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Asymmetric synthesis of novel immunosuppressive agents

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ASYMMETRIC SYNTHESIS

of

NOVEL IMMUNOSUPPRESSIVE AGENTS

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Department of Chemistry

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DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Matthew D. Cliff

August 1995

PUBLICATIONS

Sections of the work described in this thesis have been reported in the following publications:

M. D. Cliff, S. G. Pyne, 'Synthesis of 4,4'-Biimidazoles' *Synthesis,* 1994, *7*, 681-682.

M. D. Cliff, S. G. Pyne, 'Direct Synthesis of Trimethylvinylstannanes from Aldehydes,' *Tetrahedron Lett.*, 1995, *36*, 763-766.

M. D. Cliff, S. G. Pyne, 'Asymmetric Synthesis of 2-Acetyl-4(5)-(1,2,4-trihydroxybutyl)imidazoles,' *J. Org. Chem.*, 1995, *60*, 2378-2383.

M. D. Cliff, S. G. Pyne, 'Asymmetric Synthesis of (1*R*,2*S*,3*R*)-2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazoles,' *Tetrahedron Lett.*, 1995, *36*, 5969-5972.

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ABBREVIATIONS

The following abbreviations have been used throughout this thesis.

[α]	specific rotation
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	α,α'-azobis(isobutyronitrile)
Ar	aryl
atm	atmosphere
Bn	benzyl
bp	boiling point
BHT	butylated hydroxytoluene
Bu	butyl
^{t}Bu	*tert*-butyl
°C	degrees Celsius
calcd	calculated
CI	chemical ionisation
COSY	correlation spectroscopy
CSA	camphorsufonic acid
δ	chemical shift in parts per million
d	doublet
dba	dibenzylideneacetone
de	diastereomeric excess
decomp	decomposes
DHQ	dihydroquinine
DHQD	dihydroquinidine
DMA	dimethylacetamide
DMAP	4-(*N*,*N*-dimethyl)aminopyridine

DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv.	(molar) equivalents
ES	electrospray
Et	ethyl
FAB	fast atom bombardment
g	gram
HETCOR	heteronuclear correlation spectroscopy
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
h	hours
HRMS	high-resolution mass spectrum
Hz	hertz
Imid.	imidazole
IND	indoline
IR	infrared
J	coupling constant
k	kilo
L	litre(s)
LAH	lithium aluminium hydride
lit.	literature
LDA	lithium diisopropylamine
m	multiplet (spectral), milli
M	mols per litre
Me	methyl
MHz	megahertz

min	minutes
mol	mole(s)
mp	melting point
MTPA	α-methoxy-α -trifluoromethylphenylacetate
MS	mass spectrometry
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOD	non-obese diabetic
p	pentet
Ph	phenyl
PHAL	phthalazine
ppm	parts per million
Pr	propyl
*i*Pr	isopropyl
PYR	pyrimidine
q	quartet
R_f	retention factor
rt	room temperature
s	singlet, second
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
t	tertiary
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran

THI	(1*R*,2*S*,3*R*)-2-Acetyl-4(5)-(1,2,3,4-tetrahydroxy butyl)imidazole
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilane
tosyl	*p*-toluenesufonyl
trityl	triphenylmethyl

ABSTRACT

This thesis presents the synthesis of several structural analogues of the immunosuppressant THI. In the first Chapter a review is made of the human immune system and its response to solid organ transplants. Current immunosuppressive drug therapies are examined with regard to organ transplantation as well as autoimmune diseases such as diabetes. The biological significance of THI is tabulated, as well as the detailed aims and synthetic strategies of this project.

A number of preliminary model studies are presented in Chapter 2 towards the synthesis of 2-acetyl-4-substituted imidazole compounds. A number of different synthetic routes are reported including C4 metallation and Heck reactions to introduce the C4-substituent onto imidazole. In addition, a synthetic route to a new 4,4'-biimidazole heterocyclic system is presented.

In Chapter 3 the Stille coupling reaction and the Sharpless asymmetric dihydroxylation reaction were developed to suit the synthesis of several mono- and trihydroxy-THI analogues. The enantiomeric purity and the stereochemical outcome of the Sharpless asymmetric dihydroxylation reactions is presented, which was based upon ^{1}H NMR analysis of Mosher MTPA esters.

The synthesis of all eight stereoisomers of THI is presented in Chapter 4. The Stille coupling and Sharpless asymmetric dihydroxylation reactions using chiral substrates were investigated and the limitations of these reactions examined. The eight stereoisomers of THI were isolated as their tetraacetates and the stereochemical assignments confirmed *via* chemical correlation. A direct synthetic route for the conversion of aldehydes into (*E*)-

trimethylvinylstannanes is also described.

A brief summary of all THI analogues synthesised is presented in Chapter 5, as well as current and future work in this area.

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CHAPTER 1

INTRODUCTION

1.1 The Immune System

The immune system is a diffuse organ which weighs about 1,000 g in adult humans. It is comprised of approximately 10^{12} lymphocytes (a specific type of leucocyte)[1] and accessory cells (e.g. polymorphonuclear leucocytes), 10^{20} antibody molecules and millions of molecules of various effector and regulatory substances that regulate proliferation, maturation and the differentiation of cells in the immune system.[2] It is also composed of numerous other complementary components.

The fundamental role of the immune system is to recognise 'self' from 'non-self' so as to maintain the health of an individual. This is achieved by the system fulfilling two main functions; to carry out an immunological surveillance of the body and to act as a defence against foreign substances (antigens) as depicted in Figure 1.1.

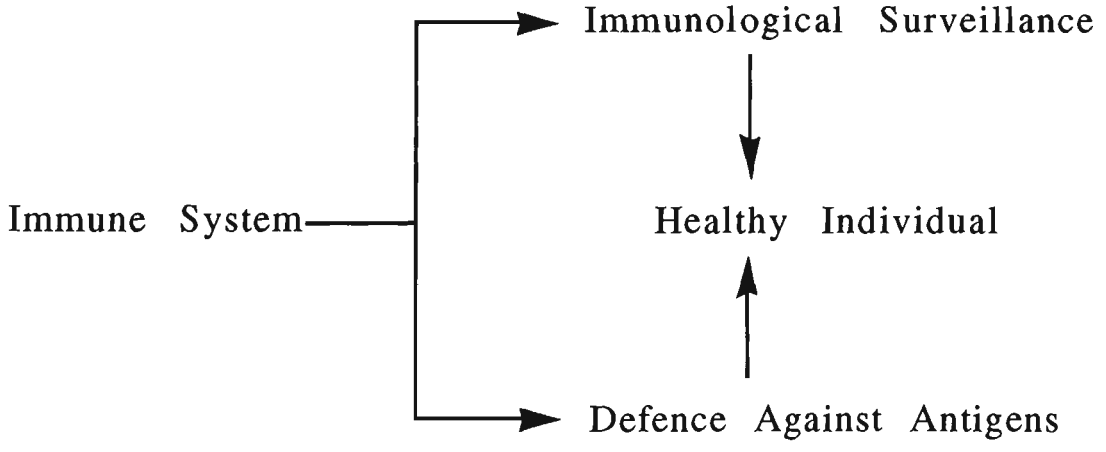


Figure 1.1 Functions of the immune system.

The immune system is triggered by the presence of foreign antigens, which set off a series of complex reactions known as an immune response. This response can be regarded as useful,

indifferent or harmful to the individual. Defence against infectious diseases is a typical advantageous response. The harmful type of immune response, however, can lead to various allergic reactions (hypersensitivity) to an individual's immediate environment. Hay fever is a common allergic reaction to atmospheric dust and pollen that causes watering of the eyes and nose due to inflammation of the mucous membranes in the sinus.[3]

The immune system is not only triggered by foreign antigens, but also by the bodies own cells. Antigenically altered cells and molecules that are recognised as foreign are capable of inducing an immune response (Figure 1.2). This can also be regarded as a useful (immunity against tumours) or harmful response (autoimmune diseases such as diabetes mellitus and rheumatoid arthritis).

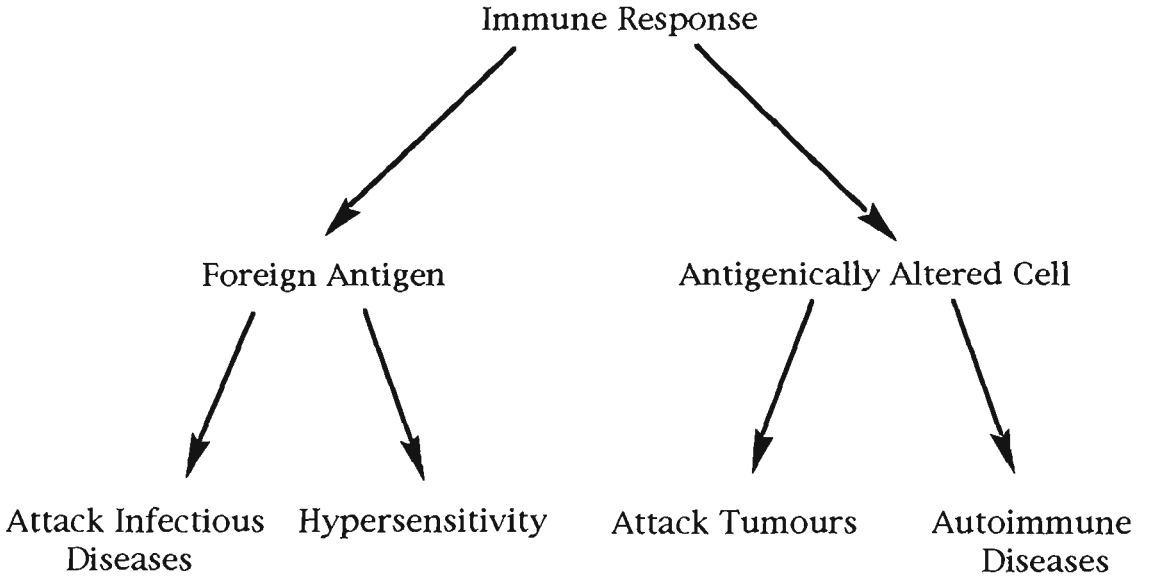


Figure 1.2 Types of immune reponses.

White blood cells (leucocytes) form the primary defence against invading organisms and other foreign material. The leucocyte count is typically about 10,000 cells per mm^3 of blood,[3] and is also found in large quantities in tissue such as the thymus, spleen and kidney.

The lymphocytes are the smallest of the leucocytes and comprise 20-35% of the total white blood count.[1] They are produced from stem cells in bone marrow[4] and are then transported to the primary lymphoid organs where they gain immunocompetence (the ability to recognise and respond to a foreign antigen) as part of their development.[5]

All vertebrates including humans have two types of primary lymphoid organs:
i) the thymus where lymphocytes called T-lymphocytes (T-cells) gain immunocompetence, and
ii) the bursa of Fabricius in birds, or its equivalent in mammals, where lymphocytes called B-lymphocytes (B-cells) are developed.[2,4]

After gaining immunocompetence, both lymphocyte types settle in secondary peripheral lymphoid organs (lymph nodes, spleen and certain aggregates of lymphoid tissue) or circulate freely in the blood.

The B- and T-lymphocytes contain antigen receptors on their surface. One end of the receptor is anchored to the phospholipid bilayer of the cell, while the second end protrudes out. The end of the receptor molecule that is protruding away from the lymphocyte surface contains a binding site that has a structure complementary to a specific antigen type. Similarly, the antigen can only bind to a single antigen receptor. Each key (antigen receptor) fits a single lock (antigen) (Figure 1.3). There exist millions of different binding sites throughout the lymphocyte population, as many as there are

antigen types present. However, each lymphocyte contains identical receptors with identical binding sites. Thus, of the millions of lymphocytes circulating within the body, only a tiny population possesses receptors suitable for a specific antigen, the rest contain other types of receptors.

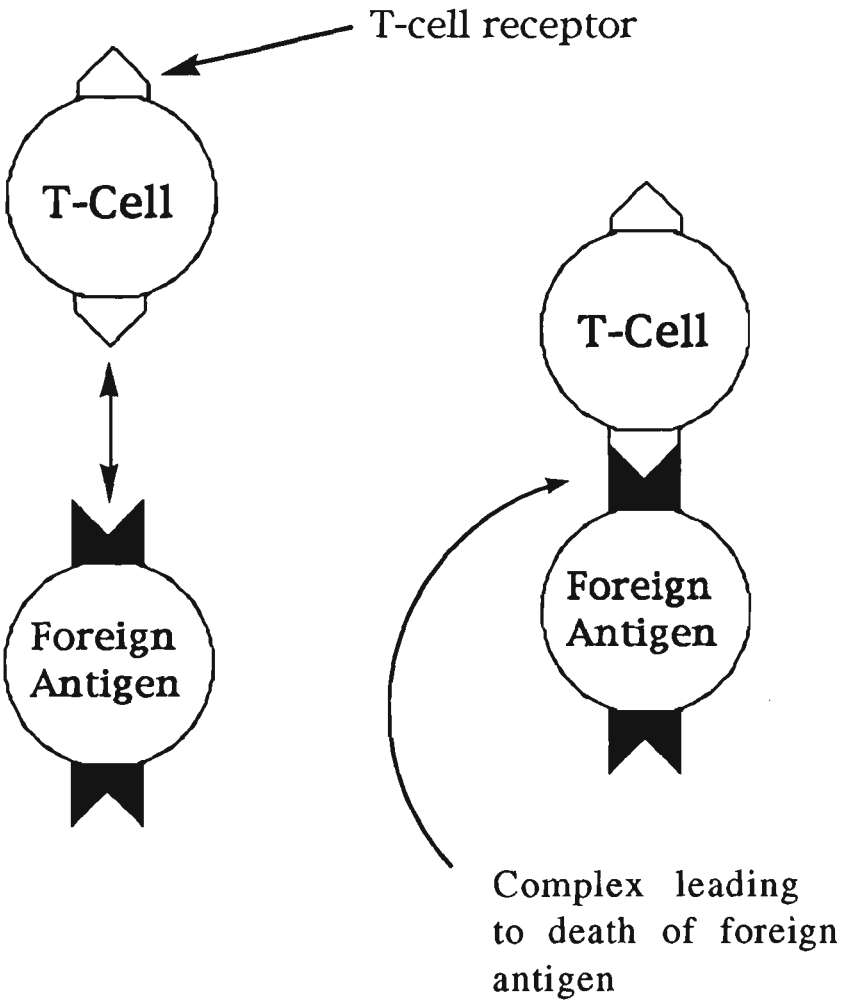


Figure 1.3 Binding of T-cell to foreign antigen.

1.1.1 Immune Mechanism

The immune response consists of two basic mechanisms, humoral immunity and cellular immunity.[2,4] When an antigen activates certain B-lymphocytes, the cells synthesise and secrete antibodies

(IgM, IgG, IgA, IgB and IgD) that are capable of recognising the antigen. The antibodies are responsible for the humoral type of immune response. When an antigen activates a T-lymphocyte however, antibodies are not produced. Instead various regulatory, cytotoxic and delayed-type hypersensitivity reactions occur. These are controlled by a number of T-lymphocyte sub-populations known as inducer or helper, suppressor and cytotoxic T-lymphocytes, as well as their products, the lymphokines and interleukins.

The helper T-cells (T_H-cells) assist in B-cell recognition of antigen and the subsequent production of antibodies. They are also the origin of cytotoxic T-cells. Suppressor T-cells (T_S-cells) suppress the initial phase of the immune response. This is achieved by one T_S-cell population blocking initial antibody formation in the B-cells, while other populations suppress the production of antigen cells, which are immune themselves to the body's immune system, particularly to cytotoxic T-cells. The overall effect of the T_S-cells provides a more vigorous immune response to foreign antigen.

Cytotoxic T-cells (T_C-cells) possess activity toxic to the antigen and have the ability to damage and kill target cells. The attack is target cell specific and does not harm surrounding tissue.

The effector and regulatory T-lymphocytes are involved in the immune mechanism either directly or *via* various chemical substances that they secrete. These substances are lymphokines and interleukins and act as immunohormones. They influence the activity and function of individual cell populations and other cell

types. The main producers of interleukins are believed to be the T_H-cells.

A particular lymphocyte population known as memory cells 'remember' specific antigens after the first encounter. The memory cells are responsible for a more rapid and intense immune response upon later contact with the same antigen. This type of immunity is known as acquired immunity.

The immune mechanisms and lymphocyte roles can be summarised in Figure 1.4. Although both mechanisms rely on different pathways, no immune mechanism can perform its function separately, both cooperate mutually and complement each other.

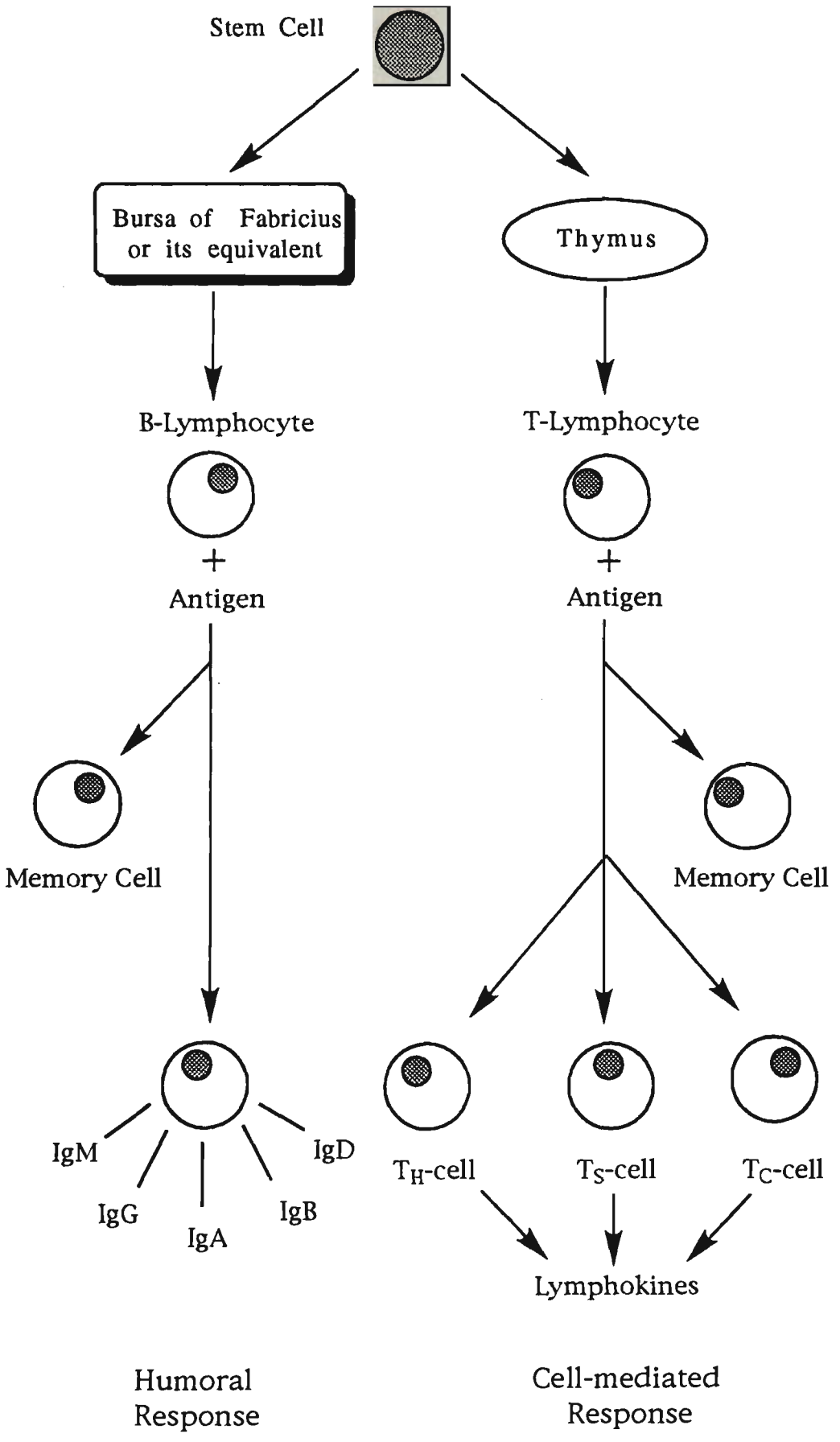


Figure 1.4 Immune mechanisms.

1.2 Organ Transplantation

The complexity of surgical transplantations has increased dramatically over the last 60 years. Initial studies on skin grafts of soldiers who had suffered various wounds and burns during World War II showed that grafts taken from the individuals own body were accepted, with the patient's chances of survival greatly increased. Grafts taken from other donors however, were regularly rejected within four weeks.[6] This seemingly simple observation lead to the awarding of the Nobel Prize to P. D. Medawar in 1960 and has been the starting point to the extensive study of transplantations by numerous groups. The complexity of such transplants has since increased to such a point that kidney replacements are common and even complete heart/lung transplantations no longer receive front page media attention.

Today both the number and survival rate of patients undergoing solid organ transplants have markedly increased. This has been due to a number of advances in the medical field, including the refinement of surgical procedures and medical and nursing managements, improved organ retrieval and storage and the development of modern drug therapies.[1]

1.2.1 Transplantation Types

There are four basic types of transplants used in modern surgery (Table 1.1).[2] Autografts are used where the donor tissue is able to be taken directly from the patient. Autografts are commonly used for skin grafts. Allografts come from different individuals of the

same biological species and are the most frequently used for human solid organ transplants. Isografts are a form of allograft where both the donor and recipient are genetically identical individuals of the same species. Transplantations between identical twins are surgically favoured due to the biological similarity of organs and the likelihood of human leucocyte matching. The final type of transplantation, a xenograft, is used between individual of two different biological species. This type is common in experimental trials between animals,[7,8] but will become increasingly important for humans as the procedure is refined and shortages in donor organs become more prevalent.

Table 1.1 Graft type *vs.* recipient-donor relationship.

Graft Designation	*Tissue Type*	*Recipient-Donor Genetic Relationship*
Autograft	Autogenous Autochtonous	The same individual (donor = recipient)
Isograft	Syngeneic Isogeneic	Genetically identical individuals of the same strain (homozygous twins)
Allograft	Allogenic	Genetically different individuals of the same species
Xenograft	Xenogeneic	Individuals of two different biological species

1.2.2 Graft Rejection

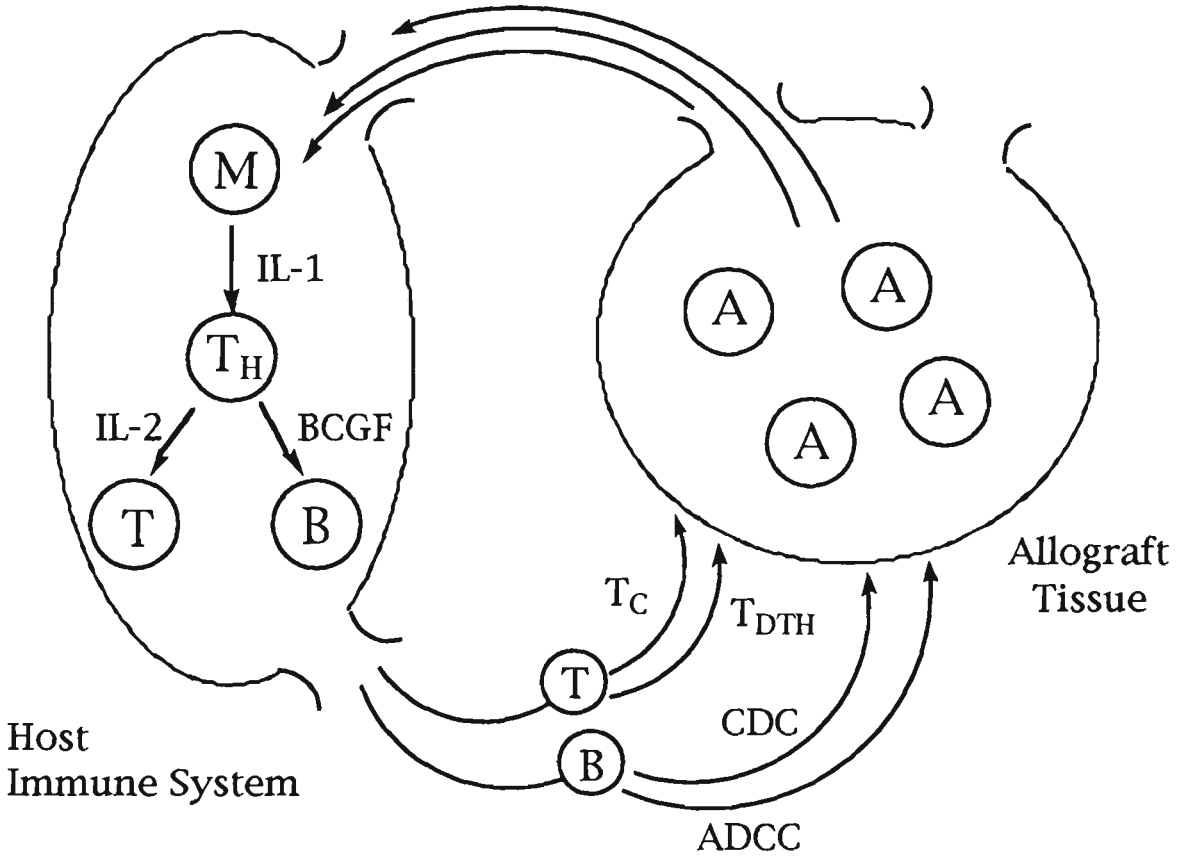
For a transplantation to be successful the recipients immune system must accept the donor organ and not identify the tissue as

antigenic. The current level of success of organ transplants is due primarily to drug mediated suppression of the immune system.[9] With the exception of rare organ transplantations between monozygotic twins, lifelong administration of multiple drug therapy is usually required for continual function and stability of the transplanted organ.

The rejection response to an allograft begins with the recognition of alloantigens (donor tissue and soluble antigens) by the host within the allograft and in the local lymphoid tissue.[10] Host lymphoid cells that enter the graft are confronted by foreign tissue, while donor lymphoid cells and soluble antigen from the transplanted organ begin to accumulate in the host lymph nodes. Alloantigen is first processed by macrophages (a cell type whose primary function is to remove 'debris' from the body) and then presented to the T- and B-lymphocytes of the host. Once the lymphocytes are activated, their subsequent division and proliferation leads to both cell-mediated and humoral immune response mechanisms, which participate in graft destruction.

Both *in vitro* and *in vivo* studies have been used to investigate the cell-mediated immune response. Results from both studies support roles for both T_H-cells and T_C-cells in allograft rejection.[11,12] Following activation of the host T-lymphocyte population by specific antigen, the T_H-cells become responsive to accessory cell derived Interleukin 1 (IL-1) and are triggered to proliferate, releasing the soluble mediator Interleukin 2 (IL-2). Simultaneously, the T_C-cells are activated by the alloantigen and acquire responsiveness to T_H-cell secreted IL-2. Upon receipt of this second

signal, the T_C-cells proliferate and differentiate. This results in a population of mature T_C-cells carrying the necessary receptors to attack the alloantigen from the graft tissue,[1,10] effecting cell lysis and rejection of donor tissue (Figure 1.5).



A: Allograft Tissue, M:Macrophage, T: T-Lymphocyte, B:B-Lymphocyte.

Figure 1.5 Immune response to and rejection of allograft.

The role of delayed type hypersensitivity (DTH) in graft rejection has been clarified over recent years. Loveland *et al.* showed during *in vivo* studies on laboratory mice that the cell responsible for DTH is a T-cell subset known as Lyl+ cell.[13] Upon contact with target antigen, the Lyl+ or 'T_{DTH}-cell' releases lymphokines, that result in intense local inflammation at the graft site.[14]

The humoral immune response to the allograft is also depicted in Figure 1.5. Following alloantigen recognition, IL-2 production from the T_H-cells triggers the release of T-cell derived B-cell growth factors (BCGF),[15] resulting in the clonal expansion and differentiation of alloantigen-activated B-cells and antibody secretion. The graft endothelium, a layer of flattened cells one cell thick that lines the blood vessels within the graft, is the primary site of antibody bonding. Target cell destruction is then effected either by the complement cascade, resulting in complement dependant cytotoxicity (CDC) or by antibody-dependant cell mediated cytotoxicity (ADCC).

1.2.3 Host/Graft Adaptation

In addition to the immune response following transplantation, changes also occur progressively in both the host and graft, which in time result in mutual adaptation and reduce the intensity of the immune response. The immune rejection response outlined above is under continuous regulation. Antigenetic stimulation of the immune system results not only in cytotoxic T-lymphocyte proliferation, but also in the production of cells with suppressor ability (T_S-cells). In man, T_S-cells are detected in the peripheral blood of transplant recipients. This may induce either a global impairment of the humoral and cell-mediated immune response, or inhibit specifically the T-cell proliferation to donor antigen.[16] The suppressor cells are derived from either macrophage or lymphocytes and long-term graft survival may be accompanied by a subtle shift in the ratio of helper/suppressor T-cell population, with donor-specific suppressor activity increasing within the latter group.[17]

The humoral response to the allograft is also regulated. Upon recognition of specific alloantigen the lymphocyte population expands to produce T_C-cells and specific antibodies with receptor sites determined by the alloantigen. The variable binding site on the T- or B-cell receptors are thus present in increasing amounts during lymphocyte expansion and serve as endogenous antigens themselves. This results in the production of a series of regulatory antibodies directed against this region, thus decreasing the severity of the humoral response.

1.3 Immunosuppressive Drugs

While the process of host/graft adaptation does occur after transplantation, the over-riding effect of the immune response is to attack the allograft and reject the donor organ. In an effort to alleviate this, surgeons attempt to control the immune system though drug therapy and the use of immunosuppressants. For test mammals and rodents this procedure is relatively simple, with a short course of immunosuppressive drug therapy often being all that is required. In large animals and humans however, therapy must generally be continued indefinitely.[18]

At present multiple-drug therapy is used on patients following organ transplantation.[1,19] This often comprises of a triple therapy of, for example, cyclosporine A, azathioprine and prednisone,[18,20] although other therapies using azathioprine/prednisone and prednisone/ cyclosporine are also used.[10] The logic behind multiple-drug therapy is that each drug acts at a different stage in the immune response and that a combined therapy will require lower doses of each individual drug.

All immunosuppressive agents used in modern medicine suffer from two main drawbacks:

i) the agents are either directly toxic in themselves, or

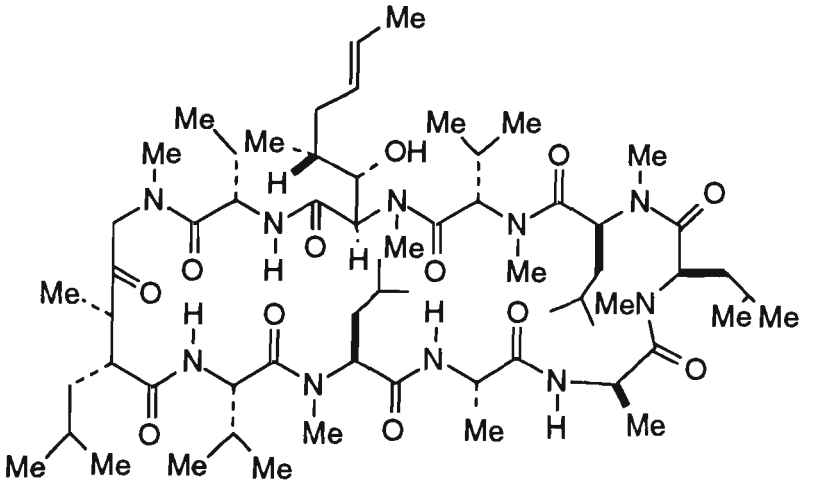
ii) they fail to give a balanced immunosuppression.

This latter problem is of two extremes, inadequate suppression of the immune response leading to rejection, or over-suppression which may allow the development of opportunistic infections and diseases.

A balanced immunosuppression remains the key to a successful transplant. Nearly 50% of graft losses result from rejection by the hosts immune system.[21] The second most common cause of graft loss is due to infection brought on by a weakened immune system. Treatment usually requires alteration or even cessation of immunosuppressive therapy, that leads again to graft loss.[18,22]

1.3.1 Cyclosporine A

Cyclosporine A **1** is a neutral, lipophilic, cyclic polypeptide containing 11 amino acids.[23] It has a molecular weight of 1203 Daltons and is extracted from the soil fungus *tolypocladium inflatum gams.* The amino acids in positions 10, 11, 1, 2 and 3 form a hydrophilic immunosuppressive active site (Figure 1.6).



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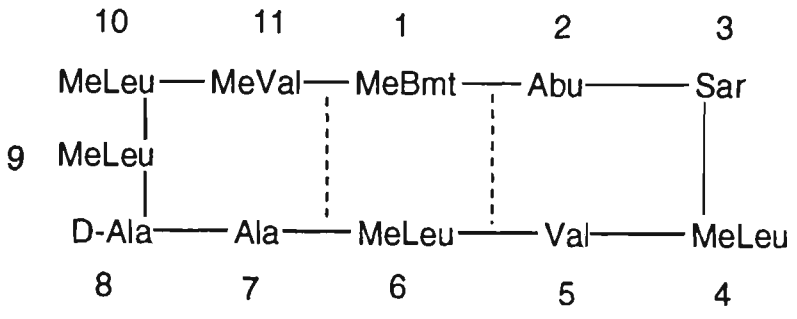


Figure 1.6 Alignment of amino acids in cyclosporin A. Numbers 10, 11, 1, 2 and 3 form the immunosuppressive active site.

Over 700 natural, synthetic and semisynthetic structural analogues of cyclosporine have been produced and tested in the search for safer and more effective agents, with all having a lower suppressive ability than the parent molecule.[24]

The immunosuppressive effect of cyclosporine A is mediated through the inhibition of T-cell function. When a T-cell receptor (TCR) is stimulated by a foreign antigen, a signal is transduced through the cell cytoplasm *via* an unknown mechanism to the nucleus.[25] Translation of this message results in the secretion of IL-2, which causes the division and proliferation of T_C-cells, resulting in a population of mature T_C-cells carrying the necessary receptors to attack the alloantigen. Cyclosporine inhibits the calcium dependent signal in both T- and B-cells (Figure 1.7) and reduces IL-2 synthesis.[9,26] The resulting T_C-cell proliferation is therefore diminished.

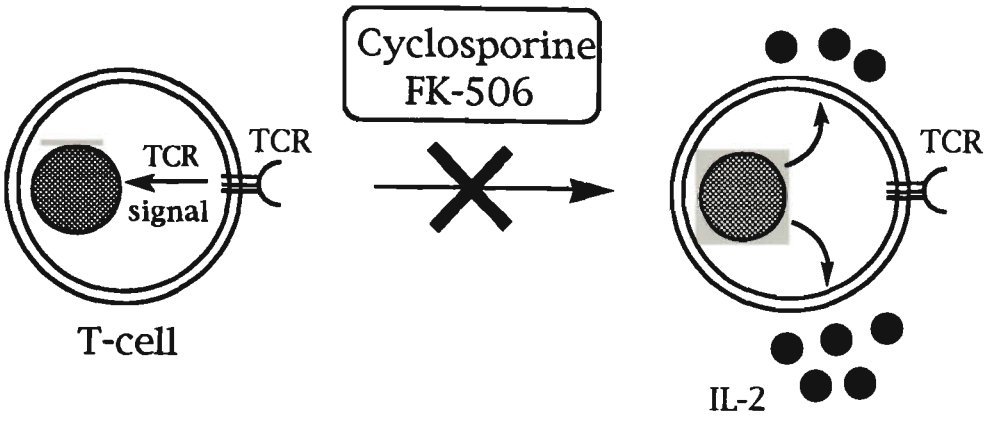


Figure 1.7 Blocking of the Ca^{+} T-cell receptor signal to the T-cell nucleus.

1.3.1.1 Clinical Use and Efficiency

Cyclosporine A is stabilised with castor-oil and olive-oil for clinical intravenous and oral administration respectively.[23] The drug is usually given orally once or twice daily as a solution or as capsules containing 25 or 100 mg of cyclosporine A.[1] Adsorption of oral cyclosporine A from the small intestine is slow, incomplete and highly variable. The bioavailability of the drug is only about 30%[10,23] with a mean time of 3.8 h to peak drug levels in the body. Cyclosporine A is converted rapidly (median half-life 6.4-8.7 h) to more than 15 metabolites by the hepatic cytochrome P-450 enzyme family in the liver. Less than 0.1% of the absorbed drug is excreted in the urine unchanged with the vast majority of metabolites (94%) disposed of by fecal excretion.[23]

A number of drug therapies have been investigated in an effort to decrease the rate of metabolism by P-450 enzymes, thereby allowing various cyclosporine A levels to be achieved. Agents such as diltiazem and erythromycin are able to increase total cyclosporine A levels by inhibiting the P-450 enzyme function. On

the other hand, agents such as rifamycin and phenobarbital can be used to decrease cyclosporine levels by activating the P-450 enzyme system (Table 1.2). The use of all such agents however, has been found to be hazardous, and patients treated have a higher incidence of allograft rejection or drug-induced toxicity.[27]

Table 1.2 Pharmacokinetic drug effects on cyclosporine A levels.

Drug	*Effect on Cyclosporine A Level*	*Mechanism*
Diltiazem	Increase	P-450*
Ketoconazole	Increase	P-450*
Metaclopramide	Increase	Absorption
Erythromycin	Increase	P-450*
Octreotide	Decrease	Absorption
Phenobarbital	Decrease	P-450†
Phenytoin	Decrease	P-450†
Rifamycin	Decrease	P-450†
Cotrimoxazole	Decrease	Unknown

* Caused by a decrease in P-450 activity, † Caused by an increase in P-450 activity.

Despite its rapid metabolism and low bioavailability, cyclosporine A has revolutionised the field of organ transplantation. It has resulted not only in improved initial and long-term survival of renal allografts,[28] but has also minimised the impact of immunological risks such as Human Leucocyte A (HLA) mismatching and the absence of pre-transplantation blood transfusions. In addition, it

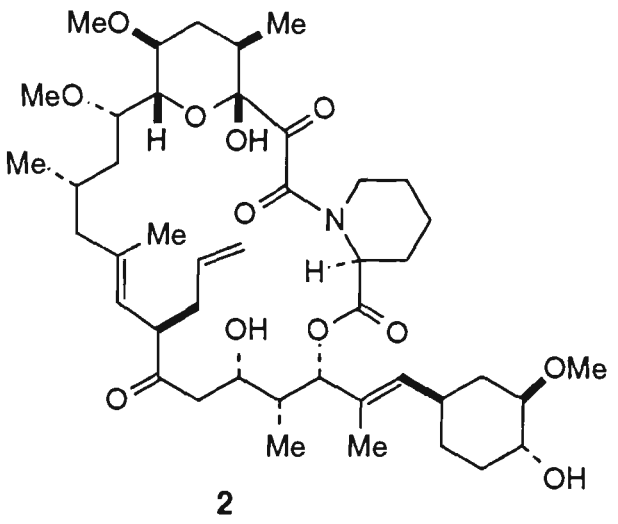
has reduced the likelihood of disease, the period of initial hospitalisation and the rate of re-admission.[29] The rate of rejection of kidney replacement, cardiac, hepatic heart-lung, single lung and multiple-organ transplants has also decreased.[10,23]

1.3.1.2 Adverse Effects

The two most common adverse effects associated with cyclosporine A use are nephrotoxicity and heptotoxicity.[23,30] Drug induced nephrotoxicity is usually treated as organ rejection until proved otherwise. Only after a diagnosis of rejection is excluded will cyclosporine A dosages be altered. Premature cyclosporine A reductions to combat suspected nephrotoxicity can lead to rejection and loss of the graft. Other side-effects include hypertension, increased cholesterol levels, increased incidence of infection, gum growth, nausea, vomiting and diarrhoea.

1.3.2 FK-506

During the 11th International Congress of the Transplantation Society held in Helsinki in August 1986, Ochiai[31] first described the properties of a newly discovered naturally occurring immunosuppressant, FK-506 **2**. This came one decade after the first published account of cyclosporine A.[32]



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FK-506 was discovered during routine screening for naturally occurring immunosuppressants in 1984 by the Fujisawa Pharmaceutical Company in Japan. It is a novel 23-membered macrolide lactone, which was isolated from the fermentation broth of a strain of the soil fungus *steptomyces tsukubaensis* No. 9993.[33,34] A yield of 13.6 g of highly pure FK-506 from 1,500 L of the fermentation broth was achieved after exhaustive extraction and purification (Figure 1.8).

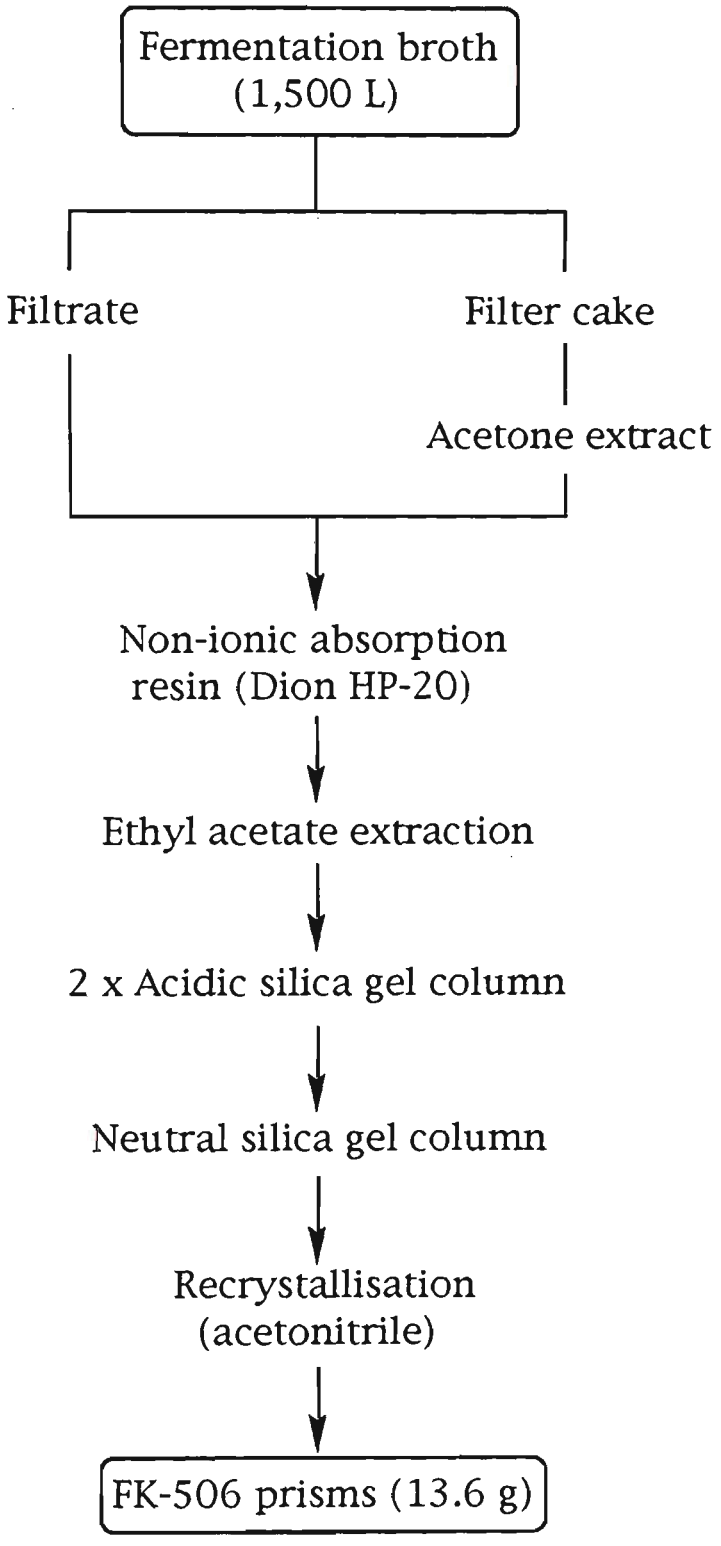
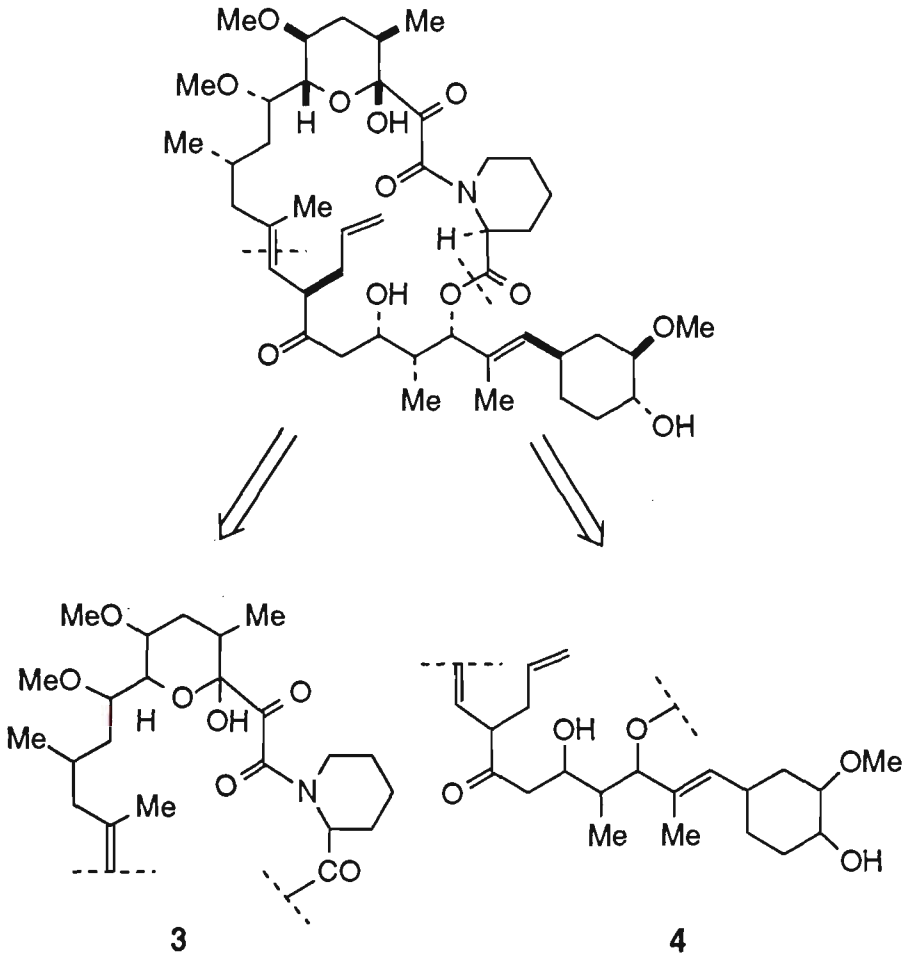


Figure 1.8 Isolation of FK-506 from *steptomyces tsukubaensis* no. 9993.

FK-506 forms solid crystalline prisms of X-ray crystallography standard[33] and is stable at room temperature for many months. Like cyclosporine A, it is insoluble in water but dissolves readily in

organic solvents such as methanol, acetone and ethanol.[35] The structure of FK-506 was evaluated by the chemical breakdown of **2** and examination of the resulting products. Partial structures **3** and **4** were concluded from the resulting data with the final stereochemical assignments coming from X-ray analysis of FK-506 itself.[33]



3 **4**

FK-506 has a similar mode of action to cyclosporine A by inhibiting T-cell function and preventing the secretion of IL-2 (Figure 1.7).[9,32] The similarity of modes of action is surprising as the two agents are structurally dissimilar. The advantage of FK-506, however, is its very high immunosuppressive potency, which has been shown to be 10-100 times that of than cyclosporine A.[36] Studies both *in vitro* and *in vivo* have shown that FK-506 can achieve an identical

suppression to cyclosporine A at only a fraction of the concentration (Table 1.3).[32] This not only lowers the quantities of immunosuppressant required, but also assists in eliminating undesirable side-effects due to the small amounts of drug used. Although the reason behind its high activity in comparison to cyclosporine A is not understood, it may simply reflect different bioavailability and/or metabolism of the two immunosuppressants.

Table 1.3 Comparison of the antilymphocytic and immunosuppressive activities of FK-506 and cyclosporine A.

		*Dose**	
Response Suppressed	*Species*	*FK-506*	*Cyl A†*
In vitro			
Generation of T_C-cells	Human	0.2 nM	14 nM
IL-2 and IL-3 production	Human	0.1 nM	10 nM
In vivo			
Antibody production	Mouse	4.4 mg kg^{-1}	39 mg kg^{-1}
	Rat	1 mg kg^{-1}	25 mg kg^{-1}
Allograft rejection	Rat (heart)	0.1 mg kg^{-1}	10 mg kg-1
	(skin)	0.3 mg kg^{-1}	32 mg kg^{-1}
	(limb)	0.32 mg kg^{-1}	15 mg kg^{-1}
	Dog (liver)	1.0 mg kg^{-1}	20 mg kg^{-1}
	(pancreas)	0.2 mg kg^{-1}	20 mg kg^{-1}

* Concentration causing 50% inhibition (*in vitro* responses) or minimal effective dose (*in vivo* responses), † Cyl A: Cyclosporine A

1.3.2.1 Clinical Use and Efficiency

The first clinical trials of FK-506 in liver transplantations was reported in 1989 from the University Health Centre of Pittsburgh.[37] The agent was used on ten patients that had previously rejected liver allografts despite conventional (cyclosporine A) immunosuppressive therapies. After transplantation all ten patients showed a sustained improvement in at least some liver functions, with seven of the ten liver grafts still in place and providing normal liver function one to six months after treatment. This was achieved using low oral doses of 0.15 mg kg^{-1} every 12 or 24 h.

Over the next 12 months the use of FK-506 was expanded at Pittsburgh to encompass a total of 111 transplant patients. This number included 102 liver transplants, 9 kidney, 5 pancreatic, 3 heart and 2 double-lung transplants (with some patients receiving multi-organ replacement).[38] Of this number, only 8 patients died with a further 3 taken off the program due to complications. The remaining patients were successfully treated using FK-506 doses as low as 0.075 mg kg^{-1} twice daily.

Unlike cyclosporine A, the use of FK-506 in multi-drug therapy has not received a great deal of attention, although this may merely reflect its potency in single drug therapy. FK-506 and cyclosporine A, however, have been found to have a synergistic relationship both *in vitro* and *in vivo*.[39] A combination of low doses of both drugs, which on their own were ineffective, inhibited both primary and secondary alloantigen-induced human T-cell activation. In addition, there is also evidence that FK-506 and azathioprine show

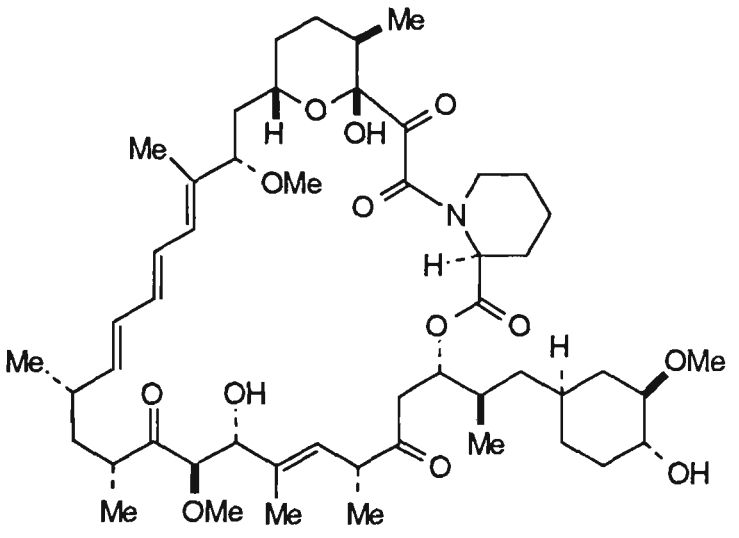
synergistic inhibitory effects on primary human T-cell activation. Pretreatment of lymphocytes with FK-506 has been shown to increase cell uptake of radiolabelled cyclosporine A, but the mechanism of this is not understood.[32,40]

1.3.2.2 Adverse Effects

FK-506 results in less hypertension than cyclosporine A, but still induces both acute and chronic nephrotoxicity. The dosages required to achieve such effects, however, are at least 10-fold larger than that used clinically.[30] This contrasts with cyclosporine A with which acute and chronic nephrotoxicity can be produced by doses that are close to those used clinically. FK-506 treated patients show minor side-effects such as nausea, vomiting, anorexia and burning of the feet.[37]

1.3.3 Rapamycin

Rapamycin **5** is a macrolide structurally similar to FK-506, but it exerts its immunosuppressive activity at a different point in the immune response. FK-506 is able to inhibit the secretion of IL-2, whereas rapamycin has no such ability. T-cell activation involves not only IL-2 secretion, but also expression of the lymphokine receptor IL-2R on the surface of the cell. While rapamycin allows the secretion of IL-2, it hinders binding of IL-2 to IL-2R and thus diminishes the immune response (Figure 1.9).[9,25]



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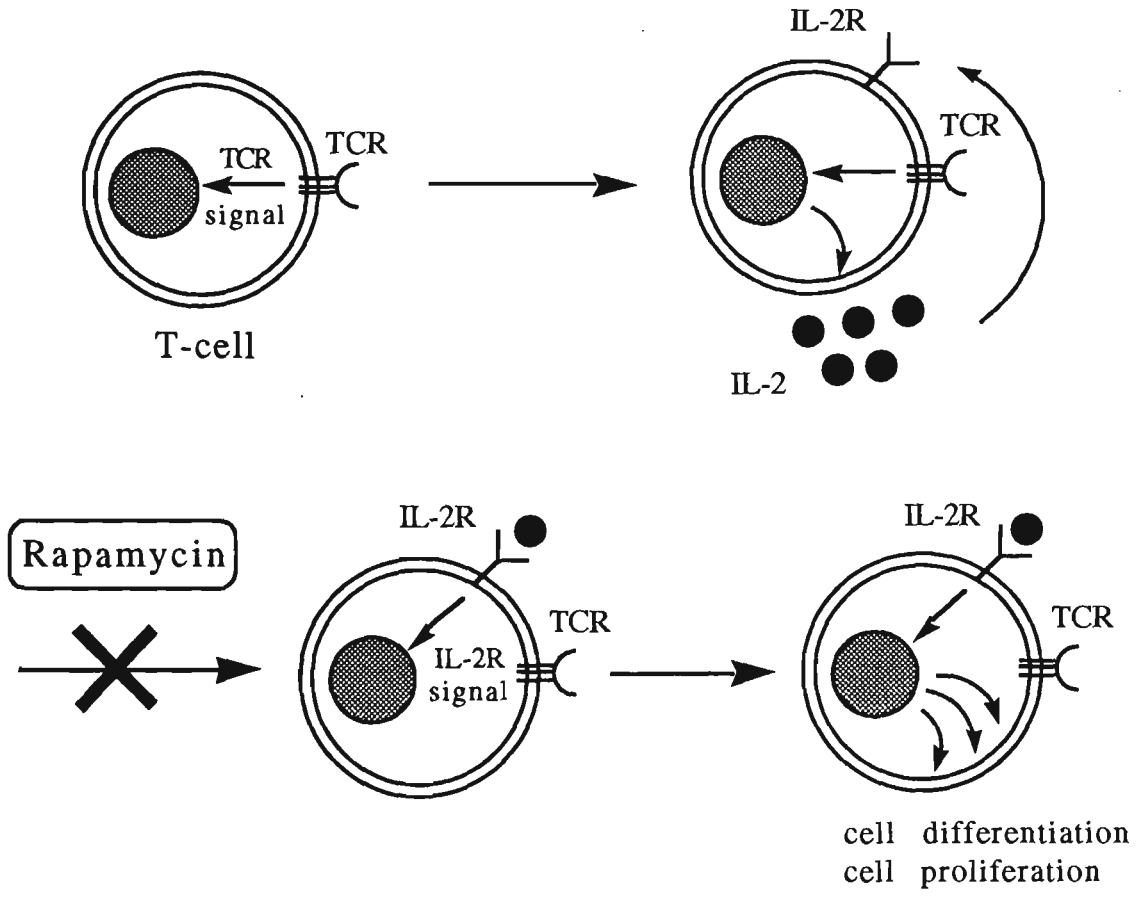


Figure 1.9 Rapamycin inhibition of IL-2/IL-2R binding.

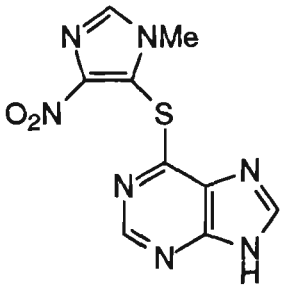
Both rapamycin and FK-506 compete for the same immunosuppressant binding proteins (immunophilins) and thus act as pharmacological antagonists, offering no benefits for use in multi-drug therapy. Cyclosporine A, however, binds to a different

immunophilin and does not inhibit the action of rapamycin. The two drugs have been found to exert synergistic immunosuppressive effects, with cyclosporine A preventing the secretion of IL-2 and rapamycin inhibiting binding to IL-2R.[9,30]

Studies on the toxicity of rapamycin are incomplete, with most results coming from animal studies. Rapamycin has been shown to induce diabetes mellitus in rodents and also affect renal function. Nephrotoxicity data are also incomplete, but the fact that rapamycin and cyclosporine A are synergistic for immunosuppression makes studies discerning whether or not they are synergistic for nephrotoxicity imperative.

1.3.4 Azathioprine

Azathioprine **6** was originally synthesised in the early 1950's as a pro-drug of the antitumor agent 6-mercaptopurine **7**.[1] It was subsequently found to have a lower toxicity at equivalent immunosuppressive doses and has been used extensively as a component in multi-drug treatment for over 25 years. It is used with both cyclosporine A and/or prednisone for both pre- and post-transplant immunosuppression and also for the maintenance of grafts.[10]



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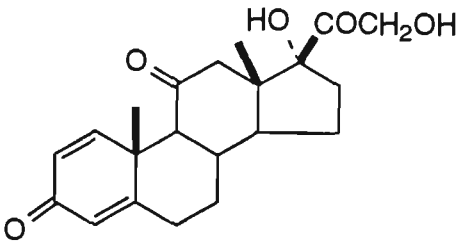
Azathioprine is absorbed rapidly from the gastrointestinal tract and has a bioavailability of approximately 80%. Breakdown of the drug occurs in the liver to give a number of active metabolites that result in increased immunosuppressive activity and toxicity. Azathioprine acts as a purine antagonist and functions as an effective T-cell antiproliferation agent in much the same way as rapamycin by preventing the binding of IL-2 to IL-2R.[41] Its activity is more specific for T-lymphocytes than B-lymphocytes, but has also been shown to decrease the rate of synthesis of IgM and IgG antibodies in the humoral response.

The most common adverse effect associated with the use of azathioprine is bone marrow depletion, which may lead to leukopenia, although bone marrow recovery rapidly occurs when the drug is withdrawn. Instances of azathioprine induced heptotoxicity have been reported, but the most serious toxicities associated with its use are hepatitis and cholestasis. Other adverse effects include fever, headache, hypertension, anorexia and nausea, although these symptoms usually resolve when dosages are lowered.

1.3.5 Prednisone

Prednisone **8** is formed *via* the dehydrogenation of cortisone and was first characterised in 1955.[42] It was found to be 3-5 times more active as the parent steroid by a variety of biological and therapeutic criteria.[43] The dehydrogenation is effected by the reaction of cortisone with Difco yeast extract at ambient temperature for periods ranging between 3-24 h.[44]



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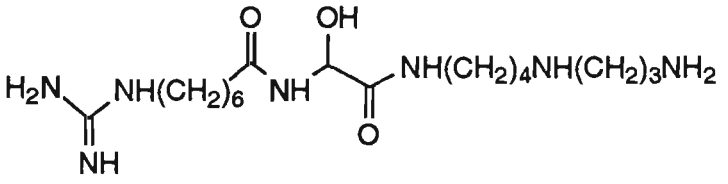
Prednisone is an effective agent in multidrug therapy, but is itself not used as the primary immunosuppressant for transplantations. Before the introduction of cyclosporine A in the early 1980's, immunosuppressive therapy consisted mainly of azathioprine and prednisone.[29,45] The discovery of cyclosporine A as a powerful immunosuppressant transferred the use of prednisone to pre- and post-operative drug therapy. In conjunction with azathioprine or cyclosporine A, prednisone is used to induce immunosuppression before a transplantation and as a maintenance agent to stabilise allografts and prevent rejection. The dosage requirements of prednisone varies depending upon its use. Initial drug therapy usually consists of prednisone intakes of 2-3 mg/kg/day at the time of transplantation, with intake levels tapering off over the ensuring post-operative period to a maintenance level of 0.15-0.35 mg/kg/day after 3 months.[10]

1.3.6 15-Deoxyspergualin

15-Deoxyspergualin (DSG) **9** is a synthetic analogue of spergualin, a natural product produced in culture by the bacteria strain *bacillus laterosporus*.[46,47] DSG is a powerful immunosuppressive agent, which shows strong activity in animal models. It is effective in the maintenance of skin allografts in male F344 rats and in preventing

delayed-type hypersensitivity reactions in mice by inhibiting antibody formation.[48,49] One of its most remarkable achievements in animal studies has been to prolong cardiac xenografts in recipient male F344 rats using donor hearts from male golden hamsters.[8] Used alone, DSG was able to prolong xenograft survival from 2 days to a median period of 5 days at dosages of 10 mg/kg/day. In comparison, cyclosporine A (25 mg/kg/day) and FK 506 (0.5 mg/kg/day) were ineffective in preventing graft rejection, with recipient rats surviving only 2 days. DSG and FK 506 also display synergistic activity, with cardiac xenograft recipients surviving up to 16 days when placed on a mutidrug therapy.



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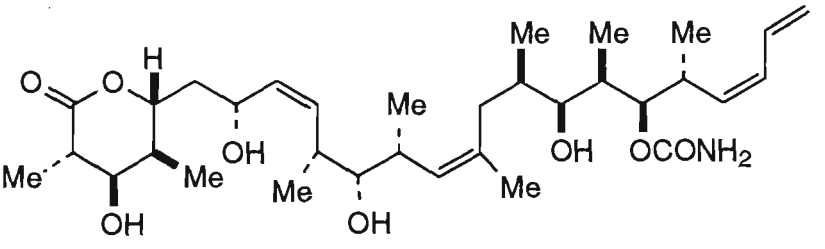
DSG's clinical use is restricted mainly to the maintenance of allografts and as a rescue drug for renal transplants. [9,18] In a clinical study involving 6 medical institutes in Japan, DSG was used to treat renal rejection cases that had failed to respond to high dose corticosteroid therapy.[50] DSG treatment was effective in 79% of cases and succeeded in stabilising renal allografts. DSG's adverse side-effects are also quite mild. Unlike cyclosporine A and FK 506, DSG has not been associated with nephrotoxicity. Its adverse reactions include a reduction in white blood cells and platelets, anaemia and gastrointestinal disorders, but these symptoms are so mild that cessation of therapy is not usually required.

The mode of action of DSG is still unknown, but has been shown to affect both the humoral and cell-mediated immune responses. DSG inhibits antibody production, lymphocyte proliferation and the onset of delayed-type hypersensitivity, but does not effect IL-2 production.[8]

1.3.7 Discodermolide

Discodermolide **10** is a crystalline polyhydroxylated lactone isolated from the Caribbean marine sponge *discodermia dissoluta.* It was first collected and isolated by the Harbour Branch Oceanographic Institute in Florida and its structure reported in 1990.[51] Discodermolide is a new immunosuppressant whose mode of action is still unknown.[25] It has been shown to inhibit *in vitro* growth of P388 murine leukemia cells and to be active in two-way mixed-lymphocyte culture assays.[52]



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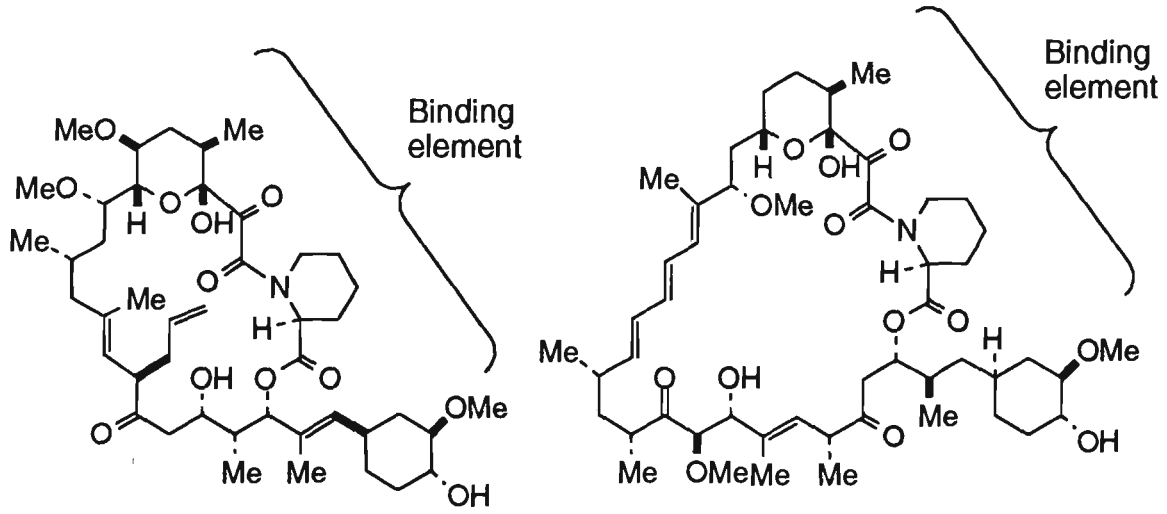
1.4 Immunosuppressants and Immunophilins

Although immunosuppressants used in today's surgery are becoming increasingly effective, they do not have the ability to act alone. Proteins (immunophilins) within the body bind the drug and it is the bound pair that becomes the active suppressant. The predominant cyclosporine A immunophilin, isolated in 1984 and characterised five years later, is appropriately named cyclophilin.[53] The major form of human cyclophilin has a mass of 17,737 Daltons and has been identified as an enzyme that catalyses the interconversion of the *cis*- and *trans*-rotamers of proline-containing peptides or proteins.[25] Shortly after this discovery, the major isoform of the family of immunophilins for FK-506 called FK-binding protein (FKBP) was discovered.[54] Like cyclophilin, FKBP was found to have rotamase activity towards peptide substrates.

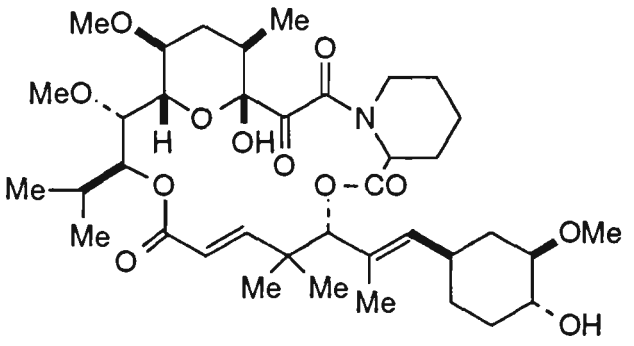
These discoveries gave the first insight into the mechanisms of immunosuppression of these two major drugs. An hypothesis emerged that proline *cis-trans* isomerisation may be involved in the calcium signal transduction in T-cells and that cyclosporine A and FK-506, as powerful rotamase inhibitors, prevent signal passage. One of the implications of this hypothesis was that any rotamase inhibitor would possess immunosuppressive activity and that new and less toxic agents could be obtained based upon this assumption. The theory was soon abandoned, however, as a number of immunosuppressants were found to have no rotamase-inhibiting ability, while agents that bound rotamase catalysing proteins and diminished their activity showed no immunosuppressive action.[53]

Rapamycin was found also to bind to FKBP in an identical way to FK-506 (Figure 1.10).[25] The fact that both compounds act as dual domain agents, yet inhibit the immune response at different stages, raises the possibility that immunophilins may function merely as general presenting molecules. Studies have shown that FK-506 and rapamycin are composed of two domains, one important for binding to the immunophilin (binding element) and one essential for biological activity (effector element). Schreiber synthesised an abbreviated analogue of FK-506 which he called 506BD (for binding domain) **11**.[25,36] This synthetic agent contained only the FK-506/rapamycin binding element. It was found to bind effectively to FKBP, but showed no immunosuppressive ability as expected for a molecule that contains no effector element.



FK-506 **Rapamycin**

Figure 1.10 Identical binding elements of FK-506 and rapamycin.



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A second possibility is that the immunophilins have a more general function and perhaps assist in protein folding *in vivo* by acting as 'foldases', and only when combined with its immunosuppressive ligand do they inhibit T-cell function.[25] The 15-deoxyspergualin immunophilin has recently been identified as a member of the heat shock protein 70 family (Hsp70).[55] Hsp70 also participates in the folding of proteins and like cyclophilin and FKBP is immunosuppressively inactive on its own. The possibility still exists however that Hsp70 may also be acting as merely a carrier of the drug.

1.5 Autoimmune Diseases

Autoimmune diseases occur when the immune system identifies the bodies own cells as antigenic and responds to attacking them. Autoimmunity has been recognised as an important interaction since it was first observed in 1900 by Ehrlich and Morgenroth.[56] At the time such conditions were considered as abnormal in the body and were classified under the term *horror autotoxicus*. Sixty years later however, Pierre Grabar hypothesised that such occurrences might be important in the body's function and effect the elimination of defective or denatured molecules.[57]

The reality of such conditions falls somewhere between these two extremes. Autoimmunity is a mechanism of fundamental importance for shaping the normal immune response. In certain cases however, control over autoimmunity is weakened or lost and diseases such as diabetes mellitus, rheumatoid arthritis and multiple sclerosis are induced.

1.5.1 Combating Autoimmune Diseases

Combating autoimmune diseases revolves around the ability of medical practitioners to control a patient's immune system. Ideally the immune response that is attacking the bodies 'self-antigen' needs to be halted, while still allowing the immune system to function in a normal manner beneficial to the patient.

1.5.1.1 Plasmapheresis

When plasma is removed from a patient the procedure is called plasmapheresis or plasma exchange (PE). The use of PE in combating autoimmune diseases started as an experimental approach to the treatment of rare conditions but has shown its effectiveness in many diseases as a therapeutic measure.[58] In certain diseases one or more of its manifestations involves an abnormal plasma component (or a deficiency of normal plasma), which can be readily removed by plasmapheresis. The procedure involves drawing blood from the patient, separating and removing the plasma and returning the blood to the patient in a 'solution' of fresh frozen plasma or plasma protein fraction. Plasmapheresis is considered the treatment of choice for autoimmune diseases such as multiple myeloma, antibody-mediated hemolytic disorders, myasthenia gravis and Goodpasture's syndrome.

