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The Synthesis of Hydroxy-*iso*-Evoninic Acid *via* a Benzilic Ester Rearrangement



Thesis submitted for the partial fulfilment of a PhD degree

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Finally, I thank my partner, Freddie Parks, who has has always remained sympathetic and supportive. He is even supporting me moving to Germany in the near future to continue research after this PhD for which I am truly grateful. It is to him that this thesis is dedicated.

Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
BAR	benzilic acid rearrangement
BER	benzilic ester rearrangement
Bn	benzyl
boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
Bu	butyl
Bz	benzoyl
c	concentration in g/100 mL
calcd	calculated
cf	*confer*
DAD	diode array detector
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DIBAL-H	di*iso*butylaluminium hydride
DIPT	di*iso*propyl tartrate
DMAP	dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EC_{50}	half maximal effective concentration

ee	enantiomeric excess
Et	ethyl
eq	equivalents
FC	flash chromatography
Fu	furyl
g	grams
GC	gas chromatography
h	hours
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
LDA	lithium diisopropylamide
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MG	migrating group
min	minutes
mmol	millimoles
mL	millilitres
mp	melting point
MS	mass spectrometry
MS	molecular sieves
Ms	methanesulfonyl

MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NS	no suppression
Ph	phenyl
Pr	propyl
Py	pyridine
QUIPHOS	(2*R*,5*S*)-3-phenyl-2-(8-quinolinoxy)-1,3-diaza-2-phosphabicyclo- [3.3.0]-octane
rds	rate determining step
rt	room temperature
TBHP	*tert*-butyl hydrogen peroxide
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TI	therapeutic index
TLC	thin layer chromatography
TMS	trimethylsilyl

Abstract

Hydroxy-*iso*-evoninic acid is a pyridine diacid alkaloid present in nine natural products belonging to the Celastraceae plant family. The relative and absolute stereochemistry of the two stereocentres in this compound, which invariably occurs as a macrocyclic esterifying ligand between the C-3 and C-13 alcohols of β-dihydroagarofuran sesquiterpenes, were not assigned during isolation and no synthesis has yet been reported. The natural products containing hydroxy-*iso*-evoninic acid are of medicinal interest because of their high anti-HIV activity.

This thesis contains an overview of the pyridine alkaloids present in the Celastraceae plant family and background to the benzilic ester rearrangement (BER), a variant of the benzilic acid rearrangement (BAR) discovered by Liebig in 1838.

The majority of this thesis describes the first synthesis of the pyridine alkaloid hydroxy-*iso*-evoninic acid which utilises a BER as the key synthetic step. The development of a tunable diastereoselective BER is also reported, along with the initiation of the development of an asymmetric variant. The synthesis of a model of dihydro-β-agarofuran core euonyminol is also detailed to enable future assignment of the currently unknown stereochemistry of natural hydroxy-*iso*-evoninic acid.

Declaration: I declare that I have personally prepared this thesis, and the work described here is my own, carried out personally unless otherwise stated. All sources of information are acknowledged by means of references.

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1 Introduction

1.1 Celastraceae Sesquiterpenoids

1.1.1 Introduction to the Celastraceae Sesquiterpenoid Family

The Celastraceae plant family has been a rich source of biologically active secondary metabolites, consisting of an array of terpenoids, maytansinoids, alkylamines and flavonoids.[1] The family is widespread in tropical and subtropical regions, including North Africa, South America and South East Asia. The crude plant extracts of the Celastraceae have been used abundantly for their medicinal, insecticidal and stimulating effects. Their use in traditional Chinese medicine is extremely varied, with use in therapies for diseases including rheumatoid arthritis, nephritis, psoriasis and cancer.[2] They have also been widely used in China as insecticides and insect anti-feedants.[3]

The most diverse and arguably most biologically interesting class of compounds isolated from the Celastraceae are the Celastraceae sesquiterpenoids. These compounds are all based on a dihydro-β-agarofuran skeleton with various degrees of oxygenation ranging from two additional oxygen groups in the case of boariol,[4] to up to nine in the case of euonyminol[5] (**Figure 1.1**).

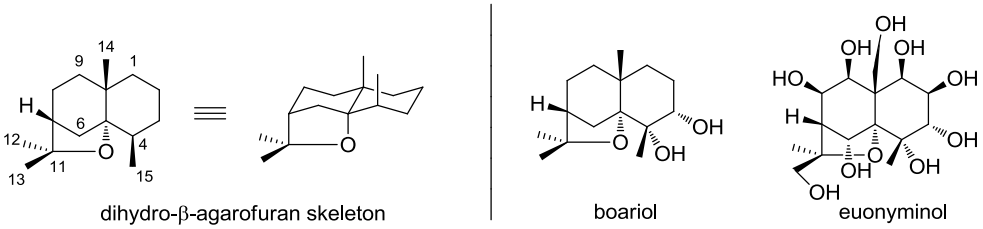


Figure 1.1 - General dihydro-β-agarofuran skeleton for Celastraceae sesquiterpenoids.[6]

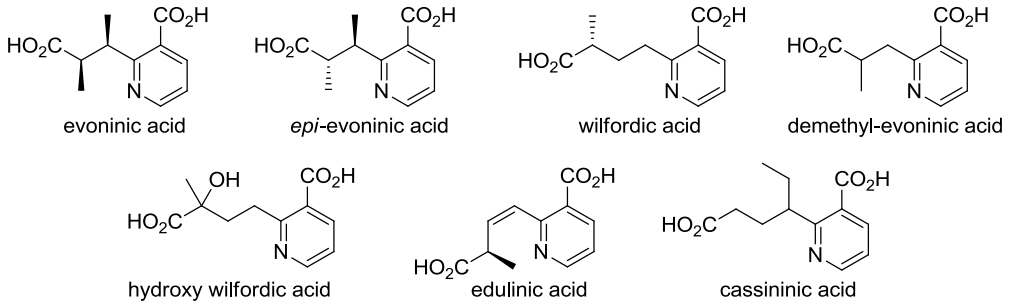
These oxygenated cores are decorated with a range of esterifying residues including aliphatic acids, and aromatic and heterocyclic acids including, elaborated nicotinic dicarboxylic acids. Changes in the relative positions, the number and configuration of these esterifying ligands around the various oxygenated dihydro-β-agarofuran cores, leads to the occurrence of over 460 Celastraceae sesquiterpenoids.

Due to the number of previous reviews of the Celastraceae sesquiterpenoids published in journals and previous PhD theses from the Spivey group,[2,6,7] the focus of this introduction will be on the pyridine dicarboxylic acid ligands, as this thesis details the synthesis of pyridine dicarboxylic acid, hydroxy-*iso*-evoninic acid.

1.1.2 Macrocycle Forming Sesquiterpene Pyridine Alkaloids

Twelve pyridine dicarboxylic acid based esterifying ligands have been identified and characterised from the Celastraceae over the past 30 years. They can be separated into 2,3- and 3,4-disubstituted pyridines which contain a carboxylic acid group at the 3-position (**Figure 1.2**).[6]

2,3-Substituted pyridines:



3,4-Substituted pyridines:

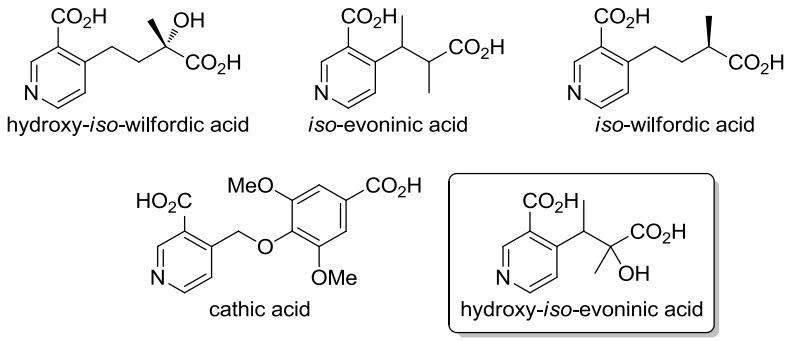


Figure 1.2 - Macrolactone forming pyridine based alkaloids.[6]

The macrolactones are either 14- or 15-membered rings where the dihydro-β-agarofuran is esterified at the C-3 and C-13 positions of one of six of the more highly oxygenated cores: evoninol, 4-deoxyevoninol, euonyminol, *iso*-euonyminol, 4-deoxy-*iso*-euonyminol and 4-deoxyeuonyminol. Evonine and neoevonine were the first macrocyclide sesquitepene pyridine alkaloids to have their structure elucidated in 1972,[8] though well over 100 have since been characterised (**Figure 1.3**).

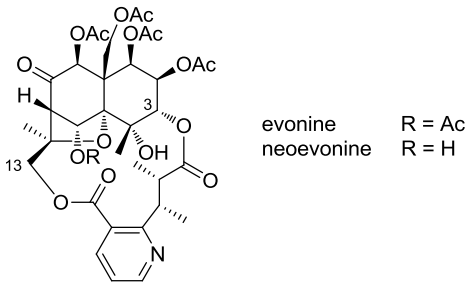


Figure 1.3 - Macrolactone sesquitepene pyridine alkaloids evonine and neoevonine.[8]

Evoninic acid is the most prevalent of the pyridyl esterifying ligands, currently identified in 77 Celastraceae sesquiterpenoids isolated from over 15 different plant species.[6] Two dimacrolide sesquiterpenoids have also been isolated; triptonines A and B, in which one macrolide is formed with a pyridyl dicarboxylic acid unit between C-3 and C-13 and the other with a monoterpene moiety between C-8 and C-10.[9]

The absolute stereochemistry of the sesquiterpenoid cores was determined in 1972 by anomalous dispersion x-ray diffraction after introduction of a bromine atom.[10] From this assignment and from formal syntheses, the absolute stereochemistry of the majority of the pyridyl dicarboxylic acid units have been assigned.[11-15] However, six remain in which the stereochemistry is still unassigned (where no stereochemistry is shown in **Figure 1.2**, it remains unassigned).

1.1.3 Biosynthesis of the Pyridyl Diacid Ligands

It has been suggested that the pyridyl diacid family of ligands originates from either nicotinic acid or nicotinamide. It has been proposed that nicotinic acid or a derivative is alkylated *via* a radical coupling process when *in vivo* (**Figure 1.4**).[16]

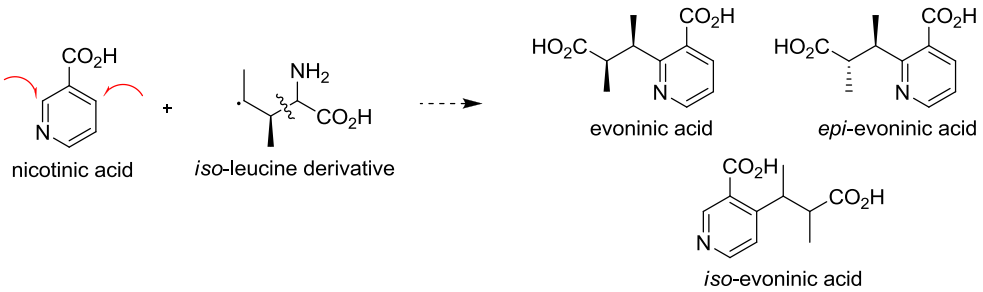
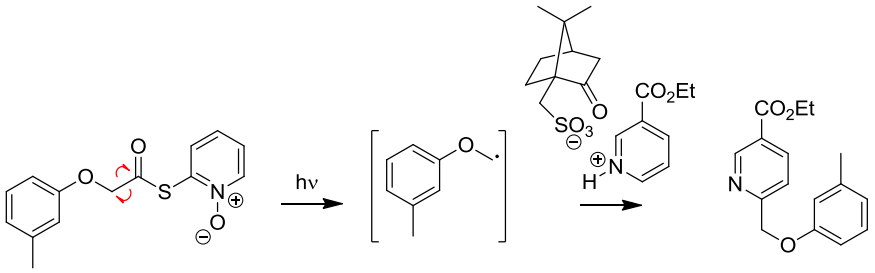


Figure 1.4 – Whiting's proposed biosysnthesis of the pyridyl diacid ligands.[16]

It is suggested that a radical centre is generated on a C_5 *iso*-leucine derivative which then undergoes regioselective addition to yield the 2- and 4-alkylated diacids. This proposed biosynthesis has been supported by a model study in which a nicotinate ester salt and an alkyl radical generated *in situ* by photolysis combine *in vitro* to give alkylation at the pyridine C-6 position (**Scheme 1.1**).



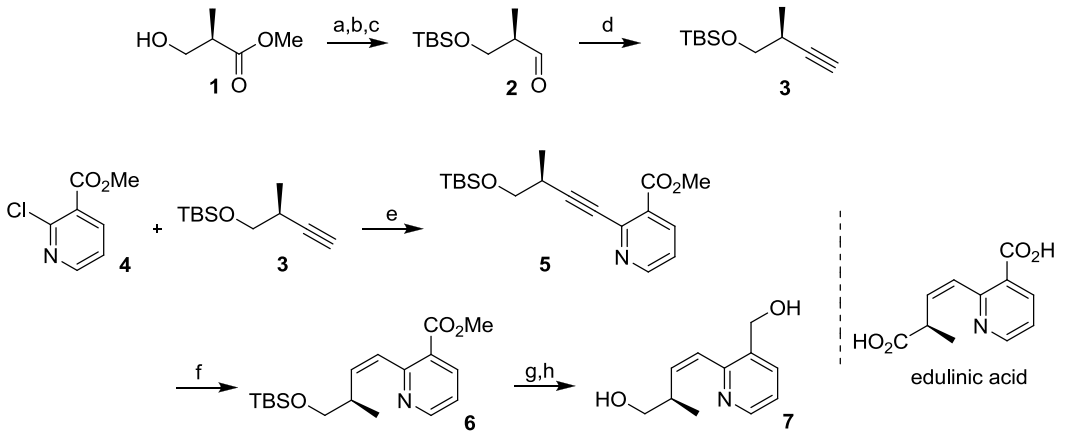
Scheme 1.1 – Whiting's biomimetic radical alkylation of a nicotinate salt.[16]

Alkylation was observed exclusively at the less hindered C-6-position to give the 3,6-disubstituted product in 41% yield, and this was considered to provide proof-of-concept for the proposed biosynthetic pathway.

The generation of the carbon radical in the biosynthetic pathway is thought to occur through the action of a P-450 enzyme. No biosynthetic pathway has been proposed for the introduction of the α-hydroxyl group present in many of the pyridyl diacid ligands and therefore it seems unlikely that the unknown stereochemistry of two of these ligands can currently be proposed by consideration of their biosynthesis.

1.1.4 Previous Syntheses of the Pyridyl Diacid Ligands

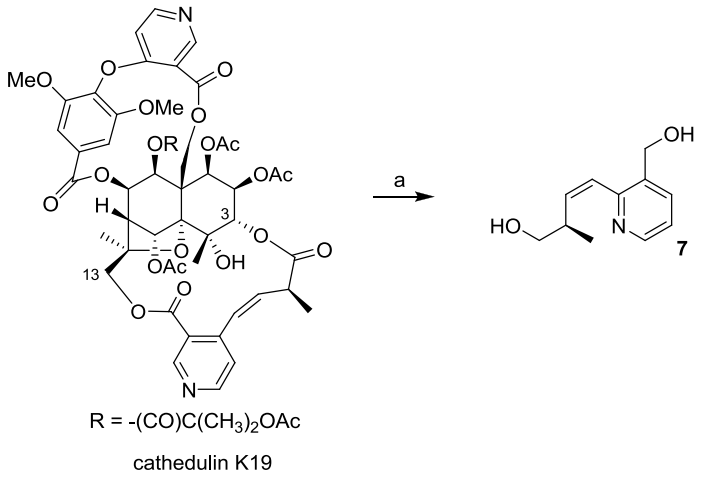
Only a handful of diacid units have previously been synthesised. White *et al.* assigned the stereochemistry of edulinic acid by synthesis of reduced edulinic acid diol **7**, although the formal synthesis was not completed (**Scheme 1.2**).[14]



Reagents and Conditions; (a) TBSCl, 1H-imidazole, rt; (b) BH_3·THF, THF, 0 °C; (c) DMSO, $(COCl)_2$, then Et_3N (84% over 3 steps); (d) $(MeO)_2POCHN_2$, ^tBuOK, THF (90%); (e) $(Ph_3P)PdCl_2$, CuI, Et_2NH (61%); (f) H_2, Lindlar catalyst, MeOH (76%); (g), 5% HF/MeCN (100%); (h) $LiAlH_4$, THF, 0 °C (72%).

Scheme 1.2 – White's synthesis of reduced edulinic acid **7** to assign the stereochemistry.[14]

From commercially available methyl (*R*)-3-hydroxy-2methylpropionate (**1**), aldehyde **2** was prepared using a literature 3-step procedure consisting of TBS protection, ester reduction to the primary alcohol and oxidation to aldehyde **2**.[17,18] Condensation with dimethyl diazomethylphosphonate gave terminal alkyne **3** which underwent a Sonogashira coupling with 2-chloro nicotinic ester **4** to afford alkyne **5**. Partial-hydrogenation with Lindlar's catalyst afforded (*Z*)-alkene **6** contaminated with 10% of the (*E*)-isomer which could be separated by column chromatography. Deprotection and then reduction of the ester to diol **7** allowed for comparison of the optical rotations with material obtained by treatment of cathedulin K-19 with $LiAlH_4$ (**Scheme 1.3**).[14]

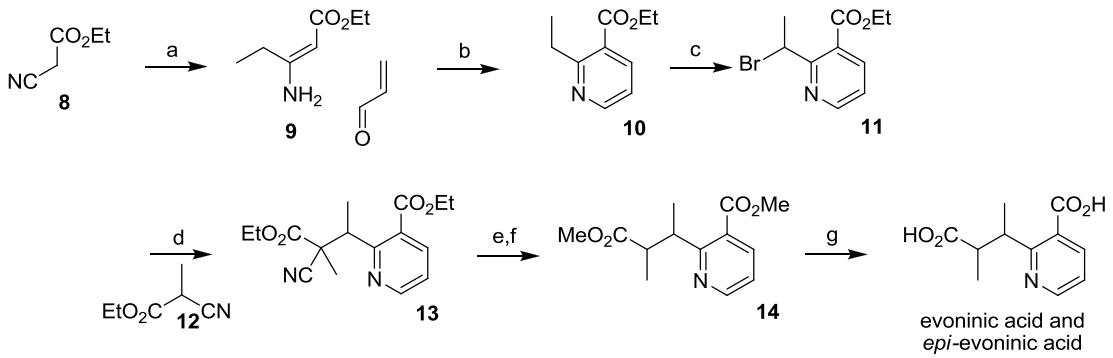


Reagents and Conditions; (a) $LiAlH_4$, THF/Et_2O, 0 °C to rt (28%).

Scheme 1.3 – White's degradation of cathedulin K-19 to obtain the reduced form of edulinic acid, diol **7**.[14]

From this partial synthesis, (*R*)-edulinic acid was determined to be the naturally occurring stereoisomer. It was not reported if the oxidation of diol **7** to edulinic acid was possible.

Both the racemic and asymmetric syntheses of the most prevalent ligand, evoninic acid, have been reported. The racemic synthesis was completed in 1976 and gave access to evoninic and *epi*-evoninic acid which could be separated by preparative GC (**Scheme 1.4**).[19]



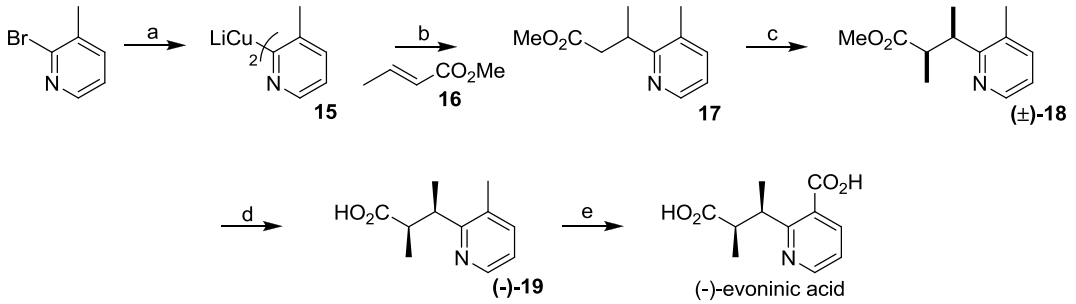
***Reagents and Conditions*;** (a) EtMgBr, Et_2O, rt; (b) heat (60%); (c) NBS, CCl_4 (59%); (d) Na, EtOH, 70 °C (36%); (e) conc. HCl; (f) CH_2N_2, $MeOH/H_2O$ (61% over 2 steps); (g) KOH, MeOH (51-60%).

Scheme 1.4 – Pailer and Pfleger's synthesis of evoninic acid and *epi*-evoninic acid.[19]

The 2,3-subsititution pattern was set up in the formation of the pyridyl ring by the reaction of unsaturated ester **9** (prepared by ethyl Grignard reagent addition to cyano ester **8**)[20] and propenal. Bromination at the benzylic position followed by

addition of α-methyl malononitrile **12** lengthened the alkyl chain to the required 3-carbon chain present in diester **13**. Decyanation and ester hydrolysis under acidic conditions, followed by diazomethane-mediated *bis*-esterification of the resulting diacid, afforded *bis*-methyl ester **14**. The two diastereoisomers could be separated at this stage by preparative GC allowing (albeit in yields of just 29% and 45%), after hydrolysis, (±)-evoninic acid and (±)-*epi*-evoninic acid to be isolated in an overall yield of 4.6% over the 7 steps.

More recently, Spivey *et al.* reported the first asymmetric synthesis of naturally occurring (-)-evoninic acid using an enzymatic kinetic resolution (**Scheme 1.5**).[21]

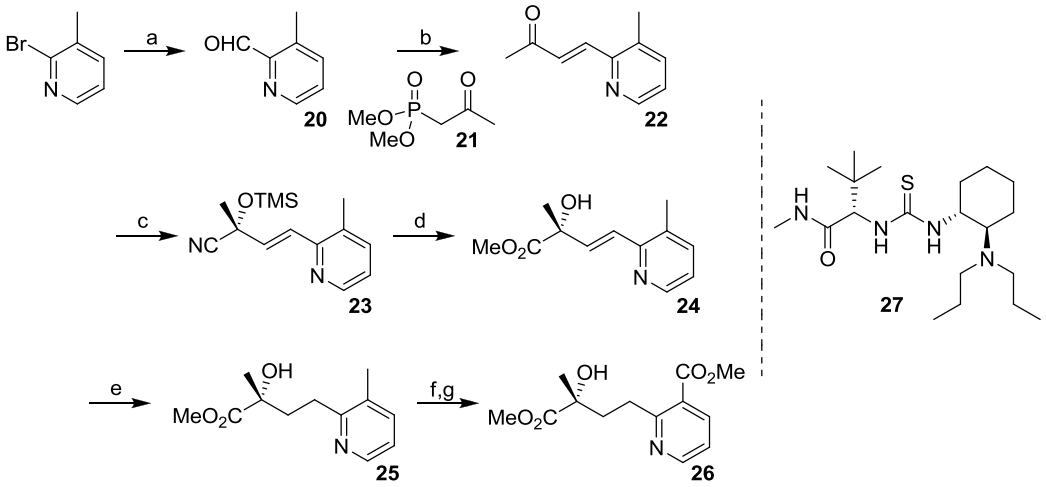


***Reagents and Conditions*;** (a) ^{n}BuLi, Et_2O, -78 °C, then CuI, SBu_2, Et_2O, 0 °C; (b) Et_2O, rt (70%); (c) KHMDS, MeI, toluene, -78 °C (*dr* 96:4, 98%); (d) Lipase *P. Fluorescens*, pH 7.0 buffer (*dr* 97:3, *ee* >95%, 46%); (e) $KMnO_4$, H_2O, 100 °C (85%).

Scheme 1.5 – Spivey's asymmetric synthesis of evoninic acid.[21]

Cuprate **15** was generated after halogen-lithium exchange with commercially available 2-bromo-3-picoline. This 2-pyridyl Gilman homocuprate underwent 1,4-addition to unsaturated ester **16** to afford 2,3-dialkyl substituted pyridine **17**. α-Methylation of the potassium enolate of ester **17** with methyl iodide afforded the desired *syn* dimethyl compound **18**, with a high level of *de*, as a racemate. Following a screen of hydrolytic enzymes, a lipase was identified to effect efficient enantioselective hydrolysis of ester **18** affording acid (-)-**19** in high *ee*. The benzylic methyl group was then oxidised by $KMnO_4$ to afford (-)-evoninic acid in an overall yield of 30% over 4-steps in >95% *ee*. This provided not only an asymmetric route to evoninic acid, but also one that was shorter and more efficient than that reported by Pailer and Pfleger (4.6% yield over 7 steps, see **Scheme 1.4**).[19]

Another 2,3-disubstituded pyridyl ligand, hydroxy wilfordic acid, has also recently been synthesised. Although the naturally occurring stereochemistry of this alkaloid is currently unassigned, an asymmetric synthesis was developed allowing access to both enantiomers, which were isolated as dimethyl ester **26** (**Scheme 1.6**).[22]



***Reagents and Conditions*;** (a) ^{n}BuLi, DMF, THF (95%); (b) **21**, NaH, THF (85%); (c) TMSCN, chiral urea catalyst **27**, CF_3CH_2OH, CH_2Cl_2, -78 °C (*ee* 50%, 82%); (d) 6M HCl, MeOH, 90 °C (59%); (e) H_2, Pd/C, MeOH, rt (83%); (f) $KMnO_4$, H_2O, 100 °C; (g) HCl, MeOH (45% over 2 steps).

Scheme 1.6 – Eun and Seo's asymmetric synthesis of hydroxy wilfordic acid.[22]

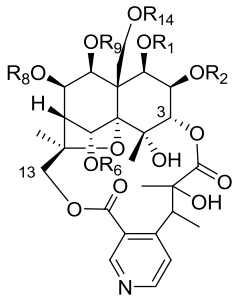
The synthesis starts with commercially available 2-bromo-3-picoline which is converted to aldehyde **20**, which then undergoes a Horner-Wadsworth-Emmons reaction to afford enone **22**. Asymmetric cyanosilylation proceeded with an *ee* of just 50% when using chiral urea catalyst **27** to give TMS-ether **23**. Treatment with methanolic HCl converted the cyano group to the corresponding methyl ester while also deprotecting the TMS group to give alkene **24**. Hydrogenation of the alkene afforded ester **25**. Benzylic oxidation with $KMnO_4$ (as developed in the Spivey synthesis of evoninic acid) followed by methylation, afforded dimethyl ester protected hydroxy wilfordic acid **26**. Thus, the first asymmetric synthesis of diesterified hydroxy wilfordic acid was reported *via* a 7-step synthetic sequence and an overall yield of 14.6% with an *ee* of 50%.

These are the only reported syntheses of the pyridine diacid ligands to date. None of the 3,4-disubstituted pyridines have previously been synthesised.

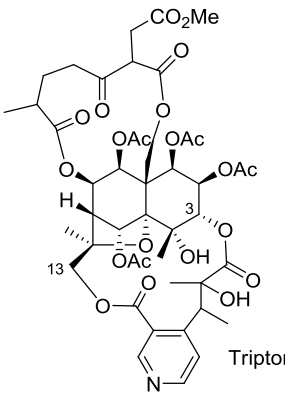
1.2 Hydroxy-*iso*-Evoninic Acid

1.2.1 Background

Hydroxy-*iso*-evoninic acid is one of the 3,4-disubstituted pyridine ligands found in Celastraceae sesquiternepoid natural products and its synthesis is the focus of this thesis. It has been identified in nine Celastraceae sesquiterpenoids, isolated from the root barks of *Tripteygium wilfordii* and *Tripterygium hypoglaucum* by a methanol extraction. All nine natural products contain hydroxy-*iso*-evoninic acid and in all cases this compound forms a 14-membered macrolactone bridge to the most highly oxygenated dihydro-β-agarofuran core, euonyminol. The bridge is formed between the primary C-13 and the secondary C-3 hydroxyl group on the bottom face of the molecule. The products differ in the other esterifying groups present (**Table 1.1**).



28-30 and **32-36**



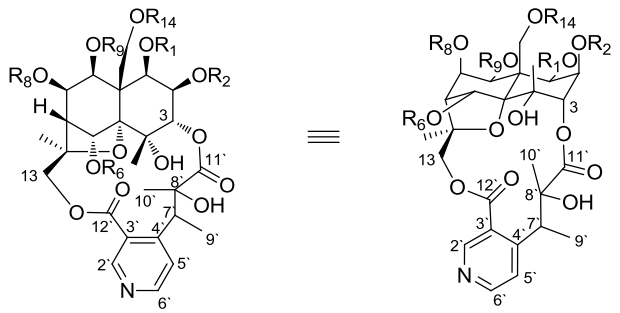
Triptonine B **31**

Sesquiterpenoid	R_1	R_2	R_6	R_8	R_9	R_{14}	Isolated From
Hypoglaunine A (28)[23]	Ac	Ac	Ac	Ac	Ac	^{3}Fu	*T. hypoglaucum*
Hypoglaunine B (29)[23]	Ac	^{3}Fu	Ac	Ac	Ac	Ac	*T. hypoglaucum*
Hypoglaunine C (30)[9,23]	Ac	Bz	Ac	Ac	Ac	Ac	*T. hypoglaucum* *T. wilfordii*
Triptonine B (31)[9,24]	-	-	-	-	-	-	*T. hypoglaucum* *T. wilfordii*
Wilfordinine (32)[15]	Ac	Bz	Bz	Ac	Ac	Ac	*T. wilfordii*
Wilfordinine B (33)[9]	Ac	Ac	Ac	Ac	Ac	Ac	*T. wilfordii*
Wilfordinine C (34)[9]	Bz	Ac	Ac	Ac	Ac	Ac	*T. wilfordii*
Wilfordconine (35)[25]	Ac	H	Ac	^{3}Fu	Ac	Ac	*T. wilfordii*
Wilfordlongine (36)[26]	Ac	H	Ac	Ac	Ac	Ac	*T. wilfordii*

Table 1.1 – Celastraceae sesquiterpenoids containing hydroxy-*iso*-evoninic acid.

Even though the naturally occurring absolute and relative stereochemistry of euonyminol has previously been assigned,[10] as no single crystal x-ray crystallographic structure assignment has been reported for any of the nine natural products containing hydroxy-*iso*-evoninic acid and because even the relative stereochemistry on the diacid ligand could not be determined by spectroscopic methods, the stereocentres in hydroxy-*iso*-evoninic acid remain unassigned. Both the absolute and relative stereochemistry of the two chiral centres are unknown. A methyl ether protected model of the euonyminol core containing the full functionality on the bottom half of the molecule from C-3 to C-13, has previously been prepared within the Spivey group. It is integral in our strategy for the assignment of natural hydroxy-*iso*-evoninic acid, which will be discussed later.

Additionally, there have been no reports on the attempted degradation of any of the natural products listed in **Table 1.1** and therefore there is no data reported for isolated hydroxy-*iso*-evoninic acid. However, proton and carbon NMR data reported for these compounds show very little variation in the peaks corresponding to the carbons and protons of the esterifying ligand hydroxy-*iso*-evoninic acid, suggesting that it exists as the same single stereoisomer in all compounds isolated to date (**Table 1.2** and **Table 1.3**)



Sesquiterpene	H-2`	H-5`	H-6`	H-7`	H-9`	H-10`
28[23]	8.98	7.82	8.69	4.23	1.21	1.36
29[23]	9.00	7.83	8.69	4.24	1.19	1.38
30[9,23]	9.00	7.85	8.69	4.26	1.20	1.39
31[9,24]	8.99	7.81	8.69	4.24	1.19	1.34
33[9]	8.98	7.83	8.68	4.23	1.18	1.35
34[9]	9.00	7.83	8.69	4.25	1.20	1.43
35[25]	8.98	7.82	8.69	4.23	1.20	1.36
36[26]	9.03	7.85	8.70	4.21	1.18	1.37

Table 1.2 – Comparison of the proton NMR chemical shifts (δ_H/ppm) of the esterifying ligand hydroxy-*iso*-evoninic acid in sesquiterpenoids **28**-**36** taken in $CDCl_3$.

Sesquiterpene	C-2`	C-3’	C-4’	C-5’	C-6’
28[23]	151.4	127.9	151.9	123.6	152.6
29[23]	151.7	127.7	152.0	123.6	152.7
30[9,23]	151.3	128.5	151.8	123.5	152.5
31[9,24]	151.5	127.5	151.8	123.6	152.7
33[9]	151.3	127.4	151.7	123.5	152.5
34[9]	151.5	127.5	151.7	123.5	152.6
35[25]	152.6	123.5	151.6	127.5	151.2
36[26]	152.6	123.5	151.6	127.5	151.2

Sesquiterpene	C-7’	C-8’	C-9’	C-10’	C-11’	C-12’
28[23]	42.3	77.1	17.4	24.3	175.2	167.7
29[23]	42.3	77.1	17.4	24.2	175.2	167.7
30[9,23]	41.8	77.2	17.2	24.0	174.9	167.6
31[9,24]	41.9	76.8	17.3	24.1	175.2	167.7
33[9]	41.8	76.8	17.2	24.0	174.9	167.6
34[9]	41.9	76.7	17.3	24.0	175.1	167.7
35[25]	41.8	77.2	17.1	24.0	175.1	167.7
36[26]	41.7	77.2	41.9[a]	23.8	174.8	167.7

a. The chemical shift and assignment as a triplet in this report would appear to be erroneous.

Table 1.3 – Comparison of the carbon NMR chemical shifts (δ_C/ppm) of the esterifying ligand hydroxy-*iso*-evoninic acid in sesquiterpenoids **28**-**36** taken in $CDCl_3$.

When considering the 3D structures of the sesquiterpenoids containing hydroxy-*iso*-evoninic acid, the similarity in the NMR spectra is unsurprising (**Figure 1.5**).

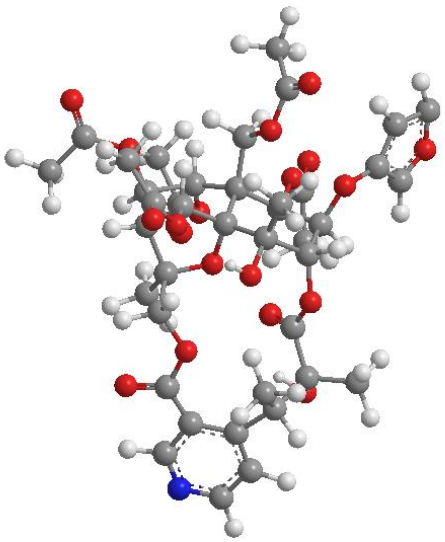
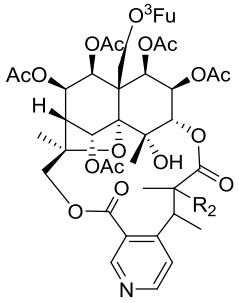


Figure 1.5 – Computed molecular structure of (7'*S*,8'*R*)-hypoglaunine B (**29**) following energy minimisation (MM2).

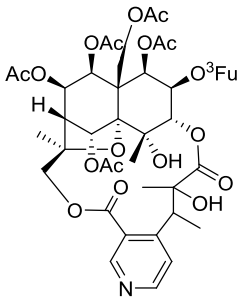
The esterifying ligand is situated underneath the molecule, distant from the varying esterifying groups through bonds, and also through space.

1.2.2 Biological Activity

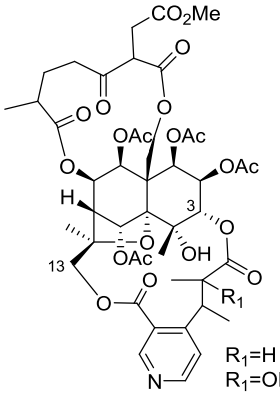
As previously discussed, the Celastraceae sesquiterpenoids are known for their wide variety of biological properties. Of particular interest for the compounds containing hydroxy-*iso*-evoninic acid is their anti-HIV activity,[9,24,27] as has been highlighted in a recent *anti*-HIV natural products review.[28] Three of the sesquiterpenoids containing hydroxy-*iso*-evoninic acid have been tested and been found to be highly active inhibitors of HIV replication in human lymphocyte cells, although the mechanism of this inhibition has yet to be understood (**Table 1.4**).[24]



R_2=OH Hypoglaunine A **28**
R_2=H Hypoglaunine D **37**



Hypoglaunine B **29**



R_1=H Triptonine A **38**
R_1=OH Triptonine B **31**

Sesquiterpenoid	IC_{50}	EC_{50}	TI
Hypoglaunine A (28)	>100	0.13	>769
Hypoglaunine B (29)	>100	0.10	>1000
Triptonine B (31)	>100	<0.1	>1000
Hypoglaunine D (37)	22.2	NS	-
Triptonine A (38)	>100	2.5	>39.4

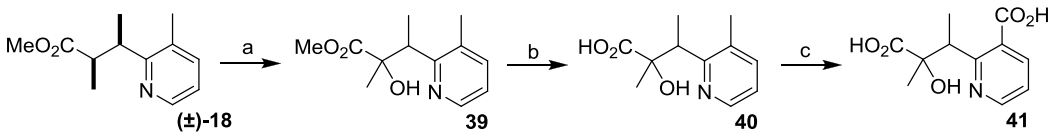
IC_{50} = concentration of test sample that was toxic to 50% of the mock-infected cells. EC_{50} = concentration of test sample that was able to suppress HIV replication by 50%. TI = therapeutic index, the ratio of the IC_{50} and EC_{50}. NS = no suppression.

Table 1.4 – *Anti*-HIV activity of the sesquiterpenoids containing hydroxy-*iso*-evoninic acid and the importance of the C-8` hydroxyl group.[24]

Including the three hydroxy-*iso*-evoninic acid containing sesquiterpenoids **28**, **29** and **31**, a total of 20 compounds were tested for their *anti*-HIV activity and SAR analysis was performed. It was found that an acetoxy group at C-6 increased the activity and that whether the pyridyl ligand was 2,3- or 3,4-substituted had no effect on the activity. It was also concluded, as highlighted in **Table 1.4**, that the C-8` hydroxy group is important for high *anti*-HIV activity. When hydroxy-*iso*-evoninic acid is replaced by evoninic acid and all other esterifying groups around the dihydro-β-agarofuran core are kept unchanged (hypoglaunine A **28** *cf.* hypoglaunine D **37** and also triptonine B **31** *cf.* triptonine A **38**), a dramatic reduction in activity is observed. The three sesquiterpenoids containing hydroxy-*iso*-evoninic acid also have unusually high therapeutic indexes in comparison with other active natural products (usually a TI of >5 is considered significant).

1.2.3 Previous Synthetic Efforts Towards Hydroxy-*iso*-Evoninic Acid

Previously within the Spivey group, the synthesis of hydroxy-*iso*-evoninic acid was attempted using the same strategy as was applied in the synthesis of evoninic acid (see **Scheme 1.5**).[21] It was found that the unnatural 2,3-substituted regioisomer of the natural product, which is not a known compound and which we called hydroxy evoninic acid (**41**), could be synthesised from an intermediate *en route* to evoninic acid: compound **18** (**Scheme 1.7**).[29]

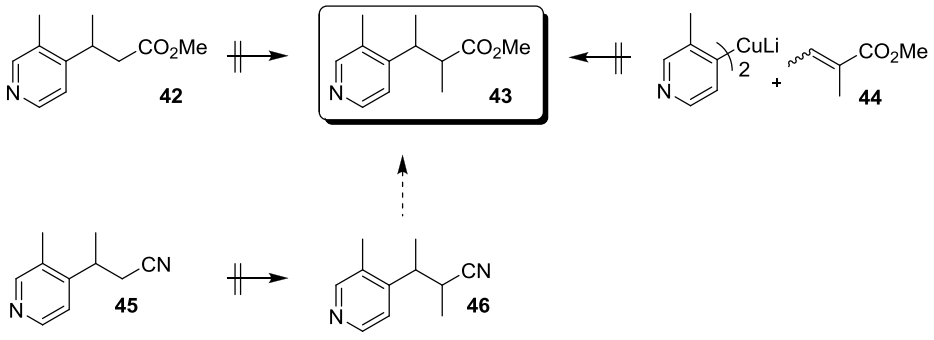


***Reagents and Conditions*;** (a) Davis oxaziridine, KHMDS, 25 °C (*dr* 75:25, 78%); (b) NaOH, MeOH, 60 °C (*dr* 70:30, 96%); (c) $KMnO_4$, H_2O, 100 °C (*dr* 70:30, 92%).

Scheme 1.7 – Shukla's synthesis of hydroxy evoninic acid (**41**) from intermediate **18** (see **Scheme 1.5**).[29]

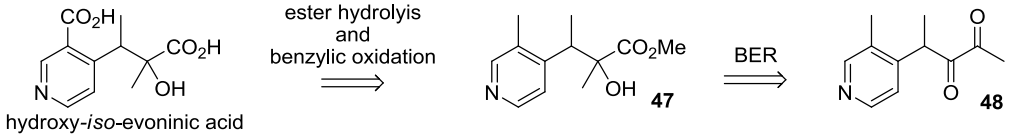
Installation of the α-hydroxy group proceeded with Davis oxaziridine to afford α-hydroxy ester **39**, which was hydrolysed to form acid **40**. Oxidation of the benzylic methyl group with $KMnO_4$ afforded hydroxy evoninic acid (**41**) in a yield of 61% over the final three-steps.

Unfortunately, the enolate methylation chemistry used to introduce the methyl group α- to the ester in intermediate **18** was unsuccessful when attempted on the analogous 3,4-substituted compound. The synthesis of the requisite α,β-dimethyl ester **43** (the regioisomer of ester **18**) *via* direct conjugate addition to a tiglate (or angelate) was also unsuccessful (**Scheme 1.8**).[29]



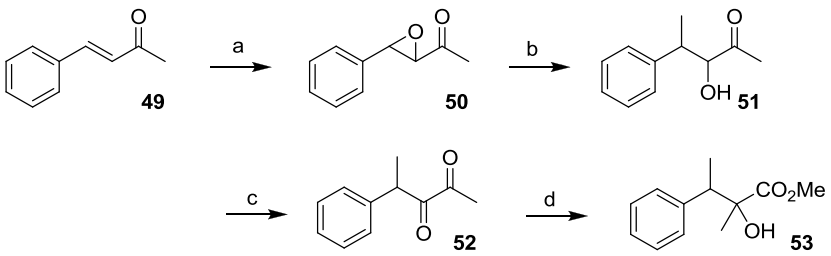
Scheme 1.8 – Shukla's attempts at the formation of α,β-dimethyl ester **43**.[29]

Shukla found that ester **42** could be obtained by addition of the Gilman cuprate obtained from 4-bromo-3-picoline, to methyl crotonate. However, inexplicably, no conditions could be found to effect α-methylation of this ester despite the success of this reaction on regioisomer **17**. It is possible that the success of the α-methylation in the case of the 2-pyridyl system can be attributed to transient pyridine *N*-methylation then intramolecular methyl transfer. This would be geometrically precluded for the 4-pyridyl system. Attempts to avoid α-methylation by performing the 1,4-addition with methyl tiglate [(*E*)-**44**] were also unsuccessful. Nitrile **45** was also synthesised by an analogous 1,4-addition process, but α-methylation of this substrate to give α-methyl nitrile **46** could not be realised without methylation of the nitrile nitrogen to afford an iminoketene. This led to the design of a new retrosynthetic strategy incorporating a benzilic ester rearrangement (BER) as the key step to install the α-hydroxy quarternary centre (**Scheme 1.9**).



Scheme 1.9 – New retrosynthetic strategy towards hydroxy-*iso*-evoninic acid incorporating a BER.

In this strategy, the benzylic acid is masked as a methyl group as in the syntheses of evoninic acid and hydroxy wilfordic acid.[21,22] Access to methyl ester **47**, prior to ester hydrolysis and benzylic oxidation, was envisaged by promotion of a BER in MeOH (the BER will be introduced later in **Chapter 1.3**). To test this new strategy, model phenyl diketone **52** was synthesised and a BER was attempted (**Scheme 1.10**).[30]



***Reagents and Conditions*;** (a) H_2O_2, MeOH, 1M NaOH (52%); (b) $AlMe_3$, H_2O, CH_2Cl_2 (64%); (c) $VOCl_3$, CH_3CN (51%); (d) $Cu(OAc)_2$, MeOH (*dr* 50:50, 60%).

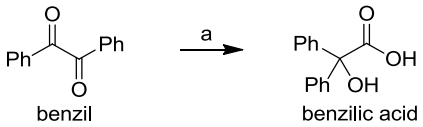
Scheme 1.10 – Sheng's synthesis of model phenyl diketone **52** and a trial BER.[30]

Epoxidation of commercially available enone **49** using hydrogen peroxide[31] gave epoxy ketone **50** which was ring opened with Me_3Al in the presence of water to afford α-hydroxy ketone **51**.[32,33] This could in turn be oxidised to diketone **52** with $VOCl_3$.[34] Using $Cu(OAc)_2$ as the Lewis acid promoter, a BER was effected and quarternary α-hydroxy ester **53** was formed as a 1:1 mixture of diastereoisomers. Although the BER was quite slow (60% conversion in 140 h), the retrosynthetic approach envisioned in **Scheme 1.9** was shown to be feasible.

1.3 The Benzilic Ester Rearrangement

1.3.1 Background and Mechanism

The BER is analogous to the benzilic acid rearrangement (BAR) reported by J. Liebig in 1838, which was the first rearrangement reaction to be discovered. The rearrangement is named after benzilic acid, the product of this first reported BAR which ensued on treatment of benzil with alcoholic potassium hydroxide at elevated temperature (**Scheme 1.11**).[35]



***Reagents and Conditions*;** (a) KOH, MeOH, 65 °C.

Scheme 1.11 – Liebig's benzilic acid rearrangement.[35]

The BER was reported later by Doering *et al.* in 1956.[36] The nucleophile in a BER is an alkoxy group rather than a hydroxy group and hence results in the formation of quarternary α-hydroxy esters rather than acids.

A mechanism for the BAR was first proposed by Ingold[37] and later corroborated by Yamabe[38] in a detailed computational study (**Figure 1.6**).

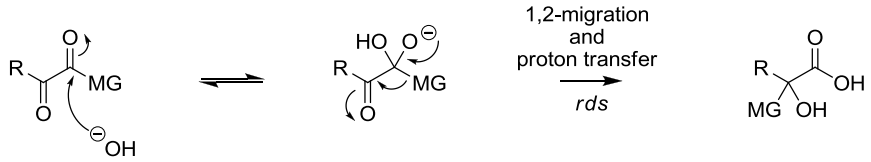


Figure 1.6 – Proposed mechanism of the BAR according to Ingold[37] and Yamabe.[38]

The process begins with the reversible 1,2-addition of an alcohol to one of the carbonyl groups of the 1,2-diketone substrate to form a deprotonated ketone hydrate intermediate. 1,2-Migration then occurs in the rate determining step and the quarternary α-hydroxy acid is formed. An investigation into effects on the rate of 1,2-migration under basic conditions have been performed by Bowden *et al.* They investigated a variety of 2,2`-, 3,3`- and 4,4`-substituted benzils with electron donating (-OMe) and electron withdrawing (-Cl) groups.[39] They found that the rates significantly increased when the benzils contained electron withdrawing groups, suggesting that a there is a build-up of negative charge on the migrating carbon during the 1,2-migration. This observation has also been corroborated in the computational study performed by Yamabe.[38] It was also found that *ortho*-substituents slowed the reactions, probably as the result of proceeding *via* a more sterically hindered transition state. Although no studies have been performed on the rates of the BER under neutral or acidic conditions, it is likely that the same effects observed for Lewis acid promoted pinacol rearrangements hold for the BER.[40] It has been shown through both experimental and computational work, that groups which can stabilise carbon cationic character at the migratory carbon show greater migratory aptitude. This supports the proposal of a build up of positive charge on the migrating group during the 1,2-migration. The different transition states are shown in the figure below (**Figure 1.7**).

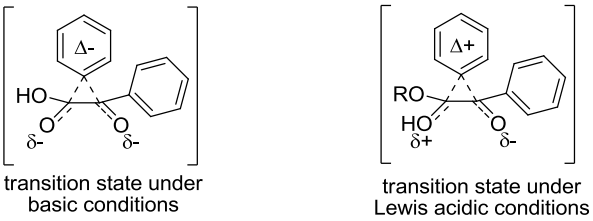
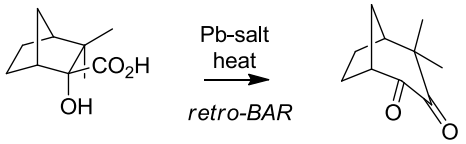


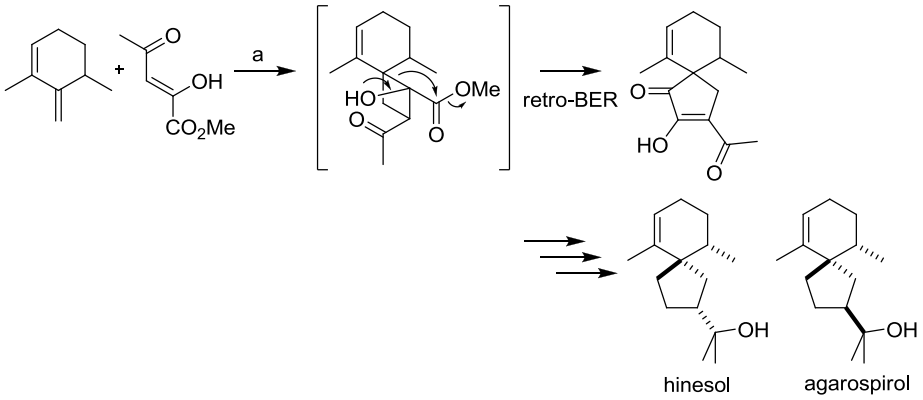
Figure 1.7 – 1,2-Migration transition states under basic and Lewis acidic conditions.

The 1,2-migration has been shown to be irreversible whether promoted under basic or Lewis acidic conditions.[41] However, there are some exceptions. To the best of our knowledge, there is only one reported case of a *retro*-BAR, and in this example there is an expansion from a 5- to 6-membered ring (**Scheme 1.12**).[42]



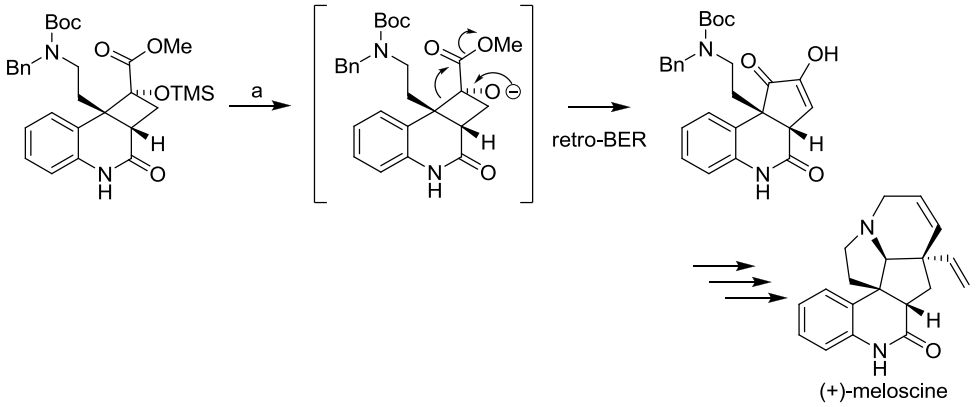
Scheme 1.12 – Wallach's first reported *retro*-BAR.[42]

Retro-BER's on the other hand, appear to occur more commonly but apparently only when there is a release of ring strain. Since the work of Takeshita *et al.* on the *retro*-BER of [2+2]-cycloaddition products,[43,44] this reaction has been utilised in the synthesis of natural product stereoisomers hinesol and agarospirol, and also meloscine (**Schemes 1.13** and **1.14**).



Reagents and Conditions; (a) hν, EtOAc, 7 h, then Na_2CO_3 (aq.) (79%).

Scheme 1.13 – Takeshita's use of the *retro*-BER for the synthesis of hinesol and its epimer agarospirol.[45]

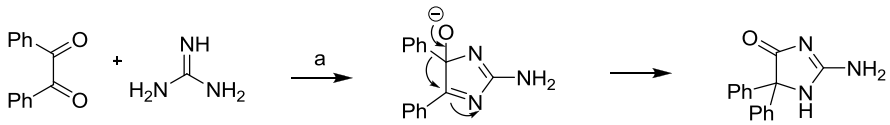


Reagents and Conditions; (a) K_2CO_3, MeOH, rt (98%).

Scheme 1.14 – Bach's use of the *retro*-BER for the synthesis of meloscine.[46]

In both examples, the *retro*-BER is spontaneous due to the release of ring-strain when expanding from a 4- to a 5-membered ring. In the first example (**Scheme 1.13**), the *retro*-BER occurs after [2+2] cycloaddition and in the second example (**Scheme 1.14**), after deprotection of the TMS ether. In both cases, the 5-membered ring 1,2-diketone is isolated in its mono-enol form.

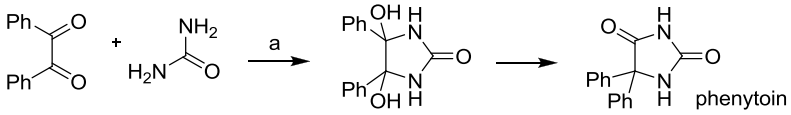
The first reported BER's were promoted under basic conditions (e.g. LiOH,[47] KOH[48]). An unusual variant of the BER, also promoted under basic conditions, has been found to occur with benzil using guanidine as the nucleophile (**Scheme 1.15**).[49]



***Reagents and Conditions*;** (a) NaOH, MeOH, 65 °C, 5 min (92%).

Scheme 1.15 – Kitajima's BER variant after treatment of benzil with guanidine.[49]

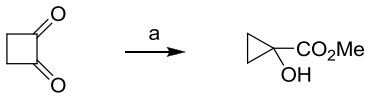
In an analogous example, a base promoted BER with urea was utilised in an expedient synthesis of phenytoin, an *anti*-epileptic pharmaceutical (**Scheme 1.16**).[50]



Reagents and Conditions; (a) KOH, heat.

Scheme 1.16 – Blitz's synthesis of phenytoin utilising a base promoted BER.[50]

However, a variety of other conditions not involving bases have since been employed to promote BER's.[51] Examples of Lewis acid BER promoters include $ZnCl_2$,[52] CuCl[53] and $Cu(OAc)_2$.[54] High temperature water (HTW), defined as water at 300-380 °C in the report, has also been used to promote a BAR.[55,56] In this work, Savage *et al.* found that a BAR was promoted under neutral and basic conditions, though it is thought the reaction occurs under the neutral conditions due to the presence of hydroxide anions in HTW. They also report the occurrence of a BAR under acidic HTW conditions, the first and only report of a BAR catalysed by a Brønsted acid. HTW promoted BAR's are not synthetically useful yet however, as high conversion is only achieved at pH>10 and under these highly basic conditions, mainly decomposition products of benzilic acid are isolated, including diphenyl methane, benzophenone, phenylacetophenone and 2-phenylmethylphenol. There is one other report in which a BER is promoted under neutral conditions, although the substrate is a strained 4-membered ring (**Scheme 1.17**).[57]



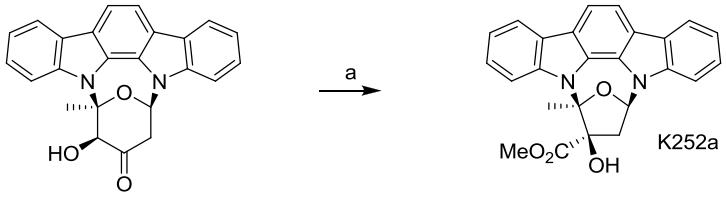
Reagents and Conditions; (a) MeOH, heat.

Scheme 1.17 – Denis's BER under neutral conditions.[57]

It was found that by simply stirring cyclobutan-1,2-dione in methanol, a BER was realised affording the ring-contracted 3-membered ring product.

