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Studies on the Stereoselective Synthesis of the C₁₇ Backbone of the *Alternaria* Toxins using Chiral Sulfoxide Methodology

by

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SUMMARY

TA and TB toxins are host-specific phytotoxins produced by the fungus *Alternaria alternata* f. sp. *lycopersici*, the causative agent of *Alternaria* stem canker disease in tomato. Both compounds are isolated as an equilibrium mixture of the esters formed by either the C(13) or C(14) hydroxy groups with the *Re* prochiral carboxy group of tricarballylic acid. The design and execution of syntheses for these toxins is necessary in order to study structure-function relationships for TA and TB toxins and their application as natural herbicides.

The aim of the synthetic study presented in this thesis is to develop and implement a methodology for the synthesis of the C(1)–C(9) unit of the C₁₇ aminopentol backbone of the TA and TB toxins with the required functional groups and appropriate stereochemistry using a chiral sulfoxide as an auxiliary to control the stereochemistry in key steps of the synthetic route.

(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-aminononane-2,4,5,9-tetrol, synthon **A** were identified by retrosynthetic analysis of the C₁₇ aminopentol backbone of TA toxin as key intermediates for a proposed synthesis. Further analysis of synthon **B** identified a C₅ synthon that can be obtained from (2*S*)-malic acid by functional group transformations, chiral sulfoxide methodology and an appropriate protective group strategy.

The work presented in the thesis shows that a protected intermediate corresponding to the abovementioned C₅ synthon, (2*S*,4*S*)-2,4,5-trihydroxy-pentanal can be prepared from (2*S*)-malic acid, but that using either Sharpless methodology or chiral sulfoxide methodology for the introduction of the third stereogenic centre and chain extension to a C₉ unit, failed as a result of the steric crowding caused by the acetonide protecting group. As a result a different synthetic route is proposed.

The results obtained in the work on TA toxin were applied to the synthesis of the C(1)–C(9) aminotetrol unit of the backbone of TB toxin.

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. Beide verbindings word geïsoleer as 'n ewewigsmengsel van die esters wat gevorm word deur die reaksie van of die C(13)- of die C(14)-hidroksigroepe met die *Re* groep van trikarballiëlsuur. Die ontwerp en uitvoering van sinteses vir hierdie toksiene is nodig teneinde struktuur-funksie verwantskappe van TA- en TB-toksien te kan bestudeer asook hulle toepassing as natuurlike plantdoders.

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 C₁₇-ruggraat van TA- en TB-toksien, met die nodige funksionele groepe en toepaslike stereochemie, deur gebruik te maak van 'n chirale sulfoksied om die stereochemie te beheer tydens sleutelstappe in die sintese.

(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 is deur retrosintetiese analise van die C₁₇-aminopentolruggraat van TA-toksien as uiters-belangrike sleutelverbindings in 'n voornemende sintese geïdentifiseer. Verdere analise van bousteen A toon dat 'n C₅-bousteen van (2*S*)-appelsuur verkry kan word deur 'n reeks funksionele groep omskakelings, chirale sulfoksiedmetodiek en 'n toepaslike beskermende groep strategie.

Die werk wat in die verhandeling aangebied word toon dat 'n beskermde tussenganger wat ooreenstem met bogenoemde C₅ bousteen, (2*S*,4*S*)-2,4,5-trihidroksipentanaal wel vanaf (2*S*)-appelsuur berei kan word maar dat nóg Sharpless- nóg chirale sulfoksiedmetodiek gebruik kan word vir die inbou van die derde stereogeniese senter en die kettingverlenging tot 'n C₉-eenheid as gevolg van die steriese hindernis wat deur die asetonied-beskermende groep veroorsaak word. 'n Veranderde sintetiese roete word gevolglik voorgestel.

Die resultate van die werk op TA-toksien is toegepas op die sintese van die C(1)–C(9) aminotetrol-eenheid van TB-toksien.

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CONTENTS

CHAPTER 1	INTRODUCTION	
1.1	GENERAL	1
1.2	IDENTIFICATION, ISOLATION AND STRUCTURAL ELUCIDATION OF THE AAL TOXINS.	1
1.2.1	Identification of the AAL toxins	1
1.2.2	Isolation of the AAL toxins	2
1.2.3	Structural elucidation and stereochemical analysis of the AAL toxins.	4
1.3	BIOLOGICAL STUDIES ON THE AAL AND STRUCTURALLY-RELATED MYCOTOXINS.	13
1.3.1	Mechanism and mode of action.	14
1.3.2	Structure-activity relationships.	14
1.4	SYNTHETIC STUDIES ON THE AAL TOXINS	17
1.5	REFERENCES	28
CHAPTER 2	CHEMISTRY OF CHIRAL SULFOXIDES.	
2.1	INTRODUCTION	32
2.2	CHEMISTRY OF CHIRAL SULFOXIDES	32
2.2.1	Synthesis of chiral sulfoxides.	32
2.2.2	Synthesis of β -ketosulfoxides.	33
2.2.3	Selective reduction of β -ketosulfoxides.	34
2.2.4	α -Alkylation of β -hydroxysulfoxides.	36
2.2.5	Functional group transformations involving the sulfoxide moiety.	38
2.3	REFERENCES	41
CHAPTER 3	USE OF ACETONIDES IN SYNTHESIS	44



	3.1	INTRODUCTION	44
	3.2	FORMATION OF ACETONIDES	44
	3.3	CLEAVAGE OF THE ACETONIDE GROUP	45
	3.4	THE USE OF ¹³ C NMR TO DETERMINE THE STEREO- CHEMISTRY OF 1,3-DIOL ACETONIDES	46
	3.5	CONFORMATIONAL ANALYSIS OF ANTI-1,3-DIOL ACETONIDES	49
	3.6	CONCLUSION	49
	3.7	REFERENCES	50
CHAPTER	4	RETROSYNTHETIC ANALYSIS OF THE AAL TOXINS	52
	4.1	INTRODUCTION	52
	4.2	RETROSYNTHETIC ANALYSIS OF TA TOXIN	53
	4.3	RETROSYNTHETIC ANALYSIS OF TB TOXIN	55
	4.4	REFERENCES	57
CHAPTER	5	SYNTHESIS OF THE C(1)–C(9) MOIETY OF TA AND TB TOXIN	58
	5.1	INTRODUCTION	58
	5.2	SYNTHESIS OF THE C(1)–C(9) UNIT OF TA TOXIN	58
	5.2.1	Synthesis of the C(1)–C(5) unit of TA toxin	58
	5.2.2	Chain extension of the C ₅ unit to a C ₇ unit	61
	5.2.3	Extension of the C ₇ unit to a C ₉ unit	64
	5.3	SYNTHESIS OF THE C(1)–C(9) UNIT OF TB TOXIN	66
	5.4	REFERENCES	69
CHAPTER	6	EXPERIMENTAL	70
	6.1	INTRODUCTION	70
	6.2	PREPARATION OF REAGENTS	71
	6.3	PREPARATION OF THE C(1)–C(6) UNIT OF THE TA SERIES	75
	6.4	PREPARATION OF THE C(1)–C(7) UNIT OF TA TOXIN VIA THE EPOXIDATION METHOD	91



6.5	PREPARATION OF THE C(1)–C(9) UNIT OF TB TOXIN	96
6.6	REFERENCES	102

LIST OF ABBREVIATIONS

Ac ₂ O	acetic anhydride
BaSO ₄	barium sulfate
BCl ₃ .Me ₂ S	boron trichloride-methyl sulfide complex
BF ₃ .Et ₂ O	boron trifluoride diethyl etherate
BnBr	benzyl bromide
<i>n</i> -Bu ₄ N ⁺ I ⁻	tetrabutylammonium iodide
<i>n</i> -BuLi	<i>n</i> -butyl lithium
<i>t</i> -BuMe ₂ SiCl	<i>t</i> -butyldimethylchlorosilane
<i>t</i> -BuOH	<i>t</i> -butanol
<i>t</i> -BuPh ₂ SiCl	<i>t</i> -butyldiphenylchlorosilane
C ₆ H ₆	benzene
CaCO ₃	calcium carbonate
CCl ₄	carbon tetrachloride
CF ₃ CO ₂ H	trifluoroacetic acid
CH ₂ Cl ₂	dichloromethane
CH ₂ N ₂	diazomethane
CH ₃ CN	acetonitrile
CH ₃ I	methyl iodide
CS ₂	carbon disulfide
CSA	camphor-10-sulfonic acid
CsOAc	cesium acetate
DCC	dicyclohexylcarbodiimide
DHQD-IND	dihydroquinidine indoliny carbamate
DIBALH	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
EDC	<i>N</i> -ethyl- <i>N</i> -(3-dimethylaminopropyl)carbodiimide
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOH	ethanol
H ₂ O ₂	hydrogen peroxide
H ₂ SO ₄	sulfuric acid
HBr	hydrobromic acid
HCl	hydrochloric acid
HCOOH	formic acid
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
I ₂	iodine
Im	imidazole
K ₂ CO ₃	potassium carbonate
KOH	potassium hydroxide
LDA	lithium diisopropylamide
LiAlH ₄	lithium aluminium hydride



LiHMDS	lithium hexamethyldisilazide
LiOH	lithium hydroxide
MCPBA	<i>m</i> -chloroperbenzoic acid
MeI	methyl iodide (iodomethane)
MeOH	methanol
MOMCl	chloromethyl methyl ether
Na(s)	sodium metal
Na ₂ CO ₃	sodium carbonate
NaBH ₄	sodium borohydride
NaClO ₂	sodium chlorite
NaCN	sodium cyanide
NaH	sodium hydride
NaHCO ₃	sodium hydrogencarbonate
NaN ₃	sodium azide
NaOH	sodium hydroxide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
OsO ₄	osmium tetroxide
<i>i</i> -Pr ₂ NEt	diisopropylethylamine
Pd	palladium
Pd(OH) ₂	palladium hydroxide
PPh ₃	triphenylphosphine
PPL	porcine pancreatic lipase
Py	pyridine
Raney-Ni	Raney-nickel
TBDPSCI	<i>t</i> -butyldiphenylsilyl chloride
TBSCI	<i>t</i> -butyldimethylsilyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TrCl	triphenylmethyl chloride
Trityl	triphenylmethyl
TsCl	toluene-4-sulfonyl chloride
TsIm	1-(toluene-4-sulfonyl)imidazole
TsOH	toluene-4-sulfonic acid
ZnCl ₂	zinc chloride

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 Although it is a stem disease with the characteristic appearance of a dark brown to black canker on the stem, it 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 AAL toxins was coined.²⁻⁴ The AAL toxins were previously reported as host-specific to tomato plants,⁵ but were later found to affect many weed and crop species such as jimsonweed,⁶ black nightshade⁷ and duck weed.⁸ The TA-toxin one of the AAL toxins shows phytotoxicity against tomato cultivars susceptible to stem canker disease (genotype *casc/asc*), whereas the resistant cultivars to the disease (genotype *asc/asc*) show a high tolerance level to the toxins.^{2,9,10}

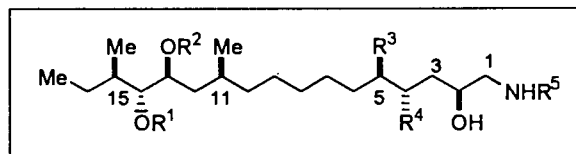
1.2 IDENTIFICATION, ISOLATION AND STRUCTURAL ELUCIDATION OF THE AAL TOXINS.

1.2.1 Identification of the AAL toxins

Bottini and Gilchrist reported in two separate papers the presence of two ninhydrin-positive substances in the TLC analysis of the cell-free culture filtrates of the fungus *A. alternata*^{11,12} 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. The purified compounds produce the characteristic necrotic symptoms, showing specific genotype induced necrosis and toxicity at equal molar concentration. These two compound pairs were designated TA₁ (1), TA₂ (2) and TB₁ (3), TB₂ (4).

Caldas *et al.*¹³ identified three new AAL toxins by spraying the developed TLC plate with *p*-anisaldehyde. These compounds were identified as three new pairs of regeoisomeric AAL toxins and were designated as TC₁ (5) and TC₂ (6); TD₁ (7) and TD₂ (8); and TE₁ (9) and TE₂ (10). (See Table 1 for the structures of the compounds).

These compounds also caused the characteristic necrotic symptoms typical of the other AAL toxins.



	R ¹	R ²	R ³	R ⁴	R ⁵
1 TA ₁	H	TCA	OH	OH	H
2 TA ₂	TCA	H	OH	OH	H
3 TB ₁	H	TCA	H	OH	H
4 TB ₂	TCA	H	H	OH	H
5 TC ₁	H	TCA	H	H	H
6 TC ₂	TCA	H	H	H	H
7 TD ₁	H	TCA	H	OH	Ac
8 TD ₂	TCA	H	H	OH	Ac
9 TE ₁	H	TCA	H	H	Ac
10 TE ₂	TCA	H	H	H	Ac

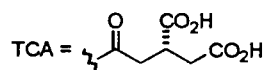


Table 1: Structures of the AAL toxins

1.2.2 Isolation of the AAL toxins

Clouse *et al.*¹⁴ inoculated 300 ml of sterile medium in low form Pyrex flask with a 1ml suspension of the fungal extract from naturally infected tomato plants. This contained ca 10⁵ AS 27-3 conidial/ml as described by Grogan *et al.*¹ The medium used for the AAL toxin accumulation contained: 5.0 mM (S)-malic acid, 8.0 mM L-asparagine, 1.7 mM sodium chloride, 4.4 mM dipotassium hydrogen phosphate, 2.0 mM magnesium sulfate, 8.8 mM calcium chloride, 0.05% yeast extract and 0.12 mM glucose. The medium was adjusted to pH 6 prior to autoclaving for 20 min. at 120 psi. The glucose solution was autoclaved separately from the medium to prevent caramelization. Stock solutions of (S)-malic acid (0.1 g/ml) were sterilized by passing through a 22- μ m filter (Millipore) and added aseptically to the cooled, autoclaved

media. Liquid cultures were grown on laboratory shelves for 18 to 20 days at room temperature under cool-white fluorescent lighting. Cultures were harvested by sequential filtration through Miracloth, Whatman No.1, Whatman GF/C glass fiber 0.45- and 0.22- μm cellulose acetate filters (Millipore).

The initial method of isolation of the AAL toxins from culture filtrates involved the treatment of the cell-free culture with barium acetate to a concentration of 0.4M, centrifugation, extraction of the supernatant solution with n-butanol, exchange into water and concentration under vacuum on a rotary evaporator at 30-35°C, followed by gel permeation chromatography on polyacrylamide biogel to yield the pure sample of the TA and TB pairs.^{16,17} Clouse *et al.*¹⁴ optimized the isolation technique by absorption of the filtrate, partitioning on C₁₈ reversed-phase column and cleaning up by gel filtration. The toxins were analysed by HPLC.¹⁷ Isocratic HPLC is needed to separate the individual structural isomers of the TA and TB toxins with a binary gradient (60 min. analysis time).

Shephard *et al.*¹⁵ developed a rapid, sensitive, and reproducible method for the isolation and determination of the AAL toxins. Lyophilized cultures of *A. alternata* f. sp. *lycopersici* were used to inoculate autoclaved ground moist yellow maize. The maize cultures were incubated in the dark at 25°C for 16 days after which the material was dried (45 °C, 24h) and ground in a laboratory mill. The method involves extraction by blending the culture material with chloroform - methanol (10:3, v/v). The mixture was filtered, washed with the extraction solvent, and dried under vacuum. The dried filtrate, was further extracted with water, the homogenate was centrifuged and all the supernatants pooled, acidified to pH 2.7 with 2M HCl and then re-centrifuged. The clear supernatant was applied to a pre-washed (1:1 methanol-water) column of Amberlite XAD-2 resin (35×3.0 cm I.D). The resin was again washed with water and after the application of the sample with a mixture of methanol -water (1:3, v/v). The toxins were eluted with methanol and the solvent evaporated under reduced pressure at 40°C. The residue was dissolved in ethyl acetate-acetic acid-water (12:6:1, v/v/v), and fractionated again on a silica gel 60 column using the same solvent system. Fractions were tested for the presence of TA and TB toxins by TLC, developing the plates with an ethyl acetate- acetic acid-water mixture (6:3:1, v/v/v). The toxins were revealed as purple spots by spraying with *p*-anisaldehyde reagent.¹⁸ The fractions were further purified using C₁₈ solid phase extraction, pre-column derivatisation with *o*-phthalaldehyde and reversed-phase HPLC with fluorescence detection.

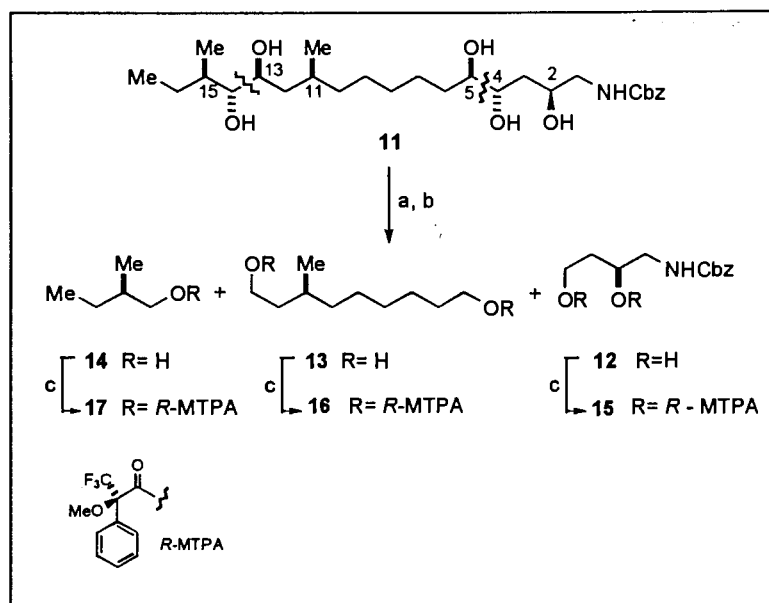
Caldes *et al.*¹³ employing the method developed by Shephard *et al.*,¹⁵ detected and separated three new pairs of regioisomeric AAL toxins. The toxins were eluted from Amberlite XAD-2 resin using methanol and the eluent fractionated using silica gel column chromatography. *p*-Anisaldehyde was used to detect the presence of the toxins on developed TLC plates as this reagent reacts not only with the primary amine like ninhydrin but also has the ability to detect the hydroxy groups. This led to the detection and isolation of the TD₁ (7), TD₂ (8) and TE₁ (9), TE₂ (10) designated AAL toxins, which constituted 40% of the toxins produced under these conditions. The non-reactivity of the TD and TE isomers to ninhydrin proved that the primary amino group either is absent or has been blocked. It was later proved to be the latter by mass spectrometry. The fifth toxin designated TC₁ (5) and TC₂ (6), although ninhydrin-positive, was only detected in highly concentrated chromatographic fractions of the column eluates due to its low concentration (<5%) compared to the TA and TB toxins.

1.2.3 Structure Elucidation and Stereochemical Analysis of the AAL Toxins

Bottini *et al.*^{11,12} used high-resolution mass spectrometry and ¹H and ¹³C NMR spectroscopy to determine the structure of TA toxin and propose the structure of the TB toxins. Positive ion fast atom bombardment (FAB) mass spectrometry together with NMR spectroscopy were employed by Caldes *et al.*¹³ to identify and determine the structures of the TC, TD and TE compounds. This technique also confirmed the proposed structure of TB toxin

The absolute configuration of the AAL toxins was determined by Oikawa *et al.*^{19,20} and by Kishi *et al.*²¹

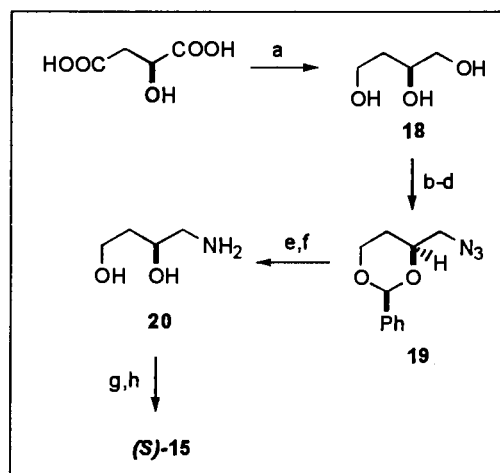
The absolute configuration of the C(1)–C(5) fragment of TA toxin as reported by the Oikawa group, involved the degradation of the aminopentol backbone of the toxin into three fragments by oxidative cleavage of the C(4)–C(5) and C(13)–C(14) bonds with NaIO₄. The resultant aldehydes were reduced with NaBH₄ to the corresponding alcohols 11, 12, and 13. These alcohols were then further converted to their (*R*)- α -methoxy- α -trifluoromethyl-phenylacetate esters 14, 15, and 16, respectively (see Scheme 1.1).



Scheme 1.1: Degradation of the aminopentol backbone of TA toxin.

Reagents: a) NaIO_4 , THF- H_2O (1:1); b) NaBH_4 ; c) (*R*)-(+)-MTPA, DCC, DMAP, CH_2Cl_2 .

The (*R*)-MTPA derivative **15** was synthesised from (*2S*)-malic acid by reduction to the triol **18**, and protection of the 1,3-diol system as the *O,O*-benzylidene (see Scheme 1.2). Conversion of the primary alcohol group to the azide **19** proceeded via

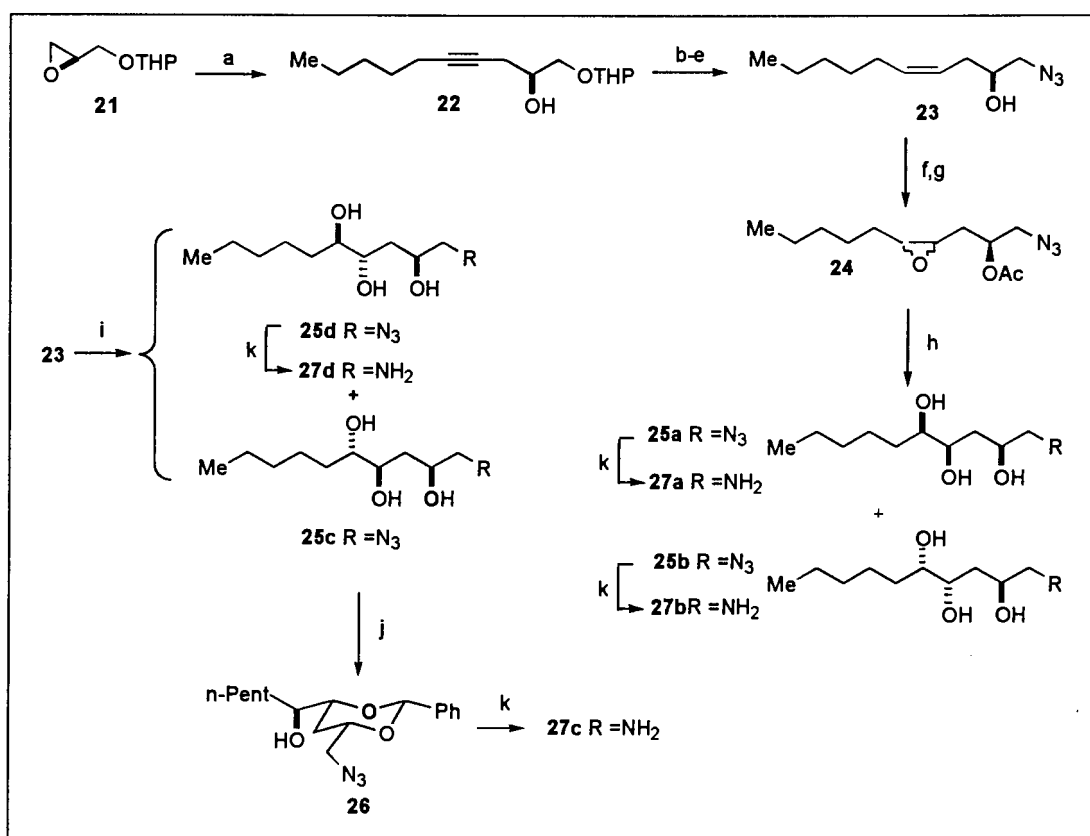


Scheme 1.2: Synthesis of the (*R*)-MTPA derivative of **15** from (*S*)-malic acid.

Reagents: a) BMS, $\text{B}(\text{OEt})_3$; 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 .

the tosylate derivative. Catalytic hydrogenation of the azide followed by removal of the *O,O*-benzylidene group gave the aminodiol **20** that was then converted to the (*R*)-MTPA derivative **15**. Comparison of the ^1H NMR spectrum of the (*R*)-MTPA of **15** with that of the synthetic product obtained from (*2S*)-malic acid showed that the two compounds were identical and established the *2S* configuration for the backbone of TA toxin.

Model compounds **27a-27d**, representing the four possible stereoisomers of the (*2S*)-1-amino-2,4,5-triol unit [C(1)–C(5)] of the TA backbone, were synthesised (see Scheme 1.3) The synthesis commences with the condensation of epoxide **21** and 1-heptyne in high yield. The coupled product **22** was hydrogenated to the corresponding *cis*-olefin that was converted to the azide **23** by deprotection of the THP ether, tosylation of the formed primary alcohol and displacement of the tosylate with

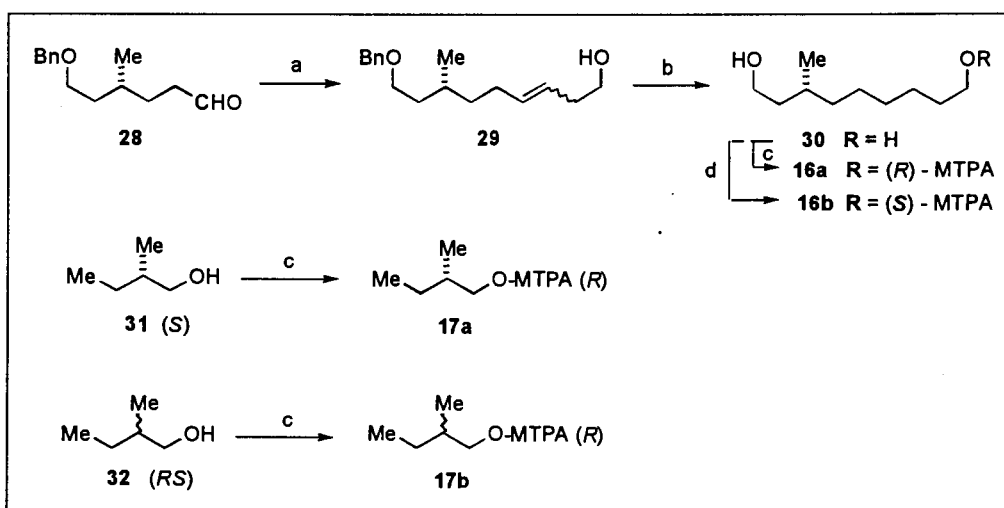


Scheme 1.3: Synthesis of the different stereoisomers of the (*2S*)-1-amino-2,4,5-triol fragment of TA toxin.

Reagents: a) 1-heptyne, *n*-BuLi, HMPA/THF (82%); b) H₂, Pd-BaSO₄, quinoline; c) 1M HCl-MeOH (94%, 2 steps); d) TsCl, Py (70%); e) NaN₃, DMF (47%); f) Ac₂O, Py; g) *m*CPBA (quant., 2 steps); h) aq. 7% HClO₄, dioxane, 60°C, then 0.3M KOH (90%); i) OsO₄, NMO (96%); j) PhCHO, ZnCl₂, (48%); k) H₂, Pd-black, 0.1% HCl-MeOH, (quant.)

azide. Treatment of the *O*-acetate of **23** with *m*-CPBA gave the diastereomeric epoxides **24**. Subsequent hydrolysis with perchloric acid and treatment with aq. KOH yielded a 2:1 mixture of the 4,5-*syn* triols **25a** and **25b** that was easily separated by chromatography. The 4,5-*anti* triols were prepared by catalytic dihydroxylation of the azide **23** with OsO₄. Treatment of the mixture with benzaldehyde and ZnCl₂ affords the benzylidene acetal **26** derived from the 2,4-*syn* diastereomer **25c** while the unreacted 2,4-*anti* stereoisomer **25d** was recovered. Hydrogenation of the compounds **25d** and **26** under acidic conditions leads to the formation of the corresponding aminotriols **27d** and **27c** as hydrochloride salts. Comparison of the ¹H-NMR spectra of the four diastereomers with that of the aminopentol backbone established the absolute configuration of the C(1)–C(5) unit of TA toxin as 2*S*,4*S*,5*R*. (Scheme 1.3).

Oikawa *et al.*²⁰ in a later report determined the complete configuration of the TA backbone. Following the same approach as that used for the determination of the stereochemistry of the C(1)–C(5) unit, authentic samples of the MTPA esters **16** and **17** were prepared (see Scheme 1.4). (*S*)- and (*RS*)-2-Methylbutanol are commercially available and were converted to their (*R*)-MTPA derivatives **17a** and **17b**.



Scheme 1.4: Synthesis of the MTPA esters for the determination of the absolute configuration at C(15) and C(11) of TA toxin.

Reagents: a) HO(CH₂)₃PPh₃Br, *n*-BuLi, THF (53%); b) H₂, Pd(OH)₂ (49%); c) (*R*)-MTPA, DCC, DMAP, CH₂Cl₂; d) (*S*)-MTPA, DCC, DMAP, CH₂Cl₂.

The preparation of the (*R*)-diol **30** began with the reaction of the aldehyde **28**, derived from from (*R*)-citronellal, in a Wittig reaction with the ylide prepared from 3-hydroxy-

propylphosphonium bromide to give the alkenol **29** that was subjected to hydrogenation and concomitant debenzoylation to afford the diol **30** (see Scheme 1.4). Comparison of the ^1H NMR spectra of the (*R*)- and (*S*)-MTPA esters **16a** and **16b** prepared from diol **30** with the ^1H -NMR spectrum of the compound derived from the degradation product of the backbone of TA toxin established the absolute configuration as 2*S*, 4*S*, 5*R*, 11*S*, 13*S*, 14*R*, 15*R* as indicated in (**33**) (Figure 1.1)

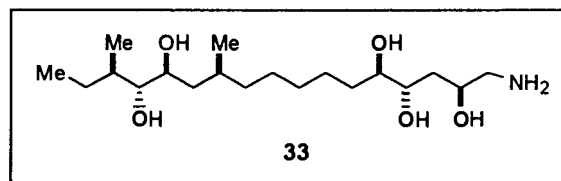


Figure 1.1: Absolute configuration of the backbone of TA toxin.

Kishi *et al.*²¹, following a different approach in the determination of the absolute stereochemistry of the C_{17} aminopentol backbone of the TA_1 toxin, proved the correctness of the absolute configuration proposed by the Oikawa group. Kishi exploited the fact that the right side of the toxin with three stereogenic centers has no effect on the spectroscopic properties of the left side of the molecule. The disconnection of the C(9)–C(10) bond of the C_{17} aminopentol backbone **33** of TA toxin, identifies two distinct synthons. The synthesis of model compounds of all eight diastereomers possible for the left side of the backbone (e.g. **35a-35d**) were synthesised from (*S*)-(-)-citronellal whereas all four possible diastereomers with the 2*S* configuration, **34a-34d**, were prepared from D-mannose or D-glucose. ^1H NMR studies established that the stereoisomers **35a** and **34c** represented the relative stereochemistry of the left and right side of the C_{17} aminopentol backbone of TA toxin, respectively. The absolute configuration was established by the synthesis of the C_{17} backbone with synthons corresponding to the relative stereochemistry shown in **35a** and **34c** and once again comparison of the ^1H NMR data with that of the aminopentol derived from TA toxin. The results confirmed the findings of the Oikawa group.

