

**Synthetic studies toward pavettamine, the
active principle from *Pavetta harborii*.**

by

SAMSON YEBIO GEBRETNSAE

Submitted in partial fulfillment of the requirement for the degree.

MAGISTER SCIENTIAE

In the Faculty of Natural & Agricultural Sciences

**UNIVERSITY OF PRETORIA
PRETORIA**

Supervisor: Prof. R. Vleggaar

January 2005

SUMMARY

Gousiekte (“quick” disease) is a plant-induced cardiomyopathy of livestock in South Africa, that is characterized by the sudden death of animals within a period of 3-6 weeks after the initial ingestion of toxic plant material. Six species of three genera of the Rubiaceae family *viz.* *Pachystigma pygmaeum*, *P. thamnus*, and *P. latifolium*; *Pavetta harborii* and *P. schuman-niana*, and *Fadogia homblei* have been identified as the causative agents of the disease. The toxin responsible for the poisoning, named pavettamine, has been isolated and the structure and absolute configuration established as (2*S*,4*R*,8*R*,10*S*)-1,11-diamino-6-aza-undecane-2,4,8,10-tetraol, or the enantiomer, by mass spectrometry and NMR spectroscopy.

Retrosynthetic analysis of the pavettamine molecule as outlined in the dissertation showed that the secondary amine function could be obtained from the amide functional group in an intermediate such as (2*R*,4*S*)-*N*-[(2'*R*,4'*S*)-2,4,5-trihydroxypentan-1'-yl]-2,4,5-trihydroxypentanamide **A**. Disconnection of the amide bond then generated two C₅ building blocks *viz.* an amine **B** and a carboxylic acid **C** which through a set of functional group transformations led to a common C₅ building block, a pentane-1,2,4,5-tetraol **D**. The terminal primary hydroxy groups required different protecting groups at all times in order to safe-guard the integrity of the two stereogenic centres. In addition identical protecting groups but different to those used for the primary hydroxy groups, were necessary for the secondary hydroxy groups. Further analysis of the C₅ building block **D** showed that it could be obtained from (2*S*)-malic acid by functional group transformations, chiral sulfoxide methodology and an appropriate protective group strategy.

A suitable protective group strategy was developed and an 11 step synthetic route for the C₅ building block established. The successful conversion of this moiety through functional group transformations provided the C₅ amine **B** and C₅ carboxylic acid **C** which were linked to give the target compound, the amide **D** but with the hydroxy groups protected.

The synthetic study presented in the dissertation provides an efficient methodology toward the synthesis of any of the 10 possible stereoisomers of pavettamine.

ACKNOWLEDGEMENTS

To **God** our **Creator** who knows the destiny of every living being on this earth. It is through his **Grace** and **Love** that I am what I am today, tomorrow and forever.

To my supervisor **Professor Robert Vlegaar**, thank you for your guidance and our discussions throughout the project as well as financial support. I have acquired much from your supervision and have been inspired by your knowledge. Thank you for letting me be very close to you. I will always remember you.

To my **family**, your encouragement, love and support were the things that kept me going to fulfillment of my dream.

To my friend and brother in Christ, **Eyob Habte**, thank you for your prayers, for always being there at the time of need and for your encouragement.

I am grateful to **Dr. Lynne Collett** and **Dr. Janine Chantson**, for letting me use their laboratories and chemicals, and for their proofreading of some of my chapters.

I wish to thank the Honours students, **Daniella**, **Richard**, and **Bernel**, and Nick Brannen for their acceptance, friendship and love they showed me during my study.

I would like to thank **Mr. Eric Palmer** for NMR training and **Robin Muir** for making and repairing all the glass needed during the course of the project.

Many thanks also go to **Louisa Stuurman**, **Binnur** and **Ronald van Pomeran** for their support, and for they made my stay in South Africa colourfull.

Finally I would like to thank the **Human Resource Development of Eritrea**, and the **Department of Chemistry, University of Pretoria** for financial assistance. Without your support I would not have been able to sustain myself while studying.

LIST OF ABBREVIATIONS

AcOH	Acetic acid
Ac ₂ O	Acetic anhydride
AgNO ₃	Silver nitrate
Ag ₂ O	Silver oxide
AlCl ₃	Aluminium trichloride
BF ₃ .Et ₂ O	Borontrifluoride diethyl etherate
BH ₃ .NHMe ₂	Borane dimethylamine complex
BH ₃ .SMe ₂	Borane dimethyl sulfide complex
BH ₃ .THF	Borane tetrahydrofuran complex
BnBr	Benzyl bromide
<i>n</i> -BuLi	<i>n</i> -Butyllithium
<i>t</i> -BuOH	<i>t</i> -Butanol
<i>t</i> -BuOOH	<i>t</i> -Butyl hydroperoxide
CBr ₄	Carbon tetrabromide
CCl ₄	Carbon tetrachloride
CF ₃ CO ₂ H	Trifluoroacetic acid
CH ₂ Cl ₂	Dichloromethane
CSA	Camphorsulfonic acid
CuCl ₂	Copper(II) chloride
CuSO ₄	Copper(II) sulfate
DIBALH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	<i>N,N</i> -Dimethylformamide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	Dimethylsulfoxide
DEAD	Diethyl azodicarboxylate
Et ₂ AlCN	Diethylaluminum cyanide
HBr	Hydrogen bromide
HCl	Hydrogen chloride
HgCl ₂	Mercury(II) chloride
HN ₃	Hydrazoic acid
KH	Potassium hydride
KI	Potassium iodide
K ₂ CO ₃	Potassium carbonate

LDA	Lithium diisopropylamide
LiAlH ₄	Lithium aluminium hydride
Li ₂ S	Lithium sulfide
MeCN	Acetonitrile
MeMgI	Methylmagnesium iodide
MeOH	Methanol
MOM	Methoxymethyl
NaClO ₂	Sodium chlorite
NaCN	Sodium cyanide
NaBH ₄	Sodium borohydride
NaH	Sodium hydride
NaHCO ₃	Sodium hydrogencarbonate
NaN ₃	Sodium azide
NaOAc	Sodium acetate
NaOCH ₃	Sodium methoxide
NaOH	Sodium hydroxide
NBS	<i>N</i> -Bromosuccinimide
NH ₄ OH	Ammonium hydroxide
O ₃	Ozone
PhCHO	Benzaldehyde
Ph ₃ CCl	Triphenylmethyl chloride
PPh ₃	Triphenylphosphine
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Pyr	Pyridine
SOCl ₂	Thionyl chloride
TBAF	Tetrabutylammonium fluoride
TBDPS	<i>t</i> -Butyldiphenylsilyl
TBDPSOTf	<i>t</i> -Butyldiphenylsilyl triflate
TBS	<i>t</i> -Butyldimethylsilyl
TBS-Cl	<i>t</i> -Butyldimethylsilyl chloride
TBSOTf	<i>t</i> -Butyldimethylsilyl triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Triflic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TiCl ₃	Titanium trichloride
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography

TMSI	Trimethylsilyl iodide
TMS-OTf	Trimethylsilyl triflate
Tr	Triphenylmethyl or trityl
TsCl	Toluene-4-sulfonyl chloride
TsOH	Toluene-4-sulfonic acid
ZnBr ₂	Zinc bromide
ZnI ₂	Zinc iodide
Zn(OTf) ₂	Zinc triflate

CONTENTS

1	INTRODUCTION	
1.1	General	1
1.2	Isolation of the active principle	2
1.3	Structural elucidation of pavettamine	3
1.4	Natural polyamines	5
2	RETROSYNTHETIC ANALYSIS	
2.1	Introduction	8
2.2	Retrosynthetic analysis of pavettamine	9
2.2.1	Disconnection of the central C-N bond	9
2.2.2	Retrosynthetic analysis of the C ₅ primary alcohol synthon F	11
2.3	Retrosynthetic analysis of the stereoisomers of pavettamine	12
2.4	Literature synthesis for the C ₅ synthons F and M	13
3	CHEMISTRY OF CHIRAL SULFOXIDES	
3.1	Introduction	18
3.2	Synthesis of chiral sulfoxides	18
3.2.1	Synthesis of β -ketosulfoxides	19
3.3	Reaction of β -ketosulfoxides	21
3.3.1	Nucleophilic addition of β -ketosulfoxides	21
3.3.2	Selective reduction of β -ketosulfoxides	22
3.3.3	Reactions of α -sulfinyl carbanions	25
3.3.4	Functional group transformations involving the sulfoxide moiety	28
4	PROTECTING GROUP STRATEGY OF HYDROXY GROUPS	
4.1	Introduction	31
4.2	Benzylidene protecting group	31
4.2.1	Formation of benzylidene acetals	31
4.2.2	Cleavage of benzylidene acetals	33

4.3	Acetonide protecting group	37
4.3.1	Formation of acetonides	37
4.3.2	Cleavage of acetonides	39
4.3.3	The use of ^{13}C NMR to determine the stereochemistry of 1,3-diols	41
4.4	Benzyl protecting group	42
4.4.1	Formation of benzyl ethers	43
4.4.1	Cleavage of benzyl ethers	44
4.5	Silyl ether protecting groups	44
4.5.1	<i>t</i> -Butyldimethylsilyl ether	45
4.5.1.1	Formation of <i>t</i> -butyldimethylsilyl ethers	45
4.5.1.2	Cleavage <i>t</i> -butyldimethylsilyl ethers	46
4.5.2	<i>t</i> -Butyldiphenylsilyl ethers	46
4.5.2.1	Formation of <i>t</i> -butyldiphenylsilyl ethers	47
4.5.2.2	Cleavage <i>t</i> -butyldiphenylsilyl ethers	47
4.5.3	Trityl protecting group	47
4.5.3.1	Formation of trityl protecting groups	48
4.5.3.2	Cleavage of trityl protecting groups	48
5	PREPARATION OF AMINES	
5.1	Introduction	49
5.2	Methods of transformation	49
5.2.1	Method 1: Amines via reduction	49
5.2.2	Method 2: Amines via rearrangement	50
5.2.3	Method 3: Amines via nucleophilic substitution	51
5.2.3.1	Three-step methodology	52
5.2.3.2	The Mitsunobu reaction: a two-step methodology	53
5.2.3.3	One-pot methodology	55
6	SYNTHETIC STUDIES	
6.1	Introduction	57
6.2	Synthesis of the C_5 unit	57

6.2.1	The lactone approach	57
6.2.2	Synthesis of the C ₅ synthon: the open-chain ester approach	60
6.2.2.1	Route 1: Benzylidene protecting group	60
6.2.2.2	Route 2: Acetonide and trityl protecting group	63
6.2.2.3	Route 3: TBDPS protecting group	66
6.3	Linkage of the two C ₅ units	70
6.4	Conclusion and Future Work	74
7	EXPERIMENTAL	
7.1	General	75
7.2	Preparation of Reagents	76
7.2.1	Spraying reagents	76
7.2.2	Other reagents	76
7.3	Procedures	79
7.3.1	The lactone approach	79
7.3.2	Synthesis of the C ₅ synthon: the open-chain ester approach	83
7.3.2.1	Route 1: Benzylidene protecting group	83
7.3.2.2	Route 2: Acetonide and trityl protecting group	87
7.3.2.3	Route 3: TBDPS protecting group	95
7.3.3	Linkage of the two C ₅ units	104

1 INTRODUCTION

1.1 General

Southern Africa with its rich diversity and beauty of its flora also has an unequalled variety of poisonous plants. The importance of poisonous plants to the livestock industry cannot be overestimated. About 600 indigenous poisonous plants are known to occur in southern Africa. Under adverse conditions caused by drought, overstocking and uncontrolled fires, animals are often forced to eat plants that they would normally avoid. Devastating outbreaks of poisonings have been reported under these conditions. Losses are still incurred almost annually as a result of ingestion of poisonous plants such as *Senecio* spp., *Geigeria* spp., *Dichapetalum cymosum* or gifblaar, cardiac glycoside containing plants and members of the Rubiaceae that cause gousiekte. Authorities estimate that in certain years up to 25% of stock losses can be attributed to plant poisonings.^{1,2}

Gousiekte (“quick” disease), one of the six most important plant toxicoses of livestock in South Africa, is a plant-induced cardiomyopathy of domestic ruminants that is characterized by the sudden death of animals within a period of 3-6 weeks after the initial ingestion of toxic plant material. The six species of the three genera of the Rubiaceae family viz. *Pachystigma pygmaeum*,³ *P. thamnus*, and *P. latifolium*;⁴ *Pavetta harborii*⁵ and *P. schumanniana*, and *Fadogia homblei*⁶ have been identified as the causative agents of the disease.⁷ The disease was first identified in 1908 but because of the irregular outbreaks the matter was not pursued until a severe outbreak in 1915 was reported in which 1047 out of a flock of 1761 sheep died. Gousiekte is the last of the major plant poisonings in southern Africa to be investigated and the causal toxin was not identified until 1995. Investigations were hampered by the variations

¹ Kellerman, T.S.; Coetzer, J.A.W.; Naude, T.W. *Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa*, Oxford University Press Southern Africa, Cape Town, **1988**.

² Mulholland, D.A.; Drewes, S.E. *Phytochemistry* **2004**, *65*, 769.

³ Theiler, A.; du Toit, P.J.; Mitchell, D.T. *Report of the Director of Veterinary Education and Research, Union of South Africa*, **1923**, 9-10, 9.

⁴ Adelaar, T.F.; Terblanche, M. *J.S. Afr. Vet. Med. Assoc.* **1967**, *38*, 25.

⁵ Uys, P.L.; Adelaar, T.F. *J.S. Afr. Vet. Med. Assoc.* **1957**, *28*, 5.

⁶ Hurter, L.P.; Naude, T.W.; Adelaar, T.F.; Smit, J.D.; Codd, L.E. *Onderstepoort J. Vet. Research*, **1972**, *39*, 71.

⁷ Kellerman, T.S.; Coetzer, J.A.W.; Naude, T.W. *Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa*, Oxford University Press Southern Africa, Cape Town, **1988**, p. 114.

in the clinical signs of the disease, variability in toxicity of the plants, differences in animal susceptibility to intoxication, and diminishing toxicity of the plants during drying. Although there is strong evidence that shows that a small dose of plant material is occasionally fatal, generally fairly large quantities of plant material have to be ingested for intoxication to occur.

1.2 Isolation of the active principle⁸

Pavetta harborii was collected near Ellisras in Limpopo Province (South Africa) on a farm with a high prevalence of gousiekte. This particular plant was selected for extraction of the toxin because it was the most readily obtainable of the gousiekte bushes and the dried material reportedly maintained its toxicity during storage. Sheep or goats were used for toxicity testing of extracts and the various fractions during the isolation procedure.

P. harborii is a perennial shrublet with subterranean branches giving rise to groups of aerial stems. One plant can cover an area of *ca.* 2 m in diameter. The erect, smooth, grayish to pale-yellow, woody stems persist through the winter, though the leaves drop off. The opposite, sessile, oblanceolate leaves, measuring 30-45 mm by *ca.* 10 mm, are sparsely hairy on the upper surface, and pale and felt-like on the under surface. As in all *Pavetta* species, opaque bacterial spots may be visible when the leaves are held up to the light. Clusters of white scented tubular flowers with star-shaped corolla lobes and protruding styles appear in early summer on the previous season's growth. The fruits are small pea-sized drupes that become shiny-black with age.^{5,9,10}

Coarsely milled, dried *P. harborii* leaves (4 kg) were extracted with warm ethanol and the extract discarded. The residual plant material was then extracted with hot water for 24 h. The water extract was proven to be toxic and concentrated to a volume of 2 l on a rotary evaporator. Addition of 96% ethanol (4 l) gave a toxic precipitate (150 g). This precipitate was redissolved in water (1.5 l) and treated with methanol (3 l) to give once again a toxic precipitate (125 g). A solution of part of this material (100 g) in water (500 ml) was dialysed

⁸ Fourie, N.; Erasmus, G.L.; Schultz, R.A.; Prozesky, L. *Onderstepoort J. Vet. Research* **1995**, *62*, 77.

⁹ Codd, L.E.; Voorendyk, S. *Bothalia*, **1966**, *8*, 47.

¹⁰ Vahrmeijer, J. *Poisonous plants of Southern Africa that cause stock losses*, Tafelberg Publishers, Cape Town, **1981**.

against water for 2 days. The dialysate was evaporated to give *ca.* 90 g of toxic material. In the next step this material was fractionated on a column of weakly acidic cation-exchange resin CM Sephadex C-25 (NH₄⁺ form) eluting first with water (2 l) and then successively with ammonium acetate (pH 7) solutions at concentrations of 0.25M (2 l), 0.5M (1 l) and 1.0M (1 l). The elutions were concentrated on a rotary evaporator and freeze-dried to remove most of the ammonium acetate. The lyophilisate of the 1.0M NH₄OAc elution (2 g) was further purified by gel filtration on Sephadex G-10 eluting with water to give a fraction (80 mg) that was purified by column chromatography on silica gel using 2-propanol-water-acetic acid (60:40:2.5) as eluant. In the end 40 mg of purified toxin was obtained *i.e.* a yield of 10 mg/kg of dried leaves.

1.3 Structure elucidation of pavettamine¹¹

The toxin isolated as described above was named pavettamine. Electrospray ionization mass spectrometry (ESI-MS) established the molecular mass of pavettamine as 251 and the molecular formula as C₁₀H₂₅N₃O₄ by accurate mass determination of the [M+H]⁺ and [M+Na]⁺ ions as well as the fragment ions formed from the [M+H]⁺ ion.¹² The ¹³C NMR spectrum showed only 5 signals for the proton-bearing carbon atoms (see Table 1) and the ¹H NMR spectrum multiplet signals for only 8 protons. The signals of the proton-bearing carbon atoms were correlated with specific proton resonances in two-dimensional (2-D) ¹³C{¹H} heteronuclear chemical shift correlation experiments (HETCOR) utilizing the one-bond (¹³C,¹H) spin-spin couplings. The assignments of the signals in the ¹H NMR spectra are based on first-order analysis of the spin systems and were confirmed by a two-dimensional (2D) (¹H,¹H)-homonuclear chemical shift correlation (COSY) experiment. It was evident from the NMR data that the pavettamine molecule contained a symmetry element: either a C₂ axis or a symmetry plane. The structure **1** (see Scheme 1) was assigned to pavettamine *i.e.* 1,11-diamino-6-aza-undecane-2,4,8,10-tetraol on the basis of above data.¹³

The relative stereochemistry of pavettamine was established by ¹³C NMR analysis of the acetamide derivative of the 1,3-diol system present in the compound, a method developed by

¹¹ Data relevant to the structure elucidation were provided by Professor R. Vleggaar.

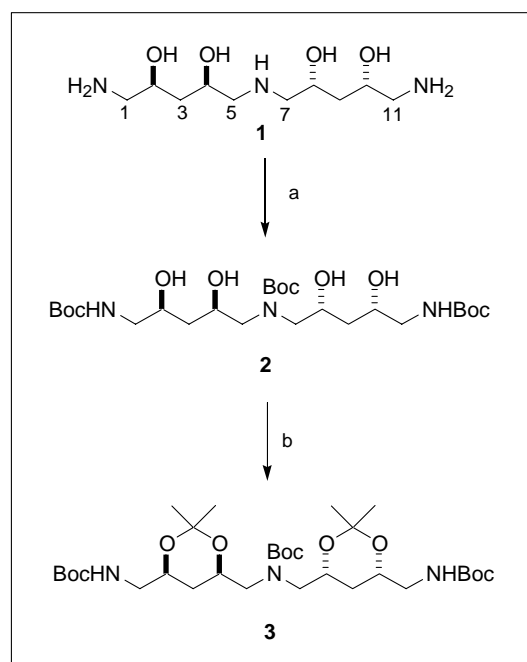
¹² Gates, P.J.; Vleggaar, R., unpublished results.

¹³ Vleggaar, R., unpublished results.

Table 1 NMR Data for pavettamine 1*

δ_H		δ_C	
H-1a	2.851 (dd, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 9.5)	C(1)	46.65 T
H-1b	3.058 (dd, $J_{1a,1b}$ 13.0, $J_{1b,2}$ 3.0)		
H-2	3.952 (m, $J_{1a,2}$ 9.4, $J_{1b,2}$ 3.1, $J_{2,3}$ 6.5)	C(2)	67.18D
H-3	1.679 (m)	C(3)	40.97 T
H-4	4.057 (m, $J_{4,5a}$ 10.0, $J_{4,5b}$ 2.8, $J_{3,4}$ 6.3)	C(4)	66.27 D
H-5a	3.000 (dd, $J_{5a,5b}$ 13.0, $J_{4,5a}$ 10.0)	C(5)	54.56 T
H-5b	3.143 (dd, $J_{5a,5b}$ 13.0, $J_{4,5b}$ 2.9)		

* in D₂O.


Scheme 1: Determination of the relative stereochemistry of pavettamine 1.

Reagents: a) Boc₂O, Na₂CO₃; b) 2,2-Dimethoxypropane, TsOH.

Rychnovsky.^{14,15,16,17,18,19} The amino groups present in pavettamine were protected by converting the compound to the tri-Boc derivative **2** by treatment with Boc₂O and Na₂CO₃ in aqueous dioxane. The 1,3-diol system of **2** was protected as the acetonide **3** by acid catalysed (TsOH) transacetalisation with 2,2-dimethoxypropane. The signals at δ_C 30.00Q and 19.88Q for the 2,2-dimethyl groups of the formed dioxane ring as well as the signal at δ_C 98.73S for the acetal carbon atom established the *syn* stereochemistry of pavettamine.

The presence of a C₂ symmetry element in pavettamine was established by the fact that the compound was optically active and showed a specific rotation of -19.5 . The absolute value remained in doubt as a result of solvent retained in the natural toxin obtained from the isolation procedure but the result excluded the presence of a symmetry plane and thus the two possible *meso* stereoisomers for pavettamine. The absolute configuration as shown in **1** *i.e.* (2*S*,4*R*,8*R*,10*S*) (or *ent*-**1**) was therefore assigned to pavettamine.

1.4 Natural polyamines

The polyamines putrescine **4**, spermidine **5**, and spermine **6** are found in all eukaryotes and are essential to cell growth. Although polyamine moieties have been identified in spider toxins²⁰ and in squalamine²¹ very few natural products contain polyamines in which the methylene backbone itself has been modified. The notable exceptions are hydroxyputrescine,²² the triamines (*S*)-6- (**7**) and (*S*)-7-hydroxyspermidine (**8**), and hypusine (**9**). Whereas (*S*)-7-hydroxyspermidine **8** occurs free in *Pseudomonas* species,^{23,24} (*S*)-6-hydroxyspermidine **7** is a component of several alkaloids isolated from marine microorganisms.^{25,26} Hypusine, (2*S*,9*R*)-

¹⁴ Rychnovsky, S.D.; Griesgraber, G. *J. Am. Chem. Soc.* **1994**, *116*, 2623.

¹⁵ Rychnovsky, S.D.; Skalitzyk, D.J. *Tetrahedron Lett.* **1990**, *31*, 945.

¹⁶ Rychnovsky, S.D.; Roger, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

¹⁷ Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* **1993**, *58*, 5251.

¹⁸ Rychnovsky, S.D.; Griesgraber, G.; Schegel, R. *J. Am. Chem. Soc.* **1995**, *117*, 197.

¹⁹ Rychnovsky, S.D.; Richardson, T.I. *J. Org. Chem.* **1996**, *61*, 4219.

²⁰ Moya, E.; Blagbrough, I.S. *Tetrahedron Lett.* **1994**, *35*, 2061.

²¹ Moore, K.S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J.N.; McCrimmon, D.; Zasloff, M. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 1354.

²² Kullnig, R.K.; Rosano, C.L.; Coulter, M.E.; Hurwitz, C. *J. Biol. Chem.* **1973**, *248*, 2487.

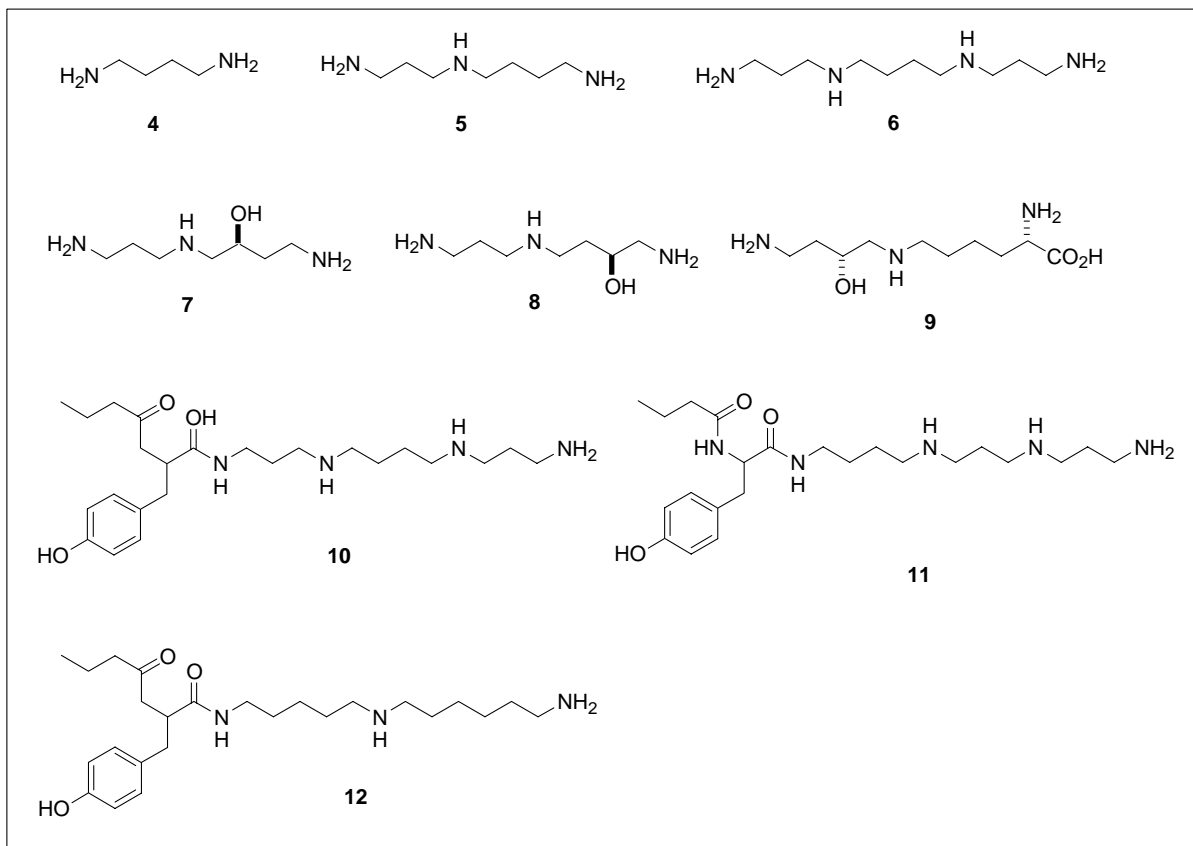
²³ Hamana, K.; Matsuzaki, S. *FEMS Microbiol. Lett.* **1990**, *70*, 353.

²⁴ Rosano, C.L.; Hurwitz, C.; Bunce, S.C. *J. Bacteriol.* **1978**, *135*, 805.

²⁵ Palagiano, E.; DeMarino, S. Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carre, J.B.; Debitus, C.; Lucarain, L.; Prevost, J. *Tetrahedron*, **1995**, *51*, 3675.

²⁶ Jares-Erijman, E.A.; Sakai, R.; Rinehart, K.L. *J. Org. Chem.* **1991**, *56*, 5712.

2,11-diamino-9-hydroxy-7-azaundecanoic acid (**9**)²⁷ is an unusual amino acid which plays a role in the replication of HIV.²⁸ It is formed by the post-translational modification of eukaryotic initiation factor 5A.²⁹ Lysine 50 of this protein is coupled with an aminobutyl fragment derived from spermidine followed by hydroxylation at C(9).³⁰



Scheme 2: Examples of some polyamine natural products.

There are also polyamine containing toxins, such as philanthoxine-433 (PhTX-433) (**10**), isolated from the Egyptian digger wasp *Philanthus triangulum*,³¹ and its synthetic analogue PhTX-343 (**11**)³² which are antagonists of a broad range of ionotropic receptors such as

²⁷ Shiba, T.; Mizote, H.; Kaneko, T.; Nakajima, T.; Sano, I. *Biochim. Biophys. Acta* **1971**, *244*, 523.

²⁸ Ruhl, M.; Himmelspach, M.; Bahr, G.M.; Hammerschmidt, F.; Jaksche, H.; Wolff, B.; Aschauer, H.; Farrington, G.K.; Probst, H.; Bevec, D.; Hauber, J. *J. Cell Biol.* **1993**, *123*, 1309.

²⁹ Park, M.H.; Cooper, H.L.; Folk, J.E. *J. Biol. Chem.* **1982**, *257*, 7217.

³⁰ Park, M.H.; Wolff, E.C.; Folk, J.E. *Trends Biochem. Sci.* **1993**, *18*, 475.

³¹ Eldefrawi, A.T.; Eldefrawi, M.E.; Konno, K.; Mansour, N.A.; Nakanishi, K.; Oltz, E.; Usherwood, P.N.R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *43*, 493.

³² Andersen, T.F.; Stromgaard, K. *Tetrahedron Lett.* **2004**, *45*, 7929.

iGluRs. This polyamine has little selectivity between the different subtypes of these receptors.^{33,34} However modification of the polyamine moiety of these two philanthotoxins has led to selective compounds with increased potency and the synthesized PhTX-56 (**12**) is a very potent and highly selective antagonist of this receptor. This effect has therapeutic potential for the range of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.³⁵

The biological interest in polyamines and polyamine toxins has stimulated an interest in the synthesis of these compounds and their derivatives and analogues for investigations into structure-activity relationships and as leads for new medicinal agents.

³³ Stromgaard, K.; Mellor, I.R. *Med. Res. Rev.* **2004**, *24*, 589.

³⁴ Mellor, I.R.; Usherwood, P.N.R. *Toxicon* **2004**, *43*, 4.

³⁵ Weiss, J.H.; Sensi, S.L.; *Trends Neurosci.* **2000**, *23*, 365.

2 RETROSYNTHETIC ANALYSIS

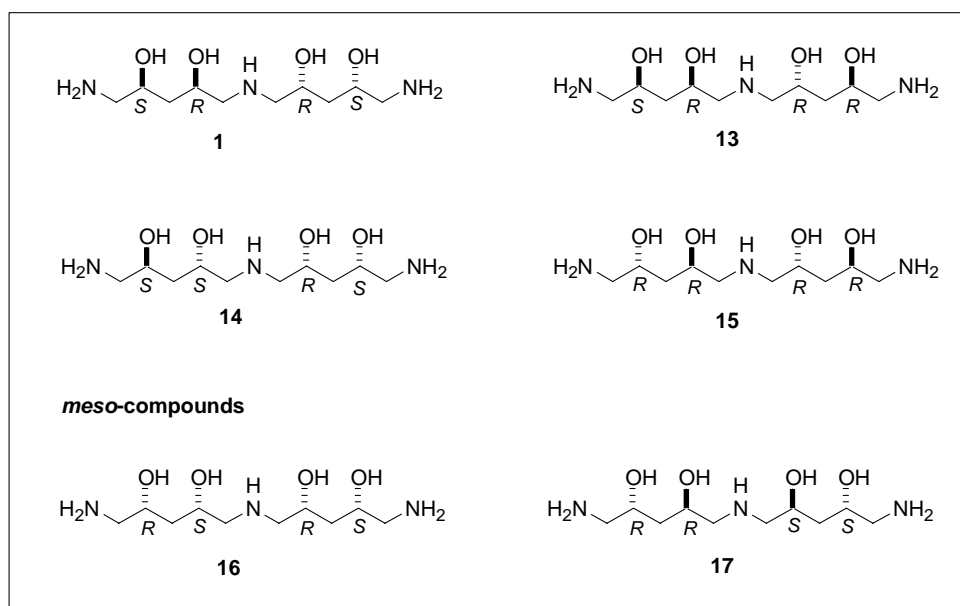
2.1 Introduction

Organic synthesis is a creative science that entails the design and execution of synthetic routes for the preparation of compounds for agricultural, pharmaceutical and material use. The ability to synthesize a particular compound from commercially available materials is of fundamental importance in organic chemistry. The appropriate selection of a suitable starting material for the synthesis of complex organic compounds can be a demanding and tedious exercise. In the early days of organic synthesis procedures 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 it to the desired product (synthetic target). With an increasing need for the synthesis of more complex products, this approach with its frustrating and time-limited success rate was no longer viable. 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 are 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 Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1989.

The evaluation of the different alternative synthetic pathways is sometimes immediate and straightforward, but in general it is difficult and a number of factors have to be taken into consideration such as the number of steps involved, availability of different starting materials, familiarity with the reactions involved and their yield. In addition the experience of the chemist in some specific fields (e.g. sulfur chemistry) introduces a degree of subjectivity to the decision.



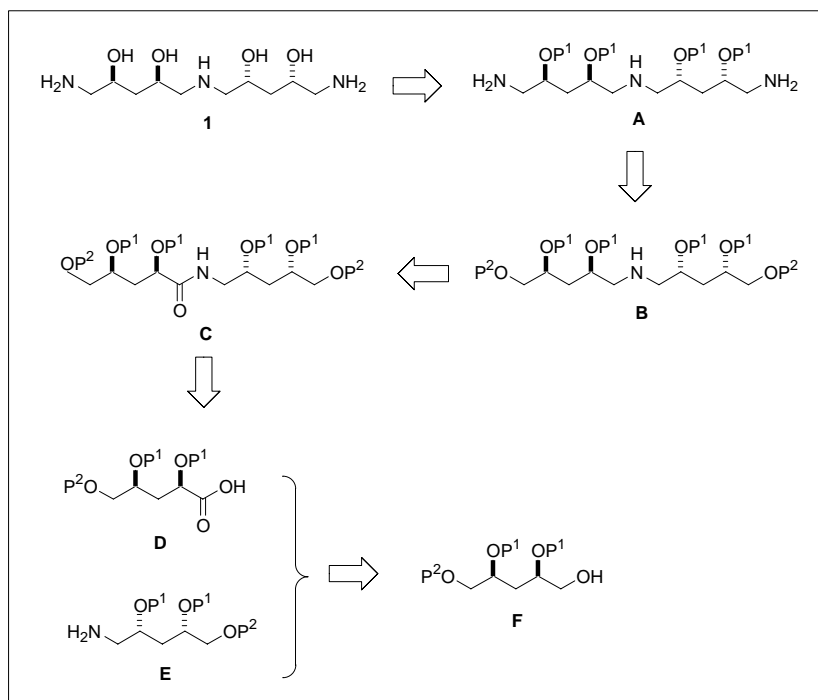
Scheme 1: Possible diastereomers for pavettamine.

2.2 Retrosynthetic analysis of pavettamine

The primary goal of the project on pavettamine (**1**) (or *enant-1*) is to determine the absolute configuration of the stereogenic centres present in the molecule as at the outset of the project only the relative configuration was known. X-ray crystallography of an appropriate crystalline derivative of pavettamine would solve this problem but the lack of quantities of the natural product precluded this approach. It was therefore decided to combine the main goal of the project with a secondary goal, the synthesis of all the stereoisomers possible for pavettamine for structure-activity studies. Thus a synthetic route had to be devised that would allow for the synthesis of all 10 stereoisomers: the 4 C_2 -symmetric stereoisomers **1** and **13-15** (and their enantiomers) and the two *meso*-compounds **16** and **17** (Scheme 1).

2.2.1 Disconnection of the central C-N bond

It was decided to use the C_2 -symmetric stereoisomer **1** as the target molecule in the retrosynthetic analysis of pavettamine as the C_2 symmetry identifies the central C-N bond as a strategic bond that can be disconnected after a series of functional group transformations into a single C_5 -unit **F** (Scheme 2).



Scheme 2: Retrosynthetic analysis of pavettamine: disconnection of the central C-N bond.

The presence of both the hydroxy and primary amino groups in the target molecule (**1**) requires that a protecting group strategy must be developed that will allow in the synthetic direction for the conversion of a protected primary alcohol into a primary amine. The initial step in the retrosynthetic analysis of (**1**) is therefore the introduction of a protecting group to give synthon **A** (where P^1 is a benzyl group). The choice of a particular protecting group is dictated by the type of reaction conditions that will be carried out in the eventual synthetic sequence, and on the ease and versatility with which the protecting group is cleaved at the end of the synthesis. As these hydroxy groups are not involved in any of the reactions throughout the synthesis a permanent protecting group able to withstand the conditions of a variety of reactions is required.

The terminal primary amine groups can be transformed into the protected hydroxy groups of synthon **B** (where P^2 is a TBDPS group) by functional group transformations. In the

synthetic direction the OTBDPS group can be deprotected by treatment with TBAF and the hydroxy group converted to the azide using Mitsunobu methodology.^{2,3} Subsequent reduction with LiAlH₄ would afford the amine **B**. An alternative route to the amine **B** involves a three-step sequence in which the hydroxy group is converted to the *O*-tosylate derivative followed by nucleophilic substitution by azide and once again reduction of the azido compound. Prior protection of the secondary amine is necessary as this functional group will be converted to the *N*-tosyl derivative using this synthetic methodology and thus result in an additional two steps in the synthetic sequence.

Functional group interconversion (FGI) of the secondary amine synthon **B** gives the amide synthon **C**. Disconnection of the amide bond generates two C₅ fragments: a carboxylic acid **D** and a primary amine **E**. Functional group interconversions of both the synthons **D** and **E** identify the common C₅ primary alcohol intermediate **F**. In the synthetic direction the primary alcohol **F** can be converted to the acid **D** by oxidation of the alcohol to the aldehyde with either the Dess-Martin periodinane or the Swern reagent, and the subsequent oxidation of the aldehyde to the carboxylic acid using hydrogen peroxide–sodium chlorite (NaClO₂). The synthesis of the amine **E** is envisaged to proceed by initial conversion of the alcohol **F** to the *O*-tosylate (*p*-tolylsulfonyl chloride-DMAP) followed by an S_N2 reaction with NaN₃ to give the azido derivative that in turn is reduced by LiAlH₄ to afford the amine **E**. The linkage of the acid **D** and the amine **E** is carried out using carbonyldiimidazole to give the amide **C**. The reduction of the amide functionality in **C** with either LiAlH₄ or BH₃ is expected to lead to the amine synthon **B**.

2.2.2 Retrosynthetic analysis of the C₅ primary alcohol synthon **F**

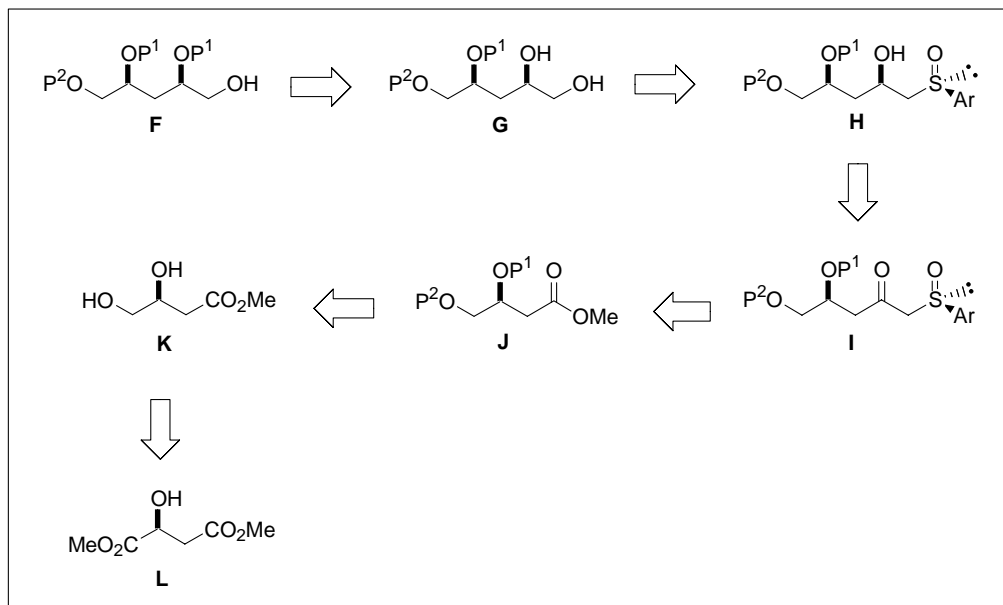
The retrosynthetic analysis of the C₅ primary alcohol synthon **F** involves a series of functional group transformations and the use of a chiral auxiliary to control the configuration (Scheme 3). Thus the removal of one of the protecting groups P¹ (= benzyl) generates the 1,2-diol system of synthon **G** which by a functional group transformation corresponds to the β-hydroxysulfoxide **H**. In the synthetic direction synthon **H** is subjected to a Pummerer rearrangement⁴ using Ac₂O–NaOAc to generate an *O*-acetyl-*S*-tolyl acetal as a mixture of two diastereomers, that on LiAlH₄ reduction forms the 1,2-diol, synthon **G**.

² Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.*, **1967**, *40*, 2380.

³ Mitsunobu, O. *Synthesis*, **1981**, 1.

⁴ Pummerer, R. *Ber.* **1910**, *43*, 1401.

Protection of the 1,2-diol **G** as the benzylidene using α,α -dimethoxytoluene in the presence of an acid catalyst TsOH, followed by regioselective ring opening of the benzylidene acetal with DIBALH or $\text{BH}_3\cdot\text{NHMe}_2$ leads to the formation of the required key intermediate **F**.