1.3.2 Stereoselective Variants of the BER

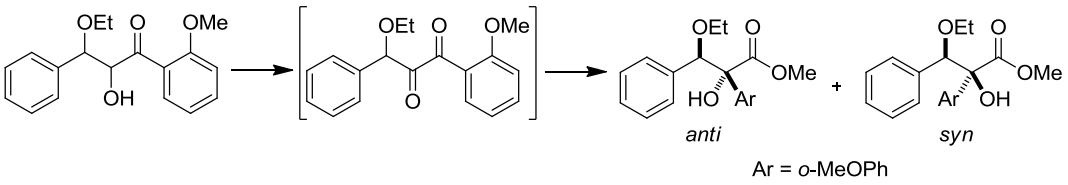
Although there are many examples of high diastereoselectivity in BER's, these are only reported for cyclic substrates where the BER results in a ring-contraction and the ring constraints control the diastereoselectivity. For example, the BER used in the synthesis of carbohydrate moiety K252a is completely diastereoselective and the CuCl promoter is used to oxidise the substrate to the 1,2-diketone as well as promoting the BER (**Scheme 1.18**).[53]



Reagents and Conditions; (a) CuCl, MeOH/CH_2Cl_2 (95%).

Scheme 1.18 –Wood's highly diastereoselective BER of a cyclic substrate *en route* to K252a.[53]

To date, there is only one report where the diastereoselectivity of a BER has been influenced beyond that determined by the substrate itself.[54] Burke *et al.* found that for their substrate, by lowering the concentration of the BER promoter $Cu(OAc)_2$ (also used to oxidise their α-hydroxy ketone precursor to the 1,2-diketone *in situ*), the diastereoselectivity was increased (**Table 1.5**).



Entry	$Cu(OAc)_2$ (mol%)	Yield (%)	*anti*:*syn*
1	100	70	2.1:1
2	50	75	2.7:1
3	25	74	3.6:1
4	10	87	4.5:1
5	5	73	4.6:1

Table 1.5 – Burke's study of the influence of promoter concentration on the diastereoselectivity in a BER.[54]

Burke rationalised the increased diastereoselectivity by looking at the copper bound and unbound intermediates and later performed a ^{13}C-labelling study to confirm that the benzylic group migrates exclusively in preference to the phenyl group in these reactions (**Figure 1.8**).[54,58]

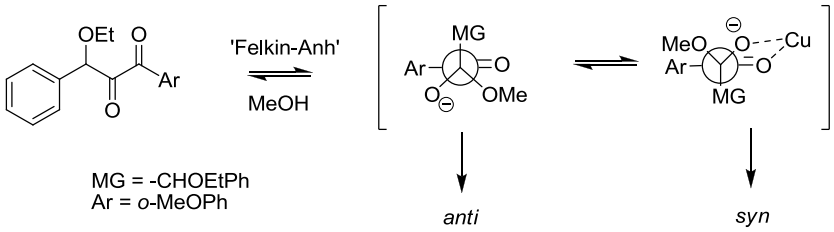


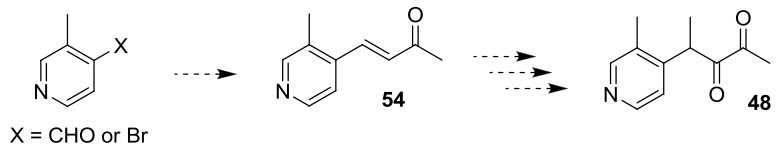
Figure 1.8 – Burke's rationalisation of the change in diastereoselectivity with promoter concentration.[54]

Burke proposes that nucleophilic addition to the 1,2-diketone occurs according to the Felkin-Anh model. At lower concentrations of $Cu(OAc)_2$, more material proceeds *via* the intermediate conformation leading to the *anti*-diastereoisomer as in this conformation, the carbonyl is *anti*-periplanar to the adjacent alkoxy group. As the migrating group has an orthogonal approach to maximise orbital overlap according to the Deslongchamps model,[59] the major product is the *anti*-diastereoisomer. However, as copper is moderately oxophilic and can chelate between the carbonyl and alkoxy oxygen as shown in the intermediate leading to the *syn*-diastereoisomer, a reduced selectivity for the *anti*-diastereoisomer is observed when more promoter is present. In other words, a balance between the copper-chelated and copper-free intermediates is proposed. However, the substrate investigated contains four oxygen atoms and a variety of copper chelates can be envisaged.

1.4 Aims and Objectives

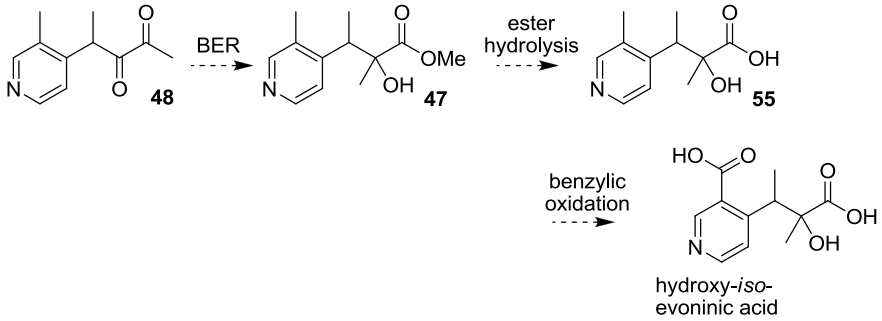
1.4.1 Synthesis of (±)-Hydroxy-*iso*-Evoninic Acid

The primary target of the work described in this thesis, was to achieve the first synthesis of (±)-hydroxy-*iso*-evoninic acid. With the successful promotion of a BER of model diketone **52** (see **Scheme 1.10**) it was decided to follow the retrosynthetic strategy demonstrated in **Scheme 1.9**, making 1,2-diketone **48** the first key intermediate target. As enone **54** is not commercially available, the synthesis of this was first required before the subsequent steps used in the model synthesis demonstrated in **Scheme 1.10** could be tested on the desired system (**Scheme 1.19**).



Scheme 1.19 – Proposed strategy for the synthesis of 1,2-diketone **48**.

A BER of 1,2-diketone **48** was then to be explored in order to obtain methyl ester **47**. Finally, by following Shukla's synthesis of unnatural hydroxy evoninic acid (see **Scheme 1.7**), the synthesis was to be completed by hydrolysing the ester followed by benzylic oxidation to afford the target compound hydroxy-*iso*-evoninic acid (**Scheme 1.20**).



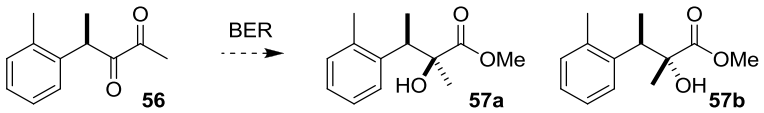
Scheme 1.20 – Proposed final steps for the synthesis of hydroxy-*iso*-evoninic acid.

This strategy was anticipated to give access to all four possible stereoisomers of hydroxy-*iso*-evoninic acid but had the potential to be adapted to the preparation of a single stereoisomer by performing an asymmetric epoxidation of enone **54** and then later performing a diastereoselective BER of chiral 1,2-diketone **48**.

1.4.2 Development of a Diastereoselective BER

As the study by Burke *et al.*, described above, is the only previous investigation in which the diastereoselectivity of a BER has been attempted to be manipulated, and because their substrate is highly oxygenated and thus their findings unlikely to prove general, it was planned to investigate control of diastereoselectivity in acyclic BERs further. It was recognised that it would be highly advantageous to develop switchable conditions so that once the relative stereochemistry present in natural hydroxy-*iso*-evoninic acid had been determined, the required diastereoisomer could be targeted by choice of appropriate conditions.

Envisaging possible complications in the synthesis of diketone **48** due to the basicity of the pyridyl nitrogen and because many of the common BER promoters are known to chelate strongly to pyridyl nitrogens, it was decided to initially employ *ortho*-tolyl diketone **56** as a model substrate on which to develop the BER conditions and to prepare this substrate using the same synthetic sequence as used in the synthesis of the phenyl diketone **52** (see **Scheme 1.10**) (**Scheme 1.21**).



Scheme 1.21 – Proposed model diketone **56** for methodology studies towards a diastereoselective BER.

It was planned to determine the ratio of the diastereomeric esters **57a** and **57b** by proton NMR or failing that, by GC or HPLC. Influencing the diastereoselectivity was to be attempted by investigating different BER promoters, then by varying temperature, concentration, solvent, nucleophile and investigating additives in the reaction.

1.4.3 Assignment of the Stereochemistry of Hydroxy-*iso*-Evoninic Acid

A dimethyl ether protected model of the dihydro-β-agarofuran core euonyminol (the common core in the nine sesquiterpenoids containing hydroxy-*iso*-evoninic acid) in which all the functionality of the bottom face is present, has previously been synthesised within the Spivey group (**Figure 1.9**).[7]

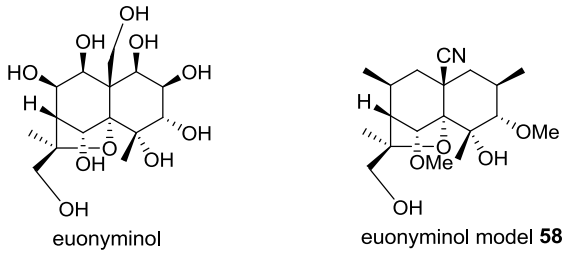
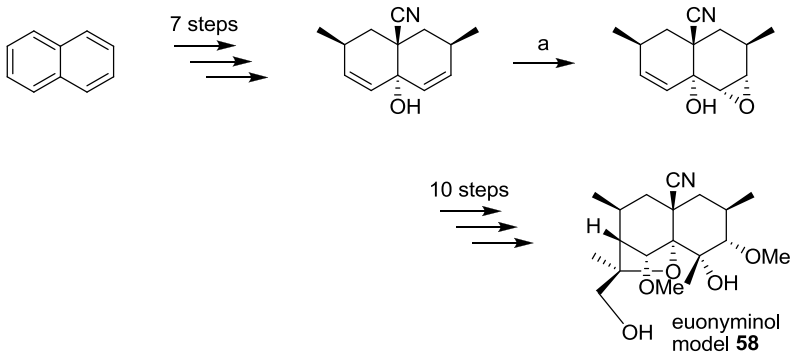


Figure 1.9 – Euonyminol and Webber's model containing the full functionality of the bottom face.[7]

Previously, only <1 mg of dimethyl ether protected euonyminol model **58** was isolated following the 18-step asymmetric synthesis in which the chirality is

introduced by desymmetrisation in a Zr-based Sharpless-type epoxidation (**Scheme 1.22**).[7,60]

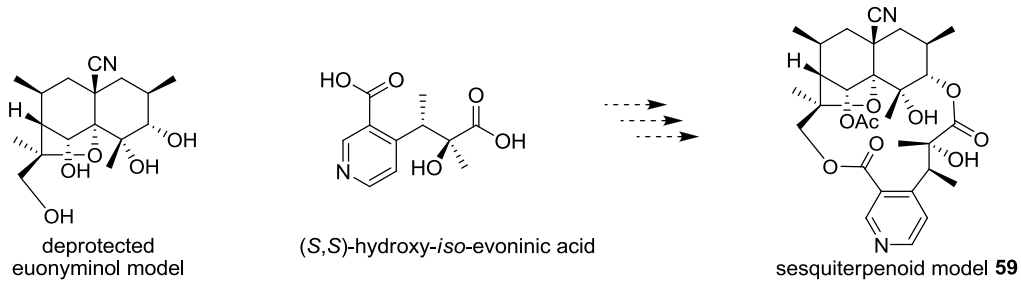


***Reagents and Conditions*;** (a) $Zr(O^iPr)_4$, L-(+)-DIPT, CH_2Cl_2, TBHP, 4 Å MS, -20 °C (92% *ee*, 90%).

Scheme 1.22 – Outline of Webber's 18-step synthesis of euonyminol model **58**.[7,60]

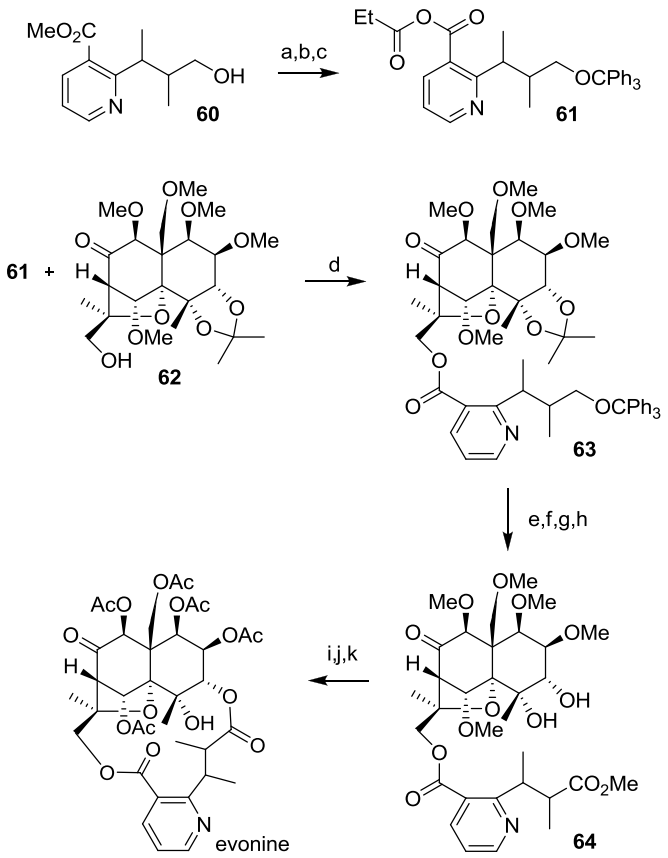
Since only small quantities of material had been brought through this synthesis, not all of the compounds had been fully characterised and the final methyl ether deprotection had not been attempted. Therefore, an additional aim of this project was to repeat the synthesis of euonyminol model **58** to allow for complete characterisation of all intermediates and to look for conditions to perform the final methyl ether deprotection.

As demonstrated by **Tables 1.2** and **1.3**, the NMR peaks corresponding to the esterifying ligand hydroxy-*iso*-evoninic acid show very little variation with changes to the esterifying ligands on the top face of the dihydro-β-agarofuran core. As the enantiomerically enriched euonyminol model **58** contains the full functionality on the bottom face, it is an ideal substrate to link with all four possible stereoisomers of synthesised hydroxy-*iso*-evoninic acid and compare the NMR data to the natural sesquiterpenoids with the intention of assigning the naturally occurring stereochemistry (**Scheme 1.23**).



Scheme 1.23 – Strategy for assigning the naturally occurring stereoisomer of hydroxy-*iso*-evoninic acid.

There is only one literature report on the successful linking of a pyridyl diacid esterifying ligand with a sesquiterpenoid core to form the 14-membered lactone characteristic of this class of compounds. Yamada *et al.* successfully linked evoninic acid to an evonine-derived β-dihydroagarofuran core **62** in their semi-synthesis of evonine using intermediates obtained from degradation of natural evonine (**Scheme 1.24**).[61]



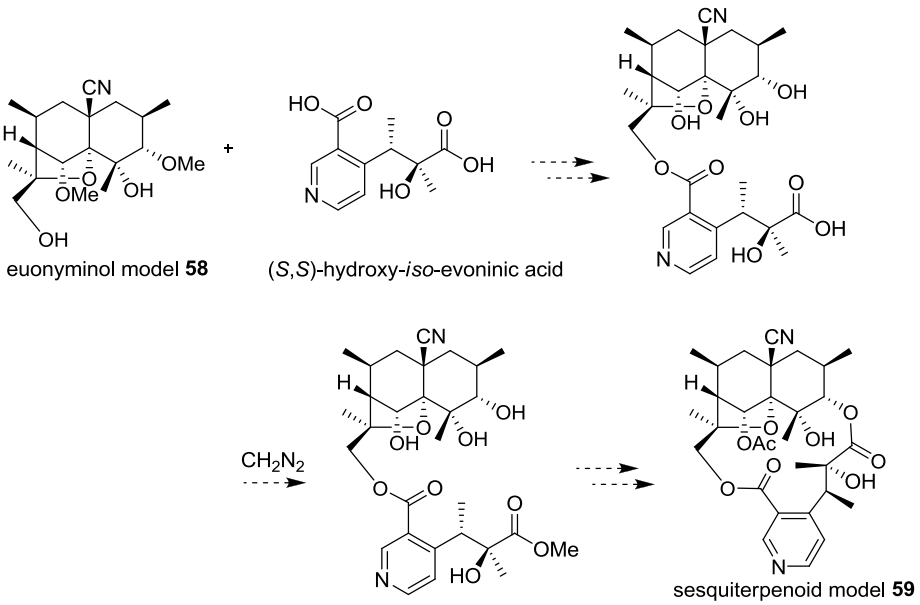
Reagents and Conditions; (a) Ph_3CCl, pyridine, 60 °C (95%); (b) 10% KOH/MeOH, 70 °C (71%); (c) ethyl chloroformate, Et_3N, DME, rt; (d) 4-DMAP, Et_3N, DME, 90 °C (34% over 2 steps); (e) 80% AcOH, 50 °C (82%); (f) CrO_3, pyridine, 65 °C (70%); (g) 50% AcOH, 85 °C (68%); (h) CH_2N_2; (i) NaH, DMF, rt (12%); (j) BCl_3, CH_2Cl_2, rt; (k) Ac_2O, pyridine, 70 °C (35% over 2 steps).

Scheme 1.24 – Yamada's macrolactone formation in the synthesis of evonine.[61]

Alcohol **60** was prepared from methyl ester protected evoninic acid using a known 3-step procedure.[8] Alcohol **60** was protected by forming a trityl derivative, the ester group was hydrolysed and the resulting acid treated with ethyl chloroformate to afford mixed anhydride **61**. Anhydride **61** was then esterified with primary alcohol **62** (a derivative of sesquiterpenoid core evoninol), to afford ester **63**. Deprotection of the trityl group, oxidation to the corresponding carboxylic acid, then deprotection of the acetonide moiety and finally esterification of the acid group, afforded methyl ester **64** ready for macrolactonisation. Treatment of methyl ester **64** with NaH successfully promoted macrolactonisation without requirement of protection of the tertiary alcohol albeit in a yield of just 12%. Deprotection of the

methyl ether groups followed by acetylation resulted in the semi-synthesis of evonine. It was found that all required secondary alcohol groups could be esterified leaving the tertiary alcohol free as required for the natural product.

There is much room for improvement in the formation of the macrolactone, as the current method requires several protecting group manipulations. However, it is encouraging that following treatment of the diol obtained from acetonide deprotection of compound **64** with NaH, the desired secondary alcohol cyclises onto the hindered methyl ester. In the light of this precedent, the same strategy of esterifying the primary alcohol with the benzylic ester present in the esterified hydroxy-*iso*-evoninic acid derivative, followed by an equivalent cyclisation, was envisaged in our work. It was anticipated that conditions could be found to selectively esterify the primary C-13 alcohol without the need to protect the free secondary and tertiary alcohols. As benzylic acids are generally more reactive towards carbodiimide assisted esterification than aliphatic esters, and because the α-quarternary centre present in hydroxy-*iso*-evoninic acid would probably hinder attack at this position, it was considered likely that the benzylic acid would also esterify more rapidly than the aliphatic one leading to the following synthetic plan (**Scheme 1.25**).

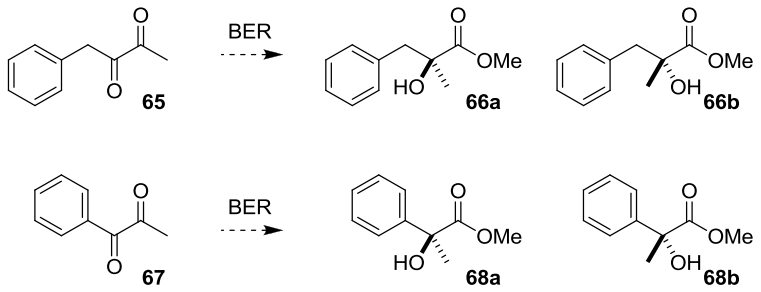


Scheme 1.25 – Plan for linking hydroxy-*iso*-evoninic acid with model core **58** to enable assignment of the naturally occurring stereochemistry of the Celastraceae diacid pyridine alkaloids.

In the event that the desired selectivity for ester formation at the benzylic over the aliphatic acid could not be achieved, the acid functionalities on the hydroxy-*iso*-evoninic acid derivative could be manipulated to ensure this outcome.

1.4.4 Development of an Asymmetric BER

As previously discussed, there is currently no reported asymmetric BER. Although, due to the presence of a chiral centre present in diketone **48**, only a diastereoselective BER is required for the asymmetric synthesis of hydroxy-*iso*-evoninic acid; it was envisaged that an asymmetric BER would be of wide utility and to that end it was hoped that it would be possible to also initiate an investigation into an asymmetric variant of the BER. Two substrates were planned to be investigated: 1,2-diketones **65** and **67** (**Scheme 1.26**).



Scheme 1.26 - Target substrates with which to investigate an asymmetric BER.

Benzyl diketone **65** was selected as it is known that benzylic groups can migrate under mild conditions in BER's, increasing the chances of developing conditions for inducing asymmetry in the reaction. It was also planned to prepare the possibly more challenging phenyl diketone **67** as the esters **68a** and **68b**, which would be formed upon a BER, show more prevalence in pharmaceuticals and natural products. The plan was to explore chiral ligands in conjugation with whichever transition metal proved to be most effective in promoting a diastereoselective BER in the aforementioned investigation.

2 Results and Discussion

2.1 Synthesis of Hydroxy-*iso*-Evoninic Acid

2.1.1 Synthesis of 1,2-Diketone Using the Model Route

In order to adapt Sheng's synthesis of phenyl diketone **52** (see **Scheme 1.10**) for the synthesis of desired picoline diketone **48**, the preparation of picoline enone **54** was first required. Three methods were considered: *via* an aldol condensation, *via* a Wittig reaction and *via* a Heck coupling reaction (**Figure 2.1**).

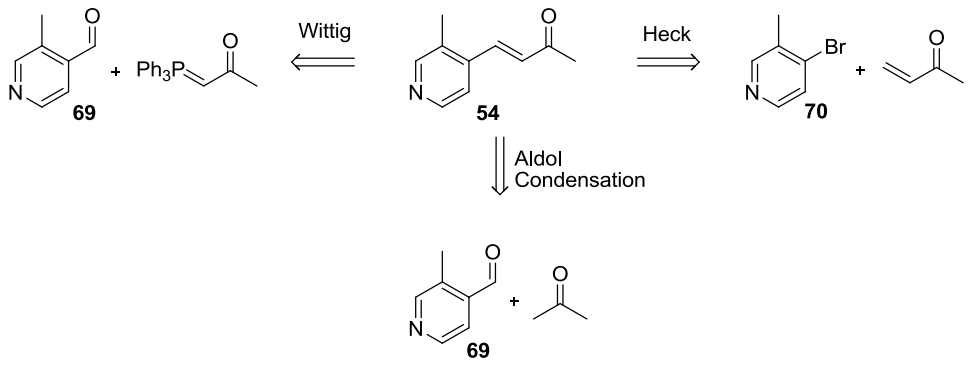
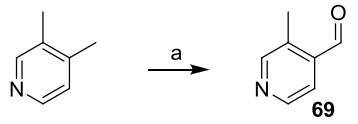


Figure 2.1 – Possible routes to picoline enone **54**.

Before attempts could be made at an aldol condensation or a Wittig reaction, the synthesis of known aldehyde **69** was required. It is known that commercially available 3,4-lutidine can be selectively oxidised to the alcohol[62] or the carboxylic acid[63] at the 4-methyl group, as this benzylic position is better able to accommodate a negative charge by delocalisation onto the pyridyl nitrogen, when compared to the 3-methyl group. Due to the higher yield reported for oxidation of the 4-methyl group to the carboxylic acid using SeO_2, it was decided to repeat this literature reaction and then reduce the ester derived from this acid to the aldehyde using DIBAL-H. In the procedure reported for the oxidation to the carboxylic acid, 3,4-lutidine is heated in diphenyl ether at 150 °C in the presence of SeO_2. However, it was found that by performing the reaction in dioxane and only heating to 105 °C, the 4-methyl group was only oxidised as far as the desired aldehyde **69** (**Scheme 2.1**).

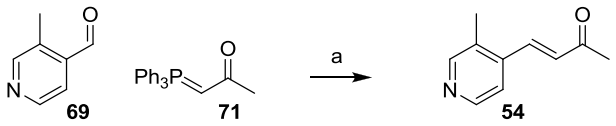


Reagents and Conditions; (a) SeO_2, dioxane, 105 °C, 20 h (47%).

Scheme 2.1 - Selective oxidation of 3,4-lutidine to aldehyde **69** using SeO_2.

Formation of aldehyde **69** was confirmed by comparison of its NMR data with the literature values and by mass spectrometry. This provides an improved procedure over those reported in the literature for accessing known aldehyde **69**. Previous one-step procedures either require a gaseous reagent at 400 °C[64] or show poor selectivity between oxidation to the aldehyde and the carboxylic acid.[65]

With aldehyde **69**, a Wittig reaction using commercially available ylide **71** was explored (**Scheme 2.2**).

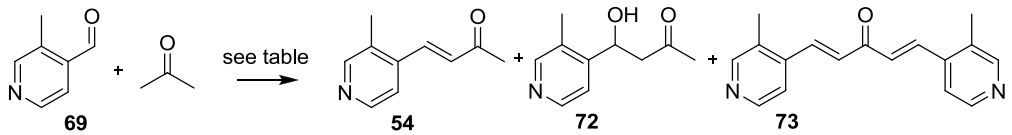


Reagents and Conditions; (a) 1.1 eq. ylide **71**, H_2O, 100 °C, 2 h (55%).

Scheme 2.2 – Formation of enone **54** *via* a Wittig reaction.[66]

The reaction was performed in water, as this solvent is known to accelerate Wittig reactions of stabilised ylides.[66] A ratio of 77:23 of the *trans*- and *cis*-enones was formed and to facilitate the analysis of subsequent NMR spectra, it was decided to separate the two isomers. The predominant *trans*-isomer could be separated from the *cis*-isomer by flash chromatography, however, it could not be isolated from the triphenylphosphine oxide by-product.

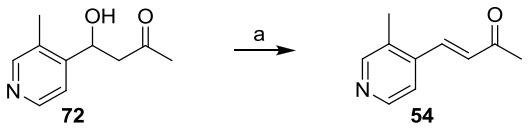
To avoid the formation of triphenylphosphine oxide, an aldol condensation reaction was investigated (**Table 2.1**).



Entry	Conditions	Outcome
1[67]	10% NaOH, EtOH, 0 °C to rt, 4.5 h	Consumption of aldehyde **69**, no desired products
2[68]	10% NaOH, EtOH, -20 °C, 30 min	Aldol **72** in 38% yield
3	10% NaOH, EtOH, -10 °C, 30 min	62% yield of aldol **72**
4	10 eq. TFA, MeOH, 60 °C, 17 h	Recovered aldehyde **69**

Table 2.1 – Attempts at the formation of enone **54** *via* an aldol condensation.

Following a procedure for the aldol condensation between 2-methylbenzaldehyde and acetone, although consumption of aldehyde **69** was observed, no desired enone **54** or aldol product **72** was observed (entry 1).[67] A paper detailing the aldol reactions of pyridine aldehydes with acetone, demonstrated the difficulty in performing the aldol reaction when the aldehyde is at the 4-position of a pyridyl ring.[68] They found that a temperature of -20 °C was optimal, though a yield of just 20.7% was obtained. When repeating these conditions with a 3-methyl substituent the aldol product **72** was successfully formed in a yield of 38% which was compromised by the competitive formation of symmetrical dibenzylacetone derivative **73** in 32% yield (entry 2). By increasing the temperature to -10 °C, the yield was increased to 62% and afforded aldol product **72** exclusively (entry 3). No reaction was observed when the aldol reaction was attempted using acidic conditions (entry 4). Heating aldol product **72** under acidic conditions allowed for conversion to *Z*-enone **54** in a high yield (**Scheme 2.3**).

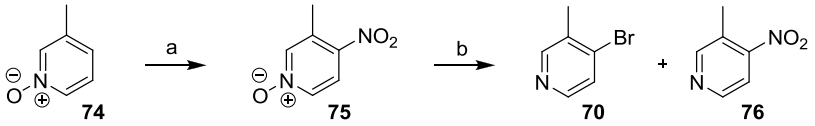


Reagents and Conditions; (a) 20% HCl, MeOH, 65 °C (89%).

Scheme 2.3 – Dehydration of aldol **72** to form enone **54**.

Due to the moderate yields of the aldol condensation route over the 3-steps from 3,4-lutidine, it was decided to also investigate the possibility of a Heck reaction of 4-bromo-3-picoline (**70**) with MVK before proceeding with the synthesis of 1,2-

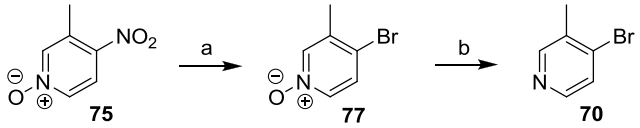
diketone **48**. Although 4-bromo-3-picoline is not commercially available, its synthesis is known. Its preparation from 3-picoline-*N*-oxide by nitration and then a 1-step procedure for aromatic substitution and deoxygenation, was investigated first (**Scheme 2.4**).[69,70]



Reagents and Conditions; (a) conc. HNO_3/conc. H_2SO_4, 0 to 100 °C (52%); (b) 15 eq. PBr_3, EtOAc, 0 to 65 °C, 3 h (10-50%).

Scheme 2.4 – Two-step synthesis of 4-bromo-3-picoline (**70**).[69,70]

Standard conc. HNO_3/conc. H_2SO_4 conditions successfully nitrated *N*-oxide **74** at the 4-position to afford 4-nitro pyridine **75**.[69] Reaction with PBr_3 to effect aromatic substitution followed by deoxygenation was found to be irreproducible.[70] If deoxygenation of 4-nitro pyridine *N*-oxide **75** occurred first, the pyridyl system was not electrophilic enough to participate in the aromatic substitution and 4-nitro-3-picoline **76** was isolated as a major product alongside oligomerisation products. It was thought that splitting this procedure into separate steps by following a more recent synthesis of 4-bromo-3-picoline (**70**) might provide a more reliable route (**Scheme 2.5**).[71]

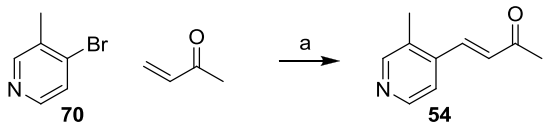


Reagents and Conditions; (a) AcOH/AcBr, 80 °C, 3 h (91%); (b) 4 eq. PBr_3, EtOAc, 65 °C, 30 min (72%).

Scheme 2.5 - Three-step synthesis of 4-bromo-3-picoline (**70**).[71]

From 4-nitro pyridine **75**, aromatic substitution was found to proceed in high yield when HBr was generated *in situ* from a AcBr/AcOH mixture.[71] No reaction was observed when refluxing in aqueous HBr. The resulting 4-bromo-*N*-oxide **77** was deoxygenated by heating with PBr_3. It was found that PPh_3 was not competent for this transformation.

With an efficient procedure established for the synthesis of 4-bromo-3-picoline, a Heck reaction with MVK using a procedure reported for the coupling of MVK with 2-bromotoluene was attempted (**Scheme 2.6**).[72]

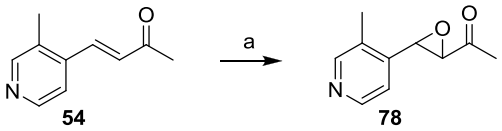


Reagents and Conditions; (a) 4 eq. MVK, 10 mol% $Pd(OAc)_2$, 40 mol% PPh_3, 2 eq. Et_3N, DMF, 100 °C (34%).

Scheme 2.6 – Heck coupling of 4-bromo-3-picoline with MVK.[72]

It was initially considered that the reaction was unsuccessful because no product was obtained following work-up. However, by avoiding aqueous work-up and using 4 equivalents of MVK, a yield of 34% of enone **54** was achieved. Although it is likely this yield could be further optimised, with the synthesis of 4-bromo pyridine **70** requiring 3-steps, it was clear that an aldol reaction after a 1-step synthesis of aldehyde **69** was the best method to synthesise enone **54** on the scale required to complete the synthesis of hydroxy-*iso*-evoninic acid and so no further work was carried out to optimise this Heck reaction (see **Table 2.1**, entry 3).

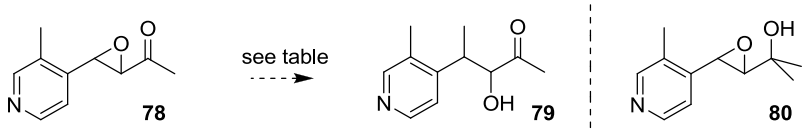
With enone **54** in hand, the synthetic route developed for the model system was followed (see **Scheme 1.10**), and epoxidation of enone **54** was performed (**Scheme 2.7**).



Reagents and Conditions; (a) 35% H_2O_2, 2M NaOH, MeOH, rt, 2.5 h (54%).

Scheme 2.7 – Nucleophilic epoxidation of enone **54**.

Nucleophilic epoxidation occurred in 54% yield, which is comparable with that obtained on the model (52%, **Scheme 1.10**) and no *N*-oxide formation was observed which was considered to be a likely by-product if electrophilic epoxidation had been attempted. The synthesis was continued by attempting to ring-open epoxide **78** with Me_3Al (**Table 2.2**).[32]



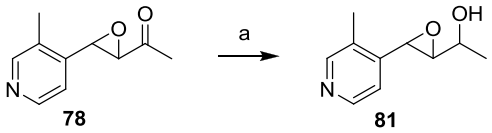
Entry	Temperature	Outcome
1[32]	-78 °C	Recovered epoxy ketone **78**
2	-78 to 0 °C	82% yield of epoxy alcohol **80**
3	-40 °C	50% conversion to epoxy alcohol **80**

Reagents and Conditions; 4 eq. Me_3Al, 4 eq. H_2O, CH_2Cl_2, 2.5 h.

Table 2.2 – Attempted ring-opening of epoxide **78** with Me_3Al.

On attempting the reaction at -78 °C under the same conditions as used on the model, no reaction was observed (entry 1). Allowing the reaction to warm up to 0 °C afforded only epoxy alcohol **80** which was isolated in 82% yield and presumably arises from 1,2-addition to the carbonyl group (entry 2). By repeating the reaction at -40 °C no desired α-hydroxy ketone **79** was formed, only a slower conversion to epoxy alcohol **80** was observed by inspection of ^{1}H NMR spectra (entry 3).

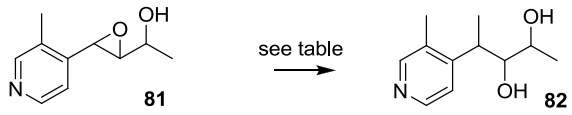
To eliminate the possibility of 1,2-addition to ketone **78**, it was decided to reduce the ketone to epoxy alcohol **81** before ring-opening the epoxide. This would add just one step to the sequence if the resulting 1,2-diol **82** could be dioxidised to 1,2-diketone **48**. The reduction was achieved with $NaBH_4$ (**Scheme 2.8**).



Reagents and Conditions; (a) $NaBH_4$, MeOH, 0 °C to rt, 15 min (*dr* 57:43, 95%).

Scheme 2.8 – Reduction of epoxy ketone **78** to epoxy alcohol **81**.

The reduction gave a 57:43 ratio of *erythro* and *threo* diastereoisomers which were assigned by comparison to similar substrates in the literature.[73] The ring-opening of this epoxide was then attempted under various conditions (**Table 2.3**).



Entry	Conditions	Outcome
1[33]	3 eq. $AlMe_3$, CH_2Cl_2, 0 °C to rt, 16 h	Recovered epoxide **81**
2[33]	10 eq. $AlMe_3$, 6 eq. H_2O, CH_2Cl_2, 0 °C to rt, 16 h	Recovered epoxide **81**
3[74]	$Me_2Cu(CN)Li_2$, Et_2O, -78 °C to rt, 18 h	Recovered epoxide **81**
4	5 eq. MeLi, THF, 0 °C, 30 min	Unidentified product
5	2 eq. MeLi, THF, 0 °C, 30 min	Unidentified products
6	2 eq. MeLi, THF, -78 °C, 30 min	Recovered epoxide **81**
7[75]	1.1 eq. Me_4AlLi, hexane/CH_2Cl_2, 0 °C to rt, 16 h	Recovered epoxide **81**
8[75]	3 eq. Me_4AlLi, CH_2Cl_2, 40 °C, 18 h	Unidentified products
9[74]	4 eq. MeMgBr, THF, 0 °C, 17 h	Recovered epoxide **81**

Table 2.3 – Attempts at ring-opening epoxy alcohol **81** with methyl organometallic reagents.

Attempts at the ring-opening reaction with varying equivalents of Me_3Al and in the presence or absence of water, resulted only in recovery of epoxy alcohol **81** (entries 1 and 2).[33] Upon addition of $Me_2Cu(CN)Li_2$, for which addition to epoxides is known to proceed with inversion as opposed to retention as observed with Me_3Al, a gummy complex immediately formed, probably due to chelation of the pyridyl nitrogen to the copper.[74] Hence, no desired reaction occurred under these conditions (entry 3). Reaction with excess MeLi resulted in conversion to an unidentified product (entry 4). By reducing the amount of MeLi to 2 equivalents, 1 equivalent to deprotonate the alcohol and 1 equivalent to perform the ring-opening, the formation of the same undesired product could not be avoided, though this product was isolated in a 1:1 ratio with a new product which appeared to contain an epoxide (entry 5). Cooling the reaction to -78 °C in the hope of avoiding unwanted side reactions resulted in recovery of the starting material (entry 6). It was therefore decided to return to aluminium complexes with the addition of the more reactive species Me_4AlLi. However, using only 1 equivalent resulted simply in recovery of starting material and using an excess resulted in a mixture of unidentified products (entries 7 and 8).[75] Finally, addition of a methyl Grignard reagent failed to instigate a reaction (entry 9).[74] It is possible the aryl methyl group is sterically hindering the addition to the epoxide, and/or that the

pyridyl nitrogen is making the build up of positive charge at the benzylic position less favourable than in the case of the successful model system. Alternatively, the pyridyl lone pair of electrons may coordinate too strongly to the aluminium metal reagents to allow them to act as effective methyl nucleophiles.

2.1.2 New Strategy Towards 1,2-Diketone 48

Without even trace amounts of diol **82** observed up to this point, an alternate route to diketone **48** was considered (**Figure 2.2**).

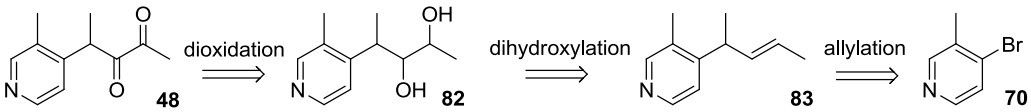
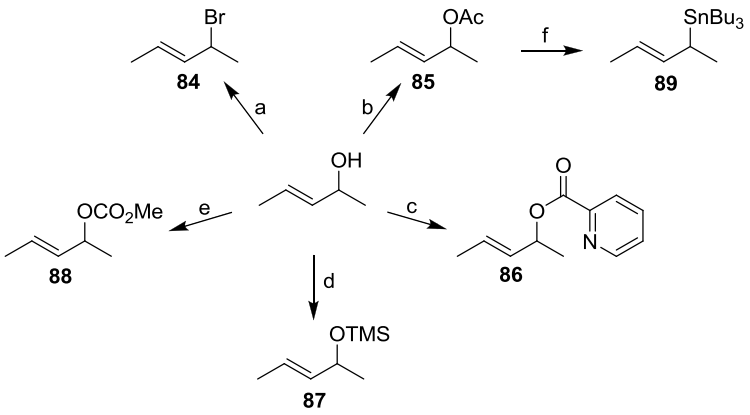


Figure 2.2 – New retrosynthetic strategy to diketone intermediate **48**.

It was hoped that 4-bromo pyridine **70** would participate in an allylation with an allylic electrophile obtained from commercially available 3-penten-2-ol. This approach takes advantage of the symmetry of the allyl intermediate and so requires no consideration of S_N2 or S_N2' selectivity. Problems with dihydroxylation of alkene **83** or dioxidation of the resulting 1,2-diol **82** were not envisaged.

Due to 4-bromo pyridine **70** requiring a 3-step synthesis (see **Scheme 2.3**), it was decided to target *ortho*-tolyl alkene **92** as a model substrate on which to develop allylation reaction conditions using 2-bromotoluene as the aryl bromide. Before discussion of this, the following scheme summarises the synthesis of the various allylic electrophiles that were investigated in the allylations discussed in this section (**Scheme 2.9**).

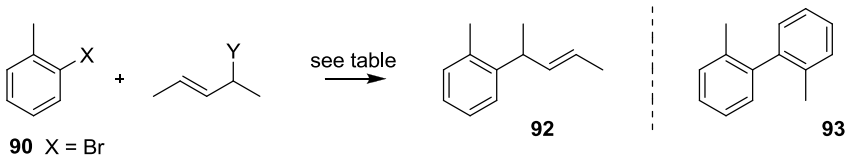


Reagents and Conditions; (a) 0.5 eq. PBr_3, Et_2O, 0 °C, 2 h,then rt, 1 h (68%); (b) 1.1 eq. Ac_2O, 1.1 eq. pyridine, Et_2O, rt, 21 h (69%); (c) 1.2 eq. 2-picolinic acid, 1.3 eq. DCC, 1.2 eq. 4-DMAP, CH_2Cl_2, 0 °C to rt, 1 h (95%); (d) 1.1 eq. TMSCl, pyridine/Et_2O (1:10), 0 °C to rt, 2.5 h (72%); (e) 1.1 eq. $ClCO_2Me$, 1.1 eq. pyridine, Et_2O, 0 °C to rt (53%); (f) 1.5 eq. $Bu_3SnAlEt_2$, 5 mol% $Pd(PPh_3)_4$, THF, -78 to 0 °C to rt, 2 h (70%).

Scheme 2.9 – Allylic compounds synthesised from 3-penten-2-ol for use in allylation reactions.

The yields for the synthesis of allylic bromide **84**,[76] acetate **85**,[77] formate **88**[78] and TMS ether **87** were limited by their volatility. To maximise these yields, only volatile solvents were used in the reactions and during work-up. These solvents were then removed carefully under a flow of nitrogen. Previously unknown picolinate ester **86** was synthesised according to standard Steglich esterification conditions.[79] The synthesis of allylic stannane **89** was also successful using $(SnBu_3)_2$[80] rather than $Bu_3SnAlEt_2$[81] when catalysed by $Pd(PPh_3)_4$, though the reaction produced a large amount of tin by-products which were difficult to remove from the extremely apolar allylic stannane **89**. $Bu_3SnAlEt_2$ was prepared by deprotonation of Bu_3SnH followed by addition of Et_2AlCl and was used directly as a THF solution.

A range of model allylation reactions were attempted that could be used directly with the commercially available 2-bromotoluene (**90**) or following its conversion to an aryl metal *in situ* (**Table 2.4**).



90 X = Br
91 X = MgBr

Entry	X	Y	Conditions	Outcome
1[82]	Br	OAc	3 eq. Et_4NCl, 4 eq. $^nBuMe_2N$, 0.5 eq. Pd/C, DMF, 1 eq. H_2O, 100 °C, 16 h	Recovered **90**
2[83]	Br	OAc	0.1 eq. PhBr, 3.3 eq. Zn, 0.2 eq. $CoBr_2$, 0.1 eq. $ZnBr_2$, AcOH, MeCN, 60 °C, 16 h	Recovered **90** and **85**
3[84]	Br	OAc	1.5 eq. $(SnBu_3)_2$, 0.1 eq. $Pd(dppf)Cl_2$, DMF, 120 °C, 16 h	38%
4	Br	Br	2 eq. ^{t}BuLi or 1 eq. ^{n}BuLi, -78 to 0 °C, 2 h	11% yield
5[85]	MgBr	OAc	4 mol% $NiCl_2(PPh_3)_2$, THF, rt, 16 h	17% yield
6[86]	MgBr	OTMS	4 mol% $NiCl_2(PPh_3)_2$, THF, rt, 16 h	Only biaryl **93** observed
7[86]	MgBr	OTMS	4 mol% $Pd(dppf)Cl_2$, THF, rt, 16 h	0.1:1, alkene **92** : biaryl **93**
8[87]	MgBr	OCO-(2-pyridyl)	0.5 eq. $CuBr{\cdot}SMe_2$, THF, -78 to 0 °C, 1 h	99% yield

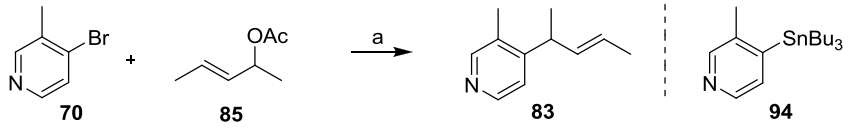
Table 2.4 – Allylation reactions with aryl bromide **90**.

A Pd/C catalysed reaction with allylic acetate **85** was attempted first which did not require transmetallation.[82] Although examples were only provided for the allylation of aryl iodides, it was decided to attempt the reaction with 2-bromotoluene (**90**). The mechanism proposed starts with oxidative addition into the aryl-halide bond and as the aryl bromide was recovered intact from the reaction mixture, it was clear that this bromide was not reactive enough under these conditions (entry 1). Gosmini's cobalt catalysed procedure has been successfully used with aryl bromides, though only with allyl acetate itself.[83] The mechanism proposed is reduction of Co(II) to Co(I) by zinc dust which immediately forms a strong (*ŋ*2-allylOAc)-cobalt(I) complex. These complexes have been shown to be highly reactive towards aryl halides. However, it appears that this cobalt(I) complex did not form with secondary allylic acetate **85** as it was recovered and no reaction was observed (entry 2). Another procedure in which an aryl bromide can be used directly is *via* Stille coupling. Addition of $(SnBu_3)_2$ to an aryl bromide in the presence of a Pd

catalyst and allyl acetate can afford the allylated product.[84] No investigation into whether the reaction proceeds *via* the allyl or aryl stannane has previously been performed and only examples employing allyl acetate itself have been reported. Pleasingly, the reaction between 2-bromotoluene and allylic acetate **85** was successful, and afforded alkene **92** in a moderate yield (entry 3). As the yield was not particularly high and removal of the tin by-products was laborious, it was decided to continue to look for alternative methods. Performing halogen-lithium exchange and quenching with allylic bromide **84** did result in the formation of a small amount of alkene **92**, although the majority of the material was lost due to isomerisation to the presumably more thermodynamically stable styrene (entry 4). Kumada couplings were then considered. Using a nickel catalyst with allylic acetate **85** resulted in the formation of product in just 17% yield (entry 5).[85] Using TMS protected allylic ether **87** under the same conditions resulted in complete conversion to biaryl **93** (entry 6) and switching the catalyst to a palladium catalyst appeared to only slightly slow down the rate of formation of this biaryl, allowing co-formation of the desired alkene **92** in just 10% yield (entry 7).[86] Finally, a S_N2' reaction with allylic picolinate **86** as the electrophile using conditions developed by Kobayashi *et al*. was attempted.[87] After formation of the aryl Grignard reagent, transmetallation with copper occurs to generate $MgBr_2$, which coordinates to the picolinate making this a particularly effective leaving group. Although not required for our symmetrical allylic moiety, the substitution has been shown to proceed exclusively through a S_N2' mechanism with a range of substrates. It has also been shown that the substitution occurs with extremely high levels of chirality transfer, allowing for an asymmetric synthesis, as chiral 3-penten-2-ol is readily accessed through a kinetic resolution of the carbonate[88] or by a lipase resolution.[89] The reaction between the aryl Grignard reagent obtained from 2-bromotoluene and allylic picolinate ester **86** afforded desired alkene **92** in essentially quantitative yield (entry 8).

The optimal allylation conditions (**Table 2.4**, entry 8) were applied to the pyridyl system. Unfortunately, the reaction was unsuccessful, as upon addition of the Cu(I) complex, a viscous mixture formed presumably as the result of coordination of the

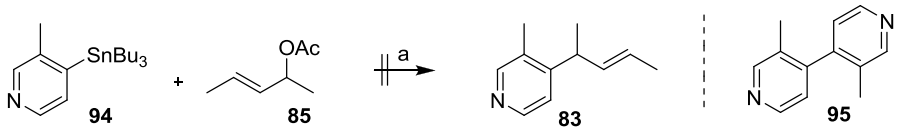
pyridyl nitrogen to the copper centre and no desired product was isolated. Efforts therefore focused on optimising the Stille coupling (**Table 2.4**, entry 3) on the required pyridyl system (**Scheme 2.10**).



Reagents and Conditions; (a) 1.5 eq. $(SnBu_3)_2$, 10 mol% $Pd(dppf)Cl_2$, DMF, 120 °C, 16 h (39%).

Scheme 2.10 – Optimisation of the Stille coupling between bromo pyridine **70** and allylic acetate **85**.

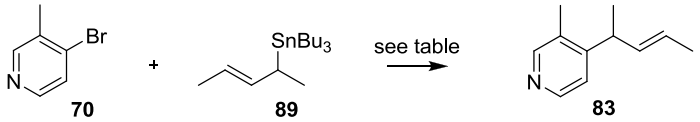
Repeating the Stille coupling on the pyridyl system did afford some of the desired alkene **83**, though a major product was aryl stannane **94**. As mentioned above, no study into whether the reaction proceeds *via* the aryl or allyl stannane has been reported. Therefore, aryl stannane **94** was isolated and resubjected to the reaction conditions (**Scheme 2.11**).



Reagents and Conditions; (a) 0.1 eq. $Pd(dppf)Cl_2$, DMF, 120 °C, 16 h.

Scheme 2.11 – Attempted Stille coupling using preformed aryl stannane **94**.

No alkene **83** was observed and biaryl **95** was the major product formed during the reaction, as deduced by analysis of the LCMS data recorded on the crude reaction mixture. It was therefore presumed that the reaction was proceeding *via* the allylic stannane and so it was decided to prepare allylic stannane **89** as described by Trost[81] (see **Scheme 2.9**). The Stille coupling between aryl bromide **70** and allyl stannane **89** was then investigated (**Table 2.5**).

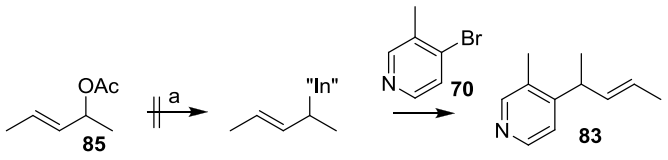


Entry	Conditions	Outcome
1[84]	1 eq. **70**, 1.3 eq. **89**, 10 mol% $Pd(dppf)Cl_2$, DMF, 120 °C, 16 h	0%
2[90]	1 eq. **70**, 1.3 eq. **89**, 10 mol% $Pd(PPh_3)_4$, toluene, 100 °C, 16 h	17% conversion to alkene **83**
3	1 eq. **70**, 1.3 eq. **89**, 10 mol% $Pd(PPh_3)_4$, DMF, 120 °C, 16 h	54% yield of alkene **83**

Table 2.5 – Stille coupling with preformed allyl stannane **89**.

When performing the reaction using the same solvent and catalyst as used successfully for the model coupling (*cf*. **Table 2.4,** entry 3), surprisingly, no alkene **83** was observed (entry 1). It was therefore decided to change the catalyst and solvent to those commonly used in Stille couplings with allylic stannanes, i.e. $Pd(PPh_3)_4$ and toluene.[91] This resulted in the formation of a small quantity alkene **83**, though the majority of aryl bromide **70** was recovered (entry 2). Switching the solvent back to DMF but keeping the catalyst as $Pd(PPh_3)_4$, the isolated yield was improved to 54% with complete consumption of aryl bromide **70** (entry 3). Formation of biaryl **95** limited the yield. Increasing the amount of allylic stannane **89** did not improve the yield so the amount of this was held at 1.3 eq. to minimise problems with tin removal during work-up. It was originally decided to proceed with this method to synthesise alkene **83**, though when performing the reaction on a scale greater than 250 mg, the yields decreased significantly. As the reaction is heated at 120 °C, the cause of this is unclear.

Another catalysed cross-coupling reaction was attempted where an allylic indium species is formed *in situ* (**Scheme 2.12**).

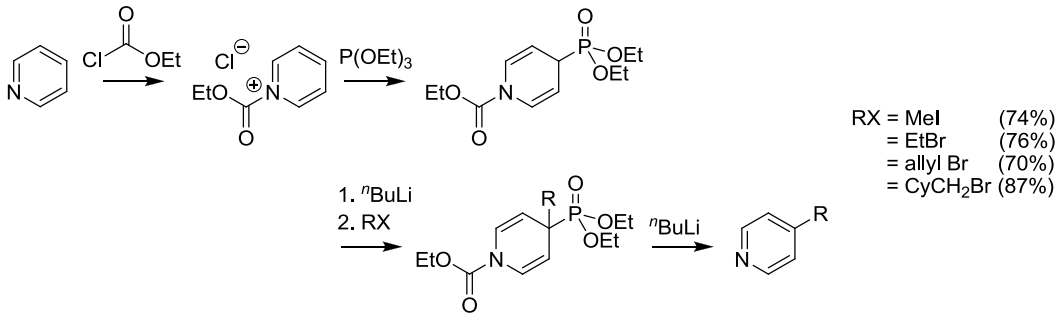


Reagents and Conditions; (a) 5 mol% $Pd_2dba_3{\cdot}CHCl_3$, 20 mol% Xantphos, 2 eq. In, 0.5 eq. $InCl_3$, 3 eq. LiCl, 2 eq. $^{n}BuNMe_2$, DMF, rt, then 1 eq. **70**, 100 °C.

Scheme 2.12 – Allylation by *in situ* formation of an allylic indium species.[92]

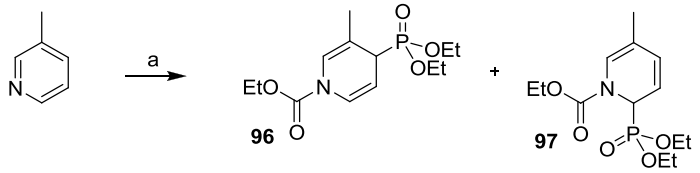
This followed a procedure from a paper which described the first successful reactions of aryl bromides with allyl indium species. The success of these coupling reactions was attributed to the larger bite angle of Xantphos as compared to previous investigated ligands. However, the conditions did not afford alkene **83**, possibly due to the presence of the γ-substituent, and/or the basicity of the pyridyl nitrogen, and/or the steric hindrance caused by the 3-methyl substituent on the aryl bromide **70**.

In view of the limited success thus far achieved for allylation reactions with aryl bromide **70** and due to its 3-step preparation, it was decided not to investigate allylations of the corresponding aryl iodide as this derivative requires a 4-step synthesis which has been shown to be low yielding.[29] Instead, chemistry developed by Akiba *et al.* was considered. Akiba has reported that 1,4-dihydropyridine phosphonates can act as equivalents of a pyridine that is nucleophilic at the 4-position.[93] Allyl bromide and a selection of alkyl halides were reported as potential electrophiles (**Scheme 2.13**).



Scheme 2.13 – Akiba's use of 1,4-dihydropyridinesphosphonates in the formation of 4-substituted pyridines.[93]

Akiba reported that by using ethyl chloroformate, the phosphonate ester formed exclusively at the 4-position. Deprotonation and then trapping with an alkyl halide electrophile, installed the alkyl substituent α to the phosphonate ester. A further 2 equivalents of base are then required to remove the formate and phosphonate esters. The procedure was attempted using 3-picoline in the hope that the 3-methyl substituent wouldn't reduce the selectivity for the 4-position (**Table 2.6**).