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

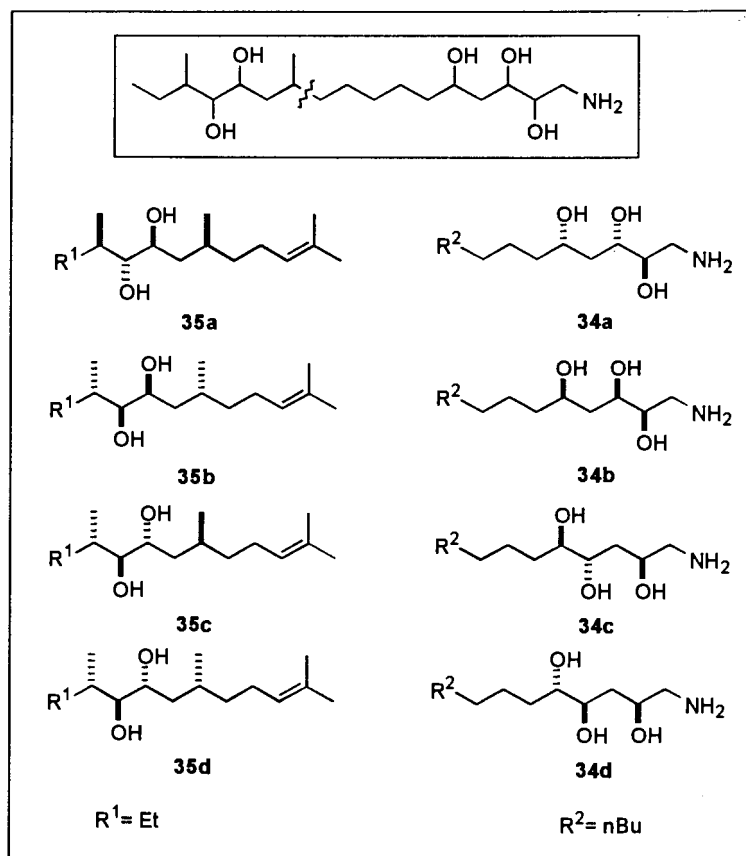
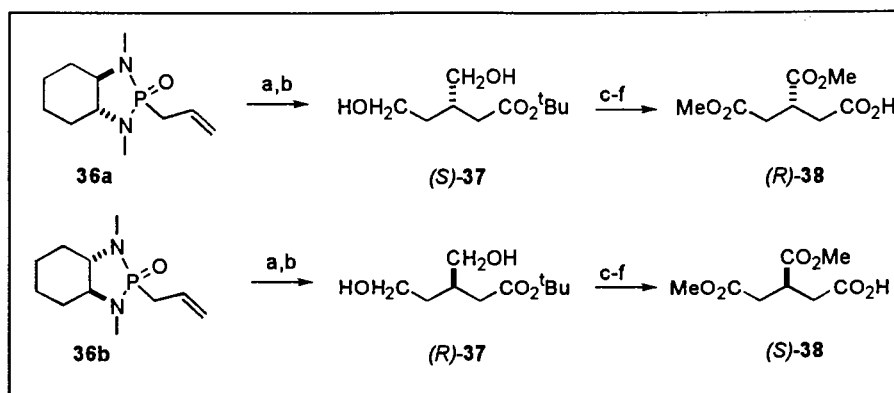


Figure 1.2: Stereoisomers prepared by Kishi to determine the absolute configuration of the backbone of TA toxin.

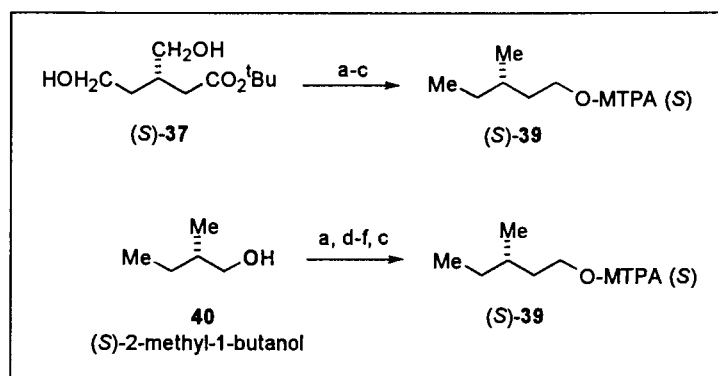
Kishi *et al.*²¹ synthesised both stereoisomers of tricarballylic acid dimethyl ester. The procedure involves a modification of the Hanessian protocol for the asymmetric Michael addition of a chiral allylphosphonamide to *t*-butyl sorbate.²² The modification involves the addition of LiHMDS to a mixture of allylphosphonamide and *t*-butyl sorbate at -78°C instead of deprotonation of the allylphosphonamide by *n*-BuLi at -78°C , followed by the immediate addition of *t*-butyl sorbate. A cleaner reaction and higher yields were obtained in this way. Ozonolysis of the Michael adduct followed by reductive work-up using NaBH_4 produced (*S*)- and (*R*)-**38** (Scheme 1.5).

Hanessian originally assigned the absolute configuration of (*S*)-**37** and this assignment was verified by the correlation with the compound derived from (*S*)-2-methyl-1-butanol (see Scheme 1.6). Although the optical purity of (*S*)- and (*R*)-**37** was in each case greater than 95:5, that of (*S*)- and (*R*)-**38** were determined by derivatisation with (–)-menthol to give a ca. 5:1 mixture of diastereomers in each case.²³



Scheme 1.5: Synthesis of the two isomers of the tricarballylic acid moiety.

Reagents: a) LiHMDS, ^tbutyl sorbate, THF, -78°C ; b) O_3 , NaBH_4 ; c) Swern oxidation; d) NaClO_2 ; e) CH_2N_2 ; f) $\text{CF}_3\text{CO}_2\text{H}$.

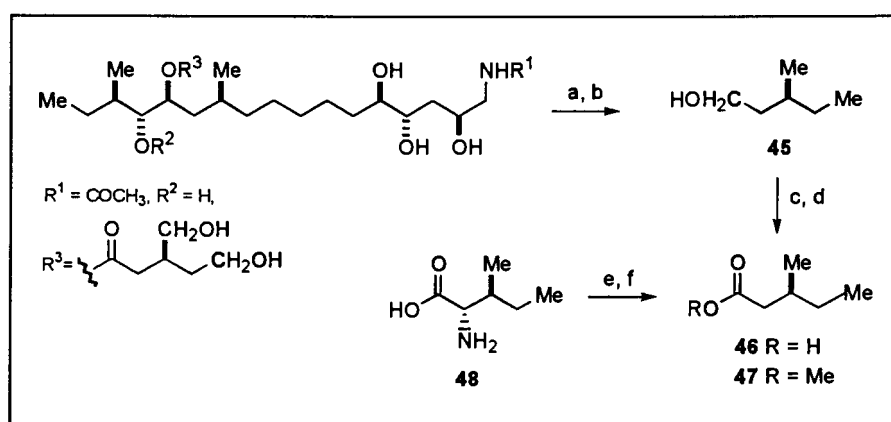


Scheme 1.6: Preparation of (S)-39 from (S)-2-methyl-1-butanol .

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

The tricarballylic acid dimethyl esters (S)- and (R)-38 were linked by an ester bond to either the C(13) or the C(14) hydroxy group of the protected C₁₇ backbone obtained from TA toxin as outlined in Scheme 1.7, to give the esters 42, 43 and 44. Comparison of the ¹H NMR spectra of these esters with that of the protected TA derivative 41 established the R configuration of the tricarballylic ester moiety in the AAL toxins (see Figure 1.3)

The reduced product was immediately tosylated and reduced to 3-methyl-1-pentanol **45**. Racemic **45** could not be resolved into two peaks by gas chromatography on chiral columns. Thus the oxidation of the released side chain **45** was carried out to give the carboxylic acid **46** which was converted to the methyl ester **47** as the acid also could not be resolved (Scheme 1.8). A reference compound was prepared from L-isoleucine **48**. Treatment with hydroxylamine-O-sulfonic acid under alkaline conditions and esterification of the product with diazomethane produces the methyl ester **47** identical with that obtained from the natural product. In this way the (*S*) configuration was established for the stereogenic center of the tricarballylic ester moiety.

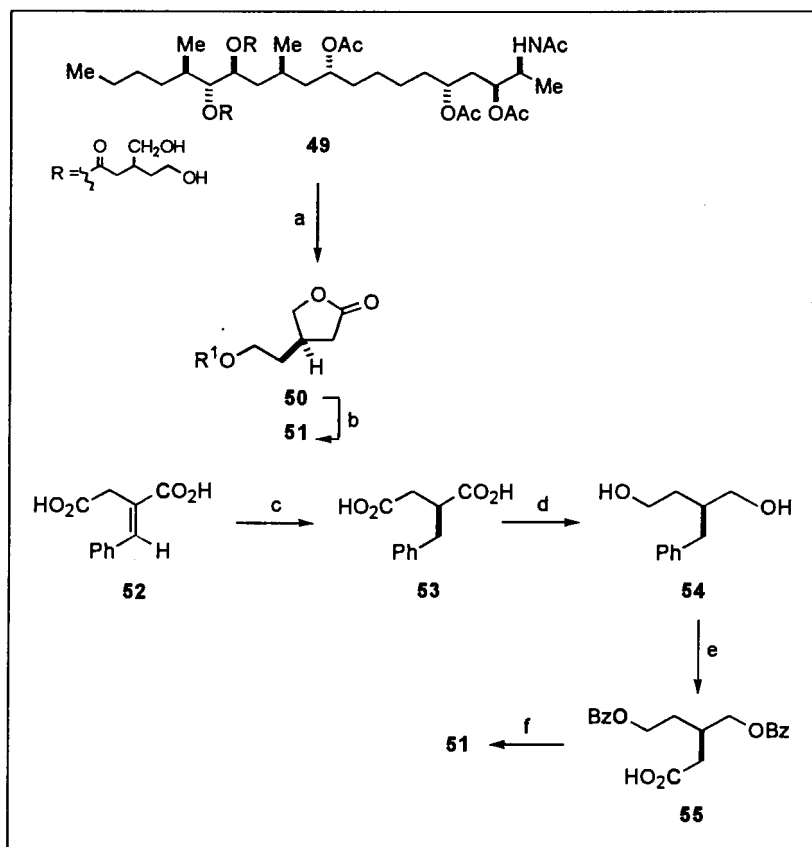


Scheme 1.8: Synthesis of the tricarballylic acid moiety derivative.

Reagents: a) TsCl, Py; b) LiAlH₄, THF; c) CrO₃, H₂SO₄; d) CH₂N₂; e) H₂N-OSO₃H, NaOH; f) CH₂N₂.

Edwards *et al.*²⁵ provided evidence that supported the *R* configuration proposed by Kishi. The approach involves stabilization of the stereogenic centre in the tricarballylic ester moiety in fumonisin B₁ (a closely related compound to TA toxin) by borane reduction of the free carboxyl groups to give **49** (see Scheme 1.8). Hydrolysis of all the ester groups in **49** using KOH in aqueous MeOH, followed by acidification and extraction with chloroform gave a mixture rich in the γ -lactone **50**. Benzoylation and separation by chromatography afforded **51** in high yield. An authentic sample of **51** was prepared from *E*-phenylitaconic acid **52**, the stereochemistry of which was assigned by X-ray crystallography. Stereoselective reduction of **52** gave (*S*)-(-)-2-benzylsuccinic acid **53** that was converted by reduction with diborane to the diol **54**. Benzoylation of the hydroxy groups and oxidation of the phenyl group with ruthenium tetroxide gave the dibenzoyloxy acid **55**.

Alkaline hydrolysis followed by acidification afforded (*R*)-(-)-hydroxy γ -lactone **51**. Comparison of the MS, IR, ^{13}C and ^1H NMR spectra of the two samples established the structure and the specific rotation the *R* absolute configuration.



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

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

1.3 BIOLOGICAL STUDIES ON THE AAL AND STRUCTURALLY-RELATED MYCOTOXINS.

The AAL toxins are structurally related to the fumonisins e.g. fumonisin B₁ (FB₁) and B₂ (FB₂), mycotoxins produced by *Fusarium moniliforme*. The mycotoxins produced by this fungus have been implicated in cancer,²⁶⁻³⁰ equine leucencephalomalacia,³¹ immunosuppression in poultry,³² porcine pulmonary edema and hydrothorax in swine.^{31,33-37} The toxins produced by *F. moniliforme* are the fumonisins FA₁ **61**, FA₂ **62**, FB₁ **63**, FB₂ **64**, FB₃ **65** and FB₄ **66**^{29,30,38,39} (see Figure 1.4). FB₁ **63** is a

non-host specific phytotoxin for a wide range of dicotyledonous weed and crop species.⁴⁰⁻⁴⁷

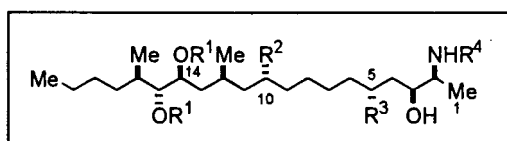
1.3.1 Mechanism and mode of action.

The fumonisins and AAL toxins are structurally related to the sphingosines (Figures 1.4 and 1.5) and exert their physiological and toxicological action on plants and animal species by disrupting sphingolipid metabolism.⁴⁸⁻⁵¹ Both the AAL toxins and the fumonisins inhibit sphinganine *N*-acyl transferase (ceramide synthase in animals).^{49, 50} Sphingolipids are important constituents of cell membranes in both plant and animals,⁵²⁻⁵⁵ but their role in plants has not been well studied.

The structural relationship between the toxins and the sphingosines suggests that the toxins are competitive inhibitors of the enzymes sphingonine (sphingosine) *N*-acyl transferase. AAL toxins are thought to compete with sphingonine and other sphingolipids for the enzyme sphingonine (sphingosine) *N*-acyl transferase, and causes accumulation of sphinganine, depletion of the complex sphingolipids, an increase in the degradation products of catabolism of free sphingoid bases, increase in the lipid product derived from the increase in sphingoid base degradation product and an increase in free sphingosine presumably from inhibition of reacylation of sphingosine.⁵⁶ Abbas *et al.*⁵⁷ reported a significant increase in the concentration of free phytosphingosine and sphinganine in duckweed, tomato leaf discs, intact tomato plants, and tobacco callus on their exposure to TA toxin and fumonisin B₁. Significant increases in free phytosphingosine and free sphinganine were observed within 30 minutes of exposure of duckweed to the toxins whereas it took two hours to observe the same physiological effect in the leaf discs of susceptible tomato plants. A similar response was observed in intact tomato plants exposed to TA (≥ 95% purity) or fumonisin B₁ (≥ 93% purity). These results indicated that disruption of sphingolipid metabolism occurs early in the sequence of events leading to cell death. Scheme 1.10 shows the biosynthetic pathway for the production of the sphingolipids in plants and animals and the proposed point of disruption in the sequence by the TA toxin and fumonisin B₁.

1.3.2 Structure-Activity Relationship.

The aminopentol backbones derived from FB₁ (**63**) of the fumonisins and the TA toxins (**1** and **2**), and the aminotetrol backbones derived from FB₂ (**64**) of the fumonisins and TB toxin (**3** and **4**), resemble the sphingosine and sphinganine more



Fumonisin	R ²	R ³	R ⁴
FA ₁ 61	OH	OH	Ac
FA ₂ 62	H	OH	Ac
FA ₁ 63	OH	OH	H
FA ₂ 64	H	OH	H
FA ₃ 65	OH	H	H
FA ₄ 66	H	H	H

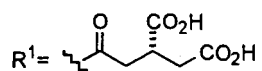
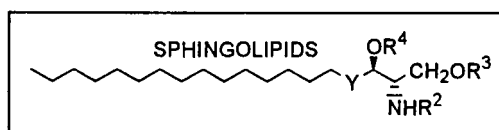
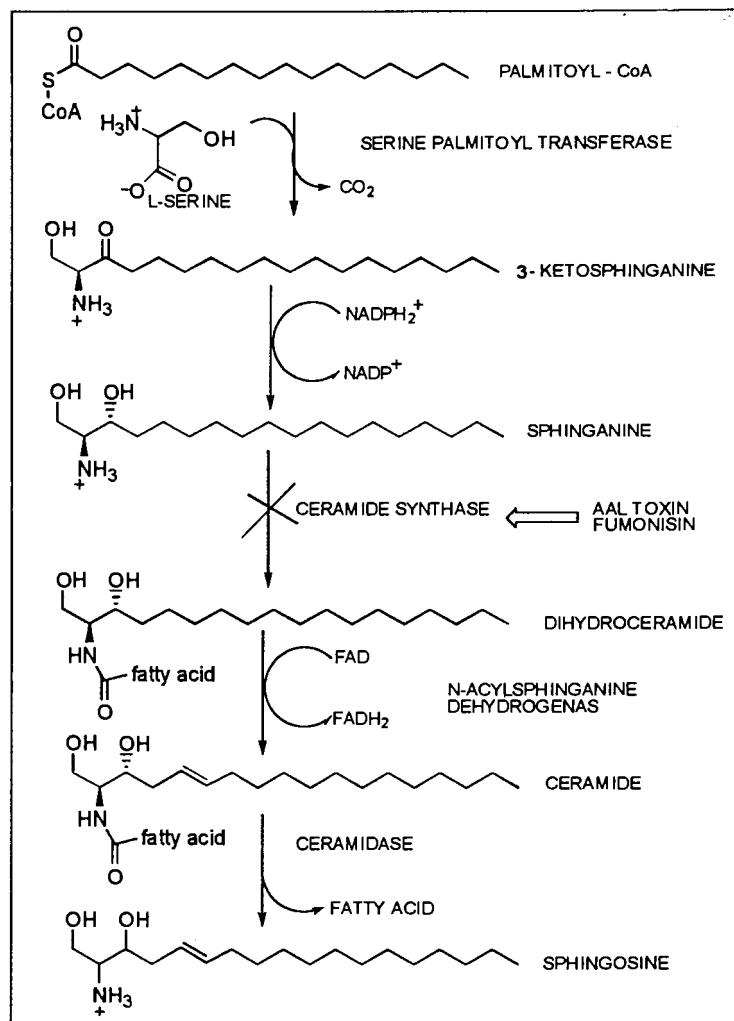


Figure 1.4: Structures of the fumonisins



	Y	R ²	R ³	R ⁴
Sphingolipid 67				
Sphingosine 68	-CH ₂ =CH ₂ -	H	H	H
Phytosphingosine 69	-CH ₂ CH(OH)-	H	H	H
Sphingonine 70	-CH ₂ -CH ₂ -	H	H	H
Tetraacetyl phytosphingosine 71	-CH ₂ CHOAc-	Ac	Ac	Ac
N-Lignoceroyl-DL-sphinganine 72	-CH ₂ -CH ₂ -	-CO(CH ₂)CH ₃	H	H

Fig 1.5: Structure of some sphingolipids.



Scheme 1.10: Biosynthetic pathway leading to the production of sphingolipids in plants and animals.

closely than the toxins themselves as they lack the propane-1,2,3-tricarboxylic acid moiety. The aminopentol and aminotetrol of the fumonisins have relatively little biological activity in the *L. pausicostata* bioassay⁴⁴ but show more phytotoxic activity in jimsonweed leaf disc than the fumonisins.⁵⁸ The aminopentol and aminotetrol back bones of the fumonisins and AAL toxins are 15- and 400-fold less phytotoxic than the parent compounds in tomato leaflets.¹⁰

Questions have been raised whether the aminopentols and the aminotetrols are the active inhibitor in plant ceramide synthase. If this is the case, then the fumonisins and AAL toxins are pro-toxins that must be metabolised to the active form to establish activity. Shier⁵² suggested that fungi producing these toxins add the propane-1,2,3-tricarboxylic acid moiety to the aminopentols and the aminotetrols in order to detoxify these compounds and producing the AAL toxins in the process. It

was also suggested that in affected organisms fumonisin and AAL toxins are hydrolysed to aminopentols or aminotetrols by carboxyesterase.

The AAL toxins are more toxic in plants than the most active fumonisin^{44, 59} whereas the opposite is the case in animals.^{59,60} The A-series of fumonisins are much less active than the B-series as phytotoxins.^{10,44} Acetylation of the terminal amino group of both the AAL toxins and the fumonisins renders them inactive in animals.⁵⁹

1.4 SYNTHETIC STUDIES ON THE AAL TOXINS.

Synthetic studies on the AAL toxins have been undertaken in order to study the structure-activity relationship of the toxin. Oikawa *et al.*⁶¹ achieved the synthesis of the AAL toxin TA₁, by retrosynthetically dividing the toxin into a left- **73** and right-half **74**, and the tricarballylic acid unit (*S*)-**75** (see Figure 1.6).

The synthesis of the left-half segment **73a** started with the Evans alkylation product⁶² **76a**, 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 1.11). The oxazolidinone chiral auxiliary was removed by a standard procedure⁶³ that involved hydrolysis of the imide with basic hydrogen peroxide. The formed acid was reduced with LiAlH₄ to the alcohol **77**. This alcohol

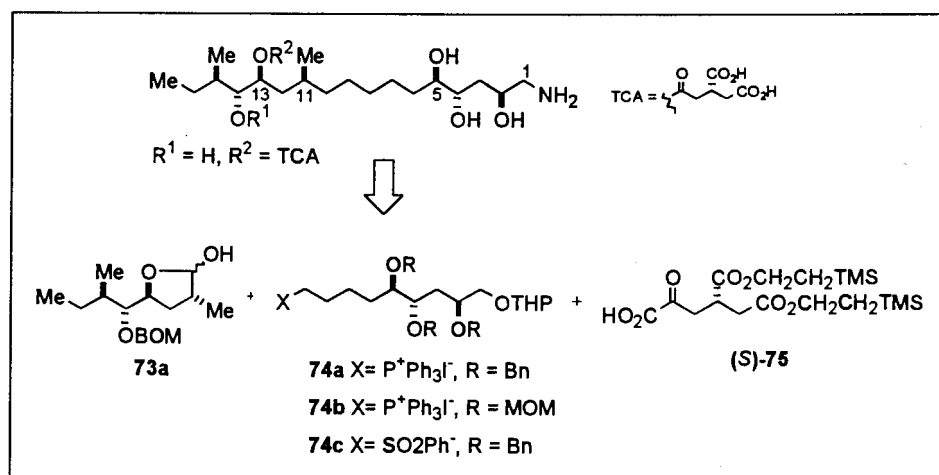
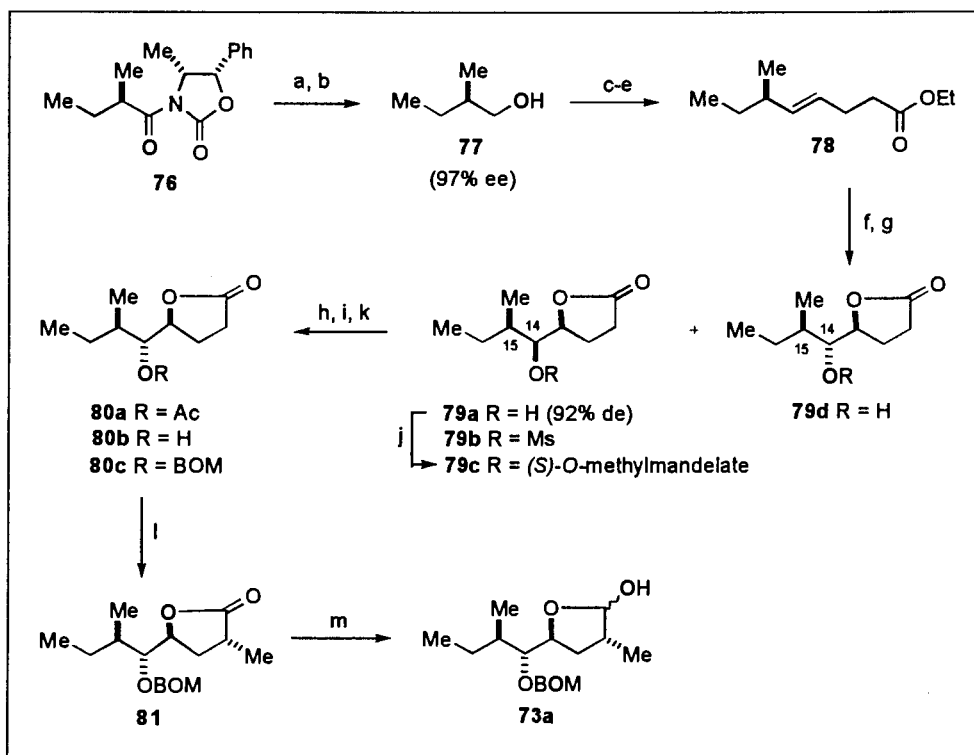


Fig 1.6: Retrosynthesis of the AAL toxin TA₁.

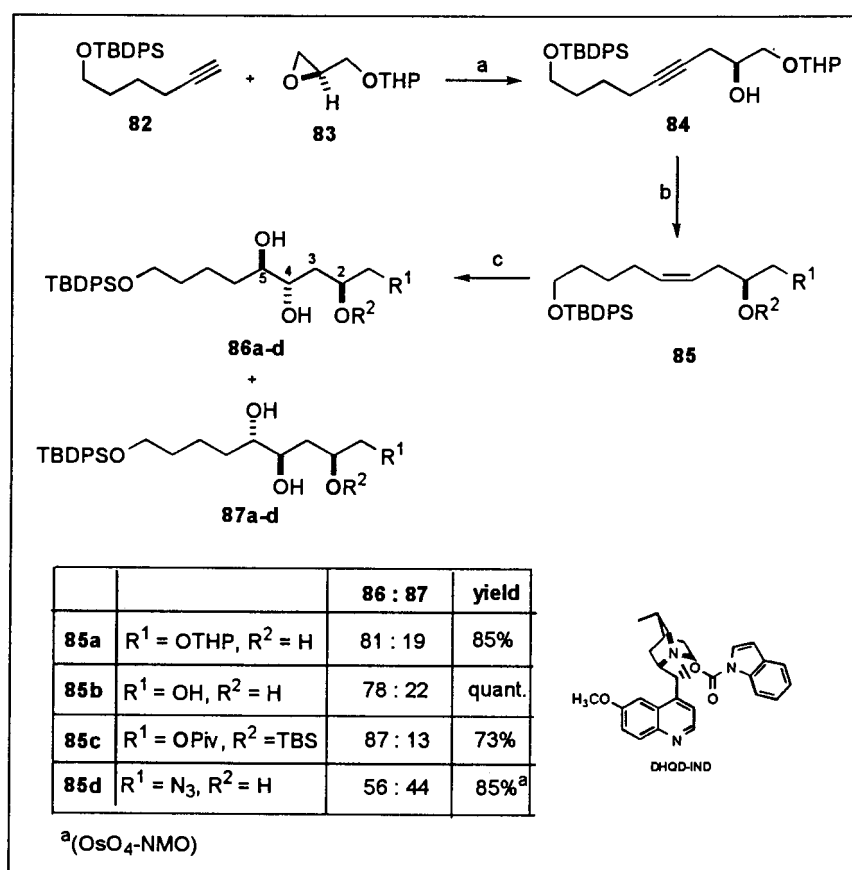
was converted to the *E*-olefin **78**. Thus Swern oxidation of **77** followed by the addition of vinyl magnesium bromide to the formed aldehyde, gave an epimeric mixture of alcohols that underwent an orthoester-Claisen rearrangement to give **78**. Asymmetric dihydroxylation of **78** with AD-mix- α and concomitant lactonization furnished lactones **79a** and **79d** in 92:8 d.r. The diastereoselectivity was determined from the (*S*)-*O*-methylmandelate ester **79c** using HPLC. Inversion of stereochemistry at C(14) of diastereomer **79a** was achieved with Ikegami's procedure⁶⁴ as the Mitsunobu protocol led to the elimination of water. The lactone **79a** was mesylated and treated with CsOAc in the presence of 18-crown-6 to give **80a**. After hydrolysis and protection of the hydroxy group as the BOM ether, the compound was methylated with LiHMDS and methyl iodide to give **82** in 8.7:1 d.r. Reduction of the lactone with DIBALH furnished the left-half segment, the lactol **73a**.



Scheme 1.11: Synthesis of the left-half **73a** of the AAL TA₁ toxin.

Reagents: a) 30% H₂O₂, LiOH; b) LiAlH₄, EtO₂, (77%, 2 steps); c) Swern oxidation; d) CH₂=CHMgBr, THF, -78°C; e) CH₃C(OEt)₃, CH₃CH₂CO₂H, reflux (53%, 3 steps); f) AD-mix- α , (75%); g) MsCl, Et₃N, CH₂Cl₂; h) CsOAc, 18-crown-6, C₆H₆, reflux; i) KOH, EtOH-H₂O, (70%, 3 steps); j) (*S*)-*O*-methylmandelic acid, DMAP, DCC, CH₂Cl₂; k) BOMCl, *i*-Pr₂NEt, CH₂Cl₂; l) LiHMDS, CH₃I, THF, -78°C, (60%, 2 steps); m) DIBALH, EtO₂, -78°C, (96%).

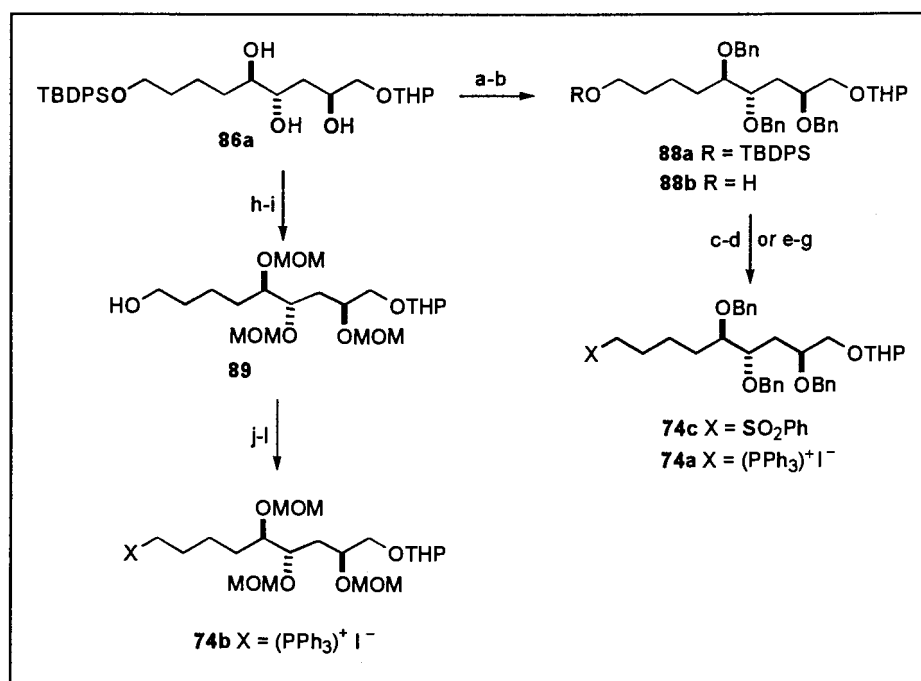
The synthesis of the right-half segment of the AAL TA₁ toxin was achieved as outlined in Scheme 1.12. Lithium acetylide, derived from **82**, was reacted in the presence of BF₃·OEt₂^{65,66} with epoxide **83**, prepared from (*R*)-glycidol, to give the acetylenic alcohol **84**. Partial hydrogenation of the triple bond led to the formation of the *Z*-olefin **85a**. This olefin was converted into the differently protected analogues **85b-85d** in order to investigate the introduction of the 1,2-diol group by an asymmetric dihydroxylation reaction using DHQD-IND and catalytic OsO₄. In all cases the desired 2,4-*anti* diols **86a-86b** were obtained as the major product together with the minor 2,4-*syn* products in the ratios indicated and which could be separated by chromatography. The required product **86a** from the asymmetric dihydroxylation step was converted to different units suitable for linking with the left-half segment **73a** (see Scheme 1.13). Benzylation of the triol **88a** and removal of the TBDPS group using TBAF afforded the primary alcohol **88b**. Sulfination of **88b**, followed by *m*CPBA



Scheme 1.12: Synthesis of the right-half of the AAL toxin TA₁.]