1.5.1.2 Cyclosporine A

In addition to being an effective agent for prolonging allograft survival, cyclosporine A has considerable use in the fight against autoimmune diseases. By suppressing the patient's immune system, it is able to inhibit the response of T-lymphocytes to the bodies self-antigen. Cyclosporine A has proved effective in animal models and also against human rheumatoid arthritis and Crohn's disease.[59] Unfortunately all of the adverse effects associated with cyclosporine A treatment such as nephrotoxicity are also manifested in patients suffering from autoimmune diseases. Thus

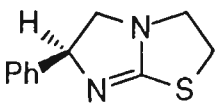
cyclosporine A is unsuitable for life-long diseases such as insulin-dependent diabetes mellitus.

1.5.1.3 Total Lymphoid Irradiation

Total lymphoid irradiation (TLI) is a technique where high doses of radiation (greater than LD_{50} for man) are delivered to lymphoid tissues while other tissue is shielded. TLI produces a number of alterations in the immune system and causes a suppression of the cell-mediated immune response. It induces a marked lymphopenia, but the lymphocyte count gradually returns to normal within 1 to 2 years after treatment.[60] TLI is used as a routine treatment for human lymphoid malignancies such as Hodgkin's disease. Only a few trials on human autoimmune diseases have been performed using TLI and these have been shown to be beneficial in the treatment of rheumatoid arthritis and systemic lupus erythematosus.

1.5.1.4 Levamisole

Originally developed in 1966 as an antihelminthic agent, levamisole **12** has been shown to modulate T-cell function,[61] with the exact effect on T-cell sub-populations dependent on the conditions employed.[62] B-cell activity is also able to be increased depending on whether T_S-cells or T_H-cells are stimulated.



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Human trials of levamisole have shown long term improvements in 49% of rheumatoid arthritis patients, equalling the clinical efficiency of penicillamine and gold salts therapy in trials lasting one year.[63] Levamisole is relatively safe, with minor ailments such as headaches, insomnia and allergic rashes being the most common side-effects.

1.5.1.5 Dietary Manipulation

Diet therapy for autoimmune diseases has attracted considerable attention, especially in the treatment and prevention of rheumatoid arthritis[64,65] and diabetes.[66] Diet manipulations have been shown to be effective in numerous animal models and offers both treatment and prevention of autoimmune diseases free of drug induced side-effects. Both low calorie and low protein diets have been shown to reduce autoantibody levels in mice, but still maintain T-cell responsiveness.[67]

1.6 Diabetes Mellitus

Along with rheumatoid arthritis, diabetes mellitus is the most well known disease associated with autoimmunity. It is caused by a lack of insulin produced in the pancreas and results in elevated blood glucose levels. Diabetes can be divided into two types reflecting their medical treatment: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). NIDDM is the most common form of the disease covering about 80% of patients.[57] It mainly effects older, usually overweight patients whose pancreas still produces insulin, but in insufficient amounts to keep glucose levels normal. NIDDM responds well to diet, especially in overweight patients.[66] If diet alone is not enough, then oral medication to stimulate insulin secretion and in some cases insulin injections may be necessary to control the disease.

IDDM affects 20% of all patients and is the most serious of the two types of diabetes. In the normal state, glucose arrives at the pancreas in waves following digestion of meals. Receptors on β-cells in the islets of Langerhans within the pancreas transport the glucose molecules into the cells, which respond by secreting insulin. About half the insulin produced is used by the liver while the rest goes into general blood circulation. In all cells where it acts, insulin stimulates the uptake of glucose for energy and storage.[68] In IDDM, the underlying pathology is characterised by a specific destruction of β-cells in the pancreatic islets by the immune system. The loss of β-cells ultimately leads to insulin deficiency, which requires life-long insulin replacement.[69]

1.6.1 IDDM and the Human Environment

Exactly who is susceptible to IDDM and why is unclear. Despite strong evidence for inherited susceptibility of diabetes, studies on identical twins suggest that this only accounts for 30-40% of IDDM incidents.[70] Environmental factors must therefore play an important role.

Northern European countries such as Norway, Sweden and Finland have extremely high incidences of IDDM, with between 20-35 people per 100,000 per year at risk. In comparison Romania, Israel and Kuwait only have about 5 per 100,000 per year at risk. Japan is even lower at about 2 per 100,000 (Figure 1.11).[71]

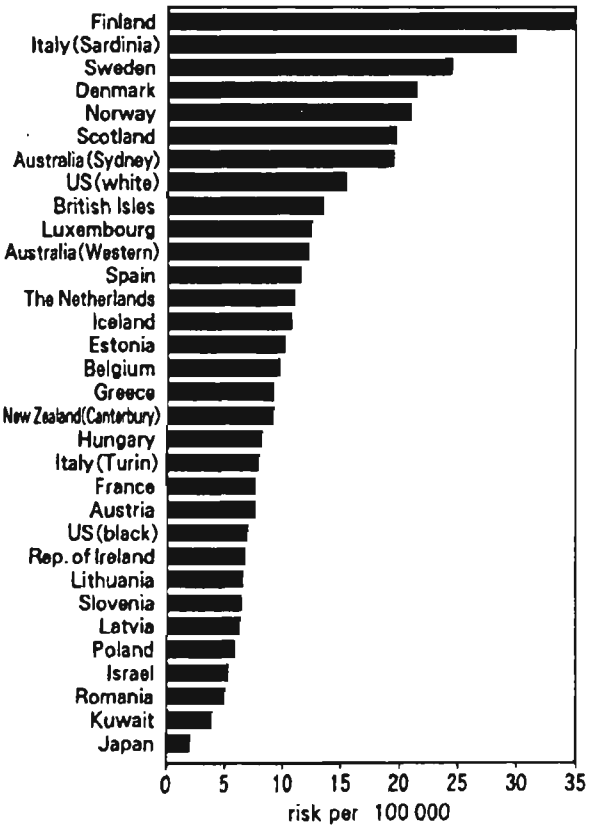


Figure 1.11 Risk of IDDM per 100,000 per year.[71]

Migrants moving from low to high risk regions also assume the higher risk of the host country. Japanese migrants to Hawaii and French to Canada have a greater chance of IDDM induction.[72] One possible explanation of IDDM onset is that the disease is initiated in genetically susceptible individuals following exposure to unidentified agents such as a virus, which triggers autoimmune β-cell destruction.[73]

1.6.2 Effector Cells leading to IDDM

A number of different cell types within the immune system are thought to be involved in the onset of IDDM. A large body of data from animal models, however, indicates that it is a T-cell mediated disease. Multiple studies have provided evidence that T-cells are critical to the progress of β-cell destruction, while elevated T-cell levels in the pancreas of human patients with accompanying islet lesions support their role.[74] Islet cell surface antibodies (ICSA) have also been detected frequently in sera from IDDM patients.[75] The serum was able to alter β-cell function and was cytotoxic to β-cells in the presence of complement (the protein components of blood serum that can bind to antigen/antibody groups). There is no evidence though that ICSA induces IDDM.

A key role is played by macrophages during the onset of IDDM. Macrophage infiltration of islets has been seen to precede T- and B-lymphocyte infiltration and may act as a presenting cell for the T-cells.

1.6.3 Prevention and Treatment

IDDM can be combated at various stages during its onset (Figure 1.12).[76]

Stage one: Genetic Predisposition. Prevention of IDDM by susceptible individuals includes avoiding suspected environmental 'triggers'. Dietary strategies including maintenance of ideal body weight and balanced intakes have been shown to be an effective preventative measure. Vaccination against viruses suspected of initiating insulitis is also effective. These include the rubella and mumps virus, retrovirus and cytomegalovirus.[77]

Stage two: Early Insulitis. β-Cell mass is still normal, but insulin levels start to decrease. Potential early insulitis managements include the aforementioned dietary and vaccination considerations, but oral insulin and preventative drugs may also be necessary.

Stage three: Progressive Insulitis. β-Cell damage in progress due to T-cell assault, with insulin levels decreasing. Drug therapies include the use of sulfonylureas and non-traditional drugs such as pioglitaizone **13**, and CP-72467 **14** to stimulate undamaged β-cells into insulin secretion. Various aldose reductase inhibitors such as tolrestat **15** can also be used to convert excess glucose to sorbitol.[68] Antioxidant therapy can be employed to reduce oxidation damage by free radicals within the islets. Although free radical damage is not an initiating event in IDDM, their release from macrophages within the islet lesions is likely to accelerate β-cell destruction.

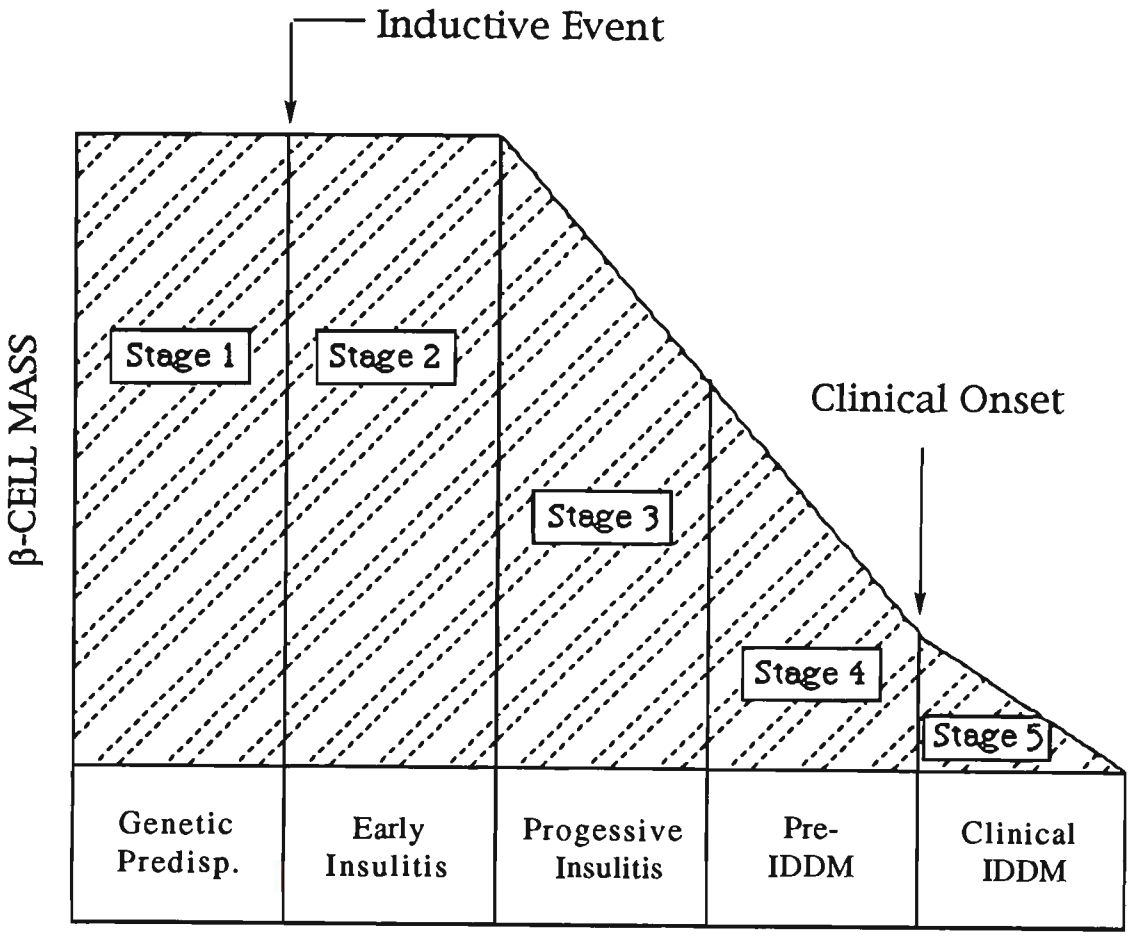
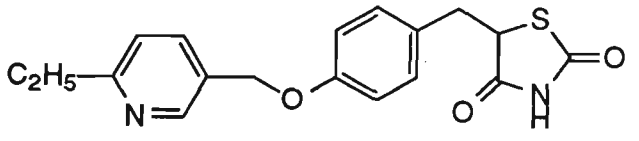


Figure 1.12 Opportunities for intervention to prevent IDDM.



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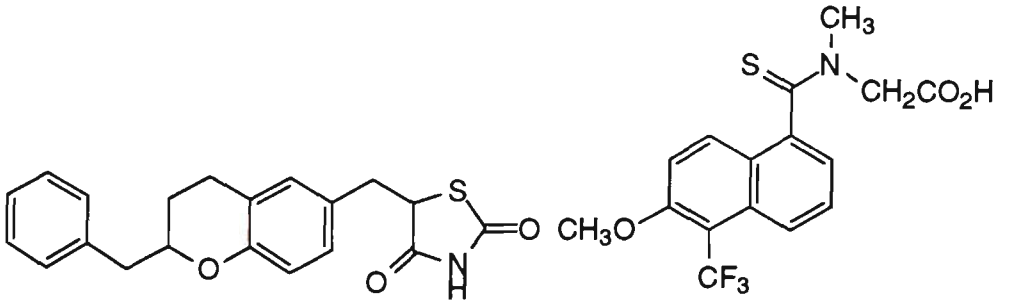

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Stage four: Pre-IDDM. This stage offers the last opportunity for IDDM prevention. Large masses of β-cells have been lost and therapies are focussed on saving the remaining active β-cells and

halting the autoimmune response. Immunosuppressants are used in an effort to halt β-cell destruction and allow recovery.

Stage five: Clinical IDDM. Most β-cells have been destroyed but early detection of new patients with IDDM may enable the preservation of residual β-cells. Insulin therapy is necessary with the patient receiving either pig (porcine) or calves (bovine) insulin.

1.6.4 Use of Immunosuppressants

Being an autoimmune disease, the ideal treatment of IDDM would be an immunosuppressant affecting only the T-lymphocyte population within the pancreas, while leaving that present in lymphoid tissue and circulating blood untouched. The agents presently used however are all non-specific suppressants and have had only marginal success in combating IDDM.[76] Cyclosporine A has had some success in slowing the progress of IDDM or inducing remission in newly diagnosed patients, although the remissions have not been permanent.[78] The risks associated with nephrotoxicity and the uncertain chance of recovery thus restrict the use of cyclosporine A to incidences in which a very great likelihood of IDDM is thought to exist. A recent study among 192 patients with autoimmune diseases who received cyclosporine A treatment revealed 41 cases of nephropathy.[79] The use of dosages greater that 5 mg/kg per day was associated with significant nephrotoxicity, with doses of 10 mg/kg per day typically used to combat IDDM and other autoimmune diseases.[59] FK-506, like cyclosporine A, is also associated with nephrotoxicity and is considered less favourable for IDDM treatment.

Azathioprine has had significantly more success than either cyclosporine A or FK-506.[80] It effects β-cell stabilisation in both pre- and early IDDM without increased lymphoma or the onset of opportunistic diseases. Patients given doses of up to 3 mg/kg per day have been able to decrease external insulin requirements for periods of one year or longer, however prolonged azathioprine treatment has been associated with initial and persistent relative lymphopenia.[81]

1.7 New Immunosuppressants

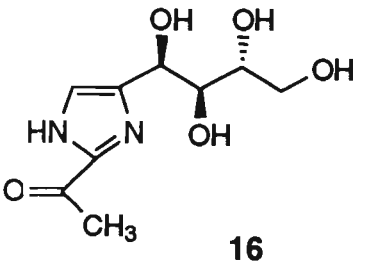
The fact that current immunosuppressants perform so poorly in combating autoimmune diseases and IDDM in particular makes the search for new agents crucial. The number of drugs available to fight such diseases is indeed varied, but focussing on the causes of the disease rather than the treatment of symptoms is by far the preferred therapy. It is preferable to prevent T-cell destruction of β-cells in IDDM rather than rely on exogenous insulin replacement.

The agents used in the fight against autoimmunity are those used commonly in the prevention of allograft loss, and while potent, suffer from significant adverse side-effects. It is also these effects that hinder their use in many transplant procedures. New immunosuppressant drugs must therefore be discovered and evaluated for use in both solid organ transplants and autoimmune diseases. Their mode of action, toxicity and side-effects must all be investigated. Only in this way can the above treatments be perfected and novel clinical agents be employed.

1.7.1 THI: An Immunosuppressant from Food Colouring

(1*R*,2*S*,3*R*)-2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) **16**, a constituent of caramel colour III, has been found to decrease blood lymphocyte counts in both mice and rats.[82] THI produces lymphopenia, apparently without side-effects, in mice and rats in quite small quantities (0.1-5 mg/kg/day) in drinking water[83] and has been reported to prevent spontaneous and

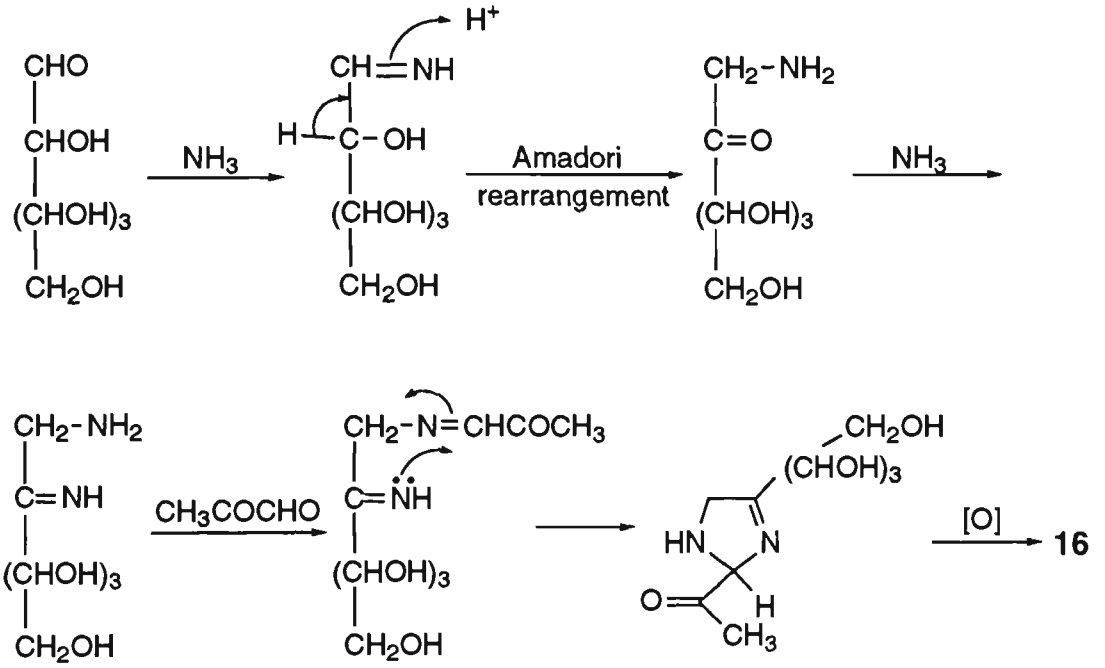
cyclophosphamide induced IDDM in non-obese diabetic (NOD) mice.[84]



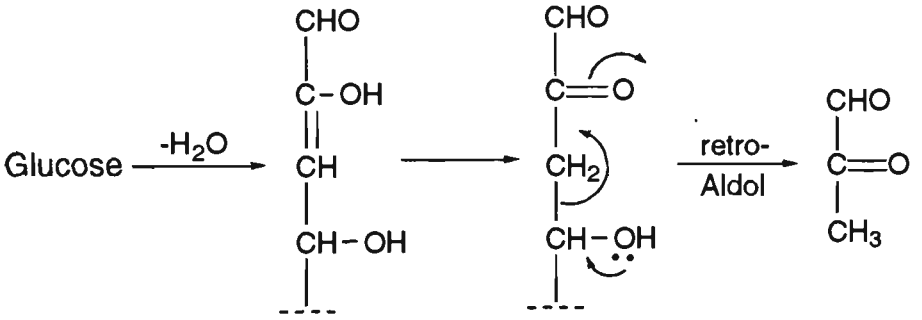
16

THI was first isolated and characterised by the Coca-Cola Company in 1985 by chromatographic separation of caramel colour III, and was found to comprise 0.06% of the original caramel solids.[85] THI is an amorphous, off-white solid and structurally comprises of a disubstituted imidazole containing a 1,2,3,4-tetrahydroxybutyl side-chain at the 4-position and an acetyl group in the 2-position. It is surprisingly insoluble in both water and common organic solvents, but dissolves in DMSO and upon reflux in water. THI is formed during the ammonium caramelisation of glucose. One possible mode of formation involves a condensation reaction between two moles of ammonia and one mole of fructosamine and pyruvaldehyde.[85] Fructosamine is known to be formed from the reaction of glucose with ammonia *via* the Amadori rearrangement (Scheme 1.1). Pyruvaldehyde is also known to be produced as a breakdown product of glucose. A possible mechanism for this reaction is shown in Scheme 1.2.

Scheme 1.1

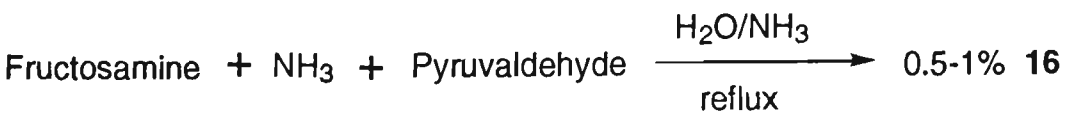


Scheme 1.2



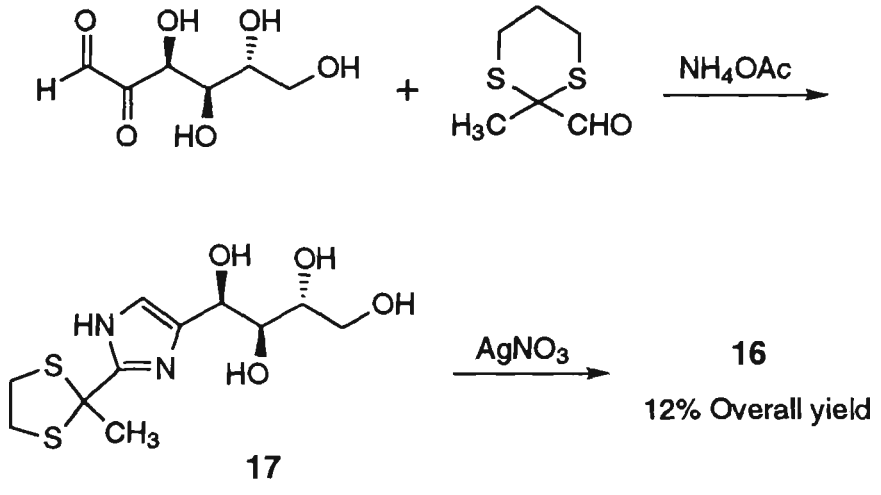
This reaction was able to be reproduced by refluxing fructosamine acetate and excess pyruvaldehyde in 25% aqueous ammonia. THI was obtained in a 0.5-1% yield based on fructosamine[85] (Scheme 1.3).

Scheme 1.3



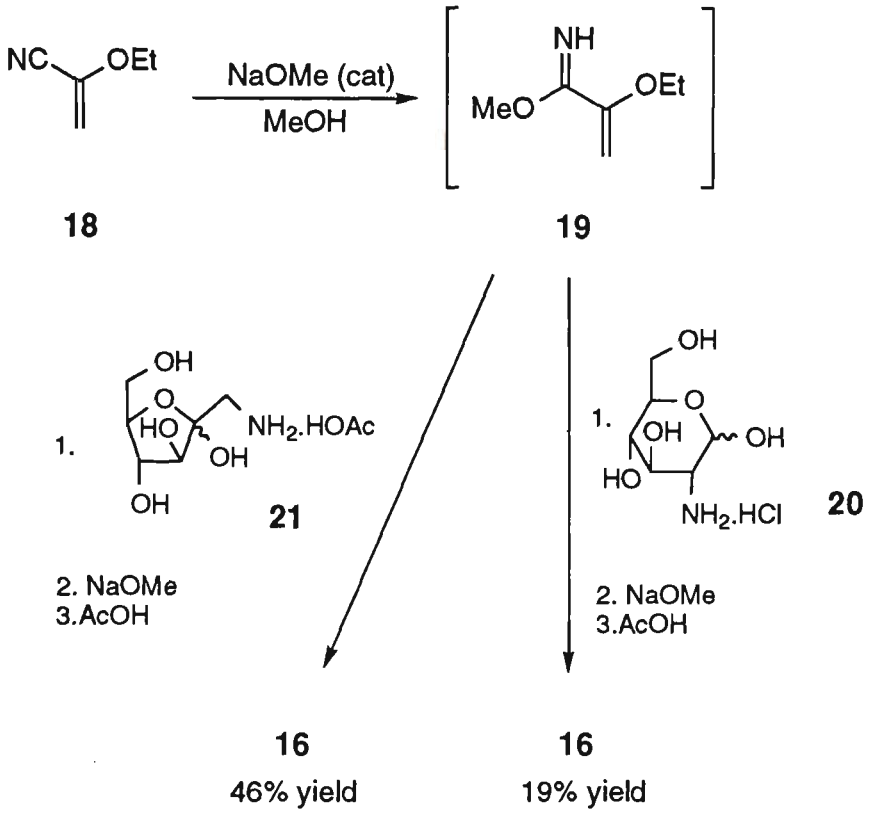
Two syntheses of THI have been developed and published.[86,87] These have confirmed the molecule's structure and enabled multigram quantities of the imidazole to be obtained. The method of Sweeny *et al.* relies upon the condensation of D-glucosone with the dithioketal of pyruvaldehyde in the presence of ammonium acetate (Scheme 1.4).[86] In a similar reaction to the caramelisation process, dithiane **17** was obtained in 30% yield, with 12% overall yield of THI after silver nitrate deprotection.

Scheme 1.4



The second synthesis is the most efficient of the two.[87] 2-Ethoxyacrylonitrile **18** reacts in the presence of sodium methoxide in methanol to give the intermediate **19**. Addition of commercially available D-(+)-glucosamine hydrochloride **20** and one equivalent of sodium methoxide gave THI in 19% yield after acetic acid work-up. The yield can be increased to 46% by the use of 1-amino-1-deoxy-D-fructose acetate **21**, which is prepared from glucose in near quantitative yield (Scheme 1.5).

Scheme 1.5



1.7.1.1 Biological Properties

Before THI was isolated in 1985, caramel colours were known to produce both short and long term lymphopenia in rats.[88,89] In a short term study lasting 13 weeks, rats fed on diets comprising 8% and 16% caramel showed lymphocyte counts less than half that of the control group. When the length of the study was increased to one year, rats on 6% caramel diets were still showing suppressed lymphocyte levels with no adverse or carcinogenic effects evident.[89]

Most studies on THI itself have been carried out on laboratory rats using oral administration. THI has been found to decrease blood lymphocyte counts within 16-24 h of administration, with B- and

T-cell levels returning to normal within 48 h of treatment cessation.[83] Using THI levels of 1 mg/kg/day over a 7 day trial on male F344 rats, both B- and T-cell counts were significantly reduced to a fractional value of the control rodents. The total T-cell population was decreased by about 97% with B-cell count down 84%. Both helper and cytotoxic/suppressor T-cell sub-populations were effected during the trial, with the T_H-cell count only 6% that of the control (Table 1.4).[90]

Table 1.4 Effect of THI at 1 mg/kg per day on lymphocyte counts per mm^3 of peripheral blood in rats. Mean value plus standard deviation.

Cell Type	*Control*	*Cell Count ($10^3/mm^3$)*		
		Day 1	*Day 3*	*Day 7*
B-Cell	5.60 (2.21)	2.70 (0.60)	2.00 (0.34)	0.88 (0.16)
T-Cell	8.02 (1.46)	2.41 (1.75)	0.41 (0.19)	0.21 (0.06)
T_H-Cell	5.19 (1.40)	1.59 (1.14)	0.32 (0.16)	0.30 (0.12)
$T_{C/S}$-Cell	3.37 (0.82)	1.32 (0.78)	0.60 (0.19)	0.76 (0.18)

Although tests on THI's ability to suppress an immune response during allograft transplantation on rats are still in their infancy, they show promising results. Mixed spleen cells of F1 hybrid F344 and Brown Norway rats were injected into the footpads of F344 rats to imitate a graft *vs.* host reaction. THI doses of 0.1-5 mg/kg/day inhibited the mixed lymphocyte reaction in a dose dependant manner.[91]

The use of THI for the inhibition of IDDM in NOD mice has been met with considerable success. NOD mice spontaneously become diabetic upon maturation. Continual administration of THI at 400 ppm in drinking water has been shown to reduce the prevalence of spontaneous diabetes in female NOD mice from 63% to 8% in treated rodents. Diabetes in the NOD mouse can also be accelerated and intensified by the administration of cyclophosphamide. Cyclophosphamide-induced IDDM effected 100% of untreated mice. THI treatment either concurrently or from 14 days previous deceased diabetes incidence to 13-14%.[84]

1.7.1.2 THI - A Potential Agent for Modulating the Human Immune System?

To date, THI has proved to be both non-carcinogenic and non-toxic in model animal studies[84] and has been shown to be an effective immunosuppressant. Its potential for modulating and suppressing the immune system in man is thus raised. As a constituent of caramel colour III, THI is consumed in low doses over extended periods by western man. According to data in Martindale's 'Extra Pharmacopoeia', the estimated daily intake of caramel colour made by the ammonia process is 100 mg/kg body weight[84]. For a person weighing 70 kg, this would correspond to about 7 g per day caramel colour, with a daily THI intake of 1.4 mg. There are no known long-term toxic effects of THI to man at such low dosages, and thus it may be useful in treatments requiring prolonged exposure to immunosuppressants. (While no chronic toxicity has been observed at such low doses, it should be noted that these dosage levels would

be below that required for therapeutic treatment, and are most likely below the level required to induce a toxic response).

In IDDM, where the side-effects of the immunosuppressants cyclosporine A and azathioprine exclude them from long-term therapy, an agent such as THI may prove extremely beneficial. Primarily effecting T-lymphocyte populations,[83,91] low dosage THI treatment to prevent β-cell damage could be implemented at both the early and progressive insulitis stages and be continued long-term.

The potential use of THI in surgical transplants as an agent for manipulating the immune response requires significantly more work and evaluation on animal models. Studies as to whether islet allografts and xenografts in NOD mice can survive under the influence of THI are underway at the Walter and Eliza Hall Institute of Medical Research in Melbourne, but results are yet to appear in print. While THI is unlikely to present a more potent immunosuppressive alternative to cyclosporine A or FK-506, its long-term lack of known toxicity may potentially be useful in immunomodulatory treatment for graft preservation and stabilisation.

1.8 Aims of Project

With THI being such a structurally simple yet biologically intriguing molecule, its structure/activity relationship is well worth further investigation. Primarily inducing lymphopenia, THI's mode and site of action need to evaluated. Data obtained from such studies would lead to a greater understanding of THI's biomechanism and may potentially lead to new agents whose bioactivity surpasses the parent molecule itself.

The most effective way of assessing the structure/activity relationship of a molecule is *via* biological evaluation of structural analogues. Subtle changes in a molecule's structure may yield significant alterations in bioactivity and lead to valuable data on the parent molecule's immunological mechanism.

THI comprises of three basic units which could be altered to give numerous structural analogues:

i) the 2-acetyl group

ii) the heterocyclic imidazole ring

iii) the 1,2,3,4-tetrahydroxybutyl side-chain.

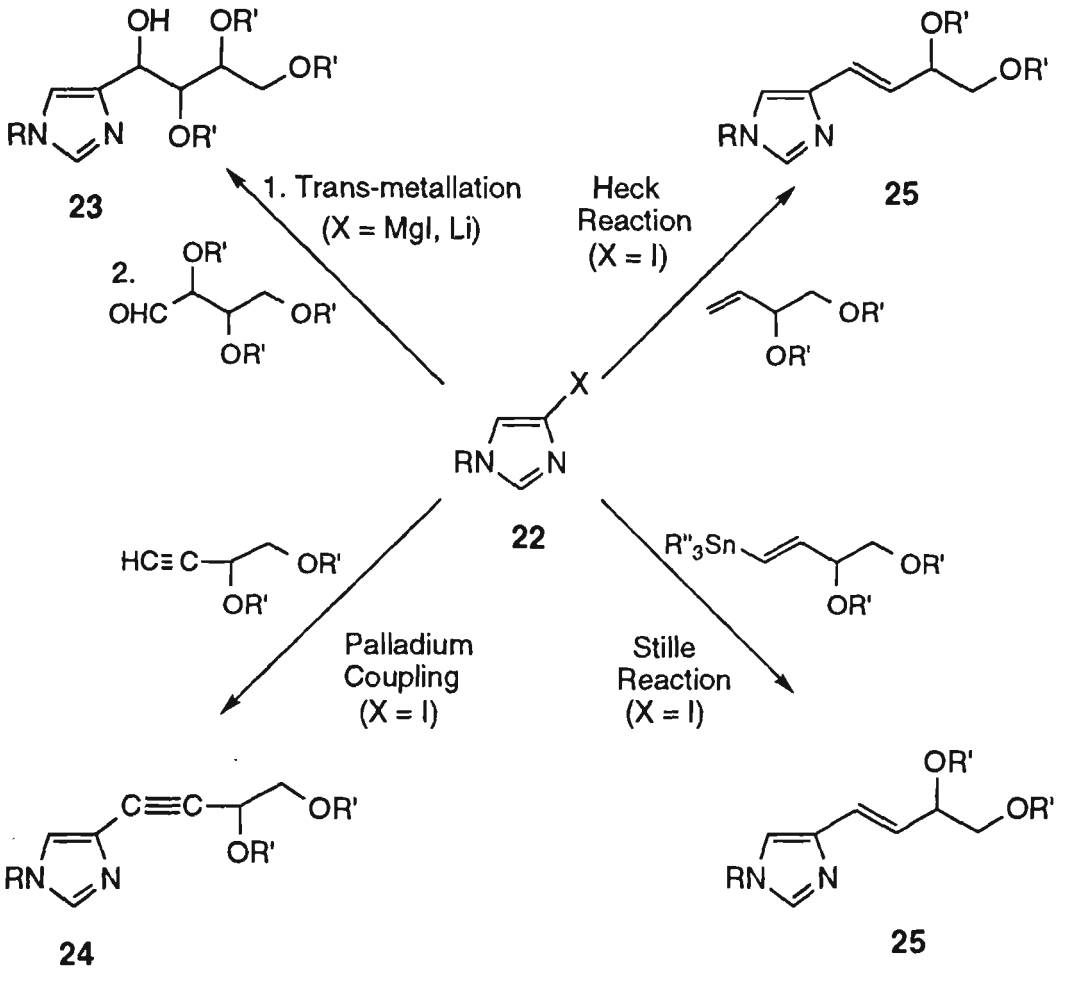
Work on altering the 2-acetyl group has already been investigated by our group. It was found that manipulating the methyl ketone resulted in reduced or negligible immunosuppressive activity. Reduction of the carbonyl group to an alcohol or amine moiety or replacement of acetyl with benzoyl or alkyl groupings gave analogues of diminished activity.[92]

The aim of the project was to develop a flexible, synthetic route that would allow all eight stereoisomers of THI to be synthesised. In addition, various mono, di, and triol analogues would be synthesised during preliminary model work or as intermediates to the tetraol analogues. This would enable a large range of THI analogues with various numbers of hydroxyl groups and stereochemistries on the butyl side-chain to be obtained. These analogues would then be sent to the Walter and Eliza Hall of Medical Research in Melbourne and the John Curtin School of Medical Research at the Australian National University, Canberra for assessment *in vivo* and *in vitro*.

1.8.1 Synthetic Approach

In principle, a number of synthetic strategies could be utilised for the synthesis of THI analogues. Rather than construct the imidazole ring as has been employed in the previous syntheses of THI,[85,86,87] it was decided to use an *N*-protected 4-iodoimidazole **22** and then attach a suitably functionalised butyl side-chain to the 4-position of the imidazole nucleus (Scheme 1.6). This would provide a more flexible route than the three previous approaches, which relied on sugar derivatives to prepare the tetrahydroxybutyl side-chain of THI.

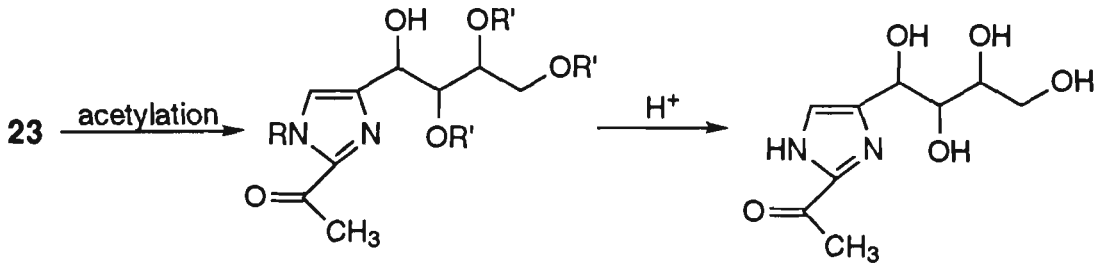
Scheme 1.6



An on-line search of the literature revealed that the majority of work involving the preparation of 4-substituted imidazoles employed either Grignard[93,94] or organolithium reagents.[95,96,97] Such a method could be adapted to the synthesis of tetraols of structure **23** employing the organometallic compounds **22** (X = Li or MgI) and chiral protected 2,3,4-trihydroxybutanals (Scheme 1.6).

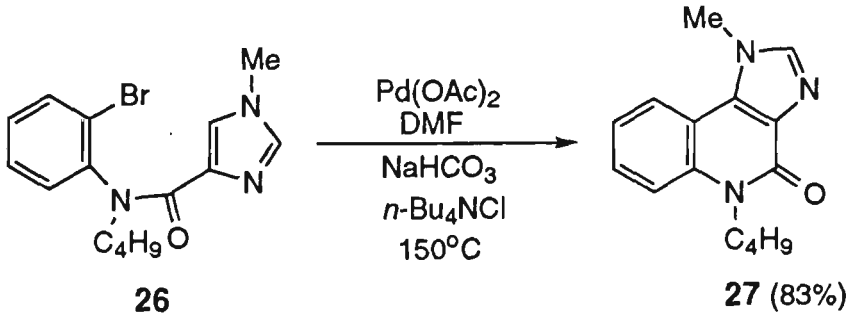
Addition of the acetyl group into the 2-position of **23** followed by deprotection would complete analogue construction of those molecules employing trans-metallation of **22** (X = I) as a method for the addition of the butyl side-chain (Scheme 1.7).

Scheme 1.7



Only two papers were found which described the palladium coupling of imidazole compounds.[98,99] Of these, the only efficient reaction involved an intramolecular annulation of imidazole **26** to give the heterocycle **27** in 83% yield (Scheme 1.8).[99]

Scheme 1.8

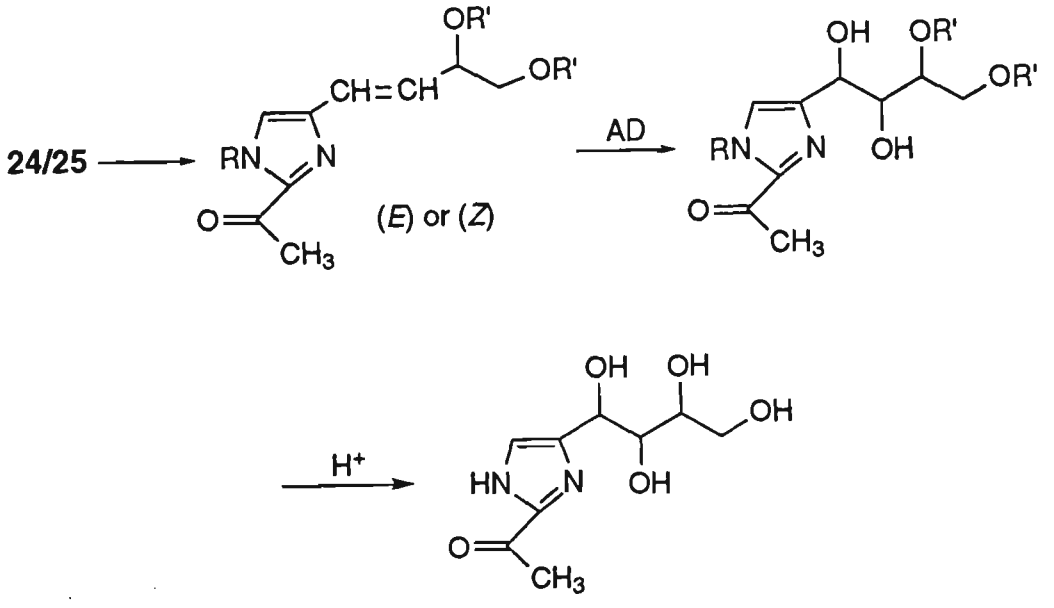


26 **27** (83%)

Despite the lack of published work involving imidazoles, a recent review revealed many examples of similar palladium catalysed coupling reactions to those proposed in Scheme 1.6 with other heterocyclic systems.[100] Adaptation of these methods to our own system should enable suitable 4-substituted imidazoles **24** and **25** to be sucessfully prepared *via* palladium catalysed alkyne coupling, and Heck and Stille reactions respectively from 4-iodoimidazole **22** (X = I) (Scheme 1.6).

Sharpless's asymmetric dihydroxylation (AD) reaction on the 2-acetyl compounds of **24** and **25** followed by deprotection would complete construction of analogues synthesised *via* palladium coupling (Scheme 1.9).[101]

Scheme 1.9



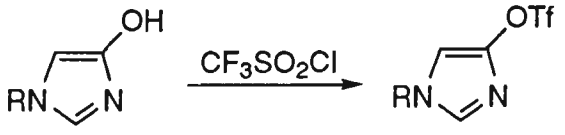
CHAPTER 2

MODEL STUDIES

2.1 Synthesis of *N*-Protected 4-Iodoimidazoles

For the synthesis of THI and its analogues, an *N*-protected 4-iodoimidazole was chosen as the most versatile starting material. The 4-iodo group readily undergoes transmetallation to form organolithium and Grignard reagents and performs exceedingly well in Heck and Stille coupling reactions.[102,103] Organic triflates outperform their organohalide equivalents in Stille reactions as a general rule[104,105] and have also received attention in the Heck coupling.[106] Synthesis of the appropriate triflate **29**, however, would require the *N*-protected 4-hydroxyimidazole **28** (Scheme 2.1). Synthesis of the alcohol **28** would be expected to be time consuming and of low yield, due to the manipulations needed to provide the hydroxyl group.

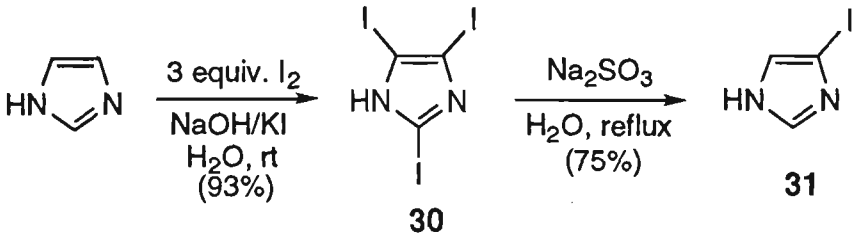
Scheme 2.1



28 **29**

Synthesis of the mono-iodoimidazole was achieved by reaction of imidazole with three molar equivalents of iodine in basic media to give the triiodide **30** in 93% yield.[107] Regioselective reduction with sodium sulfite, at the 2- and 5-positions, gave 4(5)-iodoimidazole **31** in 75% yield[108] (Scheme 2.2). Attempts to obtain the monoiodide **31** using a single equivalent of iodine failed and gave a mixture of the starting imidazole plus the mono-, di- and triiodinated species.

Scheme 2.2



30 **31**

Addition of protecting groups to the nitrogen of the imidazole ring of **31** can occur at either the τ or π positions, depending upon which nitrogen atom of the conjugate base of **31** is more readily accessible (Figures 2.1, 2.2). Sterically demanding protecting groups such as trityl and tosyl form the 1,4-disubstituted isomer in preference to the sterically less favoured 1,5-isomer.[109] Reaction of **31** with such groupings under base catalysed conditions gave the *N*-protected 4-iodoimidazoles in good to excellent yields. Reaction of **31** with trityl chloride, tosyl chloride or benzenesulfonyl chloride for 16 h in the presence of one molar equivalence of triethylamine gave derivatives **32**, **33** and **34** in 76%, 78% and 94% yields respectively after recrystallisation (Scheme 2.3).

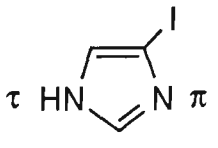
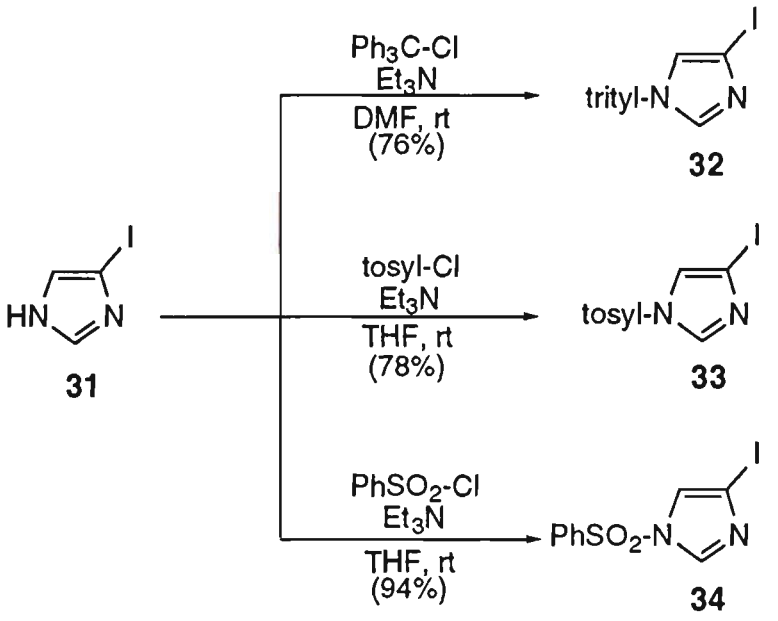


Figure 2.1 τ and sterically hindered π positions on imidazole **31**.

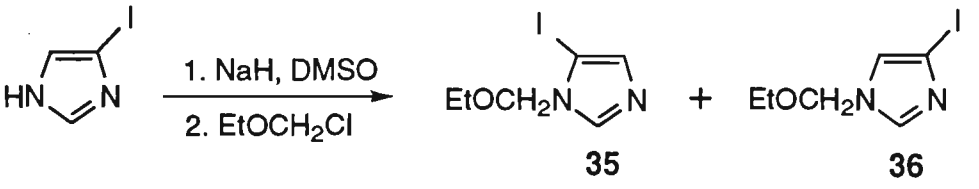
Figure 2.2 Resonance forms of the conjugate base of **31**.

Scheme 2.3



The use of less sterically demanding protecting groups often gives mixtures of regioisomeric *N*-protected imidazole derivatives.[110] Treatment of **31** with sodium hydride at 80 °C followed by quenching of the resulting imidazole anion with chloromethyl ethyl ether gave the isomeric 5-iodo and 4-iodo 1-ethoxymethyl ethers **35** and **36** in 5% and 47% yields respectively[111] (Scheme 2.4). Despite numerous attempts to suppress the formation of **35**, we were unable to significantly increase the ratio of **36**:**35** from 9.4:1. Reduction in the reaction temperature to ambient temperature surprisingly gave **35** as the major product with a ratio of **35**:**36** of 1.6:1, while the use of different solvents such as THF and dichloromethane/triethylamine, which had proved advantageous in the preparation of other derivatives, all gave increased quantities of **35**.

Scheme 2.4



35 **36**

The structure of the isomers **35** and **36** were assigned on the basis of a number of ^{1}H NMR experiments.[112] The aromatic protons of 1,4- (H2 and H5) and 1,5- (H2 and H4) disubstituted imidazoles are coupled across the ring with associated coupling constants $J_{2,5}$ and $J_{2,4}$ respectively. Matthews *et al.* have found empirically that $J_{2,5}$ is larger than $J_{2,4}$ and that $J_{2,5}$ typically falls in the range 1.1-1.5 Hz, while $J_{2,4}$ generally varies from 0.9-1.0 Hz. This result has also been confirmed by other workers.[109,113,114]

Although this empirical rule can be used to assign the 1,4 and 1,5 disubstituted patterns of the imidazole derivatives **32-36** that were prepared in this study (Table 2.1), the difference between $J_{2,5}$ and $J_{2,4}$ seems to be a slender distinction. Overlapping of signals in the aromatic region and signal broadening, as in the case of **35**, can make measuring coupling constants difficult or impossible.

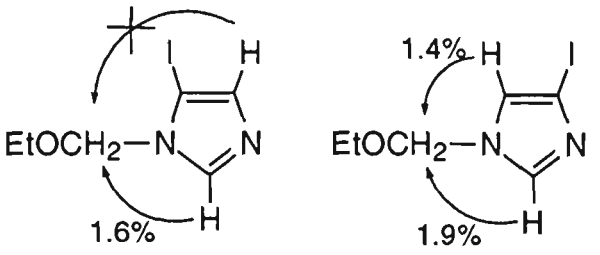
Table 2.1 Imidazole proton chemical shifts and coupling constants for compounds **32-36**.

Compound	*δ (ppm) H2, H5(4)*	*Assigned Isomeric Form*	$J_{2,5(4)}$ *(Hz)*
32	7.32, 6.91	1,4-Isomer	1.2
33	7.88, 7.37	1,4-Isomer	1.2
34	7.90, 7.40	1,4-Isomer	1.2
35	7.75, 7.15	1,5-Isomer	-*
36	7.49, 7.14	1,4-Isomer	1.2

* Resonances appeared as singlets at 400 MHz.

More substantial support for the structural assignments to **35** and **36** was obtained from 1D nOe experiments. Upon saturation of either of the aromatic protons of **36**, an enhancement of the signal due to the methylene group of the *N*-protecting moiety at ca. 5.25 ppm would be expected due the proximity of this methylene group to both H2 and H5. For **35** however, only irradiation at H2 would result in such an enhancement, since H4 is too remote to affect the methylene signal.[109]

Irradiation of H2 and H5 of **36** resulted in an enhancement of the methylene signal of 1.9% and 1.4% respectively when compared to the unperturbed spectrum. In comparison, the same experiment carried out on **35** resulted in an increase in signal strength of 1.6% for H2 irradiation only. No enhancement was observed upon saturation of the H4 singlet at 7.15 ppm (Figure 2.3).



35 **36**

Figure 2.3 nOe enhancements of the methylene signal upon saturation of both aromatic protons.

Subtraction of the perturbed spectra from the unperturbed blank (with irradiation off-resonance) showed a clear enhancement of the methylene signal in all cases except upon irradiation at H4 of **35**, thus confirming its 1,5 disubstituted structure (Figures 2.4, 2.5).

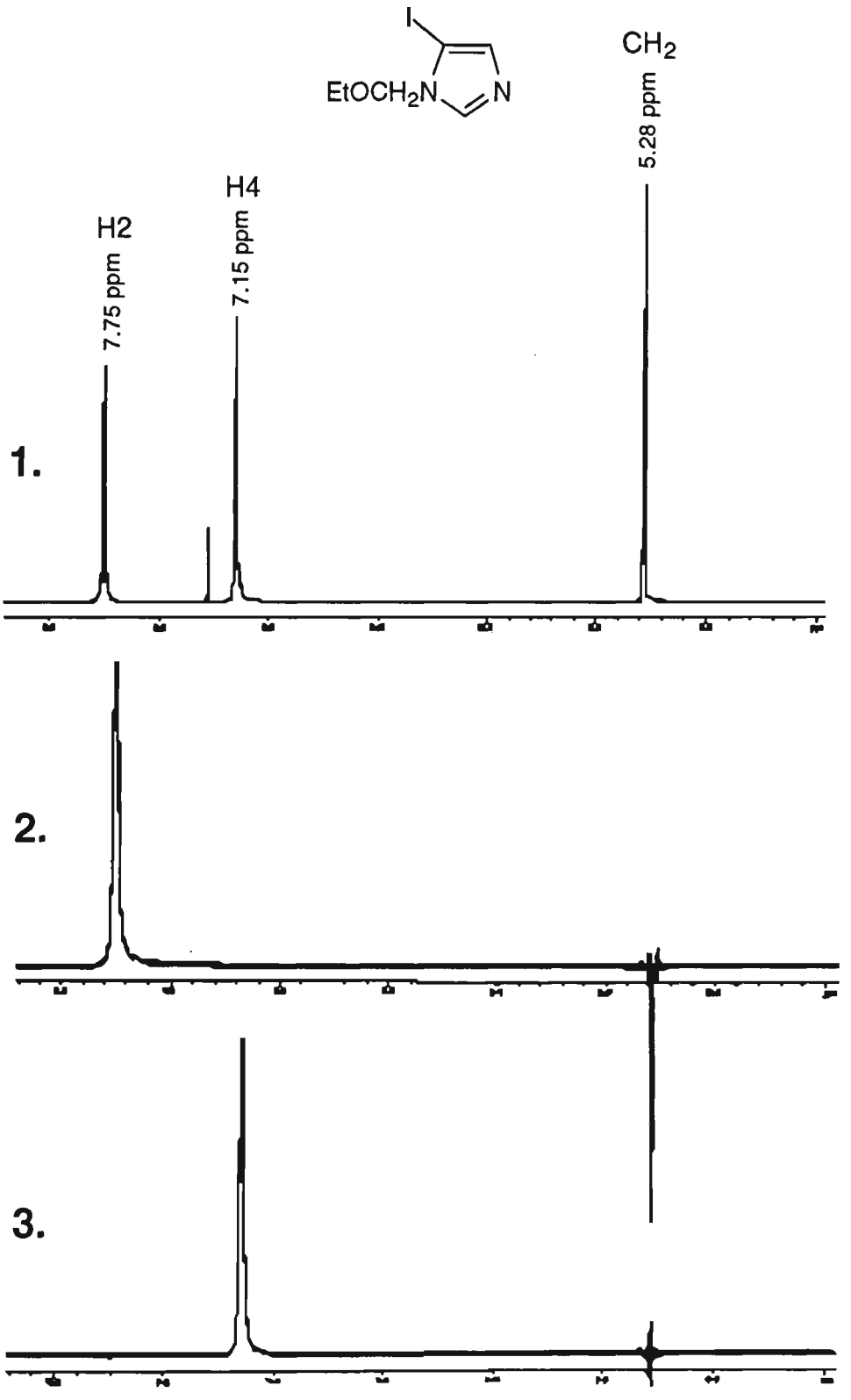


Figure 2.4 Difference ^{1}H NMR spectra from 1D nOe experiment on imidazole **35**. 1. Unperturbed spectra with irradiation off-resonance. 2. Irradiation of H2. 3. Irradiation of H4.

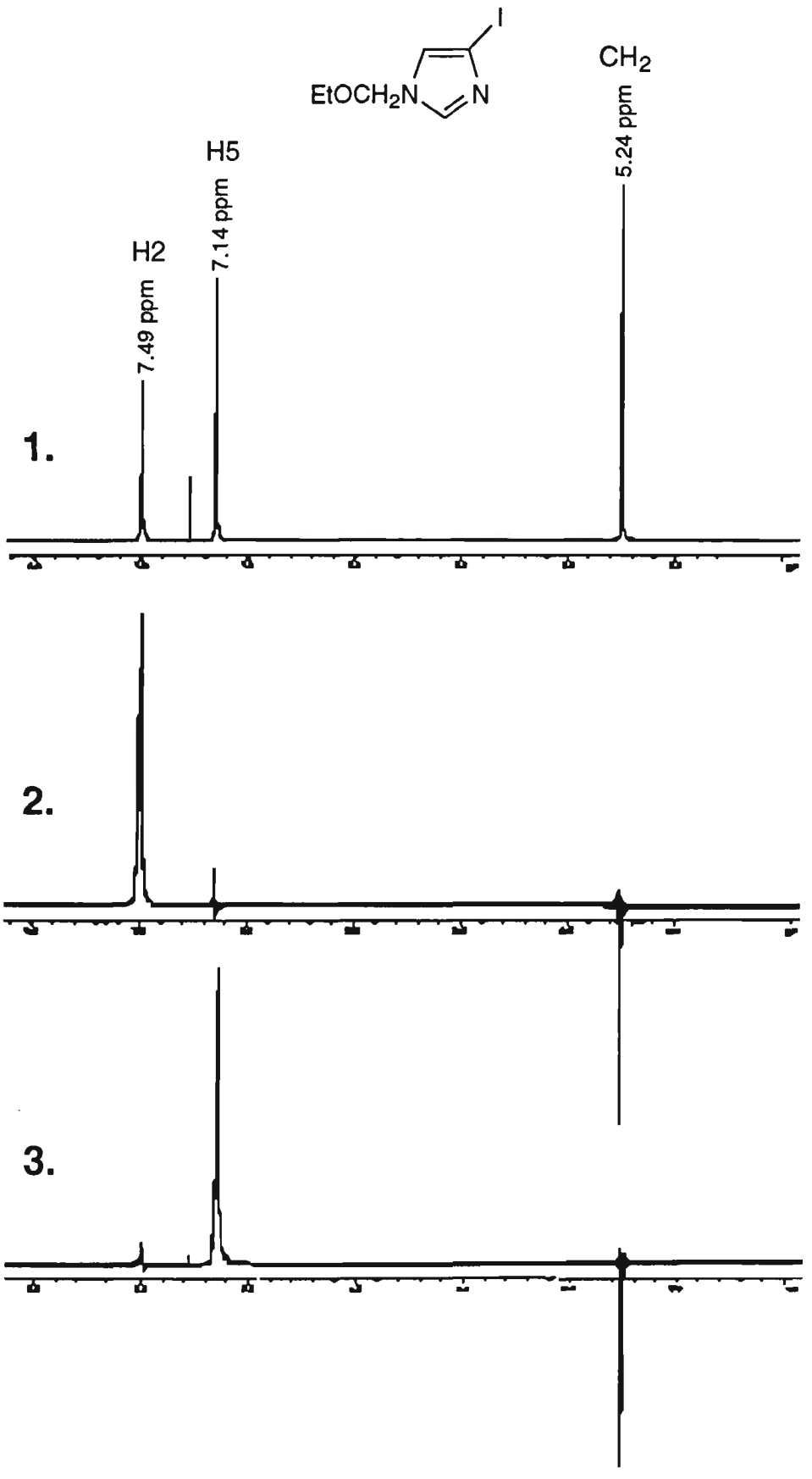


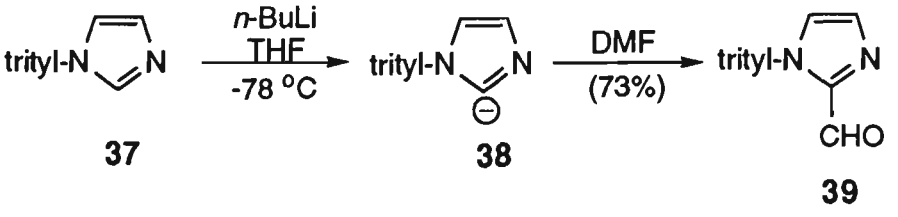
Figure 2.5 Difference ^{1}H NMR spectra from 1D nOe experiment on imidazole **36**. 1. Unperturbed spectra with irradiation off-resonance. 2. Irradiation of H2. 3. Irradiation of H4.

2.2 Addition of a 2-Acetyl Group to Imidazole

Numerous methods have been reported in the literature for the addition of groups onto the C2 position of imidazole.[115,116,117] Lithiation at C2 is readily achieved by treating *N*-protected 2-haloimidazoles or *N*-protected imidazoles with *n*-BuLi. The 2-lithioimidazoles can be quenched with a variety of electrophiles to give 2-substituted species in good to excellent yields.[95,96,97] The choice of the electrophile, however, is critical in effecting efficient, high yielding reactions. While certain electrophiles react efficiently with imidazoles containing specific *N*-protecting groups, they may be less or non-reactive with others.

Initial work to develop a method for introducing an acetyl grouping to C2 of imidazole was carried out using 1-tritylimidazole **37** and other *N*-protected, mono-substituted imidazoles. Carbanion formation at C2 of **37** was achieved efficiently using *n*-BuLi in anhydrous THF at -78 °C, with deuterium oxide quenching of the 2-lithiated species **38** giving a quantitative yield of the *N*-protected 2-deuterated imidazole. Quenching **38** with DMF also proceeded efficiently to give the 2-formyl product **39** in 73% yield (Scheme 2.5).

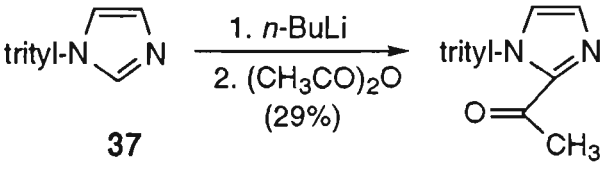
Scheme 2.5



37 **38** **39**

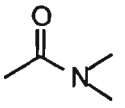
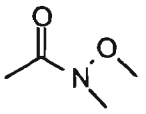
Quenching **38** with *N,N*-dimethylacetamide (DMA), however, under identical conditions to those employed above failed to give any of the methyl ketone **40** and resulted in recovery of the starting material only. A number of different electrophilic acetylating agents were trialed in an attempt to obtain high yields of **40**, but all failed to give significant quantities of the ketone (Table 2.2). Quenching **38** with acetic anhydride gave **40** in 29% yield, but this reaction was not reproducible (Scheme 2.6), while phenyl and ethyl acetate gave only trace amounts of the desired product. *N*-Methoxy-*N*-methyl acetamide **41**[118] gave a 13% yield of **40** upon quenching of **38**. This low yield was disappointing as such amides have proved to be extremely useful acylating agents, with the leaving amine anion stabilised by the electron-withdrawing oxygen.[118,119] The use of HMPA or TMEDA to increase the reactivity of the anion had no effect on the yields of **40** obtained. Reactions carried out on *N*-benzenesulfonyl imidazole also failed to give any of the acetylated product.

Scheme 2.6



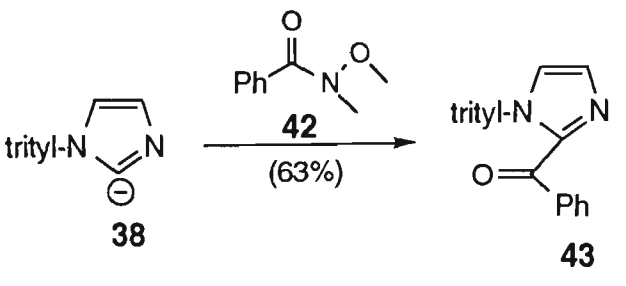
37 **40**

Table 2.2 Yields of **40** after reaction with various acetylating agents.

Acetylating Agent	*% Yield (40)*
 (DMA)	0
 (41)	13
Acetic Anhydride	29
Ethyl Acetate	Trace
Phenyl Acetate	Trace
^{t}Butyl Acetate	0

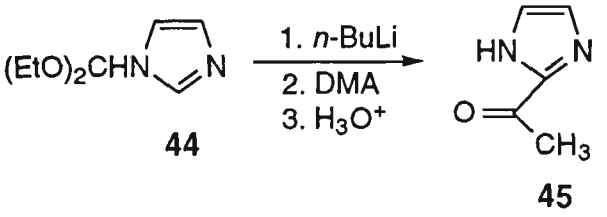
The high reactivity of **38** towards DMF, yet reluctance to react with the structurally similar DMA, or even **41**, suggested that the C2 carbanion in **38** was being quenched by abstraction of α-protons from the acetylating agents. Further support for this hypothesis came from the following experiment in which the phenyl ketone **43** was obtained in 63% yield when the acylating agent *N*-methoxy-*N*-methyl benzamide **42**, which is devoid of acidic α-protons, was used (Scheme 2.7).

Scheme 2.7



A search of the literature revealed only one example of the addition of acetyl into the C2 position of imidazole.[120] Brown *et al.* reacted *N*-diethoxymethylimidazole **44** with *n*-BuLi and DMA to give the methyl ketone **45** in 80% yield upon acidic workup (Scheme 2.8).

Scheme 2.8



44 **45**

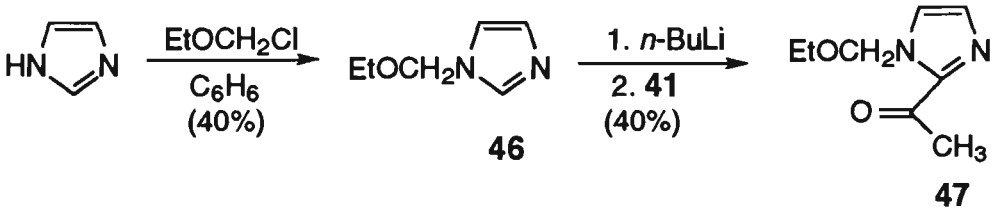
In our hands a yield of 39% for **45** was the best that could be achieved, despite numerous attempts with and in the absence of HMPA and TMEDA. The diethoxymethyl protecting group also proved too labile for our purposes, being readily removed upon exposure to silica gel. Despite its unsuitability however, the diethoxymethyl moiety provided an insight to the system necessary to enable addition of the acetyl grouping to C2. The less sterically hindered ethoxymethyl group was found to be far more stable, yet retained similar electronic properties.

Imidazole and chloromethyl ethyl ether were stirred at ambient temperature in benzene for 2 h to give **46** in 40% yield. Lithiation at C2 followed by addition of *N*-methoxy-*N*-methyl acetamide **41** gave **47** in 40% yield with the ethoxymethyl moiety still intact (Scheme 2.9).

Dropwise addition of **41** as a solution in THF was crucial to the success of the reaction. Addition of the amide as a neat liquid

resulted in localised heating and a rapid reaction occurred that produced a thick tan oily product that contained little of the acetylated compound or starting imidazole.

Scheme 2.9



In addition to being sterically less hindered than either the trityl or benzenesulfonyl moieties, the ethoxymethyl protecting group is thought to assist in stabilising the C2 anion.[121,122] Chelation of lithium to the protecting groups oxygen provides a stabilising effect to the imidazol-2-yl lithium species, allowing greater control of subsequent reactions and minimising the possibility of anion migration to either C4 or C5 on the imidazole ring[97,122] (Figure 2.6).

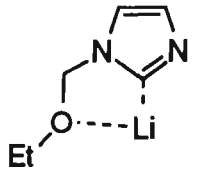


Figure 2.6 Stabilisation of the C2 carbanion of **46**.

A second imidazole protecting group that could be employed is the SEM moiety.[123] This group has been used in numerous imidazole studies and would provide a stabilising effect to the 2-lithio imidazole species.[95] The SEM group, however, offers no distinct advantages over the structurally simple ethoxymethyl group already used, with SEM chloride considerably more expensive to obtain.

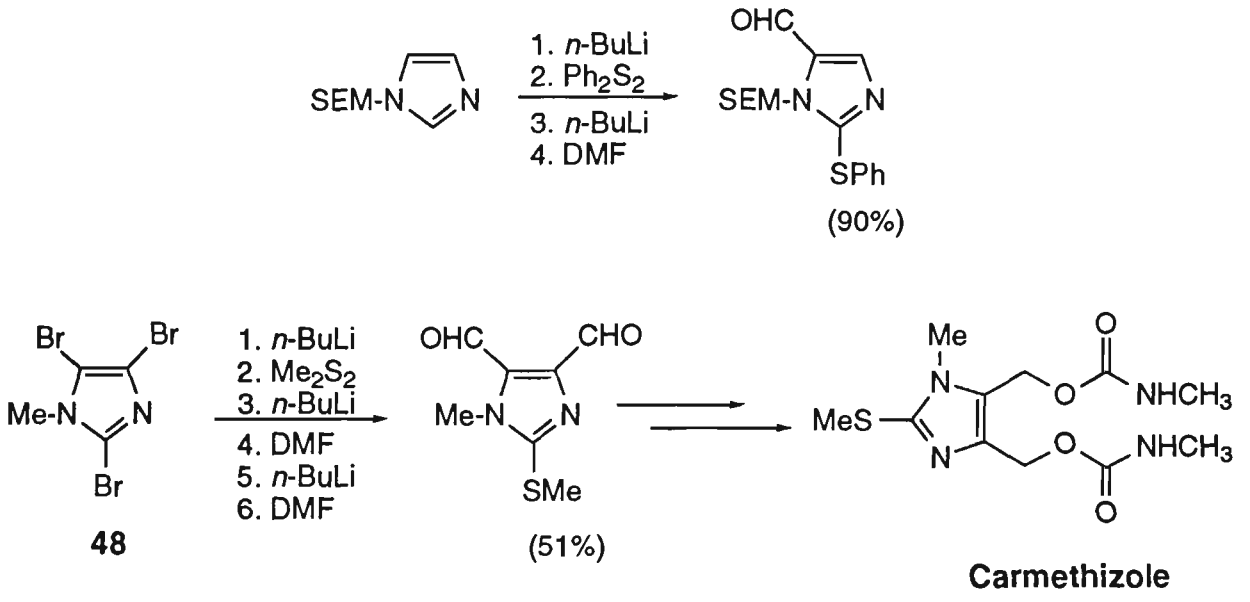
2.3 Metallation at C4

Carbanion formation at C4 on **22** (Chapter 1, Scheme 1.6) *via* metallation reactions provides a simple, convenient means of addition of side chains to the imidazole moiety. This technique has been used extensively in the production of imidazole based bioactive compounds [93,124] and for the synthesis of heterocyclic intermediates.[97] Metallations can be effected by the use of organolithium reagents or Grignard formation from haloimidazoles, with each having its own benefits.

2.3.1 Lithiation

Lithiation of imidazole has been extensively utilised in the synthesis of substituted imidazoles due the ability of organolithium reagents to create anions at C2, C4 and C5 on *N*-protected imidazoles without the need for metal/halogen exchange. Carbanion formation is also site selective on the ring, with the order of reactivity being C2 > C5 > C4.[97] Mono-, di- and trisubstituted imidazoles can be synthesised from suitably protected imidazoles in one-pot reactions provided that the electrophile moieties are added onto the imidazole ring in order of ring reactivity. Lipshutz *et al.* successfully synthesised a series of disubstituted imidazoles by selective lithiations at the C2 and C5 positions.[95,96] Trisubstituted imidazoles were also synthesised in a one-pot reaction from the tribromide **48**, including the bioactive molecule carmethizole (Scheme 2.10).

