Studies toward the Stereoselective Synthesis of the C(10)-C(20) Unit of the Fumonisins using Sharpless Methodology

by

HAPPY HAZEL MSIBI

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Supervisor : Prof. R Vleggaar

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DECLARATION

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously, in its entirety or in part, submitted it at any university for a degree.

Signature: ……. **Date**: ……..

H.H. Msibi

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SUMMARY

Fusarium verticillioides (=Fusarium moniliforme) 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. The main mycotoxin, fumonisin B_1 consists of the diester formed by the C(14) and C(15) hydroxy groups of (2*S*,3*S*,5*R*,10*R*,12*S*,14*S*,15*R*,16*R*)-2-amino-12,16-dimethyleicosane-3,10,14,15-pentaol with the *Si* carboxy group of propane-1,2,3-tricarboxylic acid.

A comparison of the structures of the 28 known fumonisins isolated since 1988 reveals that they share a common structural motif for the C(11)–C(20) unit, and probably also the same stereochemistry for the 4 stereogenic centres present in this part of the C_{20} backbone. Disconnection of the C(9)–C(10) bond in a retrosynthetic analysis of the fumonisins identifies (3*S*,5*S*,6*R*,7*R*)-3,7-dimethylundecane-1,5,6-triol as a common building block for the synthesis of any of the fumonisins.

In the dissertation the retrosynthetic analysis of this 3,7-dimethylundecane-1,5,6-triol building block identifies a simple precursor, ethyl 2-heptenoate, as the starting material for the proposed synthetic route toward this target. The Sharpless asymmetric epoxidation reaction plays a pivotal role in this synthetic route as all 4 stereogenic centres present in the 3,7-dimethylundecane-1,5,6-triol target are generated by this methodology at three different stages of the proposed synthesis. The epoxy alcohol formed at each stage was subjected to regioselective ring opening followed by a protective group strategy which allowed for the protection of the secondary hydroxyl group as the benzyl ether and left the primary hydroxyl group, available after oxidation to the aldehyde, for a two-carbon chain extension to an α,β-unsaturated ester. This ester in turn was reduced to an allylic alcohol which formed the starting material for a second cycle of reactions. In this manner a synthetic route towards the target compound was developed and problems associated with the route investigated.

The dissertation shows that a viable route was developed with complete stereochemical control in the formation of the stereogenic centres, even though the final product, the protected

3,7-dimethylundecane-1,5,6-triol was not obtained due to time constraints and material shortages.

LIST OF ABBREVIATIONS

$AlCl_3$	Aluminium trichloride
Ar	Argon
BuLi	Butyllithium
*t*BuOOH	*t*-Butylhydroperoxide
*t*BuOK	Potassium *t*-butoxide
BH_3	Borane
CH_2Cl_2	Dichloromethane
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated chlorofom
$CHCl_3$	Chloroform
$(COCl)_2$	Oxalyl chloride
DET	Diethyl tartrate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMFCl	*N*-(Chloromethylene)-*N*-methylmethanaminium chloride
DMP	2,2-Dimethoxypropane
Et_3N	Triethylamine
Et_2O	Diethyl ether
DHP	Dihydropyran
DIBALH	Diisobutylalaminium hydride
DMSO	Dimethyl sulfoxide
DMS	Dimethyl sulfide
EtOH	Ethanol
H_2O_2	Hydrogen peroxide
HETCOR	Heteronuclear correlation
HMPA	Hexamethylphosphoric amide
I_2	Iodine
HCl	Hydrochloric acid
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminium hydride
MCPBA	*m*-Chloroperoxybenzoic acid
MeOH	Methanol
Me_2O	Acetone
Me_3Al	Trimethyl aluminium
$(MeO)_3P$	Trimethylphosphite
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
MTPACl	α-Methoxy-α-trifluoromethylphenylacetyl chloride
Na(s)	Sodium metal
NaH	Sodium hydride
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium hydrogen carbonate
NMR	Nuclear magnetic resonance
Pyr	Pyridine
PCC	Pyridinium chlorochromate

PPTS	Pyridinium *p*-toluenesulfonate
$PHCH(OMe)_2$	α,α-Dimethoxytoluene
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
$SOCl_2$	Thionyl chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	Toluene-4-sulfonyl chloride
TsOH	Toluene-4-sulfonic acid
$Ti(iPrO)_4$	Titanium isopropoxide

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1 FUMONISINS

1.1 INTRODUCTION

Mycotoxins are toxic secondary metabolites produced by fungi and they are the causative agents of various diseases in man and his domestic animals. Human beings and animals get the diseases, commonly called mycotoxicoses through the ingestion of foods or feeds contaminated by these toxic fungal metabolites. 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 resulted in the current international awareness of mycotoxins. 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 verticilloides* Nirenberg commonly known as *Fusarium moniliforme* Sheldon, a common fungal contaminant of maize throughout the world, has been associated with diseases in both man and animals.[2] The mycotoxins produced by this fungus, called fumonisins, accumulate in the liver and kidney in all animal species when contaminated feed or food is ingested. The fumonisins have been shown to cause equine leukoencephalomalacia, pulmonary edema in pigs and liver cancer in rats. Epidemiological studies performed in South Africa and China revealed that there might be a correlation between the intake of fumonisins and increased oesophageal cancer incidence.[3]

Twenty-eight fumonisin analogs have been characterized since 1988 and are separated into four main groups, which are identified as the fumonisin A, B, C and P series. Fumonisin B

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[1] Wyllie, T.D. and Morehouse, L.G. (Editors), Mycotoxic Fungi, Mycotoxins, Mycotoxicoses, An Encyclopedia Handbook, Marcel Dekker, USA, **1987**, 2.
[2] Bacon, C.W.; Williams, T.W. *Mycopathologia*, **1992**, *117*, 65.
[3] Rheeder, J.P.; Marasas, W.F.O.; Thiel, P.G.; Sydenham, E.W.; Shephard, G.S. and van Schalkwyk, D.J. *Phytopathology*, **1992**, *82*, 352.

(FB) analogs are the most abundant natural fumonisins and therefore the most important toxicologically. This series comprise of FB_1, FB_2 and FB_3 with FB_1 predominating and usually occurring at higher levels.[4,5] According to Bullerman *et al*. the carcinogenicity of the fumonisins appears to be a combination of tumor-initiating and tumor-promoting activity.[6]

1.2 ISOLATION AND STRUCTURE 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*.[7,8] followed an investigation into the cause of the high rate of oesophageal cancer in the Transkei as well as the outbreaks of equine leukoencelo-phalomalacia in a number of countries including South Africa. The structures of the members of the fumonisin A (**1**-**3**), B (**4**-**7**) and C (**8**-**12**) series are illustrated in Table 1.1 and 1.2.

1.2.1 Isolation of the fumonisins.

The purification techniques used by Gelderblom and co-workers[9] 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.[8] The extraction and purification steps reported earlier[9] 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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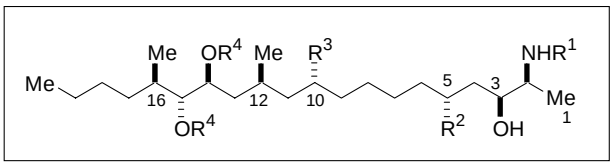
[4] Rheeder, J.P. *Appl. Environ. Microbiol*., **2002**, *68*, 2101.
[5] Marasas, W.F.O., *Fumonisins in Food*, **1996**, 1.
[6] Bullerman, L.B. and Draughon, F. *J. Food Protection*, **1994**, *57*, 512.
[7] Bezuidenhout, S.C.; Gelderblom, W.C.A.; Gorst-Allman, C.P.; Horak, R.M.; Marasas, W.F.O.; Spiteller, G.; Vleggaar, R. *J. Chem. Soc. Chem. Commun*., **1988**, 743.
[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] 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



	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

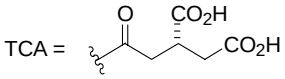
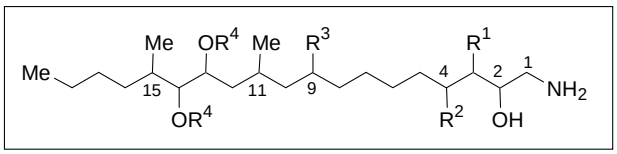


Table 1.1 Structures of the fumonisins of the A and B series



	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

The culture materials were 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 first evaporated and dried *in vacuo*. The dried residues were partitioned between methanol-water (3:1) and chloroform to remove any remaining lipid-soluble material and the

aqueous methanol solution was applied to an Amberlite XAD-2 column. The column was washed with methanol-water before the fumonisins were eluted with methanol. 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 **4-10**.

Fusarium moniliforme (strain KSU 819) accumulates no fumonisin B_1 (**4**) or B_2 (**5**) but produces fumonisin A_3 (**3**),[10] B_3 (**6**), B_4 (**7**), and C_4 (**12**) in high concentration. Poling and Platter[11,12] 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 (Table 1.2) e.g. fumonisin C_1 (**8**),[13,14] isofumonisin C_1 (**9**),[15] hydroxy-fumonisin C_1 (**10**) and fumonisin C_3 (**11**), and fumonisin C_4 (**12**)[14,16] all lack the C(1) 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 compounds has been reported. The P series of fumonisins has been isolated by Plattner from *Fusarium moniliforme* (M-2285) grown on solid maize and characterized by UV, LC-

[10] Plattner, R.D.; Weisleder, D.; Poling, S.M. in *Fumonisins in Food*, (Ed. Jackson, L.S.; deVries, J.W.; Buller-man, L.B.), Plenum Press, New York, **1996**, 57.
[11] Poling, S.M.; Plattner, R.D. *J. Agric. Food Chem.*, **1996**, *44*, 2792.
[12] Poling, S.M.; Plattner, R.D. *J. Agric. Food Chem.*, **1999**, *47*, 2349.
[13] Branham, B.E.; Plattner, R.D. *J. Nat. Prod.*, **1993**, *56*, 1630.
[14] Seo, J.-A.; Kim, J.-C.; Lee, Y.-W. *J. Nat. Prod.*, **1996**, *59*, 1003.
[15] Seo, J.-A.; Kim, J.-C.; Lee, Y.-W. *J. Nat. Prod.*, **1999**, *62*, 355.
[16] Plattner, R.D. *Nat. Toxins*, **1995**, *3*, 294.

MS, ^{1}H-NMR and ^{13}C NMR.. The new compounds fumonisin P_1 (**14**), P_2 (**15**) and P_3 (**16**) correspond to fumonisin B_1 (**4**), B_2 (**5**), and B_3 (**6**), respectively, but contain a *N*-linked 3-hydroxy-pyridinium moiety instead of an amino group at C(2) of the backbone.[17] The LC-MS analysis indicated that (**14**) occurs at up to approximately one-third the amount of its amino analogue (**7**).[18]

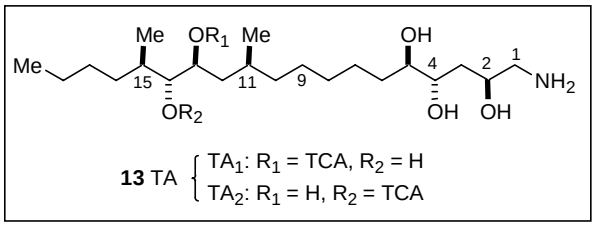


Figure 1.1: The structure of TA toxin

1.2.2 Structure elucidation.

The chemical nature of the mycotoxins produced by *F. moniliforme* remained unknown until 1988, when Bezuidenhout *et al*. 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-pentahydroxyeicosane (**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.

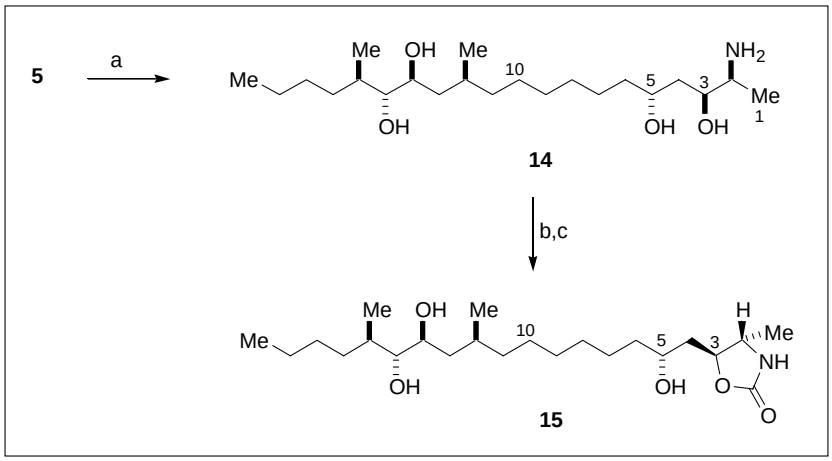
1.2.3 Stereochemical analysis of the backbone of the fumonisins.

The strategy by Boer[19] to establish the configuration of the stereogenic centres of the backbone of fumonisin B_1 (**4**) and B_2 (**5**), involved 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**) which was

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

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



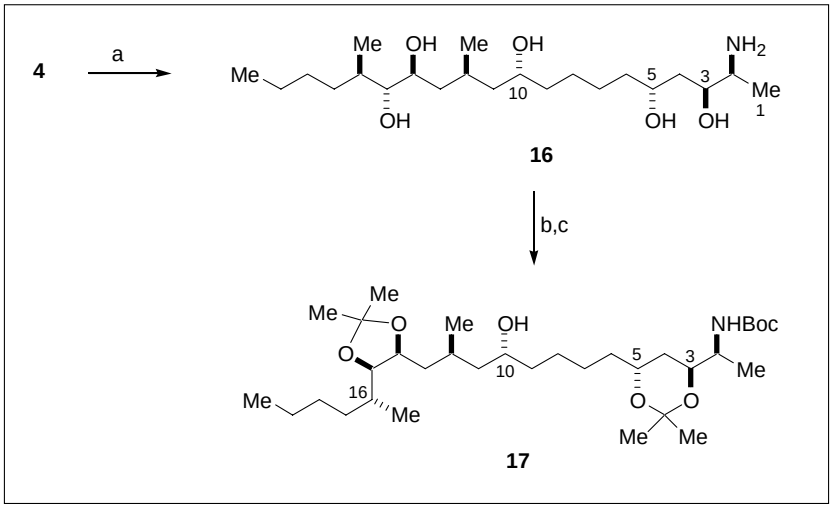
Scheme 1.1 *Reagents*: (a) 1M KOH; (b) $(Boc)_2O$; (c) NaOEt.

Rychnovsky[20] 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

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

followed from the coupling constant of 5.3 Hz for the C(14) and C(15) protons of the 3,4:14,15-diacetonide (**17**). The value indicated a *cis* relationship for these protons and therefore an *anti* relationship for the corresponding hydroxy groups in the fumonisins. The *anti* relationship for the C(16) methyl group and the C(15) hydroxy group in the fumonisins followed from NOE studies on (**17**).

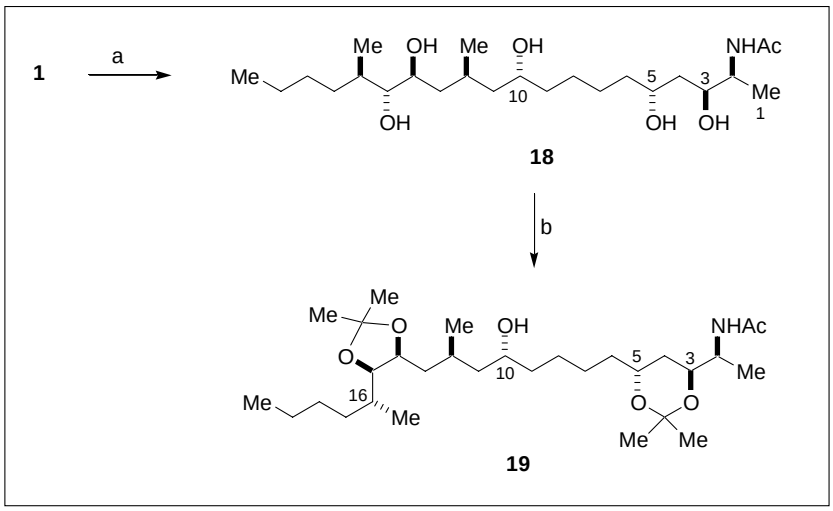


Scheme 1.2 *Reagents*: (a) 1M KOH; (b) $(Boc)_2O$; (c) $Me_2C(OMe)_2$, TsOH

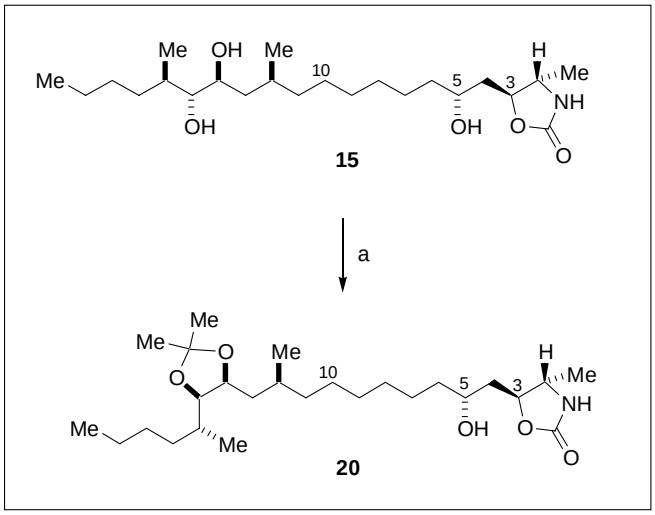
The absolute configuration of the C(10) stereogenic centre in fumonisin B_1 was determined by the method of Horeau[21,22] as *R* using the *N*-acetyl diacetonide derivative (**19**) (see Scheme 1.3) in the esterification reaction with an excess of racemic α-phenylbutyric anhydride. The absolute configuration 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*S*,5*R* absolute configuration on the basis of the earlier determined relative stereochemistry.

The absolute configuration of the C(16) stereogenic centre in the fumonisins was determined by 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

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



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



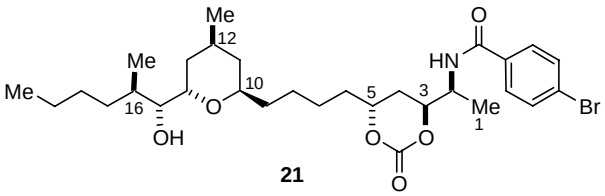
Scheme 1.4 *Reagents*: (a) $Me_2C(OMe)_2$, TsOH.

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 by Boer on the basis of biosynthetic arguments. Enzymatic methylations at the different active methylene sites of a polyketide precursor appear to follow the same stereochemical course.[23] 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.

[23] Turner, W.B.; Aldridge, D.C. Fungal Metabolites II, Academic Press, London, **1983**, p. 112.

The relative stereochemistry of the C(1)–C(5) unit of fumonisin B_1 (**4**) was confirmed by ApSimon *et al.*[24] using NMR studies of the 2,3-oxazolidinone and the 3,5-carbonate derivatives. Poch *et al.*[25] 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.*[26]



21

The relative and absolute configuration of the eight stereogenic centres of the fumonisin B_1 backbone assigned by Hoye *et al.*[27] are based on NMR studies of a number of derivatives and confirmed the findings of Boer. Thus the absolute configuration of the C(10) stereogenic centre was determined as *R* by Mosher analysis[28,29] of the *R*- and *S*-α-methoxy-α-trifluoromethylphenyl acetate (MTPA) esters of the C(10) hydroxy group in (**19**) (see Scheme 1.5)

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* 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[30] 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.

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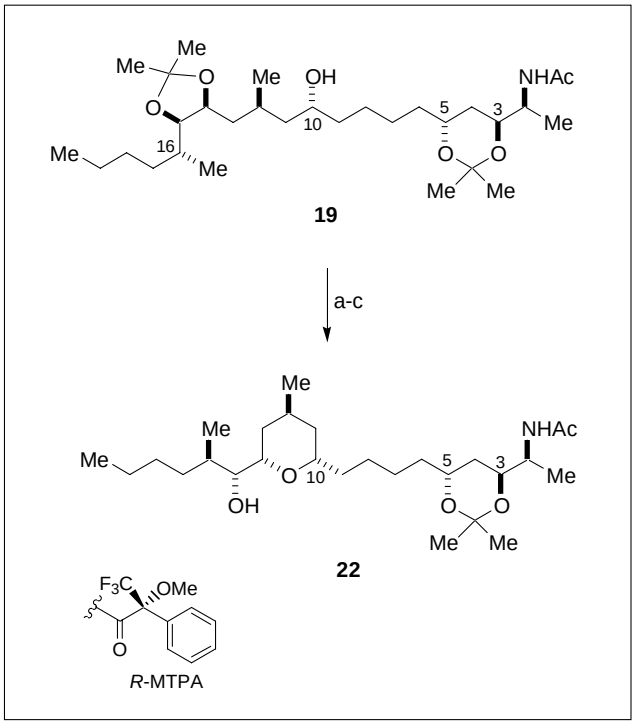
[24] ApSimon, J.W.; Blackwell, B.A.; Edwards, O.E.; Fruchier, A. *Tetrahedron Lett.*, **1994**, *35*, 7703.
[25] Poch, G.K., Powell, R.G., Plattner, R.D.; Weisleder D., *Tetrahedron Lett.*, **1994**, *35*, 7707.
[26] Blackwell, B.A.; Edwards,O.E.; ApSimon, J.W.; Fruchier, A. *Tetrahedron Lett.*, **1995**, *36*, 1973.
[27] Hoye, T.R.; Jiménez, J.I.; Shier, W.T. *J. Am. Chem. Soc.*, **1994**, *116*, 9409.
[28] Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, *95*, 512.
[29] Sullivan, G.R.; Dale, J.A.; Mosher, H.S. *J. Org. Chem.*, **1973**, *38*, 2143.
[30] Hartl, M.; Humpf, H.-U. *Tetrahedron Asymmetry*, **1998**, *9*, 1549.



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

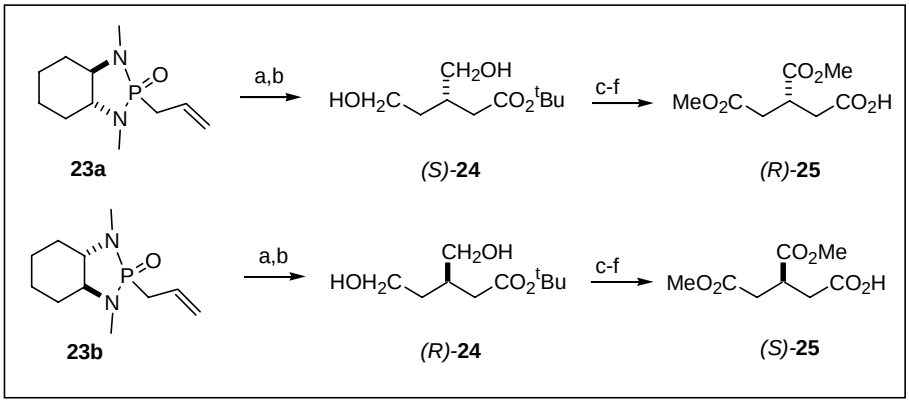
Using the *p*-dimethylaminobenzoate chromophore, the stereochemistry of fumonisin B_1 (**4**) was confirmed as 2*S*,3*S*,5*R* and that of fumonisin B_3 (**6**) as 2*S*,3*S*.

1.2.4 Stereochemical analysis of the tricarballylic acid moiety.

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

Boyle *et al.*[31] 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.[32] Addition of LiHMDS to a mixture of allylphosphonamide (**23**) and *t*-butyl sorbate at –78°C gave the Michael adduct which on ozonolysis followed by reductive work-up with $NaBH_4$ produced (*S*)-and (*R*)-**24** (Scheme 1.6).

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



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

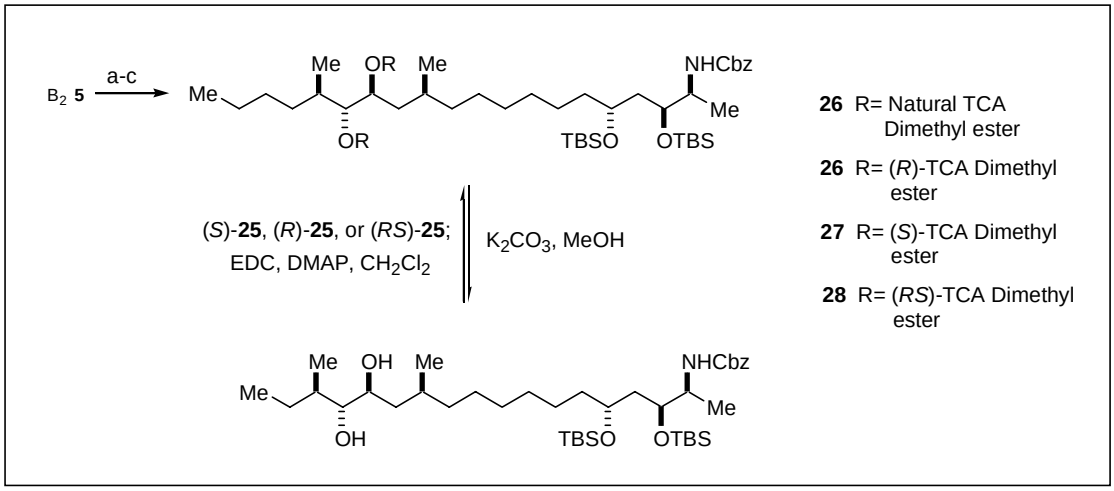
Reagents: (a) LiHMDS, *t*-butyl sorbate, THF, –78°C; (b) O_3, $NaBH_4$; (c) Swern oxidation; (d) $NaClO_2$; (e) CH_2N_2; (f) CF_3CO_2H.

Hanessian originally assigned the absolute configuration of (*S*)-**24** and this assignment was verified by the correlation with the compound derived from (*S*)-2-methyl-1-butanol. Although the optical purity of (*S*)- and (*R*)-**24** was in each case greater than 95:5, that of (*S*)- and (*R*)-**25** were determined by derivatisation with (–)-menthol to give a ca. 5:1 mixture of diastereomers in each case.

The tricarballylic acid dimethyl esters (*S*)-and (*R*)-**25** 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 (**27**)**,** (**28**) and (**29**)**.** Comparison of the ^1H NMR spectra of these esters with that of the protected fumonisin B_2 derivative **26** established the *R* configuration of the tricarballylic ester moiety in fumonisin B_2 A similar approach established the *R* configuration for the tricarballyllic acid moiety in fumonisin B_1.[33]

The Shier group[34] used chiral gas chromatography to determine the absolute configuration of the tricarballylic acid moiety in fumonisin B_1 (**4**). Selective reduction of the free carboxyl groups in the *N*-acetyl derivative (≡ fumonisin A_1) (**1**) was carried out using diborane in THF (Scheme 1.8). The reduced product was immediately tosylated and reduced to give 3-methyl-1-pentanol **30.** Oxidation of the primary alcohol **30** with CrO_3 gave the carboxylic acid **31** which was converted to the methyl ester **32** which was

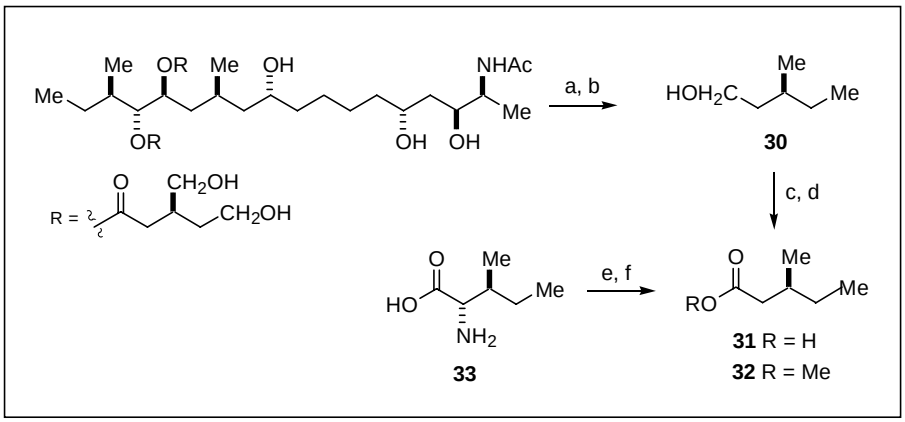
[33] Boyle, C.D.; Kishi, Y. *Tetrahedron Lett.* 1995, **36**, 5695.
[34] Shier, W.T.; Abbas, H.K.; Badria, F.A. *Tetrahedron Lett.*, **1995**, *36*, 1571.



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.

identical with the compound prepared from L-isoleucine **33**. In this way the *(S)* configuration was established for the stereogenic center of the tricarballylic ester moiety of the fumonisins.



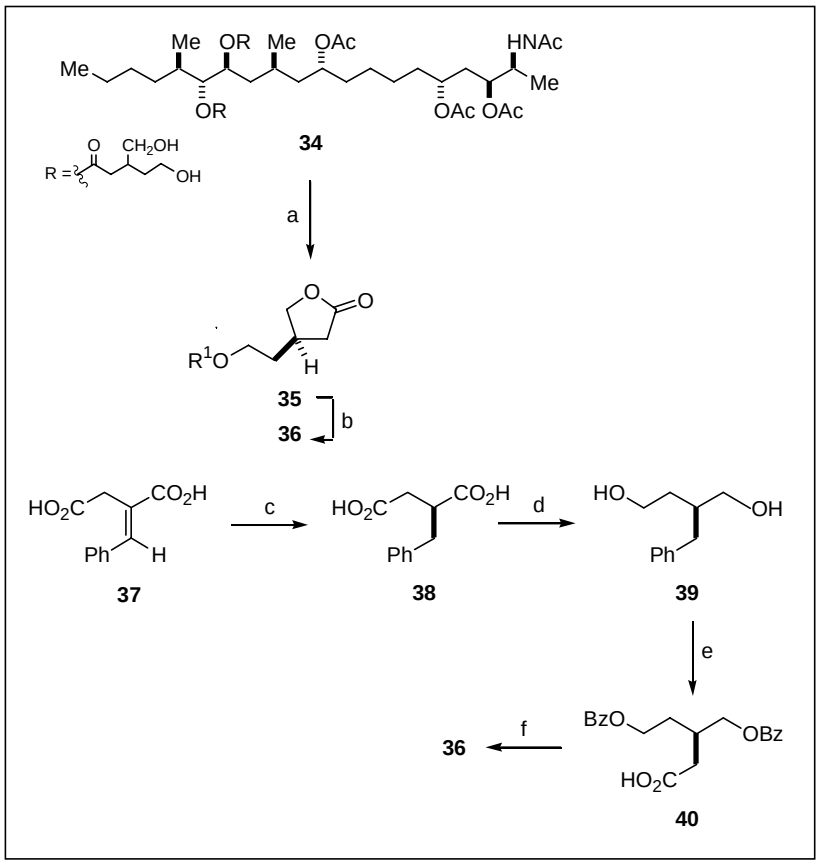
Scheme 1.8: Synthesis of the tricarballylic acid moiety derivative

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

Edwards *et al.*[35] provided evidence that supported the *R* configuration proposed by Kishi. Borane reduction of the free carboxyl groups fumonisin B_1 gave (**34**) (see Scheme 1.9). Hydrolysis of all the ester groups in (**34**) using KOH in aqueous MeOH, followed by

[35] Edwards, O.E.; Blackwell, B.A.; Driega, A.B.; Bensimon, C.; ApSimon, J.W. *Tetrahedron Lett.*, **1999**, *40*, 4515

acidification and extraction with chloroform gave a mixture rich in the γ-lactone (**35**). Benzoylation and separation by chromatography afforded the benzoate derivative (**36**) in high yield. An authentic sample of (**36**) was prepared from *E*-phenylitaconic acid (**37**), the stereochemistry of which was assigned by X-ray crystallography.[36]



Scheme 1.9 Synthesis of the (*R*)-(-)-hydroxy-γ-lactone **36**

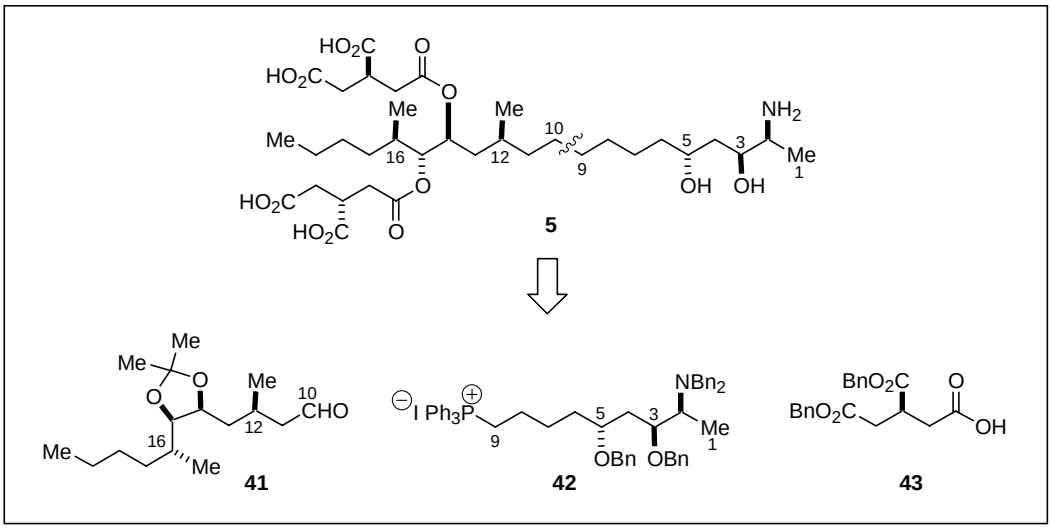
Reagents: (a) KOH, MeOH, then H^+; (b); BzCl; (c) [(–)-phenyl-CAPP]RhCl, H_2; (d) BH_3, THF; (e) i. BzCl, Py, ii. RuO_4; (f) KOH, then H^+.

