Synthetic Studies on the C(1)-C(9) Unit of TA Toxin using Nucleophilic Opening of Chiral Epoxides

by

ZSUZSANNA FÖLDVÁRI

Submitted in partial fulfilment of the requirements for the degree

MAGISTER SCIENTIAE

in the Faculty of Natural & Agricultural Sciences

UNIVERSITY OF PRETORIA
PRETORIA

Supervisor: Prof. R. Vleggaar

September 2002

SUMMARY

TA and TB toxins are host-specific phytotoxins produced by the fungus *Alternaria alternata* f. sp. *lycopersici*, the causative agent of stem canker disease in tomato. The two toxins are similar in structure: TB lacks the C(5) hydroxy group present in TA toxin. Both compounds are isolated as an equilibrium mixture of the two esters formed by either the C(13) or C(14) hydroxy groups of the (2*S*,4*R*,5*R*,11*R*,13*S*,14*R*,15*R*)-1-amino-11,15-dimethylhepta-decane-2,4,5,13,14-pentol backbone with the *Re* prochiral carboxy group of tricarballylic acid. The synthesis for these toxins is necessary in order to study their structure-activity relationships.

The aim of the synthetic study outlined in this dissertation is the development and implementation of methodology for the synthesis of the C(1)-C(9) unit of the C_{17} aminopentol backbone of TA toxin with the appropriate stereochemistry.

Retrosynthetic analysis of the C_{17} aminopentol backbone of TA toxin identifies (2*R*,4*S*,-5*R*,6*R*)-2,6-dimethyloctane-1,4,5-triol, synthon **B**, and (2*S*,4*R*,5*R*)-1-amino-nonane-2,4,5,9-tetrol, synthon **A** as key intermediates for the proposed synthesis. Further analysis of synthon **A** identifies the C_9 synthon (2*S*,4*R*,5*R*)-nonane-1,2,4,5,9-pentol, as the target molecule which can be derived from the C_7 synthon (2*S*,3*R*)-1,2-epoxyheptane-3,7-diol. The work presented in this dissertation shows that the protected intermediate corresponding to the abovementioned C_7 synthon, can be prepared from 1,5-pentanediol by a number of functional group trans-formations using appropriate protecting group strategy (*O*-TBS, *O*-TBDPS and *O*-benzyl groups) and introduction of the two stereogenic centres by using Sharpless epoxidation/kinetic resolution methodology. Nucleophilic opening of the terminal epoxide using cyanide was successful but using chiral sulfoxide methodology for the introduction of the third stereogenic centre and the concomitant one-carbon chain extension, failed: in the case of both an acetonide and a dibenzyl protected C_8 intermediate a rearrangement occurred. Alternative methods for nucleophilic opening of the terminal epoxide ring and concomitant or subsequent chain extension were investigated and as a result a different synthetic route is proposed.

OPSOMMING

TA- en TB-toksien is gasheerspesifieke fitotoksiene wat deur *Alternaria alternata* f. sp. *lycopersici*, die fungus verantwoordelik vir die voorkoms van stingelkanker by tamaties, geproduseer word. Die twee toksiene is struktureel nouverwant: die C(5) hidroksigroep teenwoordig in TA-toksien ontbreek in TB-toksien. Beide verbindings word geïsoleer as 'n ewewigsmengsel van die esters gevorm deur die reaksie van of die C(13)- of die C(14)-hidroksigroep van die (2*S*,4*R*,5*R*,11*R*,13*S*,14*R*,15*R*)-1-amino-11,15-dimetielheptadekaan-2,4,-5,13,14-pentol ruggraat met die *Re* karboksigroep van trikarballielsuur. Die sintese van hierdie toksiene is nodig teneinde struktuur-aktiwiteitsverwantskappe te bestudeer.

Die doel van die sintetiese studies wat in hierdie verhandeling beskryf word, is om metodiek te ontwikkel en toe te pas vir die sintese van die C(1)–C(9)-eenheid van die C_{17}-ruggraat van TA-toksien met die toepaslike stereochemie.

Retrosintetiese analise van die C_{17}-aminopentolruggraat van TA-toksien identifiseer (2*R*,-4*S*,5*R*,6*R*)-2,6-dimetieloktaan-1,4,5-triol, bousteen **B**, en (2*S*,4*R*,5*R*)-1-aminononaan-2,4,5,9-tetrol, bousteen **A** as sleutelverbindings in 'n voornemende sintese. Verdere analise van bousteen **A** toon dat die C_9-bousteen (2*S*,4*R*,5*R*)-nonaan-1,2,4,5,9-pentol kan dien as die doelwitmolekule wat op sy beurt weer vanaf die C_7-bousteen (2*S*,3*R*)-1,2-epoksiheptaan-3,7-diol verkry kan word. Die werk wat in hierdie verhandeling beskryf word, wys dat die beskermde tussenverbinding, wat ooreenstem met bogenoemde C_7-bousteen, berei kan word vanaf 1,5-pentaandiol deur 'n aantal funksionele groep omskakelings en die gebruik van 'n toepaslike beskermende groep strategie (*O*-TBS-, *O*-TBDPS- en *O*-bensielgroepe) terwyl die twee stereogeniese sentra deur middel van Sharpless epoksidasie/kinetiese resolusie geskep kan word. Nukleofiliese opening van die terminale epoksied met sianied was suksesvol maar die gebruik van chirale sulfoksiedmetodiek vir die daarstelling van die derde stereogeniese sentrum en die gepaardgaande een-koolstof kettingverlenging, het gefaal: in die geval van beide 'n asetonied- en 'n dibensielbeskermde C_8-nitriel tussenverbinding het 'n herrangskikking plaasgevind. Alternatiewe metodes vir die nukleofiliese opening van die terminale epoksiedring en die gepaardgaande of daaropvolgende kettingverlenging is ondersoek en 'n veranderde sintetiese roete gegrond op hierdie resultate word gevolglik voorgestel.

ACKNOWLEDGEMENTS

A sincere word of gratitude and appreciation is given to the following individuals:

My supervisor Professor Robert Vleggaar for the insight and scientific knowledge imparted to me throughout this study.

Dr. Thomas Logothetis, Dr Moira Bode and my research group during 2000-2002 for useful discussions.

Mr Eric Palmer for NMR training, and Mrs Linda Prinsloo and Ljiljana Popović for introduction to the Bruker 113v FT-IR software.

The National Research Foundation (NRF) and the University of Pretoria for financial assistance.

Toni Van Schoor, who is my spiritual guider, for her encouragement and wisdom throughout the course of my study.

Tracey Laban, HATS society and my home group for their unconditional love and moral support.

My parents and sister for serving me and showing unfailing love throughout my studies.

Finally, my Hope and Light, Jesus Christ and the Holy Spirit for Guidance, Strength, Courage and Love.

TABLE OF CONTENTS

CHAPTER 4 CHEMISTRY OF CHIRAL SULFOXIDES

CHAPTER 5 SYNTHETIC STUDIES ON THE C(1)-C(9) UNIT OF TA TOXIN

CHAPTER 6 EXPERIMENTAL

List of abbreviations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
BMS	Borane-dimethylsulfide
BnCl	Benzyl chloride
BnBr	Benzyl bromide
BOMCl	Benzyloxymethyl chloride
BuLi	Butyl lithium
CbzCl	Benzyloxycarbonyl chloride
DCC	Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
DHQD-IND	Dihydroquinidine indolinylcarbamate
$(DHQD)_2PHAL$	1,4-bis(Dihydoquinidinyl)-phthalazine
DET	Diethyl tartrate
DIBALH	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DMT	Dimethyl tartrate
EDC	*N*-Ethyl-*N*-(3-dimethylaminopropyl)carbodiimide
HPLC	High-performance liquid chromatography
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
MCPBA	*m*-Chloroperbenzoic acid
MsCl	Methanesulfonyl chloride
MTPA	α-Methoxy-α-trifluoromethylphenyl acetic acid
Na/Hg	Sodium amalgam

$Pd(AcO)_2$	Palladium(II) acetate
$Pd\text{-}BaSO_4$	Palladium on barium sulfate
Pd-C	Palladium on activated carbon
PPL	Porcine pancreatic lipase
PPTS	Pyridinium toluene-4-sulfonate
$i\text{-}Pr_2NEt$	Diisopropylethylamine
Py	Pyridine
Raney-Ni	Raney nickel
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPSCl	*t*-Butyldiphenylchlorosilane
TBHP	*t*-Butylhydroperoxide
TBSCl	*t*-Butyldimethylchlorosilane
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
$Ti(iPrO)_4$	Titanium(IV) isopropoxide
TLC	Thin layer chromatography
TMSCl	Trimethylchlorosilane
TMS-CN	Trimethylsilyl cyanide
TrCl	Triphenylmethyl chloride
TsCl	Toluene-4-sulfonyl chloride
TsIm	1-(Toluene-4-sulfonyl)imidazole
TsOH	Toluene-4-sulfonic acid
$VO(acac)_2$	Vanadyl acetylacetonate

1. Introduction

1.1 GENERAL

The fungus *Alternaria alternata* f.sp. *lycopersica* is the cause of stem canker in susceptible tomato cultivars. The disease was first noticed in San Diego, California in the early part of 1960 and the etiology was confirmed 15 years later.[1] Since then AAL-toxin of *A. alternata f.sp. lycopersici* has been isolated from several geographical areas including Mississippi (USA)[2], Illinois (USA)[3] and Japan.[4] The susceptibility to AAL-toxin in tomato is controlled by one genetic locus (Asc).[5] Although it is a stem disease with the characteristic appearance of a dark brown canker on the stem, it also sometimes causes interveinal necrosis of the leaves by translocation of the fungal toxins. The cause of the disease has been linked to the production of phytotoxins for which the name of AAL-toxins was coined.[6,7,8] The AAL-toxins were previously reported as host-specific to tomato plants[9] (*Lycopersicon esculentum* Mill), but were later found to affect many weed and crop species such as jimsonweed[2], black nightshade[10] and duckweed[11] and was also found to induce cell death in rat liver[12] and dog kidney[12]. AAL-toxins show phytotoxicity against tomato cultivars susceptible to stem canker diseases (genotype asc/asc), whereas the resistant cultivars (genotype Asc/Asc) show high tolerance level to the toxins.[6,5,13]

1.2 BIOLOGICAL EFFECTS OF AAL-TOXIN

Stem canker symptoms caused by AAL-toxin in *planta* include initiation of necrosis within interveinal areas of tomato leaflets.[1,14] There's evidence that the toxin moves in the phloem, since one of the disease symptoms is the browning of phloem tissue in the whole

---

[1] Grogan, R.G.; Kimble, K.A.; Misaghi, I. *Phytopathol.*, **1975**, *65*, 880.
[2] Abbas, H.K.; Vesonder, R.F.; Boyette, C.D.; Peterson, S.W. *Can. J. Bot.*, **1993**, *71*, 155.
[3] Vesonder, R.F.; Peterson, R.E.; Labeda, D.; Abbas, H.K. *Arch. Environ. Contam. Toxicol.*, **1992**, *23*, 464.
[4] Kohmoto, K.; Verma, V.S.; Nishimura, S.; Tagami, M.; Scheffer, R.P. *J. Fac. Agric., Tottori Univ.*, **1982**, 17, 1.
[5] Clouse, S.D. and Gilchrist, D.G. *Phytopathology*, **1977**, *77*, 80.
[6] Siler, D.J.; Gilchrist, D.G. *Physiol. Plant Pathol.*, **1983**, *23*, 256.
[7] Gilchrist, D.G.; Clouse, S.D.; McFarland, B.L.; Martensen, A.N. *Molecular Genetics of Filamentous Fungi,* **1985**, 405.
[8] Nishimura, S.; Kohmoto, K. *Annu. Rev. Phytopathol.*, **1983**, *21*, 87.
[9] Fuson, G.B.; Pratt, D. *Phytopathol.*, **1988**, *78*, 1641.
[10] Abbas, H.K.; Paul, R.N. *Weed Sci. Sci. Amer. Abstr.*, **1993**, *33*, 178.
[11] Vesonder, R.F.; Peterson, R.E.; Labeda, D.; Abbas, H.K. *Arch. Environ. Contam. Toxicol.*, **1992**, *23*, 464.
[12] Mirocha, C.J.; Gilchrist, D.G.; Shier, W.T.; Abbas, H.K.; Wen, Y.J.; Vesonder, R.F. *Mycopathologia*, **1992**, *117*, 47.
[13] Gilchrist, D.G.; Ward, B.; Moussatos, V.; Mirocha, C.J. *Mycopathologia*, **1992**, *117*, 57.
[14] Gilchrist, D.G.; Grogan, R.G. *Phytopathology*, **1976**, *66*, 165.

plant.[1] AAL-toxin transported through the phloem moves rapidly into the interveinal areas of tissues. This results in an increase in the uptake of AAL-toxin. The interaction of Asc and sucrose transport was observed both in the presence and in the absence of AAL-toxin. Therefore, it appears that there's a relationship between the normal physiological function of the Asc gene product and sucrose influx.[15] Normally, sucrose uptake is rapid in youngest leaves and then decreases with age. It was found that the youngest asc/asc leaflets were most sensitive to AAL-toxin whereas the intermediate asc/asc leaflets were the second most sensitive. Tissue that was sensitive to AAL-toxin suffered a perturbation of sucrose influx while the response of the tissue from the insensitive genotype showed less change in the presence of the AAL-toxin. The length of time that the leaflets were exposed to the toxin played an important role on the sucrose transport. AAL-toxin was, therefore, found to have an impact on the regulation of sucrose transportation, but not on the sucrose metabolism itself.[16]

Epinasty, a classical ethylene reaction is a common symptom of stem canker disease prior to visible cell death.[17] Studies were conducted to determine whether AAL-toxin stimulates accumulation of the ethylene precursor 1-aminocyclopropane-1-carboxylic acid, ACC, in tomato leaves.[18] It was found that ethylene appears to enhance necrosis by AAL-toxin, but did not induce cell death on its own.

AAL-toxins were found also to induce changes in the endoplasmic reticulum and in mitochondria of inoculated leaves. In toxin-treated leaves mitochondria were swollen, the matrix was leached and there was a reduction in the number of cristae, whereas the endoplasmic reticulum was swollen and vesiculated.[19] McFarland and Gilchrist indicated that this host-specific toxin inhibited the activity of aspartate transcarbamylase, ACTase, the enzyme involved in nucleotide synthesis of susceptible, and, to a lesser extent, of resistant tomato leaflets.[20] Interestingly, ACTase has been found in chloroplasts of several plant species.[21,22,23] The first step in the biosynthesis of uridine 5'-monophosphate, UMP **7** is the condensation of aspartate **1** and carbamoyl phosphate **2** catalysed by ACTase to form N-carbamoyl-L-aspartate **3**. This is followed by the conversion of **3** to dihydroorotate **4** by

[15] Moussatos, V.V.; Lucas, W.J.; Gilchrist, D.G. *Mol. Plant Pathol.*, **1993**, *42*, 359.
[16] Giaquinta, R. *Plant Physiol.*, **1992**, *57*, 872.
[17] Hansen, E.; Hartmen, H. *Oreg. Agric. Exp. Stn. Bull.*, **1935**, *342*, 1.
[18] Moussatos, V.V.; Yang, S.F.; Ward, B.W.; Gilchrist, D.G. *Physiol. Mol. Plant Pathol.*
[19] Park, P.; Nishimura, S.; Kohmoto, K.; Otani, H. *Ann. Phytopathol. Soc. Japan*, **1981**, *47*, 488.
[20] McFarland, B.L.; Gilchrist, D.G. *Phytopathology*, **1981**, *71*, 240.
[21] Doremus, H.D.; Jagendorf, A.T. *Plant Physiol.*, **1985**, *79*, 856.
[22] Shibita, H.; Ochiai, H.; Sawa, Y.; Miyoshi *Plant Physiol.*, **1986**, *80*, 126.
[23] Shibita, H.; Sawa Y.; Ochiai, H.; Kawasima, T. and Yamane, K. *Plant Sci.*, **1987**, *51*, 129.

intramolecular dehydration as well as cyclization. Dihydroorotate is converted to orotate **5** by another enzyme, dihydroorotate dehydrogenase. Conversion of **5** to orotidine 5'-mono-phosphate **6** is catalysed by orotate phosphoribosyl transferase. The pyrimidine nucleotide **7** is then formed by the enzymatic decarboxylation of **6**. It was also found that **7** inhibits the ACTase step via a negative feedback mechanism. Gilchrist *et al.* found that in the presence of **7**, AAL toxin interferes with the binding of **2** in a competitive manner for ACTase from both Asc/Asc and asc/asc genotypic tomatoes.[7] Moreover, a synergism takes place between the toxin and **7** for the asc/asc ACTase and was twice as great as that for the ACTase from tolerant tissue (Asc/Asc) at saturation level of **1**. The degree of the synergistic interaction of **7** and AAL-toxin is dependent upon the concentration of **1** in the reaction mixture. The binding of AAL-toxin to the allosteric site of ACTase from tomato leads to a conformational change that enhances the sensitivity to the natural feedback inhibitor **7**. Kinetic data prove that the synergistic interaction between AAL-toxin and **7** results in ACTase activity reaching zero at concentrations of **7** that are normally not inhibitory.

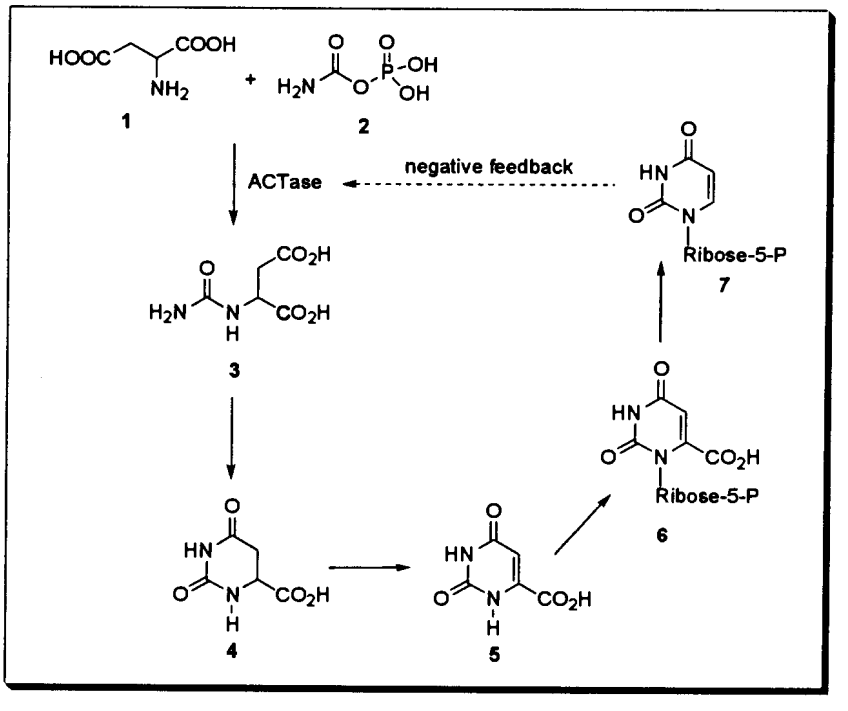


Figure 1.1 Orotic acid pathway of pyrimidine biosynthesis in higher plants.

Fuson and Pratt[24] found that AAL-toxin in susceptible tomato cultivars inhibited the uptake of [^{3}H]uridine and [^{3}H]thymidine, the building blocks of RNA and DNA, respectively, but

[24] Fuson, G.B.; Pratt, D. *Physiol. Biochem.*, **1988**, *78*, 1641.

that uptake of neither DNA nor RNA was inhibited by the failure in uptake of uridine or thymidine.

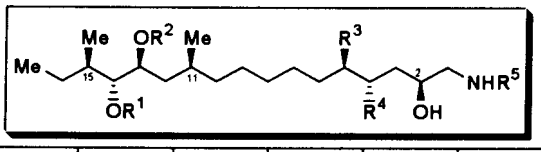
Tanaka *et al.* [25] carried out studies on the physiological mode action of AAL-toxin and found that the mechanism by which AAL toxin causes toxicity in plants involves the disruption of sphingolipid metabolism via inhibition of ceramide synthesis. Sphingolipids are important constituents of cell membranes in animals and plants,[26,27,28,] but their role in plants is not well studied. AAL-toxin inhibits the enzyme sphinganine (sphingosine) N-acyltransferase (ceramide synthase), suggesting that these compounds are competitive inhibitors of the enzyme due to the structural similarities between the toxins and sphingolipids.[29,30] AAL-toxin is thought to compete with sphinganine and other sphingolipids for the enzyme ceramide synthase and causes the accumulation of sphinganine, the depletion of complex sphingolipids, an increase in degradation products from the catabolism of free sphingoid bases, and an increase in free sphingosine presumably from inhibition of the reacylation of sphingosine.[31] Therefore, the effect of AAL-toxin can be determined by measuring the increase of free sphingoid bases in plant and animal systems.

1.3 ISOLATION, STRUCTURAL ELUCIDATION AND STEREOCHEMICAL ANALYSIS OF AAL-TOXIN

Bottini and Gilchrist reported in two separate papers the presence of two ninhydrin-positive substances in the thin layer chromatography (TLC) analysis of the cell-free culture filtrates of the fungus *A. alternata*.[32,33] The two substances, TA and TB, each consists of an equilibrium mixture in which either the C(13) or the C(14) hydroxy group is linked by an ester linkage with one of the prochiral carboxyl groups of tricarballylic acid. Both purified compounds produce the necrotic symptoms of the disease and are genotype specific in the induction of necrosis, and are toxic at equal molar concentrations. These toxins were named TA_1 (**8**) and TA_2 (**9**), and TB_1 (**10**) and TB_2 (**11**).[32,33] More recently three new regioisomeric AAL-toxin pairs TC_1 (**12**) and TC_2 (**13**), TD_1 (**14**) and TD_2 (**15**), TE_1 (**16**) and TE_2 (**17**) have

[25] Tanaka, T.; Abbas, H.K.; Duke, S.O.; *Phytochemistry*, **1993**, *33*, 779.
[26] Shier, W.T. *J. Toxicol-Toxin Rev.*, **1992**, *11*, 241.
[27] Dharmawardhane, S.; Rubinstein, B.; Stern, A. *Plant Physiol.*, **1989**, *89*, 1345.
[28] Hannum, Y.A.; Bell, R.M. *Science (Washington)*, **1989**, *243*, 500.
[29] Riley, R.T.; Hinton, D.M.; Chamberlain, W.J.; Bacon, C.W.; Merrill, A.H.; Voss, K. *J. Nutr.*, **1994**, *124*, 594.
[30] Wang, E.; Norred, W.P.; Bacon, C.W.; Riley, R.T.; Merrill, A.H. Jr. *J. Biol. Chem.*, **1991**, *266*, 14486.
[31] Riley, R.T.; Voss, K.A.; Yoo, H.S.; Gelderblom, W.C.A.; Merrill, A.H. Jr. *J. Food Prot.*, **1994**, *57*, 638.
[32] Bottini, A.T.; Gilchrist, D.G. *Tetrahedron Lett.*, **1981**, *22*, 2719.
[33] Bottini, A.T.; Bowen, J.R.; Gilchrist, D.G. *Tetrahedron Lett.*, **1981**, *22*, 2723.

been isolated,[34] All regioisomeric pairs induce the genotype-specific necrosis characteristic of TA in tomato bioassays but differ markedly in relative toxicity.



	R¹	R²	R³	R⁴	R⁵
8 TA_1	H	TCA	OH	OH	H
9 TA_2	TCA	H	OH	OH	H
10 TB_1	H	TCA	H	OH	H
11 TB_2	TCA	H	H	OH	H
12 TC_1	H	TCA	H	H	H
13 TC_2	TCA	H	H	H	H
14 TD_1	H	TCA	H	OH	Ac
15 TD_2	TCA	H	H	OH	Ac
16 TE_1	H	TCA	H	H	Ac
17 TE_2	TCA	H	H	H	Ac

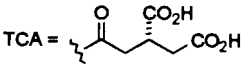


Table 1.1 Structures of the AAL-toxins.

1.3.1 Isolation of the AAL-toxins

There have been quite a few methods for the isolation of the AAL-toxin from the culture filtrates of *A. alternata*. At first only TA (**8/9**) and TB (**10/11**) were isolated. Siler *et al.*[35] used a procedure involving barium acetate precipitation, butanol extraction, gel filtration and semi-preparative thin-layer chromatography. Clouse *et al.*[36] directly absorbed and partitioned the filtrate on C_{18} reversed-phase columns and cleaned up the products by gel filtration. The toxins were analysed by high-performance liquid chromatography (HPLC) of their maleyl derivatives.[35] Although these derivatives of TA and TB could be separated by isocratic HPLC,

[34] Caldas, E.D.; Jones, A.D.; Ward, B.; Winter, C.K.; Gilchrist, D.G. *J. Agric. Food Chem.*, **1994**, *42*, 327.
[35] Siler, D.J.; Gilchrist, D.G. *J. Chromatogr.*, **1982**, *238*, 167.
[36] Clouse, S.D.; Martensen, A.N.; Gilchrist, D.G. *J. Chromatogr.*, **1985**, *350*, 255.

a binary gradient (60 min analysis time) was required for partial separation of the individual structural isomers of the toxins.

It was only when Shephard *et al.*[37] developed a rapid, sensitive and reproducible method for the determination of the AAL-toxins that it was possible for Caldas *et al.*[34] to detect three new pairs of biologically active regioisomeric toxins.This method involved the blending of the ground culture material with chloroform-methanol (10:3, v/v). The mixture was filtered, washed with extraction solvent and dried. Subsamples of this dried culture material were further extracted with water. After each extraction, the homogenate was centrifuged and supernatants from all extractions were pooled, acidified to pH 2.7 with 2M hydrochloric acid and then centrifuged. The clear supernatant was applied to a column of Amberlite XAD-2 resin. After application of the sample, the resin was washed with water, methanol-water (1:3, v/v) and the toxins were eluted with methanol, which was removed under vacuum. The residue was dissolved in ethyl acetate-acetic acid-water (12:6:1, v/v/v) and fractionated on a silica gel column with the same solvent as eluant. The fractions were tested for toxins by TLC using ethyl acetate-acetic acid-water (6:3:1, v/v/v) as eluant. The toxins appeared as purple spots by spraying with *p*-anisaldehyde reagent.[38] Further clean-up and purification consisted of C_{18} solid-phase extraction, pre-column derivatisation with *o*-phthaldialdehyde and reversed-phase HPLC with fluorescence detection. Caldas *et al.*[34] adapted this method to separate the three new pairs of *p*-anisaldehyde positive toxins. They first used the less polar eluant (ethyl acetate/acetic acid/hexane/water, 6:2:2:1) before switching to the eluant used for TLC development. Since *p*-anisaldehyde does not only react with primary amines but also with hydroxy groups, Caldas *et al.*[34] were able to detect two additional biologically active compounds, designated TD (**14/15**) and TE (**16/17**) which constituted up to 40% of the total AAL toxins produced under these conditions. These compounds were ninhydrin negative as they lacked a free amino group. The fifth AAL-toxin designated TC (**12/13**), is ninhydrin positive and occurred at <5% of the concentration of TA (**8/9**) and TB (**10/11**).

1.3.2 Structure elucidation and stereochemical studies of AAL-toxin

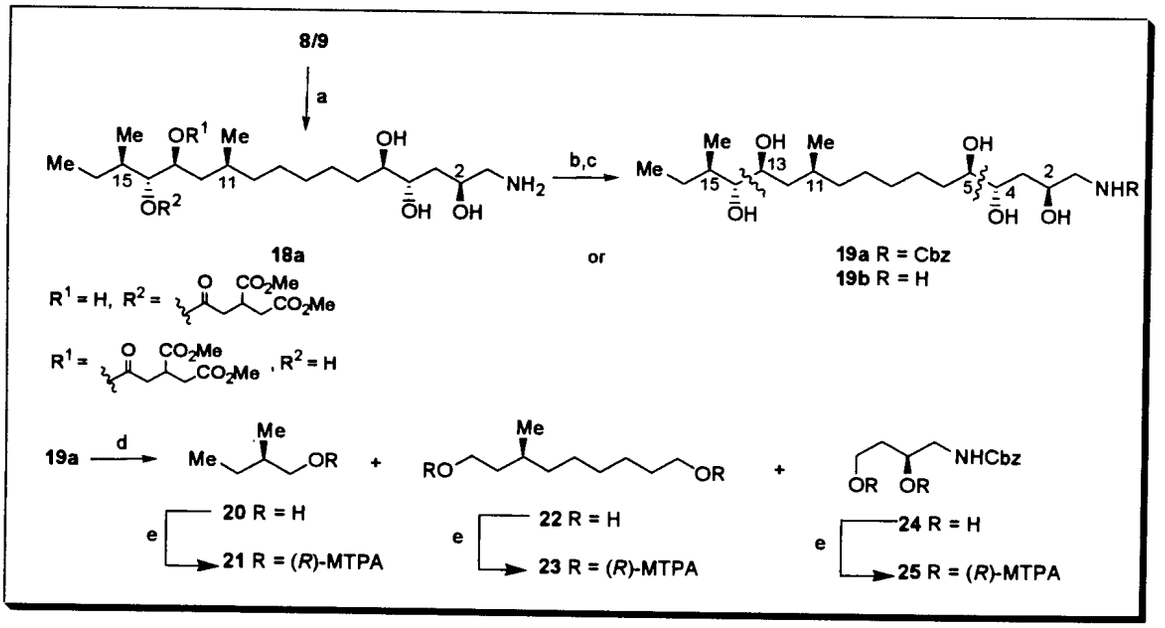
Bottini *et al.*[32,33] determined the 2D-structure of TA (**8/9**) and TB (**10/11**) by using high-resolution mass spectrometry, ^{1}H- and ^{13}C-NMR spectroscopy. Caldas *et al.*[34] employed

[37] Shephard, G.S.; Thiel, P.G.; Marasas, W.F.O.; Sydenham, E.W.; Vleggaar, R. *J. Chromatogr.*, **1993**, *641*, 95.
[38] 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.

positive ion fast atom bombardment (FAB) mass spectrometry and NMR spectroscopy to identify and determine the structures of the TC, TD and TE compounds.

The relative and absolute configuration of the AAL toxins was determined by Oikawa *et al.*[39,40] and Kishi *et al.*[41]

The absolute configuration of seven of the stereogenic centres present in TA toxin (**8/9**) were reported by the Oikawa group[39,40] and involved the degradation of the aminopentol backbone. TA toxin (**8/9**), isolated from cultures of the tomato pathotype *Alternaria alternata* f.sp. *lycopersici* (O-227)[42], was converted to the tetramethyl ester derivative **18a**. The amino group was protected as the carbobenzyloxy (Cbz) derivative and the tricarballylic ester moieties removed by base hydrolysis to give the *N*-Cbz protected aminopentol backbone **19a**.



Scheme 1.1 Degradation of the aminopentol backbone of TA toxin.

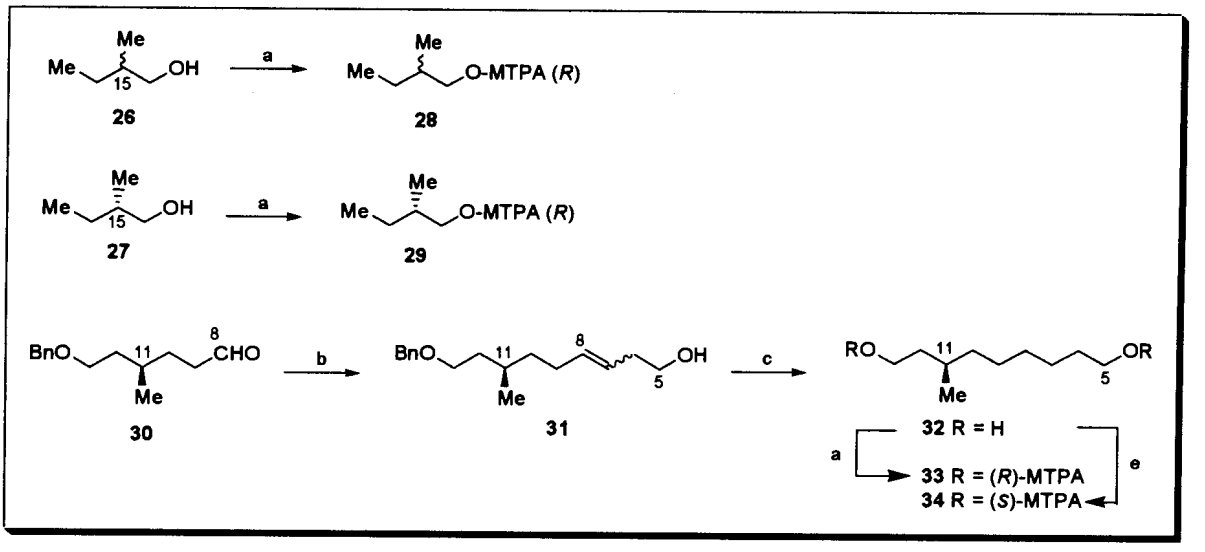
Reagents : a. CH_2N_2, MeOH; b. CbzCl, $NaHCO_3$, H_2O; c. NaOH, MeOH; d. $NaIO_4$ THF-H_2O (1:1), then $NaBH_4$; e. (*R*)-MTPA, DCC, DMAP, CH_2Cl_2.

Oxidative cleavage of the C(4)-C(5) and C(14)-C(15) bonds in **19a** with $NaIO_4$ and reduction of the formed aldehydes with $NaBH_4$ yielded the alcohols **20, 22** and **24**. These alcohols were

[39] Oikawa, H.; Matsuda, I.; Ichihara, A.; Kohmoto, K. *Tetrahedron,* **1994**, *35,* 1223.
[40] Oikawa, H.; Matsuda, I.; Kagawa, T.; Ichihara, A.; Kohmoto, K. *Tetrahedron*, **1994**, *50*, 13347.
[41] Kishi, Y.; Boyle, C. *Tetrahedron Lett.,* **1995**, *36*, 5695.
[42] Kohmoto, K.; Verma, V.S.; Nishimura, S.; Takagi, M.; Scheffer, R.P. *J. Fac. Agric., Tottori Univ.* **1982**, *17,* 1.

then converted to the (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate (MTPA) esters **21, 23** and **25**, respectively (see Scheme 1.1).

(*RS*)- and (*S*)-2-Methylbutanol are commercially available and were converted to their (*R*)-MTPA derivatives **28** and **29**, respectively (see Scheme 1.2). Comparison of the ^{1}H NMR spectrum of the degradation product **20** with those of the synthetic samples, **28** and **29** established the C(15) configuration as *R*.

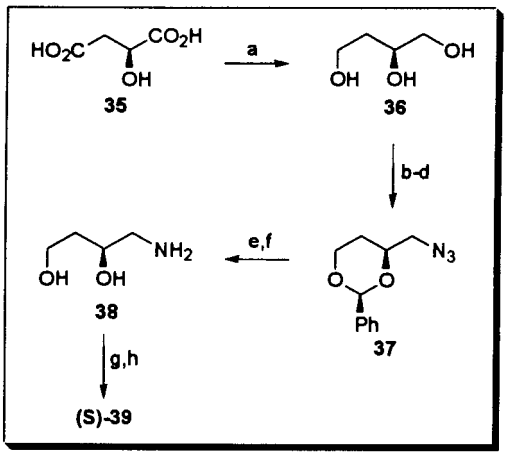


Scheme 1.2 Synthesis of authentic samples for the determination of the absolute configuration at C(11) and C(15) of TA toxin (TA toxin numbering).

Reagents: a. (*R*)-MTPA, DCC, DMAP, CH_2Cl_2; b. $HO(CH_2)_3PPh_3Br$, n-BuLi, THF (53%); c. H_2, $Pd(OH)_2$ (49%); d. (*S*)-MTPA, DCC, DMAP, CH_2Cl_2.

The preparation of the C_9 unit containing the C(11) stereogenic unit of the TA toxin backbone, the (*R*)-diol **32**, started from the aldehyde **30,** derived from (*R*)-citronellal. The aldehyde **30** was reacted with the Wittig ylide obtained from 3-hydroxypropylphosphonium bromide to give a mixture of the *E*- and *Z*-alkenol **31**. Catalytic hydrogenation of the double bond of **31** proceeded with concomitant debenzylation to give the (*R*)-diol **32** in an overall yield of 23%. The (*R*)-diol **32** was esterified with both (*R*)-MTPA and (*S*)-MTPA to form the esters **33** and **34**, respectively. Comparison of the ^{1}H NMR spectrum of the (*R*)-MTPA ester **23**, obtained from the degradation of TA toxin, with that of **34** proved that **23** is the enantiomer of **34** and therefore that the configuration at C(11) in TA toxin is *S*.

The absolute configuration at C(2) of the backbone of TA toxin was determined through the synthesis of an authentic sample of the di-(*R*)-MTPA derivative **25** (see Scheme 1.3). Reduction of (2*S*)-malic acid using borane-dimethylsulfide complex in the presence of triethyl-borate gave the triol **36**. The 1,3-diol moiety in **36** was protected as the *O,O*-benzylidene. The conversion of the primary alcohol group to the azide **37** proceeded via the tosylate derivative. Catalytic hydrogenation of the azide followed by the removal of the *O,O*-benzylidene group gave the aminodiol **38** that was converted to the di-(*R*)-MTPA derivative **39**. Comparison of the ^{1}H NMR spectrum of the degradation product **25** with that of **39** showed that the two compounds were identical and established the 2*S* configuration for the backbone of TA toxin.



Scheme 1.3 Synthesis of the di-(*R*)-MTPA derivative **39** from (2*S*)-malic acid.

Reagents: a. BMS, $B(OEt)_3$; b. PhCHO, $ZnCl_2$; c. TsCl, Py; d. NaN_3; e. H_2, Pd-C; f. 1M HCl, MeOH; g. CbzCl, Na_2CO_3; h. (*R*)-MTPA, DCC, DMAP, CH_2Cl_2.

With the knowledge of the 2*S* configuration for the backbone of TA toxin the absolute configuration of the other two stereogenic centers of the C(1)–C(5) unit were determined by synthesis of the model compounds **40a-40d** (Figure 1.2). These four diastereomers represent the four possible stereoisomers of the (2*S*)-1-amino-2,4,5-triol unit of the TA toxin backbone. Comparison of the ^{1}H NMR spectrum of each of the four diastereomers with that of the aminopentol backbone **19b** established the absolute configuration of the C(1)–C(5) unit of TA toxin as 2*S*, 4*S* and 5*R*.

Attention now turned to the three stereogenic centres present in the C(10)–C(17) unit of the backbone of TA toxin. The established 15*R* configuration (see earlier) in conjunction with

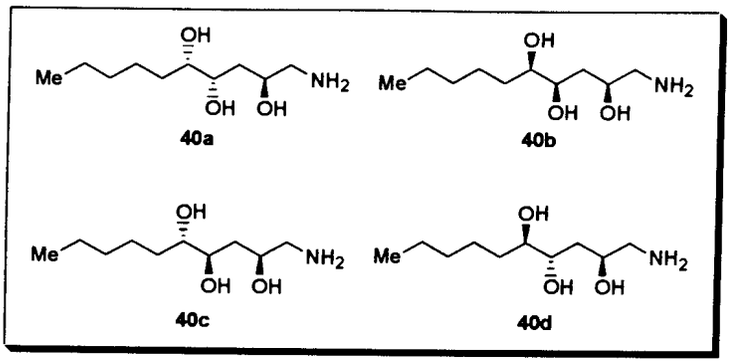


Figure 1.2 The four stereoisomers of the (2*S*)-1-amino-2,4,5-triol unit of the TA backbone.

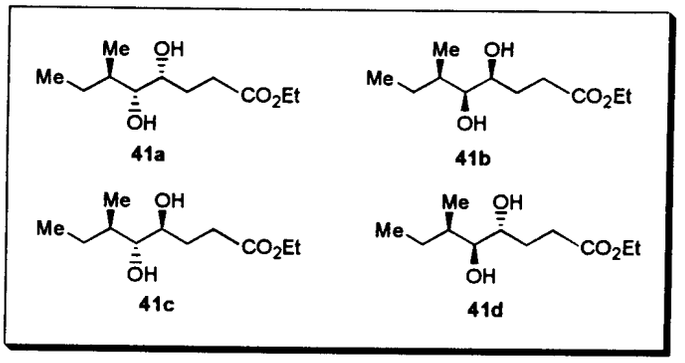


Figure 1.3 The four stereoisomers of the (15*R*)-15-methyl-13,14-diol unit of the TA backbone.

the unknown configuration of the C(13) and C(14) stereogenic centres required the synthesis of four diastereomeric model compounds, **41a-41d** in order to establish the absolute configuration of all three stereogenic centres. The synthetic route employed by Oikawa[40] provided these four model compounds as the acetonide derivatives. Comparison of the ^{1}H NMR spectra of these four diastereomeric derivatives with that of the aminopentol backbone **19b** of TA toxin established the absolute configuration of the left-hand unit of TA toxin as 13*S*, 14*R* and 15*R*.

Kishi *et al.*[43] recognised, and later proved, that the C_{17} backbone, **19b,** of TA toxin consists of two distinct halves, exhibiting characteristic spectroscopic properties that are independent from the remote stereogenic centres of the other half of the molecule. Thus, the assignment of the relative stereochemistry of **19b** was reduced to determining the relative

[43] Boyle, C.D.; Harmange, C.; Kishi, Y. *J. Am. Chem. Soc.*, **1994**, *116*, 4995.