Scheme 2.10



The major disadvantage with lithiations on imidazole is that a carbanion formed at C4 or C5 migrates to the more stable C2 position. In the absence of a blocking group at C2, anion formation at C4 or C5 is only possible *via* metal/halogen exchange, with subsequent carbanion migration to C2 occurring rapidly. Groziak *et al.* found that even at -78 °C, anion migration from C5 to C2 occurred within 35 minutes even in the presence of stabilising protecting groups[122] (Figure 2.7). Metal/halogen exchange at C4 is further complicated by the adjacent electron lone pair on N3, resulting in a rapid migration to C2.[125]

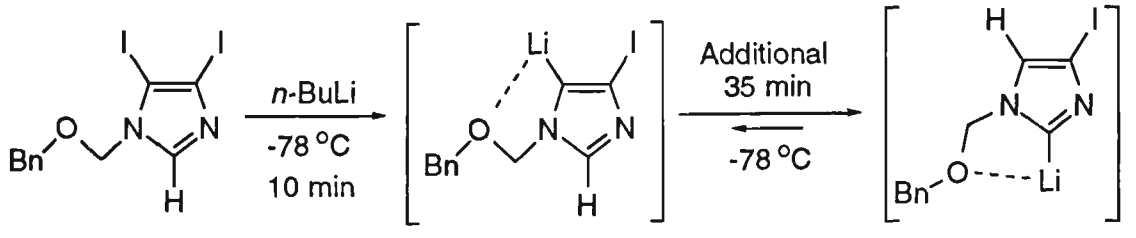
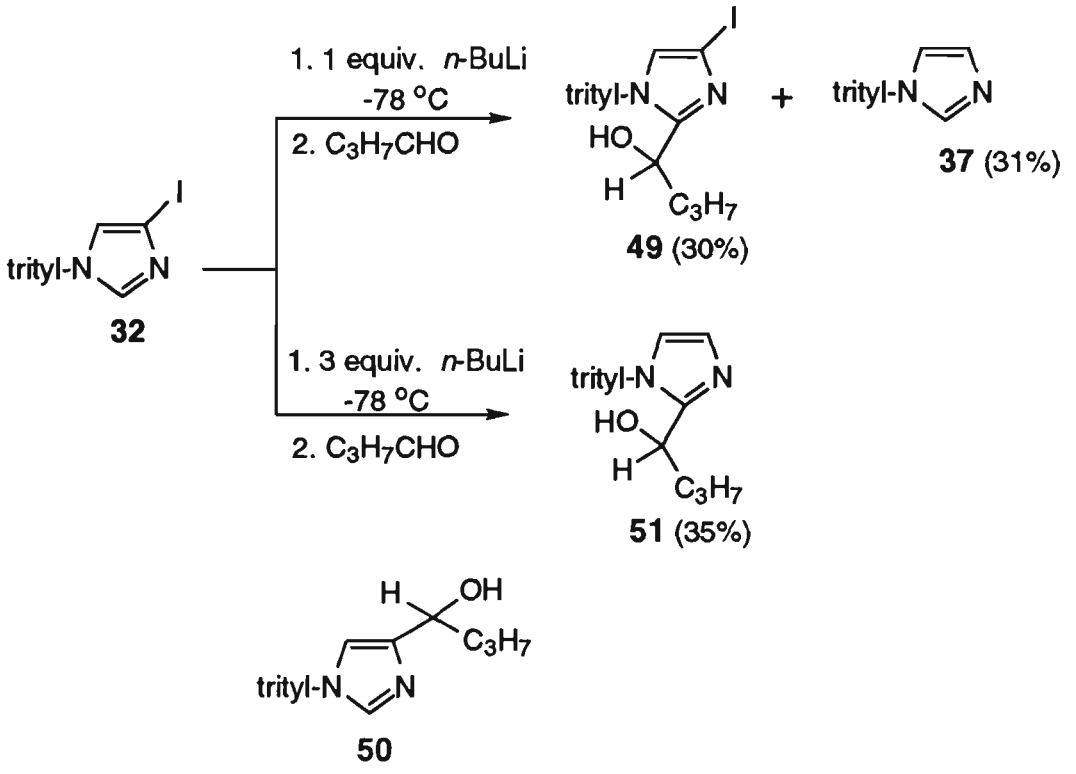


Figure 2.7 Carbanion Migration to C2.

Despite these potential complications, the ease with which such reactions can be performed warranted an attempt to create a carbanion at C4 and subsequently trap it by quenching with butanal.

Imidazole **32** in anhydrous THF was lithiated with a stoichiometric quantity of *n*-BuLi at -78 °C and then quenched with butanal to give imidazoles **49** and **37** in 30% and 31% yields respectively, with none of the desired alcohol **50** being isolated (Scheme 2.11). Despite the presence of a bulky, non-chelating protecting group at N1, carbanion formation at C2 still occurred to a significant extent when using a stoichiometric quantity of *n*-BuLi, leaving the halogen at C4 untouched. Where metal/halogen exchange did occur, however, the resulting carbanion failed to react with the aldehyde and was instead quenched to give the unsubstituted imidazole **37**. It is reasonable to assume that anion migration from C4 to C2 had not occurred since imidazole **51** was not isolated.

Scheme 2.11

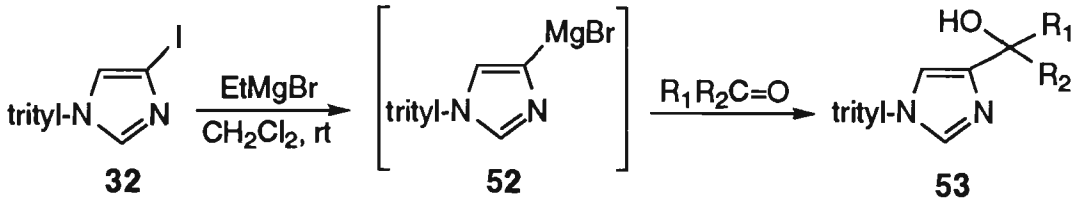


The reaction was repeated using an excess of *n*-BuLi in an effort to effect carbanion formation at C4, but resulted only in the isolation of alcohol **51** in 35% yield (Scheme 2.11).

2.3.2 Grignard Reactions

Unlike the use of lithium reagents, Grignard reagents require the presence of a halogen atom on imidazole to effect carbanion formation. The advantage of Grignards, however, is that they are more selective and will not remove H2 on compounds **32-34** and **36**. Formation of imidazol-4-yl magnesium iodide intermediates from magnesium metal requires entrainment techniques to be used.[97] A more elegant method has been to react the *N*-protected 4-iodoimidazole with ethyl magnesium bromide and exchange the Grignard to the more stable aromatic system (Scheme 2.12).[93,94]

Scheme 2.12

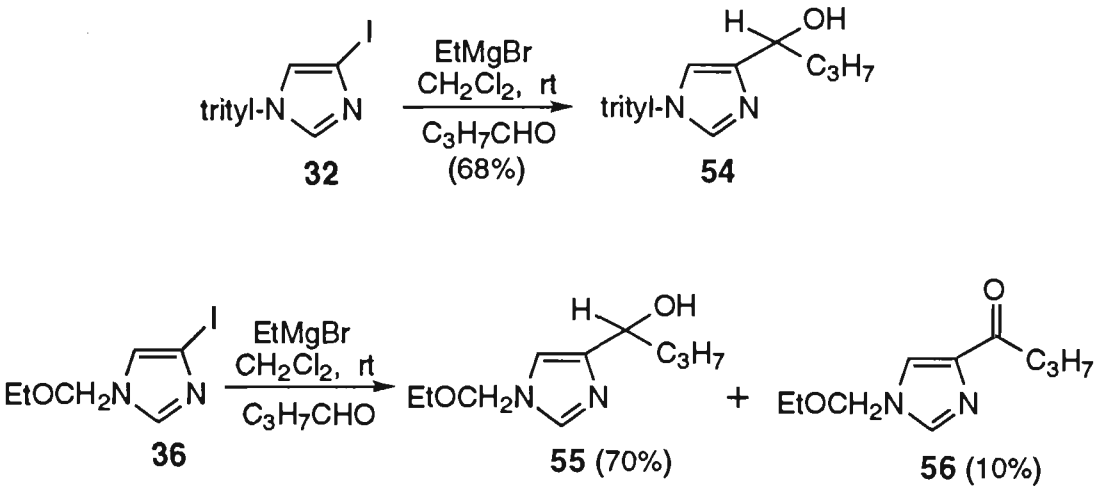


32 **52** **53**

Ley *et al.* found that this technique not only provided an efficient means of forming the imidazol-4-yl anion, but by carrying out the reaction in anhydrous dichloromethane also suppressed anion migration to C2.[93] The use of THF in the same reaction, however, resulted in the formation of 2-alkylated products. The greater covalent character of the organomagnesium intermediate in the noncomplexing dichloromethane made the intermediate **52** less susceptible to equilibrate with the C2 Grignard equivalent, leading to the exclusive formation of alcohol **53**.

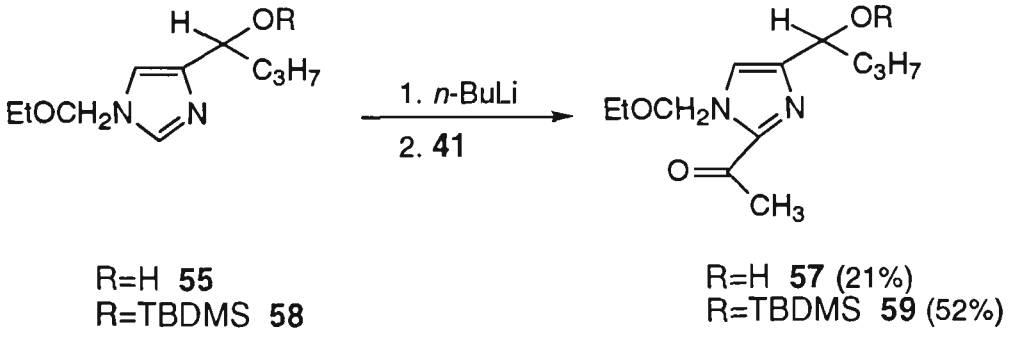
Iodoimidazole **32** was treated with ethylmagnesium bromide in dichloromethane at room temperature for 30 minutes as reported by Ley and then quenched with butanal to give the alcohol **54** in 68% yield (Scheme 2.13) with no trace of the 2-alkylated products **49** and **51** or reduced product **37** (Scheme 2.11). While this method enabled the butyl side chain to be added onto C4, the use of the trityl protecting group would not allow effective addition of the methyl ketone to C2. Repeating this reaction sequence starting with imidazole **36** gave the alcohol **55** in 70% yield plus the ketone **56** in 10% yield (Scheme 2.13). The latter product most likely arose from oxidation of the magnesium salt of **55**.

Scheme 2.13



Reaction of **55** with 2.2 molar equivalents of *n*-BuLi and quenching with the amide **41** gave the alcohol **57** in a disappointingly low yield of 21%, with a 73% recovery of starting material. Despite the distance between C2 and the C1' hydroxyl group, dianion formation from **55** resulted in low yields of the acetylated product. Conversion of the alcohol to the corresponding silyl ether with TBDMS chloride in DMF gave **58** in 70% yield. Reaction of **58** with 1.2 molar equivalents of *n*-BuLi followed by the addition of the amide **41**, gave the ketone **59** in 52% yield (Scheme 2.14).

Scheme 2.14

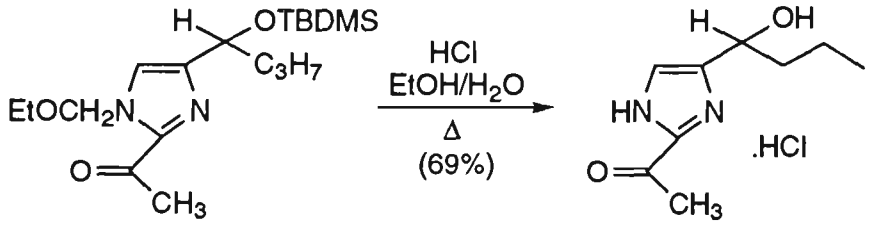


R=H **55**
R=TBDMS **58**

R=H **57** (21%)
R=TBDMS **59** (52%)

Deprotection of **59** under acidic conditions gave the imidazolium chloride salt **60** as a racemate in 69% yield (Scheme 2.15).

Scheme 2.15



59 **60**

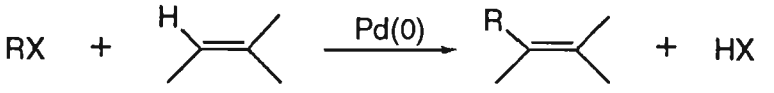
Although present as a racemic mixture, **60** was obtained as a simple, monohydroxylated analogue of THI. The reaction schemes 2.13-2.15 above represent a general method for the synthesis of more complex THI analogues. Initial studies, however, on the synthesis of some of the requisite aldehydes for producing THI analogues proved difficult and the optical purity of these aldehydes was questionable.[126,127,128] Coupled with the difficulties found in controlling the stereochemistry at C1' using the Grignard route with chiral aldehydes,[129] it was considered more efficient to introduce the hydroxyl groupings stereoselectively onto derivatives of type **24** and **25** (Chapter 1, Scheme 1.6).

2.4 The Heck Reaction

2.4.1 Mechanistic Studies and Product Formation

Palladium-catalysed olefination of organic halides with alkenes provides a simple means of carbon-carbon bond formation. Reaction conditions are usually mild and reactions are often complete within a few hours.[102] They are typically used in the coupling of aryl or vinyl halides with terminal alkenes and allow unsaturated products to be formed using only a catalytic amount of palladium (0) (Scheme 2.16).

Scheme 2.16



The Heck reaction makes use of a cyclic mechanism which regenerates the palladium catalyst (Scheme 2.17). The reaction mechanism comprises of four stages:

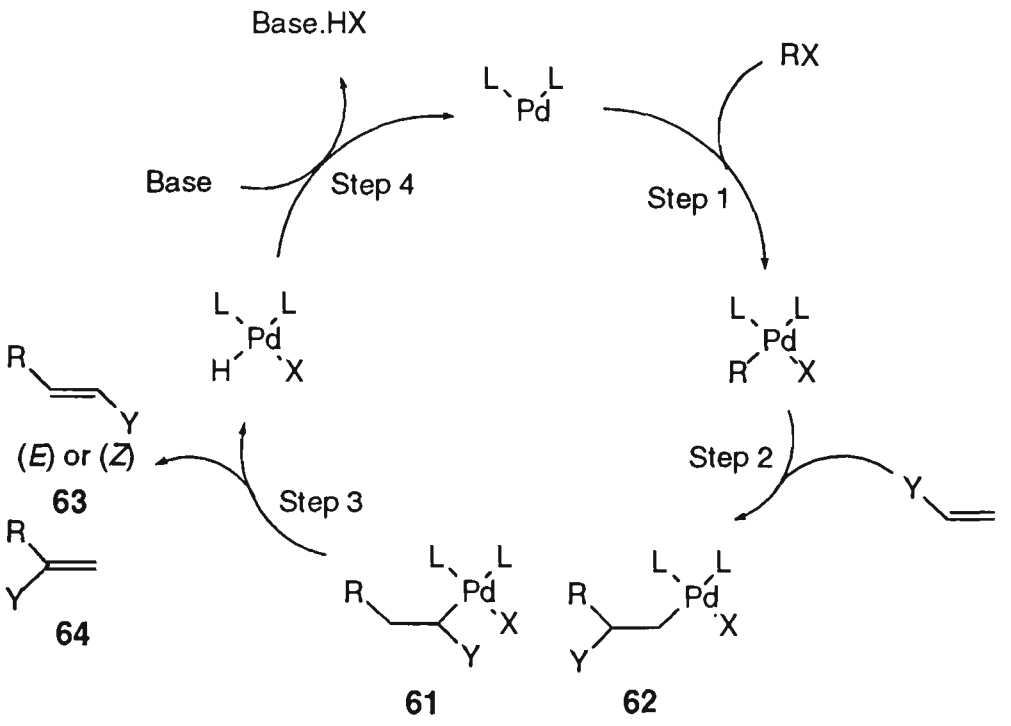
Step 1: Oxidative Addition. Palladium (0) is oxidatively added into the R-X bond. Except in the case of certain aryl iodides, the presence of chelating ligands (L) is necessary to effect addition. Monodentate triphenylphosphine is the most commonly used ligand, although numerous mono and bidentate phosphines have also been employed.

Step 2: Coordination/Insertion. Depending upon the system used, the square planar palladium complex loses either a ligand or halide (X) upon coordination with the alkene. The alkene then inserts into the palladium/carbon bond to give the intermediates **61** or **62**.

Step 3: Product Dissociation. Alkenes **63** and **64** dissociate from palladium to give a Pd(II) hydride salt.

Step 4: Palladium (0) Regeneration. $L_2Pd(0)$ is regenerated from L_2PdHX by base. Typical bases used are trialkylamines (triethylamine) or inorganic salts (K_2CO_3, etc.).

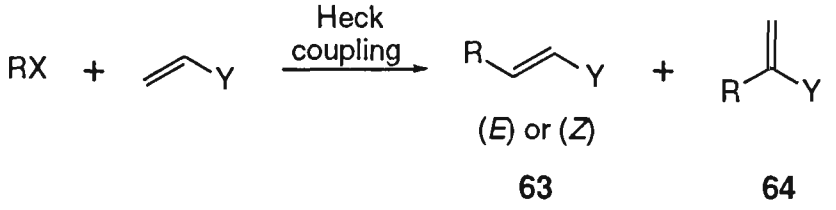
Scheme 2.17



Heck coupling between a monosubstituted alkene and an aryl or vinyl halide can occur on either end of the double-bond to give two possible products, **63** and **64** (Scheme 2.18). In general, the new grouping attaches to the less substituted carbon atom on the double-bond,[130] however, electronic factors also play an important role. If an electron-withdrawing group is attached to one end of the double bond then addition of the aryl moiety R takes place mainly or exclusively on the other carbon atom, giving the (*E*)-alkene **63** as the major product. The presence of an electron-donating

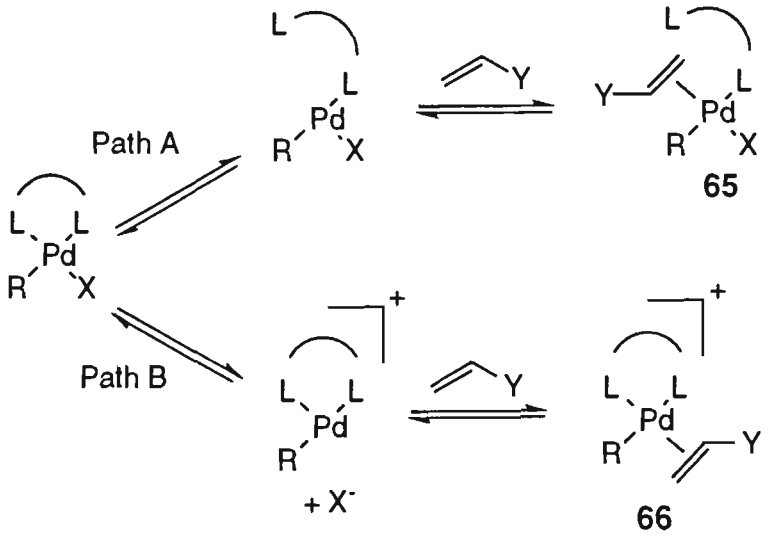
substituent, however, often causes a mixture of products **63** and **64** to be formed.[102]

Scheme 2.18



Independent of the nature of the alkene substituent, however, it is possible to alter the reaction conditions and reagents to obtain predominantly **63** or **64**. During the coordination/insertion step in the cyclic mechanism, the alkene can coordinate to the palladium *via* one of two pathways (Scheme 2.19).[106] Path A involves coordination of the alkene *via* dissociation of a neutral ligand, while path B involves alkene coordination *via* the dissociation of the anionic ligand.

Scheme 2.19



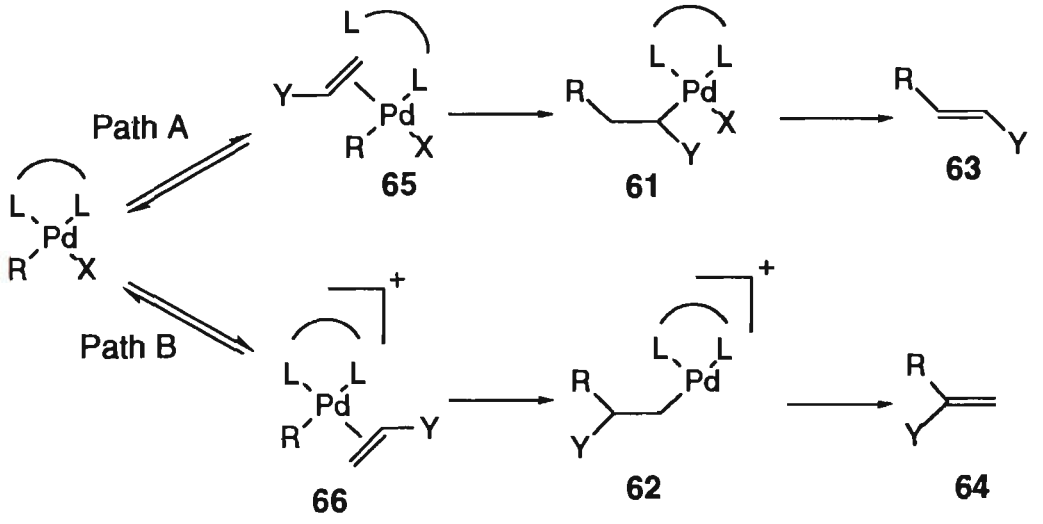
Of the four available coordination sites on the square planar complexes **65** and **66**, two are occupied by the alkene and the organic fragment R that has to migrate onto the π-system. Therefore, the regioselectivity exerted by the palladium catalyst depends upon the two remaining ligands, which are neutral and ionic in the neutral complex **65** (path A), or both neutral in the cationic complex **66** (path B).

Under 'traditional' Heck conditions employing monodentate phosphines (i.e. PPh_3 or $P(o\text{-}Tol)_3$) and aryl halides, a palladium (II) square planar complex containing weak Pd-PR_3 bonds and a strong Pd-I (Br, Cl) bond is generated.[131] Therefore, coordination of the unsaturated system takes place *via* path A and leads to the complex **65**. The use of triflates as the leaving group and bidentate ligands, however, alters the reaction significantly. The Pd-OTf bond is extremely labile and the triflate rapidly leaves the palladium complex,[132] while bidentate phosphine ligands chelate strongly to palladium and are not easily removed. (Bidentate phosphine ligands chelate palladium so strongly that their use with aryl halides decreases the reaction rate and may even suppress Heck product formation completely).[133,134] The cationic complex **66** is thus formed *via* path B.

Migration of the fragment R onto the olefinic π-system depends upon which intermediate complex (**65** or **66**) has been formed. Steric factors always favour the migration of the R moiety to the least substituted alkene carbon on complex **65** (path A), leading to the complex **61** and dissociation of the 1,2-bisubstituted alkene **63**. Coordination of the π-system to the cationic complex **66**, however,

leads to an increase in bond polarisation and selective migration of the aryl moiety R onto the carbon with the lowest charge density, leading to the palladium complex **62** and ultimately to the dissociation of the 1,1-bisubstituted alkene **64** (Scheme 2.20).[106]

Scheme 2.20



Tailoring reaction conditions to give predominantly **63** or **64** from reaction paths A or B can be readily achieved so as to allow attack at either olefinic carbon. The use of monodentate ligands with aryl halides promotes attack onto the unsubstituted alkene carbon to give alkenes of type **63** (Figure 2.8), while aryl triflates and bidentate phosphorous ligands promote path B and results in molecules of type **64** (Figure 2.9).[106]

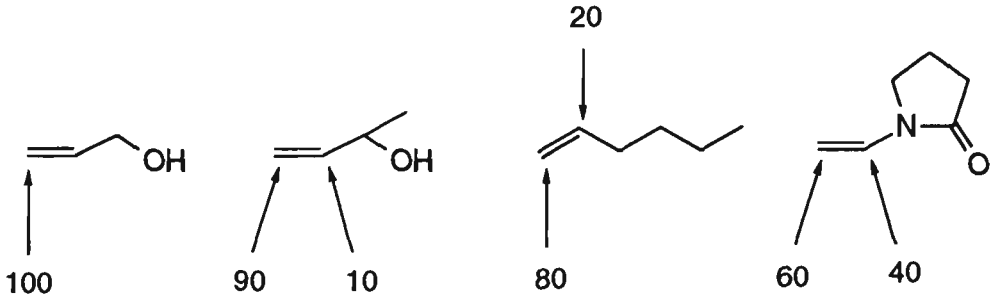


Figure 2.8 Ratio of sites of attack using conditions favouring path A.

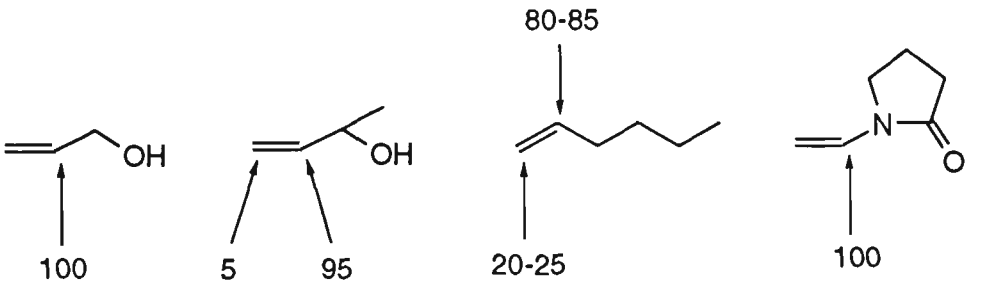
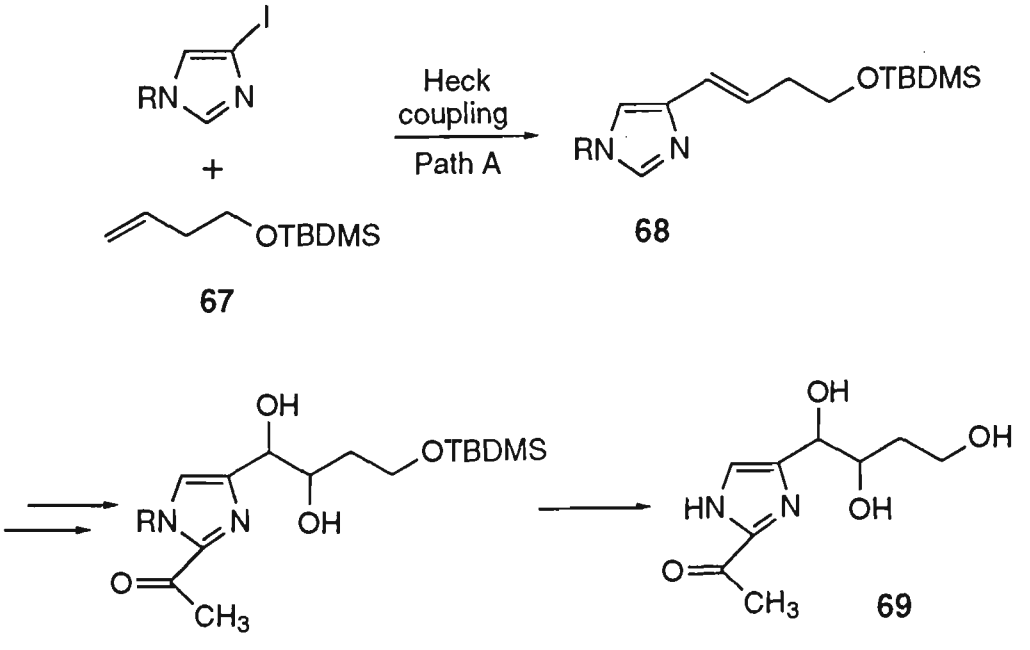


Figure 2.9 Ratio of sites of attack using conditions favouring path B.

2.4.2 Imidazole-Alkene Coupling

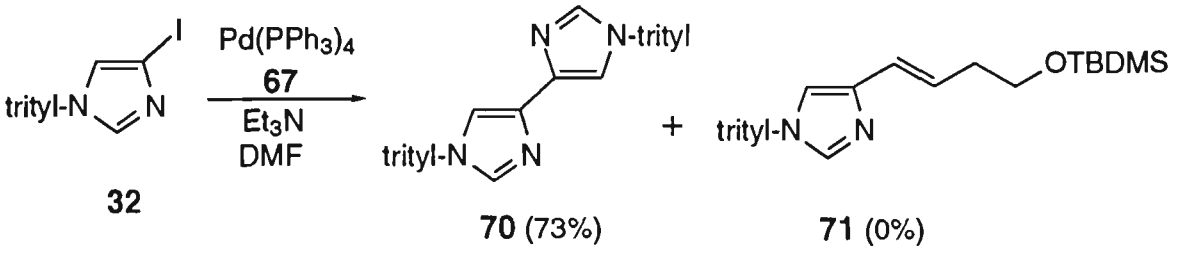
The use of monodentate triphenylphosphine and *N*-protected iodoimidazoles should enable addition to the monosubstituted alkene **67** to take place *via* path A, resulting in the (*E*)-1,2-alkene **68**. Addition of the acetyl grouping to the 2-position followed by the Sharpless AD reaction would thus enable a series of THI triol analogues **69** to be isolated after deprotection (Scheme 2.21).

Scheme 2.21



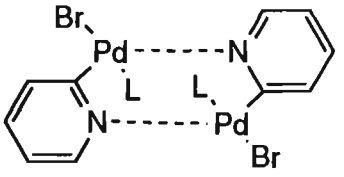
Iodoimidazole **32** and alkene **67** were treated under Heck conditions in the presence of 4 mole % $Pd(PPh_3)_4$ and triethylamine in DMF.[102] A white solid had precipitated after 24 h, which upon ^1H NMR and mass spectrometric analysis was found to be the 4,4'-biimidazole dimer **70**, isolated in 73% yield. Examination of the reaction mixture revealed complete consumption of the starting iodide, with none of the expected alkene **71** having been formed (Scheme 2.22). The use of acetonitrile as solvent and different palladium catalysts again resulted in only formation of the dimer **70**, albeit at lower yields, with no cross-coupled product formed.

Scheme 2.22

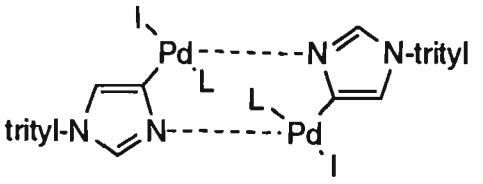


32 **70** (73%) **71** (0%)

While oxidative addition of palladium into the carbon/iodine bond of **32** had obviously taken place to allow the dimer **70** to be formed, the subsequent coordination/insertion reaction with alkene **68** had failed to occur. Similar dimerisations have been reported in the literature.[135,136] Attempted Heck coupling using 2-bromopyridine fails, resulting in the stable complex **72** being formed (L=PPh_3). The reaction also fails with 2-iodopyridine and gives homocoupled material as the only isolatable product.[137] Complex **72** is readily isolated and has been characterised by X-ray analysis.[135] Presumably, the imidazole equivalent **73** is formed as an intermediate, which leads ultimately to the biimidazole **70**.

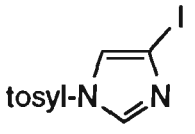


72



73

In an attempt to suppress dimer formation and effect Heck coupling, the iodoimidazole **33** was used in the cross-coupling reaction. By replacing the electron-donating trityl moiety on N1 with the electron-withdrawing tosyl group, it was expected that the decreased electron density of the ring of **33** would prevent the formation of intermediates of type **73** and allow the coordination/insertion reaction to take place.

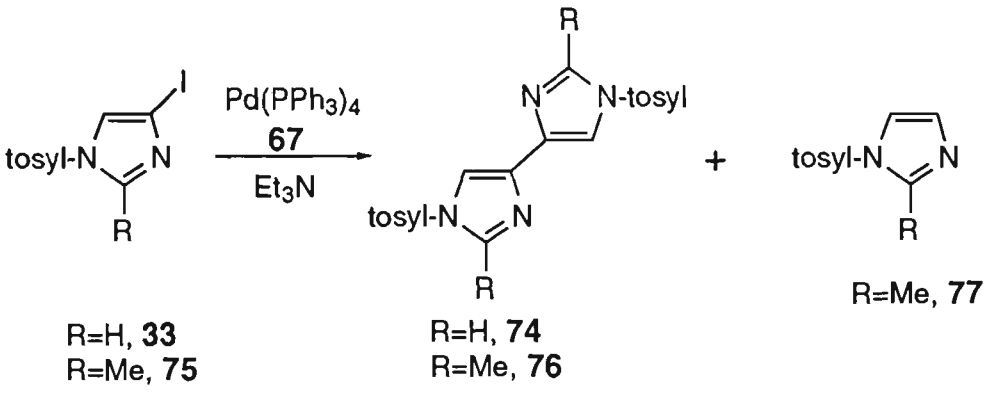


33

Attempted coupling of **33** and **67** in acetonitrile under identical conditions that were used for the analogous reaction of imidazole **32** and **67**, however, failed to yield any cross-coupled product, with **74** formed in 55% yield (Scheme 2.23). The isolation of lower quantities of homocoupled product indicated that the electron-withdrawing tosyl moiety was assisting in the reduction of dimer formation, even though no Heck product was detected. The same reaction was again run using the bulkier 2-methyl substituted iodoimidazole **75**. Alkene **67**, being sterically less hindering than a second imidazole derivative would hopefully cross-couple to give the 1,2-alkene in preference to forming a palladium complex of type **73** and ultimately the 4,4'-biimidazole dimer. Treatment of **75** and **67** in the presence of $Pd(PPh_3)_4$ and triethylamine under

standard Heck conditions again resulted in formation of the dimer **76** in 19-40% yield. The reduced imidazole **77** was also isolated (11-46% yield), but none of the desired cross-coupled alkene was detected (Scheme 2.23).

Scheme 2.23



The *N*-tosyl and 2-methyl moieties on iodoimidazole did assist in suppressing the quantity of dimer formed, but were unable to effect the formation of any cross-coupled product. Despite numerous reactions performed under various conditions, compounds **76** and **77** were isolated in each case (Table 2.3).

Table 2.3 Yields of **76** and **77** under various Heck conditions.

Solvent	*Catalyst*	*Yield %*	
		76	*77*
Acetonitrile	$Pd(PPh_3)_4$	40	31
Acetonitrile	$Pd(OAc)_2/P(o\text{-}tol)_3$	20	11
DMF	$Pd(PPh_3)_4$	19	23
Acetonitrile*	$Pd(PPh_3)_4$	37	46

* No Alkene used, Iodoimidazole **75** only.

2.4.3 Synthetic Potential of 4,4'-Biimidazoles

While the synthesis and chemistry of the 2,2'-biimidazole class of dimers has been well developed, with their formation and subsequent reactions extensively documented,[138,139,140] 4,4'-biimidazoles represent a new class of heterocycles not previously reported in the literature. Such heterocyclic systems may potentially be useful as metal-ion chelators or as precursors in the synthesis of new heterocyclic compounds. The dimerisation of iodoimidazoles was thus explored in more detail.

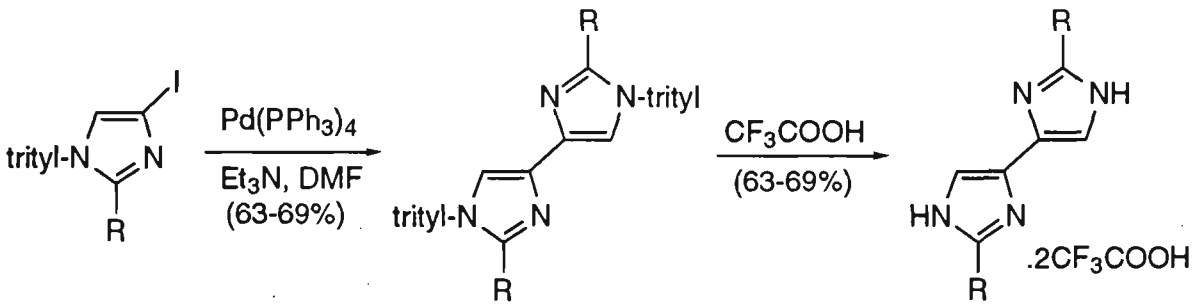
Dimerisation proceeds efficiently in both anhydrous DMF and acetonitrile, with a 5 mole % $Pd(PPh_3)_4$ catalyst loading effecting efficient catalyst turnover. Under these conditions, the reaction is usually complete within 24 h at 100-110 °C. In the event of incomplete consumption of starting iodide, the addition of an extra 5 mole % palladium catalyst usually resulted in complete reaction after a further 24 h.

The dimerisation reaction of 4-iodoimidazoles proceeds in the absence of alkenes to give 4,4'-biimidazoles without any loss in yield. The synthesis could also be scaled up to yield multigram quantities of biimidazoles, albeit with slightly longer reaction times. The use of a 4-iodo substituted imidazole, however, was crucial for the successful dimerisation. Identical reactions to those above using 4-bromoimidazoles failed to give any dimerisation products under a variety of conditions, resulting only in the decomposition of the starting 4-bromoimidazoles after four days of continual treatment.

Similarly, triethylamine was necessary in the reaction mixture, with starting iodoimidazole only recovered in its absence.

To demonstrate this procedure, iodoimidazoles **32** or **78** were treated in the presence of $Pd(PPh_3)_4$ and triethylamine in DMF to give the dimers **70** or **79** in 69% and 63% yields respectively. The dimers were then cleanly deprotected with trifluoroacetic acid to give microanalytically pure bi-trifluoroacetates **80** and **81** in 69% and 63% yields respectively[141] (Scheme 2.24).

Scheme 2.24



R=H, **32**
R=Me, **78**

R=H, **70**
R=Me, **79**

R=H, **80**
R=Me, **81**

The ease with which the 4,4'-biimidazoles were synthesised with substituents in the 2-position and different *N*-protecting groups potentially allows a large number of new heterocyclic compounds to be formed. Further substitution of this class of heterocycles might then be readily achieved by the application of known imidazole chemistry.

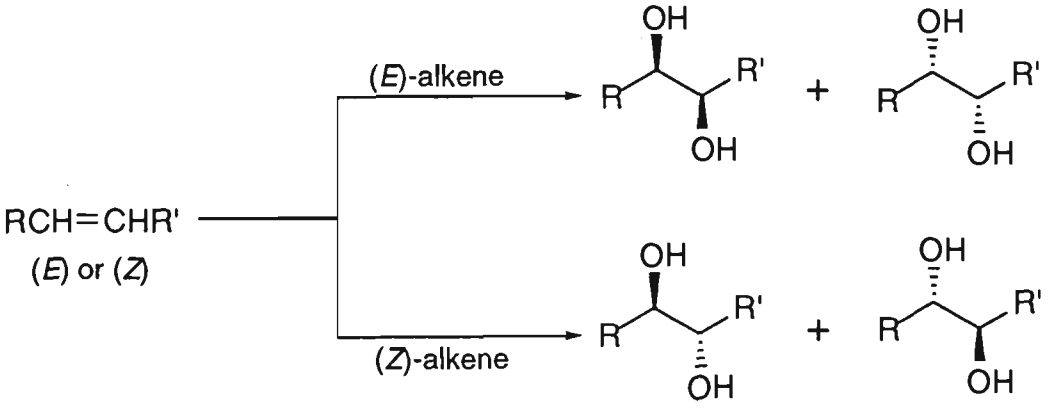
CHAPTER 3

THI TRIOL ANALOGUES

3.1 Introduction

Despite the failure of *N*-protected 4-iodoimidazoles **32**, **33** and **75** to undergo Heck coupling reactions, introducing an unsaturated side-chain onto the C4 imidazole position should still be possible *via* a palladium/alkyne or Stille coupling reaction as outlined in Scheme 1.6 of Chapter 1. Such reactions have been used successfully on other heteroaromatic systems with similar electronic and steric properties to imidazole.[98,100] In order to obtain the maximum number of THI analogues, it is necessary that the coupling reactions provide both *cis*- and *trans*-alkenes, with the former derived from a suitably coupled alkyne. Application of the Sharpless AD reaction would thus enable four different stereoisomers to be obtained (Scheme 3.1).

Scheme 3.1



3.1.1 Palladium/Alkyne Coupling Reactions

Palladium(0)/alkyne coupling provides a means of introducing a 1-alkynyl substituent onto an aryl moiety, which can then be modified to give a (*Z*)-alkene *via* a Lindlar reduction.[142,143] Reaction conditions are typically mild with coupling proceeding to

completion within a few hours at ambient temperature[144,145] or with mild heating.[146] In a mechanism similar to that of the Heck reaction, the coupling of alkynes to aryl halides in the presence of palladium(0) proceeds *via* a cyclic route. To effect high yields, however, the terminal alkyne is activated *in situ* by base (e.g. triethylamine) and the resulting acetylene anion stabilised as an organocuprate. The reaction therefore requires excess base and a catalytic amount of Cu^+, usually as CuI, to form and stabilise the carbanion. The cuprate **82** reacts with the aryl-palladium complex **83** to give the final coupled product after reductive elimination of palladium(0) (Figure 3.1).

$$\text{Ar-X} + \text{HC}\equiv\text{CR} \xrightarrow[\text{CuI, Et}_3\text{N}]{\text{Pd(0)}} \text{Ar-C}\equiv\text{CR}$$

$$\text{HC}\equiv\text{CR} \xrightarrow[\text{Et}_3\text{N}]{\text{CuI}} \underset{\mathbf{82}}{\text{Cu}^+ {}^-\text{C}\equiv\text{CR}}$$

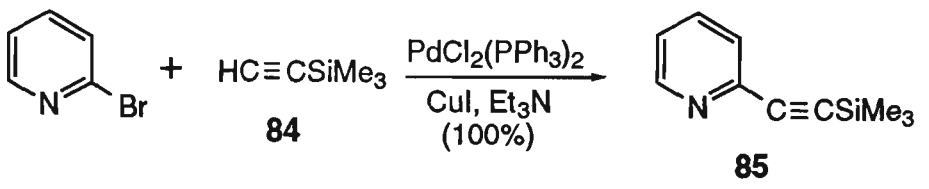
$$\text{Ar-X} \xrightarrow{\text{Pd(0)}} \underset{\mathbf{83}}{\text{Ar-Pd-X}}$$

$$\text{Ar-Pd-X} \xrightarrow{\text{Cu}^+ {}^-\text{C}\equiv\text{CR}} \text{Ar-C}\equiv\text{CR} + \text{CuX} + \text{Pd(0)}$$

Figure 3.1 Palladium/alkyne coupling reaction and mechanism.

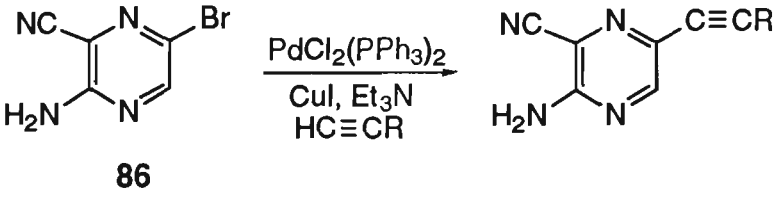
Palladium/alkyne coupling is excellent for the formation of unsaturated compounds that fail to form *via* a Heck reaction. 2-Bromopyridine is readily coupled with trimethylsilyl acetylene **84** to give **85** in a quantitative yield[147] (Scheme 3.2). Under Heck conditions, however, the stable complex **72** is formed, with no coupled products obtained.

Scheme 3.2



Sakamoto *et al.* successfully reacted nineteen different nitrogen containing heteroaromatic compounds with trimethylsilyl acetylene to give alkynes in 74-100% yields.[147] Taylor *et al.* demonstrated that this type of coupling can also be used on sterically less favourable alkynes than **84**. The 5-bromopyrazine derivative **86** was reacted with various terminal alkynes, including the hindered *t*-butyl acetylene, to give the desired coupled products **87-90** in 54-75% yields[148] (Scheme 3.3).

Scheme 3.3



87 R=Ph (75%) **89** R=t-butyl (65%)
88 R=butyl (60%) **90** R=CH_2CH_3 (54%)

3.1.2 The Stille Reaction

Stille coupling provides an excellent means of carbon-carbon bond formation and can be used to provide substrates containing (*E*)- or (*Z*)-alkene or alkyne functional groups. The reaction is similar to both the Heck and palladium/alkyne coupling routes, but utilises stannane-activated alkenes and alkynes that are synthesised prior

to the coupling reaction. The Stille reaction is palladium catalysed, with one of the four tin moieties entering into the reaction (Scheme 3.4).

Scheme 3.4

$$RX + R'SnR''_3 \xrightarrow{Pd(0)} R\text{-}R' + XSnR''_3$$

R = aryl, vinyl

The transfer of a single group from the stannane to the palladium complex does not present a problem if a relatively simple organic moiety, for example methyl, is to be transferred since tetramethyltin can be used. If the substrate is more expensive or difficult to synthesise, however, the transfer of only one of four identical groups would be a distinct disadvantage. However, different types of groups transfer from tin at different rates, with the simple alkyl group having the slowest transfer rate.[149] Thus by using a trialkylvinyl, aryl or alkynylstannane, the unsaturated group bound to the tin atom can be transferred exclusively to the aryl halide (Figure 3.2).

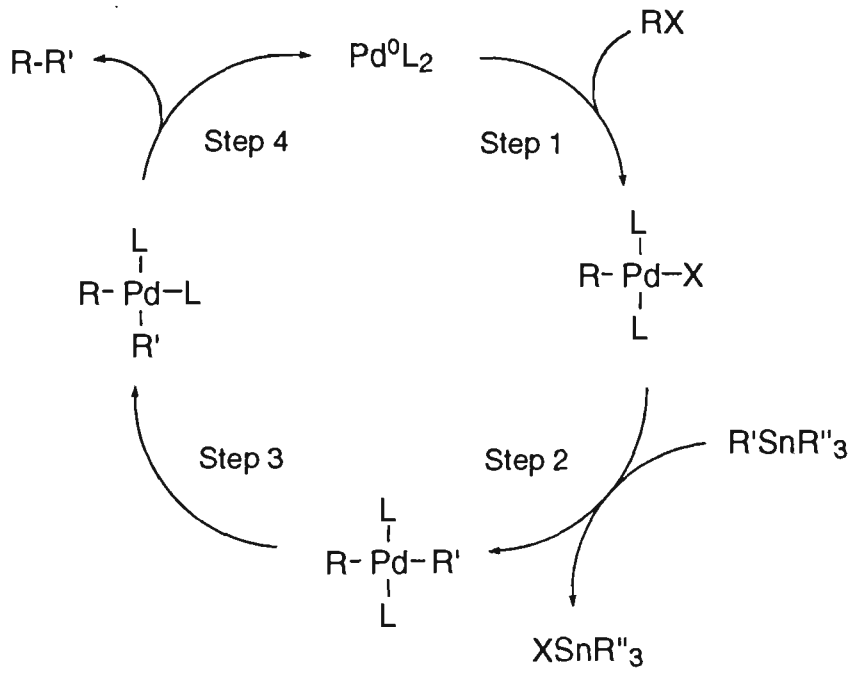
$$RC{\equiv}CR > RCH{=}CH > Aryl > RCH{=}CH\text{-}CH_2 \approx ArylCH_2 > CH_3OCH_2 > Alkyl$$

Figure 3.2 Relative rates of transfer of representative organic moieties from tin substrates.

3.1.2.1 Stille Mechanism

The Stille reaction follows a cyclic mechanism that is similar to that of the Heck reaction and palladium/alkyne coupling[149] (Scheme 3.5). Oxidative addition of the palladium(0) complex with aryl halides (step 1) occurs at a comparable rate to the Heck reaction at moderate temperatures. The rate determining step for the Stille reaction is transmetallation between tin and palladium(0) (step 2), after which *trans/cis* isomerisation (step 3) and reductive elimination of palladium(0) (step 4) occur rapidly.

Scheme 3.5

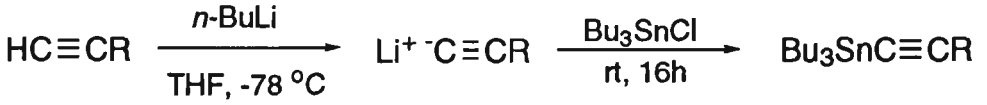


3.1.2.2 Organotin Reagents

Organotin compounds for use in the Stille reaction can be prepared by a number of routes. Organostannanes are not particularly oxygen or moisture sensitive and can be synthesised using

commercially available tributyltin hydride and tributyltin or trimethyltin chlorides. 1-Alkynylstannanes are obtained from the reaction of terminal alkynes with *n*-BuLi, followed by quenching of the anion with trialkyltin chloride[150] (Scheme 3.6). Trimethyltin chloride is the preferred electrophile despite its higher cost, as the final stannane is more reactive than the sterically hindered tributyltin equivalent. The tin by-product of the Stille reaction, Me_3SnX, is also preferred as it is readily removed from the reaction mixture by aqueous washing. Tributyltin halides, resulting from the use of tributylstannane reagents, are more difficult to remove from the reaction mixture. Their separation usually requires conversion to insoluble tributyltin fluoride by exhaustive treatment with aqueous potassium fluoride solutions.[151]

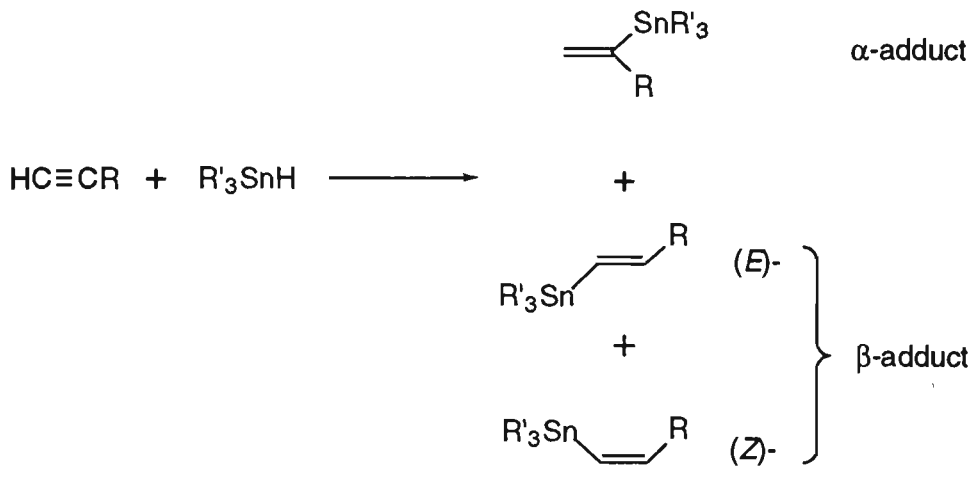
Scheme 3.6



R = Ph, 81% R = Me_3Si, 91%
R = $EtOCH_2$, 88% R = *t*-Bu, 69%

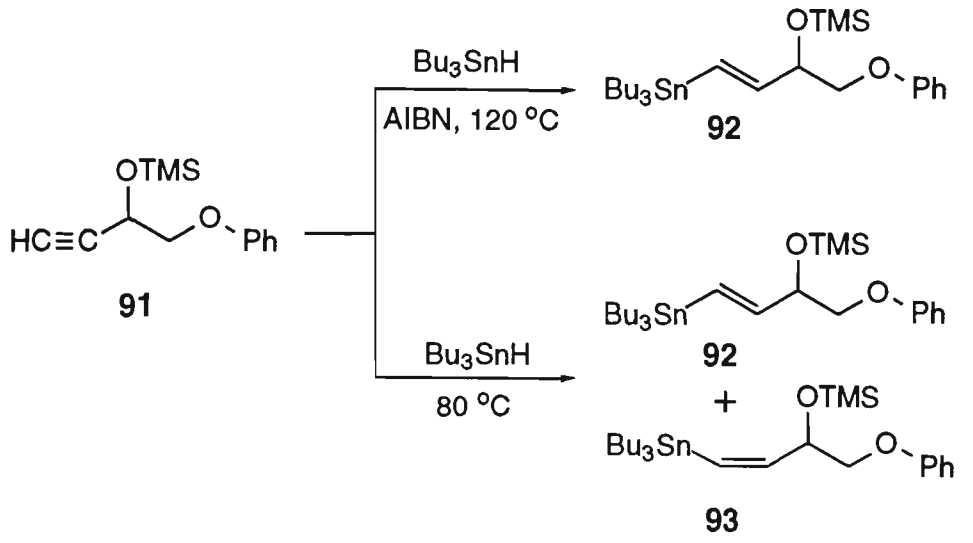
The synthesis of vinylstannanes is usually achieved by the hydrostannylation of alkynes. The use of terminal alkynes results in the formation of two possible regioisomers. Where the stannane moiety adds onto C2 of the alkyne, the so-called α-adduct is formed, whilst addition to the terminal carbon leads to the β-adduct[152] (Scheme 3.7). The β-adduct is further differentiated into (*E*)- and (*Z*)-isomers.

Scheme 3.7



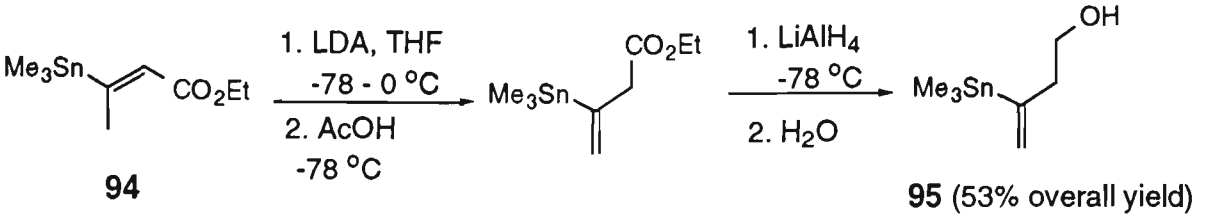
Hydrostannylation of alkynes can be carried out in the absence of solvent and occurs *via* a free-radical mechanism. Acetylenes bearing strong electron-withdrawing substituents (CO_2R, C≡N, etc.) afford mainly, or even exclusively, the α-adduct. Electron donating (alkyl, OR, etc.) or weakly electron-withdrawing (CR_2OH, Ph, etc.) substituents, however, afford mainly the β-adduct.[153,154] The thermodynamically more stable (*E*)-vinylstannane is the major β-adduct formed. Formation of the (Z)-β-adduct can be suppressed by the use of elevated temperatures and AIBN as a radical initiator, rather than rely on thermal initiation of the radical reaction. Tolstikov *et al.* reacted the terminal alkyne **91** with tributyltin hydride and catalytic AIBN at 120 °C to give the (*E*)-β-adduct **92** exclusively. The same reaction carried out in the absence of AIBN and at 80 °C, however, resulted in a 1:1 mixture of (*E*)- and (Z)-isomers **92** and **93** respectively[155] (Scheme 3.8).

Scheme 3.8



The tin-carbon bond is relatively stable, with a bond energy of about 50 kcal/mol.[156] Organostannanes can be subjected to further modification before use in the Stille reaction to give new tin reagents, with the Sn-C bond left intact. The Sn-C bond survives Grignard reactions and can withstand permanganate and chromium oxidation. Lithium aluminium hydride reduction of esters, nitriles and ketones to alcohols and amines and the use of strong bases such as LDA also does not effect stannane degradation.[103,156] The vinylstannane **94** was subjected to LDA isomerisation, followed by $LiAlH_4$ reduction to give **95** in 53% overall yield, with no decomposition of the stannane[157] (Scheme 3.9).

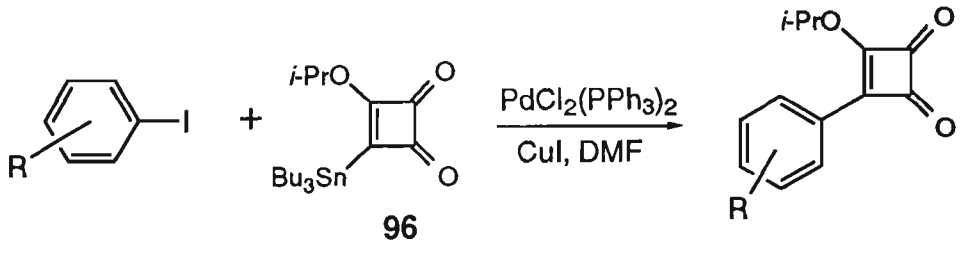
Scheme 3.9



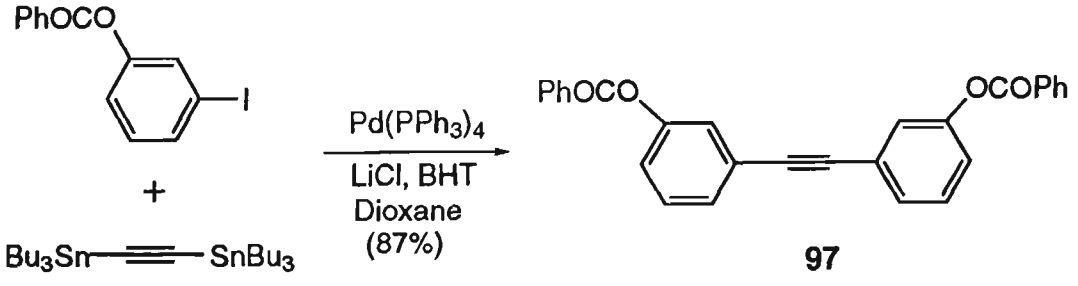
3.1.2.3 Stille Coupling of Aryl Substrates

The coupling reaction between stannanes and aryl halides and triflates proceeds efficiently under various conditions. Liebeskind and Fergl successfully introduced a hindered cyclobutenedione derivative **96** onto a number of sterically and electronically different iodobenzene substrates in good to excellent yields.[158] Similarly, Cummins was able to synthesise the alkyne **97** in 87% yield by carrying out a double Stille coupling on bis(tributylstannyl)acetylene[159] (Scheme 3.10).

Scheme 3.10



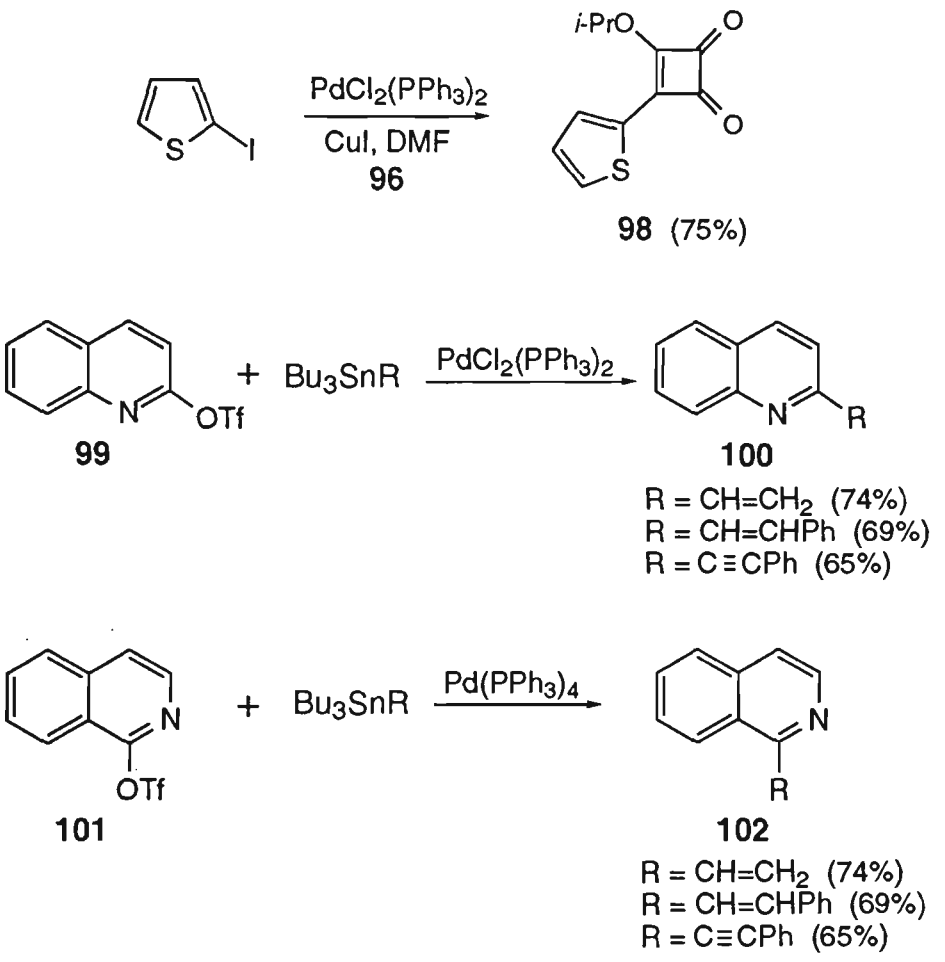
R = H (99%) R = CO_2Me (68%)
R = OMe (80%) R = CH_2OH (57%)



Of more importance to this project, however, is the efficiency in which vinylstannanes couple to heteroaromatic systems. 2-Iodothiophene was coupled with stannane **96** to give **98** in 75% isolated yield.[158] Using the quinolyl and isoquinolyl triflates **99** and

101, Crisp *et al.* introduced both vinyl and acetylene moieties *via* their tributylstannanes to give the substituted heteroaromatics **100** and **102** in good yields[160] (Scheme 3.11).

Scheme 3.11

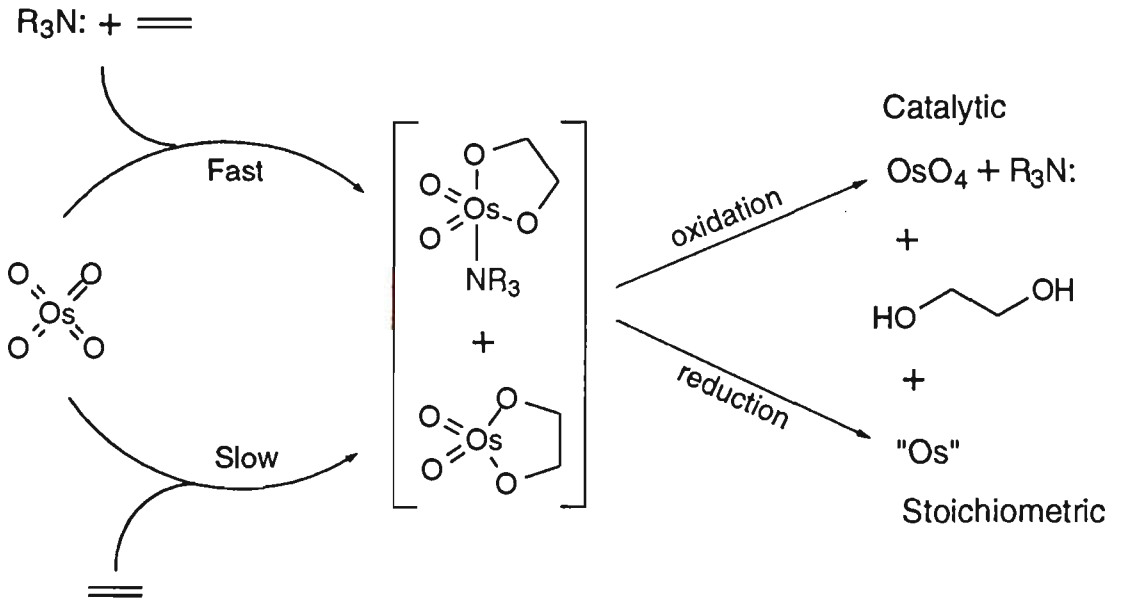


3.1.3 Sharpless Catalytic Asymmetric Dihydroxylation

The past decade has seen the advancement of numerous catalytic asymmetric reactions.[161] They have become increasingly important as the need for optically pure compounds has increased, and are far more cost effective than their stoichiometric counterparts. One of the most published catalytic processes to be refined over the past

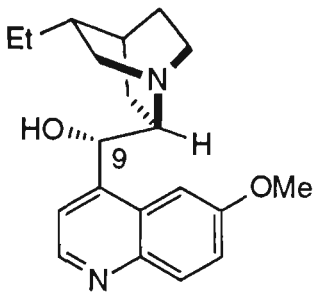
decade is the catalytic asymmetric dihydroxylation (AD) of alkenes. The AD reaction utilises a catalytic quantity of OsO_4 along with an amine ligand to accelerate the reaction. The effectiveness of amine ligand accelerants has been known since the early work of Criegee in the 1930's,[162,163] however, his work and that of the period utilised osmium in stoichiometric quantities. To overcome this uneconomical approach, cooxidants such as sodium chlorate[164] or hydrogen peroxide[165] were originally used to reoxidise osmium back to its tetroxide, but superior results have been obtained with *N*-methylmorpholine-*N*-oxide (NMO)[166] or more recently, $K_3Fe(CN)_6$ in the presence of potassium carbonate.[167] The overall AD process using both stoichiometric and catalytic OsO_4 is illustrated in Scheme 3.12.

Scheme 3.12



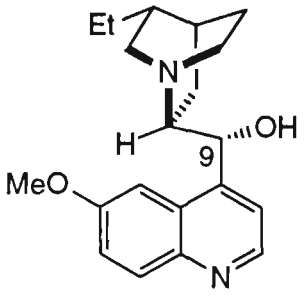
The ability of amine ligands to accelerate the AD reaction lead to attempts by Sharpless and Hentges to induce enantioselectivity into the osmylation *via* the use of chiral pyridine derivatives.[168]

Although initial attempts failed due to the low affinity the pyridine ligands displayed towards osmium, greater success was achieved with the use of quinuclidine derivatives. The use of C9 acetates of the cinchona alkaloids dihydroquinidine **103** (DHQD) and dihydroquinine **104** (DHQ) as chiral ligands, however, gave diols with moderate to good ee's.



Dihydroquinidine

103



Dihydroquinine

104

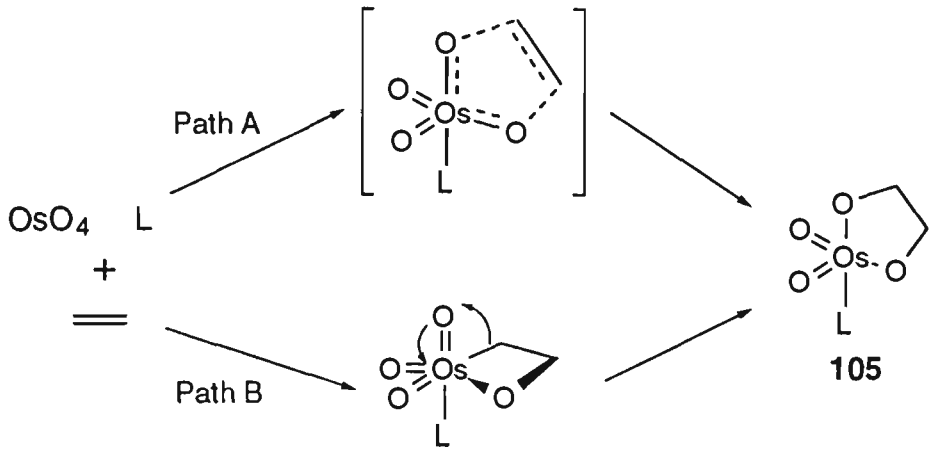
3.1.3.1 AD Mechanisms

The mechanism by which OsO_4 adds to olefin substrates is unclear, with one of two pathways possible. Böseken originally proposed a concerted [3+2] pathway[169] (Scheme 3.13, Path A), while Sharpless *et al.* has suggested a stepwise reaction, which is initiated by a [2+2] cycloaddition, followed by a rearrangement to the glycolate intermediate **105**[170] (Scheme 3.15, Path B). Both pathways A and B lead to the same osmium glycolate intermediate.

