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STUDIES TOWARDS THE TOTAL SYNTHESIS OF (-)-ANISOMYCIN.

THE TOTAL SYNTHESIS OF

(-)-2-*epi*-ANISOMYCIN

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A Thesis Submitted for the Degree of

Doctor of Philosophy

School of Life Science,

Department of Chemistry

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I dedicate this thesis to my parents

John Alfred Henry and Marian Ruth Brann

and to my son Dalton Jonathan Brann.

Without their love, support and encouragement I would not have made it.

I hereby declare that this thesis has not been submitted,
Either in the same or different form, to this or any other
University for a degree.

Signature:

"If we knew what we were doing, it wouldn't
     be called research, would it?".

            Albert Einstein.

"Completum est itineris mei, adipem domina cecinisse".

            Anonymous.

Contents.

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Abstract.
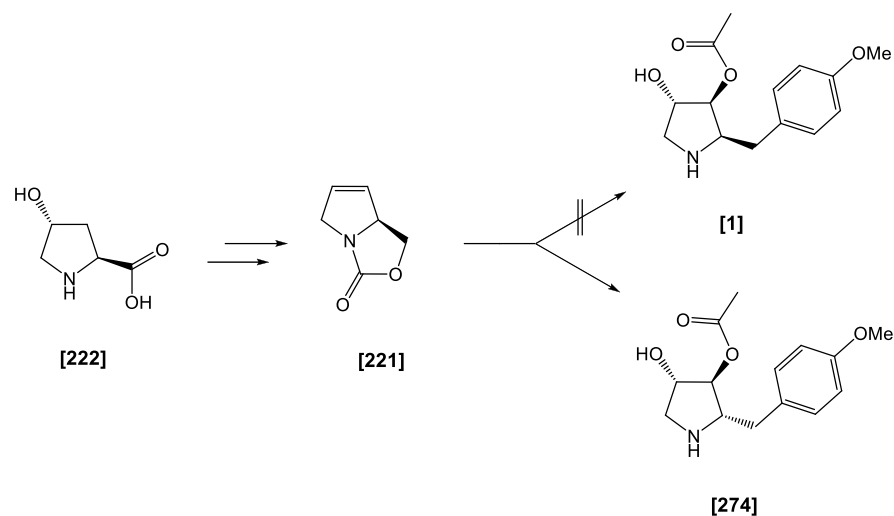
Exploitation of the asymmetric electron density at the crown of the oxazolidinone **[221]** allowed for high diastereofacial selectivity when converting the olefin to an epoxide. Regiocontrolled fragmentation of the epoxide enabled us to introduce the three essential stereocentres of the target alkaloid (-)-anisomycin **[1]** both contiguously and with the correct geometry. Installation of the remaining aromatic appendage allowed us to complete the molecular skeleton of the natural product; however, the synthetic step to facilitate this addition reaction also compromised the chiral integrity of the C2 position. Whilst the desired bioactive alkaloid, (-)-anisomycin **[1]** was not achieved upon completion of the synthesis, construction of the rare stereoisomer, (-)-2-*epi*-anisomycin **[274]** in a 9.4% overall yield demonstrates the routes future potential to deliver (-)-anisomycin **[1]**.

Abbreviations.

Å	Ångstrom
Ac	acetyl
AD-mix-α	potassium osmate
AIBN	2,2'-azobis(2-methylpropionitrile
Aq	aqueous
Bn	benzyl
Boc	*tert* butoxycarbonyl
B.p.	boiling point
Bu	butyl
^{t}Bu	*tert* butyl
^{o}C	degrees Celsius
cat	catalytic
Cbz	benzyoxycarbonyl
Cm	centimetre
Conc	concentrated
DAST	*N,N*-diethylaminosulfur trifluoride
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DE	diethyl ether
DIBAL-H	diisobutylaluminium Hydride
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N, N*-dimethylformamide
DMM	dimethoxymethane
DMSO	dimethyl sulfoxide
EA	ethyl acetate
E^+	electrophile
EDTA	ethylenedianinetetraacetic acid
ee	enantiomeric excess

ESI-MS	electron Spray Ionisation Mass Spectrometry
Equiv	equivalence
g	gram(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
HCl	hydrochloric acid
HRMS	high resolution mass spectrometry
Hz	Herts
IR	Infra-Red
IUPAC	International Union of Pure and Applied Chemistry
J	*J* coupling
LAED	lithium acetylide ethylenediamine
LDA	lithium di-*iso*-propylamide
M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
Min	minute(s)
mL	millilitre
mol	mole
mmol	millimole
MOM	methoxymethyl
m.p.	melting point
M.S	molecular sieve
MS	mass spectrometry
MW	molecular weight
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	4-methylmorpholine *N*-oxide
NOESY	nuclear Överhauser effect spectroscopy
Nu⁻	nucleophile
PE	petroleum ether (40-60)

Ph	phenyl
PMA	phosphomolybdic acid
Ppm	parts per million
PPTA	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
*i*Pr	*iso*-propyl
pyr	pyridine
Rf	retention factor
Rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butylmethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triiospropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
Quant	quantitative
UV	ultraviolet light

1. Introduction

1.1 Introduction to (-)-Anisomycin.

1.1.1. Structure and initial isolation.

The isolation of the monobasic pyrrolidine antibiotic (-)-anisomycin **[1]** (Flagecidin®)[1] was first reported in August 1954 by Sobin and Tanner at the Pfizer Research Laboratories in New York[1]. It was isolated as long white needle-like crystals by altering the pH of the fermentation medium filtrate of two different *Streptomyces* species, *Streptomyces griseolous* and *Streptomyces roseochromogens*, to pH 9.0 and extracting with methyl isobutyl ketone, water and then chloroform[1]. (-)-Anisomycin **[1]** (Fig 1.1) was also obtained from two further related *Streptomyces* species, No. 638 in 1974 by Ishida *et al.*[2] and strain SA 3097 in 1993 by Hosoya *et al*[3].
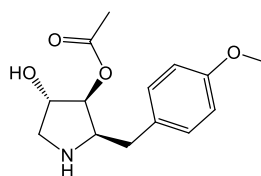
[1]

Figure 1.1: (-)-Anisomycin.

The alkaloid consists of a cyclic secondary amine core; a pyrrolidine ring with asymmetric centres at C2, C3 and C4 in an *R, S,* and *S* configuration. A second cyclic entity, an aromatic *p*-methoxybenzyl moiety is attached to C2 of the pyrrolidine via a methylene group and is arranged *cis* to the acetyl ester of C3. The remaining appendage at C4 is a simple hydroxyl group and is set *trans* relative to the acetoxy group.

(+)-Anisomycin **[1a]** and some of its various isomers[4] have also been isolated and characterised since Sobin and Tanner initially isolated (-)-anisomycin **[1]** and are shown in Figure 1.2.

Figure 1.2: Anisomycin stereoisomers.
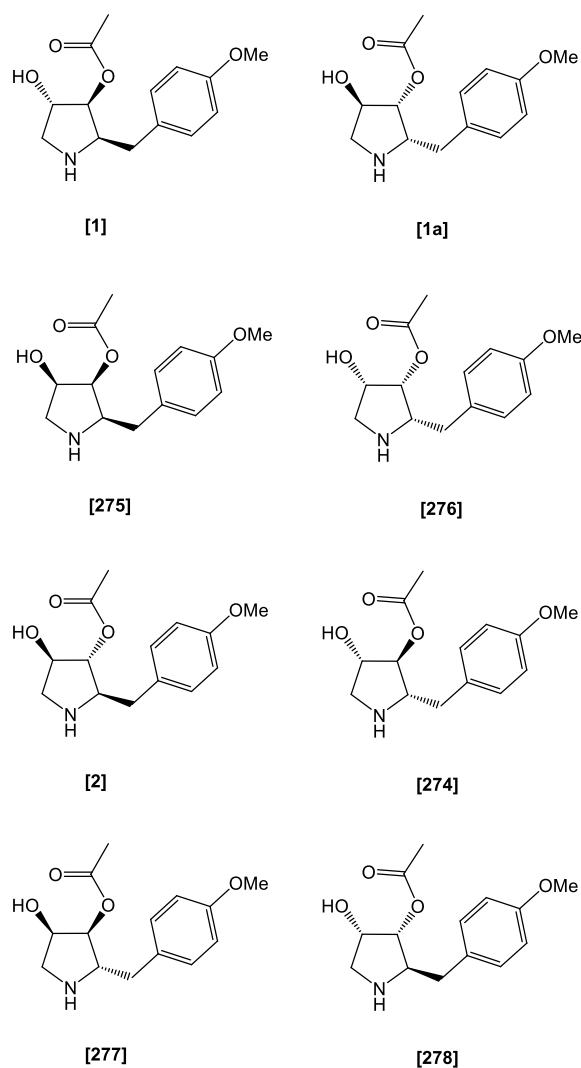
Whilst most groups have concentrated on synthesising the biologically active compound **[1]** or its enantiomer (+)-anisomycin **[1a]**, and others have conducted formal synthesis by reaching (-)-deacetyl anisomycin **[4]**; Park *et al.*[4] is the only group which has attempted the synthesis of the stereoisomers of anisomycin and these will be discussed later in this report.

1.1.2. Biological properties.

(-)-Anisomycin [1] possesses strong and effective activity against certain pathogenic protozoa[1] particularly *Trichomonas vaginitis* and *Endamoeba histolytica*, both *in vitro* and *in vivo*[5], and has also been successful in the clinical treatment of intestinal amebiasis[6]. It has been found to interfere with peptide bond formation on *eukaryotic ribosomes*[7] whereby the transpeptidation step of protein synthesis is reversibly inhibited by the binding of anisomycin [1] to the peptidyltranferase centre of the large ribosomal subunit[8,9].

(-)-Anisomycin [1] and a number of its derivatives have also found use as a fungistatic agent in the eradication of bean mildew[10] and as an inhibitor to various other strains of phytopathogenic fungi found within the agricultural environment[11].

A study by Venrooij *et al.*[12] reported that (-)-anisomycin's [1] treatment of Ehrlich ascites tumour cells suggested that the antibiotic was responsible for a defect in the binding of native 60S subunits and a later report by Hosoya *et al.*[3] in 1993 concluded that the alkaloid and three derivatives (3097-B1, 3097-B2 and 3097-C2) showed high cytotoxic activity against certain human tumour cell lines.

Recently, research has been directed towards the area of memory inhibition, whereby protein synthesis is required for brain memory retention. (-)-Anisomycin [1] has been shown to interfere with long-term memory function due to its ability to act as a protein synthesis inhibitor and is thought to have the potential to selectively control or remove "fear or trauma", memories[13,14].

1.1.3. Stereochemistry and absolute configuration.

Whilst the elucidation of the general structure of (-)-anisomycin [1] was comparatively trivial, exposition of the relative stereochemistry was not entirely straightforward. Beereboom *et al.*[6] conducted a study of anisomycin [1] in 1965 by the use of chemical analysis in an attempt to unlock its structure and stereochemistry. Titration of (-)-anisomycin [1] indicated the presence of nitrogen as an amine with a pKa of 7.9, whilst infra red and ultraviolet absorption revealed the existence of a hydroxyl group, an ester and an aromatic portion. The UV spectrum suggested that the aromatic ring system of anisomycin was analogous to that of *p*-anisyl alcohol, but oxidative degradation of [1] to draconic or *p*-anisic acid with "Condy's crystals" in water and sodium hydroxide left no doubt as to the presence of the *p*-methoxyphenyl group. Definition of the ester group was concluded via acid and base hydrolysis reactions which gave only deacetylanisomycin [4] and acetic acid as final products. With the external architecture of the molecule all but identified and the molecular formula indicating the presence of a second ring, the core of the compound came under scrutiny. Zinc dust steam distillation confirmed the existence of a pyrrolic material, whilst bromine and a platinum catalyst established the absence of any sp^2 hybridised carbons, thus confirming the pyrrolidine ring nucleus as opposed to a pyrrol or pyrroline[6].

A further series of reactions and chemical analysis was conducted on the antibiotic [1] and Beerboom *et al.* finally reported the structure as 2-*p*-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolidine [2] (Fig 1.3), whereby he stated, albeit incorrectly, that the substituent's on the pyrrolidine ring were *trans* in relation to the adjacent substituents[6].
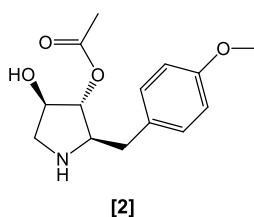
[2]

Figure 1.3: Beerboom's proposed structure for (-)-anisomycin[6], illustrating his all-*trans* configuration for the three asymmetric centres.

An x-ray crystallographic study by Schaefer *et al.*[15] into a derivative of anisomycin, *N*-acetylbromoanisomycin **[3]** (Fig 1.4), together with ^{1}H NMR analysis[6] and a private communication from the Connecticut group in 1967 concluded that the *p*-methoxybenzyl appendage was in fact *cis* to the adjacent acetate group[15].

[3]

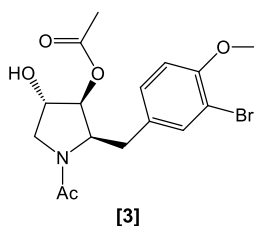Figure 1.4: *N*-acetylbromoanisomycin[15].

Wong *et al.* finally resolved any ambiguity and deduced the absolute configuration in 1968 to be 2*R*,3*S*,4*S*, via chemical correlation studies with the amino acid L-tyrosine[16] and further verified this deduction with the synthesis of (-)-deacetylanisomycin **[4]** and (+)-deacetylanisomycin **[5]** from (+)-tartaric acid later that same year[17]. (Fig 1.5).
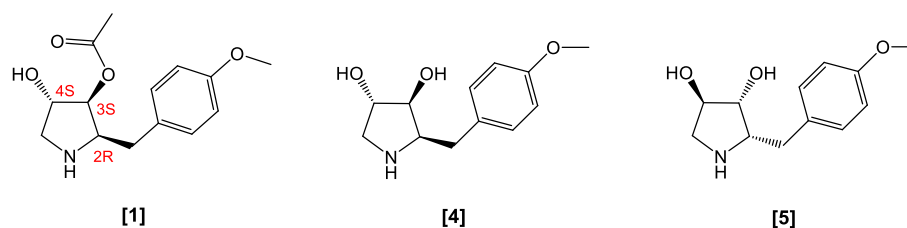
Figure 1.5: Wong *et al's.* absolute configuration of (-)-anisomycin together with (-) and (+)-deacetylanisomycin[16,17].

1.1.4. Biosynthesis.

Notwithstanding the erroneous assignment of the *trans* substituents on the pyrrolidine ring, Dr Kenneth Butler from Pfizer's Connecticut laboratories, published a biosynthesis of anisomycin **[1]** in 1966. Whilst investigating both the structure and extraction techniques of anisomycin **[1]** it became apparent to Butler that the alkaloid could be derived from several amino acids, namely tyrosine, phenylalanine and proline, and thus, these amino acids could be used as precursors in a total synthesis.[18]

A series of a labelled amino acid and degradation studies concluded that deacetylanisomycin **[4]** was converted to anisomycin **[1]** in the assimilation phase of the fermentation process when the acetic acid concentrations had peaked; it was clear however, that its antecedent did not accrue from proline during the logarithmic phase of growth.
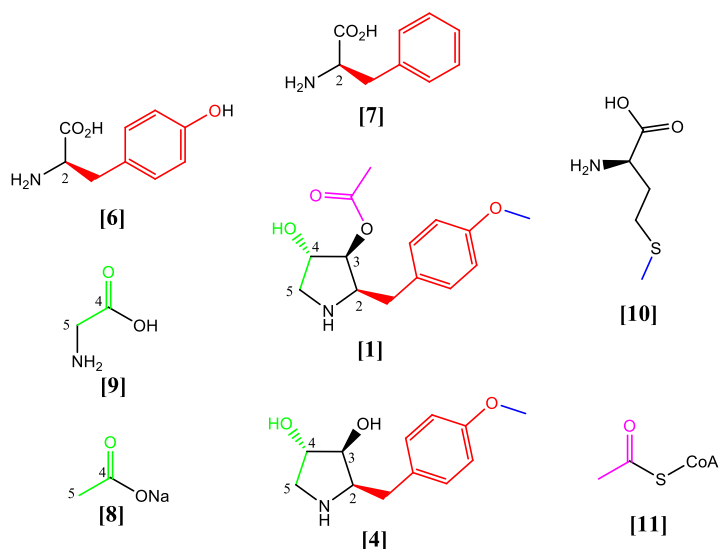
Figure 1.6: Butler's biosynthesis study results.[18]

Both tyrosine [6] and phenylalanine [7] were shown to be major precursors in the formation of the antibiotic's aromatic moiety together with C2 of the pyrrolidine ring; however, the non-essential amino acid was shown to be incorporated foremost, with phenylalanine [7] 40 times less efficient. (Fig 1.6)[18]

Attention now, was turned to anisomycin [1] and deacetylanisomycin [4] isolated from the fermentation broth incorporating labelled acetate [8], glycine [9] and methionine [10]. It was anticipated that by measuring the radioactivity in the remnants of degradation, the remainder of the puzzle could be realised.

Structured disintegration of deacetylanisomycin [4] with the 2-^{14}C glycine isotope [9] was instigated by exhaustive methylation to N-methyldeacetylanisomycin methiodide [12] via refluxing potassium carbonate and methyl iodide in acetone. Execution of the concluding element of the Hofmann degradation[18] was to fragment the pyrrolidine core with refluxing

sodium hydroxide to give 1-(*p*-methoxyphenyl)-3,4-dihydroxy-5-dimethylamino-1-pentene **[13]**.[18] Glycolic cleavage of the vicinal diol **[13]** to *p*-methoxycinnamaldehyde **[14]** and dimethylaminoacetaldehyde **[15]** was achieved by way of lead tetraacetate oxidation. With the glycine isotope activity measured as an uneven split of 43.5% in aldehyde **[14]** and 56.5% in the tertiary amine **[15]**; carbon 4 and 5 of the pyrrolidine ring had been identified. (Scheme 1.1)

Further oxidation of **[15]** with potassium permanganate lead to N,N-dimethylglycine **[16]** which was absorbed onto calcium oxide before pyrolysis gave trimethylamine **[21]**. Radioactive analysis of the amine salt of **[21]** reconfirmed the presence of [14]carbon at C5 of the anisomycin core.[18]

Reagents & conditions: i. H_2O, H^+ ii. K_2CO_3, CH_3I, C_3H_6O, Reflux. iii. NaOH, Reflux. iv. $Pb(C_2H_3O_2)_4$. v. O_3/O_2. vi. $KMnO_4$. vii. $KMnO_4$. viii. CaO, Heat. iv. H_2O, Heat. x. $KMnO_4$.

Scheme 1.1: Butler's biosynthesis degradation study[18].

The chemical analysis of **[1]** using a labelled methionine **[10]** and acetate **[8]** isotopes was largely inconclusive due to solubility issues, fermentation acetic acid concentration and the low boiling points of the degradation relics. Butler reported that the methionine **[10]** presumably undertook its customary role as a biological methylating agent and accounted for the aromatic methoxy group; and acetate **[8]**, probably as acetyl co-enzyme A **[11]** was responsible for the acetyl group, considered to be the final step in the biosynthesis. The origin of C3 was not thought to come from the tyrosine or phenylalanine's carboxylic acid group due to decarboxylation in the early stages of fermentation, thus the source of C3 was undetermined together with that of the nitrogen[18].

1.1.5. Previous syntheses.

Anisomycin's biological profile has attracted considerable interest from the scientific community over the last half century and many organic chemists have been tempted into resolving an efficient synthetic route to what is a comparatively simple molecular structure with a chirally challenging configuration. (-)-Anisomycin [1] has been successfully synthesized through 21 different routes, with chemists generally employing the readily available chiral pool of amino acids and carbohydrates. However, because of the necessity of continued protecting group chemistry and the inherent difficulty in separating undesirable stereoisomers, the efficiency of many of these routes has been compromised resulting in syntheses frequently in excess of 20 steps.

The first successful total synthesis of anisomycin [1], albeit racemic, was published in 1969 by Oida *et al*[19]. whereby the strategy for the synthesis drew upon their previous work on 3,4-*trans*-disubstituted pyrrolidines[20] and the biosynthesis of Butler three years earlier[18].

Reagents & conditions: i. NaH, C_6H_6, reflux.
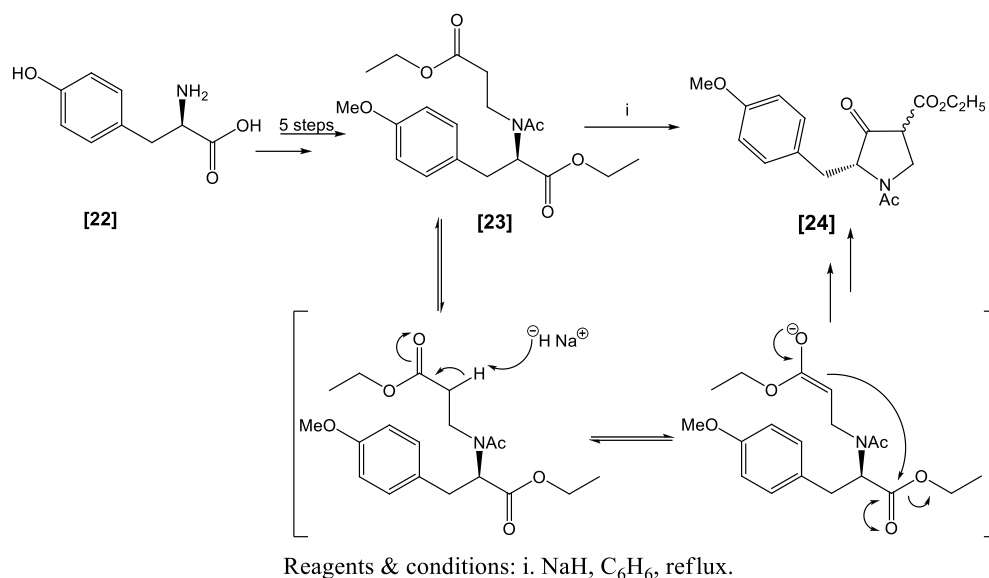
Scheme 1.2

The Sanko group reasoned their pertrifluoroacetic acid oxidation[21] to form an epoxide across the double bond of a pyrroline would serve as a target intermediate **[26]** for the synthesis, with the proteinogenic amino acid tyrosine **[22]** chosen as the suitable starting material[19].

Tyrosine **[22]** was converted to the methoxybenzyl-propanoate **[23]** in 4 steps by way of McKinney's cyanoethylation procedure[22] and successive treatment with hydrogen chloride in ethanol. Amine protection with acetic anhydride in methanol was followed by *O*-methylation with dimethyl sulfate in acetone in the presence of potassium carbonate. The 1,6-diester **[23]** lent itself favourably to undergo intramolecular cyclisation to form the pyrrolidine ring via the Dieckmann cyclisation to give β-keto ester **[24]** (scheme 1.2).
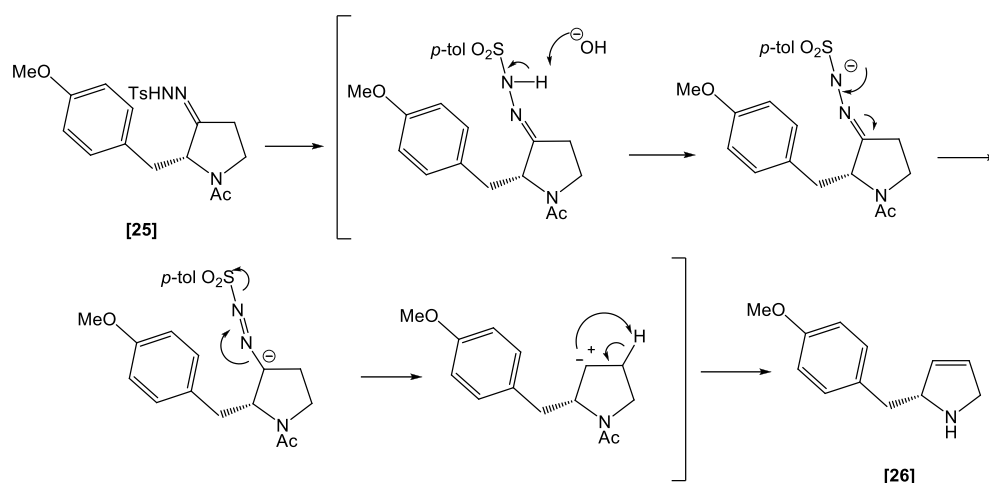

Reagents: $(HOC_2H_2)_2O$, H_2O, KOH. (49%).

Scheme 1.3

The keto functionality introduced at C3 of **[24]** by the cyclisation enabled the molecule to be manipulated to the key intermediate **[26]** relatively efficiently. Removal of the adjacent carboxylate with HCl in acetic acid followed by Stoichometric addition of tosyl hydrazine furnished tosyl hydrazide **[25]**. Potassium hydroxide in the protic solvent diethylene glycol instigated the

Bamford-Stevens reaction necessary to install the double bond at carbon 3 and 4 of the ring with concomitant amine deprotection (Scheme 1.3).
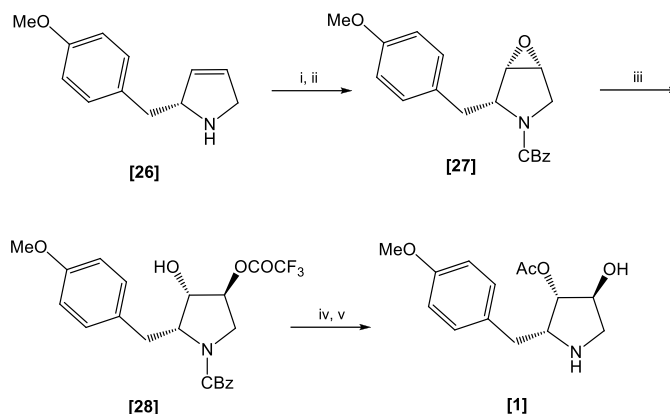
Reagents: i. BnOCOCl, NaHCO$_3$, C$_6$H$_6$ ii. (CF$_3$CO)$_2$O, H$_2$O$_2$, Cl$_2$CH$_2$, Na$_2$CO$_3$, (7%). iii.CF$_3$CO$_2$H, CF$_3$CO$_2$Na. iv.(CH$_3$CO)$_2$O, pyr, H$_2$O. v. Pd/C/H$_2$, (11.4% over three steps).
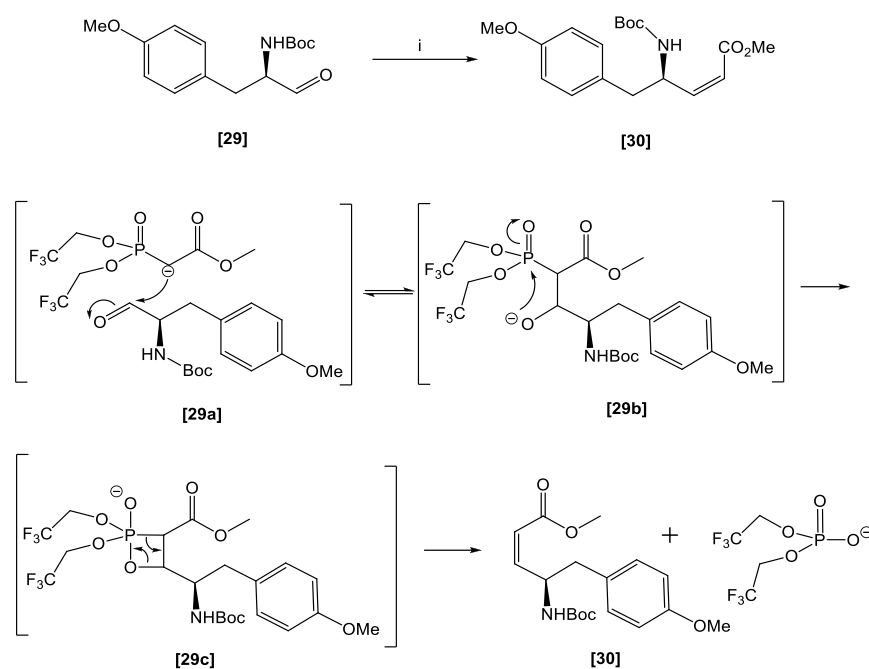
Scheme 1.4

Alternate amine protection was sought with benzoxycarbonyl chloride before treatment of the double bond with pertrifluoroacetic acid to form the desired α-epoxide [27]. Addition of trifluoroacetic acid with sodium trifluoroacetate promoted solvolysis, whereby interaction with the acid fragmented the strained three-membered ring to yield the required pyrrolidine skeleton [28] containing the elusive yet crucial chiral centres on carbons 2, 3 and 4 and a redundant inseparable stereoisomer[19]. (Scheme 1.4)

Acetylation of alcohol [28] with acetic anhydride in pyridine completed the architecture of C3, whilst the unstable trifluoroacetyl group was removed with dilute HCl and water to concluded C4. The mixture of stereoisomeric monoacetates was subjected to hydrogenation over palladium and charcoal to remove the benzyloxycarbonyl protection and reveal anisomycin together with the analogous stereoisomer. Separation of the monoacetates by

recrystalisation in ethyl acetate and hexane (5:1) completed Oida's 13 step route and the first total synthesis of anisomycin[19].

Oida *et al's.* target intermediate, (*R*)-2-(*p*-methoxyphenyl)methyl-2,5-dihydropyrrole [26] was also the objective for Jegham *et al's.* formal synthesis of (-)-anisomycin [1] from D-tyrosine, together with (+)-anisomycin [1a] from L-tyrosine [22]. Formation of an α,β-unsaturated methyl ester prior to cyclisation was the key step in the synthesis[23].
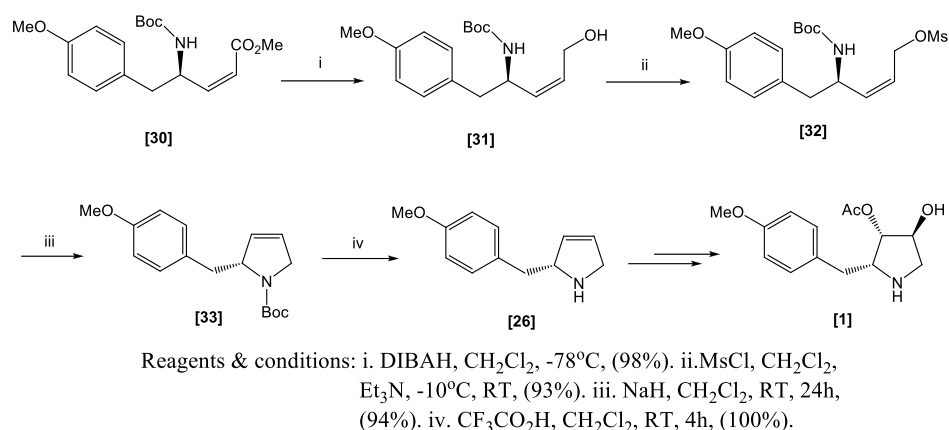

Reagents & conditions: i. $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(Me_3Si)_2NK$, THF, -78°C.

Scheme 1.5

Reduction to the alcohol of the ortho-methyl, Boc protected methyl ester fashioned from D-tyrosine, was achieved with sodium borohydride and lithium chloride. This was followed by a Swern oxidation[30] to give aldehyde [29]. The chain elongation and olefination was made possible by the Horner-Wadsworth-Emmons reaction with the anion derived from bis-(2,2,2-

trifluoroethyl)-(methoxycarbonylmethyl)-phosphonate. The use of the trifluoroethyl ligands on the phosphonate are thought to enhance the rate of elimination when the oxaphosphetane [29c] intermediate is formed, thus ensuring the all important *cis* configuration is achieved to enable cyclisation. This represents the Still-Gennari[123] modification of this reaction and formed the (Z)-γ-amino-α,β-unsaturated methyl ester [30]. (Scheme 1.5)

Conversion of the ester group to the alcohol [31] and then onto the mesylate [32] for S_n2 leaving functionality, allowed sodium hydride persuasive intramolecular cyclisation to take place and form pyrroline [33] without racemisation of the chiral centre. Trivial removal of the Boc protection completed this formal synthesis to [26] in an overall yield of 62%. (Scheme 1.6)
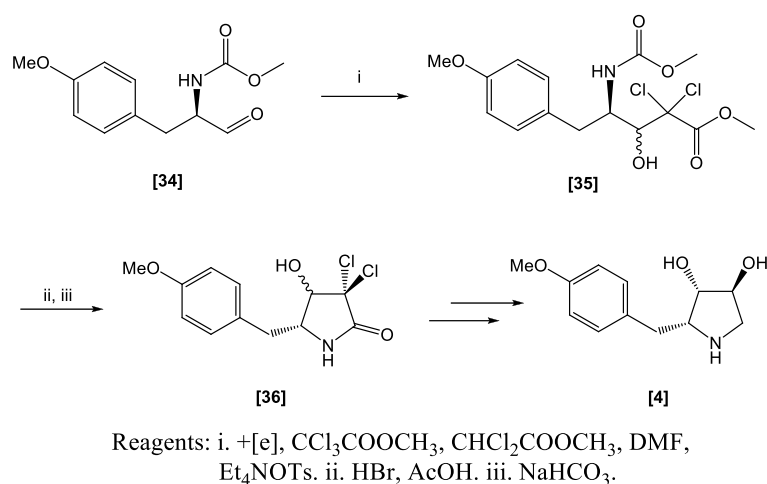

Reagents & conditions: i. DIBAH, CH$_2$Cl$_2$, -78°C, (98%). ii.MsCl, CH$_2$Cl$_2$, Et$_3$N, -10°C, RT, (93%). iii. NaH, CH$_2$Cl$_2$, RT, 24h, (94%). iv. CF$_3$CO$_2$H, CH$_2$Cl$_2$, RT, 4h, (100%).

Scheme 1.6

Acknowledgement was attributed to Hall *et al*[24]. and Meyers *et al*[25]. for the conversion of [26] to [1] and these two routes will be discussed further in this review.

Shono *et al's.* sparse report in 1987 on the formal synthesis of (-)-anisomycin [1][26] also utilised D-tyrosine as a starting material and employed an

intramolecular cyclisation to form the core of the compound, but the key reaction was the electro-generated (methoxycarbonyl)-methyl anion for addition to an aldehyde to form the cyclisation halosynthon[27].

DIBAL reduction of the methyl ester on the methoxycarbonyl protected D-tyrosine gave access to aldehyde [34]. Electrochemical reduction of the chloro-acetates formed the DMM anion and on addition to [34] generated an α-geminal chloride on the methyl pentanoate [35] prior to cyclisation. Hydrolysis with acid followed by treatment with sodium bicarbonate induced formation of the γ-lactam [36] in a 65% yield. A further 4 step manipulation of the γ-lactam gave the *trans* diol of (-)-deacetylanisomycin [4][26]. (Scheme 1.7)

Reagents: i. +[e], CCl$_3$COOCH$_3$, CHCl$_2$COOCH$_3$, DMF, Et$_4$NOTs. ii. HBr, AcOH. iii. NaHCO$_3$.

Scheme 1.7

An efficient synthesis of enantiomerically pure (-)-deacetylanisomycin [4] from D-tyrosine, which also constitutes a formal synthesis of (-)-anisomycin [1] was reported by Chandrasekhar *et al.* in 2002[28]. Several classic named reactions were employed in this synthesis, but possibly the key reaction was the modified Sharpless asymmetric dihydroxylation[29] to install the chiral diol.
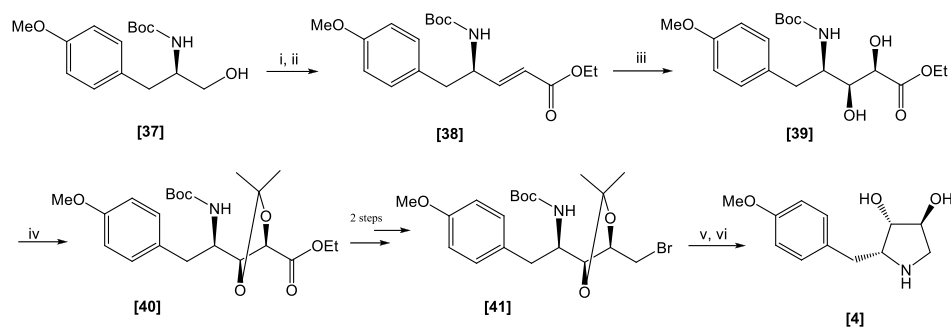
Reagents & conditions: i. (COCl)$_2$, DMSO, DCM, Et$_3$N, -78°C. ii. Ph$_3$P=CHCOOEt, CH$_2$Cl$_2$, RT. (73% over two steps). iii. AD-mix-a, ^{t}BuOH, H$_2$O 0°C, (60%). iv. 2,2-DMP, CSA, CH$_2$Cl$_2$. (72%). v. TFA, CH$_2$Cl$_2$. vi. Et$_3$N, MeOH, 0°C. (70%).
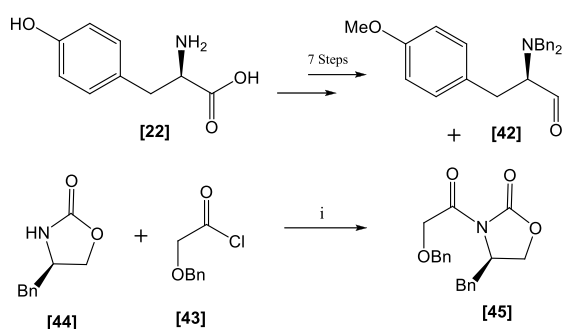
Scheme 1.8

The Boc protected alcohol [37] residue of D-tyrosine was subjected to a Swern oxidation[30] and followed up without purification by a Wittig reaction with (ethylcarbonylmethylene)-triphenylphosphorane to form the γ-amino-*trans*-α,β-unsaturated ethyl ester [38] in a 73% yield.

The *trans* geometry of the olefin enabled the creation of the (2*R*, 3*S*, 4*R*) configured chiral diol [39] using the Sharpless asymmetric dihydroxylation with AD-mix-α. Following osmylation, the two hydroxyl groups were bound by acetonation to allow unimpeded manipulation of the ethyl ester [40] to the required period 4 halogen [41] over two steps. The protecting groups were removed via TFA induced acidolysis and the resultant amine was tempted to cyclise with triethylamine to give (-)-deacetylanisomycin [4] in a 70% yield[28]. (Scheme 1.8)

Hulme *et al.* considered an aldol based approach to (-)-anisomycin [1][31] and reported a successful 13 step synthesis of (-)-anisomycin [1] in 2002 from D-tyrosine [22] and a glycolate derivative of Evans' oxazolidinone [45][32]. Drawing upon experience gained on their previous synthesis of the α-glucosidase inhibitor 1,4-dideoxy-1,4-imino-D-arabinitol, the Edinburgh

group employed a similar strategy to construct the pyrrolidine cyclisation precursor **[47]**.

Reagents & conditions: i. ^{n}BuLi, -78°C, 1.5h. (80%).

Scheme 1.9

The Swern oxidised aldehyde **[42]** was converted from D-tyrosine in 7 steps to form one half of the aldol system, with the second element fashioned from benzyloxyacetyl chloride and (*R*)-4-benzyloxazolidin-2-one to assemble the Evans type oxazolidinone **[45]**. (Scheme 1.9)
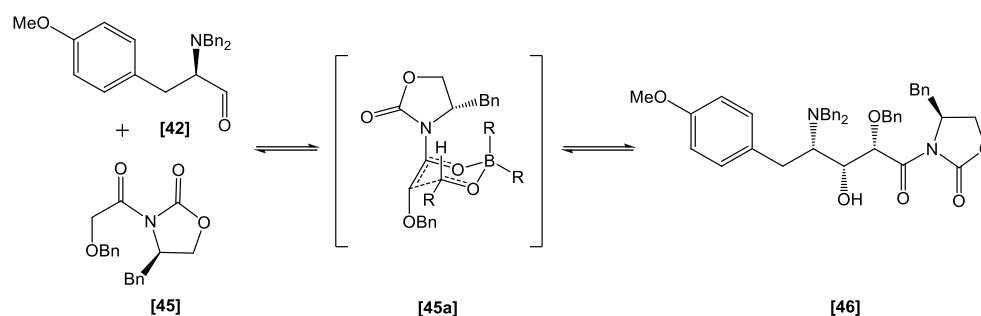
Reagents & conditions: i.Et$_3$N, CH$_2$Cl$_2$, Bu$_2$BOTf -78°C, 6h. (75%).

Scheme 2.0

Formation of the (*Z*)-boron enolate **[45a]** (Scheme 2.0) gave rise to the *syn*-aldol adduct **[46]** before metal hydride reductive cleavage of the benzyl

oxazolidinone moiety revealed the desired 1,3-diol **[47].** Selective primary alcohol tosylation with tosyl chloride and DMAP, encourage spontaneous ring closure to give the pyrrolidinium tosylate salt, which upon treatment with 1% HCl on Dowex ion exchange resin was converted to the chloride salt **[48]**. A further 3 step manipulation of gave (-)-anisomycin **[1]** as its hydrochloride salt **[49]** in a 35% overall yield[31]. (Scheme 2.1)
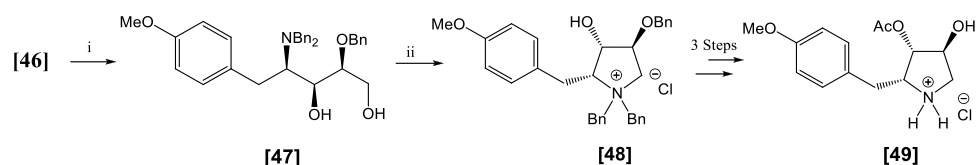

Reagents: i. LiBH$_4$, MeOH. (80%). ii. TsCl, DMAP, CH$_2$Cl$_2$. iii. Dowex Cl$^-$. (85%).

Scheme 2.1

D-Tyrosine was again utilised in a recent novel approach to (-)-anisomycin **[1]** by Ham *et al.*[33] who used a palladium catalysed stereoselective intramolecular oxazine ring formation as the penultimate target before successfully converting it to **[1]**.

Familiar formation of the D-tyrosine amino protected methyl ester derivative was also employed by Ham *et al.* as a starting point in the most recent synthesis of **[1]**. However, in a deviation to the previous syntheses whereby aldehyde mediated chain extension was used,[23,26,28,31] conversion of the methyl ester to the Weinreb amide **[50]** enabled tin radical chemistry to furnish an α,β-unsaturated ketone **[51]**. Stereoselective reduction of the ketone was necessary to generate the anti-periplainer relationship between the amine and the alcohol **[52]** to facilitate the *p*-nitrobenzoic acid catalysed Mitsunobu type *trans* oxazoline **[53]** formation. (Scheme 2.2)
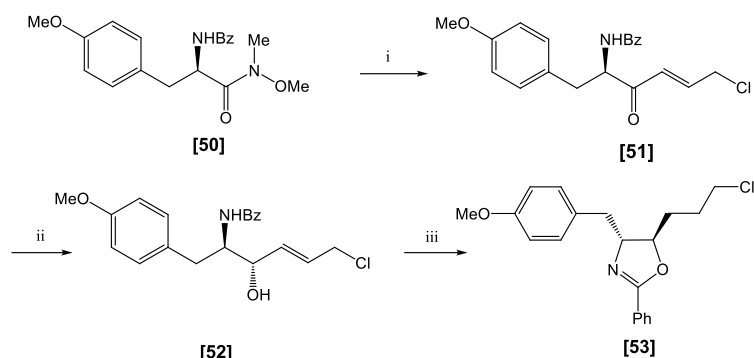
Reagents & conditions: i. Bu$_3$SnCH=CHCH$_2$Cl, MeLi, THF, -78°C, (86%).
ii. LiALH(t-BuO)$_3$, EtOH, -78°C, (93%). iii. DEAD,
PPh$_3$, *p*-ArNO$_2$, THF, RT, (83%).

Scheme 2.2

Acid catalysed hydrolysis followed by moderate *p*H elevation secured the *syn*-amino alcohol, which was subsequently silyl protected **[54]** before palladium mediated ring formation at 0°C ensured the kinetically formed *syn*-oxazine **[55]**.