Stereoselective reduction of (**37**) gave (*S*)-(–)-2-benzylsuccinic acid (**38**) that was converted by reduction with diborane to the diol (**39**)**.** Benzoylation of the hydroxy groups and oxidation of the phenyl group with ruthenium tetroxide gave the dibenzoyloxy acid (**40**). Alkaline hydrolysis followed by acidification afforded (*R*)-(–)-hydroxy-γ-lactone (**35**)**.** 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.

[36] Jendralla, J. *Tetrahedron Lett*. **1991**, *32*, 3671.

1.2.5 Enantioselective synthesis of the left segment of fumonisins B_2

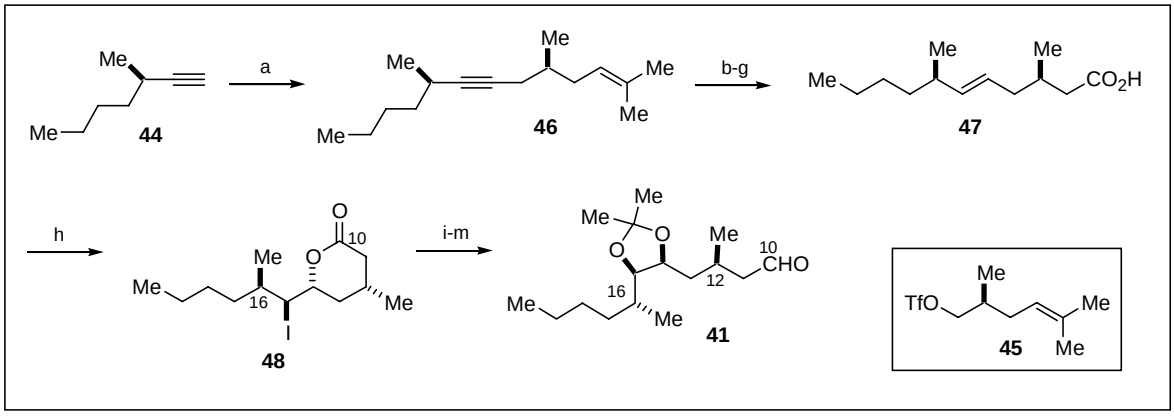
Fumonisin B_2 (FB_2) (**5**) possesses two distinct halves containing clustered stereogenic centers on its backbone, which are separated by six methylene units. Shi *et al.*[37] adopted a convergent approach and divided the molecule into three units — the left unit (**41**), the right unit (**42**), and the tricarballylic unit (**43**) (see Scheme 1.10).



Scheme 1.10 Retrosynthetic analysis of fumonisin B_2 (**5**).

Shi *et al.* began their synthesis of the left unit (**41**) by coupling the chiral alkyne (**44**) with the triflate (**45**) to give the alkyne (**46**) (see Scheme 1.11), which was then transformed to the *trans*-alkene acid (**47**) via (1) site-selective osmylation, (2) the resultant diol was cleaved using $Pb(OAc)_4$ 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 (**47**). The vicinal C(14) and C(15) hydroxy groups were stereoselectively introduced on the backbone of (**47**) in three steps: (1) iodolactonisation of (**47**) under equilibrium conditions in MeCN at –30°C to give the iodolactone (**48**) 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 alcohol was reduced to a triol, the two vicinal hydroxy groups protected as the acetonide and Swern oxidation of the primary alcohol gave the aldehyde (**41**).

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



Scheme 1.11: Synthesis of the left unit of fumonisin B_2.

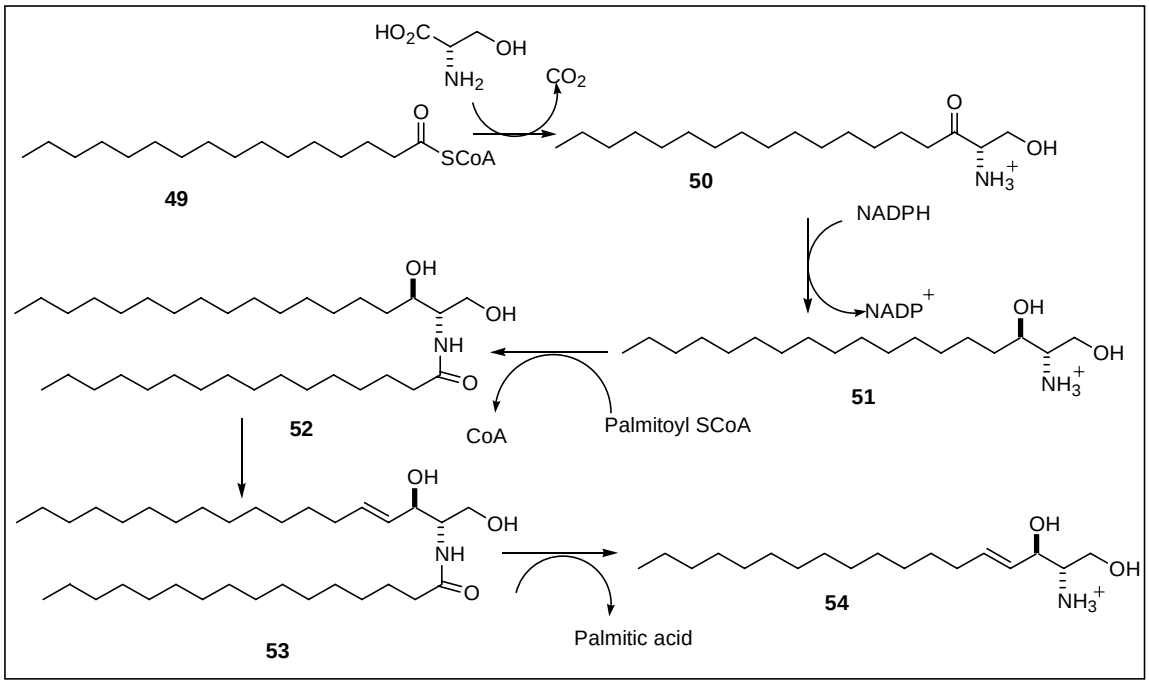
Reagents: (a) *n*-BuLi, then **45**; (b) $K_2OsO_4.2H_2O$; (c) $Pb(OAc)_4$; (d) $NaBH_4$; (e) Na/liq. NH_3; (f) Swern oxidation; (g) $NaClO_2$; (h) I_2, MeCN; (i) BnONa; (j) Pd-C, H_2, TsOH; (k) TsOH, acetone; (l) Swern oxidation.

1.2.6 Effect of fumonisins on sphingolipid biosynthesis

Sphingolipids are building blocks of the plasma membrane of eukaryotic cells; they are the second type of lipid found in cell membranes, particularly nerve cells and brain tissue. They 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. Their function is to anchor lipid bound carbohydrates to cell surfaces and construct the epidermal water permeability barrier. They do not contain glycerol but retain the two alcohols with the middle position occupied by an amine. In mammals sphingolipid biosynthesis can occur in all kinds of tissue. The biosynthesis consists of a cascade of reactions that are regulated and catalyzed by several enzymes.

The first step in the biosynthesis of (2*S*,3*R*)-sphingosine (**54**) and the sphingolipids, involves the condensation of palmitoyl-SCoA (**49**) 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 (**50**) (Scheme 1.12). The reaction has been reported as the rate-limiting step and is catalysed by the pyridoxalphosphate dependent enzyme, serine palmitoyltransferase. 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 (**50**) to give sphinganine (**51**) which is acylated to dihydroceramide (**52**) 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 (**52**) to D-*erythro*-ceramide (**53**). The hydrolysis of ceramide (**53**) catalysed by ceramidase is reported to be the only established pathway for production of D-*erythro*-sphingosine **(54)** in cells. Ceramide (**53**) is also the precursor of sphingomyelins (**55**) **(Fig. 1.2)**, cerebrosides and gangliosides, compounds which are prevalent in neuron cells.



Scheme 1.12: Biosynthetic pathway of sphingosine

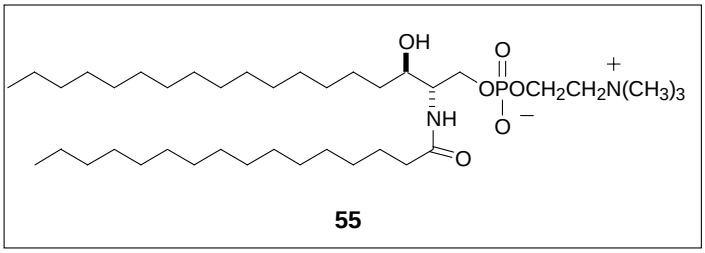


Figure 1.2: Structure of sphingomyelin

The remarkable structural similarity of the fumonisins and sphinganine **(51)**, 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[38] to involve the same enzyme ceramide synthase which catalyses the amide linkage of palmitoyl SCoA with sphinganine **(51)** and has the ability to reacylate

[38] Voss, K.A.; Plattner, R.D.; Riley R.T.; Meredith F.I. and Norred W.P. *Mycopathologia*, **1998**, *141*, 44.

sphingosine **(54)** generated by the hydrolysis of ceramide (**53**). 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.[39,40] The tricarballylic acid moiety and the C(5) hydroxy group are important but not decisive for inhibition.[41]

The mode of action of the fumonisins is primarily explained by the interference with *de novo* synthesis of complex glycosphingolipids. This results in disturbances of cellular processes such as cell growth, cell differentiation and cell morphology, endothelial cell permeability and apoptosis (programmed cell death). The molecular mechanisms by which fumonisins cause apoptosis, cytotoxicity and *in vivo* pathogenesis are not fully understood. Inhibition of the biosynthesis of sphingolipids is seen at different levels and is reflected in changes of the sphingonine:sphingosin ratio.

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.[42] 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 inhibition of the biosynthesis of glycosphingolipids is already seen a few hours after oral exposure to FB_1. 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.

[39] Merrill, A.H.; van Echten, G.; Wang E.; Sandhoff, K. *J. Biol. Chem*., **1993**, *268*, 27299.
[40] Norred, W.P.; Wang, E.; Yoo, H.; Riley, R.T.; Merrill, A.H. *Mycopathologia*, **1992**, *117*, 73.
[41] Kolter, T and Sandhoff, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 153
[42] Vance, D.E.; Vance, J. *Biochemistry of Lipids, Lipoproteins and Membranes*, **1996**, *31*, 309.

2 RETROSYNTHETIC ANALYSIS OF THE FUMONISINS

2.1 INTRODUCTION

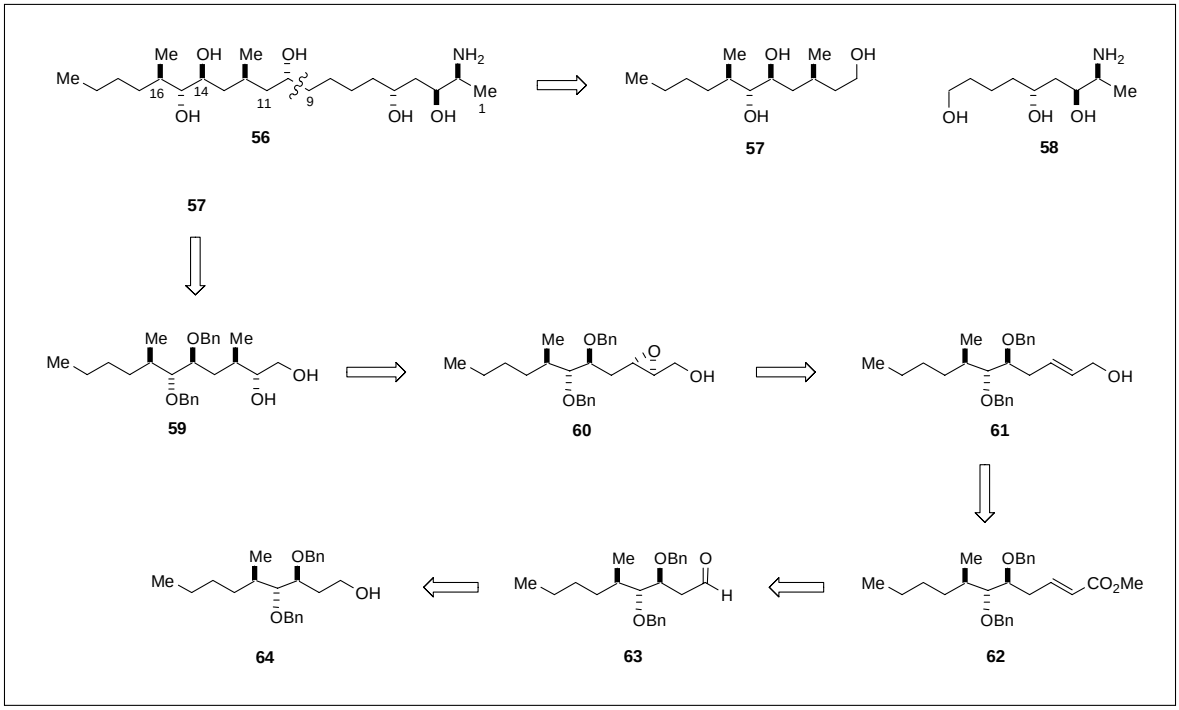
Selection of a suitable starting material for the synthesis of a complex organic compound can be a demanding and tedious exercise. In the early days of organic synthesis the focus was on chemical change in the direction of chemical reactions *i.e.* reactants → products. Most syntheses were developed 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.

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

2.2 ANALYSIS OF THE C_{11} LEFT SIDE UNIT

Base hydrolysis of fumonisin B_1 (**4**) results in cleavage of the tricarballylic ester moiety to give the C_{20} backbone (**56**) with its eight stereogenic centres. The first step in the retrosynthetic analysis (see Scheme 2.1) is 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.



Scheme 2.1: Retrosynthetic analysis of the fumonisin B_1 C_{20} backbone (**56**).

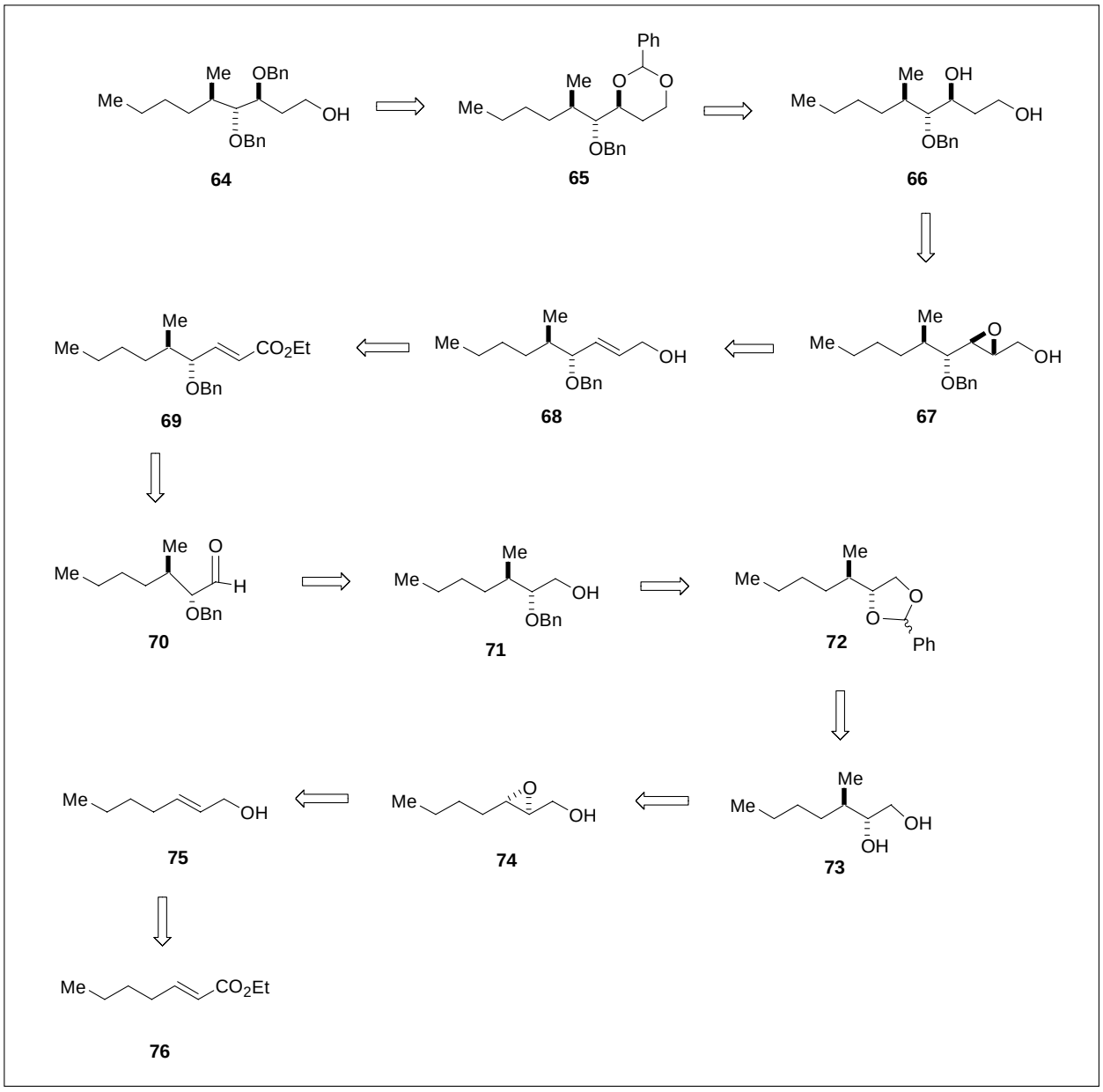
In the present study it was decided to disconnect the C(9)–C10) bond to give the C_{11} unit (**57**) which contains the stereogenic centres common to all of the known fumonisins. Following the protection of the secondary hydroxy groups the 1,2-dihydroxy-3-methyl motif present in (**59**) is envisaged as the precursor for the synthon (**57**) by removal of the C(11) hydroxy group (fumonisin numbering).

The 1,2-dihydroxy-3-methyl motif of (**59**) can be obtained from the regioselective ring opening of the epoxide (**60**) using Me_3Al whereby the methyl group is selectively introduced at C(12). The epoxide (**60**) can be synthesized by Sharpless epoxidation methodology[2] which requires an allylic alcohol (**61**) for the introduction of the C(12) stereogenic centre. The required allylic alcohol can be formed by the DIBALH reduction of the α,β-unsaturated ester (**62**). Wadsworth-Emmons methodology[3,4] can be used in the synthesis of this α,β-unsaturated ester by reaction of the aldehyde (**63**) with triethylphosphonate. The required aldehyde (**63**) is available from the primary alcohol (**64**) by Swern oxidation.[5]

The retrosynthetic analysis of the alcohol (**64**) is illustrated in Scheme 2.2. The alcohol (**64**) can be obtained from the regioselective cleavage of a C–O bond of the 1,3-benzylidene acetal group of (**65**) by DIBALH. The dioxane (**65**) is the product of the reaction of the 1,3-diol (**66**) with α,α–dimethoxytoluene, and the required 1,3-diol (**66**) can be formed from the reductive ring opening of an epoxide (**67**) by Red-Al reduction. This epoxide is derived from the allyllic alcohol (**68**) by Sharpless epoxidation methodology. The allylic alcohol is obtained by a functional group transformation of the α,β–unsaturated ester (**69**) by DIBALH reduction. The disconnection of the C(13)–C(14) bond in (**69**) (fumonisin numbering) represents a two-carbon chain extension to give the C_7 aldehyde (**70**). The conversion of the monoprotected alcohol (**71**) is envisaged to proceed by a Swern oxidation of the primary alcohol group to give the aldehyde (**70**) which can undergo a Wadsworth-Emmons reaction[3,4] to form the α,β-unaturated ester (**69**) with the *E* configuration. The monoprotected diol (**71**) is derived from the dioxolane derivative (**72**), by regioselective cleavage of the more accessible C–O bond by DIBALH reduction. The dioxolane derivative (**72**) is derived from the diol (**73**). Once again the 1,2-dihydroxy-3-methyl motif appears in the analysis: compound (**73**) can be obtained from the regioselective ring opening of the epoxide (**74**) using Me_3Al whereby the methyl group is selectively introduced at C(16) (fumonisin numbering). This epoxide is derived from an allylic alcohol (**75**) using once again Sharpless epoxidation methodology. This transformation results in the introduction of the first two stereogenic centres in the synthesis of

[2] Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[3] Hulme, A.H.; Howells, G.E.; Walker, R.H. *Synlett*, **1998**, 828.
[4] Gosselin, F.; Lubell, W.D. *J. Org. Chem.*, **1998**, *63*, 7463.
[5] Osmura, S.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651.

the C_{11} left-side unit. The starting material in the synthesis direction is identified as the α,β–unsaturated ester (**76**) as DIBALH reduction leads to the formation of the allylic alcohol (**75**).



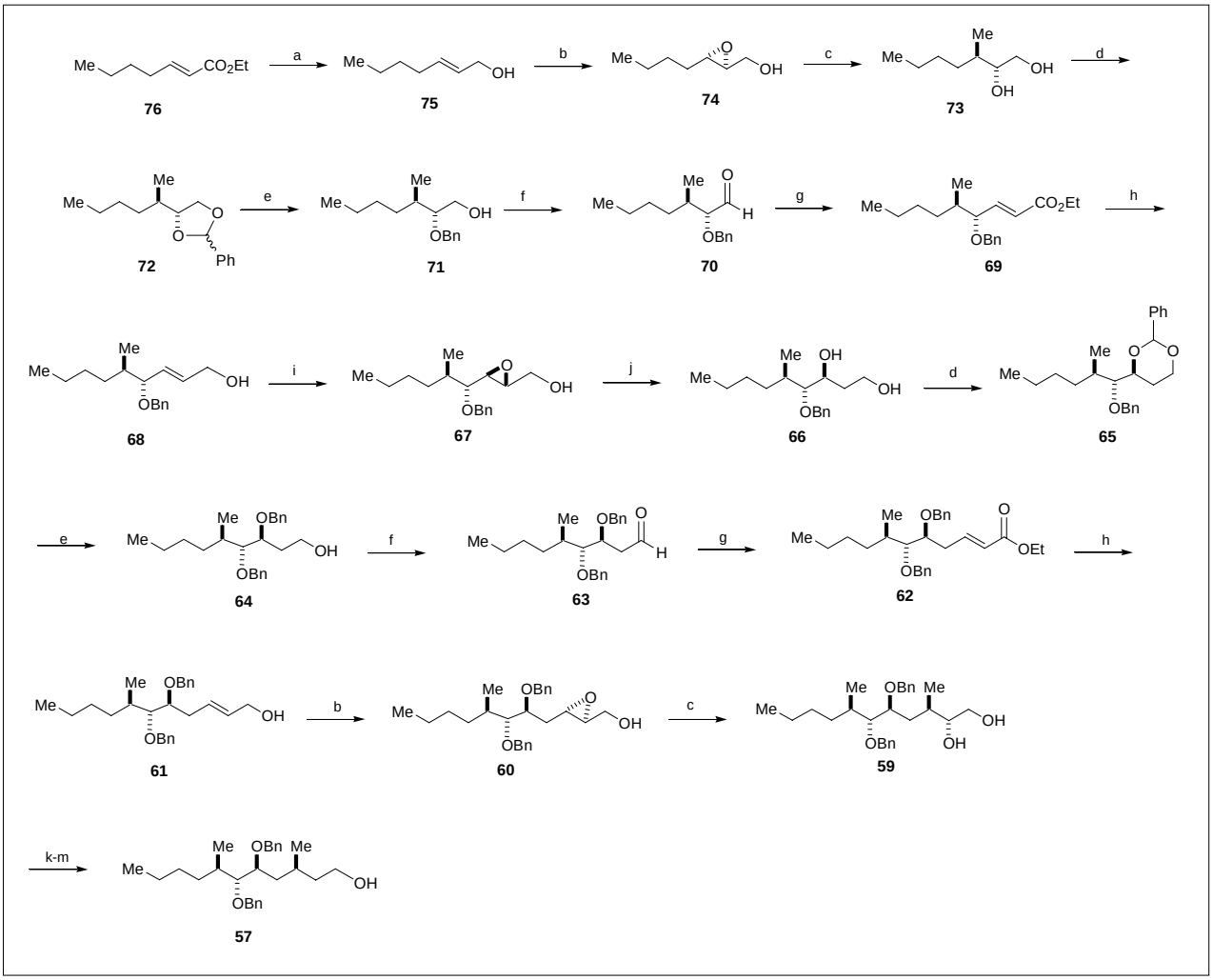
Scheme 2.2: Retrosynthetic analysis of the C_9 alcohol (**64**).

2.3 PROPOSED SYNTHETIC STUDIES

The proposed synthesis of the C(10)-C(20) unit of the fumonisins is outlined in Scheme 2.3

and uses ethyl 2-heptenoate (**76**) as starting material. DIBALH reduction of this ester gives the allylic alcohol (**75**) needed as the substrate for the Sharpless epoxidation using diethyl (*R*,*R*)-(–)-tartrate to give the epoxide (**74**) with the required stereochemistry. The epoxide ring is then opened by attack at C(3) using Me_3Al which introduces the C(3) methyl group in an S_N2 reaction that proceeds with inversion of configuration to give the 3-methyl-1,2-diol motif of (**73**) with the (2*R*,3*R*) configuration thus introducing the first two stereogenic centres of the C_{11} left-side unit of the fumonisins. Selective protection of the secondary hydroxy group as the *O*-benzyl ether (**71**) is achieved by formation of the 1,2-*O*-benzylidene derivative (**72**) which is regioselectively opened by reduction with DIBALH. It is now possible to extend the backbone by two carbon atoms using a two-step process. Swern oxidation of the primary alcohol (**71**) gives the aldehyde (**70**). The Wadsworth-Emmons reaction of this aldehyde with the ylid obtained by treatment of diisopropyl 1-(methoxycarbonyl)ethylphosphonate and *t*BuOK gives the (*E*)-α,β-unsaturated ester (**69**).

Once again a DIBALH reduction is employed to convert the (*E*)-α,β-unsaturated ester (**69**) to the allylic alcohol (**68**) required for the subsequent Sharpless epoxidation but this time using (*S*,*S*)-DET to give the epoxide (**67**) with the required stereochemistry. Regioselective reductive ring opening of this epoxide with Red-Al gives the 1,3-diol (**66**). This 1,3-diol can be selectively protected as the 3-*O*-benzyl ether (**64**) by conversion of the diol (**66**) to the benzylidene acetal (**65**) followed by reduction with DIBALH. The alcohol (**64**) now serves as the starting point of a sequence of reactions that will terminate in the formation of another 3-methyl-1,2-diol motif as shown in (**59**). Swern oxidation of the alcohol **(64)** gives the aldehyde (**63**) which is converted to the (*E*)-α,β-unsaturated ester (**62**) using diisopropyl 1-(methoxycarbonyl)ethylphosphonate in a Wadsworth-Emmons reaction. DIBALH reduction of this ester gives the allylic alcohol (**61**) which in a Sharpless epoxidation reaction using diethyl (*R*,*R*)-(–)-tartrate gives the epoxide (**60**). The required C(3) methyl group is introduced by ring opening of the epoxide in an S_N2 process using Me_3Al to give the diol (**59**). The final stages in the proposed synthetic route involve the removal of the C(2) secondary hydroxy group. This transformation is seen as a two-step process in which the 1,2-diol is first converted to an alkene (**A**) by a procedure in which the *O*-tosylate derivative is treated with sodium



Scheme 2.3: Synthesis of the C_{11} left-hand unit of the fumonisins.

Reagents: a) DIBALH; b) (*R*,*R*)-DET, Ti(*i*PrO)$_4$, *t*BuOOH; c) Me_3Al; d) $PhCH(OMe)_2$, TsOH; e) DIBALH; f) Swern oxidn: g) $(iPrO)_2POCH_2CO_2Et$; h) DIBALH; i) (*S*,*S*)-DET, Ti(*i*PrO)$_4$, *t*BuOOH; j) Red-Al; k) TsCl; l) Zn(Cu), NaI; m) i. BH_3, ii. H_2O_2, HO^-.

iodide in the presence of Zn(Cu) couple in DMF solution.[6] The subsequent hydroboration-oxidation step leads to the required target compound (**57**).

The theoretical background of the methodologies employed during this synthetic study is outlined in Chapter 3.

[6] Radatus, B.K. and Clarke, I.S., *Synthesis*, **1980**, 47.

3 SYNTHETIC METHODOLOGIES

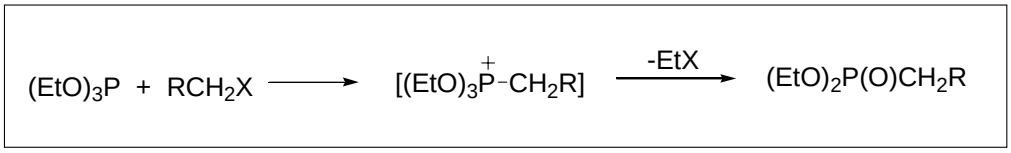
3.1 INTRODUCTION

The objective of this project is the synthesis of the C(10)–C(20) unit of fumonisin B_1, common to all the fumonisins, using the Sharpless asymmetric epoxidation methodology with its requirement of an allylic alcohol structural motif. The epoxides produced by this method can be used as chiral building blocks during the organic synthesis. This methodology has been proven to be one of the best in providing key intermediates in the preparation of complex enantiomerically pure bioactive compounds. The background to the different methodologies identified in the retrosynthetic analysis and used in the subsequent synthetic route are presented below.