A recent observation by Sharpless has shown a non-linear Eyring relationship between ee and reaction temperature, which is inconsistent with a one-step [3+2] mechanism, but can be explained by a pathway with at least two selectivity determining steps.[171,172] High level quantum mechanical calculations have also indicated that

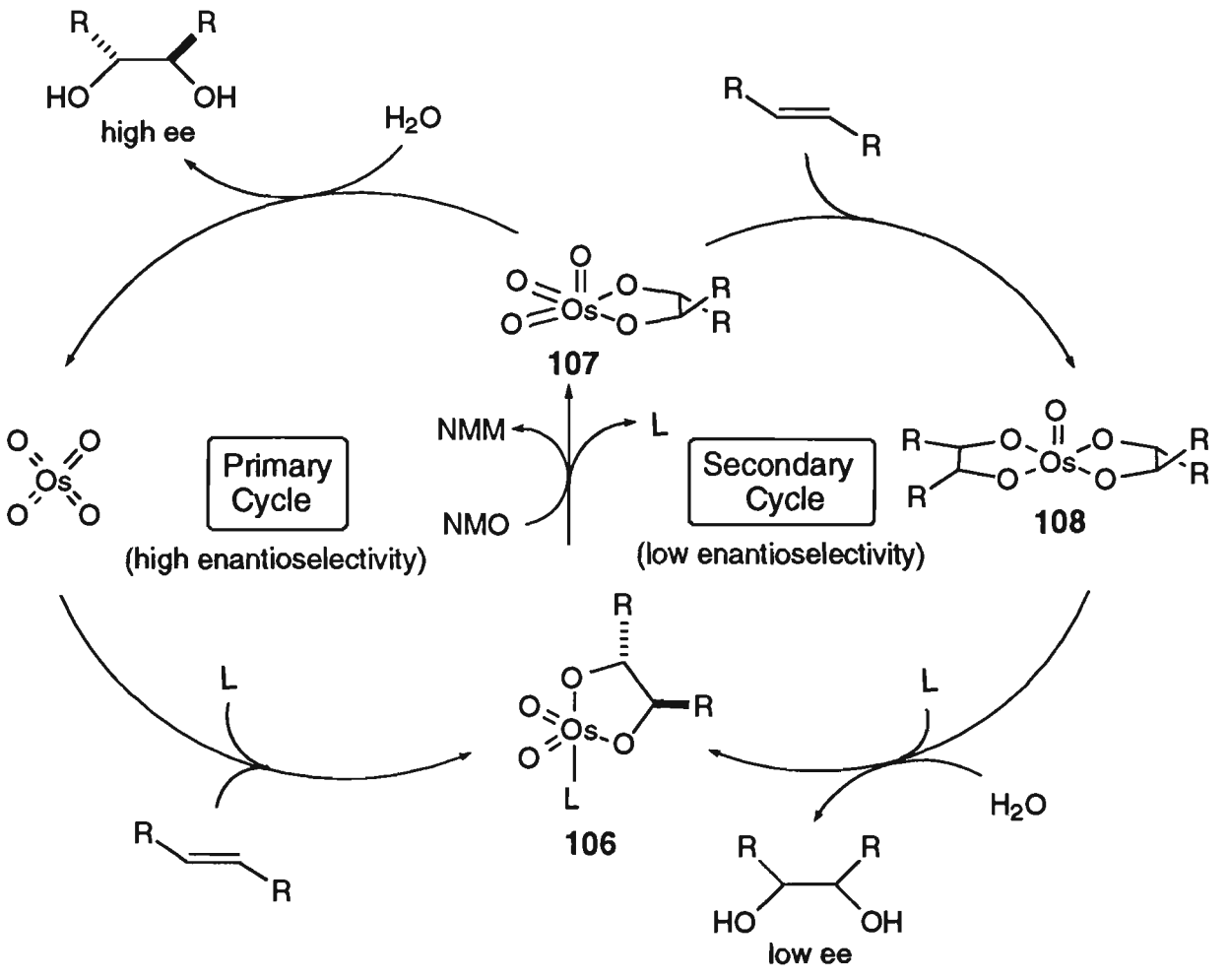
the [2+2] cycloaddition intermediate is plausible in the AD reaction.[173]

Scheme 3.13



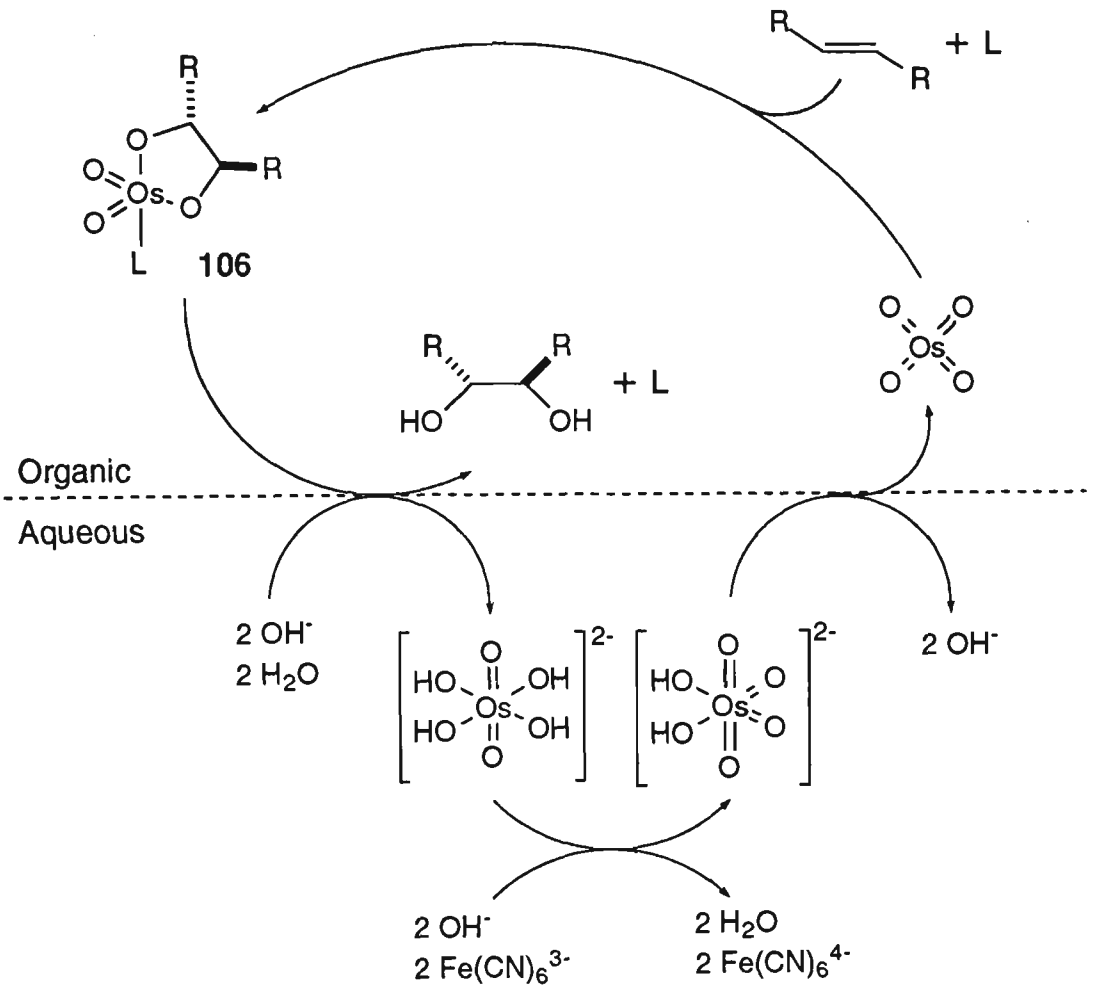
The AD reaction itself can proceed *via* one of two possible cyclic mechanisms depending upon the cooxidant and the use of a single or two-phase reaction system. The use of NMO as the cooxidant in an organic, single phase reaction gives rise to two catalytic cycles[174] (Scheme 3.14). In the primary cycle, high enantioselectivity is obtained by reaction of OsO_4 with a single olefin and chiral ligand to give the glycolate **106**. Oxidation with NMO to give the trioxo osmium intermediate **107**, followed by hydrolysis, gives the diol in high ee, plus recycled OsO_4. Alternatively, **107** can react with a second olefin to give the osmium (VI) bisglycolate **108**. Hydrolysis of this species results in the production of alkenes of low optical purity and the monoglycolate **106**.[170,175]

Scheme 3.14



The use of an organic/aqueous two phase system and $K_3Fe(CN)_6/K_2CO_3$ cooxidant, however, is able to suppress the low enantioselective second cycle.[176] In contrast to the homogenous conditions used in Scheme 3.14 above, there is no oxidant other than OsO_4 present in the organic layer. As the osmylation takes place in this layer, the monoglycolate **106** undergoes hydrolysis and releases the diol and chiral ligand into the organic layer before reoxidation of the osmium can take place. Once **106** has released the diol and chiral ligand, the osmium species liberated is transferred to the aqueous phase as an inorganic salt where it is reoxidised to OsO_4 by ferricyanide[170,175] (Scheme 3.15).

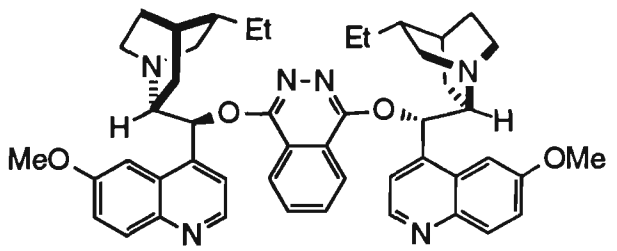
Scheme 3.15



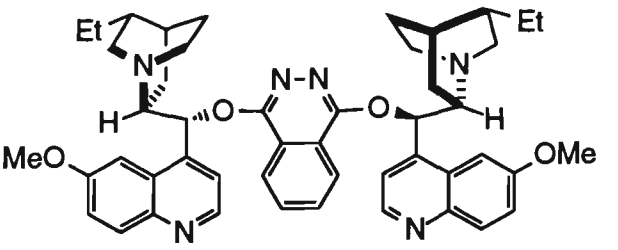
3.1.3.2 Chiral Ligand Auxiliaries

Since the discovery of the dihydroquinidine and dihydroquinine derivatives by Hentges and Sharpless, over 350 cinchona alkaloid based ligands have been tested in the AD reaction.[170] DHQD and DHQ act as enantiomers in the AD reaction, directing attack to opposite faces of the olefin substrate. They are in fact diastereomers, with one of the five chiral centres present on the alkaloids having an identical stereochemistry, and are therefore termed 'pseudo-enantiomers'.[175] Of the hundreds of chiral cinchona ligands tested, only three classes have been found that give consistently good to excellent results over the six possible olefin classes. The phthalazine

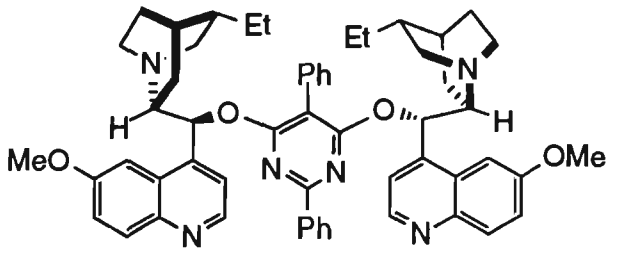
(PHAL)[101] and pyrimidine (PYR)[177] class of chiral ligands are comprised of two cinchona alkaloid moieties, either DHQD or DHQ, with an aromatic spacer. The phthalazine ligands are designated $(DHQD)_2PHAL$ **108** and $(DHQ)_2PHAL$ **109**, while the corresponding pyrimidine ligands are designated $(DHQD)_2PYR$ **110** and $(DHQ)_2PYR$ **111**. Five of the six olefin classes undergo the AD reaction to give good to excellent ee's with either the PHAL or PYR ligands (Table 3.1). The PHAL class gives the optimum results for 1,1-disubstituted, trisubstituted and *trans*-alkenes,[101] while the PYR class routinely give high ee's for terminal alkenes.[177] Both classes can be used for the AD of tetrasubstituted alkenes.[178]



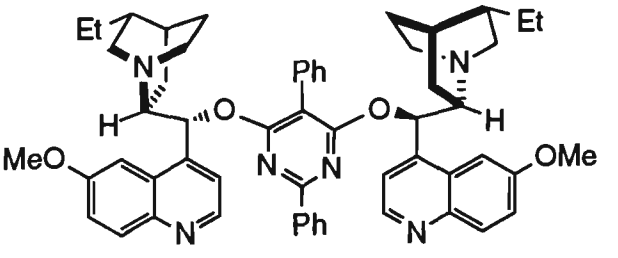
108 $(DHQD)_2PHAL$



109 $(DHQ)_2PHAL$



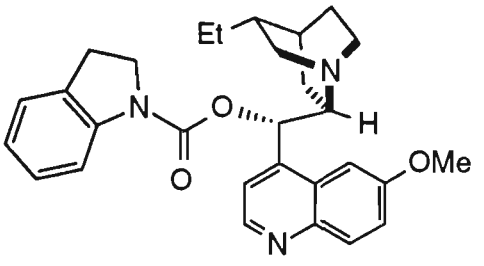
110 $(DHQD)_2PYR$



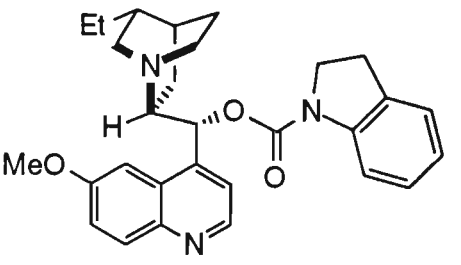
111 $(DHQ)_2PYR$

The third class of cinchona alkaloid ligands are unique in that only a single alkaloid moiety is attached to the aromatic spacer.[179] The indoline (IND) based class of ligands, designated DHQD-IND **112** and DHQ-IND **113** are used primarily for the AD of *cis*-alkenes. They give ee's typically in the range 20-80%, and while lower than that

obtained with other olefin classes and their accompanying ligands, are superior to previously obtained results[179] (Table 3.1).

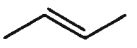
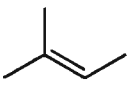
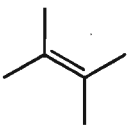


112



113

Table 3.1 Recommended ligands for each olefin class.

Olefin Class						
Preferred Ligand	PYR PHAL	PHAL	IND	PHAL	PHAL	PYR PHAL
ee range	30-97%	70-97%	20-80%	90-99.8%	90-99%	20-97%

Extensive experimentation on the origin of the high enantioselectivity of the AD reactions has demonstrated the importance of an enzyme-like binding pocket or cleft present in the dimeric cinchona alkaloid derivatives (e.g. the phthalazine based ligands).[180,181] The pocket set up by the quinoline and phthalazine ring systems forms an ideal binding site for aromatic alkenes, and stabilises the intermediate glycolate (Figure 3.2). Osmium binds to a single quinuclidine nitrogen, which then forms the osmium glycolate intermediate upon contact with aromatic alkenes such as styrene.[182] The binding cleft within the phthalazine ligand stabilises the glycolate intermediate through aromatic stacking interactions with the phthalazine 'floor', and edge-to-face interactions with the

second methoxyquinoline unit.[170,183] For aliphatic substrates, stacking interactions within the binding cleft may result from van der Waals and solvophobic effects,[184] but they would be less effective and lead to lower enantioselectivies.[182]

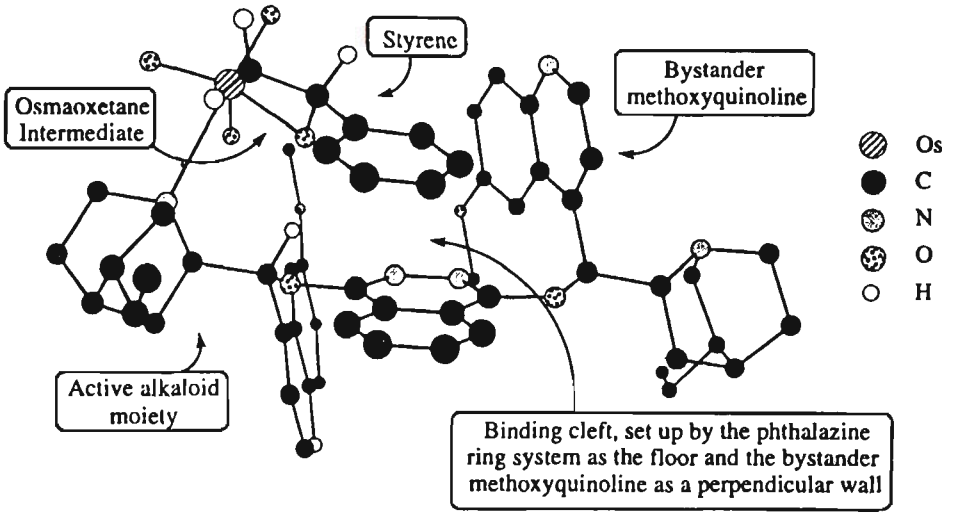


Figure 3.2 Structure of the osmaoxetane intermediate derived from $(DHQD)_2PHAL$, styrene and OsO_4. The aromatic portion of the olefin is positioned inside the binding cleft.[173]

Aromatic stabilisation effects also operate in the indoline class of monomeric cinchona alkaloid ligands, but are reduced due to the absence of a binding pocket. Therefore, dimeric ligands **108-111** result in the highest enantioselectivity.

Extensive experimentation has been carried out by Sharpless *et al.* to examine the structure/enantioselectivity relationship of the cinchona ligand systems.[182] It was found that alteration of the various sections of the moiety lead to either a reduction in reaction rate or binding to osmium or both, which in turn affects the enantioselectivity (Figure 3.3).

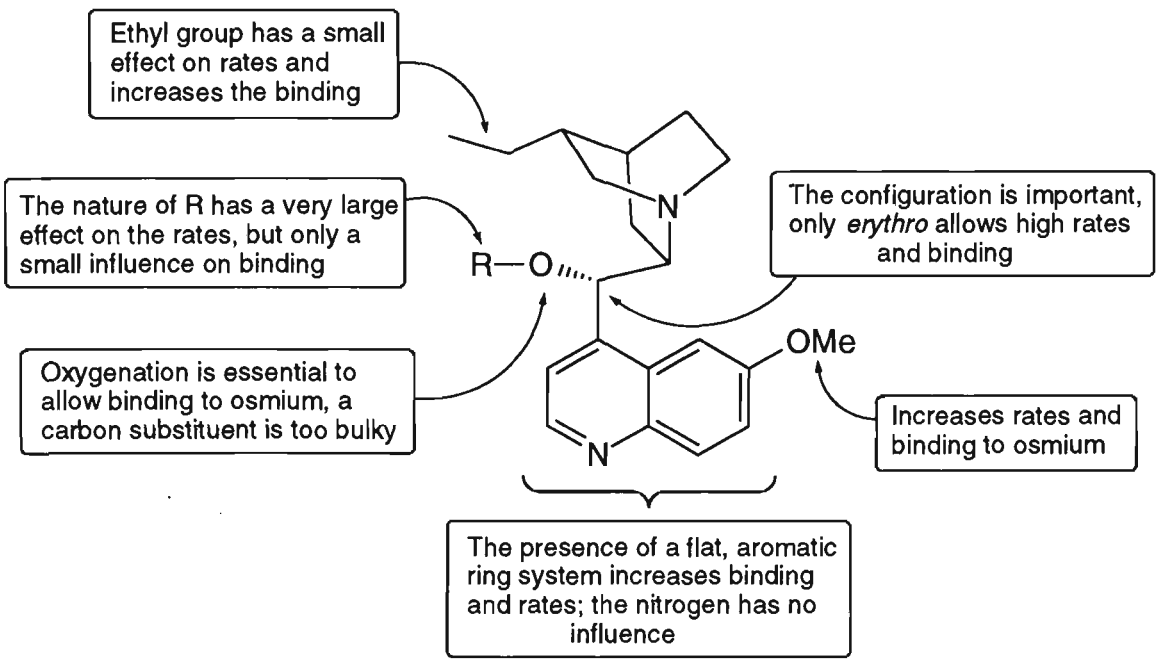


Figure 3.3 Structural features on cinchona alkaloid ligands leading to high stereoselectivity.[182]

The presence of a flat aromatic ring system such as quinoline was found to increase both the binding of substrates within the pocket and also the reaction rate due to face-to-edge interactions. The substituent and stereochemistry at C9 was also of vital importance to the AD reaction. Only the *erythro* conformation allows both high reaction rates and binding, with the nature of the R moiety affecting reaction rates. The introduction of bulky carbon groups onto C9, for example RCH_2 instead of RO, reduces the binding capacity of the ligand significantly. Other minor structure/enantioselectivity relationships are shown in Figure 3.3.

3.1.3.3 Enantioselective Mnemonic

The large number of cinchona alkaloid ligand derivatives developed by Sharpless has lead to an empirical mnemonic that can be used to predict the stereochemical outcome of the AD reaction.[101,175] In the

original mnemonic, the olefin was orientated so that its substituents fit into three size constraints, where R_L=largest substituent, L_M=medium-sized substituent and L_S=smallest substituent (Figure 3.4). The AD reaction then delivers the two hydroxyl groups from the top or β-face in the case of dihydroquinidine derivatives (**108**, **110**, **112**), or the bottom or α-face in the case of dihydroquinine derivatives (**109**, **111**, **113**).[175]

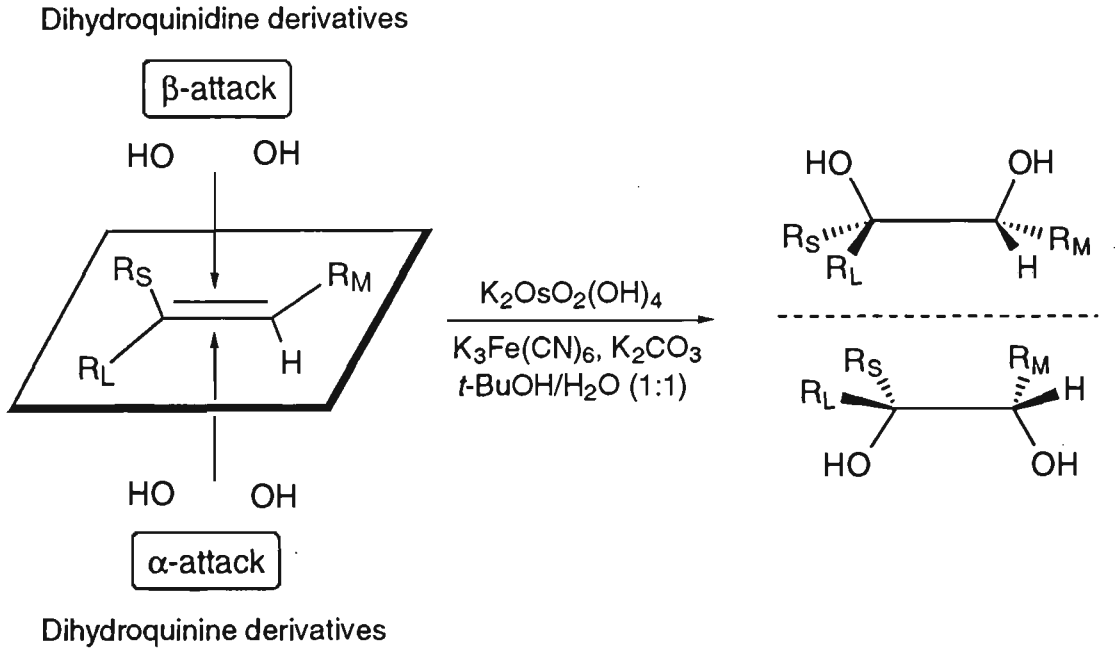


Figure 3.4 Mnemonic scheme for predicting stereochemistry of diols synthesised in the Sharpless AD reaction.[175]

Recent results and the recognition of the importance of the binding pocket have lead to a revised mnemonic device[170,182] (Figure 3.5). The southwest quadrant in this scheme can be regarded as an attractive area that is well suited to accommodate flat, aromatic substituents or, in their absence, large aliphatic groups. The southeast quadrant and to a lesser extent the northwest quadrant present steric barriers, whereas the northeast quadrant is relatively open for olefinic substituents of moderate size. An olefin orientated according to the constraints of this revised mnemonic

will again be attacked from either the β-face with dihydroquinidine derivatives, or in the case of dihydroquinine derivatives, the α-face.[182] Recent studies have shown, however, that the northwest quadrant can also play an attractive role towards certain allylic and homoallylic alcohols. Thus for substrates containing allylic and homoallylic alcohol moieties, orientation of the olefin may differ from that described above.[170]

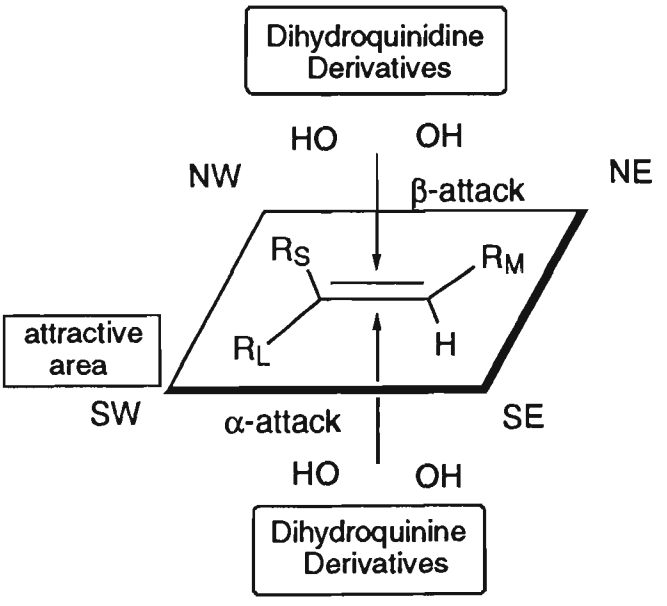


Figure 3.5 Revised AD mnemonic.[170]

3.1.3.4 Experimental Conditions

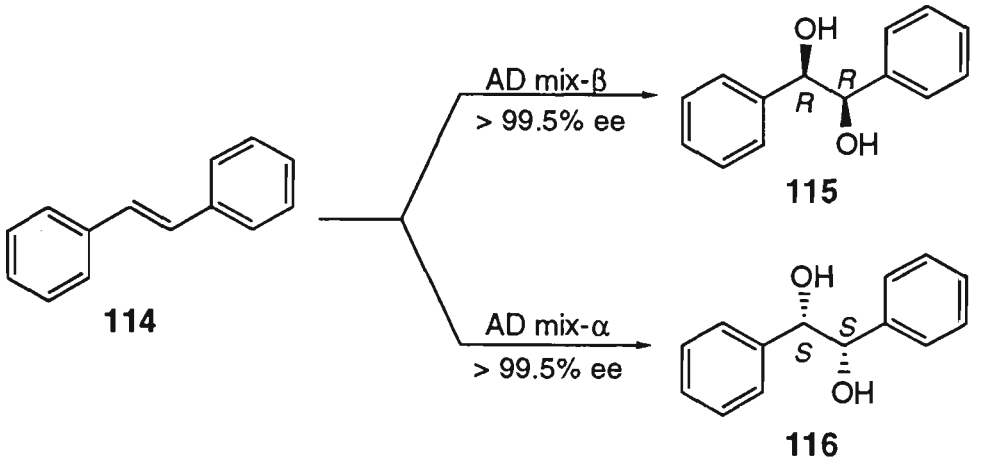
Due to the wide use of Sharpless's AD ligands, both the phthalazine and pyrimidine derivatives have become commercially available. The cinchona alkaloid indoline derivatives **112** and **113** are yet to appear on the market but can be synthesised in good yield in a two-step reaction from indoline.[170,179] The phthalazine based ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ can be obtained as prepacked reaction mixtures, called AD mix-α (for α-face attack) and AD mix-β (for β-face attack) respectively. The AD mixes are an

orange powder containing the osmium tetroxide as a non-volatile potassium salt, the chiral ligand and the ferricyanate cooxidant. One kilogram of AD mix-α or AD mix-β contains $K_2OsO_2(OH)_4$ (1.04 g), $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ (5.52 g), $K_3Fe(CN)_6$ (699.6 g) and K_2CO_3 (193.9 g). The AD reaction is carried out at 0 °C in a two-phase water/*t*-BuOH (1:1) system, using 1.4 g of AD mix-α or AD mix-β per millimole of olefin. Under these conditions, 0.4 mole % osmium and 1.0 mole % chiral ligand are present relative to the olefin. Methanesulfonamide (1 molar equivalent) is also used in the reaction (except in cases involving terminal alkenes) to assist in the hydrolysis of the osmium glycolate. In the presence of this sulfonamide, reaction times can be reduced by up to a factor of 50.[101]

For reactions using the pyrimidine (**110**, **111**) and indoline (**112**, **113**) based ligands, the reagents must be added separately. In a reaction involving one millimole of olefin, the usual reagent quantities used are 0.4 mole % $K_2OsO_2(OH)_4$, 1-2 mole % chiral ligand, 3 molar equivalents $K_3Fe(CN)_6$, 3 molar equivalents K_2CO_3 and 1 molar equivalent methanesulfonamide.

Under the above reaction conditions, complete consumption of the olefin usually takes place within 24 hours to give diols in high yields and optical purity. Sharpless *et al.* have used the aforementioned ligand systems on numerous olefin classes. The catalytic AD of *trans*-stilbene **114** using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ gives the *R,R*- and *S,S*-diols **115** and **116** respectively in near 100% optical purity[101] (Scheme 3.16). This system shows one of the highest ee's reported for a nonenzymic catalyst.[185]

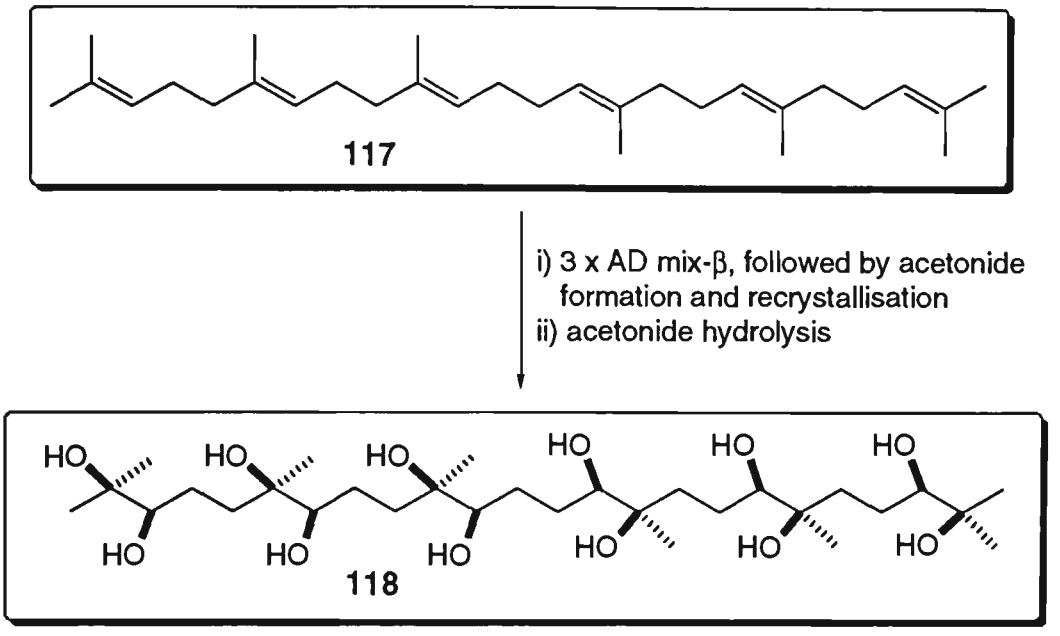
Scheme 3.16



114 **115** **116**

The efficiency of Sharpless's AD system is effectively demonstrated by the exhaustive hydroxylation of squalene **117** to give its dodecahydroxy derivative[185] (Scheme 3.17). Reaction of **117** with AD mix-β ultimately gave the crude dodecahydroxylated species in 88.3% yield, containing 89.3% of the desired polyol **118**. An overall yield of 78.9% of enantiomerically pure **118** (based upon an 88.3% isolated yield of 89.3% pure crude product) was therefore obtained for the six reactions, one of which was enantioselective and five that were diastereoselective. This yield requires that each of the six AD reactions performed must have proceeded in 98% ee or de, *and* 98% yield on average, as $(78.9\%)^{1/12} = 98\%$.

Scheme 3.17

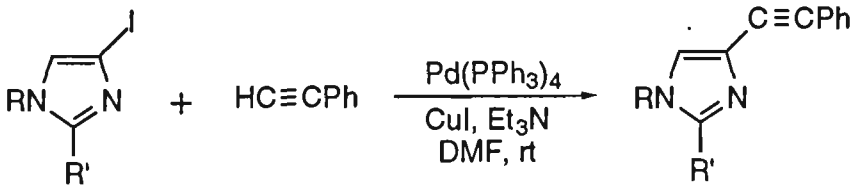

117
i) 3 x AD mix-β, followed by acetonide formation and recrystallisation
ii) acetonide hydrolysis
HO
HO
HO
HO
HO
HO
HO
HO
HO
HO
HO
HO
118

3.2 Synthesis of Olefinic Imidazole Substrates

3.2.1 (Z)-Alkene Synthesis

The addition of butyl side chains onto C4 of imidazole *via* palladium/alkyne cross-coupling was initially modelled on imidazoles **32**, **34** and **75**, of which large quantities were readily available. Imidazoles **32** and **75** were treated at ambient temperature with excess phenylacetylene in the presence of palladium(0), CuI and triethylamine under standard coupling conditions[186] to give imidazoles **119** and **120** in 47% and 69% yields respectively (Scheme 3.18).

Scheme 3.18

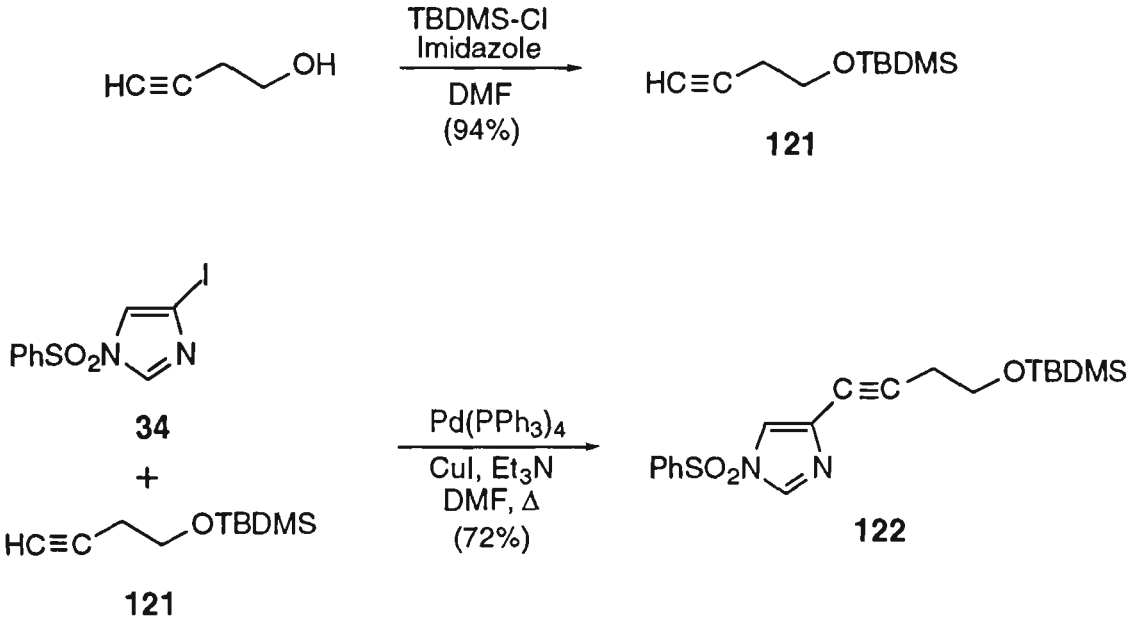


32 R = trityl, R' = H
75 R = tosyl, R' = Me

119 R = trityl, R' = H (47%)
120 R = tosyl, R' = Me (69%)

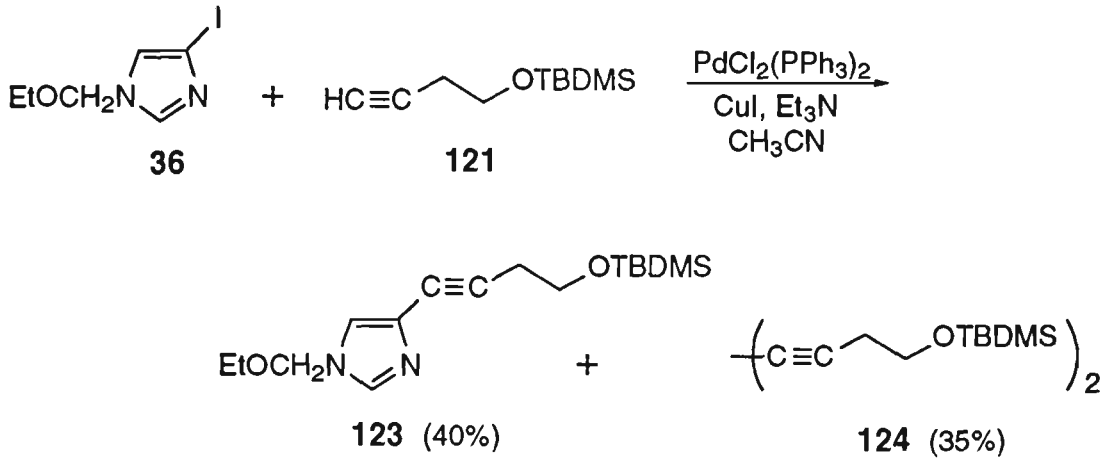
The side-chain **121**, necessary for the synthesis of THI triol analogues, was synthesised from the free alcohol and TBDMS chloride in the presence of imidazole in 94% yield.[187] Reaction of **75** and **121** at 70 °C for 5 hours under standard coupling conditions gave the cross-coupled product **122** in 72% yield (Scheme 3.19).

Scheme 3.19



The use of electron-withdrawing protecting groups (e.g. tosyl, benzenesulfonyl) are thought to assist the reaction by polarising the carbon-iodine bond, thus allowing a more rapid oxidative addition of palladium and assisting in stabilising the palladium(II) intermediate. Such protecting groups, however, will not allow effective addition of the acetyl moiety onto the imidazole C2 position. The ethoxymethyl protected equivalent **36** was therefore trialed. Imidazole **36** was reacted with the alkyne **121** in the presence of $PdCl_2(PPh_3)_2$ to give the cross-coupled product **123** in 40% yield, plus the dialkyne **124** in 35% yield (Scheme 3.20).

Scheme 3.20



36 **121** **123** (40%) **124** (35%)

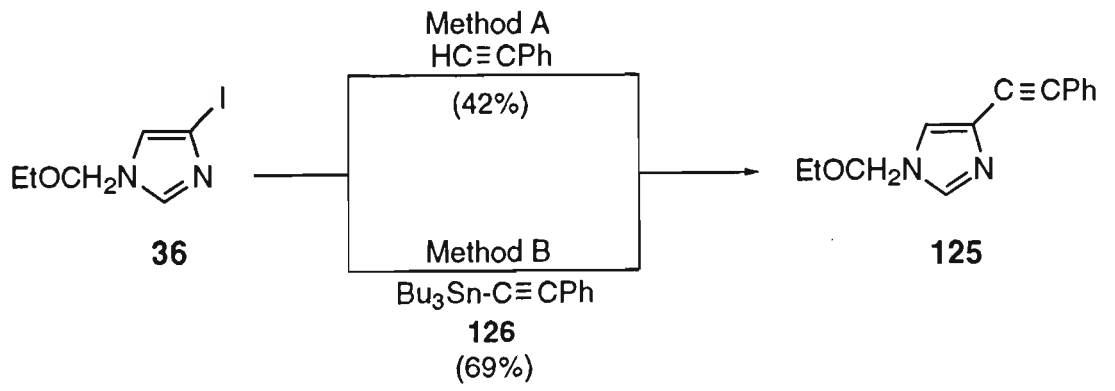
Synthesis of the dialkyne **124** accounts for the consumption of much of the alkyne **121** necessary for the cross-coupling reaction. Reaction conditions used for palladium/alkyne cross-coupling also favour dialkyne formation[188] and can be used specifically for the synthesis of dialkynes.[189] The use of an electron-donating ethoxymethyl protecting group on imidazole does not favour stabilisation of the imidazole/palladium(II) complex intermediate. Under such conditions dialkyne formation proceeds competitively with the cross-coupling reaction. The use of large excesses of alkyne **121** had no effect on the quantity of cross-coupled product formed and resulted in the increased synthesis of **124**. The reaction accounts for only 40% of the starting iodoimidazole. Unlike the attempted Heck coupling, however, no biimidazoles were isolated from the reaction.

Despite numerous attempts under various conditions to increase the yields of cross-coupled imidazole **123**, no improvements were able to be made. The use of triethylamine as reaction solvent has been successful in the cross-coupling reaction with numerous

heteroaromatic halides,[147] but was less so in this instance. When triethylamine was used as solvent this lead to a reduction in the solubility of CuI and the palladium catalyst, with **123** being isolated in 34% yield.

In order to improve cross-coupled yields using the ethoxymethyl protected imidazole **36**, tin activated alkyne side-chains were trialed using a Stille coupling reaction. Imidazole **36** was reacted with phenylacetylene under palladium/alkyne coupling conditions to give the cross-coupled imidazole **125** in 42% yield (Scheme 3.21, Method A). The equivalent Stille reaction, however, utilising the commercially available phenylethynyltributylstannane **126** gave the desired imidazole **125** in 69% yield (Scheme 3.21, Method B).

Scheme 3.21

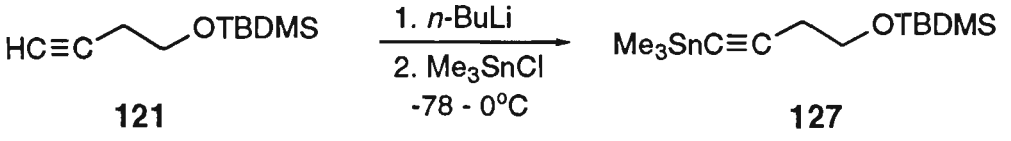


Method A: 5 mol % $Pd(PPh_3)_4$, 10 mol % CuI, Et_3N, CH_3CN
Method B: 5 mol % $Pd(PPh_3)_4$, THF

Although both of the above reactions gave quantities of the dialkyne 1,4-biphenyl-1,3-butadiyne (from mass spectrometric analysis of the crude reaction mixture), the Stille reaction resulted in a significant increase in the yield of the final cross-coupled product. Synthesis of the stannane equivalent of alkyne **121** for

coupling to imidazole **36** was achieved by treatment of **121** with *n*-BuLi, followed by quenching of the resulting 1-lithio alkyne with trimethyltin chloride to give the stannane **127** in 86% yield (Scheme 3.22).

Scheme 3.22



121 **127**

Tin/proton coupling was observed in the ^{1}H NMR spectrum from the trimethyltin moiety of **127** (Figure 3.6). A singlet was present at 0.26 ppm due to the trimethyltin moiety. In addition, two small doublets were also observed from coupling to ^{119}Sn and ^{117}Sn, which are naturally occuring tin isotopes with I = 1/2 (relative abundance 8.6% and 7.6% respectively).[190] The doublets observed had coupling constants of $^{2}J_{119Sn,H}$ = 60.4 Hz and $^{2}J_{117Sn,H}$ = 58.0 Hz. The ratio $^{2}J_{119Sn,H}$ / $^{2}J_{117Sn,H}$ = 1.0414, which represents a 0.5% deviation from the expected theoretical value of 1.0465.[190]

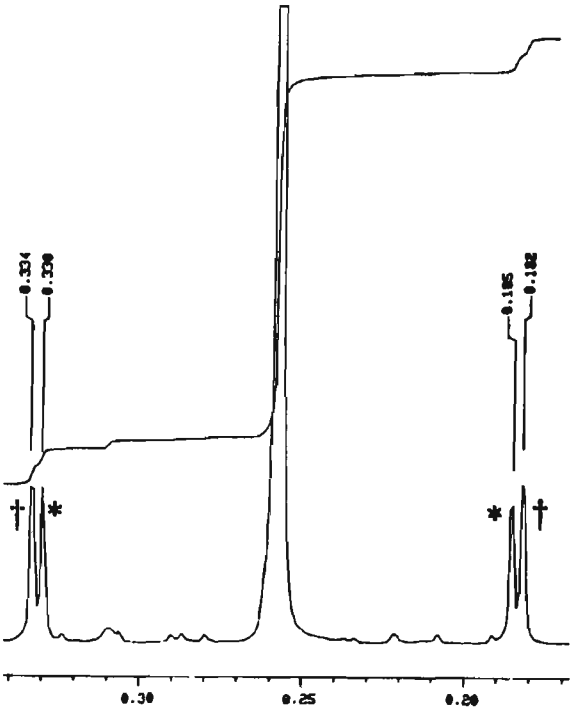
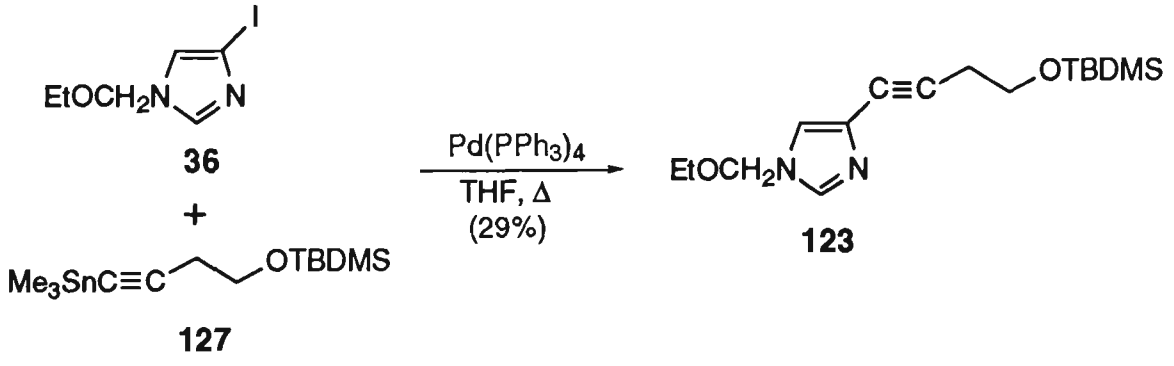


Figure 3.6 Tin/proton coupling for the singlet at 0.26 ppm (Me_3Sn) in the ^1H NMR spectrum of **127** in $CDCl_3$. † Doublet due to ^{119}Sn. * Doublet due to ^{117}Sn.

Reaction of **127** with **36** in the presence of $Pd(Ph_3P)_4$ in refluxing THF gave the alkyne **123** in a disappointingly low yield of 29% (Scheme 3.23).

Scheme 3.23



Numerous reactions, carried out under different conditions,[191] all failed to give an improved yield of **123** (Table 3.2). The use of DMF

as the reaction solvent in conjunction with tetrakis(triphenylphosphine)palladium(0), did however, lead to a significantly improved 59% yield of imidazole **123**.[192] This was expected as polar aprotic solvents enhance the coupling rate substantially,[193] with coupling rates increasing in the following order:

$$CHCl_3 < THF < CH_3CN < DMF, DMSO, NMP$$

It has been suggested that by utilising DMF, the reaction turnover rate is increased and leads to the formation of larger quantities of cross-coupled product before decomposition of the palladium catalyst can occur.[193]

Table 3.2 Stille reaction conditions for the synthesis of alkyne **123** from compounds **36** and **127**.

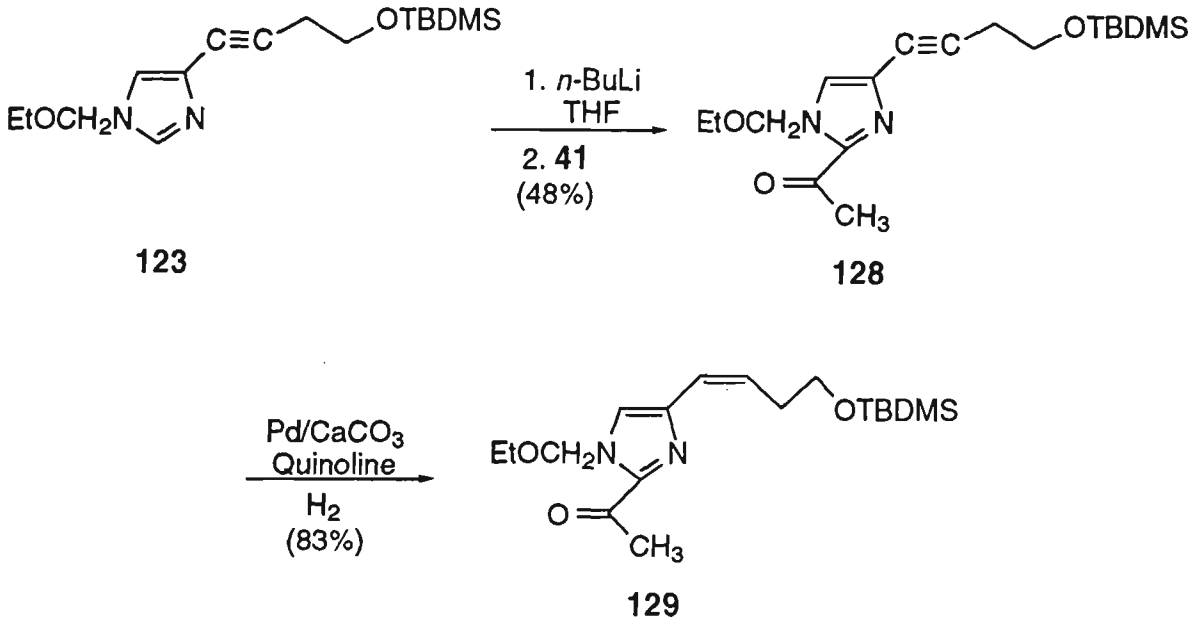
Solvent	*Catalyst*	*Reaction Conditions*	*Yield (%)*
THF	$Pd(PPh_3)_4$	A	29
THF	$PdCl_2(PPh_3)_2$	A	39
Dioxane	$Pd(PPh_3)_4$	A	34
Dioxane	$Pd_2(dba)_3$, P(*o*-tol)$_3$	B	11
Acetonitrile	$PdCl_2(PPh_3)_2$	A	21
Acetonitrile	$Pd_2(dba)_3$, P(*o*-tol)$_3$	B	11
DMF	$Pd(PPh_3)_4$	C	59

A: excess stannane, reflux. B: excess stannane, 80 °C. C: excess stannane, 80 °C, sealed reaction vessel.

Treatment of the alkyne **123** with *n*-BuLi in anhydrous THF followed by quenching with the amide **41** gave the methyl ketone

128 in 48% yield. Lindlar reduction[142] of **128** using 10% Pd on $CaCO_3$ and 1 molar equivalent of quinoline under a H_2 atmosphere gave the (Z)-alkene **129** in 83% yield, ready for use in the Sharpless AD reaction (Scheme 3.24).

Scheme 3.24



123 **128** **129**

The olefinic protons H1' and H2' on the alkene **129** displayed a coupling of 11.6 Hz across the double bond, characteristic of a *cis* alkene. H1' and H2' were also coupled to the two H3' protons, with coupling constants of 1.6 Hz and 7.2 Hz respectively. The signal for H1' (ca. 6.37 ppm) and H2' (ca. 5.75 ppm) were both a doublet of triplets. All couplings were within the expected ranges for *cis*-alkenes (Figure 3.7).[194]

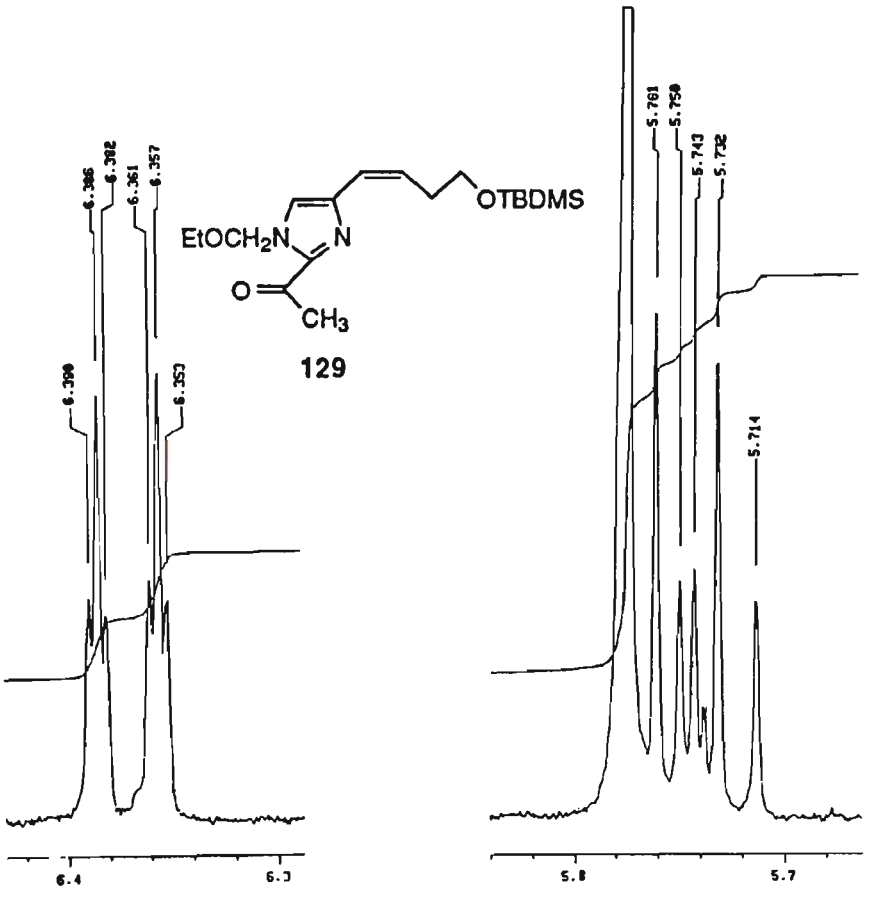
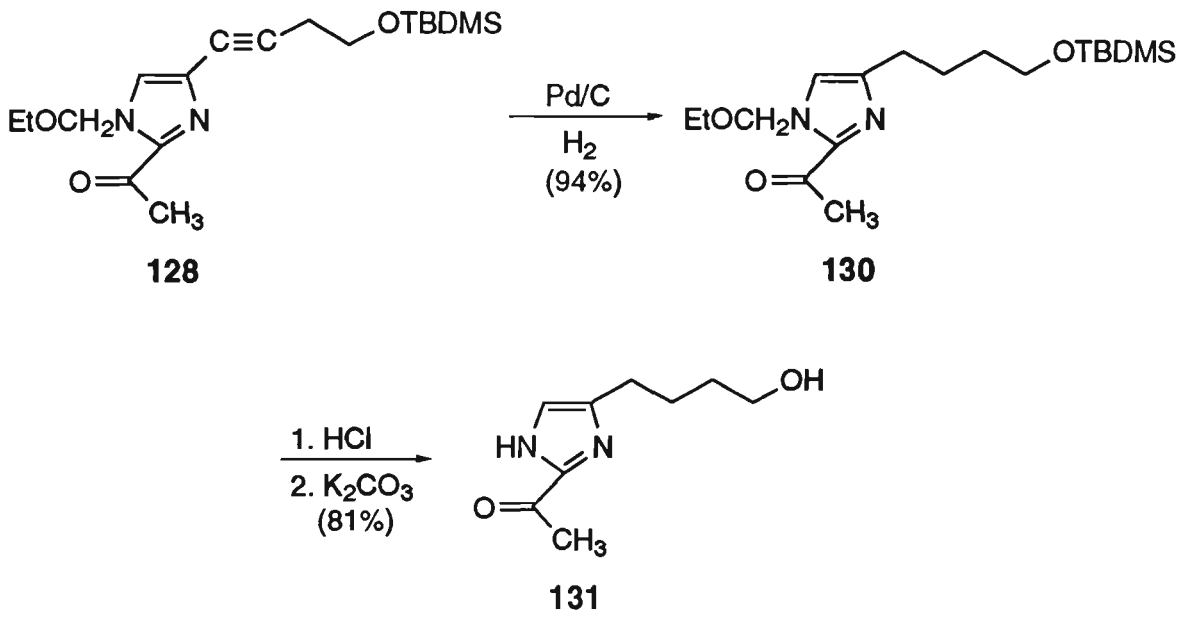


Figure 3.7 ^{1}H NMR olefinic coupling patterns for H1' (δ 6.39-6.53 ppm) and H2' (δ 5.76-5.71 ppm) for the (*Z*)-alkene **129** in $CDCl_3$.

3.2.2 Synthesis of the 4'-Monohydroxy THI Analogue

The methyl ketone **128** lends itself to a simple conversion to a monohydroxylated THI analogue. Hydrogenation of the alkyne **128** with 10% Pd on carbon under a H_2 atmosphere gave the imidazole **130** in 94% yield. Acid hydrolysis of **130** in 1:1 ethanol/H_2O at reflux followed by basification with solid K_2CO_3 gave the deprotected imidazole **131** in 81% yield (Scheme 3.25).

Scheme 3.25



128 **130** **131**

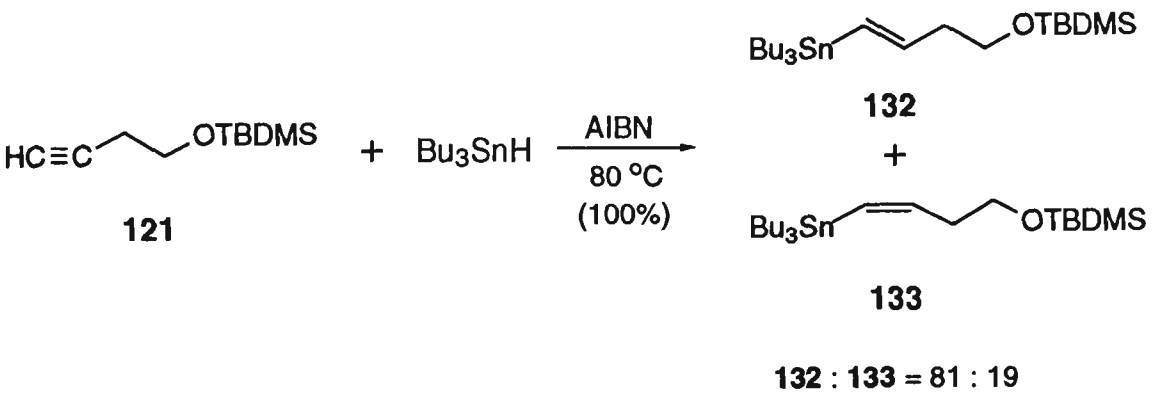
3.2.3 (*E*)-Alkene Synthesis

Synthesis of the (*E*)-alkene equivalent to the methyl ketone **129** was expected to be readily achievable *via* a *cis/trans* isomerisation. Preliminary experiments, however, using this method did not present sufficiently satisfactory results to warrant further investigation. Instead, the direct synthesis of the (*E*)-alkene from (*E*)-vinylstannanes was pursued. This method was superior to one that would involve *cis/trans* isomerisation as it would enable two steps to be eliminated from the reaction scheme, namely the Lindlar reduction and the *cis/trans* isomerisation.

Synthesis of the necessary (*E*)-vinylstannanes was achieved *via* hydrostannylation of the alkyne **121**.[155] Excess alkyne **121** was reacted with tributyltin hydride and catalytic AIBN at 80 °C to give

an 81:19 mixture of the (*E*)- and (*Z*)-vinylstannanes **132** and **133** respectively in quantitative yield (Scheme 3.26).

Scheme 3.26



The ^{1}H NMR olefinic signals displayed by **132** were present as a multiplet at 5.97-5.95 ppm. Olefinic proton coupling constants were therefore unable to be determined. The (*Z*)-vinylstannane **133**, however, displayed characteristic *cis*-alkene coupling. The ^{1}H NMR signal for H1 at ca. 5.89 ppm was a doublet of triplets, with coupling constants of 1.2 Hz and 12.4 Hz to H3 and H2 respectively. The H2 signal at ca. 6.51 ppm, also a doublet of triplets, displayed a coupling of 6.8 Hz and 12.8 Hz to H3 and H1 respectively.

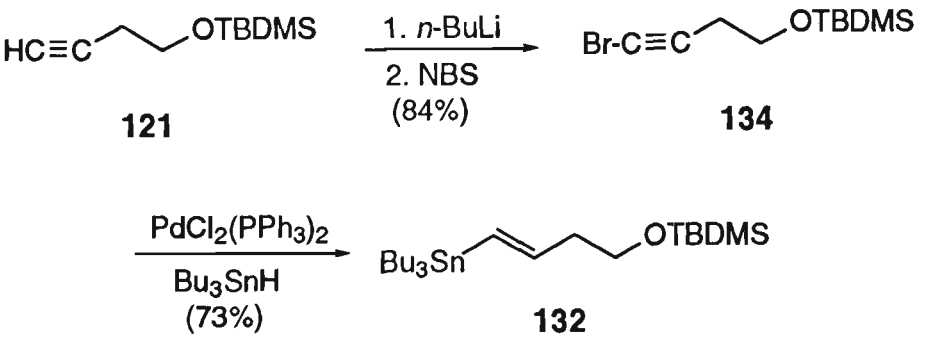
Increases in reaction temperature up to 120 °C resulted in a reduction in the amount of the thermodynamically less stable (*Z*)-alkene **133** but failed to eliminate its formation (Table 3.3). Reaction at all temperatures resulted in quantitative yields of the stannanes. The (*E*)-and (*Z*)-vinylstannane mixture was used directly in the Stille coupling reaction. Attempts to obtain pure (*E*)-vinylstannane **132** *via* separation on silica column chromatography lead to a significant decomposition of the stannane.

Table 3.3 Temperature effects on hydrostannylation of alkyne **121** with tributyltin hydride and AIBN

Run	*Temperature*	*Ratio 132/133*
1	80 °C	81:19
2	95 °C	89:11
3	120 °C	90:10

A complete suppression of the (*Z*)-vinylstannane **133** was achieved *via* a 2-step reaction involving the palladium(0) catalysed addition of tributyltin hydride to the C1 bromide equivalent of alkyne **121**. Anion formation at C1 using *n*-BuLi in anhydrous THF followed by quenching with *N*-bromosuccinimide gave the bromide **134** in 84% yield. Reaction of the bromide with 2 equivalents of tributyltin hydride in the presence of $PdCl_2(PPh_3)_2$ gave the (*E*)-alkene **132** exclusively in 73% yield (Scheme 3.27).[195,196]

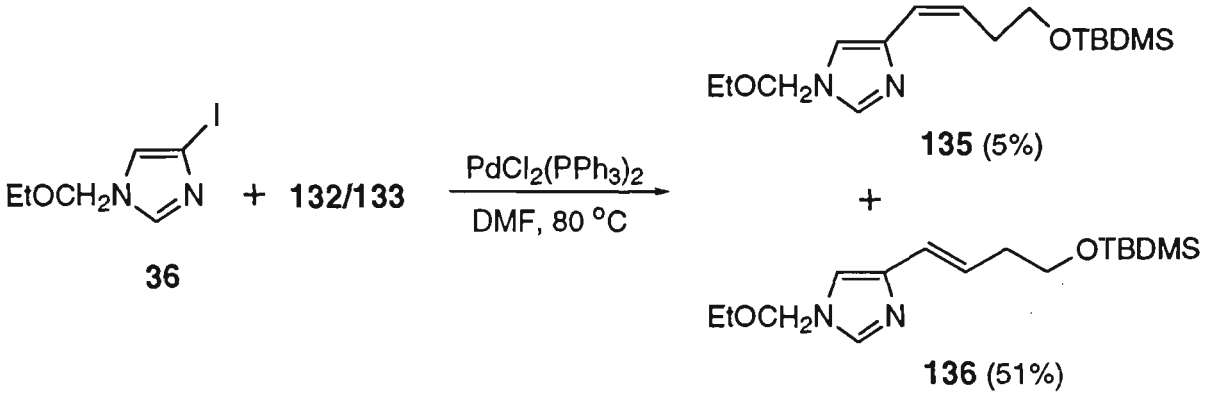
Scheme 3.27



Reaction of the iodoimidazole **36** with an 81:19 mixture of **132** and **133** in the presence of $PdCl_2(PPh_3)_2$ gave the cross-coupled (*Z*)- and (*E*)-alkenes **135** and **136** in 5% and 51% yields respectively (Scheme 3.28). The (*Z*)-alkene **135** displayed characteristic *cis*-

alkene proton coupling constants across the double bond (J = 11.6 Hz). The (*E*)-alkene **136** olefinic signals were again present as a multiplet at 6.33-6.31 ppm, with the coupling constants unable to be determined.

Scheme 3.28



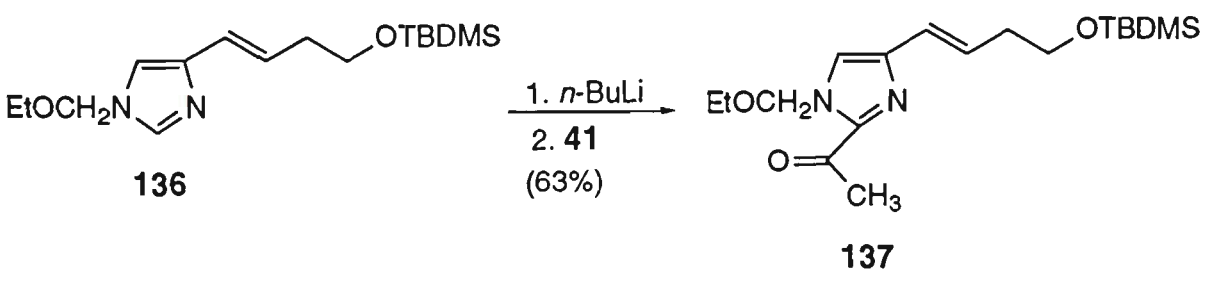
36

135 (5%)

136 (51%)

Treatment of **136** with *n*-BuLi at -78 °C in anhydrous THF followed by quenching of the resulting C2 carbanion with the amide **41** gave the methyl ketone **137** in 63% yield, plus a 21% recovery of the starting imidazole **136** (Scheme 3.29).

Scheme 3.29



136

137

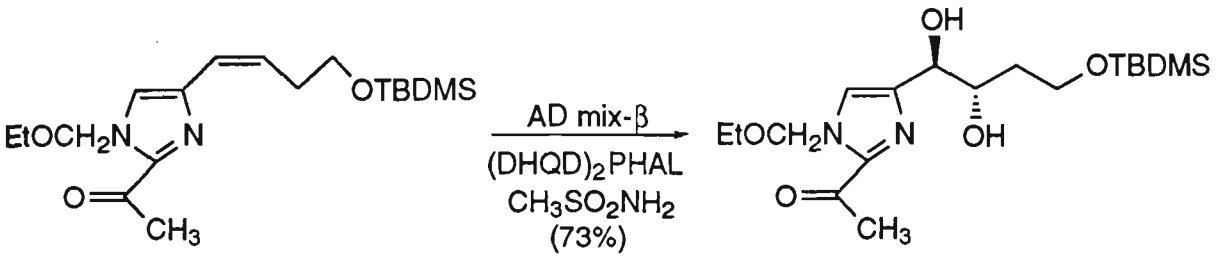
3.3 Asymmetric Dihydroxylation of Imidazole Substrates

3.3.1 The AD of (Z)-Alkenes

The ligands of choice for use in the AD of (Z)-alkenes are the indoline based alkaloids **112** and **113**.[179] At the time at which this work was performed, however, ligands **112** and **113** were unavailable for use in the AD reactions. The dihydroxylation was therefore performed using the phthalazine ligands **108** and **109** within commercially available AD mix-β and AD mix-α respectively. Initial AD reactions under standard conditions using the (Z)-alkene **129** proceeded sluggishly and were incomplete after several days at 0 °C.[101] As most AD's are complete within 24 hours using standard substrates, the low turnover rate is most likely due to coordination of the imidazole nitrogen to osmium. In order to effect efficient reaction rates, an increased ligand loading of 5 mole % compared with the standard 1 mole % present within the AD mixes was used.[197] Methanesulfonamide loading was also increased from 1 to 2-3 molar equivalents, based on the olefin substrate, to effect rapid hydrolysis of the osmium/glycolate intermediate.

Imidazole **129** was treated with commercial AD mix-β, an additional 4 mole % of $(DHQD)_2PHAL$ and methanesulfonamide in *t*-BuOH/H_2O (1:1) at 0 °C. TLC analysis showed complete consumption of starting (Z)-alkene after 3 days, at which time the diol **138** was isolated in 73% yield (Scheme 3.30).

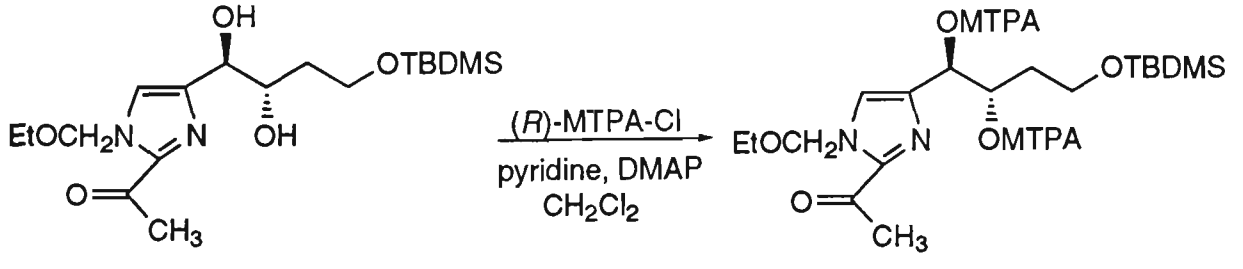
Scheme 3.30



129 **138**

The stereochemical assignment of **138** was made based upon Sharpless's mnemonic, in which the imidazole ring is orientated into the northeast quadrant and the side-chain into the northwest quadrant (Figure 3.5). The optical purity of the diol was determined by ^{1}H NMR analysis of the corresponding MTPA diester of **138**.[198,199] A small quantity of the diol **134** and excess (*R*)-(-)-MTPA chloride were reacted in a dichloromethane solution containing pyridine and a catalytic quantity of *N*,*N*-dimethylaminopyridine to give the (*S*)-MTPA diester **139** after 24 hours (Scheme 3.31). The diester was used directly in the ^{1}H NMR study without any further purification to avoid any loss of the minor diastereomer.

Scheme 3.31



138 **139** ee = 26%

^{1}H NMR analysis of the diester **139** showed the diol had a disappointingly low 26% ee. Although results in the 70-80% ee

range were not expected as the indoline cinchona alkaloid ligands were not used, a higher enantioselectivity was nonetheless expected. The ^1H NMR signals used to examine the MTPA diester **139** included the H1' doublets at 6.33-6.30 ppm, and the methyl ketone singlets at 2.55-2.51 ppm (Figure 3.8).