Ham *et al.*[34] demonstrated that temperature was critical in obtaining the correct diastereoselectivity. It was postulated that the molecule would adopt the chair-like transition state with the bulky silyl group sitting in an equatorial orientation to minimise the conformational energy. Whilst the initial π-allyl palladium complex, in the axial configuration **[54a]** at 0°C, does suffer slight *synclinal* alignment repulsion due to the 60° torsion angle with the vicinal silyl group; it does not suffer the destabilising steric inhibitions that it undoubtedly would if it were equatorial **[54b]**.
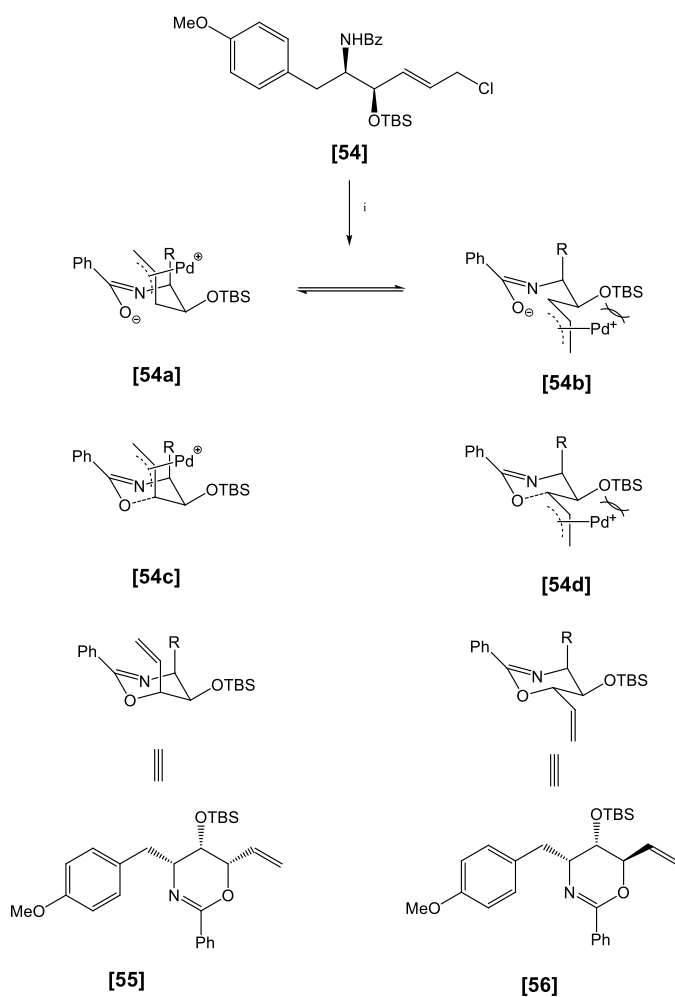
Reagents & conditions: i. Pd(PPH$_3$)$_4$, NaH, $_n$-Bu$_4$NI, THF. 0°C,
(15:1 *syn* 79%). 50°C, (1:9 *anti* 68%).

Scheme 2.3

Upon formation of the secondary intermediate **[54c]** and onto cyclic completion, the *syn* product **[55]** is undoubtedly preferred over the sterically impeded transitional state of **[54b]** even allowing for the 1,3-psuedioaxial interaction of the pendant vinyl group with the aromatic moiety **[54e]**. However, an increase in reaction temperature enables the higher energy barrier for the formation of transition state **[54b]** to be overcome and on

completion of ring formation and loss of the palladium the steric issues for the thermodynamic product [56] vanish.[34] (Scheme 2.3)

Hydroxyl group protection exchange via acetylation [57] enabled ozonolysis of the pendant vinyl group prior to the second employment of the group 10 metal, this time as Pearlman's catalyst. Hydrogenation of the oxazine and aldehyde groups enabled spontaneous cyclisation of the aminoaldehyde intermediate to reveal (-)-anisomycin as a single stereoisomer in an overall yield of 27%.[33] (Scheme 2.4)

Reagents & conditions: i. O_3, MeOH, -78°C. ii. Pd(OH)$_2$/C/H$_2$, MeOH/AcOH, (9:1), (65% over 2 steps).
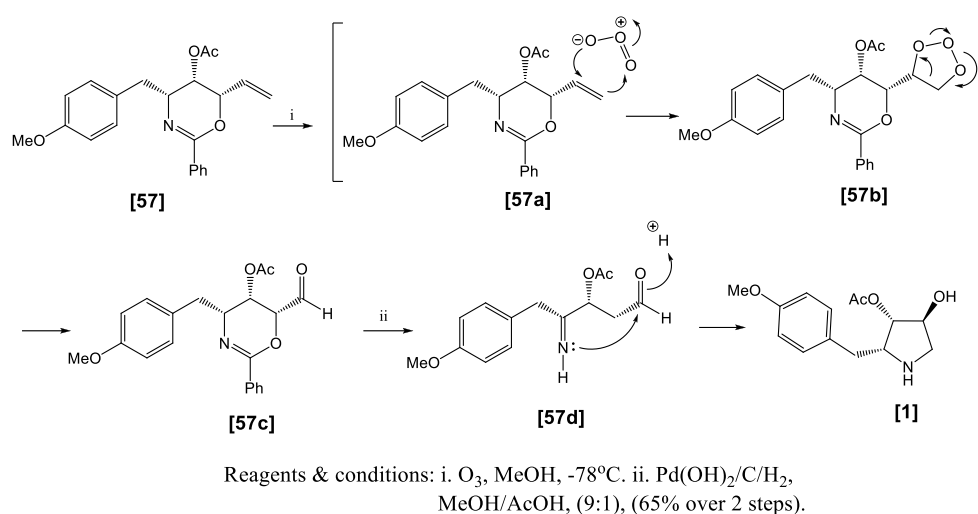
Scheme 2.4

Verheyden's 1978 selective chiral synthesis of anisomycin[35] took advantage of the carbohydrate chiral pool instead of the amino acids. The Syntex Research group considered that the asymmetric carbons at the centre of [1] were also mimicked in the core of the aldohexose, D-glucose. The formation of the amino-β-L-talofuranose key intermediate [61] enabled the resultant bicyclic furo-pyrrolidine to contain the necessary regio and stereo-chemical functionalities to complete an efficient synthesis.
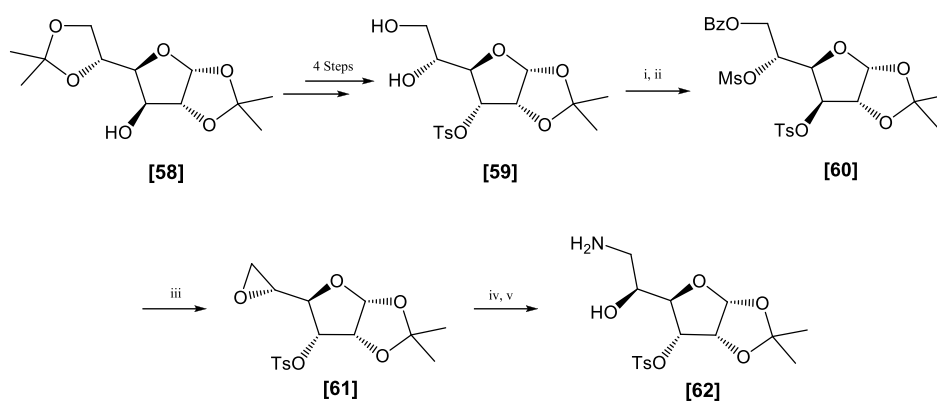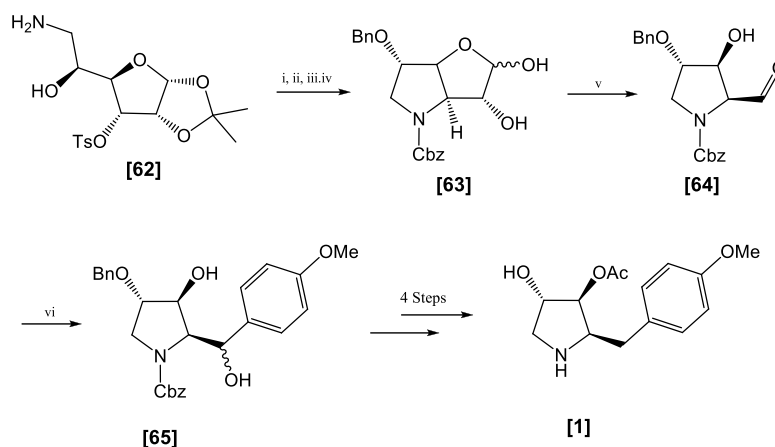
Reagents: i. PhCOCl, NaOH, (69%). ii. CH$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, (90%). iii. NaOMe, MeOH, (91%). iv. NaN$_3$, DMF, NH$_4$Cl, (84%). v. Pd/C/H$_2$.

Scheme 2.5

The diacetonide protected α-D-glucofuranose **[58]** allowed for tosyl conversion of the solitary alcohol together with its stereochemical volte-face, before selective hydrolysis of the 5,6-acetonide revealed the 1,2-diol **[59]** in an 88% yield. Selective benzoate protection of the primary alcohol permitted formation of the mesyl ester on the remaining hydroxyl group **[60]** and this in turn allowed for translation to the oxirane **[61]**. Reaction of the epoxide with sodium azide initiated attack at the least hindered primary position thus installing the azido group and the resultant alcohol. Reduction to the amine via palladium catalysed hydrogenation completed the key amino-β-L-talofuranose intermediate **[62]**. (Scheme 2.5)

Cyclisation to form the pyrrolidine ring was instigated by refluxing **[62]** with sodium acetate in ethanol before installation of the carbamate protection. Sodium hydroxyl assisted benzylation covered the alcohol at C3 of the pnictogen heterocycle prior to treatment with tri trifluoroacetic acid to cleave the 1,2-acetonide to form an anomeric mixture of diol **[63]** in 92%. Key oxidative fragmentation of the furan ring not only revealed the skeleton of the target alkaloid complete with the correct stereochemistry but also provided

the aldehyde **[64]** functionality to facilitate the final aryl architecture. Successful attachment of the arene **[65]** was completed by the *p*-magnesium bromide Grignard of anisole in THF followed with a further 4 steps to conclude the natural compound **[1]** in an overall yield of 8%.[35] (Scheme 2.6)

Reagents: i. CH_3COONa, EtOH, (62%). ii. $PhCH_2OCOCl$, Et_3N, CH_2Cl_2.
iii. PhCOCl, NaOH, DMF, (98%). iv. TFA, (92%). v. $NaIO_4$,
H_2O, Et_2O, TEAA, $NaHCO_3$. vi. MeOPhMgBr, THF. (54%).

Scheme 2.6

Buchanan *et al*. also exploited the carbohydrate pool and reported the use of the monosaccharide, D-ribose for an enantiospecific synthesis of (-)-anisomycin. The cyano-dioxolane cyclisation precursor **[68]** was the target intermediate following addition of the aryl group.[36,37]
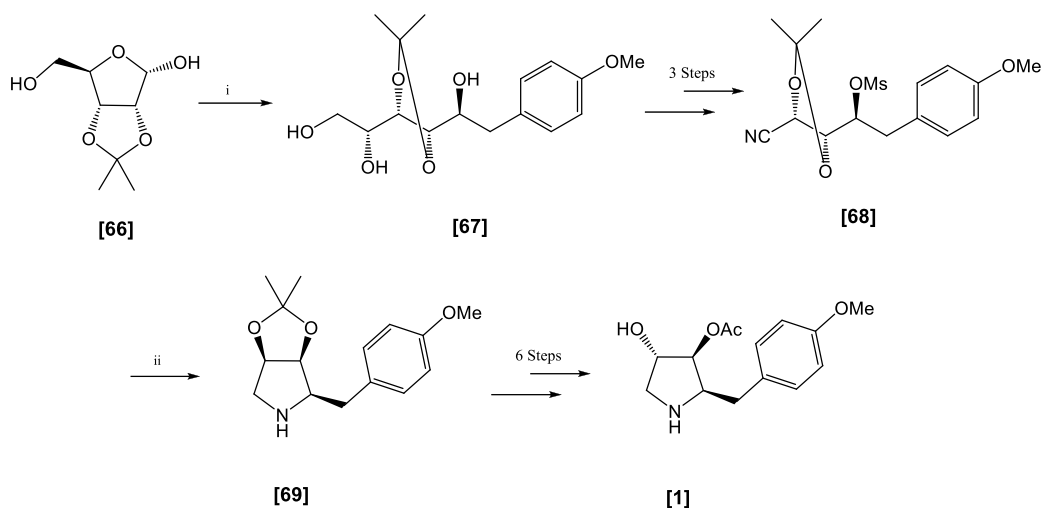
Reagents & conditions: i. MeOPhCH$_2$MgCl, THF, RT, 1hr. (70%).
ii. Et$_2$O, LiALH$_4$, 2hr, EtOAc, 1hr. (51%).

Scheme 2.7

Grignard attachment to install the anisole group effected collapse of the furanose ring and gave rise to the triol **[67]**. Further manipulation through to the hemiacetal and onto the oxime finally resulted in the desired nitrile key intermediate **[68]**. Lithium aluminium hydride reduction enabled forced mesyl displacement and creation of the pyrrolidine ring with an all *cis* configuration **[69]** before progression to the natural product **[1]** in an overall yield of 10%.[36,37] (Scheme 2.7)

An early exponent of the synthesis of (-)-anisomycin **[1]** was von Felner *et al.* in 1970 whereby the formation of a γ-thiolactam key intermediate from diethyl-L-tartrate **[70]** enabled addition of the methoxy-aryl moiety via Eschenmoser's sulfide contraction.[38,39,40]
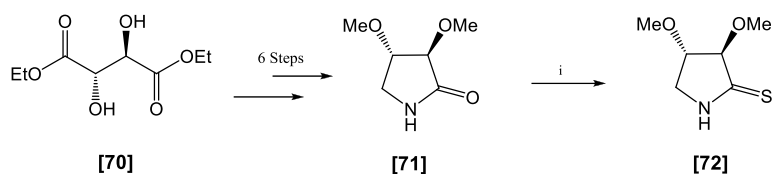
Reagents & conditions: i. P_4S_{10}, C_6H_6, Reflux 10 mins. (58%).

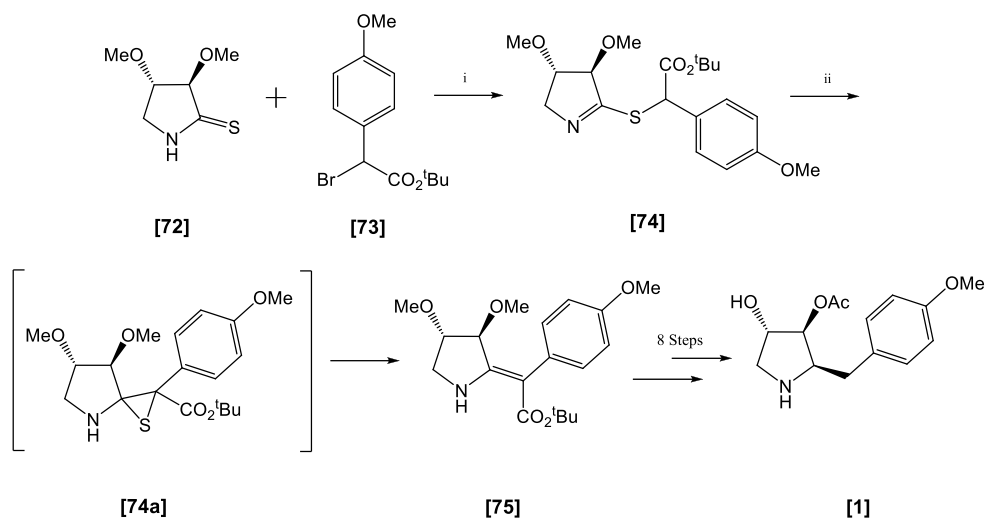Scheme 2.8

Following an unsuccessful attempt to attach the methoxy arene moiety to an imino-ester derivative of [71] von Felner *et al.* modified their approach by conversion of lactam [71] to the γ-thiolactam [72]. (Scheme 2.8)

Reagents & conditions: i. P_4S_{10}, C_6H_6, Reflux 10 mins. (58%). ii. $P(OMe)_3$, DMSO, $(Me)_3COK$, 100°C.

Scheme 2.9

The addition of [72] with tert-butyl-2-bromo-2-(4-methoxyphenyl)-acetate [73] together with phosphorus pentasulfide in benzene translated to the sulfur bridged aryl-pyrroline [74]. Eschenmoser's sulfide contraction initialised with trimethyl phosphate, dimethyl sulfoxide and catalytic potassium *tert*-butoxide induced formation of the spiro-thiirane intermediate [74a] before phosphate abstraction of the sulfur collapsed the 3 membered ring to give the

benzylidene **[75]**. (Scheme 2.9) A further 3 and 8 step manipulation proceeded to give (-)-deacetyl anisomycin **[4]** and (-)-anisomycin **[1]** respectively.[38,39,40]

Although mentioned earlier in this report for clarifying the absolute stereochemistry of **[1]**,[16] Wong *et al's.* configurational studies concluded in reporting the synthesis of (-)-anisomycin **[1]** and (+)-anisomycin **[1a]** together with (-)-deacetyl anisomycin **[4]** and (+)-deacetyl anisomycin **[5]** from both L-tartaric acid **[76]** and α-anisyl pyrrole **[81]**.[17,41]
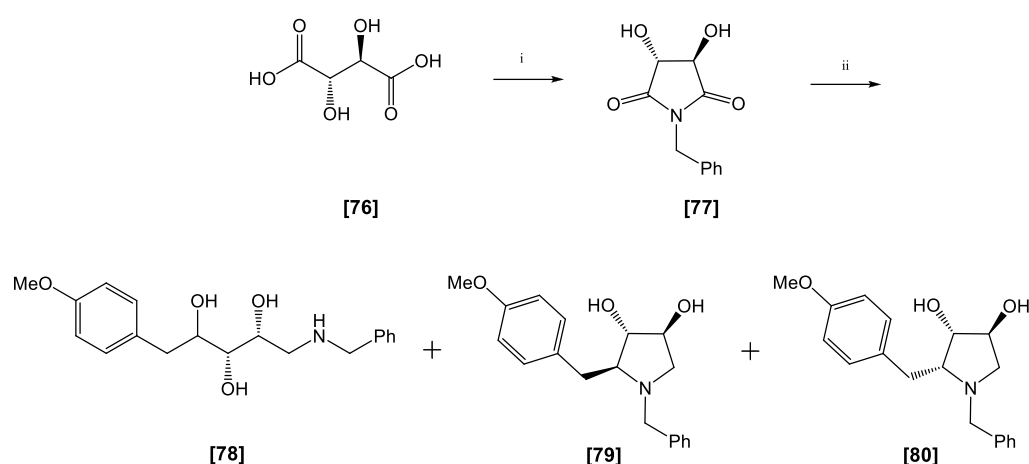
Reagents & conditions: i. BnNH₂, Xylene. Reflux. ii. MeOPhMgCl THF, LiAlH. (**78** (2%), **79** (12%), **80** (3%)).

Scheme 3.0

The addition of the aromatic moiety to *N*-Benzyl tartrimide **[77]**, fashioned from L-tartaric acid **[76]**, was achieved by reacting an in-situ formed anisyl-magnesium chloride Grignard reagent with tartrimide **[77]** in THF. However, Wong *et al.* discovered that if lithium aluminium hydride was added to the reaction mixture before the excess Grignard was quenched, three products were formed, **[78], [79]** and the desired **[80]** in 2%, 12% and 3% yields respectively.[17,41] (Scheme 3.0)

Debenzylation of the conformationally correct *trans* diol **[80]** with Pd/C in acidified ethanol gave the hydrochloride salt of (-)-deacetyl anisomycin **[4]** with liberation to its free base via sodium hydroxide.[41]

Wong *et al's*. second approach to anisomycin was to use the target molecule's aromatic portion combined with the 5-membered core as the starting material. A Clemmenson reduction[42] of α-anisyl pyrrole **[81]** with a zinc/mercury chloride amalgam furnished the vital sp^2 hybridised function at carbons 2 and 3 **[82]**. Treatment of the newly formed alkene **[82]** with acetic anhydride followed by peracetic acid oxidation gave way to epoxides **[83]** and **[84]**.[41] (Scheme 3.1)
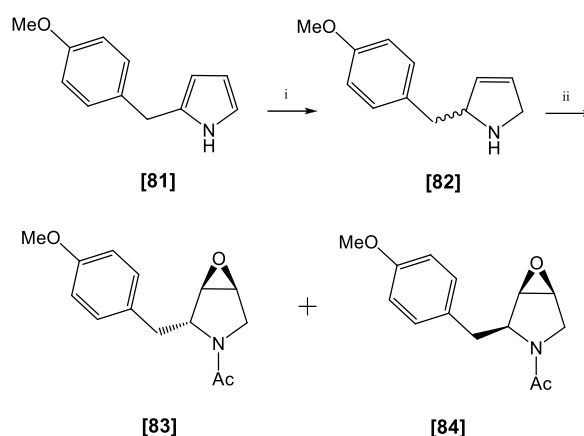
Reagents & conditions: i. Zn/HgCl, HCl, EtOH, Reflux.
ii.(CH$_2$CO)$_2$O, CH$_3$CO$_3$H.

Scheme 3.1

Conversion of epoxide **[84]** to a racemic mixture of deacetyl anisomycin was concluded by refluxing in glacial acetic acid followed by basic hydrolysis.[41]

N-Protection of (+)-deacetyl anisomycin **[5]** with benzyl bromide gave the enantiomorph of **[80]** which in turn was treated with acetic anhydride to form

the *N*-benzyl-anisomycin **[86]**. Wong *et al.* suggested that the selective acetylation of the C2 hydroxy group was achieved due to the pyrrolidine ring adopting its most stable conformation **[85a]** with the lone pair of electrons on the nitrogen in a *cis* configuration with the aromatic group and the C2 hydroxyl group.[17,41] (Scheme 3.2)

Reagents: i. (Ch$_2$CO)$_2$O.   R = OCH$_3$C$_6$H$_4$
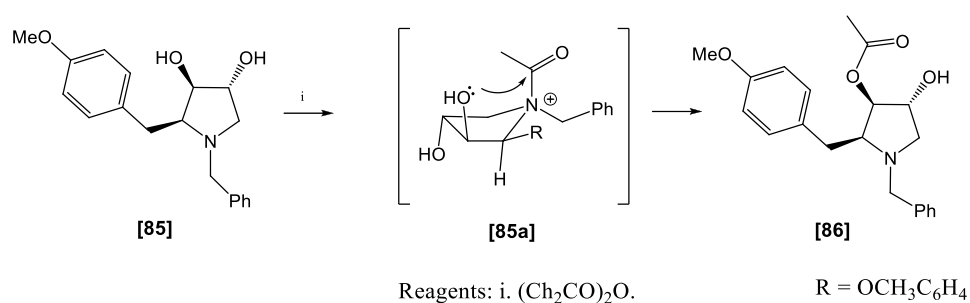
Scheme 3.2

Debenzylation of the nitrogen with 5% Pd/C with HCl gave the hydrochloride salt of (+)-deacetyl anisomycin before sodium hydroxide treatment released the monobasic pyrrolidine **[5]**.

Wong *et al.* affirmed that the conversion of **[80]** to **[1]** was achieved using the same method which formed (+)-anisomycin **[1a]**, however the experimental data is not reported.[41]

Hall *et al's.* synthesis of (±)-anisomycin also employed Wong's 2-(*p*-methoxy-benzyl)-pyrrole **[81]** route by uniting pyrrole-2-carboxaldehyde **[87]** and anisyllithium in a tandem alkylation-reduction procedure. Whilst utilisation of this technique was fundamental at the onset of the synthesis, the regioselective and stereospecific opening of the *syn*-epoxide was arguably the significant reaction step. The lithium-benzyl-alkoxide intermediate **[88]** was reduced to the α-anisyl pyrrole **[81]** via sequential treatment with ammonia,

lithium and ammonium chloride in a 98% yield with no adverse reduction of the pyrrole in accordance with O'Brien and Smith.[43,44,] (Scheme 3.3)

[87] [88] [81]

Reagents: i. OCh$_3$C$_6$H$_4$Li, Et$_2$O. ii. Li, NH$_3$, NH$_4$Cl
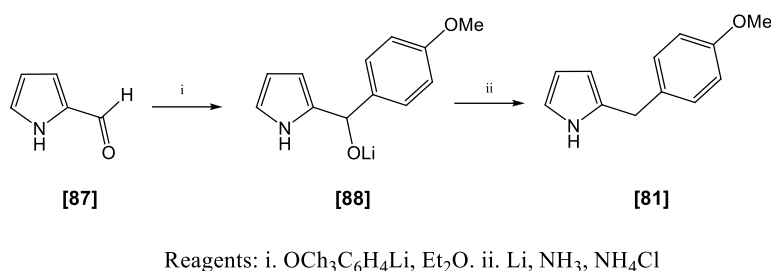
Scheme 3.3

With the molecular framework fabricated efficiently in the one-pot tandem reaction, partial reduction of the pyrrole [81] to 2-(*p*-methoxybenzyl)-3-pyrroline [82] was concluded by the McElvain procedure[45] rather than the Clemmenson reduction[42] in a modest 67%. Hall's strategy relied on forming an epoxide across the double bond at the head of the emergent molecule to enable the vicinal appendages to be set by regio and stereospecific fragmentation. Reaction of the olefin with NIS in perchloric acid and THF formed the short-lived iodiranium cation [89] before collapsing to form iodohydrin [90] as a single stereoisomer. Hall *et al.* suggested that the steric influence of the bulky methoxyaryl group focused regioselective attack to the rear of the C4 position of the strained iodiranium.[24] (Scheme 3.4)

[82] [89] [90]

Reagents & conditions: i.NIS, HClO$_4$ (aq)/THF.   R = OCH$_3$C$_6$H$_4$
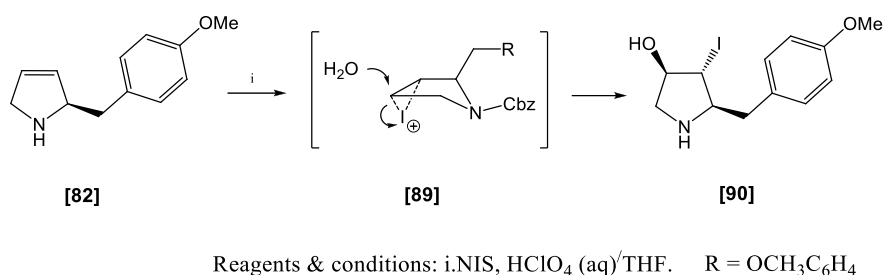
Scheme 3.4

Potassium hydroxide (10% in ethanol) converted the halohydrin to the desired epoxide before removal of the carbamate protecting group. It was firmly advocated that reduction to the free amine was necessary to ensure success of the second regio and stereospecific ring fragmentation to form (-)-deacetyl anisomycin [4]. Refluxing trifluoroacetic acid with sodium trifluoroacetate induced cleavage of the *syn* epoxide before reintroduction of the amine protection.[24] (Scheme 3.5)

Reagents & conditions: i. CF_3CO_2H, CF_3CO_2Na, 120°C $R = OCH_3C_6H_4$
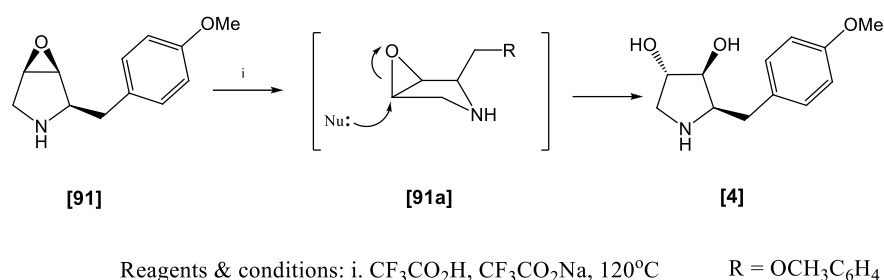
Scheme 3.5

Selective trichloroethyl carbamate protection of the 4α-hydroxy group in DCM with pyridine enabled acetylation of the remaining hydroxyl group with acetic anhydride. Sequential hydroxyl and amine deprotection with zinc in THF and acetic acid followed by conventional catalytic hydrogenation finalised the synthesis in an 8% overall yield.[24]

An efficient 11 step synthesis of (-)-anisomycin [1] exploiting both the Sharpless asymmetric epoxidation and asymmetric dihydroxylation reactions was utilised by Lin *et al.* in 1995 and culminated in an elegant intramolecular cyclisation final step to complete the alkaloid in a 12% overall yield.[46]

Conversion of divinylcarbinol [92] to the epoxide via the titanium IV mediated Sharpless asymmetric epoxidation reaction followed by trimethylsilyl protection of the alcohol gave the oxirane [94]. Successful

bromomagnisium Grignard coupling of the anisyl group to the unhindered position of the cyclic ether not only installed the aromatic entity but also allowed the oxirane residue to provided the functionality to establish the future amine presence.[46] (Scheme 3.6)

[92]   [93]   [94]   [95]
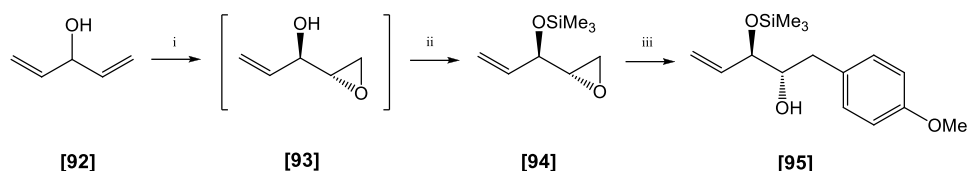
Reagents & conditions: i. D-(-)-DIPT, TBHP, Ti(OPr^i)$_4$, CH$_2$Cl$_2$, -20°C. ii. TMSCl, Et$_3$N, DMAP, CH$_2$Cl$_2$. (65%). iii. OCH$_3$C$_6$H$_4$MgBr, CuI, THF, -10°C. (85%).

Scheme 3.6

Asymmetric dihydroxylation on olefin [96] with catalytic osmium tetroxide and chiral ligand DHQ-CLB enabled formation of the 2,3-*erythro*-triol [97].[46] (Scheme 3.7)

[96]   [97]
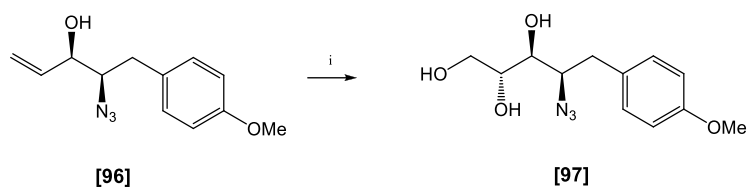
Reagents & conditions: i. OsO$_4$ (cat), K$_3$Fe(CN)$_6$, K$_2$CO$_3$, DHQ-CLB, ^{t}BuOH/H$_2$O. r.t. (95%).

Scheme 3.7

Sequential manipulation of the three hydroxyl groups over 5 steps resulted in the bromo-azide [98] penultimate compound. Hydrogenation of the bromohydrin [98] with catalytic palladium on charcoal followed by a sodium acetate in methanol reflux revealed (-)-anisomycin [1] in a 58% yield.[46] (Scheme 3.8)
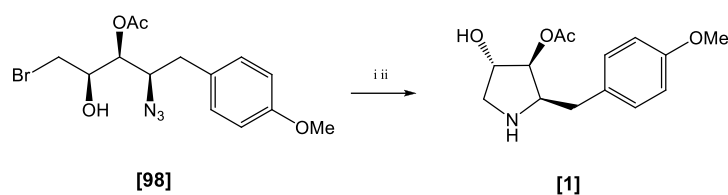
Reagents & conditions: i.H_2, 10% Pd/C, r.t. ii. NaOAc, MeOH, Reflux. (58%).

Scheme 3.8

Kang *et al.* demonstrated that aziridines, like their chalcogenic analogues, could also be used in conjunction with an identical Grignard to introduce the aromatic substituent to the emerging alkaloid.[47]
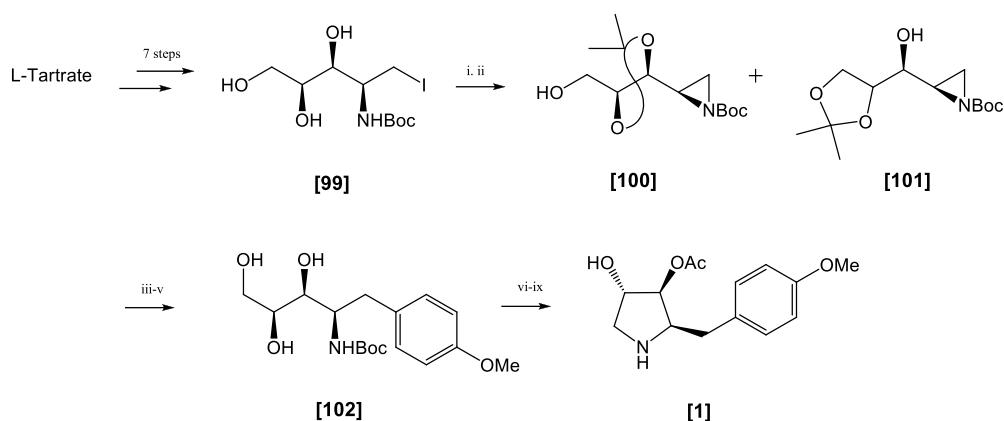
Reagents & conditions: i. CF_3COOH, $(CH_3)_2CO$, 20°C. ii. LDA,THF, -20°C. iii. $OCH_3C_6H_4MgBr$, CuBr-Me_2S, PhMe, -30°C.iv. CF_3COOH, 20°C. v.Boc_2O, $NaHCO_3$, MeOH, 0°C. vi. DEAD, Ph_3P, PPTS, THF, 0°C. vii. TBSCl, imidazole, DMF, 20°C. viii. Ac_2O, DMAP, Et_3N, CH_2Cl_2. ix. HCl, MeOH, 20°C.

Scheme 3.9

Treatment of the acetonide aziridines [**100**] and [**101**], fashioned from the aminoiodotriol [**99**], with anisylmagnesium bromide in the presence of a cuprous bromide dimethyl sulfide complex followed by acid hydrolysis of the acetonide and Boc protection of the amine gave the amino-triol [**102**] as

Kang's key intermediate. Cyclisation to (-)-deacetyl anisomycin [4] under PPTS modified Mitsunobu conditions followed by successive silylation and acetylation enabled simple acid hydrolysis to gain the target alkaloid [1].[47] (Scheme 3.9)

In a recent attempt, Reissig's devised an ambitious synthesis involving a diacetone-fructose substituted allene coupling with an *N*-protected imine precursor before subjecting the resultant molecule to a base catalysed intramolecular cyclisation.[48]

Reissig *et al.* envisages that the chiral entity of the 1,2:4,5-di-*O*-isopropylidenefructose would ensure high diastereoselectivity in the lithiated allene/imine reaction. It was considered that with its sterically hindered rear side, the allene would attack the *Si* face of the imine to provide the desired (*R*)-configuration at the newly formed stereocentre; however, a modest 2:1 ratio in favour of the desired isomer was not improved upon.[48] (Scheme 4.0)

preffered attack to the
Si face of the imine

Major diastereoisomer
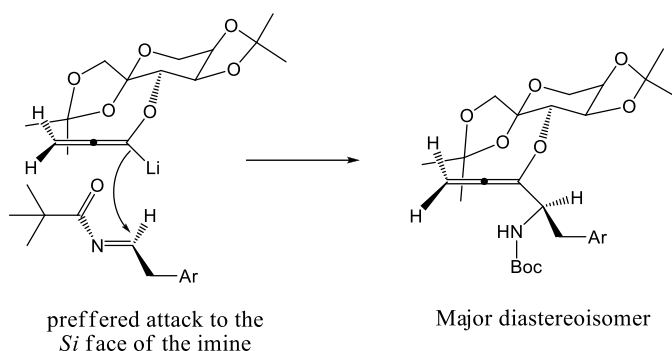
Scheme 4.0

The *N*-Boc-protected allenylamines [105] were cyclised under strong basic potassium tertiary butoxide in DMSO conditions to afford a mixture of the two diastereoisomers of pyrroline [106] in a 65% yield with no change in the ratio. After separation pyrroline [106] was taken forward in a further 6 steps

to successfully complete the synthesis as the hydrochloride salt of **[1]** in an overall yield of 8%.[48] (Scheme 4.1)
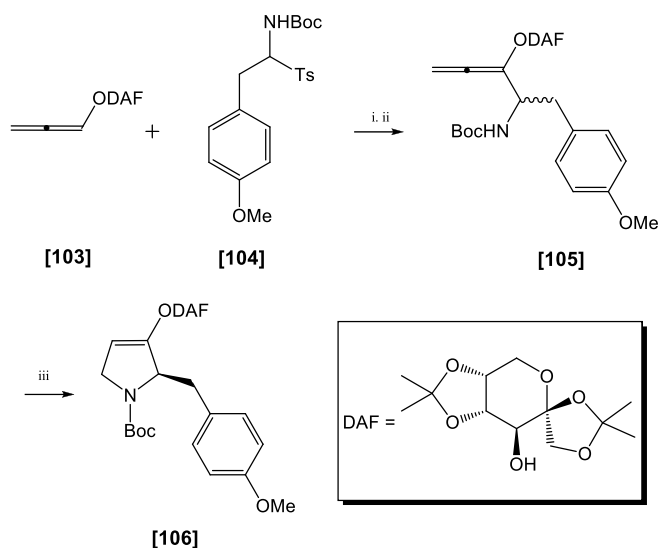
Reagents & conditions: i.BuLi (3 equiv) -78°C, 20 min. ii. [104],
BuLi (1 equiv) -50°C to -20°C, 4h, (73%)
iii. KO^{t}Bu, DMSO, 50°C, 8h (65%).

Scheme 4.1

Kibayashi's highly selective synthesis of (-)-anisomycin **[1]** starting from diethyl-L-tartrate **[107]**, attempted an unsuccessful Grignard addition of the aryl moiety to the L-threitol derived aldehyde **[108]**. However, catalytic deprotection of the terminal benzyl of **[108]** induced cyclisation to the lactol **[109]** which in turn, did succumb to Grignard addition forming the diastereoisomers **[110a]** and **[110b]** in a 79:21 ratio in favour of the undesired *xylo*-isomer **[110a]**.[49] (Scheme 4.2)
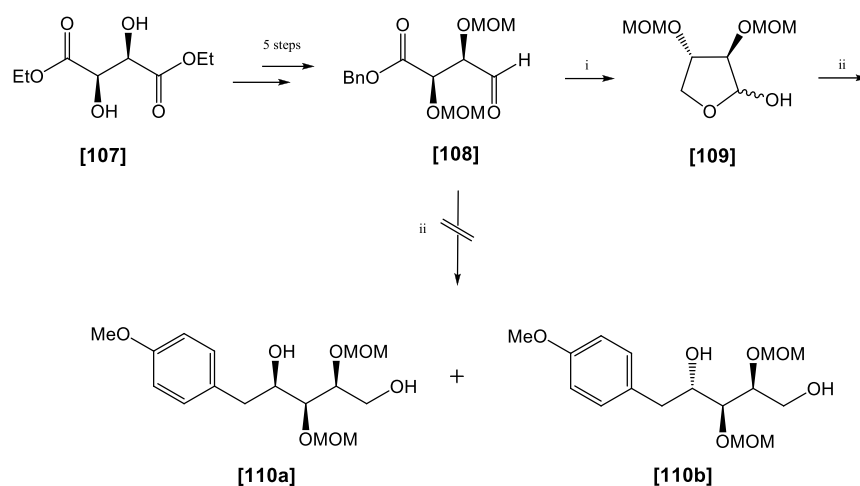
Reagents & conditions: i.Pd/C/H_2, MeOH. ii. Mg, THF, $OCH_3C_6H_4Cl$,
-10°C 14h. (69%) Ratio 79:21.

Scheme 4.2

Inversion of the 4-hydroxyl group was required to enable formation of the azide key intermediate [113] crucial to obtain the necessary 2*R*,3*S*,4*S* configuration in the final product.
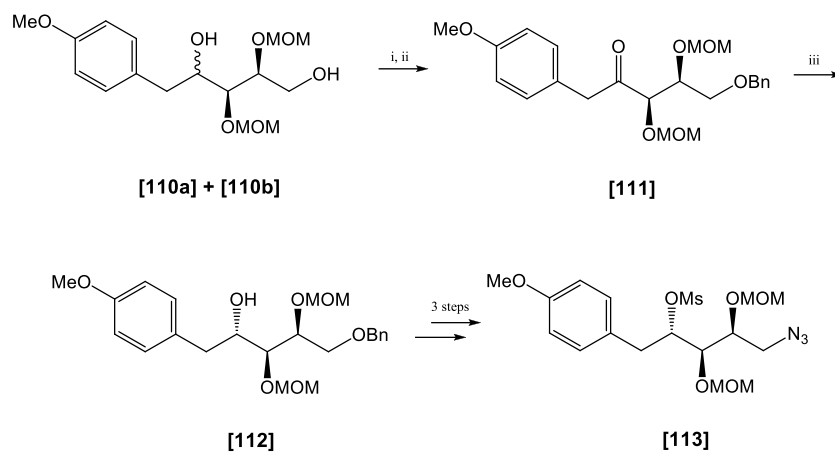
Reagents & conditions: i.BnCl, NaOH, (^{n}Bu)$_4$NBr, CH_2Cl_2. (69%), Ratio 79:21.
ii. Mg, THF, $C_2O_2Cl_2$, CH_2Cl_2, Me_2SO_3, Et$_e$N, -78°C.
(93%). iii. Zn(BH$_4$)$_2$, Et$_2$O, (91%).

Scheme 4.3

Selective benzylation of the diastereoisomeric mixture with successive Swern oxidation furnished ketone [111] and treatment with zinc borohydride enabled diastereofacial control of the α,β-alkoxy carbonyl chelation for the hydride reduction.[49,50] (Scheme 4.3) Spontaneous cyclisation of [113] via intramolecular mesyl displacement following catalytic hydrogenation caused configuratory inversion to give dimethoxymethyl protected deacetyl anisomycin with the correct stereochemistry. A further six steps including selective benzyl and silyl protection of the amine and 4-hydroxy group respectively allowed unimpeded acetylation followed by systematic deprotection to give the desired target [1] in a 2% yield over 18 steps.[49]

Baer *et al.* like their predecessors, Verheyden and Buchanan *vida supra*, also elected to utilize the carbohydrate pool as a chiral template. It was considered that the *trans* glycol motif of D-galactose would serve well to form the awkward stereochemical C3 and C4 embodied in the final product and the C5 and C6 pendant would elaborate to the benzylic substituent.[51]

D-galactose was converted to the glycol protected *β*-D-galactofuranoside [114] over five multigram standard reactions before periodate oxidation gave the dibenzyloxy aldehyde [115]. Treatment with *in situ* generated (4-methoxyphenyl)-magnesium bromide attached the aryl group forming a mixture of epirmeric alcohols [116].[51] (Scheme 4.4)
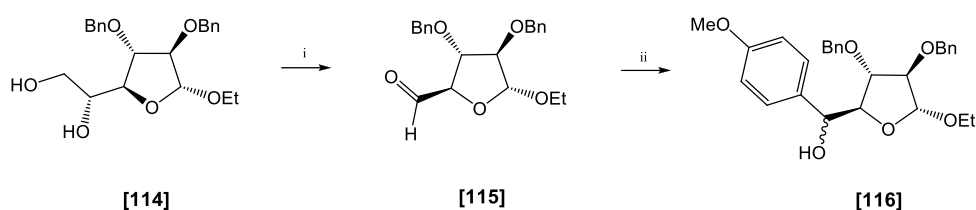
Reagents & conditions: i.NaIO$_4$, EtOH, H$_2$O. (95%). ii. CH$_3$OC$_6$H$_4$Br, Et$_2$O, Mg, Br$_2$, Reflux, 2h. (87%).