Reagents: a) *n*-BuLi, BF₃·EtO₂, THF, 78^oC (.81%); b) H₂, Pd-BaSO₄, quinoline (93%); c) cat.OsO₄, DHQD-IND, K₃Fe(CN)₆, K₂CO₃, *t*-BuOH, H₂O.

oxidation gave the sulfone **74c**. The alcohol **88b** was also converted to the phosphonium salt **74a** by standard procedures. The sluggish reaction and low yield (45%) encountered in the conversion of the iodide to the phosphonium salt led to the preparation of the MOM protected analogue **74b** by identical procedures in a 76% yield.

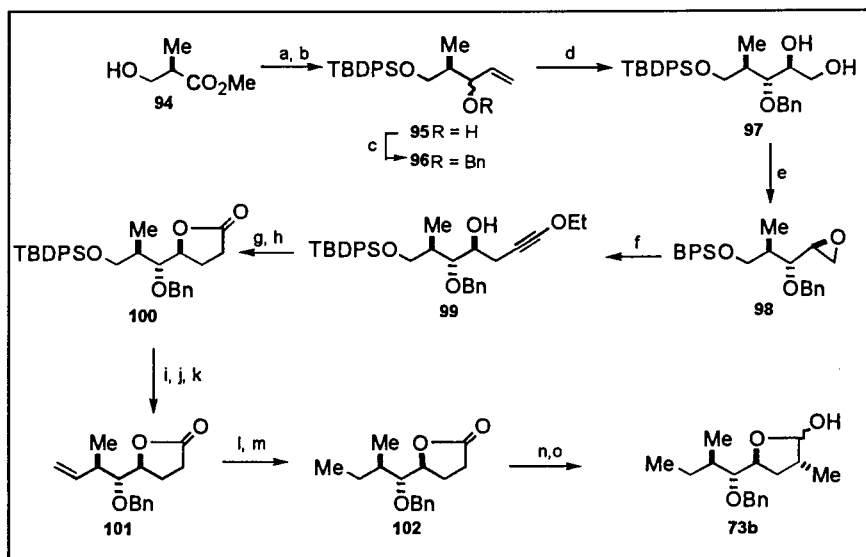


Scheme 1.13 Synthesis of the different right-half units for linking to the left-half.

Reagents: a) NaH, BnBr, *n*-Bu₄NI, THF, reflux, (81%); b) TBAF, THF, 89%; c) (PhS)₂, *n*-Bu₃P, CH₂Cl₂; d) *m*CPBA, CH₂Cl₂, 89% (2 steps); e) TsCl, Et₃N, CH₂Cl₂; f) NaI, acetone, (83%; 2 steps); g) Ph₃P, *i*-Pr₂NEt, CH₃CN, reflux, (45%); h) MOMCl, *i*-Pr₂NEt, CH₂Cl₂; i) TBAF, THF, (83%, 2 steps); j) TsCl, Et₃N, CH₂Cl₂; k) NaI, acetone (76%, 2 steps); l) Ph₃P, *i*-Pr₂NEt, CH₃CN, reflux, (76%).

Lipase-catalysed kinetic resolution was employed in the synthesis of the tricarballylic ester unit (see Scheme 1.14). (*2RS*)-2-benzylsuccinate **90** was hydrolysed with porcine pancreatic lipase, PPL. After 28% conversion, (*S*)-**91** was obtained in 82% e.e. This material was re-esterified with diazomethane and subjected to a second PPL-hydrolysis to afford (*S*)-**91** in 95% e.e (55% conversion). The recovered diester (*R*)-**92** from the first hydrolysis (84% e.e at 22% conversion) was also subjected to a second PPL-hydrolysis. (*S*)-**91** was hydrolysed and the corresponding diacid protected as the trimethylsilylethyl ester to give (*S*)-**93**. Catalytic

lactone as a separable mixture (8.7:1 d.r.) that was reduced to the lactol **73b** with DIBALH.



Scheme 1.15: Alternative route for the synthesis of the left-half segment **73b** of TA toxin.

Reagents: a) TBDPSCI, 1m, DMF, quant; b) DIBALH, EtO₂, -78^oC then CH₂=CHMgBr, (77%); c) NaH, BnBr, *n*-Bu₄NI, THF (91%), chromatographic separation; d) OsO₄, NMO, acetone:H₂O, (8:1), (6:1, 91%) e) i. MeC(OMe)₃, cat. PPTS, CH₂Cl₂; ii. AcBr, CH₂Cl₂; K₂CO₃, MeOH, (77%); f) ethyl ethynyl ether, *n*-BuLi, BF₃.EtO₂, THF, -78^oC; g) HgCl₂, EtOH; h) K₂CO₃, MeOH, then 3M HCl, (59%, 3 steps); i) TBAF, THF, (80%); j) Swern oxidation; k) Ph₃PCH₃Br, *n*-BuLi, THF, (19%, 2 steps; recovered aldehyde 70%); l) H₂, Pd-C, EtAcO; m) CCl₃(=NH)OBn, TfOH, CH₂Cl₂:cyclohexane(1:1), (57%, 2 steps); n) LiHMDS, CH₃I, THF, -78^oC, (8.7:1, 68%) o) DIBALH, EtO₂, -78^oC, (96%).

The second method involves the reaction of aldehyde **103**,⁶⁹ readily prepared from L-glutamate, with various crotylboronate reagents⁷⁰ as shown in Figure 1.7. The reaction proceeds smoothly to give all possible diastereomers **104a-104d** in good yield. Hydrogenation and benzylation of **104a** and **104b** afforded the intermediate **102** and its diastereomer.

Attempts to condense the left- and right-half segments via Wittig (**73b** and **74b** or **74a**) or Julia coupling (**74b** and **74c**) gave poor results. Thus, the one-carbon shorter homologue **105** (= nor-**88a**) of the right-half segment was prepared by the

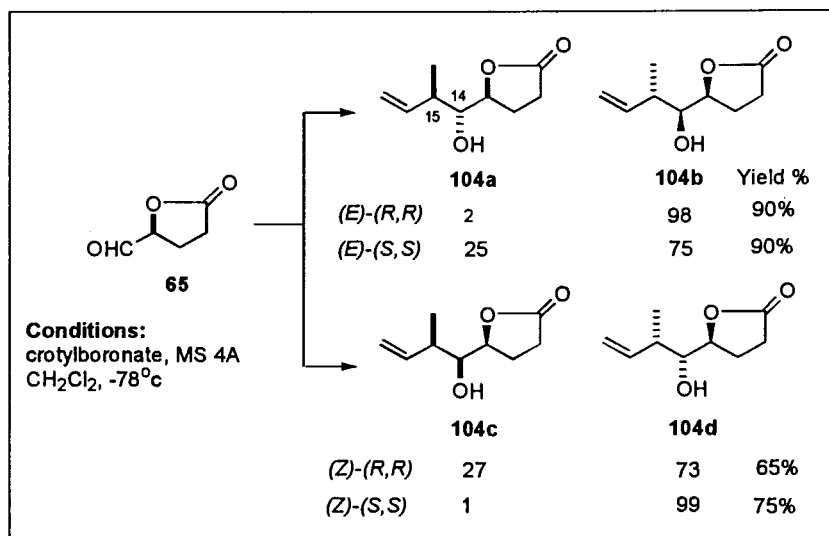
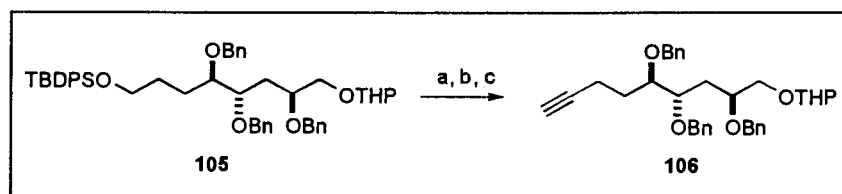


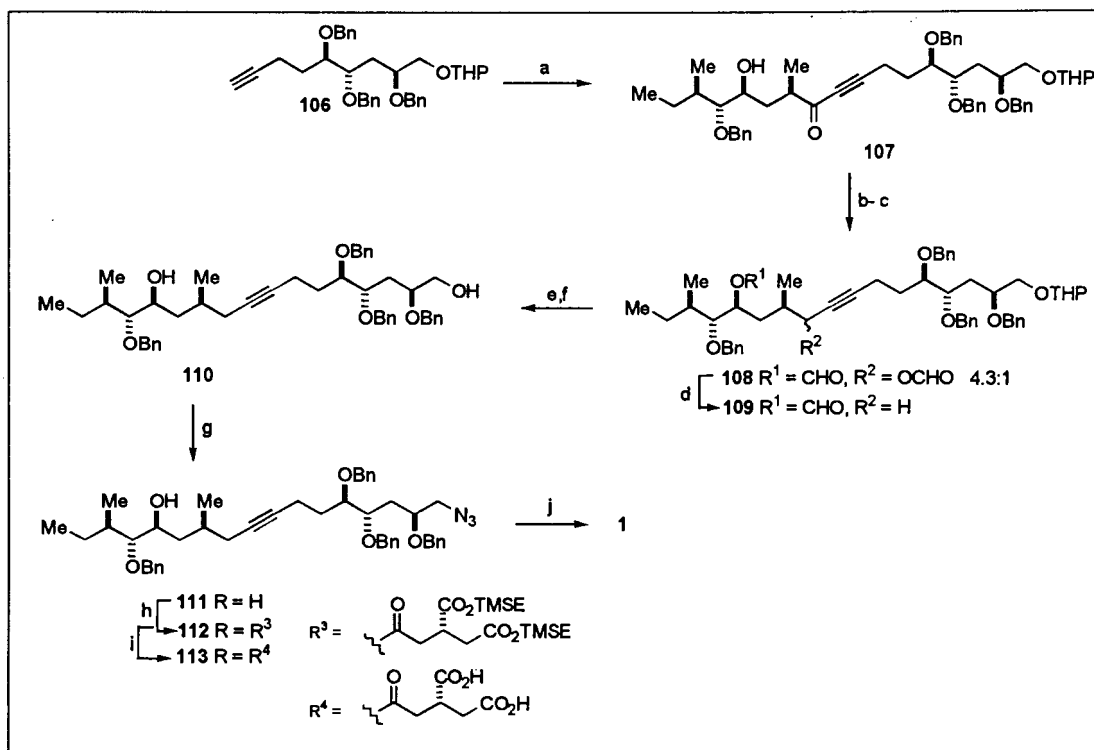
Fig 1.7: Short synthesis of the intermediate 104 in the synthesis of 102.

route described for 88a (see Scheme 1.12 and 1.13) and converted to the acetylene 106 (Scheme 1.16). The acetylene in turn was condensed with the left-half 74b to afford 107 in good yield. Luche⁷¹ reduction of 107, followed by formylation gave formate 108 that was catalytically deoxygenated using palladium(II) acetate to give 109. Sequential deprotection of the acyl and THP groups afforded diol 110 which was regioselectively converted to azide 111 under Mitsunobu conditions.⁷² The azide 111 was acylated with the tricarballic acid segment (S)-75 by the Yamaguchi method⁷³ to afford 112. Removal of the trimethylsilyl ester groups with TBAF gave 113. The reduction of the azide and triple bonds followed by hydrogenolysis of all benzyl groups under conditions described by Shi *et al.*⁷⁴ afforded the AAL TA₁ toxin 1 (Scheme 1.17).



Scheme 1.16: Synthesis of the acetylene analog of 74.

Reagents: a) TBAF, THF, (89%); b) CBr₄, i-Pr₂NEt, CH₂Cl₂, (75%); c) *n*-BuLi, Et₂O, THF, -78°C (75%).

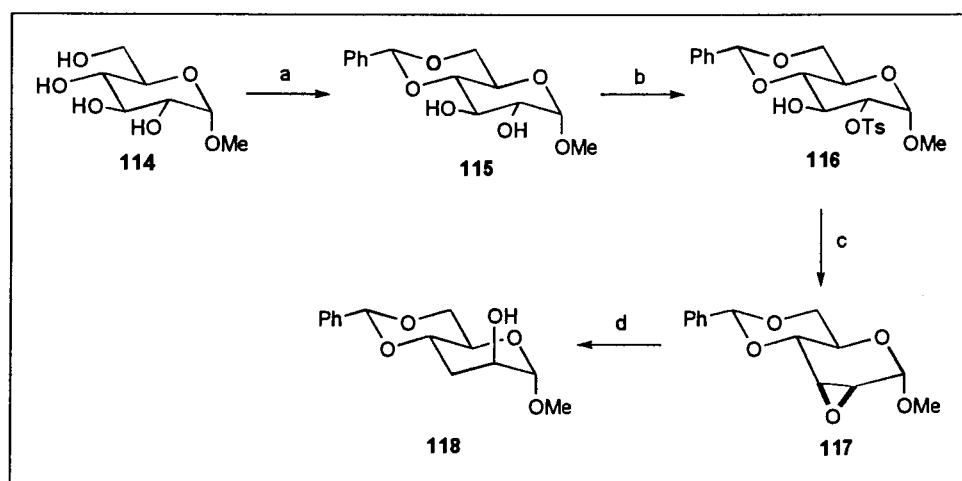


Scheme 1.17: Coupling of the segments 73b, 106 and (S)-75 to afford AAL TA₁ toxin.

Reagents: a) n-BuLi, Et₂O, -20°C, 73b (72%); b) NaBH₄, CeCl₃, MeOH, (85%); c) Ac₂O, HCO₂H, Py, (97%); d) Pd(OAc)₂, n-Bu₃P, THF, (84%); e) LiAlH₄, THF; f) PPTS, EtOH, (89%, 2 steps); g) HN₃, Ph₃P, DEAD, toluene, (69%); h) 2,4-NO₂C₆H₄COCl, (S)-75, EtN₃, toluene, then 78, DMAP, (71%); i) TBAF, THF; j) H₂, Pd-C, *t*-BuOH-THF-1M HCl (3:1:0.04), (76%, 2 steps)

Although the Oikawa group was able to achieve the synthesis of the three retrosynthetic fragments of the AAL TA₁ toxin, and subsequently the total synthesis of the toxin, there were a few drawbacks in the routes followed. In the first reported synthesis of the left-half segment 73a (Scheme 1.11), the opposite stereochemistry was produced at C(14) and the conversion to the desired stereochemistry introduced three additional steps in the reaction sequence. Alternative methods proposed in later reports to maximise the synthesis were not better either as Scheme 1.15 is very laborious and the Wittig reaction step to prepare 101 has a very low yield (19%). Although the yield obtained in the Scheme proposed for the rapid synthesis of the intermediate 104 is high (Figure 1.7), the desired diastereomer is always the minor product and as such the synthesis is not maximised.

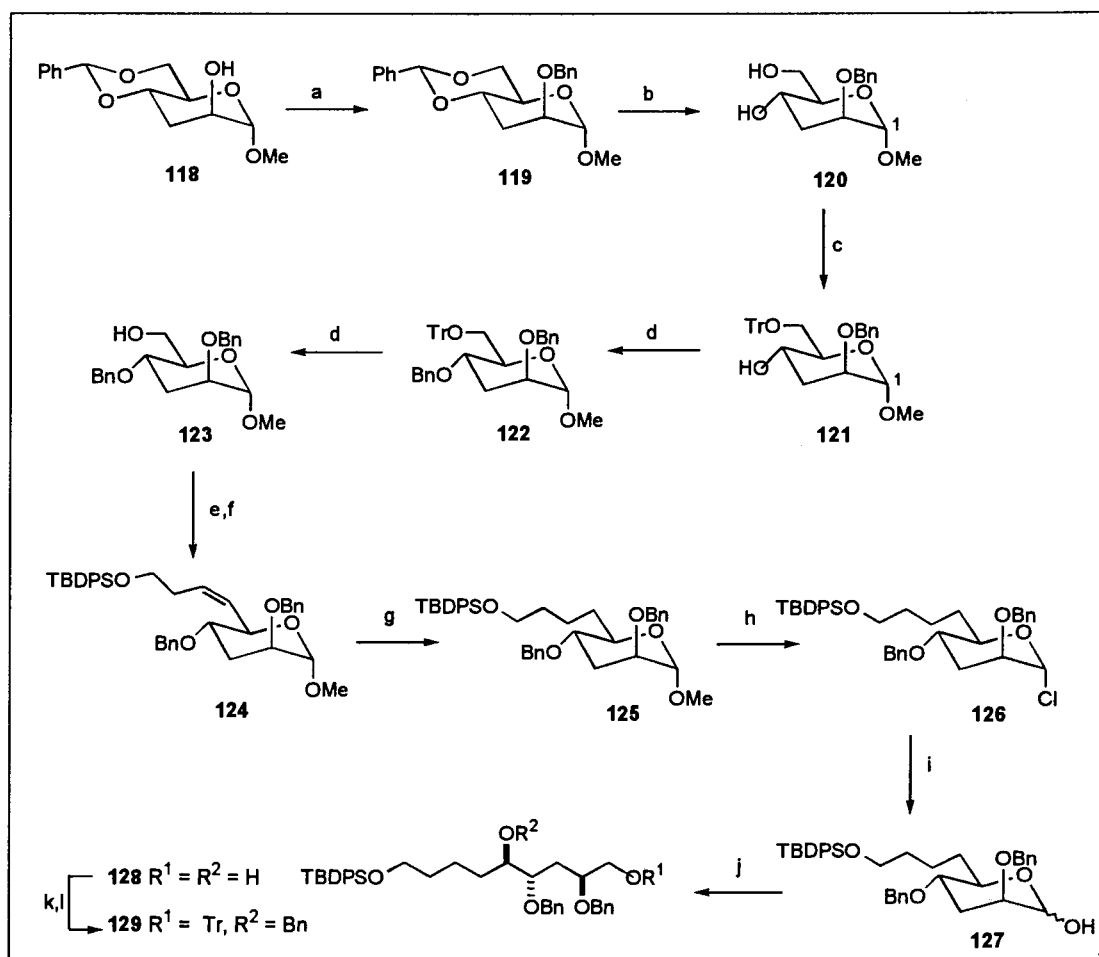
As a result of the shortcomings in the Oikawa synthesis, alternative synthetic routes were proposed for the synthesis of the C(1)-C(9) unit of the AAL toxin TA and consequently for its total synthesis in our research group.⁷⁵ The retrosynthetic analysis of the aminopentol backbone of TA toxin identifies (2*R*,4*S*,5*R*,6*R*)-2,6-dimethyloctane-1,4,5-triol, synthon A and (2*S*,4*R*,5*R*)-1-amino-nonane-2,4,5,9-tetraol, synthon B (see Chapter 4.2) as proposed by Oikawa. Further analysis of synthon B, the C(1)–C(9) unit of the aminopentol backbone, suggested that it could be derived from a C₆ carbohydrate such as methyl 3-deoxy- α -D-*arabino*-hexopyranoside **114**, prepared from D-glucose in a series of transformations as outlined in Scheme 1.18, followed by C₃ chain elongation at the C(6) terminus. The transformations involve the selective protection of the C(4) and C(6) hydroxy groups of methyl α -D-glucopyranoside by the formation of the thermodynamically-favoured six-membered benzylidene derivative **115**. Tosylation of the C(2) hydroxy group of **115** was accomplished using *N*-tosylimidazole and sodium methoxide to afford **116**. Treatment of the 2-O-tosyl derivative **116** with sodium methoxide, formed by addition of sodium metal to the methanol solution of **116**, afforded the *manno*-epoxide **117** in excellent yield. LiAlH₄ reduction of **117** proceeds by regioselective hydride attack at C(3) resulting in the formation of methyl 4,6-benzylidene-3-deoxy- α -D-*arabino*-hexopyranoside **118** with the required stereochemistry at C(2).



Scheme 1.18: Synthesis of methyl 4,6-benzylidene-3-deoxy- α -D-*arabino*-hexopyranoside **118**.

Reagents: a) PhCH(OMe)₂, CSA (97%); b) NaOMe, TsIm (92%); Na(s), MeOH (72%); d) LiAlH₄ (89%).

Protection of the C(2) hydroxy group in **118** as the benzyl ether gave **119**. Treatment of **119** with TsOH in methanol regenerated the diol **120**. The C(6) hydroxy group was selectively protected as the trityl ether **121**, followed by benzylation of the C(4) hydroxy group and subsequent deprotection of the C(6) trityl ether to give the alcohol **123**. Swern oxidation of the C(6) primary alcohol gave an aldehyde which was immediately used in a Wittig reaction with the ylide generated from 3-[(*t*-butyldiphenylsilyloxy)-propyltriphenylphosphonium iodide using BuLi, to afford the



Scheme 1.19: Chain elongation of methyl 4,6-benzylidene-3-deoxy- α -D-arabino-hexopyranoside **118** to a C(9) unit.

Reagents: a) TsOH, MeOH, H₂O (95%); b) TrCl, DMAP, Pyridine, CH₂Cl₂ (74%); c) BnBr, KH (96%); d) TsOH, MeOH, H₂O (89%); e) Swern oxidation; f) BuLi, **123** (58%); g) Raney-Ni, H₂ (98%); h) BCl₃.SMe₂; i) SiO₂, H₂O (53%, 2 steps); j) NaBH₄, EtOH (87%).

alkene **124**. Hydrogenation of **124** with freshly prepared Raney nickel afforded **125**. The methyl glycoside bond of **125** was cleaved using excess of BCl₃.Me₂S reagent to



give **126**, followed by absorption on moist silica gel and elution after 24 h to give the hemiacetal **127**, a mixture of α,β -anomers in the ratio 1.4:1. Reduction of the hemiacetal **127** using NaBH_4 in ethanol gave **128**, the (C1)-C(9) segment of the AAL TA₁ toxin which was protected as the trityl derivative **129** (Scheme 1.19).

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2 CHEMISTRY OF CHIRAL SULFOXIDES

2.1 INTRODUCTION

The synthesis of homochiral molecules, and especially natural products with novel physiological properties, is an important part of modern organic chemistry. Organosulfur compounds have been found over the years to be an attractive tool in such syntheses.^{1,2,3,4} Sulfoxides are one of the most important groups of organosulfur compounds due to their relative ease of preparation, selective elaboration into more complex sulfoxides and ready conversion to other functional groups not containing sulfur.⁵ Sulfoxides have become associated with many diverse areas of synthetic chemistry; indeed, their ability to act as a handle for the stereoselective generation of chirality at proximate centers has attracted much research worldwide.

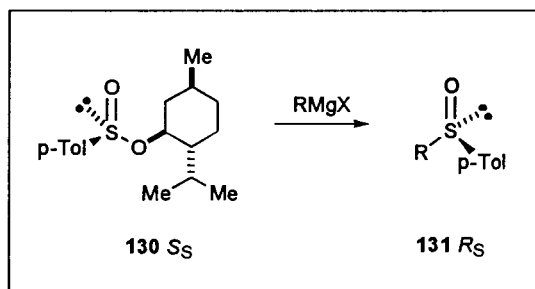
2.2 CHEMISTRY OF CHIRAL SULFOXIDES

The development of sulfoxide chemistry started in 1926 with the pioneering work of Harrison⁶ on the optical resolution of sulfoxides. Since then there has been an exponential growth in the synthesis of chiral sulfoxides and their application in natural product synthesis as shown by the number of reviews published on the subject.⁷⁻¹⁴ Attention is therefore directed only to those aspect that have a direct bearing on the work covered in this thesis in order to create a general background.

2.2.1 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. Optical resolution was later achieved by the introduction of an acidic or a basic group into the molecule⁶ or via a transition metal complex such as *trans*-dichloro-[ethyl *p*-tolylsulfoxide][α -methylbenzyl-mine]-platinum(II). Asymmetric oxidation of sulfides using optically active peracids has also been investigated but the optical yields in general were poor.¹⁵⁻²⁰

Anderson,^{21,22} following the method proposed by Gilman,²³ prepared optically active sulfoxides from the optically active sulfinate esters using a Grignard reaction. Solladié *et al.*²⁴ was able to optimise the production of (+)-(*R*)-methyl *p*-tolylsulfoxide on a large scale using the Grignard reaction methodology. The method involves the reaction of methyl magnesium iodide with (*S*)-(-)-menthyl *p*-toluenesulfinate **130** at 0°C in benzene (Scheme 2.1). (+)-(*R*)-Methyl *p*-tolylsulfoxide **131** is obtained exclusively and in high enantiomeric excess (e.e) (>98%) by this method and is purified by crystallization from hexane- ether (1:1) at -5°C.



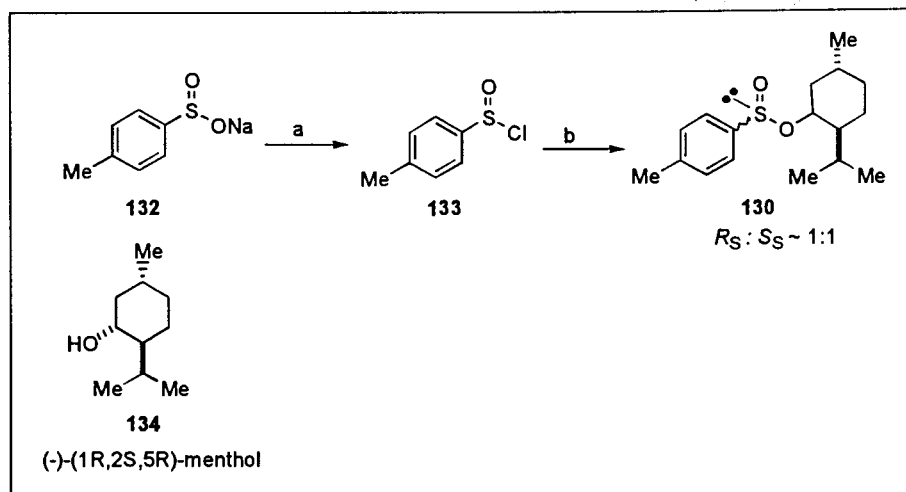
Scheme 2.1: Synthesis of (*R*)-sulfoxides proceeds by S_N2 inversion.

(-)-Menthyl (*S*)-*p*-toluenesulfinate **130** is obtained from the reaction of (-)-menthol **134** with *p*-toluenesulfinyl chloride **133**.²⁵ The esterification reaction shows no particular stereoselectivity and gives a 1:1 mixture of diastereomers epimeric at sulfur. The desired (*S*)-diastereomer **130** is crystalline and is obtained by crystallization at -20°C in pure form and high yield (between 80 - 90%). The corresponding (*R*)-diastereomer is an oil that undergoes acid-catalysed epimerisation to give once again a mixture of diastereomers from which the (*R*)-diastereomer is obtained by crystallization.²⁴ (Scheme 2.2).

2.2.2 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 number of ways, the most important of which is in carbon-carbon bond formation.²⁶ Racemic mixtures of β -ketosulfoxides were first prepared by Corey,^{27,28} and the first optically pure compound was prepared by Kunieda,²⁹ while Solladié^{30,31} has successfully optimized the reaction conditions.

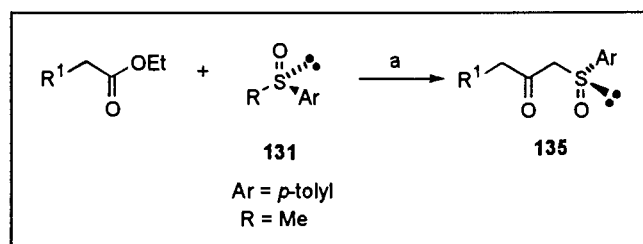
The reaction involves the addition of an ester to a cold solution of two equivalents of the α -carbanion of (+)-(*R*)-methyl *p*-tolylsulfoxide **131** (Scheme 2.3)



Scheme 2.2: Synthesis of (-)-(S)-menthyl *p*-toluenesulfinate.

Reagents: a) SOCl_2 , 10°C ; b) pyridine, **134**.

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.



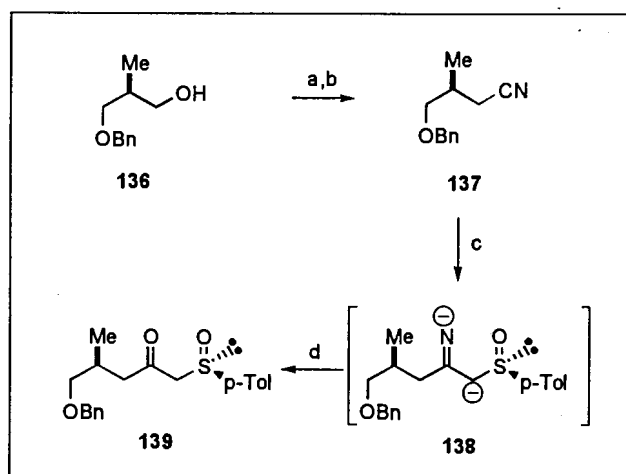
Scheme 2.3: Preparation of β -ketosulfoxide.

Reagent: a) LDA, -78°C .

Vleggaar and Zeevaart³² reported the use of nitriles 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 (**138**). Aqueous acidic work-up generates an imine that in turn is hydrolysed under the work-up conditions to form the β -ketosulfoxide (Scheme 2.4).

2.2.3 Selective reduction of β -ketosulfoxides

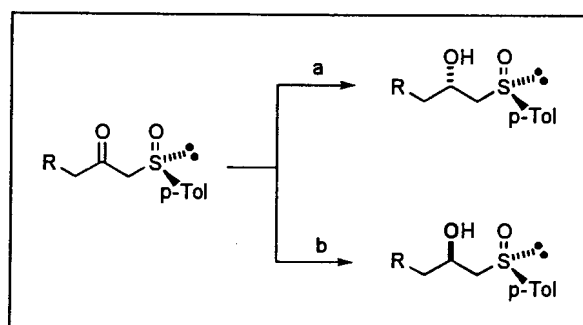
The great advantage of chiral sulfoxides in synthesis is the stereoselectivity attainable in the reduction of the β -ketosulfoxide using diisobutyl aluminium hydride



Scheme 2.4: Preparation of β -ketosulfoxide from nitriles.

Reagents: a) TsCl, DMAP (90%); b) NaCN, DMF (92%); c) LDA, **131**, $0^{\circ}\text{C}\rightarrow\text{rt}$.; d) aq. HCl (pH 2) (85%).

