Studies on the Stereoselective Synthesis of the C_{20} Backbone of Fumonisin B_3 and B_4 using Sharpless Methodology

by

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"I used my wisdom to test all this
I was determined to be wise,
But it was beyond me
How can anyone discover what
Life means? It is too deep for us,
Too hard to understand.
But I devoted myself to knowledge
And study, I was determined to find
Wisdom and the answers to my questions
And to learn how wicked and foolish stupidity is!

This is all that I have learnt:
God made us plain and simple
But we have made ourselves
Very complicated."

Ecclesiastes 7:23-25/29

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Finally, to Jesus Christ my only Lord and personal Saviour and Holy Spirit, my best companion.

SUMMARY

Fusarium moniliforme Sheldon a common fungal contaminant of maize throughout the world has been associated with diseases in both man and animals. The structure of the fumonisins, a family of structurally related mycotoxins isolated from cultures associated with the high incidence of human oesophageal cancer in the Transkei region in South Africa and with equine leucoencephalomalacia, a neurological disorder in horses and donkeys, has been established. These mycotoxins in the case of fumonisin B_3 and B_4 consist of the diester formed by the C(14) and C(15) hydroxy groups of 2-amino-12,16-dimethyl-3,10,14,15-tetrahydroxyicosane and the C(10) deoxy analogue, respectively, with the *Si* carboxy group of propane-1,2,3-tricarboxylic acid.

The aim of the synthetic study outlined in this dissertation is the development and implementation of methodology for the synthesis of the C(1)–C(8) unit of the C_{20} backbone of fumonisin B_3 and B_4 with the appropriate stereochemistry. Retrosynthetic analysis of the C_{20} backbone identifies (6*S*,7*S*)-7-amino-1,6-octanediol as the target structure. The use of *t*-butyldimethylsilyl and *t*-butyldiphenylsilyl, methoxymethyl and benzyl protecting groups in the proposed synthetic route, the stereochemical control in the creation of the stereogenic centres using Sharpless asymmetric epoxidation–kinetic resolution, and the introduction of the amino group, were initially investigated using pentane-1,5-diol as starting material. The findings were then applied in the synthesis of (2*S*,3*S*)-3-benzyloxy-2-(*t*-butyloxycarbonyl)amino-8-[(*t*-butyldimethylsilyl)oxy]-octane, the synthetic intermediate corresponding to the target structure, from hexane-1,6-diol using *t*-butyldimethylsilyl and benzyl protecting groups.

The structures of 3-*epi*-fumonisin B_3 and -fumonisin B_4 were deduced from ^1H and ^{13}C NMR data and confirmed by the data for a model compound, (5*R*,6*S*)-6-amino-1,5-heptanediol, prepared from pentane-1,5-diol using the methodology established earlier in the dissertation.

OPSOMMING

Fusarium moniliforme Sheldon is 'n algemene swamkontaminant van mielies dwarsoor die wêreld en word reeds lank met siektes in mens en dier verbind. Die strukture van die fumonisiene, 'n familie van struktureelverwante mikotoksiene geïsoleer vanuit kultuurmateriaal van *F. moniliforme* geassosieer met die hoë voorkoms van menslike slukdermkanker in die Transkei-gebied van Suid-Afrika en met 'n neurologiese aandoening, harsingverweking, in perde en donkies, is reeds eerder vasgestel. Hierdie mikotoksiene bestaan uit die diester gevorm deur die C(14) en C(15) hidroksi-groepe van 2-amino-12,16-dimetiel-3,10,14,15-trihidroksi-ikosaan en die C(10) deoksi analoog in die geval van fumonisien B_3 en B_4, respektiewelik, met die *Si* karboksi-groep van propaan-1,2,3-trikarboksielsuur.

Die doel van die sintetiese studie wat in hierdie verhandeling beskryf word, is die ontwikkeling en implementering van metodiek vir die sintese van die C(1)–C(8) eenheid van die C_{20}-ruggraat van fumonisien B_3 en B_4 met die toepaslike stereochemie. Retrosintetiese analise van die C_{20}-ruggraat identifiseer (6*S*,7*S*)-7-amino-1,6-oktaandiol as die doelwitstruktuur. Die gebruik van *t*-butieldimetielsiliel en *t*-butieldifenielsiliel, metoksimetiel en bensiel beskermende groepe in die voorgestelde sintetiese roete, die stereochemiese beheer tydens die vorming van die stereogeniese sentra deur gebruik te maak van Sharpless asimmetriese epoksidasie–kinetiese resolusie, en die daarstelling van die aminogroep, is eers ondersoek deur pentaan-1,5-diol as uitgangstof te gebruik. Die bevindings is daarna toegepas in die sintese van (2*S*,3*S*)-3-bensieloksi-2-(*t*-butieloksikarboniel)amino-8-[(*t*-butieldimetielsiliel)oksi]-oktaan, die sintetiese tussenproduk wat ooreenstem met die doelwitstruktuur, vanaf heksaan-1,6-diol en die gebruik van *t*-butieldimetielsiliel en bensiel beskermende groepe.

Die strukture van 3-*epi*-fumonisien B_3 en –fumonisien B_4 is afgelei vanaf die ^1H en ^{13}C KMR data en is bevestig deur die data van 'n modelstof, (5*R*,6*S*)-6-amino-1,5-heptaandiol, berei vanaf pentaan-1,5-diol deur gebruik te maak van die metodiek wat reeds eerder in hierdie verhandeling daargestel is.

CONTENTS

CHAPTER 6 EXPERIMENTAL

LIST OF ABBREVIATIONS

AcOH	Acetic acid
Ac_2O	Acetic anhydride
AIBN	α,α'-Azo-isobutyronitrile
$BaCO_3$	Barium carbonate
BCl_3	Boron trichloride
$BCl_3.Me_2S$	Boron trichloride-methyl sulfide complex
$BF_3.Et_2O$	Boron trifluoride diethyl etherate
BnCl	Benzyl chloride
BnBr	Benzyl bromide
Bn_2NH	Dibenzylamine
$(Boc)_2O$	Di-*t*-butyldicarbonate
BOMCl	Benzyloxymethyl chloride
BuLi	Butyl lithium
n-Bu_4NI	Tetrabutylammonium iodide
t-BuOH	Butanol
t-BuOK	Potassium *t*-butoxide
t-BuOOH	*t*-Butyl hydroperoxide
Bu_3P	Tributylphosphine
t-$BuPh_2SiCl$	*t*-Butyldiphenylchlorosilane
Bu_3SnH	Tributyltin hydride
BzOH	Benzoic acid
$CaCO_3$	Calcium carbonate
CbzCl	Benzyloxycarbonyl chloride
CCl_4	Carbon tetrachloride
CF_3CO_2H	Trifluoroacetic acid
C_6H_6	Benzene
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3I	Methyl iodide
CH_2N_2	Diazomethane
$(COCl)_2$	Oxalyl chloride
CSA	Camphor-10-sulfonic acid
CS_2	Carbon disulfide
CsOAc	Cesium acetate
DCC	Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
DET	Diethyl tartrate
DHQD-IND	Dihydroquinidine indolinylcarbamate
DIBALH	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	*N*-Ethyl-*N*-(3-dimethylaminopropyl)carbodiimide
Et_2O	Diethyl ether
Et_3N	Triethylamine

EtOH	Ethanol
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HCOOH	Formic acid
H_2O_2	Hydrogen peroxide
HPLC	High performance liquid chromatography
I_2	Iodine
Im	Imidazole
K_2CO_3	Potassium carbonate
$K_3Fe(CN)_6$	Potassium hexacyanoferrate(III)
KH	Potassium hydride
KI	Potassium iodide
KOH	Potassium hydroxide
$K_2OsO_4.2H_2O$	Potassium osmium(VI) oxide dihydrate
$LiAlH_4$	Lithium aluminium hydride
LiHMDS	Lithium hexamethyldisilazide
LiOH	Lithium hydroxide
MCPBA	*m*-Chloroperbenzoic acid
MeCN	Acetonitrile
$Me_2C(OMe)_2$	2,2-Dimethoxypropane
MeI	Methyl iodide (iodomethane)
MeOH	Methanol
Me_3SiBr	Trimethylsilyl bromide
Mg	Magnesium
MOMCl	Chloromethyl methyl ether
MTPA	α-Methoxy-α-trifluoromethylphenyl acetic acid
Me_2CuLi	Lithium dimethyl cuprate
Me_2S	Dimethyl sulfide
$Me_3S^+I^-$	Trimethylsulfonium iodide
MsCl	Methanesulfonyl chloride
Na(s)	Sodium metal
Na/liq. NH_3	Sodium liquid ammonia
$NaBH_4$	Sodium borohydride
$NaClO_2$	Sodium chlorite
NaCN	Sodium cyanide
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
$NaHCO_3$	Sodium hydrogen carbonate
NaI	Sodium iodide
NaN_3	Sodium azide
NaOMe	Sodium methoxide
NaOEt	Sodium ethoxide
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
O_3	Ozone
OsO_4	Osmiumtetroxide

Pd-C	10% Palladium on activated carbon
$Pd(OH)_2$	Palladium hydroxide
PMBCl	*p*-Methoxybenzyl chloride
PPh_3	Triphenylphosphine
i-Pr_2NEt	Diisopropylethylamine
$(iPrO)_2POCH(Me)CO_2Me$	Diisopropyl (methoxycarbonylmethyl) phosphonate
py	Pyridine
Raney-Ni	Raney-nickel
Red-Al	Sodium *bis*(2-methoxyethoxy)aluminium hydride
RuO_4	Ruthenium(VIII) oxide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	Tetrabutylhydroperoxide
TBSCl	*t*-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
$Ti(iPrO)_4$	Titanium(IV) isopropoxide
TLC	Thin layer chromatography
TrCl	Triphenylmethyl chloride
Trityl	Triphenylmethyl
TsCl	Toluene-4-sulfonyl chloride
TsIm	1-(Toluene-4-sulfonyl)imidazole
TsOH	Toluene-4-sulfonic acid
Zn-Cu	Zinc-copper couple

1 INTRODUCTION

1.1 GENERAL

Mycotoxins, toxic secondary metabolites produced by fungi, are the causative agents of various disorders in man and his domestic animals and have been part of mankind's environment throughout the ages. The diseases caused by the ingestion of foods or feeds contaminated by these toxic fungal metabolites are commonly called mycotoxicoses and are characterised by their sporadic regional and seasonal occurrence. The current international awareness of mycotoxins is the result of the outbreak of a mycotoxicosis that caused the death of 100 000 turkeys, 14 000 ducklings and thousands of partridge and pheasant poults in 1960 in England. The origin of the disease was traced to Brazilian peanut meal contaminated by aflatoxins, highly carcinogenic secondary metabolites of the ubiquitous fungi, *Aspergillus flavus* and *Aspergillus parasiticus.*[1]

Organic chemists, mycologists, plant pathologists, toxicologists and epidemiologists have extensively investigated fungal related problems and mycotoxins since the discovery of the aflatoxins. Cultures of *Fusarium* species, isolated from a wide variety of hosts, and their metabolites have been the subject of numerous investigations and continue to receive considerable attention due to their impact on human health and agricultural products. *Fusarium moniliforme* Sheldon, a common fungal contaminant of maize throughout the world, has been associated with diseases in both man and animals.[2] Although the liver is affected in most instances other target organs appear to be species specific: for instance, the lungs and pancreas of pigs (pulmonary edema and hydrothorax),[3,4] It has also been reported that *F. moniliforme* exhibits cancer promoting effects and dysfunction in rat liver [5,6,7,8,9,10] and cancer of the

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1 Wyllie, T.D.; L.G. Morehouse (Editors), *Mycotoxic Fungi, Mycotoxins, Mycotoxicoses, An Encyclopedia Handbook,* Marcel Dekker, USA, **1987**, *2*.
2 Bacon, C.W.; Williams, T.W. *Mycopathologia*, **1992**, *117*, 65.
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4 Haschek, W.M; Motelin, G; Ness, D.K.; Harlin, K.S.; Hall, W.F.; Vesonder, R.F.; Peterson, R.E.; Beasley, V.R.; *Mycopathologia*, **1992**, *117*, 83.
5 Gelderblom, W.C.A.; Semple, E.; Marasas, W.F.O.; Farber, E.; *Carcinogenesis*, **1992**, *13*, 433.
6 Gelderblom, W.C.A.; Jaskiewicz, K; Marasas, W.F.O.; Thiel, P.G.; Horak, R.M.; Vleggaar, R.; Kriek, N.P.J. *Appl. Environ. Microbiol.*, **1988**, *54*, 1806.
7 Gelderblom, W.C.A.; Marasas, W.F.O.; Vleggaar, R.; Thiel, P.G.; Cawood, M.E. *Mycopathologia*, **1992**, *117*, 11.
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9 Voss, K.A.; Plattner, R.D.; Bacon, C.W.; Norred, W.P. *Mycopathologia*, **1990**, *112*, 81.
10 Voss, K.A.; Norred, W.P.; Plattner, R.D.; Bacon, C.W. *Fd. Chem. Toxic.*, **1989**, *27*, 89.

oesophagus in humans.[11] The most widely reported animal fatal neurotoxic syndrome associated with the ingestion of *F. moniliforme* contaminated feed is equine leucoencephalomalacia (LEM).[12,13,14,15,16] Field outbreaks of LEM occur sporadically in many countries including South Africa, the United States of America and China. LEM is the only mycotoxicosis for which the causative role of a fungus, *F. moniliforme* has been established beyond doubt.

1.2 ISOLATION AND STRUCTURAL ELUCIDATION OF THE FUMONISINS.

The discovery and structural elucidation in South Africa of a new family of mycotoxins from a culture of *F. moniliforme* (strain MRC 826), called the fumonisins, as reported by Gelderblom *et al.*[6,17,18] followed an investigation into the cause of the high rate of oesophageal cancer in the Transkei as well as the outbreaks of LEM in a number of countries including South Africa. The structures of the fumonisins of the A (**1-3**) and B (**4-7**) series are illustrated in Table 1.2.

1.2.1 Isolation of the fumonisins.

The first isolation and purification of fumonisin B_1 (**4**) and B_2 (**5**) dealt mainly with the detection of cancer-promoting compounds produced by *F. moniliforme*. The purification techniques used by Gelderblom *et al.*[6] yielded both FB_1 (**4**) and FB_2 (**5**) with a purity of approximately 90%. The need to know more about the biological effects of the fumonisin toxins in both humans and animals, led to the development of more efficient and cost-effective methods for purifying sufficient quantities of the fumonisins.[18] The extraction and purification steps reported earlier[6] were used with minor modifications for the isolation of fumonisin B_1 (**4**) and other related compounds on a quantitative basis.

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[11] Sydenham, E.W.; Thiel, P.G.; Marasas, W.F.O.; Shephard, G.S.; van Schalkwyk, D.J.; Koch, K.R. *J. Agric. Food Chem.*, **1990**, *38*, 1900.
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[14] Sydenham, E.W.; Marasas, W.F.O.; Shephard, G.S.; Thiel, P.G.; Hirooka, E.Y. *J. Agric. Food Chem.*, **1992**, *40*, 994.
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[16] Thiel, P.G.; Shephard, G.S.; Sydenham, E.W.; Marasas, W.F.O.; Nelson, P.E.; Wilson, T.M. *J. Agric. Food Chem.*, **1991**, *39*, 109.
[17] Bezuidenhout, S.C.; Gelderblom, W.C.A.; Gorst-Allman, C.P.; Horak, R.M.; Marasas, W.F.O.; Spiteller, G.; Vleggaar, R. *J. Chem. Soc. Chem. Commun.*, **1988**, 743.
[18] Cawood, M.E.; Gelderblom, W.C.A.; Vleggaar, R.; Behrend, Y.; Thiel, P.G.; Marasas, W.F.O. *J. Agric. Food Chem.*, **1991**, *39*, 1958.

The culture material was first extracted with ethyl acetate to remove all the lipid-soluble matter and then with methanol-water (3:1) before the combined aqueous fractions were evaporated and dried *in vacuo*. The dried residues were partitioned between methanol-water (3:1) and chloroform to remove any remaining lipid-soluble material that could hamper the Amberlite XAD-2 column purification step. The aqueous methanol solution was applied to an Amberlite XAD-2 column that was equilibrated and washed with methanol-water before it was eluted with methanol to obtain the fumonisin mycotoxins. The effective separation of the individual fumonisins was achieved by silica gel chromatography using two different mobile phases. The first column separated most of the unwanted pigments from the fumonisin B series compounds but did not manage to completely separate fumonisin B_1 from B_2 and B_3. The complete separation was achieved in the second silica gel chromatography step that was followed for each fumonisin by a final purification step on a reversed phase C_{18} column. The use of the method led to the isolation of the fumonisins A_1 (**1**), A_2 (**2**), B_1 (**4**), B_2 (**5**), B_3 (**6**), and B_4 (**7**).

Fusarium moniliforme (strain KSU 819) accumulates no fumonisin B_1 (**4**) or B_2 (**5**) but produces fumonisin A_3 (**3**),[19] B_3 (**6**), B_4 (**7**), and C_4 (**12**) in high concentration. Poling and Platter[20,21] have reported the use of solid-phase extraction (SPE) columns for the isolation and separation of fumonisin B_3 and B_4. A CH_3CN-H_2O (1:1) extract of the culture material was stirred with IRA-68, a weak anion-exchange resin. The fumonisins were desorbed with 5% acetic acid in the same solvent. After dilution with water the desorbed fumonisins were separated into fumonisin B_3 and B_4 fractions with a tC_{18} SPE cartridge. Each fraction was subsequently purified on an SPE cartridge with a propylamine (NH_2)-bonded phase with 5% acetic acid in methanol and increasing amounts of acetonitrile in water to give fumonisin B_3 (**6**) and B_4 (**7**) with 90-95% purity.

A number of minor fumonisin metabolites have been isolated and characterised from cultures of *F. moniliforme* and *F. oxysporum* (KCTC 16654). The C series of fumonisins (see Table 1.2) *e.g.* fumonisin C_1 (**8**),[22,23] isofumonisin C_1 (**9**),[24] hydroxy-fumonisin C_1 (**10**) and fumonisin C_3 (**11**),[23] and fumonisin C_4 (**12**)[23,25] all lack the C(1)

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[19] Plattner, R.D.; Weisleder, D.; Poling, S.M. in *Fumonisins in Food*, (Ed. Jackson, L.S.; deVries, J.W.; Bullerman, L.B.), Plenum Press, New York, **1996**, 57
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[24] Seo, J.-A.; Kim, J.-C.; Lee, Y.-W. *J. Nat. Prod.*, **1999**, *62*, 355.
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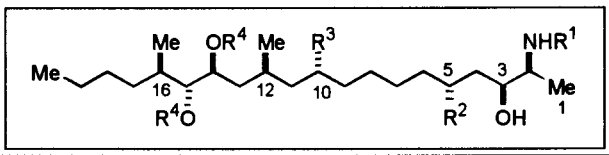
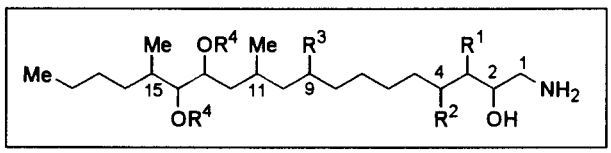


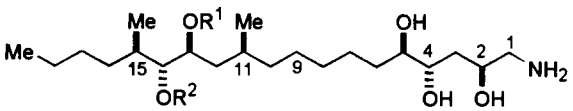
	Name	R^1	R^2	R^3	R^4	MW
1	FA_1	Ac	OH	OH	TCA	763
2	FA_2	Ac	OH	H	TCA	747
3	FA_3	Ac	H	OH	TCA	747
4	FB_1	H	OH	OH	TCA	721
5	FB_2	H	OH	H	TCA	705
6	FB_3	H	H	OH	TCA	705
7	FB_4	H	H	H	TCA	689

Table 1.1 Structure of the fumonisins of the A and B series

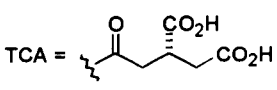


	Name	R^1	R^2	R^3	R^4	MW
8	FC_1	H	OH	OH	TCA	707
9	Iso-FC_1	OH	H	OH	TCA	707
10	HO-FC_1	OH	OH	OH	TCA	723
11	FC_3	H	H	OH	TCA	691
12	FC_4	H	H	H	TCA	675

Table 1.2 Structures of the fumonisins of the C series



13 TA { TA_1 R^1 = TCA, R^2 = H
TA_2 R^1 = H, R^2 = TCA



methyl group present in the fumonisin A and B series and thus show a close resemblence to the AAL toxins *e.g.* TA toxin (**13**). The isolation of the *N*-acetyl derivatives of the three fumonisin C_1 compounds has been reported.[24] The P series of fumonisins has been isolated from maize cultures of a strain of *F. moniliforme*. The new compounds fumonisin P_1, P_2 and P_3 correspond to fumonisin B_1 (**4**), B_2 (**5**), B_3 (**6**), respectively but contain a *N*-linked 3-hydroxypyridinium moiety instead of an amino group at C(2) of the backbone.[26]

1.2.2 Structure elucidation.

The chemical nature of the mycotoxins produced by *F. moniliforme* remained unknown until 1988, when Bezuidenhout *et al.*[17] isolated and purified fumonisin B_1 (**4**) and B_2 (**5**), the two major members of the fumonisin family. The structures of these compounds were elucidated by mass spectrometry and NMR spectroscopy as the diesters of propane-1,2,3-tricarboxylic acid and 2-amino-12,16-dimethyl-3,5,10,14,15-pentahydroxyicosane (**4**) as well as the C-10 deoxy analogue (**5**). In all cases both the C(14) and C(15) hydroxy groups are involved in ester formation with a terminal carboxy group of propane-1,2,3-tricarboxylic acid. In addition, several other structurally related compounds *viz.* fumonisin B_3 (**6**), A_1 (**1**) and A_2 (**2**) were isolated and the structures determined.

1.2.3 Stereochemical analysis of the backbone of the fumonisins.

The strategy by Boer[27] to establish the configuration of the stereogenic centres of the backbone of fumonisin B_1 (**4**) and B_2 (**5**), is based on the formation of conformationally rigid 1,3-oxazolidinone, 1,3-dioxolane and 1,3-dioxane derivatives and the use of NMR techniques.

Fumonisin B_2 (**5**) was hydrolysed with 1M KOH to give the aminotetrol (**14**). The aminotetrol (**14**) was converted to the oxazolidinone (**15**) by formation of the *N*-Boc derivative and treatment with sodium ethoxide (see Scheme 1.1). The fact that an NOE was observed between the C-1 protons and H(3), but not H(4), as well as an NOE between H(2) and both the C(4) protons in the oxazolidinone (**15**) established the *trans*

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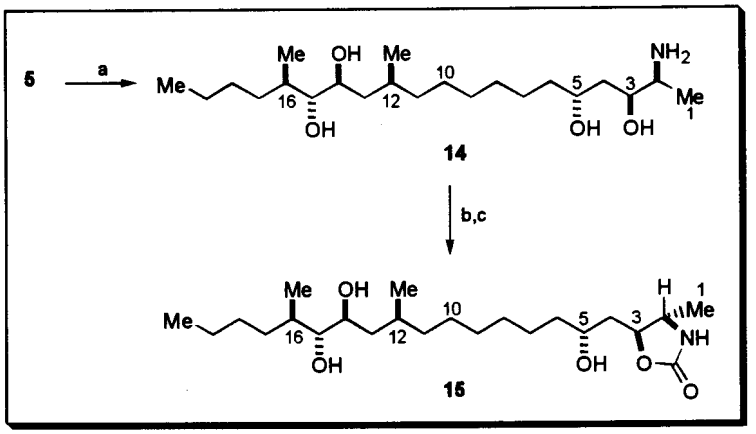
[26] Musser, M.M.; Gay, M.L.; Mazzola, E.P.; Plattner, R.D. *J. Nat. Prod.*, **1996**, *59*, 970.
[27] Boer, A. Stereochemical studies on the fumonisins, metabolites of *Fusarium moniliforme*, M.Sc Dissertation, University of Pretoria, **1992**.



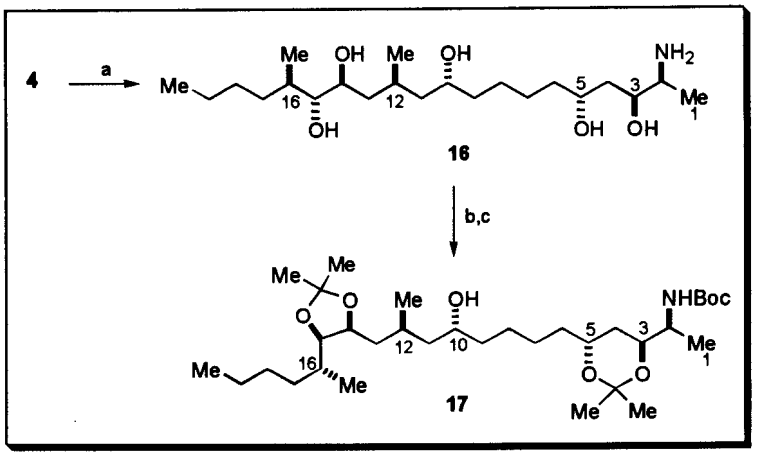
Scheme 1.1 *Reagents*: (a) 1M KOH; (b) $(Boc)_2O$; (c) NaOEt.

relationship between C(1) and C(4). The 2-amino and 3-hydroxy groups in the fumonisins must therefore have the *syn* relative configuration.

Rychnovsky[28] has shown that the acetonides of *syn* and *anti* 1,3-diols (4,6-dialkyl-2,2-dimethyl-1,3-dioxanes) can be unambiguously distinguished by the ^{13}C chemical shifts of the acetonide methyl groups and the acetal carbon atom. The ^{13}C NMR spectra of *syn* 1,3-diol acetonides show an axial methyl group carbon atom at δ_C 19.6 and the corresponding equatorial one at δ_C 30.0. This is in contrast to the spectra of the *anti* 1,3-diol acetonides which show the methyl resonances at δ_C 24.7. The acetal carbon chemical shifts are also indicative of the stereochemistry: δ_C 98.5 for the *syn* 1,3-diol acetonides and δ_C 100.4 for the *anti* stereoisomer. The 3,5:14,15 diacetonide derivative (**17**) was prepared as indicated in Scheme 1.2. The aminopentol (**16**) obtained from fumonisin B_1 (**4**) by hydrolysis was converted to the *N*-Boc derivative and then to the diacetonide (**17**). The ^{13}C chemical shifts observed for the methyl groups (δ_C 24.57 and 26.12) and the acetal carbon atom (δ_C 100.37) confirmed the *anti* relationship for the C-3 and C-5 oxygen atoms in (**17**) and thus the corresponding hydroxy groups in the fumonisins.

The relative configuration of the C-14 and C-15 stereogenic centres in the fumonisins was deduced from the magnitude of the proton-proton coupling constants observed for the 3,4:14,15-diacetonide (**17**). The observed coupling constant of 5.3 Hz for the C(14) and C(15) protons indicated a *cis* relationship for these protons and therefore an *anti* relationship for the corresponding hydroxy groups in the fumonisins.

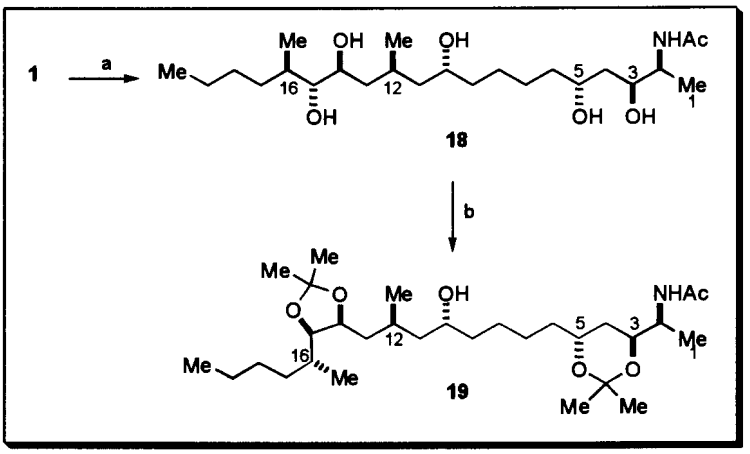
[28] Rychnovsky, S.D.; Rogers, B.; Yang, G. *J. Org. Chem.*, **1993**, *58*, 3511.



Scheme 1.2 *Reagents*: (a) 1M KOH; (b) $(Boc)_2O$; (c) $Me_2C(OMe)_2$, TsOH

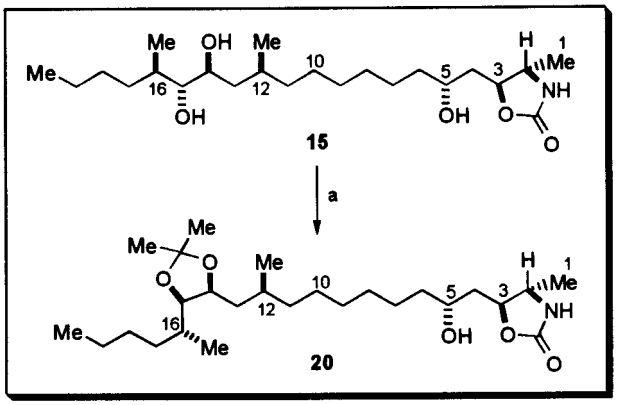
The *anti* relationship for the C(16) methyl group and the C(15) hydroxy group in the fumonisins followed from NOE studies on (**17**).

The absolute configuration of the C(10) stereogenic centre in fumonisin B_1 was determined by the method of Horeau[29,30] as *R* using the *N*-acetyl diacetonide derivative (**19**) (see Scheme 1.3) in the esterification reaction with an excess of racemic α-phenylbutyric anhydride. The absolute configuration of the C(5) stereogenic centre was established as *R* by the same methodology using the 14,15-acetonide (**20**), obtained from the triol (**15**)(see Scheme 1.4), and consequently the 2*S*,3*R*,5*R* absolute configuration on the basis of the earlier determined relative stereochemistry.



Scheme 1.3 *Reagents*: (a) 1M KOH; (b) $Me_2C(OMe)_2$, TsOH.

[29] Horeau, A. *Tetrahedron Lett.*, **1961**, 506; **1962**, 965.
[30] Horeau, A.; Kagan, H.B. *Tetrahedron*, **1964**, *20*, 2431.



Scheme 1.4 *Reagents*: (a) $Me_2C(OMe)_2$, TsOH.

The strategy for the determination of the absolute configuration of the C(16) stereogenic centre in the fumonisins is based on the oxidative cleavage of the 15,16-diol moiety in (**18**) with CrO_3-H_2SO_4 (Kiliani reagent) to give a single enantiomer of 2-methylhexanoic acid which was converted to the (*S*)-α-methyl-*p*-nitrobenzylamide derivative. The correlation of the HPLC retention time of this diastereomer with those of the (*S*)-α-methyl-*p*-nitrobenzylamide derivatives of each of the enantiomers of 2-methylhexanoic acid established the 2*R* configuration of the 2-methylhexanoic acid obtained in the oxidative cleavage reaction and thus the 16*R* configuration of the fumonisins. The 14*S*,15*R*,16*R* configuration followed from the relative stereochemistry of these stereogenic centres.

The absolute configuration of the C(12) stereogenic centre was assigned on the basis of biosynthetic arguments. Enzymatic methylations at the different active methylene sites of a polyketide precursor follow the same stereochemical course.[31] As a consequence the absolute configuration of the C(12) and C(16) methyl groups should be the same and C(12) must have the *R* configuration.

The relative stereochemistry of the C(1)–C(5) unit of fumonisin B_1 (**4**) was confirmed by ApSimon *et al.*[32] using NMR studies of the 2,3-oxazolidinone and the 3,5-carbonate derivatives. Poch *et al.*[33] also confirmed the 2,3-*syn* stereochemistry. The relative stereochemistry of the C(10)–C(16) fragment was confirmed by NMR studies of the 10,14-cyclic ether derivative (**21**) by Blackwell *et al.*[34]

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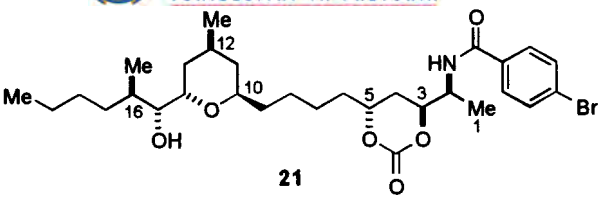
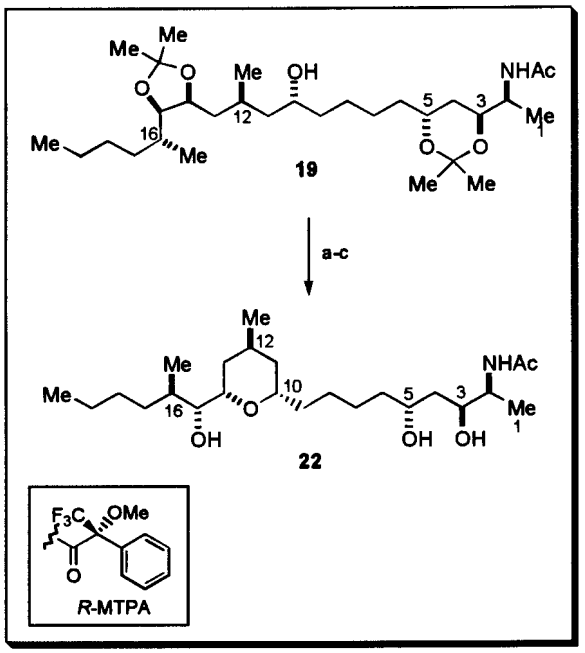
[31] Turner, W.B.; Aldridge, D.C. Fungal Metabolites II, Academic Press, London, **1983**, p. 112.
[32] ApSimon, J.W.; Blackwell, B.A.; Edwards, O.E.; Fruchier, A. *Tetrahedron Lett.*, **1994**, *35*, 7703.
[33] Poch, G.K., Powell, R.G., Plattner, R.D.; Weisleder D., *Tetrahedron Lett.*, **1994**, *35*, 7707.
[34] Blackwell, B.A.; Edwards,O.E.; ApSimon, J.W.; Fruchier, A. *Tetrahedron Lett.*, **1995**, *36*, 1973.



21

The relative and absolute configuration of the eight stereogenic centres of the fumonisin B_1 backbone assigned by Hoye et al.[35] are based on NMR studies of a number of derivatives and confirmed the findings of Boer.[27] Thus the absolute configuration of the C(10) stereogenic centre was determined as *R* by Mosher analysis[36,37] of the *R*- and *S*-α-methoxy-α-trifluoromethylphenyl acetate (MTPA) esters of the C(10) hydroxy group in (**19**) (see Scheme 1.5)



Scheme 1.5 *Reagents*: (a) MsCl, Et_3N, DMAP, CH_2Cl_2; (b) MeOH, Dowex; (c) NaH, THF.

The diacetonide (**19**) was converted to the C(10) mesylate by treatment with MsCl, the acetonides were removed by stirring with Dowex H^+ resin in methanol and the pyran (**22**) was formed with inversion of configuration at C(10) by treatment with NaH in THF. Finally the tri-(*S*) and tri-(*R*)-MPTA esters were prepared. Analysis of the ^1H NMR data for the protons of the pyran ring in (**22**) indicated the *cis* relationship between the C(10) and C(14) protons and that both these protons are axially oriented. The C(12) methyl group is axial on the pyran ring. Mosher analysis established the 15*R*

[35] Hoye, T.R.; Jiménez, J.I.; Shier, W.T. *J. Am. Chem. Soc.*, **1994**, *116*, 9409.
[36] Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, *95*, 512.
[37] Sullivan, G.R.; Dale, J.A.; Mosher, H.S. *J. Org. Chem.*, **1973**, *38*, 2143.

configuration. The 16*R* configuration was established by sodium periodate cleavage of the aminopentol (**16**) to give (2*R*)-methylhexanal identified by chiral gas chromatography using racemic and enantiopure standards.

Hartl and Humpf[38] applied the circular dichroism (CD) exciton chirality method to determine the absolute configuration of the C(1)–C(5) unit of the backbone of the fumonisins. Using the *p*-dimethylaminobenzoate chromophore, the stereochemistry of fumonisin B_1 (**4**) was confirmed as 2*S*,3*S*,5*R* and that of fumonisin B_3 (**6**) as 2*S*,3*S*.

Harmange *et al.*[39] followed a different approach to establish the absolute configuration of (**14**), the C_{20} backbone of fumonisin B_2 (**5**) and exploited the fact that the right-side with three stereogenic centres has no effect on the spectroscopic properties of the left-side with five stereogenic centres. The disconnection of the C(8)–C(9) bond in (**14**) identifies two distinct synthons: the phosphonium salt (**23**) and the aldehyde (**24**)(see Figure 1.1).

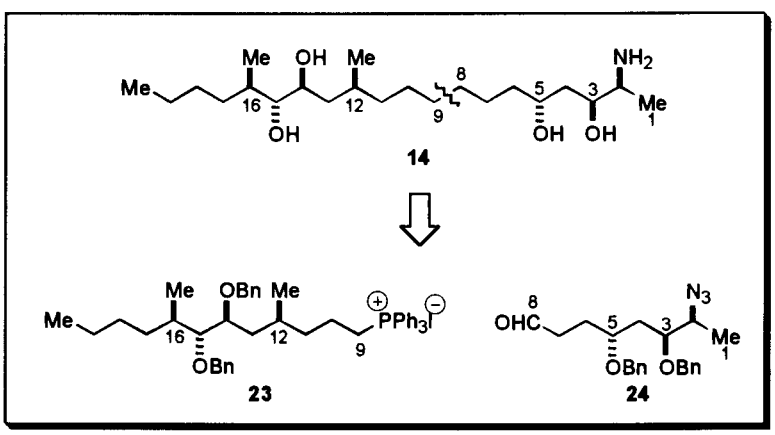


Figure 1.1 Retrosynthetic analysis of the backbone (**14**) of fumonisin B_2.

The phosphonium salt *ent*-(**23**) corresponding to the left-side was prepared from (2*S*)-2-methyl-1-hexanol and (*R*)-(–)citronellyl bromide. For the right-side the diastereomeric azido aldehydes *ent*-(**24**) and (**25**), both with the 2,3-*syn* configuration, were prepared from (2*S*)-glutamic acid — note that all three synthetic targets correspond to the antipode of (**14**). The synthetic amino alcohol hydrochloride salts (**26a**)•**HCl** and (**27a**)•**HCl** were obtained by Wittig olefination (n-BuLi, THF,–78°C→ RT) and hydrogenation/hydrogenolysis (H_2,Pd-C, H^+, MeOH) (see Figure 1.2). The ^{1}H NMR spectrum of (**14**)•**HCl** was found to be clearly different from that of (**27a**)•**HCl** but

[38] Hartl, M.; Humpf, H.-U. *Tetrahedron Asymmetry*, **1998**, *9*, 1549.
[39] Harmange, J.-C.; Boyle, C.D.; Kishi, Y. *Tetrahedron Lett.*, **1994**, *35*, 6819.

superimposable on that of (**26a**)•**HCl**. This experiment established that *ent*-(**23**) and *ent*-(**24**) represented the relative stereochemistry of the left- and right-sides and that the relative stereochemistry of (**14**), the backbone of fumonisin B_2, was represented by either (**26a**)•**HCl** or the diastereomer (**28a**)•**HCl**. Therefore the hydrochloride salt (**28a**)•**HCl** was synthesised from *ent*-(**23**) and (**24**). As expected both (**26a**)•**HCl** and (**28a**)•**HCl**, as well as (**14**)•**HCl** gave identical ^{1}H NMR spectra.