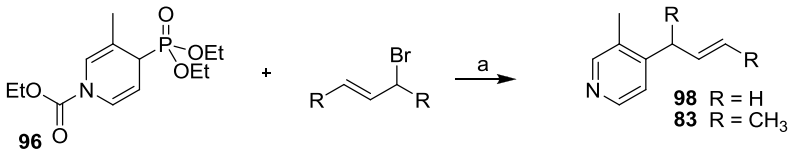


Entry	Solvent	Ratio of 96:97 (yield)
1	THF	1:0.3
2	MeCN	1:0 (88%)

Reagents and Conditions; (a) 1 eq. EtOCOCl, 0 °C, 30 min then 1 eq. $P(OEt)_3$, rt, 16 h.

Table 2.6 – Formation of phosphonate ester **96**.

Using THF as the solvent, as was used by Akiba *et al.*, resulted in a mixture of 4- and 6-substituted phosphonate esters (entry 1). However, by switching the solvent to MeCN, 4-substituted phosphonate ester **96** was formed exclusively in a high yield and this compound could be taken through to the next step with no purification required after removal of the solvent (entry 2). Using commercially available allyl bromide, a trial allylation was performed and upon its success, 3-bromopent-2-ene (**84**) was used to obtain the desired alkene **83** (**Table 2.7**).



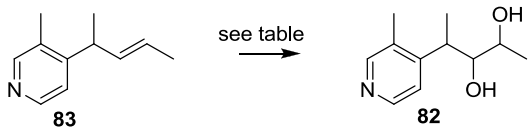
Entry	R	Yield
1	H	79% of alkene **98**
2	CH_3	53% of alkene **83**

Reagents and Conditions; (a) 1.1 eq. ^{n}BuLi, THF, -78 °C, 40 min, then 1.1 eq. allyl bromide, 30 min, then 0 °C, 40 min, then -78 °C, 2.2 eq. ^{n}BuLi, then 0 °C, 45 min.

Table 2.7 – Alkylation reactions of 4-phosphonate ester **96**.

The yield with commercially available allyl bromide (entry 1) was higher than that achieved for 3-bromopent-2-ene (entry 2) likely due to the greater steric hindrance of the secondary bromide. However, a yield of 53% was considered a significant improvement in all previous routes given the low cost of the starting materials and the avoidance of the 3-step synthesis of aryl bromide **70**. It was therefore decided to proceed with this procedure in future for the synthesis of intermediate alkene **83**.

Returning to the synthesis of the BER precursor diketone **48** (see **Figure 2.2**), dihydroxylation of alkene **83** was attempted (**Table 2.8**).



83 **82**

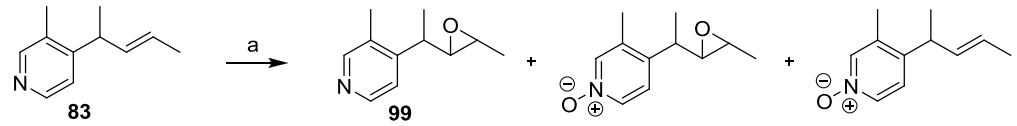
Entry	Conditions	Outcome
1[94]	0.4 mol% K_2OsO_4, 2.2 eq. NMO, 3 eq. citric acid, $^tBuOH/H_2O$ (1:1), rt, 18 h	Irreproducible
2[95]	1 mol% OsO_4, 2.2 eq. NMO, THF/H_2O (10:1), rt, 17 h	Irreproducible
3	0.4 mol% OsO_4, 2.2 eq. NMO, acetone/H_2O (4:1), rt, 6 h	Recovered alkene **83**
4[96]	0.4 eq. $NaIO_4$, 0.3 eq. LiBr, AcOH, 95 °C, 18 h; then conc. *in vacuo*; then 3.3 eq. K_2CO_3, MeOH, rt, 30 min	Unidentified product, possibly glycol bond cleavage to acid
5[97]	0.5 mol% $RuCl_3$, 1.5 eq. $NaIO_4$, 1M H_2SO_4, EtOAc, MeCN, H_2O, 0 °C, 5 min	Glycol bond cleavage to aldehyde (36% yield)

Table 2.8 – Attempts at dihydroxylation of alkene **83**.

Although moderate yields of 1,2-diol **82** were obtained using standard Sharpless dihydroxylation conditions (entry 1),[94] the reaction was found to be highly unreliable and when low yields were obtained, alkene **83** had largely decomposed. Under these conditions the reaction mixture is at pH 4 and at this acidity it is possible that alkene **83** is in the aqueous layer due to protonation of the pyridyl nitrogen. It was therefore decided to use OsO_4 in a high THF/H_2O ratio; unfortunately, this showed no improvement (entry 2).[95] By switching the solvent mixture to acetone/H_2O, decomposition was prevented though the starting material

was completely recovered (entry 3). $NaIO_4$ was used in acetic acid as the acidic conditions have been reported to avoid cleavage of the glycol bond. However, it was found that with alkene **83**, cleavage could not be avoided and a mixture of products was formed (entry 4).[96] Dihydroxylation was then attempted with RuO_4 with which it has also been shown that under highly acidic conditions, cleavage of the glycol bond is prevented.[97] However, alkene **83** was cleaved within 5 min and only the aldehyde cleavage product was observed (entry 5).

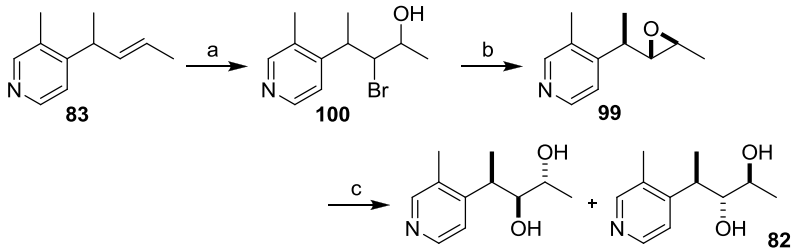
It was therefore decided to form diol **82** in a stepwise procedure *via* epoxide **99** which could be ring-opened to diol **82**. Epoxidation was attempted with *m*-CPBA (**Scheme 2.14**).



Reagents and Conditions; (a) 1 eq. *m*-CPBA, CH_2Cl_2, 0 °C, 2 h.

Scheme 2.14 – Epoxidation of alkene **83**.

Although just 1 equivalent of *m*-CPBA was used, a mixture of *N*-oxide and epoxide/alkene products was obtained. Envisaging that *N*-oxide formation may be hard to avoid, it was decided to obtain epoxide **99** from bromohydrin **100** (**Scheme 2.15**).



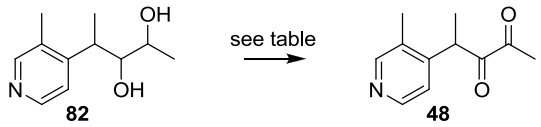
Reagents and Conditions; (a) 1 eq. NBS, THF/H_2O, 0 °C, 1 h (*regioisomers* 60:40); (b) 2M NaOH, MeOH, 60 °C, 1 h (*dr* 52:48, 84% over 2 steps); (c) 10% $HClO_4$ (aq.), MeCN, rt, 16 h (*dr* 52:48, 70% over 3 steps).

Scheme 2.15 – Formation of 1,2-diol **82** *via* bromohydrin **100** and epoxide **99**.

Formation of bromohydrin **100** proceeded cleanly without any bromination of the pyridyl ring. The reaction proceeded with higher regioselectivity when performed in

MeCN/H_2O rather than in THF/H_2O (with the major regiosomer shown above), but in a slightly lower yield. As the regioselectivity is inconsequential following epoxide formation, THF/H_2O was selected as the solvent system. Ring-closure to epoxide **99** proceeded smoothly upon treatment under basic conditions and this epoxide could then be opened to 1,2-diol **82** under highly acidic conditions.[98] Although some elegance is lost in this 3-step procedure, the sequence can comfortably be completed in 24 h as column chromatography is required just once after formation of epoxide **99**.

Dioxidation of 1,2-diol **82** was investigated next (**Table 2.9**).



82 **48**

Entry	Conditions	Outcome
1[99]	2.5 eq. IBX, DMSO, rt, 2 h	Trace amounts of diketone **48**
2[100]	3 eq. $PhICl_2$, 5 mol% TEMPO, 6 eq. pyridine, $CHCl_3$, 50 °C, 2.5 h	Complex mixture
3[101]	10 eq. DMSO, 3 eq. TFAA, -60 °C, 1 h; then 7 eq. Et_3N, THF, 5 °C, 15 min	55%
4	10 eq. DMSO, 3 eq. TFAA, -60 °C, 1 h; then 7 eq. $^{i}Pr_2NEt$, THF, 5 °C, 15 min	47%
5[102]	2.2 eq. $(COCl)_2$, 4.4 eq. DMSO, -78 °C, 15 min; then 6 eq. Et_3N, CH_2Cl_2, 0 °C, 15 min	53%
6	2.2 eq. $(COCl)_2$, 4.4 eq. DMSO, -78 °C, 15 min; then 6 eq. Et_3N, CH_2Cl_2, -78 °C, 2 min	75%

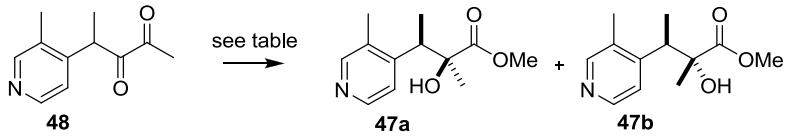
Table 2.9 – Dioxidation of 1,2-diol **82**.

For all of the reactions summarised in **Table 2.9**, aqueous work-up was avoided to maximise the potential yields. IBX was first considered as an oxidant as it has been reported as a mild oxidant for which glycol bond cleavage products are not generally observed[99] although these are not unknown.[103] Unfortunately, the IBX dioxidation of 1,2-diol **82** resulted predominantly in cleavage products and only trace amounts of diketone **48** were observed (entry 1). Radical oxidation using TEMPO resulted in a complex mixture of products possibly due to the potential to form stable benzylic radicals (entry 2).[100] It was then decided to attempt a Swern

oxidation. Activating the DMSO with TFAA afforded the desired diketone in a yield of 47% accompanied by the formation of decomposition products (entry 3).[101] It was hoped that by switching to a more hindered base the amount of decomposition products could be limited, however, this did not materialise and a similar yield was achieved when employing Hünig's base in place of Et_3N (entry 4). Switching the DMSO activator to oxalyl chloride also did not improve the yield of the reaction (entry 5),[102] but the attractiveness of the shorter reaction time led to these conditions being used in optimising the quenching procedure. It was noted that during the above Swern oxidations, the bright yellow colour characteristic of 1,2-diketones was darkening after addition of the base. By shortening the time after addition of the base to 2 min at -78 °C and immediately eluting the solution onto a silica column before the mixture had the opportunity to warm, the yield was increased to 75% and was found to be reproducible on a scale of up to 250 mg (limited by the volume of the reaction mixture due to the rate it could be transferred to the column of silica before decomposition) (entry 6). This dioxidation procedure was selected as the final step in the synthesis of diketone **48**.

2.1.3 BER and the Completion of the Synthesis of Hydroxy-*iso*-Evoninic Acid

With a route to diketone **48** established, promotion of a BER was investigated (**Table 2.10**).



48 **47a** **47b**

Entry	Conditions	*dr* (47a:47b)[a,b]	Yield
1	CuCl	-	0%
2	$Ca(OH)_2$[c]	45:55	64%
3	$ZnCl_2$	36:64	90%
4	0.05M NaOH	57:43	81%
5	0.05M BaO	57:43	80%

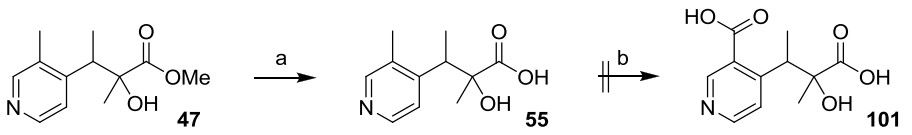
*a. dr calculated by integration of the ^{1}H NMR spectrum of Me esters and the two benzylic signals. b. diastereoisomers were assigned by comparison of NMR spectra with spectra of tolyl esters **57a** and **57b** which were assigned previously. c. 48 h reaction time.*

Reagents and Conditions; (a) 1 eq. BER promoter, MeOH, 40 °C, 16 h.

Table 2.10 – Promotion of a BER of diketone **48**.

A few common BER promoters were investigated. When CuCl was added to a solution of diketone **48** in MeOH, a viscous substance immediately formed, likely due to the pyridyl nitrogen coordinating to the azaphilic copper centre. This resulted in decomposition of diketone **48** (entry 1). $Ca(OH)_2$ and $ZnCl_2$ were both successful in promoting a BER, although the reaction in the presence of $ZnCl_2$ was much faster (64% in 48 h *cf*. 90% in 16 h, entries 2 and 3). Both conditions slightly favoured diastereoisomer **47b**. A BER also occurred under basic conditions and interestingly slightly favoured the opposite diastereoisomer **47a** (entry 5). This selectivity switch will be discussed later. Without knowing which diastereoisomer of hydroxy-*iso*-evoninic acid was required for the synthesis of naturally occurring hydroxy-*iso*-evoninic acid, an investigation into improving the levels of *dr* on this substrate was not pursued, though the switch in selectivity observed was considered to be extremely promising for the eventual development of a stereoselective synthesis.

To complete the synthesis, hydrolysis of methyl ester **47** was required followed by benzylic oxidation, as employed in the synthesis of evoninic acid (**Scheme 2.16**).[21]



Reagents and Conditions; (a) 2M NaOH, MeOH, 65 °C, 1 h (*dr* 45:55, 83%); (b) 4 eq. $KMnO_4$, H_2O, 100 °C, 16 h.

Scheme 2.16 – Ester hydrolysis and attempted benzylic oxidation.

Basic ester hydrolysis afforded acid **55** in a high yield. Due to the poor solubility of acid **55** in organic solvents, salts were removed after neutralisation with 1M HCl, by sonication in MeCN and then passing the resulting suspension through a pad of C18 silica using MeCN as the eluent. Benzylic oxidation of the resulting monoacid **55** was unsuccessful in water[21] due to cleavage of the glycol bond. This cleavage was not observed by Shukla in the synthesis of its regioisomer, hydroxy evoninic acid,[29] possibly due to the quarternary alcohol forming a hydrogen bond to the pyridyl nitrogen to give a stable 6-membered ring (**Figure 2.3**).

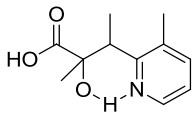
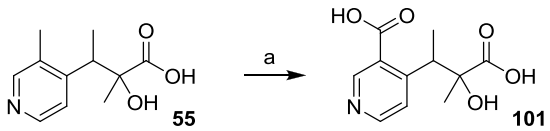


Figure 2.3 – Possible intramolecular hydrogen bonding in the precursor to Shukla's hydroxy evoninic acid.

However, it was found that if the oxidation was performed under basic conditions, as was originally reported by Criegee, no glycol bond cleavage was observed as long as care was taken to remove all salts from mono-acid **55** (**Scheme 2.17**).[104]



Reagents and Conditions; (a) 4.5 eq. $KMnO_4$, 1M NaOH, 100 °C, 1 h (*dr* 45:55, 92%).

Scheme 2.17 – Benzylic oxidation under basic conditions.[104]

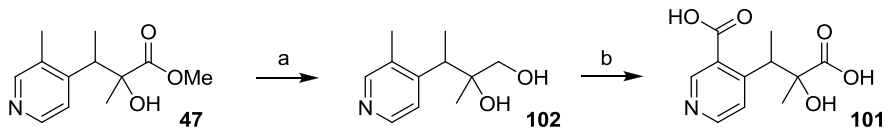
Diacid **101** was found to only be soluble in DMSO or H_2O making removal of salts formed after neutralisation problematic. However, it was found that salts could be removed by passing the aqueous solution of diacid **101** through a ZipTip®. The C18 ZipTip® is prepared with a 5% TFA (aq.) solution and an aqueous solution of diacid

101 is passed through the tip. When eluting with 100% H_2O, diacid **101** sticks to the ZipTip® allowing for the removal of salts. Diacid **101** can then be retrieved from the ZipTip® by washing with 50% MeCN/H_2O. The *dr* remains constant through both the ester hydrolysis and benzylic oxidation steps.

This completed the first synthesis of (±)-hydroxy-*iso*-evoninic acid (**101**). The synthesis developed is a 9-step sequence which requires purification by column chromatography just 4 times and was completed in an overall yield of 25%.

2.1.4 Isolation and Assignment of the Four Possible Stereoisomers

As the stereochemistry of naturally occurring hydroxy-*iso*-evoninic acid is unknown and no spectral data for it is available, a method of separating the four stereoisomers was required. To allow for easier separation by chiral HPLC of the enantiomers, it was decided to attempt to convert the diastereoisomers of ester **47** to a compound for which the diastereoisomers could be separated by flash chromatography. Ester **47** was reduced to 1,2-diol **102** in the hope that the resulting diastereoisomers would separate by flash chromatography (**Scheme 2.18**).

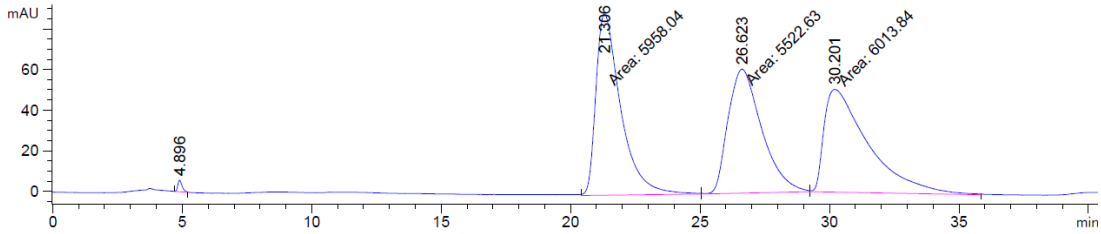


Reagents and Conditions; (a) 4 eq. $LiAlH_4$, THF, rt, 16 h (76%); (b) 6 eq. $KMnO_4$, 1M NaOH, 100 °C, 2 h (64%).

Scheme 2.18 – Reduction of ester **47** to 1,2-diol **102** and oxidation to diacid **101**.

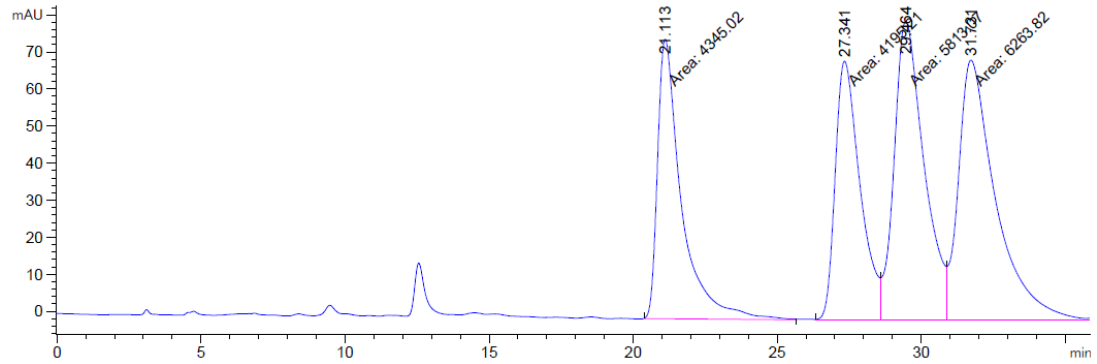
Although the reduction proceeded smoothly with $LiAlH_4$, the resulting diastereoisomers of 1,2-diol **102** appeared as a single spot on the TLC plate. It was shown however, that these could also be oxidised to diacid **101** by treatment with $KMnO_4$ under basic conditions in a yield of 64%.

Separation of the mixture of the four methyl ester stereoisomers by chiral HPLC was then investigated. It was found that the (+)-(*S*,*S*)-ester **47b** could be isolated using a Chiralcel® OD-H column (**Figure 2.4**) and that the (-)-(*S*,*R*)-ester **47a** could be isolated using a Chiralcel® IC column (**Figure 2.5**).



Conditions; Chiralcel ODH; Temp: 8 °C; Flow Rate: 0.75 ml/min; Injection: 7 microlitres; Solvent: hexane/IPA = 90:10; Sample Conc.: 10 mg/mL in IPA/EtOAc, 9:1.
Peak 1 – 21.3 min, (+)-(*S*,*S*)-ester **47b**; ***Peak 2*** – 26.6 min, (*S*,*R*)- and (*R*,*S*)-ester **47a**; ***Peak 3*** – 30.2 min, (-)-(*R*,*R*)-ester **47b**.

Figure 2.4 – HPLC conditions to isolate (+)-(*S*,*S*)-ester **47b**.



Conditions; Chiralcel IC; Temp: 10 °C; Flow Rate: 1.2 ml/min; Injection: 5 microlitres; Solvent: hexane/IPA = 85:15; Sample Conc.: 10 mg/ml in IPA.
Peak 1 – 21.1 min, (-)-(*S*,*R*)-ester **47a**; ***Peak 2*** – 27.3 min, (+)-(*R*,*S*)-ester **47a**; ***Peak 3*** – 29.5 min, (*R**,*R**)-ester **47b**; ***Peak 4*** – 31.7 min, (*R**,*R**)-ester **47b**.

Figure 2.5 – HPLC conditions to isolate (-)-(*S*,*R*)-ester **47a**.

An imbalance of diastereoisomers was injected into the HPLC which allowed each diastereoisomer to be assigned to a peak by comparison of the integration in the HPLC trace and ^{1}H NMR spectra. A semi-preparative OD-H column was available allowing easy isolation of (+)-(*S*,*S*)-ester **47b**, which was found to be highly crystalline after slow evaporation of CH_2Cl_2. A small quantity of (-)-(*S*,*R*)-ester **47a** was isolated from the analytical IC column as a white solid. Enantiomeric purity was confirmed by analytical chiral HPLC of both isolated stereoisomers.

2.1.5 Configurational Assignment of the Stereoisomers

With HPLC methods developed to isolate a single enantiomer of each diastereoisomer of ester **47**, assignment of their stereochemistry was required. Cocrystallisation with single enantiomer chiral carboxylic acids that could hydrogen bond to the pyridyl nitrogen were considered so that the stereochemistry in ester

47 could be determined by a standard x-ray diffraction experiment. A search of the crystal structure database revealed that tartaric acid and malic acid were found to be the most common chiral acids to cocrystallise with pyridyl containing molecules (**Table 2.11**).

Entry	Enantiomer of ester 47	Chiral acid	Description
1	(+)-(2*S*,3*S*)-ester **47b**	(+)-tartaric acid	Flat cubic crystals
2	(+)-(2*S*,3*S*)-ester **47b**	(-)-malic acid	Unsuitable fan-like crystals
3	(-)-(2*S*,3*R*)-ester **47a**	(+)-tartaric acid	Amorphous solid
4	(-)-(2*S*,3*R*)-ester **47a**	(-)-malic acid	Amorphous solid

Conditions; Cocrystallisation performed using the vapour diffusion method in MeOH/hexane.[105]

Table 2.11 – Cocrystallisation attempts with (+)-tartaric acid and (-)-malic acid.

Flattened cubic crystals were isolated when (+)-(2*S*,3*S*)-ester **47b** was cocrystallised with (+)-tartaric acid though the x-ray diffraction pattern was too weak to resolve (entry 1). Cocrystallising with (-)-malic acid afforded a highly crystalline substance, although unfortunately the crystals were fan-like and so unsuitable for x-ray diffraction (entry 2). Attempts at cocrystallising (-)-(2*S*,3*R*)-ester **47a** with these acids only resulted in amorphous solids (entries 3 and 4).

As isolated (+)-(2*S*,3*S*)-ester **47b** was highly crystalline following slow evaporation of CH_2Cl_2, assignment of the stereochemistry was attempted by anomalous dispersion x-ray diffraction, made possible by the high ratio of heteroatoms to carbon atoms.[106] Pleasingly, this was found possible by analysis of the Flack parameters (**Figure 2.6**).[107,108]



Figure 2.6 – Molecular structure of (+)-(2*S*,3*S*)-ester **47b** assigned by a single crystal anomalous dispersion x-ray structure determination.

After successful assignment of the (+)-(2*S*,3*S*)-ester **47b**, efforts focused on obtaining a high quality crystal of (-)-(2*S*,3*R*)-ester **47a**. This was eventually achieved by the vapour diffusion method using CH_2Cl_2/hexane as the solvent system and leaving for a number of days. Needle-like crystals were obtained and pleasingly, were of high enough quality to assign the stereochemistry, again by analysis of the Flack parameters from a single crystal x-ray structure determination experiment (**Figure 2.7**).[107,108]

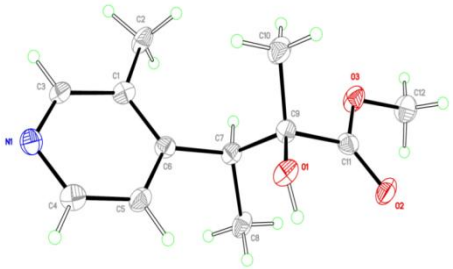
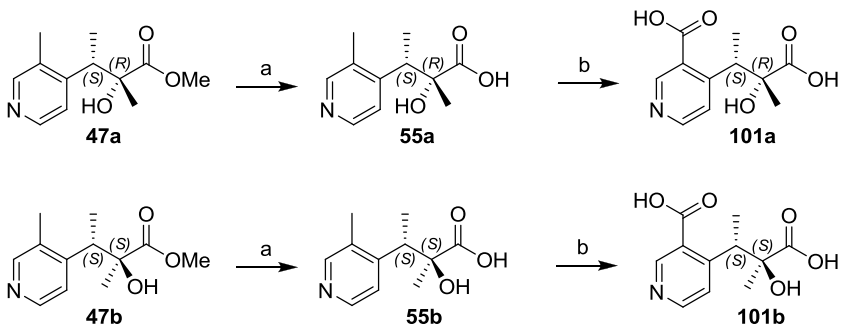


Figure 2.7 - Molecular structure of (-)-(2*S*,3*R*)-ester **47a** assigned by a single crystal anomalous dispersion x-ray structure determination.

To allow for future assignment of the natural configuration of hydroxy-*iso*-evoninic acid, e.g. after hydrolysis of one of the natural products containing the ligand, the final steps of the synthesis were completed with each of the isolated single enantiomers to obtain spectroscopic data and optical rotation values for the two diastereomeric hydroxy-*iso*-evoninic acids **101a** and **101b** (**Scheme 2.19**).



Reagents and Conditions; (a) 2M NaOH, MeOH, 65 °C, 1 h (82%); (b) 4 eq. $KMnO_4$, 1M NaOH, MeOH, 100 °C, 1 h (83%).

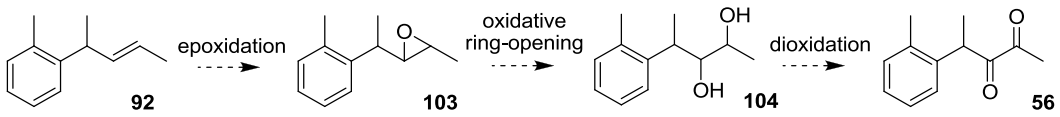
Scheme 2.19 – Synthesis of enantiomerically pure (+)-(2*S*,3*R*)-diacid **101a** and (+)-(2*S*,3*S*)-diacid **101b**.

The final diacid enantiomers (+)-**101a** and (+)-**101b** were purified by reverse phase HPLC to complete the synthesis and optical rotation values of $[\alpha]^{20}_{D}$ +12.8 (*c* = 0.20, H_2O) for (2*S*,3*R*)-**101a** and $[\alpha]^{20}_{D}$ +6.7 (*c* = 0.25, H_2O) for (2*S*,3*S*)-**101b**, were obtained.

2.2 Development of a Diastereoselective BER

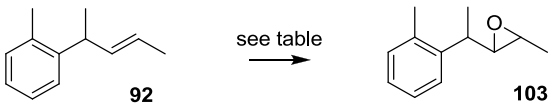
2.2.1 Synthesis of Tolyl Diketone

Following the successful completion of the synthesis of hydroxy-*iso*-evoninic acid from alkene **83**, and the discovery of a high yielding procedure to obtain tolyl alkene **92** (**Table 2.4**, entry 8), it was decided to follow the same strategy for the synthesis of model tolyl diketone **56** as was successfully employed in the synthesis of pyridyl diketone **48** (**Scheme 2.20**).



Scheme 2.20 – Strategy for accessing model diketone **56**.

In the absence of the pyridyl nitrogen, potential problems with *N*-oxide formation during epoxidation of alkene **92**, as previously encountered, were no longer a concern. Hence, there was no need to form the bromohydrin, and direct epoxidation of alkene **92** was attempted (**Table 2.12**).

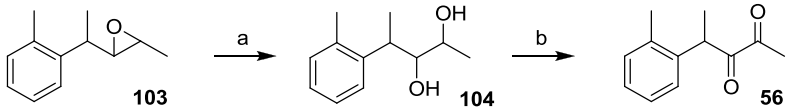


Entry	Conditions	Yield	*dr*
1	1.2 eq. *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2 h	26%	66:34
2[109]	4 x 10^{-4} M Na_2.EDTA, 11 eq. CF_3COCH_3, 7.7 eq. $NaHCO_3$, 5 eq. Oxone®, MeCN, 2 h, 0 °C	76%	43:57

Table 2.12 – Epoxidation of alkene **92**.

Epoxidation with *m*-CPBA was low yielding (entry 1). Generation of a reactive dioxirane generated *in situ* under neutral conditions wherein a pH 7-7.5 was maintained by the presence of $NaHCO_3$, afforded epoxide **103** in an improved yield of 76% (entry 2). A switch in the major diastereoisomer was observed under each

set of conditions. It is likely that one diastereoisomer decomposes faster in the reaction with *m*-CPBA and hence a lower yield is obtained. Ring-opening, again under the same conditions as used previously for the pyridyl series (see **Scheme 2.15**), afforded 1,2-diol **104** which could be oxidised using IBX in DMSO to afford diketone **56** (**Scheme 2.21**).



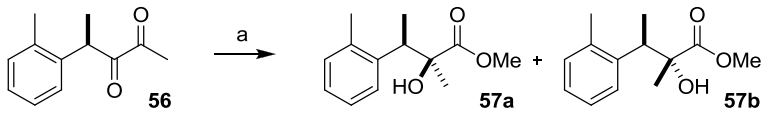
Reagents and Conditions; (a) 10% $HClO_4$ (aq.), MeCN, 0 °C to rt, 19 h (82%); (b) 2.5 eq. IBX, DMSO, rt, 19 h (80%).

Scheme 2.21 – Final steps in the synthesis of model diketone **56**.

IBX, which is a cheaper alternative (and precurosor) to the Dess-Martin periodinane, was prepared from 2-iodobenzoic acid and found to oxidise 1,2-diol **104** to 1,2-diketone **56** which was again isolated as a bright yellow liquid.[99] The reaction was performed in DMSO due to the poor solubility of IBX in other common organic solvents, though it was easily removed by repeated aqueous washings followed by FC.

2.2.2 Development of a Diastereoselective BER

With an expedient route to diketone **56** developed, the promotion of a BER with $Cu(OAc)_2$, as used with model phenyl diketone **52**, was attempted (**Scheme 2.22**).



Reagents and Conditions; (a) 1 eq. $Cu(OAc)_2$, MeOH, 40 °C, 5 days (91% conversion).

Scheme 2.22 –BER of diketone **56** with $Cu(OAc)_2$.

Unlike with phenyl diketone **52**, a BER did not occur at room temperature. This is likely due to the *ortho*-methyl group causing greater steric hindrance in the transition state and so increasing the activation energy. Warming the reaction to 40 °C resulted in a BER albeit the reaction was very slow with the reaction requiring 5 days to reach 91% conversion. No diastereoselectivity was observed in the reaction

though it was found that the *dr* could be conveniently measured by integration of the proton signals highlighted in the figure below (**Figure 2.8**).

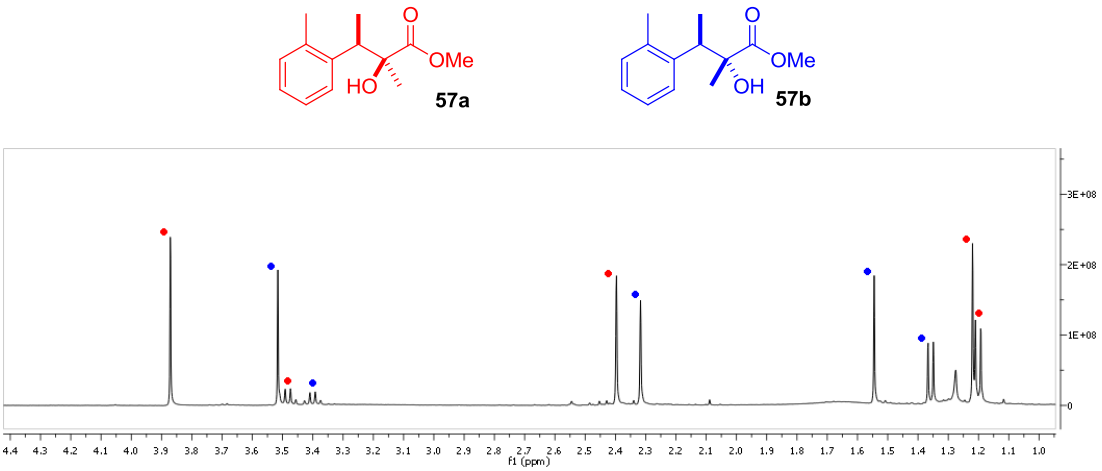
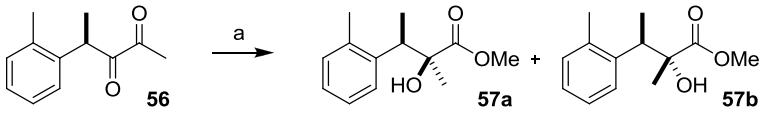


Figure 2.8 – ^{1}H NMR spectrum of a crude reaction mixture and the peaks integrated to measure the *dr* in the BER studies.

A range of Cu(II) Lewis acids were then screened to investigate their influence on the *dr* of a BER (**Table 2.13**).



Entry	Lewis acid	Conversion to ester 57	*dr* (57a:57b)
1[a]	$Cu(OAc)_2$	91%	50:50
2	$Cu(OTf)_2$	9%	50:50
3	CuF_2	100%	47:53
4	$CuCl_2$	23%	45:55
5	$CuBr_2$	30%	44:56
6	$CuSO_4{\cdot}5H_2O$	9%	50:50
7	CuO	39%	55:45

a. Reaction left for 5 days.

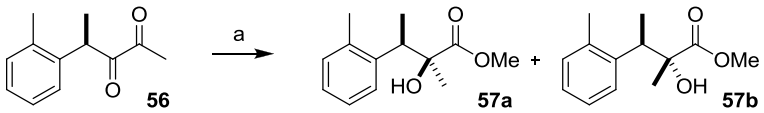
Reagents and Conditions; (a) 1 eq. diketone **56**, 1 eq. Lewis acid, MeOH, 40 °C, 72 h.

Table 2.13 – BER's of diketone **56** with Cu(II) Lewis acids.

Replacing the counter-ion acetate (entry 1) with triflate (entry 2) resulted in a much slower reaction possibly due to a more electron deficient copper centre destabilising the build up of positive charge in the transition state. Cu(II) halides also promoted a BER (entries 3-5). The halide counter-ion had little effect on the *dr*

though the rate was significantly faster with a fluoride counter-ion (entry 3). As we have seen that EWG groups decrease the reaction rate, it is possible that this increase in rate is due to the smaller size of fluoride anion creating less steric hindrance in the transition state. $CuBr_2$ did promote a faster reaction than $CuCl_2$ as was expected (entries 4 and 5). $CuSO_4{\cdot}5H_2O$ gave poor conversion and a 1:1 *dr* (entry 6). Interestingly, CuO favoured the opposite diastereoisomer (entry 7), a likely reason for which will be discussed later.

As a more electron deficient copper centre has been found to decrease the rate of reaction, Cu(I) promoters were also investigated (**Table 2.14**).



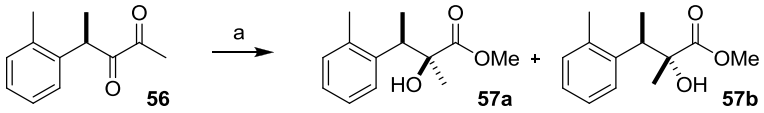
Entry	Lewis acid	Conversion to ester 57	*dr* (57a:57b)
1	CuCl	91%	45:55
2	CuBr	100%	47:53
3	CuI	4%	50:50
4	CuCN	12%	48:52
5	$CuBF_4$	50%	46:54
6	$CuBr{\cdot}SMe_2$	100%	50:50
7	$CuBr{\cdot}PPh_3$	0%	-
8	Cu_2O	100%	53:47

Reagents and Conditions; (a) 1 eq. diketone **56**, 1 eq. Lewis acid, MeOH, 40 °C, 72 h.

Table 2.14 – BER's of diketone **56** with Cu(I) Lewis acids.

In general, Cu(I) complexes gave an improved rate of reaction, although, little variation in diastereoselectivity was observed with different halide counter-ions (entries 1-3). The rate was significantly lower when promoted by CuI, fitting with the hypothesis that the size of the counter-ion can hinder the rate of the reaction (entry 3). CuCN and $CuBF_4$ promoted BER's but without greatly effecting the *dr* (entries 4 and 5). Having dimethyl sulfide coordinated to the copper complex had little effect on the reaction (entry 6) though triphenylphosphine completely prevented the reaction (entry 7). Again, the metal oxide Cu_2O promoted a switch in the favoured diastereoisomer relative to the other Cu(I) salts (entry 8).

Zn(II) complexes were investigated next (**Table 2.15**).



Entry	Lewis acid	Conversion to ester 57	*dr* (57a:57b)
1	$ZnCl_2$	9%	25:75
2[a]	$ZnCl_2$	100%[b]	38:62
3	$ZnBr_2$	22%	34:66
4	ZnI_2	24%	30:70
5	$Zn(OTf)_2$	0%	-
6	$Zn(CN)_2$	0%	-
7	ZnO	10%	54:46

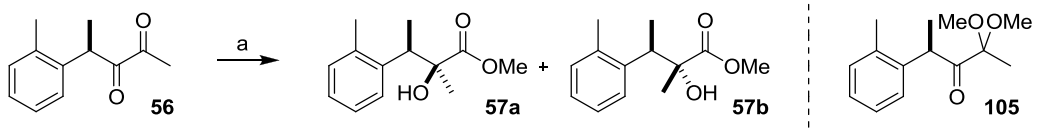
a. Reaction heated at 60 °C. b. Conversion after 48 h.

Reagents and Conditions; (a) 1 eq. diketone **56**, 1 eq. Lewis acid, MeOH, 40 °C, 72 h.

Table 2.15 – BER's of diketone **56** with Zn(II) Lewis acids.

In general, BER's promoted by Zn(II) complexes were considerably slower than observed previously with Cu(I) and Cu(II) complexes. Promoting a BER with $ZnCl_2$ resulted in a much improved *dr* of 25:75 though the reaction rate was extremely slow (entry 1). By heating the reaction to a higher temperature the rate was increased so that after 48 h the reaction had gone to completion (entry 2). Unfortunately, this improved rate resulted in a reduction in the *dr* to 38:62. Changing the halide to iodide or bromide resulted in a drop in *dr* (entries 3 and 4). Triflate and cyanide complexes failed to promote BER's (entries 5 and 6). Yet again, the metal oxide, ZnO, favoured the opposite diastereoisomer though the conversion was a considerably lower than previously observed (entry 7).

A variety of other metal chlorides were also investigated (**Table 2.16**).



56 **57a** **57b** **105**

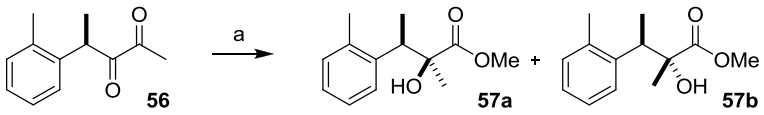
Entry	Metal halide	Conversion to ester **57**	*dr* (**57a:57b**)
1	AgCl	<1%	50:50
2-12	$RuCl_3$, $TiCl_4$, $PdCl_2$, $SnCl_4$, $IrCl_3$, $CeCl_3$, $LaCl_3$, $AlCl_3$, BCl_3, $ZrCl_4$, $HfCl_4$	0% to ester **57**, conversion to acetal **105**	-
13-15	$NiBr_2$, $InCl_3$, $BaCl_2$	0%	-
16	$FeCl_3$	3% (40% conv. to acetal **105**)	31:69

Reagents and Conditions; (a) 1 eq. metal halide, MeOH, 40 °C, 72 h.

Table 2.16 – BER's of diketone **56** with other metal halides.

In the presence of AgCl, only a very small amount of diketone **56** was converted to ester **57** with no influence on the *dr* (entry 1). Lewis acids that are known to be highly oxophilic only resulted in the formation of acetal **105** from addition of MeOH to the least hindered ketone with no BER products detected (entries 2-12).[110] $NiBr_2$, $InCl_3$ and $BaCl_2$ all failed to promote a BER (entries 13-15). $FeCl_3$ was the only Lewis acid to produce a mixture of ester **57** and acetal **105** (entry 16).

The interesting switch in the favoured diastereoisomer when the BER was promoted by a metal oxide was investigated and is summarised in the table below (**Table 2.17**).



56 57a 57b

Entry	BER promoter	Conversion to ester 57	*dr* (57a:57b)
1	CuO	40%[a]	55:45
2	Cu_2O	100% [a]	54:56
3	ZnO	10% [a]	53:47
4	BaO	100% [b]	62:38
5	NaOH	100% [b]	60:40
6	NaH	100% [b]	56:44

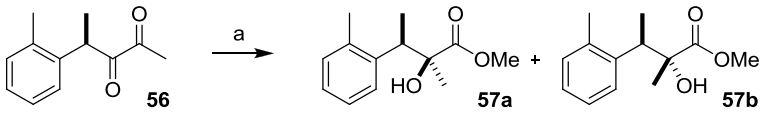
a. Conversion after 72 h. b. Conversion after 18 h.

Reagents and Conditions; (a) 1 eq. Lewis acid, MeOH, 40 °C.

Table 2.17 – BER conditions favouring ester **57a**.

Of the metal oxides investigated (entries 1-4), BaO gave the highest diastereoselectivity (entry 4). It was noted that BaO is the most basic of the metal oxides screened due to its highly ionic character,[111] and so bases NaOH and NaH were also assayed. Both gave comparable diastereoselectivities to that observed with BaO (entries 5 and 6) supporting the hypothesis that it is the basicity of the metal oxides that is responsible for the switch in diastereoselectivity relative to other metal salts/Lewis acids.

Concentration studies were performed and it was found that although the rate increased with concentration in the presence of Lewis acids to an extent, the diastereoselectivity was not affected (**Table 2.18**).



56 57a 57b

Entry	Equivalents of CuCl	Conversion to ester 57	*dr* (57a:57b)
1	2	67%	43:57
2	4	79%	43:57
3	8	63%	43:57
4	16	49%[a]	43:57

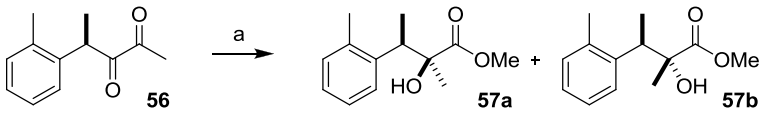
*a. 2% conversion to acetal **105**.*

Reagents and Conditions; (a) CuCl, MeOH, 40 °C, 72 h.

Table 2.18 – Effect on rate and *dr* with the concentration of Lewis acid present.

An optimum rate was reached when 4 equivalents of CuCl were used (entry 2). Increasing the concentration of CuCl further than this resulted in a decreased rate of reaction (entries 3 and 4). This could be due to the hemiacetal intermediate formed prior to 1,2-migration, spending more time coordinated to multiple copper centres thereby restricting the lone pairs of electrons on the sp^3 hybridised oxygen atoms from assisting the migration. The concentration of Lewis acid BER promoter having no effect on the *dr* is contrary to what was observed in Burke's study.[54]

In the presence of metal oxides or bases, there was a large increase in the diastereoselectivity with concentration (**Table 2.19**).



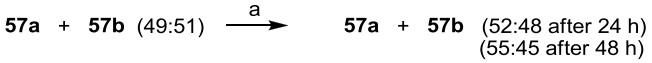
Entry	Concentration of NaOH in MeOH	*dr* (57a:57b)
1	0.05 M	60:40
2	0.10 M	63:37
3	0.21 M	68:32
4	0.42 M	84:16
5[a]	0.42 M	55:45

a. Reaction performed at 20 °C for 22 h.

Reagents and Conditions; (a) NaOH, MeOH, 40 °C, 18 h.

Table 2.19 – Effect of concentration on base promoted BER's.

Increasing the molarity to 0.42M improved the diastereoselectivity to 84:16 although a number of decomposition products were observed for the first time in these BER's (entry 4). In the attempt to reduce the amount of decomposition products, the temperature was reduced to 20 °C (entry 5). However, this resulted in a much lower *dr* of 55:45. Although, as previously discussed, BER's are generally considered not to be reversible, it was thought that an equilibrium could explain the drop in selectivity with temperature. To test this theory, a known ratio of esters **57a** and **57b** were treated to base promoted BER conditions to look for a change in selectivity (**Scheme 2.23**).

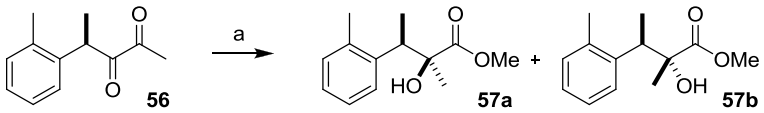


Reagents and Conditions; (a) 0.42M NaOH in MeOH, 40 °C.

Scheme 2.23 – Test to investigate the possibility of a reversible 1,2-migration in the base promoted BER of diketone **56**.

Although a small change in *dr* was observed over time, it was not comparable to that observed in the BER of diketone **56** with 0.42M NaOH in MeOH (see **Table 2.19**, entry 4). It appears that this change in diastereoselectivity arises from the faster degradation of diastereoisomer **57b** over **57a** and that 1,2-migration is irreversible.

The use of co-solvents was also investigated, firstly in the presence of a Lewis acid; $CuCl_2$ was selected as the Lewis acid due to the slow rate of reaction and modest *dr* observed in MeOH (**Table 2.20**).

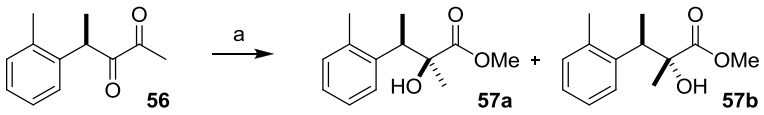


Entry	Solvent	Outcome
1	CH_2Cl_2/MeOH (1:1)	Majority converted to a mixture of unidentified products but no ester **57** detected
2	THF/MeOH (1:1)	Recovered the majority of diketone **56**
3	toluene/MeOH (1:1)	Recovered the majority of diketone **56**

Reagents and Conditions; (a) 1 eq. diketone **56**, 1 eq. $CuCl_2$, solvent, 40 °C, 72 h.

Table 2.20 – The effect of co-solvents on the BER of diketone **56** promoted by $CuCl_2$.

No ester **57** was detected in any of the reactions containing co-solvents (entries 1-3), only decomposition products were observed in a CH_2Cl_2/MeOH mixture (entry 1). These solvent mixtures were also investigated for use with the NaOH promoted BER (**Table 2.21**).



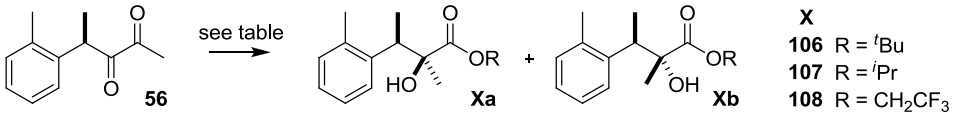
Entry	Solvent System	Outcome
1	CH_2Cl_2/MeOH (1:1)	Mixture of unidentified products
2	THF/MeOH (1:1)	Mixture of unidentified products
3	toluene/MeOH (1:1)	Mixture of unidentified products

Reagents and Conditions; (a) 0.05M NaOH in MeOH, 40 °C, 16 h.

Table 2.21 - The effect of co-solvents on the BER of diketone **56** promoted by NaOH.

Again, no desired ester **57** was observed using co-solvents (entries 1-3) so no further efforts were made in this direction.

Changing the alcohol/solvent was also explored (**Table 2.22**).



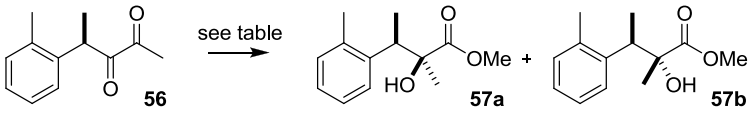
Entry	Conditions	Outcome	*dr* (a:b)
1	0.42M ^{t}BuOK in ^{t}BuOH, rt, 22 h	^{t}Bu ester **105** : diketone **56** 74:26	61:39
2	0.42M KOH in ^{i}PrOH, rt, 22 h	Mixture of unidentified products	-
3	1 eq. $CuCl_2$, CF_3CH_2OH, 40 °C, 18 h	Recovered diketone **56**	-
4	1 eq. $CuCl_2$, ^{t}BuOH, 40 °C, 18 h	Recovered diketone **56**	-

Table 2.22 – Changing the solvent/nucleophile.

With a bulkier alcohol under basic conditions at room temperature, greater diastereoselectivity was achieved than was previously observed with MeOH at the same molarity (entry 1 *cf.* **Table 2.19**, entry 5). This could be explained by an increase in the energy of the transition states due to greater steric strain and hence greater selectivity is observed as well as lower conversion. Using ^{i}PrOH as the solvent resulted in a complex mixture with complete consumption of diketone **56** and with no ester **107** observed (entry 2). To look at solvent effects in the presence of Lewis acids, $CuCl_2$ was selected due to the moderate rates of reaction it gives and

observable diastereoselectivity. Unfortunately, it would not promote a BER with the more electron deficient alcohol solvent CF_3CH_2OH (entry 3) or the sterically hindered alcohol solvent ^tBuOH (entry 4).

The table below summarises the optimal procedures found for promoting a diastereoselective BER of diketone **56** (**Table 2.23**).

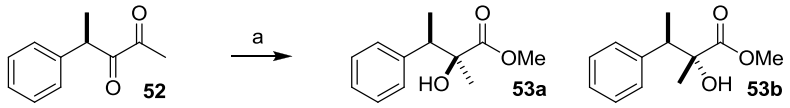


56 **57a** **57b**

Entry	Conditions	*dr* (57a:57b*)*
1	0.42M NaOH in MeOH, 40 °C, 18 h	84:16
2	1 eq. $ZnCl_2$, MeOH, 40 °C, 72 h	25:75
3	1 eq. $ZnCl_2$, MeOH, 60 °C, 72 h	38:62

Table 2.23 – Optimal conditions for promoting diastereoselective BER's of diketone **56**.

Although synthetically useful *dr*'s were obtained which favour either diastereoisomer of ester **57**, the extremely slow reaction time of the BER promoted by Lewis acids limits their usefulness (entry 2) and warming the reaction causes a significant reduction in the *dr* (entry 3). It would have been expected that the BER of pyridyl diketone **48** would be slower than tolyl diketone **56** when promoted by Lewis acids, due to the unfavourable build-up of positive charge *para*- to the pyridyl nitrogen in the transition state of the 1,2-migration. However, this was not the case with the $ZnCl_2$ promoted BER of pyridyl diketone **48** which went to completion in 16 h compared with the tolyl diketone **56** undergoing only 9% conversion after 72 h. It was considered that the basicity of the pyridyl lone pair may be increasing the rate of reaction, possibly by ligating to the metal centre. To test this hypothesis, the effects of adding pyridine and 2,6-lutidine into the BER were investigated (**Table 2.24**).



Entry	Lewis acid	Additive	Conversion	*dr* (53a:53b)	Colour
1	$CuCl_2$	-	16%	47:53	Yellow
2	$CuCl_2$	pyridine	47%	47:53	Deep green/blue
3	$CuCl_2$	2,6-lutidine	100%	47:53	Lilac
4	$ZnCl_2$	-	5%	47:53	Bright yellow (no change)
5	$ZnCl_2$	pyridine	13%	47:53	Bright yellow (no change)
6	$ZnCl_2$	2,6-lutidine	15%	42:58	Bright yellow (no change)
7	$Ca(OH)_2$	-	52%	43:57	Dark yellow
8	$Ca(OH)_2$	pyridine	75%	46:54	Dark yellow
9	$Ca(OH)_2$	2,6-lutidine	70%	42:58	Dark yellow

Reagents and Conditions; (a) 1 eq. Lewis acid, 2 eq. additive, rt, 30 h.

Table 2.24 – The effects of pyridine and 2,6-lutidine on the BER of phenyl diketone **52**.

The most dramatic rate effect was observed with $CuCl_2$ though the additives did not affect the *dr* (entries 1-3). A dramatic increase in conversion from 16% to 100% in the presence of 2,6-lutidine was observed over the 30 h reaction duration (entry 3). Interestingly, the colour of the reaction mixtures with $CuCl_2$ and the additives varied greatly suggesting that pyridyl copper complexes are formed, which is an interesting observation when considering an asymmetric BER. It is possible that the pyridyl nitrogen coordinated to the copper is decreasing the electropositivity of the copper centre and hence decreasing the destabilisation of the build-up of positive charge in the rearrangement transition state.

No colour differences were observed when using additives with $ZnCl_2$ and a less dramatic increase in rate was observed (entries 4-6). A slight change in *dr* was observed in the presence of 2,6-lutidine (entry 6). Again, there was an increase in rate in the presence of the additives in combination with $Ca(OH)_2$ and no distinctive

colour differences between the three reactions were observed (entries 7-9). Slight variations in the *dr* were found in these reactions promoted by $Ca(OH)_2$. A possible explanation for the increase in rate with $ZnCl_2$ and $Ca(OH)_2$ is shown in the figure below (**Figure 2.9**).

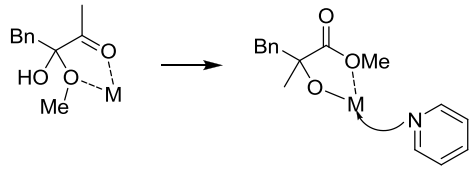
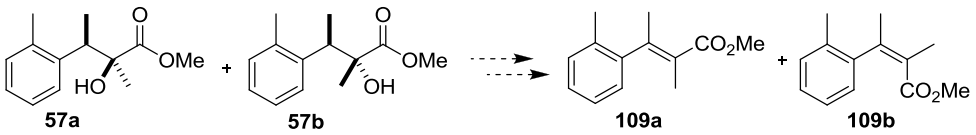


Figure 2.9 – Possible rational for the increase in rate with pyridyl additives in the BER promoted by $ZnCl_2$ and $Ca(OH)_2$.

It is conceivable that the pyridyl nitrogen helps to free the metal centre from the tertiary hydroxy group after assisting the 1,2-migration, freeing the metal centre to promote further BER reactions.

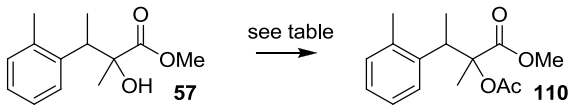
2.2.3 Stereochemical Assignment of the Diastereoisomers from the Model BER's

Burke *et al.* assigned the diastereoisomers of the resulting ester obtained from a BER of his diketone substrate (see **Scheme 1.5**) by performing a stereospecific E2-elimination to give stereodefined alkenes.[112] It was hoped that the same tactic could be employed for ester **57** if the elimination was performed on an imbalance of diastereoisomers (**Scheme 2.24**).



Scheme 2.24 – Proposed E2-elimination of a derivative of esters **57a** and **57b**.