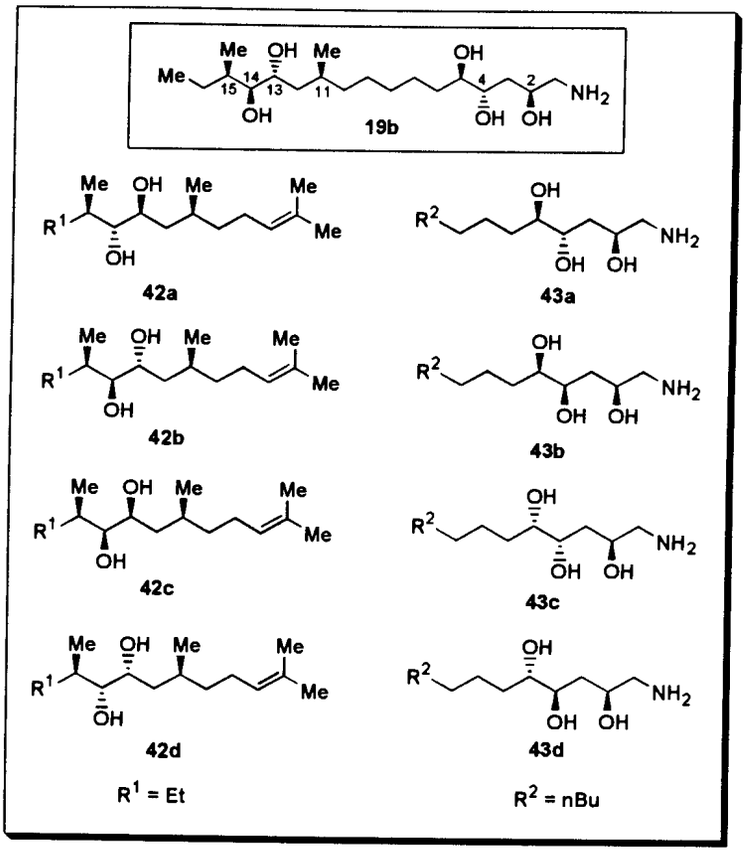
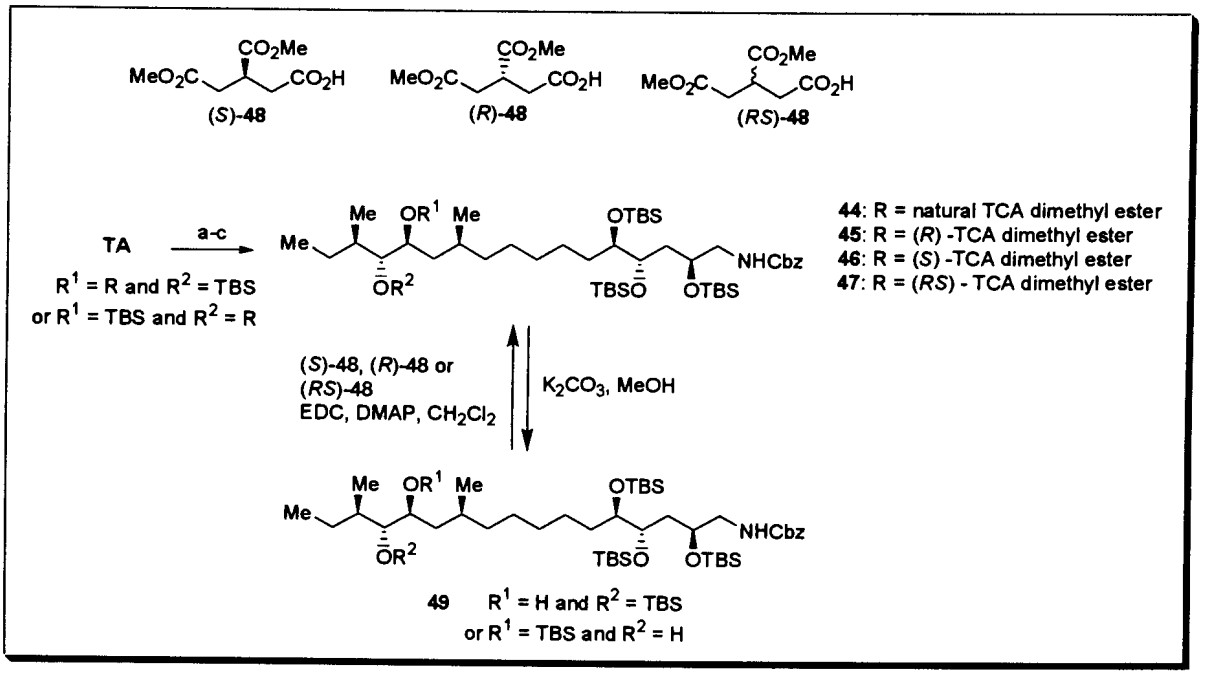


Figure 1.4 Stereoisomers prepared by Kishi[43] to determine the relative configuration of the left and right halves of the backbone of TA toxin

stereochemistry of the left- and right-half halves separately. For this purpose all eight diasteromers possible for **42**, representing the left half of **19b**, were synthesised from *S*-(-)-citronellal and subjected to ^{1}H NMR studies. Four of the diastereomers viz. **42a-42d** are shown in Figure 1.4. All eight compounds had different spectroscopic properties and the ^{1}H NMR spectrum of **42a** was virtually superimposable on the appropriate region of the spectrum of **19b**. Similarly, all four diastereomers **43a-43d**, representing the right half of **19b**, were synthesised from D-mannose or D-glucose. ^{1}H NMR studies established that the stereo-isomers **43a** represented the relative stereochemistry of the right half of the C_{17} aminopentol backbone of TA toxin. The absolute configuration was established by the synthesis of the C_{17} aminopentol backbone with synthons corresponding to the relative stereochemistry shown in **42a** and **43a** and once again a comparison of the ^{1}H NMR data with that of the aminopentol derived from TA toxin. The results confirmed the findings of the Oikawa group.

Two research groups who arrived at different conclusions published their results on the absolute configuration of the stereogenic centre present in the tricarballylic acid (TCA) moiety of the AAL toxins in the same year. Kishi *et al.*[44] established the stereochemistry as *R*, the opposite stereochemistry to that proposed by Shier *et al.*.[45]



Scheme 1.4 Stereochemistry of the TCA moiety of TA toxin as determined by Kishi *et al.*[44]

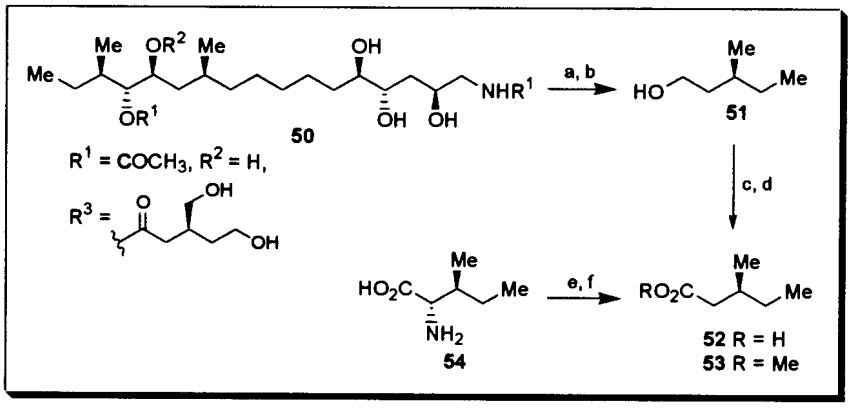
Reagents: a. CH_2N_2, MeOH; b. CbzCl, $NaHCO_3$; c. TBSCl, imidazole, DMF.

Kishi's group[46] synthesised (*R*)-, (*S*)-, and (*RS*)-tricarballylic acid dimethyl ester **48a-c** and prepared a protected derivative of the C_{17} backbone of TA toxin as a mixture of the C(13) and C(14) alcohols **49** as shown in Scheme 1.4. Compound **49** was then converted to the ester derivatives **45, 46** and **47**, using the monocarboxylic acids (*S*)-**48**, (*R*)-**48**, (*RS*)-**48**, respectively. A comparison of the signals in the methyl ester region of the ^{1}H NMR spectra of the derivatives **45, 46** and **47** with that of **44** showed that the stereochemistry of the TCA moiety in TA is *R*.

Shier *et al.*[45] used chiral gas chromatography column methodology to determine the absolute configuration of the tricarballylic acid moiety in TA toxin. Since tricarballylic acid is

[44] Boyle, C.D.; Kishi, Y. *Tetrahedron Lett.*, **1995**, *36*, 5695.
[45] Shier, W.T.; Abbas, H.K.; Badria, F.A. *Tetrahedron Lett.*, **1995**, *36*, 1571.
[46] Boyle, C.D.; Kishi, Y. *Tetrahedron Lett.*, **1995**, *36*, 4579.

achiral, it is necessary to differentiate the free carboxyl groups from the esterified carboxyl group in the tricarballylic acid moiety in TA toxin prior to separation from the backbone. Selective reduction of the free carboxyl groups with diborane in THF[47] was chosen over sodium borohydride reduction of the ester linkage in order to avoid the formation of a compound with a stereogenic centre α to a free carboxyl group as the latter reaction would result in racemisation under the alkaline conditions. TA toxin, **18a** was converted to its *N*-acetyl derivative **50**[48] in order to increase its solubility in THF and thus facilitate the reduction of the toxin by diborane in THF. In order to minimize the possibility that the side-chain might be lost through intramolecular transesterification, the reduced product was immediately tosylated with tosyl chloride in pyridine and reduced with lithium aluminium hydride to give 3-methyl-1-pentanol **51** (see Scheme 1.5). Racemic **51** could not be resolved into two peaks on the chiral column. Thus, the released side-chain **51** was subjected to Jones oxidation[49] to yield carboxylic acid **52** followed by esterification to form the methyl ester **53**, which could be resolved. Comparison of the retention time of the ester **53** on a chiral GC column with that of a reference compound prepared from L-isoleucine **54**, led to the deduction that the stereogenic centre in the tricarballylic acid moiety has the *S* configuration.



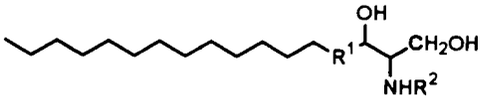
Scheme 1.5 Synthesis of the tricarballylic acid moiety derivative **53.**

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.

1.4 STRUCTURE-ACTIVITY RELATIONSHIP

[47] Yoon, N.M.; Pak, C.S.; Brown, H.C.; Krishnamurthy, S.; Stocky, T.P. *J. Org. Chem.*, **1973**, *38*, 2786.
[48] Pan, S.C.; Dutcher, J.D. *Anal. Chem.*, **1956**, *28*, 836.
[49] Brown, H.C.; Grag, C.P.; Liu, K.T. *J. Org. Chem.*, **1971**, *36*, 387.

The AAL-toxins show structural resemblances to the sphingolipids (see Table 1.2). They contain a C_{17} backbone, with a varying number of hydroxy groups and an amino group, that is responsible for the lipophobic character of the molecule, and a polar tricarballylic acid moiety. Gilchrist *et al.*[12] investigated and compared the toxicity of the parent compound AAL-toxin, TA toxin with that of the hydrolysis product, the C_{17} backbone. They found that the C_{17} aminopentol backbone also showed toxicity in both animal and plant tissues. Abbas *et al.*[50] found that the aminopentol derivative of TA toxin was 400-fold less phytotoxic than the parent compound in tomato leaflets. The lower activity of the aminopentol backbone was ascribed to its poor uptake by intact plants due to the absence of the TCA which is postulated to aid in the transportation of the compounds across the cellular membrane of the leaf tissues.[45] The question was raised whether aminopentols could be the active inhibitors of the plant equivalent of ceramide synthase. If this were so then the AAL-toxins would be pro-toxins that have to be metabolized to the active form for activity. Shier *et al.*[26] suggested that fungi producing these toxins add the tricarballylic acid moiety to aminopentols in order to detoxify the toxin. It was also suggested that in affected organisms the AAL-toxin is hydrolysed to the corresponding aminopentol by carboxylesterase enzymes.



Sphingolipid	R^1	R^2
55 Sphingosine	CH=CH	H
56 Phytosphingosine	CH_2-CHOH	H
57 Sphinganine	CH_2-CH_2	H
58 *N*-Lignoceroyl-DL-sphinganine	CH_2-CH_2	CO-$(CH_2)_{22}$-CH_3

Table 1.2 Structures of some sphingolipids

Gilchrist *et al.*[37] investigated the role of the amino group of TA and TB toxin by treatment with maleic anhydride, which caused >97 % inhibition of the AAL-toxin activity. Demaleylation of AAL-toxin derivative restored its original structure and therefore its phytotoxicity. The low level of biological activity that was observed in some maleylated samples was due to demaleylation during bioassay, since the maleylation reaction is reversible. However, irreversible acetylation of TA and TB toxin using acetic anhydride leads

[50] Abbas, H.K.; Duke, S.O.; Tanaka, T. *Toxicol.-Toxin Reviews*, **1993**. *12*, 225.

to the formation of the N-acetyl derivatives and resulted in complete and permanent loss of biological activity. Hence, it can be concluded that the free amino group plays an important role in the toxicity of AAL-toxins.

1.5 SYNTHETIC STUDIES OF AAL-TOXIN

Oikawa and co-workers[51] developed a synthesis for the AAL toxin, TA toxin **8/9** by retrosynthetically dividing the toxin into a left- **59** and right-half **60**, and the tricarballylic acid unit *S*-**61**.

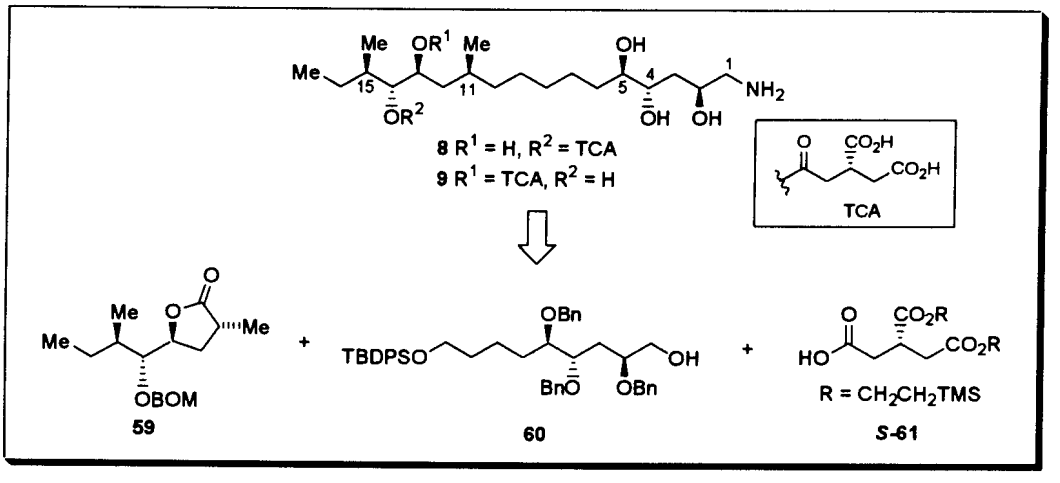
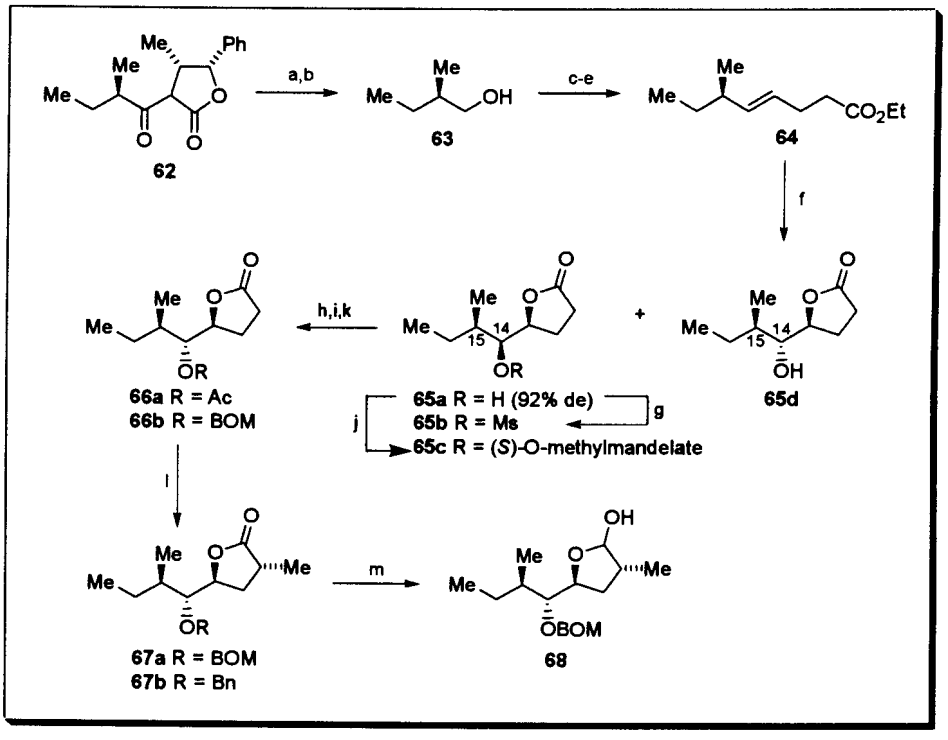


Figure 1.5 Retrosynthetic analysis of TA toxin **8/9**.

The synthesis of the left-half segment **59** started with the Evans alkylation product[52] **62** obtained by methylation of (4*R*,5*S*)-4-methyl-5-phenyl-3-propanoyl-2-oxazolidinone and separation of the formed diastereomeric mixture by silica gel chromatography (see Scheme 1.6). The oxazolidinone chiral auxiliary was removed by standard procedures[53] and involved the hydrolysis of the imide with basic hydrogen peroxide. The formed acid was reduced with $LiAlH_4$ to the alcohol **63**. This alcohol was converted to the *E*-olefin **64**. Thus Swern oxidation of **63** followed by the addition of vinyl magnesium bromide to the formed aldehyde, gave an epimeric mixture of alcohols that was subjected to an orthoester-Claisen rearrangement to give **64**. Asymmetric dihydroxylation of **65** with AD-mix-α and concomitant lactonization furnished the lactones **66a** and **66b** in 92:8 d.r. The diastereoselectivity was determined from (*S*)-*O*-methylmandelate ester **66c** using HPLC. Inversion of stereochemistry at C(14) of

[51] Oikawa, H.; Kagawa, T. Kobayashi, T;. Ichihara, A. *Tetrahedron Lett.*, **1996,** 37, 6169.
[52] Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.*, **1982**, *104*, 1737.
[53] Ichihara, A.; Miki, S.; Kawagishi, H.; Sakamura, S. *Tetrahedron Lett.*, **1989**, *30*, 4551.

diastereomer **66a** was achieved by Ikegami's procedure.[54] The lactone **65a** was mesylated and treated with CsOAc in the presence of 18-crown-6 to give **66a**. After hydrolysis and protection of the hydroxy group as the BOM ether **66b**, the compound was methylated with LiHMDS and methyl iodide to give **67a** as a 8.7:1 mixture of diastereomers. Reduction of the lactone with DIBALH furnished the left-half segment, the lactol **68**.



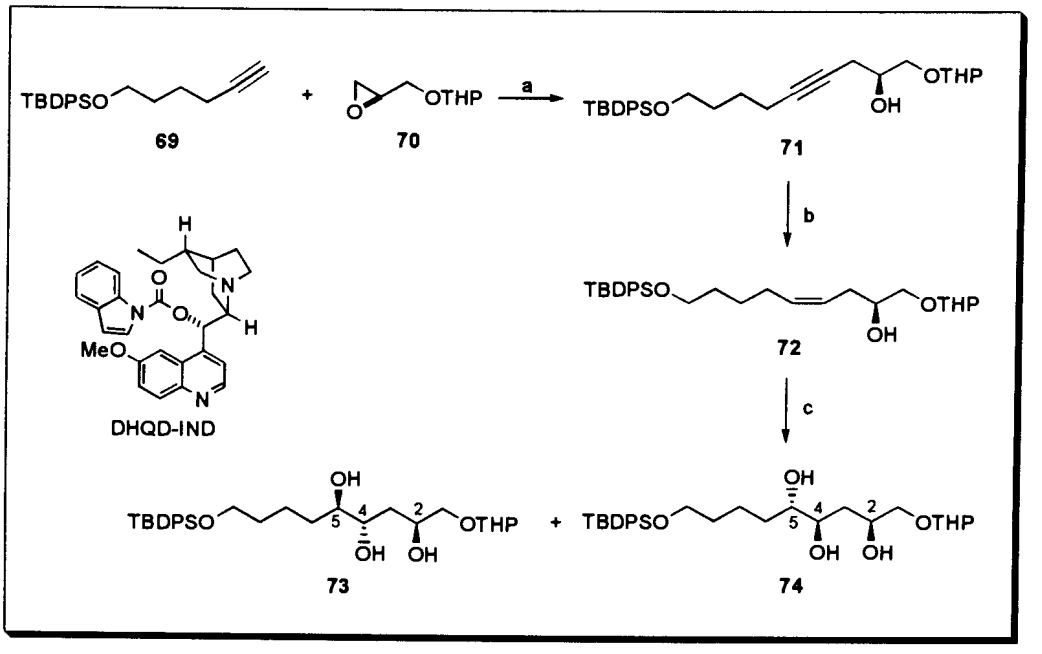
Scheme 1.6 Synthesis of the C_8 left-half unit of TA toxin.

Reagents: a. 30% H_2O_2, LiOH; b. $LiAlH_4$, Et_2O, (77%, 2 steps); c. Swern oxidation; d. CH_2=$CHMgBr$, THF, –78°C; e. $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, reflux, (53%, 3 steps); f. AD-mix-α, (75%); g. MsCl, Et_3N, CH_2Cl_2; h. CsOAc, 18-crown-6, C_6H_6, reflux; i. KOH, EtOH-H_2O, (70%, 3 steps); j. (*S*)-*O*-methylmandelic acid, DMAP, DCC, CH_2Cl_2; k. BOMCl, *i*-Pr_2NEt, CH_2Cl_2; l. LiHMDS, CH_3I, THF, –78°C, (60%, 2 steps); m. DIBALH, Et_2O, –78°C, (96%).

The synthetic route to the right-half unit of TA toxin is outlined in Scheme 1.7. The lithium acetylide obtained from **69** was coupled in the presence of $BF_3.OEt_2$[55,56] with epoxide **70** prepared from (*R*)-glycidol to give the internal acetylene adduct **71** in 75% yield. The *Z*-olefin **72**, formed by partial hydrogenation of the triple bond using a Pd-$BaSO_4$ catalyst, was subjected to a Sharpless asymmetric dihydroxylation procedure using DHQD-IND as ligand to

[54] Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.*, 1984, 1555.
[55] Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.*, 1983, *24*, 391.
[56] Eis, M.J.; Wrobel, J.E.; Ganem, B. J. *J. Am. Chem. Soc.*, 1984, *106*, 3693.

give the required 2,4-*anti* diol **73** as the major product, which was separable from the minor 2,4-*syn* product **74** by column chromatography.



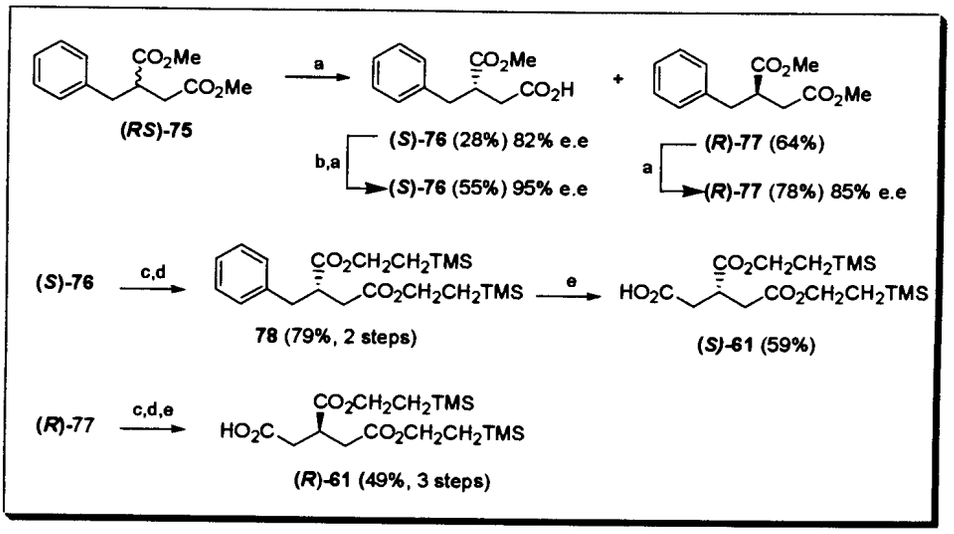
Scheme 1.7 Synthesis of the right-half of TA toxin.

Reagents: a. *n*-BuLi, $BF_3.Et_2O$, THF, –78°C (81%); b. H_2, Pd-$BaSO_4$, quinoline (93%); c. cat. OsO_4, DHQD-IND, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, H_2O.

Lipase-catalysed kinetic resolution was employed in the synthesis of the tricarballylic ester unit (see Scheme 1.8). Porcine pancreatic lipase, PPL hydrolysis of the terminal ester group of the (2*S*) enantiomer of (2*RS*)-2-benzylsuccinate **75** resulted in the formation of (*S*)-**76** in 82 % ee after 28 % conversion through kinetic resolution.[57]. This material was re-esterified with diazomethane and subjected to a second PPL-hydrolysis to afford (*S*)-**76** in 95% ee (55 % conversion). The recovered diester, (*R*)-**77** from the first hydrolysis was re-subjected to PPL-hydrolysis to give (*R*)-**77** with 84% ee. The (*S*)-**76** compound was hydrolysed and the corresponding diacid protected as the trimethylsilylethyl ester to give (*S*)-**78**. Catalytic oxidation using RuO_4 led to the formation of the tricarballylic acid segment (*S*)-**61**. (*R*)-**77** was similarly treated to afford (*R*)-**61**.

In a subsequent publication Oikawa[58] described two alternative synthetic routes leading to the left-half unit **67b** of the backbone of TA toxin. Attempts to link the left- and right-half unit

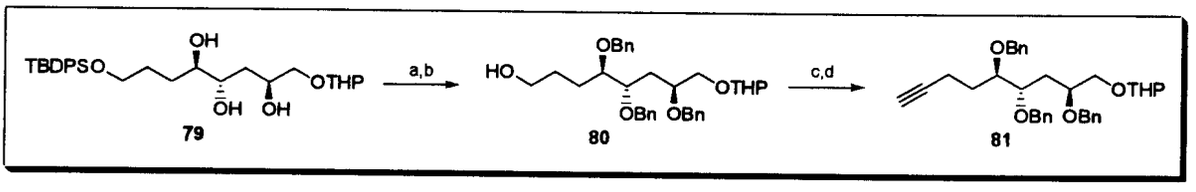
[57] Guibé-Jampel, E.; Pousseau, G.; Salaün, J. *J. Chem. Soc., Chem. Commun.*, **1987,** 1080.
[58] Oikawa, H.; Yamawaki, D.; Kagawa, T.; Ichihara, A. *Tetrahedron Lett.*, **1999**, *40*, 6621.



Scheme 1.8 Synthesis of the tricarballylic acid unit.

Reagents: a. PPL, 0.1M KH_2PO_4 (pH 7.2). b. CH_2N_2; c. 1M NaOH, MeOH; d. $TMSCH_2CH_2OH$, EDC, Et_3N, DMAP, CH_2Cl_2; e. $RuCl_2$, $NaIO_4$, CCl_4-CH_3CN-H_2O (2:2:3).

via Wittig or Julia coupling gave poor results and an alternative strategy was tried. Thus, the C_8 homologue of the right-half unit **73**, *i.e.* compound **79** was prepared by the route described for **73** (see Scheme 1.7). Protection of the hydroxy groups as the benzyl ethers and removal of the TBDPS protecting group using TBAF gave the alcohol **80** which was converted to the terminal acetylene **81** (Scheme 1.9).



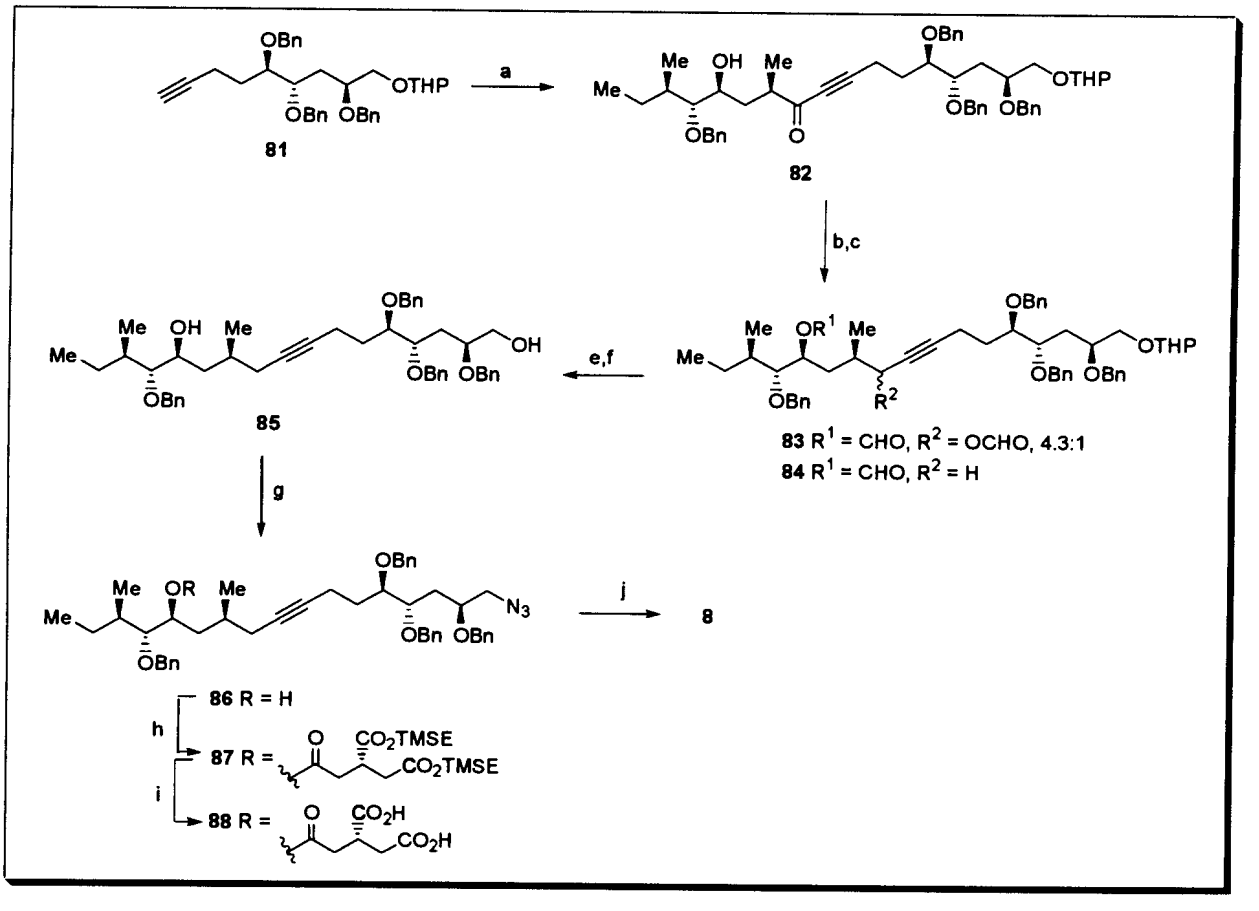
Scheme 1.9 Synthesis of the acetylene **81**

Reagents: a. NaH, BnBr, n-Bu_4NI, THF, reflux, (81%); b. TBAF, THF, (89%); c. CBr_4, Ph_3P, i-Pr_2NEt, CH_2Cl_2, (75%); d. *n*-BuLi, $BF_3.Et_2O$, THF, –78°C (75%).

The lactone **67b** was condensed with the acetylide prepared from **81** to give the adduct **82** in excellent yield (see Scheme 1.10). Luche[59] reduction of **82** followed by formylation gave the formate **83**. Catalytic deoxygenation of **83** was achieved by palladium(II) acetate to give **84.** Sequential deprotection of the formyl and THP groups in **84** afforded the diol **85,** which

[59] Luche, J.-L. *J. Am. Chem. Soc.*, **1978**, *100*, 2226.

was regioselectively converted in 69% yield to the azide **86** using the Mitsunobu[60] reaction. Acylation of **86** with the tricarballylic acid moiety (*S*)-**61** followed the Yamaguchi[61] method to afford the diacid **87**. The TMSE protecting groups were removed with TBAF to afford the diacid **88**. The reduction of the azide and the triple bond followed by hydrogenolysis of all the benzyl groups under conditions described by Shi *et al.*[62] gave the AAL-toxin TA_1 **8** (Scheme 1.10).

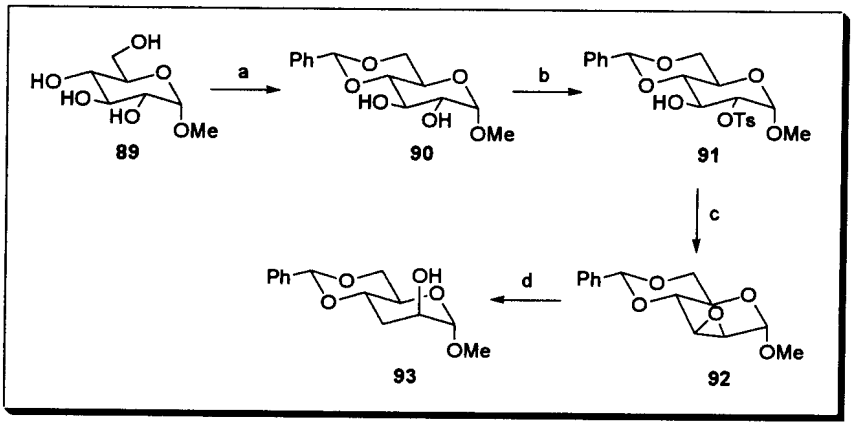


Scheme 1.10. Linkage of the left- and right-halves of the TA toxin backbone and formation of the ester bond leading to TA_1 **8**.

Reagents: a. *n*-BuLi, ether, –20°C, **67b**, (72%); b. $NaBH_4$, $CeCl_3$, MeOH, (85%); c. Ac_2O, HCO_2H, Py (97%); d. $Pd(OAc)_2$, *n*-Bu_3P, THF, (84%); e. $LiAlH_4$, THF; f. PPTS, EtOH, (89%, 2 steps); g. HN_3, Ph_3P, DEAD, toluene, (69%); h. 2,4-$NO_2C_6H_4COCl$, (*S*)-**61**, Et_3N, toluene then **86**, DMAP, (71%); i. TBAF, THF; j. H_2, Pd-C, *t*-BuOH-THF-1M HCl (3:1:0.04), (76%, 2 steps).

[60] Mitsunobu, O. *Synthesis*, **1981**, 1.
[61] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1989.
[62] Shi, Y.; Peng, L.F.; Kishi, Y. *J. Org. Chem.*, **1997**, *62*, 5666.

An alternative synthetic route has been proposed for the synthesis of the C(1)-C(9) unit of TA toxin, and thus an alternative synthesis for the backbone, by another member of our research group.[63] The retrosynthetic analysis of the C(1)-C(9) unit of the aminopentol backbone, (2S,4R,5R)-1-aminononane-2,4,5,9-tetraol, suggested that it could be derived from a C_6 carbohydrate such as methyl 3-deoxy-α-D-*arabino*-hexopyranose **89**, prepared from D-glucose in a series of transformations as outlined in Scheme 1.11, followed by C_4 chain elongation at the C(6) terminus. The selective protection of the C(4) and C(6) hydroxy groups of methyl 3-deoxy-α-D-*arabino*-hexopyranose **89** yielded the thermodynamically-favoured six-membered benzylidene derivative **90**. Tosylation of C(2) hydroxy group of **90** was accomplished using *N*-tosylimidazole and sodium methoxide to give **91**. Treatment of the 2-*O*-tosyl derivative **91** with sodium methoxide formed the *manno*-epoxide **92** in excellent yield. $LiAlH_4$ reduction of **92** proceeded regioselectively to form methyl 4,6-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside **93** with the required stereochemistry at C(2).



Scheme 1.11: Synthesis of methyl 4,6-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside **93**.

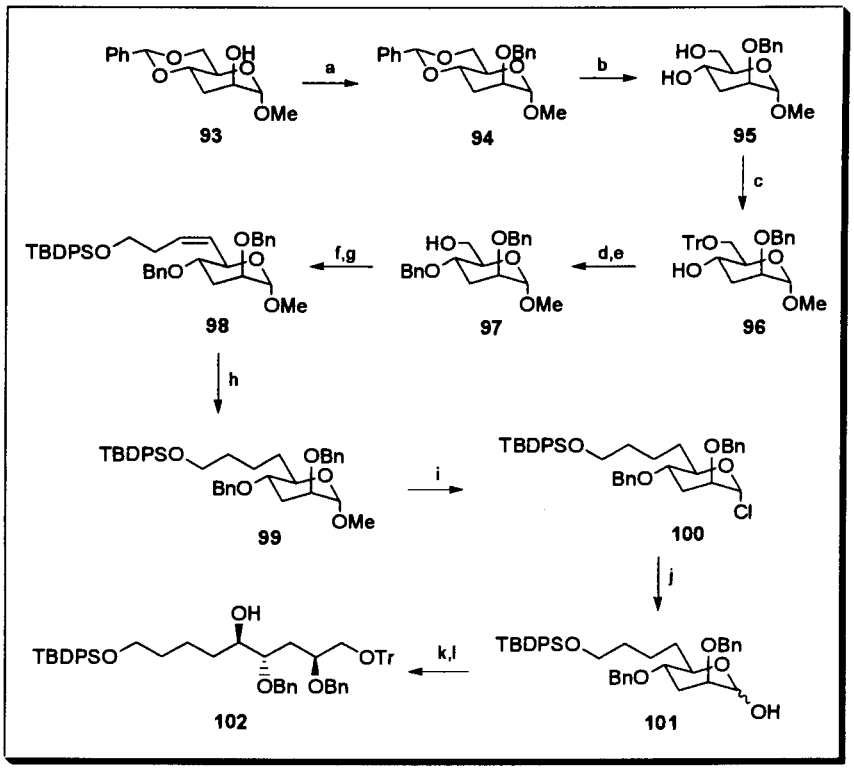
Reagents: a) $PhCH(OMe)_2$, CSA (97%); b) NaOMe, TsIm (92%); Na(s), MeOH (72%); d) $LiAlH_4$ (89%).

Protection of the C(2) hydroxy group in **93** as the benzyl ether gave **94** which on treatment with TsOH in methanol regenerated the diol **95** (see Scheme 1.12). The C(6) hydroxy group was selectively protected as the trityl ether **96**, followed by benzylation of the C(4) hydroxy group and subsequent deprotection of the C(6) primary alcohol to give alcohol **97**. Swern oxidation of the C(6) primary alcohol gave an aldehyde which was immediately used in a Wittig reaction to afford the alkene **98**. Hydrogenation of **98** with freshly prepared

[63] Wallhorn, D. *Synthetic Studies on the C_{17} Backbone of the Alternaria Toxins using Carbohydrates as Chiral Templates*, M.Sc. Thesis, University of Pretoria, **1997**.

Raney nickel afforded **99**. The methyl glycoside bond of **99** was cleaved using excess of $BCl_3.Me_2S$ reagent to give the pyranosyl chloride **100,** which was hydrolysed by absorption on moist silica gel and elution after 24 h to give the hemiacetal **101** as a 1.4:1 mixture of α-, and β-anomers. Reduction of the hemiacetal **101** using $NaBH_4$ in ethanol followed by tritylation of the primary hydroxy group yielded the C(1)-C(9) unit **102** of TA toxin.

Compound **102**, by removal of the C(5) hydroxy group, can serve as the C(1)-C(9) unit of the backbone of TB toxin.



Scheme 1.12: Chain elongation of methyl 4,6-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside **93** to a C_9 unit.

Reagents: a. BnCl, NaH, DMF; b. TsOH, MeOH, H_2O (95%); c. TrCl, DMAP, Pyridine, CH_2Cl_2 (74%); d. BnBr, KH (96%); e. TsOH, MeOH, H_2O (89%); f. Swern oxidation; g. BuLi, $TBDPSOCH_2CH_2CH_2PPh_3I$ (58%); h. Raney-Ni, H_2 (98%); i. $BCl_3.SMe_2$; j. SiO_2, H_2O (53%, 2 steps); k. $NaBH_4$, EtOH (87%); l. TrCl, DMAP, Pyridine, CH_2Cl_2.

2. Retrosynthetic Analysis of TA Toxin

2.1 GENERAL

In the early days of organic synthesis the focus was on chemical change in the direction of chemical reactions i.e. reactants → products. Chemists developed most syntheses 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). A different approach was needed for the synthesis of more complex compounds. In the mid-1960s Corey's[1] development of a totally new approach to the synthesis of complex natural products from readily available starting materials led to the beginning of a new era in organic synthesis. This new approach depends on the structural features in the *reaction products* and the manipulation of structures in the reverse sense. This method became known as retro-synthetic analysis, which can be described as a simplified and accelerated planning process of synthetic routes.

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 leads to simple or commercially available starting materials. A convenient notation that shows how two molecules are related with respect to their synthetic interconversion is the transform. A transform is defined by Corey as "the exact reverse of a synthetic reaction to a target structure". Each structure derived antithetically from a target then becomes itself a target for further analysis. Repetition of this process eventually produces a tree of intermediates having different chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the synthetic target.

But which is the best synthetic route? The simplest strategy is where the number of synthetic steps is kept to a minimum. The choice of a synthetic route also depends on a variety of factors including the cost and availability of the reagents and starting materials. Simple homochiral starting materials, the so-called chiral building blocks obtainable from Nature, are often commercially available and are of great value in stereoselective syntheses.

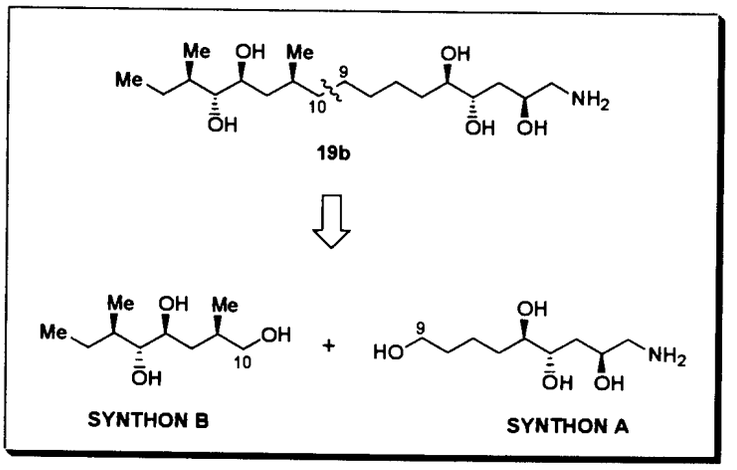
[1] Corey, E.J.; Cheng, X-M. The Logic of Chemical Synthesis, John Wiley & Sons, New York, **1989.**

It is important to note that in retrosynthetic analysis there is often more than one 'correct' answer and the synthetic route eventually chosen may come down simply to personal choice.

2.2 RETROSYNTHETIC ANALYSIS OF TA TOXIN

Retrosynthetic analysis of the C_{17} aminopentol **19b**, obtained by base hydrolysis of TA toxin **8/9**, indicates that various bond disconnections (the reactions in the synthetic direction) between C(6) to C(8) are equally feasible. Thus from the outset of the synthetic work on the AAL-toxins in the research group, it was decided on a strategy of disconnecting the C(9)–C(10) bond in order to generate two synthons that would be of use in other projects underway in the group.