(DIBALH). The stereochemistry of the stereogenic centre formed in the reduction of the β -carbonyl group is determined by the presence or absence of ZnCl_2 or ZnBr_2 in the DIBALH reduction (Scheme 2.5).^{33,34} Early work on the reduction of β -ketosulfoxides using NaBH_4 or LiAlH_4 gave a disappointingly low d.e of 60-70%.³⁵ Solladié³³ found an increase in diastereoselectivity when DIBALH was added to the substrate at low temperature instead of adding the substrate to the reducing agent. The relative ease of controlling the stereochemistry of the hydroxy group formed in the selective reduction of the β -ketosulfoxide has made the use of chiral sulfoxides very attractive for asymmetric synthesis. This is especially evident from the number of natural product syntheses in which it has been employed.^{30,31,36-41}



Scheme 2.5: 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-ZnCl₂ is shown in Figure 2.1 and is based on an early proposal formulated by Solladié³³ and Garcia Ruano.⁴² 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 ZnCl₂ 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.

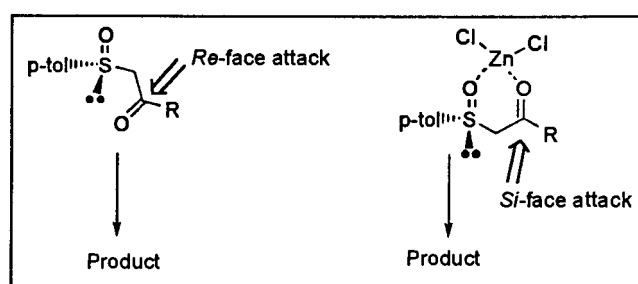


Figure 2.1: First mechanistic explanation for the stereoselective reduction

In subsequent publications Solladié and Garcia Ruano⁴³⁻⁴⁵ proposed a new and more complicated model (Figure 2.2). They postulated that hydride transfer is intramolecular and not intermolecular as previously believed. In the favoured twisted conformation C₁, in which the *p*-tolyl group is pseudo-equatorial, DIBAL will approach by forming a complex with the geometrically well-located chlorine atom, leading to a bimetallic-bridged species, M₁. The hydride transfer will now be intramolecular from the top to the *Si*-face, leading to the (*R*) configuration at C-2. The *p*-tolyl group in the other possible conformation, C₂, is in an unfavourable pseudo-axial position that will greatly hinder transfer from the bottom to the *Re*-face. For the reduction reaction without ZnCl₂, they also postulated a bimetallic-bridged species, M₃ that will, through intramolecular hydride transfer, lead to the (*S*) configuration at C-2.

2.2.4 α -Alkylation of β -hydroxysulfoxides.

The introduction of an alkyl group at the α -position to the sulfoxide group through carbon-carbon bond formation is of importance in the context of this thesis as it forms the basis for a chain extension method of a synthon identified by retrosynthetic analysis (see Chapter 4).

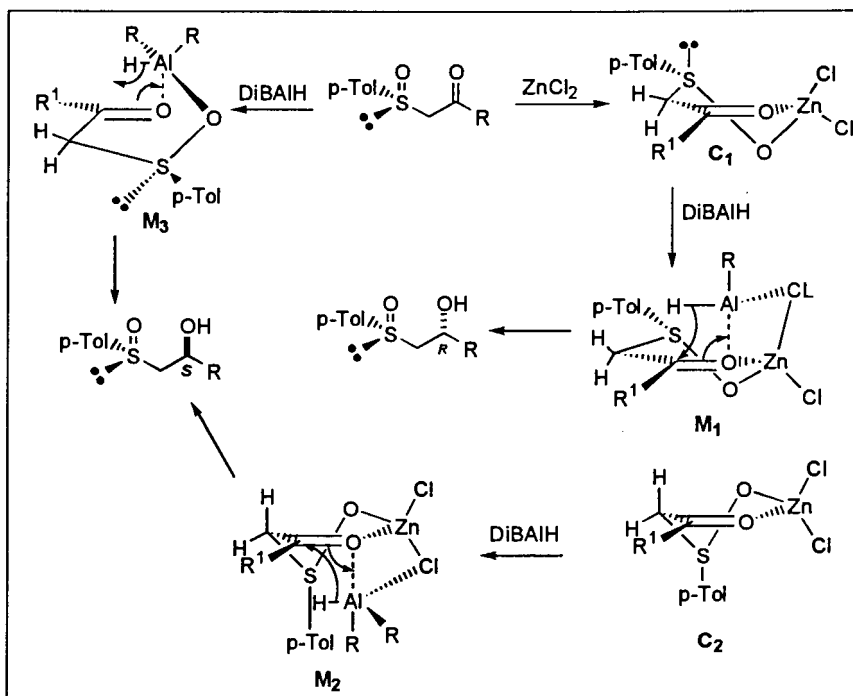


Figure 2.2: Stereoselective reducton: Intramolecular hydride transfer model.

The acidity of the proton α to the sulfoxide group is between those of a benzylic proton and a proton α to the carboxylate function.⁴⁶ Addition of two equivalents of a strong base such as LDA or *n*-BuLi abstracts one of the methylene protons α to the sulfoxide group as well as the hydroxy proton to form a dianion. It was proposed that the dianion forms a six-membered ring through chelation of the oxygen atoms with the lithium cation. (Figure 2.3)

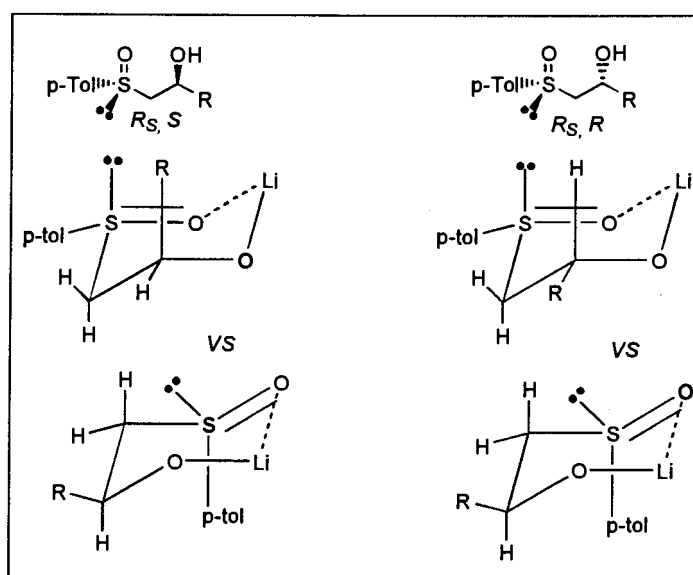


Figure 2.3: Chelation of the β -hydroxysulfoxide anion with a lithium cation

The chair conformation in which both the aryl and alkyl groups are in the equatorial position is expected to be the most stable conformation. This is expected to cause the alkylation of the dianion to be highly stereoselective. Results have shown that the alkylation of β -hydroxysulfoxides depends mainly on the configuration of the hydroxy-bearing stereogenic center^{7,47,48} with little or no influence from the sulfur stereogenic center. The *threo* product [in which the hydroxyl and the alkyl (R^1) groups are *anti*] is favored over the *erythro*, (in which the hydroxy and the alkyl (R^1) groups are *syn*) in ratios varying from 1:1 to 95:5 (Figure 2.4). Also, the larger the size of the alkyl group (R and R^1), the slower the reaction proceeds and as such, the yield is low.

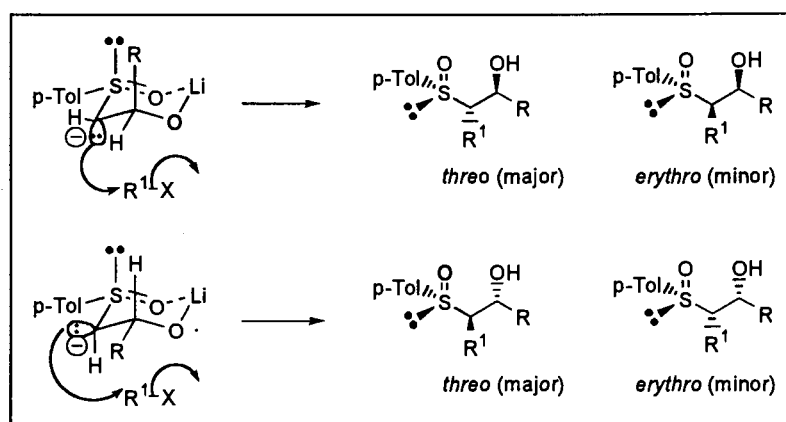
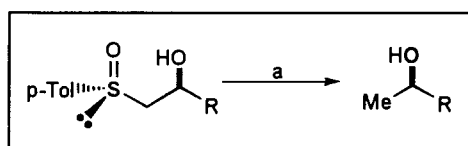


Figure 2.4: Alkylation of β -hydroxysulfoxides

2.2.5 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,^{49,50} sodium-



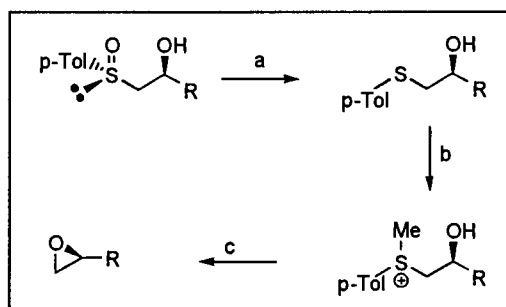
Scheme 2.6: Reductive removal of the sulfoxide group.

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

amalgam with disodium hydrogen phosphate (Na_2HPO_4)⁵¹ or lithium metal⁵² in diethylamine at -78°C . These methods replace the sulfoxide group with a hydrogen atom (Scheme 2.6).

Another well-documented procedure for the removal of the sulfoxide groups involves the formation of an epoxide. The sulfoxide is firstly reduced to a sulfide using LiAlH_4 ,⁴³ $\text{Zn}/\text{Me}_3\text{SiCl}$,^{53,54} or trifluoroacetic anhydride and NaI in acetone,⁵⁵ or $^t\text{BuBr}$ in CHCl_3 ,⁴¹ and then treatment with Me_3OBF_4 ^{41,55} to form the sulfonium salt which is immediately reacted with aqueous base such as NaOH or K_2CO_3 ^{41,54} to form the epoxide (Scheme 2.7).

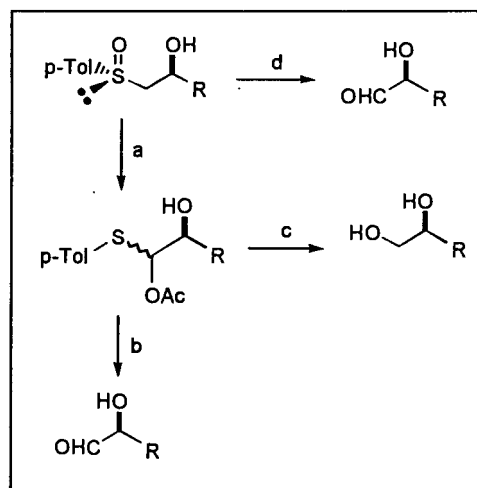
Conversion of the sulfoxide group to the alcohol via Pummerer rearrangement is a well-known procedure. The method allows the removal of the sulfur group while retaining the functionality at the carbon atom carrying it. The sulfoxide is converted to the sulfide, an O,S acetal using sodium acetate and acetic anhydride at 145°C which



Scheme 2.7: Conversion of β -hydroxysulfoxides to epoxides.

Reagents: a) LiAlH_4 ; b) Me_3OBF_4 ; c) aq NaOH

is then cleaved by a number of methods. This procedure was employed in the course of this research to allow for the extension of the C_5 to a C_9 carbon chain of the synthetic target. Cleavage with DIBALH in CH_2Cl_2 at -78°C ⁴⁰, Cu(II) or Mg(II) salts in aqueous $\text{NaOH}/\text{CH}_3\text{CN}$ ^{55,56} produces the β -hydroxyaldehyde, whereas reduction with LiAlH_4 ^{39,57} or desulfurisation by catalytic hydrogenation using Raney nickel⁵⁵ 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 $\text{NaHCO}_3/\text{H}_2\text{O}$ ⁵⁸ (Scheme 2.8).



Scheme 2.8: Pummerer rearrangement and cleavage of the sulfur group.

Reagents: a) Ac_2O , NaOAc ; b) $\text{HgCl}_2/\text{MeCN}/\text{H}_2\text{O}$ or $\text{CuCl}_2/\text{MeCN}/\text{H}_2\text{O}$ or DIBALH , CH_2Cl_2 , -78°C ; c) LiAlH_4 , Et_2O ; d) i. 2,6-Lutidine/TFAA/ CH_3N ; ii. aq. NaHCO_3 .

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3 USE OF ACETONIDES IN SYNTHESIS

3.1 INTRODUCTION

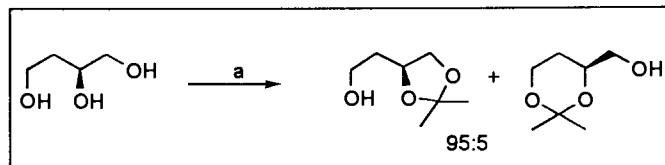
Protecting groups play a pivotal role in organic synthesis and acetonides (also known as isopropylidene acetals) have been extensively employed in the protection of both 1,2- and 1,3-diol systems. Their ease of formation and relative stability to most reaction conditions (except for protic and Lewis acids), and their ready removal, both in high percentage yields, have made the acetonide group a very attractive tool.¹ The characteristic ¹³C chemical shifts of acetonides have in recent times been widely used in the assignment of the relative stereochemistry of diol systems in complex polyhydroxy natural products.

3.2 FORMATION OF ACETONIDES

The oldest method used to prepare acetonides involves the use of dry acetone in the presence of an acid catalyst such as TsOH. Azeotropic removal of the water formed in the reaction is not feasible due to the low boiling point of acetone and other methods using molecular sieves or an inorganic dehydrating agent such as anhydrous CuSO₄ must be used.^{2,3} In some cases reaction of a diol with acetone using a Lewis acid such as FeCl₃⁶ or AlCl₃⁷ has been reported. Acetal exchange using 2,2-dimethoxypropane is an alternative method that avoids the need for a dehydrating agent since two moles of methanol are formed in the reaction. The exchange will go to completion provided the equilibrium is favourable, as it is in most cases when 2,2-dimethoxypropane is present in excess as both a reagent and a solvent. 2-Methoxypropene or 2-trimethylsilyloxypropene can be used in less favourable circumstances.

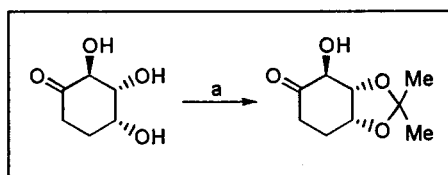
Acetonide formation is a thermodynamically driven process: thus in cases where two or more acetals can be formed, the more stable product will prevail.⁸⁻¹⁰ Hence in the reaction of 1,2,4-butanetriol the formation of the 5-membered 1,3-dioxolane ring is thermodynamically favoured over the formation of the 6-membered

1,3-dioxane ring in a ratio of 95:5 (Scheme 3.1). Furthermore *cis*-fused dioxolanes are favoured over *trans*-fused systems (Scheme 3.2)



Scheme 3.1 1,3-Dioxolane vs. 1,3-dioxane formation.

Reagents: a) Acetone, TsOH, CuSO₄, 62h, r.t., (85%).

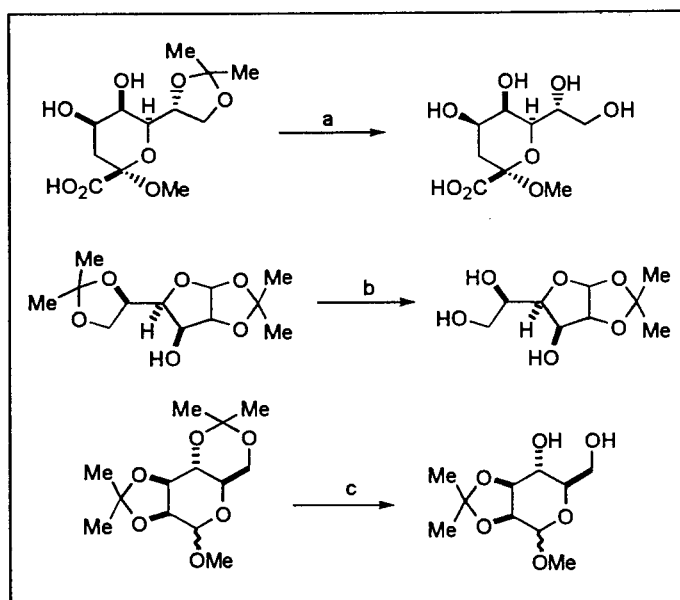


Scheme 3.2 Preferential formation of *cis*-fused over *trans*-fused systems.

Reagents: a) H₂C=C(Me)OTMS, HCl_(g), CH₂Cl₂, r.t. 2h, (95%).

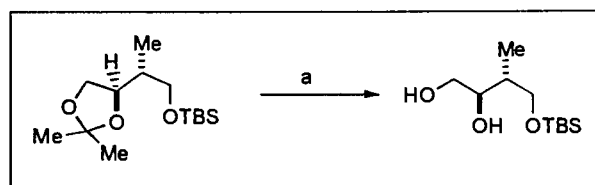
3.3 CLEAVAGE OF THE ACETONIDE GROUP

Acid-catalysed hydrolysis is the most common method for deprotecting acetonides. The reaction times and acid strengths can vary widely. In most cases aqueous acetic acid, dilute HCl in THF or an exchange resin such as Dowex 50W with its sulfonic acid group, will rapidly cleave the ring.¹¹ Similarly catalytic amounts of TsOH in aqueous methanol will result in removal of the acetonide group. A wide difference in reactivity is observed as shown in Scheme 3.3. 1,3-Dioxanes hydrolyse faster than 1,3-dioxolanes but *trans*-fused 1,3-dioxolanes hydrolyse faster than 1,3-dioxanes.¹² Deprotection of an acetonide in the presence of other acid labile groups such as a *t*-butyldimethylsilyl ether group has been accomplished by treatment of the acetal with ethanethiol and acid (Scheme 3.4).¹³ The use of Lewis acids has also been reported¹⁴ to lead to cleavage of the acetonide group. Another reagent that has proved effective in the high yield cleavage of the acetonide group is catalytic I₂ in methanol.¹⁵



Scheme 3.3: Cleavage of the acetonide ring under different conditions.

Reagents: a) Dowex 50w (H⁺), H₂O, 80^o C, 1.5h (44%); b) H₂SO₄, H₂O-MeOH, r.t, 22h, (95%); c) AcOH-H₂O.



Scheme 3.4: Cleavage of the acetonide ring in compounds with acid sensitive groups.

Reagents: a) EtSH (7eq), TsOH, CH₃Cl₃.

3.4 THE USE OF ¹³C NMR TO DETERMINE THE STEREOCHEMISTRY OF 1,3-DIOL ACETONIDES

Natural products such as the polyene macrolide antibiotics contain alternating (1,3.5....)-polyol chains and the determination of both the relative and absolute configuration of these chains is a daunting and challenging task. Single crystal X-ray crystallography allows us to determine the stereochemistry of compounds that exhibit good crystalline properties but in the case of the polyene macrolides the stereochemistry of only two of more than 200 compounds have been determined by this method *viz.* amphotericin B¹⁶ and roxaticin.¹⁷ The stereochemistry of other polyene macrolides such as mycotycin¹⁸⁻²⁰, nystatin,²¹⁻²³ and roflamycin²⁴ has been

determined by chemical degradation and synthesis of the formed fragments as well as NMR analyses (Figure 3.1).

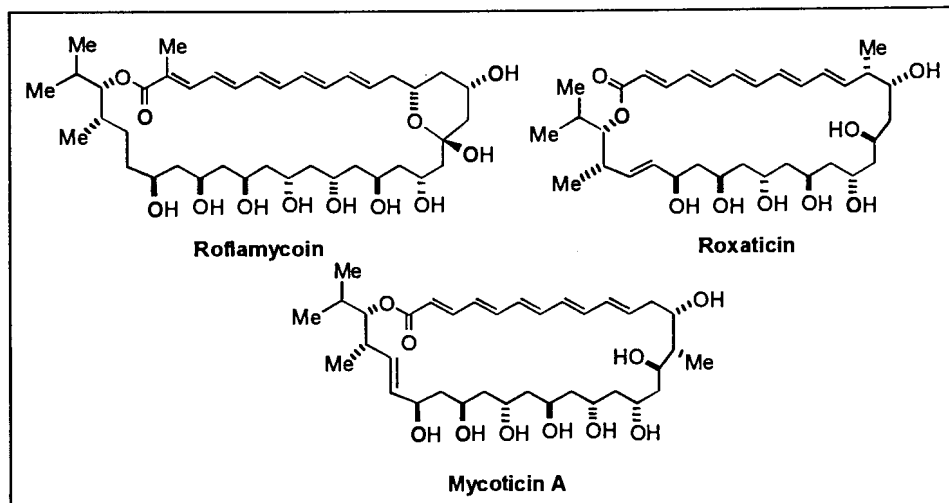


Figure 3.1: Structures of some polyene macrolide antibiotics.

Rychnovsky²⁴⁻²⁹ has made an extensive study of the ¹³C chemical shifts of a large number of 1,3-diol acetonide derivatives and concluded that *syn* and *anti* 1,3-diol acetonides (4,6-dialkyl-2,2-dimethyl-1,3-dioxanes) can be readily and unambiguously distinguished by ¹³C NMR spectroscopy. The difference in the ¹³C chemical shift values for the *syn* and *anti* diastereomers is attributed to their different conformational properties. The *syn* acetonide exists in a well-defined chair conformation with the C(4) and C(6) alkyl substituents in equatorial positions. The *anti* acetonide, however, exists in a twist-boat conformation with the C(4) and C(6) alkyl substituents in pseudo-equatorial positions in order to avoid the 1,3-diaxial interactions between an axial methyl group and one of the two substituents at C(4) and C(6) in either of two possible chair conformations (see Figure 3.2)^{30,31} The steric bulk of the substituent groups at C(4) and C(6) also plays an important role in *anti* 1,3-diol acetonides. When R¹ and R² are large (e.g. R¹, R² = CH₂R), the 1,3-diaxial interaction with the appropriate C(2) methyl group destabilises both possible chair conformations and forces the acetonide to adopt a twist-boat form. In those cases where R¹ is small (e.g. R¹=H), the 1,3-diaxial interaction with the appropriate C(2) methyl group is small and the acetonide will adopt a chair conformation with R¹ in the axial position.²⁶

The chair and the twist-boat conformations of the *syn* and *anti* 1,3-diol acetonides, and thus the relative stereochemistry of the corresponding diols, can be

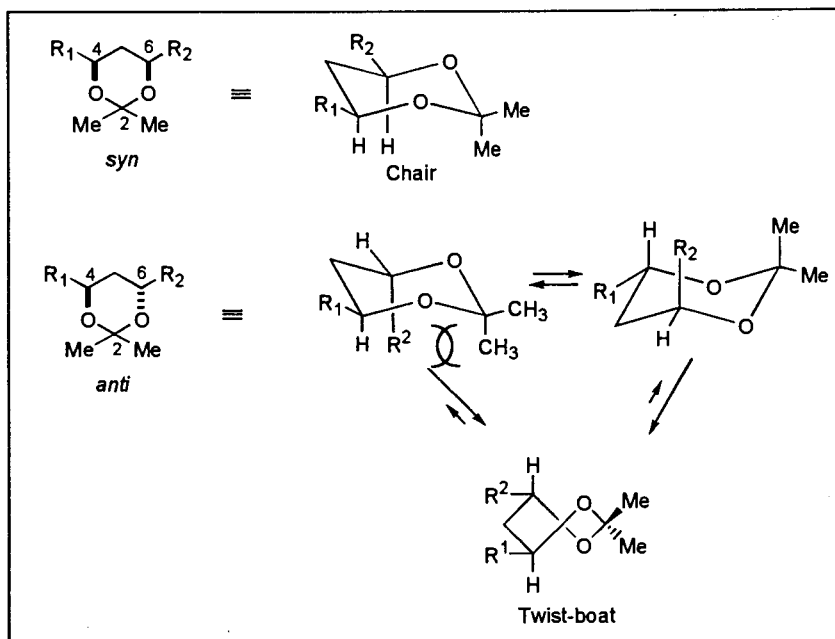


Figure 3.2: Conformations of *syn*-1,3- and *anti*-1,3-diol acetonides.

distinguished by the ^{13}C chemical shift values of the acetonide. The two ring conformations can also be distinguished by analysis of the appropriate ($^1\text{H}, ^1\text{H}$) coupling constants and ^1H NOE experiments and this procedure has been used to assign the stereochemistry of some 1,3-diols.³² A similar procedure has been used to determine the stereochemistry of 1,2-diol acetonides.³³

The ^{13}C NMR spectrum of a typical *syn*-1,3-diol acetonide shows the axial C(2) methyl group at ca. 19 ppm and the equatorial C(2) methyl group at ca. 30 ppm. In the case of the *anti*-1,3-diol acetonide both C(2) methyl groups have the same

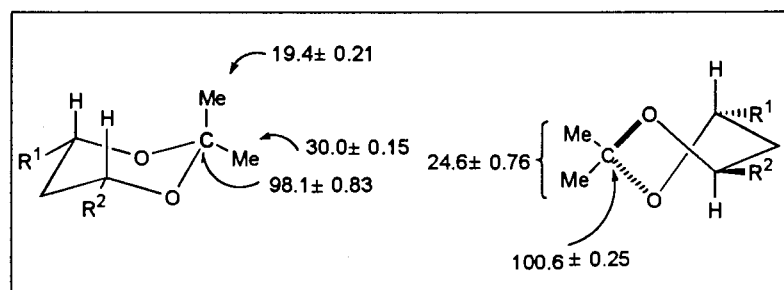


Figure 3.3: ^{13}C Chemical shift values for *syn* and *anti* 1,3-diol acetonides.

chemical shift value of ca. 25 ppm.^{26,33} (see Figure 3.3). The ^{13}C chemical shift value for the quaternary acetal carbon atom in 1,3-diol acetonides can also be used to

deduce the stereochemical relationship between the 1,3-diols used in the formation of the acetonide group. Acetal carbon chemical shift values of 98.1 ± 0.8 ppm indicate a *syn* stereochemical relationship whereas values of 100.5 ± 0.25 ppm are indicative of the *anti* relationship. The use of the chemical shift value of the acetal carbon atom to assign the stereochemistry of 1,3-diol acetonide systems is of use especially in polypropionate-derived natural products that contain a multitude of methyl groups.²⁶

33

3.5 CONFORMATIONAL ANALYSIS OF ANTI-1,3-DIOL ACETONIDES.

The data reported by Rychnovsky *et al.*²⁶, showed that the twist-boat conformation for *anti* 1,3-diol acetonides is dependent on the nature of the C(4) and C(6) substituents. The influence of these substituents was confirmed by dividing the *anti* 1,3-diol acetonides into two different groups in which the C(5) methyl substituent is either absent, as in polyacetate-derived natural products, or present as in many polypropionate-derived natural products. In the absence of a C(5) methyl group the chemical shifts of the C(2) methyl groups vary by only 0.25 ppm. Even in cases where the two alkyl substituents are different the two C(2) methyl groups are still in similar environments and as such have similar chemical shifts. The presence of a C(5) methyl group has a significant effect on the chemical shift of the C(2) methyl groups: values can differ by ca. 1.3 ppm. The lack of symmetry introduced by the presence of the C(5) methyl group does not significantly change the conformation and the molecule prefers to adopt a slightly distorted twist-boat conformation rather than significantly populating the chair conformation.

3.6 CONCLUSION

The use of the acetonide protecting group for the 1,3- and 1,2-diol system identified in the retrosynthetic analysis of the C₁₇-backbone of the TA *Alternaria alternata* toxin proved to be extremely valuable in the subsequent synthesis of a number of synthetic targets. The relative stereochemistry of the 1,3-diol system could be monitored at each step of the reaction sequence to determine whether epimerisation had occurred at one of the stereogenic centres, by analysing the ¹³C chemical shifts of the carbon atoms of the acetonide system.

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4 RETROSYNTHETIC ANALYSIS OF THE AAL TOXINS

4.1 INTRODUCTION

Organic synthesis has been from the beginning an integral part of organic chemistry. In the early days of organic synthesis the focus was on chemical change in the direction of chemical reactions i.e. reactants → products. Most syntheses were developed by selecting a suitable starting material (often by trial and error) and searching for a set of reactions that in the end transformed that material to the desired product (synthetic target). By the mid-1960s a different and more systematic approach started to become more popular with synthetic chemists. This approach depends on the structural features in the *reaction products* (as contrasted with starting materials) and the manipulation of structures in the reverse-synthetic sense. This method became known as *retrosynthetic* or *antithetic* analysis and its merits and power is evident from the way it has simplified and accelerated the planning process of synthetic routes and from the explosion in the number of natural products synthesised over the last few decades.¹

Retrosynthetic analysis is a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structures along a pathway that ultimately leads to simple or commercially available starting materials. The application of a transform, the exact reverse of a synthetic reaction, to a target structure, accomplishes the transformation of a molecule to a synthetic precursor. Each structure derived antithetically from a target then itself becomes a target for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the synthetic target.¹

Simple homochiral starting materials, the so-called chiral building blocks obtainable from Nature, are often commercially available and have been used in stereoselective syntheses: nonactin from (*S*)-lactic acid,² (*S*)-sulcatol from (*R*)-

glutamic acid,³ disparlure from (S,S)-tartaric acid,⁴ biotin from L-cysteine,⁵ picrotoxinin from (-)-carvone.⁶

4.2 RETROSYNTHETIC ANALYSIS OF TA TOXIN.

When one applies the process of retrosynthetic analysis to the C₁₇ backbone of TA toxin 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 synthons that would be of use to other members of the group.