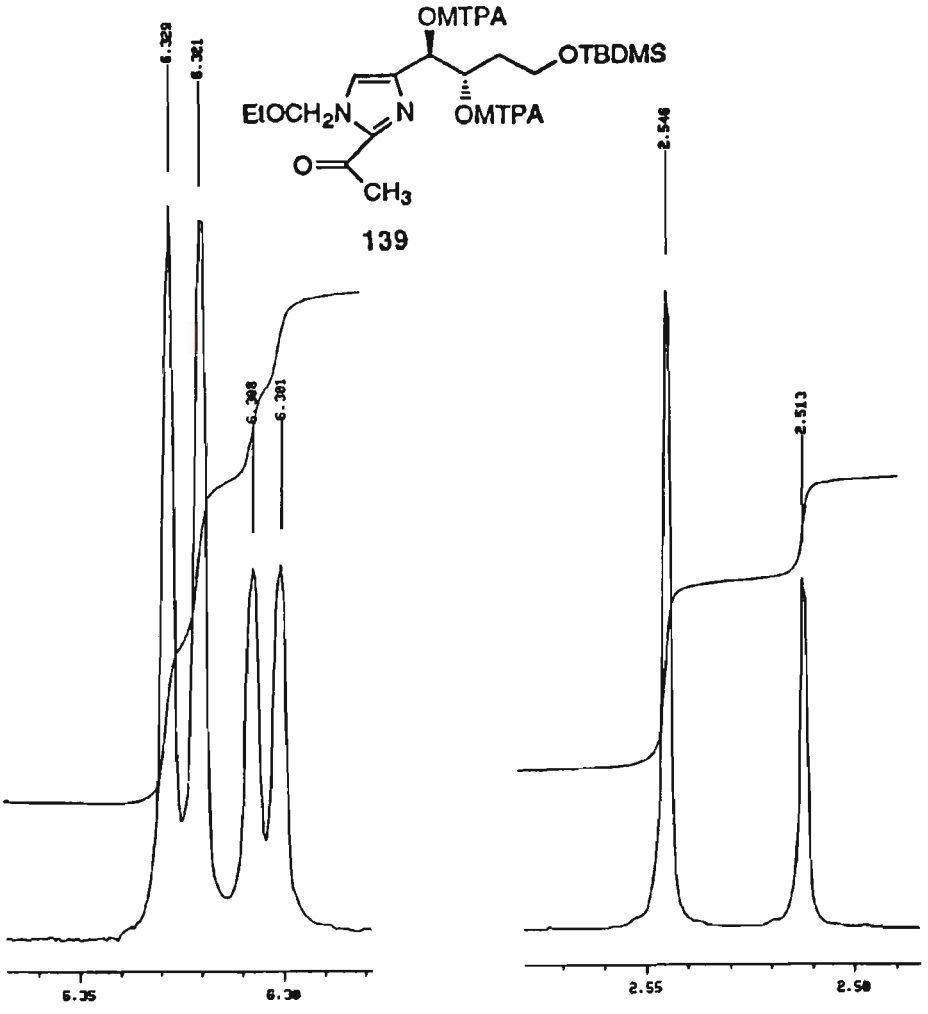
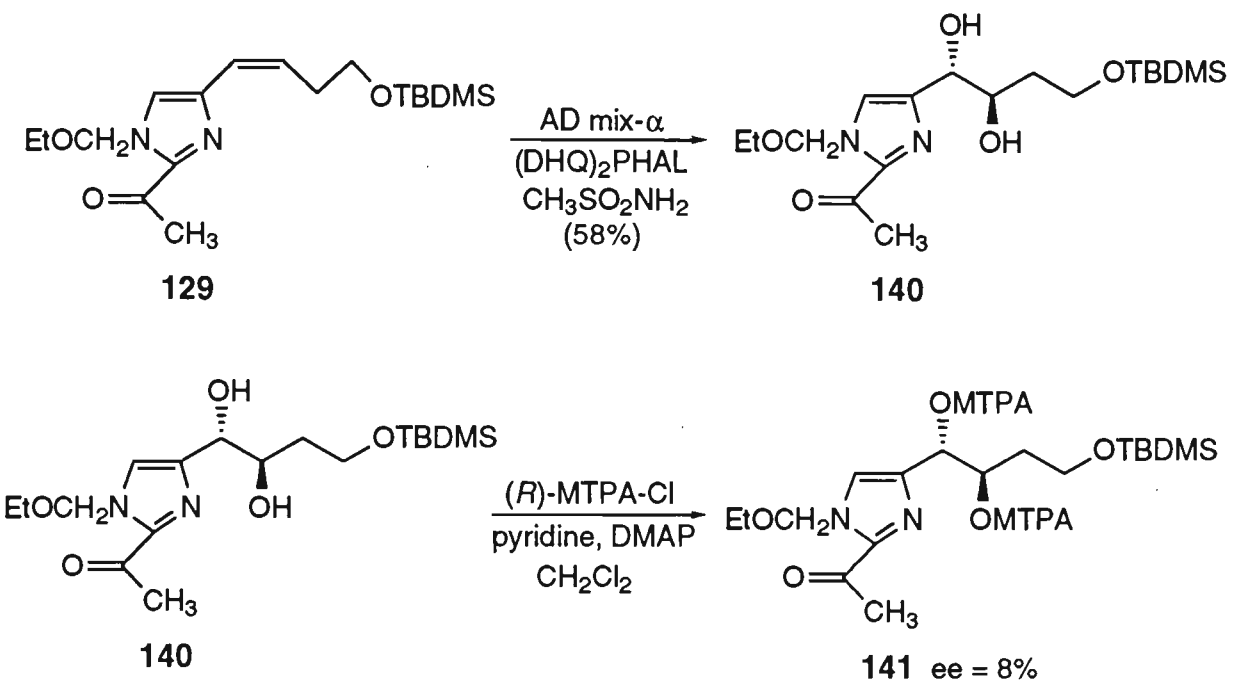


Figure 3.8 H1' doublets (δ 6.33-6.30 ppm) and methyl ketone singlet peaks (δ 2.546 and 2.513 ppm) from the ^1H NMR spectrum of (*S*)-MTPA diester **139** in $CDCl_3$ solution.

To obtain the second enantiomer, imidazole **129** was treated with commercial AD mix-α, plus an additional 4 mole % of $(DHQ)_2PHAL$ and methanesulfonamide to give the diol **140** in 58% yield. Conversion of a small quantity of the diol to the (*S*)-MTPA diester

using excess (*R*)-(-)-MTPA chloride, as described above, gave the diester **141** after 24 hours at ambient temperature (Scheme 3.32).

Scheme 3.32



^{1}H NMR analysis revealed that the diol **140** had an extremely low 8% ee. Stereochemical assignment of the diol was again based upon Sharpless's revised mnemonic. The low optical purity obtained, however, makes a confident assignment of the major enantiomeric diol somewhat dubious. The lower ee of **140** in comparison to **138** is expected as the cinchona alkaloid ligands are not true enantiomers. The $(DHQD)_2PHAL$ ligand **108** in general gives superior ee's to that of its $(DHQ)_2PHAL$ counterpart **109**.[170] If dihydroquinine were a true enantiomer of dihydroquinidine, then comparable optical purities would be expected. The optical purity of the diol **140** was assessed by examination of the H1' doublets and the methyl ketone singlets in the aforementioned ^{1}H NMR regions (Figure 3.9).

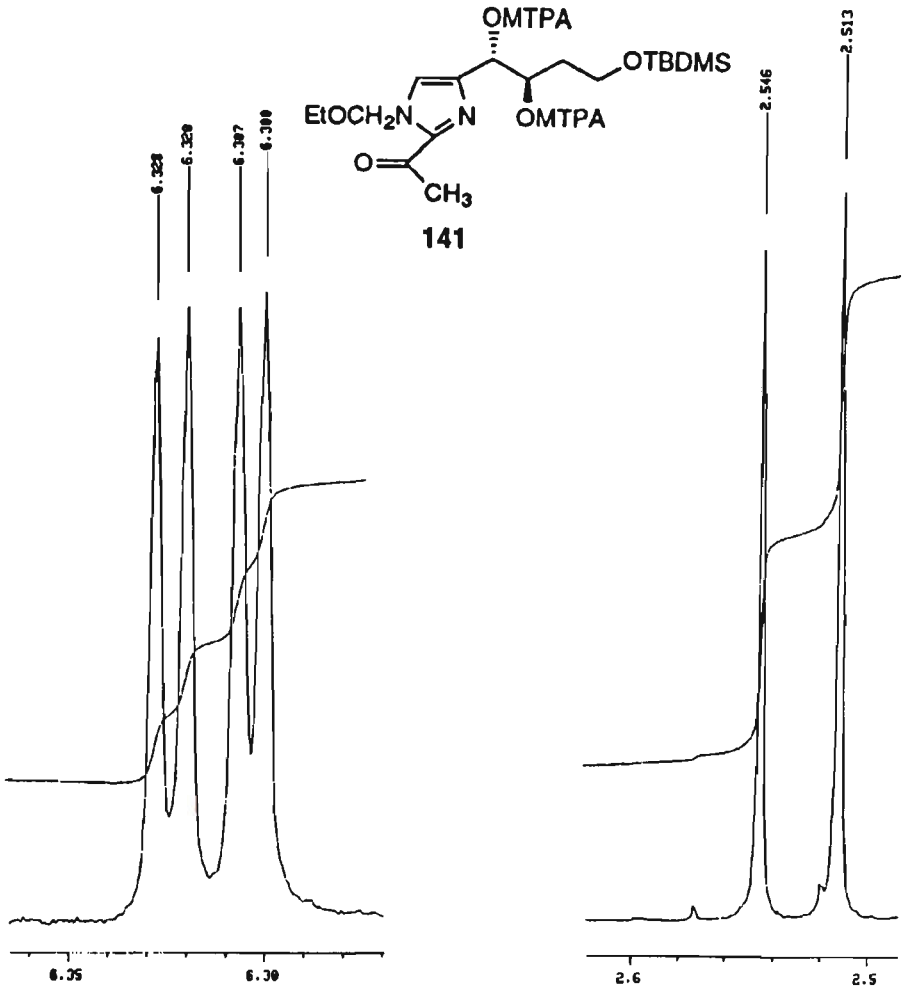


Figure 3.9 H1' doublets (δ 6.33-6.30 ppm) and methyl ketone singlet peaks (δ 2.546 and 2.513 ppm) from the ^1H NMR spectrum of (*S*)-MTPA diester **141** in $CDCl_3$ solution.

3.3.2.1 The AD of (*Z*)-alkenes possessing homoallylic alcohols

The major limitation in obtaining high ee's in the AD of *cis*-alkenes is the so-called 'meso-effect'.[179] For the general *cis*-alkene **142** depicted in Figure 3.10, when $R_1 = R_2$, then the AD of this symmetrical *cis*-disubstituted alkene leads to the formation of a meso diol. As R_1 approaches R_2 in size, the vanishing prochiral asymmetry of the olefin renders enantiofacial selection increasingly more difficult. Therefore, the enantioselectivity of the AD when $R_1 \neq$

R_2 can be rationalised as size recognition of the olefinic substituents.

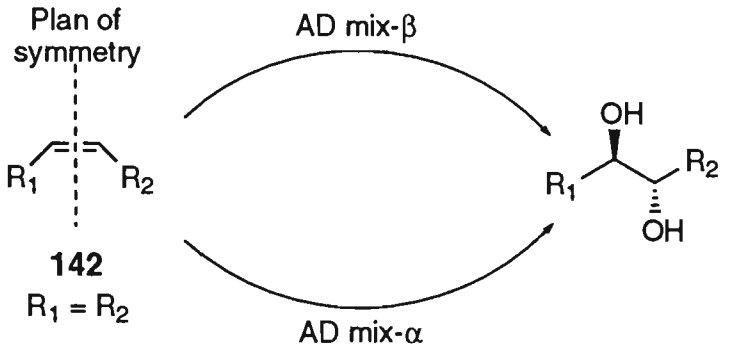
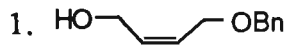
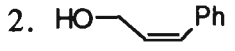
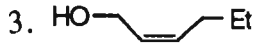
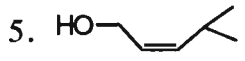


Figure 3.10 Synthesis of the meso-diol using AD mix-α or β when R_1=R_2.

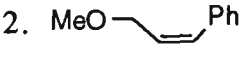
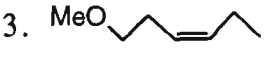
Recent results by VanNieuwenhze and Sharpless, however, have shown an improvement in the ee's obtained from *cis*-olefins containing an allylic or homoallylic alcohol.[200] This improvement was obtained using the phthalazine class of chiral ligands, with the ee's achieved equal or superior to those obtained using the indoline based chiral ligands. A number of allylic and homoallylic alcohols were subjected to an AD reaction using both $(DHQD)_2PHAL$ and DHQD-IND and their ee's assessed (Table 3.4).

Table 3.4 Enantiomeric excesses of *cis*-alkenes possessing allylic or homoallylic alcohol moieties.

Substrate	*enantiomeric excess (%)*	
	$(DHQD)_2PHAL$	*DHQD-IND*
1. 	64	31
2. 	71	72
3. 	74	52
4. 	54	-
5. 	64	-

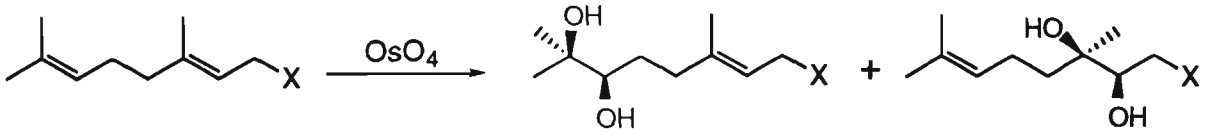
It is believed that hydrogen bonding by the free hydroxyl to an oxo group on osmium may be responsible for the enhanced enantioselectivity seen with this class of *cis*-olefins,[201] as the phthalazine ligands generally give poor enantioselectivities with other *cis*-olefin classes. When the equivalent methyl ethers to entries 1, 2 and 4 in Table 3.4 were treated with $(DHQD)_2PHAL$ in the AD reaction, however, a dramatic decrease in the enantioselectivity was observed (Table 3.5).

Table 3.5 AD data of methyl ether derivatives with $(DHQD)_2PHAL$.

Substrate	*% ee*
1. 	23
2. 	13
3. 	0

The ability of a free hydroxyl group to hydrogen bond to OsO_4 and direct attack has been examined by Sharpless using the geraniol diene **143**[201] (Scheme 3.33). Under both stoichiometric and catalytic conditions, the AD of **143** gives a mixture of the 6,7-diol **144** and the 2,3-diol **145** in an 80:20 ratio. In contrast, the AD of the methyl ether **146** and the acetate **147** gave the diol **144** due to oxidation of the remote double bond almost exclusively. Although a preference for remote double bond oxidation is anticipated due to the electron-withdrawing effect of the allylic oxygen substituents, the drop in regioselectivity for geraniol **143** is indicative of an attractive interaction between the hydroxyl group and OsO_4, which partly counters the repulsive electronic effects.

Scheme 3.33



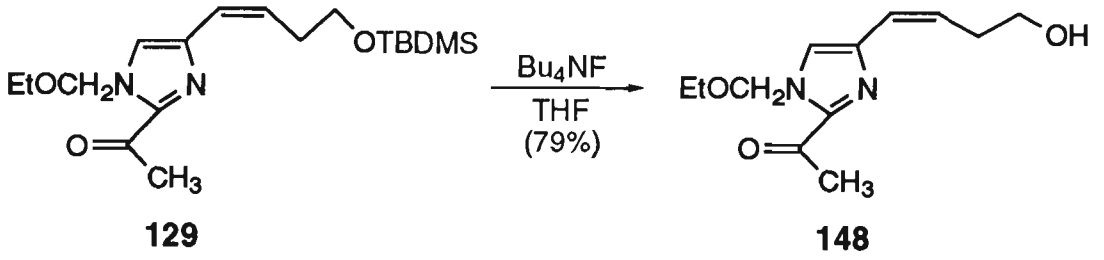
143, X = OH
146, X = OMe
147, X = OAc

144 (6,7-diol) **145** (2,3-diol)

X	144 : 145
143	80 : 20
146	>98 : 2
147	>99 : 1

Application of this theory to our own system should allow an increase in enantioselectivity in the AD reaction. The (Z)-alkene **129** was subjected to fluoride deprotection of the silyl ether group using Bu_4NF in THF at ambient temperature to give the alcohol **148** in 79% yield[187] (Scheme 3.34).

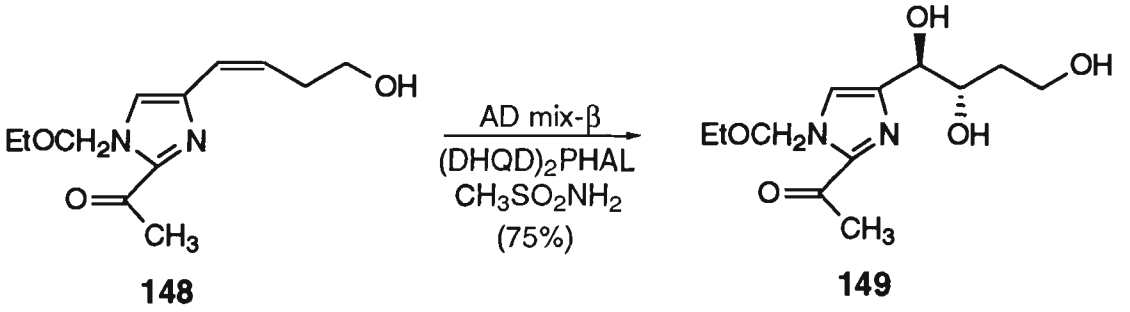
Scheme 3.34



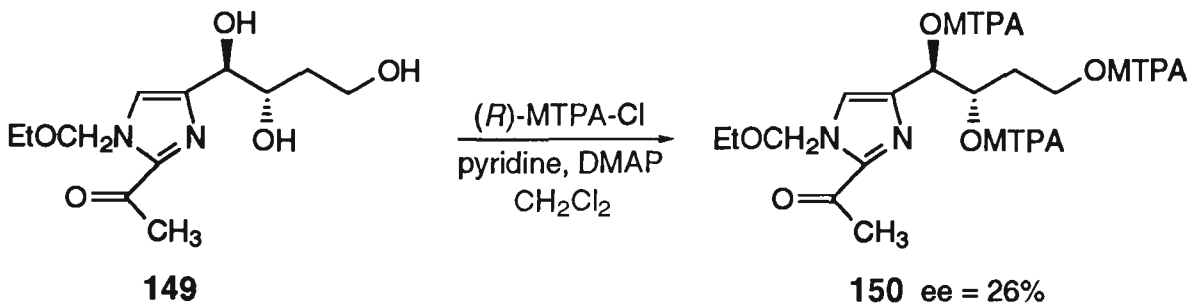
129 **148**

The alcohol **148** was treated with AD mix-β and an additional 5 mole % of $(DHQD)_2PHAL$ at 0 °C for 5 days to give the triol **149** in 75% yield. The AD proceeded sluggishly in comparison to that of the (*Z*)-alkene **129**, possibly due to hydrogen bonding of the homoallylic alcohol to the oxo groups on osmium. Conversion of a small quantity of the triol to its (*S*)-MTPA triester **150** with (*R*)-(-)-MTPA chloride followed by ^1H NMR analysis showed that the triol had an ee of 26% (Scheme 3.35).

Scheme 3.35



148 **149**



149 **150** ee = 26%

The low enantioselectivity of this reaction gave an identical result to that achieved using the (*Z*)-alkene **129** and AD mix-β. This result was both surprising and disappointing as removal of the silyl protecting group from **129** enabled both i) the meso effect to be reduced, as the (*Z*)-alkene substituents are more sterically different, and ii) the homoallylic alcohol to direct attack.

The advantage in obtaining the triol **149**, however, in comparison to the silylated diol **138** is that it is present as a solid and therefore lends itself to enantiomeric enrichment *via* recrystallisation. This process was not performed, however, as the initial low level of optical purity of the triol would have made multiple recrystallisations necessary to obtain a high degree of optical purity and therefore result in the loss of large quantities of the triol.

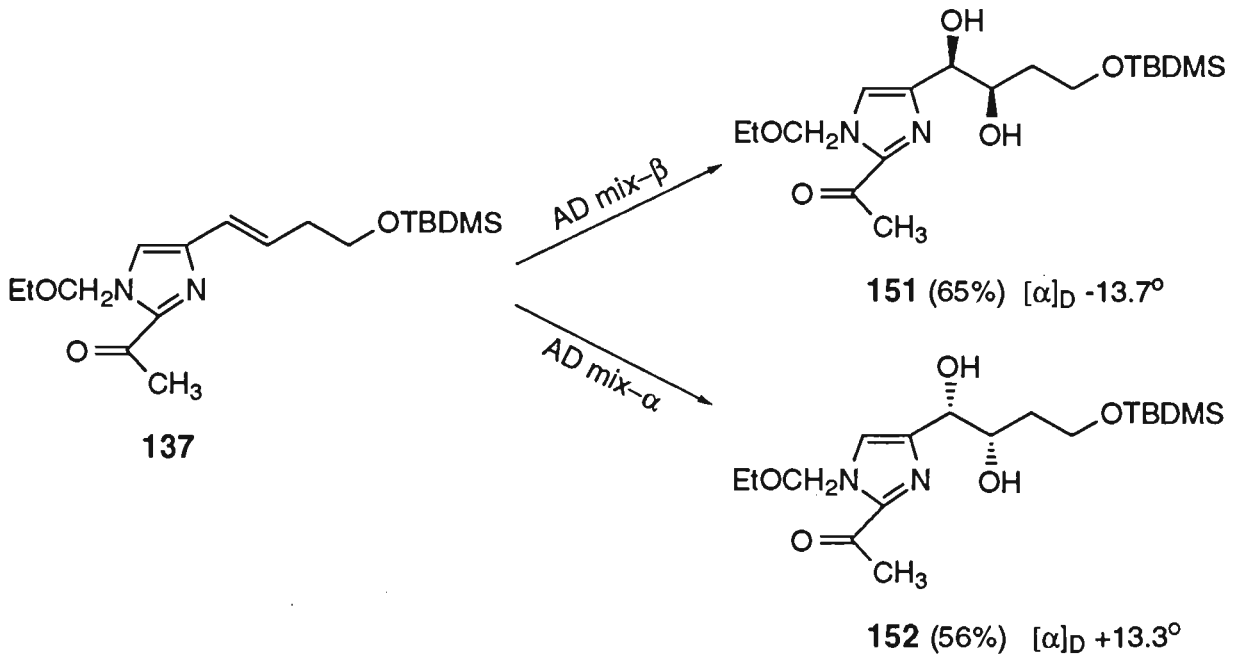
The means by which high enantiomerically pure diols could be obtained from the (*Z*)-alkenes **129** and **148** had been exhausted, with no satisfactory results obtained. Use of other chiral ligand systems, and the indoline based cinchona alkaloids in particular, would therefore be necessary to effect reasonable results.

3.3.3 The AD of (*E*)-alkenes

Although poor results were obtained from the AD of (*Z*)-alkenes **129** and **148**, a large improvement would be expected from the corresponding (*E*)-alkenes. *Trans*-alkenes typically give ee's within the range 90-99% using the phthalazine ligand class.[101,170]

The (*E*)-alkene **137** was treated separately with AD mix-β and AD mix-α, plus an additional 4 mole % of the chiral phthalazine ligand and 2.2 molar equivalents methanesulfonamide to give the diols **151** and **152** in 65% and 56% yields respectively (Scheme 3.36). Both reactions took 3 days to complete at 0 °C.

Scheme 3.36

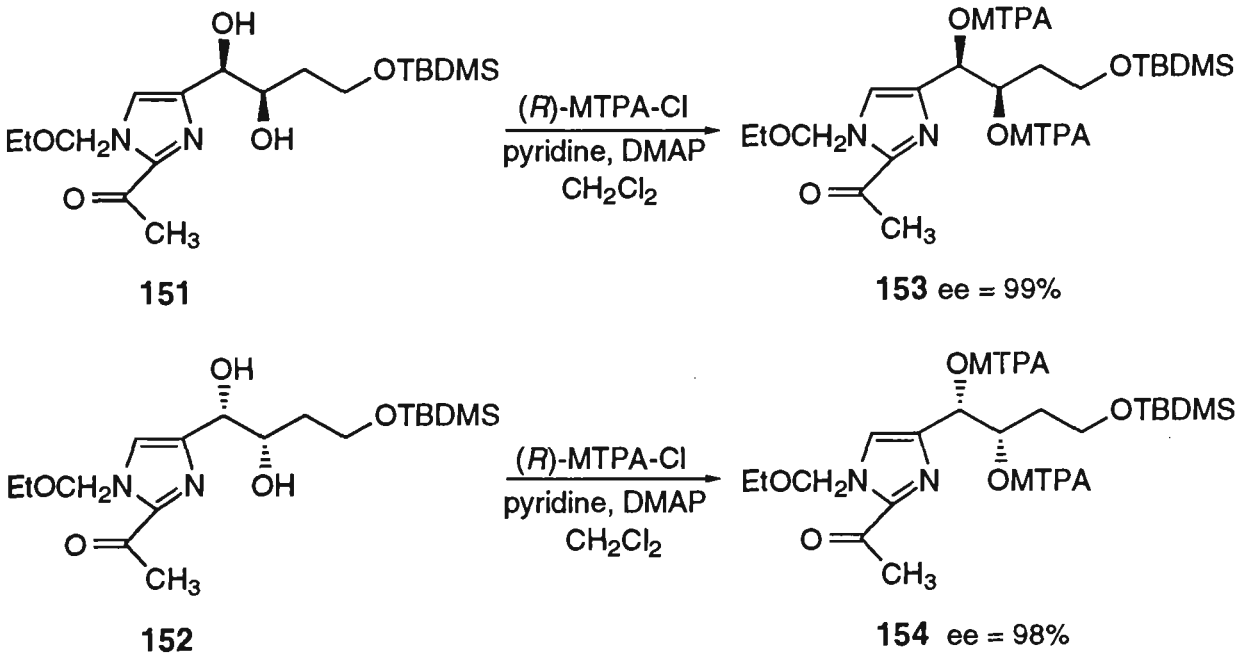


The stereochemical assignments of the diols was made using Sharpless's mnemonic by positioning the flat, aromatic imidazole ring onto the attractive, southwest quadrant and the side-chain onto the northeast quadrant. AD mix-β would then deliver the hydroxyl moieties from the top face, while AD mix-α delivers them from the bottom face of the alkene (Figure 3.5).

Conversion of a small quantity of diols **151** and **152** to the corresponding (*S*)-MTPA diesters **153** and **154** proceeded sluggishly and required 5 equivalents of (*R*)-(-)-MTPA chloride to effect a complete conversion (Scheme 3.37). The stereochemistries

at C1' and C2' resulted in a sterically hindered enviroment, with the addition of the two MTPA moieties to the two adjacent hydroxyl groups taking 48 hours to complete.

Scheme 3.37



151 **153** ee = 99%

152 **154** ee = 98%

^{1}H NMR analysis of the methyl ketone region of the MTPA diesters revealed that the diols **151** and **152** were present in a highly optically pure state, with ee's of 99% and 98% respectively (Figure 3.11). The minor diastereomer in each case was barely distinguishable above the baseline noise. The optical rotations of the two enantiomers were essentially equal and opposite. Diol **151** gave a negative rotation of -13.7°, while **152** gave a rotation of +13.3°.

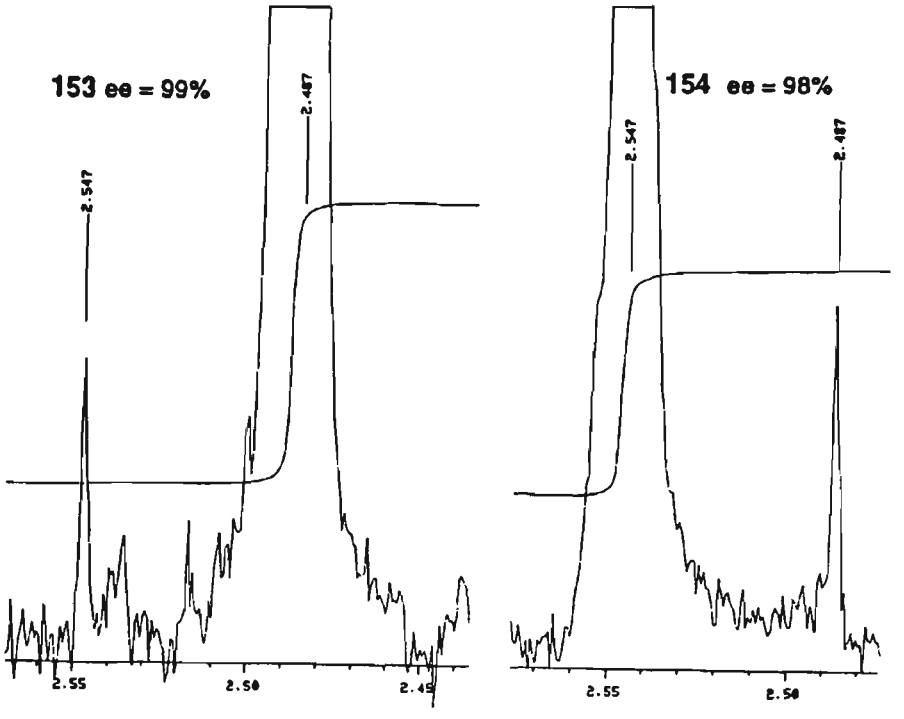


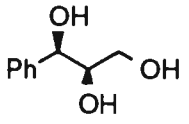
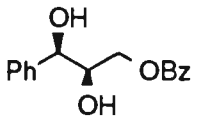
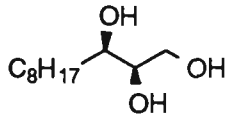
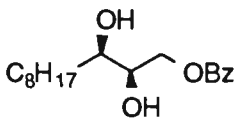
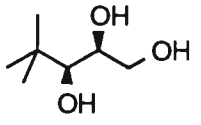
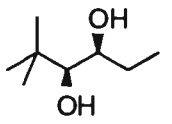
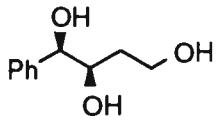
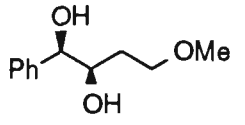
Figure 3.11 Methyl ketone signals from the ^1H NMR spectra of the (*S*)-MTPA diesters **153** and **154** in $CDCl_3$ solution.

3.3.4 The AD of (*E*)-alkenes possessing homoallylic alcohols

Although excellent results were obtained from the AD of the (*E*)-alkene **137**, a comparison was also made with the AD reaction of the corresponding free alcohol to examine the effect of hydrogen bonding to the OsO_4/chiral ligand complex. Unlike the expected enhancement of enantioselectivity for (*Z*)-alkenes possessing an allylic or homoallylic alcohol moiety, literature precedent suggested that in the case of (*E*)-alkenes, a decrease in enantioselectivity would be expected.[201] Using both allylic and homoallylic alcohols along with the corresponding protected substrates, Xu *et al.* carried out a number of AD trials.[201] Their results showed that the presence of a free hydroxyl group had a deleterious effect upon the AD reaction and lead to lower ee's (Table 3.6). The effect was most

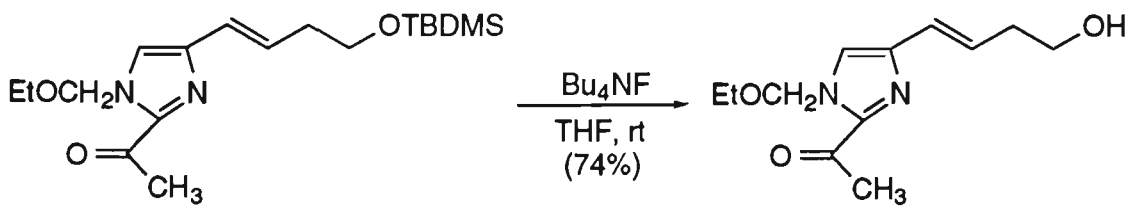
marked for allylic alcohols (entries 1, 2, 3), with only a small decrease in optical purity displayed for the homoallylic moiety (entry 4).

Table 3.6 Products from the AD reaction of *trans*-alkenes possessing hydroxyl and ether moieties.

From Free Alcohol	*% ee*	*From Protected Alcohol*	*% ee*
1. 	97		99
2. 	93		99
3. 	74		95
4. 	98		99

Alkene **137** was desilylated using Bu_4NF in THF to give the alcohol **155** in 74% yield[187] (Scheme 3.38).

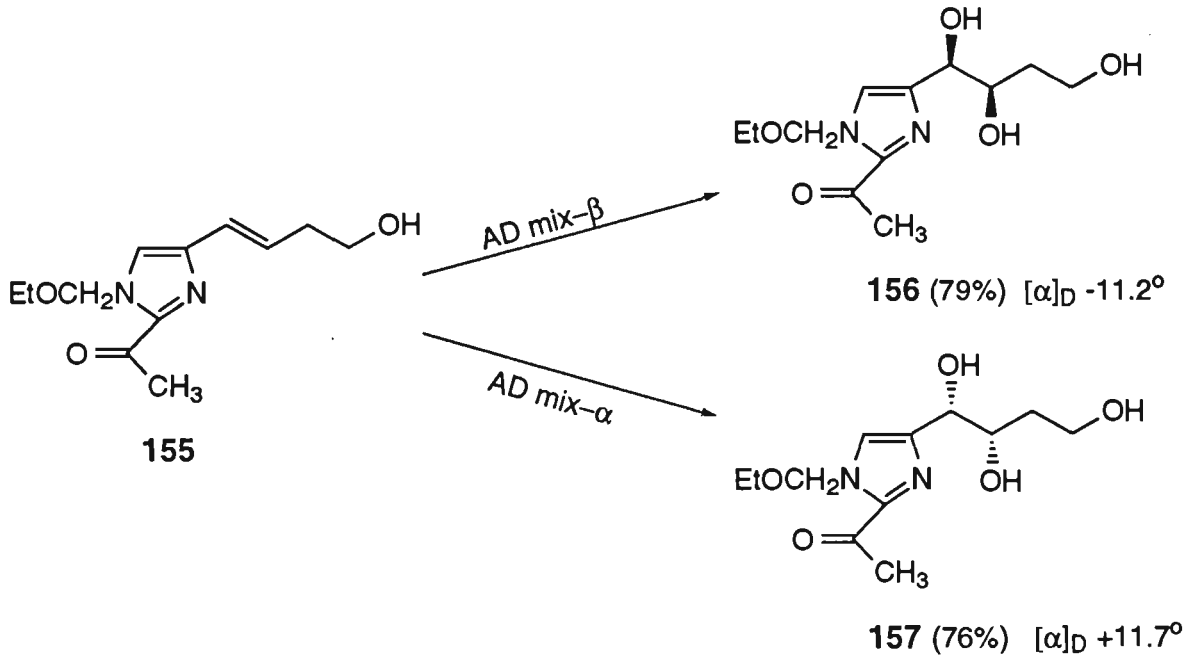
Scheme 3.38



137 **155**

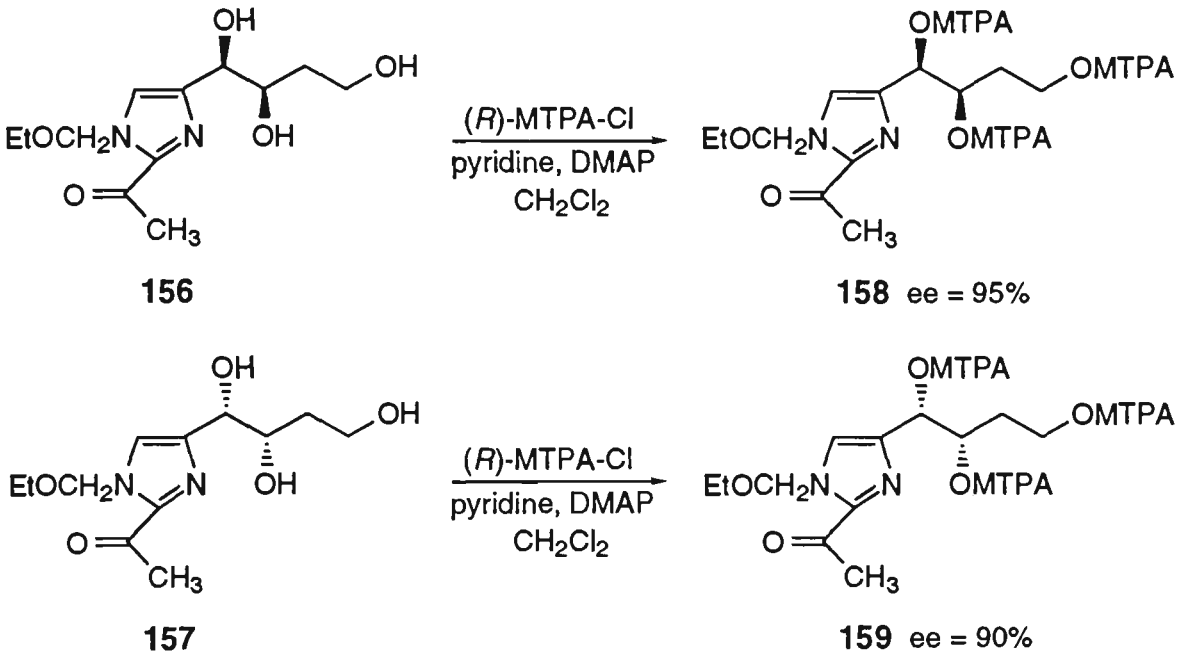
The (*E*)-alkene **155** was subjected to separate AD reactions using AD mix-β and AD mix-α along with an additional 4 mole % of the chiral ligand and 2.2 molar equivalents of methanesulfonamide in *t*-BuOH/H_2O (1:1), to give the triols **156** and **157** in 79% and 76% yields respectively (Scheme 3.39). As with the AD of the homoallylic alcohol **148**, the reaction proceeded sluggishly and took 4 days to complete at 0 °C. The optical rotations of **156** and **157** were again essentially equal and opposite, with rotations of -11.2° and +11.7° respectively.

Scheme 3.39



Conversion of a small quantity of the triols **156** and **157** to their (*S*)-MTPA triesters as previously described gave the esters **158** and **159** respectively (Scheme 3.40). The esterification again proceeded slowly due to the sterically unfavourable stereochemistries presented at C1' and C2' and required 6 equivalents of (*R*)-(-)-MTPA chloride to effect a complete conversion to the triesters.

Scheme 3.40



^{1}H NMR analysis of the methyl ketone region of the (*S*)-MTPA esters showed the original triols to be present in 95% and 90% ee respectively (Figure 3.12). As with the AD of the (*Z*)-alkene **129**, the ee of the diols synthesised using $(DHQD)_2PHAL$ (**151** and **156**) was superior to that obtained with the pseudo-enantiomer $(DHQ)_2PHAL$.

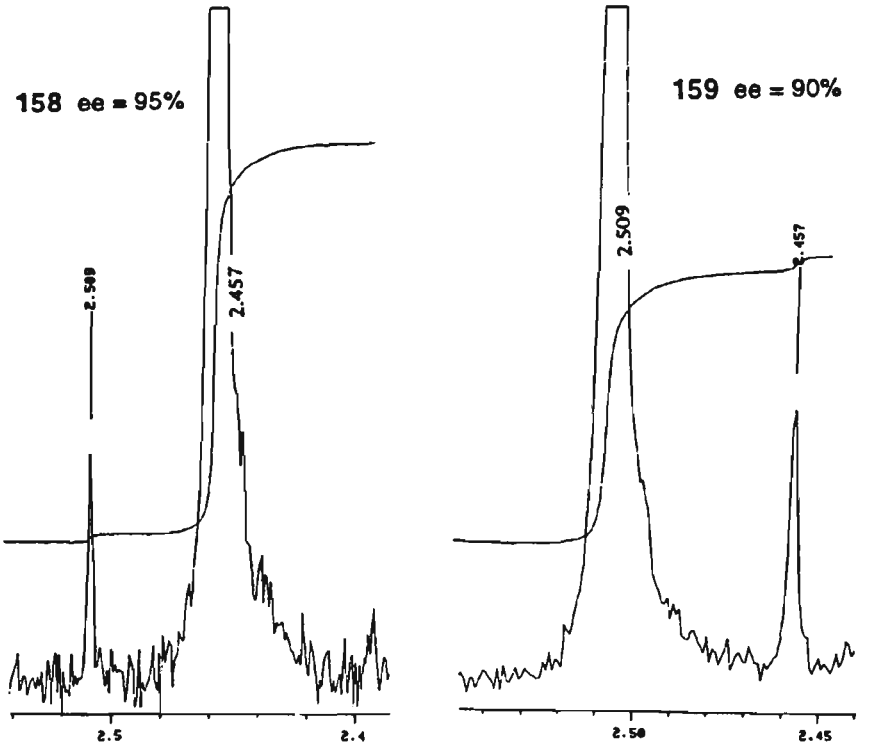


Figure 3.12 Methyl ketone signals from the ^1H NMR spectra of the (*S*)-MTPA triesters **158** and **159** in $CDCl_3$ solution.

3.4 Determination of the Absolute Configurations of Diols Synthesised by the Sharpless Asymmetric Dihydroxylation

Sharpless's revised mnemonic has been successfully used to predict the stereochemical outcome of numerous AD reactions.[170] The stereochemical assignments at C1' and C2' for the diols **138**, **140**, **151** and **152** can therefore be assigned with a good deal of confidence. In the absence of an authentic comparative diol sample, however, a secondary technique for confirming the assigned configurations was desirable. The most secure physical method for determining absolute configuration is to incorporate a chiral auxiliary into the diol and obtain an X-ray crystal structure of the diastereoisomer. Suitable crystals of the Mosher esters could not be obtained, however, and therefore a chemical technique was required. The MTPA esters of our chiral diols were used to evaluate their enantiomeric purity and were also utilised to determine their absolute configurations.[199,202]

3.4.1 The Modified Mosher Method for Determination of Absolute Configuration

In Mosher's original method it was proposed that, in solution, the methine proton, the ester carbonyl and the trifluoromethyl groups on the MTPA moiety lie in the same plan[202] (Figure 3.11). With the MTPA group in this hypothesised conformation, the ^{1}H NMR signals of the substituent R_1 of the (*R*)-MTPA ester will appear upfield relative to those of R_1 of the (*S*)-MTPA ester due to the diamagnetic effect of the benzene ring. A comparison of the ^{1}H NMR spectra would therefore provide evidence for a specific configuration.[202]

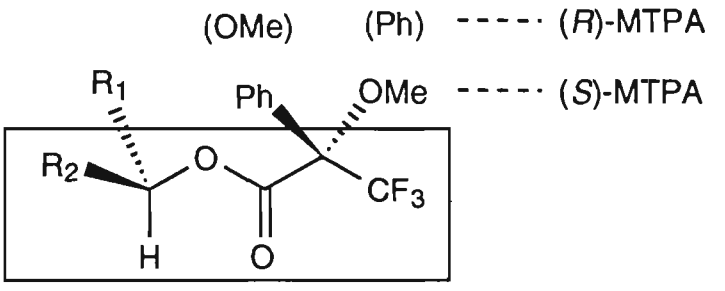


Figure 3.11 Ideal conformation of the (*R*)- and (*S*)-MTPA esters. The methine proton, carbonyl and trifluoromethyl moieties lie in a single plane.[202]

Molecular modelling of various MTPA esters[203] have shown that the conformation proposed by Mosher is one of two possible stable states, the second of which has the methoxy group close to the ester carbonyl. X-ray and IR studies, however, have shown that the MTPA adopts a conformation that is almost identical to that proposed by Mosher.[203,204,205]

When Mosher first proposed his method for determining absolute configurations, the NMR instrumentation available at the time consisted mainly of 60-100 MHz instruments, thus leading to difficulties in complete proton assignments for a molecule.[206] Modifications of Mosher's method that used ^{19}F NMR[202] or lanthanide-shift reagents[204,205] have therefore been employed.

Relying on a chemical shift difference between the CF_3 group (^{19}F NMR) or OMe group (^{1}H NMR) of diastereomeric derivatives, however, meant that the assignment of absolute configuration was based upon only two data points, one each from the (*R*)- and (*S*)-MTPA diastereomeric esters. An improvement of Mosher's method, however, has been utilised by Kakisawa *et al.*[206] which relies on a

larger number of data points. The basic principle of this modification is essentially the same as that proposed by Mosher, but with the advancement of NMR instrumentation and 2D spectral assignments, a large number of proton assignments can be made to the parent molecule. In Kakisawa's adaptation, the ideal MTPA conformation is the same as that proposed by Mosher (Figure 3.12). Due to the diamagnetic effect of the benzene ring, the $H_{A,B,C...}$ ^1H NMR signals due to the (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester. The reverse should hold true for the protons $H_{X,Y,Z}$.[206] Therefore, for the predefined $\Delta\delta = \delta_S - \delta_R$, then protons on the bottom side of the MTPA plane must have positive $\Delta\delta$ values ($\Delta\delta > 0$) and protons on the top side of the plane must have negative $\Delta\delta$ values ($\Delta\delta < 0$)[206] (Figure 3.13).

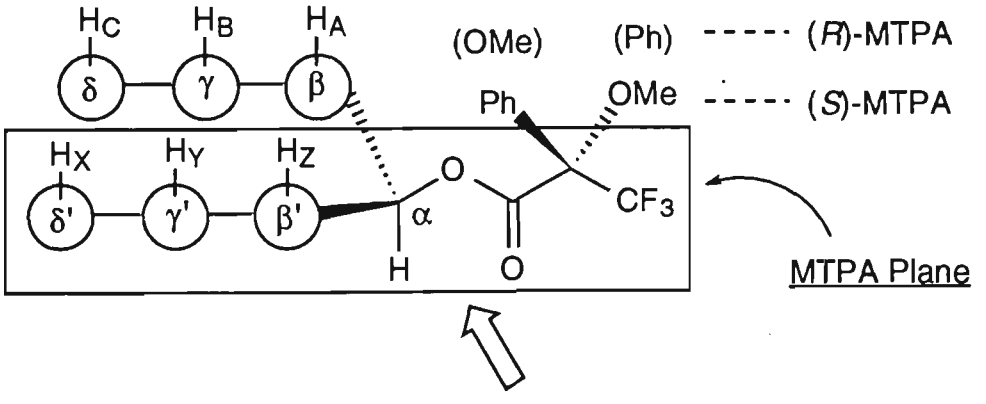


Figure 3.12 MTPA plane containing the ester for Kakisawa's modified Mosher analysis.[206]

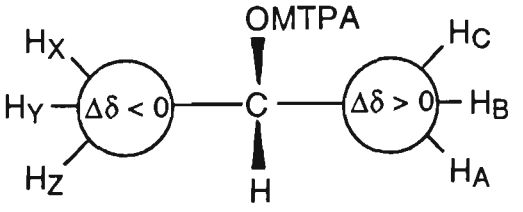


Figure 3.13 MTPA plane for Kakisawa's modified Mosher analysis from the direction indicated by the arrow in Figure 3.12.[206]

Mosher's modified method can thus be applied as follows:

i) assign as many signals as possible on both the (*R*)- and (*S*)-MTPA esters

ii) obtain $\Delta\delta$ values for the proton signal pairs

iii) put the protons with positive $\Delta\delta$ on the right side of the model depicted in Figure 3.13 and those with negative $\Delta\delta$ on the left side

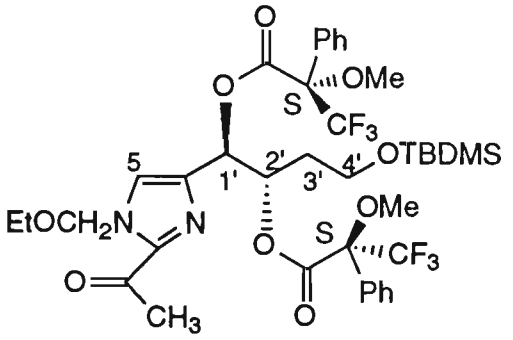
iv) construct a molecular model of the compound and confirm that all the assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane respectively.

The absolute values of $\Delta\delta$ must be proportional to the distance from the MTPA moiety. When all of these conditions are met, the model depicted in Figure 3.13 should indicate the absolute configuration of the compound.

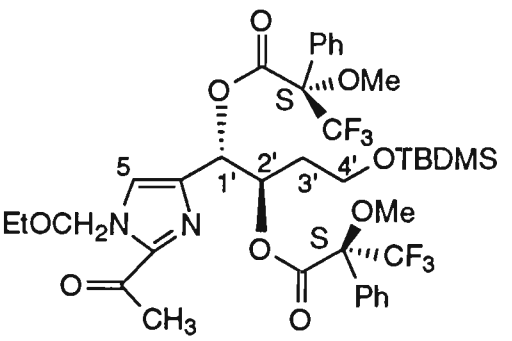
3.4.2 Application of Mosher's Modified Method to THI Analogues

To apply Mosher's method to the diols synthesised in this Chapter, a modification must be made. Rather than synthesise both the (*R*)- and (*S*)-MTPA esters of all four diols (**138**, **140**, **151** and **152**), the absolute configurations can be evaluated by using a *single* hand of the MTPA chloride with each *pair* of enantiomers (**138/140** and **151/152**). Application of Mosher's modified method can then be applied to the diastereomeric pair as described above.

Diols **138** and **140** were converted to the (*S*)-MTPA diesters **139** and **141** respectively as described above in section 3.3.1.



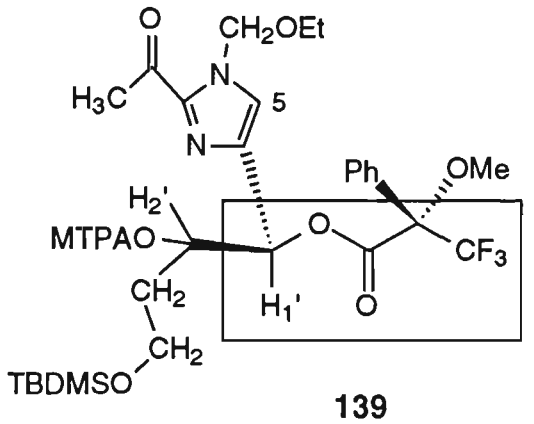
139



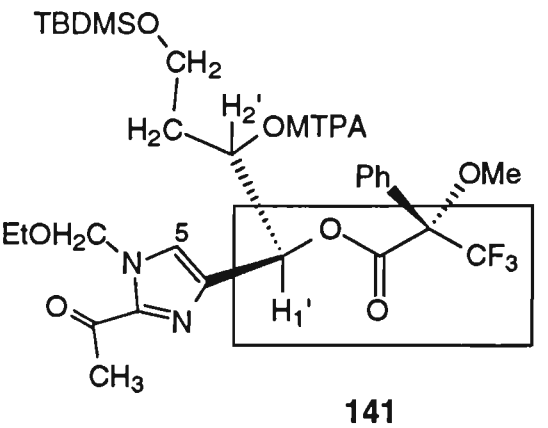
141

Either of the two chiral centres present on the butyl side-chain could be used in the Mosher analysis. The MTPA ester at C2' is the preferred site for this analysis as it is situated roughly half-way along the molecule, allowing an even number of ^{1}H NMR signals on either side to be examined. The low enantioselectivity of the AD reaction, however, rendered the multiplet signals for H3' and H4' on the esters **139** and **141** indistinguishable, with no definite assignments able to be made to either diastereomer. Therefore, the C1' MTPA ester was chosen as the centre from which to evaluate the absolute configuration.

Using the absolute configurations predicted by the Sharpless mnemonic, the (*S*)-MTPA diesters **139** and **141** were projected onto the idealised MTPA plane (Figure 3.14). Due to the diamagnetic effect of the benzene ring, the side-chain ^{1}H NMR signals of **139** should appear upfield relative to those of **141**. The reverse should hold true for the imidazole ring signals. Therefore, for the predefined $\Delta\delta = \delta_{139} - \delta_{141}$, the side-chain $\Delta\delta$ values should be negative while $\Delta\delta$ for the imidazole signals should be positive. The ^{1}H NMR data is presented in Table 3.7.



139



141

Figure 3.14 Projection of the MTPA ester at C1' of **139** and **141** onto the MTPA plane.

Table 3.7 $\Delta\delta$ values for the (*S*)-MTPA esters **139** and **141** in $CDCl_3$. Analysis was performed at C1'.

Proton Signal	δ_{139} *(ppm)*	δ_{141} *(ppm)*	$\Delta\delta$
H5	7.111	6.648	+0.463
$COCH_3$	2.567	2.534	+0.033
H2'	5.730*	5.802*	-0.072
H1'	6.346†	6.326†	+0.020

* Centre of doublet signal. † Centre of multiplet signal.

It can be seen from the $\Delta\delta$ data presented in Table 3.7 that the methine proton at C1' has a positive $\Delta\delta$. According to Mosher's scheme, if the MTPA is in the ideal conformation, then this value should be zero. [202] Kakisawa *et al.* [206] have observed non-zero $\Delta\delta$ values for the methine proton and suggest that this is due to deviations of the MTPA moiety from the ideal conformation. Molecular models constructed of both **139** and **141** confirm this to be the case, with both MTPA moieties showing deviations from the ideal conformation (Figures 3.15, 3.16).

With the modified Mosher analysis followed according to the aforementioned constraints, the absolute configuration of the diols **138** and **140** is confirmed. The AD reactions utilising both phthalazine ligands **108** and **109** therefore delivered the hydroxyl groups according to the mnemonic.

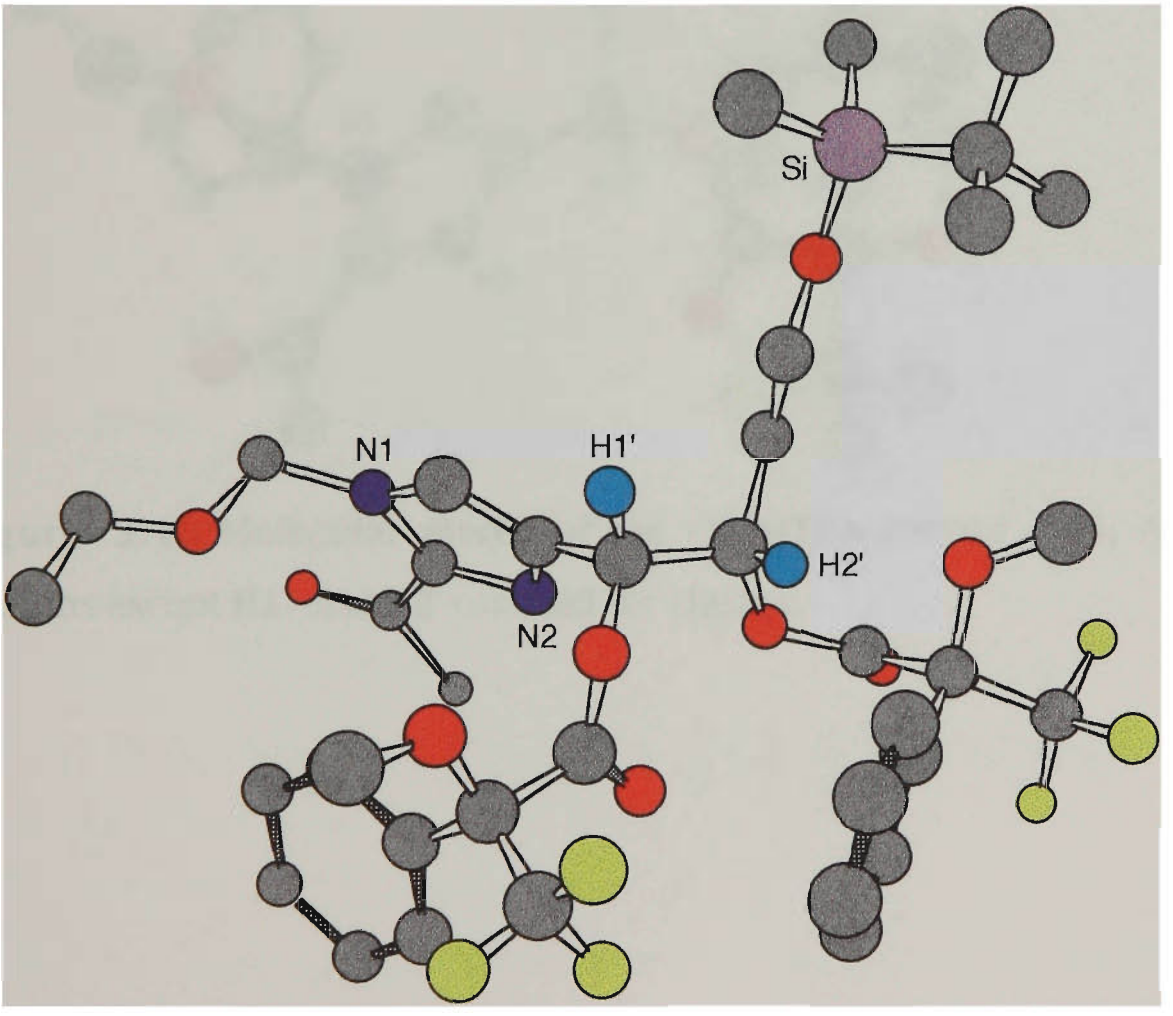


Figure 3.15 Molecular model of the (*S*)-MTPA diester **139**. All protons except H1' and H2' omitted for clarity.

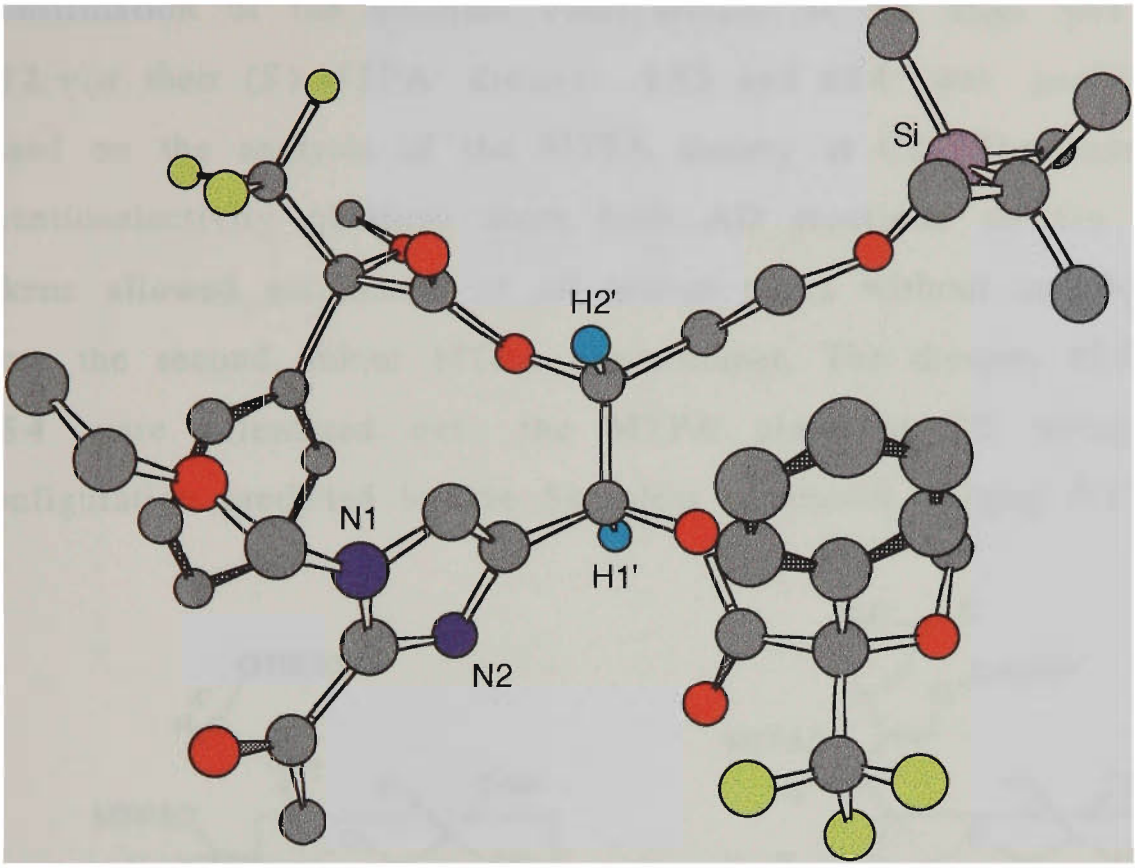


Figure 3.16 Molecular model of the (*S*)-MTPA diester 141. All protons except H1' and H2' omitted for clarity.

Confirmation of the absolute configuration of the diols **151** and **152** *via* their (*S*)-MTPA diesters **153** and **154** was performed based on the analysis of the MTPA moiety at C2'. The excellent enantioselectivity obtained from both AD reactions on the (*E*)-alkene allowed assignment of all proton peaks without interference from the second, minor MTPA diastereomer. The diesters **153** and **154** were orientated onto the MTPA plane at C2' using the configuration predicted by the Sharpless mnemonic (Figure 3.17).

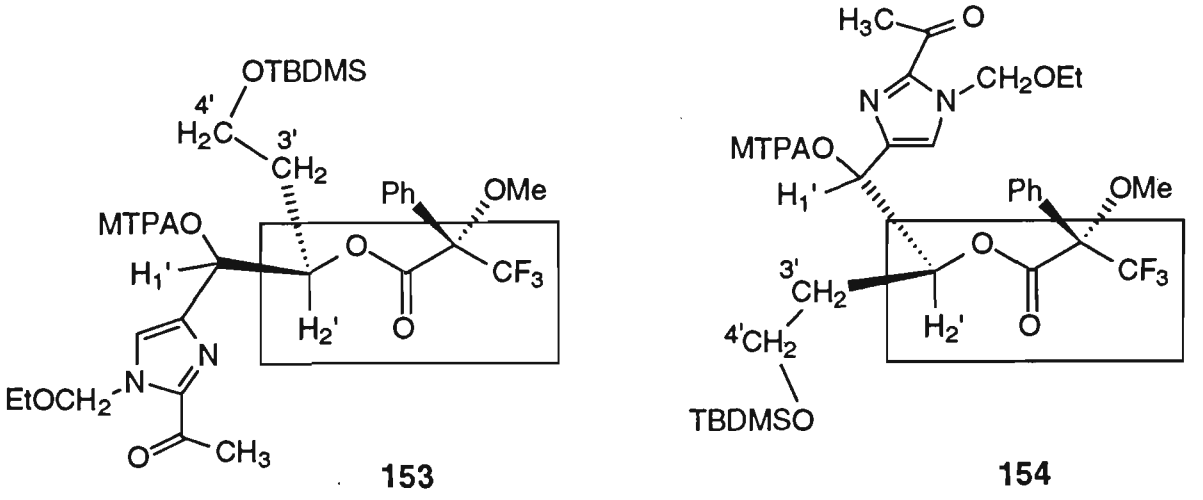


Figure 3.17 Projection of the MTPA diester of **153** and **154** at C2' onto the MTPA plane.

With the esters orientated according to the modified Mosher's method, the 'imidazole' proton signals and that of H1' of **153** should appear upfield from those of **154**. Similarly, due to the diamagnetic effect of the benzene ring, the side-chain protons H3' and H4' should appear downfield. Thus, for the predefined $\Delta\delta = \delta_{153} - \delta_{154}$, the side-chain $\Delta\delta$ values should be positive, while the imidazole and H1' signals should be negative. The ^{1}H NMR analysis is shown in Table 3.8.

Table 3.8 Δδ values for the (*S*)-MTPA esters **153** and **154**. Analysis performed at C2'.

Proton Signal	δ_{153} *(ppm)*	δ_{154} *(ppm)*	*Δδ*
H5	6.849	6.896	-0.047
$COCH_3$	2.489	2.549	-0.060
H1'	6.242*	6.290*	-0.048
H3'	3.673†	3.587†	+0.086
H4'	1.999†	1.845†	+0.154
H2'	5.794†	5.890†	+0.096

* Centre of doublet signal. † Centre of multiplet signal.

The Δδ values shown in Table 3.8 match those expected for the assigned configurations. Both side-chain Δδ values for H3' and H4' were positive, while H1', H5 and the methyl ketone signals all gave the expected negative Δδ. In addition, the absolute values of Δδ were directly proportional to their distance from the MTPA moiety at C2'. The methine proton signal at H2' again gave a non-zero Δδ. Examination of the molecular models of **153** and **154** showed deviations from the ideal MTPA conformation, leading to a non-zero Δδ (Figures 3.18, 3.19).

The absolute configurations of the diols **151** and **152** were therefore consistent with that predicted by the Sharpless mnemonic.

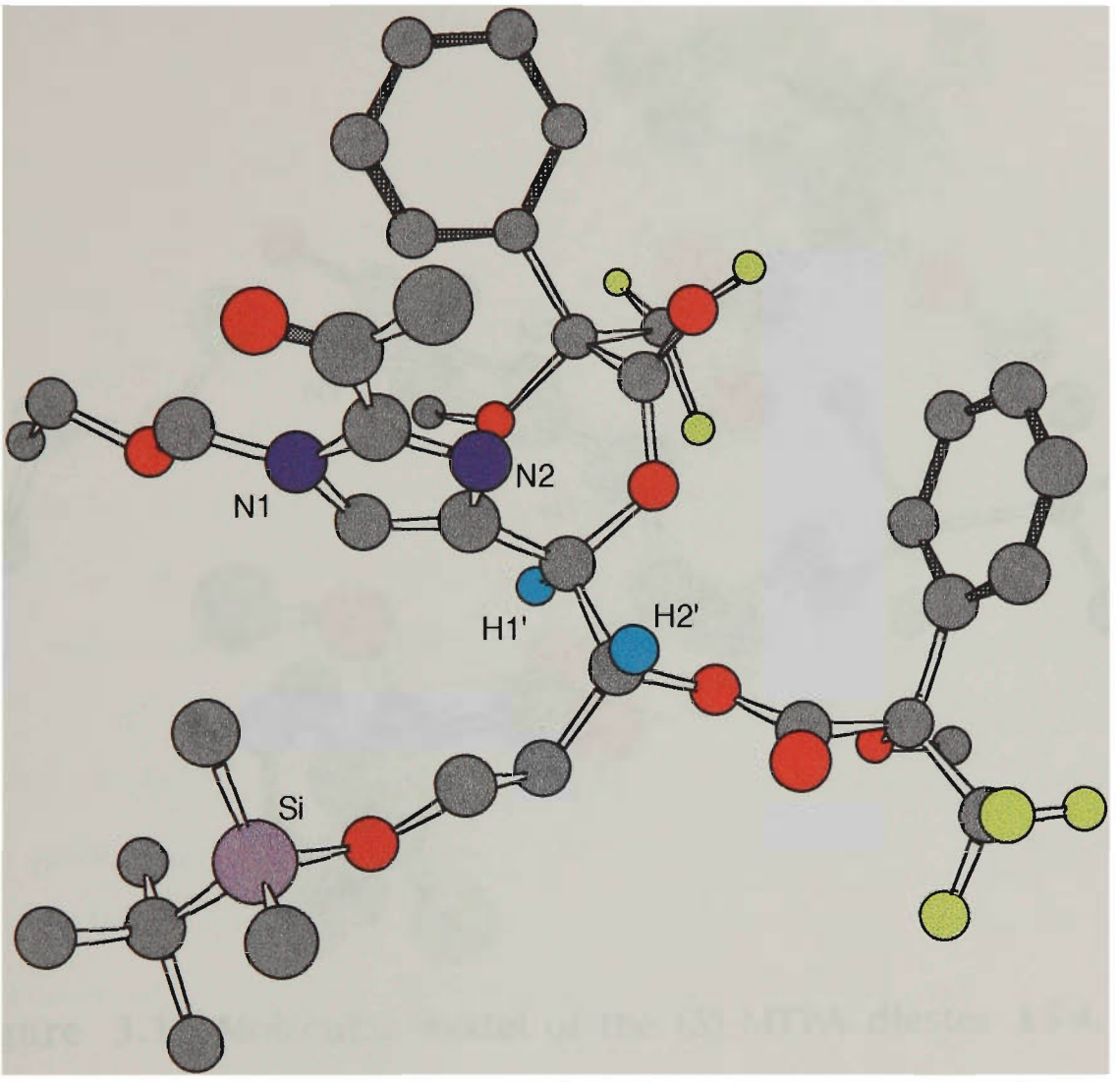


Figure 3.18 Molecular model of the (*S*)-MTPA diester 153. All protons except H1' and H2' omitted for clarity.

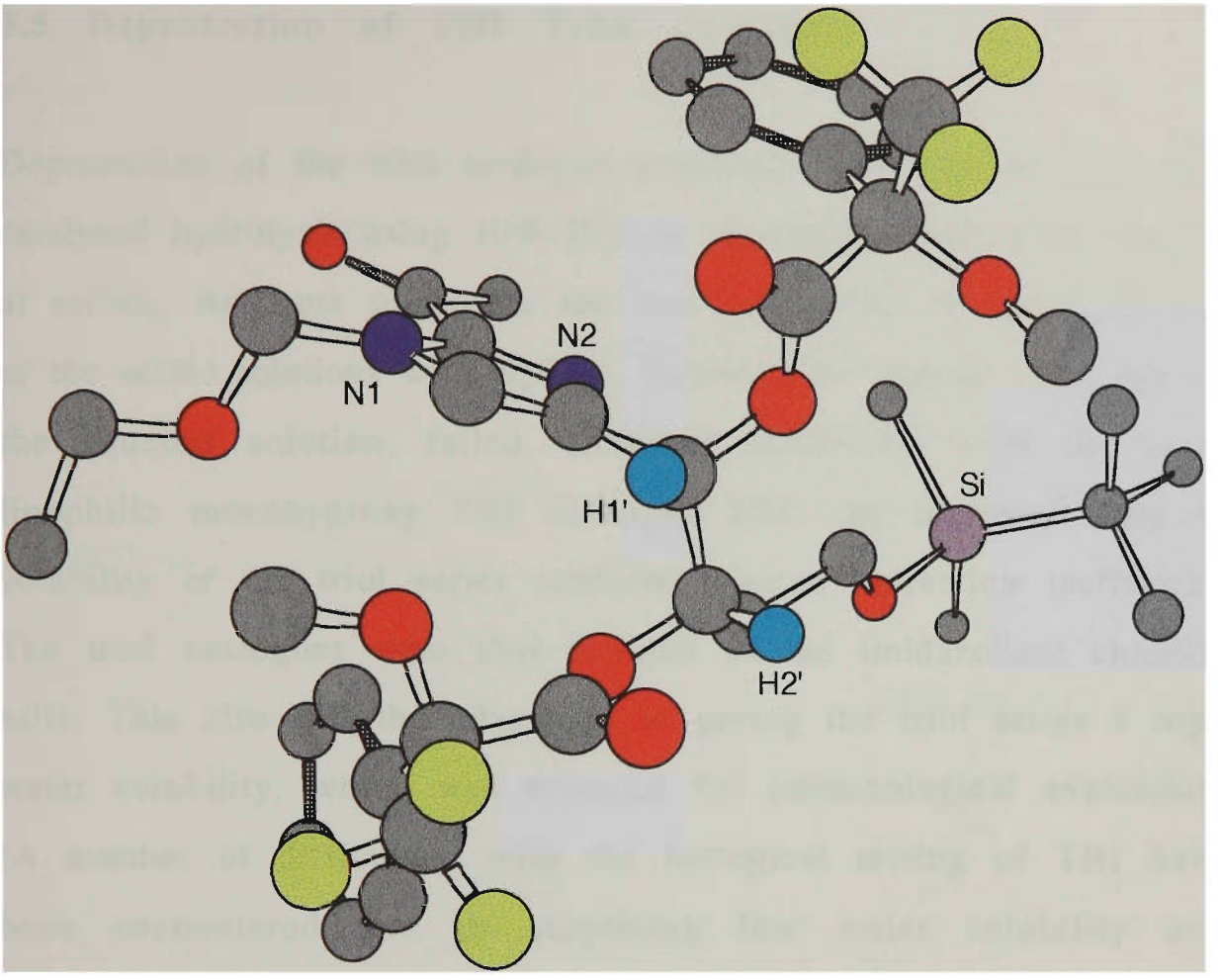


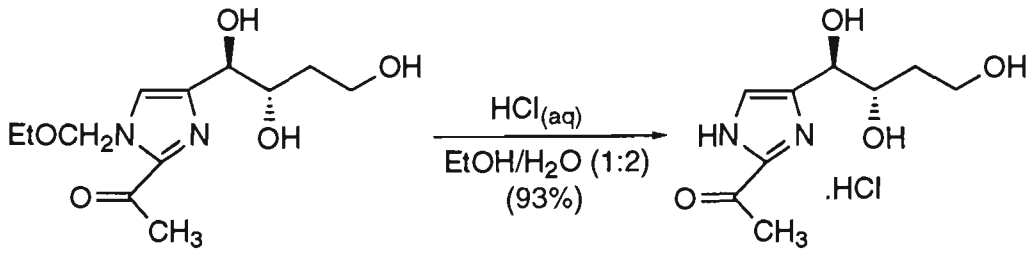
Figure 3.19 Molecular model of the (*S*)-MTPA diester 154. All protons except H1' and H2' omitted for clarity.