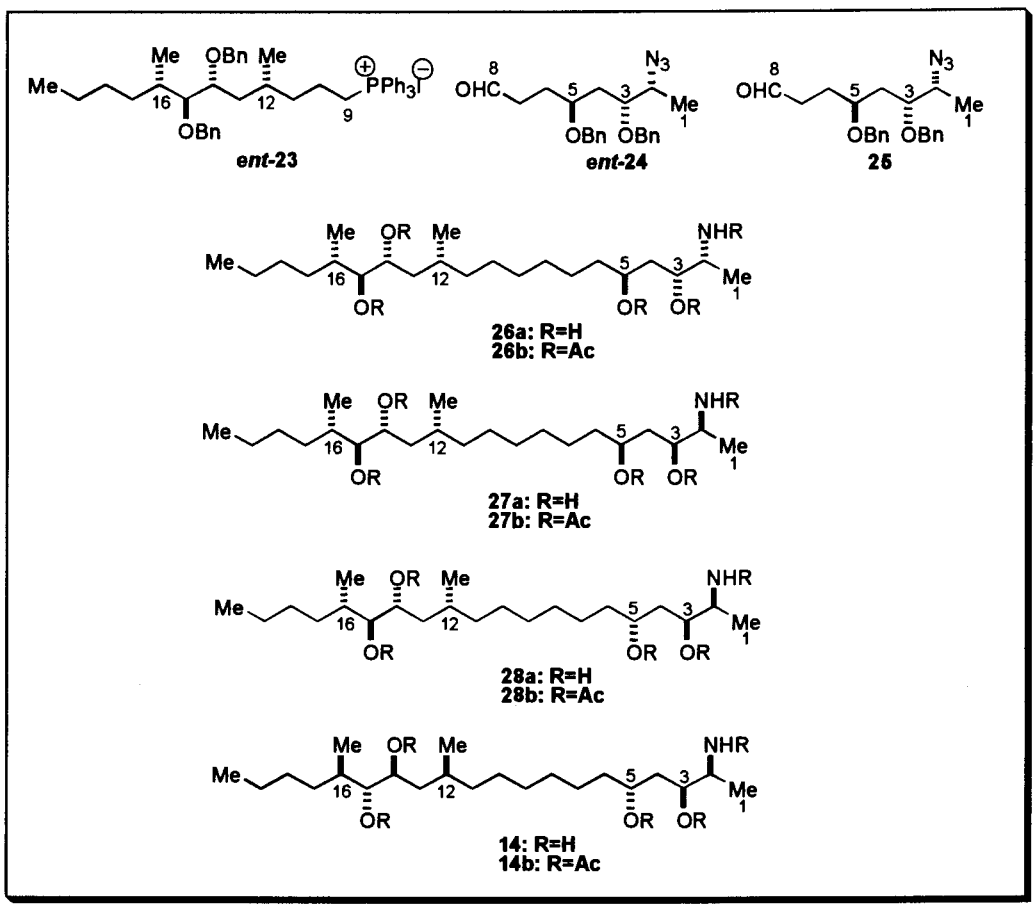


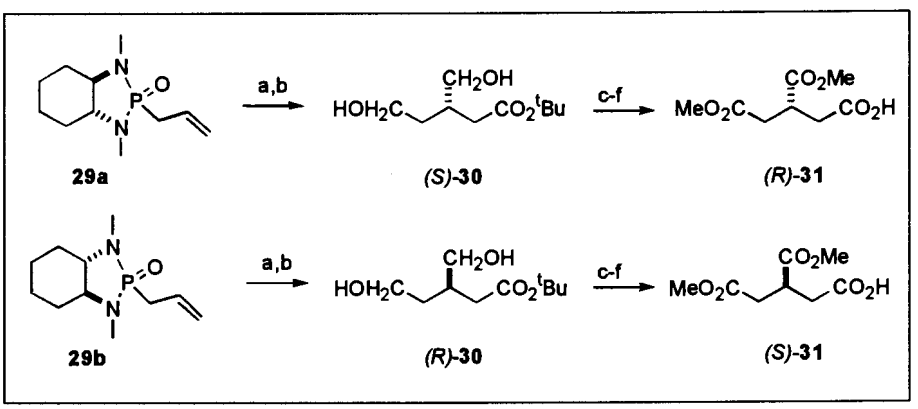
Figure 1.2 Structures of the stereoisomers used in determining the absolute configuration of the fumonisin B_2 backbone.

In order to differentiate (**26**) and (**28**), the corresponding pentaacetates (**26b**) and (**28b**) were prepared and the ^{1}H NMR spectra compared with that of (**14b**) in the presence of Eu(fod)$_3$. A 2:1 mixture of (**28b**) and (**14b**) behaved as two different compounds in the presence of Eu(fod)$_3$ but a 2:1 mixture of (**14b**) and (**26b**) acted as a single compound. Thus (**26a**) represents the relative stereochemistry of the fumonisin B_2 backbone. The absolute stereochemistry of the backbone was established as (**14**); a 2:1 mixture (**14b**) and (**26b**) behaved as two different compounds in the presence of a chiral shift reagent (+)-Eu(thf)$_3$. In addition the signs of the specific rotation observed for (**26b**) ($[\alpha]_D$ +27) and (**14b**) ($[\alpha]_D$ –29) supported this conclusion.

1.2.4 Stereochemical analysis of the tricarballylic acid moiety.

Two different groups who arrived at different conclusions determined the absolute configuration of the stereogenic centre present in the tricarballylic ester moiety of the fumonisins.

Boyle *et al.*[40] synthesised both stereoisomers of tricarballylic acid dimethyl ester. The procedure involves a modification of the Hanessian protocol for the asymmetric Michael addition of a chiral allylphosphonamide to *t*-butyl sorbate.[41] The modification involves the addition of LiHMDS to a mixture of allylphosphonamide (**29**) and *t*-butyl sorbate at –78°C instead of deprotonation of the allylphosphonamide by *n*-BuLi at –78°C, followed by the immediate addition of *t*-butyl sorbate. A cleaner reaction and higher yields were obtained in this way. Ozonolysis of the Michael adduct followed by reductive work-up using $NaBH_4$ produced (*S*)-and (*R*)-**30** (Scheme 1.6).



Scheme 1.6: Synthesis of the two isomers of the tricarballylic acid moiety.

Reagents: (a) LiHMDS, *t*-butyl sorbate, THF, –78°C; (b) O_3, $NaBH_4$; (c) Swern oxidation; (d) $NaClO_2$; (e) CH_2N_2; (f) CF_3CO_2H.

Hanessian originally assigned the absolute configuration of (*S*)-**30** and this assignment was verified by the correlation with the compound derived from (*S*)-2-methyl-1-butanol (see Scheme 1.7). Although the optical purity of (*S*)- and (*R*)-**30** was in each case greater than 95:5, that of (*S*)- and (*R*)-**31** were determined by derivatisation with (–)-menthol to give a ca. 5:1 mixture of diastereomers in each case.[40]

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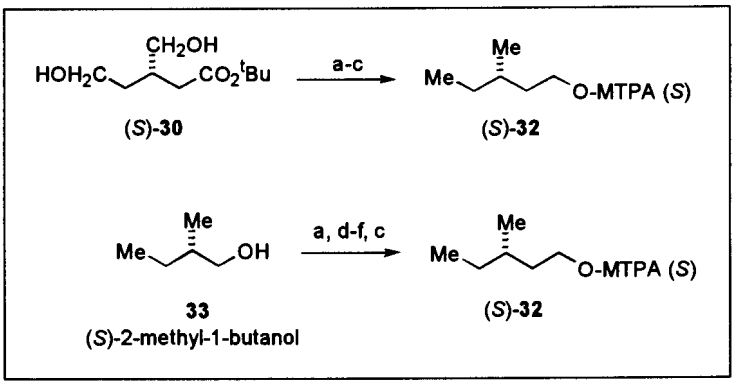
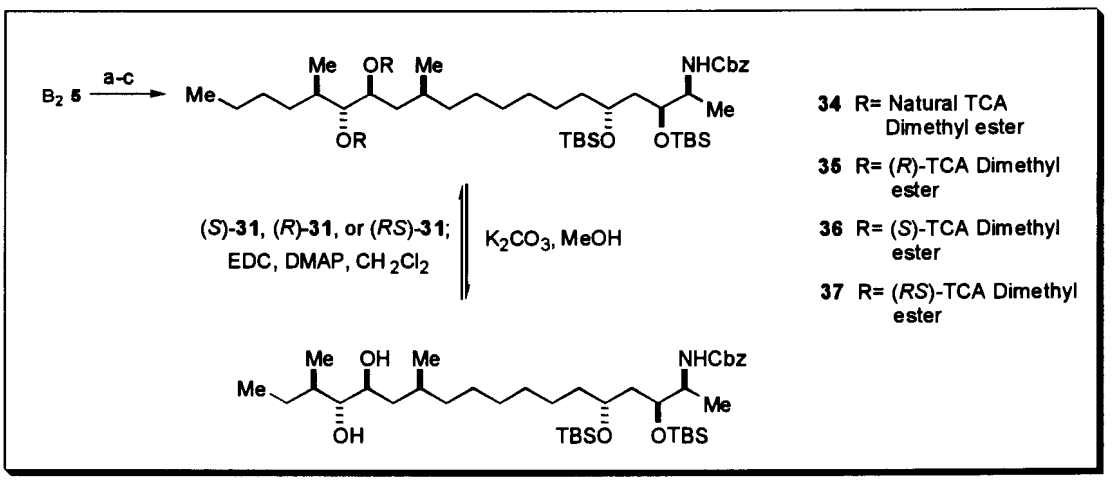
[40] Boyle, C.D, Kishi, Y. *Tetrahedron Lett.*, **1995**, *36*, 4579.
[41] Hanessian, S, Gomtsyan, A.; Payne, A.; Harvé, Y.; Beaudoin, S. *J. Org. Chem.*, **1993**, *58*, 5032.



Scheme 1.7: Preparation of (*S*)-**32** from (*S*)-2-methyl-1-butanol (**33**).

Reagents: (a) TsCl, Py; (b) $LiAlH_4$, Et_2O; (c) (*S*) MTPA, EDC, DMAP; (d) NaCN; (e) DIBALH; (f) $NaBH_4$

The tricarballylic acid dimethyl esters (*S*)-and (*R*)-**31** were linked by an ester bond to the C(14) and C(15) hydroxy group of the protected C_{20} backbone obtained from fumonisin B_2 as outlined in Scheme 1.8, to give the esters (**35**), (**36**) and (**37**). Comparison of the ^1H NMR spectra of these esters with that of the protected fumonisin B_2 derivative **34** established the *R* configuration of the tricarballylic ester moiety in fumonisin B_2 (see Figure 1.3). A similar approach established the *R* configuration for the tricarballyllic acid moiety in fumonisin B_1.[42]



Scheme 1.7: Fumonisin B_2 analogues with different tricarballylic acid dimethyl ester stereoisomers.

Reagents: (a) CH_2N_2, MeOH; (b) CbzCl, $NaHCO_3$; (c) TBSCl, imidazole, DMF.

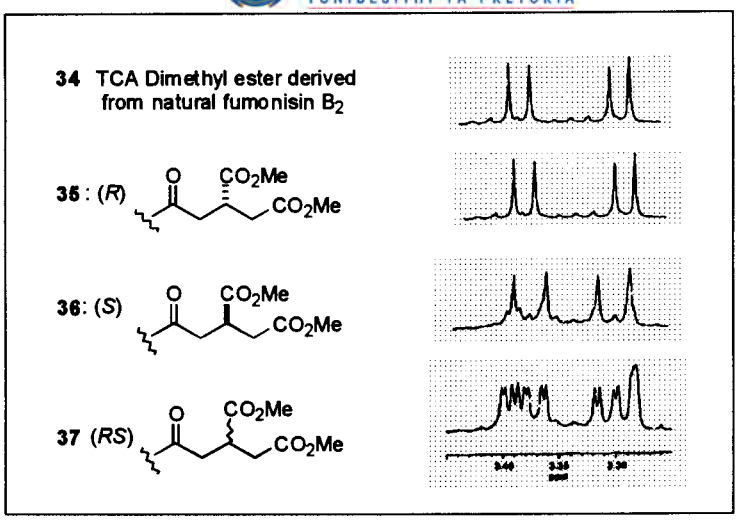
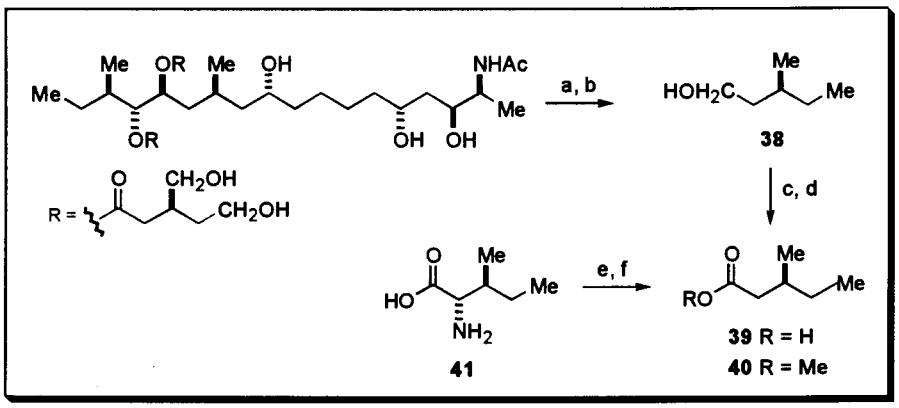


Figure 1.3: ^{1}H NMR (400 MHz, C_6D_6) spectra of the methyl ester region of fumonisin B_2 analogues with different tricarballylic ester stereoisomers.[40]

The Shier group[43] used chiral gas chromatography to determine the absolute configuration of the tricarballylic acid moiety in fumonisin B_1 (**4**) and the AAL toxins. Since the free propane-1,2,3-tricarboxylic acid is achiral, it was necessary to differentiate the free carboxyl groups from the ones involved in the ester linkage prior to separation from the backbone.



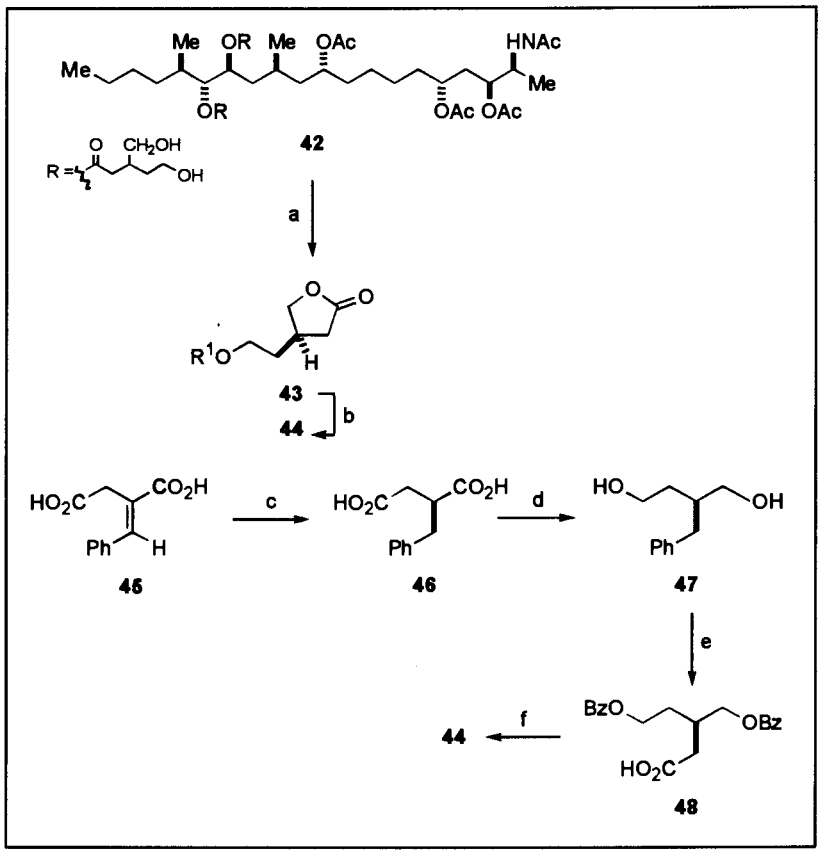
Scheme 1.8: Synthesis of the tricarballylic acid moiety derivative.

Reagents: (a) TsCl, Py; (b) $LiAlH_4$, THF; (c) CrO_3, H_2SO_4; (d) CH_2N_2; (e) H_2N-OSO_3H, NaOH; (f) CH_2N_2.

Diborane in THF was used to selectively reduce the free carboxyl groups in the *N*-acetyl derivative (≡ fumonisin A_1) (**1**) and to avoid the formation of a compound with a stereogenic centre α to a free carboxyl group in order to prevent racemisation under the alkaline conditions. This is usually the case in the reduction of the ester linkage

[42] Boyle, C.D.; Kishi, Y. *Tetrahedron Lett.* 1995, **36**, 5695.

using borohydride salts. The reduced product was immediately tosylated and reduced to 3-methyl-1-pentanol **38.** Racemic **38** could not be resolved into two peaks by gas chromatography on chiral columns. Thus the oxidation of the released side chain **38** was carried out to give the carboxylic acid **39** which was converted to the methyl ester **40** as the acid also could not be resolved (Scheme 1.8). A reference compound was prepared from L-isoleucine **41**. Treatment with hydroxylamine-*O*-sulfonic acid under alkaline conditions and esterification of the product with diazomethane produced the methyl ester **40** identical with that obtained from the natural product. In this way the *(S)* configuration was established for the stereogenic center of the tricarballylic ester.



Scheme 1.9 Synthesis of the (*R*)-(-)-hydroxy-γ-lactone **51**

Reagents: (a) KOH, MeOH, then H^+; (b); BzCl; (c) [(–)-phenyl-CAPP]RhCl, H_2; (d) BH_3, THF; (e) i. BzCl, Py, ii. RuO_4; (f) KOH, then H^+.

Edwards *et al.*[44] provided evidence that supported the *R* configuration proposed by Kishi. The approach involves stabilization of the stereogenic centre in the tricarbal-

[43] Shier, W.T.; Abbas, H.K.; Badria, F.A. *Tetrahedron Lett.*, **1995**, *36*, 1571.
[44] Edwards, O.E.; Blackwell, B.A.; Driega, A.B.; Bensimon, C.; ApSimon, J.W. *Tetrahedron Lett.*, **1999**, *40*, 4515

lylic ester moiety in fumonisin B_1 by borane reduction of the free carboxyl groups to give (**42**) (see Scheme 1.9). Hydrolysis of all the ester groups in (**42**) using KOH in aqueous MeOH, followed by acidification and extraction with chloroform gave a mixture rich in the γ-lactone (**43**). Benzoylation and separation by chromatography afforded (**44**) in high yield. An authentic sample of (**44**) was prepared from *E*-phenylitaconic acid (**45**), the stereochemistry of which was assigned by X-ray crystallography. Stereo-selective reduction of (**45**) gave (*S*)-(–)-2-benzylsuccinic acid (**46**) that was converted by reduction with diborane to the diol (**47**). Benzoylation of the hydroxy groups and oxidation of the phenyl group with ruthenium tetroxide gave the dibenzoyloxy acid (**48**). Alkaline hydrolysis followed by acidification afforded (*R*)-(–)-hydroxy-γ-lactone (**44**). Comparison of the MS, IR, ^{13}C and ^{1}H NMR spectra of the two samples established the structure and the specific rotation the *R* absolute configuration.

1.2.5 Synthetic Studies.

Synthetic studies on the fumonisins have been undertaken in order to develop a synthetic route that will allow the synthesis of analogs in order to study structure= activity relationships. Shi *et al.*[45] have reported the enantioselective synthesis of fumonisin B_2 (**5**): a convergent approach was adopted with the molecule being divided in three units — the left unit (**49**), the right unit (**50**), and the tricarballylic unit (**51**)(see Figure 1.4).

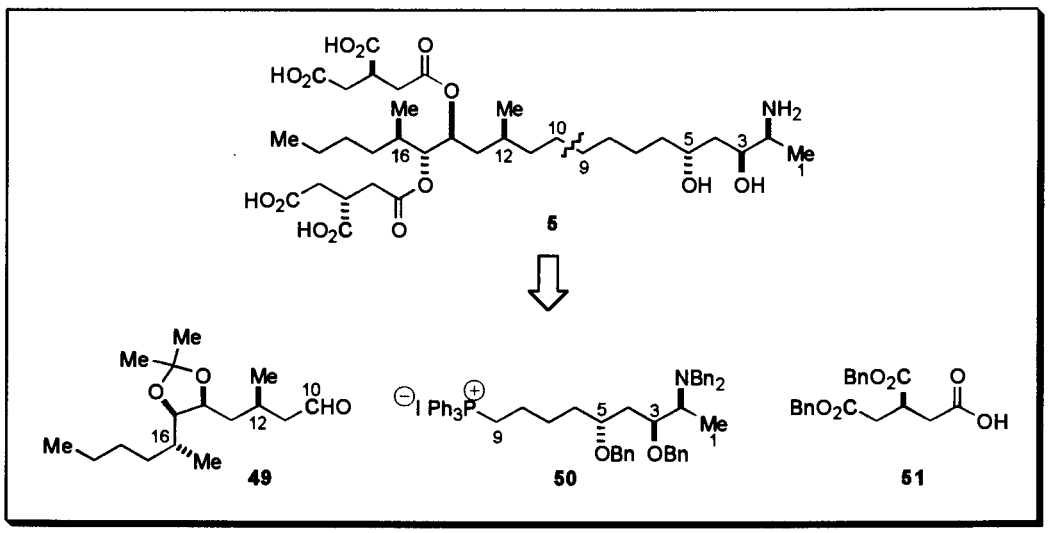
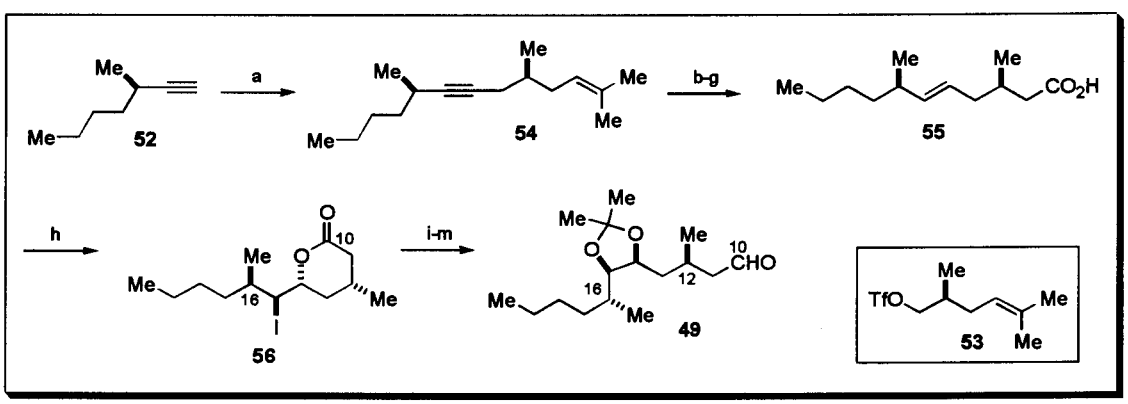


Figure 1.4 Retrosynthesis of fumonisin B_2 (**5**).

[45] Shi, Y; Peng, L.F.; Kishi, Y. *J.Org. Chem.*, **1997**, *62*, 5666.

The synthesis of the left unit (**49**) began with coupling of the chiral alkyne (**52**) with the triflate (**53**) to give the alkyne (**54**)(see Scheme 1.10). The alkyne (**54**) was transformed to the *trans*-alkene acid (**55**) via (1) site-selective osmylation, (2) $Pb(OAc)_4$ cleavage of the resultant diol, followed by $NaBH_4$ reduction, (3) Na/NH_3 reduction of the alkyne to a *trans*-alkene, and (4) Swern and then $NaClO_2$ oxidations of the primary alcohol to the acid (**55**). The vicinal C(14) and C(15) hydroxy groups were stereoselectively introduced on the backbone of (**55**) in three steps: (1) iodolactonisation of (**55**) under equilibrium conditions in MeCN at –30°C to give the iodolactone (**56**) in 84% yield with a diastereomeric ratio greater than 20:1, (2) ring opening of the lactone with $PhCH_2ONa$ to yield the C(14)-C(15) epoxide benzyl ester, and (3) deprotection (Pd-C, H_2) of the resultant benzyl ester with concomitant epoxide ring opening, to give the lactone alcohol with the desired stereochemistry at both C(14) and C(15). The lactone alchol was reduced to a triol, the two vicinal hydroxy groups protected as the acetonide and Swern oxidation of the primary alcohol gave the aldehyde (**49**).

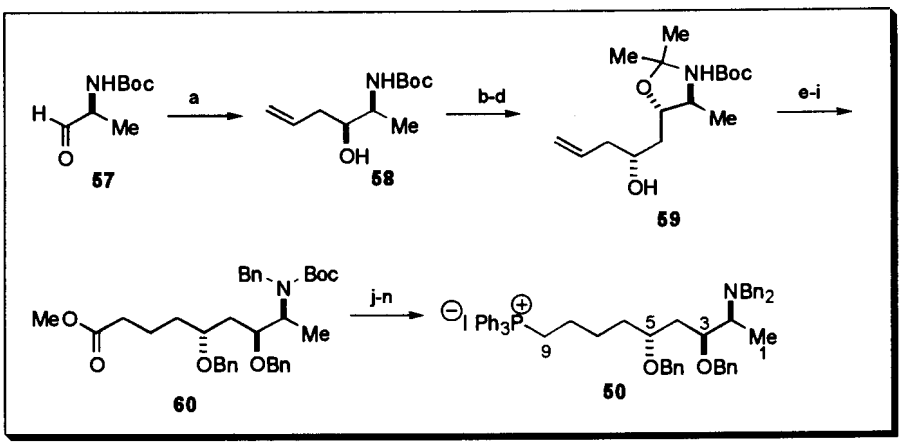


Scheme 1.10 Synthesis of the left unit of fumonisin B_2.

Reagents: (a) n-BuLi, then **53**; (b) $K_2OsO_4.2H_2O$; (c) $Pb(OAc)_4$; (d) $NaBH_4$; (e) Na/liq. NH_3; (f) Swern oxidation; (g) $NaClO_2$; (h) I_2, MeCN; (i) BnONa; (j) Pd-C, H_2, TsOH; (k) TsOH, acetone; (l) Swern oxidation.

The synthesis of the right unit is outlined in Scheme 1.11. Allylation of α-amino aldehyde (**57**) with Brown's chiral (–)-*B*-allyldiisopinocampheylborane gave *syn*-amino alcohol (**58**) in 75% yield and 94% diastereoselectivity. Protection of (**58**) as the acetonide and ozonolysis of the alkene with reductive workup provided an aldehyde, which was then reacted with (+)-*B*-allyldiisopinocampheylborane to give the *anti*-alcohol (**59**) with a diastereomeric ratio of 10:1 in 65% yield. Acetonide deprotection of (**59**) followed by benzyl group protection provided an alkene, which was converted into

an aldehyde by ozonolysis with dimethyl sulfide workup. A two-carbon chain extension in two steps, *i.e.*, (1) Wadsworth-Emmons olefination and (2) hydrogenation, gave the ester (**60**) in 70% overall yield from (**59**). Removal of the Boc-group, protection of the resultant amine and DIBALH reduction of the ester group gave an alcohol which was transformed into an alkyl halide and then treated with Ph_3P in acetonitrile to give the phosphonium salt (**50**).



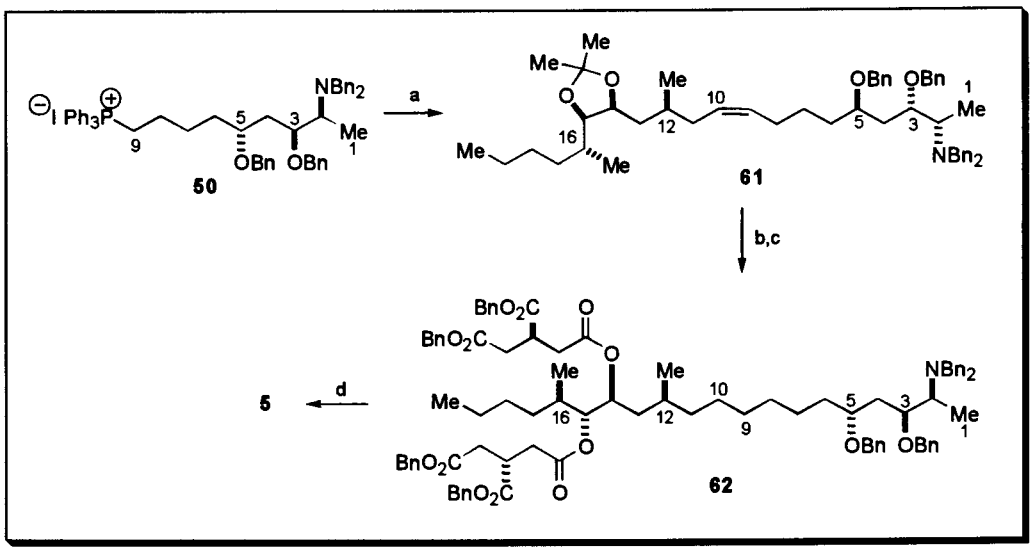
Scheme 1.10 Synthesis of the right unit of fumonisin B_2.

Reagents: (a) (–)-Ipc_2B-allyl; (b) TsOH, acetone; (c) O_3, then Me_2S; (d) (+)-Ipc_2B-allyl; (e) TsOH, MeOH; (f) NaH, BnBr, TBAI; (g) O_3, then Me_2S; (h) $(MeO)_2POCH_2CO_2Me$; (i) Lindlar catalyst, H_2; (j) TFA, CH_2Cl_2; (k) BnBr, K_2CO_3: (l) DIBALH; (m) I_2, Ph_3P; (n) Ph_3P, CH_3CN.

The completion of the fumonisin B_2 synthesis is depicted in Scheme 1.11. The backbone (**61**) was formed through a Wittig reaction of the ylide generated from the phosphonium salt (**50**) with the aldehyde (**49**) in 80% yield. TFA treatment to remove the acetonide and acylation of the resultant diol with the tricarballylic ester moiety (**51**) gave the fully protected fumonisin B_2 (**62**) in 90% yield. Hydrogenation of the alkene and hydrogenolysis of all the benzyl protecting groups with $Pd(OH)_2$ gave fumonisin B_2 (**5**)

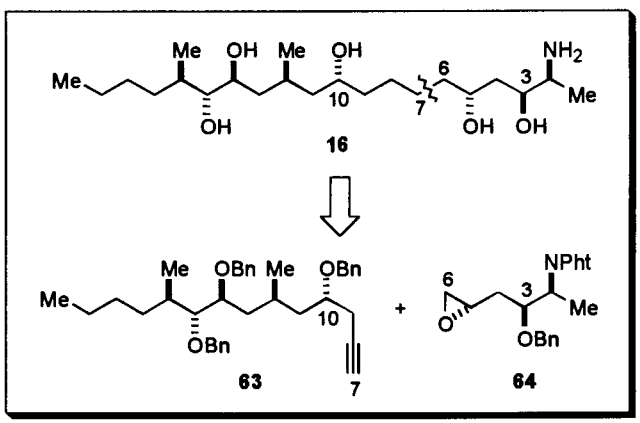
Carbohydrates constitute an inexpensive source in modern organic synthesis of chiral compounds that can be transformed through specific chemical reactions into versatile synthetic intermediates with predetermined functional groups and stereogenic centres. Gurjar *et al.*[46] have reported the use of carbohydrates in the synthesis of the C_{20} backbone (**16**) of fumonisin B_1. Disconnection of the C(7)–C(8) bond in (**16**)

[46] Gurjar, M.K.; Rajendren, V.; Rao, B.V. *Tetrahedron Lett.*, **1998**, *39*, 3803.



Scheme 1.12 Synthesis of fumonisin B_2 (**5**).

Reagents: (a) n-BuLi, then (**49**); (b) TFA, H_2O; (c) (**51**), EDC, DMAP; (d) H_2, $Pd(OH)_2$, *t*-BuOH-THF.

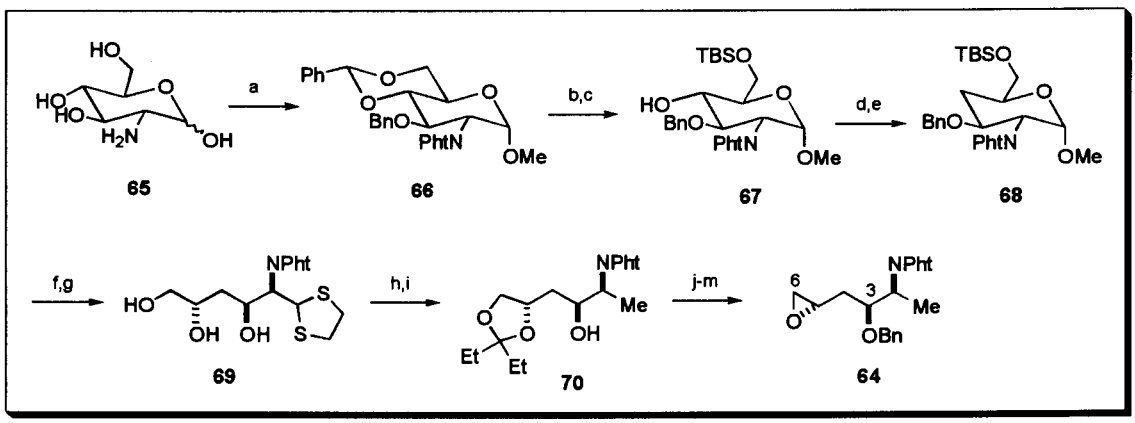


Scheme 1.13 Retrosynthesis of the backbone of fumonisin B_1 according to Gurjar.[46]

identified the C_{14} intermediate (**63**) available from D-glucose, and the C_6 *N*-phthalimide derivative (**64**) formed from D-glucosamine (see Scheme 1.13). The synthesis of (**64**) started from D-glucosamine (**65**) that was converted to the *N*-phthalimido methyl glycoside (**66**) by a route reported earlier[47] (see Scheme 1.14). Subsequent cleavage of the benzylidene group and selective protection of the primary hydroxy group as the TBS ether gave (**67**). Barton radical deoxygenation then provided the 4-deoxy compound (**68**) that was converted to the ring-opened thioacetal (**69**). Reductive

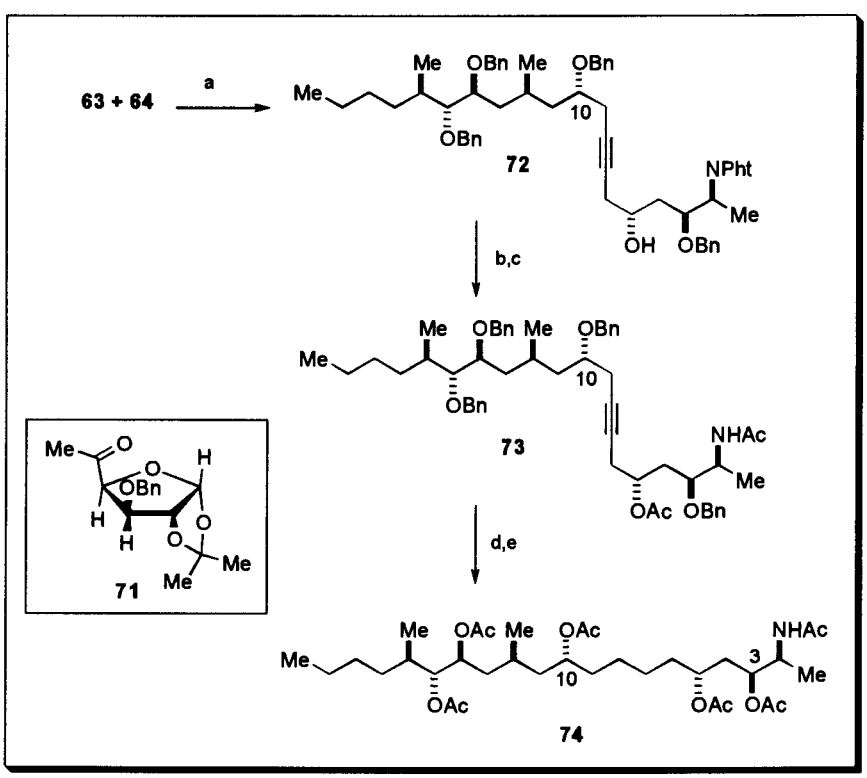
[47] Shigehiro, H. *Carbohydr. Res.*, **1971**, *6*, 229.

desulfurisation over Raney-Ni and protection of the 1,2-diol as the 3-pentylidene gave (**70**) which was converted in four steps to the epoxide derivative (**64**).



Scheme 1.14 Synthesis of (**64**) from D-glucosamine

Reagents: (a) Ref. 47; (b) 60% aq. HOAc: (c) TBS-Cl, imidazole, CH_2Cl_2; (d) NaH, CS_2, MeI, THF; (e) Bu_3SnH, AIBN, toluene; (f) MeOH, TsOH; (g) $BF_3.Et_2O$, $HSCH_2CH_2SH$, CH_2Cl_2; (h) Ra-Ni, EtOH; (i) Et_2CO, CSA, CH_2Cl_2; (j) NaH, BnBr; (k) MeOH, TsOH; (l) TsCl, pyridine, CH_2Cl_2; (m) NaH, THF.



Scheme 1.15 Formation of the backbone of fumonisin B_1 according to Gurjar.[46]

Reagents: (a) n-BuLi, $BF_3.Et_2O$; (b) $MeNH_2$, MeOH; (c) Ac_2O, Et_3N, CH_2Cl_2; (d) $Pd(OH)_2$-C, H_2; (e) Ac_2O, Et_3N, CH_2Cl_2.

The acetylene (**63**) was prepared from the 5-ulose derivative (**71**), available from D-glucose,[48] in 20 steps. The carbon-carbon bond formation between the acetylene (**63**) and the epoxide (**64**) was carried out with n-BuLi mediated with $BF_3.Et_2O$.to give the C_{20} backbone (**72**). Removal of the phthalimido protective group with methylamine followed by acetylation gave the diacetate derivative (**73**) that was exhaustively hydrogenolysed over $Pd(OH)_2$ to afford after acetylation the peracetate derivative (**74**) of (**16**).

Snyman[49] reported on the synthesis of the C(1)–C(10) unit of the fumonisin B_1 and B_2 backbone usng D-glucose as a chiral building block. The same approach was followed by Netshiozwi in the synthesis of the corresponding unit of the fumonisin B_3 and B_4 backbones.[50] Disconnection of the C(10)–C(11) bond in (**75**) and (**76**), the backbones of fumonisin B_3 and B_4, respectively, identified the synthetic target (**77**) for the right-side of these fumonisins.

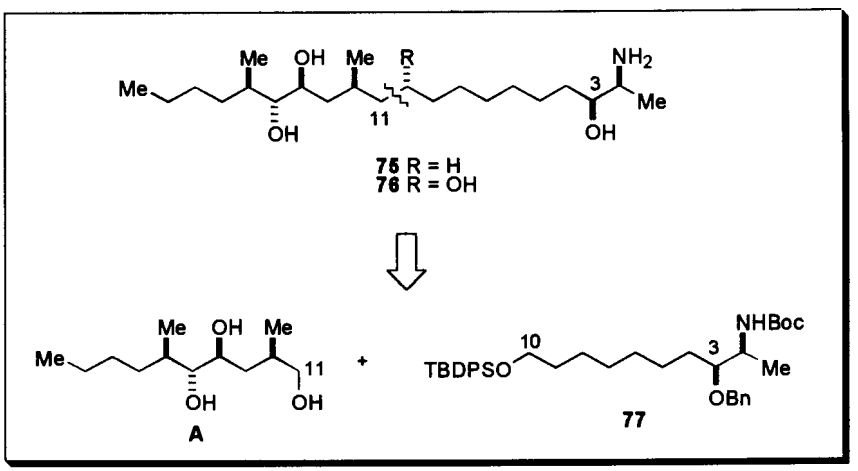
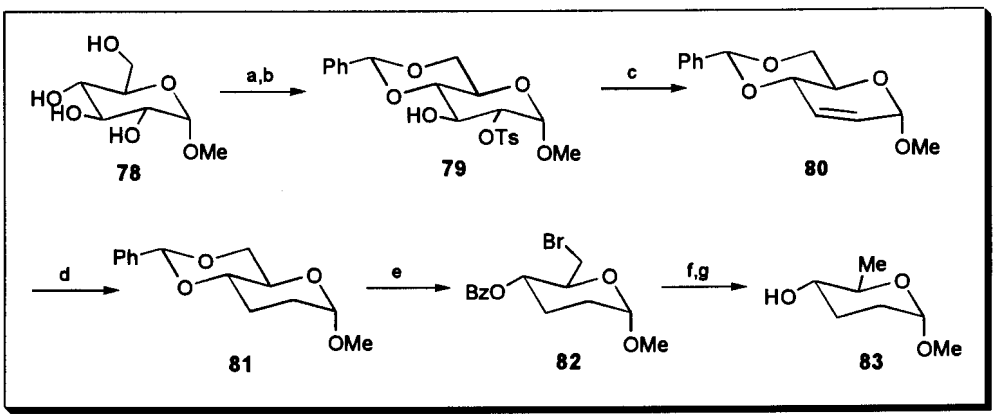


Figure 1.4 Retrosynthesis of fumonisin B_3 and B_4.