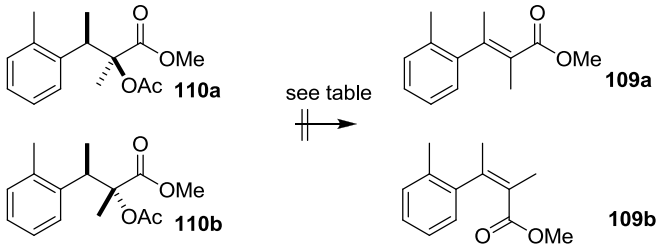
This first required the conversion of the α-hydroxy group into a leaving group. A high yield was required for this transformation to ensure that the major diastereoisomer of ester **57** remained the major diastereoisomer after conversion to the leaving group. As Burke converted his α-hydroxyl group to an acetate, this was attempted first (**Table 2.25**).



Entry	Conditions	Outcome
1	2.2 eq. Ac_2O, 1.1 eq. pyridine, 0.1 eq. 4-DMAP, Et_2O, 45 °C, 5 h	Recovered ester **57**
2	Ac_2O, 12% H_2SO_4, 45 °C, 19 h	65% yield of acetate **110**

Table 2.25 – Conversion of the hindered α-hydroxyl group to acetate **110**.

Using standard acetylation conditions as used previously by Burke, no reaction was observed (entry 1). Heating the reaction offered no improvement and it is likely that sterics are preventing the acetylation. However, by warming under acidic conditions with acetic anhydride as the solvent, acetate **110** was obtained in a yield of 65%, but with complete retention of *dr* (entry 2). E2-elimination of acetate **110** was then explored (**Table 2.26**).

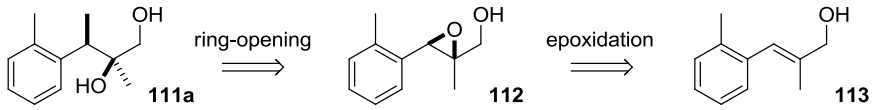


Entry	Conditions	Outcome
1	5 eq. Ac_2O, AcOH, 16 h	Recovered acetate **110**
2	5 eq. NaH, THF, 60 °C, 16 h	Mixture of undesired products
3	DBN (neat), 100 °C, 16 h	Mixture of undesired products

Table 2.26 – Attempted E2-elimination to assign the diastereoisomers of ester **57**.

No trace of unsaturated esters **109a** and **109b** could be detected following treatment with base, due to either decomposition or recovery of starting ester **110** (entries 1-3). Attempts at converting the α-hydroxy group to a mesyl or tosyl derivative were unsuccessful. An alternate assignment method was therefore required.

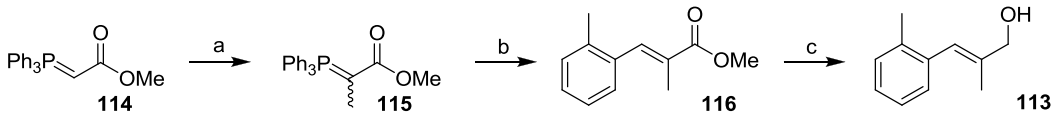
It was decided to assign the diastereoisomers by performing a diastereoselective synthesis of diol **111a** (**Scheme 2.25**).



Scheme 2.25 – Strategy for assigning the diastereoisomers of ester **57** by a diastereoselective synthesis.

The synthesis of (*E*)-allylic alcohol **113** has previously been reported,[113] so it was planned to epoxidise and then stereospecifically open the epoxide with retention of configuration at the benzylic position.[33] This would afford 1,2-diol **111a** which could either be oxidised to methyl ester **57a** or a known ratio of esters **57a** and **57b** could be reduced to give this compound. Assignment of the diastereoisomers could then be made by comparison of ^{1}H NMR data for the authentic diol **111a** with the unequal mixture of diols obtained from the reduction.

The 3-step procedure reported by Stratakis was followed to synthesise (*E*)-allylic alcohol **113** (**Scheme 2.26**).[113]

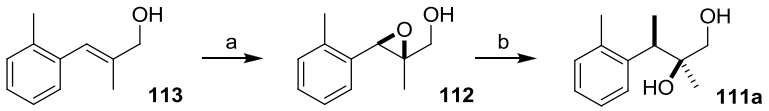


Reagents and Conditions; (a) 1.5 eq. MeI, CH_2Cl_2, 0 °C to rt, 18 h (*rotamers* 1:1, 75%); (b) 1.2 eq. *o*-tolylaldehyde, CH_2Cl_2, rt, 17 h (49%); (c) 2.6 eq. $LiAlH_4$, 0.2 eq. $AlCl_3$, Et_2O, 0 °C to rt, 2 h (82%).

Scheme 2.26 – Synthesis of (*E*)-allylic alcohol **113**.[113]

As ylide **114** is commercially available and inexpensive, methylation of it was used to form ylide **115** rather than treatment of the required α-halo ester with triphenylphosphine. This reaction was relatively high yielding and afforded a 1:1 ratio of rotamers of ylide **115**, as was observed previously. A Wittig reaction of the stabilised ylide **115** with *ortho*-tolylaldehyde afforded (*E*)-unsaturated ester **116** exclusively which was then reduced to (*E*)-allylic alcohol **113** (assigned previously by Stratakis).[114]

Epoxidation of (*E*)-allylic alcohol **113** followed by ring-opening was then performed (**Scheme 2.27**).



Reagents and Conditions; (a) 10 mol% $VO(acac)_2$, 1.2 eq. TBHP, toluene, 40 °C, 16 h (76%); (b) 3 eq. Me_3Al, hexane, -78 to 0 °C, 4 h (76%).

Scheme 2.27 - Synthesis of 1,2-diol **111a** as a single diastereoisomer.

Epoxidation successfully yielded epoxide **112** after *syn*-addition of the peroxide, with the distinctive colour change to orange/red then back to dark green being observed. Epoxide **112** was ring-opened with Me_3Al to afford 1,2-diol **111a** as a single diastereoisomer as was expected from the transition state proposed by Roberts (**Figure 2.10**).[33]

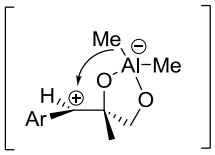
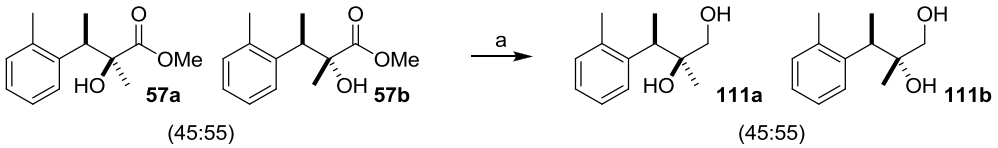


Figure 2.10 – Transition state explaining the retention of stereochemistry at the benzylic position after epoxide ring-opening with Me_3Al.[33]

By consideration of available material, it was then decided to reduce a known ratio of esters **57a** and **57b** to a mixture of primary alcohols **111a** and **111b** (**Scheme 2.28**).



Reagents and Conditions; (a) 2.2 eq. $LiAlH_4$, THF, 0 °C to rt, 2 h (100%).

Scheme 2.28 – Reduction of a known ratio of esters **57a** and **57b** to 1,2-diols **111a** and **111b** to allow diastereoisomer assignment.

As the reduction was quantitative, a mixture containing ester **57b** as the major diastereoisomer was reduced with $LiAlH_4$ to a mixture containing diol **111b** as the major diastereoisomer. Overlaying the proton and carbon NMR spectra allowed for unambiguous assignment of the diastereoisomers: the major diastereoisomer

formed by Lewis acidic BER's was the (2*R**,3*R**) diastereoisomer, whereas the major diastereoisomer formed under basic conditions is the (2*R**,3*S**) diastereoisomer.

2.2.4 ^{13}C-Labelling Studies

On the basis of migratory aptitude, the benzylic group is expected to have migrated during these rearrangements rather than the methyl group. Although the same product is observed whichever group migrates, in order to investigate the role of Lewis acidic and basic promoters, and when contemplating the design of an asymmetric BER, it was considered important to know which group migrated.[40] To confirm the hypothesis that the benzylic group is migrating, ^{13}C-labelling studies were performed. By mapping the carbon atoms during a BER in which the methyl and benzyl groups could migrate, the required position of a ^{13}C-label to determine the migratory group could be determined (**Figure 2.11**).

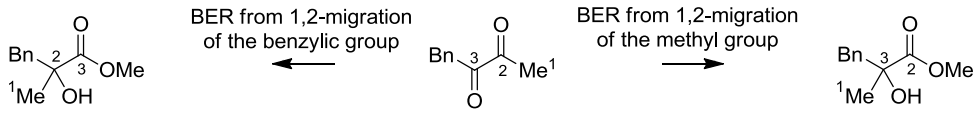
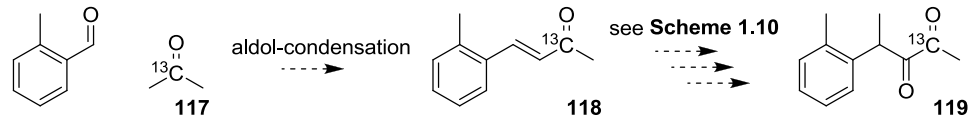


Figure 2.11 – Mapping of carbon atoms after 1,2-migration of the benzylic or methyl groups in the BER.

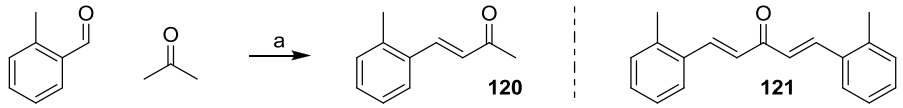
It is clear that a ^{13}C-label at C-2 or C-3 should suffice to confirm which group is migrating. The location of the label was expected to be easily be determined by ^{13}C NMR spectrometry due to the large difference in chemical shifts of an alkyl or carbonyl carbon in the spectrum. It was found that a potential source of a ^{13}C-label was from acetone which is available as mono-labelled 2-^{13}C or di-labelled 1,3-^{13}C. To simplify the analysis, it was decided to proceed with mono-labelled 2-^{13}C acetone in order to install a ^{13}C-label at C-2 in the 1,2-diketone.

It was hoped that an aldol reaction of ^{13}C-labelled acetone **117** with *o*-methylbenzaldehyde would afford labelled enone **118** which could in turn be taken through to labelled tolyl diketone **119** according to the chemistry used in the synthesis of model phenyl diketone **52** (see **Scheme 1.10**) (**Scheme 2.29**).



Scheme 2.29 – Strategy for installing a ^{13}C-label at C-2 to afford ^{13}C-labelled diketone **119**.

Due to the high cost of ^{13}C-labelled acetone **117**, the synthesis was first attempted using unlabelled acetone. Known conditions to perform an aldol-condensation between acetone and *o*-methylbenzaldehyde were attempted (**Scheme 2.30**).[115]

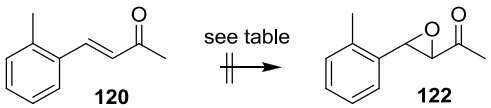


Reagents and Conditions; (a) 1.3 eq. acetone, 0.37M NaOH (aq.), EtOH, 0 °C, 4 h (75%).

Scheme 2.30 – Aldol-condensation of acetone with *o*-methylbenzaldehyde to afford enone **120**.[115]

No aldol product was observed in the reaction though the yield of enone **120** was compromised by the formation of dba derivative **121** which could be removed by performing multiple FCs. The similarity in R_f values, presumably as the result of π-interactions, made this separation particularly difficult.

With enone **120** in hand, epoxidation was explored (**Table 2.27**).

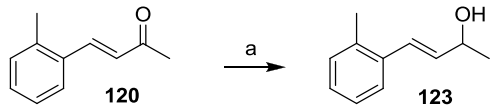


Entry	Conditions	Outcome
1[31]	35% H_2O_2, 2M NaOH, MeOH, rt, 16 h	Recovered enone **120**
2	35% H_2O_2, 2M NaOH, MeOH, 50 °C, 16 h	Recovered enone **120**
3[116]	TBHP, DBU, DCM, 0 °C to rt. 18 h	Recovered enone **120**
4[117]	Et_2Zn, O_2, toluene, 16 h	Recovered enone **120**

Table 2.27 – Attempted epoxidation of enone **120**.

No epoxidation was observed when repeating the conditions successfully applied by Sheng on the phenyl system (entry 1) and moreover heating the solution also did not allow the reaction to proceed (entry 2).[31] A procedure using a mixture of TBHP and DBU, which was apparently developed for unreactive α,β-unsaturated lactones

where epoxidation is often very slow when using hydrogen peroxide, was attempted next. However, again, no reaction was observed (entry 3).[116] It was considered that the extreme unreactivity of enone **120** might be due to strong intermolecular π-interactions caused by restricted rotation brought about by the tolyl methyl group (*cf.* the phenyl analogue). It was therefore decided to make one final attempt using a procedure performed in toluene in an attempt to break up such π-interactions. However, epoxidation using the autoxidation product of diethylzinc in toluene was also unsuccessful (entry 4).[117] Concluding that we would need to reduce the conjugation in the system to allow epoxidation, enone **120** was reduced to allylic alcohol **123** using a Luche reduction (**Scheme 2.31**).[118]

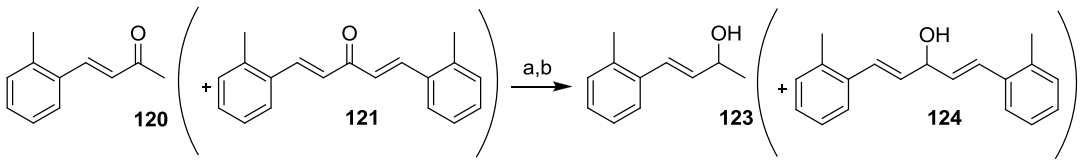


Reagents and Conditions; (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH (61%).

Scheme 2.31 – Luche reduction of enone **120**.[118]

The required reduction was successful in the presence of $CeCl_3 \cdot 7H_2O$, giving allylic alcohol **123** in 61% yield. Interestingly, in the absence of this Lewis acid the corresponding allylic methyl ether was obtained in 69% yield, rather than the desired allylic alcohol **123**.

To avoid the laborious purification of enone **120** when bringing material through the sequence, it was decided to perform the Luche reduction on a mixture of enone **120** and dba derivative **121** formed during the aldol-condensation (see **Scheme 2.30**) (**Scheme 2.32**).

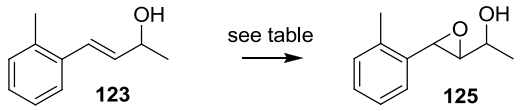


Reagents and Conditions; (a) 1.3 eq. acetone, 0.37M NaOH (aq.), EtOH, 0 °C, 4 h; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH (64% over 2 steps).

Scheme 2.32 – Luche reduction to ease the removal of the dba derivative **121** formed in the aldol-condensation.

The Luche reduction was successful and as anticipated, made separation of diallylic alcohol **124** from desired allylic alcohol **123** by FC much easier. It was therefore decided use this device to avoid laborious purification after the aldol-condensation when repeating the synthesis using ^{13}C-labelled material.

Efficient conditions for epoxidation of allylic alcohol **123** to give epoxy alcohol **125** were then explored (**Table 2.28**).

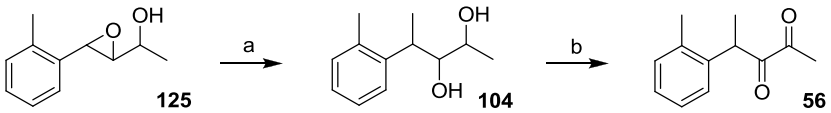


Entry	Conditions	Outcome (*dr*)
1	*m*-CPBA, CH_2Cl_2, rt, 16 h	70% (60:40)
2[119]	$VO(acac)_2$, TBHP, toluene, 40 °C, 18 h	85% (62:38)

Table 2.28 – Electrophilic epoxidation of allylic alcohol **125**.

Although *m*-CPBA afforded desired epoxy alcohol **125** in good yield (entry 1), it was found that using TBHP with $VO(acac)_2$ gave a more consistent and also improved yield of 85% (entry 2).[119] Under both sets of conditions, a similar *dr* was observed. By analogy with similar reactions in the literature, the major diastereoisomer from this epoxidation was tentatively assigned as being the *erythro* isomer.[120,121]

Ring-opening followed by oxidation completed the synthesis of required 1,2-diketone **56** in a reaction sequence suitable for ^{13}C-label introduction (**Scheme 2.33**).

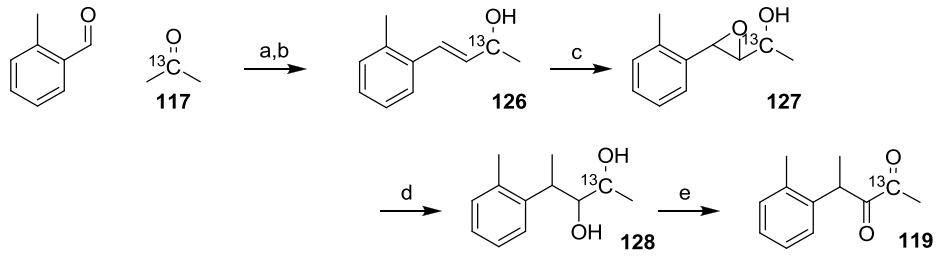


Reagents and Conditions; (a) Me_3Al, hexane, -78 to 0 °C (*dr* 66:34, 67%); (b) IBX, DMSO, rt (80%).

Scheme 2.33 – Completion of the synthesis of 1,2-diketone **56**.

The *dr* was maintained in the ring-opening of epoxide **125** with Me_3Al which was regioselective due to chelation of aluminium to the hydroxyl and epoxide oxygen atoms with a build-up of positive charge occurring at the benzylic position (see **Figure 2.10** above).[33] This afforded previously synthesised 1,2-diol **104** which could be oxidised to 1,2-diketone **56** with IBX (see **Scheme 2.21** above).

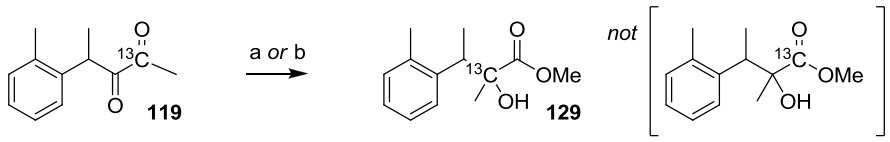
The optimised sequence of reactions was repeated using 2-^{13}C-labelled acetone **117** to access ^{13}C-labelled diketone **119** (**Scheme 2.34**).



Reagents and Conditions; (a) 1.3 eq. **117**, 0.37M NaOH (aq.), EtOH, 0 °C, 4 h; (b) 1 eq. $CeCl_3 \cdot 7H_2O$, 1.5 eq. $NaBH_4$, 0 °C to rt, 15 min (51% over 2 steps); (c) 10 mol% $VO(acac)_2$, 1.2 eq. TBHP, toluene, 40 °C, 16 h (*dr* 41:59, 65%); (d) 3 eq. Me_3Al, hexane, -78 to 0 °C, 4 h (*dr* 43:57, 67%); (e) 2.5 eq. IBX, DMSO, rt, 18 h, (79%).

Scheme 2.34 – Synthesis of 2-^{13}C-labelled diketone **119**.

All steps proceeded in comparable yields to those observed using unlabelled material as would be expected. ^{13}C-Labelled diketone **119** was then exposed to both Lewis acid and base promoted BER conditions (**Scheme 2.35**).



Reagents and Conditions; (a) 1 eq. CuCl, MeOH, 40 °C, 66 h (*dr* 45:55); (b) 0.21M NaOH, MeOH, 40 °C, 16 h (*dr* 59:41).

Scheme 2.35 – BER of ^{13}C-labelled diketone **119** under Lewis acidic and basic conditions to investigate which group is migrating.

Under both sets of conditions, the ^{13}C-label ended up in the α-position to the carbonyl group in ester **129**. No product was observed containing the ^{13}C-label in the carbonyl group by ^{13}C NMR. This confirmed that as expected, the benzylic group is exclusively migrating in these BER reactions.

2.2.5 Proposed BER Transition States

With the diastereoisomers of ester **57** assigned[†] and confirmation that the benzylic group is exclusively migrating established, transition states were proposed to rationalise the diastereoselectivity observed (**Figure 2.12**).

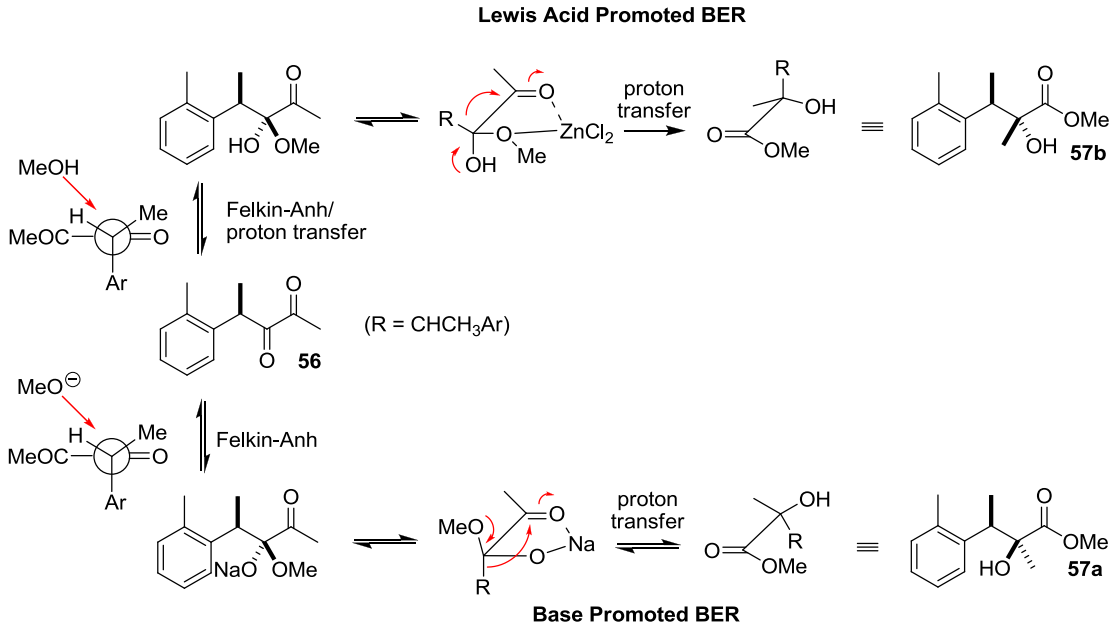


Figure 2.12 – Predicted transition states to rationalise the diastereoselectivity observed in the BER of diketone **56**.

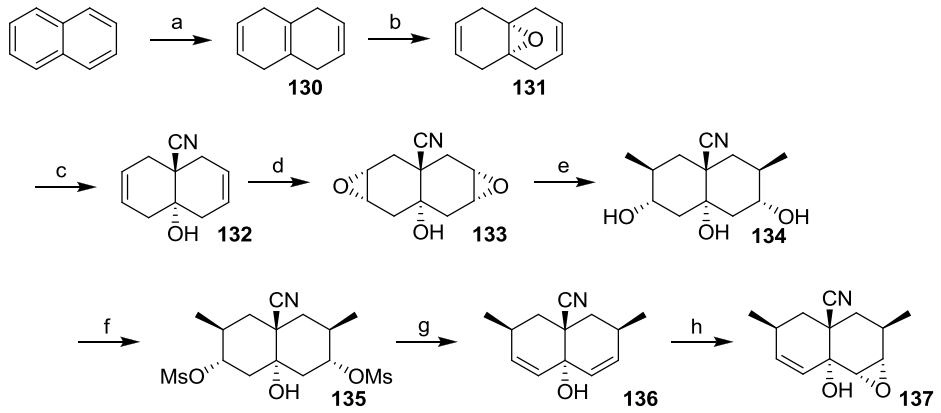
We propose that the major intermediate in both pathways is the hemiacetal 'Felkin-Anh' product. We then propose that under Lewis acid promoted conditions, the Lewis acid chelates between the methyl ether and carbonyl oxygens allowing for smooth orbital overlap for 1,2-benzylic group migration assisted by the hydroxyl group lone pair of electrons. This leads to ester diastereoisomer **57b**. By contrast, the base deprotonates the hydroxy group forming the alkoxide which chelates to the carbonyl oxygen *via* the counter-ion allowing for smooth orbital overlap for 1,2-benzylic group migration assisted in this case by the methyl ether lone pair. This leads to the formation of ester diastereoisomer **57a** as the major product.

Interestingly, this contrasts with the transition states predicted by Burke *et al.* for the $Cu(OAc)_2$ promoted BER of their diketone substrate (see **Figure 1.8**).[54] Using their predicted transition state, a BER promoted by Lewis acids would lead to the formation of ester **57a** as the major diastereoisomer. As previously discussed, it is possible that their system is complicated by the presence of extra heteroatoms.

[†] Note that all previous depictions of diastereoisomers of BER's on diketone **56** in this thesis show the correct relative stereochemistry.

2.3 Synthesis of Euonyminol Model

The synthesis of the euonyminol model up to the key desymmetrisation step has previously been published.[60] Using the procedures reported therein, a large scale synthesis of epoxide **137** was completed starting from 100 g of naphthalene (**Scheme 2.36**).



Reagents and Conditions; (a) NH_3 (aq.), 5.6 eq. Na, EtOH/Et_2O, -78 °C, 3 h (89%); (b) 1.8 eq. NaOAc, CH_2Cl_2, 1.2 eq. peracetic acid in AcOH, 0 °C to rt, 1.5 h (67%); (c) 10 eq. KCN, H_2O/MeCN, 85 °C, 4 days (64%); (d) 0.1 eq. $VO(acac)_2$, 4 eq. TBHP, CH_2Cl_2/toluene, 70 °C, 21 h (72%); (e) 4 eq. Me_3Al, CH_2Cl_2/hexane, 50 °C, 16 h (87%); (f) 3 eq. MsCl, 3 eq. Et_3N, CH_2Cl_2, -10 °C to rt, 17 h (69%); (g) DBU, 110 °C, 17 h (74%); (h) 1.1 eq. L-(+)-DIPT, 1.1 eq. $Zr(O^iPr)_4.{}^iPrOH$, 2.4 eq. TBHP, 4 Å MS, CH_2Cl_2, -42 °C then 1 eq. diallylic alcohol **136**, then -20 °C, 42 h (*ee* 48%, 95%).

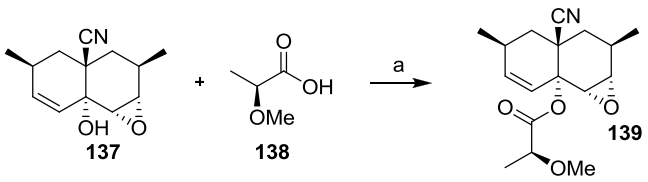
Scheme 2.36 – Synthesis of euonyminol model up the desymmetrisation step.

Due to the large quantities of reagents and solvents required, the final 7 steps in the above synthesis were performed in 3 batches. The Birch reduction of naphthalene proceeded in high yield as complete conversion to triene **130** was observed allowing the avoidance of a difficult work-up to remove the mono-reduced product. Epoxidation of resulting triene **130** proceeded in a moderate yield due to the formation of some *bis*-epoxide despite careful monitoring of the reaction. Due to a rise in the cost of Et_2AlCN which was originally used to ring-open epoxide **131**, a large excess of KCN was used instead (as has also been done previously within the Spivey group).[122] Although this required a longer reaction time, it afforded the desired cyanohydrin **132** in a yield of 64%. Diastereoselective *bis*-epoxidation controlled by chelation to the hydroxy group on the bottom face of the molecule, afforded *bis*-epoxide **133** which was then regioselectively ring-opened with Me_3Al

to afford triol **134**. Selective mesylation of the two secondary hydroxyl groups was followed by *anti*-elimination in neat DBU to furnish *meso*-diallylic alcohol **136**. A Zr-based Sharpless-type asymmetric epoxidation then afforded the desired (+)-epoxide **137** in high yield although the high enantioselectivity achieved previously was not reproduced.[60] The reaction was repeated 5 times and *ee*'s of 22%, 38%, 32%, 28% and 39% were obtained (as determined by HPLC).[60] Webber also failed to reproduce the high *ee* reported originally by Weston,[60] but did not use molecular sieves when performing the reaction, unlike the conditions reported by Weston.[7] It is therefore likely that the *ee* was compromised by the presence/quality of the molecular sieves.

As methyl ether deprotection of euonyminol model compound **58** has not been achieved yet, it was decided to hold the majority of material as stable crystalline chiral epoxide **137**. To this end, the synthesis was continued on a small scale (~500 mg of allylic alcohol **137**).

Thus, a Yamaguchi esterification with enantiomerically pure (-)-(*S*)-2-methoxypropionic acid was performed according to the method developed by Webber (**Scheme 2.37**).[7]



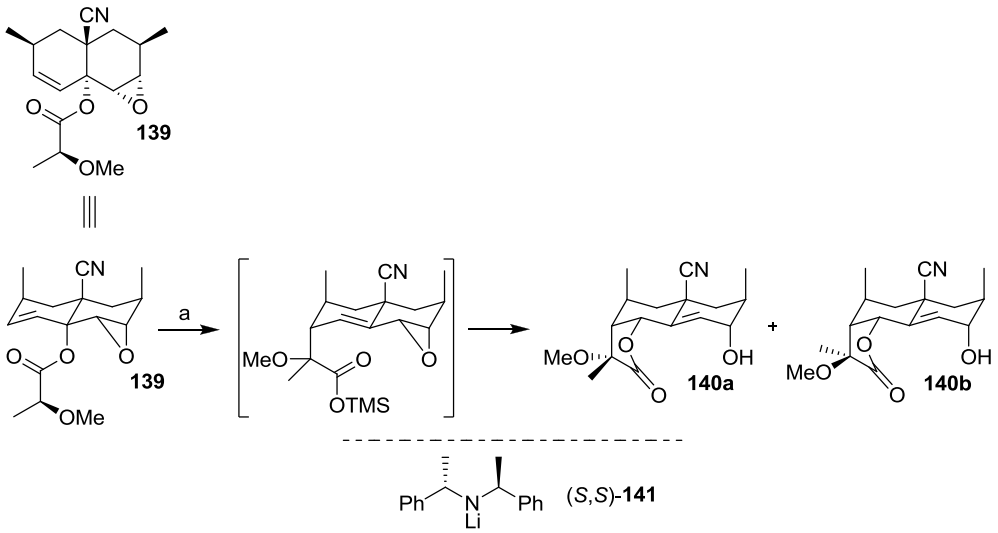
Reagents and Conditions; (a) 1 eq. **138**, 1.05 eq. 2,4,6-trichlorobezoyl chloride, 1.05 eq. Et_3N, 0.55 eq. 4-DMAP, toluene, 60 °C, 20 h (79%).

Scheme 2.37 – Yamaguchi esterification with (-)-(*S*)-2-methoxypropionic acid (**138**).

It was found that the *dr* could be determined by integration of the methyl ether peaks in the ^1H NMR spectrum. A kinetic resolution occurred during the esterification. For example, allylic alcohol **137** with an *ee* of 22% improved to a *de* of 48% after esterification to ester **139**. Unfortunately, the diastereoisomers of ester **139** were not separable by FC and when passed through the HPLC, they could not be detected using our DAD (i.e. no absorption in the region >200 nm).

Webber had performed some optimisation on the next step in the synthesis, which is an Ireland-Claisen rearrangement, that under the reaction conditions proceeds to give two epimers lactones **140a** and **140b** which Webber was able to assign by x-ray crystallography.[7] The ratio of these epimers reflects both the ratio of silyl ketene acetal stereoisomers formed following ester α-deprotonation/silylation and the proportion proceeding through a boat *vs.* a chair transition state.[123] For cyclic systems, particularly cyclohexenyl systems, both boat- and chair-like transition states are plausible, making prediction of the stereochemical outcome of the reaction difficult.[124]

After determining the optimal order of addition of reagents, the effect of the nature of the base was examined by Webber (**Table 2.29**).



Entry	Base	Conversion to 140	Ratio of epimers 140a:140b
1[a]	LHMDS	51%	53:47
2[a]	(*S*,*S*)-**141**	82%	54:46
3[a]	(*R*,*R*)-**141**	39%	58:42

a. Reported by M. Webber.

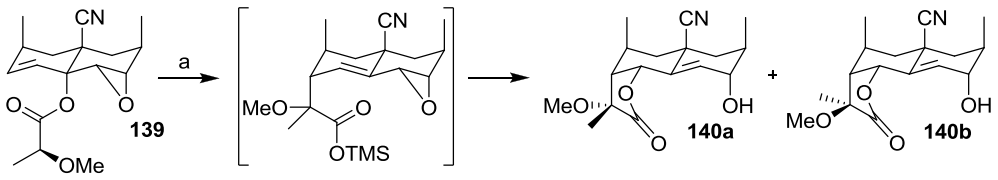
Reagents and Conditions; (a) 2 eq. TMSCl, -78 °C, then 1 eq. base, 1h, then rt, 16 h.

Table 2.29 – Webber's findings during optimisation of the Ireland-Claisen rearrangement.[7]

LHMDS was first investigated due to its success in Ireland-Claisen rearrangements that were not lactate variants.[125] This base afforded little selectivity for the desired epimer **140a** (entry 1). Considering the work of Zakarian which employed Koga-type

bases to install quarternary stereocentres by matching the chirality of the ester and the base,[126] chiral amine bases were applied (entries 2 and 3). It appeared that in this case, the chirality of the base had little effect on the selectivity although the conversion was much greater when using (*S*,*S*)-**141** as the base (entry 2). When this procedure was repeated by Webber on a large scale to bring material through to the final product, a significant amount of material was lost and it was noted that even on a small scale the reaction was capricious.

Cognisant of this reported irreproducibility and bearing in mind the new realisation that the *dr* of ester **139** could be measured by inspection of its ^{1}H NMR spectrum, I decided to do a further brief investigation into this lactate variant of the Ireland-Claisen rearrangement (**Table 2.30**).



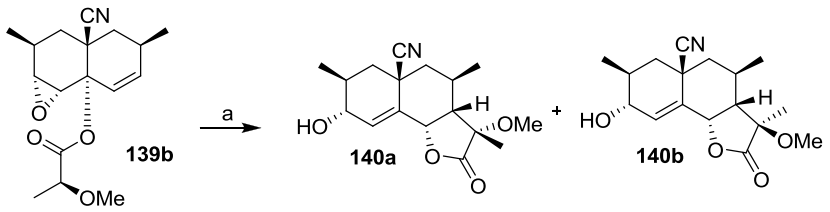
Entry	Base	Ester 139 : Lactone 140	Change in *dr* of ester 139	Epimers 140a:140b
1	(*S*,*S*)-**141**	1:0	no change	-
2	(*S*,*S*)-**141**·^{n}BuLi	decomposition	-	-
3	Et_2NLi	1:0	77:23 to 65:35	-
4	NaHMDS	1:0	77:23 to 68:32	-
5	LHMDS	1:1	77:23 to 0:1	65:35

Table 2.30 – Investigation into the lactate variant of the Ireland-Claisen.

When repeating Webber's conditions using (*S*,*S*)-**141** as the base, no reaction was observed (entry 1). It was noted that previously when preparing the lithium amide from the secondary amine, an excess of ^{n}BuLi was used. It was therefore thought that a more reactive (*S*,*S*)-**141**·^{n}BuLi complex could have been formed inadvertently by Webber during formation of the silyl ketene acetal and hence this complex was deliberately prepared. Unfortunately, only decomposition products were observed (entry 2). Treatment with Et_2NLi or NaHMDS, two bases that had not been screened previously, did not result in the formation of any lactone **140** although a change in the *dr* of starting ester **139** was observed suggesting that

deprotonation/reprotonation or some decomposition was occurring under these conditions. In both cases there was a greater consumption of the diastereoisomer containing the required chirality on the decalin core (entries 3 and 4). Repeating the conditions using LHMDS as the base resulted in a 50% conversion to lactone **140** in an improved epimeric ratio of 65:35 to that previously reported (entry 5, *cf.* 53:47 entry 1, **Table 2.29**). Interestingly, only the minor diastereoisomer ester **139b** was recovered from the reaction suggesting that a kinetic resolution is occurring in favour of the reaction of ester **139a** containing the desired chirality on the decalin core (entry 5).

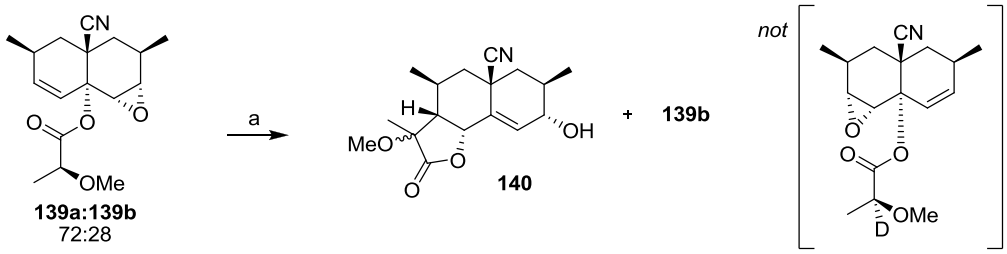
To confirm the hypothesis that a kinetic resolution is occurring and not simply a reprotonation of the silyl ketene acetal, recovered ester **139b** was resubmitted to the reaction conditions (**Scheme 2.38**).



Reagents and Conditions; (a) 2.2 eq. TMSCl, 1.1 eq. LHMDS, THF, -78 °C, 30 min, then 60 °C, 15 h (*dr* 62:38, 9% conv.).

Scheme 2.38 – Ireland-Claisen rearrangement of the minor diastereoisomer ester **139b**.

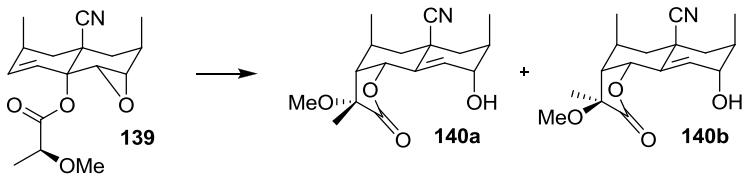
The reaction proceeded with only 9% conversion, a much lower conversion than that observed previously with the mixture of diastereoisomers of ester **139** (*cf* 55% with 72:28, **140a**:**140b**). A comparable ratio of epimers was obtained to that previously observed. Although it was shown that the reaction was much slower with ester **139b**, it was decided to perform a D_2O quench to rule out the possibility that one face of the silyl ketene acetal is simply just reprotonating selectively over the other (**Scheme 2.39**).



Reagents and Conditions; (a) 2.2 eq TMSCl, 2.2 eq. LHMDS, THF, -78 °C, 30 min; then 60 °C, 4 h.

Scheme 2.39 – D_2O quench following exposure of esters **139a** and **139b** to rearrangement conditions.

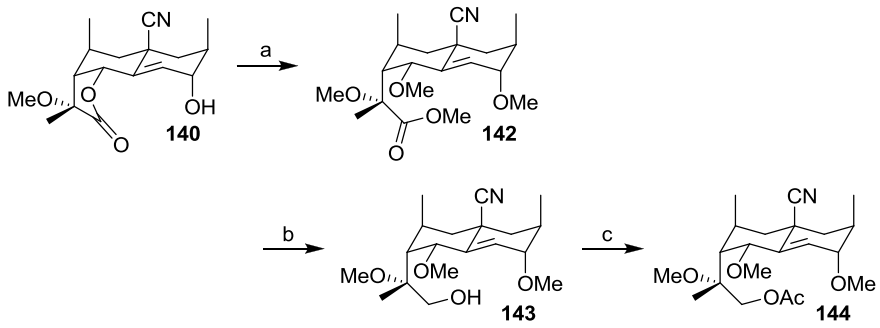
Again, only minor diastereoisomer ester **139b** was recovered from the reaction and no incorporation of deuterium was observed. We concluded that a kinetic resolution is occurring. Although this would compensate for the poor enantioselectivity obtained in the desymmetrisation epoxidation step, the primary goal was to complete the synthesis in order to repeat the chemistry later in the sequence on a larger scale and to fully characterise these intermediates. Therefore, the rearrangement in which LHMDS was used as the base was driven to completion to allow the synthesis of a sufficient quantity of required epimer **140a** (**Scheme 2.40**).



Reagents and Conditions; (a) 2.2 eq. TMSCl, 2.2 eq. LHMDS, THF, -78 °C, 30 min; then 60 °C for 14.5 h (38% yield of **140a**, 20% yield of **140b**).

Scheme 2.40 – Conditions for the Ireland-Claisen rearrangement to bring material through the final steps of the synthesis.

Considering that the fully oxygenated system required in the synthesis of euonyminol itself may show different selectivity in the Ireland-Claisen, it was decided to proceed with the synthesis bringing through material in 50 mg batches despite the low yield of 38% of epimer **140a**. The proceeding 3 steps were thereafter repeated without major complications (**Scheme 2.41**).

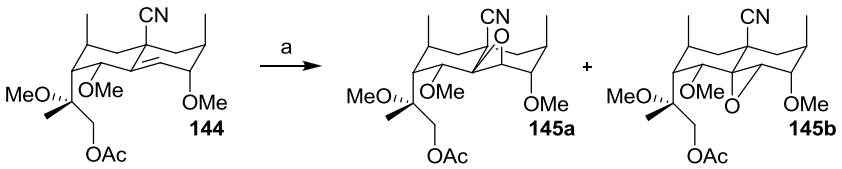


Reagents and Conditions; (a) 10 eq. KOH, 10 eq. MeI, THF, 60 °C, 3 h (96%); (b) 4.2 eq. $LiAlH_4$, THF, 0 °C, 2.5 h (63%); (c) 3 eq. Ac_2O, 1 eq. 4-DMAP, pyridine, rt, 1 h (99%).

Scheme 2.41 – Synthetic steps from lactone **140** to acetate **144**.

Lactone-opening under basic conditions in the presence of MeI afforded methyl ether protected ester **142** in a yield of 96%. When the reduction of ester **142** to alcohol **143** was first attempted, reduction of the nitrile group was also observed, as confirmed by loss of nitrogen from the mass spectrum. It is thought that this was caused by a combination of using a fresh bottle of $LiAlH_4$ and the larger scale the reaction was performed on. By repeating with extra care to keep the temperature below 0 °C and adding $LiAlH_4$ in small portions, nitrile reduction was avoided and alcohol **143** was isolated in a yield of 63%. Acetylation of primary alcohol **143** then afforded acetate **144** in a quantitative yield.

The synthesis was continued with epoxidation of alkene **144** with *m*-CPBA (**Table 2.31**).



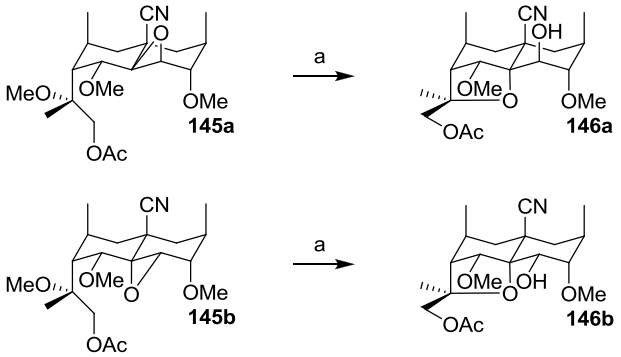
Entry	Scale	Ratio of 145a:145b	Yield of 145a and 145b
1	10 mg	96:4	96%
2	26 mg	66:34	88%

Reagents and Conditions; (a) 1.3 eq. *m*-CPBA, CH_2Cl_2, rt, 3.5 h.

Table 2.31 – Change in selectivity as a function of the scale of reaction in the epoxidation of alkene **144**.

When the reaction was repeated on a 10 mg scale, a small amount of the undesired epoxide diastereoisomer **145b** was also formed, though at this point due to there being only 4% conversion to this diastereoisomer, it was only later identified as epoxide **145b**, resulting from epoxidation on the more hindered bottom face of the C-3 - C-4 alkene (entry 1). It is likely that the larger scale reaction generates more heat and hence the selectivity is reduced. As epoxide **145b** had not yet been identified, when the reaction was repeated on a larger scale of 26 mg, precaution to cool the reaction were not taken. This larger scale caused the ratio of epoxides **145a**/**145b** to decrease from 96:4 to 66:34 (entry 2). However, this did allow for isolation of minor diastereoisomer **145b** which allowed us subsequently to gain insight into the mechanism of the next step, which was THF ring formation.

It was found that THF ring formation proceeded with both diastereoisomers of epoxide **145** to afford epimeric alcohols **146a** and **146b** (**Scheme 2.42**).



Reagents and Conditions; (a) 3 eq. BBr_3, 5 eq. LiI, CH_2Cl_2, -78 °C, 3 h (78% of **146a**, 52% of **146b**).

Scheme 2.42 – THF-ring formation from diastereoisomeric epoxides **146a** and **146b**.

As previously reported, upon treatment of epoxide **145a** with BBr_3, the 12-OMe cyclises to ring-open the epoxide. However, as the cyclisation was found to also occur with epoxide **145b**, this suggests that this substitution process is proceeding through a S_N1-type mechanism with the generation of at least a partial cation at the ring-fusion carbon (**Figure 2.13**).

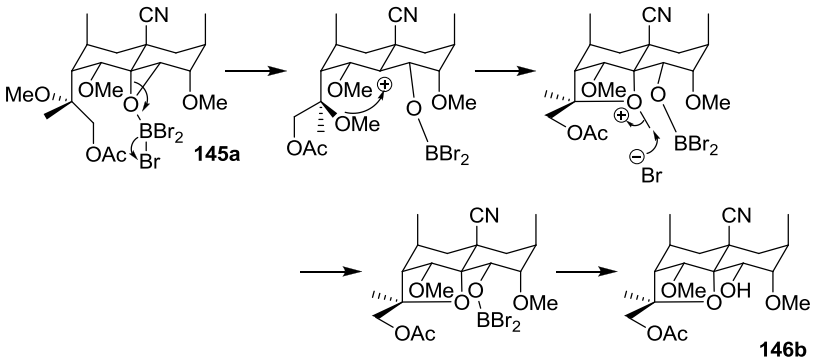
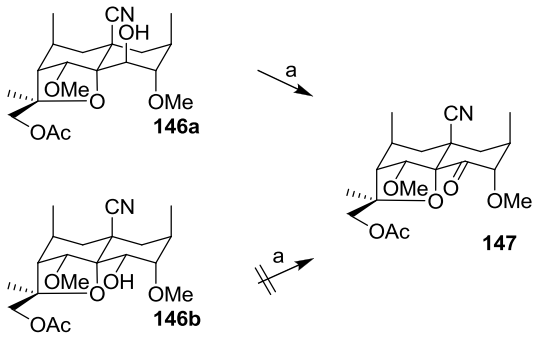


Figure 2.13 – Proposed mechanism for the formation of alcohol **146b**.

We propose that the BBr_3 coordinates to the epoxide causing it to open and generate a tertiary carbocation at the ring-fusing carbon atom. The methyl ether oxygen then closes onto the empty p-orbital to form a 5-membered ring. The generated bromide anion then attacks the carbon atom of the methyl ether to generate methyl bromide in an S_N2-type reaction. After aqueous work-up, alcohol **146b** is obtained.

Oxidation of the secondary alcohol using the Dess-Martin periodinane was then required. It was hoped that this would allow both epimers to converge to ketone **147** (**Scheme 2.43**).

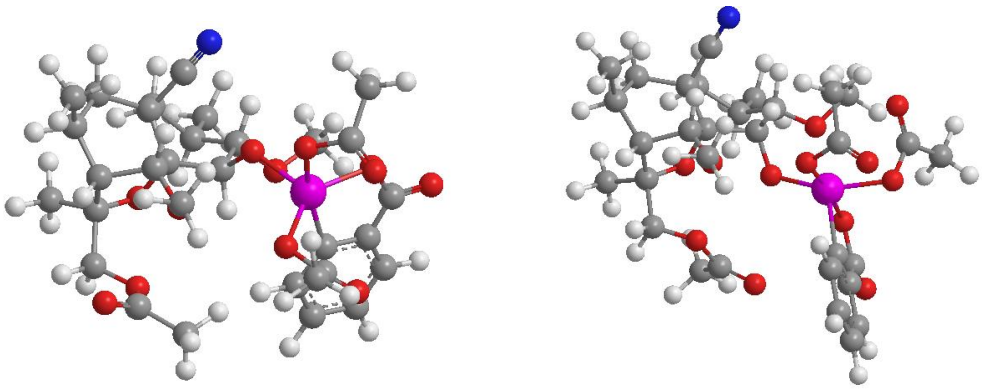


Reagents and Conditions; (a) 1.5 eq. DMP, CH_2Cl_2, rt, 2 h (92% for the oxidation of **146a**).

Scheme 2.43 – Expected convergence of alcohols **146a** and **146b** to give ketone **147** by oxidation with DMP.

As previously observed, alcohol **146a** was oxidised to ketone **147** in a high yield. Epimer **146b**, unfortunately, would not oxidise to ketone **147** and instead was converted to a mixture of products as evidenced by analysis of the methyl ether peaks in the ^{1}H NMR spectrum of the crude reaction mixture. Due to the small scale

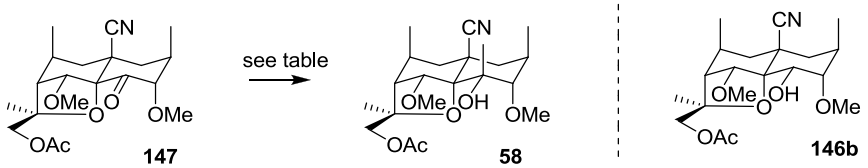
the reaction was performed on, no attempt was made to isolate and identify the resulting products. The failure of epimer **146b** to undergo clean oxidation might be explained by the proximity of the acetate protecting group to the iodine centre in the intermediate formed following reaction of the alcohol with the DMP. This is clearly demonstrated when the intermediates are modelled in 3D (**Figure 2.14**).



*Axial epimer **146a*** *Equatorial epimer **146b***

Figure 2.14 – Computed molecular structure of the intermediates of alcohols **146a** and **146b** when reacted with DMP following energy minimisation (MM2).

To complete the synthesis of the methyl ether protected model **58**, 1,2-addition to the least hindered face of ketone **147** was attempted (**Table 2.32**).



Entry	Conditions	Scale	Outcome
1[a]	4 eq. MeMgCl, THF, rt, 4 h	1 mg	75% yield
2	4 eq. MeMgCl, THF, rt, 4h	3 mg	no reaction
3	8 eq. MeMgCl, THF, rt, 4 h	6 mg	50% yield of 2° alcohol **146b**
4[127]	5 eq. $CeCl_3$, 10 eq. MeMgCl, THF, -78 °C to rt, 4 h	1 mg	no reaction
5	4 eq. MeLi, THF, -78 °C, 1 h	1 mg	decomposition
6	4 eq. MeMgI, THF/Et_2O, 0 °C to rt, 4 h	4 mg	Conversion to unknown product
7	4 eq. MeMgBr, 1 eq. LiCl, THF, rt, 3 h	2 mg	Conversion to unknown product

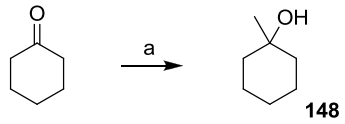
a. Reaction performed by M. Webber.[7]

Table 2.32 – 1,2-Addition of methyl organometallic reagents to ketone **147**.

Webber reported a 75% yield of alcohol **58** from addition of MeMgCl to ketone **147** at room temperature in THF (entry 1).[7] Unfortunately, this result could not be repeated. Upon addition of 4 eq. MeMgCl, as used by Webber, no reaction was observed (entry 2). It was thought that because of the very small scale the reaction was originally performed on, a larger excess of MeMgCl may have been added than was reported. Therefore, the reaction was attempted with 8 eq. MeMgCl (entry 3). This did not result in the formation of desired alcohol **58**, though reduced product alcohol **146b** was obtained in 50% yield. Due to the absence of any β-hydrogens on the Grignard reagent, this reduced product must be obtained from a single-electron transfer (SET) mechanism,[128] as has previously been observed in cyclic ketones flanked by two α-ether groups.[129] Use of $CeCl_3$ to enhance the rate of Grignard reagent addition and hence potentially limit the extent of undesired side reactions was then explored.[127] After adding MeMgCl to a premixed solution of ketone **147** and $CeCl_3$, no reaction was observed (entry 4). Due to the apparent lack of activity and with signals corresponding to the enolate of the acetate group observed in the ^{1}H NMR spectra of the crude material of the above reactions, it was decided to attempt addition with MeLi due to its higher nucleophilicity. Using an excess of

MeLi at -78 °C resulted in decomposition into a complex mixture (entry 5). Due to the small scale these trial reactions were performed on, addition of just the required 2 equivalents of MeLi would be difficult to accurately achieve. Wanting to avoid decomposing more of valuable ketone **147**, it was decided to generate MeMgI immediately prior to use and attempt addition of this Grignard reagent which is reported to be slightly more reactive than MeMgCl as previously used. It was clear that the acetate group was no longer present, though the ^{1}H NMR spectrum did not correspond to that of the desired alcohol product **58** previously formed (entry 6). Addition of LiCl to break up the aggregates of MeMgCl to generate a more reactive species resulted in consumption of ketone **147** but afforded no desired product (entry 7).[130]

As a control reaction, the addition of MeMgCl to cyclohexanone was performed (**Scheme 2.44**).



Reagents and Conditions; (a) 3 eq. MeMgCl, THF, rt, 3 h (94%).

Scheme 2.44 – Addition of MeMgCl to cyclohexanone.

Unsurprisingly, this reaction gave the expected *tert*-alcohol **148** in good yield following work-up, clearly indicating that the Grignard reagent was of good quality. The reason for the failure to reproduce MeMgCl addition to ketone **147** is therefore unclear. As alluded to above, the deshielding of the diastereotopic C-13 signals in the ^{1}H NMR spectrum after aqueous work-up and their return after passing through a plug of silica, suggests that the acetate is enolising in the reaction. This explains why the acetate group is unreacted though it is still unclear why the ketone remains intact. Alkoxides formed during Grignard reagent additions are known to cause complexities throughout the course of the reaction and it is possible that formation of the enolate is doing this.[131] Both the alkoxide species formed during the reaction and the Schlenk equilibrium, including equilibria involving association, must be considered (**Figure 2.15**).[132]

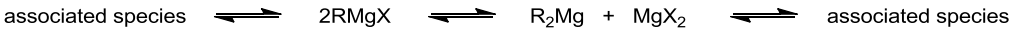


Figure 2.15 – Schlenk equilibrium.[133]

Unlike in diethyl ether, Grignard reagents in THF solutions differ very little in terms of their state of association/aggregation with varying concentration, therefore variances in the level of association of MeMgCl as a function of the scale on which the reactions were performed is unlikely to be a strong factor in the irreproducibility.[134] Due to the small Schlenk equilibria constant in THF, there is a higher concentration of R_2Mg and MgX_2 in THF than in diethyl ether where RMgX is the predominant species.[135] It is not always clear which species is active within the Schlenk equilibrium, so small variations in other variables including temperature, concentration and the presence of salts, can greatly affect the course of a reaction.

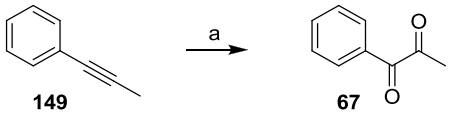
Unlike most of the intermediates *en route* to it, euonyminol model dimethyl ether **58** was previously fully characterised by Webber. This, and the fact that time constraints precluded the re-synthesis of ketone **147**, meant that a deeper investigation into the irreproducibility of the Grignard addition was not conducted. Unfortunately, this also meant that it was not possible to investigate the coupling of the euonyminol model with the four diastereoisomers of hydroxy-*iso*-evoninic acid.

2.4 Asymmetric BER

2.4.1 Synthesis of Diketone Substrates

As discussed earlier, two substrates were selected with which to develop an asymmetric BER. Benzyl diketone **65** was selected due to the high migratory aptitude of benzyl groups, whereas phenyl diketone **67** was selected because the products contain a structural motif found in many bioactive products.

