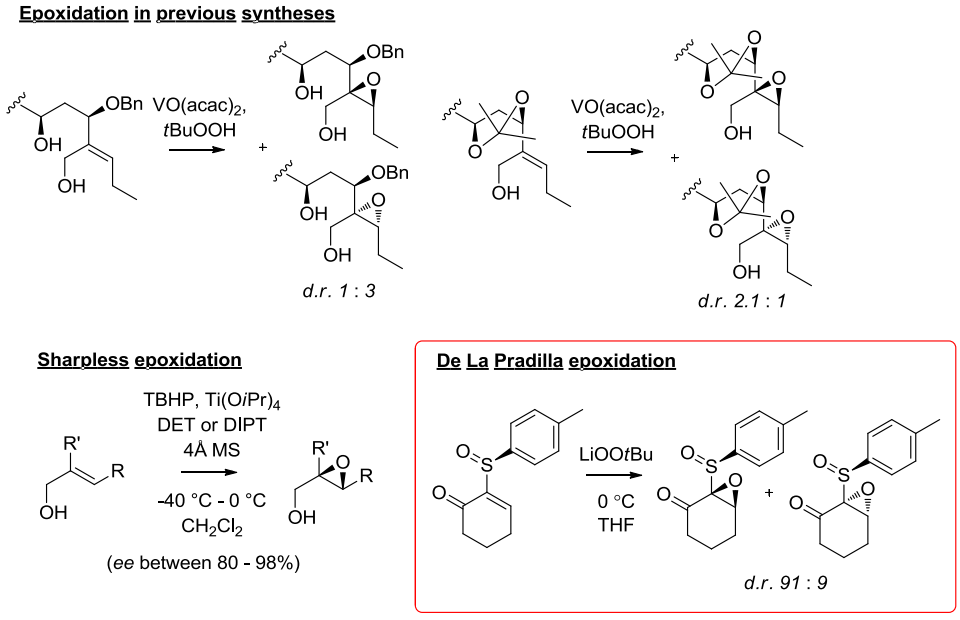


Fig 2.2 – Directed epoxidation reactions

2.2 Routes to the epoxide precursor 2.2.2.

2.2.1 Retrosynthetic analysis for routes (a) and (b)

With the aim of utilizing the procedure of De La Pradilla *et al*., access to the preceding alkene **2.2.2** was necessary, and a number synthetic strategies were envisaged (Fig **2.1**).[33] The first strategy involved synthesis of alkene **2.2.4**, which would then be carboxylated to arrive at the alkene **2.2.2** (route **a**). The second route (route **b**) would involve the synthesis of the α-sulfinylester **2.2.5** followed by its condensation with propionaldehyde to arrive at **2.2.2**.

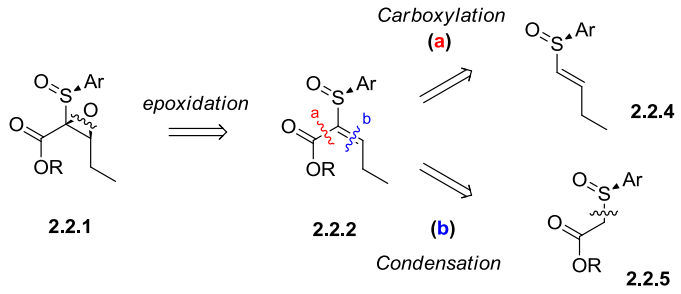


Fig 2.1 – Access to the epoxide **2.2.1**

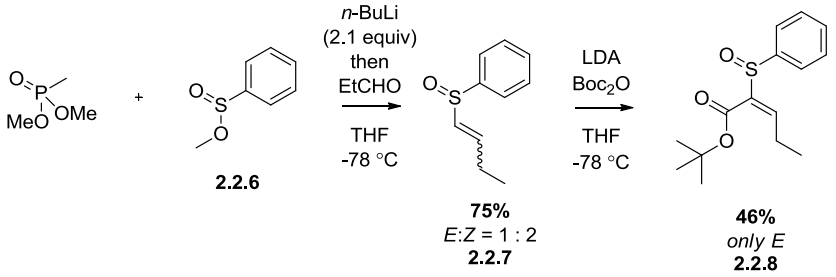
2.2.2 Route (**a**)

Folowing the work of Craig, route (**a**) was investigated with some good results (Scheme **2.1**).[34] The initial composite reaction, which forms the sulfinylmethylene phosphonate ester, followed by immediate Wittig reaction *in situ*, gave the vinylsulfoxide **2.2.7**, forming the separable *E* and *Z* isomers in good yield (75%) with an *E* : *Z* ratio of approximately *1* : *2*. Unlike the method of Craig, methyl phenylsulfinate ester **2.2.6** was used instead of *i*-propyl tolylsulfinate ester given the commercial availability of the methyl ester **2.2.6**.

After unsuccessful attempts at introducing the carboxylic acid onto the α carbon of the vinylsulfoxide **2.2.7** directly, it was found that deprotonation of the vinylsulfoxide **2.2.7** with freshly prepared LDA gave the vinyl anion in THF. This anion solution was then quenched with BOC anhydride to give the desired alkene **2.2.8** in modest yield. The configuration of the double bond in the product **2.2.8** was found to be independent of the configuration of the starting vinyl sulfoxide **2.2.7**. The yield of the reaction was found to be highly dependent on

the rate at which the vinyl sulfoxide **2.2.7** was added to the LDA solution with rapid additions leading to reduced yields. The highest yield obtained for this reaction was modest however (46%).

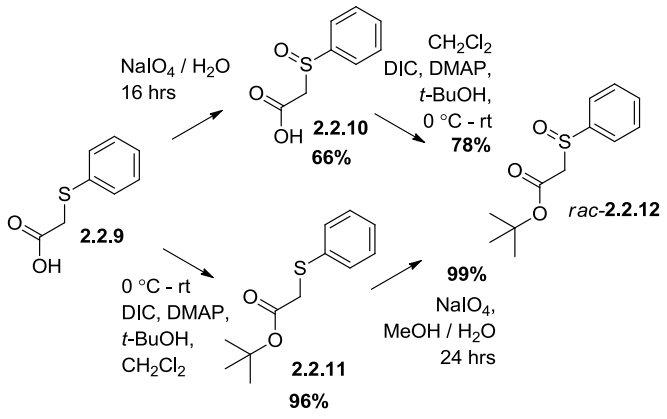
Scheme 2.1 – Route (**a**)



2.2.2 Route (**b**) –Synthesis of the α-sulfinylester **2.2.12**

The synthesis of α-sulfinylester **2.2.12** in route (**b**) initially was achieved by functionalization of phenylthioacetic acid **2.2.9** (Scheme **2.2**). This was accomplished through oxidation of the thiol **2.2.9** followed by esterification; or esterification and subsequent oxidation, with the latter sequence affording the highest yield of the sulfoxide **2.2.12**.

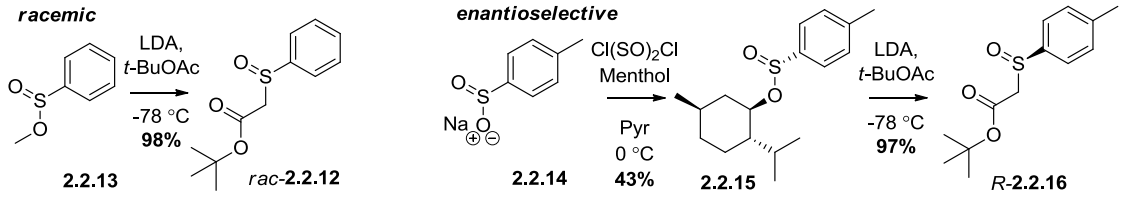
Scheme 2.2 – *rac*-Route (**b**)



Alternatively, addition of the preformed enolate of *t*-butylacetate to methyl phenylsulfinate ester **2.2.13** allowed access to the sulfoxide **2.2.12** in excellent yield (98%) directly (Scheme **2.3**). This reaction was easily amenable to the enantioenrichment of sulfoxide *R*-**2.2.16**, by

using the enantiopure menthol sulfinate ester **2.2.15**. This menthol derivative was prepared from sodium *p*-toluenesulfinate **2.2.14** or bought commercially and then reacted with the lithium enolate of *t*-butyl acetate. The reaction affords the enantiopure sulfoxide *R*-**2.2.16** in excellent yield (97%).

Scheme 2.3 – Enantioselective *R*-Route (**b**)



2.2.3 Route (**b**) – Condensation reaction to alkene **2.2.8**.

A number of conditions were then investigated on the ester **2.2.12** for the condensation reaction to give the alkene **2.2.8** and these are summarised in Table **2.1** (Scheme **2.4**). Conditions were inspired by precedent by Tankikaga *et al*. where a similar condensation had been achieved using Knoevenagel conditions.[35] Surprisingly however, yields of the desired alkene were found to be very low. With weaker bases, such as in entry 1, no reaction was observed. When a stronger base was used (entry 3), the product produced was then consumed by an ill-favoured pathway. From numerous other examples, it is known that this pathway involved the initial shift of the double bond from the α,β position to the β,γ position, after which a rapid and favoured [2,3]-sigmatropic rearrangement can occur (Scheme **2.5**).[36] This makes the precedent of Tankikaga *et al.* even more surprising as Knoevenagel conditions were low yielding and slow, with variations around known conditions failing to kinetically resolve the two products **2.2.8** and **2.2.17** (entry 5 - 8).[37] When NaH/$TiCl_4$ was used (entry 4), substantial decarboxylation was observed, inferred by the presence of phenylmethylsulfoxide in the crude. Ultimately the use of MeLi/$ZnCl_2$, optimised through minor modifications, yielded the best results (entry 9 -11), giving maximum yields of 28% of the alkene **2.2.8**, whilst supressing formation of the undesired γ-hydroxyl-α,β-unsaturated ester **2.2.17**.

Scheme 2.4 – Condensation reaction (Table **2.1**)

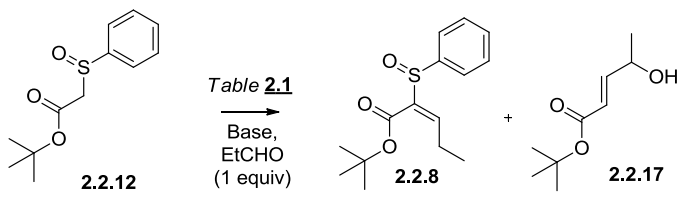
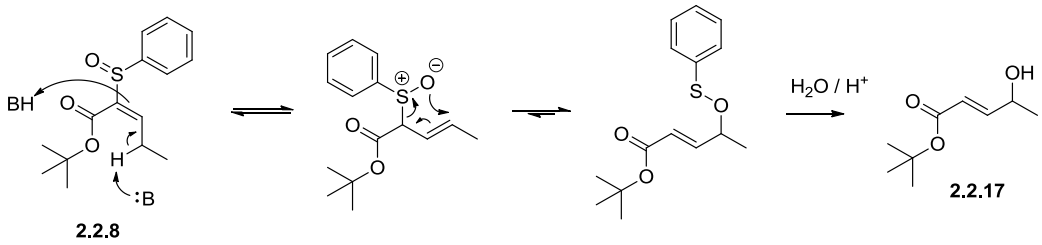


Table 2.1 – Optimisation of condensation reaction;

Entry	Reagents, Conditions & Solvent	Yield (%) **2.2.12**	**2.2.17**	**2.2.8**
1	Et_3N (as Solvent, ≈ 1 M), rt, 48 h	100	-	-
2	Piperidine (1 equiv) or imidazole (1 equiv), Pyridine, 100 ºC, >48 h	100	-	-
3	DBU (1 equiv), C_6H_6 (0.7 M), rt, 16 h	3	35	
4	NaH (1.5 equiv), $TiCl_4$ (1.5 equiv), THF (0.14 M), 0 ºC, 20 h	methylphenylsulfoxide		
5	Piperidine (1 equiv), acetic acid (1 equiv), MeCN, 0 ºC (24 h) – rt (48 h)	8[a]	0[a]	1[a]
6	Piperidine (0.05 equiv), acetic acid (0.01 equiv), MeCN, 0 ºC (24 h) – rt (48 h)	63[a]	1[a]	1[a]
7	Piperidine (0.1 equiv), MeCN (0.25 M), 0 ºC, 16 h	61	13	7
8	Piperidine (0.05 equiv), MeCN, 0 ºC (24 h) – rt (48 h)	8[a]	1[a]	1[a]
9	MeLi (1.2 equiv), $ZnCl_2$ (1.5 equiv), EtCHO (1.2 equiv), THF (0.14 M), 0 ºC – reflux, 20 h	-	57	10
10	MeLi (1.2 equiv), $ZnCl_2$ (1.5 equiv), EtCHO (5 equiv), Et_2O (0.14 M), 0 ºC – rt, 48 h	-	-	25
11	MeLi (1.2 equiv), $ZnCl_2$ (1.5 equiv), EtCHO (5 equiv), THF (0.14 M), 0 ºC – rt, 48 h	-	-	13-28

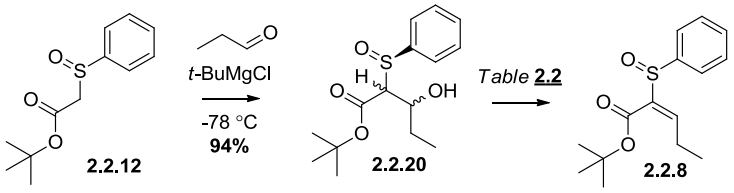
[a] Ratio by ^{1}H NMR (**2.2.12** : **2.2.17** : **2.2.8**)

Scheme 2.5 – Rearrangement of the alkene **2.2.8** to γ-hydroxyl-α,β-unsaturated ester **2.2.17**



2.2.4 *rac*-Route (**b**) – Addition then elimination to alkene **2.2.8**

Scheme 2.6 – Addition then elimination to alkene **2.2.8**



Given the poor yields of the trialled condensation reaction, and encouraged by the work of Mioskowski and Solladie, we sought to overcome these limitations by conducting the addition and elimination reactions in two separate steps.[38] The first addition reaction, using the magnesium enolate of ester **2.2.12** proceeded in good yield (94%). The elimination reaction was then optimised (*see* Table **2.2**) by choosing suitably inert solvents/reagents from the optimisation of the condensation reaction (Table **2.1**). It was found that adding a cooled excess of MsCl in pyridine facilitated the elimination in good yield (90%), with minimal formation of the γ-hydroxy-α,β-unsaturated ester **2.2.17**.

Table 2.2 – Optimisation of the elimenation reaction – ratio

Entry	Conditions	*E*:*Z* ratio[a]	Yield (**2.2.8**)	Ratio (**2.2.8** : **2.2.20** : **2.2.17**)[a]
1	AcCl (1.2 equiv), Pyridine (1.25 equiv), Et_2O, rt	-	< 30%[a]	Complicated mixture of products
2	MsCl (4 equiv), Et_3N (4 equiv), CH_2Cl_2, 0 ºC	*1* : *2*	< 30%[a]	*2* : *2* : *12*
3	MsCl (1.2 equiv), Pyridine (as solvent), 0 ºC	*4* : *1*	48%	*21* : *11* : *2*
4	MsCl (3 equiv), Pyridine (as solvent), 0 ºC	*8* : *1*	90%	*40* : *0* : *1*

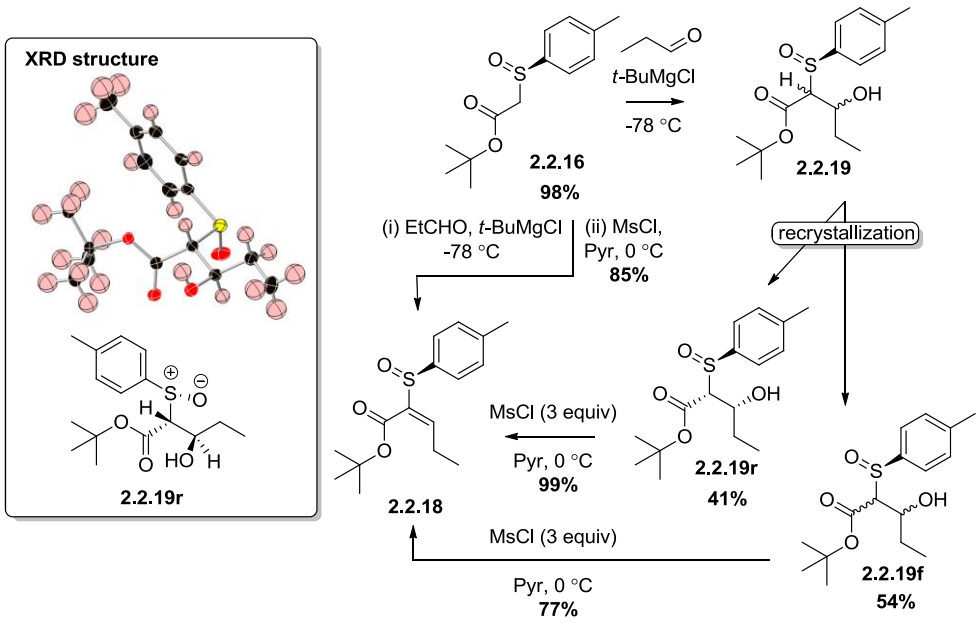
[a] measured by ^{1}H NMR.

2.2.5 *R*-Route (**b**) – Addition then elimination to alkene **2.2.18**

With a good route to the alkene **2.2.8** in hand, route (b) was completed by using the optimised addition / elimination procedures to obtain the enantiopure alkene **2.2.18**. The

obvious substitution of phenyl **2.2.8** for *p*-tolyl **2.2.18**, as the aromatic sulfoxide substituent in the enantioenriched substrate was made for availability reasons. Nevertheless, it would be equally possible to perform the sequence without this substitution. The sulfoxide **2.2.16** was reacted as the magnesium enolate with propionaldehyde, giving the addition product as a mixture of diastereomers **2.2.19m**. This mixture was recrystallized to a single diastereomer of very high purity **2.2.19r** and the filtrate recovered as a mixture of diastereomers **2.2.19f**. The structure of single diastereomer **2.2.19r** was analysed by XRD and the structure has been included in Scheme **2.7**.[3]

Scheme 2.7 – Finishing route (b) and XRD structure of single diastereomer **2.2.19r**



From the single diastereomer **2.2.19r**, the elimination could be achieved in near quantitative yield (99%), giving the alkene **2.2.18** exclusively as the *E* isomer. From the filtrate mixture **2.2.19f** was isolated. A lower yield of alkene **2.2.18** was obtained under the same conditions (77%) with baseline impurities observed in the ^{1}H NMR. Avoiding the recrystallization altogether and subjecting the un-separated mixture of diastereomers **2.2.19** directly to the

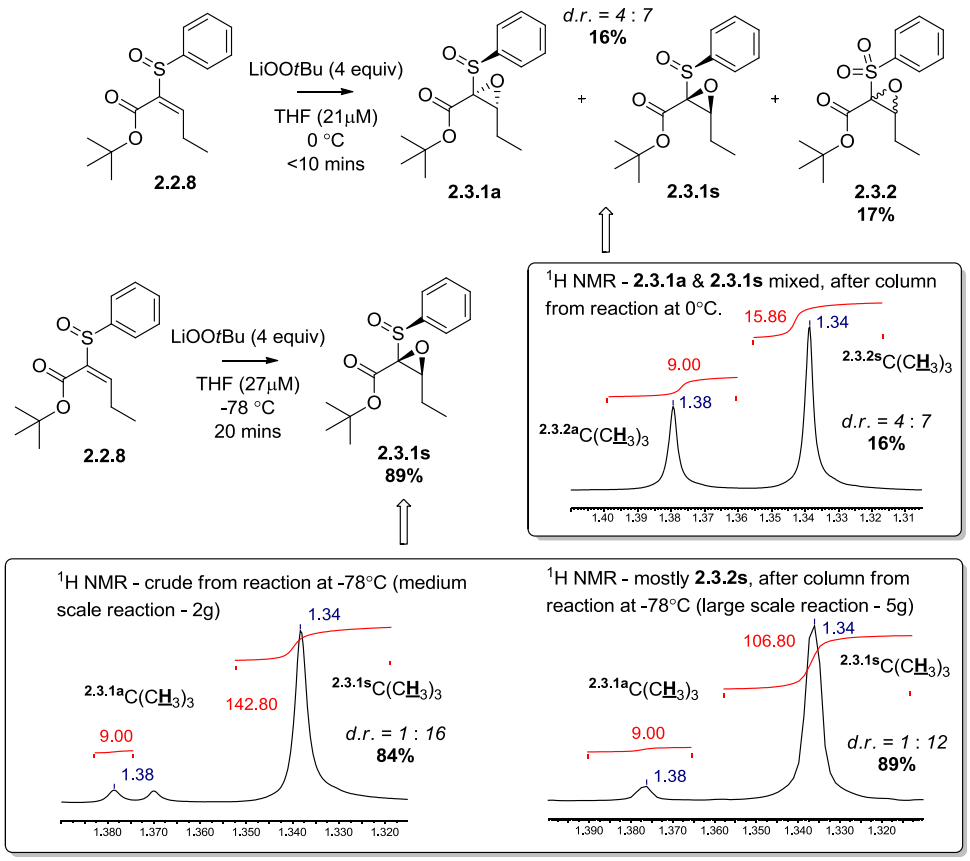
[3] **m** – Denotes mixture of isomers, **f** – denotes from the filtrate of recrystallization, **r** – denotes the recrystallized substance.

elimination conditions gave the most efficient preparation of the alkene **2.2.18** as the *E* isomer, it being formed in 85% yield over the two steps from the sulfoxide **2.2.16**.

2.3 Epoxidation & Proof of diastereoselection

2.3.1 Epoxidation

Scheme 2.8 – Epoxidation of the racemic alkene **2.3.1**

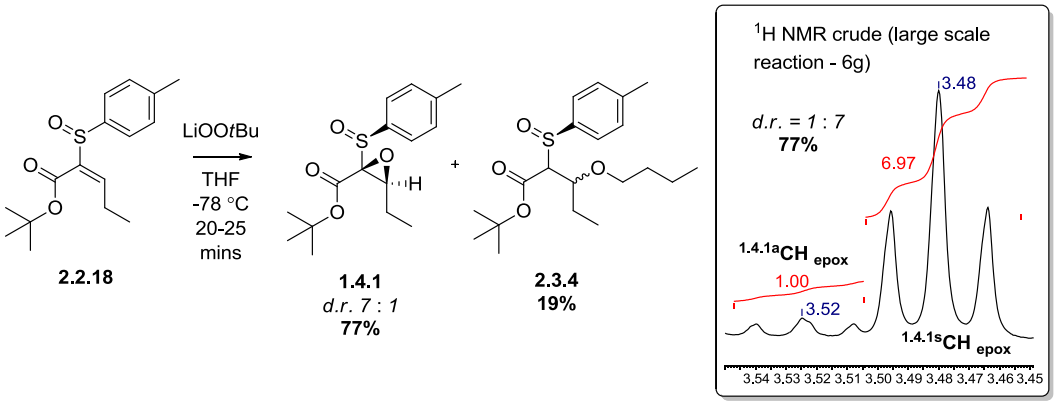


Initial investigations into the epoxidation were carried out on the *rac* phenyl substituted vinylsulfoxide **2.2.8**. Direct replication of the conditions of De La Pradilla *et al.* bestowed only a low yield and selectivity of the corresponding epoxide diastereomers **2.3.1s** and **2.3.1a**, as well as a significant proportion of the over oxidised sulfone epoxide **2.3.2**. On cooling of the reaction to -78 ºC, a good yield and very high diastereoselectivity was observed for the epoxide **2.3.1a** with very little or no sulfone detected. The reaction went to completion rapidly (<20 min), even at cryogenic temperatures, but on repetition of the reaction it was

found critical to ensure a high dilution was used in order to avoid sulfone formation and maintain high diastereoselectivity. The best conditions, diastereoselectivity and yield for this transformation are summarised in Scheme **2.8** with the associated supporting ^{1}H NMR expansions (for diastereoselectivities).

When the reaction conditions were applied to the *p*-tolyl substituted vinylsulfoxide **2.2.18**, lower diastereoselectivity was observed. This result was unexpected and no explanation for this discrepancy could be found. Strangely, lowering the reaction temperature (-95 ºC) further eroded diastereoselectivity for the desired epoxide **1.4.1s**. An inseparable diastereomeric mixture of an undesired sideproduct (**2.3.4**) was also recovered from the reaction (see Scheme **2.9**). This unusual product was thought to arise from Michael addition of lithium *n*-butoxide under the reaction conditions, where *n*-butoxide arose directly as a result of the reaction between TBLiP and any excess *n*-BuLi, before the addition of the alkene **2.3.4**. (TBLiP was preformed from *n*-BuLi and TBHP). The ^{1}H NMR proton environments used to determine diastereoselectivity for **2.3.1s** and **1.4.1s** were different for each compound. As in each of the compound's different spectra, different environment signals were obscured.

Scheme 2.9 – Epoxidation of the *R*-alkene **2.3.1**

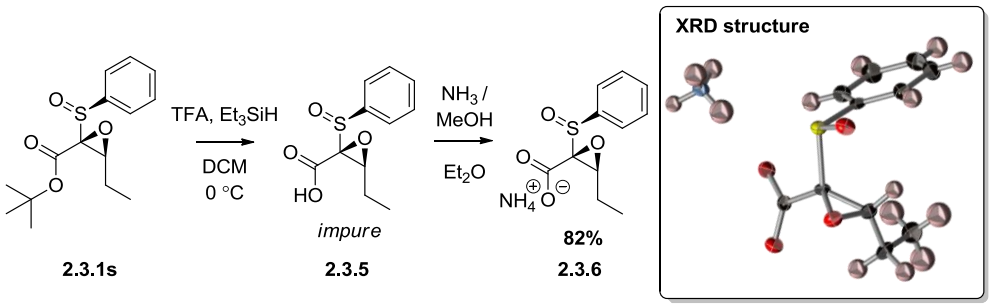


2.3.2 Derivation as the acid ammonium salt for XRD

Deprotection of the *t*-butyl α-epoxyester **2.3.1s** to the carboxylic acid **2.3.5** was examined and the best conditions given in Scheme **2.10**. Unfortunately, the free acid was difficult to purify and it was necessary to precipitate this as its ammonium salt **2.3.6** to isolate

pure compound. Crystallization of the precipitate enabled XRD studies which imparted crucial experimental proof of the epoxidation diastereoselection. This would enable the correct enantiomer of menthol sulfinate to be chosen to give the desired epoxide configuration for luminacin D in the sequence to afford **1.4.1s**.

Scheme 2.10 – Crystallization of epoxide ammonium salt **2.3.8**



Chapter 3 The oxiranyl anion and reactions of α-sulfinyl-α-epoxide esters

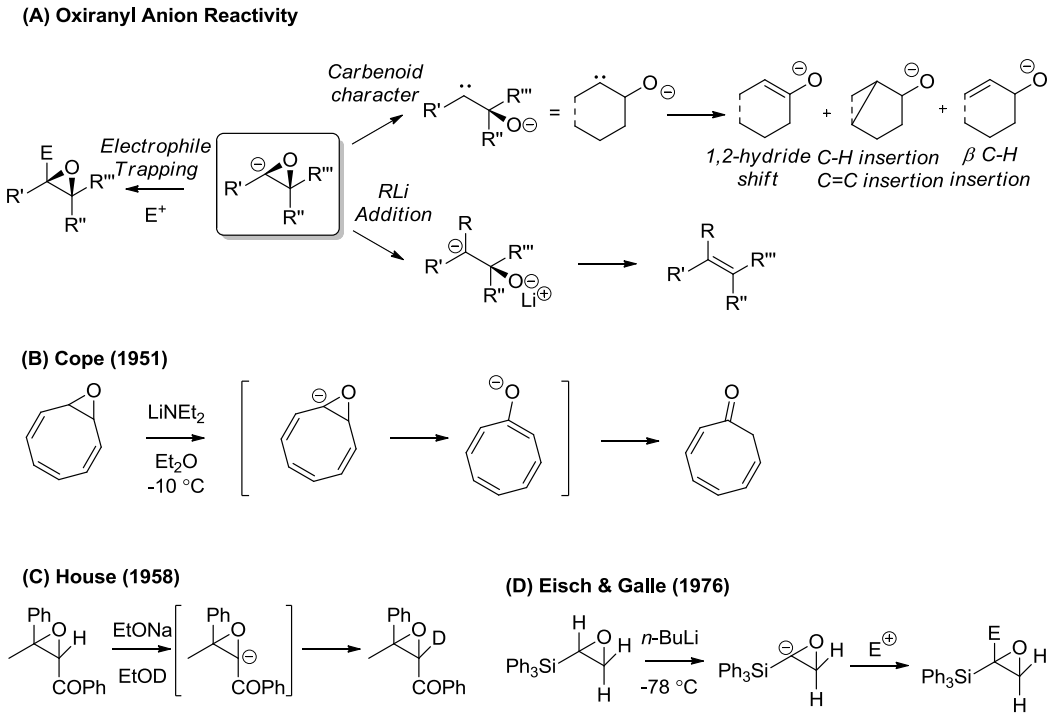
3.1 Reactivity of oxiranyl anions & the chemistry of sulfoxides

3.1.1 Oxiranyl Anions

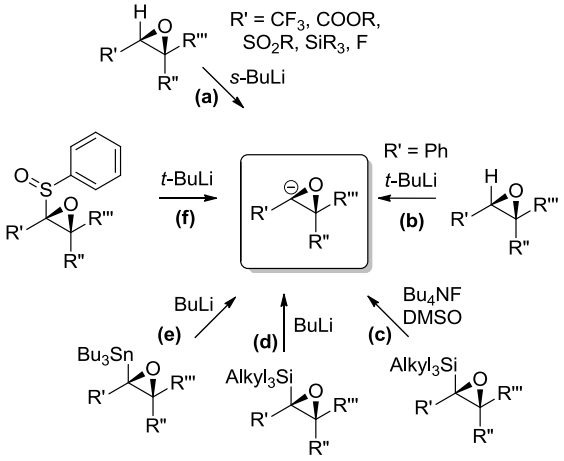
Oxiranyl anions or α-lithiated epoxides have seen much recent interest for their unusual reactivity and application in synthetic chemistry as carbenoids, nucleophiles, organometallic reagents and even as electrophiles (Scheme **3.1 – A**). Much of their chemistry has been extensively reviewed in recent years.[39] The existence of oxiranyl anions as transient intermediates was first hypothesised by Cope in 1951 to explain the base promoted formation of 1,3,5-cyclooctatrie-7-one from cyclooctatraene oxide (Scheme **3.1 - B**).[39c] Various experiments then followed notably by House *et al*. (**C**), who showed that in the presence of sodium ethoxide and deuterioethanol, deuterium was incorporated at the α position of an epoxide, and then by Eisch and Galle (**D**), who were the first to trap an α-lithiated silyl epoxide with an electrophile, generating a more substituted epoxide.[40] For the purposes of our synthesis, it is this nucleophilicity (electrophile trapping ability) exhibited by oxiranyl anions that is of interest.

Lithiated epoxides are readily available from a number of different precursors. They can be formed by direct deprotonation at the α-position or by lithium exchange reactions (Scheme **3.2**). Stabilising groups such as an α-sulfone, ester, trifluoromethyl or alkyl silane favour direct deprotonation (**a**) but it is also possible to directly deprotonate unstabilised epoxides under the correct conditions without excessive ring opening of the epoxide (**b**).[41] Perhaps a more unusual method for the generation of oxiranyl anions is the fluoride promoted desilylation of silyloxiranes which has been investigated by Chan, using similar conditions to those used for the deprotection of silyl protecting groups (**c**).[39b] Lithium-silicon (**d**) and lithium-tin (**e**) exchange are also possible, as well as desulfinylation (**f**), which is known to be incredibly rapid, and hence possible in the presence of other labile functional groups.[42]

Scheme 3.1 – Oxiranyl Anion Reactivity and early mechanistic insights



Scheme 3.2 – Oxiranyl Anion generation

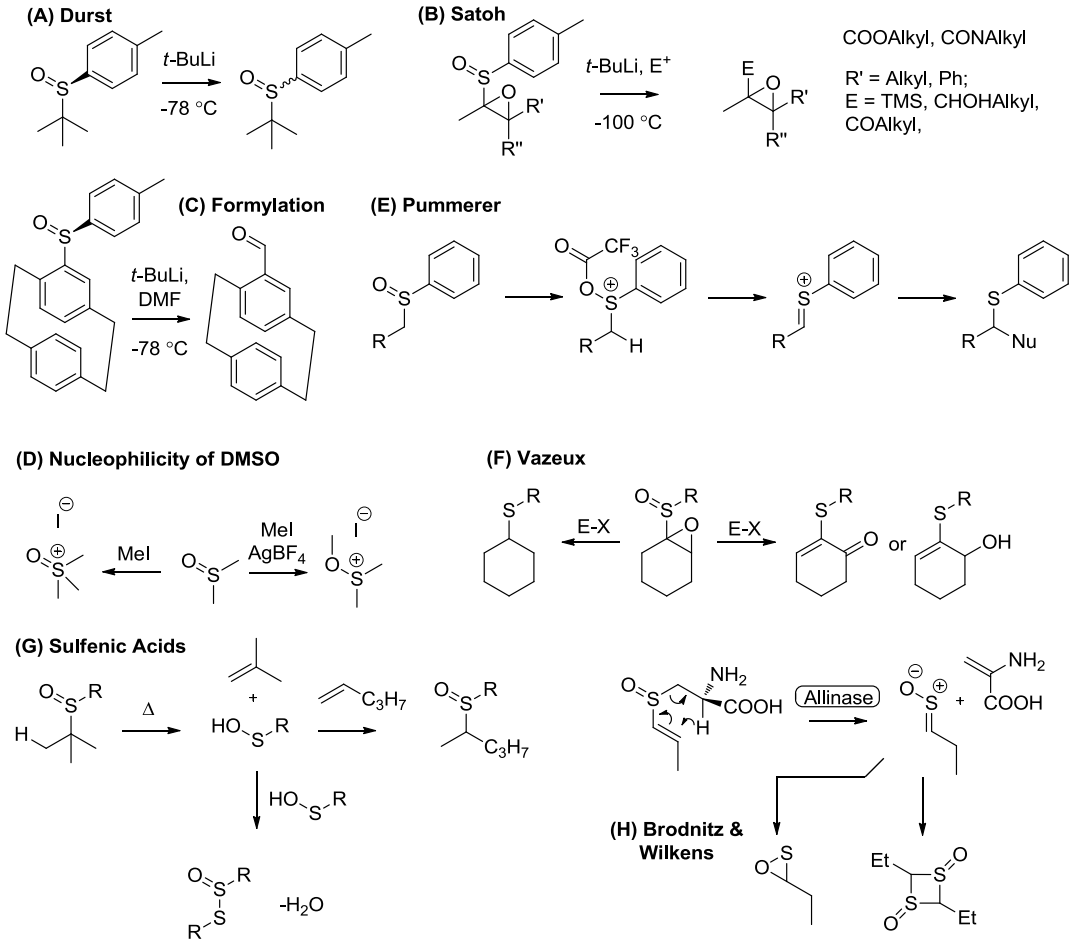


3.1.2 Sulfoxide chemistry

Sulfoxides readily react with organolithium and organomagnesium reagents, either by abstraction of α-protons or by cleavage of C-S bond by nucleophilic displacement at sulfur. For example, it was noted by Durst *et al*. that enantiopure *t*-butyl phenylsulfoxide rapidly racemizes in minutes, at -78 ºC, upon addition of *t*-butyl lithium, due to the latter effect

(Scheme **3.3** - **A**).[43] This chemistry is now commonly employed to generate anions and notable contributions have been made by Satoh *et al*. who have specifically generated many unstable oxiranyl anions and explored their chemistry (**B**).[39c, 42, 44] When a formyl donor is used, C-CHO bonds can be formed by generation of the carbanion from the corresponding C-SOTol, however α-epoxyaldehydes had not been generated in this manner before our investigations (**C**).[45] Sulfoxides are also thermally unstable and although chiral may racemize on heating or irradiation.

Scheme 3.3 – Sulfoxide reactions and reactivity



As well as displaying electrophilic character, sulfoxides readily act as nucleophiles. Their nucleophilicity can come from the lone pair on sulfur or oxygen, as exemplified when DMSO is reacted with either MeI alone or in the prescence of Ag^+ (**D**).[46] In the Pummerer rearrangement, activation of oxygen (the nuceophile) leads to its elimination by α-proton

abstraction. This leads to a transient thionium ion intermediate which is readily quench by addition of a nucleophile to the α carbon (**E**).[47] When the sulfoxide is flanked by an α-epoxy substituent, complications can occur depending on the electrophile and substrate, leading to a number of different pathways and products (**F**).[48] Electrocyclic cleavage of C-S bonds is also possible through [2,3]-rearrangement (as discussed in Scheme **2.2**) or protolytic β-elimination of sulfenic acids (**G**). In fact many other sulfoxide rearrangements, forming labile sulfurous compounds (including sulfines) occur naturally on splitting the bulb of an onion (or any member of genus *Allium*), and are the primary odour and lacrimation agents (**H**).[49] The reactivities displayed by sulfoxides may help in rationalising the various problems encountered when trying to derivate the sulfoxide **1.4.1** (Section **3.3**) when investigating approaches to luminacin D.

3.2 The story of two approaches

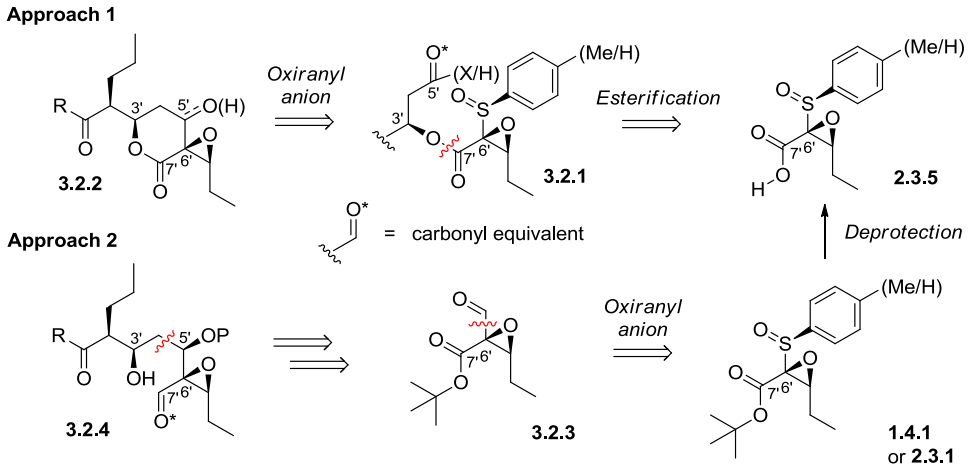


Fig 3.1 – Retrosynthetic disconnections of the two approaches (extended from Fig **1.9**)

As outlined in Section **1.4**, two separate approaches were investigated. In approach 1, it was anticipated that desulfinylation of a progenitor intermediate **3.2.1** would allow access to the cyclised aliphatic fragment of luminacin D **3.2.2**. This approach clearly would be dependent on very fast sulfoxide-lithium exchange, as well as ensuring carbonyl addition occurs as opposed to an ester elimination reaction. The intermediate **3.2.1** would then be available through the esterification of the α-epoxy-α-sulfinyl acid **2.3.5**, to the appropriate alcohol fragment bearing a β carbonyl equivalent. Approach 2 took a linear approach to the

problem, exchanging the sulfoxide (**1.4.1**) for the formyl group (**3.2.3**). The aldehyde **3.2.3** would then be further functionalised by diastereoselective addition.

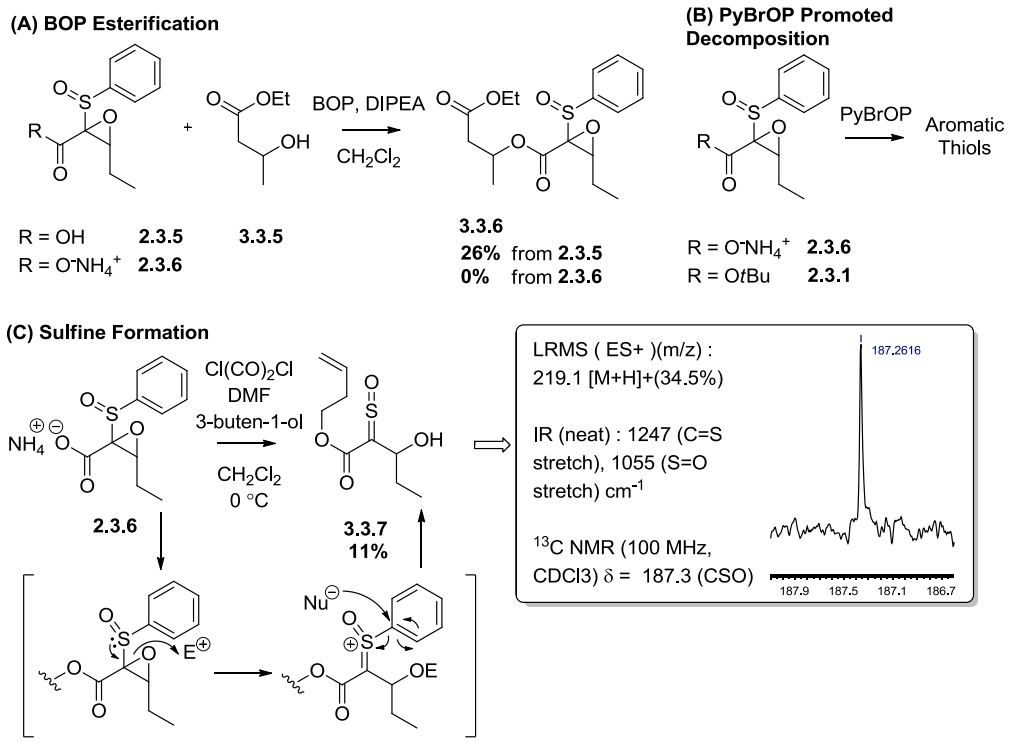
3.3 Attempted esterification reactions (Approach 1)

With the acid intermediate **2.3.5** available (see Section **2.3.2**), a number of different methods were tried to allow the formation of an ester (**3.3.6**) which may then be subsequently cyclised through intramolecular oxiranyl anion chemistry. The alcohol fragment chosen for investigative purposes was ethyl 3-hydroxybutyrate **3.3.5**, where in the real synthesis the 4 methyl group would contain the remainder of the luminacin D skeleton. Although a number of coupling conditions and reagents were tested (DIC, HATU, PyAOP, PyBrOP, BOP), none gave the desired ester in high yield. The starting acid was rarely recovered in these trials and it was assumed this was due to decomposition as the crude mixtures were often complex. A frequently isolated compound in these reactions was phenylsulfenic acid (amongst other pungent aromatic compounds). When the salt **2.3.6** was treated with PyBrOP decomposition was observed. This was also the case when the ester **2.3.1** was subjected to the same conditions (Scheme **3.4 – B**). This hinted towards cleavage of the S-C_{epox} bond by activation of the sulfoxide with these electrophilic reagents.

The best result from this trial was when using BOP coupling conditions as this gave low yield of the desired ester **3.3.6** (Scheme **3.4 - A**). It was found that the product **3.3.6** degraded over time back to the acid, highlighting the difficulty of this esterification procedure. The inherent tendency of the reaction product to undergo E_{1CB} elimination is another likely source of the low observed yields. When substituting the acid **2.3.5** for the ammonium salt **2.3.6**, which was substantially purer, no product was recovered using the same BOP esterification conditions. Again increasing the basicity of the reaction mixture is likely to promote an E_{1CB} reaction (**A**). Yamaguchi esterification conditions (activation as the mixed anhydride) from the acid **2.3.5** also did not lead to the correct product (no reaction) and Mitsunobu conditions using a substitute ammonium salt gave very low yields (<10%). Attempts to make the acid chloride from the ammonium salt **2.3.6** *in situ* with oxalyl chloride led to an unusual compound thought to be the sulfine **3.3.7** (Scheme **3.4 - C**). In this reaction ethyl 3-hydroxybutyrate (Scheme **3.1**) was substituted for 3-buten-1-ol as the alkene could serve as a carbonyl equivalent (giving the

aldehyde after ozonolysis). Although uncommon, this functionality is known in the literature. Its mechanism of formation under the reactions condition was unknown and but was speculated to involve a number key features. It is likely that the mechanism involved pre-activation of the epoxide and involvement of the sulfur lone pair to open the epoxide. The possible pentavalent sulfinium cation could then activate the phenyl ring for *ipso* nucleophilic substitution, which would then lead to the sulfine **3.3.7**. The obtained data does support the isolation of this compound.[50] (Scheme **3.1 - C**)

Scheme 3.4 – Esterification using coupling reagent BOP ([a] – Me group would be exchanged for the rest of luminacin D skeleton in the real system, see Fig **3.1**, approach 1)



3.4 Oxiranyl anion reactions

3.4.1 Intermolecular variants

The lack of success with approach 1 (Fig **3.1**) prompted a rethink of the strategy towards luminacin D. Before approach 2 (Fig **3.1**) was conceived, the idea of intermolecular addition of the oxiranyl anion of the ester **2.3.1** directly to the aliphatic system was also

investigated (see Fig **3.2** - approach 1 reordered). Using simple propionaldehyde as a mimic of the aliphatic luminacin D precursor a complex mixture of products was recovered. To simplify the reaction, aromatic aldehydes *p*-methoxybenzaldehyde and *p*-fluorobenzaldehyde were used and the results of this study have been tabulated in Table **3.1**. No products were recovered where the aldehyde had reacted directly with the oxiranyl anion (**3.4.1**). Rather, *t*-butylphenylsulfoxide **3.4.2** and ortholithiation addition products of *t*-butylphenylsulfoxide **3.4.4**, as ≈ *1* : *1* mixture of diastereomers were obtained. It was found that a couple of electrophiles were able to trap the oxiranyl anion under the trialled conditions. Notably, TMSCl gave a moderate yield of the TMS substituted epoxide **3.4.4** (Scheme **3.5**) while DMF gave aldehyde **3.2.3** on workup (discussed in Section **3.4.2**). Potential use of the TMS substituted epoxide as an oxiranyl 'anion' precursor was not investigated further.

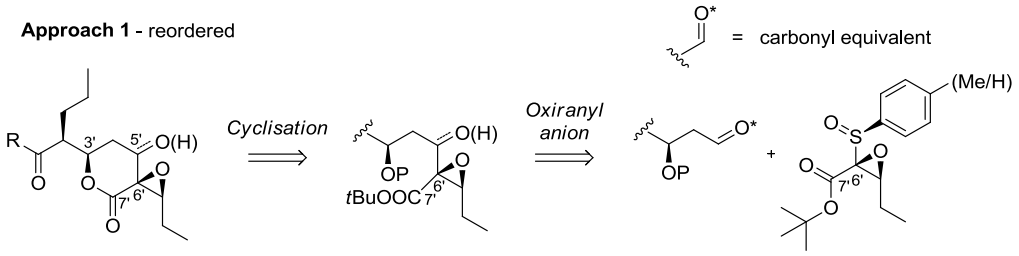


Fig 3.2 – Retrosynthesis - Intermolecular oxiranyl anion additions in the synthesis of luminacin D

Scheme 3.5 – Intermolecular oxiranyl anion additions

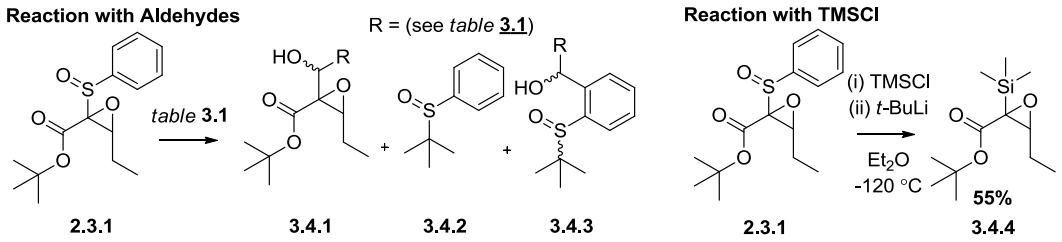


Table 3.1 – Intermolecular additions of oxiranyl anions to aldehydes (Scheme **3.2**).

Entry	Reagents, Conditions & Solvent	R =	Yield /(%) **3.4.1**	**3.4.2**	**3.4.3**
1	*t*-BuLi (2.5 equiv), **2.3.1** (1 equiv), RCHO (2.5 equiv), THF, -100 ºC	CH_2CH_3	Inseparable mixture		
2	*t*-BuLi (2.5 equiv), **2.3.1** (1 equiv), RCOOMe (1 equiv), THF, -100 ºC	C_6H_5	Inseparable mixture		
3	*t*-BuLi (2.5 equiv), **2.3.1** (1 equiv), RCHO (2.5 equiv), Et_2O, -120 ºC	4-FC_6H_4	0	49	26
4	*t*-BuLi (2.5 equiv), **2.3.1** (1 equiv), RCHO (2.5 equiv), Et_2O, -120 ºC	4-$MeOC_6H_4$	0	63	29

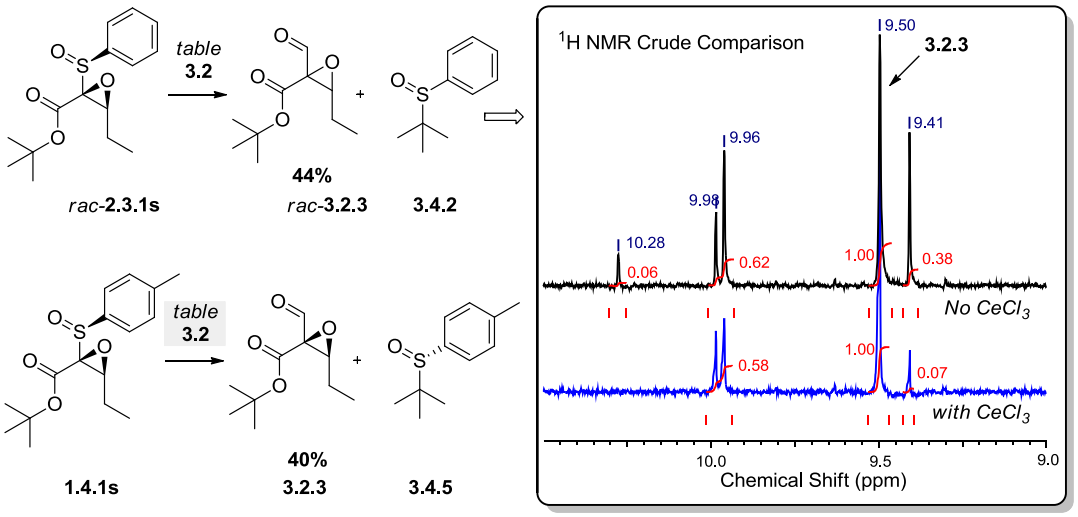
3.4.2 Oxiranyl anion formylation (Approach 2)

Preparation of aldehyde *rac*-**3.2.3** from ester **2.3.1** allowed us to examine our approach 2 strategy (Fig **3.1**) towards the luminacin aliphatic fragment. From this aldehyde **3.2.3**, nucleophilic additions would install the remaining skeleton and stereocentres diastereoselectively. The initial reaction, using un-optimised conditions, gave a low yield of the desired aldehyde *rac*-**3.2.3** (after purification) (Table **3.2** - entry 2). Knowledge present in the Linclau group an allylation reactions, made the formation of aldehyde **3.2.3** promising despite the modest yield (discussed in Chapter **4**). To increase the nucleophilicity and moderate the reactivity of the oxiranyl anion, a lanthanide salt ($CeCl_3$) was added, leading to an increase in selectivity for the desired aldehyde **3.2.3** (see Scheme **3.6**, entry 4).[51] However this posed problems during reaction workup as aqueous quenching gave thick emulsions which proved difficult to separate. This was overcome by exchanging for a methanol based quench, allowing easy filtering of the cerium salts (entry 5).

t-Butylmagnesium chloride also gave the desired aldehyde **3.2.3** in low yield but with substantially less side products (entry 3 - further systematic optimisation of the reaction with *t*-butylmagnesium chloride here may lead to better conditions). Also, magnesium metal (with

LiCl) did not yield any of the target product **3.2.3** (entry 1) under Knochel conditions.[52] *t*-Butyllithium, in combination with $CeCl_3$, was found to be the best reagent for the oxiranyl anion reaction under the studied conditions, giving the highest yield (entry 5). There were a number of associated difficulties with the reaction arising from the volatility of the aldehyde **3.2.3** and substantial efforts were made to reduce losses from this factor during the workup and purification, these included keeping the compound under low vacuum and temperature during evaporation of solvent and the use of pentane/diethylether column eluents. Attempts to purify the reaction mixture by distillation were unsuccessful due to the contamination by a number of other volatile reaction side products. The best conditions for the reaction were found when the reaction duration was reduced down to 5 min and the quantity of $CeCl_3$ used in the reaction reduced, but even these conditions only gave a modest yield. The reaction conditions trialled are summarised in Table **3.2** for the racemic aldehyde **3.2.3** (Scheme **3.3**).

Scheme 3.6 – Formylation of the oxiranyl anion



The conditions optimised on the racemic ester **2.3.1** were then translated to the enantioenriched, *p*-tolyl ester **1.4.1** and the reaction conditions further fine-tuned. Direct repetition of the best conditions for the racemic ester **2.3.1** on the single enantiomer **1.4.1** gave an initial drop in yield (entry 6), this was offset by a drop in equivalence of $CeCl_3$ to sub-stoichiometric quantities bringing the yield back to comparable levels (entry 9 - 40%). This affect was thought to arise from improved processing of the quenched crude reaction mixture. Exchange of $CeCl_3$ for $Yb(OTf)_3$ gave no improvement in reaction performance (entry 8),

similarly using a more hydrophobic formyl donor (thought to give more anhydrous conditions), *N*-formylpiperidine did not lead to a better reaction (entry 7). The reaction again suffered from scaling problems, showing a drop in yield on up-scaling. The yield for the *p*-tolyl substituted sulfoxide **3.4.5** under the optimised conditions varied between 32 – 40%.

Table 3.2 – Optimisation of formylation reaction, from esters **2.3.1s** and **1.4.1s** respectively.

Entry	Reagents & Conditions	Yield / (%) Aldehyde (**3.2.3**)	Sulfoxide (**3.4.2** or **3.4.5**)	Recovered SM **2.3.1s**
1	**2.3.1** (1 equiv), Mg (2.5 equiv), LiCl (1.25 equiv), DMF (1.5 equiv), THF, -78 ºC.	0	-	-
2	**2.3.1** (1 equiv), *t*-BuLi (2.5 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - NH_4Cl sat.)	3	26	4
3	**2.3.1** (1 equiv), t-BuMgCl (2.5 equiv), DMF (2 equiv), THF, -78 ºC.	13	24	34
4	**2.3.1** (1 equiv), *t*-BuLi (2.5 equiv), $CeCl_3$ (2 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - NH_4Cl sat.)	35	-	-
5	**2.3.1** (1 equiv), *t*-BuLi (2.5 equiv), $CeCl_3$ (2 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - MeOH)	44	-	-
6	**1.4.1** (1 equiv), *t*-BuLi (2.5 equiv), $CeCl_3$ (2 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - MeOH)	27	-	-
7	**1.4.1** (1 equiv), *t*-BuLi (2.8 equiv), $CeCl_3$ (0.8 equiv), *N*-formylpiperidine (3 equiv), Et_2O, -120 ºC. (quench - MeOH)	32	-	-
8	**1.4.1** (1 equiv), *t*-BuLi (2.5 equiv), $Yb(OTf)_3$ (0.8 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - MeOH)	33	-	-
9	**1.4.1** (1 equiv), *t*-BuLi (2.5 equiv), $CeCl_3$ (0.8 equiv), DMF (2 equiv), Et_2O, -120 ºC. (quench - MeOH)	40	-	-

Despite the shortcomings of the desulfinylation/formylation reaction, approach 2, where the epoxide is introduced diastereoselectively by means of an enantiopure sulfoxide was the best and chosen strategy. This enabled further diastereoselective additions which eventually led to

the luminacin D synthesis, the first of which was the allylation reaction promoted by magnesium bromide (Chapter 4).

Chapter 4 Aldehyde Allylation

4.1 Diastereoselection in carbonyl additions (Fig 4.1)

The diastereoselection of nucleophilic additions to carbonyl compounds are greatly affected by α-chiral substituents on the carbonyl component and many models have been proposed to rationalise the experimental observations of such 1,2-asymmetric induction reactions. All of the models proposed prioritise specific physical phenomena as the cause of attack on the *Re* or *Si* face of the carbonyl and these phenomena result from the nature of the α-substituent. A major assumption of all the models is that the nucleophile approaches from the least sterically congested face where the transition state is reactant like.

4.1.1 Pre-Bürgi-Dunitz

The Cram acyclic model was the earliest hypothesis put forward to rationalise carbonyl additions.[53] It assumes a perpendicular approach of the nucleophile to the carbonyl, considering the rotamer which minimises steric clash between the carbonyl and the largest α-substituent to dominate in the transition state. The torsional strain encountered on transition of reactant rotamer to the corresponding product diastereomer is not considered. This is a similar concession made in the later Conforth model however the dominant rotamer chosen for the Conforth model is not dependent on sterics but instead minimisation of dipoles, it states that "…where the dipoles are antiparallel, the polarization of the carbonyl group would be easiest".[54] This ensures the lowest transition state energy and puts any polar substituent 180º to the carbonyl C=O bond. The original Felkin model considers the torsional effect[4] to be of key significance and because of this, places the largest group perpendicular to the carbonyl plane.[55] To determine which face this large group is aligned perpendicular to, a secondary steric effect comes into play. The carbonyl R group (R = H for aldehydes) is assumed to be more sterically demanding in comparison to the carbonyl oxygen and the smallest α-substituent is then placed closest to R. The placement of the polar substituent away from the approaching nucleophile was said to achieve a favourable polar effect in this model.

[4] Torsional effect - Energy barrier experienced when vicinal groups eclipse when passing from sp^2 hybridised C=O to sp^3 hybridised alcohol.

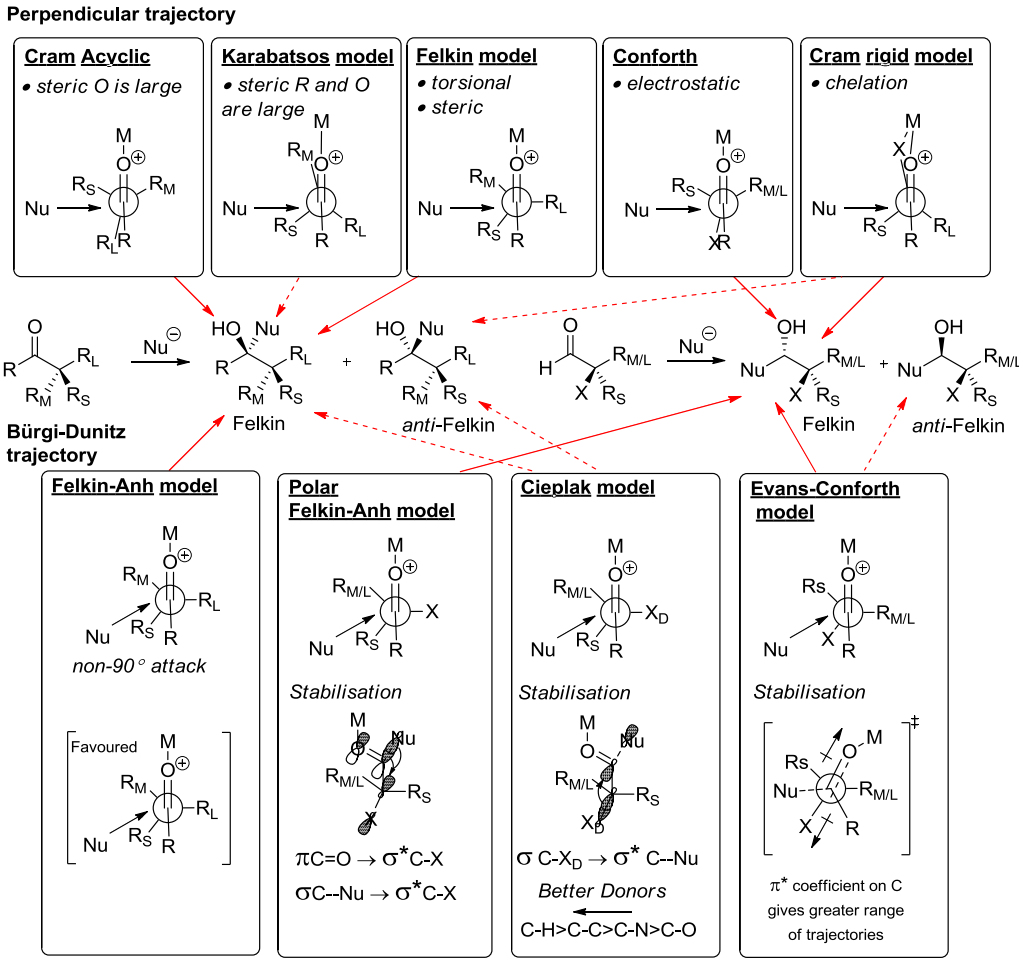


Fig 4.1 – Models for carbonyl addition.

The Karabatsos model was an attempt at rationalising some experimental results that clearly did not fit with the Cram acyclic model.[56] Karabatsos' explanation was that the Cram transition state was incorrect and instead the important steric effect to consider was the steric interaction between the carbonyl oxygen and R_M (medium group), when compared to the steric interaction between the carbonyl oxygen and R_L (large substituent). This was because the favoured conformer leading to the major diastereomer eclipsed the medium group with the carbonyl, whereas the minor diastereomer was formed from the 2nd best conformer where R_L was eclipsed with the carbonyl.[5] In the case where R_L = Ph and R_M = Me or *i*-Pr it was calculated that diastereoselection would be increased when replacing Me with *i*-Pr. However,

[5] This was based on equivalent imine structures and molecular modelling

the assumption that one α-substituent eclipses the carbonyl is not substantiated. Another perturbation of the Cram model is in the case where a polar chelating group is present which can then actually tether such a α-substituent in an eclipsing position leading to the anti-Felkin product in some cases.[57]

4.1.2 Post-Bürgi-Dunitz

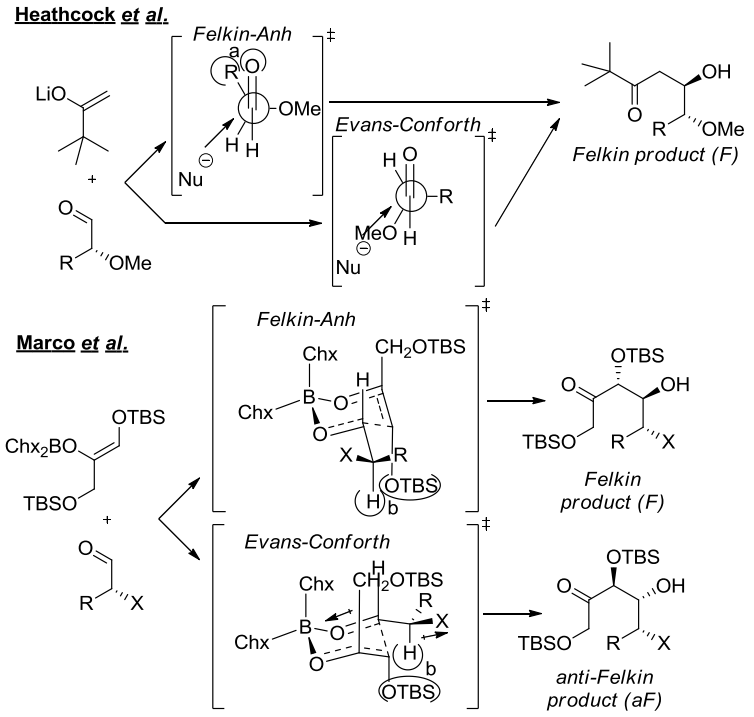
After this mix of ideas, informed by some specific experimental examples which fitted each of the respective models, the work of Bürgi and Dunitz gave a different take on the actual behaviour of these reactions.[58] They stated that approach of the nucleophile was not 90º but aligned with the π* orbital of the carbonyl. This allows an angle of approach of around 107º for the trajectory of the incoming nucleophile. A number of assumptions associated with the Felkin model where addressed by Anh giving the Felkin-Anh model and Polar Felkin-Anh model.[59] Firstly, the low justification for the so called polar affect was solved by orbital arguments. The best σ* acceptor is aligned parallel to the π* and π orbitals of the carbonyl bond stabilising the incoming nucleophile. The best σ* acceptor is normally the most electronegative substituent (hence the polar substituent). The second adjustment to the Felkin model was the breakdown for aldehydes where the R substituent is small and not sterically demanding. In this case the inclusion of the Bürgi-Dunitz trajectory alleviates the requirement as an uncongested approach of the nucleophile, requires the smaller substituent to lie away from the carbonyl C=O bond (towards the nucleophile's trajectory). (Fig 4.1)

Another approach to orbital effects was put forward by Cieplak and can be applied to carbonyl additions (Cieplak Model).[60] Here, it is the relative electron donor abilities of the α-substituent σ bonds, the best of which sits aligned with the σ* orbital of the forming C-Nu bond giving alleged stabilization. Although ample experimental observations exist which support the Cieplak effect, there is still much disagreement whether Cieplak's mechanism is the cause of such reaction selectivities. More recently Evans has taken a number of the best features of the Felkin-Anh and Conforth models and created a new model the Evans electrostatic model.[61] Like the Felkin-Anh model attack of the carbonyl along the Bürgi-Dunitz angle leads directly to the staggered conformation avoiding torsional strain and like the Conforth model, it assumes greater ionic character in the transition state where columbic

interactions are important. The dipoles of the carbonyl and α-polar substituent are minimised but importantly for the Evans model this stabilization increases when moving from an sp^2 to sp^3 hybridisation on attack of the carbonyl. The greater stabilization and greater π* coefficient (at the carbon of the C=O) may also allow the nucleophiles angle of approach to be within a larger range of trajectories.

4.1.3 Experimental evidence (Scheme **4.1**)

Scheme 4.1 (Section 4.1.3) – Experimental evidence of carbonyl addition models – [a] steric interaction between more demanding R and O, should erode diastereoselectivity, [b] *syn* pentane steric interaction.



Heathcock	*d.r.*	
R =	*aF*	*F*
Me	42	58
Et	24	76
i-Pr	8	92
i-Bu	7	93

Marco		*d.r.*	
R =	X =	*aF*	*F*
Ph	NBn_2	2	8
CH_2OBn	OBn	8	2
CH_2OBn	F	19	1
CH_2OTPS	Me	17	1

It is poignant to note that even though distinct differences exist between the Felkin-Anh and the Evans-Conforth model, both are expected to give the Felkin product. Conclusive separation of the two models is not normally possible under most reaction scenarios. Heathcock *et al*. noted that when an enolate was reacted with various α-R-α-methoxy substituted aldehydes,[62] the selectivity increased when the other, non-polar, α-substituent became more sterically demanding. This result is the opposite of what would be expected in the Felkin-Ahn model where an increase in the size of R would lead to a greater steric clash

with the carbonyl oxygen atom. However, in the Evans-Conforth model, as observed in Heathcock's experiments, as the steric demand of R increases so does the selectivity of reaction. This is a result of the conformation becoming "locked" in the Evans' favoured conformation as R increases in steric bulk.

Experiments by Marco *et al*. went a little further by distinguishing the two models with different reaction outcomes.[63] During aldol reaction through a Zimmerman-Traxler type transition state (see Section **5.3.1**) a number of rotamers of the electrophilic aldehyde are available whilst the tethered boron enolate attacks as the nucleophile. Critically, *syn* pentane interactions with a *Z* enolate substituent mean that only hydrogen as an aldehyde α-substituent can align 1,3-diaxial. This then leaves the choice between the Felkin-Anh or Evans-Conforth rotamers for a single aldehyde enantiomer. Each aldehyde rotamer demands attack of the aldehyde from a different face to ensure the lowest possible transiton state energy is achieved. Hence with a small caveat, the requirement of a hydrogen α-substituent, the two models of carbonyl addition can be distinguished.

4.2 Unambiguous stereochemical probes of the Conforth-Evans and Felkin-Ahn models

The magnesium bromide promoted allylation reactions of aldehydes with α-substitutions are of interest in the Linclau group. Some of these containing α-heteroatoms have been investigated experimentally and the results are summarised in Scheme **4.2** and Table **4.2**. Contributions to this work have included computational calculations (conformational analysis) using DFT methods of all the described reactions and experimental investigation of the allylation of the α-epoxyaldehyde ester **3.2.3** to alcohol **4.2.14** (which will be discussed below). All other experimental work, although included for discussion in relation to the computational work, is the result of others toil and as such, has been credited where relevant.[64]

The allylation reactions which have been investigated involve chelation of magnesium bromide to the aldehyde substrates at two positions. These positions are the β oxygen substituent and the aldehyde oxygen which chelate and in the process activates the aldehydes

for reaction with the allyltributyltin nucleophile. "Flexible" rings are formed from the bidentate aldehydes and solubilised magnesium bromide and these rings can then adopt different conformations in solution. However, due to stereoelectronic effects resulting from the α-substituent of the various aldehydes, one conformation for each aldehyde will exist in preference (at higher populations), and hence the face upon which the majority of nucleophilic attack of the aldehydes proceeds will be determined by this conformation.

Table 4.1 – Assumptions made in the computational investigations of chelated aldehyde conformation.

Assumption	Justification & control
Bi-dentate chelated aldehyde (BCA)	• Keck *et al*. proof by low temperature ^{1}H NMR studies.[65]
BCA requirement for reaction	• No reaction with mono-chelated aldehyde using $MgBr_2.(OEt_2)_x$, previous work by Martin Jeffrey.[66]
Octahedral coordination at magnesium	• Control calculations showed that when tetrahedral or octahedral magnesium was used very little change in the ring conformation of the chelate occurred. • In solution magnesium is more likely to adopt its octahedral coordination, enthalpic benefits.
BCA mimics the transition state (TS) of reaction	• Ideally TS would be preferential for understanding reactivity however: ➞ Acyclic addition of the allyl nucleophile gives high levels of conformational flexibility in TS, massively increasing the computational cost ➞ The stepwise reaction mechanism in the allyl addition is poorly understood/unknown increasing area of investigation and computational cost ➞ The BCA encapsulates all major selectivity determining features of the TS whilst minimising computational cost ➞ Sn atom would require optimisation of basis sets as 6-31G* may no longer be appropriate
Use of B3LYP method and 6-31G* basis set	• Evans and Cramer have shown this combination appropriate in the conformational study of simple chelated aldehydes.[61b]
En Vacuo calculations	• CH_2Cl_2 is an aprotic solvent which is expected to exhibit minimal effect on conformation when compared to vacuum conditions. • Octahedral coordinate magnesium to mimic solubilised magnesium characteristics.

In these chelated aldehyde systems, the two ring-flip conformations are closely related to the Conforth-Evans and Felkin-Ahn arrangement of α-substituents for carbonyl additions where facial attack avoiding twist-boat intermediates leads to a different diastereomer for the

Conforth-Evans ring-flip compared to the Felkin-Ahn ring-flip conformer. This makes such systems excellent probes for the discrimination of the two models as it is possible to determine the chelated species conformation based on the experimental outcome of the reactions. Detailed qualitative insights into the structure and relative energies of the conformations were sought through DFT calculations which accurately account for both steric and orbital contributions to molecular conformation. However, a large number of assumptions were made in these investigations and these are explained and justified in Table **4.1**.

Scheme 4.2 – Allylation reactions investigated in the Linclau group. [a] – Experimental work involving the synthesis and allylation reactions of highlighted compounds carried out by Leona Gross[64a]

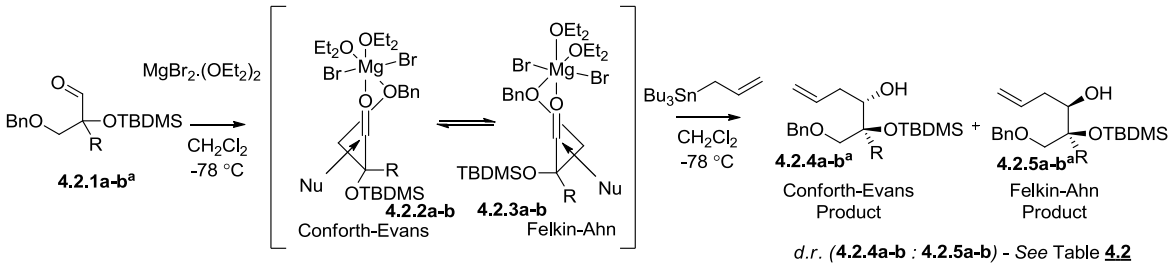


Table 4.2 – Summary of computational and experimental results, including calculated relative free energy of Conforth-Evans and Felkin-Ahn conformer as well as experimentally obtained *d.r.*

	entry	X group	R group	angle C=O C-X	angle C=O C-R	ΔG /Kjmol^{-1}	*d.r.*	yield
1	**4.2.5a**[a]	OTBDMS	H	75	165	+17	<5	53%[a]
2	**4.2.4a**[a]	OTBDMS	H	177	60	0	>95	
3	**4.2.5b**[a]	OTBDMS	Me	94	144	+19	<5	87%[a]
4	**4.2.4b**[a]	OTBDMS	Me	145	94	0	>95	

[a] – Experimental work involving the synthesis and allylation reactions of highlighted compounds carried out by Leona Gross.[64a]

4.2.2 The allylation of α-OTBDMS aldehydes

For the α-OTBDMS substrates a strong preference for the Conforth-Evans conformer **4.2.2a-b** was observed by DFT calculations (Fig **4.2**, Scheme **4.2** and Table **4.2**). An increase in the Gibbs energy difference between the Felkin-Ahn and Conforth-Evans conformer for the

α-methyl substrate **4.2.1b** (ΔG = +19 KJmol^{-1}) over the α-hydrogen substrate **4.2.1a** (ΔG = +17 KJmol^{-1}) was calculated. However the experimental results of Leona Gross seem to show a higher diastereoselectivity for the α-hydrogen product **4.2.4a** (*only one diastereomer observed*) over the α-methyl product **4.2.4b** (*measured d.r. 97 : 3*).[64a] This discrepancy may well lie within experimental error, for the α-hydrogen aldehyde **4.2.1a** the reaction does not reach near completion and the *d.r.* may well differ through longer reaction duration. The difference in free energy difference between substrate conformers is quite small as well, so effects not encapsulated in the conformer analysis, with regard of the approaching nucleophile in the actual transition state may have an effect but are left unquantified in our analysis.

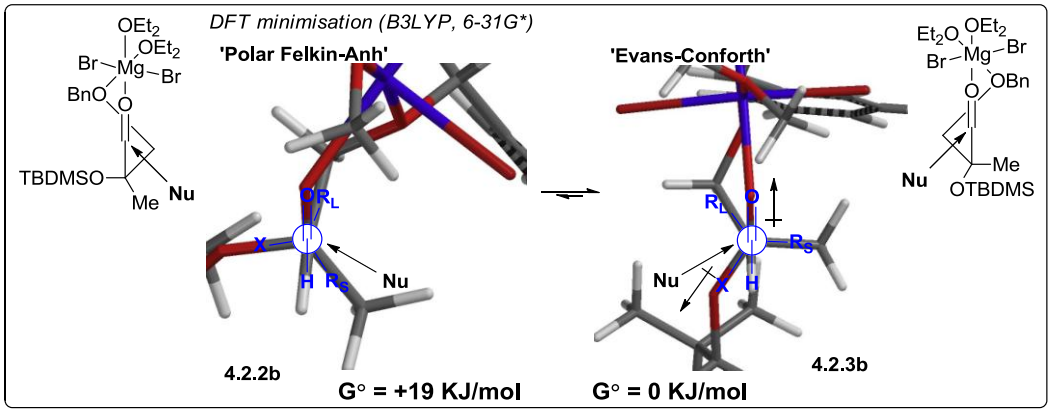


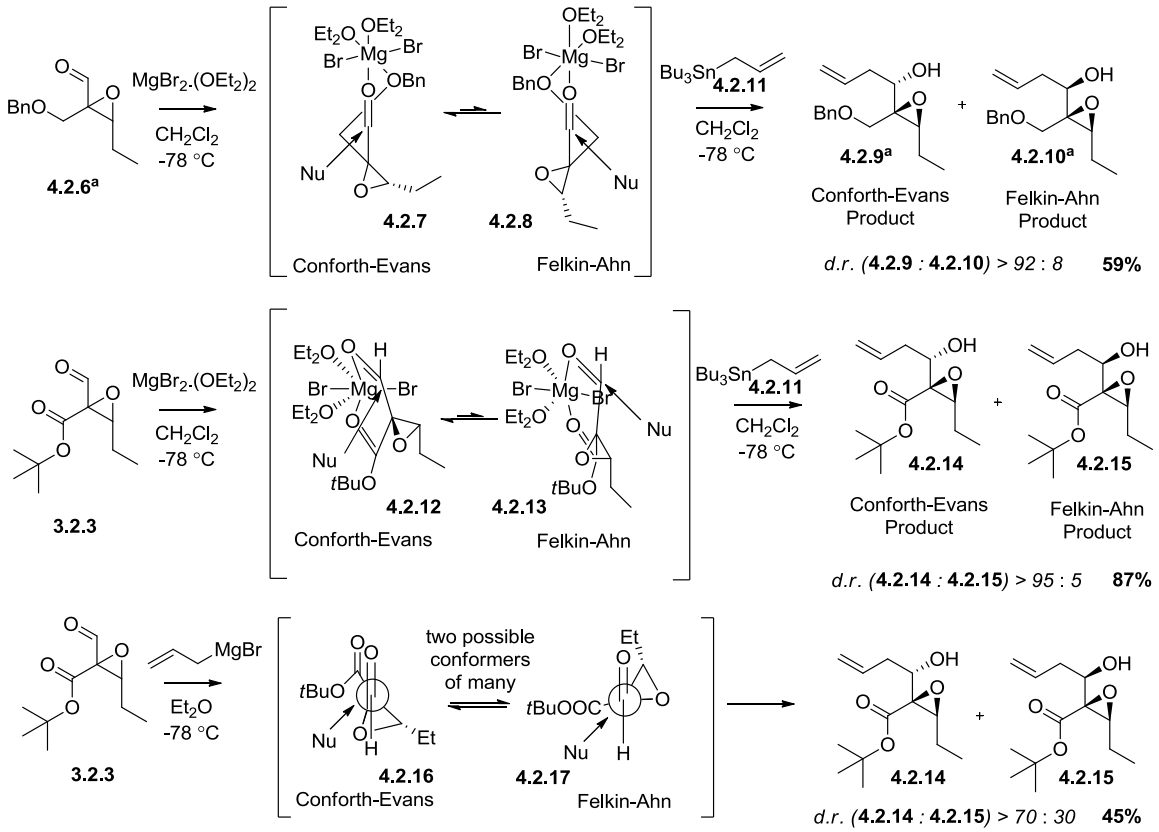
Fig 4.2 – Newman projections and interpretation of calculations on chelated aldehyde **4.2.1b**

4.2.4 The allylation of α-Epoxyaldhydes

In relation to our route to luminacin D, the allylation of α-epoxyaldehydes **4.2.6** and **3.2.3** were investigated, experimentally and computationally (Scheme **4.3** and Table **4.3**). Most preceding examples of additions to such α-epoxyaldehydes were concerned with additions to mono-chelated species and as such both the Conforth-Evans and Felkin-Ahn models would be expected to lead to the same diastereomeric product.[67] In fact, when BF_3 (mono-dentate) was trialled to activate and enable allylation of substrate **3.2.3** only decomposition of the epoxide was observed and this outcome was expected for most strong Lewis acids both mono-dentate and poly-dentate. When using a more reactive allyl nucleophile such as allylmagnesium bromide, preference for the *anti*-product **4.2.14** was observed. However the selectivity was much lower as chelation of the aldehyde **3.2.3** was not

required before reaction and the difference between transition state energies for either diastereomer was probably much less, mainly because of the higher chemical potential of the allyl Grignard. This also means that the Conforth-Evans **4.2.16** and the Felkin-Ahn **4.2.17** conformer would favour the same diastereomer assuming that the C-O of the epoxide would take the 'polar position' (C-X) in preference to the *t*-butyl ester (see Scheme **4.3**).

Scheme 4.3 – Allylation reactions investigated towards luminacin D. [a] – Experimental work involving the synthesis and allylation reactions of highlighted compounds carried out by Leona Gross[64a]



For the transformation of benzyloxyaldehyde **4.2.6** to alcohols **4.2.9** and **4.2.10** computational analysis of the two ring-flip conformation showed the Conforth-Evans conformer **4.2.7** to be more stable than the Felkin-Ahn conformer **4.2.8** (ΔG = +11 KJmol^{-1}) and this was confirmed experimentally, with a reaction *d.r. 92* : *8* in favour of the Conforth-Evans product **4.2.9** (Fig **4.3**). When compared to the allylation of luminacin D intermediate **3.2.3**, giving the alcohol **4.2.14**, computational results showed a much bigger energy difference between the Conforth-

Evans **4.2.12** and Felkin-Ahn **4.2.13** conformers (ΔG = +43 $KJmol^{-1}$), the Conforth-Evans ring-flip **4.2.12** being the most stable (Fig **4.3**). Pleasingly this result was confirmed experimentally with a higher diastereoselectivity for the Conforth-Evans product **4.2.14** where none of the Felkin-Ahn product **4.2.15** was recovered in the reaction (*d.r. > 95 : 5*).

Table 4.3 – Summary of computational and experimental results, including calculated relative free energy of Conforth-Evans and Felkin-Ahn conformer as well as experimentally obtained *d.r*

	entry	angle C=O C-O_{epox}	angle C=O C-C_{epox}	ΔG /$Kjmol^{-1}$	*d.r.*	Yield
9	**4.2.10**[a]	85	150	+11	8	59%[a]
10	**4.2.9**[a]	167	129	0	92	
11	**4.2.15**	80	145	+43	<5	87%
12	**4.2.14**	168	129	0	>95	

[a] – Experimental work involving the synthesis and allylation reactions of highlighted compounds carried out by Leona Gross.[64a].