3.5 Deprotection of THI Triol Analogues

Deprotection of the triol analogue precursors was achieved *via* acid catalysed hydrolysis using 10% HCl in an ethanol/H_2O (1:2) solution at reflux. Attempts to obtain the free imidazoles by neutralisation of the acidic solutions with K_2CO_3, followed by organic extraction of the aqueous solution, failed. Although successful with the more lipophilic monohydroxy THI analogue **131**, the increased aqueous solubility of the triol series rendered organic extraction inefficient. The triol analogues were thus isolated as the imidazolium chloride salts. This also had the advantage of giving the triol series a high water solubility, which was essential for immunological evaluation. (A number of difficulties with the biological testing of THI have been encountered due its surprising low water solubility and tendency to precipitate from aqueous test solutions).

The triol **149** was heated at reflux in an ethanol/H_2O (1:2) solution containing 10% HCl. Concentration of the solution gave the imidazolium chloride salt **160** as a hydroscopic solid in 93% yield (Scheme 3.41).

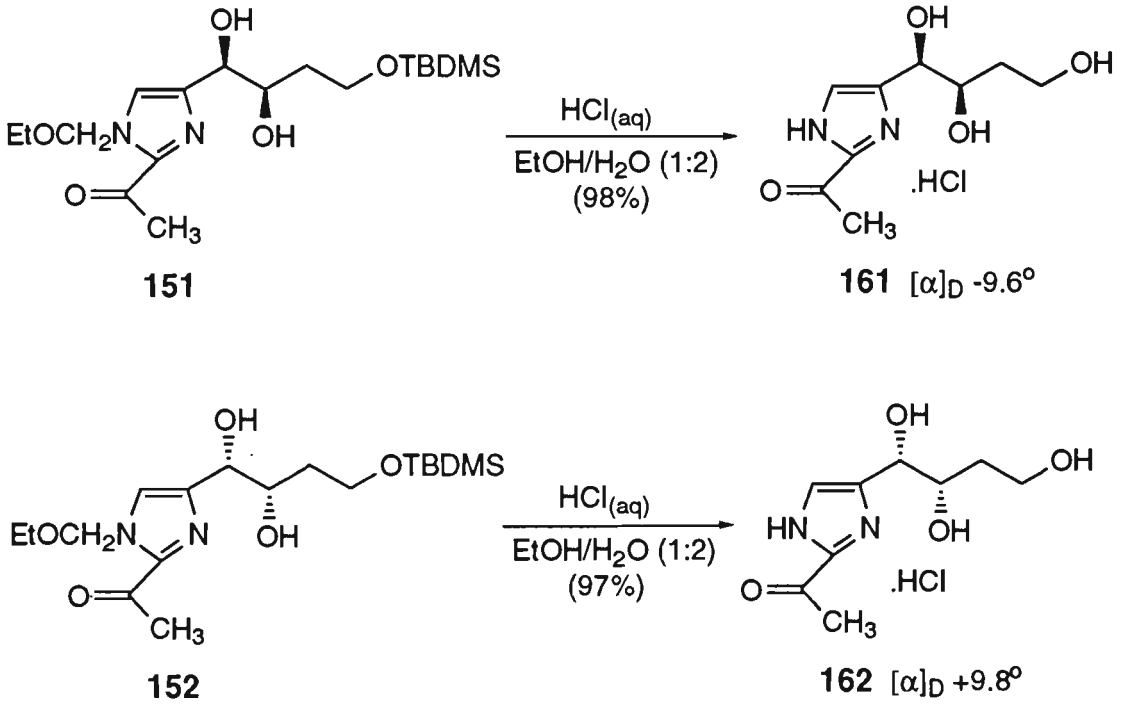
Scheme 3.41



149 **160**

Diols **151** and **152** were deprotected in an identical manner to **149** above. Ether extraction of the aqueous phase to remove silyl residues and concentration gave the imidazolium chloride salts **161** and **162** in 98% and 97% yields respectively (Scheme 3.42).

Scheme 3.42

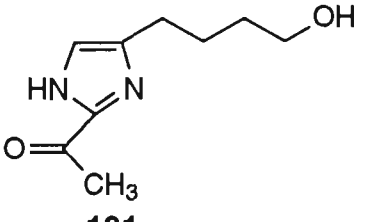


The optical rotations of the triols **161** and **162** were essentially equal and opposite. Triol **161** had a negative rotation of -9.6° while **162** had an optical rotation of +9.8°.

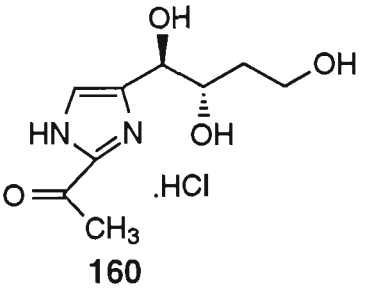
3.6 Conclusion

In summary, a general synthetic method has been developed for the synthesis of THI 1',2',4'-triol analogues. The introduction of the necessary side-chains onto the 4-position of imidazole could be readily achieved by either a palladium/alkyne coupling reaction or Stille coupling, with the latter the most effective. The Sharpless AD reaction gave 1,2-diols with enantioselectivities ranging from poor, for the (*Z*)-alkene precursors, to excellent for the (*E*)-alkenes. Stereochemical assignment of the chiral diols was made using Sharpless's mnemonic and verified *via* a modified Mosher ^{1}H NMR analysis.

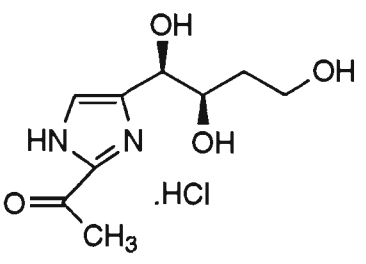
Acidic deprotection of the THI analogues gave four compounds for biological assessment. The simple monohydroxylated analogue **131** was obtained as the free base while the triol analogues **160**, **161** and **162** were isolated as imidazolium chloride salts.



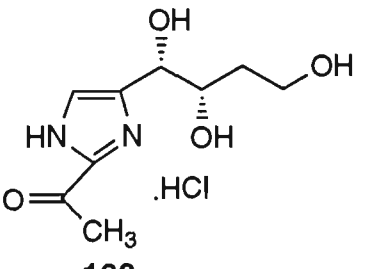
131



160



161



162

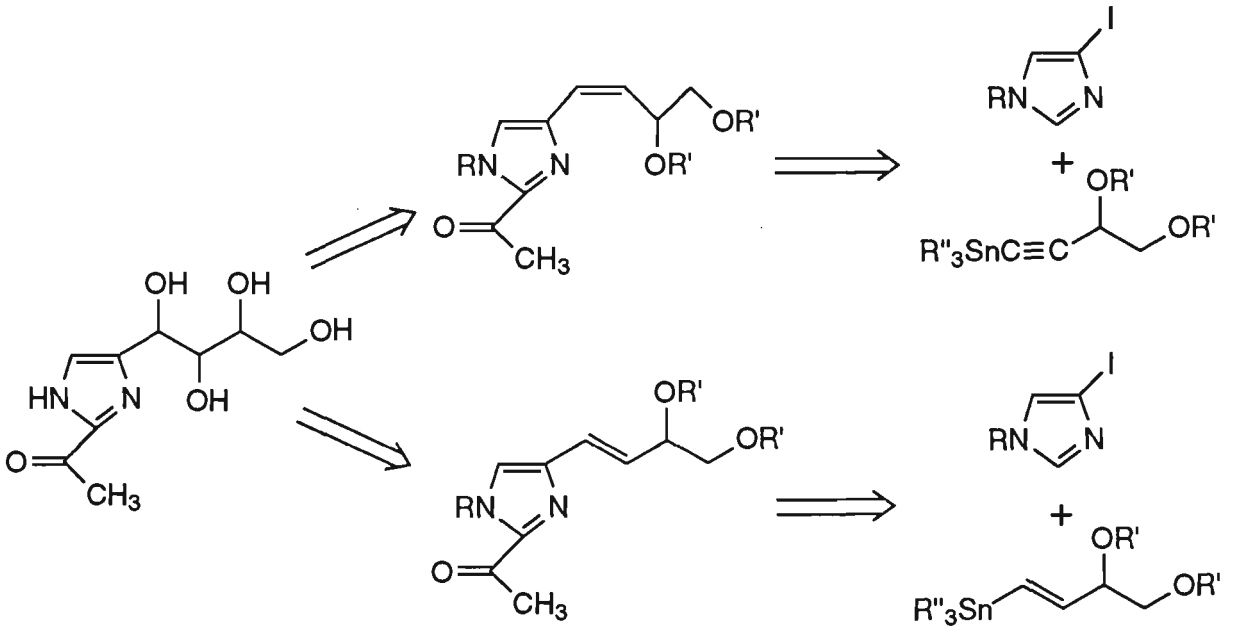
The methods used in this Chapter were found to be reproducible. Modifications of these synthetic techniques allowed other THI analogues, including the tetraol series, to be successfully synthesised as discussed in the following Chapter.

CHAPTER 4

SYNTHESIS OF THI TETRAOL ANALOGUES

The synthesis of the 1',2',4'-triol THI analogue series provided not only a number of valuable compounds for immunological assessment, but also served as a model system for the synthesis of the tetraol analogue series. The eight possible stereoisomers, including THI itself, were required to fully assess the biological significance of the tetrahydroxybutyl side-chain. A retrosynthetic analysis showed that the required synthetic strategy was essentially identical to that used in Chapter 3 (Scheme 4.1).

Scheme 4.1

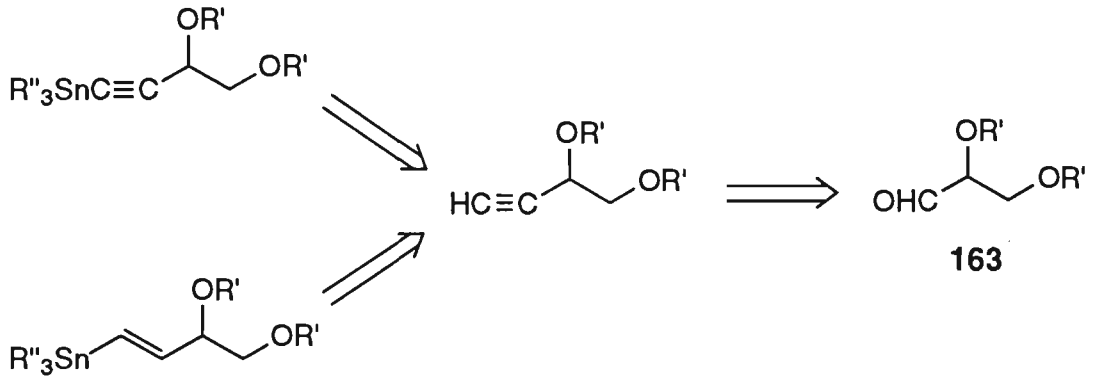


The major difference in obtaining the tetraol series is the introduction of a chiral side-chain containing two hydroxy groups. Once synthesised, the side-chains could be introduced onto the C4 imidazole position and manipulated to obtain the desired tetraols.

4.1 Synthesis of Chiral Side-Chains

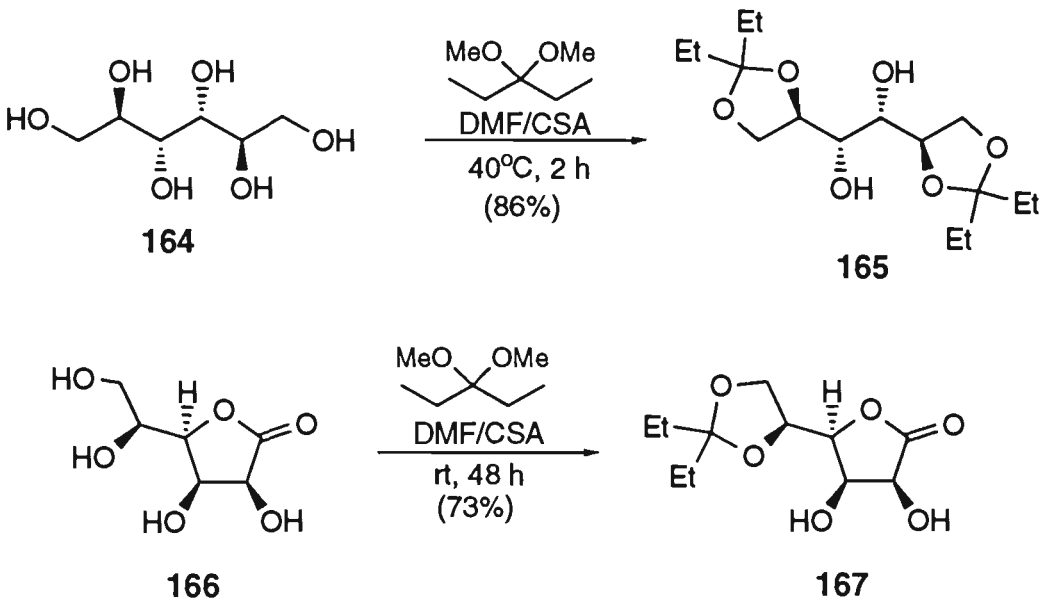
To obtain the necessary side-chains for the tetraol series, the enantiomeric (*R*)- and (*S*)-aldehydes **163** had to be prepared (Scheme 4.2).

Scheme 4.2



Synthesis of the enantiomeric aldehydes was achieved by the method of Schmid.[207] Commercially available D-mannitol **164** and L-gulono-1,4-lactone **166** in DMF were treated with 3,3-dimethoxypentane[208] in the presence of a catalytic amount of camphorsulfonic acid. Reaction for periods of 2 and 48 hours respectively, gave the dioxolanes **165** and **167** in 86% and 73% yields respectively (Scheme 4.3).

Scheme 4.3

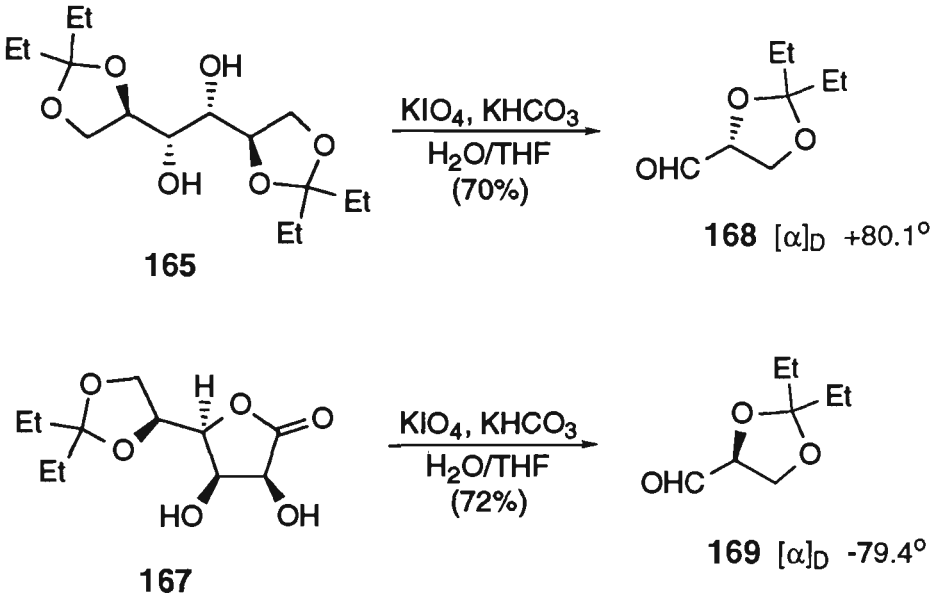


164 **165** **166** **167**

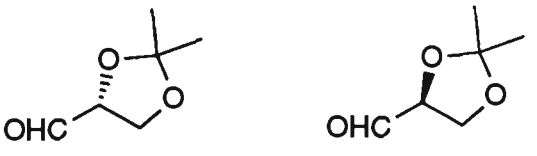
Cleavage of the glycol **165** and the lactone **167** was achieved *via* potassium periodate in aqueous solution. The use of KIO_4 for such cleavages is uncommon, with the sodium equivalent, $NaIO_4$, normally the reagent of choice. Schmid *et al.*[207] reported poor results with sodium periodate due to the highly acid sensitive nature of the substrates used. In solution, $NaIO_4$ forms a buffered phase of pH 3.0-3.5, leading to a significant decomposition of both **165** and **167**. Potassium periodate, however, gives a higher pH (5-6) due to its low aqueous solubility (0.66 g / 100 mL at 13 °C).[209] Addition of 10 mole % $KHCO_3$ buffers the solution at pH 7.0-7.5, enabling oxidation of the glycol and lactone substrates without any ketal hydrolysis.[207]

Reaction of **165** and **167** with KIO_4 and 10 mole % $KHCO_3$ for 3 hours gave the enantiomeric aldehydes **168** and **169** in 70% and 72% yields respectively (Scheme 4.4). The optical rotations of the two aldehydes were essentially equal and opposite.

Scheme 4.4



Synthesis of the 2,2-diethyl dioxolanes **168** and **169** rather than the more common 2,2-dimethyl analogues **170** and **171** had the advantage of making the aldehydes more hydrophobic, thus enabling them to be readily extracted from the aqueous reaction mixture.

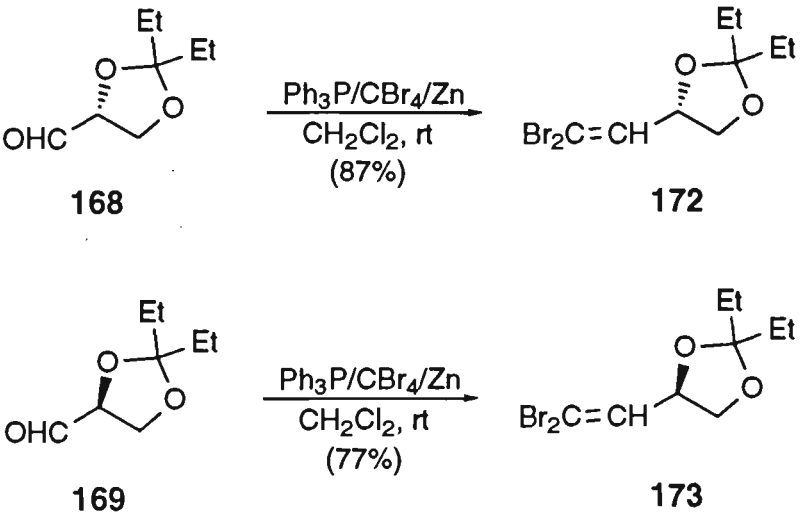


170 **171**

Conversion of the aldehydes **168** and **169** to 1,1-dibromoolefins as precursors to alkynes is usually achieved *via* treatment with triphenylphosphine and carbon tetrabromide.[210,211] The subsequent Wittig type reaction between the aldehyde and 1,1-dibromomethylenetriphenylphosphorane results in the synthesis of the dibromoolefin. In our hands, however, this method failed to yield significant quantities of the dibromoolefin equivalents of **168**

and **169**. Products obtained were contaminated with large quantities of triphenylphosphine residues which were difficult to remove. An improvement of this technique was to prepare the Ph_3P/CBr_4 Wittig reagent in the presence of zinc dust.[212] Triphenylphosphine, carbon tetrabromide and zinc dust in anhydrous dichloromethane were stirred vigorously for 24 hours before addition of the aldehydes **168** and **169**. Reaction for a further 24 hours at ambient temperature gave the 1,1-dibromoolefins **172** and **173** in 87% and 77% yields respectively[212] (Scheme 4.5).

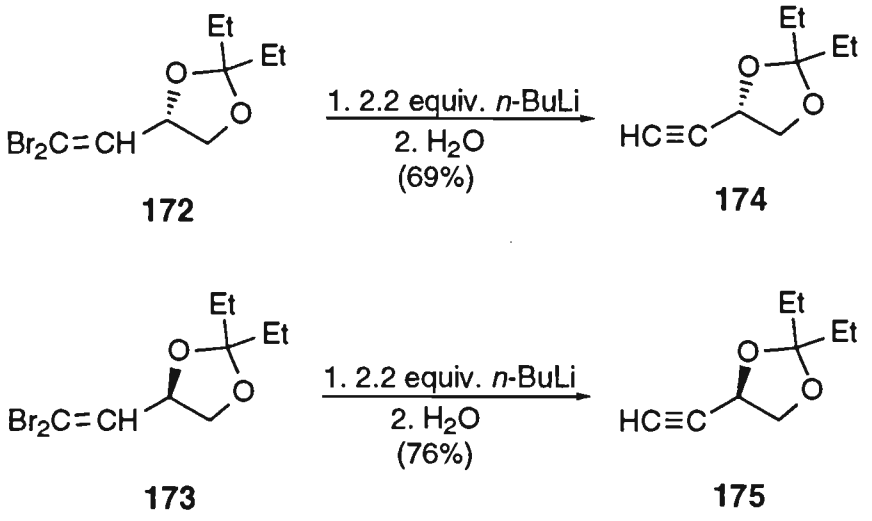
Scheme 4.5



Inclusion of zinc dust into the reaction mixture assists formation of the Wittig reagent and generates $ZnBr_2$ which presumably coordinates the aldehyde, thereby enhancing the reaction rate. The use of zinc allowed lower quantities of triphenylphosphine to be used, however, it was still necessary to utilise 3 molar equivalents of Ph_3P, CBr_4 and Zn. Lower quantities resulted in an incomplete consumption of the aldehyde after 24 hours with accompanying low yields of the 1,1-dibromoalkene.

Reaction of the olefins **172** and **173** with 2.2 molar equivalents of *n*-BuLi in anhydrous THF followed by quenching with water gave the alkynes **174** and **175** in 69% and 76% yields respectively[210,212] (Scheme 4.6). The alkynes were isolated by bulb-to-bulb distillation to give the enantiomeric pair as clear oils.

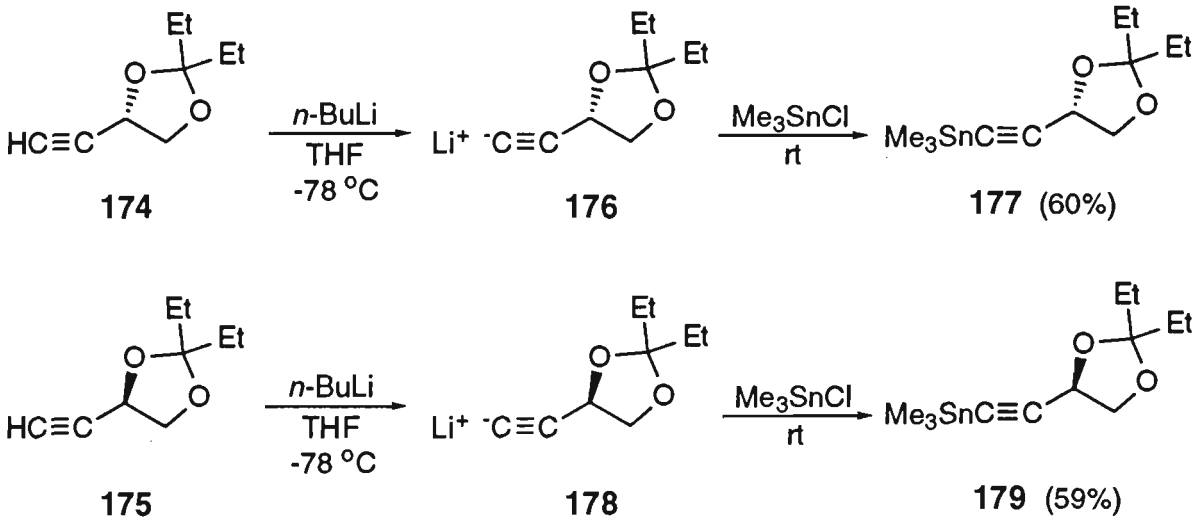
Scheme 4.6



4.2 Synthesis of Chiral Stannanes for use in the Stille Reaction

In order to obtain both the (*Z*)- and (*E*)-alkene precursors for use in the Sharpless AD reaction, the chiral alkynes **174** and **175** were converted to their alkynyl and (*E*)-alkenylstannanes. Alkynes **174** and **175** were reacted with *n*-BuLi in anhydrous THF to create the carbanions **176** and **178**. Quenching with a solution of Me_3SnCl in THF gave the stannanes **177** and **179** in 60% and 59% yields respectively[150] (Scheme 4.7).

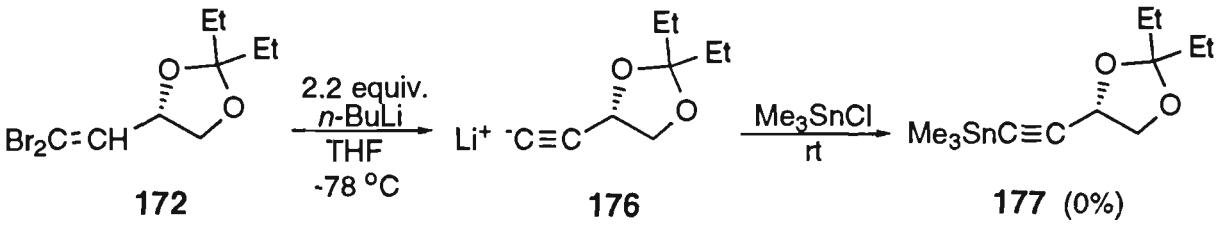
Scheme 4.7



The carbanions **176** and **178** were remarkably unreactive towards the electrophilic stannane. Reaction occurred upon warming to ambient temperature and was complete once LiCl precipitation ceased. Both stannanes were isolated as bright, fluorescent green oils upon distillation from the black, crude product. The unusual colour of the stannanes slowly dissipated upon standing to give a dull yellow oil after several days. Redistillation, however, gave the originally coloured material which was used directly in the Stille

coupling reaction. Attempts to convert the 1,1-dibromoolefin **172** directly to the stannane **177** by reaction with 2.2 molar equivalents *n*-BuLi followed by Me_3SnCl failed, resulting only in the isolation of the alkyne **174** (Scheme 4.8).

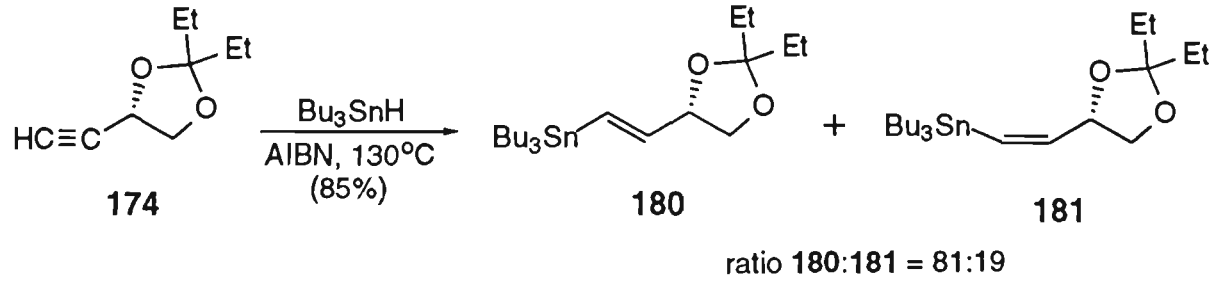
Scheme 4.8



172 **176** **177** (0%)

The (*E*)-vinylstannanes were synthesised *via* a hydrostannylation reaction.[155] The alkyne **174** was reacted with Bu_3SnH and catalytic AIBN at 130 °C to give the (*E*)- and (*Z*)-vinylstannanes **180** and **181** in 85% overall yield, with an *E:Z* ratio of 81:19 (Scheme 4.9). Higher reaction temperatures were not trialed, as hydrostannylation results obtained from the alkyne **121** indicated that temperature increases above ca. 130 °C was unlikely to lead to a significantly improved *E:Z* ratio.

Scheme 4.9



174 **180** **181**

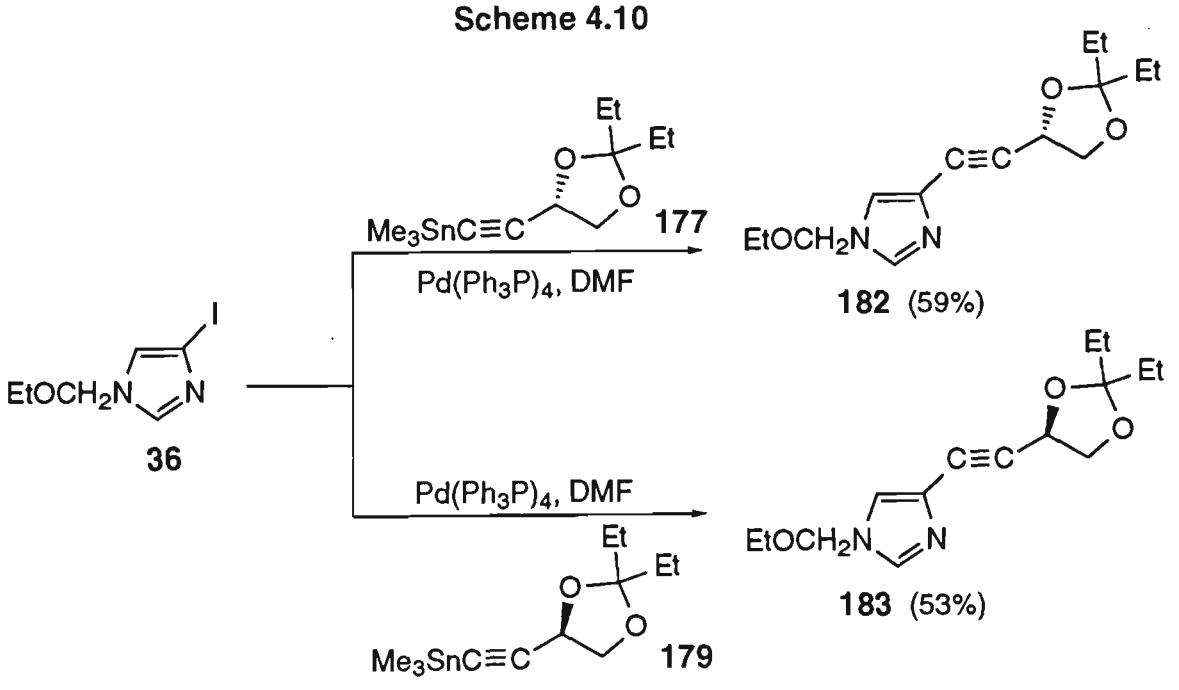
ratio **180**:**181** = 81:19

4.3 Synthesis of Chiral Olefinic Imidazole Substrates

4.3.1 Synthesis of (Z)-Alkenes

The synthesis of (Z)-alkenes for use in the Sharpless AD reaction was performed under the Stille conditions optimised in section 2.1 of Chapter 3. The iodoimidazole **36** was reacted with the alkynylstannanes **177** and **179** in the presence of $Pd(Ph_3P)_4$ in anhydrous DMF to give the coupled imidazoles **182** and **183** in 59% and 53% yields respectively (Scheme 4.10).

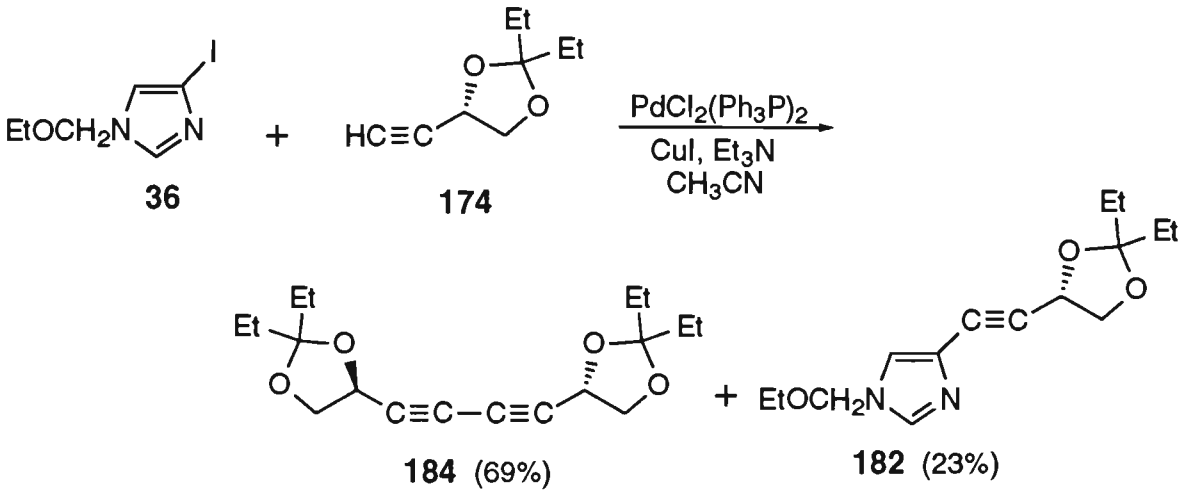
Scheme 4.10



Although the coupled products were isolated in modest yields, the Stille coupling method gave results that were superior to other attempted methods. In a comparative reaction, iodoimidazole **36** and the alkyne **174** were reacted under palladium/alkyne coupling conditions using $PdCl_2(Ph_3P)_2$, CuI and triethylamine in acetonitrile. The reaction was complete by TLC after 4 hours at reflux to give the target imidazole **182** in 23% yield, plus the undesired dialkyne

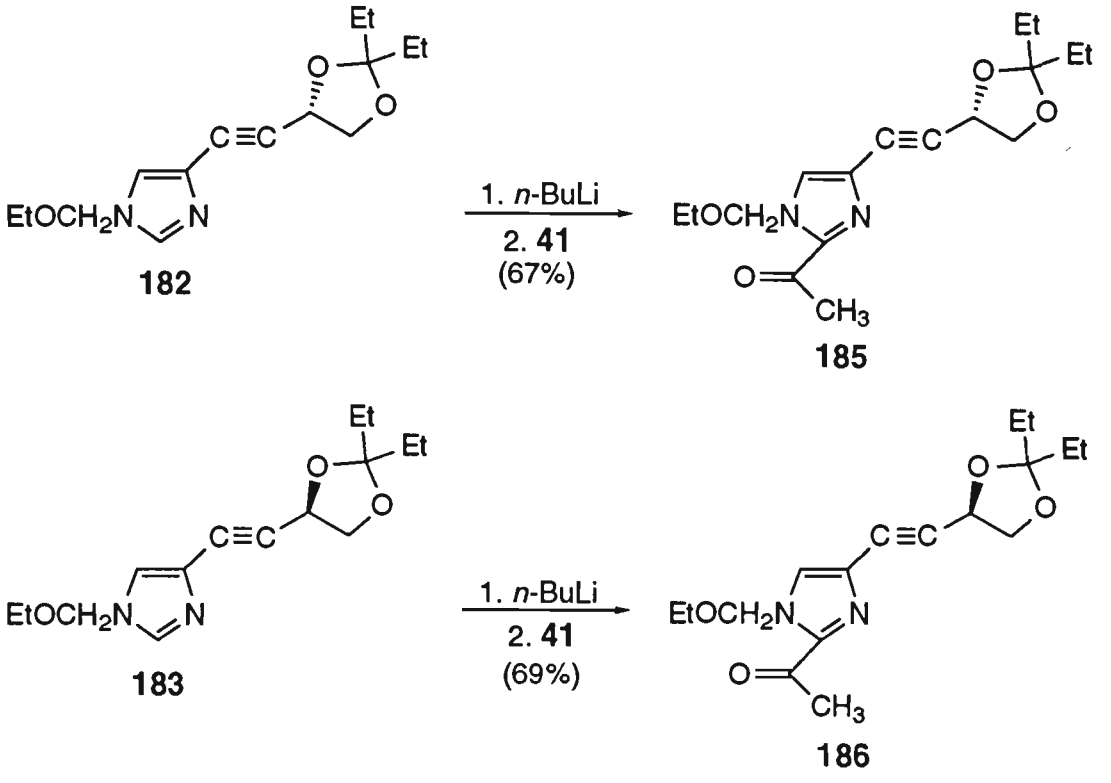
184 in 69% yield (Scheme 4.11). Dialkyne **184** was the major reaction product, despite the reaction being carried out using an excess of the iodoimidazole **36** over the alkyne **174**.

Scheme 4.11



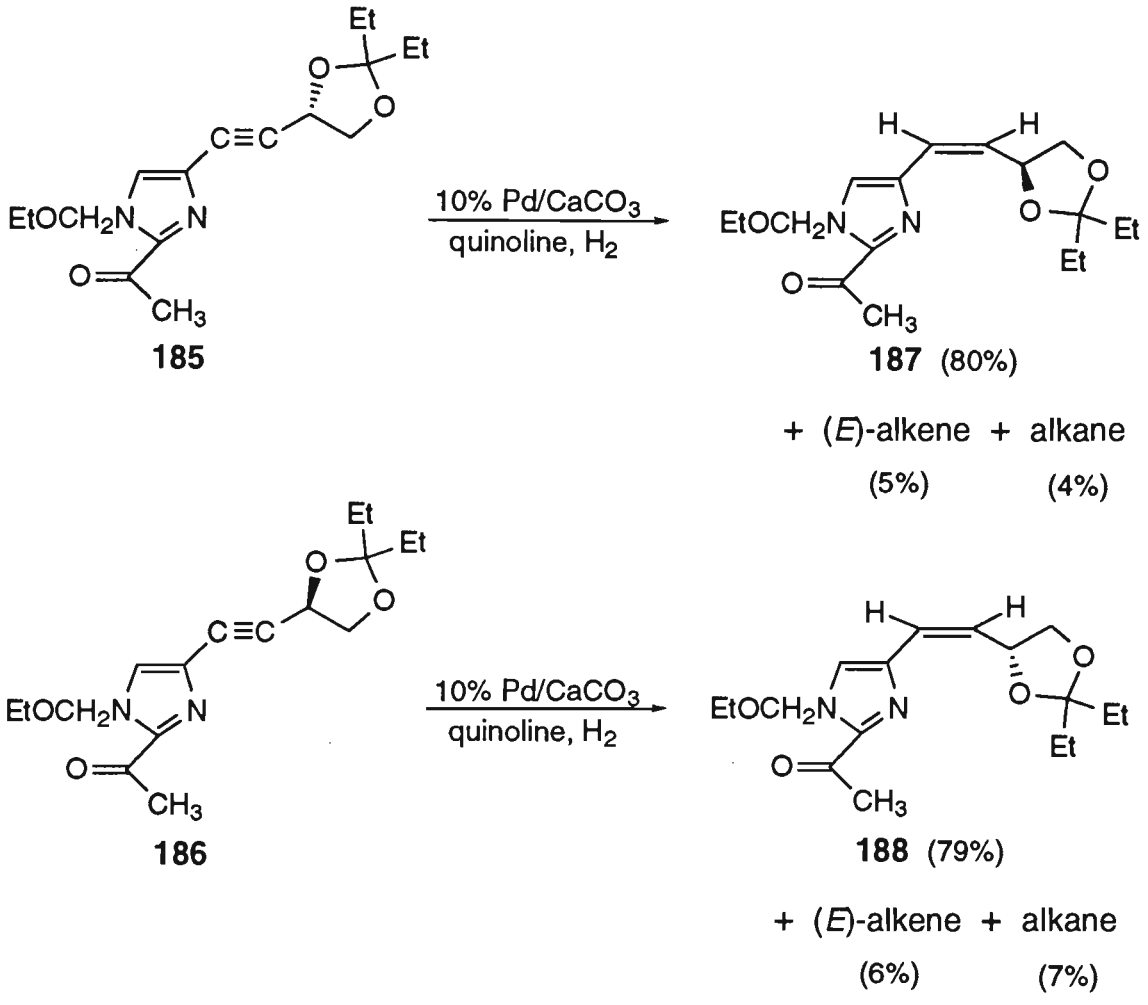
The coupled imidazoles **182** and **183** were treated with *n*-BuLi at -78 °C in THF to effect carbanion formation at C2, before quenching with the amide **41**. Imidazole **182** gave the methyl ketone **185** in 67% corrected yield, allowing for a 27% recovery of the starting imidazole. The enantiomeric imidazole **183** gave the methyl ketone **186** in a comparable 69% corrected yield with a small quantity of the starting imidazole (11%) also recovered (Scheme 4.12).

Scheme 4.12



Reduction of the alkynes **185** and **186** to their (*Z*)-alkene counterparts was performed *via* an hydrogenation reaction over Lindlar's catalyst.[142] Imidazole **185** was treated with 10% Pd on $CaCO_3$ and one molar equivalent of quinoline under a hydrogen atmosphere to give the (*Z*)-alkene **187** in 80% yield, plus a small quantity of the (*E*)-alkene (5%) and over-reduced alkane (4%). An identical reaction with the methyl ketone **186** gave its (*Z*)-alkene counterpart **188** in 79% yield, with the (*E*)-alkene (6%) and over-reduced alkane (7%) also isolated (Scheme 4.13). The hydrogenation was followed by ^1H NMR as the starting alkyne and (*Z*)-alkene had an identical R_f by TLC analysis.

Scheme 4.13



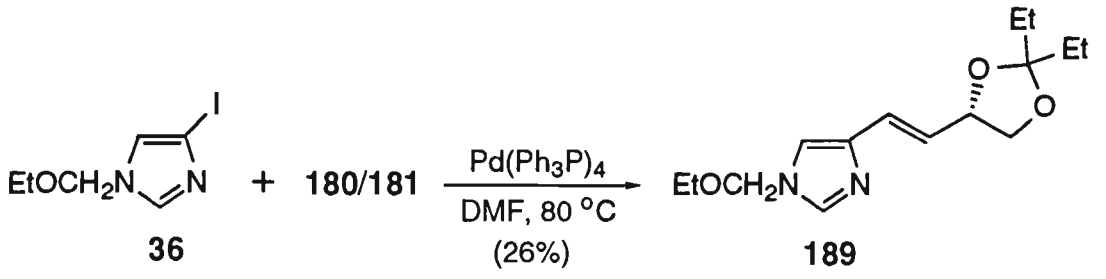
The olefinic proton H1' (ca. 6.39 ppm) for **187** and **188** displayed characteristic *cis*-alkene proton coupling across the double bond, with coupling constants of 1.2 Hz and 7.6 Hz to H3' and H2' respectively. The H2' signal at ca. 5.66 ppm displayed a complex multiplicity, with the coupling constants unable to be evaluated.

4.3.2 Synthesis of (*E*)-Alkenes

The synthesis of (*E*)-alkenes was initially carried out by application of the Stille reaction in a manner similar to that described in section 4.3.1 above. Iodoimidazole **36** and an 81:19 mixture of stannanes **180/181** were reacted in the presence of 10 mole % $Pd(Ph_3P)_4$ in

DMF to give the cross-coupled alkene **189** in a disappointingly low 26% yield (Scheme 4.14). None of the coupled (Z)-alkene was isolated from the reaction.

Scheme 4.14



The reaction was repeated under a variety of conditions to give **189** in 26-45% yield (Table 4.1).

Table 4.1 Yields of **189** obtained from the Stille coupling reaction of **36** and **180/181** under various conditions.

Run	*Solvent*[a]	*Catalyst*	*Yield (189)*
1	DMF	$Pd(Ph_3P)_4$	26%
2	THF	$Pd(Ph_3P)_4$	28%
3	Acetonitrile	$Pd(Ph_3P)_4$	31%
4	DMF	$Pd_2(dba)_3$, $AsPh_3$, CuI	45%

[a]All reactions carried out in sealed reaction vessels at 80 °C under argon.

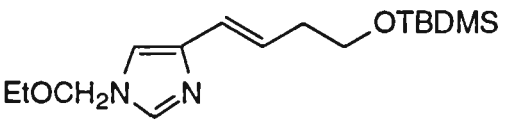
The coupling reaction carried out in DMF solvent gave a lower yield than that performed in THF or acetonitrile. This result is contrary to that found in section 3.2.1 above, in which DMF gave superior results to all other solvent systems trialed. The coupling reaction that provided the highest yield of **189** used a novel ligand system involving 5 mole % $Pd_2(dba)_3$, 10 mole % $AsPh_3$ and 10 mole % CuI

as a co-catalyst. The so-called 'ligandless' catalyst $Pd_2(dba)_3$[213] has received considerable attention over the last few years due to its ability to enhance reaction rates.[214] It is recognised that ligands which readily dissociate from Pd(II) complexes produce the fastest coupling rates. Farina *et al.*[214] have carried out an extensive study on Stille coupling rates using $Pd_2(dba)_3$ in the presence of numerous ligand systems. It was found that $Pd_2(dba)_3$ in the presence of $AsPh_3$ produced reaction rates almost 1500 times that of $Pd(Ph_3P)_4$. Thus, reactions were able to proceed to completion before decomposition of the palladium catalyst occurred.

The use of CuI as a co-catalyst in the Stille reaction has also seen dramatic improvements in the Stille reaction over recent years.[158,215] Under certain conditions, copper iodide reacts with organostannanes to produce transient organocopper species.[216] The cuprates are presumably more reactive than their organostannane counterparts towards transmetallation with palladium, a key step in the cross-coupling reaction, and lead to enhanced reaction rates and yields.

Despite an improvement in the synthesis of **189** using the $Pd_2(dba)_3$ ligand system, the low yields still obtained were hindering progress towards the final target 1',2',3',4'-tetraol molecules. The major obstacle to the reaction seemed to be the sterically hindered stannane **180** and its associated bulky tributyltin moiety. Although this had not presented a problem in the synthesis of imidazole **136** from the tributylstannane **132** and iodoimidazole **36**, the sterically hindered stannane **180** with the large pentylidene protecting group was reluctant to react.

132



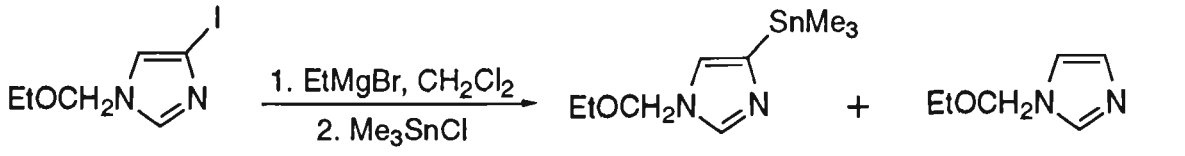
136

Synthesis of the trimethyltin analogue of **180** seemed the obvious solution to this synthetic dilemma. Hydrostannylation of the alkyne **174** with Me_3SnH[217]/AIBN, however, would have most likely lead to a mixture of (*E*)- and (*Z*)-vinylstannanes with low stereoselectivity.[155] While Bu_3SnH gave an acceptable ratio of (*E*)- and (*Z*)-vinylstannanes (81:19), the sterically less hindered trimethyltin moiety would fair considerably worse, thereby achieving little by its synthesis.

A second alternative was to convert the iodoimidazole **36** into its trimethyltin equivalent, and the tributylstannane **180** into the (*E*)-vinyliodide. The subsequent Stille coupling was expected to give the cross-coupled product **189** in a considerably improved yield.[151]

Iodoimidazole **36** was treated with ethylmagnesium bromide in anhydrous dichloromethane for 30 minutes at ambient temperature.[93] Quenching of the C4 carbanion with an excess of Me_3SnCl gave the organostannane **190** in 66% yield and the reduced imidazole **46** in 16% yield (Scheme 4.15).

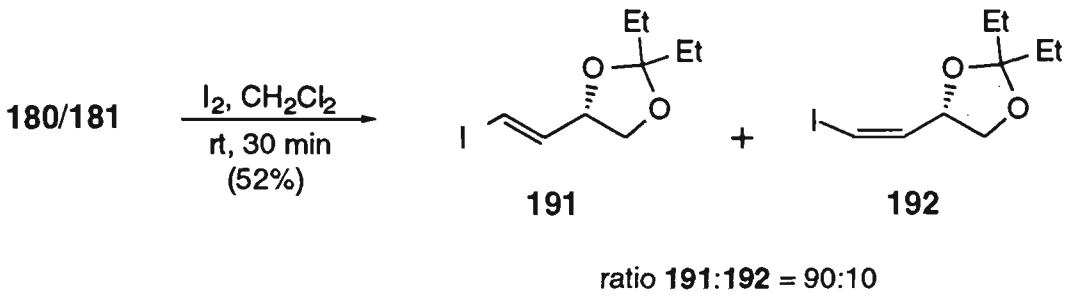
Scheme 4.15



36 **190** (66%) **46** (16%)

Conversion of the (*E*)-vinylstannane **180** to its vinyliodide was achieved *via* treatment with iodine.[218] An 81:19 mixture of vinylstannanes **180/181** in anhydrous dichloromethane was treated with an excess of iodine for 30 minutes at ambient temperature. Removal of excess iodine and Bu_3SnI with saturated aqueous $Na_2S_2O_3$ and KF gave a 90:10 mixture of the (*E*)- and (*Z*)-vinyliodides **191** and **192** in 52% overall yield (Scheme 4.16).

Scheme 4.16

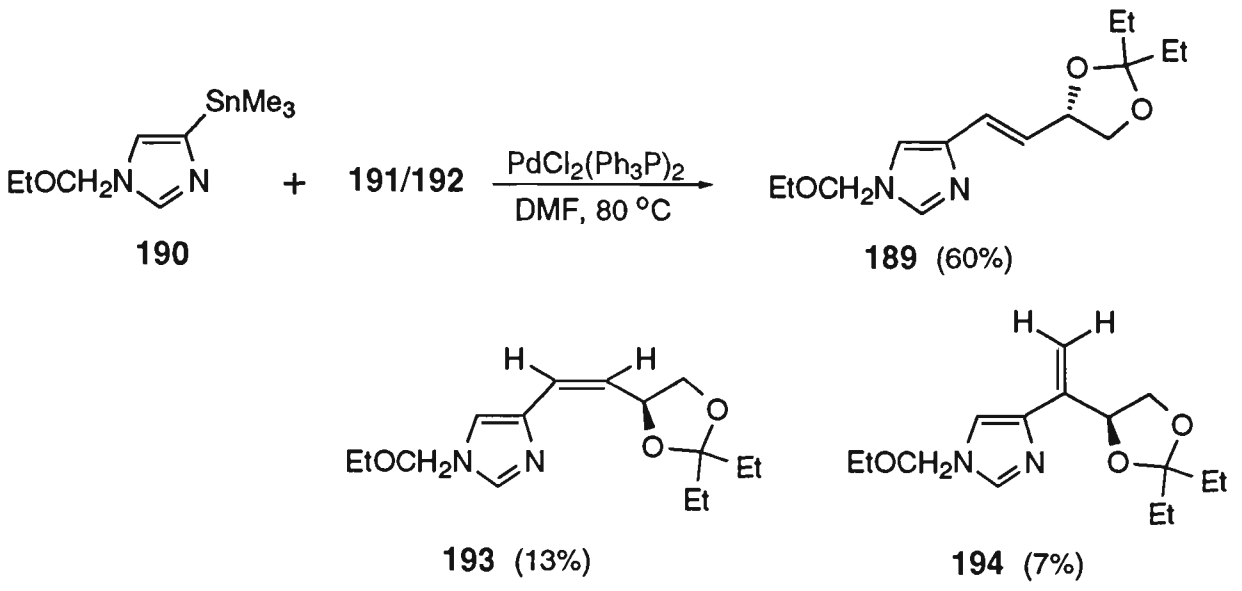


191 **192**

ratio **191**:**192** = 90:10

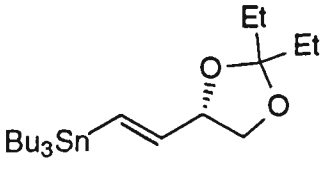
The arylstannane **190** was treated with a 90:10 mixture of the vinyliodides **191/192** in the presence of 5 mole % $PdCl_2(Ph_3P)_2$ in DMF. Three products were isolated from the coupling reaction. The target (*E*)-alkene **189** and coupled (*Z*)-alkene **193** were isolated in 60% and 13% yields respectively based on the starting imidazole **190**. The third product obtained was the 1,1-dialkene **194**, isolated in 7% yield. This minor product might arise *via* an initial Heck type reaction followed by deiodination (Scheme 4.17). The terminal olefin protons of **194** were present as apparent triplets at 5.73 ppm and 5.45 ppm. Both protons displayed a coupling of 1.6 Hz, consistent with that of *gem*-olefinic protons.[194]

Scheme 4.17



4.3.3 Direct Synthesis (*E*)-Trimethylvinylstannanes for use in the Stille Cross-Coupling Reaction

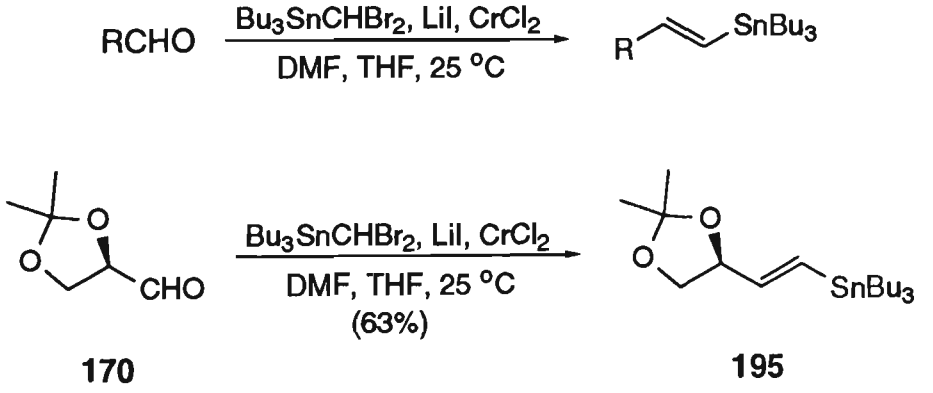
Although the reaction between the arylstannane **190** and vinyliodide **191** produced the desired (*E*)-alkene **189** in an improved 60% yield (Scheme 4.17), the additional reactions necessary to complete this synthetic sequence had reduced the overall yield of **189**, thereby rendering the route unviable. None the less, the reaction demonstrated the beneficial effect of utilising a trimethyltin moiety rather than the more sterically hindered tributyltin equivalent. Solving this synthetic problem thus hinged upon finding an efficient route to the trimethyltin equivalent of **180**.



180

Recently Hodgson reported a method for converting aldehydes directly to (*E*)-tributylvinylstannanes using $Bu_3SnCHBr_2$, chromium(II) chloride and lithium iodide[219,220] (Scheme 4.18). Of significance to this project, however, was the successful conversion of the aldehyde **170** to its (*E*)-vinylstannane **195** in 63% yield with no loss of optical purity.[220] It was therefore hoped that by an analogous route, this method could be adapted to produce (*E*)-trimethylvinylstannanes directly from the aldehydes **168** and **169**.

Scheme 4.18



170 **195**

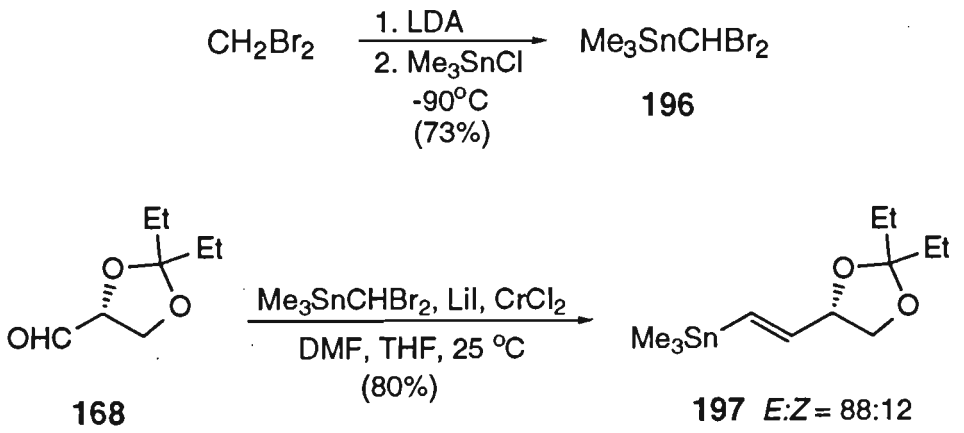
The dibromomethylstannane **196** was prepared from the modified literature procedure of Villieras *et al.*[221] Dibromomethane in a 1:1 solution of anhydrous THF/ether was treated with LDA at -90 °C. Quenching of the resulting carbanion with trimethyltin chloride gave the stannane **196** in 73% yield (Scheme 4.19).

The reaction was found to be extremely sensitive to changes in temperature and solvent. Executing the reaction at the more convenient -78 °C (dry ice/acetone) rather than -90 °C resulted in diminished yields of **196**, which was difficult to separate from unreacted Me_3SnCl. Similarly, changes in the THF/ether solvent

ratio from 1:1 lead to lower yields of the product stannane. The use of anhydrous THF only as reaction solvent resulted in an almost quantitative recovery of Me_3SnCl, with only trace quantities of **196** detected by ^1H NMR.

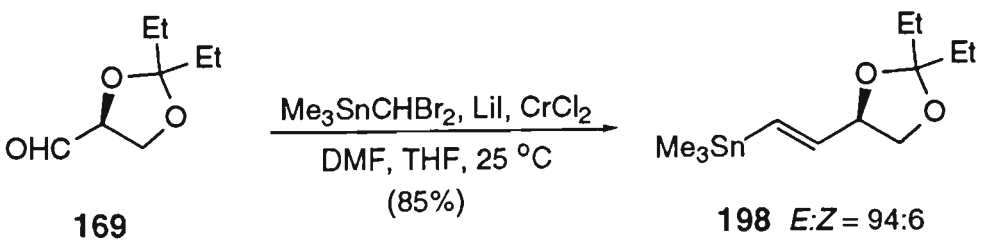
Treatment of freshly distilled aldehyde **168** with $Me_3SnCHBr_2$, $CrCl_2$ and LiI in THF/DMF gave the trimethylvinylstannane **197** in an 80% yield and an improved *E:Z* ratio of 88:12 (Scheme 4.19).

Scheme 4.19



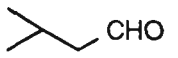
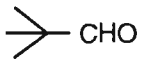
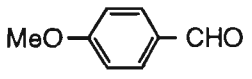
The equivalent reaction using the aldehyde **169** gave the trimethylvinylstannane **198** in 85% yield, with an improved *E:Z* ratio of 94:6 (Scheme 4.20).

Scheme 4.20



To examine this new system further, a number of representative aliphatic aldehydes were treated with $Me_3SnCHBr_2$ in the presence of $CrCl_2$ and LiI[222] (Table 4.2). In all cases the desired trimethylvinylstannanes were obtained in good yield and high purity by bulb-to-bulb distillation. The trimethylvinylstannanes were isolated as a mixture of (*E*)- and (*Z*)-isomers, with the *E:Z* ratio improved as the steric demand of the aldehyde was increased. Compared with the method of Hodgson using $Bu_3SnCHBr_2$, this method gave improved yields of the vinylstannanes, however, the former method gave only the (*E*)-isomer. For example, the reaction of pivaldehyde with $Bu_3SnCHBr_2$, $CrCl_2$ and LiI has been reported to give only a 6% yield of the (*E*)-tributylvinylstannane,[219] whereas using $Me_3SnCHBr_2$ in this study gave a ten fold increase in yield of the trimethylstannane equivalent (60%, *E:Z* = 84:16). In the case of *p*-methoxybenzaldehyde a mixture of *p*-methoxystyrene and unreacted aldehyde were isolated. None of the target arylstannane was detected by ^1H NMR. A similar result was obtained by Hodgson with benzaldehyde.[219]

Table 4.2 Direct conversion of representative aldehydes to vinylstannanes *via* $Me_3SnCHBr_2$.

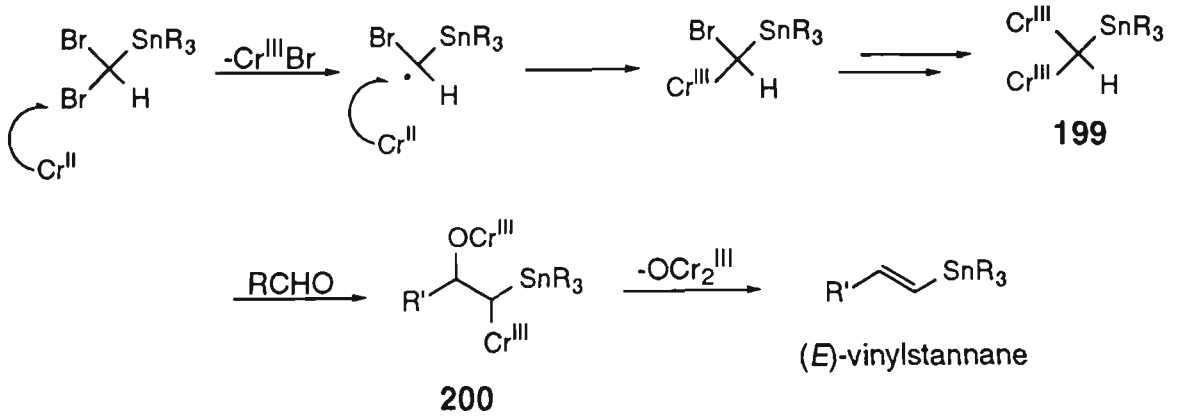
Aldehyde	*Yield*[a] *(%)*	*(E) : (Z)*[b]
168	80	88 : 12
169	85	94 : 6
	77	69 : 69 : 31
	82	73 : 27
	60	84 : 16
	0[c]	-

[a] Isolated yield after distillation. [b] Determined by 1H NMR.

[c] p-Methoxystyrene formed.

The reaction is believed to proceed *via* two successive halogen atom transfers to $CrCl_2$, with the intermediate radical immediately reduced by Cr(II) to give the *gem*-dichromium species **199**.[223] Addition of the aldehyde results in the formation of the chromium salt **200**, which leads predominantly to the (*E*)-vinylstannane following β-elimination of dichromium oxide[220] (Scheme 4.21).

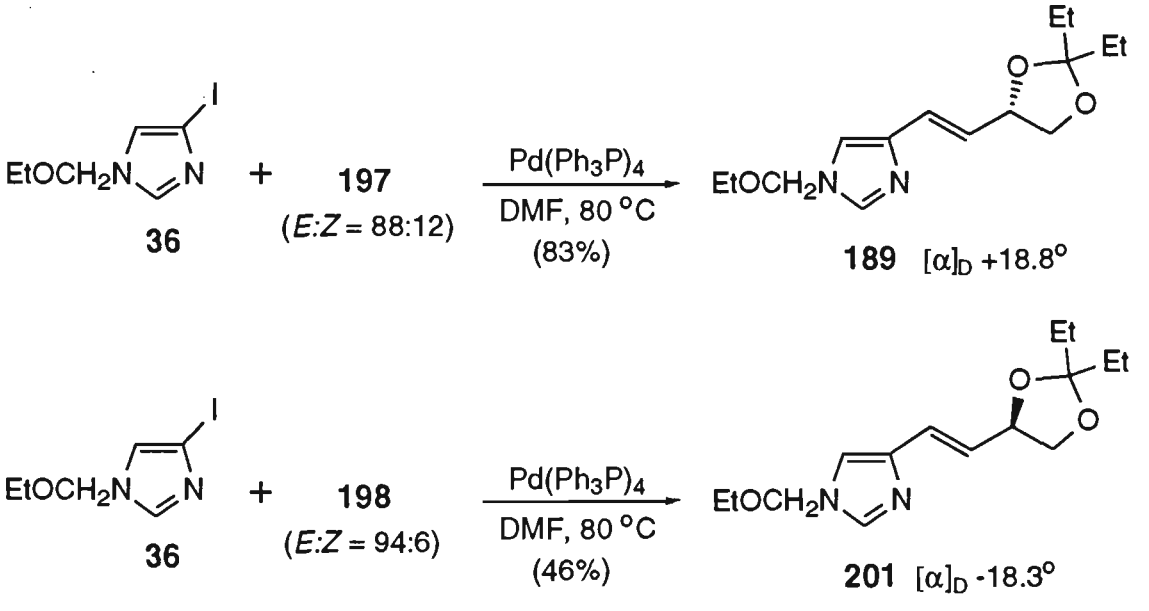
Scheme 4.21



4.3.4 (*E*)-Alkene Synthesis *via* Trimethylvinylstannanes

The successful synthesis of **197** and **198** removed much of the steric demand of the tributylstannanes which had hindered the Stille cross-coupling reaction. The iodoimidazole **36** was treated with the trimethylstannane **197** (*E:Z* = 88:12) in the presence of $Pd(Ph_3P)_4$ in anhydrous DMF. Reaction for 12 hours at 80 °C gave the coupled imidazole **189** in a good 83% yield. None of the (*Z*)-isomer was isolated (Scheme 4.22). An analogous reaction with a 94:6 mixture of (*E*)- and (*Z*)-vinylstannanes **198** gave the cross-coupled product **201** in a significantly lower 46% yield, with none of the (*Z*)-isomer isolated (Scheme 4.22).

Scheme 4.22



The ^1H NMR coupling constants for the olefinic protons H1' and H2' of both **189** and **201** were identical and characteristic of *trans*-alkenes.[194] H1' and H2' were coupled across the double bond with a coupling constant of 15.6 Hz. The signal for H2' was present as a

doublet of doublets, with a coupling to the H3' proton of 7.5 Hz (Figure 4.1).

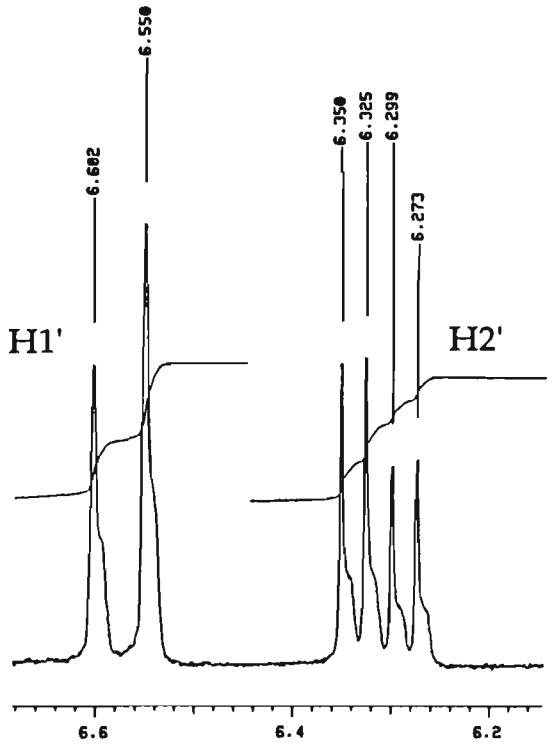
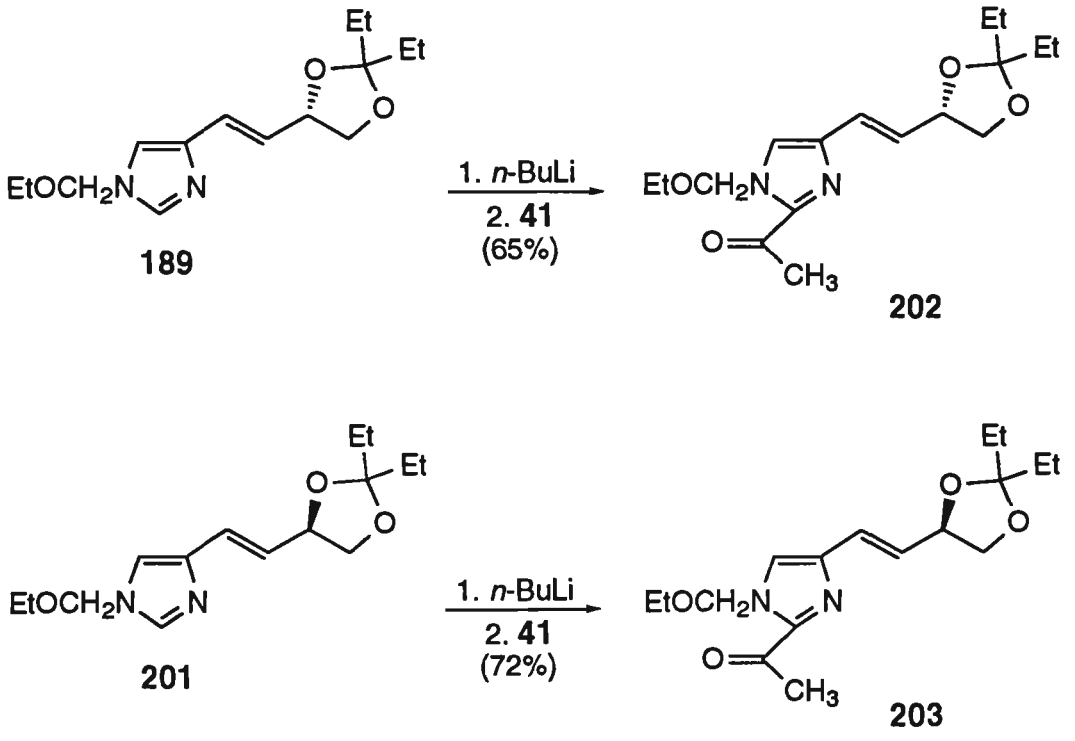


Figure 4.1 ^{1}H NMR olefinic coupling pattern of H1' and H2' for the *trans*-alkene **189** in $CDCl_3$.

Conversion of the (*E*)-alkenes **189** and **201** to their methyl ketone equivalents was performed as previously described. The imidazoles **189** and **201** were treated with *n*-BuLi in anhydrous THF. Quenching of the resulting C2 imidazole carbanions with a solution of the amide **41** in THF gave the methyl ketones **202** and **203** in 65% and 72% yields respectively (Scheme 4.23). The (*E*)-alkene **201** gave a 19% recovery of starting imidazole.

Scheme 4.23


Et
Et
O
O
EtOCH2N
N
189
1. n-BuLi
2. 41
(65%)
Et
Et
O
O
EtOCH2N
N
O
CH3
202
Et
Et
O
O
EtOCH2N
N
201
1. n-BuLi
2. 41
(72%)
Et
Et
O
O
EtOCH2N
N
O
CH3
203

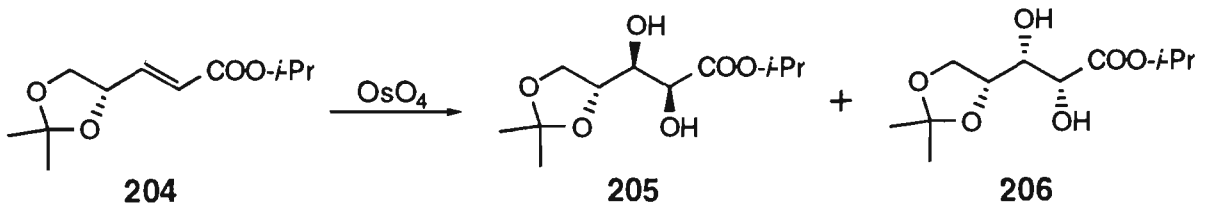
4.4 Sharpless AD of Chiral (Z)-Alkenes

Application of the Sharpless AD reaction to alkenes containing a chiral centre leads to the synthesis of two diastereomers. If the stereogenic centre is distant from the double bond, then its presence may have little effect on the subsequent AD reaction. For molecules containing the centre in close proximity to the alkene moiety, however, the possibility exists for the 'matching and mismatching' of diastereofacial selectivity with the selectivity of the AD process.[224]

To maximise the effectiveness of the AD process, a knowledge of the diastereoselectivity for a given olefin is needed. The alkene substrate can thus be correctly matched to the appropriate cinchona alkaloid ligand to obtain high diastereofacial selectivity. In many cases this can be done by an inspection of the molecular model of the chiral olefin, which may suggest a diastereoselective preference for the dihydroxylation.[175] The best way to determine the intrinsic diastereoselectivity, however, is to perform the dihydroxylation in the absence of the chiral ligand and determine the ratio and stereochemistry of the resulting diols.[170] One of the simplest examples of this work was carried out by Morikawa and Sharpless using the chiral allylic ether **204**[175,225] (Scheme 4.24). In the absence of chiral ligands, the dihydroxylation gave a 2.8:1 ratio of the diols **205** and **206** respectively, with osmium approaching preferentially from the upper, less hindered face of the olefin. When this reaction was performed in the presence of the matched ligand $(DHQD)_2PHAL$, a 39:1 ratio of diols **205/206** was achieved.