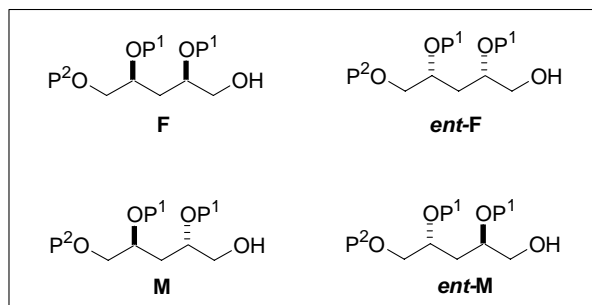
Scheme 3: Retrosynthetic analysis of the C₅ primary alcohol **F**.

The introduction of the chiral sulfoxide group at C(5) of synthon **H** 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 the carbonyl group in synthon **I**. In the synthetic direction the β -ketosulfoxide **I** is reduced using DIBALH–ZnBr₂ to give β -hydroxy-sulfoxide **H** with the required *R* configuration. β -Ketosulfoxides, as outlined in Chapter 4, are obtained by reaction of an ester with a chiral sulfoxide such as (+)-(*R*)-methyl *p*-tolylsulfoxide. This functional group transformation thus identifies synthon **J** with its ester functionality. Removal of the two different protecting groups P¹ and P² leads to the 1,2-diol **K** which by a functional group transformation corresponds to dimethyl (2*S*)-malate **L**. The dimethyl ester is obtained by esterification of commercially available (2*S*)-malic acid and is reduced by $\text{BH}_3\cdot\text{SMe}_2\text{--NaBH}_4$ to the 1,2-diol ester **K**. Selective protection of the primary alcohol as the OTBDPS ether and the secondary hydroxy group as the benzyl ether leads to the synthon **J**.

2.3 Retrosynthetic analysis of the stereoisomers of pavettamine

A similar retrosynthetic analysis of each of the stereoisomers of the C₂ symmetric

stereoisomers **13–15** (and their enantiomers) of pavettamine as well as the two diastereomeric *meso* compounds **16** and **17**, identifies the synthons **F** and **M** (and their enantiomers *ent-F* and *ent-M*)(Scheme 4).



Scheme 4: C₅ synthons for the synthesis of the stereoisomers of pavettamine.

In the synthesis direction the *ent-F* and *ent-M* synthons can be derived from synthons **F** and **M** (where P¹ = benzyl and P² = TBDPS), respectively by a simple protection-deprotection sequence: thus protection of the primary hydroxy group as the trityl ether using trityl chloride and pyridine and removal of the TBDPS protecting group with TBAF in THF gives the *ent-F* and *ent-M* synthons where P¹ = benzyl and P² = trityl.

The synthon **M** can be derived from synthon **I** by a similar set of reactions as outlined for synthon **F** except that the reduction of the β-ketosulfoxide moiety of synthon **I** is carried out using DIBALH to give the β-hydroxysulfoxide with the *anti* 1,3-diol arrangement.

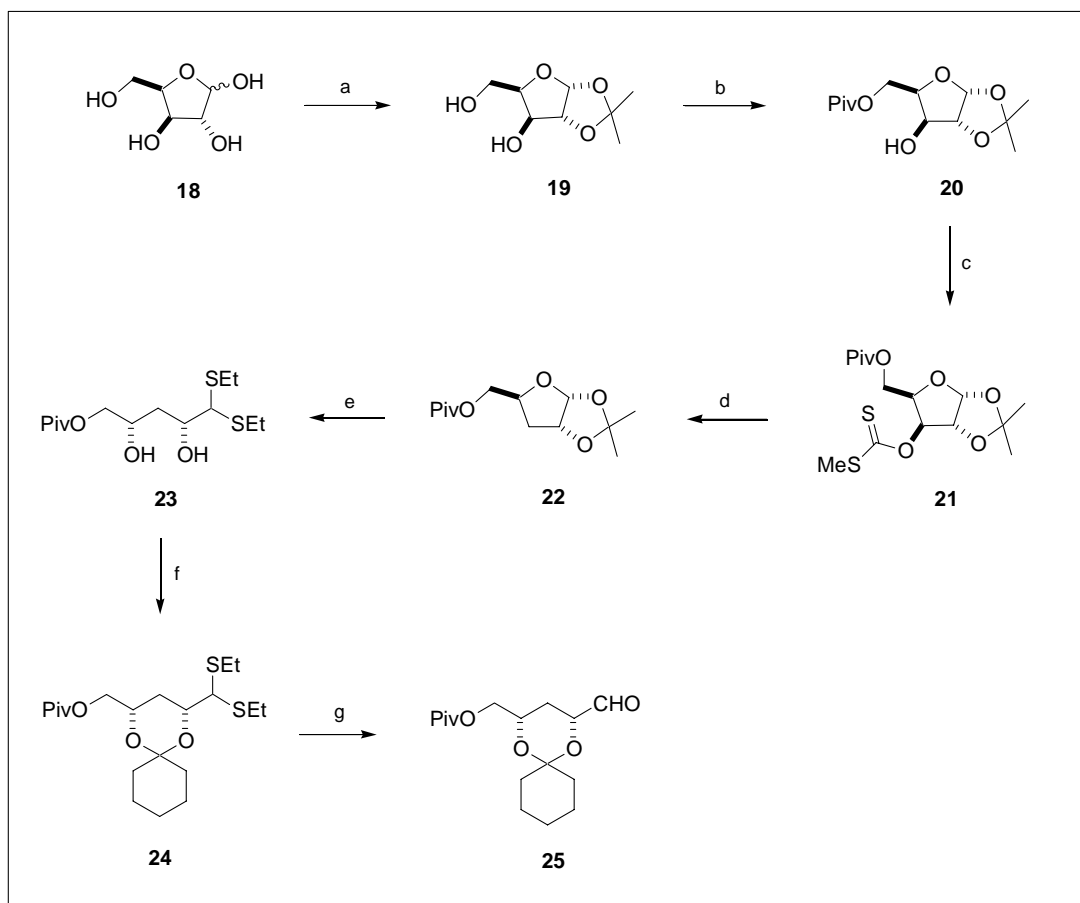
2.4 Literature syntheses for the C₅ synthons **F** and **M**

The synthesis of *syn*- and *anti*-1,3-diols as key precursors of the extended 1,3-polyol units of the polyene macrolides has received considerable attention. Early work has been reviewed⁵ and has mainly been based on the enantioselective reduction of β-ketoesters and 1,3-diketones, the diastereoselective reduction of β-hydroxyketones and the Sharpless epoxidation of allylic alcohols and subsequent epoxide opening.

Two syntheses with a direct bearing on the work described in this dissertation have been reported in the literature. Thus James⁶ reported the preparation of a C₅ unit corresponding

⁵ Oishi, T.; Nakata, T. *Synthesis* **1990**, 635.

⁶ James, D.W.; Scott, C.J. *J. Org. Chem.* **1996**, *61*, 2600.



Scheme 5: Preparation of a C₅ unit from D-(+)-xylose

Reagents: a) i. Me₂CO, CuSO₄, H₂SO₄, ii. 0.2% HCl; b) Me₃CCOCl, pyridine; c) NaH, CS₂, THF, then MeI; d) *n*Bu₃SnH, AIBN, toluene; e) EtSH, 6M HCl; f) cyclohexanone, TsOH; g) HgCl₂, CaCO₃, MeCN-H₂O (4:1).

to synthon **F** using a carbohydrate, D-(+)-xylose **1** as a chiral template (Scheme 5). The D-(+)-xylose **18** starting material was converted in a two-step sequence into the 1,2-*O*-acetonide derivative **19**. The primary alcohol in **19** was then selectively protected as the pivaloate ester by treatment with pivaloyl chloride and pyridine to afford **20**. Scission of the C(3) carbon-oxygen bond was carried out using the Barton–McCombie deoxygenation reaction:⁷ the C(3) hydroxy group was converted to the xanthate **21** which on radical deoxygenation with tri-*n*-butyltin hydride in refluxing toluene furnished **22**. Conversion of **22** to the open-chain *S,S*-acetal **23** proceeded under acidic conditions in the presence of excess ethanethiol. The *syn*-1,3-diol system of **23** was protected as the cyclohexylidene derivative **24** and the protected aldehyde functional group of **24** unmasked by treatment with HgCl₂ in aqueous acetonitrile to give the aldehyde **25**. Although this procedure of preparing the C₅ synthon **F** is short and efficient the method is limited to the synthesis of

⁷ Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

only the 1,3-*syn* stereoisomer. The enantiomeric arrangement can of course be obtained by using L-(–)-xylose as starting material.

The stereocontrolled synthesis of both *syn*- and *anti*-1,3-diols from a common intermediate was recently reported by Brückner⁸ (Scheme 6). The synthesis starts from 2,3-dibromopropene **26**, obtained from allyl bromide in a 2-step sequence,⁹ which is converted to the benzyl ether **27** by treatment with sodium benzyloxide in a Williamson reaction. The bromoolefin moiety of the ether **27** underwent a Heck coupling¹⁰ in DMF with methyl acrylate using Pd(OAc)₂ as catalyst and Bu₄NCl, LiCl and K₂CO₃ as additives to give the dienoate ester **28**.¹¹ The ester functionality of **28** was reduced with DIBALH to furnish the 2,4-pentadien-1-ol **29**. Sharpless epoxidation of the allylic double bond of the 2,4-pentadien-1-ol moiety of **29** using diisopropyl L-(+)-tartrate gave the epoxy alcohol **30**. The hydroxy group of **30** was protected as the TBDPS ether **31** which was then subjected to ozonolysis and reductive workup with Ph₃P to afford the epoxyketone **32**. The epoxyketone **32** is the progenitor to both the *syn* and *anti* 1,3-diol building blocks by reduction of the carbonyl group and cleavage of the epoxide moiety to generate a 1,3-diol system. The *syn/anti* relationship of the formed 1,3-diol is dictated by the sequence in which these two reactions are carried out.

Anti-selective reduction of *trans*-configured epoxyketones can be effected by exploiting chelation control of diastereoselectivity.^{12,13} Thus Zn(BH₄)₂ reduction of the epoxyketone **32** in toluene, the optimum solvent for chelation control,^{14,15,16} instead of diethyl ether, gave the *anti* epoxyalcohol **33** as a single diastereomer. Regioselective opening of the epoxide ring in **33** by *in situ* prepared cp₂Ti(III)Cl and an excess of 1,4-cyclohexadiene gave the *anti* 1,3-diol **34** which was protected as the acetonide **35**.

The *syn*-1,3-diol relationship was established by first carrying out the regioselective

⁸ Weigand, S.; Brückner, R. *Synlett*. **1997**, 225.

⁹ Lespieau, R.; Bourguet, M. *Org. Synth. Coll. Vol. 1* (Gilman, H.; Blat, A.H., Eds.), 2nd Ed., John Wiley & Sons, New York, pp. 209-211.

¹⁰ de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2379.

¹¹ Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *Liebigs Ann.* **1996**, 899.

¹² Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, 22, 4723.

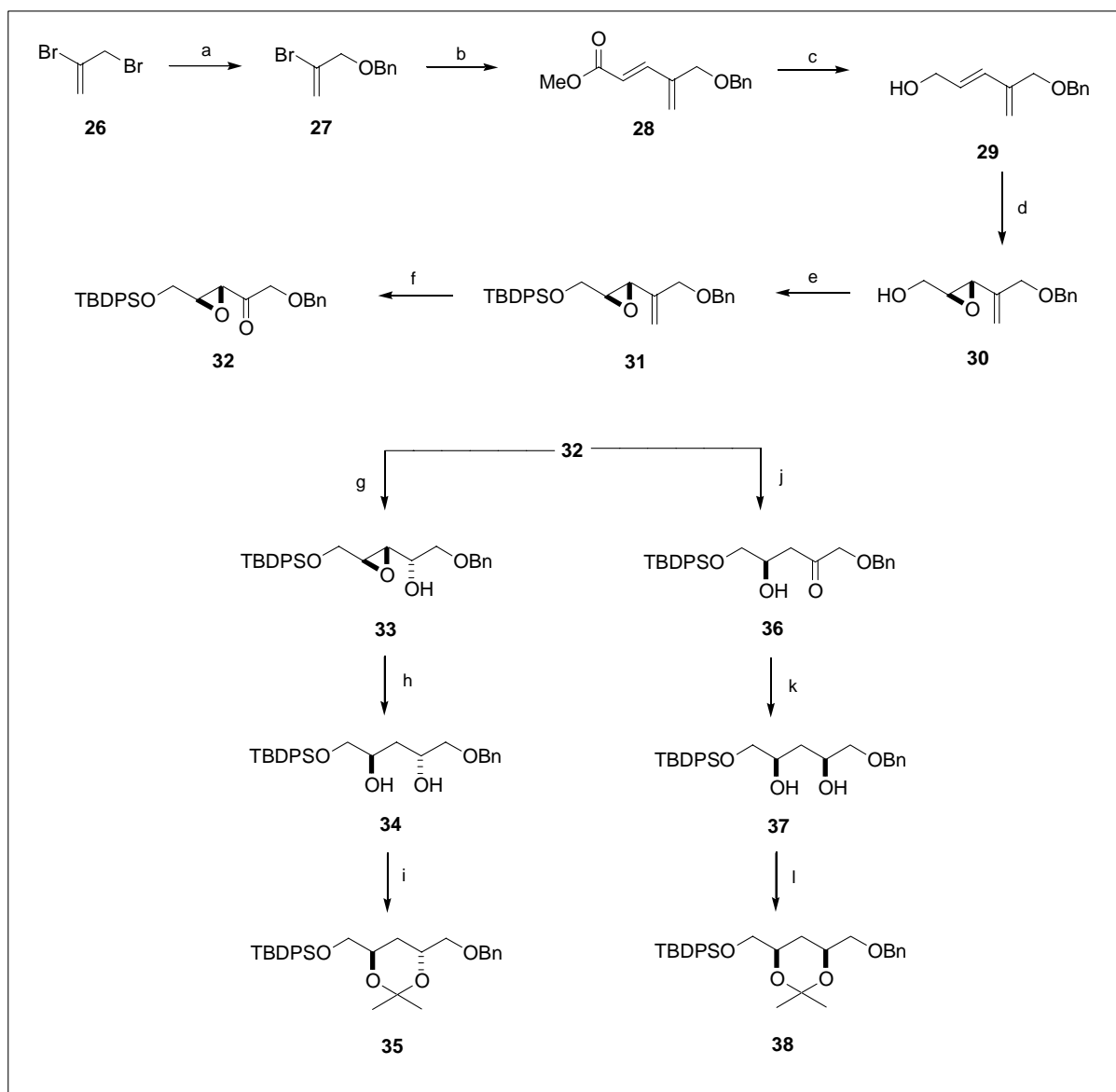
¹³ Aoyama, Y.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1991**, 32, 6731.

¹⁴ Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, 30, 6529.

¹⁵ Menges, M.; Brückner, R. *Synlett*. **1994**, 809.

¹⁶ Menges, M.; Brückner, R. *Liebigs Ann.* **1995**, 365.

epoxide ring cleavage of the epoxyketone **32** using *in situ* prepared Cp₂Ti(III)Cl and an



Scheme 6: Synthesis of *syn* and *anti* 1,3-diol building blocks.

Reagents: a) PhCH₂OH, NaH, THF (90%); b) Pd(OAc)₂, LiCl, Bu₄NCl, K₂CO₃, H₂C=CH-CO₂Me, DMF (57%); c) DIBALH (85%); d) Ti(O^{*i*}Pr)₄, diisopropyl L-(+)-tartrate, *t*BuOOH, 4 Å molecular sieves, CH₂Cl₂ (89%); e) *t*BuPh₂SiCl, imidazole, THF (90%); f) i. O₃, ii. Ph₃P (81%); g) Zn(BH₄)₂ (73%); h) Zn, Cp₂TiCl₂, 1,4-cyclohexadiene (67%); i) 2,2-dimethoxypropane, CSA, acetone (79%); j) Zn, Cp₂TiCl₂, 1,4-cyclohexadiene (60%); k) i. Et₃B, MeOH, THF, ii. NaBH₄ (73%); l) 2,2-dimethoxypropane, CSA, acetone (85%).

excess of 1,4-cyclohexadiene to give the β-hydroxyketone **36**. Treatment of the β-hydroxyketone **36** with Et₂BOMe resulted in the formation of a boron-bridged six-membered chelate which was reduced exclusively to the *syn* 1,3-diol **37** with NaBH₄ in MeOH. The *syn*-diol **37** was then protected as the acetonide **38**.

The enantiomeric building blocks *ent*-**35** and *ent*-**38** can be prepared by the same chemistry too; their common progenitor would be the epoxy alcohol *ent*-**30** prepared by Sharpless epoxidation of the 2,4-pentadien-1-ol **29** using diisopropyl D-(–)-tartrate.

In this dissertation a totally different route using a chiral starting material was developed for the stereocontrolled synthesis of both *syn*- and *anti*-1,3-diols in a C₅ unit corresponding to synthon F. The reactions used are comparatively easy to handle and yields are better than those obtained by the Brückner procedures. In addition the number of steps in the synthetic route are less.

3 CHEMISTRY OF CHIRAL SUFOXIDES

3.1 Introduction

Organosulfur compounds play a major role in organic synthesis. Enantiomerically pure sulfur compounds are increasingly important in asymmetric synthesis as stereocontrol elements. Chiral sulfoxides which can serve as chiral auxiliaries are an important class of compounds due to their ease of preparation, the ability of the sulfoxide moiety to control the stereochemical course of the reduction of β -ketosulfoxides. The ready conversion of the sulfoxide moiety to other functional groups not containing sulfur as well as the ability of the sulfur atom to stabilize α -carbanions have led to the extensive use of these compounds in organic synthesis research.

3.2 Synthesis of chiral sulfoxides

In recent years the ever-increasing importance of enantiomerically pure chiral sulfoxides, both as bioactive compounds and as chiral auxiliaries in asymmetric synthesis,¹ has stimulated the development of new synthetic procedures for chiral sulfoxides. Many approaches have been developed to synthesize optically active sulfoxides, of which asymmetric oxidation and asymmetric nucleophilic substitution at sulfur are the two most important procedures for making sulfoxides as single enantiomers.

Different approaches have been reported for the enantioselective oxidation of prochiral sulfides including the use of chiral oxaziridines,^{2,3} enzymatic oxidation^{4,5} and modified Sharpless oxidation of sulfides.⁶ The latter is the most popular and reliable method and involves treatment of sulfides e.g. **39** with the oxidant *t*-butyl hydroperoxide or cumene hydroperoxide in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ and either (*R,R*)- or (*S,S*)-diethyl tartrate (Scheme 1). This methodology is a direct and versatile method of making sulfoxides with

¹ Solladié, G. *Synthesis* **1982**, 185.

² Davis, F. A.; Reddy, R.T.; Weismiller, M.C. *J. Am. Chem. Soc.* **1989**, *111*, 5964.

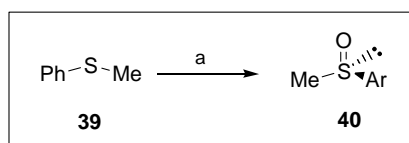
³ Weismiller, M. C.; Murphy, C.K.; Thimma, R. *J. Org. Chem.* **1992**, *57*, 7274.

⁴ Pitchen, P.; Dunach, E.; Deshmukh, M.N.; Kagan, H.B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

⁵ DiFuria, F.; Modena, G.; Seraglia, G. *Synthesis* **1984**, 325.

⁶ Andersen, K.K. *Tetrahedron Lett.* **1962**, 93.

varying substituents at sulfur, and much research effort has been directed in optimizing the yield and enantioselectivity of this oxidation.



Scheme 1: Synthesis of (*R*)-sulfoxides by oxidation.

Reagents: a) $\text{Ti}(\text{O}^i\text{Pr})_4$, (*R,R*)-diethyl tartrate, *t*-BuOOH, H_2O

On the other hand the method based on nucleophilic substitution is the most frequently used. The method involves the reaction of an optically active sulfinate ester with a Grignard reagent^{7,8} resulting in inversion of configuration at sulfur. In the context of this thesis (+)-(*R*)-methyl *p*-tolyl sulfoxide (**40**)⁹ was made using this methodology (Scheme 2). Thus the optically-active ester menthyl (–)-(*S*)-methyl *p*-toluenesulfinate **43**, which is used to make the (+)-(*R*)-methyl *p*-tolylsulfoxide **40** is obtained from the reaction of (–)-menthol **42** with *p*-toluenesulfinyl chloride **41**. The esterification reaction shows no particular stereoselectivity and gives a 1:1 mixture of diastereomers epimeric at sulfur. The desired (*S*)-diastereomer **43** is crystalline and is obtained by recrystallization at -20°C in pure form and high yield. The corresponding (*R*)-diastereomer **44** is an oil that undergoes acid catalyzed epimerisation to give once again a mixture of diastereomers from which the (*S*)-diastereomer **43** is obtained by crystallization.¹⁰

3.2.1 Synthesis of β -ketosulfoxides

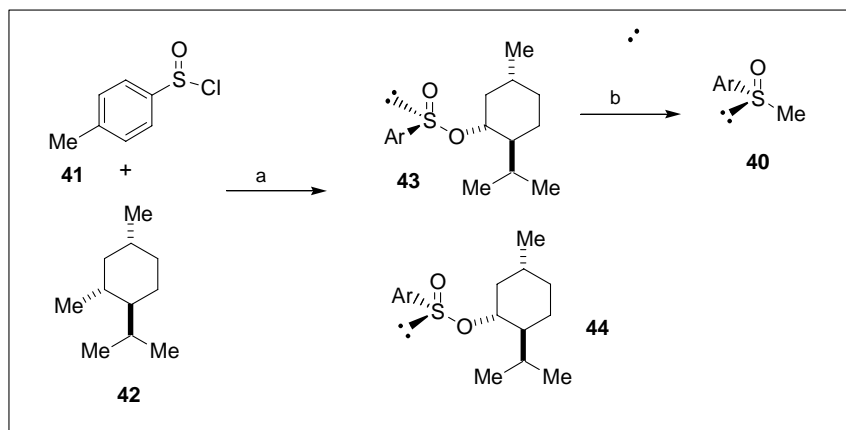
Chiral β -ketosulfoxides have been extensively investigated and are commonly used in the synthesis of natural products and biologically active compounds. The synthetic importance of chiral β -ketosulfoxides arises from the ability of the sulfoxide moiety to stereoselectively direct the reduction of the carbonyl group, to stabilize α -carbanions and the ease with which it can be removed or transformed to other functionalities that don't contain sulfur.

⁷ Andersen, K.K. *J. Org. Chem.* **1964**, 1953.

⁸ Gilman, H.; Robinson, J.; Beaber, N.H. *J. Am. Chem. Soc.* **1926**, 48, 2715.

⁹ Solladié, G.; Hutt, J.; Gigardin, A. *Synthesis*, **1987**, 173.

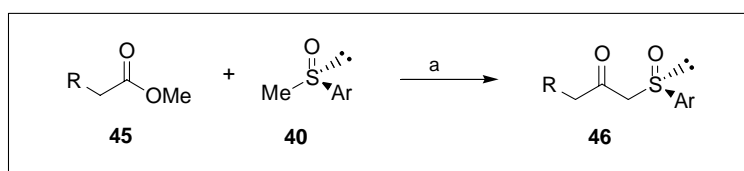
¹⁰ Mioskowski, C.; Solladié, G. *Tetrahedron Lett.* **1980**, 36, 227.



Scheme 2: Synthesis of (*R*)-sulfoxides by S_N2 nucleophilic substitution

Reagents: a) Pyridine; b) MeMgI.

Acyclic β -ketosulfoxides are generally prepared according to a procedure based on the reaction of an α -sulfinyl anion with esters.^{11,12,13} (+)-(*R*)-Methyl *p*-tolylsulfoxide **40** is treated with the base lithium diethylamide (LDA) to give the corresponding sulfinyl anion and the anion is coupled with an ester at -78°C (Scheme 3). In making the β -ketosulfoxide, two equivalents of the (+)-(*R*)-methyl *p*-tolylsulfoxide **40** are required as the α -proton of the formed β -ketosulfoxide **46** is more acidic than that of the reagents. The low nucleophilicity of the formed product anion prevents it from reacting with the ester functionality present in the substrate.



Scheme 3: Preparation of β -ketosulfoxides.

Reagents: a) LDA, -78°C

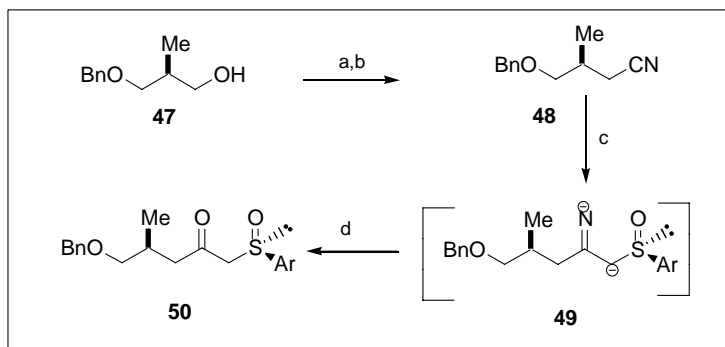
β -Ketosulfoxides can also be prepared from nitriles by nucleophilic attack of an α -sulfinyl anion on the carbon atom of a nitrile **48** to form a carbon-carbon bond via an iminide intermediate **49**.¹⁴ Aqueous acid work-up generates an imine that in turn is hydrolyzed under the work-up conditions to form the β -ketosulfoxide **50** (Scheme 4).

¹¹ Kunieda, N.; Nokami, J.; Kinoshita, M. *Chem. Lett.* **1974**, 369.

¹² Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1995**, 6, 559.

¹³ Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas*, **1995**, 144, 153.

¹⁴ Vleggaar, R.; Zeevaart, J.G. *Tetrahedron Lett.* **1999**, 40, 9301.



Scheme 4: Preparation of β -ketosulfoxides from nitriles

Reagents: a) TsCl, DMAP; b) NaCN, DMF; c) LDA, (*R*)-methyl *p*-tolylsulfoxide, 0°C; d) aq. HCl (pH 2)

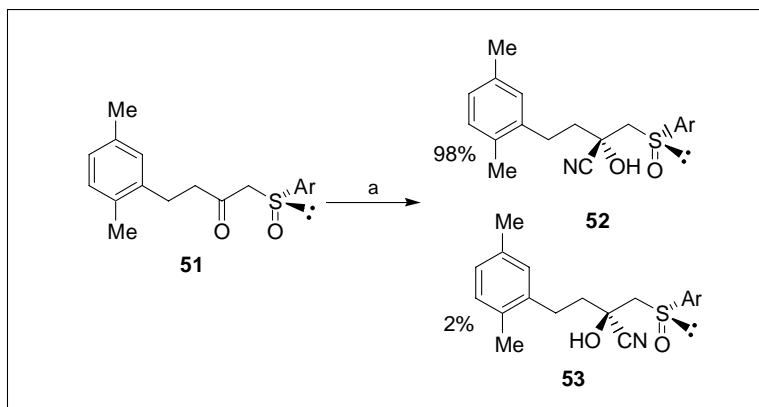
3.3 Reactions involving β -ketosulfoxides

3.3.1 Nucleophilic additions to β -ketosulfoxides

Nucleophilic addition to enantiomerically pure β -ketosulfoxides has been widely used in asymmetric synthesis of optically active tertiary β -hydroxysulfoxides. Recently **Gracia Ruano *et al.***¹⁵ reported that the reaction of β -ketosulfoxides with Et_2AlCN proceeds with high stereoselectivity to give cyanohydrins in high yield and with a diastereomeric excess of more than 96%. The chirality at the newly created stereogenic center is controlled only by the sulfoxide configuration. To account for the diastereoselective outcome of the nucleophilic attack it is assumed that the nucleophilic attack proceeds intramolecularly via a pentacoordinated aluminium intermediate. The use of Lewis acid additives to the reagent Et_2AlCN has little or no effect on the stereoselectivity of the reaction. Similar stereoselectivity has been observed for alkylation reactions of enantiomerically pure β -ketosulfoxides with aluminium reagents to give optically-active tertiary alcohol products (Scheme 5).¹⁶ Moreover, the influence of the configuration of an α -substituent on the stereochemical course of the reaction of α -substituted β -ketosulfoxides with nucleophiles in the synthesis of tertiary alcohols has been studied. In this case the stereoinduction from a β -ketosulfoxide in the reduction of the carbonyl group is so strong that it overrides any induction from an α -chiral center.

¹⁵ Bueno, B.A.; Carreno, M.C.; Garcia Ruano, J.L.; Arrayas, R.G.; Zarzuelo, M.M. *J. Org. Chem.* **1997**, *62*, 2139.

¹⁶ Garcia Ruano, J.L.; Paredes, C.G. *Tetrahedron Lett.* **2000**, *41*, 261.



Scheme 5: Nucleophilic attack on β -ketosulfoxides.

Reagents: a) Et_2AlCN , $\text{Y} = \text{CN}$, 97%; b) $\text{Me}_3\text{Al}/\text{ZnBr}_2$ $\text{Y} = \text{Me}$, 64%.

3.3.2 Selective reduction of β -ketosulfoxides

Chiral sulfoxides have received considerable attention over the last two decades as key intermediates in asymmetric synthesis where they are used as chiral auxiliaries to control the stereochemistry of newly created stereogenic centres^{17,18,19} or as pharmaceutical goals.^{20,21,22} This is evident from the number of natural products synthesized in which the chiral sulfoxides are used as intermediates. The ever-increasing importance of chiral sulfoxides in the field of organic synthesis arises from their ability to act as stereocontrol auxiliaries in the reduction of β -ketosulfoxides. The stereoselective sulfoxide directed reduction of a β -ketosulfoxide is a useful method of preparing enantiomerically pure hydroxy compounds and has been used in the synthesis of natural products such as (+)-isobretonein A,²³ (+)-vitrol C,²⁴ or (-)-macrolactin A.²⁵

The reduction of the carbonyl group of a β -ketosulfoxide using DIBALH proceeds with high diastereoselectivity to give either of the diastereomeric β -hydroxysulfoxides (S,R_S)-**54**

¹⁷ Mikolajczyk, M.; Drabowicz, J. *Topics Stereochem.* **1982**, *13*, 435.

¹⁸ Davis, F.A.; Zhou, P.; Chen, B.C. *Chem. Soc. Rev.* **1998**, *27*, 13.

¹⁹ Davis, F.A.; Portonovo, P.S.; Reddy, R.E.; Reddy, G.V.; Zhou, P. *Phosphorus, Sulfur, Silicon Related Elem.* **1997**, *120-121*, 291-303.

²⁰ Pitchen, P. *Chem. Ind. (London)* **1994**, 636.

²¹ von Unge, S.; Langer, V.; Sjolín, L. *Tetrahedron: Asymmetry* **1997**, *8*, 1967.

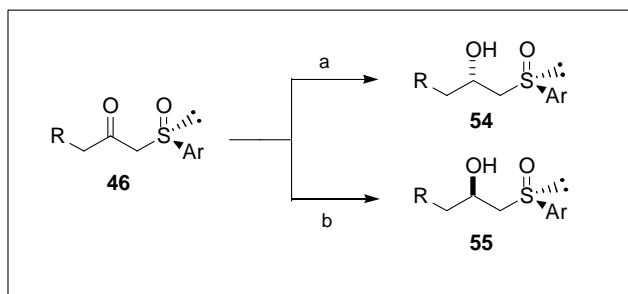
²² Holland, H.; Brown, F.M. *Tetrahedron: Asymmetry* **1998**, *9*, 535.

²³ Solladié, G.; Adamy, M.; Colobert, F. *J. Org. Chem.* **1996**, *61*, 4369.

²⁴ Stefani, H.A.; Menezes, P.H.; Costa, I.M.; Silva, D.O.; Petragnani, N. *Synlett.* **2002**, *8*, 1335.

²⁵ Marino, J.P.; McClue, M.S.; Holub, D.P.; Comasseto, J.V.; Tucci, F.C. *J. Am. Chem. Soc.* **2002**, *124*, 1664.

or (*R,R*)-**55** depending on the absence or presence of ZnCl₂ in the reduction.^{26,27,28} However, reduction of β-ketosulfoxides using lithium aluminium hydride and sodium borohydride gave low diastereomeric excesses.



Scheme 6: Stereoselective reduction of β-ketosulfoxides

Reagents: a) DIBALH, THF, -78°C; b) DIBALH, ZnX₂, THF, -78°C

The influence of an alkyl α-substituent on stereoselectivity during the reduction of β-ketosulfoxides using either DIBALH or DIBALH/ZnCl₂ has been studied. The presence of an alkyl substituent in the α-position has little influence in the DIBALH/ZnCl₂ reduction^{29,30,31} but treatment of α-alkylated β-ketosulfoxides with DIBALH generally produced diastereomeric mixtures.

Different explanations have been proposed for the high stereoselectivity observed in the DIBALH reduction of β-ketosulfoxides. Earlier explanations were based on the intermolecular transfer of hydride from the DIBALH to the carbonyl.^{32,33} In the absence of chelating Lewis acid the dipoles of the sulfoxide and carbonyl groups are assumed to be directed away from each other as shown in **56** (Scheme 7). The resulting conformation will favour *Re*-face attack of the hydride due to steric effects that lead to the formation of the (*S*)-alcohol **54**. When ZnCl₂ is added, the metal chelates with the oxygens of both the

²⁶ Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211.

²⁷ Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, 26, 435.

²⁸ Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, 50, 1552.

²⁹ García Ruano, J.L.; Maestro, M.C.; Sanchez Sancho, F. *Tetrahedron: Asymmetry*, **1995**, 6, 2299.

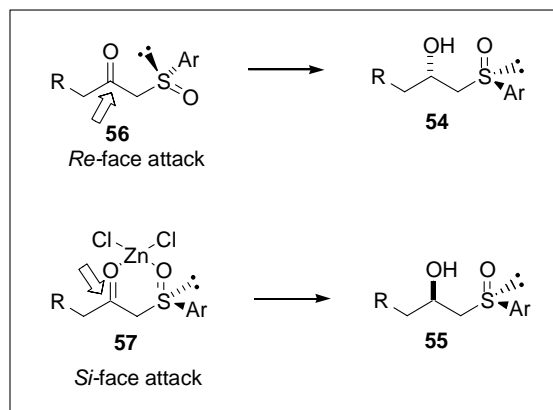
³⁰ García Ruano, J.L.; Maestro, M.C.; Barros, D.; Gonzales-Vadillo, A.M. *Tetrahedron: Asymmetry* **1996**, 7, 1819.

³¹ García Ruano, J.L.; Maestro, M.C.; Gonzales-Vadillo, A.M. *Tetrahedron: Asymmetry* **1999**, 8, 3283.

³² Solladié, G.; Demailly, G.; Greck, C.; *Tetrahedron Lett.* **1985**, 26, 435.

³³ Carreno, C.; García Ruano, J.L.; Martín, A.M.; Pedregal, C.; Rodríguez, J.H.; Rubio, A.; Sanchez, J.; Solladié G. *J. Org. Chem.* **1990**, 55, 2120.

sulfoxide and carbonyl groups causing the *Si*-face of the carbonyl to be less sterically hindered and consequently the (*R*)-alcohol **55** is formed. (Scheme 7)



Scheme 7: First mechanistic explanation for the stereoselective reduction.

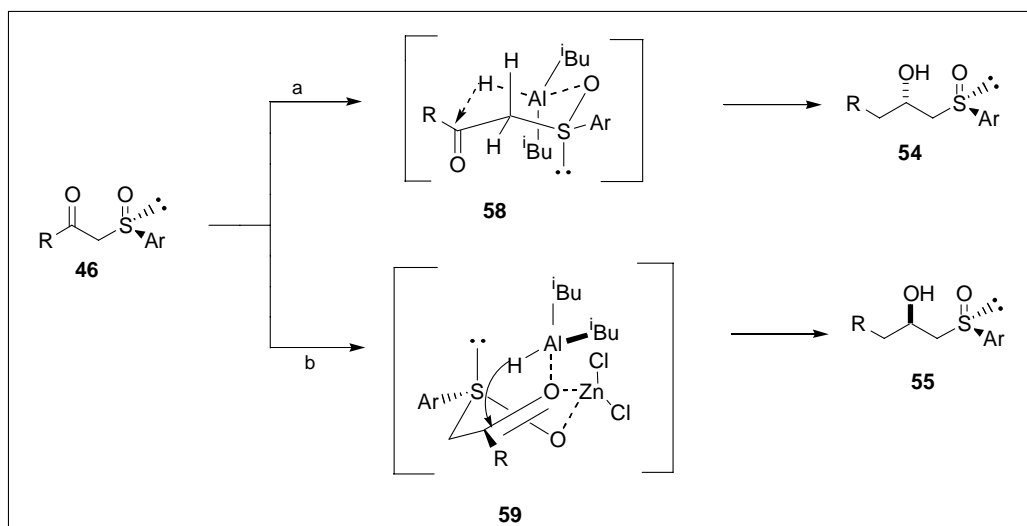
Subsequent proposals^{34,35,36} (Scheme 8) however concluded that the stereoselectivity observed in the DIBALH reduction is derived from the ability of the aluminium to associate with the unshared electron pair of the oxygen in the sulfoxide moiety. In the absence of a chelating Lewis acid a six-membered cyclic transition state **58** is formed resulting in intramolecular hydride attack. In contrast the DIBALH reduction in the presence of a Lewis acid, $ZnCl_2$, gives the epimer at the hydroxy center. This finding is rationalized by a conformationally rigid six-membered cyclic intermediate **59** involving chelation of the Lewis acid to the sulfinyl and carbonyl oxygen in the favoured twisted conformation where the *p*-tolyl group is pseudo-equatorial. DIBALH will approach by complexation with the geometrically well-located chlorine atom leading to the bimetallic-bridged species and hydride transfer will now be intramolecular from the top to the *Si*-face leading to the *R* configuration at C-2. In the other possible conformation the *p*-tolyl group is in a unfavorable pseudo-axial position which will greatly hinder hydride transfer from the bottom to the *Re*-face.

On the basis of the last mechanism given to account for the stereoselectivity in DIBALH reductions, it could be expected that the presence of other groups able to compete with the

³⁴ Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, 3, 1649.

³⁵ Solladié, G. *Organosulfur Chemistry. Synthetic Aspects* (P. Page, Ed.), Academic Press, London, **1995**, 13.

³⁶ Garcia Ruano, J.L. *Phosphorus, Sulfur. Silicon Related Elem.* **1993**, 74, 233.



Scheme 8: Stereoselective reduction of β -ketosulfoxides: Mechanistic aspects.

Reagents: a) DIBALH, THF, -78°C ; b) DIBALH, ZnCl_2 , THF, -78°C .

sulfinyl group for association to the metal has significant influence on the stereoselectivity. In order to expand the scope of the methodology and evaluate the influence of those groups highly functionalized substrates bearing alkoxy,^{37,38,39} keto,⁴⁰ ester,^{41,42} and carboxylic groups⁴³ have been studied and the predominant role of the sulfinyl group in the stereoselectivity was generally observed. By contrast in the presence of ZnX_2 when the additional functionality is able to compete with the sulfinyl group for chelating with the metal, the reduction is less stereoselective and yielded mixtures of epimers at the β -hydroxy center. For instance DIBALH/ ZnI_2 reduction of β -ketosulfoxide **60** and **61** (Scheme 9), bearing an ester or amide in the γ -position, produces the β -hydroxysulfoxides **62** and **63**, respectively, but with a much lesser diastereoselectivity (Scheme 9).

3.3.3. Reactions of α -sulfinyl carbanions

The introduction of an alkyl group at the α -position to the sulfoxide group through carbon-

³⁷ Solladié, G.; Almario, A. *Tetrahedron Lett.* **1994**, *36*, 1937.

³⁸ García Ruano, J.L.; Maestro, M.C.; Sanchez Sancho, F. *Tetrahedron: Asymmetry* **1995**, *6*, 2299.

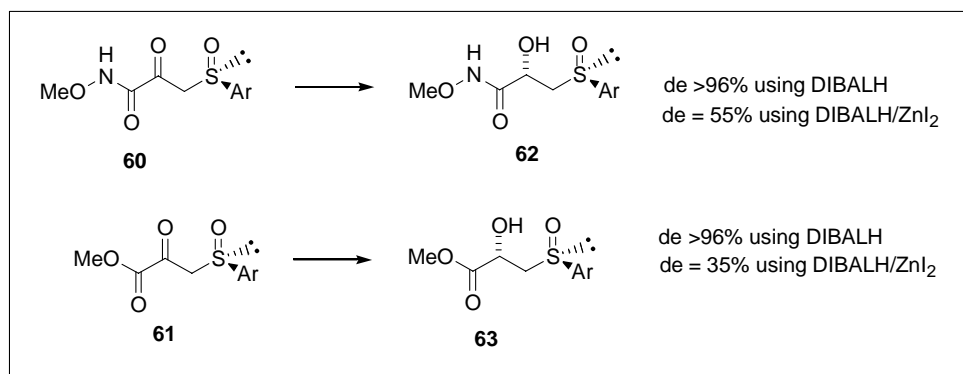
³⁹ García Ruano, J.L.; Maestro, M.C.; Barros, D.; Gonzalez-Vadillo, A.M. *Tetrahedron: Asymmetry* **1996**, *7*, 819.

⁴⁰ Solladié, G.; Ghiatou, N. *Bull. Soc. Chim. Fr.* **1994**, *131*, 575.

⁴¹ Solladié, G.; Almario, A. *Tetrahedron Lett.* **1992**, *33*, 2477.