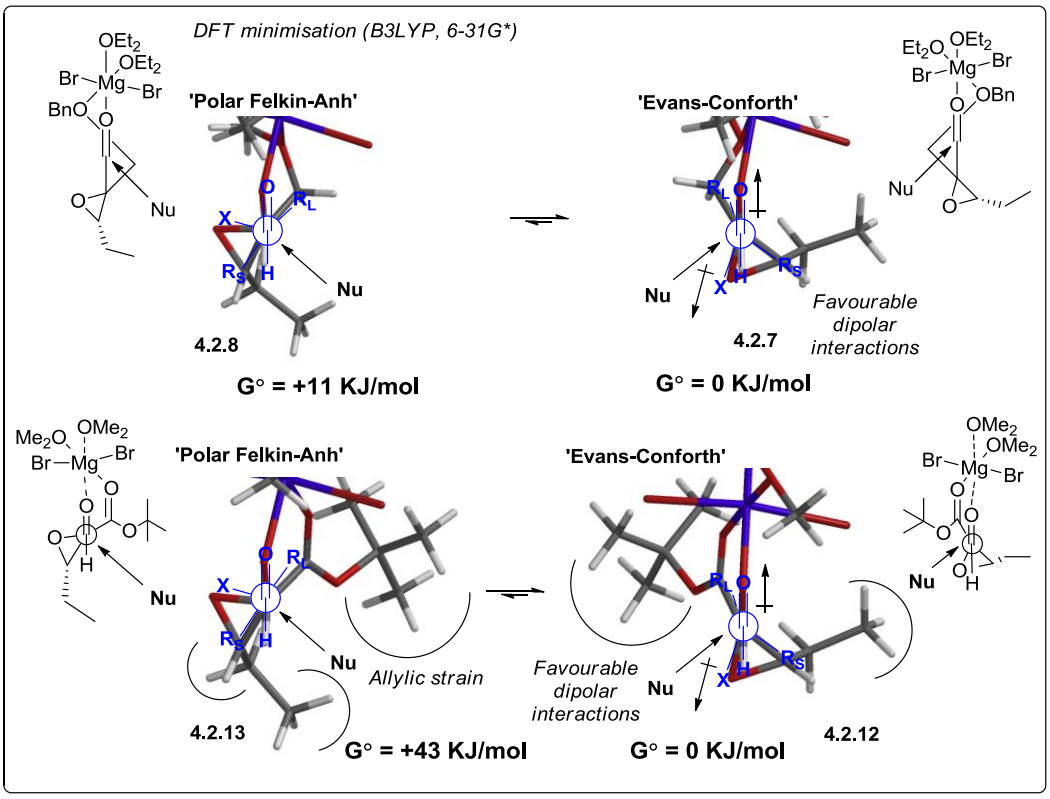


Fig 4.3 – Newman projections and interpretation of calculations on chelated aldehydes **4.2.6** and **3.2.3**

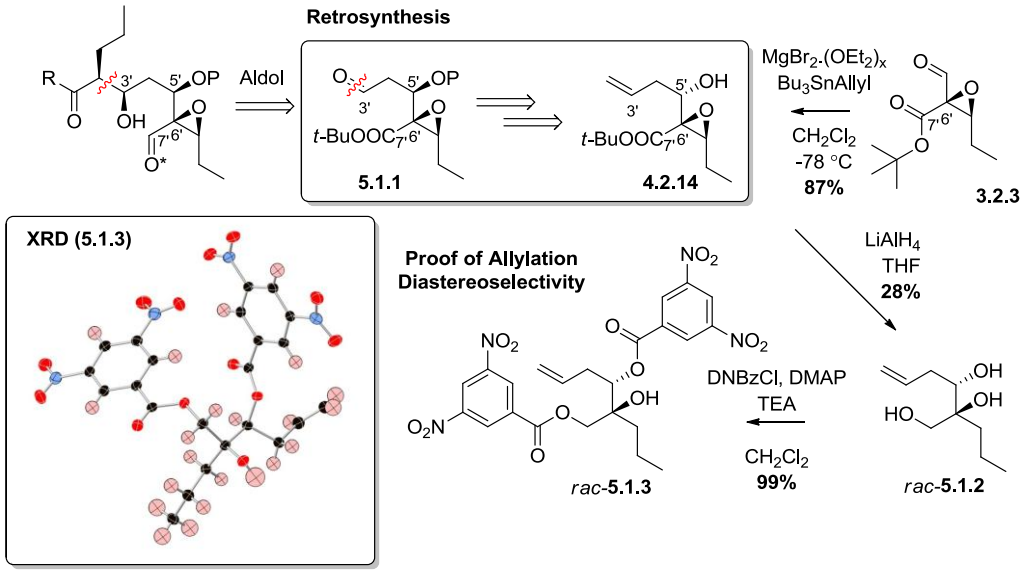
This effect can be explained by a number of differences between the two substrates. Firstly, the greater rigidity of a dicarbonyl aldehyde (**4.2.12**) destabilises the higher energy conformation **4.2.13**, whereas the flexibility of the CH_2OBn ring arm (**4.2.7**) puts less torsional strain on the disfavoured conformer **4.2.8**. This effect is compounded on the chelated aldehyde **4.2.12** as the sterically demanding *t*-butyl ester and epoxide ethyl substituent exhibit allylic strain interactions locking the Conforth-Evans conformation **4.2.12** (*see* Fig **4.3**). These effects lead to a very high diastereoselectivity of the alcohol **4.2.14** and make this allylation of the aldehyde **3.2.3** an ideal candidate reaction for the selective introduction of C5' hydroxyl stereochemistry of luminacin D, from the epoxide C6',C8' stereochemistry.

Chapter 5 Aldol Reactions and the chemistry of aldol products

5.1 Incorporation of allylation into the synthesis of luminacin D

The relevance of the computational and experimental results of Chapter 4 should be defined with regard to the synthesis of luminacin D. The highly selective allylation reaction of the aldehyde **3.2.3** gave the undesired alcohol diastereomer **4.2.14** only. This was confirmed by converting the alcohol product **4.2.14** by global reduction to the triol **5.1.2** and then derivatising the triol as the dinitrobenzoyl ester **5.1.3** which was crystalline allowing XRD structure to be obtained (see Scheme **5.1**). To tailor the alcohol **4.2.14** for luminacin D an inversion of the alcohol would be required, followed by protection and ozonolysis to reveal the C3' aldehyde **5.1.1**. This would then allow an aldol reaction to install the next two chiral centres as outlined in the retrosynthesis of Scheme **5.1**.

Scheme 5.1 – Retrosynthesis of luminacin aliphatic system in relation to the allylation reaction and experimental proof of diastereoselection



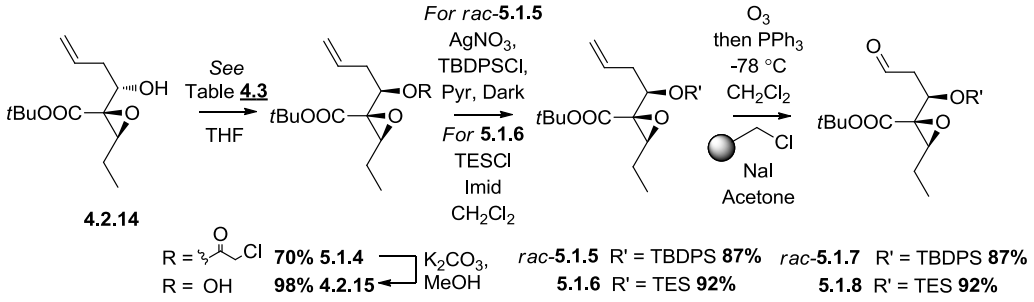
To invert the alcohol **4.2.14** to the desired diastereomer required for luminacin D a number of Mitsunobu conditions were investigated, the results of which are summarised in Table **5.1** (Scheme **5.2**). It was found that the choice of carboxylate nucleophile was critical to the efficiency of the reaction. Acetic acid was found to be the worst nucleophile for the inversion

(23%) and with 4-nitrobenzoic acid only a marginal improvement was observed (36%), similar in performance to the related inversion in the previously discussed patent of Fang *et al*.[15] However, chloroacetic acid allowed the transformation in good yield (70%). The alcohol **4.2.14** is a challenging substrate for Mitsunobu reaction due to the steric requirements resulting from the close proximity of the quaternary carbon centre, the –I effect of the epoxide and acidity requirements of the Mitsunobu reaction itself, most of which are satisfied by chloroacetic acid.[68] The formed ester **5.1.4** was cleaved in near quantitative yield by action of K_2CO_3 in methanol to give the inverted alcohol **4.2.15**.

Table 5.1 – Optimisation of Mitsunobu reaction (see Scheme **5.2**)

Entry	Reagents	(*see* Scheme **5.2**) R =	Yield
1	DIAD, PPh_3, $HOOCCH_3$	$OOCCH_3$	23%
2	DIAD, PPh_3, 4-NO_2BzOH	4-NO_2BzO	36%
3	DIAD, PPh_3, $HOOCCH_2Cl$	$OOCCH_2Cl$	70%

Scheme 5.2 – From the allylation product **4.2.14** to the aldehyde **5.1.8**



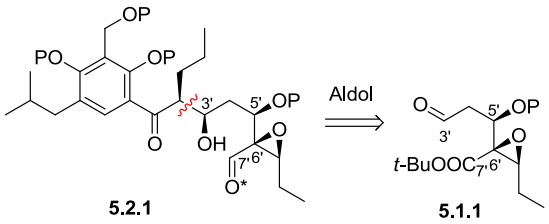
The subsequent protection proved to be more difficult however. We intended to instal a bulky protecting group to improve the selectivity of the aldol reaction and standard conditions were unsuccessful at preparing any substantial quantities of the bulky TBDPS ether **5.1.5**, it was thought that this was due to steric crowding around the alcohol functional group. The use of silver nitrate to force the reaction gave a more desirable yield (87%). To avoid this problem, the alcohol could also be protected as the less sterically demanding TES ether **5.1.6**, which could be prepared from TESCl and imidazole in good yield (92%) (*see* Scheme **5.2**). Both

protected forms could then be ozonolyzed to give the respective aldehydes **5.1.7** and **5.1.8**, which would then enable the subsequent aldol reactions. It was found that purification of the ozonolysis reaction mixture by column chromatography allowed the aldehyde to be separated from triphenylphoshine oxide, but not from unreacted triphenylphosphine. Triphenylphoshine could be effectively scavenged from the crude reaction mixture by using the method developed by Lipshultz *et al*., which employed Merrifield's resin.[69]

5.2 Diastereoselective aldol reaction in luminacin D synthesis

We were initially attracted to diastereoselective aldol reactions to introduce the aromatic fragment of luminacin D. The reaction would introduce C2' and C3' chiral centres diastereoselectively by remote stereocontrol from the C5' protected alcohol of aldehyde **5.1.1** (Scheme **5.3**). This was a strategy utilised by Shipman *et al*. when synthesising luminacin D, the crucial difference being that in our synthesis the epoxide is already installed.[22] This limited the options available to transform the aldehyde **5.1.1** to aldol product **5.2.1** as the present epoxide would be sensitive to Lewis acids, such as the $TiCl_4$ used by Shipman. However, this approach would lead to a highly convergent approach to luminacin D.

Scheme 5.3 – Retrosynthesis in relation to the aldol reaction



5.3 Remote stereocontrol in aldol reactions with aromatic ketone enolates

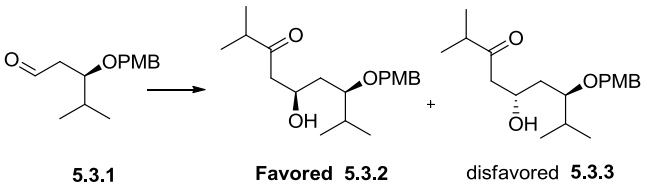
5.3.1 Selectivity in aldol reactions

The possibility of stereocontrol by a remote β-benzyloxy-stereocenter of the aldehyde fragment is known. The effect can be explained by examining the lowest energy, 'open' or 'closed' transition state geometries. Evans *et al*. have described 'open' transition states in

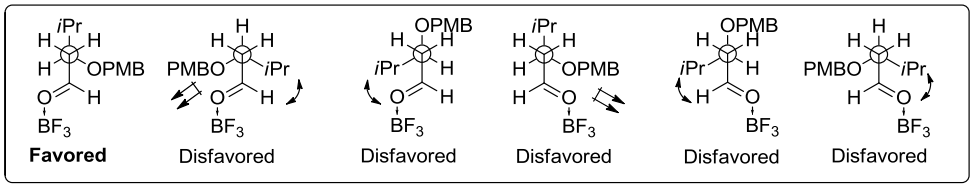
reference to diastereoselective aldol reactions stereodirected by a β-alkoxyaldehyde **5.3.2**, similar to our β-OP aldehyde **5.1.1** (*see* Scheme **5.4**).[70] Importantly, in the Evans example, the *i*-propyl substituent prefers to sit distantly from the C-CHO bond to avoid steric interactions and the OPMB substituent prefers to oppose dipolar interactions with the C=O of the aldehyde (Scheme **5.4**). Both of these factors cause the activated aldehyde to present the *Re* face, which when attacked by the enolate gives the major product **5.3.2**.

For 'closed' transition states and with respect to the C2' and C3' stereochemical outcome of aldol reactions, it has been well demonstrated that *Z*-enolates, derived from ketones are *syn*-selective. For an *E*-enolate, the opposing *anti* selectivity is observed and both these observations can be explained by the 'closed' Zimmerman-Traxler transition state model (*see* Scheme **5.5**).[71] This model assumes that the chair transition state with the lowest energy conformation will lead to the major reaction product.

Scheme 5.4 – Evans example of 'Open' transition state[70]



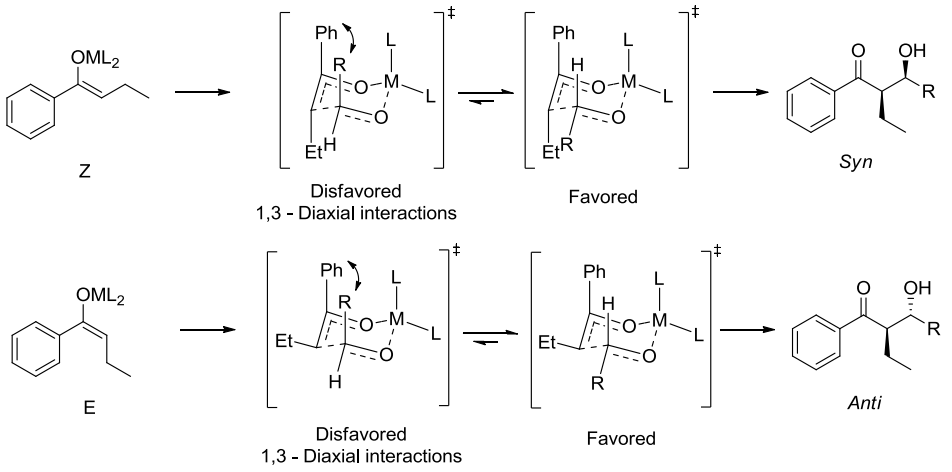
Entry	Metal	**5.2.2** : **5.2.3**
A	TMS / $BF_3.OEt_2$	*92* : *08*
B	Li	*71* : *29*
C	$TiCl_4$	*60* : *40*
D	9-BBN	*42* : *58*



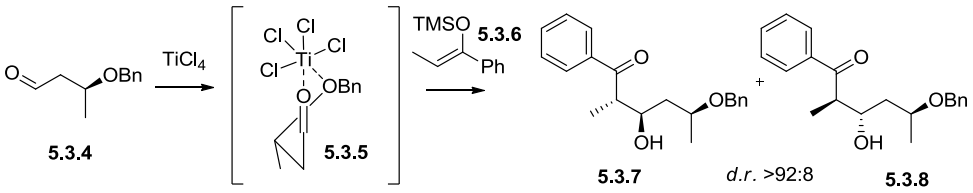
It is also possible to achieve chiral induction in these systems through chelation of the aldehyde followed by nucleophilic attack in an 'open' transition state. If the Lewis acid used is able to accept multiple coordinating ligands, then reaction selectivity is determined by the lowest energy geometry of the chelate **5.3.5**. The selectivity of such aldol addition to β-alkoxyaldehyde **5.3.4** has been outlined by Reetz *et al*. (Scheme **5.6**).[72] They describe such a

chelation mediated addition on model systems with high diastereoselectivity. The action of a *Z*-silylenol ether **5.3.6** on a β-chiral β-alkoxyaldehyde **5.3.4**, complexed to $TiCl_4$, leads to a high selectivity for the product **5.3.7** with the desired stereo-relationship for luminacin D synthesis. However, Shipman achieved much lower selectivity using similar conditions.[22]

Scheme 5.5 – Zimmerman-Traxler transition state[71]



Scheme 5.6 – Selective aldol additions on β-alkoxy aldehydes (Reetz *et al.*)[72]



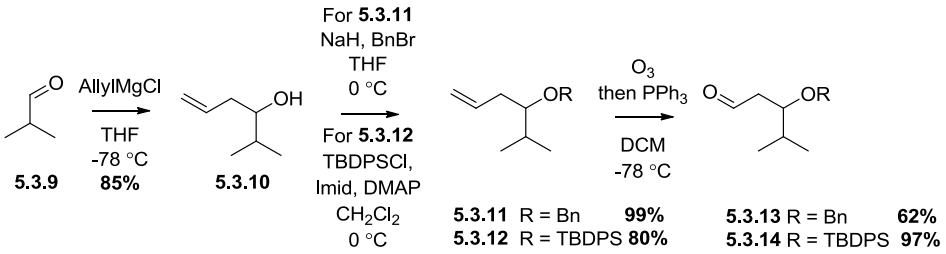
5.3.2 Investigation of aldol on aryl ketone enolates

To investigate remote stereocontrol in diastereoselective aldol reactions with aromatic enolates, model aldehydes **5.3.13** and **5.3.14**, sharing the major skeletal features of aldehyde **5.1.1** were prepared. The syntheses were short and high yielding from the commercially available alcohol **5.3.10**, which could also be prepared from *i*-butyraldehyde **5.3.9**. Both the β-OBn **5.3.13** and β-OTBDPS **5.3.14** aldehydes were prepared (*see* Scheme **5.7**).

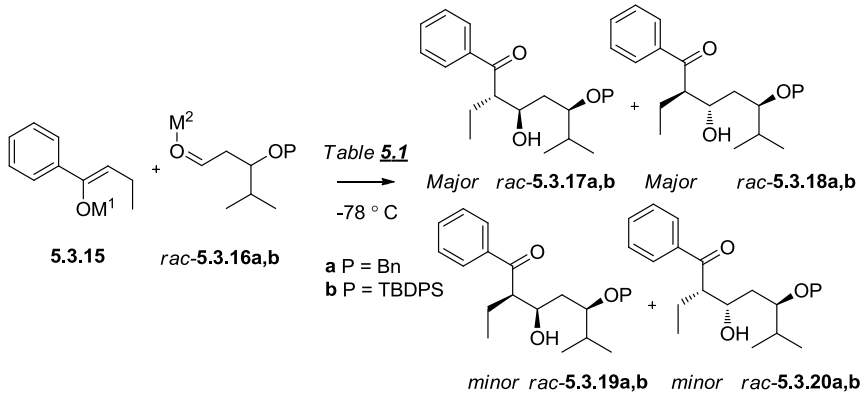
The aldehyde **5.3.13** was then used to investigate mild aldol conditions. Stronger Lewis acids like $TiCl_4$, such as in the example of Reetz *et al.*, were avoided as it is known that the epoxide

functionality of the aldehyde **5.1.1** would be unlikely to survive exposure to such harsh conditions.[73] Instead, magnesium bromide was investigated as a milder alternative, which is also a well-known chelating species. The results of these aldol reaction studies are summarised in Table **5.2** (Scheme **5.8**).

Scheme 5.7 – Preparation of model aldehydes



Scheme 5.8 – Trial diastereoselective aldol reactions on model aldehyde **5.2.13** and **5.2.14** – stereochemistry tentatively assigned.



Entries 1 and 2 were both unsuccessful at producing any product and it was thought for entry 1 that activation with $MgBr_2.(OEt_2)_x$, was not strong enough under the reaction conditions to enable the desired reactivity. For entry 2, a possible cause of the reaction failure, is $MgBr_2$ chelating with the aldehyde and blocking chelation with the dibutylboron enolate. For the enolate to become reactive the boron needs to chelate both aldehyde and enolate giving the active boronate species, in which intramolecular reaction through Zimmerman-Traxler transition state can occur. Heathcock *et al*. have however, shown that under suitable activation boronate enolates can react with aldehydes. Key here is an additional coordination available on the enolate.[62]

The successful $MgBr_2.(OEt_2)_x$ activated reactions (Entries 3 - 5) had only low to modest selectivities. It was thought that the major diastereomer obtained (**5.3.18**) had the undesired relative stereochemistry for luminacin D. The low selectivities can be explained by the large number of possible enolate approaches to the chelated aldehyde **5.3.21** and **5.3.22** and high reactivity of the enolate. The favoured approach of these reactions leading to the undesired relative stereochemistry **5.3.18**, must come from approach to the disfavoured face of the chelated aldehyde to obtain the major product **5.3.18a** (Scheme 5.9). This is likely when pre-coordination of the enolate oxygen is considered before approaching the transition state, meaning the true transition state is more dependent on the lowest conformation of a bicyclic [6,6] ring system. However the relative stereochemistry was not proven and little can be justified conclusively. The selectivity issues are further confounded if the enolate exists as a mixture of *E* and *Z* isomers, which may well be expected when lithium or magnesium enolates are prepared and used *in situ* in such reactions.[74]

The selectivity is better with a mono-dentate Lewis acid such as BF_3 (entry 6), although it is unlikely the epoxide of aldehyde **5.1.1** would survive such reaction conditions. The selectivity in this case is determined in a similar manner as that described for the Evans example in Scheme **5.4**. Again the approach of the nucleophile is critical for the reaction selectivity and a large number of possible transition state conformations are available (Scheme **5.9**). The lowest energy transition state **5.3.23** minimises steric clashes and dipolar interactions leading to the major diastereomer **5.3.17a**.

The highest diastereoselectivities were obtained in entries 7 and 8. For these entries the Zimmerman-Traxler transition state determines the C2' and C3' relative stereochemistry giving the two major products **5.3.17** and **5.3.18**. However it is surprising that any of the disfavoured (*anti* – **5.3.19** and **5.3.20**) product is formed from the 'closed' transition state and it must be assumed that some of the *E*-enolate was formed. The relative orientation of this chair to aldehyde chain then determines the relative C3 and C5 stereochemistry. The relative C3 and C5 stereochemistry was assumed different in the two major products and this was justified when it was observed that a superior diastereoselectivity between the two major

products was found on changing the OBn (entry 7) to the more sterically demanding OTBDPS (entry 8) (*see* Scheme **5.10**).

Table 5.2 – Trial diastereoselective aldol reactions

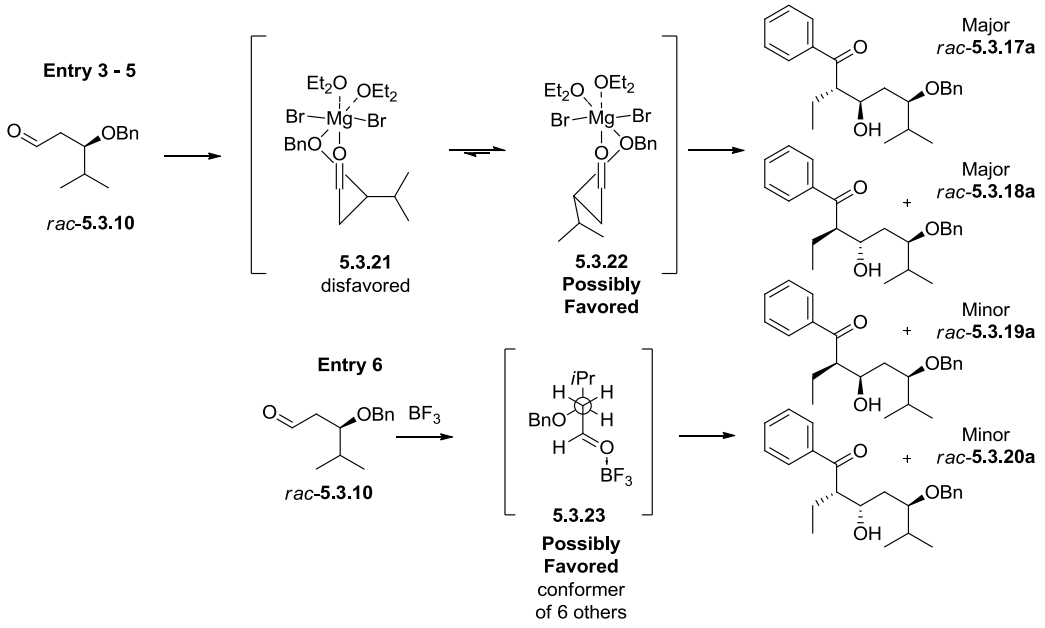
Entry	M^1 =	M^2 =	Yield /(%)	P =	Solvent	Diasteroselectivity[6] **5.3.17** : **5.3.18** : **5.3.19** : **5.3.20**
1	TMS	$MgBr_2.(OEt_2)_x$	0	Bn	CH_2Cl_2	-
2	Bu_2BOTf	$MgBr_2.(OEt_2)_x$	0	Bn	CH_2Cl_2	-
3	Li	$MgBr_2.(OEt_2)_x$	24	Bn	CH_2Cl_2 / Et_2O	*2* : *2* : *1* : *1*
4	MgCl	$MgBr_2.(OEt_2)_x$	47	Bn	CH_2Cl_2 / Et_2O	*4* : *6* : *3* : *1*
5	Li	$MgBr_2.(OEt_2)_x$	64	Bn	Et_2O	*3* : *5* : *3* : *2*
6	TMS	BF_3	18	Bn	CH_2Cl_2	*6* : *4* : *1* : *1*
7	Bu_2BOTf	-	56	Bn	CH_2Cl_2	*13* : *7* : *2* : *1*
8	Bu_2BOTf	-	25	TBDPS	CH_2Cl_2	*6* : *2* : *2* : *1*

The moderate diastereoselectivity obtained in entry 8 (Table **5.2**) prompted an investigation of these conditions using a ketone which better represented the aromatic ketone that would be required for our synthesis of luminacin D. The ketone chosen was resorcinol derivative **5.3.24b** which was subjected to a number of conditions of which, the successful experiments are described in Scheme **5.11**. A major problem associated with this reaction is the Lewis acid promoted, *ortho*-debenzylation of ketone **5.3.24b** which led to low yields for this transformation. The *ortho*-debenzylated ketone **5.3.24a** formed a very stable enolate with

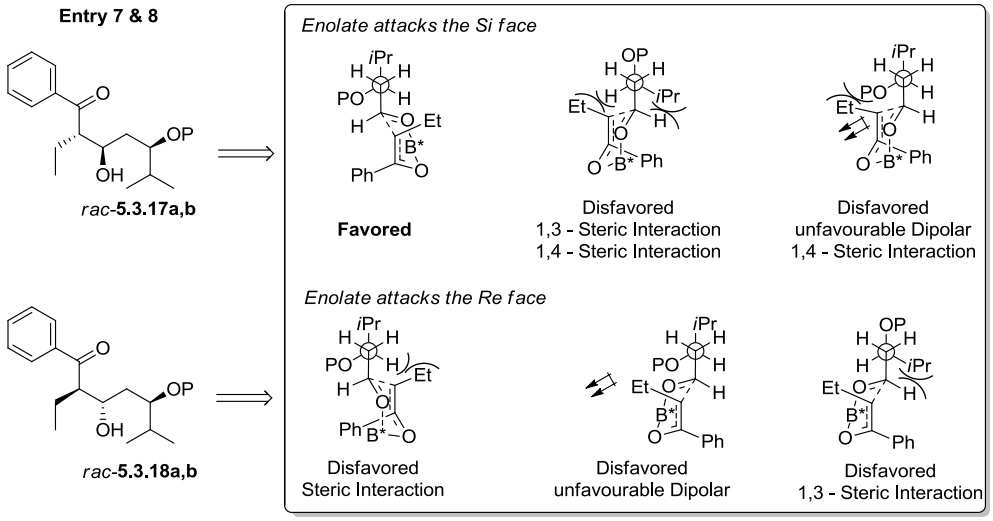
[6] The diastereoselectivity was measured from the ^{13}C NMR spectrum because the crowded nature of the ^{1}H NMR spectrum made it difficult to distinguish individual signals. The diastereomer mixtures could not be separated by column chromatography or HPLC and hence chemical correlation to determine which diastereomer is responsible for each chosen signal was not practical. It was assumed therefore that from the hypothetical selectivity the two major isomers obtained are those shown in Scheme **5.6**, out of four possible stereochemistry permutations. Given the low selectivities no attempt was made to determine the absolute stereochemistries.

Bu_2BOTf and did not react with the aldehyde under the conditions. For reactions with the ketone **5.3.24b**, only two diastereoisomers are observed, however the selectivity was low. Use of the larger boron Lewis acid, dicyclohexylboron triflate decreased the diastereoselectivity between the two products (Scheme **5.11**). This result is interesting as it suggests an ideal size for the Lewis acid or ideal Lewis acid pocket which, when correctly filled, will give the largest diastereoselectivity.

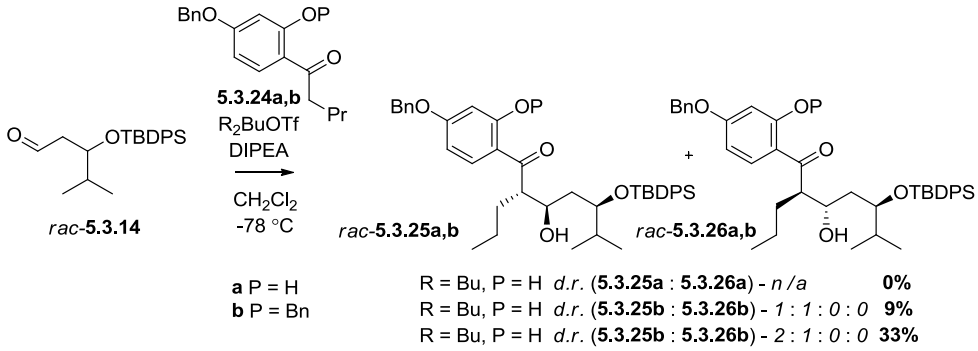
Scheme 5.9 – Tentative origin of diastereoselectivity for entries 3-6. (Table **5.2**)

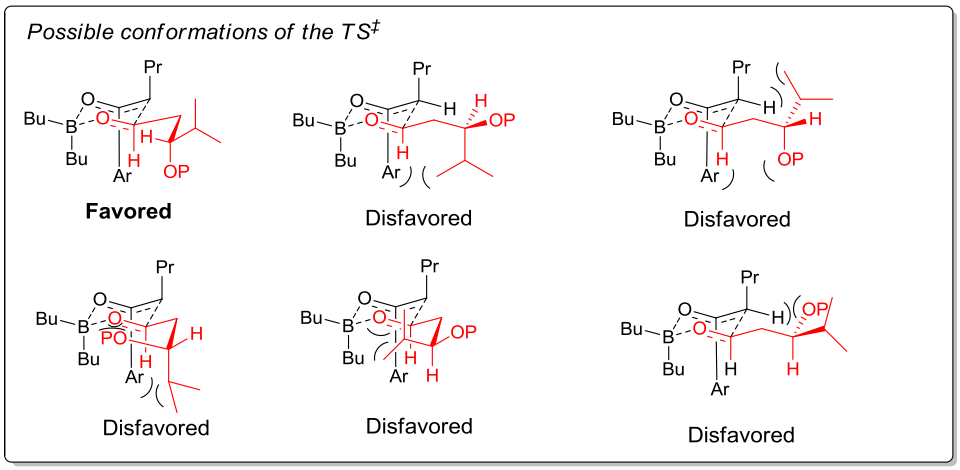


Scheme 5.10 – Tentative origin of diastereoselectivity for entries 7-8. Table **5.2**



Scheme 5.11 – Diastereoselective aldol reaction with resorcinol derived model enolate and the tentative origin of diastereoselectivity for resorcinol derived enolate.[7]





The expected diastereoselectivity of the reaction can be explained by comparing the steric interactions in the various possible transition state conformations (*see* Scheme **5.11**). Only when the directing, exocyclic stereocentre is positioned away from the 6 membered transition state chair and rotated such that the stereoelectronic and steric energies are minimized, is the most stable conformation found. The aromatic ring is orientated such that the dipolar interactions between the *ortho* benzyloxy-substituent and the reacting carbonyl groups of the chair transition state are minimised. Again the diastereomeric products of the reaction were inseparable and the relative stereochemistries of the isomers were not elucidated. Given the

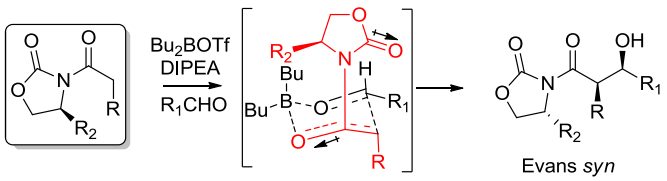
[7] Only the lowest energy conformations have been shown and some low energy conformers are excluded because of their symmetrical degeneracies.

low diastereoselectivity of these reactions and the poor overall conversions, an Evans aldol approach was then considered for our route and this is described in the next section.

5.4 Evans aldol reactions to complete the luminacin D aliphatic fragment

It is well known that the use of amides such as Evans' acyl oxazolidinones can mediate aldol reactions with very good diastereoselectivity. Enantioenriched chiral oxazolidinones can then give enantioenriched aldol products. The use of different metals and conditions in these reactions can select for a number of different relative stereoconfigurations of the aldol product obtained. This is apparent from the many reaction variations, and major contributions to the field have come from Evans and Crimmins amongst others (*see* Scheme **5.12**).[75] There have been numerous applications of Evans aldol methodology to natural product synthesis and this is testament to the technology's robust nature.[76] Evans' standard method is of interest for the relative configuration desired for our purposes.

Scheme 5.12 – Evans aldol chemistry – Evans *syn* aldol[75d]



5.4.1 Investigation of remote stereocontrol in Evans-'like' systems

Due to the modest selectivities obtained for aldol reactions with aromatic enolates the use of oxazolidinone enolates was investigated, given the demonstrated high diastereoselectivities of these substrates. The remote stereocontrol of these reactions with a β aldehyde substituent was not precedented (to our knowledge) and this was of interest in the applicability of this aldol reaction to our luminacin D synthesis.

Our efforts into Evans aldol chemistry started with aldol reactions of the boron enolates of oxazolidinones **5.4.1a,b** with model aldehydes **5.3.13** and **5.3.14**. The stereoinduction of the β-OP aldehyde substituent was found to favour aldol product **5.4.2** (*see* Scheme **5.13**) as was

expected from previously discussed stereoelectronic effects (see Scheme **5.10**). Diastereoselectivity improved when β-O protecting group was changed from benzyl to the more sterically demanding TBDPS and when the ketone α-alkyl chain was extended from ethyl to propyl (*see* Table **5.3**, max *d.r. 5* : *1*).

Scheme 5.13 – Diastereoselection in *racemic* Evans aldol reaction

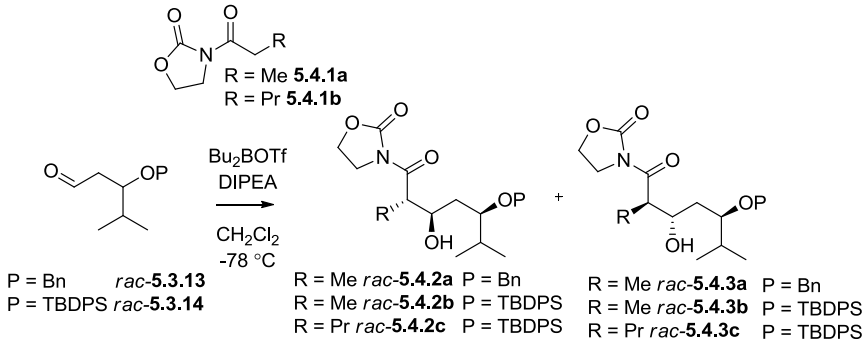


Table 5.3 – Diastereoselection in *racemic* Evans aldol reaction

Entry	Yield	*d.r.* **5.4.2** : **5.4.3**	R =	P
1	49%	*2* : *1*	Me	Bn
2	34%	*3* : *1*	Me	TBDPS
3	75%	*5* : *1*	Pr	TBDPS

With a reasonable diastereoselectivity obtained for the model system **5.4.2c** it was important to prove experimentally the relative configuration of the product. This would ensure that the major isomer had the correct relative stereochemistry for application in the synthesis.

This was achieved fortuitously by deprotection of the inseparable mixture of TBDPS ethers (**5.4.2c** : **5.4.3c**, *d.r. 5* : *1*) (Scheme **5.14**). Initial attempts at deprotection with TBAF only led to elimination to give alkene **5.4.4** (mechanism of formation discussed in Section **5.5.2**). However, treatment with HF / pyridine facilitated removal of the silyl group and cyclisation onto the amide, expelling the oxazolidinone and forming the lactone **5.4.5a**. The lactone was obtained as an inseparable mixture of major lactone **5.4.5a** (from **5.4.2c**) and minor lactone

5.4.5b (from **5.4.3c**) as well as lactone **5.4.5d** (Scheme **5.14**). This lactone **5.4.5d** was thought to originate from the tautomerism of lactone **5.4.5b** under the deprotection conditions, not from the aldol reaction (*d.r.*- **5.4.5a** : **5.4.5b** : **5.4.5d** - *11* : *2* : *1*). The absolute configuration of this lactone was then inferred by measurement of the ^{1}H NMR proton coupling constants. These measured coupling constants were then compared to calculated coupling constants for each of the four possible lactone configurations (Table **5.4**). The coupling constants were calculated by obtaining energy minimised structures for the four possible lactones (DFT, B3LYP, 6-31G*) and from these structures measuring the C-H dihedral angles and calculating coupling constant values from the Karplus equation.[77]

Scheme 5.14 – Deprotection of major diastereomer.

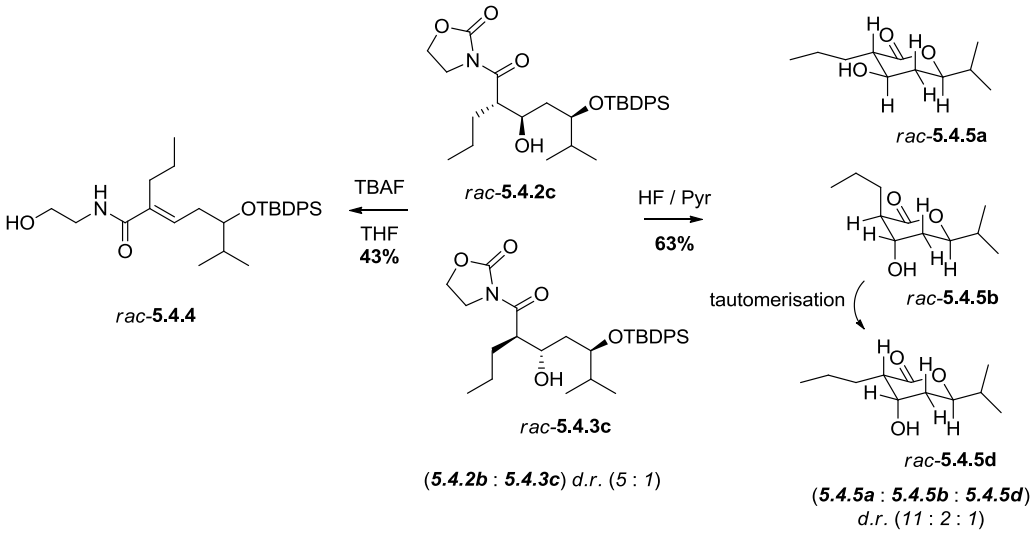


Table 5.4 – A comparison of the calculated and measured coupling constants, highlighting the correlation with calculated structure **5.4.5a** and measured **5.4.5a**.

Proton Relationship	Calculated Coupling Constants / (Hz)				Measured / (Hz)
	5.4.5a	**5.4.5b**	**5.4.5c**	**5.4.5d**	**5.4.5a**
Hc-Hb	1.6[a]	1.7	1.6	1.8	4[a]
Hc-He	**2.1**	2.8	3.0	2.3	**2.5**
Hc-Hd	9.2[a,b]	9.2	9.2	9.2	13.1[a,b]
Hd-Hb	**9.2**	2.3	9.2	2.1	**9.8**
Hd-He	**9.2**	9.0	8.9	9.2	**11.9**
Ha-Hb	**8.8**	0.4	3.5	3.1	**9.1**

[a] - n.b. calculated and measured values differ by a substantial quantity but **5.4.5a** is still the best fit given other possible matches, [b] – germinal coupling (not measurable with the Karplus relationship)

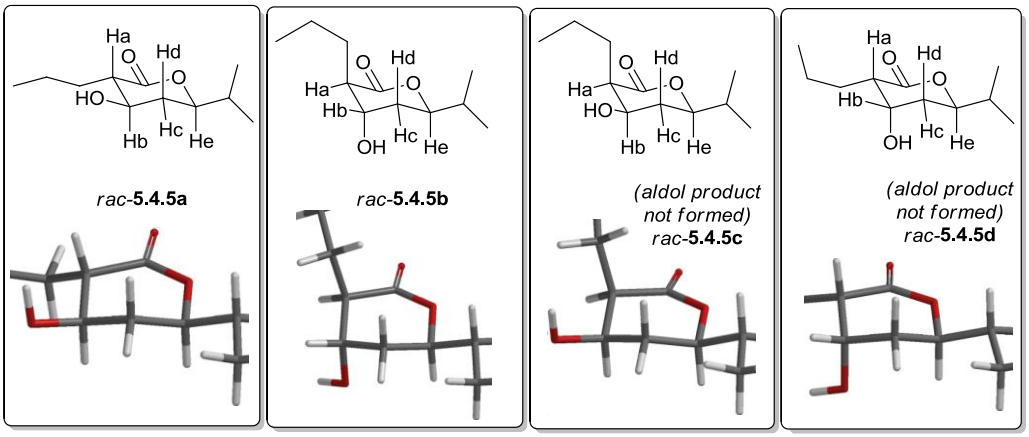
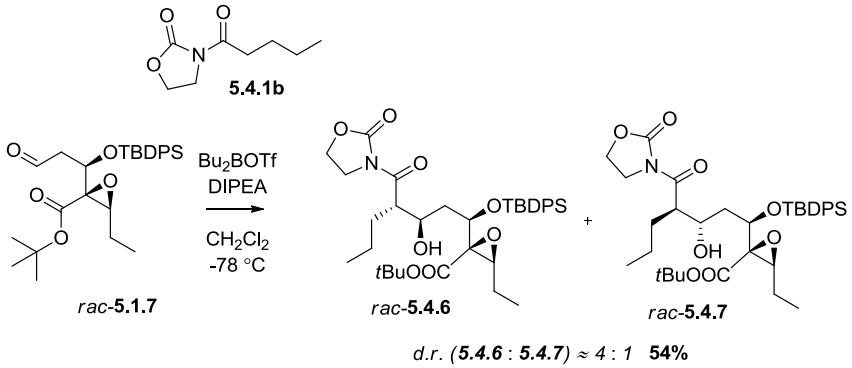


Fig 5.1 – Calculated energy minimised structures (B3LYP, 6-31G*) and the corresponding lactone structure.

The measured pattern was distinctive for the lactone with all equatorial subtituents **5.4.5a** only obtained by cyclisation of the desired aldol diastereomer **5.4.2b**. This gave a sufficient proof which showed that the aldol reaction on the model aldehyde **5.3.14**, led to the diastereomer **5.4.2b** as the major reaction product.

5.4.2 Translation to luminacin D synthesis

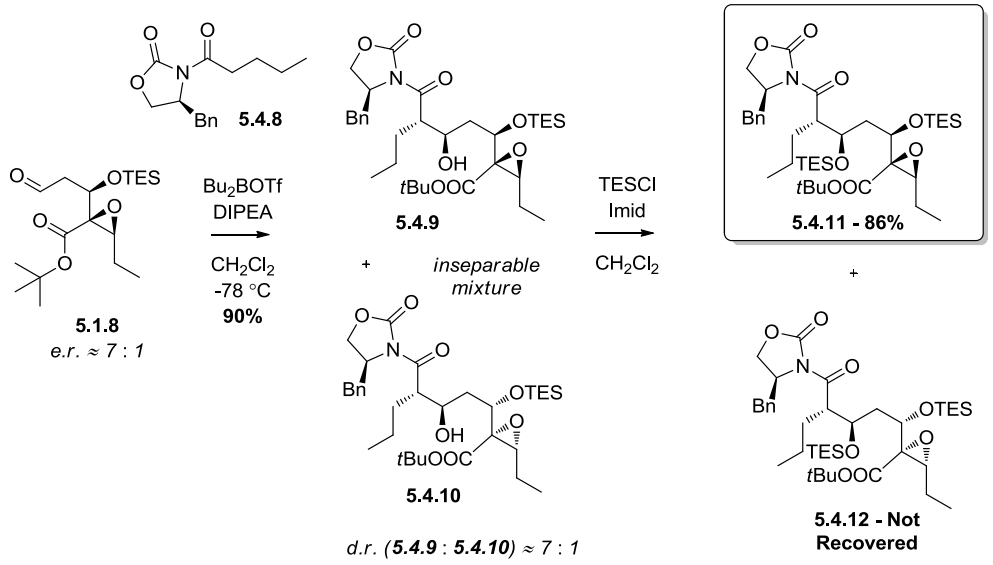
Scheme 5.15 – Translation of the diastereoselective Evans 'type' aldol reaction to the natural product system.



This diastereoselective Evans 'type' aldol reaction was then performed on the racemic natural product intermediate **5.1.7**. A slightly diminished level of selectivity was obtained for the desired aldol diastereomer **5.4.6** with minor quantities of aldol product **5.4.7** present in the

product mixture (Scheme **5.15**). The relative configuration of diastereomer **5.4.6** was proven and will be discussed in Section **5.5.1**.

Scheme 5.16 – Translation of the Evans aldol reaction to the enantioenriched natural product intermediate **5.1.8**.



Given the modest diastereoselectivity, we sought to amplify the desired diastereoselectivity by using double diastereodifferentiation, an opportunity offered by using a chiral oxazolidinone based auxiliary. The enantiopure oxazolidinone **5.4.8** was used on the enantioenriched aldehyde **5.1.8** (*e.r. ≈ 7 : 1, ee 75%*) to achieve selectivity for the desired enantiomer **5.4.9** (Scheme **5.16**). In this reaction a matched situation was anticipated, where the diastereoselection by the amide enolate and diastereoselection by the aldehyde **5.1.8** would enable excellent overall selectivity for the Evans aldol reaction. This was indeed the case with the desired diastereomer **5.4.9** (*d.r. > 20 : 1*) obtained for luminacin D along with a minor compound **5.4.10** in good yield. The minor product was thought to be the result of the reaction between the minor enantiomer of the aldehyde **5.1.8** and the oxazolidinone **5.4.8**, where diastereoselection in the reaction was determined by the amide component **5.4.8**. This is testimony to the dominance of oxazolidinone chiral auxiliary's stereocontrol over the remote stereocontrol of the aldehyde β substituent, the effect of which is completely occluded. These two isomers could be separated with some difficulty by HPLC only after protection as the TES ether which enabled an excellent yield of the pure enantiomer required for the synthesis (max

yield of **5.4.11** possible – 87.5%). The minor compound **5.4.12**, although separated, was not recovered from the separation.

5.5 Attempts to complete the aliphatic fragment

5.5.1 Acid catalysed formation of the cyclised aliphatic fragment of luminacin D

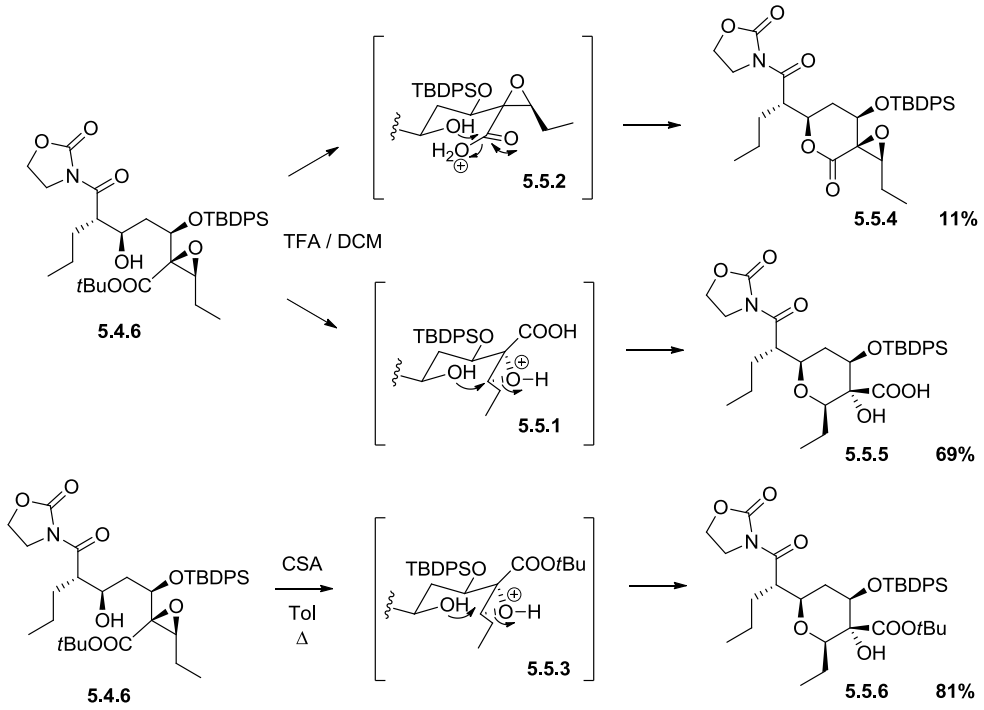
It was envisaged that the aliphatic fragment could be completed at this stage by *t*-butyl deprotection and lactone formation under acid catalysis. The subsequent reduction of the lactone would give the lactol, completing the aliphatic system of luminacin D. Some plausible conditions were investigated for the cyclisation of the aldol product **5.4.6** to lactone **5.5.4** (Scheme **5.17**). When the aldol product **5.4.6** was subjected to acidic conditions two products were formed, the minor product was unfortunately found to be the desired lactone **5.5.4** (11%). Surprisingly, the major product was found to the tetrahydropyran **5.5.5** (69%), where attack of the unprotected alcohol led to opening of the epoxide. This cyclisation onto the epoxide was also observed when the aldol product was heated with CSA in toluene, however in this case, no *t*-butyl deprotection occurred, and the product **5.5.6** was recovered in good yield (81%).

For the cyclised product **5.5.6**, strong HMBC correlations matched the anticipated structure of the epoxide opened product proving that it was in fact the 6-*exo*-tet cyclisation product **5.5.6** and not the hypothetical 5-*exo*-tet product **5.5.7** or other non-cyclised epoxide opened compounds (Fig **5.2**). Similarly, for the cyclised product **5.5.5** with the free carboxylic acid, the strong HMBC correlation (not shown) matched the hypothetical structure of the epoxide opened product **5.5.5** at the C8’ position, proving that the 6-*exo*-tet cyclisation product was formed in both cases.

Closer examination of tetrahydropyran **5.5.5** by nOe NMR measurements did reveal crucial structural information (Fig **5.3**). The nOe experiments gave essential proof of the relative stereochemistry between the epoxide, OTBDPS and the OH formed during the aldol reaction. The relationship between $H^{3'}$ and $H^{2'}$ could not be proven by this method however, but given the results from the model system and the vast amount of literature precedent, their relationship can be assigned with virtual certainty. The nOe measurements also prove unequivocally that the product **5.5.5** is the 6-*exo*-tet cyclisation product and not that of 5-*exo*-

tet cyclisation **5.5.7** as this structure would have a through space interaction with $H^{4'}$, when $H^{8'}$ is irradiated in compound **5.5.7** and this was not observed. Similarly an analysis by nOe (not shown) of the cyclised product **5.5.6**, which retained the *t*-butyl protection, confirmed the same stereo configuration and structural information.

Scheme 5.17 – Deprotection and unexpected cyclisation of the Aldol product **5.4.6**.



Supporting Assignments

5.5.4

IR (neat) : 1777, **1754**, 1697 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 2.81 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1.0 H), 1.90 - 1.72 (C$\underline{H}_{2\ Et}$, CHOTBDPSC$\underline{H}_{2\ Eq}$, C$\underline{H}_2CH_2CH_3$, m, 3H), 1.70 - 1.40 (C$\underline{H}_2$* $_{Et}$, C$\underline{H}_2CH_2CH_3$*, m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5 (**C**OOCH),

5.5.5

IR (neat) : 1779, 1699 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 3.14 (CHOC**H**Et, dd, *J* = 2.0, 10.6 Hz, 1Hz), 1.82 (C$\underline{H}_{2\ Et}$, dsxt, *J* = 2.0, 7.3 Hz, 1H), 1.35 - 1.22 (C$\underline{H}_2$* $_{Et}$, *app.*m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9 (**C**OOH),

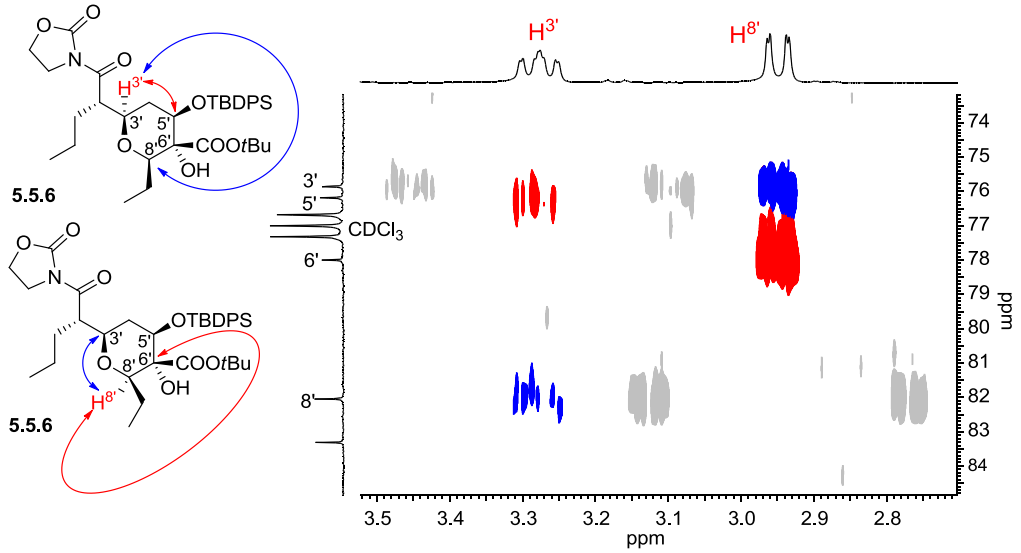


Fig 5.2 – Expansion of HMBC of the cyclised product **5.4.6**

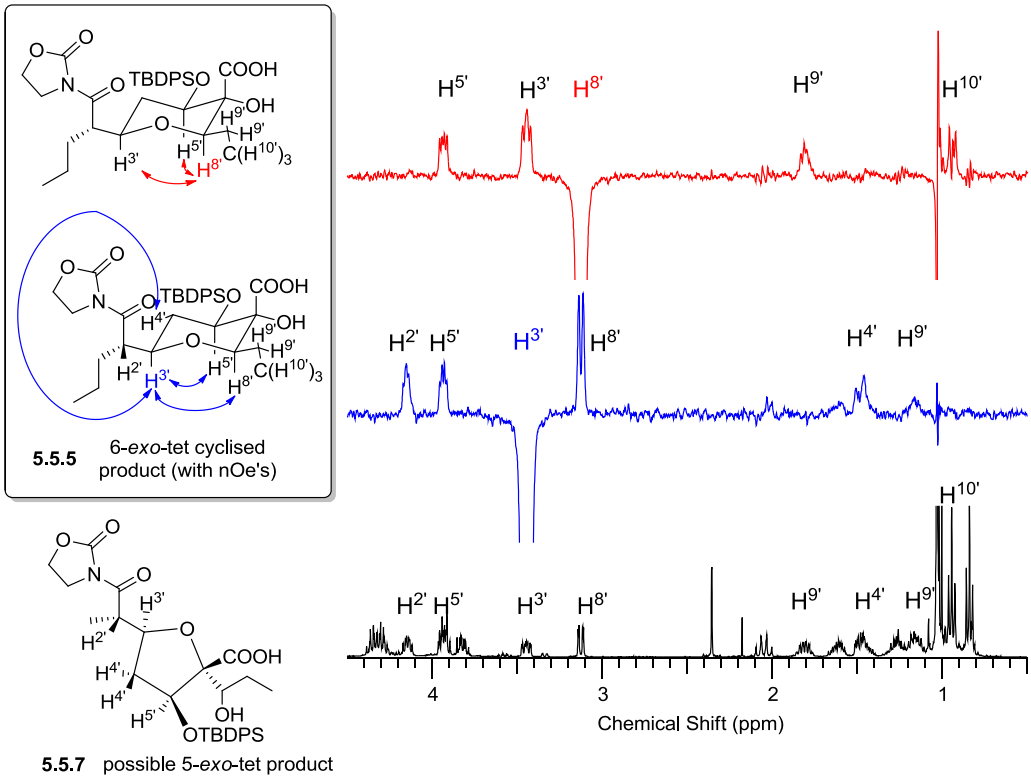


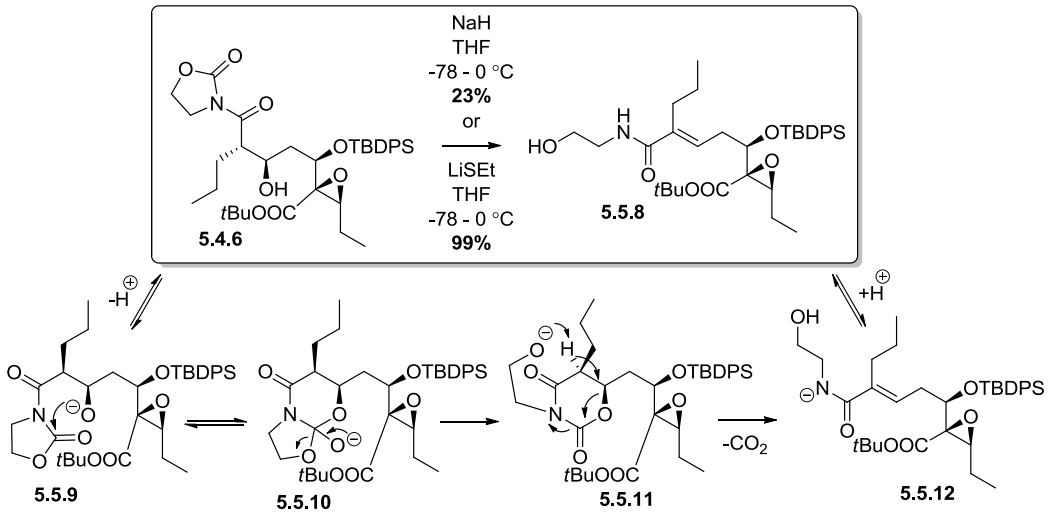
Fig 5.3 – nOe couplings on the cyclisation product **5.4.5** with the structure of the possible 5-exotet structure (not observed)

The formal 5-*exo*-tet cyclisation product **5.5.7** is likely to be disfavoured for two reasons. Firstly the steric crowding of the C6' carbon and destabilisation of any partial positive charge at this position by the acid group would disfavour S_N2 reaction. Secondly the epoxide geometry is such that the attacking oxygen lone pair would need to attack in an equivalent manner to a 5-*endo*-trig cyclisation (not the stated *5-exo*-tet approach) as the C-O σ* protrudes in a similar orientation to an *endo*-cyclic π* lobe, and this is a disallowed cyclisation.

5.5.2 Base catalysed cyclisation attempts

Attempts were then made to cyclise the aliphatic fragment under basic conditions, which also gave surprising results. On treatment of the aldol product **5.4.6** with sodium hydride the elimination product **5.5.8** was obtained in low yield (Scheme **5.18**). This product was also obtained in quantitative yield when the aldol product **5.4.6** was subjected to lithium ethylthiolate. The mechanism of formation of this product **5.5.8** is thought to be initiated by the deprotonation of the hydroxyl (**5.5.9**). This anion then cyclises onto the carbamate (**5.5.10**), expelling the primary alkoxide (**5.5.11**) which intramolecularly eliminates carbon dioxide via deprotonation (**5.5.11**). The amide anion **5.5.12** is then protonated to give the elimination product **5.5.8**. This is also the likely mechanism of formation of elimination product **5.4.4** from model aldol product **5.4.2c** (*see* Scheme **5.14**).

Scheme 5.18 – Base catalysed elimination of aldol product **5.4.6**



5.6 Chapter 5 Conclusions

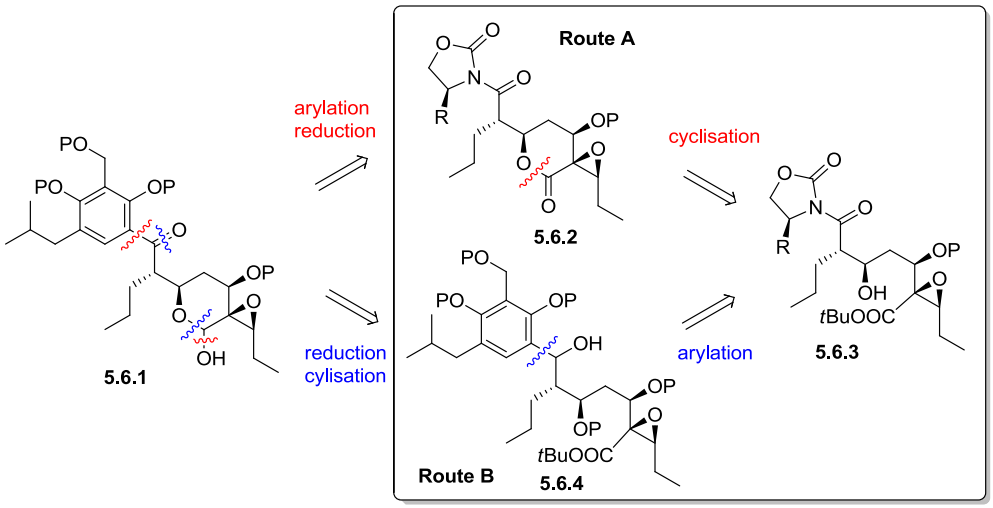


Fig 5.4 – Retrosynthesis, after the Evans aldol reaction.

Remote stereocontrol from the β aldehyde substituent was found to induce only moderate selectivity in the aldol reaction involving aromatic enolates. A less convergent approach involving an oxazolidinone based enolate was then used. From the aldol product intermediate **5.6.3**, two possible routes were under investigation to enable the synthesis of luminacin D (Fig **5.4**). Route A involved the cyclisation of the β-alcohol onto the ester functionality to give a lactone intermediate **5.6.2** forming the natural product aliphatic ring. The surprisingly selectivity for the epoxide in the acid catalysed cyclisation reaction prompted an investigation into an alternative strategy. Route B involed the inverted strategy, first, after protection of reactive functionality, the oxazolidinone could be exchanged for the thioester or aldehyde enabling arylation to **5.6.4**. Then reduction of the ester and subsequent cyclisation would give the hemiacetal **5.6.1**. Route B is the subject of Chapter **6**.

Chapter 6 Synthesis of the aromatic fragment and completion of Lum D

6.1 A different approach avoiding pre-cyclisation of the aliphatic fragment

Given the unexpected reactivity of the aldol product when attempts were made to cyclise the aliphatic fragment, another approach was investigated (Scheme **6.1**). This approach (route **B** – Fig **5.4**) would introduce the aromatic fragment on to the acyclic aliphatic fragment and this was envisaged by Fukuyama coupling (Sceme **6.1**). Cyclisation of the aliphatic fragment would then be undertaken in the finishing stages of the synthesis.

In this new approach, to enable coupling of the aromatic and aliphatic fragments, the Evans aldol product **5.4.11** would be converted to an intermediate which would facilitate arylation. Aroylation was envisaged by two methods, Fukuyama coupling with the thioester **6.1.2** of the aliphatic fragment or direct arylation of the aldehyde **6.1.4** of the aliphatic fragment with the aryllithium (Scheme **5.18**). Both these arylations will be discussed in detail in this Chapter.

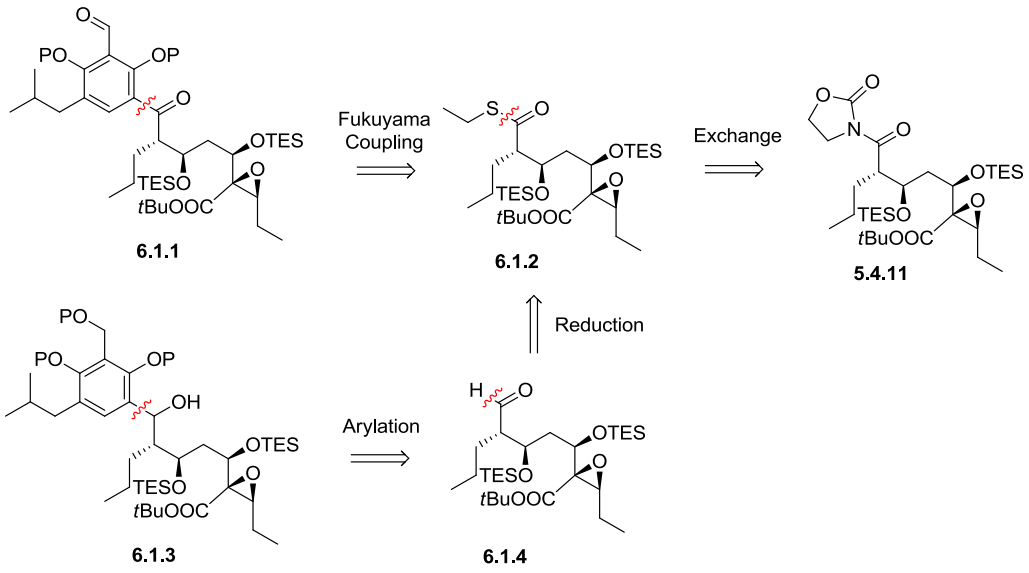


Fig 6.1 – Retrosynthesis – A detailed examination of approach B (Fig **5.4**)

The conversion of the Evans aldol product **5.4.11** to the thioester **6.1.2** and subsequent conversion to aldehyde **6.1.4** was optimised and the results are summarised in Table **6.1** (Scheme **6.1**). The time of reaction and concentration of reactants was found to be critical for

good conversion to the thioester **6.1.2** from aldol product **5.4.11**. Under high concentrations of EtS^-, small quantities of the product **6.1.5** were recovered, and this was a result of ethylthiolate anion attack on the less sterically encumbered side of the epoxide. The subsquent conversion of thioester **6.1.2** to aldehyde **6.1.4** was straight forward with yields ranging from 66% - 75%.

Scheme 6.1 – Tailoring the aliphatic fragment before arylation

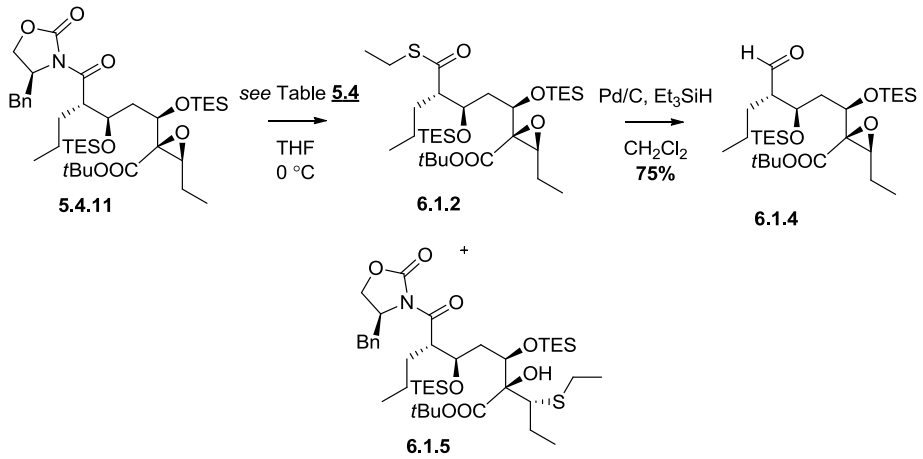


Table 6.1 – Optimisation of thioester **6.1.2** formation.

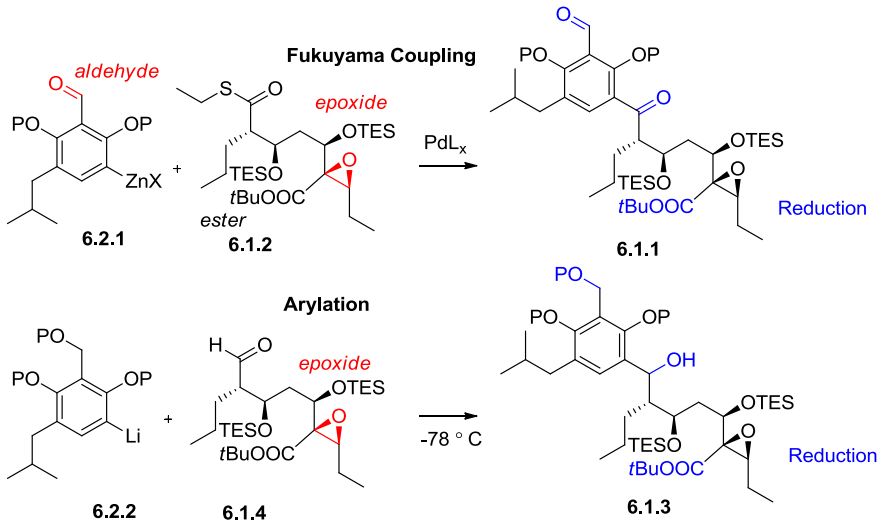
Entry	[MSEt] /(M)	[**5.4.11**] /(M)	Time /(h)	Yields **5.4.11**	**6.1.5**	**6.1.2**
1[a]	1.27	0.127	2	28%	12%	24%
2[b]	0.09	0.033	0.5	100%[c]	-	-
3[b]	0.33	0.033	0.5	39%	-	48%
4[b]	0.39	0.019	2	19%	-	51%
5[b]	2.84	0.136	2	56%	-	28%
6[b]	0.64	0.153	6	-[d]	-	77%
7[b]	0.46	0.132	6	-[d]	-	87%

[a] - base used KH; 0 ºC → rt. [b] - base used nBuLi, -78 ºC → 0 ºC. [c] - as observed from the crude 1H NMR. [d] - mass of **5.4.11** not recorded.

6.2 Reaction choice when connecting the aliphatic and aromatic fragments

Upon joining the protected aromatic and aliphatic fragments of luminacin D, the natural product skeleton would need only minor modifications and deprotections to give the finished natural product. As briefly discussed in Section **6.1**, two options were to be investigated; to join the aliphatic and aromatic fragments of luminacin D, aroylation via the aryllithium **6.2.2** and Fukuyama coupling via the aromatic zincate **6.2.1** (Scheme **6.2**). The aryllithium **6.2.2** was expected to possess a high reactivity and hence, low functional group tolerance, but had been used previously in luminacin syntheses.[20-21] Alternatively, Fukuyama coupling conditions could allow the tolerance of more sensitive functional groups. In examples from Fukuyama *et al*. the reaction was observed to tolerate aliphatic aldehydes as well as aromatic ketones on the thioester fragment of reaction.[78] Other examples have shown that electron rich zincates are also tolerated in the reaction.[79] For our purposes the reaction would need to tolerate a number of sensitive functional groups including an epoxide and aromatic aldehyde (red). The Fukuyama approach would decrease the required pre and post coupling reactions.

Scheme 6.2 – Tailoring the aliphatic



After a successful coupling the choice of reaction would lead to additional complications when attempting the necessary selective reduction of the C7' *t*-butyl ester to the aldehyde. If Fukuyama coupling were successful, difficulties may arise when selectively reducing the ester

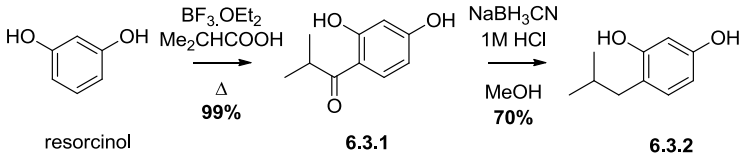
in the presence of the aromatic ketone and aldehyde. No single step methods are currently available for this transformation with the desired selectivity. If the aryllithium approach was undertaken no selectivity issues would be present however additional steps would be required to obtain the correct oxidation states at the highlighted positions (blue). Additional steps would also be required prior to the arylation to obtain suitable aliphatic and aromatic fragments. In order to investigate these scenarios fully the viability of both reactions would need to be investigated and the appropriate aromatic fragment prepared for both instances.

6.3 Synthesis of the aromatic fragments

6.3.1 The Aromatic fragment for Fukuyama coupling

It was envisaged that any aromatic synthesis would be most efficient when protecting group chemistry was avoided to the latest stage possible. For the aromatic fragment of the luminacins, an appropriate starting material was resorcinol, as phenols are generally difficult to introduce synthetically. From resorcinol the *i*-butyl chain could be introduced in quantitative yield via a Friedel-Crafts reaction (**6.3.1**), followed by reduction of the ketone to alkane **6.3.2.** Both reaction were previously investigated by Helen Gale, formerly of the Linclau group (Scheme **6.3**), and methodology utilized from literature precedent.[80]

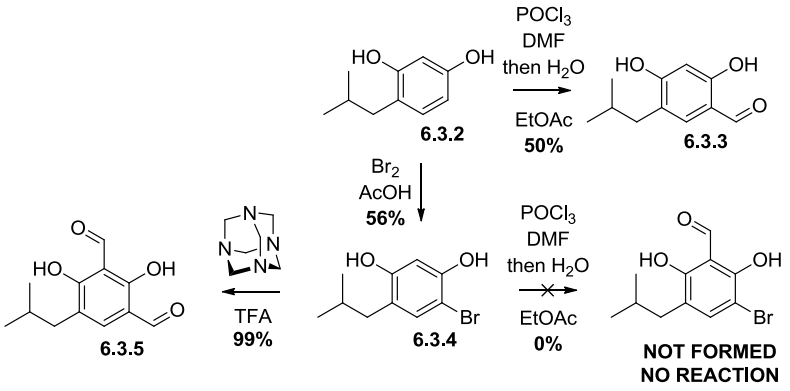
Scheme 6.3 – Introducing *i*-butyl in the aromatic synthesis



From intermediate **6.3.2**, attempts were made to introduce the formyl group at the C2 position (Scheme **6.4**). This was found to be less than straightforward. Vilsmeier-Haak formylation gave only reaction at C6, leading to the undesired aldehyde regioisomer **6.3.3**. To alleviate this problem, resorcinol derivative **6.3.2** was converted to the corresponding bromide **6.3.4**. With the C6' position now blocked, Vilsmeier-Haak formylation conditions gave no reaction. Other formylation conditions such as those of the Duff reaction involving hexamine and TFA gave the dialdehyde **6.3.5**, where unsurprisingly the C-Br bond is cleaved by the strongly acidic

conditions, and both nucleophilic aromatic sites of the intermediate **6.3.2** formed *in situ* are formylated (Scheme **6.4**).

Scheme 6.4 – Attempts to prepare the correct aldehyde regioisomer



Scheme 6.5 – Synthesis of the MOM protected aldehyde **6.3.7** and attempted bromination

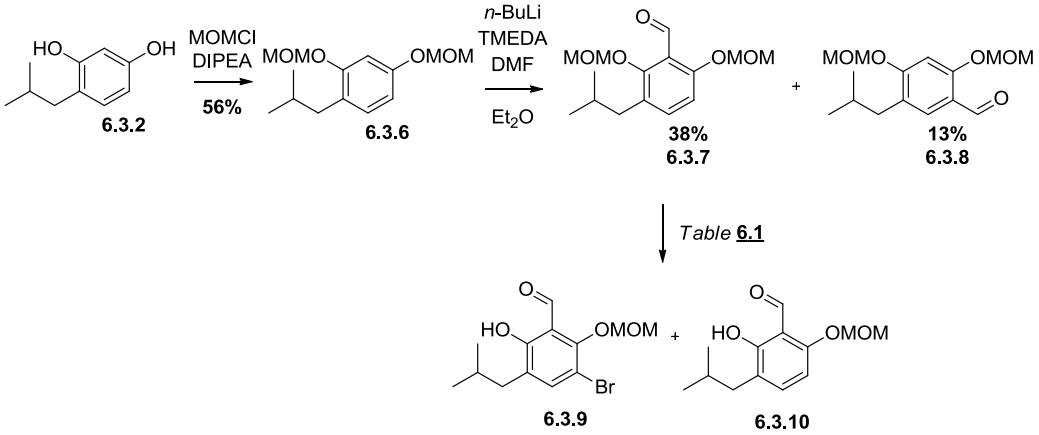


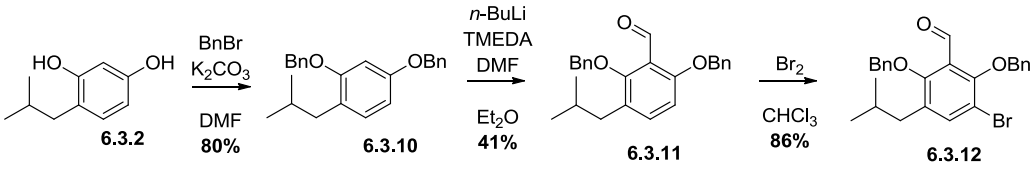
Table **6.2** – bromination of intermediate **6.3.7** – [a] complex mixture of products

Entry	Reagents and Conditions	Product yield /(%) **6.3.10**	**6.3.9**
1	Br_2, TEA, CH_2Cl_2	-	-
2	Br_2, AcOH	[a]	[a]
3	NBS, DMF	86	9
4	Oxone, NH_4Br, MeOH	22	12
5	Br_2, $CHCl_3$	23	-

To avoid the difficulties with this formyl introduction, other protection strategies were investigated. MOM-protection of resorcinol derivative **6.3.2** gave compound **6.3.6** and then *ortho*-lithiation enabled the desired aldehyde **6.3.7** to be prepared with the separable undesired regioisomer **6.3.8** (Scheme **6.5**). From here the bromination was investigated (*see* Table **6.2**), however the desired bromide could not be formed without MOM deprotection, and complex mixtures were formed.

Given the low stability of the MOM ether protecting group to bromination conditions, benzyl protecting groups were investigated as a more resistant protecting group (Scheme **6.6**). From resorcinol derivative **6.3.2**, benzylation gave a good yield of the protected intermediate **6.3.10**. This could then be formylated in moderate yield, using the same conditions as used for the MOM ether **6.3.6**. This aldehyde **6.3.11** could then be easily brominated without issue to give aromatic fragment **6.3.12** ready for a trial Fukuyama coupling.

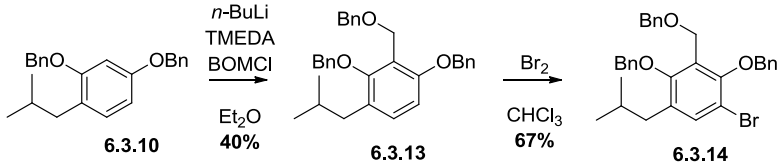
Scheme 6.6 – Synthesis of the benzyl protected aromatic fragment **6.2.12**



6.3.2 Synthesis of the aromatic fragment for organolithium arylation

With the aromatic intermediate **6.3.12** required for Fukuyama coupling in hand, a suitable aromatic fragment for organolithium arylation was prepared. A suitable latent functional group for the reactive aldehyde of intermediate **6.3.12** was found to be methylenebenzyloxy functionality. This group would be stable to organolithium conditions whilst allowing access to the aldehyde upon benzyl deprotection. From **6.3.10**, *ortho*-lithiation and reaction with BOMCl yielded the intermediate **6.3.13** which was then brominated in good yield **6.3.14** (Scheme **6.7**). Both the bromination and reaction with BOMCl were performed and optimised by Joe Watts.[81]

Scheme 6.7 – Synthesis of the benzyl protected aromatic **6.3.14** for arylation

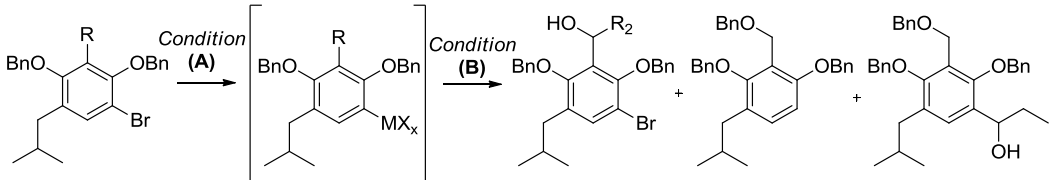


6.4 Joining the aromatic and aliphatic fragments of luminacin D

6.4.1 Trial couplings on a model compounds

With appropriate aromatic fragments available for trial couplings a number of conditions were investigated (Scheme **6.8** and Table **6.3**). For the Fukuyama coupling, *S*-ethyl butylthioate (**6.4.1**) was used as a simple model of the aliphatic system for reaction optimisation. Initial attempts to produce the organozincate with activated zinc produced by the activation of zinc powder with dibromoethane and TMSCl were unsuccessful (entry 1), only stating material was recovered. Using Rieke zinc, formed by the action of lithium metal on a $ZnCl_2$ solution in THF, did give a reaction. However, the mixture of products recovered was inseparable and complex. The green colour of the zincate solution was however present. Attempts to form the Grignard reagent, *i*-PrMgCl and exchange with $ZnCl_2$ did give reaction. But instead of halogen metal exchange, nucleophilic addition of *i*-PrMgCl as well as reduction of the aldehyde occurred giving products **6.4.3** and **6.4.2** respectively (entry 3).

Scheme 6.8 – Trial Fukuyama couplings and arylation reactions (*see* Table **6.3**)



Attempts to optimise the reaction, even on fragment **6.3.14** devoid of the aldehyde, gave no reaction under halogen metal exchange conditions with *i*-PrMgCl (entry 4). Halogen metal exchange with *n*-BuLi and exchange to the organozinacate with $ZnCl_2$, gave only the debrominated **6.3.13** after being subjected to Fukuyama coupling conditions (entry 5). Given

the difficulty associated with the Fukuyama reaction, arylation was then investigated using the aryllithium of **6.3.14**, using propionaldehyde as a mimic of the aliphatic aldehyde **6.1.4** (entry 6). Slight modification of the concentrations enabled better yields to be obtained for this arylation (entry 7).