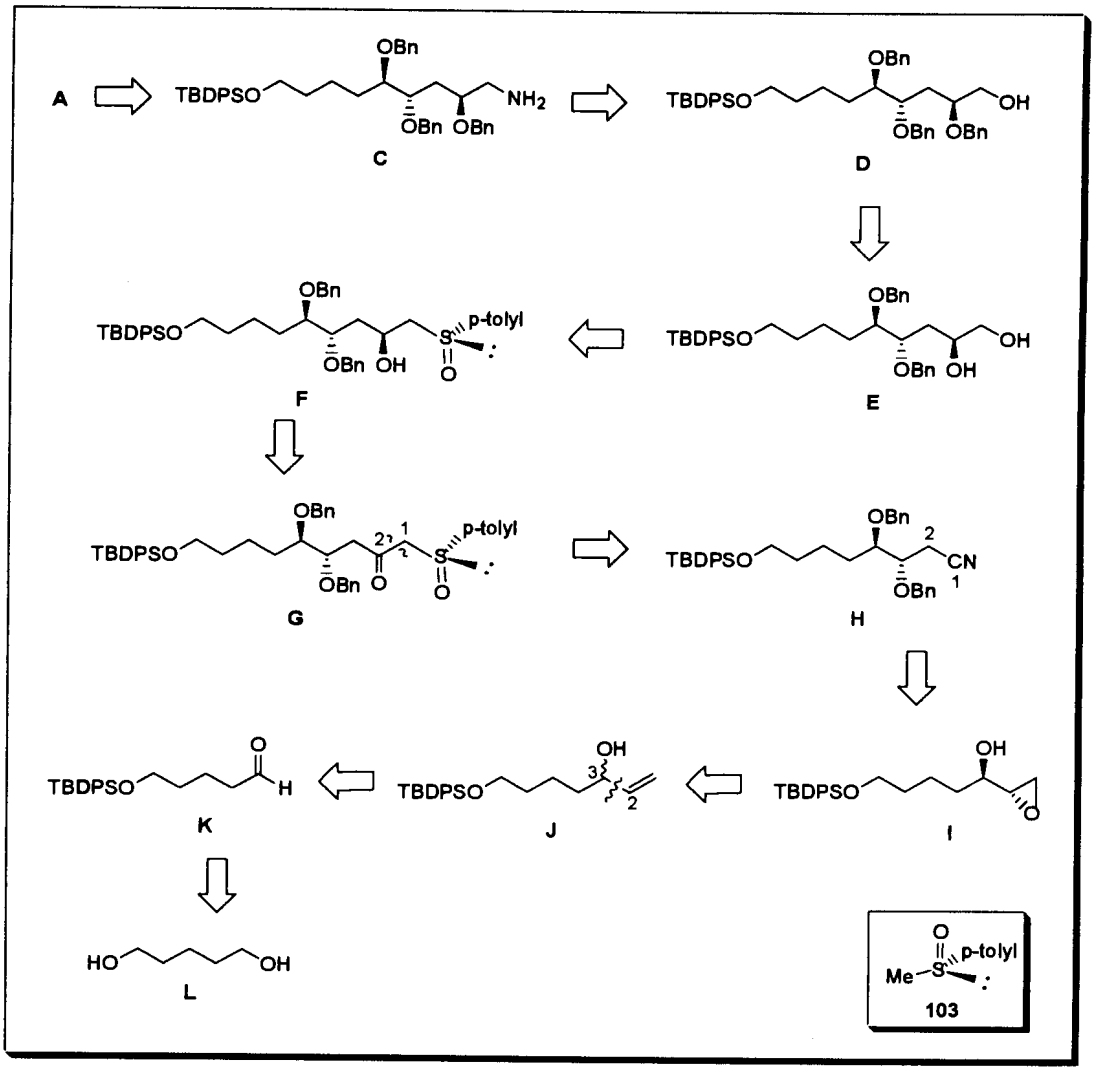
Disconnection of the C(9)–C(10) bond of the C_{17} aminopentol **19b** generates a synthon **B** with 4 stereogenic centres, common to all of the AAL toxins, and synthon **A** with 3 stereogenic centres (Scheme 2.1).



Scheme 2.1 Retrosynthetic analysis of the C_{17} aminopentol backbone of TA toxin: Disconnection of the C(9)–C(10) bond.

Synthon **A** is the target molecule for the research described in this dissertation. In the next stage of the analysis a protective group strategy leads to the synthon **C** (see Scheme 2.2). The exact nature of the protecting groups is dependent on the type of reaction and the conditions used in the eventual synthetic sequence. It is envisaged that the primary hydroxy group present in **A** can be protected using a TBS or TBDPS group whereas a benzyl group would suffice for the secondary hydroxy groups. The amino group in synthon **C** can be transformed to the primary hydroxy group of synthon **D** by functional group transformations. In

the synthetic direction the hydroxy group can be converted to the *O*-tosylate that undergoes an S_N2 reaction with NaN_3 to give an azide that is converted to an amino group by catalytic hydrogenation using Pd-C as catalyst or by $LiAlH_4$ reduction. Alternatively, the azide group can be introduced into synthon **C** under Mitsunobu conditions[2] using hydrazoic acid, HN_3 followed by reduction to give the amino group.



Scheme 2.2 Retrosynthetic analysis of the C_9 right-half unit of TA toxin.

The 1,2 relationship between the C(2) benzyloxy and C(1) hydroxy groups in synthon **D** identifies a 1,2-diol unit in synthon **E**. In the synthesis the 1,2-diol can be converted to a benzylidene derivative using benzaldehyde dimethyl acetal and TsOH catalysis. Regioselec-

[2] Mitsunobu, O. *Synthesis,* **1981**, 1.

tive opening of the dioxolane ring using DIBALH results in the formation of a secondary benzyloxy group and a primary alcohol.

The introduction of the chiral sulfoxide group at C(1) of synthon **F** in the retrosynthetic analysis is dictated by the strategic control over the stereochemistry in the formation of the C(2) stereogenic centre in the reduction of the C(2) carbonyl group in synthon **G**. In the synthetic direction the β-ketosulfoxide moiety is reduced with DIBALH in the presence of $ZnCl_2$ to achieve the correct stereochemistry at C(2). The β-ketosulfoxide then undergoes a Pummerer rearrangement using acetic anhydride and sodium acetate and the *O*,*S*-acetal product is reduced with $LiAlH_4$ to give the diol functionality present in synthon **E**.

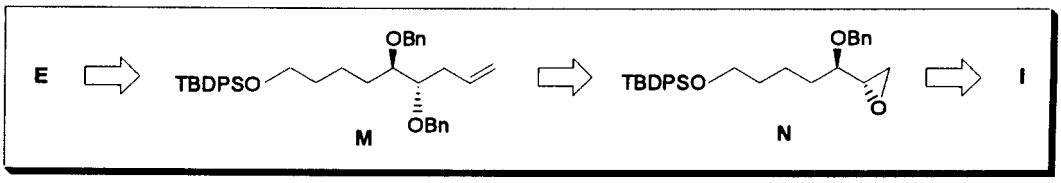
β-Ketosulfoxides, as discussed in Chapter 4, are obtained by the reaction of an ester or a nitrile with a chiral sulfoxide such as (+)-(*R*)-methyl *p*-tolylsulfoxide **103**. The functional group transformation thus involves the disconnection of the C(1)–C(2) bond in synthon **G** and identifies synthon **H** with its nitrile functionality, or as alternative, an ester functionality. In the latter case, an additional two steps are required to convert the nitrile to its corresponding acid followed by esterification of the acid to form the corresponding ester in the synthesis.

Removal of the *O*-benzyl groups and disconnection of the C(1)–C(2) bond in synthon **H** identifies the epoxy alcohol, **I** and cyanide as a C_1 source. In the synthetic direction nucleophilic opening of the epoxide ring by cyanide anion followed by protection of the diol functionality as the benzyl ethers, results in the formation of **H**.

Chiral *anti* epoxy alcohols such as **I** are formed from racemic allylic alcohols by Sharpless epoxidation/kinetic resolution methodology and this transformation identifies the racemic secondary allylic alcohol **J** in the retrosynthetic analysis. The secondary allylic alcohol group can be derived from a C_5 aldehyde **K** by a Grignard reaction using vinyl magnesium bromide. Aldehyde **K** can be obtained from 1,5-pentanediol **L** by selective monoprotection followed by Swern oxidation

An alternative retrosynthetic analysis recognizes that the terminal 1,2-diol unit present in synthon **E** can be obtained by Sharpless asymmetric dihydroxylation of the terminal alkene moiety in synthon **M** as outlined in Scheme 2.2. Deprotection of the C(4) *O*-benzyl group and disconnection of the C(2)–C(3) bond in synthon **M** identifies the *O*-benzyl protected epoxy

alcohol **N** as a key intermediate. In the synthetic direction the hydroxy group present in synthon **I** is protected as the benzyl ether and the epoxide ring opened using a Cu(I)-catalysed Grignard reaction with vinyl magnesium bromide or by reaction with lithium divinyl-cuprate.



Scheme 2.2 Alternative strategy for the introduction of the third stereogenic centre of the C(1)–C(9) unit of TA toxin.

The chemistry of epoxides and an overview of methods for the ring opening of epoxides are discussed in Chapter 3.

3. Chemistry of Epoxides

3.1 GENERAL

Epoxides (oxiranes) are versatile and important intermediates in organic reactions due to their ease of formation, which results in the creation of two contiguous stereogenic centers with known relative configuration, and their ready reactivity towards nucleophiles. The epoxide functional group is an important structural feature of numerous natural products. The biological activity of many natural products is due to the presence of this functional group *e.g.* (+)-disparlure[1] (**104**), the sex pheromone of the gypsy moth and the trichothecenes diacetoxyscirpenol (**105**) and roridin A (**106**). The mycotoxin aflatoxin B_1 (**107**) is a pre-carcinogen that requires transformation of the vinyl ether double bond to an epoxide (**108**), the highly toxic carcinogen, by liver enzymes.

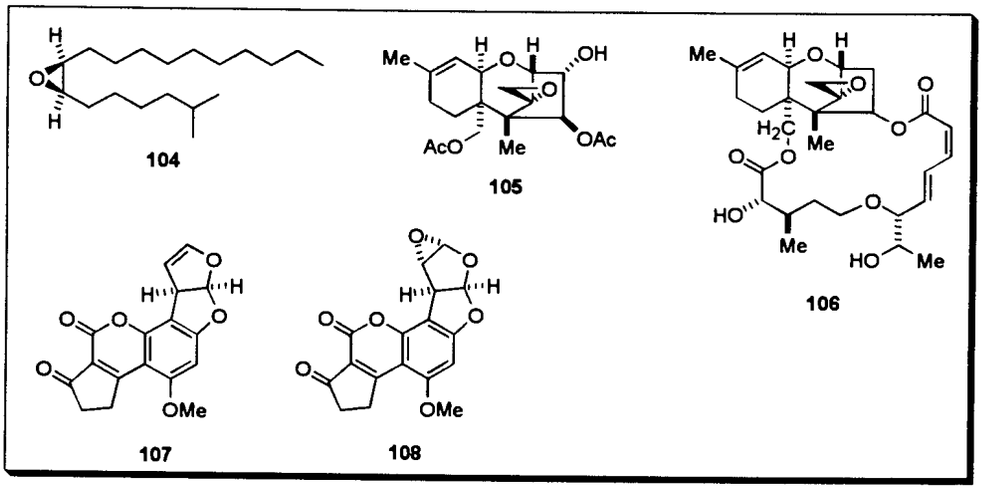


Figure 3.1 Biologically active natural products with an epoxide functional group.

3.2 FORMATION OF EPOXIDES

3.2.1 Epoxidation by peracids

The simplest epoxide ethylene oxide (or oxirane) can be produced on the tonne scale by the direct oxidation of ethane by O_2 at high temperatures over a silver oxide catalyst. The conditions are hardly suitable for general laboratory use and the most commonly used

[1] Mori, K.; Takigawa, T.; Matsui, M.; *Tetrahedron*, **1979**, *35*, 833.

epoxidising reagents are peroxycarboxylic acids (peracids).[2] Peracids are halfesters of hydrogen peroxide and are less acidic than the corresponding acid because their conjugate base is not stabilised by delocalisation into the carbonyl group. They are, however, electrophilic at oxygen because attack there by a nucleophile displaces a carboxylate, a good leaving group. In 1909, the Russian chemist N. Prileschajew[3] discovered epoxidation by organic peracids and found that the olefinic unit acts as the nucleophile and the peroxy acid as the electrophile. Thus, either increasing the electron density of the olefin or decreasing that of the peracid serves to increase the rate of the reaction. The most commonly used peracid is *m*-chloroperbenzoic acid (MCPBA). The essence of the mechanism is nucleophilic attack of the double bond π orbital on the outer oxygen atom of the weak, polarised O–O bond. The proton of the epoxide oxygen is transferred to the carboxylic acid by-product (see Figure 3.2). The reaction is stereospecific as both new C–O bonds are formed on the same face of the alkene's π bond and the geometry of the alkene is therefore reflected in the stereochemistry of the epoxide. Thus *cis*-alkenes give rise to *cis* epoxides whereas the *trans* alkene leads to the formation of the *trans* epoxide.

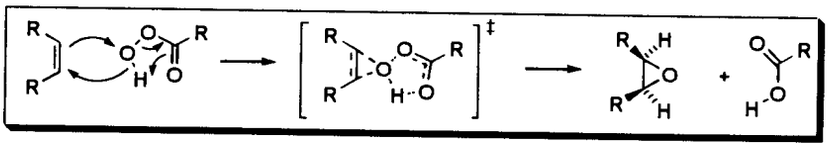


Figure 3.2 General mechanism of epoxidation by peracids.

Epoxidation of an allylic alcohol (both cyclic and acyclic) with MCPBA occurs by attack of the face of the alkene *syn* to the hydroxy group and the *syn* epoxy-alcohol is formed as the major diastereomer (95:5).[4] The reason for the diastereoselectivity is shown in the transition state for the reaction in Figure 3.3. The only important conformer in the transition state has the hydrogen of the stereogenic centre eclipsing the double bond. The hydrogen of the hydroxy group can then form a hydrogen bond to the oxygen of the peracid, stabilising the transition state when *syn* epoxidation occurs.[5] This hydrogen bonding means that peracid epoxidations of alkenes with adjacent hydroxy groups are much faster than simple alkenes even when no stereochemistry is involved.[6]

---

[2] Helmchen, G.; Hoffman, R.W.; Mulzer, J.; Schaumann, E. *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), Thieme Stuttgart, 4th Ed., Vol. E21e, **1995**, p. 4599.
[3] Prileschajew, N. *Chem. Ber.*, **1909**, *42*, 4811.
[4] Henbest, H.B.; Wilson, R.A.L. *J. Chem. Soc.* (B), **1957**, 1958.
[5] Chautemps, P.; Pierre, J.L. *Tetrahedron*, **1976**, *32*, 549.

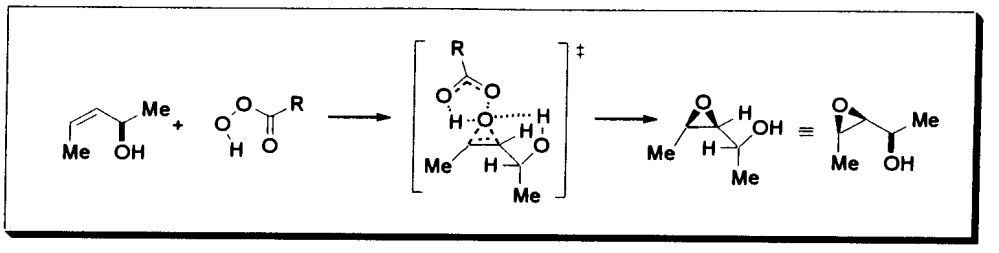


Figure 3.3 Stereofacial selectivity in the epoxidation of allylic alcohols.

3.2.2 Epoxidation using vanadium(V) reagents

Oxidation of cyclic allylic alcohols and cyclic alkenols with *t*-butyl hydroperoxide in the presence of a vanadium(V) catalyst, $VO(acac)_2$ gives the *cis* epoxide with complete diastereoselectivity. The active catalyst is represented by structure **109**, where one of the 'acac' ligand is displaced by *t*-BuOOH and the allylic alcohol. Epoxidation then takes place *cis* to the hydroxy group by in-line attack on the O–O bond by the π orbital of the double bond. These vanadium(V)-catalysed epoxidations can also be highly diastereoselective with acyclic alkenols in which the geometrical constraints present in cyclic substrates are absent. The mechanistic course of this epoxidation is illustrated in Figure 3.4 for an allylic alcohol system.

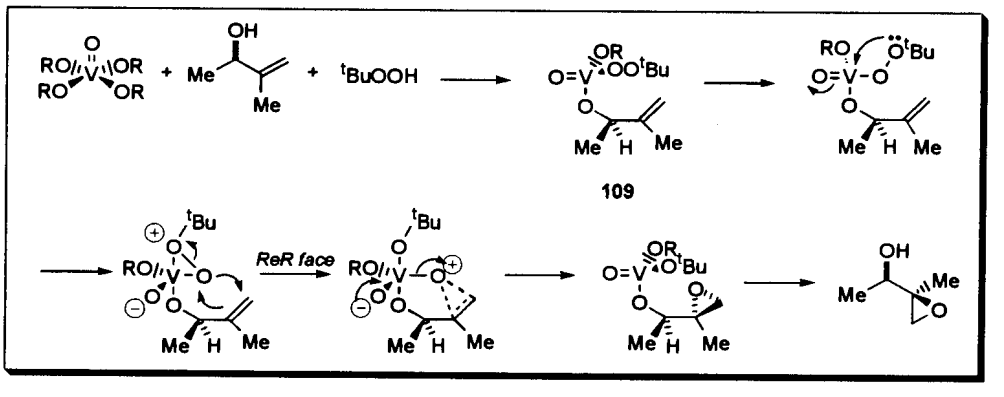


Figure 3.4 Epoxidation mechanism for a vanadium(V) reagent.

The stereochemical course of the reaction is determined by the dihedral angle y in (**110**) and (**111**). Me-Me interactions in the conformation depicted in (**111**) result in steric strain. The conformation **110** has minimal steric repulsion and reaction thus occurs preferentially by attack of the *ReR* face of the double bond (see Figure 3.5).[7,8,9]

---

[6] Adam, W.; Wirth, T. *Acc. Chem. Res.*, **1999**, *32*, 703.
[7] Jørgensen, K.A. *Chem. Rev.*, **1989**, *89*, 432.
[8] Mihelich, E.D.; Daniels, K.; Eickhoff, D.J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.
[9] Besse, P.; Veschambre, H. *Tetrahedron*, **1994**, *50*, 8885.

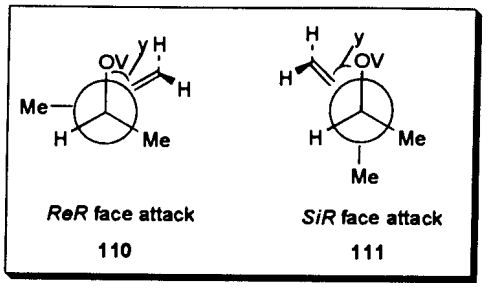


Figure 3.5 Conformational analysis of the vanadium(V) intermediate in the epoxidation reaction.

3.3 ENANTIOSELECTIVE METAL-CATALYZED EPOXIDATION REACTIONS

3.3.1 Jacobsen methodology

In 1990 Jacobsen[10,11,12] reported the highly enantioselective epoxidation of alkyl- and aryl-substituted alkenes using a manganese(III) catalyst (**112**) (a manganese(III)-salen complex) prepared from either of the homochiral enantiomers of 1,2-diamino-cyclohexane and the aromatic aldehyde, 2-hydroxy-3,5-di(*t*-butyl)-benzaldehyde. The complexes are inexpensive, easy to prepare with a range of substituent groups and robust enough for commercial bleach to be used as the oxidant. Substrate selectivity studies and the effect of structural changes in the ligands have led to a model that accounts for the observed stereochemical aspects of the reaction. It is thought that a manganese(IV) oxo species is the oxidant and that only *cis* alkenes can approach properly. The bulky *t*-butyl groups are important for high enantioselectivity as they are considered to prevent approach from the substrate from

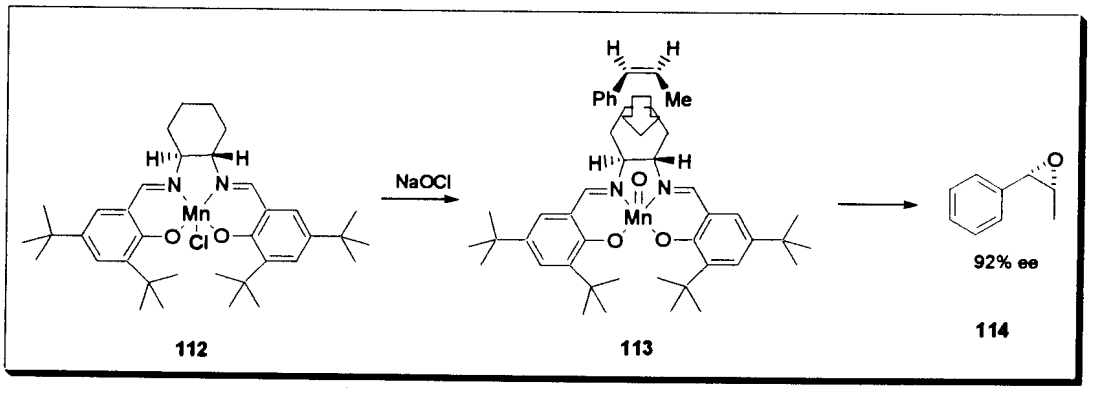


Figure 3.6 Jacobsen epoxidation of alkenes.

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

directions other than that indicated in Figure 3.6. The sense of enantioselection is in agreement with a perpendicular approach of the alkene to the manganese-oxo bond with transfer of the oxo oxygen to the *Re* face of the alkene. In this approach the phenyl substituent of the alkene is directed away from the axial hydrogen on the bridge (H*) and steric repulsion between the catalyst and the substrate will be minimised. This model predicts that *cis* alkenes will be epoxidised with higher enantioselectivity than *trans* alkenes, which is found to be the case.

3.3.2 Katsuki-Sharpless methodology

The synthesis of enantiomerically pure compounds is one of the most important goals in organic synthesis and is a major target in industrial syntheses of physiologically active compounds. The 1980s witnessed the emergence of reagent-control strategy that employs powerful enantiomerically pure catalysts and auxiliaries for the purpose of constructing chiral molecules in a diastereo- and enantioselective fashion. In 1980 Katsuki and Sharpless reported an unusually efficient method for the epoxidation of primary allylic alcohols[13,14] and later the kinetic resolution of secondary allylic alcohols.[15] This new strategy involves epoxidation by a transition-metal catalyst in the presence of chiral auxiliries in order to achieve stereochemical control. The reagents required for the preparation of the catalyst are commercially available at moderate cost using titanium(IV) tetraisopropoxide, *t*-butyl hydroperoxide (TBHP) as the oxidising agent, and either diethyl (*S*,*S*)-(–)- or (*R*,*R*)-(+)-(natural) in dichloromethane. The reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. The asymmetric epoxidation and the kinetic resolution of allylic alcohols by Sharpless are similar in nature to other earlier transition metal-catalyzed epoxidation reactions.[16] The difference between the titanium-catalyzed epoxidation and other metal-catalyzed epoxidations is that it is able to successfully use dialkyl tartrates and tartamides as ligands to induce asymmetry in the reaction.[17] The reaction is highly predictable. When the (*S*,*S*)-(–)-tartrate ligand is used in the reaction the oxygen is delivered to the top face of the olefin when the allylic alcohol is depicted as in Figure 3.7. The (*R*,*R*)-(+)-tartrate ligand, on the other hand, allows the bottom face of the olefin to be epoxidised. When achiral alcohols are used the Sharpless asymmetric epoxidation reaction exhibits exceptional

[13] Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1980,** *102*, 5974.
[14] Michaelson, R.C.; Palermo, R.E.; Sharpless, K.B. *Ibid.*, **1977,** *99*, 1990.
[15] Martin, V.S.; Woordard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.*, *103*, **1981,** 6237.
[16] Finn, M.G.; Sharpless, K.B. *In "Asymmetric Synthesis"* (J. Morrison, Ed.), *Vol.5*, Academic Press. Orlando, **1985,** p. 247.
[17] Lu, L.D.-L.; Johnson, R.A.; Finn, M.G.; Sharpless, K.B. *J. Org. Chem.*, **1984,** *49*, 728.

enantiofacial selectivity (*ca.* 100:1) and provides convenient access to synthetically versatile epoxy alcohols.[18,19]

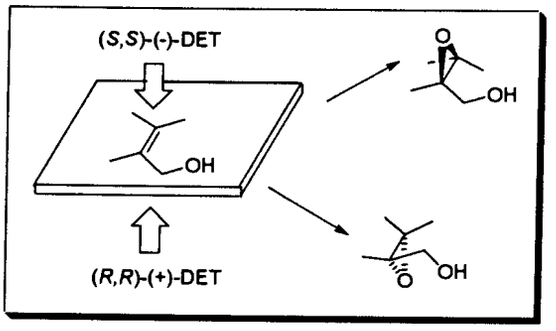


Figure 3.7 Stereofacial selectivity rule for the Sharpless epoxidation reaction.

Kinetic evidence suggests that initially a ligand exchange takes place between the titanium (IV) alkoxide and the tartrate ester, diethyl (*R,R*)-(+)-tartrate, to form a binuclear Ti-tartrate complex.

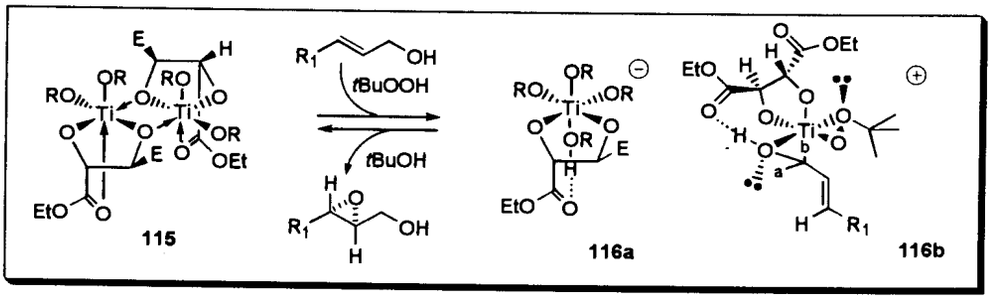
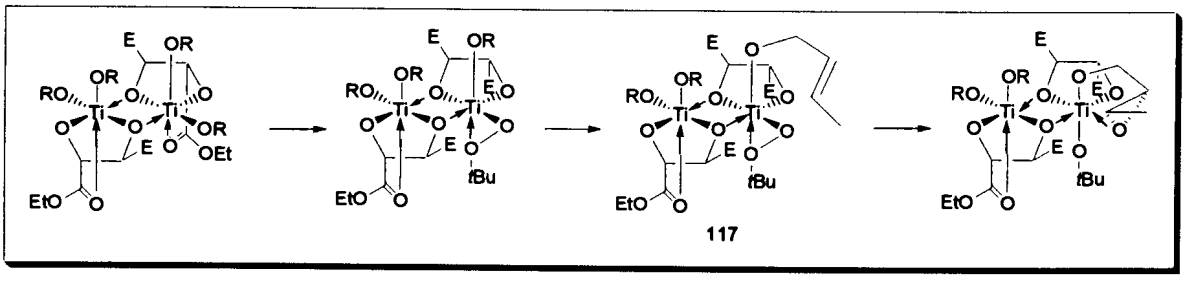


Figure 3.8 Nature of the catalytic species in the Sharpless epoxidation reaction.of allylic alcohols.

Addition of the allylic alcohol and the oxidant *t*-BuOOH leads to the formation of the transition state assembly (**116b**) (see Figure 3.8) in a reaction that is first-order in **115**, the allylic alcohol and *t*-BuOOH, in agreement with the observed kinetics. The assembly (**116b**) represents the cationic species, whilst **116a** indicates the anionic species. The formation of the epoxy alcohol from **116** would clearly lead to the regeneration of **115** by dissociation of the epoxy alcohol from the catalytic site.

[18] Rossiter, B.E. in *Asymmetric Synthesis*, (J.D. Morrison Ed.), *Vol. 5,* Academic Press, New York, **1985**, p. 193.
[19] Pfenninger, A. *Synthesis*, **1986**, 89.

Corey[20,21] proposed that the assembly of the titanium-tartrate catalyst system is not a dimer, but an ion pair (see Figure 3.8). A single molecule of diethyl (*R,R*)-(-)-tartrate is complexed with the Ti atom of the cationic species in **116**. The hydroxy group of the allylic alcohol is coordinated with the Ti in such a way that hydrogen bonding with the carbonyl group of the tartrate ester can occur. The geometry of the H-bond is linear and close to ideal with an O–H····O distance of 2.7 Å. The *t*-BuOOH group is coordinated to the Ti atom through the terminal O atom in such a way that this O is *cis* and the *t*-BuO group is *trans* to the coordinated allylic hydroxy group. The O of the *t*-BuO group is pyrimidal and has the *R* configuration in order for this bulky group to be adjacent to the vacant coordination site of the octahedral Ti and away from the other ligands present on the Ti atom. Any other arrangement leads to extreme steric repulsion between the *t*-Bu group and the ligands *cis* to it. The specific arrangement of ligands on Ti results in a titanium stereogenic centre with the chirality sense determined by the tartrate ester ligand. The chirality sense of the catalytic Ti species and the fixed hydrogen bonding favours the intemal epoxidation at a specific face of the double bond as this bond approaches the peroxy O–O with its midpoint nearly co-linear with the O–O axis and the double bond axis perpendicular to the plane of the peroxy chelate ring: the optimum stereoelectronic arrangement for epoxidation.[20,21,22] The two C-O bonds in the epoxide ring form by the interactions of the appropriate orbitals of the oxygen with that of the C-C double bond. One of the interactions is between the π^*-orbital of the alkene and the lone pair of electrons on the equatorial peroxygen. The second interaction is between the π-orbital of the alkene and the antibonding orbital of the titanium-peroxygen bond.



117

Figure 3.9 Structure of the catalytically active Ti-tartrate complex proposed by Sharpless.

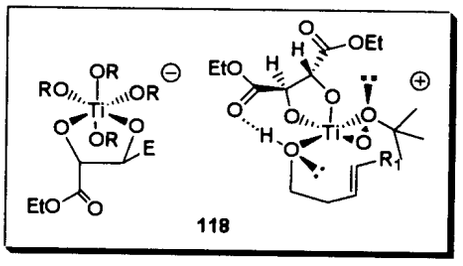
Sharpless *et al.*[23] suggested that the active Ti(IV)-tartrate ester complex is a dimer in solution (Figure 3.9). The proposed structure **117** has a high degree of symmetry as the

[20] Corey, E.J. *J. Org. Chem.*, **1990**, *55*, 1693.
[21] Corey, E.J. *Pure Appl. Chem.*, **1990**, *62*, 1209.
[22] Adam, W.; Richter, M.J. *Acc. Chem. Res.*, **1994**, *27*, 57.
[23] Sharpless, K.B.; Woodard, S.S.; Finn, N.G. *Pure Appl. Chem.*, **1983**, *55*, 1823.

titanium atom in this dimer has a local C_2 symmetry. One difference between Corey's proposed catalyst and that of Sharpless is that in the latter's model the oxygen of the *tert*-butoxy group is bound in an axial position and the peroxygen equatorially[24] whilst in the Corey structure **116** both oxygens of the *tert*-butylperoxy unit are bound in equatorial positions.

Both transition state assemblies are unambigous with regard to the absolute stereochemical preference that is implied for the epoxidation reaction. The chirality sense expected for the epoxy alcohol from the transition state assembly (**116**) accords with the experimental facts and also explains the much faster reaction rate for substrates in which a = alkyl or a = b = H relative to b = alkyl.

Interestingly, the enantiofacial selectivity in the Sharpless epoxidation of homoallylic alcohols is the reverse of that found for allylic alcohols. This result can be explained in terms of the transition state assembly (**118**) (see Figure 3.10), which is similar to the assembly (**116**) for allylic alcohols.



118

Figure 3.10. Nature of the catalytic species in the Sharpless epoxidation of homoallylic alcohols.

3.4 KINETIC RESOLUTION IN THE SHARPLESS EPOXIDATION REACTION

A kinetic resolution is a chemical reaction of a racemate in which one of the enantiomers forms its product more rapidly than the other one does. The rate difference arises from the difference in E_a, the activation energy, to reach the transition states for the respective enantiomers of the substrate. As the reaction proceeds towards the product, the enantiomeric excess of the product (e.e) decreases, whilst the e.e of the starting material increases. If the reaction is allowed to go to completion the product is racemic. Kinetic resolution in a reaction only occurs when $k_R \neq k_S$ and the reaction is stopped at some point

[24] Jorgensen, K.A.; Wheeler, R.A.; Hoffman, R. *J. Am. Chem. Soc.*, **1987**, *109*, 3240.

before 100% conversion. Adjustment of either the reaction time or the reaction stoichiometry may be used to control the extent of conversion. The ideal situation is the one in which only the one enantiomer reacts so that at 50% conversion a mixture of 50% of the starting material and 50% of the product is obtained both with 100% e.e.

It must be emphasised that the efficiency of kinetic resolutions depends on the conversion (C), which can only be 0<C<1, and the rate constants of the two competing reactions of the enantiomers, k_R and k_S.[25] More precisely, it is the relative rate of the two enantiomers (k_R/k_S = s, the stereoselectivity factor) that plays a crucial role. The efficiency is measured by the enantiomeric excess of the unreacted substrate (ee_R) and that of the product (ee_P) at a given degree of conversion, C, illustrated by the equations 1 and 2.

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

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

Combination of the two eq.1 and 2, gives equation 3:

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

Since eq. 1 is applicable to all types of reactions, kinetic resolution can be considered as a practical and general route to obtain an enantiopure product from a racemate. This seems, especially true for reactions having a stereoselectivity factor **s**>10. Stated in words, in order to obtain unreacted resolution substrate having a 99% ee, a kinetic resolution having a relative rate ratio of 10 would have to be taken to 72.1% conversion. That is, the yield of the unreacted substrate would be 27.9%. The latter value must, of course, be compared to the maximum yield of one enantiomer obtainable in any resolution, *i.e.* 50%. Eq. 2 relates *C* and **s** to the enantiomeric purity, ee_P of the product of a kinetic resolution. Combining eqs. 1 and 2 gives eq. 3. Eq. 3 illustrates that the enantiomeric purity of the unreacted substrate and the chiral product of a kinetic resolution are necessarily related yet independent of the stereoselective factor, **s**. It also shows that as the enantiomeric purity of the starting material goes up, the product's needs to go down. It is therefore evident that it is impossible to maximize both the enantiomeric purity of the unreacted substrate and its yield.

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

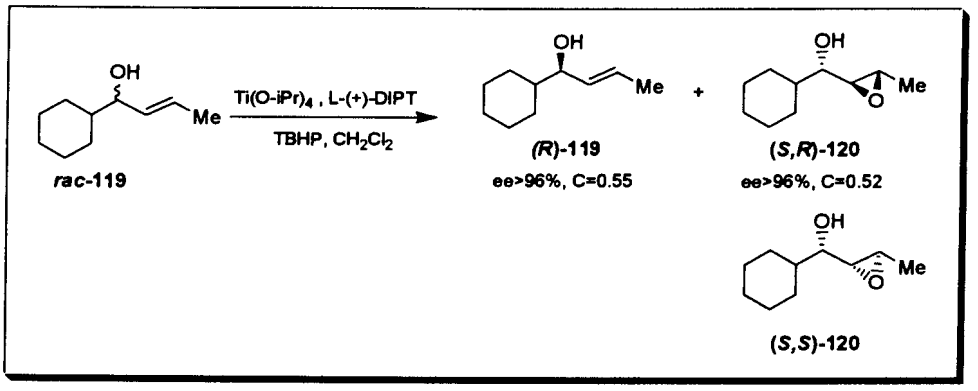


Figure 3.11 Kinetic resolution of racemic (*E*)-1-cyclohexylprop-2-enylcarbinol using L-(+)-DIPT.

Martin and co-workers in 1981 were the first to report on the kinetic resolution of a variety of secondary racemic allylic alcohols during enantioselective epoxidation.[26] Sharpless epoxidation of the racemic secondary allylic alcohol (**119**) (see Figure 3.11) was carried out using diisopropyl (*R*,*R*)-(+)-tartrate and only 0.6 equivalent of the oxidant *t*BuOOH. The unreacted *R*-**119** that was isolated had an e.e.>96%. The estimated value for the conversion was *C* = 0.55 and the stereoselectivity factor **s** were determined experimentally as 104. The epoxide products of the reaction were obtained as a diastereomeric mixture of *syn* and *anti* diastereomers, (*S*,*S*)-**119** and (*S*,*R*)-**119** in a ratio of 97:3. The *anti* diastereomer (*S*,*R*)-**119** had >96% e.e. when *C* = 0.52. The dependence of the yield and e.e. of the diastereomeric epoxy alcohols on the % conversion is shown in Figure 3.12.

The simple mnemonic model shown in Figure 3.13 can be applied to the epoxidation of secondary allylic alcohols and the stereoselectivity predicted. The stereofacial selectivity in the epoxidation reaction is controlled by the tartrate ester that is used. For a given tartrate enantiomer one of the enantiomers of the general secondary allylic alcohol (**121**) will react faster. Since (*S*,*S*)-(–)-tartrate requires the *S* enantiomer of **121** to undergo epoxidation on the face shielded by the R group (the *SSi* face) it reacts more slowly than the *R* enantiomer in which the *SiR* face is much more accessible ($k_R > k_S$). Two possible stereoisomers (**122**) and (**124**) will thus be formed in unequal amounts. The use of (*R*,*R*)-(+)-tartrate will lead to the formation of the (**123**) and (**125**) also in unequal amounts. One prediction that follows from the model which is validated by experimental results, is that of the four epoxy alcohols,

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

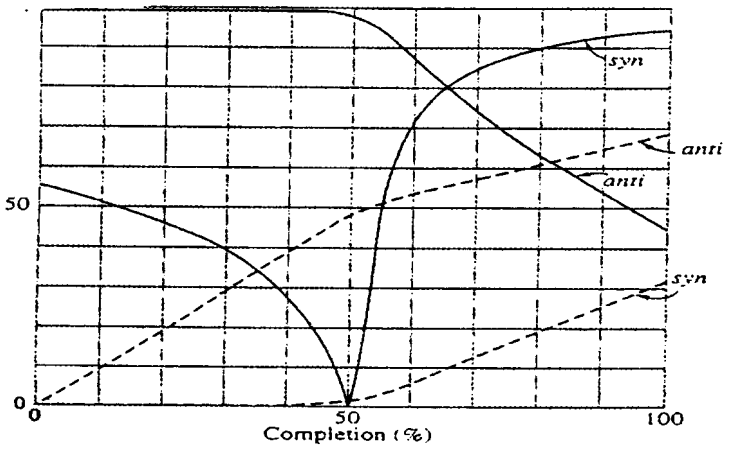


Figure 3.12 Dependence of yield (---) and e.e. (—) on % completion for the Sharpless epoxidation of a racemic secondary allylic alcohol.

(**122-125**), the two *syn* stereoisomers, **122** and **125**, are expected to form in much smaller quantities than the corresponding *anti* stereoisomers, **123** and **124**. It can therefore be deducted that Sharpless epoxidation is not only enantioselective but also diastereoselective.

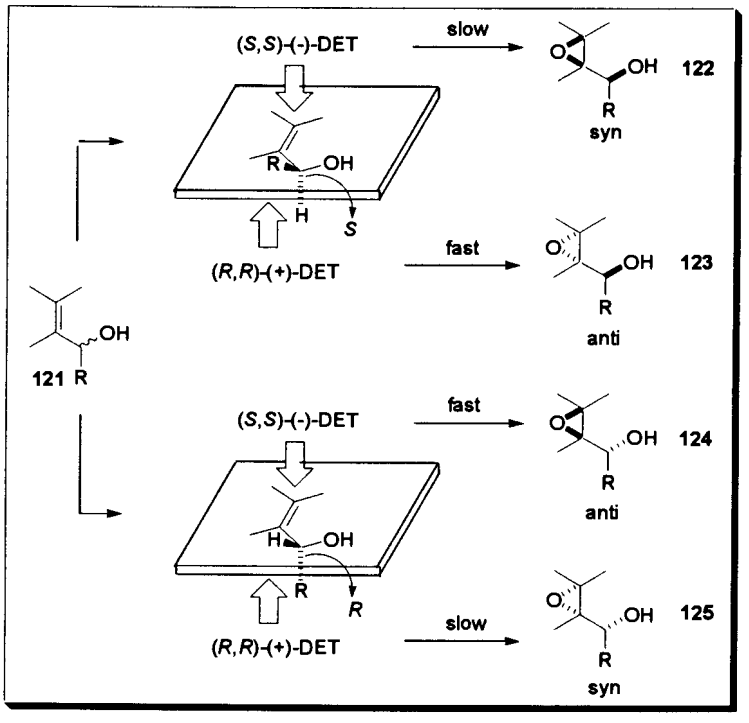


Figure 3.13 Mnemonic model to predict the products formed in the kinetic resolution of a secondary allylic alcohol (**121**).

If there is only enough *t*-BuOOH oxidant present to transform the faster reacting enantiomer, and the stereoselectivity factor **s** is sufficiently high (a ratio of rates of 25 is

usually enough) then the reaction will effectively stop once one enantiomer has reacted, leaving the slower reacting enantiomer of the allylic alcohol unreacted (see Figure 3.13). Hydroperoxides, other than TBHP can be used in asymmetric epoxidation. Secondary hydroperoxides such as phenethyl and very bulky tertiary hydroperoxides, such as triphenylmethyl have been used successfully in enantioselective epoxidation of allylic alcohols. These hydroperoxides have, however, different equilibrium constants for the binding to the titanium. However, it is interesting to note that primary hydroperoxides are not useful for asymmetric epoxidation.