⁴² Solladié, G.; Huser, N.; Garcia Ruano, J. L.; Adrio, J.; Carreno, M. C.; Tito, A. *Tetrahedron Lett.* **1994**, *35*, 5297.

⁴³ Garcia Ruano, J. L.; Fuerte, A.; Maestro, M. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1443.



Scheme 9: Influence of functional groups on DIBALH and DIBALH/ZnX₂ reduction.

carbon bond formation has been used as one of the key steps in the synthesis of several natural products. The hydrogen on the α -carbon to the sulfoxide group in the β -hydroxysulfoxide is acidic and is abstracted by a strong base such as LDA or *n*-BuLi.⁴⁴ Two equivalents of base are required to abstract both the hydroxy group proton and the proton on the α -carbon to form the dianion. Due to the high binding ability of the β -hydroxysulfinyl moiety to alkali or alkaline earth metal ions, the dianion forms a six membered ring by chelating the lithium ion between the oxygens of the sulfinyl and hydroxy group (Scheme 10).

This six-membered ring intermediate is expected to adopt the most stable conformation with the aryl and alkyl groups in an equatorial position. As a result of this conformational preference alkylation of the dianion intermediate is expected to be highly stereoselective. Results have shown that the alkylation of β -hydroxysulfoxide depends mainly on the configuration of the hydroxy-bearing stereogenic center with little or no influence from the sulfur stereogenic center.^{45,46,47} The *anti* product is favoured over the *syn* in ratios varying from 1:1 to 95:5 (Scheme 11). Increasing the size of the alkyl groups (R, R¹) slows the reaction resulting in low yields.

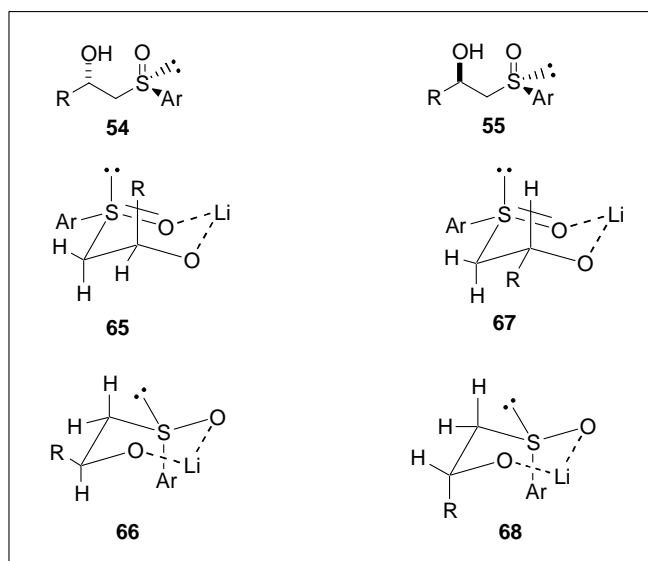
Saturated α -sulfinyl carbanions can also be condensed with aldehydes and ketones but the

⁴⁴ Lowry, T. H.; Schueller-Richardson, K.; *Mechanism and Theory in Organic Chemistry*, Harper and Row, London, **1976**.

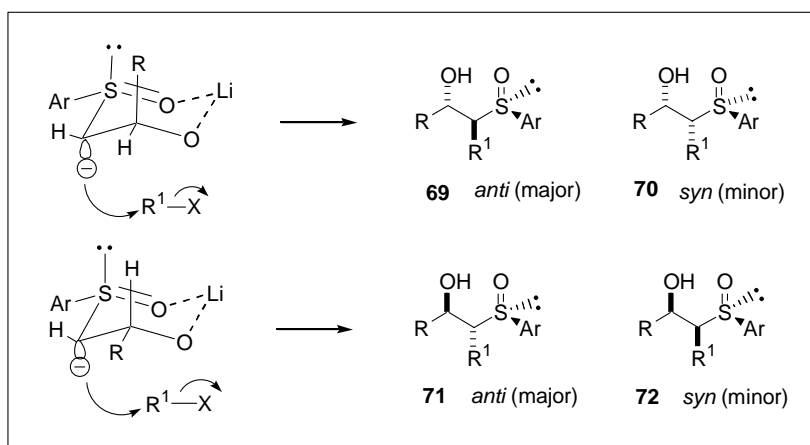
⁴⁵ Walker, A. J. *Tetrahedron: Asymmetry* **1992**, 3, 961.

⁴⁶ Tanikaga, R.; Honoya, B.; Hamamura, K.; Kaji, A. *Tetrahedron Lett.* **1987**, 28, 3705.

⁴⁷ Sato, T.; Itoh, T.; Fujisawa, T. *Tetrahedron Lett.* **1987**, 28, 5677.



Scheme 10: Chelation of the β -hydroxysulfoxide anion with a lithium cation



Scheme 11: Alkylation of β -hydroxysulfoxides.

reaction affords diastereomeric products.^{48,49} However, when a trimethylsilyl group is in the β -position, the diastereoselectivity of this condensation is very high.⁵⁰ To account for this remarkable diastereoselectivity Nakamura *et al.*⁵¹ postulated a silicon-carbonyl oxygen interaction in the condensation transition state on the basis of stereochemical results. In the

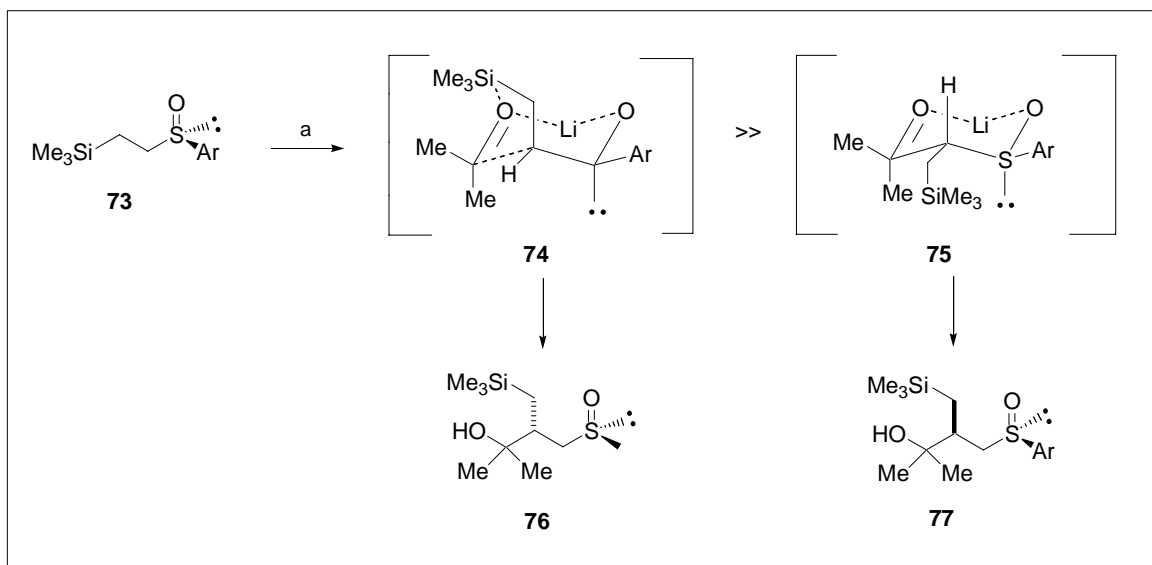
⁴⁸ Fitjer, L.; Schlotmann, W.; Noltemeyer, M.; *Tetrahedron Lett.* **1995**, 36, 4985.

⁴⁹ Nakamura, S.; Takemoto, H.; Ueno, Y.; Kakumoto, T.; Hagiwara, T.; Toru, T. *J. Org. Chem.* **2000**, 65, 469.

⁵⁰ Bravo, P.; Piovosi, G.; Resnati, G. *J. Chem. Soc., Perkin Trans. I* **1989**, 12.

⁵¹ Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *J. Chem. Soc., Perkin Trans. I* **2000**, 3143.

transition state the six-membered conformation **74** with the axial trimethylsilyl group is more stable than conformation **75** where this group is equatorial (Scheme 12).



Scheme 12: Condensation of α -sulfinyl carbanions with ketones.

Reagent: a) Acetone.

3.3.4 Functional group transformations involving the sulfoxide moiety

In addition to the high stereochemical induction observed when chiral sulfoxides are used as auxiliaries, the relative ease with which the sulfoxide group can be converted into several other functionalities, which don't contain sulfur, makes this class of compounds very attractive. Depending on the functionality that is needed for further manipulation, several methods are employed to convert the sulfoxide moiety to other functional groups. Catalytic hydrogenation using Raney nickel, reduction with aluminium sodium amalgam using disodium hydrogen phosphate, or lithium metal in diethyl amine at -78°C may be used to replace the sulfoxide group by a hydrogen atom. Epoxides, which are versatile building blocks in natural products synthesis, may also be prepared from sulfoxide groups. The reaction involves initial carbonyl reduction of a β -ketosulfoxide followed by subsequent reduction of the sulfoxide to the sulfide by LiAlH_4 ,⁵² $\text{Zn}/\text{Me}_3\text{SiCl}$,^{52,53} or trifluoroacetic anhydride and NaI in acetone,⁵⁴ or BuBr in CHCl_3 .⁵⁵ The treatment of the

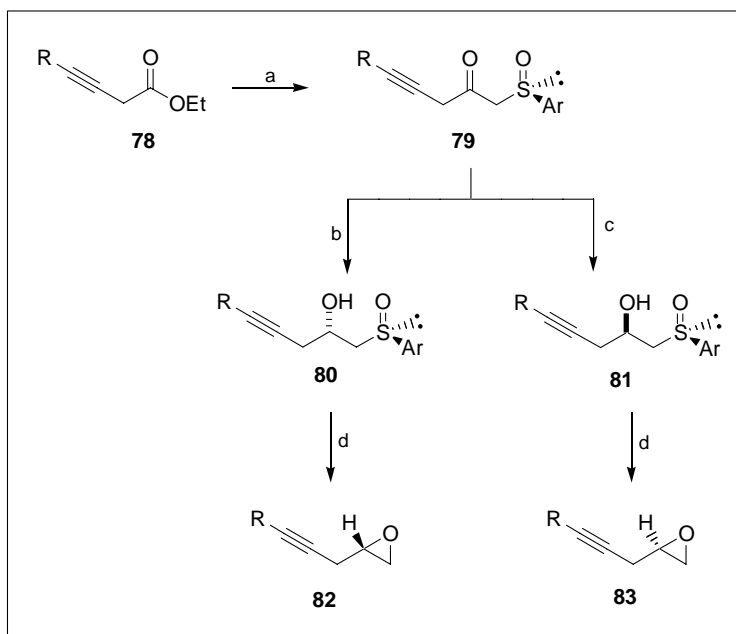
⁵² Bravo, P.; Piovisi, G.; Resnati, G. *J. Chem. Soc., Perkin Trans. 1*, **1989**, , 1201.

⁵³ Bravo, P.; Piovisi, G.; Resnati, G.; Fronza, G. *J. Org. Chem.* **1989**, *54*, 5171.

⁵⁴ Solladié, G.; Frechon, C.; Hutt, J.; Demailly, G. *Bull. Soc. Chim. Fr.* **1987**, *5*, 827.

⁵⁵ Solladié, G.; Salom-Roig, X.J.; Hanquet, G. *Tetrahedron Lett.* **2000**, *41*, 551.

resultant β -hydroxysulfide with $\text{Me}_3\text{O}\cdot\text{BF}_4$ ^{54,55} leads to the formation of the sulfonium salt that is immediately reacted with an aqueous base such as NaOH or K_2CO_3 to give the epoxide product.^{53,55} Recently the synthesis of chiral α -acetylenic epoxides **82** and **83** from propargylic esters **78** via the β -ketosulfoxides **80** and **81** was reported⁵⁶ (Scheme 13).



Scheme 13: Conversion of β -hydroxysulfoxides to epoxides.

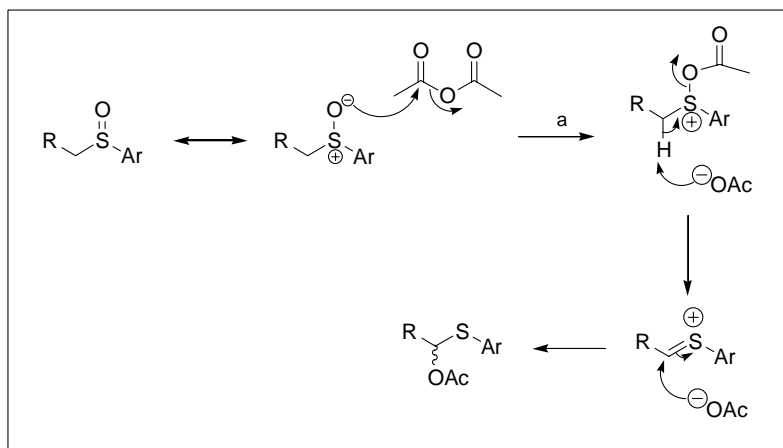
Reagents: a) (*R*)-methyl *p*-tolylsulfoxide (2 equiv.); LDA (2 equiv.), THF; b) Dibal-H, -78°C , THF; c) Dibal-H/ ZnBr_2 , THF, -78°C ; d) TiCl_3 , EtOH, 15 min; then $\text{Me}_3\text{O}\cdot\text{BF}_4$, CH_2Cl_2 , 3h, K_2CO_3 , H_2O .

The sulfoxide moiety can furthermore be transformed into an *O,S* acetal by the Pummerer rearrangement.^{57,58} (Scheme 14). A leaving group, created by acylation of the oxygen atom of the sulfoxide group, is lost from the sulfur atom of a sulfonium ylid to create a cationic intermediate that immediately captures a nucleophile at the α -carbon atom to give the acetal. The classical Pummerer reaction in which the chirality is transferred from sulfur to the adjacent α -carbon involves heating of the sulfoxide in acetic anhydride in the presence of sodium acetate. However this reaction proceeds with no diastereoselectivity and as a result the two diastereomers are present in equal ratios. The formed *O,S*-acetal can be cleaved either by simple hydrolysis to the aldehyde or reduction to the alcohol by various

⁵⁶ Sanchez-Obregon R.; Ortiz, B.; Walls, F.; Yuste, F.; Garcia Ruano, J.L. *Tetrahedron: Asymmetry*. **1999**, *10*, 947.

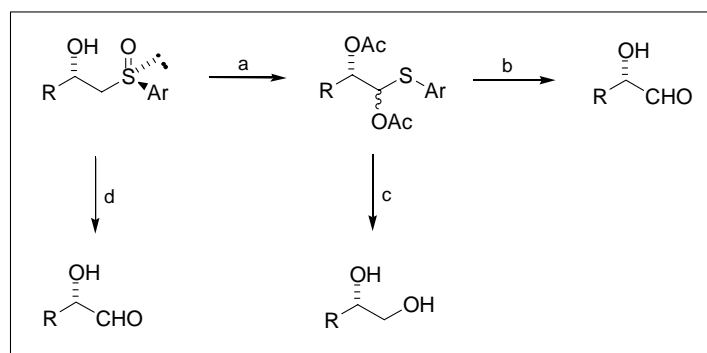
⁵⁷ Pummerer, R. *Ber.* **1909**, *42*, 2275 and 2282.

⁵⁸ Horner, L. *Liebigs Ann. Chem.* **1959**, *626*, 19; *Ibid.* **1960**, *631*, 198.



Scheme 14: Mechanism of the Pummerer rearrangement.

methods. Cleavage with DIBALH in dichloromethane at -78°C ,⁵⁹ Cu(II) or Mg(II) salts in aqueous $\text{CH}_3\text{CN}/\text{NaOH}$ ^{55,60} produces the β -hydroxyaldehyde, whereas reduction with LiAlH_4 ^{61,62} or desulfurisation by catalytic hydrogenation using Raney nickel⁵⁵ yields the diol. The sulfoxides can also be directly converted to the β -hydroxyaldehyde by using TFAA and 2,6-lutidine in acetonitrile and work-up of the reaction mixture with aqueous NaHCO_3 .⁶³ (Scheme 15)



Scheme 15: Pummerer rearrangement and cleavage of the sulfur group.

Reagents: a) Ac_2O , NaOAc ; b) HgCl_2 or CuCl_2 , aq. MeCN ; or DIBALH , CH_2Cl_2 , -78°C ; c) LiAlH_4 , Et_2O ; d) i. 2,6-Lutidine, TFAA, CH_3CN ; ii. aq. NaHCO_3 .

⁵⁹ Arroyo-Gomaz, Y.; Rodriguez-Amo, J.F.; Santos-Garcia, M.; Sanz-Tejedor, M.A, *Tetrahedron: Asymmetry* **2002**, *11*, 789.

⁶⁰ Sugihara, H.; Tanigaka, R.; Kaji, A. *Synthesis*, **1978**, 88.

⁶¹ Solladié, G.; Fernandez, I.; Maestro, M.C. *Tetrahedron Lett.* **1987**, *28*, 6.

⁶² Schmidt, A.H.; Russ, M. *Chem. Ber.* **1981**, *11*, 4822.

⁶³ Solladié, G.; Ziani-Cherif, C. *Tetrahedron Lett.* **1992**, *33*, 3.

4 PROTECTING GROUP STRATEGY FOR HYDROXY GROUPS

4.1 Introduction

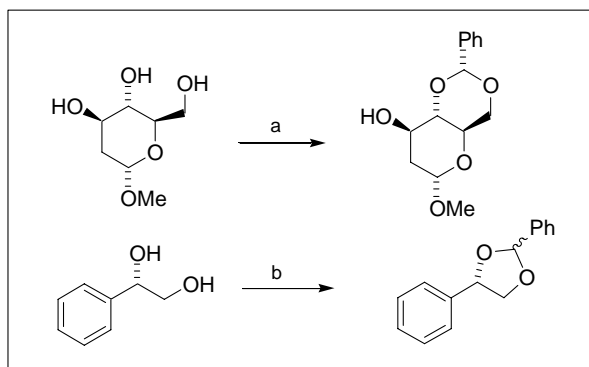
In the synthesis of complex organic compounds the need to carry out a selective reaction at one functional group without affecting other functional groups or the same functional group located at a different position in the same molecule requires the use of protecting groups in order to control the chemo-, regio- and stereoselectivity of a particular reaction. Many protecting groups have been developed for each of the many functional groups encountered in order to temporarily render those groups from interfering. The choice of protecting group employed for a specific functional group is dictated mainly by the eventual reaction conditions used in the synthetic route and the ease with which the protecting group can be introduced and removed at a later stage of the synthesis. In the work described in this dissertation a protecting group strategy had to be developed for the hydroxy groups present in the pavettamine molecule and a brief overview of the different protecting groups employed for the hydroxy group is presented.

4.2 Benzylidene protecting group

Benzylidene acetals are widely used to protect 1,2- and 1,3-diols in organic synthesis due to their ease of formation and tolerance to a variety of chemical conditions. This protecting group is stable to strong bases, mild oxidants and metal hydrides in the absence of Lewis acids. As a result the benzylidene acetal group has found extensive applications in the synthesis of oligosaccharides and glycoconjugates. The possible selective cleavage of benzylidene acetals allows formation of a benzyl ether under reductive conditions or benzoate esters under oxidative conditions at either the less or more hindered hydroxy group and makes the use of benzylidene protecting groups an attractive strategy in the synthesis of a variety of natural products. A disadvantage associated with the use of this protecting group is the possible formation of a mixture of diastereomers as a result of the new stereogenic center at the acetal carbon.

4.2.1 Formation of benzylidene acetals

Benzylidene acetals are formed by the reaction of a diol with benzaldehyde in the presence of either a Lewis or a protic acid catalyst (Scheme 1).^{1,2,3} The transformation can also be accomplished by acetal exchange by treatment of the diol with α,α -dimethoxytoluene in the presence of a catalytic amount of TsOH in dichloromethane (Scheme 1).⁴



Scheme 1: Preparation of benzylidene acetals

Reagents; a) PhCHO, ZnCl₂, b) α,α -Dimethoxytoluene, TsOH, CH₂Cl₂

In the absence of substituents and for cases where two or more acetals can be formed, the thermodynamic product is expected to prevail. Hence treatment of a cyclic 1,2,3 or 1,2,4-triol with benzaldehyde and acid results in the formation of the most stable 1,3-dioxane ring. However, the composition of the product is strongly dependent on temperature and substituents. It has been reported that the treatment of 1,2,3-triols with benzaldehyde in DMF in the presence of TsOH⁵ leads rapidly to the formation of 1,3-dioxolanes (kinetic product) that isomerise to give the 1,3-dioxanes (thermodynamic product) (Scheme 2).

In more complex systems a variety of factors may play a role in determining the structure of the final product. Thus benzylidenation of D-(+)-arabitol⁶ led to selective formation of only one 1,3-dioxane derivative incorporating the C(1) and C(3) hydroxy functions. None of the corresponding isomeric dioxane derived from the C(3) and C(5) hydroxy groups was formed (Scheme 3). The observed selectivity is the result of intramolecular hydrogen bonding.

¹ Richtyter, N.K. *Methods Carbohydr. Chem.* **1962**, *1*, 107.

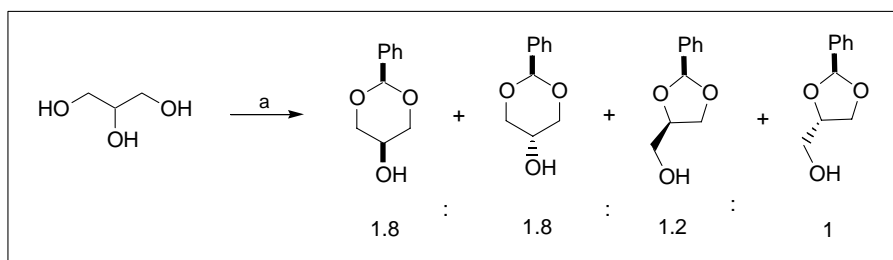
² Fletcher, H.G. *Methods Carbohydr. Chem.* **1962**, *2*, 307.

³ Kakinuma, K.; Otake, N.; Yonehara, H. *Tetrahedron Lett.* **1980**, *21*, 167.

⁴ Kocienski, P.J.; Street, S.D.A. *Synth. Commun.* **1984**, *14*, 1087.

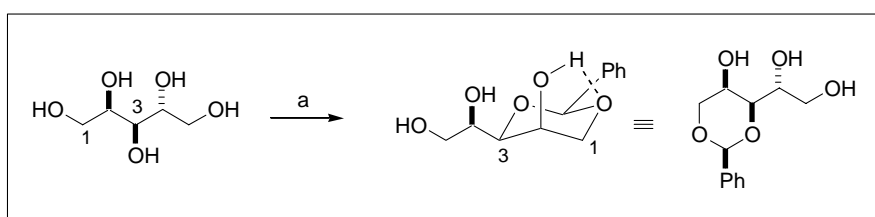
⁵ Baggett, N.; Duxbury, J.M.; Foster, A.B.; Webber, J.M. *Carbohydr. Res.* **1966**, *55*, 7.

⁶ Baggett, N.; Brimaconbe, J.S.; Foster, A.B.; Stacey, M.; Whiffen, D.H. *J. Chem. Soc.* **1960**, 2574.



Scheme 2: Formation of all stereoisomers during benzylidene formation.

Reagents: a) PhCHO, TsOH, DMF.



Scheme 3: Selectivity in the formation of a benzylidene acetal.

Reagents: a) PhCHO, TsOH

The ring size and conformation of benzylidene acetals can be determined by ^1H and ^{13}C NMR spectroscopy.^{7,8} The 2-phenyl-1,3-dioxanes give signals for the acetal proton at δ_{H} 5.5 whereas the corresponding signal for the 2-phenyl-1,3-dioxolanes appears at δ_{H} 5.9-6.3. Caution must be exercised in using ^{13}C chemical shift values for determining the ring size and conformation of benzylidene acetals as the acetal carbon atom of both 1,3-dioxolanes and 1,3-dioxanes appear in the 102-106 ppm region.

4.2.2 Cleavage of benzylidene acetals

Different methods have been employed to cleave benzylidene acetals to the corresponding diols and acid catalysis is the cheapest, mildest and most efficient method⁹ (Scheme 4). For acid sensitive substrates transacetalization using ethanethiol in the presence of a mild Lewis acid such as $\text{Zn}(\text{OTf})_2$ has been used.¹⁰ Catalytic hydrogenation is an efficient method for cleaving benzylidene acetals to toluene and the corresponding diol¹¹ but the

⁷ Neszmelyi, A.; Lipta K.A.; Nanasi, P. *Carbohydr. Res.* **1977**, *58*, c7.

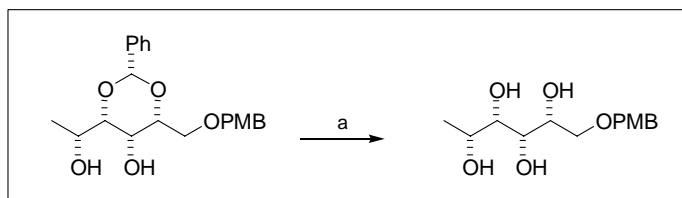
⁸ Grindley, T.B.; Gulasekharam, V. *Carbohydr. Res.* **1979**, *74*, 7.

⁹ Hann, R.E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919.

¹⁰ Nicolaou, K.C.; Veale, C.A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C.V.C; Ogilvie, W.W. *Angew. Chem Int. Ed. Engl.* **1991**, *30*, 299.

¹¹ Smith, A.B.; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037.

incompatibility of alkenes, alkynes and alkyl halides, and the catalyst poisoning experienced with thioether substrates are its main limitation. Benzylidene acetals can also be cleanly removed under Birch reduction conditions using Na or Li in liquid ammonia in the presence of proton source such as *t*-BuOH despite the obvious narrow range of functional groups compatible with such powerful reducing conditions.¹²



Scheme 4: Cleavage of a benzylidene acetal.

Reagents: a) 0.005M H₂SO₄, 100°C, 3h.

Partial deprotection of benzylidene acetals yields a monoprotected diol *i.e.* with one free hydroxy group and is a useful procedure for selectively liberating one of the hydroxy groups for further manipulation and leaving behind a protected hydroxy group. Reductive benzylidene acetal opening which gives *O*-benzyl protected diols has been shown to be a useful technique for protecting group manipulations and has found wide application not only in carbohydrate chemistry but also in the synthesis of natural products.

The regioselectivity observed in reductive ring opening of benzylidene acetals varies with the reagent and solvent used. For the preparation of an *O*-benzyl ether at the less hindered hydroxy group (the primary hydroxy group) and a free hydroxy group at the more hindered position NaBH₃CN-HCl in THF gives the best results.¹³ Other reagents such as Et₃SiH-TFA,¹⁴ Me₂NH.BH₃-BF₃.OEt₂ in CH₃CN,¹⁵ and BH₃.NMe₃-AlCl₃ in THF¹⁶, are also effective. It has recently been reported that the presence of water in the reductive opening of benzylidene acetals with BH₃.NMe₃ and AlCl₃ improves the yield and regioselectivity. In this methodology the acid reagent formed *in situ* from anhydrous AlCl₃ and H₂O in a 3:1 ratio is much more efficient for the reductive opening of the cyclic benzylidene acetals

¹² Ireland, R.E.; Wipf, P. *Tetrahedron Lett.* **1989**, 30, 919.

¹³ Garegg, P.J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, 108, 97.

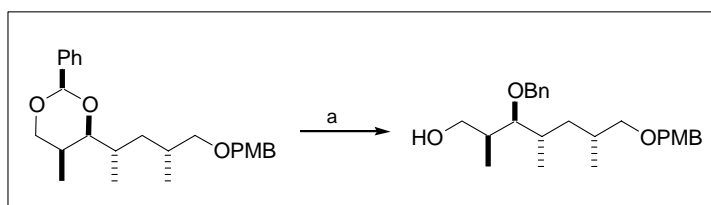
¹⁴ De Ninno, M.P.; Etienne, J.B.; Duplantier, K.C. *Tetrahedron Lett.* **1995**, 36, 669.

¹⁵ Okawa, M.; Liu, W.C.; Nakai, Y.; Koshida, S.; Fukase, K.; Kusumoto, S. *Synlett.* **1996**, 1179.

¹⁶ Ek, M.; Garegg, P.J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, 2, 305.

with $\text{Me}_3\text{N}.\text{BH}_3$ in THF than the use of AlCl_3 only.¹⁷

On the other hand there are a number of mild and effective reagents for the regioselective reductive ring opening of benzylidene acetals leading to the *O*-benzyl ether derivative at the more hindered hydroxy group with the free hydroxy group at the less hindered position. The reagents employed for such transformations are DIBALH¹⁸ (Scheme 5), $\text{LiAlH}_4\text{-AlCl}_3$ in THF,^{19,20,21,22} $\text{Me}_2\text{NH}.\text{BH}_3\text{-BF}_3.\text{OEt}_2$ in CH_2Cl_2 ¹⁶ (not sufficiently regioselective), $\text{Me}_3\text{N}.\text{BH}_3\text{-AlCl}_3$ in toluene¹⁷ (modest yield). Other reagents based on borane such as $\text{BH}_3.\text{THF-Bu}_2\text{BOTf}$ ²³ and $\text{Me}_2\text{BBr-BH}_3.\text{THF}$ ²⁴ were recently reported as efficient reagents for cleaving benzylidene acetals in good yield and better regioselectivity to give benzyl protected secondary (more hindered) hydroxy groups.⁷



Scheme 5: Regioselective benzylidene cleavage.

Reagents: a) DIBALH, hexane- CH_2Cl_2

Oxidative cleavage of benzylidene acetals leading to the formation of benzoate derivatives was first reported in 1973 and has found widespread use in organic synthesis. Various reagents such as tritylfluoroborate ($\text{Ph}_3\text{C}.\text{BF}_4$),²⁵ *t*-butyl hydroperoxide,^{26,27,28} $\text{NBS-H}_2\text{O}$,²⁹ $\text{NaBrO}_3\text{-Na}_2\text{S}_2\text{O}_4$,³⁰ and 2,2'-bipyridiniumchlorochromate-*m*-CPBA,³¹ have been employed for this transformation with varying degree of regioselectivity. However, most of these

¹⁷ Sherman, A.A.; Mironov, Y.V.; Yudina, O.N.; Nifantiev, N.E. *Carbohydr. Res.* **2003**, 338, 697.

¹⁸ Bhattacharjee, S. S.; Gorin, P.A. *Can. J. Chem.* **1969**, 47, 1195.

¹⁹ Liptak, A.; Imre, J.; Harangi, J.; Nanasi, P. *Tetrahedron* **1982**, 38, 3721.

²⁰ Gejas, J. *Adv. Carbohydr. Chem. BioChem.* **1981**, 39, 71.

²¹ Garegg, P. *J. Pure App. Chem.* **1984**, 56, 845.

²² Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. I* **1984**, 2371.

²³ Jiang, L.; Chan, T.-K. *Tetrahedron Lett.* **1998**, 39, 355.

²⁴ Yvan G.; Sylviel B.; Vida, G.; Rene, L.; Christiane, Y. *Can. J. Chem.* **1990**, 68, 897.

²⁵ Hanessian, S.; Staub, A.P.A. *Tetrahedron Lett.* **1973**, 37, 3551.

²⁶ Hosokawa, T.; Imada, Y.; Murahashi, S.I. *J. Chem. Soc., Chem. Commun.* **1983**, 1245.

²⁷ Sato, K.; Igarashi, T.; Yanagisawa, Y.; Kawauchi, N.; Hashimoto, H.; Yoshimura. *Chem. Lett.* **1988**, 1699.

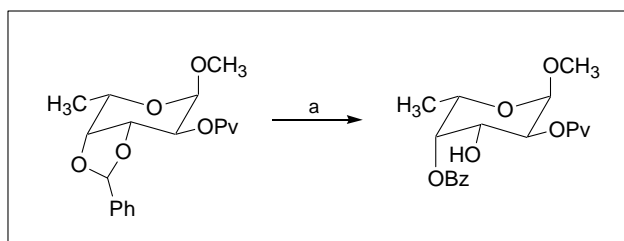
²⁸ Ziegler, F.E.; de Groot, F.M.H.; van Rozendaal, H.L.M.; Scheeren, H.W. *J. Org. Chem.* **1996**, 61, 7092.

²⁹ Binkley, R.W.; Goewey, G.S.; Johnston, J.C. *J. Org. Chem.* **1984**, 49, 992.

³⁰ Bhat, S.; Ramesha, A.R.; Chandrasekaram, S. *Synlett* **1995**, 329.

³¹ Luzzio, F.A.; Bobb, R.A. *Tetrahedron Lett.* **1997**, 38, 1733.

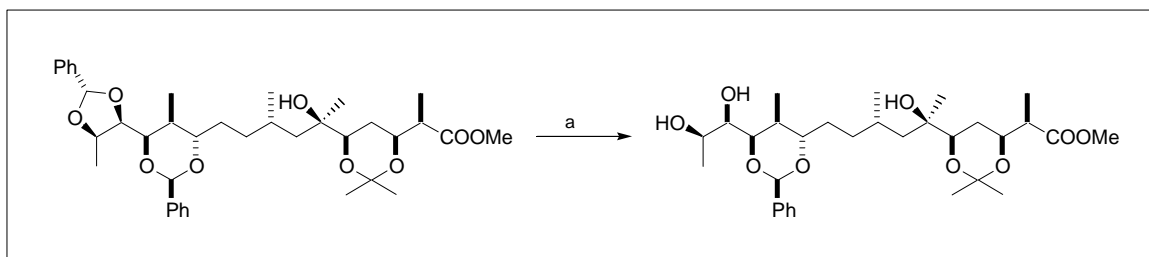
procedures suffer from the use of rather harsh or environmentally harmful conditions, but recently a new mild oxidant, NHPI/Co(OAc)₂-O₂ was reported to cleave benzylidene acetals to benzoate esters in improved yield and reasonable regioselectivity.³²



Scheme 6: Oxidative cleavage of benzylidene acetals.

Reagent: a) NBS, CCl₄

A difference in the rate of ozonolysis for 1,3-dioxolanes and 1,3-dioxanes has been observed and exploited in synthetic methodology. Thus in the presence of both systems, the 1,3-dioxolane can be selectively removed to unmask the 1,2-diol system leaving the 1,3-dioxane moiety intact.³³ (Scheme 7)



Scheme 7: Ozonolysis of benzylidene protecting groups.

Reagents: a) O₃, CH₂Cl₂.

Benzylidene acetals are cleaved by *N*-bromosuccinimide to the corresponding bromo benzoate esters. These have great synthetic importance as the alkyl halides are the major precursors for synthesizing a number of natural products such as pseudomonic acid,³⁴ boromycin,³⁵ thienamycin,³⁶ and rifamycin.³⁷ (Scheme 8)

³² Yongsheng C.; Peng G.W. *Tetrahedron Lett.* **2001**, 42, 4955.

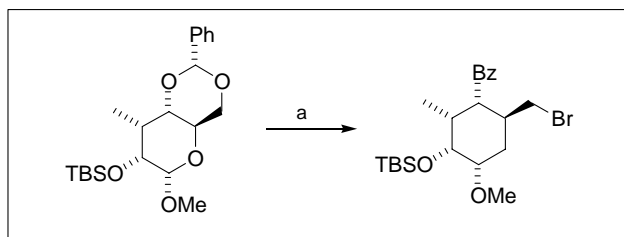
³³ Deslongchamps, P.; Moreau, C.; Frehel, D.; Chenevert, R. *Can. J. Chem.* **1975**, 53, 1204.

³⁴ Beau, J.M.; Aburaki, S.; Pougny, J.R.; Sinay, P. *J. Am. Chem. Soc.* **1983**, 105, 621.

³⁵ Hanessian, S.; Tyler, P.C.; Demailly, G.; Chapleur, Y. *J. Am. Chem. Soc.* **1981**, 103, 6243.

³⁶ Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, 60, 2292.

³⁷ Nakata, M.; Ikeyama, Y.; Takao, H.; Kinoshita, M.; *Bull. Chem. Soc. Jpn.* **1980**, 53, 3252.



Scheme 8: Benzylidene cleavage to bromobenzoate.

Reagents: a) NBS, BaCO₃, CCl₄, Δ

4.3 Acetonide protecting group

Acetonide protecting groups have been extensively used to protect 1,2- and 1,3-diols. This protecting group strategy finds wide application in carbohydrate chemistry to selectively mask the hydroxy groups of many different sugars.³⁸ The ease with which this protecting group is formed and its stability to nucleophiles, bases, organometals, reduction and oxidation conditions and the high yield cleavage of acetonides using protic or Lewis acids has led to their widespread use in synthesis. Rychnovsky has reported that the characteristic ¹³C chemical shifts of acetonides can be used to readily and unambiguously determine the relative stereochemistry of 1,2- and 1,3-diols.

4.3.1 Formation of acetonides

The classical method to prepare acetonides involves the reaction of a diol with acetone and an acid catalyst such as TsOH. The reaction is reversible and in order for the reaction to go to completion the formed water must be removed by molecular sieves or inorganic dehydrating agents such as anhydrous CuSO₄.^{39,40} (Scheme 9A). In those cases where the functional groups present in a compound are stable to Lewis acids, acetonides can be formed in good yield by the use of acetone and a Lewis acid such as FeCl₃⁴¹ or AlCl₃.⁴² Acetal exchange^{43,44} is a milder and more common procedure that involves the use of 2,2-dimethoxypropane and a catalytic amount of a strong acid such as TsOH or camphor-sulfonic acid (CSA). The reaction conditions are compatible with acid sensitive protecting

³⁸ Rychnovsky, S.D; Griesgraber, G. *J. Am. Chem. Soc.* **1994**, *116*, 2623.

³⁹ Kocienski, P.J.; Yeates, C.; Street, S.D.A.; Campbell, S.F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2183.

⁴⁰ Mori, K.; Iwasawa, H. *Tetrahedron Lett.* **1980**, *36*, 87.

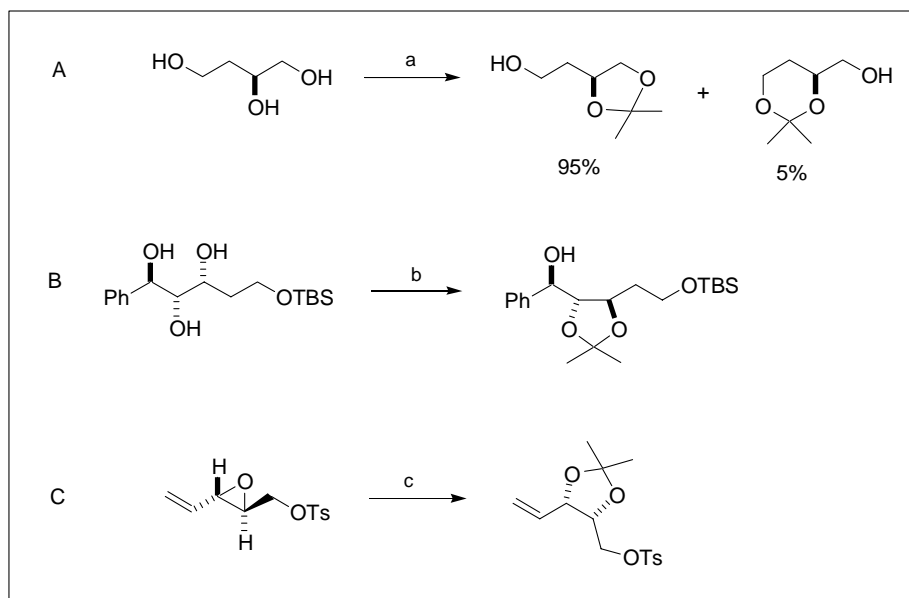
⁴¹ Dumortier, L.; van der Eychen, J.; Vandewalle, M. *Tetrahedron Lett.* **1989**, *30*, 3201.

⁴² House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* **1969**, *43*, 2324.

⁴³ Evans, D.A.; Dow, R.L.; Shih, T.L.; Takacs, J.M.; Zahler, R.; *J. Am. Chem. Soc.* **1990**, *112*, 5290.

⁴⁴ Schmid, C.R.; Bryant, J.D.; Dowlatzedah, M.; Philips, J.L.; Prather, D.E.; Schentz, R.D.; Sear, N.L.; Vianco, C.S. *J. Org. Chem.* **1991**, *54*, 4058.

groups such as the TBDPS group. The use of PPTS as a milder acid catalyst than TsOH is recommended (Scheme 9B). In addition acetonides can be prepared by Lewis acid-catalysed opening of an epoxide ring using acetone as solvent (Scheme 9C).⁴⁵



Scheme 9: Preparation of acetonides.

Reagents: a) acetone, TsOH, CuSO₄; b) (CH₃)₂C(OCH₃)₂, PPTS, DMF, 8 h; c) acetone, AlCl₃.

Acetonide formation is a thermodynamic driven process: thus in situations where two or more acetonides can be formed, the most stable product will be favoured.^{46,47,48} Hence in the preparation of the acetonide derivative of a triol, the thermodynamically more stable 1,2-derivative is favoured over the 1,3-derivative which in turn is favoured over the 1,4-derivative. The extent to which the more stable acetal is favoured is dependent upon the structure of the triol. In cases where two 1,2-acetonides are possible, the thermodynamically more stable product will prevail. Therefore in the 1,2,3-triol **84** with two secondary and one primary hydroxy group, acetonide formation will preferentially involve the two secondary alcohols.⁴⁹ (Scheme 10A). Furthermore acetonide formation involving a *cis* 1,2-diol is favoured over a *trans* 1,2-diol system as shown for **85** in Scheme

⁴⁵ Wershofen, S.; Scharf, H-D.; *Synthesis* **1988**, 854.