An identical reaction using the mismatched ligand $(DHQ)_2PHAL$, however, resulted in a 1:1.3 ratio of the diols **205/206**.

Scheme 4.24

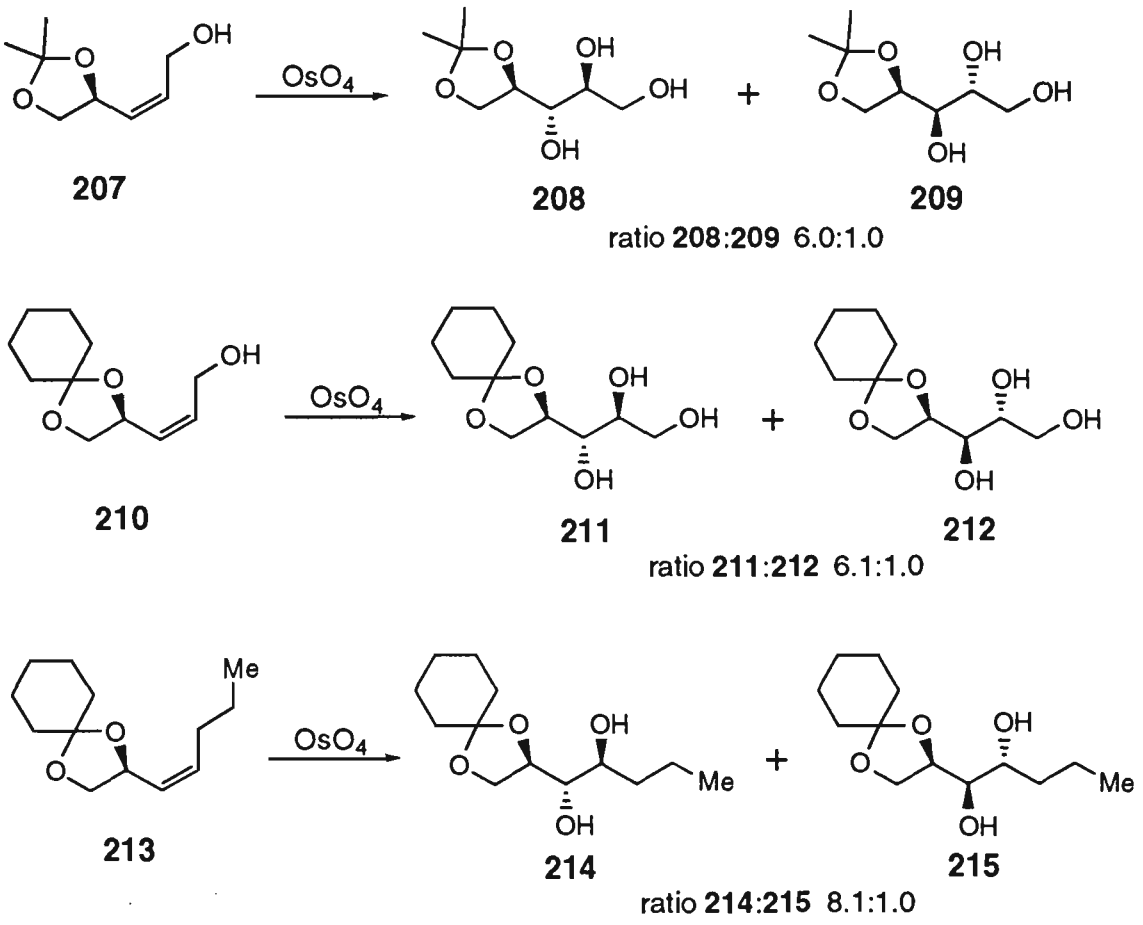


204 **205** **206**

Reagent	Ratio 205:206
no ligand	2.8:1
$(DHQD)_2PHAL$	39:1
$(DHQ)_2PHAL$	1:1.3

Very little work has been done on the dihydroxylation of chiral (*Z*)-alkenes, with only one example found in the literature which utilised chiral ligands.[226] The dihydroxylation of the (*Z*)-alkenes **207**, **210** and **213**, however, provides an insight into the diastereoselectivity that could be expected for the (*Z*)-alkenes **187** and **188** used in this study.[227] When treated with catalytic OsO_4 in the absence of a chiral ligand, the alkenes **207**, **210** and **213** gave a mixture of diastereomeric diols (Scheme 4.25). In each case the major diol (**208**, **211** and **214**) resulted from OsO_4 attack at the alkene face *anti* to the chiral ether moiety.

Scheme 4.25



Based upon these results, it could be assumed that the diastereofacial selectivity of the chiral alkenes **187** and **188** also favours attack *anti* to the allylic ether moiety. The (*Z*)-alkenes used in this study, however, are considerably more complex than those in Scheme 4.25 above. The intrinsic diastereoselectivity of the system must therefore be evaluated with a high degree of confidence to enable correct assignment of stereochemistries and matching with the appropriate cinchona alkaloid ligand.

4.4.1 Diastereoselectivity of Chiral (*Z*)-Allylic Ethers

In general, the stereochemical outcome for reactions of allylic compounds can be predicted or accounted for *via* one of three allylic ground or transition state models.[228] The three models proposed by Kishi[227,229], Vedejs[230,231] and Houk[232,233,234] all predict the same stereochemical outcome for the OsO_4 dihydroxylation of (*Z*)-allylic ethers.

In the model of Kishi,[227] an eclipsed conformation is adopted, with the allylic C-H bond *syn* co-planar with the olefinic double bond (Figure 4.2). This conformation is considered to be preferred since it reduces 1,3-allylic strain.[235] The major dihydroxylation product then arises from the approach of OsO_4 to the face opposite to that containing the alkoxy group. Addition to this face reduces electrostatic interactions between the electron rich OsO_4 and the alkoxy group.

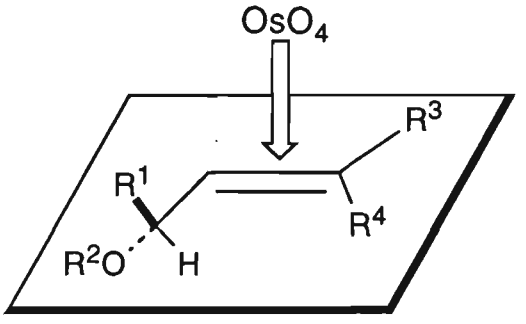
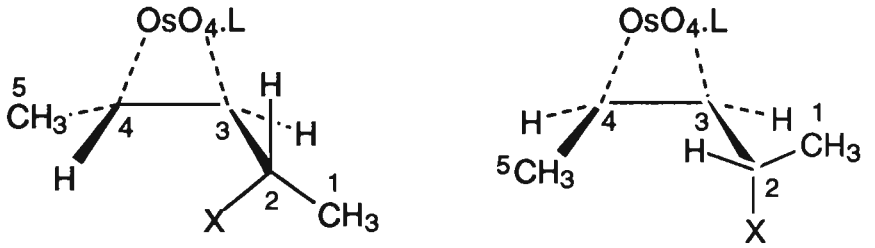


Figure 4.2 Kishi's model for OsO_4 addition to chiral allylic ethers.[227]

The model developed by Vedejs[230] varies depending upon the presence of an (*E*)- or (*Z*)-allylic ether moiety. The model is a refined version of Kishi's and takes into account steric interactions between the allylic ether and the osmium reagent in the reaction's

transition state. It also allows for the accompanying osmium ligands. For (*E*)-alkenes, the steric requirements for the osmium ligands are dominant and a conformation with the hydrogen at C2 near osmium is adopted. For (*Z*)-alkenes, however, ligand interactions can be reduced by distorting the osmium heterocycle towards the unsubstituted olefinic side. The dominant steric effects are now between the two alkene substituents, and the C2 hydrogen is faced into the double bond (Figure 4.3). The (*Z*)-alkene conformation is identical to that predicted by Kishi, as depicted in Figure 4.2 above.



(*E*)-alkene transition state (*Z*)-alkene transition state

Figure 4.3 Transition states for osmylation of (*E*)- and (*Z*)-alkenes with OsO_4 as proposed by Vedejs.[230]

The model of Houk[232] differs significantly from both of those proposed by Kishi and Vedejs. It is based upon the stereoselectivity of nitrile oxide cycloadditions to a variety of substituted alkenes. Experimental results and theoretical studies by Houk have lead to the proposal that the alkoxy group of chiral allylic ethers adopts an *inside* conformation, with the alkyl substituent (R^1) preferring the sterically less crowded *anti* position (Figure 4.4). With the alkene in this conformation, OsO_4 attacks from the opposite face to that containing the alkyl moiety.[228]

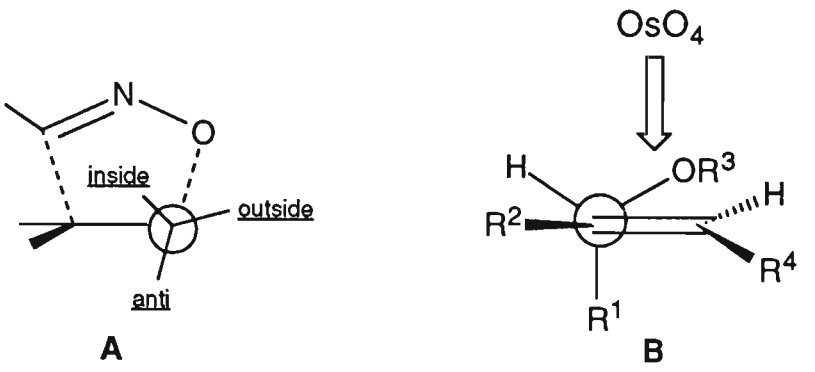
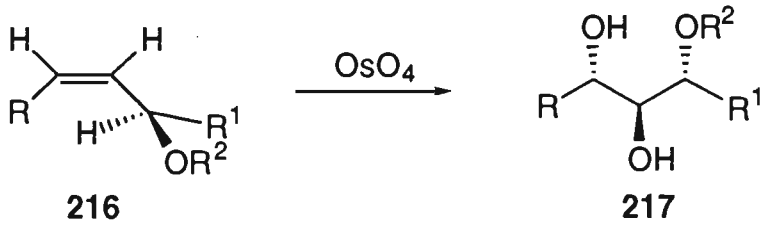


Figure 4.4 A: Houk's proposed model based upon nitrile oxide cycloadditions,[232] and **B**: Application to OsO_4 dihydroxylation.[228]

Application of the three models can be summarised in Figure 4.5. Addition of OsO_4 to the olefin **216** occurs at the same face in all three cases. The transition states proposed by Kishi and Vedejs are identical, with the allylic hydrogen adopting an inside conformation. The transition state proposed by Houk, while conformationally different, still leads to the same diol **217**.



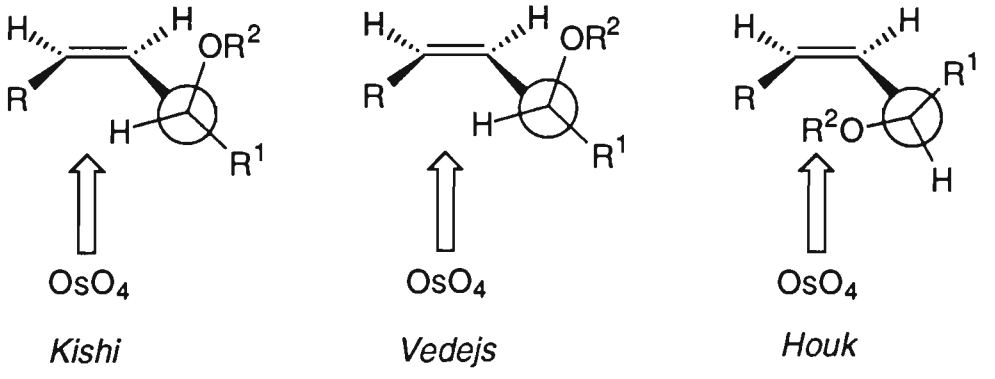
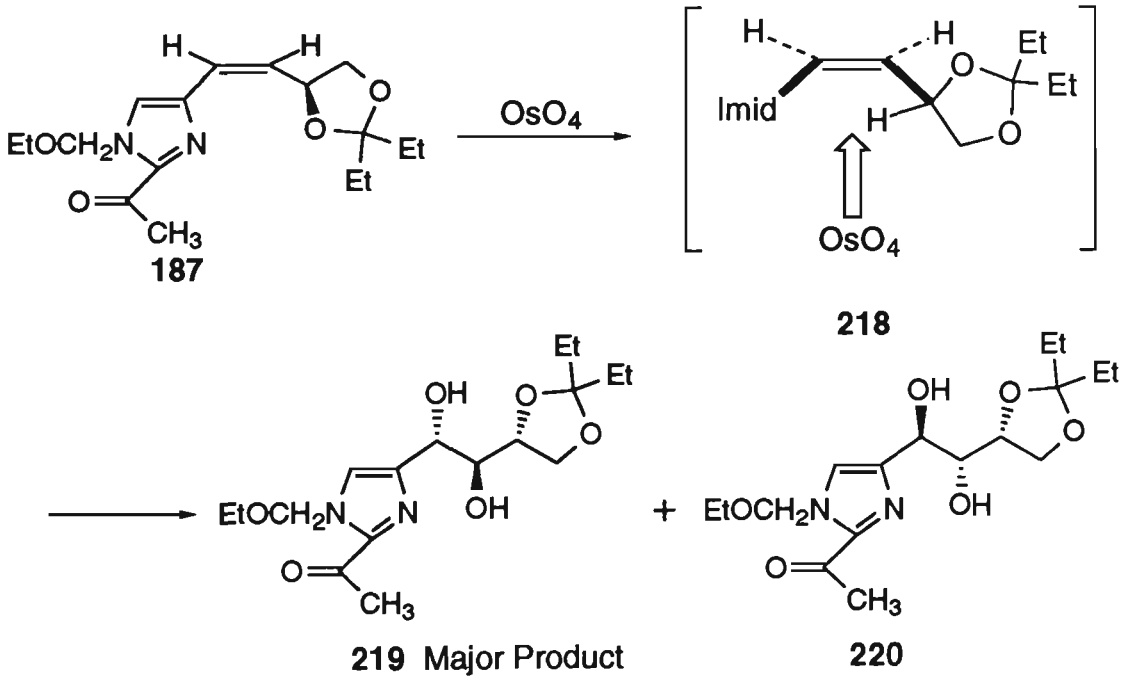


Figure 4.5 Osmylation of chiral (Z)-allylic ethers. Newman projections of the models of Kishi, Vedejs and Houk predict the same stereochemical outcome.

4.4.2 Dihydroxylation of the (Z)-Alkene 187

Construction of a molecular model of the alkene **187** shows that the adopted conformation is similar to that proposed by both Kishi and Vedejs for (Z)-allylic ethers (Figure 4.6). Using this conformation for the dihydroxylation of **187** with OsO_4 in the absence of a chiral ligand, there would be a slight preference for addition of OsO_4 to the α-face of the alkene, *anti* to the ether moiety as shown in Scheme 4.26. The diols **219** and **220** would thus be produced, with the former diol the major product.

Scheme 4.26



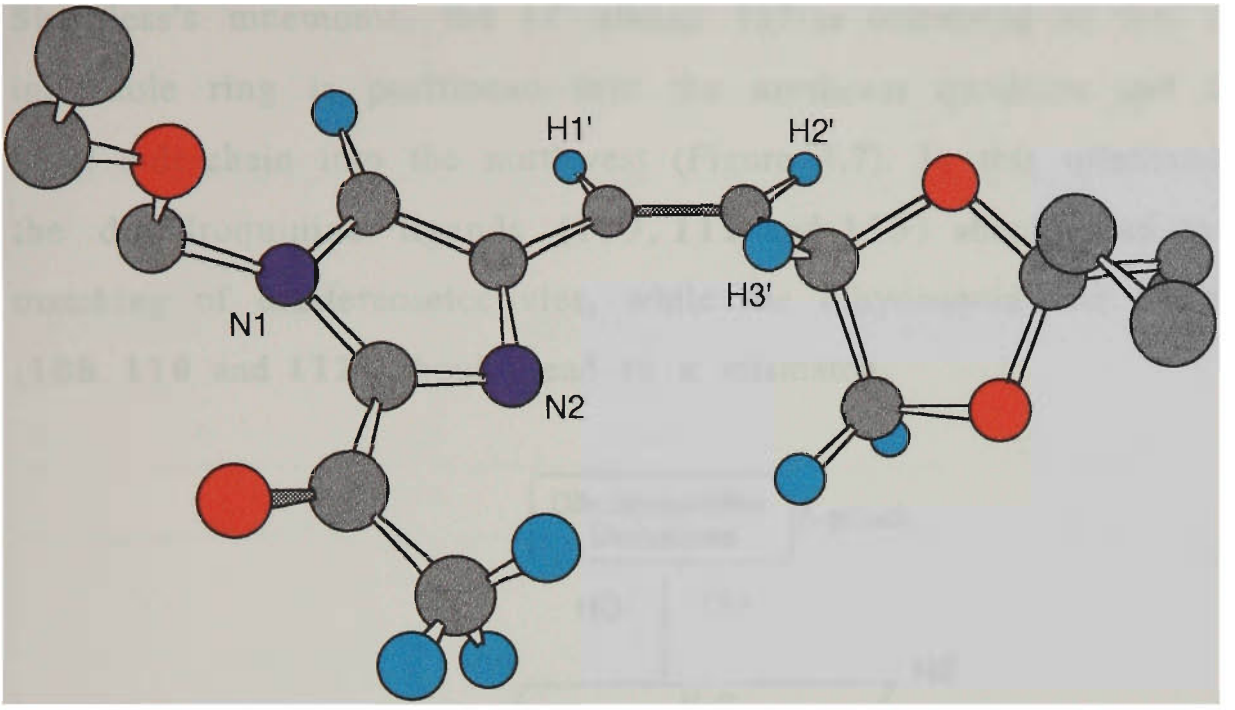


Figure 4.6 Molecular model of the (*Z*)-alkene 187. Conformation consistent with that proposed by Kishi with the allylic hydrogen H3' adopting an inside position. Ethoxymethyl and pentylidene protons omitted for clarity.

The (*Z*)-alkene 187 was treated with 3 mole % $K_2OsO_4.2H_2O$ at 0 °C in the presence of 3 molar equivalents of each of $K_3Fe(CN)_6$, K_2CO_3 and methanesulfonamide. The reaction was complete within 16 hours and gave a mixture of the diastereomeric diols 219 and 220 in a 2.1:1 ratio. (The stereochemical assignment of the diols is confirmed later in section 4.7.2). The quantity of 219 was lower than that expected, as ratios of greater than 6:1 have been obtained from similar substrates[227] (Scheme 4.25 above).

To assess the effectiveness of the cinchona alkaloid ligand family, the dihydroxylation was repeated six times using the phthalazine, pyrimidine and indoline based ligands 108-113. According to

Sharpless's mnemonic, the (Z)-alkene **187** is orientated so that the imidazole ring is positioned into the northeast quadrant and the butyl side-chain into the northwest (Figure 4.7). In this orientation, the dihydroquinine ligands (**109**, **111** and **113**) should lead to a matching of diastereoselectivies, while the dihydroquinidine ligands (**108**, **110** and **112**) should lead to a mismatch.

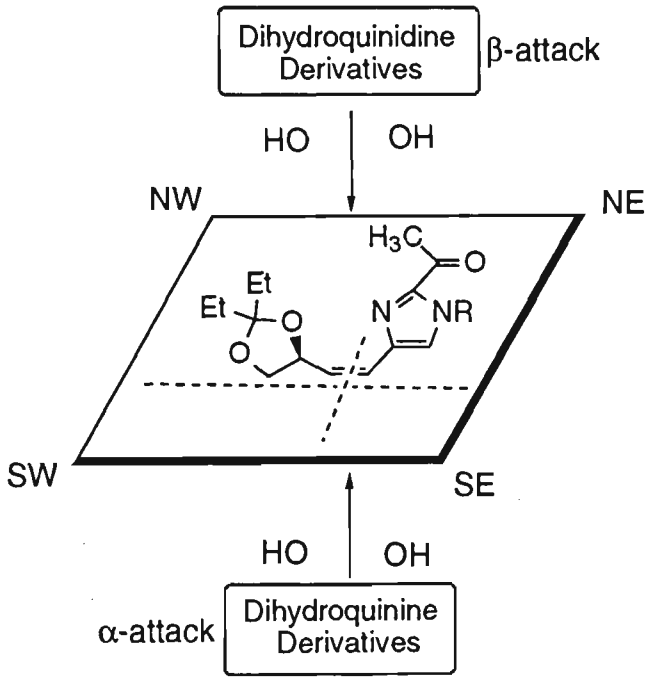
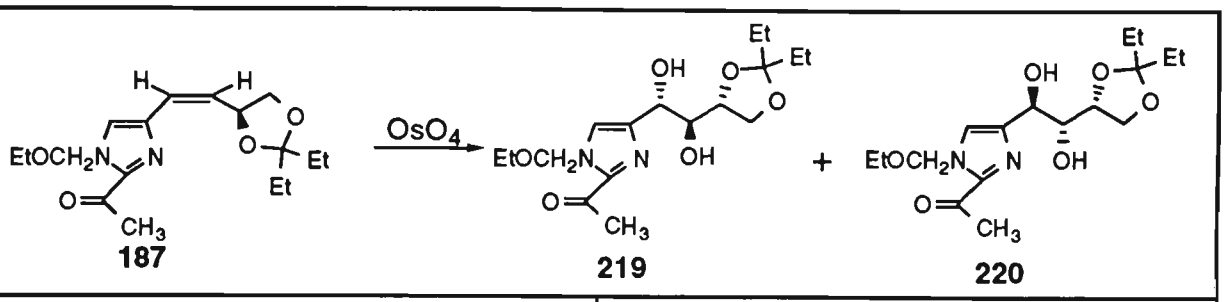


Figure 4.7 (Z)-Alkene **187** orientated according to Sharpless's mnemonic.

The (Z)-alkene **187** was treated with 3 mole % $K_2OsO_4.2H_2O$ in the presence of 5 mole % chiral ligand as described above. All six reactions were complete after 16 hours at 0 °C. The ratio **219**:**220** was determined by ^1H NMR analysis of the H1' doublet signals at ca. 4.86 ppm and the methyl ketone signals at ca. 2.55 ppm for the diastereomeric diol products (Table 4.3).

Table 4.3 Ratio of diols **219** : **220** from the AD reaction using the cinchona alkaloid ligands **108-113**.



187 **219** **220**

Ligand	*ratio 219 : 220*
none	2.1 : 1
$(DHQD)_2PHAL$	1.7 : 1
$(DHQ)_2PHAL$	1 : 2.0
$(DHQD)_2PYR$	1.2 : 1
$(DHQ)_2PYR$	2.0 : 1
DHQD-IND	1.6 : 1
DHQ-IND	3.2 : 1

The results obtained using $(DHQ)_2PHAL$ were opposite to that expected, with the diol **220** obtained as the major product. A matching of diastereoselectivies was expected with this ligand, with **219** being the major product. $(DHQD)_2PHAL$ gave a **219/220** ratio of 1.7:1. While this is lower than that obtained in the absence of a chiral ligand, the $(DHQD)_2PHAL$-osmium catalyst was unable to overcome the intrinsic diastereofacial control imposed by the chiral allylic ether moiety. The pyrimidine and indoline based ligands showed the expected matched/mismatched results, but neither $(DHQD)_2PYR$ nor DHQD-IND were able to overcome the intrinsic diastereofacial control imposed by the alkene substrate. In both cases the diol **219** was obtained as the major product, but in lower quantities than in the absence of a chiral ligand. The indoline based

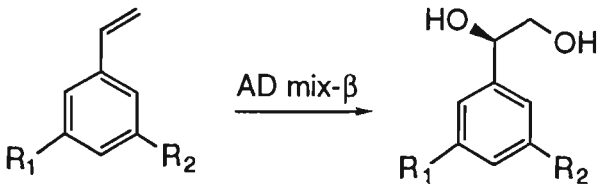
ligand DHQ-IND showed the only effective matching of diastereoselectivities. The diol **219** was obtained as the major product, with **219**:**220** in a ratio of 3.2:1. Superior results than those obtained were expected with both DHQD-IND and DHQ-IND, as these are the ligands of choice for the AD of *cis*-alkenes.[179]

4.4.3 Limitations of the Sharpless AD Reaction

The cinchona alkaloid family of ligands has been shown to effect excellent AD results on numerous olefinic systems.[170] Their effectiveness, however, seems to be limited for substrates of moderate to high complexity and steric bulk. Sharpless *et al.*[236] carried out a series of AD reactions using substituted styrene derivatives. Their findings showed that as the substituents on the styrene ring became more complex, unfavourable stacking arrangements within the ligand binding cleft resulted, leading to a decrease in the ee of the product diols[182] (Table 4.4).

Olefinic substrates such as **187** are considerably more complex than the styrenes used by Sharpless and coworkers, and also contain an unfavourable *cis*-alkene geometry. This alkene stereochemistry would most likely induce unfavourable steric interactions within the binding cleft as the two large alkene substituents are 'brought' together on the same side.

Table 4.4 Decrease in enantiomeric purity with increasing steric bulk of styrene substituents.

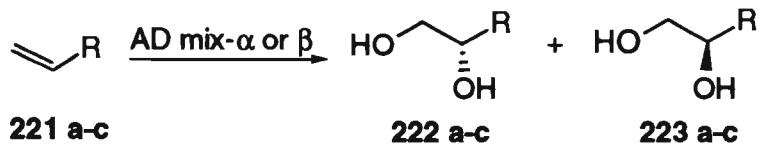


R 1	*R 2*	*ee (%)*
H	H	97
H	CH_3	99
H	^{t}Bu	95
^{t}Bu	^{t}Bu	49
2,4-dimethyl		35

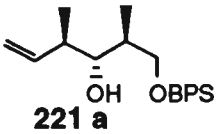
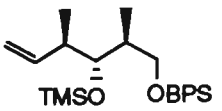
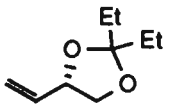
A similar synthetic dilemma in which Sharpless's ligands were unable to overcome the intrinsic diastereoselectivies of olefinic substrates has been reported by Smith *et al.*[237] During their work on the synthesis of calyculins, a number of diol precursors were required. Smith found that the use of AD mix-α and β gave a number of anomalous results that were contrary to that predicted by the Sharpless mnemonic (Table 4.5). The AD of **221b** gave the opposite stereochemistry using both $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ than was obtained when a ligandless dihydroxylation was performed. The only effective AD was obtained upon use of the pyrimidine based ligand $(DHQ)_2PYR$. Alkene **221c** is similar to the alkene **187** used in this study. The intrinsic diastereoselectivity displayed a dominant directing effect. Both the matched ligands $(DHQD)_2PHAL$ and $(DHQD)_2PYR$ enhanced the ratio **223**:**222**. The dihydroquinine ligands $(DHQ)_2PHAL$ and $(DHQ)_2PYR$ displayed a

mismatched effect, but neither ligand was able to provide **222** as the clearly dominant diol product.

Table 4.5 Inconsistent AD results displayed by Sharpless's cinchona alkaloid ligands with chiral alkene substrates.[237]



221 a-c **222 a-c** **223 a-c**

Substrate	PHAL ligands		PYR ligands	
	α or β	222 : 223	α or β	222 : 223
 **221 a**	DHQ DHQD None	5.2 : 1 1 : 1.5 3.5 : 1	DHQ DHQD	25.9 : 1 1 : 1.2
 **221 b**	DHQ DHQD None	3.2 : 1 1.6: 1 1 : 6.6	DHQ DHQD	31.3 : 1 1 : 1.2
 **221 c**	DHQ DHQD None	1 : 2.1 1 : 5.3 1 : 2.8	DHQ DHQD	1 : 1.6 1 : 4.5

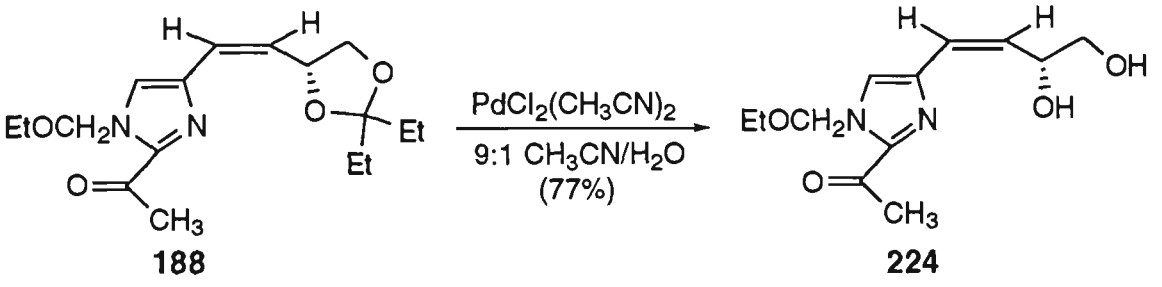
4.4.4 AD of (Z)-Allylic Alcohols

A second potentially useful method of obtaining high diastereoselective AD reactions from the alkene **187** and **188** is to utilise the directing effects of the protected hydroxyl groups. Although the AD reaction on the homoallylic alcohol **148** displayed no enhanced effects over its TBDMS precursor **129** in Chapter 3, removal of the pentylidene protecting group from **187** and **188** would present an allylic alcohol moiety. Hydroxyl groups in the allylic position display a greater directing effect in the AD process

than hydroxyl groups in the homoallylic position,[200] thus the subsequent AD reaction may lead to an enhanced selectivity.

The alkene **188** and 10 mole % of freshly synthesised $PdCl_2(CH_3CN)_2$[238] were refluxed in acetonitrile/H_2O (9:1) for 2 hours to give the deprotected diol **224** in 77% yield[239] (Scheme 4.27).

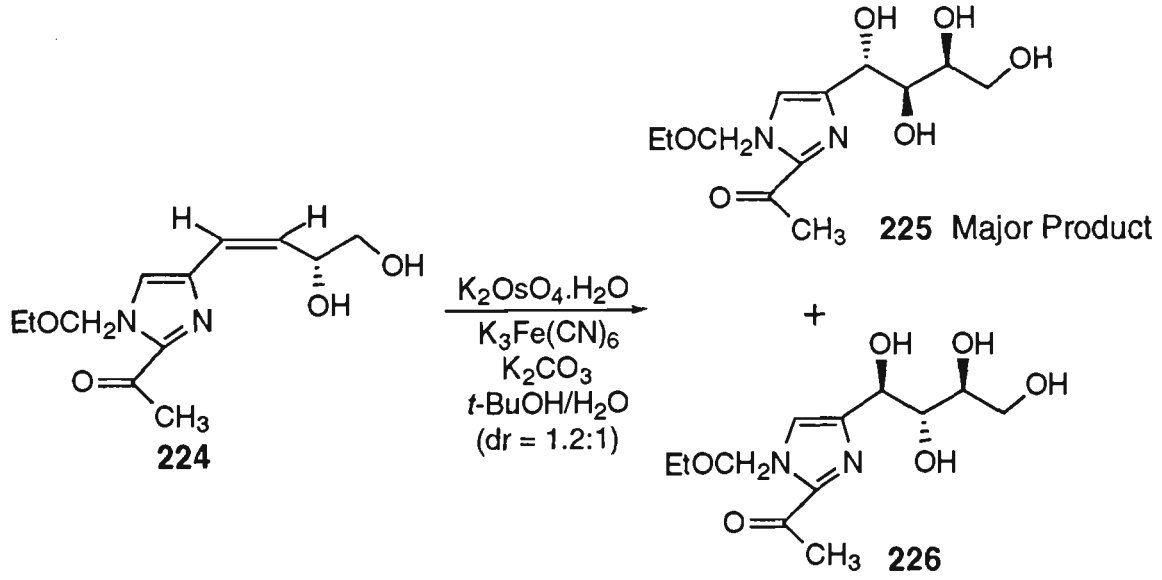
Scheme 4.27



188 **224**

Treatment of the diol **224** with 3 mole % $K_2OsO_4.2H_2O$ and 3 molar equivalents of each of $K_3Fe(CN)_6$, K_2CO_3 and methanesulfonamide at 0 °C gave the tetraols **225** and **226** in a 1.2:1 ratio (Scheme 4.28).

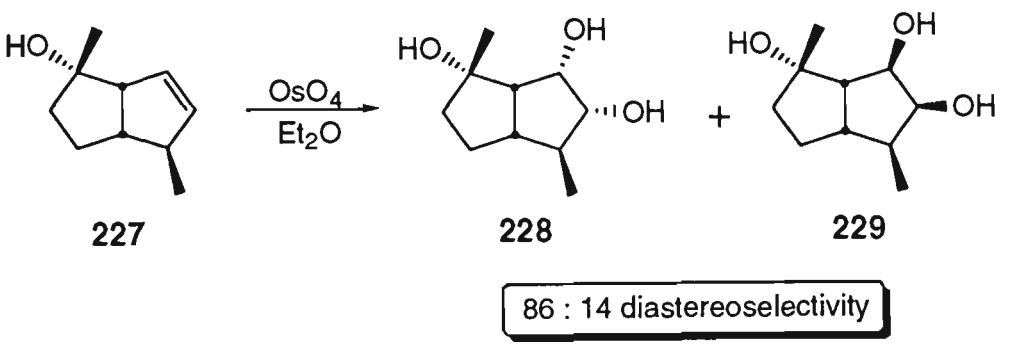
Scheme 4.28



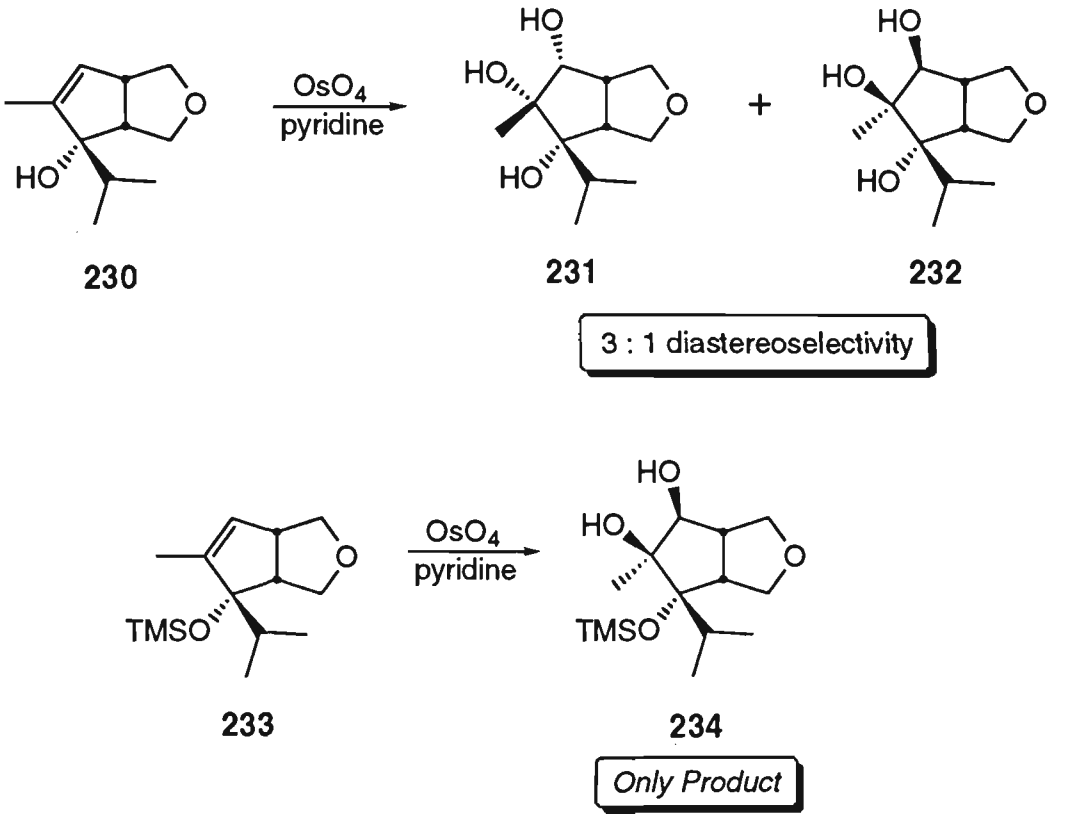
224 **225** Major Product **226**

The major tetraol product **225** had the opposite stereochemistry at C1' and C2' to the major diol product that was obtained from the AD of the parent alkene **188**. Steric directing factors are no longer dominant in this deprotected system, with the directing effect of the allylic hydroxyl group dictating the stereochemical outcome. Two reports have appeared in the literature involving dihydroxylations directed *via* hydrogen bonding to OsO_4. In the first example, the bicyclic system **227** was treated with OsO_4 to give the triols **228** and **229** with an 86:14 diastereoselectivity. The major product **228** resulted from attack by osmium from the face of the molecule that contains the free alcohol group[240] (Scheme 4.29). Similarly, the allylic alcohol **230** was dihydroxylated to give a 3:1 ratio of products **231** and **232**, with the major product again due to the directing effect of the free allylic hydroxy group. In contrast, however, the silyl ether **233** gave the diol **234** exclusively, with dihydroxylation occurring on the face of the molecule that is *anti* to the silyl ether moiety[241] (Scheme 4.30).

Scheme 4.29

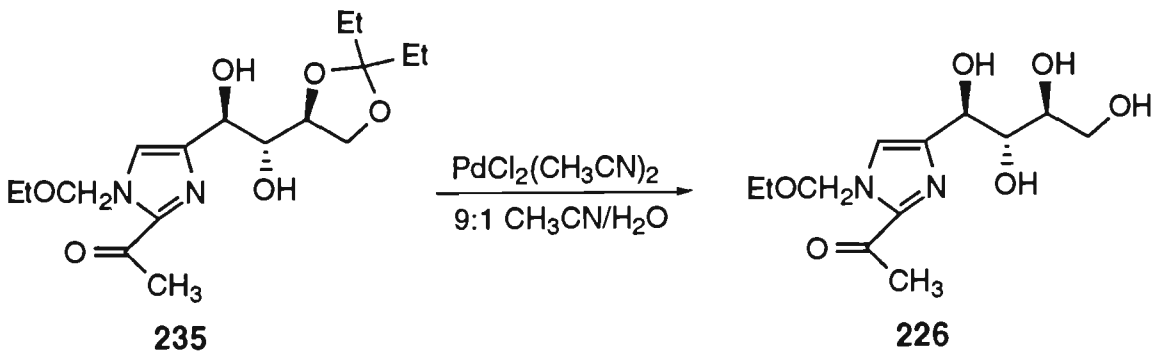


Scheme 4.30



To confirm the stereochemical outcome of the dihydroxylation of **224**, a known sample of the diol **235**, synthesised *via* the AD of **188**, was deprotected using $PdCl_2(CH_3CN)_2$ in refluxing acetonitrile/H_2O (9:1) to give the tetraol **226** (Scheme 4.31). ^1H NMR analysis of this tetraol sample showed an identical spectrum to the minor tetraol synthesised *via* the dihydroxylation of **224** in Scheme 4.28.

Scheme 4.31



To assess the effectiveness of the chiral ligands **108-113**, the deprotected alkene **224** was subjected to six separate AD reactions. The dihydroxylations were performed using 3 mole % $K_2OsO_4.2H_2O$, 5 mole % chiral ligand and 3 molar equivalents of each of $K_3Fe(CN)_6$, K_2CO_3 and methanesulfonamide in 1:1 *t*-BuOH/H_2O at 0 °C. The reactions were complete after 3 days vigorous stirring and the diastereomeric tetraol products **225** and **226** taken into deuterated acetone for ^1H NMR analysis. The ratio **225**:**226** was determined by the integration of the H1' doublets at 4.76 ppm and 4.85 ppm for **225** and **226** respectively (Table 4.6).

Table 4.6 Ratio of tetraols **225** : **226** from the AD of the (*Z*)-alkene **224** with the cinchona alkaloid ligands **108-113**.

Ligand	*ratio 225:226*
none	1.2 : 1
$(DHQD)_2PHAL$	1 : 1.1
$(DHQ)_2PHAL$	1 : 3.5
$(DHQD)_2PYR$	1.4 : 1
$(DHQ)_2PYR$	1.3 : 1
DHQD-IND	1.2 : 1
DHQ-IND	1 : 1

With the diol **224** orientated according to the Sharpless mnemonic so that the imidazole ring is positioned into the northeast quadrant and the diol side-chain into the potentially hydrogen-bonding, attractive northwest quadrant,[170] the dihydroquinine ligands (**109**, **111** and **113**) were expected to give products from the matched double diastereoselectivity. Similarly, the dihydroquinidine ligands

(**108**, **110** and **112**) would be expected to give products from the mismatched double diastereoselectivity (Figure 4.8).

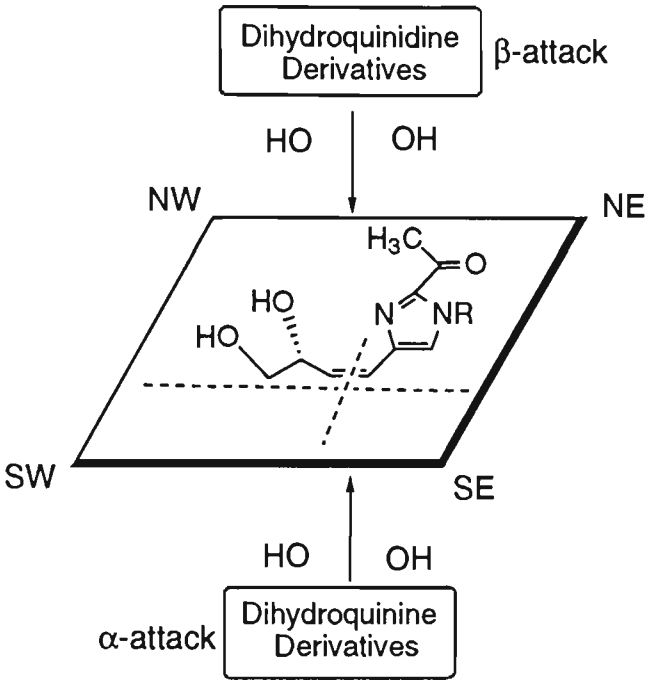


Figure 4.8 (Z)-Alkene **224** orientated according Sharpless's mnemonic.

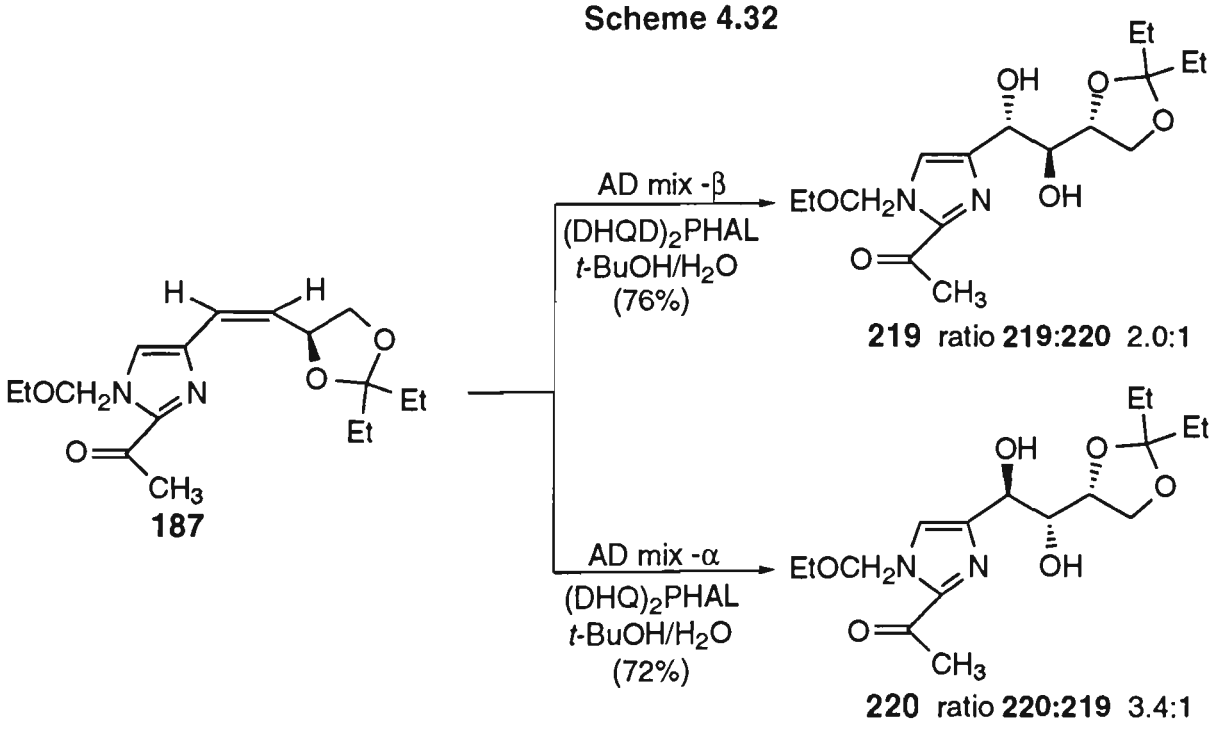
The only ligand that showed any selectivity, however, was $(DHQ)_2PHAL$, giving the tetraols **225** and **226** in a 1:3.5 ratio. Moreover, this ligand was expected to give the tetraol **225** as the major product and not **226** as found in this study! The remaining five cinchona alkaloid ligands showed little or no selectivity. The pyrimidine based ligands resulted in little enhancement of the diastereofacial selectivity, while $(DHQD)_2PHAL$ and both indoline based ligands gave a near 1:1 mixture of diastereomers **225** and **226**.

4.4.5 The AD of (Z)-Alkenes 186 and 187

Of the twelve AD reactions trialed using the alkene **187** and deprotected diol **224**, the most effective reactions involved the use of the former protected alkene **187** with the phthalazine ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$. This system was therefore used for a large scale synthesis of the tetraols.

The (Z)-alkene **187** was treated in two separate reactions with AD mix-α and AD mix-β. Each reaction used an additional 1 mole % $K_2OsO_4.2H_2O$, 4 mole % of the appropriate phthalazine ligand and 2 molar equivalents of methanesulfonamide in 1:1 *t*-$BuOH/H_2O$ and were complete after 48 hours at 0 °C. Treatment of **187** with AD mix-α gave the diol **220** as the major diol product in 72% yield. The ratio **219:220** was 1:3.4 by ^1H NMR analysis. An analogous reaction of **187** with AD mix-β gave the diol **219** as the major product in 76% yield. The ratio **219:220** was 2.0:1 by ^1H NMR analysis (Scheme 4.32).

Scheme 4.32

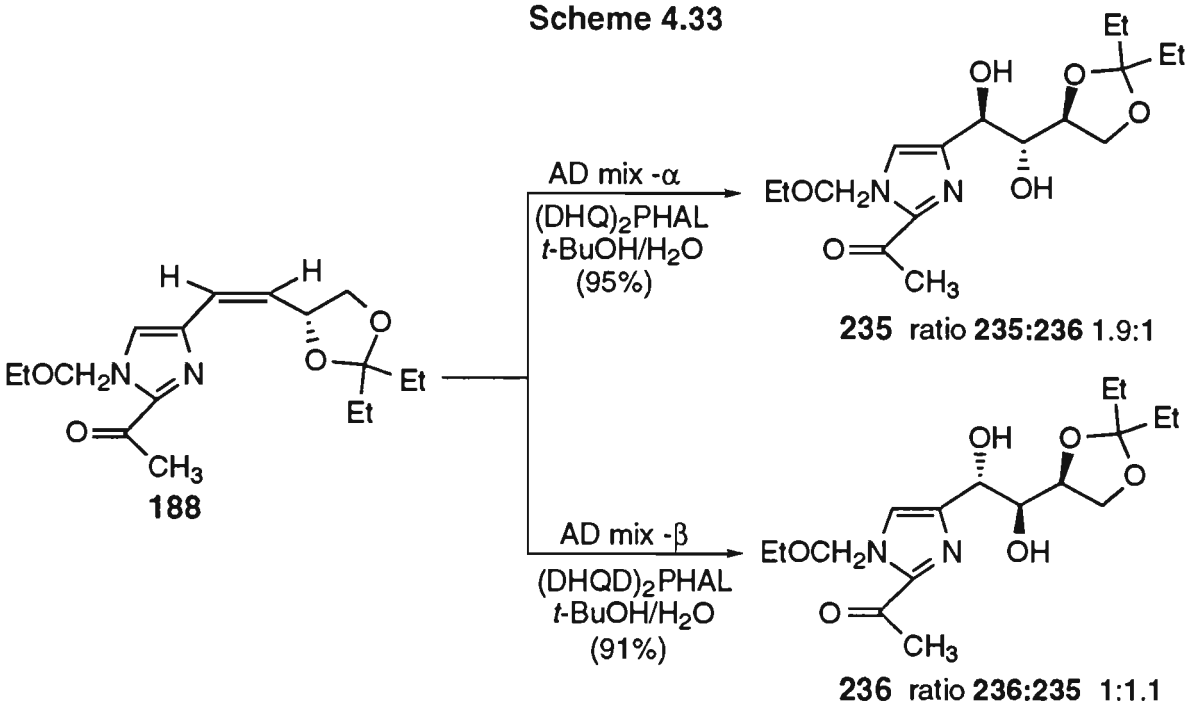


Both of the above AD reactions gave superior diastereoselectivities than was found upon performing the dihydroxylations on a smaller scale (Table 4.3). In the former case, the ratio **219**:**220** was 1:2.0 and 1.7:1 for AD mix-α and AD mix-β respectively.

Treatment of the (*Z*)-alkene **188** with AD mix-α and AD mix-β was carried out in the presence of an additional 1 mole % $K_2OsO_4.2H_2O$, 4 mole % chiral phthalazine ligand and 2 molar equivalents of methanesulfonamide in 1:1 *t*-BuOH/H_2O. Reaction of **188** with AD mix-α for 48 hours at 0 °C gave the diastereomeric diols **235** and **236** in 95% yield. The ratio **235**:**236** was 1.9:1 by ^1H NMR analysis, with the major diol **235** showing an identical proton spectrum to its (1'*S*, 2'*S*, 3'*R*) enantiomer **219** (Scheme 4.33).

The analogous reaction of **188** with AD mix-β failed to give the diol **236** as the major diol product. The ratio **236**:**235** was 1:1.1 by ^1H NMR analysis with an overall yield of 91%. The diol **236** showed an identical proton spectrum to its (1'*R*, 2'*R*, 3'*R*) enantiomer **220** in Scheme 4.32.

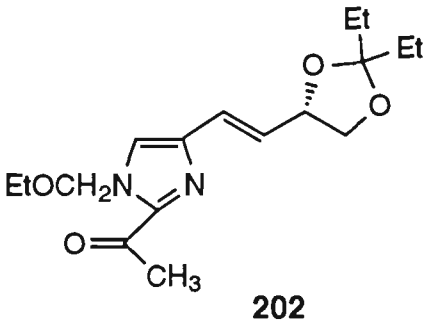
Scheme 4.33



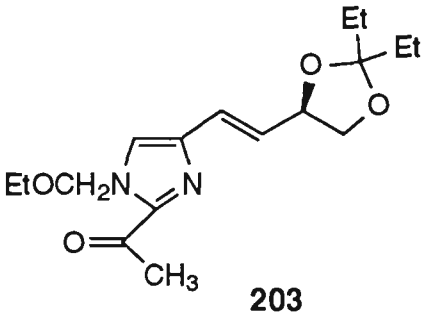
Both diastereomeric pairs **219/220** and **235/236** were unable to be separated by column chromatography to give diastereomerically homogeneous tetraols. Subsequent deprotection and manipulations of the tetraols was performed on the diastereomeric mixtures, although only one diastereomer for each mixture is shown for simplicity.

4.5 The AD of Chiral (*E*)-Alkenes

Despite the chiral (*Z*)-alkenes **187** and **188** proving to be poor substrates for the AD reactions, their chiral *trans* counterparts **202** and **203** provided enhanced results.



202

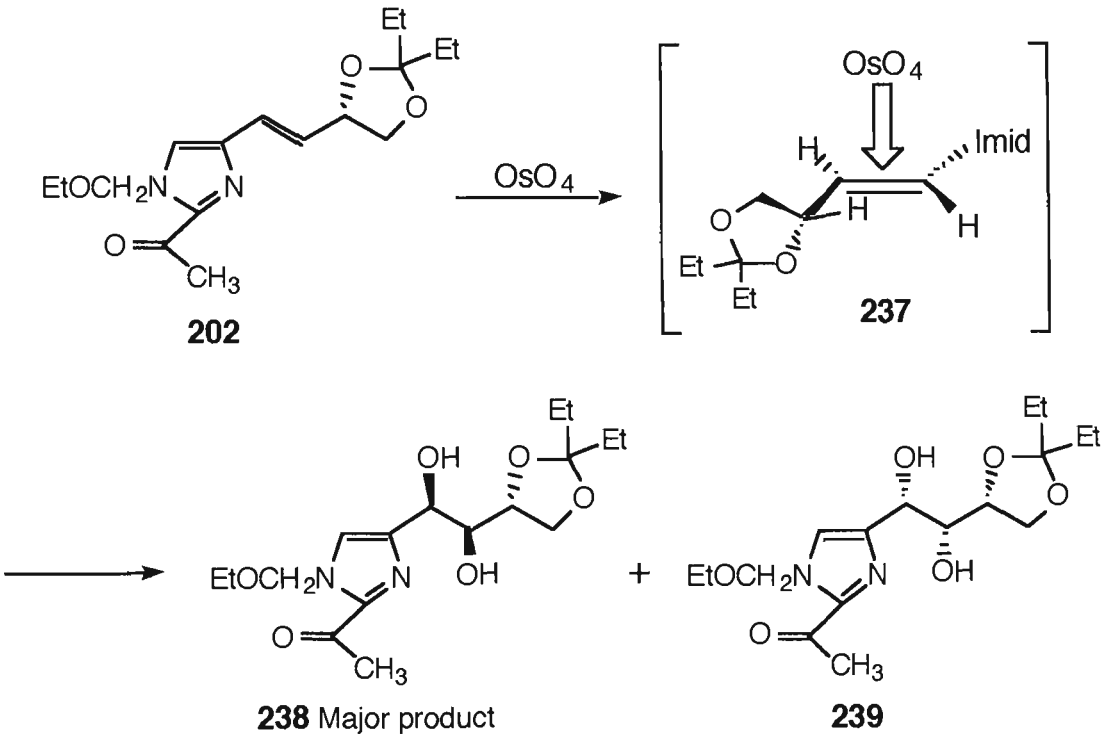


203

The intrinsic diastereofacial selectivity of the (*E*)-alkenes was evaluated using catalytic osmylation in the absence of a chiral ligand. Application of the Kishi model to **202** suggests the transition state **237** in which the allylic hydrogen atom is positioned 'inside' the double bond. Addition of OsO_4 to the upper face away from the allylic ether moiety would result in the synthesis of **238** as the major dihydroxylation product (Scheme 4.34). The diol **238** has identical stereochemistry to THI.

Inspection of the molecular model of **202** showed a conformation consistent with that proposed by Kishi (Figure 4.9), in which the allylic C-H bond has the 'inside' position with respect to the double bond.

Scheme 4.34



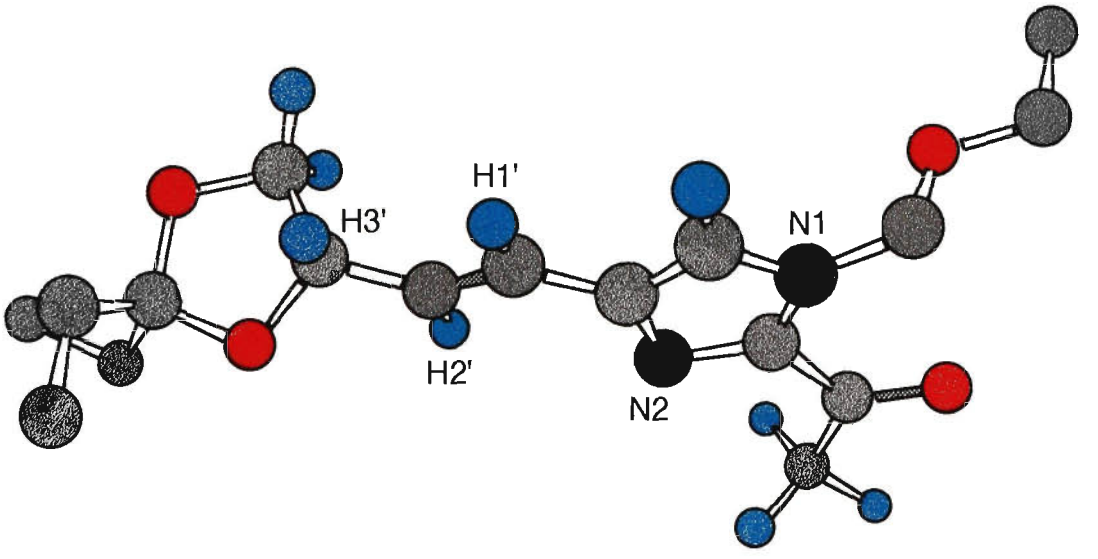


Figure 4.9 Molecular model of the (*E*)-alkene 202 with allylic hydrogen H3' eclipsing the double bond. Ethoxymethyl and pentylidene protons omitted for clarity.

The models proposed by Vedejs and Houk present different transition and ground states respectively to that proposed by Kishi, however, both still predict the diol 238 as the major

dihydroxylation product. Application of Vedejs's model leads to a transition state in which the hydrogen atom is faced towards the incoming OsO_4. This conformation is similar to that proposed by Houk. In Houk's model, the chiral ether moiety is orientated inside the double bond. The osmium species then attacks from the upper, less hindered face. In both cases the diol **238** is predicted as the major dihydroxylation product (Figure 4.10).

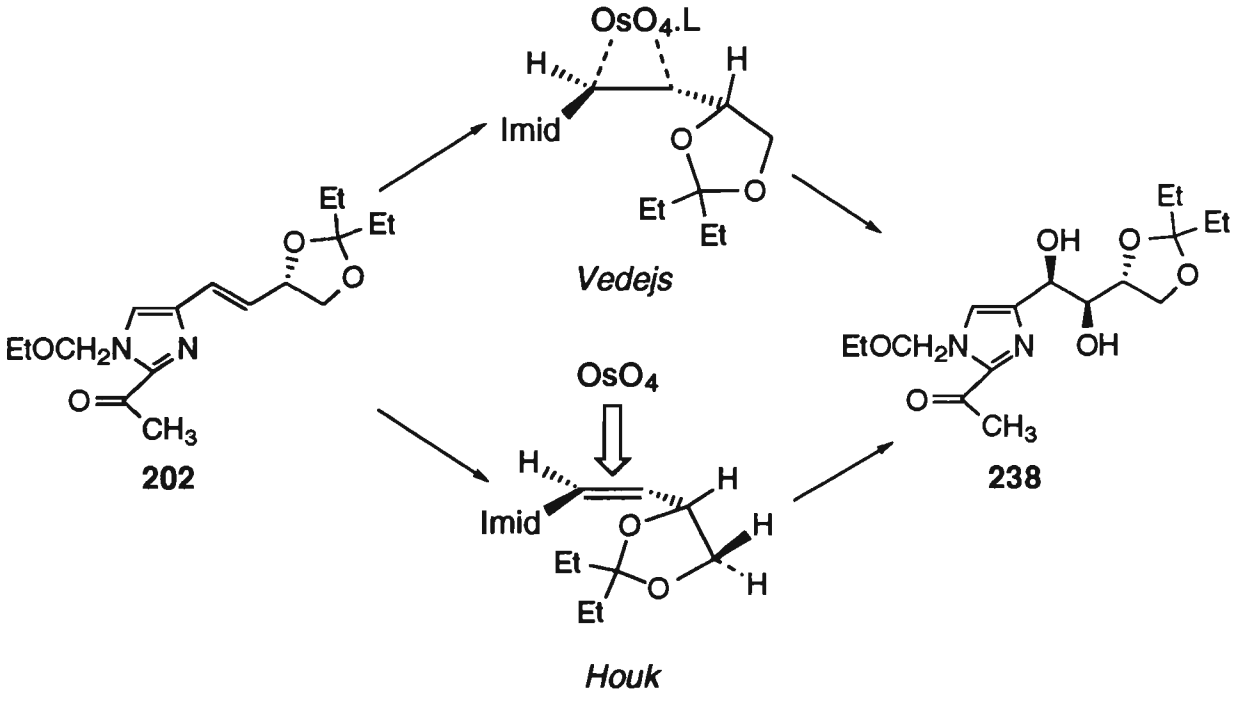
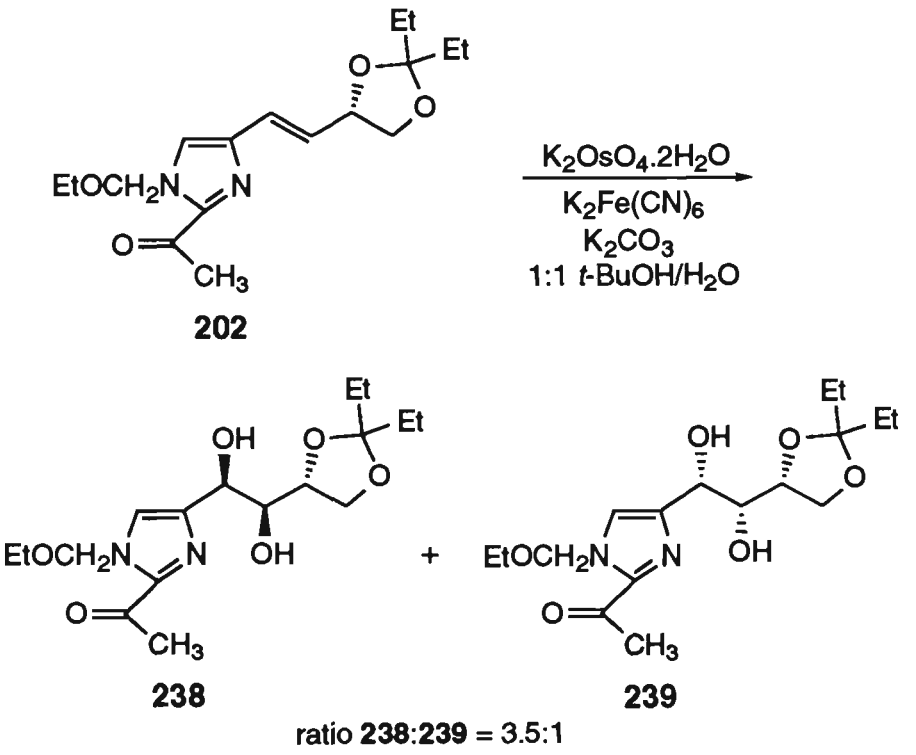


Figure 4.10 Synthesis of **238** predicted by the models of Vedejs and Houk.

The (*E*)-alkene **202** was treated with 5 mole % $K_2OsO_4.2H_2O$, 3 molar equivalents of $K_3Fe(CN)_6$ and K_2CO_3 and 2 molar equivalents methanesulfonamide in *t*-$BuOH/H_2O$ (1:1). The reaction was complete after 3 days at 0 °C to give a mixture of the diastereomeric diols **238** and **239** (Scheme 4.35).

Scheme 4.35



202

^{1}H NMR analysis of the diol mixture showed a 3.5:1 ratio of **238/239**. This ratio was determined by integration of the individual ^{1}H NMR signals for H1' (doublets at 4.89-4.80 ppm) and the methyl ketone group (singlets at 2.64-2.62 ppm) for the two diastereomeric diols (Figure 4.11).

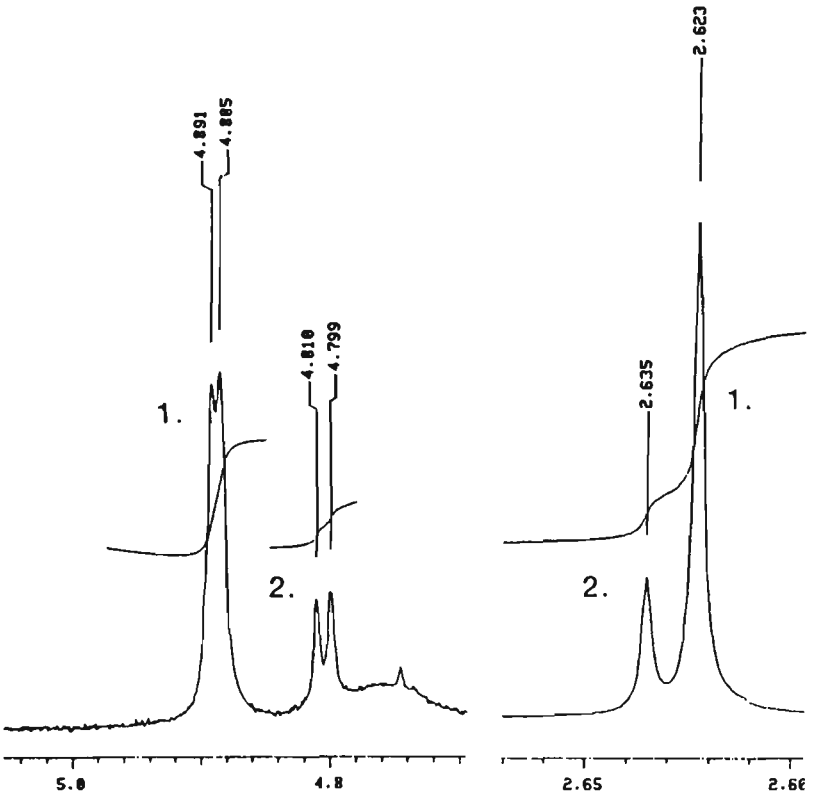


Figure 4.11 ^{1}H NMR (d^6-acetone) signals for H1' (doublet) and the methyl ketone group (singlet) for the diols **238** (1) and **239** (2).

4.5.1 AD of (*E*)-Alkenes 202 and 203

Orientation of the alkene **202** according to the Sharpless mnemonic shows an expected matching of the intrinsic diastereofacial selectivity and the diastereoselectivity of the AD process using the dihydroquinidine based ligands. Conversely, the use of dihydroquinine based ligands would lead to a mismatching of diastereoselectivities (Figure 4.12).

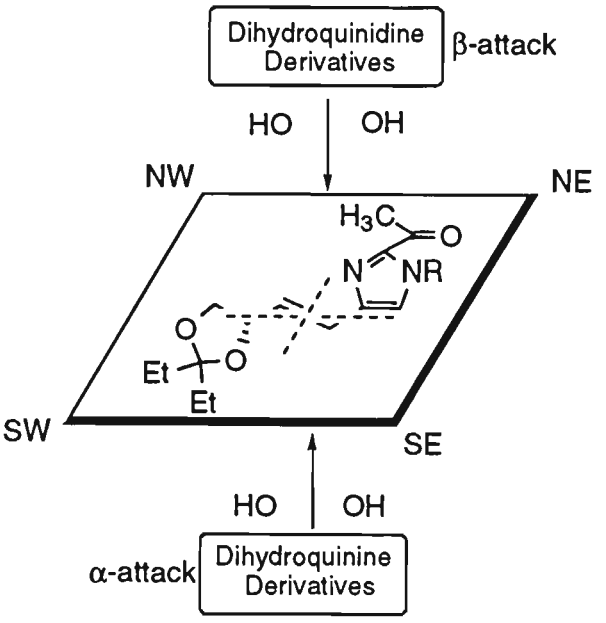


Figure 4.12 Orientation of the diol **202** according to the Sharpless mnemonic.

Analogous conclusions can also be drawn from the enantiomeric (*E*)-alkene **203**, in which treatment with OsO_4 would result in the synthesis of diols **240** and **241**, with **240** the major product. Orientation of this alkene according to the mnemonic would lead to a matching of selectivities for the dihydroquinine based ligands and a mismatching for the dihydroquinidine derivatives (Figure 4.13).