The synthesis of the C_{10} unit started from methyl α-D-glucopyranoside (**78**) that was converted to the 4,6-*O*-benzylidene derivative upon treatment with α,α-dimethoxy-toluene and a catalytic amount of camphorsulfonic acid (see Scheme 1.16). Selective tosylation of the C(2) hydroxy group with *N*-tosylimidazole gave the 2-*O*-tosylate derivative (**79**). This compound was transformed into the 2-hexenopyranoside (**80**) using NaI and Zn -Cu couple in a reaction that proceeds via the *manno*-epoxide.[51] The

[48] Araki, Y.; Arai, Y.; Endo, T.; Ishido, Y. *Chem. Lett.*, **1989**, 1.
[49] Snyman, R.M., Studies directed to ward the total synthesis of fumonisins, metabolites of *Fusarium moniliforme*, Ph.D. Thesis, University of Pretoria, **1995**.
[50] Netshiozwi, T.E. Carbohydrates as chiral templates for the synthesis of the C_{20} backbone of fumonisin B_3 and B_4, M.Sc. Dissertation, University of Pretoria, **1997**.
[51] Radatus, B.K.; Clarke, I.S. *Synthesis*, **1980**, 47.

newly formed double bond was saturated by catalytic hydrogenation using Raney-nickel to give (**81**) in 89% yield. Cleavage of the benzylidene group using NBS in CCl_4 in the presence of $CaCO_3$ gave the 6-bromo compound (**82**).[52,53] Base hydrolysis of (**82**) with sodium methoxide in anhydrous methanol gave an alcohol which on reductive debromination with Raney-nickel gave the key intermediate 2,3,6-trideoxy-α-D-*erythro*-hexapyranoside (**83**).

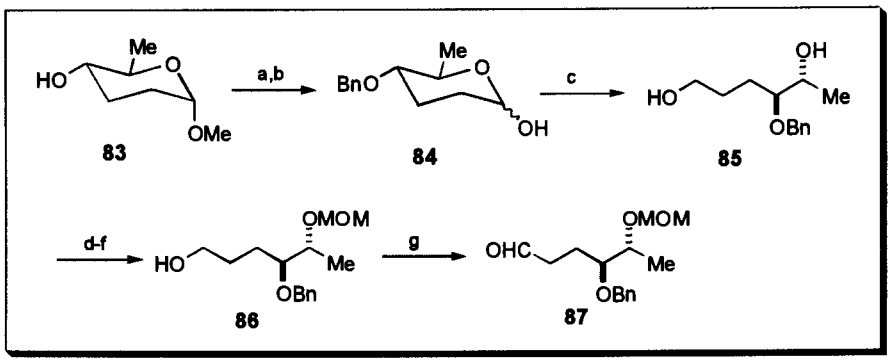


Scheme 1.16 Synthesis of the C(1)–C(10) unit of the fumonisin B_3/B_4 backbone.

Reagents: (a) α,α-dimethoxytoluene, CSA, CH_3CN (77%); (b) TsIm, NaOMe (80%); (c) Zn-Cu, NaI, DMF-DME, Δ (73%); (d) Raney-nickel, H_2, MeOH (89%); (e) NBS, CCl_4, $CaCO_3$ (95%); (f) Na(s), MeOH, (65%); (g). Raney-nickel, H_2, MeOH (63%).

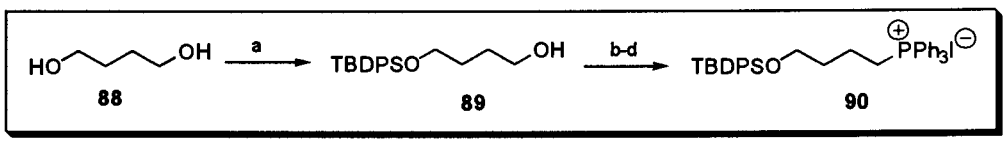
The alcohol (**83**) was protected as the benzyl ether and the methyl glycoside bond cleaved using 1M HCl in acetic acid (2:7) to give the hemiacetal (**84**) (see Scheme 1.17). Attempts at chain extension of this masked aldehyde with the Wittig reagent (**90**) (see Scheme 1.18) failed. A different strategy was therefore followed. $NaBH_4$ reduction of (**84**) gave the diol (**85**) which was transformed in three steps to the MOM ether (**86**) by (1) selective protection of the primary alcohol as the TBDPS ether, (2) protection of the secondary alcohol as the MOM ether and (3) deprotection of the TBDPS ether using TBAF. The primary alcohol group in (**86**) was converted to the aldehyde (**87**) by Swern oxidation. The chain elongation of this aldehyde required the C_4 Wittig reagent (**90**) which was prepared in four steps from 1,4-butanediol (**88**). Monosilylation with TBDPSCl using the procedure of McDougal *et al.*[54] for symmetric diols gave the monoprotected silyl ether (**89**) in 89% yield. Conversion of the hydroxy

[52] Hanessian, S. *Carbohydr. Res.*, 1966, **2**, 86
[53] Crétiene, F.; Khaldi, M.;Chapleur, Y. *Synth. Commun.* **1990**, *20*, 1589.
[54] McDougal, P.G.; Rico, J.G.; Oh, Y.-I.; Condon, B.D. *J. Org. Chem.*, **1986**, *51*, 3388.



Scheme 1.17 Synthesis of the C(1)–C(10) unit of the fumonisin B_3/B_4 backbone (contd.)

Reagents: (a) BnBr, NaH, DMF (78%); (b). CH_3CO_2H: 1M HCl (7:2) (74%); (c) $NaBH_4$ (75%); (d) TBDPSCl, imidazole, DMF (74%); (e) MOMCl, Hünig's base, THF (78%); (f) TBAF, THF (88%); (g) Swern oxidation (79%).



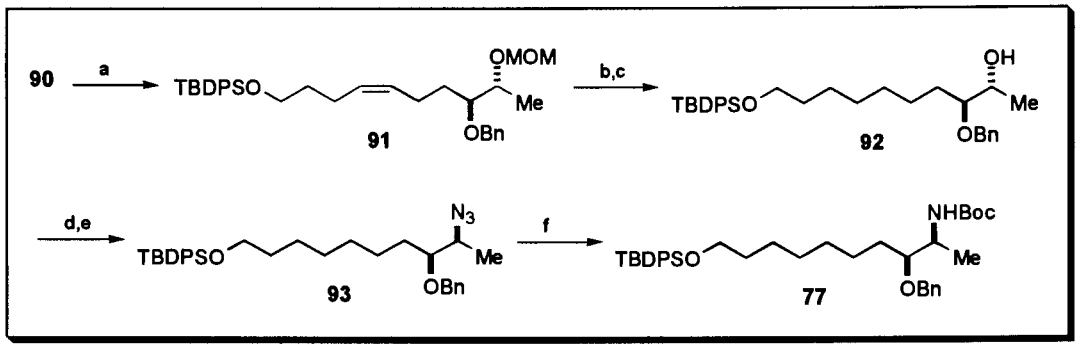
Scheme 1.18 Preparation of the C_4 Wittig reagent.

Reagents: (a) TBDPSCl, NaH, THF (85%); (b) TsCl, DMAP, pyridine, CH_2Cl_2 (82%); (c) NaI, acetone (81%); Ph_3P, toluene, Δ (82%).

group in (**89**) to an *O*-tosylate and displacement of the tosylate group with iodide gave the alkyl iodide which was converted to the phosphonium salt (**90**).

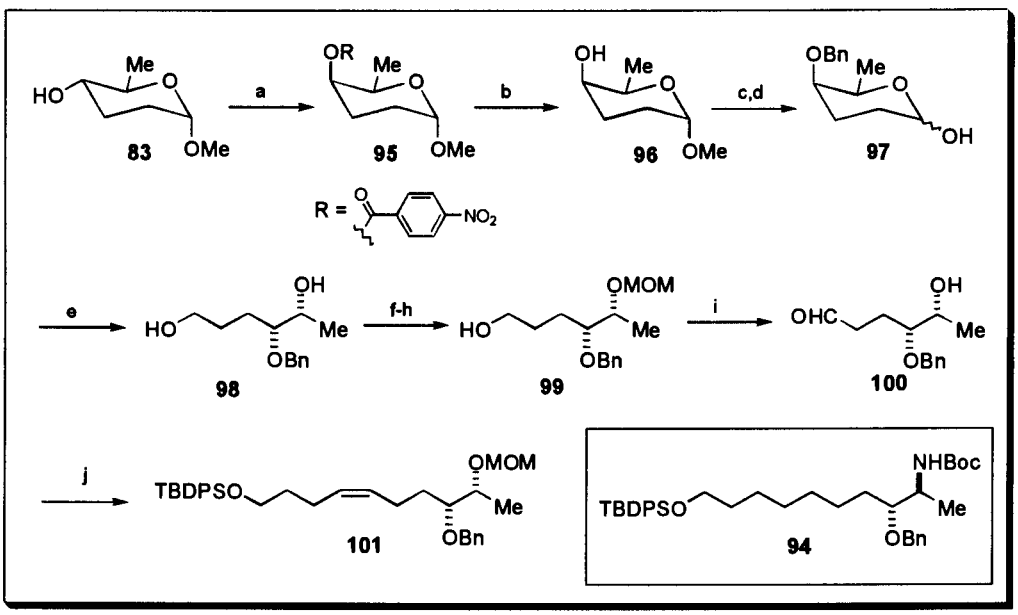
The (*Z*)-alkene (**91**) was formed by reaction of the ylid generated from the phosphonium salt (**90**) and *n*-BuLi, and the aldehyde (**97**) in a mixture of THF-HMPA in 41% yield. Catalytic hydrogenation of the double bond over $Pd(OH)_2$-C was followed by cleavage of the C(2) MOM ether using TMS-Br at –50°C, a reagent developed by Hanessian[55] for the deprotection of MOM ethers in the presence of TBDPS and benzyl ethers. The resulting secondary alcohol (**92**) was converted to the azide (**93**) using two methods: (1) a one-step Mitsunobu reaction using hydrazoic acid in the presence of Ph_3P and DEAD (in 65% yield) or (2) a two-step process (56% overall yield) that involved the conversion of the hydroxy group to an *O*-tosylate and displacement of the tosylate group with azide. The introduction of the azide group occurred with inversion of configuration to generate the required stereochemistry at the two stereogenic centres.

[55] Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.*, **1984**, *25*, 2515.



Scheme 1.19 Synthesis of the C(1)–C(10) unit of the fumonisin B_3/B_4 backbone (contd.).

Reagents: (a) n-BuLi, **87**, THF-HMPA 4:1 (41%); (b) $Pd(OH)_2$-C, H_2 (78%); (c) Me_3SiBr, CH_2Cl_2, –50°C (80%); (d) TsCl, DMAP, pyridine, CH_2Cl_2 (75%); (e) NaN_3, DMF (74%); (f) 10% Pd-C, Boc_2O, H_2, EtOAc (81%).



Scheme 1.20 Synthetic route to the C(1)–C(10) unit of the 3-*epi*-fumonisin B_3 and B_4 compounds

Reagents: (a) Ph_3P, DEAD, 4-nitrobenzoic acid (42%); (b) 10% KOH, THF (54%); (c) BnBr, NaH, DMF (78%); (d) HOAc: 1M HCl 7:2 (74%); (e) $NaBH_4$ (75%); (f) TBDPSCl, imidazole, DMF (56%); (g) MOMCl, iPr_2NEt, THF (84%); (h) TBAF (84%); (i) Swern oxidation (73%); (j) n-BuLi, **100**, THF-HMPA (35%).

The protocol reported by Saito *et al.*[56] for the catalytic reduction of the azide moiety over Pd-C in the presence of Boc_2O using EtOAc as solvent, led to the formation of the *N*-Boc derivative (**77**) with the 2,3-*syn* stereochemistry. The *N*-Boc derivative (**94**) with the *anti*-2,3 stereochemistry corresponds to the C(1)–C(10) unit of

[56] Saito, S.; Nakajima, H.; Inaba, M.; Mariwake, T. *Tetrahedron Lett.*, **1989**, *30*, 837.

the 3-*epi*-fuminisin B_3 and B_4 compounds (see Chapter 5) and its synthesis requires the availability of the methyl 2,3,6-trideoxy-α-D-*threo*-hexopyranoside (**96**)(see Scheme 1.20) The Mitsunobu reaction on the C(4) hydroxy group in (**83**) with Ph_3P, DEAD, and 4-nitrobenzoic acid instead of benzoic acid, occurs with inversion of configuration and led to the formation of the 4-nitrobenzoate ester (**95**) in poor yield (42%). Base hydrolysis of the ester group gave the alcohol (**96**) that was converted to the hemi-acetal (**97**) by benzylation of the C(4) hydroxy group and cleavage of the methyl glycoside bond. The subsequent elaboration of (**97**) to the alkene (**101**) follows the same route as that outlined for the alkene (**91**).

The work presented in this dissertation utilises Sharpless asymmetric epoxi-dation–kinetic resolution methodology for a more efficient stereoselective synthesis of the C(1)–C(8) units of the backbone of fumonisin B_3 and B_4 as well as the 3-*epi* series using achiral starting materials.

1.2.6 Biosynthetic studies on the fumonisins.

The fumonisins are structurally similar to (2*S*,3*R*)-sphingosine (**102**), the base backbone of sphingolipids The biosynthesis of (2*S*,3*R*)-sphingosine (**102**) is initiated with the condensation of (2*S*)-serine with palmitoyl-SCoA (**103**), by serine palmitoyl transferase, a pyridoxalphosphate-dependent enzyme, and involves the loss of CO_2 to form 3-ketosphinganine (**104**)(see Figure 1.5).[57] In the case of the fumonisins it was envisaged that (2*S*)-alanine and a polyketide-derived-SCoA are involved in a similar condensation reaction. In early biosynthetic studies directed more towards the preparation of ^{14}C-labelled fumonisins it was shown that the C(10) and C(16) methyl groups of fumonisin B_1 are derived from the methyl group of (2*S*)-methionine.[58,59] Branham and Platter[60] reported that alanine is a precursor in the biosynthesis of fumonisin B_1.

These findings were confirmed by Blackwell *et al.*[61;62] The label from (2*S*)-[3-^{13}C]-alanine was incorporated at C(1) of fumonisin B_1 (**4**) by a factor of 4 as determined by

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[57] Braun, P.E.; Snell, E.E. *J. Biol. Chem.*, **1968**, *243*, 3775.
[58] Plattner, R.D.; Shackelford, D.D. *Mycopathologia*, **1992**, *117*, 17.
[59] Alberts, J.F.; Gelderblom, W.C.A.; Vleggaar, R.; Marasas, W.F.O.; Rheeder, J.P. *Appl. Environ. Microbiol.*, **1993**, *59*, 2673.
[60] Branham, B.E.; Plattner, R.D. *Mycopathologia,* **1993**, *124*, 99.
[61] Blackwell, B.A.; Miller, J.D.; Savard, M.E. *JAOAC International*, **1994**, 77, 506.
[62] Blackwell, B.A.; Edwards, O.E.; Fruchier, A.; ApSimon, J.W.; Miller, J.D. *Fumonisins in Food*, (Eds. Jackson, L.S.; DeVries, J.W.; Bullerman, L.B.), Plenum Press, New York, **1996**, p. 75.

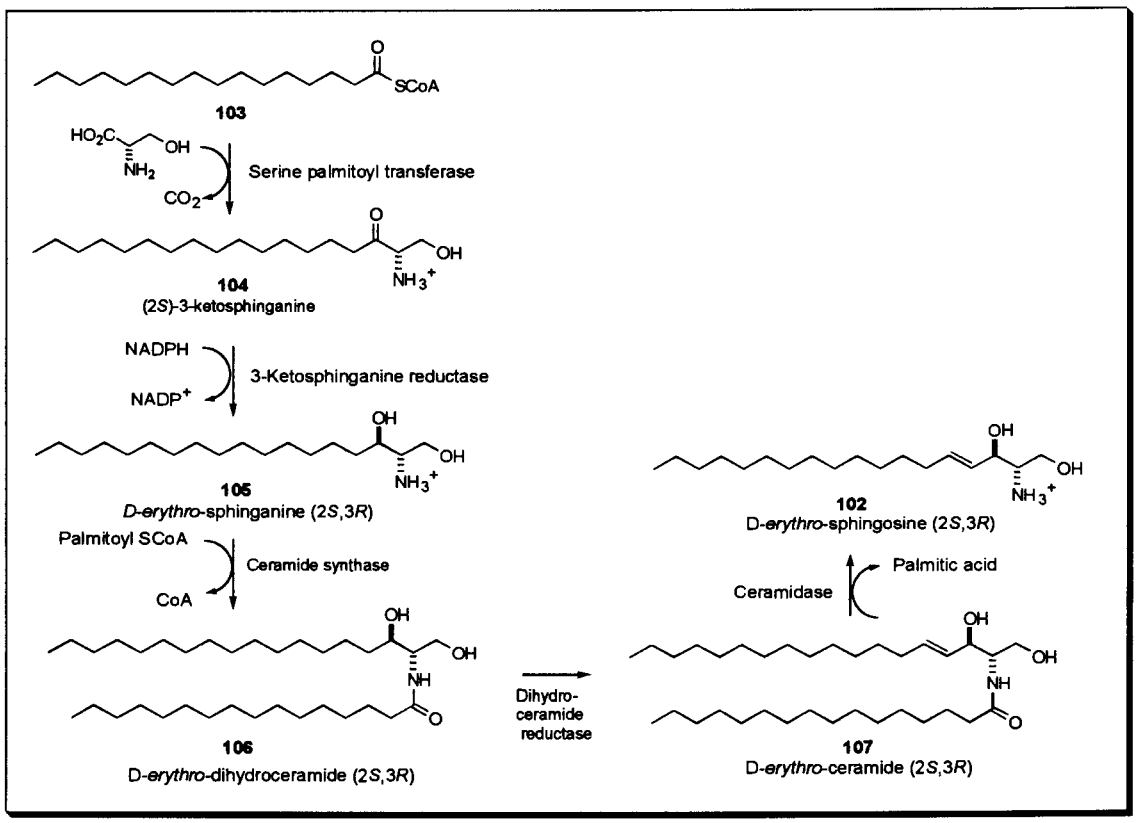

Figure 1.5 Biosynthetic pathway of sphingosine.

^{13}C NMR spectroscopy. The pattern of acetate incorporation into the C_{20} backbone is consistent with polyketide biosynthesis in which a starter acetyl-SCoA unit is extended by malonyl-SCoA to a C_{18}-polyketide-SCoA unit that is subsequently condensed with (2*S*)-alanine. Label from [1-^{13}C]acetate resulted in enrichment of C(3), C(5), C(7), C(9), C(11), C(13), C(15), C(17), and C(19) (*ca.* 4) whereas [2-^{13}C]acetate labelled C(4), C(6), C(8), C(10), C(12), C(14), C(16), C(18) and C(20). It was notable that no incorporation was observed for the resonances assigned to C(1) and C(2). Enrichment by acetate in the tricarballylic acid moiety is less (*ca.* 2) than in the backbone and is unevenly distributed – the two carbons of the ester carbonyl group are less enriched than those of the free carboxyl groups. This would suggest that a C_4 unit is formed first, most likely from the Krebs citric acid cycle and a third acetate unit is added at a later stage. The precursor to the esterification step must therefore be unsymmetric since symmetry would produce an even labelling pattern. Incorporation of (2*S*)-[5-^{13}C]-glutamate showed enrichment of the carbon atom of the secondary carboxy group of the tricarballylic acid moiety. This result in conjunction with the results from the acetate incorporation, indicated that the precursor to esterification involved a condensation

between α-ketoglutarate and a second acetyl-SCoA unit. The results of the labeling studies are shown in Figure 1.6.

The biosynthesis of the fumonisins, however, requires further research as the origins of the oxygen atoms on the backbone have not been established. The results obtained with ^{18}O precursors and mass spectrometry analysis are ambiguous and doubtful.[63] The principles of polyketide biosynthesis would indicate that the C(3) and C(5) oxygen atoms are derived from acetate. The C(14) oxygen atom could be derived from acetate or molecular oxygen and the C(15) oxygen atom from water. Molecular oxygen contributes the C(10) oxygen atom.

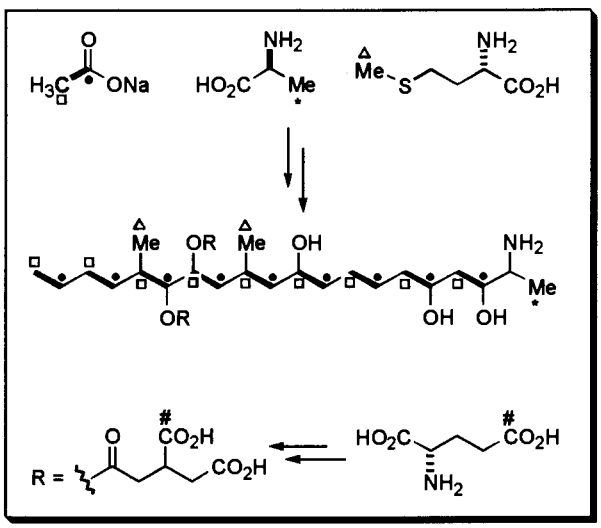

Figure 1.6 ^{13}C Labelling studies in the biosynthesis of fumonisin B_1.

1.2.7 Effect of fumonisins on sphingosine biosynthesis.

Sphingolipids are prominent components of cellular membranes, lipoproteins and more importantly, components of the myelin sheath that protect and electrically insulate cells of the central nervous system. They encompass a complex family of phospho- and glycosyl-ceramides that are found in mammalian cells. The sphingolipids on the other hand, are derivatives of the C_{18} amino alcohols, dihydrosphinganine and sphingosine (**102**) and are involved in cell-cell communication, immunorecognition, intercellular signal transduction such as regulation of cell growth, differentiation of cell function and programmed cell death.[64]

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[63] Caldas, E.D.; Sadilkova, K.; Ward, B.L.; Jones, A.D.; Winter, C.K.; Gilchrist, D.G. *J.Agric. Food Chem.*, **1998**, *46*, 4734.
[64] Wang, J. *Biol. Chem.* **1991**, *266*, 14486.

As already stated in section 1.2.6 (see Figure 1.5) the first step in the biosynthesis of (2*S*,3*R*)-sphingosine (**102**) and the sphingolipids, involves the condensation of palmitoyl-SCoA (**103**) and (2*S*)-serine and is accompanied by the loss of the carboxyl group of serine as carbon dioxide and the production of 3-ketosphinganine (**104**). The reaction has been reported as the rate-limiting step and is catalysed by the pyridoxalphosphate dependent enzyme, serine palmitoyltransferase.[57] The next step is the reduction of the carbonyl group by the transfer of a hydrogen atom from NADPH to C-3 of 3-ketosphinganine (**104**) to give sphinganine (**105**) which is acylated to dihydroceramide (**106**) by ceramide synthase. The introduction of the 4*E* double bond occurs by the action of the enzyme dihydroceramide reductase which converts D-*erythro*-dihydroceramide (**106**) to D-*erythro*-ceramide (**107**). The hydrolysis of ceramide (**107**) catalysed by ceramidase is reported to be the only established pathway for production of D-*erythro*-sphingosine **(102)** in cells. Ceramide (**107**) is also the precursor of sphingomyelins, cerebrosides and gangliosides, compounds which are prevalent in neuron cells.

The remarkable structural similarity of the fumonisins and sphinganine **(105)**, has led to the hypothesis that these toxins could be responsible for the inhibition of crucial steps in the *de novo* biosynthesis of sphingolipids. The primary mode of action of the fumonisins is reported to involve the same enzyme ceramide synthase which catalyses the amide linkage of palmitoyl SCoA with sphinganine **(105)** and has the ability to reacylate sphingosine **(102)** generated by the hydrolysis of ceramide (**107**). Fumonisin inhibition of sphinganine N-acyltranferase occurs in an apparent competitive manner with both sphinganine and stearyl-CoA for the binding sites. The fact that this inhibition is not easily reversible suggests that fumonisin binds tightly to the enzyme. The ability of the fumonisin to interact with both the binding sites might account for its potency.[65],[66]

The observation of a decrease in radio-labelled sphingosine and ceramides as well as an increase in labelled sphinganine in hepatocytes treated with fumonisin B_1, is consistent with inhibition of the ceramide synthase catalysed reaction in the *de novo* pathway.[21] The greater accumulation of sphinganine compared to sphingosine, provides further evidence that introduction of the 4*E* double bond of sphingosine **(102)** occurs after the acylation of sphinganine **(105)**. A corollary to this hypothesis is that free sphingosine arises from the turnover of cellular sphingolipids rather than as an intermediate of the *de novo* biosynthetic pathway.[65]

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[65] Merrill, A.H.; van Echten, G.; Wang E.; Sandhoff, K. *J. Biol. Chem.*, **1993**, *268*, 27299.
[66] Norred, W.P.; Wang, E.; Yoo, H.; Riley, R.T.; Merrill, A.H. *Mycopathologia*, **1992**, *117*, 73.

Fumonisin B_1 not only blocks the *de novo* sphingosine biosynthesis pathway, but also causes the accumulation of free sphinganine and sometimes sphingosine in both blood and urine of animals exposed to these mycotoxins.[67] Elevations in sphinganine and 2-hydroxysphinganine levels are also seen in plants exposed to fumonisins; therefore, the accumulation of sphinganine provides a useful biomarker for exposure of organisms to these mycotoxins.

The potent action of fumonisins on sphingolipid biosynthesis may be the mechanism of the known and suspected toxic effect of fumonisin that has been observed. Sphingolipids belong to a broad class of bioactive compounds, a sub-class of which consists of the cerebrosides known to play an important role in the brain and have been shown to possess a long-chain fatty acid attached to sphingosine through an amide linkage, which in turn is coupled to a hexose sugar galactose. The necrotic lesions in the brain as well as the mobility problems observed in horses suffering from equine leucoencephalomalacia (LEM) could be the end results of inhibition of sphingolipid biosynthesis.

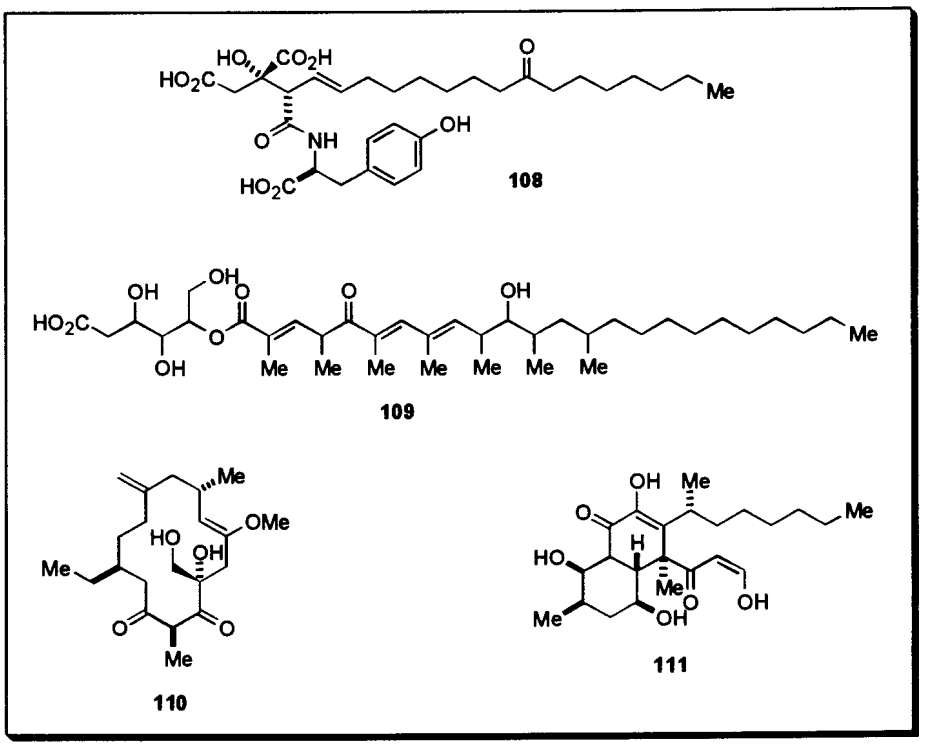

Figure 1.7 Structures of natural product inhibitors of sphingolipid synthesis.

[67] Vance, D.E.; Vance, J. *Biochemistry of Lipids, Lipoproteins and Membranes*, **1996**, *31*, 309.

The fumonisins are the first group of naturally occurring mycotoxins known to inhibit sphingolipid biosynthesis. Other sphingolipid inhibitors identified to date *viz.* viridiofungin (**108**), khafrefungin (**109**), rustimicin (**110**), and australifungin (**111**) have poor solubility in an aqueous environment.[68]

[68] Madala, S.M.; Harris, G.H. *Methods in Enzymology*, 2000, **311**, 335.

2 CHEMISTRY OF CHIRAL EPOXIDES.

2.1 INTRODUCTION

Epoxides (oxiranes) are versatile and important intermediates in organic synthesis due to their ease of formation and ready reactivity towards nucleophiles. The three-membered ring is strained (bond angles: C–C–O 59.2° and C–O–C 61.5°) and tends to undergo reactions by cleavage of one of the C–O bonds. There is an important difference in the regiochemistry of ring-opening reactions of epoxides depending on the reaction conditions. Thus epoxide ring cleavage by anionic nucleophiles occurs by an S_N2 mechanism at the less substituted site in unsymmetrical epoxides, whereas acid-catalysed ring opening occurs primarily by an S_N1-like mechanism by attack at the more substituted epoxide carbon.[1]

The epoxide functional group is a structural feature of numerous natural products isolated to date. The biological activity of many natural products is due to the presence of this functional group *e.g.* (+)-disparlure[2] (**112**), the sex pheromone of the gypsy moth and the trichothecenes diacetoxyscirpenol (**113**) and roridin A (**114**). The mycotoxin

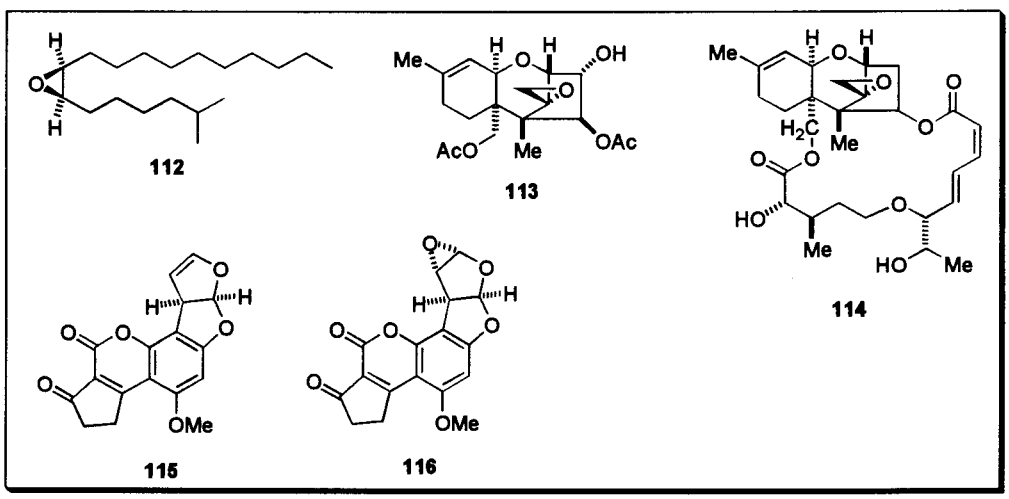

Figure 2.1 Biologically active natural products with an epoxide functional group.

[1] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, Oxford University Press, **2001**, p. 513-514.
[2] Mori, K.; Takigawa, T.; Matsui, M.; *Tetrahedron*, **1979**, *35*, 833.

aflatoxin B_1 (**115**) is a pre-carcinogen that requires transformation of the vinyl ether double bond to an epoxide (**116**), the highly toxic carcinogen, by liver enzymes.

2.2 FORMATION OF EPOXIDES

2.2.1 Epoxidation using peracids

Epoxidation of compounds with electrophilic double bonds, e.g., conjugated enones, α,β-unsaturated acids, esters and aldehydes, proceeds very slowly, if at all, when peracids (electrophilic reagents) are used as the epoxidation reagents. Furthermore, Baeyer-Villiger oxidation can succesfully compete with epoxidation. The simplest epoxide ethylene oxide (or oxirane itself) can be produced on the tonne scale by the direct oxidation of ethane by O_2 at high temperatures over a silver oxide catalyst. The conditions are hardly suitable for general laboratory use and the most commonly used epoxidising reagents are peroxycarboxylic acids (peracids).[3] Peracids are halfesters of hydrogen peroxide and are less acidic than the corresponding acid because their conjugate base is not stabilised by delocalisation into the carbonyl group. They are, however, electrophilic at oxygen because attack there by a nucleophile displaces a carboxylate, a good leaving group. Epoxidation using organic peracids was first reported by Prisleschajew.[4] The most commonly used peracid is *m*-chloroperbenzoic acid (MCPBA). The essence of the mechanism is nucleophilic attack of the double bond π orbital on the outer oxygen atom of the weak, polarised O–O bond. The proton of the epoxide oxygen is transferred to the carboxylic acid by-product (see Figure 2.1). The reaction is stereospecific as both new C–O bonds are formed on the same face of the alkene's π bond and the geometry of the alkene is therefore reflected in the stereochemistry of the epoxide. Thus *cis*-alkenes give rise to *cis*-epoxides whereas the *trans*-alkene leads to the formation of the *trans*-epoxide.

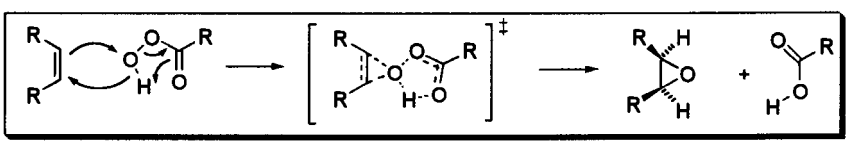

Figure 2.2 General mechanism of epoxidation by peracids.

[3] Helmchen, G.; Hoffman, R.W.; Mulzer, J.; Schaumann, E. *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), Thieme Stuttgart, 4th Ed., Vol. E21e, **1995**, p. 4599-4633.
[4] Prisleschajew, N. *Ber.*, **1909**, *2*, 4811.

Epoxidation of an allylic alcohol (both cyclic and acyclic) with MCPBA occurs by attack of the face of the alkene *syn* to the hydroxy group and the *syn* epoxy-alcohol is formed as the major diastereomer (95:5).[5] The reason for the diastereoselectivity is shown in the transition state for the reaction in Figure 2.2. The only important conformer in the transition state has the hydrogen of the stereogenic centre eclipsing the double bond. The hydrogen of the hydroxy group can then form a hydrogen bond to the oxygen of the peracid, stabilising the transition state when *syn* epoxidation occurs.[6] This hydrogen bond means that peracid epoxidations of alkenes with adjacent hydroxy groups are much faster than simple alkenes even when no stereochemistry is involved.[7]

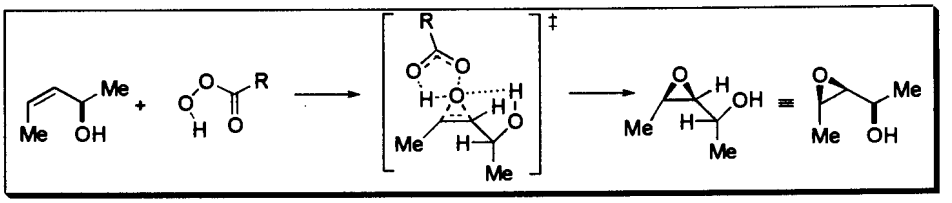

Figure 2.3 Stereofacial selectivity in the epoxidation of allylic alcohols.

2.2.2 Epoxidation using vanadium(IV) reagents

Oxidation of cyclic allylic alcohols and cyclic alkenols with *t*-butyl hydroperoxide in the presence of a vanadium(V) catalyst, $VO(acac)_2$, gives the *cis* epoxide with complete diastereoselectivity. $VO(acac)_2$ is a square pyramidal complex of two molecules of the enolate of acetylacetone and the vanadyl (V=O) dication. It can easily accept another ligand to form an octahedral complex so there is plenty of room for the alcohol to bind to the vanadium atom and for the *t*-BuOOH to displace one of the 'acac' ligands. Epoxidation then takes place *cis* to the hydroxy group by in-line attack on the O–O bond by the π orbital of the double bond. These vanadium(V) catalysed epoxidations can also be highly diastereoselective with acyclic alkenols in which the geometrical constraints present in cyclic substrates are absent. The mechanistic course of this epoxidation is illustrated in Figure 2.4 for an allylic alcohol system.

The stereochemical course of the reaction is determined by the dihedral angle y in (**117**) and (**118**). Me-Me interactions in the conformation depicted in (**118**) result in

[5] Henbest, H.B.; Wilson, R.A.L. *J. Chem. Soc.* (B), **1957**, 1958.
[6] Chautemps, P.; Pierre, J.L. *Tetrahedron*, **1976**, *32*, 549.
[7] Adam, W.; Wirth, T. *Acc. Chem. Res.*, **1999**, *32*, 703.

steric strain. The conformation **117** has minimal steric repulsion and reaction thus occurs preferentially by attack of the *ReR* face of the double bond (see Figure 2.5). [8,9,10]

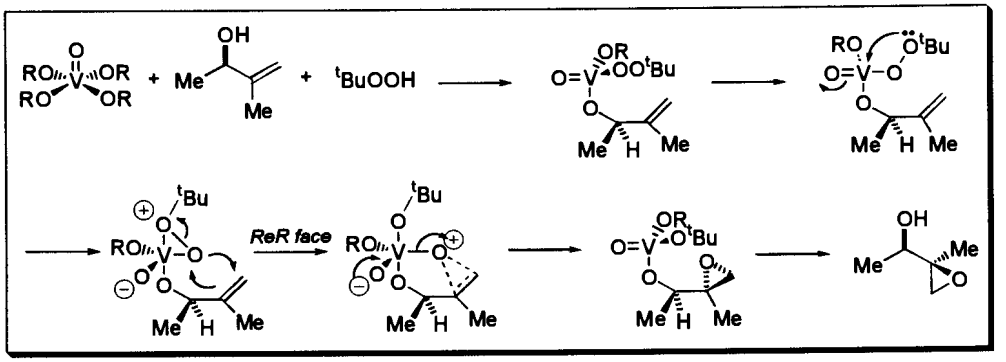

Figure 2.4 Epoxidation mechanism : vanadium (V) reagent.

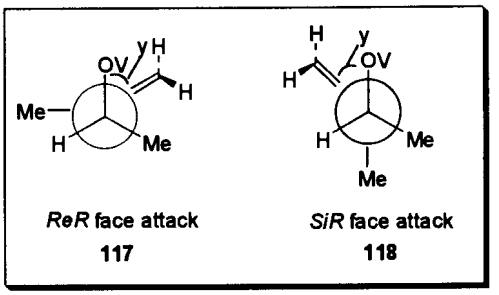

Figure 2.5 Conformational analysis of the vanadium(V) intermediate in the epoxidation reaction.

2.2.3 Formation of epoxides using sulfonium ylids

An important method for the formation of epoxides is the reaction of ketones and aldehydes with a sulfonium ylid such as dimethylsulfonium methylide[11] ($Me_2S^+CH_2^-$). The reaction of dimethyl sulfide with methyl iodide leads to the formation of the trimethylsulfonium iodide salt that is converted to the sulfonium ylid (**120**) by treatment with base. The subsequent reaction of the ylid with a carbonyl functional group results in C-C bond formation followed by formation of the epoxide ring (**122**) through expulsion of dimethyl sulfide[12] as shown in Figure 2.6.

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[8] Jørgensen, K.A. *Chem. Rev.*, **1989**, *89*, 432.
[9] Mihelich, E.D.; Daniels, K.; Eickhoff, D.J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.
[10] Besse, P.; Veschambre, H. *Tetrahedron*, **1994**, *50*, 8885.
[11] Whitham, G.H. *Organosulfur Chemistry,* Oxford University Press, Oxford, **1995**, p. 32.
[12] Alcarez, L.; Hamett, J.J.; Mioskowski, C.; Martel, J.P.; Gall, T.L.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* **1994**, *35*, 5449.