Scheme 4.4

Ionic deoxygenation using triethylsilane with trifluororacetic acid converted the benzylic hydroxyl groups to the methylene and gave ethyl-2,3-di-*O*-benzyl-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside, whilst an acetic acid reflux afforded the alcohol **[117]** as an anomeric mixture.[51]
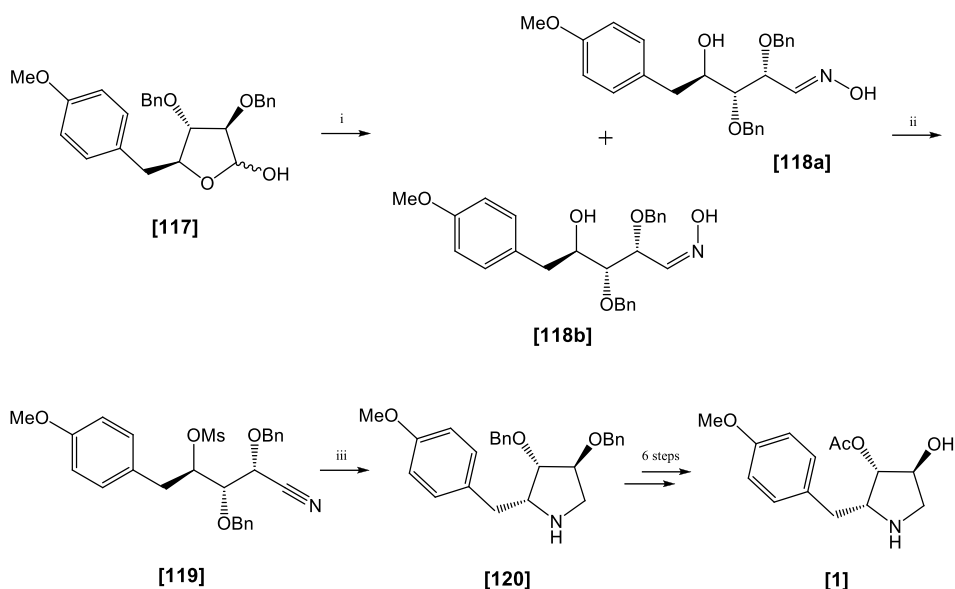
Reagents & conditions: i.NH$_2$OH.HCl, C$_5$H$_6$N, EtOH, Reflux (86%). ii. MsCl, C$_5$H$_6$N, H$_2$O, (71%). iii. BH$_3$, THF, HCl, MeOH, KOH, (86%),

Scheme 4.5

Formation of the oximes **[118a]** and **[118b]** as an *E,Z* mixture was achieved by fragmentation of the furanoside with hydroxylamine hydrochloride in pyridine and ethanol. Treatment of the aldoximes with methanesulfonyl chloride induced dehydration with simultaneous *O*-mesylation to give the nitrile mesylate cyclisation precursor **[119]**. Whilst employing Buchanan *et al's* precedent to their analogous reductive cyclisation reaction to achieve similar results, Baer's preference was to use diborane in THF to ensure a greater yield of the desired pyrrolidine **[120]**. Debenzylation via catalytic hydrogenation in the presence of formic acid completed the formal synthesis in an 18% overall yield.[51] (Scheme 4.5)

Yoda *et al.* developed an economic route to (-)-deacetyl anisomycin **[4]**, and like Shono *et al.* previously, formed a substituted γ-lactam as the key intermediate via intramolecular cyclisation.[26] Amination of commercially available 2,3,5-tri-*O*-benzyl-*β*-L-arabinofuranose with benzylamine replaced the solitary hydroxyl to form the furanosylamine **[121]**.
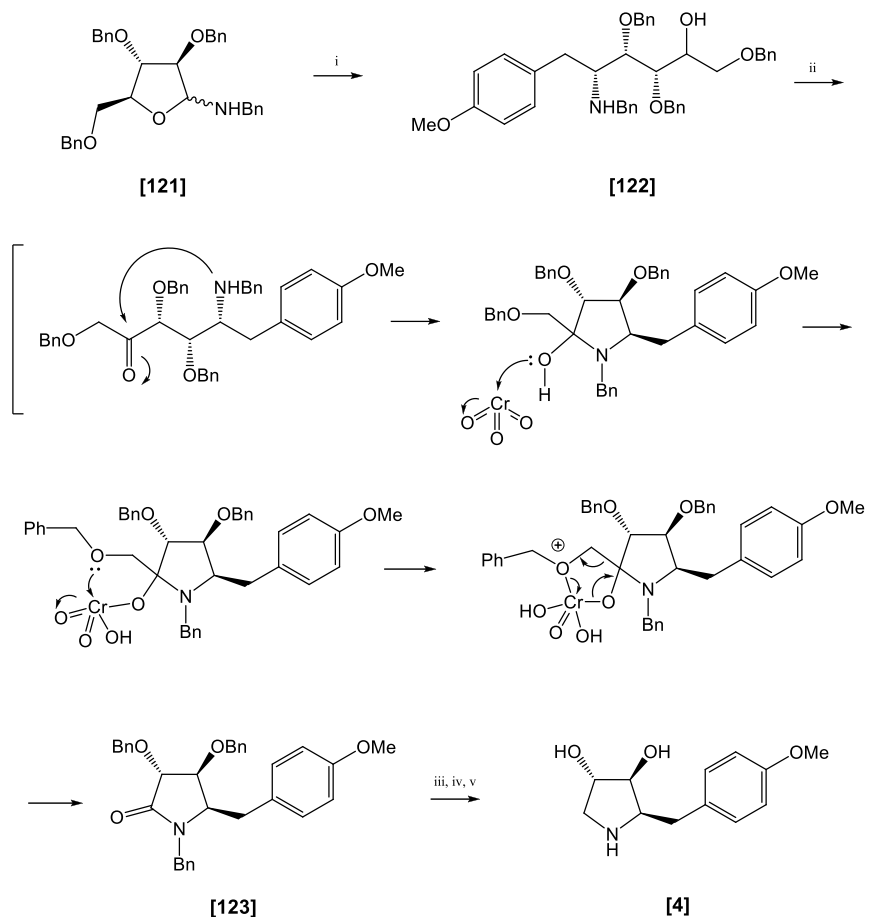
Reagents & conditions: i. Mg, THF, OCH$_3$C$_6$H$_4$Cl, -78°C. (78%). ii. PCC, MS 4A, CH$_2$Cl$_2$, (63%). iii. Pd-black, HCO$_2$H, MeOH. (99%). iv. LiAlH$_4$, THF, (91%). v. Pd-black, HCO$_2$H, MeOH.

Scheme 4.6

Grignard fragmentation of the ring via approach to the least hindered side ensured a high yield of the single stereoisomer **[122]**. Treatment with pyridinium chlorochromate enabled ring closure to form the desired γ-lactam

[123] with the correct stereogenic centres, whilst catalytic debenzylation and hydride reduction of the carbonyl concluded the global deprotection and the formal synthesis.[52] (Scheme 4.6)

Petrini *et al.* considered a different approach into uniting both rings of the alkaloid. It was felt that the nitrogen within the pyrrolidine ring could be integrated as part of a nitrone functionality and that the carbon α to the nitrogen would be electrophilic enough to undergo attack from a suitable Grignard reagent. *N*-benzyl tartrimide **[77]** prepared from L-tartaric acid **[76]**, parallel to the Wong *et al.*[17] procedure, underwent methoxymethyl protection of the *trans* diol and debenzylation to give the secondary amine **[124]**.
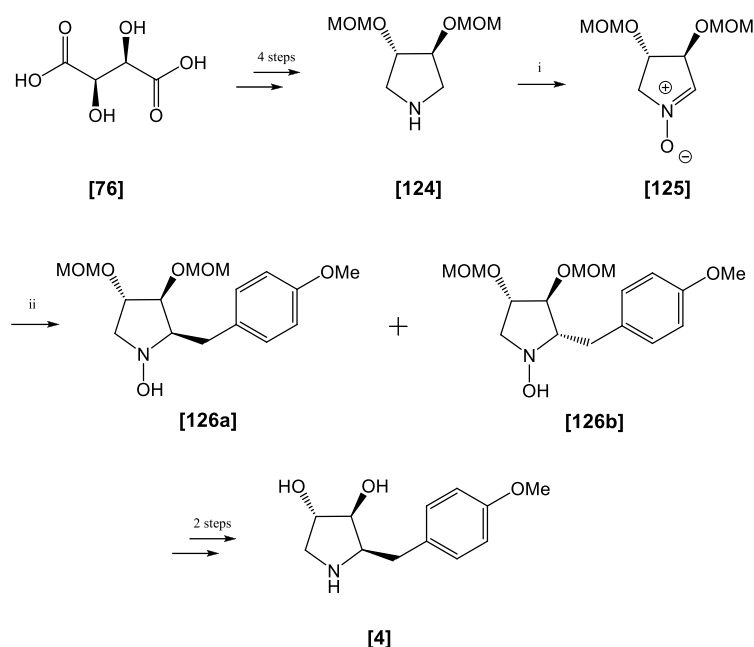
Reagents & conditions: i. SeO$_2$, (CH$_3$)$_2$CO, 30% H$_2$O$_2$ 0°C. (60%). ii. MgBr$_2$.Et$_2$O, OCH$_3$C$_6$H$_4$MgCl, 0°C, 30min. (42%).

Scheme 4.7

Translation to the nitrone **[125]** via hydrogen peroxide oxidation in the presence of catalytic selenium dioxide enabled addition of the aryl group. The

reaction of (*p*-methoxybenzyl)-magnesium chloride in THF produced a mixture of diastereomers **[126a]** and **[126b]** in a 2:3 ratio in favour of the undesired isomer **[126b]**. However, the addition of 1 equivalent of magnesium bromide diethyl etherate in DCM allowed for magnesium/oxygen coordination, thus altering the diastereoselectivity to give predominantly the desired *cis* product **[126a]**. Catalytic hydrogenation with Raney nickel and subsequent acid hydrolysis gave (-)-deacetyl anisomycin **[4]** in a 12% overall yield.[53] (Scheme 4.7)

In 2000, Larchevêque *et al.* reported a formal synthesis of (-)-anisomycin based on a stereoselective reductive alkylation of a polyhydoxylnitrile derivative.[54] Previous work by the Paris group on 2,3-dialkylnitriles provided sound evidence that they were able to control the reaction to give the all *syn*-protected aminodiol in high enantiomeric purity.[55]
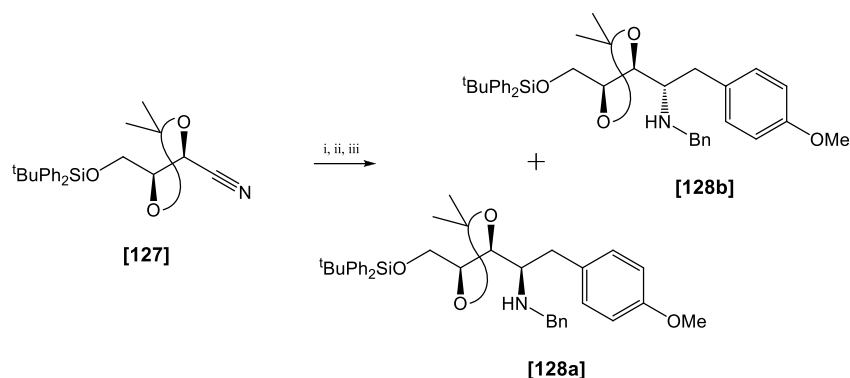
Reagents: i. OCH₃C₆H₄CH₂MgCl, Et₂O, ii. BnNH₂, MeOH, iii. NaBH₄, (80%).

Scheme 4.8

Formation of the protected trihydroxynitrile **[127]** target intermediate was achieved from both L-tartaric acid **[76]** and L-threonic acid over five steps via two different routes. Nucleophilic attack of the cyano group with *p*-anisyl magnesium chloride formed the metalloimine intermediate before yielding *in*

situ to the primary imine. Addition of benzylamine allowed for trans-imination of the unsubstituted imine before reduction with sodium borohydride gave a mixture of *syn* and *anti* diastereomeric *N*-benzylamines **[128a]** and **[128b]** in an 81:19 ratio in favour of the desired *threo* product.[54] (Scheme 4.8)

Manipulation of the *syn* protected amine **[128a]** to the mesylate from the primary alcohol **[129]** enable acidic cleavage of the acetonide before base assisted ring closure via the familiar intramolecular S_n2 displacement reaction[23,28,31,49] gave *N*-benzyl deacetyl anisomycin **[129]**, whilst standard debenzylation completed the ten step synthesis.[54] (Scheme 4.9)

[129]

[130]

[131]
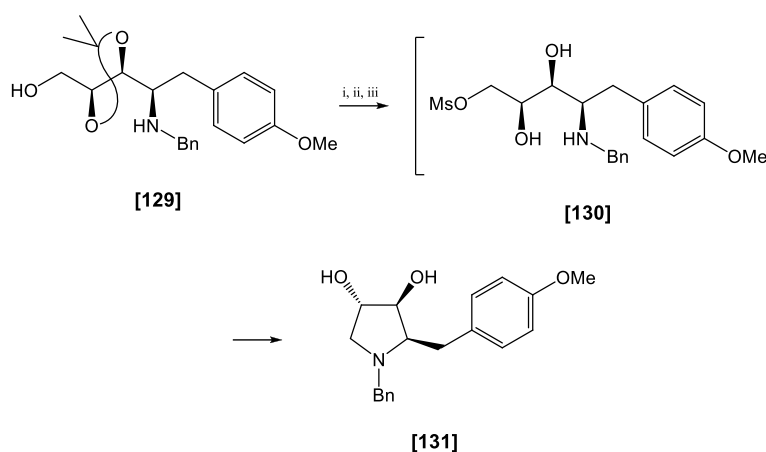
Reagents & conditions: i. MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$. ii. HCl, THF, Reflux 12h, iii. NaHCO$_3$, (80%).

Scheme 4.9

Merino *et al.* like Petrini,[53] also employed nitrone functionality in order to attach the anisyl group; however, stereoselective nucleophilic addition to an acyclic α-alkoxy nitrone[56,57] instead of the nitrone being incorporated within the pyrrolidine would pave the way to (-)-deacetyl anisomycin **[4]**. Nitrone **[133]** was prepared by treatment of the protected D-threitol aldehyde derivative **[132]** with *N*-benzylhydroxylamine and magnesium sulfate. The addition of the *p*-methoxybenzyl Grignard yielded almost exclusively the *syn*

adduct **[134]** thus setting the final chiral centre. Reduction of the hydroxylamine **[134]** with a zinc/copper(II)acetate couple allowed debenzylation to Larchevêque *et al's* cyclisation precursor **[129]**. In a slight deviation to Larchevêque's final procedures to produce (-)-deacetyl anisomycin **[4]**, an overall yield of 28% concluded the synthesis.[57] (Scheme 5.0)
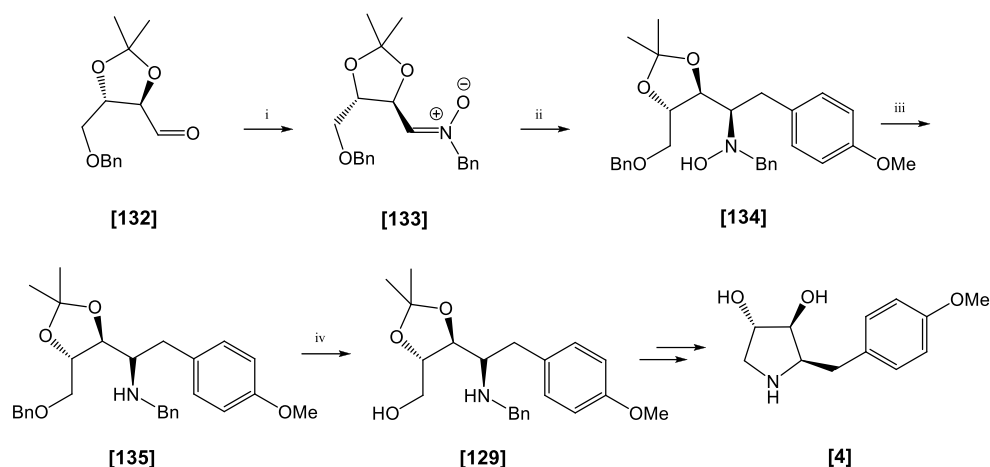
Reagents & conditions: i. $PhCH_2NHOH$, CH_2Cl_2, $MgSO_4$ 4h. (86%). ii. $CH_3C_6H_4CH_2MgCl$, THF, -20°C. (84%). iii. Zn, $Cu(OAc)_2$, CH_3COOH, H_2O, EDTA, NaOH. (82%). iv. Na, NH_3, Et_2O, NH_4Cl, H_2O. (100%).

Scheme 5.0

Jäger's approach to (-)-deacetyl anisomycin **[4]**[58] in 1996 developed an L-threose imine key intermediate starting from monobenzylated L-threitol **[136]** via 1,2-diol protection with acetone and *p*-toluene sulfonic acid[59] followed by Sarett oxidation to form the aldehyde **[137]**. Condensation of the aldehyde with benzylamine gave the imine **[138]** necessary for the aryl coupling reaction. Treatment of the imine **[138]** with the *p*-methoxymethylbenzene Grignard produced the familiar analogous skeletal backbone[31,47,54,57] of the cyclisation precursor **[139]**; and modified Mitsunobu conditions finalised the ring. Removal of the *N*-benzyl protection afforded the hydrobromide salt of (-)-deacetyl anisomycin **[4]** in 34% yield over 7 steps.[58] (Scheme 5.1)

[136]   **[137]**   **[138]**

[139]   **[140]**   **[141]**
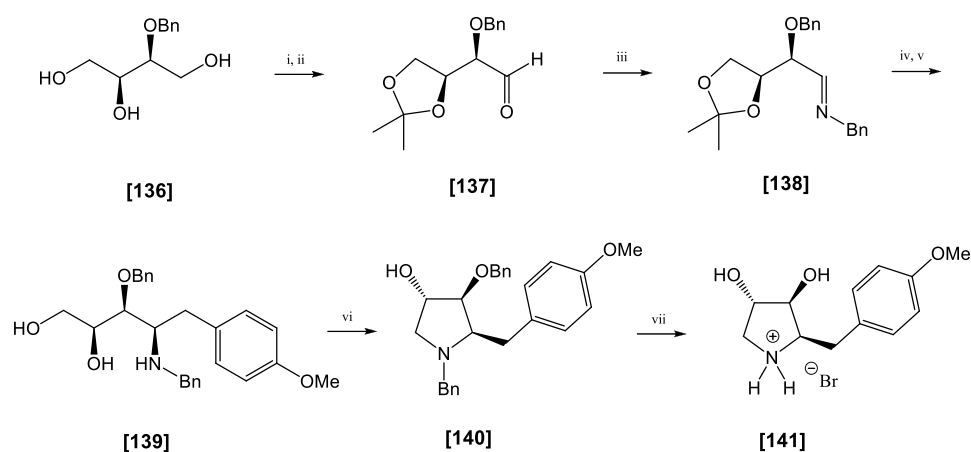
Reagents & conditions: i. $(CH_3)_2CO$, PTSA. (98%). ii. CrO_3 C_6H_5N. (74%). iii. Al_2O_3, $BnNH_3$, (100%). iv. $OCH_3C_6H_4CH_2MgCl$, Et_2O, 0°C, NH_4Cl. (62%). v. HCl, $H_2O/C_4H_8O_2$. vi. DEAD, Ph_3P, C_5H_5N, 0°. H_2O, LiOH. (77%). vii. Pd/C/H_2, MeOH. (99%).

Scheme 5.1

An interesting, if not tortuous route to Kibayashi's key intermediate **[110b]**[49] was developed by Akita *et al.* and included a stereoselective nucleophilic substitution coupled with a 1,2 aryl migration.

[142]   **[143]**

[144]   **[145]**
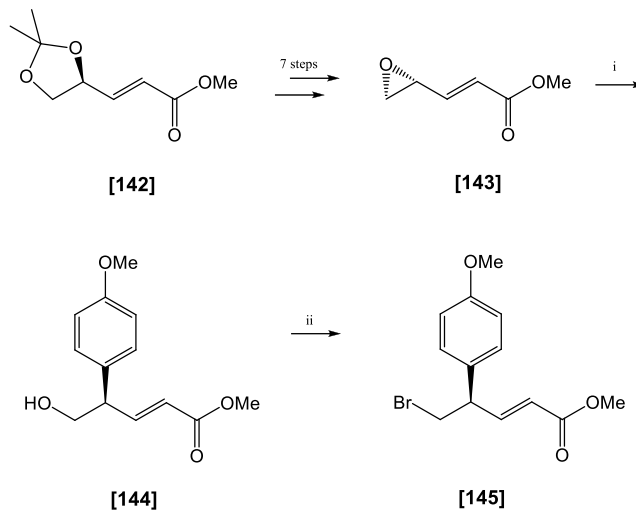
Reagents: i. $OCH_3C_6H_5$, $BF_3.Et_2O$, CH_2Cl_2, (47%). ii. CBr_4, Ph_3P, CH_2Cl_2. (92%).

Scheme 5.2

The (*E*)-unsaturated methyl ester **[142]** from D-mannitol was converted to the (*R*)-epoxide **[143]** over seven steps. Introduction of the anisole group with

boron trifluoride diethyl etherate at the expense of the epoxide furnished alcohol **[144]** which was then converted to the bromide **[145]**. (Scheme 5.2) To induce aryl migration, the bromo-methyl ester **[145]** was treated with silver nitrate in nitromethane with 4Å molecular sieves. Akita suggested that a cationic spiro-cyclopropane intermediate species would form, whereby nucleophilic fragmentation via the ambident anion would complete the aromatic shift and establish the nitrate functionality with inversion at the C4 position **[146]**.[60,61] (Scheme 5.3)
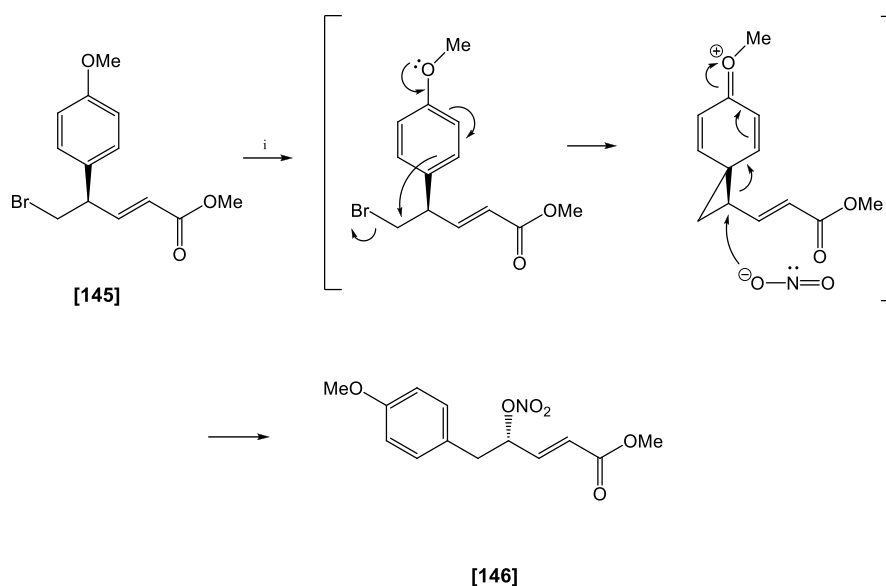
Reagents & conditions: i. AgNO$_3$, MS 4 A°, MeNO$_2$, 12h. (91%).

Scheme 5.3

Conversion of the nitrate **[146]** to the (4*S*)-alcohol **[147]** allowed for catalytic osmium tetroxide to bind to the least sterically hindered *β*-side of the *trans* olefin to undergo dihydroxylation before treatment with *N*-morpholine-*N*-oxide to produce the 3,4-*anti*-γ-lactone **[148]**. Protection of the diol was concluded with chloromethyl methyl ether and Hünig's base before DIBAL reduction gave Kibayashi's intermediate **[110b]**.[60,61] (Scheme 5.4)
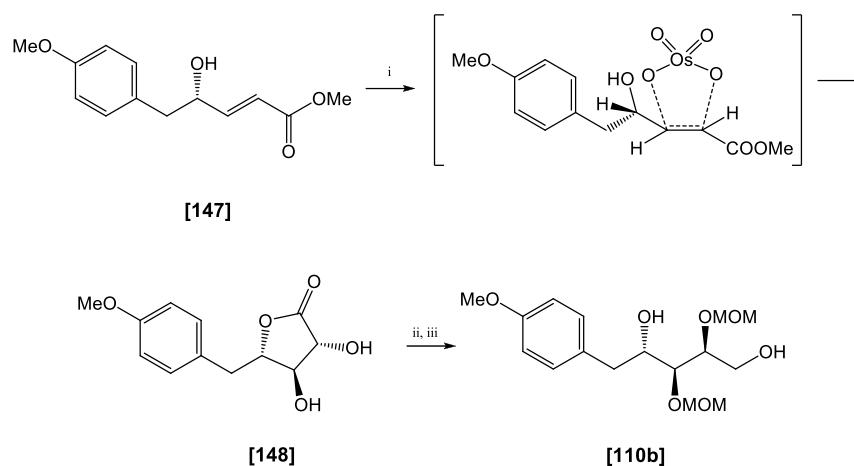
Reagents: i. OsO$_4$, NMNO, (CH$_3$)$_2$O, H$_2$O. (78%). ii. CH$_3$OCH$_2$Cl, DIPEA, MeCN. (78%). iii. DIBAL,C$_6$H$_6$. (81%).

Scheme 5.4

Takano *et al*. devised an enantioconvergent route to Oida's 3-pyrroline intermediate [26][20] for their formal synthesis, utilising both the (*S*)- [149] and (*R*)- [150] enantiomers of epichlorohydrin. Although both could be fashioned from D-mannitol via McClure's synthesis,[63] commercially available supplies were employed as the starting materials. Transformation of both (*S*)- and (*R*)-epichlorohydrin to the single key epoxide target [151] together with installation of the anisole moiety was achieved in two and seven steps respectively.
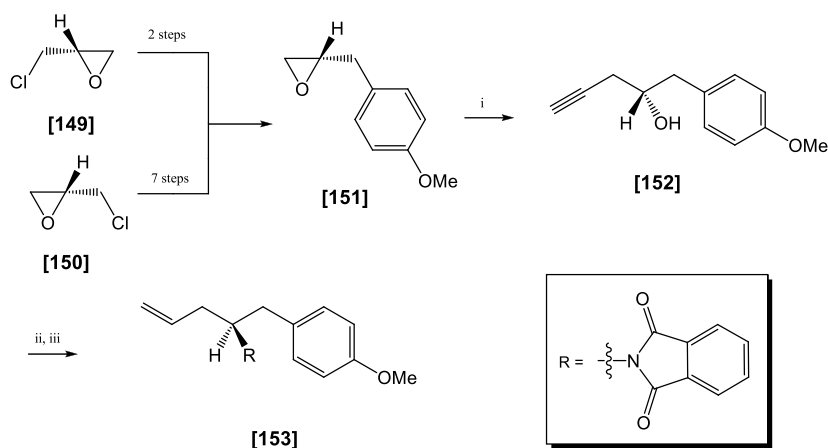
Reagents & conditions: i. LAED, DMSO, (85%). ii. Pd/CaCO$_3$, AcOEt, (100%). iii. DIAC, PPh$_3$, THF, -20°C.

Scheme 5.5

The oxirane **[151]** was converted to the acetylene **[152]** by reaction with lithium acetylide ethylenediamine and subsequently reduced to the alkene with Lindlar's catalyst. The secondary alcohol was subjected to Mitsunobu conditions to give the phthalimide **[153]** with inversion of the stereochemistry, before reduction to the primary amine.[62] (Scheme 5.5)
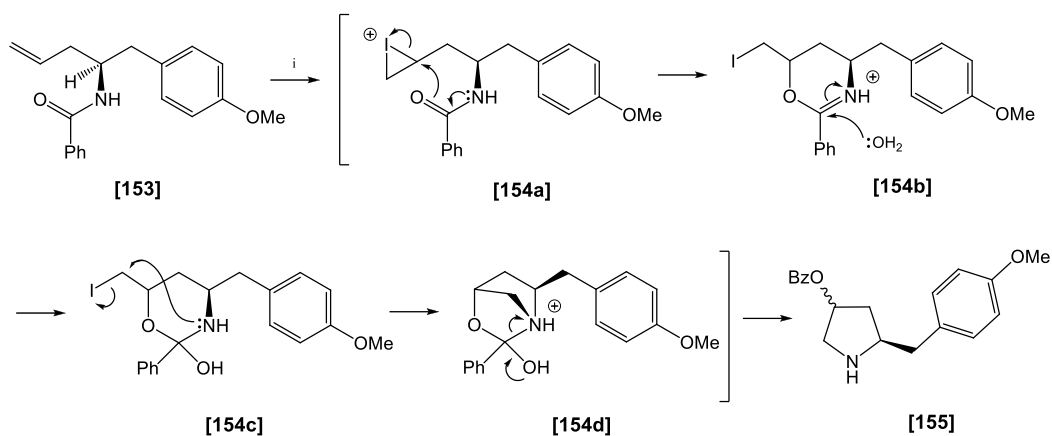
Reagents: i.I$_2$ (3 equi), H$_2$O/MeCN (1:1), (90%).

Scheme 5.6

The selection of the benzoyl protection for amine was essential in that the amide created would be intrinsic in the formation of the cyclisation product. Treatment of the amide [153] with three equivalence of iodine in acetonitrile proceeded to form the iodiranium 3-membered ring [154a] across the alkene, which in turn collapsed following formation of the dihydro-oxazinium species [154b]. The intermediate evolved further into the bicyclic-oxazolidinium [154d] with the water present in the reaction, before finally resolving to a 2:1 mixture of epimers of the pyrrolidine benzoate [155]. (Scheme 5.6) The amine [155] was once again protected but to the benzyl carbamate which allowed for benzoyl conversion to the xanthate [156] via the hydroxyl. High temperature reflux in *ortho*-dichlorobenzene ejected the xanthate and installed the double bond and base hydrolysis completed the synthesis.[62] (Scheme 5.7)
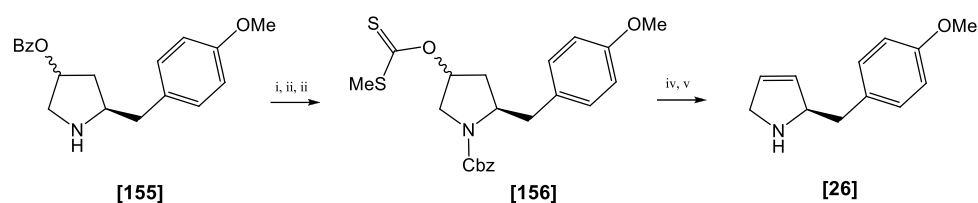
Reagents & conditions: i. BnCOOCl, Et$_3$N, CH$_2$Cl$_2$, ii. K$_2$CO$_3$, MeOH, iii. CS$_2$, NaOH, ^{n}Bu$_4$NHSO$_4$, MeI, C$_6$H$_6$, (87% over 3 steps). iv. *O*-C$_6$H$_4$Cl$_2$, Reflux, (70%). v. NaOH, (CH$_2$OH)$_2$, 120°C, (89%).

Scheme 5.7

Takahata *et al.* also developed an enantioconvergent strategy from a racemic starting material to deliver Oida's 3-pyrroline intermediate [26][20] for (-)-anisomycin [1]; however in addition to this, the synthetic route also diverged at a common key intermediate to complete the synthesis of (-)-detoxinine [164]. *N*-(*tert*-butoxycarbonyl)-3-hydroxy-4-pentenylamine [159] was readily obtained using a Sharpless kinetic resolution protocol to give the optically pure (*R*) isomer in 36% yield from racemic [158] and >90% ee.

Stereoselective amidomercuration followed by replacement of the acetate with bromide **[160]** allowed for silyl protection of the hydroxyl group and subsequent oxidation to give the primary alcohol **[163]**. The same Sharpless asymmetric oxidation using the opposite chiral tartrate diester formed the (3S,4R)-epoxy alcohol which in turn surrendered to the *cis*-1,3-pyrrolidine-diol **[161]** via intramolecular amidation in 33% yield and >92% ee. A shorter sequence of converting the diol **[161]** to the primary alcohol **[162]** used the same silyl protection procedure, before selective monodesilylation with acetic acid completed the convergence.[64] (Scheme 5.8)
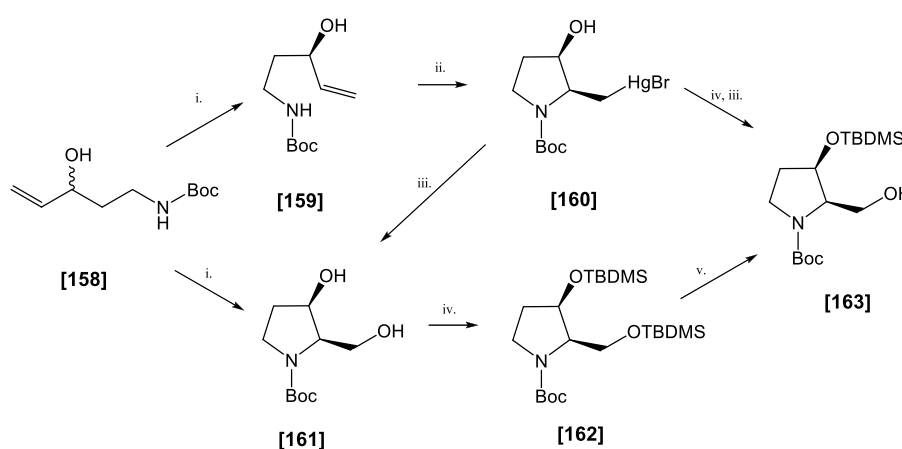
Reagents: i. L-(+)-DIPT/D-(-)-DIPT, TBHP, Ti(*O-I*-Pr)$_4$/4A MS. (36%), (33%). ii. Hg(OAc)$_2$, THF, NaHCO$_3$/H$_2$O, KBr, (90%). iii. O$_2$, NaBH$_4$, DMF, (64%), (93%). iv. C$_3$H$_4$N$_2$, TBDMSCl, DMF, Et$_2$O. (64%), (93%) v. AcOH, THF, H$_2$O, (52%).

Scheme 5.8

The alcohol **[163]** underwent Swern oxidation treatment to form the aldehyde **[165]** and it is at this key intermediate where the synthetic routes separate to the different biologically active compounds. *In situ* formed 4-anisyllithium afforded the coupled product which was then exposed to strong acid conditions causing simultaneous desilylation, benzylic hydroxyl reduction and butoxycarbonyl elimination. With the two functional groups exposed,

amine protection was re-instigated in the form of a carboxybenzyl group followed by conversion of the alcohol to the xanthate [167], identical to Takano's [156] but for the regiochemistry. Pyrolysis under reduced pressure provoked Chugaev's 6 membered cyclic transition state terminating in the *syn* elimination and the new alkene. Completion of the formal synthesis was accomplished with removal of the amine protection by sodium in aqueous ammonia.[64] (Scheme 5.9)
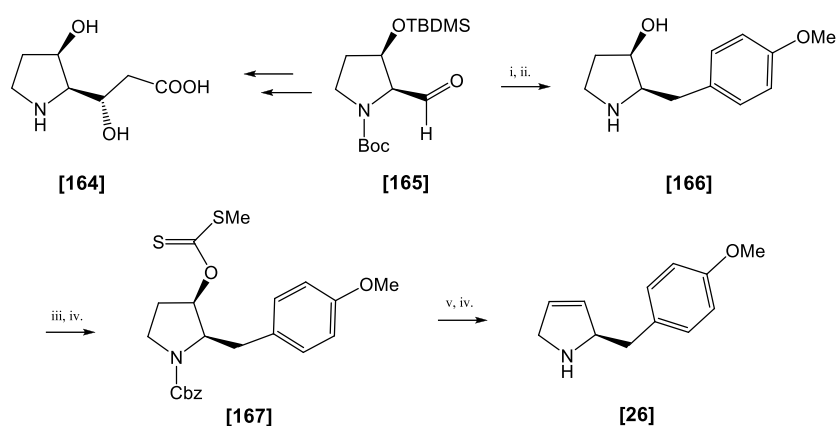
Reagents & conditions: i. $CH_3OC_6H_5Br$, ^nBuLi, THF, -78^oC, (76%). ii. Et_3SiH, CF_3CO_2H, HCl, iii. $C_6H_5CH_2OCOCl$, Et_3N, CH_2Cl_2, (62%). iv. NaH, $C_3H_4N_2$, CS_2, MeI Reflux, 4h, (81%). v. 170^oC, (77%). vi. NH_3/H_2O, Na, (100%).

Scheme 5.9

Somfai utilised a microwave-assisted rearrangement of a vinylaziridine derivative in a recent formal synthesis of (-)-anisomycin [1], again reaching the 3-pyrroline [26].

Reagents & conditions: i. CH_2CHCH_2Cl, $LiNCy_2$, (+)-Ipc_2BOMe, $BF_3.Et_2O$,
-95°C, 6h. ii. MeOH, NH_4OH, 130°C, 10 min, (52%).
iii. TsCl, KOH, THF. (93%).
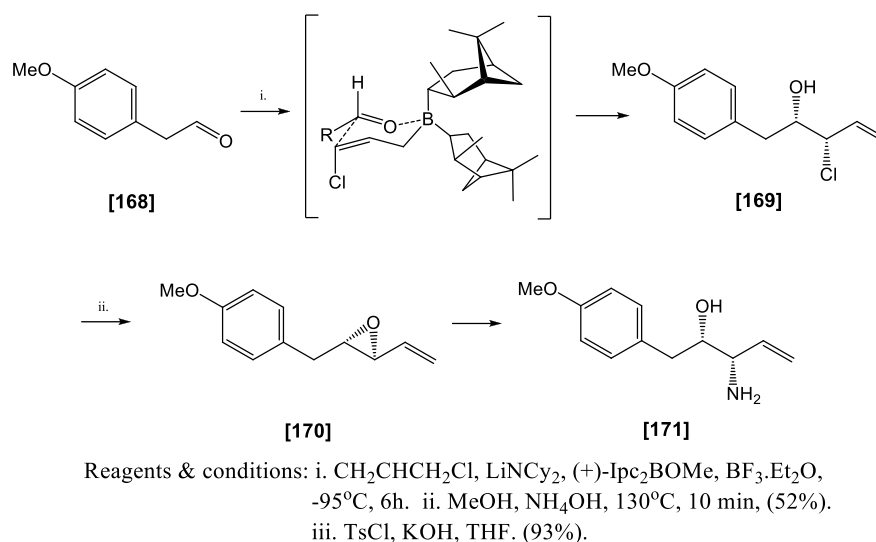
Scheme 6.0

A modified Brown allylation[65] on *p*-methoxyphenyl acetaldehyde **[168]** with allyl chloride allowed for boron assisted coupling with *re* face attack[65] to give the chlorohydrin **[169]**. Treatment with aqueous ammonia in methanol formed the amino alcohol **[171]** via the vinyloxirane **[170]** in 52% yield over 2 steps and >95% ee.[66] (Scheme 6.0)

Tosylation and ring closure of the amino alcohol **[171]** with potassium hydroxide and 5 equivalence of tosyl chloride gave the *cis*-vinyl-aziridine **[172]** which when treated with lithium iodide under microwave irradiation rearranged to the N-tosyl pyrroline in an impressive 92% yield. Simple amine deprotection completed the route in a 37% overall yield.[66] (Scheme 6.1)
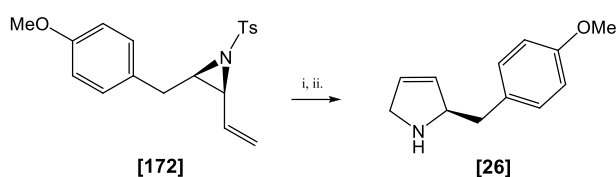
Reagents & conditions: i. LiI, M.I. 200°C, 30 min. (92%). ii. Na,
naphthalene, THF, -78°C. (84%).

Scheme 6.1

Initially starting with (*S*)-malic acid **[173]**, Huang *et al.* reported in two publications over 6 years the construction of Oida's aryl methoxy dihydro-1*H*-pyrrole **[26]**[20] featuring a highly regio and stereoselective reductive alkylation to attach the anisole group. Huang's assembly of the *N*-benzyl malamide **[174]** was analogous to that of both Wong and Petrini *vida supra*, as well as the Grignard reagent chosen to attack the ketone. Reaction with the Grignard installed the anisole substructure at the C2 position in near perfect regeoselectivity producing a 2:1 diastereomeric mixture of the α-hydroxylactam **[175]**. Lewis acid mediated reductive deoxygenation gave rise to the 2-pyrrolidinonium ion intermediate **[176]** before setting the stereochemistry predominantly in the *trans* orientation of the resulting γ-lactam **[177]**.[67,68] (Scheme 6.2)
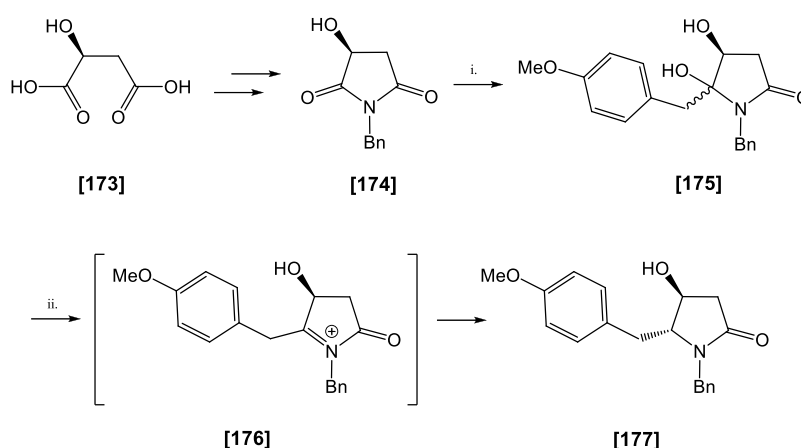
Reagents & conditions: i. $CH_3OC_6H_5CH_2MgCl$, THF, -15°C. (95%).
ii. $BF_3.Et_2O$, Et_3SiH, -78°C. (95%).

Scheme 6.2

Reduction of the ketone in the presence of lithium aluminium hydride followed by substitution of the amine protection via Pearlman's catalyst gave **[178]**; the diastereoisomer of Takahata's pyrrolidine **[166]**. This allowed for familiar hydroxyl elaboration to make use of Chugaev's elimination protocol.

Trivial amine deprotection concluded the synthesis of **[26]** in a 39% yield over 8 steps from **[174]**.[67,68] (Scheme 6.3)
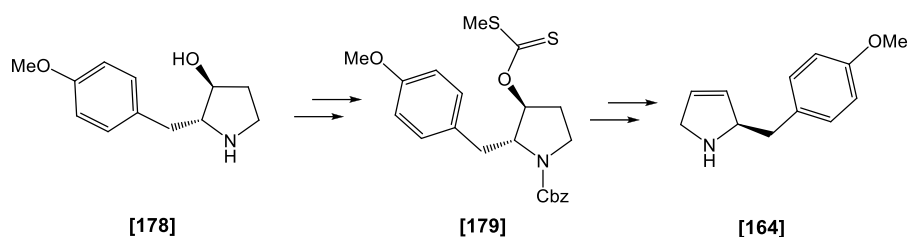
Scheme 6.3

In an interesting deviation from the general cyclisation theme; Greene *et al.* in 1999 drew upon their experience in their synthesis of (+)-preussin **[180]**, a related natural product, a year earlier[69] and used an asymmetric 2+2 cycloaddition reaction on their route to Takahata's *cis*-disubstituted pyrrolidine **[166]**[64] before expanding the resultant cyclobutanone.
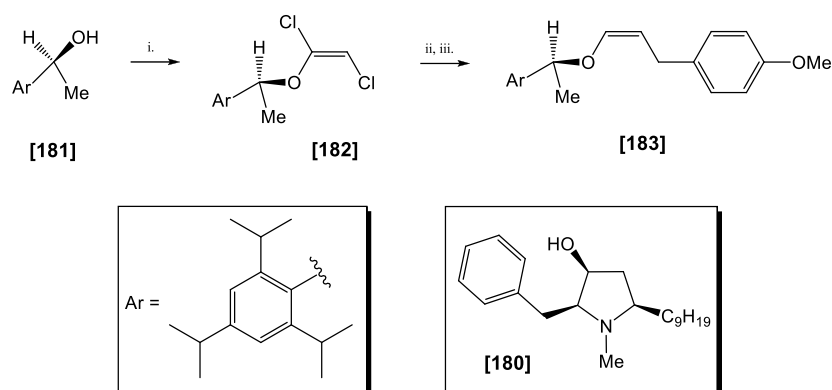
Reagents & conditions: i. KH, THF, Cl_2CCHCl, 20°C, 1h. (82%). ii. ^{n}BuLi, THF, $CH_3OC_6H_5CH_2Br$, HMPA -78°C. iii. H_2, Pd/$BaSO_4$, C_5H_5N, $KHCO_3$, 0°C, 48h. (81%).