Table 6.3 – Coupling conditions and respective yields

Entry	Condition (A)	Condition (B)	Yield (%) **6.4.2**	**6.4.3**	**6.3.13**	**6.4.4**
1	(i) Zn, TMSCl, $BrCH_2CH_2Br$, (ii) **6.3.12**, THF, rt	BuCOSEt **6.3.1**, $PdCl_2(PPh_3)_2$, THF, rt	No reaction			
2	(i) Li, $ZnCl_2$, ○))) THF, (ii) **6.3.12**, THF, rt	BuCOSEt **6.3.1**, $PdCl_2(PPh_3)_2$, THF, rt	Complex mixture of products			
3	(i) **6.3.12**, *i*-PrMgCl, (ii) $ZnCl_2$, THF, -78 ºC	BuCOSEt **6.3.1**, $PdCl_2(PPh_3)_2$, THF, rt	29	11	-	-
4	(i) **6.3.14**, *i*-PrMgCl, (ii) $ZnCl_2$, THF, -78 ºC	BuCOSEt **6.3.1**, $PdCl_2(PPh_3)_2$, THF, rt	No reaction			
5	(i) **6.3.14**, *n*-BuLi, (ii) $ZnCl_2$, THF, -78 ºC	BuCOSEt **6.3.1**, $PdCl_2(PPh_3)_2$, THF, rt	-	-	quant	-
6	(i) **6.3.14**, *n*-BuLi, THF, -78 ºC	EtCHO	-	-	-	38
7	(i) **6.3.14**, *n*-BuLi, THF, -78 ºC	EtCHO	-	-	-	58

6.4.2 The coupling on luminacin D and cyclisation of the aliphatic system

With a method available to join the aromatic and aliphatic fragments, demonstrated by the successful reaction between organolithium of aromatic intermediate **6.3.14** and propionaldehyde, these arylation conditions were then translated to the reaction between aliphatic aldehyde **6.1.4** and aromatic **6.3.14** (Scheme **6.9**). It was found that higher equivalence of the aromatic lithium intermediate was necessary to give good conversion to the coupled intermediate **6.4.5**. The timing of reaction after formation of the aryllithium was also important and a reaction time of 45 min was found to be optimal (Table **6.4**).

From the intermediate **6.4.5**, the aliphatic *hemi*-acetal group was then obtained by reduction of the *t*-butyl ester to the aldehyde **6.4.6** which was then easily cyclised upon TES deprotection with TBAF (Scheme **6.10**). The reduction was however capricious and highly dependent on the purity of the epimeric mixture **6.4.5**. The yields were variable, the best obtained being 83%. If the reaction was not run to completion, the remaining starting material proved difficult to separate from the aldehyde product **6.4.6,** even following TES deprotection. Further optimisation may be required here to ensure repeatability of the procedure.

Scheme 6.9 – Arylation reaction for luminacin D synthesis (*see* Table **6.4**)

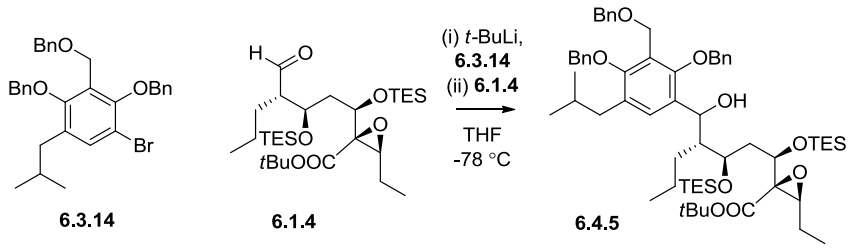
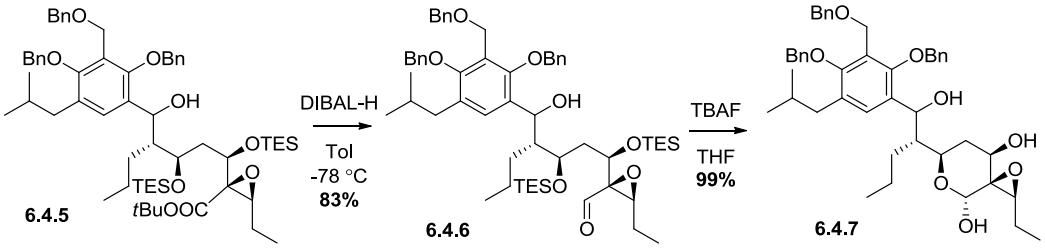


Table 6.4 – Arylation optimisation

		Yield /(%)	
Entry	Equivalence and Timing	**6.4.5**	**6.3.14**
1	(i) *t*-BuLi, **6.3.14** (1.5 equiv), 10 min. (ii) **6.1.4** (1 equiv), 30 min.	33	56
2	(i) *t*-BuLi, **6.3.14** (1.5 equiv), 15 min. (ii) **6.1.4** (1 equiv), 2.5 h.	20	-
3	(i) *t*-BuLi, **6.3.14** (5 equiv), 15 min. (ii) **6.1.4** (1 equiv), 30 min.	65	-
5	(i) *t*-BuLi, **6.3.14** (5 equiv), 15 min. (ii) **6.1.4** (1 equiv), 45 min.	99	-

Scheme 6.10 – Completion of luminacin D aliphatic system by reduction and TES deprotection

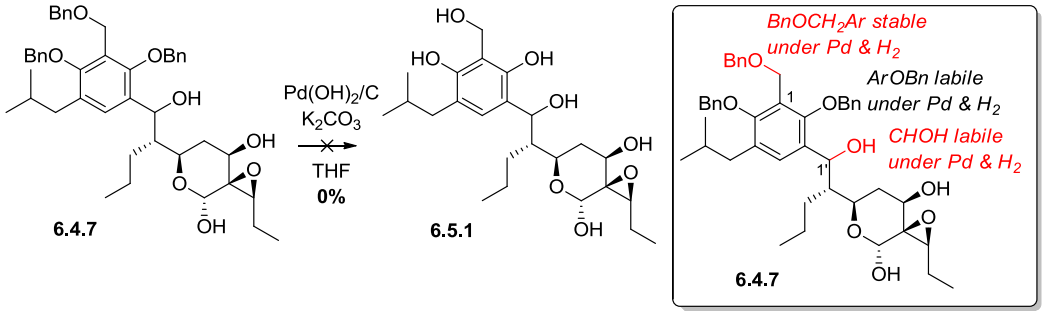


6.5 Completing the synthesis of luminacin D

6.5.1 Unanticipated debenzylation selectivity issues

It was anticipated that from late stage intermediate **6.4.7** debenzylation and subsequent oxidation of the two remaining benzylic alcohols would yield luminacin D. Initial hydrogenation conditions gave surprisingly complicated product profiles, and it became clear that a number of selectivity issues were present in our substrate which prevented conversion to triol **6.5.1** (Scheme **6.11**). Firstly, the dibenzyl ether linkage of C1 position was found difficult to cleave under basic hydrogenation conditions whilst the primary benzyl alcohol formed after its debenzylation was relatively easy to reduce to the methyl group. The secondary benzylic alcohol at the C1' position was also found to be unstable, being reductively labile relative to the C1 dibenzylether linkage under the same conditions. The two benzyl protected phenols were very easy to remove under any hydrogenation conditions (Scheme **6.11**).

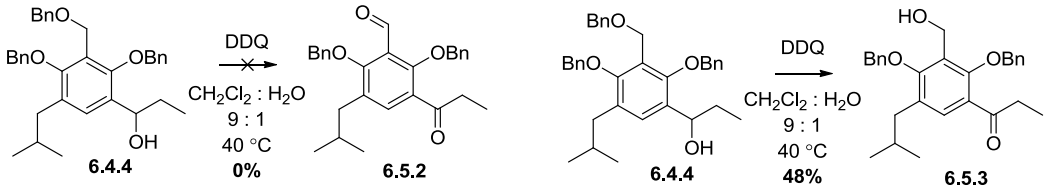
Scheme 6.11 – Attempted debenzylation of intermediate **6.4.7**



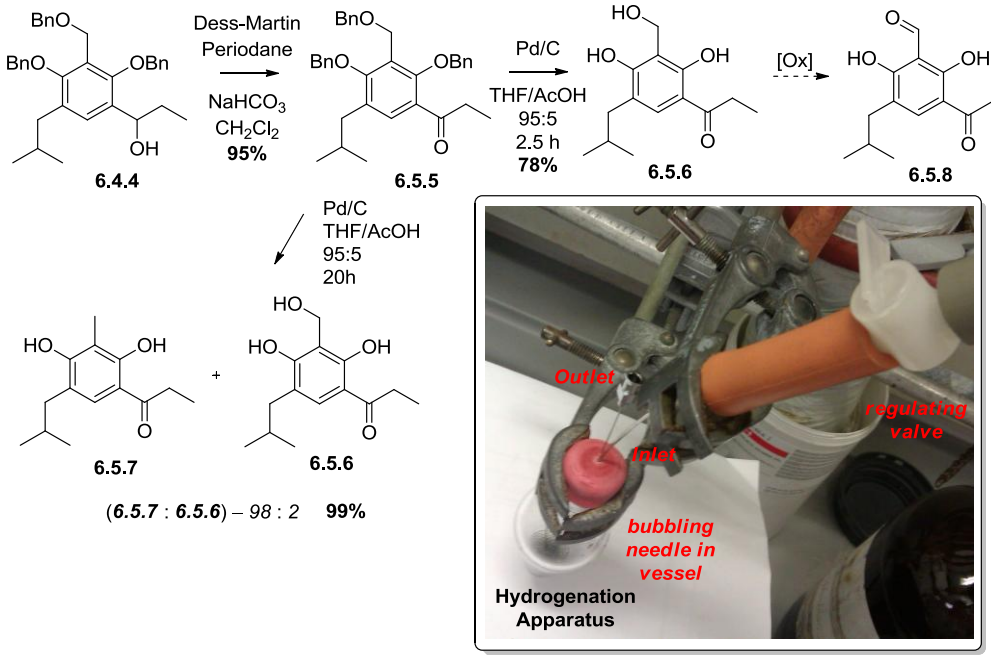
Conditions to enable the removal of the protecting benzyl groups were then explored on model aromatic compound **6.4.4** and it was envisaged that with the electron rich aromatic ring of this compound, DDQ could enable the removal of the benzyl groups with concomitant oxidation of the key alcohol positions at C1 and C1' to give product **6.5.2** (Scheme **6.12**). A number of conditions were explored based on known examples where similar transformations had been achieved.[82] The reactions were all unsuccessful at achieving the desired transformation, and many different inseparable products were formed in the reactions. The most promising example is given in Scheme **6.12**. In this case the secondary alcohol of compound **6.4.4** was oxidised, and the bis-benzyl ether cleaved giving **6.5.3**, but no further oxidation of the formed primary alcohol occurred. This may be due to the deactivating effect of the aromatic ketone

formed during the reaction or just down to reaction conditions. It is likely that these reactions could reveal novel chemistry under a more exhaustive investigation.

Scheme 6.12 – DDQ promoted oxidation/debenzylation example



Scheme 6.13 – oxidation, reduction, oxidation sequence avoiding selectivity issues



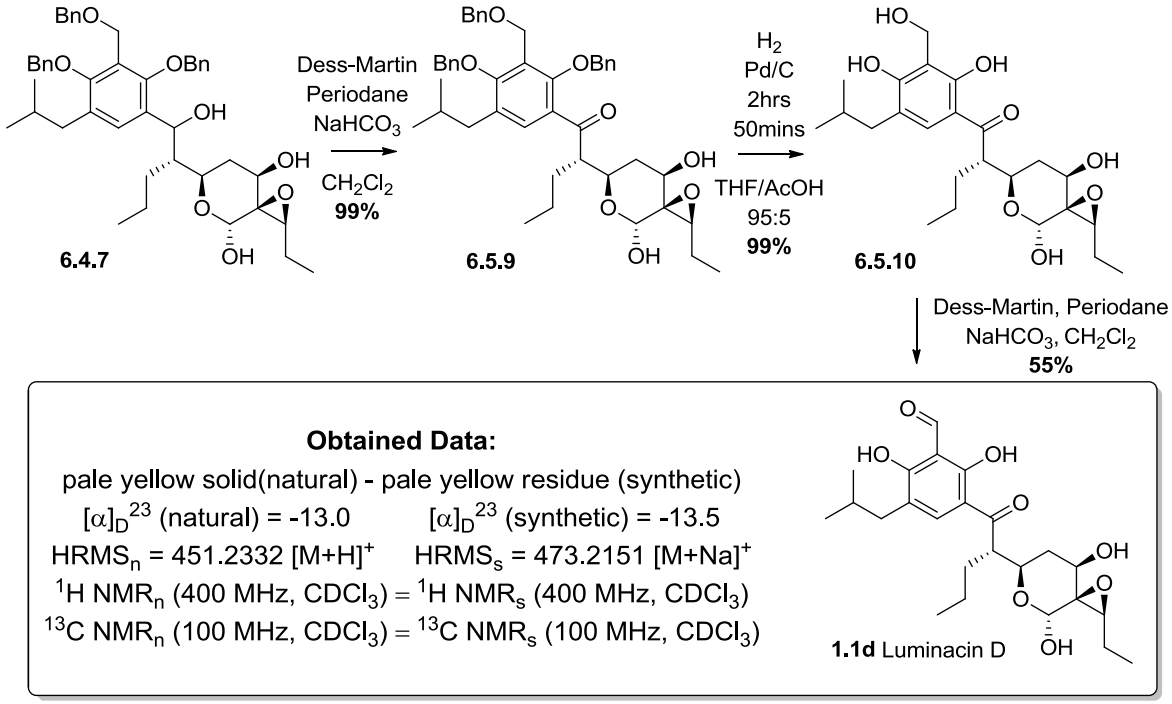
Given this unsuccessful approach to the selectivity requirements for the last stages of the synthesis a longer approach was taken to ensure the successful completion of luminacin D. Again this was first investigated on a model system **6.4.4** (Scheme **6.13**). In this route, Dess-Martin oxidation of the C1' alcohol to the ketone **6.5.5** blocks reduction of this position during debenzylation. Manganese dioxide was found ineffective at this transformation on small scale. The full debenzylation from the ketone **6.5.5** was achieved under acidic conditions to give the triol **6.5.6.** However, the reaction duration was critical as the triol **6.5.6** was easily converted to the diol **6.5.7**. The delivery of hydrogen to the reaction was also important to ensure

repeatable results and this was achieved by valve controlled bubbling of hydrogen gas directly into the reaction suspension. The same oxidation would have then lead to the completed aromatic fragment **6.5.8**, analogous to luminacin D.

6.5.2 Completion of luminacin D

These successful reactions on the aromatic system **6.4.4** were then applied to intermediate **6.4.7**. Gratifyingly, the initial Dess-Martin oxidation to ketone **6.5.9** proceeded in quantitative yield, as did the subsequent debenzylation reaction to triol **6.5.10**. The final primary oxidation to give luminacin D **1.1d** was less pleasing giving only a moderate yield of the natural product. Attempts to modify the reaction by removing the $NaHCO_3$ buffer only exacerbated the situation (<15% impure). Given constraints on available material no further optimisation of this final step was undertaken.

Scheme 6.13 – Last steps to luminacin D



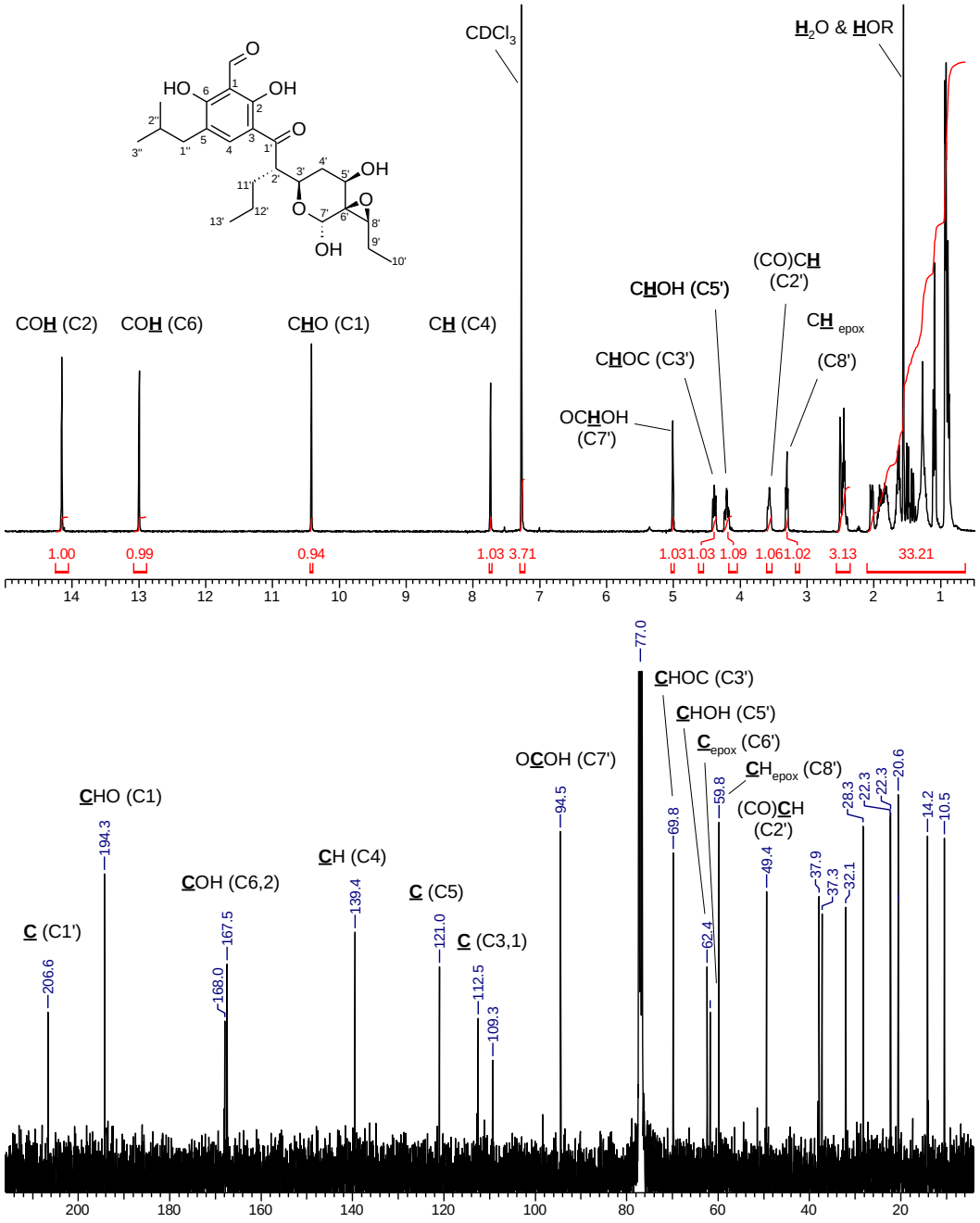


Fig 6.2 – ^{1}H and ^{13}C NMR of luminacin D with diagnostic peaks assigned.

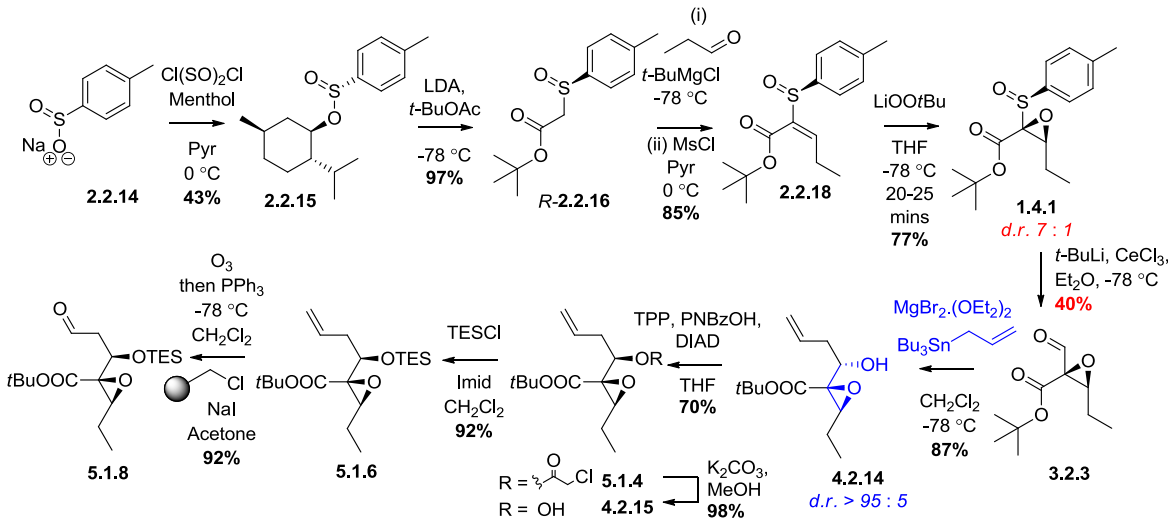
It was found that both ^{1}H and ^{13}C NMR data of our synthetic luminacin D **1.1d** closely matched the published data of Wakabashi *et al*.[1] The $[\alpha]_D$ value obtained was amicably close to that of the natural material, supporting the enantioselectivity of our synthesis. The many challenges faced during the synthesis were overcome to arrive at a route to luminacin D as the pure enantiomer a feat not convincingly achieved in the other older syntheses. This has enabled sufficient material for intial biological testing and gives a method for the further

preparation of luminacin D. More general conclusions on this work will be discussed in the last chapter.

Chapter 7 Conclusions and Future Works

7.1 Conclusions

Scheme 7.1 – Summary of linear route to luminacin D – *pre aldol*

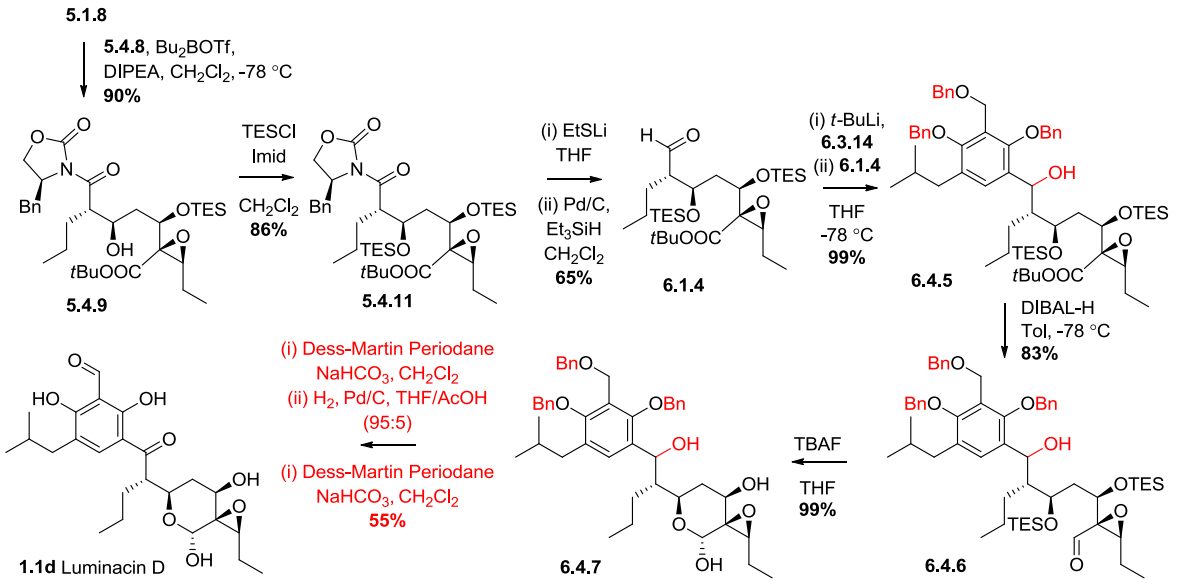


In general, as depicted in Scheme **7.1** and **7.2** our route to luminacin D has a number of high yielding transformations. The route enabled the synthesis of (-)-luminacin D in 20 linear steps from commercially available starting materials, with an overall yield of 2.9% (from commercially available materials). Further repetition of our synthesis would allow preparation of enough luminacin D for in-depth biological investigation of this interesting natural product. However, there were a number of weaker steps in the synthesis that could be addressed.

This includes the epoxidation of alkene **2.2.18** to epoxide **1.4.1** and subsequent formylation of epoxide **1.4.1** to aldehyde **3.2.3** (Scheme **7.1**). As well as the reaction involving the reduction of ester **6.4.5** to aldehyde **6.4.6**, this could be optimised to ensure repeatability (Scheme **7.2**). Also, a significant improvement could be made to the end sequence of the synthesis as well and all these points will be discussed below (Scheme **7.2**, red). Of additional interest is the computational work undertaken on related chelated α-substituted aldehydes, relevant to allylation of our synthesis (Scheme **7.1**, blue, see Chapter 4), a lot of the substrates studied through calculations have yet to be synthesised and studied experimentally (some distantly related substrates have and are included in Section **7.4**).

These calculations will be discussed in this Chapter for completeness and where relevant should be tested by subsequent experimental studies.

Scheme 7.2 – Summary of linear route to luminacin D – *post aldol*



7.2 Proposed improvements to the synthesis

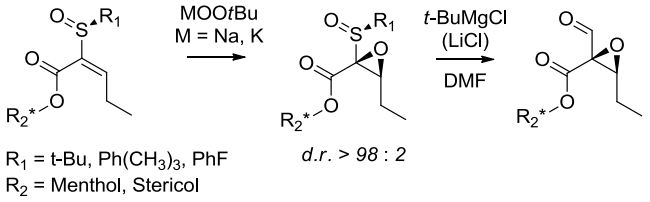
A number of improvements could be made to the current epoxidation in the synthesis (Scheme **7.1**). An investigation into the sulfoxide aromatic substituent of alkene **2.2.18** would be interesting. Changing from phenyl **2.2.8** to tolyl **2.2.18**, when changing from the racemic to enantioselective synthesis had a surprisingly pronounced effect on reaction diastereoselectivity (*d.r. 94 : 6 → 7 : 1*). Sulfoxide ligands which may make interesting substrates include *t*-butyl, mesityl and F-phenyl (electron poor) and these could be introduced in a similar manner to the tolyl in the enantioselective synthesis (Scheme **7.3**). The origin of altered reaction diastereoselectivity may however arise from changing to an enatioenriched environment from a racemic environment, where one could envisage a templating or anisotropic phase phenomena becoming important. It may only be possible to rule this out through investigating reaction with racemic and enantioenriched tolyl epoxide **2.2.18**.

As discussed by De La Pradilla *et al*. the use of other alkali metal peroxides may improve selectivity, such as the use of NaOO*t*Bu as a substitute for LiOO*t*Bu.[33] To avoid the formation of side products and to enable a low concentration to be used effectively on

large scales, a flow chemistry procedure could also be employed. It may also be prudent to use a different ester alkyl group as opposed to *t*-butyl group utilised. Another sterically demanding alcohol devoid of any acidic positions and perhaps pocessing chirality would be suitable (for example menthol). This could enable higher enantioselectivities to be achieved in the epoxidation by double diastereoselection whilst also enabling easier separation of the undesired diastereomer.

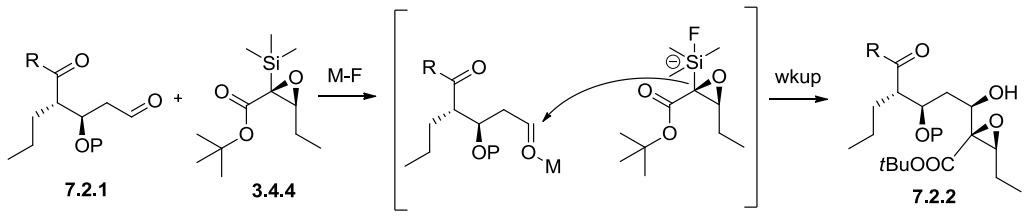
Further optimisation of the proceeding oxiranyl anion formylation is also required to improve the route to aldehyde **3.2.3**. The use of *t*-butyl Grignard should be further investigated as it was observed here that less side reactions were present from the reaction (Scheme **7.3**). A systematic approach to the investigation of this reaction could yield more information that could lead to a much better reaction outcome.

Scheme 7.3 – Possible improvements to the epoxidation and formylation reaction



Another approach involving a substantial route change could utilize the silyl epoxide **3.4.4** formed in Scheme **3.5**. Metal fluoride activation of this substrate may enable its nucleophilic addition to an appropriate aldehyde to give the desired aliphatic stereoisomer **7.2.1**. It is unknown if the selectivity of such a reaction would be appropriate for total synthesis.

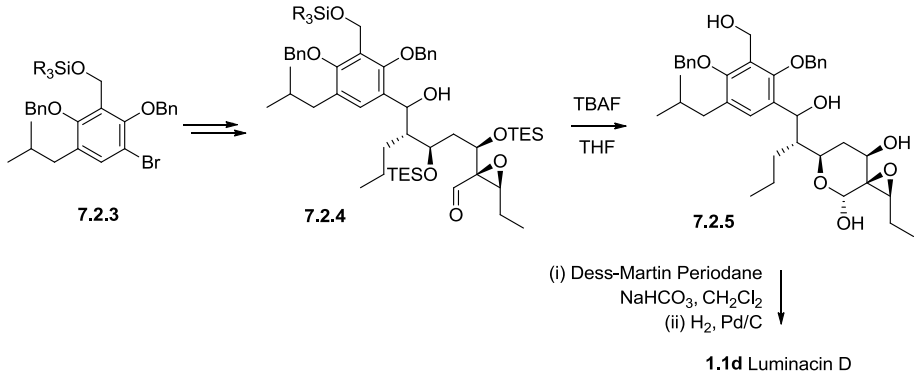
Scheme 7.4 – A different approach to luminacin D using silyl epoxide **3.4.4**



In the later stages of the synthesis, the reduction of the *t*-butyl ester **6.4.5** with DIBAL should be further investigated. Although a good yield was achieved for this transformation

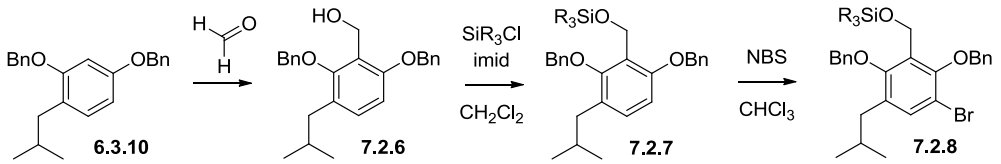
a reliable procedure needs to be found to ensure pure intermediates can be formed in the later stages of the synthesis. This should only require adjustments in reaction timing and reagent equivalence to ensure complete conversion to the aldehyde **6.4.6**. Perhaps the best improvements in the synthesis can be achieved through changes to the protecting group strategy at the end of the synthesis. If aromatic moiety **7.2.3** is incorporated into the synthesis you would arrive at late stage intermediate **7.2.4** by repetition of the required steps (Scheme **7.4**). From here deprotection using TBAF would reveal both benzylic alcohols at the C1 and C1' positions (**7.2.4**). These could then be oxidised to the aldehyde and ketone in one pot, giving the benzyl protected luminacin D, which upon subjecting to standard hydrogenation conditions should give luminacin D **1.1d**. This sequence would then eliminate the low yielding final oxidation and shorten the synthesis by one step.

Scheme 7.4 – A different protecting group strategy in the luminacin D synthesis.



The relevant aromatic fragment **7.2.3** could be prepared by hydroxymethylation of aromatic moiety **6.3.10** (Scheme **7.5**)**.** The alcohol **7.2.6** could then be protected with an appropriate silyl protecting group and the protected aromatic **7.2.7**, brominated to give the fragment **7.2.8** ready for coupling to the aliphatic fragment through its organolithium species (Scheme **7.5**).

Scheme 7.5 – A different protecting group strategy in the luminacin D synthesis.



These discussed points are the main areas required to refine the synthesis to more efficiently produce luminacin D synthetically via our route. However there is further work to be done on the allylation reactions discussed in Chapter **4**. This was prompted by the computational studies which are discussed below.

7.3 Computational studies of α-substituted aldehydes

Scheme 7.6 – Allylation reactions investigated in the Linclau group. [a] – Experimental work involving the synthesis and allylation reactions of highlighted compounds to be undertaken in future work.

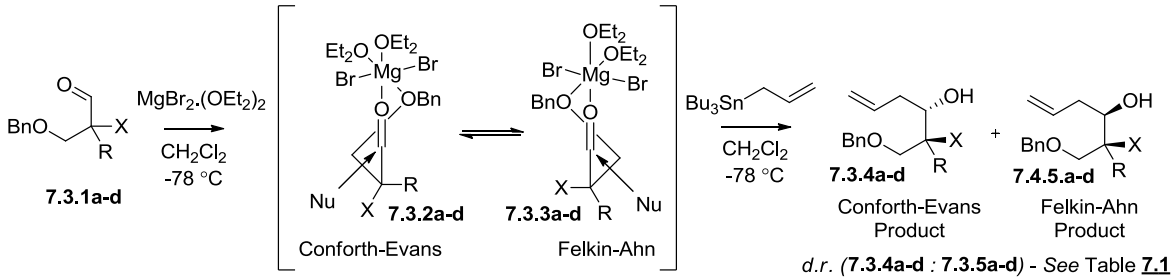


Table 7.1 – Summary of computational and experimental results, including calculated relative free energy of Conforth-Evans and Felkin-Ahn conformer as well as experimentally obtained *d.r.*

entry		X group	R group	angle C=O C-X	angle C=O C-R	ΔG /Kjmol^{-1}	*d.r.*	yield
1	**7.3.5a**[a]	F	H	66	176	+15	minor	n/a[a]
2	**7.3.4a**[a]	F	H	172	70	0	major	
3	**7.3.5b**[a]	F	Me	61	179	+47	minor	n/a[a]
4	**7.3.4b**[a]	F	Me	152	91	0	major	
15	**7.3.5c**[a]	STr	H	97	149	0	major	n/a[a]
16	**7.3.4c**[a]	STr	H	170	71	+1	minor	
7	**7.3.5d**[a]	STr	Me	94	140	0	major	n/a[a]
18	**7.3.4d**[a]	STr	Me	124	11	+2	minor	

[a] – Experimental results have not been obtained at time of writing.

A number of other magnesium chelated, α-substituted aldehydes were studied with DFT calculation, in relation to the allylation reaction and conformational models discussed (Chapter **4**). The results are summarised in Table **7.1**. The answer to the question of

whether the Evans-Conforth or Polar Felkin-Anh models operate in these substrates is still to be confirmed through experimental investigations.

7.3.1 The allylation of α-Fluoroaldehydes

A set of β-benzyloxy-α-hetereoatom aldehyde substrates were investigated computationally, with both α-heteroatom-α-hydrogen tertiary centres and α-hetereoatom-α-methyl substitution (see Scheme **7.6** and Table **7.1**), results showed that for the α-fluoro substrates **7.3.1a-b**, the Felkin-Ahn conformation **7.3.3a-b** was of a higher energy relative to the Conforth-Evans **7.3.2a-b** conformation for both the α-hydrogen **7.3.3a** (ΔG = +15 KJmol^{-1}) and α-methyl **7.3.3b** variants (ΔG = +47 KJmol^{-1}). With the α-methyl **7.3.1b** example having a much greater preference for the Conforth-Evans conformation **7.3.2b**, this means that the Conforth-Evans product is expected for both in the experimental investigation. But, for the α-methyl **7.3.1b** example a much greater selectivity should be observed. Presently, full experimental results have not been acquired for this example.

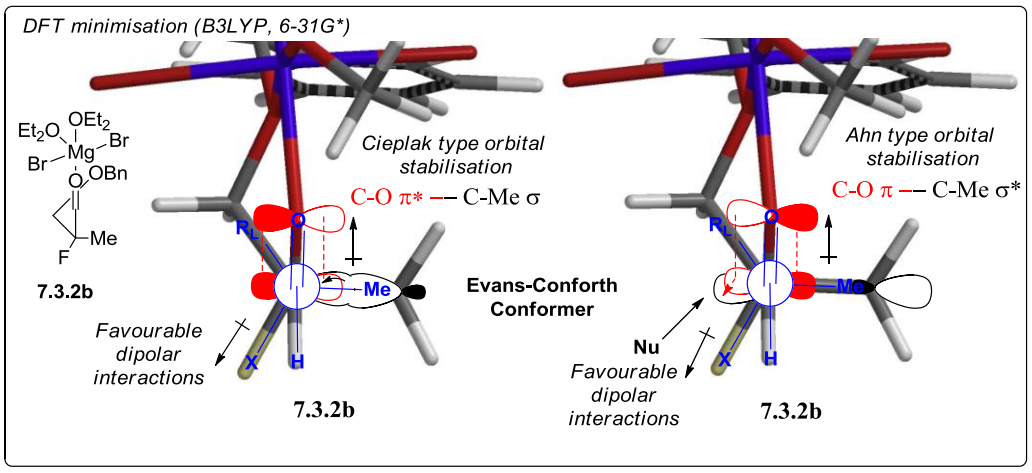


Fig 7.1 – Secondary orbital effects in the Evans-Conforth conformer **7.3.2b**.

The origin of the stability calculated for the Conforth-Evans conformers **7.3.2a-b** must primarily be a result of the favourable dipolar interactions experienced when aligning the carbonyl and C-F bonds close to antiparallel. However the fact that the free energy difference greatly increases between the Conforth-Evans and Felkin-Ahn conformers for the α-hydrogen **7.3.1a** to α-methyl substrate **7.3.1b** hints at another underlying effect. The result is likely to be down to sterics as in the Felkin-Ahn conformer **7.3.3b** the aldehyde C-H and C-Me approach an eclipsing dihedral angle. However there may be other secondary

orbital interaction as are described in Fig **7.1**. Ahn stabilisation maybe operating where the C-Me σ* orbital is accepting electron density from the C=O π orbital, alternatively, Cieplak stabilisation maybe occurring where C-Me σ orbital is donating density to the LUMO (C=O π* orbital). The latter effect is less probable from the calculations as a C-H σ bond would be expected from Cieplak's work to be a better donor and stabilise the Conforth-Evans conformer more than for the α-hydrogen example **7.3.2a**.[60]

7.3.2 The allylation of α-Stritylaldehydes

An interesting exception to the Conforth-Evans model is the case of α-thiol aldehydes. Computational analysis shows a small but significant preference for Felkin-Ahn conformer **7.3.3c-d** over the Conforth-Evans conformer **7.3.2c-d**. The reason for the preference of the Felkin-Ahn conformer can be explained by thiols diminished bond polarisation but excellent σ* acceptor properties as noted by Evans and Cramer in their calculations for aldol reactions.[61b] This means Ahn orbital interactions (C=O π → C-S σ*) are dominant in α-thiol substrates.

The preference for the Felkin-Ahn conformer **7.3.3c-d**, was true for both the α-hydrogen aldehyde **7.3.1c** ($\Delta G = +1$ KJmol^{-1})[8] and the α-methyl aldehyde **7.3.1d** ($\Delta G = +2$ KJmol^{-1}), the difference in free energies for the α-methyl example **7.3.1d** again was slightly larger. The torsional eclipsing interaction between C-H of the aldehyde and C-Me does not hold here as an increase steric bulk of C-R for **7.3.1c-d** should destabilise the Felkin-Ahn conformer **7.3.3c-d**. If the described eclipsing interaction was important the opposite result would be observed. An explanation for this discrepancy may be a result of the slight puckering in the ring of the minimised α-hydrogen Felkin-Ahn conformer **7.3.3c**, which allows a greater dipolar stabilisation to be achieved for this conformer shrinking the energy difference between the α-hydrogen conformers **7.3.2c** and **7.3.3c**, relative to the α-methyl substrate conformer's energy difference **7.3.2d** and **7.3.3d**. It is likely that this is more a result of the method by which the conformer was found and minimised computationally, rather than an effect which would be observed experimentally. What is however of key importance is a change in preference for the Felkin-Ahn conformer **7.3.3c-d**. It is also noteworthy that the low energy difference between the conformers should mean only a

[8] free energy difference between the Felkin-Ahn and Conforth-Evans conformer, Felkin-Ahn conformer set at 0 KJmol^{-1}

moderate diastereoselectivity is achieved experimentally. The experimental investigations for these substrates have yet to be undertaken.

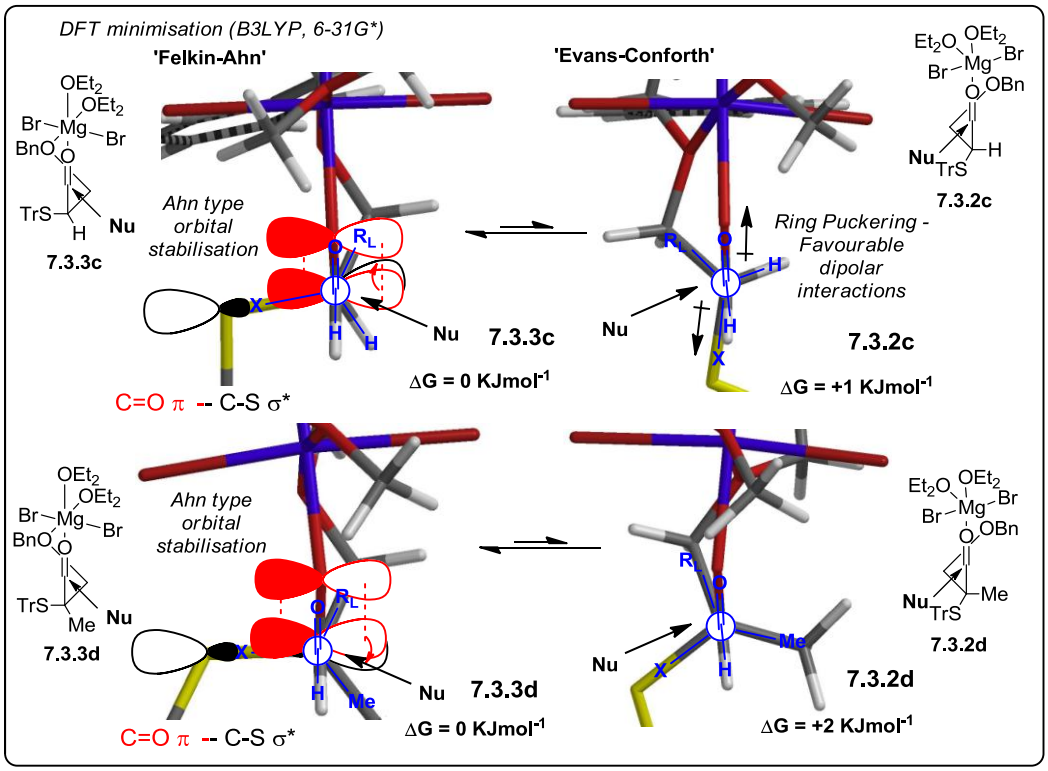


Fig 7.2 – Newman projections and interpretation of calculations on chelated aldehyde **7.3.1c-d**

7.4 Allylation of aldehydes with α-*All*-*C* quaternary centres

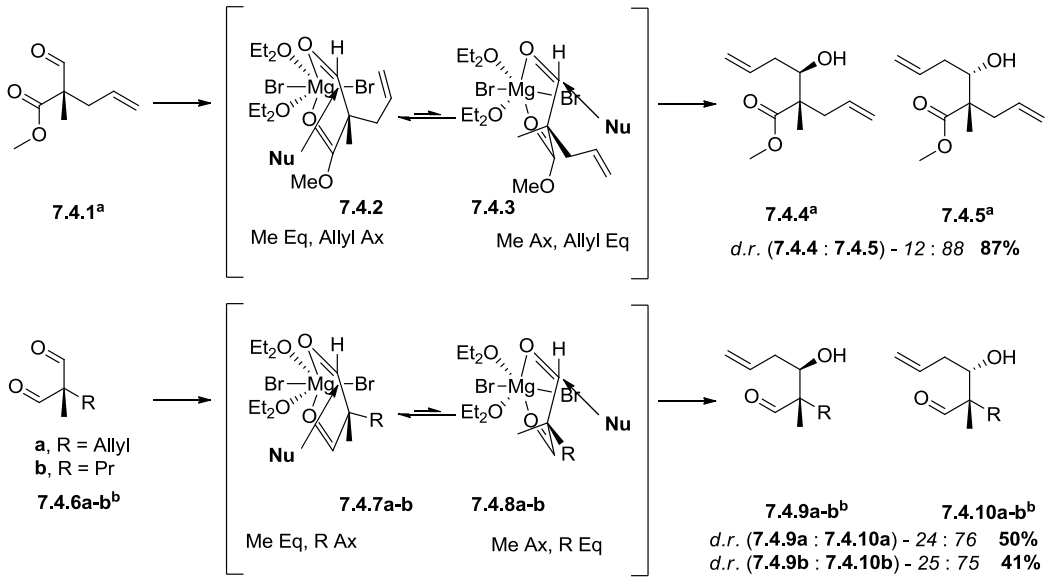
7.4.1 In relation to the work of Mulzer *et al.*

Investigations into the selectivity of allylation reactions were also extended to substrates without α-heteroatoms but instead *all* carbon substituents. The experimental work of Mulzer and Prantz using a similar allylation methodology was of interest and was analysed with conformational DFT calculation.[83] This analysis was extended to other substrates and the calculations were supported by the experimental work of Catherine Oakes (see Scheme **7.7** and Table **7.2**).[64b]

For the computational analysis the allyl substituent (for **7.4.1** and **7.4.6a**) sits *pseudo*-axial in the favoured conformer in preference to the methyl which sits in the *pseudo*-equatorial position (Scheme **7.7**). This allows the nucleophile to approach from the less sterically congested face past the methyl as shown in **7.4.2** and **7.4.7a**, this result is supported by the

experimentally obtained, reaction diastereoselectivities. For the substrate **7.4.6b**, analysis of conformations by DFT methods shows the propyl substituent sits *pseudo*-equatorial **7.4.8b** in preference to *pseudo*-axial **7.4.7b** (ΔG = +9 KJmol^{-1}). However experimental results of Oakes show the diastereoselectivity of reaction is again in preference for facial attack as in **7.4.7b**.[64b]

Scheme 7.7 – Allylation of aldehydes with α-*All-C* quaternary centres: [a] – Experimental results of Mulzer and Prantz,[83] [b] – Experimental work of Catherine Oakes.[64b]



The origin of the computational results can be broken down into two effects (Fig **7.3**). Importantly the C-R bond lengths are longer in the axial position relative to the equatorial site and this shows the importance of the C=O π donor → C-R σ* acceptor hyperconjugation effect, noted by Eisenstein and Ahn.[59] The relative C-R σ* acceptor abilities of groups can be expressed C-Allyl > C-Pr ≈ C-Me as deduced from a related study.[84] So from the Ahn effect alone a preference for the axial position would be observed for the allyl substituent but perhaps no strong preference between the methyl or propyl. The second effect which becomes important is that of steric stain. This is greatest in the conformation **7.4.3** where the *pseudo*-equatorial position of the allyl substituent experiences allylic stain interactions with the OMe of the ester chelating group. When looking at the analogues conformation **7.4.8a** for the α-methyl-α-allyldialdhyde **7.4.6a**, a much diminished allylic strain interaction is present and this explains the greater selectivity observed with the ester aldehyde **7.4.1** substrate in comparison to the dialdehyde **7.4.6a** substrate. This is also reflected in the computationally calculated difference in free energy

between the two conformers for both aldehydes (**7.4.1** - ΔG = +19KJmol^{-1}, **7.4.6a** - ΔG = +4 KJmol^{-1}).

Table 7.2 – Computational and experimental studies on the allylation of aldehydes with α-*All-C* quaternary centres.

Entry		Other Chelating group	R group	angle C=O C-R	angle C=O C-Me	ΔG KJmol^{-1}	*d.r.*	yield
1	**7.4.2**[a]	COOMe	Allyl	92	143	0	88	87%[a]
2	**7.4.3**[a]	COOMe	Allyl	141	100	+19	12	
3	**7.4.7a**[b]	CHO	Allyl	95	146	0	76	50%[b]
4	**7.4.8a**[b]	CHO	Allyl	139	101	+4	24	
5	**7.4.7b**[b]	CHO	Pr	99	142	+9	75	41%[b]
6	**7.4.8b**[b]	CHO	Pr	139	101	0	25	

[a] – Experimental results of Mulzer and Prantz,[83] [b] – Experimental work of Catherine Oakes.[64b]

Another steric effect not discussed but which may play an important role for the last entry from aldehyde **7.4.6b**, in Table **7.2**, is that of 1,4-flagpole interaction. As substrate **7.4.6b** is a dialdehyde, allylic strain interactions are less important but when the propyl is in the *pseudo*-axial position steric interactions with freely rotating propyl group and bromide (possible entropic restrictions created - ΔS – 6 KJmol^{-1}) increase the energy of this conformation **7.4.7b** relative to the conformation where the methyl take the *pseudo*-axial position **7.4.8b**. With only minor contributions from the Ahn orbital effect as both groups have approximately equal σ*, C-R acceptor abilities, the flagpole interaction then becomes the important effect (see Fig **7.3**). However, this still does not match the experimental observations of Oakes and this disagreement could be due to steric interaction energies of the approaching nucleophile, in the true transition state, which is not encapsulated in this conformational analysis of the chelated aldehyde **7.4.6b**.[64b]

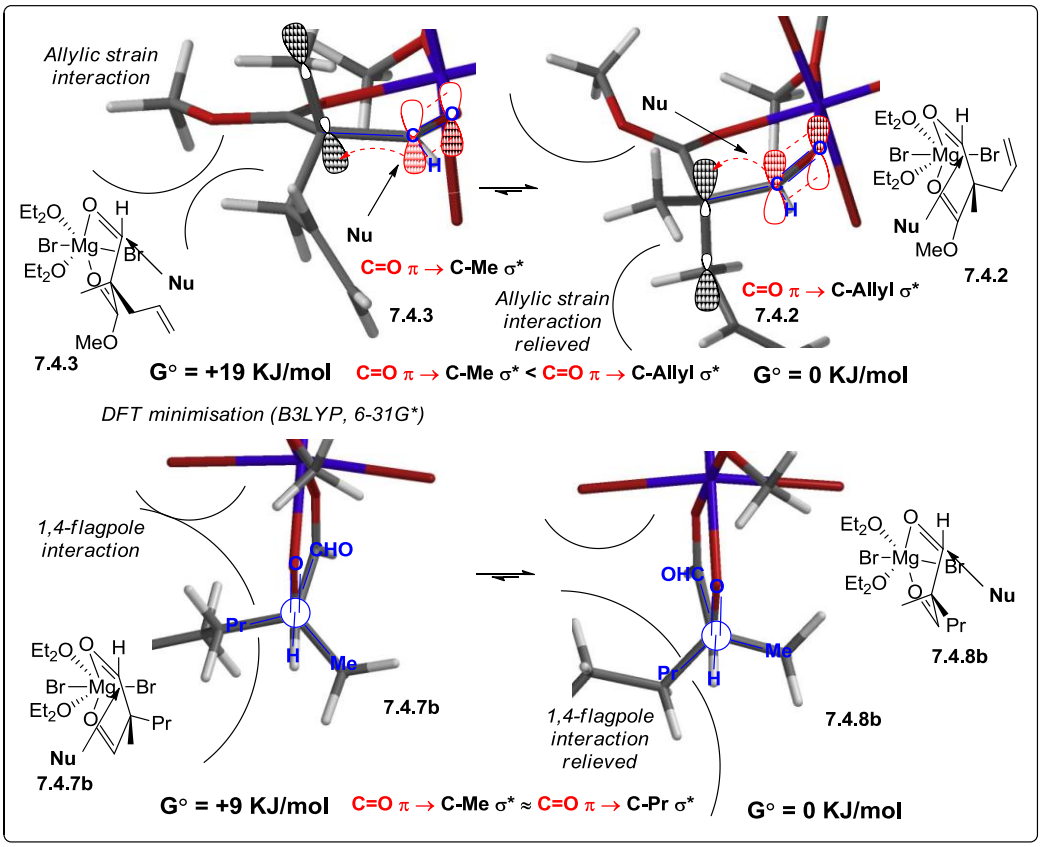


Fig 7.3 – Newman projections and interpretation of calculations on chelated aldehyde **7.4.1** and **7.4.6b**

7.4.2 The allylation of α-methyl-α-CH_2OR aldehydes

Our computational investigations were further extended to other aldehydes containing α-methyl-α-CH_2OR substitution. The normal method, used for previously discussed systems, were unsuccessful when employed to find ring flip conformations for these α-methyl-α-CH_2OR chelated species. Instead only a minimised structure could be found in these cases. The other higher energy ring flip conformation was either too unstable meaning, it is an effectively an unpopulated molecular state or too labile, meaning it is not a local minimum. The latter point also means that the unstable state realistically, would not exist or effect reaction outcome. However the following results will be discussed with respect to the computed energy minimised structures.

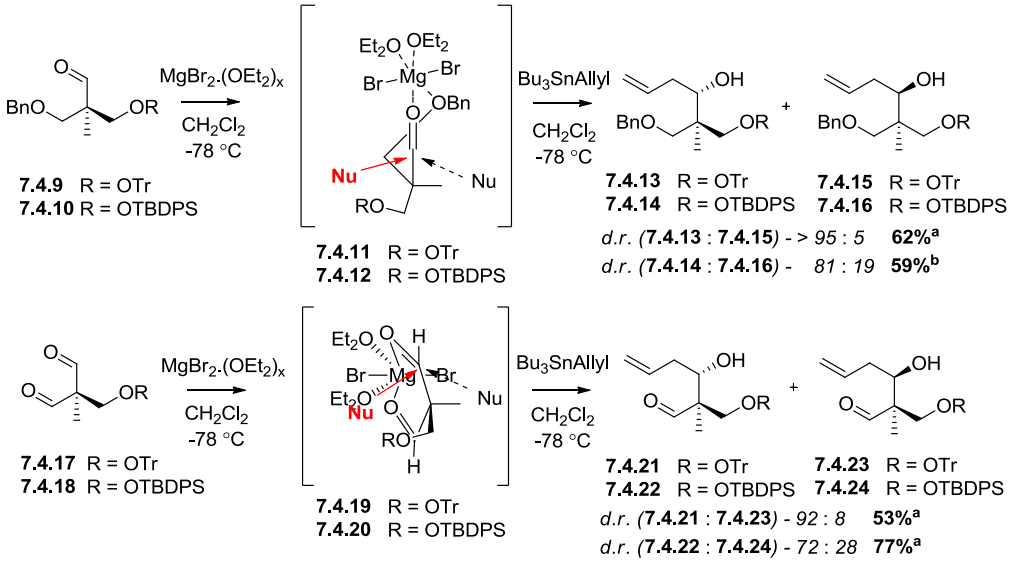
All the reactions (Scheme **7.8**) proceed giving a major product that corresponds to nucleophile approach from the same face as the CH_2OR group. Calculations show that the chelated species adopt structures with this larger and polarised group in the *pseudo*-equatorial position, allowing the nucleophile to approach from the same face and enabling

the reaction to pass through a 'chair' like transition state. Attack on the other face of the same conformer would induce a higher energy, twist boat transition state and hence would be disfavoured.

Two other trends are apparent in the experimental results of Oakes and Smith.[64b, 64c] the OTr (**7.4.9** and **7.4.17**) gives a better diastereoselectivity to the OTBDPS (**7.4.10** and **7.4.18**) protection and the CH_2OBn (**7.4.9** and **7.4.10**) substrates give higher diastereoselectivities than the dialdehydes (**7.4.17** and **7.4.18**). The first of these trends can be explained by the slight difference in steric hindrance between the two protecting groups. More interestingly, the second trend is likely to be a result of the two slightly different conformations adopted by the two chelate types. For the CH_2OBn aldehydes (**7.4.9** and **7.4.10**) the half-chair conformation makes a strong distinction between facial attack leading to a chair or twist boat transition state. For the dialdehydes (**7.4.17** and **7.4.18**) the 'open-book' transition conformation is much flatter and attack from the disfavoured face, passing the methyl substituent, does not impart such a drastic difference in transition states. Hence, the energies of the two transitions are likely to be closer leading to a lower reaction diastereoselectivity. (The energy minimised, chelated aldehydes are illustrated in Fig **7.4**).

The allylation reactions investigated are interesting because of the diverse factors which effect overall reaction outcome. For the α-heteroatom substituted aldehydes minimisation of dipole interactions as well as stabilisation through the Anh effect seems to be important and even with carbon based substituents these effects still play a role. However different types of steric interactions can become important in different substrates and these factors can have a pronounced effect on the expected selectivity of the reaction outcome. It is clear that these investigations could be further extended to different substrates and other nucleophilic additions.

Scheme 7.8 – Summary of experimental results on the allylation of aldehydes with α-*All-C* quaternary centres. [a] – Experimental results of Catherine Oakes,[64b] [b] – Experimental results of Craig Smith.[64c]



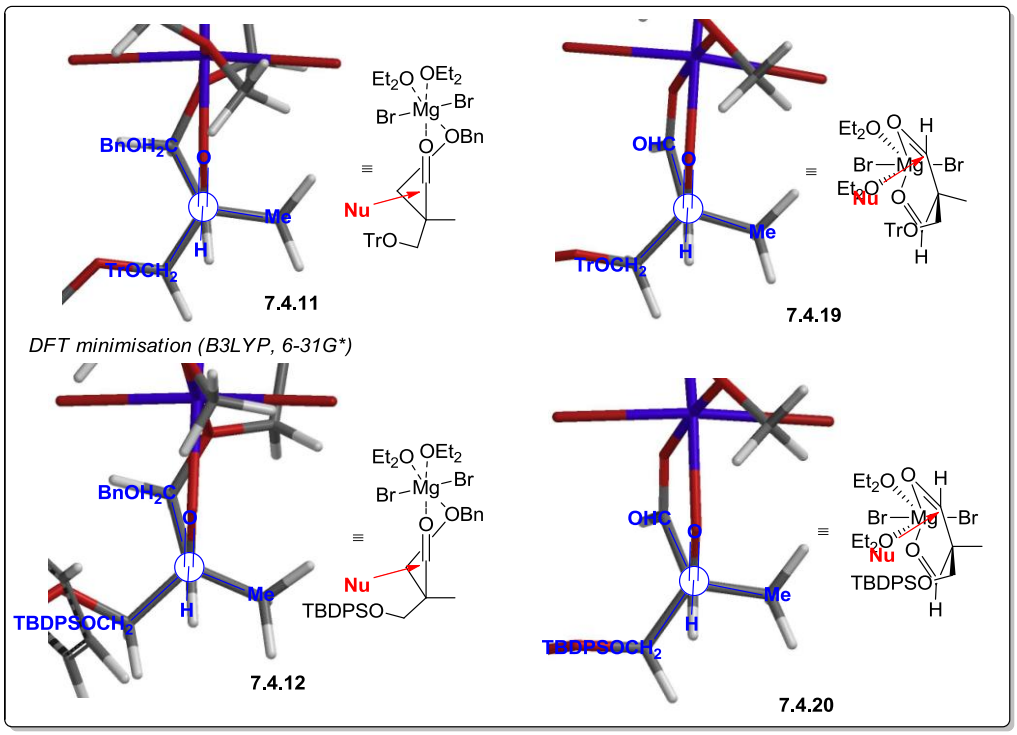


Fig 7.4 – Newman projections on chelated aldehydes **7.4.11**, **7.4.12**, **7.4.19** and **7.4.20**.

Chapter 8 Experimental

General Method

All reaction vessels were flame dried under vacuum and cooled under nitrogen prior to use. All water sensitive experiments were carried out under nitrogen or argon atmosphere, using dry solvents. For the reactions performed at low temperatures, dry ice was used as a cryogenic substance.

CH_2Cl_2, Et_3N and EtOAc were distilled from CaH_2; THF, Benzene and Et_2O from Na/benzophenone. MeCN was dried over molecular sieves. All chemical reagents were ordered from Acros Organics, Alfa Aesar, Fisher Scientific, Merck (VWR), Sigma-Aldrich and TCI.

All reactions were monitored by TLC (Kiesgel 60 F_{254} MERCK Art. 5735 aluminium sheet). The TLC dyes used included a solution of *p*-anisaldehyde for nucleophilic compounds (186 mL of EtOH, 6.9 mL of H_2SO_4, 2.1 mL of AcOH, 5.1 mL of *p*-anisaldehyde), a solution $KMnO_4$ for oxidizable compounds (A solution of 3 g $KMnO_4$, 20 g K_2CO_3 and 5 mL NaOH (aq., 5 w%) in 300 mL H_2O), DNPH solution for aldehydes and ketones (A solution of 12g DNPH, H_2SO_4 conc. 60 mL, water 80 mL and ethanol 200 mL) and a solution of $PdCl_2$ for sulfur containing compounds (0.5% $PdCl_2$ *w/w* in 200 mL water, 1 mL conc. HCl).

Column chromatography was performed on silica gel (60 Å). Particle size 35–70 µm, or 40–63 µm. All reported solvent mixtures are volume measures. Preparative HPLC was carried out using Biorad Bio-Sil D 90-10 columns (250 × 22 mm at 15–20 mL min^{-1} and 250 × 10 mm at 5 mL min^{-1}).

NMR spectra were recorded on a BRUKER AV300 at 300 MHz (^1H) and 75 MHz (^{13}C), or on a BRUKER AV400 at 400 MHz (^1H) and 100 MHz (^{13}C) using the residual solvent as the internal standard. The coupling constants (*J*) are expressed in hertz and the chemical shift in ppm. IR spectra were recorded on a THERMO MATSON Fourier Transform spectrometer. The wave numbers (υ) are given in cm^{-1}. LRMS spectra were accomplished with ThermoQuest Trace MS, single quadrupol GC. This instrument was used for electron ionisation (EI) and chemical ionisation (CI) spectra. HRMS spectra were recorded on a

VG Analytical 70-250-SE normal geometry, double focusing. This apparatus was used for all the HRMS. Optical rotations were recorded on an Optical Activity Polaar 2001 polarimeter at 589 nm. Melting points were recorded on a Gallenkamp electrothermal melting point apparatus and are uncorrected.

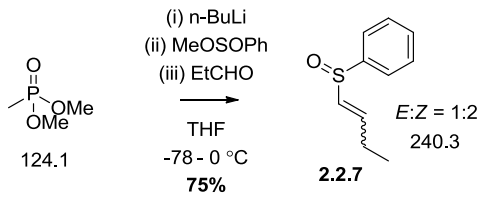
General Computational Methods

All calculations were run on the Spartan '08 (Wavefunction) program on a desktop computer running windows XP.[85] All energy minimisations were calculated using an initial molecular mechanics approximation followed by DFT minimisation using the Becke, three-parameter, Lee-Yang-Parr (B3LYP) method. All calculation used the 6-31G* basis set.[86]

To determine appropriate starting conformations for energy minimizations in the investigation of chelated aldehydes, molecular mechanics was used to calculate energy profiles by varying appropriate *endo*-cyclic internal dihedral angles and the minimal structures chosen from these calculated profiles. Angles were chosen such that ring flip would be induced when varying angles in the energy profile. For example for dialdehydes this was often the O=C-C_α-X dihedral and for β-benzyloxyaldehydes this was often the Mg-O(Bn)-CH_2-C_α dihedral. The calculated free energies of specific minimised conformations were compared and relative energies were stated.

Individual methods

But-1-enylsulfinylbenzene 2.2.7



To a solution dimethyl methylphosphonate (1.747 mL, 16.12 mmol, 2.2 equiv) in THF (15 mL) at -78 ºC under N_2 was added *n*-BuLi (6.155 mL, 15.39 mmol, 2.1 equiv). After 10 min methyl benzene sulfinate (959 μL, 7.33 mmol, 1 equiv) in THF (5 mL) was added via cannula and after a further 10 min freshly distilled propionaldehyde (582 μL, 8.06 mmol,

1.1 equiv) was added dropwise. The reaction was allowed to warm to 0 ºC for 10 min then quenched with sat. NH_4Cl (12.5 mL), extracting with CH_2Cl_2 (38 mL) followed by two further portions of CH_2Cl_2 (2×12.5 mL). The organic phases were the combined, then dried over $MgSO_4$ (anh), filtered and concentrated under reduced pressure. The crude was then purified by column chromatography (20→50% ethyl acetate in light petroleum ether 40/60) to yield (*E*)-(but-1-enylsulfinyl)benzene **2.2.7*E*** (326 mg, 1.81 mmol. 25%) then (*Z*)-(but-1-enylsulfinyl)benzene **2.2.7*Z*** (665 mg, 3.69 mmol. 50%) as colourless oils.

(*E*)-(But-1-en-1-ylsulfinyl)benzene **2.2.7*E***

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 - 7.57 (C**H** $_{Ar}$, m, 2 H), 7.56 - 7.43 (C**H** $_{Ar}$, m, 3 H), 6.67 (C**H**=CHSO, td, *J* = 6.3, 15.2 Hz, 1 H), 6.23 (CH=C**H**SO, td, *J* = 1.6, 15.2 Hz, 1 H), 2.26 (C$\mathbf{H}_2$, ddq, *J* = 1.6, 6.0, 7.4 Hz, 2 H), 1.07 (C$\mathbf{H}_3$, t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.0 (**C**SO Ar *I*), 142.6 (**C**H Ar *P*), 134.0 (**C**H Ar *O*), 130.6 (**C**H Ar *M*), 129.1 (**C**H=CHSO), 124.2 (CH=**C**HSO), 25.0 (**C**H_2), 12.0 (**C**H_3).

MS (ES^+)(m/z) : 181 $[M+H]^+$ (35%), 203 $[M+Na]^+$ (100%), 235 $[M+MeOH+Na]^+$ (73%). 383 $[2M+Na]^+$ (76%).

Data matches literature. [87]

(*Z*)-(But-1-en-1-ylsulfinyl)benzene **2.2.7*Z***

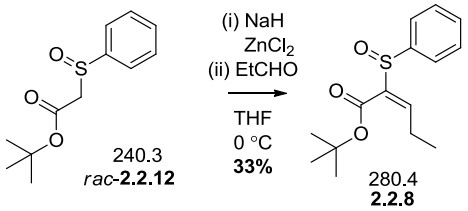
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 - 7.55 (C**H** $_{Ar}$, m, 2 H), 7.55 - 7.41 (C**H** $_{Ar}$, m, 3 H), 6.28 - 6.13 (C**H**=C**H**SO, m, 2 H), 2.76 - 2.45 (C$\mathbf{H}_2$, m, 2 H), 1.15 (C$\mathbf{H}_3$, t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6 (**C**SO Ar *I*), 143.6 (**C**H Ar *P*), 136.2 (**C**H Ar *O*), 130.6 (**C**H Ar *M*), 129.2 (**C**H=CHSO), 124.0 (CH=**C**HSO), 22.9 (**C**H_2), 13.7 (**C**H_3).

MS (ES^+)(m/z) : 181 $[M+H]^+$ (41%), 203 $[M+Na]^+$ (100%), 235 $[M+MeOH+Na]^+$ (58%). 383 $[2M+Na]^+$ (53%).

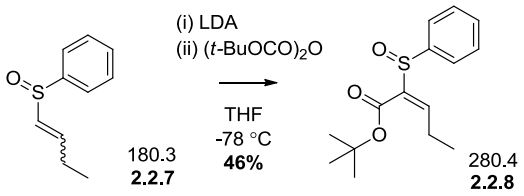
Data matches literature. [87]

(*E*)-*tert*-Butyl 2-(phenylsulfinyl)pent-2-enoate 2.2.8



(*E*)-*tert*-Butyl 2-(phenylsulfinyl)pent-2-enoate **2.2.8** from *tert*-butyl (phenylsulfinyl) acetate *rac*-**2.2.12**

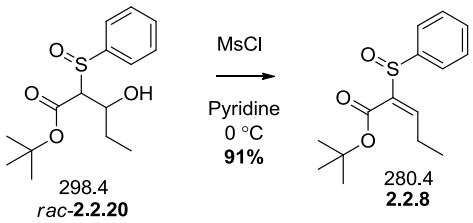
To a solution of *tert*-butyl (phenylsulfinyl) acetate *rac*-**2.2.12** (1.00 g, 4.16 mmol, 1 equiv) in THF (30 mL) stirred at 0 ºC under N_2 was added sodium hydride (60% dispersion in mineral oil, 249.6 mg, 6.24 mmol, 1.5 equiv) in one portion, after effervescence had ceased, zinc chloride (1M in Et_2O, 6.24 mL, 6.24 mmol, 1.5 equiv) was added dropwise. After 15min the propionaldehyde (360 μL, 4.99 mmol, 1.2 equiv) was added dropwise and the solution was allowed to warm to rt and then heated at reflux for 48 hours monitoring by TLC (25% ethyl acetate in light petroleum ether 40/60), the reaction was then quenched with 0.1M HCl (aq) (50 mL) and extracted with ethyl acetate (2×20 mL). The combined organic phases were then washed with $NaHCO_3$ (sat) solution (40 mL) and then brine (30 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. The mixture was then purified by column chromatography (20% ethyl acetate in light petroleum ether 40/60) to yield pure product as oil (0.387 g, 1.38 mmol. 33%).



(*E*)-*tert*-Butyl 2-(phenylsulfinyl)pent-2-enoate **2.2.8** from (but-1-en-1-ylsulfinyl)benzene **2.2.7**

To a solution of diisopropylamine (5.03 mL, 36.1 mmol, 2.6 equiv) in THF (60 mL) at -78 ºC under N_2 (g) was added *t*-butyl lithium (1.6M in pentane, 21.7 mL, 34.7 mmol, 2.5 equiv) dropwise. The solution was stirred for 10 min after which (but-1-en-1-ylsulfinyl)benzene **2.2.7** (2.50 g, 13.9 mmol, 1 eqiuv) in THF (30 mL) at -78 ºC was added

dropwise via cannula over 10 min the solution was stirred for a further 10 min at -78 ºC. The pale yellow anion solution was then added to a solution of di-*tert*-butyl dicarbonate (15.1 g, 69.4 mmol, 5 equiv) in THF (70 mL) at -78 ºC, dropwise over 1 h. On completion the reaction mixture was stirred for a further 10 min. After which the reaction was quenched with ammonium chloride ½ sat. (100 mL) and after warming to rt was extracted with portions of ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (75 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (20% ethyl acetate in light petroleum ether 40/60) to yield a colourless oil (1.79 g, 6.38 mmol. 46%).



(*E*)-*tert*-Butyl 2-(phenylsulfinyl)pent-2-enoate **2.2.8** from *tert*-butyl 3-hydroxy-2-(phenylsulfinyl)pentanoate *rac*-**2.2.20**

To a solution of *tert*-butyl 3-hydroxy-2-(phenylsulfinyl)pentanoate *rac*-**2.2.20** (10.6 g, 35.5 mmol, 1 equiv) in pyridine (120 mL) at 0 ºC under N_2 (g) was added methanesulfonyl chloride (8.25 mL, 107 mmol, 3 equiv) dropwise. The solution was stirred for a further 16 hours at 0 ºC. After completion the mixture was partioned between HCl (2M, 400 mL) and diethyl ether (300 mL). The aqueous phase was then extracted with further portions of diethyl ether (2 × 300 mL); the combined extracts were then washed with sodium hydrogen carbonate sat. (300 mL) and brine (200 mL). The organic phase was then dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (15% ethyl acetate in light petroleum ether 40/60) to yield an oil (9.10 g, 32.5 mmol. 91%).

R_f (ethyl acetate / light petroleum ether 40/60) (20 : 80) : 0.25

R_f (ethyl acetate / light petroleum ether 40/60) (35 : 65) : 0.48

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 - 7.74 (C**H**$_{Ar}$, m, 2 H), 7.41 - 7.53 (C**H**$_{Ar}$, m, 3 H), 7.05 (C=C**H**, t, *J* = 7.6 Hz, 1 H), 2.79 (C**H**$_2$, dquin, *J* = 15.3, 7.5 Hz, 1 H), 2.73 (C**H**$_2^*$, dquin, *J* = 15.2, 7.5 Hz, 1 H), 1.31 (C**H**$_{3\ t\text{-Bu}}$, s, 9 H), 1.19 (C**H**$_3$, t, *J* = 7.5 Hz, 3 H).

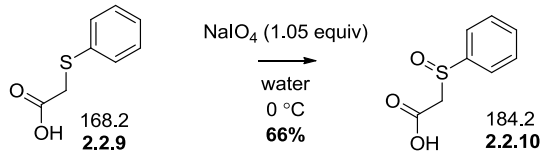
^{13}C NMR ($CDCl_3$, 75 MHz) 161.5 (**C**OO*t*Bu), 148.4 (C=**C**H), 143.9 (**C**=CH), 136.5 (**C** Ar), 131.5 (**C**H Ar *P*), 129.1 (**C**H Ar *O*), 126.4 (**C**H Ar *M*), 83.0 (**C**Me_3), 27.9 (C**Me**$_3$), 22.8 (**C**H_2), 13.3 (**C**H_3).

IR (neat) : 3060 (w), 2975 (m), 1714.3 (s), 1230 (s), 1155cm^{-1}.

MS (ES^+) m/z (%): 583 $[2M+Na]^+$ (100%), 303 $[M+Na]^+$ (76%), 281 $[M+H]^+$ (8.4%), 247 $[M-t\text{Bu}+H+Na]^+$ (29%) 225 $[M+t\text{Bu}+2H]^+$ (30%).

HRMS (ES^+) for $C_{15}H_{20}O_3SNa$ $(M+Na)^+$, Calcd. 303.1031; Found. 303.1025.

(Phenylsulfinyl)acetic acid *rac*-2.2.10



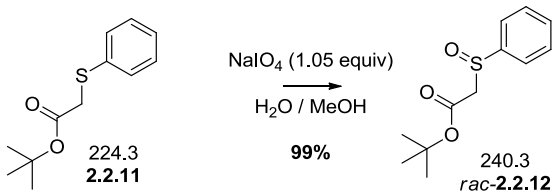
To a stirred solution of sodium metaperiodate (6.68 g, 31.2 mmol, 1.05 equiv) in water (50 mL) at 0 ºC was added (phenylthio) acetic acid **2.2.9** (5.00 g, 29.7 mmol, 1 equiv) portionwise. The reaction was stirred for 24 hours at 0 ºC after which the reaction mixture was filtered, washing with portions of cooled (0 ºC, 4×10 mL) CH_2Cl_2 and water. The filtrate was collected and continually extracted with CH_2Cl_2 for approximately 6 hours with a small portion of activated carbon. The resultant organic CH_2Cl_2 extract was filtered through celite, dried over Na_2SO_4 (anh) and concentrated in vacuo to yield crude product (4.71g). The crude product was then recrystallised from toluene to yield a white crystalline product (3.62 g, 0.0197 mmol. 66%).

^{1}H NMR (300 MHz, DMSO – d_6) δ 13.19 (COO**H**, *b*s, 1H), 7.69-7.76 (C**H** $_{Ar}$, m, 2H), 7.53-7.62 (C**H** $_{Ar}$, m, 3H), 4.01 (C$\mathbf{H}_2$*, d, 1H, *J* = 14.3 Hz), 3.78 (C$\mathbf{H}_2$, d, 1H, *J* = 14.3 Hz).

^{13}C NMR (75 MHz, DMSO – d_6) δ, 166.8 (**C**), 143.7 (**C**), 131.2 (**C**H), 129.3 (**C**H), 124.3 (**C**H), 61.3 (**C**H_2).

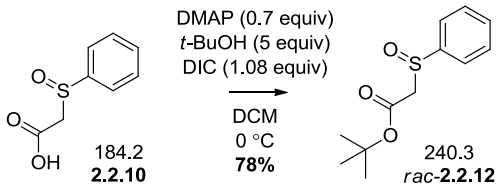
Data matches literature. [88]

tert-Butyl (phenylsulfinyl) acetate _rac_-2.2.12



tert-Butyl (phenylsulfinyl) acetate *rac*-**2.2.12** from *tert*-butyl (phenylthio) acetate **2.2.11**

To a stirred solution of *tert*-butyl (phenylthio)acetate **2.2.11** (460 mg, 2.05 mmol, 1 equiv) in water/dioxane (2 mL / 8 mL) at rt, was added sodium metaperiodate (460 mg, 2.15 mmol, 1.05 equiv). The reaction was stirred for a further 12 days monitoring by TLC (10% ethyl acetate in light petroleumether 40/60), after which the reaction was diluted with water (10 mL) and filtered washing with CH_2Cl_2 portions (3×10 mL). The organic phase was separated, dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. The crude product (434.9 mg) was then purified by column chromatography (20% ethyl acetate in light petroleumether 40/60) to yield pure product as an oil (351 mg, 1.46 mmol. 71%).



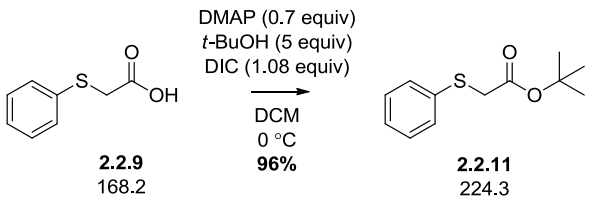
tert-Butyl (phenylsulfinyl)acetate *rac*-**2.2.12** from (phenylsulfinyl)acetic acid *rac*-**2.2.10**

To a stirred solution of (phenylsulfinyl) acetic acid **2.2.10** (3.00 g, 16.3 mmol, 1 equiv) in CH_2Cl_2 at 0 ºC under N_2 was added sequentially, DMAP (1.39 g, 11.4 mmol, 0.7 equiv) and *tert*-BuOH (6.04 g, 81.4 mmol, 5 equiv). The mixture was stirred at 0 ºC for 15min upon which DIC (2.22 g, 2.73 mL, 17.6 mmol, 1.08 equiv) was added dropwise. The reaction was stirred for a further 16 hours monitoring by TLC (30% MeOH in ethyl acetate and 20% ethyl acetate in light petroleumether 40/60) after which the reaction mixture was filtered through celite washing with CH_2Cl_2 (3×15 mL). The filtrate was then washed sequentially with 1M HCl (2×100 mL), sat. $NaHCO_3$ (1×100 mL) and Brine (50 mL),

dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. The crude green/black slurry was then purified by column chromatography (20% ethyl acetate in light petroleumether 40/60) to yield pure product as oil (3.05 g, 12.7 mmol. 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.72 (C**H** $_{Ar}$, m, 2H), 7.51-7.56 (C**H** $_{Ar}$, m, 3H), 3.81 (C**H**$_2$, d, 1H, *J* = 13.6 Hz), 3.61 (C**H**$_2^*$, d, 1H, *J* = 13.6 Hz), 1.40 (C(C**H**$_3$)$_3$, s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (**C**), 143.3 (**C**), 131.6 (**C**H), 129.3 (**C**H), 124.4 (**C**H), 83.2 (**C**), 62.6 (**C**H_2), 27.9 (**C**H_3).
Data matches literature. [89]

***tert*-Butyl (phenylthio)acetate 2.2.11**



2.2.9
168.2

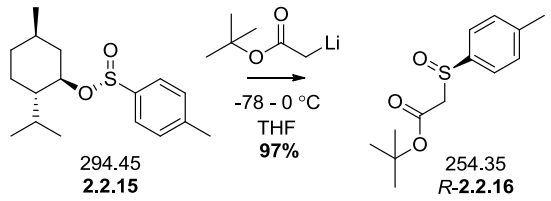
2.2.11
224.3

To a stirred solution of (phenylthio)acetic acid **2.2.9** (5.00 g, 29.7 mmol, 1 equiv) in CH_2Cl_2 (60 mL) at 0 ºC under N_2, was added sequentially, DMAP (2.54 g, 20.8 mmol, 0.7 equiv) and *t*-BuOH (11.0 mL, 149 mmol, 5 equiv). The mixture was stirred at 0 ºC for 15min, after which DIC (4.08 g, 5 mL, 32.3 mmol, 1.08 equiv) was added dropwise, the reaction was then stirred for a further 19 hours checking by TLC (10% MeOH in CH_2Cl_2 and 5% ethyl acetate in light petroleumether 40/60). On completion, the reaction mixture was filtered through celite washing with CH_2Cl_2 portions (3×15 mL), the filtrate was then washed sequentially with 1M HCl (2×100 mL), sat. $NaHCO_3$ (1×100 mL) and Brine (50 mL). The organic phase was separated, dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. The resultant orange oil with solid precipitate was diluted with hexane (15 mL) and filtered through cotton wool, and then concentrated in vacuo to yield pure product as oil (6.43 g, 28.7 mmol. 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.35 (C**H** $_{Ar}$, m, 2H), 7.11-7.24 (C**H** $_{Ar}$, m, 3H), 3.48 (**C**H_2, s, 2H), 1.33 (C(C**H**$_3$)$_3$, s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (**C**), 135.3 (**C**), 129.8 (**C**H), 128.9 (**C**H), 126.7 (**C**H), 81.9 (**C**), 37.7 (**C**H_2), 27.9 (**C**H_3).

Data matches literature. [90]

(*R*)-*tert*-Butyl 2-(*p*-tolylsulfinyl)acetate 2.2.16



To a solution of di*iso*propyl amine (19.1 mL, 136 mmol, 2 equiv) in THF (510 mL) under N_2 (g) was added *n*-butyl lithium (54.3 mL, 135.8 mmol, 2 equiv) via cannula, dropwise at -78 ºC. The solution was stirred for 15 min before adding *t*-butyl acetate (27.5 mL, 204 mmol, 3 equiv) dropwise at -78 ºC. After stirring for a further 1 h at -78 ºC a solution of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-p-toluenesulfinate **2.2.15** (20.0 g, 67.9 mmol, 1 equiv) in THF (70 mL) was added via cannula. The solution was warmed to 0 ºC before stirring for 1 h. The reaction was then quenched with NH_4Cl sat. (100 mL) and diluted with a water (100 mL); extracted with portions of diethyl ether (2 × 200 mL); dried over magnesium sulfate (anh) and filtered. The solvent was then evaporated under vacuum. The crude was purified by column chromatography (10% - 50 % ethyl acetate in light petroleum 40/60). The product was obtained as a pale oil (15.8 g, 65.9 mmol. 97%).

R_f (ethyl acetate / light petroleum 40/60) (3 : 7) : 0.28

$[\alpha]_D$: 135.2 (c 0.560, $CHCl_3$, 31 ^oC) (lit. 127.6)

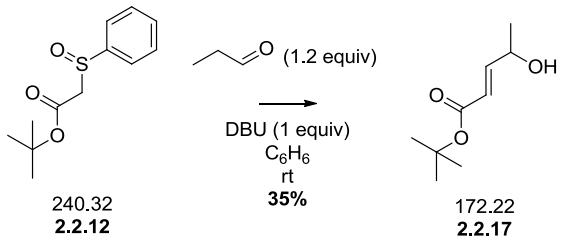
^1H NMR (400 MHz, $CDCl_3$) δ = 7.59 (C**H** $_{Ar}$, d, *J* = 8.1 Hz, 2 H), 7.34 (C**H** $_{Ar}$, d, *J* = 8.3 Hz, 2 H), 3.80 (C**H**$_2$, d, *J* = 13.5 Hz, 1 H), 3.58 (C**H**$_2^*$, d, *J* = 13.6 Hz, 1 H), 2.42 (C**H**$_{3\ tol}$, s, 3 H), 1.40 (C**H**$_{3\ t\text{-Bu}}$, s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8 (**C**OO*t*-Bu), 142.2 (**C** $_{Ar\ P}$), 140.1 (**C**-SO $_{Ar\ I}$), 130.0 (**C**H $_{Ar\ O}$), 124.5 (**C**H $_{Ar\ M}$), 83.1 (**C**Me$_3$), 62.7 (**C**H$_2$), 27.9 (**C**H$_{3\ t\text{-Bu}}$), 21.5 (**C**H$_{3\ tol}$).