Although phenyl diketone **67** is commercially available, it was decided to synthesise it from commercially available alkyne **149** as a trial reaction for the synthesis of analogues in the future due to the ready availability of aryl alkynes. Alkyne **149** was oxidised according to Seebach's procedure (**Scheme 2.45**).[136]

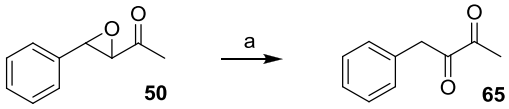


Reagents and Conditions; (a) 4.1 eq. $NaIO_4$, 2 mol% $RuO_2 \cdot XH_2O$, CCl_4/MeCN/H_2O, rt, 1 h (72%).

Scheme 2.45 – Oxidation of alkyne **149** to phenyl diketone **67**.[136]

The oxidation was high yielding and phenyl diketone **67** was isolated after simply passing the material, after aqueous work-up, through a plug of silica making the synthesis extremely time efficient.

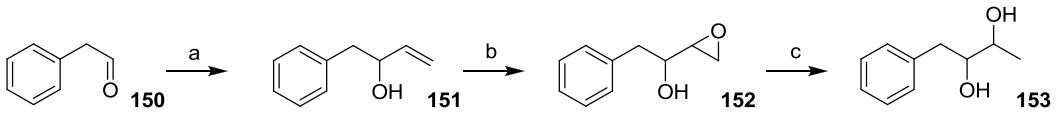
The synthesis of benzyl diketone **65** was then explored. Diketone **65** is a known compound and a 2-step procedure has previously been reported, whereby the oxidation of epoxy ketone **50** is the key step in the sequence (**Scheme 2.46**).[137]



Reagents and Conditions; (a) 2 mol% Fe(tpp)OTf, dioxane, reflux, 15 min (85%).

Scheme 2.46 – Suda's key step in the 2-step preparation of diketone **65**.[137]

However, as the catalyst for this transformation requires a 2-step preparation from an expensive Fe-porphyrin precursor, it was decided to target 1,2-diol **153** first, as oxidation with IBX had been shown earlier in this thesis to be high yielding when employing similar tolyl 1,2-diol **104** as a substrate (**Scheme 2.47**).



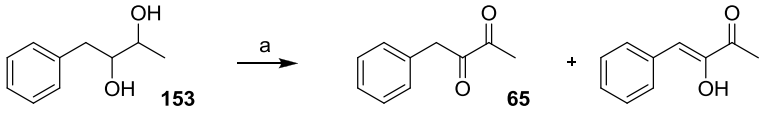
Reagents and Conditions; (a) 1.1 eq. vinyl magnesium bromide, THF, 0 °C to rt, 30 min (40%); (b) 1.2 eq. *m*-CPBA, CH_2Cl_2, 0 °C to rt, 16 h (*dr* 58:42, 98%); (c) 1.1 eq. $LiAlH_4$, THF, rt, 18 h (99%).

Scheme 2.47 – Preparation of 1,2-diol **153**.

1,2-Addition of vinyl magnesium bromide to commercially available phenylacetaldehyde **150** afforded allylic alcohol **151** in a moderate yield. It is thought likely, however, that this can be improved by transmetallating the vinyl nucleophile to an organocerate to minimise enolisation of this substrate.

Epoxidation with *m*-CPBA proceeded in high yield to afford epoxy alcohol **152** which could then be reductively opened to afford targeted 1,2-diol **153**.

Dioxidation of 1,2-diol **153** with IBX gave diketone **65** (**Scheme 2.48**).



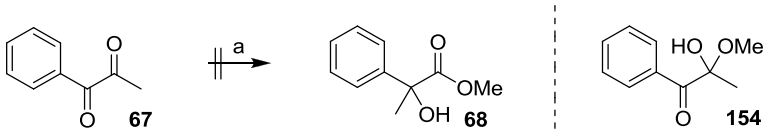
Reagents and Conditions; (a) 2.5 eq. IBX, DMSO, rt, 16 h (23%).

Scheme 2.48 – Formation of benzyl diketone **65**.

A yield of just 23% was achieved for the oxidation, possibly due to the volatility of diketone **65**, 44% of which, by analysis of its ^{1}H NMR spectrum, was isolated in the enol form. It is possible that a Swern oxidation to avoid the required work-up for removal of DMSO, will give an improved yield.

2.4.2 Promoting a BER of the Asymmetric Substrates

Attempts at promoting a BER of phenyl diketone **67** were made first (**Table 2.33**).



Entry	Temperature	Additives	Reaction Time	Conversion to hemiacetal 154
1	40 °C	-	18 h	0%
2	60 °C	-	22 h	10
3	50 °C	1 eq. pyridine	66 h	100%
4	50 °C	1 eq. 2,6-lutidine	66 h	100%

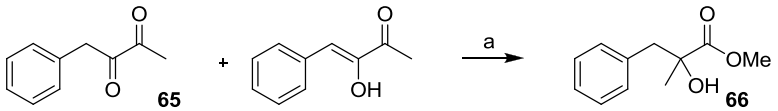
Reagents and Conditions; (a) 1 eq. CuCl, MeOH.

Table 2.33 – Attempts to promote a BER of phenyl diketone **67** using CuCl, with and without additives.

In light of the interesting observations regarding copper-pyridyl complexation when promoting a BER of tolyl diketone **56** (see **Table 2.24**), it was decided to try and promote the BER of phenyl diketone **67** with copper based Lewis acids. When using CuCl as a promoter alone at 40 °C, no reaction was observed (entry 1). Increasing the temperature to 60 °C gave a 10% conversion to previously unreported

hemiacetal **154** (entry 2). As phenyl groups are known to be poorer migrating groups than benzyl groups, it is likely that this is the reason for the failure of the reaction. The use of pyridine (entry 3) and 2,6-lutidine (entry 4) as additives in the reactions only increased the conversion to hemiacetal **154**.

In view of time limitations, it was decided to focus further studies on benzyl diketone **65** (**Scheme 2.49**).



Reagents and Conditions; (a) 1 eq. CuCl, MeOH, 50 °C, 20 h (86%).

Scheme 2.49 – BER of benzyl diketone **65**.

As expected, the tautomers obtained from the oxidation with IBX (see **Scheme 2.48**) are in equilibrium under the Lewis acid promoted BER conditions, and so full conversion to α-hydroxy ester **66** was observed from a mixture of starting materials using CuCl as promoter in a yield of 86%. As the enantiomers of ester **66** have previously been assigned,[138] only separation of the enantiomers by chiral HPLC and comparison of optical rotation values is required for rationalising any stereoselectivity obtained.

Unfortunately, time constraints did not permit the exploration of chiral catalysts to effect an asymmetric BER though the planned strategy to achieve this is described in the future work section below.

3 Conclusions

In summary, the first synthesis of (±)-hydroxy-*iso*-evoninic acid has been achieved. By obtaining the optical rotations for the enantiomers of both possible diastereoisomers, the assignment of naturally occurring hydroxy-*iso*-evoninic acid is now possible if e.g. hydrolysis of one of the Celastraceae sesquiterpenoids is performed.

A diastereoselective BER has been developed allowing a specific diastereoisomer to be targeted by altering the reaction conditions. Although the levels of *dr* are not yet optimal, tunable conditions have been demonstrated for the first time in a BER reaction.

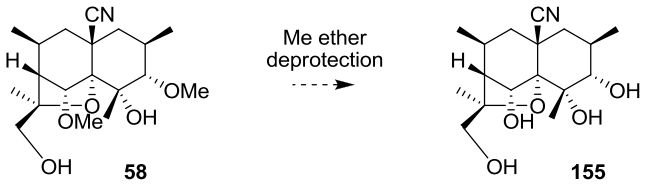
All intermediates *en route* to euonyminol model **58** have been fully characterised despite the unexpected failure of the final methyl addition to ketone **147**.

4 Future Work

4.1 Assigning the Naturally Occurring Stereochemistry

It is likely that the formation of an enolate of the acetate group is interfering in the Grignard reagent addition to ketone **147**. Therefore, when repeating the synthesis from chiral epoxy alcohol **137**, a different non-enolisable protecting group will be introduced.

After completion of the synthesis of euonyminol model **58**, conditions for methyl ether deprotection will be explored (**Scheme 4.1**).



Scheme 4.1 – Required methyl ether deprotection of model euonyminol **58**.

Due to the stability of model compound **58**, there is high confidence that one of the many known methyl ether deprotection methods, including Me_3SiI,[139] BBr_3,[140] AlX_3/EtSH,[141] $AlCl_3$/TBAI,[142] $SiCl_4$/NaI[143], will be successful in affording tetraol euonyminol model **155**.

As previously discussed, the formation of the 14-membered macrolactone of euonyminol model **155** with each of the stereoisomers of hydroxy-*iso*-evoninic acid is planned. Due to the high steric hindrance of addition to the aliphatic acid in hydroxy-*iso*-evoninic acid and as the aromatic acid has higher acidity, it is likely that this will esterify faster when subjected to carbodiimide coupling conditions (**Figure 2.16**).

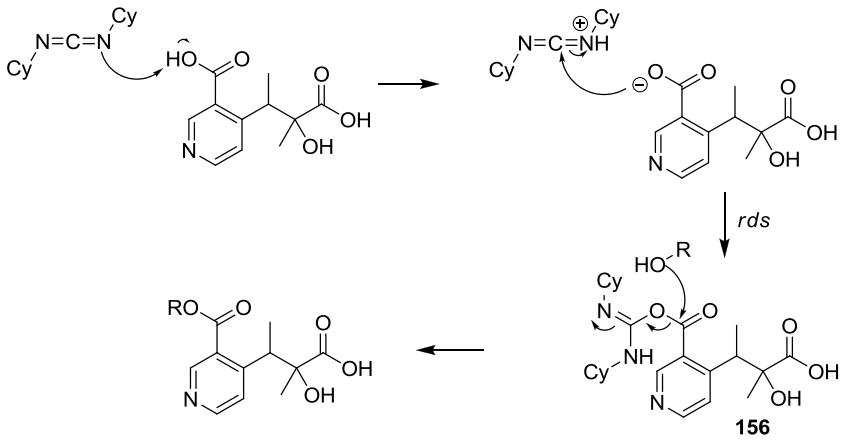
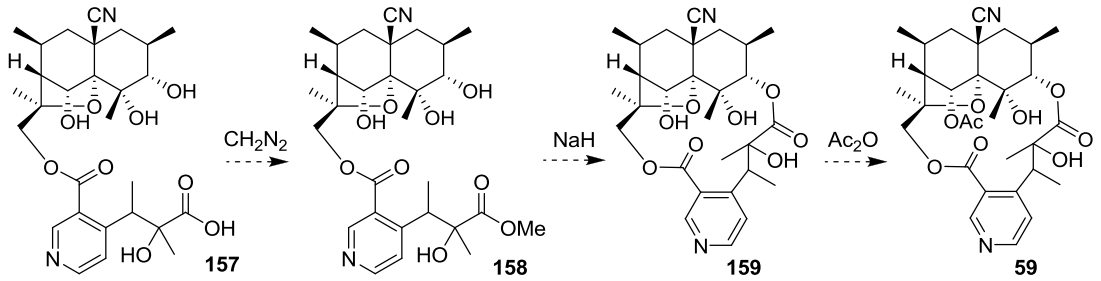


Figure 4.1 – Proposed selective esterification of the aromatic acid group.

The rate determining step in DCC coupling reactions has been shown to be the formation of the *O*-acylisourea intermediate **156**.[144] Due to the higher acidity of the aromatic acid, *O*-acylisourea intermediate **156** should form selectively from the reaction with a carbodiimide. It can be expected that the only primary alcohol present in deprotected euonyminol model **155** will act as the nucleophile to form ester **157** from which a 3-step sequence to close the macrolide ring can be envisioned (**Scheme 4.2**).



Scheme 4.2 – Proposed synthesis of macrocycle sesquiterpenoid model **59**.

Esterification of the remaining free acid with diazomethane would afford methyl ester **159** and based on the successful macrolactonisation performed by Yamada,[61] it is expected that treatment with NaH would afford 14-membered lactone **159**. After acetylation of the secondary alcohol, the ^{1}H and ^{13}C NMR data of model sesquiterpenoids **59** containing all 4 possible stereochemistries will be compared to that reported for the natural Celastraceae sesquiterpenoids (see **Tables 1.2** and **1.3**).

4.2 Asymmetric Synthesis of Hydroxy-*iso*-Evoninic Acid

Once the stereochemistry of naturally occurring hydroxy-*iso*-evoninic acid has been assigned, an asymmetric synthesis targeting the correct enantiomer of the required diastereoisomer will be attempted. The absolute stereochemistry will be set up in the allylation of a 3-picoline derivative (**Figure 4.2**).

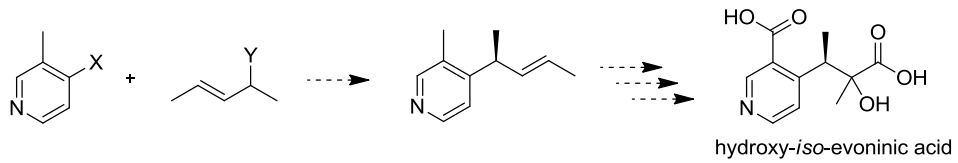
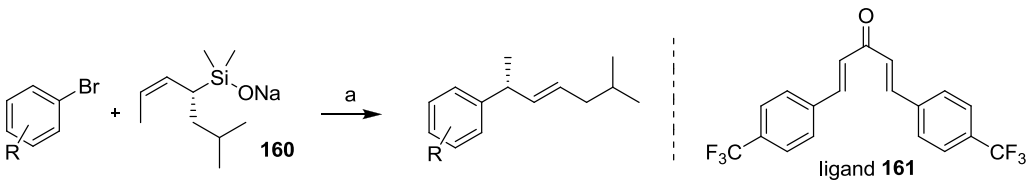


Figure 4.2 – Required asymmetric allylation for the stereoselective synthesis of hydroxy-*iso*-evoninic acid.

As previously discussed, 4-bromo-3-picoline is not very stable and requires a 3-step preparation from commercially available 3-picoline-*N*-oxide. Conversion of this aryl bromide to an aryl metal complex or aryl iodide to perform asymmetric allylation reactions is therefore unattractive.

However, a recent report by Denmark *et al.* details the asymmetric cross-coupling reaction of aryl bromides and allylic silanoate **160** (**Scheme 4.3**).[145]



Reagents and Condtions; (a) 2.5 mol% allylpalladium chloride dimer, 20 mol% ligand **161**, toluene, 70 °C, 6-24 h (66-78%, *er* > 98:2).

Scheme 4.3 – Denmark's asymmetric Pd-catalysed cross-coupling of allylic silanoates and aryl bromides.[145]

A selection of aryl bromides were successfully coupled under these conditions, including a heterocycle and aryls containing *ortho*-substituents. All examples proceeded with high chirality transfer which was rationalised by consideration of the relevant transition states (**Figure 4.3**).

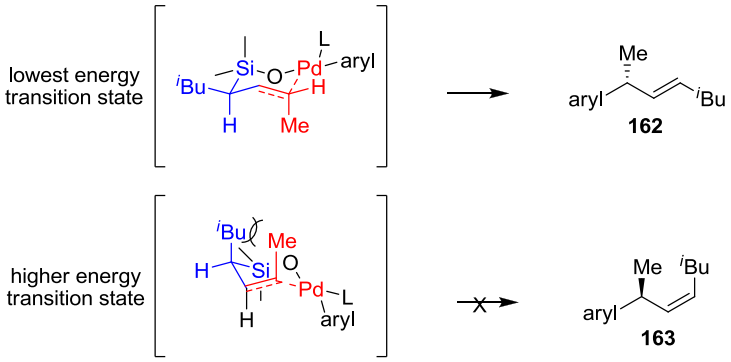
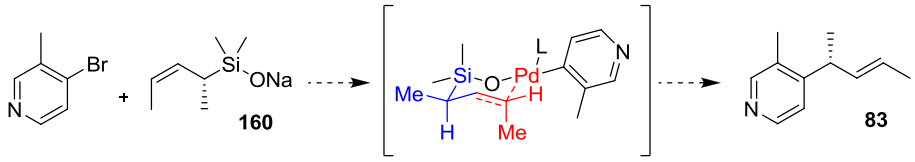


Figure 4.3 – Denmark's proposed transition states to rationalise the high levels of chirality transfer.

Due to the steric clash caused by the two alkyl groups in axial positions, no (*Z*)-alkene containing product **163** was observed. Unfortunately, an investigation into different alkyl groups on the allylic moiety has not yet been reported. It is likely however, that two methyl substituents, as required for the synthesis of hydroxy-*iso*-evoninic acid, would suffice to give a sufficient energy difference between the two possible transition states to allow for high levels of chirality transfer (**Scheme 4.4**).



Scheme 4.4 – Proposed application of Denmark's procedure to the synthesis of chiral alkene **83** *en route* to hydroxy-*iso*-evoninic acid.

Although this method requires an 11-step synthetic sequence for the preparation of chiral allylic silanolate **160**, the high levels of enantiomeric excess achievable, the number of suitable aryl bromides reported, and the avoidance of increasing the number of linear steps, makes this method attractive.

The relative stereochemistry can then be controlled later in the synthesis by applying a diastereoselective BER as developed in this thesis.

4.3 Development of an Asymmetric BER

With the selection and preparation of benzyl diketone **65** as the substrate with which to investigate an asymmetric variant of the BER now completed, catalytic conditions must be found to avoid the use of large amounts of potentially expensive chiral ligands. Although the BER can be promoted with sub-stoichiometric amounts of Lewis acid promoter,[54] the rate of the reaction becomes too slow to be of synthetic use. As previously discussed, a dramatic rate increase was observed when using pyridyl additives with a $CuCl_2$ promoter and this was postulated to be due to the formation of Cu-pyridyl complexes. It is therefore thought that success is likely when using chiral electron rich pyridine based ligands like those depicted below, with a copper-based Lewis acid (**Figure 4.4**).

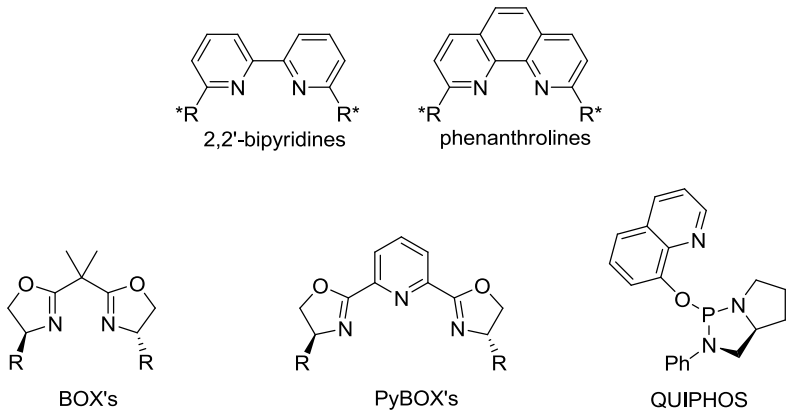


Figure 4.4 – Potential chiral catalysts for the promotion of an asymmetric BER.

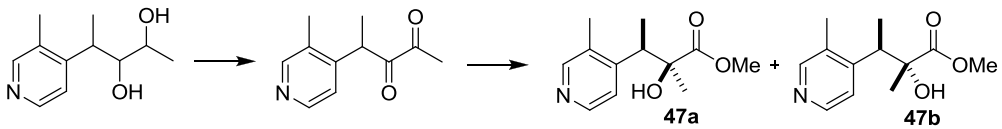
2,2'-Bipyridines,[146] phenanthrolines,[147] and electron rich BOX,[148] PyBOX[149] and QUIPHOS[150] ligands that form complexes with Cu(I) and Cu(II) salts should be considered initially.

Experimental

General Directions

All reactions were performed under anhydrous conditions, in oven-dried glassware and under a nitrogen atmosphere. *Anhydrous Solvents:* MeCN, Et_2O, CH_2Cl_2 and THF were used directly following passage under nitrogen through Al_2O_3 columns in a Grubb dry-solvent system (Innovative Technology Inc.). MeOH was used after distillation over CaH_2. *Reagents:* These were purchased from commercial sources and handled according to COSHH regulations. TMSCl was distilled over CaH_2 prior to use. *Chromatography:* Flash chromatography (FC) was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) and reverse phase chromatography on C18 silica gel (Fluka Kieselgel 90 F_{254} 230-400 mesh) according to the method of W. C. Still.[151] Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F254) which were visualized either by quenching of ultraviolet fluorescence (λmax = 254 nm) or by charring with $KMnO_4$ TLC dip. *HPLC:* see Appendices for conditions. *Melting points:* were determined on a Khofler hot stage. *Infra red spectra:* were recorded as neat liquids on Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (ν_{max}) are reported. *^{1}H NMR spectra:* These were recorded at 400 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referenced to $CDCl_3$ or D_2O, the residual solvent peak. Coupling constants (*J*) are reported to the nearest 2 significant figures. *^{13}C NMR spectra:* These were recorded at 100 MHz on a Bruker AMX-400 instrument. Chemical shifts (δ_C) are quoted in ppm and referenced to the $CDCl_3$, the residual solvent peak. ^{13}C multiplicities were determined by DEPT or/and by comparison of integrals. *Mass spectra:* Low resolution mass spectra (*m/z*) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+, MH^+, MNH^{4+}) and major peaks being reported with intensities quoted as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5ppm.

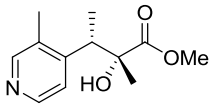
(2*S,3*R**)-** and **(2*R**,3*R**)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate (47a** and **47b)**



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

Oxalyl chloride (229 µL, 2.71 mmol, 2.2 eq.) in CH_2Cl_2 (1.6 mL) was cooled to – 78 ˚C. DMSO (384 µL, 5.41 mmol, 4.4 eq) was added and the solution stirred for 5 min. 1,2-Diol **82** (240 mg, 1.23 mmol, 1 eq.) in CH_2Cl_2 (1.5 mL) was added dropwise and the solution was stirred for a further 15 min. Triethylamine (1.02 mL, 7.38 mmol, 6 eq.) was added dropwise. After 3 min the reaction mixture was quickly pushed onto a short silica column while the solution was transferred *via* a pipette and then the column was eluted with CH_2Cl_2. After concentration *in vacuo*, the bright yellow liquid 1,2-diketone **48** was redissolved in MeOH (25 mL) and $ZnCl_2$ (203 mg, 1.23 mmol, 1 eq.) was added. The mixture was stirred at 40 ˚C for 18 h then concentrated *in vacuo* to leave a yellow oil. CH_2Cl_2 (20 mL) was added followed by $NaHCO_3$ (aq.) (15 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (1:49, MeOH/CH_2Cl_2) afforded esters **47a** and **47b** (235 mg, 1.05 mmol, 86%, *dr* 35:65) as a pale yellow oil. R_f 0.47 (MeOH/CH_2Cl_2, 1:9); ν_{max}/cm^{-1} (neat) 3505 (OH), 1730 (C=O), 1596 (pyr), 1452 (CH_3), 1255 (CH), 1175 (C-O), 1116 (C-O), 840 (C-O-C); ***47a*****:** δ_H ($CDCl_3$, 400 MHz) 8.40-8.35 (2H, NCH), 7.49 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.89 (3H, s, OCH_3), 3.43 (1H, q, *J* 7.0 Hz, ArCH), 2.38 (3H, s, $ArCH_3$), 1.20 (3H, s, COHCH_3), 1.18 (3H, d, *J* 7.0 Hz, ArCHCH_3); δ_C ($CDCl_3$, 100 MHz) 177.30 (s), 150.60 (d), 149.45 (s), 147.38 (d), 131.81 (s), 123.08 (d), 76.87 (s), 53.12 (q), 40.53 (d), 24.59 (q), 16.90 (q), 16.20 (q). ***47b*****:** δ_H ($CDCl_3$, 400 MHz) 8.40-8.35 (2H, NCH), 7.47 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.54 (3H, s, OCH_3), 3.35 (1H, q, *J* 7.2 Hz, ArCH), 2.30 (3H, s, $ArCH_3$), 1.55 (3H, s, COHCH_3), 1.35 (3H, d, *J* 7.0 Hz, ArCHCH_3); δ_C ($CDCl_3$, 100 MHz) 176.69 (s), 150.64 (d), 150.53 (s), 147.46 (d), 130.73 (s), 122.05 (d), 76.42 (s), 52.41 (q), 40.90 (d), 25.31 (q), 16.24 (q), 14.92 (q); MS (ESI) *m/z* 224 (MH^+, 100), 225 (13); HRMS (ESI) 224.1281 calcd for $C_{12}H_{18}NO_3^+$ (MH^+), found 224.1281, Δ = 0.0 ppm.

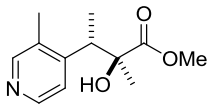
(-)- (2*S*,3*R*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate (47a)



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

After the above procedure a small sample of (-)-(*S*,*R*)-ester **47a** was isolated as white crystals by chiral HPLC using an analytical IC column (see Appendix). Data as above. mp 54-56 ˚C (CH_2Cl_2); $[\alpha]^{25}_D$ -8.4 (*c* = 0.33, CH_2Cl_2).

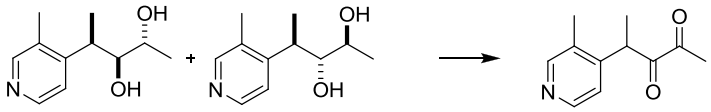
(+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate (47b)



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

After the above procedure a small sample of (+)-(*S*,*S*)-ester **47b** was isolated as a white soide by chiral HPLC using a semi-prep OD-H column. Data as above. mp 55-57 ˚C (CH_2Cl_2); $[\alpha]^{25}_D$ +11.2 (*c* = 0.92, CH_2Cl_2).

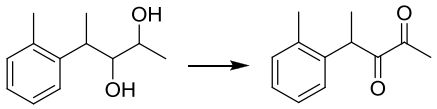
(±)-4-(3-Methylpyridin-4-yl)pentane-2,3-dione (48)



Chemical Formula: $C_{11}H_{13}NO_2$
Molecular Weight: 191.2264

Oxalyl chloride (464 µL, 3.21 mmol, 2.2 eq.) in CH_2Cl_2 (2 mL) was cooled to – 78 ˚C. DMSO (278 µL, 6.42 mmol, 4.4 eq) was added and the solution stirred for 5 min. 1,2-Diol **82** (290 mg, 1.49 mmol, 1 eq.) in CH_2Cl_2 (1.5 mL) was added dropwise and the solution was stirred for a further 15 min. Triethylamine (1.24 mL, 8.94 mmol, 6 eq.) was added dropwise. After 3 min the reaction mixture was quickly pushed onto a short silica column while the solution was transferred *via* a pipette and then the column was eluted with CH_2Cl_2. Purification by FC ($MeOH/CH_2Cl_2$, 0:100 to 1:99) afforded 1,2-diketone **48** (214 mg, 1.12 mmol, 75%) as a bright yellow liquid. R_f 0.45 ($MeOH/CH_2Cl_2$, 1:19); ν_{max}/cm^{-1} (neat) 2982 (CH_3), 2930 (CH_3), 1716 (C=O), 1594 (pyr), 1405 (CH), 1031 (pyr), 954 (CH); δ_H ($CDCl_3$, 400 MHz) 8.59 (1H, s, NCH), 8.52 (1H, d, *J* 5.6 Hz, NC*H*CH), 7.31 (1H, d, *J* 5.6 Hz, NCHC*H*), 4.84 (1H, q, *J* 7.0 Hz, ArCH), 2.54 (3H, s, $ArCH_3$), 2.34 (3H, s, $COCH_3$), 1.45 (3H, d, *J* 7.0 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 197.72 (s), 196.89 (s), 151.56 (d), 147.90 (d), 146.13 (s), 131.68 (s), 121.19 (d), 40.43 (d), 24.34 (q), 16.22 (q), 15.94 (q); MS (ESI) *m/z* 192 (MH^+, 100), 193 (16), 233 (7), 251 (6); HRMS (ESI) 192.1019 calcd for $C_{11}H_{14}NO_2^+$ (MH^+), found 192.1020, Δ = +0.5 ppm.

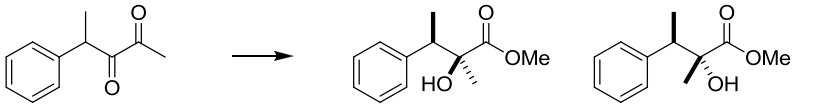
(±)-4-*ortho*-Tolylpentane-2,3-dione (52)



Chemical Formula: $C_{12}H_{14}O_2$
Molecular Weight: 190.2384

Solid IBX (10.1 g, 59% pure by ^{1}H NMR, 21.2 mmol, 2.5 eq.) was added to 1,2-diol **104** (1.65 g, 8.48 mmol, 1 eq.) in DMSO (10 mL) and the mixture was stirred at room temperature for 19 h. The resulting suspension was passed through a pad of Celite® washing with CH_2Cl_2. The filtrate was washed with water (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a bright yellow oil. Purification by FC (CH_2Cl_2/hexane, 1:4) afforded 1,2-diketone **52** (1.30 g, 6.83 mmol, 80%) as a bright yellow liquid. R_f 0.86 (CH_2Cl_2); ν_{max}/cm^{-1} (neat)2931 (CH_3), 2873 (CH_3), 1712 (C=O), 1453 (CH_3), 1355 (CH), 1029 (aromatic); δ_H ($CDCl_3$, 400 MHz) 7.20 (1H, m, ArH), 7.15 (2H, m, ArH), 6.94 (1H, m, ArH), 4.77 (1H, q, *J* 6.8 Hz, ArC*H*CH_3), 2.46 (3H, s, ArCH_3), 2.24 (3H, s, $COCH_3$), 1.38 (3H, d, *J* 6.8 Hz, ArCHCH_3); δ_C ($CDCl_3$, 100 MHz) 199.32 (s), 198.39 (s), 136.89 (s), 136.56 (s), 131.23 (d), 127.43 (d), 126.72 (d), 126.52 (d), 40.96 (d), 24.80 (q), 19.63 (q), 16.26 (q); MS (EI) *m/z* 190 (M$^+$, 13), 147 (14), 119 (100), 85 (16), 71 (18); HRMS (EI) 190.0994 calcd for $C_{12}H_{14}O_2$, found 190.0991, Δ = -1.6 ppm.

(2*S,3*R**)-** and **(2*R**,3*R**)-Methyl 2-hydroxy-2-methyl-3-phenylbutanoate (52a** and **53b)**[30]

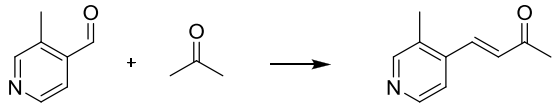


Chemical Formula: $C_{12}H_{16}O_3$
Molecular Weight: 208.2536

Typical procedure (entry 3, **Table 2.24**):

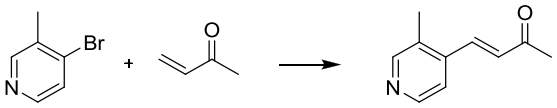
$CuCl_2$ (15 mg, 0.114 mmol, 1 eq.) and 2,6-lutidine (13 µL, 0.114 mmol, 1 eq.) were added to 1,2-diketone **52** (20 mg, 0.114 mmol, 1 eq.) in MeOH (2 mL). The mixture was stirred at 40 °C for 66 h then diluted with CH_2Cl_2 (15 mL) and washed with brine (15 mL). The organic layer was dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (CH_2Cl_2) afforded ester **53** (23 mg, 0.109 mmol, 97%, *dr* 47:53) as a clear oil. Data was consistent with that previously reported.[30] ***53a*****:** δ_H ($CDCl_3$, 400 MHz) 7.37-7.23 (5H, ArH), 3.79 (3H, s, OCH_3), 3.13 (1H, m, ArCH), 1.53 (3H, s, C(OH)C*H*$_3$), 1.43 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$). ***53b*****:** δ_H ($CDCl_3$, 400 MHz) 7.37-7.23 (5H, ArH), 3.63 (3H, s, OCH_3), 3.13 (1H, m, ArCH), 1.28 (3H, d, *J* 7.0 Hz, ArCHC*H*$_3$), 1.24 (3H, s, C(OH)C*H*$_3$). MS (EI) *m/z* 208 (8, M$^+$), 105 (100), 91 (31), 43 (43).

(*E*)-4-(3-Picoline)but-3-en-2-one (54)



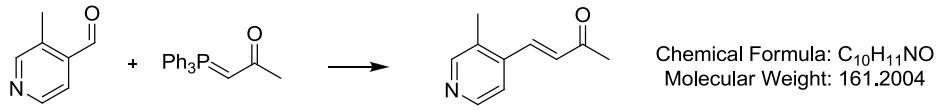
4-Carbaldehyde-3-picoline (150 mg, 1.24 mmol, 1 eq.) and acetone (128 µL, 1.74 mmol, 1.4 eq.) in EtOH (0.75 mL) and water (1.85 mL), was cooled to -10 °C. 10% NaOH (aq.) (1.51 mL) was added dropwise. The reaction was warmed to -4 °C over 50 min and was then neutralised with 1M HCl. 15% HCl/MeOH (15 mL) was added and the mixture was refluxed for 3 h. After allowing to cool to room temperature, the reaction mixture was neutralised with 1M NaOH and sat. $NaHCO_3$ (aq.) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo* to leave a yellow oil. Purification by FC (EtOAc/Et_2O, 1:4 to 3:2) afforded enone **54** (124 mg, 0.768 mmol, 62%) as a pale yellow oil. R_f 0.35 (EtOAc/Et_2O, 1:4); ν_{max} / cm^{-1} (neat) 3392 (NH), 1674 (C=O), 1618 (C=N), 1361 ($COCH_3$); δ_H ($CDCl_3$, 400 MHz) 8.51 (2H, m, NC*H*), 7.70 (1H, d, *J* 16 Hz, COCHC*H*), 7.38 (1H, d, *J* 5.1 Hz, NCHC*H*), 6.77 (1H, d, *J* 16 Hz, COC*H*CH), 2.43 (6H, s, CH_3); δ_C ($CDCl_3$, 400 MHz) 197.60 (s), 151.87, 150.01, 148.08, 147.99, 137.80, 132.13, 120.07, 28.17 (q), 16.47 (q); MS (EI) *m/z* 161 (M^+, 48), 146 (100), 117 (37), 91 (22); HRMS (EI) 161.0841 calcd for $C_{10}H_{11}NO$ (M^+), found 161.0836, Δ = -3.1 ppm.

or



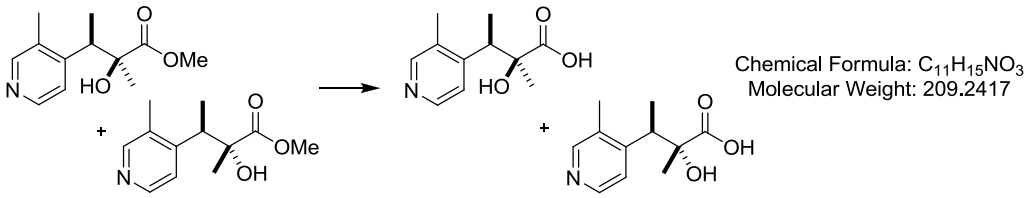
4-Bromo-3-picoline (54 mg, 0.314 mmol, 1 eq.) and MVK (90 µL, 1.26 mmol, 4 eq.) in DMF (1 mL) was added to a mixture of $Pd(OAc)_2$ (7 mg, 0.0314 mmol, 0.1 eq.), PPh_3 (31 mg, 0.126 mmol, 0.4 eq.) and $^iPr_2EtN$ (107 µL, 0.628 mmol, 2 eq.) in DMF (0.5 mL). The mixture was heated at 110 °C for 40 h then allowed to cool to room temperature and diluted with EtOAc. The suspension was passed through a plug of Celite® then concentrated *in vacuo*. Purification by FC (EtOAc/hexane, 1:19 to 1:4) afforded enone **54** (7 mg, 0.0434 mmol, 14%) as a pale yellow oil. Data as above.

or



Aldehyde **69** (518 mg, 4.28 mmol, 1 eq.) and ylide **71** (2.88 g, 5.56 mmol, 1.3 eq.) were dissolved in water (20 mL) and heated at 100 °C for 2 h. After allowing to cool to room temperature, the aqueous solution was extracted with CH_2Cl_2 (4 x 30 mL) and the combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a pale yellow solid. Purification by FC (EtOAc/hexane, 1:9 to 1:4) afforded enone **54** (380 mg, 2.36 mmol, 55%) as a pale yellow oil. Data as above.

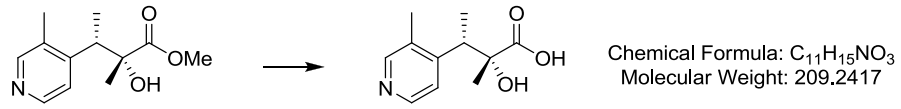
(2*S,3*R**)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid** and **(2*R**,3*R**)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (55a** and **55b)**



Ester **47** (27 mg, 0.121 mmol, *dr* 45:55) was dissolved in MeOH (2.7 mL) and 2M NaOH (2.7 mL) was added. The solution was stirred at 65 °C for 2 h after which time it had turned pale yellow. The solution was acidified to pH 5 with 2M HCl then concentrated *in vacuo* to leave a white solid. MeCN (10 mL) was added and the solution was sonicated for 15 min. The resulting suspension was purified by reverse phase C18 FC (MeCN) to afford monoacid **55** (21 mg, 0.100 mmol, 83%, *dr* 45:55) as a white solid. Rf 0.15 (MeCN/H_2O, 4:1); mp 108-109 °C (MeCN); ν_{max}/cm^{-1} (neat) 3379 (OH), 2974 (CH), 1721 (C=O), 1636 (pyr), 1488 (pyr), 1254 (CH), 1167 (C-O), 829. ***55a*****:** δ_H (D_2O, 400 MHz) 8.54 (1H, s, NCH), 8.49 (1H, d, *J* 6.0 Hz, NC*H*CH), 8.08 (1H, d, *J* 6.2 Hz, NCHC*H*), 3.77 (1H, q, *J* 6.5 Hz, ArCH), 2.68 (1H, s, CCH_3OH), 2.54 (3H, s, $ArCH_3$), 1.26 (3H, d, *J* 7.7 Hz, $ArCHCH_3$), 1.22 (3H, s, CCH_3OH); δ_C (D_2O, 100 MHz) 161.58 (s), 146.80 (s), 137.21 (d), 139.62 (d), 136.38 (d), 125.70 (s), 48.03 (s), 40.59 (d), 22.62 (q), 15.26 (q), 13.14 (q). ***55b*****:** δ_H (D_2O, 400 MHz) 8.48 (1H, s, NCH), 8.45 (1H, d, *J* 5.5 Hz, NC*H*CH), 8.17 (1H, d, *J* 5.9 Hz, NCHC*H*), 3.70 (1H, q, *J* 6.5 Hz, ArCH), 2.51 (1H, s, CCH_3OH), 2.48 (3H, s, $ArCH_3$), 1.58 (3H, s, CCH_3OH), 1.33 (3H, d, *J* 7.0 Hz, $ArCHCH_3$); δ_C (D_2O, 100 MHz) 162.86 (s), 146.80 (s), 139.67 (d), 136.85 (d), 136.73 (d), 124.95 (s), 48.03 (s), 40.63 (d), 23.32 (q),

15.78 (q), 14.18 (q); MS (ESI) *m/z* 208 (22), 210 (MH^+, 100), 213 (34), 215 (13); HRMS (ESI) 210.1125 calcd for $C_{11}H_{16}NO_3^+$ (MH^+), found 210.1052, Δ = -3.4 ppm.

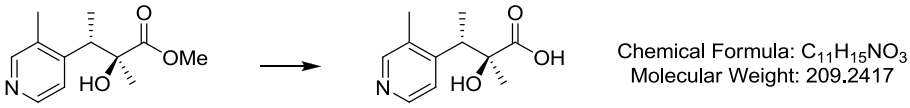
(+)-(2*S*,3*R*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (55a)



Chemical Formula: $C_{11}H_{15}NO_3$
Molecular Weight: 209.2417

Ester (-)-**47a** (9 mg, 0.0403 mmol) was dissolved in MeOH (0.9 mL) and 1M NaOH (1 mL) was added. The solution was heated at 60 °C for 1 h then concentrated *in vacuo* to remove MeOH. The aqueous solution was acidified to pH 5 with 1M HCl then concentrated under a flow of nitrogen to afford a white solid. MeCN (10 mL) was added and the mixture was sonicated for 15 min then passed through a pad of C18 silica eluting with MeCN. Concentration under a flow of nitrogen afforded monoacid (+)-**55a** (2.5 mg, 0.0119 mmol, 30%) as a clear oil. Data as above. $[\alpha]^{20}_D$ +31.6 (*c* = 0.25, MeCN).

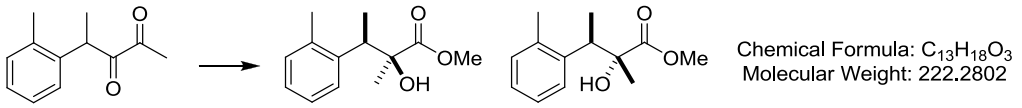
(-)-(2*S*,3*S*)-2-Hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoic acid (55b)



Chemical Formula: $C_{11}H_{15}NO_3$
Molecular Weight: 209.2417

Ester (+)-**47b** (13 mg, 0.0582 mmol) was dissolved in MeOH (1.3 mL) and 2M NaOH (1.3 mL) was added. The solution was heated at 60 °C for 1 h then concentrated *in vacuo* to remove all MeOH. The aqueous solution was acidified to pH 5 with 1M HCl then concentrated *in vacuo* to afford a white solid. MeCN (15 mL) was added and the mixture was sonicated for 15 min then passed through a pad of C18 silica eluting with MeCN to afford monoacid (-)-**55b** (10 mg, 0.0478 mmol, 82%) as a clear oil. Data as above. $[\alpha]^{20}_D$ -0.5 (*c* = 1.0, MeCN).

(2*S, 3*R**)-** and **(2*R**, 3*R**)-Methyl 2-hydroxy-2-methyl-3-*ortho*-tolylbutanoate (57a** and **57b)**



Chemical Formula: $C_{13}H_{18}O_3$
Molecular Weight: 222.2802

A typical procedure for a Lewis acid promoted BER (entry 1, **Table 2.14**):

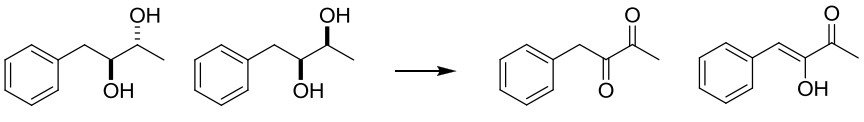
Diketone **56** (35 mg, 0.184 mmol, 1 eq.) was dissolved in MeOH and warmed to 40 °C before CuCl (18 mg, 0.184 mmol, 1 eq.) was added. The solution was held at 40 °C for 3

d, then diluted with CH_2Cl_2 (10 mL) followed by the addition of brine (10 mL). The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a yellow oil. Purification by FC (CH_2Cl_2) afforded an inseparable mixture of esters **57a** and **57b** (61 mg, 0.274 mmol, 80%, *dr* 45:55) as a clear oil. R_f 0.45 (CH_2Cl_2); ν_{max}/cm^{-1} (neat) 3521 (OH), 1733 (C=O), 1456 (CH_3), 1251 (ArH), 1162 (R_3COH). ***57a*****:** δ_H ($CDCl_3$, 400 MHz) 7.22-7.09 (4H, m, ArH), 3.87 (3H, s, OCH_3), 3.47 (1H, q, *J* 7.0 Hz, Ar*CH*CH_3), 2.40 (3H, s, $ArCH_3$), 1.22 (3H, s, COHCH_3), 1.20 (3H, d, *J* 7.1 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 177.99 (s), 140.25 (s), 135.13 (s), 130.17 (d), 128.22 (d), 126.43 (d), 126.12 (d), 77.53 (s), 53.06 (q), 24.53 (d), 19.68 (q), 16.74 (q), 15.41 (q). ***57b*****:** δ_H ($CDCl_3$, 400 MHz) 7.22-7.09 (4H, m, ArH), 3.52 (3H, s, OCH_3), 3.40 (1H, q, *J* 7.1 Hz, Ar*CH*CH_3), 2.32 (3H, s, $ArCH_3$), 1.54 (3H, s, COHCH_3), 1.36 (3H, d, *J* 7.1 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 177.24 (s), 141.27 (s), 136.25 (s), 130.03 (d), 127.28 (d), 126.48 (d), 126.07 (d), 76.92 (s), 52.30 (q), 24.95 (d), 20.39 (q), 16.75 (q), 15.41 (q). MS (EI) *m/z* 222 (M^+, 5), 119 (100), 84 (29), 49 (37); HRMS (EI) 222.1256 calcd for $C_{13}H_{18}O_3$ (M^+), found 222.1259, Δ = +1.4 ppm.

A typical procedure for a base promoted BER (entry 3, **Table 2.19**):

Diketone **56** (30 mg, 0.158 mmol, 1 eq.) was dissolved in MeOH (3 mL) and warmed to 40 °C. NaOH (50.5 mg, 1.262 mmol, 8 eq.) was added and the solution was stirred at 40 °C for a further 16 h. The solution was diluted with CH_2Cl_2 (10 mL) and brine was added (10 mL). The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave an orange oil. Purification by FC (CH_2Cl_2) afforded an inseparable mixture of esters **57a** and **57b** (12 mg, 0.054 mmol, 34%, *dr* 68:32) as a clear oil. Data as above.

1-Phenylbutane-2,3-dione and **(3*Z*)-3-Hydroxy-4-phenylbut-3-en-2-one (65)**[152]

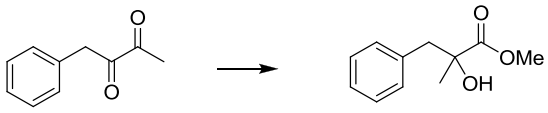


Chemical Formula: $C_{10}H_{10}O_2$
Molecular Weight: 162.1852

1,2-Diol **153** (85 mg, 0.511 mmol, 1 eq.) was dissolved in DMSO (1 mL) and IBX (358 mg, 1.28 mmol, 2.5 eq.) was added. The solution was allowed to stir at room

temperature for 16 h after which time it had turned bright yellow. CH_2Cl_2 (10 mL) was added and the suspension was passed through a plug of Celite® then washed with water (3 x 15 mL). The organic extract was dried over $MgSO_4$ then concentrated *in vacuo* to afford a bright yellow liquid. Purification by FC (CH_2Cl_2) afforded 1,2-diketone **65** (23 mg, 0.117 mmol, 23%, ketone:enol 45:55) as a bright yellow liquid. Data was consistent with that previously reported.[152] ***Dione*****:** R_f 0.65 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.87 (2H, d, *J* 7.4 Hz, ArH), 7.45-7.23 (3H, ArH), 4.08 (2H, s, $ArCH_2$), 2.35 (3H, s, $COCH_3$). ***Enol*****:** R_f 0.65 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.87 (2H, d, *J* 7.4 Hz, ArCH), 7.45-7.23 (3H, ArH), 6.49 (1H, d, *J* 0.84 Hz, ArCH), 2.55 (3H, s, $COCH_3$). MS (CI) *m/z* 163 (29, MH^+), 180 (100, MNH_4^+), 181 (24).

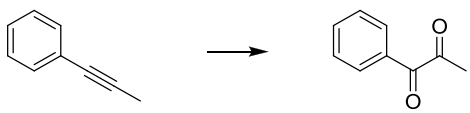
(±)-2-Hydroxy-2-methyl-3-phenyl-propionic acid methyl ester (66)[153]



Chemical Formula: $C_{11}H_{14}O_3$
Molecular Weight: 194.2271

Diketone **65** (3 mg, 0.0185 mmol, 1 eq.) was dissolved in MeOH (0.5 mL) and CuCl (2.7 mg, 0.0185 mmol, 1 eq.) was added. The mixture was heated at 50 °C for 20 h the concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (10 mL) then washed with sat. $NaHCO_3$ (aq.) (10 mL) and the organic extract was dried over $MgSO_4$ then concentrated *in vacuo* to afford a clear film. Purification by FC (CH_2Cl_2) afforded methyl ester **66** (3.1 mg, 0.0160 mmol, 86%) as a clear film. Data was consistent with that previously reported.[138,153] R_f 0.40 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.31-7.19 (5H, ArH), 3.76 (3H, s, OCH_3), 3.11 (1H, d, *J* 13 Hz, ArC*H*H), 3.04 (1H, s, OH), 2.94 (1H, d, *J* 13 Hz, ArCH*H*), 1.53 (3H, s, C(OH)CH_3); MS (CI) *m/z* 213 (13), 212 (100, MNH_4^+), 210 (16).

1-Phenyl-1,2-propanedione (67)[136]

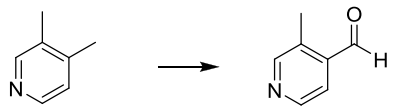


Chemical Formula: $C_9H_8O_2$
Molecular Weight: 148.1586

Alkyne **149** (0.5 mL, 3.99 mmol, 1 eq.) was dissolved in a mixture of CCl_4 (18 mL), MeCN (18 mL) and H_2O (27 mL). $NaIO_4$ (3.5 g, 16.4 mmol, 4.1 eq.) was added and the biphasic mixture was stirred vigorously for 5 min at room temperature before $RuO_2{\cdot}XH_2O$ (15 mg, 0.0828 mmol, 0.022 eq.) was added, turning the mixture black. After stirring for a further 1 h, H_2O (70 mL) was added and the organic layer was removed. The aqueous layer was further extracted with CH_2Cl_2 (3 x 40 mL) and the

combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FC (CH_2Cl_2) afforded diketone **67** (422 mg, 2.85 mmol, 72%) as a bright yellow liquid. Data was consistent with that previously reported.[154] R_f 0.70 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 8.04 (2H, d, *J* 8.1 Hz, *o*-H), 7.68 (1H, td, *J* 7.7 and 0.8 Hz, *p*-H), 7.53 (2H, t, *J* 7.4 Hz, *m*-H), 2.56 (3H, s, $C(O)CH_3$); MS (EI) *m/z* 148 (6, M^+), 105 (100, $[M\text{-}C(O)CH_3]^+$), 77 (62, $[M\text{-}(CO)_2CH_3]^+$), 51 (22).

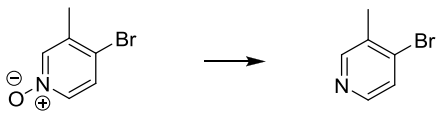
4-Carbaldehyde-3-picoline (69)[63]



Chemical Formula: C_7H_7NO
Molecular Weight: 121.1366

SeO_2 (9.09 g, 81.9 mmol, 2.3 eq.) was stirred in 1,4-dioxane (8 mL) at room temperature and 3,4-lutidine (4 mL, 35.6 mmol, 1 eq.) was added dropwise. The reaction mixture was heated at 105 °C for 20 h and was filtered while hot, washing with ether and hot water. The filtrate was concentrated *in vacuo,* then water (50 mL) was added and the resulting suspension was extracted with CH_2Cl_2 (3 x 50 ml). The organic extracts were combined and dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (EtOAc/hexane, 1:4) yielded 4-carbaldehyde-3-picoline (2.03 g, 16.8 mmol, 47%) as a pale yellow oil. Data was consistent with that previously reported.[63] R_f 0.42 (EtOAc/hexane, 1:4); δ_H ($CDCl_3$, 400 MHz) 10.34 (1H, s, CHO), 8.72 (1H, d, *J* 4.9 Hz, NC*H*CH), 8.65 (1H, s, NCH),7.62 (1H, d, J 4.9 Hz, NCHC*H*), 2.66 (3H, s, CH_3); MS (EI) *m/z* 121 (M^+, 100), 92 (73), 84 (60), 65 (48), 49 (78).

4-Bromo-3-picoline (70)[71]

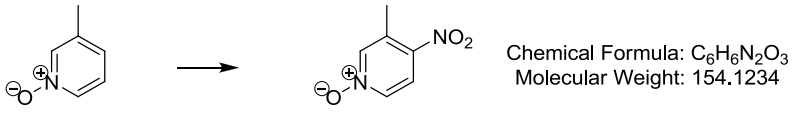


Chemical Formula: C_6H_6BrN
Molecular Weight: 172.0225

4-Bromo-3-picoline-*N*-oxide (300 mg, 1.60 mmol, 1 eq.) was dissolved in EtOAc (20 mL) and PBr_3 (0.60 mL, 6.38 mmol, 4 eq.) was added dropwise. The reaction was heated at 70 °C for 30 min then allowed to cool to room temperature and extracted with Et_2O (30 mL). The aqueous layer was basified to pH 10 with NaOH (aq.) then extracted with Et_2O (5 x 30 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC ($MeOH/CH_2Cl_2$, 1:49) afforded 4-bromo-3-picoline (210 mg, 1.22 mmol, 76%) as a pale yellow oil. Data was consistent with that previously reported.[71] R_f 0.35 ($MeOH/CH_2Cl_2$, 1:19); δ_H ($CDCl_3$,

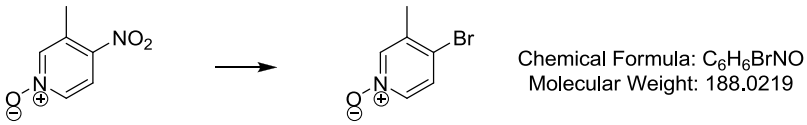
400 MHz) 8.44 (1H, s, NCH), 8.25 (1H, d, *J* 4 Hz, NC*H*CH), 7.50 (1H, d, *J* 4 Hz, NCHC*H*); MS (EI) *m/z* 173 (M^+, 98), 171 (M^+, 100), 92 (64), 65 (59).

4-Nitro-3-picoline-*N*-oxide (75)[69]



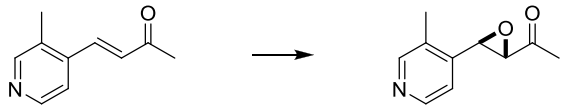
3-Picoline-*N*-oxide (10 g, 91.6 mmol) was dissolved in conc. H_2SO_4 (35 mL) and cooled to 0 °C. HNO_3 (27.5 mL) was added dropwise and the mixture was heated at 100 °C for 2 h. The reaction mixture was cooled to 0 °C and water was added dropwise followed by Na_2CO_3 (aq.) until no more precipitate formed. The mixture was filtered under suction washing with water to leave a pale yellow solid. The solid was purified by FC (EtOAc/hexane, 2:3 to 7:3) to yield 4-nitro-3-picoline-*N*-oxide (7.46 g, 48.4 mmol, 53%) as yellow crystals. Data was consistent with that previously reported.[69] R_f 0.55 ($MeOH/CH_2Cl_2$, 1:20); mp 135-136 °C ($CHCl_3$); δ_H ($CDCl_3$, 400 MHz) 8.15 (1H, s, NCH), 8.12 (1H, d, *J* 7.1 Hz, NC*H*CH), 8.03 (1H, d, *J* 7.1 Hz, NCHC*H*), 2.62 (3H, s, CH_3); MS (EI) *m/z* 154 (M^+, 100), 137 (11), 124 (9), 83 (15).

4-Bromo-3-picolin-*N*-oxide (77)[71]



4-Nitro-3-picoline-*N*-oxide (6.71 g, 43.6 mmol, 1 eq.) was dissolved in AcOH (92 mL) under a nitrogen atmosphere. AcBr (54.6 mL, 739 mmol, 17 eq.) was added dropwise and the reaction was stirred at 80 °C for 3 h, then allowed to cool to room temperature. Water (40 mL) was added and the mixture was neutralised with 1M NaOH and extracted with CH_2Cl_2 (5 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FC ($MeOH/CH_2Cl_2$, 1:20) afforded 4-bromo-3-picoline-*N*-oxide (7.60 g, 40.4 mmol, 93%) as a white solid. Data was consistent with that previously reported.[71] R_f 0.52 ($MeOH/CH_2Cl_2$, 1:9); δ_H ($CDCl_3$) 8.13 (1H, s, NCH), 7.96 (1H, d, *J* 6.2 Hz, NC*H*CH), 7.53 (1H, d, *J* 6.2 Hz, NCHC*H*), 2.34 (3H, s, CH_3); MS (EI) *m/z* 189 (M^+, 98), 187 (M^+, 100), 173 (24), 171 (25), 92 (21).