Scheme 6.4

Starting with (*S*)-1-(2,4,6-triisopropylphenyl)ethanol **[181]** as the chiral auxiliary with trichlororthene; the (*E*)-dichloro-enol ether **[182]** was successfully prepared for the addition of the aromatic. Formation of the lithium acetylide with ^{n}butyllithium allowed for alkylation with 4-methoxybenzyl bromide to yield the relatively unstable acetylenic ether. (Scheme 6.4)

Lindlar's barium sulfate catalyst with a pyridine modifier as opposed to the conventional quinoline, allowed for reduction to the (*Z*)-enol ether **[183]** before diastereofacially selective 2+2 cycloaddition reaction with *in situ* generated dichloroketene produced the desired dichlorocyclobutanone **[184]**. With the use of Tamura's reagent **[185]**, a Beckmann ring expansion of the cyclobutanone **[184]** installed the essential nitrogen component and gave the γ-lactam **[186]**, which was subsequently de-chlorinated with a zinc/copper couple. Protection of the newly establish nitrogen with benzyl chloroformate sanctioned the reduction of the lactam's carbonyl constituent with lithium triethylborohydride and triethylsilane in boron trifluoride diethyl etherate. Treatment with trifluoroacetic acid removed the chiral auxiliary appendage and finalised the formal synthesis in a 27% overall yield.[70] (Scheme 6.5)
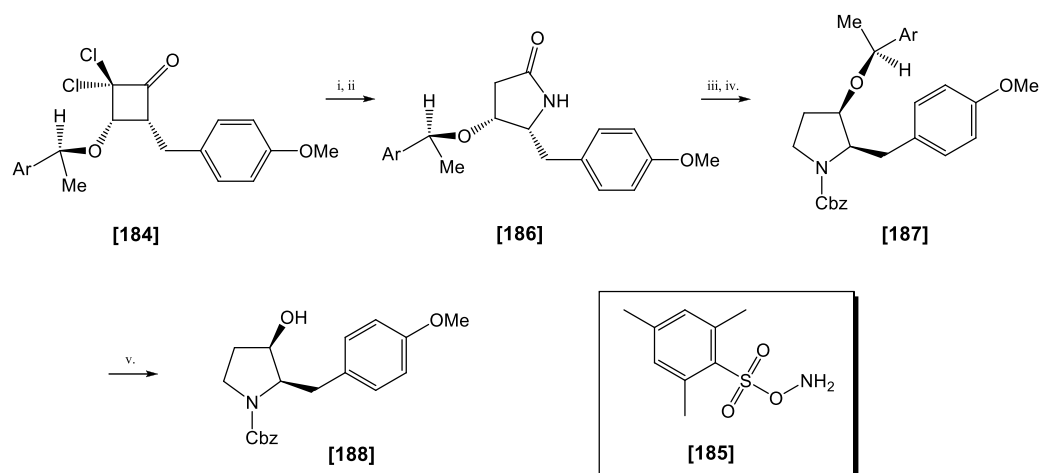
Reagents & conditions: i. O-mesityenesulfonylhydroxylamine [185], CH$_2$Cl$_2$, Al$_2$O$_3$, MeOH, 20°C, ii. Zn/Cu, MeOH, NH$_4$Cl (68%). iii. CbzCl, (C$_2$H$_5$)$_3$N, THF. 0°C, 1h. (98%). iv. Li(C$_2$H$_5$)$_3$BH, (C$_2$H$_5$)$_3$SiH, BF$_3$.Et$_2$O, CH$_2$Cl$_2$, -78°C. 1h. (62%). v. CF$_3$CO$_2$H, CH$_2$Cl$_2$, 20°C, 1h. (99%).

Scheme 6.5

In 2003 Chang *et al.* sought a more direct and efficient route to Takano's key intermediate [193][62] from *trans*-4-hydroxyproline [189]. Quantitative methylation of the carboxylic acid with thionyl chloride permitted protection of the amine with di-*tert*-butyl dicarbonate and *tert*-butyldimethylsilyl chloride protection of the alcohol to give methyl ester [190]. Sodium borohydride reduction with lithium chloride converted the methyl ester to the primary alcohol which in turn allowed for Swern oxidation to form the electrophilic target [191] for Grignard addition of the anisole group. Treatment with trifluoroacetic acid and triethylsilane ensured deprotection of both functional groups along with benzylic hydroxide elimination. Restoration of the amine protection finalised the conversion to Takano's intermediate [193] in 8 steps and a good 56% overall yield.[71] (Scheme 6.6)
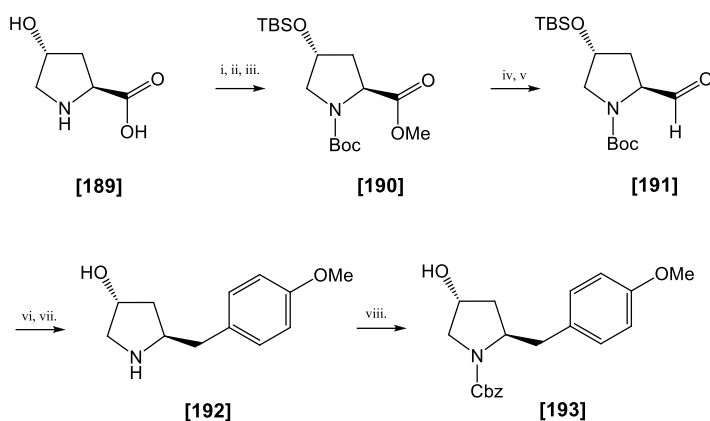
Reagents & conditions:
i. SOCl$_2$, MeOH, -78°C, 3h. (100%). ii. Boc$_2$O, NaHCO$_3$, THF, H$_2$O, 0°C, 2h. (92%).iii. TBDSCl, C$_3$H$_4$N$_2$, DMF, 0°C, 2h. (93%). iv. NaBH$_4$, LiCl, THF, MeOH, 25°C, 12h. (97%) v. C$_2$O$_2$Cl$_2$, (CH$_3$)$_2$SO, Et$_3$N. -78°C, 3h. vi. CH$_3$OC$_6$H$_4$Br, THF, -.78°C, 3h. (85%) vii. CF$_3$CO$_2$H, Et$_3$SiH, 25°C, 15h. viii. CbzCl, Et$_3$N. THF 0°C, 3h. (98%).

Scheme 6.6

Sudalai's 2009 elegant parallel strategy for the formation of both (-)-deacetyl anisomycin **[4]** and Akita's cyclisation precursor **[148]**, employed a proline-catalysed α-amination/α-aminoxylation with a sequential Horner-Wadsworth-Emmons olefination.
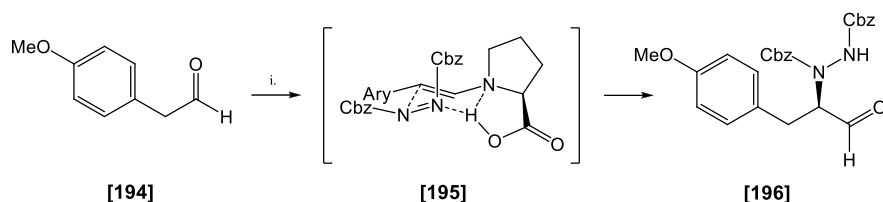
Reagents & conditions: i. DBAD, L-proline, CH$_3$CN, 0-10°C, 3h.

Scheme 6.7

Whilst both routes started with the same 3-(4-methoxyphenyl)-propanal **[194]** the α-amination used dibenzyl azodicarboxylate as the source of the nitrogen whereas the inclusion of nitrosobenzene enabled the α-aminoxylation.[72]

On addition of L-proline, the newly created enamine formed a chair-like conformational transition state [195] as the DBAD approached from the *re*-face with the assistance of the hydrogen bonding from the carboxyl group. Formation of the carboxypyrrolidinium ion caused the transitory ring to collapse with molecular rearrangement to give the α-aminoaldehyde [196].[72,73] (Scheme 6.7)
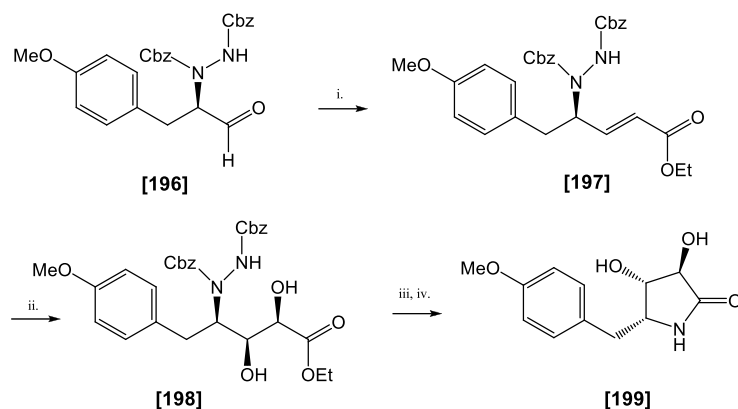
Reagents & conditions:
i. (Et$_2$O)$_2$P(O)CH$_2$CO$_2$Et, LiCl, DBU, CH$_3$CN, 5°C, 45 min, (88%). ii. OsO$_4$, NMO, (CH$_3$)$_2$O/H$_2$O. iii. Raney-Ni, MeOH, H$_2$, 80psi, 24h. iv. EtOH Reflux, 4h, (66% over 2 steps).

Scheme 6.8

Reaction of the α-aminoaldehyde [196] with an *in situ* formed ylide of trimethyl phosphonoacetate increased the carbon chain length by installing the *trans* double bond [197], while osmium catalysed stereoselective dihydroxylation yielded the predominant *syn* product [198] in a 7:1 relationship to the *anti* artefact.

Reagents & conditions: i. Cu(OAc)$_2$, EtOH, 25°C, 12h, (70%). ii.OsO$_4$, NMO, (CH$_3$)$_2$O/H$_2$O, 2h, (82%).
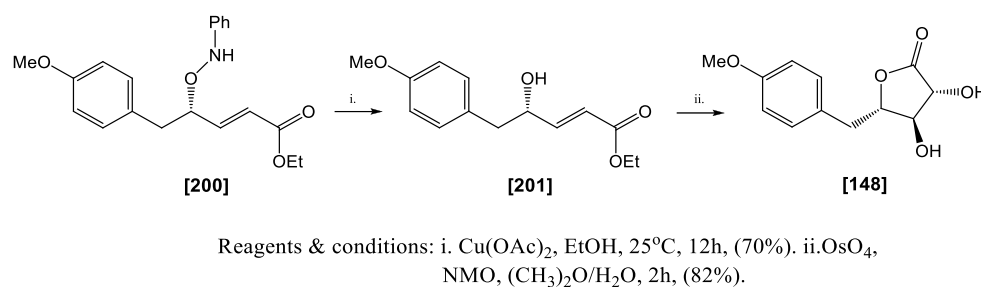
Scheme 6.9

Raney nickel high pressure reductive cyclisation with an ethanol reflux successfully gave the lactam [199] in a modest 66% yield, and (-)-deacetyl anisomycin [4] was completed with a borane dimethyl sulfide complex reduction of the amide carbonyl in 45% overall yield.[72] (Scheme 6.8)

Sudalai's second strategy followed very similar reaction protocols, however for the α-aminoxylation, the electrophilic component was nitrosobenzene and D-proline was used as the catalyst. Reduction of the anilinoxy [200] with copper(II)acetate in ethanol revealed the hydroxyl [201] and identical dihydroxylation induced cyclisation as the single lactone diastereomer [148] of Akita's 1999 synthesis in 30% overall yield.[72] (Scheme 6.9)

The most recent total synthesis of (-)-anisomycin was reported by Lui *et al.* in 2012. Whilst the strategy bore echoes of earlier syntheses, their efficiency and ultimate success was in finding a solution to the historical problem of multiple alternating protection steps. The use of acetic anhydride in the first step would not only suffice as amine protection on the D-tyrosine starting material, it would also serve as an integral unit for a key reaction during the synthesis and end as a final motif in the target molecule. Reduction of the methyl ester to the primary alcohol and then ultimately onto the aldehyde [202] allowed for conversion to Ramirez's dibromoölefin,[74] before treatment under the Corey-Fuchs protocol[75] furnished the propargyl alcohol [203].

Partial reduction of the triple bond with Lindlar's catalyst gave the (*Z*)-olefin **[204]** within the carbon tether, almost identical to that of Jegham **[31]**, save for the amine protection.[76] (Scheme 7.0)
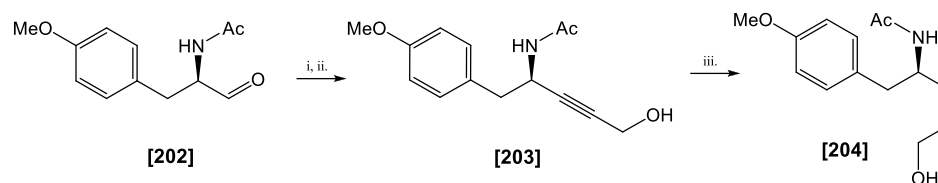
Reagents & conditions: i. PPh$_3$, CBr$_4$, CH$_2$Cl$_2$, ii. BuLi, (CH$_2$O)$_n$, THF, -78°C, (82% over 2 steps). iii. H$_2$, Pd/CaCO$_3$-PbO$_2$, (97%).

Scheme 7.0

Sharpless asymmetric epoxidation of the allylic alcohol **[204]** followed by conversion to the mesylate enabled a thermo-induced intramolecular cascade to form the oxazoline intermediate with the terminal oxirane. This key reaction not only inverted the C3 position to the correct stereochemistry but under acid hydrolysis also installed the acetate beta to the benzylic methylene. The epoxide **[206]** also succumbed to acid hydrolysis to give the diol and Boc protection of the amine allowed for chemoselective mesylation. The recognizable *syn* substituted carbon backbone **[207]** was subjected to cyclisation via sodium hydride in dimethyl formamide before Boc deprotection concluded the synthesis in 11 steps with a 9% overall yield.[76] (Scheme 7.1)
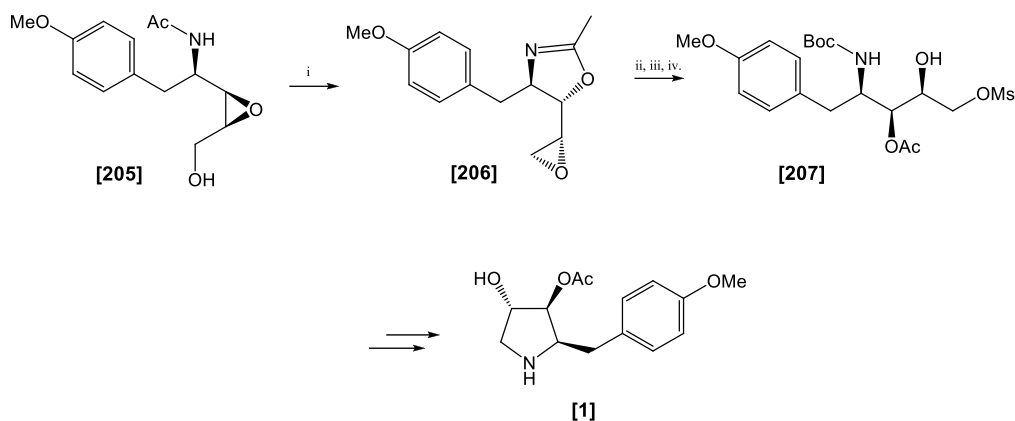
Reagents & conditions: i. MsCl, Et$_3$N, 0°C -Reflux, (69%). ii. HCl/THF. iii. NaHCO$_3$, Boc$_2$O, (79% over 2 steps). iv. MsCl, Et$_3$N, 0°C, (88%).

Scheme 7.1

Whilst the natural levorotatory anisomycin **[1]** and (-)-deacetyl anisomycin **[4]** contain the important biologically active conformations, several groups have reported syntheses of their enantiomers and diastereoisomers. The first synthesis of unnatural (+)-anisomycin **[1a]** was reported by Meyers and Dupre in 1987. The approach for this enantioselective route was drawn from the groups' previous study into the synthesis of (+)-metazocine[77] where a *tert*-butylformamidine tether was used to guide the metal-halogen exchange alkylation. The pyrrolidine formamidine was subjected to ^{t}butylithium to give the α-lithioanion **[208]**, which in turn allowed for alkylation with anisole chloride to form the 2-aryldihydropyrrole formamidine **[209]** in a 77:23 ratio together with an undesired regio-isomer **[210]**. Treatment of this mixture with hydrazine ensured destruction of the isomer and produced 2-(*p*-methoxybenzyl)-3-pyrroline **[211]** in 53% yield and 95% ee. Conversion of the alkene to (+)-anisomycin **[1a]** followed Hall's[43] route to the natural product **[4]** and completed the synthesis.[78] (Scheme 7.2)
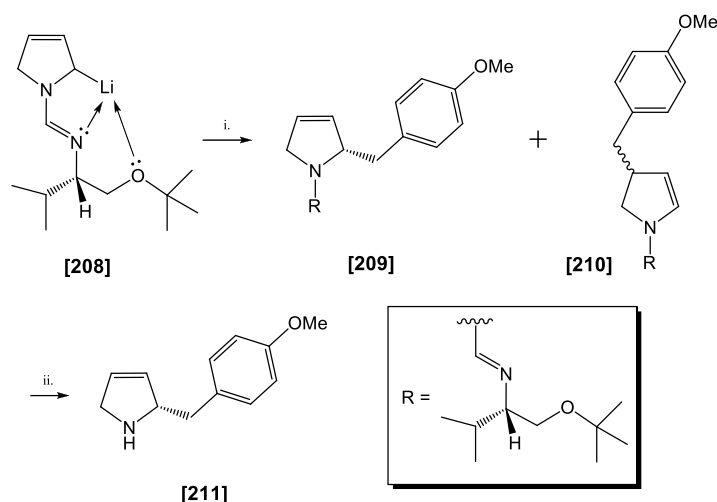
Reagents & conditions: i. p-CH$_3$OC$_6$H$_4$CH$_2$Cl, THF, -100°C (85%). ii. H$_2$NNH$_2$, EtOH/H$_2$0, HOAc, 55°C, 5h, (53%).

Scheme 7.2

Rao *et al*. published a formal synthesis of (+)-anisomycin **[1a]** in 2005 using a fully protected *O*-isopropylidine D-mannitol **[212]** starting material. Conversion to the terminal epoxide **[213]** over 6 steps in 34% yield enabled Grignard addition, similar to that of Lin *et al*.[46] to attach the aryl moiety **[214]**. Translation of the newly formed hydroxyl group to the azido functionality via the mesylate permitted further manipulation to give the Boc protected amine and the customary pre-cyclisation cognate **[215]**. Debenzylation and conversion to the mesylate followed by trifluoroacetic acid to remove the acetal protection allowed formation of (+)-deacetyl anisomycin **[5]** with triethylamine in methanol in an 11% overall yield.[79] (Scheme 7.3)
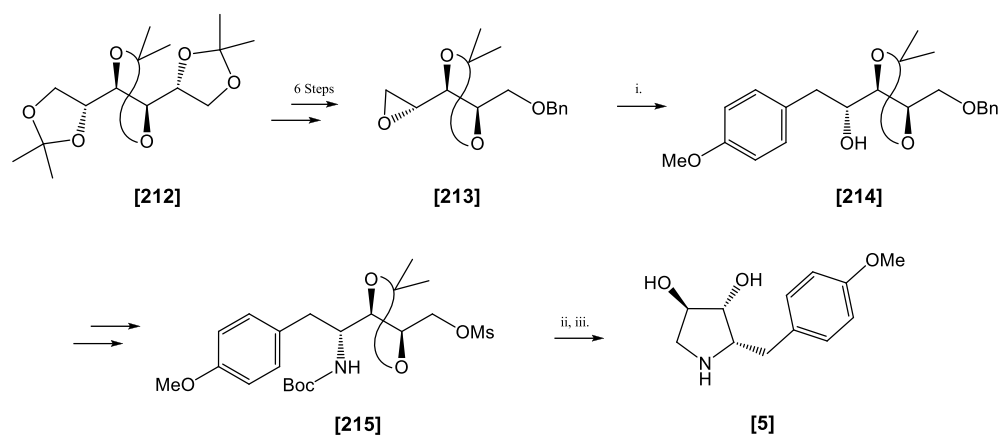
Reagents & conditions: i. p-CH$_3$OC$_6$H$_4$Br, Mg, I$_2$, CuI, 0°C, 24h, (86%). ii. TFA, CH$_2$Cl$_2$, 0°C, 10h. iii. Et$_3$N, MeOH, 0°C, 5h.

Scheme 7.3

The most recent synthesis of (+)-anisomycin **[1a]** was reported by Maarseveen *et al.* in 2011 following a lengthy study of copper catalysed propargylic substitution reactions. Enantioselective amination of the propargyl ester **[217]** with *o*-anisidine, cuprous iodide, Hünig's base and a chiral 2,6-bis(oxazolinyl-diphenyl)pyridine or PyBOX ligand **[216]** fashioned over 6 steps afforded the benzyl-substituted propargylic amine **[218]** in 59% yield and 90% ee.
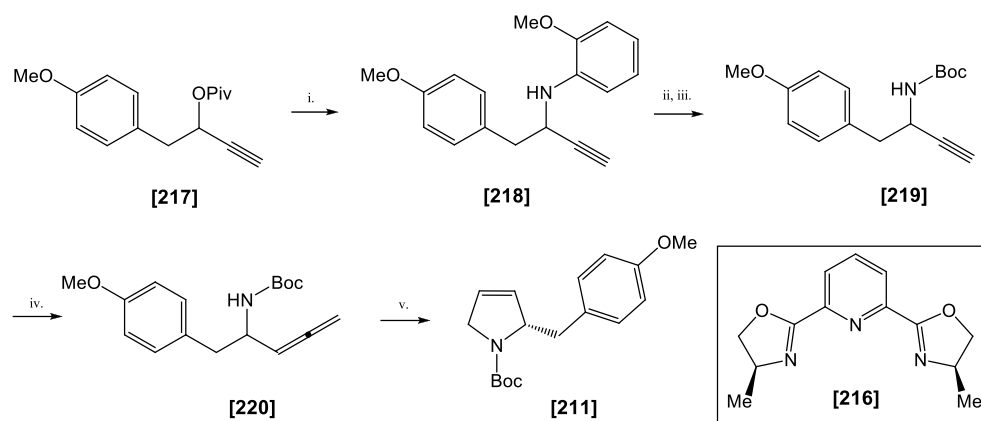
Reagents & conditions: i. CuI, **[216]** *o*-CH$_3$OC$_6$H$_4$NH$_2$, DIPEA, MeOH, 25°C, (59%). ii. PhI(OAc)$_2$, CH$_2$CN, MeOH, iii, Boc$_2$O, CH$_2$Cl$_2$, (29%). iv. ^{i}Pr$_2$NH, p-CH$_2$O, CuI, 1,4-dioxane, Reflux, (60%). v. AuPPh$_3$, AgOTF, Tol, 0°C, 10h. iii. Et$_3$N, MeOH, 25°C, 5h, (72%).

Scheme 7.4

Treatment with iodo-benzene diacetate in acetonitrile and methanol ensured oxidative removal of the anisidyl subunit followed by Boc protection of the primary amine **[219]**. Formation of the aminoallene **[220]** under Crabbé reaction[81] conditions allowed for formation of the protected 2-(*p*-methoxybenzyl)-3-pyrroline **[211]** via gold-catalysed ring closure in 7% overall yield.[80] (Scheme 7.4)

2. Results and Discussion

2.1 Introduction to results and discussion.

The Parsons group have had a long tradition in the synthesis of natural products at Sussex University including (-)-Kainic acid,[82] Galbondolide B,[83] (-)-Tetrahydrolipstsatin,[84] (±)-Anatoxin A,[85] and Brevioxime.[86] We wished to add to this impressive list of natural compounds with a total synthesis of (-)-anisomycin **[1]**, a biologically active alkaloid. The intentions of this research project are to:

1. Utilize the oxazolidinone as the synthetic starting material and attempt to improve upon any of the sequences in the multigram preparation.

2. Develop an efficient and practical synthesis of (-)-anisomycin.
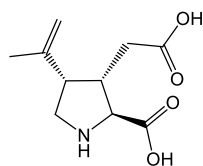
(-)-Kainic acid
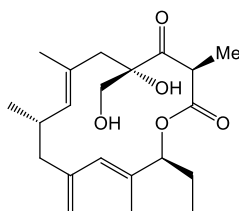
Galbondolide B
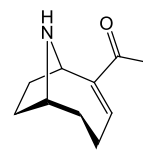
(±)-Anatoxin A
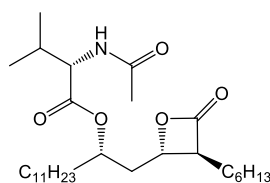
(-)-Tetrahydrolipstatin
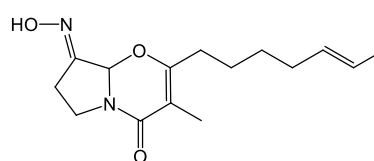
Brevioxime

2.2 Investigating the synthesis of (-)-anisomycin.

2.2.1 Formation of the Oxazolidinone [221].

In the continuation of developing a program of concise and efficient syntheses of biologically important molecules, successive members of the Parsons group have been working towards a generic chiral starting material with sufficient inbuilt functionality that it can be taken forward to different target alkaloids. This oxazolidinone precursor [221], originally developed by Greenwood[87] together with modifications by Murray can be fashioned from the inexpensive, commercially available amino acid derivative *trans*-4-hydroxy-L-proline [222] in multigram quantities.
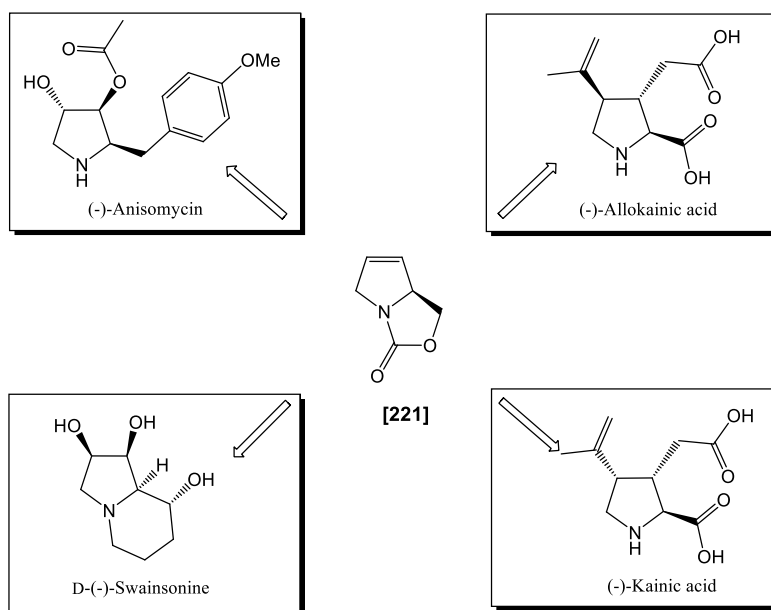
Figure 1.7

Fischer–Speier esterification of *trans*-4-hydroxy-L-proline [222] with thionyl chloride in methanol led to the pyrrolidine methyl-ester hydrochloride salt [223] followed by subsequent Boc protection of the secondary amine [224] in

95% yield. Transformation of the lone hydroxyl to give the mesyloxy-prolinate **[225]** allowed for a two step process to install the essential double bond at the crown of the molecule. Treatment of the prolinate **[225]** with an *in situ* generated anionic phenyl-selenide species ensured displacement of the newly established mesylate together with concomitant solvent induced transesterification. Oxidation of the selenide **[226]** with hydrogen peroxide and successive *syn* elimination gave the desired alkene **[227]** in 62% yield.

[222]　　　**[223]**　　　**[224]**　　　**[225]**

[226]　　　**[227]**　　　**[228]**　　　**[221]**
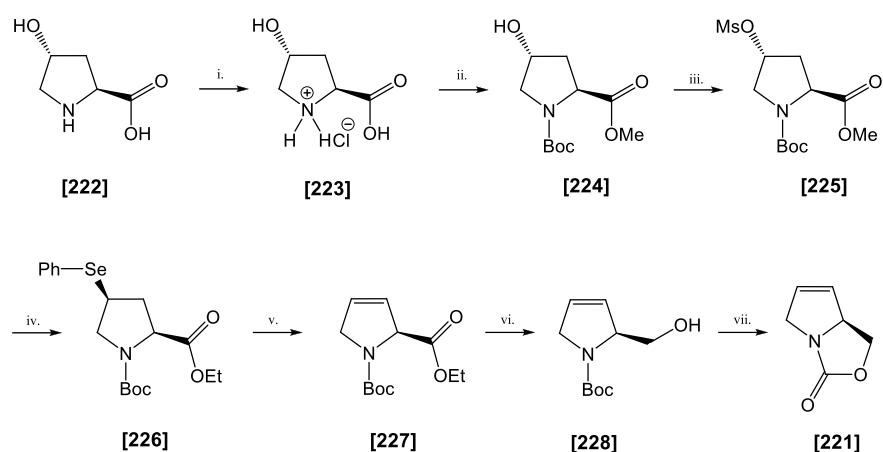
Reagents & conditions:
i. SOCl$_2$, MeOH, Reflux. ii. Boc$_2$O, ^{i}Pr$_2$(Et)N, 1,4-dioxane. 25°C. (95% over 2 steps). iii.. MsCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 25°C. (93%). iv. (PhSe)$_2$, NaBH$_4$, EtOH, Reflux. v. H$_2$O$_2$, pyr, CH$_2$Cl$_2$, -78°C to rt. (62% over 2 .steps) vi. NaBH$_4$, MeOH, THF, 0°C to rt. (63%). vii. DAST, CH$_2$Cl$_2$, 0°C to rt. (75%).

Scheme 7.5

The resultant ethyl ester **[227]** was reduced to the primary alcohol **[228]** originally with lithium aluminium hydride but Murray showed that the reduction could also be performed using diisobutylaluminium hydride and would have the advantage of negating the difficult work-up procedure and decomposition of the product. This reduction step has now been modified further with the use of 3 equivalents of sodium borohydride in dry THF and methanol. Although the reaction proceeds at a slower rate with this favoured lewis acid, sodium borohydride is a significantly milder reducing agent than

either LiAlH$_4$ or DiBAL and has delivered an increase in yield by a further 6%.

The final step of ring closure to complete the oxazolidinone [221] was achieved by reaction of the alcohol [228] with (diethylamino)sulfur trifluoride and gave the bicyclic compound [221] as viscous pale yellow oil in 75% yield. (Scheme 7.5)

Whilst conversion rates in the initial route of the Boc protected methyl ester [224] to the olefin [227] were of appreciable quantity, the use of the highly toxic selenium reagents and the exothermic volatility of the procedure during scale up necessitated an alternate procurement of the alkene [227].

Reagents & conditions: i. PPh$_3$, I$_2$, PhMe, CH$_3$CN, C$_3$H$_4$N$_2$, 0 - 25°C. 72h.
(82%). ii. DBU, PhMe, 85°C, 8h. (80%)
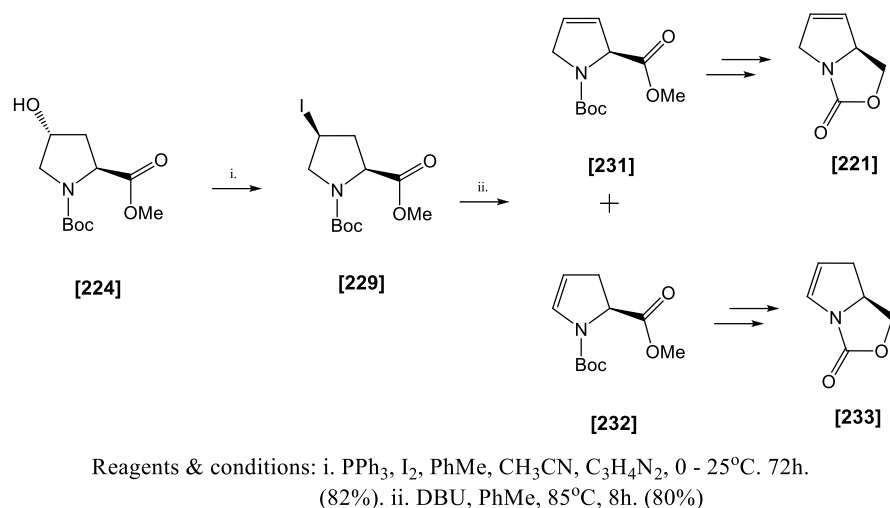
Scheme 7.6

In an adaptation of both Garegg's[88] method for conversion of hydroxyl groups to iodo groups in carbohydrate chemistry and Viaud's[89] synthesis of a chiral spiranic aminochroman derivative, treatment of the methyl ester [224] with triphenylphosphine, iodine and imidazole afforded the *cis* crystalline iodo-pyrrolidine [229] in a very good 82% yield. Separation of the

stereoisomers was unnecessary and reaction of diazabicyclo-[5.4.0]-undecene with the crude mixture yielded an 8:1 ratio of regio-isomeric 3,4- **[231]** and 4,5-dihydro-prolines **[232]** in favour of the desired 3,4-product **[231]**. (Scheme 7.6)

2.2.2 Retrosynthesis of (-)-Anisomycin [1].

The strategy for the construction of (-)-anisomycin **[1]** was to set the three stereocentres at the outset of the synthesis then manipulate each of the limbs independently to their individual final architecture. With the amine and the masked alcohol mutually protected within the cyclic carbamate, the double bond of the advanced precursor **[221]** could be converted to the desired epoxide **[234]** by taking full advantage of its prejudice to form *endo* face compounds. Regioselective fragmentation of the ring would then complete the molecular stereochemistry followed by protection of both new functional groups **[235]**. Carbamate ring opening followed by amine protection would allow unencumbered access to the primary alcohol **[235a]** and subsequent conversion of this to a suitable leaving group **[235b]** would enable addition of the aryl moiety. Selective deprotection at the C3 position and conversion to the acetate **[235c]** would leave global deprotection to yield the natural alkaloid **[1]**. (Scheme 7.7)
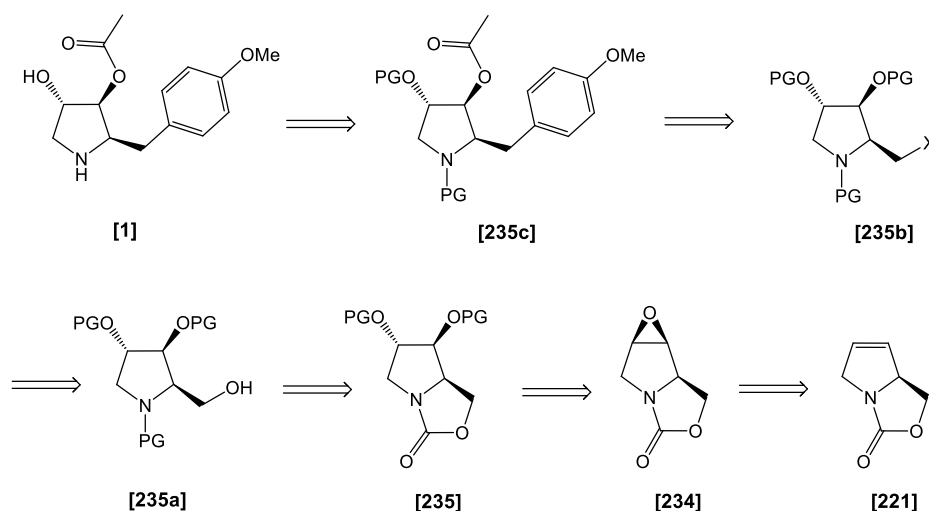
Scheme 7.7

2.2.3 Epoxidation of the oxazolidinone [221].

Previously, both Greenwood[87] and Murray[90] had independently investigated the stereoselective nature of the alkene **[221]** and found that not only did a series of [2+2] photocycloadditions give impressive diastereofacial selectivity but electrophilic addition demonstrated the same bias. Pyne *et al*; whose ring closing metathesis is the only other documented route to the oxazolidinone **[221]**, observed a similar pattern when treatment of the alkene **[221]** with osmium tetroxide revealed a *syn* diol.[91] Pyne suggested that the "butterfly" type conformation adopted by the oxazolidinone **[221]** ensured that the pseudo-axial protons at carbons 2 and 5 presented a steric hindrance to the *exo* face. However, a theoretical molecular model study by Viseux[92] in the same year concluded that an inequality in the distribution of electron density surrounding the π-bond favoured addition to the internal face.
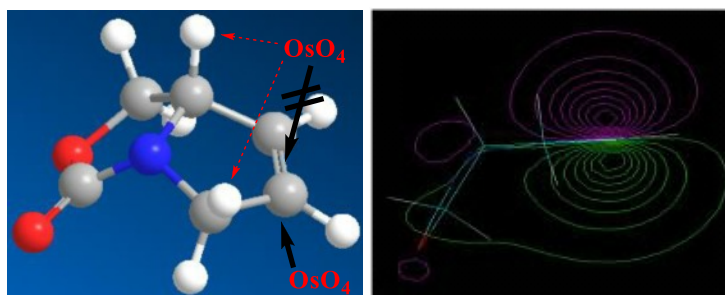
Figure 1.8: Pyne's pseudo-axial hindrance protons and Viseux's representation of the oxazolidinone **[221]** HOMO[90]

Epoxidations to the oxazolidinone **[221]** have previously been carried out by both Greenwood[93] and Murray[90] on their respective routes to members of the kainoid amino acid family. Although both were successful in achieving the desired product **[234]**; varying degrees of success in terms of yield were experienced. Greenwood's methods of using *m*CPBA and isolated dimethyldioxirane were both low yielding and impractical for scale-up

quantities respectively. Murray's adaptation of a Shi *et al. in situ* generated DMDO however, obtained the epoxide **[234]** in an impressive 77% yield. [94]

Our strategy necessitated formation of the epoxide **[234]** and whilst we felt Murray's version of the *in situ* generated DMDO had merit with regard to delivering multigram yields, the precise and critical pH control together with the laborious and prolonged reagent additions demanded a less complex solution. Hashimoto[95] had investigated the use of *in situ* generated DMDO from Oxone® and acetone for the epoxidation of olefins and his biphasic system did not require the use of a phase transfer catalyst nor the toxic acetonitrile of the Shi method. Hashimoto considered DMDO to be more lipophilic than the parent ketone and therefore likely to migrate into the organic phase even in the absence of a PTC. [95] We explored Hashimoto's method and noted that although he had used several different organic solvents and toluene had showed early promise in his methodology, ethyl acetate clearly produced the best conversion rates.
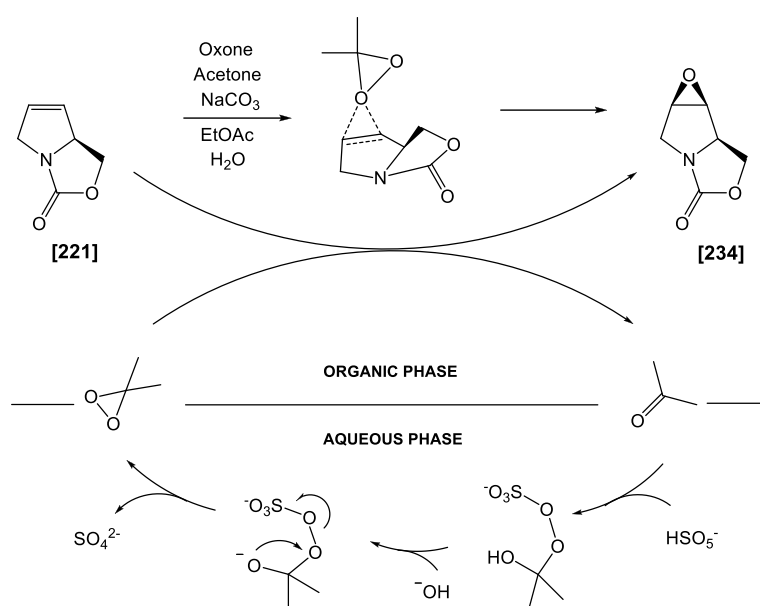
Figure 1.9: Formation of DMDO and epoxidation of Epoxide **[234]**.

This was mirrored in our experiments whereby the ethyl acetate led to yields in the high seventy percent range while DCM and toluene gave significantly lower yields. (Table 1.1)
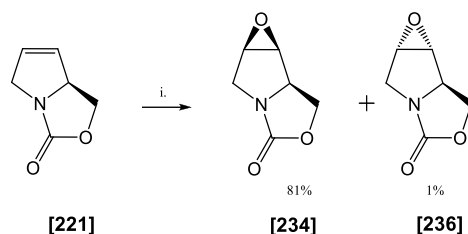
Reagents & conditions: i. Oxone, NaHCO$_3$, (CH$_3$)$_2$O, EtOAc, H$_2$O 25°C, 4h.

Scheme 7.7

Epoxide **[234]** was purified and revealed as white Mayan profile pyramidal crystals in a maximum 81% yield whereby its structure was clarified by way of x-ray analysis.

Entry	Solvent	Oxone (equiv)	Acetone (equiv)	Yield (%)
1	Toluene	1.3	10	36
2	Dichloromethane	1.3	10	21
3	Ethyl Acetate	1.3	10	81
4	Toluene	3.0	10	29
5	Dichloromethane	3.0	10	17
6	Ethyl Acetate	3.0	10	41

Table 1.1: Conditions used to form epoxide **[234]**.

We consider this method of epoxidation of the oxazolidinone **[221]** an advancement on the Murray adapted Shi protocol, not only because the

practical nature of the reaction simplifies the procedure, but it delivers an increase in final yield and removes the toxic element from the reaction. It was interesting to note that with this epoxidation method a small amount of the diastereoisomer **[236]** was isolated indicating that the diastereofacial selectivity is not 100% exclusive. (Scheme 7.7)
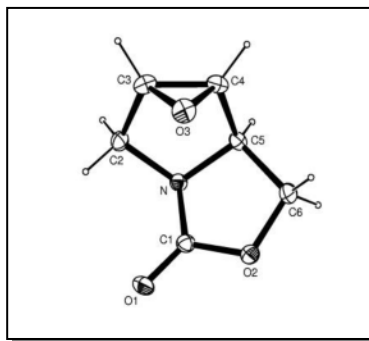
Figure 2.0: X-ray structure of epoxide **[234]**.

2.2.4 Regio-selective ring opening of epoxide [234].

With a reaction that allows us to form multigram quantities of the pure epoxide **[234]** our attention turned to the regio- and stereoselective opening of the newly formed ring. We considered that benzyl alcohol would not only serve as a suitable nucleophile, but on successful opening there would be inbuilt oxygen functionality provided at C4 in the target compound, with the added bonus that this delivered oxygen functionality would carry with it its own protection.

Smith *et al.* showed in their total synthesis of (+)-Jatropholones A **[239]** that a simple acid catalysed ring opening of cyclopentene oxide **[237]** with benzyl alcohol[96] was an almost a perfect mimic of our system. (Scheme 7.8)
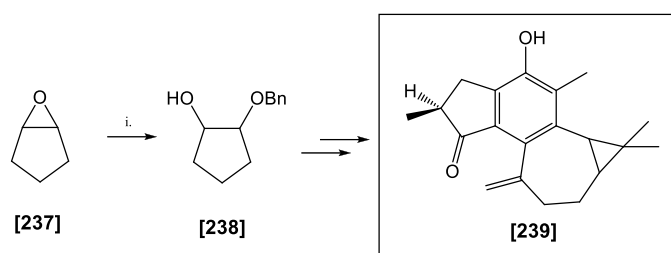
Reagents & conditions: i. , H_2SO_4, $C_6H_5CH_2OH$, 95°C, 2h.

[237]   [238]   [239]

Scheme 7.8

We were confident that the rear side attack of the benzyl alcohols would occur at the least hindered side of the epoxide **[234]** to give the three correct contiguous stereocentres of the final compound. Whilst Smith enjoyed a 97% conversion rate, [96] fragmentation of our epoxide **[234]** was unsuccessful even when conducted in a succession of organic solvents. After futile attempts to open the epoxide **[234]** with sodium hydride and benzyl alcohol in THF we considered the use of group three elements as catalysts as the use of lewis acids to promote the epoxide cleavage is well documented. Posner demonstrated that a range of nucleophiles, including benzyl alcohol, coupled with catalytic amounts of aluminium oxide was successful in opening a variety of symmetric and asymmetric epoxides;[97] again all attempts to open our epoxide **[234]** failed.