A number of factors are of importance in the kinetic resolution epoxidation reaction. The obvious parameter of interest in the system is the ratio of the rates of epoxidation of the two enantiomers ($k_{fast}/k_{slow,}$) or the relative rate (k_{rel}). According to reports[16,27] in the literature the relative rate values increase remarkably with the bulk of the tartrate ester group, DIPT (104)> DET (36) > DMT (19)[15] but no notable differences in the e.e.'s of the epoxy alcohol products were observed. As expected, electron-withdrawing groups, such as nitro, decrease the rate of epoxidation, while electron-donating groups increase the rate. It was also found that the more highly substituted the double bond is, the greater is the rate of epoxidation. Furthermore, when a stoichiometric amount of tartrate to titanium is used, the rate decreases due to the formation of $Ti(tartrate)_2$ which is catalytically inactive because of its inability to monodentate allylic alcohol and TBHP to displace one of the bidentate tartrate ligands.[28].Therefore, the use of ~1:1.2 ratio of titanium to tartrate is recommended. Kinetic resolution could instead be due to different affinities of the enantiomeric substrates for the chiral metal centre. If one enantiomer were a substantially better ligand than the other one and both enantiomers epoxidized at the same rate, once bound to the metal centre, kinetic resolution would occur. This plays an important role, especially when the rates of epoxidation for both enantiomers are the same.

Kinetic resolution/asymmetric epoxidation has been carried out under catalytic conditions using only 5-10% catalyst.[29] Several researchers have successfully used a 1:1 catalyst:substrate ratio in kinetic resolution studies.[30,31,32,33] Gao *et al.*[27] reported the

[27] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. J. Am. Chem. Soc., 1987, 109, 5765.
[28] Woodard, S.S. PhD Dissertation, Stanford University, Stanford, California **1981.**
[29] Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.*, **1986**, *51*, 1922.
[30] Yang, Z.; Jiang, X.; Wang, Z.; Zhou, W. *J. Chem. Soc., Perkin Trans. 1.* **1997**, 317.
[31] Roush, W.R.; Brown, R.J.; *J. Org. Chem.* **1983**, *48*, 5093.
[32] Honda, T.; Mizutani, H.; Kanai, K. *J. Chem. Soc., Perkin Trans.*, **1996**, 1729.
[33] Yang, Z.; Jiang, X.; Wang, Z.; Zhou, W. *J. Chem. Soc., Chem. Commun.*, **1995**, 2389.

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

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

Sharpless epoxidation/kinetic resolution of secondary allylic alcohols has certain limitations, which are worth mentioning. There are two major classes of substrates that are not suitable for epoxidation by such a catalyst: (1) substrates that react slowly and to a poor ee, for example, some (*Z*)-allylic alcohols and a few severely hindered molecules of other substituted types,[34] (2) substrates that are epoxidized at a rapid rate and with a high selectivity but yield epoxy alcohols that are unstable to the reaction conditions.[35]

3.5 NUCLEOPHILIC OPENING OF EPOXIDE

3.5.1 Background

The strain and the polarity of the three-membered oxirane ring with bond angles of C-C-O 59.2° and C-O-C 61.5° allow it to undergo cleavage of one of the C-O bonds with both electrophiles and nucleophiles. Epoxides can be ring-opened by a variety of nucleophiles in both acidic and basic medium.[36] In basic medium the reaction proceeds via nucleophilic attack on the neutral epoxide by an S_N2 mechanism whereas in acidic medium protonation of the epoxide precedes nucleophilic attack and opening occurs by a mechanism that is termed

[34] Reed, L.A.; Ito, Y.; Masamune, S.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1982**, 104, 6468.
[35] Morgans, D.J..; Sharpless, K.B.; Traynor, S.G. *J. Am. Chem. Soc.*, **1981**, *103*, 462.
[36] Smith, J.G. *Synthesis*, **1994**, 629.

as a borderline S_N2.[37,38] In general the position of nucleophilic attack for 1,2- and 2,3-epoxides is governed by both the structure of the epoxide and the reaction conditions.

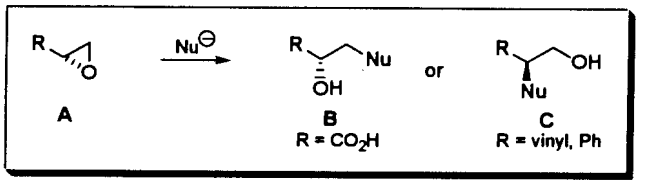


Figure 3.14 Nucleophilic opening of a terminal epoxide.

Ring opening of the 1,2-epoxide **A** by nucleophilic attack under different reaction conditions is outlined in Figure 3.14. In basic solution attack occurs predominantly at the sterically less hindered site yielding **B**. In acidic 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 **C.** It was found that when the substituent on the epoxide ring is for example, a phenyl or a vinyl group, which can stabilize an intermediate positive charge by conjugation, attack at the more substituted carbon atom to form **C** is favoured. When the substituent is an electron-withdrawing group formation of **B** is preferred. Similarly, 2,3-epoxy alcohols can be opened by nucleophiles as outlined in Scheme 3.15.

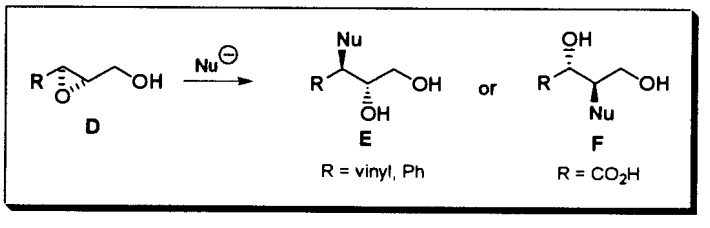


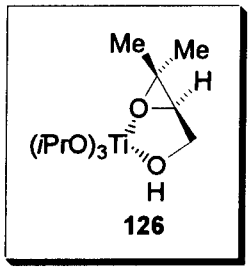
Figure 3.15. Nucleophilic opening of 2,3-epoxy alcohol **D.**

3.5.2 Metal-chelated opening of epoxides by cyanide

Smiley and Arnold[39] in 1960 reported the preparation of nitriles in high yields and short reaction times by the reaction of primary and secondary halides with alkali metal cyanides in DMSO at high temperatures (between 100-150°C). These conditions are not suitable for heat-labile compounds. In the early 1980s much milder reaction conditions were reported [35,40]

[37] Parker, R.E.; Isaacs, N.S. *Chem. Rev.*,**1959**, 737.
[38] Buchanan, J.G.; Sable, H.Z. in *Selective Organic Transformations,* (B.S. Thyagarajan, Ed.), *Vol.2,* John Wiley & Sons, New York, **1967.**
[39] Smiley, R.A.; Arnold, C. *J. Org. Chem.*, **1960,** *25*, 257.
[40] Fujiwara, S.; Aoki, M.; Uyehara, T.; Kato, T. *Tetrahedron Lett.*, **1984,** *25*, 3003.

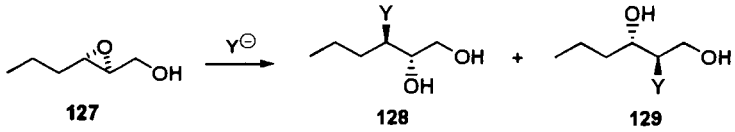
for the nucleophilic ring opening of 2,3-epoxy alcohols. High regioselectivity and stereo-chemical control were facilitated by the co-ordination of the oxirane oxygen atom to the metal alkoxide in a rigid bidentate manner (see Figure 3.16). The presence of the hydroxy functional group enhances this coordination even though epoxides are weak Lewis bases and titanium alkoxides are weak Lewis acids.



126

Figure 3.16 Bidentate coordination of an epoxy alcohol to the Ti metal centre.

The opening of 3-propyloxiranemethanol **127** in the presence of the Lewis acid $Ti(OiPr)_4$ was investigated by Sharpless *et al.* with a variety of nucleophiles. They found that the presence of $Ti(O\text{-}iPr)_4$ is essential since it markedly increased the rate and the regioselectivity of the opening process. The increase in rate and regioselectivity was also found to be dependent on the type of nucleophile used: isopropanol, benzoic acid and pivalic



127 **128** **129**

	NUCLEOPHILE, Y	REGIOSELECTIVITY C-3:C-2 128:129	YIELD, %
A	*i*-PrOH	100 : 1	88
B	KCN	1.3 : 1	91
C	Me_3SiCN	4.9 : 1	32
D	NH_4Cl	3.0 : 1	71
E	$PhCO_2H$	100 : 1	74

Figure 3.17 Nucleophilic opening of epoxide **127.**

acid resulted in ratio of 100:1 for the C_3:C_2 regioselectivity (see Figure 3.17). The lowest selectivity was observed when potassium cyanide and a catalytic amount of tetrabutyl-ammonium iodide (TBAI) were used and a 1.3:1 ratio for the C_3:C_2 ring opening was found.[41]

3.5.3 Alternative methods for the opening of oxiranes

Cyanotrimethylsilane (TMS-CN) which is known to exist as an equilibrium mixture of nitrile and isocyanide forms,[42] is a versatile reagent for the synthesis of nitriles and isonitriles.[43] Ring-opening reactions of epoxides (internal and terminal) with TMS-CN and Lewis acid catalysis with for example diethylaluminium chloride, has been studied thoroughly by various research groups.[43,44] The cyano group of TMS-CN binds to the catalyst either via the nitrogen or the carbon atom. In general the cyano group binds to hard Lewis acids (*e.g.* those containing aluminium) through the nitrogen atom and this results in the formation of nitriles as products.[45] Initially, TMS-CN reacts with a catalytic amount of diethylaluminium chloride to give the CN-Al species[44,46] and trimethylsilyl chloride. Diethylaluminium cyanide then reacts with the epoxide to yield the ring-opened product. Finally, exchange between additional TMS-CN and diethylaluminium alkoxide serves to regenerate the diethylaluminium cyanide and give the nitrile as the product. Examples of the use of TMS-CN in the presence of a catalyst to afford nitriles from 1,2-epoxides are as follows.

Sassaman, Prakash and Olah[47] studied the opening of the 1,2-epoxide **130** using KCN and TMS-CN with 18-crown-6 as a phase transfer catalyst. The coordination of the nitrogen atom of the cyanide ion with the silicon atom of TMS-CN results in the formation of a trigonal-bipyramidal complex that is involved in nucleophilic attack at the less-hindered side of the epoxide (see Figure 3.18). The limitation of the reaction is that ring cleavage takes place only with monosubstituted epoxides as the unfavourable interaction in the transition state between the methyl groups on the silicon and the substituents on the epoxide prevent ring opening of more highly substituted epoxides.

Lidy and Sundermeyer[48] found that the addition of cyanide in the reaction of TMS-CN with 2,2-dimethyloxirane **130** in the presence of catalytic aluminium trichloride occurred at the

---

[41] Caron, M;. Sharpless, K.B. *J. Org. Chem.*, **1985,** *50*, 1557.
[42] Seckar, J.A.; Thayer, J.S. *Inorg. Chem.*, **1976**, *15*, 501.
[43] Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.*, **1987,** *52*, 1013.
[44] Mullis, J.C.; Weber, W.P. *J. Org. Chem.*, **1982,** *47*, 2873.
[45] Ho, T. *Hard and Soft Acids and Bases Principle in Organic Chemistry,* Academic Press: New York, **1977.**
[46] Nagata, W.; Yoshioka, M;. Okumura, T. *Tetrahedron Lett.*, **1966,** 847.
[47] Sassaman, M.B.; Surya Prakash, G.K.; Olah, G.A. *J. Org. Chem.*, **1990,** *55*, 2016.
[48] Lidy, W.; Sundermeyer, W. *Tetrahedron Lett.*, **1973,** 1449.

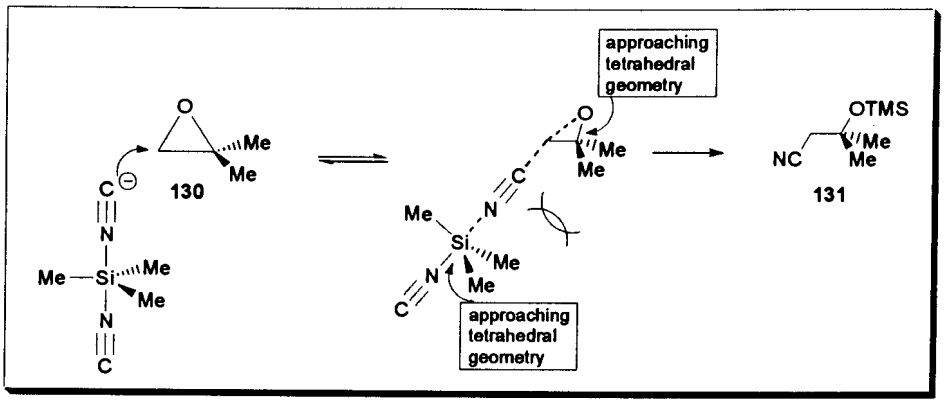
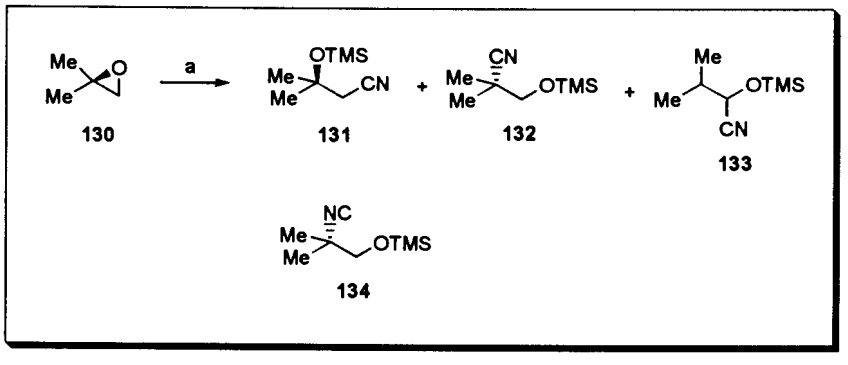


Figure 3.18 Proposed transition-state for the ring-opening of a terminal epoxide with CN^-.

more highly substituted carbon to form compound **132** (see Scheme 3.1). Mullis and Weber[44] on the other hand, reported that the same substrate undergoes ring cleavage in the presence of either aluminum trichloride or diethylaluminum chloride catalyst at the least substituted carbon to give **131**.



Scheme 3.1 Nucleophilic opening of 2,2-dimethyloxirane by TMS-CN.

Reagents: a. TMS-CN, $AlCl_3$ or Et_2AlCl

Two other research groups[43,49] also investigated nucleophilic opening of **130** by TMS-CN in the presence of Et_2AlCl and obtained the same results, namely a mixture of nitriles **131**, **132** and isonitrile, **134**, the main product, and a rearranged product **133**. Imi *et al.*[43] also reported that in the presence of either $Pd(CN)_2$, $SnCl_2$ or Me_3Ga the regioselective addition of the nucleophile to **130** favours the formation of **134**. Katsuharu *et al.*[49] explained that the formation of **133** is the result of the isomerization of **130** to 2-methylpropanal which undergoes nucleophilic attack by TMS-CN to give **133**. They also found that the use of (*i*-

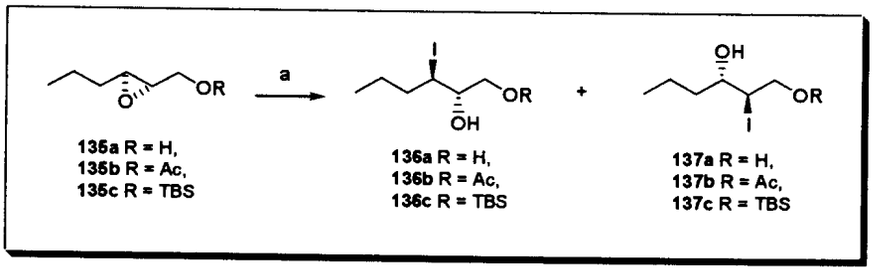
[49] Katsuharu, I.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.*, **1987**, *52*, 1013.

$Bu)_2AlO$*i*Pr suppresses the formation of isonitrile **134** and thus leads to the regio- and stereoselective production of the nitrile **131**.

Chini *et al.*[50] discovered a methodology for the opening of 1,2-epoxides by potassium cyanide using catalytic metal salts such as $LiClO_4$, $Mg(ClO_4)_2$, $NaClO_4$, $KClO_4$ and NH_4Cl, to afford β-hydroxynitriles. The reactions are highly regioselective with attack of the cyanide nucleophile on the less substituted carbon. The reaction conditions are mild and the yields are above average even when highly substituted epoxides are used.

3.5.4 Opening of epoxides to form halohydrins

Bonini *et al.*[51] reported on the opening of 2,3-epoxy alcohols such as **135**, **136** and **137** with MgI_2 to yield 3-iodo-1,2-diols with regioselectivities and chemical yields comparable or superior to other methods[52,41] (see Scheme 3.2). They found that protected (an acetyl or TBS group) and hindered epoxy alcohols also undergo ring opening. This is in contrast to other known procedures in which a free hydroxy group plays an essential part in the rate and regioselectivity of the ring opening[41] and which can only be used to open unhindered epoxy alcohols. The mechanism of the opening involves the formation of a chelate complex between the Mg(II) and the two oxygens of the epoxy alcohol without the need of another coordinating species such as $Ti(O$*i*$Pr)_4$.[41,52] This chelate also forms in the case where a protected epoxy alcohol is used as a substrate.



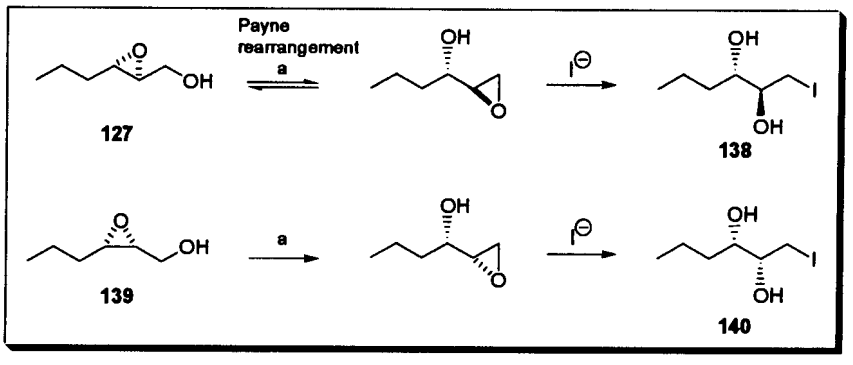
Scheme 3.2 Nucleophilic opening of 2,3-epoxy alcohols by MgI_2.

Reagents: a. MgI_2, CH_2Cl_2, –60°C

Bonini *et al.*[53] also investigated the lithium halide opening of *trans*- and *cis*-2,3-epoxy alcohols **127** and **139**. (see Scheme 3.3). They proposed a simple methodology for the formation of 1-halo-2,3 diols *e.g.* **138**, under mild conditions with a high degree of regio-

[50] Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.*, **1991**, *32*, 4775.
[51] Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.*, **1991**, *56*, 6206.
[52] Alverez, E.; Nunez, M.T;. Martin, V.S. *J. Org. Chem.*, **1990**, *55*, 3429.

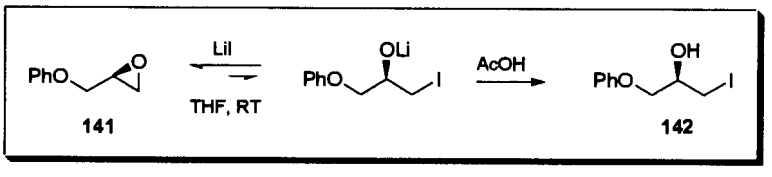
selectivity. The 2,3-epoxy alcohol **127** undergoes an initial Payne rearrangement[54] to a 1,2-epoxy alcohol that is ring opened at the less substituted carbon atom by nucleophilic attack of the halide, I^- to give the iodohydrin **138**. This method can also be used on benzyl, TBS and TBDPS derivatives and also in the presence of an olefin functional group.



Scheme 3.3 Formation of 1-iodo-2,3-diols from 2,3-epoxy alcohols **127** and **139**.

Reagents: a. LiI, DME, 70°C.

Baiwa *et al.*[55] found that lithium halides regioselectively open the 1,2-epoxide **141** by to form the halohydrin **142**. The reactivity of lithium halides in decreasing order is LiI>LiBr>LiCl. The reaction involves a reversible epoxide ring opening by nucleophilic attack of a halide ion.[56] The addition of acetic acid is to drive the reaction to completion by protonating the intermediate alkoxide (see Scheme 3.4). The addition of acetic acid or any acid with a pK_a <16,[57] is important since only starting material is recovered when this step is omitted.

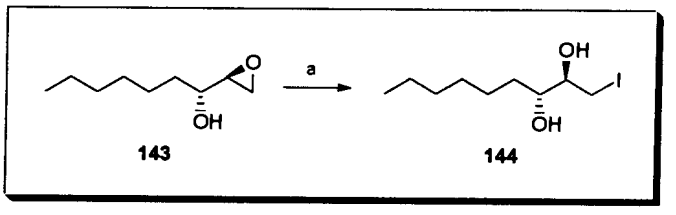


Scheme 3.4 Nucleophilic opening of epoxides.

Alverez *et al.*[52] reported the regioselective opening of 1,2-epoxy alcohol **143** to the iodohydrin **144** with I_2 in the presence of a stoichiometric amount of $Ti(OiPr)_4$ The only draw-

[53] Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.*, **1995,** 60, 4803.
[54] Payne, G.B. *J. Am. Chem. Soc.*, **1962**, 27, 3819.
[55] Bajwa, J.S.; Anderson, C. *Tetrahedron Lett.*, **1991,** *32*, 3021.
[56] Rickborn, B.; Gerkin, R.M. *J. Am. Chem. Soc.*, **1971,** *93,* 1693.
[57] March, J. *Advanced Organic Chemistry;* John Wiley and Sons, Inc.; New York, **1985,** 220.

back of this method is that it is not applicable when acid-sensitive groups are present.[58,59] The increase in the rate and regioselectivity of the opening reaction of **143** with dihalogen in the presence of $Ti(OiPr)_4$ suggested that complexation of the epoxy alcohol to the Ti metal centre, as proposed by Sharpless *et al.*[60] for other Ti-assisted openings, takes place. The reaction requires a free hydroxy group to bind to the metal as epoxy alcohol acetates show negligable activity under the described conditions.



143 **144**

Scheme 3.5 Nucleophilic opening of 1,2-epoxy alcohols.

Reagents: a. $Ti(iPrO)_4$, I_2, 0°C.

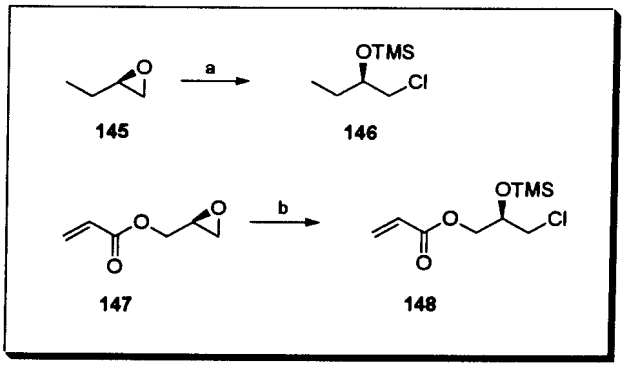
The thermal uncatalysed insertion of silicon halides into oxiranes has been known for long.[61,62] In 1981 Andrews *et al.*[63] found a milder method using silyl halides in the presence of a catalyst (*e.g.* Bu_4NCl, Bu_4NBr, Bu_4NI or Ph_3P) to afford primary halohydrins **146** and **148** from the terminal epoxides **145** and **147**, respectively. They found that the catalysed reactions gave higher regioselectivities than the uncatalysed reaction. The regioselectivity is furthermore temperature dependent. In general 1,2-epoxide opening by trialkylsilyl halides results in high yields at low temperature *i.e.* 0 ^{0}C but in the case of TBSCl and TBDPSCl higher temperatures and longer reaction times are needed.

3.5.5 Opening of epoxides with Grignard reagents

Numerous groups[64,65,66,67] have reported comparative studies of the reaction of organolithium, organomagnesium and organocopper reagents with epoxides. Acker[66] found that direct nucleophilic opening of styrene oxide **149** could occur at either the more electrophilic carbon of the epoxide to form **150**, or at the more accessible site to form **151**.

---

[58] Doherty, A.M.; Ley, S.V. *Tetrahedron Lett.*, **1986,** *27*, 105.
[59] Evans, D.A.; Bender, S.L.; Morr, J. *J. Am. Chem. Soc.*, **1988,** *110*, 2506.
[60] Caron, M;. Sharpless, K.B. *J. Org. Chem.*, **1985,** 1560.
[61] Sauer, R.O.; Patnode, W. *J. Am. Chem. Soc.*, **1945,** *67*, 1548.
[62] Ditty, M.R;. Seidler, M.D. *J. Org. Chem.*, **1981,** *46*, 1283.
[63] Andrews, G.C.; Crawford, T.C.; Contillo, L.G.Jr. *Tetrahedron Lett.*, **1981,** *22*, 3803.
[64] Posner, G.H. *Org. React.* **1975**, *22*, 253.
[65] Johnson, C.R.; Herr, R.W.; Wieland, D.M. *J. Org. Chem.* **1973,** *38*, 4263.
[66] Acker, R.D. *Tetrahedron Lett.*, 1977, 3407.
[67] Davies, S.G.; Wollowitz, S. *Tetrahedron Lett.*, **1980**, *21*, 4175.



Scheme 3.6 Nucleophilic opening of 1,2-epoxides by Cl^-.

Reagents: a. TMSCl, TBAI, $CHCl_3$, –50°C; b. TMSCl, TBAI, $CHCl_3$, 25°C

When organometallic reagents with sufficient Lewis acidity are used, the epoxide **149** can also rearrange to an intermediate aldehyde **152** which can undergo nucleophilic attack to afford **153**. The yield of addition adduct **151** predominates when dialkylmagnesium reagents or heterocuprates prepared from an organolithium reagent and copper cyanide were used as shown in Table 3.1. A complete reversal of regioselectivity is seen when higher order mixed cuprates $R_2Cu(CN)Li_2$ are used and **151** is then the major product. In the case of a Grignard reagent such as methylmagnesium bromide isomerization to an intermediate aldehyde **152** becomes a significant competing reaction and the alcohol **153** is formed.

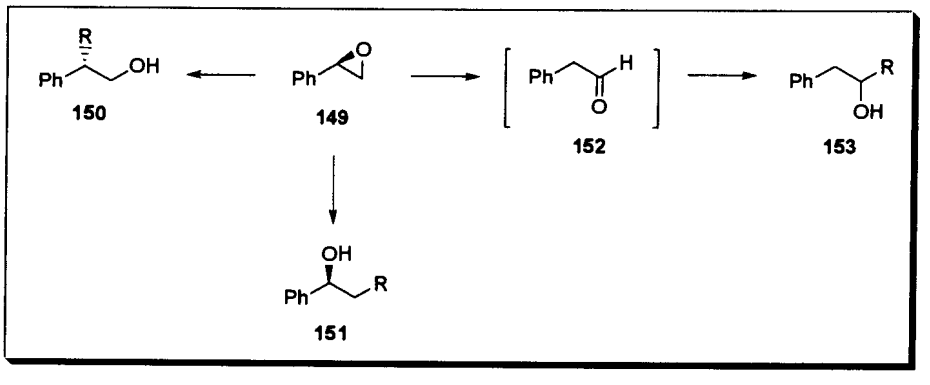


Figure 3.19 Nucleophilic opening of styrene oxide **149** by organometallic reagents.

Courtois *et al.*[68] reported that the nucleophilic opening of propylene oxide **154** by an unsymmetrical allyl Grignard reagent can be achieved with high regioselectivity in the presence of copper(I) iodide (Figure 3.21). Attack of the α-carbon of the isoprenylmagnesium

[68] Coutrois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

	Yield (%)		
Reagent	**150**	**151**	**153**
Me_2Mg	100	–	–
MeMgBr	50	–	50
(Me)Cu(CN)Li	81	18	–
$(n\text{-}C_4H_9)Cu(CN)Li$	74	21	–
$(n\text{-}C_4H_9)_2Cu(CN)Li_2$	8	85	–

Table 3.1 Nucleophilic opening of **149** by different organometallic reagents.

bromide on the less substituted carbon atom of the epoxide **154** occurs predominantly when Cu(I)I is present to afford **156**. If the copper catalyst is absent γ-attack by the Grignard reagent is favoured forming **155**.

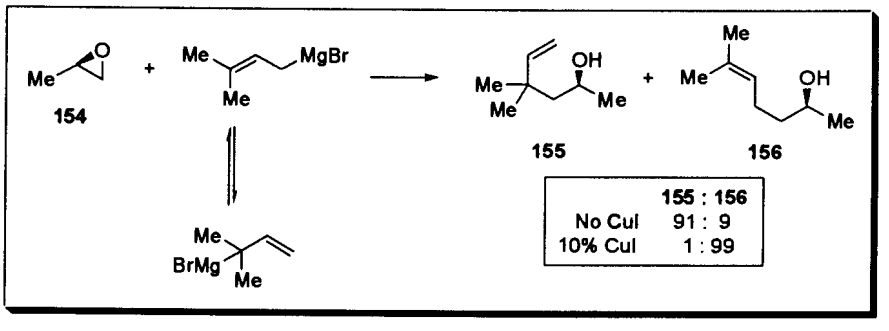


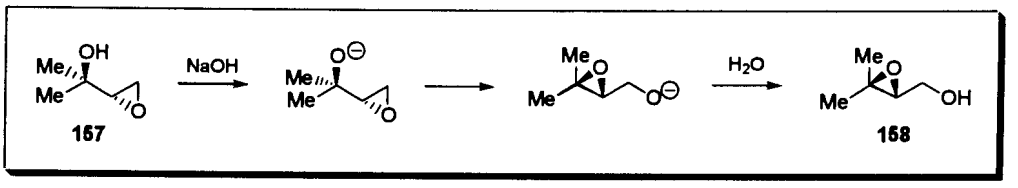
Figure 3.20 Reaction of propylene oxide **154** with isoprenylmagnesium bromide

3.5.6 Payne Rearrangement

Epoxide migration in sugars has been reported by Angyal *et al.*[69] as early as 1957. This observation led Payne[54] to investigate epoxide migration in the aliphatic 1,2-epoxy alcohol **157** using NaH and THF as solvent. However the extent of isomerization was very low <2%. In 0.5M aqueous sodium hydroxide solution the epoxy alcohol **157** isomerised and gave a mixture of **157/158** in the ratio 92:8 in 82% yield after 1 h. The isomerization that was observed is the result of the generation of a "free" anion (see Scheme 3.7). It is postulated that the sodium cation is tightly bound to the alkoxide anionin THF solution precluding intramolecular nucleophilic attack on the oxirane ring. **157**. Payne proposed a mechanism where the alkoxide anion approaches the epoxide ring resulting in stretching of the adjacent

[69] Angyal, S. J.; Gilham, P. T. *J. Chem. Soc.*, **1957**, 3691.

ring C-O bond therefore increasing the carbocation character at the receptor centre, i.e. intramolecular nucleophilic substitution is S_N2[70] type of reaction, thus forming a new C-O bond. Payne also found that 1,2- and 2,3-epoxy alcohols with less highly substituted carbinol carbon in general are favoured over the more highly substituted isomer (See Figure 3.21).



Scheme 3.7 Mechanism of the Payne rearrangement of epoxide **157.**

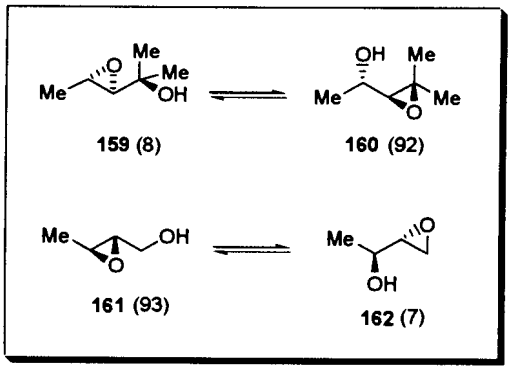


Figure 3.21 Equilibration of 1,2-epoxy alcohols in 0.5M NaOH solution.

The favoured isomer was found to be the one having the more highly substituted epoxide group.[71] In the absence of steric effects, the ratio of isomers is >10:1 which correlates with the relative acidic strengths of carbinols. The relative acidic strength of simple aliphatic alcohols in decreasing order is primary> secondary>tertiary.[72]

[70] Dua, S.; Taylor, M. S.; Buntine, M.A.; Bowie, J.H. *J. Chem. Soc., Perkin Trans. 2*, **1997,** 1991.
[71] Parker, R.E.; Isaacs, N.S. *Chem. Rev.*, **1959**, *59*, 737.
[72] Hine, J.; Hine, M. *J. Am. Chem. Soc.*,**1952,** 74, 5266.

4. Chemistry of Chiral Sulfoxides

4.1 INTRODUCTION

The synthesis of homochiral molecules, and especially natural products with novel physiological properties, is an important part of modern organic chemistry. Organic sulfur compounds have become increasingly useful and important in organic synthesis in the past decade.[1,2,3,4] The sulfoxide group is of special interest because of the sulfur stereogenic center that allows it to act as a chiral auxiliary in asymmetric syntheses for the stereoselective generation of chirality at proximate centres.

4.2 CHEMISTRY OF CHIRAL SULFOXIDES

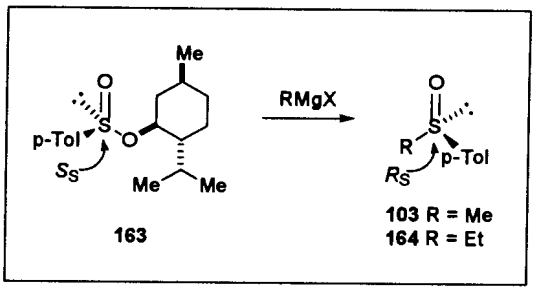
4.2.1 Synthesis of chiral sulfoxides

Many approaches have been followed over the years in the synthesis of optically active sulfoxides. In the initial stage of the development the sulfoxide group was introduced as the racemic mixture in synthesis. Later, optically active sulfoxides were obtained by optical resolution, asymmetric synthesis, kinetic resolution and stereospecific synthesis. In the pioneering work of Harrison *et al.*,[5] optical resolution was achieved by the introduction of an acidic or basic group in the molecule. Later, Mikolajczyk[6] reported a thorough study on the optical resolution of racemic sulfoxides. Montanari[7,8] and Balenovic[9] first reported the asymmetric oxidation of sulfides with optically active peracids but the optical yields in general were poor (<10%). Later, Kagan[10,11] improved the enantiomeric excess obtained in asymmetric oxidations of simple alkyl aryl sulfides to as high as 90% using $Ti(O\text{-}iPr)_4$ and either (*R*,*R*)- or (*S*,*S*)-tartrate and *t*-BuOOH as oxidant (Sharpless conditions). Enzymatic oxidation of sulfides has been a successful alternative for the preparation of chiral sulfoxides in a

---

[1] Field, L. *Synthesis,* **1972**, 101; **1978,** 713.
[2] Grobel, B.-T.; Seebach, D. *Synthesis*, **1977**, 357.
[3] Trost, B. *Chem. Rev.;* **1978**, *78,* 363.
[4] Oae, S. Ed, *Organic Chemistry of Sulfur*, Plenum Press, New York, **1977.**
[5] Harrison, P.W.B.; Kenyon, J.; Phillips, H. *J. Chem. Soc.*, **1979,** *128*, 2079.
[6] Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *The Chemistry of Sulfones and Sulfoxides* (Patai, S.; Rappoport, Z. and Srirling, C.J.M., Eds), 233, Wiley, New York, **1988.**
[7] Macconi, A.; Montanari, F.; Secci, M.; Tramontini, M. *Tetrahedron Lett.*, **1961**, 607.
[8] Folli, U; Iarossi, D.; Montanari, F.; Torre, G. *J. Chem. Soc. C.*, **1968,** 1317.
[9] Balenovic, K.; Bregant, N.; Francetic, D. *Tetrahedron Lett.*, **1960,** 20.
[10] Pitchen, P.; Dunach, F.; Deshmukh, M.N.; Kagan, H.B. *J. Am. Chem. Soc.*, **1984,** *106*, 8188.
[11] Dunach, E.; Kagan, H.B. *Nouv. J. Chim.*, **1985,** *9*, 1.

number of cases.[6,12,13] Even though all of the above-mentioned methods can be used to give very good results with specific substrates, a more general method was needed. Andersen[14,15,16] following the method proposed by Gilman,[17] prepared optically active sulfoxides from the optically active sulfinate esters using a Grignard reaction: thus the reaction of diastereoisomerically pure (–)-(*S*)-menthyl-*p*-toluenesulfinate **163** with Grignard reagent, ethyl magnesium iodide gives (+)-(*R*)-ethyl *p*-tolyl-sulfoxide **164** (see Scheme 4.1).

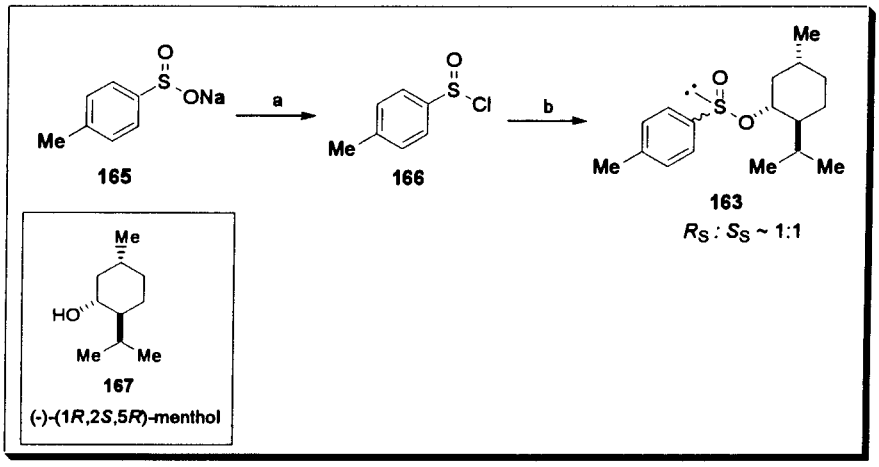


Scheme 4.1 Synthesis of (+)-(*R*)-alkyl *p*-tolylsulfoxide proceeds by S_N2 inversion.

The Andersen sulfoxide method is a general reaction applicable even to the synthesis of complex homochiral sulfoxides. The initial drawback of the reaction was the requirement of quantities of optically pure **163**. Andersen,[14,15,16] Mislow *et al.*[18,19,20] and others[21,22,23] obtained **163** by esterification of (–)-menthol with racemic *p*-toluenesulfinyl chloride (see Scheme 4.2). The esterification reaction shows no particular stereoselectivity and gives a 1:1 mixture of diastereomers epimeric at sulfur. The desired (S_S)-diastereomer **163** is crystalline and is obtained by crystallisation at –20°C in pure form. The corresponding (R_S)-diastereomer is an oil. Solladie *et al.*[24] subsequently improved this method by using the acid-catalysed epimerization of sulfinates to epimerise the (R_S)-diastereomer to an equilibrium mixture of diastereoisomers from which the (*S*)-menthyl *p*-toluenesulfinate **163** can be obtained by crystallisation. The final yield of **163** can be as high as 90%.[24,25]

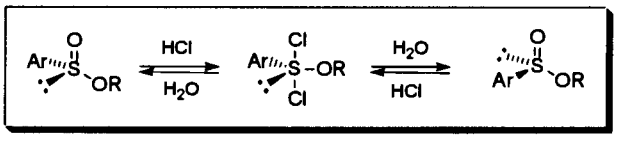
---

[12] Auret, B.J.; Boyd, D.R.; Henbest, H.B.; Ross, S. J. *Chem. Soc. C.*, **1968,** 2371.
[13] Colonna, S.; Gaggero, M.; Casella, L.; Carrea, G.; Pasta, P. *Tetrahedron Asym.*, **1992,** *3*, 95.
[14] Andersen, K.K. *Tetrahedron Lett.*, **1962** , 93.
[15] Andersen, K.K.; Gaffield, W.; Papanikolaou, N.E.; Foley, J.W.; Perkins, R.I. *J. Am. Chem. Soc.*, **1964,** *86*, 5637.
[16] Andersen, K.K. *J. Org. Chem.*, **1964,** *29*, 1953.
[17] Gilman, H.; Robinson, J.; Beaber, N.H. *J. Am. Soc.*, **1926,** *48*, 2715.
[18] Mislow, K.; Green, M.M.; Laur, P.; Melillo, J.P.; Simmons, T.; Ternay, A.L. *J. Am. Chem. Soc.*, **1965,** *87*, 1958.
[19] Mislow, K.; Ternay, A;. Melillo, J.T. *J. Am. Chem. Soc.*, **1963,** *85*, 2329.
[20] Mislow, K.; Simmons, T.; Melillo, J.T.; Ternay, A.L. *J. A. Chem. Soc.*, **1964,** *86*, 1452.
[21] Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M.M.; Mislow, K. *J. Am. Chem. Soc.*, **1968,** *90*, 4835.
[22] Nishio, M.; Nishihata, K. *J. Chem. Soc., Chem. Commun.*, **1970,** 1485.
[23] Stirling, C.J.M. *J. Chem. Soc.*, **1963,** 5741.
[24] Mioskowski, C.; Solladié, G. *Tetrahedron*, **1980,** *36*, 227.
[25] Solladié, G.; Hutt, J.; Gigardin, A. *Synthesis*, **1987,** 173.



Scheme 4.2: Synthesis of (–)-(*S*)-menthyl *p*-toluenesulfinate.

Reagents: a) $SOCl_2$, 10°C; b) pyridine, **167**.



Scheme 4.3 Epimerization of chiral sulfoxides in the presence of aqueous HCl.

Initially, the reaction of arenesulfinates with Grignard reagents was carried out in ethyl ether to afford chiral sulfoxides in moderate to low yield depending on the sulfinic ester structure and the Grignard reagent. Mikolajczyk[26] later reported that chiral sulfoxides could be prepared in high chemical yield and optical purity when the Grignard reaction is carried out in benzene instead of diethyl ether solution. This procedure was followed for the multigram synthesis of (+)-(*R*)-methyl *p*-tolylsulfoxide **103** with >98% e.e.[25] using the Grignard reaction of methyl magnesium iodide with (*S*)-(–)-menthyl *p*-toluenesulfinate **163** at 0°C in benzene. The (–)-menthol is separated by column chromatography and the product **103** is purified by crystallization from hexane-ether (1:1) at –5°C.