Disconnection of the C(9)–C(10) bond of the C₁₇ aminopentol backbone **33** of TA toxin, generates a synthon **B** with 4 stereogenic centers, common to all the AAL toxins, and synthon **A** with 3 stereogenic centers (see Figure 4.1)

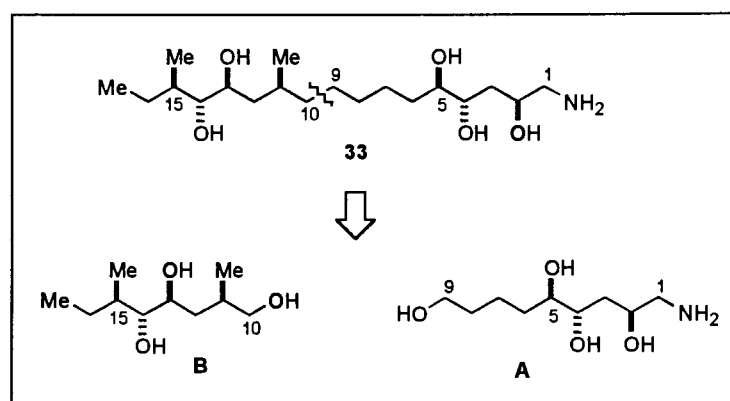
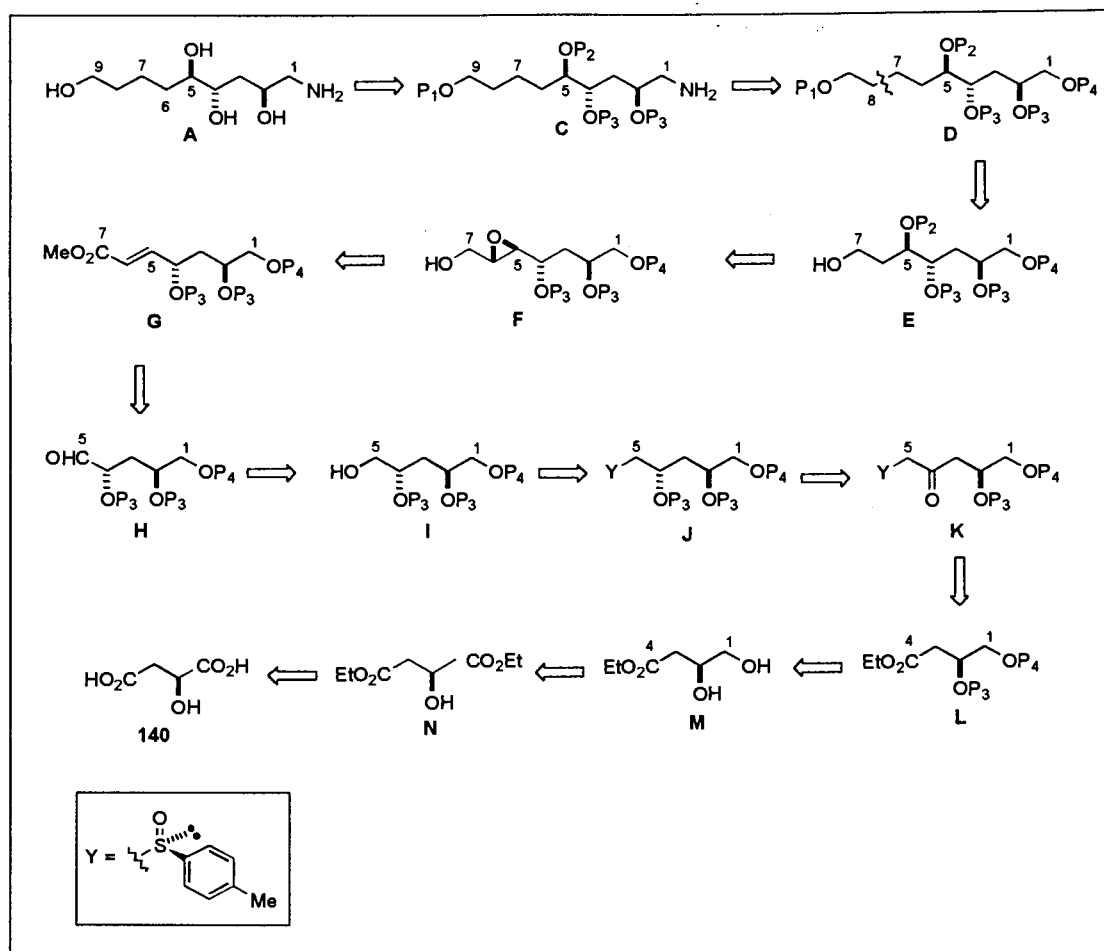


Figure 4.1: Retrosynthetic analysis of the C₁₇ aminopentol backbone of TA toxin: disconnection of the C(9)–C(10) bond.

Synthon **A** is the target molecule for the research described in this thesis. In the next stage of the analysis a protective group strategy leads to the synthon **C**. The exact nature of the protecting groups is dependent on the type of reaction and conditions used in the eventual synthetic sequence. The amino group can be transformed to the protected 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 NaN₃ to give an azide that is converted to an amino group by catalytic hydrogenation using Pd-C as catalyst.



Scheme 4.1: Retrosynthetic analysis of TA toxin: Analysis of synthon A

The C(7)–C(8) bond in synthon D was projected to arise from Wadsworth-Emmons methodology and functional group manipulations. In the synthesis direction the primary alcohol is oxidized under Swern conditions to the aldehyde that on treatment with diisopropyl methoxycarbonyl methylphosphonate and a base leads to a two-carbon chain-extended α,β -unsaturated ester. DIBALH reduction of the ester group and catalytic reduction of the double bond of the allylic alcohol completes this transformation.

The 1,3-diol relationship between the C(7) and C(9) hydroxy groups in E identifies the epoxy alcohol functionality present in synthon F. Regioselective reduction of an epoxy alcohol to a 1,3-diol is possible using Red-Al as reducing agent. Epoxy alcohols such as F are available with complete stereocontrol over the epoxidation process by using the Sharpless methodology. The requisite epoxy

alcohol in turn identifies the synthon **G** as a precursor. In the synthesis direction the α,β -unsaturated ester is reduced by DIBALH to the allylic alcohol.

The α,β -unsaturated ester group in synthon **G** is envisaged to arise as earlier in the sequence by Wadsworth–Emmons methodology. The α,β -unsaturated ester group present in synthon **G** thus identifies the aldehyde functionality present in synthon **H**. The aldehyde in turn can be obtained from the C(5) primary hydroxy group of synthon **I**. The introduction of the chiral sulfoxide group at C(5) of synthon **J** in the retrosynthetic analysis is dictated by the strategic control over the stereochemistry in the formation of the C(4) stereogenic center in the reduction of a in synthon **K**. In the synthesis direction the β -ketosulfoxide is reduced using DIBAL to give the C(4) hydroxy group with the correct stereochemistry, Protection of the hydroxy group is followed by a Pummerer rearrangement and LiAlH_4 reduction to give the C₅ alcohol represented by synthon **I**.

β -Ketosulfoxides, as outlined in Chapter 2, are obtained by reaction of an ester with a chiral sulfoxide such as (+)-(*R*)-methyl *p*-tolylsulfoxide **131**. This functional group transformation thus identifies synthon **L** with its ester functionality. Protective group manipulations in going from **L** to synthon **N**, diethyl (2*S*)-malate, identify (2*S*)-malic acid **140** as the starting material in the proposed synthesis.

4.3 RETROSYNTHETIC ANALYSIS OF TB TOXIN.

The structural difference between TA and TB toxin lies in the absence of the C(5) hydroxy group in TB toxin. It is therefore expected that the retrosynthetic analysis of the C₁₇ aminotetrol backbone **141** of TB toxin should share a number of common features and be more straightforward than that of TA toxin as the absence of a stereogenic center at C₅ will simplify matters. Figure 2.2 shows the disconnection of the C(9)–C(10) bond and the structures of the two synthons, **B** and **P** that are formed. The analysis of synthon **P** to generate the C(1) hydroxy group of synthon **R** is identical to the process described earlier for TB toxin. Functional group addition to the C(6)–C(7) bond gives an alkene synthon **S** that can be formed from a C₄ Wittig reagent and the synthon **H**, common to both analyses. Thus (2*S*)-malic acid **140** also serves as starting material for the synthesis of the backbone of TB toxin and the aldehyde synthon **H** will serve as the branch point in the synthetic routes.

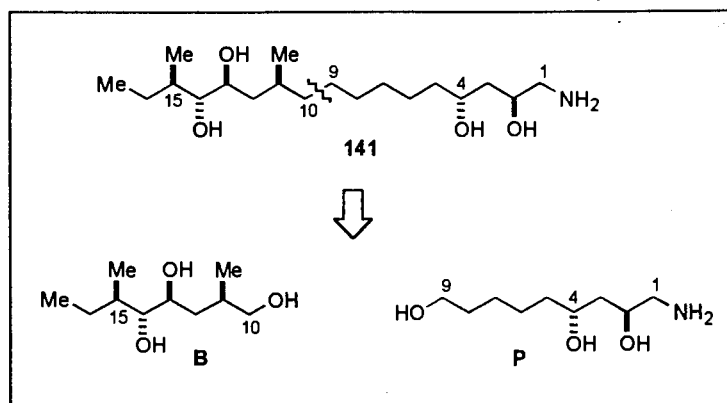
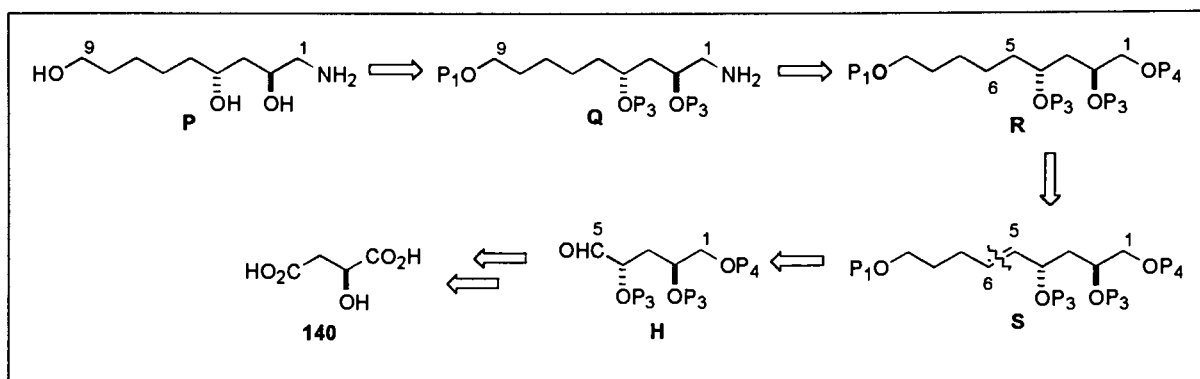


Figure 4.2: Structure of the C₁₇ backbone of TB toxin and disconnection of the C(9)–C(10) bond.



Scheme 4.2: Retrosynthetic analysis of the backbone of TB toxin.

4.4 REFERENCES

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5 SYNTHESIS OF THE C(1)–C(9) MOIETY OF TA AND TB TOXIN

5.1 INTRODUCTION

Retrosynthetic analysis of the backbone of the TA and TB toxins indicated that the first part of the proposed syntheses shared a common route for the C(1)–C(5) unit with two of the stereogenic centers. The common intermediate is a C₅ aldehyde that can be utilised for extending the carbon chain and, when required to introduce the third stereogenic centre. (2S)-Malic acid, the starting material identified in the analysis (see Chapter 4) is commercially available.

5.2 SYNTHESIS OF THE C(1)–C(9) UNIT OF TA TOXIN.

5.2.1 Synthesis of the C(1)–C(5) unit of TA toxin

The synthesis is outlined in Scheme 5.1. (2S)-Malic acid **140** was converted to the diethyl ester **142** in a Fischer esterification procedure according to the protocol of Ianni *et al.*¹ and Adkin *et al.*² The regioselective reduction of the C(1) ester functionality to the diol **143** was achieved using borane-dimethyl sulfide complex (BMS) and catalytic quantities of NaBH₄ following the protocol as described by Saito *et al.*³ The BMS was added to a solution of the diester **142** of THF. When the evolution of hydrogen ceased a catalytic quantity of NaBH₄ was added to the cooled (<10°C) reaction mixture as the reaction is exothermic. The mechanism of the reaction shows that the BMS forms a complex with the oxygen of the hydroxy group and the oxygen of the α-ester carbonyl group. Reduction commences only upon addition of NaBH₄ with the formation of BH₃. The catalytic cycle is completed when the BH₃ abstracts an H⁻ from the tetracoordinated boron complex and regenerates

the BH_4^- (see Figure 5.1). It is important to use only freshly opened NaBH_4 as old material leads to the formation of mixtures containing the lactone **144**

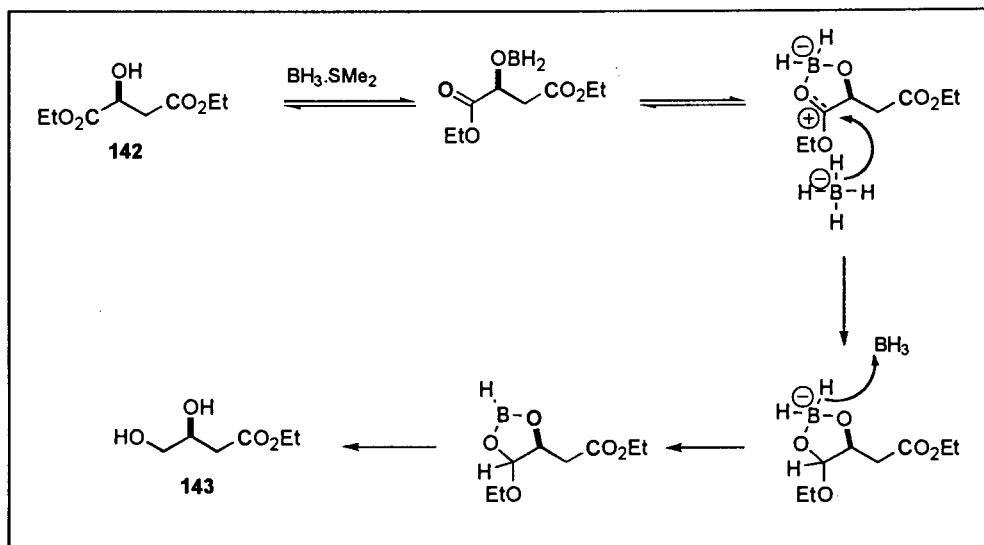
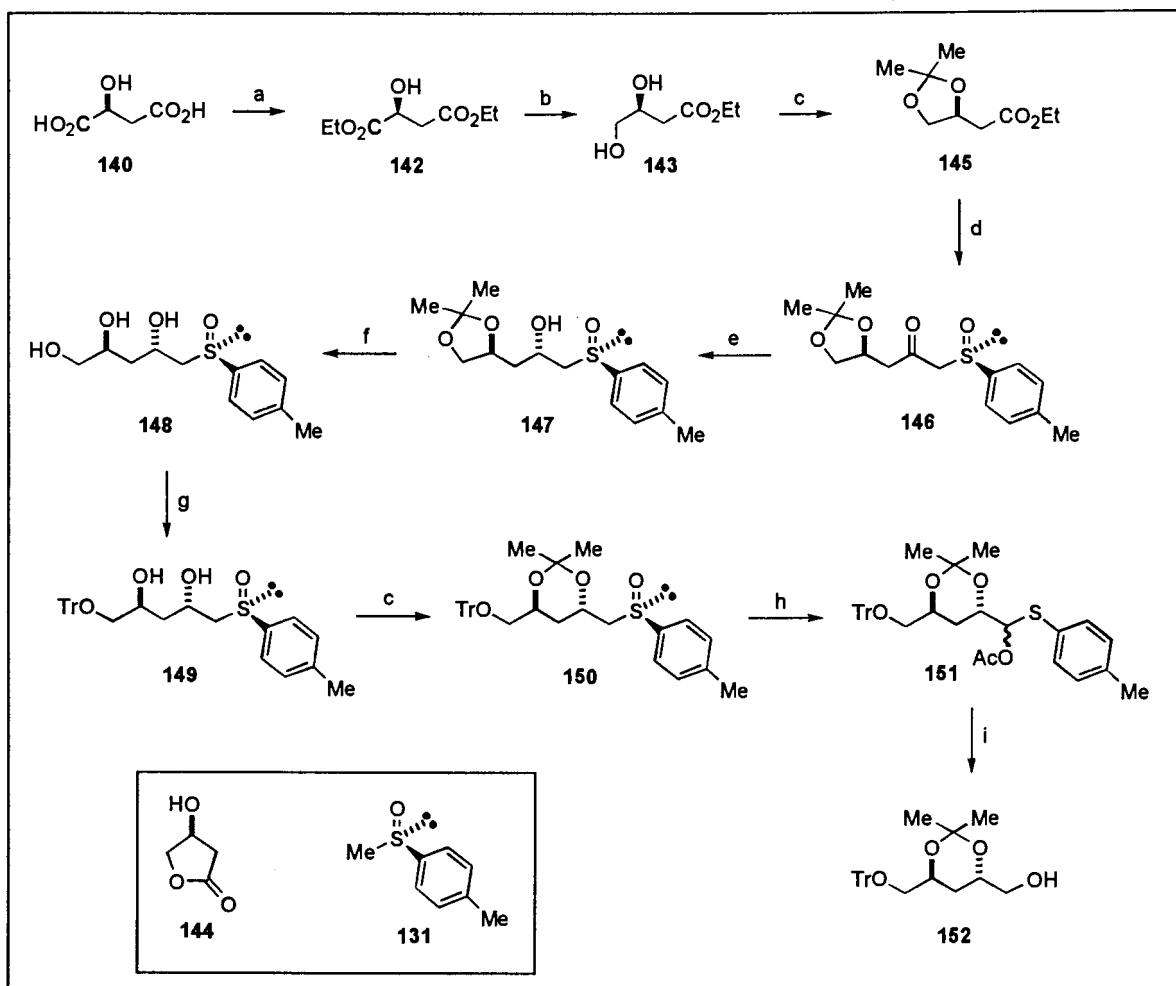


Figure 5.1 Mechanism for the reduction of the ester using BMS and NaBH_4 ³

The 3,4-diol **143** was protected as the acetonide by reaction with 2,2-dimethoxypropane under acid catalysis. The ^{13}C NMR spectrum of the acetonide **145** showed a signal at $\delta 109.01\text{S}$, characteristic of the C(2) quaternary carbon atom of the dioxolane ring. The ester function of **145** was used in the preparation of the β -ketosulfoxide **146** using 2 equivalents of the anion formed from (*R*)-methyl *p*-tolylsulfoxide **131** and LDA at -78°C . The necessity of working at -78°C for the generation of the sulfoxide anion and the carbon-carbon bond formation must be emphasised as higher temperatures lead to unwanted by-products and lower yields. Two equivalents of the (*R*)-methyl *p*-tolylsulfoxide anion are required as the α -protons of the formed β -ketosulfoxide are more acidic than those of the starting material **131**. The β -ketosulfoxide **146** showed a carbonyl absorption band at 1720 cm^{-1} in the IR spectrum and a signal at 199.35S in the ^{13}C NMR spectrum. The reduction of β -ketosulfoxides is under the control of the chiral sulfoxide auxiliary and the stereoselectivity is controlled by the use of either DIBALH or DIBALH- ZnCl_2 (see Chapter 2). Thus reduction of the β -ketosulfoxide **146** with DIBALH gives the 2,4-*anti* diol **147** in $>98:2$ d.r.^{4,5} This diastereomeric ratio is probably higher as ^1H NMR could not detect the presence of the 2,4-*syn* diastereomer. The C(1) methylene protons form part of an ABX spin system and appeared at $\delta_{\text{H}} 2.975$ (dd, J 13.4 and 9.0 Hz) and 2.786 (dd, J 13.4 and 2.2 Hz) typical of (*S*)(*R*),2*S*) β -hydroxysulfoxides.^{6,7,8}



Scheme 5.1: Synthesis of the C(1)–C(5) unit of TA toxin.

Reagents: a) SOCl_2 , EtOH, (85%); b) BMS, NaBH_4 {5 mol%}, THF (78%); c) Acetone, TsOH, 2,2-Dimethoxypropane (91%); d) **131**, LDA, THF, and then **145** (62%); e) DIBALH, THF (67%); f) MeOH, TsOH, H_2O (89%); g) TrCl, Py, DMAP, CH_2Cl_2 (95%); h) NaOAc, Ac_2O (72%); i) LiAlH_4 , Et_2O (77%).

At this stage of the synthesis the protective group strategy required differentiation between the primary and secondary hydroxy groups present in the C_5 unit as the primary alcohol would at the completion of the synthesis of the C_9 chain be converted to an amino group. The acetonide protective group was removed by acid catalysis using TsOH in aqueous MeOH to give the water-soluble triol **148** that was isolated by continuous extraction with EtOAc. The primary hydroxy group of the triol **148** was selectively protected as the trityl ether **149**. The chemical shift of the protons of the C-2 and C-4 hydroxy groups (δ_{H} 4.651, d, J 4.1 Hz and δ_{H} 3.286, d, J

3.9 Hz, respectively) is indicative of hydrogen bonding between the C(2) hydroxy group and the oxygen of the sulfoxide group. The two secondary hydroxy groups in **149** were protected as the acetonide by treatment with 2,2-dimethoxypropane and TsOH to give **150**. The use of this protecting group was favoured at this stage as the characteristic ^{13}C chemical shifts of the methyl groups and the C(2) quaternary carbon of the 1,3-dioxane ring provided a method of monitoring the stereochemical integrity of the 2,4-diol system in subsequent steps of the synthetic route. The ^{13}C NMR spectrum of **150** showed the signals of the two methyl groups at δ_{C} 24.84Q and 24.53Q and the C(2) quaternary carbon atom of the 1,3-dioxane ring at δ_{C} 101.00S. These values are characteristic of a 1,3-*anti* diol system (see Chapter 3). The *syn*-1,3-diol acetonides have signals at ca. 19 ppm for the axial methyl group and ca. 30 ppm for the equatorial methyl group. The quaternary carbon appears at ca 99 ppm⁹ (see Chapter 3). The values observed for **150** confirmed that the DIBALH reduction of the β -ketosulfoxide **146** gave the 2,4-*anti* diastereomer in keeping with literature precedents.

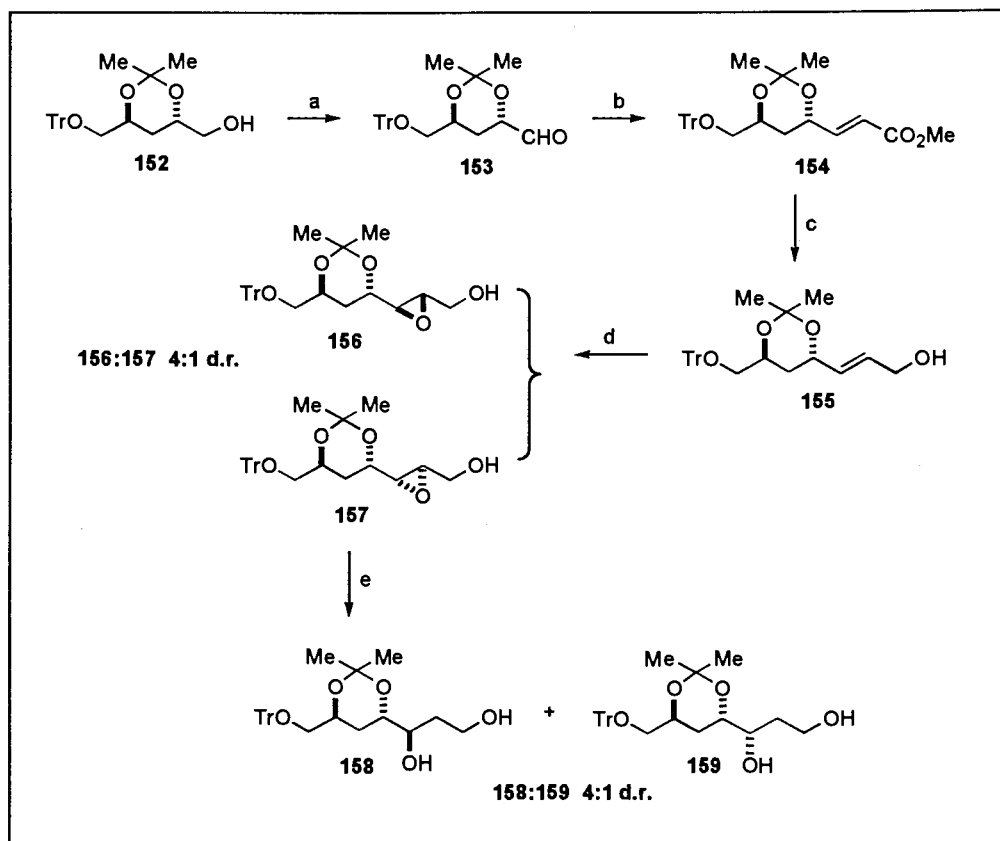
The role of the chiral sulfoxide auxilliary in **150** is done at this stage. The Pummerer rearrangement¹⁰ of the sulfoxide group using Ac_2O and NaOAc at 130–140 °C gave the *O,S*-acetal **151** as a ca. 4:3 diastereomeric mixture. The C(1) acetal proton of the two diastereomers appeared in each case as a doublet, at δ_{H} 6.102 (J 4.1 Hz) and 6.084 (J 6.5 Hz). LiAlH_4 reduction in diethyl ether of the *O,S*-acetal gave the alcohol **152** (Scheme 5.1). Acidic conditions were avoided during the work-up of the reaction in order to prevent the loss of the 1,3-acetonide protecting group or its rearrangement to a 1,2-acetonide. The ^{13}C spectrum showed the typical signal of the C(2) quaternary carbon atom of a 1,3-dioxane at δ_{C} 100.40.

5.2.2 Chain extension of the C_5 unit to a C_7 unit.

Two different approaches were considered for the extension of the carbon chain and the introduction of the third stereogenic centre.

A. First approach.

Swern oxidation¹¹ of the alcohol **152** gave the aldehyde **153** (see Scheme 5.2). The NMR data of a purified sample showed the signals of the aldehyde group at δ_{H} 9.790(s) and δ_{C} 202.17D. More importantly the ^{13}C signal at δ_{C} 100.18S confirmed



Scheme 5.2: Introduction of the third stereogenic centre and extension to a C₇ unit.

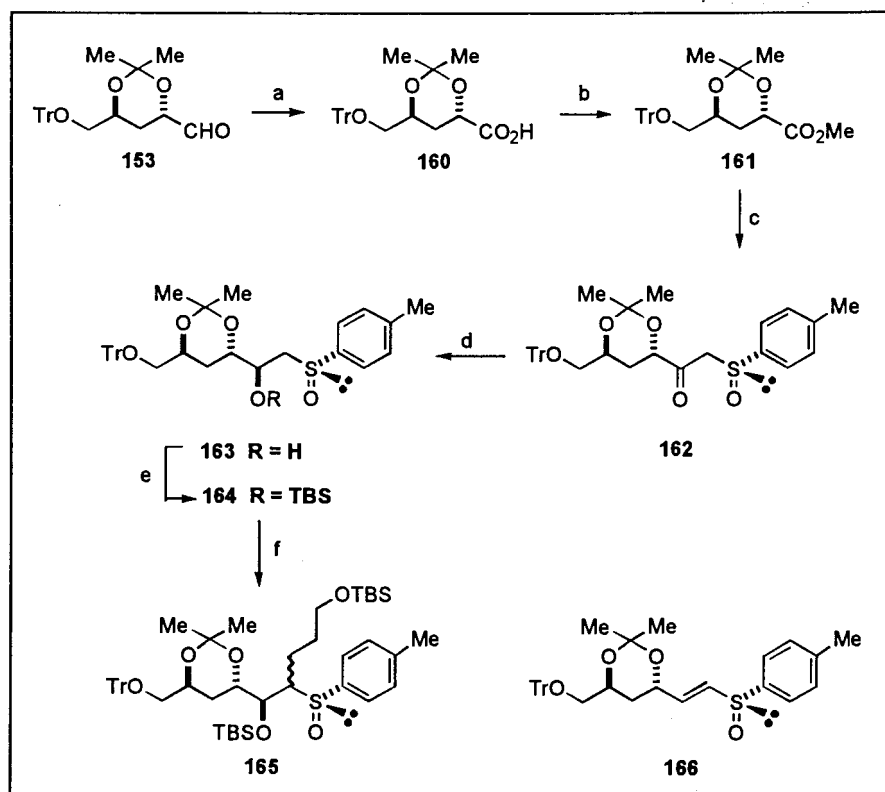
Reagents: a) Oxalyl chloride, *N,N*-diisopropyl-*N*-ethylamine, CH₂Cl₂, DMSO (67%); b) *(iPrO)*₂P(O)CH₂CO₂Me, ^tBuOK, then **153**, THF (77%); c) DIBALH, THF (94%); d) *t*-BuOOH, Ti(*Oi*-Pr)₄, (*R,R*)-DET, CH₂Cl₂, -20°C, 5 days (55%); e) Red-Al, 0°C, THF (70%).

that no epimerisation at the C(2) stereogenic centre had occurred during the reaction. The Wadsworth-Emmons reaction of the aldehyde **153** with the anion obtained from diisopropyl methoxycarbonyl methylphosphonate and a base, potassium butoxide, led to a two-carbon chain-extended α,β -unsaturated ester **154**. The presence of only the *E* diastereomer was evident from the coupling constant of 15.8 Hz for the signals of the double bond protons at δ_H 6.929 and 6.017 in the ¹H NMR spectrum. Once again no epimerisation occurred at the C-2 stereogenic centre of the aldehyde starting material or the α,β -unsaturated ester **154** [C(4) of the product] as was evident from the signal at δ_C 100.54S. The reduction of the α,β -unsaturated ester **154** with DIBALH gave the allylic alcohol **155**. Sharpless epoxidation^{12,13} of the allylic alcohol **155** using (*R,R*)-DET proceeded exceedingly slow at -20°C and gave a diastereomeric mixture of the epoxides **156:157** in a d.r. of 4:1 as was evident from

both the ^1H and ^{13}C NMR spectra. The *trans* configuration of the disubstituted epoxide was evident from the coupling constant of 2.3 Hz for the C(2) and C(3) protons. The use of the (*R,R*)-DET according to literature^{14,15} leads to preferential (*2Re,3Re*)-face attack and this face is also favoured by the C(4) stereogenic centre. As a consequence a high d.r. should be obtained in the epoxidation reaction. This was not the case and is ascribed to steric hindrance in the allylic alcohol. The diastereomers have the same R_f values and could not be separated by chromatography. Reduction of the epoxy alcohol **156:157** with Red-Al gave only the 1,3-diol derivative **158:159** also as an inseparable 4:1 diastereomeric mixture. The signal at δ_{H} 3.810 (t, $J_{1,2}$ 5.8 Hz) confirmed the regioselectivity in the ring opening reaction. The above results led to the decision to investigate an alternative route for the chain extension of the C_5 unit and the introduction of the third stereogenic centre.

Second approach.

In the second approach it was decided to introduce the third stereogenic centre using chiral sulfoxide methodology once again. The aldehyde **153** served as starting material (see Scheme 5.3) and was oxidised to the acid **160** using sodium chlorite (NaClO_2) and hydrogen peroxide in a buffer solution at pH 4.^{16,17} The crude acid was esterified to the methyl ester **161** (ν_{max} 1742 cm^{-1}) using an ether solution of diazomethane. The ^{13}C NMR spectrum showed the typical signal for the *anti* 1,3-acetonide at δ_{C} 100.73S and the carbon of the ester carbonyl group δ_{C} 172.41S. The ester **161** was used in the preparation of the β -ketosulfoxide **162** (95% yield) using 2 equivalents of the anion formed from (*R*)-methyl *p*-tolylsulfoxide **131** and LDA at -78°C . It was interesting to note the much higher yield recorded in this reaction using a methyl ester compared to the yield obtained for the similar reaction for the ethyl ester **145** (62% yield). Due care must be taken though to avoid the use of excess BuLi in generating the LDA from diisopropylamine as transesterification of the methyl ester **161** to a butyl ester was observed. The β -ketosulfoxide **162** showed a carbonyl absorption band at 1725 cm^{-1} in the IR spectrum and a signal at 201.63S in the ^{13}C NMR spectrum. The protons of the C(1) methylene group appeared as an AB spin system at δ_{H} 4.143 and 4.022 with J 13.7 Hz. The ketosulfoxide **162** is prone to epimerisation at C(3) if left too long at room temperature or during extended chromatographic clean-up procedures and was promptly used in the next step of the synthetic sequence. The reduction of the β -ketosulfoxide with DIBALH proceeded stereoselectively to give the 2,3-*anti* diol **163** in >98:2 d.r.^{4,5} The C(1) methylene



Scheme 5.3: Introduction of the C(6) stereogenic centre and chain elongation.