Data matches literature. [91]

($[\alpha]_D$ [92])

(*E*)-*tert*-Butyl 4-hydroxypent-2-enoate 2.2.17



To a solution of *tert*-butyl 2-(phenylsulfinyl)acetate **2.2.12** (335 mg, 1.41 mmol, 1 equiv) in C_6H_6 (2 mL) was added DBU dropwise in benzene at rt (under N_2 (g)). After 5 min propionaldehyde (122 µL, 1.69 mmol, 1.2 equiv) was added dropwise and the reaction was stirred at rt for 16 h. The solvent was then removed under reduced pressure and the resultant residue purified by column chromatography (20% ethyl acetate in light petroleumether 40/60) to yield a colourless oil (84.8 mg, 0.492 mmol. 35%).

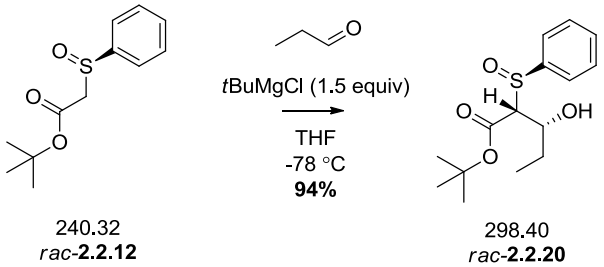
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.81 (C**H**$_\beta$, dd, *J* = 15.7, 4.9 Hz, 1 H), 5.88 (C**H**$_\alpha$, dd, *J* = 15.6, 1.6 Hz, 1 H), 4.41 (C**H**OH, qdd, *J* = 6.5, 5.0, 1.6 Hz, 1 H), 2.65 - 2.86 (O**H**, m, 1 H), 1.44 (C**H**$_3$ *t*-Bu, s, 9 H), 1.28 (C**H**$_3$, d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 166.0 (**C**OO*t*-Bu), 150.0 (**C**H=CHCOO*t*-Bu), 121.2 (CH=**C**HCOO*t*-Bu), 80.5 (C $_{t\text{-Bu}}$), 66.9 (**C**HOH), 28.0 (**C**H$_3$ $_{t\text{-Bu}}$), 22.6 (**C**H$_3$CHOH).

MS (ES$^+$)(m/z) : 195 [M+Na]$^+$ (31%), 227 [M+MeOH+Na]$^+$ (26%), 311 (100%).

Data matches literature. [93]

rac-(2*R*,3*R*)-*tert*-Butyl 3-hydroxy-2-((*R*)-phenylsulfinyl)pentanoate _rac_-2.2.20



To a solution of tert-butyl 2-(phenylsulfinyl)acetate **2.2.12** (1.00 g, 4.16 mmol, 1 equiv) in THF (30 mL) at -78 ºC (under N_2 (g)) was added *t*-butylmagenesium chloride (2 M in

ether, 3.12 mL, 6.24 mmol, 1.5 equiv) at 0 ºC (no colder, avoids precipitate). The solution was then stirred for 1 h at -78 ºC. After which propionaldhyde (919 µL, 12.5 mmol, 1 equiv) was added dropwise. The solution was then stirred for a further 1 h at -78 ºC. The reaction was then quenched with (30 mL) NH_4Cl (sat) and extracted with portions of diethylether (3×100 mL), the combined ethereal extracts were then dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure to yield a crude oil. The crude was then immediately purified by column chromatography (35% ethylacetate in light petroleumether 40/60), TLC (30% ethylacetate in light petroleum ether 40/60) to yield a white crystalline solid (1.12 g, 3.90 mmol. 94%).

R_f (ethylacetate / light petroleum 40/60) (30 : 70) : 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 - 7.68 (C**H** $_{Ar}$, m, 2 H), 7.58 - 7.50 (C**H** $_{Ar}$, m, 3 H), 3.83 (C**H**OH, dtd, *J* = 5.1, 6.7, 8.1 Hz, 2 H), 3.44 (C**H** $_{\alpha}$, d, *J* = 5.1 Hz, 2 H), 3.18 (O**H**, d, *J* = 8.1 Hz, 4 H), 1.75 - 1.55 (C**H**$_2$, m, 2 H), 1.38 (C**H**$_{3\ t\text{-Bu}}$, s, 9 H), 0.96 (C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 3 H).

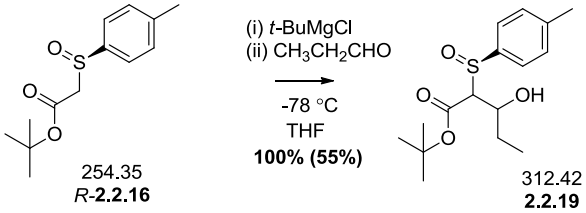
^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3 (**C**OO*t*-Bu), 141.8 (**C**SO $_{Ar\ I}$), 131.47 (**C**H $_{Ar\ P}$), 129.1 (**C**H $_{Ar\ O}$), 124.9 (**C**H $_{Ar\ M}$), 83.7 (**C**Me$_3$), 74.7 (**C**H α), 71.1 (**C**HOH), 28.4 (**C**H$_{2\ Et}$), 27.9 (**C**H$_{3\ t\text{-Bu}}$), 9.9 (**C**H$_{3\ Et}$).

IR (cm^{-1}) : 3415.9, 2975.4, 2927.7, 1718.6, 1366.4, 1256.5.

MS (ES^+)(m/z) : 335 $[M+Na]^+$ (51%), 376 $[M+Na+MeCN]^+$ (100%).

HRMS (ES^+) : $(M+Na)^+$; Calcd. 335.1288; Found. 335.1285.

(2*R*,3*R*)-*tert*-Butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate 2.2.19



To a solution of *t*-butyl magnesium chloride (1.7M in THF, 52 mL, 88.5 mmol, 1.5 equiv) in THF at -78 ºC under N_2 (g) was added (*R*)-*tert*-butyl 2-(*p*-tolylsulfinyl)acetate **2.2.16** (15.0 g, 59.0 mmol, 1 equiv) in THF (410 mL) at -78 ºC. The mixture was then stirred at -78 ºC for 1 h before propionaldehyde (15.6 mL, 183 mmol, 3.1 equiv) was added dropwise. The reaction was then stirred for a further 1 h before quenching with NH_4Cl sat.

(100 mL). The mixture was then allowed to warm to 0 ^{o}C before diluting with water (100 mL) and diethyl ether (200 mL). The layers were separated and the aqueous phase extracted with further portions of diethyl ether (2 × 200 mL). The combined organic extracts were then collected, dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (15% - 50% ethyl acetate in light petroleum ether 40/60). To yield a partially crystalline slurry (mixture of diasteromers) **2.2.19f**. (15.3 g, 52.0 mmol. 88%). The mixture could be purified to a single diastereomer by recrystallization from boiling ethyl acetate, filtering at 0 ºC gave a white solid **2.2.19r** (9.66 g, 32.4 mmol. 55%).

(2*R*,3*R*)-*tert*-Butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate **2.2.19** to be used as impure mixture in the formation of (*S*,*E*)-*tert*-butyl 2-(*p*-tolylsulfinyl)pent-2-enoate **2.2.18**

To a solution of *t*-butyl magnesium chloride (1.7 M in THF, 37.3 mL, 63.4 mmol, 1.5 equiv) in THF (50 mL) at -78 ºC under N_2 (g) was added (*R*)-*tert*-butyl 2-(*p*-tolylsulfinyl)acetate **2.2.16** (10.8 g, 42.3 mmol, 1 equiv) in THF (200 mL) at -78 ºC. The mixture was then stirred at -78 ºC for 1 h before propionaldehyde (11.2 mL, 131.0 mmol, 3.1 equiv) was added dropwise. The reaction was then stirred for a further 1 h before quenching with NH_4Cl sat. (100 mL). The mixture was then allowed to warm to 0^{o}C before diluting with water (100 mL) and diethyl ether (200 mL). The layers were separated and the aqueous phase extracted with further portions of diethyl ether (2 × 200 mL). The combined organic extracts were then collected, dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (15% - 50% ethyl acetate in light petroleum ether 40/60), to yield a partially crystalline slurry (impure mixture of diasteromers) (14.5 g, 42.3 mmol. 100%).

R_f (ethyl acetate / light petroleum ether 40/60) (3 : 7) : 0.25

$[\alpha]_D$: 276.7 (c 0.49, $CHCl_3$, 27^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (C**H**$_{Ar}$, d, *J* = 8.3 Hz, 2 H), 7.35 (C**H**$_{Ar}$, d, *J* = 8.0 Hz, 2 H), 3.76 (C**H**OH, tt, *J* = 5.3, 7.9 Hz, 1 H), 3.43 (C**H**$_{\alpha}$, d, *J* = 4.6 Hz, 1 H), 3.14 (O**H**, d, *J* = 8.4 Hz, 1 H), 2.43 (C**H**$_{3\ Tol}$, s, 3 H), 1.67 - 1.55 (C**H**$_2$, m, 2 H), 1.42 (C**H**$_{3\ t\text{-Bu}}$, s, 9 H), 0.95 (C**H**$_{3\ Et}$, t, *J* = 7.4 Hz, 3 H).

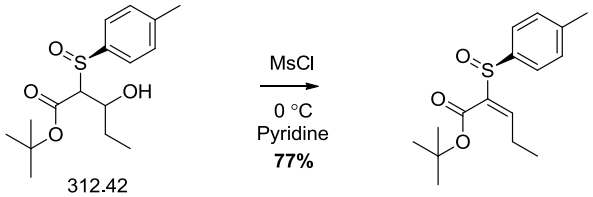
^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7 (**C**OO*t*-Bu), 142.1 (**C** $_{Ar\ P}$), 138.5 (**C** -SO $_{Ar\ I}$), 129.8 (**C**H $_{Ar\ O}$), 124.9 (**C**H $_{Ar\ M}$), 83.8 (**C**Me_3), 75.1 (**C**H α), 71.1 (**C**HOH), 28.8 (**C**$H_{2\ Et}$), 28.0 (**C**$H_{3\ t\text{-}Bu}$), 21.5 (**C**$H_{3\ t\text{-}Bu}$), 9.9 (**C**$H_{3\ Et}$).

IR (cm^{-1}) : 3415.9, 2975.4, 2927.7, 1718.6, 1366.4, 1256.5.

MS (ES^+)(m/z) : 335 $[M+Na]^+$ (51%), 376 $[M+Na+MeCN]^+$ (100%).

HRMS (ES^+) : $(M+Na)^+$, Calcd. 335.1288; Found. 335.1285.

(S,E)-*tert*-Butyl 2-(*p*-tolylsulfinyl)pent-2-enoate 2.2.18



(S,E)-*tert*-Butyl 2-(*p*-tolylsulfinyl)pent-2-enoate **2.2.18** from pure (2*R*,3*R*)-*tert*-butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate **2.2.19r**

To a solution of *tert*-butyl (2*R*,3*R*)-*tert*-butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate **2.2.19r** (9.00 g, 28.8 mmol, 1 equiv) in pyridine (100 mL) at 0 ºC under N_2 (g) was added methanesulfonyl chloride (6.69 mL, 86.4 mmol, 3 equiv) dropwise. The reaction was stirred at 0 ºC for 16 h before quenching with hydrochloric acid (1M, 400 mL). The mixture was extracted with portions of diethylether (3× 300 mL) and the combined extracts washed with brine (300 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (15 → 25% ethyl acetate in light petroleum ether 40/60), to yield an orange oil (8.36 g, 28.4 mmol. 99%).

(*S,E*)-*tert*-Butyl 2-(*p*-tolylsulfinyl)pent-2-enoate **2.2.18** from impure *tert*-butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate **2.2.19**

To a solution of *tert*-butyl 3-hydroxy-2-((*R*)-*p*-tolylsulfinyl)pentanoate **2.2.19** (13.2 g, 42.3 mmol, 1 equiv) in pyridine (150 mL) at 0 ºC under N_2 (g) was added methanesulfonyl chloride (10.8 mL, 139 mmol, 3 equiv) dropwise. The reaction was stirred at 0 ^{o}C for 16 h before quenching with hydrochloric acid (1M, 400 mL). The mixture was extracted with

portions of diethylether (3× 300 mL) and the combined extracts washed with brine (300 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude product was then purified by column chromatography (15% ethyl acetate in light petroleum ether 40/60), to yield an orange oil (10.5 g, 35.8 mmol. 85%).

R_f (ethyl acetate / light petroleum ether 40/60) (35 : 65) : 0.48

$[\alpha]_D$: +195.6 (c 0.262 g/100 mL, $CHCl_3$, 26°C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (C**H** $_{Ar}$, d, *J* = 8.2 Hz, 2 H), 7.28 (C**H** $_{Ar}$, d, *J* = 8.9 Hz, 2 H), 7.05 (C=C**H**, t, *J* = 7.7 Hz, 1 H), 2.77 (C**H**$_{2\ Et}$, quin, *J* = 7.6 Hz, 2 H), 2.41 (C**H**$_{3\ Tol}$, s, 3 H), 1.33 (C**H**$_{3\ t\text{-}Bu}$, s, 9 H), 1.20 (C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 3 H).

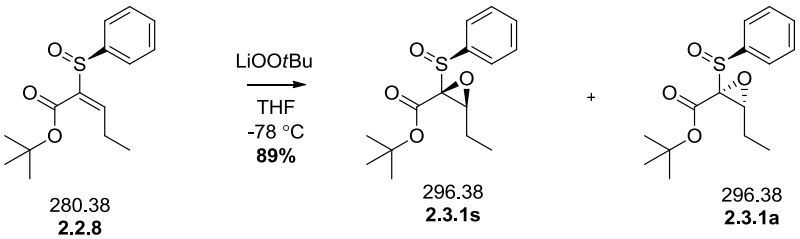
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6 (**C**OO*t*-Bu), 148.0 (C=**C**H), 142.1 (**C** $_{Ar\ I}$), 140.8 (**C**=CH), 136.6 (**C**-SO $_{Ar\ P}$), 129.7 (**C**H $_{Ar\ O}$), 126.5 (**C**H $_{Ar\ M}$), 82.8 (**C** $_{t\text{-}Bu}$), 27.9 (**C**H$_{3\ t\text{-}Bu}$), 22.7 (**C**H$_{2\ Et}$), 21.4 (**C**H$_{3\ Tol}$), 13.3 (**C**H$_{3\ Et}$).

IR (cm^{-1}) : 2975.6, 2933.8, 1713.7 1629.4, 1367.7

MS (ES^+)(m/z) : 295 $[M+H]^+$ (33%), 358 $[M+MeCN+Na]^+$ (14%), 589.4 $[2M+H]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$, Calcd. 317.1182; Found. 317.1183, Date.

rac-Epoxide 2.3.1

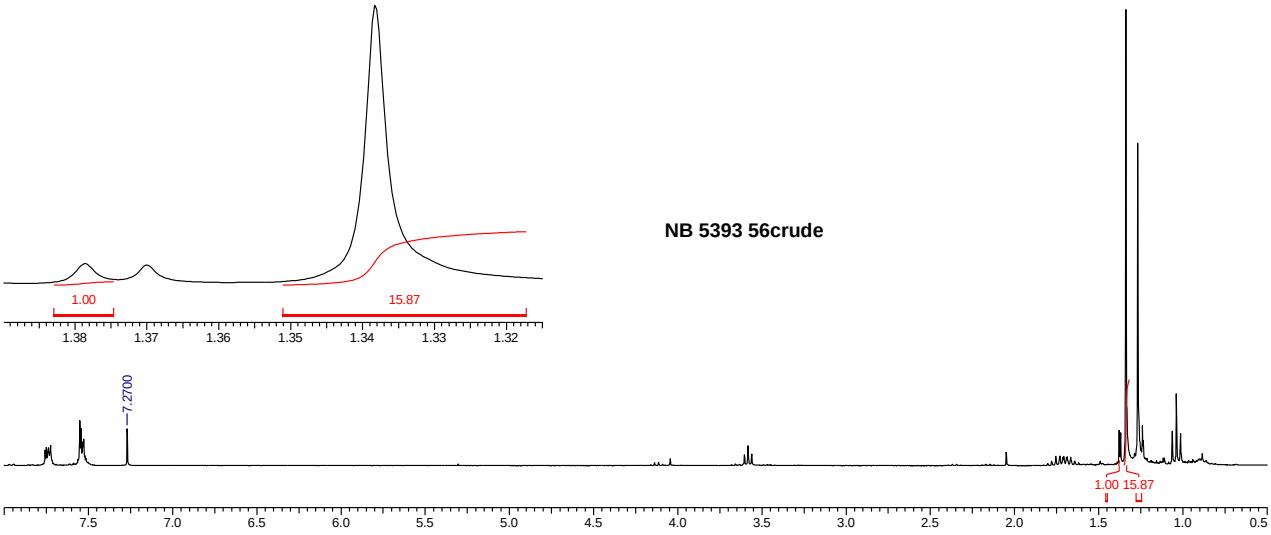


d.r. (syn : anti) 94 : 6

To a solution of *t*-butyl hydrogenperoxide (5M in decane, 13.0 mL, 71.3 mmol, 4 equiv) in THF (500 mL) under nitrogen at -78 ºC was added *n*-butyl lithium (2.5M in hexane, 35.7 mL, 89.2 mmol, 5 equiv) dropwise via cannula. The resultant solution was stirred at -78 ºC for 20 min before adding a solution of (*E*)-*tert*-butyl 2-(phenylsulfinyl)pent-2-enoate **2.2.8** (5.00 g, 17.8 mmol, 1 equiv) in THF (150 mL) at -78 ºC under nitrogen. The reaction was then stirred at the same temperature for a further 20 min before immediately quenching with sodium thiosulfate solution (sat. 500 mL). The mixture was then allowed to warm to 0 ºC before extracting with portions of ethyl acetate (3 × 250 mL). The combined organic extracts were then dried over sodium sulfate (anh), before filtering and evaporating the

solvent under vacuum. The crude was then purified by column chromatography (35% ethyl acetate in light petroleum ether 40/60) to yield a colourless oil (4.69 g, 15.8 mmol. 89%).

d.r. *from* ^{1}H NMR – NB 5393 56crude



rac-(2*R*,3*S*)-*tert*-Butyl 3-ethyl-2-((*S*)-phenylsulfinyl)oxirane-2-carboxylate **2.3.1**

R_f (ethyl acetate / light petroleum 40/60) (20 : 80) : 0.28

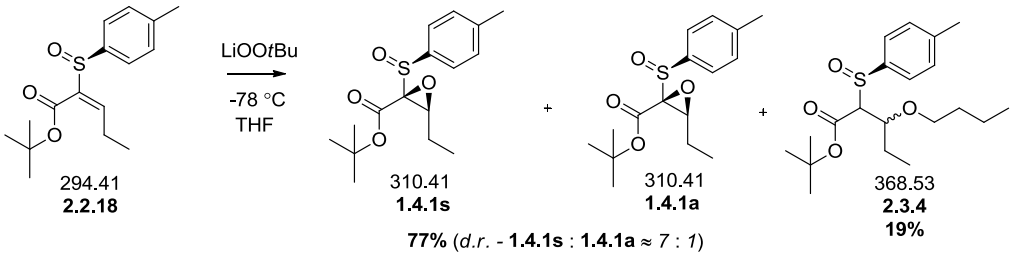
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.78 - 7.69 (^{a,s}C**H** $_{Ar}$, m, 2H), 7.59 - 7.47 (^{a,s}C**H** $_{Ar}$, m, 3H), 3.61 (^{a}C**H** $_{epox}$, dd, *J* = 5.9, 6.8 Hz, 0.1 H), 3.58 (^{s}C**H** $_{epox}$, t, *J* = 6.4 Hz, 1H), 1.84 - 1.60 (^{a,s}C**H**$_2$CH$_3$, m, 2H), 1.38 (^{a}C(C**H**$_3$)$_3$, s, 0.6H), 1.34 (^{s}C(C**H**$_3$)$_3$, s, 9H), 1.11 (^{a}CH$_2$C**H**$_3$, t, *J* = 7.6 Hz, 0.4H), 1.04 (^{s}CH$_2$C**H**$_3$, t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.3 (**C**OO*t*Bu), 140.5 (**C** Ar *I*), 131.8 (**C** Ar *P*), 129.0 (**C** Ar *O*), 125.5 (**C** Ar *M*), 84.5 (**C**Me$_3$), 75.2 (**C** epox), 61.5 (**C**H epox), 27.8 (**C**H$_3$ *t*-Bu), 21.7 (**C**H$_2$ Et), 10.0 (**C**H$_3$).

IR (neat) : 3060, 2977, 2937, 2879, 1734, 1582cm^{-1}.

LRMS (ES$^+$)(m/z) : 241 [M-*t*Bu+2H]$^+$ (15%), 263 [M-*t*Bu+H+Na]$^+$, 319 [M+Na]$^+$ (42%), 615.3 [2M+Na]$^+$.

Epoxide 1.4.1



To a solution of *t*-butyl hyroperoxide (5M in decane, 16.3 mL, 81.5 mmol, 4 equiv) in THF (500 mL) at -78^{o}C under N_2 (g) was added n-butyl lithium (2.5M, 40.8 mL, 102 mmol, 5 equiv) via cannula. The resultant solution was stirred at -78 ºC for a further 20 min before adding a solution of (*S,E*)-*tert*-butyl 2-(*p*-tolylsulfinyl)pent-2-enoate **2.2.18** (6.00 g, 20.4 mmol, 1 equiv) at -78 ºC via cannula over 5 min. The reaction was then stirred at -78 ºC for a further 20 min before quenching with sodium thiosulfate sat. (500 mL) immediately. The mixture was allowed to thaw before extracting with ethyl acetate (3 × 250 mL). The combined organic extracts were then washed with brine (400 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated in vacuum. The crude product was then purified by column chromatography (10% - 20% ethyl acetate in light petroleum ether 40/60) to yield a colourless oil. (4.89 g, 15.7 mmol. 77%) Column chromatography also yielded *tert*-butyl 3-butoxy-2-((*R*)-p-tolylsulfinyl)pentanoate **2.3.4** was isolated (1.43 g, 3.87 mmol. 19%).

Epoxide mixture **1.4.1**

d.r. - (*syn* : *anti)*- 7 : 1

R_f (ethyl acetate / light petroleum ether 40/60) (20 : 80) : 0.20

$[\alpha]_D$: +56.2 (c 0.697 g/100 mL, $CHCl_3$, 25^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (^{a,s}C**H** $_{Ar}$, d, *J* = 8.2 Hz, 2.5H), 7.33 (^{a,s}C**H** $_{Ar}$, d, *J* = 7.9 Hz, 2.5H), 3.59 (^{a}C**H** $_{epox}$, dd, *J* = 5.8, 6.8 Hz, 0.2H), 3.55 (^{s}C**H** $_{epox}$, t, *J* = 6.3 Hz, 1H), 2.42 (^{s}PhC**H**$_3$, s, 3H), 2.40 (^{a}PhC**H**$_3$, s, 0.5H), 1.83 - 1.59 (^{a,s}C**H**$_2$CH$_3$, m, 3H), 1.35 (^{a,s}C(C**H**$_3$)$_3$, s, 9.7H), 1.10 (^{a}CH$_2$C**H**$_3$, t, *J* = 7.5 Hz, 0.5H), 1.04 (^{s}CH$_2$C**H**$_3$, t, *J* = 7.5 Hz, 3H).

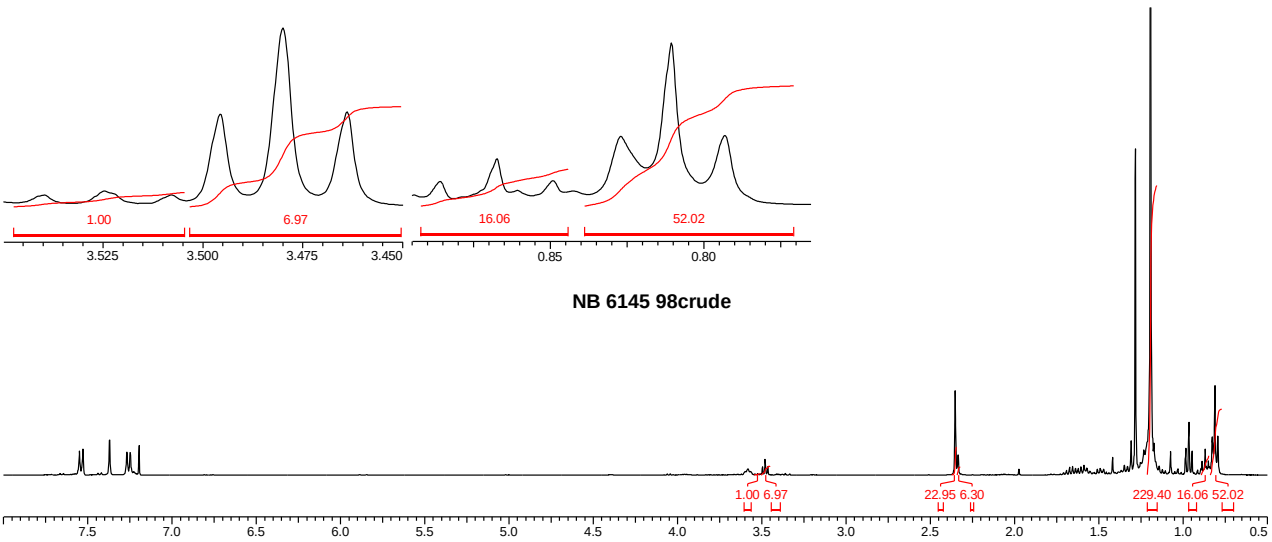
^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (**C**OO*t*-Bu), 142.5 (**C** $_{Ar\ P}$), 137.1 (**C**-SO $_{Ar\ I}$), 129.7 (**C**H $_{Ar\ O}$), 125.6 (**C**H $_{Ar\ M}$), 84.4 (**C** $_{t\text{-}Bu}$), 75.3 (**C** $_{epox}$), 61.1 (**C**H $_{epox}$), 27.7 (**C**H$_3$ $_{t\text{-}Bu}$), 21.7 (**C**H$_2$ $_{Et}$), 21.4 (**C**H$_3$ $_{Tol}$), 10.0 (**C**H$_3$ $_{Et}$).

IR (cm^{-1}) : 2976, 2935, 1736, 1459, 1369.

MS (ES^+)(m/z) : 318 $[M\text{-}t\text{-Bu}+H+MeCN+Na]^+$ (40%), 374 $[M+MeCN+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$, Calcd. 333.1131; Found. 333.1130, Date : 01/09/2011.

d.r. *from* ^{1}H NMR – NB 6145 98crude



syn-Epoxide **1.4.1s**

R_f (ethyl acetate / light petroleum ether 40/60) (20 : 80) : 0.20

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (C**H** $_{Ar}$, d, *J* = 8 Hz, 2 H), 7.33 (C**H** $_{Ar}$, d, *J* = 8 Hz, 2 H), 3.55 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.42 (C**H**$_{3\ tol}$, s, 3 H), 1.59 - 1.83 (C**H**$_{2\ Et}$, m, 2 H), 1.33 - 1.37 (C**H**$_{3\ t\text{-}Bu}$, m, 9 H), 1.04 (C**H**$_{3\ Et}$, t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (**C**OO*t*-Bu), 142.5 (**C** $_{Ar\ P}$), 137.1 (**C**-SO $_{Ar\ I}$), 129.7 (**C**H $_{Ar\ O}$), 125.6 (**C**H $_{Ar\ M}$), 84.4 (**C** $_{t\text{-}Bu}$), 75.3 (**C** $_{epox}$), 61.1 (**C**H $_{epox}$), 27.7 (**C**H$_{3\ t\text{-}Bu}$), 21.7 (**C**H$_{2\ Et}$), 21.4 (**C**H$_{3\ Tol}$), 10.0 (**C**H$_{3\ Et}$).

IR (cm^{-1}) : 2976, 2935, 1736, 1459, 1369

MS (ES^+)(m/z) : 318 $[M\text{-}t\text{-Bu}+H+MeCN+Na]^+$ (40%), 374 $[M+MeCN+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$, Calcd. 333.1131; Found. 333.1130.

tert-Butyl 3-butoxy-2-((*R*)-p-tolylsulfinyl)pentanoate **2.3.4**

R_f (ethylacetate / light petroleum 40/60) (20 : 80) : 0.31

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (^{b}C**H** $_{Ar,}$ d, *J* = 8.6 Hz, 1.5 H), 7.50 (^{a}C**H** $_{Ar,}$ d, *J* = 8.1 Hz, 2.0 H), 7.31 (^{a}C**H** $_{Ar,}$ d, *J* = 8.1 Hz, 2.0 H), 7.29 (^{b}C**H** $_{Ar,}$ d, *J* = 7.6 Hz, 1.8 H), 4.07 - 3.98 (^{a,b}C**H**OBu, m, 1.8 H), 3.75 - 3.68 (^{a,b}CHOC**H**$_2$Pr, m, 1.5 H), 3.68 - 3.60 (^{a,b}CHOC**H**$_2$Pr*, m, 2.0 H), 3.50 (^{b}*t*BuOOCC**H**, d, *J* = 3.5 Hz, 0.7 H), 3.42 (^{a}*t*BuOOCC**H**, d, *J* = 10.6 Hz, 1.0 H), 2.41 (^{a,b}PhC**H**$_3$ s, 5.5 H), 1.94 - 1.74 (^{a,b}OCH$_2$C**H**$_2$Et, m, 2.1 H), 1.72 - 1.57 (^{a,b}OCH$_2$C**H**$_2$CH$_2$CH$_3$, m, 4.7 H), 1.54 - 1.38 (*n*BuOH, ^{a,b}OCH$_2$CH$_2$C**H**$_2$CH$_3$, m, 8.8 H), 1.26 (*t*BuOH, ^{b}C(C**H**$_3$)$_3$, s, 49 H), 1.15 (^{a}C(C**H**$_3$)$_3$, s, 8.7 H), 1.03 - 0.82 (*n*BuOH, ^{a,b}CHCH$_2$C**H**$_3$, ^{a,b}OCH$_2$CH$_2$CH$_2$C**H**$_3$, m, 15.1 H).

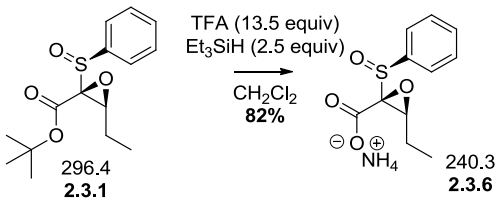
^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.2 (^{b}*t*BuOO**C**), 163.8 (^{a}*t*BuOO**C**), 142.3 (^{b}**C** Ar *P*), 141.0 (^{a}**C** Ar *P*), 139.8 (^{b}**C** Ar *I*), 138.6 (^{a}**C** Ar *I*), 129.7 (^{b}**C**H Ar *O*), 129.5 (^{a}**C**H Ar *O*), 125.9 (^{b}**C**H Ar *M*), 124.6 (^{b}**C**H Ar *M*), 82.5 (HO**C**Me$_3$), 82.0 (^{b}Me$_3$**C**OOCCH), 80.7 (^{a}Me$_3$**C**OOCCH), 77.2 (^{b}**C**HOBu), 76.7 (^{b}*t*BuOOC**C**H), 76.0 (^{a}**C**HOBu), 72.7 (^{a}*t*BuOOC**C**H), 71.1 (^{b}CHO**C**H$_2$Pr), 70.8 (^{a}CHO**C**H$_2$Pr), 39.3, 32.2 (^{b}CH**C**H$_2$CH$_3$), 32.1 (^{a}CH**C**H2CH3), 31.2, 29.6, 29.5, 29.2, 27.8 (^{b}C(**C**H$_3$)$_3$), 27.6 (^{a}C(**C**H$_3$)$_3$), 26.3 (^{b}OCH$_2$**C**H$_2$Et), 25.7 (HOC(**C**H$_3$)$_3$), 24.9 (^{a}OCH$_2$**C**H$_2$CH$_2$CH$_3$), 23.4, 22.6, 21.4 (^{b}Ph**C**H$_3$), 21.3 (^{a}Ph**C**H$_3$), 19.3 (^{a}OCH2CH2**C**H2CH3), 19.2 (^{b}OCH2CH2**C**H2CH3), 14.1 (^{b}CHCH$_2$**C**H$_3$), 13.9 (^{a}CHCH$_2$**C**H$_3$), 10.0 (^{b}OCH$_2$CH$_2$CH$_2$**C**H$_3$), 8.2 (^{a}OCH$_2$CH$_2$CH$_2$**C**H$_3$).

IR (neat) : 2961, 2930, 2872, 1724, 1459 cm^{-1}

MS (ES$^+$)(m/z) : 391 [M+Na]$^+$ (100%), 760 [2M+Na]$^+$ (37%).

HRMS (ES$^+$) : [M+Na]$^+$, Calcd. 391.1914; Found. 391.1920.

rac-Ammonium (2R,3S)-3-ethyl-2-((S)-phenylsulfinyl)oxirane-2-carboxylate 2.3.6



To a solution of *rac*-epoxide **2.3.1** (500 mg, 1.69 mmol, 1 equiv) in CH_2Cl_2 (17.5 mL) was added TFA (1.69 mL, 22.8 mmol, 13.5 equiv) dropwise followed by triethylsilane (673 µL, 4.23 mmol, 2.5 equiv). The solution was then monitored by TLC (25% ethyl acetate in light petroleumether 40/60 and 40% MeOH in ethyl acetate) after 20 hours the reaction run

to completion. The resultant solution was then concentrated in vacuo azeotropically removing TFA traces with toluene (3 × 50 mL), the resultant crude oil was then dried on high vacuum for 2 hours to give a colourless oil (110 mg, 0.843 mmol), the crude free acid (>90%). The crude oil was then dissolved in ether (20 mL), addition of NH_3 in methanol (289 μL, 7 M, 1.2 equiv) formed a white precipitate. The mixture was filtered and the precipitate washed with further portions of ether. The white precipitate was then dried on high vacuum, recrystalising from hot ethanol if necessary (354 mg, 1.38 mmol. 82%).

(*E*)-3-Ethyl-2-(phenylsulfinyl)oxirane-2-carboxylic acid **2.3.6imp**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 - 7.67 (C**H** $_{Ar}$, 2 H, m) 7.67 - 7.53 (C**H** $_{Ar}$, 3 H, m) 3.77 (C**H** $_{epox}$, 1 H, t, *J* = 6.40 Hz) 1.98 - 1.65 (C**H**$_2$, 2 H, m) 1.13 (C**H**$_3$, 3 H, t, *J* = 7.50 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0 (CH_3), 20.9 (CH_2), 67.8 (CH), 124.8 (CH), 129.9 (CH), 133.1 (CH). LRMS (ES^-) *m/z* 239.1 $[M-H]^-$, 353.1, 125.0 $[C_6H_5SO]^-$.

LRMS (ES^+) *m/z* 241 $[M+Na]^+$, 319 [**SM**+Na]$^+$, 615 [2(**SM**)+Na]$^+$.

rac-Ammonium (2*R*,3*S*)-3-ethyl-2-((*S*)-phenylsulfinyl)oxirane-2-carboxylate **2.3.6**

m.p. : 156 ºC

^{1}H NMR (CD_3OD, 300 MHz): δ = 7.68 - 7.74 (C**H** $_{Ar}$, m, 2 H), 7.54 - 7.65 (C**H** $_{Ar}$, m, 3H), 2.99 (C**H**, t, *J* = 6.4 Hz, 1 H), 1.56 (C**H**$_2$, qd, *J* =7.5, 6.4 Hz, 2 H), 0.84 (C**H**$_3$, t, *J* = 7.5 Hz, 3 H).

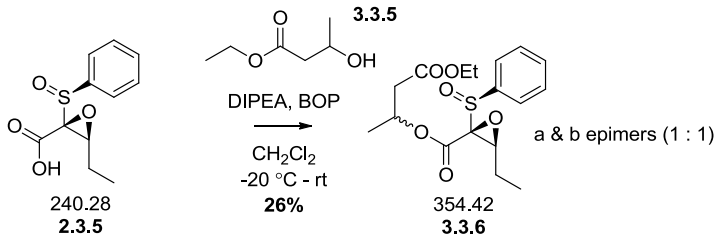
^{13}C NMR (CD_3OD, 75 MHz): δ = 169.3 (**C**=O), 142.5 (**C**H Ar *I*), 132.9 (**C**H Ar *P*), 130.0 (**C**H Ar *O*), 127.7 (CH Ar *M*), 78.4 (**C** epox), 61.2 (**C**H epox), 22.0 (**C**H$_2$), 10.4 (**C**H$_3$).

IR (neat) : 3171 *br*, 3048, 2967, 1617 *s*, 1400cm^{-1}

LRMS (ES^-)(m/z) : 121 (100%), 125 (51%), 239 $[M-NH_4^+]^-$ (22%).

HRMS (ES^-) : $[M-NH_4]^-$, Calcd. 239.0384; Found. 239.0389.

4-Ethoxy-4-oxobutan-2-yl 3-ethyl-2-(phenylsulfinyl)oxirane-2-carboxylate 3.3.6



To a solution (2*R*,3*S*)-3-ethyl-2-((*S*)-phenylsulfinyl)oxirane-2-carboxylic acid **2.3.6imp** (100 mg, 0.416 mmol, 1 equiv) and ethyl 3-hydroxybutyrate (59.5 µL, 0.458 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) at -20 ºC under N_2 (g) was added DIPEA (73 µL, 0.416 mmol, 1 equiv) followed by BOP (184 mg, 0.416 mmol, 1 equiv) in one portion. The reaction was stirred at -20 ºC for 2 h before warming to rt for an additional 16 h. The solvent was then evaporated under reduced pressure and the crude purified by column chromatography (20 → 30% ethylacetate in light petroleum ether 40/60) to yield an impure residue which was further purified by HPLC (35% ethylacetate in hexane) to yield a colourless residue as a 1:1 mixture of epimers (39 mg, 0.11 mmol. 26%).

R_f (ethylacetate / light petroleumether 40/60) (40 : 60) : 0.28

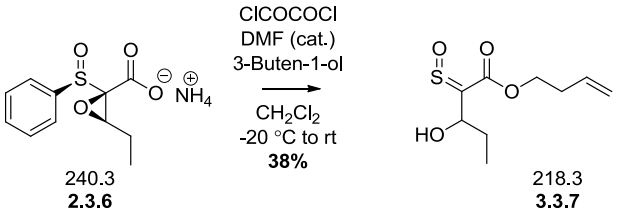
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 - 7.68 (^{a,b}C**H** $_{Ar}$, m, 2 H), 7.59 - 7.47 (^{a,b}C**H** $_{Ar}$, m, 3 H), 5.35 - 5.23 (^{a,b}C**H**OOC$_{epox}$, m, 1 H), 4.11 (^{a,b}CH$_3$**C**H$_2$OOC, q, *J* = 7.3 Hz, 2 H), 3.60 (^{a}C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 3.57 (^{b}C**H** $_{epox}$, t, *J* = 6.3 Hz, 0.5 H), 2.58 (^{a,b}EtOOCC**H**$_2$, dd, *J* = 7.5, 16.1 Hz, 0.5 H), 2.43 (^{a,b}EtOOCC**H**$_2^*$, ddd, *J* = 4.4, 5.5, 16.1 Hz, 1 H), 1.76 - 1.58 (^{a,b}CHC**H**$_2$CH$_3$, m, 2 H), 1.25 (^{a}CHCH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 1.5 H), 1.24 (^{b}CHCH$_2$C**H**$_3$, t, *J* = 7.2 Hz, 1.5 H), 1.22 (^{a}CH$_2$CH(OOC)C**H**$_3$, d, *J* = 6.3 Hz, 1.5 H), 1.16 (^{b}CH$_2$CH(OOC)C**H**$_3$, d, *J* = 6.3 Hz, 1.5 H), 1.01 (^{a}C**H**$_3$CH$_2$OOC, t, *J* = 7.5 Hz, 1.5 H), 1.01 (^{b}C**H**$_3$CH$_2$OOC, t, *J* = 7.5 Hz, 1.5 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5 (^{a}**C**OOEt), 169.5 (^{b}**C**OOEt), 162.7 (^{a}ROO**C**C epox), 140.4 (^{a}**C** Ph), 140.3 (^{b}**C** Ph), 132.0 (^{a}**C**H Ph), 132.0 (^{b}**C**H Ph), 129.1 (^{a,b}**C**H Ph), 125.5 (^{a}**C**H Ph), 125.5 (^{b}**C**H), 75.1 (^{a}**C** epox), 74.8 (^{b}**C** epox), 70.1 (^{a}**C**H epox), 70.1 (^{b}**C**H epox), 61.9 (^{a}**C**HOOCC epox), 61.6 (^{b}**C**HOOCC epox), 60.8 (^{a}CH$_3$**C**H$_2$OOC), 60.8 (^{b}CH$_3$**C**H$_2$OOC), 40.4 (^{a}EtOOC**C**H$_2$), 40.2 (^{b}EtOOC**C**H$_2$), 21.7 (^{a}CH**C**H$_2$CH$_3$), 21.6 (^{b}CH**C**H$_2$CH$_3$), 19.7 (^{a}CH$_2$CH(OOC)**C**H$_3$), 19.5 (^{b}CH$_2$CH(OOC)**C**H$_3$), 14.1 (^{a,b}**C**H$_3$CH$_2$OOC), 10.0 (^{a}CHCH$_2$**C**H$_3$), 10.0 (^{b}CHCH$_2$**C**H$_3$).

IR (cm^{-1}) : 3062, 2979, 2938, 2880, 1732, 1445 cm^{-1}.

MS (ES$^+$)(m/z) : 377 [M+Na]$^+$ (76%), 731 [2M+Na]$^+$ (100%).

But-3-en-1-yl 3-hydroxy-2-thioxopentanoate S-oxide 3.3.7



240.3
2.3.6

218.3
3.3.7

To a suspension of *rac*-(2*R*,3*S*)-3-ethyl-2-((*S*)-phenylsulfinyl)oxirane-2-carboxylic acid **2.3.6** (100 mg, 0.389 mmol, 1 equiv) in CH_2Cl_2 was added a single drop of DMF. The mixture was then cooled to 0 ºC, oxalyl chloride was then added dropwise the solution was stirred at 0 ºC for a further hour. 3-Buten-1-ol (68 μL, 0.778 mmol, 2 equiv) was then added dropwise. The reaction was allowed to warm to room temperature stirring for a further 16 hours after which the mixture was diluted with CH_2Cl_2 (10 mL) and washed with portions of 1M HCl (3×10 mL). The separated organic phase was then dried over Na_2SO_4 (anh) and the solvent was evaporated under vacuum. The crude product was then purified by column chromatography (10 → 20% ether in light petroleum 40/60), (Phenyl)hydroxythiol was recovered as well as a colourless oil (32.1 mg, 14.7 mmol. 38%) (After HPLC 9.1 mg, 0.04 mmol. 11 %).

R_f (diethylether / light Petroleum 40-60) (20 : 80) : 0.53

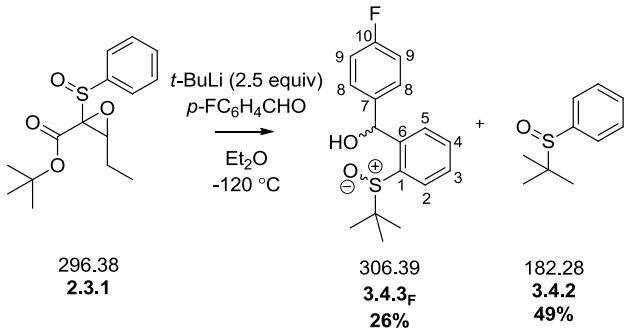
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.80 (C**H**=CH_2, tdd, *J* = 6.8, 10.3, 17.1 Hz, 1 H), 5.17 (CH=C**H**$_2$ *trans*, qd, *J* = 1.5, 17.2 Hz, 2 H), 5.13 (CH=C**H**$_2$ *cis*, qd, *J* = 1.3, 10.3 Hz, 2 H), 4.86 (C**H**OH, dd, *J* = 5.5, 8.1 Hz, 1 H), 4.38 (COOC**H**$_2$, dt, *J* = 0.6, 6.7 Hz, 2 H), 2.51 (C**H**$_2$CH=CH_2, tq, *J* = 1.4, 6.7 Hz, 2 H), 2.13 (CH_3C**H**$_2$CHOH, dqd, *J* = 5.4, 7.3, 14.6 Hz, 1 H), 1.95 (CH_3C**H**$_2$CHOH*, qdd, *J* = 7.4, 8.0, 14.6 Hz, 1 H), 1.59 (CHO**H**, br. s., 1 H), 1.08 (C**H**$_3$$CH_2$CHOH, t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.3 (**C**SO), 160.7 (**C**OO), 132.9 (**C**H=CH_2), 118.1 (CH=C**H**$_2$), 65.7 (COO**C**H_2), 60.4 (**C**HOH), 32.7 (**C**H_2CH=CH_2), 25.8 (CH_3**C**H_2), 10.4 (**C**H_3CH_2).

IR (neat) : 3081, 2976, 1732, 1247, 1055 cm^{-1}

LRMS (ES^+)(m/z) : 219 $[M+H]^+$ (35%), 259 $[?]^+$ (100%), 291.1 $[?]^+$ (16%).

rac-(2-(_tert_-Butylsulfinyl)phenyl)(4-fluorophenyl)methanol 3.4.3$_F$



To a solution of *rac*-(2*R*,3*S*)-*tert*-butyl 3-ethyl-2-((*S*)-phenylsulfinyl)oxirane-2-carboxylate **2.3.1** (100 mg, 0.34 mmol, 1 equiv) in diethylether (1 mL) at -120 ºC under nitrogen was added *t*-butyllithium (1.9 M in pentane, 527 µL, 0.843 mmol, 2.5 equiv) in one portion. After 5 min 4-fluorobenzaldehyde in diethylether (4 mL) was added via cannula dropwise and the reaction was stirred for a further 10 min at -120 ºC. The reaction was then quenched with NH_4Cl (sat. 2 mL) and the mixture allowed to warm to rt. The mixture was then extracted with diethylether (3×5 mL) and the combined extracts dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (10 → 60% ethylacetate in light petroleumether 40/60) to yield *rac*-(2-(*tert*-butylsulfinyl)phenyl)(4-fluorophenyl)methanol a colourless glass. (27.1 mg, 88.4 µmol. 26%) Column chromatography also yielded (*tert*-butylsulfinyl)benzene as a solid (30.6 mg, 168 µmol. 49%).

rac-(2-(*tert*-Butylsulfinyl)phenyl)(4-fluorophenyl)methanol **3.4.3$_F$**

R_f (ethylacetate / light petroleumether 40/60) (60 : 40) : 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (C**H** $_{C2}$, dd, *J* = 2.5, 6.1 Hz, 1 H), 7.51 - 7.43 (C**H** $_{C2, C4, C5}$, m, 3 H), 7.37 (C**H** $_{C8}$, dd, *J* = 5.3, 8.3 Hz, 2 H), 7.02 (C**H** $_{C9}$, CH t, *J* = 8.8 Hz, 2 H), 6.40 (C**H**OH, s, 1 H), 1.32 (C(C**H**$_3$)$_3$, s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.8 (**C** C6), 137.3 (**C** C7), 131.8 (**C**H C4), 127.9 (**C**H C8, d, *J* = 7.3 Hz), 127.5 (**C**H C3), 126.9 (**C**H C2), 115.4 (**C**H C9, d, *J* = 22.0 Hz), 70.9 (**C**HOH), 57.7 (**C**(CH$_3$)$_3$), 23.3 (C(**C**H$_3$)$_3$).

IR (neat) : 3326, 3063, 2965, 2927, 1508 cm^{-1}.

MS (ES$^+$)(m/z) : 370 [M+Na+MeCN]$^+$ (100%), 635 [2M+Na]$^+$ (93%), 941 [3M+Na]$^+$ (37%).

HRMS (ES^+) : $[M+Na]^+$, Calcd. 329.0982; Found. 329.0989.

(*tert*-Butylsulfinyl)benzene **3.4.2**

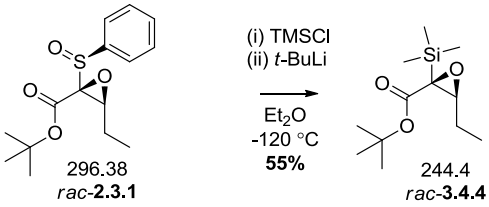
R_f (ethylacetate / light petroleumether 40/60) (60 : 40) : 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.53 (C**H** *t*BuSOAr, m, 2 H), 7.53 - 7.45 (C**H** *t*BuSOAr, m, *J* = 2.6 Hz, 3 H), 1.17 (*t***Bu**SOAr s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.9 (*t*BuSOAr **C** *I*), 130.9 (*t*BuSOAr **C**H *P*), 128.1 (*t*BuSOAr **C**H *O*), 126.0 (*t*BuSOAr **C**H *M*), 55.4 (*t***Bu**SOAr **C**) 53.4 (CH_2Cl_2), 22.4 (*t***Bu**SOAr **C**H_3).

Data matches literature. (JACS *120, 32,* **1998**, 8019)

***rac*-(2*R*,3*S*)-*tert*-Butyl 3-ethyl-2-(trimethylsilyl)oxirane-2-carboxylate 3.4.4**



To a solution of *rac*-epoxide **2.3.1** (200 mg, 0.675 mmol, 1 equiv) in diethyl ether (1 mL) at -78 ºC under N_2 (g) was added chlorotrimethylsilane (171 µL, 1.35 mmol, 2 equiv) dropwise. Separately to a flask of diethyl ether (1 mL) at -120 ºC (N_2 (l), ethanol) under N_2 (g) was added *t*-butyl lithium (1.6 M in pentane, 843 µL, 2 equiv). The solution of epoxide and chlorotrimethylsilane was then added to the *t*-butyl lithium dropwise via cannula. The resultant solution was stirred for 15 min at -120 ºC. The reaction was then quenched immediately with ammonium chloride sat. (2 mL). The mixture was allowed to warm to rt and was then diluted with water (2 mL). The mixture was then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were collected, dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The resultant crude was then purified by column chromatography (2% → 100% ethyl acetate in light petroleum ether 40/60) to yield a colourless oil (90.4 mg, 0.370 mmol. 55%).

R_f (ethylacetate / light petroleum ether 40-60) (2 : 98) : 0.75

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.87 (C**H** $_{epox}$, t, *J* = 6.2 Hz, 1 H), 1.77 - 1.59 (C**H**$_2$, m, 1 H), 1.59 - 1.38 (C**H**$_2^*$, m, 1 H), 1.48 (*t***Bu**, s, 9 H), 1.03 (CH_2C**H**$_3$, t, *J* = 7.5 Hz, 3 H), 0.13 (Si**Me**$_3$, s, 9 H).

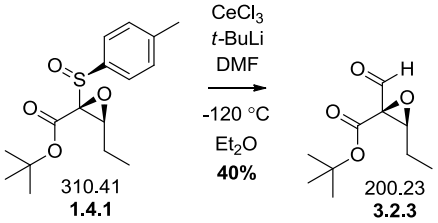
^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2 (**C**OO*t*Bu), 81.5 (**C**Me$_3$), 60.6 (**C**H epox), 57.4 (**C** epox), 28.2 (C**Me**$_3$), 22.4 (**C**$H_2$$CH_3$), 10.2 ($CH_2$**C**$H_3$), 3.4 (Si**Me**$_3$).

IR (neat) : 2971, 1737, 1704, 1393, 841 cm^{-1}

LRMS (ES$^+$)(m/z) : 267 [M+Na]$^+$ (7%), 308 [M+MeCN+Na]$^+$ (100%).

HRMS (ES$^+$) : [M+Na]$^+$, Calcd. 267.1387; Found. 267.1389.

α-Epoxyaldehyde 3.2.3



To a predried flask was added predried cerium (III) chloride (1.42 g, 5.75 mmol, 0.8 equiv). The cerium chloride was then dried in the flask at 140 ºC under high vacuum >15h. Seperately a flask containing epoxide **1.4.1** (2.23 g, 7.18 mmol, 1 equiv) was dried under high vacuum >15h. Both flasks were then purged with N_2 (g). The epoxide was then dissolved in diethyl ether (10 mL) and DMF (1.11 mL, 14.4 mmol, 2 equiv); and the cerium chloride suspended in diethyl ether (20 mL), both flasks were then cooled to -120 ºC (N_2 (l) and ethanol bath). Then to the cerium chloride suspension was added *t*-butyl lithium (11.2 mL, 18.0 mmol, 2.5 equiv) dropwise. After 5 min at -120 ºC the epoxide solution was then added rapidly via cannula at -120 ºC, the mixture was stirred for a further 10min at the same temperature becoming orange/red from colourless and then quenched with methanol (5 mL) immediately. The mixture was then allowed to thaw before filtering through celite and washing with dichloromethane (60 mL). The filtrate was then partioned with sodium hydrogen carbonate sat. (40 mL), the aqueous phase extracted with further portions of CH_2Cl_2 (2 × 20 mL). The combined organic phases were then washed with brine (20 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum (< 500 mbar, 30 ºC, **product is volatile**). The crude was then purified by column chromatography (10% - 25% diethyl ether in pentane) to yield a pale yellow oil (645 mg,

90% purity with 10% diethyl ether, 2.90 mmol. 40%) (*ee* 75% from *7* : *1 d.r.* of (2*R*,3*S*)-*tert*-butyl 3-ethyl-2-((*S*)-p-tolylsulfinyl)oxirane-2-carboxylate).

α-Epoxyaldehyde **3.2.3**

R_f (diethyl ether / pentane) (30 : 70) : 0.13 (+ve *p*-anisaldehyde; -ve UV)

$[\alpha]_D$: +40.7 (c 0.39 g/100 mL, $CHCl_3$, 24°C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 9.58 (C**H**O, s, 1 H), 3.26 (C**H** $_{epox,}$ t, *J* = 6.2 Hz, 1 H), 1.61 - 1.86 (C$\mathbf{H}_2$, m, 2 H), 1.52 - 1.59 (C$\mathbf{H}_{3\ t\text{-Bu}}$, m, 9 H), 1.10 (C$\mathbf{H}_{3\ Et}$, t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.8 (**C**HO), 163.9 (**C**OO*t*-Bu), 84.2 (**C** $_{t\text{-Bu}}$), 65.0 (**C**H $_{epox}$), 64.0 (**C** $_{epox}$), 28.1 (**C**$H_{3\ t\text{-Bu}}$), 21.7 (**C**$H_{2\ Et}$), 10.0 (**C**$H_{3\ Et}$).

IR (cm^{-1}) : 2977, 2938, 2880, 1749, 1726cm^{-1}

MS (CI)(m/z) : 218 $[M+CH_5]^+$ (32%).

MS (EI)(m/z): 145 $[M-t\text{Bu}+H]^+$ (50%), 127 $[M-O t\text{Bu}]^+$ (127%), 100 $[M-COO t\text{Bu}+H]^+$ (54%), 57 $[t\text{Bu}]^+$ (100%).

HRMS (ES^+) : $[M+MeOH+Na]^+$, Calcd. 255.1203; Found. 255.1208.

(*S*)-1-(*tert*-Butylsulfinyl)-4-methylbenzene **3.4.5**

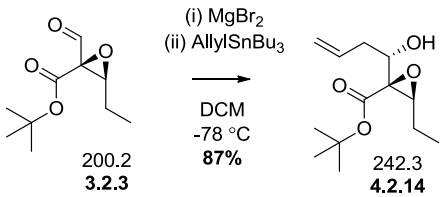
R_f (ethylacetate / light petroleumether 40-60) (30 : 70) : 0.20

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (C**H** $_{t\text{BuSOAr}}$, d, *J* = 8.1 Hz, 2 H), 7.21 (C**H** $_{t\text{BuSOAr}}$, d, *J* = 8.1 Hz, 2 H), 2.34 (Ar**Me**, s, 3 H), 1.09 (*t***Bu**SOAr, s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.5 (*t*BuSOAr **C**), 136.7 (*t*BuSOAr **C**), 129.0 (*t*BuSOAr **C**H *O*), 126.2 (*t*BuSOAr **C**H *M*), 55.6 (**C**Me_3), 22.7 (C**Me**$_3$), 21.4 (Ar**Me**).

Data matches literature. [91]

α-Epoxyaldehyde allylation to give the allyl alcohol 4.2.14



To a suspension of magnesium granules (132 mg, 5.44 mmol, 1.6 equiv) in diethyl ether (5 mL) was added 1,2-dibromoethane (469 µL, 5.44 mmol, 1.6 equiv) under N_2 (g). The

mixture started to spontaneously reflux and was stirred for approximately 2 h until complete dissolution of the solid magnesium. After initial reflux, some intermittent periods of heating, with a heat gun were carried out to promote dissolution. The diethyl ether was then evacuated from the flask under vacuum to yield a white solid which was dissolved in CH_2Cl_2 (17 mL). Separately a flask containing α-epoxyaldehyde **3.2.3** (680 mg, 3.37 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was prepared under N_2 (g). Again separately another flask containing a solution of allyltributylstannane (1.086 mL, 3.54 mmol, 1.05 equiv) in CH_2Cl_2 (3 mL) under N_2 (g). All flasks were then cooled to -78 ºC. The aldehyde solution was then transferred to the solution of magnesium bromide via cannula and the solution stirred for 10 min at -78 ºC after which the solution of allyltributylstannane was then transferred via cannula and the solution stirred for a further 1 h 30 min. The reaction was then quenched with sodium hydrogen carbonate (40 mL) and mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then washed with brine (20 mL) and dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum. The crude was then immediately purified by column chromatography (10% → 20% ethyl acetate in light petroleum ether 40/60) to yield a colourless oil (709 mg, 2.92 mmol. 87%).

R_f (ethyl acetate / light petroleum ether 40/60) (15 : 85) : 0.25

$[\alpha]_D$: -16.1 (c 0.686 g/100 mL, $CHCl_3$, 24^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.88 (C**H**=CH_2, tdd, *J* = 6.8, 10.2, 17.1 Hz, 1 H), 5.20 - 5.08 (CH=C**H**$_2$, m, 2 H), 3.70 (C**H**OH, dd, *J* = 4.3, 8.3 Hz, 1 H), 3.08 (C**H**$_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.56 - 2.46 (C**H**$_{2\ allyl}$, m, *J* = 6.1 Hz, 1 H), 2.37 - 2.27 (C**H**$_2^{*}{}_{allyl}$, m, *J* = 1.0 Hz, 1 H), 1.75 - 1.54 (C**H**$_{2\ Et}$, m, 2 H), 1.52 (C**H**$_{3\ t\text{-}Bu}$, s, 9 H), 1.05 (C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 3 H).

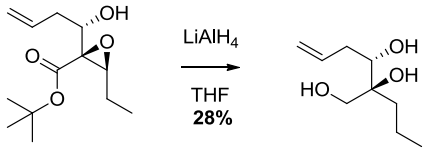
^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0 (**C**OO*t*-Bu), 133.8 (**C**H=CH_2), 117.8 (CH=**C**H_2), 83.4 (**C**Me_3), 71.8 (**C**HOH), 64.2 (**C**$_{epox}$), 62.3 (**C**H$_{epox}$), 37.9 (**C**$H_{2\ allyl}$), 28.1 (**C**$H_{3\ t\text{-}Bu}$), 21.5 (**C**$H_{2\ Et}$), 10.2 (**C**$H_{3\ Et}$).

IR (neat) : 3494, 2976, 2936, 1725, 1369cm^{-1}

LRMS (ES$^+$)(m/z) : 306 (M+MeCN+Na)$^+$ (100%).

HRMS (ES$^+$) : (M+Na)$^+$, Calcd. 265.1410; Found. 265.1415.

rac-(2*S*,3*S*)-2-Propylhex-5-ene-1,2,3-triol



242.3
rac-**4.2.14**

174.24
rac-**5.1.3**

To a solution of *rac*-allyl alcohol **4.2.14** (35 mg, 0.14 mmol, 1 equiv) in THF (1 mL) was added lithium aluminium hydride (27 mg , 0.72 mmol, 5 equiv) in one portion under N_2 (g). The reaction effervesced violently for 1 h, after 3 h the reaction was quenched with water/THF mixture (40 : 60, 1 mL). The white emulsion was then filtered through filter paper on a sinter. The collected solid was triturated with CH_2Cl_2 and filtered through a plug of cotton wool. The solvent of the filtrate was then evaporated under vacuum to yield a crude product which was purified by HPLC (7.5% methanol in CH_2Cl_2) to yield an amorphous residue (6.8 mg, 39 µmol. 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.87 (C**H**=CH_2, dtd, *J* = 5.8, 8.9, 17.9 Hz, 1H), 5.21 (CH=C**H**$_2$, d, *J* = 4.5 Hz, 1H), 5.18 (CH=C**H**$_2^*$, br s, 1H), 4.74 (O**H**, br. s., 2H), 3.72 (C**H**$_2$OH, d, *J* = 11.1 Hz, 1H), 3.73 (C**H**OH, dd, *J* = 3.0, 10.1 Hz, 1H), 3.60 (C**H**$_2$OH*, d, *J* = 11.6 Hz, 1H), 2.40 (C**H**$_2$CH=CH_2, d, *J* = 14.1 Hz, 1H), 2.25 (C**H**$_2$CH=CH_2^*, td, *J* = 9.1, 14.1 Hz, 1H), 1.60 - 1.21 (C**H**$_2$C**H**$_2$$CH_3$, m, 4H), 0.93 (t, *J* = 6.8 Hz, 3H).

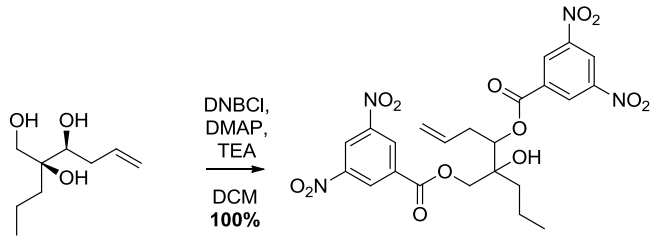
^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0 (**C**H=CH_2), 118.7 (CH=**C**H_2), 74.4 (**C**HOH), 67.2 (**C**H_2OH), 36.1 (**C**H_2CH=CH_2)[a], 35.6 (**C**$H_2CH_2CH_3$)[a], 16.4 (CH_2**C**H_2CH_3), 14.8 (CH_2CH_2**C**H_3).

[a] – some ambiguity between different noted carbons.

IR (neat) : 3358, 2959, 2875, 1413, 1051cm^{-1}

HRMS (ES$^+$) : [M+Na]$^+$, Calcd. 197.1150; Found. 197.1148.

rac-(4_S_,5_S_)-5-Hydroxyoct-1-ene-4,5-diyl bis(3,5-dinitrobenzoate) 5.1.3



174.24
rac-**5.1.2**

562.44
rac-**5.1.3**

To a solution of *rac*-(2S,3S)-2-propylhex-5-ene-1,2,3-triol **5.1.2** (5 mg, 29 µmol, 1 equiv) in CH_2Cl_2 (1 mL) under N_2 (g) was added triethylamine (20 µL, 0.144 mmol, 5 equiv), dimethylamino pyridine (<1 mg, cat.) and 3,5-dinitrobenzoyl chloride (33 mg, 0.144 mmol, 5 equiv) sequentially and portionwise. The reaction was then stirred for 16 h after which the mixture was subjected to standard acid/base work up (1M hydrochloric acid, sodium hydrogen carbonate sat. and brine), filtered and the solvent removed under vacuum. The crude product was purified by HPLC (32.5% ethyl acetate in hexane) to yield an amorphous solid (18.8 mg, 33.4 µmol. 100%). This solid was then recrystallized from chloroform to yield crystals suitable for XRD.

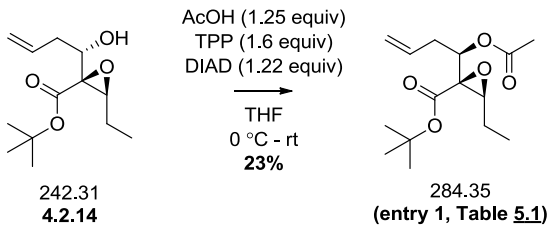
^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ = 9.19 - 9.06 (C**H** $_{Ar}$, m, 6H), 5.94 - 5.81 (C**H**=CH_2, dddd, *J* = 6.2, 8.1, 10.1, 17.2 Hz, 1H), 5.65 (C**H**OH, dd, *J* = 3.0, 9.6 Hz, 1H), 5.14 (CH=C**H**$_2$, dd, *J* = 1.5, 17.2 Hz, 1H), 4.96 (CH=C**H**$_2^*$, br d, *J* = 10.1 Hz, 1H), 4.70 (CO**H**, s, 1H), 4.59 (C**H**$_2$ODNP, s, 2H), 2.88 - 2.70 (C**H**$_2$CH=CH_2, H_2O, m, 4H), 1.88 - 1.81 (C**H**$_2$$CH_2CH_3$, m, *J* = 8.6 Hz, 2H), 1.73 - 1.51 (CH_2C**H**$_2$$CH_3$, m, 2H), 0.98 ($CH_2CH_2$C**H**$_3$, t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.1 (Ar**C**OO), 163.9 (**C** Ar), 163.9 (**C*** Ar), 150.4 (**C** Ar), 136.0 (**C**H Ar), 134.9 (**C** Ar), 134.9 (**C*** Ar), 130.7 (**C**H Ar), 130.6 (**C**H* Ar), 124.0 (**C**H Ar), 119.0 (CH=**C**H_2), 79.5 (**C**HODNP), 75.6 (**C**OH), 69.0 (**C**H_2ODNP), 38.2 (**C**$H_2CH_2CH_3$), 35.1 (**C**H_2CH=CH_2), 17.5 (CH_2**C**H_2CH_3), 15.6 CH_2CH_2**C**H_3).

IR (neat) : 3547, 3101, 3962, 1731, 1544 cm^{-1}

HRMS (ES^+) : $[M+Na]^+$, Calcd. 585.1076; Found. 585.1066.

Mitsunobu inversion of the allyl alcohol to the acetate



242.31
4.2.14

284.35
(entry 1, Table 5.1)

To a solution of *rac*-allyl alcohol **4.2.14** (100 mg, 0.413 mmol, 1 equiv) in THF (2 mL) was added triphenylphosphine (173 mg, 0.660 mmol, 1.6 equiv), DIAD (99 µL, 0.504 mmol, 1.22 equiv) sequentially under N_2 (g) at 0 ºC. The reaction was then stirred for 3 h, before warming to rt and stirring for 48 h. The solvent was then evaporated under reduced pressure and the crude residue dissolved in diethylether (5 mL) and filtered through a plug of silica, washing with further portions of diethylether (4 × 5 mL). The solvent from the combined filtrates was then evaporated under reduced pressure and crude residue purified by HPLC (10% ethylacetate in hexane) to yield a colourless oil (27 mg, 93.6 µmol. 23%).

^{1}H NMR (400 MHz, $CHCl_3$) δ = 5.75 (C**H**=CH_2, tdd, *J* = 7.5, 9.9, 17.1 Hz, 1 H), 5.26 (C**H**OAc, t, *J* = 6.8 Hz, 1 H), 5.14 (CH=C**H**$_2$ *trans*, dd, *J* = 1.5, 17.2 Hz, 1 H), 5.08 (CH=C**H**$_2$ *cis*, dd, *J* = 1.0, 10.1 Hz, 1 H), 2.99 (C**H** epox, t, *J* = 6.3 Hz, 1 H), 2.59 - 2.44 (C**H**$_2$CH=CH_2, m, 2 H), 2.06 (OOCC**H**$_3$, s, 3 H), 1.68 - 1.53 (C**H**$_2$$CH_3$, m, 2 H), 1.51 (C(C**H**$_3$)$_3$, s, 9 H), 1.02 (CH_2C**H**$_3$, t, *J* = 7.6 Hz, 3 H).

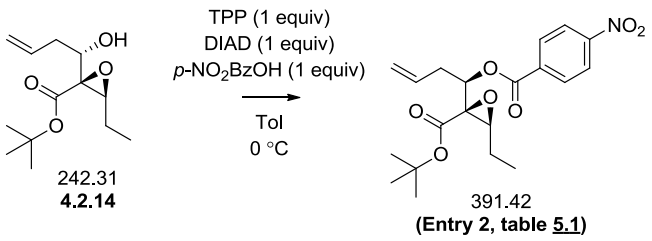
^{13}C NMR (100 MHz, $CHCl_3$) δ = 169.8 (OO**C**Me), 166.3 (**C**OO*t*Bu), 132.7 (**C**H=CH_2), 118.6 (CH=C**H**$_2$), 83.0 (**C**Me_3), 71.9 (**C**HOAc), 63.9 (**C** epox), 61.3 (**C**H epox), 35.9 (**C**H_2CH=CH_2), 28.0 (C(C**H**$_3$)$_3$), 21.3 (C**H**$_2$$CH_3$), 20.9 (OOC**C**$H_3$), 10.0 ($CH_2$C**H**$_3$).

IR (cm^{-1}) : 2977, 2938, 1745, 1369 1226 cm^{-1}.

MS (ES^+)(m/z) : 307 $[M+Na]^+$ (19%), 348 $[M+Na+MeCN]^+$ (100%).

HRMS (ES^+) : $[M+K]^+$; Calcd. 323.1255; Found. 323.1258.

Mitsunobu inversion of the allyl alcohol to the *p*-nitrobenzoate



To a solution of allyl alcohol **4.2.14** (110 mg, 0.454 mmol, 1 equiv) in toluene (1 mL) was added, triphenylphoshine (119 mg, 0.454 mmol, 1 equiv) and *p*-nitrobenzoic acid (76 mg, 0.454 mmol, 1 equiv). The solution was then cooled to 0 ºC and di*iso*propyl azodicarboxylate (89 µL, 0.454 mmol, 1 equiv) was added dropwise over 1 h. After 6 h the reaction was diluted with toluene and filtered through silica pad (wetted with toluene), washing with toluene and then CH_2Cl_2. The solvent of the combined washings was removed under reduced pressure and the crude residue purified by column chromatography (15% diethylether in light petroleumether 40/60), TLC (15% diethylether in light petroleumether 40/60), to yield a colourless oil (65.4 mg, 0.167 mmol. 37%).

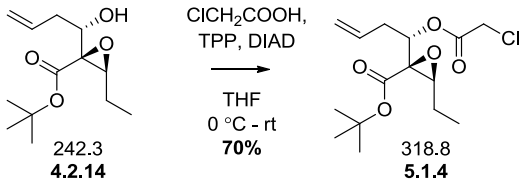
R_f (diethylether / light petroleumether 40-60) (15 : 85) : 0.15

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (Ar $_{C\underline{\mathbf{H}}}$, d, *J* = 8.9 Hz, 2 H), 8.18 (Ar $_{C\underline{\mathbf{H}}}$, d, *J* = 8.8 Hz, 2 H), 5.80 (C**H**=CH_2, tdd, *J* = 7.2, 10.0, 17.1 Hz, 1 H), 5.45 (C**H**OAr, t, *J* = 7.1 Hz, 1 H), 5.18 (CH=C**H**$_{2\ trans}$, dd, *J* = 1.5, 17.1 Hz, 1 H), 5.09 (CH=C**H**$_{2\ cis}$, d, *J* = 10.2 Hz, 1 H), 3.04 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.68 (C**H**$_2$CH=CH_2, t, *J* = 7.1 Hz, 2 H), 1.72 - 1.57 (C**H**$_2$$CH_3$, m, 1 H), 1.56 - 1.45 (C**H**$_2$$CH_3$*, m, 1 H), 1.53 (*t***Bu**, s, 9 H), 1.02 (CH_2C**H**$_3$, t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0 (Ar**C**OO), 163.5 (**C**OO*t*Bu), 150.7 (Ar **C**), 135.1 (Ar **C**), 132.2 (**C**H=CH_2), 130.8 (Ar **C**H), 123.6 (Ar **C**H), 119.1 (CH=**C**H_2), 83.2 (**C**Me_3), 74.3 (**C**HOOCAr), 63.8 (**C** epox), 61.5 (**C**H epox), 35.9 (**C**H_2CH=CH_2), 28.0 (C**Me**$_3$), 21.4 (**C**$H_2$$CH_3$), 10.0 ($CH_2$C**H**$_3$).

(Sample decomposed before obtaining LRMS, HRMS and IR data)

Mitsunobu inversion of the allyl alcohol to the α-chloroacetate 5.1.4



To a solution of allyl alcohol **4.2.14** (973 mg, 4.02 mmol, 1 equiv) in THF (25 mL) under N_2 (g) at 0 ºC was added sequentially triphenylphosphine (1.69 g, 6.43 mmol, 1.6 equiv), chloroacetic acid (474 mg, 5.02 mmol, 1.25 equiv) and di*iso*propyl azodicarboxylate (965 µL, 4.90 mmol, 1.22 equiv) dropwise under N_2 (g) at 0 ºC. The reaction was then stirred at 0 ºC for 3 h and then at rt for 18 h. After which the solvent was evaporated under vacuum and the crude purified by column chromatography (5% diethyl ether in light petroleum ether 40/60), loading the mixture as a solution in CH_2Cl_2. The inverted ester was obtained as a colourless oil (899 mg, 2.82 mmol. 70%).

R_f (diethyl ether / light petroleum ether 40/60) (15 : 85) : 0.18

$[\alpha]_D$: -12.6 (c 0.51 g/100 mL, $CHCl_3$, 23^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (C**H**=CH_2, tdd, *J* = 7.1, 10.0, 17.1 Hz, 1 H), 5.29 (C**H**OOCCH_2Cl, dd, *J* = 6.6, 7.6 Hz, 1 H), 5.15 (CH=C**H**$_{2\ trans}$, dd, *J* = 1.5, 17.1 Hz, 1 H), 5.09 (CH=C**H**$_{2\ cis}$, dd, *J* = 1.5, 10.1 Hz, 1 H), 4.04 (OOCC**H**$_2$Cl, d, *J* = 1.5 Hz, 2 H), 3.02 (C**H**$_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.61 - 2.46 (C**H**$_{2\ allyl}$, m, 3 H), 1.61 (C**H**$_{2\ Et}$, dt, *J* = 7.1, 14.4 Hz, 2 H), 1.50 (C**H**$_{3}$ *t*-Bu, s, 9 H), 1.01 (C**H**$_{3\ Et}$, t, *J* = 7.3 Hz, 3 H).

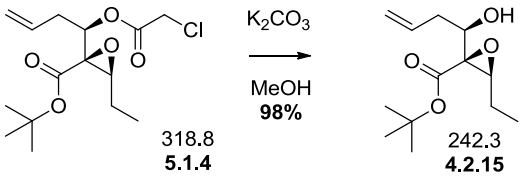
^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2 (**C**OO*t*-Bu), 165.9 (CH_2**C**OO), 132.1 (**C**H=CH_2), 119.1 (CH=**C**H_2), 83.2 (**C**Me_3), 74.1 (**C**HOOCCH_2), 63.5 (**C**$_{epox}$), 61.3 (**C**H $_{epox}$), 40.6 (**C**$H_{2\ allyl}$), 35.7 (**C**H_2Cl), 27.9 (**C**$H_{3\ t\text{-Bu}}$), 21.2 (**C**$H_{2\ Et}$), 10.0 (**C**$H_{3\ Et}$).

IR (neat) : 2977, 2938, 1744, 1369, 1135cm^{-1}

LRMS (ES^+)(m/z) : 341 $[M+Na]^+$ (13%), 382 $[M+MeCN+Na]^+$ (^{35}Cl, 100%), 384 $[M+MeCN+Na]^+$ (^{37}Cl, 35%).

HRMS (ES^+) : $(M+Na)^+$, Calcd. 341.1126; Found. 341.1131.

Methanolysis of the α-chloroacetate 5.1.4 to the inverted allyl alcohol 4.2.15



To a solution of α-chloroacetate **5.1.4** (210 mg, 0.659 mmol, 1 equiv) in MeOH (6 mL) was added potassium carbonate (anh, 455 mg, 3.29 mmol, 5 equiv) in one portion. The mixture was stirred for 2 h before removing most of the methanol by evaporation; the slurry was then dissolved in diethyl ether (15 mL) and water (10 mL). The phases were then separated and the organic phase was then washed with water (10 mL) and brine (5 mL); dried over sodium sulfate (anh), filtered and the solvent evaporated under vacuum to yield a colourless oil (156 mg, 0.645 mmol. 98%).

R_f (diethyl ether / light petroleum ether 40/60) (20 : 80) : 0.20

$[\alpha]_D$: -1.6 (c 0.739 g/100 mL, $CHCl_3$, 24°C)

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.87 (C**H**$_{ene}$, ddt, *J* = 16.7, 10.1, 7.6 Hz, 1 H), 5.17 (C**H**$_{2\ ene\ E\ CH}$, dd, *J* = 8.1, 1.0 Hz, 1 H), 5.13 (C**H**$_{2\ ene\ Z\ CH}$, *br*d, *J* = 1.0 1 H), 4.11 (C**H**OH, td, *J* = 7.8, 4.5 Hz, 1 H), 3.19 (C**H**$_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.31 - 2.47 (C**H**$_{2\ allyl}$, m, 2 H,), 1.87 (O**H**, d, *J* = 9.1 Hz, 1 H), 1.54 - 1.69 (C**H**$_{2\ Et}$, m, 2 H), 1.50 (C**H**$_{3\ t\text{-}Bu}$, s, 9 H,), 1.04 ppm (C**H**$_{3\ Et}$, t, *J* = 7.3 Hz, 3 H).

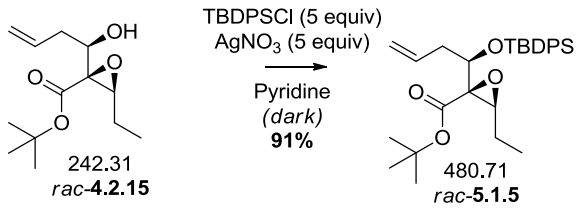
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.4 (**C**OO*t*Bu), 133.5 (**C**H$_{ene}$), 118.7 (**C**H$_{2\ ene}$), 82.8 (**C**$_{t\text{-}Bu}$), 68.9 (**C**HOH), 66.0 (**C**$_{epox}$), 60.3 (**C**H$_{epox}$), 38.3 (**C**H$_{2\ allyl}$), 28.0 (**C**H$_{3\ t\text{-}Bu}$), 21.4 (**C**H$_{2\ Et}$), 10.2 (**C**H$_{3\ Et}$).

IR (neat) : 3485, 3078, 2975, 1743, 1642 cm^{-1}.

LRMS (ES^+)(m/z) : 242 *exp* 243 *calc* $[M+H]^+$ (100%), 281 $[M+K]^+$ (13%), 306 $[M+MeCN+Na]^+$ (18%).

HRMS (ES^+) : $(M+Na)^+$, Calcd. 265.1416; Found. 265.1410.

TBDPS protection of the inverted allyl alcohol 4.2.15



To a solution of inverted allyl alcohol **4.2.15** (150 mg, 0.619 mmol, 1 equiv) in pyridine (7.5 mL) under N_2 (g) in the dark, was added silver (I) nitrate (523 mg, 3.10 mmol, 5 equiv) in one portion followed by TBDPSCl (805 µL, 3.10 mmol, 5 equiv) dropwise (slowly). The reaction was then stirred in the dark for 4 h. The reaction was then diluted with diethylether (60 mL) and washed with portions of $CuSO_4$ (sat, 4 × 20 mL) and brine (2 × 20 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (2.5% ethylacetate in light petroleumether 40/60), further purifying by HPLC (7.5% ethylacetate in hexane) to give a colourless oil (227 mg, 0.472 mmol. 91%).

R_f (diethylether / light petroleumether 40/60) (15 : 85) : 0.50

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 - 7.66 (C**H** $_{Ar}$, m, 4 H), 7.47 - 7.34 (C**H** $_{Ar}$, m, 6 H), 5.49 (C**H**=CH_2, tdd, *J* = 7.6, 9.6, 17.2 Hz, 1 H), 4.88 (CH=C**H**$_{2\ trans}$, *br*d, *J* = 17.2 Hz, 1 H), 4.84 (CH=C**H**$_2$, *cis br*s, 1 H), 3.73 (C**H**OTBDPS, dd, *J* = 5.1, 9.1 Hz, 1 H), 2.94 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.69 (C**H**$_{2\ allyl}$, td, *J* = 8.4, 13.5 Hz, 1 H), 2.21 (C**H**$_2^*$ $_{ally,l}$ ddd, *J* = 5.6, 7.1, 13.6 Hz, 1 H), 1.67 - 1.56 (C**H**$_{2\ Et}$, m, 1 H), 1.53 (C**H**$_3$, $_{t\text{-}Bu}$ s, 9 H), 1.47 - 1.34 (C**H**$_2^*$ $_{Et}$, m, 1 H), 1.10 (C**H**$_{3\ TBDPS}$, s, 9 H), 0.99 (C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 2 H).

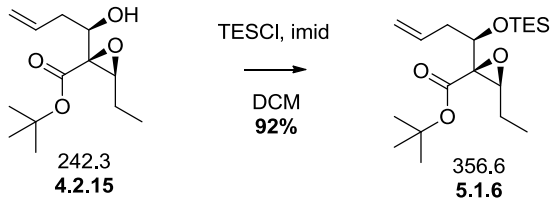
^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0 (**C**OO*t*-Bu), 136.1 (**C**H $_{Ar\ M}$), 135.9 (**C**H* $_{Ar\ M}$), 134.1 (**C** $_{Ar\ I}$), 133.6 (**C**H=CH_2), 133.0 (**C*** $_{Ar\ I}$), 129.7 (**C**H $_{Ar\ P}$), 129.6 (**C**H* $_{Ar\ P}$), 127.5 (**C**H $_{Ar\ O}$), 127.5 (**C**H* $_{Ar\ O}$), 117.9 (CH=C**H**$_2$), 82.1 (**C**Me_3), 76.0 (**C**HOTBDPS), 66.1 (**C** $_{epox}$), 61.4 (**C**H $_{epox}$), 40.0 (**C**$H_{2\ allyl}$), 28.1 (**C**$H_{3\ t\text{-}Bu}$), 26.9 (**C**$H_{3\ TBDPS}$), 21.7 (**C**$H_{2\ Et}$), 19.4 (**C** $_{t\text{-}Bu\ TBDPS}$), 10.1 (**C**$H_{3\ Et}$).

IR (cm^{-1}) : 3072.4, 2970.0, 2932.4, 1747.5, 1427.5 cm^{-1}.

MS (ES^+)(m/z) : 503 $[M+Na]^+$ (100%), 544 $[M+MeCN+Na]^+$ (20%).

HRMS (ES^+) : $[M+Na]^+$; Calcd. 503.2588; Found. 503.2569.