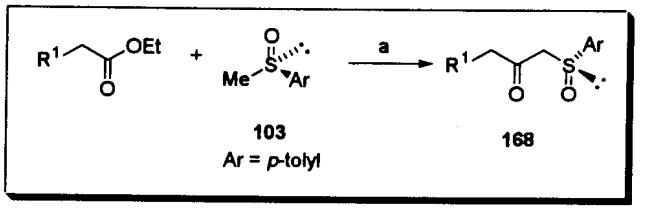
4.2.2 Synthesis of β-ketosulfoxides

The synthetic usefulness of the sulfoxide group arises from its ability to stabilise a negative charge on an α-carbon atom. The formed α-carbanion can then be exploited in a

[26] Drabowicz, J.; Bujnicki, B.; Mikolajczyk, M.M. *J. Org. Chem.*, **1982**, *47*, 3325.

number of ways, the most important of which is in carbon-carbon bond formation.[27] Racemic mixtures of β-ketosulfoxides were first prepared by Corey,[28,29] and the first optically pure compound was prepared by Kunieda,[30] while Solladié[31,32] has successfully optimized the reaction conditions.

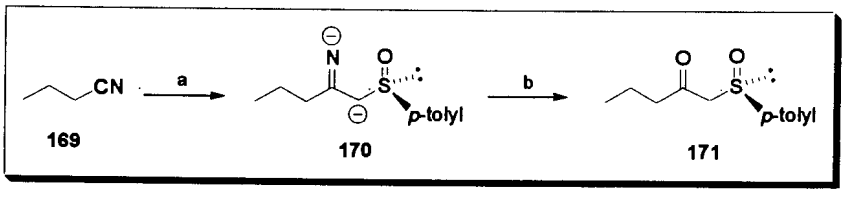
The reaction involves the addition of an ester to a cold solution of two equivalents of the α-carbanion of (+)-(*R*)-methyl *p*-tolylsulfoxide **103** (Scheme 4.4). Two equivalents are essential as the α-protons of the formed ketosulfoxide are more acidic than those of the reagent. The low nucleophilicity of the formed product anion prevents it from reacting with the ester present.



Scheme 4.4 Preparation of a β-ketosulfoxide from an ester.

Reagent: a) LDA, –78°C.

Zeevaart and Vleggaar[33] investigated the reaction of nitriles with (+)-(*R*)-methyl *p*-tolylsulfoxide **103** to prepare β-ketosulfoxides by exploiting the fact that nucleophilic attack of an α-sulfinyl anion on the carbon atom of a nitrile group leads to carbon-carbon formation via an iminide intermediate (**170**). Aqueous acidic work-up generates an imine that in tum is hydrolysed under the work-up conditions to form the β-ketosulfoxide **171** (Scheme 4.5).



Scheme 4.5 Synthesis of a β-keto sulfoxide from a nitrile.

Reagents: a) LDA, **103**, 0°C→rt; b) aq. HCl (pH 2) (85%).

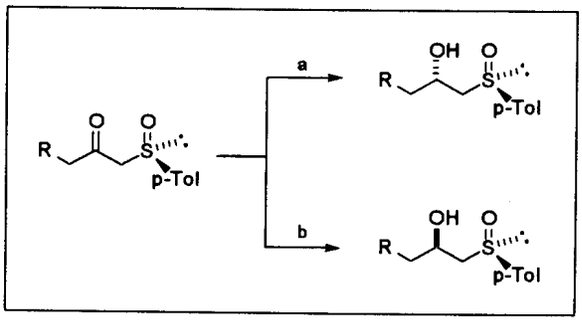
---

[27] Carreño, M.C.; *Chem. Rev.*, **1995**, *95*, 1717.
[28] Corey E.J, Chaykowski M, *J. Am. Chem. Soc.* **1962**, *84*, 866.
[29] Corey, E.J, Chaykowski, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
[30] Kunieda, N.; Nokami, J.; Kinoshita, M.; *Chem. Lett.* **1974**, 369.
[31] Solladié, G.; Almario, A. *Tetrahedron Asym.* **1995**, *6*, 559.
[32] Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas*, **1995**, *144*, 153.

The reaction proceeds in excellent yield even when double bonds and protected hydroxy groups are present in the nitrile. The reaction failed only in the case of phenylacetonitrile.

4.2.3 Stereoselective reduction of β-ketosulfoxides

The great advantage of chiral sulfoxides in synthesis is the stereoselectivity attainable in the reduction of the β-ketosulfoxide moiety. Early work by Annunziata and Cinquini[34] on the stereoselective reduction of β-ketosulfoxides using $NaBH_4$ and $LiAlH_4$ at –70°C gave diasappointingly low diastereomeric excess (d.e.) of 60-70%. Solladié *et al.*[35] investigated the reduction of β-ketosulfoxides with many different reducing agents. They obtained the same results as Annunziata for $LiAlH_4$ and $NaBH_4$ but observed a high d.e. for the β-hydroxy-sulfoxide product when β-ketosulfoxides were reduced by diisobutyl aluminium hydride, DIBALH. An increase in the diastereoselectivity could be achieved when DIBALH was added to the β-ketosulfoxide solution kept at –78°C, instead of adding the substrate to a solution of DIBALH.[36] They[36] and Kosugi *et al.*[37] found that the stereochemistry of the stereogenic centre formed in the reduction of the β-carbonyl group is determined by the presence or absence of anhydrous $ZnCl_2$ or $ZnBr_2$ in the DIBALH reduction (see Scheme 4.6).



Scheme 4.6 Stereoselective reduction of β-ketosulfoxides.

Reagents: a) DIBALH, THF, –78°C; b) DIBALH, $ZnCl_2$, THF, –78°C

Different explanations have been proposed to account for the high stereoselectivity achieved in the reduction of β-ketosulfoxides. The mode of action of DIBALH and DIBALH-

---

[33] Vleggaar, R;. Zeevaart, J.G. *Tetrahedron Lett.*, **1999**, *40*, 9301.
[34] Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1687
[35] Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.*,**1982**, *23*, 5047.
[36] Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.*, **1985**, *26*, 435.
[37] Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc. Chem. Commun.*, **1985**, 211.

$ZnCl_2$ is shown in Figure 4.1 and is based on an early proposal formulated by Solladié.[36,38] The theory is based on the fact that the two polar groups (*i.e.* the sulfoxide and carbonyl groups) will be directed away from each other. The *Re*-face of the carbonyl will then be less sterically hindered than the *Si*-face and attack from the less-hindered face will lead to the formation of the (*S*) alcohols. The addition of $ZnCl_2$ to the reaction leads to the formation of a chelated complex with the carbonyl and the sulfoxide groups parallel, with the result that the *Si*-face is now less sterically hindered and consequently the (*R*) alcohol is formed.

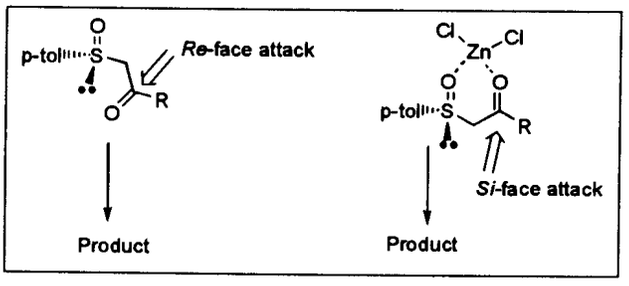


Figure 4.1 First mechanistic explanation for the stereoselective reduction.

In subsequent publications Solladié[39,40]and Garcia Ruano[41] proposed a new and more complicated model (Figure 4.2). They postulated that hydride transfer is intramolecular and not intermolecular as previously believed. The $ZnCl_2$-chelated β-ketosulfoxide adopts the favoured twisted conformation C_1, in which the *p*-tolyl group is pseudo-equatorial, and the absolute configuration at sulfur is *R*. The approach of DIBALH is directed by complexation with the chlorine atom of zinc already chelated with the substrate, resulting in a bimetallic bridged species, M_1. In this model, the hydride is just at the right position to be transferred intramolecularly to the *Si*-face of the carbonyl group, from the top, leading to the (*R*)-alcohol. In the other possible conformation C_2, the *p*-tolyl group is located in an unfavourable pseudo-axial position, hindering the hydride transfer to the *Re* face of the carbonyl group, forming (S)-alcohol.

When only DIBALH is used in the reduction of β-ketosulfoxides, the aluminium atom chelates to the oxygens of the carbonyl and the sulfoxide group of the substrate. The DIBALH-chelated β-ketosulfoxide complex then adopts a conformation in which the *p*-tolyl group is in

[38] Carreno, C.; Garcia Ruano, J.L.; Martin, AM.; Pedregal, C.; Rodriguez, J.H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990,** *55,* 2120.
[39] Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990,** *31,* 6649.
[40] Solladié, G. in *Organosulfur Chemistry, Synthetic Aspects* (P. Page, Ed.), Academic Press, London, **1995**, 13.
[41] Garcia Ruano, J.L. *Phosphorus Sulfur*, **1993,** *74,* 233.

the most favourable equatorial position and an intramolecular hydride transfer to the *Re* face of the carbonyl group occurs to form the (*S*)-alcohol (see Figure 4.3).

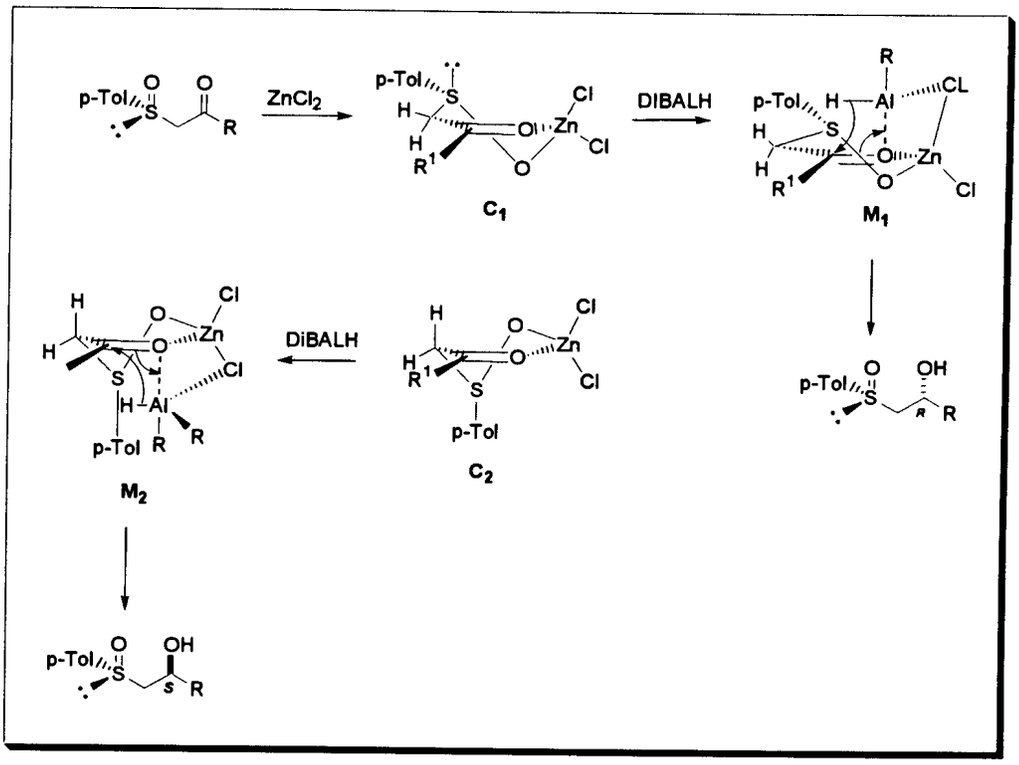


Figure 4.2 Intramolecular hydride transfer from DIBALH to a β-ketosulfoxide in the presence of $ZnCl_2$.

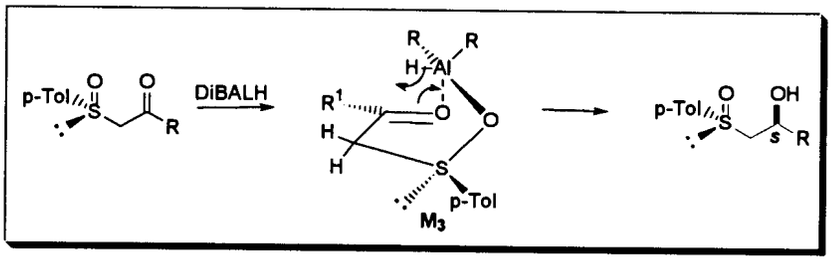
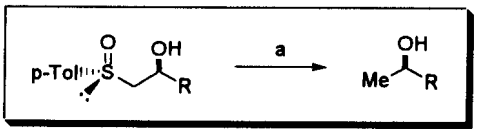


Figure 4.3 Intramolecular hydride transfer from DIBALH to a β-ketosulfoxide in the absence of $ZnCl_2$.

4.2.4 Functional group transformations involving the sulfoxide moiety

One of the advantages of sulfoxides in synthesis is the relative ease with which it can be converted by various reactions into several other functionalities. Some of the methods reported include the removal of the sulfoxide group by reduction using catalytic hydrogenation

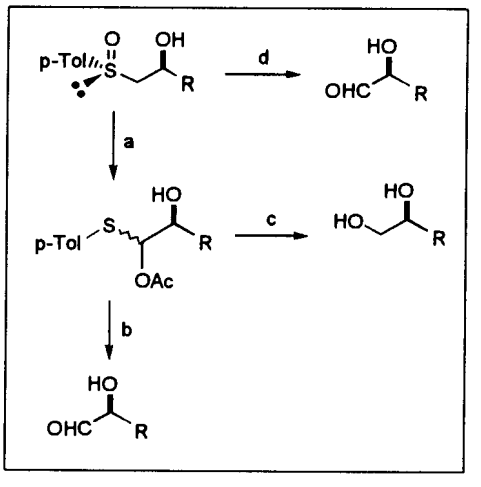
in the presence of Raney nickel,[35,42] sodium-amalgam with disodium hydrogen phosphate (Na_2HPO_4)[43] or lithium metal in diethylamine at –78°C.[44] These methods replace the sulfoxide group with a hydrogen atom (Scheme 4.7).



Scheme 4.7 Reductive removal of the sulfoxide group.

Reagent: a) Raney Ni, EtOH, or Na/Hg, Na_2HPO_2 or Li, Et_2NH, –78°C.

Conversion of the sulfoxide group to the alcohol via Pummerer rearrangement is a well-known procedure. The method allows the removal of the sulfur group while retaining the functionality at the carbon atom carrying it. The sulfoxide is converted to the sulfide, an *O,S*



Scheme 4.8 Pummerer rearrangement and cleavage of the sulfur group.

Reagents: a) Ac_2O, NaOAc; b) $HgCl_2$ or $CuCl_2$ in aq. MeCN or DIBALH, CH_2Cl_2, –78°C; c) $LiAlH_4$, Et_2O; d) i. TFAA , 2,6-lutidine, MeCN; ii. aq. $NaHCO_3$.

acetal, using sodium acetate and acetic anhydride at 145°C, which is then cleaved by a number of methods. This procedure when employed in the course of this research would allow the extension of the C_5 to the C_9 carbon chain of the synthetic target. Cleavage with DIBALH in

[42] Solladié, G.; Demailly, G.; Greack, C.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982,** *23,* 5047.
[43] Cinquini, M.; Cozzi, F.; Gilardi, A. *J. Chem. Soc., Chem. Commun.* **1984,** 551.
[44] Solladié, G.; Demailly, G.; Greack, C. *J. Org. Chem.* **1985,** *50,* 1552.

CH_2Cl_2 at –78°C,[45] Cu(II) or Mg(II) salts in aqueous $NaOH/CH_3CN$[46,47] produces the β-hydroxyaldehyde, whereas reduction with $LiAlH_4$[48,49] or desulfurisation by catalytic hydrogenation using Raney nickel[47] yields the diol. The sulfoxide can also be directly converted to the β-hydroxy-aldehyde by using TFAA and 2,6-lutidine in acetonitrile and work-up of the reaction mixture with aqueous $NaHCO_3$ solution.[50] (Scheme 4.8).

[45] Arroyo-Gomez, Y.; Rodriguez-Amo, J.F.; Santos-Garcia, M.; Sanz-Tejedor, M.A.; *Tetrahedron Asym.* **2000,** *11,* 789.
[46] Sugihara, H.; Tanigaka, R.; Kaji, A. *Synthesis*, **1978**, 881.
[47] Solladié, G.; Frechon, C.; Hutt, J.; Demailly, G. *Bull. Soc. Chim. Fr,* **1987**, *5*, 827.
[48] Solladié, G.; Fernandez, I.; Maestro, M.C. *Tetrahedron Lett.* **1991,** *32,* 509.
[49] Schmidt, A.H.; Russ, M. *Chem. Ber.* **1981,** *11,* 4822.
[50] Solldié, G.; Zian-Cherif, C. *Tetrahedron Lett.*, **1992,** *33*, 31.

5. Synthetic Studies on the C(1)–C(9) Unit of TA Toxin

5.1 INTRODUCTION

Retrosynthetic analysis of the C_{17} backbone **19b** of TA toxin as outlined in Chapter 2 indicated that 1,5-pentanediol **172** can serve as the starting material for the synthesis of the C(1)–C(9) unit. In this chapter the methodologies used for extending the C_5 carbon chain as well as the creation of the three stereogenic centres using Sharpless asymmetric epoxidation/ kinetic resolution, nucleophilic opening of epoxides and chiral sulfoxide chemistry is discussed. Protection of the functional groups played a crucial role at various stages in this synthetic route.

5.2 SYNTHETIC STUDIES ON THE C(1)–C(9) UNIT

5.2.1 Synthesis of (3*RS*)-7-[(*t*-butyldimethylsilyl)oxy]- 177 and (3*RS*)-7-[(*t*-butyl-diphenylsilyl)oxy]-hept-1-en-3-ol 178

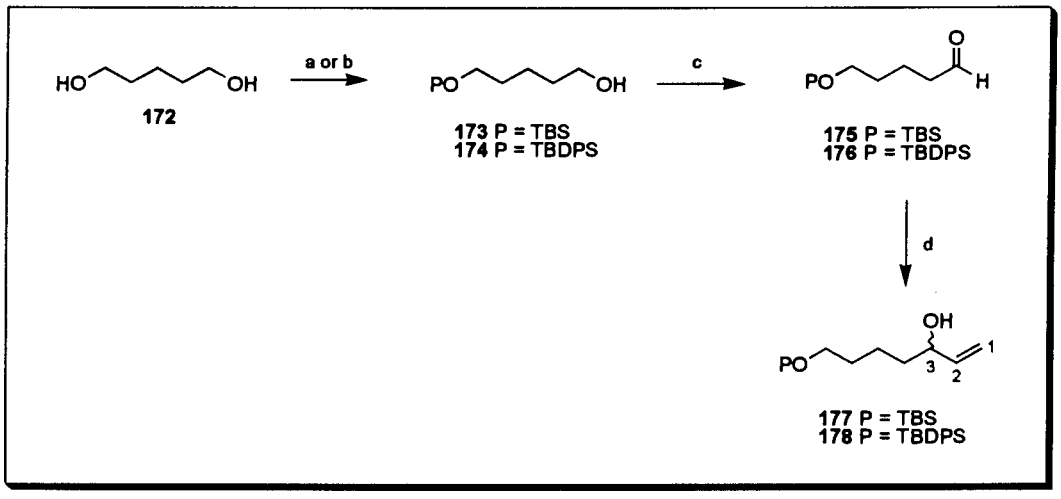
Silyl ethers are used extensively in organic synthesis for the protection of hydroxy groups due to their ease and selectivity of formation and their compatibility with a variety of synthetic transformations and reaction conditions. The relative stability of silyl ethers towards both acidic and basic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

The *t*-butyldiphenylsilyl (TBDPS) group was introduced by Hanessian *et al.*[5] for the protection of the hydroxy group. As a result of the steric bulk of the *t*-butyl and phenyl groups, preferential silylation of a primary over a secondary hydroxy group occurs. In addition the TBDPS ether is more stable towards acid hydrolysis and hydrogenolysis than *t*-butyldimethylsilyl (TBS) and benzyl ethers. The parent alcohol can be regenerated by treatment with

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

tetrabutylammonium fluoride (TBAF) in THF at room temperature, reaction conditions that do not affect the benzyl ether group.

The initial steps of the synthetic route towards the C(1)–C(9) unit of TA toxin are outlined in Scheme 5.1. A method for the selective monosilylation of symmetrical primary 1,n-diols has been developed by McDouglas.[6] In this procedure the silylating reagent is added to the insoluble sodium alkoxide suspension in THF formed by reaction of the diol with 1 equivalent NaH.

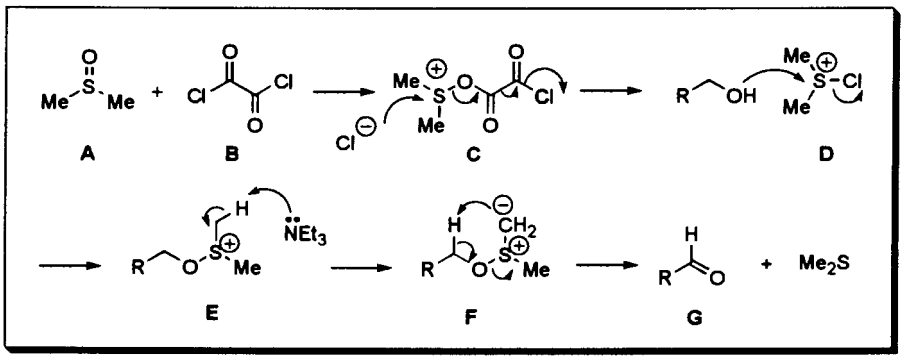


Scheme 5.1 Synthesis of the C_7 racemic allylic alcohols **177/178**.

Reagents: a. TBSCl, NaH, THF; b. TBDPSCl, NaH, THF; c. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; d. vinylbromide, Mg, THF

In the initial work in the synthetic route use was made of the TBS protecting group but this was changed to the TBDPS group when unexpected problems arose during the course of the Grignard reaction using vinyl magnesium bromide (see later). Selective monosilylation of 1,5-pentanediol **172** following the McDouglas procedure using TBSCl or TBDPSCl gave the protected diols **173** and **174**, respectively. The ^1H NMR spectrum of **173** indicated two sets of triplets at δ_H 3.609 and 3.625 for H(1) and H(5), respectively. The corresponding signals in the ^{13}C NMR spectrum were observed at δ_C 62.94T for C(1) and 63.10T for C(5). The IR spectrum of the TBS ether **173** showed a broad signal for the OH group at ν_{max} 3356 cm^{-1}. The NMR data for the TBDPS ether **174** is similar to that of the TBS ether and the assignments have been collated in Chapter 6.

The two-carbon chain extension of the silyl ethers **173** and **174** is based on Grignard methodology and requires the aldehydes **175** and **176**, respectively. The Swern oxidation[7] is one of the most widely used methods for the oxidation of a primary alcohol to an aldehyde and uses dimethylsulfoxide, oxalyl chloride and triethylamine, at low temperature to achieve oxidation. The mechanism is outlined in Scheme 5.2. Initially, a dimethylchlorosulfonium ion (**D**) is formed by the reaction of dimethylsulfoxide with oxalyl chloride at –78°C. The reaction of the alcohol with (**D**) then gives a new sulfonium ion (**E**) which is treated with a base Et_3N. The most acidic proton in (**E**) is located on the carbon atom α to the positively charged sulfur atom, and is abstracted as the formed carbanion can be stabilised by the positive charge on the sulfur. This carbanion (**F**) then removes a proton on the carbon adjacent to the oxygen atom of the alcohol, creating a flow of electrons towards the positively charged sulfur. In this process the aldehyde and dimethylsulfide are formed.



Scheme 5.2 Reaction mechanism for the Swern oxidation.

Swern oxidation of the primary alcohol group in **173** gave the aldehyde **175** in high yield (87%). The ^1H NMR spectrum showed the aldehyde proton as a triplet at δ_H 9.744 (J 1.8 Hz) whereas the aldehyde carbon atom appeared at δ_C 202.57D in the ^{13}C NMR spectrum. The IR spectrum of **175** showed the aldehyde carbonyl absorption at ν_{max} 1720 cm^{-1}. Similarly, Swern oxidation of the TBDPS protected alcohol **174** gave the corresponding aldehyde **176** in 99 % yield (see spectral details in Chapter 6).

The Grignard reaction is one of the oldest and yet most widely used methods for generating alcohols from carbonyl compounds. The required C_2 Grignard reagent was formed by reacting a solution of vinyl bromide in THF with magnesium metal to give vinyl magnesium

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

bromide. The reaction of this Grignard reagent with the aldehyde **175** gave the racemic allylic alcohol **177** in 68% yield. When a new batch of vinyl bromide was used loss of the TBS protecting group was observed. The protecting group was hence changed to the more acid-stable protecting group, TBDPS. The presence of the acid sensitive TBS ether group in the allylic alcohol **177** required work-up of the reaction under neutral conditions using saturated ammonium chloride solution as a proton source rather than aqueous acid. In the same way, the racemic allylic alcohol **178** was produced from the reaction of aldehyde **176** with vinyl magnesium bromide (76%). The assignment of the protons in the allylic system of **177** is based on the following analysis of the signals in the ^{1}H NMR spectrum of the allylic alcohol. The H(2) proton appeared at δ_H 5.833 and exhibited a *trans* coupling of 17.2 Hz with H(1a) (δ_H 5.190) and a *cis* coupling of 10.4 Hz with H(1b) (δ_H 5.070). In addition the signal for H(2) also exhibited a coupling of 6.2 Hz with H(3) (δ_H 4.066). A geminal coupling of 1.4 Hz between H(1a) and H(1b) as well as allylic coupling (J 1.4 Hz) between each of these protons and H(3) was observed. The signals of the carbons of the allylic system appeared at δ_C 114.55T [C(1)], 141.22D [C(2)] and 73.04D [C(3)] in the ^{13}C NMR spectrum. In the IR spectrum the absorption of the OH group appeared at ν_{max} 3402 cm^{-1} and the C=C bond at ν_{max} 1596 cm^{-1}. The ^{1}H and ^{13}C NMR spectra of the TBDPS protected allylic alcohol **178** were similar to those of **177** (see details in Chapter 6).

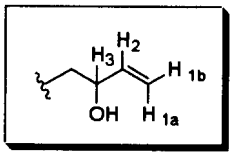


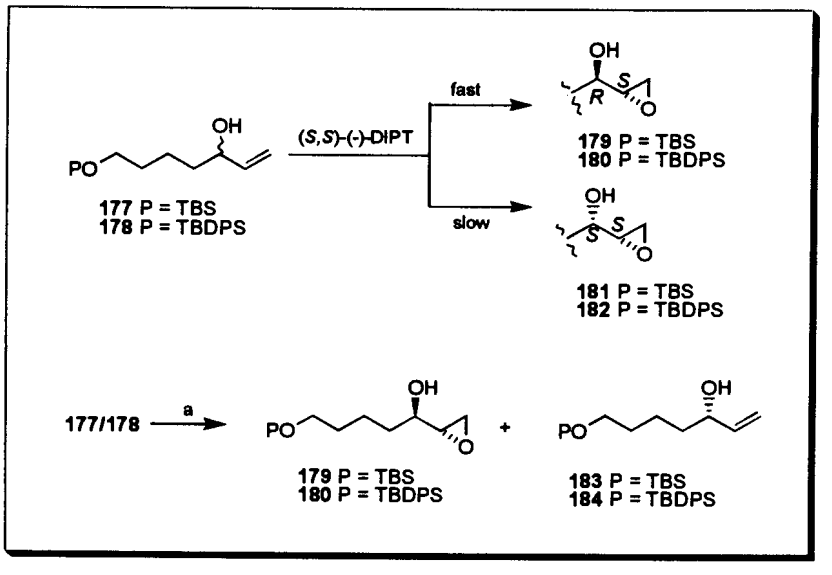
Figure 5.1 Numbering of the protons of the allylic system in **177/178.**

5.2.2 Asymmetric epoxidation-kinetic resolution of the racemic allylic alcohols 177 and 178

Racemic allylic alcohols such as **177** and **178** are key intermediates in the synthetic route towards the C(1)–C(9) unit of TA toxin as asymmetric epoxidation in conjunction with kinetic resolution leads to a single stereoisomer of an epoxy alcohol with the appropriate stereochemistry at the two stereogenic centres. The absolute configuration of the epoxy alcohol formed follows from the stereochemistry of the tartrate ester used in the experiment. The background to the method has been discussed in Chapter 3.

The racemic allylic alcohol **177** was treated with 0.6 equivalent of the Ti catalyst, formed from Ti(IV) isopropoxide, (*S,S*)-(–)-DIPT, and *t*-butylhydroperoxide (TBHP) at –20°C. The

(*S,S*)-(–)-DIPT determines the stereofacial selectivity in the epoxidation reaction. (*S,S*)-(–)-DIPT requires that epoxidation of the *S*-enantiomer of **177** by the active titanium catalyst occurs on the face that is sterically hindered by the alkyl chain (the *SiS* face) and it therefore reacts slower than the *R*-enantiomer in which the *SiR* face is much more accessible. The outcome of the reaction is shown in Scheme 5.3 with the formation of the *anti*-epoxy alcohol favoured over the *syn*-epoxy alcohol. The (2*S*,3*R*)-epoxy alcohol **179** was formed in 34% yield and the unreacted (3*S*)-allylic alcohol **183** was isolated in 32% yield. Similarly, asymmetric epoxidation/kinetic resolution of the racemic TBDPS protected allylic alcohol **178** was applied gave the (2*S*,3*R*)-epoxy alcohol **180** and the (3*S*)-allylic alcohol **184** both in 37 % yield (50% is the highest yield possible in kinetic resolution).

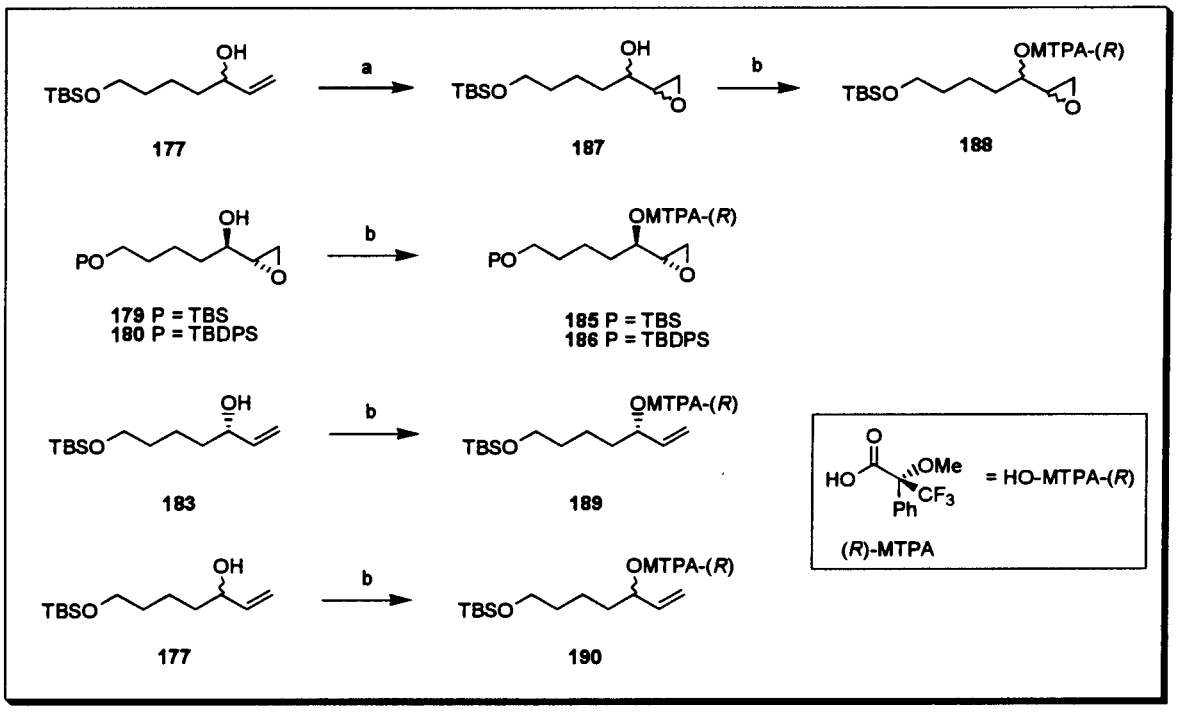


Scheme 5.3 Kinetic resolution of the allylic alcohols **177/178.**

Reagents: a. (*S,S*)-(–)-DIPT, $Ti(O\textit{i}Pr)_4$, TBHP, 4Å molecular sieves, CH_2Cl_2, –20°C.

The ^{13}C NMR spectrum showed the typical signals of the terminal epoxide group in **179**: the C(1) signal appeared at δ_C 43.43 as a triplet and the C(2) signal at δ_C 54.50 as a doublet. The epoxide protons were found as three sets of signals in the ^1H NMR spectrum. The assignment of the C(1) protons was deduced from the magnitude of the vicinal coupling constants.[8] The H(2) signal appeared at δ_H 2.965 (ddd) with a *trans* coupling of 4.0 Hz with H(1a) (δ_H 2.687 dd) and a *cis*-coupling of 3.0 Hz with H(1b) (δ_H 2.765 dd). A geminal coupling of 5.2 Hz was observed between H(1a) and H(1b). In addition the *anti* arrangement gave rise to a 3.0

Hz coupling between H(2) and the C(3) proton at δ_H 3.769. Low intensity multiplet at δ_H 2.926 in the ^{1}H NMR spectrum was assigned to the C(2) proton of the *syn* epoxy alcohol **181** and established the diastereoselectivity as 98:2 d.r.



Scheme 5.4 Determination of the enantioselectivity of the products of the asymmetric epoxidation–kinetic resolution reaction.

Reagents: a. MCPBA, CH_2Cl_2; b. (*R*)-MTPA, $(COCl)_2$, DMAP, Et_3N, CH_2Cl_2.

The enantioselectivity of the reaction was determined by the conversion of the (2*S*,3*R*)-epoxy alcohol **179** to the (*R*)-α-methoxy-α-trifluoromethylphenylacetate [(*R*-MTPA)] derivative **185** and ^{19}F NMR spectroscopy. The protocol developed by Ward and Rhee[9] was followed. (*R*)-α-Methoxy-α-trifluoromethylphenylacetic acid [(*R*)-MTPA] was converted to the (*S*) acid chloride derivative by addition of oxalyl chloride to a solution of [(*R*)-MTPA] in a mixture of DMF-hexane. The white precipitate of DMFCl formed during the reaction was removed by filtration. A solution of epoxide **179**, Et_3N, and DMAP in CH_2Cl_2 was then added to the acid chloride and the reaction stirred for 15 h to ensure that all of the epoxide is derivatized. Work-up of the reaction and purification by column chromatography gave the pure Mosher ester derivative **185**.

---

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

The ^{1}H NMR spectrum of the Mosher ester **185** showed the signal of H(3) at δ_H 5.082 (dt, $J_{3,4}$ 6.2 Hz, $J_{3,2}$ 4.7 Hz) and the methoxy group appeared as a quartet ($J_{H,F}$ 1.2 Hz) at δ_H 3.528. The H(2) signal resonated at δ_H 3.039 and exhibited a *trans* coupling of 3.6 Hz with H(1a) (δ_H 2.723) and a *cis* coupling of 2.6 Hz with H(1b) (δ_H 2.709). An additional coupling of 4.7 Hz was observed between H(2) and H(3). The ^{19}F spectrum showed a single major signal at δ_F –71.82 (A) and four minor signals at –71.89 (B), –71.97 (C), –72.07 (X) and –72.17 (D). In order to determine the enantioselectivity of the epoxidation in the kinetic resolution reaction using ^{19}F NMR data, it was necessary to prepare a sample of the epoxy alcohol that contained all four possible stereoisomers. Thus the racemic secondary allylic alcohol **177** was epoxidised with MCPBA and the product epoxide **187** converted to the (*R*)-MTPA derivative **188**.

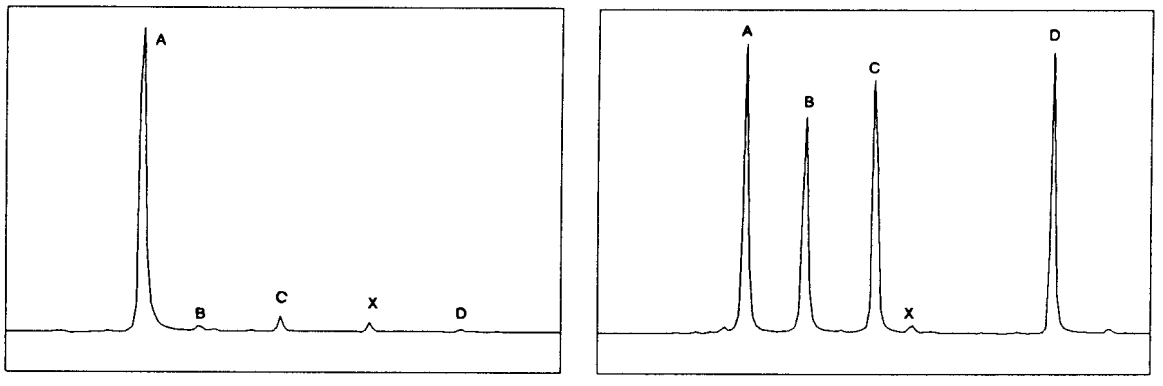


Figure 5.1 ^{19}F NMR spectra of the Mosher derivatives (**185**)(at left) and (**188**)(at right). The signals marked A and C represent the *anti* stereoisomers and B and D the *syn* stereoisomers. X is an impurity.

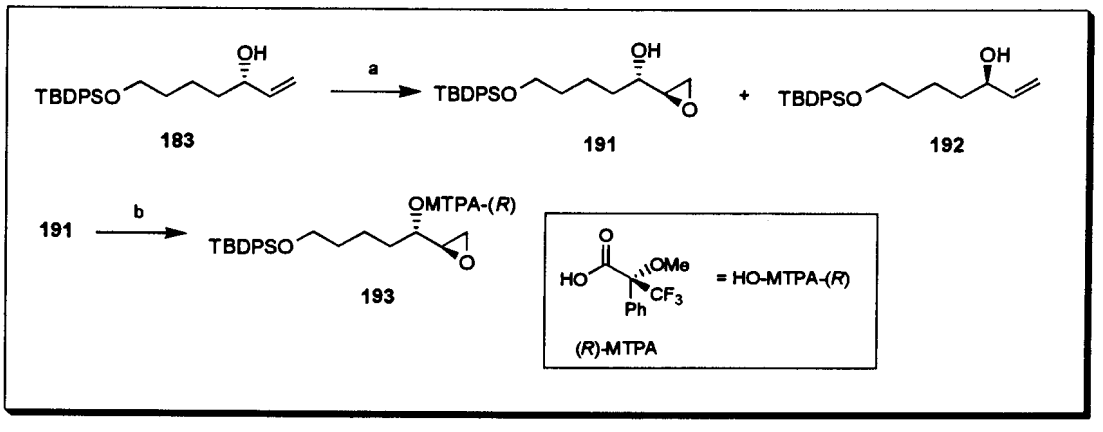
The ^{19}F spectrum showed four major signals at δ_F –71.86 (A), -71.92 (B), -72.00 (C) and –72.19 (D) in the ratio of 1.4:1:1.2:1.3. The signal at –72.07 (X) is due to an impurity. With the available knowledge of the ^{19}F chemical shifts of the four diastereomers it was now possible to determine the diastereo- and enantioselectivity as 99:1 d.r. and 97:3 e.e., respectively.

The enantio- and diastereoselectivity achieved in the asymmetric epoxidation/kinetic resolution of the TBDPS protected allylic alcohol **178** was determined by conversion of the epoxy alcohol **180** to its Mosher ester **186**. The ^{19}F spectrum showed a single major signal at –71.81 Hz and four minor signals at –71.87, –71.90, –72.05 (impurity) and –72.10. Once

again the four possible stereoisomers of the TBDPS protected epoxy alcohol, obtained by epoxidation of the racemic allylic alcohol **178,** were converted to the Mosher ester derivative and the ^{19}F chemical shifts obtained for reference purposes. The diastereo- and enantio-selectivity were established as 97:3 d.r.and 95:5 e.e. from the ^{19}F NMR data.

The (*R*)-MTPA derivative **189** of the unreacted (*S*) allyl alcohol **183** showed a major signal at δ_F –71.95 Hz and a minor signal at –71.84 Hz which established the enantio-selectivity as 95:5. The ^{19}F NMR spectrum of the Mosher ester **190**, derived from the racemic allylic alcohol **177**, showed two signals at δ_F –71.89 and –71.95 in the ratio of 1:1.2.

Asymmetric epoxidation/ kinetic resolution of the racemic allylic alcohol **177** using the same protocol as mentioned but using DET instead of DIPT resulted in both poor enantio- and diastereoselectivity in the reaction in agreement with findings by Martin *et al.* [10]. DIPT is therefore the reagent of choice in Sharpless epoxidation/kinetic resolution procedures.



Scheme 5.5 Asymmetric epoxidation–kinetic resolution of non-racemic allylic alcohol **183**.

Reagents: a. (*R,R*)-(+)-DIPT, $Ti(OiPr)_4$, TBHP, 4Å molecular sieves, CH_2Cl_2, –20°C; b. (*R*)-MTPA, $(COCl)_2$, DMAP, Et_3N, CH_2Cl_2, RT.

The non-racemic allylic alcohol **183** which was obtained from a number of different Sharpless epoxidation/kinetic resolution experiments, was treated with 0.6 equivalent of the Ti catalyst, formed from Ti(IV) isopropoxide, (*R,R*)-(+)-DIPT, and *t*-butylhydroperoxide (TBHP) at –20°C. The epoxide **191** was converted to its (*R*)-MTPA derivative **193** which showed a major signal at δ_F –71.92 in the ^{19}F NMR spectrum. Analysis of the spectrum established the

[10] Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1981,** *103*, 6237.

enantio- and diastereoselectivity in the formation of the epoxy alcohol **191** as 99:1 and 98:2, respectively.

5.2.3 Introduction of the benzyl protecting group

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

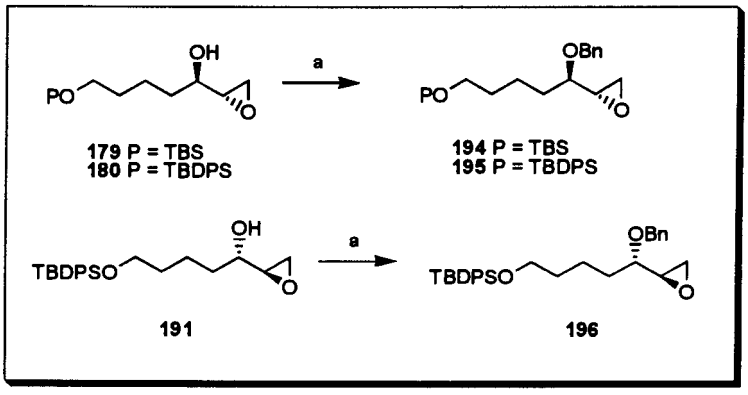
The ease of ring opening of epoxides by acids and bases renders them difficult to work with under these conditions. Benzylation of alcohols is carried out using NaH and BnBr. The formation of an alkoxide in the case of an epoxy alcohol can result in ring opening of the epoxide and formation of complex mixtures of benzyl ethers. An alternative method for the preparation of benzyl ethers employs *O*-benzyl trichloroacetimidate in the presence of an acid such as triflic acid,[11,12,13] and an epoxide may not survive these conditions.