3.2 PHOSPHONATE CARBANIONS (PHOSPHONO YLIDES)

3.2.1 Introduction

Phosphonate carbanions have been known since 1927 and they have been employed as nucleophiles in numerous reactions. In 1958 it was found that phosphonate carbanions would effect olefination of aldehydes and ketones in a reaction similar to that of phosphonium ylides (Wittig reaction). The phosphonate carbanions are often prepared by a straightforward deprotonation of phosphonates. In 1898[1] the reaction of alkyl halides with trialkylphoshites, (usually triethylphosphite) to produce phosphonates was discovered and it has been widely employed since because of its simplicity and good yields.



Scheme 3.1: The reaction of alkyl halides with triethylphosphite

This reaction is most effective with primary alkyl halides, but is of limited use with secondary

[1] Michaelis, A.; Kaehne, R. *Ber*. **1898**, *60*, 291.

halides.[2,3,4,5] The mechanism involves the nucleophilic attack of phosphorus on the alkyl halide in an S_N2 reaction and the displaced halide ion then attacks the *O*-alkyl group to form an alkyl halide and expel phosphonate.

3.2.2 The properties of phosphonate carbanions

Phosphonate carbanions are seldom isolated and instead they are formed by deprotonation either in the presence of another reactant or immediately prior to its addition and the reaction occurs immediately. The anion stability varies with the nature of the alkoxy group attached to phosphorus, decreasing in the order *i*-PrO> EtO> MeO> $OCH_2C(CH_3)_2O$ the latter being unstable at –50°C whereas the isopropoxy is stable for several hours at 0°C. The acidity of phosphonates varies with the nature of the carbon substituents and the alkoxy groups and in all cases is less than the corresponding phosphonium salt. When the common keto, ester, phenyl, or cyano groups are attached to the α-carbon to stabilize the formed carbanion, sodium hydride, sodium ethoxide or potassium *t*-butoxide seem to be the bases of choice. In the absence of such groups stronger bases are necessary, usually organolithium or alkali amide reagents. Teulade *et al.* [6] used organolithium exchange to determine the acidity differences among a series of phosphonates [$(RO)_2P(O)CH_2R'$] with the acidity decreasing in the order R= $OCH_2C(CH_3)_2CH_2O$>MeO>EtO>*i*-PrO and R′= Ph>Cl>Me>Et>*i*-Pr.

3.3 THE WADSWORTH-EMMONS REACTION

3.3.1 Introduction

Wadsworth and Emmons were the first to study in detail the reaction between the phosphonate carbanion and a carbonyl compound to produce an alkene and phosphate, and they developed it into a useful and important synthetic tool. The alkene usually is formed stereoselectively often with ratios of >90:10 and usually with *E*-stereochemistry. Both the Wittig reaction and Wadsworth-Emmons reaction have similar advantages over other methods of alkene synthesis.

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2 Crofts, P. C. *Quart. Rev*. **1958**, *12*, 341.
3 Arbuzov, B.A. *Pure Appl. Chem*. **1964**, *9*, 307.
4 Worms, K.A.; Schmidt-Dunker, M. in *Organic Phosphorus Compounds*; Kosolapoff, G.M. and Maier, L., Eds.; Wiley-Interscience: New York, **1976.**
5 Battacharya, A. K.; Thyagarajan, G. *Chem. Revs*. **1981**, *81*, 415.
6 Teulade, M.P.; Savignac, P. *Tetrahedron Lett.* **1987**, *28*, 405.

Both alkene-producing reactions rarely form byproducts. They have the ability to substitute on the carbanions of both phosphonium ylides and phosphonate carbanions prior to carbonyl condensation, thereby providing access to more highly substituted alkenes. The Wittig reaction and Wadsworth-Emmons reactions are both regiospecific and they have the ability to effect variable stereochemical control in alkene formation in many instances. The starting phosphonate is usually dissolved in an aprotic solvent and treated with an appropriate base to produce the carbanion, usually at low temperatures. The carbonyl compound is then added and the reaction allowed to continue, often for many hours while warming to 0°C or room temperature but occasionally with heating. Quenching with water to dissolve the phosphate and then extraction provides the crude product.

3.3.2 The mechanism of the Wadsworth-Emmons reaction

The mechanism illustrated in Scheme 3.2 represents the Wadsworth-Emmons reaction of the phosphonate carbanions with aldehydes.[7] The mechanism involves initial nucleophilic attack of the carbanion on the electrophilic carbonyl carbon to form betaines, which form oxaphosphetanes followed by ring opening, to afford alkene and phosphate anion. Larsen *et al.* [8] reported that the reaction with triethyl phosphonoacetate (R=COOEt) and ethoxide as the base, appeared to be third order; first order in each of ethoxide, phosphonate and benzaldehyde (R=Ph). They also found that the rate of alkene formation was approximately equal to that of carbonyl disappearance and that there was no evidence for the formation of intermediates. The issue of the precise nature of the intermediate in the Wadsworth-Emmons reaction is still very much open as there is no conclusive evidence and observation of either a betaine or an oxaphosphetane.[9] Most authors continue to represent the reaction as proceeding formally through a discrete betaine intermediate even though no NMR spectral evidence has been reported for betaines during the course of Wadsworth-Emmons reaction, nor have any been isolated. β-Hydroxyphosphonates (BHPs), the conjugate acids of the betaines, have been isolated from numerous Wadsworth-Emmons reactions, leading to the assumption that they are derived from betaines.[19]

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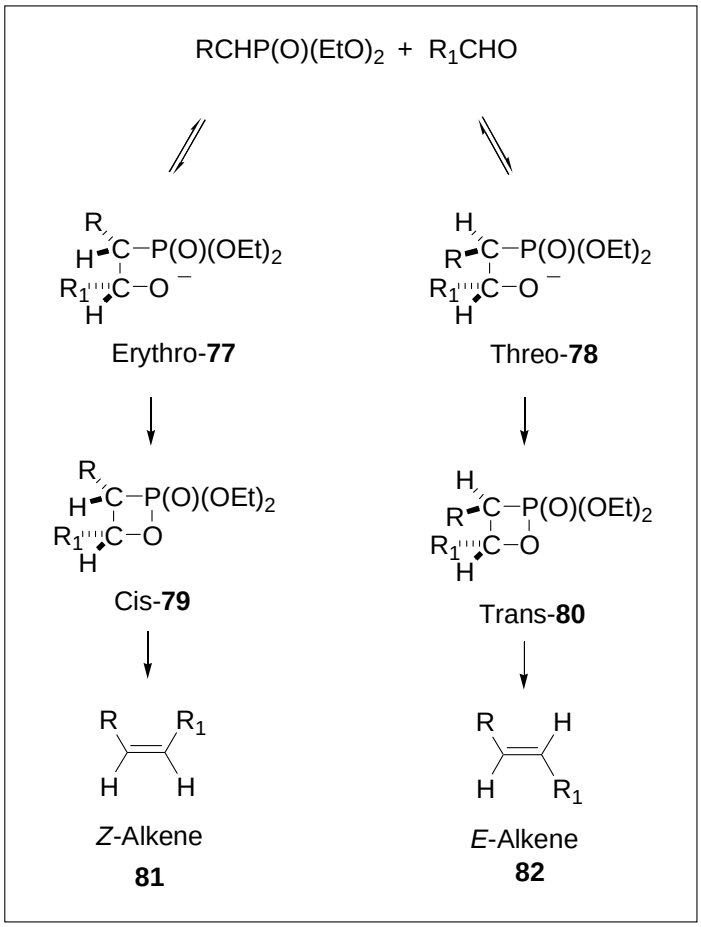
[7] Wadsworth, W.S.; Emmons, W.D. *J. Am. Chem. Soc*. **1961**, *83*, 1733.
[8] Larsen, R.O.; Aksnes, G. *Phosphorus Sulfur* **1983** , *15*, 219.
[9] Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkoska, B.; Gross, H.; Costisella, B. *Tetrahedron* **1978**, *34*, 3081.



Scheme 3.2: The mechanism of the Wadsworth-Emmons reaction

3.3.3 Stereochemistry of the Wadsworth-Emmons reaction

Initially it was concluded that the Wadsworth-Emmons reaction was not stereospecific.[10] However in most cases that were studied, generally those with electron-withdrawing groups on the carbanion, an *E*-alkene was produced as the dominant if not the exclusive product[11,12,13,14] similar to the results obtained using the corresponding stabilized phosphonium ylides.[15] The Wadsworth-Emmons reaction has now developed to the point where it is an important complement to the Wittig reaction, with numerous examples known where a

[10] Wadsworth, D.H.; Schupp, O.E.; Seus, E.J.; Ford, J.A. *J. Org. Chem.* **1965**, *30*, 680.
[11] Boutagy, J.; Thomas, R. *Chem. Revs*. **1974**, *74*, 87.
[12] Wadsworth, W.E. *Org. React*. **1977**, *25*, 73.
[13] Walker, B.J. in *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J.I., Ed.; Academic Press; London, **1979**, Ch. 3.
[14] Gushurst, A.J.; Jorgensen, W.L. *J. Org. Chem*. **1988**, *53*, 3397.
[15] Nesterov, N.I.; Belyaev, N.N.; Stadnichuk, M.D.; Mingaleva, K.S.; Sigolaev, Y.F. *J. Gen. Chem*. **1980**, *50*, 63.

phosphonium ylide reacted with a carbonyl compound to afford the usual *E*-alkene, but the use of the corresponding phosphonate carbanion under specialized conditions provided dominant *Z*-alkene formation.[16,17] The Wadsworth-Emmons reaction with aldehydes and ketones most often produces a dominance of *E*-alkene, but many variables make the stereochemistry somewhat controllable. The *E*-alkene arises from a *trans*-OPA (**80**) perhaps involving a *threo*-betaine (**78**) precursor, whereas the *Z*-alkene arises from *cis*-OPA (**79**) perhaps involving an *erythro*-betaine (**77**) (as illustrated in Scheme 3.2). It has been generally accepted and available evidence is consistent with the conclusion that the thermodynamically favoured route is via *trans*-OPA-(**80**) to *E*-alkene (**82**).

3.4 THE WITTIG REACTION

3.4.1 Introduction

George Wittig was the first to discover a way of adding a phosphorus-stabilized carbanion to a ketone or an aldehyde[18]. The Wittig reaction is important in organic synthesis and its use in the synthesis of naturally occurring molecules and as a general method for the preparation of alkenes has made it one of the cornerstones of synthetic chemistry[19]. The Wittig reaction converts the carbonyl group of a ketone or an aldehyde into a new double bond where no double bond existed before. The phosphorus ylides are prepared by S_N2 reaction of primary and some secondary alkyl halides (not tertiary)[20] with triphenylphosphine followed by treatment with a base. The first step is the nucleophilic attack by triphenylphosphine on an unhindered (usually primary) alkyl halide (Scheme 3.3). The product is an alkyl triphenylphos-phonium salt. The phosphonium salt is then treated with a strong base to abstract a proton from the α-carbon atom. The phosphorus ylide has two resonance forms, one with a double bond between the carbon and phosphorus atom (**85**) and another with charges on carbon and phosphorus (**84**). The double-bonded resonance form requires ten electrons in the valence shell of phosphorus, using a *d* orbital. The π-bond between carbon and phosphorus is weak, and the charged structure is the major contributor (**84**).

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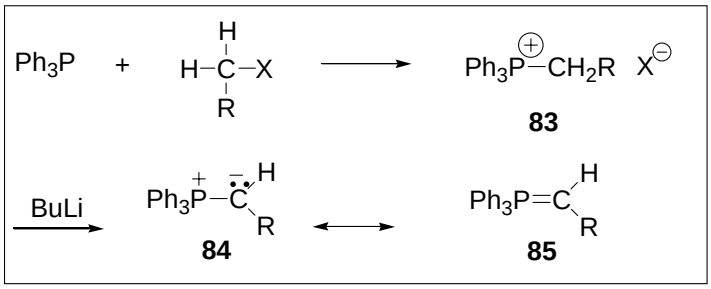
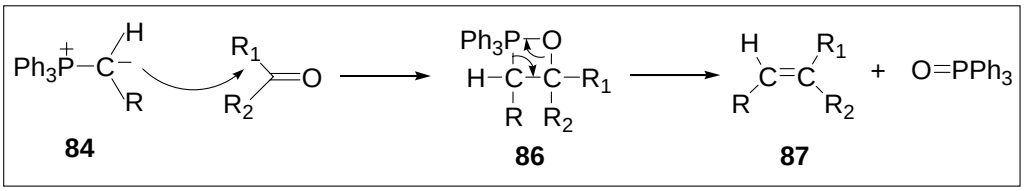
16 Oppolzer, W.; Grayson, J. I.; Wegmann, H.; Urrea, M. *Tetrahedron* **1983**, *39*, 3695.
17 Denmark, S.E.; Sternberg, J.A. *J. Am. Chem. Soc.* **1986**, *108*, 8277.
18 Wade, L.G. in *Organic Chemistry* **1999**, 4th Edition.
19 Johnson, A.W. in *Ylides and Imines of Phosphorus*, Wiley-Interscience: New York, **1993.**
20 McMurry, J. in *Organic Chemistry*, **1988**, 2nd Edition.



Scheme 3.3: The formation of a phosphorus ylide.

The carbon atom actually bears a partial negative charge, balanced by a corresponding positive charge on phosphorus. Because of its carbanion character, the ylide carbon atom is strongly nucleophilic; it attacks a carbonyl group to give a charge-separated intermediate called a betaine.



Scheme 3.4 The formation of the four-membered oxaphosphetane ring

3.4.2 The stereochemistry of the Wittig reaction

The Wittig reaction is known to involve a *syn*-elimination of phosphine oxide by virtue of the observation that the configuration of the phosphorus was retained throughout.[21,22] The Wittig reaction can produce one or both geometric isomers of the alkene product, with the stereochemistry of the alkene being ordained by the stereochemistry of the precursor oxaphosphetane, and regardless of whether or not betaines are involved as discrete species. A betaine contains negatively charged oxygen and positively charged phosphorus on adjacent carbon atoms (**84**). Phosphorus and oxygen form strong bonds and the attraction of opposite charges promotes the fast formation of a four-membered oxaphosphetane ring (**86**). The four-membered ring quickly collapses to give the alkene (**87**) and triphenylphosphine oxide as illustrated in Scheme 3.4. The mechanism of the Wittig reaction is illustrated in Scheme 3.5.

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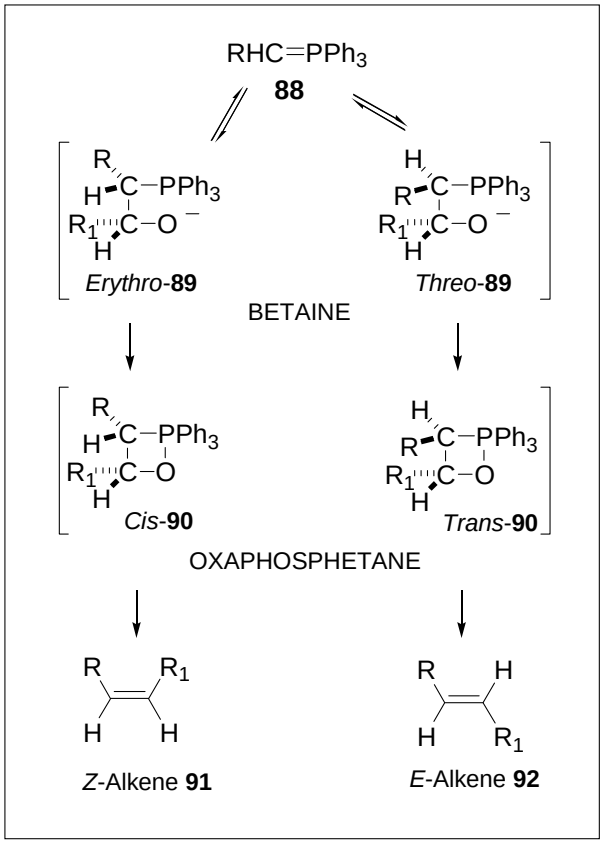
[21] Blade-Font, A.; Vanderwerf, C.A.; McAwen, W.E. *J. Am. Chem. Soc.* **1960**, *82*, 2396.
[22] Horner, L.; Winkler, H. *Tetrahedron Lett*. **1964**,3265.



Scheme 3.5: The mechanism of the Wittig reaction

Nonstabilized triphenylphosphorus ylides generally react with aldehydes to afford mainly *Z*-alkenes. Stabilized phosphonium ylides, those carrying strong electron-withdrawing groups such as carbonyl on the ylide carbon, normally afford predominantly *E*-alkenes, with proportions of 95% not being unusual but the reaction conditions may influence the ratio. The stereochemistry of such reactions can be influenced by a variety of experimental conditions like the choice of base to generate the ylide, the solvent, the reactant ratios, the additives, the catalyst, the temperature and the pressure.

Stabilized ylides, which normally produce *E*-alkenes with high stereoselectivity, usually are reacted in nonpolar solvents such as benzene and methylenechloride. The Wittig reactions using stabilized or semistabilized ylides usually are conducted at room temperature or under gentle reflux since they tend to be endothermic. Polar aprotic solvents, exclusion of lithium salt and low reaction temperatures; maximize *Z*-stereoselectivity however a strong preference for *E*-alkene is rarely observed. Optically active/pure phosphonium salts retain their

stereochemistry during the reaction. In cases where the betaine formation is reversible the thermodynamically more stable diastereoisomer will predominate prior to the *syn*-elimination of the Ph_3PO and thus a *trans* olefin is formed, usually in the case of ylides with stabilizing groups.

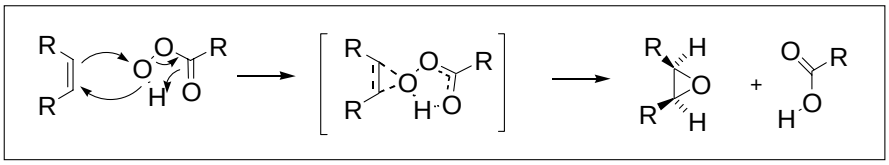
3.5 EPOXIDATION (SHARPLESS EPOXIDATION)

3.5.1 Introduction

Stereoselective synthesis constitutes one of the central challenges of modern organic synthesis. Epoxides are very important chiral building blocks in organic synthesis because they can be used as key intermediates in the preparation of more complex homochiral compounds. The strain of the three-membered ether ring makes epoxides highly reactive and confers unique chemical reactivity on them. In the laboratory epoxides are normally prepared by treatment of an alkene with a peroxy acid, RCO_3H. A variety of peroxy acids can be used to accomplish epoxidation but *m*-chloroperoxybenzoic acid is the preferred reagent on laboratory scale. *m*-Chloroperoxybenzoic acid is a stable, crystalline solid which is easily handled in contrast to other peroxy acids which are highly reactive and readily decompose.

Among numerous diastereoselective and/or enantioselective transformations that have been developed in recent years the Sharpless epoxidation of allylic alcohols has been found to be one of the most valuable. It uses commercially available and affordable reagents to produce synthetically useful epoxy alcohols from various substituted allylic alcohols with high stereocontrol.

The oxidation of an alkene to an epoxide is concerted. The nature of the transition state is illustrated in Scheme 3.6. Alkyl groups and other electron donating substituents on the alkene increase the rate of epoxidation, and the electron accepting substituents increases the reactivity of the peroxyacid. The peroxyacid acts as an electrophile in the reaction. Hydroxyl groups exert a directive effect on the epoxidation process and favour the approach from the side of the double bond closest to the hydroxyl group. Hydrogen bonding between the hydroxyl group and the reagent stabilizes the transition state.



Scheme 3.6: The mechanism of alkene epoxidation

The epoxidation of an allylic alcohol is effected by *t*-butylhydroperoxide and titanium tetraisopropoxide. The catalyst in the reaction is a complex prepared from titanium iso-propoxide and enantiomerically pure tartaric acid ester. When these enantiomerically pure tartrate esters are included in the system, the reaction is highly enantioselective. This reaction is called the Sharpless asymmetric epoxidation. Either (+) or (–)-tartrate ester can be used in the Sharpless epoxidation reaction resulting in the formation of either enantiomer of the epoxy alcohol. The use of the tartrate has to be carefully selected, depending on whether a primary or a secondary allylic alcohol is used.

The mechanism by which the enantioselective oxidation occurs is generally similar to that for vanadium catalyzed oxidations. The allylic hydroxyl group serves to coordinate the reactant to titanium, which creates a chiral environment. Oxidation occurs through an intermediate in which both the allylic hydroxyl and the *t*-butylhydroperoxide are both complexed to the titanium ion. The orientation of the reactive ligand is governed by the chirality of the tartrate ester. In the transition state an oxygen atom from the hydroperoxide is transferred to the double bond. The epoxidation employs a stoichiometric amount of catalyst, even though reactions of certain substrates can be carried out with as little as 10% catalyst with loss of enantioselectivity and some increase in yield. Using at least 10% tartrate is important, if too little is used (<10% excess) tartrate will result in a lowering of selectivity and too much (>100% excess) tartrate will slow the reaction unnecessarily.[23] The key feature of the catalytic modification is the use of molecular sieves (zeolites) to protect the catalyst from adventitious water in the reaction medium. In the stoichiometric reaction substrate concentration must be

[23] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y..; Masamune, H. and Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

kept low (*ca* 0.1M) in order to minimize side reactions (epoxide opening) arising from a large amount of titanium-tartrate species and isopropyl alcohol solution.

3.5.2 Titanium(IV) and dialkyltartrates

Sharpless asymmetric epoxidation converts the double bond of allylic alcohols into epoxides using transition metal catalyst titanium tetraisoproxide and a chiral additive diethyl tartrate. Titanium tetraisoproxide is a mild Lewis acid which exists in its highest oxidation state (d0) and has a low redox potential, it is labile to alkoxide ligand substitution like the other good epoxidation catalysts such as vanadium(V), molybdenum(VI) and tungsten(VI). One of the important differences between titanium(IV) alkoxides and most other highly active catalysts is that the titanium species have four covalently bound alkoxide ligands whereas the others do not. Co-ordination of the chiral ligand DET and the oxidant source tBuOOH to the metal centre forms the catalytically active species. The metal catalyst is a dimer consisting of two dialkyl tartrates or tartramides covalently bound through the hydroxylic functions to two titaniums (Figure 3.1).[24]

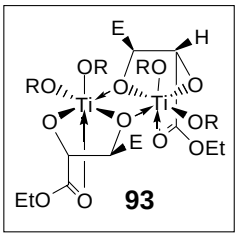


Figure 3.1: Catalyst dimer proposed by Sharpless. (R= *i*Pr)

In the epoxidation reaction the allylic alcohol and alkylhydroperoxide are bound to either of the two equivalent metal centers. In other words the catalyst centre must have the ability to accept four hydroxylic ligands to promote asymmetric epoxidation or kinetic resolution with the dialkyl tartrates or tartramides, one from each of the two chiral ligands and one from each of the reactants (allylic alcohol and hydroperoxide). Titanium does not readily accept oxo ligands therefore does not easily form Ti=O species whereas vanadium(IV), molybdenum(VI) and tungsten(VI) are stable with one, two and two oxo ligands, respectively. Thus these metal

[24] Finn, M.G. and Sharpless, K.B., in *Asymmetric Synthesis,* (J. Morrison, Ed.), **1985**, *5*, 247, Academic Press, New York.

oxo species can only be covalently bound to three, two and two alkoxide ligands, respectively as illustrated by **95** and **96** in Figure 3.2 and as such are unable to coordinate simultaneously with the hydroperoxide, allylic alcohol and a divalent ligand. The main function of the molecular sieves is the protection of the catalyst from adventitious water in the reaction medium[25] since water reacts with the titanium complex but not initially in the irreversible manner.

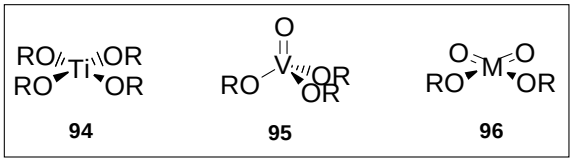


Figure 3.2: The ligand patterns of epoxidation catalysts. M=Mo, W

Although many different ligands have been used with various metals, dialkyltartrates and tartramides with titanium are by far the best combination known to date to effect asymmetric epoxidation. Scheme 3.1 illustrates the use of tartrates in the epoxidation of primary and secondary allylic alcohols. The steric bulk of the esters seems to be the deciding factor in the modification of catalyst properties. Rossiter *et al.*[26] reported that in cases where diadamantyl and di-*t*-butyl tartrates were used, reactions were very slow and products of low enantiomeric excess were obtained.

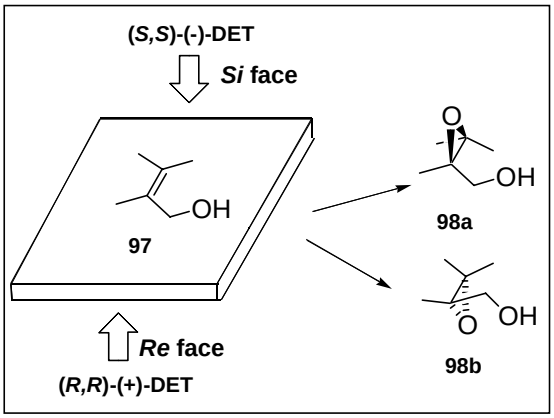
The best work-up method for most stable, water insoluble epoxy alcohols is by shaking or stirring the reaction mixture with 10% aqueous tartaric acid solution or citric acid. This leads to two homogeneous phases in which the titanium is present in the aqueous phase as a tartaric acid or citric acid complex. The organic phase contains the epoxy alcohol product, the tartrate diester, unreacted TBHP and *t*-butanol. Iron(II) sulfate may be added to the aqueous acid solution in which case this single treatment destroys excess TBHP in addition to removing titanium. In cases where the epoxy alcohol is acid sensitive and/or water-soluble an alternative to the tartaric acid wash is required. The addition of a saturated solution of sodium sulfate to the reaction mixture gives an insoluble titanium species that may be removed by

[25] Sheldon, R.A. and Kochi, J.K. in *Metal catalyzed oxidations of organic compounds*, **1981**, Ch. 3, Academic Press, New York.
[26] Rossiter, B.E. in *Asymmetric Synthesis*, (J. Morrison, Ed.), **1985**, *5*, Ch. 7, Academic Press, New York.

filtration.[26,27,28] The recommended procedure for tartrate ester removal is by hydrolysis in a two-phase system of diethyl ether and NaOH in brine.[29] The early procedures of asymmetric epoxidation called for dilute NaOH solution to effect tartrate ester hydrolysis, but the use of a brine solution of NaOH is the recommended procedure.

3.5.3 Stereoselectivity

The stereochemical outcome of the asymmetric epoxidation is consistent with (*S*,*S*)-(–)-DET inducing the epoxide formation on the *Si* face and the (*R*,*R*)-(+)-DET inducing the epoxide formation on the *Re* face of the allylic alcohol as is illustrated in Scheme 3.7. Similarly for kinetic resolution of the secondary allylic alcohols one can predict the stereochemical outcome of a given reaction by predicting which enantiomer will react faster and what the stereochemistry of the resulting epoxide will be. The stereochemical rule for the asymmetric epoxidation of primary allylic alcohols is illustrated in Scheme 3.7.

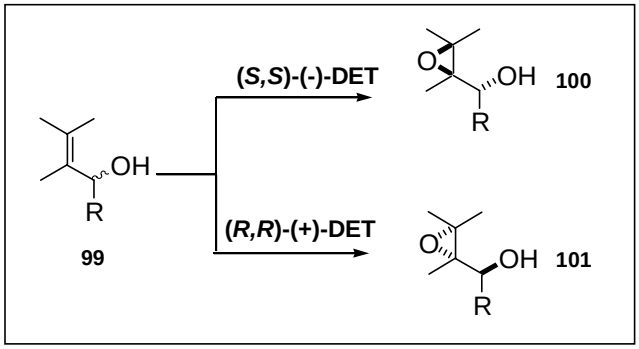


Scheme 3.7: Asymmetric epoxidation of primary allylic alcohols

For a given tartrate or tartramide, the system delivers the epoxide oxygen from the same enantioface of the olefin regardless of the olefinic substitution pattern. For most allylic alcohols the asymmetric induction is generally high (>90%ee) but there have been instances in which this is not the case. (*Z*)-Allylic alcohols with steric bulk at the C(4) position have lower

[27] Reed, L.A.; Ito, Y.; Masamune, S. and Sharpless, K.B., *J. Am. Chem, Soc.***1982**, *104*, 6468.
[28] Sharpless, K. B. In *Asymmetric synthesis* (J Morrison, Ed.), **1985**, *5*, Ch. 8, Academic Press, New York.
[29] Hill, J.G.; Sharpless, K.B.; Exon, C.M. and Regenye R., *Org. Synth.*, **1984**, *63*, 66.

rates and enantioselectivities. Few examples exist in which little or no selectivity is manifested, in these cases the allylic alcohol is not only *Z* but has chiral centres adjacent to the olefin. In these cases it is often possible to obtain primarily one of the two possible diastereomers by using *m*CPBA or $VO(OEt)_3$ / TBHP.



Scheme 3.8 : Asymmetric epoxidation/ kinetic resolution of racemic secondary alcohol.

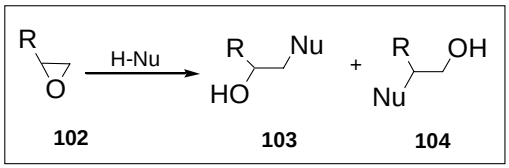
The olefinic portion of the molecule in Scheme 3.8 is shown in the plane of the paper, as is the carbinol hydrogen while the –OH and –R groups are either above or below the plane. When using (*S*,*S*)-(–)-DET, the fast reacting isomer having –OH below the plane, gives an epoxide whereas the slow reacting isomer having the –OH above the plane of the paper is left largely unreacted. Use of (*R*,*R*)-(+)-DET will give the opposite results, this pattern is consistently observed except in the case of bulky *Z* substituents.

3.6 RING OPENING OF EPOXIDES

3.6.1 Introduction

Epoxides are versatile intermediates in organic chemistry because the inherent polarity and strain of the three-membered ring makes them susceptible to reaction with a large number of reagents. The ring opening of epoxides can be achieved by variety of nucleophiles; these include oxygen compounds (water, alcohols and phenols), nitrogen compounds (amines and derivatives of amines, azides, isocyanates), acids (hydrogen halides, hydrogen cyanide, sulfonic acids, and carboxylic acids), sulfur compounds (hydrogen sulfide, thiols, thiophenols, sulfides, thioacids and several sulfur anions) and various carbon nucleophiles. Ring opening can occur in neutral, basic or acidic solution but it is known that the presence of acid

accelerates ring opening. In neutral and basic media, the reaction proceeds via nucleophilic attack on the neutral epoxide, while in acidic media, protonation of the epoxide precedes nucleophilic attack. The reaction in neutral or basic media follows an S_N2 mechanism but in acidic solution the mechanism has most often been termed borderline S_N2 (or modified A_2) though this has been the subject of much discussion.[30]



Scheme 3.9: Nucleophilic attack of an epoxide ring.