TES protection of the inverted allyl alcohol 4.2.15



To a solution of inverted allyl alcohol **4.2.15** (575 mg, 2.37 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added imidazole (646 mg, 9.49 mmol, 4 equiv), followed by chloro triethylsilane (1.19 mL, 7.12 mmol, 3 equiv) dropwise. The reaction was then stirred for 16 h before quenching with potassium hydrogen sulfate (10% w/w, 50 mL). The organic phase was then washed with portions of water (2 × 25 mL), dried over sodium sulfate (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (5% diethyl ether in light petroleum) to yield a colourless oil (779 mg, 2.18 mmol. 92%).

R_f (diethyl ether / light petroleum ether 40/60) (20 : 80) : 0.55

$[\alpha]_D$: -3.0 (c 0.706 g/100mL, $CHCl_3$, 23^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.80 (C**H**=CH_2, tdd, *J* = 7.6, 10.1, 17.2 Hz, 1 H), 5.12 (CH=C**H**$_2$ *trans*, dd, *J* = 1.5, 17.2 Hz, 1 H), 5.05 (CH=C**H**$_2$ *cis*, dd, *J* = 1.0, 10.1 Hz, 1 H), 3.78 (C**H**OTBDPS, t, *J* = 6.8 Hz, 1 H), 3.02 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.53 (C**H**$_{2\ allyl}$, tddd, *J* = 1.1, 6.9, 7.1, 13.6 Hz, 1 H), 2.46 (C**H**$_2^*$ $_{allyl}$, tddd, *J* = 1.0, 6.9, 7.1, 13.6 Hz, 1 H), 1.69 - 1.54 (C**H**$_{2\ Et}$, m, 1 H), 1.49 (s, 9 H), 1.53 - 1.39 (C**H**$_2^*$ $_{Et}$, m, 1 H), 1.03 (C**H**$_{3\ TESOH\ impurity}$, t, *J* = 7.6 Hz, 3 H (9H)), 0.97 (C**H**$_{3\ TES}$, t, *J* = 8.1 Hz, 9 H), 0.93 (**?**, t, *J* = 8.1 Hz, 3 H), 0.63 (C**H**$_{2\ TES}$, q, *J* = 8.1 Hz, 6 H), 0.52 (C**H**$_{2\ TESOH\ impuritiy}$, q, *J* = 8.1 Hz, 2 H (6H)).

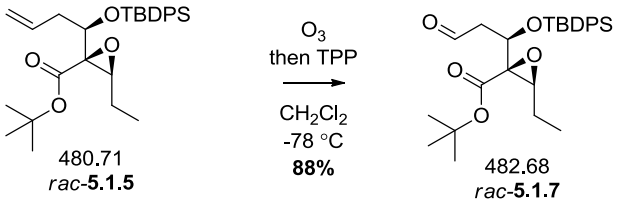
^{13}C NMR (100 MHz $CDCl_3$) δ = 167.1 (**C**OO*t*-Bu), 134.4 (**C**H=CH_2), 117.7 (CH=C**H**$_2$), 82.1 (**C**Me$_{3\ t\text{-Bu}}$), 74.1 (**C**HOTBDPS), 66.5 (**C** $_{epox}$), 61.3 (**C**H $_{epox}$), 40.2 (**C**H$_{2\ allyl}$), 28.0 (**C**H$_{3\ t\text{-Bu}}$), 21.7 (**C**H$_{2\ Et}$), 10.1 (**C**H$_{3\ Et}$), 6.8 (**C**H$_{3\ TESOH\ impurity}$), 6.7 (**C**H$_{3\ TES}$), 6.4 (**C**H$_{2\ TESOH\ impurity}$), 4.8 (**C**H$_{2\ TES}$).

IR (neat) : 2955, 2912, 2878, 1750, 1723, 1368cm^{-1}.

LRMS (ES$^+$)(m/z) : 364 [M+Li]$^+$ (20%), 379 [M+Na]$^+$ (13%), 420 [M+MeCN+Na]$^+$ (100%).

HRMS (ES$^+$) : [M+Na]$^+$, Calcd. 379.2275; Found. 379.2274.

Ozonolysis of the TBDPS protected inverted allyl alcohol 5.1.5 to the aldehyde 5.1.7



To a solution of *rac*-TBDPS protected allyl alcohol **5.1.5** (208 mg, 0.432 mmol, 1 equiv) in CH_2Cl_2 (20 mL) at -78 ºC was bubbled O_3 (excess). After 20 min the solution became a deep blue colour from colourless and O_2 was then bubbled through the solution at -78 ºC until the colour had dissipated (≈ 40 min). The flow of gas was then terminated and triphenylphosphine (125 mg, 0.476 mmol, 1.1 equiv) was added in one portion after stirring for 15 min the reaction checked with starch iodide paper and allowed to warm to rt. The solvent was then evaporated under reduced pressure. The crude residue was redissolved in acetone (HPLC grade, 5 mL) under N_2 (g) and merrifield's resin (~3.5 mmol/g, 0.817g, 2.86 mmol, 5 equiv) was added followed by NaI (429 mg, 2.86 mmol, 5 equiv) in single portions. The suspension was then stirred in the dark for 16 h and then filtered, washing with acetone (2 × 20 mL), toluene (2 × 20 mL) and acetone (2 × 20 mL) sequentially. The solvent of the combined filtrates was then evaporated under reduced pressure and the crude purified by column chromatography (10% ethylacetate in hexane) loading the crude in CH_2Cl_2 solution (183 mg, 0.378 mmol. 88%).

R_f (ethylacetate / hexane) (10 : 90) : 0.20

^{1}H NMR (400 MHz , $CDCl_3$) δ = 9.47 (C**H**O, t, *J* = 1.8 Hz, 1 H), 7.77 - 7.62 (C**H** $_{Ar}$, m, 4 H), 7.50 - 7.34 (C**H** $_{Ar}$, m, 6 H), 4.27 (C**H**OTBDPS, dd, *J* = 5.1, 7.1 Hz, 1 H), 3.06 (C**H** $_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.91 (C**H**$_2$ $_{allyl}$, ddd, *J* = 1.8, 6.9, 17.1 Hz, 1 H), 2.65 (C**H**$_2^*$ $_{allyl}$ ddd, *J* = 2.0, 5.1, 17.2 Hz, 1 H), 1.70 - 1.57 (C**H**$_2$ $_{Et}$, m, 1 H), 1.53 (C**H**$_3$ $_{t\text{-}Bu}$, s, 9 H), 1.39 (C**H**$_2^*$ $_{Et}$, quind, *J* = 7.2, 14.3 Hz, 1 H), 1.14 - 1.06 (C**H**$_3$ $_{TBDPS}$, s, 9 H), 0.97 (C**H**$_3$ $_{Et}$, t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.7 (**C**HO), 166.7 (**C**OO*t*-Bu), 136.0 (**C**H $_{Ar\ M}$), 135.8 (**C**H $_{Ar\ M}$), 133.3 (**C** $_{Ar\ I}$), 132.3 (**C*** $_{Ar\ I}$), 130.0 (**C**H $_{Ar\ P}$), 130.0 (**C**H* $_{Ar\ P}$), 127.7 (**C**H $_{Ar\ O}$), 127.7 (**C**H* $_{Ar\ O}$), 82.8 (**C**Me$_3$ $_{t\text{-}Bu}$), 70.8 (**C**HOTBDPS), 66.4 (**C** $_{epox}$), 61.7 (**C**H $_{epox}$), 49.2

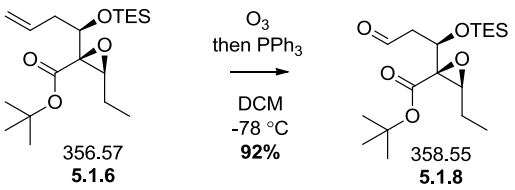
(**C**H_2CHO), 28.1 (**C**H_3 *t*-Bu), 26.8 (**C**H_3 TBDPS), 21.7 (**C**H_2 Et), 19.4 (**C** *t*-Bu TBDPS), 10.0 (**C**H_3 Et).

IR (cm^{-1}) : 3071.6; 2969.2; 2933.1; 1746.5; 1721.4; 1368.1 cm^{-1}.

MS (ES^+)(m/z) : 505 $[M+Na]^+$ (100%), 546 $[M+MeCN+Na]^+$.

HRMS (ES^+) : $[M+Na]^+$; Calcd. 505.2381; Found. 505.2369.

Ozonolysis of the TES protected inverted allyl alcohol 5.1.6 to the aldehyde 5.1.8



To a solution of TES protected allyl alcohol **5.1.6** (778 mg, 2.18 mmol, 1 equiv) in CH_2Cl_2 (130 mL) at -78 ºC was bubbled O_3 (g) for ≈20 min. The colourless solution became blue. The flow of O_3 (g) was stopped and O_2 (g) was bubbled through the solution for a further 40 min. After the solution had become colourless the flow of oxygen was stopped and triphenylphosphine (629 mg, 2.40 mmol, 1.1 equiv) was added in one portion the reaction was stirred for 5 min at -78 ºC before allowing to warm to rt and testing with starch iodide paper. The solvent was then evaporated under vacuum and the crude dissolved in acetone (30 mL). To this solution was added merrifield's resin (3.5 – 4.5 mmol/g loading, 3.11 g, ≈10.9 mmol, 5 equiv) and sodium iodide (1.63 g, 10.9 mmol, 5 equiv). The resultant suspension was stirred in the dark for 20 hr before filtering and washing the filter cake with acetone (2 × 40 mL), toluene (2 × 40 mL) and acetone (2 × 40 mL) respectively. The solvent was then evaporated from the filtrate under vacuum and crude purified by column chromatography (20% diethyl ether in light petroleum 40/60) to yield a colourless oil (717 mg, 2.00 mmol. 92%).

R_f (diethylether / light petroleum 40/60) (20 : 80) : 0.38

$[\alpha]_D$: +6.1 (c 0.69 g/100 mL, $CHCl_3$, 26ºC)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (C**H**O, t, *J* = 1.5 Hz, 1H), 4.26 (C**H**OTES, dd, *J* = 5.1, 7.1 Hz, 1H), 3.05 (C**H** epox, t, *J* = 6.3 Hz, 1H), 2.96 (C**H**$_2$CHO, ddd, *J* = 2.0, 7.1, 16.7 Hz, 1H), 2.80 (C**H**$_2$CHO*, ddd, *J* = 1.5, 5.1, 16.7 Hz, 1H), 1.64 (C**H**$_2$$CH_3$, spt, *J* = 7.6 Hz,

1H), 1.51 (s, 9H), 1.46 (C**H**$_2$CH$_3$*, spt, *J* = 7.6 Hz, 1H), 1.02 (CH$_2$C**H**$_3$, t, *J* = 7.6 Hz, 3H), 0.95 (C**H**$_{3\ TES}$, t, *J* = 7.6 Hz, 9H), 0.64 (C**H**$_{2\ TES}$, q, *J* = 8.1 Hz, 6H).

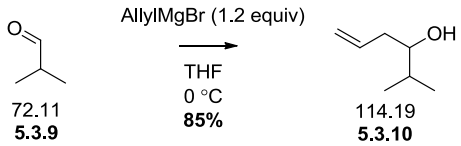
^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.2 (**C**HO), 166.6 (**C**OO*t*Bu), 82.7 (**C**Me$_3$), 69.6 (**C**HOTES), 66.5 (**C** epox), 61.5 (**C**H epox), 49.3 (**C**H$_2$CHO), 28.0 (C**Me**$_3$), 21.7 (**C**H$_2$CH$_3$), 10.1 (CH$_2$**C**H$_3$), 6.6 (**C**H$_3$ TES), 4.6 (**C**H$_2$ TES).

IR (neat) : 2956, 2878, 1722, 1369, 1136cm^{-1}

LRMS (ES$^+$)(m/z): 366 [M-*t*Bu+H+Na+MeCN]$^+$ (25%), 381 [M+Na]$^+$ (32%), 422 [M+Na+MeCN]$^+$ (100%).

HRMS (ES$^+$) : [M+Na]$^+$, Calcd. 381.2068; Found. 381.2069.

2-Methylhex-5-en-3-ol 5.3.10



To a solution of allylmagneisum chloride in THF (2 M, 84.9 mL, 170 mmol, 1.2 equiv) at 0 ºC in a dried 3-neck RBF under nitrogen was added *i*-butyraldehyde **5.3.9** dropwise (10.0 g, 140 mmol, 1 equiv). The reaction mixture was stirred at 0 ºC (15min) before allowing to warm to rt and stirring for a further hour monitoring by TLC (5% ethylacetate in heptane). The reaction was then poured into saturated NH_4Cl (sat) (100 mL) and extracted with (3 × 200 mL) portions of diethylether. The combined organic extracts were then dried over $MgSO_4$ (anh) filtered and the solvent evaporated under reduced pressure (20 ºC, low vacuum) to yield (~ 50 mL) of colourless oil as crude product. Because of the high volatility the crude was purified by distillation (130 ºC – 143 ºC, fraction 2) (14.4 g, 94% purity by 1H NMR, 119 mmol. 85%).

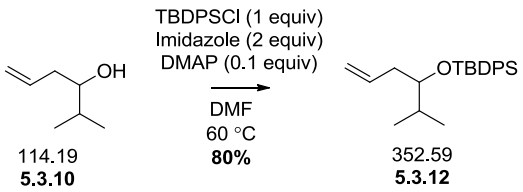
(The product was stored over 4Å MS)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (C**H**=CH$_2$, m, 1H), 5.16 (CH=C**H**$_2$, br d, *J* = 7.6 Hz, 1H), 5.13 (CH=C**H**$_2$*, br s, 1H), 3.41 (C**H**OH, td, *J* = 4.2, 8.2 Hz, 1H), 2.33 (C**H**$_2$CH=CH$_2$, dddd, *J* = 1.0, 3.5, 5.1, 14.1 Hz, 1H), 2.13 (C**H**$_2$CH=CH$_2$,* td, *J* = 8.3, 14.1 Hz, 1H), 1.70 (C**H**Me$_2$, qd, *J* = 6.5, 13.3 Hz, 1H), 1.57 (CHO**H**, br. s., 1H), 0.95 (CH**Me**$_2$, t, *J* = 5.8 Hz, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.4 (**C**H=CH_2), 117.9 CH=CH_2), 75.4 (**C**HOH), 38.8 (**C**H_2CH=CH_2), 33.1 (**C**HMe_2), 18.7 (CH**Me**$_2$), 17.5 (CH**Me**$_2$*).

Data matches literature. [94]

tert-Butyl((2-methylhex-5-en-3-yl)oxy)diphenylsilane 5.3.12



To a solution of 2-methyl-5-hexene-3-ol **5.3.10** (5 g, 40 mmol, 1 equiv) in DMF (25 mL) under N_2 (g) at rt was added imidazole (5.55 mL, 83.2 mmol, 2 equiv) and DMAP (51.9 mg, 0.416 mmol, 0.01 equiv) portion wise and sequentially under nitrogen. After complete dissolution of the imidazole, TBDPSCl (10.8 mL, 41.5 mmol, 1 equiv) was added dropwise. The reaction was then warmed to 60 ºC and stirred for 24 hours. After which it was quenched with water (100 mL) and extracted with ether (3×50 mL), the combined organic extracts were then dried over $MgSO_4$ (anh). The crude mixture was then purified by column chromatography (0-20% ethylacetate in heptane) to yield a colourless oil (11.8 g, 33.4 mmol. 80%).

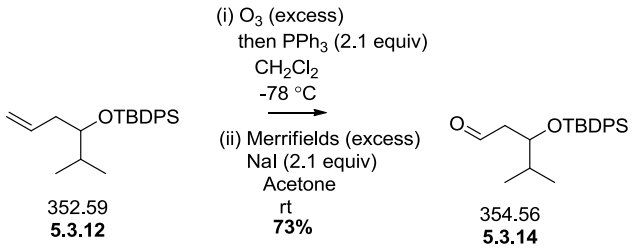
R_f (diethylether / light petroleumether 40/60) (10 : 90) : 0.93

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 - 7.66 (C**H** $_{Ar}$, m, 4H), 7.47 - 7.33 (C**H** $_{Ar}$, m, 6H), 5.62 (C**H**=CH_2, tdd, *J* = 7.3, 10.2, 17.1 Hz, 1H), 4.91 - 4.88 (CH=C**H**$_2$, m, 1H), 4.85 (CH=C**H**$_2$*, d, *J* = 9.6 Hz, 1H), 3.60 (C**H**OTBDPS, dt, *J* = 4.0, 5.6 Hz, 1H), 2.24 - 2.09 (C**H**$_2$CH=CH_2, m, 2H), 1.73 (C**H**Me_2, dtd, *J* = 4.0, 6.8, 13.6 Hz, 1H), 1.56 - 1.53 (H_2O, br s, 1H), 1.07 (*t*Bu $_{TBDPS}$, s, 9H), 0.91 (CH**Me**$_2$, d, *J* = 6.6 Hz, 3H), 0.86 (CH**Me**$_2$*, d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.1 (**C**H Ar), 135.6 (**C**H=CH_2), 134.8 (**C**H Ar), 134.3 (**C** Ar), 129.5 (**C**H Ar), 129.4 (**C**H Ar), 127.4 (**C**H Ar), 127.3 (**C**H Ar), 116.3 (CH=**C**H_2), 77.6 (**C**HOTBDPS), 38.4 (**C**H_2CH=CH_2), 32.1 (**C**HMe_2), 27.1 (C**Me**$_3$), 19.6 (**C**Me_3), 18.7 (CH**Me**$_2$), 16.8 (CH**Me**$_2$*).

Data matches literature. [95]

3-(TBDPSO)-4-methylpentanal 5.3.14



To a solution of *tert*-butyl((2-methylhex-5-en-3-yl)oxy)diphenylsilane **5.3.12** (12.0 g, 34.0 mmol, 1 equiv) in CH_2Cl_2 (500 mL), cooled to -78 ºC, was bubbled O_3 gas. After 20 min the CH_2Cl_2 became a rich blue colour and the ozonolyzer was turned off. Oxygen was then bubbled through the solution for 20 min. PPh_3 (18.7 g, 71.3 mmol, 2.1 equiv) was then added portionwise at -78 ºC and the solution stirred for another 20 min. The mixture was then tested with starch iodide paper for the presence of ozonide (starch/iodide paper). The solvent was then evaporated under reduced pressure and the resultant oil and precipitate purified by column chromatography (0% - 100% ethylacetate in heptane). This resulted in a crude product that was a mixture of PPh_3 and the desired product, which was then treated with a small quantity of heptane and cooled to approximately (-70 to -50 ºC) and filtered cold. The white PPh_3 precipitate was then washed with further portions of cold heptane and the filtrate reduced in volume under reduced pressure to yield colourless oil. A small quantity of PPh_3 remained in the product so further purification was undertaken. 11.73g (impure crude product). To a solution of the impure crude product (2.00 g, containing 448 mg, 1.71 mmol, 1 equiv of PPh_3) in acetone (20 mL), was added merrifield's resin (**3.5** – 4.5 mmol/g, 1.04 g, 3.6 mmol, 2.1 equiv) and NaI (512 mg, 3.42 mmol, 2 equiv) portionwise at rt (under N_2 (g)). After 18 h the mixture was filtered and the resin washed sequentially with acetone (20 mL), toluene (2 × 20 mL) and acetone (20 mL). The solvent of the combined filtrates was then removed under reduced pressure and the crude purified by column chromatography (0 – 10% ethyl acetate in toluene), a colourless oil was recovered as the pure product (1.48 g, 4.17 mmol. Corrected yield 73%).

R_f (diethylether / light petroleumether 40/60) (5 : 95) : 0.14

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.56 (C**H**O, dd, *J* = 2.1, 2.9 Hz, 1H), 7.72 - 7.64 (C**H** $_{Ar\ M}$, m, 4H), 7.49 - 7.36 (C**H** $_{Ar\ O\ \&\ P}$, m, 6H), 4.12 (C**H**OTBDPS, ddd, *J* = 4.1, 5.1, 6.5 Hz, 1H), 2.49 (C**H**$_2$CHO, ddd, *J* = 2.9, 6.5, 16.2 Hz, 1H), 2.38 (C**H**$_2$CHO*, ddd, *J* = 2.1, 5.1,

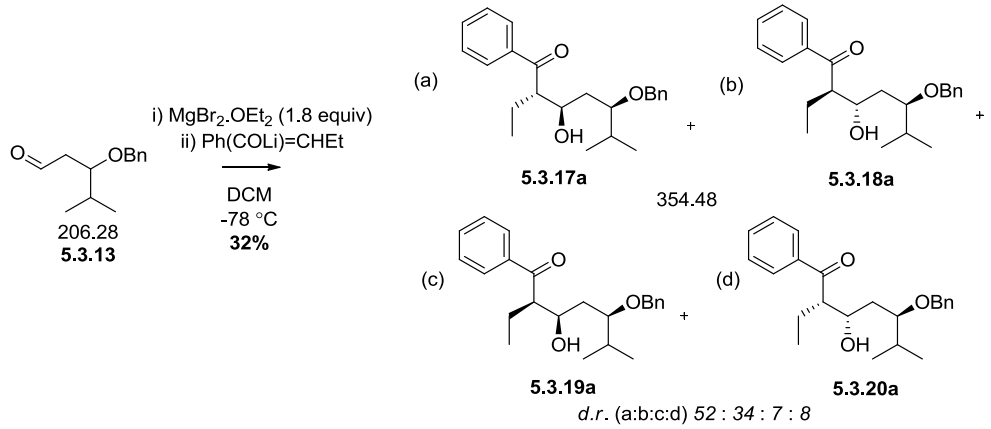
16.1 Hz, 1H), 1.82 (C**H**Me_2, dspt, *J* = 4.1, 6.8 Hz, 1H), 1.07 (*t*Bu $_{TBDPS}$, s, 9H), 0.94 (CH**Me**$_2$, d, *J* = 6.8 Hz, 3H), 0.80 (CH**Me**$_2$, d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.1 (**C**HO), 135.9 (**C**H Ar), 135.3, 133.8 (**C** Ar), 133.7 (**C** Ar), 129.8 (**C**H Ar), 127.6 (**C**H Ar), 127.6 (**C**H Ar), 73.2 (**C**HOTBDPS), 47.0 (**C**H_2CHO), 33.8 (**C**HMe_2) 27.0 (C**Me**$_3$), 19.4 (**C**Me_3), 18.0 (CH**Me**$_2$), 17.1 (CH**Me**$_2$*).

Data matches literature. [95]

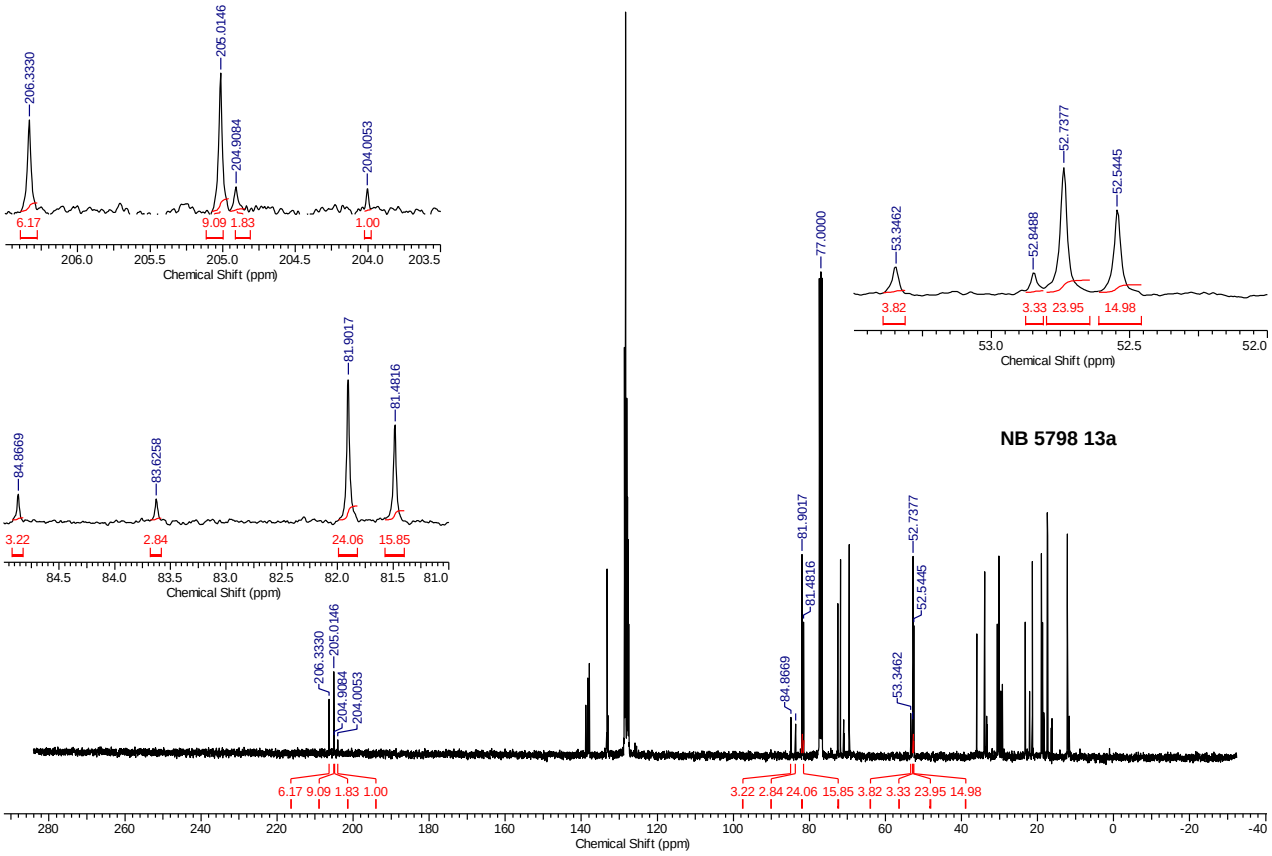
5-(Benzyloxy)-2-ethyl-3-hydroxy-6-methyl-1-phenylheptan-1-one (inseperable mixture of diastereomers)

Entry 6 (*nb 5798 13a*)

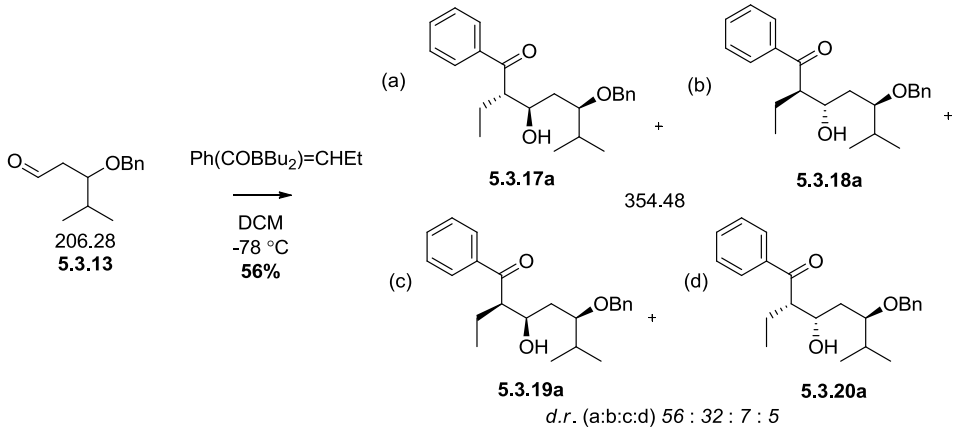


To a solution of BF_3.OEt_2 (108 µL, 0.873 mmol, 1.8 equiv) in CH_2Cl_2 (2 mL) at -78 ºC under N_2 (g) was added a solution of 3-(benzyloxy)-4-methylpentanal **5.3.13** (100 mg, 0.485 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC. (Z)-Trimethyl((1-phenylbut-1-en-1-yl)oxy)silane (118 mg, 0.534 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was then added dropwise at -78 ºC and the reaction stirred for a further 3 h at -78 ºC. The reaction mixture was then quenched with $NaHCO_3$ (4 mL, sat) and diluted with CH_2Cl_2 (4 mL) and water (6 mL). The layers were separated and the aqueous phase further extracted with CH_2Cl_2 (2 × 4 mL), the combined organic extracts were then washed with brine (5 mL), dried over Na_2SO_4 (anh), filtered and solvent evaporated under reduced pressure. The crude was then purified by column chromatography (15% diethylether in light petroleumether 40/60) (55 mg, 0.155 mmol. 32%) *d.r.* (a:b:c:d) *34* : *52* : *7* : *8*.

d.r. *from* ^{13}C NMR – **Entry 6** - NB 5798 13a



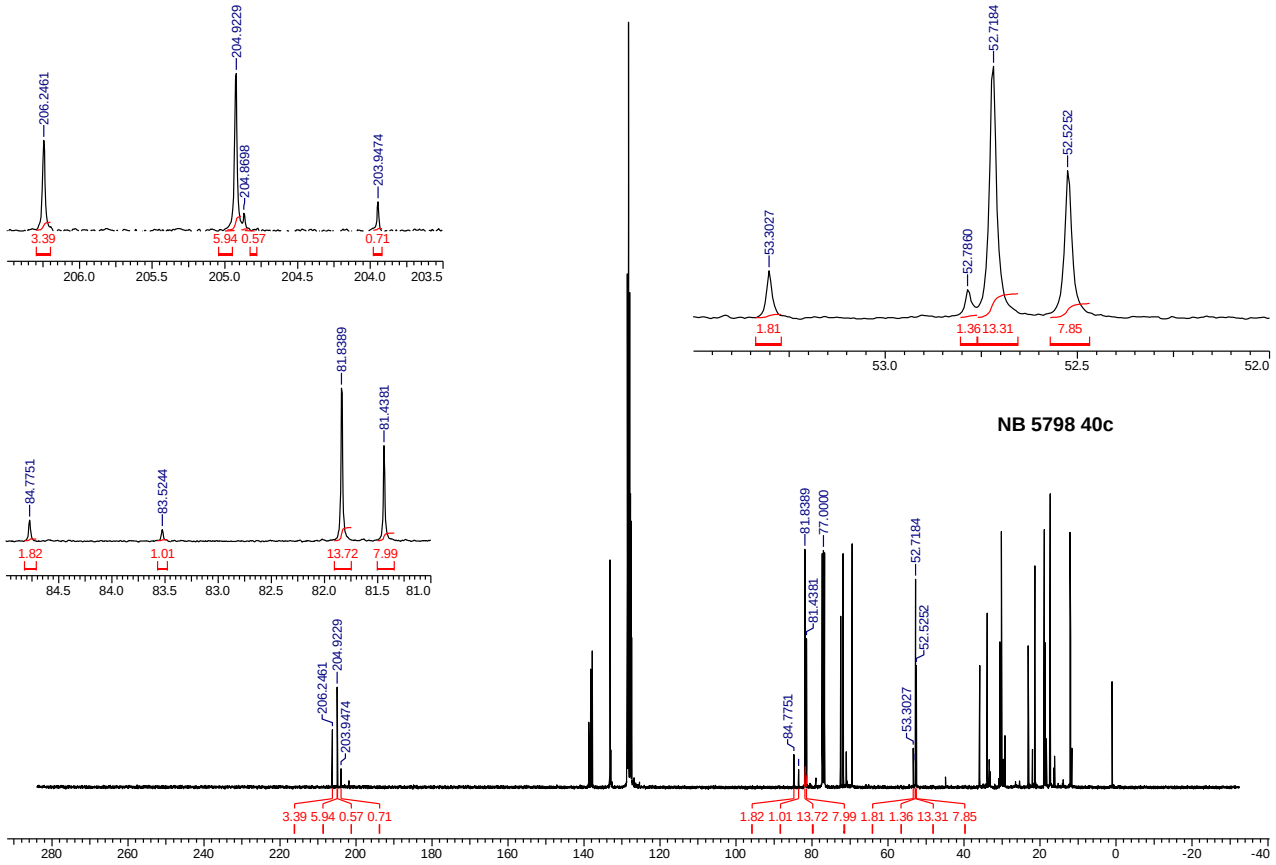
Entry 7 (*nb 5798 40c*)



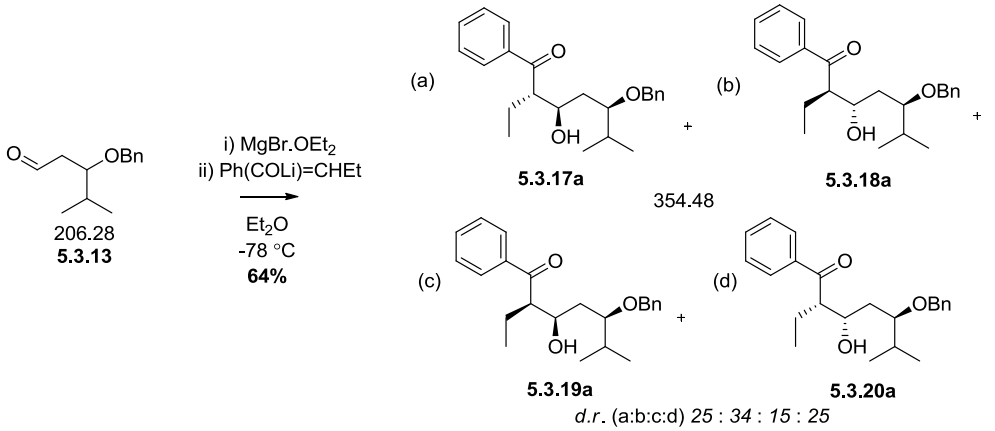
To a solution of butyrophenone (106 µL, 0.728 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) at 0 ºC (under N_2 (g)) was added DIPEA (127 µL, 0.728 mmol, 1.5 quiv) followed by $Bu_2B(OTf)$ (1M in CH_2Cl_2, 728 µL, 0.728 mmol, 1.5 equiv) dropwise. After 5 min the mixture was cooled to -78 ºC, separately a solution of a solution of 3-(benzyloxy)-4-methylpentanal (100 mg, 0.485 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was prepared and cooled to -78 ºC

(under N_2 (g)). The solution of boron enolate was then added to solution of aldehyde via cannula and stirred for 1 h (at -78 ºC). The reaction mixture was then quenched with $NaHCO_3$ (4 mL, sat) and diluted with CH_2Cl_2 (10 mL) and water (6 mL). The layers were separated and the aqueous phase further extracted with CH_2Cl_2 (2 × 10 mL), the combined organic extracts were then dried over Na_2SO_4 (anh), filtered and solvent evaporated under reduced pressure. The crude was then purified by column chromatography (15% diethylether in light petroleumether 40/60) to give a colourless oil (97 mg, 0.272 mmol. 56%) *d.r.* (a:b:c:d) *56* : *32* : *7* : *5*.

d.r. *from* ^{13}C NMR – **Entry 7** - NB 5798 40c

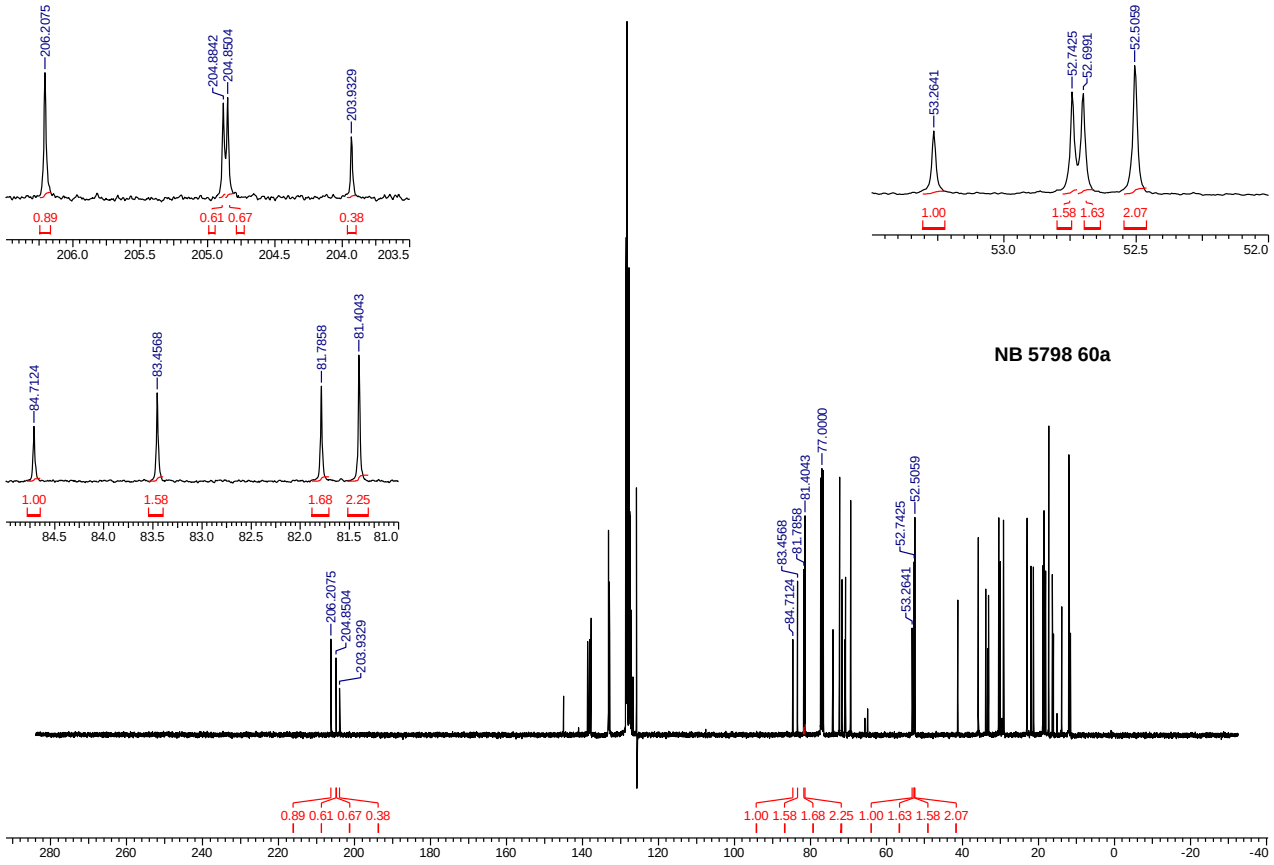


Entry 5 (*nb 5798 60a*)

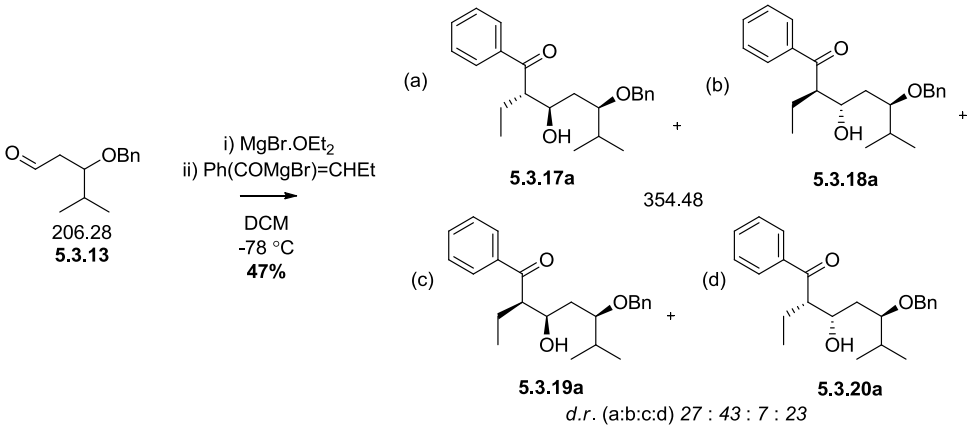


To a suspension of magnesium turnings (21 mg, 0.873 mmol, 1.8 equiv) in diethylether (2 mL) was added 1,2-dibromoethane (75 µL, 0.873 mmol, 1.8 equiv) dropwise (under N_2 (g)). The mixture was then heated (with a heatgun) to initiate reaction. The suspension was stirred until complete dissolution (≈ 3h), separately to a solution of DIPA (75 µL, 0.534 mmol, 1.1 equiv) in diethylether (2 mL) at -78 ºC (under N_2 (g)) was added *n*-BuLi (2.5 M in hexanes, 214 µL, 0.534 mmol, 1.1 equiv) dropwise. After 5 min butyrophenone (77 µL, 0.534 mmol, 1.1 equiv) was added dropwise and immediately a yellow colour became visible. 3-(Benzyloxy)-4-methylpentanal (100 mg, 0.485 mmol, 1 equiv) in diethylether (1 mL) was then added to the solution of $MgBr_2$ and cooled to -78 ºC. After 15 min the enolate solution was added to the chelated aldehyde solution via cannula. The reaction was then stirred for 1 h (at -78 ºC) before quenching with $NaHCO_3$ (sat, 5 mL), water (5 mL). The mixture was then extracted with (3 × 10 mL) CH_2Cl_2 before drying the combined organic phases over Na_2SO_4 (anh), filtering and evaporating the solvent under reduced pressure to yield a crude oil. The crude was then purified by column chromatography (10% diethylether in light petroleumether 40/60) to give a colourless oil (110 mg, 0.310 mmol. 64%) *d.r.* (a:b:c:d) *25* : *34* : *15* : *25*.

d.r. *from* ^{13}C NMR – **Entry 5** - NB 5798 60a



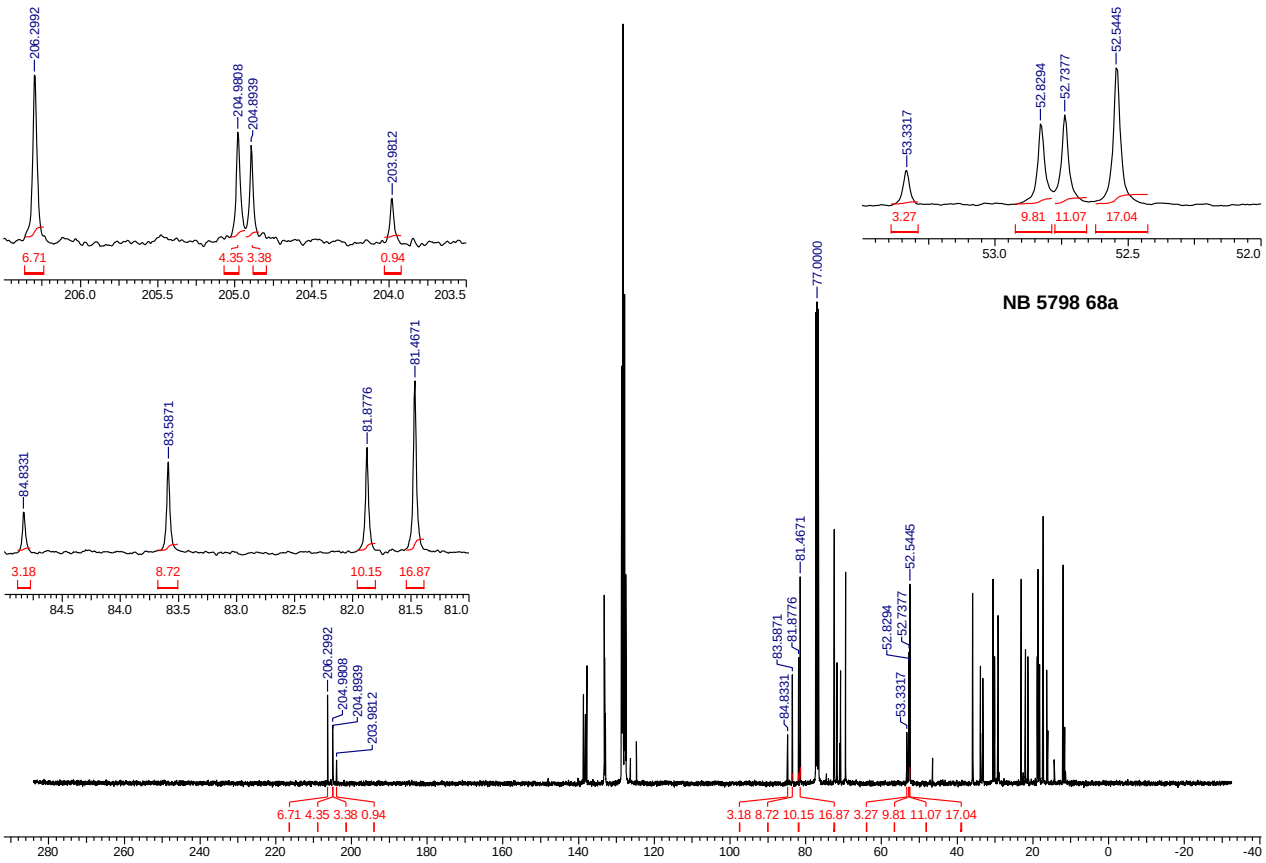
Entry 4 (*nb 5798 68a*)



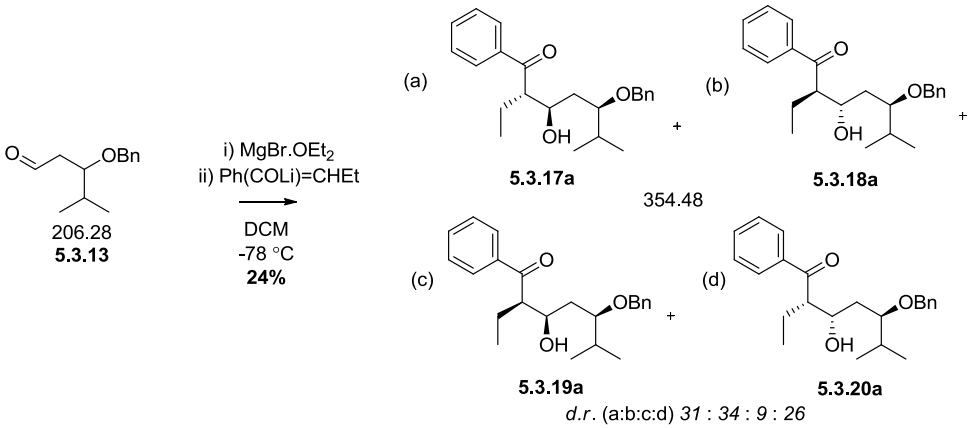
To a suspension of magnesium turnings (21 mg, 0.873 mmol, 1.8 equiv) in diethylether (2 mL) was added 1,2-dibromoethane (75 µL, 0.873 mmol, 1.8 equiv) dropwise (under N_2 (g)). The mixture was then heated (with a heatgun) to initiate reaction. The suspension was stirred until complete dissolution (≈ 3h), the solvent was then evaporated and the residues re-dissolved in CH_2Cl_2 (3 mL) and cooled to -78 ºC. A solution of 3-(Benzyloxy)-4-

methylpentanal (100 mg, 0.485 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was then added dropwise. Seperately to a solution of DIPA (102 µL, 0.728 mmol, 1.5 equiv) in diethylether (1 mL) was added methylmagnesium bromide (3M in diethylether, 243 µL, 0.728 mmol, 1.5 equiv). A white precipitate was formed which was suspended by addition of more diethylether (2 mL). Butyrophenone (106 µL, 0.873 mmol, 1.5 equiv) was then added dropwise to yield a yellowish suspension. Allowing the mixture to warm to rt caused dissolution. The solution of magnesium enolate was then added dropwise to the chelated aldehyde solution at -78 ºC. The reaction was stirred for 2 h before quenching with $NaHCO_3$ (sat, 5 mL), water (5 mL). The mixture was then extracted with (3 × 10 mL) diethylether, before drying the organic phases over Na_2SO_4 (anh), filtering and evaporating the solvent under reduced pressure to yield a crude oil. The crude was then purified by column chromatography (15% diethylether in light petroleumether 40/60) to give a colourless oil (80 mg, 0.226 mmol. 47%) *d.r.* (a:b:c:d) *27* : *43* : *7* : *23*.

d.r. *from* ^{13}C NMR – **Entry 4** - NB 5798 68a

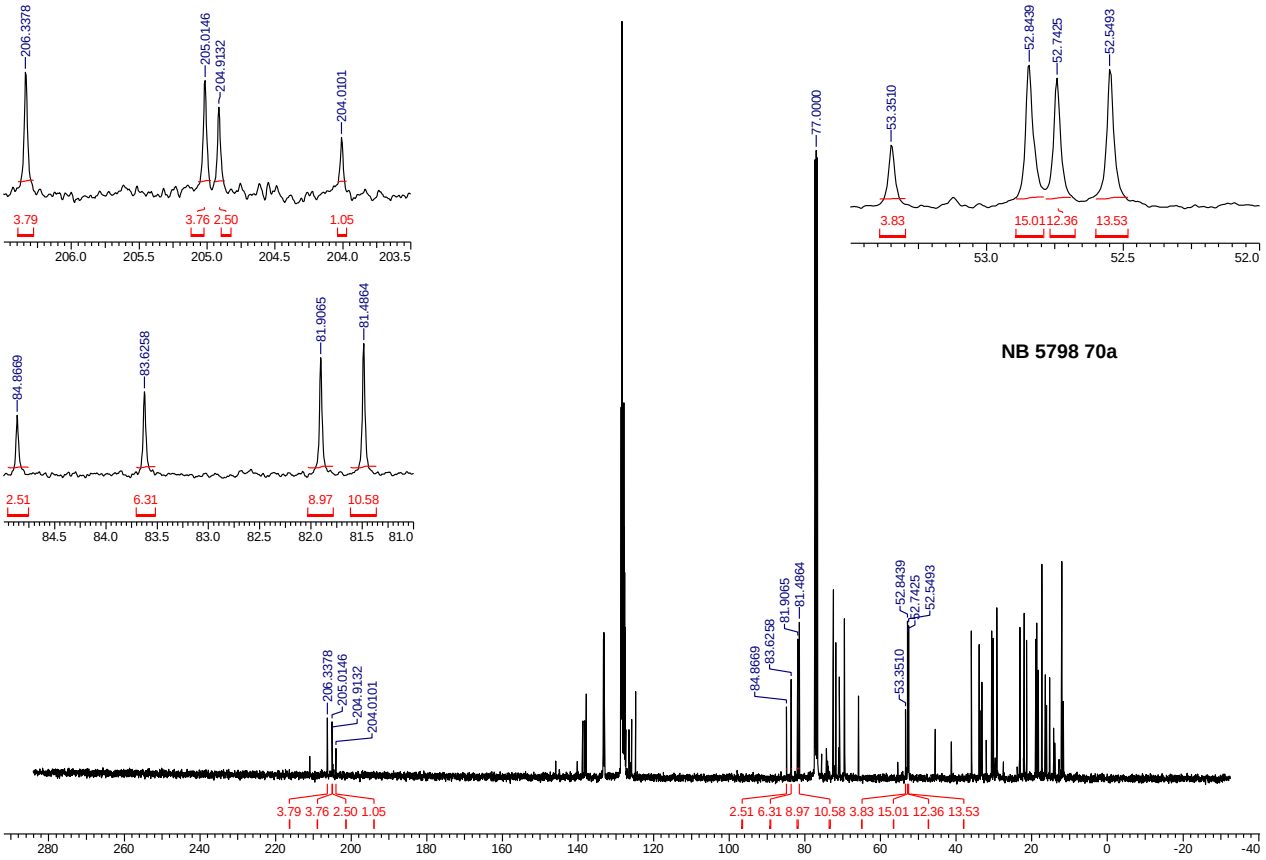


Entry 3 (*nb 5798 70a*)



To a suspension of magnesium turnings (21 mg, 0.873 mmol, 1.8 equiv) in diethylether (2 mL) was added 1,2-dibromoethane (75 µL, 0.873 mmol, 1.8 equiv) dropwise (under N_2 (g)). The mixture was then heated (with a heatgun) to initiate reaction. The suspension was stirred until complete dissolution (≈ 3h), the solvent was then evaporated and the residues re-dissolved in CH_2Cl_2 (3 mL) and cooled to -78 ºC. A solution of 3-(Benzyloxy)-4-methylpentanal (100 mg, 0.485 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was then added dropwise. Separately to a solution of DIPA (75 µL, 0.534 mmol, 1.1 equiv) in diethylether (1 mL) at -78 ºC (under N_2 (g)) was added *n*-BuLi (2.5 M in hexanes, 214 µL, 0.534 mmol, 1.1 equiv) dropwise. After 5 min butyrophenone (77 µL, 0.534 mmol, 1.1 equiv) was added dropwise and immediately a yellow colour became visible. After 5 min the enolate solution was transferred via cannula to the chelated aldehyde solution and the reaction stirred for 3 h (at -78 ºC). The reaction mixture was then quenched with $NaHCO_3$ (5 mL, sat) and diluted with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated and the aqueous phase further extracted with CH_2Cl_2 (2 × 10 mL), the combined organic extracts were then dried over Na_2SO_4 (anh), filtered and solvent evaporated under reduced pressure. The crude was then purified by column chromatography (15% diethylether in light petroleumether 40/60) to give a colourless oil (41 mg, 0.117 mmol. 24%) *d.r.* (a:b:c:d) *31* : *34* : *9*: *26*.

d.r. *from* ^{13}C NMR – **Entry 3** - NB 5798 70a



R_f (diethylether / light petroleumether 40/60) (10 : 90) : 0.08

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 - 7.83 ($^{a\text{-}d}$C**H** $_{Ar}$, m, 2 H), 7.56 - 7.49 ($^{a\text{-}d}$C**H** $_{Ar,}$ m, 1 H), 7.45 - 7.38 ($^{a\text{-}d}$C**H** $_{Ar,}$ m, 2 H), 7.33 - 7.21 ($^{a\text{-}d}$C**H** $_{Bn}$, m, 5 H), 4.63 - 4.33 ($^{a\text{-}d}$C**H**$_2$ $_{Bn}$, m, 2 H), 4.21 - 4.10 (^{a,b}C**H**OH, m, 0.8 H), 4.09 - 4.01 (^{c,d}C**H**OH, m, 0.2 H), 3.54 (^{b,c}C**H**OBn, ~dt, *J* = 4.5, 8.3 Hz, 0.5 H), 3.47 - 3.34 (^{a,d}C**H**OBn & $^{a\text{-}d}$C**H**CHOH, m, 1.8 H), 2.11 - 1.50 ($^{a\text{-}d}$C**H**Me$_2$, $^{a\text{-}d}$CHOHC**H**$_2$ & $^{a\text{-}d}$C**H**$_2$CH$_3$, m, 5 H), 0.91 - 0.78 ($^{a\text{-}d}$CH(C**H**$_3$)$_2$ & $^{a\text{-}d}$CH$_2$C**H**$_3$, m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.4 (^{b}**C**=O), 205.0 (^{a}**C**=O), 204.9 (^{d}**C**=O), 204.0 (^{c}**C**=O), 138.8 (^{c}**C** Ar Bn), 138.3 (^{a}**C** Ar Bn), 138.3 (^{d}**C** Ar Bn), 137.9 (^{b}**C** Ar Bn), 133.3 (^{b}**C**H Ar *P*), 133.2 (^{a}**C**H Ar *P*), 133.0 (^{d}**C**H Ar *P*), 133.0 (^{c}**C**H Ar *P*), 128.7 (**C**H Ar), 128.6 (**C**H Ar), 128.6 (**C**H Ar), 128.5 (**C**H Ar), 128.4 (**C**H Ar), 128.4 (**C**H Ar), 128.3 (**C**H Ar), 128.0 (**C**H Ar), 127.9 (**C**H Ar), 127.8 (**C**H Ar), 127.7 (**C**H Ar), 127.7 (**C**H Ar), 127.5 (**C**H Ar), 84.9 (^{c}**C**HOBn), 83.6 (^{d}**C**HOBn), 81.9 (^{a}**C**HOBn), 81.5 (^{b}**C**HOBn), 72.6 (^{d}C**H**OH), 72.5 (^{c}C**H**OH), 72.5 (^{b}**C**H$_2$Ph), 71.8 (^{a}**C**H$_2$Ph), 71.0 (^{c}**C**H$_2$Ph), 70.8 (^{d}**C**H$_2$Ph), 69.5 (^{b}C**H**OH), 69.5 (^{a}C**H**OH), 53.3 (^{c}**C**HCHOH), 52.8 (^{d}**C**HCHOH), 52.7 (^{a}**C**HCHOH), 52.5

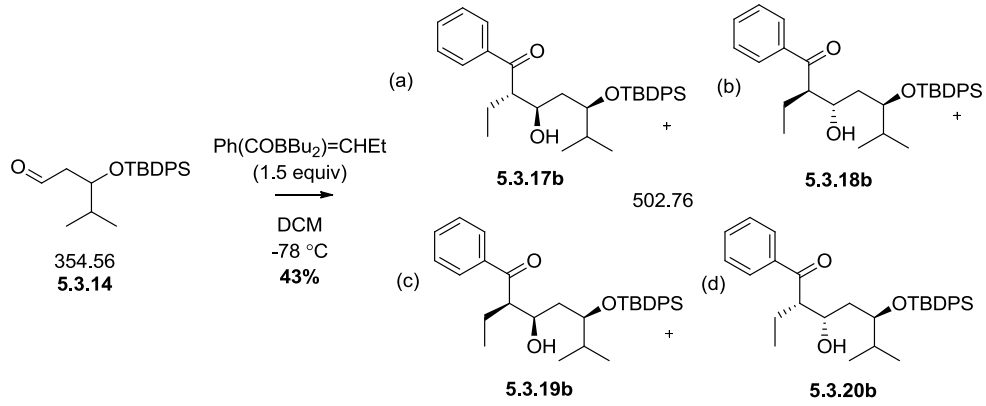
(^{b}**C**HCHOH), 35.9 (^{b}CHOH**C**H$_2$), 33.9 (^{a}CHOH**C**H$_2$), 33.3 (^{c}CHOH**C**H$_2$), 33.2 (^{d}CHOH**C**H$_2$), 30.6 (^{b}**C**HMe$_2$), 30.1 (^{a}**C**HMe$_2$), 29.2 (^{c}**C**HMe$_2$), 23.1 (^{b}C**H**$_2$CH$_3$), 22.0 (^{c}C**H**$_2$CH$_3$), 21.3 (^{a}C**H**$_2$CH$_3$), 18.9 (^{a}CH(**C**H$_3$)$_2$), 18.7 (^{b}CH(**C**H$_3$)$_2$), 18.4 (^{c}CH(**C**H$_3$)$_2$), 18.2 (^{d}CH(**C**H$_3$)$_2$), 17.3 (^{a}CH(**C**H$_3$)$_2$*), 16.4 (^{d}CH(**C**H$_3$)$_2$*), 16.1 (^{c}CH(**C**H$_3$)$_2$*), 12.1 (^{a}CH$_2$**C**H$_3$), 12.0 (^{b}CH$_2$**C**H$_3$), 11.6 (^{c}CH$_2$**C**H$_3$).

IR (neat) : 3481, 2961, 2874, 1672, 1596, 1579, 1064 cm^{-1}.

MS (ES$^+$)(m/z) : 377 [M+Na]$^+$ (100%), 418 [M+MeCN+Na]$^+$ (17%).

HRMS (ES$^+$) : [M+Na]$^+$; Calcd. 377.2087; Found. 377.2090.

5-(TBDPSO)-2-ethyl-3-hydroxy-6-methyl-1-phenylheptan-1-one



d.r. (a : b : c : d) (from 13C) *56* : *19* : *16* : *9*, (from dept) *52* : *19* : *17* : *12*.

To a solution of butyrophenone (125 mg, 0.846 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) at 0 ºC was added DIPEA (147 µL, 0.846 mmol, 1.5 equiv) followed by $Bu_2B(OTf)$ (1M in CH_2Cl_2, 846 µL, 0.846 mmol, 1.5 equiv) dropwise. After 5 min the mixture was cooled to -78 ºC under N_2 (g) and added to a solution of 3-(TBDPSO)-4-methylpentanal (200 mg, 0.564 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC via cannula. The reaction was stirred at the same temperature for 3 h before quenching with $NaHCO_3$ (10 mL, sat), diluting with water (10 mL), the mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The combined portions were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (5 →10% diethylether in light petroleum) to give a colourless oil (122 mg, 0.243 mmol. 43%) *d.r.* (a : b : c : d) (from ^{13}C) *56* : *19* : *16* : *9*, (from dept) *52* : *19* : *17* : *12*.

R_f (diethylether / light petroleumether 40/60) (10 : 90) : 0.15

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 - 7.84 (C**H** $_{Ar}$, m, 3.3H), 7.78 - 7.52 (C**H** $_{Ar}$, m, 15.4H), 7.40 (C**H** $_{Ar}$, d, *J* = 7.1 Hz, 23.1H), 4.03 - 3.86 ($^{a\text{-}d}$C**H**OH, ^{b}C**H**OTBDPS, m, *J* = 3.5 Hz, 2.5H), 3.79 (^{a}C**H**OTBDPS, td, *J* = 4.0, 7.6 Hz, 1H), 3.68 (^{c}C**H**OTBDPS, ddd, *J* = 3.3, 4.8, 7.6 Hz, 0.2H), 3.33 - 3.21 (^{a}C**H**CHOH, m, 0.7H), 3.29 (^{b}C**H**CHOH, td, *J* = 4.4, 9.3 Hz, 1H), 3.12 - 3.05 (^{c}C**H**CHOH, m, 0.34H), 2.67 (^{b}O**H**, d, *J* = 1.0 Hz, 0.34H), 2.47 (^{a}O**H**, d, *J* = 2.0 Hz, 1H), 2.41 (^{c}O**H**, s, 0.2H), 2.42 (^{d}O**H**, s, 0.2H), 1.94 - 1.74 (C**H**Me_2, C**H**$_2CH_3$, m, 3.2H), 1.74 - 1.62 (C**H**$_2CH_3$, m, 3.1H), 1.61 - 1.56 (C**H**$_2CH_3$, m, 1.6H), 1.56 - 1.49 (C**H**$_2$CHOTBDPS, m, 3.1H), 1.49 - 1.36 (C**H**$_2$CHOTBDPS, m, 0.8H), 1.09 (^{a}C**Me**$_{3\ TBDPS}$, s, 12.9H), 1.07 (^{d}C**Me**$_{3\ TBDPS}$, s, 2.6H), 1.05 (^{c}C**Me**$_{3\ TBDPS}$, s, 5.4H), 1.05 (^{b}C**Me**$_{3\ TBDPS}$, s, 8.7H), 0.91 - 0.85 (CH**Me**$_2$, m, 6.3H), 0.82 (C**H**$_2CH_3$, t, *J* = 7.6 Hz, 3.6H), 0.79 (C**H**$_2CH_3$, t, *J* = 7.1 Hz, 2.5H), , 0.72 (CH**Me**$_2$, d, *J* = 7.1 Hz, 2.4H), 0.72 (CH**Me**$_2$, d, *J* = 7.1 Hz, 1.6H), 0.68 (CH**Me**$_2$, d, *J* = 7.1 Hz, 1.3H), 0.49 (CH**Me**$_2$, d, *J* = 7.1 Hz, 0.6H).

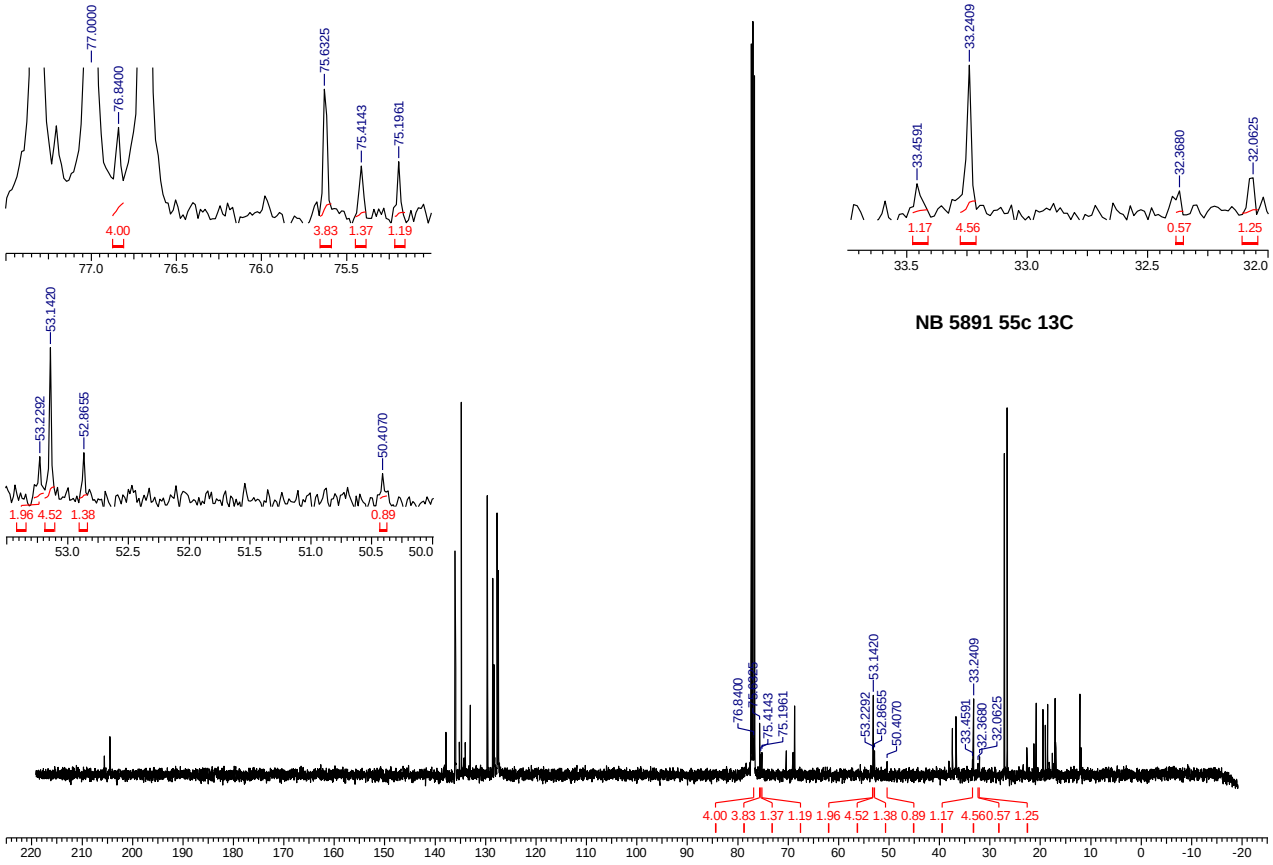
^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.6 (^{b}Ph**C**O), 204.5 (^{c}Ph**C**O), 204.5 (^{a}Ph**C**O**)**, 137.9 (**C** Ph), 136.1 (**C**H Ar), 135.9 (**C**H Ar), 134.8 (**C**H Ar), 134.0 (**C**H Ar), 134.0 (**C** TBDPS), 134.0 (**C** TBDPS), 133.1 (**C**H Ar), 133.0 (**C**H Ar), 129.6 (**C**H Ar), 128.6 (**C**H Ar), 128.3 (**C**H Ar), 128.2 (**C**H Ar), 127.7 (**C**H Ar), 127.6 (**C**H Ar), 127.5 (**C**H Ar), 127.5 (**C**H Ar), 127.5 (**C**H Ar), 76.8 (^{b}**C**HOTBDPS), 75.6 (^{a}**C**HOTBDPS), 75.4 (^{c}**C**HOTBDPS), 75.3 (^{d}**C**HOTBDPS), 70.5 (^{d}**C**HOH), 70.4 (^{b}**C**HOH), 69.0 (^{c}**C**HOH), 68.7 (^{a}**C**HOH), 53.2 (^{c}**C**HCHOH), 53.1 (^{a}**C**HCHOH), 52.9 (^{b}**C**HCHOH), 50.4 (^{d}**C**HCHOH), 37.4 (^{b}**C**H_2CHOTBDPS), 36.7 (^{a}**C**H_2CHOTBDPS), 33.5 (^{c}**C**HMe_2), 33.2 (^{a}**C**HMe_2), 32.4 (^{d}**C**HMe_2), 32.1 (^{b}**C**HMe_2), 27.1 (^{b}C**Me**$_3$ TBDPS), 26.5 (^{a}C**Me**$_3$ TBDPS), 22.7 (^{c}**C**H_2CH_3), 21.2 (^{b}**C**H_2CH_3), 20.8 (^{a}**C**H_2CH_3), 19.5 (CH**Me**$_2$), 19.5 (CH**Me**$_2$), 19.0 (CH**Me**$_2$), 18.5 (CH**Me**$_2$), 17.6 (CH**Me**$_2$), 17.1 (CH**Me**$_2$), 16.9 (CH**Me**$_2$), 16.9 (CH**Me**$_2$), 12.2 (^{a}CH_2**C**H_3), 11.9 (CH_2**C**H_3), 11.9 (CH_2**C**H_3).

IR (neat) : 3482, 3070, 2959, 2931, 1669 cm^{-1}.

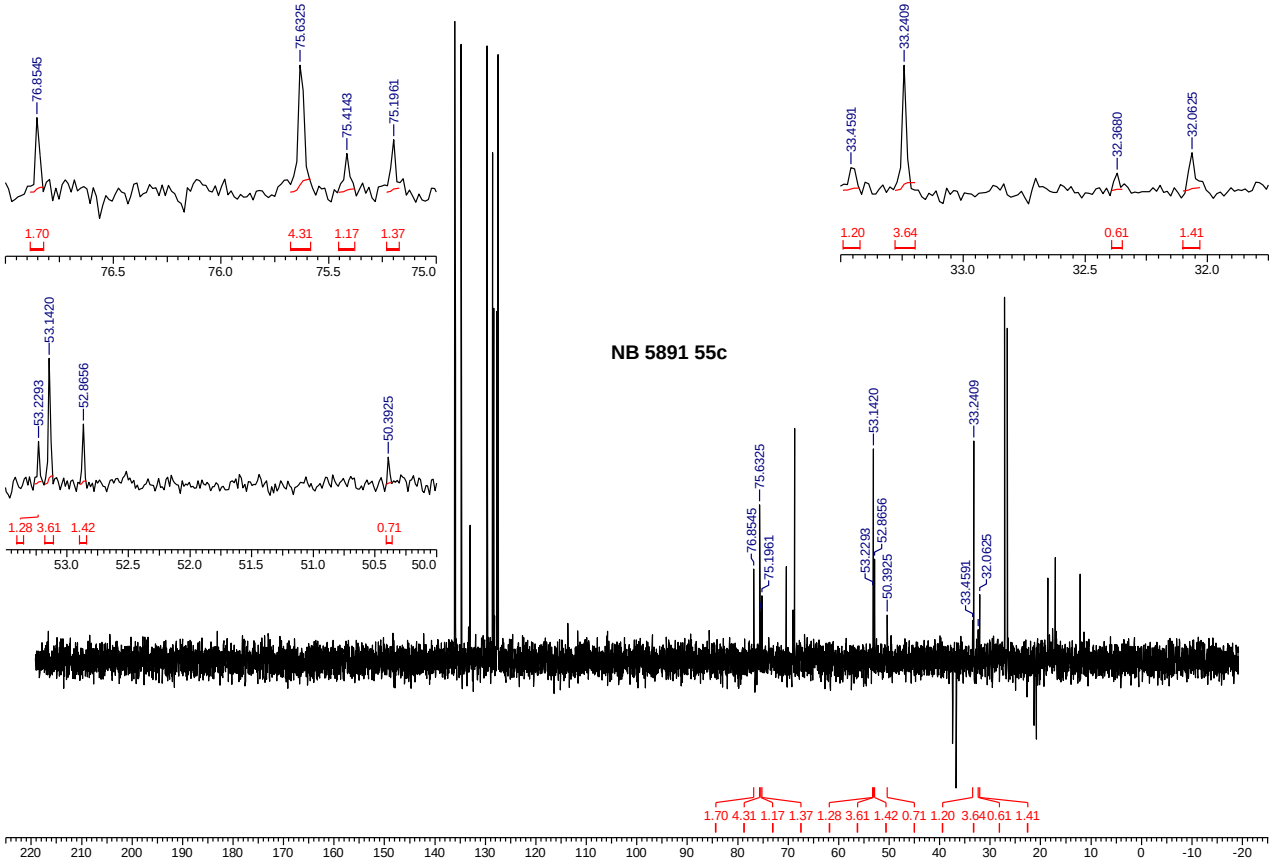
MS (ES^+)(m/z) : 525 $[M+Na]^+$ (100%), 566 $[M+Na+MeCN]^+$.

HRMS (ES^+) : $[M+Na]^+$, Calcd. 525.2795; Found. 525.2805.

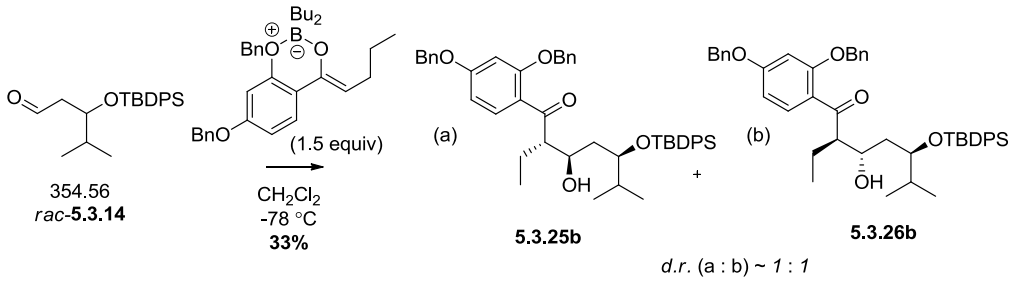
d.r. *from* ^{13}C NMR – **Entry 8 -** NB 5798 55c



d.r. *from* dept ^{13}C NMR – **Entry 8** - NB 5798 55c



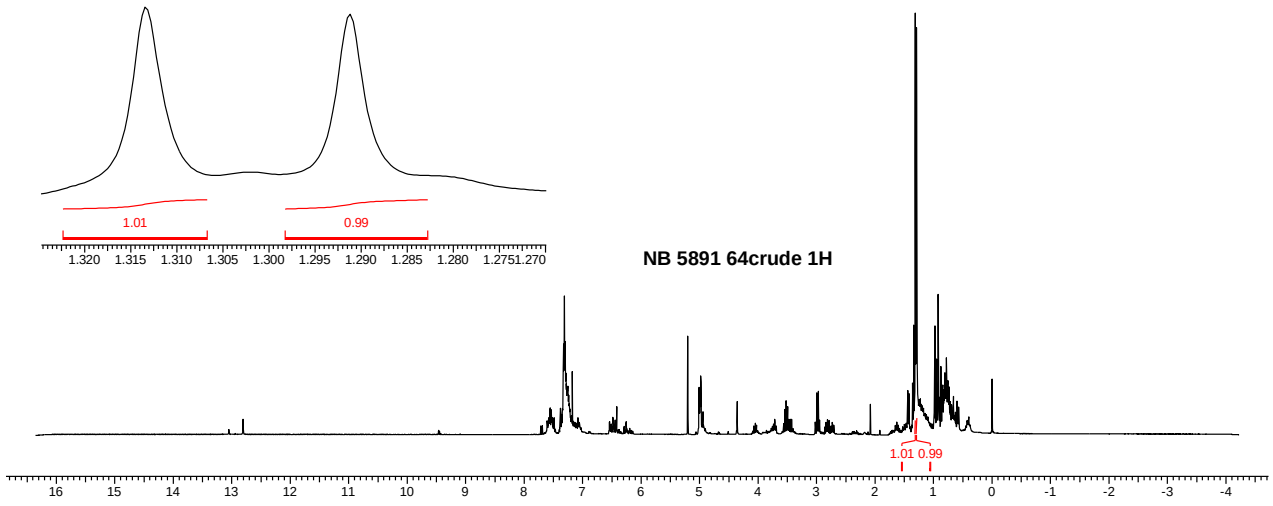
(2*R*,3*S*,5*S*)-1-(2,4-Bis(benzyloxy)phenyl)-5-(TBDPSO)-3-hydroxy-6-methyl-2-propylheptan-1-one



To a solution of 1-(2,4-bis(benzyloxy)phenyl)pentan-1-one (525 mg, 1.46 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) at 0 ºC was added DIPEA (253 µL, 1.46 mmol, 1.5 equiv) dropwise followed by $Bu_2B(OTf)$ (1M in CH_2Cl_2, 1.46 mL, 1.46 mmol, 1.5 equiv) dropwise. The mixture was cooled to 0 ºC before cooling to -78 ºC and transferring via cannula, to a solution of 3-((tert-butyldiphenylsilyl)oxy)-4-methylpentanal (200 mg, 0.970 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC. The reaction was stirred for 4 h before quenching with $NaHCO_3$ (1/2 sat, 10 mL) and extracting with CH_2Cl_2 (3 × 10 mL). The

combined organic phases were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure to yield a crude oil. The crude was then purified by column chromatography (10 → 20% diethylether in light petroleumether 40/60) to yield a colourless oil (233 mg, 0.320 mmol. 33%) *d.r.* (a : b) ≈ *1* : *1*.

d.r. *from* ^{1}H NMR – NB 5891 64 crude



R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 - 7.62 (^{a,b}C**H** $_{Ar}$, C**H** $_{TBDPS}$, m, 8.9H), 7.60 - 7.56 (^{a,b}C**H** $_{Ar}$, m, 1.4H), 7.48 - 7.26 (^{a,b}C**H** $_{Bn}$, ^{a,b}C**H** $_{TBDPS}$, m, 36.1H), 6.67 - 6.51 (^{a,b}C**H** $_{Ar}$, m, 4.5H), 5.13 - 4.99 (^{a,b}OC**H**$_2$Bn, m, 9.1H), 4.04 - 3.93 (^{a}C**H**OH, m, 1.2H), 3.92 - 3.79 (^{b}C**H**OH, ^{a,b}C**H**OTBDPS, m, *J* = 2.5 Hz, 3.0H), 3.58 (^{a}C**H**CHOH, td, *J* = 4.0, 9.1 Hz, 1.1H), 3.50 (^{b}C**H**CHOH, td, *J* = 4.2, 8.8 Hz, 1.0H), 2.50 - 2.40 (^{a}O**H**, *br* s, 1.0H), 2.36 - 2.18 (^{b}O**H**, *br* s, 1.4H), 1.88 - 1.13 (^{a,b}C**H**$_2$CHOTBDPS, ^{a,b}C**H**Me$_2$, ^{a,b}C**H**$_2$CH$_2$CH$_3$, ^{a,b}CH$_2$C**H**$_2$CH$_3$, m, 19H), 1.10 (?), 1.06 (^{a}C**H**3 *t*Bu, s, 9H), 1.02 (^{b}C**H**$_3$ *t*Bu, s, 9H), 0.99 (?), 0.87 (^{a}CH**Me**$_2$, d, *J* = 7.1 Hz, 3H), 0.84 (^{b}CH**Me**$_2$, d, *J* = 6.6 Hz, 4H), 0.77 (^{b}CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 7H), 0.73 (^{a}CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 2H), 0.69 (^{a}CH**Me**$_2$, d, *J* = 6.6 Hz, 3H), 0.68 (^{b}CH**Me**$_2$, d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.2 (^{b}**C**=O), 205.2 (^{a}**C**=O), 163.1 (^{a,b}**C**O Ar *O*), 159.2 (^{a}**C**O Ar *P*), 159.2 (^{b}**C**O Ar *P*), 136.2 (**C** Ar), 136.2 (**C** Ar), 136.0 (**C**H Ar), 136.0 (**C**H Ar), 135.9 (**C**H Ar), 135.9 (**C** Ar), 135.8 (**C** Ar), 134.8 (**C** Ar), 134.7 (**C** Ar), 134.4 (**C** Ar), 134.4 (**C** Ar), 134.4 (**C** Ar), 134.2 (**C** Ar), 132.8 (^{a}**C**H Ar *O*), 132.7 (^{b}**C**H Ar *O*), 132.6 (**C**H Ar), 129.5 (**C**H Ar), 129.5 (**C**H Ar), 129.4 (**C**H Ar), 128.7 (**C**H Ar), 128.6 (**C**H Ar),

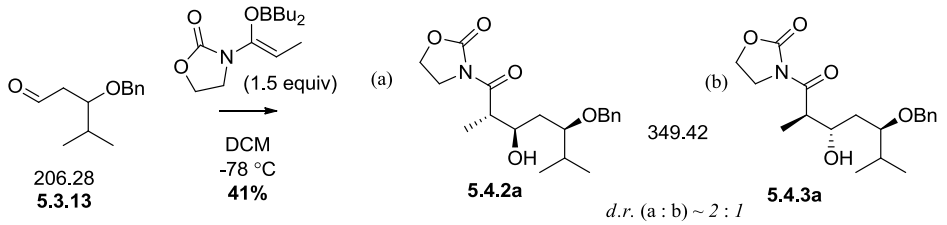
128.3 (**C**H Ar), 128.3 (**C**H Ar), 127.7 (**C**H Ar), 127.7 (**C**H Ar), 127.6 (**C**H Ar), 127.5 (**C**H Ar), 127.4 (**C**H Ar), 127.4 (**C**H Ar), 127.3 (**C**H Ar), 122.6 (^{b}**C** Ar *I*), 122.6 (^{a}**C** Ar *I*), 106.4 (^{a,b}**C**H Ar *M*), 100.6 (^{a,b}**C**H Ar *M*), 100.4 (?), 76.2 (^{b}**C**HOTBDPS), 75.1 (^{a}**C**HOTBDPS), 70.7 (^{b}OCH2Ph *O*), 70.7 (^{a}OCH2Ph *O*), 70.2 (^{a,b}OCH$_2$Ph *P*), 69.9 (^{b}CHOH), 68.2 (^{a}CHOH), 55.1 (^{a}**C**HCHOH), 55.0 (^{b}**C**HCHOH), 38.1 (^{b}CH$_2$CHOTBDPS), 36.6 (^{a}CH$_2$CHOTBDPS), 33.3 (^{a}C**H**Me$_2$), 31.5 (^{b}C**H**Me$_2$), 29.2 (^{b}**C**H$_2$CH$_2$CH$_3$), 28.9 (^{a}**C**H$_2$CH$_2$CH$_3$), 27.1 (^{a,b}C(**C**H$_3$)$_3$), 27.0 (?), 21.0 (^{b}CH$_2$**C**H$_2$CH$_3$), 20.8 (^{a}CH$_2$**C**H$_2$CH$_3$), 19.5 (^{b}**C**Me$_3$), 19.5 (^{a}**C**Me$_3$), 18.5 (^{b}CH(**C**H$_3$)$_2$), 18.4 (^{a}CH(**C**H$_3$)$_2$), 16.8 (^{a}CH(**C**H$_3$)$_2$*), 16.2 (^{b}CH(**C**H$_3$)$_2$*).

IR (neat) : 3507, 3068, 2957, 2930, 1597 cm^{-1}.

MS (ES$^+$)(m/z) : 752 [M+Na]$^+$ (100%).