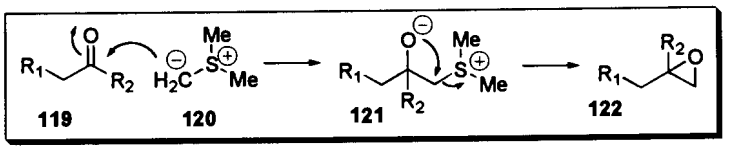

Figure 2.6 Epoxide formation using sulfur ylids.

2.3 ENANTIOSELECTIVE EPOXIDATION REACTIONS

2.3.1 Jacobsen methodology

In 1990 Jacobsen[13,14,15] reported the highly enantioselective epoxidation of alkyl and aryl-substituted alkenes using a manganese(III) catalyst (**123**) (a manganese(III)-salen complex) prepared from either of the homochiral enantiomers of 1,2-diamino-cyclohexane and the aromatic aldehyde, 2-hydroxy-3,5-di(t-butyl)-benzaldehyde. The complexes are inexpensive, easy to prepare with a range of substituent groups and robust enough for commercial bleach to be used as the oxidant.

Substrate selectivity studies and the effect of structural changes in the ligands have led to a model that accounts for the observed stereochemical aspects of the reaction. It is thought that a manganese(IV) oxo species is the oxidant and that only *cis*-alkenes can approach properly. The bulky *t*-butyl groups are most important for high enantioselectivity, and are considered to prevent approach from the substrate from directions other than that indicated in Figure 2.7. The sense of enantio-selection is in agreement with a perpendicular approach of the alkene to the manganese-oxo bond with transfer of the oxo oxygen to the *Re* face of the alkene. In this approach the phenyl substituent of the alkene is directed away from the axial hydrogen on the bridge (H*) and steric repulsion between the catalyst and the substrate will be minimised. This model predicts that *cis*-alkenes will be epoxidised with higher enantioselectivity than *trans*-alkenes, which is found to be the case.

Whatever the detailed mechanism of the process, it is an extremely easy and potentially very valuable method for enantioselective epoxidation and will undoubtedly find widespread use in organic synthesis.

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[13] Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am.Chem. Soc.* **1990**, *112*, 2801.
[14] Zhang, W.; Jacobsen, E.N. *J. Org. Chem.* **1991**, *56*, 2296.
[15] Jacobsen, E.N.; Zhang, W.; Güler, M.L. *J. Am. Chem.Soc.* **1991**, *113*, 6703.

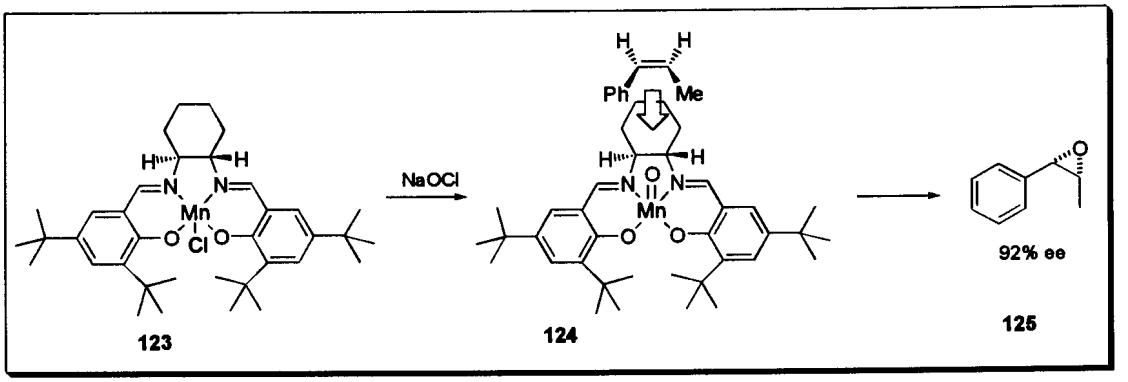

Figure 2.7 Jacobsen epoxidation of alkenes

2.3.2 Katsuki-Sharpless methodology

The synthesis of enantiomerically pure compounds is one of the most important goals in organic synthesis and is a major target in industrial syntheses of physiologically active compounds. Even more important are asymmetric transformations under catalytic conditions and high turnover rates. The 1980s witnessed the emergence of reagent-control strategy that employs powerful enantiomerically pure catalysts and auxiliaries for the purpose of constructing chiral molecules in a diastereo- and enantioselective fashion. The development of the reagent-control strategy has been the subject of some excellent discussions and reviews. The Sharpless asymmetric epoxidation reaction of allylic alcohols catalysed by a transition metal, discovered in 1980, is exemplary of this new strategy for the achievement of stereochemical control.[16] The reagents required for the preparation of the catalyst are commercially available at moderate cost: using titanium(IV) tetraisopropoxide, *t*-butyl hydroperoxide (TBHP) as the oxidising agent, and either diethyl (*R*,*R*)-(+)-tartrate (natural) or (*S*,*S*)-(–)-tartrate in dichloromethane, the reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. The reaction is highly predictable. When the (*S*,*S*)-(–)-tartrate ligand is used in the reaction the oxygen is delivered to the top face of the olefin when the allylic alcohol is depicted as in Figure 2.8. The (*R*,*R*)-(+)-tartrate ligand, on the other hand, allows the bottom face of the olefin to be epoxidised. When achiral alcohols are used the Sharpless asymmetric epoxidation reaction exhibits exceptional enantiofacial selectivity (*ca.* 100:1) and provides convenient access to synthetically versatile epoxy alcohols.[17,18]

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[16] Katsuki, T.; Sharpless, K.B. *J. Am. Soc.* **1980**, *102*, 5974.
[17] Rossiter, B.E. in *Asymmetric Synthesis*, Vol. 5, (Ed. Morrison, J.D.), Academic Press, New York, **1985**, p. 193.
[18] Pfenninger, A. *Synthesis*, **1986**, 89.

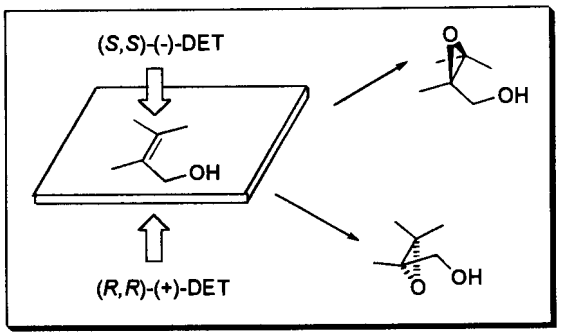


Figure 2.8 Stereofacial selectivity rule for the Sharpless epoxidation reaction.

The procedure originally reported by Katsuki and Sharpless has been modified and can be conducted very successfully with a catalytic amount of the titanium-tartrate complex, provided that molecular sieves are added to the reaction medium.[19]

Kinetic evidence suggests that an initial ligand exchange occurs between the titanium(IV) alkoxide and the tartrate ester, diethyl (*R*,*R*)-(+)-tartrate, to form a binuclear Ti–tartrate complex (**126**). The structures of a number of this type of complex have been established by X-ray crystallography.[20] Addition of the allylic alcohol and the oxidant *t*-BuOOH leads to the formation of the transition state assembly (**127**) (see Scheme 2.7) in a reaction that is first-order in (**126**), the allylic alcohol and *t*-BuOOH, in agreement with the observed kinetics. The assembly (**127**) contains the cationic catalytic species. The formation of the epoxy alcohol from (**127**) would clearly lead to regeneration of (**126**) by dissociation of the epoxy alcohol from the catalytic site.

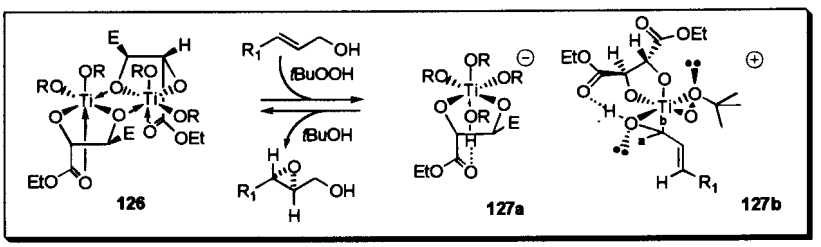


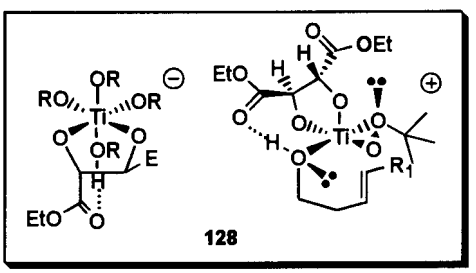
Figure 2.9 Nature of the catalytic species in the Sharpless epoxidation reaction.of allylic alcohols.

A single molecule of diethyl (*R*,*R*)-(+)-tartrate is complexed with the titanium atom of the cationic species in (**127b**). The hydroxy group of the allylic alcohol is coordinated with the Ti in such a way that hydrogen bonding with the carbonyl group of

[19] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
[20] Finn, M.G.; Sharpless, K.B. in *Asymmetric Synthesis*, Vol. 5, (Ed. Morrison, J.D.), Academic Press, New York, **1985**, p. 247.

the tartrate ester can occur. The geometry of the H-bond is linear and close to ideal with an O–H····O distance of 2.7 Å. The *t*BuOOH group is coordinated to the Ti atom through the terminal O atom in such a way that this O is *cis* and the *t*-BuO group is *trans* to the coordinated allylic hydroxy group. The O of the *t*-BuO group is pyrimidal and has the *R* configuration in order for this bulky group to be adjacent to the vacant coordination site of the octahedral Ti and away from the other ligands present on the Ti atom. Any other arrangement leads to extreme steric repulsion between the *t*-Bu group and the ligands *cis* to it. The specific arrangement of ligands on Ti results in a titanium stereogenic centre with the chirality sense determined by the tartrate ester ligand. The chirality sense of the catalytic cationic Ti species and the fixed hydrogen bonding favours the internal epoxidation at a specific face of the double bond as this bond approaches the peroxy O–O with its midpoint nearly co-linear with the O–O axis and the double bond axis perpendicular to the plane of the peroxy chelate ring: the optimum stereoelectronic arrangement for epoxidation.[21,22,23]

The transition state assembly is unambigous with regard to the absolute stereochemical preference that is implied for the epoxidation reaction. The chirality sense expected for the epoxy alcohol from (**127**) accords with the experimental facts. The transition state assembly (**127**) also explains the much faster reaction rate for substrates in which a = alkyl or a = b = H relative to b = alkyl.



128

Figure 2.10 Nature of the catalytic species in the Sharpless epoxidation reaction of homoallylic alcohols.

Interestingly, the enantiofacial selectivity in the Sharpless epoxidation of homoallylic alcohols is the reverse of that found for allylic alcohols. This result can be explained in terms of the transition state assembly (**128**) (see Figure 2.10), which is similar to the assembly (**127**) for allylic alcohols.[21,22]

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[21] Corey, E.J. *J. Org. Chem.* **1990**, *55*, 1693.
[22] Corey, E.J. *Pure Appl. Chem.* **1990**, *62*, 1209.
[23] Adam, W.; Richter, M.J. *Acc. Chem. Res.* **1994**, *27*, 57.

An alternative transition state assembly that correctly explains the observed enantiofacial selectivity for the Sharpless epoxidation of allylic alcohols, has been proposed and is illustrated in Figure 2.11. The model, however, does not explain the enantiofacial selectivity observed in the epoxidation of homoallylic alcohols.[20]

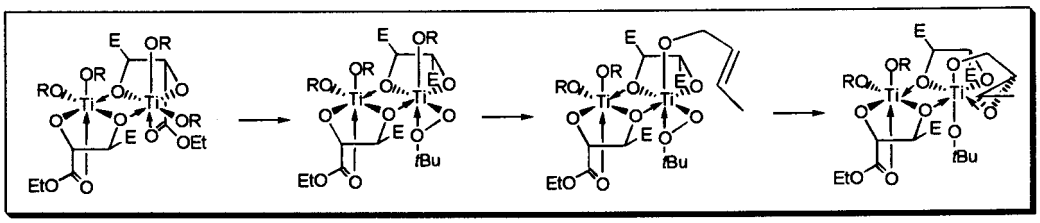

Figure 2.11 Alternative transition state assembly for the Sharpless epoxidation of allylic alcohols.

2.4 KINETIC RESOLUTION IN THE SHARPLESS EPOXIDATION REACTION.

A kinetic resolution is a chemical reaction of a racemate in which one of the enantiomers forms a product more rapidly than the other. The rate difference arises from the difference in E_a, the activation energy, to reach the transition states for the respective enantiomers of the substrate. The maximum yield is 100% but the enantiomeric excess (e.e.) of the product decreases as the reaction proceeds. In contrast the e.e. of the starting material increases as the reaction proceeds. If the reaction is allowed to go to completion the product is racemic. Thus kinetic resolution occurs in a reaction if $k_R \neq k_S$ and the reaction is stopped at some point before 100% conversion is achieved Adjustment of either the reaction time or the reaction stoichiometry may be used to control the extent of conversion. The ideal situation is the one in which only the one enantiomer reacts so that at 50% conversion a mixture of 50% of the starting material and 50% of the product is obtained both with 100% e.e.

It should be noted that the efficiency in kinetic resolutions depends on the conversion (C), which can only be $0<C<1$ and the rate constants k_R and k_S for the competing reactions of the enantiomeric substrates.[24] More precisely, it is the relative rate of reaction of the two enantiomers (k_R / k_S = **s**, the stereoselectivity factor) that dictates the efficiency. The efficiency is measured by the enantiomeric excess, ee_R of the reaction substrate (unreacted starting material) following the resolution. The fundamental relationship between these three variables is given by eq.1.

---

[24] Kagan, H.B.; Fiaud, J.C. *Topics in Stereochemistry*, **1988**, *18*, 249.

$$\mathbf{s} = \frac{\ln[(1-C)(1-ee_R)]}{\ln[(1-C)(1+ee_R)]} \qquad \text{eq. 1}$$

$$\mathbf{s} = \frac{\ln[1-C(1+ee_P)]}{\ln[1-C(1-ee_P)]} \qquad \text{eq. 2}$$

$$\frac{ee_R}{ee_P} = \frac{C}{1-C} \qquad \text{eq. 3}$$

Since eq. 1 is applicable to all types of reactions, kinetic resolution appears to be a practical and general route to obtaining an entantiopure product from a racemate; this would seem to be true for reactions having a stereoselectivity factor **s**>10. Stated in words, in order to obtain unreacted resolution substrate having a 99% ee, a kinetic resolution having a relative rate ratio of 10 would have to be taken to 72.1% conversion. That is, the yield of the unreacted substrate would be 27.9%. The latter value must, of course, be compared to the maximum yield of one enantiomer obtainable in any resolution, *i.e.* 50%. Eq. 2 relates *C* and **s** to the enantiomeric purity, ee_P, of the product of a kinetic resolution. Combining eqs. 1 and 2 gives eq. 3. The last equation illustrates the fact that the e.e.'s of the unreacted substrate and the product of a kinetic resolution are necessarily related and independent of the stereoselectivity factor **s**. As the enantiomeric purity of the starting material goes up, so must that of the product go down. From eq. 3 it also follows that it is impossible to maximise both the enantiomeric purity of the unreacted substrate *and* its yield.

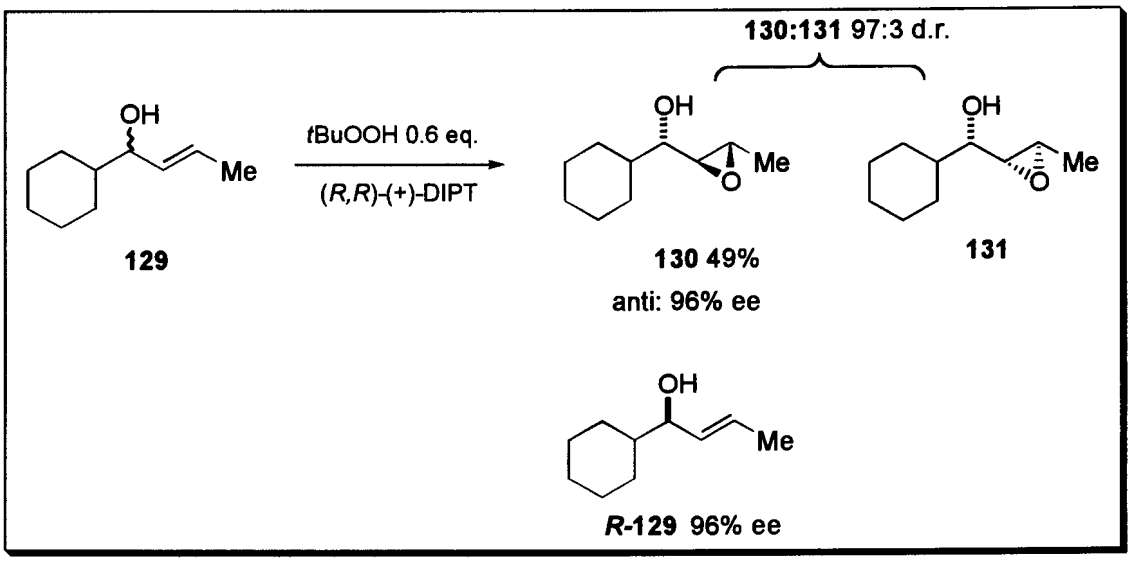

Figure 2.12 Kinetic resolution of a racemic allylic alcohol.

Kinetic resolution of a racemic secondary allylic alcohol was first reported by Martin *et al.*[25] Sharpless epoxidation of the racemic secondary allylic alcohol (**129**) (see Figure 2.12) was carried out using diisopropyl (*R*,*R*)-(+)-tartrate and only 0.6 equivalent of the oxidant *t*BuOOH. The unreacted *R*-**129** that was isolated had an e.e.>96%. The estimated value for the conversion was *C* = 0.55 and the stereoselectivity factor **s** was determined experimentally as 104. The epoxide products (**130** and **131**) of the reaction were obtained as a diastereomeric mixture of *syn*:*anti* diastereomers in a ratio of 97:3. The *anti* diastereomer **55** had >96% e.e. when *C* = 0.52. The dependence of the yield and e.e. of the diastereomeric epoxy alcohols on the % conversion is shown in Figure 2.13.

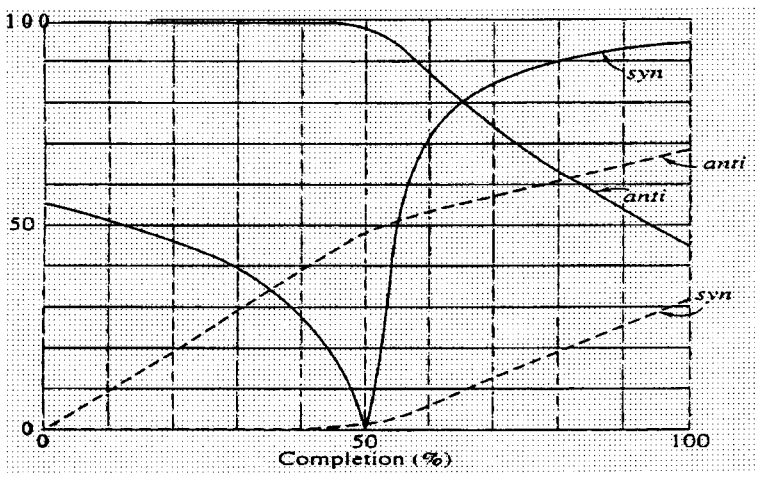

Figure 2.13 Dependence of yield (---) and e.e. (—) on % completion for the Sharpless epoxidation of a racemic secondary allylic alcohol.

The simple mnemonic model shown in Figure 2.14 can be applied to the epoxidation of secondary allylic alcohols and the stereoselectivity predicted. The stereofacial selectivity in the epoxidation reaction is determined by the tartrate ester that is used. For a given tartrate enantiomer one of the enantiomers of the general secondary allylic alcohol (**132**) will react faster. Since (*S*,*S*)-(–)-tartrate requires the *S* enantiomer of (**132**) to undergo epoxidation on the face shielded by the R group (the *SSi* face) it reacts more slowly than the *R* enantiomer in which the *SiR* face is much more accessible ($k_R > k_S$)(see Scheme 2.10). Two possible stereoisomers (**133**) and (**135**) will thus be formed in unequal amounts. The use of (R,R)(+)-tartrate will lead to the formation of the (**134**) and (**136**) also in unequal amounts. One prediction that follows from the model in Scheme 2.10 which is validated by experimental results, is

[25] Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *109*, 6237.

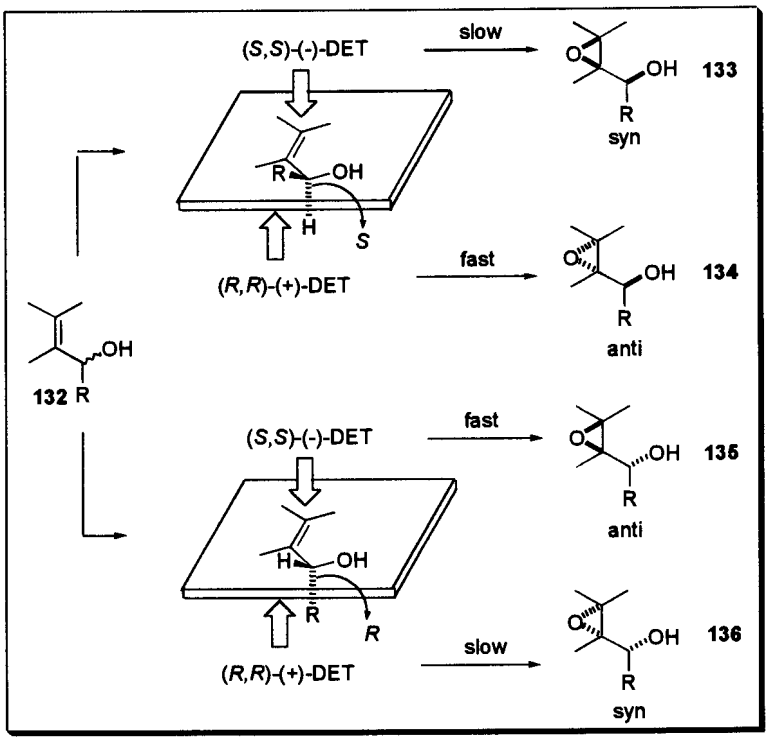

Figure 2.14 Mnemonic model to predict the products formed in the kinetic resolution of a secondary allylic alchol (**132**).

that of the four possible epoxy alcohols, (**133-136**), the two *syn* stereoisomers, (**133**) and (**136**), should be formed in smaller quantities than the corresponding *anti* stereoisomers (**134** and **135**). The Sharpless epoxidation reaction is not only enantio-selective but is also diastereoselective.

If there is only enough *t*-BuOOH oxidant present to transform the faster reacting enantiomer, and the stereoselectivity factor **s** is sufficiently high (a ratio of rates of 25 is usually enough) then the reaction will effectively stop once one enantiomer has reacted, leaving the slower reacting enantiomer of the allylic alcohol unreacted (see Figure 2.13).

A number of factors are of importance in the kinetic resolution epoxidation reaction and have been optimised. The obvious parameter of interest in the system is the ratio of the rates of epoxidation of the two enantiomers ($k_{fast}/k_{slow,}$) or the relative rate (k_{rel}). According to reports[19,20] in the literature the relative rate values increase remarkably with the bulk of the tartrate ester group, DIPT (104)> DET (36) > DMT (19)[25] but no notable differences in the e.e.'s of the epoxy alcohol products were observed.

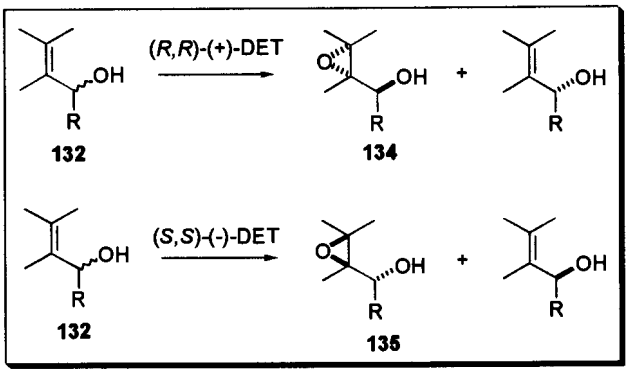

Figure 2.15 Products formed in the Sharpless asymmetric epoxidation–kinetic resolution reaction of secondary allylic alcohols.

Although structural features present in the secondary allylic alcohol are of importance for the rate of epoxidation, the reaction of both acyclic and cyclic substrates can take a few hours to several weeks to complete the kinetic resolution. Shorter reaction times can be achieved using more TBHP (up to 2 equivalents) for sluggish substrates but require careful monitoring of the degree of conversion. The optimal recommended amount of TBHP, however, is 0.6 equivalents of a 4-6 M solution in CH_2Cl_2 or toluene.

An important aspect of kinetic resolution that deserves special attention is the concentration of the catalyst. The titanium(IV) reagent is a Lewis acid and is a good catalyst to effect epoxide ring opening. The formed diol binds or complexes with the chiral complex and renders it inactive[26,27]. The effect of catalyst stoichiometry in the kinetic resolution reaction has been studied and a 10% excess of the tartrate ester over $Ti(^iPrO)_4$ has been recommended.[20] Too little (<10% excess) tartrate results in low selectivity and too much (≥100% excess) tartrate slows down the reaction rate. A $Ti(^iPrO)_4$: tartrate ratio of 5:6 is in fact the most suitable for all asymmetric epoxidation reactions.

Kinetic resolution/asymmetric epoxidation has been carried out under catalytic conditions using only 5-10% catalyst.[28] Several researchers have successfully used a 1:1 catalyst:substrate ratio in kinetic resolution studies.[20,29,30,31,32] Gao *et al.*[21] reported the importance of substrate concentration in stoichiometric reactions with *ca.* 0.1M

[26] Morgans, D.J. Jr.; Sharpless, K.B.; Traynor, S.G. *J. Am.Chem. Soc.*, **1981**, *103*, 462.
[27] Roush, W.R.; Brown, R.J.; Dimare, M. *J. Am. Chem. Soc*, **1983**, *48*, 5083.
[28] Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.***1986**, *51*, 1922.
[29] Yang, Z.; Jiang, X.; Wang, Z.; Zhou, W. *J. Chem. Soc., Perkin Trans. 1.* **1997**, 317.
[30] Roush, W.R.; Brown, R.J.; *J. Org. Chem.* **1983**, *48*, 5093..
[31] Honda, T.; Mizutani, H.; Kanai, K. *J. Chem. Soc., Perkin Trans. 1,* **1996**, 1729.

regarded as optimal in order to minimize side-reactions such as epoxide ring opening arising from the large amounts of titanium-tartrate species and 2-propanol present. For catalytic titanium-tartrate complexes, the substrate concentration can be increased up to 1.0 M but for for more sensitive alcohols, 0.1M is ideal.

All asymmetric epoxidation (AE)–kinetic resolution (KR) reactions are carried out at –20^{0}C in the presence of activated powdered 4Å molecular sieves (zeolites). The use of molecular sieves in catalytic reactions results in higher turnover and/or higher facial stereoselectivity. The main function of the molecular sieves is to protect the catalyst from adventitious water in the reaction as the catalyst is irreversibly destroyed by water. TBHP solutions are therefore stored over molecular sieves in sealed brown-glass containers immediately after preparation. TBHP preparations in dichloromethane are stored at 4°C but solutions in toluene and isooctane are stable at room temperature.

2.5 CONCLUSIONS

The Sharpless asymmetric epoxidation reaction and its use in kinetic resolution of racemic secondary allylic alcohols has been rapidly accepted for the synthesis of a large variety of enantiomerically pure compounds in the field of natural products. The main reasons that led to the success of the method are as follows:

- Simplicity. All reagents are inexpensive and commercially available.
- Reliability. The asymmetric epoxidation succeeds with most allylic alcohols.
- High optical purity. Generally >90% e.e. and often >95% e.e..
- Absolute stereochemistry of the epoxy alcohols is predictable.
- Relatively insensitive to existing chirality in the allylic alcohol. The chiral titanium-tartrate catalyst is able to override the diastereofacial preferences inherent in the chiral olefinic substrate.
- Kinetic resolution of secondary racemic allylic alcohols is easily done and the outcome is predictable,
- 2,3-Epoxy alcohols are versatile synthetic intermediates in natural product synthesis.

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[32] Yang, Z.; Jiang, X.; Wang, Z.; Zhou, W. *J. Chem. Soc., Chem. Commun.*, **1995**, 2389.

The above considerations played a major role in the planning of the synthetic studies on the backbone of the fumonisins and AAL toxins in the research group.. The successful application of the Sharpless asymmetric epoxidation–kinetic resolution reaction to the synthesis of fumonisin B_3 and B_4 and in the synthesis of model compounds for the structure elucidation of the 3-*epi*-fumonisin B compounds is described in this dissertation.

3 RETROSYNTHETIC ANALYSIS OF FUMONISINS B_3 AND B_4

3.1 BACKGROUND

Selection of a suitable starting material for the synthesis of a complex organic compound can be a demanding and tedious exercise. In the early days of organic synthesis the focus was on chemical change in the direction of chemical reactions *i.e.* reactants → products. Most syntheses were developed by selecting a suitable starting material (often by trial and error) and searching for a set of reactions that in the end transformed that material to the desired product (synthetic target). With the discovery of ever more complex natural products this approach with its frustrations and limited success rate was no longer viable. By the mid-1960s a different and more systematic approach towards synthesis able to deal with the most complex of synthetic targets was developed by Corey.[1] This approach depends on the structural features in the *reaction products* (as contrasted with starting materials) and the manipulation of structures in the reverse-synthetic sense. This method became known as *retrosynthetic* or *antithetic* analysis and its merits and power is evident from the way it has simplified and accelerated the planning process of synthetic routes and from the explosion in the number of natural products synthesised over the last few decades.

Retrosynthetic analysis is a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structures along a pathway that ultimately leads to simple or commercially available starting materials. The application of a transform, the exact reverse of a synthetic reaction, to a target structure, accomplishes the transformation of a molecule to a synthetic precursor. Each structure derived antithetically from a target then itself becomes a target for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the synthetic target.

Simple homochiral starting materials, the so-called chiral building blocks, obtain-

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[1] Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**.

able from Nature, are often commercially available and have been used extensively in stereoselective syntheses.

3.2 RETROSYNTHETIC ANALYSIS OF FUMONISIN B_3.

3.2.1 Analysis of the C_{12} left-side unit.

Base hydrolysis of fumonisin B_3 (**6**) results in cleavage of the tricarballylic ester moiety to give the C_{20} backbone (**75**) with its seven stereogenic centres. The first step in the retrosynthetic analysis (see Scheme 3.2) is the protection of the hydroxy and amino groups using a benzyl protecting group followed by the disconnection of one of the C–C bonds. The question that immediately comes to mind: which C–C bond? One of the tenets of retrosynthesis is to disconnect the bond that will result in the formation of two units of about equal size. Disconnection of both the C(10)–C(11) and the C(9)–C10) bond involves the C(10) stereogenic centre. The corresponding bond formation step in the synthesis direction must also lead to the creation of a new stereogenic centre with complete stereochemical control over the outcome of the reaction. This is not a trivial matter and an indirect synthetic route that corresponds to the C(10)–C(11) disconnection step using chiral sulfoxide methodology has been proposed by Zeevaart[2] (see Scheme 3.1). The disconnection of the C(8)–C(9) bond is an attractive alternative that circumvents the above stereochemistry problem and leads to the formation of a C_{12} unit (**137**) and a C_8 unit (**138**). Bond formation in the synthesis direction involves a Wittig reaction[3] or a Cu(I) catalysed Grignard reaction.

The disconnection of the C(10)–C(11) bond in (**137**) (fumonisin numbering) represents a two-carbon chain extension to give the C_{10} unit (**139**). The conversion of (**139**) is envisaged to proceed by Wadsworth-Emmons methodology[4,5] to give an α,β-unaturated ester. Reduction of the ester functional group generates an allylic alcohol required for the introduction of the stereogenic centre by Sharpless epoxidation methodology[6]. Functional group manipulations will then give the target alcohol (**137**).

Disconnection of the C(12)–C(13) bond in (**139**) removes another stereogenic centre and leads to the loss of a two-carbon unit. This disconnection is made up of

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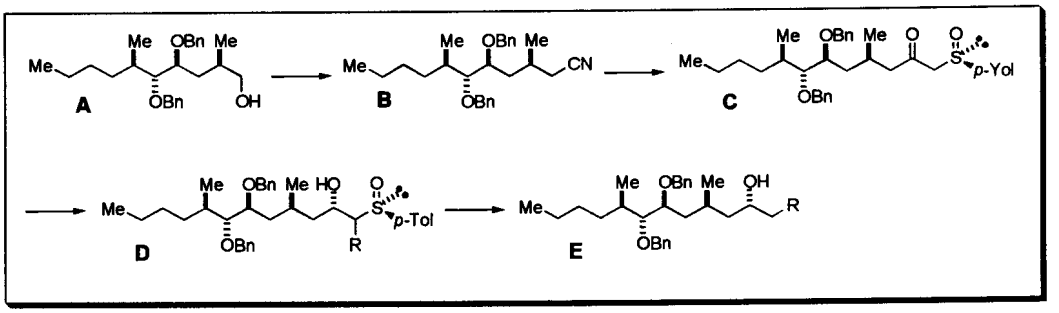
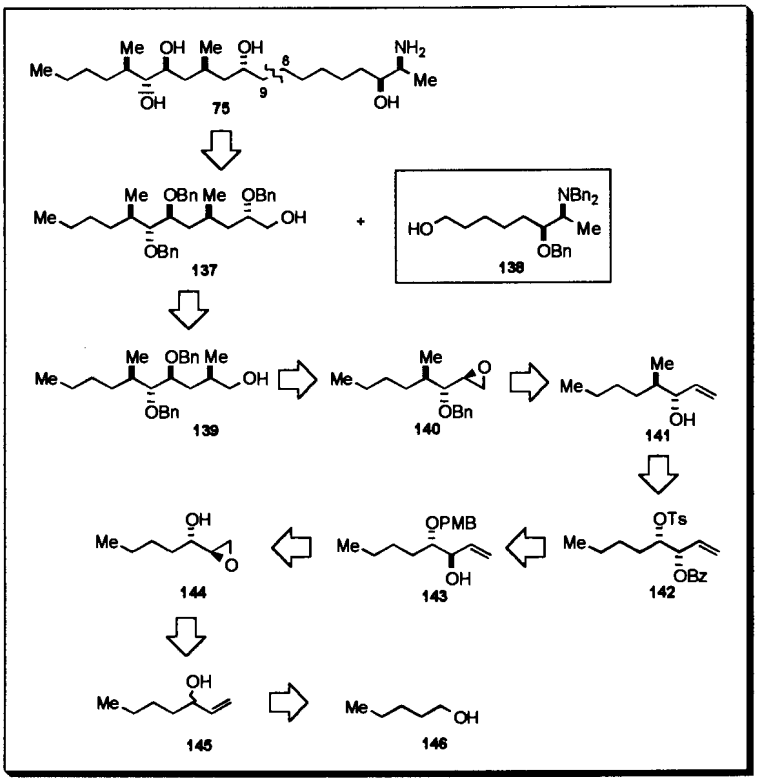
[2] Zeevaart, J.G. Synthetic studies on the C_{20} backbone of the fumonisins using chiral sulfoxides, M.Sc. Dissertation, University of Pretoria, **1997**.
[3] Ireland, R.E.; Thaisrivongs, P.H.; Dussault, P.H. *J. Am. Chem. Soc.* **1988**, *110*, 5768.
[4] Hulme, A.H.; Howells, G.E.; Walker, R.H. *Synlett*, **1998**, 828.
[5] Gosselin, F.; Lubell, W.D. *J. Org. Chem.*, **1998**, *63*, 7463.
[6] Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.



Scheme 3.1 Zeevaart synthetic route corresponding to the C(10)-C(11) disconnectionstep using chiral sulfoxide methodology.

functional group transformations in (**139**) to generate a trisubstituted α,β-unsaturated ester that is envisaged to be formed from the epoxide (**140**) by reaction of a stabilised dimethylsulfonium ylide[7] derived from methyl 2-bromopropionate. Removal of the benzyl protective group in (**140**) generates an epoxy alcohol that is obtained by Sharpless epoxidation methodology from the allylic alcohol (**141**). The transformation of the C(16) methyl group using a higher-order methyl cuprate reagent proceeds with



Scheme 3.2 Retrosynthetic analysis of the C_{20} backbone of fumonisin B_3 by disconnection of the C(8)–C(9) bond: the C_{12} left-side unit

[7] Whitham, G.H. *Organosulfur Chemistry,* Oxford Chemistry Press, Oxford, **1995**, p. 32.

inversion of configuration to generate the *O*-tosylate (**142**). The protective group transformation in the retrosynthesis of (**142**) from an *O*-tosyl to a *p*-methoxy-benzyl group generates an intermediate in which the *O*-benzoate group is transformed to a hydroxy group with inversion of stereochemistry by Mitsunobu methodology[8,9] to give (**143**). The C_8 allylic alcohol (**143**) can be derived from the epoxy alcohol (**144**) by a one-carbon chain extension using dimethylsulfonium methylide. Chiral *anti* epoxy alcohols such as (**144**) are formed from racemic allylic alcohols by Sharpless epoxidation/kinetic resolution methodology and this transformation identifies the racemic allylic alcohol (**145**) in the retrosynthetic analysis. The secondary allylic alcohol group can be derived from a C_5 aldehyde, obtained by Swern oxidation of 1-pentanol (**146**), by a Grignard reaction using vinyl magnesium bromide[10].

3.2.2 Analysis of the C_8 right-side unit.

The retrosynthetic analysis of the C_8 right-side unit (**138**) involves mainly a series of functional group transformations (see Scheme 3.3). Thus the transformation of the *N*,*N*-dibenzyl group of the C_8 right-side unit (**138**) generates the *N*-Boc group in synthon **A** (where P is a suitable protecting group) that is formed from azide **B**. The next step in the analysis identifies the alcohol **C** as azides are formed with inversion of configuration under Mitsunobu conditions from alcohols. The secondary hydroxy group in **C** is formed by reductive ring opening of the terminal epoxide **D** after protection of the secondary hydroxy group as the benzyl ether. Chiral *anti* epoxy alcohols such as **D** are formed from racemic allylic alcohols by Sharpless epoxidation/kinetic resolution methodology and this transformation identifies the racemic allylic alcohol (**E**) in the retrosynthetic analysis. The disconnection of the C(2)–C(3) bond involves a Grignard reaction[11] on the aldehyde **F** using vinyl magnesium bromide. The aldehyde functional group is obtained from the Swern oxidation[11,12,13] of a monoprotected 1,6-diol which in turn is available from 1,6-hexanediol (**147**).