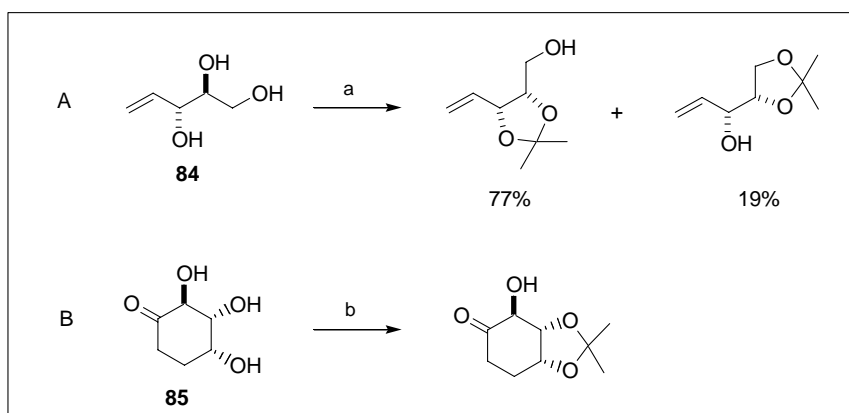
⁴⁶ Jager, V.; Hafele, B.; *Synthesis*. **1987**, 801.

⁴⁷ Coe, J.W.; Roush, W.R. *J. Org. Chem.* **1989**, *54*, 915.

⁴⁸ Mulzer, J.; de Lasalle, P.; Friessle, A.; *Liebigs. Ann. Chem.* **1986**, 1152.

⁴⁹ Grieco, A.P.; Yokoyama, Y.; Withers, P.G.; Okuniewicz, J.F.; Wang, J-L.C. *J. Org. Chem.* **1978**, *43*, 4178.

10B. In general acetonide formation involving a primary hydroxy group is preferred over that involving two *trans* secondary alcohols.



Scheme 10: Formation of thermodynamically more stable acetonide products.

Reagents: a) $\text{Me}_2\text{C}(\text{OMe})_2$, SnCl_2 ; b) $\text{H}_2\text{C}=\text{C}(\text{Me})\text{OTMS}$, $\text{HCl}(\text{g})$, CH_2Cl_2 .

The use of bulkier acetalization reagents for acetal formation can influence the ratio of the dioxane to dioxolane isomers formed from a 1,2,4-triol system. Thus the triol **86** (Scheme 11) gave a 9:1 mixture of dioxolane and dioxane products (**87** and **88**), respectively when acetone was used as the acetalisation reagent but the dioxolane product was formed exclusively using the much bulkier acetalization reagent 3-pentanone.⁵⁰

4.3.2 Cleavage of acetonides

Acetonides are susceptible to acid-catalysed hydrolysis and a number of acids have been used to cleave this protecting group in high yield. Thus aqueous acetic acid,⁵¹ dilute HCl in THF,⁵² aqueous $\text{CF}_3\text{CO}_2\text{H}$ in THF,⁵³ TsOH in aqueous methanol⁵⁴ or an ion exchange resin such as Dowex IR120 with its sulfonic acid group are some of the acids that have been reported (Scheme 12). For substrates with acid-sensitive protecting groups like TBS, deprotection of the acetonide can be accomplished using ethanethiol and an acid without affecting the TBS protecting group.⁵⁵ Alternatively acetonides can be removed using

⁵⁰ Lavalee, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, 27, 679.

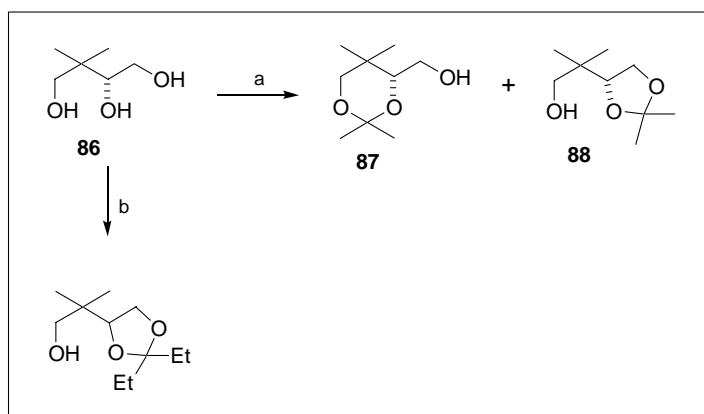
⁵¹ Garegg, J. P. *Acc. Chem. Res.*, **1992**, 25, 575.

⁵² Munavu, M.R.; Szmant, H.H., *Tetrahedron Lett.* **1975**, 4543.

⁵³ Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, 37, 1015.

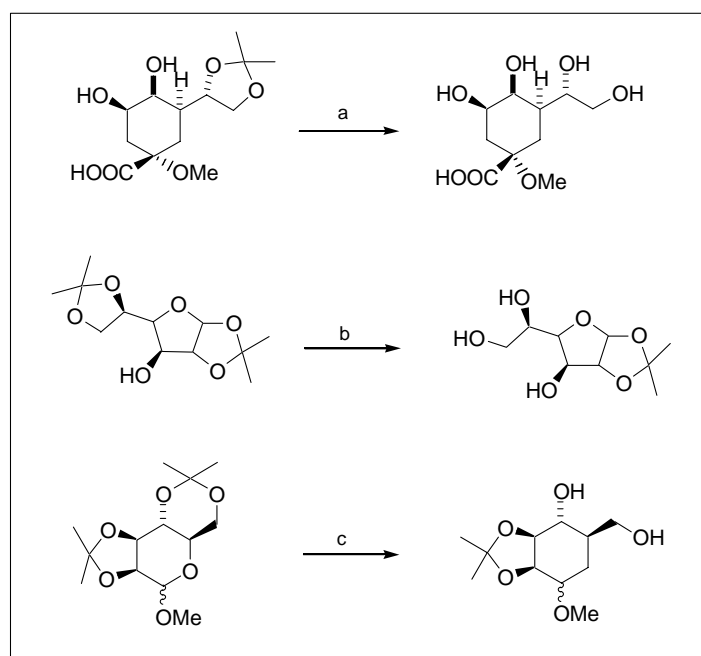
⁵⁴ Jiang, L.; Chan, T-H. *Tetrahedron Lett.* **1998**, 39, 355.

⁵⁵ Williams, D.R.; Sit, S.Y. *J. Am. Chem. Soc.*, **1984**, 106, 2949.



Scheme 11: Steric effect of acetalisation reagents.

Reagents: a) acetone, TsOH, CuSO₄, b) 3-pentanone, THF, TsOH, CuSO₄



Scheme 12: Acetonide cleavage using different reagents.

Reagents: a) Dowex IR120 (H⁺), H₂O, 80°C, 1.5h; b) H₂SO₄, aq. MeOH; c) aq. AcOH

Lewis acids provided that the substrate is stable to the reaction conditions.⁵⁶ Another reagent that has proven effective is catalytic I₂ in methanol.⁵⁷ In substrates that have more than one acetonide moiety difference in the rate of cleavage is observed. Thus 1,3-dioxanes hydrolyse faster than 1,3-dioxolanes but *trans*-fused 1,3-dioxolanes cleave at a

⁵⁶ De Laszlo, S.E.; Ford, M. J.; Ley, S.V.; Maw, G.N. *Tetrahedron Lett.* **1990**, *31*, 5525.

⁵⁷ Evans, M.E.; Parrish, F.W.; Long, L. *Carbohydr. Res.*, **1967**, *3*, 453.

faster rate than 1,3-dioxanes.⁵⁸

4.3.3 The use of ¹³C NMR to determine the stereochemistry of 1,3-diol acetonides

Nature provides enantiomerically pure compounds of great value such as the polyene macrolide antibiotics containing alternating (1,3,5....)-polyol chains. A change in configuration in one of the stereogenic centers present will lead to a stereoisomer that may not have the same biological activity as the one that is found in nature. It is therefore very important to determine the relative and absolute configuration of the stereogenic centers in the natural product using a simple NMR technique as single crystal X-ray crystallography of these compounds is not always possible.

Rychnovsky established an empirical method to determine the relative configuration of *syn* and *anti*-1,3-diol systems using the ¹³C chemical shift values of their acetonide derivatives.^{59,60,61,62,63} The difference in ¹³C chemical shift values for the *syn* and *anti* diastereomers is attributed to the different conformation that these systems adopt. In general, a *syn*-1,3-diol acetonide adopts a chair conformation with the C(4) and C(6) alkyl substituents in equatorial positions and the one acetonide methyl group axial and the other equatorial (Scheme 13). Since these methyl groups are chemically and magnetically non-equivalent, they will exhibit different chemical shifts in the NMR spectrum. Thus the ¹³C NMR spectrum of a typical *syn* 1,3-diol acetonide shows the axial C(2) methyl group at *ca.* 19.4 ppm and the equatorial C(2) methyl group at *ca.* 30 ppm (Scheme 14). On the other hand the *anti* 1,3-diol acetonide exists in a twisted boat conformation with the C(4) and C(6) alkyl substituents in pseudo-equatorial positions (Scheme 13) in order to relieve the 1,3-diaxial interactions between an axial methyl group and one of the two substituents at C(4) or C(6) in either of the two possible chair conformations.^{64,65} In this twisted conformation the two acetonide methyl groups are in nearly identical environments and thus both exhibit the same ¹³C chemical shift at *ca.* 24.6 ppm.⁶⁶ (Scheme 14)

⁵⁸ Gelas, J.; Horton, D., *Heterocycles*, **1981**, *16*, 1587.

⁵⁹ Rychnovsky, S.D.; Skalitzky, D.J. *Tetrahedron Lett.* **1990**, *31*, 945.

⁶⁰ Rychnovsky, S.D.; Roger, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

⁶¹ Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* **1993**, *58*, 5251.

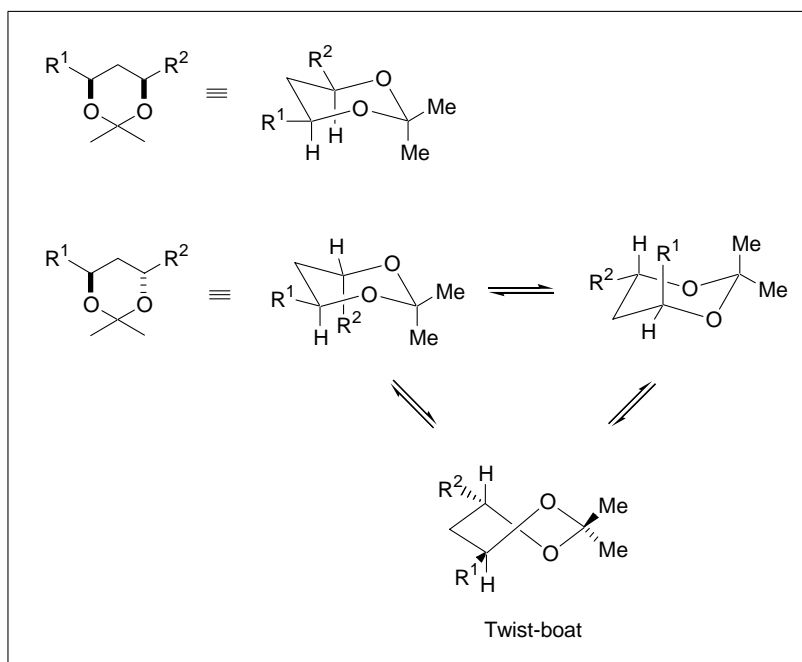
⁶² Rychnovsky, S.D.; Griesgraber, G.; Schegel, R. *J. Am. Chem. Soc.* **1995**, *117*, 197.

⁶³ Rychnovsky, S.D.; Richardson, T.I. *J. Org. Chem.* **1996**, *61*, 4219.

⁶⁴ Anteonis, M.J.O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293.

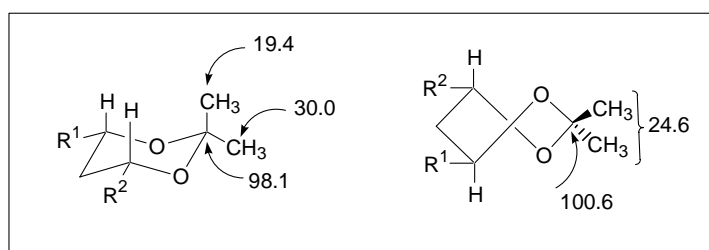
⁶⁵ Pilhaja, K.; Nurmi, T. *Isr. J. Chem.* **1980**, *20*, 160.

⁶⁶ Evans, D.A.; Rieger, D.L.; Gage, J.R. *Tetrahedron Lett.* **1990**, *31*, 7099.



Scheme 13: Conformations of *syn*- and *anti*-1,3-diol acetonides.

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 R^1 and R^2 are large, the 1,3-diaxial interaction between the substituent and one of the C(2) methyl groups will force the system to adopt a twist-chair conformation. In those cases where R^1 is small, the 1,3-diaxial interaction with the appropriate C(2) methyl group is small and the acetonide will adopt a chair conformation with R^1 in the axial position. In addition Evans noted that ^{13}C chemical shift values for the quaternary carbon atom in 1,3-diol acetonides can be used to deduce the stereochemistry of 1,3-diols. The acetal carbon of *syn* 1,3-diol acetonides resonates at *ca.* 98.1 ppm whereas that for the *anti* 1,3-diol acetonides appears at 100.6 ppm.⁶⁹ (Scheme 14).



Scheme 14: ^{13}C Chemical shift values for *syn* and *anti* 1,3-diol acetonides.

4.4 Benzyl protecting group

Benzyl ethers have been widely used in organic synthesis as typical hydroxy protecting groups because of their tolerance to a wide range of chemical conditions. Thus the benzyl group is stable to most metal hydride reducing agents, and mild oxidizing agents such as the Swern, Dess-Martin periodinane, and Jones' reagents, as well as PCC, PDC, sodium periodate, and lead tetraacetate. In addition this protecting group is resistant to a wide range of aqueous acidic and basic conditions and stable to the conditions required to cleave TBDPS and TBS ethers using TBAF.

4.4.1 Formation of benzyl ethers

The most common method used for the protection of the hydroxy group as a benzyl ether is the Williamson ether synthesis using benzyl bromide or chloride and NaH as base.^{67,68} A catalytic amount of KI or Bu₄NI is used to accelerate the alkylation of more hindered hydroxy groups because iodide displaces the bromine or chlorine atom to give benzyl iodide *in situ* which is much better alkylating agent. For substrates that contain base sensitive functional groups benzylation of the hydroxy group can be achieved using benzyl bromide in the presence of silver oxide in DMF,⁶⁹ a method that is very effective for the monobenzylation of diols.⁷⁰ Alternatively benzyl ethers can be prepared under acidic conditions using benzyl 2,2,2-trichloroacetimidate (freshly prepared) in the presence of TfOH⁷¹ or TMS-OTf.⁷²

Benzyl ethers can also be prepared by nucleophilic cleavage of oxiranes by the alkali metal derivatives of benzyl alcohol.⁷³ In addition this protecting group can be obtained by regioselective cleavage of asymmetrically substituted benzyldene acetals.⁷⁴ The cleavage results in the formation of a monoprotected benzyl ether and a free hydroxy group. The position of the benzyl group is dependent on the reagent and conditions used (see Scheme 5).

⁶⁷ Czerniecki, S.; Georgoulis C.; Provelenghiou, C. *Tetrahedron Lett.*, **1976**, 3535.

⁶⁸ Willson, T.M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P.M.; Faller, A.; Campbell, S.F. *Tetrahedron*, **1990**, *46*, 1767.

⁶⁹ Kuhn, R.; Low, I.; Trishmann, H. *Chem. Ber.* **1975**, *90*, 203.

⁷⁰ Bouzide A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945.

⁷¹ Wessel, H.P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

⁷² Xuesong C.; Yu-Lin, W.; Dihua C. *Tetrahedron Lett.* **2002**, *43*, 3529.

⁷³ Posner, G.H.; Rogers, D.Z.; *J. Am. Chem. Soc.* **1977**, *99*, 8208.

⁷⁴ Curtis, N.R.; Holmes, A.B.; Looney, M.G. *Tetrahedron Lett.* **1992**, *33*, 671.

4.4.2 Cleavage of benzyl ethers

Catalytic hydrogenation using Pd-C in THF is the commonest method for cleaving benzyl ethers.^{75,76} The method is undoubtedly convenient from the viewpoint of easy work-up, but the reproducibility of reductive debenylation depends on the activity of the catalyst. Raney-Ni⁷⁷ and Rh-Al₂O₃⁷⁸ are also used as alternative catalysts. The method is of course incompatible with the presence of alkenes, alkynes, and alkyl halides, and catalytic poisoning occurs with substrates that contain a thioether group. As alternative the benzyl ether group can be cleaved by catalytic transfer hydrogenation using formic acid,⁷⁹ cyclohexadiene,⁸⁰ or ammonium formate⁸¹ as a suitable source of hydrogen. Furthermore the deprotection can be performed under strongly basic conditions with sodium or lithium in ammonia but few substrates survive such conditions.⁸² Debenylation can also be accomplished under UV irradiation by using NBS-H₂O through a reaction pathway presumably involving radical bromination at the benzylic position and subsequent hydrolysis of the resulting bromo ether.⁸³

Various Lewis acids in CH₂Cl₂ or ClCH₂CH₂Cl offer mild conditions for cleaving benzyl ethers in the presence of some sensitive function groups. Typical reagents used include TMSI,⁸⁴ SnCl₄,⁸⁵ PhSSiMe₃-ZnI₂⁸⁶ (tolerates ester functions), BCl₃⁸⁷ and FeCl₃.⁸⁸

4.5 Silyl ether protecting groups

Silyl ethers are well established protecting groups in organic synthesis due to their ease of formation and removal and their stability to a wide range of reagents and reaction conditions. The reactivity of these groups (both formation and cleavage) can readily be

⁷⁵ Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.

⁷⁶ Hartung, W.H.; Simonoff, C. *Organic React.*, **1953**, *7*, 263.

⁷⁷ Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonenitsu, O. *Tetrahedron* **1986**, *42*, 3021.

⁷⁸ Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647.

⁷⁹ Rao, V.S.; Perlin, A.S. *Carbohydr. Res.* **1980**, *83*, 175.

⁸⁰ Hanessian, S.; Liak, T.J.; Vanasse, B. *Synthesis* **1981**, 396.

⁸¹ Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

⁸² Kocienski, P.J.; Street, S.D.A.; Yeates, C.; Campbell, S.F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171.

⁸³ Bingley, R.W.; Hehemann, D.G. *J. Org. Chem.* **1990**, *55*, 378.

⁸⁴ Jung, M.E.; Lyster, M.A.; *J. Org. Chem.* **1977**, *42*, 3761.

⁸⁵ Hori, H.; Nishida, Y.; Ohru, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346.

⁸⁶ Nicolaou, K.C.; Pavia, M.R.; Seitz, S.P. *J. Am. Chem. Soc.* **1982**, *104*, 2027.

⁸⁷ Williams, D. R.; Brown, D. L.; Benbow, J.W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.

⁸⁸ Park, M.H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823.

modulated by the appropriate choice of the groups attached to the silicon. Thus the stability of silyl ethers to hydrolysis and other nucleophilic conditions is generally proportional to the degree of steric hinderance at the silicon atom. As a result, a large number of alkylsilanes possessing various degree of steric bulk have been prepared and utilized as alcohol protecting groups. However, their stability is not solely a function of steric bulk since electronic effects play a role as well which can be exploited to differentiate stability under acidic or basic conditions. Thus electron-withdrawing groups on the silicon cooperate with the steric effect to enhance stability under acidic conditions whereas under basic conditions the effects are opposed.⁸⁹

Silicon has a high affinity for fluorine and this is exploited in selective cleavage of silyl ethers in the presence of other protecting groups in the compound. In this dissertation only the *t*-butyldimethylsilyl (TBS) and *t*-butyldiphenylsilyl (TBDPS) protecting groups were used.

4.5.1 *tert*-Butyldimethylsilyl ether

The use of the *t*-butyldimethylsilyl (TBS) protecting group was first reported in 1972 and has become one of the most highly used protecting groups in chemical synthesis. It is easily introduced with a variety of reagents and is quite stable to chromatography, metal hydrides such as LiAlH₄ and mild bases but is relatively sensitive to acids. TBS ethers are stable to non-protic bases, Grignard reagents, enolates, and metallated sulfonates at temperatures below 0°C but they are susceptible to migration from one hydroxy group to another. Migration usually occurs under basic conditions and proceeds intramolecularly through pentacoordinate silicon. *t*-Butyldimethylsilyl chloride (TBS-Cl), the reagent used to prepare *O*-TBS ethers, is expensive but it can be readily prepared in high yield by the reaction of *t*-BuLi with dimethyldichlorosilane.⁸⁹

4.5.1.1 Formation of *t*-butyldimethylsilyl ethers

Treatment of the substrate containing a hydroxy group with TBS-Cl and imidazole in DMF or CH₂Cl₂ is the most commonly used procedure for the introduction of the TBS group in

⁸⁹ Kocienski, P.J..*Protecting groups*, Georg Thieme Verlag, Stuttgart, New York, **1994**.

high yield.⁹⁰ This combination of reagents also silylates phenols,⁹¹ hydroperoxides,⁹² and hydroxylamines,⁹³ but is not effective with thiols, amines, and carboxylic acids. For more hindered hydroxy groups the use of TBSOTf and 2,6-lutidine as base,⁹⁴ or alternatively using TBS-Cl, KH, and 18-crown-6 in THF⁹⁵ has been reported.

4.5.1.2 Cleavage of *t*-butyldimethylsilyl ethers

The deprotection of TBS ethers (and all other silyl ethers) is usually carried out with tetrabutylammonium fluoride (TBAF),⁹⁶ aqueous CF₃COOH (which cleaves the TBS group preferentially in the presence of TBDPS and TIPS groups),⁹⁷ aqueous HF–CH₃CN (cleaves a primary allylic TBS group in the presence of a hindered secondary TBS group)⁹⁸ or various Lewis acids. The HF.pyridine complex in MeOH has also been suggested for the removal of a TBS ether in acid- and base-sensitive substrates.⁹⁹ Many other methods which are not chemoselective have also been reported including catalytic transfer hydrogenations using Pd,¹⁰⁰ reductive cleavage by DIBALH,¹⁰¹ oxidative cleavage by DDQ¹⁰² and ultrasonic cleavage in MeOH–CCl₄,¹⁰³ together with the use of PdCl₂(CH₃CN)₂,¹⁰⁴ I₂,¹⁰⁵ K₂CO₃ in aqueous ethanol,¹⁰⁶ and chloride ion.¹⁰⁷ Recently sodium periodate has also been reported as a mild and efficient method for the deprotection of silyl ethers.¹⁰⁸

4.5.2 *t*-Butyldiphenylsilyl ethers

Since first reported by Hanessian in 1975, the TBDPS group has been widely used for the

⁹⁰ Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *61*, 1165.

⁹¹ Hansen, D.W.; Pilipauskas, D. *J. Org. Chem.* **1985**, *50*, 945.

⁹² Clark, G.R.; Nikaido, M.M.; Fair, C.K.; Lin, J. *J. Org. Chem.* **1985**, *50*, 1994.

⁹³ Keana, J.F.W.; Heo, G.S.; Gaughan, G.T. *J. Org. Chem.* **1985**, *50*, 2346.

⁹⁴ Corey, E.J.; Cho, H.; Rucker, C.; Hua, D.H.; *Tetrahedron Lett.* **1981**, 3455.

⁹⁵ Braish, T.F.; Fuchs, P.L. *Synth. Commun.* **1986**, *16*, 111.

⁹⁶ Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

⁹⁷ Baker, R.; Cummings, W.J.; Hayes, J.F.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1237.

⁹⁸ Newton, R.F.; Reynolds, D.P.; Finch, M.A.W.; Kelly, D.R.; Roberts, S.M. *Tetrahedron Lett.* **1979**, 3981.

⁹⁹ Nicolaou, K.C.; Webber, S.E. *Synthesis*, **1986**, 453.

¹⁰⁰ Coqmier, J.F. *Tetrahedron Lett.* **1991**, *32*, 187.

¹⁰¹ Corey, E.J.; Jones, G.B. *J. Org. Chem.* **1992**, *57*, 1028.

¹⁰² Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997.

¹⁰³ Lee, A.S.Y.; Yeh, H.C.; Tsai, M.H. *Tetrahedron Lett.* **1995**, *36*, 6891.

¹⁰⁴ Wilson, N.S.; Keay, B.A. *Tetrahedron Lett.* **1996**, *37*, 153.

¹⁰⁵ Vaino, A.R.; Szarek, W.A. *Chem. Commun.* **1996**, 2351.

¹⁰⁶ Maiti, G.; Roy, S.C. *Tetrahedron Lett.* **1997**, *38*, 187.

¹⁰⁷ Jaume, F.; Carme, S.; Jaume, V. *Tetrahedron Lett.* **1998**, *39*, 327.

¹⁰⁸ Mijuan, W.; Chun, L.; Dali, Y.; Xiao-Tian, L. *Tetrahedron Lett.* **2002**, *43*, 8727.

selective protection of primary hydroxy groups. It has also been found to be valuable for the masking of secondary alcohols due to its excellent stability under acidic, basic and oxidizing agents. The TBDPS protecting group has several advantages over the TBS group. Thus TBDPS ethers are 100 times more stable than TBS ethers toward acid hydrolysis which makes it stable to the conditions used to cleave acetals and THP ethers. In general the TBDPS group, in contrast to the TBS group, shows greater stability to many reagents. Even more so the TBDPS ethers exhibit a steric induced differentiation between **primary and secondary** hydroxy groups that enhances its selective introduction and/or removal. The TBDPS ethers are stable to hydrogenolysis (which cleaves benzyl ethers), K_2CO_3 in CH_3OH , 9M NH_4OH , $NaOCH_3$ (cat.) in CH_3OH , and 80% $AcOH$ (used to cleave TBS, Tr, and THP ethers).

4.5.2.1 Formation of *t*-butyldiphenylsilyl ethers

Traditionally, TBDPS ethers are prepared by treatment of the substrate alcohol with TBDPS-Cl in DMF or CH_2Cl_2 by employing either imidazole as acid scavenger¹⁰⁹ or DMAP.¹¹⁰ TBDPSOTf with 2,6-lutidine¹¹¹ as base has also been employed for the synthesis of TBDPS ethers.

4.5.2.2 Cleavage of *t*-butyldiphenylsilyl ethers

TBDPS ethers are generally cleaved under the same conditions as those used for TBS ethers *i.e.* TBAF-THF or HF.pyridine-THF but longer reaction times are frequently necessary and as a consequence the selective removal of a TBS group in the presence of a TBDPS group is quite common.

4.5.3 Trityl protecting group

Trityl (or triphenylmethyl) ethers are the most commonly used protecting group due to its ease of formation/removal and stability towards a variety of reaction conditions. This group preferentially protects primary hydroxy groups in polyols due to its steric bulk. The trityl group is more easily introduced but a bit more difficult to remove, as it requires acidic conditions which, in some cases, compromise other protecting group in the

¹⁰⁹ Nicolaou, K.C.; Pavia, M.R.; Seitz, S.P. *J. Am. Chem. Soc.* **1981**, *103*, 1224.

¹¹⁰ Ireland, R.E.; Obrecht, D.M. *Helv. Chim. Acta* **1986**, *69*, 1272.

¹¹¹ Grieco, P.A.; Henry, K.J.; Nunes, J.J.; Matt, J.E. *J. Chem. Soc., Chem. Commun.* **1992**, 368.

molecule. As a result the use of a mono- or dimethoxy substituted trityl group, which are easier to cleave, has been developed.

4.5.3.1 Formation of trityl protecting groups

The classical method for the preparation of the trityl ethers involves the reaction of a primary alcohol with trityl chloride in pyridine.¹¹² Other convenient procedures which involve DMAP¹¹³ or DBU,¹¹⁴ have been reported. Other combinations of reagents which have been employed to introduce this group, include Ph₃CCl, 2,4,6-collidine, CH₂Cl₂, Bu₄NClO₄,¹¹⁵ and Ph₃COSiMe₃, Me₃SiOTf, CH₂Cl₂.¹¹⁶

4.5.3.2 Cleavage of trityl protecting groups

Trityl ethers are typically removed using protic acids such as formic acid,¹¹⁷ acetic acid¹¹⁸ or trifluoroacetic acid (TFA),¹¹⁹ and alternatively acid-catalyzed reactions such as 1% methanolic solution of iodine have been employed for deprotection.¹²⁰ However, in acid sensitive compounds several methods using ZnBr₂,¹²¹ AlClEt₂,¹²² Yb(OTf)₃,¹²³ BCl₃¹²⁴ and Ce(NH₄)₂(NO₃)₆¹²⁵ as Lewis acids have been reported. In addition Na in liquid ammonia has been employed in deprotection¹²⁶ but most substrates and protecting groups are not compatible with such conditions. Recently CBr₄-MeOH,¹²⁷ column chromatography,¹²⁸ and silica-supported sodium hydrogen sulfate¹²⁹ have been reported as mild and efficient conditions for cleavage.

¹¹² Garcia, M.L.; Pascual, J.; Borrás, L.; Andreu, J.A.; Fos, E.; Mauleon, D.; Carganico, G.; Arcamone, F. *Tetrahedron* **1991**, *47*, 10023.

¹¹³ Chaudary, S.C.; Hernandez, O.; *Tetrahedron Lett.* **1979**, 99.

¹¹⁴ Colin-Messenger, S.; Girard, J.P.; Rossi, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2689.

¹¹⁵ Reddy, M.P.; Rampal, J.B.; Beaucage, S.L. *Tetrahedron Lett.* **1987**, *28*, 23.

¹¹⁶ Murata, S.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 2107.

¹¹⁷ Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579.

¹¹⁸ Micheal, F. *Ber.* **1932**, *65*, 262.

¹¹⁹ MacCoss, M.; Cameron, D. *J. Carbohydr. Res.* **1978**, *60*, 206.

¹²⁰ Wahlstrom, J.L.; Ronald, R.C. *J. Org. Chem.* **1998**, *63*, 6021.

¹²¹ Kholi, V.; Blocker, H.; Koster, H.; *Tetrahedron Lett.* **1980**, *21*, 2683.

¹²² Fuentes, J.; Cuevas, T.; Pradera, M.A. *Syn. Commun.* **1994**, *24*, 2237.

¹²³ Lu, R.J.; Liu, D.; Giese, R.W. *Tetrahedron Lett.* **2000**, *41*, 2817.

¹²⁴ Jones, G.B.; Hynd, G.; Wright, J.M.; Sharma, A. *J. Org. Chem.* **2000**, *65*, 263.

¹²⁵ Hwu, J.H.; Jain, M.L.; Tsay, S.-C.; Hakimelahi, G.H. *Chem. Commun.* **1996**, 545.

¹²⁶ Hanessian, S.; Cooke, N.G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.

¹²⁷ Jhillu, S.; Yadav, Basi V.; Reddy, S. *Carbohydr. Res.* **2000**, *329*, 885.

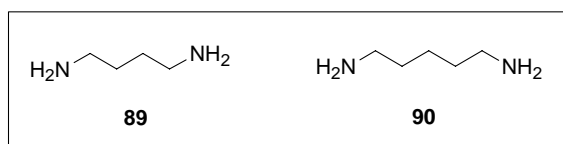
¹²⁸ Ashish, K.; Pathak, V.P.; Laine, E.; Kamal, N.; Tiwari, M.S.; Akhtar, Robert, C.R. *Tetrahedron Lett.* **2001**, *42*, 7755.

¹²⁹ Biswanath, D.; Gurram, M.; Vooturi, S.K.; Nikhil, C. *Tetrahedron Lett.* **2004**, *45*, 6709.

5 PREPARATION OF AMINES

5.1 Introduction

The simple polyamines that play an important role in biological processes are formed by enzymatic decarboxylation of the corresponding amino acid. Thus putrescine (**89**) and cadaverine (**90**) found in decaying flesh and rotten meat, is formed in the cell by decarboxylation of ornithine and lysine, respectively. Similarly the amines that influence and control brain function are derived from the corresponding amino acid as the latter are not able to cross the blood brain barrier.



Amines can be synthesized using different functional group transformations, but in this chapter the focus will be on the transformation of primary alcohols to primary amines via nucleophilic substitution, as this transformation is one of the reactions that was carried out in this project on pavettamine synthesis.

5.2 Methods of transformation

The methods used for the preparation of amines can be classified into three major groups depending on the reaction employed for the functional group transformation.

5.2.1 Method 1: Amines via reduction

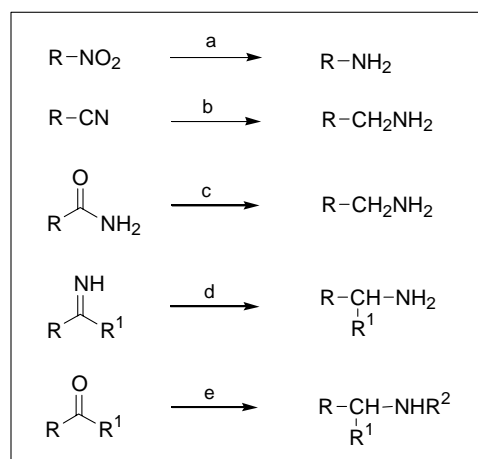
Amines can be synthesized by the reduction of nitro compounds,¹ nitriles,² amides and imines,³ and by reductive amination of aldehydes and ketones using a variety of reducing agents.⁴ (Scheme 2).

¹ Downing, R. .; Kunkeler, P.J.; van Bekkum, H. *Catalysis Today*, **1997**, 37, 121.

² Guido C.; Margherita, G.; Guido, S.; Aldo, S.; Giuseppe, S. *J. Org Chem.*, **1987**, 52, 2301

³ Krishnamurthy, S. *Tetrahedron Lett.*, **1982**, 23, 3315.

⁴ Eleveld, M.B.; Hogeveen, H.; Schudde, E.P. *J. Org. Chem.*, **1986**, 51, 3635.

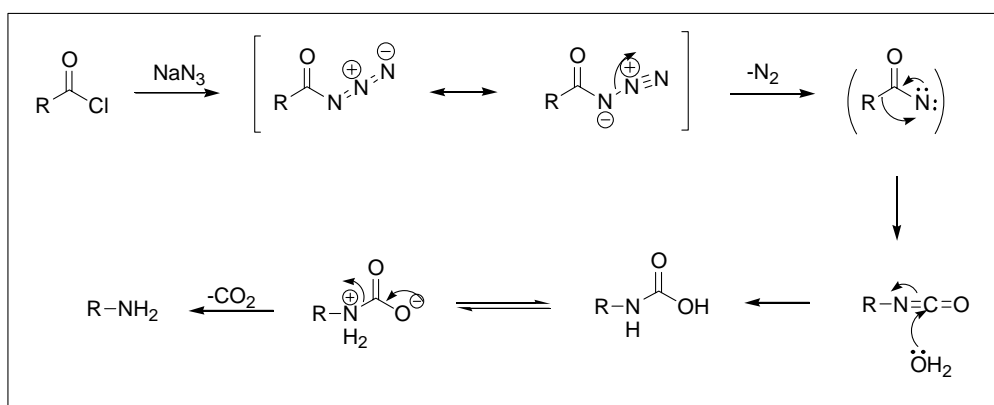


Scheme 2: Preparation of amines by reduction.

Reagents: a) H_2 , Raney Ni, HOAc, b) $LiAlH_4$, c) $BH_3 \cdot SMe_2$;
 d) $LiAlH_4$ or $NaBH_4$; e) R^2NH_2 , H_2 , cat Pd-C.

5.2.2 Method 2: Amines via rearrangement

The method developed by Hoffman and Curtius for the conversion of amide and acyl azides, respectively, involves in each case a rearrangement (named after the developer) that leads to the formation of an amine and the concomitant loss of a single carbon atom. These methods are applicable to the formation of primary amines.



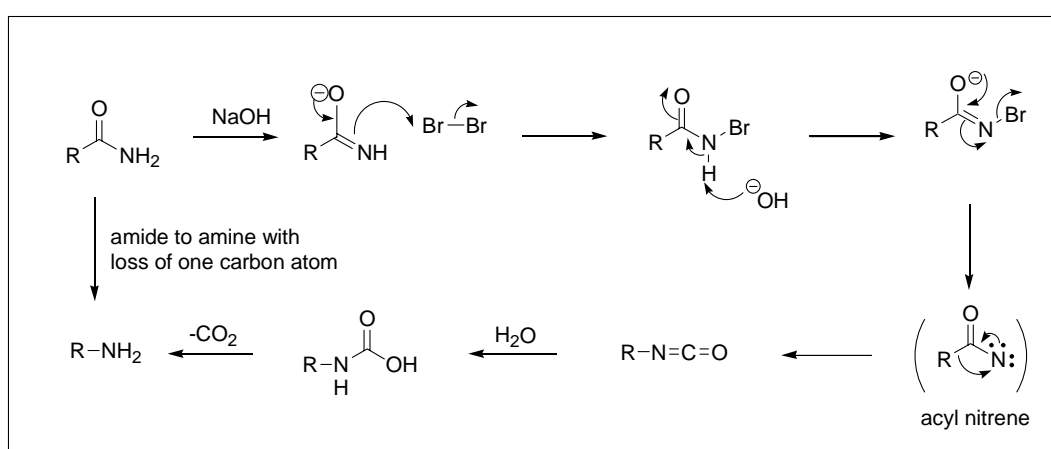
Scheme 3: Curtius rearrangement

The Curtius rearrangement⁵ involves the initial reaction of an acyl chloride with sodium azide to provide an acyl azide. This acyl azide on heating loses N_2 to give a nitrene that undergoes a rearrangement in which the R group migrates from carbon to nitrogen to give

⁵ Curtius, T. Ber. **1890**, 23, 3023.

an isocyanate. The rearrangement follows a concerted mechanism. Addition of water to the isocyanate leads to the formation of an unstable carbamic acid that loses carbon dioxide to give the required amine (Scheme 3).

The Hoffman rearrangement⁶ uses a primary amide as starting material and involves a base-promoted bromination followed by the reaction of the formed *N*-bromoamide with base to give a nitrene which undergoes once again migration of the R group from carbon to nitrogen to generate an isocyanate which can be hydrolysed to an amine (Scheme 4).



Scheme 4: Hoffman rearrangement

5.2.3 Method 3: Amines via nucleophilic substitution

Nucleophilic substitution at a saturated carbon center is used widely in a variety of synthetic operations particularly in the interconversion of functional groups. In this dissertation the focus is on the conversion of a primary alcohol to an amine. The direct conversion of alcohols to amines by nucleophilic substitution using ammonia or azide as nucleophiles is not possible as the hydroxide ion is basic, reactive and a poor leaving group. It is therefore necessary either to convert the hydroxy group into a better leaving group or to activate the alcohol for nucleophilic attack. There are three methods by which the interconversion of the alcohol to the amine can proceed. Each of these methods is discussed below.

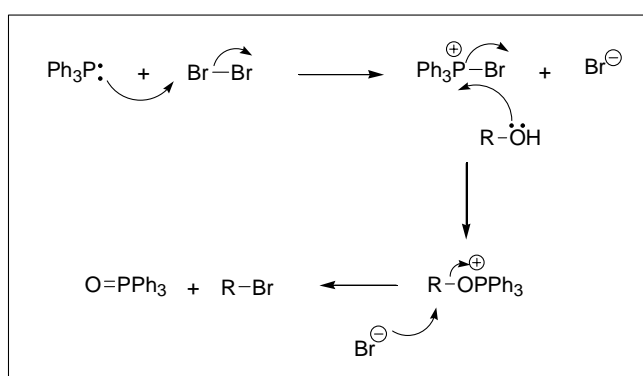
⁶ Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic chemistry*, Oxford University Press, 2001.

5.2.3.1 Three-step methodology

This method involves the initial conversion of the hydroxy group via an S_N2 reaction to a better leaving group that in turn undergoes nucleophilic substitution with azide. The subsequent reduction of the azide gives the amine. Halides and sulfonate esters are well known good leaving groups and conversion of the hydroxy group to the corresponding halide or sulfonate allows the nucleophilic substitution with azide to proceed in good yield.

Alcohols are the most common precursors for alkyl halides and a variety of methods for this transformation have been developed. The choice of an appropriate reagent and reaction condition is dictated by the sensitivity of the alcohol and any other functional groups present in the molecule to the reaction conditions.

For acid insensitive substrates primary alcohols can be converted to the corresponding halides by treating the substrate with HBr or HCl.⁷ The reaction proceeds by an S_N2 mechanism and hence elimination and rearrangement are not a problem for primary halides. Alternatively the reaction of the alcohols with halides of nonmetallic elements such as thionyl chloride, phosphorus trichloride or phosphorus tribromide gives the corresponding halide in good yield.⁸ During the reaction a very acidic solution is generated and hence this method is also limited to acid stable molecules. Therefore for substituted alcohols with acid-labile functional groups much milder methods are required.



Scheme 5: Alkyl halide preparation.

⁷ Reid, E.E.; Ruhoff, J.R.; Burnett, E.R. *Org. Synth.* **1941**, *I*, 142.

⁸ Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* **1952**, *74*, 308.

The activation of alcohols toward nucleophilic substitution by converting the substrate alcohol to alkoxyphosphonium ions is the most general method of converting highly functionalized sensitive alcohols to the corresponding halides.⁹ The alkoxyphosphonium ions are very reactive toward nucleophilic attack, with the driving force for substitution being formation of the strong phosphoryl bond. For instance the triphenylphosphine–bromine reagent converts an alcohol to the corresponding bromide.¹⁰

Generally sulfonate esters are prepared by the reaction of the alcohol with sulfonyl chloride in pyridine at room temperature.^{10,11} Alternatively the reaction can be carried out in dichloromethane at 0°C using 1 equivalent of pyridine as an acid scavenger and catalytic DMAP. In cases where an especially good leaving group is required the very reactive trifluoromethanesulfonate group is used.