Reagent: a) NaClO_2 , H_2O_2 , CH_3CN ; b) CH_2N_2 , Et_2O (95%, 2 steps); c) **131**, LDA , **161**, THF (95%); d) DIBALH , THF (83%); e) TBSCl , Im , DMF (47%); f) **164**, LDA , THF , TMEDA , $\text{TBSO}-(\text{CH}_2)_3\text{I}$ **161** (no reaction).

protons form part of an ABX spin system and appeared at δ_{H} 2.920 (dd, J 13.5 and 9.3 Hz) and 2.794 (dd, J 13.6 and 2.3) typical of (*S*(*R*),*2S*)- β -hydroxysulfoxides.^{6,7,8} The C(3) proton appeared at δ_{H} 3.823 and showed a coupling of 6.2 Hz with the C(2) proton.

5.2.3 Extension of the C₇ unit to a C₉ unit.

The next step in the synthetic sequence required extending the C₆ carbon chain of the β -hydroxysulfoxide **163** by introduction of a suitably protected C₃ unit. The C(2) hydroxy group of **163** was first protected as the TBS ether **164** that was obtained in only 47% yield after 30 hours at 50°C. The remaining starting material could be recovered. This is an improvement over the yield reported for the same reaction by Sanz-Tejedor¹⁸ on a similar system (maximum yield of 15% after 3 days

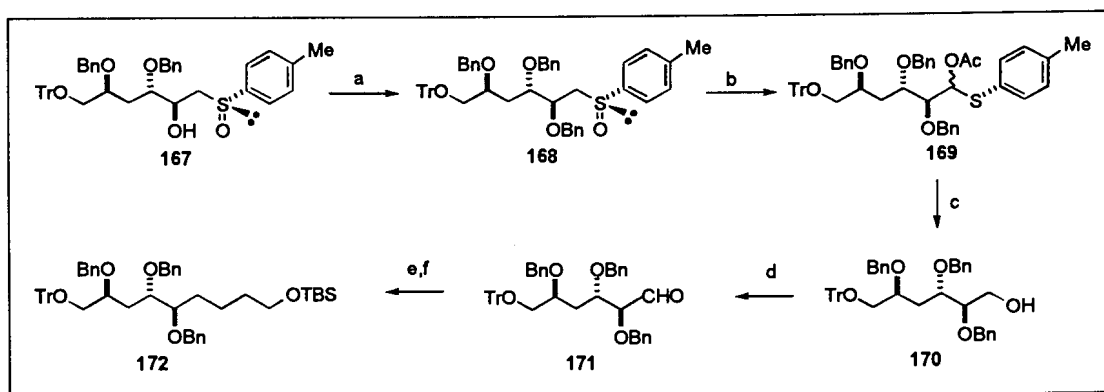
at 70°C). The signals for the protons of the C(2) OTBS group appeared at δ_{H} 0.908 (*t*-Bu) and 0.084 (Me₂Si) but the corresponding signals in the ¹³C spectrum at δ_{C} 26.63Q (*t*-Bu) and -3.61Q (Me₂Si) were barely discernible. This result is an indication of the steric crowding around the C(2) stereogenic centre and the resultant restricted rotation of the OTBS group that leads to poor relaxation of the carbon atoms.

Alkylation at C(1) of the protected β -hydroxysulfoxide **164** was initiated by the abstraction of one of the acidic protons α to the sulfoxide group using LDA (2.2 equivalents) in the presence of TMEDA (2.5 equivalents) in THF solution at -20 °C. 1-((*t*-Butyldimethylsilyl)oxy-3-propyl iodide **181** was used to alkylate the formed anion. Work-up of the reaction and column chromatography of the reaction product gave the α,β -unsaturated sulfoxide **166** and no indication that any of the C₉ chain-extended product **165** had formed. The structure of **166** was confirmed by the characteristic signals of the olefinic protons at δ_{H} 6.583 (dd, J 15.1 and 3.8 Hz, H-2) and 6.413 (dd, J 15.1 and 1.7 Hz, H-1) and the coupling constant of 15.1 Hz established that only the *E* diastereomer had formed. The formation of the α,β -unsaturated sulfoxide **166**, although unexpected and unwanted, is readily explained by the loss of the *t*-butyldimethylsilyloxy group from the C(1) anion intermediate. The removal of the bulky OTBS group from the molecule and the resultant formation of the *E* double bond relieves the steric crowding and is the driving force for the reaction.

The use of a benzyl group as a less bulky alternative for the TBS group in **164** was a solution that warranted investigation but attempts to benzylate the C(2) hydroxy group of the β -hydroxy-sulfoxide **163** following a procedure recently reported by Sanz-Tejedor *et.al.*,¹⁸ failed and the α,β -unsaturated sulfoxide **166** was formed.

The failure at this stage of the synthesis was disappointing and the approach was abandoned due to time constraints that did not allow the investigation of a viable alternative route using a different protecting group to the acetonide protection used at present. It is believed that the use of an acetonide for the protection of the *anti* 1,3-diol system is responsible for the steric crowding. The 1,3-dioxane ring is present in a twist-boat conformation with the bulky C(4) and C(6) substituents in pseudo-equatorial positions. To confirm the effect of the acetonide group on the reactivity at the C(1) and C(2) centres of the sulfoxide **163** an alternative proposal is outlined in Scheme 5.4.

The synthetic route requires the benzyl protected β -hydroxysulfoxide **167** available from (2*S*)-malic acid. Protection of the hydroxy group as the benzyl ether **168** followed by a Pummerer rearrangement leads to the formation of the *O,S*-acetal **169** that is reduced to the primary alcohol **170**. Swern oxidation¹¹ of **170** gives the aldehyde **171**. The Wittig reaction of the aldehyde with a C₃ Wittig reagent derived from 1-((*t*-butyldimethylsilyl)oxy)-3-iodopropane **181** followed by catalytic hydrogenation of the formed double bond leads to the synthetic target **172**. The investigation of this synthetic route is outside the scope of the present thesis and will form a new research project.



Scheme 5.4: Proposal for the elongation of the C₆ to a C₉ moiety of TA toxin.

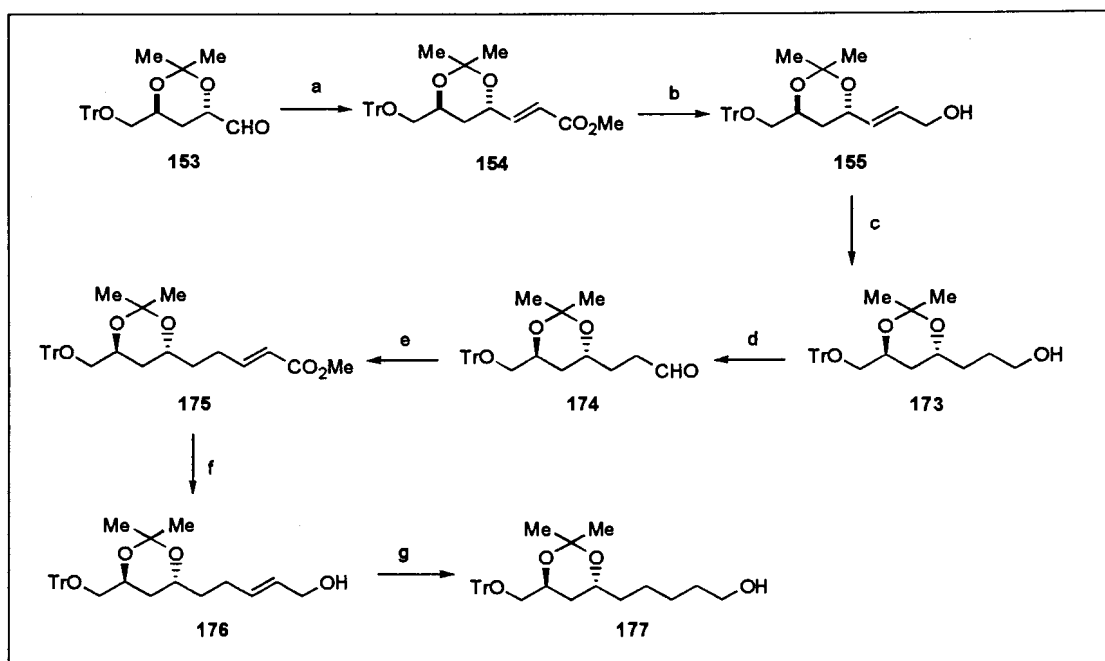
Reagents: a) NaH, BnBr; b) Ac₂O, NaOAc; c) LiAlH₄; d) Swern oxidation; e) Wittig reaction: TBSOCH₂CH₂CH₂PPh₃I, BuLi; f) Pd-C, H₂.

5.3 SYNTHESIS OF THE C(1)–C(9) UNIT OF TB TOXIN

The difference between the C(1)–C(9) fragment of the C₁₇ backbone of the TA and TB toxins is the absence of the C(5) hydroxy group in TB toxin. As a result the synthesis of the C(1)–C(5) unit is the same as that described in Scheme 5.1 and identifies the aldehyde **153** as the key intermediate in both syntheses.

The obvious next step in the synthesis is the reaction of the aldehyde **153** with a C₄ Wittig reagent derived from 1-((*t*-butyldiphenylsilyl)oxy)-3-iodobutane using *n*-BuLi, to give a C₉ alkene. Catalytic reduction of the double bond would then give the synthetic target. However all attempts using the Wittig reaction failed and a much longer method was carried out to extend the carbon chain of the C₅ aldehyde **153** to the desired C₉ unit (see Scheme 5.5).

The aldehyde **153** was transformed to the allylic alcohol **155** in a two-step sequence described in Scheme 5.2. Catalytic hydrogenation of **155** using Pd-C as catalyst gave the C₇ saturated alcohol **173**. Swern oxidation¹¹ of the alcohol **173** gave the aldehyde **174**. The NMR spectra showed the signals of the aldehyde group at δ_{H} 9.742(dd, *J* 1.8 and 1.5 Hz) and δ_{C} 202.13D. The Wadsworth-Emmons reaction of the aldehyde **174** with the anion obtained from diisopropyl methoxycarbonyl methylphosphonate and a base, potassium butoxide, led to a two-carbon chain-extended α,β -unsaturated ester **175**. The presence of only the *E* diastereomer was



Scheme 5.5: Synthesis of the C₉ unit of TB toxin.

Reagents: a) $(i\text{PrO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, ^tBuOK, then **153**, THF (77%); b) DIBALH, THF (94%); c) Pd-C, H₂, MeOH-EtOAc (90%); d) Swern oxidation, (93%); e) $(i\text{PrO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, ^tBuOK, then **174**, THF (94%); f) DIBALH, THF, (95%), g) Pd-C, H₂, MeOH-EtOAc, (88%).

evident from the coupling constant of 15.8 Hz for the signals of the double bond protons at δ_{H} 6.976 and 5.820 in the ¹H NMR spectrum. The reduction of the α,β -unsaturated ester **175** with DIBALH gave the allylic alcohol **176** in 94% yield. Catalytic hydrogenation over Pd-C gave the C₉ alcohol **177** with the correct absolute configuration of the two stereogenic centres of the corresponding unit of the TA toxin backbone.



The alcohol **177** will be used in the linkage of the left-hand C₈ unit of the AAL toxins prepared in another project. The methodology for the conversion of the O-trityl group to an amino group has been established¹⁹ and will only be implemented after the linkage of the two backbone units by other workers.

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6 EXPERIMENTAL

6.1 INTRODUCTION

Air- and/or moisture-sensitive reactions were carried out under a positive pressure of nitrogen or argon in oven-dried (120°C) glassware. Air- and moisture-sensitive reagents were transferred via syringe and/or double-ended needle techniques into rubber-septum-capped reaction vessels. Room temperature (RT) refers to 18-25°C. Evaporations were done under reduced pressure. All reagents were of synthetic grade and were used without any further purification. When necessary, solvents and reagents were dried according to standard methods prior to use.¹ Solvents used for chromatography or extractions were distilled.

Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined with a Perkin Elmer 241 polarimeter for solutions in chloroform (CHCl₃). Specific rotations are given in units of 10⁻¹ deg.g⁻¹.cm². 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 Bomem Michelson 100 spectrometer (for KBr pellets), or with a Bruker 113v FTIR instrument as a thin layer between ZnSe disks under reduced pressure. 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 CDCl₃ solutions (unless otherwise indicated) on a Bruker AMX-300 (7.0T) spectrometer operating at 300 MHz for ¹H and 75.47 MHz for ¹³C. All chemical shifts are reported as δ values downfield from Me₄Si using CDCl₃ as internal standard (δ_H 7.24 or δ_C 77.00 ppm, respectively). Proton-proton coupling constants (*J*) are given in Hz. Spectral coupling patterns are designated as follows: s/S: singlet; d/D: doublet; t/T: triplet; q/Q: quartet; m: multiplet; bs: broad signal. The assignments of the signals in the ¹H NMR spectra are based on first-order analysis of the spin systems and when required were confirmed by ¹H{¹H} decoupling experiments and two-dimensional (2-

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

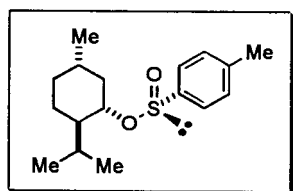
The course of reactions was followed on thin-layer chromatography (TLC) using glass or aluminium plates coated with silica gel 60 F₂₄₅ (Merck). Relative front values (R_f) in various solvent systems were recorded for all products and intermediates. Column chromatography was performed on Merck silica gel 60 (60-200 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 Spray Reagent.

A spray solution was prepared from cerium(IV) sulfate (1% w/v) dissolved in 6N sulfuric acid. The non-UV active organic compounds were visualised by spraying followed by heating at 130°C to develop the colours.

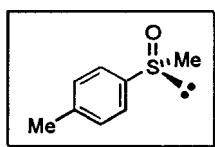
6.2.2 Sulfoxide Reagent.



(1*R*,2*S*,5*R*)-(-)-Menthyl (*S*)-*p*-toluenesulfinate 130^{1,2}

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 (100 cm³, 1.40 mol) in benzene (300 cm³) 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 cm³) and evaporation under

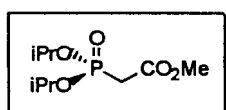
reduced pressure. The residue was diluted with anhydrous diethyl ether (500 cm³) (formation of a white precipitate of sodium chloride) and cooled at 0°C. A solution of (-)-menthol (69.4 g, 0.440 mol) in pyridine (70 cm³) was added dropwise. After the addition was complete the mixture was stirred for 1 h at RT and hydrolysed with water (200 cm³). The organic layer was washed with 10% HCl (200 cm³) and saturated brine (100 cm³), dried over Na₂SO₄ and concentrated. The residue was diluted with acetone (200 cm³), ~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 cm³, 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)-sulfinic acid as a white crystalline material (102.5 g, 78%); mp 108-109 °C (Lit.³ 105-107 °C), [α]_D²¹ -199 (c 2.5, acetone), [Lit.⁴ [α]_D²¹ -201 (c 2.0, acetone)]; R_f 0.90 (EtOAc).



(R)-(+)-Methyl *p*-tolylsulfoxide 131^{1,2}

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 cm³) was slowly added to a solution of (-)-(S)-menthyl-*p*-toluenesulfinic acid 130 (60.0 g, 204 mmol) in anhydrous benzene (200 cm³) between 0–10°C. After addition, the mixture was stirred at room temperature for 2 h and then hydrolyzed with saturated aq. NH₄Cl solution (200 cm³). The aqueous solution was extracted with EtOAc (3 x 100 cm³). The organic layers were washed with saturated brine (100 cm³), dried (Na₂SO₄) and concentrated *in vacuo*. The oily residue was mixed with hot hexane till formation of a light white cloudy precipitate. Crystallization occurs 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.⁵ 73-74.5°C); [α]_D²¹ +192 (c 4.0, CHCl₃), (Lit.¹⁰ [α]_D²¹ +192, (c 1.2, CHCl₃)), [α]_D¹⁵ +146 (c 2.0, acetone), (Lit.⁵ [α]_D²¹ +145.5);

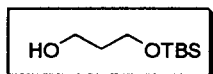
6.2.3 Wadsworth-Emmons Reagent.



Diisopropyl methoxycarbonyl methylphosphonate 178

A mixture of tri-isopropylphosphite (18.7 g, 100 mmol) and methyl chloroacetate (10.8 g, 100 mmol) was refluxed for 24 h (~130°C). The product was obtained after distillation at 100 °C/0.5 mm Hg as a clear liquid (22.0g, 92%); R_f 0.16 (hexane: EtOAc, 4:1), (only visible with I_2).

6.2.4 Wittig Reagent.

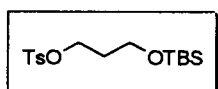


3-((*t*-butyldimethylsilyl)oxy)-propan-1-ol 179

Sodium hydride (60% dispersion in oil, 8.28 g, 207 mmol) was washed with dry hexane and suspended in dry THF (250 cm³). Propane-1,3-diol (15.75 g, 207 mmol) was added and the mixture stirred at room temperature for 45 min with the formation of an opaque white precipitate. TBSCl (56.88 g, 207 mmol) was added and the reaction was allowed to proceed with stirring for 90 min. The solvent was evaporated and the residue partitioned between CH₂Cl₂ and water. The organic phase was dried (Na₂SO₄), filtered and evaporated. Column chromatography of the residue using hexane-EtOAc (4:1) yielded the TBS ether 179 (34.24g, 87%) as an oil; R_f 0.33 (EtOAc-hexane 1:4).

δ_H 3.744 (t, 2H, , H-3)
 3.699 (td, 2H, $J_{1,2}$ 5.4, $J_{1,OH}$ 5.2, H-1)
 1.699 (quintet, 2H, $J_{1,2}$ 5.4, $J_{3,2}$ 5.4, H-2)
 0.832 (s, 9H, *t*-Bu)
 0.004 (s, 6H, Me₂Si)

δ_C 62.26T (C-1); 61.61T (C-3); 34.41T (C-2); 25.73Q (*t*-Bu); -5.46Q (Me₂Si).



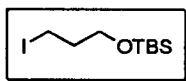
3-((*t*-Butyldimethylsilyl)oxy)-propan-1-ol *p*-toluenesulfonate 180.

TsCl (26.98g, 151.9 mmol) and DMAP (17.29g, 151.9mmol) were added to a solution of 179 (24.10 g, 126.6 mmol) in CH₂Cl₂ (250 cm³) in one portion. The

reaction mixture was stirred at room temperature for 12 h, washed with H₂O (2×cm³), dried (Na₂SO₄) and concentrated. Column chromatography using EtOAc-hexane (9:1) afforded the tosylate derivative **180** as an oil (34.11g, 78%).

δ_{H} 7.769 (d, 2H, J 8.0, aromatic H-2).
 7.752 (br d, 2H, J 8.0, aromatic H-3).
 4.107 (t, 2H, J_{1,2} 6.0, H-1).
 3.591 (t, 2H, J_{3,2} 6.0, H-3).
 2.402 (s, 3H, tolyl Me).
 1.793 (quintet, 2H, J 6.0, H-2).
 0.791 (s, 9H, *t*-Bu).
 -0.045 (s, 6H, Me₂Si).

δ_{C} 144.52S (aromatic C-1); 133.09S (aromatic C-4); 129.69D and 127.74D (aromatic carbons); 67.42T (C-1); 58.29T (C-3); 31.88T (C-2); 25.67Q (*t*-Bu); 21.42Q (tolyl Me); 18.00S (*t*-Bu); -5.66Q (Me₂Si).



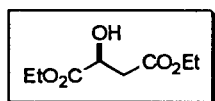
1-((*t*-Butyldimethylsilyl)oxy)-3-iodopropane **181**

The tosylate **180** (34.00 g, 68.0 mmol) and NaI (34.02 g, 227.0 mmol) was dissolved in anhydrous acetone (300 cm³). The reaction was stirred at RT for 10 h. The solid material was removed by filtration and the solvent evaporated. The residue was dissolved in diethyl ether (400 cm³) and washed with Na₂S₂O₃ solution (10%, 100 cm³). The diethyl ether solution was dried. The mixture was extracted with ether, dried (Na₂SO₄), filtered and evaporated. The residual oil was purified by column chromatography using hexane-EtOAc (9:1) to give the iodide **181** as an oil (22.76 g, 77%), R_f 0.40 (hexane-EtOAc (9:1)).

δ_{H} 3.642 (t, 3H, J_{1,2} 5.7, H-1)
 3.249 (t, 2H, J_{3,2} 6.7, H-3).
 1.964 (tt, 2H, J_{1,2} 5.7, J_{2,3} 6.7, H-2).
 0.874 (s, 9H, *t*-Bu).
 0.047 (s, 6H, Me₂Si).

δ_c 62.32T (C-1); 36.18T (C-2); 25.89Q (t-Bu); 18.25S (t-Bu); 3.45T (C-3); -5.33Q (Me₂Si).

6.3 PREPARATION OF THE C(1)–C(6) UNIT OF THE TA SERIES.



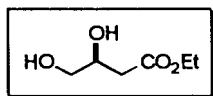
Diethyl (2S)-malate **142**

Thionyl chloride (12.5 cm³) was added dropwise to a cooled (0°C) solution of (2S)-malic acid **140** (50.0 g, 373 mmol) in absolute ethanol (250 cm³). The solution was refluxed for 3 h and the solvent evaporated under reduced pressure. The residue was dissolved once again in absolute ethanol (250 cm³) and thionyl chloride (12.5 cm³) added. The solution was refluxed for a further 3 h. The solvent was evaporated and the residue diluted with diethyl ether (500 cm³). The diethyl ether solution was washed with brine (3x300 cm³), 6M NaHCO₃ solution (4x200 cm³), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by kugelrohr distillation (115°C/1 mmHg) to give the diester **142** (60.1g, 85%), R_f 0.55 (EtOAc-hexane 19:1); [α]_D -5.5 (c, 2.45, CHCl₃), ν_{max} 1737 cm⁻¹

δ_H 4.449 (dd, 1H, J_{2,3a} 4.7, J_{2,3b} 6.0 Hz, H-2).
4.248 (dq, 1H, J 10.9, J 7.2, OCH₂CH₃).
4.229 (dq, 1H, J 10.9, J 7.2, OCH₂CH₃).
4.200 (q, 2H, J 7.0, OCH₂CH₃).
3.52 (s, 1H, OH).
2.808 (dd, 1H, J_{2a,2b} 16.3, J_{2a,3} 4.7, H-2a).
2.751 (dd, 1H, J_{2a,2b} 16.3, J_{2a,3} 6.0, H-2b).
1.270 (t, 3H, J 7.0, Me).
1.235 (t, 3H, J 7.0, Me).

δ_c 173.22S (CO), 170.38S (CO), 67.16D (C-3), 61.74T (OCH₂), 60.77T (OCH₂), 38.61T (C-3), 13.91Q (2xMe),

FAB-MS: *m/z* 191 [M+H]⁺.



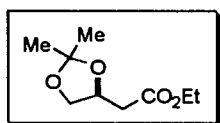
Ethyl (3S)-3,4-dihydroxybutanoate **143**

Borane dimethyl sulfide (BMS) was added dropwise over a period of 30 min to a stirred solution of diethyl (2S)-malate **142** (5.00 g, 0.03mol) in dry THF (50 cm³) at 20^o C. When the evolution of hydrogen ceased (30 min) the solution was cooled to 10^o C in a water-ice bath, NaBH₄ powder (50 mg, 0.05 eq) was added in one portion to the vigorously stirred solution (exothermic reaction!). The reaction was stirred at room temperature after the exothermic reaction subsided and monitored by TLC until **142** disappeared. EtOH (30 cm³) and *p*-TsOH (0.25 g, 1.32 mmol) were added to the reaction and the resulting cloudy solution was stirred for 30 min. at room temperature. Concentration under reduced pressure gave a colourless gum. The gum was dissolved in benzene-EtOH (1:1, 100 cm³) and the solvent evaporated under reduced pressure. This process was repeated. Benzene (100 cm³) was added to the residue and the solvent evaporated in order to remove EtOH and B(OEt)₃. The evaporation with benzene was repeated until a clear, colourless gum was obtained. Column chromatography of the crude product using EtOAc-hexane (19:1) gave **143** (3.02 g, 78%); R_f 0.23; [α]_D -21.1^o (c 2.3, CHCl₃).

δ_H 4.117 (q, J_{CH₂,CH₃} 7.0, OCH₂).
 4.083 (dddd, 1H, J_{2a,3} 8.0, J_{4b,3} 6.5, J_{2a,3} 4.9, J_{4a,3} 3.4, H-3).
 3.780 (m, 1H, OH).
 3.610 (dd, 1H, J_{4a,4b} 11.4, J_{4a,3} 3.4, H-4a).
 3.464 (dd, 1H, J_{4a,4b} 11.4, J_{4b,3} 6.5, H-4b).
 3.171 (s, 1H, OH).
 2.481 (dd, 1H, J_{2a,2b} 16.3, J_{2a,3} 8.0, H-2a).
 2.429 (dd, 1H, J_{2a,2b} 16.3, J_{2a,3} 4.9, H-2b).
 1.220 (t, 3H, J_{CH₃,CH₂} 7.2, Me).

δ_C 172.48S (C-1); 68.56D (C-3); 65.65T (C-4); 60.83T (OCH₂CH₃); 37.72T (C-2); 14.04Q (Me).

FAB-MS *m/z* 149 [M+H]⁺



Ethyl (3S)-3,4-O-isopropylidene-butanoate **145**

A solution of ethyl (3S)-3,4-dihydroxybutanoate **143** (1.82 g, 12.3 mmol), acetone (6.50 cm³), 2,2-dimethoxypropane (1.70 cm³) and *p*-toluenesulfonic acid (0.12g, 0.63 mmol) were stirred at RT for 20 min. The reaction mixture was neutralized with Et₃N (0.2 cm³) and diluted with diethyl ether (30 cm³). The mixture was filtered through a pad of silica gel, dried (Na₂SO₄) and concentrated to give the pure oil of **145** (2.10 g, 91%); R_f 0.45 (hexane-EtOAc 4:1); [α]_D +19.2 (c 1.4, CHCl₃); ν_{max} 1732 cm⁻¹.

δ_H 4.373 (dddd, 1H, J_{2b,3} 7.2, J_{2a,3} 6.2, J_{4b,3} 6.2, J_{4a,3} 5.9, H-3).

4.070 (q, 2H, J_{CH₂,CH₃} 7.2, OCH₂CH₃).

4.069 (dd, 1H, J_{4a,4b} 8.3, J_{4a,3} 5.9, H-4a).

3.568 (dd, 1H, J_{4a,4b} 8.3, J_{4b,3} 6.2, H-4b).

2.625 (dd, 1H, J_{2a,2b} 15.8, J_{2a,3} 6.2, H-2a).

2.426 (dd, 1H, J_{2a,2b} 15.8, J_{2b,3} 7.2, H-2b).

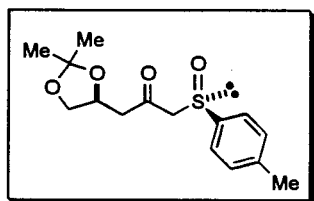
1.326 (s, 3H, Me, acetonide).

1.269 (s, 3H, Me, acetonide).

1.180 (t, 3H, J_{CH₃,CH₂} 7.2, OCH₂CH₃).

δ_C 170.42S (C-1); 109.01S (acetonide C-2); 71.95D (C-3); 69.01T (C-4); 60.47T (OCH₂), 38.89T(C-2); 25.36Q and 26.72Q (acetonide Me); 13.98Q (Me);

FAB-MS: *m/z* 189 [M+H]⁺. Exact mass: Calculated for C₉H₁₆O₄, 189.1127; Found, 189.1127.



(S(R),4S)-4,5-O-isopropylidene-1-(*p*-tolylsulfinyl)-2-pentanone **146**

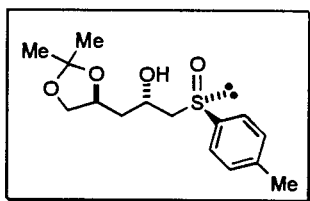
LDA (2.2 eq) was prepared *in situ* by the reaction of *n*-BuLi (60.4 cm³, 96.6 mmol) and diisopropylamine (13.3 cm³, 96.6 mmol) in THF (60 cm³) at -78^oC. A solution of

methyl *p*-tolylsulfoxide **131** (2.1 eq, 13.9 g, 90.1 mmol) in THF (40 cm³) was added and stirred for 1h. The ester **145** (5.64 g, 30.0 mmol) in THF (40 cm³) was added to the reaction mixture which was stirred for 2 h at -78^o C. The reaction was quenched with saturated NH₄Cl solution (80 cm³), acidified with 1M HCl (30 cm³) to pH 4, and extracted with EtOAc. The EtOAc solution was dried (Na₂SO₄), and evaporated under reduced pressure. Column chromatography of the crude product using EtOAc as eluent yielded the ketosulfoxide **146** (9.20 g, 69%) as yellowish solid); m.p 77-79^oC; R_f 0.63 (EtOAc); [α]_D +148.9^o (c 1.0, CHCl₃); ν_{max} 1720 cm⁻¹

δ_H 7.462 (d, 2H, J 8.0, aromatic protons).
 7.277 (d, 2H, J 8.0, aromatic protons).
 4.330 (dddd, 1H, J_{3b,4} 6.5, J_{3a,4} 6.5, J_{5b,4} 6.5, J_{5a,4} 6.0, H-4).
 4.024 (dd, 1H, J_{5a,5b} 8.3, J_{5a,4} 6.0, H-5a).
 3.804 (s, 2H, H-1).
 3.392 (dd, 1H, J_{5a,5b} 8.3, J_{5b,4} 6.5, H-5).
 2.889 (dd, 1H, J_{3a,3b} 17.3, J_{3a,4} 6.5, H-3a).
 2.570 (dd, 1H, J_{3a,3b} 17.3, J_{3b,4} 6.5, H-3b).
 2.353 (s, 3H, tolyl Me).
 1.252 (s, 3H, acetonide Me).
 1.188 (s, 3H, acetonide Me).

δ_C 199.35S (C-2). 142.14S, 139.36S (*ipso* carbons, tolyl); 130.02D, 123.94D (aromatic carbon); 108.96S (acetonide C-2); 71.09D (C-4); 68.98T (C-3); 67.90T (C-5); 49.04T (C-1); 26.67Q and 25.31Q (acetonide Me); 21.28Q (tolyl Me);

FAB-MS: *m/z* 297 [M+H]⁺. Exact mass: Calculated for C₁₅H₂₀SO₄, 297.1161;
 Found, 297.1161.