3.3 RETROSYNTHETIC ANALYSIS OF FUMONISIN B_4.

Fumonisin B_4 (**7**) lacks the C(10) stereogenic of fumonisin B_3 (**6**) and the retro-

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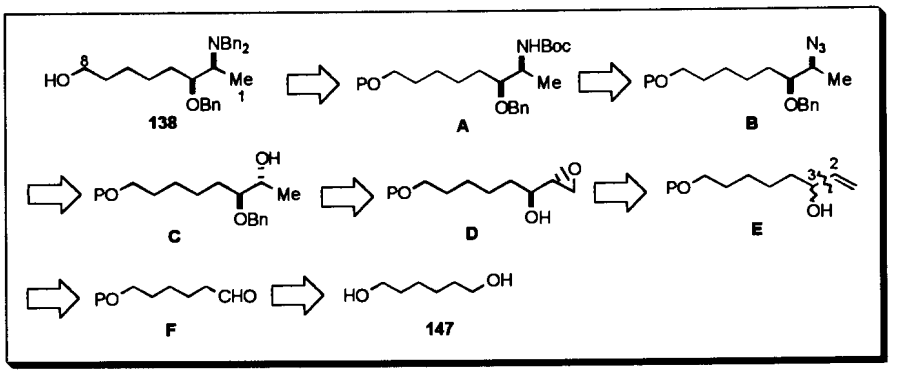
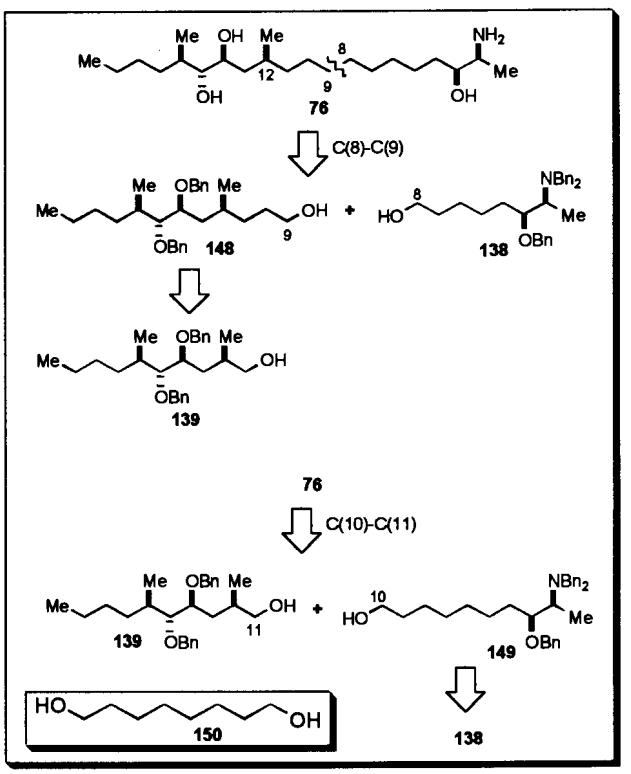
[8] Mitsunobu, O. *Synthesis*, **1981**, 1.
[9] Gajda, T.; Nowalinska, M.; Zawadzki, S.; Zwierzak, A. *Phosphorus Sulfur and Silicon and the related elements*, **1995**, *105*, 45.
[10] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Textbook of practical Organic Chemistry*, John Wiley & Sons, New York, 5th Ed., **1989**, p. 539.
[11] Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677.
[12] Osmura, S.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651.
[13] Hudlický, M. *Oxidation in Organic Chemistry*, Am. Chem. Soc., Washington, D.C. **1990**, p. 45 & 145.



Scheme 3.3 Retrosynthetic analysis of the C_{20} backbone of fumonisin B_3 by disconnection of the C(8)–C(9) bond: the C_8 right-side unit (**138**).

synthetic analysis of its C_{20} backbone (**76**) (see Scheme 3.4) is therefore expected to be closely related to that of fumonisin B_3 described in Section 3.2 but more straightforward as the absence of the stereogenic center at C(10) will simplify matters. Following the protection of the hydroxy and amino groups the disconnection of the C(8)–C(9) bond leads to the left-hand C_{12} unit (**148**) and once again the C_8 right-side unit (**138**). The disconnection of the C(10)–C(11) bond in (**148**) represents a two-carbon chain extension and leads to the common synthetic target (**139**), already identified in the retrosynthetic analysis of the backbone of fumonisin B_3 (see Scheme 3.2) as transformation of the C(10)–C(11) bond to a double bond leads to an allylic



Scheme 3.4 Retrosynthetic analyses of the C_{20} backbone of fumonisin B_4.

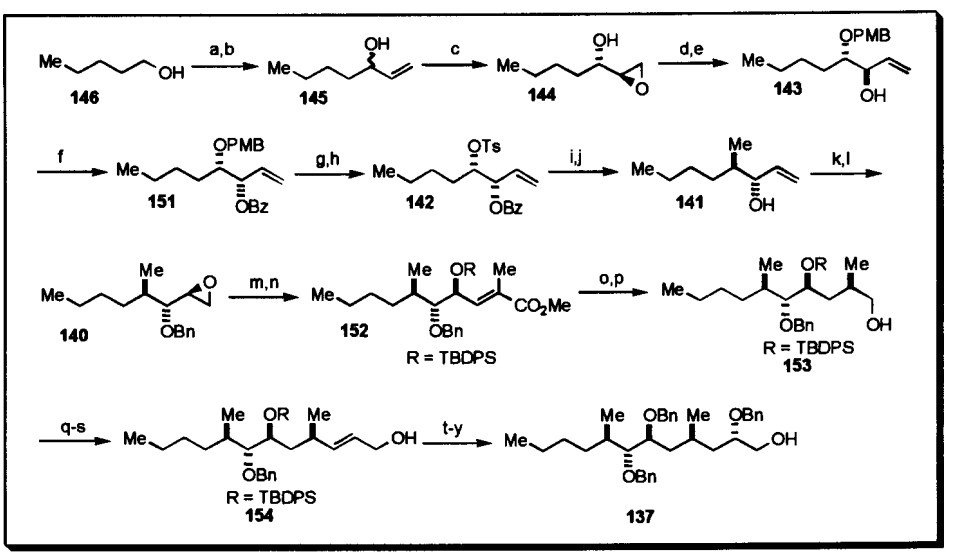
alcohol that can be derived from the alcohol (**139**) through Swern oxidation followed by Wadsworth-Emmons methodology to give an α,β-unsaturated ester that is reduced to the allylic alcohol and the double bond saturated by catalytic hydrogenation to give the target (**148**).

An alternative retrosynthetic analysis of the backbone of fumonisin B_4 involves the disconnection of the C(10)–C(11) bond and provides once again the intermediate (**139**) and the C_{10} right-side unit (**149**). Disconnection of the C(8)–C(9) bond in (**149**) represents a two-carbon chain extension as described above and leads to the alcohol (**138**). An alternative retrosynthetic analysis for (**149**) is similar to that described for (**138**) but identifies 1,8-octanediol (**150**) as starting material in the synthetic direction.

3.4 PROPOSED SYNTHETIC STUDIES.

3.4.1 The C_{12} left-side unit of the fumonisin B_3 backbone.

The proposed synthesis is outlined in Scheme 3.5 and uses 1-pentanol (**146**) as starting material. Swern oxidation of (**146**) gives the aldehyde that is converted in a

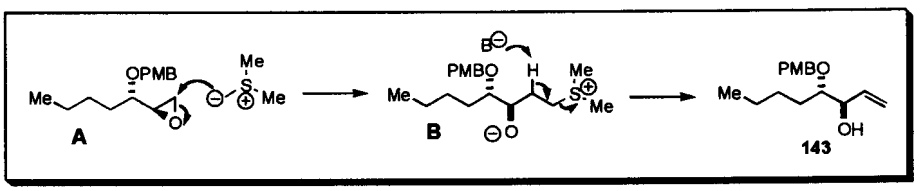


Scheme 3.5 Proposed synthesis of C(9)-C(20) unit.

Reagents: (a) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (b) Vinyl bromide, Mg, THF; (c) (*R*,*R*)-(+)-DIPT, Ti(*i*PrO)$_4$, TBHP, 4Å mol sieves, CH_2Cl_2, –20°C; (d) NaH, PMBCl; (e) $Me_3S^+I^-$, n-BuLi; (f) DEAD, Ph_3P, BzOH; (g) CSA, MeOH; (h) TsCl, DMAP, pyridine; (i) Me_2CuLi, Et_2O, (j) $LiAlH_4$; (k) (*S*,*S*)-(–)-DET, Ti(*i*PrO)$_4$, TBHP, 4Å mol sieves, CH_2Cl_2, –20°C (l) BnCl, NaH, DMF; (m) n-BuLi, Me_3S^+–$^-C(Me)CO_2Me$, THF, –25°C; (n) TBDPSCl, DMAP,CH_2Cl_2; (o) Pd-C, H_2; (p) $LiAlH_4$; (q) Swern oxidation (see(a)); (r) (*i*PrO)$_2$POCH$_2$CO$_2$Me, *t*BuOK; (s) DIBALH; (t) (*S*,*S*)-(–)-DET, Ti(*i*PrO)$_4$, TBHP, 4Å mol sieves, CH_2Cl_2, –20°C; (u) Red-Al; (v) PhCH(OMe)$_2$, TsOH; (w) TBAF; (x) BnCl, NaH, DMF; (y) DIBALH.

Grignard reaction with vinyl magnesium bromide to the racemic allylic alcohol (**145**). The predictable outcome of the Sharpless epoxidation/kinetic resolution of secondary allylic alcohols as outlined in Chapter 2, requires the use of diisopropyl (*R,R*)-(+)-tartrate to generate the required epoxy alcohol (**144**).

Mioskowski[14] has reported the conversion of epoxides to allylic alcohols using a sulfur ylide. The ylide reacts regioselectively at the less hindered end of the epoxide, transferring a methylene group with concomitant loss of dimethyl sulfide. The use of the Sharpless epoxidation reaction in tandem with the sulfur ylide reaction is a powerful iterative process for the production of polyoxygenated compounds.[15] The one reaction produces epoxides from allylic alcohols, the other allylic alcohols from epoxides. The result is then a simple protocol for the homologation of allylic alcohols. Protection of the hydroxy group of the epoxy alcohol (**144**) as the *p*-methoxybenzyl ether (**A**) is followed by a sulfur ylide reaction. Treatment of trimethylsulfonium iodide with n-butyl lithium produces the requisite dimethylsulfonium methylidene. Reaction of 3 equivalents of this reagent with the epoxide gives the allylic alcohol (**143**)(see Scheme 3.6).



Scheme 3.6 Conversion of an epoxide to an allylic alcohol.

The configuration of the C(3) stereogenic centre is inverted using the Mitsunobu procedure to give the benzoate ester (**151**). The *p*-methoxybenzyl ether is cleaved under acidic conditions with CSA and the alcohol converted to the *O*-tosyl derivative (**142**). The displacement of the O-tosylate group in the reaction with lithium dimethyl cuprate or a higher-order cuprate reagent, leads to the introduction of a methyl group in an S_N2 reaction that proceeds with inversion of configuration. The subsequent reductive removal of the benzoate group gives the allylic alcohol (**141**). Sharpless epoxidation of (**141**) using diethyl (*S,S*)-(–)-tartrate gives the epoxide with the required stereochemistry. The hydroxy group is protected as the benzyl ether to give (**140**).

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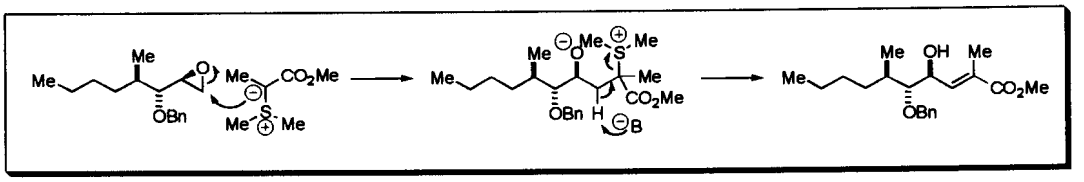
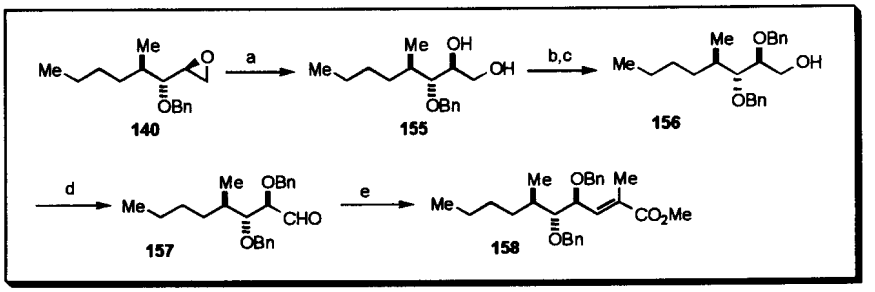
[14] Alcarez, L.; Hamett, J.J.; Mioskowski, C.; Martel, P. J. Gall, T.L.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* **1994**, *35*, 30, 5449.
[15] Davoille, R.J.; Rutherford, D.T.; Christie, S.D.R. *Tetrahedron Lett.* **2000**, *41*, 1255.

The transformation of the protected epoxide to the α,β-unsaturated ester (**152**) using stabilised sulfonium ylides must be regarded as speculative and requires an in-depth investigation using model compounds. The mechanism is outlined in Scheme 3.7.



Scheme 3.7 Mechanism of the chain extension reaction using a stabilised sulfur ylid.

An alternative procedure is outlined in Scheme 3.8 and converts the epoxide (**140**) to the diol (**155**). Selective protection of the secondary hydroxy group as the benzyl ether is a two-steps process and involves the regioselective reduction of the benzylidene derivative with DIBALH to give the alcohol (**156**). Swern oxidation of (**156**) gives the aldehyde (**157**). The Wadsworth-Emmons reaction of the aldehyde (**157**) with the ylid obtained by treatment of diisopropyl 1-(methoxycarbonyl)ethylphosphonate and *t*BuOK gives the α,β-unsaturated ester (**158**).



Scheme 3.8 Introduction of the C(12) methyl group using the Wadsworth-Emmons reaction.

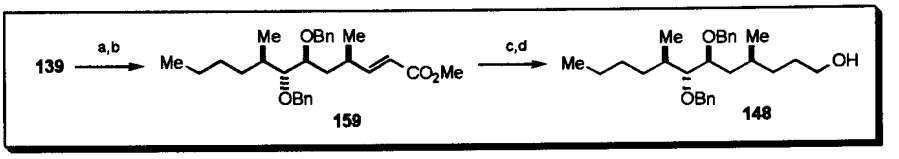
Reagents: (a) $BF_3.Et_2O$, H_2O; (b) $PhCH(OMe)_2$, TsOH; (c) DIBALH; (d) Swern oxidation; (e) $(iPrO)_2POCH(Me)CO_2Me$, *t*BuOK.

Stereoselective catalytic reduction of the double bond in (**152**) in Scheme 3.5 followed by $LiAlH_4$ reduction gives the alcohol (**153**). This alcohol can be converted to the two-carbon chain extended alcohol (**154**) by a sequence of reactions *viz*. Swern oxidation to the aldehyde followed by a Wadsworth-Emmons reaction using diisopropyl (methoxycarbonylmethyl)phosphonate to give an α,β-unsaturated ester. This ester is reduced to the allylic alcohol (**154**) using DIBALH. Compound (**154**) is converted to an epoxy alcohol in a Sharpless epoxidation using diethyl (S,S)-(–)-tartrate. Reduction of the epoxy alcohol with Red-Al leads to the formation of a 1,2-diol which is selectively protected by conversion to the benzylidene derivative. Removal of the TBDPS group

and protection as the benzyl ether is followed by cleavage of the benzylidene group using DIBALH to give the C_{12} synthetic target (**137**).

3.4.2 The C_{12} left-side unit of fumonisin B_4.

The intermediate (**139**) is common to the synthetic routes leading to the C_{12} left-side unit of both fumonisin B_3 and B_4. The subsequent elaboration of (**139**) to the C_{12} unit of fumonisin B_4 is straightforward and presents little difficulty, as there is no need to generate an additional stereogenic centre.



Scheme 3.9. Two-carbon chain extension of alcohol (**139**) to alcohol (**148**) following Wadsworth-Emmons reaction.

Reagents: (a) Swern oxidation; (b) $(i\text{PrO})_2\text{POCH}_2\text{CO}_2\text{Me}$, *t*BuOK, THF; (c) DIBALH; (d) Pd-C, H_2.

Swern oxidation of the alcohol (**139**) gives an aldehyde that is converted to the α,β-unsaturated ester (**159**) by a Wadsworth-Emmons reaction using diisopropyl (methoxy-carbonylmethyl)phosphonate. Reduction of the ester group in (**159**) with DIBALH gives an allylic alcohol that on catalytic hydrogenation over Pd-C provides the target molecule (**148**).

4 SYNTHETIC STUDIES: THE C_8 UNIT OF FUMONISIN B_3 AND B_4.

4.1 INTRODUCTION

Retrosynthetic analysis of the C_{20} backbone of both fumonisin B_3 (**6**) and B_4 (**7**) identified a common C_8 intermediate (**138**) that can be derived from 1,6-hexanediol (**147**) using Sharpless asymmetric epoxidation–kinetic resolution as discussed in Chapter 2. This synthetic route and the associated protective group strategy as well as the route to the model compound (**213**) corresponding to the 3-*epi* series (see Chapter 5), was investigated using 1,5-pentanediol (**160**) as starting material. A synthetic route based on 1,n-alkanediols will also allow the synthesis of analogs of the fumonisins with different chain lengths between the left- and right-side units.

4.2 Synthesis of (3*RS*)-7-[*tert*-butyldiphenylsilyl(oxy)]-1-hepten-3-ol 163.

Silyl ethers are used extensively in organic synthesis for the protection of hydroxy groups due to their ease and selectivity of formation and their compatibility with a variety of synthetic transformations and reaction conditions. The relative stability of silyl ethers towards both acidic and basic conditions can be finely tuned by varying the nature of the three alkyl groups on the silicon atom.[1,2,3,4] They are relatively stable towards most oxidizing and reducing agents and are unaffected in electrophilic and nucleophilic reactions.

The *t*-butyldiphenyl silyl (TBDPS) group was introduced by Hanessian *et al.*[5] for the protection of the hydroxy group. As a result of the steric bulk of the *t*-butyl and phenyl groups, preferential silylation of a primary over a secondary hydroxy group occurs. In addition the TBDPS ether is more stable towards acid hydrolysis and hydrogenolysis than *t*-butyldimethylsilyl (TBS) and benzyl ethers and in some instances also survives the conditions for the cleavage of the MOM group. The parent alcohol

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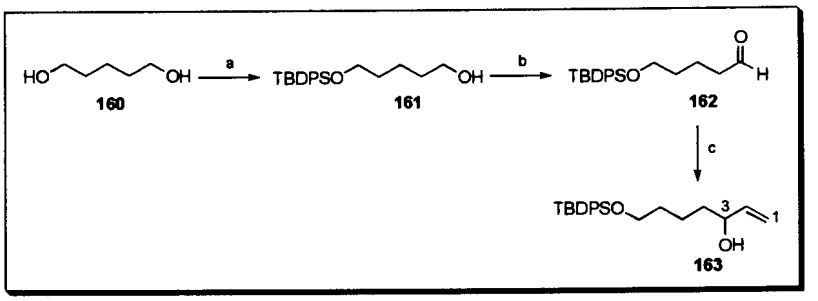
[1] Greene, T.W.; Wuts, P.G.M. *Protecting Goups in Organic Synthesis*, 3rd Ed., Wiley, **1999**.
[2] Kocieński, P.J. *Protecting Groups*, Thieme, Stuttgart, **1994**.
[3] Van Look, G. *Silylating Reagents*, Fluka Chemie AG, Buchs, Switzerland, **1988**.
[4] Nelson, T.D.; Crouch, R.D. *Synthesis,* **1996**, 1031.
[5] Hanessian, S.; Lavalle, P. *Can. J. Chem.*, **1975**, *53*, 2975.

can be regenerated by treatment with tetrabutylammonium fluoride (TBAF) in THF at room temperature, reaction conditions that do not affect the benzyl and MOM ether groups.



Scheme 4.1 Synthesis of the racemic secondary allyl alcohol (**163**)

Reagents: (a) TBDPSCl, NaH, THF (72%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, (91%); (c) H_2C=CH-Br, Mg, THF (100%).

The initial steps in the synthetic investigation are outlined in Scheme 4.1. Selective monosilylation of 1,5-pentanediol (**160**) using TBDPSCl was achieved in 72% yield using the protocol developed by McDougal *et al.*[6] In this procedure the silylating reagent is added to the insoluble sodium alkoxide suspension in THF formed by reaction of the diol with 1 equivalent NaH. The IR spectrum of the TBDPS ether (**161**) showed a broad signal for the OH group at ν_{max} 3337 cm^{-1}.

The two-carbon chain extension of the silyl ether (**161**) is based on Grignard methodology and requires the aldehyde (**162**). The Swern oxidation[7] is one of the most widely used methods for the oxidation of a primary alcohol to an aldehyde and uses dimethylsulfoxide, oxalyl chloride and triethylamine, at low temperature to achieve oxidation. The mechanism is outlined in Scheme 4.2 and involves the formation of a dimethylchloro-sulfonium ion (**D**) by reaction of dimethylsulfoxide with oxalyl chloride at –78°C. The reaction of the alcohol with (**D**) gives a new sulfonium ion (**E**) which is treated with a base, Et_3N. The most acidic proton in (**E**), located on the carbon atom α to the positively charged sulfur atom, is abstracted as the formed carbanion (**F**) can be stabilised by the positive charge on sulfur. This carbanion then removes a proton on the carbon adjacent to the oxygen atom derived from the alcohol, creating a flow of electrons toward the positively charged sulfur. In this process the aldehyde and dimethylsulfide are formed.

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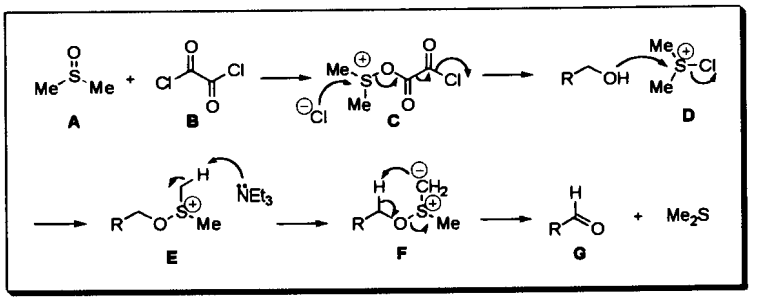
[6] McDougal, P.G.; Rico, J.G.; Oh, Y.-I.; Condon, B.D. *J. Org. Chem.*, **1986**, *51*, 3388.
[7] Omura, S.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651.



Scheme 4.2 Reaction mechanism for the Swern oxidation.

Swern oxidation of the primary alcohol in (**161**) proceeded in excellent yield (91%) to give the aldehyde (**162**) (ν_{max} 1727 cm^{-1}). The ^1H NMR spectrum showed the aldehyde proton as a triplet at δ_H 9.750 (J 1.8 Hz) whereas the aldehyde carbon atom appeared at δ_C 202.25S in the ^{13}C NMR spectrum.

The Grignard reaction is one of the oldest and yet most widely used method for generating alcohols from carbonyl compounds. The required C_2 Grignard reagent was formed by reacting a solution of vinylbromide in THF with magnesium metal. The formed vinyl magnesium bromide was reacted with the aldehyde (**162**) to give the racemic secondary allylic alcohol (**163**) in 100% yield and which often required no chromatographic purification. The presence of the acid sensitive TBDPS ether group in the aldehyde required work-up of the reaction under neutral conditions using saturated ammonium chloride solution as a proton source rather than aqueous acid.

In the IR spectrum the absorption of the alcohol OH group of (**163**) appeared at ν_{max} 3360 cm^{-1} and the C=C double bond at ν_{max} 1643 cm^{-1}. The assignment of the protons of the allylic spin system (see Figure 4.1) is based on the following analysis of the signals in the ^1H NMR spectrum of the allylic alcohol (**163**). The C(2) proton appeared at δ_H 5.849 and exhibited a *trans* coupling (J 17.2 Hz) with H(1a) (δ_H 5.207) and a *cis* coupling (J 10.3 Hz) with H(1b) (δ_H 5.091). In addition the signal for H(2) also exhibited a coupling of 6.0 Hz with H(3) (δ_H 4.071). A vicinal coupling of 1.4 Hz between H(1a) and H(1b) as well as allylic coupling (J 1.4 Hz) between each of these protons and H(3) was observed.

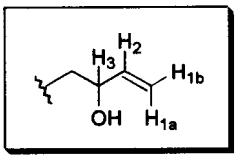
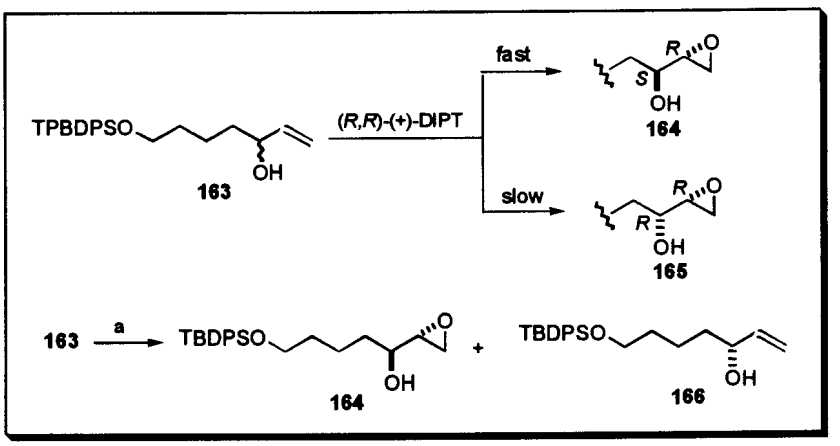


Figure 4.1 Numbering of the protons of the allylic system in (**163**).

4.3. Asymmetric epoxidation–kinetic resolution of the racemic allylic alcohol.

Racemic allylic alcohols such as (**163**) are key intermediates in the synthetic route towards the right-side of the backbone of fumonisin B_3 and B_4 as asymmetric epoxidation in conjunction with kinetic resolution will lead to a single stereoisomer of the epoxy alcohol with the appropriate stereochemistry at the two stereogenic centres. The absolute configuration of the epoxy alcohol product follows from the stereochemistry of the tartrate ester used in the experiment. The background to the method is discussed in Chapter 2.

The allylic alcohol (**163**) was treated with 0.6 equivalent of the Ti catalyst formed from Ti(IV) isopropoxide, (*R*,*R*)-(+)-DIPT, and *t*-butylhydroperoxide (TBHP) at –20°C. The (*R*,*R*)-(+)-DIPT determines the stereofacial selectivity in the epoxidation reaction. Since (*R*,*R*)-(+)-DIPT requires the *R* enantiomer of (**163**) to undergo epoxidation on the face shielded by the alkyl chain (the *ReR* face) it reacts more slowly than the *S* enantiomer in which the *ReS* face is much more accessible (see Scheme 2.12, Chapter 2). The outcome of the reaction is shown in Scheme 4.3 with the formation of the *anti* epoxy alcohol (**164**) favoured over that of the *syn* epoxy alcohol (**165**). The (2*R*,3*S*)-epoxy alcohol (**164**) was formed in 43.5% yield and the unreacted (3*R*)-allylic alcohol (**166**) was isolated in 46% yield.



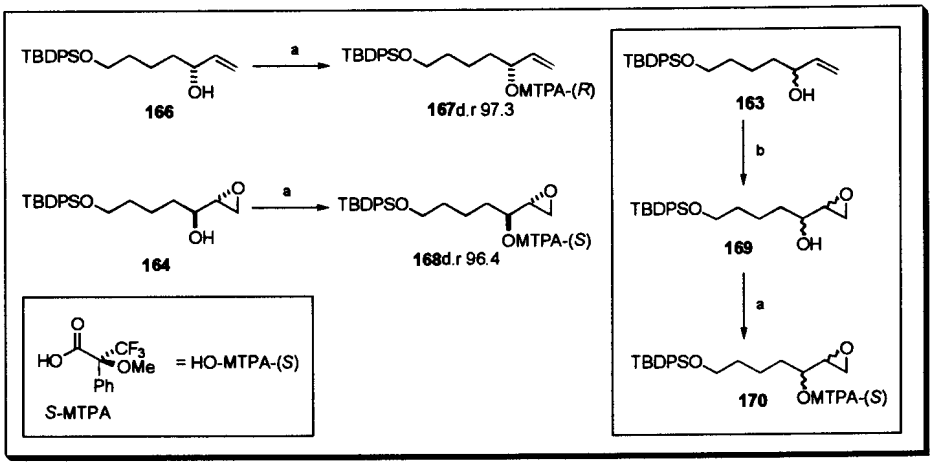
Scheme 4.3 Kinetic resolution of the allylic alcohol (**163**).

Reagents: (a) (*R*,*R*)-(+)-DIPT, Ti(*i*PrO)$_4$, TBHP, 4Å molecular sieves, CH_2Cl_2, –20°C (87%).

The ^{13}C NMR spectrum showed the typical signals of a terminal epoxide group: the C(1) signal appeared at δ_C 43.35T and the C(2) signal at δ_C 54.44D. In the ^1H NMR spectrum the epoxide protons were found as three sets of signals. The assignment of

the C(1) protons followed from the magnitude of the vicinal coupling constants.[8] The H(2) signal appeared at δ_H 2.970 (ddd) and exhibited a *trans* coupling of 4.0 Hz with H(1a) (δ_H 2.698 dd) and a *cis* coupling of 2.9 Hz with H(1b)(δ_H 2.779 dd). A geminal coupling of 5.0 Hz was observed between H(1a) and H(1b). The *anti* arrangement gave rise to a 3.0 Hz coupling for the C(2) and C(3) protons. The diastereoselectivity of the reaction was determined from the low intensity signals of the *syn*-epoxy alcohol (**165**) at δ_H 2.676 [dd, H(1b)] and δ_H 2.938 [ddd, H(2)] as 98:2 d.r.

The enantioselectivity of the reaction was determined by conversion of the (2*R*,3*S*)-epoxy alcohol (**164**) to the (*S*)-α-methoxy-α-trifluoromethylphenylacetate [(*S*)-MTPA] derivative (see Scheme 4.4) and ^{1}H and ^{19}F NMR spectroscopy. The protocol developed by Ward and Rhee[9] was followed. The Mosher acid chloride was prepared by addition of oxalyl chloride to a solution of either the (*R*)- or the (*S*)-MTPA in a mixture of DMF-hexane and stirring for 1 h at room temperature. The presence of hexane was beneficial as the DMFCl contaminant that forms, precipitates and can be removed by filtration. A solution of epoxy alcohol in DMF and Et_3N was added to the solution of the Mosher acid chloride and the reaction stirred for 90 min. Work-up of the reaction and purification by filtration through a short column of silica gel gave the pure Mosher ester derivative.



Scheme 4.4 Determination of the enantioselectivity in the products of the asymmetric epoxidation–kinetic resolution reaction.

Reagents: (a) i. (*R*)- or (*S*)-MTPA, $(COCl)_2$, DMF-hexane, ii. Epoxy alcohol, Et_3N, CH_2Cl_2; (b) MCPBA, CH_2Cl_2.

[8] Karplus, M. *J. Am. Chem. Soc.*, **1963**, *85*, 2870.
[9] Ward, D.E.; Rhee, C.K. *Tetrahedron Lett.*, **1991**, *32*, 7165.

The ^{1}H NMR spectrum of the Mosher ester (**168**) showed the signal of the C(3) proton at δ_H 5.082 (dt, $J_{2,3}$ 4.4, $J_{3,4}$ 5.7 Hz) and that of the methoxy group as a quartet ($J_{H,F}$ 1.3 Hz) at δ 3.539 (q, 3H, OMe). The H(2) signal appeared at δ_H 3.033 (ddd) and exhibited a *trans* coupling of 3.9 Hz with H(1a) (δ_H 2.729 dd) and a *cis* coupling of 2.7 Hz with H(1b)(δ_H 2.709 dd). A geminal coupling of 5.2 Hz was observed between H(1a) and H(1b). The ^{19}F spectrum showed a single major signal at δ_F –71.82 (A) and three minor signals at δ_F –71.88 (B), –71.92 (C), and –72.05 (X)(see Figure 4.1)

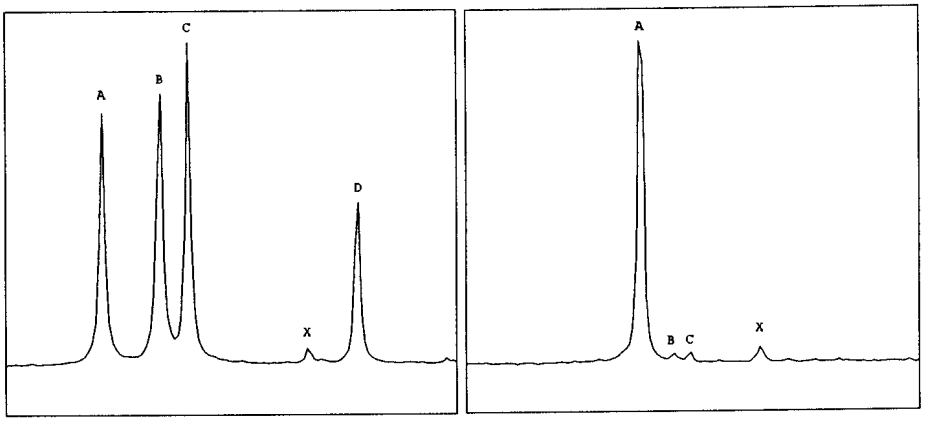


Figure 4.1 ^{19}F spectra of the Mosher derivatives (**170**)(at left) and (**168**)(at right). The signals marked A and C represent the *anti* stereoisomers and B and D the *syn* stereoisomers. X is an impurity.

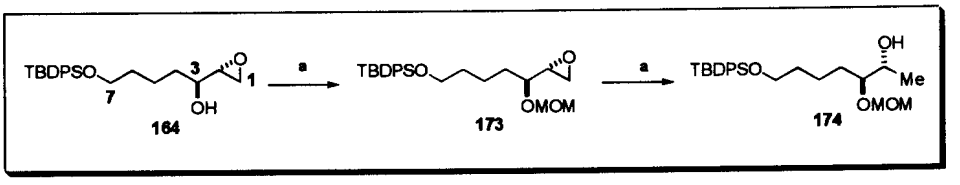
In order to facilitate the determination of the enantioselectivity in the kinetic resolution reaction using both ^{1}H and ^{19}F NMR data, it was necessary to prepare a sample of the epoxy alcohol that contained all four possible stereoisomers. Thus the racemic secondary allylic alcohol (**163**) was epoxidised using MCPBA and the product converted to the (*S*)-MTPA derivative (**170**). The overlap of the signals of the four diastereomers in the ^{1}H NMR spectrum led to the decision not to use the ^{1}H NMR data for the assay. The ^{19}F spectrum of (**170**) showed four major signals at δ_F –71.81 (A), –71.87 (B), –71.90 (C), and –72.10 (D) as well as a small signal at δ_F –72.05 (X) due to a contaminant (see Figure 4.1). With the knowledge of the ^{19}F chemical shifts of the four diastereomers to hand it was possible to determine the diastereo- and the enantioselectivity as 96:4 d.r. and 96:4 e.e., respectively.

The (*R*)-MTPA derivative (**167**) of the unreacted (*R*) allyl alcohol (**166**) showed a major signal at δ_F –71.88 and a minor one δ_F –71.73 in a 97:3 d.r.

4.4 PROTECTING GROUPS IN THE SYNTHESIS

4.4.1 The use of MOM group protection

Protection of the secondary alcohol in the epoxy alcohol (**164**) was readily achieved using chloromethyl methyl ether (MOM-Cl) in the presence of Hünig base (diisopropyl-ethylamine) in THF following the procedure described by Stock and Takahashi.[10] (see Scheme 4.5). The sensitivity of the epoxide group toward both acids and bases renders them difficult to handle under the conditions required for the introduction of many protecting groups. The essentially neutral conditions to introduce the MOM group and the fact that silyl ethers can be cleaved with TBAF without affecting the MOM group, led to its choice as protective group.



Scheme 4.5 The use of the MOM protecting group.

Reagents: (a) iPr$_2$NEt, MOM-Cl, CH_2Cl_2, 0°C→RT (76%); (b) $LiAlH_4$, THF (77%).

The MOM ether (**173**) was obtained in good yield (76%) as a colourless oil. The ^{1}H NMR spectrum showed a pair of doublets (J 6.8 Hz) at δ_H 4.575 and δ_H 4.711 and a singlet at δ_H 3.352 (3H) characteristic of the protons of the MOM group. The corresponding signals in the ^{13}C spectrum appeared at δ_C 95.96T (OCH_2O) and δ_C 55.35Q (OMe), respectively.

A drawback of the use of the MOM protecting group is the almost impossible task of obtaining MOM-Cl from overseas chemical suppliers. As a result the reagent was prepared by passing a rapid stream of hydrogen chloride gas into a mixture of methanol (1 mole equivalent) and formaldehyde solution (37%, 3 mol equivalent) following the procedure developed by Marvel and Porter.[11] The excess hydrogen chloride present in the freshly-prepared MOM-Cl was removed following the method used by Wedekind[12] by passage of a stream of CO_2 through the reagent. The presence of HCl in the reagent leads to epoxide ring opening and the formation of a chlorohydrin.

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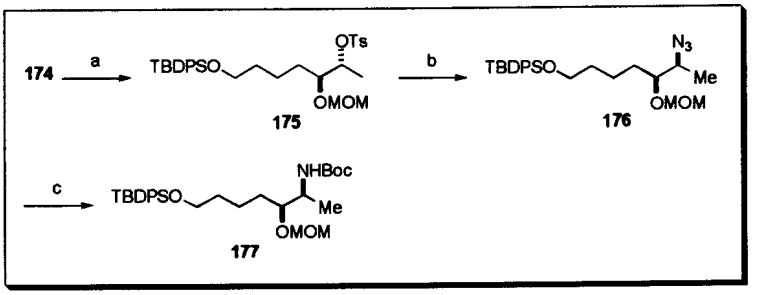
[10] Stock, G.; Takahashi, T. *J. Am. Chem. Soc.*, **1977**, *99*, 1275.
[11] Marvel, C.S.; Porter, P.K. *Organic Synthesis,* Coll. Vol. 1, 2nd Ed., John Wiley & Sons, London, **1951**, 377.
[12] Wedekind, E. *Ber.*, **1903**, 1383.

The above problems led to the consideration of the benzyl group as a viable alternative protecting group.

Lithium aluminum hydride reduction of the MOM protected epoxide (**173**) resulted in the regioselective ring opening of the epoxide ring to give the secondary alcohol (**174**) in 77% yield. The ^{1}H NMR spectrum showed the signal of the newly-formed methyl group at δ_H 1.115 as a doublet (J 6.7 Hz), the C(2) proton at δ_H 3.735 (dqd, $J_{2,OH}$ 7.5, $J_{2,1}$ 6.7, $J_{2,3}$ 2.6 Hz) and the proton of the hydroxy group at δ_H 3.100 (d, $J_{OH,2}$ 7.5 Hz). The C(1) signal appeared at δ_C 17.09Q in the ^{13}C spectrum.

The next step in the synthetic route requires the introduction of the amino group at C(2) of the MOM protected alcohol (**174**). This conversion must proceed with inversion of configuration to generate the required *syn* relationship of the two stereogenic centers. A two-step procedure was followed: (1) conversion of the C(2) hydroxy group to the *O*-tosylate derivative (**175**) and (2) displacement of the *O*-tosylate group by the azide ion in an S_N2 reaction to give the 2-azido compound (**176**) (see Scheme 4.6). The C(2) proton appeared as a doublet of quartets at δ_H 3.526 ($J_{2,1}$ 6.7, $J_{2,3}$ 5.0 Hz) and the carbon atom at δ_C 59.29D.



Scheme 4.6 Formation of the 2,3-*syn* amino alcohol unit using MOM protection.

Reagents: (a) TsCl, pyridine, DMAP, CH_2Cl_2, (61%); (b). NaN_3, DMF (88%); (c) $(Boc)_2O$, 10% Pd-C, H_2, EtOAc (81%)..

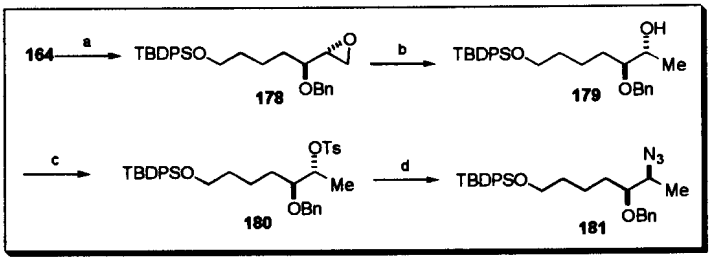
The reduction of the azide group to an amino group can be achieved by $LiAlH_4$ reduction or catalytic hydrogenation. As a result of the polar nature and the basic properties of the amino group it was decided that the amino group had to be protected before the primary TBDPS ether was deprotected and utilized in a subsequent chain extension reaction. A convenient one-pot protocol to convert an azido compound directly into the corresponding *N-t*-(butyloxycarbonyl)amino derivative has been

reported by Saito *et al.*[13] Catalytic hydrogenation of the azide (**176**), followed by *in situ* protection of the formed amino functionality, is accomplished using a suspension of 10% Pd-C in ethyl acetate in the presence of di-*tert*-butyl dicarbonate (Boc_2O). The *N*-Boc derivative (**177**) was obtained in 67% yield as a colourless oil. The presence of the *t*-Boc group was evident from the signal at δ_H 1.418 (s, 9H) in the ^1H NMR and the signals at δ_C 28.40Q, 78.96S and 155.57S in the ^{13}C spectrum. The C(2) signal appeared at δ_C 48.25D.