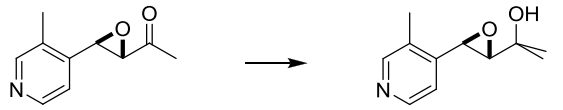
1-[(2*R,3*S**)-3-(3-Methylpyridin-4-yl)oxiran-2-yl]ethan-1-one (78)**



Chemical Formula: $C_{10}H_{11}NO_2$
Molecular Weight: 177.1998

Enone **54** (154 mg, 0.955 mmol, 1 eq.) was dissolved in MeOH (1.5 mL) and cooled to 0 °C. 35% H_2O_2 (aq.) (300 µL, 3.09 mmol, 3.3 eq.) was added dropwise followed by 2M NaOH (296 µL). The reaction was stirred at 0 °C for 15 min and then allowed to warm to room temperature. After 1.5 h, the reaction was quenched with sat. $Na_2S_2O_3$ (aq.) and neutralised with $NaHCO_3$ (aq.). The mixture was extracted with CH_2Cl_2 (4 x 25 mL) and the combined organic extracts were dried over $MgSO_4$, then concentrated *in vacuo* to leave a yellow oil. Purification by FC (EtOAc/Et_2O, 3:17) afforded epoxy ketone **78** (110 mg, 0.621 mmol, 65%) as a clear oil; R_f 0.27 (EtOAc/Et_2O, 3:7); δ_H ($CDCl_3$, 400 MHz) 8.48 (1H, d, *J* 5 Hz, NCH), 8.44 (1H, s, NC*H*CH), 7.14 (1H, d, *J* 5 Hz, NCHC*H*), 4.12 (1H, d, *J* 1.5 Hz, C*H*$COCH_3$), 3.39 (1H, d, *J* 1.5 Hz, ArC*H*), 2.38 (3H, s, ArCH_3), 2.25 (3H, s, $COCH_3$); δ_C ($CDCl_3$, 400 MHz) 203.41 (s), 150.66 (s), 148.18 (d), 142.31 (d), 130.95 (s), 118.29 (d), 62.12 (d), 54.50 (d), 24.93 (q), 25.65 (q); MS (EI) *m/z* 177 (M^+, 29), 134 (19), 120 (12), 107 (18), 85 (22), 43 (100); HRMS (EI) 177.0790 calcd for $C_{10}H_{11}NO_2$ (M^+), found 177.0788, Δ = -1.1 ppm

2-[(2*R,3*S**)3-(3-Methylpyridin-4-yl)oxiran-2-yl]propan-2-ol (80)**

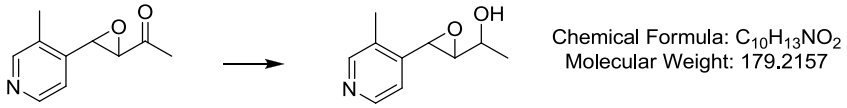


Chemical Formula: $C_{11}H_{15}NO_2$
Molecular Weight: 193.2423

Epoxy ketone **78** (61 mg, 0.344 mmol, 1 eq.) was dissolved in CH_2Cl_2 (2 mL) and water (25 µL, 1.38 mmol, 4 eq.) and then cooled to -78 °C. Me_3Al (2M solution in hexane, 690 µL, 1.38 mmol, 4 eq.) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h then allowed to warm to 0 °C and stirred for a further 1 h. The reaction was quenched with sat. NH_4Cl (aq.) and allowed to warm to room temperature. The mixture was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a yellow oil (123 mg). Purification by FC (EtOAc/Et_2O, 1:4 to 1:1) afforded epoxy alcohol **80** (54 mg, 0.279 mmol, 81%) as a clear oil. R_f 0.20 (EtOAc/Et_2O, 1:4); ν_{max}/cm^{-1} (neat) 3229 (OH), 2974 (CH_3), 1601 (C=N), 1451 (C=C), 1408 (CH), 1378 (epoxide), 1186 (C-O),1105 (C-O); δ_H ($CDCl_3$, 400 MHz) 8.44 (1H, d, *J* 5.0 Hz, NC*H*CH), 8.39 (1H, s, NCH), 7.17 (1H, d, *J* 5.0 Hz,

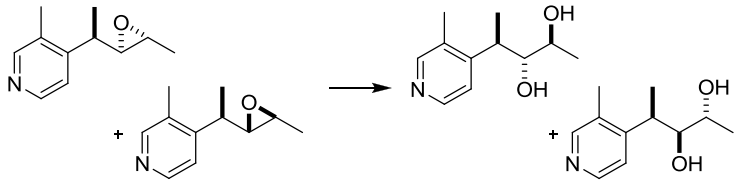
NCHC*H*), 4.09 (1H, d, *J* 2.1 Hz, ArCH), 2.86 (1H, d, *J* 2.1 Hz, C*H*COH(CH_3)$_2$), 2.39 (3H, s, ArCH_3), 1.42 (3H, s, COH(CH_3)$_2$), 1.36 (3H, s, COH(CH_3)$_2$); δ_C ($CDCl_3$, 400 MHz) 149.88, 147.69, 144.94, 130.66 (s), 118.50 (d), 68.43 (d), 67.72 (s), 52.26 (d), 27.72 (q), 25.27 (q), 15.78 (q); MS (Cl^+) *m/z* 210 (MNH_4^+,48), 194 (MH^+, 100); HRMS (Cl^+) 194.1176 calcd for $C_{11}H_{16}NO_2$ (MH^+), found 194.1182, Δ = +3.1 ppm.

(*R)-1-[(2*R**,3*R**)-** and **(*S**)-1-[(2*R**,3*R**)-3-(3-Methylpyridin-4-yl)oxiran-2-yl]ethanol (81)**



Epoxy ketone **78** (369 mg, 2.08 mmol, 1 eq.) was dissolved in anhydrous MeOH (6 mL) and cooled to 0 °C. $NaBH_4$ (87 mg, 2.29 mmol, 1.1eq.) in MeOH (8 mL) was added dropwise and the reaction was stirred at 0 °C for 1 h 15 min, then at room temperature for a further 15 min. Water (5 mL) was added and the mixture was concentrated *in vacuo* to remove all MeOH, then extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil (393 mg). Purification by FC (EtOAc/Et_2O, 1:2 to 2:3) afforded epoxy alcohol **81** (311 mg, 1.73 mmol, 84%, *dr* 57:43) as a pale yellow oil. R_f 0.20 (EtOAc/Et_2O, 1:2); ν_{max} / cm^{-1} (neat) 3228 (OH), 2972 (CH_3), 1602 (C=N), 1450 (C=C), 1408 (CH), 1372 (epoxide), 1106 (C-O), 1060 (C-O). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.40 (1H, d, *J* 5.0 Hz, NCHC*H*), 8.35 (1H, s, NCH), 7.12 (1H, d, *J* 5.0 Hz, NC*H*CH), 4.12 (1H, qd, *J* 6.4 and 2.9 Hz, C*H*OH), 4.06 (1H, d, *J* 2.0 Hz, ArC*H*O), 2.90 (1H, m, ArCHC*H*), 2.36 (3H, s, ArCH_3), 1.35 (3H, d, *J* 6.4 Hz, CHOHCH_3); δ_C ($CDCl_3$, 400 MHz) 149.97 (d), 147.73 (d), 144.84 (d), 130.77 (s), 118.49 (s), 65.66 (d), 64.38 (d), 51.46 (d), 19.20 (q), 15.72 (q). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.40 (1H, d, *J* 5.0 Hz, NCHC*H*), 8.35 (1H, s, NCH), 7.12 (1H, d, *J* 5.0 Hz, NC*H*CH), 3.96 (1H, d, *J* 2.0 Hz, ArC*H*O), 3.89 (1H, qd, *J* 6.5 and 1.6 Hz, C*H*OH), 2.90 (1H, m, ArCHC*H*), 2.35 (3H, s, ArCH_3), 1.37 (3H, d, *J* 6.5 Hz, CHOHCH_3); δ_C ($CDCl_3$, 400 MHz) 150.02 (d), 147.80 (d), 144.58 (d), 130.73 (s), 118.51 (s), 66.96 (d), 66.05 (d), 53.02 (d), 20.02 (q), 15.72 (q). MS (EI) *m/z* 179 (M^+, 9), 163 (21), 136 (71), 122 (100), 106 (27), 94 (29), 58 (62); HRMS (EI) 179.0946 calcd for $C_{10}H_{13}NO_2$ (M^+), found 179.0942, Δ = -2.2 ppm.

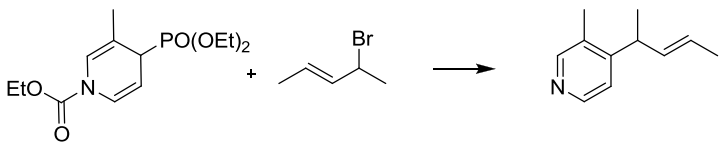
(2*S,3*R**,4*R**)-** and **(2*R**,3*S**,4*R**)-4-(3-Methylpyridin-4-yl)pentane-2,3-diol (82)**



Chemical Formula: $C_{11}H_{17}NO_2$
Molecular Weight: 195.2582

Epoxide **81** (1.60 g, 9.02 mmol, 1 eq., *dr* 52:48) was dissolved in MeCN (19 mL) and water (9.6 mL). 60% $HClO_4$ (1.6 mL) was added dropwise and the solution was stirred at room temperature for 40 h. The solution was neutralised with sat. $NaHCO_3$ (aq.) then concentrated *in vacuo* to remove all MeCN. The remaining aqueous solution was extracted with CH_2Cl_2 (4 x 30 mL) and the combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a pale yellow oil. Purification by FC ($MeOH/CH_2Cl_2$, 1:19) afforded 1,2-diol **82** (1.469 g, 7.52 mmol, 83%, *dr* 52:48) as a clear oil. R_f 0.34 ($MeOH/CH_2Cl_2$, 1:9); ν_{max}/cm^{-1} (neat) 3331 (OH), 2969 (CH_3), 2926 (CH_3), 1600 (pyridyl), 1074 (C-O), 734 (pyridyl). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.40-8.30 (2H, NCH), 7.16 (1H, d, *J* 5.2 Hz, NCHC*H*), 4.00 (1H, qd, *J* 6.4 and 3.7 Hz, C*H*OHCH$_3$), 3.87 (1H, dd, *J* 9.0 and 3.6 Hz, ArCHC*H*OH), 3.19-3.07 (1H, ArCH), 2.37 (3H, s, ArCH$_3$), 1.19 (3H, d, *J* 7.0 Hz, ArCHC*H*$_3$), 1.16 (3H, d, *J* 6.3 Hz, CHOHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 152.42 (s), 150.49 (d), 147.35 (d), 132.43 (s), 121.06 (d), 78.61 (d), 68.00 (d), 37.05 (d), 16.99 (q), 16.64 (q), 16.01 (q). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.40-8.30 (2H, NCH), 7.21 (1H, d, *J* 5.1 Hz, NCHC*H*), 3.81 (1H, dd, *J* 7.2 and 4.4 Hz, ArCHC*H*OH), 3.71 (1H, qd, *J* 6.3 and 4.5 Hz, C*H*OHCH$_3$), 3.19-3.07 (1H, ArCH), 2.33 (3H, s, ArCH$_3$), 1.34 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$), 1.30 (3H, d, *J* 6.3 Hz, CHOHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 152.09 (s), 150.90 (d), 147.42 (d), 130.86 (s), 121.69 (d), 77.46 (d), 68.17 (d), 36.47 (d), 17.56 (q), 16.62 (q), 16.28 (q). MS (ESI) *m/z* 196 (MH^+, 100), 179 (4), 178 (7), 150 (3); HRMS (ESI) 196.1332 calcd for $C_{11}H_{18}NO_2$ (MH^+), found 196.1336, Δ = +2.4 ppm.

(±)-3-Methyl-4-[(*E*)-pent-3-en-2-yl]pyridine (83)

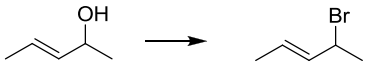


Chemical Formula: $C_{11}H_{15}N$
Molecular Weight: 161.2435

Phosphonate ester **96** (9.74 g, 30.45 mmol, 1 eq.) was dissolved in THF (60 mL) and cooled to -78 ˚C. ^{n}BuLi (1.6 M solution in THF, 20.9 mL, 33.5 mmol, 1.1 eq.) was added dropwise and the brown solution was stirred at -78 ˚C for 40 min. Allylic bromide **84**

(5.00 g, 33.5 mmol, 1.1 eq.) in THF (5 mL) was added dropwise and after 30 min the reaction mixture was allowed to warm to 0 ˚C and stirred for another 40 min. The mixture was cooled down to -78 ˚C again and ^{n}BuLi (1.6 M solution in THF, 41.8 mL, 67.0 mmol, 2.2 eq.) was added. After the addition, the solution was allowed to warm to 0 ˚C and stirred for another 45 min. Et_2O (20 mL) was added, followed by water (5 mL). The mixture was concentrated *in vacuo* to leave an orange/yellow liquid. Purification by FC (1:9 to 1:3, EtOAc/hexane) afforded alkene **83** (2.60 g, 16.1 mmol, 53%) as a pale yellow liquid. R_f 0.18 (EtOAc/hexane, 3:7); ν_{max}/cm^{-1} (neat) 2965 (CH_3), 2929 (CH_3), 2874 (CH_3), 1593 (C=C), 1451 (pyridine), 1404 (pyridyl), 966 (CH), 834 (CH); δ_H ($CDCl_3$, 400 MHz) 8.36 (1H, d, *J* 5.1 Hz, NC*H*CH), 8.31 (1H, s, NC*H*), 7.07 (1H, d, *J* 5.1 Hz, NCHC*H*), 5.33-5.38 (2H, C*H*C*H*CH_3), 3.58 (1H, p, *J* 6.9 Hz, ArC*H*), 2.27 (3H, s, ArCH_3), 1.66 (3H, dt, *J* 6.1 and 1.2 Hz, CHCHCH_3), 1.29 (3H, d, *J* 7.1 Hz, ArCHCH_3); δ_c ($CDCl_3$, 100 MHz) 152.97 (s), 150.81 (d), 147.81 (d), 133.78 (d), 130.99 (s), 125.02 (d), 120.92 (d), 37.52 (d), 20.01 (q), 17.88 (q), 16.08 (q); MS (ESI) *m/z* 162 (MH^+, 100), 155 (4), 150 (4), 147 (4); HRMS (ESI) 162.1277 calcd for $C_{11}H_{16}N^+$ (MH^+), found 162.1275, Δ = -1.2 ppm.

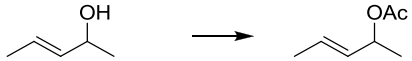
(±)-(*E*)-4-Bromopent-2-ene (84)[155]



Chemical Formula: C_5H_9Br
Molecular Weight: 149.0290

3-Penten-2-ol (1 mL, 9.79 mmol, 1 eq.) was dissolved in Et_2O (6 mL) and cooled to 0 °C. PBr_3 (0.92 mL, 9.79 mmol, 1 eq.) was added dropwise. The solution was stirred at 0 °C for 2 h then allowed to warm to room temperature and stirred for a further 1 h. The yellow solution was cooled to 0 °C again and water (10 mL) was added dropwise. The aqueous layer was removed and the organic layer washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated under a flow of nitrogen to afford allylic bromide **84** (986 mg, 6.62 mmol, 68%) as a pale yellow liquid. Data was consistent with that previously reported.[156] δ_H ($CDCl_3$, 400 MHz) 5.90-5.70 (2H, C*H*C*H*), 4.73 (1H, p, *J* 6.8 Hz, CHBr), 1.79 (3H, d, *J* 6.6 Hz, C*H*BrCH_3), 1.73 (3H, d, *J* 5.0 Hz, CHCHCH_3); MS (EI) *m/z* 151 (MH^+, 9), 149 (MH^+, 7), 111 (14), 109 (17), 97 (23), 95 (22), 82 (98), 80 (100), 71 (39), 69 (54), 57 (56).

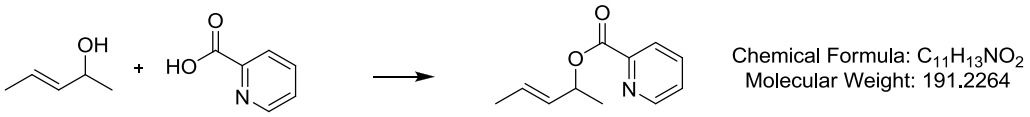
(±)-(*E*)-pent-3-en-2-yl acetate (85)[157]



Chemical Formula: $C_7H_{12}O_2$
Molecular Weight: 128.1690

3-Penten-2-ol (4 mL, 39.2 mmol, 1 eq.) was dissolved in Et_2O (40 mL). Pyridine (3.41 mL, 43.1 mmol, 1.1 eq.) was added followed by Ac_2O (4.07 mL, 43.1 mmol, 1.1 eq.). The solution was stirred at room temperature for 40 h then washed with 10% $CuSO_4$ (aq.) (2 x 20 mL). The organic layer was dried over $MgSO_4$ then concentrated under a flow of nitrogen to afford allylic acetate **85** (3.42 g, 27.1 mmol, 69%) as a clear oil. Data was consistent with that previously reported.[157] δ_H ($CDCl_3$, 400 MHz) 5.76 (1H, ddd, *J* 15, 6.3 and 0.8 Hz, CH=CH), 5.51 (1H, ddq, *J* 15, 5.4 and 1.5 Hz, CH=CH), 5.33 (1H, p, *J* 6.5 Hz, C*H*OAc), 2.07 (3H, s, C(O)CH_3), 1.72 (3H, dt, *J* 7.3 and 0.8 Hz, $CHCH_3$), 1.31 (3H, d, *J* 6.5 Hz, CH(OAc)CH_3).

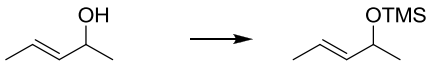
(±)-(*E*)-Pent-3-en-2-yl picolinate (86)[158]



Chemical Formula: $C_{11}H_{13}NO_2$
Molecular Weight: 191.2264

2-Picolinic acid (2.89 g, 23.4 mmol, 1.2 eq.), DCC (5.25 g, 25.4 mmol, 1.3 eq.) and 4-DMAP (2.87 g, 23.4 mmol, 1.2 eq.) were dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. 3-Penten-2-ol (2 mL, 19.6 mmol, 1 eq.) was added dropwise and after 10 min the reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The reaction mixture was passed through a plug of silica eluting with CH_2Cl_2 and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (CH_2Cl_2) afforded (*E*)-pent-3-en-2-yl picolinate (3.56 g, 18.6 mmol, 95%) as a clear oil. R_f 0.60 (MeOH/CH_2Cl_2, 1:9); δ_H ($CDCl_3$, 400 MHz) 8.78 (1H, dd, *J* 4.1 and 1.7 Hz, NCH), 8.14 (1H, dd, *J* 7.8 and 1.1 Hz, NCCH), 7.84 (1H, dt, *J* 7.8 and 1.7 Hz, NCHCHC*H*), 7.47 (1H, ddd, *J* 1.1, 4.8 and 7.7 Hz, NCHC*H*), 5.86 (1H, m, C*H*CH_3), 5.67 (2H, m, CHO and CHOC*H*), 1.72 (3H, d, *J* 6.8 Hz, CHOCH_3), 1.49 (3H, d, *J* 6.2 Hz, $CHCH_3$); δ_C ($CDCl_3$, 400 MHz) 164.44 (s), 149.82 (d), 148.53 (s), 136.86 (d), 130.34 (d), 129.03 (d), 126.63 (d), 125.02 (d), 72.94 (d), 20.30 (q), 17.64 (q); MS (EI) *m/z* 190 (M^+, 1), 146 (23), 124 (42), 120 (28), 106 (54), 78 (90), 69 (100).

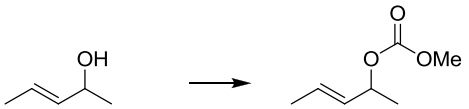
(±)-[(*E*)-pent-3-en-2-yloxy]trimethylsilane (87)[159]



Chemical Formula: $C_8H_{18}OSi$
Molecular Weight: 158.3134

3-Penten-2-ol (0.2 mL, 1.96 mmol, 1 eq.) was dissolved in pyridine (0.33 mL) and cooled to 0 °C. TMSCl (273 µL, 2.15 mmol, 1.1 eq.) was added dropwise then the reaction mixture was allowed to warm to room temperature. Et_2O (2 mL) was added to dissolve the white precipitate and the solution was stirred at room temperature for a further 2.5 h. The reaction was quenched with water (1 mL) and after addition of Et_2O (10 mL), the organic layer was washed with 5% $CuSO_4$ (aq.) (2 x 15 mL). The organic layer was dried over $MgSO_4$ then concentrated under a flow of nitrogen to afford TMS ether **87** (200 mg, 1.41 mmol, 72%) as a clear oil. Data was consistent with that previously reported.[159] δ_H ($CDCl_3$, 400 MHz) 5.62-5.47 (2H, CH=CH), 4.26 (1H, p, *J* 6.3 Hz, CHOTMS), 1.69 (3H, dt, *J* 6.0 and 0.88 Hz, CH=CHC*H*$_3$), 1.23 (3H, d, *J* 6.2 Hz, CH(OTMS)C*H*$_3$), 0.14 (9H, s, Si(CH_3)$_3$).

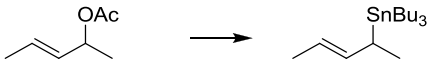
(±)-Methyl (*E*)-pent-3-en-2-yl carbonate (88)[160]



Chemical Formula: $C_7H_{12}O_3$
Molecular Weight: 144.1684

3-Penten-2-ol (0.5 mL, 4.89 mmol, 1 eq.) was dissolved in Et_2O (5 mL) and pyridine (435 µL, 5.38 mmol, 1.1 eq.) and cooled to 0 °C. Methyl chloroformate (416 µL, 5.38 mmol, 1.1 eq.) was added dropwise and the mixture was allowed to warm to room temperature and stirred for a further 17 h. The mixture was filtered through a pad of Celite® then washed with 5% $CuSO_4$ (aq.) (2 x 30 mL). The organic layer was dried over $MgSO_4$ then concentrated under a flow of nitrogen to afford allylic formate ester **88** (371 mg, 2.57 mmol, 53%) as a pale yellow oil. Data was consistent with that previously reported.[160] δ_H ($CDCl_3$, 400 MHz) 5.80 (1H, m, CH=C*H*CH_3), 5.56 (1H, ddq, *J* 14, 6.8 and 1.4 Hz, C*H*=$CHCH_3$), 4.28 (1H, p, *J* 6.4 Hz, C*H*(OCO_2CH_3)), 3.78 (3H, s, OCH_3), 1.36 (3H, d, *J* 6.5 Hz, CH=CHC*H*$_3$), 1.27 (3H, d, *J* 6.3 Hz, C(OR)C*H*$_3$).

(±)-Tributyl[(*E*)-pent-3-en-2-yl]stannane (89)[161]

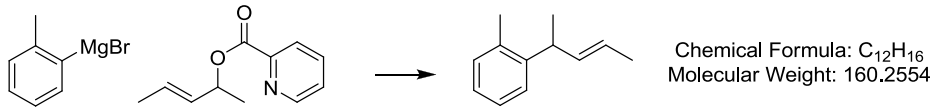


Chemical Formula: $C_{17}H_{36}Sn$
Molecular Weight: 359.1777

Bu_3SnH (6.2 mL, 11.7 mmol, 1.5 eq.) was dissolved in THF (10 mL) and cooled to 0 °C. ^{n}BuLi (2.5M solution in hexane, 4.7 mL, 11.5 mmol, 1.5 eq.) was added dropwise and

the solution was stirred at 0 °C for 20 min. After cooling to -78 °C, Et_2AlCl (1M solution in THF, 11.7 mL, 11.7 mmol, 1.5 eq.) was added and the solution was stirred at -78 °C for 1 h. A solution of $Pd(PPh_3)_4$ (225 mg, 0.195 mmol, 2.5 mol%) and allylic acetate **85** (982 mg, 7.67 mmol, 1 eq.) in THF (2 mL) was added and the mixture was stirred at 0 °C for 30 min then room temperature for 18 h. The mixture was cooled in an ice bath and quenched with 26% NH_3 (aq.) (2 mL). Water (20 mL) was added, then the mixture was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to afford a brown oil. Purification by FC (hexane) then washing the combined fractions with MeCN (2 x 40 mL) and concentrating *in vacuo*, afforded allylic stannane **89** (2.802 g, 5.46 mmol, 70%) contaminated with 30% tin impurities. Data was consistent with that previously reported.[161] δ_H ($CDCl_3$, 400 MHz) 5.69 (1H, m, CH=CH), 5.17 (1H, ddd, *J* 15, 6.4 and 1.4 Hz, CH=CH), 2.12 (1H, p, *J* 7.4 Hz, CHSn), 2.55-0.81 (33H, CH_3 and CH_2).

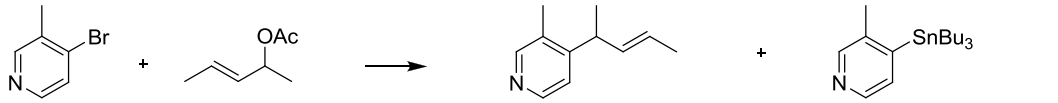
(±)-1-Methyl-2-[(*E*)-pent-3-en-2-yl]benzene (92)



2-Bromotoluene (990 µL, 8.23 mmol, 2 eq.) was added to magnesium turnings (200 mg, 8.23 mmol, 2 eq.) in THF (4.5 mL). The mixture was heated at 65 °C for 2 h, after which time all the magnesium turnings had been consumed. After the reaction mixture had cooled to room temperature, it was transferred to a solution of $CuBr{\cdot}SMe_2$ (842 mg, 4.11 mmol, 1 eq.) in THF (40 mL) at 0 °C and stirred for 30 min. The solution was then cooled to -78 °C and allylic ester **86** (786 mg, 4.11 mmol, 1 eq.) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was allowed to warm to 0 °C and was kept at this temperature for 1 h. The mixture was partitioned between Et_2O (30 mL) and water (25 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo* to leave a pale yellow liquid. Purification by FC (EtOAc/petroleum ether, 1:19) afforded alkene **92** (660 mg, 4.11 mmol, 99%) as a clear liquid. R_f 0.95 (EtOAc/petroleum ether, 1:20); ν_{max} / cm^{-1} (neat) 2966 ($ArCH_3$), 2931 ($ArCH_3$), 1654 (C=C), 1458 (CH_3); δ_H ($CDCl_3$, 400 MHz) 7.10–7.22 (4H, ArH), 5.61 (1H, ddd, *J* 1.5, 6.3 and 16 Hz, ArCHC*H*), 5.45 (1H, m, ArCHCHC*H*), 3.67 (1H, m, ArC*H*), 2.37 (3H, s, $ArCH_3$), 1.70 (3H, dt, *J* 6.3 and 1.1 Hz, ArCHCH_3), 1.34 (3H, d, *J* 6.9 Hz, CHCHCH_3);

δ_C ($CDCl_3$, 100 MHz)) 144.38, 135.86, 135.76, 132.41, 129.87, 129.35, 123.59, 123.59, 37.78 (d), 20.78 (q), 19.88 (q), 18.00 (q); MS (EI) *m/z* 160 (M^+, 38), 145 (100), 130 (18), 105 (17), 91 (19), 86 (53), 84 (84); HRMS (EI) 160.1252 calcd for $C_{12}H_{16}$ (M^+), found 160.1249, Δ = -1.9 ppm.

(±)-3-Methyl-4-[(*E*)-pent-3-en-2-yl]pyridine (83) and **4-(Tributylstannyl)-3-methylpyridine (94)**[162]

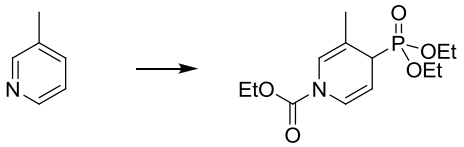


Chemical Formula: $C_{11}H_{15}N$
Molecular Weight: 161.2435

Chemical Formula: $C_{18}H_{33}NSn$
Molecular Weight: 382.17

$Pd(dppf)Cl_2$ (237 mg, 0.291 mmol, 5 mol%) was added to a solution of allylic acetate **85** (1.12 g, 8.72 mmol, 1.5 eq.) and 4-bromo-3-picoline (1 g, 5.81 mmol, 1 eq.) in DMF (4 mL). $(SnBu_3)_2$ (4.4 mL, 8.72 mmol, 1.5 eq.) was added and the reaction mixture was heated at 120 °C for 2 h. After allowing to cool to room temperature, the mixture was passed through a plug of silica and concentrated *in vacuo* to leave a dark oil. Purification by FC (EtOAc/hexane, 1:19 to 1:9) afforded alkene **83** (365 mg, 2.26 mmol, 39%) as a clear oil and aryl stannane **94** (459 mg, 1.20 mmol, 21%) as a clear oil. ***Alkene 83*****:** Data as above. ***Stannane 94*****:** Data was consistent with that previously reported.[162] R_f 0.50 (EtOAc/hexane, 1:4); δ_H ($CDCl_3$, 400 MHz) 8.34 (1H, s, NCH), 8.30 (1H, d, *J* 4.4 Hz, NC*H*CH), 7.41 (1H, d, *J* 4.4 Hz, NCHC*H*), 2.34 (3H, s, $ArCH_3$), 1.51 (6H, m, CH_2), 1.24 (6H, m, CH_2), 1.14 (6H, m, CH_2), 0.80 (9H, t, *J* 13 Hz, CH_2CH_3).

Diethyl 1-ethoxycarbonyl-1,4-dihydroxy-3-methylpyridine-4-phosphonate (96)

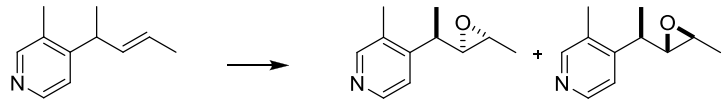


Chemical Formula: $C_{13}H_{22}NO_5P$
Molecular Weight: 303.2912

3-Picoline (3.56 mL, 36.6 mmol, 1 eq.) was dissolved in MeCN (23 mL) and cooled to 0 °C. Ethyl chloroformate (3.5 mL, 36.6 mmol, 1 eq.) was added dropwise and the red solution was stirred at 0 °C for 40 min. $P(OEt)_3$ (5.89 mL, 36.6 mmol, 1 eq.) was added dropwise and the solution was allowed to warm to room temperature and stirred for a further 17 h, after which time, a colour change to yellow was observed. The mixture was concentrated *in vacuo* to leave phosphonate **96** (9.76 g, 32.2 mmol, 88%) as a yellow oil. R_f 0.21 ($MeOH/CH_2Cl_2$, 1:19); ν_{max}/cm^{-1} 2982 (CH_3), 1716 (C=O), 1312 (C-N), 1018 (C-O), 958 (phosphonate), 746 (P-O-C); δ_H ($CDCl_3$, 400 MHz) 6.72 (1H, bd, *J* 42 Hz,

NCH), 6.53 (1H, bd, *J* 46 Hz, NCH), 4.78 (1H, bd *J* 24 Hz, NCHC*H*), 4.08 (2H, q, *J* 7.2 Hz, NCO_2CH_2), 3.95 (4H, m, $P(O)OCH_2$), 3.14 (1H, dd, *J* 27 and 4.7 Hz, PCH), 1.69 (3H, d, *J* 2.1 Hz, NCHCCH_3), 1.17-1.11 (9H, OCH_2CH_3); δ_c ($CDCl_3$, 100 MHz) 170.73 (s), 124.74 (d, *J* 27 Hz), 120.73 (d), 110.48 (d, *J* 46 Hz), 101.24 (d, *J* 46 Hz), 62.30 (t), 60.06 (t), 39.31 (d, *J* 145 Hz), 20.66 (q), 14.17 (q), 13.92 (q); δ_P ($CDCl_3$, 160 MHz) 21.20 (d, *J* 26 Hz); MS (ESI) *m/z* 230 ([M-COOEt]$^+$), 180 (9), 162 (12); HRMS (ESI) 230.0941 calcd for $C_{10}H_{17}NO_3P^+$ ([M-COOEt]$^+$), found 230.0940, Δ = -0.4 ppm.

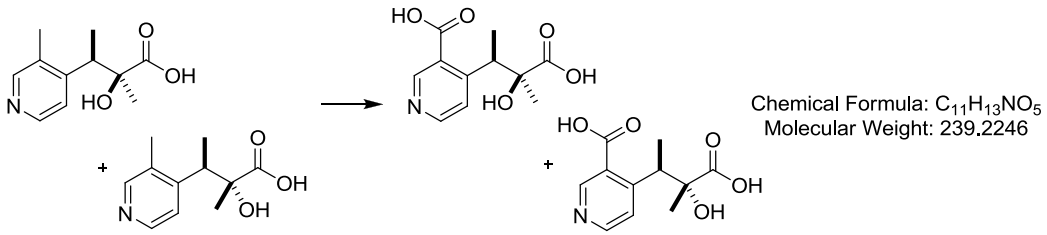
3-Methyl-4-((*R)-1-((2*S**,3*S**)-3-methyloxiran-2-yl)ethyl)pyridine** and **3-Methyl-4-((*R**)-1-((2*R**,3*R**)-3-methyloxiran-2-yl)ethyl)pyridine (99)**



Chemical Formula: $C_{11}H_{15}NO$
Molecular Weight: 177.2429

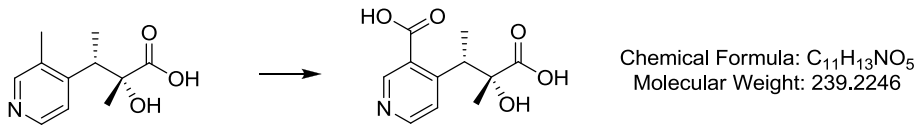
Alkene **83** (2.60 g, 16.1 mmol, 1 eq.) was dissolved in a mixture of THF (25 mL) and water (25 mL) and cooled to 0 ˚C. NBS (2.77 g, 16.1 mmol, 1 eq.) was added turning the solution yellow. After stirring at 0 ˚C for 1 h, $NaHCO_3$ (aq.) (30 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (5 x 20 mL) and the combined extracts dried over $MgSO_4$ then concentrated *in vacuo* to leave a mixture of bromohydrins as a cream solid. MeCN (20 mL) was added, followed by 1M NaOH (20 mL) and the solution was heated at 65 ˚C for 1 h. MeCN was removed *in vacuo* and the remaining aqueous solution was extracted with CH_2Cl_2 (4 x 60 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to afford epoxide **99** (2.40 g, 13.6 mmol, 84%*, dr* 52:48) as a clear oil. R_f 0.49 (MeOH/CH_2Cl_2, 1:9); ν_{max}/cm^{-1} (neat) 2970 (CH), 1594 (pyridyl), 1404 (CH_3), 1381 (CH_3), 902 (epoxide), 834 (epoxide). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.43 (1H, d, *J* 5.2 Hz, NC*H*CH), 8.38 (1H, s, NCH), 7.20 (1H, d, *J* 5.1 Hz, NCHC*H*), 2.97 (1H, p, *J* 6.8 Hz, ArCH), 2.87-2.79 (2H, CHO), 2.31 (3H, s, $ArCH_3$), 1.35-1.28 (6H, $CHCH_3$); δ_c ($CDCl_3$, 100 MHz) 150.94 (d), 150.09 (s), 147.83 (d), 131.49 (s), 120.92 (d), 62.46 (d), 53.47 (d), 36.21 (d), 17.52 (q), 16.73 (q), 16.34 (q). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 8.42 (1H, d, *J* 5.1 Hz, NC*H*CH), 8.39 (1H, s, NCH), 7.16 (1H, d, *J* 5.1 Hz, NCHC*H*), 3.06 (1H, p, *J* 7.1 Hz, ArCH), 2.87-2.79 (2H, CHO), 2.32 (3H, s, $ArCH_3$), 1.35-1.28 (6H, $CHCH_3$); δ_c ($CDCl_3$, 100 MHz) 151.03 (d), 150.45 (s), 147.90 (d), 131.04 (s), 121.16 (d), 62.74 (d), 53.47 (d), 36.54 (d), 17.47 (q), 16.73 (q), 16.31 (q). MS (ESI) *m/z* 178 (MH^+, 100), 155 (3), 150 (3); HRMS (ESI) 178.1226 calcd for $C_{11}H_{16}NO^+$ (MH^+), found 178.1228, Δ = +1.1 ppm.

4-[(2*R,3*S**)-** and **4-[(2*R**,3*R**)-3-Carboxy-3-hydroxybutan-2-yl]pyridine-3-carboxylic acid (101)**



Mono-acid **55** (30 mg, 0.143 mmol, 1 eq., *dr* 25:75) was dissolved in 1M NaOH (3 mL) and stirred at room temperature for 5 min. $KMnO_4$ (91 mg, 0.574 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature MeOH (10 mL) was added and the MnO_2 precipitate was removed by filtering under suction. The filtrated was concentrated *in vacuo* to afford a white solid. Salt removal of an aqueous solution by Ziptip® and concentration under a flow of nitrogen afforded diacid **101** (22 mg, 0.0920 mmol, 64%, *dr* 25:75) as a white solid. R_f 0.15 (MeCN/H_2O, 4:1); mp >250 ˚C (H_2O); ν_{max}/cm^{-1} (neat) 3397 (OH), 1603 (C=O), 1571 (C=O), 1397 (CH), 1387 (CH), 1163 (C-O); ***101a*****:** δ_H (D_2O, 400 MHz) 8.59 (1H, s, NCH), 8.53 (1H, d, *J* 5.8 Hz, NC*H*CH), 7.68 (1H, d, *J* 5.4 Hz, NCHC*H*), 3.82 (1H, q, *J* 7.2 Hz, ArCH), 1.30 (3H, d, *J* 7.1 Hz, ArCHCH_3). ***101b*****:** δ_H (D_2O, 400 MHz) 8.55 (1H, s, NCH), 8.51 (1H, d, *J* 5.7 Hz, NC*H*CH), 7.66 (1G, d, *J* 5.4 Hz, NCHC*H*), 3.80 (1H, q, *J* 6.4 Hz, ArCH), 1.39 (3H, d, *J* 7.2 Hz, ArCHCH_3), 1.39 (3H, s, ArCH_3); δ_C (D_2O, 100 MHz) 170.14 (s), 164.10 (s), 149.69 (d), 146.99 (d), 145.96 (d), 127.85 (s), 122.81 (s), 77.53 (s), 41.57 (q), 22.35 (d), 21.49 (q), 14.30 (q); MS (ESI) *m/z* 281 (22), 241 (13), 240 (100, MH^+); HRMS (ESI) 240.0866 calcd for $C_{11}H_{14}NO_5^+$ (MH^+), found 240.0870, Δ = +1.6 ppm.

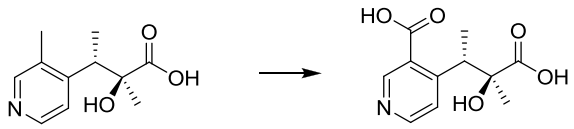
(+)-[(2*S*,3*R*)-3-Carboxy-3-hydroxybutan-2-yl]pyridine-3-carboxylic acid (101a)



Mono-acid **55** (2.0 mg, 0.00956 mmol, 1 eq.) was dissolved in 1M NaOH (0.5 mL) and stirred at room temperature for 5 min. $KMnO_4$ (6 mg, 0.0382 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature, MeOH (5 mL) was added and the MnO_2 precipitate was removed by filtration under suction. The filtrate was concentrated *in vacuo* to remove all MeOH. After neutralisation to pH 5 with 1M HCl the aqueous solution was concentrated under

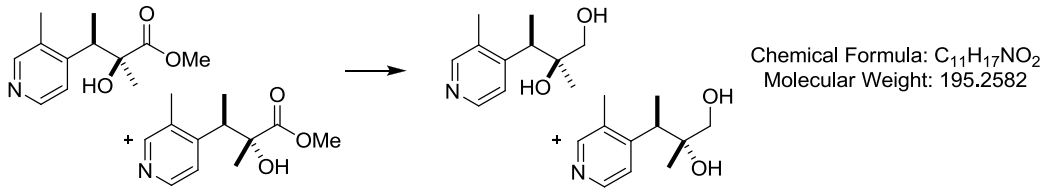
a flow of nitrogen. Salt removal from an aqueous solution by Ziptip® and purification by reverse phase (C18 silica) HPLC (MeCN/H_2O, 9:1), afforded diacid (+)-**101a** (1.9 mg, 0.00794 mmol, 83%) as a white solid. Data as above. $[\alpha]^{20}_D$ +12.8 (*c* = 0.20, H_2O).

(+)-[(2*S*,3*S*)-3-Carboxy-3-hydroxybutan-2-yl]pyridine-3-carboxylic acid (101b)



Mono-acid **55** (10 mg, 0.0478 mmol, 1 eq.) was dissolved in 1M NaOH (1 mL) and stirred at room temperature for 5 min. $KMnO_4$ (30 mg, 0.191 mmol, 4 eq.) was added and the mixture was heated at 100 °C for 1 h. After allowing to cool to room temperature, MeOH (5 mL) was added and the MnO_2 precipitated was removed by filtration under suction. The filtrate was concentrated *in vacuo* to remove all MeOH. After neutralisation to pH 5 with 1M HCl (aq.) the aqueous solution was concentrated under a flow of nitrogen. Salt removal from an aqueous solution by Ziptip® and purification by reverse phase (C18 silica) HPLC (MeCN/H_2O, 9:1), afforded diacid (+)-**101b** (2.7 mg, 0.0113 mmol, 24%) as a white solid. Data as above. $[\alpha]^{20}_D$ +6.7 (*c* = 0.25, H_2O).

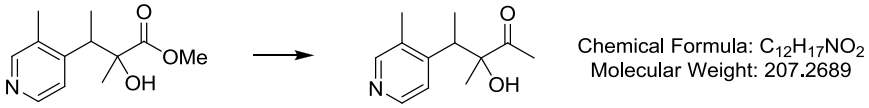
(2*S,3*R**)-** and **(2*S**,3*S**)-2-Methyl-3-(3-methylpyridin-4-yl)butane-1,2-diol (102)**



Ester **47** (20 mg, 0.0896 mmol, 1 eq., *dr* 45:55) was dissolved in THF (0.6 mL) and $LiAlH_4$ (27 mg, 0.716 mmol, 8 eq.) was added. The suspension was stirred at room temperature for 15 h then water (5 mL) was added and the resulting solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (MeOH/CH_2Cl_2, 1:49 to 1:4) afforded 1,2-diols **102a** and **102b** (15 mg, 0.0768 mmol, 80%, *dr* 45:55) as a clear oil. Rf 0.35 (MeOH/CH_2Cl_2, 1:49); ν_{max}/cm^{-1} (neat) 3355 (OH), 2974 (CH), 2925 (CH), 1599 (pyr), 1457 (CH), 1052 (C-O). ***102a:*** δ_H ($CDCl_3$, 400 MHz) 8.35 -8.33 (2H, NCH), 7.34 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.58-3.44 (2H, CH_2OH), 3.23 (1H, q, *J* 7.1 Hz, ArCH), 2.38 (3H, s, ArCH_3), 1.33 (3H, d, *J* 7.1 Hz, ArCHCH_3), 1.15 (3H, s, ArCH_3); 151.56 (s), 150.78 (d),

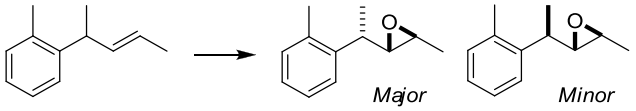
147.06 (d), 132.15 (s), 122.73 (d), 74.58 (s), 68.24 (d), 39.89 (t), 22.28 (q), 17.04 (q), 15.46 (q). ***102b:*** δ_H ($CDCl_3$, 400 MHz)8.35-8.33 (1H, NC*H*CH), 8.31 (1H, s, NCH), 7.31 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.58 -3.44 (2H, CH_2OH), 3.35 (1H, q, *J* 7.2 Hz, ArCH), 2.37 (3H, s, ArCH_3), 1.30 (3H, d, *J* 7.2 Hz, ArCHCH_3), 1.26 (3H, s, C(CH_3)OH); δ_C ($CDCl_3$, 100 MHz) 151.48 (s), 150.59 (d), 146.80 (d), 132.84 (s), 123.05 (d), 75.36 (s), 68.60 (d), 39.39 (t), 21.35 (q), 17.25 (q), 15.82 (q). MS (ESI) *m/z* 197 (12), 196 (100, MH^+), 159 (4); HRMS (ESI) 196.1332 calcd for $C_{11}H_{18}NO_2^+$ (MH^+), found 196.1330, Δ = -1.0 ppm.

(3*S,4*R**)-** and **(3*S**,4*S**)-3-Hydroxy-3-methyl-4-(3-methylpyridin-4-yl)pentan-2-one**



Ester **47** (10 mg, 0.0448 mmol, 1 eq., *dr* 50:50) and (1*S*)-(−)-2,10-camphorsultam (13 mg, 0.0538 mmol, 1.2 eq.) were dissolved in 1,3-diisopropyl benzene (0.5 mL). Me_3Al (2M solution in hexanes, 147 µL, 0.296 mmol, 6.6 eq.) was added and the solution was heated at 160 ˚C for 15 h. After allowing the solution to cool to room temperature, sat. $NaHCO_3$ (aq.) (5 mL) was added and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (MeOH/CH_2Cl_2, 1:49 to 3:17) afforded the titled compound (7 mg, 0.0338 mmol, 75%, *dr* 55:45) as a clear oil. R_f 0.45 (MeOH/CH_2Cl_2, 1:9); ν_{max}/cm^{-1} (neat) 3162 (OH), 2970 (CH_3), 1707 (C=O), 1597 (pyr), 1454 (CH), 1408 (CH), 1181 (C-O), 841 (C-O). ***Major diastereoisomer*:** δ_H ($CDCl_3$, 400 MHz) 8.43 (1H, d, *J* 5.2 Hz, NC*H*CH), 8.43 (1H, s, NCH), 7.55 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.41 (1H, q, *J* 7.0 Hz, ArCH), 2.41 (3H, s, ArCH_3), 2.38 (3H, s, OCH_3), 1.13 (3H, s, C(CH_3)(OMe)), 1.09 (3H, d, *J* 7.0 Hz, ArCHCH_3); δ_C ($CDCl_3$, 100 MHz) 211.65 (s), 150.81 (d), 149.26 (s), 147.80 (d), 131.33 (s), 123.27 (d), 80.77 (s), 39.34 (q), 25.13 (q), 23.74 (d), 17.03 (q), 15.80 (q). ***Minor diastereoisomer*:** δ_H ($CDCl_3$, 400 MHz) 8.53 (1H, s, NCH), 8.33 (1H, d, *J* 5.2 Hz, NC*H*CH), 7.48 (1H, d, *J* 5.2 Hz, NCHC*H*), 3.31 (1H, q, *J* 7.0 Hz, ArCH), 2.34 (3H, s, ArCH_3), 1.99 (3H, s, OCH_3), 1.50 (3H, s, C(CH_3)(OMe)), 1.38 (3H, d, *J* 7.0 Hz, ArCHCH_3); δ_C ($CDCl_3$, 100 MHz) 211.28 (s), 151.08 (d), 150.49 (s), 148.00 (d), 130.08 (s), 121.78 (d), 81.02 (s), 39.91 (q), 24.00 (q), 23.74 (d), 16.52 (q), 15.68 (q). MS (ESI) *m/z* 198 (8), 208 (MH^+, 100), 209 (14); HRMS (ESI) 208.1332 calcd for $C_{12}H_{18}NO_2^+$ (MH^+), found 208.1328, Δ = -1.0 ppm.

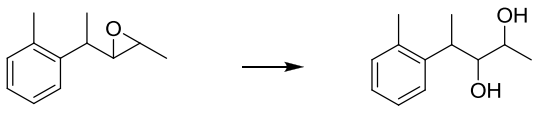
(2*S, 3*R**, 1'*S**)-** and **(2*S**, 3*R**, 1'*R**)-2-Methyl-3-(1-*ortho*-tolylethyl)oxirane (103)**



Chemical Formula: $C_{12}H_{16}O$
Molecular Weight: 176.2548

Alkene **92** (242 mg, 1.51 mmol, 1 eq.) was dissolved in a solution of MeCN (11 mL) and Na_2·EDTA ($4x10^{-4}$ M aqueous solution, 7.6 mL) and was cooled to 0 °C. CF_3COCH_3 (1.48 mL, 16.6 mmol, 11 eq.) was added *via* a cooled syringe. $NaHCO_3$ (981 mg, 11.3 mmol, 7.5 eq.) and Oxone® (1.45 g, 7.55 mmol, 5 eq.) were added in portions over 1 h. After 2 h at 0 °C, water (10 mL) was added and the resulting solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a yellow oil. Purification by FC (EtOAc/hexane, 1:49 to 1:19) afforded epoxide **103** (236 mg, 1.34 mmol, 89%, *dr* 57:43) as a clear oil. R_f 0.41 (EtOAc/hexane, 1:19); ν_{max}/cm^{-1} (neat) 2968 ($ArCH_3$), 2929 ($ArCH_3$), 2361, 1653, 1558, 1490 (epoxide), 1457 (CH_3), 1379, 757 (epoxide). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.14-7.40 (4H, m, ArH), 3.22 (1H, m, ArCH), 2.88 (2H, m, CHO), 2.37 (3H, s, $ArCH_3$), 1.36 (3H, d, *J* 5.3 Hz, $ArCHC\mathit{H}_3$), 1.27 (3H, d, *J* 7.0 Hz, $CHOCH_3$); δ_C ($CDCl_3$, 100 MHz) 141.35, 135.92, 130.37, 126.35, 126.31, 126.23, 63.26 (d), 53.16 (d), 36.00 (d), 20.50 (q), 17.83 (q), 16.67 (q). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.14-7.40 (4H, ArH), 3.12 (1H, m, ArCH), 2.96 (1H, m, CHO), 2.88 (1H, m, CHO), 2.36 (3H, s, $ArCH_3$), 1.36 (3H, d, $ArCHC\mathit{H}_3$), 1.31 (3H, d, *J* 5.0 Hz, $CHOCH_3$); δ_C ($CDCl_3$, 100 MHz) 141.84, 135.49, 126.35, 126.23, 126.16, 63.91 (d), 53.92 (d), 37.07 (d), 19.69 (q), 17.83 (q), 16.67 (q). MS (EI) *m/z* 176 (M^+, 9), 143 (39), 132 (32), 119 (100), 117 (84), 91 (33); HRMS (EI) 176.1201 calcd for $C_{12}H_{16}O$ (M^+), found 176.1200, Δ = -0.6 ppm.

4-*ortho*-Tolylpentane-2,3-diol (104)

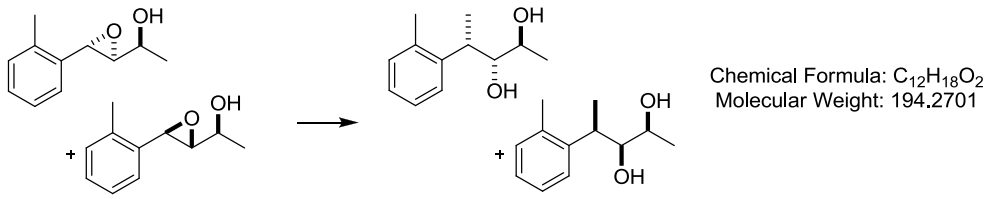


Chemical Formula: $C_{12}H_{18}O_2$
Molecular Weight: 194.2701

2-Methyl-3-(1-*o*-tolylethyl)oxirane (235 mg, 1.33 mmol) was dissolved in MeCN (5 mL) and water (1.2 mL) and cooled to 0 °C. 60% $HClO_4$ (206 µL) was added dropwise. After 5 min, the mixture was allowed to warm to room temperature and stirred for a further 19 h. The reaction mixture was quenched with $NaHCO_3$ (aq.) then extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and then concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:4 to 9:1)

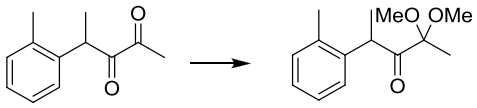
afforded 1,2-diol **104** (186 mg, 0.959 mmol, 72%) as a colourless oil and a complex mixture of diastereoisomers. R_f 0.11 (EtOAc/hexane, 2:3); ν_{max}/cm^{-1} (neat) 3381 (OH), 2970 (CH_3), 2927 (CH_3), 1461 (CH_3), 1376 (CH), 1057 (C-O). δ_H ($CDCl_3$, 400 MHz) 7.37-7.13 (4H, ArH), 4.46-4.03 (1H, C*H*OHCHOHCH$_3$), 3.86-3.44 (1H, C*H*OHCH$_3$), 3.26-2.99 (1H, ArC*H*CH$_3$), 2.40-2.36 (3H, ArCH$_3$), 1.9 (2H, bs, OH), 1.35-1.11 (6H, CHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 137.86, 137.10, 130.73, 130.59, 127.77, 126.60, 126.41, 126.25, 126.17, 126.11, 125.99, 125.82, 79.16, 78.38, 69.29, 68.49, 68.30, 67.88, 522.94, 50.77, 37.25, 36.91, 22.29, 20.38, 19.96, 19.77, 19.61, 18.11, 17.65, 16.85, 15.71; MS (EI) *m/z* 194 (M^+, 5), 149 (27), 132 (92), 120 (100), 117 (59), 105 (72), 91 (48); HRMS (EI) 194.1307 calcd for $C_{12}H_{18}O_2$ (M^+), found 194.1306, Δ = -0.5 ppm.

or



Epoxy alcohol **125** (500 mg, 2.81 mmol, 1 eq., *dr* 64:36) was dissolved in hexane (20 mL) and cooled to -78 °C. Me_3Al (2M solution in hexane, 4.21 mL, 8.42 mmol, 3 eq.) was added dropwise and the reaction was stirred a -78 °C for 1h then at 0 °C for 3 h. 10% potassium sodium tartrate (aq.) (50 mL) was added and the aqueous layer was extracted with Et_2O (4 x 30 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:3 to 2:3) afforded 1,2-diol **104** (362 mg, 1.86 mmol, 67%, *dr* 66:34) as a clear oil. ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.19-7.13 (4H, ArH), 3.66 (1H, m, C*H*OH), 3.45 (1H, dd, *J* 10 and 5.2 Hz, C*H*OH), 3.26 (1H, p, *J* 6.9 Hz, ArC*H*), 2.39 (3H, s, ArCH$_3$), 2.11 (1H, bs, OH), 2.07 (1H, bd, *J* 5.4 Hz, OH), 1.32 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$), 1.23 (3H, d, *J* 6.4 Hz, CH(OH)C*H*$_3$). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.24-7.17 (4H, ArH), 3.88 (1H, m, C*H*OH), 3.73 (1H, m, C*H*OH), 3.13 (1H, p, *J* 6.9 Hz, ArC*H*), 2.36 (3H, s, ArCH$_3$), 2.12 (1H, bs, OH), 1.36 (1H, bs, OH), 1.34 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$), 1.13 (3H, d, *J* 6.3 Hz, CH(OH)C*H*$_3$). Data as above.