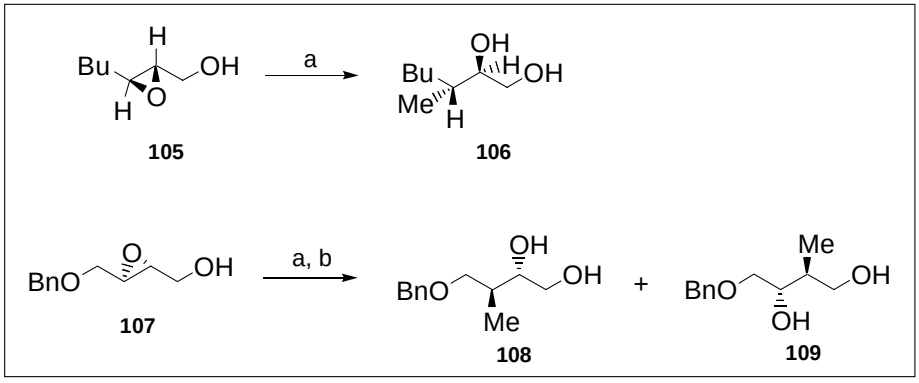
With unsymmetrical epoxides the position of nucleophilic attack is governed by both the epoxide and the exact reaction conditions. In neutral and basic solution attack at the sterically less hindered site occurs predominately yielding (**103**). In acid solution, there is a greater tendency for nucleophilic attack at the carbon atom which can better accommodate a positive charge in the transition state, that is, the more substituted carbon to form addition adduct (**104**). When R is a substituent such as phenyl or vinyl that can stabilize an intermediate positive charge by conjugation, attack in acid solution at the more substituted carbon atom to form (**104**) is even more strongly favoured. When R is an electron-withdrawing group, attack at the β-carbon is favoured. Many carbon nucleophiles are known to undergo addition reactions to epoxides and these include organomagnesium, organocopper, organoaluminium and organoboron compounds.

3.6.2 Ring opening of epoxides using Me_3Al

The regioselective epoxide ring opening by nucleophiles such as dialkylcuprate and Red-Al to produce 1,3-diols has been well studied and has found wide application in the synthesis of natural products. However, few examples are known for the regioselective production of 1,2-diols. Suzuki *et al.*[31] reported that the treatment of some 2,3-epoxy alcohols with trialkylaluminium compounds led to the regioselective formation of 1,2-diols. Nonpolar

[30] Smith, J.G. *Org. Synth.*, **1984**, 629.
[31] Suzuki,T.; Saimoto, H.; Tomioka, H.; Oshimo, K. and Nozaki, H. *Tetrahedron Lett.*,**1982**, 23, 3597.

solvents such as hexane or dichloromethane give the best results but the reaction does not take place in diethylether and THF solutions. The methyl group is introduced regioselectively at position 3 with inversion of configuration. Suzuki also reported that the epoxy alcohol generated from (*E*)-allylic alcohol and *threo* epoxy alcohols provide 1,2-diols smoothly in good yields and with high stereoselectivity, whereas epoxides derived from (*Z*)-allylic alcohols and *erythro* epoxy alcohols react sluggishly with organoaluminium reagents to give 1,2-diols in relatively low yields and with less stereoselectivity. The coordination of the epoxy-oxygen atom to the aluminium in *erythro* epoxy alcohols possibly interferes by steric repulsion with the alkyl group C(3) and alkyl groups attached on aluminium. Complementary regioselectivity was realized when (**107**) was treated with Me_3Al (3 equiv.) in CH_2Cl_2 (0^oC to 25^oC) whereby a mixture of **108**:**109** was produced with (**108**) being a major product (5:1).[32]



Scheme 3.10: Ring opening of epoxy alcohols using Me_3Al to give 1,2-diols

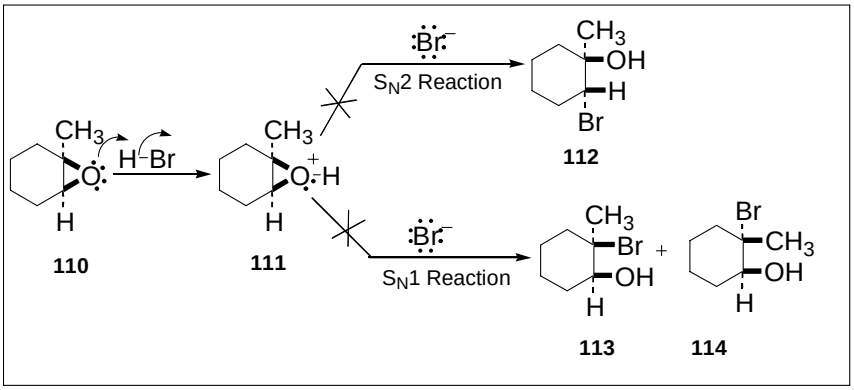
Reagents: (a) Me_3Al (b) CH_2Cl_2, 0→23°C

The stereochemical outcome of the reaction can be explained as follows: the hydroxyl group is converted into aluminium alkoxide by the first trialkylaluminium molecule. The epoxy-oxygen coordinates to the aluminium and this coordination plays an important role in the product- and rate-determining ring opening steps. The epoxide carbon-oxygen bond is thus loosened at C_3 and the bond is cleaved by the attack of the alkyl anion liberated from the second molecule of the trialkylaluminium possibly coordinated on another substrate molecule. This S_N2 type reaction via tight ion pair is well precedented.

[32] Roush, W.R.; Adam, M.A. and Peseckis, S.M. *Tetrahedron Lett.*, **1982**, *24*, 1377.

3.6.3 Ring opening of epoxides by acids

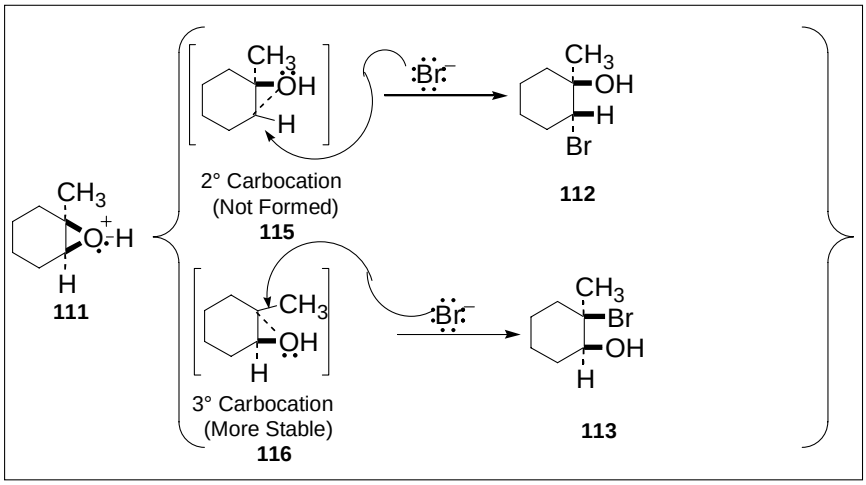
The direction in which an unsymmetrical epoxide ring is opened depends on the conditions used. If acidic conditions are used attack of the nucleophile occurs primarily at the more highly substituted carbon atom. Acid-catalyzed epoxide ring opening is particularly interesting from a mechanistic viewpoint because it appears to be midway between a pure S_N1 reaction and a pure S_N2 reaction. Take the reaction of 1,2-epoxy-1-methylcyclohexane with HBr in Figure 3.12. If this were a pure S_N2 reaction, bromide ion would attack the less highly substituted carbon atom; displacing the epoxide oxygen atom from the backside to give (**112**) with the bromo and hydroxyl groups *trans* to each other. On the other hand if this was a pure S_N1 reaction protonation of the epoxide oxygen atom followed by ring opening would yield a carbocation that could react with bromide ion from either side to give a mixture of two isomers (**113**) and (**114**). One isomer would have the bromo and hydroxyl group *cis*, the other would have the bromo and hydroxyl group *trans*. In fact neither of the reaction courses shown in Scheme 3.10 is observed.



Scheme 3.11: The reaction product from hypothetical S_N1 and S_N2 ring opening of 1,2-epoxy-1-methylcyclohexane

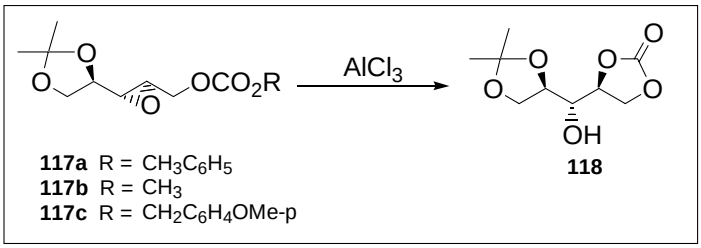
Instead the reaction of 1,2-epoxy-1-methylcyclohexane with HBr (Scheme 3.10) yields a single isomer (**114**) in which the bromo and hydroxyl groups are *trans* to each other. The observed regiochemistry can be accounted for by assuming that the reaction has characteristics of both S_N1 and S_N2 reactions. The fact that the single product formed has the entering bromine and the leaving oxygen on opposite sides of the ring is clearly an S_N2-like result and the fact that bromide ion attacks the tertiary side of the epoxide rather than the secondary side

is clearly S_N1-like result. Both facts can be accommodated by postulating that the transition state for the acid-induced epoxide ring opening has an S_N2-like geometry but a high degree of S_N1-like carbocationic character. Although the protonated epoxide is not a full carbocation, it is strongly polarized so that the more highly substituted carbon atom shares the positive charge. Thus attack of the nucleophile occurs at the more highly substituted site.



Scheme 3.11: Acid induced ring opening of 1,2-epoxy-1-methylcyclohexane.

The opening of an epoxide ring under acidic conditions via nucleophilic attack at the more highly substituted site was also illustrated by Minami *et al.* [33] (Scheme 3.12) who reported the ring opening of the carbonate (**117b**) under acidic conditions and found that it was sluggish and yet that of the carbonate (**117c**) seemed to be slightly faster than that of carbonate (**117a**), but the chemical yields were similar. The Lewis acids [$AlCl_3$, $TiCl_4$, $EtAlCl_4$, $(Me)_2AlCl$, $BF_3.Et_2O$] were found effective to ensure ring opening but $AlCl_3$, $TiCl_4$ or $EtAlCl_4$ generally gave the best results.



Scheme 3.12: Epoxide ring opening using Lewis acids

[33] Minami, N.; Ko, S.S.; Kishi, Y. *J. Am. Chem, Soc*., **1982**, *104*, 6468.

3.6.4 Ring opening of epoxides using Red-Al

The reductive ring opening of epoxides derived from allylic alcohols using Red-Al gives 1,3-diols in excellent yields. The primary factor controlling the regioselectivity seems to be the hydroxyl group at position 1. This became evident when the epoxide **(122)** was recovered unchanged under the same conditions and also because epoxide **(123)** yielded exclusively the alcohol **(124)** (Figure 3.3) The Sharpless epoxidation and the subsequent Red-Al reduction provides a stereo- and regiocontrolled route to 1,3-polyhydroxylated systems as shown in Scheme 3.13 for the synthesis of (**126**) and (**128**). The use of Red-Al leads to the (almost) exclusive formation of the 1,3-diols.

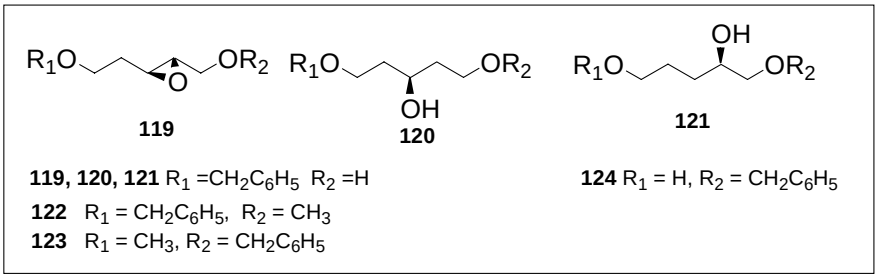
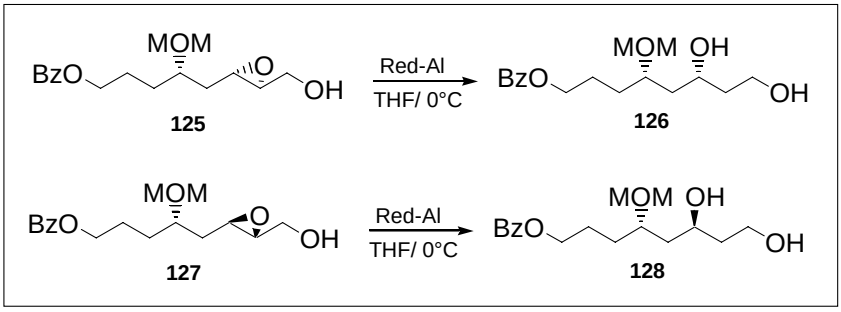


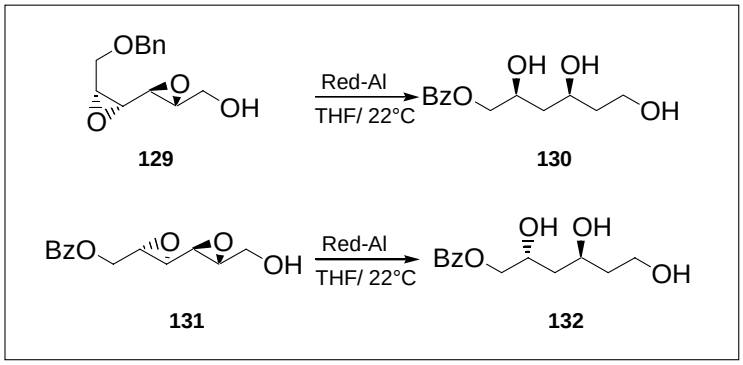
Figure 3.3: The hydroxyl group as the controlling factor during the ring opening of the epoxide



Scheme 3.13: The ring opening of epoxides by Red-Al to give 1,3-diols as products

The regioselectivity demonstrated by Red-Al in the reductive ring opening of epoxy alcohols is not limited to the reduction of monoepoxy alcohols. Minami *et al.* also reported that a diepoxy alcohol can undergo ring opening by Red-Al to give the 1,3,5-triol. The 2,3: 4,5-diepoxy alcohol (**129**) prepared from the 4,5-epoxy allylic alcohol via asymmetric epoxidation undergoes clean double ring opening to provide a single product the 1,3,5-triol (**130**). The

same result was observed for the ring opening of the diepoxy alcohol (**131**) using Red-Al, to produce exclusively the 1,3,5-triol (**132**).[34] (Scheme 3.14).



Scheme 3.14: The ring opening of the diepoxy alcohols using Red-Al

Although further experiments are needed to provide a mechanistic explanation for the observed results, the Red-Al reduction seems to involve initial complexation of the reducing agent with the hydroxyl group, followed by intramolecular hydride reduction. In contrast to Red-Al, DIBALH reductions of the epoxide (**119**) (see Figure 3.3) yielded the 1,2-diol (**121**) as the major product, although the degree of regioselectivity varies with substrate. The DIBALH reduction also seems to involve initial formation of a complex with the hydroxyl group, in which the aluminium serves as a Lewis acid to facilitate intermolecular hydride reduction.[35,34]

3.7 DETERMINATION OF OPTICAL PURITY USING MOSHER ACIDS

Mosher's acid (α-methoxy-α-(trifluoromethyl)phenylacetic acid) is the popular chiral derivatizing agent for the determination of the enantiomeric purity of alcohols and amines. In order for Mosher acid methodology to be used to establish the enantioselectivity in kinetic resolution reactions it is necessary to prepare a sample of racemic epoxy alcohol that contains all possible stereoisomers. This is done by epoxidizing the allylic alcohol with MCPBA. The product is then converted to the Mosher ester and analysed using ^{19}F NMR spectroscopy.. Typical procedures for the derivatization of alcohols or amines require the Mosher acid

[34] Minami, N; Ko, S.S.; and Kishi, Y. *J. Org. Chem,* , **1982**, *47*, 1378.
[35] Finan, J.M. and Kishi, Y. *Tetrahedron Lett.,* **1982**, *23*, 2719.

chloride (MTPACl), which is prepared from MTPA by prolonged refluxing with $SOCl_2$ followed by distillation. The reaction of MTPA with $SOCl_2$ can lead to varying amounts of the anhydride and α-methoxy-α-(trifluoromethyl)toluene depending on the reaction conditions.[36]

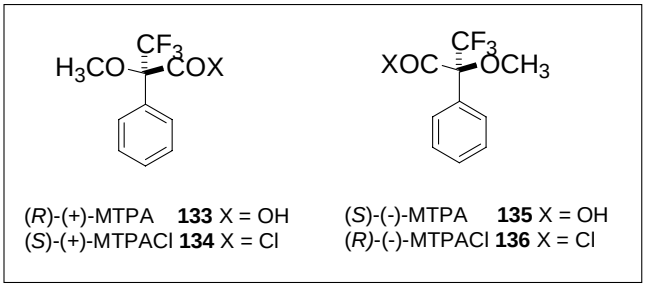


Figure 3.4: The structure of MTPA and MTPACl

The reaction of carboxylic acids with oxalyl chloride gives acid chlorides with CO, CO_2 and HCl as the only byproducts. This reaction is catalyzed by DMF and involves the intermediacy of *N*-(chloromethylene)-*N*-methylmethanaminium chloride (DMFCl). MTPA is quantitatively converted into MTPACl within one hour (microscale) at room temperature by treatment with excess oxalyl chloride in the presence of DMF. Concentration of the reaction mixture (to remove excess oxalyl chloride and HCl) gives MTPACl contaminated only by DMFCl. DMFCl is more reactive than MTPACl and reacts with alcohols to produce alkylhalides and/or formate esters. The yield of Mosher's acid derivative obtained from crude MTPACl decreases as the amount of DMF used in the preparation increases. Ward *et al.* [36] found that the offending DMFCl can be removed from MTPACl by simple filtration if the reaction is conducted in hexane. Concentration of the resulting filtrate gives essentially homogeneous MTPACl in 85-95% yield which is suitable for use without further purification. On the basis of GC-MS measurements, Jeanneret-Gris *et al.* [37] found that the major contaminant of impure MTPACl is α-methoxy-α-(trifluoromethyl)-α-phenyl-chloromethane, which is formed by decarboxylative chlorination of MTPA or MTPACl. The specific rotation of this compound is around ±5 (*c*1.5 in CCl_4) and consequently its contribution to the overall optical rotation is low. This chloride is much less reactive than the acid chloride. Therefore it does not interfere with the substrate to be reacted, particularly if MTPACl is in excess. Their experiments

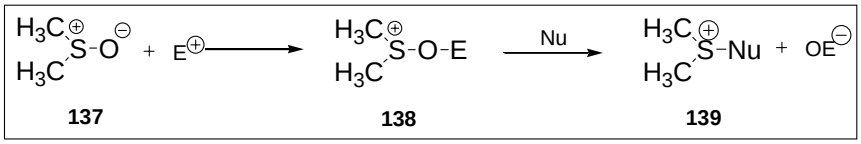
[36] Ward, D.E. and Rhee, C.K. *Tetrahedron Lett.*, **1991**, *32*, 7165.
[37] Jeanneret-Gris, G. and Pousaz, P. *Tetrahedron Lett.*, **1989**, *21*,75

showed that no racemization occurs on Mosher's acid chloride, which means that MTPACl is a well-suited chiral derivatizing reagent.

3.8 OXIDATION OF ALCOHOLS – THE SWERN OXIDATION

3.8.1 Introduction

One of the most valuable reactions of alcohols is their oxidation to yield carbonyl compounds. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones and tertiary alcohols don't react with most oxidizing agents. The method for the oxidation of alcohols employed in the present synthetic study of the C(11)-C(20) unit of fumonisin B_1 was the Swern oxidation, which uses dimethyl sulfoxide as the oxidizing agent. The advantage of this method compared to chromium(VI) reagents such as Jones reagent (chromic acid) or PCC (pyridiniumchlorochromate) are the use of less toxic substances and that further oxidation to the carboxylic acid is not possible with this reagent. One problem is that the by-product (dimethylsulfide) is a volatile liquid with a boiling point of 37°C, and has an unpleasant odour so the work-up needs to be performed in the fumehood. Dimethyl sulfoxide undergoes reactions in which nucleophilic attack occurs on the sulfur atom.[38]



Scheme 3.15: Nucleophilic attack on the sulfur atom of dimethyl sulfoxide

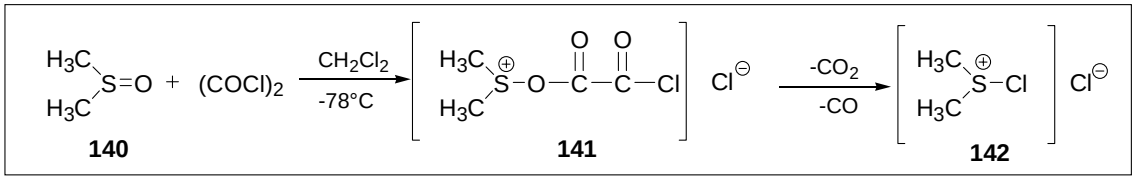
The lone pair of electrons on sulfur, however, cannot be expected to favour the approach of a nucleophile, in spite of the presence of a partial positive charge and vacant d-orbital on the sulfur. It is therefore not surprising that most reactions in which nucleophilic attack takes place readily on sulfur are aided by prior electrophilic attack on the oxygen atom to give (**138**). A nucleophile can now perform a facile displacement on sulfur with the departure of a leaving group as shown in Scheme 3.15. The formation of the sulfonium species (**139**) is usually followed by further reactions. The electrophilic reagents that activate the dimethyl

[38] Mancuso, A.J. and Swern, D. *Synth. Revs*. **1981**, 165.

sulfoxide include: trifluoroacetic acid, thionyl chloride, oxalyl chloride, *t*-butyl hypochlorite, chlorine, acetic anhydride, acetyl chloride, benzoyl, methanesulfonyl and toluenesulfonyl chlorides, carbonochloridates, sulfurtrioxide/pyridine, trifluoromethanesulfonic anhydride, dicyclohexylcarbodiimide, phosphorus pentoxide, polyphosphoric acid, bromine, ethoxy-acetylene and diphenylket-*N*-*p*-tolylimine. The usual nucleophiles are alcohols, phenols, enols, amines and oximes.

3.8.2 Dimethyl sulfoxide – Oxalyl chloride

Oxalyl chloride is the most efficient and generally useful of all the activators examined. It was also found to be superior to trifluoroacetic anhydride as an activator of dimethyl sulfoxide for the conversion of alcohols to their alkoxysulfonium salt, which upon basification results in generally higher and frequently quantitative yields of the corresponding carbonyl compound. The oxalyl chloride reacts violently and exothermically with dimethyl sulfoxide at room temperature, thus successful activation requires low temperatures (–78°C) to form the activated intermediate (**142**) obtained by the spontaneous loss of carbon dioxide and carbon monoxide from (**141**).[41]

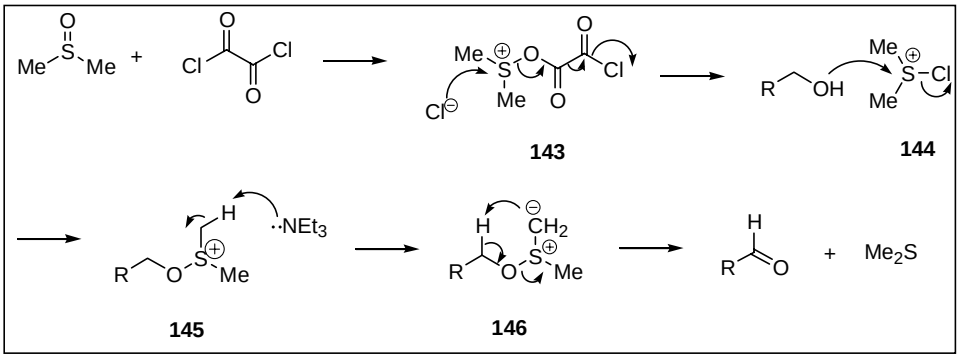


Scheme 3.16: The activation of dimethyl sulfoxide by oxalyl chloride

3.8.3 The Swern oxidation mechanism

The mechanism of the Swern oxidation involves the formation of a dimethylchlorosulfonium ion by reaction of dimethyl sulfoxide with oxalyl chloride at –78°C. The reaction of the alcohol with the dimethylchlorosulfonium ion (**144**) gives a new sulfonium ion (**145**), which is treated with a base, Et_3N. The most acidic proton in the sulfonium ion is located on the carbon atom α to the positively charged sulfur atom and is abstracted as the formed carbanion can be stabilized by the positive charge on the sulfur. This carbanion (**146**) then removes a proton on the carbon adjacent to the oxygen atom derived from the alcohol, creating a flow of electrons

towards the positively charged sulfur. The end products of this process are the aldehyde and dimethyl sulfide.[39]



Scheme 3.17: The Swern oxidation mechanism

3.9 THE PROTECTION OF ALCOHOLS

3.9.1 Introduction

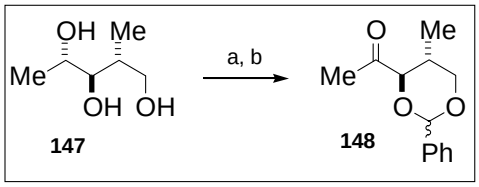
During the synthesis of complex molecules, one functional group may interfere with the intended reaction of a second functional group elsewhere in the same molecule. When this kind of incompatibility arises other reactive sites must be temporarily blocked. There are a number of requirements that must be fulfilled by a protective group: it must react selectively in good yields to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available and preferably nontoxic reagents that do not attack the regenerated functional group. It should form a derivative (without the generation of new stereogenic centers) that can easily be separated from the byproducts associated with its formation or cleavage. The protective group should have a minimum of additional functionality to avoid further sites of reaction.

3.9.2 The protection of 1,2- and 1,3-diols

The prevalence of diols in synthetic planning and in natural sources has led to the development of a number of protective groups of varying stability to a substantial array of reagents. Dioxolanes and dioxanes are the most common protective groups for diols. In some cases the formation of a dioxolane or dioxane ring can result in the generation of new

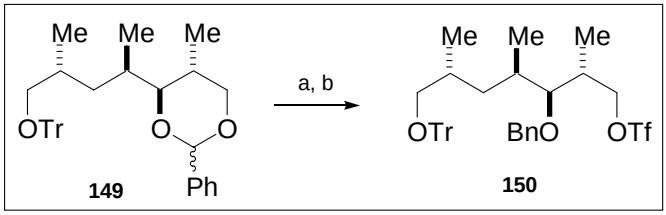
[39] Tenza, K. M.Sc. Dissertation, *Studies on the stereoselective synthesis of the C_{20} backbone of fumonisin B_3 and B_4 using Sharpless methodology*, University of Pretoria, **2001.**

stereogenic centres, either with complete selectivity or as a mixture of two possible isomers. A benzylidene acetal is a commonly used protective group for 1,2- and 1,3-diols. Tsunashima *et al.*[40] also used this protection to selectively protect the triol (**147**) as its benzylidene acetal using dimethoxytoluene. The remaining hydroxyl group was oxidized with PCC to give the methyl ketone (**148**).



Scheme 3.18 Protection of 1,3-diols as the benzylidene acetal

Reagents: (a) $PhCH(OMe)_2$, CSA, DMF; (b) PCC, 3Å molecular sieves , CH_2Cl_2.



Scheme 3.19: Benzylidene acetal cleavage using DIBALH

Reagents: (a) DIBALH, toluene; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C.

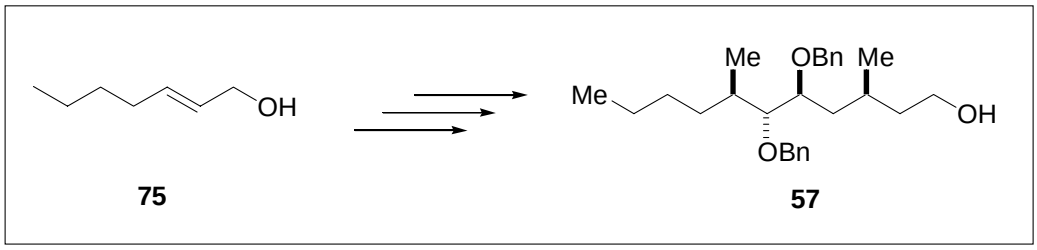
The benzylidene acetal has the advantage that it can be removed under neutral conditions by acid hydrolysis. Benzyl groups and isolated olefins have been hydrogenated in the presence of 1,3-benzylidene acetals. The benzylidene acetal of 1,2-diols is more susceptible to hydrogenolysis than those of 1,3-diols. Benzylidene acetals have the useful property that one of the two C-O bonds can be selectively cleaved. The direction of cleavage is dependent upon steric and electronic factors, as well as on the nature of the cleavage reagent. DIBALH in dichloromethane at 0°C yields generally ≥80% of the least hindered alcohol as illustrated in Scheme 3.3 with (**150**) being the favorable product.

[40] Tsunashima, K.; Ide, M.; Kadoi, H.; Hirayama, A. and Nakata, M. *Tetrahedron Lett.* **2001**, *42*, 3607.

4 SYNTHETIC STUDIES ON THE C(10)–C(20) UNIT OF THE FUMONISINS

4.1 INTRODUCTION

Retrosynthetic analysis of the C_{20} backbone **(56)** of fumonisin B_1 as outlined in Chapter 2 indicated that 2-heptenol **(75)** could serve as the starting material for the synthesis of the C(10)–C(20) unit (**57**). The four stereogenic centres present in this unit are common to all the known fumonisins and a synthetic route for (**57**) would thus be of importance for the synthesis of each of the known fumonisin mycotoxins. In this chapter the methodologies used for the creation of the four stereogenic centres *viz.* Sharpless asymmetric epoxidation followed by nucleophilic opening of the formed chiral epoxide, is discussed. Protection of the functional groups played a crucial role at various stages in this synthetic route.