Montgomery *et al.* used an alternate Lewis Acid to open a similar epoxide system to Smith and we were optimistic that this electron acceptor would work for us.[98] We adapted Montgomery's procedure and boron trifluoride diethyl etherate in benzyl alcohol produced an 8:1 mixture of regioisomers in favour of the desired alcohol **[240]**. (Scheme 7.9)
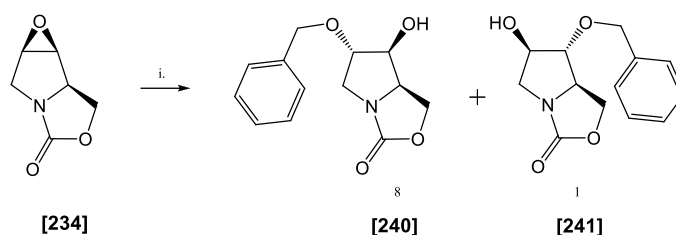
Reagents & conditions: i. BnOH, BF$_3$.Et$_2$O, 25°C, 24h. (89%)

Scheme 7.9
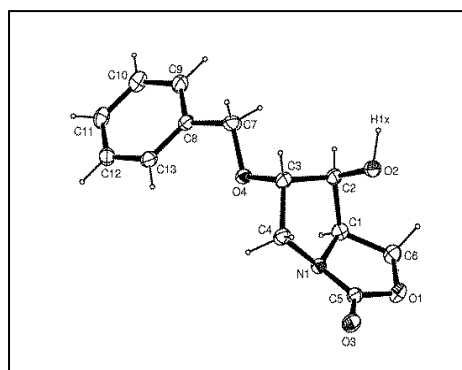
Figure 2.1: X-ray structure of opened epoxide **[240]**.

Optimisation of the reaction dictated that a minimum of 33 equivalents of benzyl alcohol were needed to ensure high yields and on careful purification and recrystalisation a white needle-type crystalline solid was revealed. (Figure 2.1)

2.2.5 Carbamate ring opening and amine protection.

With the second step of the synthesis completed we reconsidered the retrosynthesis with regards to the protection of the new hydroxyl group **[240]**. In an attempt to preserve the efficiency of the synthesis we took the view that once the carbamate ring was opened, the reactivity of the newly exposed primary alcohol would take precedent over the secondary alcohol, therefore protection would be unnecessary. Lithium hydroxide mediated hydrolysis

gave the 1,3-diol **[242]** cleanly as a white powder in 95% yield.[99,100] (Scheme 8.0)
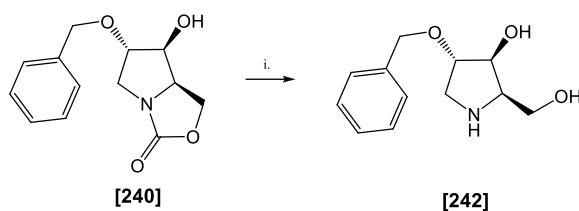
Reagents & conditions: i. LiOH, EtOH, 80°C, 72h. (95%)

Scheme 8.0

A series of crystallisations in various solvents successfully concluded in growing crystals suitable for x-ray clarification. (Figure 2.2)
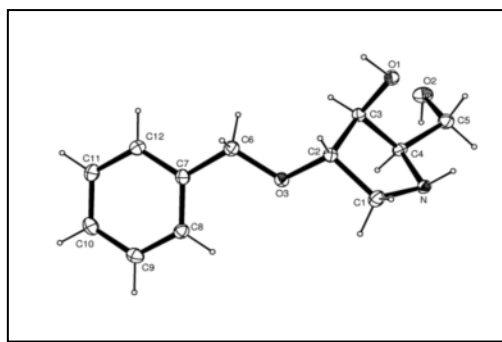
Figure 2.2: X-ray structure of 1,3-diol **[242]**.

With the subordinate ring cleaved and ready access to the primary alcohol secured, a suitable amine protection group was required before manipulation of the primary alcohol could begin. The protection group required would need to satisfy a select criterion in that it would not only need to be easy and practical to install and return high yields, but it would be resilient enough to endure all of the subsequent reaction conditions to the end of the synthesis and then be selectively removed simply and efficiently. A benzyl carboxylate group was chosen and benzyl chloroformate under Schotten-Baumann

conditions[101] gave the *N*-protected-1,3-diol **[243]** in an excellent 90% yield. (Scheme 8.1)

Reagents & conditions: i. CbzCl, $(CH_3)_2O$, Na_2CO_3, H_2O, $0^{\circ}C$, 2h. (90%)
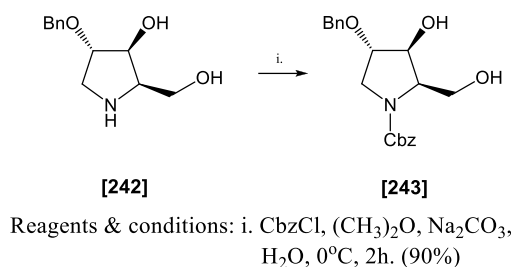
Scheme 8.1

Although the successful addition of the benzyl carboxylate to form the carbamate **[243]** in high yields was a welcome step forward, with it came the inherent problem of the compounds ability to form rotamers and its obscuring effect on the clarity of the NMR analysis. We were confident that the desired *N*-protected 1,3-diol **[243]** had been secured as the general structural entities of the molecule were able to be identified despite the doubling and broad peaks in the NMR spectra; coupled together with the ancillary data of a correct accurate mass and the significant peaks in the IR spectra. In an attempt to resolve the quality of the NMR data we undertook a series of variable temperature NMR experiments ranging from $30^{\circ}C$ to $100^{\circ}C$, the results however were only of limited success. Finally we also subjected the newly formed pyrrolidine diol **[243]** to catalytic hydrogenation under $Pd/C/H_2$ conditions which successfully returned the parent 1,3-diol **[242]**.

2.2.6 Attempted introduction of the anisole appendage.

It was envisaged that conversion of the primary alcohol into a suitable leaving group would allow for attachment of the methoxyphenyl appendage without compromising the stereochemistry at C2. Following treatment of the *N*-

protected 1,3-diol **[243]** with mesyl chloride, an unexpected cyclisation took place. Instead of the expected terminal mesylate product **[235]**, reformation of the bicyclic mono-protected *trans* diol **[240]** resulted. The same cyclisation product was also observed when tosyl chloride was used.[102] (Scheme 8.2)

[245]

[240]

[243]

[246]

[240]
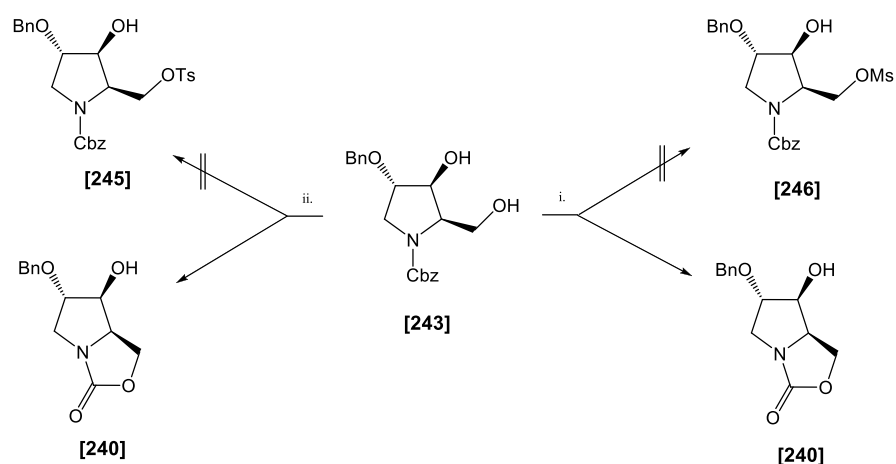
Reagents & conditions: i. MsCl, DMAP, CH_2Cl_2, Et_3N, 0°C, 24h. ii. TsCl, Pyr, 0°C, 24h

Scheme 8.2

Although the synthetic retreat was both unexpected and interesting, in that it was not envisaged that the carboxylate would undergo intramolecular participation when choosing the amine protecting group, neither facilitated progression towards the target alkaloid **[1]**; therefore an adjustment to the addition step was required.

Sharpless had previously shown that cyclic sulfates were capable of reacting in a similar ring opening manner to epoxides.[103,104] Whilst Sharpless was successful in opening many different 1,2-diol systems with selective external nucleophiles, Denmark[105] reported successful formation of a 1,3-diol derived cyclic sulfate which was subject to attack from an internal nucleophile, thus we were optimistic that the formation of a six membered cyclic sulfate from

our 1,3-diol **[243]** would share the same auspicious properties as its vicinal cousins.

Treatment of 1,3-diol **[243]** with thionyl chloride in carbon tetrachloride was monitored by TLC and the formation of the two chiral cyclic sulfites were identified **[247]** and **[248]**. All attempts to separate the diastereoisomers by column chromatography for data analysis failed due to rapid decomposition, however as both isomers were to be oxidised to the cyclic sulfate **[249]** the crude mixture was taken forward without purification. (Scheme 8.3)
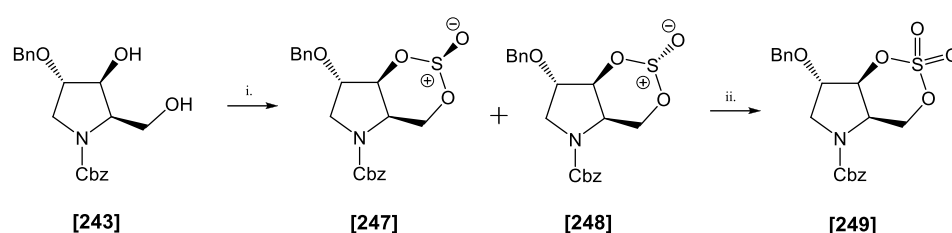
Reagents & conditions: i. $SOCl_2$, CCl_4. Reflux, 1h. ii. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN/H_2O, 25°C, 2h. (77% over 2 steps)

Scheme 8.3

Even though Denmark's conversion of sulfite to sulfate required expensive stoichometric quantities of ruthenium tetroxide the reaction still delivered good yields. Sharpless however, developed a far more parsimonious ruthenium trichloride catalytic system with sodium periodate as the stoichometric commodity. This method worked well in our system and the cyclic sulfate **[249]** was delivered in a 77% yield over the 2 steps.[103,104,105] (Scheme 8.3)

As Sharpless had reported that his 1,2-diol derived cyclic sulfate would succumb to attack from an aryl Grignard reagent,[103] it was hoped that this would also be true with an anisole Grignard on our 1,3-diol arrangement.

Treatment with freshly prepared *p*-methoxyphenylmagnesium bromide in diethyl ether disappointedly proved that this was not the case. A small series of different anisole Grignard reagents was tested which also failed to open the ring; interestingly a small amount of the mono-protected *trans* diol **[240]** was recovered when *p*-methoxyphenyl magnesiumbromide was used in THF. (Table 1.2)
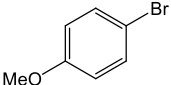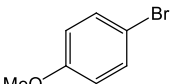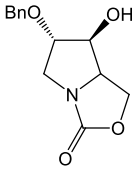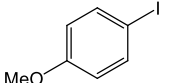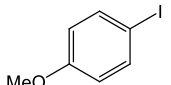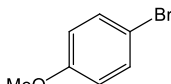
Entry	Grignard	Reagents	Solvent	Products
1	MeO–C₆H₄–Br	Mg, I₂,	Et₂O	Starting material
2	MeO–C₆H₄–Br	Mg, I₂,	THF	(BnO, OH bicyclic pyrrolidinone carbamate structure)
3	MeO–C₆H₄–I	Mg, I₂,	Et₂O	Starting material
4	MeO–C₆H₄–I	Mg, I₂,	THF	Starting material
5	MeO–C₆H₄–Br	Mg, I₂, Li₂CuCl₄	Et₂O	Decomposition

Table 1.2

2.2.7 Revised addition of the anisole appendage.

Following the second return to the mono-protected *trans* diol **[240]** an adaptation to the cyclic sulfate route was necessary. It appeared clear that the carbamate moiety was intrinsic in the re-cyclisation process to **[240]** therefore; formation of a cyclic sulfamidate **[250c]** would mitigate the

reactive carbonyl target of the benzyl ester. This however, would necessitate pre-protection of the exposed crown hydroxyl group. (Scheme 8.4)
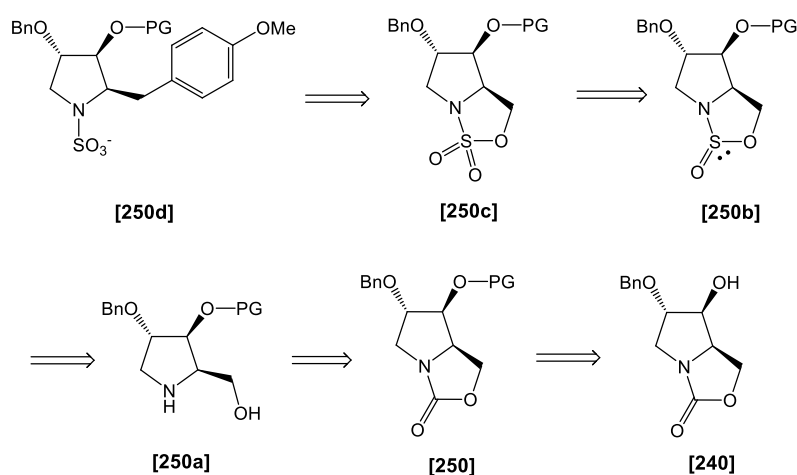
Scheme 8.4

For the sake of completeness and due to the formation of the 1,3-diol **[242]** in multigram quantities, we attempted formation of the cyclic sulfamidite **[251]**, using the same method as for the *N*-protected-1,3-diol **[243]** described previously, on the naked diol **[242]**; reasoning that the unprotected secondary amine would be more reactive than the secondary alcohol. Unfortunately our logic was not rewarded. (Scheme 8.5)
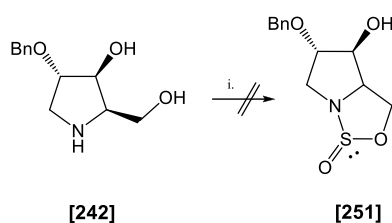
Reagents & conditions:
i. SOCl$_2$, CCl$_4$, 80°C, 24h.

Scheme 8.5

Treatment of mono-protected *trans* diol **[240]** with *tert*-butyl dimethyl silyl trifluoromethanesulfonate in dichloromethane and two equivalence of 2,6-lutidine gave the dihydroxy protected oxazolidinone **[252]** in 79% yield. As the cyclic carbamate ring opening protocol had already been established previously in the synthesis to give high yields of the 1,3-diol **[242]**, we saw no reason to alter this on the new silyl oxazolidinone **[252]**.
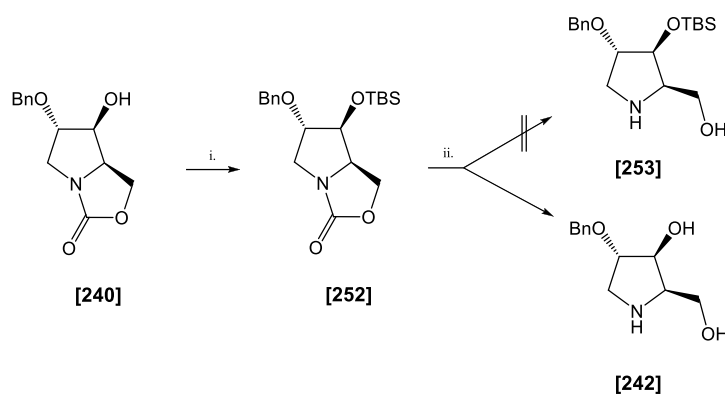
Reagents & conditions: i. TBDMSOTF, 2,6-lutidine, CH₂Cl₂, (79%). ii. LiOH, EtOH, Reflux. 5 days. **[242]**. (91%)

Scheme 8.6

Whilst the lithium hydroxide in ethanol procedure was once again successful in opening the oxazolidinone's cyclic carbamate ring, the highly basic solution was remarkably efficient in the total cleavage of the silyl protection group, thus returning the earlier 1,3-diol **[242]**, albeit in excellent yield. (Scheme 8.6)

With the inability of the silyl protection to remain in place it was hoped that a tetrahydropyran group would remain stable under the harsh hydroxide/ethanol conditions. Weiss *et al*'s synthesis of prostaglandins and their congeners successfully employed the use of tetrahydropyran protecting groups on both a secondary alcohol and a carboxylic acid group on a cyclopentenone

intermediate.[106] Their procedure of 3,4-dihydro-2*H*-pyran in dichloromethane with *p*-toluenesulfonic acid monohydrate unfortunately returned only the mono-protected *trans* diol **[240]** starting material (Scheme 8.7) regardless of equivalence or solvent. (Table 1.3)
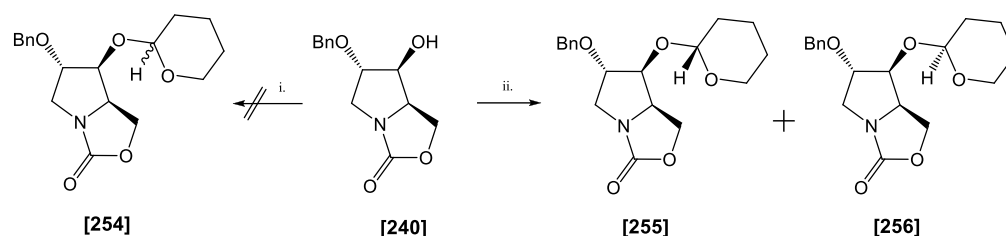
Reagents & conditions: i.Table 1.3. ii. 3,4-dihydro-2*H*-pyran, PPTS, CH$_2$Cl$_2$, 4h, 25°C. (96%)

Scheme 8.7

Entry	Solvent	PTSA (equiv)	Product
1	Dichloromethane	0.5	Starting material
2	Dichloromethane	2.0	Starting material
3	Dichloromethane	5.0	Starting material
4	Tetrahydrofuran	5.0	Starting material

Table 1.3

Grieco[107] used a slightly different procedure for tetrahydropyranylation of a series of hydroxyl groups on different molecular systems with quantitative or near quantitative conversions on each. Whilst accepting that *p*-toluenesulfonic acid was superior as a catalyst when measured against hydrochloric acid, phosphoryl chloride and boron trifluoride diethyl etherate, he reported that the use of freshly prepared pyridinium *p*-toluenesulfonate was more efficient and delivered greater yields in the preparation of alcohol derived THP ethers.[102]

Treatment of *p*-toluenesulfonic acid with dry pyridine in dichloromethane gave a white crystalline solid which was added without delay to the mono-protected *trans* diol **[240]** with 3,4-dihydro-2*H*-pyran in dichloromethane. The reaction was monitored via TLC over 4 hours and returned the two diastereoisomers of the desired pyran **[255]** and **[256]**. (Scheme 8.7)

After purification and recrystalisation from diethyl ether, small white needle crystals in an excellent 96% yield were harvested and subject to x-ray crystallographic analysis. (Figure 2.3)
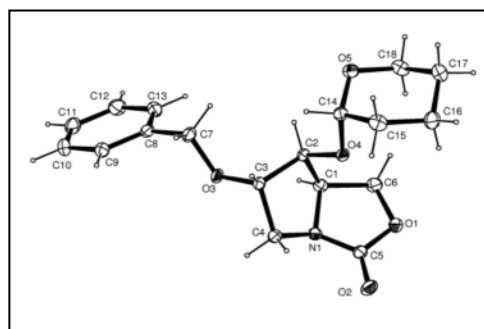
Figure 2.3: X-ray structure of tetrahydropyran oxazolidinone **[256]**.

The mixture of the two diastereoisomers of the tetrahydropyran oxazolidinone **[255]** and **[256]** were subjected to the same lithium hydroxide ring opening protocol which gave the 1,3-diol **[242]** previously and recovered the desired, although inseparable, diastereoisomeric mixture of the pyrrolidine alcohol **[257]** in an 86% yield. (Scheme 8.8)
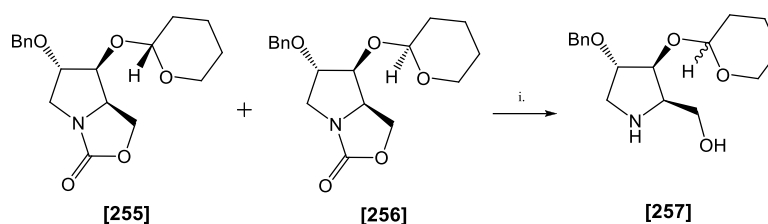
Reagents & conditions: i. LiOH, EtOH, Reflux, 5 days. (86%).

Scheme 8.8

Employing the previous method used to generate the cyclic sulfite on the *N*-protected-1,3-diol **[243]**, the diastereoisomeric mixture of pyrans **[257]**, were treated with thionyl chloride in carbon tetrachloride over 24 hours. The reaction was monitored via TLC but no indication of cyclic sulfamidite **[259]** formation was found. (Scheme 8.9)

[257]   **[259]**

Reagents & conditions: i. $SOCl_2$, CCl_4, 80^oC, 24h.
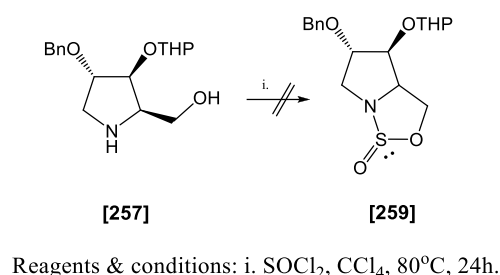
Scheme 8.9

It was clear from our results that the cyclic sulfate route to facilitate the addition of the anisole moiety was futile and it was therefore abandoned. We took heart that we had successfully protected the *trans* diol and were able to expose the primary alcohol whilst maintaining the integrity of the three contiguous centres along with the diol protection and returned to our retrosynthetic strategy, confident that correct manipulation of the primary alcohol would smooth the progression to the next step.

In an effort to reduce the number of synthetic steps we briefly explored the possibility of not only opening the subordinate ring but concomitantly protecting the amine under the same reaction. Kerns *et al.* reported a tandem opening and methyl carbamate protection of a ring-fused D-glucose oxazolidinone derivative with cesium carbonate in methanol.[108]
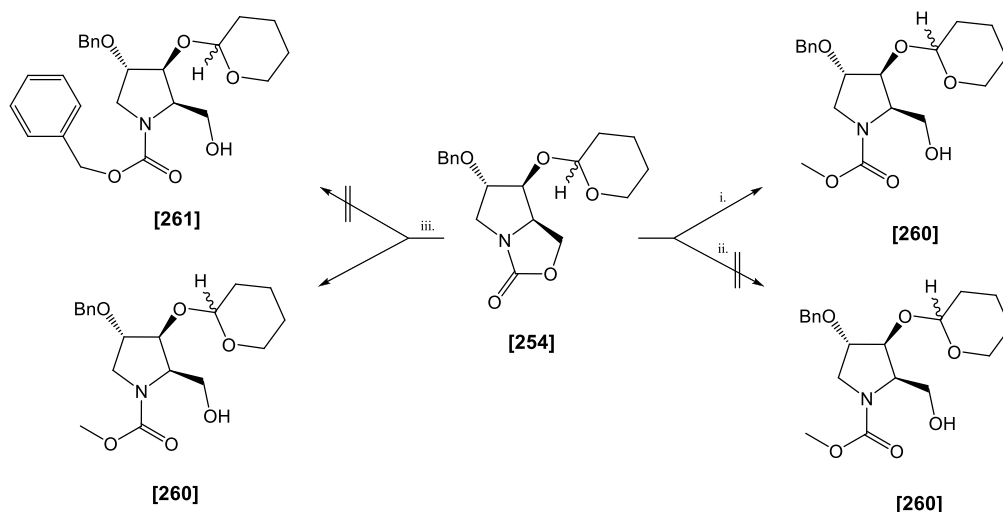
Reagents & conditions: i. Cs$_2$CO$_3$, MeOH. 25°C, 2 days (9%). ii. Cs$_2$CO$_3$, MeOH. silica, ultrasound. 25°C, 24h. iii. Cs$_2$CO$_3$, BnOH, MeOH. 25°C, 2 days (2%)

Scheme 9.0

Whilst this protocol showed hesitant promise in our system, with crude analysis showing the correct mass and clear methoxy peaks in the NMR at 3.75 ppm, the yield was disappointingly low. An analogous procedure was attempted with the addition of benzyl alcohol in the hope of securing the benzyl carbamate [261] but this unfortunately proved to be a futile endeavour and only ever delivered trace quantities of the equivalent methyl product [260]. (Scheme 9.0)
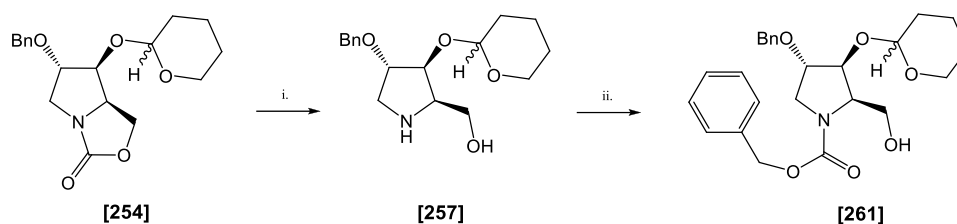
Reagents & conditions: i. LiOH, EtOH, Reflux, 5 days. (86%). ii. C$_8$H$_7$O$_2$Cl, (CH$_3$CH$_2$)$_2$O, Na$_2$CO$_3$, H$_2$O, 25°C, 2h. (88%)

Scheme 9.1

With the benzyl failure and the low yield of the methyl carbamate protection **[260]**, maximum 9%, we abandoned this route in favour of the tried and tested lithium hydroxide in ethanol technique to deliver alcohol **[257]** in an 86% yield of inseparable stereoisomers. (Scheme 9.1)

We repeated the Schotten-Baumann conditions from earlier in the synthesis which gave the *N*-protected-1,3-diol **[243]** in high yields and was rewarded with alcohol **[261]** in an 88% yield. (Scheme 9.1)

2.2.8 Aldehyde formation.

We now chose to convert the primary alcohol of **[261]** to the aldehyde **[265]** as this would give several options with which to attach the anisole group. A limited series of oxidation reactions were undertaken to establish which procedure would give the best results for our system.[109-113] (Table 1.4)

Entry	Reaction Conditions	Product	Yield (%)
1	Oxalyl Chloride, DMSO, Et$_3$N, DCM	Starting material	-
2	TFAA, DMSO, Et$_3$N, DCM	Aldehyde	58
3	TEMPO, TBACl, NCS, DCM, K$_2$CO$_3$, NaHCO$_3$, H$_2$O	Starting material	-
4	TEMPO, NaOCl, KBr, DCM H$_2$O	Aldehyde	Trace
5	TPAP, NMNO, MS 4A DCM/CNCH$_3$,	Aldehyde	11

Table 1.4

Joullie *et al.* used a trifluoroacetic anhydride variation of the Swern oxidation with good success on their intermediate alcohol **[262]** in a total synthesis of (-)-Detoxinine **[264]**.[109] (Scheme 9.2)
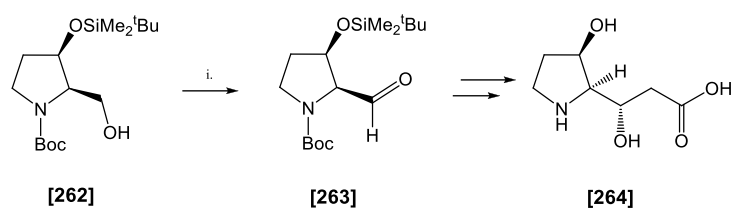
Reagents & conditions: i. TFAA, DMSO, CH_2Cl_2, Et_3N, -78°C, 1.5h, (88%)

Scheme 9.2

The intermediate alcohol **[262]** in the Joullie synthesis bore a close resemblance to our system, but whilst the oxidation reaction delivered an 88% yield for **[264]**, the same procedure gave aldehyde **[266]** in a modest 58% maximum yield for us.[109] Purification of the aldehyde **[266]** proved to be a difficult undertaking due to its propensity to decompose during column chromatography.

Although the formation of the aldehyde **[266]** would finally allow the addition of aryl group, this key reaction would prove later in the synthesis to have compromised the stereochemistry at C2 whereby it is believed that the inclusion of triethylamine over the more sterically hindered Hünig's base, *N,N*-diisopropylethylamine, induced epimerisation alpha to the newly formed carbonyl. Whilst the correct mass was determined at m/z 462.18 as its sodiated ion and the identity of the all important aldehyde peaks between 9.4 and 9.8 ppm in the NMR spectrum; the rest of the NMR spectrum proved difficult to accurately assign due not only to the diastereoisomers of the tetrahydropyran groups and notwithstanding the fragile stability of the compound itself, but also for the benzyl carboxylate's penchant to broaden the peaks of the spectrum because of the rotameric effect. (Scheme 9.3)
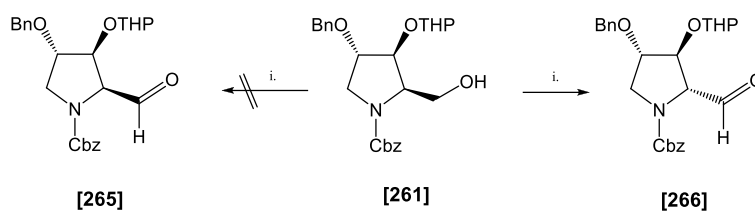
Reagents & conditions: i. TFAA, DMSO, CH$_2$Cl$_2$, Et$_3$N, -78°C, 3h, (58%)

Scheme 9.3

As we were not aware of the stereochemical compromise at the C2 position of the aldehyde **[266]** at the time, we proceeded forward to the next step of the synthesis.

2.2.9 Successful introduction of the anisole appendage.

The addition reaction required the instalment of a *p*-methoxyphenyl moiety; therefore the obvious choice was a derived anisole-halogen reagent. This would allow for the option to create a Grignard nucleophile or to exploit a metal-halogen exchange reaction. The latter method was chosen due in no small part to the Grignard failures earlier in the synthesis and the wish to try new reactions. Bailey and Punzalan[114] conducted a study to find a convenient and general method of preparation of alkyllithium reagents by lithium-iodine exchange. In an adaptation of their methods *p*-bromoanisole was treated with *n*butyllithium in THF and added to the aldehyde **[266]**; this resulted in the attachment of the major appendage and pyrrolidine **[267]** was extracted in a 31 % yield. The same reaction was undertaken with *p*-iodoanisole as the aryl-halogen reagent and delivered the identical diastereoisomeric pyrrolidines **[267]** in a 44% yield. (Scheme 9.4)
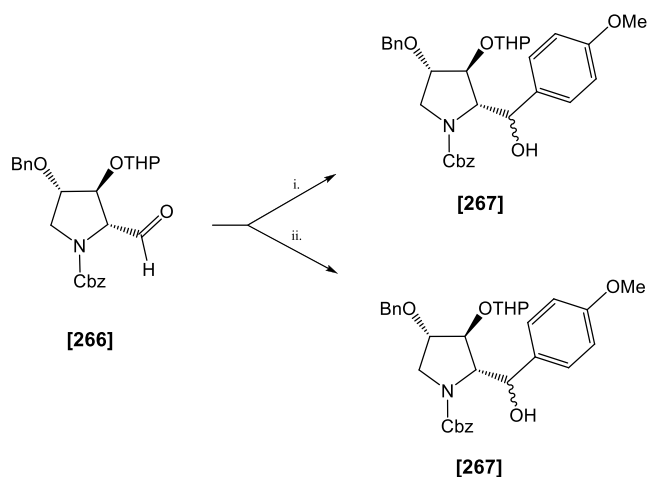
Reagents & conditions: i. C_7H_7BrO, ^nBuLi, THF. -78°C, 1h (31%).
ii. C_7H_7IO, ^nBuLi, THF. -78°C, 1h (44%).

Scheme 9.4

With the new pyrrolidine compounds **[267]**, containing the additional chiral centre of the pyran protecting group, together with the newly formed benzylic alcohol's undefined stereochemistry; separation of the diastereoisomers proved to be impossible by column chromatography, and with the carbamate group's persistence in obscuring the ^{1}H NMR spectra, clear and definitive NMR data analysis was not possible. It was clear however, that the anisomycin skeletal framework was now in place as the significant architectural groups could be identified with ease. An obvious methoxy peak of the anisole group was recorded at 3.77 ppm together with the benzyl *meta* and *ortho* peaks of the same group which were unambiguous at 6.92 and 7.29 ppm. The methanediyil of the protective pyran group were visible at the lower end of the spectra, 1.50-1.90 ppm and the aromatics of the benzyl ether and benzyl carboxylate groups could be seen at 7.29-7.37 ppm. The absence of the aldehyde peaks **[267]** at 9.4 and 9.8 ppm indicated that all of the starting material had been consumed, however, whilst the pyrrolidine hydrogens, the chiral pyran and the new benzylic proton at the addition site were generally

identifiable though the HSQC NMR and via ^{1}H integration, correct individual assignments was not possible.

This data coupled with the correct accurate mass recording and, from a synthesis progression standpoint, the redundant necessity of diastereoisomeric separation, allowed us to concentrate on removing the hydroxyl remnant of the parent aldehyde.
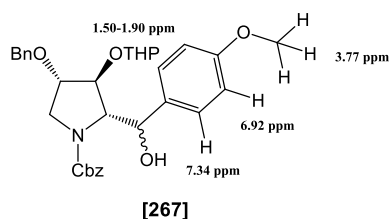
Figure 2.4

2.2.10 Reduction of benzylic hydroxyl group.

Mayr, in 1997, had reported an investigative study into the ionic reduction of a series of alcohols and ketones with triethylsilane and trifluoroacetic acid solutions[115] and we were optimistic that this system could serve to reduce the benzylic alcohol to the methylene. As the tetrahydropyran protecting group was slated for removal at the next step in the synthesis so that the resultant alcohol could receive the final architectural group, we were hopeful that silane/brønsted acid treatment would effect the tandem elimination of this group too.

Reagents & conditions: i. Et$_3$SiH, CF$_3$CO$_2$H, 1h. (81%).
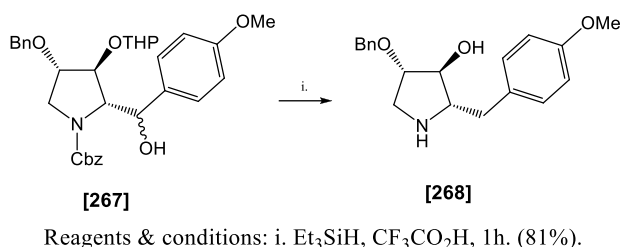
Scheme 9.5

Treatment of the mixture of alcohol diastereomers **[267]** with excess triethylsilane and trifluoroacetic acid confirmed that our optimism was well placed as the benzylic alcohol and the tetrahydropyran groups were removed; however, the acidic solution also efficiently dispatched the amine protection and delivered the all but naked pyrrolidinol **[268]** in a maximum 81% yield. (Scheme 9.5)

With the removal of the benzylic alcohol, the carboxylate and the tetrahydropyran diastereomers, we took the opportunity to establish an $[\alpha]_D$ value for the pyrrolidinol **[268]** to compare with the literature values of (-)-anisomycin **[1]**. Kibayashi reported a value of $[\alpha]_D^{20}$ -30° (c 0.3 EtOH)[49] and Hall reported $[\alpha]_D^{26}$ -26° (c 0.15 MeOH). Whilst we had not formed the acetoxy group or removed the benzyl ether, our $[\alpha]_D^{23}$ -18.006° (c 0.1 MeOH) value appeared to bode well although we were still not aware at the time of the inversion of the C2 stereocentre.

2.2.11 Introduction of the acetoxy group.

With the pyrrolidinol **[268]** exposed as its free base, the conversion of the lone alcohol to the acetoxy group would have to defer to the reinstatement of the amine protection. The Schotten-Baumann conditions with benzyl chloroformate from earlier in the synthesis were thus re-employed to again establish the carbamate protection and gave the alcohol **[269]** in 78% yield. (Scheme 9.6)

[268]   **[269]**

Reagents & conditions: i. $C_8H_7O_2Cl$, $(CH_3)_2O$, Na_2CO_3,
H_2O, 25°C, 48h. (78%)
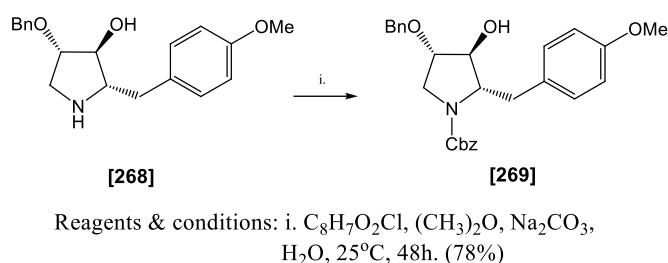
Scheme 9.6

To furnish the remaining architectural component on the solitary crown hydroxyl group to fulfil the anisomycin framework, a simple and efficient method of acetylation was required. Chandler *et al. en route* to the potent anti-influenza compound, 4-guanidino Neu5Ac2en **[272]**, performed a global acetylation of the key intermediate **[270]** in the synthesis and returned an impressive 96% yield on this penta-acetylation.[116] (Scheme 9.7)
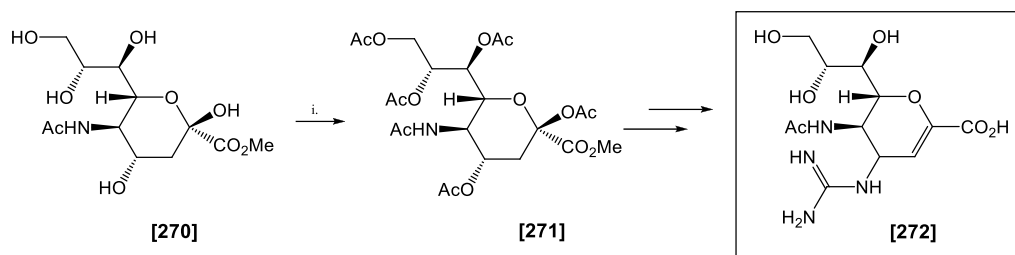
Reagents & conditions: i. Ac$_2$O, Pyr, DMAP, CH$_2$Cl$_2$, 0-25°C, 18h. (96%)

Scheme 9.7

The Chandler protocol was translated to the alcohol **[269]** and the acetoxy pyrrolidine **[273]** was delivered in a very good 84% yield. (Scheme 9.8)
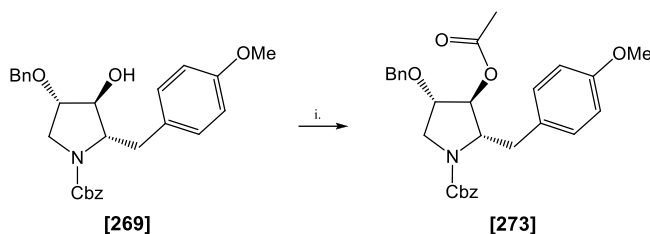
Reagents & conditions: i. Ac$_2$O, Pyr, DMAP, CH$_2$Cl$_2$, 0-25°C, 18h. (84%)

Scheme 9.8

2.2.12 Global deprotection.

The concluding step in the synthesis was to remove the remaining protecting groups to unveil the final compound. Whilst both the benzyl groups were different and in turn protecting different functional groups, they were equivalent in their inability to resist purging via catalytic hydrogenation. The acetoxy pyrrolidine [273] was treated in ethanol with 10% palladium on charcoal under an atmosphere of hydrogen over 4 days to give the final compound [274] as a white powder in 93% yield and 9.4% overall yield. (Scheme 9.9)
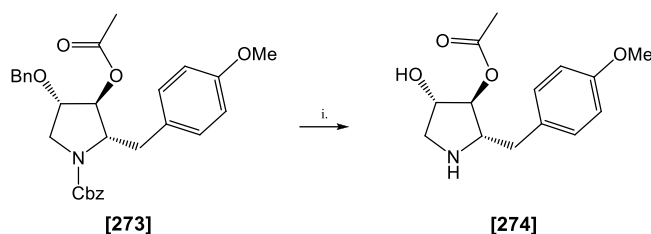
Reagents & conditions: i. Pd/C/H_2, 25°C, 4 days. (93%)

Scheme 9.9

2.2.13 Authentication of the final product [274].

With the pure final compound [274] in hand we set about confirming its authenticity as the natural alkaloid [1]. A clean accurate mass was recorded of m/z 266.1384 as the protonated ion and the NMR spectra revealed peaks for the methyl of the benzyl methoxy at 2.16 ppm, the methyl of the acetoxy at 3.74 ppm and the benzylic *ortho* and *meta* protons at 6.80 and 7.05 ppm all of which were concurrent with the general literature data values when recorded in deuterated chloroform. However, the peaks indicated for the pyrrolidine hydrogen atoms and the benzylic methylene were significantly skewed as to warrant further investigation. An $[\alpha]_D^{21}$ -2.8002° (c 1.0 MeOH) value for our

anisomycin **[274]** did not compare favourably with the natural product **[1]**, $[\alpha]_D^{25}$ -29.0° (c 1.0 MeOH), thus a further incentive to establish the correct identity of our final compound **[274]**.

The literature data values for the ^1H and ^{13}C NMR in the different publications of the total synthesis of (-)-anisomycin **[1]** vary due to the final products data being collected in different deuterated solvents and the use of equipment with varying degrees of antiquity and operating frequencies ranging from 60 MHz–500 MHz for ^1H and 20 MHz–125 MHz for ^{13}C.
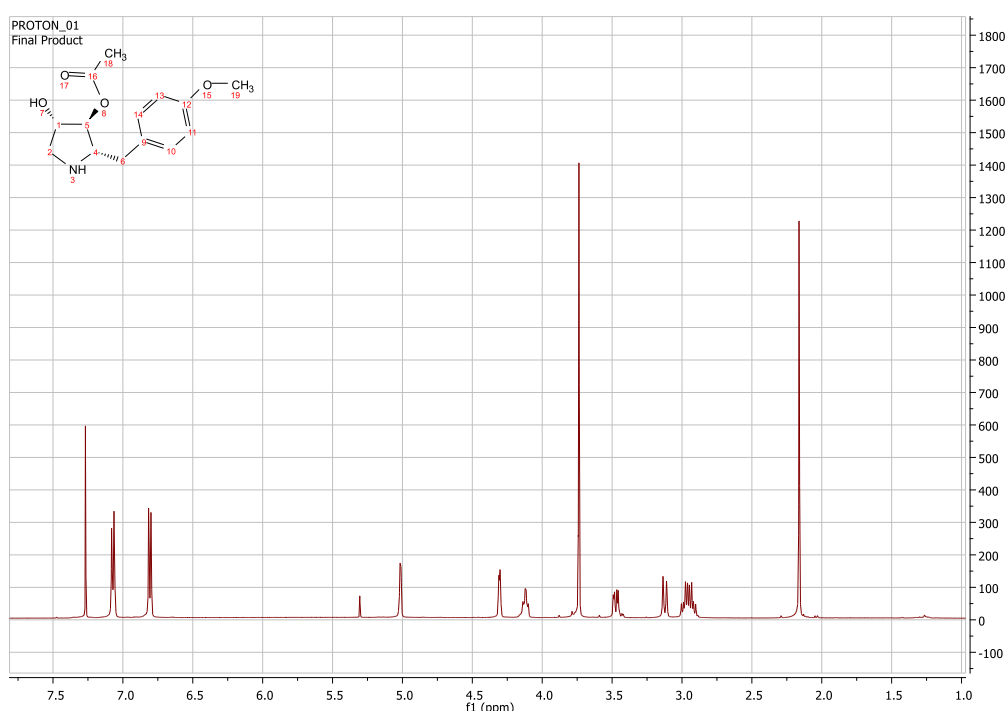
Figure: 2.5 ^1H NMR spectra of Anisomycin **[274]**

In an attempt to mitigate any disparity, NMR data was collected for our final product in both deuterated chloroform and deuterated methanol and the results compared with the data from comparable equipment. Ham *et al.*[33] recorded clear and comprehensive ^1H and ^{13}C NMR data for (-)-anisomycin **[1]** in CDCl₃ whilst Lin[46] and LeFevre[117] recorded ^1H and ^{13}C NMR data

96

respectively in CD₃OD. This comparison left little, if no doubt to the conclusion that our compound **[274]** was not that of the natural alkaloid **[1]**. To remove any lingering reservations, we obtained a pure and authentic sample of (-)-anisomycin **[1]** and the contrast was absolute in both CDCl₃ and CD₃OD. (Figure 2.5)
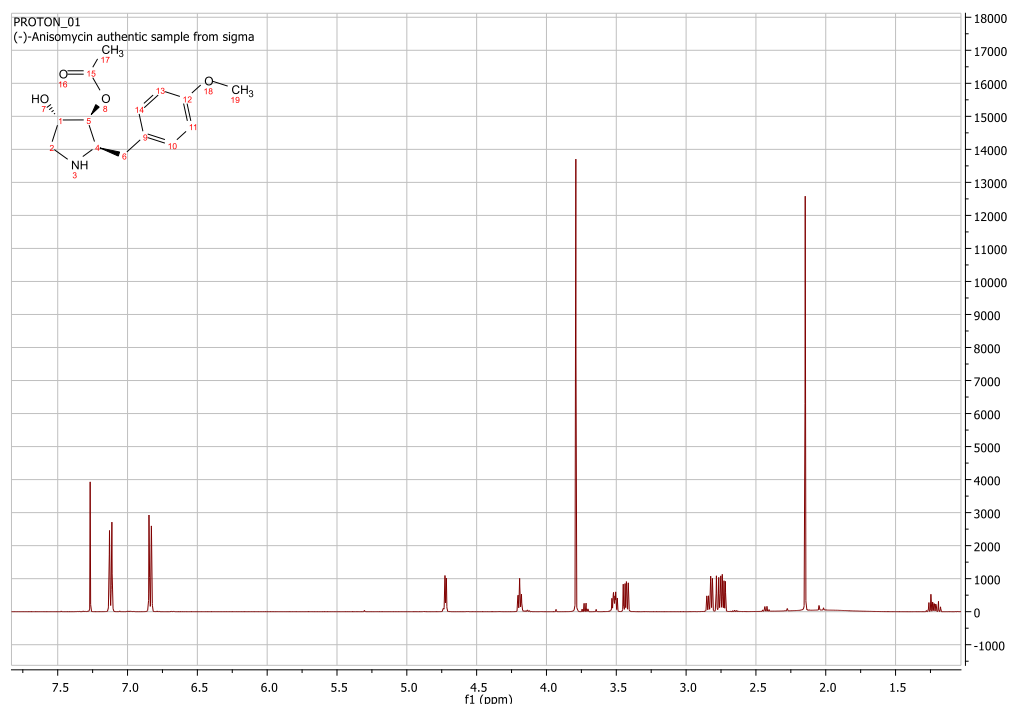
Figure: 2.5 ¹H NMR spectra (-)-anisomycin **[1]** in CDCl₃.