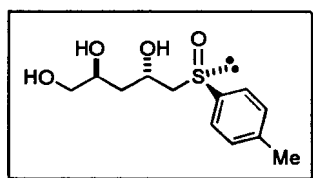
(S(R),2S, 4S)- 4,5-O, O- Isopropylidene-1-(*p*-tolylsulfinyl)-2-pentanol 147

To the solution of **146** (7.00 g, 20.0 mmol) in THF at -78°C was added DIBALH (3.98 g, 30.0 mmol). The reaction mixture was stirred at -78°C for 1 h, quenched with MeOH (very violent) and allowed to reach RT. The solvent was evaporated and the opaque solid was dissolved in CH_2Cl_2 , and washed with saturated NH_4Cl solution and 1M HCl. The organic layer was washed with brine solution, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography of the oily residue using EtOAc as eluent gave the hydroxysulfoxide **147** (4.69 g, 67%) as a white solid); m.p 104-106 $^{\circ}\text{C}$; R_f 0.35 (EtOAc);; $[\alpha]_D^{25} +197.4$ (c, 0.5, CHCl_3)

δ_{H} 7.481 (d, 2H, J 8.5, aromatic protons).
 7.296 (d, 2H, J 8.0, aromatic protons).
 4.689 (d, 1H, 2-OH).
 4.306 (m, 1H, H-2).
 4.152 (dddd, 1H, $J_{3b,4}$ 7.5, $J_{5b,4}$ 7.2, $J_{5a,4}$ 6.0, $J_{3a,4}$ 4.7, H-4).
 4.017 (dd, 1H, $J_{5a,5b}$ 8.0, $J_{5a,4}$ 6.0, H-5a).
 3.510 (dd, 1H, $J_{5a,5b}$ 8.0, $J_{5b,4}$ 7.2, H-5b).
 2.975 (dd, 1H, $J_{1a,1b}$ 13.4, $J_{1a,2}$ 9.0, H-1a).
 2.786 (dd, 1H, $J_{1a,1b}$ 13.4, $J_{1b,2}$ 2.2, H-1b).
 2.376 (s, 3H, tolyl Me).
 1.763 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3a,2}$ 8.0, $J_{3a,4}$ 4.7, H-3a).
 1.691 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3b,4}$ 7.5, $J_{3b,2}$ 4.1, H-3b).
 1.319 (s, 3H, acetonide Me).
 1.213 (s, 3H, acetonide Me).

δ_{C} 141.47S, 139.73S (*ipso* tolyl), 130.00D, 123.93D (aromatic carbons), 108.69S (acetonide C-2), 73.18D (C-4), 69.52T (C-5), 64.49D (C-2), 62.53T (C-1), 40.32T (C-3), 26.81Q, 25.61Q (acetonide Me), 21.29Q (tolyl Me).

FAB-MS: m/z 299. $[\text{M}+\text{H}]^+$. Exact mass: Calculated for $\text{C}_{15}\text{H}_{22}\text{SO}_4$, 299.1317;
 Found, 299.1317.



(S(R),2S,4S)-2,4,5-Trihydroxy-1-(p-tolylsulfinyl)-pentane 148

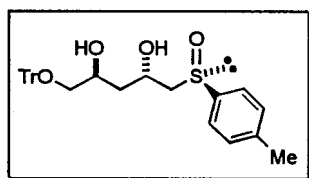
p-Toluenesulfonic acid (0.15 g, 0.062 mmol) was added to a solution of the protected ketosulfoxide **147** (3.70 g, 12.0 μ mol) in MeOH-H₂O (5:2, 40 cm³). The reaction was refluxed for 1h, neutralised by addition of Et₃N (0.5 cm³) and concentrated under reduced pressure. The residue was dissolved in water and the product extracted into EtOAc on a continuous extractor to yield a pure white crystals of **148** (2.84 g, 89%); m.p 139-141°C; R_f 0.43 (CHCl₃-MeOH 4:1); [α]_D +196.8 (c, 0.53, MeOH).

δ_H 7.425 (d, 2H, J 8.0, aromatic protons).
 7.403 (d, 2H, J 8.0, aromatic protons).
 4.202 (dddd, 1H, J_{1b,2} 10.2, J_{3a,2} 9.3, J_{3b,2} 3.6, J_{1a,2} 2.8, H-2).
 3.784 (dddd, 1H, J_{3b,4} 9.6, J_{5b,4} 6.5, J_{5a,4} 4.1, J_{3a,4} 4.1, H-4).
 3.447 (dd, 1H, J_{5a,5b} 11.6, J_{5a,4} 4.1, H-5a).
 3.353 (dd, 1H, J_{5a,5b} 11.6, J_{5b,4} 6.5, H-5b).
 3.006 (dd, 1H, J_{1a,1b} 13.7, J_{1a,2} 2.8, H-1a).
 2.812 (dd, 1H, J_{1a,1b} 13.7, J_{1b,2} 10.2, H-1b).
 2.237 (s, 3H, tolyl Me).
 1.538 (ddd, 1H, J_{3a,3b} 14.6, J_{3a,2} 9.3, J_{3a,4} 4.1, H-3a).
 1.445 (ddd, 1H, J_{3a,3b} 14.6, J_{3b,4} 9.6, J_{3b,2} 3.6, H-3b).

δ_C* 143.81S, 137.82S, (*ipso* tolyl); 130.82D, 124.98D (aromatic carbons); 68.56 D (C-4); 66.23T (C-5); 64.34D (C-2); 62.84T (C-1); 39.85T (C-3); 21.00Q (tolyl Me).

* recorded in (D₂O).

FAB-MS: *m/z* 259 [M+H]⁺. Exact mass: Calculated for C₁₂H₁₈SO₄, 259.1004;
 Found, 259.1004



(S(R),2S, 4S)-2,4-dihydroxy-5-(trityloxy)-1-(*p*-tolylsulfinyl)-pentane 149

Pyridine (4.2 cm³, 54.2mmol), triphenylmethyl chloride (3.21 g, 11.5 mmol), and dimethylaminopyridine (DMAP) (0.26 g, 2.1 mmol) were added to a solution of the triol **148** in CH₂Cl₂ (60 cm³) The reaction mixture was refluxed for 6 h, allowed to

cool, and washed with 3M HCl and twice with brine. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography of the residue using EtOAc as eluent yielded the *O*-trityl derivative **149** (4.98 g, 95%); m.p. 143-145°C; R_f 0.58 (EtOAc); $[\alpha]_D^{25} +112.6$ (c, 1.03, CHCl_3).

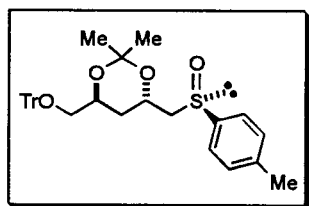
δ_H 7.51 - 7.17 (m, 19H, aromatic protons).
4.651 (d, 1H, $J_{2,\text{OH}}$ 4.1, 2-OH).
4.467 (m, 1H, H-2)
4.028 (m, 1H, H-4).
3.286 (d, 1H, J 3.9, 4-OH);
3.085 (d, 2H, $J_{5,4}$ 5.4, H-5).
3.007 (dd, 1H, $J_{1a,1b}$ 13.3, $J_{1a,2}$ 9.8, H-1a).
2.748 (dd, 1H, $J_{1a,1b}$ 13.3, $J_{1b,2}$ 2.2, H-1b).
2.392 (s, 3H, Me, toluene).
1.624 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3a,4}$ 9.1, $J_{3a,2}$ 3.6, H-3a).
1.540 (ddd, 1H, $J_{3a,3b}$ 14.0, $J_{3b,2}$ 8.3, $J_{3b,4}$ 2.8, H-3b).

After D_2O exchange

4.467 (dddd, 1H, $J_{1a,2}$ 9.8, $J_{3b,2}$ 8.3, $J_{3a,2}$ 3.6, $J_{1b,2}$ 2.2, H-2)
4.028 (dddd, 1H, $J_{3a,4}$ 9.1, $J_{5b,4}$ 6.5, $J_{5a,4}$ 4.9, $J_{3b,4}$ 2.8, H-4).
3.095 (dd, 1H, $J_{5a,5b}$ 9.6, $J_{5a,4}$ 4.9, H-5a).
3.073 (dd, 1H, $J_{5a,5b}$ 9.6, $J_{5b,4}$ 6.5, H-5b).

δ_C 143.84 (*ipso* trityl); 141.50S, 139.58S (*ipso* tolyl); 130.00D, 128.58D, 127.70D, 126.89D, 123.98D (aromatic carbons); 86.49S (OTr); 67.65T (C-5); 67.39D (C-4); 63.49T (C-1); 63.30D (C-2); 40.05T (C-3); 21.28Q (tolyl Me).

FAB-MS: m/z 501 $[\text{M}+\text{H}]^+$. Exact mass: Calculated for $\text{C}_{31}\text{H}_{32}\text{SO}_4$, 501.2100;
Found, 501.2099.



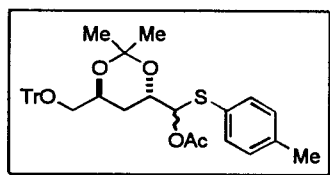
(S(R),2S,4S)-2,4-O-isopropylidene-5-(trityloxy)-1-(p-tolylsulfinyl)-pentane 150

A solution of the O-trityl derivative **149** (5.70 g, 11.4 mmol) and *p*-toluenesulfonic acid (0.15g, 0.79 mmol) in acetone (115 cm³) and 2,2-dimethoxypropane (28.6 cm³,) was stirred at RT for 1 h. The reaction mixture was neutralized with Et₃N (0.5 cm³) and the solvent evaporated. The residue in diethyl ether (100cm³) was washed with brine, dried (Na₂SO₄) and evaporated. Column chromatography of the residue with hexane-EtOAc (1:1) as the eluent yielded white crystals of **150** (5.97 g, 97%); mp. 113-115°C; R_f 0.56 (hexane-EtOAc 1:1); [α]_D +68.0 (c, 0.28, CHCl₃)

δ_H 7.54 - 7.19 (m, 19H, aromatic protons).
4.431 (dddd, 1H, J_{1b,2} 10.1, J_{3b,2} 9.8, J_{3a,2} 6.0, J_{1a,2} 3.2, H-2).
4.028 (dddd, 1H, J_{3a,4} 9.1, J_{5a,4} 6.3, J_{3b,4} 6.3, J_{5b,4} 5.0, H-4).
3.285 (dd, 1H, J_{5a,5b} 9.8, J_{5a,4} 6.3, H-5a).
3.013 (dd, 1H, J_{5b,5b} 9.8, J_{5b,4} 5.0, H-5b).
2.814 (dd, 1H, J_{1a,1b} 13.2, J_{1a,2} 3.2, H-1a).
2.779 (dd, 1H, J_{1a,1b} 13.2, , J_{1b,2} 10.1, H-1b).
2.387 (s, 3H, tolyl Me).
1.706 (ddd, 1H, J_{3a,3b} 12.9, J_{3a,4} 9.1, J_{3a,2} 6.0, H-3a).
1.594 (ddd, 1H, J_{3a,3b} 12.9, J_{3b,2} 9.8, J_{3b,4} 6.3, H-3b).
1.479 (s, 3H, acetonide Me).
1.443 (s, 3H, acetonide Me).

δ_C 143.96S (*ipso* trityl); 141.53S, 141.26S (*ipso* tolyl); 123.74D, 129.89D, 128.63D, 127.85D, 127.69D, 126.90D (aromatic carbons); 101.00S (acetonide C-2); 86.41S (OTr); 66.34T (C-5); 66.10D (C-4); 64.12T (C-1); 61.05D (C-2); 34.49T (C-3); 24.53Q, 24.84Q (acetonide Me); 21.28Q (tolyl Me).

FAB-MS: *m/z* 540 [M+H]⁺. Exact mass: Calculated for C₃₄H₃₆SO₄, 540.2334;
Found, 540.2334



(1R,2S,4S)-1-Acetoxy-2,4-O,O-isopropylidene-5-(trityloxy)-1-(*p*-tolylsulfanyl)-pentane 151

A mixture of the protected ketosulfoxide **150** (5.97g, 11.0 mmol) and anhydrous sodium acetate (6.34 g) in acetic anhydride (100 cm³) was stirred for 5 h at 140°C. The reaction was allowed to cool and diluted with toluene (100 cm³). The solvents were evaporated *in vacuo* and the residue dissolved in toluene (100 cm³) and evaporated *in vacuo* to remove the acetic anhydride. The residue was suspended in diethyl ether (100 cm³), filtered to remove salts and the filtrate evaporated. The residue was purified by column chromatography hexane-EtOAc (4:1) as eluent to give the *O,S*-acetal **151** as an oil (4.50 g, 72%); *R*_f 0.47 (hexane-EtOAc 4:1).

δ_{H} 7.52 - 7.10 (m, 19H, aromatic protons).

6.102 (d, 1H, *J*_{1,2} 4.1, H-1).

6.084 (d, 1H, *J*_{1,2} 6.5, H-1).

4.15-4.00 (m, 2H, H-2 and H-4).

3.281 (dd, 1H, *J*_{5a,5b} 9.6, *J*_{5a,4} 6.5, H-5a).

3.277 (dd, 1H, *J*_{5a,5b} 9.6, *J*_{5a,4} 6.5, H-5a).

3.047 (dd, 1H, *J*_{5a,5b} 9.8, *J*_{5b,4} 4.7, H-5b).

2.342 (s, 3H, tolyl Me).

2.074 (s, 3H, CH₃CO).

2.059 (s, 3H, CH₃CO)

2.00-1.65 (m, 2H, H-3)

1.480 (s, 3H, acetonide Me)

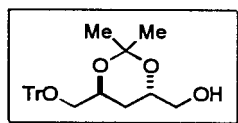
1.446 (s, 3H, acetonide Me)

1.456 (s, 3H, acetonide Me)

1.376 (s, 3H, acetonide Me)

δ_{C} 169.63s and 169.56s (acetate CO); 144.04S (*ipso* trityl); 138.445S, 138.36S, 129.74S, and 129.68S (*ipso* tolyl); 133.81D, 129.72d, 128.67d, 127.69d, and 126.88d (aromatic carbons); 100.90S and 100.81S (acetonide C-2); 86.39S (*ipso* trityl); 83.40D and 82.13D (C-1); 68.09D and 67.94D (C-4); 66.43T (C-5); 66.22D and 66.38D (C-2); 31.67T and 30.84T (C-3); 24.96Q, 24.68Q, and 24.58Q (acetonide Me); 20.89Q and 21.07Q (tolyl Me);

FAB-MS: *m/z* 583 [M+H]⁺. Exact mass: Calculated for C₃₆H₃₈SO₅, 582.2400;
Found, 582.2400

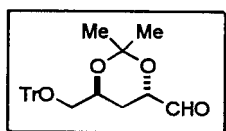


(2S,4S)-2,4-O,O-Isopropylidene-5-(trityloxy)-1-pentanol 152

A solution of **151** (6.90 g, 11.9 mmol) in diethyl ether (50 cm³) was added to a suspension of LiAlH₄ (0.90g, 23.7 mmol) in diethyl ether (200 cm³) and the mixture stirred at RT for 4 h. The excess LiAlH₄ was destroyed by careful quenching of the reaction with 2M NaOH (1 cm³). The solution was dried (Na₂SO₄), filtered and evaporated. The residue was purified by column chromatography with hexane-EtOAc (1:1) as eluent to give the alcohol **152** as a white powder (3.90 g, 79%); mp 63-65°C; R_f 0.49 (hexane-EtOAc 1:1); [α]_D -32.9 (c, 1.04, CHCl₃).

- δ_H 7.48-7.21 (m, 15H, aromatic protons).
 4.002 (dddd, 1H, H-4).
 3.923 (dddd, 1H, H-2).
 4.002 (dddd, 1H, J_{1b,2} 7.1, J_{3b,2} 9.5, J_{3a,2} 6.2, J_{1a,2} 3.2, H-2).
 3.923 (dddd, 1H, J_{3a,4} 9.5, J_{5a,4} 6.3, J_{3b,4} 6.3, J_{5b,4} 4.9, H-4).
 3.591 (dd, , 1H, J_{1a,1b} 11.4, J_{1a,2} 3.2, H-1a).
 3.502 (dd, , 1H, J_{1a,1b} 11.4, J_{1b,2} 7.1, H-1b).
 3.276 (dd, 1H, J_{5a,5b} 9.6, J_{5a,4} 6.3, H-5a).
 3.017 (dd, 1H, J_{5b,5b} 9.6, J_{5b,4} 4.9, H-5b).
 1.627 (ddd, 1H, J_{3a,3b} 12.8, J_{3a,4} 9.5, J_{3a,2} 6.2, H-3a).
 1.542 (ddd, 1H, J_{3a,3b} 12.8, J_{3b,2} 9.5, J_{3b,4} 6.3, H-3b).
 1.420 (s, 3H, acetonide Me).
 1.394 (s, 3H, acetonide Me).
- δ_C 144.09S (*ipso* Trityl);. 128.70D, 127.70D, 126.90D (aromatic carbons, trityl);
 100.40S (acetonide C-2); 86.41S (OTr); 67.48D (C-4); 66.57T (C-5); 66.27D (C-2); 65.36T (C-1); 30.37T (C-3); 24.99Q and 24.87Q (acetonide Me);

FAB-MS: *m/z* 419 [M+H]⁺. Exact mass: Calculated for C₂₇H₃₁O₄, 419.2222; Found, 419.2222



(2S,4S)-2,4-O,O-Isopropylidene-5-(trityloxy)-pentanal 153

DMSO (0.75 cm³, 10.5 mmol) was added by syringe to a solution of oxalyl chloride (0.46 cm³, 5.26 mmol) in CH₂Cl₂ (20 cm³) at -78°C and the mixture stirred for 30 min. (evolution of gas occurred). A solution of the alcohol **152** (2.00 g, 4.79 mmol) in CH₂Cl₂ (10 cm³) was added over 10 min by syringe to the reaction mixture and then allowed to stir for 30 min at -78°C. *N,N*-diisopropylethylamine (4.3 cm³, 23.9 mmol) was added to the reaction mixture, the solution stirred for 30 min at -78°C and then allowed to reach RT. After 30 min water (40 cm³) was added to the reaction mixture. The organic phase was washed with brine, dried (Na₂SO₄) and evaporated to give smelly oil. Column chromatography of the crude product using hexane-EtOAc (1:1) as eluent gave the aldehyde **153** (1.33 g, 67%) as an oil; R_f 0.49 (hexane-EtOAc 1:1).

δ_H 9.790 (s, 1H, C-1).

7.47 -7.21 (m, 15H, aromatic protons)

4.294 (dd, 1H, J_{2,3a}, 6.4, J_{2,3b} 7.2, H-2).

3.945 (dddd, 1H, J_{3b,4} 10.5, J_{4,5a} 5.9, J_{4,5b} 5.0, J_{3a,4} 4.8, H-4).

3.260 (dd, 1H, J_{5a,5b}, 9.7, J_{5a,4} 5.9, H-5a).

3.043 (dd, 1H, J_{5a,5b}, 9.7, J_{5b,4} 5.0, H-5b).

2.015 (ddd, 1H, J_{3a,3b} 13.2, J_{3a,2} 6.4, J_{3a,4} 4.8, H-3a).

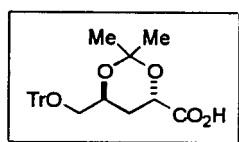
1.797 (ddd, 1H, J_{3a,3b} 13.2, J_{3b,4} 10.5, J_{3b,2} 7.2, , H-3b).

1.435 (s, 3H, acetonide Me).

1.421 (s, 3H, acetonide Me).

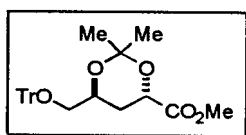
δ_C 202.17D (C-1); 143.95S (*ipso* Trityl); 128.69D, 127.75D, and 126.97D aromatic carbons); 100.18S (acetonide C-2); 86.51S (OTr); 73.58D (C-4); 66.54T (C-5); 65.89D (C-2); 27.49T (C-3); 27.06Q and 23.90Q (acetonide Me).

FAB-MS: *m/z* 417 [M+H]⁺. Exact mass: Calculated for C₂₇H₂₈O₄, 417.2066; Found, 417.2066



(2S,4S)-2,4-O,O-isopropylidene-5-(trityloxy)-pentanoic acid 160.

Sodium chlorite (80% purity, 0.552g, 4.88 mmol) in water (5.3 cm³) was added over a period of 2 h at 3-5 °C to a mixture of **153** (1.33g, 3.19mmol) in a mixture of acetonitrile (5.3 cm³), NaH₂PO₄ buffer (2.7 cm³, pH 4-5; prepared by dissolving 0.4 g in 4.0 cm³ water), and H₂O₂ (30%, 0.38 cm³). The reaction was allowed to warm to RT and left to stir for an additional 3 h. Sodium sulfite (0.132 g, 1.05 mmol) was added to destroy any HOCl or H₂O₂ present in the reaction. The reaction mixture was extracted with EtOAc (3 times), the organic phase dried (Na₂SO₄) and concentrated. TLC showed the characteristic pattern of an carboxylic acid on silica (tailing). The crude product was converted to the ester without any further clean-up.



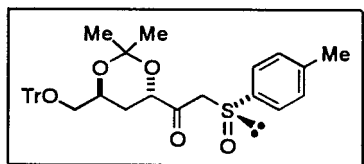
Methyl (2S,4S)-2,4-O,O-isopropylidene-5-(trityloxy)-pentanoate 161.

A diethyl ether solution of diazomethane (300 mmol) (prepared from 2.14 g *N*-methyl-*N*-nitroso-4-tolylsulfonamide in 40 cm³ Et₂O and 0.4 g KOH in 10 cm³ 96% ethanol) was added to a solution of the acid **160** (1.52 g) in diethyl ether. Nitrogen gas was immediately given off. After 15 min the excess diazomethane was evaporated in a stream of nitrogen gas. The solvent was evaporated and the residue purified by column chromatography using hexane-EtOAc (3:1) as eluent to give the methyl ester **161** as a colourless oil (1.32 g, 95%, 2 steps); *R*_f 0.46 (hexane-EtOAc 3:1); [α]_D -17.2 (*c.* 0.30, CHCl₃); *v*_{max} 1742 cm⁻¹.

- δ_H 7.48 -7.19 (m, 15H, aromatic protons).
 4.436 (dd, 1H, *J*_{2,3a} 8.3, *J*_{2,3b} 6.7, H-2).
 4.072 (dddd, 1H, *J*_{3b,4} 9.6, *J*_{4,5a} 6.0, *J*_{3a,4} 5.4, *J*_{4,5b} 4.9, H-4).
 3.754 (s, 3H, OMe).
 3.257 (dd, 1H, *J*_{5a,5b} 9.6, *J*_{5a,4} 6.0, H-5a).
 3.037 (dd, 1H, *J*_{5a,5b} 9.6, *J*_{5b,4} 4.9, H-5b).
 2.042 (ddd, 1H, *J*_{3a,3b} 13.2, *J*_{3a,2} 8.2, *J*_{3a,4} 5.4, H-3a).
 1.897 (ddd, 1H, *J*_{3a,3b} 13.2, *J*_{3b,4} 9.6, *J*_{3b,2} 6.6, H-3b).
 1.449 (s, 3H, acetonide Me).
 1.411(s, 3H, acetonide Me).
- δ_C 172.41S (C-1); 144.00S (*ipso* trityl); 128.72D, 127.78D, and 126.96D (aromatic carbons); 100.73S (acetonide C-2); 86.48S (OTrityl); 66.92D (C-4);

66.49T (C-5); 65.89D (C-2); 52.14Q (OMe); 30.81T (C-3); 26.18Q and 23.79Q (acetone Me);

FAB-MS: m/z 447 $[M+H]^+$. Exact mass: Calculated for $C_{28}H_{31}O_5$, 447.2172; Found, 447.2172



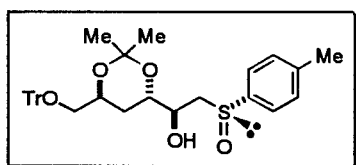
(S(R),3S,5S)-3,5-O,O-isopropylidene-1-(p-tolylsulfinyl)-6-(trityloxy)-2-hexanone 162

n-BuLi (1.58 cm³, 2.52 mmol) was added to a solution of *N,N*-diisopropylamine (0.42 cm³, 3.03 mmol), in THF (10 cm³) at -78°C . After 30 min a solution of the chiral sulfoxide 131 (0.40 g, 12.6 mmol) in THF (5 cm³) was added by syringe to the solution and stirring at -78°C continued for 1 h.. A pre-cooled solution of the ester 161 (0.56 g, 1.26 mmol) in THF (2 cm³) was slowly added by syringe to the reaction mixture and stirring at -78°C continued for 1 h (TLC control). The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (2x30 cm³). The combined organic solution was dried (Na_2SO_4) and evaporated. Column chromatography using EtOAc-hexane (2:3) yielded the ketosulfoxide 162 (0.61g, 82 %); R_f 0.47 (EtOAc-hexane 2:3); ν_{max} 1725 cm⁻¹

δ_{H} 7.55-7.18 (m, 19H, aromatic protons).
 4.143 (dd, 1H, $J_{3,4b}$ 8.8, $J_{3,4a}$ 6.9, H-3).
 4.090 (d, 1H, $J_{1a,1b}$ 13.7, H-1a).
 4.022 (d, 1H, $J_{1a,1b}$ 13.7, H-1b).
 3.940 (m, 1H, $J_{4b,5}$ 9.6, $J_{6a,5}$ 6.2, $J_{4a,5}$ 6.0, $J_{6b,5}$ 4.9, H-5).
 3.218 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6a,5}$ 6.2, H-6a).
 2.996 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6b,5}$ 4.9, H-6b).
 2.395 (s, 3H, tolyl Me).
 1.910 (ddd, 1H, $J_{4a,4b}$ 13.5, $J_{4a,5}$ 6.0, $J_{4b,3}$ 8.8, H-4a).
 1.758 (ddd, 1H, $J_{4a,4b}$ 13.5, $J_{4b,5}$ 9.6, $J_{4b,3}$ 7.0, H-4b).
 1.399 (s, 3H, acetone Me).
 1.362 (s, 3H, acetone Me).

δ_c 201.63S (C-2); 143.94S (*ipso* trityl); 142.15S and 140.23S (*ipso* tolyl), 128.68D, 127.75D, and 126.96D (trityl aromatic carbons), 130.06D and 124.20D (tolyl carbons); 101.06S (acetone C-2); 86.48S (OTr), 72.99D (C-3), 66.28T (C-6), 66.07D (C-5), 65.13T (C-1), 29.45T (C-4), 25.57Q and 24.24Q (acetone Me), 21.40Q (tolyl Me),

FAB-MS: m/z 569 $[M+H]^+$. Exact mass: Calculated for $C_{35}H_{37}SO_5$, 569.2362; Found, 569.2363



(S(R),2S,3S,5S)-3,5-O,O-Isopropylidene-1-(p-tolylsulfinyl)-6-(trityloxy)-2-hexanol 163

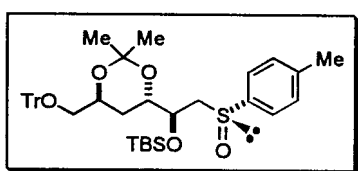
DIBALH (4.10 cm³, 23.0 mmol) was added by syringe to a solution of the ketosulfoxide **162** (11.00 g, 18.0 mmol) in THF (100 cm³) at -78°C. The reaction was stirred for 1 h, quenched with MeOH (very violent) and then concentrated *in vacuo*. The opaque solid formed was partitioned between CH₂Cl₂ and saturated NH₄Cl solution. The organic solution was dried (Na₂SO₄) and evaporated. Column chromatography of the residue using hexane-EtOAc (3:2) as eluent gave the hydroxysulfoxide **163** (9.00 g, 82%); mp. 145-147°C; R_f 0.33 (hexane-EtOAc 1:1); $[\alpha]_D^{25} +65.4$ (c, 0.53, CHCl₃)

δ_H 7.53 -7.17 (m, 19H, aromatic protons).
4.140 (dddd, 1H, $J_{1a,2}$ 9.3, $J_{2,3}$ 6.2, $J_{OH,2}$ 4.1, $J_{1b,2}$ 2.3, H-2).
3.919 (dddd, 1H, $J_{4b,5}$ 9.5, $J_{6a,5}$ 6.5, $J_{4a,5}$ 6.2, $J_{6b,5}$ 4.7, H-5).
3.823 (ddd, 1H, $J_{4a,3}$ 9.3, $J_{2,3}$ 6.2, $J_{4b,3}$ 6.2, H-3).
3.610 (d, 1H, $J_{OH,2}$ 4.1, 2-OH) disappears on addition of D₂O
3.224 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6a,5}$ 6.5, H-6a).
2.960 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6b,5}$ 4.7, H-6b).
2.874 (dd, 1H, $J_{1a,1b}$ 13.5, $J_{1a,2}$ 9.3, H-1a).
2.794 (dd, 1H, $J_{1a,1b}$ 13.6, $J_{1b,2}$ 2.3, H-1b).
2.408 (s, 3H, tolyl Me).
1.715 (ddd, 1H, $J_{4a,4b}$ 13.2, $J_{4a,3}$ 9.3, $J_{4a,5}$ 6.2, H-4a).
1.548 (ddd, 1H, $J_{4a,4b}$ 13.2, $J_{4b,3}$ 6.2, $J_{4b,5}$ 9.5, H-4b).

1.331 (s, 6H, acetonide Me).

δ_C 144.05S (*ipso* trityl); 141.59S and 140.01S (*ipso* tolyl); 128.70D, 127.73D, 126.92D (trityl aromatic carbons); 130.08D and 123.99S (tolyl carbons); 100.47S (acetonide C-2); 86.43S (OTr); 69.20D (C-2); 69.00D (C-3); 66.581T (C-6); 66.30D (C-5); 58.42T (C-1); 30.07T (C-4), 25.03Q and 24.73Q (acetonide Me), 21.37Q (tolyl Me).

FAB-MS: m/z 571 $[M+H]^+$. Exact mass: Calculated for $C_{35}H_{39}SO_5$, 571.2518; Found, 571.2513



(S(R),2S,3S,5S)-2-((*t*-Butyldimethylsilyl)oxy)-3,5-O,O-isopropylidene-1-(*p*-tolylsulfinyl)-6-(trityloxy)-hexane 164

Imidazole (50 mg, 0.73 mmol) was added to a solution of the hydroxysulfoxide **163** (280 mg, 0.48 mmol) in DMF (1 cm³) and the mixture stirred at room temperature for 10 min. TBSCl (90 mg, 0.58 mmol) was added and the reaction stirred at 50°C for 10 h. The reaction was quenched with MeOH and diluted with diethyl ether (20 cm³). The organic solution was washed with brine, dried (Na₂SO₄), and evaporated. The product mixture was purified by column chromatography to give starting material **163** (120 mg) and the TBS ether **164** (160 mg, 48%); mp. 144-146°C; R_f 0.80 (hexane-EtOAc 1:1);

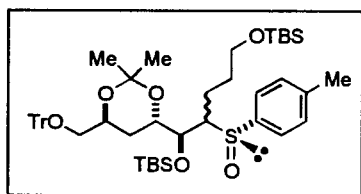
δ_H 7.53 -7.17 (m, 19H, aromatic protons).
4.147 (dddd, 1H, $J_{1a,2}$ 8.8, $J_{2,3}$ 6.2, $J_{OH,2}$ 4.1, $J_{1b,2}$ 3.1, H-2).
3.932 (dddd, 1H, $J_{4b,5}$ 9.5, $J_{6a,5}$ 6.5, $J_{4a,5}$ 6.2, $J_{6b,5}$ 4.9, H-5).
3.814 (ddd, 1H, $J_{4a,3}$ 9.3, $J_{2,3}$ 6.2, $J_{4b,3}$ 6.2, H-3).
3.230 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6a,5}$ 6.5, H-6a).
2.960 (dd, 1H, $J_{6a,6b}$ 9.8, $J_{6b,5}$ 4.9, H-6b).
2.895 (dd, 1H, $J_{1a,1b}$ 13.5, $J_{1a,2}$ 8.8, H-1a).
2.842 (dd, 1H, $J_{1a,1b}$ 13.6, $J_{1b,2}$ 3.1, H-1b).
2.399 (s, 3H, tolyl Me).
1.729 (ddd, 1H, $J_{4a,4b}$ 12.9, $J_{4a,3}$ 9.3, $J_{4a,5}$ 6.2, H-4a).