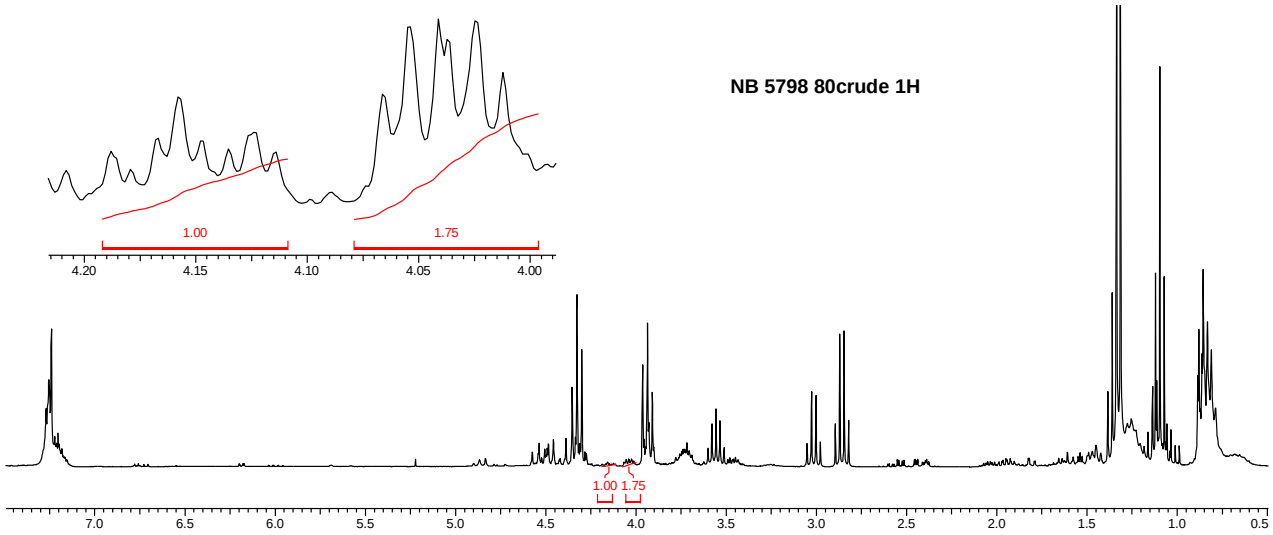
HRMS (ES$^+$) : [M+Na]$^+$; Calcd. 751.3789; Found. 751.3778.

OBn aldehyde directed 'Evans like' aldol reaction.



To a solution of 3-propionyloxazolidin-2-one (104 mg, 0.728 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) at -78 ºC under N_2 (g) was added $Bu_2B(OTf)$ (1M in CH_2Cl_2, 728 µL, 0.728 mmol, 1.5 equiv) dropwise., followed by DIPEA (127 µL, 0.728 mmol, 1.5 equiv). The solution was then stirred for 20 min at -78 ºC before transferring to a solution of 3-BnO-4-methylpentanal (100 mg, 0.485 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC dropwise. The reaction was then stirred for a further 3 h. The reaction was quenched with $NaHCO_3$ (5 mL, sat). Upon warming to rt the layers were then separated and the aqueous extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (5 → 60% ethylacetate in light petroleumether 40/60) to yield a colourless oil (as a mixture of diastereomers) (70 mg, 0.200 mmol. 41%) *d.r.* (a : b) ≈ *2* : *1*.

d.r. *from* ^{1}H NMR – NB 5891 80 crude



R_f (ethylacetate / light petroleumether 40/60) (60 : 40) : 0.55

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 - 7.10 (^{a,b}C**H** $_{Bn\ Ar}$, m, 7H), 4.55 (^{a}C**H**$_{2\ Bn}$, d, *J* = 11.1 Hz, 1H), 4.49 (^{b}C**H**$_{2\ Bn}$, d, *J* = 7.6 Hz, 0.7H), 4.36 (^{a}C**H**$_2^{*}$ $_{Bn}$, d, *J* = 11.1 Hz, 1H), 4.33 - 4.22 (^{a,b}OC**H**$_2$CH$_2$N, m, 3.2H), 4.14 (^{b}C**H**OH, td, *J* = 3.0, 10.1 Hz, 0.5H), 4.03 (^{a}C**H**OH, td, *J* = 3.5, 8.6 Hz, 1H), 3.95 - 3.85 (^{a,b}OCH$_2$C**H**$_2$N, m, 3.3H), 3.76 - 3.67 (^{a,b}C**H**CHOH, m, *J* = 4.0, 7.1 Hz, 1.5H), 3.46 (^{a}C**H**OBn, td, *J* = 3.9, 9.5 Hz, 1H), 3.49 - 3.39 (^{b}C**H**OBn, m, 0.5H), 2.04 (^{a}C**H**Me$_2$, sptd, *J* = 4.3, 6.9 Hz, 1H), 1.93 (^{b}C**H**Me$_2$, dt, *J* = 6.8, 13.0 Hz, 0.5H), 1.69 - 1.57 (^{a,b}C**H**$_2$CHOBn, m, 1.5H), 1.55 - 1.41 (^{a,b}C**H**$_2$CHOBn*, m, *J* = 3.3, 3.3 Hz, 1.5H), 1.14 (d, *J* = 7.1 Hz, 1.5H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.87 (^{b}CH**Me**$_2$, d, *J* = 6.6 Hz, 1.5H), 0.86 (^{a}CH**Me**$_2$, d, *J* = 6.6 Hz, 3H), 0.84 (^{a}CH**Me**2, d, *J* = 6.6 Hz, 9H), 0.89 - 0.81 (^{b}CH**Me**$_2$, m, 1.5H).

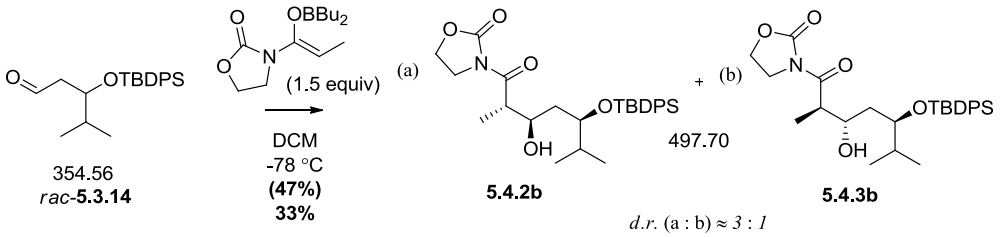
^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0 (^{b}**C**ON), 175.9 (^{a}**C**ON), 153.2 (^{a}O**C**ON), 153.1 (^{b}O**C**ON), 138.7 (^{b}**C** Bn), 138.2 (^{a}**C** Bn), 128.3 (^{a}**C**H Bn), 128.2 (^{b}**C**H Bn), 127.6 (^{a}**C**H Bn), 127.5 (^{b}**C**H Bn), 127.4 (^{a,b}**C**H Bn), 83.8 (^{a}**C**HOBn), 81.4 (^{b}**C**HOBn), 72.1 (^{b}**C**H$_2$ Bn), 71.3 (^{a}**C**HOH), 70.9 (^{a}**C**H$_2$ Bn), 68.5 (^{b}**C**HOH), 61.7 (^{a,b}O**C**H$_2$CH$_2$N), 42.6 (^{a,b}OCH$_2$**C**H$_2$N), 42.5 (^{a}**C**HCHOH), 42.4 (^{b}**C**HCHOH), 33.7 (^{b}**C**H$_2$CHOBn), 33.1 (^{a}**C**H$_2$CHOBn), 30.6 (^{b}**C**HMe$_2$), 29.3 (^{a}**C**HMe$_2$), 18.7 (^{b}CH**Me**$_2$), 18.2 (^{a}CH**Me**$_2$), 17.4 (^{b}CH**Me**$_2$*), 16.4 (^{a}CH**Me**$_2$*), 11.0 (^{b}**C**H$_3$), 10.7 (^{a}**C**H$_3$).

IR (neat) : 3483, 2962, 2875, 1774, 1697cm^{-1}

MS (ES^{+})(m/z) : 372 [M+Na]$^{+}$ (100%), 413 [M+Na+MeCN]$^{+}$ (11%).

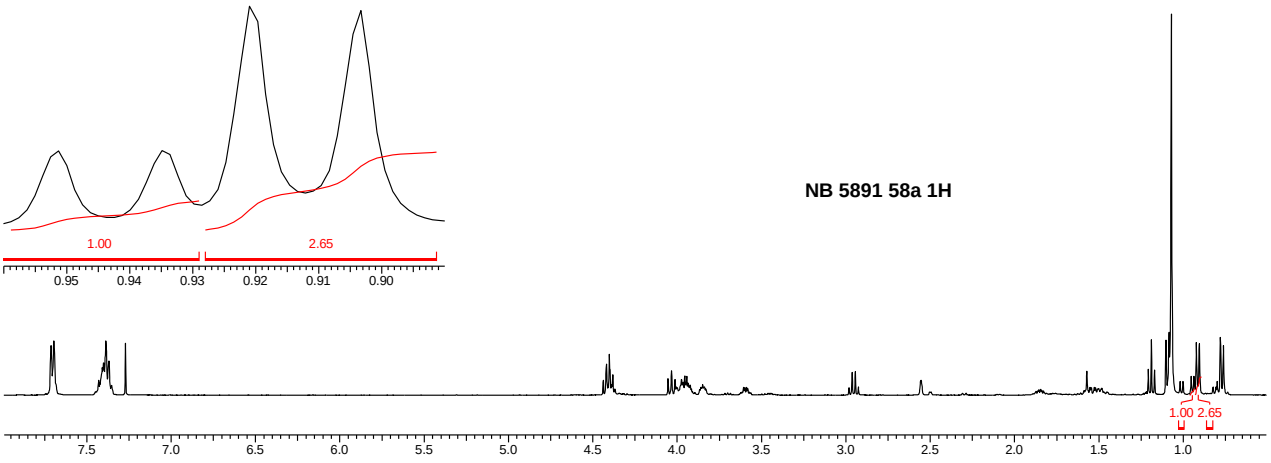
HRMS (ES^{+}) : [M+Na]$^{+}$, Calcd. 372.1781; Found. 372.1783.

OTBDPS aldehyde directed 'Evans like' aldol reaction



To a solution of 3-propionyloxazolidin-2-one (208 mg, 1.47 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) at -78 ºC, under N_2 (g) was added $Bu_2B(OTf)$ (1M in CH_2Cl_2, 1.46 mL, 1.46 mmol, 1.5 equiv) dropwise, followed by DIPEA (254 µL, 1.46 mmol, 1.5 equiv). The solution was then stirred for 20 min at -78 ºC before transferring via cannula to a solution of 3-(TBDPSO)-4-methylpentanal (200 mg, 0.970 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC (under N_2 (g)) dropwise. The combined solutions were then stirred for a further 4 h at the same temperature. The reaction was then quenched with $NaHCO_3$ (1/2 sat, 10 mL) and extracted with (3 × 10 mL) CH_2Cl_2, the combined extracts were then dried over Na_2SO_4 (anh), filtered and solvent evaporated under reduced pressure. The crude product was then purified by column chromatography (20 → 30% ethylacetate in light petroleumether 40/60) to give a colourless oil. 344 mg, 0.691 mmol. 47%. The product was then further purified by HPLC (30% ethylacetate in hexane) (165 mg, 0.323 mmol. 33%).

d.r. *from* ^{1}H NMR – NB 5891 58a



R_f (ethylacetate / light petroleumether 40/60) (30 : 70) : 0.24

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (^{a,b}C**H** $_{TBDPS\ Ar}$, d, *J* = 6.1 Hz, 5.3H), 7.48 - 7.32 (^{a,b}C**H** $_{TBDPS\ Ar}$, m, 7.9H), 4.47 - 4.25 (^{a,b}OC**H**$_2$CH$_2$N, m, *J* = 7.6 Hz, 4.2H), 4.03 (^{a}OCH$_2$C**H**$_2$N, t, *J* = 8.3 Hz, 1.6H), 4.01 - 3.90 (^{a,b}C**H**OH, ^{b}OCH$_2$C**H**$_2$N, m, 3.7H), 3.85 (^{a}C**H**OTBDPS, dt, *J* = 3.0, 8.6 Hz, 1.3H), 3.70 (^{b}C**H**OTBDPS, dt, *J* = 13.1, 6.7 Hz, 0.2H), 3.59 (^{a}C**H**CHOH, dq, *J* = 3.0, 6.9 Hz, 1.1H), 3.45 (^{b}C**H**CHOH, ddd, *J* = 3.0, 7.1, 14.1 Hz, 0.3H), 2.55 (^{a}O**H**, s, 0.9H), 2.50 (^{b}O**H**, d, *J* = 3.0 Hz, 0.2H), 1.85 (^{a}C**H**Me$_2$, sptd, *J* = 4.0, 6.9, Hz, 1H), 1.76 (^{b}C**H**Me$_2$, sptd, *J* = 3.0, 6.9 Hz, 0.5H), 1.60 - 1.42 (^{a,b}C**H**$_2$CHOBn, m, 3.2H), 1.09 (^{a}CHC**H**$_3$, d, *J* = 7.1 Hz, 3.2H), 1.07 (^{a,b}C**H**$_{3\ t\mathrm{Bu}}$, s, 12.2H), 1.01 (^{b}CHC**H**$_3$, d, *J* = 6.6 Hz, 0.8H), 0.94 (^{b}CH**Me**$_2$, d, *J* = 6.6 Hz, 1.1H), 0.91 (^{a}CH**Me**$_2$, d, *J* = 7.1 Hz, 3H), 0.81 (^{b}CH**Me**$_2$, d, *J* = 7.1 Hz, 0.5H), 0.77 (^{a}CH**Me**$_2$, d, *J* = 7.1 Hz, 3.1H).

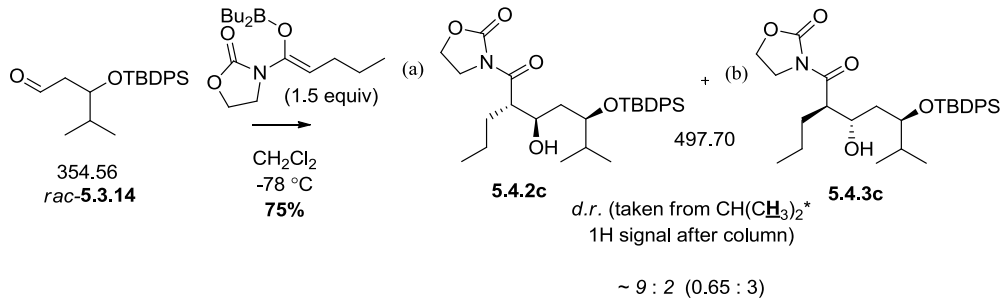
^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.9 (^{a}**C**ON), 176.4 (^{c}**C**ON), 174.2 (^{b}**C**ON), 153.1 (^{a,b}O**C**ON), 136.1 (**C**H Ar *M*), 136.1 (**C**H* Ar *M*), 134.7 (**C** Ar *I*), 133.9 (**C** Ar *I*), 129.6 (**C**H Ar *P*), 129.3 (**C**H Ar *P*), 127.5 (**C**H Ar *O*), 127.4 (**C**H Ar *O*), 75.4 (**C**HOTBDPS), 69.1 (**C**HOH), 62.2 (O**C**H$_2$CH$_2$N), 62.0 (O**C**H$_2$CH$_2$N), 61.8 O**C**H$_2$CH$_2$N, 42.6 (**C**HOH), 42.5 (OCH$_2$CH$_2$N), 42.4 (**C**HCHOH), 36.7 (^{b}**C**H$_2$OTBDPS), 36.1 (^{a}**C**H$_2$CHOTBDPS), 33.4 (**C**HMe$_2$), 27.1 (^{a}**C**H$_3$ *t*Bu), 27.1 (^{b}**C**H$_3$ *t*Bu), 19.6 (^{a}**C**Me$_3$), 19.5 (^{b}**C**Me$_3$), 18.2 (^{a}CH**Me**$_2$*), 18.0 (^{b}CH**Me**$_2$), 17.3 (^{a}CH**Me**$_2$), 16.8 (^{b}CH**Me**$_2$*), 10.6 (^{a}CH**C**H$_3$), 10.0 (^{b}CH**C**H$_3$).

IR (neat) : 3524, 3071, 2959, 2932, 1776, 1699cm^{-1}.

MS (ES$^+$)(m/z) : 520 [M+Na]$^+$ (100%).

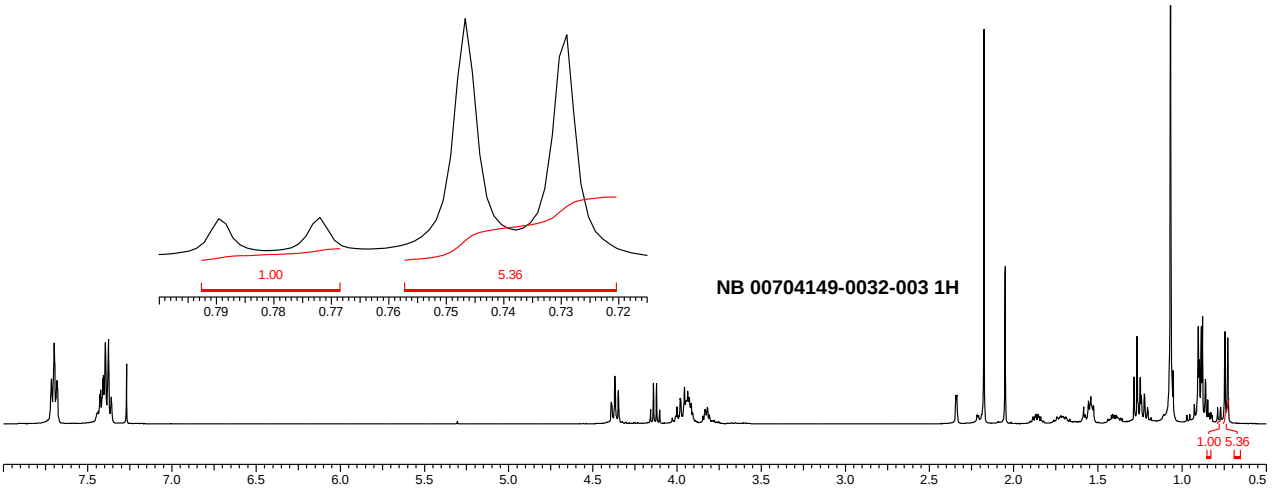
HRMS (ES$^+$) : [M+Na+MeOH]$^+$, Calcd. 552.2752; Found. 552.2761.

OTBDPS aldehyde directed 'Evans like' aldol reaction, using 3-pentanoyloxazolidin-2-one.



To a solution of the 3-pentanoyloxazolidin-2-one (200 mg, 1.17 mmol, 1.2 equiv) in CH_2Cl_2 (4 mL) was added $Bu_2B(OTf)$ (1M in CH_2Cl_2, 1.17 mL, 1.17 mmol, 1.2 equiv) dropwise, followed by DIPEA (0.204 mL, 1.17 mmol, 1.2 equiv) dropwise under N_2(g) at 0 ºC. After 15 min the reaction was cooled to -78 ºC and a solution of 3-TBDPSO-4-methylpentanal (345 mg, 0.973 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at -78 ºC, under nitrogen was added dropwise. The reaction was then stirred monitoring by TLC for 1 h at -78 ºC, the reaction was then allowed to warm to rt over 1 h. The reaction was then quenched with pH 7 phoshate buffer and diluted with H_2O_2 (30% aq), (1 : 1, 20 mL). The mixture was then extracted with portions of CH_2Cl_2 (3 × 20 mL) before drying over Na_2SO_4 (anh), filtering and evaporating the solvent under reduced pressure. The crude product was then purified by column chromatography, (0 → 40% *t*-butylmethylether in heptane, detector 220 nm) to yield the desired product as a colourless oil (384 mg, 0.731 mmol. 75%) *d.r.* (a : b) ≈ *5* : *1*.

d.r. *from* ^{1}H NMR – NB 00704149-0032-003



R_f (ethylacetate / light petroleumether 40/60) (20 : 80) : 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 - 7.59 (^{a,b}C**H** $_{Ar}$, m, 5.3 H), 7.48 - 7.34 (^{a,b}C**H** $_{Ar}$, m, *J* = 7.6 Hz, 7.7 H), 4.37 (^{a,b}OC**H**$_2$CH$_2$N, t, *J* = 8.6 Hz, 2.4 H), 4.04 - 3.87 (^{a,b}OCH$_2$C**H**$_2$N, ^{a}C**H**OH, ^{a}C**H**CON, ^{b}CHOTBDPS, m, *J* = 7.1 Hz, 5.0 H), 3.86 - 3.74 (^{a}CHOTBDPS, ^{b}C**H**OH, m, 1.5 H), 3.71 - 3.56 (^{b}C**H**CON, m, *J* = 7.6 Hz, 0.2 H), 2.34 (^{a}O**H**, d, *J* = 2.0 Hz, 1.1 H), 2.21 (^{b}O**H**, d, *J* = 3.5 Hz, 0.5 H), 1.86 (^{a,b}C**H**Me$_2$, dspt, *J* = 6.8, 11.4 Hz, 1.1 H), 1.79 - 1.65 (^{a,b}CHC**H**$_2$Et, m, 1.5 H), 1.60 - 1.51 (^{a,b}CHOHC**H**$_2$, m, 2.6 H), 1.45 - 1.35 (^{a,b}CHC**H**$_2$CH$_2$CH$_3$, m, *J* = 4.0 Hz, 1.4 H), 1.23 (^{a,b}CHCH$_2$C**H**$_2$CH$_3$, sxt, *J* = 8.1 Hz, 2.9

H), 1.07 (^{a,b}C**Me**$_3$, s, 11.5 H), 0.90 (^{b}CH**Me**$_2$, d, *J* = 7.1 Hz, 3 H), 0.88 (^{a}CHCH$_2$CH$_2$**C**H$_3$, t, *J* = 7.6 Hz, 3 H), 0.99 - 0.81 (^{b}CH**Me**$_2$, ^{b}CHCH$_2$CH$_2$**C**H$_3$, m, 1.4 H), 0.78 (^{b}CH**Me**$_2$, d, *J* = 7.1 Hz, 0.7 H), 0.74 (^{a}CH**Me**$_2$, d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6 (^{a}CH**C**ON), 175.5 (^{b}CH$_2$**C**ON), 153.6 (O**C**ON), 153.3 (ox-ket, O**C**ON), 136.1 (^{b}**C**H Ar *O*), 136.0 (^{a}**C**H Ar *O*), 134.6 (^{b}**C**H Ar *I*), 134.4 (^{a}**C**H Ar *I*), 134.3 (^{b}**C**H Ar *I**), 134.0 (^{a}**C**H Ar *I**), 129.6 (^{b}**C**H Ar *P*), 129.5 (^{a}**C**H Ar *P*), 127.5 (^{a}**C**H Ar *M*), 127.4 (^{b}**C**H Ar *M*), 76.1 (^{b}**C**HOTBDPS), 75.3 (^{a}**C**HOTBDPS), 70.4 (^{b}**C**HOH), 69.1 (^{a}**C**HOH), 62.0 (ox-ket, O**C**H$_2$CH$_2$N), 61.7 (^{b}O**C**H$_2$CH$_2$N), 61.7 (^{a}O**C**H$_2$CH$_2$N), 47.9 (**C**HCON), 47.8 (**C**HCON), 42.7 (^{a}OCH$_2$**C**H$_2$N), 42.7 (^{b}OCH$_2$**C**H$_2$N), 42.5 (ox-ket, OCH$_2$**C**H$_2$N), 37.3 (^{b}CHOHC**H**$_2$), 35.7 (^{a}CHOHC**H**$_2$), 34.8 (ox-ket, **C**H$_2$CH$_2$CH$_2$CH$_3$), 33.4 (^{a}**C**HMe$_2$), 31.9 (^{b}**C**HMe$_2$), 29.4 (^{a}CH**C**H$_2$Et), 28.7 (^{b}CH**C**H$_2$Et), 27.2 (^{a}C(**C**H$_3$)$_3$), 27.1 (^{b}C(**C**H$_3$)$_3$), 26.3 (ox-ket, CH$_2$**C**H$_2$CH$_2$CH$_3$), 22.2 (ox-ket, CH$_2$CH$_2$**C**H$_2$CH$_3$), 20.8 (^{a}CHCH$_2$**C**H$_2$CH$_3$), 20.7 (^{b}CHCH$_2$**C**H$_2$CH$_3$), 19.6 (^{a}**C**Me$_3$), 19.5 (^{b}**C**Me$_3$), 18.4 (^{b}CH(**C**H$_3$)$_2$), 18.3 (^{a}CH(**C**H$_3$)$_2$), 17.0 (^{a}CH(**C**H$_3$)$_2$*), 16.5 (^{b}CH(**C**H$_3$)$_2$*), 14.2 (CHCH$_2$CH$_2$**C**H$_3$), 13.8 (ox-tet. CH$_2$CH$_2$CH$_2$**C**H$_3$).

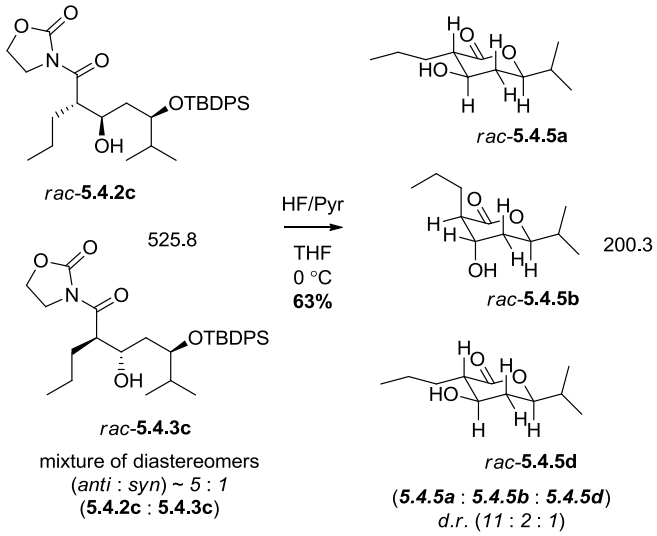
ox-ket = 3-pentanoyloxazolidin-2-one

IR (neat) : 3508, 2959, 2860, 1779, 1698, 1387cm^{-1}.

MS (ES$^+$)(m/z) : 548 [M+Na]$^+$ (100%).

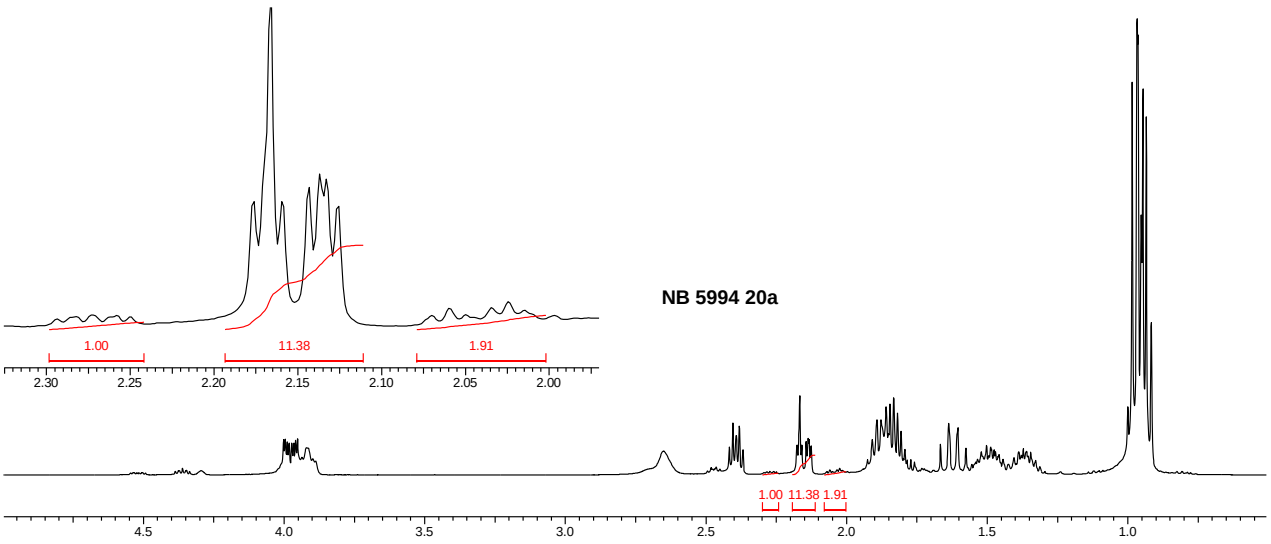
HRMS (ES$^+$) : [M+Na]$^+$; Calcd. 548.2803; Found. 548.2801.

HF/pyr promoted cyclisation of aldol product mixture (5.4.2c & 5.4.3c)



To a solution of *rac*-aldol product (**5.4.2c** and **5.4.3c**) (with minor quantities of the 3,5-*syn*-diastereomer, *d.r. ~ 2.5 : 1*, 150 mg, 0.285 mmol, 1 equiv) in THF (1 mL) at 0 ºC under N_2 (g) was added HF/pyridine (70/30% respectively, 1 mL). The reaction was then allowed to warm to rt over 2 h and stirred for a further 16 h. The reaction was then quenched with $NaHCO_3$ (10 mL), before extracting with (3 × 10 mL) CH_2Cl_2 portions. The combined organic phases were then washed with brine (10 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude product was then purified by column chromatography (1% MeOH in CH_2Cl_2) to yield a colourless residue as a mixture of isomers (36 mg, 0.179 mmol. 63%) *ratio of isomers* (a : b : c) ~ *11* : *2* : *1*.

ratio of isomers *from* ^{1}H NMR – NB 5994 20a



R_f (ethylacetate / light petroleumether 40/60) (20 : 80) : 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.52 (^{d}COOC**H**, ddd, *J* = 3.5, 5.6, 12.1 Hz, 0.06 H), 4.36 (^{b}COOC**H**, ddd, *J* = 4.3, 5.8, 10.1 Hz, 0.12 H), 4.32 - 4.26 (^{d}C**H**OH, m, 0.07 H), 3.98 (^{a}COOC**H**, ddd, *J* = 2.5, 5.3, 11.9 Hz, 1H), 3.92 (^{a}C**H**OH, dt, *J* = 4.0, 9.8 Hz, 1H), 2.65 (^{a}O**H**, br. s., 1H), 2.47 (^{b}C**H**COO, td, *J* = 5.2, 7.2 Hz, 0.18H), 2.39 (^{a}C**H**COO, td, *J* = 5.1, 9.1 Hz, 1H), 2.27 (^{d}C**H**COO, ddd, *J* = 3.0, 4.5, 9.6 Hz, 0.09H), 2.15 (^{a}CHOHC**H**$_{2\ Eq}$, ddd, *J* = 2.5, 4.0, 13.1 Hz, 1H), 2.04 (^{b}CHOHC**H**$_{2\ Eq}$, td, *J* = 4.0, 14.1 Hz, 0.12H), 1.94 - 1.79 (^{a}C**H**$_2$CH$_2$CH$_3$, ^{a}C**H**Me2, m, 3H), 1.62 (^{a}CHOHC**H**$_{2\ Ax}$, td, *J* = 11.6, 13.1 Hz, 1H), 1.56 - 1.43 (^{a}CH$_2$C**H**$_2$CH$_3$, m, 1H), 1.42 - 1.31 (^{a}CH$_2$C**H**$_2$CH$_3$*, m, 1H), 0.98 (^{a}CH**Me**$_2$, d, *J* = 7.1 Hz, 3H), 0.95 (^{a}CH**Me**$_2$*, d, *J* = 7.1 Hz, 3H), 0.93 (^{a}CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.2 Hz, 3H).

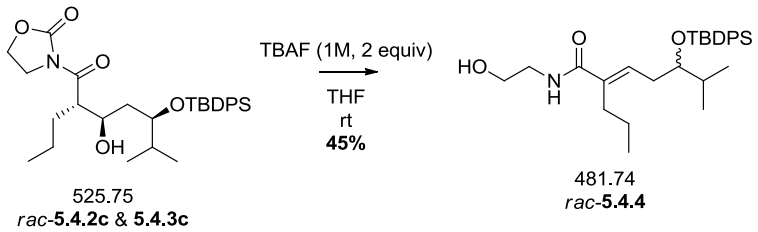
^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3 (^{b}**C**OO), 173.6 (^{a}**C**OO), 80.9 (^{a}COO**C**H), 80.2 (^{b}COO**C**H), 79.8 (^{c}COO**C**H), 67.6 (^{a}**C**HOH), 67.5 (^{b}**C**HOH), 64.4 (^{c}**C**HOH), 50.1 (^{a}**C**HCOO), 47.8 (^{b}**C**HCOO), 46.1 (^{c}**C**HCOO), 34.7 (^{a}CHOH**C**H_2), 32.9 (^{b}CHOH**C**H_2), 32.7 (^{c}CHOH**C**H_2), 32.4 (^{a}**C**HMe_2), 32.0 (^{b}**C**HMe_2), 31.8 (^{b}**C**$H_2CH_2CH_3$), 30.3 (^{a}**C**$H_2CH_2CH_3$), 28.4 (^{c}**C**$H_2CH_2CH_3$), 20.7 ($^{b}CH_2$**C**H_2CH_3), 20.1 ($^{c}CH_2$**C**H_2CH_3), 19.7 ($^{a}CH_2$**C**H_2CH_3), 17.8 ($^{?}$**C**HMe_2), 17.7 ($^{?}$**C**HMe_2), 17.6 (^{a}**C**HMe_2), 17.5 (^{a}CH**Me**$_2^{*}$), 17.4 ($^{?}$**C**HMe_2^{*}), 14.2 ($^{a}CH_2CH_2$**C**H_3), 14.0 ($^{b}CH_2CH_2$**C**H_3), 13.9 ($^{c}CH_2CH_2$**C**H_3).

IR (neat) : 3426, 2961, 2873, 1695, 1374 cm^{-1}.

MS (ES^+)(m/z) : 264 $[M+Na+MeCN]^+$ (100%), 305 $[M+Na+2MeCN]^+$ (18%), 423 $[2M+Na]^+$ (31%).

HRMS (ES^+) : $[M+Na]^+$; Calcd. 223.1305; Found. 223.1304.

TBAF promoted elimination of aldol product 5.4.2c and 5.4.3c



525.75
rac-**5.4.2c** & **5.4.3c**

481.74
rac-**5.4.4**

To a solution of *rac*-aldol product **5.4.2c** and **5.4.3c** (315 mg, 0.599 mmol, 1 equiv) in THF (2 mL) at rt (under N_2 (g)) was added TBAF in THF (1M, 1.2 mL, 1.20 mmol, 2 equiv). The solution turned pale green then yellow within seconds. The reaction was stirred for 3 h, after which the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (50% ethylacetate in light petroleumether 40/60) to yield a colourless oil (129 mg, 0.269 mmol. 45%).

R_f (ethylacetate / light petroleumether 40/60) (50 : 50) : 0.63

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 - 7.65 (**C**H $_{Ar}$, m, 4H), 7.50 - 7.35 (**C**H $_{Ar}$, m, *J* = 4.0 Hz, 6H), 5.94 (C=C**H**, t, *J* = 6.8 Hz, 1H), 5.62 (N**H**, br t, *J* = 4.5 Hz, 1H), 3.65 (O**C**H_2CH_2N, C**H**OTBDPS, dd, *J* = 4.0, 8.6 Hz, 3H), 3.38 - 3.24 (OCH_2**C**H_2N, m, *J* = 5.3, 5.3 Hz, 2H), 2.89 (O**H**, t, *J* = 5.1 Hz, 1H), 2.30 - 2.16 (C=CHC**H**$_2$, m, 2H), 2.08 (C**H**$_2CH_2CH_3$, t, *J* = 7.8 Hz, 2H), 1.77 (C**H**Me_2, dtd, *J* = 3.5, 6.8, 13.6 Hz, 1H), 1.67 (H_2O, s, 1H), 1.27 (CH_2C**H**$_2CH_3$, ddd, *J* = 3.5, 7.3, 14.9 Hz, 2H), 1.06 (*t*Bu, s, 9H), 0.96

(CH**Me**$_2$, d, *J* = 6.6 Hz, 3H), 0.88 (CH**Me**$_2$*, d, *J* = 7.1 Hz, 3H), 0.81 (CH_2CH_2C**H**$_3$, t, *J* = 7.3 Hz, 3H).

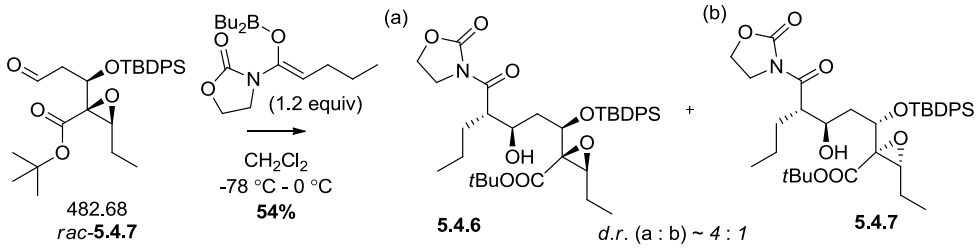
^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.2 (**C**ON), 137.6 (**C**=CH), 136.0 (**C**H Ar), 135.9 (**C**H Ar), 134.8 (**C** Ar), 133.6 (**C** Ar), 132.2 (C=**C**H), 129.8 (**C**H Ar), 129.5 (**C**H Ar), 127.7 (**C**H Ar), 127.5 (**C**H Ar), 77.5 (**C**HOTBDPS), 63.0 ($NHCH_2$**C**H_2OH), 42.9 ($NHCH_2CH_2OH$), 33.1 (**C**HMe_2), 31.9 (C=CH**C**H_2), 29.2 (**C**$H_2CH_2CH_3$), 27.0 (C**Me**$_3$), 21.8 (CH_2**C**H_2CH_3), 19.6 (**C**Me_3), 18.1 (CH**Me**$_2$), 17.2 (CH**Me**$_2$*), 13.9 (CH_2CH_2**C**H_3).

IR (neat) : 3339, 3071, 2958, 1618, 1525cm^{-1}

MS (ES^+)(m/z) : 504 $[M+Na]^+$ (100%).

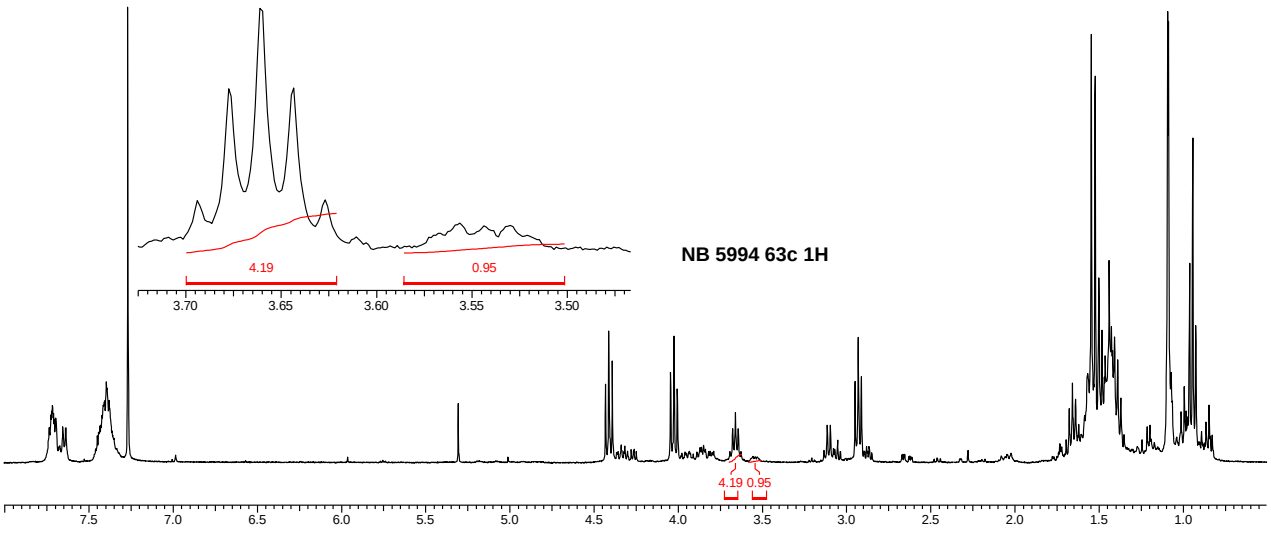
HRMS (ES^+) : $[M+Na]^+$; Calcd. 504.2904; Found. 504.2903.

Aldehyde directed 'Evans like' aldol reaction using TBDPS protected aldehyde 5.4.7



To a solution of 3-pentanoyloxazolidin-2-one (77 mg, 0.447 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) at 0 ºC under N_2 (g) was added $Bu_2B(OTf)$ (1M in CH_2Cl_2, 447 µL, 0.447 mmol, 1.2 equiv) dropwise (red/brown colour developed), followed by DIPEA (77.9 µL, 0.447 mmol, 1.2 equiv). The reaction was stirred for 15 min at 0 ºC before cooling to -78 ºC. A solution of TBDPS protected aldehyde **5.4.7** (180 mg, 0.373 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was then added at -78 ºC under N_2 (g). The reaction was then stirred for 5 h at -78 ºC before warming to 0 ºC, over 1 h. The reaction was then quenched with pH 7 phoshate buffer and diluted with H_2O_2 (30% aq), (1 : 1, 5 mL). The mixture was then extracted with portions of CH_2Cl_2 (3 × 5 mL) before drying over Na_2SO_4 (anh), filtering and evaporating the solvent under reduced pressure. The crude product was then purified by column chromatography, (20% ethylacetate in light petroluemether 40/60) to yield the desired product as a colourless oil (132 mg, 0.200 mmol. 54%) *d.r.* (a : b) ≈ *4* : *1*.

d.r. *from* ^{1}H NMR – NB 5994 63c



R_f (ethylacetate / light petroleumether 40/60) (25 : 75) : 0.10

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 - 7.66 (^{a,b}C**H** $_{Ar}$, m, 5.26 H), 7.48 - 7.34 (^{a,b}C**H** $_{Ar}$, m, 8.10 H), 4.40 - 4.26 (^{a,b}NCH$_2$C**H**$_2$O, m, 2.69 H), 4.20 - 4.16 (^{b}C**H**OTBDPS**,** m, 0.20 H), 4.01 - 3.77 (^{a,b}NC**H**$_2$CH$_2$O, ^{a}C**H**OTBDPS, ^{a,b}C**H**OH, m, 5.51 H), 3.54 (^{a}COHC**H**CON, td, *J* = 3.5, 11.1 Hz, 1.01 H), 3.21 (^{b}C**H** $_{epox}$, t, *J* = 6.3 Hz, 0.25 H), 2.87 (^{a}C**H** $_{epox}$, t, *J* = 6.3 Hz, 1.00 H), 2.33 (^{b}O**H**, d, *J* = 3.0 Hz, 1 H), 2.05 (^{a}CHOTBDPSC**H**$_2$, dd, *J* = 8.6, 14.1 Hz, 1.00 H), 1.74 (^{a}CHOTBDPSC**H**$_2^{*}$, ddd, *J* = 3.5, 11.1, 14.7 Hz, 1 H), 1.73 (^{a}O**H**, d, *J* = 3.5 Hz, 2 H), 1.67 – 1.29 (^{b}CHOTBDPSC**H**$_2$, ^{a,b}CH$_{2\ Et}$, ^{a,b}CHC**H**$_2$CH$_2$CH$_3$, m, 8.64 H), 1.55 (^{a}C**H**$_{3\ t\text{-Bu}}$, s, 9 H), 1.50 (^{b}C**H**$_{3\ t\text{-Bu}}$, s, 2.25 H), 1.19 (^{a,b}CHCH$_2$C**H**$_2$CH$_3$, m, 4.47 H), 1.09 (^{a,b}C**H**$_{3\ TBDPS}$, s, 12 H), 0.99 (^{a,b}C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 4.12 H), 0.85 (^{a}CHCH$_2$CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 3.31 H), 0.84 (^{b}CHCH$_2$CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 0.75 H).

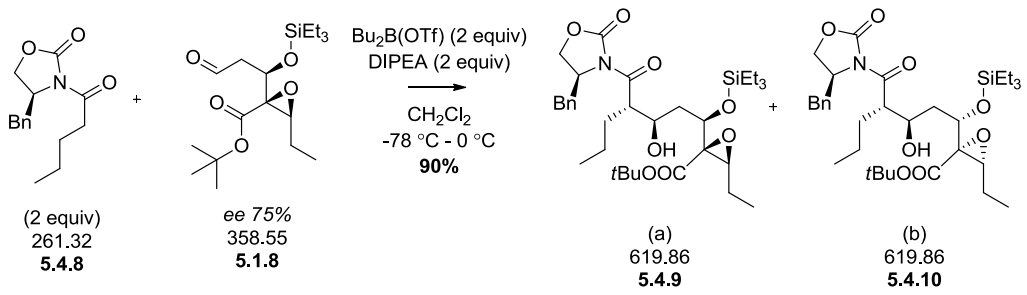
^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6 (^{b}**C**ON), 175.3 (^{a}**C**ON), 167.2 (^{b}**C**OO*t*-Bu), 167.1 (^{a}**C**OO*t*-Bu), 153.5 (^{b}N**C**OO), 153.4 (^{a}N**C**OO), 136.2 (^{a}**C**H Ar *M*), 136.1 (^{b}**C**H Ar *M*), 136.0 (^{a,b}**C**H* Ar *M*), 134.2 (^{a,b}**C** Ar *I*), 132.6 (^{a,b}**C*** Ar *I*), 129.9 (^{a,b}**C**H Ar *P*), 129.6 (^{b}**C**H* Ar *M*) 129.6 (^{a}**C**H* Ar *P*), 127.6 (^{a,b}**C**H Ar *O*), 127.5 (^{a,b}**C**H* Ar $_{O}$), 82.4 (^{a}**C**Me$_3$), 82.3 (^{b}**C**Me$_3$), 74.3 (^{a}**C**HOTBDPS), 74.2 (^{b}**C**HOTBDPS), 68.7 (^{b}**C**HOH), 68.4 (^{a}**C**HOH), 67.1 (**C** $_{epox}$), 66.0 (**C** $_{epox}$), 61.7 (^{b}NCH$_2$**C**H$_2$O), 61.6 (^{a}NCH$_2$**C**H$_2$O), 61.4 (^{b}**C**H $_{epox}$), 61.3 (^{a}**C**H $_{epox}$), 47.6 (^{a}CHOH**C**HCON), 47.5 (^{b}CHOH**C**HCON), 42.6 (^{a,b}NH**C**H$_2$CH$_2$OH), 39.5 (^{a}CHOTBDPS**C**H$_2$CHOH), 38.4 (^{b}CHOTBDPS**C**H$_2$CHOH), 29.8 (^{a}**C**H$_{2\ Et}$), 29.2 (^{b}**C**H$_{2\ Et}$), 28.1 (^{a,b}**C**H$_{3\ t\text{-Bu}}$), 26.9 (^{b}**C**H$_{3\ TBDPS}$), 26.9 (^{a}**C**H$_{3\ TBDPS}$), 21.9 (^{a,b}CH**C**H$_2$CH$_2$CH$_3$), 20.8 (^{a}CHCH$_2$**C**H$_2$CH$_3$), 20.7 (^{b}CHCH$_2$**C**H$_2$CH$_3$), 19.6 (^{b}**C**Me$_{3\ TBDPS}$), 19.4 (^{a}**C**Me$_{3\ TBDPS}$), 14.1 (^{a,b}CHCH$_2$CH$_2$**C**H$_3$), 10.2 (^{a}CH$_{3\ Et}$), 10.0 (^{b}**C**H$_{3\ Et}$).

IR (cm^{-1}) : 3521, 2963, 2932, 1777, 1741, 1697cm^{-1}.

MS (ES^+)(m/z) : 620 $[M-tBu+H+Na]^+$ (11%), 676 $[M+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$; Calcd. 676.3276; Found. 676.3265.

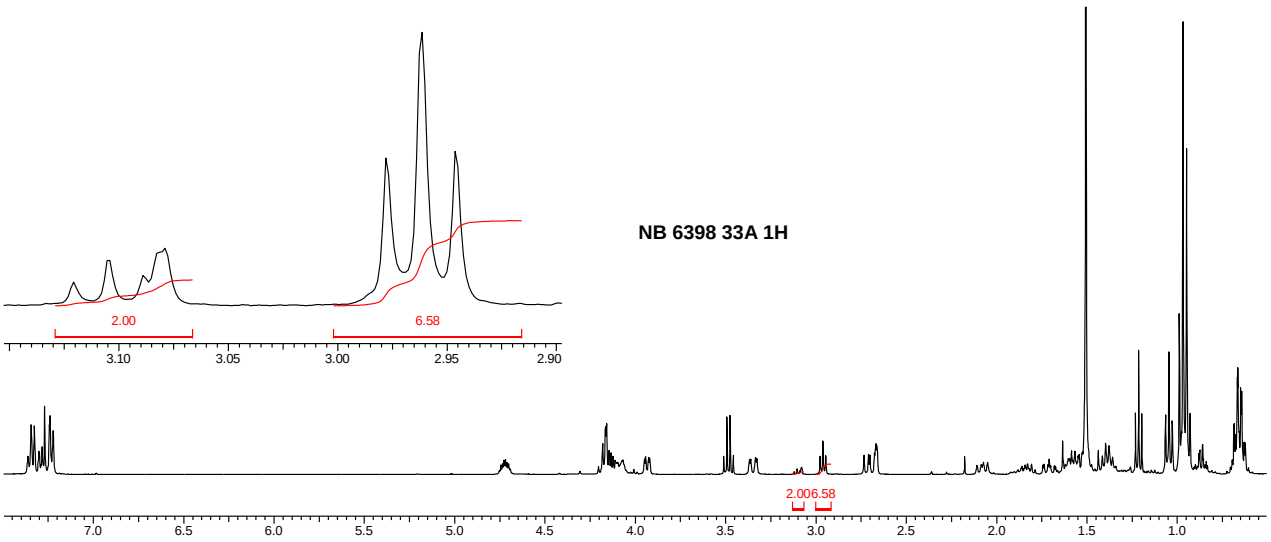
Enolate directed Evans aldol reaction using TES protected aldehyde 5.1.8



(2 equiv) 261.32 **5.4.8** + *ee 75%* 358.55 **5.1.8** → (a) 619.86 **5.4.9** + (b) 619.86 **5.4.10**

To a stirred solution of (*S*)-4-benzyl-3-pentanoyloxazolidin-2-one **5.4.8** (*ee >99%*, 1.04 g, 3.96 mmol, 2 equiv) in CH_2Cl_2 (3.6 mL) at 0 ºC under nitrogen was added dibutylborontrifluoromethanesulfonate (1M in CH_2Cl_2, 3.96 mL, 3.96 mmol, 2 equiv) to give an orange solution. After 5 min DIPEA (690 µL, 3.96 mmol, 2 equiv) was added dropwise and the solution became yellow. After another 5 min the solution was cooled to -78 ºC and transferred via cannula to a solution of TES protected aldehyde **5.1.8** (*ee ≈75%*, 710 mg, 1.98 mmol, 1 equiv) in CH_2Cl_2 (3.6 mL) at -78 ºC. The reaction was then stirred at the same temperature for 4 h before warming to 0 ºC, slowly over 2 h. The reaction was then quenched with 30% v/v H_2O_2 (aq) and pH 7 phosphate buffer (1:1, 10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were then scrubbed with brine (10 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (20 → 40% diethylether in light petroleumether 40/60) to give a mixture of (a) major aldol product **5.4.9** and (b) minor aldol product **5.4.10** (*d.r. - a*:*b, 7* : *1*) (1.11 g, 1.78 mmol. 90%).

d.r. *from* ^{1}H NMR – NB 6398 33a



R_f (diethylether / light petroleumether 40/60) (40 : 60) : 0.13

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.19 (^{a,b}C**H** Ar, m, 6.6 H), 4.72 (^{a,b}NC**H**BnCH$_2$O, tdd, *J* = 3.3, 6.9, 10.2 Hz, 1.2 H), 4.22 - 4.04 (^{a,b}NCHBnC**H**$_2$O, ^{a,b}C**H**OH, ^{a,b}C**H**CON, m, 4.8 H), 4.01 (^{b}C**H**OTES, t, *J* = 7.1 Hz, 0.19 H), 3.93 (^{a}C**H**OTES, dd, *J* = 2.8, 9.3 Hz, 1.0 H), 3.35 (^{a,b}C**H**$_2$Ph, dd, *J* = 3.0, 13.1 Hz, 1.2 H), 3.13 - 3.07 (^{b}C**H** epox, ^{b}O**H**, m, *J* = 12.6 Hz, 0.3 H), 2.96 (^{a}C**H** epox, t, *J* = 6.3 Hz, 1.0 H), 2.71 (^{a,b}C**H**$_2$Ph*, dd, *J* = 10.1, 13.1 Hz, 1.2 H), 2.67 (^{a}O**H**, d, *J* = 2.0 Hz, 1.0 H), 2.08 (^{a,b}CHOTESC**H**$_2$, dd, *J* = 9.3, 14.4 Hz, 1.1 H), 1.94 - 1.76 (^{a,b}C**H**$_2$CH$_2$CH$_3$, m, 1.4 H), 1.71 (^{a,b}CHOTESC**H**$_2$*, ddd, *J* = 3.0, 11.1, 14.1 Hz, 1.1 H), 1.65 - 1.52 (^{a,b}CH$_2$C**H**$_2$CH$_3$, m, 2.6 H), 1.51 (^{a,b}C(C**H**$_3$)$_3$, s, 11.3 H), 1.46 - 1.33 (^{a,b}C**H**$_2$CH$_3$ epox, m, 3.2 H), 1.05 (^{a,b}CH$_2$**C**H$_3$ epox, t, *J* = 7.3 Hz, 3.6 H), 0.97 (^{a,b}CH$_2$C**H**$_3$ TES, t, *J* = 8.1 Hz, 10.7 H), 0.95 (^{a,b}CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.6 Hz, 3.6 H), 0.91 - 0.82 (^{b}C**H**$_2$CH$_3$ TES, m, *J* = 2.5, 4.0 Hz, 1.8 H), 0.71 - 0.60 (^{a}C**H**$_2$CH$_3$ TES, m, 7.2 H).

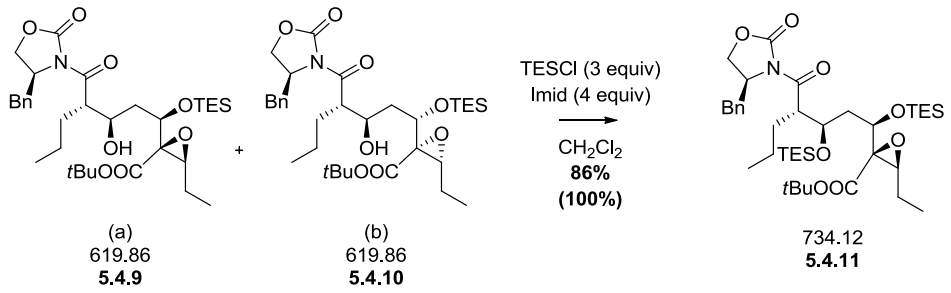
^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5 (^{a}CH**C**ON), 167.0 (^{a}**C**OO*t*Bu), 153.8 (^{a}N**C**OO), 135.2 (^{a}**C** Ar), 129.4 (^{a}**C**H Ar), 129.0 (^{a}**C**H Ar), 127.4 (^{a}**C**H Ar), 82.5 (^{b}**C**(CH$_3$)$_3$), 82.3 (^{a}**C**(CH$_3$)$_3$), 73.2 (^{b}**C**HOH), 71.8 (^{a}**C**HOH), 70.1 (^{b}**C**HOTES), 68.9 (^{a}**C**HOTES), 67.0 (^{a}**C** epox), 66.2 (^{b}**C** epox), 65.9 (^{a}NCHBn**C**H$_2$O), 61.4 (^{b}CH epox), 61.0 (^{a}CH epox), 55.6 (^{b}N**C**HBnCH$_2$O), 55.5 (^{a}NCHBn**C**H$_2$O), 47.9 (^{a}**C**HCON), 38.4 (^{a}CHOTES**C**H$_2$), 38.0 (^{a}**C**H$_2$Ph), 30.1 (^{a}**C**H$_2$CH$_2$CH$_3$), 29.6 (^{b}**C**H$_2$CH$_2$CH$_3$), 28.0 (^{a}C(**C**H$_3$)$_3$), 21.9 (^{a}CH$_2$**C**H$_2$CH$_3$), 20.7 (^{a}**C**H$_2$CH$_3$ epox), 14.3 (^{a}CH$_2$CH$_2$**C**H$_3$), 10.2 (^{a}CH$_2$**C**H$_3$ epox), 6.8 (^{a}CH$_3$ TES), 6.7 (^{b}**C**H$_3$ TES), 4.7 (^{a}**C**H$_2$ TES), 4.6 (^{b}**C**H$_2$ TES).

IR (neat) : 3513, 2958, 2876, 1780, 1747, 1697 cm^{-1}.

MS (ES^+)(m/z) : 642 $[M+Na]^+$ (100%), 586 $[M-t\text{Bu}+H+Na]^+$ (6%).

HRMS (ES^+) : $[M+Na+MeOH]^+$ Calcd. 674.3695; Found. 674.3686.

TES protection of the aldol product mixture 5.4.9 and 5.4.10



To a solution of (a) major aldol product and (b) minor aldol product (*d.r.* - *a*:*b*, *7* : *1*, 1.07 g, 1.72 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added imidazole (427 mg, 6.87 mmol, 4 equiv) and TESCl dropwise (864 µL, 5.15 mmol, 3 equiv). The reaction was stirred under nitrogen at rt for 16 h before quenching with $KHSO_4$ (aq. 10% w/w, 20 mL) and extracting with CH_2Cl_2 (40 mL). The organic phase was then washed with water (2×20 mL), the organic layer was then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (10% diethylether in light petroleumether 40/60) to yield a colourless oil 1.263 g, 1.72 mmol. 100%. The diastereomers could then be separated by HPLC (8% ethylacetate in hexane) to give the desired isomer as an oil (1.09 g, 1.48 mmol. 86%).

R_f (diethylether / light petroleumether 40/60) (40 : 60) : 0.93

$[\alpha]_D$: +31.9 (c 0.633, $CHCl_3$, 25°C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 - 7.20 (C**H** $_{Ar}$, m, 5 H), 4.67 (NC**H**BnCH$_2$O, tdd, *J* = 3.1, 6.6, 9.9 Hz, 1 H), 4.25 - 4.07 (NCHBnC**H**$_2$O, C**H**CON, m, 3 H), 3.99 (C**H**OTESCHCON, ddd, *J* = 2.3, 5.7, 7.9 Hz, 1 H), 3.54 (C**H**OTESCH$_2$, dd, *J* = 2.1, 9.6 Hz, 1 H), 3.34 (C**H**$_2$Ph, dd, *J* = 3.0, 13.2 Hz, 1 H), 2.85 (C**H** epox, t, *J* = 6.4 Hz, 1 H), 2.73 (C**H**$_2$Ph*, dd, *J* = 10.2, 13.2 Hz, 1 H), 2.37 (CHOTESC**H**$_2$, ddd, *J* = 2.3, 9.8, 15.1 Hz, 1 H), 1.87 (CHOTESC**H**$_2^*$, ddd, *J* = 2.3, 8.0, 15.0 Hz, 1 H), 1.82 - 1.69 (C**H**$_2$CH$_2$CH$_3$, m, 1 H), 1.66 - 1.53 (C**H**$_2$CH$_2$CH$_3^*$, C**H**$_2$CH$_3$ $_{epox}$, m, 3 H), 1.52 (C(C**H**$_3$)$_3$, s, 9 H), 1.48 - 1.29 (CH$_2$C**H**$_2$CH$_3$, m, 2 H), 1.05 (CH$_2$C**H**$_3$ $_{epox}$, t, *J* = 7.5 Hz, 3 H), 0.99 (C**H**$_3$ $_{TES}$, t, *J* = 8.3 Hz,

9 H), 1.00 – 0.93 ($CH_2CH_2C\underline{\mathbf{H}}_3$, t(m), 3 H) 0.95 ($C\underline{\mathbf{H}}_3{}^{*}{}_{TES}$, t, J = 7.9 Hz, 9 H), 0.75 - 0.55 ($C\underline{\mathbf{H}}_{2\ TES}$, m, J = 7.9 Hz, 12 H).

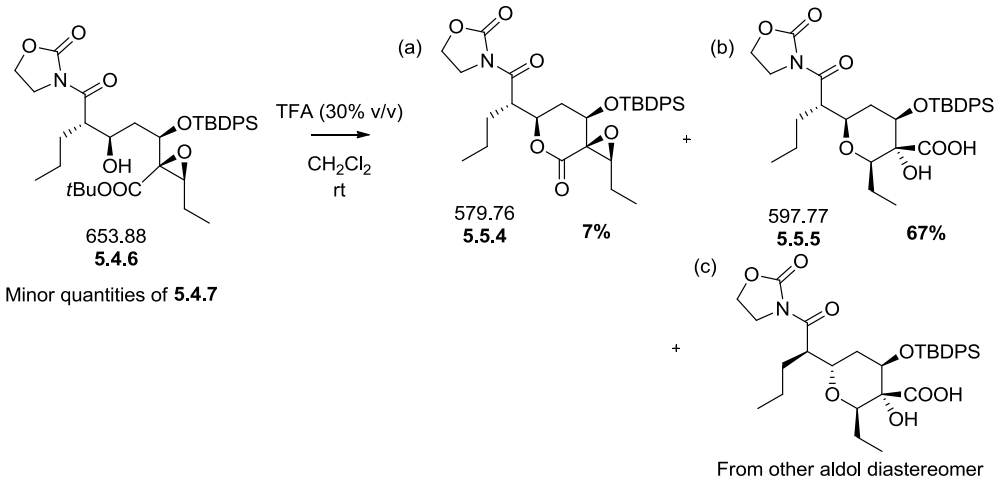
^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3 (CH**C**ON), 166.6 (**C**OO*t*Bu), 153.2 (O**C**ON), 135.6 (**C** Ar), 129.4 (**C**H Ar), 128.9 (**C**H Ar), 127.2 (**C**H Ar), 82.0 (**C**Me_3), 74.1 (**C**HOTESCH_2), 71.5 (**C**HOTESCHCON), 67.3 (**C** epox), 65.8 (NCHBn**C**H_2O), 61.4 (**C**H epox), 55.8 (N**C**HBnCH_2O), 48.3 (**C**HCON), 41.3 (CHOTES**C**H_2), 37.9 (**C**H_2Ph), 31.6 ($\underline{\mathbf{C}}H_2CH_2CH_3$), 28.1 ($C(\underline{\mathbf{C}}H_3)_3$), 21.9 ($\underline{\mathbf{C}}H_2CH_3$ epox), 20.4 ($CH_2\underline{\mathbf{C}}H_2CH_3$), 14.2 ($CH_2CH_2\underline{\mathbf{C}}H_3$), 10.3 ($CH_2\underline{\mathbf{C}}H_3$ epox), 7.0 ($\underline{\mathbf{C}}H_3$ TES), 6.9 ($\underline{\mathbf{C}}H_3$* TES), 5.4 ($\underline{\mathbf{C}}H_2$ TES), 5.1 ($\underline{\mathbf{C}}H_2$* TES).

IR (neat) : 2956, 2872, 1781, 1747, 1699 cm^{-1}.

MS (ES^+)(m/z) : 756 $[M+Na]^+$ (100%), 700 $[M-t\text{Bu}+H+Na]^+$ (26%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 756.4297; Found. 756.4281.

TFA catalysed cyclisation of the aldol product 5.4.6



To a solution of *rac*-aldol product **5.4.6** (38 mg, 58.1 µmol, 1 equiv) in CH_2Cl_2 (700 µL) was added TFA (300 µL, excess) dropwise at 0 ºC under N_2 (g). The solution was allowed to warm to rt before stirring for 4 h. The reaction solvent was then evaporated under reduced pressure, removing TFA traces by azeotropically distilling with portions of toluene (2 × 5 mL). The crude residue was then purified by column chromatography (40% ethylacetate in light petroleumether 40/60), further purifying by HPLC (40% ethylacetate in hexane) to yield to colourless oils.

(b) *rac*-major 6-*exo*-tet cyclisation product

(23.2 mg, 38.8 µmol. 67%) (contaminated with a small quantity of (c)).

R_f (ethylacetate / light petroleumether 40/60) (40 : 60) : 0.18.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 - 7.64 (C**H** $_{Ar}$, m, 4H), 7.49 - 7.34 (C**H** $_{Ar}$, m, 6H), 4.34 ($NCH_2C\mathbf{H}_2O$, dtd, *J* = 7.1, 9.1, 23.7 Hz, 2H), 4.16 (C**H**CON, dt, *J* = 5.3, 8.0 Hz, 1H), 3.98 - 3.91 ($NC\mathbf{H}_2CH_2O$, C**H**OTBDPS, m, 2H), 3.87 - 3.79 ($NC\mathbf{H}_2CH_2O^*$, m, *J* = 9.1 Hz, 1H), 3.46 (C**H**OCHEt, ddd, *J* = 2.0, 7.3, 11.9 Hz, 1H), 3.14 (CHOC**H**Et, dd, *J* = 2.0, 10.6 Hz, 1H), 2.37 (OH, s, 1H), 2.06 (CHOTBDPSC$\mathbf{H}_{2\ Ax}$, td, *J* = 11.6, 13.6 Hz, 1H), 1.82 (C$\mathbf{H}_{2\ Et}$, dsxt, *J* = 2.0, 7.3 Hz, 1H), 1.70 - 1.56 ($C\mathbf{H}_2CH_2CH_3$, m, *J* = 6.1 Hz, 1H), 1.54 - 1.39 (CHOTBDPSC$\mathbf{H}_{2\ Eq}$, m (ddd), *J* = 2.0, 5.8, 13.6 Hz, 1H), 1.54 - 1.39 ($C\mathbf{H}_2CH_2CH_3^*$, m, 1H), 1.35 - 1.22 (C$\mathbf{H}_2^*$ $_{Et}$, m, 2H), 1.22 - 1.11 ($CH_2C\mathbf{H}_2CH_3$, m, 2H), 1.04 (*t*Bu, s, 9H), 0.95 (C$\mathbf{H}_{3\ Et}$, t, *J* = 7.3 Hz, 3H), 0.85 ($CH_2CH_2C\mathbf{H}_3$, t, *J* = 7.3 Hz, 3H).

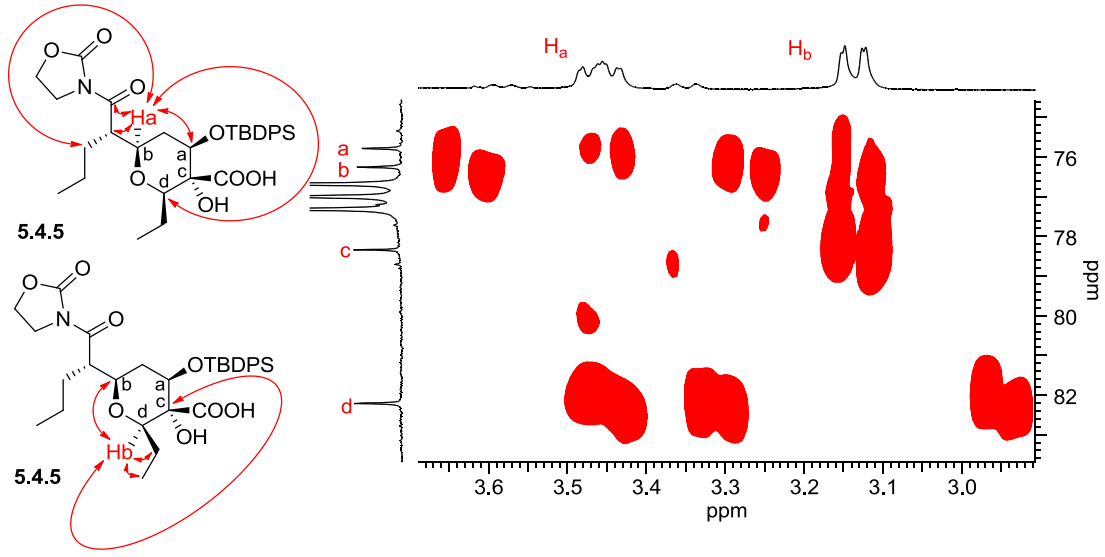
^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9 (**C**OOH), 173.8 (**C**ON), 153.0 (N**C**OO), 136.0 (**C**H Ar *M*), 135.9 (**C**H* Ar *M*), 134.2 (**C** Ar *I*), 132.7 (**C*** Ar *I*), 129.9 (**C**H Ar *P*), 129.6 (**C**H Ar *P*), 127.7 (**C**H Ar *O*), 127.6 (**C**H* Ar *O*), 82.2 (CHO**C**HEt), 78.3 (**C**OHCOOH), 76.3 (**C**HOCHEt), 75.8 (**C**HOTBDPS), 61.7 ($NCH_2C\mathbf{H}_2O$), 46.0 (**C**HCON), 42.7 ($NC\mathbf{H}_2CH_2O$), 34.6 (CHOTBDPS**C**H_2), 30.7 ($\mathbf{C}H_2CH_2CH_3$), 26.7 ($C(C\mathbf{H}_3)_3$), 22.3 (**C**H_2 Et), 20.1 ($CH_2\mathbf{C}H_2CH_3$), 19.3 (**C**Me_3), 14.0 ($CH_2CH_2\mathbf{C}H_3$), 10.6 (**C**H_3 Et).

IR (neat) : 3480, 2960, 2859, 1779, 1699, 1108cm^{-1}.

MS (ES^-)(m/z) : 596 $[M-H]^-$ (100%); MS (ES^+)(m/z) : 620 $[M+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$; Calcd. 620.2651; Found. 620.2650.

HMBC expansion of the cyclised product **5.4.5**



(a) *rac*-lactone **5.5.4 (b)** *rac*-major 6-*exo*-tet cyclisation product **5.5.5** & **(c)** *rac*-minor 6-*exo*-tet cyclisation product **5.5.5m**

3.8 mg ([a]2.5 mg), 4.29 µmol. 7%, *Ratio* (a) : (b) : (c) ~ *4* : *1.1* : *1*.

R_f (ethylacetate / light petroleumether 40/60) (40 : 60) : 0.26

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 - 7.59 ([a]C**H** $_{Ar}$, [b]C**H** $_{Ar}$, m, 5.7 H), 7.54 - 7.33 ([a]C**H** $_{Ar}$, [b]C**H** $_{Ar\ O\ \&\ P}$, m, 8.5 H), 5.20 ([a]COOC**H**, ddd, *J* = 3.5, 6.7, 11.6 Hz, 1.0 H), 4.40 ([a]OC**H**$_2$CH$_2$N, ddd, *J* = 2.6, 7.5, 8.6 Hz, 2.1 H), 4.36 - 4.29 ([a]C**H**CON, [b]NCH$_2$C**H**$_2$O, m, *J* = 2.6, 2.6, 8.9 Hz, 1.6 H), 4.25 - 4.17 ([c]C**H**CON, m, *J* = 3.2 Hz, 0.5 H), 4.17 - 4.10 ([b]C**H**CON, m, *J* = 1.5, 7.6 Hz, 0.4 H), 4.06 - 3.89 ([a]NC**H**$_2$CH$_2$O, [b]NC**H**$_2$CH$_2$O, [b]C**H**OTBDPS, m, 2.8 H), 3.89 - 3.81 ([b]NC**H**$_2$CH$_2$O*, m, *J* = 7.2, 8.5 Hz, 0.5 H), 3.74 ([a]C**H**OTBDPS, d, *J* = 3.2 Hz, 0.9 H), 3.66 - 3.55 ([c]C**H**OCHEt, m, *J* = 9.6 Hz, 0.5 H), 3.53 - 3.44 ([b]C**H**OCHEt, m, *J* = 2.0, 5.6 Hz, 0.3 H), 3.37 ([c]CHOC**H**Et, dd, *J* = 1.6, 10.2 Hz, 0.3 H), 3.16 ([b]CHOC**H**Et, dd, *J* = 2.2, 10.5 Hz, 0.3 H), 2.81 ([a]C**H** $_{epox}$, t, *J* = 6.3 Hz, 1.0 H), 2.35 - 2.25 ([c]CHOTBDPSC**H**$_2$, m, *J* = 8.3 Hz, 0.3 H), 2.20 ([a]CHOTBDPSC**H**$_{2\ Ax}$, t, *J* = 12.9 Hz, 1.1 H), 2.10 - 1.99 ([b]CHOTBDPSC**H**$_{2\ Ax}$, m, 0.4 H), 1.90 - 1.72 ([b]C**H**$_{2\ Et}$, [a]CHOTBDPSC**H**$_{2\ Eq}$, [a]C**H**$_{2\ Et}$, [a]C**H**$_2$CH$_2$CH$_3$, m, *J* = 3.9, 3.9, 14.2 Hz, 3.4 H), 1.70 - 1.40 ([a]C**H**$_{2\ Et}$*, [a]C**H**$_2$CH$_2$CH$_3$*, [b]C**H**$_2$CH$_2$CH$_3$, [b]CHOTBDPSC**H**$_{2\ Eq}$, [b]C**H**$_2$CH$_2$CH$_3$*, m, 5.6 H), 1.38 - 1.21 ([a]CH$_2$C**H**$_2$CH$_3$, [b]C**H**$_{2\ Et}$*, [b]CH$_2$C**H**$_2$CH$_3$, m, *J* = 6.6, 6.6, 9.9, 13.4 Hz, 3.5 H), 1.09 ([a]C**H**$_{3\ TBDPS}$, s, 9.0 H), 1.05 ([b]C**H**$_{3\ TBDPS}$, s, 1.8 H), 1.03 ([c]C**H**$_{3\ TBDPS}$, s, 1.5 H), 0.96 ([a]C**H**$_{3\ Et}$, [b]C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 3.5 H), 0.91 ([a]CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 3.4 H), 0.85 ([b]CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 1 H), 0.84 ([c]CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.2 Hz, 1 H).

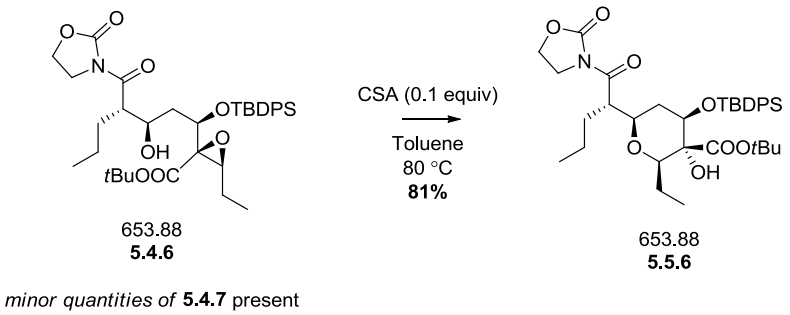
^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1 ([a]**C**ON), 167.5 ([a]**C**OOCH), 136.1 ([a]**C**H Ar *M*), 135.9 ([b]**C**H Ar *M*), 135.9 ([b]**C**H* Ar *M*), 135.8 ([a]**C**H* Ar *M*), 133.4 ([a]**C** Ar *I*), 132.1 ([a]**C*** Ar *I*), 130.0 ([a]**C**H Ar *P*), 129.9 ([a]**C**H* Ar *P*), 127.8 ([a]**C**H Ar *O*), 127.7 ([b]**C**H Ar *O*), 127.7 ([a]**C**H* Ar *O*), 127.6 ([b]**C**H* Ar *O*), 77.2 ([a]COO**C**H), 71.6 ([a]**C**HOTBDPS), 64.6 ([a]**C**H epox), 62.3 ([a]**C** epox), 61.8 ([a]NCH$_2$**C**H$_2$O), 45.8 ([a]**C**HCON), 42.7 ([a]N**C**H$_2$CH$_2$O), 33.5 ([a]CHOTBDPS**C**H$_2$), 30.2 ([a]**C**H$_2$CH$_2$CH$_3$), 26.8 ([a]C(**C**H$_3$)$_3$), 26.8 ([b]C(**C**H$_3$)$_3$), 20.3 ([a]CH$_2$**C**H$_2$CH$_3$), 19.9 ([a]**C**H$_2$ Et), 19.3 ([a]**C**Me$_3$), 14.0 ([a]CH$_2$CH$_2$**C**H$_3$), 10.1 (**C**H$_3$ Et).

IR (neat) : 3049, 2960, 2860, 1777, 1754, 1697 cm^{-1}.

MS (ES$^+$)(m/z) : 602 [[a]M+Na]$^+$ (40%), 620 [[b,c]M + Na]$^+$ (100%), 643 [[a]M+Na+MeCN]$^+$ (63%), 1182 [2[a]M + Na]$^+$ (19%).

HRMS (ES$^+$) : [M+Na]$^+$; Calcd. 602.2548; Found. 602.2545.

CSA promoted 6-*exo*-tet-cyclisation of the aldol product 5.4.6



653.88
5.4.6

minor quantities of **5.4.7** present

653.88
5.5.6

To a solution of aldol product **5.4.6** (70 mg, 0.107 mmol, 1 equiv) in toluene (5 mL) was added CSA (2.5 mg, 10.7 µmol, 0.1 equiv) portionwise. The solution was then stirred and heated to 80 ºC for 16 h before the solvent was evaporated under reduced pressure. The crude was then purified by column chromatography (20% ethylacetate in light petroleumether 40/60) to yield a colourless oil (56 mg, 86.3 µmol. 81%).

R_f (ethylacetate / light petroleumether 40/60) (30 : 70) : 0.59

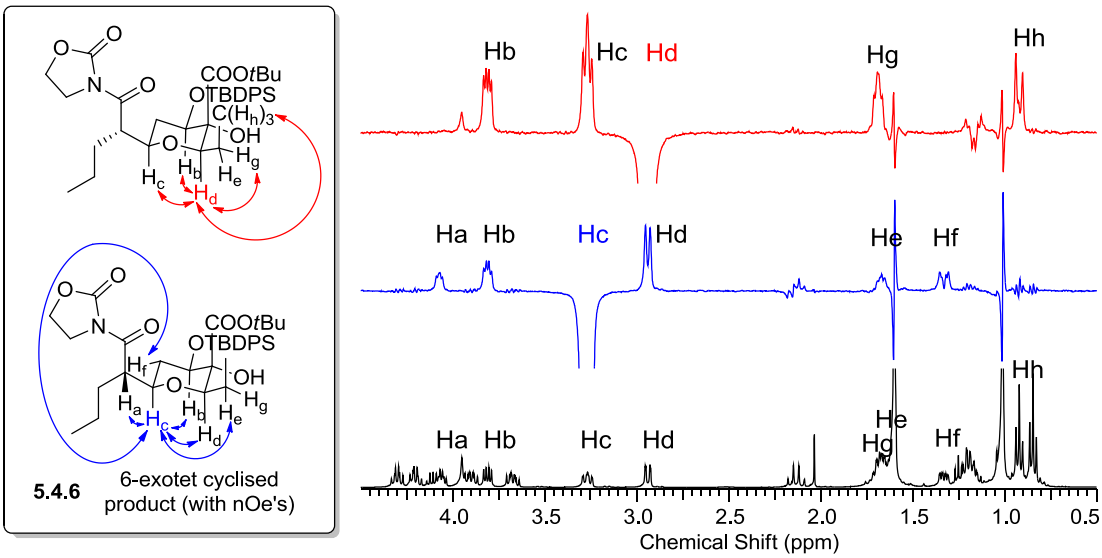
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 - 7.62 (C**H** $_{Ar}$, m, 4H), 7.54 - 7.31 (C**H** $_{Ar}$, m, 6H), 4.32 ($NCH_2C\mathbf{H}_2O$, dt, *J* = 7.1, 8.8 Hz, 1H), 4.22 ($NCH_2C\mathbf{H}_2O^*$, dt, *J* = 6.8, 9.0 Hz, 1H), 4.07 (C**H**CON, dt, *J* = 5.3, 8.2 Hz, 1H), 3.96 - 3.95 (O**H**, br s, 1H), 3.91 ($NC\mathbf{H}_2CH_2O$, ddd, *J* = 7.1, 9.6, 11.0 Hz, 3H), 3.82 (C**H**OTBDPS, dd, *J* = 5.6, 11.6 Hz, 1H), 3.69 ($NC\mathbf{H}_2CH_2O^*$, ddd, *J* = 2.5, 6.6, 8.1 Hz, 1H), 3.28 (C**H**OCHEt, ddd, *J* = 1.5, 8.3, 11.4 Hz, 1H), 2.95 (CHOC**H**Et, dd, *J* = 1.5, 10.6 Hz, 1H), 2.14 (CHOTBDPSC$\mathbf{H}_2$, q, *J* = 11.6 Hz, 1H), 1.78 - 1.63 ($C\mathbf{H}_2CH_2CH_3$, $C\mathbf{H}_{2\ Et}$, m, 3H), 1.61 (COO***t*Bu**, s, 9H), 1.34 (CHOTBDPSC$\mathbf{H}_2^*$, ddd, *J* = 2.0, 5.6, 12.1 Hz, 1H), 1.24 - 1.13 ($CH_2C\mathbf{H}_2CH_3$, $C\mathbf{H}_2^{*}{}_{Et}$, m, 3H), 1.02 (OTBDPS $_{t\mathrm{Bu}}$, s, 9H), 0.93 ($C\mathbf{H}_{3\ Et}$, t, *J* = 7.6 Hz, 2H), 0.86 ($CH_2CH_2C\mathbf{H}_3$, t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.4 (**C**OO*t*Bu), 172.0 (**C**ON), 152.9 (N**C**OO), 136.0 (**C**H Ar *M*), 135.8 (**C**H* Ar *M*), 134.7 (**C** Ar *I*), 132.7 (**C*** Ar *I*), 129.8 (**C**H Ar *P*), 129.4 (**C**H Ar *P*), 127.6 (**C**H Ar *O*), 127.3 (**C**H* Ar *O*), 83.3 (COO**C**Me_3), 82.0 (CHO**C**HEt), 78.0 (**C**OHCOO*t*Bu), 76.2 (**C**HOTBDPS), 75.9 (**C**HOCHEt), 61.4 ($NCH_2C\mathbf{H}_2O$), 47.0 (**C**HCON), 42.6 ($NC\mathbf{H}_2CH_2O$), 35.7 (CHOTBDPS**C**H_2), 31.1 (**C**$H_2CH_2CH_3$), 28.3 (COOC**Me**$_3$), 26.8 (C**Me**$_3$ TBDPS), 22.2 (**C**H_2 Et), 20.3 ($CH_2\mathbf{C}H_2CH_3$), 19.3 (**C**Me_3 TBDPS), 14.1 ($CH_2CH_2\mathbf{C}H_3$), 11.1 (**C**H_3 Et).