The use of ammonia as a nucleophile is problematic as it rarely gives a single product. The primary amine that is produced in the reaction is at least as nucleophilic as the nucleophilic starting material and hence it will undergo further alkylation to give a mixture of primary, secondary and tertiary amines. The reaction comes to an end only when a tetra–alkyl ammonium salt is formed. In order to overcome these problems the triatomic azide ion is used as a nucleophile as the formed product is no longer a nucleophile. Reduction of the formed azide using catalytic hydrogenation over a Pd catalyst, lithium aluminum hydride reduction or triphenylphosphine–water leads to the formation of the amine.

5.2.3.2 The Mitsunobu reaction: a two step methodology

Reactions involving the oxidation of phosphorus(III) into phosphorus(V) have been widely used in organic synthesis. These include the Arbuzov and Perkow reactions that use reagents formed by the combination of tertiary phosphines or triaryl phosphites with carbon tetrahalides or with halogens, the Wittig reaction, Mukaiyama's redox condensation as well as the Mitsunobu reaction.

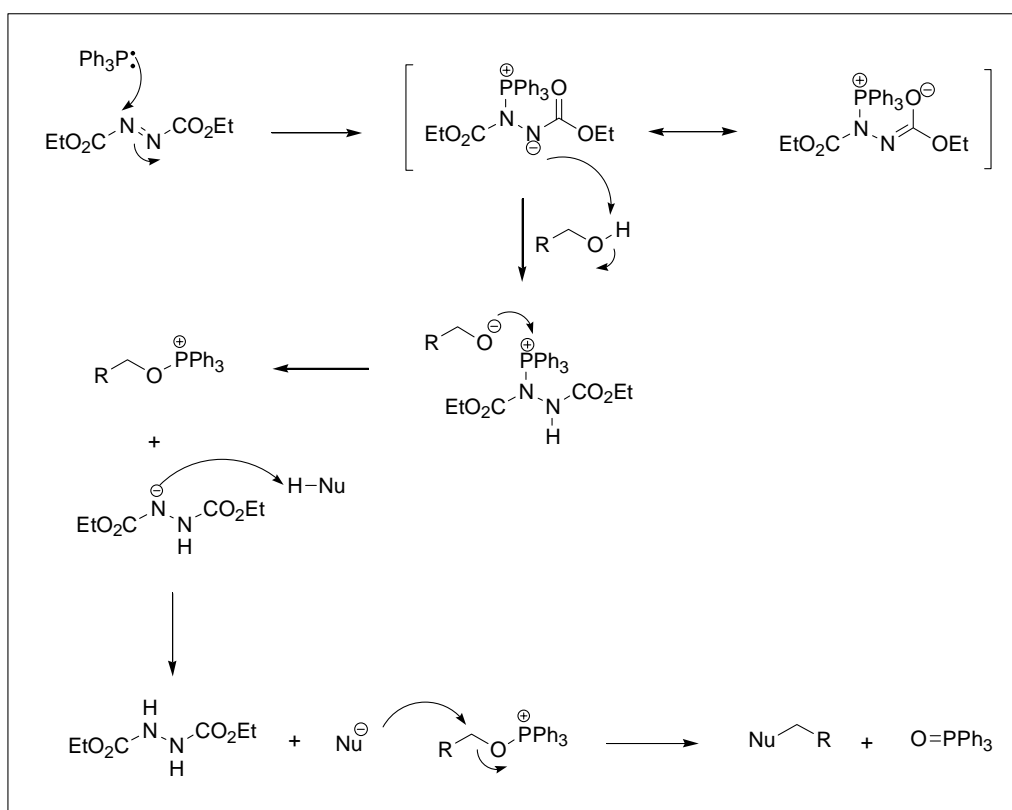
The Mitsunobu reaction involves the use of diethyl azodicarboxylate (DEAD) and

⁹ Castro, B.P. *Org. React.* **1983**, 29, 1.

¹⁰ Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. *J. Am. Chem. Soc.* **1964**, 86, 964.

¹¹ Kabalka, G.W.; Varma, M.; Varma, R.W.; Srivastava, P.C.; Knapp, F.F. *J. Org. Chem.* **1986**, 51, 2386.

triphenylphosphine.¹² The methodology has been used for the esterification of carboxylic acids, esterification of phosphoric mono- and diesters, alkylation of phenols and heterocyclic compounds and the preparation of azides. In this dissertation the preparation of azides using this methodology is discussed. This reaction proceeds under mild neutral conditions and is stereospecific with inversion of configuration when the hydroxy group is bound to a stereogenic centre (*e.g.* a chiral secondary alcohol). The reaction has been widely used in synthesis.



Scheme 6: Mechanism of the Mitsunobu reaction.

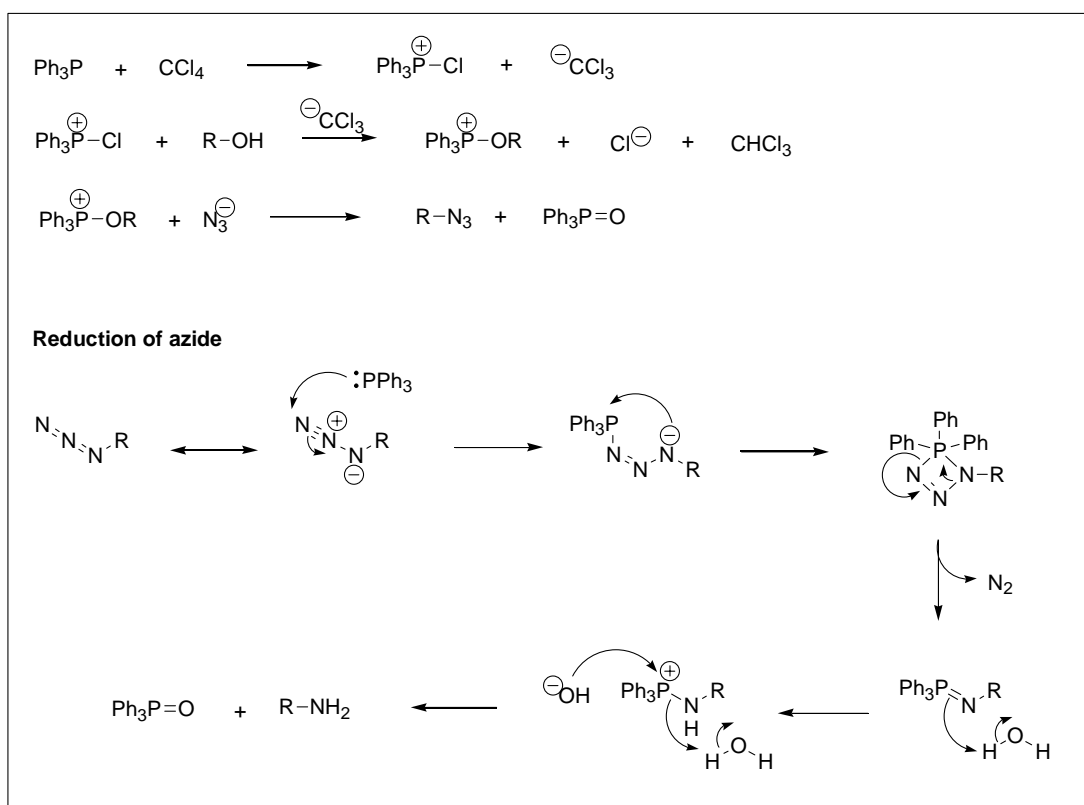
The reaction is generally believed to proceed by initial addition of triphenylphosphine to DEAD giving a quaternary phosphonium salt that abstracts a proton from the alcohol. The newly formed alkoxide ion immediately attacks the positively charged phosphorus atom to form an alkoxyphosphonium salt displacing in the process a nitrogen anion stabilized by the ester functionality. This basic nitrogen anion removes a proton from an added nucleophile NuH to reveal an anionic nucleophile. Finally this anion attacks the

¹² Mitsunobu, O. *Synthesis* **1981**, 1.

phosphorus derivative of the alcohol in a normal S_N2 reaction at carbon with phosphine oxide as leaving group (Scheme 6). When hydrazoic acid is used as nucleophile an azide is formed which can be reduced to an amine using various reducing agents.

5.2.3.3 One-pot methodology

The one-pot conversion of primary alcohols to azides/amines was reported in 1987 and involves a combination of Mitsunobu and Staudinger reactions.¹³ The method involves treatment of an alcohol with NaN₃ and two equivalents of triphenylphosphine in CCl₄-DMF (1:4) at 90°C to afford the amine. The use of one equivalent of triphenylphosphine allows for the isolation of the azide intermediate whereas the second equivalent was employed for reduction of the azide to amine upon addition of water.



Scheme 7: Formation and reduction of azide.

The reaction is initiated by *in situ* generation of chlorophosphonium ions by reaction of

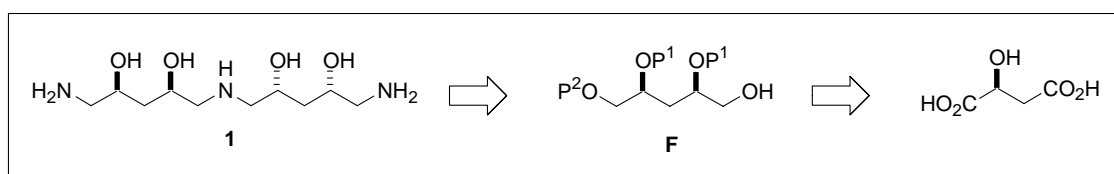
¹³ Vidya, S.R.G.; Venkat Rao, G.; Subramanyam, R.V.K.; Iyengar, D.S. *Syn. Commun.* **2000**, *30*, 2233.

triphenylphosphine with the chlorine source carbon tetrachloride. The chlorophosphonium ion then reacts with the alcohol to give an alkoxyphosphonium ion. At this stage the reaction mixture contains both chloride and azide nucleophiles but the alkoxyphosphonium ion undergoes an S_N2 reaction with the stronger nucleophilic azide ion to give the alkyl azide. The resulting azide then complexes with the second equivalent of triphenylphosphine to give the primary amine upon addition of water (Scheme 7).

6 SYNTHETIC STUDIES

6.1 Introduction

The primary goal of the project on pavettamine (**1**) (or *enant-1*) is to determine the absolute configuration of the stereogenic centres present in the molecule and to establish a synthetic route for pavettamine (and its stereoisomers) that will provide gram quantities for structure-activity studies. The retrosynthetic analysis of pavettamine as outlined in Chapter 2 identified the C₅ synthon F (where P¹ is benzyl) as a key intermediate that can be derived from (2*S*)-malic acid (Scheme 1). In the synthesis direction the first aim was to develop a protecting group strategy that would allow for the conversion of (2*S*)-malic acid into the synthon F.



Scheme 1: Retrosynthetic analysis of pavettamine **1**.

6.2 Synthesis of the C₅ unit

6.2.1 The lactone approach

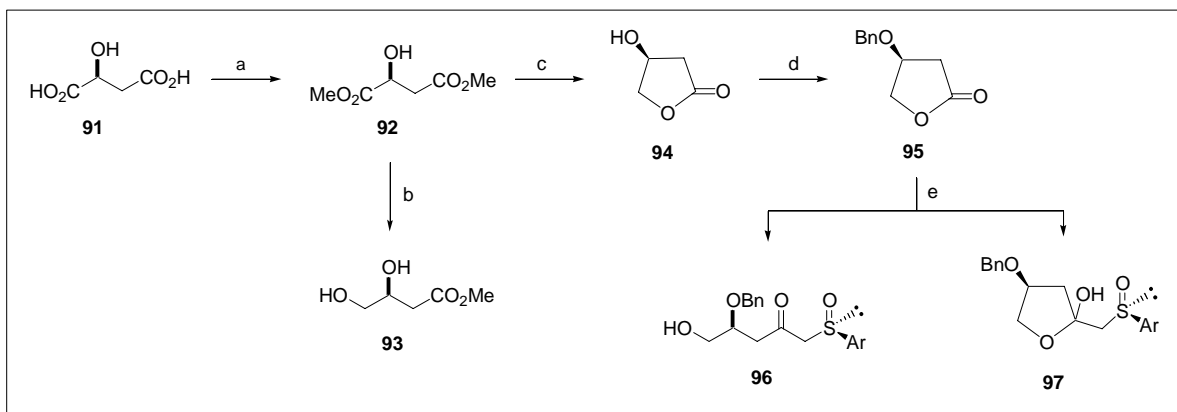
The initial steps of the synthesis are outlined in Scheme 2. (2*S*)-Malic acid **91** was converted to the dimethyl ester **92** in 72% yield by Fischer esterification using SOCl₂ and methanol.^{1,2} The regioselective reduction of the C(1) ester functionality to the diol **93** was achieved using borane-dimethyl sulfide complex (BMS) and a catalytic quantity of NaBH₄ following the protocol as described by Saito *et al.*³ The BMS was added to a solution of the diester **92** of THF. When the evolution of hydrogen ceased a catalytic quantity (5 mol%) of NaBH₄ was added to the cooled (<10°C) solution, 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 C(1) carbonyl group. Reduction commences only upon addition of the NaBH₄ with the formation of BH₃. The first catalytic cycle is

¹ Ianni, J.D.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 1675.

² Adkins, H.; Billica, H.R. *J. Am. Chem. Soc.* **1948**, *70*, 3121.

³ Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

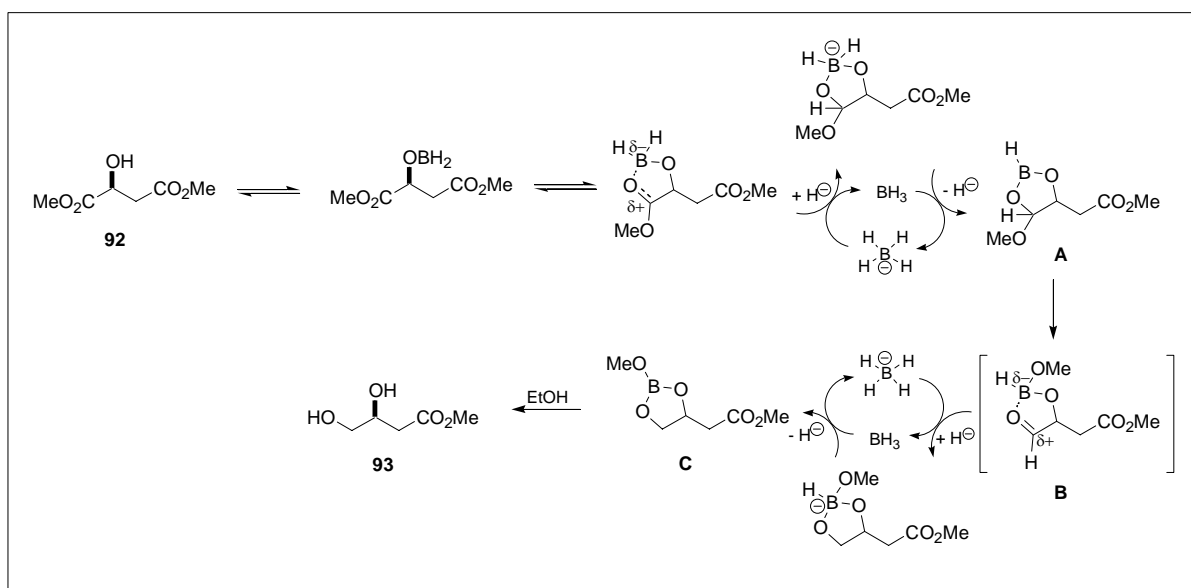
completed when the BH_3 abstracts an H^- from the tetracoordinated boron complex and regenerates the BH_4^- with the formation of the dioxyborane **A** (Scheme 3).



Scheme 2: Synthesis of the C_5 synthon: lactone approach.

Reagents: a) SOCl_2 , MeOH (72%); b) i. $\text{BH}_3 \cdot \text{Me}_2\text{S}$, NaBH_4 (5 mol%), ii. TsOH (5 mole%) (72%); c) i. $\text{BH}_3 \cdot \text{Me}_2\text{S}$, NaBH_4 (5 mol%), ii. TsOH (excess) (72%); d) TMS-OTf, benzyl trichloroacetimidate (70%); e) LDA, (+)-(*R*)-methyl *p*-tolylsulfonide, THF, -78°C .

The rearrangement of the dioxyborane through loss of methoxide and immediate transfer to the boron atom results in the formation of the activated transient aldehyde **B**. A second catalytic NaBH_4 - BH_3 cycle results in the formation of the reduced borate **C** which on work-up by addition of ethanol is converted to the diol **93** (Scheme 3).



Scheme 3: Mechanism for the reduction of dimethyl malate **92** according to Saito.³

The amount of TsOH added during the work-up procedure is of crucial importance to the outcome of the reaction. The use of ≤ 5 mol% of TsOH results in the formation of the diol **93** whereas an excess of TsOH (>5 mol%) leads to the formation of the lactone **94** as the only product. The two compounds can be readily distinguished by their NMR spectra. The ^1H and ^{13}C spectra of the diol **93** showed the signals of the methyl ester functional group at δ_{H} 3.640, and δ_{C} 172.74S and 51.76Q, respectively. The signals of the C(2) and C(4) methylene carbons appeared at δ_{C} 37.62T and 65.62T, respectively and C(3) at δ_{C} 68.57D. The signal of the lactone carbonyl group of the lactone **94** appeared at 177.32S and those of the methylene carbons at δ_{C} 37.60T [C(2)] and 76.33T [C(4)]. The signal for C(3) appeared at δ_{C} 67.17D.

It was envisaged that both the diol **93** and the lactone **94** could be converted to a common intermediate along the synthetic route. The route from the (3*S*)-3-hydroxybutanolide **94** required the protection of the hydroxy group as the benzyl ether. Unfortunately the usual basic conditions using NaH and benzyl bromide for the preparation of benzyl ethers were not suitable for the base-sensitive lactone **94** and alternative methods were investigated. The use of freshly prepared Ag_2O and benzyl bromide yielded the benzyl ether in an unsatisfactory low yield (20%).⁴ However, the protection was effected in good yield (70%) by treating a mixture of the precursor **94** and freshly prepared benzyl trichloroacetimidate, prepared by the procedure developed by Hans-Peter *et al.*⁵ with a catalytic amount of TMS-OTf⁶ to afford the benzyl ether **95**.⁷ The methylene protons of the benzyl group appeared as an AB-spin system with J 11.7 Hz at δ_{H} 4.495 and 4.519. The corresponding signal in the ^{13}C NMR spectrum appeared at δ 71.12T.

The lactone function in **95** was expected to lead to the formation of the β -ketosulfoxide **96** using 2 equivalents of the anion formed from (*R*)-methyl *p*-tolylsulfoxide **40** and LDA at -78°C . The subsequent reaction of the anion with the lactone **94** was carried out at -40°C and gave the unexpected product **97** in 60% yield. The structure was evident from the ^{13}C NMR spectrum which lacked a signal for the carbonyl carbon atom but showed a signal for a quaternary carbon at δ_{C} 105.28.

⁴ Tanabe, M.; Peters, R.H. *Org. Synth.* **1990**, Coll.7, 386.

⁵ Hans-Peter W.; Tommy I.; David, R.B. *J Chem. Soc., Perkin Trans. I* **1985**, 2247.

⁶ Demuth, M.; Mikhail, G. *Chem. Commun.* 1982, 827.

⁷ Xuesong C.; Yu-Lin, W.; Dihua C. *Tetrahedron Lett.* **2002**, 43, 3529.

Attempts to convert the lactone **94** to the diol ester **93** were unsuccessful: both acid-catalysed ring-opening of **94** in refluxing MeOH with TsOH gave starting material after work-up and base-catalysed ring opening using NaOMe in MeOH afforded some starting material together with decomposition products. As a consequence the lactone approach was abandoned and attention shifted to the use of the open-chain diol ester **93** in the synthetic route.

6.2.2 Synthesis of the C₅ synthon: the open-chain ester approach

The C₅ synthon F (where P¹ is benzyl) (Scheme 1) was identified as a key intermediate in the synthetic sequence identified by retrosynthetic analysis. The preference for the benzyl protecting group is due to the ease and versatility with which the benzyl ether can be formed and cleaved as well as its stability under a variety of reaction conditions. Thus the benzyl ether can be formed under basic, acidic or neutral reaction conditions depending on the sensitivity of the substrate. Furthermore it can be prepared by regioselective ring opening of benzylidene protecting groups using various reagents. Cleavage of the benzyl ether protecting group in the final stages of the synthetic route is envisaged to occur by catalytic hydrogenation using Pd/C⁸ as pavettamine is acid- and base-sensitive. Various routes by which the benzyl groups could be introduced and the timing of their introduction were investigated.

6.2.2.1 Route 1: Benzylidene protecting group

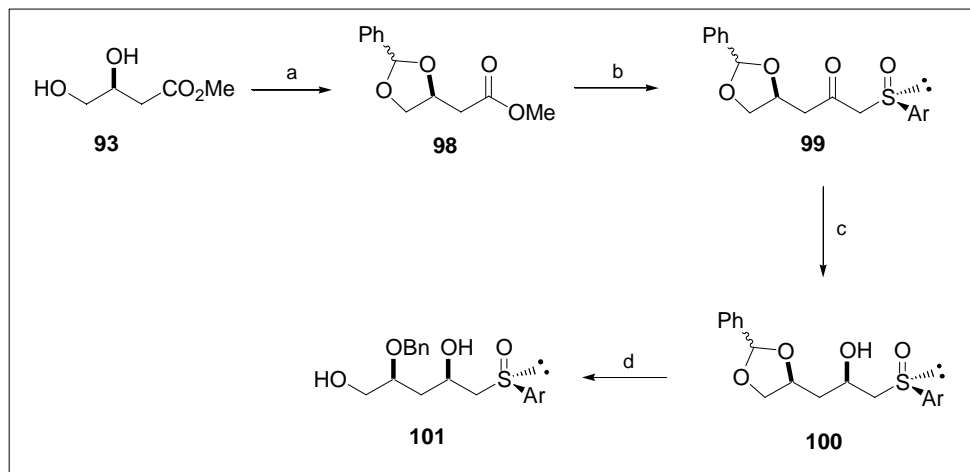
The synthetic strategy of this approach involves the protection of the 3,4-diol of **93** as the benzylidene derivative and the regioselective opening of the dioxolane ring to give a primary hydroxy group and a secondary *O*-benzyl group at a later stage in the synthetic route (Scheme 4).

The 3,4-diol **93** was protected as the benzylidene by reaction with α,α -dimethoxytoluene under acid catalysis using TsOH to give the benzylidene **98** in 64% yield as a 4:3 diastereomeric mixture. The signals at δ_C 104.12D (major) and 103.21D (minor) in the ¹³C NMR spectrum and at δ_H δ 5.925 (major) and 5.785 (minor) in the ¹H NMR spectrum are characteristic signals of the dioxolane ring. The difference in diastereomeric ratio is caused

⁸ Wilson, T.M.; Kocienski, P.J.; Jarowicki, K.; Isaac, K.; Hitchcock, P.M.; Faller, A.; Campbell, S.F. *Tetrahedron* **1990**, *46*, 1767

by the presence of the C(3) stereogenic centre that favours the *S* configuration at the newly-formed acetal stereogenic center due to steric effects.

The ester function of **98** was used in the preparation of the β -ketosulfoxide **99** using 2 equivalents of the anion formed from (*R*)-methyl *p*-tolylsulfoxide **40** and LDA at -78°C .



Scheme 4: Synthesis of the C₅ synthon: Use of the benzylidene protecting group.

Reagents: a) α,α -dimethoxytoluene, TsOH, CH_2Cl_2 (64%); b) LDA, (+)-(*R*)-methyl *p*-tolylsulfoxide, THF, -78°C (70%); c) DIBALH, ZnBr_2 , THF, -78°C (70%); d) DIBALH or $\text{BH}_3\cdot\text{Me}_2\text{NH}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , -40°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 **40**. The β -ketosulfoxide **99** was present as a 4:3 diastereomeric mixture as was evident from the signals for the benzylidene acetal carbon atoms at δ_{C} 103.89D (major) and 103.13D (minor) in the ^{13}C NMR spectrum. The C(1) methylene protons that arose from the formation of the new C-C bond for the major diastereomer appeared as a two-proton singlet at δ_{H} 3.798 and for the minor diastereomer as an AB spin system at δ_{H} 3.839 (d) and 3.802 (d) with J 13.2 Hz.

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 3).^{9,10} The reduction of β -ketosulfoxide **99** using DIBALH/ZnBr₂¹¹, proceeded stereoselectively to give the desired 2,4-*syn* β -hydroxysulfoxide **100** as a 3:2 diastereomeric mixture due to the presence of the benzylidene acetal stereogenic centre. The C(1) methylene protons appeared as part of an ABX spin system at δ_{H} 3.068 (dd, $J_{1a,1b}$ 13.2, $J_{1b,2}$ 8.0 Hz) and 2.874 (dd, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.6 Hz) for the minor diastereomer and at δ_{H} 3.053 (dd, $J_{1a,1b}$ 13.2, $J_{1b,2}$ 8.2 Hz) and 2.862 (dd, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.4) for the major diastereomer. The ABX spin system observed in the ¹H NMR spectrum are typical of the C(1) methylene protons of (S(R),2R)- β -hydroxysulfoxides.^{12,13,14} The ¹³C and ¹H NMR spectrum gave no evidence for the presence of the 2,4-*anti* β -hydroxysulfoxide diastereomers and this indicated that the reaction proceeded in >99:1 diastereoselectivity.

Selective protection of a secondary hydroxy group as the benzyl ether in the presence of a primary hydroxy group in a 1,2-diol system can be achieved through conversion of the 1,2-diol to the benzylidene derivative followed by reductive ring opening using DIBALH¹⁵ (see Chapter 3). However, the regioselective reductive ring opening of the benzylidene acetal **100** using DIBALH failed and decomposition occurred. It is believed that both elimination of water from the β -hydroxysulfoxide and concurrent reduction of the sulfoxide moiety occurs but no single product could be isolated from the reaction mixture. An alternative method for the reductive ring opening reaction involves the treatment of **100** in dichloromethane at -40°C with BH₃.Me₂NH followed by BF₃.Et₂O¹⁶ but these conditions also resulted in extensive decomposition of the starting material. It is therefore apparent that the presence of the sulfoxide moiety is incompatible with the conditions required for the reductive ring opening.

It is evident that the reductive ring opening of the benzylidene acetal must be carried out after the removal of the sulfoxide chiral auxiliary. A synthetic route based on this concept is outlined in Scheme 5. The Pummerer rearrangement^{17,18} of **100** using Ac₂O and NaOAc

⁹ Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982**, 23, 5047.

¹⁰ Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, 50, 1552.

¹¹ Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, 26, 435.

¹² Solladié, G.; Chu, G-H. *Tetrahedron Lett.* **1996**, 37, 114.

¹³ Solladié, G.; Fernandez, I.; Maestro, C. *Tetrahedron Lett.* **1991**, 32, 509.

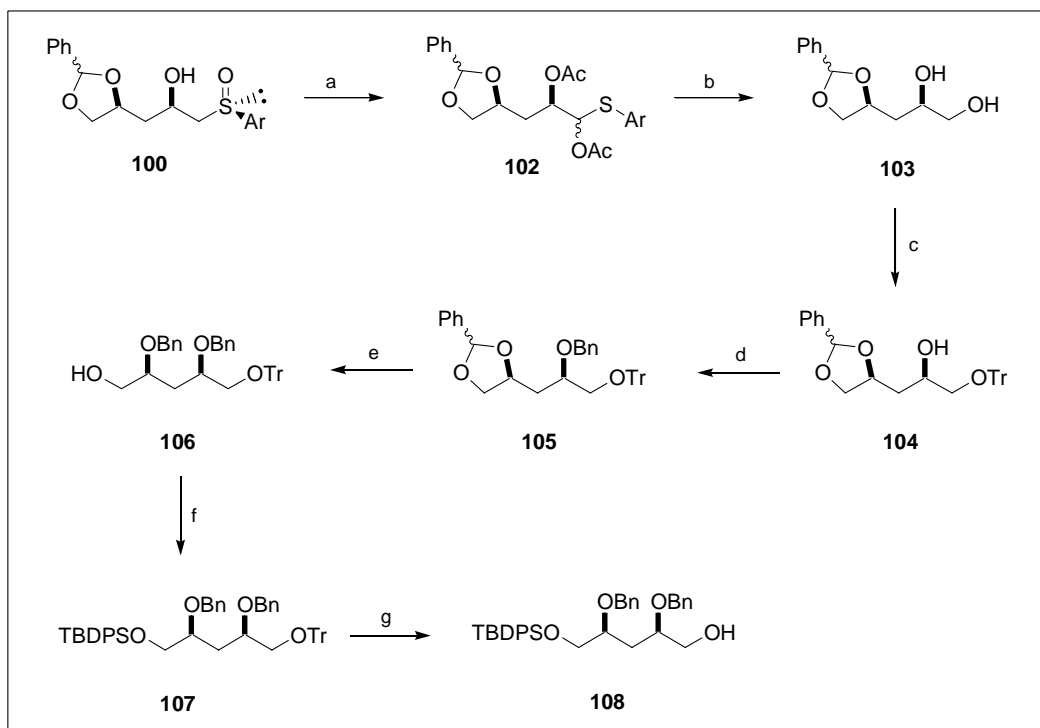
¹⁴ Khiar, N.; Singh, K.; Garcá, M.; Martín-Lomas, M. *Tetrahedron Lett.* **1999**, 40, 5779.

¹⁵ Bhattacharjee, S.S.; Gorin, P.A. *Can. J. Chem.* **1969**, 47, 1195.

¹⁶ Koichi, F.; Yoshiyuki, F.; Masato, O.; Wen-Chi, L.; Yasuo, S.; Shoichi, K. *Tetrahedron*, **1998**, 54, 4033.

¹⁷ Pummerer, R. *Ber.* **1909**, 42, 2275 and 2282.

results in the formation of the *O*-acetyl-*S*-tolyl acetal **102** as a mixture of two diastereomers which on LiAlH₄ reduction forms the 1,2-diol **103**. Selective protection of the primary hydroxy group as the *O*-trityl ether **104** followed by conversion of the secondary hydroxy group as the *O*-benzyl ether gives the fully protected C₅ unit **105**. Regioselective reductive cleavage of the benzylidene moiety in **105** with BH₃.Me₂NH-BF₃.Et₂O now results in the formation of the primary alcohol **106** which is protected as the



Scheme 5: Proposed synthetic route for the formation of the C₅ synthon **108** from the β-hydroxysulfoxide **100**.

Reagents: a) Ac₂O, NaOAc; b) LiAlH₄; c) TrCl, pyridine; d) NaH, PhCH₂Br; e) BH₃.Me₂NH, BF₃.Et₂O, -40°C; f) TBDPSCl, DMAP, CH₂Cl₂; g) aqueous MeOH, TsOH.

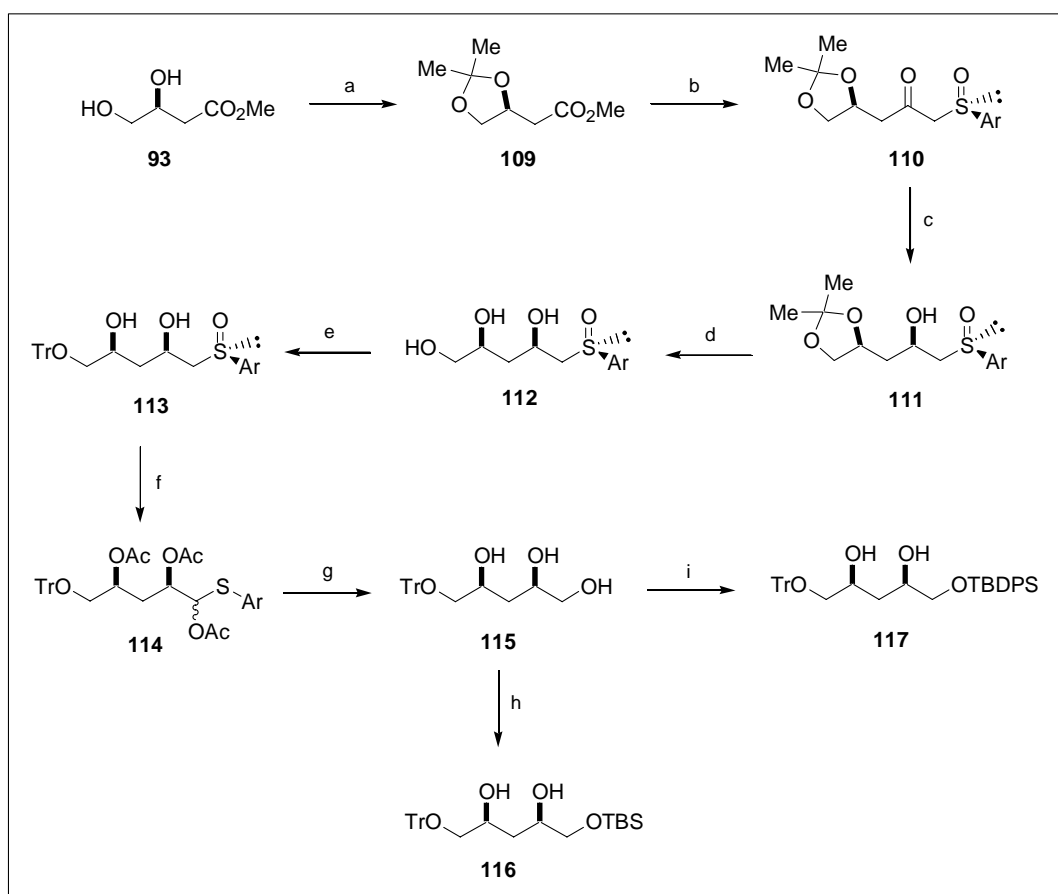
TBDPS ether **107**. Removal of the trityl protecting group using TsOH in aqueous methanol results in the formation of the primary alcohol **108**, a C₅ synthon. Time constraints and lack of material did not allow for the investigation of the proposed route.

6.2.2.2 Route 2: Acetonide and trityl protecting groups

The synthetic route for this approach is outlined in Scheme 6 and was initiated by treating the 3,4-diol **93** with 2,2-dimethoxypropane under acid catalysis using TsOH to afford the

¹⁸ Horner, L. *Liebigs Ann.* **1959**, *19*, 626.

acetonide derivative **109** in 82% yield. The ^{13}C NMR spectrum of the acetonide **109** showed a signal at δ 109.17S, characteristic of the C(2) quaternary carbon atom of the dioxolane ring. The ester functionality of **109** was used in the preparation of the β -ketosulfoxide **110** using 2 equivalents of the anion formed from (*R*)-methyl *p*-tolylsulfoxide **40** and LDA at -78°C . The β -ketosulfoxide **110** showed a carbonyl absorption band at 1720 cm^{-1} in the IR spectrum and a signal at δ 199.35S in the ^{13}C NMR spectrum, characteristic of the carbonyl group of β -ketosulfoxides. The protons of the newly-formed methylene group, C(1), appeared as a singlet at δ_{H} 3.805 whereas the C(3) protons are part of an ABX spin system and appeared at 2.888 (dd, $J_{3\text{a},3\text{b}}$ 17.1, $J_{3\text{b},4}$ 6.3 Hz) and 2.574 (dd, $J_{3\text{a},3\text{b}}$ 17.1, $J_{3\text{a},4}$ 6.5 Hz).



Scheme 6: Synthesis of the C₅ unit: use of the acetonide protecting group.

Reagents: a) 2,2-Dimethoxypropane, TsOH (82%); b) LDA, (+)-(*R*)-methyl *p*-tolylsulfoxide, -78°C (70%); c) DIBALH, ZnBr_2 , THF, -78°C (100%); d) aqueous MeOH, TsOH (85%); e) TrCl, DMAP, pyridine (80%); f) Ac_2O , NaOAc (86%); g) LiAlH_4 , Et_2O (83%); h) TBSCl, DMAP, CH_2Cl_2 (84%); i) TBDPSCl, DMAP, CH_2Cl_2 (87%).

The reduction of β -ketosulfoxides is under the control of the chiral sulfoxide auxiliary and the stereoselectivity is determined by the presence or absence of a Lewis acid, ZnX_2 . The reduction of the β -ketosulfoxide **110** with DIBALH/ $ZnBr_2$ gave the 2,4-*syn* diol **111** in >98:2 d.r. The C(1) methylene protons form part of an ABX spin system and appeared at δ_H 3.035 (dd, J 13.2 and 7.8 Hz) and 2.822 (dd, J 13.2 and 3.9 Hz), typical of (*S*(*R*),2*R*) β -hydroxysulfoxides.^{12,13,14}

At this stage of the synthesis the protective group strategy required differentiation between the primary and secondary hydroxy groups present in the C₅ unit as the primary alcohol would at the completion of the synthesis of pavettamine be converted to an amino group. The acetonide protective group was therefore removed by acid catalysis using TsOH in aqueous MeOH to give the water-soluble triol **112** that was isolated by continuous extraction with EtOAc. The primary hydroxy group of the triol **112** was selectively protected as the trityl ether **113**. The signal at δ_C 86.75S in the ¹³C NMR spectrum is assigned to the quaternary carbon of the trityl group bonded to an oxygen atom.

The role of the chiral sulfoxide auxiliary in **113** is done at this stage. The Pummerer rearrangement^{17,18} of the sulfoxide group using Ac₂O and NaOAc at 130–140 °C results in the transfer of chirality from the sulfur stereogenic centre to the C(1) carbon atom and gave rise to the formation of the *O,S*-acetal **114** as a *ca.* 1:1 diastereomeric mixture as was evident from the two sets of signals in both the ¹H and ¹³C NMR spectra. The C(1) acetal proton of the two diastereomers appeared in each case as a doublet at δ_H 6.141 (J 3.6 Hz) and 6.132 (J 6.0 Hz). The corresponding signals for the acetal carbon signals appeared at δ_C 81.96D and 81.32D, respectively.

The reduction of the *O,S*-acetal **114** using LiAlH₄ in diethyl ether afforded the triol **115** in 83% yield. The signals for the protons of the newly-formed methylene group appeared at δ_H 3.566 (dd, $J_{1a,1b}$ 11.2, $J_{1b,2}$ 3.5 Hz) and 3.437 (dd, $J_{1a,1b}$ 11.2, $J_{1a,2}$ 6.0 Hz) in the ¹H NMR spectrum and the carbon signal at δ_C 66.53T. At this stage of the synthesis the protection of the two secondary alcohols as the *O*-benzyl ethers is the next step in the protecting group strategy. However, the presence of a free primary hydroxy group does not allow for the selective protection of the secondary hydroxy groups. It is therefore necessary to protect the primary alcohol prior to the benzylation of the secondary hydroxy groups

with a protecting group that is orthogonal¹⁹ to both the trityl and benzyl groups *i.e.* this protecting group can be selectively deprotected in the presence of the benzyl and trityl protecting groups at a later stage. Thus the triol **115** was treated with TBS-chloride and DMAP in dichloromethane to give the *O*-TBS derivative **116** in 95% yield. The signals at δ_C 26.87Q, 18.27S and -5.40Q are characteristic of the TBS group. The TBS protecting group can be cleaved with tetrabutylammonium fluoride (TBAF), conditions that do not affect the benzyl and trityl ethers. The attempt to protect both secondary hydroxy groups in **116** as the benzyl ethers using NaH and freshly distilled BnBr failed and a mixture of two compounds was obtained. Benzylation of the secondary hydroxy group did take place but at the same time migration of the TBS group to the secondary hydroxyl group occurred and benzylation of the primary hydroxyl group followed.