Protection of the secondary alcohol in the epoxy alcohol **179** was readily achieved by using benzyl bromide in the presence of a base, NaH and catalytic amount of TBAI. The procedure involved the sequential addition of the reagents: BnBr, catalytic amount of TBAI and NaH to a THF solution of the epoxy alcohol **179** at 0°C under argon. The reaction mixture was kept at this temperature for 2 h and allowed to warm to room temperature over 2 h and stirred overnight.[14] The benzyl ether **194** was obtained in moderate yield (56%) as a yellowish oil. The ^{1}H NMR spectrum of **194** showed the presence of a pair of doublets at δ_H 4.490 and 4.640 with coupling of J 11.6 Hz, characteristic of the methylene protons of the O-benzyl group. The corresponding signal in the ^{13}C NMR spectrum appeared at δ_C 72.31T.

Similarly, benzyl ether **195** was synthesized by addition of epoxide **180**, BnBr, TBAI to NaH suspended in THF at 0°C under argon. The reaction yielded 48% of the final product, benzyl ether **195**. In an investigation to improve the yield of this reaction it was found that benzylation is best carried out with benzyl bromide that has been freshly distilled under reduced pressure. When this quality of benzyl bromide was used in the benzylation of epoxy

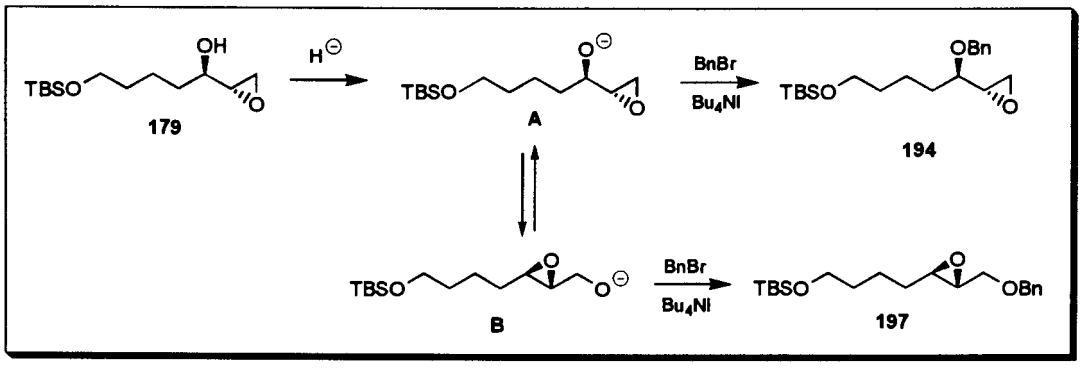
[11] Wessel, H.-P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.
[12] Widmer, U. *Synthesis*, **1987**, 568.
[13] Iversen, T.; Bundle, D.R. *J. Chem. Soc. Chem. Comm.* **1981**, 1240.
[14] Jin, J.; Weinreb, S.M. *J. Am. Chem. Soc.*, **1997**, *119*, 2050.

alcohol **191** the benzyl ether **196** was obtained in 91% yield. The ^{1}H NMR spectrum of **195** and **196** showed a pair of doublets (J 11.6 Hz) at δ_H 4.475 and 4.630. The corresponding signal in the ^{13}C spectrum appeared at δ_C 72.34T.



Scheme 5.6 Synthesis of the benzyl ethers **194**, **195** and **196**.

Reagents: a. BnBr, TBAI, NaH, THF.



Scheme 5.7 Benzylation of the epoxy alcohol **179**.

Initially benzyl chloride was used to prepare the *O*-benzyl ethers but yields were low and complex mixtures of products were obtained. This difference in behaviour between benzyl chloride and benzyl bromide can be rationalised by the mechanism of the reaction (see Scheme 5.7).

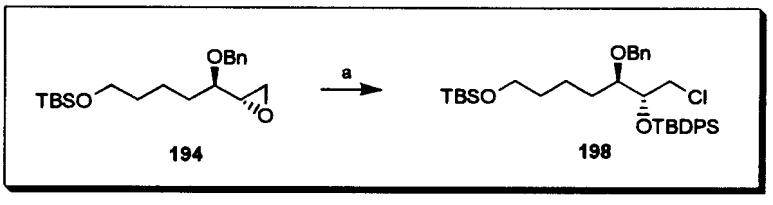
The bromide ion is a better leaving group than the chloride ion and is therefore displaced much faster by the I^- nucleophile in an S_N2 reaction. The formed benzyl iodide is thus the actual benzylating reagent. The H^- base abstracts the proton of the hydroxy group, the most acidic proton, to form an alkoxide intermediate **A** that can undergo a Payne

rearrangement to give the alkoxide **B**. The alkoxides can displace the iodide from the benzyl iodide to form the respective benzyl ethers **194** or **197**. Formation of the benzyl iodide must be fast to circumvent the Payne rearrangement of epoxy alcohol **179** and thus lead to a single *O*-benzyl ether **194**.

5.2.4 Nucleophilic opening of the epoxide ring

5.2.4.1 Opening of the epoxide ring: chloride as nucleophile

Opening of 1,2-epoxides is a very useful tool to produce 1,2-stereogenic centres. The background to the nucleophilic opening of epoxides has been presented in Chapter 3 where it is shown that opening of a 1,2 epoxy-3-alcohol is a powerful tool to produce 1,2-related stereogenic centres. Trialkylsilyl halides in the presence of a catalyst (*e.g.* Bu_4NI) afford a primary halohydrin from terminal epoxides. In general opening of 1,2-epoxides by trialkylsilyl halides results in high yields at low temperature *i.e.* 0^0C but in the case of TBSCl and TBDPSCl higher temperatures and longer reaction times are needed.



Scheme 5.8 Nucleophilic opening of benzyl ether **194** to form chlorohydrin **198**.

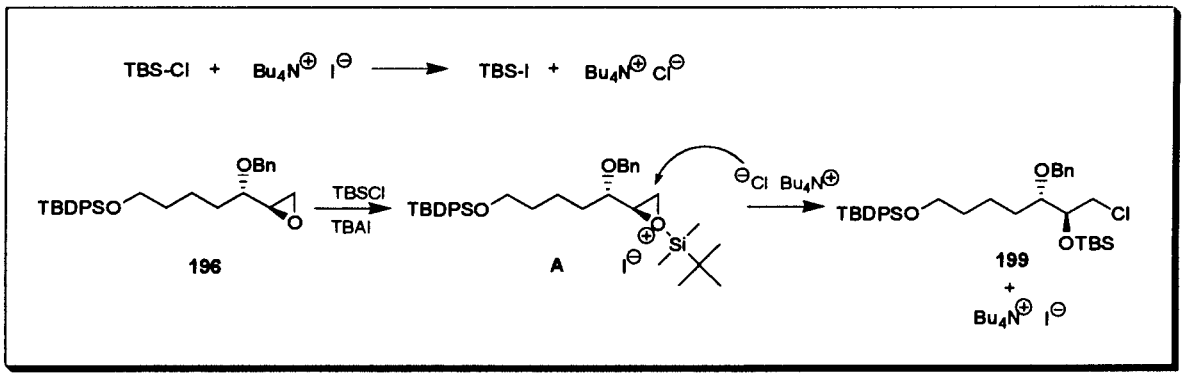
Reagents: a. TBDPSCl, TBAI, THF, heat.

The ring opening reaction of the *O*-benzyl epoxide **194** with TBDPSCl required the presence of a catalytic amount of TBAI (10%) and reflux for 15 h to give the protected chlorohydrin **198** (9% yield). The poor yield is the result of the extensive loss of the *O*-TBS protecting group and decomposition of both starting material and product. No reaction occurred in the absence of TBAI.[15] Improved yields were obtained in the ring opening of the *O*-TBDPS protected epoxide **195** to give the chlorohydrin **199** in 56% yield (Scheme 5.9).

The advantage of TBSCl (and TBDPSCl) over other chloride sources is that ring opening of the epoxide and protection of the formed hydroxy group occurs in the same

[15] Andrews, G.C.; Crawford, T.C.; Contillo, L.G. Jr. *Tetrahedron Lett.*, **1981**, *22*, 3803.

reaction. The silicon of the TBS-I, formed through reaction of the TBS-Cl reagent with TBAI, acts as a Lewis acid binding to the oxirane oxygen and forming the intermediate **A** as shown in Scheme 5.9. The activated oxirane ring then undergoes nucleophilic attack by chloride ion to give the protected halohydrin **199** with regeneration of the TBAI catalyst. The ^{1}H NMR spectrum of **199** showed the signal of the TBS dimethyl groups at δ_H 0.091. The protons of the *t*-butyl groups of the TBS and TBDPS protecting groups appeared at δ_H 0.912 and 1.048. The protons of the C(1) methylene group bonded to the chlorine atom appeared as part of an ABX spin system at δ_H 3.696 (dd, J_{gem} 11.2, J_{vic} 4.0 Hz) and 3.680 (dd, J_{gem} 11.2, J_{vic} 6.7 Hz). The C(2) proton, the X-part of the spin system, appeared at δ_H 3.51. In the ^{13}C NMR spectrum the C(1) signal appeared at δ_C 47.37T and that of C(2) at δ_C 72.77D, values that are typical for a chlorohydrin moiety.



Scheme 5.9 Mechanism of nucleophilic opening of benzyl ether **195** with TBSCl.

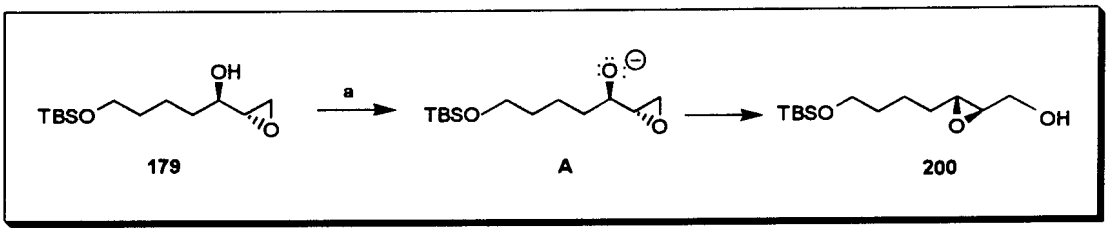
5.2.4.2 Opening of the epoxide ring: cyanide as nucleophile.

Opening of a terminal epoxide with cyanide leads to a one–carbon chain-extended nitrile. This methodology would be of use in the synthesis of the C(1)–(9) unit of TA toxin as it would convert the C_7 epoxy alcohol **179** into a C_8 nitrile that could be transformed by chiral sulfoxide methodology to the required C_9 unit. Treatment of **179** with NaCN in DMSO at 80°C did not result in the formation of a nitrile by opening of the epoxide ring at C(1). Instead the terminal epoxy alcohol was converted by a Payne rearrangement[16] to the internal 2,3-epoxy alcohol **200.** The result is rationalised by the intermediacy of the alkoxide **A** which is formed when the CN^- nucleophile abstracted the proton from the hydroxy group (see Scheme 5.10).

[16] Payne, G.B. *J. Am. Chem. Soc.*, **1962**, *27*, 3819.

Nucleophilic attack of the alkoxide **A** results in the formation of a new epoxide ring with concomitant opening of the terminal epoxide ring to form **200**.

The ^{1}H NMR spectrum of **200** showed H(2) as a doublet of doublet of doublets at δ_H 2.915 with vicinal coupling of 2.3 Hz with H(1a) (δ_H 3.856) and 4.4 Hz with H(1b) (δ_H 3.557). An additional vicinal coupling of 2.6 Hz was observed with H(3) (δ_H 2.982). A geminal coupling of 12.7 Hz was observed for the C(1) protons. The corresponding signals in the ^{13}C NMR spectrum were at δ_C 55.97D for C(2), 58.54D for C(3) and 62.89T for C(1).



Scheme 5.10 Payne rearrangement of epoxide **179** triggered by CN^- in DMSO.

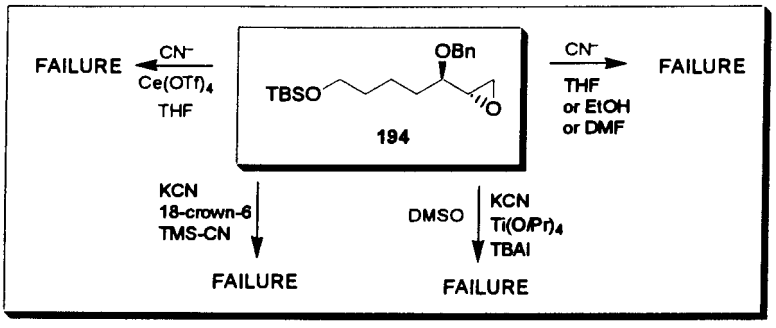
Reagents: a. NaCN, DMSO, 80°C (45%)

To prevent the Payne rearrangement of the epoxy alcohol **179** it was decided to protect the C(3) hydroxy group as the *O*-benzyl ether as outlined in Scheme 5.6. The nucleophilic opening of the epoxide ring of the benzyl ether **194** by cyanide was then investigated using different reaction conditions as outlined in Scheme 5.11. Treatment of **194** with NaCN in DMSO at 80°C;[17] NaCN in 40% ethanol;[18] NaCN in DMF; NaCN and $Ce(OTf)_4$[19,20] in THF at 70°C; TMSCN, KCN, and 18-crown-6 ether;[21] or KCN, $Ti(^iOPr)_4$, TBAI in DMSO[22] all resulted in decomposition or no reaction occurred.

Although both Et_2AlCN[23] and acetone cyanohydrin[24] give good yields for the opening of the terminal epoxide moiety neither of these two reagents was used. Et_2AlCN is both highly toxic and flammable, and work-up is dangerous under acidic conditions with the release of HCN gas in both instances.

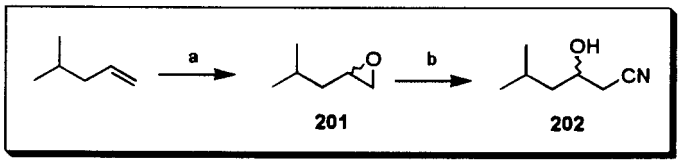
---

[17] Tsuruoka, A.; Negi, S.; Yanagisawa, M.; Nara, K.; Naito, T. *Synthetic Commun.*, **1997**, 27, 3547.
[18] Takano, S.; Morimoto, M.; Ogasawara, K. *Synthetic Commun.*,**1984,** 834.
[19] Iranpoor, N.; Shekarriz, M. *Synthetic Commun.*, **1999,** *29,* 2249.
[20] Iranpoor, N.; Shekarriz, M.; Shiriny, F. *Synthetic Commun.*, **1998**, *28*, 347.
[21] Sassaman, M.B.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.*, **1990**, *55*, 2016.
[22] Kim, Y.J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.*, **2000**, *65*, 2599.
[23] Nagata, W.; Yoshioka, M. and Okumura, T. *Tetrahedron Lett.*, **1966**, 847.
[24] Mitchell D. and Koenig, T. *Tetrahedron Lett.*, **1992**, *33*, 3281.



Scheme 5.11 Reaction conditions used in attempted ring opening of the *O*-benzyl epoxy ether **194.**

The use of $Ti(OiPr)_4$ in the nucleophilic opening of 1,2-epoxides by cyanide in DMSO was investigated using the model compound (*RS*)-1,2-epoxy-4-methylpentane **201.** The synthesis of **201** was achieved in 23% by epoxidation of 4-methyl-1-pentene in CH_2Cl_2 using MCPBA. The low yield of **201** is due to losses as a result of the compound's low boiling point and high volatility. The ^1H NMR spectrum of **201** showed the epoxide protons as three sets of signals. The C(2) proton signal appears at δ_H 2.905 with a *trans* coupling of 3.9 Hz with H(1b) (δ_H 2.736) and a *cis* coupling of 2.6 Hz with H(1a) (δ_H 2.414). H(2) also coupled with H(3b) (δ_H 1.348) with 5.4 Hz and H(3a) ((δ_H 1.421) with 6.5 Hz. A geminal coupling of 5.2 Hz was observed for the two terminal protons H(1). The ^{13}C NMR spectrum showed the C(1) signal of the epoxide group at δ_C 47.13T, C(2) at δ_C 51.21D and C(3) at δ_C 41.58D.



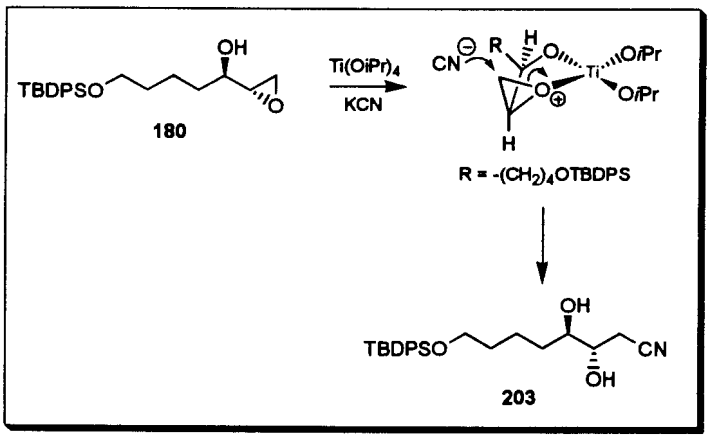
Scheme 5.12 Nucleophilic opening of epoxide **201** by cyanide.

Reagents: a. MCPBA, CH_2Cl_2, RT; b. KCN, $Ti(^iPrO)_4$, TBAI in DMSO.

The reaction of the epoxide **201** with cyanide in the presence $Ti(O{}^iPr)_4$ gave the corresponding nitrile **202** (see Scheme 5.12). The presence of the nitrile functionality was evident from the signal at δ_C 117.81S in the ^{13}C NMR spectrum. The ^1H NMR spectrum showed the C(2) methylene protons as part of an ABX spin system: H(2a) resonates at δ_H 2.514 with a vicinal coupling of 4.9 Hz with H(3) (δ_H 3.974) and H(2b) is at δ_H 2.432 with a vicinal coupling of 6.2 Hz with H(3). A geminal coupling of 16.8 Hz is present for the two H(2) protons. The corresponding signals in the ^{13}C NMR spectrum appear at δ_C 26.47T for C(2)

and at δ_C 65.68D for C(3). The result indicated that the presence of a hydroxy group at C(3) of a 1,2-epoxy alcohol is not an absolute requirement for ring opening by activation with titanium(IV). However, as shown by Martin and co-workers,[25] no ring opening occurs when a 3-benzyloxy group is present in the 1,2-epoxide. This finding was confirmed when the *O*-benzyl protected epoxy alcohol **194** was treated with Ti(O*i*Pr)$_4$ and cyanide in DMSO solution in the presence of TBAI.

However these conditions have been used for the opening of the epoxide ring of unprotected 3-hydroxy-1,2-epoxides.[22] Investigations into the ring opening of the 3-hydroxy-1,2-epoxide **180** established that TBAI could be omitted without any adverse effect on the yield. In the work-up of the reaction saturated $NaHCO_3$ solution was initially used to hydrolyse the Ti-O bonds but improved yields (80%) of the nitrile **203** were obtained with acidic work-up using 1M HCl (see Scheme 5.13).



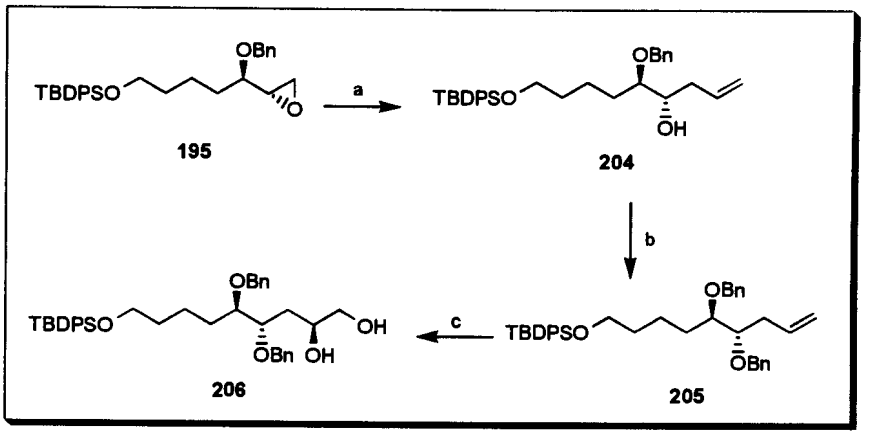
Scheme 5.13 Mechanism of nucleophilic opening of epoxide **180** by cyanide in the presence of Ti(O*i*Pr)$_4$.

The presence of the nitrile functional group in **203** was confirmed by the signal at δ_C 118.50S in the ^{13}C NMR spectrum and the absorption at ν_{max} 2255 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum indicated the typical AB portion of an ABX spin system for the C(2) protons: H(2a) resonated at δ_H 2.514 with a geminal coupling of 16.8 Hz and vicinal coupling of 4.4 Hz with H(3) (δ_H 3.786 ddd), whereas H(2b) resonated at δ_H 2.589 with a geminal coupling of 16.8 Hz and vicinal coupling of 7.8 Hz with H(3). The corresponding signal in the ^{13}C NMR spectrum for C(2) was observed at δ_C 20.96T.

[25] Alvarez, E.; Nunez, M.T.; Martin, V.S. *J. Org. Chem.*; **1990**, *55*, 3429.

5.2.4.3 Opening of the epoxide ring: copper(I) catalysed Grignard reaction.

The opening of the C_7 benzyl ether **195** by a copper(I)-catalysed Grignard reaction using vinyl magnesium bromide was identified in the retrosynthetic analysis as a method to extend the carbon chain by two carbon atoms to the C_9 unit **204**. The two hydroxy groups are protected as the benzyl ethers to give **205** and the third stereogenic centre is introduced by the Sharpless asymmetric dihydroxylation reaction to give the target compound **206** (see Scheme 5.14). The use of a Cu(I) catalyst has been suggested to aid in the opening when vinyl or allylic Grignard reagent are used.[26]



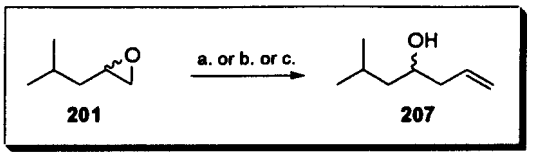
Scheme 5.14 Proposed synthesis of (2*S*,4*S*,5*R*)-[8-(*t*-butyldiphenylsilyl)oxy]-4,5-benzyloxy-1,2-nonane-diol **206.**

Reagents: a. Mg^0, $H_2C{=}CHBr$, THF, cat.Cu(I)I, b. BnBr, TBAI, NaH, THF 0°C, c. $(DHQD)_2PHAL$, OsO_4, *t*-BuOH:H_2O 1:1, $K_3Fe(CN)_6$, K_2CO_3.

1,2-Epoxy-4-methylpentane **201** was once again used as a model compound to investigate the opening of the epoxide ring by vinyl magnesium bromide. The reaction was carried out using a. 10 % Cu(I) and 1 equiv. Grignard reagent, b. 2 equiv. Cu(I) and 4 equiv. Grignard reagent, and c. no Cu(I) and 1.3 equiv. of Grignard reagent (see Scheme 5.15). The formation of the expected allylic alcohol **207** could not be effected under any of the conditions.

Attempted ring opening of the benzyl ether **195** with vinyl magnesium bromide in the presence of 10% Cu(I)I catalyst failed and resulted in the formation of a mixture of bromo and iodohydrins **208** in 56 % yield. The ^{13}C NMR spectra showed C(1) of the iodohydrin at δ_C11.82 and that of the bromohydrin at δ_C 37.20. The COSY spectrum was used to confirm the

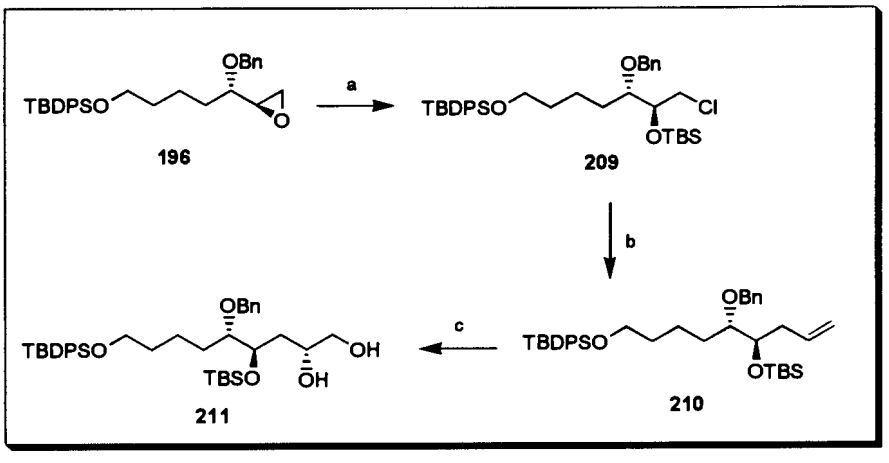
[26] Wakefield, B.J. *Organomagnesium Methods in Organic Synthesis* , **1995**.



Scheme 5.15 Nucleophilic opening of epoxide **201** by vinyl magnesium bromide

Reagents: a. H_2C=CHMgBr, cat. Cu(I)I (10%), THF, b. H_2C=CHMgBr, Cu(I)I 4:2 equiv., THF c. H_2C=CHMgBr, THF.

It was decided to first convert the epoxide ring to a halohydrin using TBS-Cl in the presence of TBAI followed by displacement of the halide with a vinyl group using a copper(I) catalysed Grignard reaction. The synthetic route is outlined in Scheme 5.16 and uses the 3-*O*-benzyl (2*R*,3*S*)-epoxide **196**, the enantiomer of compound **195** used in the earlier synthesis.



Scheme 5.16 Proposed synthesis of (2*S*,4*S*,5*R*)-[8-(*t*-butyldiphenylsilyl)oxy]-4,5-benzyloxy-1,2-nonane-diol **211.**

Reagents : a. TBSCl, TBAI, THF reflux, b. Mg^0, H_2C=CHBr, THF, cat.Cu(I), c. $(DHQ)_2PHAL$, OsO_4, ^tBuOH:H_2O 1:1, $K_3Fe(CN)_6$, K_2CO_3.

The Grignard reagent was prepared from vinyl bromide and magnesium metal in THF. The resulting solution was cooled to 0°C before the addition of 10% of Cu(I)I. The reaction mixture was stirred for 30 min to allow for the formation of the organocopper complex. After 30 min the *O*-benzyl halohydrin **209** solution was added to the organocopper reagent at 0°C. The reaction did not result in the formation of the required chain-extended product **210** but afforded a mixture of bromo, chloro and iodohydrins **212**. The ^{13}C NMR spectra showed C(1) of the chlorohydrin at δ_C 47.36, that of the bromohydrin at δ_C 37.19 and that of the iodohydrin at δ_C 11.81. The COSY spectra also confirmed the presence of the three compounds in the

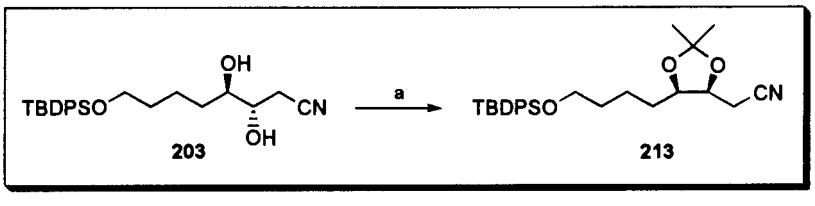
reaction product. As a consequence this approach was abandoned and an alternative methodology was investigated.

5.2.5 Chiral sulfoxide methodology for extension of the C_7 carbon chain.

The conversion of the nitrile functional group to a chiral β-ketosulfoxide moiety using (+)-(*R*)-methyl *p*-tolyl sulfoxide results in the introduction of an additional carbon atom into the molecule. The reduction of the carbonyl group of a β-ketosulfoxide can be achieved with complete control over the stereochemistry of the newly-formed stereogenic centre and leads to the formation of a β-hydroxysulfoxide (see Chapter 4). The use of chiral sulfoxide methodology would allow the conversion of the C_8 nitrile **203** to a chiral β-ketosulfoxide derivative which would then be used to introduce the third stereogenic centre but only if the two hydroxy groups present in the nitrile **203** are protected.

5.2.5.1 Protection of the hydroxy groups: acetonide formation

Acetonides (or isopropylidene acetals) are widely used for the protection of 1,2- and 1,3-diols. The acetals are easily prepared and are stable to most reaction conditions except protic and Lewis acids.[1] Treatment of the nitrile **203** with 2,2-dimethoxypropane under acid-catalysis conditions using *p*-TsOH, results in acetal exchange and the formation of the protected nitrile **213** in 80% yield (Scheme 5.17). The NMR spectra showed the signals of the two methyl groups as two singlets at δ_H 1.331 and 1.459 in the ^1H spectrum and the corresponding signals in the ^{13}C spectrum at δ_C 25.45Q and 28.130Q. The quaternary carbon atom of the signals acetonide moiety resonated at δ_C 108.93S.



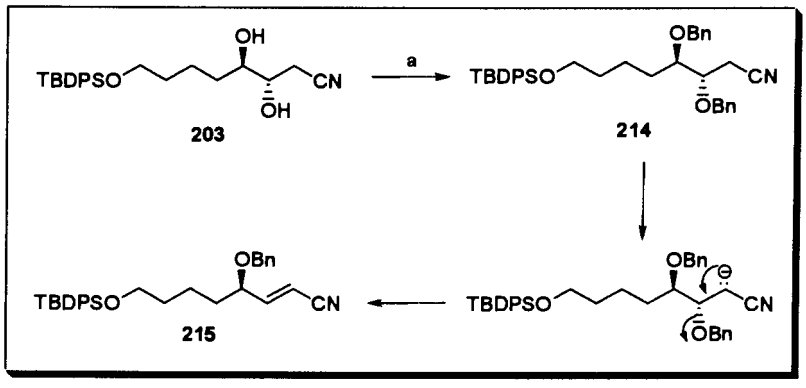
203 **213**

Scheme 5.17 Acetonide protection of (3*S*,4*R*)-[8-(*t*-butyldiphenylsilyl)oxy]-3,4-dihydroxy-octanenitrile **203.**

Reagent: a. 2,2-dimethoxypropane, TsOH, RT (80%).

5.2.5.2 Protection of the hydroxy groups: benzyl ether formation

Benzyl ethers are stable to a wide range of both acidic and basic conditions and protection of the 1,2-diol moiety of the nitrile **203** as the benzyl ether derivative would provide additional stability. The nitirile **203** was treated with NaH and BnBr in the presence of a catalytic amount of TBAI in THF to give a mixture of the dibenzyl ether **214** (48 % yield) and a by-product that was identified as the α,β-unsaturated nitrile **215** (see Scheme 5.18). The ^{1}H NMR spectrum of the dibenzyl ether **214** showed two AB spin systems δ_H 4.579 and 4.691 (J 11.3 Hz), and δ_H 4.590 and 4.610 (J 11.6 Hz), characteristic of the two benzyl methylene groups. The two benzyl carbon atoms appeared at δ_C 72.66T and 72.89T in the ^{13}C NMR spectrum.

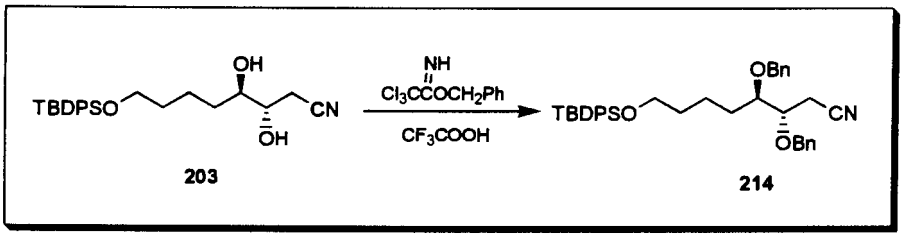


Scheme 5.18 Dibenzylation of (3*S*,4*R*)-[8-(*t*-butyldiphenylsilyl)oxy]-3,4-di(benzyloxy)-octanenitrile **203.**

Reagents: a. NaH, BnBr, TBAI, THF, 0 °C.

The by-product that formed in the reaction was identified as the α,β-unsaturated nitrile **215** by its proton-proton connectivity pattern. The ^{1}H NMR spectrum showed the presence of a typical allylic system: H(2) resonated at δ_H 5.552 with a vicinal coupling of 16.5 Hz with H(3) (δ_H 6.617) (characteristic of the protons of an *E* double bond) and a long-range coupling of 1.6 Hz with H(4) (δ_H 3.894). The signal for the C(3) proton also exhibited a 5.6 Hz coupling with H(4). The corresponding signals in the ^{13}C NMR spectrum appeared at δ_C 100.12D [C(2)], 155.03D [C(3)] and 77.94D [C(4)], respectively. The carbon atom of the nitrile group resonated at δ_C 117.00S. The formation of the α,β-unsaturated nitrile moiety is explained by abstraction of the acidic α-proton of the protected nitrile **214** by the NaH base and the formation of the α-carbanion that loses benzyloxide to give the double bond product **215**.

The formation of the dibenzyl ether derivative **214** was also attempted under acidic conditions by treating the diol **203** with *O*-benzyl trichloroacetimidate[27,28,29] in the presence of triflic acid (Scheme 5.19). It was hoped that under these conditions the formation of the α,β-unsaturated nitrile could be avoided. The reaction was unsuccessful and a complex mixture of products was obtained. It would appear that the *O*-TBDPS group does not survive the strong acid conditions.



Scheme 5.19 Dibenzylation of nitrile **203** under acidic conditions.

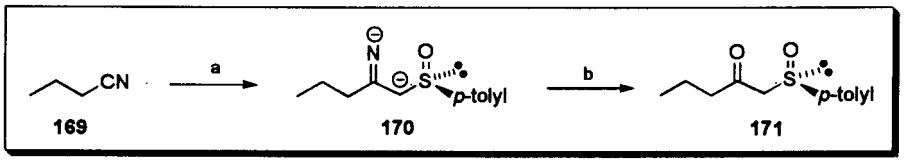
5.2.5.3 Introduction of the chiral sulfoxide moiety

The chiral sulfoxide (+)-(*R*)-methyl *p*-tolyl sulfoxide **103**, required for the synthesis of the C_9 unit of TA toxin, was synthesized from (–)-(*S*)-menthyl-*p*-toluenesulfinate **163** which in turn was prepared from *p*-toluenesulfinylchloride and (–)-menthol (Scheme 4.2). The procedure outlined by Solladié and Girardin[30] was employed. The esterification showed no stereoselectivity and gave a 1:1 mixture of diastereoisomers. This mixture was equilibrated by traces of HCl and as only the (*S*)-isomer crystallizes from acetone yields as high as 80 % yield could be obtained. Although the synthesis is relatively easy, the crystallization of a second and third crop of crystals of **163** is time consuming, as the mixture must be concentrated to a viscous liquid. The final product has a melting point of 105-107 °C and $[\alpha]_D^{20}$ –202 (c 2.0, acetone) and was stored in the deep freeze. (+)-(*R*)-Methyl *p*-tolylsulfoxide **103** can be prepared from (–)-(*S*)-menthyl-*p*-toluenesulfinate **163** by reaction with methyl magnesium bromide (Scheme 4.1). This reaction has been described extensively and the product obtained in high e.e. and chemical yield by crystallization of the crude reaction product.

In the present project the nitrile functional group was used as a substrate for the formation of the chiral β-ketosulfoxide using (+)-(*R*)-methyl *p*-tolyl sulfoxide **103**. The reaction

[27] Wessel, H.P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.
[28] Widmer, U. *Synthesis*, **1987**, 568.
[29] Iversen, T.; Bundle, D.R. J. *Chem. Soc. Chem. Commun.*, **1981**, 1240.
[30] Solladié, G.; Hutt, J.; Girardin, A. *J. Chem. Soc. Chem. Commun.*, **1987**, 173.

was practised by using butyronitrile **169** as a model substrate (Scheme 5.20). In the procedure 2 equivalents of the chiral sulfoxide **103** in THF were added to a solution of two equivalents of LDA in THF at –78°C. The LDA base abstracts the proton of the methyl group of the chiral sulfoxide, generating the chiral sulfoxide carbanion. Butyronitrile (1 equivalent) is added at 0°C and the reaction allowed to warm to room temperature. Two equivalents of base are required because the acidic α-proton of the initially formed imidine is abstracted by the second equivalent of base to form the dianion species **170**. Acidic work-up neutralises the carbanion and hydrolyses the imine to a keto group to form the β-ketosulfoxide **171**.[31]



169 170 171

Scheme 5.20 Synthesis of β-ketosulfoxide **171.**

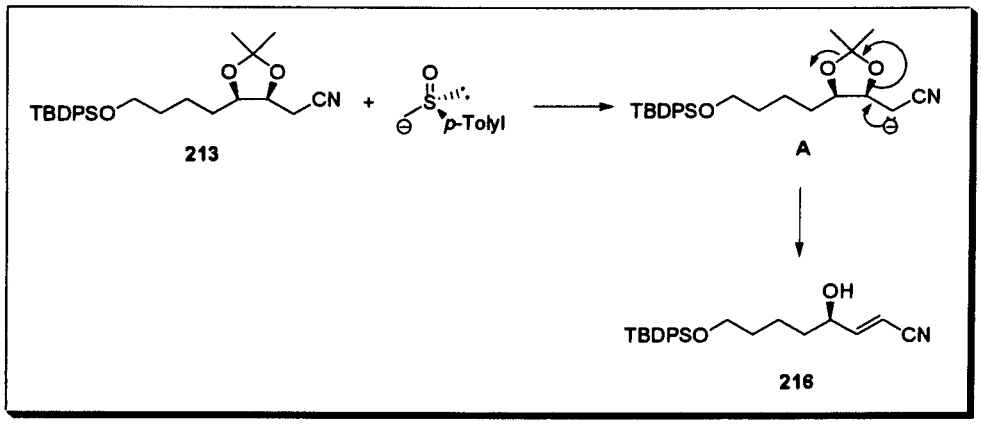
Reagents: a) LDA, **103**, 0°C→rt; b) aq. HCl (pH 2) (85%).

The ^{1}H NMR spectrum showed the C(1) protons as an AB spin system (J 13.6 Hz) at δ_H 3.691 and 3.813. The methyl group of the *p*-tolyl substituent of the sulfoxide resonated as a singlet at δ_H 2.370. The presence of the newly formed carbonyl group was evident from the signal at δ_C 201.64S in the ^{13}C NMR spectrum and the absorption band at 1713 cm^{-1} in the IR spectrum. The C(1) and C(3) signals appeared at δ_C 68.18T and 46.81T, respectively.

The reaction of the acetonide protected nitrile **213** with the anion derived from (+)-(*R*)-methyl *p*-tolyl sulfoxide under the above conditions, failed and the only formed product that could be identified was the α,β-unsaturated nitrile **216**. The formation of **216** can be explained by the mechanism as outlined in Scheme 5.21. Abstraction of the acidic α-proton of the nirile group leads to the formation of a carbanion that undergoes a rearrangement that results in formation of the double bond with concomitant loss of acetone. The ^{1}H NMR spectrum of the α,β-unsaturated nitrile showed a typical allylic system: H(2) resonated at δ_H 5.628 with a vicinal coupling of 16.2 Hz with H(3) (δ_H 6.688)(in agreement with the presence of an *E* double bond) and a long-range coupling of 2.0 Hz with H(4) (δ_H 4.245). H(3) also exhibited an additional coupling of 4.0 Hz with H(4). The corresponding signals in ^{13}C NMR spectrum

[31] Vleggaar, R.; Zeevaart, J.G. *Tetrahedron Lett.*, **1999**, *40*, 9301.

appeared at δ_C 98.67D, 156.58 and 70.83D for C(2), C(3) and C(4), respectively. The presence of the nitrile functional group was evident from the signal at δ_C 117.28S.

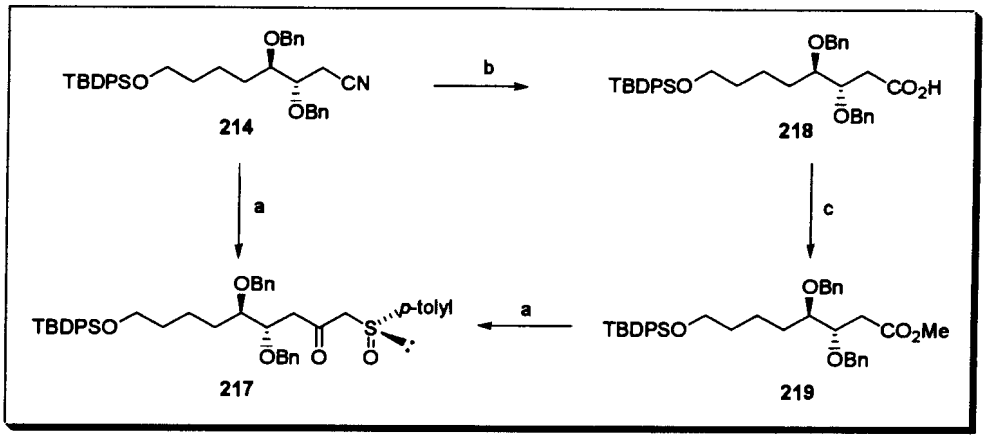


Scheme 5.21 Proposed mechanism for the formation of the α,β-unsaturated nitrile **216.**

The reaction of the dibenzyl protected nitrile **214** with the anion derived from (+)-(*R*)-methyl *p*-tolyl sulfoxide was also not successful. Although the benzyl group can withstand much harsher acidic conditions during work-up than the acetonide moiety, the only product that could be isolated and identified from the reaction was the α,β-unsaturated nitrile **215** in 20% yield.