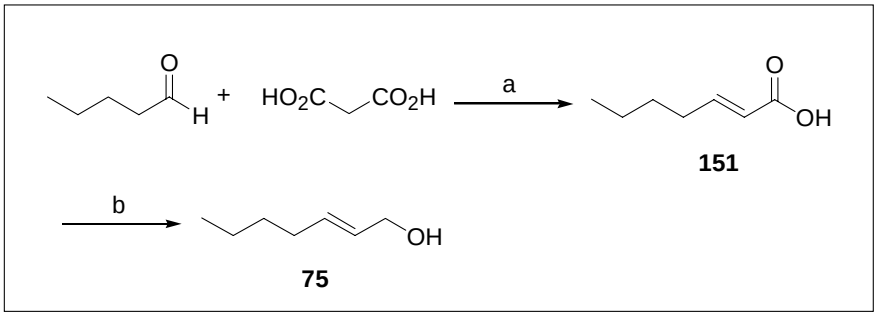
75 **57**

4.2 THE SYNTHETIC ROUTE TOWARDS THE C(10)–C(20) UNIT OF FUMONISIN B_1

4.2.1 Synthesis of (*E*)-2-hepten-1-ol (75)

The first step in the present study was the synthesis of the starting material 2-hepten-1-ol **75**, required for the introduction of two of the stereogenic centres via the epoxidation methodology. Several approaches were tried to accomplish this. The initial route to the synthesis of 2-hepten-1-ol is illustrated in Scheme 4.1 and involves the formation of the α,β-unsaturated acid (**151**) using a Knoevenagel-Doebner reaction. Thus on addition of piperidine to a solution of valeraldehyde and malonic acid in pyridine a condensation reaction occurs with concomitant loss of CO_2 and 2-heptenoic acid (**151**) was formed in 86% yield. The

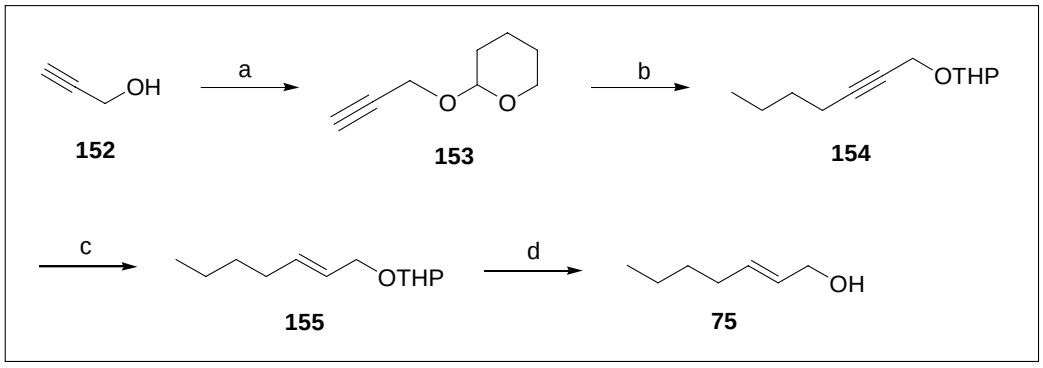
formation of the α,β-unsaturated acid with the *E* configuration was evident from the coupling constant of 15.5 Hz observed for the C(2) signal at δ_H 5.782 (dt) and the C(3) signal at δ_H 7.046 (dt). The ^{13}C NMR spectrum showed the signals of the carbons of the double bond at δ_C 152.30D [C(3)] and 120.65D [C(2)]. The carbonyl carbon signal appeared δ_C 172.23S. The reduction of the 2-heptenoic acid with $LiAlH_4$ in diethyl ether resulted in the formation of a mixture of products from which the required 2-hepten-1-ol (**75**) could not be separated. An alternative synthesis was therefore considered.



Scheme 4.1: The formation of 2-hepten-1-ol (**75**)

Reagents: a) Pyridine, piperidine, 90°C (86%); b) $LiAlH_4$.

The alternative route involved propargyl alcohol (**152**) as starting material (see Scheme 4.2).[1] Protection of the hydroxy group of (**152**) as the tetrahydropyranyl (THP) ether

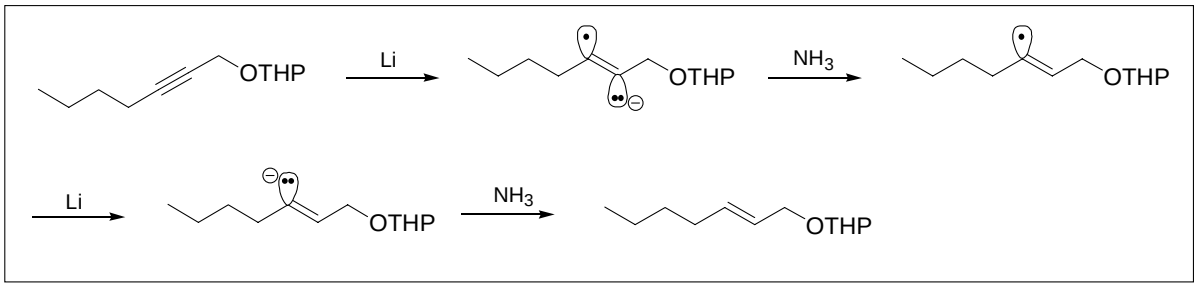


Scheme 4.2: The formation of 2-hepten-1-ol (**75**) via the acetylene route

Reagents: a) Dihydropyran, PPTS, CH_2Cl_2 (65 %); b) i. BuLi, THF, –78°C; ii. 1-iodobutane; c) Li, liq. NH_3; d) H_3O^+.

[1] Wang, Z.-M and Shen, M. *Tetrahedron: Asymmetry*, **1997**, *8*, 3393.

(**153**) was accomplished in 65% yield on treatment with dihydropyran and pyridinium *p*-toluenesulfonate (PPTS). Treatment of (**153**) with BuLi results in the removal of the acidic acetylenic proton and the formation of a carbanion which can be used in an S_N2 reaction with iodobutane to form the C_7 acetylene (**154**). The acetylene **154** would then be reduced with lithium metal in liquid ammonia in two one-electron transfer steps as shown in Scheme 4.3: the first transfer yields a radical anion which abstract a proton from the ammonia solvent to give vinylic radical. The latter is transformed by a second one-electron transfer into a vinylic anion which is quenched by the liquid ammonia solvent to give the *E* double bond.



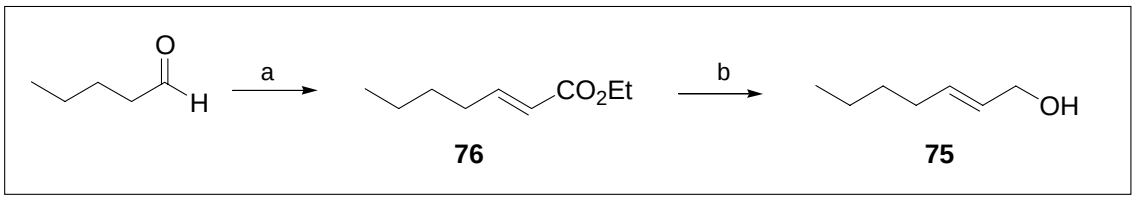
Scheme 4.3: Mechanism of alkyne reduction by Li/ liq.NH_3

The synthesis of compound (**154**) was not successful because the product obtained in the attempted alkylation step of the acetylene (**153**) was a complex mixture and from the ^{1}H NMR spectrum there was no indication that compound (**154**) had been produced. This prompted a decision to attempt another route for the synthesis of 2-heptenol.

The third approach toward the synthesis of (*E*)-2-hepten-1-ol (**75**) involved the Wadsworth-Emmons methodology[2,3] (see Chapter 3) and the synthetic pathway is illustrated in Scheme 4.4. The ethyl (*E*)-2-heptenoate (**76**) was formed in 93% yield when a vigorously stirred mixture of valeraldehyde and triethylphosphonoacetate was treated with aqueous potassium carbonate solution. The presence of the ethyl ester functionality in the product was confirmed by the triplet signal at δ_H 1.251 (J 7.0 Hz) and the quartet at δ_H 4.149 (J 7.0 Hz) in the ^{1}H NMR spectrum. The presence of the carbon-carbon double bond was confirmed by the doublet of triplet signals at δ_H 5.776 ($J_{2,3}$ 15.8, and $J_{2,4}$ 1.6 Hz, C(2)) and δ_H 6.429 ($J_{2,3}$ 15.8, and $J_{3,4}$

[2] Villieras, J. and Rambaud, M. *Organic Synthesis* **1983**, 300.
[3] Wadsworth Jr., W.S. and Emmons W.D., *J. Am. Chem. Soc*. **1961**, *83*, 1732.

7.0 Hz, C(3)). The observed value of 15.8 Hz for the coupling constant of the two olefinic protons established the *E* configuration for the double bond. The signals for the carbon atoms of the α,β-unsaturated ester moiety appeared at δ_C 121.20D [C(2)], 149.13D [C(3)] and 166.55S [C(1)] in the ^{13}C NMR spectrum.



Scheme 4.4: Formation of (*E*)-2-hepten-1-ol (**75**) using Wadsworth-Emmons methodology

Reagents: a) $(EtO)_2P(O)CH_2CO_2Et$, aq. K_2CO_3 (93%); b) DIBALH, THF, –78°C (79%).

The conversion of ethyl (*E*)-2-heptenoate (**76**) to (*E*)-2-hepten-1-ol (**75**) was achieved by reduction using two equivalents of DIBALH at –78°C. DIBALH was chosen because of its strong Lewis acidity character and the bulky isobutyl groups which ensure that the coordination of the DIBALH with the carbonyl oxygen is the dominant factor controlling the rate and regioselectivity of the reaction: only 1,2-reduction occurs.[4] This is in contrast to $LiAlH_4$: the reduction of α,β-unsaturated esters with $LiAlH_4$ proceeds in many cases by both a 1,2- and a 1,4-reduction step. The DIBALH experimental procedure produced the allylic alcohol (*E*)-2-hepten-1-ol (**75**) in an overall yield of 79%. The successful reduction of the α,β–unsaturated ester moiety was evident from the ^{1}H and ^{13}C NMR spectra. The broad singlet due to the OH group appeared at δ_H 1.45 in the ^{1}H NMR spectrum and the methylene protons of the newly-formed hydroxymethyl group at 4.057 (dt, 2H, $J_{1,2}$ 4.9, J 1.0, H-1). The corresponding signal for the C(1) atom appeared at δ_C 63.23T in the ^{13}C NMR spectrum whereas the olefinic carbon atoms now appeared at δ_C 132.83D (C-3) and 128.79D (C-2).

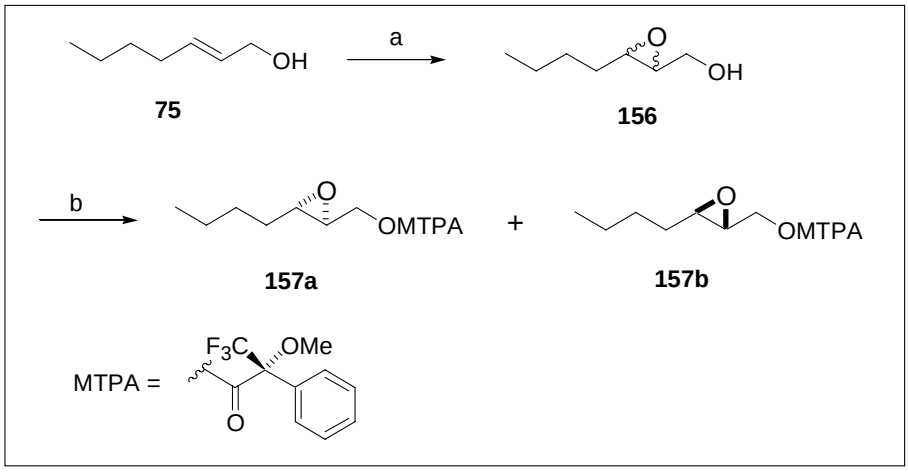
4.2.2 Synthesis of (2*S*,3*S*)-2,3-epoxyheptan-1-ol (74)

The allylic alcohol (**75**) is a key intermediate in the synthesis of the C(10)–C(20) unit (**57**) and it was envisaged that the stereogenic centres in this unit could be introduced using the

[4] Seyden-Penne J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd Ed., VCH Publishers, Weinheim, **1997**.

Sharpless asymmetric epoxidation methodology.[5] The epoxidation reaction occurs with *syn* stereoselectivity and it is therefore only necessary to establish the enantioselectivity that is achieved in the Sharpless epoxidation reaction as the absolute stereochemistry follows from the stereochemistry of the tartrate ester used in the experiment.

In order to facilitate the determination of the enantioselectivity in the Sharpless epoxidation experiment using ^{19}F NMR data, it was necessary to prepare a sample of the racemic epoxide (**156**)(see Scheme 4.5). Thus the achiral allylic alcohol (**75**) was epoxidised using *m*-chloro-peroxybenzoic acid (MCPBA) to give the racemic epoxy alcohol (**156**). The C(1) protons each appeared as a double doublet at δ_H 3.547 ($J_{1a,1b}$ 12.5, $J_{1b,2}$ 4.5) and 3.739 ($J_{1a,1b}$ 12.5, $J_{1a,2}$ 2.5). The signals at δ_H 2.872 (ddd, 1H, $J_{2.3}$ 2.3, $J_{2,1a}$ 2.6, $J_{2,1b}$ 4.4 Hz) and 2.891 (dt, 1H, $J_{2.3}$ 2.3, $J_{3,4}$ 5.4 Hz) were assigned to the C(2) and C(3) epoxide protons, respectively. In the ^{13}C NMR spectrum the corresponding signals for the epoxy alcohol moiety appeard at δ_C 61.74T [C(1)], 58.54D [C(3)] and 56.02D [C(2)]: the last two values are characteristic for an epoxide.



Scheme 4.5: Formation of the Mosher acid derivative of the racemic epoxy alcohol (**156**).

Reagents: a) MCPBA, CH_2Cl_2 (62%); b) (*S*)-MTPA-Cl, Et_3N, CH_2Cl_2 (64%).

The racemic epoxy alcohol (**156**) was converted to the (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate [(*R*)-MTPA] derivative by the protocol developed by Ward and Rhee.[6] A solution of (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid in a mixture of DMF-hexane

[5] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H. and Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

[6] Ward, D.E.; Rhee, C.K. *Tetrahedron Lett.*, **1991**, *32*, 7165.

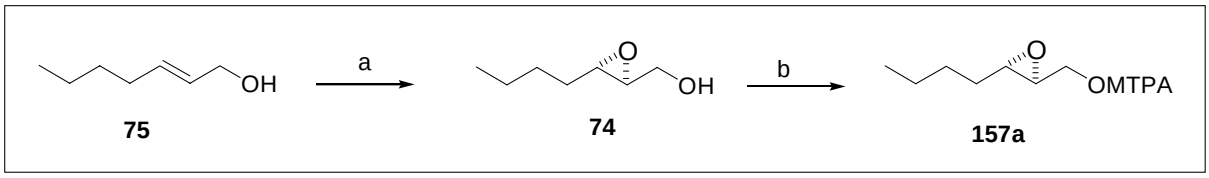
was converted to the (*S*)-acid chloride by addition of oxalyl chloride and stirring for 1 h at room temperature. The presence of hexane was beneficial as the DMFCl contaminant that forms, precipitates and can be removed by filtration. A solution of the epoxy alcohol in CH_2Cl_2 and Et_3N was added to the solution of the Mosher (*S*)-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 as a mixture of the two diastereomers (**157a**) and (**157b**). The two sets of signals for the two diastereomers were readily discernible in the ^{1}H NMR spectrum but signals could not be assigned to the protons of a specific diastereomer. The C(1) protons of the two diastereomers appeared as four double doublets at δ_H 4.208 ($J_{1a,1b}$ 11.9, $J_{1b,2}$ 5.7 Hz), 4.217 ($J_{1a,1b}$ 11.9, $J_{1b,2}$ 6.1 Hz), 4.505 ($J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.4 Hz) and 4.542 ($J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.6 Hz). The signals at δ_H 2.963 (ddd, 1H, $J_{1b,2}$ 6.0, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1 Hz) and 2.990 (ddd, 1H, $J_{1b,2}$ 5.7, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1 Hz) were assigned to the epoxide C(2) protons. Extensive overlap of the signals in the ^{1}H NMR spectrum implied that none of the signals could be used for quantitative determination of the enantiomeric excess (e.e.) obtained in the Sharpless epoxidation reaction.

The ^{19}F NMR spectrum in contrast showed only two well separated signals at δ_F −72.15 and −72.22 in a *ca.* 1:1 ratio.

The allylic alcohol (**75**) can be stereoselectively converted to either a (2*S*,3*S*)- or (2*R*,3*R*)-2,3-epoxyheptanol in a Sharpless asymmetric epoxidation[7] reaction. 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 3. The required (2*S*,3*S*)-epoxyheptanol (**74**) for the present route can be obtained if epoxidation occurs on the *Re* face of the allylic double bond and this will be the case if diethyl (*R*.*R*)-tartrate [(*R*,*R*)-DET] is used. Treatment of the allylic alcohol (**75**) with the Ti catalyst formed from Ti(IV) isopropoxide, (*R*,*R*)-DET and *t*-butylhydroperoxide in CH_2Cl_2 at −20°C led to the formation of the (2*S*,3*S*)-epoxy alcohol (**74**) in 61% yield (Scheme 4.6). Only a single set of signals was observed in the ^{1}H NMR spectrum. The enantioselectivity of the reaction was determined by

[7] Hill, J.G.; Sharpless, K.B.; Exon, M.C. and Regenye, R. *Org. Synth*. **1985**, *63*, 66.

conversion of the epoxy alcohol (**74**) to the (*R*)-α-methoxy-α-trifluoromethylphenylacetate derivative (**157a**) and ^{1}H and ^{19}F NMR spectroscopy of the product.



Scheme 4.6: Sharpless asymmetric epoxidation of the allylic alcohol (**75**).

Reagents: a) (*R,R*)-DET, Ti(*i*PrO)$_4$, *t*-BuOOH (61%); b) oxalyl chloride, (*S*)–MTPA-Cl, Et_3N, CH_2Cl_2 (43%).

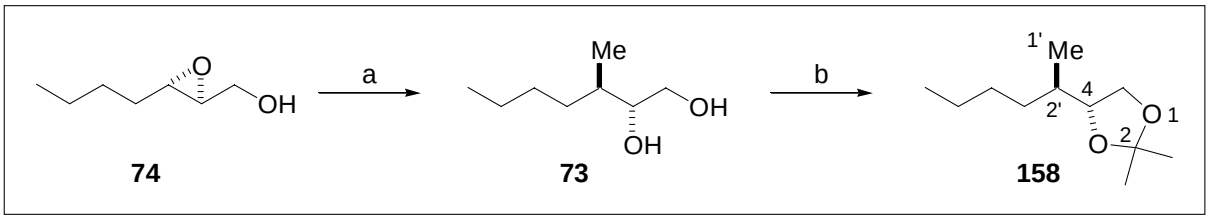
The ^{1}H NMR spectrum of the Mosher ester (**157a**) showed the signal of the C(3) proton at δ_H 2.818 (dt, $J_{2,3}$ 2.1, $J_{3,4}$ 5.7 Hz) and that of the C(2) proton at δ_H 2.984 (ddd, $J_{1b,2}$ 5.7, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1 Hz). A geminal coupling of 11.9 Hz was observed for the C(1) methylene protons at δ_H 4.202 (dd, $J_{1a,1b}$ 11.9, $J_{1b,2}$ 5.7 Hz, H-1b) and 4.536 (dd, $J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.6 Hz, H-1a). The ^{19}F spectrum showed a single peak at δ_F −72.22. With the knowledge of the ^{19}F chemical shifts of the two possible diastereomers to hand it was possible to determine the enantioselectivity of the epoxidation reaction as *ca.* 100% e.e.

4.2.3 Synthesis of (2*R*,3*R*)-3-methylheptan-1,2-diol (73)

The epoxide ring of the (2*S*,3*S*)-2,3-epoxyheptan-1-ol **74** was opened using Me_3Al.[8,9] The reaction is both regio- and stereoselective: the introduction of the methyl group at C(3) is an S_N2 reaction that occurs with inversion of configuration from the less hindered side at C(3) due to steric hindrance (see discussion in Chapter 3). The reaction selectively produced the 3-methylheptan-1,2-diol with the (2*R*,3*R*) configuration in 79% yield. The ^{1}H NMR was characterized by the overlap of the H(1) and H(2) signals and thus did not provide any indication as to whether epoxide ring opening had occurred to form a 1,2- or a 1,3-diol. The newly introduced methyl group appeared as a doublet at δ_H 0.848 (7.0 Hz). The ^{13}C spectrum

[8] Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K. and Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
[9] Oka, T. and Murai O. *Tetrahedron Lett*. **1998**, *54*, 10.

showed the signals of both a methine and a methylene oxygen-bearing carbon atom at δ_C 76.26D (C-2) and 64.59T (C-1), respectively.



Scheme 4.7: Epoxide ring opening using Me_3Al.

Reagents: a) Me_3Al, hexane, 0°C (79%); b) $MeC(OMe)_2Me$, TsOH (77%).

Acetonides (also known as isopropylidene acetals) have been extensively used in the protection of 1,2- and 1,3-diol systems. Their characteristic ^{13}C chemical shifts have been used in the assignment of the relative stereochemistry of 1,3-diol systems in complex natural products.[10] The ^{13}C chemical shift value for the quaternary acetal carbon atom in 1,3-diol acetonides (dioxanes) is in the range of 98-100 ppm whereas that of the 1,2-diol acetonides (dioxolanes) appear in the range of 108-114 ppm.[11,12] The two systems can thus be readily differentiated on the basis of ^{13}C chemical shift values.

The acetonide derivative (**158**) of the ring-opened diol (**73**) was prepared by acid catalysed treatment (TsOH) with 2,2-dimethoxypropane. The protons of the dioxolane ring system were well resolved: the C(5) protons appeared at δ_H 3.563 (dd, $J_{5b,4}$ 7.3, $J_{5a,5b}$ 7.8 Hz) and 3.950 (dd, $J_{5a,4,}$ 6.2, $J_{5a,5b}$ 7.8 Hz) and H(4) at δ_H 3.838 (dt, $J_{5a,4}$ 6.2, $J_{4,\,2'}$ 7.3, $J_{5b,4}$ 7.3 Hz). The singlet signal at δ_C 108.57 in the ^{13}C NMR spectrum was highly diagnostic and established that ring opening of the epoxide had occurred with the formation of a 1,2-diol system.

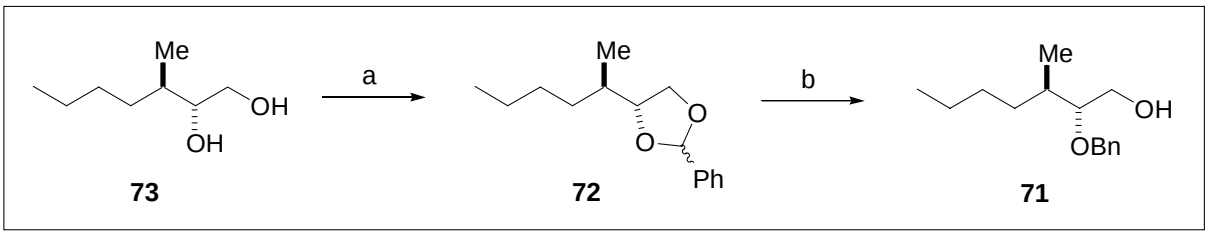
4.2.4 Synthesis of (2*R*,3*R*) 2-benzyloxy-3-methylheptan-1-ol (71)

The retrosynthetic analysis of the C(10)-C(20) synthetic target (**57**) (see Chapter 2) clearly identified the need for protection of some of the hydroxyl groups during the course of the

[10] Rychnovsky, S.D.; Rogers, B. and Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
[11] Evans, D.A.; Reiger, D.L. and Gage, J.R. *Tetrahedron Lett.* **1990**, *31*, 7099.
[12] Kocienski, P.J. *Protecting Groups*, 3rd Ed., Thieme Verlag, Stuttgart, **2005**.

synthesis. The benzyl group was selected as it is stable to the many reaction conditions employed in subsequent steps in the synthetic route. Selective protection of a secondary hydroxyl group as the benzyl ether in the presence of a primary hydroxyl group in a 1,2- or 1,3-diol system can be achieved through conversion of the 1,2-diol to the benzylidene derivative followed by reductive ring opening using DIBALH.[13,14]

The 3-methylheptan-1,2-diol (**73**) was successfully converted to the benzylidene derivative by reaction with α,α-dimethoxytoluene in dichloromethane in the presence of *p*-toluenesulfonic acid (Scheme 4.8). The ^{1}H NMR analysis of the product confirmed the presence of a 1:1 mixture of two diasteromers as a result of the formation of the acetal stereogenic centre. This was evident from the two sets of signals present in the ^{1}H spectrum and especially the two singlet signals at δ_H 5.783 and 5.908 for the acetal C(2) proton. The acetal C(2) carbon signal appeared at δ_C 103.87D and 103.45D (C-2) and that of C(4) at δ_C 81.58D and 80.81D, and C(5) at δ_C 69.04T and 68.08T.



Scheme 4.8: The formation of (2*R*,3*R*)-2-benzyloxy-3-methylheptan-1-ol (**71**)

Reagents: a) $PhCH(OMe)_2$,TsOH (54%); b) DIBALH, CH_2Cl_2, –78°C (89%).

Reductive ring opening of the benzylidene (**72**) with DIBALH[15,16,17] proceeds through preferential complexation of the aluminium atom with O(1) due to the steric bulk of the isobutyl groups. Cleavage of the C(2)–O(1) results in the formation of the O(3) oxonium ion which undergoes reduction through intramolecular hydride transfer from the aluminium anion (see Scheme 4.9) to give the secondary *O*-benzyl ether (**71**) in 89% yield.

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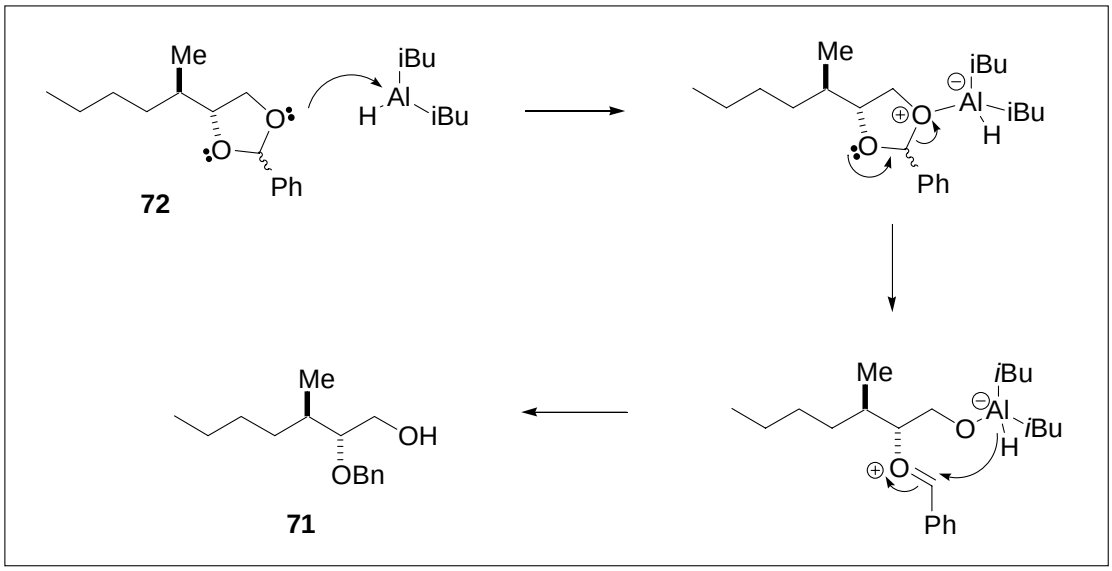
[13] Smith, A.B.; Hale, k.J.; Laakso, L.M.; Chen, k.; Riera, A. *Tetrahedron Lett.* **1989**, *30*, 6963.
[14] Evans, D.A.; Kaldor, S.W.; Jones, T.K.; Clardy, J.; Stout, T.J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
[15] Blakemore, P.R.; Schulze, V.K. and White J.D. *J. Chem. Soc., Chem. Commun*. **2000**, 1262.
[16] Liptak, A.; Imre, J.; Harungi, J. and Neszmelyi, A. *Tetrahedron Lett*. **1982**, *38*, 373.
[17] Marshall, J.A.; Trometer, J.D.; Blough, B.E. and Crute, T.D. *J. Org. Chem*. **1988**, *33*, 4273.



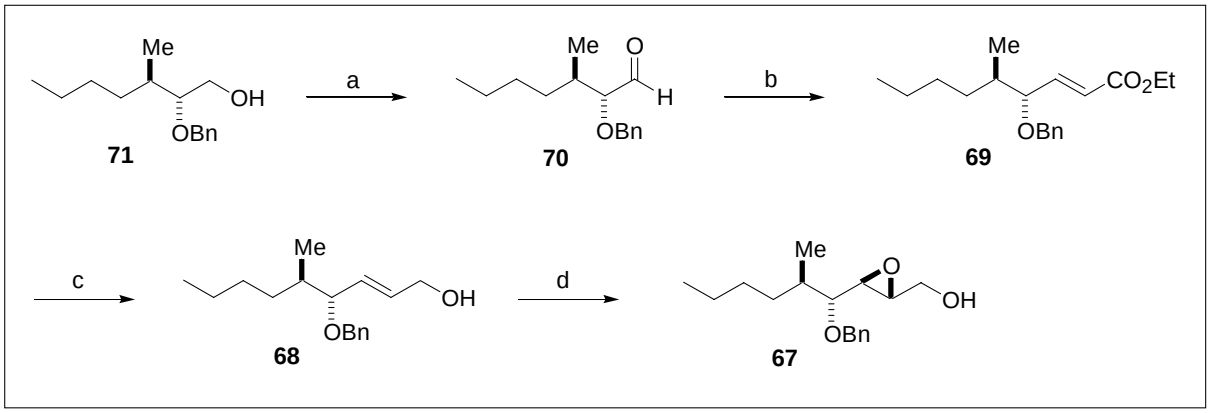
Scheme 4.9: Mechanism of the benzylidene reductive ring opening reaction.

The benzylic protons appeared as an AB spin system (J 11.4 Hz) at δ_H 4.513 and 4.616. The C(1) protons were each present as a double doublet at δ_H 3.600 ($J_{1a,1b}$ 11.6, $J_{1b,2}$ 6.7 Hz) and 3.667 ($J_{1a,1b}$ 11.6, $J_{1a,2}$ 3.5 Hz). The signal at δ_H 3.350 (ddd, 1H, $J_{1a,2}$ 3.5, $J_{1b,2}$ 6.7, $J_{2,3}$ 5.7 Hz) was assigned to H-2. A (^{13}C,^{1}H) heteronuclear (HETCOR) chemical shift correlation experiment established the assignment of the corresponding ^{13}C signals at δ_C 83.87D [C(2)]; 72.00T (OCH_2Ph) and 61.58T [C(1)].

4.2.5 Synthesis of (2*R*,3*R*,4*R*,5*R*)-4-benzyloxy-2,3-epoxy-5-methylnonan-1-ol (67)

The primary alcohol (**71**) served as the starting material for a two-carbon chain extension procedure and the subsequent introduction of a further two stereogenic centres using once again Sharpless asymmetric epoxidation (see Scheme 4.10). The first step in this sequence involved the oxidation of the primary hydroxyl group of (**71**) to an aldehyde group in 90% yield using Swern oxidation. The presence of an aldehyde moiety in (**70**) was evident from the doublet signal at δ_H 9.658 ($J_{1,2}$ 2.8 Hz) in the ^{1}H spectrum and the corresponding signal for the aldehyde carbon atom at δ_C 204.11D in the ^{13}C spectrum. The C(2) proton was a double doublet at 3.518 (dd, 1H, $J_{2,3}$ 5.7, $J_{1,2}$ 2.8, H-2) and the corresponding carbon at δ_C 87.54D. The benzylic protons formed an AB spin system (J 11.8 Hz) at δ_H 4.476 and 4.658.

In all cases samples of the aldehyde (**70**) were used directly in the next step in which the C_7 chain was extended to a C_9 chain by Wadsworth-Emmons methodology using potassium *t*-butoxide and triethylphosphonoacetate. The *E*-α,β-unsaturated ester (**69**) was obtained in 62% yield together with small quantities of the *Z* isomer.



Scheme 4.10: The formation of (2*R*,3*R*,4*R*,5*R*)-4-benzyloxy-2,3-epoxy-5-methylnonan-1-ol (**67**).