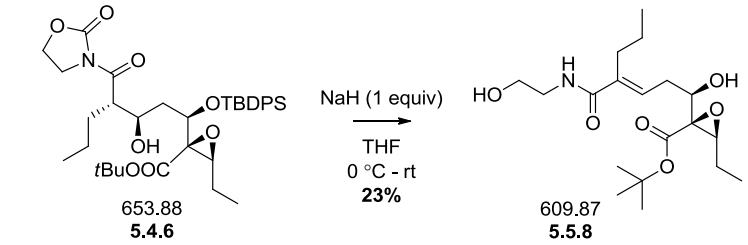
MS (ES^+)(m/z) : 620 $[M\text{-}t\mathrm{Bu}+2H]^+$ (11%), 677 $[M+Na]^+$ (100%).

HRMS (ES$^+$) : $[M+Na]^+$; Calcd. 676.3276; Found. 676.3279.

nOe couplings on the cyclisation product **5.4.5**



NaH promoted elimination of the aldol product 5.4.6



minor quantities of **5.4.7** *present*

To a solution of *rac*-aldol product **5.4.6** (24 mg, 36.1 µmol, 1 equiv) in THF (1 mL) at -78 ºC was added NaH (60% dispersion in mineral oil, 1.5 mg, 36.1 µmol, 1 equiv) under N_2 (g). The reaction was stirred for 1 h at -78 ºC before warming to 0 ºC during 1 h and stirring for a further 1 h at the same temperature. The reaction was then quenched with water (3 mL) before extracting with diethylether (3 × 3 mL). The combined organic extracts were then washed with brine (2 mL), dried over $NaSO_4$ (anh), filtered and solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (40 → 60% ethylacetate in light petroleumether 40/60) to yield a colourless oil (5.1 mg, 8.4 µmol. **23%**).

R_f (ethylacetate / light petroleum 40/60) (40 : 60) : 0.18

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (C**H** $_{Ar}$, ddd, *J* = 1.5, 8.0, 9.7 Hz, 4 H), 7.49 - 7.36 (C**H** $_{Ar}$, m, 6 H), 5.89 (CON**H**, br. s, 1 H), 5.88 (C**H**=C, t, *J* = 7.6 Hz, 1 H), 3.97 (C**H**OTBDPS, t, *J* = 7.1 Hz, 1 H), 3.65 ($NHCH_2C\mathbf{H}_2OH$, t, *J* = 5.1 Hz, 2 H), 3.39 - 3.26 ($NHC\mathbf{H}_2CH_2OH$, m, *J* = 4.5, 10.6, 14.1, 18.7 Hz, 2 H), 3.14 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.48 ($C\mathbf{H}_2CH{=}C$, tdd, *J* = 7.1, 14.1, 18.7 Hz, 2 H), 2.08 - 1.86 ($CH{=}CC\mathbf{H}_2$, m, *J* = 8.6 Hz, 2 H), 1.72 - 1.52 (C**H**$_{2\ Et}$, m, 1 H), 1.48 (C**H**$_{3\ t\text{-}Bu}$, s, 9 H), 1.40 (C**H**$_{2\ Et}$, m, *J* = 7.6 Hz, 1 H), 1.29 - 1.14 ($CH_2C\mathbf{H}_2CH_3$, m, 2 H), 1.09 (C**H**$_{3\ TBDPS}$, s, 9 H), 1.02 (C**H**$_{3\ Et}$, t, *J* = 7.6 Hz, 3 H), 0.76 ($CH_2CH_2C\mathbf{H}_3$, t, *J* = 7.3 Hz, 3 H).

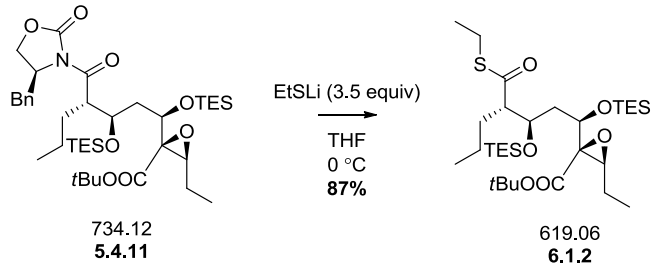
^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.2 (**C**OONH), 167.7 (**C**OO*t*-Bu), 139.2 (CH=**C**CONH), 136.0 (**C**H Ar *M*), 135.9 (**C**H* Ar *M*), 133.8 (**C** Ar *I*), 132.4 (**C** Ar *I*), 130.1 (**C**H Ar *P*), 129.9 (**C**H Ar *P*), 129.1 (**C**H=CCONH), 127.8 (**C**H Ar *O*), 127.7 (**C**H Ar *O*), 82.9 (CMe_3 *t*-Bu), 77.2, 73.9 (**C**HOTBDPS), 66.8 (**C** epox), 63.0 ($NHCH_2\mathbf{C}H_2OH$), 61.9 (C**H** epox), 43.0 ($NH\mathbf{C}H_2CH_2OH$), 33.9 ($\mathbf{C}H_2CH{=}C$), 29.7 (grease), 29.0 ($\mathbf{C}H_2CH_2CH_3$), 28.1 (CH_3 *t*-Bu), 26.9 ($\mathbf{C}H_3$ TBDPS), 22.0 ($CH_2\mathbf{C}H_2CH_3$), 21.7 (CH_2 Et), 19.5 (**C** *t*-Bu TBDPS), 13.9 ($\mathbf{C}H_3$ Et), 10.1 ($CH_2CH_2\mathbf{C}H_3$), 1.0 (silicon grease).

IR (cm^{-1}) : 3397.2, 3071.3, 2961.7, 2931.4, 2858.7, 1745.8, 1724.4 cm^{-1}.

MS (ES^+)(m/z) : 554 $[M\text{-}t\text{-}Bu+2H]^+$ (40%), 611 $[M+H]^+$ (51%), 633 $[M+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$; Calcd.632.3378; Found. 632.3372.

Thioester 6.1.2



734.12
5.4.11

619.06
6.1.2

To a solution of mercaptoethane (80 µL, 1.11 mmol, 4.2 equiv) in THF (1 mL) at -78 ºC under nitrogen was added *n*-BuLi (2.5 M in hexane, 370 µL, 0.925 mmol, 3.5 equiv). The mixture was stirred at -78 ºC for 5 min before warming to 0 ºC. A solution of aldol product **5.4.11** (194 mg, 0.264 mmol, 1 equiv) in THF (1 mL) was then added via cannula, washing with a further portion of THF (0.5 mL). The reaction was then stirred at 0 ºC for 6 h before

quenching with diethylether (10 mL) and $NaHCO_3$ (aq. 4 mL). The aqueous phase was then extracted with diethylether (10 mL) and the combined organic extracts washed with brine (3 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure to yield a crude oil. The crude was then purified by column chromatography (10 → 20% diethylether in light petroleumether 40/60) to give the product as a strong smelling, colourless oil (142 mg, 0.229 mmol. 87%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.60

$[\alpha]_D$: +20.3 (c 0.477 g/100 mL, $CHCl_3$, 27°C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 (C**H**OTESCHCOS, td, *J* = 3.7, 7.7 Hz, 1 H), 3.47 (CC**H**OTES, dd, *J* = 2.4, 9.2 Hz, 1 H), 2.88 (SC**H**$_2$CH$_3$, q, *J* = 7.2 Hz, 3 H), 2.84 (C**H** $_{epox}$, t, *J* = 6.0 Hz, 1 H), 2.72 (C**H**COS, td, *J* = 3.7, 9.9 Hz, 1 H), 2.26 (C**H**$_2$CHOTES, ddd, *J* = 3.4, 9.2, 14.9 Hz, 1 H), 1.76 (C**H**$_2$CHOTES*, C**H**$_2$CH$_2$CH$_3$, m, 2 H), 1.61 (C**H**$_2$CH$_3$ $_{epox}$, dq, *J* = 14.2, 7 Hz, 1 H), 1.51 (C(C**H**$_3$)$_3$, s, 9 H), 1.48 - 1.32 (C**H**$_2$CH$_3$* $_{epox}$, C**H**$_2$CH$_2$CH$_3$*, CH$_2$C**H**$_2$CH$_3$, m, 3 H), 1.29 - 1.20 (CH$_2$C**H**$_2$CH$_3$*, m, 1 H), 1.25 (SCH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 3 H), 1.10 - 0.86 (CH$_2$C**H**$_{3\ TES}$, CH$_2$C**H**$_{3\ epox}$, CH$_2$CH$_2$C**H**$_3$, m, 24 H), 0.78 - 0.54 (C**H**$_2$CH$_3$ $_{TES}$, m, 12 H).

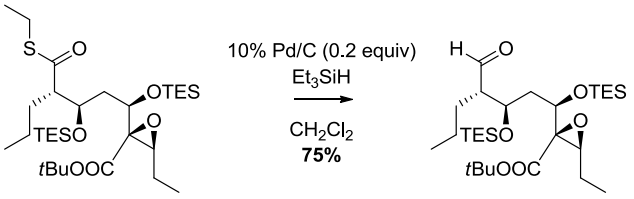
^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.4 (**C**OS), 166.4 (**C**OO*t*Bu), 82.1 (**C**Me$_3$), 74.4 (C**C**HOTESCH$_2$), 71.9 (**C**HOTESCHCOS), 67.3 (**C** epox), 61.3 (**C**H epox), 60.5 (**C**HCOS), 41.9 (**C**CHOTES), 30.4 (**C**H$_2$CH$_2$CH$_3$), 28.0 (C(**C**H$_3$)$_3$), 23.2 (S**C**H$_2$CH$_3$), 21.9 (**C**H$_2$CH$_3$ epox), 20.9 (CH$_2$**C**H$_2$CH$_3$), 14.7 (SCH$_2$**C**H$_3$), 14.1 (CH$_2$**C**H$_3$ epox), 10.1 (CH$_2$CH$_2$**C**H$_3$), 7.0 (CH$_2$**C**H$_3$ TES), 6.9 (CH$_2$**C**H$_3$* TES), 5.4 (**C**H$_2$CH$_3$ TES), 5.0 (**C**H$_2$CH$_3$* TES).

IR (neat) : 2957, 2876, 1749, 1723, 1685 cm^{-1}.

MS (ES$^+$)(m/z) : 641 [M+Na]$^+$ (100%), 585 [M-*t*Bu+H+Na]$^+$ (17%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 641.3698; Found. 641.3721.

Aliphatic fragment aldehyde 6.1.4



619.06
6.1.2

558.94
6.1.4

To a solution of thioester **6.1.2** (110 mg, 178 µmol, 1 equiv) in CH_2Cl_2 (0.5 mL) under nitrogen was added Et_3SiH (85 µL, 533 µmol, 3 equiv) followed by Pd/C (10%, 38 mg, 36 µmol, 0.2 equiv) in one portion. The mixture was stirred for 16 h before filtering through Celite, washing with CH_2Cl_2 (5 mL). The solvent of the filtrate was then evaporated under reduced pressure and the crude residue immediately purified by column chromatography (2 → 4 % diethylether in light petroleumether 40/60) to give a colourless oil (74.4 mg, 0.133 mmol. 75%).

R_f (diethylether / hexane) (20 : 80) : 0.43

$[\alpha]_D$: +39.4 (c 0.304 g/100 mL, $CHCl_3$, 25°C)

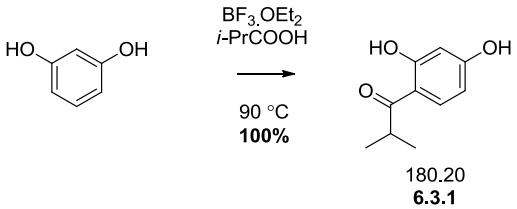
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.81 (C**H**O, d, *J* = 2.0 Hz, 1 H), 4.09 (C**H**OTESCH, td, *J* = 3.7, 7.8 Hz, 1 H), 3.62 (CC**H**OTES, dd, *J* = 3.0, 9.1 Hz, 1 H), 2.86 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.45 (C**H**CHO, dtd, *J* = 2.0, 4.0, 8.1 Hz, 1 H), 2.21 (C**H**$_2$CHOTES, ddd, *J* = 3.8, 9.2, 14.3 Hz, 1 H), 1.80 - 1.56 (C**H**$_2$CHOTES*, C**H**$_2$CH$_3$ $_{epox}$, m, 3 H), 1.49 (C(C**H**$_3$)$_3$, s, 9 H), 1.35 (C**H**$_2$CHOTES*, C**H**$_2$CH$_2$CH$_3$, C**H**$_2$* $_{epox}$, CH$_2$C**H**$_2$CH$_3$, m, 6 H), 1.03 (CH$_2$C**H**$_3$ $_{epox}$, t, *J* = 7.6 Hz, 3 H), 0.98 (C**H**$_3$ $_{TES}$, t, *J* = 7.6 Hz, 9 H), 0.96 (C**H**$_3$* $_{TES}$, t, *J* = 8.1 Hz, 9 H), 0.93 (CH$_2$CH$_2$C**H**$_3$ t, *J* = 7.6 Hz, 3 H), 0.63 (C**H**$_2$ $_{TES}$, m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.0 (**C**HO), 166.5 (**C**OO*t*Bu), 82.3 (**C**Me$_3$), 73.6 (C**C**HOTES), 70.5 (**C**HOTESCH), 67.2 (**C** epox), 61.5 (**C**H epox), 57.7 (**C**HCHO), 41.0 (**C**H$_2$CHOTES), 28.1 (C(**C**H$_3$)$_3$), 26.6 (**C**H$_2$CH$_2$CH$_3$), 21.8 **C**H$_2$CH$_3$ epox), 21.0 (CH$_2$**C**H$_2$CH$_3$), 14.2 (CH$_2$CH$_2$**C**H$_3$), 10.1 (CH$_2$**C**H$_3$ epox), 6.9 (**C**H$_3$ TES), 6.9 (**C**H$_3$* TES), 5.3 (**C**H$_2$ TES), 5.0 (**C**H$_2$* TES).

MS (ES$^+$)(m/z) : 525 [M-*t*Bu+H+Na]$^+$ (48%), 581 [M+Na]$^+$ (100%), 613 [M+Na+MeOH]$^+$ (81%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 581.3664; Found. 581.3667.

4-*i*-Propylresourcinol

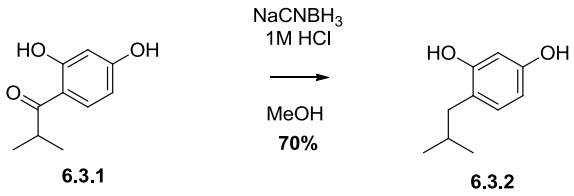


180.20
6.3.1

To a solution of resourcinol (10.0 g; 90.8 mmol; 1 equiv) in borontrifluoride etherate (60 mL, excess) in a 2 neck rbf fitted with a condenser under nitrogen, was added *i*-butyric acid (9.27 mL; 90.8 mmol; 1 equiv). The mixture was heated to 90^{o}C for 1.5 hr before allowing to cool, to rt. The mixture was then added to stirred 10% NaOAc (400 mL; aq) dropwise from a dropping funnel and allowed to stand for 4 hr, before extracting with ethylacetate (3×100 mL). The combined organic extracts were then washed with $NaHCO_3$ (100 mL; sat), dried over $MgSO_4$ (dried), filtered and the solvent removed under reduced pressure. Azeotropically removing AcOH with toluene, the crude oil was then purified by column chromatography (25% diethylether in light petroleum 40/60; R_f = 0.40). The purified product was obtained as oil (16.4 g, 90.8 mmol. 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.06 (s, 1 H), 7.70 (d, *J* = 9.5 Hz, 1 H), 6.42 (dd, *J* = 2.5, 6.8 Hz, 1 H), 6.41 (s, 1 H), 6.59 - 6.03 (*br*s, 1 H), 3.52 (spt, *J* = 6.8 Hz, 1 H), 1.24 (d, *J* = 6.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.3 (C**C**O*i*-Pr), 165.7 (**C**OH $_{Ar}$), 162.6 (**C**OH $_{Ar}$), 132.2 (COHC**C**H $_{Ar}$), 112.6 (**C**CO*i*-Pr), 107.8 (COH**C**HCOH $_{Ar}$), 103.76 (**C**HCOHCHCOH $_{Ar}$), 34.6 (**C**H), 19.4 (**C**H_3).
Data matches literature. [96]

4-*i*-Butylresourcinol



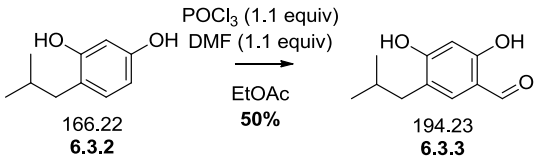
6.3.1 **6.3.2**

To a stirred solution of 1-(2,4-Dihydroxyphenyl)-2-methylpropan-1-one (12.0 g; 66.6 mmol; 1 equiv) in MeOH (180 mL) was added $NaCNBH_3$ (12.6 g; 200 mmol; 3 equiv) in one portion & methyl orange (22 mg; 0.066 mmol; 0.1 mol%). 1M HCl (aq) was added via dropping funnel at a rate to maintain the indicators acidified red colour. The reaction was then stirred for 24 hours, after all effervescence had ceased the reaction mixture was diluted with water (150 mL), before extracting with CH_2Cl_2 (4×50 mL). The combined organic extracts were then scrubbed with brine (100 mL) which was acidified by dropwise addition of 2M HCl, dried over $MgSO_4$ (dried), filtered and solvent removed under reduced pressure. The crude was then purified by column chromatography (30%

diethylether in light petroleum 40/60), TLC (20% diethylether in light petroleum 40/60, R_f = 0.36) to yield a white solid (7.77 g, 147 mmol. 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.92 (C**H** $_{Ar}$, d, *J* = 8.1 Hz, 1 H), 6.37 (C**H** $_{Ar}$, dd, *J* = 2.5, 8.1 Hz, 1 H), 6.33 (C**H** $_{Ar}$, d, *J* = 2.5 Hz, 1 H), 4.84 (O**H**, *br*s, 2 H), 2.40 (C**H**$_2$ $_{i\text{-Bu}}$, d, *J* = 7.6 Hz, 2 H), 1.93 - 1.79 (C**H** $_{i\text{-Bu}}$, tspt, *J* = 6.8 Hz, 2 H), 0.93 (C**H**$_3$ $_{i\text{-Bu}}$, d, *J* = 6.6 Hz, 6 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.6 (**C**OH $_{Ar}$), 154.4 (**C**OH $_{Ar}$), 131.8 (COHC**C**H $_{Ar}$), 119.8 (**C***i*-Bu $_{Ar}$), 107.5 (**C**HCOHCHCOH), 102.8 (COH**C**HCOH $_{Ar}$), 38.6 (**C**H_2) 29.0 (**C**H), 22.4 (**C**H_3).
Data matches literature. [97]

2,4-Dihydroxy-5-*iso*butylbenzaldehyde



To a solution of 4-*i*-butylresorcinol (500 mg, 3.01 mmol, 1 equiv) in ethylacetate (6 mL) was added DMF (256 µL, 3.31 mmol, 1.1 equiv). Phosphorous oxychloride (308 µL, 3.31 mmol, 1.1 equiv) was then added dropwise over 30 min before stirring the reaction for a further 20 h. A cream precipitate formed after a few hours. After the reaction duration the precipitate was filtered off and washed with ethylacetate (2×5 mL), suspended in water (20 mL) and refluxed for 5 min. The mixture was then extracted with ethylacetate (3×15 mL) and scrubbed with brine (2×15 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure to yield a cream solid (291 mg, 1.50 mmol. 50%).

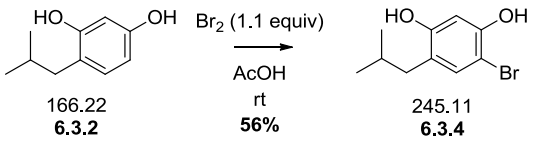
^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.25 (O**H** $_{O}$, s, 1 H), 9.69 (C**H**O, s, 1 H), 7.23 (C**H** $_{Ar\ O}$, s, 1 H), 6.35 (C**H** $_{Ar\ M}$, s, 1 H), 6.20 (O**H** $_{P}$, s, 1 H), 2.45 (C**H**$_2$CHMe$_2$, d, *J* = 7.6 Hz, 2 H), 1.92 (CH_2C**H**Me$_2$, tspt, *J* = 7.1, 7.6 Hz, 1 H), 0.94 (CH_2CH(C**H**$_3$)$_2$, d, *J* = 7.1 Hz, 44 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.6 (**C**HO), 162.5 (**C**OH *O*), 162.0 (**C**OH *P*), 136.5 (**C**H *O*), 121.0 (**C**CH_2CHMe$_2$), 115.1 (**C**CHO), 102.9 (**C**H *M*), 38.3 (**C**H_2CHMe$_2$), 28.6 (CH_2**C**HMe$_2$), 22.3 (CH_2CH(**C**H_3)$_2$).

IR (neat) : 3181, 2955, 2867, 1606, 1505 cm^{-1}.

MS (ES^-)(m/z) : 193 $[M-H]^-$ (100%).

HRMS (ES^-) : $[M-H]^-$ Calcd. 193.0871; Found. 193.0871.

4-Bromo-6-*iso*butylbenzene-1,3-diol



To a solution of 4-*i*-butylresorcinol (1.00 g, 6.02 mmol, 1 equiv) in acetic acid (10 mL) under nitrogen was added bromine (339 µL, 6.62 mmol, 1.1 equiv) the reaction was then stirred for 4 h before pouring into $NaHCO_3$ (sat. 50 mL) very carefully. After the vigorous effervescence had ceased the mixture was extracted with diethylether (30 mL) and the organic layre washed with further portions of $NaHCO_3$ (3×50 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure to yield a brown oil which was purified by column chromatography (20% ethylacetate in light petroleumether 40/60) to give an oil (829 mg, 3.38 mmol. 56%).

R_f (ethylacetate / light petroleumether 40/60) (20 : 80) : 0.18

^1H NMR (400 MHz, $CDCl_3$) δ = 7.13 (C**H** $_{5\text{-Ar}}$, s, 1H), 6.50 (C**H** $_{2\text{-Ar}}$, s, 1H), 5.38 (O**H**, br. s., 1H), 5.06 (O**H***, br. s., 1H), 2.38 (C**H**$_2$, d, *J* = 7.1 Hz, 2H), 1.96 - 1.80 (C**H**, tspt, *J* = 6.6 Hz, 1H), 0.92 (C**H**$_3$, d, *J* = 6.6 Hz, 6H).

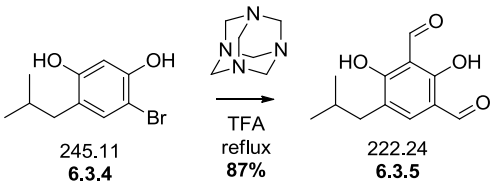
^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.3 (**C**OH), 150.9 (**C**OH), 133.2 (**C**H 2-Ar), 121.9 (**C**Br), 103.2 (**C**H 4-Ar), 100.4 (**C***i*Bu), 38.4 (**C**H_2), 28.9 (**C**H), 22.3 (**C**H_3).

IR (neat) : 3415, 2954, 2867, 1613, 1503 cm^{-1}.

MS (ES^-)(m/z) : 243 $[M-H]^-$ (Br^{79}, 100%), 245 $[M-H]^-$ (Br^{81}, 97%).

HRMS (ES^-) : $[M-H]^-$(Br^{79}); Calcd. 243.0026; Found. 243.0030.

2,4-Dihydroxy-5-isobutylisophthalaldehyde



To a solution of 4-bromo-6-*iso*butylbenzene-1,3-diol (500 mg, 2.04 mmol, 1 equiv) in TFA (10 mL) was added hexamine (1.57 g, 11.2 mmol, 5.5 equiv) portionwise. The mixture was then refluxed for 20 h. The reaction was then quenched with water (60 mL) slowly before extracting with ethyl acetate (3×50 mL). The combined organic extracts were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude solid was then purified by column chromatography (17.5% ethylacetate in light petroleumether 40/60) to yield a white solid (483 mg, 1.77 mmol. 87%).

R_f (ethylacetate / light petroleumether 40/60) (20 : 80) : 0.66

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.94 (O**H**, s, 1H), 12.37 (O**H**, s, 1H), 10.40 (C**H**O, s, 1H), 9.70 (C**H**O, s, 1H), 7.45 (C**H** $_{Ar}$, s, 1H), 2.46 (C**H**$_2$, d, *J* = 7.1 Hz, 2H), 2.01 - 1.86 (C**H**Me_2, tspt, *J* = 6.7 Hz, 1H), 0.93 (CH**Me**$_2$ d, *J* = 6.6 Hz, 6H).

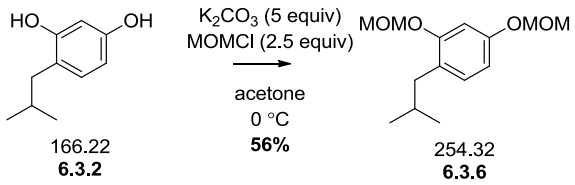
^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.5 (**C**HO), 193.7 (**C**HO*), 168.1 (**C**OH Ar), 165.8 (**C**OH Ar), 141.7 (**C**H Ar), 122.5 (**C**CHO Ar), 112.7 (**C**CHO Ar), 108.8 (**C***i*Bu Ar), 37.5 (**C**H_2), 28.2 (**C**HMe_2), 22.3 (CH**Me**$_2$).

IR (neat) : 2959, 2871, 1630, 1440, 1281cm^{-1}

MS (ES$^-$)(m/z) : 221 [M-H]$^-$ (100%).

HRMS (ES$^-$) : [M-H]$^-$, Calcd. 221.0819; Found. 221.0820.

1-*iso*Butyl-2,4-bis(methoxymethoxy)benzene



To a solution of 4-*i*-butylresorcinol (1.00 g, 6.02 mmol, 1 equiv) in DMF (20 mL) was added DIPEA (2.31 mL, 24.08 mmol, 4 equiv) dropwise, followed by MOMCl (1.83 mL,

24.1 mmol, 4 equiv) dropwise at rt. The reaction was stirred for 48 h after which the mixture was quenched by portioning between water (20 mL) and diethylether (10 mL). After separating the layers the aqueous phase was extracted with further portions of diethylether (10 mL). The combined extracts were then washed with water (2×10 mL), 5% NaOH (2×10 mL, aq), water (2×10 mL), brine (2×10 mL) sequentially. The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. To yield a yellow oil with some solid, the crude mixture was then purified by column chromatography (20% diethylether in light petroleumether 40/60) to give a colourless oil (856 mg, 3.37 mmol. 56%).

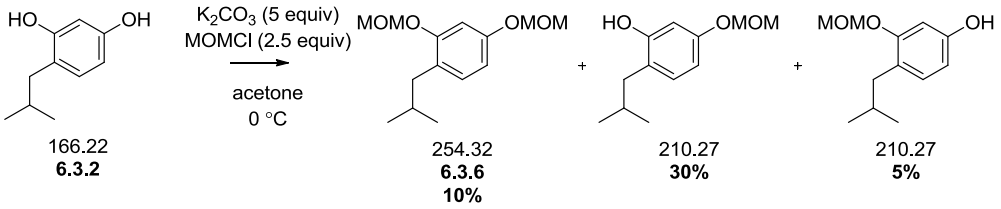
1-*iso*Butyl-2,4-bis(methoxymethoxy)benzene

R_f (diethylether / light petroleumether 40/60) (40 : 60) : 0.80

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00 (C**H** $_{Ar\ 6}$, d, *J* = 8.1 Hz, 1H), 6.79 (C**H** $_{Ar\ 3}$, d, *J* = 2.5 Hz, 1H), 6.64 (C**H** $_{Ar\ 4}$,dd, *J* = 2.5, 8.1 Hz, 1H), 5.17 (C**H**$_{2\ MOM}$, s, 2H), 5.15 (C**H**$_{2\ MOM}$, s, 2H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 2.45 (C**H**$_{2\ i\mathrm{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.88 (C**H** $_{i\mathrm{Bu}}$, tspt, *J* = 7.1, 6.7 Hz, 1H), 0.91 (C**H**$_{3\ i\mathrm{Bu}}$, d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.4 (**C**OMOM 4), 156.0 (**C**OMOM 2), 131.1 (**C**H Ar 6), 124.3 (**C** Ar 1), 108.4 (**C**H Ar 5), 103.3 (**C**H Ar 3), 94.7 (**C**H_2 MOM 4), 94.5 (**C**H_2 MOM 2), 56.0 (**C**H_3 MOM), 38.9 (**C**H_2 *i*Bu), 29.0 (**C**H *i*Bu), 22.5 (**C**H_3 *i*Bu).

Data matches literature. [21]



To a solution of 4-*i*-butylresorcinol (515 mg, 3.10 mmol, 1 equiv) in acetone (HPLC grade, 5 mL) was added K_2CO_3 (anh. 2.14 g, 15.5 mmol, 5 equiv). The mixture was then reduced in volume *en vacuo* and dried on high vacuum (red powder). The solid was then redissolved in acetone under nitrogen (5 mL) and cooled to 0 ºC. MOMCl was then added in portions over 3 h (≈ 30 µL portions, 270 µL, 3.35 mmol, 1.08 equiv). The reaction was then quenched with water (20 mL) and diethylether (15 mL). $KHSO_4$ (10% w/w) was then added to adjust the pH (≈ 4). The layers were then separated and the aqueous phase

extracted with diethylether (2 × 15 mL). The combined organic extracts were then scrubbed with brine (20 mL) dried over Na_2SO_4 (anh), filtered and the solvent removed under reduced pressure. The crude was then purified by column chromatography (10% → 50% diethylether in light petroleumether 40/60) to yield 1-*iso*butyl-2,4-bis(methoxymethoxy)benzene (79.1 mg, 0.311 mmol. 10%), 2-*iso*Butyl-5-(methoxymethoxy)phenol (199 mg, 0.944 mol. 30%) and 4-*iso*Butyl-3-(methoxymethoxy)phenol (31.2 mg, 0.148 mmol. 5%).

1-*iso*Butyl-2,4-bis(methoxymethoxy)benzene

R_f (diethylether / light petroleumether 40/60) (40 : 60) : 0.80

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00 (C**H** $_{Ar\,6}$, d, *J* = 8.1 Hz, 1H), 6.79 (C**H** $_{Ar\,3}$, d, *J* = 2.5 Hz, 1H), 6.64 (C**H** $_{Ar\,4}$,dd, *J* = 2.5, 8.1 Hz, 1H), 5.17 (C**H**$_{2\ MOM}$, s, 2H), 5.15 (C**H**$_{2\ MOM}$, s, 2H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 2.45 (C**H**$_{2\ i\mathrm{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.88 (C**H** $_{i\mathrm{Bu}}$, tspt, *J* = 7.1, 6.7 Hz, 1H), 0.91 (C**H**$_{3\ i\mathrm{Bu}}$, d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.4 (**C**OMOM 4), 156.0 (**C**OMOM 2), 131.1 (**C**H Ar 6), 124.3 (**C** Ar 1), 108.4 (**C**H Ar 5), 103.3 (**C**H Ar 3), 94.7 (**C**H_2 MOM 4), 94.5 (**C**H_2 MOM 2), 56.0 (**C**H_3 MOM), 38.9 (**C**H_2 *i*Bu), 29.0 (**C**H *i*Bu), 22.5 (**C**H_3 *i*Bu).

Data matches literature. [21]

2-*iso*Butyl-5-(methoxymethoxy)phenol

R_f (diethylether / light petroluemether 40/60) (40 : 60) : 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (C**H** $_{Ar\,3}$, d, *J* = 8.1 Hz, 1H), 6.57 (C**H** $_{Ar\,4}$, dd, *J* = 2.3, 8.3 Hz, 1H), 6.53 (C**H** $_{Ar\,6}$, d, *J* = 2.0 Hz, 1H), 5.14 (C**H**$_{2\ MOM}$, s, 2H), 4.97 (O**H**, s, 1H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 2.42 (C**H**$_{2\ i\mathrm{Bu},}$ d, *J* = 7.1 Hz, 2H), 1.89 (C**H** $_{i\mathrm{Bu},}$ tspt, *J* = 7.1, 6.6 Hz, 1H), 0.93 (C**H**$_{3\ i\mathrm{Bu},}$ d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.4 (**C**OMOM 5), 154.3 (**C**OH 1), 131.6 (**C**H Ar 3), 121.1 (**C** Ar 2), 108.3 (**C**H Ar 4), 103.7 (**C**H Ar 6), 94.5 (**C**H_2 MOM), 55.9 (**C**H_3 MOM), 38.6 (**C**H_2 *i*Bu), 28.9 (**C**H *i*Bu), 22.4 (**C**H_3 *i*Bu).

IR (neat) : 3395, 2954, 2868, 1616, 1595cm^{-1}

MS (ES^-)(m/z) : 165 $[M\text{-}MOM]^-$ (15%), 209 $[M\text{-}H]^-$ (38%), 249 $[?]^-$ (100%).

HRMS (ES^-) : $[M\text{-}H]^-$ Calcd. 209.1183; Found. 209.1183.

4-*iso*Butyl-3-(methoxymethoxy)phenol

R_f (diethylether / light petroleum 40/60) (40 : 60) : 0.40

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.94 (C**H** $_{Ar\ 5}$,d, *J* = 8.1 Hz, 1H), 6.62 (C**H** $_{Ar\ 2}$, d, *J* = 2.5 Hz, 1H), 6.42 (C**H** $_{Ar\ 6}$, dd, *J* = 2.5, 8.1 Hz, 1H), 5.16 (C**H**$_{2\ MOM}$, s, 2H), 5.19 (O**H**, s, 1H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 2.43 (C**H**$_{2\ iBu,}$ d, *J* = 7.1 Hz, 2H), 1.87 (C**H** $_{iBu,}$ tspt, *J* = 7.1, 6.6 Hz, 1H), 0.90 (C**H**$_{3\ iBu,}$ d, *J* = 6.6 Hz, 6H).

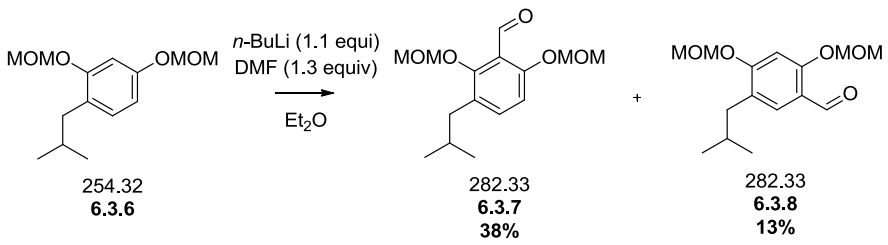
^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.0 (**C**OMOM 3), 154.6 (**C**OH), 131.4 (**C** Ar 5), 122.9 (**C** Ar 4), 108.0 (**C**H Ar 6), 101.9 (**C**H Ar 2), 94.3 (**C**H_2 MOM), 55.9 (**C**H_3 MOM), 38.8 (**C**H_2 *i*Bu), 29.1 (**C**H *i*Bu), 22.4 (**C**H_3 *i*Bu).

IR (neat) : 3379, 2954, 2867, 1614, 1601cm^{-1}

MS (ES^-)(m/z) : 165 $[M\text{-}MOM]^-$ (3%), 209 $[M\text{-}H]^-$ (77%), 249 (100%).

HRMS (ES^-) : $[M\text{-}H]^-$ Calcd. 209.1183; Found. 209.1183.

3-*iso*Butyl-2,6-bis(methoxymethoxy)benzaldehyde



254.32 **6.3.6**

282.33 **6.3.7** **38%**

282.33 **6.3.8** **13%**

To a solution of 1-*iso*butyl-2,4-bis(methoxymethoxy)benzene (450 mg, 1.77 mmol, 1 equiv) in diethylether (5 mL) was added *t*-butyl lithium (1.217 mL, 1.947 mmol, 1.1 equiv, 1.6 M in pentane) dropwise. The solution was then refluxed for 1 h before adding DMF (181 µL, 2.30 mmol, 1.3 equiv) at rt. The reaction was then stirred for 1 hr after which the mixture was diluted with diethylether (10 mL) and quenched with water. The mixture was then washed sequentially with NH_4Cl (sat. 2×10 mL), NaOH (aq. 2.5% w/w, 2×5 mL), water (2×5 mL) and brine (5 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude oil was purified by column chromatography (10% ethylacetate in light petroleum 40/60) and then HPLC (20% ethylacetate in hexane) to yield 3-*iso*butyl-2,6-bis(methoxymethoxy)benzaldehyde as a colourless oil (188 mg, 0.664 mmol. 38%) and 5-*iso*butyl-2,4-bis(methoxymethoxy)benzaldehyde was also recovered as a colourless oil (67.3 mg, 0.238 mmol. 13%).

3-*iso*Butyl-2,6-bis(methoxymethoxy)benzaldehyde

R_f (ethylacetate / light petroleumether 40/60) (10 : 90) : 0.20

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.47 (C**H**O, s, 1H), 7.30 (C**H** $_{Ar\ 4}$, d, *J* = 8.6 Hz, 1H), 6.93 (C**H** $_{Ar\ 5}$, d, *J* = 8.6 Hz, 1H), 5.26 (C**H**$_{2\ MOM\ 6}$, s, 2H), 5.05 (C**H**$_{2\ MOM\ 2}$, s, 2H), 3.59 (C**H**$_{3\ MOM\ 2}$, s, 3H), 3.52 (C**H**$_{3\ MOM\ 6}$, s, 3H), 2.52 (C**H**$_{2\ i\text{-}Bu}$, d, *J* = 7.1 Hz, 2H), 1.94 (C**H** $_{i\text{-}Bu}$, spt, *J* = 7.1 Hz, 1H), 0.91 (C**H**$_{3\ i\text{-}Bu}$, d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.6 (**C**HO), 158.6 (**C**OMOM 6), 157.3 (**C**OMOM 2), 137.1 (**C**H Ar 4), 129.2 (**C** Ar 3), 119.3 (**C** Ar 1), 110.6 (**C**H Ar 5), 101.9 (**C**H_2 MOM 2), 95.0 (**C**H_2 MOM 6), 57.5 (**C**H_3 MOM 2), 56.5 (**C**H_3 MOM 6), 38.9 (**C**H_2 *i*Bu), 28.9 (**C**H *i*Bu), 22.4 (**C**H_3 *i*Bu).

IR (neat) : 2954, 2868, 1688, 1591, 1475cm^{-1}

MS (ES^+)(m/z) : 305 $[M+Na]^+$ (17%), 346 $[M+Na+MeCN]^+$ (100%), 525 (86%).

Data matches literature. [21]

5-*iso*Butyl-2,4-bis(methoxymethoxy)benzaldehyde

R_f (ethylacetate / light petroleumether 40/60) (10 : 90) : 0.15

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.35 (C**H**O, s, 1H), 7.61 (C**H** $_{Ar\ 6}$, s, 1H), 6.89 (C**H** $_{Ar\ 3}$, s, 1H), 5.27 (C**H**$_{2\ MOM}$, s, 2H), 5.25 (C**H**$_{2\ MOM}$, s, 2H), 3.54 (C**H**$_{3\ MOM}$, s, 3H), 3.49 (C**H**$_{3\ MOM}$, s, 3H), 2.46 (C**H**$_{2\ i\text{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.89 (C**H** $_{i\text{Bu}}$, tspt, *J* = 7.1, 6.6 Hz, 1H), 0.90 (C**H**$_{3\ i\text{Bu}}$, d, *J* = 6.6 Hz, 6H).

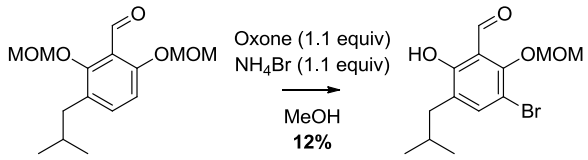
^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.6 (**C**HO), 161.5 (**C**OMOM 4), 159.9 (**C**OMOM 2), 130.3 (**C**H Ar 6), 124.8 (**C**H Ar 5), 119.4 (**C** Ar 1), 100.3 (**C**H Ar 3), 95.0 (**C**H_2 MOM 2), 94.2 (**C**H_2 MOM 4), 56.6 (**C**H_3 MOM 2), 56.4 (**C**H_3 MOM 4), 38.6 (**C**H_2 *i*Bu), 28.7 (**C**H *i*Bu), 22.4 (**C**H_3 *i*Bu).

IR (neat) : 2955, 2868, 1677, 1604, 1492 cm^{-1}

MS (ES^+)(m/z) : 305 $[M+Na]^+$ (17%), 346 $[M+Na+MeCN]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 305.1359; Found. 305.136.

3-Bromo-6-hydroxy-5-*iso*butyl-2-(methoxymethoxy)benzaldehyde



282.33 **6.3.7** 317.18 **6.3.9**

To a solution of 3-*iso*butyl-2,6-bis(methoxymethoxy)benzaldehyde (100 mg, 0.354 mmol, 1 equiv) in MeOH (3 mL) was added NH_4Br (38.1 mg, 0.389 mmol, 1.1 equiv) in one portion, oxone (120 g, 0.389 mmol, 1.1 equiv) was then added in one portion and the reaction stirred for 3 h. The reaction was then diluted with diethylether (5 mL) and filtered through a cotton wool plug, evaporating the solvent under reduced pressure. The crude was then purified by column chromatography (10 → 20% diethylether in light petroleumether 40/60) to yield a colourless oil (14 mg, 44.1 µmol. 12%). The fully deprotected product, 3-bromo-2,6-dihydroxy-5-isobutylbenzaldehyde, was also recovered but was unstable and rapidly decomposed (35 mg, 128 µmol. 36%).

R_f (diethylether / light petroleum 40/60) (25 : 75) : 0.63

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.00 (O**H**, s, 1H), 10.26 (C**H**O, s, 1H), 7.49 (C**H** $_{Ar}$, s, 1H), 5.19 (C$\mathbf{H}_{2\ MOM}$, s, 2H), 3.61 ($CH_{3\ MOM}$, s, 3H), 2.46 (C$\mathbf{H}_{2\ i\mathrm{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.94 (C**H** $_{i\mathrm{Bu}}$, tspt, *J* = 7.1 Hz, 1H), 0.92 (C$\mathbf{H}_{3\ i\mathrm{Bu}}$, d, *J* = 7.1 Hz, 6H).

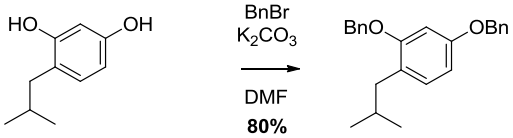
^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.6 (**C**HO), 160.4 (**C**OH), 155.6 (**C** OMOM 2), 141.6 (**C**H Ar 4), 128.7 (**C** Ar 5), 116.1 (**C** Ar 3), 104.4 (**C** Ar 1), 100.9 (**C**H_2 MOM), 58.3 (**C**H_3 MOM), 37.8 (**C**H_2 *i*Bu), 28.3 (**C**H *i*Bu), 22.3 (**C**H_3 *i*Bu).

IR (neat) : 2955, 2928, 1642, 1609, 1452cm^{-1}.

MS (ES^-)(m/z) : 314 $[M+NH_3-H_2O-H]^-$ (^{79}Br, 93%), 316 $[M+NH_3-H_2O-H]^-$ (^{81}Br, 100%).

HRMS (ES^-) : $[M+NH_3-H_2O-H]^-$ Calcd. 314.0397; Found. 314.0397.

***O,O*-Dibenzyl-4-*i*-butylresourcinol**



166.22 **6.3.2** 346.46 **6.3.10**

To a solution of 4-*i*-butylresourcinol (340 mg, 2.05 mmol, 1 equiv) in DMF (anh) (10 mL) was added potassium carbonate (1.41g, 10.2 mmol, 5 equiv) in one portion, under nitrogen. Benzyl bromide (1.22 mL, 10.2 mmol, 5 equiv) was then added dropwise to the mixture, the reaction was then stirred monitoring by TLC. After the reaction had completed it was quenched with 1N HCl (30 mL), caution was taken as the reaction effervesced **VIOLENTLY** when the quench was not controlled appropriately by slow addition. After effervescence had ceased, the mixture was extracted with diethylether (3×10 mL). The combined organic extracts were the dried over Na_2SO_4 (anh) and filtered, removing the solvent *en vacuo*. The crude oil was then purified by column chromatography (2% diethylether in light petroleum 40/60), to yield a pale oil (567 mg, 1.64 mmol. 80%).

R_f (Diethylether / Light Petroleum 40/60) (2 : 98) : 0.30

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 - 7.30 (C**H** $_{Bn}$, m, 10H), 7.04 (C**H** $_{Ar}$, d, *J* = 8.1 Hz, 1H), 6.62 (C**H** $_{Ar}$, d, *J* = 2.5 Hz, 1H), 6.54 (C**H** $_{Ar}$, dd, *J* = 2.3, 8.3 Hz, 1H), 5.06 (C**H**$_2$ $_{OBn}$, s, 2H), 5.05 (C**H**$_2$ $_{OBn}$, s, 2H), 2.52 (C**H**$_2$ $_{i\text{-}Bu}$, d, *J* = 7.1 Hz, 2H), 1.96 (C**H** $_{i\text{-}Bu}$, quind, *J* = 6.7, 13.5 Hz, 1H), 0.93 (C**H**$_3$ $_{i\text{-}Bu}$, d, *J* = 6.6 Hz, 6H).

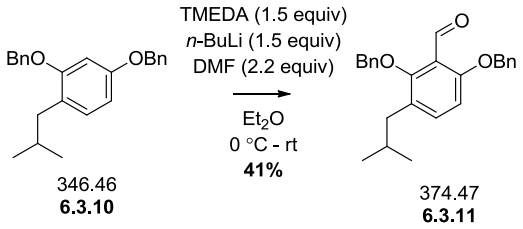
^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.1 (**C**OH $_{Ar}$), 157.5 (**C**OH $_{Ar}$), 137.4 (**C** $_{Bn}$), 137.2 (**C** $_{Bn}$), 131.0 (**C**H $_{O\ Ar}$), 128.6 (**C**H $_{Bn}$), 128.5 (**C**H $_{Bn}$), 127.9 (**C**H $_{Bn}$), 127.6 (**C**H $_{Bn}$), 127.6 (**C**H $_{Bn}$), 126.9 (**C**H $_{Bn}$), 123.3 (**C***i*Bu), 105.1 (**C**H $_{M\ Ar}$), 100.5 (COH**C**HCOH $_{Ar}$), 70.2 (**C**H$_2$ $_{OBn}$), 69.8 (**C**H$_2$ $_{OBn}$), 39.0 (**C**H$_2$ $_{i\text{-}Bu}$), 28.9 (**C**H $_{i\text{-}Bu}$), 22.6 (**C**H$_3$ $_{i\text{-}Bu}$).

IR (neat) : 3064, 3032, 2952, 2926, 2866, 1609 cm^{-1}.

MS (EI)(m/z) : 346 $[M]^+$ (36%), 303 $[M\text{-}Pr]^+$ (35%), 255 $[M\text{-}Bn]^+$ (4%), 91.1 $[Bn]^+$.

HRMS (ES^+) : $[M+H]^+$ Calcd. 347.2006; Found. 347.2006.

2,6-Bis(benzyloxy)-3-*iso*butylbenzaldehyde



346.46
6.3.10

374.47
6.3.11

To a solution of *O,O*-dibenzyl-4-*i*-butylresourcinol (610 mg, 1.567 mmol, 1 equiv) in diethylether (5 mL) was added TMEDA (440 µL, 2. 94 mmol, 1.5 equiv) under nitrogen. The solution was cooled to 0 ºC, then *n*-butyl lithium was added dropwise and the reaction was stirred for an hour at the same temperature. The reaction became an orange colour and then a dark emerald green. DMF (267 µL, 3.45 mmol, 2.2 equiv) was added dropwise and the reaction stirred for a further 2 h. The reaction was then quenched with water (20 mL) and extracted with diethylether (3×20 mL). The combined organic extracts were then scrubbed with brine (20 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (5% diethylether in light petroleumether 40/60) to yield a colourless oil (268 mg, 0.65 mmol. 41%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.50

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.60 (C**H**O, s, 1H), 7.56 - 7.29 (C**H** $_{Ar\ \&\ Bn}$, m, 12H), 6.80 (C**H** $_{Ar\ 5}$, d, *J* = 8.6 Hz, 1H), 5.19 (C**H**$_{2\ Bn}$, s, 2H), 4.95 (C**H**$_{2\ Bn}$, s, 2H), 2.42 (C**H**$_{2\ i\mathrm{Bu}}$, d, *J* = 7.6 Hz, 2H), 1.91 (C**H** $_{i\mathrm{Bu}}$, tspt, *J* = 7.6, 6.6 Hz, 1H), 0.87 (C**H**$_{3\ i\mathrm{Bu}}$, d, *J* = 6.6 Hz, 6H).

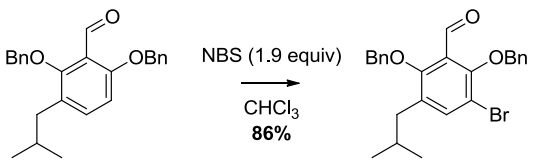
^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.6 (**C**HO), 160.0 (**C**OBn), 158.8 (**C**OBn*), 137.1 (**C**H Ar *P*), 136.3 (**C** Bn), 128.6 (**C**H Bn), 128.5 (**C**H Bn), 128.2 (**C**H Bn), 128.1 (**C**H Bn), 127.1 (**C**H Bn), 119.4 (**C** Ar *I*), 108.5 (**C**H Ar *M*), 77.3 (**C**H_2 Bn), 70.8 (**C**H_2 Bn), 38.6 (**C**H_2 *i*Bu), 29.1 (**C**H *i*Bu), 22.4 (**C**H_3 *i*Bu).

IR (neat) : 3032, 2954, 2866, 1685, 1591cm^{-1}

MS (CI)(m/z) : 91 $[Bn]^+$ (100%), 257 $[M\text{-}Bn+2H\text{-}CO]^+$ (2%), 347 $[M\text{-}CO+H]^+$ (4%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 397.1774; Found. 397.1771.

2,6-Bis(benzyloxy)-3-bromo-5-*iso*butylbenzaldehyde



374.47 **6.3.11** 453.37 **6.3.12**

To a solution of 2,6-bis(benzyloxy)-3-*iso*butylbenzaldehyde (240 mg, 0.641 mmol, 1 equiv) in $CHCl_3$ (10 mL) at 0 ºC was added NBS (219 mg, 1.23 mmol, 1.9 equiv) in one portion under nitrogen. The reaction was allowed to warm to rt and was stirred for 62 h before quenching with water (10 mL). The layers were separated and the aqueous layer extracted with further portions of chloroform (10 mL), the combined organic phases were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was purified by column chromatography (5% diethylether in light petroleumether) to yield a yellow oil (250 mg, 0.551 mmol. 86%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.28 (C**H**O, s, 1H), 7.64 (C**H** $_{Ar}$, s, 1H), 7.58 - 7.52 (C**H** $_{Bn\ P}$, m, 2H), 7.49 - 7.34 (C**H** $_{Bn\ O\ \&\ M}$, m, 8H), 5.09 (C**H**$_{2\ Bn}$, s, 2H), 4.91 (C**H**$_{2\ Bn}$, s, 2H), 2.45 (C**H**$_{2\ i\mathrm{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.94 (C**H** $_{i\mathrm{Bu}}$, quind, *J* = 6.9, 13.5 Hz, 1H), 0.91 (C**H**$_{3\ i\mathrm{Bu}}$, d, *J* = 6.6 Hz, 6H).

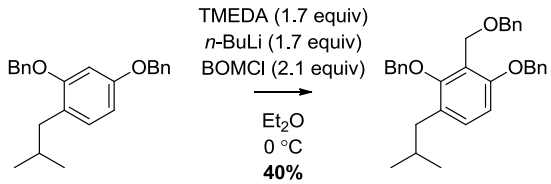
^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0 (**C**HO), 158.1 (**C**OBn Ar 6), 155.8 (**C**OBn Ar 6), 139.9 (C**H** Ar 4), 136.4 (**C** Bn 6), 135.8 (**C** Bn 2), 134.3 (**C** Ar 5), 128.8 (**C**H Bn), 128.6 (**C**H Bn), 128.6 (**C**H Bn), 128.4 (**C**H Bn), 128.2 (**C**H Bn), 125.6 (**C** Ar 1), 113.2 (**C** Ar 3), 77.9 (**C**H_2 Bn 6), 77.1 (**C**H_2 Bn 2), 38.5 (**C**H_2 *i*Bu), 29.1 (**C**H_3 *i*Bu).

IR (neat) : 3032, 2956, 2868, 1695, 1573cm^{-1}

MS (ES^+)(m/z) : 475 $[M+Na]^+$ (^{79}Br, 5%), 477 $[M+Na]^+$ (^{81}Br, 5%), 516 $[M+Na+MeCN]^+$ (^{79}Br, 5%), 518 $[M+Na+MeCN]^+$ (^{81}Br, 5%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 475.0879; Found. 475.0879.

O,O-Dibenzyl-2-((benzyloxy)methyl)-4-*i*-butylresourcinol



346.46
6.3.10

466.61
6.3.13

To a solution of (((2-((benzyloxy)methyl)-4-*iso*butyl-1,3-(dibenzyloxy)benzene (1.35 g, 3.90 mmol, 1 equiv) in Et_2O (12 mL) was added TMEDA (1.023 mL, 0.798 g, 6.87 mmol, 1.7 equiv) under nitrogen. The solution was cooled to 0°C at which point *n*-BuLi (2.5 M in

hexane, 2.73 mL, 6.81 mmol, 1.7 equiv) was added dropwise. The solution was stirred at 0°C for 0.5 h, before addition of BOMCl (1.12 mL, 8.08 mmol, 2.1 equiv) which was added dropwise and the reaction stirred for 2 h. The reaction was quenched with water (75 mL) and ether (75 mL) separating the layers and extracting the aqueous layer with further portions of diethylether (2×75 mL). The combined organic extracts were scrubbed with brine (100 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure yielding a crude oil. This was purified by column chromatography (1 → 5% diethylether in light petroleumether 40/60), yielding *O,O*-dibenzyl-2-((benzyloxy)methyl)-4-*i*-butylresourcinol as a pale liquid (721 mg, 1.55 mmol. 40%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.55

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 - 7.21 (C**H** $_{Bn}$, m, 15 H), 7.12 (C**H** $_{Ar}$, d, *J* = 8.6 Hz, 1 H), 6.77 (C**H** $_{Ar}$, d, *J* = 8.1 Hz, 1 H), 5.13 (C**H**$_2$ $_{Bn}$, s, 2 H), 5.00 (C**H**$_2$ $_{Bn}$, s, 2 H), 4.74 (C**H**$_2$ $_{Bn}$, s, 2 H), 4.63 (C**H**$_2$ $_{Bn}$, s, 2 H), 2.50 (C**H**$_2$CHMe$_2$, d, *J* = 7.1 Hz, 2 H), 1.96 (CH_2C**H**Me$_2$, sptt, *J* = 6.7, 7.1 Hz, 1 H), 0.91 ($CH_2CH(CH_3)_2$, d, *J* = 6.6 Hz, 7 H).

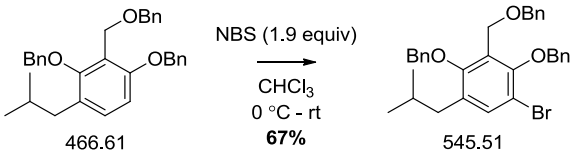
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.8 (**C**OBn), 157.0 (**C**OBn), 138.7 (**C** Bn), 138.0 (**C** Bn), 137.4 (**C** Bn), 131.1 (**C**H Ar *M*), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.2 (**C**H Bn), 127.9 (**C**H Bn), 127.9 (**C**H Bn), 127.8 (**C**H Bn), 127.6 (**C**H Bn), 127.3 (**C**H Bn), 120.5 (**C** Ar *O*), 108.2 (**C**H Ar *O*), 76.9 (**C**H$_2$ Bn), 72.8 (**C**H$_2$ Bn), 70.6 (**C**H$_2$ Bn), 62.3 (Ar**C**H$_2$OBn), 39.1 (**C**H$_2$CHMe$_2$), 29.3 (CH_2**C**HMe$_2$), 22.5 (CH_2CH(**C**H$_3$)$_2$).

IR (neat) : 3031, 2952, 2866, 1601, 1484 cm^{-1}.

MS (ES^+)(m/z) : 489 $[M+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 489.2400; Found. 489.2413.

***O,O*-Dibenzyl-2-((benzyloxy)methyl)-4-*i*-butyl-6-bromoresourcinol**



466.61 **6.3.13** 545.51 **6.3.14**

To a solution of *O,O*-dibenzyl-2-((benzyloxy)methyl)-4-*i*-butyl-resourcinol (240mg, 0.536mmol, 1 equiv) in chloroform (10 mL) was added NBS (181mg, 1.02mmol, 1.9 equiv) in one portion under nitrogen. The reaction was stirred, in the dark, until completion

(23 h). The reaction was then quenched with water (10 ml), the layers separated and the aqueous extracted with chloroform (2×10 mL). The combined organic extracts were then dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (3% diethylether in light petroleumetherff) yielding a pale yellow oil (195 mg, 0.357 mmol. 67%).

R_f (diethylether / light petroleumether 40/60) (10 : 90) : 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 - 7.37 (C**H** $_{Ar}$, m, 2 H), 7.35 - 7.23 (C**H** $_{Ar}$, m, 9 H), 7.17 (C**H** $_{Ar}$, s, 5 H), 5.01 (CH_2Ph, s, 2 H), 4.88 (OC**H**$_2$Ph*, s, 2 H), 4.57 (C**H**$_2$OCH_2Ph, s, 2 H), 4.47 (CH_2OC**H**$_2$Ph, s, 2 H), 2.39 (C**H**$_2$CHMe_2, d, *J* = 7.1 Hz, 2 H), 1.87 (CH_2C**H**Me_2, sptt, *J* = 6.6, 7.1 Hz, 1 H), 0.82 (CH_2CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 3 H), 0.82 (CH_2CH(C**H**$_3$)$_2$*, d, *J* = 6.6 Hz, 3 H).

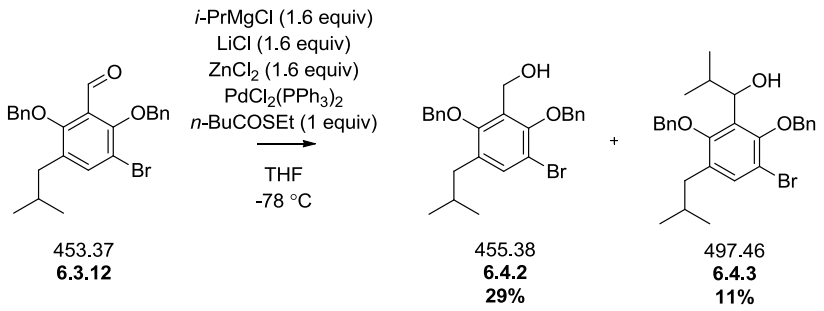
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0 (**C**OBn), 154.2 (**C**OBn*), 138.0 (**C** Bn), 137.5 (**C*** Bn), 137.3 (**C**** Bn), 134.6 (**C**H Ar), 133.1 (**C** Ar), 128.5 (**C**H Ar), 128.4 (**C**H Ar), 128.4 (**C**H Ar), 128.0 (**C**H Ar), 128.0 (**C**H Ar), 127.9 (**C**H Ar), 127.6 (**C**H Ar), 127.5 (**C** Ar), 127.4 (**C**H Ar), 112.5 (**C** Ar), 76.9 (OC**H**$_2$Ph), 76.4 (OC**H**$_2$Ph*), 73.3 (CH_2OC**H**$_2$Ph), 63.2 (**C**H_2OCH_2Ph), 39.0 (**C**H_2CH$(CH_3)_2$), 29.2 (CH_2**C**H$(CH_3)_2$), 22.5 (CH_2CH(**C**$H_3)_2$).

IR (neat) : 3031, 2954, 2927, 2867, 1452 cm^{-1}.

MS (ES^+)(m/z) : 567 $[M+Na]^+$ (Br^{79}, 96%), 569 $[M+Na]^+$ (Br^{81}, 100%).

HRMS (ES^+) : $[M+Na]^+$(Br^{79}) Calcd. 567.1505; Found. 567.1504.

2,6-Bis(benzyloxy)-3-bromo-5-*iso*butylbenzaldehyde



To a predried flask of anhydrous LiCl (20 mg, 0.47 mmol, 1.6 equiv) and 2,6-bis(benzyloxy)-3-bromo-5-*iso*butylbenzaldehyde (200 mg, 0.441 mmol, 1.5 equiv) was added THF (1 mL) the mixture was cooled to -78 ºC for 5 min before adding *i*-propylmagnesium chloride dropwise (235 µL, 0.470 mmol, 1.6 equiv). After 5 min at -78

ºC, $ZnCl_2$ (671 µL, 0.470 mmol, 1.6 equiv, 0.7 M in THF) was added dropwise and the solution allowed to warm to 0 ºC, over 15 min. Separately, a predried flask was charged with S-ethyl pentanethioate (43 mg, 0.294 mmol, 1 equiv) and THF (1 mL). $PdCl_2(PPh_3)_2$ (21 mg, 0.294 mmol, 10% mol) was then added a few minutes before transferring the aromatic zincate solution at 0 ºC and stirred for 1 h. The reaction solvent was then removed under reduced pressure and the reaction purified by column chromatography (5 → 20% diethylether in light petroleumether) to yield 1-(2,6-bis(benzyloxy)-3-bromo-5-isobutylphenyl)-2-methylpropan-1-ol (24.5 mg, 49.3 µmol. 11%) and (2,6-bis(benzyloxy)-3-bromo-5-*iso*butylphenyl)methanol (57.8 mg, 127 µmol. 29%).

1-(2,6-Bis(benzyloxy)-3-bromo-5-isobutylphenyl)-2-methylpropan-1-ol

R_f (diethylether / light petroleumether 40/60) (10 : 90) : 0.13

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.51 (C**H** $_{Ar}$, m, 2H), 7.49 - 7.34 (C**H** $_{Ar}$, m, 9H), 5.09 (C**H**$_{2\ Bn}$, s, 2H), 4.91 (C**H**$_{2\ Bn}$, s, 2H), 4.67 (C**H**$_2$OH, d, *J* = 6.6 Hz, 2H), 2.50 (C**H**$_2$CHMe$_2$, d, *J* = 7.1 Hz, 2H), 2.28 (O**H**, t, *J* = 6.6 Hz, 1H), 1.97 (CH$_2$C**H**Me$_2$, tspt, *J* = 7.1, 6.6 Hz, 1H), 0.93 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9 (**C**OBn), 153.1 (**C**OBn*), 136.9 (**C** Bn), 136.6 (**C** Bn), 134.3 (**C**H Ar *P*), 133.3 (**C** Ar), 130.1 (**C** Ar), 128.6 (**C**H Bn), 128.6 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.3 (**C**H Bn), 127.7 (**C** Ar), 112.2 (**C** Ar), 76.7 (**C**H$_2$ Bn), 76.1 (**C**H$_2$ Bn*), 58.5 (**C**H$_2$OH), 39.0 (**C**H$_2$CHMe$_2$), 29.2 (CH$_2$**C**HMe$_2$), 22.5 (CH$_2$CH(**C**H$_3$)$_2$).

IR (neat) : 3445, 3064, 3032, 2955, 2968 cm^{-1}.

MS (ES$^+$)(m/z) : 477 [M+Na]$^+$ (Br^{79}, 69%), 479 [M+Na]$^+$ (Br^{81}, 69%), 518 [M+Na+MeCN]$^+$ (Br^{79}, 94%), 520 [M+Na+MeCN]$^+$ (Br^{81}, 100%).

HRMS (ES$^+$) : [M+Na]$^+$(Br^{79}) Calcd. 477.1036; Found. 477.1029.

2,6-Bis(benzyloxy)-3-bromo-5-*iso*butylbenzaldehyde

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.28 (C**H**O, s, 1H), 7.64 (C**H** $_{Ar}$, s, 1H), 7.58 - 7.52 (C**H** $_{Bn}$, m, 2H), 7.49 - 7.34 (C**H** $_{Bn}$, m, 8H), 5.09 (C**H**$_{2\ Bn}$, s, 2H), 4.91 (C**H**$_{2\ Bn}$, s, 2H), 2.45 (C**H**$_{2\ i\text{Bu}}$, d, *J* = 7.1 Hz, 2H), 1.94 (C**H** $_{i\text{Bu}}$, quind, *J* = 6.9, 13.5 Hz, 1H), 0.91 (C**H**$_{3\ i\text{Bu}}$, d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.0 (**C**HO), 158.1 (**C**OBn Ar 6), 155.8 (**C**OBn Ar 6), 139.9 (C**H** Ar 4), 136.4 (**C** Bn 6), 135.8 (**C** Bn 2), 134.3 (**C** Ar 5), 128.8 (**C**H Bn), 128.6

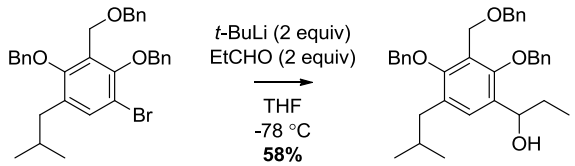
(**C**H Bn), 128.6 (**C**H Bn), 128.4 (**C**H Bn), 128.2 (**C**H Bn), 125.6 (**C** Ar 1), 113.2 (**C** Ar 3), 77.9 (**C**H_2 Bn 6), 77.1 (**C**H_2 Bn 2), 38.5 (**C**H_2 *i*Bu), 29.1 (**C**H_3 *i*Bu).

IR (neat) : 3032, 2956, 2868, 1695, 1573cm^{-1}

MS (ES$^+$)(m/z) : 475 [M+Na]$^+$ (^{79}Br, 5%), 477 [M+Na]$^+$ (^{81}Br, 5%), 516 [M+Na+MeCN]$^+$ (^{79}Br, 5%), 518 [M+Na+MeCN]$^+$ (^{81}Br, 5%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 475.0879; Found. 475.0879.

1-(2,4-Bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-ol



545.51
6.3.14

524.69
6.4.4

To a solution of *O,O*-dibenzyl-2-((benzyloxy)methyl)-4-*i*-butyl-6-bromoresourcinol (250 mg, 0.458 mmol, 1 equiv) in THF (3 mL) at -78 ºC under nitrogen was added *t*-BuLi (1.6 M in pentane, 573 µL, 0.917 mmol, 2 equiv) dropwise. The solution was stirred at -78 ºC for 5 min before adding a solution of propionaldehyde (66 µL, 0.92 mmol, 2 equiv) in THF (1 mL) at -78 ºC dropwise. The reaction was stirred for 1 h, warming to 0 ºC slowly, after which the reaction was quenched with water (10 mL). The mixture was quenched with water (10 mL) extracting with diethylether (3×10 mL), the combined extracts were then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (25% diethylether in light petroleumether 40/60) to give a colourless oil (139.2 mg, 0.265 mmol. 58%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.10

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 - 7.23 (C**H** $_{Bn}$, m, 10 H), 7.21 - 7.10 (C**H** $_{Bn}$, m, 6 H), 5.00 (C**H**$_{2\ Bn}$, s, 2 H), 4.95 (C**H**$_{2\ Bn}$, d, *J* = 11.6 Hz, 1 H), 4.91 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.81 (C**H**OH, dt, *J* = 2.0, 6.0 Hz, 1 H), 4.60 (C**H**$_{2\ Bn}$, s, 2 H), 4.47 (C**H**$_{2\ Bn}$, s, 2 H), 2.48 (C**H**$_2$CHMe$_2$, dd, *J* = 7.1, 13.1 Hz, 1 H), 2.39 (C**H**$_2$CHMe$_2^*$, dd, *J* = 7.6, 13.6 Hz, 1 H), 1.88 (C**H**$_2$CH$_3$, quind, *J* = 6.7, 13.5 Hz, 1 H), 1.81 - 1.62 (C**H**$_2$CH$_3^*$, CH$_2$C**H**Me$_2$, m, 3 H), 1.79 (O**H**, d, *J* = 2.5 Hz, 1 H), 0.85 (CH$_2$C**H**$_3$, t, *J* = 7.6 Hz, 7 H), 0.81 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 5.1 Hz, 4 H), 0.82 (CH$_2$CH(C**H**$_3$)$_2^*$, d, *J* = 5.1 Hz, 4 H).

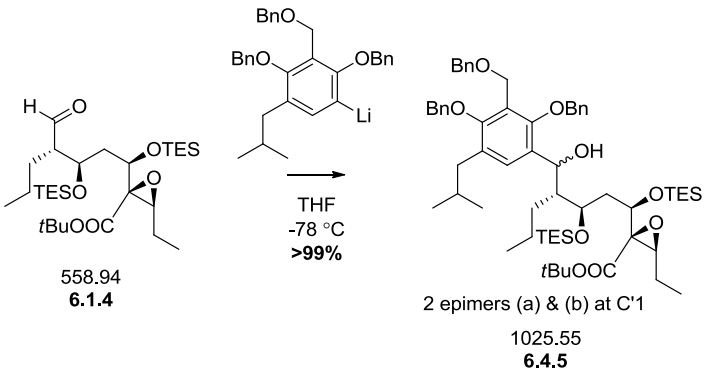
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.1 (**C**OBn), 154.7 (**C**OBn), 133.3 (**C** Ar), 131.3 (**C** Ar), 129.1 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.4 (**C**H Bn), 128.1 (**C**H Bn), 128.0 (**C**H Bn), 127.7 (**C**H Bn), 127.6 (**C**H Bn), 127.6 (**C**H Bn), 127.3 (**C**H Bn), 125.0 (**C**H Ar *O*), 77.8 (**C**H_2 Bn), 76.8 (**C**H_2 Bn), 73.3 (**C**H_2 Bn), 70.1 (**C**HOH), 63.2 (Ar**C**H_2OBn), 39.3 (**C**H_2CHMe_2), 30.9 (**C**$H_2$$CH_3$), 29.3 ($CH_2$**C**H$Me_2$), 22.6 ($CH_2$CH(**C**$H_3$)$_2$), 22.5 ($CH_2$CH(**C**$H_3$)$_2$*), 10.5 ($CH_2$**C**$H_3$).

IR (neat) : 3425 , 3031, 2955, 2869, 1453 cm^{-1}.

MS (ES^+)(m/z) : 547 $[M+Na]^+$ (100%), 603 $[M-H_2O+MeOH+MeCH+Na]^+$ (13%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 547.2819; Found. 547.2826.

The coupling of the aromatic and aliphatic fragments



558.94
6.1.4

1025.55
6.4.5

To a solution of *O*,*O*-dibenzyl-2-((benzyloxy)methyl)-4-*i*-butyl-6-bromoresourcinol (85 mg, 0.153 mmol, 5 equiv) in THF (2.5 mL) was added *t*-BuLi (1.7 M in pentane, 449 µL 0.764 mmol, 5 equiv) at -78 ºC under nitrogen. The solution was stirred at -78 ºC for 15 min before a solution of aliphatic fragment aldehyde **6.4.5** (85.4 mg, 0.153 mmol, 1 equiv) in THF (5.6 mL) was added, washing with THF (1.7 mL) at -78 ºC. The reaction was then stirred for 45 min at -78 ºC before quenching with water (10 mL) and extracting with diethylether (10 mL). The organic phase was then dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude was then purified by column chromatography (20% diethylether in hexane) to give a colourless oil (160 mg, 0.153 mmol. 100%).

R_f (diethylether / hexane) (20 : 80) : 0.20

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 - 7.29 (^{a,b}C**H** $_{Ar}$, m, 16.8 H), 7.25 - 7.15 (^{a,b}C**H** $_{Ar}$, m, 6.9 H), 5.24 (^{a,b}C**H**OH, *br*s, 1 H), 5.20 - 5.01 (^{a,b}C**H**$_2$ $_{Bn}$, m, 4.9 H), 5.00 - 4.86 (^{a,b}C**H**$_2$ $_{Bn}$,

m, 2 H), 4.74 - 4.55 (^{a,b}C**H**$_2$OBn, m, 3.3 H), 4.50 (^{a,b}C**H**$_2$ Bn, d, *J* = 11 Hz, 1.7 H), 4.45 (^{a,b}C**H**$_2$ Bn*, d, *J* = 11 Hz, 1 H), 4.10 (^{b}C**H**OTESCH, *br*d, *J* = 8.6 Hz, 0.4 H), 4.04 (^{a}C**H**OTESCH, ddd, J = 2.5, 5.1, 7.6 Hz, 1 H), 3.52 (^{b}CC**H**OTES, *br*d, *J* = 7.1 Hz, 0.4 H), 3.47 (^{a,b}O**H**, d, *J* = 2.0 Hz, 1 H), 3.33 (^{a}CC**H**OTES, dd, *J* = 4.5, 7.1 Hz, 1 H), 2.79 (^{b}C**H** epox, t, *J* = 6.3 Hz, 0.3 H), 2.71 (^{a}C**H** epox, t, J = 6.3 Hz, 1 H), 2.61 ($^{a,(b)}$C**H**$_2$CHMe$_2$, dd, *J* = 7.3, 13.4 Hz, 1 H), 2.45 ($^{a,(b)}$C**H**$_2$CHMe$_2^*$, dd, *J* = 7.1, 13.1 Hz, 1 H), 2.26 ($^{a,(b)}$C**H**$_2$CHOTES, dd, *J* = 7.3, 14.4 Hz, 1 H), 2.11 - 1.92 ($^{a,(b)}$C**H**$_2$CHOTES*, $^{a,(b)}$CH$_2$C**H**Me$_2$, ^{b}C**H**CHOH, m, 3.4 H), 1.81 (^{a}C**H**CHOH, *br*s., 1.1 H), 1.66 - 1.11 (^{a,b}C**H**$_2$CH$_2$CH$_3$, ^{a,b}C**H**$_2$CH$_3$, ^{a,b}CH$_2$C**H**$_2$CH$_3$, $_{epox}$, m, 13 H) 1.56 (^{b}C(C**H**$_3$)$_3$, s, 4 H), 1.47 (^{a}C(C**H**$_3$)$_3$, s, 9 H), 1.07 - 0.85 (^{a,b}CH$_2$C**H**$_3$ $_{epox}$, ^{a,b}C**H**$_3$ $_{TES}$, ^{a,b}CH$_2$CH(C**H**$_3$)$_2$, m, 44.3 H), 0.78 - 0.51 (^{a,b}CH$_2$CH$_2$C**H**$_3$, ^{a,b}C**H**$_2$ $_{TES}$, m, 23.3 H).

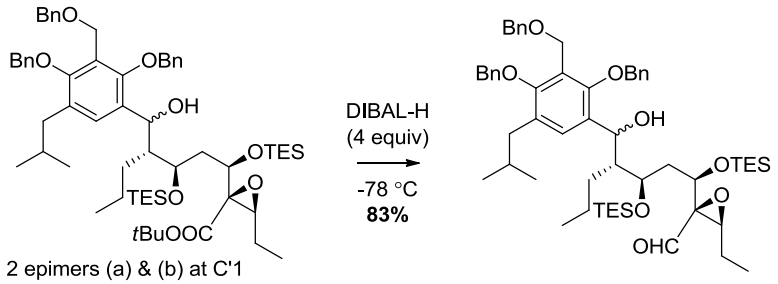
^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.4 (^{a,b}COO*t*Bu), 157.1 (^{a}**C**OBn), 156.9 (^{a}**C**OBn*), 155.6 (^{b}**C**OBn), 154.7 (^{b}**C**OBn*), 138.1 (^{a}**C** Bn), 138.1 (^{b}**C** Bn), 138.0 (^{b}**C** Bn), 138.0 (^{b}**C** Bn), 137.8 (^{a}**C** Bn), 130.7 (**C**H Bn), 129.5 (**C**H Bn), 128.8 (**C**H Bn), 128.4 (**C**H Bn), 128.4 (**C**H Bn), 128.3 (**C**H Bn), 128.3 (**C**H Bn), 128.2 (**C**H Bn), 128.1 (**C**H Bn), 128.0 (**C**H Bn), 128.0 (**C**H Bn), 127.8 (**C**H Bn), 127.7 (**C**H Bn), 127.6 (**C**H Bn), 127.5 (**C**H Bn), 127.5 (**C**H Bn), 127.4 (**C**H Bn), 127.4 (**C**H Bn), 127.3 (**C**H Bn), 124.7 (^{a,b}**C***i*Bu Ar), 117.0 (^{a,b}**C**CH$_2$OBn Ar), 82.1 (^{a,b}**C**Me$_3$), 77.5 ($^{a,(b)}$**C**H$_2$ Bn), 77.0 (^{b}**C**H$_2$ Bn), 76.8 (^{a}**C**H$_2$ Bn), 75.9 (^{a}**C**HOTESCH), 75.0 (^{a}C**C**HOTES), 74.5 (^{b}C**C**HOTES), 73.7 (^{b}**C**HOTESCH), 73.3 (^{a}**C**H$_2$ Bn) 73.3 (^{b}**C**H$_2$ Bn), 71.4 (^{a,b}**C**HOH), 67.2 (^{b}**C** epox), 67.0 (^{a}**C** epox), 63.2 (^{a}**C**H$_2$OBn), 63.0 (^{b}**C**H$_2$OBn), 61.4 (^{b}**C**H epox), 61.1 (^{a}**C**H epox), 47.4 (^{a,b}**C**HCHOH), 41.4 (^{a,b}**C**H$_2$CHOTES), 39.3 (^{a,b}**C**H$_2$CHMe$_2$), 29.5 (^{a}CH$_2$**C**HMe$_2$), 29.2 (^{b}CH$_2$**C**HMe$_2$), 28.1 (^{a}C(**C**H$_3$)$_3$), 28.0 (^{b}C(**C**H$_3$)$_3$), 24.8 (^{a,b}**C**H$_2$CH$_2$CH$_3$), 22.9 (^{a}CH$_2$**C**H$_2$CH$_3$), 22.7 (^{b}CH$_2$**C**H$_2$CH$_3$), 22.6 (^{a,b}CH$_2$CH(C**H**$_3$)$_2$), 22.5 (^{a,b}CH$_2$CH(C**H**$_3$)$_2^*$), 21.9 (^{a}**C**H$_2$CH$_3$ epox), 21.7 (^{b}**C**H$_2$CH$_3$ epox), 14.6 (^{a}CH$_2$CH$_2$**C**H$_3$), 14.1 (^{b}CH$_2$CH$_2$**C**H$_3$), 10.2 (^{b}CH$_2$**C**H$_3$ epox), 10.1 (^{a}CH$_2$**C**H$_3$ epox), 7.1 (^{b}**C**H$_3$ TES), 6.9 (^{a}**C**H$_3$ TES), 6.9 (^{b}**C**H$_3^*$ TES), 5.4 (^{a}**C**H$_2$ TES), 5.1 (^{b}**C**H$_2$ TES), 4.9 (^{a}**C**H$_2^*$ TES).

IR (neat) : 3479, 3031, 2955, 2875, 1747, 1722 cm^{-1}.

MS (ES$^+$)(m/z) : 992 [M-*t*Bu+H+Na]$^+$ (70%), 1048 [M+Na]$^+$ (100%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 1047.6172; Found. 1047.6160.

_t_-Butylester reduction on the completed luminacin D backbone 6.4.5



2 epimers (a) & (b) at C'1

1025.55
6.4.5

953.44
6.4.6

To a solution of *t*-butylester **6.4.5** (9.6 mg, 9.36 µmol, 1 equiv) in toluene (250 µL) at -78 ºC under nitrogen was added DIBAL-H (1M in heptane, 38 µL, 37.4 µmol, 4 equiv). After 45 min at -78 ºC the excess DIBALH was decomposed by addition of MeOH (250 µL) at -78 ºC. The mixture was warmed to 0 ºC, water (250 µL) was added and it was stirred for 1 h. The mixture was then filtered through cotton wool, washing with ethylacetate (4 mL). The solvent was then evaporated and the crude residue immediately purified by column chromatography (20% diethylether in hexane) to yield a colourless residue (7.4 mg, 7.8 µmol. 83%) (Further purification was undertaken by HPLC – 15% diethylether in hexane).

To a solution of *t*-butylester **6.4.5** (43.6 mg, 42.5 µmol, 1 equiv) in toluene (1.1 mL) at -78 ºC under nitrogen was added DIBAL-H (1M in heptane, 213 µL, 213 µmol, 4 equiv). After 45 min at -78 ºC the excess DIBALH was decomposed by addition of MeOH (1 mL) at -78 ºC. The mixture was warmed to 0 ºC, water (1 mL) was added and it was stirred for 1 h. The mixture was then filtered through cotton wool, washing with ethylacetate (8 mL). The filtrate was washed with brine (4 mL), dried over Na_2SO_4 (anh), filtered and the solvent was then evaporated. The crude residue immediately purified by column chromatography (20% diethylether in hexane) to yield a colourless residue (38.8 mg, 40.7 µmol). Further purification was undertaken by HPLC – 10% diethylether in hexane as SM contaminated the product (29.5 mg, 30.9 µmol. 73%).

R_f (diethylether / hexane) (20 : 80) : 0.23

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (C**H**O, s, 1 H), 7.48 - 7.30 (C**H** $_{Bn}$, m, 13 H), 7.25 - 7.17 (C**H** $_{Bn}$, m, 6 H), 5.20 (C**H**OH, *br*s, 1 H), 5.14 (C**H**$_2$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 5.09 (C**H**$_2$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 5.02 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.96 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.71 (C**H**$_2$OBn, d, *J* = 9.1 Hz, 1 H), 4.65 (C**H**$_2$OBn*, d, *J* = 9.1 Hz, 1 H), 4.50

(C**H**$_{2\ Bn}$, d, *J* = 11.6 Hz, 1 H), 4.47 (C**H**$_2^{*}{}_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.08 (C**H**OTESCH, ddd, *J* = 2.5, 5.2, 8.0 Hz, 1 H), 3.69 (CC**H**OTES, t, *J* = 6.8 Hz, 1 H), 3.54 (CHO**H**, d, *J* = 1.5 Hz, 1 H), 2.99 (C**H**$_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.61 (C**H**$_2$CHMe$_2$, dd, *J* = 7.6, 13.1 Hz, 1 H), 2.44 (C**H**$_2$CHMe$_2^{*}$, dd, *J* = 7.1, 13.1 Hz, 1 H), 2.11 (C**H**$_2$CHOTES, ddd, *J* = 6.6, 8.6, 14.1 Hz, 1 H), 2.06 - 1.94 (C**H**$_2$CHOTES*, CH$_2$C**H**Me$_2$, m, 2 H), 1.68 (C**H**CHOH, br. s., 1 H), 1.22 (t, *J* = 6.6 Hz, 1 H), 1.31 (C**H**$_2$CH$_{3\ epox}$, C**H**$_2$C**H**$_2$CH$_3$, m, 6 H), 1.08 - 0.85 (C**H**$_{3\ TES}$, CH$_2$CH(C**H**$_3$)$_2$, CH$_2$C**H**$_{3\ epox}$, m, 34 H), 0.85 - 0.48 (CH$_2$CH$_2$C**H**$_3$, C**H**$_{2\ TES}$, m, 21 H).