An alternative approach to the synthesis of the β-ketosulfoxide **217** is the use of an ester functional group instead of the nitrile group for the reaction with the carbanion derived from (+)-(*R*)-methyl *p*-tolyl sulfoxide with LDA.[32] This approach requires the conversion of the nitrile **214** into the acid **218** followed by esterification to give the methyl ester **219** (see Scheme 5.22). The reaction conditions for the hydrolysis of dibenzyl nitrile **214** were carefully chosen. Basic conditions were favoured over acidic conditions because of the greater relative stability of the TBDPS ether in basic medium (5% NaOH, 95% EtOH, 4 h, 95°C) than in acid medium (1 % HCl, 95% EtOH, 4 h, 22°C). The reaction was first carried out in 20% aqueous NaOH solution; but no hydrolysis was achieved.[2] The reaction conditions were then adjusted and 40% aq. NaOH solution was used but the silyl protecting group did not survive such harsh conditions. The chiral sulfoxide approach was then discarded for the final steps of the C_9 fragment of TA toxin.

[32] Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas.*, **1995**, *114*, 153.



Scheme 5.22 Proposed syntheses of the β-ketosulfoxide **217** using either a nitrile **214** or an ester intermediate **219.**

Reagent: a. LDA, **103,** THF; b. 40% NaOH, EtOH; c. CH_2N_2, Et_2O.

The results reported in this dissertation do not constitute a total synthesis for the the C(1)–C(9) unit of the TA toxin backbone. However some problems in the proposed synthetic route have been identified and solved. It has been clearly demonstrated that the some methodologies such as chiral sulfoxides are not suitable for the synthetic route. The opening of the *O*-benzyl protected epoxides such as **194**, **195,** and **196** by either higher-order mixed cuprates or lithium vinyl reagents followed by Sharpless dihydroxylation is a feasible route that can lead to the completion of the synthesis of the C_9 backbone of TA toxin. The investigation of this aspect of the synthetic route is, however, outside the scope of the present dissertation and will form the basis of a new research project.

6. Experimental

6.1 INTRODUCTION

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

Optical rotations were determined with a Perkin Elmer 241 polarimeter for solutions in chloroform ($CHCl_3$). Specific rotations are given in units of 10^{-1} deg.g^{-1}.cm^2. High-resolution mass spectra were performed by Dr. L. Fourie, University of Potchefstroom, on a VG 7070-E spectrometer (Xe beam, *m*-nitrobenzyl alcohol matrix, detection of positive ions with *m/z* > 99). Infrared spectra were recorded with a Bruker 113v FT-IR instrument as a thin layer between ZnSe disks. Values were rounded to 5 cm^{-1} upon manual assignment or 1 cm^{-1} upon automatic assignment.

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on a Bruker AMX-300 (7.0T) spectrometer operating at 300 MHz for ^{1}H, 75.47 MHz for ^{13}C and 284.4 MHz for ^{19}F. All chemical shifts are reported as δ values downfield from Me_4Si using $CDCl_3$ as internal standard (δ_H 7.24 or δ_C 77.00 ppm, respectively). $CFCl_3$ was used as external standard for ^{19}F with negative numbers assigned to high-field shift values. Proton-proton coupling constants (J) are given in Hz. Spectral coupling patterns are designated as follow: s/S: singlet; d/D: doublet; t/T: triplet; q/Q: quartet; m: multiplet; br: broad signal. The assignments of the signals in the ^{1}H NMR spectra are based on first-order analysis of the spin systems and when required were confirmed by ^{1}H{^{1}H} decoupling experiments and two-dimentional (2-D) (^{1}H,^{1}H) homonuclear chemical shift correlation (COSY) experiments. The ^{13}C chemical shifts were obtained from proton-decoupled spectra. The multiplicities of the different ^{13}C resonances were deduced from the proton-decoupled CH, CH_2 and CH_3 subspectra obtained using the DEPT pulse sequence. The signals of the proton-bearing carbon atoms were correlated with specific proton

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

resonances by utilizing the one-bond ($^{13}C,^{1}H$) spin-spin couplings. Standard Bruker pulse programs were used in these experiments.

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

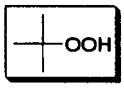
6.2 PREPARATION OF REAGENTS

6.2.1 Spraying Reagents

Cerium(IV) sulfate-sulfuric acid

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

6.2.2 Other reagents



Anhydrous *t*-butyl hydroperoxide

TBHP solution (70% v/v in water, 325 ml) and toluene (400 ml) were placed in a 1L-separating funnel. The mixture was swirled and not shaken in order to avoid the formation of emulsions. The organic phase was separated and transferred to a 1L two-necked round-bottom flask fitted with a Dean-Stark apparatus, reflux condenser, and a thermometer. The solution was refluxed for 1 h during which time about 20 ml of water was collected. When no more water collected through azeotropic distillation, the solution (*ca.* 600 ml) was allowed to cool and stored over 4Å molecular sieves in a brown glass bottle. The anhydrous TBHP solution in toluene was standardised by ^{1}H NMR spectroscopy. The molarity was determined as 3.1M by using the formula

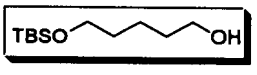
$$M = \frac{x}{0.1x + 0.32y}$$

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

δ_H 1.293 (s, 9H, CMe_3)
2.384 (s, 3H, $ArCH_3$)
7.19-7.34 (m, 5H, ArH)

6.3 PROCEDURES

6.3.1 Synthesis of the C(1)–C(9) unit of TA toxin: Use of the TBS protecting group



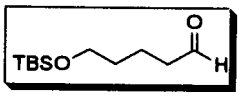
[5-(*t*-Butyldimethylsilyl)oxy]-1-pentanol 173

NaH (60% dispersion, 5.23 g, 130 mmol) was washed with hexane and suspended in THF (260 ml). 1,5-Pentanediol (13.9 g, 133 mmol) was added dropwise to this mixture at room temperature and stirred for 45 min. A white precipitate formed during the reaction. *t*-Butyldimethylsilyl chloride (20.0 g, 133 mmol) was then added dropwise and the reaction stirred for 45 min at RT. The THF was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel, using EtOAc-hexane (1:1) as eluant to afford the monoprotected diol **173** as a colourless oil (20.7 g, 71%); R_f 0.37 (EtOAc-hexane 1:1); ν_{max} 3356 cm^{-1}.

δ_H: 0.027 (s, 6H, Me_2Si)
0.873 (s, 9H, CMe_3)
1.39 (m, 2H, H-3)
1.49-1.62 (m, 4H, H-2 and H-4)
3.609 (t, 2H, $J_{1,2}$ 6.3, H-1)
3.625 (t, 2H, $J_{5,4}$ 6.5, H-5)

δ_C: –5.31Q (Me_2Si), 18.35S (CMe_3), 22.02T (C-3), 25.97Q (CMe_3), 32.51T (C-4 and C-2), 62.94T (C-1)*, 63.10T (C-5)*. * may be interchanged

FAB-MS *m/z* 219 $[M+H]^+$. Exact mass: Calculated for $C_{11}H_{27}O_2$, 219.1780; Observed, 219.1781.



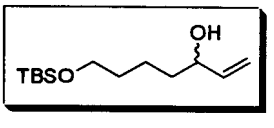
[5-(*t*-Butyldimethylsilyl)oxy]-1-pentanal 175

DMSO (6.68 g, 85.5 mmol) was added dropwise to a solution of oxalyl chloride (5.80 g, 45.7 mmol) in CH_2Cl_2 (70 ml) at –78°C under argon. After 15 min a solution of the alcohol **173** (8.88 g, 40.7 mmol) in CH_2Cl_2 (30 ml) was introduced dropwise and the solution was stirred for 90 min at –78°C. Triethylamine (20.6 g, 204 mmol) was added slowly and stirring continued for 5 h. The reaction was allowed to reach RT and the white\yellow suspension was diluted with CH_2Cl_2 (200 ml) and washed with saturated NH_4Cl (200 ml) and water (200 ml). The organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (2:1) as eluant to afford the aldehyde **175** (7.70 g, 87 %) as a yellow oil; R_f 0.60 (EtOAc-hexane 2:1); ν_{max} 2952 and 1720 cm^{-1}.

δ_H: 0.022 (s, 6H, Me_2Si)
0.868 (s, 9H, CMe_3)
1.53 (m, 2H, H-4)
1.68 (m, 2H, H-3)
2.425 (td, 2H, $J_{2,3}$ 7.0, $J_{2,1}$ 1.8, H-2)
3.602 (t, 2H, $J_{5,4}$ 6.2, H-5)
9.744 (t, 1H, $J_{1,2}$ 1.8, H-1)

δ_C: –5.36Q (Me_2Si), 18.29S (CMe_3), 18.65T (C-3), 25.91Q (CMe_3), 32.11T (C-4), 43.60T (C-2), 62.57T (C-5), 202.57D (C-1).

FAB-MS *m/z* 216 $[M]^+$. Exact mass: Calculated for $C_{11}H_{24}O_2Si$, 216.1546; Observed, 216.1546.



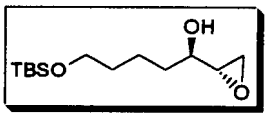
(3*RS*)-7-[(*t*-Butyldimethylsilyl)oxy]-hept-1-en-3-ol 177
A solution of vinyl bromide (5.83 g, 54.5 mmol) in THF (10 ml) was added by syringe to a mixture of Mg turnings (1.13 g, 46.3 mmol) in dry THF (300 ml). A crystal of iodine was used to initiate the reaction. After the addition of all of the vinyl bromide, the reaction mixture was

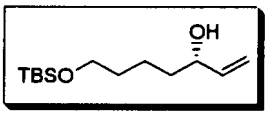
heated for 30 min. Once all of the magnesium had been consumed, the mixture was cooled to 0°C and a solution of pentanal **175** (7.69 g 35.6 mmol) in (50 ml) THF was added dropwise. After completion of the reaction, saturated NH_4Cl (50 ml) was added dropwise. The THF was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using EtOAc-hexane (1:1) as eluant to afford the allylic alcohol **177** as a yellow oil (5.90 g, 68 %); R_f 0.59 (EtOAc-hexane 1:2); ν_{max} 3402, 1596 cm^{-1}.

δ_H: 0.019 (s, 6H, Me_2Si)
0.865 (S, 9H, CMe_3)
1.38 (m, 2H, H-5)
1.46-1.57 (m, 4H, H-4 and H-6)
3.588 (t, 2H, $J_{7,6}$ 6.34, H-7)
4.05 (m, H, H-3)
5.070 (ddd, 1H, $J_{1b,2}$ 10.4, $J_{1b,1a}$ 1.4, $J_{1b,3}$ 1.4, H-1b)
5.190 (ddd, 1H, $J_{1a,2}$ 17.2, $J_{1a,1b}$ 1.4, $J_{1a,3}$ 1.4, H-1a)
5.84 (ddd, 1H, $J_{2,1a}$ 17.24, $J_{2,1b}$ 10.43, $J_{2,3}$ 6.20, H-2)

δ_C: –5.31Q (Me_2Si), 18.33S (CMe_3), 21.63T (C-5), 25.94Q (CMe_3), 32.61T (C-4), 36.67T (C-6), 63.09T (C-7), 73.04D (C-3), 114.55T (C-1), 141.22D (C-2).

FAB-MS *m/z* 245 $[M+H]^+$. Exact mass: Calculated for $C_{13}H_{29}O_2Si$, 245.1937; Observed, 245.1937.





(2*S*,3*R*)-7-[(*t*-Butyldimethylsilyl)oxy]-1,2-epoxy-3-heptanol 179 and (3*S*)-7-[*t*-butyldimethylsilyl]oxy]-1-hepten-3-ol 183

A solution of (*S*,*S*)-diisopropyl D-tartrate (2.04 g, 8.69 mmol) in CH_2Cl_2 (20 ml) was added bysyringe to a suspension of powdered 4Å molecular sieves (6.0 g) in CH_2Cl_2 (100 ml) under argon at –20°C. $Ti(^iPrO)_4$ (2.10 g, 7.39 mmol) was then added by syringe followed by a solution of TBHP (3.1M in toluene, 8.69 mmol, 2.77 ml). The resulting reaction mixture was stirred for 30 min before the allylic alcohol **177** (3.50 g, 14.3 mmol) CH_2Cl_2 (50 ml) was added dropwise. The reaction mixture was stirred at –20°C for 2 h and then at –10°C in the freezer

for 18 h. The solution was allowed to reach 0°C, filtered, and a fresh solution of iron(III) sulfate (6.1 g) and tartaric acid (4.0 g) in water (50 ml) pre-cooled to 0°C was added and stirred for 10 min. The resulting mixture was then filtered through a Celite pad in order to break the emulsion. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5x50 ml). The CH_2Cl_2 organic layer was vigorously stirred in brine solution containing NaOH (15%, 400 ml) for 1 h at 0°C and diluted with H_2O (100 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 ml). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography using EtOAc-hexane (1:2) as eluant to afford the (3*S*)-allylic alcohol **183** (1.26 g, 63 %); R_f 0.59 (EtOAc-hexane 1:2) and the epoxy alcohol **179** (714 mg, 34 %); R_f 0.39 (EtOAc-hexane 1:2).

δ_H: 0.005 (s, 6H, Me_2Si)
0.847 (s, 9H, CMe_3)
1.42-1.57 (m, 6H, H-4, H-5 and H-6)
2.687 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 3.9, H-1a)
2.765 (dd, 1H, $J_{1b,1a}$ 5.2, $J_{1b,2}$ 2.6, H-1b)
2.965 (ddd, 1H, $J_{2,1a}$ 4.0, $J_{2,1b}$ 3.0, $J_{2,3}$ 3.0, H-2)
3.585 (t, 2H, $J_{7,6}$ 6.1, H-7)
3.769 (m, 1H, H-3)

δ_C: –5.35Q (Me_2Si), 18.29S (Me_3C), 21.59T (C-5), 25.91S (Me_3C), 32.61T (C-4)*, 33.06T (C-6)*, 43.43D (C-1), 54.50D (C-2), 62.98T (C-7), 68.22D (C-3).
* may be interchanged

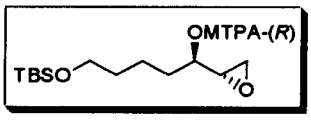
FAB-MS: *m/z* 261 $[M+H]^+$. Exact mass: Calculated for $C_{13}H_{29}O_3Si$, 261.1886; Observed, 261.1886.

MOSHER ESTER DERIVATIZATION

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

Oxalyl chloride (188 mg, 1.48 mmol) was added to a solution of (*R*)-(+)-MTPA (e.e.≥ 99%, 102 mg, 0.44 mmol) and DMF (40.0 mg, 0.55 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) (104 mg, 95 %).



b. (2*S*,3*R*)-1,2-Epoxy-7-[(*t*-butyldimethylsilyl)oxy]-3-heptyl (*R*)-α-methoxytrifluoromethyl-phenylacetate 185

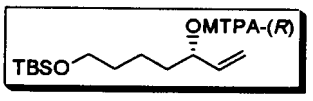
A solution of MTPACl (104 mg, 0.41 mmol) in CH_2Cl_2 (2 ml) was added to a stirred solution of epoxide **179** (64.0 mg, 0.25 mmol), triethylamine (75.0 mg, 0.74 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at RT. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl and with saturated $NaHCO_3$, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **6** (88 mg, 45 %); R_f 0.63 (EtOAc-hexane 1:2); ν_{max} 3062, 1750 cm^{-1}.

δ_H: 0.004 (s, 6H, Me_2Si)
0.857 (s, 9H, CMe_3)
1.29 (m, 2H, H-5)
1.45 (m, 2H, H-6)
1.71 (m, 2H, H-4)
2.709 (dd, 1H, $J_{1b,1a}$ 5.2, $J_{1b,2}$ 2.6, H-1b)
2.723 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 3.6, H-1a)
3.039 (ddd, 1H, $J_{2,3}$ 4.4, $J_{2,1a}$ 3.6, $J_{2,1b}$ 2.6, H-2)
3.512 (t, 2H, $J_{7,6}$ 6.2, H-7)
3.528 (q, 3H, $J_{H,F}$ 1.2, OMe)
5.082 (dt, 1H, $J_{3,4}$ 6.2, $J_{3,2}$ 4.7, H-3)
7.36-7.54 (m, 5H, ArH)

δ_C: –5.39Q ($SiMe_2$), 18.27S (CMe_3), 21.07T (H-5), 25.89Q (CMe_3), 30.98T (C-6), 32.34T (C-4), 44.64T (C-1), 51.80D (C-2), 55.34Q (OMe), 62.69T (C-7), 74.38D (C-3), 123.31S ($J_{C,F}$ 288 CF_3), 127.34D, 128.36D, 129.60D, 132.26S (aromatic carbons), 166.01S (CO).

δ_F: –71.82

FAB-MS *m/z* 460 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{35}F_3O_3Si$, 460.2257; Observed, 460.2256.



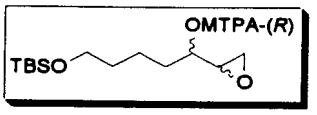
c. (3*S*)-7-[(*t*-Butyldimethylsilyl)oxy]-1-hepten-3-yl (*R*)-α-methoxy-α-trifluoro-methyl-phenylacetate 189

A solution of MTPACl (110 mg, 0.44 mmol) [prepared from (*R*)-(+) MTPA (100 mg, 0.44 mmol) as outlined in **a** above] in CH_2Cl_2 (5 ml) was added to a stirred solution of the (3*S*)-allylic alcohol **183** (60.4 mg, 0.247 mmol), triethylamine (74 mg, 0.73 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at RT. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl and saturated $NaHCO_3$ solution, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **189** (104 mg, 91 %); R_f 0.76 (EtOAc-hexane 1:2); ν_{max} 3079 and 1750 cm^{-1}.

δ_H: 0.016 (s, 6H, $SiMe_2$)
0.864 (s, 9H, CMe_3)
1.37 (m, 2H, H-5)
1.50 (m, 2H, H-6)
1.70 (m, 2H, H-4)
3.512 (q, $J_{H,F}$ 1.3, OMe)
3.572 (t, $J_{7,6}$ 6.2, H-7)
5.180 (ddd, 1H, $J_{1b,2}$ 10.3, $J_{1b,1a}$ 1.2, $J_{1b,3}$ 1.2, H-1b)
5.230 (ddd, 1H, $J_{1a,2}$ 17.3, $J_{1a,1b}$ 1.2, $J_{1a,3}$ 1.2, H-1a)
5.423 (m, 1H, $J_{3,2}$ 7.0, $J_{3,4}$ 6.2, $J_{3,1a}$ 1.2, $J_{3,1b}$ 1.2, H-3)
5.698 (ddd, 1H, $J_{2,1a}$ 17.3, $J_{2,1b}$ 10.3, $J_{2,3}$ 7.0, H-2)
7.32-7.50 (m, 5H, ArH)

δ_C: –5.39Q ($SiMe_2$), 18.26S (CMe_3), 21.43T (C-5), 25.88T (CMe_3), 32.34T (C-4), 33.80T (C-6), 55.39Q (OMe), 62.74T (C-7), 77.56D (C-3), 118.23T (C-1), 123.35S ($J_{C,F}$ 289 CF_3), 127.38D, 128.25D, 129.46D, 132.38S (aromatic carbons), 135.06D (C-2), 165.76S (CO).

δ_F: –71.95



d. (2*RS*,3*RS*)-1,2-Epoxy-7-[(*t*-butyl dimethylsilyl)oxy]-3-heptyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate 188

MCPBA (2.55 g, 14.7 mmol) was added to a solution of the racemic secondary allylic alcohol **177** (1.99 g, 8.16 mmol) in CH_2Cl_2 (55 ml) and the reaction stirred for 3 h at RT. The organic layer was then washed several times with $NaHCO_3$ solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using EtOAc-hexane (1:6) as eluant to afford the racemic epoxy alcohol **187** (580 mg, 20 %); R_f 0.13 (EtOAc-hexane 1:5).

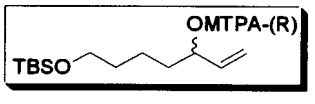
A solution of MTPACl (115 mg, 0.45 mmol) [prepared from (100 mg, 0.44 mmol) (*R*)-(+)-MTPA by the procedure as outlined in **a.**) in CH_2Cl_2 (5 ml) was added to a stirred solution of the racemic epoxy alcohol **187** (64 mg, 0.25 mmol), triethylamine (75 mg, 0.25 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at RT. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl and with saturated $NaHCO_3$ solution, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **188** (105 mg, 89 %); R_f 0.36 and 0.42 (EtOAc:hexane 1:5); ν_{max} 3068, 1753, 1596 cm^{-1}.

δ_H: 0.017 (s, 6H, $SiMe_2$)
0.019 (s, 6H, $SiMe_2$)
0.863 (s, 9H, CMe_3)
0.865 (s, 9H, CMe_3)
0.868 (s, 9H, CMe_3)
1.24-1.81 (m, 24H, H-4, H-5 and H-6)
2.572, 2.595, 2.918 and 2.931 (dd, 4H, $J_{1b,2}$ 2.6, $J_{1a,1b}$ 5.2, H-1b)
2.648, 2.730, 2.767and 2.848 (dd, 4H, $J_{1a,2}$ 3.6, $J_{1a,1b}$ 5.2, H-1a)
3.015-3.107 (m, 4H, H-2)
3.49-3.61 (m, 12H, 4(OMe))
4.778-4.912, 4.988, and 5.070 (dt, 8H, $J_{3,2}$ 4.4, $J_{3,4}$ 6.2, H-3)
7.352-7.405 (m, 10H, ArH)
7.491-7.580 (m, 10H, ArH)

δ_C: –5.39Q ($SiMe_2$), 18.28S (CMe_3), 21.07T, 21.26T, 21.45T, 21.62T (C-5), 25.89Q (CMe_3), 30.88T, 30.94T, 30.97T, 31.25T (C-6), 32.35T, 32.41T (C-4), 44.63T, 44.82T, 45.35T (C-1), 51.73D, 51.80D, 52.43D, 52.49D (C-2), 55.34Q, 55.45Q (OMe), 62.61T, 62.68T (C-7), 74.37D, 74.89D, 77.31D, 77.82 D (C-3), 123.28S ($J_{C,F}$ 288 Hz, CF_3), 127.34D, 127.51D, 128.36D, 129.02S, 129.59D and 132.17S, 132.22S, 132.27S and 132.33S (aromatic carbons), 165.97S, 166.01S (CO).

δ_F: –71.86, –71.92, –72.00 and –72.19

FAB-MS *m/z* 478 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{37}F_3O_5Si$, 478.2362; Observed, 478.2362.



e. (3*RS*)-7-[(*t*-Butyldimethylsilyl)oxy]-3-hepten-1-yl (R)-(+)-α-methoxy-α-trifluoro-methyl-phenylacetate 190

A solution of MTPACl (96.0 mg, 0.38 mmol) [obtained from (100 mg, 0.44 mmol) (*R*)-(+)-MTPA as outlined in **a.** above) in CH_2Cl_2 (5 ml) was added to a stirred solution of racemic allylic alcohol **177** (64.8 mg, 0.25 mmol), triethylamine (74.3 mg, 0.74 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at RT. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl and followed by saturated $NaHCO_3$, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **190** (91.0 mg, 80 %) as a yellow oil; R_f 0.76 (EtOAc-hexane 1:2); ν_{max} 3079, 1750 cm^{-1}.

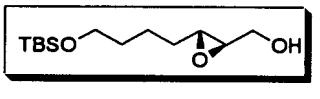
δ_H: 0.008 (s, 6H, $SiMe_2$)
0.015 (s, 6H, $SiMe_2$)
0.865 (s, 9H, CMe_3)
0.862 (s, 9H, CMe_3)
1.24-1.82 (m, 12H, H-4, H-5 and H-6)
3.519 (t, 2H, $J_{7,6}$ 6.2, H-7)
3.525 (q, $J_{H,F}$ 1.3, OMe)
3.537 (q, $J_{H,F}$ 1.3, OMe)

3.571 (t, 2H, $J_{7,6}$ 6.2, H-7)
5.168 and 5.238 (ddd, 2H, $J_{1b,2}$ 10.3, $J_{1b,3}$ 1.2, $J_{1b,1a}$ 1.2, H-1b)
5.237 and 5.337 (ddd, 2H, $J_{1a,2}$ 17.3, $J_{1a,3}$ 1.2, $J_{1a,1b}$ 1.2, H-1a)
5.385-5.480 (m, 4H, H-3)
5.704 and 5.804 (ddd, 2H, $J_{2,1a}$ 17.3, $J_{2,1b}$ 10.3, $J_{2,3}$ 7.0, H-2)
7.34-7.39 (m, 5H, ArH)
7.48-7.53 (m, 5H, ArH)

δ_C: –5.39Q ($SiMe_2$), 14.14S, 18.28S (CMe_3), 21.14T, 21.45D (C-5), 25.89Q (CMe_3), 32.29T, 32.36T (C-4), 33.66T, 33.83T (C-6), 55.38Q (OMe_3), 62.76T (C-7), 77.57D (C-3), 118.26T, 118.72T (C-1), 123.35S and 123.38S ($J_{C,F}$ 288 Hz, CF_3), 127.36D, 128.28D 129.47D, 132.39S, 132.52S (aromatic carbons), 135.08D, 135.23D (C-2), 165.78S, 165.84S (CO).

δ_f: –71.89, –71.95

FAB-MS: *m/z* 463 $[M]^+$. Exact mass: Calculated for $C_{23}H_{38}F_3O_4Si$, 463.2491; Observed, 463.2491.



(*2R,3R*)-7-[(*t*-Butyldimethylsilyl)oxy]-2,3-epoxy-1-heptanol 200

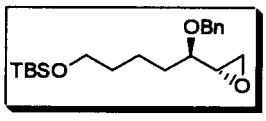
The epoxy alcohol **179** (184 mg, 0.70 mmol) was added to a solution of NaCN (188 mg, 3.84 mmol) in DMSO (5 ml) at 70°C. The reaction mixture was stirred at 70°C for 2 h, allowed to cool to RT, was diluted with diethyl ether and washed with brine (3x50 ml). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The aqueous layer was treated with NaOCl solution and tested for CN^- with aqueous $FeSO_4$ before disposal. The crude product was purified by column chromatography using EtOAc-hexane (1:1) as eluant to afford the epoxy alcohol **200** (83 mg, 45 %) as an oil; R_f 0.37 (EtOAc-hexane 1:1); ν_{max} 3774 and 3424 cm^{-1}.

δ_H: 0.011 (s, 6H, Me_2Si)
0.855 (s, 9H, Me_3C)
1.48 (m, 2H, H-5)
1.50-1.60 (m, 4H, H-4 and H-6)

2.915 (ddd, 1H, $J_{2,1b}$ 4.4, $J_{2,3}$ 2.6, $J_{1a,2}$ 2.3, H-2)
2.982 (dt, 1H, $J_{3,4}$ 5.4, $J_{2,3}$ 2.6, H-3)
3.557 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1b,2}$ 4.4, H-1b)
3.580 (t, 2H, $J_{6,7}$ 6.1, H-7)
3.856 (dd, 1H, $J_{1a,1b}$ 12.7, $J_{1a,2}$ 2.3, H-1a)

δ_C: –5.30Q (Me_2Si), 22.30T (C-5), 25.95Q (CMe_3), 31.33T (C-6), 32.45T (C-4), 55.97D (C-2), 58.54D (C-3), 61.68T (C-7), 62.89T (C-1).

FAB-MS: *m/z* 261 $[M+H]^+$. Exact mass: Calculated for $C_{13}H_{29}O_3Si$, 261.1886; Observed, 261.1886.



(2*S*,3*R*)-7-[(*t*-Butyldimethylsilyl)oxy]-3-benzyloxy-1,2-epoxyheptane 194

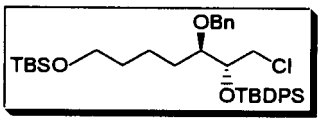
A solution of epoxy alcohol **179** (570 mg, 2.00 mmol), benzyl bromide (100 mg, 2.00 mmol) and TBAI (80 mg, 0.20 mmol) in THF (15 ml) were added to a suspension of NaH (60% dispersion, 110 mg, 2.70 mmol) in THF (10 ml) under argon at 0°C. The reaction was allowed to reach RT within 2 h and further stirred overnight. The excess BnBr was destroyed by addition of methanol. After stirring for 30 min the reaction mixture was diluted with water (100 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (5x50 ml). The diethyl ether solution was washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using first hexane and subsequently EtOAc-hexane (1:1) as eluant to give benzyl ether **194** (550 mg, 72 %); R_f 0.29 (EtOAc-hexane 1:5); $[\alpha]_D$ –7.5 (*c* 0.66, $CHCl_3$); ν_{max} 1259 cm^{-1}.

δ_H: 0.031 (s, 6H, Me_2Si)
0.884 (s, 9H, Me_3C)
1.40-1.70 (m, 6H, H-4, H-5 and H-6)
2.702 (dd, 1H, $J_{1b,1a}$ 5.4, $J_{1b,2}$ 2.6, H-1b)
2.761 (dd, 1H, $J_{1a,1b}$ 5.4, $J_{1a,2}$ 3.9, H-1a)
2.913 (dd, 1H, $J_{2,1b}$ 2.6, $J_{2,1b}$ 3.9, $J_{2,3}$ 5.4, H-2)
3.252 (td, 1H, $J_{2,3}$ 5.4, $J_{4,3}$ 6.7, H-3)
3.592 (t, 2H, $J_{6,7}$ 6.2, H-7)

4.490 (d, 1H, J 11.6, OCH_2Ph)
4.640 (d, 1H, J 11.6, OCH_2Ph)
7.25-7.36 (s, 5H, ArH)

δ_C: –5.30Q (Me_2Si), 18.34S (CMe_3), 21.58T (C-5), 25.97Q (CMe_3), 32.66T (C-4)*, 32.83T (C-6)*, 45.57T (C-1), 53.52D (C-2), 63.04T (C-7), 72.31T (OCH_2Ph), 78.11D (C-3), 127.60D, 127.68D, 128.34D, 138.58S (aromatic carbons).
* may be interchanged

FAB-MS *m/z* 351 $[M+H]^+$. Exact mass: Calculated for $C_{20}H_{34}O_4Si$, 351.2355; Observed, 351.2355.



(2*R*,3*R*)-3-Benzyloxy-1-chloro-7-[(*t*-butyldimethylsilyl)oxy]-2-(*t*-butyldiphenylsilyl-oxy) heptane 198

t-Butyldiphenylsilyl chloride (177 mg, 0.64 mmol) and TBAI (0.043 mmol, 16 mg) were added to a stirred solution of benzyl ether **194** (150 mg, 0.43 mmol) in dry THF (5 ml). The reaction mixture was refluxed for 15 h, was diluted with water (10 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (3x20 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using EtOAc-hexane (1:15) as eluant to afford the chloro compound **198** (24.0 mg, 9 %); R_f 0.31 (EtOAc-hexane 1:5); $[\alpha]_D$ –0.2 (*c* 0.48, $CHCl_3$).

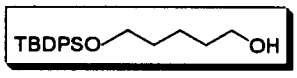
δ_H: 0.087 (s, 6H, $SiMe_2$)
0.906 (s, 9H, CMe_3)
1.062 (s, 9H, CMe_3)
1.43-1.65 (m, 6H, H-4, H-5 and H-6)
3.50 (m, 1H, H-3)
3.661 (t, 2H, $J_{6,7}$ 6.0, H-7)
3.668 (dd, 1H, $J_{1a,1b}$ 11.3, $J_{1b,2}$ 6.6, H-1b)
3.6957 (dd, H, $J_{1a,1b}$ 11.3, $J_{1a,2}$ 3.9, H-1a)
3.82 (br m, 1H, H-2)
4.542 (d, 1H, J 11.4, OCH_2Ph)

4.573 (d, 1H, J 11.4, OCH_2Ph)
7.30-7.73 (m, 15H, ArH)

δ_C: –3.60Q ($SiMe_2$), 19.00S (CMe_3), 19.22S (CMe_3), 21.34T (C-5), 26.56T (CMe_3), 26.89Q (CMe_3), 29.78T (C-4), 32.66T (C-6), 47.35T (C-1), 63.71T (C-7), 72.56T(OCH_2Ph), 72.77D (C-2), 79.58D (C-3), 127.59D, 128.45D, 129.64D, 134.09S, 134.80D, 135.22D, 135.59D, 138.14S (aromatic carbons).

FAB-MS *m/z* 625 $[M+H]^+$. Exact mass: Calculated for $C_{36}H_{53}Si_2O_3Cl$, 625.3300; Observed, 625.3302.

6.3.2 Synthesis of the C(1)-C(9) unit of TA toxin: Use of the TBDPS protecting group



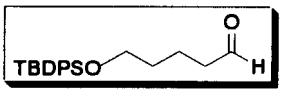
[5-(*t*-Butyldiphenylsilyl)oxy]-1-pentanol 174

NaH (60% dispersion, 2.65 g, 110 mmol) was washed with hexane (10 ml) and suspended in THF (10 ml). 1,5-Pentanediol (6.89 g, 66.2 mmol) in THF (7 ml) was added dropwise to this mixture at RT and stirred for 45 min at which a large amount of white precipitate had formed. The *t*-butyldiphenylsilyl chloride (20.0 g, 72.8 mmol) in THF (10 ml) was then added, and the reaction stirred for 90 min. Water (15 ml) was added and the THF was evaporated. The aqueous layer was extracted with CH_2Cl_2 (5x50 ml). The organic layer was then dried (Na_2SO_4), filtered and concentrated. The crude oil was purified by column chromatography on silica gel using EtOAc-hexane (1:1) as eluant to afford the mono-protected diol **174** as a colourless oil (12.3 g, 54 %); R_f 0.16 (EtOAc-hexane 1:5); ν_{max} 3337 cm^{-1}.

δ_H: 1.034 (s, 6H, $SiMe_2$)
1.40 (m, 2H, H-3)
1.49-1.63 (m, 4H, H-2 and H-4)
3.601 (t, 2H, $J_{1,2}$ 6.7, H-1)
3.656 (t, 2H, $J_{5,4}$ 6.5, H-5)
7.67-7.33 (m, 10H, ArH)

δ_C: 19.22S (CMe_3), 21.97T (C-3), 26.87Q (CMe_3), 32.26T (C-2)*, 32.46T (C-4)*, 62.95T (C-1), 63.79T (C-5), 127.61D, 129.53D, 134.06S, 135.59D (aromatic carbons).
* may be interchanged

FAB-MS *m/z* 343 $[M+H]^+$. Exact mass: Calculated for $C_{21}H_{31}O_2Si$, 343.2093; Observed, 343.2093.



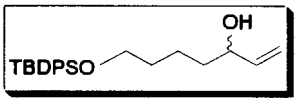
[5-(*t*-Butyldiphenylsilyl)oxy]pentanal 176

DMSO (4.89 g, 62.5 mmol) was added dropwise to a solution of oxalyl chloride (4.24 g, 33.4 mmol) in CH_2Cl_2 (20 ml) at –78°C under argon. After 15 min a solution of the alcohol **174** (10.2 g, 29.8 mmol) in CH_2Cl_2 (30 ml) was introduced dropwise and the solution was stirred for 90 min at –78°C. Triethylamine (15.1 g, 149 mmol) was slowly added and stirring continued for 4 hours. The cooling bath was then removed and the reaction mixture was allowed to reach RT. The white/yellow suspension was diluted with CH_2Cl_2 (200 ml) and washed with saturated NH_4Cl solution (200 ml) and water (100 ml). The organic solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:1) as eluant to afford the aldehyde **176** (10.1 g, 99 %) as a yellow oil; R_f 0.54 (EtOAc-hexane 2:1); ν_{max} 1727 cm^{-1}.

δ_H: 1.108 (s, 6H, $SiMe_2$)
1.63 (m, 2H, H-4)
1.77 (m, 2H, H-3)
2.415 (dt, 1H, $J_{2,1}$ 1.8, $J_{2,3}$ 7.2, H-2)
3.726 (t, 2H, $J_{5,4}$ 6.3, H-5)
7.37-7.45 (m, 6H, ArH)
7.72 (m, 10H, ArH)
9.748 (t, 1H, $J_{1,2}$ 1.8, H-1)

δ_C: 18.46T (C-3), 19.10S (CMe_3), 26.80Q (CMe_3), 31.75T (C-4), 43.37T (C-2), 63.20T (C-5), 127.65D, 129.51D, 133.87S, 135.44D (aromatic carbons), 202.24D (C-1).

FAB-MS *m/z* 341 $[M+H]^+$. Exact mass: Calculated for $C_{21}H_{29}O_2Si$, 341.1969; Observed, 341.1963.



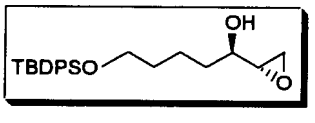
(3*RS*)-7-[(*t*-Butyldiphenylsilyl)oxy]hept-1-en-3-ol 178

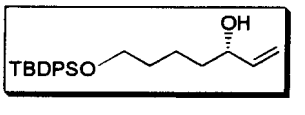
A solution of vinyl bromide (4.85 g, 45.3 mmol) in THF (10 ml) was added by syringe to a mixture of Mg turnings (79.2 mg, 32.6 mmol) in dry THF (30 ml). A crystal of iodine was used to initiate the reaction. After the addition of all of the vinyl bromide, the reaction mixture was heated for 30 min. Once all of the magnesium had been consumed, the mixture was cooled to 0°C and a solution of pentanal **176** (10.1 g, 29.6 mmol) in THF (20 ml) was added dropwise. After completion of the reaction (tlc), saturated NH_4Cl solution (50 ml) was added dropwise. The THF was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:5) as eluant to give the racemic allylic alcohol **178** as a yellow oil (8.30 g, 76 %); R_f 0.59 (EtOAc-hexane 1:2); ν_{max} 3360 and 1643 cm^{-1}.

δ_H: 1.063 (s, 6H, $SiMe_2$)
1.36-1.63 (m, 6H, H-4, H-5 and H-6)
3.683 (t, 2H, $J_{7,6}$ 6.3, H-7)
4.071 (dt, 1H, $J_{2,3}$ 6.2, $J_{3,4}$ 5.4, H-3)
5.090 (ddd, 1H, $J_{1b,2}$ 10.3, $J_{1b,3}$ 1.5, $J_{1b,1a}$ 1.3, H-1b)
5.206 (ddd, 1H, $J_{1a,2}$ 17.2, $J_{1a,3}$ 1.5, $J_{1a,1b}$ 1.3, H-1a)
5.848 (ddd, 1H, $J_{1a,2}$ 17.2, $J_{1b,2}$ 10.3, $J_{2,3}$ 6.2, H-2)
7.325-7.410 and 7.632-7.671 (m, 10H, ArH)

δ_C: 19.16S (CMe_3), 21.57T (C-5), 26.85Q (CMe_3), 32.35T (C-6), 36.66T (C-4), 63.75T (C-7), 73.06D (C-3), 114.46T (C-1), 127.53D, 129.47D, 134.05S, 135.53D (aromatic carbons), 141.21D (C-2).

FAB-MS *m/z* 369 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{33}O_2Si$, 369.2250; Observed, 369.2249.





(2*S*,3*R*)-7-[(*t*-Butyldiphenylsilyl)oxy]-1,2-epoxy-3-heptanol 180 and (3*S*)-7-[(*t*-butyldiphenylsilyl)oxy]-1-hepten-3-ol 184

A solution of (S,S)-diisopropyl D-tartrate (1.43 g, 6.11 mmol) in CH_2Cl_2 (10 ml) was added by syringe to suspension of powdered 4Å molecular sieves (6.0 g) in CH_2Cl_2 (20 ml) at –20°C under argon. $Ti(^iPrO)_4$ (1.48 g, 5.19 mmol) was then added by syringe followed by a solution of TBHP (3.1M in toluene, 6.0 mmol, 1.9 ml). The resulting reaction mixture was stirred for 30 min at –20°C before the racemic allylic alcohol **178** (3.72 g, 10.1 mmol) in CH_2Cl_2 (30 ml) was added dropwise. The reaction mixture was stirred at –20°C for 2 h and then at –10°C in the freezer for 18 h. The solution was allowed to reach 0°C, filtered, and a fresh solution of iron(III) sulfate (4.2 g) and tartaric acid (2.0 g) in water (50 ml) pre-cooled to 0°C was added to the solution with continuous stiming. The resulting mixture was filtered through a Celite pad in order to break the emulsion. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5x50 ml). The combined organic layer was vigorously stirred in brine solution containing NaOH (15%, 400 ml) for 1 h at 0°C and diluted with water (100 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 ml). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography using EtOAc-hexane (1:2) to afford the (3*S*)-allylic alcohol **184** (1.37 g, 37 %) and the epoxy alcohol **180** (1.45 g, 37 %); R_f 0.24 (EtOAc-hexane 1:2); ν_{max} 3453 cm^{-1}.

δ_H: 1.304 (s, 6H, $SiMe_2$)
1.46-1.62 (m, 6H, H-4, H-5 and H-6)
1.792 (bs, 1H, J 2.9, OH)
2.670 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1b,2}$ 3.9, H-1b)
2.778 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 2.6, H-1a)
2.970 (ddd, 1H, $J_{2,1b}$ 4.0, $J_{2,3}$ 3.0, $J_{2,1a}$ 2.9, H-2)
3.677 (t, 2H, $J_{6,7}$ 6.1, H-7)
3.80 (br m, 1H, H-3)
7.33-7.42 and 7.64-7.68 (m, 10H, ArH)

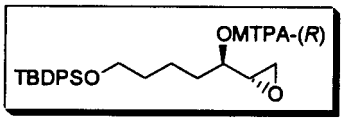
δ_C: 19.21S (CMe_3), 21.59T (C-5), 26.87Q (CMe_3), 32.46T (C-6)*, 33.13T (C-4)*, 43.34T (C-1), 54.44D (C-2), 63.72T (C-7), 68.37D (C-3), 127.59D, 129.53D, 134.06S, 135.57D (aromatic carbons).
* may be interchanged

FAB-MS: *m/z* 385 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{33}O_3Si$, 385.2199; Observed, 385.2198.

MOSHER ESTER DERIVATIZATION

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

Oxalyl chloride (188 mg, 1.48 mmol) was added to a solution of (*R*)-(+)-MTPA (e.e ≥ 99%, 102 mg, 0.436 mmol) and DMF (40 mg, 0.547 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 evaporated to yield the acid chloride (MTPACl) (104 mg, 95 %).



b. (2*S*,3*R*)-1,2-Epoxy-7-[(*t*-butyldiphenylsilyl)oxy]-3-heptyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate 186

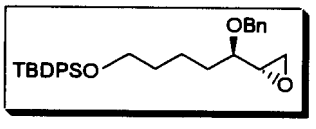
A solution of MTPACl (104 mg, 0.412 mmol) in CH_2Cl_2 (5 ml) was added to a stirred solution of epoxy alcohol **180** (64 mg, 0.247 mmol), triethylamine (75.0 mg, 0.742 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at room temperature. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl followed by saturated $NaHCO_3$ solution, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **186** (88 mg, 45 %) as a yellow oil; R_f 0.63 (EtOAc-hexane 1:2); ν_{max} 1753 cm^{-1}.