Reagents: a) Swern oxidation (90%); b) $(i\text{PrO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$, aq. K_2CO_3 (62%); c) DIBALH, THF, –78°C, (51%); d) (*S*,*S*)-DET, $\text{Ti}(i\text{PrO})_4$, *t*BuOOH (79%)

The formation of the *E* diastereomer (**69**) was evident from the coupling constant of 15.8 Hz for the signals of the double bond protons at δ_H 6.846 (dd, $J_{2,3}$ 15.8, $J_{3,4}$ 6.7 Hz, H-3) and δ_H 5.993 (dd, $J_{2,3}$ 15.8, $J_{2,4}$ 1.3, H-2) in the ^{1}H NMR spectrum. The magnitude of the coupling constant of 11.9 Hz is typical for the C(3) and C(2) protons of the *Z* stereoisomer (**69a**) which appeared as double doublets at δ_H 6.118 ($J_{3,4}$ 9.3, $J_{2,3}$11.9 Hz, H-3) and δ_H 5.946 ($J_{2,4}$ 1.0, $J_{2,3}$ 11.9 Hz, H-2). The ^{13}C signals of the two diastereomeric α,β-unsaturated ester moieties of (**69**) and (**69a**) was far less diagnostic: for the *E* stereoisomer the C(1) signal, the ester carbonyl carbon atom, was observed at δ_C 166.18S and the double bond carbons at δ_C 123.09D [C(2)] and δ_C 147.21D [C(3)]. The signals for the same carbon atoms of the *Z* stereoisomer were found at δ_C 166.01S [C(1)], 122.37D [C(2)] and 149.12D [C(3)].

The *E*-α,β-unsaturated ester (**69**) was next subjected to DIBALH reduction to produce the allylic alcohol (**68**). The structure and configuration of the newly-formed allylic alcohol (**68**)

was verified by analysis: the proton-proton connectivity pattern was established by analysis of the signals observed in the ^{1}H NMR spectrum and the cross-peaks in a COSY experiment. The signals of the proton-bearing carbon atoms were correlated with the proton chemical shifts in order to assign the signals in the ^{13}C NMR spectrum. The *E* configuration of the double bond was once again indicated by the 15.5 Hz coupling constant for the C(3) and C(2) proton signals at δ_H 5.600 (ddt, $J_{2,3}$ 15.5, $J_{3,4}$ 8.0, $J_{1,3}$ 1.4 Hz, H-3) and δ_H 5.784 (ddt, $J_{2,3}$ 15.5, $J_{2,4}$ 0.8, $J_{1,2}$ 5.4, H-2). Although the C(1) protons are diastereotopic and thus should have different chemical shifts, in this instance chemical shift equivalence caused this signal to appear as a two-proton double doublet at δ_H 4.169 ($J_{1,2}$ 5.4, $J_{1,3}$ 1.4 Hz, H-1) due to coupling with H(2) and H(3). The C(4) proton appeared as a double doublet at δ_H 3.569 ($J_{4,5}$ 6.1, $J_{3,4}$ 8.0 Hz). The signals of the olefinic carbon atoms at δ_C 132.77D (C-2) and 130.37D (C-3) were identified in a HETCOR experiment through their correlations with the assigned proton signals. The signals at δ_C 83.61D and 70.28T were assigned to C(4) and C(1), respectively.

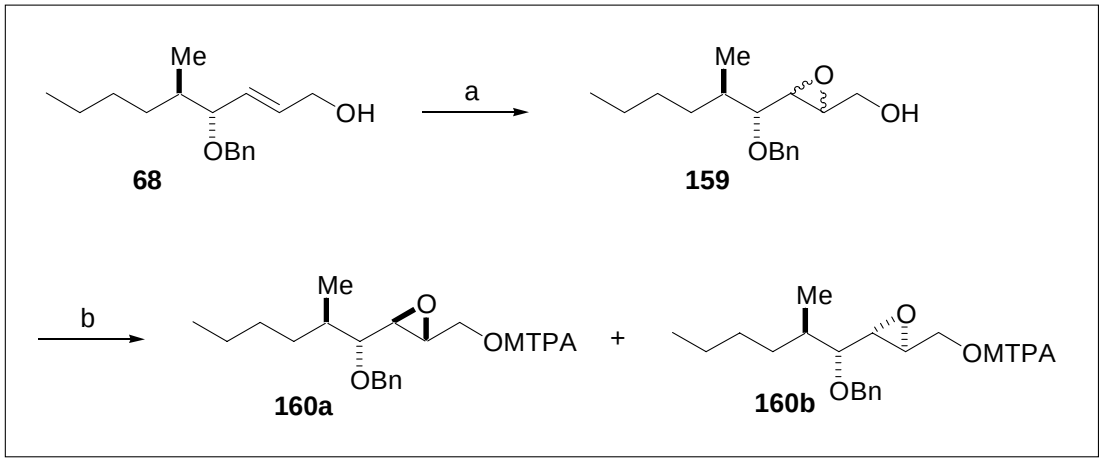
The required (2*R*,3*R*)-epoxy alcohol (**67**) for the present synthetic route can be obtained if epoxidation occurs on the *Si* face of the allylic double bond in (**68**) and this will be the case if diethyl (*S*.*S*)-tartrate [(*S*,*S*)-DET] is used. Treatment of the allylic alcohol (**75**) with the Ti catalyst formed from Ti(IV) isopropoxide, (*S*,*S*)-DET and *t*-butylhydroperoxide in CH_2Cl_2 at –20°C led to the formation of the (2*R*,3*R*)-epoxy alcohol (**67**) in 79% yield (Scheme 4.10). The signals of the C(1) protons appeared as broad unresolved humps in the ^{1}H NMR spectrum as a result of coupling with the exchangeable proton of the hydroxyl group. Sharp signals were observed on addition of D_2O to the sample: each of the protons appeared as a double doublet at δ_H 3.550 ($J_{1a,1b}$ 12.7, $J_{1b,2}$ 4.1 Hz) and 3.838 ($J_{1a,1b}$ 12.7, $J_{1b,2}$ 2.7 Hz). The multiplet signal at δ_H 3.125 (ddd, 1H, $J_{1b,2}$ 4.1, $J_{1a,2}$ 2.7, $J_{2,3}$ 2.3 Hz) was assigned to H(2) on the basis of the cross-peaks in the COSY spectrum. The coupling of 2.3 Hz is typical for a proton of a *trans* epoxide. The other epoxide proton, H(3), was represented by a double doublet at δ_H 3.004 ($J_{3,4}$ 5.2, $J_{2,3}$ 2.3 Hz) and H(4) by the double doublet at δ_H 3.241 ($J_{3,4}$ 5.2, $J_{4,5}$ 4.4 Hz). The C(2) and C(3) signals appeared at δ_C 56.23D and 55.41D, respectively in the ^{13}C NMR spectrum. The signals at δ_C 81.16D [C(4)], 72.95T (OCH_2Ph) and 61.36T [C(1)] were assigned on the basis of their multiplicity and the correlation with the corresponding assigned proton signals.

The signals of only a single diastereomer were discernible in the ^{1}H NMR spectrum of the epoxy alcohol (**67**). However, the enantiofacial selectivity achieved in the Sharpless asymmetric epoxidation reaction had to be assayed using the Mosher ester derivative and ^{19}F NMR spectroscopy. The first step in this process was the preparation of a diasteromeric mixture of the two possible epoxides that can be formed when the allylic alcohol (**68**) is epoxidised with MCPBA (Scheme 4.11). Treatment of the allylic alcohol with MCPBA gave the epoxide (**159**) as a *ca*. 1.2:1 mixture of diastereomers in which the major diastereomer arose from preferential attack on the *Si* face of the double bond as was the case with the Sharpless epoxidation reaction using (*S,S*)-DET. The diasteromeric mixture of epoxy alcohols (**159**) was converted to the (*R*)-α-methoxy-α-trifluoromethylphenylacetate derivatives (**160a**) and (**160b**) with (**160a**) the major diastereomer. Analysis of the ^{19}F NMR spectrum of the mixture of (*R*)-Mosher ester showed two signals at δ_F –72.17 and –72.12 (ratio 64:36).

The ^{19}F NMR spectrum of the (*R*)-α-methoxy-α-trifluoromethylphenylacetate derivative (**160a**) prepared from the epoxy alcohol (**67**) product from the Sharpless epoxidation also showed two signals at δ_F 72.17 (major) and –72.10 (minor) and analysis established the diastereomeric ratio of the epoxides formed in the Sharpless epoxidation as 98:2.

The next step was to reduce the epoxy alcohol **67** regioselectively using Red-Al to give the desired 1,3-diol product **66** a process that leads to the destruction of the unwanted C(2) stereogenic centre as illustrated in Scheme 4.12. The ^{1}H NMR spectrum showed the C(1) protons at δ_H 3.785 (dd, 1H, $J_{1a,1b}$ 10.9, $J_{1b,2}$ 5.0 Hz) and 3.860 (dd, 1H, $J_{1a,1b}$ 10.9, $J_{1b,2}$ 5.2 Hz). The COSY spectrum established the correlation between the H(1) signals and the multiplet at δ_H 1.768 and thus confirmed that (**66**) is in fact a 1,3-diol. The assignment of the signals of the ^{13}C NMR at δ_C 72.42D (C-3), 61.59T (C-1) and 33.65T (C-2) is based on the correlation with the proton signals in a HETCOR experiment as these values taken in isolation can not distinguish between the 1,3- and 1,2-diol system.

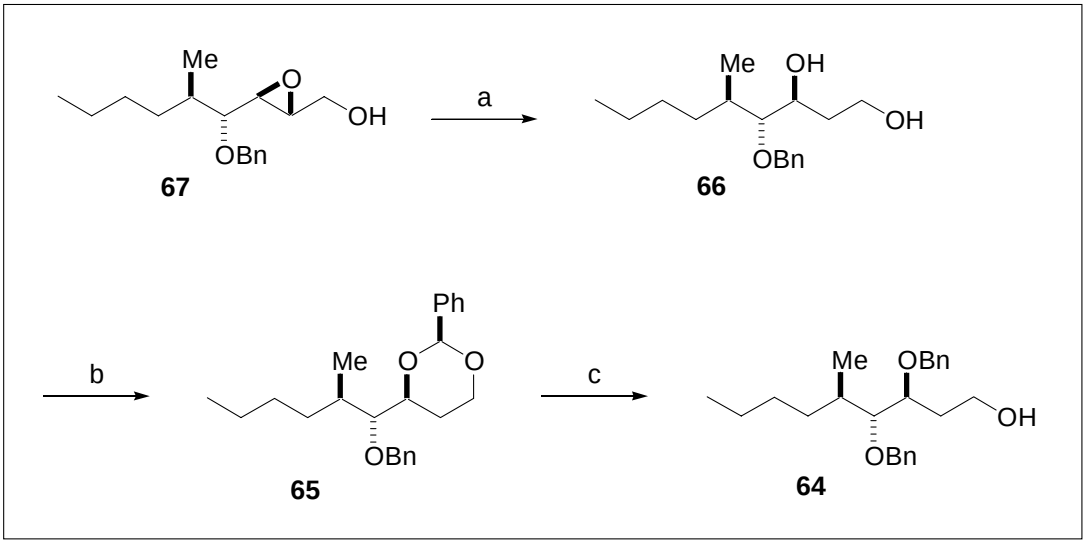
Selective protection of the secondary hydroxyl group as the benzyl ether in the presence of a primary hydroxyl group in the 1,3-diol system of (**66**) was achieved through conversion of the



Scheme 4.11: Preparation of the two diastereomeric epoxy alcohols (**159**) and their (*R*)-Mosher acid derivatives

Reagents: a) MCPBA, CH_2Cl_2 (57%); b) (*S*)-MTPA-Cl, Et_3N, CH_2Cl_2 (65%)

1,3-diol to the benzylidene derivative followed by reductive ring opening using DIBALH.[13,14] The TsOH catalysed reaction of the diol (**66**) with α,α-dimethoxytoluene in dichloromethane resulted in the formation of the benzylidene derivative (**65**). Only a single singlet signal was observed for the C(2) acetal proton at δ_H 5.496 in the ^{1}H NMR spectrum thus indicating that a single diastereomer had been formed. Analysis of the multiplet signals of the dioxane ring at δ_H 1.634 (m, 1H, $J_{5a,5b}$ 13.4 Hz, H-5b) and 2.077 (dddd, 1H, $J_{5a,5b}$ 13.4, $J_{5a,6b}$ 12.5, $J_{4,5a}$ 11.2, $J_{5a,6a}$ 5.2 Hz, H-5a), δ_H 3.963 (ddd, 1H, $J_{5a,6b}$ 12.4, $J_{6a,6b}$ 11.4, $J_{5b,6b}$ 2.6 Hz, H-6b) and 4.303 (ddd, 1H, $J_{6a,6b}$ 11.4, $J_{5a,6a}$ 5.2, $J_{5b,6a}$ 1.4 Hz, H-6a) and δ_H 4.025 (ddd, 1H, $J_{4,5a}$ 11.1, $J_{4,1'}$ 5.2, $J_{4,5b}$ 2.3 Hz, H-4) and especially the magnitude of the vicinal coupling constant of 11.1 Hz between H(4) and H(5) established the chair conformation for the dioxane ring with the C(4) substituent in the equatorial position. The C(2) phenyl group is also in the equatorial position in order to minimize 1,3-diaxial interactions and C(2) must therefore have the *S* configuration. The equatorial disposition of both substituents on the dioxane ring was confirmed by the NOE effect observed in the 2D NOESY experiment between the C(2) and C(4) protons which is only possible if this is the result of a 1,3-diaxial relationship.



Scheme 4.12: The formation of (3*S*,4*R*,5*R*)-3,4-di(benzyloxy)-5-methylnonan-1-ol (**64**)

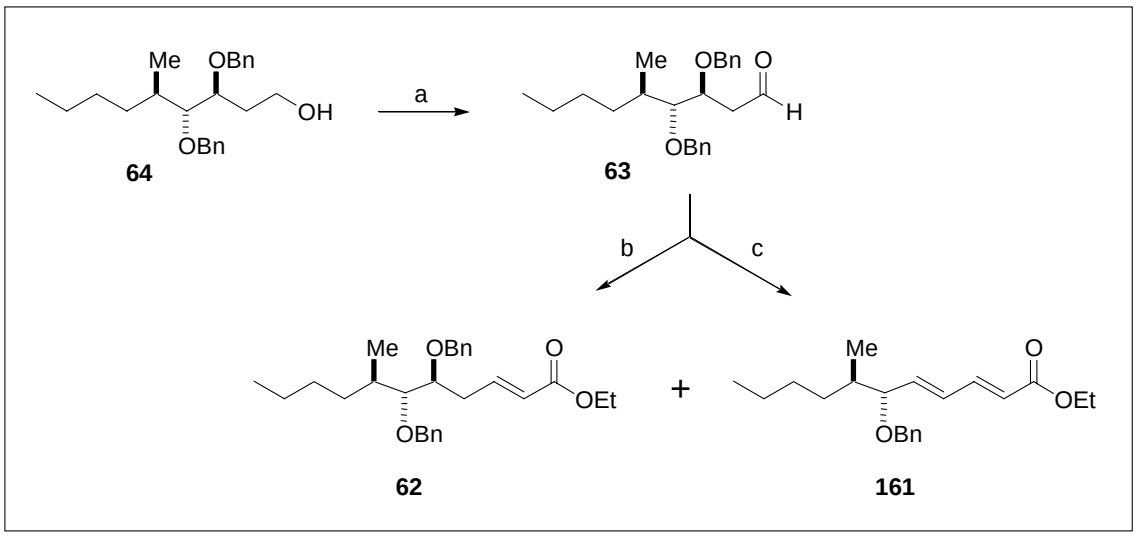
Reagents: a) Red-Al, (59%); b) $PhCH(OMe)_2$,TsOH (80%); c) DIBALH, CH_2Cl_2, –78°C (64%).

Reductive ring opening of the benzylidene (**65**) with DIBALH provided the alcohol (**64**) in 64% yield. The presence of a 1,3-diol moiety protected as a *O*-benzyl ether of the secondary hydroxyl group was evident from the proton-proton connectivity pattern deduced from the ^1H NMR data. The signals of the C(1) protons at δ_H 3.699 (ddd, 1H, $J_{1a,1b}$ 10.9, J 6.7, J 3.9 Hz) and 3.774 (ddd, 1H, $J_{1a,1b}$ 10.9, J 8.8, J 2.8 Hz) showed cross-peaks with the signals at δ_H 1.828 (dddd, 1H, $J_{2a,2b}$ 15.0, J 7.0, J 4.1, $J_{2b,3}$ 3.8 Hz) and 1.968 (dddd, 1H, $J_{2a,2b}$ 15.0, $J_{2a,3}$ 7.6, J 7.0, J 4.1 Hz) which must be assigned to the C(2) protons. The chemical shift values for H(2) established the structure of the compound (**64**) and the regioselectivity of the reductive ring opening reaction. The presence of two benzyl groups was evident from the signals at δ_C 74.49T and 71.44T in the ^{13}C NMR spectrum. The benzylic protons of the two benzyl ethers appeared as AB spin systems at δ_H 4.520 and 4.636 (J 11.6 Hz), and at δ_H 4.569 and 4.857 (J 11.1 Hz).

4.2.6 Synthesis of ethyl (2*E*,5*S*,6*R*,7*R*)-5,6-di-(benzyloxy)-7-methylundec-2-enoate (62)

With three of the required stereogenic centres in place in the di-*O*-benzyl protected alcohol (**64**) the stage was set for a further two-carbon chain extension to a C_{11} unit, using once again Wadsworth-Emmons or Wittig methodology. A structural requirement in the starting material

for this step is the presence of an aldehyde functional group and this was obtained by Swern oxidation of the primary hydroxyl group in (**64**) by Swern oxidation to give the aldehyde (**63**) (Scheme 4.13).



Scheme 4.13: Formation of the α,β-unsaturated ester (**62**) using Wittig methodology

Reagents: a) Swern Oxidation (65%); b) $Ph_3P{=}CHCO_2Et$; c) *t*BuOK, $(EtO)_2P(O)CH_2CO_2Et$

The ^1H NMR spectrum of the aldehyde (**63**) showed the diagnostic signal of the aldehyde proton as a double doublet at δ_H 9.778 ($J_{1,2a}$ 2.5, $J_{1,2b}$ 1.8 Hz) due to coupling with the C(2) protons at δ_H 2.609 (ddd, 1H, $J_{2a,2b}$ 16.8, $J_{2b,3}$ 4.4, $J_{1,2b}$ 1.8 Hz) and 2.806 (ddd, 1H, $J_{2a,2b}$ 16.8, $J_{2a,3}$ 7.0, $J_{1,2a}$ 2.5, H-2a). The signal at δ_C 201.39D was assigned to the carbon of the aldehyde carbonyl group. The presence of two *O*-benzyl groups was indicated by the doublet signals (J 11.4 Hz) at δ_H 4.555, 4.561, 4.572 and 4.758. The ^{13}C signals for the benzylic carbon atoms were found at δ_C 74.21T and 71.71T.

The initial attempt at a two-carbon chain extension reaction of the aldehyde (**63**) used Wadsworth-Emmons methodology: treatment of the aldehyde (**63**) with the anion obtained by the reaction of triethylphosphonoacetate with *t*-BuOK, gave a product that was identified as a diene ester (**161**) by the signals observed in the ^1H and ^{13}C NMR spectra. The protons of the diene system appeared at δ_H 5.874 (d, 1H, $J_{2,3}$ 15.5 Hz, H-2), 6.015 (ddd, 1H, $J_{4,5}$ 15.3, $J_{5,6}$ 7.5, $J_{3,5}$ 0.8 Hz, H-5), 6.302 (dddd, 1H, $J_{4,5}$ 15.5, $J_{3,4}$ 11.1, J 1.0, $J_{4,6}$ 0.8 Hz, H-4) and 7.294 (ddd,

1H, $J_{2,3}$ 15,5, $J_{3,4}$ 11.1, $J_{3,5}$ 0.8 Hz, H-3) and the 2*E*,4*E* configuration of the two double bonds followed from the observed coupling constant of 15.5 Hz. The signal at δ_C 166.97S was assigned to the 2,4-dienoate ester carbonyl carbon and the carbons of the diene appeared at δ_C 143.67D [C(3)], 141.76D [C(5)], 130.41D [C(4)] and 121.41D [C(2)]. The presence of a single AB system (J 11.9 Hz) for the benzylic protons at δ_H 4.330 and 4.545 confirmed that the formation of the C(4)–C(5) double bond involved the loss of one of the *O*-benzyl groups. The γ-proton of the α,β-unsaturated ester intermediate (**62**) is acidic as the anion that is formed can be stabilized by delocalization of the negative charge onto the ester carbonyl group. The formation of the dienoate ester moiety is the driving force for the loss of the benzyloxide anion. In order to prevent the loss of one of the benzyl groups and the formation of the dienoate ester (**161**) in the Wadsworth-Emmons reaction, it is recommended that a weaker base than potassium *t*-butoxide *e.g.* K_2CO_3 is used.

An alternative method for the synthesis of the α,β-unsaturated ester (**62**) that was investigated used the stabilized ylid, ethyl (triphenylphosphoranylidene)acetate, $Ph_3P{=}CHCO_2Et$, in a Wittig reaction with the aldehyde (**63**) to give the desired product (**62**). The presence of the *E* double bond was evident from the coupling constant of 15.7 Hz observed for the H(2) and H(3) signals in the ^{1}H NMR spectrum at δ_H 5.858 (ddd, $J_{2,3}$ 15.7, $J_{2,4a}$ 1.3, $J_{2,4b}$ 1.5 Hz) and 7.054 (ddd, $J_{2,3}$ 15.7, $J_{3,4a}$ 7.2, $J_{3,4b}$ 7.2 Hz), respectively. The presence of two *O*-benzyl groups followed from the two AB spin systems: one at δ_H 4.517 and 4.540 (J 11.5 Hz) and one at δ_H 4.559 and 4.738 (J 11.3 Hz).

The results reported in this dissertation do not constitute a total synthesis for the C(10)–C(20) unit of the fumonisin B_1 backbone. The work does show that the use of the Sharpless methodology offers a viable route. However some problems in the proposed synthetic route have been identified especially the two-carbon chain extension of the aldehyde (**63**) using either Wadsworth-Emmons or Wittig methodology. This aspect could not be further investigated due to a lack of material. The necessary aldehyde (**63**) supply had been exhausted and time constraints did not allow for the synthesis of this material to be repeated. The further investigation of this aspect of the synthetic route must therefore form the basis of a new research project.

5 EXPERIMENTAL

5.1 GENERAL TECHNIQUES

All air-sensitive reactions were carried out under an argon atmosphere using glassware dried overnight in an oven at 120°C. All solvents used in air-sensitive reactions were purified according to standard methods prior to use.[1] Solvents used for chromatography or extractions were distilled. All reactions were monitored by thin layer chromatography (TLC) using aluminium sheets coated with silica gel (60F-254) from Merck. Cerium(IV) sulfate/ ammonium heptamolydate reagent was used as developing reagent and UV light (254 and 236nm) was used to examine the TLC plates. Column chromatography was performed on Merck silica gel 60 (60-200 μm, 70-230 mesh). Eluant volumes are given as v/v. Yields refer to materials purified by column chromatography and their purity was established by NMR spectroscopy and mass spectrometry.

Dr. L. Fourie, University of Potchefstroom, recorded high-resolution fast atom bombardment (FAB) mass spectra on a VG7070-E spectrometer (Xe beam, *m*-nitrobenzyl alcohol matrix, detection of positive ions with $m/z > 99$). 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, respectively). $CFCl_3$ was used as external standard for ^{19}F with negative numbers assigned to highfield 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 assignment of the signals in the ^1H NMR spectra were based on the first-order analysis[2] of the spin systems and were confirmed by two dimensional (2-D) (^1H,^1H) homonuclear (COSY) and (^{13}C, ^1H) heteronuclear (HETCOR) chemical shift correlation experiments. The multiplicities of the different ^{13}C

[1] Perrin, D.D. and Armarego, W.L.F. *Purification of Laboratory Chemicals*, Oxford, **1992.**
[2] Abraham, R.J., Fisher, J. and Loftus, P. *Introduction to NMR Spectroscopy*, John Wiley & Sons, New Delhi, **1988.**

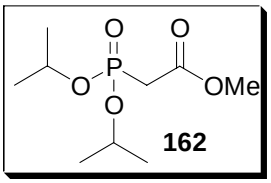
resonances were deduced from proton-decoupled CH, CH_2, and CH_3 subspectra obtained by using the DEPT pulse sequence.

5.2 SPRAYING REAGENT

Cerium(IV) sulfate spray

A spray solution of ammonium heptamolybdate (5%) and cerium(IV) sulfate (0.2%) in 3M sulfuric acid was prepared by heating and continous stirring. The solution was cooled and filtered.

5.3 FRESHLY PREPARED REAGENTS



162

Wadsworth-Emmons reagent (162)

A mixture of triisopropyl phosphite (54.14 g, 260 mmol) and methyl chloroacetate (28.22 g, 260 mmol) was refluxed for 24 h at 130°C. The crude product was purified by vacuum distillation at 120°C/0.2 mmHg to give the phosphonate **162** (55.0 g, 88%) as a colourless liquid.

FAB-MS: *m/z* 239 $[M+H]^+$. Exact mass: Calculated for $C_9H_{19}PO_5$, 239.1048; Found, 239.1046.

δ_H 1.193 (d, 12H, J 6.2, OCH(**C**H_3)$_2$)
2.786 (d, 2H, $J_{H,P}$ 22.7, C**H**$_2$$CO_2$Me)
3.584 (s, 3H, OMe)
4.604 (m, 2H, OC**H**$(CH_3)_2$)

δ_C 166.12Sd ($J_{C,P}$ 6.3 Hz, CO); 71.19 Dd ($J_{C,P}$ 6.2 Hz, CH); 52.23Q (OCH_3); 35.00Td ($J_{C,P}$ 135.5 Hz, CH_2); 23.64Qd ($J_{C,P}$ 17.5 Hz, CH_3); 23.59Qd ($J_{C,P}$ 17.5 Hz, CH_3).

Anhydrous *tert*-butyl hydroperoxide

Aqueous *t*-butyl hydroperoxide (70%, 350 ml) and toluene (700 ml) were swirled in a separatory funnel. The aqueous phase was removed and the organic solution was refluxed under argon for 5 h in a flask equipped with a Dean-Stark trap for water separation. The solution was cooled and stored in a dark bottle containing molecular sieves. The content of the *t*-butyl hydroperoxide was determined by ^{1}H NMR spectroscopy according to the following equation:

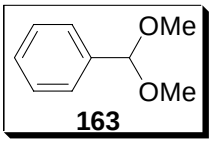
Molarity = X / (0.1X + 0.32Y) = 3.71M

X = integration of *t*-butyl resonance

Y = integration of methyl resonance

δ_H 2.805 (s, CH_3)

1.499 (*t*-butyl)



163

α,α-Dimethoxytoluene (163)

Toluene-4-sulfonic acid (1.00 g) was added to a solution of benzaldehyde (106 g, 1.00 mol) and trimethyl orthoformate (116 g, 1.10 mol) in anhydrous methanol (340 ml) and the solution allowed to stir for 30 min. Caution: exothermic reaction. The reaction mixture was refluxed for 4 h allowed to cool to room temperature, diluted with diethyl ether (900 ml) and washed with KOH (5%): NaCl (saturated) solution (1:1). The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated to give the acetal **163** (134 g, 88%).

δ_H 3.516 (s, 6H, 2x OCH_3)

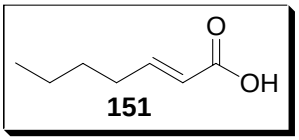
5.575 (s, 1H, PhC**H**)

7.72-7.44 (m, 5H, aromatic protons)

δ_C 53.07Q (OCH_3); 103.60D (acetal carbon); 127.07D (aromatic carbon); 128.56D (aromatic carbon); 128.81D (aromatic carbon); 138.49S (aromatic carbon).

5.4 PROCEDURES

5.4.1 First route to *E*-2-hepten-1-ol



151

***(E)*-2-Heptenoic acid (151)**

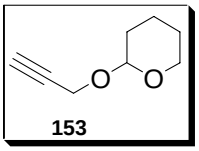
Valeraldehyde (10.0 g, 116 mmol) and malonic acid (18.0 g, 173 mmol) were dissolved in pyridine (21.0 ml, 250.5 mmol) and then piperidine (0.5 ml) was added. A vigorous exothermic CO_2 evolution started after 15 min. The reaction mixture was refluxed at 95°C for 4 h until the evolution of CO_2 ceased. The reaction mixture was cooled and acidified with a cold mixture of 1:1 H_2SO_4: H_2O. The mixture was extracted with diethyl ether and the organic solution dried (Na_2SO_4), filtered and evaporated. The product was purified by distillation at 110°C/ 0.5 mmHg to give the acid **151** (12.8 g, 86 %) as a colourless liquid.

FAB-MS: *m/z* 129 $[M+H]^+$. Exact mass: Calculated for $C_7H_{13}O_2$, 129.0916; Found, 129.0916.

δ_H 0.871 (t, 3H, J 7.1, H-7)
1.48-1.25 (m, 4H, H-5, H-6)
2.191 (ddt, 2H, $J_{2,4}$ 1.5, $J_{3,4}$ 7.0, $J_{4,5}$ 7.0, H-4)
5.782 (dt, 1H, $J_{2,3}$ 15.5, $J_{2,4}$ 1.6, H-2)
7.046 (dt, 1H, $J_{2,3}$ 15.5, $J_{3,4}$ 7.0, H-3)

δ_C 172.23S (C-1); 152.30D (C-3); 120.65D (C-2); 31.90T (C-4); 29.93T (C-5); 22.12T (C-6); 13.66Q (C-7).

5.4.2 Second route to *E*-2-hepten-1-ol

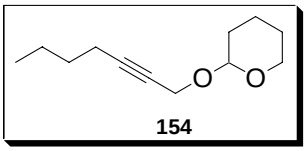


153

2-(Prop-2-ynyloxy)-tetrahydropyran (153)

A solution of dihydro-2*H*-pyran (42.2 g, 502 mmol), propargyl alcohol (19.27 g, 343.8 mmol) and pyridinium *p*-toluenesulfonate (0.79 g, 3.17 mmol) in CH_2Cl_2 (250 ml) was stirred for 4 h

at room temperature. The mixture was washed with KOH (5%):NaCl (saturated) solution (1:1) and the organic solution dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography using diethyl ether-hexane (1: 9) as eluent to give the tetrahydropyranyl ether **153** (31.7 g, 65%) as a colourless oil.

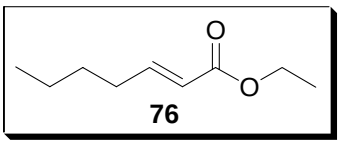


154

2-(Hept-2-yn-1-yloxy)-tetrahydropyran (154)

n-BuLi (1.6M, 12.8 ml) was added to a solution of 2-(prop-2-ynyloxy)-tetrahydropyran (2.82 g, 20.0 mmol) in dry THF (30 ml) at –78°C. The reaction mixture was stirred for 30 min and then iodobutane (3.86 g, 21.0 mmol) was added dropwise. The mixture was stirred for a further 2 h, quenched with saturated NH_4Cl solution and diluted with brine. The aqueous phase was extracted with diethyl ether. The organic solution was dried (Na_2SO_4), filtered and the solvent evaporated to give a complex mixture of products.

5.4.3 Third route to *E*-2-hepten-1-ol



76

Ethyl (*E*)-2-heptenoate (76)

A solution of K_2CO_3 (152.2 g, 1.12 mol) in water (112 ml) was added to a vigorously stirred mixture of triethylphosphonoacetate (150.2 g, 660 mmoles) and valeraldehyde (48.0 g, 558 mmoles). After 1 h the exothermic reaction ceased and additional water (200 ml) was added to dissolve residual K_2CO_3. The reaction mixture was extracted with pentane, dried (Na_2SO_4), and the solvent evaporated at 38°C (product is very volatile). The residue was purified by distillation at 60°C/0.7 mmHg to give the α,β-unsaturated ester **76** (80.7 g, 93%) as a colourless liquid.