While all of the data clearly indicated that we had successfully constructed the anisomycin skeleton with the correct ancillary architecture, we drew the conclusion from both the NMR and the polarimetry data that one or more of the chiral centres must be guilty of the discrepancy. With the specific rotation of **[274]** as a low negative value we tenuously suspected that the chirality of only one centre had been affected. We re-evaluated our route from the oxazolidinone **[221]** through to our final product **[274]** in an attempt to discern at which point and under which reaction conditions the stereochemical compromise could have taken place.

The analytical data of the oxazolidinone **[221]** was identical to that recorded in the literature and with the C2 chiral centre bound within the cyclic carbamate ring we took this as the starting point. The epoxide had a specific rotation value of $[\alpha]_D^{22}$ -8.1027° (c 1.9 CHCl$_3$) and good NMR spectra assignment, however, the x-ray crystallographic data left no doubt as to the configural orientation of the stereochemistry. The following compound, the mono-protected *trans* diol **[240]** was the first of our molecules to contain within it all three of the correct stereo centres. We established a specific rotation value of $[\alpha]_D^{23}$ -10.249° (c 1.0 CHCl$_3$) and again the effort involved in enticing crystal growth paid dividends in the ability to gain valuable x-ray crystallographic data. The mono-protected *trans* diol **[240]** was subject to both subsidiary ring opening to give the 1,3 diol **[242]** and hydroxyl THP protection to give the dual protected *trans* oxazolidinone **[254]**. Yet again the NMR data could be assigned confidently for both compounds and the luxury of x-ray crystallographic analysis discounted any ambiguity as to chiral alterations. As the mono-protected *trans* diol **[240]** had been subject to relatively harsh reaction conditions with which to open the carbamate ring and the x-ray analysis had verified that the stereochemistry of the resultant 1,3 diol **[242]** had remained unaltered, we saw no reason to suspect that the identical ring opening conditions of the dual protected *trans* oxazolidinone **[254]** would suffer any compromise in its chirality. The inseparable mixture of the diastereoisomers from the THP group impacted significantly on the ability to obtain clarity in the NMR spectra of alcohol **[257]**, although surprisingly however, the attachment of the benzyl carboxylate protection group appeared to give a certain stability and standard assignment of the *N*-protected-alcohol **[261]** proved to be relatively straightforward, even with substantial rotameric broadening. To this point it was considered that any reaction conditions that could have influenced the C2 stereocentre were unlikely; although the inability to secure sufficiently clear NMR data of the alcohol **[257]** and to some degree that of the subsequent tri-protected alcohol **[261]** to ascertain it definitively, was unfortunate if not frustrating. We did

however on balance, now believe that the aldehyde conversion was most likely the culpable reaction. Chiral lability of α-amino aldehyde derivatives during fabrication, storage and column chromatography is well documented in the literature, [118-121] and upon post mortem of the synthesis coupled with hindsight; the use of the more sterically hindered Hünig's base in place of triethylamine during the Swern oxidation could have alleviated the issue. As no comprehensible analytical NMR data was obtainable for the aldehyde **[266]**, which could categorically determine that it was this stereocentre which had been altered; together with the following compound **[267]** containing the THP diastereoisomers, the benzylic alcohol residue from the aryl addition and the carbamate rotamers, we felt that it would now be prudent to try to identify conclusively the compromised centre from the final compound **[274]** and work backwards through the synthesis.

We conducted a further set of more intrusive NMR experiments on anisomycin **[274]**, obtaining gCOSY, gHSQCAD, gHMBCAD and NOESY spectra, and compared these with the same for the authentic sample of (-)-anisomycin **[1]**.

The NOESY data provided evidence that it was indeed the C2 stereocentre which had been inverted. The (-)-anisomycin **[1]** NOESY spectra showed a clear correlation involving C2-H and C3-H implying a *cis* relationship between the two protons and no enhancement between C3-H and C4-H signifying a *trans* geometry. (Figure 2.6)

The NOESY NMR data for anisomycin **[274]** unlike its natural bioactive cousin **[1]** did not show any correlation between the key C2-H and C3-H, indicating a lack of the desired *cis* geometry; it also showed little or no relationship between C3-H and C4-H further confirming that this was also in a *trans* configuration. (Figure 2.7)
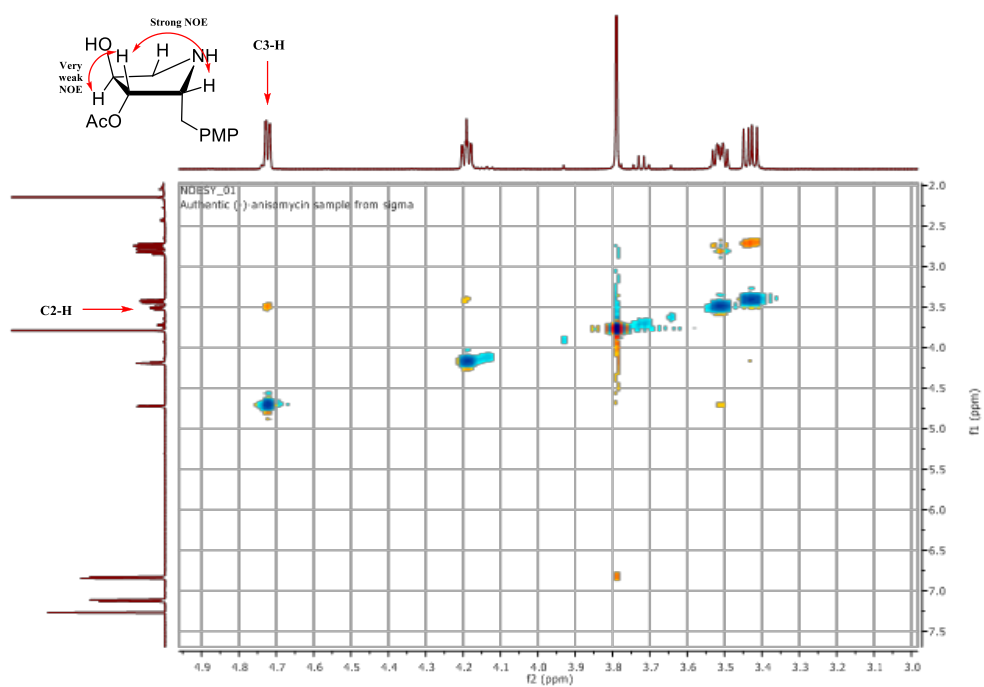
Figure: 2.6 NOESY NMR spectra of (-)-anisomycin [1]
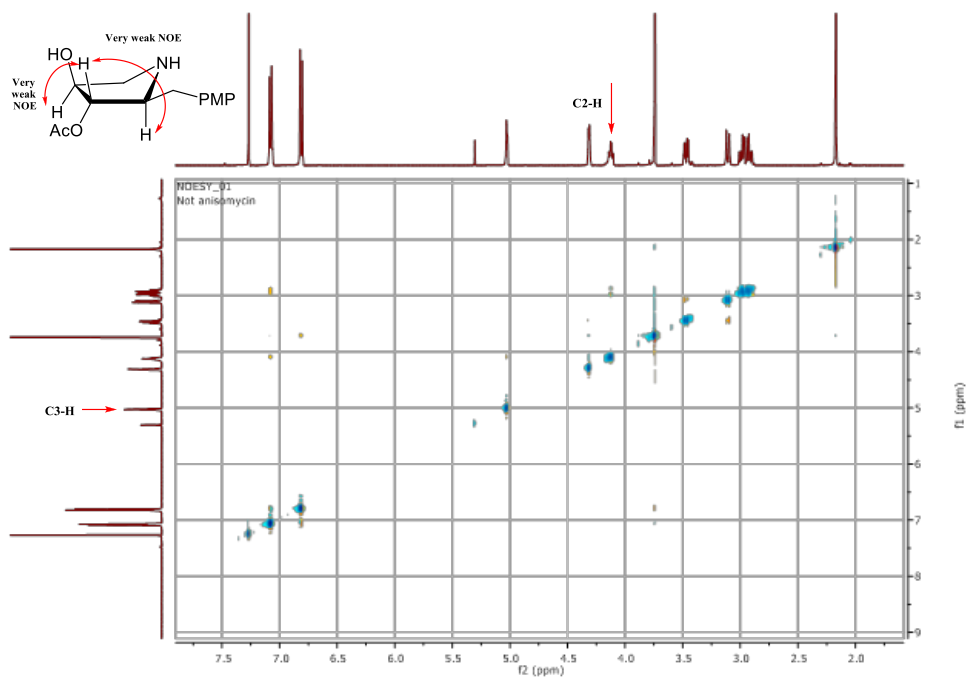
Figure: 2.7 NOESY NMR spectra of (-)-*epi*-2-anisomycin [274]

We were now confident that with the in-depth NMR data, accurate mass, specific rotation and IR evidence we had correctly identified the structure and geometry of our final product as (-)-*epi*-2-anisomycin [274]. Retreating further back through the synthesis, we obtained a NOESY NMR spectra of the pyrrolidinol [268] to further support the evidence that the C2 inversion had taken place and to try to ascertain where in the route it had happened. The NOESY NMR data for mono-protected alcohol [268] again showed no relationship between C2-H and C3-H, signifying that a *trans* configuration existed. (Figure 2.8)
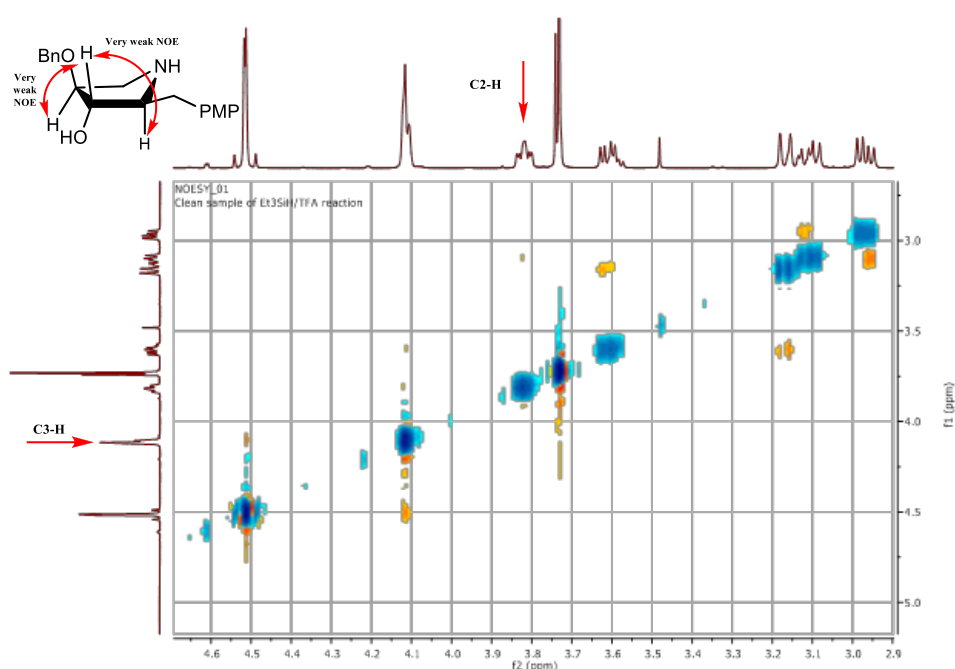
Figure: 2.8 NOESY NMR spectra of pyrrolidinol [268]

Comprehensive determination by analysis of the NMR data any further down the synthetic route was not possible as reported earlier, so we sought to validate our findings by comparing the (-)-*epi*-2-anisomycin [274] data with any identical compound reported in the literature. Park *et al.* reported the synthesis of several anisomycin and deacetyl anisomycin derivatives from D-tyrosine in 2005, unfortunately (-)-*epi*-2-anisomycin [274] was not one of the

synthesised derivatives included in the report; although its enantiomer, Beerboom's suggested configuration of (-)-anisomycin[6] **[2]** was.[4,6] (Figure 2.9)
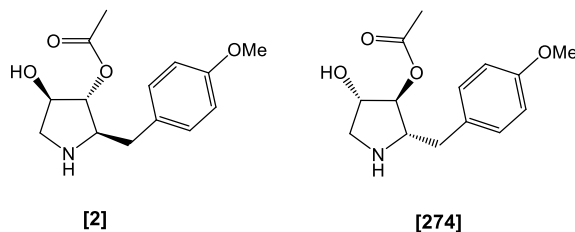
Figure: 2.9 Park *et al's* enantiomer **[2]** of our

epi-2-anisomycin **[274]**

As this enantiomer should provide an identical NMR spectrum, together with matching IR spectra and accurate mass to our final compound **[274]**, we sought comparison. A visual analysis of the IR spectra in Park's publication was not available therefore a comparison was not possible; however, there were three of the key IR peaks reported and these values, although not exact matches, were within a comparable range with our data. A reported HRMS value of M^+ 265.1305 was also stated in comparison to our m/z 266.1387 for the protonated molecular ion.

We were concerned to find that the ^{1}H NMR spectra of (-)-*epi*-2-anisomycin **[274]** did not match that of Park's enantiomer **[2]** and by some significant margin. It was noted that the author also made no reference to the extra multiplet peak at 3.16 ppm and the more significant singlet peak at 4.70 ppm.[4] (Figure 3.0)
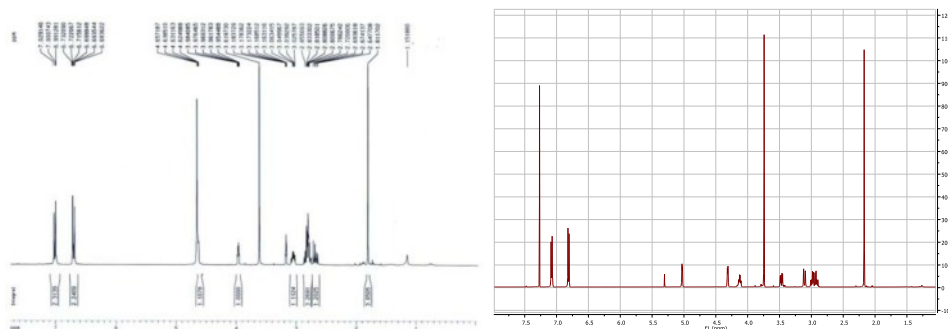
Figure: 3.0 ^{1}H NMR spectrum of Park's anisomycin [2] and
(-)-*epi*-2-anisomycin [274]

Park *et al.* also reported 3 month later in a different journal, a second series of
anisomycin and deacetyl anisomycin derivatives from D-tyrosine, including
that of (-)-*epi*-2-anisomycin [274].[4]

Park *et al's* anisomycin [2]   Park *et al's epi*-2-anisomycin [274]
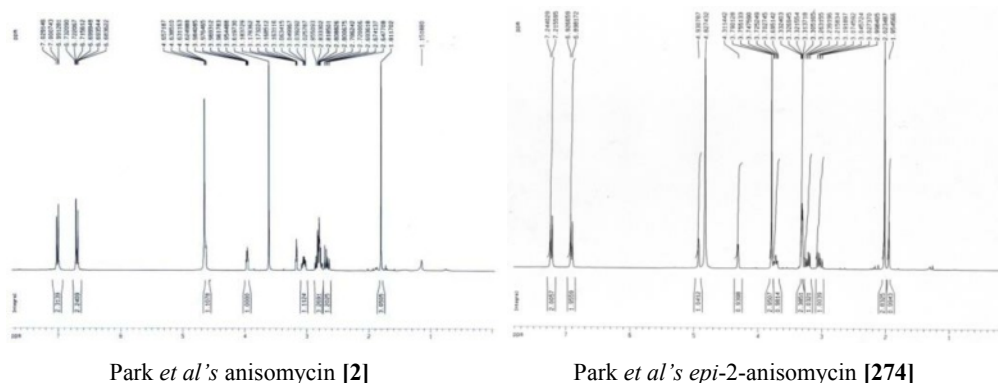
Figure: 3.1 ^{1}H NMR spectrum of both anisomycin [2] and
[274] enantiomers reported by Park.

We compared our final compound [274] ^{1}H NMR data with their reported of
the same and again found substantial anomalies; however, more significantly
the ^{1}H NMR spectra for the pair of anisomycin enantiomers from the two
publications also differed considerably.[4] (Figure 3.1)

Upon further analysis between the two publications we noted inconsistencies in the ^{13}C NMR spectral data for both the enantiomers [2] and [274], together with significant differences to our spectrum. [4]

2.3 Conclusion.

Our 11 step synthesis to (-)-*epi*-2-anisomycin successfully continues the Parsons group program of converting the oxazolidinone precursor [211] to different natural products and their derivatives. Whilst this particular synthesis failed to yield the biologically active isomer, the general route holds excellent promise to succeed to the natural alkaloid in good yield in future work.

The oxazolidinone's propensity to yield to excellent stereo- and regio-selectivity is a clear advantage in obtaining the desired *trans* geometry for the eventual hydroxy and acetoxy groups. The formation of the aldehyde [266] proved to be a paradoxical poisoned chalice; on the one hand it allowed for the addition of the aryl group after months of failures and ultimately the completion of the synthesis of anisomycin skeleton, but on the other, the compromised stereocentre stopped us achieving the total synthesis of the natural alkaloid [1].

Our diligence in determining the correct structure and configuration of our final product [274] despite the unreliability of the literature data also enabled us to suggest where in the synthesis the inversion of C2 took place. In hindsight, if the knowledge of the epimerisation had been known at the time or additional laboratory time were available when the inversion had been discovered, the reduction of the aldehyde [266] back to the parent alcohol [257] with NaBH$_4$ may have allowed us to investigate any chiral epimerisation and could have enabled us to restore the integrity of the chiral

centre. It is hoped that this work will aid any future endeavour to complete the route to the natural alkaloid **[1]**.

3. Experimental

3.1. General Experimental Procedures.

3.1.1. Reagents and Solvents.

All reactions were conducted under a nitrogen atmosphere unless otherwise stated using oven dried glassware. Reactions requiring anhydrous conditions were carried out using flame dried glassware under nitrogen. All starting materials and reagents were purchased from commercial sources and were used without any prior purification. All solvents were freshly distilled under a nitrogen atmosphere unless otherwise stated from an appropriate drying agent as described.

Solvent	Drying agent
Acetonitrile, dichloromethane, benzene, ethyl acetate, methanol.	Calcium hydride.
Tetrahydrofuran, diethyl ether.	Sodium (in the presence of benzophenone)

The solvents used in chromatography were subjected to rotary evaporation before use to remove impurities.

3.1.2. NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded on a Varian VNMRS 500 MHz spectrometer with samples run in deuterated chloroform, deuterated toluene or deuterated methanol as a solvent at 30°C and are referenced to deuterated chloroform, deuterated toluene or deuterated methanol internal reference respectively. The chemical shifts for ^{1}H NMR were recorded in parts per million (ppm) on the δ scale and the coupling constants (J) are measured in

Hz. The chemical shifts for ^{13}C NMR were recorded in parts per million (ppm) on the δ scale. ^{1}H variable temperature NMR were recorded on a Varian VNMRS 400 MHz spectrometer with samples run in deuterated toluene are referenced to deuterated toluene internal reference. The chemical shifts for were recorded in parts per million (ppm) on the δ scale and the coupling constants (*J*) are measured in Hz. The following abbreviations were used to represent multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; app, apparent; br, broad.

3.1.3. Chromatography.

All reactions were monitored using thin layer chromatography, with the solvent system as indicated. TLC was carried out using Partisil® K6F glass backed plates with a 250 μm layer of 60 Å silica gel with fluorescent indicator. Plate visualization was carried out using ultraviolet radiation (254 nm) when necessary in combination with a phosphomolybdic acid (PMA) or potassium permanganate.

Flash column chromatography was carried out using Merck Kiesel silica 60 Å, (particle size 35 – 70 μm) eluting with solvent commercially available from Fisher Scientific or Sigma Aldrich, with the solvent system specified in the procedure.

3.1.4. Mass Spectrometry.

Mass spectra were obtained on a Fisons VG Micromass 7070F and a VG AUTOSPEC instrument using Electron Spray Ionisation (ESI). All spectral data was captured by Dr. A. K. Abdul-Sada of the University of Sussex mass spectrometry centre.

3.1.5. Infra Red Spectroscopy.

Infra Red spectra were recorded using a Perkin Elmer 1710 Fourier transform spectrophotometer with a Diamond Attenuated Total Reflectance attachment with υ_{max} measured in cm^{-1}.

3.1.6. X-Ray Crystallography.

The crystallographic data was obtained on a Nonius Kappa CCD diffractometer, Program package WinGX, Refinement using SHELXL-97, Drawing using ORTEP-3 for Windows and provided by Dr Martyn Coles of the University of Sussex.

All compounds detailed in the following experimental data have been numbered to aid the reader in the identification of protons and carbons in the relevant spectra. They do not necessarily correspond with that of the I.U.P.A.C. guidelines.

3.2. Synthesis of the Oxazolidinone [221]

(2*S*,4*R*)-2-carboxy-4-hydroxypyrrolidinium chloride [223]
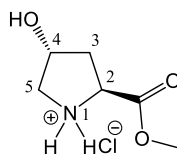
To a stirred suspension of *trans*-4-hydroxy-L-proline **[222]** (20 g, 153 mmol) in dry methanol (80 ml) at 0 °C thionyl chloride was added (12.24 mL, 168 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for a further 1 hour before warming to room temperature and stirred for 14 hours. The solution was cooled to 0 °C and adding diethyl ether (400 mL). The precipitate was filtered, washed with diethyl ether (2 x 100 mL) and dried *in vacuo* to give the crude methyl ester **[223]** as a white solid (25.2 g 91%).

δH (500 MHz, (CD$_3$)$_2$SO) (Doubling and broad peaks as a result of rotamers) 9.77 (1H, br, NH), 5.54 (1H, s, OH), 4.47 (1H, dd, *J* 7.6, 10.9 Hz 4-H), 4.41 (1H, br, 2-H), 3.75 (3H, s, CO$_2$CH$_3$), 3.35 (1H, dd, *J* 4.3, 11.9 Hz 5-H), 3.06 (1H, d, *J* 4.3 Hz 5-H), 2.19 (1H, m, 3-H), 2.09 (1H, m, 3-H), δC (125 MHz, (CD$_3$)$_2$SO) 169.6 (CO$_2$CH$_3$), 68.8 (C-4), 57.9 (C-2), 53.7 (C-5), 53.4 (CO$_2$CH$_3$) 37.4 (C-3). IR 3323, 2955, 2699, 1741, 1592, 1440 cm^{-1}; HRMS (ESI) calcd [M+H] *m/z* C$_6$H$_{12}$NO$_3$ 146.0817, found 146.0811. Spectroscopic data identical to literature values.[90]

(2S,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methylester [224]
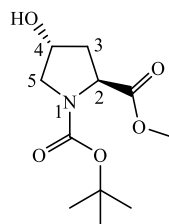
To a stirred suspension of the resulting crude methyl ester **[223]** (25.2 g) in dioxane (250 mL) at 0 °C, was added *N,N*-di-isopropylethylamine (29 mL, 167 mmol) and di-*tert*-butyl dicarbonate (31.8 g, 146 mmol). The reaction mixture was stirred for 1 hour then allowed to warm to room temperature and stirred overnight. The solution was concentrated under reduced pressure. The mixture was taken up in ethyl acetate (500 mL) and washed with a 1 M citric acid solution (500 mL). The phases were separated and the aqueous phase was further extracted with ethyl acetate (3 x 500 mL). The combined organic extracts were washed with a saturated sodium bicarbonate solution (500 mL) and a saturated sodium chloride solution (500 mL), dried over magnesium sulfate and concentrated under [143] reduced pressure to give the Boc protected methyl ester **[224]** as a yellow oil without the need for further purification (31.3 g, 93%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 4.48 -4.44 (1H, m, 4-H), 4.43-4.37 (1H, m, 2-H), 3.73 (3H, s, CO$_2$CH$_3$), 3.63-3.43 (2H, m, 5-H), 2.28 (1H, m, 3-H), 2.08 (1H, m, 3-H), 1.45 and 1.41 (9H, 2 x s, C(CH$_3$)$_3$). δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 173.6 and 173.4 (CO$_2$CH$_3$), 153.9 (N-C=O), 80.3 and 80.2 (C(CH$_3$)$_3$), 70.1 and 69.3 (C-4), 57.9 and 57.4 (C-2), 54.6 (C-5), 52.1 and 51.9 (CO$_2$CH$_3$), 39.0 and 38.4 (C-3), 28.3 and 28.2 (C(CH$_3$)$_3$). IR. 3435. 2928, 1809, 1737, 1658, 1419. cm^{-1}; HRMS (ESI) [M+Na] *m/z* calcd C$_{11}$H$_{19}$NO$_5$Na 268.1161, found 268.1146. Spectroscopic data identical to literature values.[90]

(2S,4R)-4-Methanesulphonyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl-ester-2-methyl ester [225]
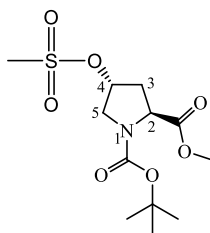
To a stirred solution of (2S,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **[224]** (177g, 720 mmol) and triethylamine (100 mL, 790 mmol) in dichloromethane (1200 mL) at 0 °C, was added methanesulfonyl chloride (82.67 mL, 790 mmol) and 4-dimethylaminopyridine (8.82 g, 72 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 24 hours, before cooling to 0 °C and adding a saturated aqueous solution of ammonium chloride (1200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 600 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate solution (500 mL) and a saturated sodium chloride solution (500 mL), dried over magnesium sulfate and concentrated under reduced pressure to reveal **[225]** as an orange crystalline solid. (223.94 g, 96%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 5.26 (1H, m, 4- H), 4.49-4.39 (1H, m, 2-H), 3.87-3.77 (2H, m, 5-H), 3.75 (3H, s, CO$_2$C$\underline{H}_3$), 3.05 (3H, s, SO$_2$C$\underline{H}_3$), 2.62 (1H, m, 3-H), 2.27 (1H, m, 3-H), 1.47 and 1.43 (9H, 2 x s, C(CH$_3$)$_3$). δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 174.7 and 172.6 ($\underline{C}$O$_2$CH$_3$), 153.3 and 150.6 (N-C=O), 80.8 ($\underline{C}$(CH$_3$)$_3$), 78.1 and 77.8 (C-4), 57.4 and 57.0 (C-2), 52.4 and 52.2 (CO$_2\underline{C}$H$_3$), 52.4 and 52.1 (C-5), 38.7 and 38.6 (SO$_2$CH$_3$), 37.4 and 36.2 (C-3), 28.2 and 28.1 (C($\underline{C}$H$_3$)$_3$). IR 2971, 1746, 1697, 1438, 1398, 1351, 1213, cm^{-1};

HRMS (ESI) calcd $C_{12}H_{21}NO_7SNa$ [M+Na] *m/z* 346.0931, found 346.0918. Spectroscopic data identical to literature values.[90]

(*S*)-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester [227]
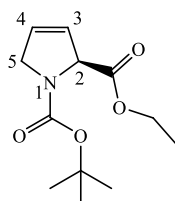
To a stirred suspension of diphenyl diselenide (19.2 g, 62 mmol) in ethanol (300 mL) at 0 °C was added sodium borohydride (5.1 g, 135 mmol) portion wise. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour, before re-cooling to 0 °C and adding (2*S*,4*R*)-4-methanesulphonyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl-ester 2-methyl ester [225] (36.2 g, 112 mmol) in ethanol (100 mL). The reaction mixture was stirred for 24 hours at room temperature before being heated to reflux and stirred for 6 hours. The solution was concentrated under reduced pressure to reveal a yellow crystalline solid. The solid was dissolved in diethyl ether (400 mL) and washed with water (250 mL). The phases were separated and the aqueous phase was further extracted with diethyl ether (3 x 200 mL). The combined organic extracts were washed with a saturated sodium chloride solution (250 mL), dried over magnesium sulfate and concentrated under reduced pressure to give the crude phenyl selenide [226] as a orange/brown oil (42.3 g 95%).

To a vigorously stirred solution of the resulting crude phenyl selenide [226] (42.3 g) and pyridine (16.8 mL, 212 mmol) in dichloromethane (725 mL) at -78 °C was added a 35 wt.% hydrogen peroxide solution (51.6 mL, 530 mol) dropwise over 1 hour. The reaction mixture was allowed to warm to room

temperature and stirred for 10 hours, before adding a saturated ammonium chloride solution (350 mL). The phases were separated and the aqueous phase was further extracted with dichloromethane (3 x 200 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (500 mL) and a saturated sodium chloride solution (500 mL), dried over magnesium sulfate and concentrated under reduced pressure to reveal a brown oil residue (32.1 g). The resulting residue was subjected to flash column chromatography on silica, eluting with 20% diethyl ether/petrol, then 50% diethyl ether/petrol to give **[227]** as a orange/brown oil (9.7 g, 38%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 5.99-5.93 (1H, m, 4-H), 5.75-5.70 (1H, m, 3-H), 5.05-4.93 (1H, m, 2-H), 4.31-4.15 (4H, m, 5-H and OC$\underline{H_2}$CH$_3$) 1.49 and 1.44 (9H, 2 x s, C(CH$_3$)$_3$), 1.28-(3H, m, OCH$_2$C$\underline{H_3}$). δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 170.5 ($\underline{C}$O$_2$Et$_3$), 153.4 (N-C=O), 129.2 and 129.1 (C-4), 124.8 and 123.6 (C-3), 80.1 and 80.0 ($\underline{C}$(CH$_3$)$_3$), 66.6 and 66.3 (C-2), 61.1 (O$\underline{C}$H$_2$CH$_3$), 53.4 and 53.2 (C-5), 28.4 and 28.2 (C($\underline{C}$H$_3$)$_3$), 14.2 and 14.1 (CO$_2$C$\underline{H_3}$). IR 2976, 1752, 1701, 1392, 1366, 1171. cm^{-1}; HRMS (ESI) calcd C$_{12}$H$_{19}$NO$_4$Na [M+Na] *m/z* 264.1212, found 264.120. $[\alpha]_D^{24}$ = -235.7. (C 1.2 CHCH$_3$) Spectroscopic data identical to literature values.[90]

(2*S*,4*S*)-1-*tert*-butyl-2-methyl-4-iodopyrrolidine-1,2-dicarboxylate [229]
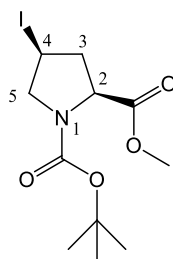
To a vigorously stirred solution of (2*S*,4*R*)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester **[224]** (34.52 g, 141 mmol)

in toluene (300 mL) and acetonitrile (150 mL) at 0 °C, was added triphenyl phospine (108.11g, 412 mmol) and iodine (108.24g, 426 mmol). The reaction mixture was left to stir for 1 hour before imidazole (56.58g, 832 mmol) was added portion wise over 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 72 hours. The reaction mixture was filtered to remove the undesired solid and the filtrate was concentrated under reduced pressure. Diethyl ether (4 x 150 mL) was added and the resultant triphenyl phospine oxide precipitate was removed via filtration. The combined filtrates were was washed with a solution of sodium thiosulphate and the aqueous phase separated and further extracted with Diethyl ether (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark orange viscous oil. The resultant oil was subjected to flash column chromatography on silica, eluting with 30% diethyl ether/hexanes to give the iodo-pyrrolidine **[229]** as a white crystalline solid (40.8 g, 82%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 4.32-4.21 (1H, dt, J 7.7 and 40.4 Hz, 2-H), 4.12-4.02 (2H, m, 3-H, 5-H$_a$), 3.75 (3H, s, CO$_2$CH$_3$), 3.66 (1H, m, 5-H$_b$), 2.86 (1H, m, 3- H$_a$), 2.34 (1H, m, 3- H$_b$), 1.46 and 1.41 (9H, 2 x s, C(CH$_3$)$_3$), δC (125 MHz, CDCl$_3$) (Doubling of peaks as a result of rotamers) 172.03 (CO$_2$CH$_3$), 154.06 (N-C=O), 80.69 (C(CH$_3$)$_3$), 59.14 and 58.56 (C-2), 56.98 and 56.59 (C-5), 52.36 and 52.17 (OCH$_3$), 42.84 and 41.87 (C-3), 28.31 and 28.18 (C(CH$_3$)$_3$), 12.68 and 11.90 (C-4) IR. 2978.84, 1732.92, 1686.18, 1394.29, 1152.04. cm^{-1}; HRMS (ESI) C$_{11}$H$_{19}$INO$_4$ [M+H] *m/z* calcd 356.0353. found 356.0352. Mp 63°C. [α]$_D^{22}$ = -23.7. (C 1.0 CHCH$_3$) TLC, (50% Et$_2$O/Hexanes) Rf = 3.2. Spectroscopic data identical to literature values.[124]

(*S*)-*tert*-butyl-2-methyl-1*H*-pyrrole-1,2-(*2H,5H*)-dicarboxylate [231]
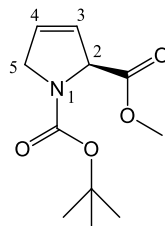
To a stirred solution of the iodo-methyl ester **[229]** (11.58g, 33 mmol) in toluene (150 mL) was added 1,8-diazabicyclo-[5.4.0]-undec-7-ene (5.36 mL, 36 mmol). The reaction mixture was heated to 85°C for 24 hours. The reaction mixture was filtered to remove the undesired precipitate and the filtrate was concentrated under reduced pressure to give a viscous orange oil as the crude product. The resultant oil was subjected to flash column chromatography on silica, eluting with 5% ethyl acetate/hexanes to give a mixture of stereoisomers as a clear orange oil for the desired product and a clear yellow/green oil as the undesired product in an 8:1 ratio in favour of **[231]**.

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 5.98-5.91 (1H, m, 4-H), 5.74-5.68 (1H, m, 3-H), 5.02-4.93 (1H, m, 2-H), 4.28-4.16 (2H, m, 5-H), 3.72,3.71 (3H, 2 x s, CO$_2$CH$_3$), 1.46 and 1.41 (9H, 2 x s, C(CH$_3$)$_3$), δC (125 MHz, CDCl$_3$) (Doubling of peaks as a result of rotamers) 171.03 and 170.71 (CO$_2$CH$_3$), 153.82 and 153.31 (N-C=O), 129.34 and 129.31 (C-4) 124.79 and 124.62 (C-3) 80.13 and 80.09 (C(CH$_3$)$_3$), 66.53 and 66.17 (C-2), 53.46 and 53.22 (C-5), 52.21 and 52.08 (OCH$_3$), 28.37 and 28.24 (C(CH$_3$)$_3$). IR. 2975, 1753, 1701, 1392, 1365, 1253, 1171, 1123. cm^{-1}; HRMS (ESI) calcd C$_{11}$H$_{17}$NO$_4$Na [M+Na] *m/z* 250.1055. found 250.1050. Mp 63°C. [α]$_D^{26.8}$ = -67.024. (C 1.15 MeOH). TLC, (25% EtOAc/Hexanes) Rf = 0.29. Spectroscopic data identical to literature values.[124]

(*S*)-*tert*-butyl-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate [228]
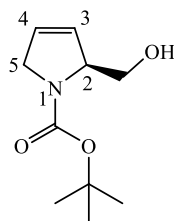
To a stirred solution of (*S*)-*tert*-butyl-2-methyl-1*H*-pyrrole-1,2-(*2H,5H*)-dicarboxylate **[231]** (9.4 g, 41 mmol) in anhydrous tetrahydrofuran (77 mL) and anhydrous methanol (39 mL) at 0°C was added portion wise sodium borohydride (4.7 g, 124 mmol). The reaction mixture was stirred at 0°C for 1 hour, warmed to room temperature and stirred for a further 24 hours. The solution was cooled to 0°C and washed with a saturated solution of ammonium chloride (115 mL). The organic portion was removed under reduced pressure and the remaining aqueous phase was filtered through celite and washed with ethyl acetate (2 x 120 mL). The phases were separated and the aqueous portion was further washed with ethyl acetate (3 x 200 mL). the combined organic fractions were dried over magnesium sulfate and concentrated under reduced pressure to reveal a yellow/orange oil residue (7.1 g). The resulting residue was subjected to flash column chromatography on silica, eluting with 60% diethyl ether/hexane to give **[228]** as a pale yellow oil (7.2 g, 67%).

δH (500 MHz, CDCl3) (Doubling and broad peaks as a result of rotamers) 5.83 (1H, br s, 4-H), 5.64 (1H, br s, 3-H), 4.72 (1H, br s, 2-H), 4.20 (1H, br m, *J* 15.1 Hz, 5-H), 4.11-4.06 (1H, m, 5-H), 3.78 (1H, dd, *J* 2.3 and 11.4 Hz, C$\underline{H}_2$OH), 3.59 (1H, m, C$\underline{H}_2$OH), 1.49 (9H, s, C(CH$_3$)$_3$). δC (125 MHz, CDCl$_3$) (Doubling of peaks as a result of rotamers) 156.4 (N-C=O), 126.8 (C-3), 126.8 (C-4), 80.4 ($\underline{C}$(CH$_3$)$_3$), 67.4 and 67.2 (C-2), 67.0 (C-5), 54.1 ($\underline{CH}_2$OH), 28. 4 (C($\underline{CH}_3$)$_3$). IR. 3416, 2974, 2930, 2867, 1696, 1672, 1397, 1365. cm^{-1}; HRMS

(ESI) m/z calcd $C_{10}H_{17}NO_3Na$ [M+Na] 222.1101, found 222.1092. $[\alpha]_D^{26.9}$ = -342.97. (C 0.85 MeOH). TLC, (25% EtOAc/Hexanes) Rf = 0.20. Spectroscopic data identical to literature values.[22,31]

(*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-3-one [221]
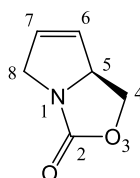
To a stirred solution of (*S*)-*tert*-butyl-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **[228]** (4.9 g, 24 mmol) in dichloromethane (50 mL) at 0°C was added (diethylamino) sulfur trifluoride (4.23 mL, 32 mmol) in dichloromethane (25 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with sodium bicarbonate (100 mL) and the phases separated. The aqueous phase was further extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to reveal an orange/brown oil residue. The resulting residue was subjected to flash column chromatography on silica, eluting with 40% ethyl acetate/hexane to give **[221]** as a pale yellow/orange oil (1.8 g, 59%).

δH (500 MHz, CDCl$_3$) 6.00-5.99 (1H, m, 7-H), 5.87-5.86 (1H, m, 6-H), 4.68 (1H, m, 5-H), 4.56 (1H, dd app. t, *J* 8.7 Hz, 4-H), 4.34-4.31 (1H, m app d, *J* 15.5 Hz, 8-H), 4.19 (1H, dd, *J* 5.1 and 8.7, 4-H), 3.78-3.75 (1H, m app d, *J* 15.5 Hz,, 8-H). δC (75 MHz, CDCl$_3$) 163.25 (C-2), 130.79 (C-7), 129.03 (C-6), 68.71 (C-4), 64.65 (C-5), 54.79 (C-8). IR. 2920, 2878, 1738, 1384, cm^{-1}; HRMS (ESI) m/z calcd $C_6H_7NO_2Na$ [M+Na] 148.0369, found 148.0370. TLC,

(60% EtOAc/Hexanes) Rf = 0.24. Spectroscopic data identical to literature values.[22,31]

3.3. Synthesis of anisomycin [274]

(1a*S*,1b*R*,5a*R*)-Tetrahydro-1,3-dioxa-4a-aza-cyclopropa[α]pentalen-4-one [234]
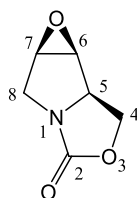
(1a*R*,1b*S*,5a*R*)-Tetrahydro-1,3-dioxa-4a-aza-cyclopropa[α]pentalen-4-one [236]
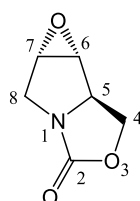
To a vigorously stirred suspension of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-3-one **[221]** (717 mg, 5.7 mmol), ethyl acetate (38 mL), water (28 mL), sodium bicarbonate (2.41 g 29mmol) and acetone (4.21 mL) at room temperature was added Oxone® (4.23 g, 6.9 mmol) in water (38 mL) dropwise over 2 hours. The reaction mixture was left to stir for 1 hour before being quenched with saturated sodium chloride (50 mL). The phases were separated and the aqueous phase was further extracted with ethyl acetate (4 x 60 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluting with 80/20% ethyl acetate/ hexane to give **[234]** as a white solid (661 mg, 81.6%).

δH (500 MHz, CDCl$_3$) 4.53 (1H, dd, app. t, J 8.3 Hz, 4-H), 4.47 (1H, dd, J 9.0 and 3.95 Hz, 4-H), 3.97 (1H, dd, J 8.4 and 4.0 Hz, 5-H), 3.95 (1H, d, J 13.4 Hz, 8-H), 3.70 (1H, d, J 2.8, 7-H), 3.64 (1H, d, J 2.8, 6-H), 3.14 (1H, d, J 13.3 Hz, 8-H). δC (125 MHz, CDCl$_3$) 162.8 (C-2), 64.5 (C-4), 58.2 (C-5), 55.5 (C-7), 55.3 (C-6), 48.3 (C-8),. IR. 3680.93, 2973.14, 2865.69, 1733.00, 1410.81, cm^{-1}; HRMS (ESI) m/z calcd C$_6$H$_7$NO$_3$Na [M+Na] 164.0318, found 164.0314. $[\alpha]_D^{23}$ = -8.9. (C 1.90 CH$_2$Cl$_2$). Mp 59-63°C. TLC, (100% EtOAc) Rf = 0.36.

(1aR,1bS,5aR)-Tetrahydro-1,3-dioxa-4a-aza-cyclopropa[α]pentalen-4-one [236]

δH (500 MHz, CDCl$_3$) 4.57 (1H, dd, app. t, J 8.3 Hz, 4-H), 4.23 (1H, dd, app. t, J 7.4 Hz, 4-H), 4.19 (1H, dd, app. t, J 8.1 Hz, 5-H), 3.97 (1H, dd, app. t, J 2.6 Hz, 7-H), 3.89 (1H, dd, J 13.2 and 2.6 Hz, 8-H), 3.71 (1H, d, J 2.74 Hz, 6-H), 3.35 (1H, d, J 13.1 Hz, 8-H). δC (125 MHz, CDCl$_3$) 148.4 (C-2), 64.7 (C-4), 61.54 (C-6), 61.0 (C-7), 60.0 (C-5), 50.1 (C-8). IR. 2949, 1735, 1405, 1354, 1304, 1251, 1202, 1166, 1071. cm^{-1}; HRMS (ESI) m/z calcd C$_6$H$_7$NO$_3$Na [M+Na] 164.0318, found 164.0319. $[\alpha]_D^{25.4}$ = +13.273. (C 0.6 MeOH). TLC, (100% EtOAc) Rf = 0.36.