δ_H: 1.0048 (s, 6H, $SiMe_2$)
1.37 (m, 2H, H-5)
1.52 (m, 2H, H-6)
1.715 (dt, 2H, $J_{4,5}$ 8.0, $J_{4,3}$ 6.2, H-4)
2.712 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1b,2}$ 2.6, H-1b)
2.730 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 3.6, H-1a)
3.035 (ddd, 1H, $J_{2,3}$ 4.4, $J_{1a,2}$ 3.6, $J_{1b,2}$ 2.6, H-2)
3.546 (q, 3H, $J_{H,F}$ 1.3, OMe)
3.597 (t, 3H, $J_{7,6}$ 6.2, H-7)
5.082 (dt, 1H, $J_{2,3}$ 4.4, $J_{3,4}$ 6.2, H-3)
7.31-7.44, 7.50-7.54 and 7.62-7.67 (m, 15H, ArH)

δ_C: 19.19S (CMe_3), 21.07T (C-5), 26.86Q (CMe_3), 30.96T (C-6), 32.13T (C-4), 44.63T (C-1), 51.81D (C-2), 55.39Q (OMe), 63.51T (C-7), 74.32D (C-3), 123.34S ($J_{C,F}$ 289 Hz, CF_3), 127.33D, 127.63D, 128.37D, 129.07S, 129.59D, 132.28S, 133.97S, 135.55D (aromatic carbons), 166.03S (CO).

δ_F: –71.81

FAB-MS: *m/z* 601 $[M+H]^+$. Exact mass: Calculated for $C_{33}H_{40}F_3O_5Si$, 601.2597; Observed, 601. 2597.



(2*S*, 3*R*)-3-Benzyloxy-7-[(*t*-butyldiphenylsilyl)oxy]-1,2-epoxyheptane 195

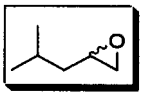
A solution of epoxy alcohol **180** (250 mg, 0.65 mmol), benzyl bromide (124 mg, 0.73 mmol) and TBAI (26.0 mg, 65.5 mmol) in DMF (5 ml) were added to suspension of NaH (60% dispersion, 28.6 mg, 1.19 mmol) in THF (5 ml) under argon at 0°C. The reaction was allowed to reach RT within 2 h and further stirred overnight. The excess BnBr was destroyed by addition of methanol. After stirring for 30 min the reaction mixture was diluted with water (10 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (5x10 ml). The diethyl ether solution was washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using first hexane and subsequently EtOAc-hexane (1:1) as eluant to afford the benzyl ether **195** (31 mg, 48 %); R_f 0.41 (EtOAc-hexane 1:5).

δ_H: 1.035 (s, 9H, Me_3C)
1.43-1.65 (m, 6H, H-4, H-5 and H-6)
2.695 (dd, 1H, $J_{1b,1a}$ 5.4, $J_{b,2}$ 2.6, H-1b)
2.755 (dd, 1H, $J_{1a,1b}$ 5.4, $J_{1a,2}$ 3.9, H-1a)
2.898 (ddd, 1H, $J_{2,3}$ 5.4, $J_{2,1a}$ 3.9, $J_{2,1b}$ 2.6, H-2)
3.238 (m, 1H, $J_{4,5}$ 6.5, $J_{2,3}$ 5.4, H-3)
3.649 (t, 2H, $J_{8,7}$ 6.2, H-7)
4.475 (d, 1H, J 11.6, OCH_2Ph)
4.630 (d, 1H, J 11.6, OCH_2Ph)

7.30-7.41 and 7.60-7.63 (m, 15H, ArH)

δ_C: 19.21S (CMe_3), 21.59T (C-5), 26.88Q (CMe_3), 32.56T (C-6)*, 32.61T (C-4)*, 45.53T (C-1), 53.53D (C-2), 63.50T (C-7), 72.34T (OCH_2Ph), 78.04D (C-3), 127.59D, 128.35D, 129.03D, 129.50D, 135.58D, 130.33S, 134.12S and 142.64S (aromatic carbons).

FAB-MS: *m/z* 475 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{39}O_3Si$, 475.2668; Observed, 475.2667.



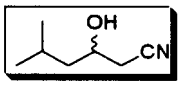
(2*RS*)-1,2-Epoxy-4-methylpentane 201

4-Methyl-1-pentene (7.00 g, 83.2 mmol) was added by syringe to a solution of MCPBA (28.7 g, 170 mmol) in CH_2Cl_2 (400 ml) at RT. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and carefully evaporated to minimize losses due to volatility of the epoxide **201** (1.90 g, 23 %).

δ_H: 0.951 (d, 3H, $J_{5,4}$ 6.7, H-5*)
0.959 (d, 3H, $J_{6,4}$ 6.7, H-6*)
1.348 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3b,4}$ 7.5, $J_{3b,2}$ 5.4, H-3b)
1.421 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3a,2}$ 6.5, $J_{3a,4}$ 6.5, H-3a)
1.812 (m, 2H, H-4)
2.414 (dd, 1H, $J_{1a,2}$ 2.6, $J_{1a,1b}$ 5.2, H-1a)
2.736 (dd, 1H, $J_{1b,2}$ 3.9, $J_{1b,1a}$ 5.2, H-1b)
2.905 (m, 1H, $J_{3a,2}$ 6.5, $J_{3b,2}$ 5.4, $J_{1b,2}$ 3.9, $J_{1a,2}$ 2.6, H-2)
*may be exchanged

δ_C: 22.39Q (C-5*), 22.91Q (C-6*), 26.39D (C-4), 41.58T (C-3), 47.13T (C-1), 51.21D (C-2).
*may be interchanged

FAB-MS *m/z* 101 $[M+H]^+$. Exact mass: Calculated for $C_6H_{13}O$, 101.0966; Observed, 101.0967.



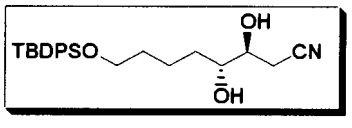
(3*RS*)-3-Hydroxy-5-methyl-pentanenitrile 202

KCN (163 mg, 2.50 mmol), TBAI (0.01 mmol, 44.0 mg) and Ti(^{i}PrO)$_4$ (2.57 mmol, 731 mg) were added to a stirred solution of epoxide **201** (100 mg, 0.10 mmol,) in dried DMSO (10 ml) at RT under argon. The reaction was stirred for 2 days and was then quenched with saturated NH_4Cl solution (10 ml). The aqueous layer was extracted with EtOAc (5x20 ml). The EtOAc solution was dried (Na_2SO_4), filtered and evaporated to give nitrile **202** as a colourless volatile oil (20 mg, 16 %).

δ_H: 0.899 (d, 3H, $J_{7,5}$ 6.5, H-6)
0.911 (d, 3H, $J_{6,5}$ 6.5, H-7)
1.309 (dddd, H, $J_{4b,4a}$ 14.0, $J_{4b,5}$ 8.8, $J_{4b,3}$ 4.4, H-4b)
1.521 (dddd, H, $J_{4a,5}$ 5.4, $J_{3,4a}$ 9.1, $J_{4a,4b}$ 14.0, H-4a)
1.74 (m, 1H, H-5)
2.432 (dd, 1H, $J_{2b,3}$ 6.2, $J_{2b,2a}$ 16.8, H-2b)
2.514 (dd, 1H, $J_{2a,3}$ 4.9, $J_{2a,2b}$ 16.8, H-2a)
3.974 (m, H, $J_{3,4a}$ 9.1, $J_{2b,3}$ 6.2, $J_{2a,3}$ 4.9, $J_{4b,3}$ 4.4, H-3)

δ_C: 21.72Q (C-7), 22.98Q (C-6), 24.40D (C-5), 26.47T (C-4), 45.40T (C-2), 65.68D (C-3), 117.81S (C-1).

FAB-MS: *m/z* 127 $[M+H]^+$. Exact mass: Calculated for $C_7H_{13}NO$, 127.0997; Observed, 127.0997.



(3*S*, 4*R*)-[8-(*t*-Butyldiphenylsilyl)oxy]-3,4-dihydroxy-octanenitrile 203

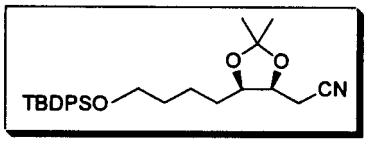
KCN (210 mg, 3.22 mmol) and Ti(*i*PrO)$_4$ (940 mg, 3.33 mmol) were added to a stirred solution of epoxy alcohol **180** (496 mg, 1.29 mmol) in DMSO (5 ml) under argon. The reaction mixture was stirred for 75 min at RT (tlc). The reaction mixture was then diluted with EtOAc (50 ml) and poured into 1M HCl (20 ml) (CAUTION: HCN gas is produced) forming a white precipitate. The white precipitate was removed by filtration and the aqueous filtrate extracted with EtOAc (5x 50 ml). The EtOAc solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with EtOAc-

hexane (1:1) as eluant to afford the nitrile **203** as a colourless oil (421 mg, 80 %); R_f 0.07 (EtOAc-hexane 1:2); $[\alpha]_D$ –0.7 (*c* 0.76, $CHCl_3$); ν_{max} 3438, 2255 cm^{-1}.

δ_H: 1.061 (s, 9H, CMe_3)
1.26-1.65 (m, 6H, H-5, H-6 and H-7)
2.514 (dd, 1H, $J_{2a,2b}$ 16.8, $J_{2a,3}$ 4.4, H-2a)
2.589 (dd, 1H, $J_{2b,2a}$ 16.8, $J_{2b,3}$ 7.8, H-2b)
3.621 (dt, 1H, $J_{3,4}$ 4.4, $J_{4,5}$ 4.1, H-4)
3.683 (t, 2H, $J_{8,7}$ 6.2, H-8)
3.786 (ddd, 1H, $J_{3,2a}$ 7.8, $J_{3,2b}$ 4.4, $J_{3,4}$ 4.4, H-3)
7.34-7.45 and 7.64-7.69 (m, 10H, ArH)

δ_C: 19.16S (CMe_3), 20.88T (C-2), 21.92T (C-6), 26.86Q (CMe_3), 32.06T (C-7)*, 32.13T (C-5)*, 63.58T (C-8), 70.39D (C-3), 73.42D (C-4), 118.50S (C-1), 127.59D, 129.56D, 133.90S, 135.50D (aromatic carbons).

FAB-MS *m/z* 412 $[M+H]^+$. Exact mass: Calculated for $C_{24}H_{34}NO_3Si$, 412.2308; Observed, 412.2308.



(3*S*,4*R*)-3,4-*O*,*O*-Isopropylidene-[8-(*t*-butyldiphenylsilyl)oxy]-octanenitrile 213

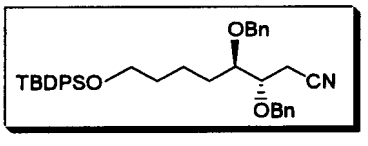
p-Toluenesulfonic acid (50 mg) was added to a solution of the nitrile **203** (383 mg, 0.93 mmol) in 2,2-dimethoxypropane (2.06 g, 19.8 mmol) at RT. After 90 min an excess of Et_3N (1.40 g, 14.0 mmol) was added and reaction mixture partitioned between water and diethyl ether. The diethyl ether solution was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:5) as eluant to afford the acetonide **213** as a colourless oil (340 mg, 80%); R_f 0.22 (EtOAc-hexane 1:5); ν_{max} 2251 cm^{-1}.

δ_H: 1.044 (s, 9H, CMe_3)
1.331 (s, 3H, acetonide Me)
1.459 (s, 3H, acetonide Me)
1.38-1.60 (m, 6H, H-5, H-6 and H-7)
2.386 (dd, 1H, $J_{2b,2a}$ 16.7, $J_{2b,3}$ 6.1, H-2b)

2.407 (dd, $J_{2a,2b}$ 16.7, $J_{2a,3}$ 6.4, H-2a)
3.676 (t, 2H, $J_{8,7}$ 6.1, H-8)
4.12 (m, 1H, H-4)
4.238 (ddd, 1H, $J_{2a,3}$ 6.4, $J_{2b,3}$ 6.1, $J_{3,4}$ 5.7, H-3)
7.67-7.33 (m, 10H, ArH)

δ_C: 19.22S (CMe_3), 20.06T (C-2), 22.81T (C-6), 25.45Q (CMe_2), 26.89Q (CMe_3), 28.13Q (CMe_2), 28.58T (C-7), 32.22T (C-5), 63.47T (C-8), 73.43D (C-3), 77.17D (C-4), 108.93S (CMe_3), 117.34S (C-1), 127.62D, 129.58D, 134.01S and 135.57D (aromatic carbons).

FAB-MS *m/z* 452 $[M+H]^+$. Exact mass: Calculated for $C_{27}H_{38}NO_3Si$, 451.2621; Observed, 452.2621.



(3*S*,4*R*)-[8-(*t*-Butyldiphenylsilyl)oxy]-3,4-dibenzyloxy-octanenitrile 214

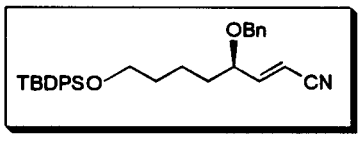
BnBr (470 mg, 2.74 mmol), TBAI (38.0 mg, 0.10 mmol) and nitrile **203** (418 mg, 1.03 mmol) in THF (5 ml) were added to NaH (60% dispersion, 91 mg, 3.79 mmol) in THF (5 ml) at –20°C under argon. The reaction mixture was stirred for 7 h. The reaction mixture was then diluted with water (5 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (7x20 ml). The diethyl ether solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:15) as eluant to afford the dibenzylated nitrile **214** as an oil (294 mg, 48%); R_f 0. 53 (EtOAc-hexane 1:2); $[\alpha]_D$ –2.9 (*c* 1.3, $CHCl_3$); ν_{max} 2250 cm^{-1} and the α,β-unsaturated compound **215** as by-product.

δ_H: 1.054 (s, 9H, CMe_3)
1.39-1.60 (m, 6H, H-5, H-6 and H-7)
2.601 (dd, 1H, $J_{2a,2b}$ 16.9, $J_{2a,3}$ 6.3, H-2a)
2.679 (dd, 1H, $J_{2b,2a}$ 16.9, $J_{2b,3}$ 4.2, H-2b)
3.583 (dt, 1H, $J_{3,4}$ 5.1, $J_{4,5}$ 6.1, H-4)
3.642 (t, 2H, $J_{7,8}$ 6.1, H-8)

3.659 (ddd, 1H, $J_{2a,3}$ 6.3, $J_{2b,3}$ 4.2, $J_{3,4}$ 5.1, H-3)
4.579 (d, 1H, J 11.3, OCH_2Ph)
4.590 (d, 1H, J 11.6, OCH_2Ph)
4.610 (d, 1H, J 11.4, OCH_2Ph)
4.691 (d, 1H, J 11.6, OCH_2Ph)
7.69-7.25 (m, 20H, ArH)

δ_C: 19.23S (CMe_3), 19.52T (C-2), 21.41T (C-6), 26.91Q (CMe_3), 30.57T (C-7), 32.63T (C-5), 63.70T (C-8), 72.66T (OCH_2Ph), 72.89T (OCH_2Ph), 76.95D (C-3), 79.11D (C-4), 118.200S (C-1), 127.63D, 127.81D, 127.96D, 128.02D, 128.07D, 128.44D, 129.58D, 134.053S, 135.58D, 137.300S and 138.07D (aromatic carbons).

FAB-MS *m/z* 591 $[M]^+$. Exact mass: Calculated for $C_{38}H_{45}NO_3Si$, 591.3169; Observed, 591.3169.



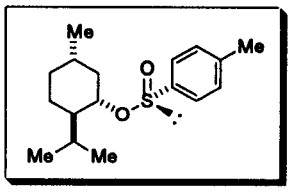
(4*R*)-[8-(*t*-Butyldiphenylsilyl)oxy]-4-benzyloxy-2-octenenitrile 215

δ_H: 1.000 (s, 9H, CMe_3)
1.35-1.55 (m, 6H, H-5, H-6 and H-7)
3.628 (t, 2H, $J_{8,7}$ 6.0 Hz, H-8)
3.894 (ddd, 1H, $J_{4,2}$ 1.6 Hz, $J_{4,5}$ 5.2 Hz, $J_{4,3}$ 5.5 Hz, H-4)
4.383 (d, 1H, J 11.8 Hz, OCH_2Ph)
4.513 (d, 1H, J 11.8 Hz, OCH_2Ph)
5.552 (dd, $J_{2,3}$ 16.5 Hz, $J_{2,4}$ 1.6 Hz, H-2)
6.617 (dd, $J_{3,2}$ 16.5 Hz, $J_{3,4}$ 5.6 Hz, H-3)
7.27-7.40 and 7.60-7.65 (m, 15H, ArH)

δ_C: 19.20S (CMe_3), 21.35T (C-6), 26.87Q (CMe_3), 32.21T (C-7)*, 34.21T (C-5)*, 63.51T (C-8), 71.46T (OCH_2Ph), 77.94D (C-4), 100.13D (C-2), 117.00S (C-1), 127.61D, 127.67D, 129.57D, 133.98S, 135.55D, 137.56S (aromatic carbons), 155.03D (C-3).
*may be interchanged

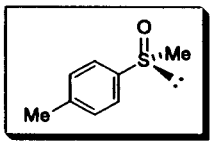
FAB-MS *m/z* 484 $[M]^+$. Exact mass: Calculated for $C_{31}H_{38}NO_2Si$, 484.2672; Observed, 484.2672.

6.3.2.1 Use of chiral sulfoxides



(1*R*,2*S*,5*R*)-(–)-Menthyl (*S*)-*p*-toluenesulfinate 163

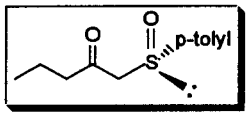
The powdered sodium salt of anhydrous *p*-toluenesulfinic acid (80.0 g, 0.44 mol) was added in small portions to a solution of thionyl chloride (1.40 mol, 100 ml) in benzene (300 ml) at 0°C. The solution was allowed to reach RT after which the solution was concentrated by distilling benzene and thionyl chloride. Excess thionyl chloride was removed by addition of benzene (200 ml) and evaporation under reduced pressure. The residue was diluted with anhydrous diethyl ether (500 ml) (formation of a white precipitate of sodium chloride) and cooled to 0°C. A solution of (–)-menthol (69.4 g, 0.440 mol) in pyridine (70 ml) was added dropwise. After the addition was complete the mixture was stirred for 1 h at RT and hydrolysed with water (200 ml). The organic layer was washed with 10% HCl (200 ml) and saturated brine (100 ml), dried over Na_2SO_4 and concentrated. The residue was diluted with acetone (200 ml), ~5 drops 10M HCl added, and allowed to crystallise at –20°C. After the filtration of the first crop of crystals, the mother liquor was concentrated to ~50 ml, 1 drop 10M HCl added and again allowed to crystallise at –20°C. This operation was repeated 3-4 times in total. Hexane was used to dilute the increasingly viscous mother liquor to improve crystallisation. The combined crops were finally recrystallised from hot acetone to give the pure (*S*)-sulfinate **163** as a white crystalline material (102.5 g, 78%); mp 108-109 °C (Lit[2] 105-107 °C), $[\alpha]_D^{21}$ –199 (*c* 2.5, acetone), [Lit.[3] $[\alpha]_D^{21}$ –201 (*c* 2.0, acetone)]; R_f 0.90 (EtOAc).



[2] Anderson, K.K.; Gaffield, W.; Papanikolaou, N.E.; Foley, N.E.; Perkins, J.W. *J. Am. Chem. Soc.*, **1964**, *86*, 5637.
[3] Anderson, K.K. *Tetrahedron Lett.*, **1962**, 93.

(*R*)-(+)-Methyl *p*-tolylsulfoxide 103

A solution of methyl magnesium iodide [prepared from iodomethane (40.6 g, 286 mmol), and magnesium (5.96 g, 245 mmol)] in diethyl ether (250 ml) was slowly added to a solution of (–)-(*S*)-menthyl-*p*-toluenesulfinate **163** (60.0 g, 204 mmol) in anhydrous benzene (200 ml) between 0–10°C. After addition, the mixture was stirred at room temperature for 2 h and then hydrolyzed with saturated aq. NH_4Cl solution (200 ml). The aqueous solution was extracted with EtOAc (3 x 100 ml). The organic layers were washed with saturated brine (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was mixed with hot hexane till formation of a light white cloudy precipitate. Crystallization occurred overnight on cooling to –5°C. The crystals were recrystallised from ether-hexane at –5°C affording white crystals (22.9 g, 73%); mp 74.5-75.5°C (Lit.[4] 73-74.5°C); $[\alpha]_D^{21}$ +192 (*c* 4.0, $CHCl_3$), (Lit.[5,6] $[\alpha]_D^{21}$ +192, (*c* 1.2, $CHCl_3$)), $[\alpha]_D^{15}$ +146 (*c* 2.0, acetone), (Lit.[4] $[\alpha]_D^{21}$ +145.5);



(S(*R*)-1-(*p*-Tolylsulfinyl)-2-pentanone 171

n-Butyl lithium (1.6M in hexane, 1.43 mmol, 0.89 ml) was added by syringe to a solution of diisopropylamine (1.43 mmol, 144 mg) in dry THF (5 ml) at –40°C under argon. After 30 min a solution of (+)-(*R*)-methyl p-tolyl sulfoxide **103** (1.30 mmol, 200 mg) in THF (5 ml) was added to the reaction mixture at –40°C. After 30 min the reaction mixture was allowed to warm to 0°C and butyronitrile (0.66 mmol, 45.0 mg) in THF (5 ml) was added by syringe and the reaction was allowed to reach RT. After 1 h the reaction was quenched with water (2 ml), the THF-hexane solvent was evaporated and the aqueous residue was diluted with saturated NH_4Cl solution (20 ml). The pH was adjusted to 3 using 1M HCl and extracted with CH_2Cl_2 (3x20 ml). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography by using EtOAc-hexane (1:5) as eluant to afford the white crystalline product **171** (85 mg, 58 %); R_f 0.44 (EtOAc-hexane 1:5); ν_{max} 1713 cm^{-1}.

δ_H: 0.828 (t, 3H, $J_{4,5}$ 7.5, H-5)

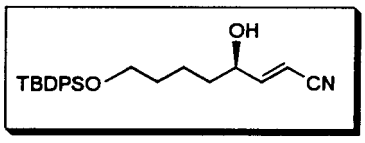
---

[4] Mislow, K.; Green, M.M.; Laur, P.; Melillo, J.T.; Simmons, T.; Ternay, A.L. *J. Am. Chem. Soc.*, **1968**, *90*, 4835.
[5] Solladié, G.; Hutt, J.; Girardin, A. *Synthesis*, **1987**, 173.
[6] Solladié, G. *Synthesis*, **1981**, 185.

1.516 (tq, 2H, $J_{4,5}$ 7.5, $J_{4,3}$ 7.5, H-4)
2.370 (s, 3H, methyl)
2.485 (t, 2H, $J_{4,3}$ 7.5, H-3)
3.691 (d, 1H, J 13.6, H-1a)
3.813 (d, 1H, J 13.6, H-1b)
7.27-7.51 (m, 4H, ArH)

δ_C: 13.44Q (C-5), 16.56T (C-4), 21.39Q (methyl), 46.81T (C-3), 68.18T (C-1), 124.06D, 130.08D, 139.90S, 142.12S (aromatic carbons), 201.64S (CO).

FAB-MS: *m/z* 225 $[M+H]^+$. Exact mass: Calculated for $C_{12}H_{21}O_2Si$, 225.0949; Observed, 225.0949.



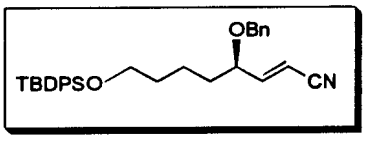
(4*R*)-[8-(*t*-Butyldiphenylsilyl)oxy]-4-hydroxy-2-octenenitrile 216

n-Butyl lithium (1.6M in hexane, 0.458 mmol, 0.3 ml) was added by syringe to a solution of diisopropylamine (0.458 mmol, 46 mg) in dry THF (5 ml) at –40°C under argon. After 30 min a solution of (+)-(*R*)-methyl p-tolyl sulfoxide (0.42 mmol, 64 mg) in THF (5 ml) was added to the reaction mixture at –40°C. After 30 min the reaction mixture was allowed to warm to 0°C and nitrile **213** (0.210 mmol, 94 mg) in THF (5 ml) was added by syringe and the reaction was allowed to reach RT. After 1 h the reaction was quenched with water (2 ml), the THF-hexane solvent was evaporated and the aqueous residue was diluted with saturated NH_4Cl solution (20 ml). The pH was adjusted to 3 using 1M HCl and extracted with CH_2Cl_2 (3x20 ml). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue with hexane-EtOAc (9:1) as eluant gave the α,β-unsaturated nitrile **216** as an oil.

δ_H: 1.055 (s, 9H, CMe_3)
1.4-1.7 (m, 6H, H-5, H-6 and H-7)
1.525 (br, 1H, OH)
3.678 (t, 2H, $J_{8,7}$ 6.1 Hz, H-8)
4.245 (br, 1H, H-4)
5.628 (dd, $J_{2,3}$ 16.2 Hz, $J_{2,4}$ 2.0 Hz, H-2)

6.688 (dd, $J_{3,2}$ 16.2 Hz, $J_{3,4}$ 4.0 Hz, H-3)
7.35-7.67 (m, 10H, ArH)

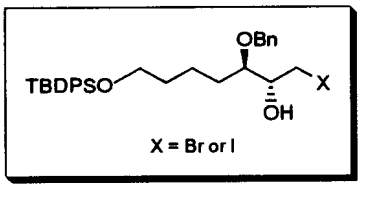
δ_C: 19.16S (CMe_3), 21.43T (C-6), 26.85Q (CMe_3), 31.96T (C-7)*, 35.88T (C-5)*, 63.47T (C-8), 70.83D (C-4), 98.67D (C-2), 117.28S (C-1), 127.61D, 129.59D, 133.86S, 135.52D (aromatic carbons),156.58D (C-3).
* maybe interchanged



(4*R*)-[8-(*t*-Butyldiphenylsilyl)oxy]-4-benzyloxy-2-octenenitrile 215

n-Butyl lithium (1.6M in hexane, 1.093 mmol, 0.68 ml) was added by syringe to a solution of diisopropylamine (1.093 mmol, 111 mg) in dry THF (5 ml) at –40°C under argon. After 30 min a solution of (+)-(*R*)-methyl p-tolyl sulfoxide (0.99 mmol, 153 mg) in THF (5 ml) was added to the reaction mixture at –40°C. After 30 min the reaction mixture was allowed to warm to 0°C and nitrile **214** (0.497 mmol, 29.4 mg) in THF (5 ml) was added by syringe and the reaction was allowed to reach RT. After 1 h the reaction was quenched with water (2 ml), the THF-hexane solvent was evaporated and the aqueous residue was diluted with saturated NH_4Cl solution (20 ml). The pH was adjusted to 3 using 1M HCl and extracted with CH_2Cl_2 (3x20 ml). The CH_2Cl_2 solution was dried (Na_2SO_4), filtered and evaporated. Column chromatography of the residue with hexane-EtOAc (9:1) as eluant gave the α,β-unsaturated nitrile **215** as an oil.

6.3.2.2 Copper(I) catalysed opening of epoxides



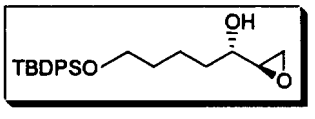
(2*R*,3*R*)-3-Benzyloxy-1-bromo- and (2*R*,3*R*)-3-benzyloxy-1-iodo-2-[(*t*-butyldimethylsilyl)-oxy]-7-[(*t*-butyldiphenylsilyl)oxy]-heptane 208

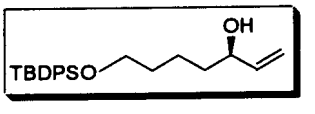
A solution of vinyl bromide (120 mg, 1.13 mmol) in THF (2 ml) was added by syringe to a mixture of Mg turnings (24 mg, 0.10 mmol) in dry THF (5 ml). A crystal of iodine was used to initiate the reaction. After the addition of all of the vinyl bromide, the reaction mixture was

heated for 30 min. Once all of the magnesium had been consumed, the mixture was cooled to 0°C and copper(I) iodide (14.3 mg, 0.08 mmol) was added. The reaction mixture was stirred at 0°C for 30 min before a solution of benzyl ether **195** (360 mg, 0.75 mmol) in THF (5 ml) was added slowly. After completion of the reaction (tlc), the reaction mixture was allowed to warm to RT and saturated NH_4Cl solution (10 ml) was added dropwise. The THF was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography of the residue using EtOAc-hexane (1:9) as eluant afforded **208** as a mixture of bromo- and iodohydrin in 59 % yield.

δ_C: 11.82T (C-1), 19.22S (CMe_3), 21.33T (C-5), 26.89Q (CMe_3), 29.46T and 29.76T (C-6), 32.65T (C-4), 37.20T (C-1), 63.70T (C-7), 72.47D (C-2), 72.52T (C-2), 72.57D (OCH_2Ph), 80.12D and 80.90D (C-3), 127.59D, 127.80D, 127.86D, 128.45D, 129.53D, 134.09S, 135.57D, 138.12S (aromatic carbons).

6.3.3 Synthesis of the *ent*-C_7 unit of TA toxin: (2*S*,3*S*)-3-benzyloxy-1-chloro-2-[*t*-butyldimethylsilyl)oxy]-7-[*t*-butyldiphenylsilyl)oxy]-heptane





(2*R*,3*S*)-7-[(*t*-Butyldiphenylsilyl)oxy]-1,2-epoxy-3-heptanol 191 and (3*R*)-7-[(*t*-butyldiphenylsilyl)oxy]-1-hepten-3-ol 192

A solution of (*R*,*R*)-diisopropyl L-tartrate (4.68 g, 20.0 mmol) in CH_2Cl_2 (100 ml) was added by syringe to suspension of powdered 4Å molecular sieves (8.0 g) in CH_2Cl_2 (100 ml) at –20°C under argon. Ti(*i*PrO)$_4$ (4.83 g, 17.0 mmol) was then added by syringe followed by a solution of TBHP (3.1M in toluene, 19.8 mmol, 6.3 ml). The resulting reaction mixture was stirred for 30 min at –20°C before the non-racemic allylic alcohol* **183** (12.2 g, 32.9 mmol) in CH_2Cl_2 (30 ml) was added dropwise. The reaction mixture was stirred at –20°C for 2 h and then at –10°C in the freezer for 18 h. The solution was allowed to reach 0°C, filtered, and a fresh solution of iron(III) sulfate (14.0 g) and tartaric acid (8.0 g) in water (50 ml) pre-cooled to 0°C, was added to the solution with continuous stirring. The resulting mixture was then filtered through a Celite pad in order to break the emulsion. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5x50 ml). The combined organic layer was vigorously stirred in brine solution containing NaOH (15%, 400 ml) for 1 h at 0°C and diluted with water (100 ml). The

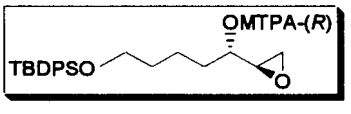
phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 ml). The combined organic layer was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography using EtOAc-hexane (1:2) to afford the (3*R*)-allylic alcohol **192** (5.90 g, 49 %) and the epoxy alcohol **191** (5.30 g, 42 %); R_f 0.24 (EtOAc-hexane 1:2); $[\alpha]_D$ +8.2 (*c* 1.3, $CHCl_3$); ν_{max} 3453 cm^{-1}.

* obtained from earlier Sharpless epoxidation/kinetic resolution experiments

δ_H: 1.043 (s, 6H, $SiMe_2$)
1.44-1.65 (m, 6H, H-4, H-5 and H-6)
1.785 (bs, 1H, J 2.9, OH)
2.697 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1b,2}$ 3.9, H-1b)
2.778 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 2.6, H-1a)
2.966 (ddd, 1H, $J_{1b,2}$ 4.0, $J_{2,3}$ 3.0, $J_{1a,2}$ 2.9, H-2)
3.677 (t, 2H, $J_{7,6}$ 6.1, H-7)
3.80 (br m, 1H, H-3)
7.33-7.44 (m, 6H, ArH)
7.64-7.68 (m, 4H, ArH)

δ_C: 19.21S (CMe_3), 21.59T (C-5), 26.87Q (CMe_3), 32.46T (C-6)*, 33.13T (C-4)*, 43.34T (C-1), 54.44D (C-2), 63.72T (C-7), 68.37D (C-3), 127.59D, 129.53D, 134.06S, 135.57D (aromatic carbons).
*may be interchanged

FAB-MS: *m/z* 385 $[M+H]^+$. Exact mass: Calculated for $C_{23}H_{33}O_3Si$, 385.2199; Observed, 385.2198.



(2*R*,3*S*)-1,2-Epoxy-7-[(*t*-butyl diphenylsilyl)oxy]-3-heptyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate 193

A solution of MTPACl (75 mg, 0.23 mmol) [prepared from (*R*)-(+)-MTPA (100 mg, 0.44 mmol) as earlier] in CH_2Cl_2 (5 ml) was added to a stirred solution of epoxy alcohol **191** (44 mg, 0.11 mmol), triethylamine (34.0 mg, 0.27 mmol) and DMAP (5.0 mg) in CH_2Cl_2 (5 ml) at room temperature. The reaction mixture was quenched after 15 h with H_2O (2 ml) and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with 0.5M HCl followed by saturated $NaHCO_3$

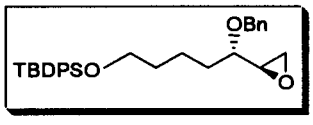
solution, then dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using EtOAc-hexane (1:2) to afford the Mosher ester **193** (35.0 mg, 52 %) as a yellow oil; R_f 0.63 (EtOAc-hexane 1:2); ν_{max} 1753 cm^{-1}.

δ_H: 1.037 (s, 6H, $SiMe_2$)
1.40-1.63 (m, 4H, H-5 and H-6)
1.76 (dt, 2H, $J_{4,5}$ 8.0, $J_{4,3}$ 6.2, H-4)
2.597 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1b,2}$ 2.6, H-1b)
2.657 (dd, 1H, $J_{1a,1b}$ 5.2, $J_{1a,2}$ 3.6, H-1a)
2.921 (ddd, 1H, $J_{2,3}$ 4.4, $J_{1a,2}$ 3.6, $J_{1b,2}$ 2.6, H-2)
3.539 (q, 3H, $J_{H,F}$ 1.3, OMe)
3.644 (t, 3H, $J_{7,6}$ 6.2, H-7)
4.982 (dt, 1H, $J_{2,3}$ 4.4, $J_{3,4}$ 6.2, H-3)
7.31-7.66 (m, 15H, ArH)

δ_C: 19.19S (CMe_3), 21.45T (C-5), 26.85Q (CMe_3), 31.22T (C-6), 32.20T (C-4), 44.83T (C-1), 51.74D (C-2), 55.46Q (OMe), 63.48T (C-7), 74.88D (C-3), 123.30S ($J_{C,F}$ 289 Hz, CF_3), 127.30D, 127.61D, 127.84D, 128.34D, 129.56D, 132.25S, 133.94S and 135.52D (aromatic carbons), 166.00S (CO).

δ_F: –71.92

FAB-MS: *m/z* 601 $[M+H]^+$. Exact mass: Calculated for $C_{33}H_{40}F_3O_5Si$, 601.2597; Observed, 601.2597.



(2*R*,3*S*)-3-Benzyloxy-7-[(*t*-butyldiphenylsilyl)oxy]-1,2-epoxyheptane 196

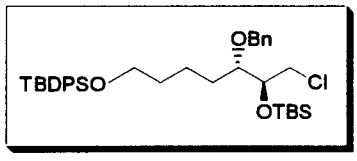
A solution of epoxy alcohol **191** (5.0 g, 13.0 mmol), benzyl bromide (6.66 g, 39.0 mmol) and TBAI (480 mg, 1.30 mmol) in DMF (30 ml) was added to suspension of NaH (60% dispersion, 730 mg, 30.3 mmol) in THF (20 ml) under argon at 0°C. The reaction was allowed to reach RT within 2 h and further stirred ovemight. The excess BnBr was destroyed by addition of methanol. After stirring for 30 min the reaction mixture was diluted with water (100 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (5x100 ml). The

diethyl ether solution was washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography on silica gel using first hexane and subsequently EtOAc-hexane (1:1) as eluant to afford the benzyl ether **196** (5.6 g, 91 %); R_f 0.41 (EtOAc-hexane 1:5).

δ_H: 1.035 (s, 9H, Me_3C)
1.43-1.65 (m, 6H, H-4, H-5 and H-6)
2.695 (dd, 1H, $J_{1b,1a}$ 5.4, $J_{b,2}$ 2.6, H-1b)
2.755 (dd, 1H, $J_{1a,1b}$ 5.4, $J_{1a,2}$ 3.9, H-1a)
2.898 (ddd, 1H, $J_{2,3}$ 5.4, $J_{2,1a}$ 3.9, $J_{2,1b}$ 2.6, H-2)
3.238 (m, 1H, $J_{4,5}$ 6.5, $J_{2,3}$ 5.4, H-3)
3.649 (t, 2H, $J_{8,7}$ 6.2, H-7)
4.475 (d, 1H, J 11.6, OCH_2Ph)
4.630 (d, 1H, J 11.6, OCH_2Ph)
7.30-7.41 and 7.60-7.67 (m, 15H, ArH)

δ_C: 19.21S (CMe_3), 21.59T (C-5), 26.88Q (CMe_3), 32.56T (C-6)*, 32.61T (C-4)*, 45.53T (C-1), 53.53D (C-2), 63.50T (C-7), 72.34T (OCH_2Ph), 78.04D (C-3), 127.59D, 128.35D, 129.03D, 129.50D, 135.58D, 130.33S, 134.12S and 142.64S (aromatic carbons).
*may be interchanged

FAB-MS: *m/z* 475 $[M+H]^+$. Exact mass: Calculated for $C_{30}H_{39}O_3Si$, 475.2668; Observed, 475.2667.



(2*S*,3*S*)-3-Benzyloxy-1-chloro-2-[(*t*-butyldimethylsilyl)oxy]-7-[(*t*-butyldiphenylsilyl)oxy]-heptane 199

t-Butylmethylsilylchloride (580 mg, 4.00 mmol) and TBAI (95 mg, 0.30 mmol) were added to a stirred solution of benzyl epoxy ether **196** (1.20 g, 2.50 mmol) in THF (25 ml). The reaction mixture was refluxed for 15 h, diluted with water (10 ml) and the THF was evaporated. The aqueous layer was extracted with diethyl ether (3x20 ml), dried (Na_2SO_4), filtered and

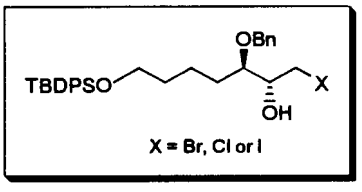
evaporated under reduced pressure. The crude product was purified by column chromatography using 1:15 (EtOAc-hexane) as eluant to afford the chloro compound **199** (880 mg, 56 %), as a yellow oil; R_f 0.39 (EtOAc-hexane 1:5); $[\alpha]_D$ –2.92 (*c* 1.3, $CHCl_3$).

δ_H: 0.091 (s, 6H, $SiMe_2$)
0.912 (s, 9H, CMe_3)
1.048 (s, 9H, CMe_3)
1.44-1.68 (m, 6H, H-4, H-5 and H-6)
3.51 (m, 1H, H-3)
3.665 (t, 2H, $J_{6,7}$ 6.0, H-7)
3.680 (dd, 1H, $J_{1a,1b}$ 11.2, $J_{1b,2}$ 6.7, H-1b)
3.696 (dd, 1H, $J_{1a,1b}$ 11.2, $J_{1a,2}$ 4.0, H-1a)
3.83 (br m, 1H, H-2)
4.548 (d, 1H, J 11.4, OCH_2Ph)
4.579 (d, 1H, J 11.4, OCH_2Ph)
7.28-7.68 (m, 30H, ArH)

δ_C: –3.58Q ($SiMe_2$), 19.22S (CMe_3), 21.34T (C-5), 25.64T (CMe_3), 26.89Q (CMe_3), 29.80T (C-6), 32.66T (C-4), 47.37T (C-1), 63.73T (C-7), 72.56T (OCH_2Ph), 72.77D (C-2), 79.59D (C-3), 127.61D, 127.80D, 127.86D, 128.45D, 129.54D, 134.09S, 135.59D, 138.16S (aromatic carbons).

FAB-MS *m/z* 625 $[M+H]^+$. Exact mass: Calculated for $C_{36}H_{53}Si_2O_3Cl$, 625.3300; Observed, 625.3302.

6.3.3.1 Copper(I) catalysed displacement of halogen



(2*S*,3*S*)-3-Benzyloxy-1-bromo-, 1-chloro- or 1-iodo-2-[(*t*-butyldimethylsilyl)oxy]-7-[(*t*-butyldiphenylsilyl)oxy]-heptane 210

A solution of vinyl bromide (92 mg, 0.86 mmol) in THF (2 ml) was added by syringe to a mixture of Mg turnings (17 mg, 0.72 mmol) in dry THF (5 ml). A crystal of iodine was used to

initiate the reaction. After the addition of all of the vinyl bromide, the reaction mixture was heated for 30 min. Once all of the magnesium had been consumed, the mixture was cooled to 0°C and copper(I) iodide (9.1 mg, 0.05 mmol) was added. The reaction mixture was stirred at 0°C for 30 min before a solution of chloro benzyl ether **199** (300 mg, 0.48 mmol) in THF (5 ml) is added slowly. After completion of the reaction (tlc), the reaction mixture was allowed to warm to RT and saturated NH_4Cl solution (10 ml) was added dropwise. The THF was evaporated and the residue partitioned between diethyl ether and water. The organic solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography of the residue using EtOAc-hexane (1:9) as eluant afforded **210,** a mixture of bromo-, chloro- and iodohydrin as an oil.

δ_C: 11.82T (C-1), 19.22S (CMe_3), 21.33T (C-5), 26.89Q (CMe_3), 29.46T and 29.76T (C-6), 32.65T (C-4), 37.19T (C-1), 47.36T (C-1), 63.70T (C-7), 72.50T (OCH_2Ph), 72.55D (C-2), 80.12D and 80.90D (C-3), 127.59D, 127.80D, 127.86D, 128.45D, 129.53D, 134.09S, 135.57D, 138.12S (aromatic carbons).