FAB-MS: *m/z* 156 $[M]^+$. Exact mass: Calculated for $C_9H_{16}O_2$, 156.1150; Found, 156.1160.

δ_H 0.876 (t, 3H, $J_{6,7}$ 7.0, H-7)

1.250 (t, 3H, J 7.0, $OCH_2C\mathbf{H}_3$)

1.48-1.28 (m, 4H, H-5, H-6)

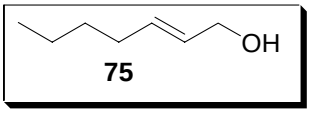
2.166 (dtt, 2H, $J_{2,4}$ 1.6, $J_{3,4}$ 7.0, $J_{4,5}$ 7.0, H-4)

4.149 (q, 2H, J 7.2, $OC\mathbf{H}_2CH_3$)

5.776 (dt, 1H, $J_{2,3}$ 15.8, $J_{2,4}$ 1.6, H-2)

6.429 (dt, 1H, $J_{2,3}$ 15.8, $J_{3,4}$ 7.0, H-3)

δ_C 166.55S (C-1); 149.13D (C-3); 121.20D (C-2); 59.90T ($O\mathbf{C}H_2CH_3$); 31.72T (C-4); 30.02T (C-6); 22.06T (C-5); 14.12Q ($OCH_2\mathbf{C}H_3$); 13.62Q (C-7)



***E*-2-Hepten-1-ol (75)**

DIBALH (21.3 g, 150 mmol) was added dropwise by syringe to a solution of the ester **76** (9.36 g, 60.0 mmol) in THF (100 ml) at –78°C and the reaction stirred for 90 min. Excess DIBALH was destroyed by careful addition of MeOH (15 ml) at –78°C using a syringe, then additional MeOH (100 ml) was added slowly using a dropping funnel followed by saturated NH_4Cl solution (100 ml) at room temperature. After stirring for 4 h at room temperature the mixture was acidified by addition of 0.05M HCl (50 ml). The solvent was evaporated and the residue extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and the solvent evaporated at 40°C. The crude product was purified by column chromatography with diethyl ether: ethyl acetate: hexane (3:4:5) as eluent to give the allylic alcohol **75** (5.40 g, 79%) as a colourless liquid; R_f 0.89 (diethyl ether: ethyl acetate: hexane 3:4:5).

FAB-MS: *m/z* 115 $[M+H]^+$. Exact mass: Calculated for $C_7H_{15}O$, 115.1123; Found, 115.1123.

δ_H 0.869 (t, 3H, J 7.0, H-7)

1.40-1.25 (m, 4H, H-5 and H-6)

1.45 (s br, 1H, O**H**)

2.02 (dt br, 2H, H-4)

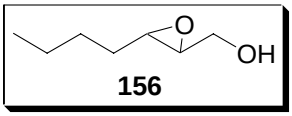
4.057 (dt, 2H, $J_{1,2}$ 4.9, J 1.0, H-1)

5.73-5.55 (m, 2H, H-2 and H-3)

δ_C 132.83D (C-3); 128.79D (C-2); 63.23T (C-1); 31.67T (C-4)*; 31.12T (C-5)*; 21.99T (C-6); 13.63Q (C-7).

* may be interchanged

5.4.4 Synthesis of (2*S*,3*S*)-2,3-epoxyheptan-1-ol (74)



156

***rac*-2,3-Epoxyheptan-1-ol (156)**

m-Chloroperoxybenzoic acid (3.14 g, 10 mmol) was added to a solution of 2-heptenol (1.14 g, 10.0 mmol) in dichloromethane (30 ml). The solution was stirred at room temperature for 1 h, washed with K_2CO_3 solution, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography with EtOAc: hexane (3:5) as eluent to give the epoxide **156** (0.81 g, 62%) as an oil R_f 0.26 (EtOAc: hexane 3:5).

δ_H 0.897 (t, 3H, $J_{6,7}$ 7.0, H-7)

1.45-1.28 (m, 4H, H-5 and H-6)

1.54 (t br, 2H, H-4)

1.72 (s, br, OH)

2.872 (ddd, 1H, $J_{2.3}$ 2.3, $J_{2,1a}$ 2.6, $J_{2,1b}$ 4.4, H-2)

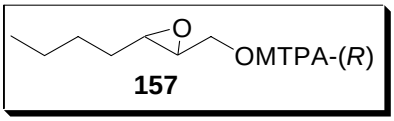
2.891 (dt, 1H, $J_{2.3}$ 2.3, $J_{3,4}$ 5.4, H-3)

3.547 (dd, 1H, $J_{1a,1b}$ 12.5, $J_{1b,2}$ 4.5, H-1b)*

3.739 (dd, 1H, $J_{1a,1b}$ 12.5, $J_{1a,2}$ 2.5, H-1a)*

* after D_2O exchange

δ_C 61.74T (C-1); 58.54D (C-3); 56.02D (C-2); 31.16T (C-4); 27.96T (C-5); 22.36T (C-6); 13.82Q (C-7);



157

***rac*-2,3-Epoxyheptan-1-yl (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate 157**

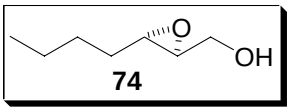
Oxalyl chloride (291 mg, 2.29 mmol) was added to a solution of (*R*)-(+)-MTPA (e.e.≥ 99%, 102 mg, 0.44 mmol) and DMF (31.0 mg, 0.43 mmol) in hexane (6 ml) at RT. A white precipitate formed immediately. After 60 min the mixture was passed through a small cotton plug to filter off the formed DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl).

A solution of *rac*-2,3-epoxyheptan-1-ol **157** (41 mg, 0.31 mmol), Et_3N (163 mg, 1.61 mmol) and DMAP (4 mg) in CH_2Cl_2 (5 ml) were added to a solution of the acid chloride in CH_2Cl_2 (2 ml) solution. The mixture was stirred for 2 h and then quenched by addition of water (2 ml). The organic solution was washed with 0.5M HCl, followed by saturated $NaHCO_3$ solution and water. The CH_2Cl_2 was dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography with diethyl ether: hexane (3:4) as eluent to give the Mosher ester **152** (70 mg, 64%) as a 1:1 mixture of diastereomers; R_f 0.63 (diethyl ether: hexane 3:4).

δ_H 0.884 (t, 3H, J 7.1, H-7)
0.881 (t, 3H, J 7.1, H-7)
1.29-1.42 (m, 12H, H-4,H-5,H-6)
2.813 (dt, 1H, $J_{2,3}$ 2.1, $J_{3,4}$ 5.7, H-3)
2.824 (dt, 1H, $J_{2,3}$ 2.1, $J_{3,4}$ 5.7, H-3)
2.963 (ddd, 1H, $J_{1b,2}$ 6.0, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1, H-2)
2.990 (ddd, 1H, $J_{1b,2}$ 5.7, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1, H-2)
3.540 (q, 3H, $J_{H,F}$ 1.3, OCH_3)
3.549 (q, 3H, $J_{H,F}$ 1.3, OCH_3)
4.208 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1b,2}$ 5.7, H-1b)
4.217 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1b,2}$ 6.1, H-1b)
4.505 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.4, H-1a)
4.542 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.6, H-1a)

7.41-7.35 (m, 10H, aromatic protons)

δ_F –72.15, –72.22



(2*S*,3*S*)-2,3-Epoxyheptan-1-ol (74)

A mixture of molecular sieves (4Å, 1.0 g) and CH_2Cl_2 (200 ml) under argon was cooled to –20°C. A solution of Ti(*i*PrO)$_4$ (21.9 mmol, 6.23 g) in CH_2Cl_2 (40 ml) was added dropwise, followed by a solution of diethyl (2*R*,3*R*)-tartrate (26.3 mmol, 5.43 g) in CH_2Cl_2 (40 ml). The solution was allowed to stir at –20°C for 30 min. A solution of 2-heptenol (43.8 mmol, 5.00 g) in CH_2Cl_2 (40 ml) was added followed by the solution of *t*-butylhydroperoxide (3.7M in toluene, 87.7 mmol, 23.7 ml) in CH_2Cl_2 (40 ml). The reaction mixture was stirred at –20°C for 6 h and then left in the freezer at –10°C for 16 h.

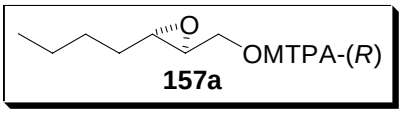
The reaction mixture was allowed to warm to 0°C, filtered and the filtrate poured into a beaker containing a solution of iron(II) sulfate (144.3 mmol, 21.9 g) and tartaric acid (8.76 g) in deionized water (88 ml), which was stirred and cooled to 10°C in an ice-bath (an exothermic reaction occurs and the temperature rises to 20°C). After the exothermic reaction had subsided and the temperature had dropped, the cooling bath was removed and the mixture was stirred at room temperature for 30 min. The aqueous layer was extracted with diethyl ether (5x30 ml) and the combined organic solutions were dried (Na_2SO_4) and filtered. The solvent was removed by evaporation at 35°C.

The crude product was dissolved in diethyl ether (100ml) and the solution cooled to 3°C in an ice-bath. A precooled (3°C) solution of NaOH (3.51 g, 87.7 mmol) in brine (88 ml) was added and the two-phase mixture stirred vigorously for 1 h with continued cooling. The aqueous phase was separated and extracted with diethyl ether (2x100 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated. The residue was purified using column chromatography with EtOAc-hexane (10: 6.5) as eluent to give the epoxy alcohol **153** (3.47 g, 61%) as a colourless oil; R_f 0.34 (EtOAc-hexane 10: 6.5).

FAB-MS: *m/z* 131 $[M+H]^+$. Exact mass: Calculated for $C_7H_{15}O_2$, 131.1072; Found, 131.1072.

δ_H 0.871 (t, 3H, J 7.0, H-7)
1.45-1.30 (m, 4H, H-5, H-6)
1.58-1.51 (m, 2H, H-4)
1.83 (br t, $J_{1,OH}$ 6.1, OH)
2.872 (ddd, 1H, $J_{2.3}$ 2.3, $J_{2,1a}$ 2.6, $J_{2,1b}$ 4.4, H-2)
2.891 (dt, 1H, $J_{2.3}$ 2.3, $J_{3,4}$ 5.4, H-3)
3.547 (dd, 1H, $J_{1a,1b}$ 12.5, $J_{1b,2}$ 4.5, H-1b)*
3.739 (dd, 1H, $J_{1a,1b}$ 12.5, $J_{1a,2}$ 2.5, H-1a)*
* after D_2O exchange

δ_C 61.78D (C-1); 58.54D (C-3); 56.02D (C-2); 31.16T (C-4); 27.96T (C-5); 22.38T (C-6); 13.82Q (C-7).



157a

(2*S*,3*S*)-2,3-Epoxyheptan-1-yl (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate 157a

Oxalyl chloride (291 mg, 2.29 mmol) was added to a solution of (*R*)-(+)-MTPA (e.e.≥ 99%, 102 mg, 0.44 mmol) and DMF (31.0 mg, 0.43 mmol) in hexane (6 ml) at room temperature. A white precipitate formed immediately. After 60 min the mixture was passed through a small cotton plug to filter off the formed DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl).

A solution of (2*S*,3*S*)-2,3-epoxyheptan-1-ol **74** (41 mg, 0.31 mmol), Et_3N (163 mg, 1.61 mmol) and DMAP (4 mg) in CH_2Cl_2 (5ml) were added to a solution of the acid chloride in CH_2Cl_2 (2 ml) solution. The mixture was stirred for 2 h and then quenched by addition of water (2 ml). The organic solution was washed with 0.5M HCl, followed by saturated $NaHCO_3$ solution and water. The CH_2Cl_2 was dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography with diethyl ether: hexane (3:4) as eluent to give the

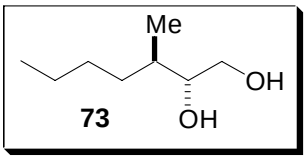
Mosher ester **157a** (50 mg, 46%) as a single diastereomer; e.e. 100%; R_f 0.63 (diethyl ether: hexane 3:4).

δ_H 0.876 (t, 3H, J 7.1, H-7)
1.29-1.55 (m, 6H, H-4,H-5,H-6)
2.818 (dt, 1H, $J_{2,3}$ 2.1, $J_{3,4}$ 5.7, H-3)
2.984 (ddd, 1H, $J_{1b,2}$ 5.7, $J_{1a,2}$ 3.6, $J_{2,3}$ 2.1, H-2)
3.538 (q, 3H, $J_{H,F}$ 1.3, OCH_3)
4.202 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1b,2}$ 5.7, H-1b)
4.536 (dd, 1H, $J_{1a,1b}$ 11.9, $J_{1a,2}$ 3.6, H-1a)
7.53-7.37 (m, 10H, aromatic protons)

δ_C 166.34 (ester CO) 132.04S; 129.68D; 128.45D; 127.33D (aromatic carbons); 123.22Sq ($J_{C,F}$ 289, CF_3); 66.01T (C-1); 56.66D (C-3); 55.46Q (OMe); 54.53D (C-2); 31.09T (C-4); 27.88T (C-5); 22.36T (C-6); 13.86Q (C-7).

δ_F –72.22

5.4.5 Synthesis of (2*R*,3*R*)-3-methylheptan-1,2-diol (73)



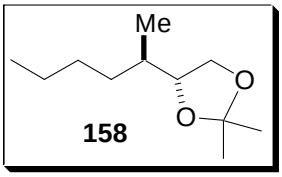
(2*R*,3*R*)-3-Methylheptane-1,2-diol (73)

A solution of (2*S*,3*S*)-2,3-epoxyheptan-1-ol **74** (2.50 g, 19.2 mmol) in hexane (29 ml) was added dropwise to a hexane solution of trimethylaluminium (2M, 28.9 ml, 57.7 mmol) at 0°C under an argon atmosphere. After stirring for 30 min at 0°C the resulting mixture was diluted with CH_2Cl_2 (150ml), treated with NaF (24.2 g, 577 mmol) and distilled water (10.6 ml, 577 mmol). The resulting suspension was vigorously stirred at 25°C for 30 min. The semisolid material was removed by filtration and washed with diethyl ether (3x20 ml). The filtrate and the diethyl ether solutions were dried (Na_2SO_4), filtered and evaporated to give the diol **73** (2.21 g, 79%) as a a colourless oil.

FAB-MS: *m/z* 147 $[M+H]^+$. Exact mass: Calculated for $C_8H_{19}O_2$, 147.1385; Found, 147.1385.

δ_H 0.848 (d, 3H, J 7.0, 3-CH_3)
0.868 (t, 3H, J 7.0, C-7)
1.42-1.04 (m, 6H, H-4, H-5, H-6)
1.59-1.45 (m, 1H, H-3)
2.68 (s br, 2H, OH)
3.66 (m, 1H, H-1a)
3.47 (m, 2H, H-1b and H-2)

δ_C 76.26D (C-2); 64.59T (C-1); 36.14D (C-3); 32.10T (C-4); 29.18T (C-5); 22.93T (C-6); 15.17Q (3-CH_3); 14.03Q (C-7);



(4*R*,2′*R*)-2,2-Dimethyl-4-(hexan-2′-yl)-[1,3]dioxolane (158)

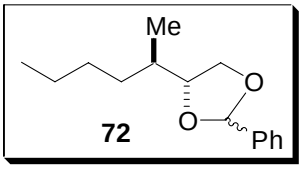
p-Toluenesulfonic acid (5 mg) was added to a solution of (2*R*,3*R*)-3-methylheptan-1,2-diol (**73**) (100 mg, 0.68 mmol) in 2,2-dimethoxypropane (1 ml). The reaction was stirred for 3 h at room temperature and the acid neutralized by the addition of Et_3N (0.5 ml). The reaction mixture was partitioned between water and diethyl ether and the organic phase dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography using EtOAc: hexane (4:1) as eluent to give the acetonide **158** (97 mg, 77%) as a colourless oil.

δ_H 0.809 (d, 3H, J 6.7, 1′-Me)
0.876 (t, 3H, J 6.7, H-6′)
1.15-1.35 (m, 6H, H-3′, H-4′, H-5′)
1.328 (s, 3H, 2-Me)
1.374 (s, 3H, 2-Me)
1.67-1.48 (m, 2H, H-3′)
3.563 (dd, 1H, $J_{5b,4}$ 7.3, $J_{5a,5b}$ 7.8, H-5b)
3.838 (dt, H, $J_{5a,4}$ 6.2, $J_{4,2'}$ 7.3, $J_{5b,4}$ 7.3, H-4)

3.950 (dd, 1H, $J_{5a,4,}$ 6.2, $J_{5a,5b}$ 7.8, H-5a)

δ_C 108.57S (C-2); 80.32D (C-4); 67.44D (C-5); 36.36D (C-2′); 32.95T (C-3′); 29.04T (C-4′); 26.68Q (2-Me); 25.61Q (2-Me); 22.90T (C-5′); 14.74Q (C-6′); 14.05Q (C-1′);

5.4.6 Synthesis of (2*R*,3*R*)-2-benzyloxy-3-methylheptan-1-ol (71)



(2*RS*,4*R*,2′*R*)-2-Phenyl-4-(hexan-2′-yl)-[1,3]dioxolane (72)

p-Toluenesulfonic acid (400 mg) was added to a solution of (2*R*,3*R*)-3-methylheptan-1,2-diol (**73**) (6.51 g, 44.6 mmol) and α,α-dimethoxytoluene (6.76 g, 44.5 mmol) in CH_2Cl_2 (5 ml) and the solution stirred for 3 h at r.t. The acid was neutralized by the addition triethylamine (3 ml) and the solution washed with water. The organic phase was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography using diethyl ether-hexane (1:4) as eluent to give the benzylidene derivative **72** (5.63 g, 54%), a colourless oil, as a *ca.* 1:1 diastereomeric mixture; R_f 0.83 (diethyl ether-hexane 1:4).

FAB-MS: *m/z* 235 $[M+H]^+$, Exact mass: Calculated for $C_{15}H_{23}O_2$, 235.1698; Found, 235.1697.

δ_H 0.864 (d, 3H, J 6.7, C-1′)

0.896 (t, 6H, J 6.9, C-6′

0.907 (d, 3H J 6.8, H-1′)

1.44-1.10 (m, 6H, H-3′, H-4′, H-5′)

3.690 (dd, 1H, $J_{5a,5b}$ 8.0, $J_{4,5b}$ 7.6, H-5b)

3.749 (m, 1H, H-5b)

3.940 (ddd, 1H, $J_{4,2'}$ 7.6, $J_{4,5b}$ 7.6, $J_{4,5a}$ 6.1, H-4)

3.97-4.06 (m, 2H, H-5a, H-4)

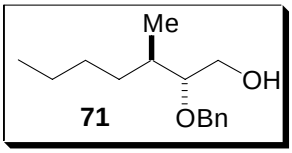
4.185 (dd, 1H, $J_{5a,5b}$ 8.0, $J_{4,5a}$ 6.1, H-5a)

5.783 (s, 1H, H-2)

5.908 (s, 1H, H-2)

7.50-7.32 (m, 10H, aromatic protons)

δ_C 138.79S, 137.95S, 129.19D, 128.95D, 128.31D, 126.69D, 126.35D (aromatic carbons); 103.87D and 103.45D (C-2); 81.58D and 80.81D (C-4); 69.04T and 68.08T (C-5); 36.38D and 36.18D (C-4); 33.03T and 32.88T (C-3′); 29.69T and 28.97T (C-4′); 22.92T (C-5′); 14.96Q (C-6′); 14.71Q and 14.05Q (C-1′).



(2*R*,3*R*)-2-Benzyloxy-3-methylheptan-1-ol (71)

DIBALH (8.38 g, 47.0 mmol) was added to a solution of the benzylidene acetal **72** (4.40 g, 18.8 mmol) in CH_2Cl_2 (50 ml) at –78°C. The reaction mixture was then allowed to warm to r.t and stirred for 2 h at r.t. Excess DIBALH was destroyed by careful dropwise addition of methanol (75 ml) followed by saturated NH_4Cl solution (50 ml). Then 0.05M HCl (15 ml) was added. The product was extracted with CH_2Cl_2 (3x30 ml) and the organic solution dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography with EtOAc-hexane (3:5) as eluent to give the primary alcohol **71** (3.93 g, (89%) as a colourless oil.

FAB-MS: *m/z* 236 $[M]^+$. Exact mass: Calculated for $C_{15}H_{24}O_2$ 236.1776; Found, 236.1776.

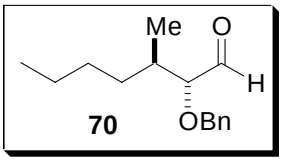
δ_H 0.885 (t, 3H, J 7.1, H-7)
0.893 (d, 3H, J 6.9, 3-Me)
1.47-1.08 (m, 6H, H-5, H-6, H-4)
1.90-1.78 (m, 1H, H-3)
1.79 (br s, 1-OH)
3.350 (ddd, 1H, $J_{1a,2}$ 3.5, $J_{1b,2}$ 6.7, $J_{2,3}$ 5.7, H-2)
3.600 (dd, 1H, $J_{1a,1b}$ 11.6, $J_{1b,2}$ 6.7, H-1b)
3.667 (dd, 1H, $J_{1a,1b}$ 11.6, $J_{1a,2}$ 3.5, H-1a)
4.513 (d, 1H, J 11.4, OCH_2Ph)

4.616 (d, 1H, J 11.4, OCH_2Ph)

7.35-7.25 (m, 5H, aromatic protons)

δ_C 138.58S, 128.47D, 127.79D, 127.74D (aromatic carbons); 83.87D (C-2); 72.00T (OCH_2Ph); 61.58T (C-1); 33.74D (C-3); 32.55T (C-4); 29.55T (C-5); 22.92T (C-6); 14.81Q (CH_3); 14.04Q (C-7);

5.4.7 Synthesis of (2*R*,3*R*,4*R*,5*R*)-4-benzyloxy-2,3-epoxy-5-nonan-1-ol (67)



(2*R*,3*R*)-2-Benzyloxy-3-methylheptanal (70)

Dry DMSO (0.37 g, 4.67 mmol) was added to a cold (–78°C), stirred solution of oxalyl chloride (0.41 g, 3.18 mmol) in CH_2Cl_2 (5 ml). After 15 min a solution of (2*R*,3*R*)-2-benzyloxy-3-methylheptanol **71** (0.50 g, 2.12 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise over a period of 5 min. The resulting mixture was stirred for 90 min, after which triethylamine (1.07 g, 10.6 mmol). The reaction mixture was stirred for 60 min, allowed to attain r.t. and diluted with CH_2Cl_2 (30 ml). The CH_2Cl_2 solution was washed with saturated NH_4Cl solution (30 ml), dried (Na_2SO_4), and evaporated to give the aldehyde **70** (0.45 g, 90%) as a colourless oil.

δ_H 0.860 (t, 3H, J 7.0, H-7)

0.946 (d, 3H, J 7.0, 3-Me)

1.21-1.03 (m, 4H, H-4, H-5)

1.50 (m, 2H, H-6)

1.945 (m, 1H, H-3)

3.518 (dd, 1H, $J_{2,3}$ 5.7, $J_{1,2}$ 2.8, H-2)

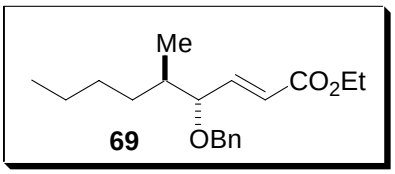
4.476 (d, 1H, J 11.8, OCH_2Ph)

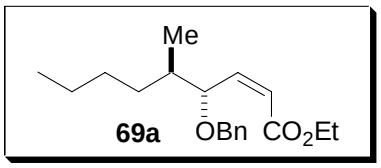
4.658 (d, 1H, J 11.6, OCH_2Ph)

7.34-7.27 (m, 5H, ArH)

9.658 (d, 1H, $J_{1,2}$ 2.8, H-1)

δ_C 204.11D (C-1); 137.54, 128.45D, 127.96D (aromatic carbons); 87.54D (C-2); 72.81T (OCH_2Ph); 35.07D (C-3); 31.47 T (C-4); 29.19 T (C-5); 22.77T (C-6); 15.57Q (3-Me); 13.97 Q (C-7)





Ethyl (2*E*,4*R*,5*R*)-4-benzyloxy-5-methylnon-2-enoate (69)

Potassium *t*-butoxide (0.48 g, 4.27 mmol) was added to a solution of triethylphosphono-acetate (0.96 g, 4.27 mmol) in dry THF (10 ml) at 0°C. The reaction mixture was stirred for 90 min and then cooled to –78°C. A solution of 2-benzyl-3-methylheptanal **70** (0.50 g, 2.14 mmol) in dry THF (5 ml) was added dropwise to the reaction mixture which was then stirred at –78°C for 90 min. The reaction was quenched by addition of saturated NH_4Cl solution and washed with brine. The crude product was extracted with CH_2Cl_2 (2x30 ml), dried (Na_2SO_4) and evaporated. Purification of the crude product was done by column chromatography with hexane-EtOAc (19:1) as eluent to give the α,β-unsaturated ester **69** (0.40 g, 62%) as a colourless oil; R_f 0.37 (hexane-EtOAc 19:1). The minor product (**69a**) had R_f 0.30 (hexane-EtOAc 19:1)

FAB-MS: *m/z* 304 $[M]^+$. Exact mass: Calculated for $C_{19}H_{28}O_3$ 304.2038; Found, 304.2037.

δ_H 0.863 (t, 3H, J 6.7, H-9)
0.864 (d, 3H, J 7.0, 5-Me)
1.15 (m, 1H, H-6b)
1.295 (t, 3H, J 7.2, $OCH_2C\underline{H}_3$)
1.24 (m, 2H, H-7b, H-8b)
1.53-1.40 (m, 2H, H-7a, H-8a)
1.82-1.70 (m, 2H. H-5)
3.760 (ddd, 1H, $J_{2,4}$ 1.3, $J_{3,4}$ 6.7, $J_{4,5}$ 5.7, H-4)
4.204 (q, 2H, J 7.2, $OC\mathbf{H}_2CH_3$)

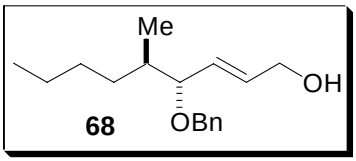
4.342 (d, 1H, J 11.9, OCH_2Ph)
4.563 (d, 1H, J11.9, OCH_2Ph)
5.993 (dd, H, $J_{2,3}$ 15.8, $J_{2,4}$ 1.3, H-2)
6.846 (dd, H, $J_{2,3}$ 15.8, $J_{3,4}$ 6.7, H-3)
7.37-7.25 (m, 5H, aromatic protons)

δ_C 166.18S (CO); 147.21D (C-3); 138.37S, 128.31D, 127.59D (C-2), 127.52D (aromatic carbons); 123.09D (C-2); 82.25D (C-4); 71.05T (OCH_2Ph); 60.42T (OCH_2CH_3); 37.45D (C-5); 32.18T (C-6); 29.21T (C-7); 22.86T (C-8); 15.13Q (OCH_2CH_3); 14.23Q (CH_3CH); 14.04Q (C-9).

Ethyl (2*Z*,4*R*,5*R*)-4-Benzyloxy-5-methylnon-2-enoate (69a)

δ_H 0.859 (t, 3H, J 7.0, H-9)
0.876 (d, 3H, J 7.0, 5-Me)
1.15-1.37 (m, 3H, H-6b, H-7, H-8)
1.252 (t, 3H, J 7.0, $OCH_2C\mathbf{H}_3$)
1.62-1.50 (m, 1H, H-6a)
1.76-1.66 (m, 1H, H-5)
4.145 (q, 2H, J 7.0, $OC\mathbf{H}_2CH_3$)
4.375 (d, 1H, J 11.6, OCH_2Ph)
4.516 (d, 1H, J 11.6, OCH_2Ph)
4.852 (ddd, 1H, $J_{2,4}$ 1.0, $J_{4,5}$ 6.5, $J_{3,4}$ 9.3, H-4)
5.946 (dd, 1H, $J_{2,4}$ 1.0, $J_{2,3}$ 11.9, H-2)
6.118 (dd, 1H, $J_{3,4}$ 9.3, $J_{2,3}$11.9, H-3)
7.31-7.20 (m, 5H, aromatic protons)

δ_C 166.01S (CO); 149.12D (C-3); 122.37D (C-2); 138.82S, 128.21D, 127.74D, 127.42D (aromatic carbons); 78.30D (C-4); 71.27T (OCH_2Ph); 60.18T (OCH_2CH_3); 37.82D (C-5); 31.79T (C-6); 29.10T (C-7); 22.98T (C-8); 15.21Q (OCH_2CH_3); 14.19Q (CH_3CH); 14.07Q (C-9)



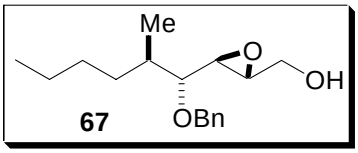
(2*E*,4*S*,5*R*)-4-Benzyloxy-5-methylnon-2-en-1-ol (68)

DIBALH (1.20 g, 8.45 mmol) was added by syringe to a solution of ethyl (2*E*,4*R*,5*R*)-4-benzyloxy-5-methylnon-2-enoate (**69**) (1.00 g, 3.29 mmol) in dry THF (10 ml) at –78°C. The reaction mixture was stirred at –78°C for 1 h. The excess DIBALH was destroyed by careful addition of methanol (10 ml) followed by saturated NH_4Cl solution (50 ml). 0.05M HCl (5 ml) was added and the mixture extracted with CH_2Cl_2 (3x30 ml). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography with diethyl ether-EtOAc-hexane (3:4:5) as eluent to give the allylic alcohol **68** (0.44 g, 51%) as a colourless oil; R_f 0.70 (diethyl ether-EtOAc-hexane 3:4:5).

FAB-MS: *m/z* 263 $[M+H]^+$. Exact mass: Calculated for $C_{17}H_{27}O_2$, 263.2011; Found, 263.2013.

δ_H 0.847 (d, 3H, J 6.7, 5-Me)
0.865 (t, 3H, J 7.0, H-9)
1.54-1.03 (m, 6H, H-6, H-7, H-8)
1.57 (br s, 1-OH)
1.69 (m, 1H, H-5)
3.569 (dd, 1H, $J_{4,5}$ 6.1, $J_{3,4}$ 8.0, H-4)
4.169 (d, 2H, $J_{1,2}$ 5.4, $J_{1,3}$ 1.4, H-1)
4.346 (d, 1H, J 11.9, OCH_2Ph)
4.553 (d, 1H, J 11.9, OCH_2Ph)
5.600 (ddt, 1H, $J_{2,3}$ 15.5, $J_{3,4}$ 8.0, $J_{1,3}$ 1.4, H-3)
5.784 (ddt,1H, $J_{2,3}$ 15.5, $J_{2,4}$ 0.8, $J_{1,2}$ 5.4, H-2)
7.34-7.20 (m, 5H, aromatic protons)

δ_C 139.04S (aromatic carbon); 132.77D (C-2), 130.37D (C-3); 127.61D, 127.29D; 128.22D (aromatic carbons); 83.61D (C-4); 70.28T (C-1); 63.11T ($O\underline{C}H_2Ph$); 37.50D (C-5); 32.39T (C-6); 29.19T (C-7); 22.96T (C-8); 15.23Q (5-$\underline{C}H_3$);14.08Q (C-9).