(6S,7S,7aR)-6-benzyloxy)-7-hydroxy-tetrahydropyrrol[1,2-c]-oxazol-3(1H)-one [240]
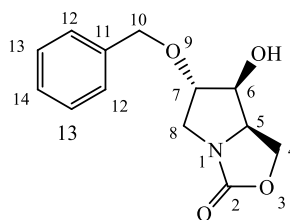
(6S,7S,7aR)-7-Benzyloxy)-6-hydroxy-tetrahydropyrrol[1,2-c]-oxazol-3(1H)-one [241]
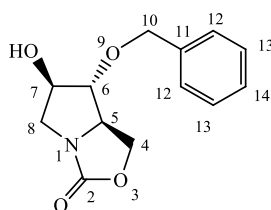
To a stirred solution of (1aS,1bR,5aR)-Tetrahydro-1,3-dioxa-4a-aza-cyclopropa[α]pentalen-4-one **[234]** (100 mg, 7 mmol) in dry benzyl alcohol (2.5 mL, 237mmol) at 0°C was added (diethyloxonio)trifluoroborate (0.89 mL, 7 mmol) dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with sodium bicarbonate (50 mL) and the phases separated. The aqueous phase was further extracted with diethyl ether (4 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting crude product was subjected to flash column chromatography on silica, eluting with 20% ethyl acetate/hexane and increasing to 40% ethyl acetate/hexane to give **[240]** and **[241]** as a clear needle type crystalline solid (5.23 g, 71%) in an inseparable mixture of regioisomers in an (8:1) ratio in favour of **[240]**.

δH (500 MHz, CDCl$_3$) 7.38 (3H, m, 13-H, 14-H,) 7.36 (2H, m, 12-H,) 4.56 (2H, m, 10-H) 4.52 - 4.46 (2H, m, 4-H), 4.14 (1H, m, 6-H), 4.12 (1H, m, 5-H), 4.11 (1H, m, 7-H), 3.90 (1H, dd, J 12.6 and 5.3 Hz, 8-H), 3.22 (1H, J 12.3 Hz, 8-H), δC (125 MHz, CDCl$_3$) 162.58 (C-2), 137.55 (C-11), 128.62 (C-14), 128.54 (C-13), 127.63 (C-12), 84.85 (C-7), 73.14 (C-5), 62.72 (C-4), 62.12 (C-6), 50.92 (C-8). TLC, (EtOAc) Rf = 0.48. IR. 3377.72, 2960.93, 1714.96, 1399.60, 1255.73 cm^{-1}; HRMS (ESI) m/z calcd C$_{13}$H$_{16}$NO$_4$ [M+H] 250.1074,

found 250.1070. HRMS (ESI) *m/z* calcd $C_{13}H_{15}NO_4Na$ [M+Na] 272.0893, found 272.0892. $[\alpha]_D^{23}$ = -10.249. (C 0.1 CHCl$_3$) M.P = 148.8 – 149.4°C.

(6*S*,7*S*,7a*R*)-7-Benzyloxy)-6-hydroxy-tetrahydropyrrol[1,2-c]-oxazol-3(1*H*)-one [241]

$^{\delta}$H (500 MHz, CDCl$_3$) 7.33 (1H, m, 14-H,) 7.31 (2H, m, 13-H,) 7.30 (2H, m, 12-H,) 4.66 (2H, m, 10-H) 4.51 (1H, m, 4-H), 4.54 (1H, m, 7-H), 4.19 (1H, m, 4-H), 3.91 (1H, m, 5-H), 3.77 (1H, s, 6-H), 3.73 (1H, m, 8-H), 3.37 (1H, m, 8-H), $^{\delta}$C (125 MHz, CDCl$_3$) 163.61 (C-2), 133.74 (C-11), 128.16 (C-14), 128.00 (C-13), 127.78 (C-12), 88.57 (C-6), 75.79 (C-7), 72.47 (C-10), 67.71 (C-4), 63.99 (C-5), 54.01 (C-8). TLC, (EtOAc) Rf = 0.48. IR. 3377.72, 2960.93, 1714.96, 1399.60, 1255.73 cm^{-1} HRMS (ESI) *m/z* calcd $C_{13}H_{16}NO_4$ [M+H] 250.1074, found 250.1070. HRMS (ESI) *m/z* calcd $C_{13}H_{15}NO_4Na$ [M+Na] 272.0893, found 272.0892. M.P = 148.8 – 149.4°C.

(2*R*,3*S*,4*S*)-4-(benzyloxy)-2-(hydroxymethyl)-pyrrolidin-3-ol [242]
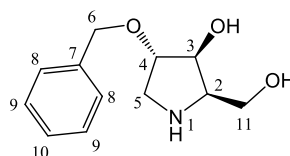
To a stirred solution of (6*S*,7*S*,7a*R*)-6-Benzyloxy)-7-hydroxy-tetrahydropyrrol-[1,2-c]-oxazol-3(1*H*)-one **[240]** (1 g, 4 mmol) in ethanol (50 mL) was added lithium hydroxide (0.5 g, 20 mmol) and the reaction mixture was subject to reflux for 5days. The solution was filtered through celite to remove the undesired precipitate and washed with cold dichloromethane (4 x 120 mL). The solution was concentrated under reduced pressure to give a yellow viscous oil. The oil was taken up in ethyl acetate and heated to 80°C and left to cool to give a white crystalline solid **[242]** (0.85 g, 95%)

δH (500 MHz, CD$_3$OD) 7.34 (1H, m, 8-H), 7.33 (2H, m, 9-H), 7.27 (2H, m, 10-H), 4.81 (2H, br s,, OH), 4.57 (2H, dd, J 11.65 and 17.52 Hz, 6-H), 4.24 (1H, d, J 3.13 Hz, 3-H), 3.93 (1H, m, 4-H), 3.78 (2H, ddd, J 38.61, 11.19 and 6.05 Hz, 11-H), 3.33 (1H, m, 5-H$_a$), 3.27 (1H, m, 2-H), 2.90 (1H, m, 5-H$_b$), δC (125 MHz, CD$_3$OD) 138.14 (C-7), 127.95 (C-8), 127.42 (C-9), 127.27 (C-10), 85.01 (C-4), 74.52 (C-3), 71.02 (C-6), 62.22 (C-2), 59.72 (C-11), 49.43 (C-5). IR. 3288, 2900, 1457, 1443, 1301, 1063. cm^{-1} HRMS (ESI) m/z calcd C$_{12}$H$_{18}$NO$_3$ [M+H] 224.1287, found 224.1276. [α]$_D^{27.4}$ = -21.330. (C 0.25 MeOH). TLC, (20/80% MeOH/CH$_2$Cl$_2$) Rf = 0.24. M.P. = 114.4-115.7°C.

(2*R*,3*S*,4*S*)-benzyl-4-(benzyloxy)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-carboxylate [243]
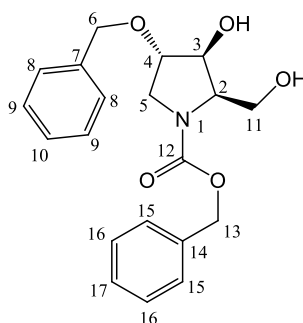
To a stirred solution of (2*R*,3*S*,4*S*)-4-(benzyloxy)-2-(hydroxymethyl)-pyrrolidin-3-ol **[242]** (0.7 g, 3 mmol) in acetone (0.45 mL) and water (6 mL) at 0°C was added benzyl chloroformate (25 mL) and sodium carbonate (0.19 g, 2 mmol). The reaction mixture was allowed to warm to room temperature and left for 2 hours. The organic solvent was removed under reduced pressure and the residue taken up in ethyl acetate and washed in 10% citric acid, aqueous sodium bicarbonate and aqueous sodium chloride successively. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a clear dark orange/brown viscous oil. The resulting crude product was subjected to flash column chromatography on silica, eluting

with 50% ethyl acetate/hexane to give **[243]** as a clear viscous pale yellow oil (1.01 g, 90%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.34 (2H, m, 8-H), 7.33 (2H, m, 9-H), 7.32 (2H, m, 15-H), 7.30 (2H, m, 16-H), 7.29 (1H, m, 10-H), 7.28 (1H, m, 17-H), 5.12 (2H, m, 6-H), 4.55 (2H, m, 13-H), 4.37 (1H, m, 2-H), 3.94 (1H, m, 3-H), 3.92 (2H, m, 11-H), 3.68 (1H, m, 4-H), 3.68-3.55 (2H, m, 5-H). δH (500 MHz, Tol-d$_8$ 90°C) 7.27 (2H, m, 8-H), 7.25 (2H, m, 9-H), 7.20 (2H, m, 15-H), 7.19 (2H, m, 16-H), 7.17 (1H, m, 10-H), 7.15 (1H, m, 17-H), 5.10 (2H, m, 6-H), 4.35 (2H, m, 13-H), 4.11 (1H, m, 2-H), 3.97 (2H, m, 11-H), 3.85 (1H, m, 3-H), 3.76 (1H, m, 4-H), 3.60 (2H, m, 5-H). δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 156.26 (C-12), 137.69 (C-13), 136.34 (C-7), 128.53 (C-8), 128.49 (C-9), 128.09 (C-15), 127.88 (C-16), 127.81 (C-10), 127.61 (C-17), 81.38 (C-3), 75.64 (C-2), 71.59 (C-13), 67.24 (C-6), 61.45 (C-11), 55.19 (C-4), 50.15 (C-5). IR. 3377.70, 2941.83, 1673.03, 1497.46, 1453.78, 1416.37, 1354.61, 1204.15/ cm^{-1}; HRMS (ESI) m/z calcd C$_{20}$H$_{23}$NO$_5$Na [M+Na] 380.1468, found 380.1471. $[\alpha]_D^{26.1}$ = -44.629. (C 1.35 MeOH). TLC, (50% EtOAc/Hexanes) Rf = 0.17.

benzyl-7-(benzyloxy)-2,2-dioxohexahydro-1,3,2λ^6,-5-[1,3,2λ^6]-dioxathiino-[5,4-b]-pyrrole-5-carboxylate [249]
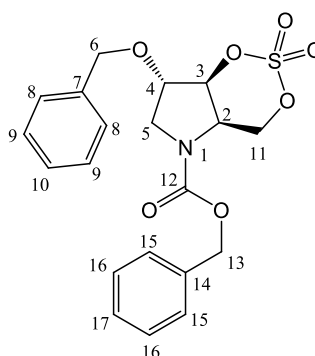
To a stirred solution of (2*R*,3*S*,4*S*)-benzyl-4-(benzyloxy)-3-hydroxy-2-(hydroxymethyl)pyrrolidin-carboxylate **[243]** (0.3 g, 0.84 mmol) in carbon tetrachloride (20 mL) at 0°C was added dropwise thionyl chloride (0.095 mL). The reaction mixture was refluxed for 30 minutes and allowed to cool to room temperature before re-cooling to 0°C. To the reaction mixture was further added acetonitrile (20 mL), ruthenium (III) chloride (0.0002 g, 0.8 mmol), sodium *meta* periodite (0.27 g, 1.26 mmol) and water (25 mL). The reaction mixture was allowed to warm to room temperature and left to stir for 1 hour. The reaction mixture was taken up in diethyl ether (200 mL) and the phases separated. The organic phase was washed successively in aqueous sodium bicarbonate and aqueous sodium chloride and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark brown viscous oil. The resulting crude product was subjected to flash column chromatography on silica, eluting with 50% diethyl ether/hexane to give **[249]** as a viscous orange oil (0.27 g, 77%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.36 (4H, m, 8-H, 15-H), 7.35 (4H, m, 9-H, 16-H), 7.26 (2H, m, 10-H, 17-H), 5.51 (1H, d, *J* 12.72 Hz, 11-H), 5.26 (1H, m, 3-H), 5.16 (2H, s, 13-H), 4.94 (1H, d, *J* 12.37 Hz, 11-H), 4.57 (2H, s, 6-H), 4.06 (1H, m, 4-H), 4.03 (1H, m, 2-H), 3.85 (1H, d, *J* 12.45 Hz, 5b-H), 3.71 (1H, dd, *J* 12.31 and 3.68 Hz, 5a-H). δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 155.62 (C-12), 136.36 (C-14), 135.93 (C-7), 128.72 (C-15), 128.59 (C-8), 128.44 (C-16), 128.30 (C-9), 127.96 (C-17), 127.71 (C-10), 85.99 (C-3), 77.74 (C-4), 71.99 (C-11), 71.87 (C-6), 67.58 (C-13), 52.28 (C-2), 51.17 (C-5). IR. 3034.21, 2954.12, 1973.94, 1699.63, 1497.75, 1455.41, 1401.52, 1352.43, 1318.65, 1304.27, 1198.51. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{21}$H$_{23}$NSO$_7$ [M+H] 442.0931, found 442.940. TLC, (50% Et$_2$O/Hexanes) Rf = 0.27.

(6*S*,7*S*,7a*R*)-6-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-tetrahydro-pyrrolo-[1,2-c]-oxazol-3(1*H*)-one [252]
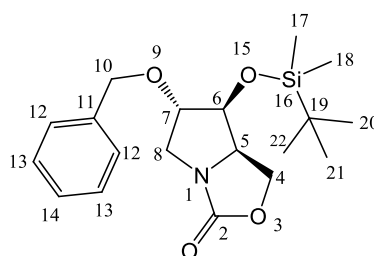
To a stirred solution of (6*S*,7*S*,7a*R*)-6-benzyloxy)-7-hydroxy-tetrahydropyrrol-[1,2-c]-oxazol-3(1*H*)-one **[240]** (1 g, 4 mmol) in dichloromethane (20 mL) at 0°C was added *tert*-butyldimethylsilyl trifluoromethane (1.4 mL, 6 mmol) and 2,6-lutidine (0.93 mL, 8 mmol). The reaction mixture was left for 2 hours before being quenched with aqueous sodium bicarbonate followed by aqueous sodium chloride. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a clear viscous pale yellow oil. The resulting crude oil was subjected to flash column chromatography on silica, eluting with 25% ethyl acetate/hexane to give **[252]** as a fine white powder (1.15 g, 79%).

δH (500 MHz, CDCl$_3$) 7.37 (2H, m, 12-H), 7.33 (2H, m, 13-H), 7.30 (1H, m, 14-H), 4.60 (1H, d, *J* 11.56 Hz, 10-H$_a$), 4.51 (1H, d, *J* 11.56 Hz, 10-H$_b$), 4.45 (1H, app t, *J* 8.33 Hz, 4-H$_a$), 4.30 (1H, dd, *J* 8.67 and 3.08 Hz, 4-H$_b$), 4.12 (1H, dt, *J* 8.26 and 2.73 Hz, 5-H), 4.01 (1H, d, *J* 1.90 Hz, 6-H), 3.96 (1H, d, *J* 5.28 Hz, 7-H), 3.82 (1H, dd, *J* 12.23 and 5.28 Hz, 8-H$_a$), 3.24 (1H, d, *J* 12.57 Hz, 8-H$_b$) 0.86(9H, s, 20-H, 21-H, 22-H), 0.08 (3H, s, 17-H), 0.04 (3H, s, 18-H). δC (125 MHz, CDCl$_3$) 162.39 (N-C=O C-2), 137.29 (C-11), 128.60 (C-12), 128.05 (C-13), 127.49 (C-14), 84.48 (C-7), 74.05 (C-6), 71.82 (C-10), 62.55 (C-4), 62.37 (C-5), 51.10 (C-8), 25.48 (C-16), 25.40 (C-20,21,22), -4.51 (C-17), -5.07 (C-18). IR. 2957, 2928, 2858, 1744, 1394, 1244, 1224, 1188,. cm^{-1};

TLC, (25% EtOAc/Hexanes) Rf = 0.52. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{19}$H$_{29}$NSiO$_4$Na [M+Na] 386.1758, found 386.1768. [α]$_D^{27.1}$ = -18.397. (C 2.3 CH$_2$Cl$_2$). TLC, (25% Et$_2$O/Hexanes) Rf = 0.52. M.P. = 51.2-52.3°C.

(6*S*,7*S*,7a*R*)-6-(benzyloxy)-7-(tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-pyrrolo[1,2-c]-oxazol-3(1*H*)-one [254]
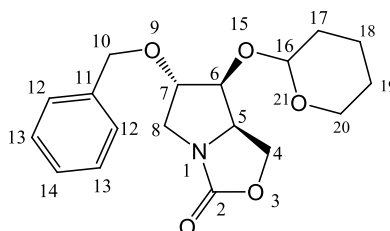
To a stirred solution of (6*S*,7*S*,7a*R*)-6-Benzyloxy)-7-hydroxy-tetrahydropyrrol-[1,2-c]-oxazol-3(1*H*)-one **[240]** (0.7 g, 2.8 mmol) in dichloromethane (40 mL) at room temperature was added freshly prepared pyridinium *p*-toluenesulfonate (0.045 g, 0.18 mmol) and 3,4-dihydro-2*H*-pyran (0.24 mL, 2.7 mmol). The reaction mixture was left for 6 hours before being diluted with diethyl ether and quenched with aqueous sodium bicarbonate followed by aqueous sodium chloride. The phases were separated and combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a clear viscous oil. The resulting crude oil was subjected to flash column chromatography on silica, eluting with 40% ethyl acetate/hexane to give **[254]** as a fine white crystalline solid (0.81 g, 87%).

^{δ}H (500 MHz, CDCl$_3$) 7.39 (2H, m, 12-H), 7.37 (2H, m, 13-H), 7.32 (1H, m, 14-H), 4.66 (1H, m, 16-H), 4.60 (1H, m, 4-H$_a$), 4.57 (2H, s, 10-H), 4.46 (1H, app t, *J* 8.53 Hz, 4-H$_b$), 4.22 (1H, dt, *J* 8.49 and 3.39 Hz, 6-H), 4.17 (1H, d, *J* 3.51 Hz, 5-H), 4.10 (1H, d, *J* 5.64 Hz, 7-H), 3.87 (1H, dd, *J* 12.62 and 5.52 Hz, 20-H$_a$), 3.81 (1H, m, 8-H$_a$), 3.54 (1H, m, 8-H$_b$), 3.25 (1H, d, *J* 12.75, 20-H$_b$), 1.79 (2H, m, 17-H), 1.67 (2H, m, 19-H), 1.53 (2H, m, 18-H). ^{δ}C (125 MHz,

CDCl$_3$) 162.04 (N-C=O C-2), 137.25 (C-11), 128.56 (C-12), 128.05 (C-13), 127.61 (C-14), 96.73 (C-16), 81.72 (C-7), 76.30 (C-6), 71.80 (C-10), 63.17 (C-8), 62.81 (C-4), 61.29 (C-5), 51.15 (C-20), 30.64 (C-17), 25.15 (C-19) 19.40 (C-18). IR. 2975, 2950, 2878, 1736, 1388. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{18}$H$_{24}$NO$_5$ [M+H] 334.1649, found 334.1657. TLC, (50% EtOAc/Hexanes) Rf = 0.46. M.P. = 96.4-97.5°C.

((2*R*,3*S*,4*S*)-4-(benzyloxy)-3-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidin-2-yl)methanol [257]
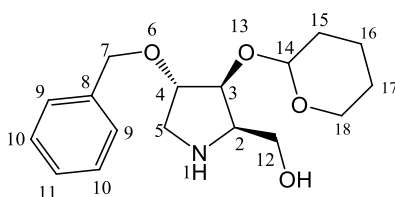
To a stirred solution of (6*S*,7*S*,7a*R*)-6-(benzyloxy)-7-(tetrahydro-2*H*-pyran-2-yloxy)-tetrahydro-pyrrolo[1,2-c]-oxazol-3(1*H*)-one **[254]** (8 g, 24 mmol) in ethanol (28 mL) was added lithium hydroxide (2.9 g, 120 mmol) and the reaction mixture was subject to reflux for 5days. The solution was filtered through celite to remove the undesired precipitate and washed with cold dichloromethane (4 x 120 mL). The solution was concentrated under reduced pressure to give a yellow viscous oil. The resultant crude oil was subjected to flash column chromatography on silica, eluting with 10% methanol /dichloromethane to give **[257]** as a clear viscous oil (6.3 g, 86%)

$^{\delta}$H (500 MHz, CDCl$_3$) 7.34 (1H, m, 8-H), 7.34 (2H, m, 9-H), 7.30 (2H, m, 10-H), 4.82 (2H, br s, NH OH), 4.62 (1H, m, 14-H), 4.58 (2H, m, 12-H), 4.23 (2H, s, 7-H), 3.96 (1H, m, 3-H), 3.81 (1H, m, 18-H$_a$), 3.79 (1H, m, 2-H), 3.76 (1H, m, 4-H), 3.50 (1H, m, 5-H$_a$), 3.42 (1H, dd, *J* 12.74 and 4.47 Hz, 5-H$_b$), 3.24 (1H, d, *J* 12.44 Hz, 18-H$_b$), 1.79 (1H, m, 15-H$_a$) 1.70 (1H, m, 17-H$_a$) 1.53 (4H,

m, 16-H, 15-H$_b$,17-H$_b$). δC (125 MHz, CDCl$_3$) 137.61 (C-8), 128.41 (C-9), 127.84 (C-10), 127.81 (C-11), 100.91 (C-14), 82.48 (C-4), 81.49 (C-3), 71.47 (C-7), 63.20 (C-5), 62.52 (C-12) 59.57 (C-2), 49.10 (C-18), 30.63 (C-15) 25.14 (C-17), 19.59 (C-16). IR. 3229 (Br), 1540, 1418, 1308, 1261, 1202, 1111. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{17}$H$_{26}$NO$_4$ [M+H] 308.1856, found 308.1852. TLC, (10% MeOH/CH$_2$Cl$_2$) Rf = 0.33.

(2*R*,3*S*,4*S*)-benzyl-4-(benzyloxy)-2-(hydroxymethyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-1-carboxylate [261]
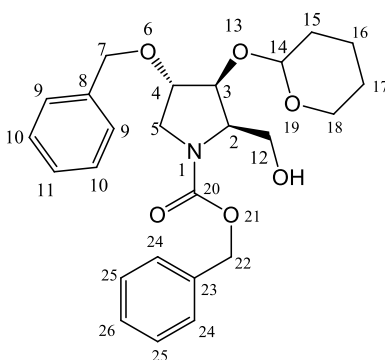
To a stirred solution of ((2*R*,3*S*,4*S*)-4-(benzyloxy)-3-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidin-2-yl)methanol **[257]** (10 g, 33 mmol) in acetone (15 mL) and water (150 mL) at 0°C was added benzyl chloroformate (5.1 mL) and sodium carbonate (2.07 g, 20 mmol). The reaction mixture was allowed to warm to room temperature and left for 2 hours. The organic solvent was removed under reduced pressure and the residue taken up in ethyl acetate and washed in 10% citric acid, aqueous sodium bicarbonate and aqueous sodium chloride successively. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark orange viscous oil. The resulting crude product was subjected to flash column chromatography on silica, eluting with 25% ethyl acetate/hexane to give **[261]** as a clear viscous pale yellow oil (12.7 g, 88%).

$^\delta$H (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.36 (4H, m, 9-H, 24-H), 7.35 (4H, m, 10-H, 25-H), 7.30 (2H, m, 11-H, 26-H), 5.15 (2H, m, 22-H), 4.60 (1H, m, 14-H), 4.55 (2H, s, 7-H), 4.40 (1H, s, 3-H), 4.13 (1H, m, 4-H), 3.96 (1H, m, 2-H), 3.94 (2H, m, 5-H), 3.90 (1H, m, 18-H$_a$), 3.61 (2H, m, 12-H), 3.52 (1H, m, 18-H$_b$), 3.12 (2H, br s, NH, OH), 1.78 (1H, m, 15-H$_a$), 1.72 (1H, m, 16-H$_a$), 1.53 (2H, m, 17-H), 1.51 (1H, m, 15-H$_b$), 1.51 (1H, m, 16-H$_b$). $^\delta$C (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 156.16 (C-20), 137.59 (C-23), 136.51 (C-8), 128.49 (C-24), 128.47 (C-9), 128.00 (C-25), 127.89 (C-10), 127.88 (C-26), 127.52 (C-11), 98.62 (C-14), 79.37 (C-2), 78.85 (C-3), 71.44 (C-7), 66.15 (C-22), 63.77 (C-18) 61.85 (C-4), 61.79 (C-5), 50.11 (C-12), 30.85 (C-15), 25.06 (C-17), 20.02 (C-15). IR. 2939, 1691, 1415, 1351, 1201, 1074, 1033. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{25}$H$_{31}$NO$_6$Na [M+Na] 464.2044, found 464.2049. TLC, (50% EtOAc/Hexanes) Rf = 0.21.

(2R,3S,4S)-benzyl 4-(benzyloxy)-2-(hydroxy(4-methoxyphenyl)methyl)-3-(tetrahydro-2H-pyran-2-yloxy)pyrrolidine-1-carboxylate [267]
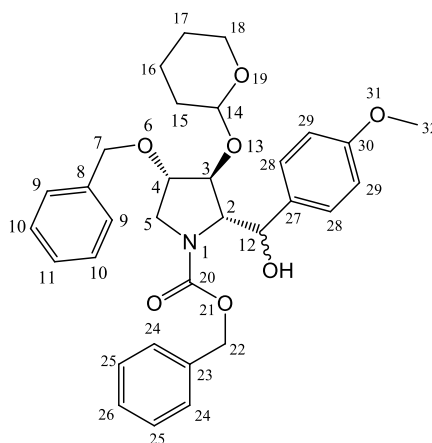
To a stirred solution of trifluoroacetic anhydride (0.5 mL, 3.5 mmol) in dichloromethane (5 mL) at -78°C was added dropwise over 10 minutes dimethyl sulfoxide (0.33 mL, 4.7 mmol) in dichloromethane (5 mL). The

reaction mixture was left to stir for 30 minutes. A solution of (2*R*,3*S*,4*S*)-benzyl-4-(benzyloxy)-2-(hydroxymethyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)-pyrrolidine-1-carboxylate **[261]** (1 g, 2.3 mmol) in dichloromethane (10 mL) at -78°C was added dropwise over 15 minutes and the reaction mixture was left to stir at -78°C for 2 hours. A further solution of triethylamine (0.93 mL, 7 mmol) in dichloromethane (10 mL) was added dropwise over 15 minutes and the reaction mixture was left for a further 1 hour before being allowed to warm to room temperature over 2 hours. The reaction was quenched with aqueous sodium bicarbonate and washed with aqueous sodium chloride and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark brown oil. The resulting crude aldehyde product **[266]** (0.6 g) was carried forward to the next step without purification.

To a stirred solution of 4-iodoanisole (1.12, 5 mmol) in tetrahydrofuran (20 mL) at -78°C was added dropwise over 10 minutes 2.5M *n*butyllithium (3.62 mL, 6.03 mmol) in tetrahydrofuran. The crude aldehyde **[266]** (2.0 g, 5 mmol) in tetrahydrofuran (25 mL) was added dropwise over 20 minutes and the reaction mixture was allowed to warm to room temperature and left to stir for 1 hour. The reaction mixture was quenched with aqueous sodium bicarbonate and washed with aqueous sodium chloride and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a viscous orange oil. The crude oil was subjected to flash column chromatography on silica, eluting with 25% ethyl acetate/hexane to give **[267]** as a clear viscous pale yellow oil (1.1 g, 44%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.37-7.29 aromatic benzyl ether/carboxylate, (10H, m, 9-11-H and 24-26-H), 7.29 (2H, m, 28-H), 6.93 (2H, d, *J* 8.92, 29-H), 5.68 (1H, d, *J* 3.58,), 5.38 (1H, d, *J* 2.66,), 4.82 (1H, m,), 4.69 (1H, m,), 4.57 (3H, m,) 4.47 (1H, d, *J* 5.20,), 4.28

(1H, d, *J* 3.48,), 4.16 (1H, d, *J* 5.53,), 4.11 (1H, m,), 4.10 (1H, m,), 4.09 (1H, m,), 3.92 (CH$_2$, m,), 3.82 (3H, s, OMe), 3.89, 3.58 (CH$_2$, m,), 3.81, 3.54 (CH$_2$, m,), 3.28 (CH$_2$, m,), 1.51-1.87 Pyran (6H, m 15,16,17-H) δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 161.5, 159.9, 137.4, 137.1, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6 (C-28), 127.5, 114.2 (C-29), 100.8, 97.0, 83.4, 81.9, 80.0, 76.1, 75.8, 71.9, 71.7, 68.7, 68.6, 63.3, 62.8, 55.3 (C-32), 51.1, 50.9, 30.7 (C-15), 25.2 (C-17), 19.5 (C-16), 19.1. IR. 2936, 2849, 1690, 1512, 1412, 1350, 1246, 1200. cm^{-1}; TLC, (25% EtOAc/Hexanes) Rf = 0.23. HRMS (ESI) *m/z* calcd C$_{32}$H$_{37}$NO$_7$Na [M+Na] 570.2462, found 570.2474.

(2*S*,3*S*,4*S*)-4-(benzyloxy)-2-(4-methoxybenzyl)pyrrolidin-3-ol [268]
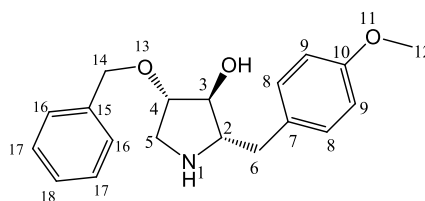
To a vigorously stirred solution of (2R,3S,4S)-benzyl-4-(benzyloxy)-2-(hydroxy(4-methoxyphenyl)methyl)-3-(tetrahydro-2H-pyran-2-yloxy)-pyrrol-idine-1-carboxylate **[267]** (1 g, 1.8 mmol) in trifluoroacetic acid (10 mL) at 0°C was added trimethyl silane (2.4 mL) dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature and left for 24 hours. The reaction mixture was taken up in ethyl acetate and washed with aqueous sodium bicarbonate and aqueous sodium chloride successively extracting with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark orange viscous oil. The resultant crude oil was subjected to flash column chromatography on silica, eluting with 10% methanol/dichloromethane to give **[268]** as a clear viscous yellow oil (0.47 g, 81%).

δH (500 MHz, CDCl$_3$) 7.32 (2H, m, 16-H), 7.29 (2H, m, 17-H), 7.26 (1H, m, 18-H), 7.16 (2H, d, *J* 8.44 Hz, 8-H), 6.80 (2H, d, *J* 8.44 Hz, 9-H), 4.51 (1H, s, 14-H), 4.12 (1H, m, 4-H), 4.11 (1H, m, 3-H), 3.82 (1H, m, 2-H), 3.73 (3H, m, 12-H), 3.61 (1H, m, 5a-H), 3.17 (1H, m, 5b-H), 3.10 (1H, m, 6a-H), 2.97 (1H, dd, *J* 13.94 and 7.26 Hz, 6b-H), δC (125 MHz, CDCl$_3$) 158.77 (C-10), 136.83 (C-15), 130.02 (C-8), 128.57 (C-16), 128.13 (C-17), 127.76 (C-7), 127.75 (C-18), 114.26 (C-9), 82.17 (C-4), 73.12 (C-3)), 71.82 (C-14), 64.33 (C-2), 55.21 (C-12), 49.21 (C-5), 30.88 (C-6). IR. 2953, 1668, 1513, 1443, 1248, 1177, 1132, 1030. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{19}$H$_{24}$NO$_3$ [M+H] 314.1751, found 314.1749. [α]$_D^{25.2}$ = -30.471. (C 0.2 MeOH). TLC, (10% MeOH/CH$_2$Cl$_2$) Rf = 0.37.

(2*S*,3*S*,4*S*)-benzyl4-(benzyloxy)-3-hydroxy-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate [269]
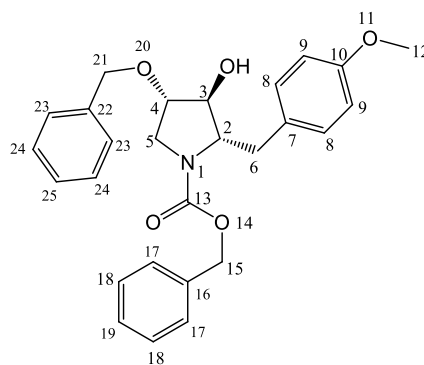
To a stirred solution of (2*S*,3*S*,4*S*)-4-(benzyloxy)-2-(4-methoxybenzyl)-pyrrolidin-3-ol **[268]** (0.7 g, 2.2 mmol) in acetone (10 mL) and water (2 mL) at -10°C was added benzyl chloroformate (0.34 mL, 2.4 mmol) and sodium carbonate (0.14 g, 1.3 mmol). The reaction mixture was allowed to warm to room temperature and left for 2 hours. The organic solvent was removed under reduced pressure and the residue taken up in ethyl acetate and washed in 10%

citric acid, aqueous sodium bicarbonate and aqueous sodium chloride successively. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a viscous yellow oil. The resulting crude product was subjected to flash column chromatography on silica, eluting with 25% ethyl acetate/hexane to give **[269]** as a clear viscous pale yellow oil (0.78 g, 88%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.37 (1H, m, 25-H), 7.37 (4H, m, 17-H, 23-H), 7.33 (4H, m, 18-H, 24-H), 7.25 (2H, m, 19-H, 25-H), 7.17 (2H, v br, 8-H), 6.79 (2H, m, 9-H), 5.17 (2H, m, 15-H), 4.46 (2H, m, H-21), 4.22 (1H, m, 4-H), 4.17 (1H, m, 3-H), 3.79 (3H, s, 12-H), 3.70 (1H, m, 2-H), 3.52 (2H, m, 5-H), 2.92 (2H, dd, J 13.20 and 8.61 Hz, 6-H), δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 174.6 (C-13), 158.1 (C-10), 152.0 (C-16), 137.6 (C-22), 130.5 (C-8), 129.2 (C-7), 128.4 (C-17), 128.4 (C-23), 127.9 (C-18), 127.8 (C-24), 127.6 (C-19), 127.6 (C-25), 113.8 (C-9), 80.8 (C-2), 74.9 (C-3), 71.6 (C-21), 66.8 (C-15) 61.2 (C-4), 48.9 (C-5), 55. 2 (C-12), 32.4 (C-6). IR. 2939, 1672, 1610, 1511, 1414, 1355, 1244, 1176, 1094. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{27}$H$_{29}$NO$_5$Na [M+Na] 470.1938, found 470.1949. $[\alpha]_D^{26.2}$ = -28.566. (C 0.4 MeOH). TLC, (25% EtOAc/Hexanes) Rf = 0.17.

(2*S*,3*S*,4*S*)-benzyl-3-acetoxy-4-(benzyloxy)-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate [273]
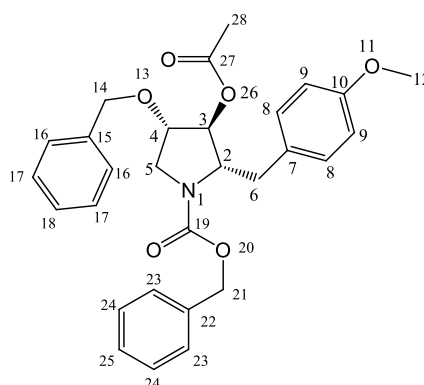
To a vigorously stirred solution of (2*S*,3*S*,4*S*)-benzyl4-(benzyloxy)-3-hydroxy-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate **[269]** (0.6 g, 1.3 mmol) in dichloromethane (10 mL) at 0°C was added pyridine (0.16 mL, 2.0 mmol) and acetic anhydride (0.14 mL, 1.5 mmol) dropwise over 10 minutes. The reaction mixture was allowed to warm to room temperature and left for 24 hours. The reaction mixture quenched with 10% citric acid and washed with aqueous sodium bicarbonate and aqueous sodium chloride successively extracting with dichloromethane. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a dark orange viscous oil. The resultant crude oil was subjected to flash column chromatography on silica, eluting with 25% ethyl acetate/hexanes to give **[273]** as a clear viscous pale orange oil (0.56 g, 84%).

δH (500 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 7.38 (2H, m, 23-H), 7.37 (2H, m, 16-H),7.31 (2H, m, 24-H), 7.30 (2H, m, 17-H), 7.25 (2H, m, 25-H, 18-H), 6.99 (2H, br s, 8-H), 6.77 (2H, br d, 9-H), 5.17 (2H, br s, 21-H), 5.07 (1H, dd ap t, *J* 4.82 Hz, 3-H), 4.51 (2H, m, 14-H), 4.43 (1H, ddd, *J* 3.79, 5.68 and 9.73 Hz, 4-H), 3.79 (3H, s, 12-H), 3.79 (1H, s, 2-H), 3.60 (1H, br s, 5a-H), 3.47 (1H, dd ap t, *J* 5.49 and 11.99 Hz, 5b-H), 2.79 (2H, dd, *J*

9.54 and 13.34 Hz, 6-H), 2.08 (1H, s, 28-H), δC (125 MHz, CDCl$_3$) (Doubling and broad peaks as a result of rotamers) 174.44 (C-19), 167.82 (C-27), 158.15 (C-10), 152.64 (C-22), 137 (C-15), 131.38 (C-7), 130.14 (C-8), 128.49 (C-23), 128.40 (C-16), 128.03 (C-24), 127.81 (C-17), 127.63 (C-18), 127.63 (C-25), 113.82 (C-9), 78.64 (C-2), 75.58 (C-3), 71.48 (C-14), 67.38 (C-21), 59.29 (C-4), 55.18 (C-12), 49.49 (C-5), 32.91 (C-6), 20.88 (C-28). IR. 2941, 1739, 1699, 1611, 1511, 1454, 1409, 1356, 1230, 1108, 1035. cm^{-1}; HRMS (ESI) *m/z* calcd C$_{29}$H$_{31}$NO$_6$Na [M+Na] 512.2049, found 512.2044. HRMS (ESI) *m/z* calcd C$_{29}$H$_{31}$NO$_6$K [M+K] 528.1783, found 528.1789. [α]$_D^{21}$ = -26.129. (C 1.9 MeOH). TLC, (25% EtOAc/Hexanes) Rf = 0.3.

(2*S*,3*S*,4*S*)-4-hydroxy-2-(4-methoxybenzyl)pyrrolidine-3-yl-acetate [274]
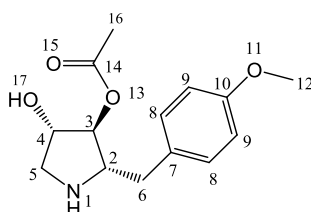
To a stirred solution of (2*S*,3*S*,4*S*)-benzyl-3-acetoxy-4-(benzyloxy)-2-(4-methoxybenzyl)-pyrrolidine-1-carboxylate **[273]** (0.3 g, 6 mmol) in ethanol (10 mL) at room temperature under a hydrogen atmosphere was added 10% palladium on carbon (0.073 g, 6 mmol). The reaction mixture was left to stir for 3 days before the solution was filtered through paper and washed with cold ethanol. The organic solvent was concentrated under reduced pressure to reveal a clear viscous pale yellow oil. The resulting crude oil was subjected to flash column chromatography on silica, eluting with 10% methanol/dichloromethane to give **[274]** as a fine white powder (0.15 g, 93%).

δH (500 MHz, CDCl$_3$) 7.08 (2H, d, *J* 8.69 Hz, 8-H), 6.81 (2H, d, *J* 8.69 Hz, 9-H), 5.30 (1H, d, *J* 3.54 Hz, 3-H), 4.31 (1H, d, *J* 4.89 Hz, 4-H), 4.12 (1H, ddd, *J*

15.54, 7.78 and 3.76, Hz, 2-H), 3.74 (3H, s, 12-H), 3.47 (1H, m, 5-H_a), 3.12 (1H, d, J 12.87, 5-H_b), 2.95 (1H, m, 5-H_a), 1.26 (3H, s, 16-H) δC (125 MHz, CDCl$_3$) 169.69 (C-14), 158.78 (C-10), 129.68 (C-8), 127.39 (C-7), 114.35 (C-9), 77.51 (C-3), 73.47 (C-4), 61.61 (C-2), 55.20 (C-12), 51.06 (C-5) 31.54 (C-6) 20.53 (C-16). IR. 3306.25, 2922.43, 1751.42, 1675.70, 1613.53, 1587.82, 1445.36, 1369.12, 1338.24, cm^{-1}; HRMS (ESI) m/z calcd C$_{14}$H$_{20}$NO$_4$ [M+H] 266.1387, found 266.1384 [α]$_D^{21}$ = -2.844. (C 1.0 MeOH). TLC, (20% MeOH/CH$_2$Cl$_2$) Rf = 0.15. M.P. = 178.7-179.5°C.

(2R,3S,4S)-4-hydroxy-2-(4-methoxybenzyl)pyrrolidin-3-yl acetate [1].
(-)-Anisomycin [1]
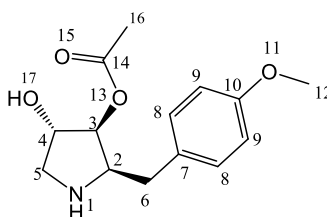
δH (500 MHz, CDCl$_3$) 7.12 (2H, d, J 8.41 Hz, 8-H), 6.84 (1H, d, J 8.31 Hz, 9-H), 4.72 (1H, d, J 5.09 Hz, 3-H), 4.19 (1H, m, 4-H), 3.79 (3H, s, 2-H), 3.74 (3H, s, 12-H), 3.51 (1H, m, 2-H), 3.43 (1H, dd, J 11.38 and 6.66 Hz, 5-H_a), 2.84 (1H, dd, J 13.78 and 6.14 Hz, 6-H_a), 2.79 (1H, m, 6-H_b), 2.74 (1H, m, 5-H_b), 2.15 (3H, s, 16-H) δC (125 MHz, CDCl$_3$) 171.57 (C-14), 158.19 (C-10), 131.03 (C-7), 129.69 (C-8), 114.01 (C-9), 82.45 (C-3), 77.94 (C-4), 61.11 (C-2), 55.24 (C-12), 52.44 (C-5), 34.60 (C-6), 21.02 (C-16).

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5. Appendices

Table 1. Crystal data and structure refinement for $C_{11}H_{18}INO_4$.

Identification code	sep109
Empirical formula	C11 H18 I N O4
Formula weight	355.16
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P 2_1$
Unit cell dimensions	a = 5.6271(2) Å $\quad\quad \alpha = 90°$.
	b = 9.1606(2) Å $\quad\quad \beta = 99.011(2)°$.
	c = 13.8330(6) Å $\quad\quad \gamma = 90°$.
Volume	704.26(4) Å^3
Z	2
Density (calculated)	1.68 Mg/m^3
Absorption coefficient	2.28 mm^{-1}
F(000)	352
Crystal size	0.20 x 0.09 x 0.08 mm^3
Theta range for data collection	3.67 to 27.08°.
Index ranges	-7<=h<=7, -11<=k<=10, -17<=l<=17
Reflections collected	5707
Independent reflections	2803 [R(int) = 0.044]
Reflections with I>2sigma(I)	2675
Completeness to theta = 27.09°	99.6 %
Absorption correction	Semi-empirical from equivalents
Tmax. and Tmin.	0.8505 and 0.6817
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2803 / 1 / 155
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0260, wR2 = 0.0600
R indices (all data)	R1 = 0.0281, wR2 = 0.0610
Largest diff. peak and hole	0.40 and -1.05 e.Å^{-3}

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for sep109. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I	10928(1)	-6(1)	1601(1)	36(1)
O(1)	5705(5)	3927(3)	3778(2)	35(1)
O(2)	7373(5)	6032(3)	3291(2)	25(1)
O(3)	6218(5)	5566(3)	1040(2)	36(1)
O(4)	9683(5)	6767(3)	1022(2)	35(1)
N	8097(6)	3924(3)	2609(2)	26(1)
C(1)	10645(7)	2130(4)	2202(3)	27(1)
C(2)	8215(7)	2334(4)	2536(3)	26(1)
C(3)	9723(6)	4663(3)	2035(2)	23(1)
C(4)	10773(7)	3386(4)	1497(3)	26(1)
C(5)	6945(7)	4584(4)	3277(3)	24(1)
C(6)	6530(6)	6980(4)	4037(2)	22(1)
C(7)	7756(7)	6529(5)	5048(3)	36(1)
C(8)	3802(6)	6948(4)	3946(3)	31(1)
C(9)	7345(7)	8481(4)	3764(3)	33(1)
C(10)	8559(6)	5786(4)	1329(2)	23(1)
C(11)	5035(9)	6675(7)	380(3)	53(1)

Table 3. Bond lengths [Å] and angles [°] for sep109.