4.4.2 The use of benzyl group protection

Benzyl ethers find great application in organic synthesis and are compatible with a wide range of chemical transformations. Thus the benzyl group, just like the MOM group, is stable under the conditions required to cleave TBDPS and TBS ethers using TBAF. The benzyl group is removed by catalytic hydrogenolysis over Pd-C.

The ease of ring opening of epoxides by acids and bases renders them difficult to work with under these conditions. Benzylation of alcohols is carried out using NaH and BnBr. The formation of an alkoxide in the case of an epoxy alcohol can result in ring opening of the epoxide and formation of complex mixtures of benzyl ethers. An alternative method for the preparation of benzyl ethers employs *O*-benzyl trichloroacetimidate in the presence of an acid such as triflic acid,[14,15,16] and an epoxide may not survive these conditions.



Scheme 4.7 The use of the benzyl protecting group in the synthetic sequence.

Reagents: (a) BnBr, NaH, TBAI, THF (48-70%); (b) $LiAlH_4$, Et_2O (82%); (c) TsCl, pyridine, DMAP, CH_2Cl_2 (72%); (d) NaN_3, DMF (68%).

These problems were circumvented to some degree by careful sequential addition of the reagents: BnBr, phase transfer catalyst tetrabutylammonium iodide and

[13] Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.*, **1989**, *30*, 837.
[14] Wessel, H.-P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.
[15] Widmer, U. *Synthesis*, **1987**, 568.

NaH to a THF solution of the epoxy alcohol (**164**) at 0°C under argon (Scheme 4.7). The reaction mixture was kept at this temperature for 2 h and allowed to warm to room temperature over 2 h.[17] Yields in the reaction varied in the range of 48-70%. It is thought that opening of the epoxide by the formed alkoxide is faster than the S_N2 attack on the BnBr. The reaction warrants further investigation/optimization. The benzylic protons of the *O*-benzyl ether (**178**) appeared as a set of doublets (J 11.6 Hz) at δ_H 4.495 and δ_H 4.662 in the ^1H spectrum. The signal at δ_H 3.262 (ddd, $J_{3,2}$ 5.2, $J_{3,4a}$ 4.8, $J_{3,4b}$ 6.7 Hz) is assigned to H(3). The benzylic carbon atom resonated at δ_C 72.30T in the ^{13}C spectrum.

The subsequent transformation of the *O*-benzyl epoxy alcohol (**178**) to the azide (**181**) was successfully accomplished in three steps similar to those described for the MOM series in section 4.4.1: (1) regioselective reductive ring opening of the epoxide ring with $LiAlH_4$ to give the alcohol (**179**), (2) preparation of the *O*-tosylate derivative (**180**), and (3) displacement of the OTs group by azide ion.

4.5 SYNTHESIS OF THE C(1)–C(8) UNIT OF THE BACKBONE

At this stage the methodology needed for the synthetic route leading to the C(1)–C(8) unit of the backbone of both fumonisin B_3 and B_4 was in place and the protecting group strategy had been investigated. Thus the synthetic route envisaged for the target molecule (**191**) would utilize benzyl group protection for the secondary hydroxy group and TBS protection of the primary hydroxy group. The change of the TBDPS to a TBS group with its greater susceptibility to both acid and base hydrolysis, was a cost consideration: the TBS-Cl reagent is cheaper.

Treatment of 1.6-hexanediol (**147**) with 1 equivalent of sodium hydride and TBS-Cl in THF using the method developed by McDougal *et al.*[6] gave the mono-silylated product (**147a**) (ν_{max} 3349 cm^{-1}) (see Scheme 4.8). Swern oxidation of the alcohol (**147a**) proceeded successfully to give the aldehyde (**182**) (ν_{max} 1717 cm^{-1}) as a colourless oil in 83% yield after chromatographic purification. The aldehyde proton appeared as a triplet signal (J 1.8 Hz) at δ_H 9.717 and the carbonyl carbon atom at δ_C 202.46S. The aldehyde (**182**) was treated with vinyl magnesium bromide to afford the C_8 secondary allylic alcohol (**183**), the key intermediate in the synthetic route. The terminal alkene was characterized by the signals for C(1) at δ_C 114.46T and C(2) at δ_C

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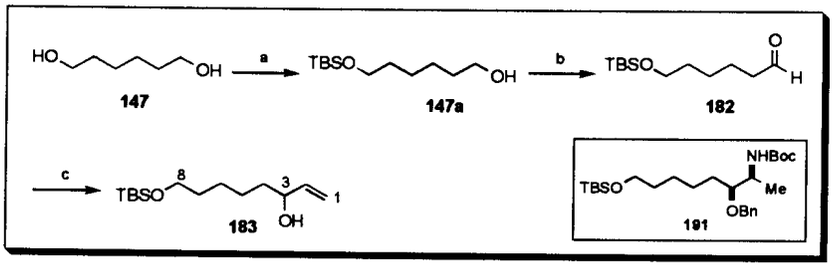
[16] Iversen, T.; Bundle, D.R. *J. Chem. Soc. Chem. Comm.* **1981**, 1240.
[17] Jin, J.; Weinreb, S.M. *J. Am. Chem. Soc.*, **1997**, *119*, 2050.

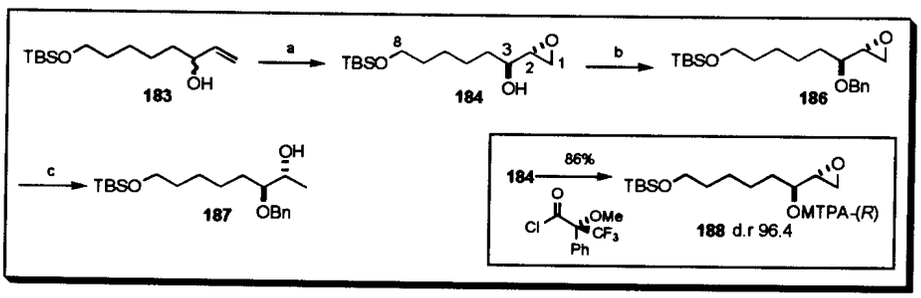
141.33D in the ^{13}C NMR spectrum. In the ^{1}H spectrum the signals of the alkene protons appeared at δ_H 5.057 [ddd, $J_{1b,2}$ 10.4, $J_{1b,1a}$ 1.5, $J_{1b,3}$ 1.3 Hz, H(1b)], 5.175 [ddd, $J_{1a,2}$ 17.2, $J_{1a,1b}$ 1.5, $J_{1a,3}$ 1.3, H(1a)] and 5.828 [ddd, $J_{2,1a}$ 17.2, $J_{2,1b}$ 10.4, $J_{2,3}$ 6.2, H(2)].



Scheme 4.8 Synthesis of the C_8 racemic secondary allylic alcohol

Reagents: (a) TBS-Cl, NaH, THF (76%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (83%); (c) CH_2=CH-Br, Mg, THF (97%).

Asymmetric epoxidation–kinetic resolution of the allylic alcohol (**183**) was carried out by treatment of (**183**) with 0.6 equivalent of Ti catalyst formed from Ti(IV) isopropoxide, (*R*,*R*)-(+)-DIPT, and *t*-butylhydroperoxide (TBHP) at –20°C (see Scheme 4.9). The (2*R*,3*S*) epoxy alcohol (**184**) was formed in 39.5% yield (maximum yield in the kinetic resolution reaction is 50%) and the unreacted (3*R*)-allylic alcohol (**185**) was isolated in 42.5% yield.



Scheme 4.9 Asymmetric epoxidation–kinetic resolution of the racemic allylic alcohol.

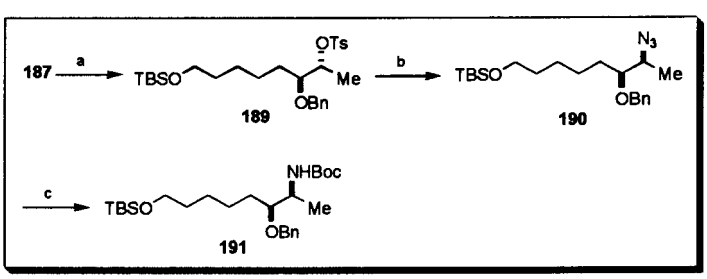
Reagents: (a) (R,R)-(+)-DIPT, Ti(^{i}PrO)$_4$, TBHP, 4Å molecular sieves, CH_2Cl_2, –20°C (79%); (b) BnBr, NaH, THF, 0°C→RT (70%); (c). $LiAlH_4$, THF (92%).

The ^{13}C NMR spectrum showed the typical signals of a terminal epoxide group: the C(1) signal appeared at δ_C 43.37T and the C(2) signal at δ_C 54.51D. In the ^{1}H NMR spectrum the epoxide protons were found as three sets of signals. Analysis indicated a set of doublet of doublets at δ_H 2.688 and δ_H 2.768 for H-1a and H-1b, respectively. The H(2) signal appeared at δ_H 2.968 (ddd) and exhibited a *trans* coupling of 3.9 Hz with H(1a) (δ_H 2.688 dd) and a *cis* coupling of 2.9 Hz with H(1b)(δ_H 2.768 dd). A geminal

coupling of 4.9 Hz was observed between H(1a) and H(1b). The *anti* arrangement gave rise to a 3.1 Hz coupling for the C(2) and C(3) protons. The diastereoselectivity of the reaction was determined from the low intensity signals of the *syn*-epoxy alcohol at δ_H 2.676 [dd, H(1b)] and δ_H 2.938 [ddd, H(2)] as 98:2 d.r

The enantioselectivity of the reaction was determined by conversion of the (2*R*,3*S*)-epoxy alcohol (**184**) to the (*R*)-α-methoxy-α-trifluoromethylphenylacetate [(*R*)-MTPA] derivative (**188**) (see Scheme 4.9) and ^{19}F NMR spectroscopy. The ratio of the signals at δ_F –71.93 and –72.09 in the ^{19}F spectrum confirmed the diastereoselectivity of the reaction as 98:2 d.r. and the ratio of the signals at δ_F –71.93 and –71.86 the enantioselectivity as 96:4.

The hydroxy group in the epoxy alcohol (**184**) was protected as the benzyl ether (**186**) in 70% yield. Regioselective reductive opening of the epoxide ring in (**186**) with $LiAlH_4$ gave the alcohol (**187**). The NMR spectra showed the signal of the formed methyl group at δ_H 1.151 (d, $J_{1,2}$ 6.5 Hz) and δ_C 17.65Q. The C(2) proton appeared as a quartet of doublets at δ_H 3.952 ($J_{1,2}$ 6.5, $J_{2,3}$ 3.4 Hz).



Scheme 4.10 Formation of the C_8 2,3-*syn* amino alcohol unit using benzyl protection

Reagents: (a) TsCl, pyridine, DMAP, CH_2Cl_2 (75%); (b) NaN_3, DMF-THF (87%); (c) $(Boc)_2O$, 10% Pd-C, H_2, EtOAc (99%).

The next step in the synthetic route requires the introduction of the amino group at C(2) of the *O*-benzyl protected alcohol (**187**). This conversion must proceed with inversion of configuration to generate the required *syn* relationship of the two stereogenic centers. A two-step procedure was followed: (1) conversion of the C(2) hydroxy group to the *O*-tosylate derivative (**189**) and (2) displacement of the *O*-tosylate group by the azide ion in an S_N2 reaction to give the 2-azido compound (**190**), ν_{max} 2105 cm^{-1} (see Scheme 4.10). The C(2) proton appeared as a doublet of quartets at δ_H 3.528 ($J_{2,1}$ 6.7, $J_{2,3}$ 5.2 Hz) and the carbon atom at δ_C 59.39D.

The number of steps in a synthetic route has a bearing on the overall yield and the cost associated with the route. The tosylate group in (**189**) is a good leaving group and therefore readily substituted by a nucleophilic reagent. The transformation of the hydroxy group in (**187**) to a dibenzylamino group would considerably shorten the synthesis. However, attempts to introduce a dibenzylamino group by displacement of the *O*-tosylate group in (**189**) by dibenzylamide, formed by reaction of Bn_2NH with butyl lithium were not successful. An alternative procedure for the direct conversion of the hydroxy group in (**187**) to an azide group can be accomplished by the Mitsunobu procedure using hydrazoic acid (HN_3) in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine.[18,19] and occurs with inversion of configuration. The hazardous nature of hydrazoic acid made it a less attractive alternative even though the synthetic route would be shortened by one step.

The azide (**190**) was converted in one step to the corresponding *N*-Boc derivative by the protocol developed by Saito.[13] Catalytic hydrogenation of the azide (**190**), followed by *in situ* protection of the formed amino functionality, is accomplished using a suspension of 10% Pd-C in ethyl acetate in the presence of di-*t*-butyl dicarbonate (Boc_2O). The *N*-Boc derivative (**191**) was obtained in 99% yield as a colourless oil. The signals at δ_H 1.413 (s, 9H) and 4.701 (br d, $J_{NH,2}$ 8.3 Hz, NHBoc) in the ^1H spectrum and those at δ_C 28.39Q, 78.93S, and 155.63S in the ^{13}C spectrum are typical of the *N*-Boc group. The C(2) signal appeared at δ_C 48.25D and the corresponding proton, H(2) at δ_H 3.819 (dqd, $J_{2,NH}$ 8.3, $J_{2,1}$ 6.7, $J_{2,3}$ 2.8 Hz).The IR spectrum showed a strong absorption at ν_{max} 1712 cm^{-1} for the carbamate carbonyl group. The benzyl ether was not affected under the catalytic hydrogenation conditions.

The completion of another project on the synthesis of the C_{12} unit corresponding to the left side of the backbone of fumonisin B_3 and B_4 and the availability of the *N*-Boc derivative (**191**) will allow the linkage of these two units to form the C_{20} backbone.

4.6 CONCLUSION

A synthetic route has been developed for a C_8 unit corresponding to C(1)–C(8) of the backbone of fumonisin B_3 and B_4 using Sharpless asymmetric epoxidation–kinetic resolution to control the stereochemistry of the two stereogenic centers. The

[18]Fieser, M.; Fieser, L.F. *Reagents for Organic Chemistry*, John Wiley & Sons, New York, **1974**, *1*, p. 447.
[19]Siah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Asym.*, 1991, 111.

stereoselectivity in this step was excellent and the yields in all the steps were high. The synthetic route can be utilized for the synthesis of analogs of the backbone with varying numbers of methylene groups between the left- and right-sides by the simple expedient of changing the length of the 1,n-alkanediol starting material.

5 STRUCTURE ELUCIDATION OF THE FUMONISIN B 3-*EPI* SERIES

5.1 INTRODUCTION

The right-side of the backbone of fumonisin B_3 and B_4 is characterised by the *syn*-2-amino-3-hydroxy group motif with the (2*S*,3*R*) absolute configuration. The same 2-amino-3-hydroxy motif is present in a number of marine natural products.

In 1989 Scheuer[1] isolated two epimeric aliphatic amino alcohols from a Papua-New Guinea sponge, *Xestospongia* sp. and proposed their structures as (2*S*,3*S*,5*E*,7*E*)- and (2*S*,3*R*,5*E*,7*E*)-2-amino-5,7-tetradecadien-3-ol, *ent*-(**192**) and *ent*-(**193**), respectively, on the basis of spectroscopic and chemical degradation studies of their diacetates and other derivatives (see Figure 5.1). The relative stereochemistry followed from NOE studies on the oxazolidinone derivative and the absolute configuration at C(2) by degradation of the diacetyl derivatives to alanine and HPLC analysis of the derivative formed with 1-fluoro-2,4-dinitrophen-5-yl-(2*S*)-alanine amide. Mori[2] assigned the opposite stereochemistry based on the total synthesis of both enantiomers of (**192**) and (**193**) since the (2*R*) isomers showed the same sign of optical rotation as the natural products. This result also necessitated a change in the stereochemistry of xestoaminol A (**194**), B (**195**), and C (**196**) originally assigned the (2*S*,3*S*) absolute configuration by Jimeńez and Crews[3] on the basis of the results obtained by Scheuer.[1]

The *anti*-2,3 stereochemistry of leucettamol A (**197**), isolated from the sponge *Leucetta microraphis* by Kong and Faulkner,[4] was deduced from NOE studies on the oxazolidinone derivative. The structures of the crucigasterins (**198**)-(**200**), isolated by Rinehart *et al.*[5] from a Mediterranean tunicate *Pseudodistoma crucigaster*, were established by NMR studies and the *anti*-2,3 relative stereochemistry from NOE studies of the

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[1] Gulavita, N.K.; Scheuer, P.J. *J. Org. Chem.*, **1989**, *54*, 366.
[2] Mori, K.; Matsuda, H. *Liebigs Ann. Chem.*, **1992**, 131.
[3] Jimeńez, C.; Crews, P. *J. Nat. Prod.*, **1990**, *53*, 978.
[4] Kong, F; Faulkner, D.J. *J. Org. Chem.*, **1993**, *58*, 970.
[5] Jares-Erijman, E.A.; Bapat, C.P.; Lithgow-Bertolloni, A.; Rinehart, K.L.; Sakai, R. *J. Org. Chem.*, **1993**, *58*, 5732

oxazolidinone derivative. The absolute configuration is based on the synthesis of the four stereoisomers of the ozonolysis product 2-amino-3-hydroxypentanoic acid.

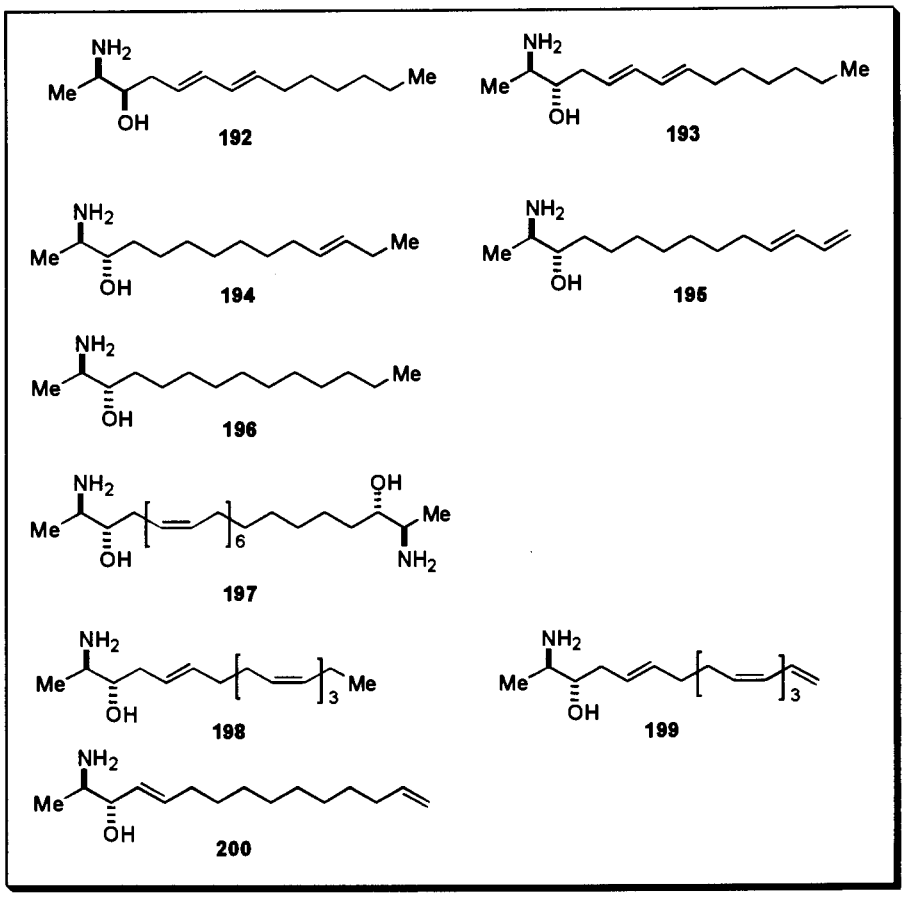

Figure 5.1 Structures of the 2,3-amino alcohols isolated from sponges.

Sata and Fusetani[6] isolated two new cytotoxic 2,3-amino alcohols, amaminol **A** (**201**) and **B** (**202**) from an unidentified tunicate of the family Polyclinidae. The stereochemical relationship between these compounds, as in the case of the amino alcohols (**192**) and (**193**) isolated by Scheuer,[1] is of particular significance to the structure elucidation of the minor metabolites of the fumonisins (see section 5.2). Amaminol **A** and **B** have the same molecular formula $C_{18}H_{31}NO$ as determined by high-resolution FAB-MS. A detailed analysis of their NMR spectra disclosed that the two compounds had identical structures but differed in the stereochemistry at the C(2) and C(3) stereogenic centres as indicated by the coupling constant between H(2) and H(3) [$J_{2,3}$ 3.1 Hz (**201**) vs. 7.3 Hz for (**202**)]. The relative stereochemistry was determined by conversion of amaminol A and B to their oxazolidinone derivatives (**201a**) and (**202a**) by treatment with *N,N'*-carbonyldiimidazole. The coupling constant (J 6.5 Hz) between

[6] Sata, N.U.; Fusetani, N. *Tetrahedron Lett.*, **2000**. *41*, 489.

H(2) and H(3) in (**201a**) as well as difference NOE experiments disclosed that the 1-methyl group and H(3) were on the same face of the oxazolidinone ring. Similarly, a *cis* relationship for H(2) and H(3) was deduced from the coupling constant and NOE experiments. Thus amaminol A (**201**) has the 2,3-*syn* and amaminol B (**202**) the 2,3-*anti* amino alcohol structure.

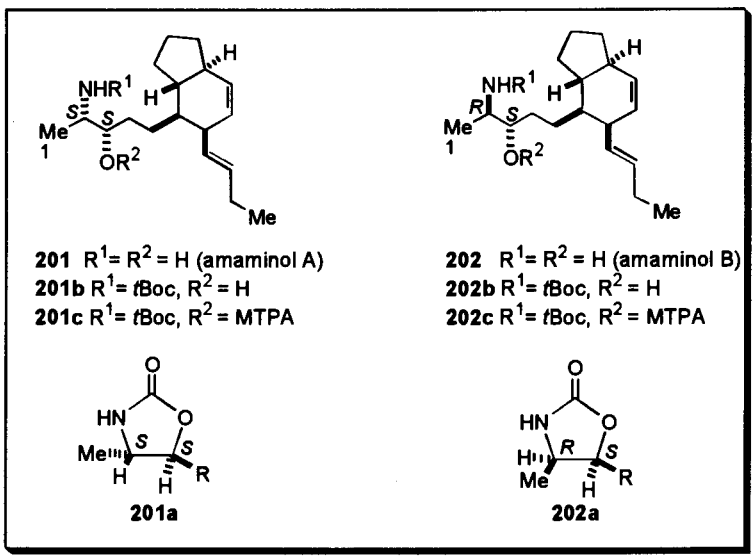

Figure 5.2 Structure of amaminol A and B and their oxazolidinone derivatives.

The *N*-Boc derivatives (**201b**) and (**202b**) were each converted to both their (*S*)- and (*R*)-MTPA esters (**201c**) and (**202c**). The Mosher analysis[7] indicated that the two compounds had the same 3*S* absolute configuration and were epimeric at C(2). This is in direct contrast to the results obtained by Scheuer[1] on the amino alcohols (**192**) and (**193**) which are C(3) epimers. The 2*S* configuration of the amaminols differs from that of all the other amino alcohols isolated from marine sources: The normal 2*R* configuration has been suggested to arise from the use of (2*R*)-alanine in the biosynthesis of these compounds.[5] Analysis of the NMR data reported by Scheuer,[1] and Mori[2] in the work on the amino alcohols (**192**) and (**193**) and by Sata and Fusitani[6] on the amaminols (**201**) and (**202**), showed characteristic chemical shift values for the methyl group of the *syn* and *anti* 2,3-amino alcohols. Thus the methyl group, C(1) in the diacetyl derivative of (**192**) appeared at δ_C 18.49 (*syn*) and in that of (**193**) at δ_C 14.93 (*anti*). The same trend is observed for the amaminols: δ_C 16.0 for the *syn* compound (**201**) and δ_C 12.1 for the *anti* compound (**202**). The *anti*-amino alcohol (**197**) showed the methyl groups at δ_C 12.1 and 11.9 whereas in the *syn*-amino alcohols such as

[7] Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

fumonisin B_3 (**6**) and B_4 (**7**) the methyl group appears at δ_C 15.61 and 15.42. It is thus evident that both *syn* and *anti* stereoisomers should be available for comparison of the ^{13}C NMR data.

5.2 STRUCTURE ELUCIDATION OF THE FUMONISIN B 3-*EPI* COMPOUNDS

Analyical standards of fumonisin B_1 (**4**), B_2 (**5**) and B_3 (**6**) have been isolated and purified according to the method described by Cawood *et al.*[8] by scientists at the MRC, Tygerberg, South Africa on a commercial basis since the early 1990s. HPLC analysis of the fumonisin samples is performed according to the method of Shephard *et al.*[9] Thus a standard solution of fumonisin B_3 (50 μg/ml in acetonitrile-water 1:1) is prepared and derivatised for fluorescence detection with o-phthaldialdehyde (OPA) reagent: 25 μl of the standard solution and 225 μl of the OPA reagent are mixed and 10 μl injected onto a Phenomenex Ultracarb 5 ODS column within one minute of mixing and eluted with methanol–0.1M NaH_2PO_4 (pH 3.4) (77:23 v/v) as mobile phase. A single peak was observed at 27.06 min in the chromatogram. Analysis of fumonisin B_3 obtained from different batches of *Fusarium moniliforme* (MRC 826) have recently shown the presence of 10-40% of a stereoisomer of fumonisin B_3 that appears as a second peak at 26.48 min in the chromatogram.

Mass spectrometry of these fumonisin B_3 samples using both FAB-MS and ES-MS showed the molecular mass at $[M+H]^+$ at 706 and established the molecular formula $C_{34}H_{59}NO_{14}$ for the two stereoisomers. The ^1H and ^{13}C NMR spectra showed in all cases the presence of a minor component (**203**). The use of two-dimensional COSY and HETCOR experiments established that the discernible signals of the minor component in the ^1H and ^{13}C spectra represent the C(1)–C(4) unit of the backbone. The coupling constant of 6.8 Hz between the C(2) and C(3) protons of fumonisin B_3 is characteristic of the *syn*-2,3 amino alcohol in these metabolites. The *anti* stereo-chemistry for the 2,3-amino alcohol unit of the minor metabolite (**203**) followed from the 3.1 Hz coupling observed for the C(2) proton with H(3)(see Table 5.1). The ^{13}C chemical shifts for the methyl group in fumonisin B_3 (δ_C 15.61Q) and the minor component (δ_C 12.01Q) confirmed the *anti*-2,3 stereochemistry of the latter.

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[8] Cawood, M.E.; Gelderblom, W.C.A.; Vleggaar, R.; Behrend, Y.; Thiel, P.G.; Marasas, W.F.O. *J. Agric. Food Chem.*, **1991**, *39*, 1958.
[9] Shephard G.S.; Sydenham, E.W.; Thiel, P.G.; Gelderblom, W.C.A. *J. Liq. Chromatogr.*,**1990** *13*, 2077.

	Fumonisin B_3 (6)		3-*epi*-Fumonisin B_3 (203)	
Atom	δ_C	δ_H	δ_C	δ_H
1	15.61 Q	1.113 d (J 6.7)	12.01 Q	1.054 d (J 6.7)
2	51.36 D	2.956 qd (J 6.7, 6.8)	50.63 D	3.125 qd (J 6.8, 3.1)
3	71.08 D	3.336 m	69.65 D	3.568 m
4	32.90 T	-----	32.46 T	------

	Fumonisin B_4 (7)		3-*epi*-Fumonisin B_4 (204)	
Atom	δ_C	δ_H	δ_C	δ_H
1	15.42 Q	1.120 d (J 6.6)	11.93 Q	1.060 d (J 6.7)
2	51.23 D	2.957 qd (J 6.7, 6.7)	50.56 D	3.120 qd (J 6.8, 3.1)
3	70.96 D	3.33 m	69.57 D	3.58 m
4	32.75 T	-----	32.37 T	-----

Table 5.1 NMR Data for the normal and 3-*epi* series of fumonisin B_3 and B_4 (solvent DMSO-d_6)

The ^1H and ^{13}C NMR spectra of samples of fumonisin B_4 (**7**) sometimes also showed the presence of up to 40% of a minor metabolite with the 2,3-*anti* stereochemistry. The *anti* stereochemistry followed once again from the coupling constant for the H(2) and H(3) protons and the ^{13}C chemical shift of the methyl group, C(1)(see Table 5.1).

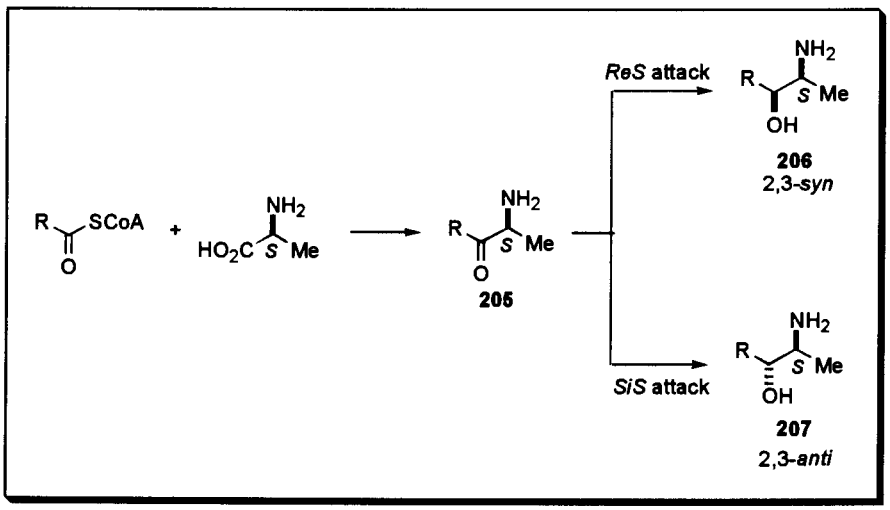


Figure 5.3 Biosynthetic formation of the 3-*epi* series of the fumonisins.

The biosynthesis of the fumonisins involves the carbon-carbon bond formation between (2*S*)-alanine and a polyketide-derived–SCoA by a pyridoxalphosphate depen-

dent enzyme, and involves the loss of CO_2 to form a 3-keto intermediate (**205**) with overall inversion of stereochemistry (see Chapter 1.2.6 and Figure 5.3). The reduction of either the *ReS* or the *SiS* face of the carbonyl group then leads to the formation of the fumonisin B 3-*normal* (**206**) and 3-*epi* (**207**) series, respectively. On the basis of this biosynthetic model the (2*S*,3*R*) configuration is assigned to the 3-*epi*-fumonisin B_3 (**203**) and B_4 (**204**) compounds.

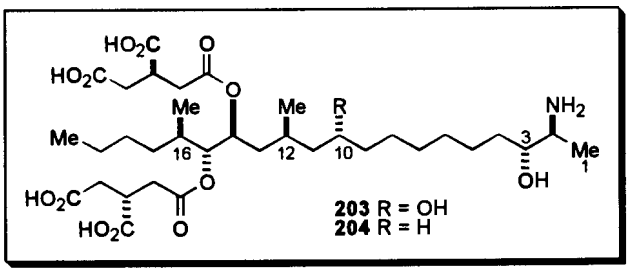


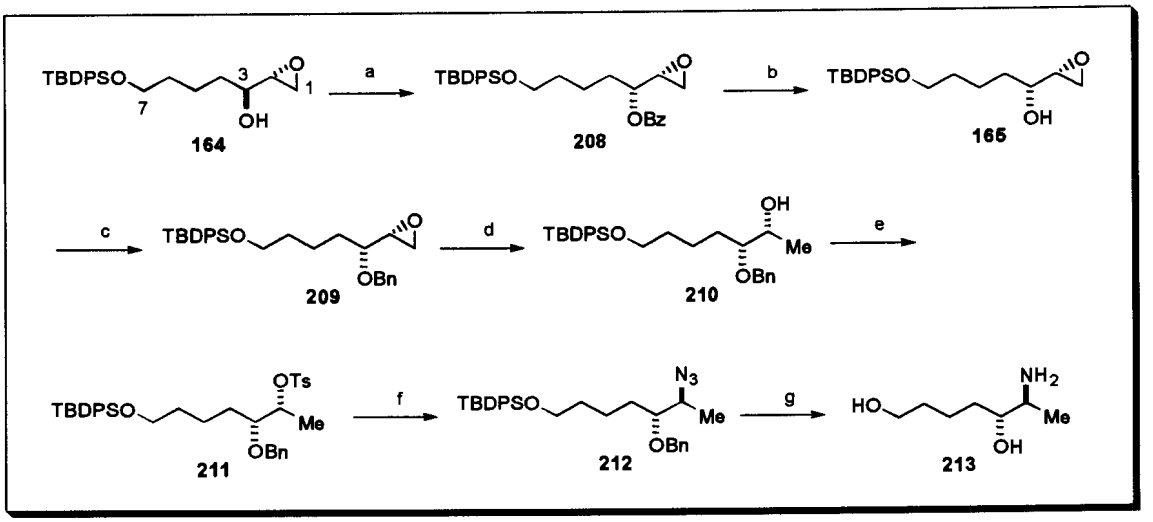
Figure 5.4 Structures of the 3-*epi*- stereoisomers of fumonisin B_3 and B_4.

5.3 SYNTHESIS OF A MODEL COMPOUND FOR THE 3-*EPI* SERIES

The aim of the synthesis of a model compound with the 2,3-*anti* amino alcohol unit was to compare its ^1H and ^{13}C NMR data with that of the right-hand moiety of 3-*epi*-fumonisin B_3 (**203**) and 3-*epi*-fumonisin B_4 (**204**).

The synthesis of the model compound (**213**) is outlined in Scheme 5.1 and uses the C_7 epoxy alcohol (**164**) as starting material. The Mitsunobu reaction[10] of (**164**) using diethyl azodicarboxylate (DEAD), triphenylsphosphine (PPh_3), and benzoic acid proceeds with inversion of configuration and gave the *syn*-epoxy benzoate (**208**) in 71% yield. The C(3) proton appeared at δ_H 5.018 and exhibited a coupling of 5.4 Hz with H(2). The benzoate ester (**208**) was saponified using anhydrous potassium carbonate in methanol,[11] at room temperature for 2 h to give the *syn*-epoxy alcohol (**165**). The H(2) signal appeared at δ_H 2.938 (ddd) in the ^1H NMR spectrum and exhibited a *trans* coupling of 3.9 Hz with H(1a) (δ_H 2.676 dd) and a *cis* coupling of 2.8 Hz with H(1b)(δ_H 2.784 dd). A geminal coupling of 5.0 Hz was observed between H(1a) and H(1b). The *syn* arrangement gave rise to a 5.2 Hz coupling for the C(2) and C(3) protons.

[10]Mitsunobu, O. *Synthesis*, **1981**, 1.
[11] Evans, D.A.; Gauchet-Prunet, J.A.; Carreira, E.M.; Charette, A.B. *J. Org. Chem.*, **1991**, *56*, 741.



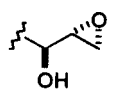
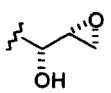
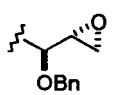
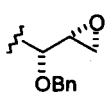
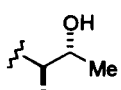
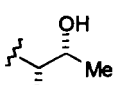
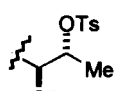
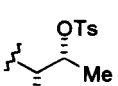
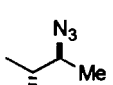
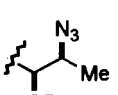
Scheme 2.1 Synthesis of a model compound with the 2,3-*anti* stereochemistry.

Reagents: (a) DEAD, $PhCO_2H$, Ph_3P, C_6C_6/THF (71%); (b) K_2CO_3, MeOH (64%); (c) BnBr, NaH, DMF/THF (56%); (d) $LiAlH_4$, Et_2O (94%), (e) i. TsCl, Py, DMAP, CH_2Cl_2; ii. NaN_3, DMF (92%); (f) 10% Pd-C, H_2, EtOAc, H^+.

The *syn*-epoxy alcohol (**165**) was reacted with NaH and BnBr to give the benzyl ether (**209**). The benzylic protons of the *O*-benzyl ether appeared as a set of doublets (J 11.7 Hz) at δ_H 4.563 and δ_H 4.826 in the ^1H spectrum. The regioselective reductive ring opening of the epoxide ring with $LiAlH_4$ gave the alcohol (**210**). The NMR spectra showed the signal of the formed methyl group at δ_H 1.157 (d, $J_{1,2}$ 6.2 Hz) and δ_C 18.98Q. The C(2) proton appeared as a quartet of doublets at δ_H 3.719 ($J_{1,2}$ 6.2, $J_{2,3}$ 5.2 Hz). The next step in the synthetic route required the introduction of the amino group at C(2) of the *O*-benzyl protected alcohol (**210**). This conversion must proceed with inversion of configuration to generate the required *anti* relationship of the two stereogenic centers. A two-step procedure was followed: (1) conversion of the C(2) hydroxy group to the *O*-tosylate derivative (**211**) and (2) displacement of the *O*-tosylate group by the azide ion in an S_N2 reaction to give the 2-azido compound (**212**). The C(2) proton appeared as a doublet of quartets at δ_H 3.596 ($J_{2,1}$ 6.7, $J_{2,3}$ 3.9 Hz) and the carbon atom at δ_C 59.39D.

The reduction of the azido group in (**212**) to an amino group was carried out by catalytic hydrogenation using 10% Pd-C under acidic conditions. As a result both the TBDPS ether and the benzyl ether were cleaved to give the amino alcohol (**213**). The ^{13}C NMR spectrum recorded in D_2O showed the signal for C(1) at δ_C 12.30Q in agreement with the *anti* stereochemistry.

The coupling constant between the C(2) and C(3) protons in both the *syn* and *anti* series of compounds obtained by the synthetic route using TBDPS and benzyl protection for the hydroxy groups, is collated in Table 5.2. In addition the ^{13}C chemicals for C(1)–C(3) are also listed in Table 5.2. From the data it is evident that the coupling constant $J_{2,3}$ of the *anti* series is always smaller than that of the *syn* series. Similarly the ^{13}C chemical shift values of the methyl group in the *syn* series are always to higher field compared to the *anti* series.

	2,3-*anti*		**2,3-*syn***		
	$J_{2,3}$ (Hz)	**δ_C**	**$J_{2,3}$ (Hz)**	**δ_C**	
 **164**	3.0	C(1) 43.35T C(2) 54.44D C(3) 68.39D	5.2	C(1) 45.01T C(2) 55.30D C(3) 71.62D	 **165**
 **178**	5.2	C(1) 45.54T C(2) 53.48D C(3) 77.95D	Note a	C(1) 43.08T C(2) 55.06D C(3) 80.50D	 **209**
 **179**	3.4	C(1) 17.62Q C(2) 68.08D C(3) 82.92D	5.2	C(1) 18.98Q C(2) 68.96D C(3) 84.02D	 **210**
 **180**	2.9	C(1) 15.36Q C(2) 81.45D C(3) 80.59D	6.5	C(1) 15.65Q C(2) 79.89D C(3) 79.32D	 **211**
 **212**	3.9	C(1) 14.36Q C(2) 59.28D C(3) 81.71D	5.2	C(1) 15.36Q C(2) 59.48D C(3) 82.00D	 **181**

[a] The H(2) and H(3) signals overlap

Table 5.2 NMR Data for compounds of the 2,3-*anti* and 2,3-*syn* series.

6 EXPERIMENTAL

6.1 General

Air- and/or moisture-sensitive reactions were carried out under a positive pressure of argon in oven-dried (120°C) glassware. Room temperature (RT) refers to 20-25°C. Evaporations were done under reduced pressure on a Büchi rotary evaporator. All reagents were of synthetic grade and were used without any further purification. When necessary, solvents and reagents were dried according to standard methods prior to use.[1] Solvents used for chromatography or extractions were distilled.

Optical rotations were determined with a Perkin Elmer 241 polarimeter for solutions in chloroform ($CHCl_3$). Specific rotations are given in units of 10^{-1} deg.g^{-1}.cm^2. High-resolution mass spectra were performed by Dr. L. Fourie, University of Potchefstroom, on a VG 7070-E spectrometer (Xe beam, *m*-nitrobenzyl alcohol matrix, detection of positive ions with $m/z > 99$).