(2*R*,3*R*,4*R*,5*R*)-4-Benzyloxy-2,3-epoxy-5-methylnonan-1-ol (67)

A mixture of molecular sieves (4Å, 0.50 g) and CH_2Cl_2 (20 ml) under argon was cooled to –20°C. A solution of Ti(*i*PrO)$_4$ (0.27 g, 0.95 mmol) in CH_2Cl_2 (4 ml) was added dropwise, followed by a solution of diethyl (2*S*,3*S*)-tartrate (1.14 mmol, 0.24 g) in CH_2Cl_2 (4 ml). The solution was allowed to stir at –20°C for 30 min. A solution of (4*R*,5*R*)-4-benzyloxy-5-methylnon-2-en-1-ol **(68)** (0.50 g, 1.91 mmol) in CH_2Cl_2 (4ml) was added followed by a solution of *t*-butylhydroperoxide (3.7M in toluene, 2.06 ml, 7.63 mmol) in CH_2Cl_2 (4 ml). The reaction mixture was stirred at –20°C for 6 h and then left in the freezer at –10°C for 16 h.

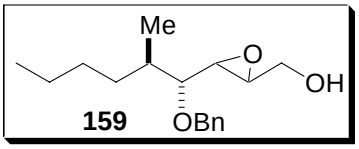
The reaction mixture was allowed to warm to 0°C, filtered and the filtrate poured into a beaker containing a solution of iron(II) sulfate (6.28 mmol, 1.75 g) and tartaric acid (0.76 g) in deionized water (7.6 ml), which was stirred and cooled to 10°C in an ice-bath (an exothermic reaction occurs and the temperature rises to 20°C). After the exothermic reaction had subsided and the temperature had dropped, the cooling bath was removed and the mixture was stirred at room temperature for 30 min. The aqueous layer was extracted with diethyl ether (5x10 ml) and the combined organic solutions dried (Na_2SO_4) and filtered. The solvent was removed by evaporation at 35°C.

The crude product was dissolved in diethyl ether (20 ml) and the solution cooled 3°C in an ice-bath. A precooled (3°C) solution of NaOH (0.30 g, 7.63 mmol) in brine (8 ml) was added and the two-phase mixture stirred vigorously for 1 h with continued cooling. The two-phase mixtures were stirred vigorously for 1 h with continued cooling. The aqueous phase was separated and extracted with diethyl ether (2x20 ml), dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography with (EtOAc-hexane (1:2) as eluent to give the epoxy alcohol **67 (**0.53 g, 79%) as a colourless oil; R_f 0.45 (EtOAc-hexane 1:2).

FAB-MS: *m/z* 278 $[M]^+$. Exact mass: Calculated for $C_{17}H_{26}O_3$, 278.1882; Found, 278.1882.

δ_H 0.979 (d, 3H, J 7.0, 5-Me)
0.875 (t, 3H, J 6.7, H-9)
1.361-1.147 (m, 4H, H-8, H-7)
1.501-1.442 (m, 2H, H-6)
1.838-1.725 (m, H, H-5)
3.004 (dd, 1H, $J_{3,4}$ 5.2, $J_{2,3}$ 2.3, H-3)
3.125 (ddd, 1H, $J_{1b,2}$ 4.1, $J_{1a,2}$ 2.7, $J_{2,3}$ 2.3, H-2)
3.241 (dd, 1H, $J_{3,4}$ 5.2, $J_{4,5}$ 4.4, H-4)
3.550 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1b,2}$ 4.1, H-1b)*
3.838 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1b,2}$ 2.7, H-1b)*
4.514 (d, 1H, J 11.9, OCH_2Ph)
4.587 (d, 1H, J 11.9, OCH_2Ph)
7.53-7.22 (m, 5H, aromatic protons)
* after D_2O exchange

δ_C 138.83S, 128.32D, 127.53D (aromatic carbons), 81.16D (C-4); 72.95T (OCH_2Ph); 61.36T (C-1); 56.23D (C-2); 55.41D (C-3); 36.45D (C-5); 31.72T (C-6); 29.52T (C-7); 22.89T (C-8); 15.44Q (5-Me); 14.05Q (C-9).



(2*R*,3*R*,4*R*,5*R*)- and (2*S*,3*S*,4*R*,5*R*)-4-Benzyloxy-2,3-epoxy-5-methylnonan-1-ol (159)

m-Chloroperoxybenzoic acid (120 mg, 0.38 mmol) was added to a solution of (4*S*,5*S*)-4-benzyloxy-5-methyl-non-2-enol **68** (100 mg, 0.38 mmol) in CH_2Cl_2 (10 ml). The solution was allowed to stir at r.t. for 1 h, washed with K_2CO_3 solution, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using EtOAc-hexane (3:5) as eluent to give a 1.2:1 diastereomeric mixture of the epoxy alcohol **159** (60 mg, 57%) as a colourless oil; R_f 0.45 (EtOAc-hexane 1:2)

δ_H 0.866 (t, 3H, J 7.0, H-9)

0.876 (t, 3H, J 7.0, H-9)

0.939 (d, 3H, J 7.0, 5-Me)

0.980 (d, 3H, J 7.0, 5-Me)

1.38-1.09 (m, 8H, H-7, H-8)

1.587-1.461 (m, 4H, H-6)

1.853-1.705 (m, 2H, H-5)

2.923 (dd, 1H, $J_{3,4}$ 7.5, $J_{4,5}$ 6.4, H-4) minor

2.954 (ddd, 1H, $J_{1b,2}$ 4.1, $J_{1a,2}$ 2.6, $J_{2,3}$ 2.3, H-2) minor

3.006 (dd, 1H, $J_{3,4}$ 4.9, $J_{2,3}$ 2.3, H-3) major

3.094 (dd, 1H, $J_{3,4}$ 7.5, $J_{2,3}$ 2.3, H-3) minor

3.126 (ddd, 1H, $J_{1b,2}$ 4.4, $J_{1a,2}$ 2.6, $J_{2,3}$ 2.3, H-2) major

3.244 (dd, 1H, $J_{4,5}$ 4.7, $J_{3,4}$ 4.9, H-4) major

3.564 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1b,2}$ 4.4, H-1b) major

3.647 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1b,2}$ 3.9, H-1b) minor

3.854 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1a,2}$ 2.6, H-1a) major

3.945 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1a,2}$ 2.6, H-1a) minor

4.515 (d, 1H, J 11.9, OCH_2Ph) major

4.515 (d, 1H, J 11.9, OCH_2Ph) major

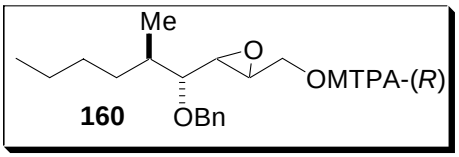
4.553 (d, 1H, J 11.9, OCH_2Ph) minor

4.802 (d, 1H, J 11.9, OCH_2Ph) minor

7.37-7.21 (m, 10H, aromatic protons)

δ_C 138.82S, 138.73S, 128.31D, 128.5D, 127.77D, 127.53D, 127.44D (aromatic carbons); 83.49D* and 81.16D (C-4), 72.94T and 72.08T* (OCH_2Ph): 61.36T and 61.23T* (C-1); 57.26D* and 56.26D (C-3); 55.41D and 55.21D* (C-2); 36.44D* and 36.23D (C-5); 32.41T* and 31.71T (C-6); 29.51T and 29.09T* (C-7), 22.87T (C-8), 15.59Q* and 15.41Q (5-Me); 14.02Q (C-9).

* major diastereomer



(2*R*,3*R*,4*R*,5*R*)- and (2*S*,3*S*,4*R*,5*R*)-4-Benzyloxy-2,3-epoxy-5-methylnonan-1-yl (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate (160)

Oxalyl chloride (291 mg, 2.29 mmol) was added to a solution of (*R*)-(−)-MTPA (e.e.≥ 99%, 102 mg, 0.44 mmol) and DMF (31.0 mg, 0.43 mmol) in hexane (6 ml) at r.t.. A white precipitate formed immediately. After 60 min the mixture was passed through a small cotton plug to filter off the formed DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl).

A solution of the racemic epoxide **159** (41 mg, 0.31 mmol), Et_3N (163 mg, 1.61 mmol) and DMAP (4 mg) in CH_2Cl_2 (5 ml) were added to a solution of the acid chloride in CH_2Cl_2 (2 ml) solution. The mixture was stirred for 2 h and then quenched by addition of water (2 ml). The organic solution was washed with 0.5M HCl, followed by saturated $NaHCO_3$ solution and water. The CH_2Cl_2 was dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography with diethyl ether: hexane (3:4) as eluent to give the Mosher ester **160** (46 mg, 65%) as a mixture of the two diastereomers; R_f 0.63 (diethyl ether: hexane 3:4).

δ_H 0.867 (t, 3H, J 7.0, H-9) major
0.898 (d, 3H, J 7.0, 5-Me) minor
0.952 (d, 3H, J 7.0, 5-Me) major
1.90-1.10 (m, H-8, H-7, H-6, H-5)
2.887 (dd, 1H, $J_{3,4}$ 7.2, $J_{4,5}$ 6.2, H-4) minor
2.878 (dd, 1H, $J_{3,4}$ 4.9, $J_{2,3}$ 2.0, H-3) major
2.982 (dd, 1H, $J_{3,4}$ 7.2, $J_{2,3}$ 2.3, H-3) minor
3.057 (ddd, 1H, $J_{1b,2}$ 5.4, $J_{1a,2}$ 3.4, $J_{2,3}$ 2.3, H-2) minor
3.182 (ddd, 1H, $J_{1b,2}$ 5.7, $J_{1a,2}$ 3.1, $J_{2,3}$ 2.0, H-2) major
3.198 (dd, 1H, $J_{3,4}$ 4.9, $J_{4,5}$ 4.7, H-4) major
3.538 (q, 3H, $J_{H,F}$ 1.3, OMe) major
3.547 (q, 3H, $J_{H,F}$ 1.3, OMe) minor

4.172 (dd, 1H, $J_{1a,1b}$ 12.2, $J_{1b,2}$ 5.7, H-1b) major

4.259 (dd, 1H, $J_{1a,1b}$ 12.2, $J_{1b,2}$ 5.4, H-1b) minor

4.469 (dd, 1H, $J_{1a,1b}$ 12.1, $J_{1a,2}$ 3.1, H-1a) major

4.487 (d, 1H, J 11.9, OCH_2Ph) major

4.515 (d, 1H, J 11.9, OCH_2Ph) minor

4.541 (d. 1H, J 11.9, OCH_2Ph) major

4.576 (dd, 1H, $J_{1a,1b}$ 12.2, $J_{1a,2}$ 3.4, H-1a) minor

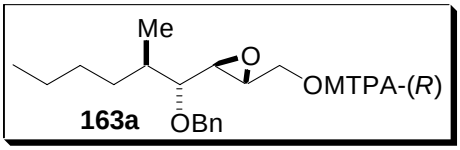
4.764 (d, 1H, J 11.9, OCH_2Ph) minor

7.60-7.24 (m, 5H, aromatic protons)

δ_C 138.67S* and 138.54S, 130.87S, 129.68D, 128.80S, 128.50D, 124.44D, 128.33D, 128.27D, 127.76D, 127.61D, 127.57D, 127.50D, 127.33D (aromatic carbons), 123.22Sq ($J_{C,F}$ 289, CF_3); 83.05D and 80.82D* (C-4); 73.04T* and 72.11T (OCH_2Ph); 65.57T* and 65.39T (C-1); 57.90D and 55.02D* (C-3); 55.46Q (OMe); 52.65D* and 51.62D (C-2); 36.36D* and 36.21D (C-5); 32.285T and 31.67T* (C-6); 29.67T* and 59.44T (C-7); 22.84T (C-8); 15.55Q and 15.27q* (5-Me); 14.02Q (C-9).

* major diastereomer

δ_F –72.17 and –72.12 (ratio 64:36)



(2*R*,3*R*,4*R*,5*R*)-4-Benzyloxy-2,3-epoxy-5-methylnonan-1-yl (*R*)-α-methoxy-α-trifluoro-methyl-phenylacetate (163a)

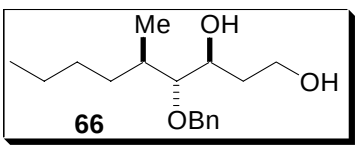
Oxalyl chloride (291 mg, 2.29 mmol) was added to a solution of (*R*)-(–)-MTPA (e.e.≥ 99%, 100 mg, 0.43 mmol) and DMF (31.0 mg, 0.43 mmol) in hexane (5 ml) at r.t.. A white precipitate formed immediately. After 60 min the mixture was passed through a small cotton plug to filter off the formed DMFCl. The filtrate was concentrated under reduced pressure to yield the acid chloride (MTPACl).

A solution of the epoxide **67** (41 mg, 0.31 mmol), Et_3N (163 mg, 1.61 mmol) and DMAP (4 mg) in CH_2Cl_2 (5 ml) were added to a solution of the acid chloride in CH_2Cl_2 (2 ml) solution. The mixture was stirred for 2 h and then quenched by addition of water (2 ml). The organic solution was washed with 0.5M HCl, followed by saturated $NaHCO_3$ solution and water. The CH_2Cl_2 was dried (Na_2SO_4), filtered and evaporated. The product was purified by column chromatography with diethyl ether-hexane (3:4) as eluent to give the Mosher ester **163a** (50.0 mg, 71%) as a colourless oil..

δ_H 0.877 (t, 3H, J 7.0, H-9)
0.965 (d, 3H, J 7.0, 5-Me)
1.90-1.10 (m, H-8, H-7, H-6, H-5)
2.882 (dd, 1H, $J_{3,4}$ 4.9, $J_{2,3}$ 2.1, H-3)
3.190 (ddd, 1H, $J_{1b,2}$ 5.9, $J_{1a,2}$ 3.1, $J_{2,3}$ 2.1, H-2)
3.200 (dd, 1H, $J_{3,4}$ 4.9, $J_{4,5}$ 4.7, H-4)
3.540 (q, 3H, $J_{H,F}$ 1.3, OMe)
4.175 (dd, 1H, $J_{1a,1b}$ 12.2, $J_{1b,2}$ 5.9, H-1b)
4.471 (dd, 1H, $J_{1a,1b}$ 12.1, $J_{1a,2}$ 3.1, H-1a)
4.489 (d, 1H, J 11.9, OCH_2Ph)
4.544 (d. 1H, J 11.9, OCH_2Ph)
7.60-7.24 (m, 5H, aromatic protons)

δ_C 166.31S (CO); 138.68S, 132.04S, 129.67D, 128.45D, 128.33D, 127.62D, 127.57D, 127.34D (aromatic carbons); 121.31Sq ($J_{C,F}$ 288, CF_3); 80.82D (C-4); 73.05T (OCH_2Ph); 65.57T (C-1); 55.92D (C-2); 55.47Q (OMe); 52.65D (C-3); 36.36D (C-5); 31.67T (C-6); 29.44T (C-7); 22.85T (C-8); 15.27Q (5-Me); 14.02Q (C-9).

δ_F –72.17, –72.10 (98:2)



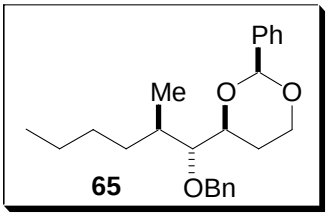
(3*S*,4*R*,5*R*)-4-Benzyloxy-5-methylnonane-1,3-diol (66)

Red-Al (3.4M in toluene, 2.0 ml) was added to a solution of the epoxy alcohol **67** (1.00 g, 3.59 mmol) in dry THF (10 ml). The mixture was stirred for 5 h and then quenched by the addition of methanol (2 ml). The reaction mixture was poured into water (x ml) and acidified with 1M HCl. The emulsion was diluted with hexane (20 ml) and extracted with EtOAc (2x20 ml). The combined organic solutions were washed with brine, dried (Na_2SO_4) and evaporated to give the 1,3-diol **66** (593 mg, 59%) as a colourless oil.

FAB-MS: *m/z* 281 $[M+H]^+$. Exact mass: Calculated for $C_{17}H_{29}O_3$, 281.2117; Found, 281.2116.

δ_H 0.924 (d, 3H, J 7.0, 5-Me)
0.881 (t, 3H, J 7.0, H-9)
1.41-1.13 (m, 5H, H-6b, H-7, H-8)
1.80-1.61 (m, 2H, H-5, H-6a)
1.768 (ddd, 2H, $J_{1a,2}$ 5.0, $J_{1b,2}$ 5.0, $J_{2,3}$ 5.0, H-2)
2.69 (br s, 2H, OH)
3.243 (dd, 1H, $J_{3,4}$ 4.7, $J_{4.5}$ 6.2, H-4)
3.785 (dd, 1H, $J_{1a,1b}$ 10.9, $J_{1b,2}$ 5.0, H-1b)
3.860 (dd, 1H, $J_{1a,1b}$ 10.9, $J_{1b,2}$ 5.2, H-1a)
3.994 (dt, 1H, $J_{2,3}$ 5.2 , $J_{3,4}$ 4.7, H-3)
4.676 (d, 2H, J 11.4, OCH_2Ph)
7.33-7.23 (m, 5H, aromatic protons)

δ_C 138.66S, 128.41D, 127.66D (aromatic carbons); 87.25D (C-4); 74.69T (OCH_2Ph); 72.42D (C-3); 61.59T (C-1); 34.85D (C-5); 33.65T (C-2); 31.89T (C-7); 29.40T (C-6); 22.99T (C-8); 16.37Q (5-Me); 14.08Q (C-9).



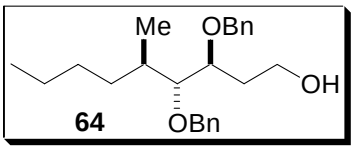
(1′*R*,2*S*,4*S*,2′*R*)-4-(1′-Benzyloxy-2′-methylhexan-1′-yl)-2-phenyl-[1,3]dioxane (65)

p-Toluenesulfonic acid (110 mg) was added to a solution of (3*S*,4*R*,5*R*)-4-benzyloxy-5-methylnonane-1,3-diol (**66**) (3.10 g, 11.1 mmol) and α,α-dimethoxytoluene (3.40 g, 22.1 mmol) in CH_2Cl_2 (30 ml) and the solution stirred for 3 h at r.t. The acid was neutralized by the addition triethylamine (3 ml) and the solution washed with water. The organic phase was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography using diethyl ether-hexane (1:4) as eluent to give the benzylidene derivative **65** (3.26 g, 80%), a colourless oil as a single diastereomer.

FAB-MS: *m/z* 369 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{33}O_3$, 369.2430; Found, 369.2429.

δ_H 0.871 (t, 3H, J 7.0, H-9)
0.974 (d, 3H, J 7.0, 2′-Me)
1.38-1.17 (m, 5H, H-3′b, H-4′, H-5′)
1.634 (m, 1H, $J_{5a,5b}$ 13.4, H-5b)
1.65-1.57 (m, 1H, H-3′a)
1.809 (m, 1H, H-2′)
2.077 (dddd, 1H, $J_{5a,5b}$ 13.4, $J_{5a,6b}$ 12.5, $J_{4,5a}$ 11.2, $J_{5a,6a}$ 5.2, H-5a)
3.391 (dd, 1H, $J_{1',2'}$ 5.9, $J_{4,1'}$ 5.2, H-1′)
3.963 (ddd, 1H, $J_{5a,6b}$ 12.4, $J_{6a,6b}$ 11.4, $J_{5b,6b}$ 2.6, H-6b)
4.025 (ddd, 1H, $J_{4,5a}$ 11.1, $J_{4,1'}$ 5.2, $J_{4,5b}$ 2.3, H-4)
4.303 (ddd, 1H, $J_{6a,6b}$ 11.4, $J_{5a,6a}$ 5.2, $J_{5b,6a}$ 1.4, H-6a)
4.605 (d, 1H, J 11.4, OCH_2Ph)
4.768 (d, 1H, J 11.4, OCH_2Ph)
5.496 (s, 1H, H-2)
7.51-7.24 (m, 10H, aromatic protons)

δ_C 138.93S, 138.88S, 128.66D, 128.28D, 128.18D, 127.92D, 127.49D,6.02D (aromatic carbons); 101.38D (C-2); 85.37D (C-1′); 78.25D (C-4); 74.48T (OCH_2Ph); 67.16T (C-6); 34.39D (C-2′); 31.76T (C-3′); 29.39T (C-4′); 26.99T (C-5); 22.98T (C-5′); 16.39Q (2′-Me); 14.07Q (C-6′).



(3*S*,4*R*,5*R*)-3,4-Di(benzyloxy)-5-methylnonan-1-ol (64)

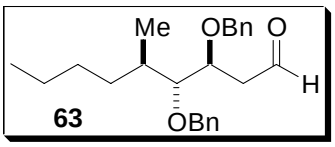
DIBALH (2.90 g, 20.3 mmol) was added by syringe to a solution of the benzylidene **(65)** (3.00 g, 8.15 mmol) in dry CH_2Cl_2 (50 ml) at –78°C. The reaction mixture was stirred r.t. for 2 h. The excess DIBALH was destroyed by careful addition of methanol (85 ml) followed by saturated NH_4Cl solution (50 ml). 0.05M HCl (15 ml) was added and the mixture extracted with CH_2Cl_2 (3x30 ml). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography with EtOAc-hexane (3:5) as eluent to give the allylic alcohol **64** (1.91 g, 64%) as a colourless oil; R_f 0.70).

FAB-MS: *m/z* 371 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{35}O_3$, 371.2586; Found, 371.2585.

δ_H 0.862 (t, 3H, J 7.0, C-9)
0.868 (d, 3H, J 7.0, 5-Me)
1.28-1.15 (m, 6H, H-6, H-8, H-7)
1.70-1.58 (m, H, H-5)
1.828 (dddd, 1H, $J_{2a,2b}$ 15.0, J 7.0, J 4.1, $J_{2b,3}$ 3.8, H-2b)
1.968 (dddd, 1H, $J_{2a,2b}$ 15.0, $J_{2a,3}$ 7.6, J 7.0, J 4.1, H-2a)
3.442 (dd,1H, $J_{4,5}$ 7.5, $J_{3,4}$ 2.9, H-4)
3.699 (ddd, 1H, $J_{1a,1b}$ 10.9, J 6.7, J 3.9, H-1b)*
3.774 (ddd, 1H, $J_{1a,1b}$ 10.9, J 8.8, J 2.8, H-1a)*
3.797 (ddd, 1H, $J_{2a,3}$ 7.8 , $J_{2b,3}$ 3.6, $J_{3,4}$ 2.9, H-3)
4.520 (d, 1H, J 11.6, OCH_2Ph)
4.569 (d, 1H, J 11.1, OCH_2Ph)
4.636 (d, 1H, J 11.6, OCH_2Ph)
4.857 (d, 1H, J 11.1, OCH_2Ph)
7.34-7.23 (m, 10H, aromatic protons)
* after D_2O exchange

δ_C 138.76S, 138.24S, 128.49D, 128.27D, 127.93D, 127.87D, 127.78D, 127.49D (aromatic carbons); 83.69D (C-4); 79.45D (C-3); 74.49T (OCH_2Ph); 71.44T (OCH_2Ph); 60.04T (C-1); 35.17D (C-5); 32.52T (C-6); 31.75T (C-2); 29.02T (C-7); 23.03T (C-8); 16.34Q (5-Me); 14.08Q (C-9).

5.4.8 Synthesis of ethyl (2*E*,5*S*,6*R*,7*R*)-5,6-di(benzyloxy)7-methylundec-2-enoate (62)



(3*S*,4*R*,5*R*)-3,4-Di-(benzyloxy)-5-methylnonanal (63)

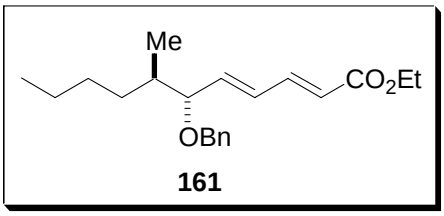
Dry DMSO (90 mg, 1.19 mmol) was added to a cooled (–78°C) solution of oxalyl chloride (100 mg, 0.81mmol) in CH_2Cl_2 (5 ml). After 15 min a solution of the alcohol **168** (200 mg, 0.54 mmol) in dry CH_2Cl_2 (2.5 ml) was added dropwise over a period of 5 min. The resulting mixture was stirred for 90 min after which triethylamine (1.07 g, 10.6 mmol) was added to the reaction mixture. After 60 min the cooling bath was removed to allow the mixture to reach 0°C. The reaction mixture was then diluted with CH_2Cl_2 (25 ml) and washed with saturated NH_4Cl solution (30 ml). The organic solution was dried (Na_2SO_4), filtered and evaporated. Column chromatography of the product with EtOAc-hexane (1:10) gave the aldehyde **63** (120 mg, 65%) as a colourless oil; R_f 0.56.

δ_H 0.857 (t, 3H, J 7.0, H-9)
0.882 (d, 3H, J 7.0, 5-Me)
2.609 (ddd, 1H, $J_{2a,2b}$ 16.8, $J_{2b,3}$ 4.4, $J_{1,2b}$ 1.8, H-2b)
2.806 (ddd, 1H, $J_{2a,2b}$ 16.8, $J_{2a,3}$ 7.0, $J_{1,2a}$ 2.5, H-2a)
3.434 (dd, 1H, $J_{4.5}$ 6.5, $J_{3,4}$ 3.4, H-4)
4.113 (ddd, 1H, $J_{2a,3}$ 7.0, $J_{2b,3}$ 4.4, $J_{3,4}$ 3.4, H-3)
4.555 (d, 1H, J 11.4, OCH_2Ph)
4.561 (d, 1H, J 11.4, OCH_2Ph)
4.572 (d, 1H, J 11.4, OCH_2Ph)
4.758 (d, 1H, J 11.4, OCH_2Ph)

7.34-7.22 (m, 10H, aromatic protons)

9.778 (dd, 1H, $J_{1,2a}$ 2.5, $J_{1,2b}$ 1.8, H-1)

δ_C 201.39D (C-1); 137.99S, 128.45D, 128.31D, 127.89D, 127.53D (aromatic carbons); 84.04D (C-4); 76.32D (C-3); 74.21T (OCH_2Ph); 71.71T (OCH_2Ph); 44.55T (C-2); 35.18D (C-5); 32.22T (C-6); 29.21T (C-7); 22.99T (C-8); 16.25Q (5-Me); 14.08Q (C-9).



161

Ethyl (6*R*,7*R*)-6-benzyloxy-7-methyl-undeca-2,4-dienoate (161)

Potassium t-butoxide (0.17g, 1.48mmol) was added to a solution of triethylphosphonoacetate (0.40g, 1.67mmol) in dry THF (10ml) at 0°C. The reaction mixture was then stirred for 60 min. and cooled to –78°C. A solution of the aldehyde (**63**) (0.12 g, 0.33 mmol) in dry THF (5 ml) was added dropwise to the phosphonate solution. The reaction mixture was then stirred at –78°C for 90 minutes, after which it was quenched with saturated NH_4Cl solution and washed with brine. The crude product was extracted with dichloromethane (2x30 ml), dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography with EtOAc-hexane (1:19) to give the diene ester (**161**) (0.15 g) as an oil.

δ_H 0.863 (t, 3H, J 7.0, H-11)

0.845 (d, 3H, J 7.0, 7-Me)

1.284 (t, 3H, J 7.2, $OCH_2C\mathbf{H}_3$)

1.53-1.10 (m, 6H, H-8, H-9, H-10)

1.731 (m, 1H, H-7)

3.669 (ddd, 1H, J 6.2, J 6.0, $J_{4,6}$ 0.8, H-6)

4.199 (q, 2H, J 7.0, $OC\mathbf{H}_2CH_3$)

4.330 (d, 1H, J 11.9, OCH_2Ph)

4.545 (d, 1H, J 11.9, OCH_2Ph)

5.874 (d, 1H, $J_{2,3}$ 15.5, H-2)

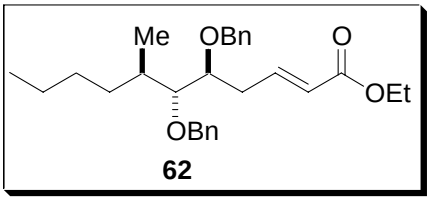
6.015 (ddd, 1H, $J_{4,5}$ 15.3, $J_{5,6}$ 7.5, H-5)

6.302 (dddd, 1H, $J_{4,5}$ 15.5, $J_{3,4}$ 11.1, J 1.0, $J_{4,6}$ 0.8, H-4)

7.294 (ddd, 1H, $J_{2,3}$ 15,5, $J_{3,4}$ 11.1, $J_{3,5}$ 0.8, H-3)

7.35-7.26 (m, 5H, aromatic protons)

δ_C 166.97S (ester CO); 143.67D (C-3); 141.76D (C-5); 130.41D(C-4); 138.60S, 128.32D, 127.62D, 127.49D (aromatic carbons); 121.41d (C-2); 83.22D (C-6); 70.73T (OCH_2Ph); 60.33T (OCH_2CH_3); 37.73D (C-7); 32.34T (C-8); 29.18T (C-9); 22.91T (C-10); 15.20Q (7-Me); 14.29Q (OCH_2CH_3); 14.06Q (C-11).



62

Ethyl (2*E*,5*S*,6*R*,7*R*)-5,6-Di-(benzyloxy)-7-methylundec-2-enoate (62)

Ethyl (triphenylphosphoranylidene)acetate (110 mg, 0.323 mmol) was added to a solution of the aldehyde (**63**) (59 mg, 0.16 mmol) in toluene (5 ml). The solution was stirred at room temperature for 24 h. The solvent was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated to give the crude α,β-unsaturated ester (**62**) (68 mg, 96%) as an oil.

δ_H 0.851 (t, 3H, J 7.0, H-11)

0.888 (d, 3H, J 7.0, 7-Me)

1.267 (t, 3H, J 7.2, $OCH_2C\mathbf{H}_3$)

2.00-1.20 (m, 7H, H-7, H-8, H-9, H-10)

2.508 (dddd, 1H, $J_{4a,4b}$ 15.1, $J_{3,4b}$ 7.3, $J_{4b,5}$ 3.6, $J_{2,4b}$ 1.5, H-4b)

2.599 (dddd, 1H, $J_{4a,4b}$ 15.1, $J_{3,4a}$ 7.3, $J_{4a,5}$ 7.4, $J_{2,4a}$ 1.3, H-4a)

3.380 (dd, 1H, $J_{6,7}$ 6.5, $J_{5,6}$ 4.2, H-6)

3.563 (ddd, 1H, $J_{4a,5}$ 7.4, $J_{5,6}$ 4.2, $J_{4b,5}$ 3.5, H-5)

4.166 (q, 2H, J 7.0, OC**H**$_2$CH$_3$)

4.517 (d, 1H, J 11.5, OCH$_2$Ph)

4.540 (d, 1H, J 11.5, OCH$_2$Ph)

4.559 (d, 1H, J 11.3, OCH$_2$Ph)

4.738 (d, 1H, J 11.3, OCH$_2$Ph)

5.858 (ddd, 1H, $J_{2,3}$ 15.7, $J_{2,4a}$ 1.3, $J_{2,4b}$ 1.5, H-2)

7.054 (ddd, 1H, $J_{2,3}$ 15.7, $J_{3,4a}$ 7.2, $J_{3,4b}$ 7.2, H-3)

7.34-7.25 (m, 10H, aromatic protons)