I-C(1)	2.142(4)
O(1)-C(5)	1.217(4)
O(2)-C(5)	1.348(5)
O(2)-C(6)	1.482(4)
O(3)-C(10)	1.331(4)
O(3)-C(11)	1.456(5)
O(4)-C(10)	1.213(4)
N-C(5)	1.351(5)
N-C(2)	1.462(4)
N-C(3)	1.468(4)
C(1)-C(4)	1.517(5)
C(1)-C(2)	1.522(5)
C(3)-C(10)	1.497(5)
C(3)-C(4)	1.553(5)
C(6)-C(9)	1.516(5)
C(6)-C(7)	1.516(5)
C(6)-C(8)	1.521(5)
C(5)-O(2)-C(6)	120.7(3)
C(10)-O(3)-C(11)	114.6(3)
C(5)-N-C(2)	121.7(3)
C(5)-N-C(3)	124.7(3)
C(2)-N-C(3)	112.5(3)
C(4)-C(1)-C(2)	103.7(3)
C(4)-C(1)-I	115.4(2)
C(2)-C(1)-I	110.8(2)
N-C(2)-C(1)	101.3(3)
N-C(3)-C(10)	115.1(3)
N-C(3)-C(4)	103.2(2)
C(10)-C(3)-C(4)	111.5(3)
C(1)-C(4)-C(3)	101.7(3)
O(1)-C(5)-O(2)	126.6(4)
O(1)-C(5)-N	123.2(3)
O(2)-C(5)-N	110.3(3)

O(2)-C(6)-C(9)	102.4(3)
O(2)-C(6)-C(7)	109.5(3)
C(9)-C(6)-C(7)	111.5(3)
O(2)-C(6)-C(8)	111.1(3)
C(9)-C(6)-C(8)	109.7(3)
C(7)-C(6)-C(8)	112.3(3)
O(4)-C(10)-O(3)	123.6(3)
O(4)-C(10)-C(3)	122.6(3)
O(3)-C(10)-C(3)	113.7(3)

Table 1. Crystal data and structure refinement for $C_6H_7NO_3$

Identification code	aug709
Empirical formula	C6 H7 N1 O3
Formula weight	141.13
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$ (No.19)
Unit cell dimensions	a = 7.7226(3) Å $\quad\alpha = 90°.$
	b = 8.5764(3) Å $\quad\beta = 90°.$
	c = 9.1061(3) Å $\quad\gamma = 90°.$
Volume	603.12(4) Å^3
Z	4
Density (calculated)	1.55 Mg/m^3
Absorption coefficient	0.13 mm^{-1}
F(000)	296
Crystal size	0.21 x 0.17 x 0.09 mm^3
Theta range for data collection	3.46 to 27.46°.
Index ranges	-9<=h<=8, -11<=k<=11, -11<=l<=10
Reflections collected	4832
Independent reflections	812 [R(int) = 0.052]
Reflections with I>2sigma(I)	773
Completeness to theta = 27.46°	99.3 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	812 / 0 / 119
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.030, wR2 = 0.073
R indices (all data)	R1 = 0.032, wR2 = 0.075
Largest diff. peak and hole	0.19 and -0.15 e.Å^{-3}

Stereochemistry defined from synthetic sequence

Data collection KappaCCD , Program package WinGX , Abs correction not applied
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for aug709. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	11228(2)	3169(2)	7527(1)	34(1)
O(2)	9419(2)	1942(2)	5991(1)	29(1)
O(3)	6690(2)	4601(1)	7307(1)	33(1)
N	8572(2)	2246(2)	8323(1)	21(1)
C(1)	9850(2)	2527(2)	7323(2)	24(1)
C(2)	8188(2)	3453(2)	9424(2)	25(1)
C(3)	6556(2)	4184(2)	8847(2)	30(1)
C(4)	5818(2)	3171(2)	7716(2)	27(1)
C(5)	6984(2)	1768(2)	7559(2)	22(1)
C(6)	7645(2)	1382(2)	6018(2)	29(1)

Table 3.   Bond lengths [Å] and angles [°] for aug709.

O(1)-C(1)	1.2128(19)
O(2)-C(1)	1.354(2)
O(2)-C(6)	1.452(2)
O(3)-C(4)	1.448(2)
O(3)-C(3)	1.451(2)
N-C(1)	1.364(2)
N-C(5)	1.4674(19)
N-C(2)	1.471(2)
C(2)-C(3)	1.502(2)
C(3)-C(4)	1.463(3)
C(4)-C(5)	1.510(2)
C(5)-C(6)	1.529(2)
C(1)-O(2)-C(6)	109.81(13)
C(4)-O(3)-C(3)	60.61(11)
C(1)-N-C(5)	109.73(12)
C(1)-N-C(2)	118.44(13)
C(5)-N-C(2)	110.56(12)
O(1)-C(1)-O(2)	121.43(15)
O(1)-C(1)-N	127.80(15)
O(2)-C(1)-N	110.75(13)
N-C(2)-C(3)	102.96(13)
O(3)-C(3)-C(4)	59.58(11)
O(3)-C(3)-C(2)	112.38(14)
C(4)-C(3)-C(2)	108.98(14)
O(3)-C(4)-C(3)	59.80(11)
O(3)-C(4)-C(5)	111.89(13)
C(3)-C(4)-C(5)	107.87(14)
N-C(5)-C(4)	103.37(13)
N-C(5)-C(6)	102.49(12)
C(4)-C(5)-C(6)	117.29(14)
O(2)-C(6)-C(5)	105.02(13)

Table 1. Crystal data and structure refinement for $C_{13}H_{15}NO_4$.

Identification code	may409
Empirical formula	C13 H15 N O4
Formula weight	249.26
Temperature	173(2) K
Wavelength	0.710703 Å
Crystal system	Orthorhombic
Space group	P $2_1 2_1 2_1$ (No.19)
Unit cell dimensions	a = 9.0340(2) Å $\alpha = 90°$.
	b = 11.4291(2) Å $\beta = 90°$.
	c = 11.7307(2) Å $\gamma = 90°$.
Volume	1211.20(4) Å^3
Z	4
Density (calculated)	1.37 Mg/m^3
Absorption coefficient	0.10 mm^{-1}
F(000)	528
Crystal size	0.38 x 0.3 x 0.2 mm^3
Theta range for data collection	3.47 to 28.24°.
Index ranges	-12<=h<=11, -14<=k<=15, -15<=l<=15
Reflections collected	19346
Independent reflections	1712 [R(int) = 0.185]
Reflections with I>2sigma(I)	1607
Completeness to theta = 28.24°	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1712 / 0 / 167
Goodness-of-fit on F^2	1.139
Final R indices [I>2sigma(I)]	R1 = 0.0523 wR2 = 0.130
R indices (all data)	R1 = 0.057, wR2 = 0.133
Absolute structure parameter	1(2)
Largest diff. peak and hole	0.22 and -0.28 e.Å^{-3}

Data collection KappaCCD , Program package WinGX
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

The hydrogen atom of the OH group was located and refined; the molecules are linked by hydrogen bonding between the OH and the carbonyl oxygen O3.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for may409. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3252(2)	7933(2)	6535(2)	38(1)
O(2)	4435(3)	5551(2)	7774(2)	39(1)
O(3)	5553(3)	8478(2)	6038(2)	40(1)
O(4)	5338(3)	4035(2)	5118(2)	34(1)
N(1)	4640(3)	6662(2)	5570(2)	28(1)
C(1)	3379(3)	5943(3)	5952(3)	32(1)
C(2)	4116(3)	5030(2)	6703(3)	31(1)
C(3)	5561(4)	4789(2)	6073(3)	32(1)
C(4)	6017(3)	5979(3)	5599(3)	35(1)
C(5)	4585(4)	7733(2)	6043(2)	30(1)
C(6)	2392(3)	6865(3)	6517(3)	37(1)
C(7)	5312(5)	2828(3)	5431(3)	44(1)
C(8)	5290(4)	2090(3)	4367(3)	32(1)
C(9)	4609(4)	1005(3)	4385(3)	38(1)
C(10)	4637(4)	291(3)	3431(3)	41(1)
C(11)	5329(4)	662(3)	2451(3)	40(1)
C(12)	6000(4)	1744(3)	2424(3)	37(1)
C(13)	5987(4)	2452(3)	3375(3)	34(1)

Table 3. Bond lengths [Å] and angles [°] for may409.

O(1)-C(5)	1.354(4)
O(1)-C(6)	1.446(4)
O(2)-C(2)	1.420(3)
O(3)-C(5)	1.221(4)
O(4)-C(7)	1.428(3)
O(4)-C(3)	1.428(3)
N(1)-C(5)	1.345(3)
N(1)-C(4)	1.469(4)
N(1)-C(1)	1.475(4)
C(1)-C(2)	1.520(4)
C(1)-C(6)	1.531(4)
C(2)-C(3)	1.526(4)
C(3)-C(4)	1.526(4)
C(7)-C(8)	1.508(4)
C(8)-C(9)	1.385(4)
C(8)-C(13)	1.386(4)
C(9)-C(10)	1.384(4)
C(10)-C(11)	1.376(5)
C(11)-C(12)	1.378(5)
C(12)-C(13)	1.379(4)
C(5)-O(1)-C(6)	109.2(2)
C(7)-O(4)-C(3)	112.5(2)
C(5)-N(1)-C(4)	120.4(3)
C(5)-N(1)-C(1)	110.7(3)
C(4)-N(1)-C(1)	110.6(2)
N(1)-C(1)-C(2)	102.7(2)
N(1)-C(1)-C(6)	101.4(2)
C(2)-C(1)-C(6)	118.4(3)
O(2)-C(2)-C(1)	108.3(2)
O(2)-C(2)-C(3)	109.3(2)
C(1)-C(2)-C(3)	102.6(2)
O(4)-C(3)-C(2)	111.6(3)
O(4)-C(3)-C(4)	106.8(2)

C(2)-C(3)-C(4)	104.3(2)
N(1)-C(4)-C(3)	104.7(2)
O(3)-C(5)-N(1)	127.3(3)
O(3)-C(5)-O(1)	121.5(3)
N(1)-C(5)-O(1)	111.2(3)
O(1)-C(6)-C(1)	105.9(2)
O(4)-C(7)-C(8)	109.1(2)
C(9)-C(8)-C(13)	118.8(3)
C(9)-C(8)-C(7)	119.6(3)
C(13)-C(8)-C(7)	121.5(3)
C(10)-C(9)-C(8)	120.4(3)
C(11)-C(10)-C(9)	120.2(3)
C(10)-C(11)-C(12)	119.7(3)
C(11)-C(12)-C(13)	120.3(3)
C(12)-C(13)-C(8)	120.5(3)

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O2-H1X	0.978	1.800	163.01	2.750	O3 [-x+1, y-1/2, -z+3/2]

Table 1. Crystal data and structure refinement for PJB100-3.

Identification code	may311
Empirical formula	C18 H23 N O5
Formula weight	333.37
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$ (No.19)
Unit cell dimensions	a = 6.6596(1) Å α= 90°.
	b = 11.6777(2) Å β= 90°.
	c = 21.7673(4) Å γ= 90°.
Volume	1692.82(5) Å^3
Z	4
Density (calculated)	1.31 Mg/m^3
Absorption coefficient	0.10 mm^{-1}
F(000)	712
Crystal size	0.40 x 0.20 x 0.04 mm^3
Theta range for data collection	3.49 to 26.69°.
Index ranges	-8<=h<=8, -14<=k<=14, -27<=l<=27
Reflections collected	30229
Independent reflections	2072 [R(int) = 0.097]
Reflections with I>2sigma(I)	1975
Completeness to theta = 26.69°	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2072 / 0 / 217
Goodness-of-fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.040, wR2 = 0.087
R indices (all data)	R1 = 0.043, wR2 = 0.088
Largest diff. peak and hole	0.20 and -0.16 e.Å^{-3}

Data collection KappaCCD , Program package WinGX , Abs correction not applied

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for may311. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4747(2)	-632(1)	2156(1)	28(1)
O(2)	7142(2)	-1849(1)	2467(1)	36(1)
O(3)	8435(2)	1929(1)	3680(1)	25(1)
O(4)	7862(2)	1323(1)	2033(1)	24(1)
O(5)	7595(2)	3111(1)	1550(1)	34(1)
N(1)	6517(3)	-167(1)	2990(1)	23(1)
C(1)	5492(3)	901(2)	2824(1)	24(1)
C(2)	7220(3)	1680(2)	2633(1)	21(1)
C(3)	8839(3)	1377(2)	3108(1)	22(1)
C(4)	8559(3)	77(2)	3215(1)	27(1)
C(5)	6252(3)	-959(2)	2535(1)	25(1)
C(6)	4012(3)	482(2)	2336(1)	29(1)
C(7)	9240(4)	3070(2)	3711(1)	30(1)
C(8)	8690(3)	3558(2)	4330(1)	26(1)
C(9)	10019(4)	3476(2)	4816(1)	31(1)
C(10)	9504(4)	3905(2)	5393(1)	37(1)
C(11)	7640(4)	4407(2)	5478(1)	39(1)
C(12)	6306(4)	4487(2)	4996(1)	39(1)
C(13)	6832(3)	4067(2)	4420(1)	34(1)
C(14)	8905(3)	2203(2)	1704(1)	26(1)
C(15)	9843(3)	1649(2)	1146(1)	34(1)
C(16)	8261(4)	1297(2)	676(1)	39(1)
C(17)	6906(4)	2316(2)	532(1)	41(1)
C(18)	6049(4)	2804(2)	1119(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for may311.

O(1)-C(5)	1.353(2)
O(1)-C(6)	1.444(2)
O(2)-C(5)	1.206(3)
O(3)-C(3)	1.427(2)
O(3)-C(7)	1.437(2)
O(4)-C(14)	1.432(2)
O(4)-C(2)	1.436(2)
O(5)-C(14)	1.414(3)
O(5)-C(18)	1.439(3)
N(1)-C(5)	1.367(3)
N(1)-C(1)	1.467(2)
N(1)-C(4)	1.473(2)
C(1)-C(2)	1.525(3)
C(1)-C(6)	1.529(3)
C(2)-C(3)	1.536(3)
C(3)-C(4)	1.548(3)
C(7)-C(8)	1.507(3)
C(8)-C(9)	1.382(3)
C(8)-C(13)	1.387(3)
C(9)-C(10)	1.396(3)
C(10)-C(11)	1.385(4)
C(11)-C(12)	1.378(3)
C(12)-C(13)	1.391(3)
C(14)-C(15)	1.512(3)
C(15)-C(16)	1.524(3)
C(16)-C(17)	1.526(3)
C(17)-C(18)	1.510(3)
C(5)-O(1)-C(6)	109.88(15)
C(3)-O(3)-C(7)	112.97(15)
C(14)-O(4)-C(2)	112.95(14)
C(14)-O(5)-C(18)	114.18(16)
C(5)-N(1)-C(1)	109.66(16)
C(5)-N(1)-C(4)	119.39(16)

C(1)-N(1)-C(4)	110.35(15)
N(1)-C(1)-C(2)	102.90(15)
N(1)-C(1)-C(6)	101.51(16)
C(2)-C(1)-C(6)	119.19(17)
O(4)-C(2)-C(1)	107.41(15)
O(4)-C(2)-C(3)	109.67(15)
C(1)-C(2)-C(3)	102.04(15)
O(3)-C(3)-C(2)	110.53(15)
O(3)-C(3)-C(4)	106.81(16)
C(2)-C(3)-C(4)	104.06(16)
N(1)-C(4)-C(3)	104.51(16)
O(2)-C(5)-O(1)	122.18(18)
O(2)-C(5)-N(1)	127.53(19)
O(1)-C(5)-N(1)	110.26(17)
O(1)-C(6)-C(1)	104.96(16)
O(3)-C(7)-C(8)	107.61(16)
C(9)-C(8)-C(13)	119.5(2)
C(9)-C(8)-C(7)	120.1(2)
C(13)-C(8)-C(7)	120.4(2)
C(8)-C(9)-C(10)	120.5(2)
C(11)-C(10)-C(9)	119.5(2)
C(12)-C(11)-C(10)	120.3(2)
C(11)-C(12)-C(13)	120.0(2)
C(8)-C(13)-C(12)	120.2(2)
O(5)-C(14)-O(4)	110.99(16)
O(5)-C(14)-C(15)	112.61(18)
O(4)-C(14)-C(15)	107.14(16)
C(14)-C(15)-C(16)	111.66(19)
C(15)-C(16)-C(17)	109.63(19)
C(18)-C(17)-C(16)	110.11(19)
O(5)-C(18)-C(17)	112.02(19)

Table 1. Crystal data and structure refinement for $C_{12}H_{17}NO_3$

Identification code	sep709
Empirical formula	C12 H17 N O3
Formula weight	223.27
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1 (No.4)
Unit cell dimensions	a = 8.8134(5) Å $\alpha = 90°$.
	b = 5.4328(2) Å $\beta = 93.985(2)°$.
	c = 11.9499(7) Å $\gamma = 90°$.
Volume	570.80(5) Å^3
Z	2
Density (calculated)	1.30 Mg/m^3
Absorption coefficient	0.09 mm^{-1}
F(000)	240
Crystal size	0.26 x 0.20 x 0.08 mm^3
Theta range for data collection	3.42 to 26.72°.
Index ranges	-9<=h<=11, -6<=k<=6, -15<=l<=14
Reflections collected	4670
Independent reflections	1338 [R(int) = 0.049]
Reflections with I>2sigma(I)	1180
Completeness to theta = 26.72°	99.4 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1338 / 1 / 157
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.035, wR2 = 0.082
R indices (all data)	R1 = 0.044, wR2 = 0.087
Largest diff. peak and hole	0.181 and -0.199 e.Å^{-3}

Absolute configuration defined from synthetic sequence only
Hydrogen atoms on oxygen and nitrogen located and refined, all others in calculated positions

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for sep709. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6210(2)	1273(3)	9244(1)	29(1)
O(2)	9474(2)	-2228(3)	10101(1)	31(1)
O(3)	6546(2)	-978(3)	6389(1)	24(1)
N	5690(2)	-3900(3)	8721(2)	20(1)
C(1)	4944(2)	-2870(5)	7680(2)	27(1)
C(2)	5793(2)	-498(4)	7389(2)	20(1)
C(3)	6925(2)	-76(4)	8413(2)	20(1)
C(4)	7199(2)	-2702(4)	8847(2)	19(1)
C(5)	7897(2)	-2934(4)	10038(2)	25(1)
C(6)	7036(3)	1195(5)	5864(2)	26(1)
C(7)	7780(2)	564(4)	4806(2)	21(1)
C(8)	7454(2)	-1601(4)	4219(2)	23(1)
C(9)	8130(2)	-2073(5)	3223(2)	26(1)
C(10)	9141(2)	-407(5)	2816(2)	28(1)
C(11)	9486(3)	1732(4)	3403(2)	28(1)
C(12)	8806(2)	2229(4)	4393(2)	26(1)

Table 3. Bond lengths [Å] and angles [°] for sep709.

O(1)-C(3)	1.417(2)
O(2)-C(5)	1.439(3)
O(3)-C(6)	1.418(3)
O(3)-C(2)	1.431(2)
N-C(1)	1.476(3)
N-C(4)	1.479(3)
C(1)-C(2)	1.542(3)
C(2)-C(3)	1.541(3)
C(3)-C(4)	1.532(3)
C(4)-C(5)	1.517(3)
C(6)-C(7)	1.504(3)
C(7)-C(8)	1.389(3)
C(7)-C(12)	1.393(3)
C(8)-C(9)	1.392(3)
C(9)-C(10)	1.382(3)
C(10)-C(11)	1.380(4)
C(11)-C(12)	1.390(3)
C(6)-O(3)-C(2)	113.04(16)
C(1)-N-C(4)	105.24(16)
N-C(1)-C(2)	108.20(17)
O(3)-C(2)-C(3)	112.22(15)
O(3)-C(2)-C(1)	107.25(17)
C(3)-C(2)-C(1)	104.07(16)
O(1)-C(3)-C(4)	108.16(16)
O(1)-C(3)-C(2)	109.81(17)
C(4)-C(3)-C(2)	102.02(17)
N-C(4)-C(5)	111.20(16)
N-C(4)-C(3)	104.82(17)
C(5)-C(4)-C(3)	116.06(18)
O(2)-C(5)-C(4)	110.71(17)
O(3)-C(6)-C(7)	110.27(19)
C(8)-C(7)-C(12)	119.23(18)
C(8)-C(7)-C(6)	121.99(19)

C(12)-C(7)-C(6)	118.8(2)
C(7)-C(8)-C(9)	120.1(2)
C(10)-C(9)-C(8)	120.3(2)
C(11)-C(10)-C(9)	119.9(2)
C(10)-C(11)-C(12)	120.2(2)
C(11)-C(12)-C(7)	120.3(2)

Table 1. Crystal data and structure refinement for $C_{11}H_{18}INO_4$.

Identification code	sep109
Empirical formula	C11 H18 I N O4
Formula weight	355.16
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2₁
Unit cell dimensions	a = 5.6271(2) Å α= 90°.
	b = 9.1606(2) Å β= 99.011(2)°.
	c = 13.8330(6) Å γ = 90°.
Volume	704.26(4) Å³
Z	2
Density (calculated)	1.68 Mg/m³
Absorption coefficient	2.28 mm⁻¹
F(000)	352
Crystal size	0.20 x 0.09 x 0.08 mm³
Theta range for data collection	3.67 to 27.08°.
Index ranges	-7<=h<=7, -11<=k<=10, -17<=l<=17
Reflections collected	5707
Independent reflections	2803 [R(int) = 0.044]
Reflections with I>2sigma(I)	2675
Completeness to theta = 27.09°	99.6 %
Absorption correction	Semi-empirical from equivalents
Tmax. and Tmin.	0.8505 and 0.6817
Refinement method	Full-matrix least-squares on F²
Data / restraints / parameters	2803 / 1 / 155
Goodness-of-fit on F²	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0260, wR2 = 0.0600
R indices (all data)	R1 = 0.0281, wR2 = 0.0610
Largest diff. peak and hole	0.40 and -1.05 e.Å⁻³

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\AA^2$x 10^3) for sep109. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I	10928(1)	-6(1)	1601(1)	36(1)
O(1)	5705(5)	3927(3)	3778(2)	35(1)
O(2)	7373(5)	6032(3)	3291(2)	25(1)
O(3)	6218(5)	5566(3)	1040(2)	36(1)
O(4)	9683(5)	6767(3)	1022(2)	35(1)
N	8097(6)	3924(3)	2609(2)	26(1)
C(1)	10645(7)	2130(4)	2202(3)	27(1)
C(2)	8215(7)	2334(4)	2536(3)	26(1)
C(3)	9723(6)	4663(3)	2035(2)	23(1)
C(4)	10773(7)	3386(4)	1497(3)	26(1)
C(5)	6945(7)	4584(4)	3277(3)	24(1)
C(6)	6530(6)	6980(4)	4037(2)	22(1)
C(7)	7756(7)	6529(5)	5048(3)	36(1)
C(8)	3802(6)	6948(4)	3946(3)	31(1)
C(9)	7345(7)	8481(4)	3764(3)	33(1)
C(10)	8559(6)	5786(4)	1329(2)	23(1)
C(11)	5035(9)	6675(7)	380(3)	53(1)

Table 3. Bond lengths [Å] and angles [°] for sep109.

I-C(1)	2.142(4)
O(1)-C(5)	1.217(4)
O(2)-C(5)	1.348(5)
O(2)-C(6)	1.482(4)
O(3)-C(10)	1.331(4)
O(3)-C(11)	1.456(5)
O(4)-C(10)	1.213(4)
N-C(5)	1.351(5)
N-C(2)	1.462(4)
N-C(3)	1.468(4)
C(1)-C(4)	1.517(5)
C(1)-C(2)	1.522(5)
C(3)-C(10)	1.497(5)
C(3)-C(4)	1.553(5)
C(6)-C(9)	1.516(5)
C(6)-C(7)	1.516(5)
C(6)-C(8)	1.521(5)
C(5)-O(2)-C(6)	120.7(3)
C(10)-O(3)-C(11)	114.6(3)
C(5)-N-C(2)	121.7(3)
C(5)-N-C(3)	124.7(3)
C(2)-N-C(3)	112.5(3)
C(4)-C(1)-C(2)	103.7(3)
C(4)-C(1)-I	115.4(2)
C(2)-C(1)-I	110.8(2)
N-C(2)-C(1)	101.3(3)
N-C(3)-C(10)	115.1(3)
N-C(3)-C(4)	103.2(2)
C(10)-C(3)-C(4)	111.5(3)
C(1)-C(4)-C(3)	101.7(3)
O(1)-C(5)-O(2)	126.6(4)
O(1)-C(5)-N	123.2(3)
O(2)-C(5)-N	110.3(3)

O(2)-C(6)-C(9)	102.4(3)
O(2)-C(6)-C(7)	109.5(3)
C(9)-C(6)-C(7)	111.5(3)
O(2)-C(6)-C(8)	111.1(3)
C(9)-C(6)-C(8)	109.7(3)
C(7)-C(6)-C(8)	112.3(3)
O(4)-C(10)-O(3)	123.6(3)
O(4)-C(10)-C(3)	122.6(3)
O(3)-C(10)-C(3)	113.7(3)

Table 1. Crystal data and structure refinement for $C_6H_7NO_3$

Identification code	aug709
Empirical formula	C6 H7 N1 O3
Formula weight	141.13
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 2_1 2_1 2_1 (No.19)
Unit cell dimensions	a = 7.7226(3) Å $\alpha= 90°$.
	b = 8.5764(3) Å $\beta= 90°$.
	c = 9.1061(3) Å $\gamma = 90°$.
Volume	603.12(4) Å^3
Z	4
Density (calculated)	1.55 Mg/m^3
Absorption coefficient	0.13 mm^{-1}
F(000)	296
Crystal size	0.21 x 0.17 x 0.09 mm^3
Theta range for data collection	3.46 to 27.46°.
Index ranges	-9<=h<=8, -11<=k<=11, -11<=l<=10
Reflections collected	4832
Independent reflections	812 [R(int) = 0.052]
Reflections with I>2sigma(I)	773
Completeness to theta = 27.46°	99.3 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	812 / 0 / 119
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.030, wR2 = 0.073
R indices (all data)	R1 = 0.032, wR2 = 0.075
Largest diff. peak and hole	0.19 and -0.15 e.Å^{-3}

Stereochemistry defined from synthetic sequence

Data collection KappaCCD , Program package WinGX , Abs correction not applied
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for aug709. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	11228(2)	3169(2)	7527(1)	34(1)
O(2)	9419(2)	1942(2)	5991(1)	29(1)
O(3)	6690(2)	4601(1)	7307(1)	33(1)
N	8572(2)	2246(2)	8323(1)	21(1)
C(1)	9850(2)	2527(2)	7323(2)	24(1)
C(2)	8188(2)	3453(2)	9424(2)	25(1)
C(3)	6556(2)	4184(2)	8847(2)	30(1)
C(4)	5818(2)	3171(2)	7716(2)	27(1)
C(5)	6984(2)	1768(2)	7559(2)	22(1)
C(6)	7645(2)	1382(2)	6018(2)	29(1)

Table 3.   Bond lengths [Å] and angles [°] for aug709.

O(1)-C(1)	1.2128(19)
O(2)-C(1)	1.354(2)
O(2)-C(6)	1.452(2)
O(3)-C(4)	1.448(2)
O(3)-C(3)	1.451(2)
N-C(1)	1.364(2)
N-C(5)	1.4674(19)
N-C(2)	1.471(2)
C(2)-C(3)	1.502(2)
C(3)-C(4)	1.463(3)
C(4)-C(5)	1.510(2)
C(5)-C(6)	1.529(2)
C(1)-O(2)-C(6)	109.81(13)
C(4)-O(3)-C(3)	60.61(11)
C(1)-N-C(5)	109.73(12)
C(1)-N-C(2)	118.44(13)
C(5)-N-C(2)	110.56(12)
O(1)-C(1)-O(2)	121.43(15)
O(1)-C(1)-N	127.80(15)
O(2)-C(1)-N	110.75(13)
N-C(2)-C(3)	102.96(13)
O(3)-C(3)-C(4)	59.58(11)
O(3)-C(3)-C(2)	112.38(14)
C(4)-C(3)-C(2)	108.98(14)
O(3)-C(4)-C(3)	59.80(11)
O(3)-C(4)-C(5)	111.89(13)
C(3)-C(4)-C(5)	107.87(14)
N-C(5)-C(4)	103.37(13)
N-C(5)-C(6)	102.49(12)
C(4)-C(5)-C(6)	117.29(14)
O(2)-C(6)-C(5)	105.02(13)

Table 1. Crystal data and structure refinement for $C_{13}H_{15}NO_4$.

Identification code	may409
Empirical formula	C13 H15 N O4
Formula weight	249.26
Temperature	173(2) K
Wavelength	0.710703 Å
Crystal system	Orthorhombic
Space group	P $2_12_12_1$ (No.19)
Unit cell dimensions	a = 9.0340(2) Å α= 90°.
	b = 11.4291(2) Å β= 90°.
	c = 11.7307(2) Å γ = 90°.
Volume	1211.20(4) Å^3
Z	4
Density (calculated)	1.37 Mg/m^3
Absorption coefficient	0.10 mm^{-1}
F(000)	528
Crystal size	0.38 x 0.3 x 0.2 mm^3
Theta range for data collection	3.47 to 28.24°.
Index ranges	-12<=h<=11, -14<=k<=15, -15<=l<=15
Reflections collected	19346
Independent reflections	1712 [R(int) = 0.185]
Reflections with I>2sigma(I)	1607
Completeness to theta = 28.24°	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1712 / 0 / 167
Goodness-of-fit on F^2	1.139
Final R indices [I>2sigma(I)]	R1 = 0.0523 wR2 = 0.130
R indices (all data)	R1 = 0.057, wR2 = 0.133
Absolute structure parameter	1(2)
Largest diff. peak and hole	0.22 and -0.28 e.Å^{-3}

Data collection KappaCCD , Program package WinGX
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

The hydrogen atom of the OH group was located and refined; the molecules are linked by hydrogen bonding between the OH and the carbonyl oxygen O3.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\mathring{A}^2$x 10^3) for may409. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3252(2)	7933(2)	6535(2)	38(1)
O(2)	4435(3)	5551(2)	7774(2)	39(1)
O(3)	5553(3)	8478(2)	6038(2)	40(1)
O(4)	5338(3)	4035(2)	5118(2)	34(1)
N(1)	4640(3)	6662(2)	5570(2)	28(1)
C(1)	3379(3)	5943(3)	5952(3)	32(1)
C(2)	4116(3)	5030(2)	6703(3)	31(1)
C(3)	5561(4)	4789(2)	6073(3)	32(1)
C(4)	6017(3)	5979(3)	5599(3)	35(1)
C(5)	4585(4)	7733(2)	6043(2)	30(1)
C(6)	2392(3)	6865(3)	6517(3)	37(1)
C(7)	5312(5)	2828(3)	5431(3)	44(1)
C(8)	5290(4)	2090(3)	4367(3)	32(1)
C(9)	4609(4)	1005(3)	4385(3)	38(1)
C(10)	4637(4)	291(3)	3431(3)	41(1)
C(11)	5329(4)	662(3)	2451(3)	40(1)
C(12)	6000(4)	1744(3)	2424(3)	37(1)
C(13)	5987(4)	2452(3)	3375(3)	34(1)

Table 3. Bond lengths [Å] and angles [°] for may409.

O(1)-C(5)	1.354(4)
O(1)-C(6)	1.446(4)
O(2)-C(2)	1.420(3)
O(3)-C(5)	1.221(4)
O(4)-C(7)	1.428(3)
O(4)-C(3)	1.428(3)
N(1)-C(5)	1.345(3)
N(1)-C(4)	1.469(4)
N(1)-C(1)	1.475(4)
C(1)-C(2)	1.520(4)
C(1)-C(6)	1.531(4)
C(2)-C(3)	1.526(4)
C(3)-C(4)	1.526(4)
C(7)-C(8)	1.508(4)
C(8)-C(9)	1.385(4)
C(8)-C(13)	1.386(4)
C(9)-C(10)	1.384(4)
C(10)-C(11)	1.376(5)
C(11)-C(12)	1.378(5)
C(12)-C(13)	1.379(4)
C(5)-O(1)-C(6)	109.2(2)
C(7)-O(4)-C(3)	112.5(2)
C(5)-N(1)-C(4)	120.4(3)
C(5)-N(1)-C(1)	110.7(3)
C(4)-N(1)-C(1)	110.6(2)
N(1)-C(1)-C(2)	102.7(2)
N(1)-C(1)-C(6)	101.4(2)
C(2)-C(1)-C(6)	118.4(3)
O(2)-C(2)-C(1)	108.3(2)
O(2)-C(2)-C(3)	109.3(2)
C(1)-C(2)-C(3)	102.6(2)
O(4)-C(3)-C(2)	111.6(3)
O(4)-C(3)-C(4)	106.8(2)

C(2)-C(3)-C(4)	104.3(2)
N(1)-C(4)-C(3)	104.7(2)
O(3)-C(5)-N(1)	127.3(3)
O(3)-C(5)-O(1)	121.5(3)
N(1)-C(5)-O(1)	111.2(3)
O(1)-C(6)-C(1)	105.9(2)
O(4)-C(7)-C(8)	109.1(2)
C(9)-C(8)-C(13)	118.8(3)
C(9)-C(8)-C(7)	119.6(3)
C(13)-C(8)-C(7)	121.5(3)
C(10)-C(9)-C(8)	120.4(3)
C(11)-C(10)-C(9)	120.2(3)
C(10)-C(11)-C(12)	119.7(3)
C(11)-C(12)-C(13)	120.3(3)
C(12)-C(13)-C(8)	120.5(3)

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O2-H1X	0.978	1.800	163.01	2.750	O3 [-x+1, y-1/2, -z+3/2]

Table 1. Crystal data and structure refinement for PJB100-3.

Identification code	may311
Empirical formula	C18 H23 N O5
Formula weight	333.37
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$ (No.19)
Unit cell dimensions	a = 6.6596(1) Å $\alpha = 90°$.
	b = 11.6777(2) Å $\beta = 90°$.
	c = 21.7673(4) Å $\gamma = 90°$.
Volume	1692.82(5) Å^3
Z	4
Density (calculated)	1.31 Mg/m^3
Absorption coefficient	0.10 mm^{-1}
F(000)	712
Crystal size	0.40 x 0.20 x 0.04 mm^3
Theta range for data collection	3.49 to 26.69°.
Index ranges	-8<=h<=8, -14<=k<=14, -27<=l<=27
Reflections collected	30229
Independent reflections	2072 [R(int) = 0.097]
Reflections with I>2sigma(I)	1975
Completeness to theta = 26.69°	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2072 / 0 / 217
Goodness-of-fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.040, wR2 = 0.087
R indices (all data)	R1 = 0.043, wR2 = 0.088
Largest diff. peak and hole	0.20 and -0.16 e.Å^{-3}

Data collection KappaCCD , Program package WinGX , Abs correction not applied
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for may311. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4747(2)	-632(1)	2156(1)	28(1)
O(2)	7142(2)	-1849(1)	2467(1)	36(1)
O(3)	8435(2)	1929(1)	3680(1)	25(1)
O(4)	7862(2)	1323(1)	2033(1)	24(1)
O(5)	7595(2)	3111(1)	1550(1)	34(1)
N(1)	6517(3)	-167(1)	2990(1)	23(1)
C(1)	5492(3)	901(2)	2824(1)	24(1)
C(2)	7220(3)	1680(2)	2633(1)	21(1)
C(3)	8839(3)	1377(2)	3108(1)	22(1)
C(4)	8559(3)	77(2)	3215(1)	27(1)
C(5)	6252(3)	-959(2)	2535(1)	25(1)
C(6)	4012(3)	482(2)	2336(1)	29(1)
C(7)	9240(4)	3070(2)	3711(1)	30(1)
C(8)	8690(3)	3558(2)	4330(1)	26(1)
C(9)	10019(4)	3476(2)	4816(1)	31(1)
C(10)	9504(4)	3905(2)	5393(1)	37(1)
C(11)	7640(4)	4407(2)	5478(1)	39(1)
C(12)	6306(4)	4487(2)	4996(1)	39(1)
C(13)	6832(3)	4067(2)	4420(1)	34(1)
C(14)	8905(3)	2203(2)	1704(1)	26(1)
C(15)	9843(3)	1649(2)	1146(1)	34(1)
C(16)	8261(4)	1297(2)	676(1)	39(1)
C(17)	6906(4)	2316(2)	532(1)	41(1)
C(18)	6049(4)	2804(2)	1119(1)	36(1)

Table 3.   Bond lengths [Å] and angles [°] for may311.

O(1)-C(5)	1.353(2)
O(1)-C(6)	1.444(2)
O(2)-C(5)	1.206(3)
O(3)-C(3)	1.427(2)
O(3)-C(7)	1.437(2)
O(4)-C(14)	1.432(2)
O(4)-C(2)	1.436(2)
O(5)-C(14)	1.414(3)
O(5)-C(18)	1.439(3)
N(1)-C(5)	1.367(3)
N(1)-C(1)	1.467(2)
N(1)-C(4)	1.473(2)
C(1)-C(2)	1.525(3)
C(1)-C(6)	1.529(3)
C(2)-C(3)	1.536(3)
C(3)-C(4)	1.548(3)
C(7)-C(8)	1.507(3)
C(8)-C(9)	1.382(3)
C(8)-C(13)	1.387(3)
C(9)-C(10)	1.396(3)
C(10)-C(11)	1.385(4)
C(11)-C(12)	1.378(3)
C(12)-C(13)	1.391(3)
C(14)-C(15)	1.512(3)
C(15)-C(16)	1.524(3)
C(16)-C(17)	1.526(3)
C(17)-C(18)	1.510(3)
C(5)-O(1)-C(6)	109.88(15)
C(3)-O(3)-C(7)	112.97(15)
C(14)-O(4)-C(2)	112.95(14)
C(14)-O(5)-C(18)	114.18(16)
C(5)-N(1)-C(1)	109.66(16)
C(5)-N(1)-C(4)	119.39(16)

C(1)-N(1)-C(4)	110.35(15)
N(1)-C(1)-C(2)	102.90(15)
N(1)-C(1)-C(6)	101.51(16)
C(2)-C(1)-C(6)	119.19(17)
O(4)-C(2)-C(1)	107.41(15)
O(4)-C(2)-C(3)	109.67(15)
C(1)-C(2)-C(3)	102.04(15)
O(3)-C(3)-C(2)	110.53(15)
O(3)-C(3)-C(4)	106.81(16)
C(2)-C(3)-C(4)	104.06(16)
N(1)-C(4)-C(3)	104.51(16)
O(2)-C(5)-O(1)	122.18(18)
O(2)-C(5)-N(1)	127.53(19)
O(1)-C(5)-N(1)	110.26(17)
O(1)-C(6)-C(1)	104.96(16)
O(3)-C(7)-C(8)	107.61(16)
C(9)-C(8)-C(13)	119.5(2)
C(9)-C(8)-C(7)	120.1(2)
C(13)-C(8)-C(7)	120.4(2)
C(8)-C(9)-C(10)	120.5(2)
C(11)-C(10)-C(9)	119.5(2)
C(12)-C(11)-C(10)	120.3(2)
C(11)-C(12)-C(13)	120.0(2)
C(8)-C(13)-C(12)	120.2(2)
O(5)-C(14)-O(4)	110.99(16)
O(5)-C(14)-C(15)	112.61(18)
O(4)-C(14)-C(15)	107.14(16)
C(14)-C(15)-C(16)	111.66(19)
C(15)-C(16)-C(17)	109.63(19)
C(18)-C(17)-C(16)	110.11(19)
O(5)-C(18)-C(17)	112.02(19)

Table 1. Crystal data and structure refinement for $C_{12}H_{17}NO_3$

Identification code	sep709
Empirical formula	C12 H17 N O3
Formula weight	223.27
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1 (No.4)
Unit cell dimensions	a = 8.8134(5) Å α = 90°.
	b = 5.4328(2) Å β = 93.985(2)°.
	c = 11.9499(7) Å γ = 90°.
Volume	570.80(5) Å^3
Z	2
Density (calculated)	1.30 Mg/m^3
Absorption coefficient	0.09 mm^{-1}
F(000)	240
Crystal size	0.26 x 0.20 x 0.08 mm^3
Theta range for data collection	3.42 to 26.72°.
Index ranges	-9<=h<=11, -6<=k<=6, -15<=l<=14
Reflections collected	4670
Independent reflections	1338 [R(int) = 0.049]
Reflections with I>2sigma(I)	1180
Completeness to theta = 26.72°	99.4 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1338 / 1 / 157
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.035, wR2 = 0.082
R indices (all data)	R1 = 0.044, wR2 = 0.087
Largest diff. peak and hole	0.181 and -0.199 e.Å^{-3}

Absolute configuration defined from synthetic sequence only
Hydrogen atoms on oxygen and nitrogen located and refined, all others in calculated positions

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for sep709. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6210(2)	1273(3)	9244(1)	29(1)
O(2)	9474(2)	-2228(3)	10101(1)	31(1)
O(3)	6546(2)	-978(3)	6389(1)	24(1)
N	5690(2)	-3900(3)	8721(2)	20(1)
C(1)	4944(2)	-2870(5)	7680(2)	27(1)
C(2)	5793(2)	-498(4)	7389(2)	20(1)
C(3)	6925(2)	-76(4)	8413(2)	20(1)
C(4)	7199(2)	-2702(4)	8847(2)	19(1)
C(5)	7897(2)	-2934(4)	10038(2)	25(1)
C(6)	7036(3)	1195(5)	5864(2)	26(1)
C(7)	7780(2)	564(4)	4806(2)	21(1)
C(8)	7454(2)	-1601(4)	4219(2)	23(1)
C(9)	8130(2)	-2073(5)	3223(2)	26(1)
C(10)	9141(2)	-407(5)	2816(2)	28(1)
C(11)	9486(3)	1732(4)	3403(2)	28(1)
C(12)	8806(2)	2229(4)	4393(2)	26(1)

Table 3. Bond lengths [Å] and angles [°] for sep709.

O(1)-C(3)	1.417(2)
O(2)-C(5)	1.439(3)
O(3)-C(6)	1.418(3)
O(3)-C(2)	1.431(2)
N-C(1)	1.476(3)
N-C(4)	1.479(3)
C(1)-C(2)	1.542(3)
C(2)-C(3)	1.541(3)
C(3)-C(4)	1.532(3)
C(4)-C(5)	1.517(3)
C(6)-C(7)	1.504(3)
C(7)-C(8)	1.389(3)
C(7)-C(12)	1.393(3)
C(8)-C(9)	1.392(3)
C(9)-C(10)	1.382(3)
C(10)-C(11)	1.380(4)
C(11)-C(12)	1.390(3)
C(6)-O(3)-C(2)	113.04(16)
C(1)-N-C(4)	105.24(16)
N-C(1)-C(2)	108.20(17)
O(3)-C(2)-C(3)	112.22(15)
O(3)-C(2)-C(1)	107.25(17)
C(3)-C(2)-C(1)	104.07(16)
O(1)-C(3)-C(4)	108.16(16)
O(1)-C(3)-C(2)	109.81(17)
C(4)-C(3)-C(2)	102.02(17)
N-C(4)-C(5)	111.20(16)
N-C(4)-C(3)	104.82(17)
C(5)-C(4)-C(3)	116.06(18)
O(2)-C(5)-C(4)	110.71(17)
O(3)-C(6)-C(7)	110.27(19)
C(8)-C(7)-C(12)	119.23(18)
C(8)-C(7)-C(6)	121.99(19)

C(12)-C(7)-C(6)	118.8(2)
C(7)-C(8)-C(9)	120.1(2)
C(10)-C(9)-C(8)	120.3(2)
C(11)-C(10)-C(9)	119.9(2)
C(10)-C(11)-C(12)	120.2(2)
C(11)-C(12)-C(7)	120.3(2)