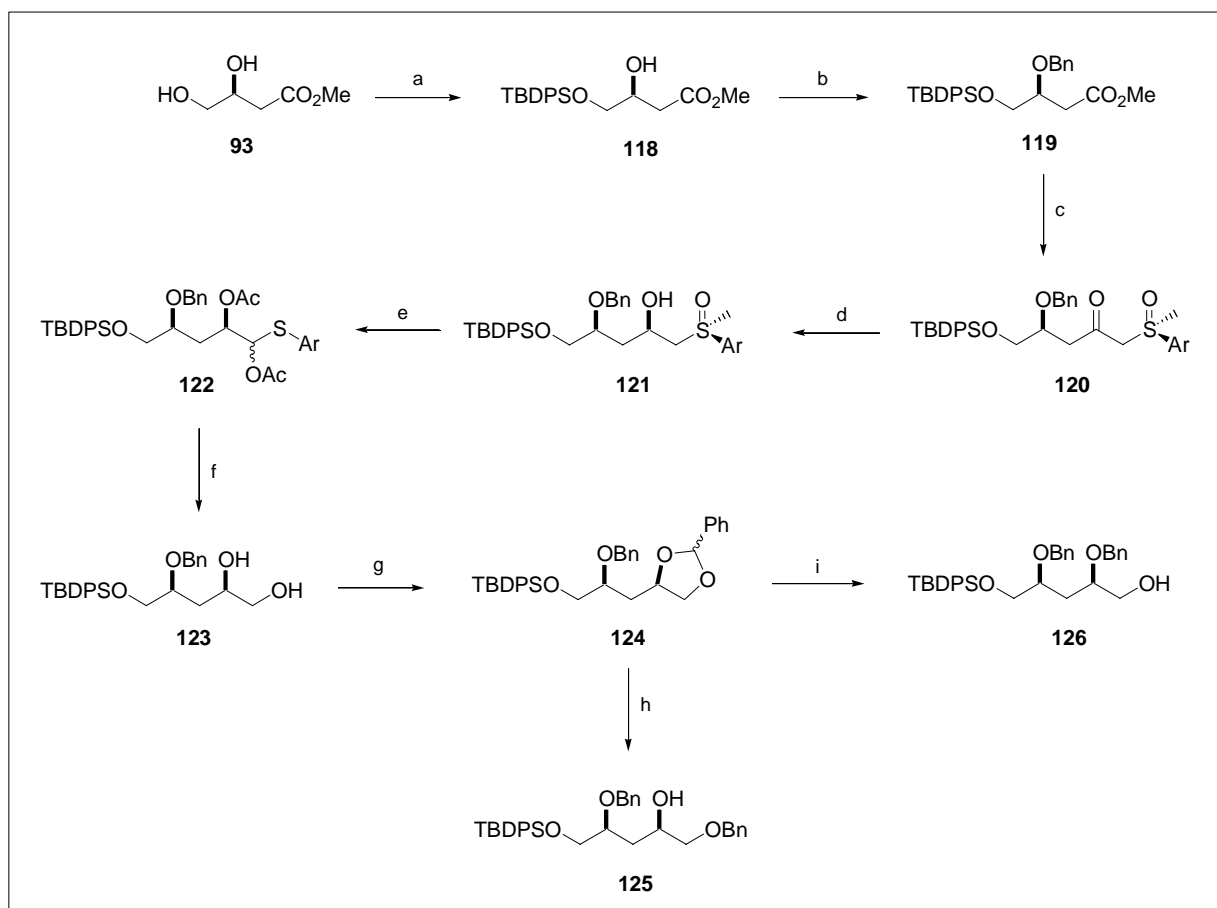
In order to circumvent the migration of the TBS protecting group it was decided to use the TBDPS protecting group as this group is less likely to migrate under the reaction conditions employed in the benzylation reaction. The triol **115** was therefore treated with TBDPSCI and imidazole to give the TBDPS ether **117**. The signals at δ_C 26.86Q and 19.22S in the ¹³C spectrum and at δ_H 1.056 (s, 9H, CMe₃) are typical of the *t*-butyl group of the TBDPS ether. Benzylation of the TBDPS derivative **117** using NaH and benzyl bromide in THF failed and only starting material was recovered. The same reaction under neutral conditions using Ag₂O and benzyl bromide also returned only starting material. The use of an acid-catalysed benzylation reaction was excluded by the presence of the acid-sensitive trityl group. The lack of reactivity in the benzylation reaction of **117** is ascribed to the presence of the trityl and TBDPS protecting groups. Nucleophilic attack by the formed alkoxide anion on the benzyl bromide electrophile is prevented by steric crowding caused by the bulky trityl and TBDPS groups.

The problems encountered in the last steps of this synthetic route and especially the benzylation step led to the decision to concentrate on an alternative approach for the synthesis of the C₅ synthon.

6.2.2.3 Route 3: TBDPS protecting group

¹⁹ Kocienski, P.J. *Protecting groups*, Georg Thieme Verlag, Stuttgart, New York, **1994**.

The third approach to the synthesis of the key C₅ intermediate synthon F, is outlined in Scheme 7 and starts once again from the diol **93**. Selective protection of the primary hydroxy group of **93** using TBDPSCl in the presence of imidazole gave the TBDPS ether **118** in 85% yield. The signals for the *t*-butyl substituent of the TBDPS group appeared at δ_{H} 1.063 (s) and at δ_{C} 26.82Q and 19.22S. The steric bulk of the TBDPS group, introduced by Hanessian as a protecting group for the hydroxy function,²⁰ ensures that the rate of



Scheme 7: Synthesis of C₅ unit: use of the TBDPS protecting group.

Reagents: a) TBDPSCl, DMAP, CH₂Cl₂ (85%); b) TMS-OTf, benzyl trichloroacetimidate (74%); c) LDA, (+)-(R)-methyl *p*-tolylsulfoxide, THF, -40°C (80%); d) DIBALH, ZnBr₂, THF, -78°C (80%); e) Ac₂O, NaOAc (85%); f) LiAlH₄, Et₂O (83%); g) α,α -dimethoxytoluene, TsOH (70%); h) DIBALH (50%); i) BH₃.Me₂NH, BF₃.Et₂O, -40°C (60%).

reaction of TBDPSCl is much greater with primary hydroxy groups than with secondary ones. In addition the TBDPS group is more stable toward acid hydrolysis and hydrogenolysis than the TBS group. Cleavage of the *O*-TBDPS group occurs by treatment

²⁰ Hanessian, S.; Lavallo, P. *Can. J. Chem.* **1975**, *53*, 2975.

with tetrabutylammonium fluoride²¹ (TBAF) in THF at room temperature, conditions that do not affect the benzyl group.

Benylation of the secondary hydroxy group in **118** was affected by treatment of the substrate with freshly prepared benzyl trichloroacetimidate and TMS-OTf⁶ in cyclohexane-dichloromethane (2:1) solution to give the benzyl ether **119**. The benzylic protons appeared as an AB spin system at 4.616 (d) and 4.561 (d) with J 11.6 Hz and the corresponding carbon atom at δ_C 72.42T.

The formation of the β -ketosulfoxide **120** proceeded in a good yield (80%) when the *O*-benzyl protected ester **119** was reacted with the anion formed from (+)-(*R*)-methyl *p*-tolylsulfoxide **40** with LDA. The formation of the anion and the addition of the ester **119** were done at -78°C . The temperature was then allowed to rise to -40°C in order for the C–C bond forming reaction to occur. The β -ketosulfoxide **120** showed a carbonyl absorption band at 1714 cm^{-1} in the IR spectrum and a signal at δ_C 200.18S in the ^{13}C NMR spectrum typical of the carbonyl carbon of β -ketosulfoxides. The protons of the newly-formed methylene group, C(1) appeared at δ_H 3.854 (d, $J_{1a,1b}$ 13.7 Hz) and 3.733 (d, $J_{1a,1b}$ 13.7 Hz). The C(3) protons form part of an ABX spin system at δ_H 2.821 (dd, $J_{3a,3b}$ 16.5, $J_{3b,4}$ 7.9 Hz) and 2.683 (dd, $J_{3a,3b}$ 16.5, $J_{3a,4}$ 4.4 Hz).

The reduction of the β -ketosulfoxide **120** with DIBALH/ZnBr₂ proceeded stereoselectively (see Chapter 3) to give the *syn* 2,4-diol **121** in >98:2 d.r. The absence of the carbonyl signal in the ^{13}C NMR spectrum and the presence of an ABX spin system with the AB-part at δ_H 3.013 (dd, 1H, $J_{1b,1a}$ 13.1, $J_{1b,2}$ 8.1 Hz) and 2.698 (dd, 1H, $J_{1a,1b}$ 13.1, $J_{1a,2}$ 3.7 Hz) assigned to the C(1) protons are indicative of the formation of the β -hydroxysulfoxide **121**. The signals for the C(3) protons now formed part of an ABXY spin system and appeared at δ_H 1.879 (ddd, $J_{3a,3b}$ 14.5, $J_{3b,2}$ 7.5, $J_{3b,4}$ 7.5 Hz) and 1.840 (ddd, $J_{3a,3b}$ 14.5, $J_{3a,2}$ 4.9, $J_{3a,4}$ 4.9 Hz). The proton of the new stereogenic centre, C(2) is a complex multiplet at δ_H 4.246 (m, $J_{2,1a}$ 3.7, $J_{2,1b}$ 8.1, $J_{2,3a}$ 4.9, $J_{2,3b}$ 7.5, H-2).

At this stage of the synthesis the role of the chiral sulfoxide auxiliary in controlling the

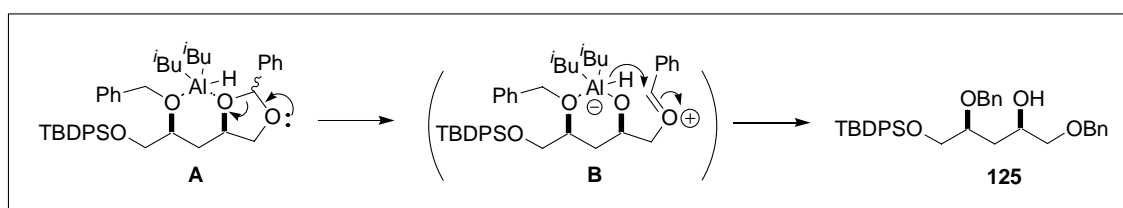
²¹ Paquette, L.A.; Doherty, A.M.; Rayner, C.M. *J. Am. Chem. Soc.* **1992**, *114*, 3910.

stereochemistry of the C(2) stereogenic centre during DIBALH/ZnBr₂ reduction has been concluded and it now only remained to convert the chiral sulfoxide functional group in **121** into a primary hydroxy group. This conversion was achieved in a two-step process. In the first step a Pummerer rearrangement of the sulfoxide group using Ac₂O and NaOAc at 130-140°C gave the *O,S*-acetal **122** as a 4:3 diastereomeric mixture due to the influence of the C(2) stereogenic centre. The C(1) acetal proton of the two diastereomers appeared in each case as a doublet at δ_{H} 6.175 (J 3.6 Hz) and δ_{H} 6.117 (J 5.7 Hz), respectively. The signals of the corresponding carbon atoms appeared at δ_{C} 82.60D and 81.40D, respectively in the ¹³C NMR spectrum. The second step of the conversion was the LiAlH₄ reduction of the *O,S*-acetal **122** in diethyl ether to give the diol **123** in 83% yield. The signals at δ_{H} 3.534 (dd, $J_{1a,1b}$ 11.1, $J_{1b,2}$ 3.6 Hz) and 3.419 (dd, $J_{1a,1b}$ 11.1, $J_{1a,2}$ 6.2 Hz) were assigned to the methylene protons of the primary alcohol group.

The acid-catalysed (*p*-TsOH) acetalisation of the diol **123** with α,α -dimethoxytoluene gave the benzylidene derivative **124** in 70% yield. The formation of two diastereomers in a 4:3 d.r., due to the generation of the new stereogenic center at the acetal carbon atom, was evident from both the ¹H and ¹³C NMR as two sets of signals could be discerned in each case. The acetal proton of the two diastereomers appeared in each case as singlets at δ_{H} 5.752 and 5.903 and the corresponding signal of the acetal carbon atom at δ_{C} 103.20D and 103.03D.

At this stage of the synthesis regioselective ring opening of the benzylidene acetal to give a benzyl protected secondary alcohol and free hydroxy group at the primary position was required. There are several reagents that can affect such a regioselective ring opening (Chapter 4). In the first attempt DIBALH was used to affect the reductive ring opening. The ¹H NMR spectrum of the formed product **125** (50% yield) showed the presence of two benzyl groups: a singlet at δ_{H} 4.541 (2H) and an AB spin-system at δ_{H} 4.696 (d) and 4.484 (d) with J 11.4 Hz. A doublet signal at δ_{H} 3.231 (J 2.3 Hz) that disappeared on addition of D₂O to the sample, gave the first indication that reductive ring opening had placed the benzyl group on the primary hydroxy group as shown in structure **125**. This was confirmed by the two-bond deuterium isotope shift ($\Delta\delta = \delta(\text{D}_2\text{O}) - \delta(\text{H}_2\text{O})$) of -0.12 ppm observed for the signal at δ_{C} 69.25D in the ¹³C NMR spectrum upon addition of a mixture of H₂O-D₂O

(1:2) to the sample.^{22,23} A plausible proposal for the observed regioselectivity of the ring opening (see Scheme 8) is that the C(4) oxygen atom directs the Lewis acid (DIBALH) to complex with the C(2) oxygen to form a six-membered cyclic structure **A**. Cleavage of the C(2)–O(3) acetal bond of the dioxolane ring leads to the formation of an oxonium intermediate **B** which undergoes intramolecular hydride reduction to give **125** the benzyl ether of the primary hydroxy group.



Scheme 8: Proposed mechanism for the reductive ring opening of the benzylidene acetal **124** using DIBALH

However, treatment of the benzylidene **124** with $\text{BH}_3 \cdot \text{Me}_2\text{NH}$ in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane at -40°C gave the desired *O*-benzyl regioisomer **126**. The ^1H NMR spectrum showed the signals of two benzyl groups as two AB spin systems at δ_{H} 4.454 (d) and 4.640 (d) with J 11.5 Hz and at δ_{H} 4.485 (d) and 4.560 (d) with J 11.7 Hz, respectively. A broad triplet at δ_{H} 2.19 ($J_{1,\text{OH}}$ 5.7 Hz) confirmed that a primary hydroxyl group had been formed in the reductive ring opening. The observed regioselectivity is due to the preference of the Lewis acid, BH_3 to complex with O(1) and subsequent cleavage of the C(2)–O(1) acetal bond of the dioxolane ring to give an oxonium ion which is reduced by intramolecular hydride delivery to give **126**.

In conclusion the approach described for Route 3 as outlined above successfully delivered the required C_5 alcohol **126** in 11 steps from commercially available (2*S*)-malic acid and an overall yield of 6.2%.

6.3 Linkage of two C_5 units

The synthetic route to pavettamine, identified by retrosynthetic analysis (Chapter 2), required the linkage of two of the C_5 building blocks **126** by means of an amide bond. The

²² Newmark, R.A.; Hill, J.R. *Org. Magn. Reson.* **1980**, *13*, 40.

²³ De Jesus, A.E.; Steyn, P.S.; van Heerden, F.R.; Vleggaar, R.; Wessels, P.L.; Hull, W.E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847.

formation of the amide bond in turn meant that the C₅ alcohol **126** had to be converted to an amine as well as into a carboxylic acid. Subsequent activation of the carboxylic acid followed by nucleophilic attack by the amine then results in the formation of an amide.

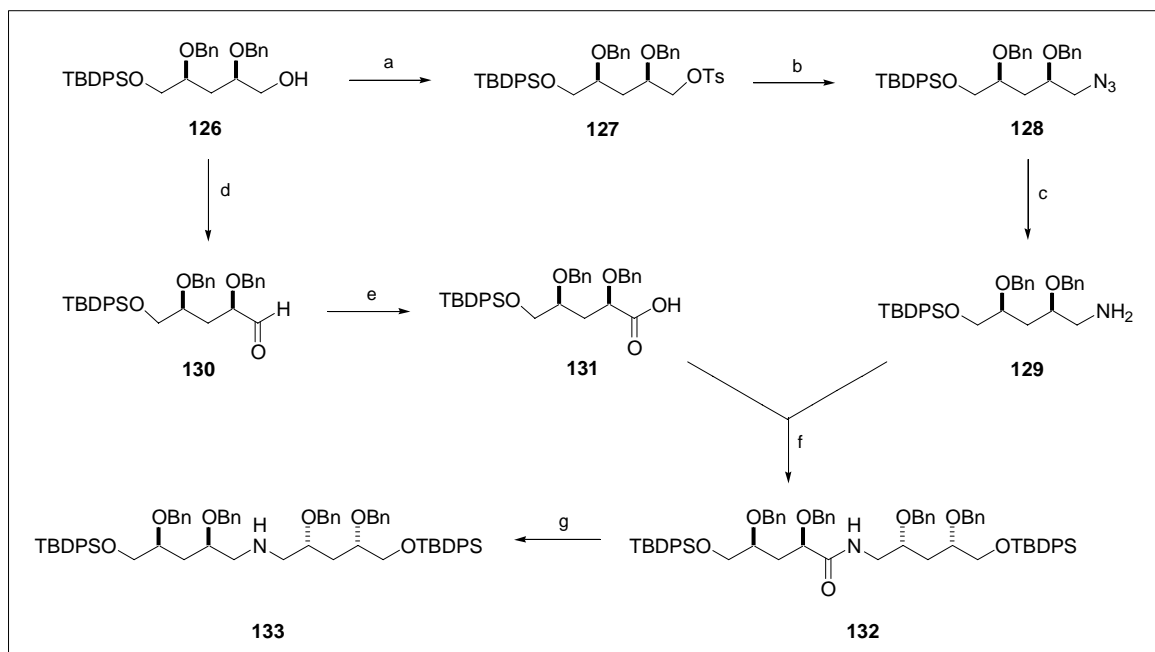
The first steps in this strategy entailed a number of functional group transformations by which the primary hydroxy group of **126** is converted into an amino group. Treatment of the alcohol **126** with *p*-toluenesulfonyl chloride in the presence of DMAP as both a catalyst and an acid scavenger, gave the *O*-tosylate **127** in 90% yield (see Scheme 9). The protons of the C(1) methylene group appeared as two sets of double doublets at δ_{H} 4.352 ($J_{1\text{a},1\text{b}}$ 10.6, $J_{1\text{b},2}$ 3.4 Hz) and 4.269 (dd, $J_{1\text{a},1\text{b}}$ 10.6, $J_{1\text{a},2}$ 6.2 Hz) and the corresponding signal in the ¹³C NMR spectrum at δ_{C} 71.94T. This *O*-tosylate served as the substrate for an S_N2 reaction with NaN₃ to give the azido derivative **128**. The C(1) carbon signal now appeared at δ_{C} 54.02T and the C(1) methylene protons at δ_{H} 3.255 (dd, $J_{1\text{a},1\text{b}}$ 12.9, $J_{1\text{b},2}$ 3.7 Hz) and 3.193 (dd, $J_{1\text{a},1\text{b}}$ 12.9, $J_{1\text{a},2}$ 6.2 Hz). Reduction of the azido group can be carried out by catalytic hydrogenation or by hydride reduction using LiAlH₄. The latter reagent was preferred as the benzyl group is stable under these conditions in contrast to catalytic hydrogenation, which could also result in reductive debenzylation. Thus LiAlH₄ reduction of the azide **128** provided the amine **129**. Both the C(1) protons and carbon atom appeared had moved upfield in their respective NMR spectra: the protons appeared at δ_{H} 2.792 (dd, $J_{1\text{a},1\text{b}}$ 13.3, $J_{1\text{b},2}$ 3.5 Hz) and 2.680 (dd, $J_{1\text{a},1\text{b}}$ 13.3, $J_{1\text{a},2}$ 6.3 Hz) and the C(1) carbon atom at δ_{C} 44.53T.

There are other, more direct methodologies by which the primary alcohol **126** can be converted to the primary amine **129**. Thus the Mitsunobu reaction²⁴ of the alcohol **126** using hydrazoic acid (HN₃) in the presence of triphenylphosphine (Ph₃P) and diethyl azodicarboxylate (DEAD) would lead to the formation of the azide **128**. The inherent dangers associated with the use of hydrazoic acid limits its application even though the number of steps in a synthetic sequence is reduced and the overall yield is much better. Recently a one-pot method of converting a primary alcohol to a primary amine was reported.²⁵ The reaction involves refluxing a solution of the primary alcohol in DMF-CCl₄ (1:4) in the presence of sodium azide (NaN₃) and 2 equivalents of Ph₃P. Two equivalents of Ph₃P are required as one is used to produce the azide and the second to complex with the

²⁴ Mitsunobu, O. *Synthesis* **1981**, 1.

²⁵ Vidya, S.R.G.; Venkat Rao, G.; Subramanyam, R.V.K.; Iyengar, D.S. *Syn. Commun.* **2000**, *30*, 2233,

azide and reduce it to the amine upon addition of water (the Staudinger reaction). Application of this methodology to the primary alcohol **126** resulted in the formation of a 1:1 mixture of the desired amine **129** and the azido derivative **128** in very low overall yield (20%). This methodology is quite fascinating and requires an in-depth investigation.



Scheme 9: Synthesis of the C₁₀ unit: Preparation of the amide **132**.

Reagents: a) *p*-Toluenesulfonyl chloride, DMAP, CH₂Cl₂ (90%); b) NaN₃, DMF (90%); c) LiAlH₄, Et₂O (80%); d) Dess-Martin periodinane (80%); e) H₂O₂, NaClO₂, NaH₂PO₄ buffer, aqueous CH₃CN (80%); f) Carbonyl diimidazole (75%); g) BH₃.SMe₂ (75%).

The primary alcohol **126** was transformed to the acid **131** in a two-step sequence. The first step involved the oxidation of the primary alcohol **126** to the aldehyde **130** in 80% yield using the Dess-Martin periodinane reagent.²⁶ The NMR spectra showed the signals of the aldehyde group at δ_{H} 9.599 (d, $J_{1,2}$ 1.2 Hz) and δ_{C} 202.42D. The C(2) proton signal was simpler than in the case of the starting material and appeared at δ_{H} 3.928 (ddd, $J_{2,1}$ 1.3, $J_{2,3a}$ 4.5, $J_{2,3b}$ 6.2 Hz). Attempts to obtain the aldehyde by Swern oxidation²⁷ of **126** using freshly distilled anhydrous DMSO and oxalyl chloride at -78°C were disappointing and gave only a 20% yield of the aldehyde. The aldehyde **130** was oxidised in an extremely mild and efficient method to the acid **131** in 80% yield using sodium chlorite (NaClO₂) and hydrogen peroxide in a NaH₂PO₄ buffer solution at pH 4.^{28,29} The ¹³C NMR spectrum of

²⁶ Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.

²⁷ Mancuso, A.J.; Huang, S.L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

²⁸ Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994**, *59*, 4749.

the purified sample showed the signal of the newly-formed carboxylic acid group at δ_C 176.26S. The C(2) proton now appeared as a simple double doublet at δ_H 4.130 ($J_{2,3a}$ 5.7 and $J_{2,3b}$ 5.7 Hz).

The availability of the two C₅ building blocks, the carboxylic acid **131** and the amine **129**, meant that the formation of an amide bond could be investigated. The formation of the amide bond entails the nucleophilic attack of the amine on the electrophile, the carbonyl group of an activated carboxylic acid. Treatment of the carboxylic acid **131** with 1,1'-carbonyldiimidazole gave an imidazolide intermediate which acts as the electrophilic reagent. Addition of the amine **129** to the reaction then resulted in the formation of the amide **132** in good yield (75%). The signal of the amide carbonyl carbon atom appeared at δ_C 172.56S and the amide NH at δ_H 6.863 (dd, J 6.2 and 5.2 Hz). The C(2) proton once again appeared as a simple double doublet at δ_H 3.969 ($J_{2,3a}$ 6.5 and $J_{2,3b}$ 5.7 Hz).

The next step in the synthetic route identified by retrosynthetic analysis, is the reduction of the secondary amide functional group to a secondary amine using either LiAlH₄ or BH₃.SMe₂, the two most commonly used reagents for this purpose. The reduction of the amide **132** using LiAlH₄ in toluene at room temperature returned only starting material. When the reaction was done at *ca.* 90°C TLC analysis showed that decomposition occurred. The reduction was also attempted using 2 equivalents of DIBALH but once again only starting material was recovered.

Treatment of a solution of the amide **132** in THF with an excess of BH₃.SMe₂ at 60°C resulted in the formation over a period of 6 h of a single product with R_f 0.80 (hexane-EtOAc, 4:1) on silica gel TLC plates. The ¹H NMR spectrum of the purified reaction product was a complex spectrum not easily analysed as a result of extensive overlap of signals. The ¹³C NMR spectrum clearly showed that the amide functional group had been reduced as no signal for the amide carbonyl carbon atom was observed. However, two sets of signals in a 1:1 ratio were observed for the carbon atoms of the backbone: δ_C 76.19D and 75.35D (C-4), 72.46D and 70.30D (C-2), 65.87T and 65.65T (C-5), 59.89T and 57.78T (C-1), 34.30T and 33.32T (C-3). In addition 4 signals were present for the *O*-benzyl methylene groups at δ_C 72.24T, 71.81T, 71.49T, and 70.36T. In all reported

²⁹ Dalcanale, E.; Montanari, F.; *J. Org. Chem.*, **1986**, *51*, 567.

reductions of amides using borane reagents,³⁰ a complex is formed between borane and the nitrogen of the formed amine. The formation of the amine **133**-borane complex in the present instance results in the creation of a 1:1 diastereomeric mixture as the N atom is now a new stereogenic centre and thus two sets of signals are observed in the ¹³C NMR spectrum. This type of complex is reportedly then decomposed through addition of TMEDA or treatment with 6M HCl. All attempts to isolate the amine from the postulated borane complex failed and either no reaction occurred with TMEDA or decomposition in the case of 6M HCl.

The exact nature of the complex remained unknown and could not be further investigated due to time constraints and lack of material.

6.4 Conclusion and future work

A suitable protective group strategy was developed and an 11 step synthetic route for the C₅ building block **126** was established. This synthetic route provides an efficient methodology toward the synthesis of each of the 10 possible stereoisomers of pavettamine. The successful conversion of the alcohol **126** through functional group transformations provided the amine **129** and the carboxylic acid **131** which were linked to give the target compound, the amide **132**.

However, the problems associated with the reduction of the amide **132** to the amine **133** require further work and must be resolved in order to complete the synthetic route towards pavettamine **1**. The exact nature of the borane complex obtained by reduction of the amide **132** with BH₃.SMe₂ and a method to obtain the free amine from the amine-borane complex is of importance in this regard.

Alternative methods for the preparation of the secondary amine **133** should be investigated. A modified Mitsunobu methodology^{31,32} in which the primary alcohol **126** is directly coupled with either the *N*-Boc or *N*-Tos derivative of the primary amine **129** in the presence of DEAD and triphenylphosphine in THF might circumvent the presently problematic amide reduction step.

³⁰ Brown, H.C.; Choi, Y.M.; Narasimhan, S *J. Org. Chem.* **1982**, *47*, 3153.

³¹ Bach, T.; Kather, K.; Kramer, O. *J. Org. Chem.* **1998**, *63*, 1910.

³² Geo, Y.; Lane-Bell, P.; Vederas, J.C. *J. Org. Chem.* **1998**, *63*, 2133.

7 EXPERIMENTAL

7.1 General

Air and/or moisture sensitive reactions were carried out under an atmosphere of argon in glassware pre-dried at temperatures above 100°C. Room temperature (RT) refers to 18-25°C. Evaporations were done under reduced pressure (*in vacuo*). All reagents were of synthetic grade and were used without any further purification. When necessary, solvent and reagents were dried according to standard methods prior to use.¹ Solvents used for chromatography or extractions were only distilled.

Melting points (mp) were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer 341 polarimeter for solutions in chloroform (CHCl₃). Mass spectra were recorded by Dr. L. Fourie, University of Potchefstroom, on a VG 7070-E spectrometer using the fast atom bombardment technique (FAB) and detection of positive ions with $m/z > 99$. A *m*-nitrobenzyl alcohol matrix was used with xenon as the bombardment gas. IR spectra were recorded on a Perkin-Elmer RX1-FT spectrophotometer for solutions in CH₂Cl₂.

Nuclear magnetic resonance (NMR) spectra were measured for CDCl₃ solutions on a Bruker AMX-300 (7.0T) or DXR-500 (11.7T) spectrometer. All chemical shifts are reported as δ values downfield from Me₄Si using CHCl₃/CDCl₃ as internal standard (δ_{H} 7.24 and δ_{C} 77.00, 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; br: broad signal.

The assignments of the signals in the ¹H NMR spectra are based on first-order analysis of the spin systems and when required were confirmed by two-dimensional (2D) (¹H, ¹H)-homonuclear chemical shift correlation (COSY) experiments. The ¹³C chemical shifts were obtained from proton-decoupled spectra. The multiplicities of the different ¹³C resonances were deduced from the proton-decoupled CH, CH₂, and CH₃ sub-spectra obtained using the DEPT pulse sequence. The signals of the proton-bearing carbon atoms were correlated

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

with specific proton resonances in two-dimensional (2-D) $^{13}\text{C}\{^1\text{H}\}$ heteronuclear chemical shift correlation experiments (HETCOR) 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 by thin-layer chromatography (TLC) using glass or aluminium plates coated with silica gel (60F₂₄₅ 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 (70-230 mesh). 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 or cerium(IV) sulfate-sulfuric acid reagent.

7.2 Preparation of reagents

7.2.1 Spraying reagents

7.2.1.2 Cerium(IV) sulfate–sulfuric acid

A cerium(IV) sulfate–sulfuric acid solution was prepared from cerium(IV) sulfate (1% w/v) dissolved in 3M sulfuric acid. The non-UV active organic compounds were visualized by spraying followed by heating with a heat-gun until the appearance of dark spots as a positive indication of the presence of compounds of interests.

7.2.1.2 Cerium(IV) sulfate– ammonium heptamolybdate

A spray solution containing ammonium heptamolybdate (5%) and cerium(IV) sulfate (0.2%) in 3M sulfuric acid was prepared by heating and continuous stirring. The solution was cooled and filtered. Chromatograms were immersed in the solution and heated with a heat-gun until the appearance of spots as a positive indication of the presence of compounds.

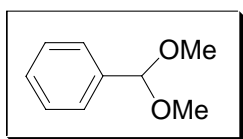
7.2.2 Other reagents

Preparation of benzyl trichloroacetimidate²

A solution of benzyl alcohol (21.8 ml, 210 mmol) in ether (30 ml) was added dropwise to a stirred suspension of sodium hydride (0.50 g, 21.0 mmol) in anhydrous diethyl ether under argon. After 20 min. at RT, the reaction mixture was cooled to 0°C with a salt-ice bath.

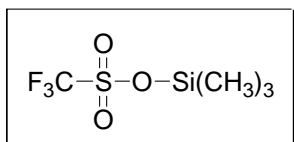
² Wessel, H-P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.

Trichloroacetonitrile (20.0 ml, 200 mmol) was then added dropwise during 15 min and the reaction mixture was allowed to warm to RT over 60 min. The reaction mixture was concentrated to a syrup and pentane (20 ml) containing anhydrous methanol (0.80 ml, 21 mmol) was added followed by vigorous shaking, filtration and concentration of the filtrate and pentane washing (2x20 ml), which gave (25.0 g, 77%) of the imidate as a clear oily brown liquid that was used without further manipulation. The imidate was stored at 5 °C for a period of up to 2 months.



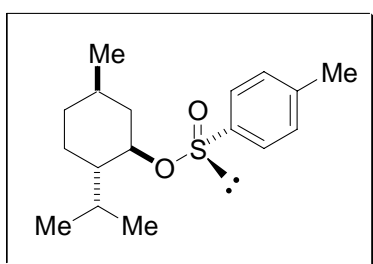
α,α -Dimethoxytoluene

p-Toluenesulfonic acid (1.0 g) was added to a stirred solution of benzaldehyde (106 g, 1.00 mol) and trimethyl orthoformate (116 g, 1.10 mol) in anhydrous methanol (340 ml) and the reaction refluxed for 4 h. The reaction mixture was cooled, then diluted with diethyl ether and washed with a 1:1 KOH (5%):brine solution. The organic layer was dried (Na_2SO_4) and evaporated to afford the acetal product (134.0 g, 88%), which was used without further purification.



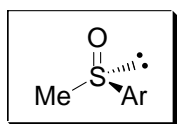
Trimethylsilyl trifluoromethanesulfonate

Trifluoromethanesulfonic acid (1.50 g, 10.0 mmol) and tetramethylsilane (1.10 g, 12.5 mmol) were mixed under an argon atmosphere at room temperature. After 1 h evolution of methane ceased and formation of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) The product was used without further purification.



(1*R*,2*S*,5*R*)-(-)-Menthyl (*S*)-*p*-toluenesulfinate **43^{3,4}**

To a solution of thionyl chloride (100 ml, 1.40 mol) in benzene (300 ml) the powdered sodium salt of anhydrous *p*-toluenesulfinic acid (80.0 g, 0.44 mol) was added in small portions at 0°C. The solution was allowed to reach RT after which the solution was concentrated by distilling benzene and thionyl chloride. Excess thionyl chloride was removed by addition of benzene (200 ml) and evaporation under reduced pressure. The residue was diluted with anhydrous diethyl ether (500 ml) (formation of white precipitate of sodium chloride) and cooled at 0°C. Then a solution of (-)-menthol (69.4 g, 0.44 mol) in pyridine (70 ml) was added dropwise. After the addition was complete the mixture was stirred for 1h at RT and hydrolyzed with water (200 ml). The organic layer was washed with 10% HCl (200 ml) and brine (100 ml), dried over sodium sulfate, and concentrated. The residue was diluted with acetone (200 ml), ~5 drops concentrated HCl was added, and allowed to crystallize at -20°C. After collecting the first crop of crystals, the mother liquor was concentrated to ~50 ml, 1 drop conc. HCl added and again allowed to crystallize at -20°C. This operation was repeated 3-4 times in total. Hexane was used to dilute the increasingly viscous mother liquor to improve crystallization. The combined portions were finally recrystallised from hot acetone to give the pure (*S*)-sulfinate **43** as a white crystalline material (102.5 g, 78%); mp. 106-108°C (Lit.,⁵ 106-107°C), $[\alpha]_D -201$ (*c* 2.0, acetone), (Lit.,⁶ $[\alpha]_D^{21} -201$ (*c* 2.0, acetone)); *R*_f 0.90 (EtOAc).


(*R*)-(+)-Methyl *p*-tolylsulfoxide **40**

A solution of methylmagnesium iodide [prepared from methyl iodide (29.3 g, 206 mmol) and magnesium (4.30 g, 178 mmol) in diethyl ether (180 ml)] was added by cannula to a solution of (-)-menthyl (*S*)-*p*-toluenesulfinate (40.0 g, 136 mmol) in anhydrous benzene (135 ml). The temperature was maintained between 0-10°C during the addition. After the addition the mixture was allowed to stir at RT for 2 h and then hydrolyzed with saturated aqueous ammonium chloride solution (155 ml). The aqueous solution was extracted with

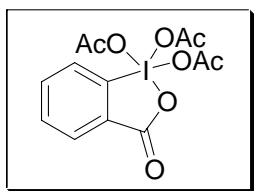
³ Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

⁴ Solladié, G. *Synthesis* **1981**, 185.

⁵ Anderson, K.K.; Gaffield, W.; Papanikolaou, N.E.; Foley, J.W.; Perkins, R.I. *J. Am. Chem. Soc.* **1964**, 86, 5637.

⁶ Anderson, K.K. *Tetrahedron Lett.* **1962**, 3, 93.

diethyl ether (300 ml) and the organic layer washed with saturated brine, dried (Na_2SO_4) and evaporated. The oily residue was mixed with hot hexane until the formation of a cloudy precipitate. Crystallization occurred overnight on cooling to -5°C . The crystals were recrystallised from diethyl ether–hexane at -5°C to give the methyl sulfoxide **40** (14.7 g, 70%) as white crystals, m.p. $74\text{--}75^\circ\text{C}$ (Lit., $73\text{--}74.5^\circ\text{C}$), $[\alpha]_{\text{D}} +192$ (c 1.2, CHCl_3) (Lit., $[\alpha]_{\text{D}}^{21} +192$ (c 1.2, CHCl_3)); $[\alpha]_{\text{D}} +146$ (c 2.0, acetone) (Lit., $[\alpha]_{\text{D}}^{21} +145.5$).



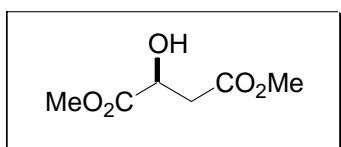
Dess-Martin Periodinane⁷

Potassium bromate (8.75 g, 52.4 mmol) was added in portions over a period of 30 min to a vigorously stirred mixture of 2-iodobenzoic acid (10.0 g, 40.3 mmol) in 0.73M H_2SO_4 (50 ml) at RT. The reaction mixture was warmed to 65°C and stirred for 4 h. The cooled mixture was filtered and the solid material thoroughly washed with water (2x100 ml) and EtOH (2x100 ml) to give 2-iodoxybenzoic acid (9.93 g, 89%) which was directly used in the next reaction.

A slurry of 2-iodoxybenzoic acid (9.93 g, 35.9 mmol) in acetic anhydride (33.0 g) and glacial acetic acid (28 ml) was heated to 100°C to give a homogeneous solution after 40 min. The solvent was evaporated at RT *in vacuo* until a slurry remained. The product was collected by filtration and washed with diethyl ether in an inert atmosphere and dried *in vacuo* to give periodinane as a white solid.

7.3 Procedures

7.3.1 The lactone approach



⁷ Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.

Dimethyl (2*S*)-malate **92**

Thionyl chloride (25 ml) was added dropwise to a solution of malic acid **91** (100 g 736 mmol) in methanol (500 ml) at 0°C and the reaction refluxed for 6 h. The solvent was evaporated and the residue dissolved in absolute methanol (500 ml). Thionyl chloride (25 ml) was added again and the reaction refluxed for a further 6 h. The solution was evaporated and the residue dissolved in dichloromethane (1 L). The organic phase was washed with saturated NaHCO₃ solution (750 ml), dried (Na₂SO₄), filtered and evaporated. The residue was purified by Kugelrohr distillation (1.5 mbar, 140 °C) to give the dimethyl ester **92** as colourless liquid (87.0 g, 72%), [α]_D +2.4 (c 1.70, CHCl₃); ν_{\max} 1742 cm⁻¹.

δ_{H} 4.452 (dd, 1H, J_{2,3a} 6.2, J_{2,3b} 4.4, H-2)

3.736 (s, 3H, OCH₃)

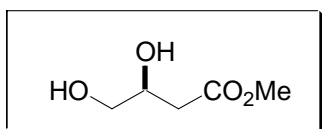
3.644 (s, 3H, OCH₃)

2.797 (dd, 1H, J_{3b,2} 4.4, J_{3a,3b} 16.0, H-3b)

2.723 (dd, 1H, J_{3a,2} 6.2, J_{3a,3b} 16.0, H-3a)

δ_{C} 173.46S (CO), 170.76S (CO), 67.03D (C-2), 52.37Q (OCH₃), 51.64Q (OCH₃), 38.26T (C-3).

FAB-MS: m/z 162 [M]⁺. Exact mass: Calculated for C₆H₁₀O₅, 162.0528; Found, 162.0528.



Methyl (3*S*)-3,4-dihydroxybutanoate **93**⁸

Borane dimethylsulfide complex, BH₃.SMe₂, (10M, 20.6 ml, 206 mmol) was added dropwise by syringe to a solution of the diester **92** (32.4 g, 200 mmol) in anhydrous THF (400 ml) over a period of 30 min at RT. The solution was stirred for 30 min until evolution of hydrogen gas ceased. The flask was then cooled to 5°C in a water-ice bath and sodium borohydride (0.39 g, 10.3 mmol) was added in one portion to the vigorously stirred reaction mixture. An exothermic reaction ensued with gas evolution. When the exothermic reaction subsided the cooling bath was removed and the reaction stirred at RT for 60 min. (TLC). The reaction was quenched by addition of ethanol (70 ml) and TsOH (**1.96 g, 10.3**

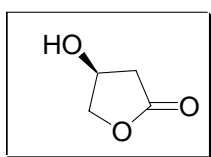
⁸ Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

mmol) and was allowed to stir for 30 min. A cloudy solution formed. The solvent was evaporated, the residue dissolved in ethanol-benzene (1:1, 500 ml) and the resulting solution evaporated. This process was repeated 4×. The residue was then dissolved in benzene (400 ml) and the solution evaporated. Repeat another 4× in order to remove ethanol and B(OEt)₃. Column chromatography of the residue using hexane:EtOAc (1:18) as eluent gave the diol **93** as a colourless oil (19.30 g, 72%); $[\alpha]_D +6.4$ (c 0.60, CHCl₃); ν_{\max} 1776 cm⁻¹; R_f 0.42 (hexane:EtOAc, 1:18).

δ_H 4.665 (m, 1H, J_{3,2a} 3.1, J_{3,2b} 6.2, J_{3,4a} 3.0, J_{3,4b} 4.5, H-3)
 4.396 (dd, 1H, J_{4b,3} 4.5, J_{4a,4b} 10.2, H-4b)
 4.268 (dd, 1H, J_{4a,3} 3.0, J_{4a,4b} 10.2, H-4a)
 3.640 (s, 3H, OMe)
 2.887 (s, 1H, OH)
 2.731 (dd, 1H, J_{2a,2b} 17.8, J_{2b,3} 6.2, H-2b)
 2.504 (dd, 1H, J_{2a,2b} 17.8, J_{2a,3} 3.1, H-2a)

δ_C 172.74S (C-1), 68.57D (C-3), 65.62T (C-4), 51.76Q (OMe), 37.62T (C-2).

FAB-MS: m/z 134 [M]⁺. Exact mass: Calculated for C₅H₁₀O₄, 134.0579; Found, 134.0578.



(3S)-3-Hydroxy-4-butanolide **94**^{9,10}

Borane dimethylsulfide complex, BH₃.SMe₂, (10M, 20.6 ml, 206 mmol) was added dropwise by syringe to a solution of the diester **92** (32.4 g, 200 mmol) in anhydrous THF (400 ml) in a 2-necked flask over a period of 30 min at RT. The solution was stirred for 30 min until evolution of hydrogen gas ceased. The flask was then cooled to 5°C in a water-ice bath and sodium borohydride (0.39 g, 10.3 mmol) was added in one portion to the vigorously stirred reaction mixture. An exothermic reaction ensued with gas evolution. When the exothermic reaction subsided the cooling bath was removed and the reaction

⁹ Hamada, Y.; Yokokawa, F.; Kabeya, M.; Hatano, K.; Kurono, Y.; Shiori, T. *Tetrahedron*, **1996**, 52, 8297.