(±)-2,2-Dimethoxy-4-*ortho*-tolylpentan-3-one (105)

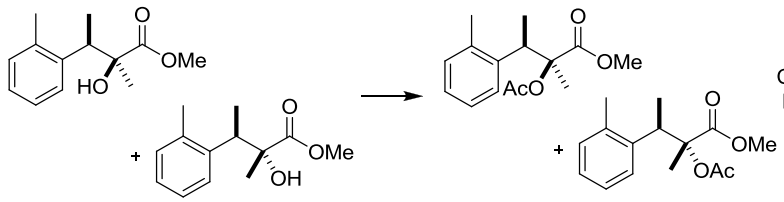


Chemical Formula: $C_{14}H_{20}O_3$
Molecular Weight: 236.3068

Typical Procedure (entry 2, **Table 2.16**):

Diketone **56** (8 mg, 0.042 mmol, 1 eq.) was dissolved in MeOH (0.8 mL) and $RuCl_3$ (8.7 mg, 0.042 mmol, 1 eq.) was added. The reaction was heated at 40 °C for 72 h then diluted with CH_2Cl_2 (5 mL) and brine was added. The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (2 x 8 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (CH_2Cl_2) afforded acetal **105** (9 mg, 0.038 mmol, 91%) as a clear oil. R_f 0.52 (CH_2Cl_2); ν_{max}/cm^{-1} (neat) 2969 (CH_3), 2933 (CH_3), 2834 (CH_3), 1725 (C=O), 1492 (C-O-C), 1146 (acetal), 1125 (acetal), 1045 (aromatic CH); δ_H ($CDCl_3$, 400 MHz) 7.20-7.10 (4H, m, ArH), 4.63 (1H, q, *J* 7.0 Hz, ArC*H*CH_3), 3.17 (3H, s, OCH_3), 3.11 (3H, s, OCH_3), 2.47 (3H, s, $ArCH_3$), 1.35 (3H, d, *J* 7.0 Hz, ArCHC*H*$_3$), 1.15 (3H, s, $C(OCH_3)_2CH_3$; δ_C ($CDCl_3$, 100 MHz) 210.04 (s), 138.51 (s), 135.88 (s), 130.60 (d), 126.97 (d), 126.67 (d), 126.11 (d), 102.91 (s), 49.81 (q), 49.38 (q), 42.54 (d), 20.98 (q), 19.58 (q), 18.30 (q); MS (CI) *m/z* 398 (88), 380 (48), 254 (MNH_4^+, 49), 222 (100), 208 (28), 190 (91), 89 (20), 52 (32); HRMS (CI) 254.1756 calcd for $C_{14}H_{24}O_3N$ (MNH_4^+), found 254.1748, Δ = -3.1 ppm.

(2*S,3*R**)-** and **(2*R**,3*R**)-Methyl 2-acetoxy-2-methyl-3-*ortho*-tolylbutanoate (110a** and **110b)**

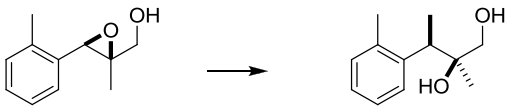


Chemical Formula: $C_{15}H_{20}O_4$
Molecular Weight: 264.3169

Ester **57** (20 mg, 0.0900 mmol, 1 eq., *dr* 45:55) was dissolved in acetic anhydride (1.2 mL) and conc. H_2SO_4 (0.02 mL) was added dropwise. The reaction was heated at 40 °C for 19 h then cooled in an ice bath before quenching with sat. $NaHCO_3$ (aq.) (5 mL) and extracting with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (CH_2Cl_2/ pet. ether, 1:1 to 1:0) afforded acetate **110** (15 mg, 0.059 mmol, 62%, *dr* 45:55) as a clear oil. R_f 0.30 (CH_2Cl_2/ pet. ether, 1:1); ν_{max}/cm^{-1} (neat) 1738 (C=O), 1454 (CH), 1371 (CH), 1245 (COC), 1118 (COC). ***110a*****:** δ_H ($CDCl_3$, 400 MHz) 7.42 (1H, d, *J* 7.6 Hz, ArH), 7.28-7.16 (3H, ArH), 3.70

(3H, s, CO_2CH_3), 3.48 (1H, q, *J* 7.1 Hz, ArCH), 2.38 (3H, s, $ArCH_3$), 2.15 (3H, s, $C(O)CH_3$), 1.56 (3H, s, $C(OAc)CH_3$), 1.35 (3H, d, *J* 7.1 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 172.36 (s), 169.82 (s), 139.73 (s), 136.35 (s), 130.33 (d), 127.94 (d), 126.69 (d), 125.96 (d), 83.64 (s), 52.17 (q), 41.55 (d), 21.52 (q), 20.26 (q), 17.79 (q), 16.59 (q). ***110b*****:** δ_H ($CDCl_3$, 400 MHz) 7.27-7.16 (4H, ArH), 3.68 (3H, s, CO_2CH_3), 3.65 (1H, q, *J* 7.2 Hz, ArCH), 2.44 (3H, s, $ArCH_3$), 2.04 (3H, s, $C(O)CH_3$), 1.61 (3H, s, $C(OAc)CH_3$), 1.30 (3H, d, *J* 7.2 Hz, $ArCHCH_3$); δ_C ($CDCl_3$, 100 MHz) 172.10 (s), 169.82 (s), 139.29 (s), 137.22 (s), 130.33 (d), 128.10 (d), 126.69 (d), 125.50 (d), 84.04 (s), 52.17 (q), 41.00 (d), 21.27 (q), 20.32 (q), 17.79 (q), 15.91 (q). MS (CI) *m/z* 282 (100, MNH_4^+), 265 (12, MH^+), 222 (28); HRMS (CI) 265.1434 calcd for $C_{15}H_{21}O_4^+$ (MH^+), found 265.1421, Δ = -4.9 ppm.

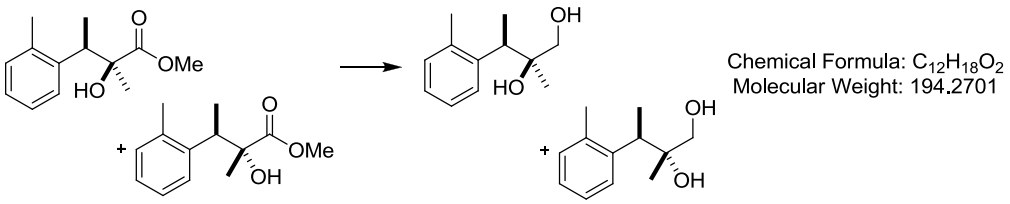
(2*S, 3*R**)-2-Methyl-3-*ortho*-tolylbutane-1,2-diol (111a)**



Chemical Formula: $C_{12}H_{18}O_2$
Molecular Weight: 194.2701

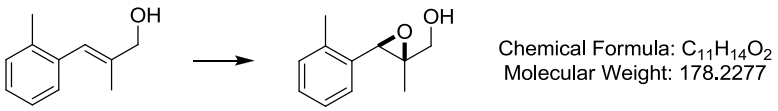
Epoxy alcohol **112** (27 mg, 0.152 mmol, 1 eq.) was dissolved in hexane (1.5 mL) and cooled to -78 °C. Me_3Al (2M solution in hexane, 0.23 mL, 0.455 mmol, 3 eq.) was added dropwise and the reaction was stirred at -78 °C for 1 h, then allowed to warm to 0 °C, and was stirred for a further 3 h. Water (5 mL) was added and after sonification, the organic layer was extracted. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 2:3) afforded 1,2-diol **111a** (19 mg, 0.116 mmol, 76%) as a clear oil. R_f 0.14 (EtOAc/hexane, 2:3); ν_{max}/cm^{-1} (neat) 3379 (OH), 2973 (CH_3), 1460 ($ArCH_3$), 1276 (CH_3), 1261 (CH_3), 1024 (CO); δ_H ($CDCl_3$, 400 MHz) 7.38 (1H, d, *J* 7.8 Hz, ArH), 7.23-7.13 (3H, ArH), 3.61 (1H, d, *J* 11 Hz, CH_2OH), 3.41 (1H, d, *J* 11 Hz, CH_2OH), 3.28 (1H, q, *J* 7.2 Hz, ArCH), 2.41 (3H, s, $ArCH_3$), 1.91 (2H, bs, OH), 3.05 (3H, d, *J* 7.2 Hz, $ArCHCH_3$), 1.19 (3H, s, $COHCH_3$); δ_C ($CDCl_3$, 100 MHz) 141.70 (s), 136.53 (s), 130.53 (d), 127.52 (d), 126.24 (d), 125.98 (d), 75.32 (s), 68.33 (t), 40.25 (d), 22.16 (q), 20.47 (q), 15.94 (q); MS (CI) *m/z* 212 (100, MNH_4^+), 194 (18), 159 (21); HRMS (EI) 212.1651 calcd for $C_{12}H_{22}O_2N$ (MNH_4^+), found 212.1649, Δ = -0.9 ppm.

(2*S, 3*R**)-** and **(2*R**, 3*R**)-2-Methyl-3-*ortho*-tolylbutane-1,2-diol (111a** and **111b)**



Ester **57** (41 mg, 0.185 mmol, 1 eq., *dr* 44:45) was dissolved in THF (1.2 mL) and cooled to 0 °C. $LiAlH_4$ (16 mg, 3.96 mmol, 2.2 eq.) was added and after 5 min the suspension was allowed to warm to room temperature and then stirred for a further 2 h. Et_2O (2 mL) was added and the mixture was filtered through Celite® and concentrated *in vacuo* to afford 1,2-diols **111a** and **111b** (**111a**:**111b**, 45:55 by ^1H NMR) as a clear oil. Purification by FC (EtOAc/hexane, 1:4 to 3:7) afforded 1,2-diols **111a** (16 mg, 0.082 mmol, 100%) and **111b** (20 mg, 0.103 mmol, 100%), both as clear oils. Data for 1,2-diol **111a** as above. ***7b*:** R_f 0.19 (EtOAC/hexane, 2:3); δ_H ($CDCl_3$, 400 MHz) 7.38 (1H, d, *J* 6.8 Hz, ArH), 7.25-7.14 (3H, ArH), 3.57 (1H, dd, *J* 11 and 6.2 Hz, C*H*$_2$OH), 3.49 (1H, dd, *J* 11 and 6.4 Hz, C*H*$_2$OH), 3.43 (1H, q, *J* 7.2 Hz, ArCH), 2.42 (3H, s, $ArCH_3$), 1.85 (1H, t, *J* 6.3 Hz, CH_2O*H*), 1.69 (1H, s, CCH_3O*H*), 1.32 (3H, d, *J* 7.2 Hz, ArCHC*H*$_3$), 1.24 (3H, s, CC*H*$_3$OH); δ_C ($CDCl_3$, 100 MHz) 141.72 (s), 136.53 (s), 130.52 (d), 127.53 (d), 126.44 (d), 125.98 (d), 75.33 (s), 68.32 (t), 40.25 (d), 21.13 (q), 20.45 (q), 15.93 (q); MS (CI) *m/z* 212 (100, MNH_4^+), 194 (18), 159 (21); HRMS (EI) 212.1651 calcd for $C_{12}H_{22}O_2N$ (MNH_4^+), found 212.1649, Δ = -0.9 ppm.

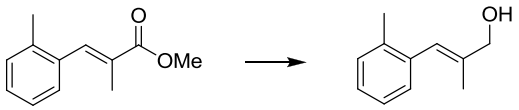
[(2*R,3*R**)-2-Methyl-3-*ortho*-tolyloxiran-2-yl]methanol (112)**



Allylic alcohol **113** (18 mg, 0.111 mmol, 1 eq.) and $VO(acac)_2$ (3 mg, 0.011 mmol, 0.1 eq.) were dissolved in toluene (0.5 mL) and warmed to 40 °C. A solution of ^{t}BuOOH (3.67M solution in toluene, 36 µL, 0.133 mmol, 1.2 eq.) was added dropwise turning the green solution deep orange/red. The reaction was stirred at 40 °C for 16 h during which time it had returned to green in colour. After dilution with CH_2Cl_2 (10 mL), 10% $Na_2S_2O_3$ (10 mL) was added. The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale green oil. Purification by FC (EtOAc/hexane, 3:7) afforded epoxy alcohol

112 (15 mg, 0.0841 mmol, 76%) as a clear oil. R_f 0.25 (EtOAc/hexane, 3:7); ν_{max}/cm^{-1} (neat) 3410 (OH), 2926 (CH_3), 1459 ($ArCH_3$), 1069 (C-O), 1040 (C-O); δ_H ($CDCl_3$, 400 MHz) 7.33-7.18 (4H, ArH), 4.22 (1H, s, ArCH), 3.92 (1H, dd, *J* 12 and 4.3 Hz, C*H*$_2$OH), 3.84 (1H, *J* 12 and 8.8 Hz, C*H*$_2$OH), 2.35 (3H, s, $ArCH_3$), 2.02 (1H, dd, *J* 8.8 and 4.3 Hz, OH), 1.06 (3H, s, CH_3); δ_C ($CDCl_3$, 100 MHz) 153.27 (s), 134.13 (s), 129.55 (d), 127.38 (d), 126.20 (d), 125.70 (d), 65.00 (t), 63.12 (s), 59.33 (d), 18.73 (q), 13.76 (q); MS (EI) *m/z* 178 (M^+, 32), 160 (27), 145 (56), 121 (83), 104 (100), 91 (68), 78 (80); HRMS (EI) 178.0994 calcd for $C_{11}H_{14}O_2$, found 178.1001, Δ = +3.9 ppm.

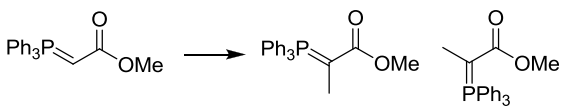
(*E*)-2-Methyl-3-*ortho*-tolylprop-2-en-1-ol (113)[114]



Chemical Formula: $C_{11}H_{14}O$
Molecular Weight: 162.2283

$LiAlH_4$ (12 mg, 0.315 mmol, 0.6 eq.) was stirred in Et_2O (1 mL) and cooled to 0 °C. $AlCl_3$ (14 mg, 0.105 mmol, 0.2 eq.) was added in two portions followed by the dropwise addition of (*E*)-methyl 2-methyl-3-*o*-tolylacrylate (100 mg, 0.526 mmol, 1 eq.) in Et_2O (1.5 mL). After 10 min the mixture was allowed to warm to room temperature and then stirred for a further 2 h. Water (10 mL) was added and the Et_2O layer extracted. The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:4) afforded allylic alcohol **113** (75 mg, 0.462 mmol, 82%) as a clear oil. Data was consistent with that previously reported.[114] R_f 0.25 (EtOAc/hexane, 1:4); δ_H ($CDCl_3$, 400 MHz) 7.26-7.17 (4H, ArH), 6.55 (1H, s, ArCH), 2.37 (2H, s, CH_2OH), 2.28 (3H, s $ArCH_3$), 1.79 (3H, s, CHCC*H*$_3$), 1.57 (1H, bs, OH).

Methyl(triphenylphosphoranylidene)propionate (115)[163]

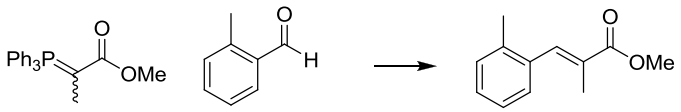


Chemical Formula: $C_{22}H_{21}O_2P$
Molecular Weight: 348.3747

Methyl (triphenylphosphoranylidene)acetate (1.00g, 2.99 mmol, 1 eq.) was dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C. Methyl iodide (279 µL, 4.49 mmol, 1.5 eq.) was added and after 15 min the solution was allowed to warm to room temperature. The pale yellow solution was stirred at room temperature for a further 18 h then concentrated *in vacuo* to leave a pale yellow foam. NaOH (240 mg, 5.98 mmol, 2 eq.) in water (10 mL) was added. After vigorous shaking the organic layer was extracted and

the aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow solid (1.117 g). The solid was dissolved in hot EtOAc and the white precipitate was filtered off while still hot. The solution was concentrated *in vacuo* to afford ylide **115** (784 mg, 2.25 mmol, 75%, rotamers 1:1) as a pale yellow solid. Data was consistent with that previously reported.[164] δ_H (CDCl3, 400 MHz) 7.81-7.48 (30H, ArH), 5.32 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 1.94 (3H, s, CH_3), 1.91 (3H, s, CH_3); MS (EI) *m/z* 348 (M+, 18), 277 (100), 262 (19), 201 (20), 183 (26), 152 (14), 77 (19).

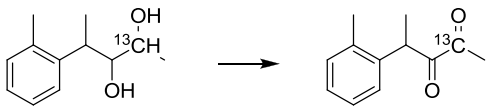
(*E*)-Methyl 2-methyl-3-*ortho*-tolylacrylate (116)[114]



Chemical Formula: $C_{12}H_{14}O_2$
Molecular Weight: 190.2384

Methyl(triphenylphosphoranylidene)propionate (162 mg, 0.465 mmol, 1 eq.) was dissolved in CH_2Cl_2 (1.5 mL) and *o*-tolylaldehyde (65 µL, 0.558 mmol, 1.2 eq.) was added. The mixture was stirred at room temperature for 17 h then concentrated *in vacuo*. Hexane (2 mL) was added and the white precipitate was filtered off under suction, washing with hexane (4 x 5 mL). The filtrate was concentrated *in vacuo* to leave a clear oil (131 mg). Purification by FC (EtOAc/hexane, 1:19) afforded the unsaturated ester **116** (109 mg, 0.573 mmol, 49%) as a clear oil. Data was consistent with that previously reported.[114] R_f 0.43 (EtOAc/petroleum ether, 1:9); δ_H ($CDCl_3$, 400 MHz) 7.77 (1H, s, ArCH), 7.23-7.21 (4H, ArH), 3.84 (3H, s, OCH_3), 2.27 (3H, $ArCH_3$), 1.98 (3H, s, CH_3).

(±)-2-[^{13}C] 4-*ortho*-Tolylpentane-2,3-dione (119)

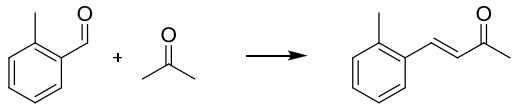


Chemical Formula: $C_{11}{}^{13}CH_{14}O_2$
Molecular Weight: 191.2310

2-[^{13}C] 4-*o*-Tolylpentane-2,3-diol (40 mg, 0.205 mmol, 1 eq.) was dissolved in DMSO (0.25 mL) and 59% IBX (245 mg, 0.512 mmol, 2.5 eq.) was added. The suspension was stirred at room temperature for 18 h after which time the reaction mixture was bright yellow. CH_2Cl_2 (5 mL) was added and the mixture was passed through a pad of Celite® eluting with CH_2Cl_2. Water (20 mL) was added and the organic layer was extracted, dried over $MgSO_4$ and concentrated *in vacuo* to leave a bright yellow oil. Purification by FC (CH_2Cl_2) afforded 1,2-diketone **119** (31 mg, 0.162 mmol, 79%) as a bright yellow

oil. R_f 0.86 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.24-7.13 (3H, ArH), 6.95 (1H, m, ArH), 4.78 (1H, q, *J* 6.9 Hz, ArCH), 2.47 (3H, s, $ArCH_3$), 2.25 (3H, d, *J* 6.4 Hz, $^{13}COCH_3$), 1.39 (3H, d, *J* 6.9 Hz, ArCHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 198.44 (s). MS (CI) *m/z* 209 (100, MNH_4^+), 182 (27), 146 (19), 132 (16), 119 (44); HRMS (CI) 209.1360 calcd for $^{13}C_1{}^{12}C_{11}H_{18}O_2N$, found 209.1371, Δ = +5.3 ppm.

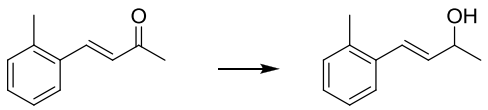
(*E*)-4-*ortho*-Tolylbut-3-en-2-one (120)[115]



Chemical Formula: $C_{11}H_{12}O$
Molecular Weight: 160.2124

Acetone (1.65 mL, 22.5 mmol, 1.3 eq.) was dissolved in EtOH (4.5 mL) and water (7.4 mL) and then cooled to 0 °C. NaOH (820 mg, 21.0 mmol, 1.18 eq.) was added followed by the dropwise addition of 2-methylbenzaldehyde (2 mL, 17.3 mmol, 1 eq.). The mixture was stirred at 0 °C for 4 h then quenched with sat. NH_4Cl (aq.) (30 mL) and extracted with CH_2Cl_2 (5 x 30 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a bright yellow oil. Purification by FC (EtOAc/hexane, 3:97) afforded enone **120** (2.09 g, 13.0 mmol, 75%) as a yellow oil. Data was consistent with that previously reported.[115] R_f 0.25 (EtOAc/hexane, 1:9); δ_H ($CDCl_3$, 400 MHz) 7.85 (1H, d, *J* 16 Hz, ArCH), 7.60 (1H, d, *J* 7.3 Hz, ArH), 7.34-7.23 (3H, ArH), 6.70 (1H, d, *J* 16 Hz, ArCHC*H*), 2.48 (3H, s, CH_3), 2.42 (3H, s, CH_3).

(±)-(*E*)-4-*ortho*-Tolylbut-3-en-2-ol (123)[165]

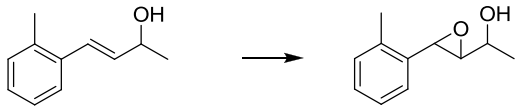


Chemical Formula: $C_{11}H_{14}O$
Molecular Weight: 162.2283

Enone **120** (580 mg, 3.58 mmol, 1 eq.) was dissolved in MeOH (8.8 mL) and cooled to 0 °C. $NaBH_4$ was added in 3 portions and the reaction was allowed to warm to room temperature and stirred for a further 30 min. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL) then the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:9 to 3:17) afforded allylic alcohol **123** (351 mg, 2.19 mmol, 61%) as a clear oil. Data was consistent with that previously reported.[165] R_f 0.60 (EtOAc/hexane, 2:3); δ_H ($CDCl_3$, 400 MHz) 7.48 (1H, m, ArH), 7.20-7.17 (3H, ArH), 6.81 (1H, d, *J* 15 Hz, ArCH), 6.19 (1H, dd, *J* 15 and 6.4 Hz, ArCHC*H*), 4.55 (1H, pd, *J* 6.4 and

1.1 Hz, C*H*OH), 2.38 (3H, s, $ArCH_3$), 1.64 (1H, bs, OH), 1.42 (3H, d, *J* 6.4 Hz , CH(OH)CH_3); MS (EI) *m/z* 162 (33, M^+), 144 (100), 119 (82), 104 (83), 91 (54), 55 (52).

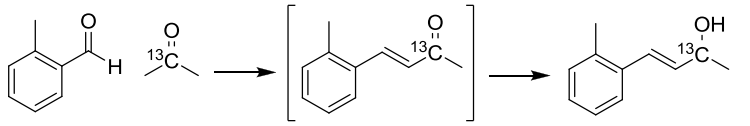
(*R)-1-(2*R**,3*R**)-** and **(*S**)-1-[(2*R**,3*R**)-3-*ortho*-Tolyloxiran-2-yl]ethanol (125)**



Chemical Formula: $C_{11}H_{14}O_2$
Molecular Weight: 178.2277

Alcohol **123** (8 mg, 0.0449 mmol, 1 eq.) and $VO(acac)_2$ (1.5 mg, 0.449 µmol, 1 mol%) were dissolved in toluene and warmed to 40 °C. TBHP (3.67M solution in toluene, 16 µL, 0.0591 mmol, 1.2 eq.) was added dropwise and the reaction turned red after 1 min and was allowed to stir at 40 °C for 16 h after which time the green colour had returned. CH_2Cl_2 (10 mL) was added and washed with 10% $Na_2S_2O_3$ (aq.) (10 mL). The organic layer was dried over $MgSO_4$ then concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (EtOAc/hexane, 1:9) afforded epoxy alcohol **125** (6.8 mg, 0.0383 mmol, 85%, *dr* 62:38) as a clear oil. R_f 0.35 (EtOAc/hexane, 3:7); ν_{max}/cm^{-1} (neat) 3422 (OH), 2975 (CH), 1492 (epoxide), 1461 (CH), 1070 (C-O), 892 (epoxide). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.29-7.18 (4H, ArH), 4.19 (1H, m, ArCH(O)C*H*), 4.14 (1H, d, *J* 2.4 Hz, ArCH), 3.00 (1H, t, *J* 2.6 Hz, C*H*OH), 2.45 (3H, s, $ArCH_3$), 1.41 (3H, d, *J* 7.4 Hz, CH(OH)CH_3); δ_C ($CDCl_3$, 100 MHz) 135.75 (s), 135.29 (s), 129.84 (d), 127.70 (d), 126.17 (d), 124.21 (d), 65.08 (d), 64.59 (d), 52.72 (d), 20.01 (q), 18.89 (q). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.29-7.18 (4H, ArH), 4.04 (1H, d, *J* 2,2 Hz, ArCH), 3.89 (1H, m, ArCH(O)C*H*), 2.97 (1H, dd, *J* 5.0 and 2.1 Hz, C*H*OH), 2.42 (3H, s, $ArCH_3$), 1.42 (3H, d, *J* 6.5 Hz, CH(OH)CH_3); δ_C ($CDCl_3$, 100 MHz) 135.29 (s), 135.06 (s), 129.84 (d), 127.79 (d), 126.21 (d), 124.30 (d), 67.71 (d), 65.74 (d), 54.84 (d), 20.01 (q), 18.93 (q). MS (EI) *m/z* 178 (9, M^+), 121 (100), 105 (38), 84 (52), 49 (58); HRMS (EI) 178.0994 calcd for $C_{11}H_{14}O_2^+$, found 178.0994, Δ = -1.7 ppm.

(±)-2-[^{13}C] (*E*)-4-*ortho*-Tolylbut-3-en-2-ol (126)

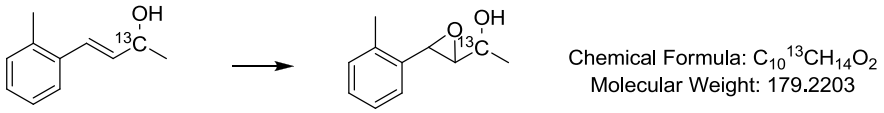


Chemical Formula: $C_{10}{}^{13}CH_{14}O$
Molecular Weight: 163.2209

To a solution of NaOH (247 mg, 6.17 mmol, 1.2 eq.) in EtOH (1.4 mL) and H_2O (2.3 mL), was added 2-[^{13}C] acetone (500 µL, 6.81 mmol, 1.3 eq.). The solution was cooled to 0 °C and 2-methylbenzaldehyde (0.61 mL, 5.14 mmol, 1 eq.) was added dropwise turning

the solution green. The mixture was stirred at 0 °C for 4 h then sat. NH_4Cl (aq.) (10 mL) was added. The solution was extracted with CH_2Cl_2 (5 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a bright yellow oil. Purification by FC (EtOAC/hexane, 2:48) afforded 2-[^{13}C] (*E*)-4-*o*-tolylbut-3-en-2-one as a pale yellow oil which was reacted directly. [R_f 0.85 (Et_2O); δ_H ($CDCl_3$, 400 MHz) 7.58 (1H, dd, *J* 16 and 6.4 Hz, ArCHC*H*), 7.60 (1H, d, *J* 7.4 Hz, ArH), 7.34-7.23 (3H, ArH), 6.68 (1H, dd, *J* 16 and 2.7 Hz, ArCH), 2.48 (3H, s, $ArCH_3$), 2.42 (3H, d, *J* 5.8 Hz, $COCH_3$); δ_C ($CDCl_3$, 100 MHz) 198.41 (s); MS (EI) *m/z* 161 (23, M^+), 146 (73), 115 (38), 91 (21), 84 (86), 49 (100); HRMS (EI) 161.0922 calcd for $^{13}C_1{}^{12}C_{10}H_{12}O$, found 161.0922, Δ = 0 ppm.] This oil was dissolved in MeOH (7.8 mL) and cooled to 0 °C. $CeCl_3.7H_2O$ (681 mg, 1.83 mmol, 1 eq.) was added. $NaBH_4$ (104 mg, 2.75 mmol, 1.5 eq.) was then added in portions and the mixture was allowed to warm to room temperature. After stirring at room temperature for 15 min, brine (10 mL) was added and the solution was extracted with CH_2Cl_2 (4 x 15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:4) afforded allylic alcohol **126** (423 mg, 2.59 mmol, 51%) as a clear oil. R_f 0.47 (EtOAc/petroleum ether, 3:7); δ_H ($CDCl_3$, 400 MHz) 7.48 (1H, m, ArH), 7.23-7.17 (3H, ArH), 6.82 (1H, dd, *J* 16 and 7.0 Hz, ArCH), 6.19 (1H, ddd, *J* 16, 6.5 and 3.6 Hz, ArCHC*H*), 4.53 (1H, ddd, *J* 150, 6.4 and 1.0 Hz, C*H*COH), 2.36 (3H, s, $ArCH_3$), 1.74 (1H, bs, OH), 1.42 (3H, dd, *J* 6.4 and 124 Hz, $CHOHCH_3$); δ_C ($CDCl_3$, 100 MHz) 69.19 (d); MS (EI) *m/z* 163 (M^+, 23), 145 (37), 130 (21), 119 (21), 104 (28), 84 (100), 49 (84); HRMS (EI) 163.1078 calcd for $^{13}C_1{}^{12}C_{10}H_{14}O$, found 163.1072, Δ = -3.7 ppm.

1-[^{13}C] 1-(3-*ortho*-Tolyloxiran-2-yl)ethanol (127)

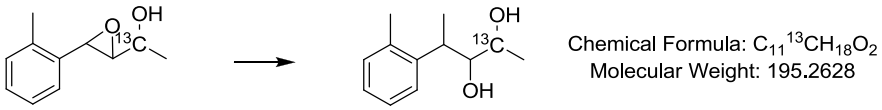


Chemical Formula: $C_{10}{}^{13}CH_{14}O_2$
Molecular Weight: 179.2203

Allylic alcohol **126** (35 mg, 0.215 mmol, 1 eq.) and $VO(acac)_2$ (6 mg, 0.022 mmol, 0.1 eq.) were dissolved in toluene (0.5 mL) and warmed to 40 °C. A solution of TBHP (3.67M solution in toluene, 36 µL, 0.133 mmol, 1.2 eq.) was added dropwise turning the green mixture deep red. The mixture was stirred at 40 °C for 16 h and then diluted with CH_2Cl_2 (10 mL) after allowing to cool to room temperature. 10% $Na_2S_2O_5$ (aq.) (10 mL) was added and the organic layer was extracted. The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL) then the combined organic extracts were dried over

$MgSO_4$ and concentrated *in vacuo* to leave a pale green oil. Purification by FC (EtOAc/hexane, 3:7) afforded epoxy alcohol **127** (25 mg, 0.140 mmol, 65%, *dr* 41:59) as a clear oil. R_f 0.28 (EtOAc/petroleum ether, 3:7); ν_{max}/cm^{-1} (neat) 3422 (OH), 2975 (CH_3), 2928 (CH_2), 1492 (epoxide), 1461 (CH_3), 1372 (CH_3), 1285 (CH), 1070 (C-O), 892 (epoxide). ***Major diastereoisomer:*** δ_H ($CDCl_3$, 400 MHz) 7.26-7.19 (4H, ArH), 4.22 (1H, dm, *J* 116 Hz, ArCHC*H*), 4.13 (1H, m, ArCH), 2.99 (1H, m, ^{13}CH), 2.44 (3H, s, $ArCH_3$), 2.04 (1H, t, *J* 2.5 Hz, OH), 1.39 (3H, dd, *J* 6.3 and 4.4 Hz, ^{13}CHCH_3); δ_C ($CDCl_3$, 100 MHz) 64.51 (d). ***Minor diastereoisomer:*** δ_H ($CDCl_3$, 400 MHz) 7.26-7.19 (4H, ArH), 4.03 (1H, m, ArCH), 3.89 (1H, dm, J 128 Hz, ArCHCH), 2.95 (1H, m, ^{13}CH), 2.42 (3H, s, $ArCH_3$), 1.96 (1H, dd, *J* 6.1 and 2.7 Hz, OH), 1.42 (3H, dd, *J* 6.6 and 4.4 Hz, ^{13}CHCH_3); δ_C ($CDCl_3$, 100 MHz) 67.60 (d). MS (EI) *m/z* 179 (M^+, 9), 146 (22), 134 (17), 121 (100), 119 (33), 105 (59), 93 (40), 91 (39); HRMS (EI) 179.1027 calcd for $^{13}C_1{}^{12}C_{10}H_{14}O_2$, found 179.1027.

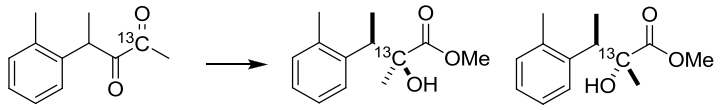
2-[^{13}C] 4-*ortho*-Tolylpentane-2,3-diol (128)



Chemical Formula: $C_{11}{}^{13}CH_{18}O_2$
Molecular Weight: 195.2628

Epoxy alcohol **127** (75 mg, 0.419 mmol, 1 eq.) was dissolved in hexane (4 mL) and cooled to -78 °C. Me_3Al (2M solution in hexane, 630 µL, 1.26 mmol, 3 eq.) was added dropwise and the mixture stirred was stirred at -78 °C for 1 h, then at 0 °C for a further 3 h. Water (15 mL) and hexane (10 mL) were added and the emulsion was sonicated until two layers formed. The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined and dried over $MgSO_4$ then concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 35:65) afforded the 1,2-diol **128** (55 mg, 0.282 mmol, 67%, *dr* 43:57) as a clear oil. R_f 0.11 (EtOAc/hexane, 2:3); ν_{max}/cm^{-1} (neat) 3381 (OH), 2970 (CH_3), 2927 (CH_3), 1461 (CH_3), 1376 (CH), 1057 (C-O). ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.29-7.12 (4H, ArH), 4.18-3.11 (3H, CH), 2.37 (3H, s, $ArCH_3$), 1.36-1.13 (6H, CHCH_3). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.29-7.12 (4H, ArH), 4.18-3.11 (3H, CH), 2.40 (3H, s, $ArCH_3$), 1.36-1.13 (6H, CHCH_3). δ_C ($CDCl_3$, 100 MHz) 68.35 (d), 67.85 (d). MS (EI) *m/z* 195 (7, M^+), 149 (27), 131 (22), 120 (100), 105 (77), 91 (34), 57 (32), 43 (32); HRMS (EI) 195.1340 calcd for $^{13}C_1{}^{12}C_{11}H_{18}O_2$, found 195.1340, Δ = 0 ppm.

(2*S,3*R**)-** and **(2*R**, 3*R**)-Methyl 2-hydroxy-2-methyl-3-*ortho*-tolylbutanoate (129a** and **129b)**



Chemical Formula: $C_{12}{}^{13}CH_{18}O_3$
Molecular Weight: 223.2729

Method A (Lewis acid promoted BER):

Diketone **119** (15 mg, 0.079 mmol, 1 eq.) was dissolved in MeOH (1.5 mL) and CuCl (7.8 mg, 0.079 mmol, 1 eq.) was added. The mixture was stirred at 40 °C for 66 h then allowed to cool to room temperature and diluted with CH_2Cl_2 (6 mL). Brine (10 mL) was added and the organic layer was extracted. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a yellow oil. Purification by FC (CH_2Cl_2) afforded esters **129a** and **129b** (*dr* 45:55) as a clear oil. ***129a*****:** δ_H ($CDCl_3$, 400 MHz) 7.55-7.49 (1H, ArH), 7.18-7.11 (3H, ArH), 3.88 (3H, s, OCH_3), 3.49 (1H, qd, *J* 7.0 and 3.1 Hz, ArCH), 3.33 (1H, d, *J* 2.9 Hz, OH), 2.40 (3H, s, $ArCH_3$), 1.23 (3H, d, *J* 4.2 Hz, $^{13}CCH_3$), 1.20 (3H, dd, *J* 7.0 and 4.5 Hz, ArCHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 77.52. ***129b*****:** δ_H ($CDCl_3$, 400 MHz) 7.55-7.49 (1H, ArH), 7.18-7.11 (3H, ArH), 3.52 (3H, s, OCH_3), 3.41 (1H, qd, *J* 7.1 and 2.8 Hz, ArCH), 3.25 (1H, d, *J* 2.8 Hz, OH), 2.40 (3H, s, $ArCH_3$), 1.55 (3H, d, *J* 4.3 Hz, $^{13}CCH_3$), 1.36 (3H, dd, *J* 7.0 and 4.2 Hz, ArCHC*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 76.92. MS (EI) *m/z* 223 (5, M^+), 164 (18), 119 (100), 105 (22), 91 (20), 84 (18), 44 (19); HRMS (EI) 223.1289 calcd for $^{13}C_1{}^{12}C_{12}H_{18}O_3$, found 223.1295, Δ = +2.7 ppm.

Method B (Base promoted BER):

Diketone **119** (15 mg, 0.079 mmol, 1 eq.) was dissolved in MeOH (1.5 mL) and NaOH (25 mg, 0.629 mmol, 8 eq.) was added. The solution was stirred at 40 °C for 16 h then allowed to cool to room temperature and diluted with CH_2Cl_2 (6 mL). Brine (10 mL) was added and the organic layer extracted. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a yellow oil. Purification by FC (CH_2Cl_2) afforded esters **129a** and **129b** (*dr* 59:41) as a clear oil. Data as above.

1,4,5,8-Tetrahydro-naphthalene (130)[60]



Chemical Formula: $C_{10}H_{12}$
Molecular Weight: 132.2023

A 3 L round-bottomed flask was fitted with a mechanical stirrer, an acetone/cardice cold finger and a pressure-equalising dropping funnel. The flask was cooled to -78 °C and ammonia was condensed through a KOH drying tower. Sodium lumps (100 g, 4.35 mmol, 5.6 eq.) were added over 45 min with vigorous stirring. A solution of naphthalene (100 g, 0.78 mmol, 1 eq.) in a mixture of EtOH (230 mL) and Et_2O (300 mL), was added *via* the dropping funnel over a course of 2.5 h. Residual naphthalene was washed from the apparatus using Et_2O (30 mL). The reaction mixture was left to stir at -78 °C for a further 3 h, then the cooling bath was removed and the mixture was left to stand for 16 h. The residual solid was cautiously quenched with ice-cooled MeOH (300 mL) followed by H_2O (2 L). The aqueous mixture was extracted with Et_2O (3 x 300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave an off-white solid. Purification by recrystallisation from MeOH afforded tetrahydro-naphthalene **130** (92.0 g, 696 mmol, 89%) as white plates. Data was consistent with that previously reported.[60] δ_H ($CDCl_3$, 400 MHz) 5.73 (4H, s, CH=CH), 2.54 (8H, s, CH_2).

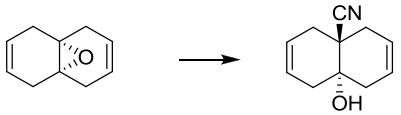
11-Oxa-tricyclo[4.4.1.0^{1,6}]undeca-3,8-diene (131)[60]



Chemical Formula: $C_{10}H_{12}O$
Molecular Weight: 148.2017

Tetrahydronaphthalene **130** (1 g, 7.56 mmol, 1 eq.) and NaOAc (1.12 g, 13.6 mmol, 1.8 eq.) were dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C. Peracetic acid (76.3 mmol, 32% wt. solution in AcOH, 9.07 mmol, 1.2 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 30 min then at rt 1 h. Water (7 mL) was added and the solution was stirred for 30 min then the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) then the combined organic extracts were washed with 5% NaOH (aq.), dried over $MgSO_4$ and concentrated *in vacuo* to leave a white crystalline solid. Purification by FC (EtOAc/hexane, 1:49) afforded epoxide **131** (748 mg, 5.05 mmol, 67%) as a white crystalline solid. Data was consistent with that previously reported.[60] δ_H ($CDCl_3$, 400 MHz) 5.48 (4H, m, HC=CH), 2.57-2.49 (4H, m, CH_2), 2.40-2.34 (4H, m, CH_2).

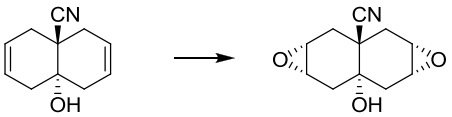
8a-Hydroxy-1,5,8,8a-tetrahydro-4*H*-naphthalene-4a-carbonitrile (132)[60]



Chemical Formula: $C_{11}H_{13}NO$
Molecular Weight: 175.2270

Epoxide **131** (31 g, 209 mmol, 1 eq.) and KCN (136.1 g, 2.09 mol, 10 eq.) was dissolved in a mixture of water (1800 mL) and MeCN (1200 mL). The solution was heated at 85 °C for 4 days, during which time it turned black. After allowing to cool to room temperature, water (100 mL) was added followed by $CHCl_3$ (200 mL). The mixture was slowly acidified with 3M HCl and the organic layer was removed. The aqueous layer was further extracted with $CHCl_3$ (6 x 500 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to leave a brown/white solid. The solid was passed through a plug of silica eluting with 20-50% MeOH/CH_2Cl_2. Purification FC (EtOAc/hexane, 2:3) followed by recrystallisation from EtOAc afforded cyanohydrin **132** (23.5 g, 134 mmol, 64%) as a white crystalline solid. Data was consistent with that previously reported.[60] R_f 0.54 (EtOAc/hexane, 1:1); δ_H ($CDCl_3$, 400 MHz) 5.73 (4H, m, HC=CH), 2.60-2.47 (4H, CH_2), 2.36-2.28 (4H, CH_2).

9β-Cyano-(2α,3α),(6α,7α)-dioxido-10α-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene (133)[60]

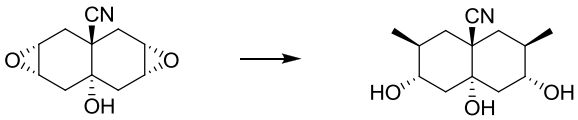


Chemical Formula: $C_{11}H_{13}NO_3$
Molecular Weight: 207.2258

Diene **132** (10 g, 57.1 mmol, 1 eq.) was dissolved in CH_2Cl_2 (61 mL) and $VO(acac)_2$ (1.51 g, 5.71 mmol, 0.1 eq.) was added and the solution was cooled to 0 °C. TBHP (3.75M solution in toluene, 60.9 mL, 228 mmol, 4 eq.) was added dropwise over 20 min turning the green solution orange/red. The solution was then heated at 70 °C for 21 h and the pale yellow solution was allowed to cool to room temperature. 10% Na_2SO_3 was cautiously added, which returned the solution to a green colour. After stirring at room temperature for 30 min, the organic layer was removed and the aqueous was further extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extractions were dried over $MgSO_4$ and concentrated *in vacuo* to leave white/brown solid. Purification by FC (CH_2Cl_2 to MeOH/CH_2Cl_2, 3:7), followed by recrystallisation (EtOAc) afforded *bis*-epoxide **133** (8.53 g, 41.2 mmol, 72%) as a white crystalline solid. Data was consistent with that previously reported.[60] R_f 0.25 (EtOAc/hexane, 1:1); δ_H ($CDCl_3$, 400 MHz) 3.44

(1H, s, OH), 3.38-3.32 (4H, CHO), 2.45-2.35 (4H, CH_2), 2.16 (2H, dd, *J* 16 and 2.1 Hz, CH_2), 2.07 (2H, d, *J* 16 Hz, CH_2).

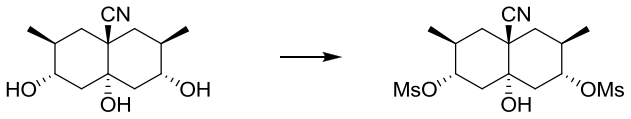
9β-Cyano-2β,7β-dimethyl-3α,6α,10α-trihydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene (134)[60]



Chemical Formula: $C_{13}H_{21}NO_3$
Molecular Weight: 239.3107

Bis-epoxide **133** (5 g, 24.13 mmol, 1 eq.) was dissolved in CH_2Cl_2 (150 mL) and Me_3Al (2.0 M solution in hexane, 48.3 mL, 96.51 mmol, 4 eq.) was added. The reaction mixture was heated to reflux for 16 h then cooled in an ice-bath. With constant cooling, 2 M aq. HCl (250 mL) was added cautiously. The organic layer was extracted and the aqueous phase was further extracted with $CHCl_3$ (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave trihydroxy **134** (5.02 g, 21.0 mmol, 87%) as a white solid. Data was consistent with that previously reported.[60] R_f 0.34 (MeOH/DCM, 1:9); δ_H ($CDCl_3$, 400 MHz) 2.19-2.13 (6H, CH_2 and C*H*CH_3), 1.89 (2H, dd, *J* 15 and 2.2 Hz, CH_2), 1.62 (2H, d, *J* 12 Hz, CH_2), 1.33 (6H, d, *J* 7.8 Hz, CH_3).

9β-Cyano-2β,7β-dimethyl-3α,6α-dimethylsulfonate-10α-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene (135)[60]

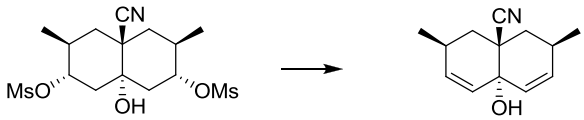


Chemical Formula: $C_{15}H_{25}NO_7S_2$
Molecular Weight: 395.4915

To a suspension of trihydroxy **134** (3 g, 12.5 mmol, 1 eq.) in CH_2Cl_2 (70 mL), Et_3N (5.24 mL, 37.6 mmol, 3 eq.) was added. The mixture was cooled to -10 °C in a water/NaCl bath and MsCl (2.92 mL, 37.6 mmol, 3 eq.) was added dropwise ensuring the temperature of the reaction mixture did not rise above 10 °C. The mixture was left to stir at room temperature for 17 h and then partitioned by the addition of saturated aq. NH_4Cl (70 mL) and CH_2Cl_2 (70 mL). The organic phase was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 70 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a brown/orange, viscous oil. Purification by FC (EtOAc/hexane, 1:4 to 1:1) afforded mesylate **135** (3.40 g, 8.60 mmol, 69%) as a white solid. Data was consistent with that previously reported.[60] R_f 0.36 (EtOAc/hexane, 1:1); δ_H ($CDCl_3$, 400 MHz) 4.87 (2H, dd, *J* = 7.7 and 3.8 Hz,

C*H*OMs), 3.24 (1H, s, OH), 3.05 (6H, s, SO_2CH_3), 2.48-2.43 (2H, CH_2), 2.37 (2H, dd, *J* 16 and 4.6 Hz, CH_2), 2.20-2.15 (4H, CH_2 and C*H*CH_3), 1.72 (2H, dd, *J* 14 and 3.0 Hz, CH_2), 1.35 (6H, d, *J* 7.7 Hz, $CHCH_3$); MS (EI) *m/z* 394 ($[M-H]^-$, 23).

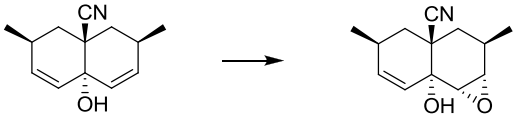
9β-Cyano-2β-7β-dimethyl-10α-hydroxy-1,2,7,8,9,10-hexahydronaphthalene (136)[60]



Chemical Formula: $C_{13}H_{17}NO$
Molecular Weight: 203.2802

A suspension of mesylate **135** (3.4 g, 8.60 mmol) in DBU (8 mL) was heated at 110 °C for 17 h. After allowing to cool to room temperature, the black solution was diluted with CH_2Cl_2 (70 mL) and 1M citric acid (aq.) (100 mL). The organic phase was extracted and the aqueous layer was then further extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated *in vacuo* to leave a white crystalline solid and a brown oil. The mixture was passed through a pad of alumina silica eluting with CH_2Cl_2 to afford diene **136** (1.29 g, 6.36 mmol, 74%) as a white crystalline solid. Data was consistent with that previously reported.[60] R_f 0.50 (EtOAc/hexane, 1:9); δ_H ($CDCl_3$, 400 MHz) 5.95 (2H, dd, *J* = 9.9 and 2.2 Hz, OCC*H*=CH), 5.90 (2H, dd, *J* = 10 and 2.7 Hz, OCCH=C*H*), 2.56 (2H, m, C*H*CH_3), 2.22 (2H, dd, *J* = 8.6 and 14 Hz, CH_2), 1.73 (2H, d, *J* 14 Hz, CH_2), 1.35 (6H, d, *J* = 7.7 Hz, $CHCH_3$).

(-)-(1*S*,2*R*,3a*R*,5*S*,7a*R*,7b*S*)-7*α*-Hydroxy-2,5-dimethyl-1a,2,3,3a,4,5,7a,7b-octahydronaphtho[1,2-b]oxirene-3a-carbonitrile (137)[60]

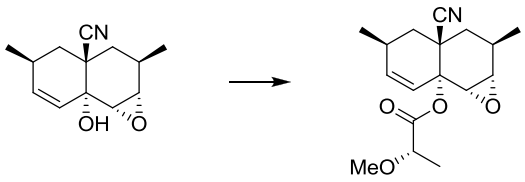


Chemical Formula: $C_{13}H_{17}NO_2$
Molecular Weight: 219.2796

L-(+)-DIPT (114 µL, 0.57 mmol, 1.1 eq.) was added to $Zr(O^iPr)_4.{}^iPrOH$ (210 mg, 0.57 mmol, 1.1 eq.) in CH_2Cl_2 (3.5 mL). The mixture was cooled to -42 °C and TBHP (3.75M solution in toluene, 315 µL, 1.25 mmol, 2.4 eq.) was added dropwise. After stirring for 15 min, diallylic alcohol **136** (100 mg, 0.52 mmol, 1 eq.) in CH_2Cl_2 (1.6 mL) was added dropwise over 5 min. The reaction mixture was left to stand at -20 °C for 42 h. The reaction was quenched with 20% Na_2SO_3 (6 mL) and the organic layer extracted. The aqueous layer was further extracted with $CHCl_3$ (3 x 15 mL)and the combined organic extractions were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow/orange oil. Purification by FC (EtOAc/hexane, 1:10 to 3:10) using silica gel washed prior with 1% Et_3N/hexane, afforded epoxide **137** (102 mg, 0.465 mmol, 95%,

ee 48%) as a white solid. Data was consistent with that previously reported.[60] R_f 0.30 (EtOAc/hexane, 1:3); δ_H ($CDCl_3$, 400 MHz) 6.00 (1H, dd, *J* 9.9 and 3.2 Hz, COHC*H*=CH), 5.93 (1H, dd, *J* 9.9 and 2.3 Hz, COHCH=C*H*), 3.48 (1H, d, *J* 3.7 Hz, CHO), 3.31 (1H, d, *J* 3.7 Hz, CHO), 2.98 (1H, s, OH), 2.56 (1H, m, C*H*CH_3), 2.42 (1H, t, *J* Hz, C*H*CH_3), 2.16 (1H, dd, *J* 14 and 8.5 Hz, CH_2), 1.77 (1H, dd, *J* 14 and 8.6 Hz, CH_2), 1.58 (1H, d, *J* 14 Hz, CH_2), 1.45 (3H, d, *J* 8/6 Hz, CH_3), 1.41 (1H, d, *J* 14 Hz, CH_2), 1.33 (3H, d, *J* 7.7 Hz, CH_3).

(-)-(2'*S*)-((1a*S*,2*R*,3a*R*,5*S*,7a*R*,7b*S*)-3a-Cyano-2,5-dimethyl-1a,2,3,3a,4,5,7a,7b-octahydronaphtho[1,2-b]oxiren-7a-yl) 2-methoxypropanoate (139)[7]

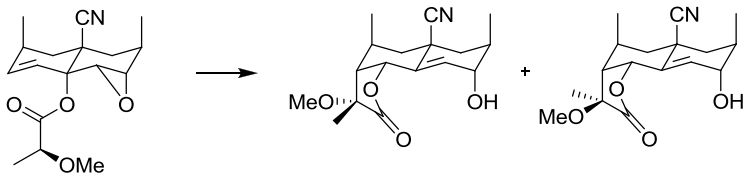


Chemical Formula: $C_{17}H_{23}NO_4$
Molecular Weight: 305.3688

Triethylamine (67 µL, 0.239 mmol, 1.05 eq., *ee* 22%) was added to a solution of (-)-(*S*)-2-methoxypropionic acid (44 µL, 0.239 mmol, 1.05 eq.) in toluene (1 mL). 2,4,6-Trichlorobenzoyl chloride (75 µL, 0.239 mmol, 1.05 eq.) was added and the solution was left to stir at room temperature for 1.5 h. Allylic alcohol **137** (50 mg, 0.228 mmol, 1 eq., *ee* 22%) and 4-DMAP (31 mg, 0.125 mmol, 0.55 eq.) in toluene (1 mL) was added, turning the solution pale yellow. The solution was heated at 60 °C for 20 h then concentrated *in vacuo* to leave a yellow solid. Purification by FC (EtOAc/hexane, 3:17) afforded ester **139** (55 mg, 0.180 mmol, 79%, *de* 48%) as a clear oil. Data was consistent with that previously reported.[7] R_f 0.27 (EtOAc/hexane, 1:4); ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 6.47 (1H, dd, *J* 9.9 and 2.6 Hz, C=C*H*, *H*-7), 5.99 (1H, dd, *J* 9.9 and 2.9 Hz, C=C*H*, *H*-6), 3.83 (1H, q, *J* 8.2 Hz, C*H*OCH_3), 3.67 (1H, d, *J* 3.3 Hz, CH(O), *H*-4), 3.40 (3H, s, OCH_3), 3.21 (1H, d, *J* 3.2 Hz, CH(O), *H*-3), 2.55 (1H, m), 2.45 (1H, dd, *J* 8.0 and 2.6 Hz), 2.25 (1H, dd, *J* 14 and 8.4 Hz, C*H*H, *H*-9), 1.94 (1H, dd, *J* 14 and 8.4 Hz, CH*H*, *H*-1), 1.69 (1H, d, *J* 14 Hz, C*H*H, *H*-9), 1.49-1.45 (4H, CH_3 and C*H*H, *H*-1), 1.36 (3H, d, *J* 6.9 Hz, CHCH_3), 1.35 (3H, d, *J* 7.7 Hz, C*H*CH_3). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 6.47 (1H, dd, *J* 9.9 and 2.6 Hz, C=C*H*, *H*-7), 5.99 (1H, dd, *J* 9.9 and 2.9 Hz, C=C*H*, *H*-6), 3.83 (1H, q, *J* 8.2 Hz, C*H*OCH_3), 3.67 (1H, d, *J* 3.3 Hz, CH(O), *H*-4), 3.37 (3H, s, OCH_3), 3.21 (1H, d, *J* 3.2 Hz, CH(O), *H*-3), 2.55 (1H, m), 2.45 (1H, dd, *J* 8.0 and 2.6 Hz), 2.25 (1H, dd, *J* 14 and 8.4 Hz, C*H*H, *H*-9), 1.94 (1H, dd, *J* 14 and 8.4 Hz, CH*H*, *H*-1), 1.70 (1H, d, *J* 14 Hz, C*H*H, *H*-9), 1.49-1.45 (4H, CH_3 and C*H*H, *H*-1), 1.36 (3H, d, *J* 6.9 Hz, CHCH_3), 1.35 (3H, d, *J* 7.7 Hz, C*H*CH_3).