1.548 (ddd, 1H, $J_{4a,4b}$ 12.9, $J_{4b,3}$ 6.2, $J_{4b,5}$ 9.5, H-4b).
 1.340 (s, 3H, acetonide Me).
 1.331 (s, 3H, acetonide Me).
 0.908 (s, 9H, t-Bu).
 0.084 (s, 6H, Me₂Si).

δ_c 144.03S (*ipso* trityl); 141.53S and 140.01S (*ipso* tolyl); 128.66D, 127.68D, 126.87D (trityl aromatic carbons); 130.02D and 123.98S (tolyl carbons); 100.42S (acetonide C-2); 86.38S (OTr); 69.05D (C-2); 68.91D (C-3); 66.561T (C-6); 66.27D (C-5); 58.97T (C-1); 30.16T (C-4), 25.63Q (t-Bu)*; 24.97Q and 24.71Q (acetonide Me), 21.33Q (tolyl Me); -3.61Q (Me₂Si)*

* very low intensity signals!

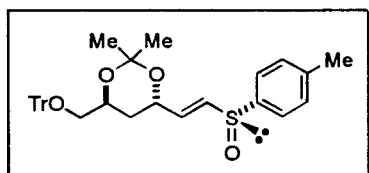
FAB MS: m/z 685 [M+H]⁺. Exact mass: Calculated for C₄₁H₅₃SSiO₅, 685.3383;
 Found, 685.3383



(S(R),1RS,2S,3S,5S)-2-((t-Butyldimethylsilyl)oxy)-1-[3-((t-butyldimethylsilyl)oxy)-propyl]-3,5-O,O-isopropylidene-1-(p-tolylsulfinyl)-6-(trityloxy)-hexane 165

The protected β -hydroxysulfoxide **164** (170 mg, 0.25 mmol) was added to a solution of LDA (2.2 eq., 0.55 mmol) in THF (5 cm³) generated *in situ*, containing TMEDA (0.55 mmol) at -40°C and the mixture stirred for 30 min. A solution of 1-((t-butyldimethylsilyl)oxy)-3-iodopropane **181** (90 mg, 0.30 mmol) in THF (1 cm³) was added and the reaction allowed to proceed at room temperature for 2 h. The reaction was quenched with NH₄Cl, the solvent evaporated and the residue partitioned between diethyl ether and brine. The diethyl ether solution was washed with 1M HCl, water and dried (Na₂SO₄), and evaporated. Column chromatography of the residue with EtOAc as eluent gave the α,β -unsaturated sulfoxide **166** as an oil.

(S(R),1E,3S,5S)-3,5-O,O-Isopropylidene-1-(p-tolylsulfinyl)-6-(trityloxy)-1-hexene 166

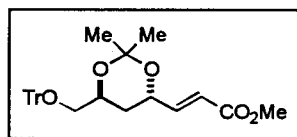


δ_H 7.52 -7.19 (m, 19H, aromatic protons).
 6.583 (dd, 1H, $J_{1,2}$ 15.1, $J_{2,3}$ 3.8, H-2).
 6.413 (dd, 1H, $J_{1,2}$ 15.1, $J_{1,3}$ 1.7, H-1).
 4.315 (ddd, 1H, $J_{4a,3}$ 8.6, $J_{4b,3}$ 6.3, $J_{2,3}$ 3.8, $J_{1,3}$ 1.7, H-3).
 3.996 (dddd, 1H, $J_{4b,5}$ 9.3, $J_{6a,5}$ 6.1, $J_{4a,5}$ 6.8, $J_{6b,5}$ 5.0, H-5).
 3.251 (dd, 1H, $J_{6a,6b}$ 9.5, $J_{6a,5}$ 6.1, H-6a).
 2.960 (dd, 1H, $J_{6a,6b}$ 9.6, $J_{6b,5}$ 5.0, H-6b).
 2.390 (s, 3H, tolyl Me).
 1.771 (ddd, 1H, $J_{4a,4b}$ 12.8, $J_{4a,3}$ 8.6, $J_{4a,5}$ 6.8, H-4a).
 1.690 (ddd, 1H, $J_{4a,4b}$ 12.9, $J_{4b,3}$ 6.3, $J_{4b,5}$ 9.3, H-4b).
 1.369 (s, 3H, acetonide Me).
 1.342 (s, 3H, acetonide Me).

δ_C 143.96S (*ipso* trityl); 141.58S and 140.59S (*ipso* tolyl); 138.05D (C-2);
 133.83D (C-1); 128.66D, 127.72D, 126.93D (trityl aromatic carbons);
 128.65D and 124.75S (tolyl carbons); 100.54S (acetonide C-2); 86.43S
 (OTr); 66.34T (C-6); 65.94D (C-5); 65.77T (C-3); 33.93T (C-4), 25.55Q and
 24.73Q (acetonide Me), 21.35Q (tolyl Me);

FAB MS: $[M+H]^+$ 685. Exact mass: Calculated for $C_{41}H_{53}SSiO_5$, 685.3383; Found,
 685.3383

6.4 PREPARATION OF THE C(1)-C(7) UNIT OF TA TOXIN VIA THE EPOXIDATION METHOD.



Methyl (2E,4S,6S)-4,6-O-isopropylidene-7-(trityloxy)-2-heptenoate 154

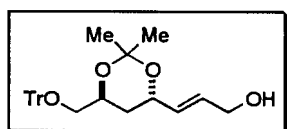
Potassium t-butoxide (1.66 g, 14.8 mmol) was added to a solution of diisopropyl methoxycarbonyl methylphosphonate 178 (4.00g, 16.8 mmol) in THF (80 cm³) at

0°C. The reaction mixture was stirred at RT for 2 h and then cooled to -78°C . The crude aldehyde **153**, prepared from the Swern oxidation of the alcohol **152** (2.07 g, 4.95 mmol) was dissolved in THF (10 cm³) and added dropwise by syringe to the reaction mixture at -78°C . The reaction mixture was quenched with saturated NH₄Cl solution and the THF evaporated. The residue was partitioned between diethyl ether (100 cm³) and brine. The aqueous phase was extracted two more times with Et₂O. The combined organic solutions were dried (Na₂SO₄) and the solvent removed. The residue was recrystallised from Et₂O-hexane (1:1) to give white crystals of the α,β -unsaturated ester **154** (1.30 g, 77%); mp 108-110°C; R_f 0.47 (hexane-EtOAc 4:1); $[\alpha]_D -31.3$ (c, 0.43, CHCl₃); ν_{max} 1717 cm⁻¹.

δ_{H} 7.47-7.20 (m, 15H, aromatic protons)
 6.929 (dd, 1H, $J_{2,3}$ 15.8, $J_{3,4}$ 4.4, H-3).
 6.017 (dd, 1H, $J_{2,3}$ 15.8, $J_{2,4}$ 2.1, H-2).
 4.482 (dddd, 1H, $J_{5b,4}$ 9.3, $J_{5a,4}$ 6.2, $J_{4,3}$ 4.4, $J_{4,2}$ 2.1, H-4),.
 4.083 (dddd, 1H, $J_{5a,6}$ 8.5, $J_{5b,6}$ 6.5, $J_{7a,6}$ 5.9, $J_{7b,6}$ 5.2, H-6)
 3.730 (s, 3H, OCH₃).
 3.271 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 5.9, H-7a)
 3.030 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7b,6}$ 5.2, H-7b)
 1.768 (ddd, 1H, $J_{5a,5b}$ 12.9, $J_{5a,6}$ 8.5, $J_{5a,4}$ 6.2, H-5a).
 1.718 (ddd, 1H, $J_{5a,5b}$ 12.9, $J_{5b,4}$ 9.3, $J_{5b,6}$ 6.5, H-5b)
 1.422 (s, 3H, acetonide Me)
 1.375 (s, 3H, acetonide Me)

δ_{C} 166.90S (C-1); 147.67D (C-2), 143.98S (*ipso* trityl); 128.66D, 127.76D, and 126.96D (trityl aromatic carbons); 119.59D (C-3); 100.54S (acetonide C-2); 86.44S (OTr); 66.39T (C-7); 65.93D (C-4 or C-6); 65.76D (C-6 or C-4); 51.55Q (OMe); 33.76T (C-5); 24.51 and 24.69Q (acetonide Me).

FAB-MS: m/z 473 [M+H]⁺. Exact mass: Calculated for C₃₀H₃₃O₅, 473.2328; Found, 473.2327.



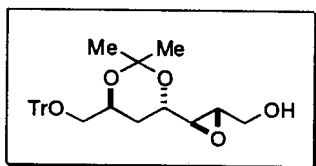
(2E,4S,6S)-4,6-O-isopropylidene-7-(trityloxy)-2-hepten-1-ol 155

DIBALH (6.75 cm³, 3.80 mmol) was added to a solution of the α,β -unsaturated ester **154** (0.83 g, 1.20 mmol) in THF (30 cm³) at -78°C and the reaction stirred for 1 h (TLC control). Excess DIBALH was destroyed by careful addition of MeOH (10 cm³). The solvent was evaporated and the residue extracted with. The combined CH₂Cl₂ solution was washed with saturated NH₄Cl solution and 1M HCl (10 cm³). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. Column chromatography of the residue using hexane-EtOAc (1:1) as eluent gave the allylic alcohol **155** (0.75 g, 94%); m.p $90\text{--}92^{\circ}\text{C}$; R_f 0.50 (hexane-EtOAc 1:1);; $[\alpha]_D -32.9$ (c, 1.0, CHCl₃);

δ_H 7.49-7.19 (m, 15H, aromatics).
 5.803 (dtd, 1H, $J_{2,3}$ 15.8, $J_{1,2}$ 5.2, $J_{2,4}$ 1.0, H-2)
 5.741 (ddt, 1H, $J_{2,3}$ 15.8, $J_{3,4}$ 5.7, $J_{1,3}$ 1.3, H-3)
 4.335 (br ddd, 1H, $J_{5b,4}$ 8.5, $J_{5a,4}$ 6.7, $J_{3,4}$ 5.7, H-4).
 4.136 (br d, 2H, H-1).
 4.047 (dddd, 1H, $J_{5a,6}$ 8.8, $J_{5b,6}$ 6.5, $J_{7a,6}$ 6.2, $J_{7b,6}$ 4.9, H-6).
 3.250 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 6.2, H-7a).
 3.000 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7b,6}$ 4.9, H-7b).
 1.723 (ddd, 1H, $J_{5a,5b}$ 13.1, $J_{5a,6}$ 8.8, $J_{5a,4}$ 6.7, H-5a).
 1.695 (ddd, 1H, $J_{5a,5b}$ 13.1, $J_{5b,4}$ 8.5, $J_{5b,6}$ 6.5, H-5b)
 1.412 (s, 3H, acetonide Me).
 1.377 (s, 3H, acetonide Me).

δ_C 144.03S (*ipso* trityl); 131.51D (C-3); 130.38D (C-2); 128.66D, 127.71D, and 126.91D (trityl aromatic carbons); 100.30S (acetonide C-2); 86.36S (OTr); 66.97D (C-4); 66.55T (C-7); 66.06D (C-6); 62.92T (C-1); 34.10T(C-5); 25.48Q and 24.86Q (acetonide Me).

FAB-MS: m/z 445 $[\text{M}+\text{H}]^+$. Exact mass: Calculated for C₂₉H₃₃O₄, 445.2379; Found, 445.2378



(2R,3R,4S,6S)-2,3-Epoxy 4,6-O,O-isopropylidene-7-(trityloxy)-1-heptanol 156

Ti(ⁱPrO)₄ (0.30 cm³, 1.0 mmol) was added to a suspension of powdered 3Å molecular sieves (0.5 g) in CH₂Cl₂ (10 cm³) at -30°C under an argon atmosphere. (*R,R*)-DET (0.20 cm³, 1.2 mmol) was added by syringe followed after 30 min by the allylic alcohol 155 C (0.89 g, 2.0 mmol) in CH₂Cl₂ (3 cm³). A pre-cooled solution of *t*-BuOOH in toluene (3.4M, 0.30 cm³, 4.0 mmol) was added and the reaction stirred at -20°C for 6 h and kept at 0°C for 5 days (TLC control). The reaction was diluted with CH₂Cl₂ and the molecular sieves filtered off. The filtrate was added to a cold (5°C) solution of FeSO₄ (0.7g, 2.5 mmol) and tartaric acid (0.2 g, 1.3 mmol) in water (10 cm³) and stirred for 30 min. After the separation of the phases and the extraction of the aqueous phase with diethyl ether, the organic solution was stirred with a solution of 30% NaOH in brine (5 cm³) for 1 h at 0°C. The diethyl ether solution was dried (MgSO₄), concentrated and subjected to column chromatography hexane-EtOAc (1:1) to the epoxide as a 4:1 diastereomeric mixture of 156:157 (0.50 g, 55%); m.p.101-103°C; R_f0.36 (hexane-EtOAc (1:1));

Major diastereomer 156

δ_H 7.47-7.22 (m, 15H, aromatics).

4.045 (dddd, 1H, J_{5a,6} 9.0, J_{5b,6} 6.5, J_{7a,6} 6.2, J_{7b,6} 4.9, H-6).

3.914 (ddd, 1H, J_{5b,4} 9.6, J_{5a,4} 6.2, J_{3,4} 3.6, H-4).

3.907 (dd, 1H, J_{1a,1b} 12.7 J_{1a,2} 2.6, H-1a).

3.633 (dd, 1H, J_{1a,1b} 12.7 J_{1b,2} 4.1, H-1b).

3.241 (dd, 1H, J_{7a,7b} 9.6, J_{7a,6} 6.2, H-7a).

2.994 (dd, 1H, J_{7a,7b} 9.6, J_{7b,6} 4.9, H-7b).

3.109 (dd, 1H, J_{3,4} 3.6, J_{2,3} 2.3, H-3).

3.070 (ddd, 1H, J_{1b,2} 4.1, J_{1a,2} 2.6, J_{2,3} 2.3, H-2).

1.733 (ddd, 1H, J_{5a,5b} 13.1, J_{5a,6} 9.0, J_{5a,4} 6.2, H-5a).

1.599 (ddd, 1H, J_{5a,5b} 13.1, J_{5b,4} 9.6, J_{5b,6} 6.5, H-5b)

1.417 (s, 3H, acetonide Me).

1.359 (s, 3H, acetonide Me).

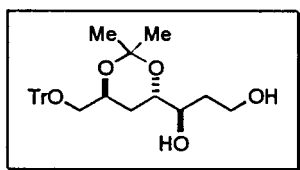
δ_C 144.01S (*ipso* trityl); 128.69D, 127.75D, and 126.94D (trityl aromatic carbons); 100.30S (acetonide C-2); 86.41S (OTr); 66.51T (C-7); 66.00D (C-6); 65.84D (C-4); 61.15T (C-1); 56.61D (C-3); 55.54D (C-2); 30.01T (C-5); 25.34Q and 24.60Q (acetonide Me).

Minor diastereomer 157

δ_H 3.253 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 6.2, H-7a).
2.997 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7b,6}$ 4.9, H-7b).
1.784 (ddd, 1H, $J_{5a,5b}$ 13.1, $J_{5a,6}$ 9.0, $J_{5a,4}$ 6.2, H-5a).
1.606 (ddd, 1H, $J_{5a,5b}$ 13.1, $J_{5b,4}$ 9.6, $J_{5b,6}$ 6.5, H-5b)

δ_C 67.13D (C-4); 60.93T (C-1); 56.73D (C-3); 55.42D (C-2); 30.88T (C-5);
25.10Q and 24.59Q (acetonide Me).

FAB-MS: m/z 461 $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{33}O_5$, 461.2328; Found, 445.2326



(3R,4S,6S)-4,6-O,O-isopropylidene-7-(trityloxy)-heptane-1,3-diol 158

Red-Al (3.4M in toluene, 0.07 cm³) was added at 0°C to a solution of the epoxy alcohol 156/157 (80 mg, 0.17 mmol) in THF (5 cm³). The mixture was stirred for 5 h and then quenched by the addition of MeOH. The reaction mixture was poured into water, and acidified with 1M HCl. The emulsion was diluted with petroleum ether, extracted with EtOAc and the organic phase washed with brine. The EtOAc solution was dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography using EtOAc to give the 1,3-diol 158:159 (70 mg, 70%), an oil, as a 4:1 diastereomeric mixture.

δ_H 7.48-7.21 (m, 15H, aromatics).
3.973 (m, 1H, H-6).
3.894 (m, 1H, H-4).
3.810 (t, 2H, $J_{1,2}$ 5.7, H-1).
3.729 (m, 1H, H-3)
3.258 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 6.5, H-7a).
3.008 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7b,6}$ 4.7, H-7b)
1.879 (ddd, 1H, $J_{5a,5b}$ 12.7, $J_{5a,6}$ 9.8, $J_{5a,4}$ 6.5, H-5a).
1.63 (m, 2H, H-2);
1.493 (ddd, 1H, $J_{5a,5b}$ 12.7, $J_{5b,4}$ 9.3, $J_{5b,6}$ 6.2, H-5b)

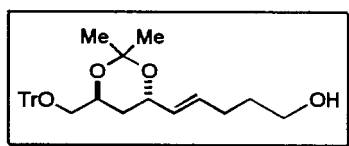
1.403 (s, 3H, acetonide Me).

1.362 (s, 3H, acetonide Me).

δ_c 144.09S (*ipso* trityl); 128.71D, 127.73D, and 126.90D (trityl aromatic carbons); 100.38S (acetonide C-2); 86.41S (OTr); 72.98D (C-4); 69.22D (C-3); 66.67T (C-7); 66.56D (C-6); 65.84D (C-4); 61.15T (C-1); 61.23T (C-1); 33.45T (C-5); 28.86T (C-2); 24.93Q and 24.71Q (acetonide Me).

FAB-MS: m/z 463 $[M+H]^+$.

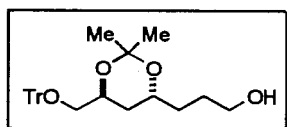
6.5 PREPARATION OF THE C(1)–C(9) UNIT OF TB TOXIN



(2E,6R,8S)-6,8-O,O-Isopropylidene-9-(trityloxy)-4-nonen-1-ol

n-Butyllithium (5.98 cm³, 9.56 mmol) was added dropwise to a solution of triphenyl 4-((*t*-butyldiphenylsilyloxy)-1-butylphosphonium iodide (4.29 g, 9.56 mmol) in THF (50 cm³) at –78°C under argon. The reaction was stirred for 1 h –78°C. The crude aldehyde **153**, prepared from the Swern oxidation of the alcohol **152** (1.0g, 2.39 mmol) in THF (10 cm³) was added dropwise to the reaction mixture at –78°C. The reaction mixture was monitored by TLC. After 5 h the reaction was quenched with NH₄Cl solution, diluted with diethyl ether (100 cm³) and partitioned between Et₂O and brine. The Et₂O solution was dried (Na₂SO₄) and concentrated *in vacuo*.

NMR showed only the recovered starting material.

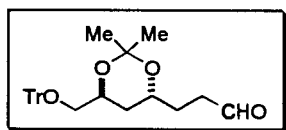


(4R,6S)-4,6-O,O-Isopropylidene-7-(trityloxy)-1-heptanol **173**

Pd-C (10%, 20 mg) was added to to a solution of the allylic alcohol **155** (200 mg.) in EtOAc (10 cm³) and the suspension stirred in a H₂ atmosphere (15 psi) for 1 h. The catalyst was removed by filtration and the filtrate concentrated. Column chromatography of the residue using EtOAc-hexane (1:1) gave the alcohol **173** (180 mg, 90%); R_f 0.50 (hexane-EtOAc 1:1);

- δ_H 7.48-7.20 (m, 15H, aromatic protons).
4.015 (m, 1H, H-4).
3.763 (m, 1H, H-6).
3.623 (m, 1H, H-1)
3.249 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 6.5, H-7a).
2.971 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 4.9, H-7a).
1.66-1.52 (m, 6H, H-2, H-3, H-5).
1.411 (s, 3H, acetonide Me).
1.368 (s, 3H, acetonide Me).
- δ_C 144.07S (*ipso* trityl). 128.68D, 127.71D, and 126.89D, (aromatic carbons);
100.37S (acetonide C-2), 86.32S (OTr); 66.82D (C-6 or C-4); 66.58T (C-7);
66.34D (C-4 or C-6); 62.63T (C-1); 35.05T (C-5); 32.51T; 29.11T; 24.79Q
and 24.69Q (acetonide Me).

FAB-MS: m/z 446 $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{34}O_4$, 446.2457; Found, 445.2457



(4R,6S)-4,6-O,O-Isopropylidene-7-(trityloxy)-heptanal 174

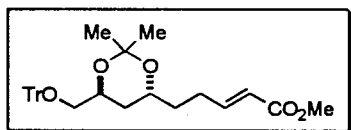
DMSO (0.11 cm³, 1.52 mmol) was added by syringe to a solution of oxalyl chloride (65 μ l, 0.76 mmol) in CH_2Cl_2 (5 cm³) at $-78^\circ C$ and the mixture stirred for 30 min. (evolution of gas occurred). A solution of the alcohol **173** (308 mg, 0.69 mmol) in CH_2Cl_2 (1 cm³) was added over 5 min by syringe to the reaction mixture and then allowed to stir for 30 min at $-78^\circ C$. *N,N*-diisopropylethylamine (0.60 cm³, 3.45 mmol) was added to the reaction mixture, the solution stirred for 30 min at $-78^\circ C$ and then allowed to reach RT. After 30 min water (10 cm³) was added to the reaction mixture. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give smelly oil. Column chromatography of the crude product using hexane-EtOAc (1:1) as eluent gave the aldehyde **174** (284 mg, 93%) as an oil; R_f 0.78 (hexane-EtOAc 1:1).

- δ_H 9.742 (dd, 1H, $J_{1,2a}$ 1.8, $J_{1,2b}$ 1.5, H-1).
7.50-7.20 (m, 15H, aromatic protons).

4.021 (dddd, 1H, $J_{5a,6}$ 9.1, $J_{5b,6}$ 6.5, $J_{7a,6}$ 6.5, $J_{7b,6}$ 4.9, H-6).
 3.762 (dddd, 1H, $J_{5b,4}$ 9.3, $J_{3b,4}$ 8.4, $J_{5a,4}$ 6.0, $J_{3a,4}$ 4.4, H-4).
 3.267 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7a,6}$ 6.5, H-7a).
 2.986 (dd, 1H, $J_{7a,7b}$ 9.6, $J_{7b,6}$ 4.9, H-7b).
 2.522 (dtd, 1H, $J_{2a,2b}$ 17.3, $J_{2a,3a}$ 7.0, $J_{1,2a}$ 1.8, H-2a)
 2.465 (dtd, 1H, $J_{2a,2b}$ 17.3, $J_{2b,3b}$ 7.0, $J_{1,2b}$ 1.5, H-2b)
 1.816 (ddd, 1H, $J_{3a,3b}$ 14.2, $J_{3a,2a}$ 7.0, $J_{3a,4}$ 4.4, H-3a)
 1.766 (ddd, 1H, $J_{3a,3b}$ 14.2, $J_{3b,2b}$ 7.0, $J_{3b,4}$ 8.4, H-3b)
 1.615 (ddd, 1H, $J_{5a,5b}$ 12.9, $J_{5a,6}$ 9.1, $J_{5a,4}$ 6.0, H-5a).
 1.561 (ddd, 1H, $J_{5a,5b}$ 12.9, $J_{5b,4}$ 9.3, $J_{5b,6}$ 6.5, H-5b)
 1.398 (s, 3H, acetonide).
 1.335 (s, 3H, acetonide).

δ_c 202.13S (C-1); 144.02S (*ipso* trityl); 128.63D, 127.68D, and 126.87D (aromatic carbons); 100.30S (acetonide C-2), 86.29S (OTr), 66.51T (C-7), 66.19D (C-6), 65.81D (C-4), 40.29T (C-2); 34.92T (C-5); 28.12T (C-3); -24.67Q (2x acetonide Me).

FAB-MS: m/z 445 $[M+H]^+$. Exact mass: Calculated for $C_{29}H_{33}O_4$, 445.2379; Found, 445.2379



Methyl (2E,6R,8S)-6,8-O,O-isopropylidene-9-(trityloxy)-2-nonenoate 175

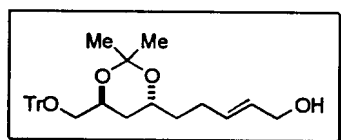
Potassium t-butoxide (160 mg, 1.46 mmol) was added to a solution of diisopropyl methoxycarbonyl methylphosphonate **178** (390 mg, 1.66 mmol) in THF (10 cm³) at 0°C. The reaction mixture was stirred at RT for 2 h and then cooled to -78°C. The aldehyde **174** (222 mg, 0.50 mmol) was dissolved in THF (1 cm³) and added dropwise by syringe to the reaction mixture at -78°C. The reaction mixture was quenched with saturated NH₄Cl solution and the THF evaporated. The residue was partitioned between diethyl ether (20 cm³) and brine. The aqueous phase was extracted two more times with Et₂O. The combined organic solutions were dried (Na₂SO₄) and the solvent removed. The product was purified by column chromatography with hexane-EtOAc (2:1) to give the α,β -unsaturated ester **175** (229

mg, 94%) as an oil; R_f 0.52 (hexane-EtOAc (1:1)); $[\alpha]_D -31.6$ (c, 2.56, CHCl_3); ν_{max} 1725 cm^{-1} .

δ_{H} 7.48 -7.17 (m, 15H, aromatic protons).
6.976 (ddd, 1H, $J_{2,3}$ 15.8, $J_{3,4a}$ 7.2, $J_{3,4b}$ 6.8, H-3).
5.820 (ddd, 1H, $J_{2,3}$ 15.8, $J_{2,4a}$ 1.5, $J_{2,4b}$ 1.5, H-2).
4.008 (m, 1H, H-8).
3.746 (m, 1H, H-6).
3685 (s, 3H, OMe).
3.251 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9a,8}$ 6.5, H-9a).
2.912 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9b,8}$ 4.9, H-9b).
2.27 (m, 2H, H-4).
1.70-1.45 (m, 4H, H-5 and H-7).
1.343 (s, 3H, acetonide).
1.333 (s, 3H, acetonide).

δ_{C} 166.81S (C-1); 148.76D (C-2); 143.94S (*ipso* trityl); 128.53D, 127.59D, and 126.77D, (aromatic carbons); 121.04D (C-3); 100.17S (acetonide C-2), 86.19S (OTr); 66.46T (C-9); 66.11D (C-6); 65.52D (C-4); 51.20Q (OMe); 34.97T (C-7); 33.72T (C-4); 28.12T (C-3), 24.69Q and 24.62Q (acetonide Me).

FAB-MS: m/z 501 $[\text{M}+\text{H}]^+$. Exact mass: Calculated for $\text{C}_{32}\text{H}_{37}\text{O}_5$, 501.2641; Found, 501.2650



(2E,6R,8S)-6,8-O,O-isopropylidene-9-(trityloxy)-2-nonen-1-ol 176

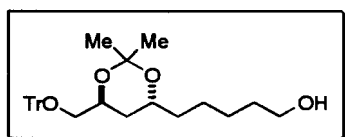
DIBALH (0.26 cm^3 , 1.45 mmol) was added to a solution of the α,β -unsaturated ester **175** (229 mg, 0.49 mmol) in THF (10 cm^3) at -78°C and the reaction stirred for 1 h (TLC control). Excess DIBALH was destroyed by careful addition of MeOH (2 cm^3). The solvent was evaporated and the residue extracted with. The combined CH_2Cl_2 solution was washed with saturated NH_4Cl solution and 1M HCl (10 cm^3). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Column chromato-

graphy of the residue using hexane-EtOAc (1:1) as eluent gave the allylic alcohol **176** (231 mg, 94%) as an oil; R_f 0.46 (hexane-EtOAc 1:1); $[\alpha]_D -31.9$ (c, 1.0, CHCl_3);

δ_H 7.55 -7.20 (m, 15H, aromatic protons).
5.650 (dt, 1H, $J_{2,3}$ 15.3, $J_{3,4}$ 5.5, H-3
5.650 (dt, 1H, $J_{2,3}$ 15.3, $J_{1,2}$ 4.7, H-2).
4.068 (d, 2H, $J_{1,2}$ 4.4, H-1).
4.044 (m, 1H, H-8).
3.849 (m, 1H, H-6).
3.266 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9a,8}$ 6.7, H-9a).
2.980 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9b,8}$ 4.9, H-9b).
2.13 (m, 2H, H-4).
1.78 (br s, 1H, OH).
1.68-1.45 (m, 4H, H-5 and H-7).
1.426 (s, 3H, acetonide Me).
1.362 (s, 3H, acetonide Me).

δ_C 144.03S (*ipso* trityl). 132.15D (C-3); 129.39D (C-2); 128.63D, 127.67D, and 126.85D (aromatic carbons); 100.23S (acetonide C-2); 86.26S (OTr); 66.62T (C-9); 66.25D (C-6); 65.78D (C-8); 63.45T (C-1); 35.12T (C-7 or C-5); 34.93T (C-5 or C-7); 28.04T (C-4); 24.80Q and 24.74Q (acetonide Me).

FAB-MS: m/z 473 $[\text{M}+\text{H}]^+$ 473. Exact mass: Calculated for $\text{C}_{32}\text{H}_{38}\text{O}_5$, 473.2615;
Found, 473.2615



Methyl (6R,8S)-6,8-O,O-isopropylidene-9-(trityloxy)-1-nonanol 177

Pd-C (10%, 20 mg) was added to to a solution of the allylic alcohol **176** (230 mg, 0.49 mmol) in EtOAc (10 cm^3) and the suspension stirred in a H_2 atmosphere (15 psi) for 1 h. The catalyst was removed by filtration and the filtrate concentrated. Column chromatography of the residue using EtOAc-hexane (1:1) gave the alcohol **177** (208 mg, 90%) as an oil; R_f 0.46 (hexane-EtOAc 1:1); $[\alpha]_D -32.0$ (c, 0.80, CHCl_3);

δ_H 7.48 - 7.19 (m, 15H, aromatic protons).
4.006 (m, 1H, H-8).
3.730 (m, 1H, H-6).
3.611 (t, 2H, $J_{1,2}$ 6.5, H-1).
3.239 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9a,8}$ 6.5, H-9a).
2.956 (dd, 1H, $J_{9a,9b}$ 9.6, $J_{9b,8}$ 4.7, H-9b).
1.58 -1.30 (m, 10H, H-2, H-3, H-4, H-5, and H-7).
1.399 (s, 3H, acetonide Me).
1.355 (s, 3H, acetonide Me).

δ_C 24.82Q and 24.86Q (acetonide Me); 25.17T; 25.62T; 32.64T; 35.25T;
35.76T; 62.87T (C-1); 66.31D (C-8); 66.55D (C-6); 66.74T (C-9); 86.32S
(OTr); 100.16S (acetonide C-2), 126.89D 127.71D, 128.71D (aromatic
carbon, trityl), 144.13S (*ipso* trityl).

FAB-MS: m/z 475 $[M+H]^+$. Exact mass: Calculated for $C_{31}H_{39}O_4$, 475.2848; Found,
475.2848

6.6 REFERENCES

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