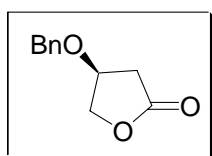
¹⁰ Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R. *Chem. Lett.* **1984**, 1389.

stirred at RT for 60 min. (TLC). The reaction was quenched by addition of ethanol (70 ml) and **excess TsOH** (2.96 g, 15.6 mmol) and was allowed to stir for 30 min. A cloudy solution formed. The solvent was evaporated, the residue dissolved in ethanol-benzene (1:1, 500 ml) and the resulting solution evaporated. This process was repeated 4×. The residue was then dissolved in benzene (400 ml) and the solution evaporated. Repeat another 4 × in order to remove ethanol and borates. The residue was purified by column chromatography using hexane:EtOAc (1:18) as eluent to give the lactone **94** as a colourless oil (14.7 g, 72%); $[\alpha]_D -40.8$ (*c* 1.2, CHCl₃), Lit.,¹¹ $[\alpha]_D -81$ (*c* 1.07, EtOH); ν_{\max} 1782 cm⁻¹; R_f 0.42 (hexane: EtOAc, 1:18).

δ_H 4.598 (m, 1H, J_{3,2a} 1.5, J_{3,2b} 5.9, J_{3,4a} 1.8, J_{3,4b} 4.4, H-3)
 4.354 (dd, 1H, J_{4b,3} 4.4, J_{4a,4b} 10.4, H-4b)
 4.232 (ddd, 1H, J_{4a,3} 1.8, J_{4a,4b} 10.4, J_{4a,2a} 1.0, H-4a)
 3.82 (br s, 1H, 2-OH)
 2.689 (dd, 1H, J_{2a,2b} 17.9, J_{2b,3} 5.9, H-2b)
 2.433 (ddd, 1H, J_{2a,2b} 17.9, J_{2a,3} 1.6, J_{4a,2a} 1.0 H-2a)

δ_C 177.32S (C-1), 76.33T (C-4), 67.17D (C-3), 37.60T (C-2).

FAB-MS: *m/z* 102 [M]⁺.



(3S)-3-Benzyloxy-4-butanolide **95**¹²

A solution of benzyl trichloroacetimidate (1.90 g, 7.50 mmol) in cyclohexane-dichloromethane (8 ml, 2:1) was added to a solution of the lactone **94** (0.490 g, 4.75 mmol) in cyclohexane-dichloromethane (25 ml, 2:1). The reaction mixture was stirred at RT for 1 h and then cooled to 0°C. TMSOTf (0.16 ml) was added to the vigorously stirred mixture. Stirring was continued at room temperature for 2 h, and then the resulting precipitate was filtered off through a cotton plug. The filtrate was washed with saturated aqueous NaHCO₃ solution, water, dried (Na₂SO₄) and evaporated. The residue was chromatographed on

¹¹ Henrot, S.; Larcheveque, M.; Petit, Y. *Synth. Commun.* **1986**, *16*, 183.

¹² Chen; X.; Wu, Y-L.; Chen, D. *Tetrahedron Lett.* **2002**, *43*, 3529.

silica gel using hexane-EtOAc (3:2) to give the benzyl ether **95** as a white solid (0.64 g, 70%); m.p. 60-62°C; $[\alpha]_D -30.3$ (c 0.46, CHCl₃); ν_{\max} 1784 cm⁻¹; R_f 0.43 (hexane-EtOAc, 3:2).

δ_H 7.37-7.25 (m, 5H, aromatic carbons)

4.519 (d, 1H, J_{a,b} 11.7, OCH₂Ph)

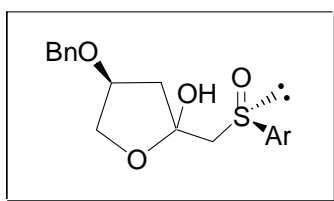
4.495 (d, 1H, J_{a,b} 11.7, OCH₂Ph)

3.39 (m, 2H, H-3 and H-4)

2.61 (m, 2H, H-2)

δ_C 175.31S (C-1), 136.94S (*ipso* aromatic carbon), 128.55D, 128.06D, 127.65D (aromatic carbons), 73.81D (C-3), 73.00T (C-4), 71.12T (OCH₂Ph), 34.87T (C-2).

FAB-MS: m/z 193 [M+H]⁺. Exact mass: Calculated for C₁₁H₁₃O₃, 193.0865; Found, 193.0865.

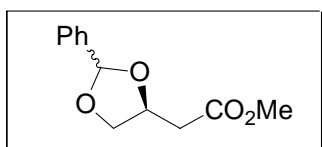


(S(R),4S)-4-(Benzyloxy)-2-hydroxy-2-(*p*-tolylsulfinylmethyl)-tetrahydrofuran **97**

A solution of (*R*)-(+)-methyl *p*-tolylsulfoxide (**40**) (2.1 eq., 3.17 g, 20.6 mmol) in THF (5 ml) was added dropwise by syringe to a cold (-78°C) solution of LDA (2.1 eq., 20.6 mmol) in THF (15 ml) (prepared *in situ* by the reaction of *n*-BuLi (1.6M, 12.9 ml, 60.3 mmol) and diisopropylamine (2.84 ml, 60.3 mmol) in THF (15 ml) at -78°C. After 1 h at -78°C the benzyl derivative **95** (2.0 g, 10.36 mmol) in THF (5 ml) was added dropwise to the reaction mixture and stirring continued for 2 h at -40°C. The reaction was quenched by addition of an aqueous saturated NH₄Cl solution (25 ml), diluted with diethyl ether (50 ml). The organic phase was washed with brine (25 ml), dried (Na₂SO₄) and the solvent evaporated. Column chromatography of the crude product using hexane-EtOAc (3:5) as eluent yielded **97** (2.52 g, 70%) as a yellowish solid; R_f 0.48 (hexane-EtOAc, 3:5).

7.3.2 Synthesis of the C₅ synthon: the open-chain ester approach

7.3.2.1 Route 1: Benzyldiene protecting group



Methyl (3*S*)-3,4-*O*-benzylidene-3,4-dihydroxybutanoate **98**

p-Toluenesulfonic acid (0.5 g, 2.60 mmol) was added to solution of methyl (3*S*)-3,4-dihydroxybutanoate **93** (3.00 g, 22.4 mmol) in α,α -dimethoxytoluene (10 ml) and the reaction mixture stirred at RT for 12 h. The reaction mixture was neutralized with Et₃N (1 ml), diluted with diethyl ether (30 ml) and washed with water. The organic layer was dried (Na₂SO₄) and evaporated. Chromatography of the residue using hexane-EtOAc (5:1) gave the benzylidene derivative **93** (4:3 diastereomeric mixture) as a colourless oil (5.33 g, 64%); ν_{\max} 1735 cm⁻¹; R_f 0.45 (hexane-EtOAc, 5:1).

δ_{H} 7.50-7.32 (m, 10H, aromatic protons),

5.925 (s, 1H, acetal proton)*

5.785 (s, 1H, acetal proton)

4.599 (m, 2H, J_{3,2a} 7.1, J_{3,2b} 6.5, J_{3,4a} 5.7, J_{3,4b} 6.7 H-3)

4.324 (dd, 1H, J_{4b,3} 6.2, J_{4a,4b} 8.4, H-4b)*

4.178 (dd, 1H, J_{4b,3} 6.7, J_{4a,4b} 8.1, H-4b)

3.829 (dd, 1H, J_{4a,3} 5.7, J_{4a,4b} 8.1, H-4a)

3.705 (dd, 1H, J_{4a,3} 6.7, J_{4a,4b} 8.4, H-4a)*

3.673 (s, 6H, OMe)

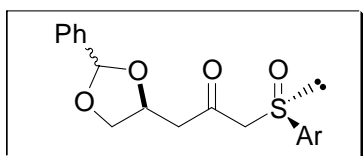
2.818 (dd, 2H J_{2a,2b} 16.1, J_{2b,3} 6.5, H-2b)

2.616 (dd, 1H, J_{2a,2b} 16.1, J_{2a,3} 7.0, H-2a)

2.593 (dd, 1H, J_{2a,2b} 16.1, J_{2a,3} 7.1, H-2a)

δ_{C} 170.68S and 170.64S* (C-1), 137.81S* and 137.22S (*ipso* phenyl), 129.21D, 129.03D, 128.19D, 126.48D, 126.25D (aromatic carbons), 104.05D* and 103.21D (acetal carbon), 72.75D and 72.25D* (C-3), 70.24T* and 69.87T (C-4), 51.63Q (OMe), 38.60T and 37.98T* (C-2).

FAB-MS: m/z 223 [M+H]⁺. Exact mass: Calculated for C₁₂H₁₅O₄, 223.0970; Found, 223.0971.

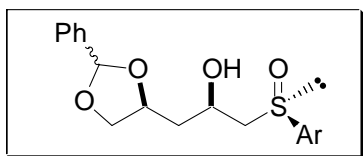


(S(R),4S,2'RS)-4,5-O-benzylidene-4,5-dihydroxy-1-(*p*-tolylsulfinyl)-pentan-2-one 99

A solution of (*R*)-(+)-methyl *p*-tolylsulfoxide (**40**) (2.1 eq, 9.30 g, 60.3 mmol) in THF (25 ml) was added dropwise to a cold (-78°C) solution of LDA (2.1eq, 60.3 mmol)(prepared *in situ* by the reaction of *n*-BuLi (1.6M, 37.7 ml, 60.3 mmol) and diisopropylamine (8.3 ml, 60.3 mmol in THF (50 ml). After stirring at -78°C for 1 h a solution of the benzylidene **98** (6.86 g, 28.7 mmol) in THF (25 ml) was added by syringe to the anion solution and stirring continued for 2 h at -78°C . The reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (70 ml), diluted with diethyl ether (100 ml) and the organic phase washed with brine (70 ml), dried (Na_2SO_4) and evaporated. Column chromatography of the crude product using hexane-EtOAc (3:5) as eluent yielded the ketosulfoxide **99** (7.29 g, 70%) (4:3 d.r.) as a white solid; R_f 0.42 (hexane-EtOAc, 3:5); ν_{max} 1720 cm^{-1} .

δ_{H} 7.54-7.21 (m, 18H, aromatic protons)
 5.854 (s, 1H, acetal proton)*
 5.716 (s, 1H, acetal proton)
 4.507 (m, 1H, $J_{4,3a}$ 3.1, $J_{4,3b}$ 9.7, $J_{4,5a}$ 5.8, $J_{4,5b}$ 6.7, H-4)
 4.268 (dd, 1H, $J_{5b,4}$ 6.2, $J_{5a,5b}$ 8.5, H-5b)*
 4.125 (dd, 1H, $J_{5b,4}$ 6.7, $J_{5a,5a}$ 8.3, H-5b)
 3.839 (d, 1H, $J_{1a,1b}$ 13.2, H-1b)
 3.802 (d, 1H, $J_{1a,1b}$ 13.2, H-1a)
 3.798 (s, 2H, H-1)
 3.627 (dd, 1H, $J_{5a,4}$ 5.8, $J_{5a,5b}$ 8.3, H-5a)
 3.501 (dd, 1H, $J_{5a,4}$ 6.7, $J_{5a,5b}$ 8.5, H-5a)*
 3.204 (dd, 1H, $J_{3a,3b}$ 13.1, $J_{3b,4}$ 9.7, H-3b)
 3.044 (dd, 1H, $J_{3a,3b}$ 17.5, $J_{3b,4}$ 6.1, H-3b)*
 2.908 (dd, 1H, $J_{3a,3b}$ 13.1, $J_{3a,4}$ 3.1, H-3a)
 2.711(dd, 1H, $J_{3a,3b}$ 17.5, $J_{3a,4}$ 6.8, H-3a)*
 2.387 (s, 3H, tolyl Me)*
 2.378 (s, 3H, tolyl Me)

δ_C 199.18S (C-2), 142.22S, 139.24S, 137.68S (*ipso* carbons), 130.08-123.97 (aromatic carbons), 103.89D and 103.13D* (acetal carbons), 72.04D and 71.48D* (C-4), 70.32T and 69.89T* (C-5), 67.79T and 67.60T* (C-1), 49.06T and 48.50T* (C-3), 21.31Q (Me).



(S(R),2R,4S,2'RS)-4,5-O-Benzylidene-1-(*p*-tolylsulfinyl)pentane-2,4,5-triol **100**

A solution of the β -ketosulfoxide **99** (500 mg, 1.45 mmol) in THF (40 ml) was added by syringe to dried ZnBr₂ (354 mg, 1.59 mmol) under an argon atmosphere. The mixture was stirred at 0°C for 1 h and then at -78°C for another hour. DIBALH (10M, 1.00 ml) was added dropwise by syringe. The reaction was quenched by addition of a saturated aqueous sodium tartrate solution (8 ml) after 1 h. The solvent was decanted and the solid residue was extracted with EtOAc (30 ml). The solvent was evaporated and the crude product purified by column chromatography using hexane-EtOAc (1:4) as eluent to give the β -hydroxysulfoxide **100** (351 mg, 70%)(d.r. 3:2) as a solid; R_f 0.48 (hexane-EtOAc, 1:4).

δ_H 7.54-7.27 (m, 18H, aromatic protons)
 5.912 (s, 1H, acetal proton)*
 5.759 (s, 1H, acetal proton)
 4.415 (m, 2H, H-4 and H-2)
 4.279 (dd, 1H, $J_{5b,4}$ 6.3, $J_{5a,5b}$ 8.5, H-5b)*
 4.125 (dd, 1H, $J_{5b,4}$ 6.7, $J_{5a,5b}$ 8.3, H-5b)
 3.990 (d, 1H, J 1.7, 2-OH)*
 3.932 (d, 1H, J 1.7, 2-OH)
 3.780 (dd, 1H, $J_{5a,4}$ 6.7, $J_{5a,5b}$ 8.3, H-5a)
 3.675 (dd, 1H, $J_{5a,4}$ 6.7, $J_{5a,5b}$ 8.5, H-5a)*
 3.068 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1b,2}$ 8.0, H-1b)*
 3.053 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1b,2}$ 8.2, H-1b)
 2.874 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.6, H-1a)*
 2.862 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.4, H-1a)
 3.389 (s, 3H, Me)*

2.387 (s, 3H, Me)

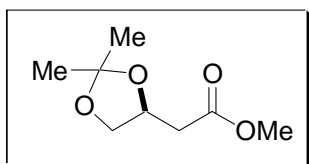
1.95 (m, 4H, H-3a and 3b)

* chemical shifts refer to one of the diastereomers

δ_C 141.83S, 140.42S, 137.82S, 137.30S (*ipso* carbons), 130.06D, 129.35D, 129.20D, 128.34D, 126.56D, 126.33D, 124.01D, 123.93D (aromatic carbons), 104.22D and 103.28D* (acetal carbons), 74.97D and 74.47D* (C-4), 71.13T* and 70.48T (C-5), 67.17D* and 67.06D (C-2), 63.09T (C-1), 40.34T and 39.97T* (C-3), 21.80 (Me).

FAB-MS: m/z 347 $[M+H]^+$. Exact mass: Calculated for $C_{19}H_{23}O_4S$, 347.1317; Found, 347.1317.

7.3.2.2 Route 2: Acetonide and trityl protecting groups



Methyl (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanoate **109**

p-Toluenesulfonic acid (1.86 mmol, 0.35 g) was added to a solution of the diol **93** (5.00 g, 37.3 mmol) in acetone (20 ml) and 2,2-dimethoxypropane (5.0 ml, 41.0 mmol). The reaction was stirred for 30min at RT and was then neutralized by addition of triethylamine (2 ml). The solvent was evaporated and the residue was purified by column chromatography with hexane-EtOAc (4:1) to yield the acetonide **109** (5.30 g, 82%) as a colourless liquid; $[\alpha]_D +17.7$ (*c* 0.30, $CHCl_3$), (Lit.; $[\alpha]_D +18.2$ (*c* 5.0, $CHCl_3$)); ν_{max} 1737 cm^{-1} ; R_f 0.71 (hexane-EtOAc, 4:1)

δ_H 4.417 (m, 1H, $J_{3,2a}$ 7.0, $J_{3,2b}$ 6.5 $J_{3,4a}$ 6.5, $J_{3,4b}$ 5.9, H-3)

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

3.649 (s, 3H, OMe)

3.596 (dd, 1H, $J_{4a,3}$ 6.5, $J_{4a,4b}$ 8.3, H-4a)

2.662 (dd, 1H, $J_{2a,2b}$ 15.9, $J_{2b,3}$ 6.4, H-2b)

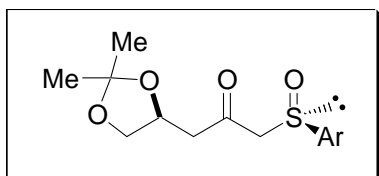
2.474 (dd, 1H, $J_{2a,2b}$ 15.9, $J_{2a,3}$ 7.0, H-2a)

1.360 (s, 3H, acetonide Me)

1.303 (s, 3H, acetonide Me)

δ_C 170.96S (C-1); 109.17S (acetone C-2); 71.99D (C-3); 69.08T (C-4); 51.67Q (OMe); 38.73T (C-2); 26.81Q and 25.44Q (acetone Me).

FAB-MS: m/z 175 $[M+H]^+$. Exact mass: Calculated for $C_8H_{15}O_4$, 175.0970; Found, 175.0971.



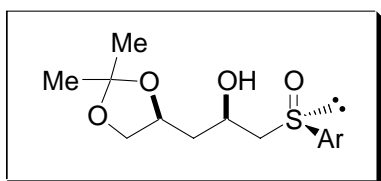
(S(R),4S)-4,5-O,O-Isopropylidene-4,5-dihydroxy-1-(*p*-tolylsulfinyl)-pentan-2-one 110

A solution of (*R*)-(+)-methyl *p*-tolylsulfoxide (**40**) (2.1 eq, 9.30 g, 60.3 mmol) in THF (25 ml) was added dropwise by syringe to a cold (-78°C) solution of LDA (2.1 eq, 60.3 mmol) in THF (50 ml) (prepared *in situ* by the reaction of *n*-BuLi (1.6M, 37.7 ml, 60.3 mmol) and diisopropylamine (8.3 ml, 60.3 mmol) in THF (50 ml) at -78°C). After 1 h at -78°C the acetone derivative **109** (5.02 g, 28.7 mmol) in THF (25 ml) was added dropwise to the reaction mixture and stirring continued for 2 h at -78°C . The reaction was quenched by addition of an aqueous saturated NH_4Cl solution (70 ml), diluted with diethyl ether (100 ml). The organic phase was washed with brine (70 ml), dried (Na_2SO_4) and the solvent evaporated. Column chromatography of the crude product using hexane-EtOAc (3:5) as eluent yielded the ketosulfoxide **110** (5.96 g, 70%) as a white solid; m.p. $77-79^\circ\text{C}$, $[\alpha]_D^{25} +150.0$ (c 1.2, CHCl_3); ν_{max} 1720 cm^{-1} ; R_f 0.42 (hexane-EtOAc, 3:5).

δ_H 7.48-7.24 (m, 4H, aromatic protons)
 4.333 (m, 1H, $J_{4,3a}$ 6.5, $J_{4,3b}$ 6.3, $J_{4,5a}$ 6.5, $J_{4,5b}$ 6.0, H-4)
 4.037 (dd, 1H, $J_{5b,4}$ 6.0, $J_{5a,5b}$ 8.3, H-5b)
 3.805 (s, 2H, H-1)
 3.395 (dd, 1H, $J_{5a,4}$ 6.5, $J_{5a,5b}$ 8.3, H-5a)
 2.888 (dd, 1H, $J_{3a,3b}$ 17.1, $J_{3b,4}$ 6.3, H-3b)
 2.574 (dd, 1H, $J_{3a,3b}$ 17.1, $J_{3a,4}$ 6.5, H-3a)
 2.355 (s, 3H, tolyl Me)
 1.314 (s, 3H, acetone Me)
 1.256 (s, 3H, acetone Me)

δ_C 199.35S (C-2); 142.15S, 129.35S, 130.04D, 123.97D (aromatic carbons); 108.97S (acetone C-2); 71.10D (C-4); 69.00T (C-1); 67.93T (C-5); 49.04T (C-3); 26.67Q and 25.31Q (acetone Me); 21.29 (tolyl Me).

FAB-MS: m/z 297 $[M+H]^+$. Exact mass: Calculated for $C_{15}H_{21}O_4S$, 297.1161; Found, 297.1161.



(S(R),2R,4S)-4,5-O,O-Isopropylidene-1-(p-tolylsulfinyl)- pentane-2,4,5-triol 111

A solution of the ketosulfoxide **110** (0.50 g, 1.69 mmol) in THF (40 ml) was added by syringe to dried zinc bromide (0.470 g, 1.86 mmol) under an argon atmosphere. The mixture was stirred for 1 h at 0°C and another 15 min at -78°C. DIBALH (10M, 0.65 ml) was added dropwise by syringe. After stirring for 1h at -78°C, the reaction was quenched by addition of methanol (10 ml) and allowed to reach RT. The solvent was evaporated and the opaque solid was dissolved in CH_2Cl_2 (20 ml) and washed with saturated NH_4Cl solution (10 ml) and acidified to pH 4 with 1M HCl. The organic layer was washed with brine (10 ml), dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography using hexane-EtOAc (1:4) R_f 0.40) as eluent to give the β -hydroxy-sulfoxide **111** (0.50 g, 100%) as a white solid; m.p. 87-89°C; $[\alpha]_D +131.1$ (c 0.33, $CHCl_3$); R_f 0.40 (hexane-EtOAc, 1:4).

δ_H 7.55-7.29 (m, 4H, aromatic protons)

4.317 (m, 1H, $J_{3b,2}$ 8.2, $J_{1b,2}$ 7.8, $J_{3a,2}$ 4.4, $J_{1a,2}$ 3.9, $J_{2,OH}$ 1.6, H-2)

4.252 (m, 1H, $J_{5a,4}$ 7.1, $J_{3b,4}$ 7.0, $J_{5b,4}$ 5.9, $J_{3a,4}$ 4.9, H-4)

4.064 (dd, 1H, $J_{5b,4}$ 5.9, $J_{5a,5b}$ 8.3, H-5b)

3.922 (d, 1H, $J_{2,OH}$ 1.6, 2-OH)

3.583 (dd, 1H, $J_{5a,4}$ 7.1, $J_{5a,5b}$ 8.3, H-5a)

3.035 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1b,2}$ 7.8, H-1b)

2.822 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.9, H-1a)

2.397 (s, 3H, tolyl Me)

1.878 (ddd, 1H, $J_{3a,3b}$ 14.2, $J_{3b,4}$ 7.0, $J_{3b,2}$ 8.2, H-3b)

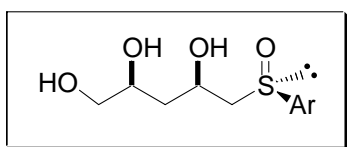
1.837 (ddd, 1H, $J_{3a,3b}$ 14.2, $J_{3a,4}$ 4.9, $J_{3a,2}$ 4.4, H-3a)

1.386 (s, 3H, acetonide Me)

1.318 (s, 3H, acetonide Me)

δ_C 141.83S and 140.53S (*ipso* tolyl), 130.08D, 124.07D (aromatic carbons); 109.37D (acetonide C-2); 74.09D (C-4); 69.41T (C-5); 66.95D (C-2); 62.93T (C-1); 39.99T (C-3); 26.83Q and 25.67Q (acetonide Me); 21.39Q (tolyl Me).

FAB-MS: m/z 299 $[M+H]^+$. Exact mass: Calculated for $C_{15}H_{23}O_4S$, 299.1317; Found, 299.1317.



(S(R),2R,4S)-1-(*p*-tolylsulfinyl)-pentane-2,4,5-triol 112

p-Toluenesulfonic acid (370 mg) was added to a solution of the β -hydroxysulfoxide **111** (3.70 g, 12.4 mmol) in MeOH-H₂O (5:2, 42 ml). The solution was refluxed for 1 h, neutralized by addition of Et₃N (1 ml) and concentrated under reduced pressure. The residue was dissolved in water (10 ml) and the product extracted into EtOAc by continuous extraction to yield the triol **112** (2.72 g, 85%) as an oil that solidified on standing; m.p. 140-142°C; $[\alpha]_D +186.8$ (c 0.53, CHCl₃).

δ_H 7.52-7.24 (m, 4H, aromatic protons)

4.315 (m, 1H, H-2)

3.903 (m, 1H, H-4)

3.563 (dd, 1H, $J_{5b,4}$ 3.6, $J_{5a,5b}$ 11.4, H-5b)

3.454 (dd, 1H, $J_{5a,4}$ 6.2, $J_{5a,5b}$ 11.4, H-5a)

3.077 (dd, 1H, $J_{1a,1b}$ 13.3, $J_{1b,2}$ 7.4, H-1b)

2.819 (dd, 1H, $J_{1a,1b}$ 13.3, $J_{1a,2}$ 4.3, H-1a)

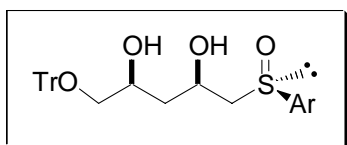
2.354 (s, 3H, tolyl Me)

1.768 (m, 1H, H-3b)

1.712 (m, 1H, H-3a)

δ_C 141.94S and 139.90S (*ipso* tolyl); 130.10D, 124.18D (aromatic carbons); 71.07D (C-4); 67.16D (C-2); 66.33T (C-5); 62.62T (C-1); 39.13T (C-3); 21.35Q (tolyl Me).

FAB-MS: m/z 259 $[M+H]^+$. Exact mass: Calculated for $C_{12}H_{19}O_4S$, 259.1004; Found, 259.1004.



(S(R),2R,4S)-1-(*p*-tolylsulfinyl)-5-(trityloxy)pentane-2,4-diol 113

Pyridine (0.30 ml, 3.90 mmol), triphenylmethyl chloride (550 mg, 2.00 mmol) and DMAP (10 mg) were added to a solution of the triol **112** (500 mg, 1.90 mmol) in CH_2Cl_2 (15 ml). 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 hexane-EtOAc (1:18) as eluent yielded the *O*-trityl derivative **113** (770 mg, 80%) as a yellowish solid; m.p. 74-76°C; $[\alpha]_D^{25} +95.0$ (c 0.80, $CHCl_3$); R_f 0.63 (hexane-EtOAc, 1:18).

δ_H 7.54-7.50 and 7.41-7.18 (m, 19H, aromatic protons)

4.34 (m, 2H, H-2 and OH)

4.016 (m, 1H, H-4)

3.26 (br s, 1H, OH)

3.095 (m, 2H, H-5)

3.017 (dd, 1H, $J_{1a,1ba}$ 13.2, $J_{1b,2}$ 8.0, H-1b)

2.772 (dd, 1H, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 3.6, H-1a)

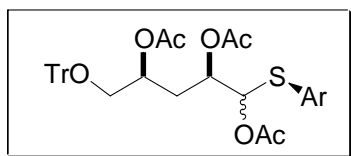
2.394 (s, 3H, tolyl Me)

1.690 (dd, 2H, $J_{2,3}$ 6.2, $J_{3,4}$ 6.2, H-3)

δ_C 143.69S, 141.77S, 140.38S (*ipso* carbons), 130.00D, 128.55D, 127.78D, 127.04D, 124.01D (aromatic carbons), 86.66S (OTr), 70.41D (C-4), 68.10D (C-2), 67.40T (C-

5), 63.04T (C-1), 39.37T (C-3), 21.34T (tolyl Me).

FAB-MS: m/z 501 $[M+H]^+$. Exact mass: Calculated for $C_{12}H_{19}O_4S$, 501.2099; Found, 501.2087.



(1R,2R,4S)-1,2,4-Triacetoxy-5-(trityloxy)-1-(*p*-tolylsulfanyl)pentane 114

A solution of the trityl derivative **113** (500 mg, 1.00 mmol) and sodium acetate (1.92 g) in acetic anhydride (30 ml) was refluxed for 7 h. The reaction was allowed to cool and diluted with toluene (30 ml). The solvent was then evaporated under vacuum, the residue dissolved in diethyl ether and salt removed by filtration through celite. After evaporation of the solvent the crude product was purified by column chromatography using hexane-EtOAc (3:1) as eluent to yield the Pummerer product **114** (1:1 d.r.) as a yellow wax (530 mg, 86%); R_f 0.37 (hexane-EtOAc, 3:1).

δ_H 7.45-7.06 (m, 19H, aromatic protons)

6.141 (d, 1H, $J_{1,2}$ 3.6, H-1)

6.132 (d, 1H, $J_{1,2}$ 6.0, H-1)

5.21-5.06 (m, 4H, H-2 and H-4)

3.207 (dd, 1H, $J_{5a,5b}$ 10.3, $J_{4,5a}$ 3.9, H-5a)¹

3.171 (dd, 1H, $J_{5a,5b}$ 10.3, $J_{4,5a}$ 3.9, H-5a)²

3.136 (dd, 1H, $J_{5a,5b}$ 10.3, $J_{4,5b}$ 5.2, H-5b)¹

3.120 (dd, 1H, $J_{5a,5b}$ 10.3, $J_{4,5a}$ 3.9, H-5b)²

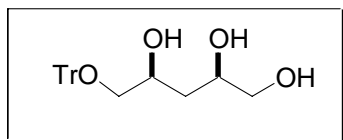
2.308 (s, 6H, tolyl Me)

2.06, 2.04, 2.02, 2.01, 1.95, 1.94 (s, each 3H, acetate Me)

1.36-1.21 and 0.96-0.79 (m, 4H, H-3)

δ_C 170.22S, 170.15S, 169.79S, 169.67S, 169.39S, 169.13S (acetate carbonyl); 143.72-127.05 (aromatic carbons); 86.54S (OTr); 81.96D and 81.32D (C-1); 71.10D and 70.73D (C-2); 70.07D and 70.00D (C-4); 64.31T and 64.18T (C-5); 31.94T and 31.02T (C-3); 21.07Q and 20.76Q (tolyl Me).

FAB-MS: m/z 626 $[M]^+$. Exact mass: Calculated for $C_{37}H_{38}O_7S$, 626.2338; Found, 626.2335.



(2*R*,4*S*)-5-(Trityloxy)-pentane-1,2,4-triol 115

A solution of compound **114** (2.00 g, 3.19 mmol) in dry diethyl ether (25 ml) was added dropwise to a suspension of lithium aluminum hydride (598 mg, 16.0 mmol) in dry diethyl ether (20 ml) and stirred at room temperature until no more starting material was present (TLC control, hexane-EtOAc, 1:28). The reaction was quenched by careful addition of 2M NaOH. The solvent was evaporated and the solid residue was extracted with hot ethyl acetate to give the triol **115** (1.00 g, 83%) as a colourless oil.

δ_H 7.42-7.19 (m, 15H, aromatic protons)

4.039 (m, 1H, H-2)

3.908 (m, 1H, H-4)

3.566 (dd, 1H, $J_{1a,1b}$ 11.2, $J_{1b,2}$ 3.5, H-1b)

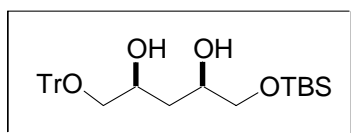
3.437 (dd, 1H, $J_{1a,1b}$ 11.2, $J_{1a,2}$ 6.0, H-1a)

3.137 (dd, 1H, $J_{5b,4}$ 4.0, $J_{5a,5b}$ 9.3, H-5b)

3.081 (dd, 1H, $J_{5a,4}$ 7.0, $J_{5a,5b}$ 9.3, H-5a)

1.60-1.47 (ddd, 2H, H-3)

δ_C 143.67S (*ipso* trityl); 128.66-127.06 (aromatic carbons); 86.84S (OTr); 71.71D (C-4); 70.89D (C-2); 67.68T (C-5); 66.53T (C-1); 35.75T (C-3).



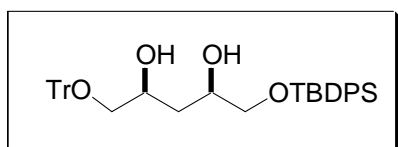
(2*R*,4*S*)-1-[(*t*-Butyldimethylsilyl)oxy]-5-(trityloxy)-pentane-2,4-diol 116

A solution of *t*-butyldimethylsilyl chloride (0.40 g, 2.64 mmol) in dichloromethane (20 ml) was added dropwise to a cold (0°C) solution of the triol **115** (1.00 g, 2.64 mmol) and imidazole (0.22 g, 3.40 mmol) in dichloromethane (30 ml). The reaction was stirred for 2 h

at 0°C, the solvent was removed under reduced pressure and the residue taken up in diethyl ether (30 ml). The organic layer was washed with water (3×), brine, dried (Na₂SO₄) and evaporated. The crude product was purified by column chromatography using hexane-EtOAc (1:4) to give the *O*-TBS derivative **116** (1.10 g, 85%) as an oil; R_f 0.89 (hexane-EtOAc, 1:4).

δ_{H} 7.45-7.20 (m, 15H, aromatic protons)
 4.023 (m, 1H, H-4)
 3.845 (m, 1H, H-2)
 3.546 (dd, 1H, $J_{1a,1b}$ 10.1, $J_{1b,2}$ 4.7, H-1b)
 3.481 (dd, 1H, $J_{1a,1b}$ 10.1, $J_{1b,2}$ 6.6, H-1a)
 3.199 (d, 1H, $J_{2,\text{OH}}$ 2.6, 2-OH)
 3.140 (dd, 1H, $J_{5a,5b}$ 9.2, $J_{5b,4}$ 5.2, H-5b)
 3.115 (dd, 1H, $J_{5a,5b}$ 9.2, $J_{5a,4}$ 6.0, H-5a)
 3.021 (d, 1H, $J_{4,\text{OH}}$ 2.8, 4-OH)
 1.691 (ddd, 1H, $J_{3a,3b}$ 14.5, $J_{3b,2}$ 3.1, $J_{3b,4}$ 3.1, H-3b)
 1.505 (ddd, 1H, $J_{3a,3b}$ 14.5, $J_{3a,2}$ 9.3, $J_{3a,4}$ 9.3, H-3a)
 0.888 (s, 9H, CMe₃)
 0.058 (s, 6H, SiMe₂)

δ_{C} 143.90S (ipso trityl); 128.66D, 127.81D, 127.04D (aromatic carbons); 86.63S (OTr); 71.91D (C-2); 70.79D (C-4); 67.57T (C-5), 67.09T (C-1); 36.17T (C-3); 26.87Q (CMe₃); 18.27S (CMe₃); -5.40Q (SiMe₂).



(2*R*,4*S*)-1-[(*t*-Butyldiphenylsilyl)oxy]-5-(trityloxy)-pentane-2,4-diol **117**

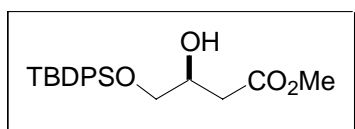
A solution of *t*-butyldiphenylsilyl chloride (2.80 g, 1.86 mmol) in dichloromethane (20 ml) was added dropwise to a cold (0°C) solution of the triol **115** (0.70 g, 1.85 mmol) and imidazole (0.16 g, 2.40 mmol) in dichloromethane (30 ml). The reaction was stirred for 2 h at 0°C, the solvent was removed under reduced pressure and the residue taken up in diethyl ether (30 ml). The organic layer was washed with water (3×), brine, dried (Na₂SO₄) and

evaporated. The crude product was purified by column chromatography using hexane-EtOAc (1:5) to give the *O*-TBDPS derivative **117** (0.78 g, 87%) as an oil; R_f 0.69 (hexane-EtOAc, 1:5).

δ_H 7.69- 7.27 (m, 25H, aromatic protons)
 4.092 (m, 1H, H-4)
 3.983 (m, 1H, H-2)
 3.575 (m, 2H, H-5)
 3.112 (m, 2H, H-1)
 1.657 (m, 2H, H-3)
 1.056 (s, 9H, C(CH₃)₃)

δ_C 143.89S (*ipso* trityl); 134.79S (*ipso* phenyl); 135.52D, 129.79D, 129.57D, 128.65D, 127.81D, 127.04D (aromatic carbons); 86.63S (OTr); 72.04D (C-2); 70.85D (C-4); 67.84T (C-5); 67.56T (C-1); 39.19T (C-3); 26.86Q (CMe₃); 19.22S (CMe₃).

7.3.2.3 Route 3: TBDPS protecting group



Methyl (3S)-4-[(*t*-butyldiphenylsilyl)oxy]-3-hydroxybutanoate **118**

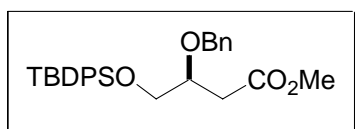
t-Butyldiphenylsilyl chloride (6.43 g, 23.0 mmol) was added dropwise to a cold (0°C) solution of the diol **93** (3.00 g, 22.4 mmol), imidazole (2.00 g, 30.0 mmol) and DMAP (20 mg) in dichloromethane (20 ml). The resulting solution was stirred for 2 h at 0°C and the solvent evaporated. The residue was partitioned between EtOAc and water (3x) and the organic phase dried (Na₂SO₄) and evaporated. The residue was purified by column chromatographed using EtOAc-hexane (1:6) to give the TBDPS ether **118** (7.00 g, 85%) as a colourless oil; $[\alpha]_D -8.7$ (*c* 0.57, CHCl₃); ν_{max} 1736 cm⁻¹; R_f 0.71 (EtOAc-hexane, 1:6).

δ_H 7.67-7.34 (m, 10H, aromatic protons)
 4.151 (m, 1H, $J_{3,2a}$ 7.4, $J_{3,2b}$ 5.3, $J_{3,4a}$ 5.7, $J_{3,4b}$ 5.2, H-3)
 3.674 (s, 3H, OCH₃)
 3.660 (dd, 1H, $J_{4b,3}$ 5.2, $J_{4a,4b}$ 10.2, H-4b)

3.630 (dd, 1H, $J_{4a,3}$ 5.7, $J_{4a,4b}$ 10.2, H-4a)
 2.883 (d, 1H, J 4.6, OH)
 2.590 (dd, 1H, $J_{2a,2b}$ 15.9, $J_{2b,3}$ 5.3, H-2b)
 2.512 (dd, 1H, $J_{2a,2b}$ 15.9, $J_{2a,3}$ 7.4, H-2a)
 1.063 (s, 9H, CMe_3)

δ_{C} 172.43S (C-1); 133.07S (*ipso* phenyl); 135.53D, 129.83D, 127.77D (aromatic carbons); 68.62D (C-3); 66.91T (C-4); 51.69Q (OMe); 37.88T (C-2); 26.82Q (CMe_3); 19.22S (CMe_3).

FAB-MS: m/z 373 $[\text{M}+\text{H}]^+$. Exact mass: Calculated for $\text{C}_{21}\text{H}_{29}\text{O}_4\text{Si}$, 373.1835; Found, 373.1833.



Methyl (3S)-3-(benzyloxy)-4-[(*t*-butyldiphenylsilyl)oxy]-butanoate **119**

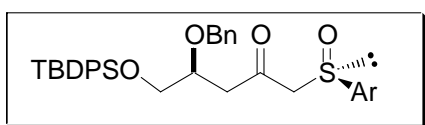
A solution of benzyl trichloroacetimidate (1.90 g, 7.50 mmol) in cyclohexane–dichloromethane (9 ml, 2:1) was added to a solution of the TBDPS ether **118** (1.77 g, 4.75 mmol) in cyclohexane–dichloromethane (24 ml, 2:1). The solution was stirred at RT for 1 h, cooled to 0°C and TMSOTf (0.16 ml) was added by syringe. The reaction mixture was then stirred at RT for 2 h. The formed precipitate was filtered off through a cotton plug. The filtrate was washed with aqueous saturated NaHCO_3 solution, dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on silica gel using hexane-EtOAc (4:1) to give the benzyl ether **119** of (1.60 g, 74%) as a colourless oil; $[\alpha]_{\text{D}} -25.0$ (c 0.35, CHCl_3); ν_{max} 1736 cm^{-1} ; R_f 0.46 (hexane-EtOAc, 4:1).

δ_{H} 7.72-7.20 (m, 15H, aromatic protons)
 4.616 (d, 1H, $J_{a,b}$ 11.6, OCH_2Ph)
 4.561 (d, 1H, $J_{a,b}$ 11.6, OCH_2Ph)
 4.056 (m, 1H, $J_{3,2a}$ 8.0, $J_{3,2b}$ 4.8, $J_{3,4a}$ 5.4, $J_{3,4b}$ 5.0, H-3)
 3.795 (dd, 1H, $J_{4b,3}$ 5.0, $J_{4a,4b}$ 10.4, H-4b)
 3.698 (dd, 1H, $J_{4a,3}$ 5.4, $J_{4a,4b}$ 10.4, H-4a)

3.668 (s, 3H, OCH₃)
 2.718 (dd, 1H, J_{2a,2b} 15.6, J_{2b,3} 4.8, H-2b)
 2.637 (dd, 1H, J_{2a,2b} 15.8, J_{2a,3} 8.0, H-2a)
 1.087 (s, 9H, CMe₃)

δ_C 172.04S (C-1), 138.45-127.50 (aromatic carbons), 76.58D (C-3); 72.42T (OCH₂Ph);
 65.26T (C-4); 51.56Q (OCH₃); 37.38T (C-2); 26.79Q (CMe₃); 19.19S (CMe₃).

FAB-MS: m/z 462 [M]⁺. Exact mass: Calculated for C₂₈H₃₄O₄Si, 462.2226; Found, 462.2222.