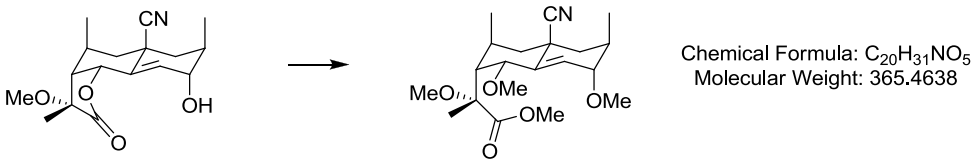
(-)-(3*R*,3a*R*,4*S*,5a*S*,7*R*,8*S*,9b*R*)-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-8-hydroxy-3-methoxy-3,4,7-trimethyl-2-oxonaphtho[1,2-b]furan-5a-carbonitrile (140a)

and **(-)-(3*S*,3a*R*,4*S*,5a*S*,7*R*,8*S*,9b*R*)-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-8-hydroxy-3-methoxy-3,4,7-trimethyl-2-oxonaphtho[1,2-b]furan-5a-carbonitrile (140b)**[7]



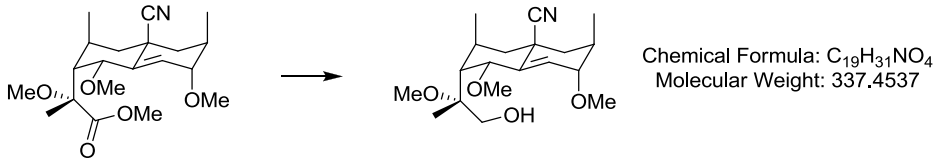
Ester **139** (50 mg, 0.164 mmol, 1 eq.) was dissolved in THF (0.5 mL) and cooled to -78 ^{o}C. TMSCl (46 µL, 0.360 mmol, 2.2 eq.) was added followed by 1M LHMDS in THF (360 µL, 0.180 mmol, 1.1 eq.). The solution was stirred at -78 ^{o}C for 30 min, then at room temperature for 30 min, then heated at 60 ^{o}C for 14.5 h. The solution was diluted with Et_2O (5 mL) and water (10 mL) was added. The mixture was concentrated *in vacuo* to remove all THF, and the mixture was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale yellow oil. Purification by FC (1:4 to 3:7, EtOAc/hexane) afforded lactone **140a** (19 mg, 0.0623 mmol, 38%) as white crystalline solid and lactone **140b** (10 mg, 0.0327 mmol, 20%) as a clear oil. Data was consistent with that previously reported.[7] ***Epimer 140a*****:** Rf 0.30 (2:3, EtOAc/hexane); δ_H ($CDCl_3$, 400 MHz) 5.91 (1H, t, *J* 2.4 Hz, C=C*H*), 5.31 (1H, dt, *J* 8.1 and 2.4 Hz, C*H*OC(O)), 3.92 (1H, m, C*H*OH), 3.24 (3H, s, OCH_3), 2.35 (1H, m, C*H*CH_3), 2.31 (1H, dd, *J* 7.8 and 3.2 Hz, C*H*CCH_3OCH_3), 2.20 (1H, dd, *J* 13 and 6.0 Hz, C*H*H, H-9), 1.99 (1H, s, C*H*CH_3), 1.97 (1H, d, *J* 2.3 Hz, C*H*H, H-1), 1.87 (1H, dd, *J* 13 and 4.3 Hz, CH*H*, H-9), 1.69 (1H, dt, *J* 13 and 6.9 Hz, CH*H*, H-1), 1.59 (1H, bs, OH), 1.41 (3H, s, CH_3), 1.40 (3H, d, *J* 6.2 Hz, CH_3), 1.16 (3H, d, *J* 6.8 Hz, CH_3); δ_C ($CDCl_3$, 100 MHz) 174.21 (s), 132.84 (s), 126.14 (d), 123.91 (s), 76.53 (s), 74.89 (d), 70.97 (d), 53.79 (d), 51.32 (q), 42.09 (d), 39.27 (t), 33.25 (s), 33.04 (t), 25.54 (d), 22.57 (q), 17.95 (q), 17.31 (q). ***Epimer 140b*****:** Rf 0.15 (2:3, EtOAc/hexane); δ_H ($CDCl_3$, 400 MHz) 5.98 (1H, dd, *J* 3.3 and 2.2 Hz, C=CH), 5.32 (1H, dt, *J* 9.7 4.6 Hz, CHOC(O)), 4.01 (1H, m, C*H*OH), 3.42 (3H, s, OCH_3), 2.75 (1H, dd, *J* 9.7 and 7.5 Hz, C*H*$COCH_3$, H-7), 2.03-1.88 (6H, m), 1.39 (3H, s, C*H*$_3COCH_3$), 1.24 (3H, d, *J* 6.7 Hz, CH_3), 1.23 (3H, d, *J* 7.0 Hz, CH_3); δ_C ($CDCl_3$, 100 MHz) 176.23 (s), 132.52 (s), 126.24 (d), 123.21 (s), 78.72 (s), 77.23 (d), 69.24 (d), 51.73 (q), 48.10 (d), 42.68 (d), 37.10 (t), 33.53 (t), 31.95 (s), 26.33 (d), 20.69 (q), 20.47 (q), 17.20 (q).

(-)-(2'*R*)-2-[(1*R*,2*R*,3*S*,4a*S*,6*R*,7*S*)-4a-Cyano-1,7-dimethoxy-3,6-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl]-2-methoxypropionic acid methyl ester (142)[7]



Lactone **140a** (20 mg, 0.0655 mmol, 1 eq.) was dissolved in THF (0.8 mL). KOH (37 mg, 0.655 mmol, 10 eq.) was added, followed by MeI (41 µL, 0.655 mmol, 10 eq.) to form a pale yellow solution. The solution was heated at 60 ^{o}C for 3 h then allowed to cool to room temperature. EtOAc (10 mL) followed by water (10 mL) was added and the organic layer was separated. The aqueous layer was further extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford ester **142** (23 mg, 0.0629 mmol, 96%) as a pale yellow oil. No further purification was required. Data was consistent with that previously reported.[7] R_f 0.75 (EtOAc/hexane, 2:3); δ_H ($CDCl_3$, 400 MHz) 5.96 (1H, t, *J* 1.8 Hz, C=C*H*), 4.21 (1H, dt, *J* 5.2 and1.8 Hz, C*H*OCH_3), 3.72 (3H, s, OCH_3), 3.60 (1H, dt, *J* 6.5 and 2.4 Hz, C*H*$COCH_3$), 3.43 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.19 (3H, s, OCH_3), 2.45 (1H, p, *J* 7.5 Hz, C*H*$COCH_3$), 2.35-2.30 (2H, CH), 1.93-1.79 (3H, CH and CH_2), 1.73 (1H, d, *J* 13 Hz, CH_2), 1.45 (3H, d, *J* 7.7 Hz, CHCH_3), 1.43 (3H, s, C(OCH_3)CH_3), 1.11 (3H, d, *J* 6.5 Hz, CHCH_3); δ_C ($CDCl_3$, 100 MHz) 174.75 (s), 133.51 (s), 125.64 (s), 122.94 (d), 80.44 (s), 79.02 (d), 77.24 (d), 58.02 (q), 52.95 (q), 51.42 (q), 51.34 (d), 41.15 (t), 40.38 (t), 34.88 (s), 30.34 (d), 28.56 (d), 22.34 (q), 21.38 (q), 17.47 (q).

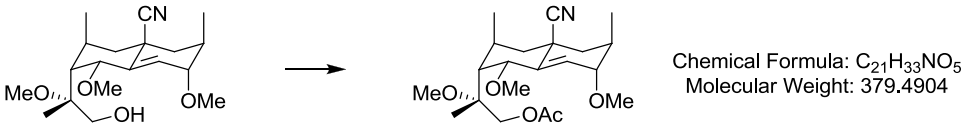
(-)-(1*R*,2*R*,3*S*,4a*S*,6*R*,7*S*)-2-[(1'*R*)-2-Hydroxy-1-methoxy-1-methyl-ethyl]-1,7-dimethoxy-3,6-dimethyl-1,3,4,5,6,7-hexahydro-2*H*-naphthalene-4a-carbonitrile (143)[7]



Ester **142** (49 mg, 0.134 mmol, 1 eq.) was dissolved in THF and cooled to -5 ˚C. $LiAlH_4$ (21 mg, 0.562 mmol, 4.2 eq) was added in 2 portions. The suspension was stirred at 0 ˚C for 2.5 h then diluted with EtOAc (15 mL) and washed with water (15 mL). The aqueous layer was further extracted with EtOAc and the combined organic extracts

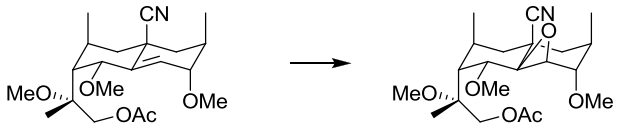
were dried over $MgSO_4$ then concentrated *in vacuo* to leave a clear oil. Purification by FC (EtOAc/hexane, 1:4 to 1:3) afforded alcohol **143** (28 mg, 0.0830 mmol, 63%) as a clear oil. R_f 0.25 (EtOAc/hexane, 2:3); ν_{max}/cm^{-1} (neat) 3484 (OH), 2934 (CH), 2165 (C≡N), 1726 (C=C), 1458 (CH), 1085 (C-O); δ_H ($CDCl_3$, 400 MHz) 5.93 (1H, s, C=CH), 4.29 (1H, m, C*H*OCH_3), 3.83 (1H, dd, *J* 11 and 4.4 Hz, C*H*$_2$OH), 3.58-3.54 (2H, C*H*$_2$OH and C*H*OCH_3), 3.46 (3H, s, OCH_3), 3.42 (1H, m, C*H*OCH_3), 3.39 (3H, s, OCH_3), 3.10 (3H, s, OCH_3), 2.45 -2.35 (2H, C7, C9 eq.), 2.05 (1H, d, *J* 5.0 Hz, C9 ax.), 1.94-1.83 (3H, C*H*$_2$ and C*H*CH_3), 1.71 (1H, d, *J* 13 Hz, C*H*CH_3), 1.44 (3H, d, *J* 7.4 Hz, CHC*H*$_3$), 1.27 (3H, s, C(OCH_3)C*H*$_3$), 1.12 (3H, d, *J* 6.6 Hz, CHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 133.36 (s), 125.47 (s), 123.43 (d), 79.83 (d), 79.27 (s), 66.27 (d), 57.77 (t), 55.62 (q), 51.53 (q), 49.01 (q), 41.20 (d), 40.38 (t), 35.40 (s), 30.63 (d), 29.20 (d), 22.61 (q), 20.91 (q), 17.72 (q); MS (ESI) *m/z* 338 (62, MH^+), 339 (17), 360 (58, MNa^+), 363 (100); HRMS (ESI) 360.2140 calcd for $C_{19}H_{31}NNaO_4^+$ (MNa^+), found 360.2151, Δ = +3.05 ppm; $[\alpha]_D^{20}$ -6.9 (*c* = 2.6, CH_2Cl_2).

(+)-Acetic acid (1*R*,2*R*,3*S*,4*R*,6*R*,8*S*,9*R*,10*R*,12*R*)-6 -hydroxy-3,12-dimethoxy-4,8,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-10-ylmethyl ester (144)[7]



Alcohol **143** (10 mg, 0.0293 mmol, 1 eq.) was dissolved in pyridine (1 mL). 4-DMAP (4 mg, 0.0293 mmol, 1 eq.) was added followed by Ac_2O (8 µL, 0.0878 mmol, 3 eq.). The solution was stirred at room temperature for 1 h then concentrated *in vacuo* to leave a yellow oil. Purification by FC (1:3, EtOAc/hexane) afforded acetate **144** (11 mg, 0.0290 mmol, 99%) as a colourless oil. Data was consistent with that previously reported.[7] R_f 0.40 (1:3, EtOAc/hexane); δ_H ($CDCl_3$, 400 MHz) 5.99 (1H, t, *J* 1.7 Hz, C=CH), 4.47 (1H, d, *J* 12 Hz, CH*H*OAc), 4.20 (1H, dt, *J* 4.4 and 1.4 Hz, C*H*OCH_3), 4.10 (1H, d, *J* 12 Hz, C*H*HOAc), 3.55 (1H, dt, *J* 6.4 and 2.1 Hz, C*H*OCH_3), 3.42 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 2.42 (1H, m, C*H*C(CH_3)(OCH_3)), 2.21 (1H, dd, *J* 14 and 7.1 Hz, C9*H*H), 2.13 (1H, t, *J* 4.2 Hz), 2.09 (3H, s, C(O)CH_3), 1.91-1.78 (3H, d, CH_2 and C*H*CH_3), 1.75 (1H, d, *J* 14 Hz, C9H*H*), 1.44 (3H, d, *J* 7.6 Hz, CHC*H*$_3$), 1.28 (3H, s, C(C*H*$_3$)(OCH_3), 1.16 (3H, d, *J* 6.4 Hz, CHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 170.87 (s), 134.16 (d), 125.19 (2C, s), 80.05 (d), 78.81 (s), 78.59 (d), 68.50 (t), 57.09 (q), 56.46 (q), 49.87 (q), 49.63 (q), 41.07 (d), 49.63 (q), 41.07 (d), 40.27 (t), 34.13 (s), 31.34 (t), 27.84 (d), 22.60 (d), 21.07 (q), 20.08 (q), 18.22 (q).

(-)-(2*R*)-2-[(S,*R*,1b*R*,3*S*,4*R*,5*R*,5a*R*,5b*R*)-1b-Cyano-5-dimethoxy-3-dimethyl-octahydro-*H*-naphtho[1,8a-b]oxiren-4-yl]-2-methoxypropylacetate (145a)[7]

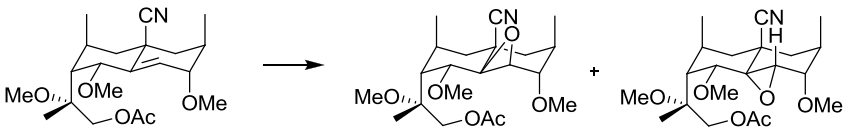


Chemical Formula: $C_{21}H_{33}NO_6$
Molecular Weight: 395.4898

Alkene **144** (10 mg, 0.0264 mmol, 1 eq.) was dissolved in CH_2Cl_2 (1 mL) and *m*-CPBA (6 mg, 0.034 mmol, 1.3 eq.) was added. The solution was stirred at room temperature for 3.5 h, then diluted with CH_2Cl_2 and sat. $NaHCO_3$ (aq.) (10 mL) was added. The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo*. Purification by FC (1:4, EtOAc/hexane) afforded epoxide **145a** (10 mg, 0.0253 mmol, 96%) as a white crystalline solid. Data was consistent with that previously reported.[7] R_f 0.35 (EtOAc/hexane, 1:3); mp 88-89 ˚C (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 4.50 (1H, d, *J* 11 Hz, C*H*HOAc), 4.28 (1H, d, *J* 11 Hz, CH*H*OAc), 4.08 (1H, d, *J* 5.3 Hz, C*H*-(O)), 3.50 (4H, s, OCH_3 and C*H*OCH_3), 3.42 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 2.92 (1H, d, *J* 9.6 Hz, C*H*OCH_3), 2.55-2.51 (2H, C*H*$CHCOCH_3$ and C9), 2.14 (1H, d, *J* 5.3 Hz, C2), 2.11 (3H, s, $C(O)CH_3$), 1.69-1.62 (2H, C*H*CH_3 and CH_2), 1.54 (1H, m, CH_2), 1.50 (3H, d, *J* 7.6 Hz, $CHCH_3$), 1.45 (1H, dd, *J* 9.8 and 3.7 Hz, CH_2), 1.29 (3H, s, $C(CH_3)(OCH_3)$), 0.99 (3H, d, *J* 6.3 Hz, $CHCH_3$); δ_C ($CDCl_3$, 100 MHz) 170.74 (s), 124.61 (s), 81.87 (d), 78.78 (s), 76.35 (d), 69.50 (t), 62.91 (s), 60.40 (d), 60.26 (q), 57.93 (q), 49.73 (q), 49.13 (q), 37.67 (t), 37.13 (s), 36.20 (t), 29.28 (d), 28.75 (d), 22.02 (d), 21.06 (q), 20.52 (q), 18.21 (q); $[\alpha]_D^{20}$ -9.9 (*c* = 0.6, CH_2Cl_2).

(-)-(2*R*)-2-[(*S*,*R*,1b*R*,3*S*,4*R*,5*R*,5a*R*,5b*R*)-1b-Cyano-5-dimethoxy-3-dimethyl-octahydro-*H*-naphtho[1,8a-b]oxiren-4-yl]-2-methoxypropylacetate (145a)[7]

and **(-)-(2*R*)-2-[(*S*,*R*,1b*R*,3*S*,4*R*,5*R*,5a*S*,5b*S*)-1b-Cyano-5-dimethoxy-3-dimethyl-octahydro-*H*-naphtho[1,8a-b]oxiren-4-yl]-2-methoxypropylacetate (145b)**

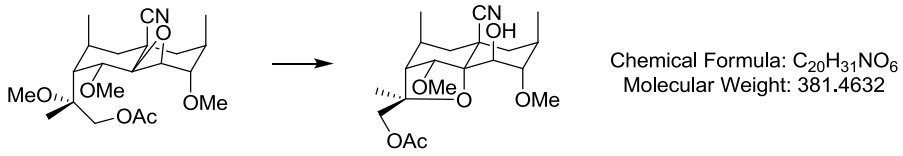


Chemical Formula: $C_{21}H_{33}NO_6$
Molecular Weight: 395.4898

Alkene **144** (26 mg, 0.0686 mmol, 1 eq.) was dissolved in CH_2Cl_2 (2.6 mL) and *m*-CPBA (15 mg, 0.0892 mmol, 1.3 eq.) was added. The solution was stirred at room temperature for 3.5 h then diluted with CH_2Cl_2 and sat. $NaHCO_3$ (aq.) (10 mL) was

added. The organic layer was extracted and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to afford a 66:34 mixture of epoxides **145a** and **145b**. Purification by FC (1:8 to 1:4, EtOAc/hexane) afforded epoxide **145a** (8 mg, 0.0202 mmol, 29%) (data identical as above), a 3:1 mixture of **145a**:**145b** (16 mg, 0.0404 mmol, 59%) and epoxide **145b** (8.5 mg, 0.0214 mmol, 30%) as fine white crystals. (Overall yield of 88% of both diastereoisomers). Data for **145a** was as above. ***145b*****:** R_f 0.39 (EtOAc/hexane, 1:3); mp 57-59 ˚C ($CHCl_3$); ν_{max}/cm^{-1} 2932 (CH), 1740 (C=O), 1385 (CH), 1462 (C-O), 1242 (C-O); δ_H ($CDCl_3$, 400 MHz) 4.51 (1H, d, *J* 11 Hz, CH*H*OAc), 4.31 (1H, d, *J* 11 Hz, C*H*HOAc), 3.82 (1H, d, *J* 5.4 Hz, CH(O)), 3.53 (3H, s, OCH_3), 3.43 (1H, s, C*H*OCH_3), 3.40 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.82 (1H, d, *J* 9.9 Hz, C*H*OCH_3), 2.44 (1H, m, C*H*CHOCH_3), 2.33 (1H, dd, *J* 14 and 5.9 Hz, C*H*CHOCH_3), 2.11 (3H, s, $OCOCH_3$), 2.03 (1H, d, *J* 5.4 Hz, CH_2), 1.78 (1H, d, *J* 14 Hz, CH_2), 1.62 (1H, m, CH_2), 1.29 (3H, s, C(OCH_3)CH_3), 1.28 (1H, m, CH), 1.12 (1H, d, *J* 14 Hz, CH_2), 1.05 (3H, d, *J* 7.6 Hz, CHCH_3), 0.99 (3H, d, *J* 6.4 Hz, CHCH_3); δ_C ($CDCl_3$, 100 MHz) 205.34 (s), 121.35 (s), 82.66 (d), 78.74 (s), 69.58 (d), 63.86 (t), 60.04 (q), 57.89 (d), 57.06 (q), 49.89 (s), 49.68 (q), 48.57 (q), 33.85 (t), 33.57 (t), 28.55 (d), 23.34 (q), 21.07 (q), 20.39 (d), 18.66 (q); MS 416 (44), 413 (MNH_4^+, 9), 399 (63), 367 (MH^+-MeOH, 49), 131 (100); HRMS (CI) 367.2115 calcd for $C_{20}H_{31}O_6^+$ ([M-HCN]$^+$), found 367.2124, Δ = +2.5 ppm; $[\alpha]_D^{20}$ -0.7 (*c* = 0.13, CH_2Cl_2).

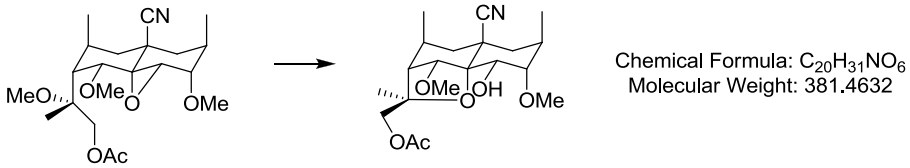
(-)-Acetic acid (1*R*,2*R*,3*S*,4*R*,6*R*,8*S*,9*R*,10*R*,12*R*)-6-cyano-2-hydroxy-3,12-dimethoxy-4,8,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-10-ylmethyl ester (146a)[7]



Epoxide **145a** (8 mg, 0.0202 mmol, 1 eq.) was dissolved in CH_2Cl_2 (1 mL) and LiI (14 mg, 0.101 mmol, 5 eq.) was added. The mixture was cooled to -78 ˚C and BBr_3 (1M solution in CH_2Cl_2, 61 µL, 0.0607 mmol, 3 eq.) was added. The mixture was stirred at -78 ˚C for 3 h then quenched with sat. $NaHCO_3$ (aq.) (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a yellow residue. Purification by FC (7:13, EtOAc/hexane) afforded alcohol **146a** (6 mg, 0.0157 mmol, 78%) as a colourless oil. R_f 0.30 (EtOAc/hexane, 1:1); ν_{max}/cm^{-1} (neat) 3498 (OH), 2924 (CH), 2230 (CΞN), 1740 (C=O), 1462 (CH), 1387 (CH), 1245 (C-O),

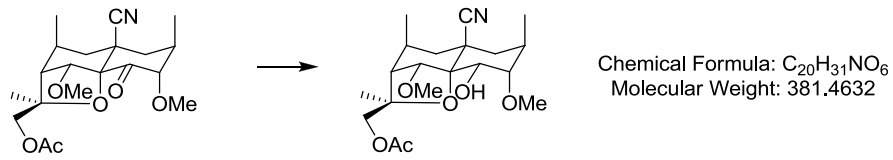
1109 (C-O), 1039 (C-O); δ_H ($CDCl_3$, 400 MHz) 4.52 (1H, s, C*H*OH), 4.40 (1H, d, *J* 11 Hz, C*H*HOAc), 4.16 (1H, d, *J* 11 Hz, CH*H*OAc), 3.45 (3H, s, OCH_3), 3.39 (3Hs, OCH_3), 3.29 (1H, dd, *J* 5.6 and 3.4 Hz, C*H*OCH_3), 2.87 (1H, d, *J* 3.8 Hz, C*H*OCH_3), 2.37-2.32 (2H, C7 and C9), 2.12 (1H, m, C2), 2.09 (3H, s, C(O)CH_3), 1.99-1.88 (3H, s, C*H*CH_3 and C9), 1.75 (1H, dd, *J* 14 and 6.1 Hz, C2), 1.62 (1H, bs, OH), 1.40 (3H, d, *J* 7.2 Hz, CHC*H*$_3$), 1.36 (3H, s, C(C*H*$_3$)CH_2OAc), 1.27 (3H, d, *J* 7.4 Hz, CHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 170.62 (s), 126.08 (s), 87.23 (s), 85.80 (s), 85.32 (d), 84.03 (d), 71.33 (d), 70.03 (t), 57.65 (q), 55.53 (q), 46.03 (t), 40.58 (t), 36.28 (s), 31.00 (d), 30.32 (q), 29.69 (d), 20.94 (d), 20.08 (q), 19.45 (q), 18.45 (q); MS (ESI) *m/z* 382 (51, MH^+), 404 (100), 405 (32); HRMS (ESI) 382.2224 calcd for $C_{20}H_{32}NO_6^+$ (MH^+), found 382.2222, Δ = -0.5 ppm; $[\alpha]_D^{20}$ -21.1 (*c* = 0.2, CH_2Cl_2).

(-)-Acetic acid (1*R*,2*S*,3*S*,4*R*,6*R*,8*S*,9*R*,10*R*,12*R*)-6-cyano-2-hydroxy-3,12-dimethoxy-4,8,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-10-ylmethyl ester (146b)



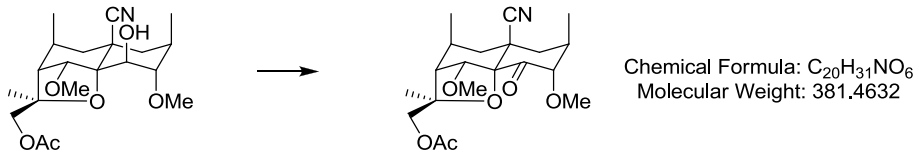
Epoxide **145b** (4 mg, 0.0101 mmol, 1 eq.) and LiI (7 mg, 0.0505 mg, 5 eq.) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to -78 ˚C. BBr_3 (1M solution in CH_2Cl_2, 31 µL, 0.0303 mmol, 3 eq.) was added dropwise and the solution was stirred at -78 ˚C for 3 h then with sat. $NaHCO_3$ (aq.) (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a yellow residue. Purification by FC (7:13, EtOAc/hexane) afforded alcohol **146b** (2 mg, 0.00524 mmol, 52%) as a colourless oil. R_f 0.36 (EtOAc/hexane, 1:1); ν_{max}/cm^{-1} (neat) 3417 (OH), 2924 (CH), 2168 (CΞN), 1739 (C=O), 1383 (CH), 1264 (C-O), 1101 (C-O); δ_H ($CDCl_3$, 400 MHz) 4.86 (1H, d, *J* 11 Hz, C*H*HOAc), 4.16-4.13 (2H, CH*H*OAc and C*H*OH), 3.66 (1H, d, *J* 3.0 Hz, C*H*OCH_3), 3.44 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.25 (1H, d, *J* 11 and 2.8 Hz, C*H*OCH_3), 3.09 (1H, s, C*H*C$HOCH_3$), 2.51-2.48 (2H, C*H*CH_3), 2.22 (1H, m, CH_2), 2.11 (3H, s, C(O)CH_3), 1.87 (1H, m, CH_2), 1.67 (1H, d, *J* 14 Hz, CH_2), 1.56 (1H, m, CH_2), 1.32 (3H, s, CH_3), 1.06 (H, d, *J* 7.1 Hz, CHC*H*$_3$), 1.05 (3H, d, *J* 6.4 Hz, CHC*H*$_3$); δ_C ($CDCl_3$, 100 MHz) 170.86 (s), 129.19 (s), 82.01 (d), 78.48 (d), 75.30 (s), 71.01 (s), 66.74 (d), 65.82 (t), 57.11 (q), 56.50 (q), 52.22 (s), 41.12 (q), 35.52 (t), 31.81 (t), 28.68 (d), 27.23 (d), 23.34 (q), 21.49 (q), 20.95 (d), 18.01 (q); MS (CI) *m/z* 402 (51), 390 (91), 388 (100), 374 (49, M-CN+NH_4), 273 (33); $[\alpha]_D^{19}$ -4.1 (*c* = 0.26, CH_2Cl_2).

(-)-Acetic acid (1*R*,2*S*,3*S*,4*R*,6*R*,8*S*,9*R*,10*R*,12*R*)-6-cyano-2-hydroxy-3,12-dimethoxy-4,8,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-10-ylmethyl ester (146b)



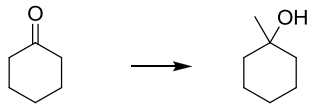
Ketone **147** (6 mg, 0.0157 mmol, 1 eq.) was dissolved in THF (0.6 mL) and MeMgCl (2M solution in THF, 63 µL, 0.126 mmol, 8 eq.). The solution was stirred at room temperature for 4 h then H_2O (3 mL) was added. The solution was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an off-white solid. Purification by FC (EtOAc/hexane, 2:3) afforded alcohol **146b** (3 mg, 0.00764 mmol, 50%) as a white solid. Data as above.

(-)-Acetic acid (1*S*,3*S*,4*R*,6*R*,8*S*,9*R*,10*R*,12*R*)-6-cyano-3,12-dimethoxy-4,8,10-trimethyl-2-oxo-11-oxatricyclo[7.2.1.0^{1,6}]dodec-10-ylmethyl ester (147)[7]



Alcohol **146a** (6 mg, 0.0157 mmol, 1 eq.) was dissolved in CH_2Cl_2 (0.4 mL) and Dess-Martin periodinane (0.3 M solution in CH_2Cl_2, 79 µL, 0.0236 mmol, 1.5 eq.) was added. The mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The white solid was dissolved in EtOAc (10 mL) and washed with saturated $NaHCO_3$ (aq.) (4 x 15 mL), dried over $MgSO_4$ then concentrated *in vacuo* to leave a white solid. Purification by FC (EtOAc) afforded ketone **147** (5.5 mg, 0.0144mmol, 92%) as a white crystalline solid. R_f 0.55 (EtOAc/hexane, 1:1); mp 118-119 ˚C (EtOAc); δ_H ($CDCl_3$, 400 MHz) 4.59 (1H, d, *J* 11 Hz, C*H*HOAc), 4.48 (1H, s, C*H*OCH_3), 4.38 (1H, d, *J* 11 Hz, CH*H*OAc), 4.21 (1H, d, *J* 7.4 Hz, C*H*OCH_3), 3.50 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 2.40-2.34 (2H, C7 and C9), 2.26-2.14 (2H, C8 and C3), 2.10 (3H, s, C(O)CH_3), 1.94 (1H, dd, *J* 15 and 7.1 Hz, CH_2), 1.83 (1H, d, *J* 14 Hz, CH_2), 1.66 (1H, d, *J* 13 Hz, CH_2), 1.43 (3H, d, *J* 7.3 Hz, CHCH_3), 1.38 (3H, d, *J* 7.4 Hz, CHCH_3), 1.37 (3H, s, CCH_3(CH_2OAc)); δ_C ($CDCl_3$, 100 MHz) 203.51 (s), 170.55 (s), 124.95 (s), 88.60 (s), 87.14 (d), 86.49 (s), 85.97 (s), 69.80 (t), 58.92 (q), 58.14 (q), 50.68 (q), 42.72 (s), 38.30 (d), 35.44 (t), 34.14 (t), 30.43 (d), 29.70 (d), 21.00 (q), 10.15 (q), 19.89 (q), 18.59 (q); MS (CI) *m/z* 397 (MNH_4^+, 100), 383 (35), 348 (MH^+ -MeOH, 100); HRMS (CI) 397.2702 calcd for $C_{21}H_{37}N_2O_5$ (MNH_4^+), found 397.2706, Δ = 1.0 ppm; $[\alpha]^{22}_D$ -2.1 (*c* = 1.2, CH_2Cl_2).

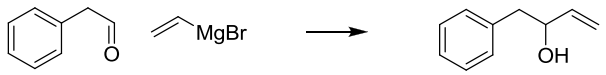
(±)-1-Methylcyclohexan-1-ol (148)[166]



Chemical Formula: $C_7H_{14}O$
Molecular Weight: 114.1855

Cyclohexanone (50 µL, 0.483 mmol, 1 eq.) was dissolved in THF (3 mL). MeMgCl (3M solution in THF, 480 µL, 1.45 mmol, 3 eq.) was added dropwise at room temperature and the solution was stirred for 3 h. Sat. NH_4Cl (aq.) (5 mL) was added and mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to afford alcohol **148** (52 mg, 0.455 mmol, 94%) as a clear oil. Data was consistent with that previously reported.[167] δ_H ($CDCl_3$, 400 MHz) 1.76-1.29 (10H, CH_2), 1.23 (3H, s, CH_3); MS (EI) *m/z* 114 (24, M^+), 99 (73), 84 (84), 71 (100), 55 (57).

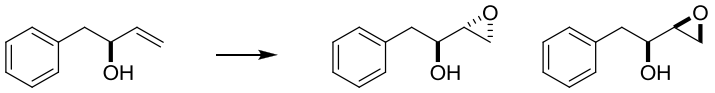
(±)-1-Phenyl-3-buten-2-ol (151)[168]



Chemical Formula: $C_{10}H_{12}O$
Molecular Weight: 148.2017

Aldehyde **150** (0.56 g, 4.66 mmol, 1 eq.) was dissolved in THF (10 mL) and cooled to 0 °C. Vinyl magnesiumbromide (1M in THF, 5.1 mL, 5.12 mmol, 1.1 eq.) was added dropwise and the yellow solution was stirred at 0 °C for 30 min. The reaction was quenched with water (10 mL) and the mixture concentrated *in vacuo* to remove the THF. The aqueous solution was acidified to pH 3 with 1M HCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ then concentrated *in vacuo* to leave a pale yellow liquid. Purification by FC (1:9, EtOAc/hexane) afforded alcohol **151** (280 mg, 1.89 mmol, 40%) as a pale yellow liquid. Data was consistent with that previously reported.[169] R_f 0.50 (CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.37-7.26 (5H, Ar), 5.97 (1H, ddd, *J* 17, 10 and 5.8 Hz, C*H*=CH_2), 5.29 (1H, dt, *J* 17 and 1.3 Hz, H_{cis}), 5.17 (1H, dt, *J* 10 and 1.1 Hz, H_{trans}), 4.39 (1H, m, C*H*OH), 2.92 (1H, dd, *J* 14 and 5.1 Hz, $ArCH_2$), 2.82 (1H, dd, *J* 14 and 7.9 Hz, $ArCH_2$), 1.64 (1H, d, *J* 3.8 Hz, OH); MS (CI) *m/z* 148 (26), 149 (5, MH^+), 166 (100, MNH_4^+), 167 (28).

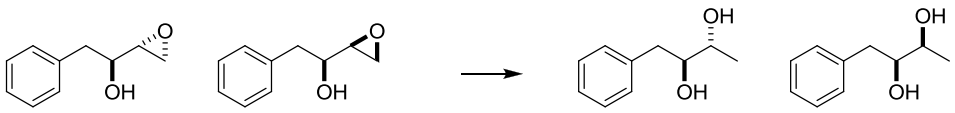
(2*R,3*S**)-** and **(2*R**,3*R**)-3,4-Epoxy-1-phenyl-2-butanol (152)**[170]



Chemical Formula: $C_{10}H_{12}O_2$
Molecular Weight: 164.2011

Allylic alcohol **151** (180 mg, 1.21 mmol, 1 eq.) was dissolved in CH_2Cl_2 (10 mL). After cooling to 0 °C, *μ*-CPBA (252 mg, 1.46 mmol, 1.2 eq.) was added and after 10 min the reaction mixture was allowed to warm to room temperature. After stirring for 16 h, sat. $NaHCO_3$ (aq.) (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (aq.), dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear liquid. Purification by FC (1:4, EtOAc/hexane to CH_2Cl_2) afforded epoxides **152a** and **152b** (*anti*:*syn* 58:42, 195 mg, 1.19 mmol, 98%) as a clear liquid. Data consistent with that previously reported.[171] R_f 0.15 (3:7, EtOAc/hexane); ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.37-7.27 (5H, ArH), 4.05 (1H, m, C*H*OH), 3.08 (1H, m, CHO), 3.03-2.78 (4H), 2.67 (1H, dd, *J* 4.9 and 2,7 Hz, CHO). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.37-7.27 (5H, ArH), 3.77 (1H, m, C*H*OH), 3.08 (1H, m, CHO), 3.03-2.78 (5H). MS (CI) *m/z* 182 (100, MNH_4^+), 183 (22).

(2*S,3*S**)-** and **(2*R**,3*S**)-1-Phenyl-2,3-butanediol (153)**[172]



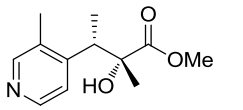
Chemical Formula: $C_{10}H_{14}O_2$
Molecular Weight: 166.2170

Epoxide **152** (188 mg, 1.14 mmol, 1 eq.) was dissolved in THF (5 mL) and cooled to 0 °C. $LiAlH_4$ (48 mg, 1.26 mmol, 1.1 eq.) was added and the solution was allowed to warm to room temperature and stirred for a further 18 h. Et_2O (15 mL) and water (20 mL) was added and the mixture was stirred for 5 min. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a clear oil. Purification by FC (1:1, EtOAc/hexane) afforded 1,2-diols **153** (176 mg, 1.06 mmol, 93%, *dr* 40:60) as a clear oil. Data was consistent with that previously reported.[172] R_f 0.60 (1:19, MeOH/CH_2Cl_2); ***Major diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.38-7.34 (2H, ArH), 7.28 (3H, ArH), 3.73 (1H, m, C*H*OH), 3.64 (1H, m, C*H*OH), 2.94 (1H, dd, *J* 14 and 4.0 Hz, $ArCH_2$), 2.77-2.69 (1H, $ArCH_2$), 2.22 (1H, d, *J* 4.6 Hz, OH), 1.99 (1H, d, *J* 4.6 Hz, OH), 1.30 (3H, d, *J* 6.3 Hz, CH_3). ***Minor diastereoisomer*****:** δ_H ($CDCl_3$, 400 MHz) 7.38-7.34

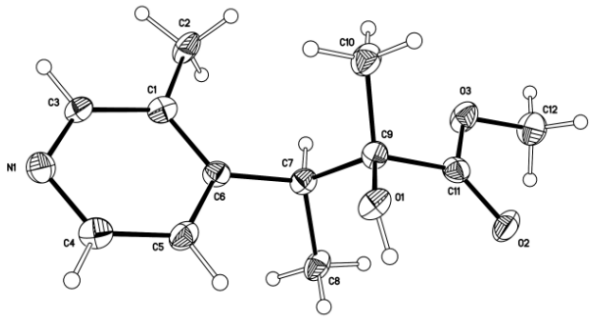
(2H, ArH), 7.28 (3H, ArH), 3.92 (1H, m, C*H*OH), 3.86 (1H, m, C*H*OH), 2.88 (1H, dd, *J* 14 and 3.7 Hz, $ArCH_2$), 2.77-2.69 (1H, $ArCH_2$), 1.96 (1H, d, *J* 4.8 Hz, OH), 1.86 (1H, d, *J* 3.3 Hz, OH), 1.30 (3H, d, *J* 6.4 Hz, CH_3). MS (CI) *m/z* 184 (100, MNH_4^+), 185 (13).

Appendix 1 - X-ray Data

(-)- (2*S*,3*R*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683



Formula	C12 H17 N O3	
Formula weight	223.27	
Temperature	173 K	
Diffractometer wavelength	Cu Kα, 1.54178	
Crystal system, space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5034(2) Å	α = 90 °
	b = 12.2919(4) Å	β = 90 °
	c = 13.0178(4) Å	γ = 90 °
Volume, Z	1200.65(6) Å^3, 4	
Reflns collected / unique	11172 / 2448 [R(int) = 0.0143]	
Reflns observed [F>4σ(F)]	2448	
Absorption correction	Analytical	
Max. transmission	0.80	
Final R indices [F>4σ(F)]	R1 = 0.0302, wR2 = 0.0734	
R indices (all data)	R1 = 0.0338, wR2 = 0.0760	
Absolute structure parameter	x+ = -0.03(17)	

Bond Lengths (Å)

C(30)-H(33)	0.9799	C(24)-C(29)	1.5336
C(30)-H(32)	0.9798	C(24)-C(25)	1.5239
C(30)-H(31)	0.9806	C(20)-H(23)	0.9791
C(25)-H(28)	0.9787	C(20)-H(22)	0.9802
C(25)-H(27)	0.9796	C(20)-H(21)	0.9798
C(25)-H(26)	0.9795	C(18)-H(19)	0.9994

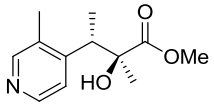
C(18)-C(24)	1.5678	C(6)-C(7)	1.5076
C(18)-C(20)	1.5328	C(6)-C(17)	1.4043
C(17)-C(18)	1.5237	C(6)-C(11)	1.3971
C(15)-H(16)	0.9501	N(5)-C(13)	1.3475
C(15)-C(17)	1.3924	N(5)-C(11)	1.3357
C(13)-H(14)	0.9500	O(4)-C(30)	1.4495
C(13)-C(15)	1.3837	O(4)-C(29)	1.3419
C(11)-H(12)	0.9495	O(3)-C(29)	1.2072
C(7)-H(10)	0.9800	O(1)-H(2)	0.8682
C(7)-H(9)	0.9800	O(1)-C(24)	1.4067
C(7)-H(8)	0.9804		

Angles (Å)

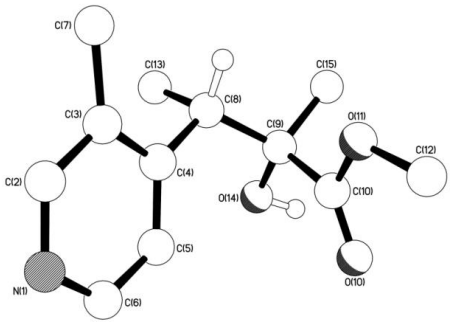
H(33)-C(30)-H(32)	109.5231	H(22)-C(20)-C(18)	109.4544
H(33)-C(30)-H(31)	109.4233	H(21)-C(20)-C(18)	109.5061
H(33)-C(30)-O(4)	109.4336	H(19)-C(18)-C(24)	107.6107
H(32)-C(30)-H(31)	109.4818	H(19)-C(18)-C(20)	107.6499
H(32)-C(30)-O(4)	109.5237	H(19)-C(18)-C(17)	107.6622
H(31)-C(30)-O(4)	109.4417	C(24)-C(18)-C(20)	111.8304
C(24)-C(29)-O(4)	112.1861	C(24)-C(18)-C(17)	110.8388
C(24)-C(29)-O(3)	124.3634	C(20)-C(18)-C(17)	111.0431
O(4)-C(29)-O(3)	123.4347	C(18)-C(17)-C(15)	120.1407
H(28)-C(25)-H(27)	109.5144	C(18)-C(17)-C(6)	122.4029
H(28)-C(25)-H(26)	109.4912	C(15)-C(17)-C(6)	117.4221
H(28)-C(25)-C(24)	109.4704	H(16)-C(15)-C(17)	119.7764
H(27)-C(25)-H(26)	109.5124	H(16)-C(15)-C(13)	119.7713
H(27)-C(25)-C(24)	109.4184	C(17)-C(15)-C(13)	120.4522
H(26)-C(25)-C(24)	109.4205	H(14)-C(13)-C(15)	118.5702
C(29)-C(24)-C(25)	110.1975	H(14)-C(13)-N(5)	118.5028
C(29)-C(24)-C(18)	107.2273	C(15)-C(13)-N(5)	122.9270
C(29)-C(24)-O(1)	109.4630	H(12)-C(11)-C(6)	117.3644
C(25)-C(24)-C(18)	110.9242	H(12)-C(11)-N(5)	117.3773
C(25)-C(24)-O(1)	106.5089	C(6)-C(11)-N(5)	125.2581
C(18)-C(24)-O(1)	112.5354	H(10)-C(7)-H(9)	109.3933
H(23)-C(20)-H(22)	109.4707	H(10)-C(7)-H(8)	109.4931
H(23)-C(20)-H(21)	109.4732	H(10)-C(7)-C(6)	109.5063
H(23)-C(20)-C(18)	109.4998	H(9)-C(7)-H(8)	109.4237
H(22)-C(20)-H(21)	109.4231	H(9)-C(7)-C(6)	109.5354

H(8)-C(7)-C(6)	109.4754	C(13)-N(5)-C(11)	116.3459
C(7)-C(6)-C(17)	123.8017	C(30)-O(4)-C(29)	114.8420
C(7)-C(6)-C(11)	118.5719	H(2)-O(1)-C(24)	111.9738
C(17)-C(6)-C(11)	117.5906		

(+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate



Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683



Identification code	AS1101	
Formula	C12 H17 N O3	
Formula weight	223.27	
Temperature	173 K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.97836(4) Å	α = 90°
	b = 12.67070(7) Å	β = 90°
	c = 15.76352(9) Å	γ = 90°
Volume, Z	1194.087(12) $Å^3$, 4	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.729 mm^{-1}	
F(000)	480	
Crystal colour / morphology	Colourless shards	
Crystal size	0.35 x 0.22 x 0.10 mm^3	
Θ range for data collection	4.48 to 72.48°	
Index ranges	-7<=h<=6, -15<=k<=15, -19<=l<=19	
Reflns collected / unique	44547 / 2366 [R(int) = 0.0283]	
Reflns observed [F>4σ(F)]	2337	
Absorption correction	Analytical	

Max. and min. transmission	0.939 and 0.839
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2366 / 1 / 152
Goodness-of-fit on F^2	1.049
Final R indices [F>4σ(F)]	R1 = 0.0262, wR2 = 0.0723
	R1+ = 0.0262, wR2+ = 0.0723
	R1- = 0.0264, wR2- = 0.0729
R indices (all data)	R1 = 0.0264, wR2 = 0.0726
Absolute structure parameter	x+ = 0.00(16), x- = 1.05(16)
Extinction coefficient	0.0157(11)
Largest diff. peak, hole	0.161, -0.104 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Bond lengths (Å)

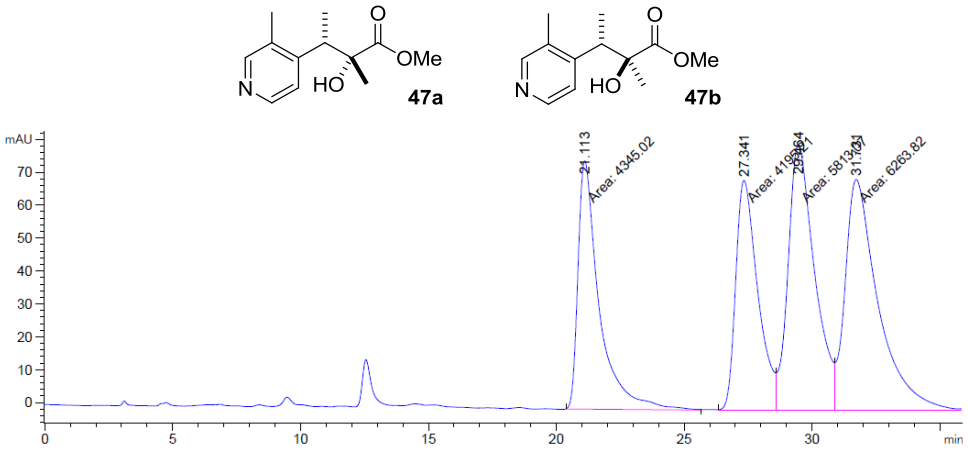
N(1)-C(2)	1.3299(18)	C(8)-C(13)	1.5373(16)
N(1)-C(6)	1.3372(16)	C(8)-C(9)	1.5496(14)
C(2)-C(3)	1.3888(16)	C(9)-O(14)	1.4115(12)
C(3)-C(4)	1.4083(14)	C(9)-C(15)	1.5345(15)
C(3)-C(7)	1.5014(17)	C(9)-C(10)	1.5371(15)
C(4)-C(5)	1.3915(16)	C(10)-O(10)	1.1985(14)
C(4)-C(8)	1.5158(14)	C(10)-O(11)	1.3395(14)
C(5)-C(6)	1.3877(15)	O(11)-C(12)	1.4454(15)

Angles (°)

C(2)-N(1)-C(6)	116.67(10)	C(13)-C(8)-C(9)	110.53(9)
N(1)-C(2)-C(3)	125.38(10)	O(14)-C(9)-C(15)	110.30(8)
C(2)-C(3)-C(4)	117.38(10)	O(14)-C(9)-C(10)	108.97(9)
C(2)-C(3)-C(7)	118.95(10)	C(15)-C(9)-C(10)	106.97(9)
C(4)-C(3)-C(7)	123.65(10)	O(14)-C(9)-C(8)	108.75(8)
C(5)-C(4)-C(3)	117.63(9)	C(15)-C(9)-C(8)	109.99(9)
C(5)-C(4)-C(8)	122.27(9)	C(10)-C(9)-C(8)	111.85(8)
C(3)-C(4)-C(8)	119.98(10)	O(10)-C(10)-O(11)	123.63(10)
C(6)-C(5)-C(4)	119.82(10)	O(10)-C(10)-C(9)	125.23(10)
N(1)-C(6)-C(5)	123.10(11)	O(11)-C(10)-C(9)	111.04(9)
C(4)-C(8)-C(13)	108.21(9)	C(10)-O(11)-C(12)	116.19(10)
C(4)-C(8)-C(9)	115.95(8)		

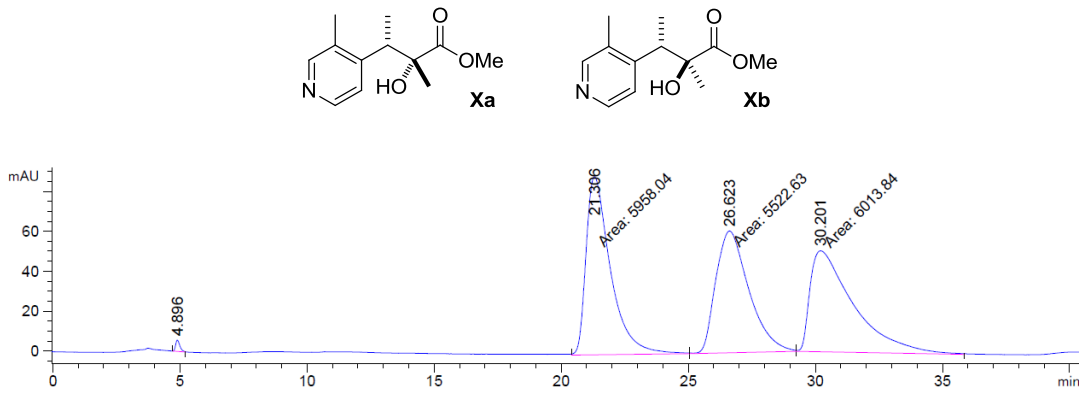
Appendix 2 - HPLC Data

Esters 47a and **47b** (*dr* 45:55).



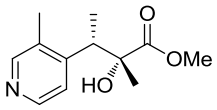
Peak 1 – 21.1 min, (-)-(*S*,*R*)-ester **47a**; ***Peak 2*** – 27.3 min, (+)-(*R*,*S*)-ester **47a**; ***Peak 3*** – 29.5 min, (*R**,*R**)-ester **47b**; ***Peak 4*** – 31.7 min, (*R**,*R**)-ester **47b**. ***Conditions;*** Chiralcel IC; 5 µm; Column Size: 0.46 cmI.D. x 25 cmL; Column number: IC00CE-LL027; Temperature: 10 °C; Flow Rate: 1.2 ml/min; Injection: 5 µL; Solvent: *n*-hexane/IPA = 85:15; Sample conc.: 10 mg/ml (IPA).

Esters 47a and **47b** (*dr* 45:55).

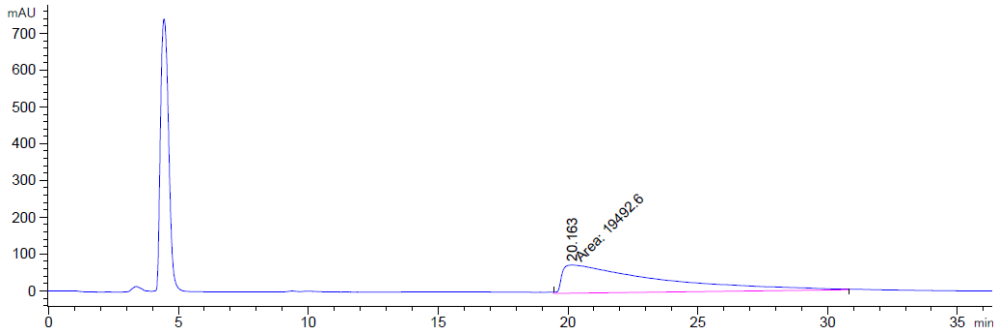


Peak 1 – 21.3 min, (+)-(*S*,*S*)-ester **47b**; ***Peak 2*** – 26.6 min, (*S*,*R*)- and (*R*,*S*)-ester **47a**; ***Peak 3*** – 30.2 min, (-)-(*R*,*R*)-ester **47b**. ***Conditions;*** Chiralcel ODH; 5 µm; Column Size: 0.46 cmI.D. x 25 cmL; Column number: ODH0CE-KK122; Temp: 8 °C; Flow Rate: 0.75 ml/min; Injection: 7 µL; Solvent: *n*-hexane/IPA, 90:10; Sample conc.: 10 mg/mL (IPA/EtOAc, 9:1).

(-)-(2*S*,3*R*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate (47a)

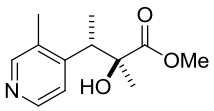


Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

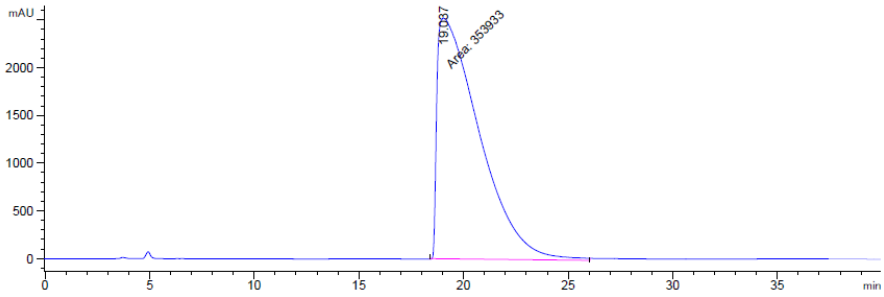


Retention time: 20.2 min. ***Conditions:*** Chiralcel IC; 5 µm; Column Size: 0.46 cmI.D. x 25 cmL; Column number IC00CE-LL027; Temperature: 10 °C; UV wavelength: 250 nm; Flow Rate: 1.2 ml/min; Injection: 5 µL; Solvent: *n*-hexane/IPA, 85:15; Pressure: 50 bar; Sample Conc. 0.3 mg/mL (IPA).

(+)-(2*S*,3*S*)-Methyl 2-hydroxy-2-methyl-3-(3-methylpyridin-4-yl)butanoate (47b)

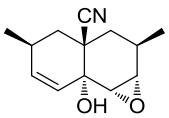


Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.2683

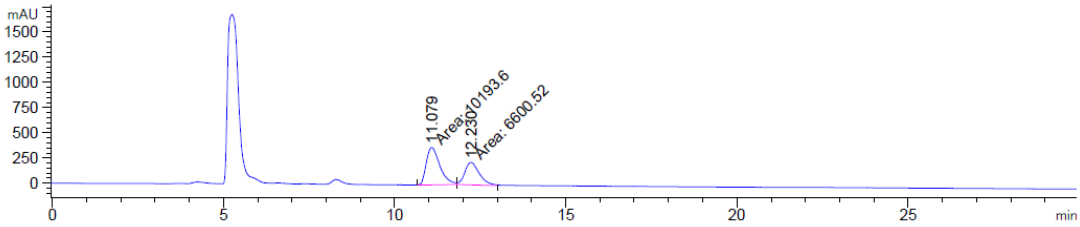


Retention time: 19.1 min. ***Conditions:*** Chiralcel OD-H; 5 µm; Column Size: 0.46 cmI.D. x 25 cmL; Column number ODH0CE-KK122; Temperature: 8 °C; UV wavelength: 254 nm; Flow Rate: 0.9ml/min; Injection: 1 µL; Solvent: *n*-hexane/IPA, 95:5; Pressure: 44 bar; Sample Conc. 7 mg/mL (EtOAc/IPA, 1:1).

(-)-(1*S*,2*R*,3a*R*,5*S*,7a*R*,7b*S*)-7*α*-Hydroxy-2,5-dimethyl-1a,2,3,3a,4,5,7a,7b-octahydronaphtho[1,2-b]oxirene-3a-carbonitrile (137)[60]



Chemical Formula: $C_{13}H_{17}NO_2$
Molecular Weight: 219.2796



Retention times: (-)-**137** = 11.1 min, (+)-**137** = 12.2 min. ***Conditions:*** Chiralcel OD-H; 5 µm; Column Size: 0.46 cmI.D. x 25 cmL; Column number ODH0CE-KK122; Temperature: 10 °C; UV wavelength: 210 nm; Flow Rate: 0.75 ml/min; Injection: 7 µL; Solvent: *n*-hexane/IPA, 80:20; Pressure: 46 bar; Sample Conc. 10 mg/mL (EtOAc/IPA, 5:1).

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