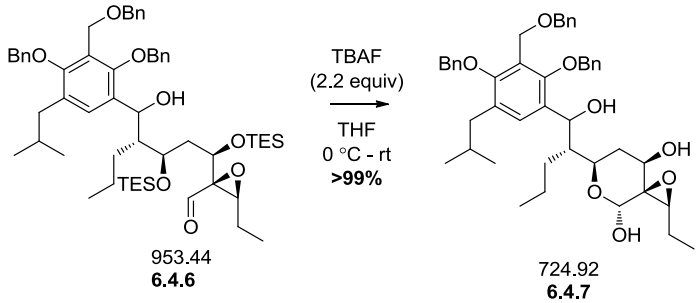
^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.2 (**C**HO), 156.9 (**C**OBn), 154.5 (**C**OBn), 138.1 (**C** Bn), 138.1 (**C** Bn), 137.8 (**C** Bn), 132.4 (**C** Ar), 130.7 (**C** Ar), 129.4 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.3 (**C**H Bn), 128.1 (**C**H Bn), 127.8 (**C**H Bn), 127.7 (**C**H Bn), 127.6 (**C**H Bn), 127.3 (**C**H Bn), 77.4 (**C**H$_2$ Bn), 76.8 (**C**H$_2$ Bn), 74.9 (**C**HOTESCH), 73.2 (**C**H$_2$ Bn), 71.9 (**C**HOH), 70.8 (C**C**HOTES), 68.7 (**C** epox), 64.0 (**C**H epox), 63.3 (**C**H$_2$OBn), 47.0 (**C**HCHOH), 40.5 (**C**H$_2$CHOTES), 39.2 (**C**H$_2$CHMe$_2$), 29.5 (CH$_2$**C**HMe$_2$), 24.2 (**C**H$_2$CH$_2$CH$_3$), 23.2 (CH$_2$**C**H$_2$CH$_3$), 22.7 (CH$_2$CH(**C**H$_3$)$_2$), 22.5 (CH$_2$CH(**C**H$_3$)$_2^{*}$), 21.2 (**C**H$_2$CH$_3$ epox), 14.5 (CH$_2$CH$_2$**C**H$_3$), 10.4 (CH$_2$**C**H$_3$ epox), 6.9 (CH$_3$ TES), 6.7 (CH$_3$* TES), 5.4 (**C**H$_2$ TES), 4.7 (**C**H$_2$* TES).

IR (neat) : 3476, 3031, 2955, 2875, 1729, 1586 cm^{-1}.

MS (ES$^+$)(m/z) : 977 [M+Na]$^+$ (100%), 1008 [M+Na+MeOH]$^+$ (42%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 975.5597; Found. 975.5566.

TES deprotection of the luminacin D backbone 6.4.6



953.44
6.4.6

724.92
6.4.7

To a solution of TES protected luminacin D backbone **6.4.7** (84 mg, 88 µmol, 1 equiv) in THF (5 mL) was added TBAF (1M in THF, 194 µL, 194 µmol, 2.2 equiv). The reaction was then stirred at 0 ºC for 1 h and rt for 1 h. After reaction completion the solvent was evaporated under reduced pressure and the crude residue purified by column

chromatography (45% ethylacetate in hexane) to yield a colourless oil which was further purified by HPLC (35% ethylacetate in hexane) (64 mg, 88 μmol. >99%).

R_f (ethylacetate / hexane) (35 : 65) : 0.24

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 - 7.28 (C**H** $_{Bn}$, m, 11 H), 7.26 - 7.17 (C**H** $_{Bn}$, m, 6 H), 5.09 (C**H**$_2$ $_{Bn}$, d, *J* = 11.1 Hz, 1 H), 5.11 - 5.05 (ArC**H**OH, m, 1 H), 5.01 (C**H**$_2$ $_{Bn}$, d, *J* = 11.1 Hz, 1 H), 4.89 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.1 Hz, 1 H), 4.88 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.75 (C**H**OHO, d, *J* = 2.0 Hz, 1 H), 4.62 (C**H**$_2$OBn, d, *J* = 9.6 Hz, 1 H), 4.59 (C**H**$_2$OBn*, d, *J* = 9.6 Hz, 1 H), 4.55 (C**H**$_2$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.50 (C**H**$_2^*$ $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 3.95 (C**H**OCOH, dt, *J* = 5.1, 11.6 Hz, 1 H), 3.78 (C**H**OHCH$_2$, *br*d, *J* = 11.1 Hz, 1 H), 3.49 (CHO**H**O, d, *J* = 2.0 Hz, 1 H), 3.17 (C**H** $_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.58 (C**H**$_2$CHMe$_2$, dd, *J* = 7.1, 13.1 Hz, 1 H), 2.38 (C**H**$_2$CHMe$_2^*$, dd, *J* = 7.6, 13.1 Hz, 1 H), 2.22 (ArCHO**H**, br. s., 1 H), 1.93 (CH$_2$C**H**Me$_2$ sptdd, *J* = 6.6, 7.1, 7.6 Hz, 1 H), 1.68 - 1.38 (C**H**$_2$CHOH, C**H**CHOH, CHO**H**CH$_2$, C**H**$_2$CH$_3$ $_{epox}$, C**H**$_2$CH$_2$CH$_3$, m, 8 H), 1.28 - 1.17 (CH$_2$C**H**$_2$CH$_3$, m, *J* = 7.6 Hz, 2 H), 0.99 (CH$_2$C**H**$_3$ $_{epox}$, t, *J* = 7.6 Hz, 3 H), 0.83 (CH$_2$CH(C**H**$_3$)$_2$,d, *J* = 6.6 Hz, 7 H), 0.86 (CH$_2$CH(C**H**$_3$)$_2^*$, d, *J* = 6.6 Hz, 1 H), 0.76 (CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 3 H).

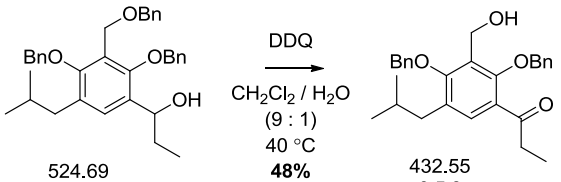
^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0 (**C**OBn), 154.0 (**C**OBn), 137.9 (**C** Bn), 137.8 (**C** Bn), 137.1 (**C** Bn), 132.7 (**C** Ar), 131.9 (**C** Ar), 129.4 (**C**H Bn), 128.6 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.3 (**C**H Bn), 128.2 (**C**H Bn), 128.0 (**C**H Bn), 127.8 (**C**H Bn), 127.7 (**C**H Bn), 127.2 (**C**H Bn), 124.8 (**C**H Ar), 94.2 (**C**OHOCH), 77.9 (**C**H$_2$ Bn), 76.9 (**C**H$_2$ Bn), 73.3 (CH$_2$O**C**H$_2$Ph), 71.1 (Ar**C**HOH), 69.5 (**C**HOHCH$_2$), 63.3 (**C**H$_2$OBn), 63.0 (**C**HOCOH), 61.8 (**C** epox), 59.6 (**C**H epox), 49.0 (**C**HCHOHAr), 39.4 (**C**H$_2$CHMe$_2$), 37.3 (CHOH**C**H$_2$), 29.3 (CH$_2$**C**HMe$_2$), 26.8 (**C**H$_2$CH$_2$CH$_3$), 23.3 (CH$_2$**C**H$_2$CH$_3$), 22.6 (CH$_2$CH(**C**H$_3$)$_2$), 22.4 (CH$_2$CH(**C**H$_3$)$_2^*$), 20.6 (**C**H$_2$CH$_3$ epox), 14.5 (CH$_2$CH$_2$**C**H$_3$), 10.6 (CH$_2$**C**H$_3$ epox).

IR (neat) : 3410, 2955, 2870, 1586, 1455 cm^{-1}.

MS (ES$^+$)(m/z) : 747 [M+Na]$^+$ (100%), 819 [M-H+O*t*Bu+Na]$^+$ (68%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 747.3867; Found. 747.3860.

1-(2,4-Bis(benzyloxy)-3-(hydroxymethyl)-5-*iso*butylphenyl)propan-1-one



524.69 **6.4.4** 432.55 **6.5.3**

To a solution of 1-(2,4-bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-ol (55 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2/H_2O (9 : 1, 5 mL) was added DDQ (119 mg, 0.524 mmol, 5 equiv) The reaction was then heated to reflux for 24 h, after which the reaction was partioned between $NaHCO_3$ (sat) (5 mL) and CH_2Cl_2 (5 mL), the separated aqueous phase was then extracted with a further portion of CH_2Cl_2 (5 mL). The combined organic extracts were then scrubbed with brine (5 mL), dried over Na_2SO_4 (anh), filtered and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography (20% diethylether in light petroleum 40/60) to yield a colourless oil (22 mg, 51 µmol. 48%) (The product was further purified by HPLC (10% acetone in hexane) 9.8 mg, 23 µmol. 22%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.15

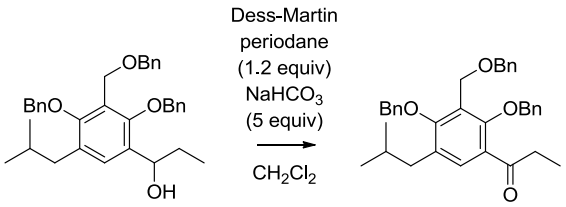
^{1}H NMR (400 MHz, CD_3CN) δ = 7.57 - 7.32 (C**H**$_{Ar}$, m, 11 H), 4.99 (C**H**$_{2\ Bn}$, s, 2 H), 4.95 (C**H**$_{2\ Bn}$, s, 2 H), 4.67 (C**H**$_2$OH, d, *J* = 4.9 Hz, 2 H), 3.08 (CH_2O**H**, t, *J* = 5.1 Hz, 1 H), 2.96 (COC**H**$_2CH_3$, q, *J* = 7.3 Hz, 2 H), 2.54 (C**H**$_2CHMe_2$, d, *J* = 7.2 Hz, 2 H), 1.94 (CH_2C**H**Me_2, sptt, *J* = 6.8, 7.2 Hz, 2 H), 1.08 ($COCH_2$C**H**$_3$, t, *J* = 7.3 Hz, 3 H), 0.88 (CH_2CH(C**H**$_3)_2$, d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.5 (**C**=O), 161.1 (**C**OBn *O*), 157.0 (**C**OBn *P*), 139.0 (OCH_2**C** Bn), 138.6 (OCH_2**C** Bn), 132.8 (**C***i*Bu *M*), 132.5 (**C**H *O*), 131.7 (**C**CH_2OH *M*), 130.6 (**C**CO *I*), 130.0 (**C**H Bn), 129.9 (**C**H Bn), 129.7 (**C**H Bn), 129.6 (**C**H Bn), 129.6 (**C**H Bn), 129.4 (**C**H Bn), 79.7 (O**C**H_2Ph), 78.1 (O**C**H_2Ph), 55.7 (**C**H_2OH), 40.2 (**C**H_2CHMe_2), 36.9 (CO**C**H_2CH_3), 30.4 (CH_2**C**HMe_2), 23.1 (CH_2CH(**C**$H_3)_2$), 9.1 ($COCH_2$**C**H_3).

MS (ES^+)(m/z) : 405 (44%), 425 (39%), 455 $[M+Na]^+$ (73%), 496 $[M+Na+MeCN]^+$ (100%), 889 $[2M+Na]^+$ (33%).

(No HRMS or IR obtained before sample decomposition)

1-(2,4-Bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-one



524.69
6.4.4

522.67
6.5.5

To a solution of 1-(2,4-bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-ol (70 mg, 0.133 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added sequentially $NaHCO_3$ (56 mg, 0.67 mmol, 5 equiv) and Dess-Martin periodane (68 mg, 0.160 mmol, 1.2 equiv) under nitrogen (g). The mixture was stirred at rt for 1 h before quenching with Na_2SO_3 (sat. 3 mL) and water (5 mL). The mixture was then extracted with portions of CH_2Cl_2 (3×10 mL) and the combined extracts washed with $NaHCO_3$ (aq, 3×7.5 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (20% diethylether in light petroleumether 40/60) to yield a colourless oil (64 mg, 123 mmol. 92%).

R_f (diethylether / light petroleumether 40/60) (25 : 75) : 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 - 7.32 (C**H** $_{Ar\ \&\ Bn}$, m, 16 H), 5.04 (C**H**$_{2\ Bn}$, s, 2 H), 5.02 (C**H**$_{2\ Bn}$, s, 2 H), 4.68 (C**H**$_{2\ Bn}$, s, 2 H), 4.56 (C**H**$_{2\ Bn}$, s, 2 H), 3.00 (C**H**$_2$CH$_3$, q, *J* = 7.4 Hz, 2 H), 2.54 (C**H**$_2$CH(CH$_3$)$_2$, d, *J* = 7.1 Hz, 2 H), 1.99 (CH$_2$C**H**(CH$_3$)$_2$, sptt, *J* = 6.6, 7.1 Hz, 2 H), 1.15 (CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 3 H), 0.92 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 6 H).

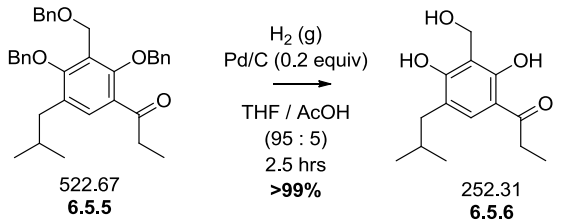
^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.8 (**C**OAr), 160.6 (**C**OBn *P*), 156.4 (**C**OBn *O*), 137.9 (**C** Bn), 137.5 (**C** Bn), 137.0 (**C** Bn), 131.8 (**C**H *O*), 131.5 (**C** *I*), 130.2 (**C***i*Bu), 128.7 (**C**H Bn), 128.7 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.0 (**C**H Bn), 127.9 (**C**H Bn), 127.7 (**C**H Bn), 127.6 (**C**H Bn), 127.3 (**C**H Bn), 126.2 (**C**CH$_2$OBn), 78.8 (**C**H$_2$ Bn), 77.0 (**C**H$_2$ Bn), 73.3 (CH$_2$O**C**H$_2$Ph), 62.7 (**C**H$_2$OBn), 39.1 (**C**H$_2$CHMe$_2$), 35.9 (CO**C**H$_2$CH$_3$), 29.2 (CH$_2$**C**HMe$_2$), 22.5 (CH$_2$CH(**C**H$_3$)$_2$), 8.5 (COCH$_2$**C**H$_3$).

IR (neat) : 3031, 2955, 2869, 1680, 1588 cm^{-1}.

MS (ES$^+$)(m/z) : 545 [M+Na]$^+$ (100%).

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 545.2662; Found. 545.2667.

1-(2,4-Dihydroxy-3-(hydroxymethyl)-5-*iso*butylphenyl)propan-1-one



To a solution of 1-(2,4-bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-one (95 mg, 0.182 mmol, 1 equiv) in THF (285 µL) was added Pd/C in one portion under nitrogen (g) followed by acetic acid dropwise (15 µL). The reaction was then purged with hydrogen (g) by bubbling through the suspension, adding THF periodically to combat evaporation. After 2.5 h under H_2 (g) the mixture was filtered through celite and washing with THF (3×3 mL), the solvent was then evaporated and the crude purified by column chromatography (20% diethylether in light petroleum ether 40/60) to yield a colourless oil (36 mg, 0.142 mmol. 78%).

R_f (diethylether / light petroleumether 40/60) (20 : 80) : 0.38

^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.02 (CO**H**, s, 1 H), 9.00 (**C**OH, s, 1 H), 7.40 (C**H**, s, 1 H), 5.09 (C**H**$_2$OH, d, *J* = 5.1 Hz, 2 H), 2.95 (C**H**$_2$CH$_3$, q, *J* = 7.1 Hz, 2 H), 2.43 (C**H**$_2$CHMe$_2$, d, *J* = 7.1 Hz, 2 H), 2.33 (CH$_2$O**H**, t, *J* = 5.3 Hz, 1 H), 1.92 (CH$_2$C**H**Me$_2$, sptt, *J* = 6.6, 7.1 Hz, 1 H), 1.23 (CH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 3 H), 0.93 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 6 H).

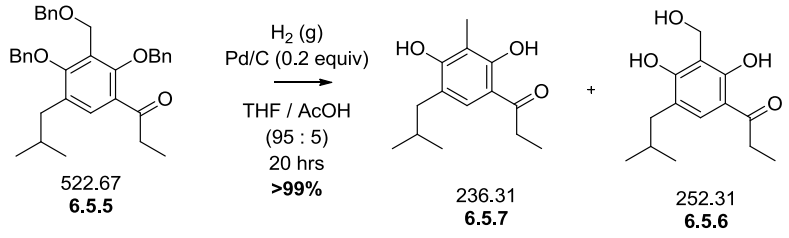
^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.7 (**C**=O), 162.1 (**C**OH *O*), 159.7 (**C**OH *P*), 131.4 (**C**H *O*), 120.6 (**C***i*Bu), 111.9 (**C**CH$_2$OH *M*), 110.4 (**C**CO *I*), 58.8 (**C**H$_2$OH), 38.8 (CO**C**H$_2$CH$_3$), 31.1 (**C**H$_2$CHMe$_2$), 28.5 (CH$_2$C**H**Me$_2$), 22.4 (CH$_2$CH(CH$_3$)$_2$), 8.7 (COCH$_2$**C**H$_3$).

IR (neat) : 3403, 3213, 2964, 2914, 1606 cm^{-1}

MS (ES$^-$)(m/z) : 316 [M+Na+MeCN]$^+$ (88%), 527 [2M+Na]$^+$ (100%).

HRMS (ES$^-$) : [M-H]$^-$. Calcd. 251.1289; Found. 251.1285.

1-(2,4-Dihydroxy-5-*iso*butyl-3-methylphenyl)propan-1-one



To a solution of 1-(2,4-bis(benzyloxy)-3-((benzyloxy)methyl)-5-*iso*butylphenyl)propan-1-one (60 mg, 0.115 mmol, 1 equiv) in THF (0.95 mL) was added Pd/C in one portion under nitrogen (g) followed by acetic acid dropwise (50µL). The reaction was then purged with hydrogen (g) by bubbling through the suspension, adding THF periodically to combat evaporation. After 20 h under H_2 (g) the mixture was filtered through celite and washing with THF (3×3 mL), the solvent was then evaporated to yield a crude mixture of the product and 1-(2,4-dihydroxy-3-(hydroxymethyl)-5-*iso*butylphenyl)propan-1-one as a pale yellow oil (28 mg, 0.115 mmol. >99%) (ratio ≈ 98 : 2).

R_f (diethylether / light petroleum 40/60) (25 : 75) : 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.97 (CO**H**, s, 1 H), 7.36 (C**H**, s, 1 H), 5.35 (CO**H**, br. s, 1 H), 2.97 ($COCH_2C\mathbf{H}_3$, q, *J* = 7.2 Hz, 2 H), 2.44 ($C\mathbf{H}_2CHMe_2$, d, *J* = 7.1 Hz, 2 H), 2.14 ($CC\mathbf{H}_3$, s, 3 H), 1.89 ($CH_2C\mathbf{H}Me_2$, tspt, *J* = 7.1 Hz, 1 H), 1.24 ($COCH_2C\mathbf{H}_3$, t, *J* = 7.3 Hz, 3 H), 0.94 ($CH_2CH(C\mathbf{H}_3)_2$, d, *J* = 7.1 Hz, 6 H).

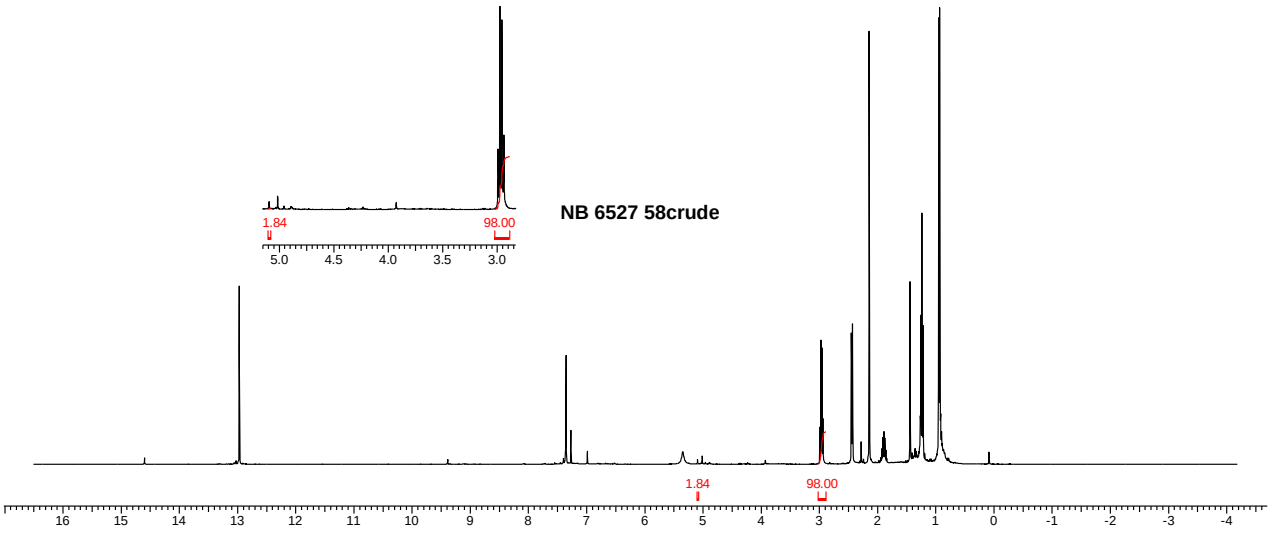
^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.7 (**C**=O), 161.1 (**C**OH *O*), 158.4 (**C**OH *P*), 129.5 (**C**H *O*), 118.3 (**C***i*Bu *M*), 112.7 (**C**Me *M*), 110.3 (**C**CO *I*), 39.2 ($\mathbf{C}H_2CHMe_2$), 31.2 ($CO\mathbf{C}H_2CH_3$), 28.7 ($CH_2\mathbf{C}HMe_2$), 22.4 ($CH_2CH(\mathbf{C}H_3)_2$), 8.7 ($C\mathbf{C}H_3$ *M*), 7.5 ($COCH_2\mathbf{C}H_3$).

IR (neat) : 3457, 2955, 2869, 1624, 1464 cm^{-1}

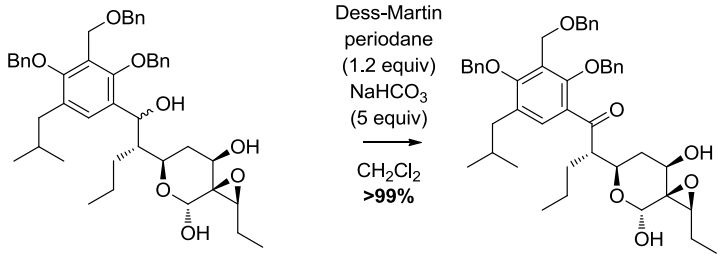
MS (ES^-)(m/z) : 235 $[M-H]^-$ (100%),

HRMS (ES^+) : $[M+Na]^+$ Calcd. 237.1485; Found. 237.1490.

ratio of products *from* ^{1}H NMR – NB 6527 58crude



Oxidation of benzylic alcohol 6.4.7



To a solution of benzylic alcohol **6.4.7** (17.5 mg, 24.1 µmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was added sequentially $NaHCO_3$ (10.1 mg, 121 µmol, 5 equiv) and Dess-Martin periodane (11 mg, 25 mmol, 1.05 equiv) under nitrogen (g). The mixture was stirred at rt for 1 h before quenching with Na_2SO_3 (sat. 3 mL) and water (1 mL). The mixture was then extracted with portions of CH_2Cl_2 (3×2 mL) and the combined extracts washed with $NaHCO_3$ (aq, 3×1.5 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (30% ethylacetate in hexane) to yield a colourless oil (16.9 mg, 23.4 µmol. 97%).

R_f (ethylacetate / hexane) (30 : 70) : 0.46

$[\alpha]_D$: -22.6 (c 0.563 g/100mL, $CHCl_3$, 25^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 - 7.32 (C**H** $_{Bn}$, m, 11 H), 7.30 - 7.21 (C**H** $_{Bn\ \&\ Ar}$, m, 8 H), 5.18 (C**H**$_{2\ Bn}$, d, *J* = 11.1 Hz, 1 H), 5.09 (C**H**$_2^{*}$ $_{Bn}$, d, *J* = 11.1 Hz, 1 H), 5.08 (C**H**$_{2\ Bn}$, d,

J = 11.1 Hz, 1 H), 5.02 (C**H**$_2$ * $_{Bn}$, d, *J* = 11.6 Hz, 1 H), 4.69 (C**H**$_2$OBn, d, *J* = 9.1 Hz, 1 H), 4.68 (C**H**$_2$OBn*, d, *J* = 9.1 Hz, 1 H), 4.67 (C**H**OHO, *br*s, 1 H), 4.58 (CH_2OC**H**$_2$Ph, d, *J* = 11.6 Hz, 1 H), 4.55 (CH_2OC**H**$_2$Ph*, d, *J* = 11.6 Hz, 1 H), 4.41 (C**H**OHCH_2, dd, *J* = 4.0, 11.1 Hz, 1 H), 4.11 (C**H**OCOH, dt, *J* = 4.5, 11.6 Hz, 1 H), 3.31 (C**H**COAr, td, *J* = 4.3, 8.6 Hz, 1 H), 3.22 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.64 (CO**H**O, *br*s., 1 H), 2.54 (C**H**$_2$CHMe$_2$, d, *J* = 7.1 Hz, 2 H), 2.03 - 1.90 (CH_2C**H**Me$_2$, CHOHC**H**$_2$, C**H**$_2CH_2CH_3$, m, 3 H), 1.68 - 1.35 (CHOHC**H**$_2^{*}$, C**H**$_2CH_2CH_3^{*}$, CH_2C**H**$_2CH_3$, C**H**$_2CH_3$ $_{epox}$, m, 6 H), 1.32 - 1.18 (m, 2 H), 1.04 (CH_2C**H**$_3$ $_{epox}$, t, *J* = 7.6 Hz, 3 H), 0.93 (CH_2CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 3 H), 0.91 (CH_2CH(C**H**$_3$)$_2^{*}$, d, *J* = 6.6 Hz, 3 H), 0.91 (CH_2CH_2C**H**$_3$, t, *J* = 7.1 Hz, 3 H).

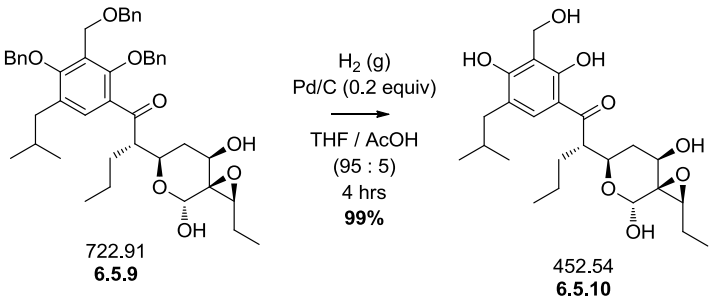
^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.1 (**C**OAr), 159.9 (**C**OBn), 155.1 (**C**OBn), 137.8 (**C** Bn), 137.5 (**C** Bn), 137.1 (**C** Bn), 131.8 (**C** Ar), 131.7 (**C** Ar), 130.5 (**C**H Bn), 128.5 (**C**H Bn), 128.5 (**C**H Bn), 128.4 (**C**H Bn), 128.1 (**C**H Bn), 128.0 (**C**H Bn), 127.9 (**C**H Bn), 127.7 (**C**H Bn), 127.3 (**C**H Bn), 126.6 (**C**CH_2OBn), 94.3 (**C**OHO), 79.5 (**C**H_2 Bn), 77.0 (**C**H_2 Bn), 73.4 (CH_2O**C**H_2Ph), 67.4 (**C**HOHCH_2), 62.9 (**C**HOCOH), 62.7 (**C**H_2OBn), 61.5 (**C** epox), 59.5 (**C**H epox), 55.0 (**C**HCOAr), 39.1 (**C**H_2CHMe$_2$), 37.1 (CHOH**C**H_2), 29.2 (CH_2**C**HMe$_2$), 27.7 (**C**$H_2CH_2CH_3$), 22.5 (CH_2CH(**C**H_3)$_2$), 22.4 (CH_2CH(**C**H_3)$_2$*), 21.0 (CH_2**C**H_2CH_3), 20.5 (**C**H_2CH_3 epox), 14.3 (CH_2CH_2**C**H_3), 10.5 (CH_2CH_3 epox).

MS (ES^{+})(m/z) : 745 [M+Na]$^{+}$ (100%).

IR (neat) : 3447, 3031, 2957, 2871, 1679 1589 cm^{-1}.

HRMS (ES^{+}) : [M+Na]$^{+}$ Calcd. 745.3711; Found. 745.3706.

(1-Hydroxymethylene) luminacin D



To a solution of hemiacetal **6.5.9** (16.8 mg, 23.2 µmol, 1 equiv) in THF (95 µL) was added Pd/C in one portion under nitrogen (g) followed by acetic acid dropwise (5 µL). The reaction was then purged with hydrogen (g) by bubbling through the suspension, adding THF periodically to combat evaporation. After 4 h under H_2 (g) the mixture was filtered

through celite and washing with THF (4×2 mL), the solvent was then evaporated and the crude purified by column chromatography (30% ethylacetate in hexane) to yield a colourless oil (10.4 mg, 22.8 µmol. 99%).

R_f (ethylacetate / hexane) (35 : 65) : 0.16

^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.28 (ArO**H**, s, 1 H), 9.23 (ArO**H**, s, 1 H), 7.47 (C**H** $_{Ar}$, s, 1 H), 5.07 (C**H**$_2$OH, d, *J* = 14.1 Hz, 1 H), 5.11 (C**H**$_2$OH*, d, *J* = 14.1 Hz, 1 H), 5.00 (C**H**OHO, *br*s, 1 H), 4.35 (C**H**OHCH$_2$ *br*t, *J* = 9.1 Hz, 1 H), 4.18 (C**H**OCOH, dt, *J* = 4.5, 11.6 Hz, 1 H), 3.57 (C**H**COAr, *br*q, *J* = 7.4 Hz, 1 H), 3.29 (C**H** $_{epox}$, t, *J* = 6.3 Hz, 1 H), 2.72 (O**H**, br. s., 1 H), 2.61 (O**H**, br. s., 1 H), 2.40 (C**H**$_2$CHMe$_2$, dd, *J* = 7.1, 13.1 Hz, 1 H), 2.47 (C**H**$_2$CHMe$_2^*$, dd, *J* = 7.1, 13.1 Hz, 1 H), 1.98 (CHOHC**H**$_2^{Eq}$, ddd, *J* = 1.3, 4.8, 12.1 Hz, 1 H), 1.91 (CH$_2$C**H**Me$_2$, sptt, *J* = 6.6, 6.8 Hz, 1 H), 1.81 (C**H**$_2$CH$_2$CH$_3$, *br*q, *J* = 7.6 Hz, 2 H), 1.70 - 1.46 (C**H**$_2$CH$_3$ $_{epox}$, m, 2 H), 1.40 (CHOHC**H**$_2^{Ax}$, q, *J* = 11.6 Hz, 1 H), 1.32 - 1.15 (CH$_2$C**H**$_2$CH$_3$, m, 2 H), 1.08 (CH$_2$C**H**$_3$ $_{epox}$, t, *J* = 7.3 Hz, 3 H), 0.91 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 4.0 Hz, 3 H), 0.93 (CH$_2$CH(C**H**$_3$)$_2^*$, d, *J* = 4.0 Hz, 3 H), 0.86 (CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.3 Hz, 3 H).

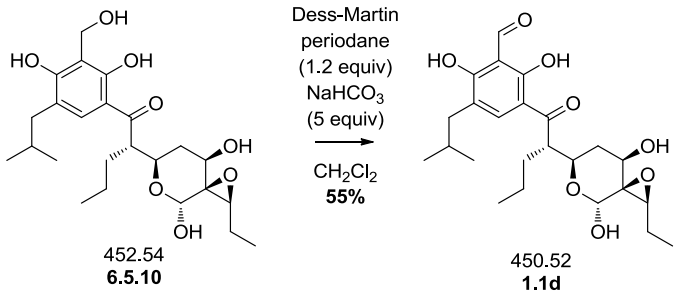
^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.5 (**C**OAr), 163.0 (**C**OH Ar), 160.5 (**C**OH Ar), 132.0 (**C**H Ar), 120.9 (**C** Ar), 113.4 (**C** Ar), 110.4 (**C**CH$_2$OH Ar), 94.4 (**C**HOHO), 69.9 (**C**HOHCH$_2$), 62.5 (**C**HOCOH), 61.9 (**C** epox), 59.9 (**C**H epox), 58.9 (**C**H$_2$OH), 49.4 (**C**HCOAr), 38.8 (**C**H$_2$CHMe$_2$), 37.6 (CHOH**C**H$_2$), 32.2 (**C**H$_2$CH$_2$CH$_3$), 28.4 (CH$_2$**C**HMe$_2$), 22.4 (CH$_2$CH(**C**H$_3$)$_2$), 22.3 (CH$_2$CH(**C**H$_3$)$_2^*$), 20.6 (**C**H$_2$CH$_3$ epox), 20.5 (CH$_2$C**H**$_2$CH$_3$), 14.2 (CH$_2$CH$_2$**C**H$_3$), 10.5 (CH$_2$C**H**$_3$ epox).

IR (neat) : 3384, 2958, 2871, 1619, 1464 cm^{-1}.

MS (ES$^+$)(m/z) : 475 [M+Na]$^+$ (100%), 547 [M-2H+*t*Bu+Na]$^+$ (76%), 928 [2M+Na]$^+$.

HRMS (ES$^+$) : [M+Na]$^+$ Calcd. 475.2302; Found. 475.2305.

Luminacin D



To a solution of (1-hydroxymethylene) luminacin D **6.5.10** (10.1 mg, 23.7 µmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was added sequentially $NaHCO_3$ (10 mg, 0.12 mmol, 5 equiv) and Dess-Martin periodane (10.6 mg, 24.9 µmol, 1.05 equiv) under nitrogen (g). The mixture was stirred at rt for 1 h before quenching with Na_2SO_3 (sat. 3 mL) and water (1 mL). The mixture was then extracted with portions of CH_2Cl_2 (3×4 mL) and the combined extracts washed with $NaHCO_3$ (aq, 4 mL), $KHSO_4$ (10% w/w, aq, 4 mL), dried over Na_2SO_4 (anh), filtered and the solvent evaporated under reduced pressure. The crude residue was then purified by column chromatography (35% ethylacetate in hexane) to yield a pale yellow residue (5.9 mg, 13.1 µmol. 55%).

R_f (ethylacetate / hexane) (35 : 65) : 0.15

$[\alpha]_D$: -13.5 (c 0.10 g/100 mL, $CHCl_3$, 23°C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.15 (ArO**H** $_{C2}$, s, 1 H), 12.99 (ArO**H** $_{C6}$, s, 1 H), 10.41 (C**H**O, s, 1 H), 7.74 (C**H** $_{Ar}$, s, 1 H), 5.00 (C**H**OHO, d, *J* = 2.5 Hz, 1 H), 4.39 (C**H**OCOH, ddd, *J* = 1.5, 9.1, 11.0 Hz, 1 H), 4.20 (C**H**OHCH$_2$, dt, *J* = 5.1, 11.6 Hz, 1 H), 3.56 (C**H**COAr, dt, *J* = 4.0, 8.6 Hz, 1 H), 3.30 (C**H** $_{epox}$, t, *J* = 6.6 Hz, 1 H), 2.53 (CO**H**O, d, *J* = 2.5 Hz, 1 H), 2.47 (C**H**$_2$CHMe$_2$, dd, *J* = 7.0, 13.6 Hz, 2 H), 2.42 (C**H**$_2$CHMe$_2$, dd, *J* = 7.1, 13.6 Hz, 1 H), 2.03 (CHOHC**H**$_2^{Eq}$, ddd, *J* = 1.5, 4.5, 12.1 Hz, 1 H), 1.97 - 1.74 (CH$_2$C**H**Me$_2$, C**H**$_2$CH$_2$CH$_3$, m, 3 H), 1.70 - 1.58 (C**H**$_2$CH$_3$ $_{epox}$, m, 2 H), 1.56 (CHO**H**CH$_2$, **H**$_2$O, s, 5 H), 1.42 (CHOHC**H**$_2^{Ax}$, q, *J* = 12.1 Hz, 2 H), 1.34 - 1.17 (CH$_2$C**H**$_2$CH$_3$, m, 2 H), 1.09 (CH$_2$C**H**$_3$ $_{epox}$, t, *J* = 7.6 Hz, 3 H), 0.92 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 6 H), 0.93 (CH$_2$CH(C**H**$_3$)$_2$, d, *J* = 6.6 Hz, 1 H), 0.89 (CH$_2$CH$_2$C**H**$_3$, t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.6 (CH**C**OAr), 194.3 (**C**HO), 168.0 (**C**HOH C2), 167.5 (**C**OH C6), 139.4 (**C**H Ar), 121.0 (**C** C5), 112.5 (**C** C3), 109.3 (**C** C1), 94.5 (**C**HOHO), 69.8 (**C**HOCOH), 62.4 (**C**HOHCH$_2$), 61.8 (**C** epox), 59.8 (**C**H epox), 49.4

(**C**HOAr), 37.9 (**C**H_2CHMe_2), 37.3 (CHOH**C**H_2), 32.1 (**C**$H_2CH_2CH_3$), 28.3 (CH_2**C**HMe_2), 22.3 (CH_2CH(**C**$H_3)_2$), 22.3 (CH_2CH(**C**$H_3)_2$*), 20.6 (CH_2**C**H_2CH_3), 20.6 (**C**H_2CH_3 epox), 14.2 (CH_2CH_2**C**H_3), 10.5 (CH_2**C**H_3 epox).

IR (neat) : 3407, 2959,2872,1629,1459 cm^{-1}.

MS (ES^+)(m/z) : 473 $[M+Na]^+$ (91%), 924 $[2M+Na]^+$ (100%).

HRMS (ES^+) : $[M+Na]^+$ Calcd. 473.2146; Found. 473.2151.

Data matches literature. [1]

Chapter 9 Appendix

9.1 XRD data

Table 9.1 Crystal data and structure refinement details.

Identification code	**2.3.6** (**2009sot0833**)
Empirical formula	$C_{11}H_{15}NO_4S$
	$C_{11}H_{11}O_4S,\ NH_4$
Formula weight	257.30
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.5956(13) Å
	b = 13.1326(10) Å β = 101.485(4)°
	c = 6.5258(5) Å
Volume	1225.81(17) Å^3
Z	4
Density (calculated)	1.394 Mg / m^3
Absorption coefficient	0.267 mm^{-1}
F(000)	544
Crystal	Lath; Colourless
Crystal size	0.34 × 0.13 × 0.02 mm^3
θ range for data collection	3.10 – 27.48°
Index ranges	$-18 \le h \le 18$, $-16 \le k \le 16$, $-8 \le l \le 8$
Reflections collected	11605
Independent reflections	2788 [R_{int} = 0.0828]
Completeness to θ = 27.48°	98.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9947 and 0.9148
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2788 / 0 / 171

Goodness-of-fit on F^2	1.204
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0847, $wR2$ = 0.1347
R indices (all data)	$R1$ = 0.1314, $wR2$ = 0.1518
Largest diff. peak and hole	0.402 and –0.369 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the NH4 which were freely refined.

Table 9.2 Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{equiv} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{equiv}	*S.o.f.*
S1	1573(1)	3705(1)	10629(2)	19(1)	1
O1	1624(2)	3128(2)	12647(4)	24(1)	1
O2	1069(2)	5120(2)	13231(4)	23(1)	1
O3	1098(2)	5375(2)	7771(4)	25(1)	1
O4	571(2)	6490(2)	9874(5)	31(1)	1
N1	–187(3)	6516(3)	4839(6)	20(1)	1
C1	2766(3)	3797(3)	10292(6)	17(1)	1
C2	3464(3)	3421(3)	11848(7)	26(1)	1
C3	4379(3)	3434(3)	11549(7)	30(1)	1
C4	4587(3)	3824(3)	9720(7)	31(1)	1
C5	3881(3)	4187(3)	8163(7)	32(1)	1
C6	2963(3)	4175(3)	8434(6)	24(1)	1
C7	1423(3)	5054(3)	11359(6)	17(1)	1
C8	2031(3)	5404(3)	13318(6)	21(1)	1
C9	2317(3)	6487(3)	13747(6)	26(1)	1
C10	3261(3)	6682(4)	13162(7)	34(1)	1
C11	990(3)	5712(3)	9506(6)	19(1)	1

Table 9.3 Bond lengths [Å] and angles [°].

S1–O1	1.508(3)
S1–C1	1.803(4)
S1–C7	1.859(4)
O2–C7	1.421(4)
O2–C8	1.443(5)
O3–C11	1.254(4)
O4–C11	1.239(5)
C1–C2	1.379(6)
C1–C6	1.391(5)
C2–C3	1.388(6)
C3–C4	1.387(6)
C4–C5	1.380(6)
C5–C6	1.386(6)
C7–C8	1.477(5)
C7–C11	1.518(5)
C8–C9	1.493(5)
C9–C10	1.523(6)
O1–S1–C1	105.03(17)
O1–S1–C7	104.06(16)
C1–S1–C7	97.62(17)
C7–O2–C8	62.1(2)
C2–C1–C6	121.3(4)
C2–C1–S1	118.4(3)
C6–C1–S1	120.2(3)
C1–C2–C3	118.8(4)
C4–C3–C2	120.5(4)
C5–C4–C3	120.1(4)
C4–C5–C6	120.1(4)
C5–C6–C1	119.2(4)
O2–C7–C8	59.7(2)

O2–C7–C11	119.1(3)
C8–C7–C11	126.6(3)
O2–C7–S1	111.1(2)
C8–C7–S1	115.9(3)
C11–C7–S1	112.9(3)
O2–C8–C7	58.2(2)
O2–C8–C9	119.2(3)
C7–C8–C9	123.8(3)
C8–C9–C10	110.2(3)
O4–C11–O3	128.4(4)
O4–C11–C7	117.3(3)
O3–C11–C7	114.3(3)

Table 9.4 Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	21(1)	16(1)	21(1)	–1(1)	6(1)	0(1)
O1	26(2)	22(2)	28(2)	8(1)	12(1)	2(1)
O2	26(2)	24(2)	23(2)	–3(1)	12(1)	–2(1)
O3	31(2)	28(2)	17(2)	3(1)	3(1)	8(1)
O4	33(2)	22(2)	35(2)	–4(1)	0(1)	8(1)
N1	25(2)	14(2)	22(2)	2(2)	5(2)	4(2)
C1	19(2)	15(2)	19(2)	–6(2)	6(2)	–2(2)
C2	24(2)	25(2)	28(2)	1(2)	5(2)	2(2)
C3	24(2)	27(2)	38(3)	2(2)	2(2)	2(2)
C4	24(2)	28(2)	43(3)	0(2)	13(2)	–1(2)
C5	31(3)	36(3)	34(3)	5(2)	18(2)	3(2)
C6	27(2)	23(2)	22(2)	5(2)	6(2)	3(2)
C7	21(2)	15(2)	16(2)	–2(2)	9(2)	2(2)
C8	26(2)	23(2)	15(2)	–2(2)	7(2)	–1(2)
C9	34(3)	25(2)	17(2)	–4(2)	3(2)	–5(2)
C10	31(3)	32(3)	40(3)	1(2)	8(2)	–7(2)
C11	15(2)	19(2)	22(2)	–2(2)	3(2)	–2(2)

Table 9.5 Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

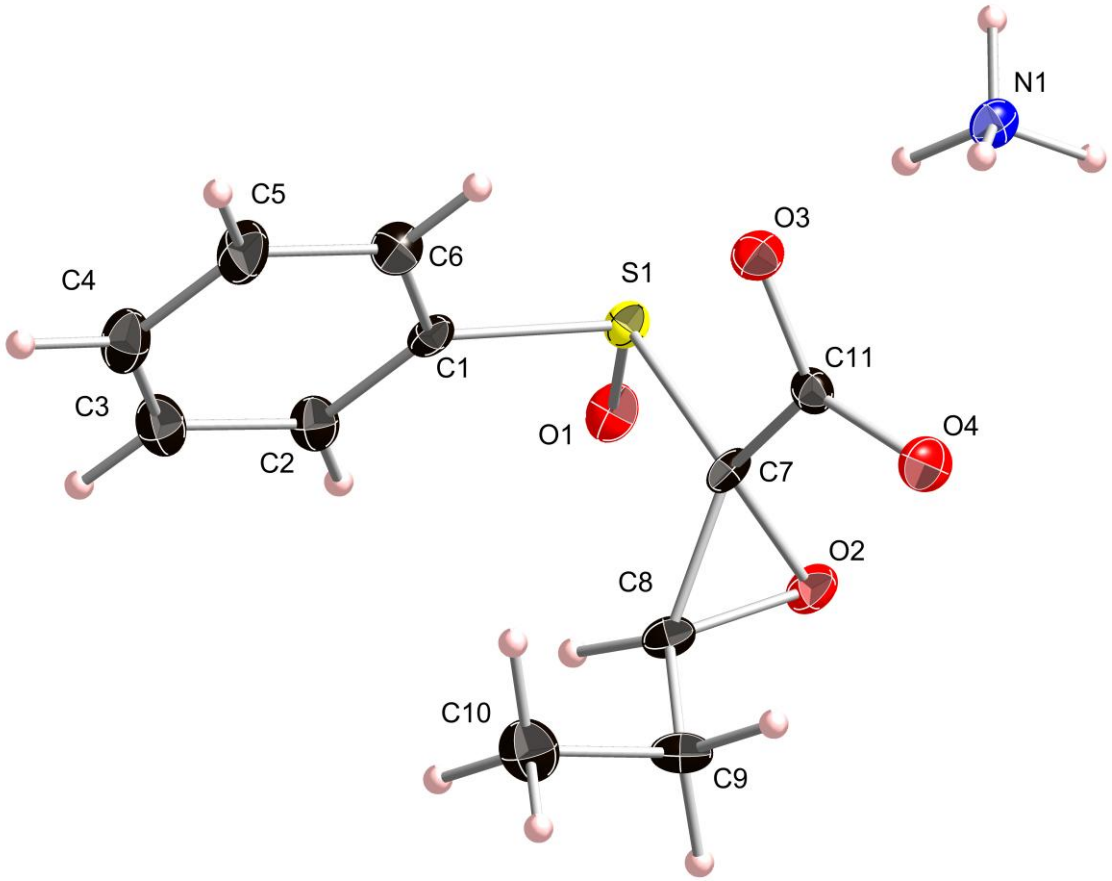
Atom	*x*	*y*	*z*	U_{equiv}	*S.o.f.*
H901	–710(30)	6610(30)	5440(70)	31(13)	1
H902	–370(40)	6140(40)	3730(90)	48(16)	1
H903	50(30)	7100(40)	4580(80)	43(15)	1
H904	290(30)	6150(30)	5680(70)	22(11)	1
H2	3321	3157	13103	31	1
H3	4867	3174	12605	36	1
H4	5217	3841	9538	37	1
H5	4024	4446	6904	39	1
H6	2474	4421	7365	29	1
H8	2500	4891	14003	26	1
H9A	2358	6638	15249	31	1
H9B	1841	6943	12928	31	1
H10A	3731	6230	13975	51	1
H10B	3444	7392	13467	51	1
H10C	3214	6549	11667	51	1

Table 9.6 Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N1–H901···O1^{i}	0.93(5)	2.03(5)	2.946(4)	167(4)
N1–H902···O3^{ii}	0.87(6)	2.38(6)	3.152(5)	149(4)
N1–H903···O4^{iii}	0.87(5)	1.99(6)	2.841(5)	163(5)
N1–H904···O3	0.93(5)	1.90(5)	2.828(5)	169(4)

Symmetry transformations used to generate equivalent atoms:

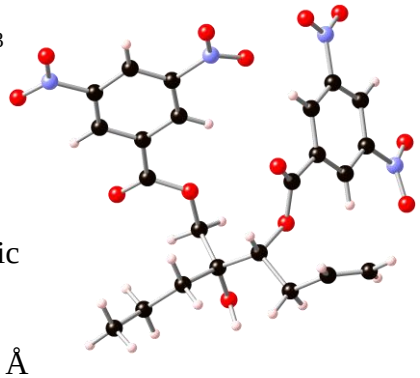
(i) –x,–y+1,–z+2 (ii) –x,–y+1,–z+1 (iii) x,–y+3/2,z–1/2



Thermal ellipsoids drawn at the 35% probability level.

Table 9.7 Crystal data and structure refinement details.

Identification code	**5.1.3** (**2011sot0021**)
Empirical formula	$C_{23}H_{22}N_4O_{13}$
Formula weight	562.45
Temperature	120(2) K
Wavelength	0.68890 Å
Crystal system	Orthorhombic
Space group	*P*212121
Unit cell dimensions	a = 5.011(3) Å
	b = 20.820(12) Å
	c = 23.075(13) Å
Volume	2407(2) Å^3
Z	4
Density (calculated)	1.552 Mg / m^3
Absorption coefficient	0.129 mm^{-1}
F(000)	1168
Crystal	Needle; Colourless
Crystal size	0.09 × 0.01 × 0.01 mm^3
θ range for data collection	2.97 – 24.30°
Index ranges	$-5 \le h \le 4$, $-24 \le k \le 24$, $-27 \le l \le 27$
Reflections collected	19589
Independent reflections	2487 [R_{int} = 0.0435]
Completeness to θ = 24.30°	99.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.768
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2487 / 0 / 366
Goodness-of-fit on F^2	1.231
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0372, *wR2* = 0.0924
R indices (all data)	*R1* = 0.0397, *wR2* = 0.0943
Largest diff. peak and hole	0.173 and –0.214 e Å^{-3}



Appendix

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, ,except fro the OH – this was identified in the difference map and freely refined.

Relative stereochemistry: C(9) = S, C(10) = S

Table 9.8 Atomic coordinates [× 104], equivalent isotropic displacement parameters [Å2 × 103] and site occupancy factors. U equiv is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	*x*	*y*	*z*	U_{equiv}	*S.o.f.*
O1	4413(5)	6728(1)	10582(1)	38(1)	1
O2	883(5)	7085(1)	10154(1)	36(1)	1
O3	−2(4)	6834(1)	8070(1)	39(1)	1
O4	3394(5)	6462(1)	7594(1)	41(1)	1
O5	8162(5)	6995(1)	6615(1)	40(1)	1
O6	11724(5)	7084(1)	6101(1)	42(1)	1
O7	16795(4)	5220(1)	5600(1)	35(1)	1
O8	15243(5)	4279(1)	5810(1)	44(1)	1
O9	10399(4)	5238(1)	9534(1)	31(1)	1
O10	9161(4)	4984(1)	8623(1)	26(1)	1
O11	5842(4)	4909(1)	7489(1)	29(1)	1
O12	9270(4)	4204(1)	7508(1)	25(1)	1
O13	12054(4)	3423(1)	8430(1)	26(1)	1
N1	3008(5)	6796(1)	10156(1)	29(1)	1
N2	2191(5)	6578(1)	8046(1)	31(1)	1
N3	10134(5)	6770(1)	6381(1)	31(1)	1
N4	15164(5)	4864(1)	5833(1)	30(1)	1
C1	3908(6)	6513(1)	9604(1)	25(1)	1
C2	2591(6)	6687(1)	9103(1)	27(1)	1
C3	3481(6)	6403(1)	8597(1)	27(1)	1
C4	5497(6)	5952(1)	8585(1)	26(1)	1
C5	6758(6)	5789(1)	9101(1)	24(1)	1
C6	5980(6)	6082(1)	9618(1)	26(1)	1
C7	8956(6)	5313(1)	9122(1)	25(1)	1
C8	11155(6)	4485(1)	8592(1)	25(1)	1
C9	9801(6)	3833(1)	8506(1)	23(1)	1
C10	8000(6)	3828(1)	7969(1)	24(1)	1
C11	7987(6)	4725(1)	7322(1)	24(1)	1
C12	9590(6)	5079(1)	6884(1)	24(1)	1

C13	9065(6)	5732(1)	6820(1)	26(1)	1
C14	10593(6)	6078(1)	6436(1)	27(1)	1
C15	12609(6)	5811(1)	6106(1)	28(1)	1
C16	13009(6)	5160(1)	6172(1)	25(1)	1
C17	11585(6)	4786(1)	6557(1)	25(1)	1
C18	8121(6)	3648(1)	9036(1)	24(1)	1
C19	9663(6)	3492(1)	9584(1)	30(1)	1
C20	7786(7)	3258(1)	10055(1)	32(1)	1
C21	7498(6)	3161(1)	7712(1)	28(1)	1
C22	5531(7)	3179(1)	7221(1)	33(1)	1
C23	6144(8)	3120(1)	6672(1)	40(1)	1

Table 9.9 Bond lengths [Å] and angles [°].

O1–N1	1.218(3)
O2–N1	1.223(3)
O3–N2	1.223(3)
O4–N2	1.228(3)
O5–N3	1.220(3)
O6–N3	1.218(3)
O7–N4	1.228(3)
O8–N4	1.220(3)
O9–C7	1.204(3)
O10–C7	1.344(3)
O10–C8	1.444(3)
O11–C11	1.204(4)
O12–C11	1.333(3)
O12–C10	1.466(3)
O13–C9	1.427(3)
N1–C1	1.474(3)
N2–C3	1.473(3)
N3–C14	1.463(3)
N4–C16	1.470(4)
C1–C6	1.373(4)
C1–C2	1.380(4)
C2–C3	1.383(4)
C3–C4	1.380(4)
C4–C5	1.388(4)
C5–C6	1.398(4)
C5–C7	1.482(4)
C8–C9	1.530(4)
C9–C18	1.534(3)
C9–C10	1.534(4)
C10–C21	1.529(3)

C11–C12	1.486(4)
C12–C13	1.393(3)
C12–C17	1.394(4)
C13–C14	1.376(4)
C14–C15	1.382(4)
C15–C16	1.378(4)
C16–C17	1.380(4)
C18–C19	1.516(4)
C19–C20	1.518(4)
C21–C22	1.503(4)
C22–C23	1.309(4)
C7–O10–C8	117.5(2)
C11–O12–C10	117.4(2)
O1–N1–O2	124.4(2)
O1–N1–C1	118.3(2)
O2–N1–C1	117.3(2)
O3–N2–O4	124.5(2)
O3–N2–C3	117.6(2)
O4–N2–C3	117.9(2)
O6–N3–O5	123.9(2)
O6–N3–C14	118.2(2)
O5–N3–C14	117.9(2)
O8–N4–O7	124.2(3)
O8–N4–C16	117.8(2)
O7–N4–C16	118.0(2)
C6–C1–C2	123.6(2)
C6–C1–N1	118.2(2)
C2–C1–N1	118.2(2)
C1–C2–C3	116.2(2)
C4–C3–C2	122.9(2)
C4–C3–N2	118.3(2)
C2–C3–N2	118.8(2)

C3–C4–C5	118.9(2)
C4–C5–C6	119.9(2)
C4–C5–C7	122.0(2)
C6–C5–C7	118.1(2)
C1–C6–C5	118.4(2)
O9–C7–O10	124.3(3)
O9–C7–C5	124.0(2)
O10–C7–C5	111.6(2)
O10–C8–C9	109.7(2)
O13–C9–C8	101.3(2)
O13–C9–C18	112.5(2)
C8–C9–C18	111.3(2)
O13–C9–C10	111.18(19)
C8–C9–C10	111.82(19)
C18–C9–C10	108.6(2)
O12–C10–C21	105.98(19)
O12–C10–C9	109.1(2)
C21–C10–C9	114.6(2)
O11–C11–O12	125.8(2)
O11–C11–C12	122.9(2)
O12–C11–C12	111.2(2)
C13–C12–C17	120.3(2)
C13–C12–C11	117.0(2)
C17–C12–C11	122.6(2)
C14–C13–C12	118.4(3)
C13–C14–C15	123.4(2)
C13–C14–N3	119.0(3)
C15–C14–N3	117.6(2)
C16–C15–C14	116.2(2)
C15–C16–C17	123.5(3)
C15–C16–N4	117.4(2)
C17–C16–N4	119.0(2)

C16–C17–C12	118.2(2)
C19–C18–C9	116.0(2)
C18–C19–C20	110.5(3)
C22–C21–C10	112.2(2)
C23–C22–C21	125.0(3)

Table 9.10 Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement

factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	46(1)	43(1)	24(1)	–4(1)	–4(1)	7(1)
O2	39(1)	32(1)	38(1)	1(1)	7(1)	9(1)
O3	33(1)	41(1)	45(1)	7(1)	–8(1)	4(1)
O4	54(2)	42(1)	25(1)	–3(1)	–6(1)	7(1)
O5	56(2)	25(1)	40(1)	0(1)	1(1)	8(1)
O6	60(2)	23(1)	41(1)	5(1)	2(1)	–9(1)
O7	36(1)	39(1)	30(1)	2(1)	5(1)	–8(1)
O8	61(2)	26(1)	44(1)	6(1)	20(1)	9(1)
O9	36(1)	28(1)	28(1)	–2(1)	–2(1)	3(1)
O10	32(1)	21(1)	27(1)	–3(1)	–2(1)	4(1)
O11	32(1)	28(1)	27(1)	3(1)	1(1)	4(1)
O12	31(1)	21(1)	24(1)	5(1)	4(1)	1(1)
O13	24(1)	22(1)	33(1)	0(1)	1(1)	2(1)
N1	35(1)	23(1)	29(1)	–1(1)	5(1)	2(1)
N2	38(2)	24(1)	30(1)	–1(1)	–7(1)	–3(1)
N3	47(2)	20(1)	27(1)	1(1)	–7(1)	–1(1)
N4	37(1)	31(1)	23(1)	4(1)	3(1)	0(1)
C1	31(2)	19(1)	25(1)	–2(1)	1(1)	–3(1)
C2	28(2)	21(1)	31(1)	1(1)	–1(1)	0(1)
C3	31(2)	23(1)	26(1)	1(1)	–5(1)	–2(1)
C4	34(2)	19(1)	25(1)	0(1)	2(1)	–1(1)
C5	26(1)	19(1)	26(1)	–1(1)	0(1)	–2(1)
C6	29(2)	21(1)	27(1)	–1(1)	–2(1)	–2(1)
C7	33(2)	17(1)	25(1)	1(1)	2(1)	–2(1)
C8	27(2)	21(1)	28(1)	–1(1)	2(1)	6(1)
C9	26(2)	19(1)	25(1)	0(1)	3(1)	3(1)
C10	28(1)	22(1)	23(1)	4(1)	4(1)	1(1)

C11	31(2)	18(1)	23(1)	−1(1)	−2(1)	0(1)
C12	29(2)	22(1)	21(1)	1(1)	−3(1)	−1(1)
C13	32(2)	23(1)	23(1)	−2(1)	−3(1)	−1(1)
C14	39(2)	19(1)	23(1)	1(1)	−5(1)	−1(1)
C15	39(2)	23(1)	22(1)	2(1)	−3(1)	−6(1)
C16	32(2)	24(1)	20(1)	−2(1)	−3(1)	1(1)
C17	31(2)	22(1)	22(1)	2(1)	−5(1)	−1(1)
C18	25(1)	24(1)	24(1)	1(1)	1(1)	1(1)
C19	34(2)	28(1)	26(1)	1(1)	−2(1)	1(1)
C20	43(2)	31(1)	24(1)	2(1)	1(1)	−7(1)
C21	35(2)	25(1)	23(1)	0(1)	0(1)	−3(1)
C22	36(2)	31(1)	33(2)	1(1)	−2(1)	0(1)
C23	61(2)	30(2)	29(1)	−1(1)	−3(2)	2(2)

Table 9.11 Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

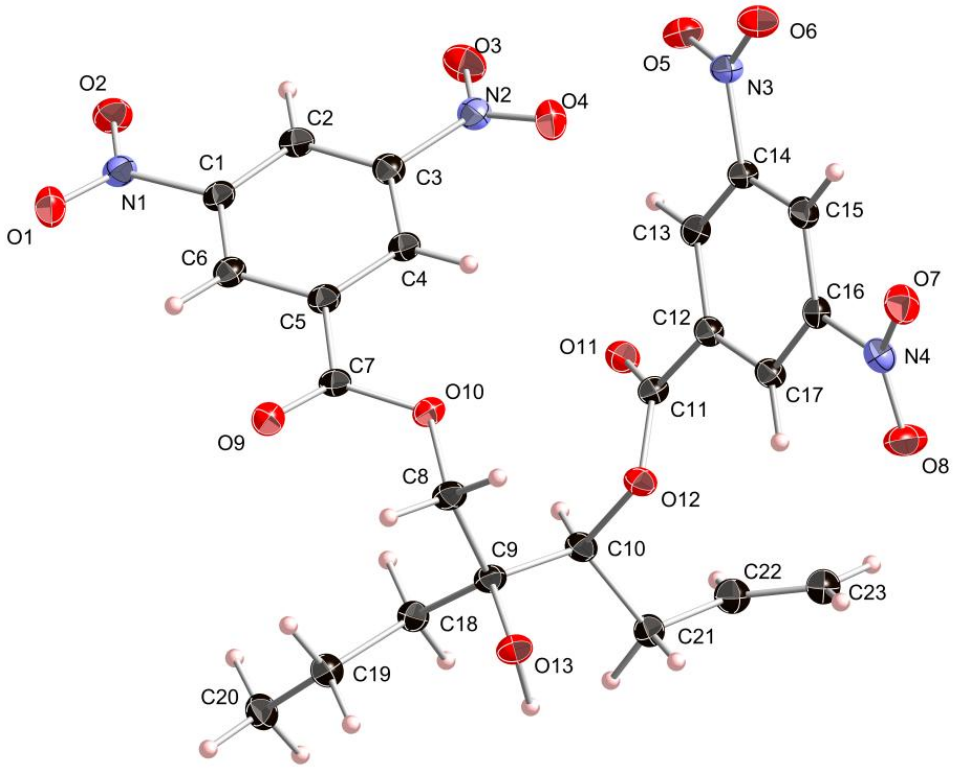
Atom	*x*	*y*	*z*	U_{equiv}	*S.o.f.*
H13A	11430(90)	3004(19)	8434(15)	66(12)	1
H2	1156	6985	9105	32	1
H4	6015	5756	8231	31	1
H6	6865	5986	9972	31	1
H8A	12216	4480	8954	30	1
H8B	12382	4571	8264	30	1
H10	6248	4029	8070	29	1
H13	7686	5933	7036	31	1
H15	13660	6062	5848	34	1
H17	11953	4340	6597	30	1
H18A	6884	4006	9122	29	1
H18B	7022	3270	8933	29	1
H19A	10617	3880	9720	36	1
H19B	11007	3156	9500	36	1
H20A	6799	2882	9915	49	1
H20B	6527	3601	10155	49	1
H20C	8821	3140	10399	49	1
H21A	9207	2982	7571	33	1
H21B	6813	2874	8020	33	1
H22	3702	3237	7316	40	1
H23A	7951	3061	6560	48	1
H23B	4781	3136	6386	48	1

Table 9.12 Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O13–H13A···O5^{i}	0.93(4)	2.11(4)	2.976(3)	154(4)

Symmetry transformations used to generate equivalent atoms:

(i) –x+2,y–1/2,–z+3/2



Thermal ellipsoids drawn at the 35% probability level.

9.2 Computation appendix

For Table 5.4 and Fig 5.1

Table 9.13 – Measured angles (^{o}) from energy minimised, DFT calculated structures of all possible Lactones and coupling constants calculated from the Karplus relationship (Hz)

				calculated coupling constant /(Hz)			
				angle	below 90	above 90	geminal
5.4.5a	vicinal	a	Ha - Hb	167.79		8.80	
		b	Hb - Hd	179.73		9.22	
		c	Hb - Hc	61.98	1.60		
		d	Hd - He	176.55		9.19	
		e	Hc - He	58.11	2.09		
	geminal	f	Hd - Hc	107.67			9.2
5.4.5b	vicinal	a	Ha - Hb	73.95	0.37		
		b	Hb - Hd	56.85	2.26		
		c	Hb - Hc	60.94	1.73		
		d	Hd - He	171.63		9.02	
		e	Hc - He	53.36	2.75		
	geminal	f	Hd - Hc	107.64			9.2
5.4.5c	vicinal	a	Ha - Hb	48.03	3.52		
		b	Hb - Hd	179.93		9.22	
		c	Hb - Hc	62.06	1.59		
		d	Hd - He	169.77		8.92	
		e	Hc - He	51.79	2.97		
	geminal	f	Hd - Hc	107.51			9.2
5.4.5d	vicinal	a	Ha - Hb	51.09	3.07		
		b	Hb - Hd	57.74	2.14		
		c	Hb - Hc	60.21	1.82		
		d	Hd - He	175.51		9.16	
		e	Hc - He	56.78	2.27		
	geminal	f	Hd - Hc	107.99			9.2

References

[1] N. Naruse, R. Kageyama-Kawase, Y. Funahashi, T. Wakabayashi, Y. Watanabe, T. Sameshima, K. Dobashi, *Journal of Antibiotics* **2000**, *53*, 579-590.

[2] J. Berdy, *Journal of Antibiotics* **2005**, *58*, 1-26.

[3] G. K. Suzuki, Izumi; Mitsutake, Kenichiro (Idemitsu Kosan co. ltd.), *Jpn. Kokai Tokkyo Koho* **1983**, *116*, 686.

[4] M. Klagsbrun, P. A. D'Amore, *Annual Review of Physiology* **1991**, *53*, 217-240.

[5] aT. E. Maione, R. J. Sharpe, *Trends in Pharmacological Sciences* **1990**, *11*, 457-461; bN. S. Grandjean, P., *Current Trends in Pharmaceutical Discovery* **2000**, *3*, 1-119; cJ. Folkman, Y. Shing, *Journal of Biological Chemistry* **1992**, *267*, 10931-10934.

[6] M. Rosenblatt, I; Azar, D, T. , *Seminars in Ophthalmology* **2006**, *21*, 151-160.

[7] J. Schlessinger, *Cell* **2000**, *100*, 293-296.

[8] A. W. Griffioen, G. Molema, *Pharmacological Reviews* **2000**, *52*, 237-268.

[9] H. E. Varmus, *Bioscience Reports* **1990**, *10*, 413-430.

[10] S. V. Sharma, C. Oneyama, Y. Yamashita, H. Nakano, K. Sugawara, M. Hamada, N. Kosaka, T. Tamaoki, *Oncogene* **2001**, *20*, 2068-2079.

[11] C. Oneyama, H. Nakano, S. V. Sharma, *Oncogene* **2002**, *21*, 2037-2050.

[12] W. Q. Xu, S. C. Harrison, M. J. Eck, *Nature* **1997**, *385*, 595-602.

[13] T. Wakabayashi, R. Kageyama-Kawase, N. Naruse, Y. Funahashi, K. Yoshimatsu, *Journal of Antibiotics* **2000**, *53*, 591-596.

[14] S. Hashimoto, M. Hiroso, A. Hashimoto, M. Morishige, A. Yamada, H. Hosaka, K. I. Akagi, E. Ogawa, C. Oneyama, T. Agatsuma, M. Okada, H. Kobayashi, H. Wada, H. Nakano, T. Ikegami, A. Nakagawa, H. Sabe, *Proceedings of the National Academy of Sciences of the United States of America* **2006**, *103*, 7036-7041.

[15] F. Fang, C. Johannes, Y. Y., X. Zhu, (Ed.: P. Appl.), **2010**.

[16] C. Oneyama, T. Agatsuma, Y. Kanda, H. Nakano, S. V. Sharma, S. Nakano, F. Narazaki, K. Tatsuta, *Chemistry & Biology* **2003**, *10*, 443-451.

[17] N. Atatreh, J. Barraclough, A. Welman, C. Cawthorne, R. A. Bryce, C. Dive, S. Freeman, *Journal of Enzyme Inhibition and Medicinal Chemistry* **2007**, *22*, 638-646.

[18] M. W. Davies, L. Maskell, M. Shipman, A. Slawin, M, Z;, S. Vidot, M, E;, J. Whatmore, L;, *Organic Letters* **2004**, *6*, 3909-3912.

[19] J. Shotwell, B;, E. Krygowski, S;, J. Hines, B. Koh, E. Huntsman, W, D;, H. Choi, W;, J. Schneekloth, S;, J. Wood, L;, C. Crews, M;, *Organic Letters* **2002**, *4*, 3087-3089.

[20] K. Tatsuta, S. Nakano, F. Narazaki, Y. Nakamura, *Tetrahedron Letters* **2001**, *42*, 7625-7628.

[21] M. Maier, R. Jogireddy, *Journal of Organic Chemistry* **2006**, *71*, 6999-7006.

[22] D. Oehlrich, S. M. E. Vidot, M. W. Davies, G. J. Clarkson, M. Shipman, *Tetrahedron* **2007**, *63*, 4703-4711.

[23] H. Gale, Ph.D. thesis, University of Southampton (Southampton), **2005**.

[24] A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chemical Reviews* **1997**, *97*, 2341-2372.

[25] M. Ballester, *Chemical Reviews* **1955**, *55*, 283-300.

[26] V. K. Aggarwal, G. Hynd, W. Picoul, J.-L. Vasse, *Journal of the American Chemical Society* **2002**, *124*, 9964-9965.

[27] N. Prileschajew, *Berichte der deutschen chemischen Gesellschaft* **1909**, *42*, 4811-4815.

[28] Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *Journal of the American Chemical Society* **1997**, *119*, 11224-11235.
[29] E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *Journal of the American Chemical Society* **1991**, *113*, 7063-7064.
[30] B. D. Brandes, E. N. Jacobsen, *The Journal of Organic Chemistry* **1994**, *59*, 4378-4380.
[31] Q. H. Xia, H. Q. Ge, C. P. Ye, Z. M. Liu, K. X. Su, *Chemical Reviews* **2005**, *105*, 1603-1662.
[32] aT. Katsuki, K. B. Sharpless, *Journal of the American Chemical Society* **1980**, *102*, 5974-5976; bY. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *Journal of the American Chemical Society* **1987**, *109*, 5765-5780.
[33] R. F. de la Pradilla, S. Castro, P. Manzano, M. Martin-Ortega, J. Priego, A. Viso, A. Rodriguez, I. Fonseca, *Journal of Organic Chemistry* **1998**, *63*, 4954-4966.
[34] D. Craig, K. Daniels, A. R. Mackenzie, *Tetrahedron* **1993**, *49*, 11263-11304.
[35] R. Tanikaga, N. Konya, T. Tamura, A. Kaji, *Journal of the Chemical Society-Perkin Transactions 1* **1987**, 825 - 830.
[36] J. Nokami, K. Kataoka, K. Shiraishi, M. Osafune, I. Hussain, S. Sumida, *Journal of Organic Chemistry* **2001**, *66*, 1228-1232.
[37] R. Tanikaga, N. Konya, K. Hamamura, A. Kaji, *Bulletin of the Chemical Society of Japan* **1988**, *61*, 3211-3216.
[38] C. Mioskowski, G. Solladie, *Tetrahedron* **1980**, *36*, 227-236.
[39] aV. Capriati, S. Florio, R. Luisi, *Chemical Reviews* **2008**, *108*, 1918-1942; bE. Abele, E. Lukevics, *Heterocycles* **2002**, *57*, 361-404; cT. Satoh, *Chemical Reviews* **1996**, *96*, 3303-3325; dD. M. Hodgson, E. Gras, *Synthesis-Stuttgart* **2002**, 1625-1642; eD. M. Hodgson, C. D. Bray, P. G. Humphreys, *Synlett* **2006**, 1-22; fE. Doris, L. Dechoux, C. Mioskowski, *Synlett* **1998**, 337-+; gG. Boche, J. C. W. Lohrenz, *Chemical Reviews* **2001**, *101*, 697-756.
[40] D. M. Hodgson, E. H. M. Kirton, S. M. Miles, S. L. M. Norsikian, N. J. Reynolds, S. J. Coote, *Organic & Biomolecular Chemistry* **2005**, *3*, 1893-1904.
[41] D. M. Hodgson, S. L. M. Norsikian, *Organic Letters* **2001**, *3*, 461-463.
[42] T. Satoh, K. Horiguchi, *Tetrahedron Letters* **1995**, *36*, 8235-8238.
[43] T. Durst, M. J. Lebelle, Vandenel.R, K. C. Tin, *Canadian Journal of Chemistry* **1974**, *52*, 761-766.
[44] T. Satoh, S. Kobayashi, S. Nakanishi, K. Horiguchi, S. Irisa, *Tetrahedron* **1999**, *55*, 2515-2528.
[45] P. B. Hitchcock, G. J. Rowlands, R. Parmar, *Chemical Communications* **2005**, 4219-4221.
[46] H. Whitman, G,, *Organosulfur Chemistry*, Oxford University Press, **1995**.
[47] B. Laleu, M. S. Machado, J. Lacour, *Chemical Communications* **2006**, 2786-2788.
[48] D. Barillier, J. Levillain, M. Vazeux, *Tetrahedron* **1994**, *50*, 5413-5424.
[49] E. Block, *Angewandte Chemie International Edition in English* **1992**, *31*, 1135-1178.
[50] aM. Baltas, K. Raouf-Benchekroun, A. De Blic, L. Cazaux, P. Tisnès, L. Gorrichon, K. Hussein, J. C. Barthelat, *Tetrahedron* **1996**, *52*, 14865-14876; bP. Kiełbasiński, B. Zwanenburg, T. J. G. Damen, M. W. Wieczorek, W. R. Majzner, G. D. Bujacz, *European Journal of Organic Chemistry* **1999**, *1999*, 2573-2578.
[51] H. B. Kagan, J. L. Namy, *Tetrahedron* **1986**, *42*, 6573-6614.
[52] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angewandte Chemie-International Edition* **2008**, *47*, 6802-6806.
[53] D. J. Cram, F. A. A. Elhafez, *Journal of the American Chemical Society* **1952**, *74*, 5828-5835.

[54] J. W. C. Cornforth, R. H.; Mathew, K. K., *J. Chem. Soc* **1959**, 112-127.
[55] M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Letters* **1968**, *9*, 2199-2204.
[56] G. J. Karabatsos, *Journal of the American Chemical Society* **1967**, *89*, 1367-1371.
[57] D. J. Cram, K. R. Kopecky, *Journal of the American Chemical Society* **1959**, *81*, 2748-2755.
[58] aH. B. Burgi, J. D. Dunitz, E. Shefter, *Journal of the American Chemical Society* **1973**, *95*, 5065-5067; bH. B. Burgi, J. D. Dunitz, J. M. Lehn, G. Wipff, *Tetrahedron* **1974**, *30*, 1563-1572.
[59] aN. T. Anh, O. Eisenstein, *Nouveau Journal De Chimie-New Journal of Chemistry* **1977**, *1*, 61-70; bN. T. Anh, O. Eisenstein, *Tetrahedron Letters* **1976**, 155-158.
[60] aA. S. Cieplak, *Journal of the American Chemical Society* **1981**, *103*, 4540-4552; bA. S. Cieplak, B. D. Tait, C. R. Johnson, *Journal of the American Chemical Society* **1989**, *111*, 8447-8462.
[61] aD. A. Evans, S. J. Siska, V. J. Cee, *Angewandte Chemie International Edition* **2003**, *42*, 1761-1765; bV. J. Cee, C. J. Cramer, D. A. Evans, *Journal of the American Chemical Society* **2006**, *128*, 2920-2930.
[62] E. P. Lodge, C. H. Heathcock, *Journal of the American Chemical Society* **1987**, *109*, 3353-3361.
[63] S. Díaz-Oltra, M. Carda, J. Murga, E. Falomir, J. A. Marco, *Chemistry – A European Journal* **2008**, *14*, 9240-9254.
[64] aL. Gross, University of Southampton, **2012**; bC. Oakes, PhD thesis, The University of Southampton **2011**; cC. Smith, University of Southampton, **2012**.
[65] aG. E. Keck, S. Castellino, *Journal of the American Chemical Society* **1986**, *108*, 3847-3849; bG. E. Keck, S. Castellino, M. R. Wiley, *The Journal of Organic Chemistry* **1986**, *51*, 5478-5480.
[66] M. Jefferey, J,, PhD thesis thesis, University of Southampton **2004**.
[67] aJ. M. Escudier, M. Baltas, L. Gorrichon, *Tetrahedron Letters* **1991**, *32*, 5345-5348; bJ. M. Escudier, M. Baltas, L. Gorrichon, *Tetrahedron* **1993**, *49*, 5253-5266; cK. Nacro, M. Baltas, J. M. Escudier, L. Gorrichon, *Tetrahedron* **1996**, *52*, 9047-9056; dI. Shibata, S. Fukuoka, N. Yoshimura, H. Matsuda, A. Baba, *Journal of Organic Chemistry* **1997**, *62*, 3790-3791; eK. Nacro, M. Baltas, L. Gorrichon, *Tetrahedron* **1999**, *55*, 14013-14030; fD. R. Williams, B. J. Myers, L. Mi, *Organic Letters* **2000**, *2*, 945-948; gG. Righi, F. Spirito, C. Bonini, *Tetrahedron Letters* **2002**, *43*, 4737-4740.
[68] aD. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *Journal of the American Chemical Society* **1988**, *110*, 6487-6491; bK. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. Kumar, *Chemical Reviews* **2009**, *109*, 2551-2651.
[69] B. H. Lipshutz, P. A. Blomgren, *Organic Letters* **2001**, *3*, 1869-1871.
[70] D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger, *Tetrahedron* **1992**, *48*, 2127-2142.
[71] H. E. Zimmerman, M. D. Traxler, *Journal of the American Chemical Society* **1957**, *79*, 1920-1923.
[72] M. T. Reetz, K. Kesseler, A. Jung, *Tetrahedron* **1984**, *40*, 4327-4336.
[73] T. Wang, W. H. Ji, Z. Y. Xu, B. B. Zeng, *Synlett* **2009**, 1511-1513.
[74] P. L. Hall, J. H. Gilchrist, D. B. Collum, *Journal of the American Chemical Society* **1991**, *113*, 9571-9574.
[75] aD. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *Journal of the American Chemical Society* **2001**, *124*, 392-393; bM. T. Crimmins, K. Chaudhary, *Organic Letters* **2000**, *2*, 775-777; cM. T. Crimmins, B. W. King, E. A. Tabet, *Journal of the American Chemical Society* **1997**, *119*, 7883-7884; dD. A. Evans, J. Bartroli, T. L. Shih, *Journal of the American Chemical Society* **1981**, *103*, 2127-2129; eM. A. Walker, C. H. Heathcock, *The Journal of Organic Chemistry* **1991**, *56*, 5747-5750.

[76] S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, D. C. Myles, *Journal of Organic Chemistry* **2003**, *68*, 6646-6660.
[77] D. Williams, H; Flemming, Ian;, *Spectroscopic methods in organic chemistry, Vol. 1*, 5 ed., McGraw Hill, **1995**.
[78] H. Tokuyama, S. Yokoshima, T. Yamashita, S. C. Lin, L. P. Li, T. Fukuyama, *Journal of the Brazilian Chemical Society* **1998**, *9*, 381-387.
[79] K. Kunchithapatham, C. C. Eichman, J. P. Stambuli, *Chemical Communications* **2011**, *47*, 12679-12681.
[80] aH. Gale, Ph.D thesis, University of Southampton **2005**; bC. A. Elliger, *Synthetic Communications* **1985**, *15*, 1315-1324; cK. Koch, M. S. Biggers, *The Journal of Organic Chemistry* **1994**, *59*, 1216-1218.
[81] J. Watts, University of Southampton, **2012**.
[82] aE. Lee-Ruff, F. J. Ablenas, *Canadian Journal of Chemistry* **1989**, *67*, 699-702; bW. Wang, T. Li, G. Attardo, *The Journal of Organic Chemistry* **1997**, *62*, 6598-6602; cM. A. Rahim, S. Matsumura, K. Toshima, *Tetrahedron Letters* **2005**, *46*, 7307-7309.
[83] K. Prantz, J. Mulzer, *Angewandte Chemie-International Edition* **2009**, *48*, 5030-5033.
[84] I. V. Alabugin, T. A. Zeidan, *Journal of the American Chemical Society* **2002**, *124*, 3175-3185.
[85] Wavefunction, *Spartan 08* **2008**.
[86] aA. D. Becke, *The Journal of Chemical Physics* **1993**, *98*, 1372-1377; bK. Kim, K. D. Jordan, *The Journal of Physical Chemistry* **1994**, *98*, 10089-10094.
[87] J. H. van Steenis, J. J. G. S. van Es, A. van der Gen, *European Journal of Organic Chemistry* **2000**, *2000*, 2787-2793.
[88] F. Batigalhia, M. Zaldini-Hernandes, A. G. Ferreira, I. Malvestiti, Q. B. Cass, *Tetrahedron* **2001**, *57*, 9669-9676.
[89] L. S. Nathan, N; Kim, B; Yun; Tam; Mustapha, (Ed.: PCT/US2008/084894), US, **2009**.
[90] M. A. Tius, D. J. Drake, *Tetrahedron* **1996**, *52*, 14651-14660.
[91] C. Mioskowski, G. Solladie, *Tetrahedron* **1980**, *36*, 227-236.
[92] C. Bauder, *Tetrahedron Letters* **2008**, *49*, 2243-2246.
[93] M. P. Acemoglu, A; Schaerer, C; Roth, P, R; , (Ed.: PCT/EP2009/065241), CH, **2010**.
[94] G. Deleris, J. Dunoguès, R. Calas, *Tetrahedron Letters* **1976**, *17*, 2449-2450.
[95] J. Bach, R. Berenguer, J. Garcia, J. Vilarrasa, *Tetrahedron Letters* **1995**, *36*, 3425-3428.
[96] H. Oelschläger, *Archiv der Pharmazie* **1955**, *288*, 102-113.
[97] P. A. Brough, W. Aherne, X. Barril, J. Borgognoni, K. Boxall, J. E. Cansfield, K.-M. J. Cheung, I. Collins, N. G. M. Davies, M. J. Drysdale, B. Dymock, S. A. Eccles, H. Finch, A. Fink, A. Hayes, R. Howes, R. E. Hubbard, K. James, A. M. Jordan, A. Lockie, V. Martins, A. Massey, T. P. Matthews, E. McDonald, C. J. Northfield, L. H. Pearl, C. Prodromou, S. Ray, F. I. Raynaud, S. D. Roughley, S. Y. Sharp, A. Surgenor, D. L. Walmsley, P. Webb, M. Wood, P. Workman, L. Wright, *Journal of Medicinal Chemistry* **2007**, *51*, 196-218.