**(S(R),4S)-4-(Benzyloxy)-5[(*t*-butyldiphenylsilyl)oxy]-1-(*p*-tolylsulfinyl)-2-pentanone
 120**

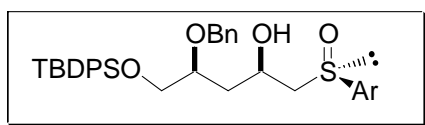
LDA (2.2 eq.) was prepared *in situ* by the reaction of *n*-BuLi (1.6M, 3.0 ml, 4.80 mmol) and diisopropylamine (0.66 ml, 4.80 mmol) in THF (10 ml) at -78°C . A solution of (*R*)-(+)-methyl *p*-tolylsulfoxide (2.1 eq., 0.70 g, 4.50 mmol) in THF (5 ml) was added by syringe to the LDA solution at -78°C and stirred for 1 h. The protected ester **119** (1.00 g, 2.00 mmol) in THF (5 ml) was then added dropwise by syringe to the reaction mixture at -78°C . The reaction mixture was allowed to stir for 2 h at -40°C . The reaction was quenched by addition of a saturated NH₄Cl solution (5 ml) and extracted with diethyl ether (30 ml). The organic phase was washed with brine, dried (Na₂SO₄) and evaporated. The residue was purified by column chromatography (hexane-EtOAc, 1:1) to give the β -ketosulfoxide **120** (1.01 g, 80%) as a colourless oil; $[\alpha]_D^{25} +53.5$ (*c* 0.20, CHCl₃); ν_{max} 1714 cm⁻¹; R_f 0.62 (hexane-EtOAc, 1:1).

δ_H 7.19-7.66 (m, 19H, aromatic protons)
 4.539 (d, 1H, J_{a,b} 11.4, OCH₂Ph)
 4.438 (d, 1H, J_{a,b} 11.4, OCH₂Ph)
 3.960 (m, 1H, J_{4,3a} 4.4, J_{4,3b} 7.9, J_{4,5a} 5.4, J_{4,5b} 4.9, H-4)
 3.854 (d, 1H, J_{1a,1b} 13.7, H-1b)
 3.733 (d, 1H, J_{1a,1b} 13.7, H-1a)

3.691 (dd, 1H, $J_{5b,4}$ 4.9, $J_{5a,5b}$ 10.7, H-5b)
 3.613 (dd, 1H, $J_{5a,4}$ 5.4, $J_{5a,5b}$ 10.7, H-5a)
 2.821 (dd, 1H, $J_{3a,3b}$ 16.5, $J_{3b,4}$ 7.9, H-3b)
 2.683 (dd, 1H, $J_{3a,3b}$ 16.5, $J_{3a,4}$ 4.4, H-3a)
 2.361 (s, 3H, tolyl CH₃)
 1.034 (s, 9H, CMe₃)

δ_C 200.18S (C-2); 141.99S, 139.79S, 138.12S, 135.50D, 133.15S, 133.08S, 130.01D, 129.74D, 128.27D, 127.71D, 124.06D (aromatic carbons); 75.76D (C-4); 72.33T (OCH₂Ph); 68.92T (C-1); 65.14T (C-5); 47.14T (C-3); 26.77Q (CMe₃); 21.37Q (tolyl Me); 19.16S (CMe₃).

FAB-MS: m/z 584 [M]⁺. Exact mass: Calculated for C₃₅H₄₀O₄SSi, 584.2417; Found, 584.2417.



(S(R),2R,4S)-4-(Benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]-1-(*p*-tolylsulfinyl)-pentan-2-ol **121**

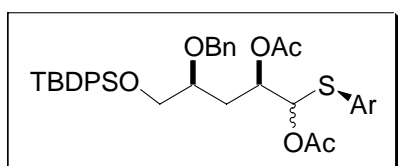
A solution of the ketosulfoxide **120** (1.80 g, 3.08 mmol) in THF (40 ml) in THF (40 ml) was added by syringe to dried zinc bromide (0.752 g, 3.38 mmol) under an argon atmosphere. The mixture was stirred for 1 h at 0°C and another 15 min at -78°C. DIBALH (10M, 1.20 ml) was added dropwise by syringe. After stirring for 1 h at -78°C, the reaction was quenched by addition of methanol (10 ml) and allowed to reach RT. The solvent was evaporated and the opaque solid was suspended in CH₂Cl₂ (20 ml); saturated NH₄Cl solution (10 ml) was added and the pH adjusted to 4 with 1M HCl. The organic layer was washed with brine (10 ml), dried (Na₂SO₄) and evaporated.. The crude product was purified by column chromatography using hexane-EtOAc (1:4) R_f 0.40) as eluent to give the β -hydroxysulfoxide **121** (1.44 g, 80%) as a colourless oil; $[\alpha]_D$ +31.1 (*c* 1.3, CHCl₃); R_f 0.40 (hexane-EtOAc, 1:4).

δ_H 7.66-7.19 (m, 19H, aromatic protons)
 4.648 (d, 1H, $J_{a,b}$ 11.5, OCH₂Ph)

4.401 (d, 1H, $J_{a,b}$ 11.5, OCH₂Ph)
 4.246 (m, 1H, $J_{2,1a}$ 3.7, $J_{2,1b}$ 8.1, $J_{2,3a}$ 4.9, $J_{2,3b}$ 7.5, H-2)
 3.761 (dd, 1H, $J_{5b,4}$ 6.5, $J_{5a,5b}$ 11.9, H-5b)
 3.724 (m, 1H, $J_{4,3a}$ 4.3, $J_{4,5a}$ 4.0, $J_{4,5b}$ 6.5, H-4)
 3.700 (dd, 1H, $J_{5a,4}$ 4.0, $J_{5a,5b}$ 11.9, H-5a)
 3.013 (dd, 1H, $J_{1a,1b}$ 13.1, $J_{1b,2}$ 8.1, H-1b)
 2.698 (dd, 1H, $J_{1a,1b}$ 13.1, $J_{1a,2}$ 3.7, H-1a)
 2.411 (s, 3H, tolyl Me)
 1.879 (ddd, 1H, $J_{3a,3b}$ 14.5, $J_{3b,2}$ 7.5, $J_{3b,4}$ 7.5, H-3b)
 1.840 (ddd, 1H, $J_{3a,3b}$ 14.5, $J_{3a,2}$ 4.9, $J_{3a,4}$ 4.9, H-3a)
 1.050 (s, 9H, CMe₃)

δ_c 141.63S, 140.70S, 138.02S, 133.23S, 133.11S (*ipso* carbons), 135.52D, 135.56D;
 129.97D, 129.78D, 128.43D, 127.89D, 127.74D, 124.08D (aromatic carbons);
 78.05D (C-4); 71.85T (OCH₂Ph); 66.77D (C-2); 65.76T (C-5); 63.44T (C-1); 38.45T
 (C-3); 26.82Q (CMe₃); 21.37Q (tolyl Me); 19.16S (CMe₃).

FAB-MS: m/z 586 [M]⁺. Exact mass: Calculated for C₃₅H₄₂O₄SSi, 586.2573; Found,
 586.2573.



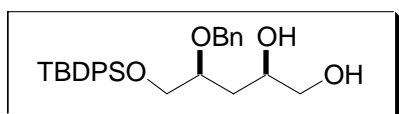
(1R,2R,4S)-1,2-Diacetoxy-4-(benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]-1-(*p*-tolylsulfanyl)-pentane **122**

A solution of the β -hydroxysulfoxide **121** (1.40 g, 2.40 mmol) and sodium acetate (1.90 g, 24.0 mmol) in acetic anhydride (20 ml) was refluxed for 7 h. The reaction was allowed to cool and diluted with toluene (20 ml). The solvent was evaporated under reduced pressure, the residue dissolved in diethyl ether (50 ml) and the salt removed by filtration through celite. After evaporation the solvent, the crude product was purified by column chromatography (hexane-EtOAc, 3:1) to yield the Pummerer product **122** (1.32 g, 85%)(a 1:1 diastereomeric mixture) as a yellow wax; R_f 0.37 (hexane-EtOAc, 3:1).

δ_H 7.68-7.63 and 7.41-7.23 (m, 19H, aromatic protons)

6.175 (d, 1H, $J_{1,2}$ 3.9, H-1)
 6.117 (d, 1H, $J_{1,2}$ 5.7, H-1)*
 5.370 (ddd, 1H, $J_{2,1}$ 3.9, $J_{2,3a}$ 3.9, $J_{2,3b}$ 14.5, H-2)
 5.325 (ddd, 1H, $J_{2,1}$ 5.7, $J_{2,3a}$ 8.0, $J_{2,3b}$ 4.8, H-2)*
 4.540 (d, 1H, $J_{a,b}$ 11.5, OCH₂Ph)
 4.526 (d, 1H, $J_{a,b}$ 11.6, OCH₂Ph)
 4.447 (d, 1H, $J_{a,b}$ 11.5, OCH₂Ph)
 4.365 (d, 1H, $J_{a,b}$ 11.6, OCH₂Ph)
 3.739 (dd, 1H, $J_{5a,5b}$ 10.6, $J_{5b,4}$ 6.2, H-5b)
 3.723 (dd, 1H, $J_{5a,5b}$ 10.6, $J_{5b,4}$ 6.2, H-5b)
 3.687 (dd, 2H, $J_{5a,5b}$ 10.6, $J_{5a,4}$ 6.2, H-5a)
 3.65-3.52 (m, 2H, H4)
 2.30-2.12 (m, 2H, H-3b)
 2.07-1.91 (m, 2H, H-3a)
 2.303 (s, 3H, acetate CH₃)
 2.282 (s, 3H, acetate CH₃)
 2.009 (s, 6H, tolyl CH₃)
 1.878 (s, 3H, acetate CH₃)
 1.866 (s, 3H, acetate CH₃)
 1.054 (s, 9H, CMe₃)
 1.043 (s, 9H, CMe₃)

δ_C 170.04S, 169.91S, 169.51S, 169.27S (CO acetate); 138.74S, 138.50S, 134.15S, 133.43S (*ipso* carbons); 135.62D, 129.86D, 129.84D, 129.69D, 128.24D, 127.71D, 27.42D (aromatic carbons); 82.60D and 81.40D (C-1); 77.14D and 76.82D (C-4); 71.89D and 71.60D (C-2); 71.76T and 71.64T (OCH₂Ph); 65.26T and 65.21T (C-5); 32.85T and 32.11T (C-3); 26.82Q (CMe₃), 21.12Q (tolyl Me); 20.86Q, 20.82Q and 20.74Q (acetate Me); 19.20S (CMe₃).



(2R,4S)-4-(Benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]-pentane-1,2-diol 123

A solution of the Pummerer product **122** (1.30 g, 1.97 mmol) in dry diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (0.185 g, 4.87 mmol) in dry diethyl ether (10 ml). The reaction mixture was stirred at RT for 90 min. The excess LiAlH₄ was destroyed by careful quenching of the reaction with 5M NaOH and extraction of the formed white solid with hot EtOAc (4x30 ml). The combined EtOAc solutions were evaporated and the residue purified by column chromatography (hexane-EtOAc, 1:5) to give the diol **123** (0.76 g, 83%) as a colourless oil; [α]_D -29.9 (*c* 0.74, CHCl₃); R_f 0.69 (hexane-EtOAc, 1:5).

δ_H 7.69-7.21 (s, 15H, aromatic protons),

4.680 (d, 1H, J_{a,b} 11.4, OCH₂Ph)

4.450 (d, 1H, J_{b,a} 11.4, OCH₂Ph)

3.867 (m, 1H, H-2)

3.80-3.67 (m, 2H, H-4 and H-5)

3.534 (dd, 1H, J_{1a,1b} 11.1, J_{1b,2} 3.6, H-1b)

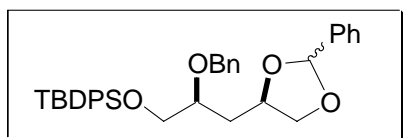
3.419 (dd, 1H, J_{1a,1b} 11.1, J_{1a,2} 6.2, H-1a)

1.78-1.67 (m, 2H, H-3)

1.065 (s, 9H, CMe₃)

δ_C 137.89S, 133.22S, 133.11S (*ipso* carbons), 135.62D, 135.59D, 129.82D, 128.50D, 127.88D, 127.77D (aromatic carbon); 79.45D (C-4); 72.06T (OCH₂Ph); 71.03D (C-2); 66.77T (C-1); 65.89T (C-5); 35.02T (C-3); 26.83Q (CMe₃); 19.17S (CMe₃).

FAB-MS: *m/z* 464 [M]⁺. Exact mass: Calculated for C₂₈H₃₆O₄Si, 464.2383; Found, 464.2381.



(2R,4S)-1,2-O-Benzylidene-4-(benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]pentane-1,2-diol **124**

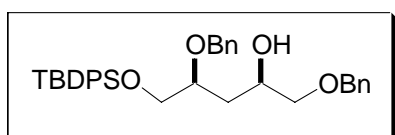
p-Toluenesulfonic acid (60 mg) was added to a solution of the diol **123** (0.70 g, 1.50 mmol) and α,α -dimethoxytoluene (4 ml) in dichloromethane (3 ml) and the solution stirred for 16 h at RT. The reaction mixture was neutralized with Et₃N (1 ml), diluted with diethyl

ether (20 ml) and washed with water. The organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography using EtOAc-hexane (1:8) as eluent. The benzylidene derivative **124** (580 mg, 70%)(a 1:1 diastereomeric mixture) was obtained as a clear colourless oil; R_f 0.48 (EtOAc-hexane, 1:8).

δ_{H} 7.71-7.67 (m, aromatic protons)
 7.26-7.48 (m, aromatic protons)
 5.903 (s, 1H, acetal CH)
 5.752 (s, 1H, acetal CH)
 4.641 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
 4.624 (d, 1H, J_{a,b} 11.7, OCH₂Ph)
 4.470 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
 4.457 (d, 1H, J_{a,b} 11.7, OCH₂Ph)
 4.321 (m, 2H, H-2)
 4.068 (dd, 1H, J_{1a,1b} 7.8, J_{1b,2} 6.0 H-1b)
 3.938 (dd, 1H, J_{1a,1b} 7.8, J_{1a,2} 6.6, H-1a)
 3.826 (dd, 2H, J_{5b,4} 5.3, J_{5a,5b} 10.9, H-5b)
 3.758 (dd, 1H, J_{5a,4} 4.6, J_{5a,5b} 10.9, H-5a)
 3.751 (dd, 1H, J_{5a,4} 4.6, J_{5a,5b} 10.9, H-5a)
 3.68-3.54 (m, 2H, H-4)
 2.16-2.05 (m, 2H, H-3b)
 1.99-1.85 (m, 2H, H-3a)

δ_{C} 138.54S, 137.92S, 133.45S, 133.35S (*ipso* carbons), 129.71-126.32 (aromatic carbons); 103.20D and 103.03D (acetal C-2); 76.75D and 76.70D (C-4); 74.48D and 73.56D (C-2); 71.78T (OCH₂Ph); 70.78T and 70.07T (C-1); 65.61T and 65.52T (C-5); 35.36T and 35.03T (C-3); 26.85Q (CMe₃); 19.20S (CMe₃).

FAB-MS: m/z 552 [M]⁺. Exact mass: Calculated for C₃₅H₄₀O₄Si, 552.2696; Found, 552.2687.



(2*R*,4*S*)-1,4-Di(benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]pentan-2-ol 125

DIBALH (10M, 0.04 ml, 0.4 mmol) was added by syringe to a solution of the benzyldiene derivative **124** (0.50 g, 0.90 mmol) in dichloromethane (5 ml) at -78°C under an argon atmosphere and the reaction stirred at room temperature for 2 h. Excess DIBALH was destroyed by careful addition of methanol (10 ml) followed by saturated NH_4Cl solution and the pH adjusted to 4 with 0.05M HCl. Additional dichloromethane (20 ml) was added and the organic phase dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography with EtOAc-hexane (3:5) as eluent to give the secondary alcohol **125** (0.28 g, 50%) as a colourless oil; R_f 0.30 (EtOAc-hexane, 1:4).

δ_{H} 7.27-7.68 and 7.47-7.24 (m, 20H, aromatic protons)

4.694 (d, 1H, $J_{\text{a,b}}$ 11.4, OCH_2Ph)

4.541 (s, 2H, OCH_2Ph)

4.485 (d, 1H, $J_{\text{a,b}}$ 11.4, OCH_2Ph)

4.001 (m, 1H, H-2)

3.83-3.70 (m, 2H, H-4 and H-5)

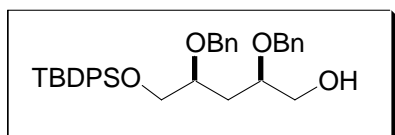
3.231 (d, 1H, $J_{2,\text{OH}}$ 2.3, 2-OH)

3.417 and 3.404 (AB part of ABX system, 2H, J_{AB} 9.6, J_{BX} 4.7, J_{AX} 6.1, H-1)

1.870 (ddd, 1H, $J_{3\text{a},3\text{b}}$ 14.5, $J_{3\text{b},4}$ 4.0, $J_{3\text{b},2}$ 4.0, H-3b)

1.750 (ddd, 1H, $J_{3\text{a},3\text{b}}$ 14.5, $J_{3\text{b},4}$ 8.3, $J_{3\text{b},2}$ 8.3, H-3b)

δ_{C} 138.23S, 138.17S, 133.35S, 133.24S (*ipso* carbons); 135.62D, 135.59D, 129.72D, 128.38D, 128.36D, 127.81D, 127.70D, 127.67D, 127.63D (aromatic carbons); 78.94D (C-4); 74.25T (C-1); 73.30T (OCH_2Ph); 71.93T (OCH_2Ph); 69.13D (C-2); 65.91T (C-5); 35.44T (C-3); 26.82Q (CMe_3); 19.16S (CMe_3).


(2*R*,4*S*)-2,4-Di(benzyloxy)-5-[(*t*-butyldiphenylsilyl)oxy]pentan-1-ol 126

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.55 ml, 4.50 mmol) was added by syringe to a solution of the benzyldiene protected compound **124** (0.50 g, 0.90 mmol) and $\text{BH}_3 \cdot \text{Me}_2\text{NH}$ complex (247 mg, 4.50 mmol) in anhydrous dichloromethane (10 ml) at -40°C . After stirring for 2 h at 0°C the

solution was quenched with saturated aqueous NaHCO₃ solution (5 ml) and extracted with CHCl₃ (15 ml). The organic phase was dried (Na₂SO₄) and evaporated. The crude product was purified by column chromatography using hexane-EtOAc (4:1) to provide the primary alcohol **126** (0.30 g, 60%) as an oil; [α]_D -35.6 (*c* 1.6, CHCl₃); R_f 0.33 (hexane-EtOAc, 4:1).

δ_H 7.72-7.65 and 7.46-7.25 (m, 20H, aromatic protons)

4.454 (d, 1H, J_{a,b} 11.5, OCH₂Ph)

4.485 (d, 1H, J_{a,b} 11.7, OCH₂Ph)

4.560 (d, 1H, J_{a,b} 11.7, OCH₂Ph)

4.640 (d, 1H, J_{a,b} 11.5, OCH₂Ph)

3.778 (dd, 1H, J_{5b,4} 5.2, J_{5a,5b} 10.4, H-5b)

3.72 (m, 3H, H-2, H-4 and H-5a)

3.600 (dd, 1H, J_{1a,1b} 11.6, J_{1b,2} 4.1, H-1b)

3.504 (dd, 1H, J_{1a,1b} 11.6, J_{1a,2} 6.0, H-1a)

2.19 (br t, 1H, J_{1,OH} 5.7, 1-OH)

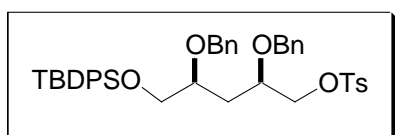
1.98-1.84 (m, 2H, H-3)

1.081 (s, 9H, CMe₃)

δ_C 138.39S, 133.41S, 133.35S (*ipso* carbons), 135.61D, 129.71-127.58 (aromatic carbons); 76.70D (C-4); 76.40D (C-2); 71.91T (OCH₂Ph); 71.07T (OCH₂Ph); 65.88T (C-5); 64.02T (C-1); 32.81T (C-3); 26.84Q (CMe₃); 19.19S (CMe₃).

FAB-MS: *m/z* 554 [M]⁺. Exact mass: Calculated for C₃₅H₄₂O₄Si, 554.2853; Found, 554.2853.

7.3.3 Linkage of the two C₅ units



(2*R*,4*S*)-2,4-Di(benzyloxy)-5-(*t*-butyldiphenylsilyloxy)-pentan-1-ol tosylate **127**

DMAP (142 mg, 1.17 mmol) and *p*-toluenesulfonyl chloride (214 mg 1.12 mmol) were added to a solution of the primary alcohol **126** (0.50 g, 0.90 mmol) in dichloromethane (7

ml) at 0°C. The reaction was stirred at RT for 16 h. Water (10ml) was added and the mixture stirred for 30 min. The organic phase was dried (Na₂SO₄) and evaporated. Column chromatography of the crude product using hexane-EtOAc (5:1) afforded the *O*-tosylate **127** (0.56 g, 90%) as an oil; [α]_D -12.7 (*c* 2.0, CHCl₃); R_f 0.30 (hexane-EtOAc, 5:1).

δ_H 7.96-7.43 (m, 20H, aromatic protons)

4.822 (d, 1H, J_{a,b} 11.6, OCH₂Ph)

4.764 (d, 1H, J_{a,b} 11.6, OCH₂Ph)

4.660 (d, 1H, J_{a,b} 11.6, OCH₂Ph)

4.629 (d, 1H, J_{a,b} 11.6, OCH₂Ph)

4.352 (dd, 1H, J_{1a,1b} 10.6, J_{1b,2} 3.4, H-1b)

4.269 (dd, 1H, J_{1a,1b} 10.6, J_{1a,2} 6.2, H-1a)

4.043 (m, 1H, J_{2,1a} 6.2, J_{2,1b} 3.4, J_{2,3a} 5.7, J_{2,3b} 6.3, H-2)

3.945 (dd, 1H, J_{5b,4} 5.3, J_{5a,5b} 10.5, H-5b)

3.894 (dd, 1H, J_{5a,4} 4.4, J_{5a,5b} 10.5, H-5a)

3.852 (m, 1H, J_{4,3a} 7.2, J_{4,3b} 4.6, J_{4,5a} 4.4, J_{4,5b} 5.3, H-4)

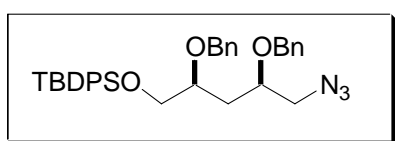
2.314 (s, 3H, tolyl CH₃)

2.135 (ddd, 1H, J_{3b,2} 6.3, J_{3a,3b} 14.5, J_{3b,4} 4.6, H-3b)

2.067 (ddd, 1H, J_{3a,2} 5.7, J_{3a,3b} 14.5, J_{3a,4} 7.2, H-3a)

δ_C 144.57S, 138.46S, 138.00S, 133.36S, 133.29S, 133.04S (*ipso* carbons); 135.60D, 129.72-127.49 (aromatic carbons); 76.00D (C-4); 73.93D (C-2); 71.94T (C-1); 71.67T (2xOCH₂Ph); 65.58T (C-5); 33.34T (C-3); 26.85Q (CMe₃); 21.56Q (tolyl Me); 19.17S (CMe₃).

FAB-MS: *m/z* 708 [M]⁺. Exact mass: Calculated for C₄₂H₄₈O₆SSi, 708.2941; Found, 708.2941.



(2*R*,4*S*)- 1-azido-2,4-di(benzyloxy)-5-(*t*-[butyldiphenylsilyl]oxy)pentane 128

Sodium azide (63 mg, 0.97 mmol) was added to a solution of the *O*-tosylate **127** (270 mg, 0.39 mmol) in DMF (4 ml) and the reaction was heated at 90°C for 3.5 h. Diethyl ether (20 ml) and brine (20 ml) were added to the cooled reaction mixture. The organic phase was washed with brine (6x10 ml), dried (Na₂SO₄) and evaporated to give the azide **128** (203 mg, 90%) as a colourless oil; [α]_D -28.6 (*c* 0.60, CHCl₃). The product was not further purified.

δ_H 7.70-7.66 and 7.47-7.23 (m, 20H, aromatic protons)

4.618 (d, 1H, *J*_{a,b} 11.6, OCH₂Ph)

4.551 (d, 1H, *J*_{a,b} 11.4, OCH₂Ph)

4.520 (d, 1H, *J*_{a,b} 11.4, OCH₂Ph)

4.424 (d, 1H, *J*_{a,b} 11.6, OCH₂Ph)

3.761 (dd, 1H, *J*_{5b,4} 5.3, *J*_{5a,5b} 10.7, H-5b)

3.667 (dd, 1H, *J*_{5a,4} 4.8, *J*_{5a,5b} 10.7, H-5a)

3.715 (m, 1H, H-2)

3.567 (m, 1H, H-4)

3.255 (dd, 1H, *J*_{1a,1b} 12.9, *J*_{1b,2} 3.7, H-1b)

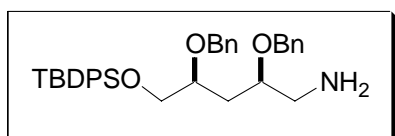
3.193 (dd, 1H, *J*_{1a,1b} 12.9, *J*_{1a,2} 6.2, H-1a)

1.905 (dd, 2H, *J*_{3,4} 6.2, *J*_{2,3} 6.2, H-3)

1.080 (s, 9H, CMe₃)

δ_C 138.06S, 133.42S, 133.33S (*ipso* carbons); 135.62D, 129.74D, 128.36D, 127.77D, 127.73D, 127.64D, 127.57D (aromatic carbons); 76.09D (C-4); 75.50D (C-2); 71.69T (OCH₂Ph); 71.37T (OCH₂Ph); 65.74T (C-5); 54.02T (C-1); 33.96T (C-3); 26.86Q (CMe₃); 19.19S (CMe₃).

FAB-MS: *m/z* 579 [M]⁺. Exact mass: Calculated for C₃₅H₄₃N₃O₃Si, 579.2917; Found, 579.2918.



(2*R*,4*S*)- 1-Amino-2,4-di(benzyloxy)-5-(*t*-[butyldiphenylsilyl]oxy)pentane 129

Method 1

The azide **128** (300 mg, 0.52 mmol) was dissolved in dry diethyl ether (40 ml) and LiAlH₄ (20 mg, 0.52 mmol) was added in one portion and the suspension stirred for 2 h at RT. The reaction was carefully quenched by addition of 5M NaOH until a white precipitate had formed. Anhydrous Na₂SO₄ was added and the precipitate collected by filtration and extracted twice with diethyl ether (40 ml). The combined diethyl ether extracts were evaporated and the residue was purified by column chromatography (CHCl₃-MeOH, 5:1), to give the amine **129** (229 mg, 80%); [α]_D -45.2 (*c* 0.04, CHCl₃); R_f 0.48 (CHCl₃-MeOH, 5:1).

The product appeared to show two spots on TLC but NMR shows signals of a single product only.

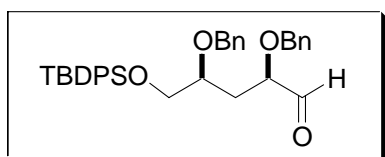
δ_{H} 7.69-7.23 (m, 20H, aromatic protons),
4.613 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
4.533 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
4.425 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
4.433 (d, 1H, J_{a,b} 11.6, OCH₂Ph)
3.941 (m, 1H, H-4)
3.751 (dd, 1H, J_{5b,4} 5.4, J_{5a,5b} 10.6, H-5b)
3.669 (dd, 1H, J_{5a,4} 4.9, J_{5a,5b} 10.6, H-5a)
3.573 (dd, 1H, H-2)
2.792 (dd, 1H, J_{1a,1b} 13.3, J_{1b,2} 3.5, H-1b)
2.680 (dd, 1H, J_{1a,1b} 13.3, J_{1a,2} 6.3, H-1a)
1.966 (m, 2H, H-3)
1.068 (s, 9H, CMe₃)

δ_{C} 138.55-127.53 (aromatic carbons); 76.79D (C-4); 76.32D (C-2); 71.86T (OCH₂Ph); 70.91T (OCH₂Ph); 65.90T (C-5); 44.53(C-1); 33.60T (C-3); 26.86Q (CMe₃); 19.19S (CMe₂).

FAB-MS: *m/z* 553 [M]⁺. Exact mass: Calculated for C₃₅H₄₃NO₃Si, 553.3013; Found, 553.3013.

Method 2¹³

A mixture of the alcohol **126** (200 mg, 0.36 mmol), sodium azide (28 mg, 0.43 mmol) and Ph₃P (200 mg, 0.76 mmol) in CCl₄-DMF (1:4, 5 ml) was warmed at 90°C for 2 h. (TLC control). The reaction mixture was diluted with water (10 ml) and extracted with diethyl ether (20 ml). The organic phase was dried (Na₂SO₄), filtered and evaporated. The crude product was purified by column chromatography with hexane-EtOAc (1:3) to give a product (40 mg); R_f 0.86 (hexane-EtOAc, 1:3). The NMR spectrum of the product showed it to be a 1:1 mixture of the azide **128** and the amine **129**.



(2*R*,4*S*)-2,4-Di(benzyloxy)-5-(*t*-[butyldiphenylsilyl]oxy)pentanal **130**

Periodinane (0.15 g, 0.36 mmol) was added to a solution of the alcohol **126** (0.20 g, 0.36 mmol) in CH₂Cl₂ (5 ml). The reaction mixture was stirred at room temperature for 4 h. More periodinane (0.30 g, 0.72 mmol) was added and stirred for 16 h. The reaction mixture was diluted with diethyl ether (20 ml), washed with NaHCO₃:Na₂S₂O₃ (1:7) solution and stirred until a colourless solution was obtained. The organic phase was dried (Na₂SO₄), filtered and evaporated. Column chromatography of the crude product using hexane-EtOAc (5:1) as eluent gave the aldehyde **130** (0.16 g, 80%) as a colourless oil; [α]_D -14.6 (*c* 0.10, CHCl₃); R_f 0.68 (hexane-EtOAc, 5:1).

δ _H	9.599 (d, 1H, J _{2,1} 1.2, H-1)
	7.67-7.23 (m, 20H, aromatic protons)
	4.675 (d, 1H, J _{a,b} 11.9, OCH ₂ Ph)
	4.541 (d, 1H, J _{a,b} 11.9, OCH ₂ Ph)
	4.454 (d, 1H, J _{a,b} 11.4, OCH ₂ Ph)
	4.443 (d, 1H, J _{a,b} 11.4, OCH ₂ Ph)
	3.928 (m, 1H, J _{2,1} 1.3, J _{2,3a} 4.5, J _{2,3b} 6.2, H-2)
	3.822 (m, 1H, J _{4,3a} 8.6, J _{4,3b} 3.7, J _{4,5a} 5.2, J _{4,5b} 5.3, H-4)
	3.713 (dd, 1H, J _{5b,4} 5.3, J _{5b,5a} 10.3, H-5b)
	3.660 (dd, 1H, J _{5a,4} 5.2, J _{5a,5b} 10.3, H-5a)

¹³ Videya, S.R.G.; Venkat Rao, G.; Subramanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* **2000**, *30*, 2233.

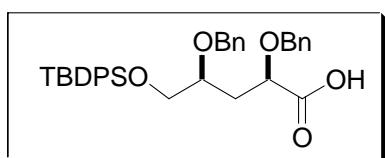
2.146 (ddd, 1H, $J_{3b,2}$ 6.2, $J_{3b,3a}$ 14.5, $J_{3a,4}$ 3.7, H-3b)

2.060 (ddd, 1H, $J_{3a,2}$ 4.5, $J_{3a,3b}$ 14.5, $J_{3a,4}$ 8.6, H-3a)

1.063 (s, 9H, CMe₃)

δ_c 202.42D (C-1), 138.37S, 137.51S, 133.77S, 133.71S (*ipso* carbons); 136.02D, 130.12-127.44D (aromatic carbons); 80.46D (C-2); 75.44D (C-4); 72.06T (OCH₂Ph); 71.97T (OCH₂Ph); 65.62T (C-5); 33.54T (C-3); 26.86Q (CMe₃); 19.23S (CMe₃).

FAB-MS: m/z 552 [M]⁺. Exact mass: Calculated for C₃₅H₄₀O₄Si, 552.2696; Found, 552.2699.



(2R,4S)-2,4-Di(benzyloxy)-5-[*t*-(butyldiphenylsilyl)oxy]pentanoic acid 131

Sodium chlorite (51 mg, 0.45 mmol) in water (0.5 ml) was added at 3-5°C over a period of 2 h to a stirred mixture of the aldehyde **130** (170 mg, 0.30 mmol,) in acetonitrile (1.0 ml), NaH₂PO₄ buffer (pH 4, 0.5 ml) (prepared by dissolving 0.20 g of NaH₂PO₄ in 2.0 ml water) and 30% H₂O₂ (35 μ l). After the addition the reaction was allowed to warm to RT and stirred for an additional 2 h. Sodium sulfite (12 mg) was added to react with any remaining HOCl or H₂O₂. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc (2x10 ml). The organic phase was dried (Na₂SO₄) and evaporated. The residue was purified by column chromatography using hexane-EtOAc (1:1) as eluent to give the acid **131** (137 mg, 80%) as a colourless oil. [α]_D -15.3 (*c* 0.30, CHCl₃); R_f 0.33 (hexane-EtOAc, 1:1).

δ_H 7.66-7.20 (m, 20H, aromatic protons)

4.634 (d, 1H, $J_{a,b}$ 11.4, OCH₂Ph)

4.557 (d, 1H, $J_{a,b}$ 11.6, OCH₂Ph)

4.495 (d, 1H, $J_{a,b}$ 11.6, OCH₂Ph)

4.422 (d, 1H, $J_{a,b}$ 11.4, OCH₂Ph)

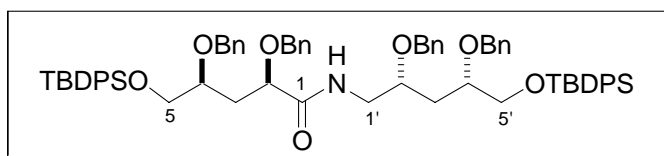
4.130 (t, 1H, $J_{2,3a}$ 5.7, $J_{2,3b}$ 5.7, H-2)

3.803 (m, 1H, $J_{4,3a}$ 7.5, $J_{4,3b}$ 4.6, $J_{4,5a}$ 5.0, $J_{4,5b}$ 4.9, H-4)

3.703 (dd, 1H, $J_{5b,4}$ 4.9, $J_{5a,5b}$ 10.7, H-5b)
 3.643 (dd, 1H, $J_{5a,4}$ 5.0, $J_{5a,5b}$ 10.7, H-5a)
 2.185 (ddd, 1H, $J_{3b,2}$ 5.7, $J_{3a,3b}$ 14.5, $J_{3b,4}$ 4.6, H-3b)
 2.118 (ddd, 1H, $J_{3a,2}$ 5.7, $J_{3a,3b}$ 14.5, $J_{3a,4}$ 7.5, H-3a)
 1.045 (s, 9H, CMe_3)

δ_{C} 176.26S (C-1); 138.50S, 137.04S, 133.41S, 133.34S (*ipso* carbons), 135.62D, 129.69-127.36D (aromatic carbons), 75.95D (C-4); 74.59D (C-2); 72.34T (OCH_2Ph); 71.96T (OCH_2Ph); 65.63T (C-5); 34.66T (C-3); 26.83Q (CMe_3); 19.19S (CMe_3).

FAB-MS: m/z 568 $[\text{M}]^+$. Exact mass: Calculated for $\text{C}_{35}\text{H}_{40}\text{O}_5\text{Si}$, 568.2646; Found, 568.2650.



(2*R*,4*S*)-*N*-{(2'*R*,4'*S*)-2,4-di(benzyloxy)-5'-[*t*-(butyldiphenylsilyl)oxy]pentan-1'-yl}-2,4-di(benzyloxy)-5-[*t*-(butyldiphenylsilyl)oxy]pentanamide **132**

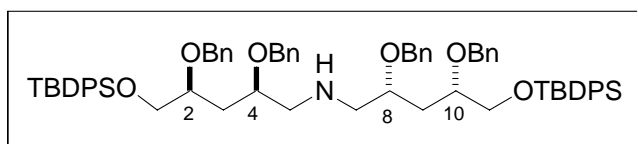
1,1'- Carbonyldiimidazole (170 mg, 1.06 mmol) was added to a solution of the acid **131** (1.0 g, 1.76 mmol) in dry DMF (8ml) and the mixture stirred at 45°C for 30 minutes. After cooling the amine **129** (0.97 g, 1.76 mmol) in dry DMF (2ml) was added and the reaction was stirred at room temperature for 3 h. The reaction was diluted with diethyl ether (30 ml) and washed with brine (4x20 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography with hexane-EtOAc (4:1) to give the amide **132** (1.45 g, 75%) as an oil; $[\alpha]_{\text{D}} -25.0$ (c 0.20, CHCl_3) R_{f} 0.44 (hexane-EtOAc, 4:1)

δ_{H} 7.67-7.14 (m, 40H, aromatic protons)
 6.863 (dd, 1H, $J_{\text{NH},1'a}$ 5.2, $J_{\text{NH},1'b}$ 6.2, NH)
 4.617 (d, 1H, J 11.6, OCH_2Ph)¹
 4.610 (d, 1H, J 11.6, OCH_2Ph)²
 4.554 (d, 1H, J 11.6, OCH_2Ph)²
 4.453 (d, 1H, J 11.6, OCH_2Ph)³
 4.437 (d, 1H, J 11.6, OCH_2Ph)¹

- 4.410 (d, 1H, J 11.3, OCH₂Ph)⁴
 4.381(d, 1H, J 11.3, OCH₂Ph)⁴
 3.969 (dd, 1H, J_{3a,2} 6.5, J_{3b,2} 5.7, H-2)
 3.82-3.77 (m, 1H, H-4)
 3.75-3.60 (dd, 6H, H-1a, H-1b, H-2', H-4', H-5'a, H-5'b,)
 3.397 (ddd, 1H, J_{1'b,NH} 6.2, J_{1'a,1'b} 13.9, J_{1'b,2'} 6.2, H-1'b)
 3.288 (ddd, 1H, J_{1'a,NH} 5.2, J_{1'a,1'b} 13.9, J_{1'a,2'} 4.5, H-1'a)
 2.039 (ddd, 1H, J_{3b,2} 5.6, J_{3a,3b} 14.3, J_{3b,4} 5.6, H-3b)
 1.924 (ddd, 1H, J_{3a,2} 6.7, J_{3a,3b} 14.3, J_{3a,4} 6.7, H-3a)
 1.856 (ddd, 1H, J_{3'b,2'} 4.9 or 7.8, J_{3'a,3'b} 14.5, J_{3'b,4'} 4.9 or 7.8, H-3'b)
 1.763(ddd, 1H, J_{3'a,2'} 4.0 or 6.8, J_{3'a,3'b} 14.5, J_{3'a,4'} 4.0 or 6.8, H-3'a)
 1.078(s, 9H, CMe₃)

Note: Identical numbers *e.g.* ^{1,2,3 or 4} imply that the protons are from the same benzyl group.

- δ_C 172.56S (C-1); 138.98-127-22 (aromatic carbons), 77.35D (C-2); 76.88D (C-4);
 76.46D (C-4'); 74.68D (C-2'); 72.48T (); 71.98T (OCH₂Ph); 71.84T (OCH₂Ph);
 70.70T (OCH₂Ph); 66.33T (C-5 or C-5'); 66.04T (C-5' or C-5); 41.06T (C-1');
 35.15T (C-3); 33.78T (C-3'); 26.86Q (CMe₃); 19.19S (CMe₃).



(2*S*,4*R*,8*R*,10*S*)-1,10-Di[(*t*-butyldiphenylsilyloxy)]-6-aza-2,4,8,10-tetra(benzyloxy)undecane **133**

Borane dimethylsulfide complex, BH₃.SMe₂, (10M, 90 μl, 0.90 mmol) was added dropwise by syringe to a solution of the amide **132** (400 mg, 0.36 mmol) in anhydrous THF (4 ml) at 0°C. The reaction was stirred at 50°C for 6 h and then quenched by addition of MeOH (3 ml). The solvent was evaporated to give a crude product which was purified by column chromatography using hexane-EtOAc (4:1) to give a 1:1 diastereomeric mixture of the borane complex of the amine **133** as an oil (270 mg); R_f 0.80 (hexane-EtOAc, 4:1).

- δ_H 7.37-7.09 (m, aromatic protons)
 4.595 (d, 1H, J 11.4, OCH₂Ph)
 4.536 (d, 1H, J 11.1, OCH₂Ph)

4.509 (d, 1H, J 11.4, OCH₂Ph)

4.430 (d, 1H, J 11.1, OCH₂Ph)

4.411 (d, 1H, J 11.4, OCH₂Ph)

4.394 (d, 1H, J 11.4, OCH₂Ph)

4.309 (d, 1H, J 11.6, OCH₂Ph)

4.234(d, 1H, J 11.6, OCH₂Ph)

4.40 (m, 1H, H-2)

3.8-3.40 (m, H-2, H-4, H-5)

3.08 (m, 1H, H-1)

2.70-2.38 (m, 3H, H-1)

2.00-1.50 (m, 4H, H-3)

1.061 (s, 9H, *t*-butyl)

1.048 (s, 9H, *t*-butyl)

δ_C 138.19-127.51 (aromatic carbons); 76.19D and 75.35D (C-4); 72.46D and 70.30D (C-2); 72.24T, 71.81T, 71.49T, and 70.36T (OCH₂Ph); 65.87T and 65.65T (C-5); 59.89T and 57.78T (C-1); 34.30T and 33.32T (C-3); 26.88Q (CMe₃); 19.21S (CMe₃).