Infrared spectra were recorded with a Bruker 113v FTIR instrument as a thin layer between ZnSe disks. Values were rounded to 5 cm^{-1} upon manual assignment or 1 cm^{-1} upon automatic assignment.

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on a Bruker AMX-300 (7.0T) spectrometer operating at 300 MHz for ^1H, 75.47 MHz for ^{13}C and 282.4 MHz for ^{19}F. All chemical shifts are reported as δ values downfield from Me_4Si using $CDCl_3$ as internal standard (δ_H 7.24 or δ_C 77.00 ppm, respectively). $CFCl_3$ was used as external standard for ^{19}F with negative numbers assigned to high-field shift values. Proton-proton coupling constants (*J*) are given in Hz. Spectral coupling patterns are designated as follows: s/S: singlet; d/D: doublet; t/T: triplet; q/Q: quartet; m: multiplet; br: broad signal. The assignments of the signals in the ^1H NMR spectra are based on first-order analysis of the spin systems and when required were confirmed by $^1H\{^1H\}$ decoupling experiments and two-dimensional (2-D) (^1H,^1H) homonuclear chemical shift correlation (COSY) experiments. The ^{13}C chemical shifts were obtained from proton-decoupled spectra. The multiplicities of the

[1] Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1992**.

different ^{13}C resonances were deduced from the proton-decoupled CH, CH_2, and CH_3 subspectra obtained using the DEPT pulse sequence. The signals of the proton-bearing carbon atoms were correlated with specific proton resonances by utilizing the one-bond (^{13}C,^{1}H) spin-spin couplings. Standard Bruker pulse programs were used in these experiments.

The course of reactions was followed on thin-layer chromatography (TLC) using glass or aluminium plates coated with silica gel 60 F_{245} (Merck). Relative front values (R_f) in various solvent systems were recorded for all products and intermediates. Column chromatography was performed on Merck silica gel 60 (60-200μm, 70-230 mesh). Eluant volumes are given as v/v. TLC plates were examined under UV light (254 and 366 nm) and/or after colouring and subsequent heating with cerium(IV) sulfate/ammonium heptamolybdate reagent.

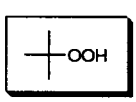
6.2 PREPARATION OF REAGENTS

6.2.1 Spraying Reagents.

Cerium(IV) sulfate-sulfuric acid.

A spray solution was prepared from cerium(IV) sulfate (1% w/v) dissolved in 3M sulfuric acid. The chromatograms were heated with a heat-gun until the appearance of dark spots as a positive indication of the presence of compounds of interest.

6.2.2 Other Reagents



Anhydrous *tert*-butyl hydroperoxide in toluene.

TBHP solution (70% v/v in water, 325 ml) and toluene (400 ml) were placed in a 1L separating funnel. The mixture was swirled and not shaken in order to avoid the formation of an emulsion. The organic phase was separated and transferred to a 1L two-necked round-bottom flask fitted with a Dean-Stark apparatus, reflux condenser, and a thermometer. The solution was refluxed for 1 h during which time about 20 ml of water was collected. When no more water collected through azeotropic distillation, the solution (*ca.* 600 ml) was allowed to cool and stored over 4Å molecular sieves in a brown glass bottle. The anhydrous TBHP solution in toluene was standardised by ^{1}H NMR spectroscopy. The molarity was determined as 4.1M by using the formula

$$M = \frac{x}{0.1x + 0.32y}$$

where x and y are the integrated value in millimetres (mm) of the *tert*-butyl group and the toluene methyl group protons, respectively,

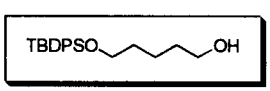
δ_H 1.293 (s, 9H, C**Me**$_3$)
2.384 (s, 3H, Ar**CH**$_3$)
7.19-7.34 (m, 5H, Ar**H**)

Chloromethyl methyl ether.

A rapid stream of hydrogen chloride gas was passed into a mixture of methanol (175 g, 5.46 mol) and formaldehyde solution (37% w/v, 450 g, 15.0 mol). The solution was allowed to reflux for 2 h by which time a layer of chloromethyl methyl ether (MOMCl) had begun to form. The stream of hydrogen chloride was continued for 1 h longer to saturate the solution. The MOMCl was then separated. The water layer was saturated with solid $CaCl_2$ and more MOMCl separated. The latter was added to the main portion that was then dried over $CaCl_2$. The crude MOMCl was neutralised by passing a stream of dry CO_2 gas through the solution and fractionally distilled to yield a pure product, b.p. 55-60°C (212 g, 63%).

6.3 PROCEDURES.

6.3.1 Synthesis of the C_7 *syn*-2,3-amino alcohol : MOM protection.



5-[(*tert*-Butyldiphenylsilyl)oxy]-1-pentanol 161.

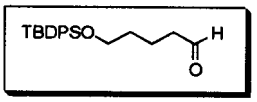
Sodium hydride (60% dispersion, 5.80 g, 150 mmol) was washed with hexane (3×) and suspended in THF (50 ml). 1,5-Pentanediol (15.6 g, 150 mmol) was added dropwise to the suspension at RT and the reaction mixture stirred for 45 min (until such time that hydrogen evolution ceased). TBDPSCl (41.2 g, 150 mmol) was added dropwise and the reaction mixture stirred for another 90 min at RT. The THF was evaporated and the residue partitioned between water and CH_2Cl_2. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:4) as eluent to

give the monoprotected ether **161** as an oil (36.8 g, 72%), R_f 0.27 (EtOAc-hexane 1:4); ν_{max} 3337 cm^{-1}.

δ_H 1.121 (s, 9H, C**Me**$_3$)
1.424 (m, 2H, H-3)
1.50-1.65 (m, 4H, H-2 and H-4)
3.623 (t, 2H, $J_{1,2}$ 6.5, H-1)
3.737 (t, 2H, $J_{5,4}$ 6.5, H-5)
7.34-7.69 (m, 10H, Ar**H**)

δ_C 19.09S (**C**Me$_3$), 21.90T (C-3), 26.80Q (C**Me**$_3$), 32.19T (C-2)*, 32.29T (C-4)*, 62.67T (C-1), 63.74T (C-5), 127.45D, 129.43D, 133.96S, and 135.44D (aromatic carbons).

FAB-MS: *m/z* 343 $[M+H]^+$. Exact mass: Calculated for $C_{21}H_{31}SiO_2$, 343.2093; Observed, 343.2093



5-[(*tert*-Butyldiphenylsilyl)oxy]-1-pentanal 162.

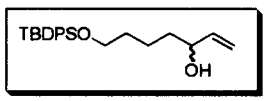
DMSO (10.3 g, 132 mmol) was added dropwise by syringe to a solution of oxalyl chloride (8.38 g, 66.0 mmol) in CH_2Cl_2 (100 ml) at –78°C under argon and the reaction stirred for 15 min. A solution of the alcohol **161** (21.0 g, 61.3 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 30 min and the reaction stirred at –78°C for 1 h. Triethylamine (30.4 g, 300 mmol) was slowly added and stirring continued for 90 min. The reaction was allowed to reach RT and the slightly white/yellow suspension was washed with 2M HCl (150 ml) and water (150 ml). The organic solution was dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by column chromatography with EtOAc-hexane (1:9) to yield the aldehyde **162** (19.0 g, 91%) as a colourless oil; R_f 0.33 (EtOAc-hexane 1:9); ν_{max} 1727 cm^{-1}.

δ_H 1.110 (s, 9H, C**Me**$_3$)
1.58-1.68 (m, 2H, H-4)
1.72-1.82 (m, 2H, H-3)
2.418 (td, 2H, $J_{2,3}$ 7.0, $J_{2,1}$ 1.8, H-2)

3.728 (t, 2H, $J_{5,4}$ 6.1, H-5)
7.37-7.74 (m, 10H, ArH)
9.750 (t, 1H, $J_{1,2}$ 1.8, H-1)

δ_C 18.46T (C-3), 19.10S (CMe_3), 26.80Q (CMe_3), 31.75T (C-4), 43.37T (C-2), 63.20T (C-5), 127.56D, 129.51D, 133.78S, and 135.44D (aromatic carbons), 202.25S (C-1).

FAB-MS *m/z* 341 $[M+H]^+$. Exact mass: Calculated for $C_{21}H_{29}SiO_2$, 341.1969; Observed, 341.1936.



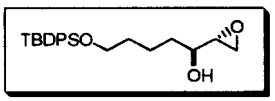
(*3RS*)-*7*-[(*tert*-Butyldiphenylsilyl)oxy]-1-hepten-3-ol 163.

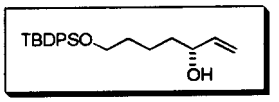
A solution of vinyl bromide (9.95 g, 93.0 mmol) in THF (15 ml) was added by syringe to a mixture of Mg turnings (1.94 g, 80.8 mmol) in THF (250 ml). The reaction was initiated by addition of a crystal of iodine. After all the Mg was consumed the solution was cooled to 20°C and a solution of the aldehyde **162** (18.0 g, 52.9 mmol) in THF (35 ml) was added dropwise to the Grignard solution. The reaction was refluxed for 2 h, cooled to 20°C and a saturated solution of ammonium chloride was added carefully. The resulting Mg salts were allowed to settle and the solvent decanted. The THF was evaporated and the residue partitioned between water (50 ml) and diethyl ether (100 ml). The diethyl ether solution was washed with sodium thiosulfate (10%, 50ml), dried (Na_2SO_4), filtered and evaporated to give the allylic alcohol **163** (19.5 g, 100%) as a thick oil; R_f 0.48 (hexane-EtOAc 1:4); ν_{max} 3360 and 1643 cm^{-1}.

δ_H 1.064 (s, 9H, CMe_3)
1.41-1.62 (m, 6H, H-4, H-5 and H-6)
3.684 (t, 2H, $J_{7,6}$ 6.4, H-7)
4.071 (m, 1H, H-3)
5.091 (ddd, 1H, $J_{1b,2}$ 10.3, $J_{1b,1a}$ 1.4, $J_{1b,3}$ 1.4, H-1b)
5.207 (ddd, 1H, $J_{1a,2}$ 17.1, $J_{1a,1b}$ 1.4, $J_{1a,3}$ 1.4, H-1a)
5.849 (ddd, 1H, $J_{2,1a}$ 17.2, $J_{2,1b}$ 10.3, $J_{2,3}$ 6.0, H-2)
7.32-7.66 (m, 10H, ArH)

δ_C 19.16S (**C**Me_3), 21.57T (C-5), 26.85Q (CMe_3), 32.35T (C-6), 36.66T (C-4), 63.75T (C-7), 73.06D (C-3), 114.45T (C-1), 127.53D, 129.47D, 134.05S, and 135.53D (aromatic carbons), 141.22D (C-2).

FAB-MS *m/z* 369 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{33}SiO_2$, 369.2250; Observed, 369.2249.





(2*R*,3*S*)-1,2-Epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]-3-heptanol 164 and (3*R*)-7-[(*tert*-butyldiphenylsilyl)oxy]-1-hepten-3-ol 166.

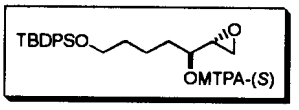
A solution of (*R*,*R*)-(+)-DIPT (762 mg, 3.25 mmol) in CH_2Cl_2 (10 ml) was added by syringe to a suspension of activated powdered 4Å molecular sieves (500 mg) in CH_2Cl_2 (30 ml) under argon at –20°C. Ti(*i*PrO)$_4$ (771 mg, 2.71 mmol) in CH_2Cl_2 (5 ml) was added by syringe followed by a solution of TBHP (3.8M in toluene, 294 mg, 3.26 mmol) pre-cooled to 0°C. The resulting solution was stirred for 30 min at –20°C before addition by syringe over a period of 10 min of a solution of the secondary allylic alcohol **163** (2.00 g, 5.43 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 4 h at –20°C and then at –10°C in the freezer for 14 h. The solution was allowed to reach 0°C, filtered, and a fresh solution of iron(II) sulfate (13.2 g) and tartaric acid (4.0 g) in water (40 ml), pre-cooled to 0°C was added with continuous stirring. The CH_2Cl_2 solution was evaporated and the residue dissolved in diethyl ether (20 ml). The aqueous layer was extracted with diethyl ether (5×30 ml). The combined diethyl ether solution was vigorously stirred with brine solution containing NaOH (5%, 80 ml) for 1 h at 0°C and diluted with water (50 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by chromatography on silica gel using EtOAc-hexane (1:3) as eluant to yield the (3*R*)-allylic alcohol **164** (915 mg, 46%), R_f 0.48 (EtOAc:hexane 1:4) and the epoxide **166** (909 mg, 43.5%), R_f 0.32 (EtOAc-hexane 1:4); ν_{max} 3453 cm^{-1}.

δ_H 1.050 (s, 9H, CMe_3)
1.48-1.61 (m, 6H, H-4, H-5 and H-6)
1.84 (bs, 1H, OH)
2.698 (dd, 1H, $J_{1a,1b}$ 5.0, $J_{1a,2}$ 4.0, H-1a)
2.779 (dd, 1H, $J_{1a,1b}$ 5.0, $J_{1b,2}$ 2.9, H-1b)

2.970 (ddd, 1H, $J_{1a,2}$ 4.0, $J_{2,3}$ 3.0, $J_{1b,2}$ 2.9, H-2)
3.728 (t, 2H, $J_{1,2}$ 6.1, H-7)
3.789 (m, 1H, H-3)
7.38-7.72 (m, 10H, ArH)

δ_C 19.19S (CMe_3), 21.57T (C-5), 26.87Q (CMe_3), 32.45T (C-6), 33.13T (C-4), 43.35T (C-1), 54.44D (C-2), 63.71T (C-7), 68.39D (C-3), 127.57D, 129.51D, 134.06S, and 135.55D (aromatic carbons).

FAB-MS *m/z* 385 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{33}SiO_3$, 385.2199; Observed, 385.2198.



MOSHER ESTER DERIVATIZATION

a. (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride

Oxalyl chloride (290 mg, 2.28 mmol) was added to a solution of (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (101 mg, 0.431 mmol) and DMF (31 mg, 0.42 mmol) in anhydrous hexane (5.0 ml) at RT. A white precipitate formed immediately. After 1 h at RT the mixture was passed through a small cotton plug to filter off the DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl) (108 mg, 94%).

b. (2*R*,3*S*)-1,2-Epoxy-7-[(tert-butyldiphenylsilyl)oxy]-3-heptyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate 168.

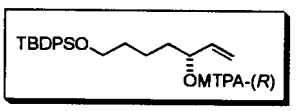
A solution of the epoxy alcohol **164** (120 mg, 0.31 mmol), triethylamine (363 mg, 3.59 mmol) and DMAP (5.0 mg) were added to a stirred solution of the acid chloride (obtained as described in **a**. above) in CH_2Cl_2 (5.0 ml). The reaction was quenched after 90 min with water (2.0 ml), and the organic layer washed with 0.5M HCl, and saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (EtOAc-hexane 1:3) to give the Mosher ester **168** (156 mg, 83%), R_f 0.57 (EtOAc-hexane 1:3); ν_{max} 1753 cm^{-1}.

δ_H 1.035 (s, 9H, C**Me**$_3$)
1.350 (m, 2H, H-5)
1.517 (m, 2H, H-6)
1.694 (dt, 2H, $J_{3,4}$ 5.7, $J_{4,5}$ 8.0, H-4)
2.709 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 2.7, H-1a)
2.729 (dd, 1H, $J_{1b,1a}$ 5.2, $J_{1b,2}$ 3.9, H-1b)
3.033 (ddd, 1H, $J_{3,2}$ 4.4, $J_{2,1b}$ 3.9, $J_{2,1a}$ 2.7, H-2)
3.539 (q, 3H, $J_{H,F}$ 1.3 OMe)
3.580 (t, 2H, $J_{7,6}$ 6.2, H-7)
5.082 (dt,1H, $J_{2,3}$ 4.4, $J_{3,4}$ 5.7, H-3)
7.34-7.67 (m, 15H, Ar**H**)

δ_C 19.16S (**C**Me$_3$), 21.04T (C-5), 26.83Q (C**Me**$_3$), 30.93T (C-6), 32.10T (C-4), 44.60T (C-1), 51.79D (C-2), 55.37Q (O**Me**), 63.49T (C-7), 74.29D (C-3), 84.79SQ (**C**CF$_3$), 123.33Q (**C**F$_3$, $J_{C,F}$ 289 Hz), 127.30D, 127.61D, 127.84D, 128.34D, 129.56D, 132.25S, 133.94S, 135.24D (C-2), 135.52D (aromatic carbons), 166.00S (**C**O).

δ_F –71.83

FAB-MS *m/z* 601 $[M+H]^+$. Exact mass: Calculated for $C_{33}H_{40}F_3SiO_5$, 601.2597; Observed, 601.2597.



c. (3*R*)-7-[(tert-butyldiphenylsilyl)oxy]-1-hepten-3-yl (*R*)-α-methoxy-α-trifluoromethylphenylacetate 167.

A solution of the (3*R*)-allylic alcohol **166** (114 mg, 0.31 mmol), triethylamine (363 mg, 3.59 mmol) and DMAP (5.0 mg) were added to a stirred solution of (*R*)-(–)-α-methoxy-α-trifluoromethylphenylacetyl chloride [obtained as described in **a**. above from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (101 mg, 0.431 mmol)] in CH_2Cl_2 (5.0 ml). The reaction was quenched after 90 min with water (2.0 ml), and the organic layer washed with 0.5M HCl, and saturated sodium hydrogen carbonate solution, dried

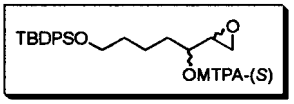
(Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (EtOAc-hexane 1:4) to give the Mosher ester **167** (171 mg, 94%), R_f 0.69 (EtOAc-hexane 1:4).

δ_H 1.032 (s, 9H, C**Me**$_3$)
1.20-1.75 (m, 6H, H-4, H-5, H-6)
3.532 (q, 3H, $J_{H,F}$ 1.3 OMe)
3.583 (t, 2H, $J_{7,6}$ 6.2, H-7)
5.245 (ddd, 1H, $J_{1a,2}$ 10.3, $J_{1b,1a}$ 1.4, $J_{1a,3}$ 1.4, H-1a)
5.207 (ddd, 1H, $J_{1b,2}$ 17.1, $J_{1a,1b}$ 1.4, $J_{1b,3}$ 1.4, H-1b)
5.440 (dt, 1H, $J_{2,3}$ 6.7, $J_{3,4}$ 6.7, H-3)
5.801 (ddd, 1H, $J_{2,1b}$ 17.1, $J_{2,1a}$ 10.3, $J_{2,3}$ 6.7, H-2)
7.34-7.67 (m, 15H, Ar**H**)

δ_C 19.18S (**C**Me$_3$), 21.14T (C-5), 26.85Q (C**Me**$_3$), 32.07T (C-6), 33.64T (C-4), 55.39Q (O**Me**), 63.58T (C-7), 77.55D (C-3), 84.79SQ (**C**CF_3), 118.75T (C-1), 123.39Q (**C**F_3, $J_{C,F}$ 288 Hz), 127.33D, 127.61D, 128.30D, 129.54D, 132.52S, 134.02S, 135.55D (aromatic carbons), 165.87S (**C**O).

δ_F –71.88 and -71.73

FAB-MS *m/z* 585 $[M+H]^+$. Exact mass: Calculated for $C_{33}H_{40}F_3SiO_4$, 585.2648, Observed, 585.2648.



d. (*2RS,3RS*)-1,2-Epoxy-1-[(*tert*-butyldiphenylsilyl)oxy]-3-heptyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate 170.

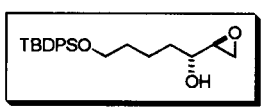
MCPBA (147 mg, 0.85 mmol) was added to a solution of the racemic secondary allyl alcohol **163** (209 mg, 0.57 mmol) in CH_2Cl_2 (10 ml), and the reaction stirred at RT for 3 h (tlc control). The organic layer was extracted with a saturated brine solution of NaOH (5%). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated to give the racemic epoxides **169** (168 mg, 77%); R_f 0.23 (EtOAc-hexane 1:4).

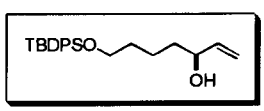
A solution of the racemic epoxides **169** (120 mg, 0.31 mmol), triethylamine (363 mg, 3.59 mmol) and DMAP (5.0 mg) were added to a stirred solution of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride [obtained as described in a. above from (*S*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (101 mg, 0.431 mmol)] in CH_2Cl_2 (5.0 ml). The reaction was quenched after 90 min with water (2.0 ml), and the organic layer washed with 0.5M HCl, and saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (EtOAc-hexane 1:3) to give the Mosher ester **170** (170 mg, 91%), R_f 0.57 (EtOAc-hexane 1:3);

δ_C 19.16S (**C**Me_3), 21.03T, 21.23T, 21.42T, and 21.60T (C-5), 26.83Q (C**Me**$_3$), 29.66T, 30.82T, 30.91T and 31.19T (C-4), 32.09T and 3217T (C-6), 44.59T, 44.79T, and 45.34T (C-1), 51.71D, 51.79D, 52.42D, and 52.48D (C-2), 55.46Q (O**Me**), 63.43T and 63.45T (C-7), 74.28D, 74.85D, 77.29D, and 77.76D (C-3), 84.79SQ (**C**CF_3), 123.28Q (**C**F_3, $J_{C,F}$ 288 Hz), 127.31D, 127.62D, 128.34D, 129.58D, 133.89S, 135.52D, (aromatic carbons), 166.00S (**C**O).

δ_F –71.81, –71.87, –71.90, –72.10

FAB-MS *m/z* 601 $[M+H]^+$. Exact mass: Calculated for $C_{33}H_{40}F_3SiO_5$, 601.2597; Observed, 601.2591.

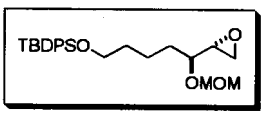




(2*S*,3*R*)-1,2-Epoxy-7-[(*tert*-butyldiphenylsilyloxy)]-3-heptanol 171.

A solution of (*S,S*)-(–)-DET (335 mg, 1.62 mmol) in CH_2Cl_2 (3.0 ml) was added by syringe to a suspension of activated powdered 4Å molecular sieves (300 mg) in CH_2Cl_2 (15 ml) under argon at –20°C. Ti(*i*PrO)$_4$ (384 mg, 1.36 mmol) in CH_2Cl_2 (3.0 ml) was added by syringe followed by a solution of TBHP (3.8M, 147 mg, 1.63 mmol) pre-cooled to 0°C. The resulting solution was stirred for 30 min at –20°C before addition of a solution of the racemic secondary allylic alcohol **163** (1.00 g, 2.71 mmol) in CH_2Cl_2 (6 ml). The reaction mixture was stirred for 8 h at –20°C and kept in the freezer at –10°C for 16 h. The solution was warned to 0°C, filtered and a fresh solution of iron(II) sulfate (6.6 g) and tartaric acid (2.0 g) in water (20 ml), pre-cooled to 0°C was added with

continuous stirring. The CH_2Cl_2 solution was evaporated and the residue dissolved in diethyl ether (20 ml). The aqueous layer was extracted with diethyl ether (4×20 ml). The combined diethyl ether solution was vigorously stirred with brine solution containing NaOH (5%, 40 ml) for 1 h at 0°C and diluted with water (40 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by chromatography on silica gel using EtOAc-hexane (1:3) as eluant to yield the epoxide **171** (420 mg, 40.5%), R_f 0.32 (EtOAc-hexane 1:3) and the (3*S*)-allylic alcohol **172** (435 mg, 43.5%), R_f 0.48 (EtOAc:hexane 1:4).



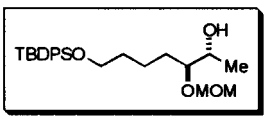
(2*R*,3*S*)-1,2-Epoxy-3-[(methoxymethyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 173.

Chloromethyl methyl ether (307 mg, 3.81 mmol) was added to a stirred solution of the epoxy alcohol **164** (508 mg, 1.32 mmol) and Hünig's base (iPr_2NEt) (334 mg, 2.58 mmol) in CH_2Cl_2 (10 ml) at 0°C. The reaction was allowed to reach RT and stirred for 14 h. Water (8.0 ml) was added and the mixture diluted with CH_2Cl_2 (15 ml). The CH_2Cl_2 solution was washed successively with 0.8M HCl (10 ml), and 6M $NaHCO_3$ solution (15 ml). The organic solution was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel with EtOAc-hexane (1:2) to give the MOM ether **173** (421 mg, 76%), as a colourless oil; R_f 0.38 (EtOAc-hexane 1:2)

δ_H 1.060 (s, 9H, C**Me$_3$**)
1.625 (m, 6H, H-4, H-5 and H-6)
2.715 (dd, 1H, $J_{1a,1b}$ 5.3, $J_{1a,2}$ 2.7, H-1a)
2.759 (dd, 1H, $J_{1b,1a}$ 5.3, $J_{1b,2}$ 4.0, H-1b)
2.886 (ddd, 1H, $J_{2,3}$ 5.4, $J_{2,1a}$ 2.7, $J_{2,1b}$ 3.9, H-2)
3.352 (s, 3H, OMe)
3.38 (m, 1H, H-3)
3.692 (t, 2H, $J_{1,2}$ 6.2, H-7)
4.575 (d, 1H, J 6.8, O**CH$_2$**O)
4.711 (d, 1H, J 6.8, O**CH$_2$**O)
7.34-7.69 (m, 10H, Ar**H**)

δ_C 19.17S (**C**Me_3), 21.49T (C-5), 26.83Q (C**Me**$_3$), 32.51T (C-6), 32.65T (C-4), 45.42T (C-1), 53.24D (C-2), 55.39Q (OMe), 63.72T (C-7), 76,14D (C-3), 95.96T (OCH_2O), 127.55D, 129.47D, 134.04S, and 135.53D (aromatic carbons).

FAB-MS *m/z* 429 $[M+H]^+$. Exact mass: Calculated for $C_{25}H_{37}SiO_4$, 429.2461; Observed, 429.2461.



(2*R*,3*S*)-3-[(Methoxymethyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanol 174.

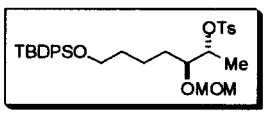
A solution of the MOM ether **173** (419 mg, 0.98 mmol) in diethyl ether (5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (43 mg 1.17 mmol) in diethyl ether (5.0 ml). The reaction was stirred at RT for 45 min (tlc control). A few drops of water were carefully added to destroy the excess $LiAlH_4$. The diethyl ether was decanted and the solid salts extracted 5 times with diethyl ether. The diethyl ether solution was dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by column chromatography with EtOAc-hexane (1:4) to yield the alcohol **174** (333 mg, 77%) as an oil; R_f 0.24; ν_{max} 3454 cm^{-1}.

δ_H 1.041 (s, 9H, C**Me**$_3$)
1.115 (d, 3H, $J_{7,6}$ 6.7, H-1)
1.34-1.60 (m, 6H, H-3, H-4 and H-5)
3.100 (d, 1H, $J_{2,OH}$ 7.5, 2-OH)
3.413 (s, 3H, OCH_3)
3.481 (ddd, 1H, $J_{3,4a}$ 8.3, $J_{3,4b}$ 3.6, $J_{3,2}$ 2.6, H-3)
3.667 (t, 2H, $J_{7,6}$ 6.2, H-7)
3.735 (dqd, 1H, $J_{2,OH}$ 7.5, $J_{2,1}$ 6.7, $J_{2,3}$ 2.6, H-2)
4.626 (d, 1H, J 6.7, OCH_2O)
4.720 (d, 1H, J 6.8, OCH_2O)
7.34-7.68 (m, 10H, Ar**H**)

δ_C 17.09Q (C-1), 19.20S (**C**Me_3), 22.31T (C-5), 26.86Q (C**Me**$_3$), 30.66T (C-6), 32.50T (C-4), 55.75Q (OMe), 63.68T (C-7), 68.97D (C-2), 85.04D (C-3),

97.61T (OCH_2O), 127.57D, 129.51D, 134.05S, and 135.54D (aromatic carbons).

FAB-MS *m/z* 431 $[M+H]^+$. Exact mass: Calculated for $C_{25}H_{39}SiO_4$, 431.2618; Observed, 431.2618.



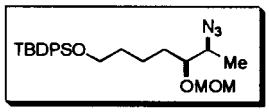
(2*R*,3*S*)-3-[(Methoxymethyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanol *p*-toluenesulfonate 175.

TsCl (429 mg, 2.25 mmol) was added to a stirred solution of the alcohol **174** (195 mg, 0.45 mmol), DMAP (55 mg, 0.45 mmol), pyridine (71 mg, 0.90 mmol) in CH_2Cl_2 (5 ml) at RT for 20 h. Water (5 ml) and CH_2Cl_2 (10 ml) were added and the aqueous layer extracted with CH_2Cl_2 (2×10ml). The combined CH_2Cl_2 solution was washed with 2M HCl, and brine, dried (Na_2SO_4), filtered and evaporated. The oily residue was purified by column chromatography using EtOAc-hexane (1:6) as eluant to give the O-tosylate derivative **175** (162 mg, 61%) as colourless oil; R_f 0.52 (EtOAc-hexane 1:4).

δ_H 1.036 (s, 9H, C**Me**$_3$)
1.237 (d, 3H, $J_{1,2}$ 6.5, H-1)
1.30-1.50 (m, 6H, H-4, H-5, H-6)
2.398 (s, 3H, Ar**CH**$_3$)
3.313 (s, 3H, OMe)
3.59 (m, 1H, H-3)
3.613 (t, 2H, $J_{1,2}$ 6.2, H-7)
4.518 (d, 1H, J 7.0, O**CH**$_2$O)
4.604 (qd, 1H, $J_{1,2}$ 6.5, $J_{2,3}$ 2.7, H-2)
4.611 (d, H, J 7.0, O**CH**$_2$O)
7.24-7.79 (m, 14H, Ar**H**)

δ_C 15.18Q (C-1), 19.16S (**C**Me$_3$), 21.55Q (Ar**C**H$_3$), 21.92T (C-5), 26.81 (C**Me**$_3$), 30.63T (C-6), 32.32T (C-4), 55.76Q (OMe), 63.51T (C-7), 78.31D (C-2), 80.57D (C-3), 96.17T (OCH_2O), 127.58D, 127.73D, 129.53D, 129.68D, 133.91S, 134.33S, 135.49D, and 144.47S (aromatic carbons).

FAB-MS *m/z* 585 $[M+H]^+$. Exact mass: Calculated for $C_{32}H_{45}SsiO_6$, 585.2706; Observed, 585.2706.



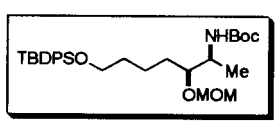
(2*S*,3*S*)-2-Azido-3-[(methoxymethyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 176.

Sodium azide (371 mg, 5.71 mmol) was added to a solution of the tosylate **175** (334 mg, 0.57 mmol) in anhydrous DMF (5 ml). The reaction mixture was stirred at 130°C for 16 h, diluted with water (30 ml) and extracted with diethyl ether (3×10 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow crude oil, which was purified by chromatography using EtOAc-hexane (1:4) to give the azide **176** (228 mg, 88%); R_f 0.63 (EtOAc-hexane 1:4).

δ_H 1.049 (s, 9H, C**Me**$_3$),
1.412-1.61 (m, 6H, H-4, H-5 and H-6)
1.259 (d, 1H, $J_{1,2}$ 6.7, H-1)
3.387 (s, 3H, OMe)
3.432 (ddd, 1H, $J_{2,3}$ 5.0, $J_{3,4a}$ 6.5, $J_{3,4b}$ 4.6, H-3)
3.526 (qd, 1H, $J_{1,2}$ 6.7, $J_{2,3}$ 5.0, H-2)
3.669 (t, 2H, $J_{1,2}$ 6.2, H-7)
4.668 (d, 1H, J 6.8, O**CH**$_2$O)
4.682 (d, 1H, J 6.8, O**CH**$_2$O)
7.34-7.68 (m, 10H, Ar**H**)

δ_C 15.14Q (C-1), 19.17S (**C**Me$_3$), 21.49T (C-5), 26.83Q (C**Me**$_3$), 30.58T (C-6), 32.57T (C-4), 55.84Q (OMe), 59.29D (C-2), 63.62T (C-7), 80.54D (C-3), 96.64T (O**CH**$_2$O), 127.57D, 129.53D, 134.00S, and 135.54D (aromatic carbons).

FAB-MS *m/z* 456 $[M+H]^+$. Exact mass: Calculated for $C_{25}H_{38}N_3SiO_3$, 456.2682; Observed, 456.2682.



(2*S*,3*S*)-2-(*tert*-Butyloxycarbonyl)amino-3-[(methoxymethyl)oxy]-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 177.

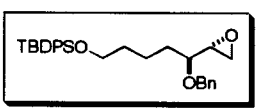
10% Pd/C (50 mg) was added to a solution of the azide **176** (298 mg, 0.65 mmol) and di-*tert*-butyldicarbonate (1.02 g, 4.67 mmol) in EtOAc (10 ml) in a hydrogenation flask. The solution was shaken under a 2 bar hydrogen atmosphere for 5 h. The Pd/C catalyst was removed by filtration, the filtrate evaporated and the residue purified by column chromatography using EtOAc-hexane (1:6) to give the *N*-Boc derivative **177** (230 mg, 67%) as a thick colourless oil; R_f 0.50 (EtOAc-hexane 1:4); ν_{max} 1714 and 3449 cm^{-1}.

δ_H 1.033 (s, 9H, CMe_3)
1.133 (d, 3H, $J_{1,2}$ 6.7, H-1)
1.418 (s, 9H, NCOOC**Me**$_3$)
1.37-1.60 (m, 6H, H-4, H-5 and H-6)
3.360 (s, 3H, OMe)
3.38 (m, 1H, H-2)
3.646 (t, 2H, $J_{1,2}$ 6.5, H-1)
3.75 (br m, 1H, H-3)
4.604 (d, 1H, J 6.8, OCH_2O)
4.641 (d, 1H, J 6.8, OCH_2O)
7.32-7.66 (m, 10H, Ar**H**)

δ_C 18.25Q (C-1), 19.19S (CMe_3), 21.91T (C-5), 26.87Q (C**Me**$_3$), 28.40Q (NCOOC**Me**$_3$), 32.55T (C-6), 32.66T (C-4), 48.25D (C-2), 55.82Q (OMe), 63.77T (C-7), 78.96S (NCOO**C**Me$_3$), 80.69D (C-3), 96.46T (OCH_2O), 127.57D, 129.49D, 134.09S, and 135.55D (aromatic carbons), 155.57S (NCOOt-Bu).

FAB-MS *m/z* 531 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{49}NSiO_5$, 531.3380; Observed, 531.3380.

6.3.2 Synthesis of the C_7 *syn*-2,3-amino alcohol: Benzyl protection.



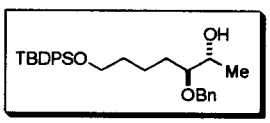
(2*R*,3*S*)-3-Benzyloxy-1,2-epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 178.

NaH (60% dispersion, 111 mg, 2.78 mmol) was washed with hexane and suspended in THF (2 ml). BnBr (649 mg, 3.79 mmol), tetrabutylammonium iodide (93 mg, 0.25 mmol) and the NaH suspension were sequentially added to a stirred solution of the epoxy alcohol **164** (973 mg, 2.53 mmol) in DMF (20 ml) at 0°C. The reaction was stirred for 4 h at RT. The excess BnBr was destroyed by addition of MeOH (2 ml). After stirring for 30 min the reaction was diluted with water (100 ml) and extracted with EtOAc (3×30 ml). The combined EtOAc solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a brown crude product which was purified by column chromatography using EtOAc-hexane (1:4) as eluant to give the benzyl ether **178** (575 mg, 48%) as colourless oil; R_f 0.61 (EtOAc:hexane 1:4).

δ_H 1.063 (s, 9H, C**Me**$_3$)
1.54-1.68 (m, 6H, H-4, H-5 and H-6)
2.724 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 2.6, H-1a)
2.778 (dd, 1H, $J_{1b,1a}$ 5.3, $J_{1b,2}$ 3.9, H-1b)
2.923 (ddd, 1H, $J_{2,3}$ 5.2, $J_{1b,2}$ 3.9, $J_{1a,2}$ 2.6, H-2)
3.262 (ddd, 1H, $J_{2,3}$ 5.2, $J_{3,4a}$ 4.8, $J_{3,4b}$ 6.7, H-3)
3.675 (t, 2H, $J_{6,7}$ 6.2, H-7)
4.495 (d, H, J 11.6, OC**H**$_2$Ph)
4.662 (d, H, J 11.6, OC**H**$_2$Ph)
7.243-7.77 (m, 15H, Ar**H**)

δ_C 19.16S (**C**Me$_3$), 21.56T (C-5), 26.83Q (C**Me**$_3$), 32.50T (C-6), 32.67T (C-4), 45.53T (C-1), 53.48D (C-2), 63.73T (C-7), 72.30T (OCH$_2$Ph), 77.95D (C-3), 127.57D, 127.66D, 128.32D, 129.49D, 134.00S, 135.53D, and 138.47S (aromatic carbons).

FAB-MS *m/z* 475 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{39}SiO_3$, 475.2668; Observed, 475.2667.



(2*R*,3*S*)-3-Benzyloxy-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanol 179.

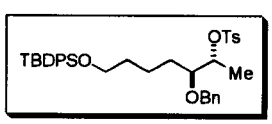
A solution of the benzyl ether **178** (964 mg, 2.01 mmol) in diethyl ether (10 ml) was added dropwise at RT to a stirred suspension of $LiAlH_4$ (159 mg, 4.19 mmol) in diethyl

ether (10 ml). The reaction was refluxed for 3 h (tlc control). A few drops of water were added carefully to destroy the excess $LiAlH_4$ reagent. The diethyl ether was decanted and the solid salt residue extracted with diethyl ether (3×20 ml). The combined diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography using EtOAc-hexane (1:4) to give the alcohol **179** (785 mg, 82%); R_f 0.36; ν_{max} 3446 cm^{-1}.

δ_H 1.050 (s, 9H, C**Me**$_3$)
1.145 (d, 3H, $J_{1,2}$ 6.5, H-1)
1.35-1.64 (m, 6H, H-4, H-5 and H-6)
2.003 (bd, 1H, $J_{2,OH}$ 3.6, 2-OH)
3.328 (ddd, 1H, $J_{3,4a}$ 8.0, $J_{3,4b}$ 4.4, $J_{2,3}$ 3.4, H-3)
3.665 (t, 2H, $J_{6,7}$ 6.2, H-7)
3.955 (qdd, 1H, $J_{1,2}$ 6.5, $J_{2,OH}$ 3.7, $J_{2,3}$ 3.4, H-2)
4.567 (d, 1H, J 11.5, OC**H**$_2$Ph)
4.579 (d, 1H, J 11.5, OC**H**$_2$Ph)
7.25-7.37 (m, 15H, Ar**H**)

δ_C 17.62Q (C-1), 19.21S (C**Me**$_3$), 22.16T (C-5), 26.87Q (C**Me**$_3$), 28.87T (C-6), 32.70T, (C-4), 63.76T (C-7), 68.08D (C-2), 72.20T (OCH_2Ph), 82.92D (C-3), 127.57D, 127.73D, 128.41D, 129.50D, 135.56S, 135.57D, 138.60S (aromatic carbons).

FAB-MS *m/z* 477 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{41}SiO_3$, 477.2825; Observed, 477.2825.



(2*R*,3*S*)-3-Benzyloxy-7-[(*tert*-butyldiphenylsilyloxy)]-2-heptanol *p*-toluenesulfonate 180.

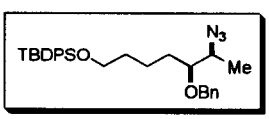
TsCl (372 mg, 1.95 mmol) and DMAP (328 mg, 2.68 mmol) were added to a stirred solution of the alcohol **179** (729 mg, 1.53 mmol) and pyridine (605 mg, 7.65 mmol) in dry CH_2Cl_2 (10 ml). The reaction was refluxed for 20 h. Water (10 ml) was added and the aqueous layer extracted with CH_2Cl_2 (3×10 ml). The combined CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated. Column chromatography of the oily residue

with EtOAc-hexane (1:6) gave the *O*-tosylate **180** (694 mg, 72%) as a colourless oil; R_f 0.47 (EtOAc:hexane 1:6)

δ_H 1.032 (s, 9H, C**Me**$_3$)
1.265 (d, 3H, $J_{1,2}$ 6,5, H-1)
1.25-1.45 (m, H-4, H-5 and H-6)
2.380 (s, 3H, Ar**Me**)
3.455 (ddd, 1H, $J_{3,4a}$ 6.7, $J_{3,4b}$ 4.1, $J_{2,3}$ 2.9, H-3)
3.588 (t, 2H, $J_{6,7}$ 6.2, H-7)
4.424 (d, 1H, J 11.4, OC**H**$_2$Ph)
4.595 (d, 1H, J 11.4, OC**H**$_2$Ph)
4.636 (qd, 1H, $J_{1,2}$ 6,5, $J_{2,3}$ 2.9, H-2)
7.32-7.77 (m, 19H, Ar**H**)

δ_C 15.36Q (C-7), 19.21S (**C**Me$_3$), 21.57Q (Ar**C**H$_3$), 22.10T (C-5), 26.88Q (C**Me**$_3$), 30.97T (C-6), 32.38T (C-4), 63.62T (C-7), 72.97T (OCH$_2$Ph), 80.59D (C-2), 81.45D (C-3), 127.62D, 127.74D, 127.83D, 128.28D, 129.54D, 129.71D, 134.04S, 134.47S, 135.55D, 138.29S, and 144.47S (aromatic carbons).

FAB-MS *m/z* 631 $[M+H]^+$. Exact mass: Calculated for $C_{37}H_{47}SsiO_5$, 631.2914; Observed, 631.2913.



(2*S*,3*S*)-2-Azido-3-benzyloxy-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 181.

Sodium azide (631 mg, 9.71 mmol) was added to a solution of the *O*-tosylate **180** (670 mg, 1.06 mmol) in dry DMF (5 ml). The reaction mixture was heated at 130°C for 20 h, diluted with water (40 ml) and extracted with diethyl ether (3×20 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and the solvent evaporated. The yellow crude oil was purified by column chromatography (EtOAc-hexane 1:6) to give the azide **181** (330 mg, 68%), an oil; R_f. 0.59; (EtOAc-hexane 1:6); ν_{max} 2105 cm^{-1}.

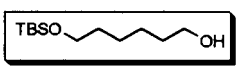
δ_H 1.049 (s, 9H, C**Me**$_3$)
1.229 (d, 3H, $J_{1,2}$ 6.7, H-1)

1.45-1.60 (m, 6H, H-4, H-5 and H-6)
3.296 (ddd, 1H, $J_{3,4a}$ 6.2, $J_{2,3}$ 5.2, $J_{3,4b}$ 5.2, H-3)
3.518 (qd, 1H, $J_{1,2}$ 6.7, $J_{2,3}$ 5.2, H-2)
3.657 (t, 2H, $J_{6,7}$ 6.2, H-7)
4.576 (s, 2H, OCH_2Ph)
7.27-7.69 (m, 15H, Ar**H**)

δ_C 15.36Q (C-1), 19.21S (CMe_3), 21.70T (C-5), 26.88Q (CMe_3), 30.39T (C-6), 32.65T (C-4), 59.48D (C-2), 63.69T (C-7), 72.80T (OCH_2Ph), 82.0D (C-3), 127.59D, 127.64D, 127.80D, 128.36D, 129.53D, 134.06S, 135.57D, 138.29S (aromatic carbons).

FAB-MS *m/z* 502 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{40}N_3SiO_2$, 502.2890; Observed, 502.2887.

6.3.3 Synthesis of the C_8 *syn*-2,3-amino alcohol.



6-[(*tert*-Butyldimethylsilyl)oxy]-1-hexanol 147a.

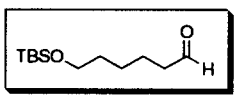
Sodium hydride (60% dispersion, 3.84 g, 95.9 mmol) was suspended in THF (20 ml) after washing with hexane (3×50 ml). A solution of 1,6-hexanediol **147** (10.0 g, 87.2 mmol) in THF (30 ml) was added dropwise over 30 min to the suspension and stirred for 45 min (until such time that hydrogen evolution had ceased). TBSCl (13.6 g, 87.2 mmol) was added dropwise and the reaction mixture stirred for another 90 min at RT. The THF was evaporated, and the residue partitioned between water (100 ml) and CH_2Cl_2 (300 ml). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue on silica gel with EtOAc-hexane (1:4) gave the monoprotected TBS ether **147a** (15.5 g, 76%), as colourless oil: R_f. 0.33 (EtOAc-hexane 1:4); ν_{max} 3338 cm^{-1}.

δ_H 0.007 (s, 6H, $SiMe_2$)
0.852 (s, 9H, CMe_3)
1.32 (m, 4H, H-3, H-4)
1.75 (br s, 1H, 1-OH)
1.51 (m, 4H, H-2, H-5)

3.566 (t, 2H, $J_{5,6}$ 6.2, H-6)
3.58 (m, 2H, H-1)

δ_C –5.31Q (Si**Me**$_2$), 18.33S (**C**Me$_3$), 25.50T and 25.57T (C-4/C-3)), 25.93Q (C**Me**$_3$), 32.70T and 32.73 (C-5/C-2), 62.81T (C-1), 63.14D (C-6).

FAB-MS *m/z* 233 $[M+H]^+$. Exact mass: Calculated for $C_{12}H_{29}SiO_2$, 233.1937; Observed, 233.1937.



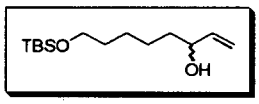
6-[(*tert*-Butyldimethylsilyl)oxy]-1-hexanal 182.

DMSO (9.90 g, 127 mmol) was added dropwise to a stirred solution of oxalyl chloride (8.21 g, 63.4 mmol) in CH_2Cl_2 (150 ml) at –78°C under argon. After 15 min a solution of the alcohol **147a** (13.4 g, 57.6 mmol) in CH_2Cl_2 (50 ml) was introduced dropwise over 30 min and the solution stirred for 1 h at –78°C. Triethylamine (29.4 g, 288 mmol) was added slowly and stirring continued for 1 h. The cooling bath was removed and the reaction mixture allowed to reach RT. The suspension was diluted with CH_2Cl_2 (200 ml) and washed with saturated NH_4Cl solution. The CH_2Cl_2 solution was dried (Na_2SO_4), and concentrated. Column chromatography on silica gel with EtOAc-hexane (1:9) gave the aldehyde **182** (11.0 g, 83%) as a colourless oil; R_f 0.51 (EtOAc:hexane 1:9); ν_{max} 1717 cm^{-1}.

δ_H –0.005 (s, 6H, Si**Me**$_2$)
0.843 (s, 9H, C**Me**$_3$)
1.34 (m, 2H, H-4)
1.48 (m, 2H, H-5)
1.60 (m, 2H, H-3)
2.382 (td, 2H, $J_{2,3}$ 7.2, $J_{2,1}$ 1.8, H-2)
3.561 (t, 2H, $J_{1,2}$ 6.2, H-6)
9.717 (t, H, $J_{1,2}$ 1.8, H-1)

δ_C –5.36Q (Si**Me**$_2$), 18.27S (**C**Me$_3$), 21.85T (C-4), 25.43T (C-5), 25.89Q (C**Me**$_3$), 32.47T (C-3), 43.83T (C-2), 62.79T (C-6) and 202.46S (C-1).

FAB-MS *m/z* 230 $[M]^+$. Exact mass: Calculated for $C_{12}H_{26}SiO_2$, 230.1702; Observed, 230.1702.



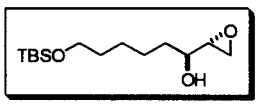
(*3RS*)-*8*-[(*tert*-Butyldimethylsilyl)oxy]-oct-1-en-3-ol 183.

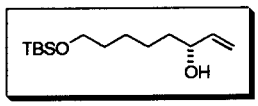
A solution of vinyl bromide (10.4 g, 95.0 mmol) in THF (15 ml) was added by syringe to a mixture of Mg turnings (1.54 g, 63.3 mmol) in THF (250 ml). The reaction was initiated by addition of a crystal of iodine. After all the Mg was consumed the solution was cooled to 20°C and a solution of the aldehyde **182** (7.30 g, 31.7 mmol) in THF (35 ml) was added dropwise to the Grignard solution. The reaction was refluxed for 2 h, cooled to 20°C and a saturated solution of ammonium chloride was added carefully. The resulting Mg salts were allowed to settle and the solvent decanted. The THF was evaporated and the residue partitioned between water (50 ml) and diethyl ether (100 ml). The diethyl ether solution was washed with sodium thiosulfate (10%, 50 ml), dried (Na_2SO_4), filtered and evaporated to give the allylic alcohol **183** as a thick oil (7.94 g, 97%); R_f 0.34 (hexane-EtOAc 1:4); ν_{max} 1645 and 3367 cm^{-1}.

δ_H 0.011 (s, 6H, Si**Me**$_2$)
0.858 (s, 9H, C**Me**$_3$)
1.35-1.66 (m, 8H, H-4, H-5, H-6 and H-7)
3.568 (t, 2H, $J_{8,7}$ 6.2, H-8)
4.056 (m, 1H, H-3)
5.057 (ddd, 1H, $J_{1b,2}$ 10.4, $J_{1b,1a}$ 1.5, $J_{1b,3}$ 1.3, H-1b)
5.175 (ddd,1H, $J_{1a,2}$ 17.2, $J_{1a,1b}$ 1.5, $J_{1a,3}$ 1.3, H-1a)
5.828 (ddd, 1H, $J_{2,1a}$ 17.2, $J_{2,1b}$ 10.4, $J_{2,3}$ 6.2, H-2)

δ_C –5.30Q (Si**Me**$_2$), 18.32S (**C**Me$_3$), 25.10T and 25.75T (C-6/C-5), 25.94Q (C**Me**$_3$), 32.76T (C-7), 37.03T (C-4), 63.12T (C-8), 73.13D (C-3), 114.46T (C-1) and 141.33D (C-2).

FAB-MS *m/z* 364 $[M+H]^+$. Exact mass: Calculated for $C_{14}H_{30}SiO_2$, 259.2093; Observed, 259.2093.





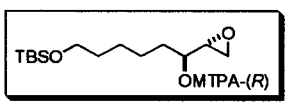
(2*R*,3*S*)-1,2-Epoxy-8-[(*tert*-butyldiphenylsilyl)oxy]-3-octanol 184 and (3*R*)-8-[(*tert*-butyldiphenylsilyl)oxy]-1-octen-3-ol 185.

A solution of (*R*,*R*)-(+)-DIPT (4.48 g, 19.1 mmol) in CH_2Cl_2 (40 ml) was added to a suspension of activated powdered 4Å molecular sieves (2.00 g) in CH_2Cl_2 (200 ml) under argon at –20°C. Ti(*i*PrO)$_4$ (4.53 g, 15.9 mmol) in CH_2Cl_2 (40 ml) was added dropwise by syringe followed by a solution of TBHP (4.1M in toluene, 1.72 g, 19.1 mmol) pre-cooled to 0°C. The resulting solution was stirred for 30 min at –30°C before addition over a period of 10 min of a solution of the secondary allylic alcohol **183** (8.25 g, 31.9 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was stirred for 8 h at –20°C and then at –10°C in the freezer for 16 h. The solution was allowed to reach 0°C, filtered, and a fresh solution of iron(II) sulfate (13.2 g) and tartaric acid (4.0 g) in water (40 ml), pre-cooled to 0°C was added with continuous stirring. The CH_2Cl_2 solution was evaporated and the residue dissolved in diethyl ether (100 ml). The aqueous layer was extracted with diethyl ether (5×30 ml). The combined diethyl ether solution was vigorously stirred with brine solution containing NaOH (5%, 80 ml) for 1 h at 0°C and diluted with water (50 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by chromatography on silica gel using EtOAc-hexane (1:4) as eluant to yield the (3*R*)-allylic alcohol **185** (3.51 g, 42.5%), R_f 0.39 (EtOAc:hexane 1:4) and the epoxide **184** (3.46 g, 39.5%), R_f 0.34 (EtOAc-hexane 1:4); $[\alpha]_D$ +9.3 (*c* 0.79, $CHCl_3$); ν_{max} 3433 cm^{-1}.

δ_H 0.017 (s, 6H, Si**Me$_2$**)
0.866 (s, 9H, C**Me$_3$**)
1.32-1.60 (m, 8H, H-4, H-5, H-6 and H-7)
1.98 (br s, 1H, OH)
2.688 (dd, 1H, $J_{1b,1a}$ 4.9, $J_{1b,2}$ 3.9, H-1b)
2.768 (dd, 1H, $J_{1a,1b}$ 4.9, $J_{1a,2}$ 2.9, H-1a)
2.968 (ddd,1H, $J_{1b,2}$ 4.0, $J_{2,3}$ 3.1, $J_{1a,2}$ 2.9, H-2)
3.582 (t, 2H, $J_{7,8}$ 6.5, H-8)
3.779 (m, 1H, H-3)

δ_C –5.33Q (Si**Me**$_2$), 18.32S (**C**Me$_3$), 25.07T (C-6), 25.88T (C-5), 25.93Q (**C**Me$_3$), 32.71T (C-7), 33.47T (C-4), 43.37T (C-1), 54.51D (C-2), 63.07T (C-8), 68.42D (C-3).

FAB-MS *m/z* $[M+H]^+$. Exact mass: Calculated for $C_{14}H_{31}SiO_3$, 275.2042; Observed, 275.2043.



MOSHER ESTER DERIVATIZATION

a. (*R*)-(–)-α-Methoxy-α-trifluoromethylphenylacetyl chloride

Oxalyl chloride (307 mg, 2.42 mmol) was added to a solution of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (105 mg, 0.45 mmol) and DMF (33 mg, 0.45 mmol) in anhydrous hexane (5.0 ml) at RT. A white precipitate formed immediately. After 1 h at RT the mixture was passed through a small cotton plug to filter off the DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl) (99 mg, 86%).

b. (2*R*,3*S*)-1,2-Epoxy-8-[(*tert*-butyldiphenylsilyl)oxy]-3-octyl (*R*)-α-Methoxy-α-trifluoromethylphenylacetate 188.

A solution of the epoxy alcohol **184** (91 mg, 0.33 mmol), triethylamine (168 mg, 1.7 mmol) and DMAP (4 mg) were added to a stirred solution of the acid chloride in CH_2Cl_2 (5.0 ml). The reaction was quenched after 90 min with water (2.0 ml), and the organic layer washed with 0.5M HCl, and saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (EtOAc-hexane 1:3) to give the Mosher ester **188** (152 mg, 93%), R_f 0.68 (EtOAc-hexane 1:4).

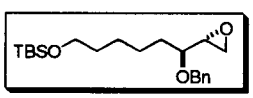
δ_H 0.025 (s, 6H, Si**Me**$_2$)
0.876 (s, 9H, C**Me**$_3$)
1.33-1.55 (m, 6H, H-5, H-6 and H-7)
1.764 (tt, 2H, $J_{4,5}$ 7.2, $J_{4,3}$ 6.5, H-4)
2.609 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 2.6, H-1a)
2.669 (dd, 1H, $J_{1b,1a}$ 5.2, $J_{1b,2}$ 3.9, H-1b)

2.933 (ddd, 1H, $J_{2,3}$ 5.2, $J_{2,1b}$ 3.9, $J_{2,1a}$ 2.6, H-2)
3.527 (q, 3H, $J_{H,F}$ 1.3, OMe)
3.574 (t, 2H, $J_{8,7}$ 6.3, H-8)
4.971 (ddd, $J_{3,4a}$ 6.5, $J_{3,4b}$ 6.5, $J_{3,2}$ 5.2, H-3)
7.32-7.53 (m, 5H, Ar**H**)

δ_C -5.31Q (Si**Me**$_2$), 18.33S (**C**Me$_3$), 24.75T (C-5), 25.59T (C-6), 25.59Q (C**Me**$_3$), 31.45T (C-7), 32.59T (C-4), 44.90T (C-1), 51.77D (C-2), 55.44D (OMe), 62.92T (C-8), 74.98D (C-3), 123.30Q (CF_3, $J_{C,F}$ 289 Hz), 127.39D, 128.34D, 129.63D, 132.21S (aromatic carbons), 166.00S (CO).

δ_F –71.93

FAB-MS *m/z* 491 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{38}SiF_3O_5$, 491.2441; Observed, 491.2441.



(2*R*,3*S*)-3-Benzyloxy-1,2-epoxy-8-[(*tert*-butyldimethylsilyl)oxy]-octane 186.

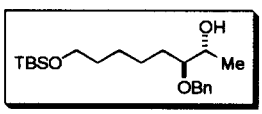
A suspension of NaH (60% dispersion, 1.17 g, 29.3 mmol) in DMF (10 ml) was added to a solution of the epoxy alcohol **184** (7.30 g, 26.6 mmol), BnBr (5.57 g, 31.9 mmol) and TBAI (2.98 g, 8.1 mmol) in DMF (50 ml) at 0°C under argon atmosphere. The reaction was stirred for 5 h at RT. MeOH (5 ml) was added to destroy excess BnBr and after 30 min the reaction was diluted with brine (300 ml) and extracted with EtOAc (3×100 ml). The EtOAc solution was dried (Na_2SO_4), and evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel with EtOAc-hexane (1:9) to give the benzyl ether **186** (6.81 g, 70%) as an oil; R_f 0.68 (EtOAc:hexane 1:4); $[\alpha]_D$ –8.6 (*c* 0.64, $CHCl_3$)

δ_H 0.328 (s, 6H, Si**Me**$_2$)
0.883 (s, 9H, C**Me**$_3$)
1.25-1.68 (m, 8H, H-4, H-5, H-6 and H-7)
2.698 (dd, 1H, $J_{1a,1b}$ 5.4, $J_{1a,2}$ 2.9, H-1a)
2.761 (dd, 1H, $J_{1b,1a}$ 5.4, $J_{1b,2}$ 3.9, H-1b)
2.913 (ddd, 1H, $J_{2,3}$ 5.2, $J_{2,1b}$ 3.9, $J_{2,1a}$ 2.9, H-2)

3.247 (ddd, 1H, $J_{3,4a}$ 6.5, $J_{3,4b}$ 5.4, $J_{3,2}$ 5.2, H-3)
3.582 (t, 2H, $J_{8,7}$ 6.5, H-8)
4.488 (d, 1H, J 11.8, OCH_2Ph)
4.643 (d, 1H, J 11.8, OCH_2Ph)
7.29-7.32 (m, 5H, Ar**H**)

δ_C –5.29Q (Si**Me**$_2$), 18.34S (**C**Me$_3$), 24.98T (C-5), 25.86 (C-7), 25.97Q (C**Me**$_3$), 32.77T (C-6), 32.87T (C-4), 45.57T (C-1), 53.53D (C-2), 63.14T (C-8), 72.29T (OCH2Ph), 78.07D (C-3), 127.5D, 127.67D, 128.33D, 138.61S (aro-matic carbons).

FAB-MS *m/z* 364 $[M]^+$. Exact mass: Calculated for $C_{21}H_{36}SiO_3$, 364.2434; Observed, 364.2434.



(2*R*,3*S*)-3-Benzyloxy-8-[(*tert*-butyldimethylsilyl)oxy]-2-octanol 187.

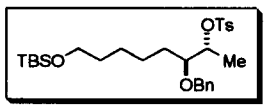
A solution of the benzyl ether **186** (3.40 g, 9.33 mmol) in diethyl ether (70 ml) was added dropwise at RT to a stirred suspension of $LiAlH_4$ (708 mg, 29.5 mmol) in diethyl ether (70 ml). The reaction was stirred for 30 min (tlc control). Water was added carefully to destroy the excess $LiAlH_4$ reagent and to form a white precipitate of aluminium salts. The diethyl ether was decanted and the solid residue extracted with diethyl ether (3×70 ml). The combined diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography using EtOAc-hexane (1:4) to give the alcohol **187** (3.14 g, 92%); R_f. 0.32 (EtOAc-hexane 1:4); $[\alpha]_D$ –7.0; (*c* 0.83, $CHCl_3$) ;ν_{max} 3434 cm^{-1}.

δ_H 0.036 (s, 6H, Si**Me**$_2$)
0.887 (s, 9H, C**Me**$_3$
1.151 (d, 3H, $J_{1,2}$ 6.5, H-1)
1.25-1.64 (m, 8H, H-4, H-5, H-6 and H-7)
2.02 (br s, 1H, OH)
3.333 (ddd, 1H, $J_{3,4a}$ 7.8, $J_{3,2}$ 3.4, $J_{3,4b}$ 3.1, H-3)
3.585 (t, 2H, $J_{8,7}$ 6.5, H-8)
3.952 (qd, 1H, $J_{1,2}$ 6.5, $J_{2,3}$ 3.4, H-2)

4.570 (d, 1H, J 11.9, OCH_2Ph)
4.586 (d, 1H, J 11.9, OCH_2Ph)
7.29-7.34 (m, 5H, Ar**H**)

δ_C –5.28Q ($SiMe_2$), 17.65Q (C-1), 18.35S (CMe_3), 25.63T (C-5), 25.98Q (CMe_3), 26.03T (C-6), 29.12T (C-7), 32.80T (C-4), 63.17T (C-8), 68.12D (C-2), 72.16D (OCH_2Ph), 82.93D (C-3), 127.67D, 127.75D, 128.40D, 138.64S (aromatic carbons).

FAB-MS *m/z* 364 $[M+H]^+$. Exact mass: Calculated for $C_{21}H_{39}SiO_3$, 367.2668; Observed, 367.2668.



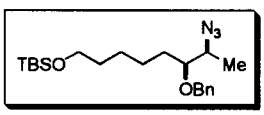
(2*R*,3*S*)-3-Benzyloxy-8-[(*tert*-butyldimethylsilyl)oxy]-2-octanol *p*-toluenesulfonate 189.

p-Toluenesulfonyl chloride (3.23 g, 16.9 mmol) and DMAP (207 mg, 1.69 mmol) were added to a stirred solution of the alcohol **187** (3.10 g, 8.46 mmol) and pyridine (2.01 g, 25.4 mmol) in CH_2Cl_2 (60ml). The reaction was refluxed for 10 h (tlc control). Water (5 ml) was added to destroy excess TsCl. The CH_2Cl_2 solution was washed with 1M HCl and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel using EtOAc-hexane (1:6) to give the *O*-tosylate **189** (3.29 g, 75%) as an oil: R_f 0.63 (EtOAc:hexane 1:4).

δ_H 0.029 (s, 6H, $SiMe_2$)
0.879 (s, 9H, CMe_3)
1.271 (d, 3H, $J_{1,2}$ 6.7, H-1)
1.20-1.48 (m, 8H, H-7, H-6, H-5 and H-4)
2.405 (s, 3H, $ArCH_3$)
3.456 (ddd, 1H, $J_{3,4a}$ 6.7, $J_{3,4b}$ 4.1, $J_{2,3}$ 2.6, H-3)
3.545 (t, 2H, $J_{7,8}$ 6.5, H-8)
4.428 (d, 1H, J 11.4, OCH_2Ph)
4.596 (d, 1H, J 11.4, OCH_2Ph)
4.627 (qd, 1H, $J_{1,2}$ 6.7, $J_{2,3}$ 2.6, H-2)
7.25-7.78 (m, 9H, Ar**H**).

δ_C -5.31Q (Si**Me**$_2$), 15.32Q (C-1), 18.39S (**C**Me$_3$), 21.58Q (Ar**C**H$_3$), 25.42T (C-5), 25.64T (C-6), 25.93Q (C**Me**$_3$), 31.06T (C-7), 32.64T (C-4), 63.03T (C-8), 72.84T (O**C**H$_2$Ph), 80.45D (C-2), 81.39D (C-3), 127.56D, 127.70D, 127.82D, 128.24D, 129.70D, 134.23S, 138.20S and 144.55S (aromatic carbons).

FAB-MS *m/z* 364 $[M+H]^+$. Exact mass: Calculated for $C_{14}H_{30}SiO_2$, 521.2757; Observed, 521.2757.



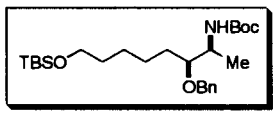
(2*S*,3*S*)-2-Azido-3-benzyloxy-8-[(*tert*-butyldimethylsilyl)oxy]-octane 190.

Sodium azide (2.00 g, 30.8 mmol), was added to a solution of the *O*-tosylate **189** (3.20 g, 6.14 mmol) in DMF (70 ml). The reaction was stirred at 130°C for 12 h (tlc control). The reaction was diluted with brine (300 ml) and extracted with diethyl ether (3×80 ml). The diethyl ether solution was dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:6) as eluant to give the azide **190** (2.10 g, 87%); R_f 0.66 (EtOAc-hexane 1:4); $[\alpha]_D$ +1.8; (*c* 0.64, $CHCl_3$); ν_{max} 2108 cm^{-1}.

δ_H 0.035 (s, 6H, Si**Me**$_2$)
0.883 (s, 9H, C**Me**$_3$)
1.230 (d, 3H, $J_{1,2}$ 6.7, H-1)
1.32-1.52 (m, 8H, H-4, H-5, H-6, H-7)
3.303 (ddd, 1H, $J_{3,4a}$ 6.7, $J_{3,4b}$ 5.2, $J_{3,2}$ 5.2, H-3)
3.528 (qd, 1H, $J_{1,2}$ 6.7, $J_{2,3}$ 5.2, H-2)
3.581 (t, 2H, $J_{7,8}$ 6.5, H-8)
4.582 (s, 2H, OC**H**$_2$Ph)
7.27-7.35 (m, 5H, Ar**H**)

δ_C –5.31Q (Si**Me**$_2$), 15.38Q (C-1), 18.33S (**C**Me$_3$), 25.01T (C-5), 25.93T (C-6), 25.93Q (C**Me**$_3$), 30.52T (C-7), 32.70T (C-4), 59.39T (C-2), 63.05T (C-8), 72.71T (O**C**H$_2$Ph), 81.92D (C-3), 127.63D, 127.80D, 128.33D, and 138.22S (aromatic carbons).

FAB-MS *m/z* 364 $[M+H]^+$. Exact mass: Calculated for $C_{14}H_{30}SiO_2$, 392.2733; Observed, 392.2734.



(2*S*,3*S*)-3-Benzyloxy-2-(*tert*-butyloxycarbonyl)amino-8-[(*tert*-butyldimethylsilyl)-oxy]-octane 191.

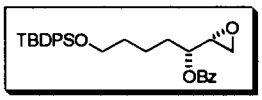
10% Pd/C (70 mg) was added to a solution of the azide **190** (1.21 g, 3.09 mmol) and di-*tert*-butyldicarbonate (1.02 g, 4.67 mmol) in EtOAc (30 ml) in a hydrogenation flask. The suspension was shaken under a 2 bar hydrogen atmosphere for 8 h. The Pd/C catalyst was removed by filtration, the filtrate evaporated and the residue purified by column chromatography using EtOAc-hexane (1:6) to give the *N*-Boc derivative **191** (1.42 g, 99%) as a thick colourless oil; R_f 0.58 (EtOAc-hexane 1:4); $[\alpha]_D$ –5.2 (*c* 0.71, $CHCl_3$); ν_{max} 3448 and 1712 cm^{-1}.

δ_H 0.024 (s, 6H, Si**Me**$_2$)
0.872 (s, 9H, C**Me**$_3$)
1.147 (d, 3H, $J_{1,2}$ 6.7, H-1)
1.31-1.50 (m, 8H, H-4, H-5, H-6 and H-7)
1.413 (s, 9H, NCOOC**Me**$_3$)
3.289 (ddd, 1H, $J_{3,4a}$ 6.7, $J_{3,4b}$ 5.2, $J_{2,3}$ 5.2, H-3)
3.568 (t, 2H, $J_{7,8}$ 6.5, H-8)
3.819 (dqd, 1H, $J_{NH,2}$ 8.3, $J_{1,2}$ 6.7, $J_{2,3}$ 2.8, H-2)
4.484 (d, 1H, J 11.4, OC**H**$_2$Ph)
4.583 (d, 1H, J 11.4, OC**H**$_2$Ph)
4.701 (br d, 1H, $J_{NH,2}$ 8.3, N**H**Boc)
7.26-7.33 (s, 5H, Ar**H**)

δ_C –5.28Q (Si**Me**$_2$), 18.32T (C-1), 25.57T (C-3), 25.97T (C-5), 25.97Q (C**Me**$_3$), 28.39Q (NCOOC**Me**$_3$), 30.69T (C-2), 32.74T (C-5), 47.97D (C-2), 63.17T (C-8), 72.50D (OC**H**$_2$Ph), 78.93S (NCOO**C**Me$_3$); 81.73T (C-3), 127.64D, 127.93D, 128.33D, and 138.52S (aromatic carbons), 155.63S (NCOOMe$_3$).

FAB-MS *m/z* 466 $[M+H]^+$. Exact mass: Calculated for $C_{25}H_{48}NSiO_4$, 466.3353; Observed, 466.3352.

6.3.4 Synthesis of the C_7 anti-2,3-amino alcohol: the Mitsunobu reaction.



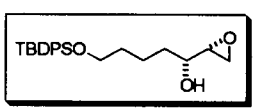
(2*R*,3*R*)-1,2-Epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]-3-heptyl benzoate 208.

To a solution of the epoxy alcohol **164** (317 mg, 0.83 mmol) and triphenylphosphine (435 mg, 1.66 mmol) in THF (10 ml) at 0°C, was added a solution of benzoic acid (506 mg, 4.14 mmol) in benzene (10 ml). After 5 min, DEAD (532 mg, 3.05 mmol) was added and the reaction stirred at RT for 12 h (tlc control). The solvents were evaporated *in vacuo* and the residue was purified by chromatography on silica gel (EtOAc-hexane 1:4) to give the benzoate ester **208** (237 mg, 71%); R_f 0.47 (EtOAc-hexane 1:4), ν_{max} 1721 cm^{-1}.

δ_H 1.021 (s, 9H, C**Me**$_3$)
1.82 (m, 2H, H-6)
1.60 (m, 2H, H-4)
1.53 (m, 2H, H-5)
2.680 (dd, 1H, $J_{1a,1b}$ 4.9, $J_{1a,2}$ 2.6, H-1a)
2.831 (dd, 1H $J_{1b.1a}$ 4.9, $J_{1b,2}$ 4.0, H-1b)
3.198 (ddd, 1H, $J_{2,3}$ 5.4, $J_{2.1b}$ 3.9, $J_{2.1a}$ 2.6, H-2)
3.668 (t, 2H $J_{6,7}$ 6.0, H-7)
5.018 (ddd, 1H, $J_{3,4a}$ 7.6, $J_{3,4b}$ 5.7, $J_{2,3}$ 5.4, H-3)
7.32-8.81 (m, 15H, Ar**H**)

δ_C 19.14S (**C**Me$_3$), 21.60T (C-5), 26.79Q (C**Me**$_3$), 31.17T (C-6), 32.26T (C-4), 44.77T (C-1), 53.05D (C-2), 63.41T (C-7), 74.12D (C-3), 127.57D, 128.32D, 129.51D, 129.70D, 130.00S, 133.01D, 133.89SS, 135.50D (aromatic carbons), 165.87S (Ph**C**OOR).

FAB-MS *m/z* 489 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{37}SiO_4$, 489.2461; Observed, 489.2461.



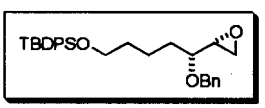
(2*R*,3*R*)-1,2-Epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]-3-heptanol 165.

Anhydrous potassium carbonate (155 mg, 1.12 mmol) was added to solution of the benzoate ester **208** (161 mg, 0.34 mmol) in dry methanol (10 ml) and the reaction was stirred for 2 h at RT (tlc control). The solvent was evaporated and the solid residue extracted with diethyl ether (4×20 ml). The solvent was evaporated and the oily residue purified by chromatography on silica gel (Et_2O-hexane 1:1) to give the epoxy alcohol **165** (84 mg, 64%) as a colourless oil; R_f 0.22 (EtOAc-hexane 1:4).

δ_H 1.042 (s, 9H, C**Me**$_3$)
1.50-1.64 (m, 6H, H-4, H-5 and H-6)
1.889 (d, 1H, $J_{3,OH}$ 5.7, 3-OH)
2.676 (dd, 1H, $J_{1a,1b}$ 4.9, $J_{1a,2}$ 2.8, H-1a)
2.784 (dd, 1H, $J_{1a,1b}$ 4.9, $J_{1b,2}$ 3.9, H-1b)
2.938 (ddd, 1H, $J_{1b,2}$ 3.9, $J_{1a,2}$ 2.8, H-2)
3.390 (dddd, 1H, $J_{3,4b}$ 6.7, $J_{3,OH}$ 5.7, $J_{2,3}$ 5.2, $J_{3,4a}$ 5.2, H-3)
3.673 (t, 2H, $J_{6,7}$ 6.2, H-7)
7.33-7.66 (m, 10H, Ar**H**)

δ_C 19.20S (**C**$\mathbf{Me}_3$), 21.61T (C-5), 26.86Q (C**Me**$_3$), 32.39T (C-6), 34.08T (C-4), 45.10T (C-1), 55.30D (C-2), 63.66T (C-7), 71.62D (C-3), 127.58D, 129.52D, 134.03S, 135.55D (aromatic carbons).

FAB-MS *m/z* 386 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{34}SiO_3$, 386.2277; Observed, 386.2277.



(2*R*,3*R*)-3-Benzyloxy-1,2-epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 209.

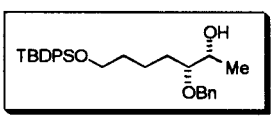
Benzylation of the *syn* epoxy alcohol **165** (587 mg, 1.59 mmol) followed the procedure outlined under 6.3.2. The product was purified by column chromatography on silica gel with EtOAc-hexane (1:6) to give the benzyl ether **209** (412 mg, 56%) as a colourless oil; R_f. 0.35 (EtOAc:hexane 1:6).

δ_H 1.039 (s, 9H, C**Me**$_3$)
1.39-1.67 (m, 6H, H-4, H-5 and H-6)

2.448 (dd, 1H, $J_{1a,1b}$ 4.9, $J_{1a,2}$ 2.5, H-1a)
2.749 (m, 1H, $J_{1a,1b}$ 4.9, $J_{1b,2}$ 4.1, H-1b)
3.01 (m, 2H, H-2 and H-3)
3.639 (t, 2H, $J_{6,7}$ 6.2, H-7)
4.563 (d, H, J 11.7, OCH_2Ph)
4.826 (d, H, J 11.7, OCH_2Ph)
7.31-7.67 (m, 15H, ArH)

δ_C 19.19S (CMe_3), 21.90T (C-5), 26.83Q (CMe_3), 32.11T (C-6), 32.41T (C-4), 43.08T (C-1), 55.06D (C-2), 63.64T (C-7), 71.67T (OCH_2Ph), 80.50D (C-3), 127.45D, 127.57D, 128.27D, 129.52D, 133.96S, 135.53D, 138.61S (aromatic carbons).

FAB-MS *m/z* 474 $[M]^+$. Exact mass: Calculated for $C_{30}H_{38}SiO_3$, 474.2590; Observed, 474.2591.



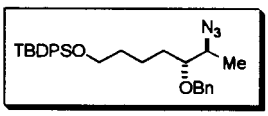
(2*R*,3*R*)-3-Benzyloxy-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanol 210.

The benzyl ether **209** (371 mg, 0.781 mmol) was reduced with $LiAlH_4$ in diethyl ether as described under 6.3.2. The crude alcohol was purified by chromatography on silica gel (EtOAc-hexane 1:6) to give the alcohol **210** (349 mg, 94%) as an oil: R_f 0.19 (EtOAc:hexane 1:6).

δ_H 1.041 (s, 9H, CMe_3)
1.157 (d, 3H, $J_{1,2}$ 6.2, H-1)
1.41-1.63 (m, 6H, H-4, H-5, H-6)
2.432 (br d, 1H, $J_{2,OH}$ 3.6, 3-OH)
3.195 (ddd, 1H, $J_{3,4a}$ 6.3, $J_{3,4b}$ 4.7, $J_{2,3}$ 5.2, H-3)
3.661 (t, 2H, $J_{6,7}$ 6.3, H-7)
3.719 (qdd, 1H, $J_{1,2}$ 6.2, $J_{2,3}$ 5.2, $J_{2,OH}$ 3.6, H-2)
4.473 (d, H, J 11.1, OCH_2Ph)
4.638 (d, H, J 11.1, OCH_2Ph)
7.32-7.67 (m, 15H, ArH)

δ_C 18.98Q (C-1), 19.19S (**C**Me$_3$), 21.21D (C-5), 26.83Q (C**Me**$_3$), 29.96T (C-6), 32.83T (C-4), 63.67T (C-7), 68.96D (C-2), 72.49T (O**C**H$_2$Ph), 84.02D (C-3), 127.58D, 127.82D, 128.46D, 129.52D, 133.98S, 135.54D, 138.30S (aromatic carbons).

FAB-MS *m/z* 476 $[M]^+$. Exact mass: Calculated for $C_{30}H_{40}SiO_3$, 476.2747; Observed, 476.2747.



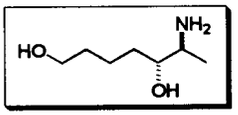
(2*S*,3*R*)-2-Azido-3-benzyloxy-7-[(*tert*-butyldiphenylsilyl)oxy]-heptane 212.

The procedure for the conversion of the hydroxy group of the *O*-benzyl ether **210** (322 mg, 0.675 mmol) to the *O*-tosyl derivative with TsCl, DMAP and pyridine in CH_2Cl_2 is decribed under 6.3.2. The O-tosylate (**211**) was directly converted to the *anti*-2,3-azide **212** by treatment with sodium azide as described under 6.3.2. The crude product was purified by chromatography on silica gel (EtOAc-hexane 1:6) to give the azide **212** (118 mg, 92%) as an oil; R_f 0.45 (EtOAc:hexane 1:4).

δ_H 1.088 (s, 9H, C**Me**$_3$)
1.276 (d, 3H, $J_{1,2}$ 6.7, H-1)
1.45-1.62 (m, 6H, H-4, H-5 and H-6)
3.410 (ddd, 1H, $J_{3,4a}$ 7.7, $J_{3,4b}$ 3.9, $J_{2,3}$ 3.9, H-3)
3.596 (qd, 1H, $J_{1,2}$ 6.7, $J_{2,3}$ 3.9, H-2)
3.689 (t, 2H, $J_{6,7}$ 6.2, H-7)
4.566 (d, H, J 11.4, O**C**H$_2$Ph)
4.673 (d, H, J 11.4, O**C**H$_2$Ph)
7.35-7.72 (m, 15H, Ar**H**)

δ_C 14.36Q (C-1), 19.17S (**C**Me$_3$), 21.95T (C-5), 26.82Q (C**Me**$_3$), 30.50T (C-6), 32.52T (C-4), 59.28D (C-2), 63.62T (C-7), 72.59T (O**C**H$_2$Ph), 81.71D (C-3), 127.57D, 127.62D, 127.81D, 128.33D, 129.51D, 133.96S, 135.53D, 138.20S (aromatic carbons).

FAB-MS *m/z* 501 $[M]^+$. Exact mass: Calculated for $C_{37}H_{47}SSiO_5$, 631.2914; Observed, 631.2913.



(5*R*,6*S*)-6-amino-1,5-heptanediol 213.

10% Pd-C was added to a solution of the azide **212** (112 mg, 0.223 mmol) in methanol (10 ml). A drop of concentrated hydrochloric acid (32%) was added and the reaction hydrogenated for 24 h under 1 atm hydrogen pressure The palladium catalyst was filtered off, the solvent evaporated and the residue partitioned between diethyl ether and water. The aqueous solution was adjusted to pH 7 with 1M NaOH. The aqueous solution was absorbed on a short column of Amberlite IR-120 (H^+) resin. The resin was washed with water and the amino alcohol eluted with NH_4OH. The NH_4OH solution was evaporated under reduced pressure. The residue was dried *in vacuo* to give the amino alcohol **213** (26.7 mg, 81%). R_f 0.26 (H_2O: 2-propanol: NH_4OH, 10:5:1).

δ_C* 12.30Q (C-7), 2282T (C-3), 32.27T (C-2), 32.99T (C-4), 52.42D (C-6), 62.88D (C-1), 71.84T (C-5).

* in D_2O