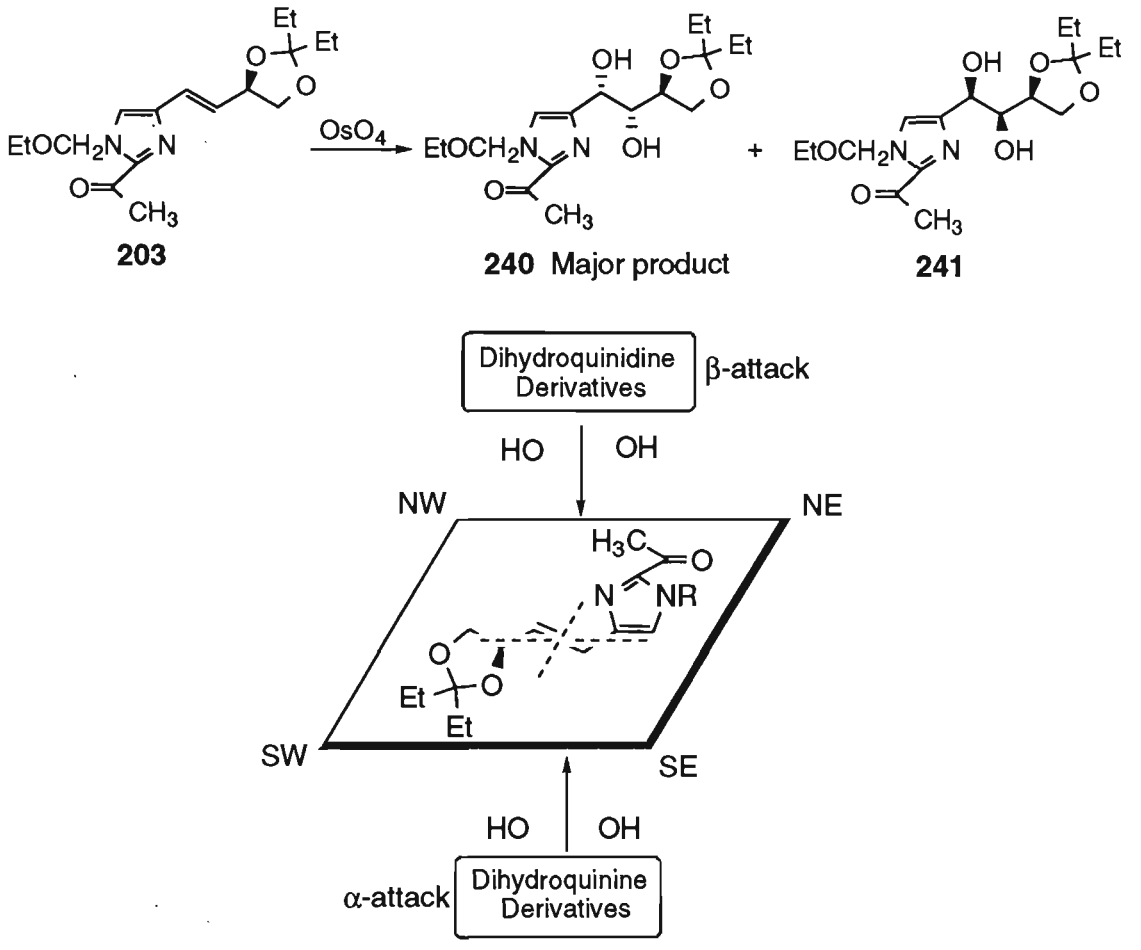
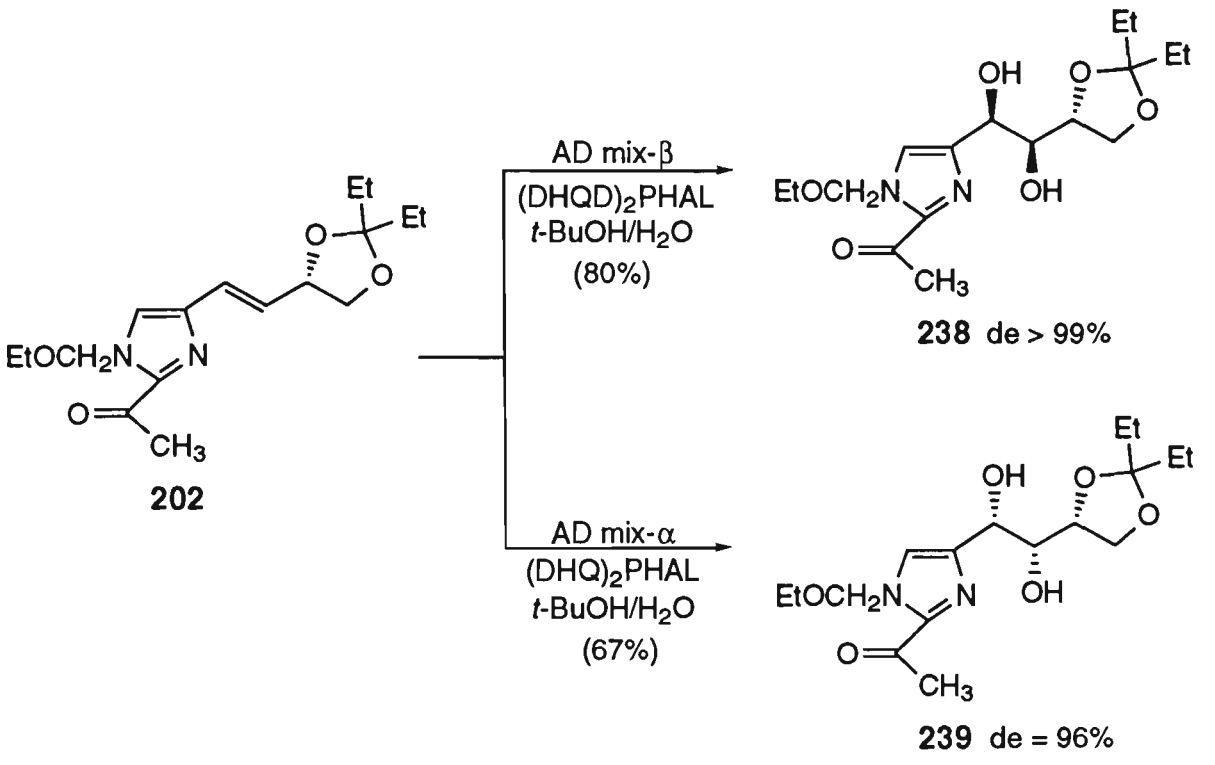


Figure 4.13 Orientation of the diol **203** according to the Sharpless mnemonic.

The diol **202** was treated separately with AD mix-β or AD mix-α, an additional 4 mole % of $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ respectively and 2 molar equivalents of methanesulfonamide in *t*-BuOH/H_2O (1:1). Consumption of the starting alkene was complete after 3 days at 0 °C. Treatment of **202** with AD mix-β gave the THI precursor **238** in 80% yield. ^1H NMR analysis of the purified diol showed **238** to be present in >99% de, with the minor diastereomer **239** not detected. Reaction of **202** with AD mix-α gave the diol **239** in 67% yield. ^1H NMR analysis showed the diol to be present in 96% de (Scheme 4.36).

Scheme 4.36



202

238 de > 99%

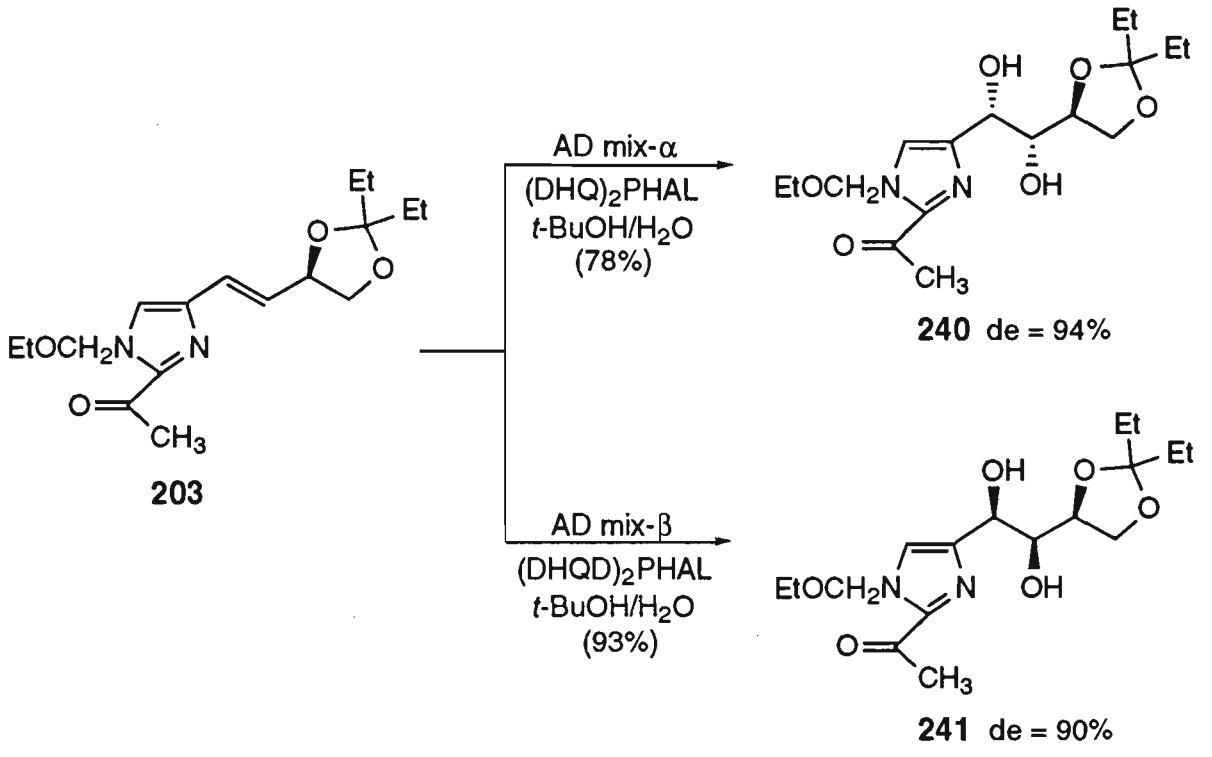
239 de = 96%

Despite mismatching of the (*E*)-alkene **202** with the chiral ligand $(DHQ)_2PHAL$ present in AD mix-α, a highly selective AD process still occurred. This result was further enhanced upon matching the alkene with the dihydroquinidine auxiliary to give the diol **238**.

Reaction of the (*E*)-alkene **203** was carried out in an analogous fashion to **202** above. The alkene was treated in two separate reactions with AD mix-α or AD mix-β, an additional 4 mole % of the appropriate chiral ligand and 2 molar equivalents of methanesulfonamide in *t*-$BuOH/H_2O$ (1:1). The dihydroxylation was complete within 3 days at 0 °C. Treatment of **203** with AD mix-α gave the diol **240** in 78% yield. ^1H NMR analysis of the H1' doublet signals at ca. 4.9-4.8 ppm showed the diol **240** to be present in 94% de. The analogous AD with the mismatched AD mix-β ligand system gave the diol **241** in 93% yield. ^1H NMR analysis of this

diastereomeric mixture showed the diol **241** to be present in 90% de (Scheme 4.37).

Scheme 4.37



The dihydroxylation reactions on the alkene **203** displayed the predicted matching and mismatching of the intrinsic diastereofacial selectivity with the diastereoselectivity of the AD process. The matching and mismatching of selectivities of **203** was opposite to that found with the enantiomeric (*E*)-alkene **202** (Table 4.7). The diols **240** and **241** had identical ^{1}H NMR spectra to their enantiomers **238** and **239** respectively.

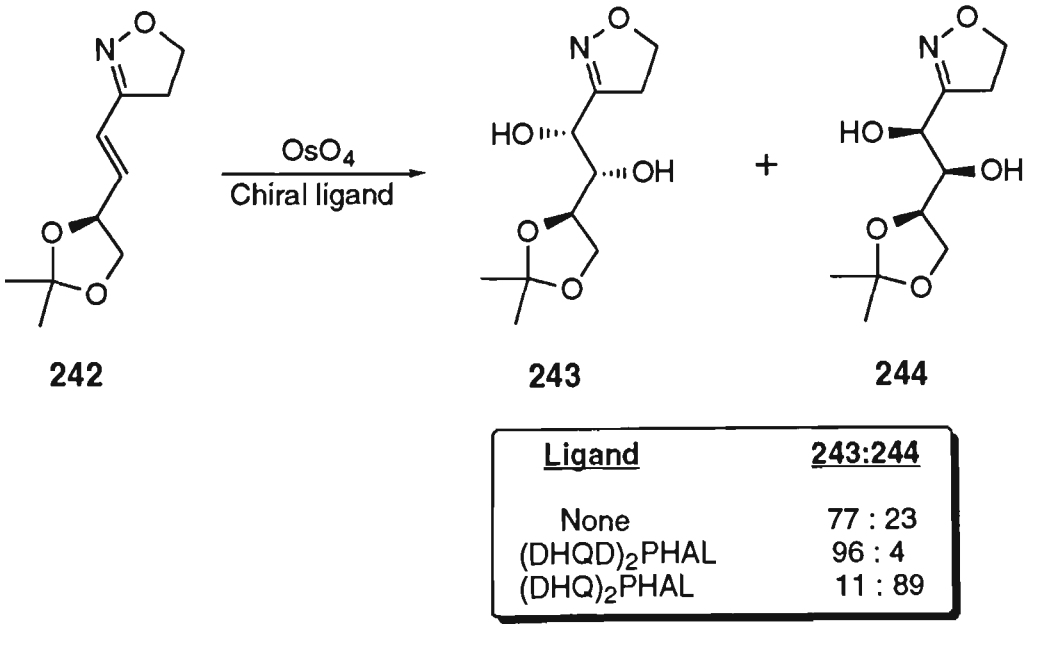
The dihydroxylation of the (*E*)-alkenes **202** and **203** showed excellent selectivity in both the matched and mismatched AD reactions. This process is uncommon, with most chiral (*E*)-alkenes displaying good to excellent selectivity in the matched reaction but a poor selectivity in the mismatched.[170] One of the few examples

found in the literature that shows good AD results in both the matched and mismatched diastereofacial selectivities involves the AD of the alkenyl dihydroisoxazole **242**.[242] Wade *et al.* subjected **242** to a number of AD reactions, which utilised different chiral ligands, to give the diols **243** and **244**. Treatment with $(DHQD)_2PHAL$ lead to a matching of selectivities and a 96:4 ratio of the diols **243/244**. Conversely, treatment with $(DHQ)_2PHAL$ resulted in a diastereoselectivity mismatch. The diol ratio 11:89 was, however, still considerably high[242] (Scheme 4.38).

Table 4.7 Matching of (*E*)-alkenes **202** and **203** with chiral phthalazine ligands.

	$(DHQD)_2PHAL$		*$(DHQ)_2PHAL$*	
Substrate	*Matched*	*ee %*	*Matched*	*ee %*
202	√	>99	X	96
203	X	90	√	94

Scheme 4.38



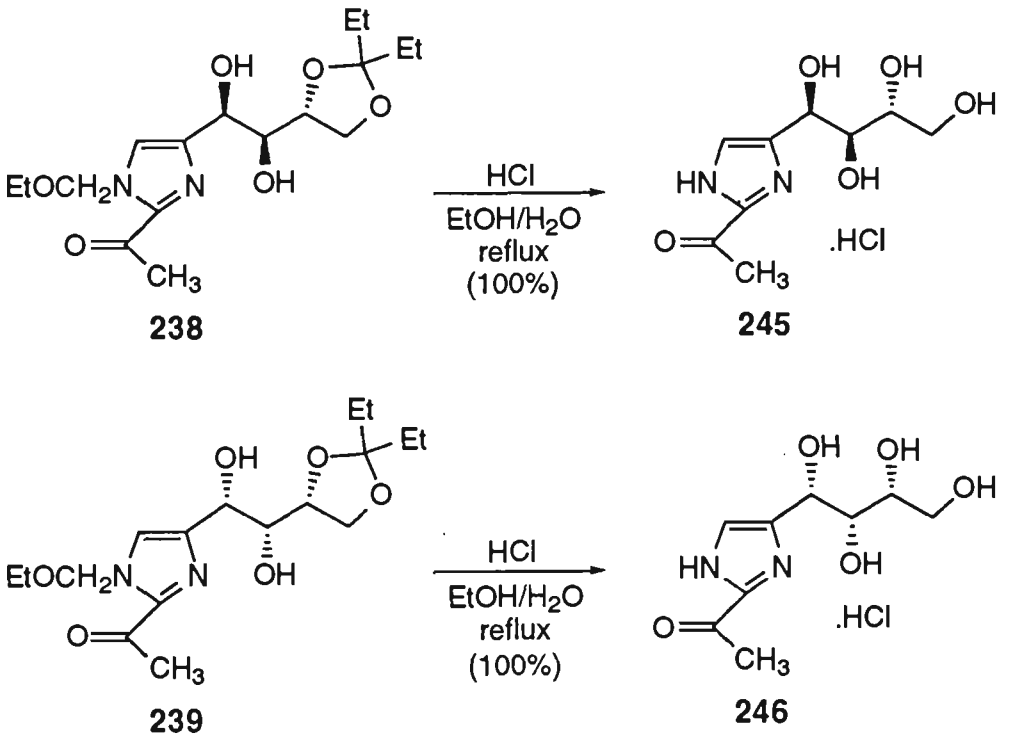
242 **243** **244**

Ligand	243:244
None	77 : 23
$(DHQD)_2PHAL$	96 : 4
$(DHQ)_2PHAL$	11 : 89

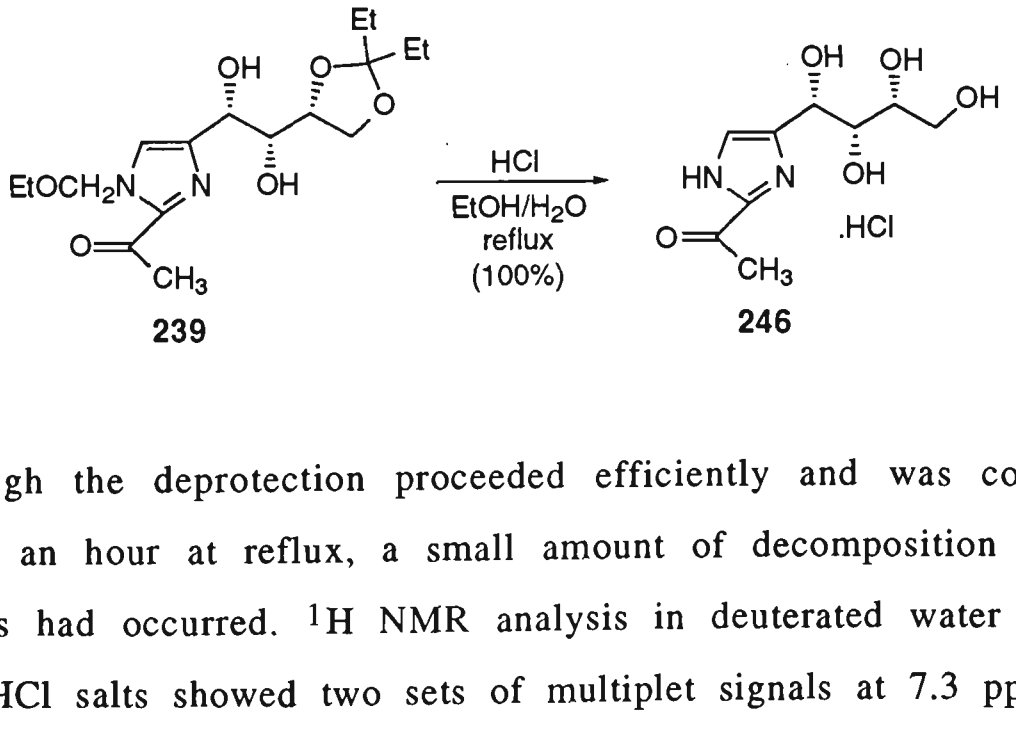
4.6 Deprotection of THI Tetraol Analogues

Removal of the ethoxymethyl and pentylidene protecting groups from the tetraol series of THI analogues was achieved *via* treatment with HCl in an ethanol/H_2O solution. The diols **238** and **239** were dissolved separately in a 1:1 ethanol/H_2O solution containing 10% HCl. The solutions were heated at reflux for 1 hour, cooled to ambient temperature and washed with ether to remove organic residues. Removal of the aqueous solvent lead to the hydrochloride salts **245** and **246** in quantitative yields (Scheme 4.39).

Scheme 4.39



238 **245**



239 **246**

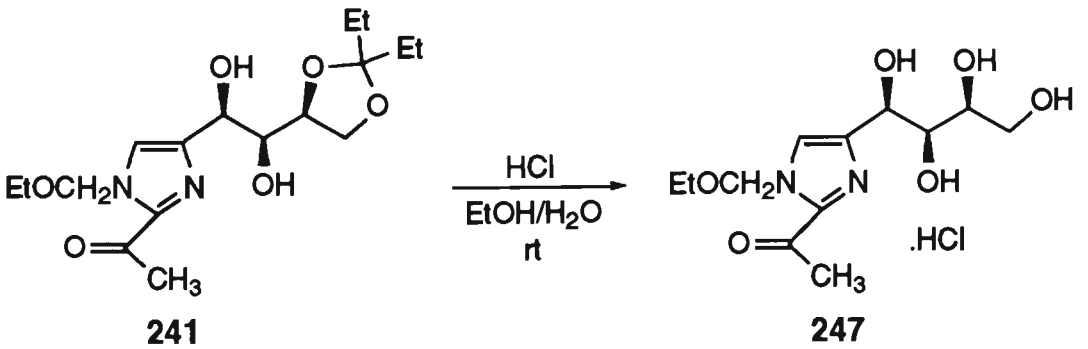
Although the deprotection proceeded efficiently and was complete within an hour at reflux, a small amount of decomposition of the tetraols had occurred. ^1H NMR analysis in deuterated water of the final HCl salts showed two sets of multiplet signals at 7.3 ppm and

1.7 ppm in addition to the expected proton signals of the tetraol species.

Decomposition of this nature had not previously been seen in the triol series of THI analogues, nor in the two monohydroxylated compounds **60** and **131**. It is reasonable to assume that degradation is occurring primarily at the hydroxyl moiety on C3', possibly due to dehydration. This moiety is not present in the aforementioned triol and monohydroxyl analogue series in which no decomposition was observed upon acidic deprotection.

In an effort to perfect the deprotection sequence, the diol **241** was examined in a number of deprotection experiments. Exposure to an acidic environment at ambient temperature led to a rapid and clean removal of the pentylidene protecting group, but did not effect cleavage of the ethoxymethyl moiety at N1. A six hour exposure of **241** to a 1:1 ethanol/H_2O solution containing 10% HCl at ambient temperature gave the ethoxymethyl protected imidazole **247** in near quantitative yield with no decomposition evident (Scheme 4.40). The imidazole was highly soluble in deuterated water and therefore assumed to be present as the hydrochloride salt. No deprotected imidazole species were present.

Scheme 4.40



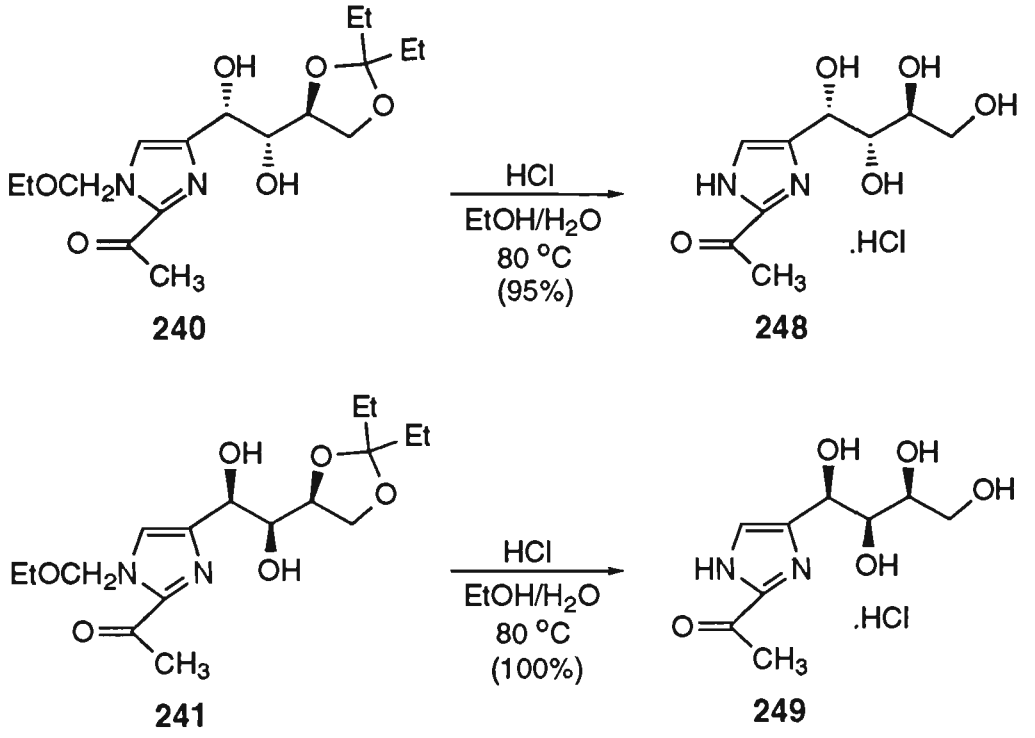
241 **247**

Heating of the imidazole **241** in 10% HCl lead to the removal of the ethoxymethyl moiety. Cleavage was evident at 40 °C, but proceeded sluggishly and appeared to cease after the reaction was approximately 50% complete. An increase in temperature to 80 °C lead to an efficient deprotection, with the reaction complete after 90 minutes. Only minimal decomposition was evident under these conditions. Removal of the aqueous solvent was achieved *via* freeze drying of the imidazole solution. Removal of the solvent by rotary evaporator on a water bath again lead to a decomposition of the tetraol hydrochloride salt. This was most likely due to a concentration of HCl at elevated temperatures upon solvent removal.

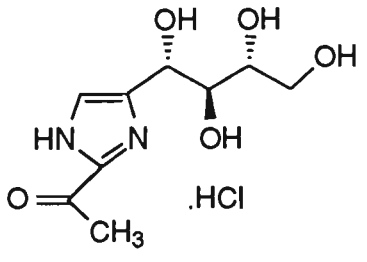
Further purification of the tetraols *via* silica, alumina and ion-exchange chromatography failed, with the tetraol being isolated after chromatography in its original state. Use of other proton sources such as acetic acid and trifluoroacetic acid were effective in removal of the pentylidene moiety, but were unable to cleave the ethoxymethyl group from the imidazole ring.

The imidazoles **240** and **241** were treated separately with a 1:1 ethanol/H_2O solution containing 10% HCl at 80 °C. The reaction was complete after 90 minutes. Ethanol was removed *in vacuo*, the aqueous phase washed with ether to remove organic residues and the solution concentrated by freeze drying to give the hydrochloride salts **248** and **249** in 95% and 100% yields respectively (Scheme 4.41).

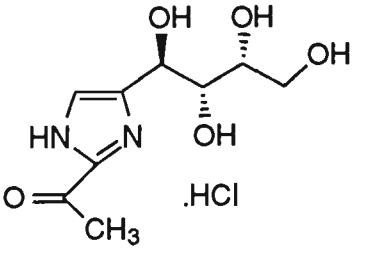
Scheme 4.41



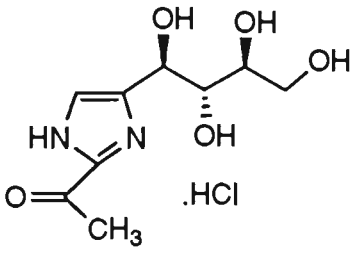
Both **248** and **249** were isolated with minimal decomposition as the hydrochoride salt. In analogous reactions to that presented in Scheme 4.41 above, the imidazoles **219**, **220**, **235** and **236** were subjected to separate deprotection using HCl at 80 °C. The four reactions were complete within a 90 minute period and gave the hydrochlorides **250**, **251**, **252** and **253** in 89%, 90%, 85% and 92% yields respectively.



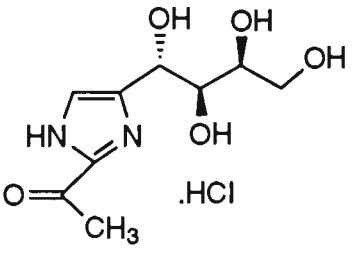
250 (89%)



251 (90%)



252 (85%)

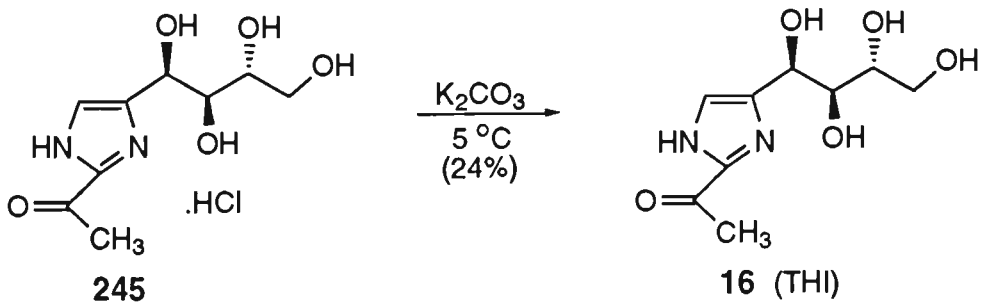


253 (92%)

4.6.1 Isolation of THI Synthesised *via* the Stille and Sharpless Reactions

As a final confirmation of the stereochemical assignments of the tetraol series of THI analogues, it was necessary to desalt the hydrochloride **245** and compare the free imidazole with an authentic sample synthesised by the method of Büchi.[87] The hydrochloride salt **245** was dissolved in a minimum volume of water and one molar equivalent of solid K_2CO_3 added. The solution was cooled to 5 °C for a period of three days and the precipitate collected by centrifuge to give the target THI **16** as a light yellow solid in 24% yield[243] (Scheme 4.42).

Scheme 4.42



245 **16** (THI)

The THI synthesised *via* the Stille and Sharpless reactions in this study was compared to an authentic sample[87] and found to exhibit similar melting points (240-244 °C and 234-236 °C respectively),

optical rotations ($[\alpha]_D^{23}$ -14.9 ° and $[\alpha]_D^{25}$ -12 ° respectively) and ^1H NMR spectra (Figure 4.14).

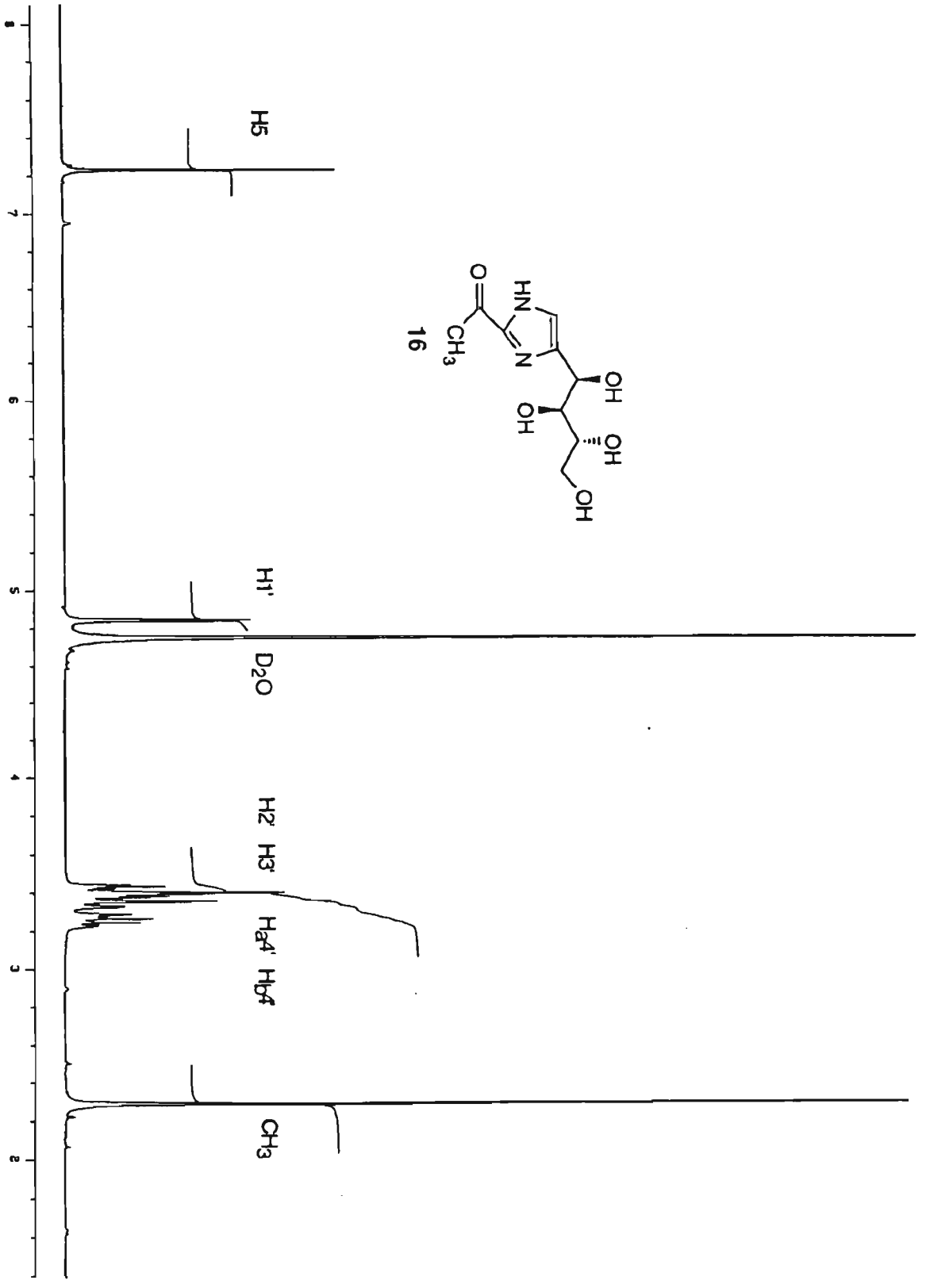


Figure 4.14 ^1H NMR spetrum for THI **16** in D_20/DCl.

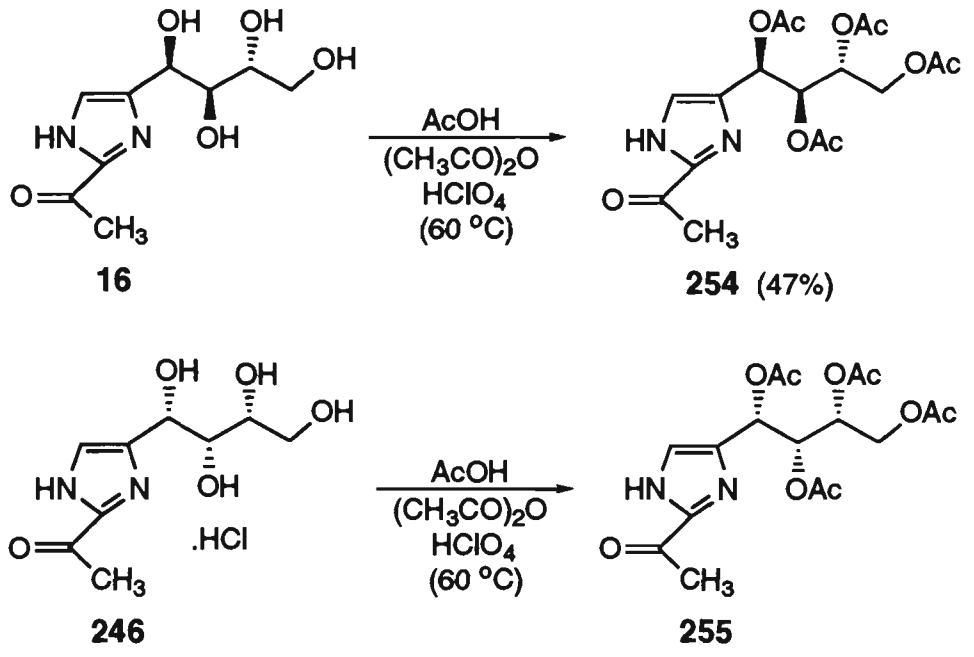
Precipitation of THI from a neutral aqueous solution is utilised by Büchi to isolate large quantities of the tetraol.[87] An identical isolation to that used in Scheme 4.42 above was attempted with the hydrochloride salt **246**, but failed to yield any of the free imidazole. Saturation with NaCl and cooling to 5 °C for an extended period resulted in the precipitation of inorganic salts only, with none of the desired imidazole precipitated from solution. The procedure thus appeared to be suitable for THI alone (and perhaps its enantiomer **248**), and was therefore not attempted on the remaining tetraol hydrochloride salts.

4.7 Tetraacetate Synthesise

The synthesis and deprotection of THI and its seven stereoisomers had been successfully achieved to provide valuable compounds for immunological assessment. From a synthetic chemist's point of view, however, the spectra obtained from the hydrochloride salts were unsatisfactory. ^1H NMR spectra run on the same compound were at times non-equivalent due to difficulties associated with referencing the D_2O solvent, and broad peaks were often observed at 400 MHz. To overcome this, a small quantity of each of the eight tetraols was converted to the corresponding tetraacetates[244] and sharp, clean NMR spectra obtained in a deuterated, organic solvent.

THI **16** synthesised in this study and the tetraol **246** were dissolved in a glacial acetic acid/acetic anhydride solution. A catalytic amount of perchloric acid was added and the solution heated for one hour at 60 °C to give the tetraacetates **254** and **255** (Scheme 4.43). The acetate **254** was obtained in 47% yield, while the yield for **255** was unable to be calculated due to KCl contamination of the starting hydrochloride **246**. (This sample was retrieved from the attempted neutralisation experiment in section 4.6.1 above).

Scheme 4.43



The tetraacetates **254** and **255** gave sharp, easily distinguishable ^{1}H NMR spectra. Both compounds appeared as a single 1,4-disubstituted imidazole. There was no evidence of a second tautomeric form present in the proton spectrum as is the case of THI in d_6-Me_2SO or D_2O, in which the 1,5-bisubstituted tautomeric form is seen[86] (Figure 4.15).

An authentic sample of THI[87] was converted to its tetraacetate **254** for comparative purposes. Both tetraacetates of THI synthesised in this study and that made by the method of Büchi had identical ^{1}H NMR spectra, with their optical rotations essentially equal and of the same sign ($[\alpha]_D^{24}$ -20.0 ° and $[\alpha]_D^{24}$ -22.6 ° respectively).

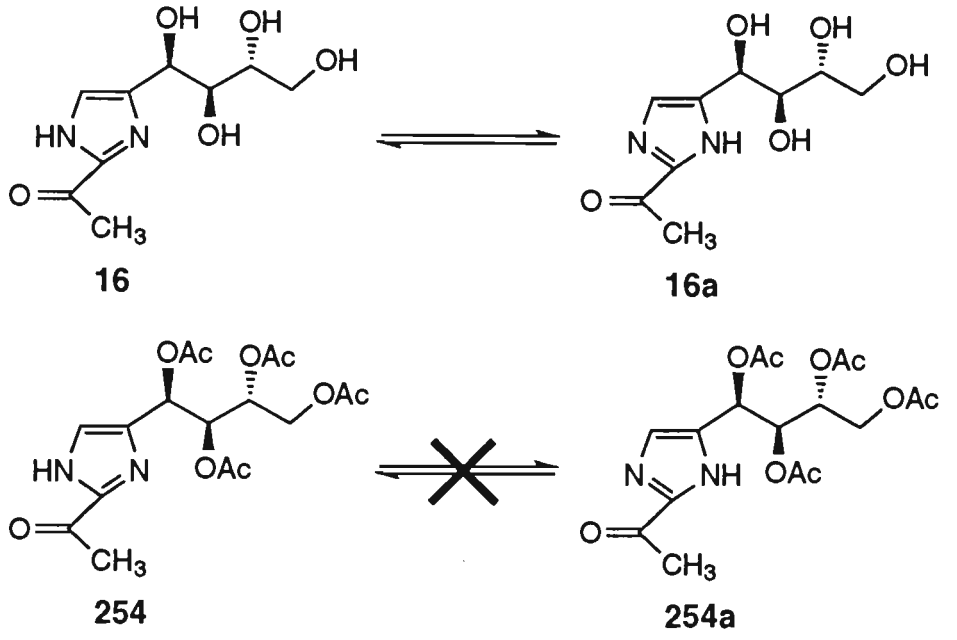
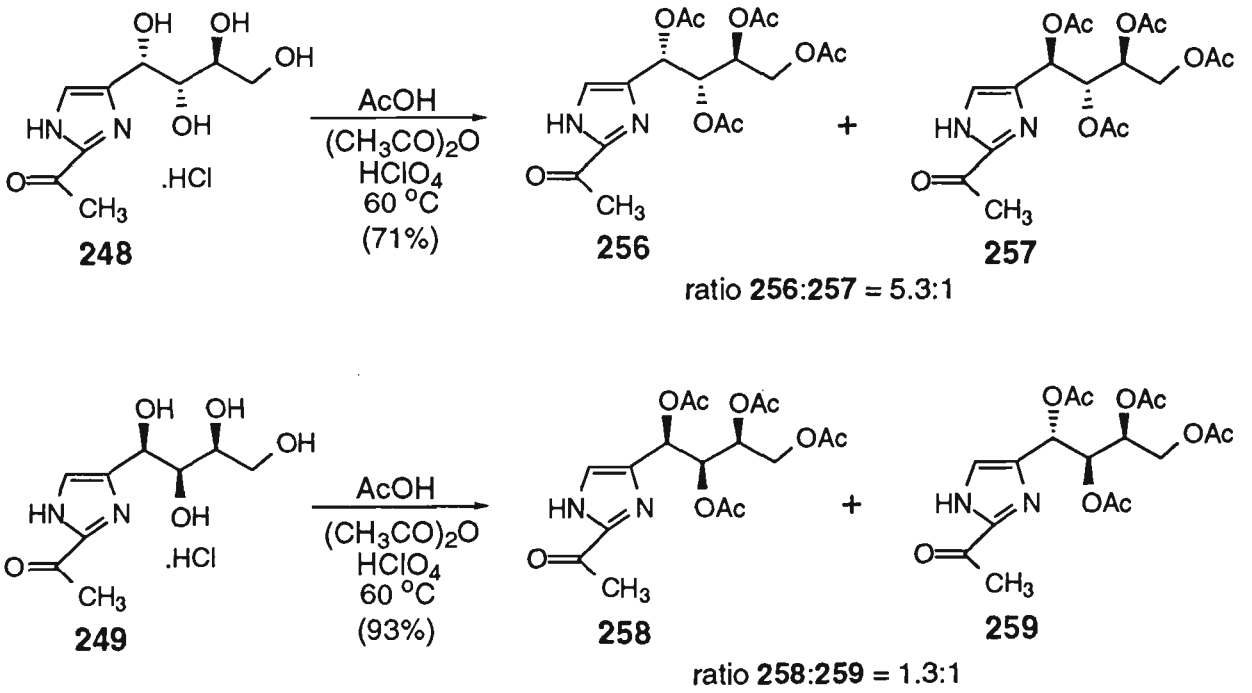


Figure 4.15 THI and its tautomer **16a**. The tetraacetate **254** displayed no tautomeric behaviour, with **254a** not evident by ^{1}H NMR.

The hydrochlorides **248** and **249** were treated with an acetic acid/acetic anhydride solution and perchloric acid catalyst as described above at 60 °C. The low solubility of the hydrochlorides, however, required a prolonged reaction time of 6 hours to effect a complete conversion. ^{1}H NMR analysis of the crude product revealed that *two* tetraacetate products had been obtained from each of the tetraols **248** and **249**. Our initial conclusions were that a mixture of two triacetates had been isolated due to an incomplete acetylation. Retreatment with acetic anhydride, acetic acid and perchloric acid catalyst, however, gave an identical mixture by ^{1}H NMR analysis to that originally obtained. Further analysis and separation of the tetraacetates showed that acetylation of the hydrochloride **248** resulted in a 5.3:1 mixture of the expected tetraacetate **256** to the (later identified) acetate **257** in a 71% combined yield. Similarly, treatment of **249** gave a 1.3:1 mixture of

the expected acetate **258** to the diastereomeric **259** in a 93% overall yield (Scheme 4.44). Tetraacetates **256** and **258** had identical ^1H NMR spectra to their enantiomer tetraacetates **254** and **255** respectively (Scheme 4.43).

Scheme 4.44



Prolonged exposure to the acidic reaction mixture appeared to have caused epimerisation of the stereochemistry at C1'. The highly acid nature of the reaction media is most likely catalysing acetate removal at C1' on the general tetraacetate **260**, with participation of the neighbouring C2' acetate assisting ionisation at C1' and leading to the carbocations **261a** and **261b**.[245] Quenching of the carbocations with acetate would lead to the formation of both the original stereoisomer **260**, plus the acetate **262** with the opposite stereochemistry at C1' (Figure 4.16).

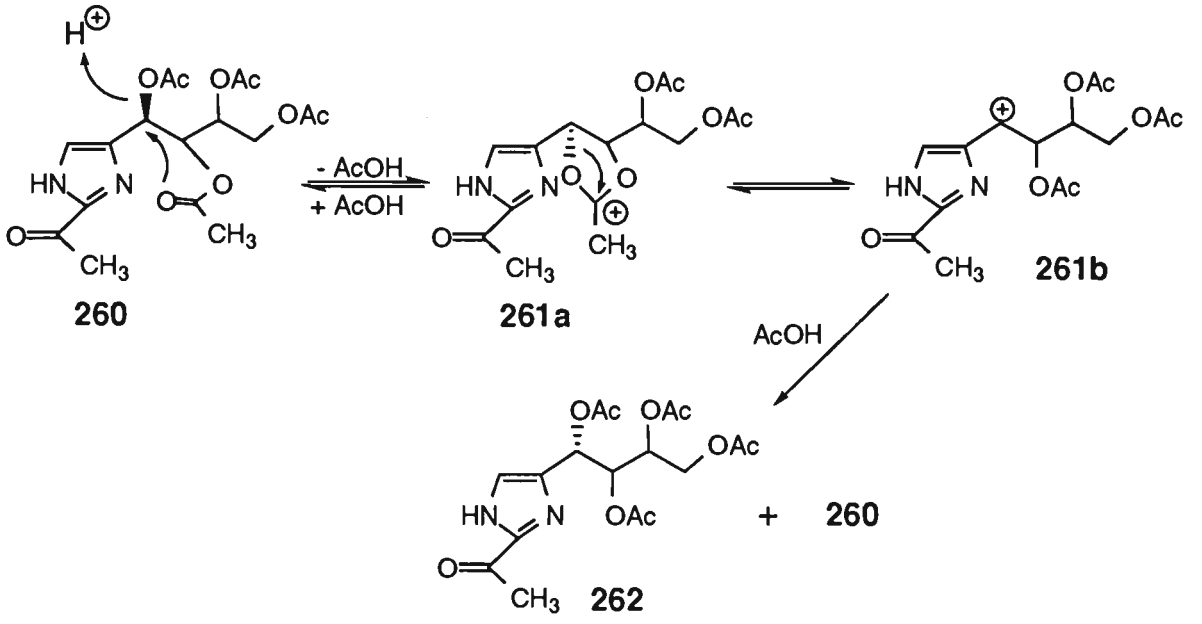
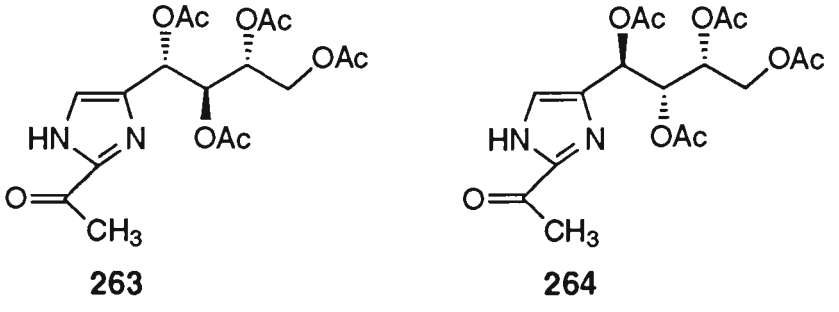


Figure 4.16 Epimerisation at C1' of the general tetraacetate species **260**.

Epimerisation at C1' was not observed in the synthesis of the tetraacetates **254** and **255** (Scheme 4.43) as both reactions are complete within one hour at 60 °C. Presumably, a prolonged exposure to the acidic reaction mixture would effect the formation of the tetraacetaes **263** and **264** respectively.



While epimerisation leads to two isomers for the tetraols **248** and **249** above, an identical treatment to the tetraol mixture of **250** and **251** and of **252** and **253** would most likely lead to *four* tetraacetate products. Synthesis of the tetraols (section 4.4.5) from the parent (*Z*)-alkenes gave inseparable mixtures of two

diastereomers. Conversion to the tetraacetates would therefore lead to a complex mixture of four isomers due to epimerisation at C1'.

The tetraol mixtures **250/251** and **252/253** were treated separately with a glacial acetic acid/ acetic anhydride solution and a catalytic quantity of perchloric acid. Reactions were complete after 6 hours at 60 °C. Purification of each reaction revealed a mixture of four tetraacetates (Table 4.8).

Table 4.8 Ratio of tetraacetates formed *via* epimerisation at C1' from the hydrochloride salts **250-253**.

Tetraol[a] *(ratio)*	*Tetraacetates Formed*	*Tetraacetate Ratio*	*Yield*[b] *(%)*
250/**251** (2:1)	**263**[c]:**254**[d]:**264**[c]:**255**[d]	6.3:1.7:3.0:1.0	65%
251/**250** (3.4:1)	**264**[c]:**255**[d]:**263**[c]:**254**[d]	4.0:2.7:1.1:1.0	63%
252/**253** (1.9:1)	**257**[c]:**256**[d]:**259**[c]:**258**[d]	3.8:1.9:2.2:1.0	47%
253/**252** (1:1.1)	**259**[c]:**258**[d]:**257**[c]:**256**[d]	2.8:1.0:3.1:1.1	37%

[a]Secondary tetraol and acetates underlined. [b]Overall acetate yield. [c]Identical stereochemistry to parent tetraol. [d]Opposite stereochemistry at C1'.

4.7.1 Separation of Diastereomeric Tetraacetates

Purification of the tetraacetate mixtures by both column and preparative layer chromatography failed to separate the individual tetraacetates. To achieve this, the mixtures were subjected to HPLC separation using a preparative scale column and 30% ethyl acetate/hexane as eluent. Separations took in the order of 3-4 hours to complete at a flow rate of 5 mL/min. Peaks were unable to

be separated out to baseline level, however, pure samples of each diastereomeric tetraacetate was obtained by shaving each peak and discarding the fractions collected between each pair of peaks. Excellent ^{1}H NMR spectra were thus obtained for all eight chiral tetraacetate diastereomers, with the enantiomeric acetate pairs **254/256**, **255/258**, **257/263** and **259/264** possessing identical proton spectra (Figures 4.17, 4.18, 4.19 and 4.20 respectively).

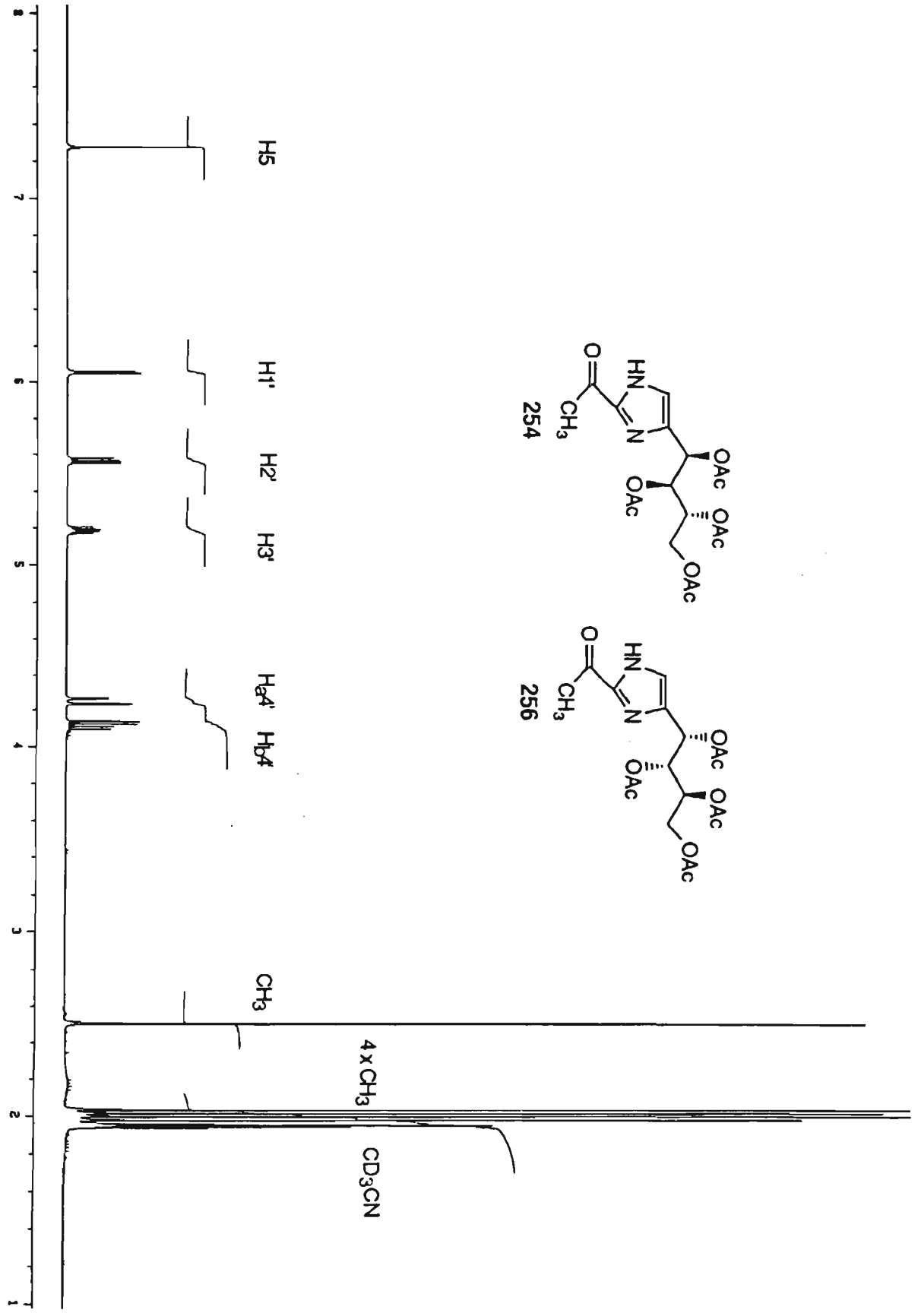


Figure 4.17 ^{1}H NMR spectra of the diasteromeric tetraacetate **254** in CD_3CN. Spectra identical to the enantiomer **256**.

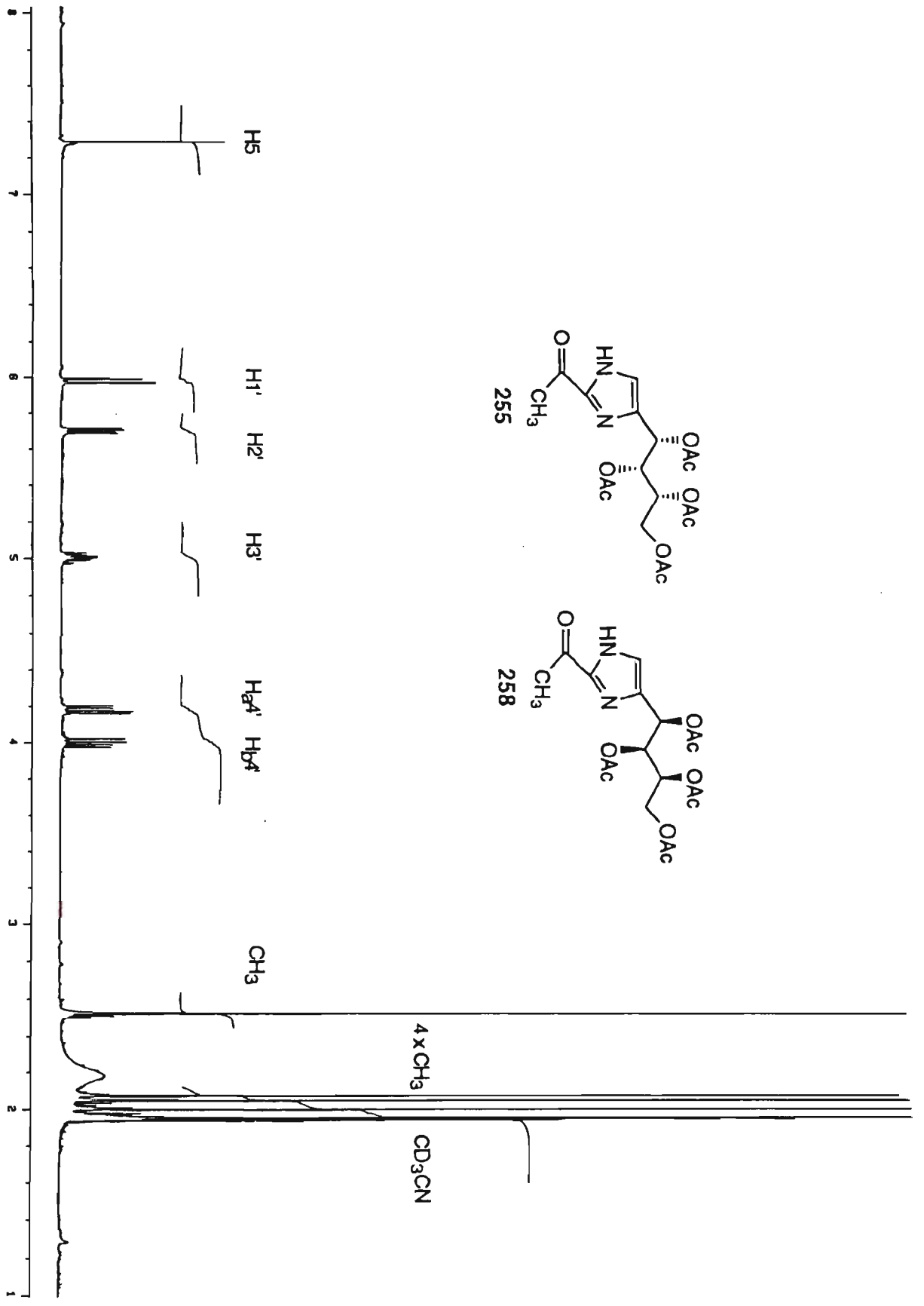


Figure 4.18 ^{1}H NMR spectra of the diasteromeric tetraacetate **255** in CD_3CN. Spectra identical to the enantiomer **258**.

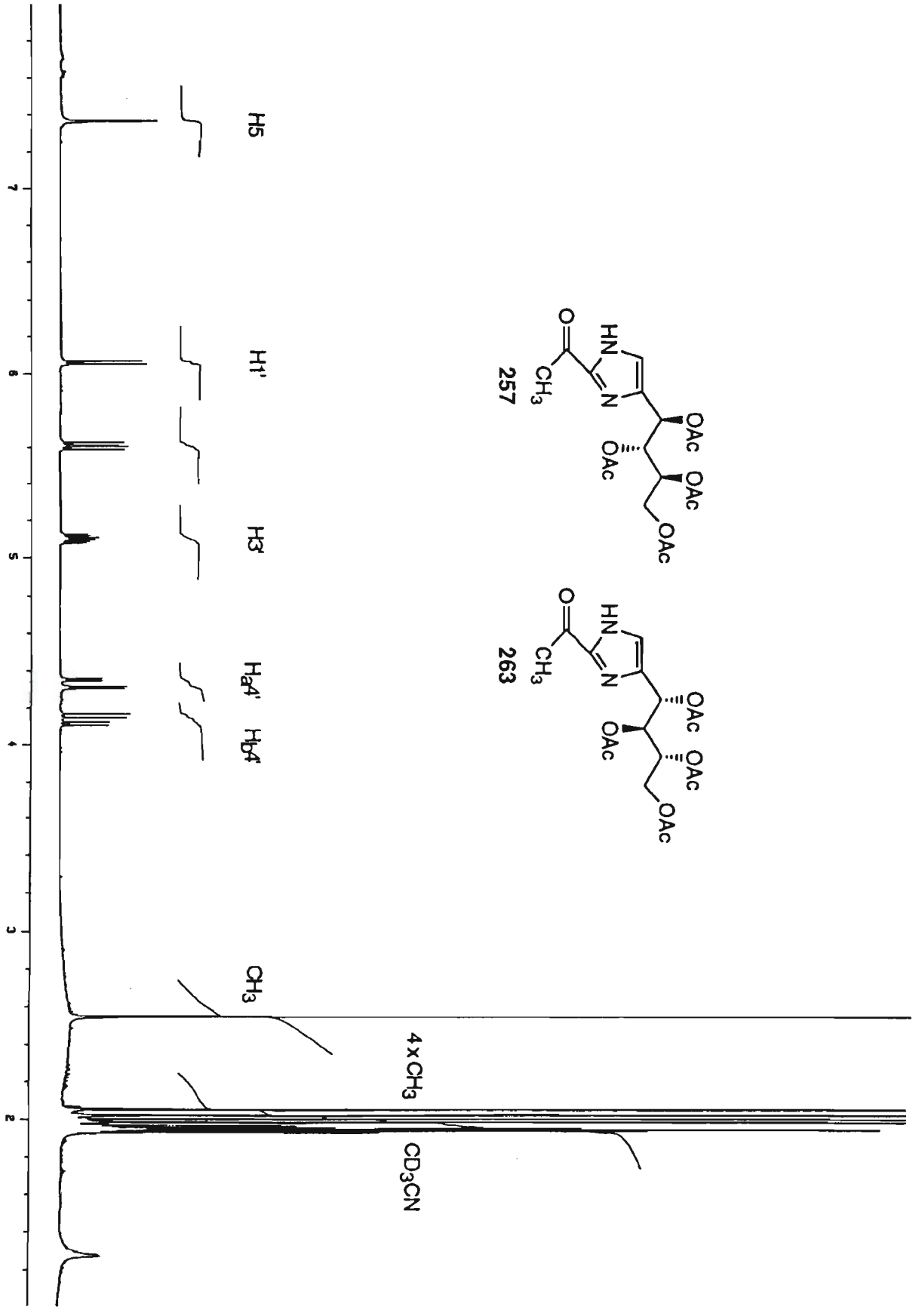


Figure 4.19 ^{1}H NMR spectra of the diasteromeric tetraacetate **263** in CD_3CN. Spectra identical to the enantiomer **257**.

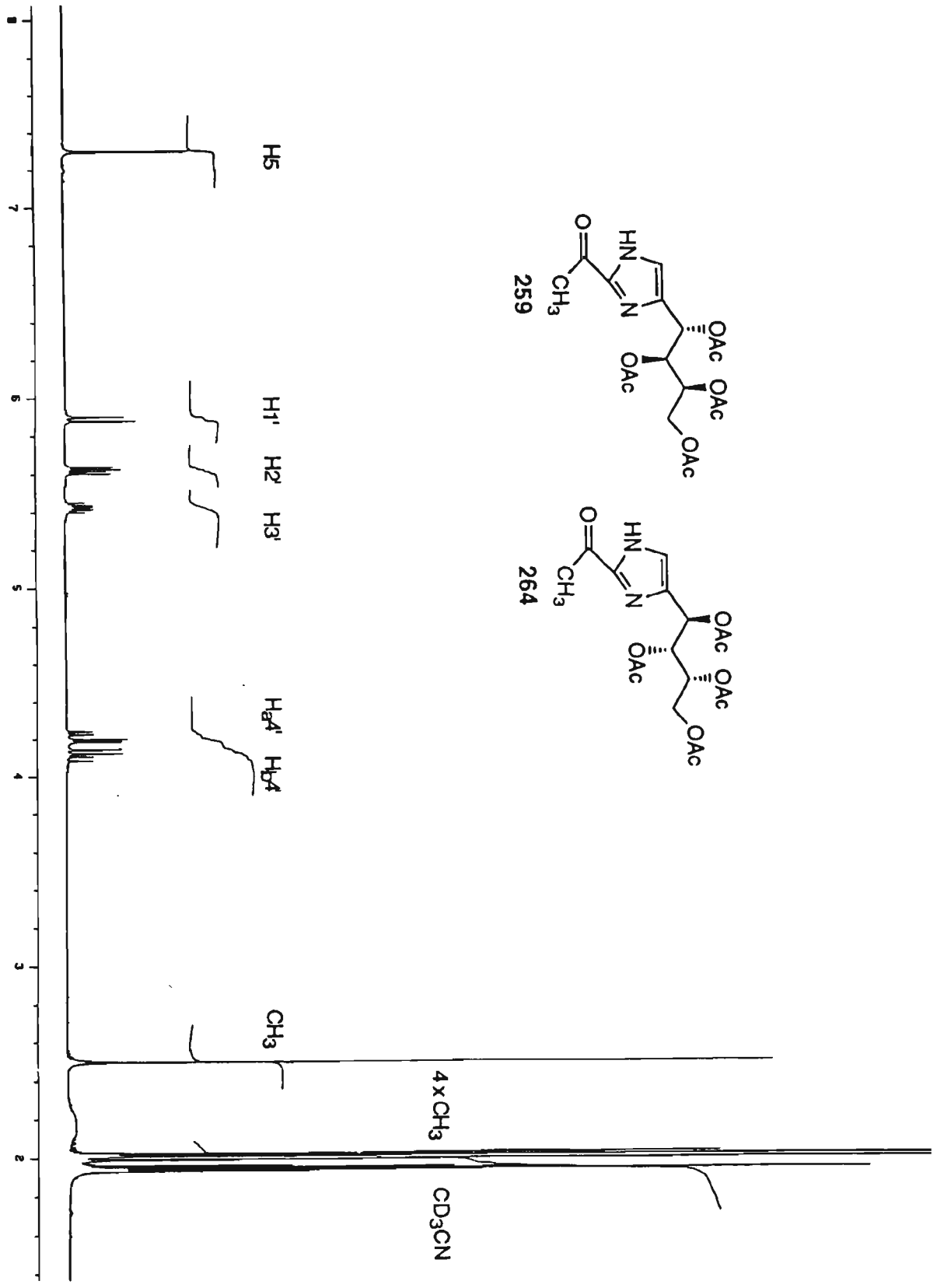


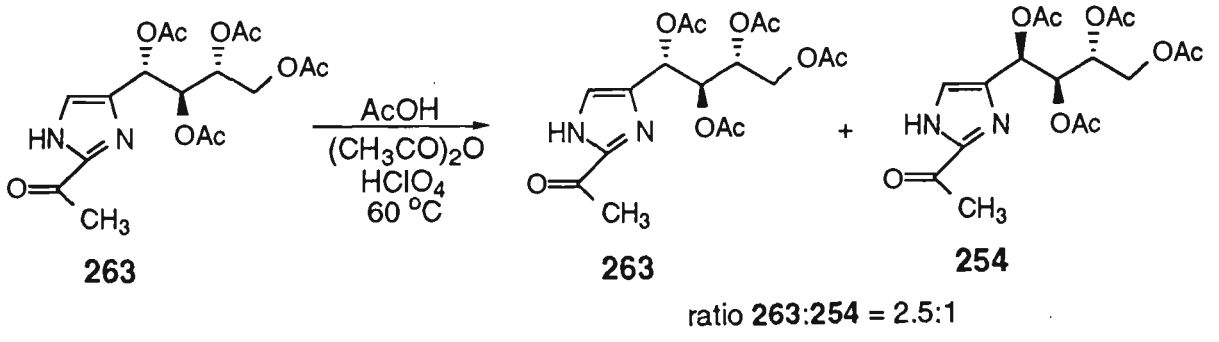
Figure 4.20 ^{1}H NMR spectra of the diasteromeric tetraacetate **259** in CD_3CN. Spectra identical to the enantiomer **264**.

4.7.2 Assignment of Tetraacetate Stereochemistry

The assignment of stereochemistries to all eight isomers relies on the assumed epimerisation of the C1' acetate moiety and a knowledge of the stereochemistry of the starting tetraol. For example, as no epimerisation occurred for the tetraacetates **254** and **255**, their respective enantiomers **256** and **258** were able to be identified *via* identical ^{1}H NMR spectra. This in turn lead to the identification of the C1' epimerised isomers **257** and **259** respectively. Classification of the final two isomers **263** and **264** was thus a simple matter of comparing ^{1}H NMR spectra along with a knowledge of the stereochemistry of the starting tetraol.

To confirm that epimerisation is occurring at C1', a small quantity of pure **263** was treated with acetic acid, acetic anhydride and perchloric acid catalyst for 6 hours at 60 °C. ^{1}H NMR analysis of the resulting tetraacetate mixture revealed both the starting acetate **263** *plus* the tetraacetate of THI **254** in a 2.5:1 ratio (Scheme 4.45). Formation of **254** was possible only though epimerisation of the stereochemistry at C1'.

Scheme 4.45



263 **263** **254**

ratio **263**:**254** = 2.5:1

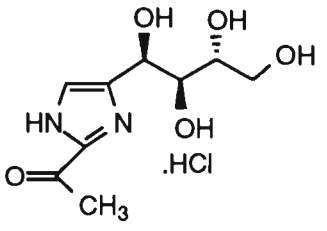
4.8 Conclusion

The fundamental chemical methodology used in this Chapter was developed in Chapter 3. The chiral side-chains necessary for incorporation onto the heteroaromatic imidazole ring were synthesised from optically pure D-mannitol and L-gulono-1,4-lactone and coupled to the iodoimidazole **36** *via* a Stille reaction. It was found that Stille cross-coupling of the hindered side-chains to 4-iodoimidazole **36** was low yielding when using the large, tributyltin moiety. Yields could be substantially improved, however, by the use of the analogous trimethylstannanes. Chiral alkynyltrimethylstannanes were synthesised from the corresponding alkynes, while the (*E*)-vinyltrimethylstannanes **197** and **198** were synthesised directly from the aldehydes **168** and **169** *via* a modified method of Hodgson.

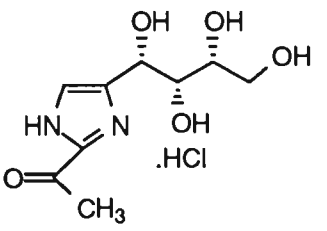
Application of the Sharpless AD reaction to the (*Z*)-alkenes **187** and **188** gave a number of anomalous results, with the cinchona alkaloid ligands unable to overcome the intrinsic diastereofacial selectivity of the chiral alkene in certain cases. Removal of the pentylidene protecting group enabled a free allylic alcohol moiety to direct attack, however, subsequent AD reactions showed poor selectivity. Asymmetric dihydroxylation of the (*E*)-alkenes **202** and **203** resulted in excellent selectivity, with de's in the range 90-99% achieved for the four diol products.

Deprotection of the eight tetraol precursors was achieved *via* treatment with HCl, with the reaction temperature and exposure time altered from that previously used. A small quantity of each

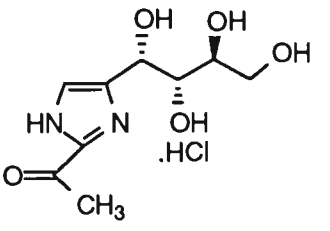
tetraol was converted to its corresponding tetraacetate to obtain clean, sharp ^1H NMR spectra of all eight tetraol products.



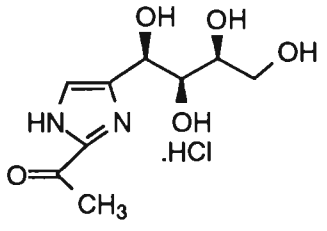
245



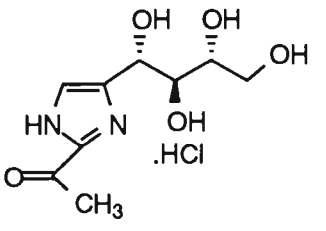
246



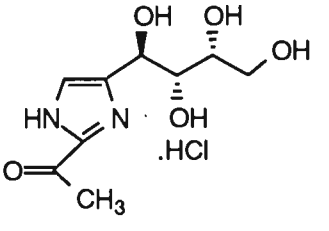
248



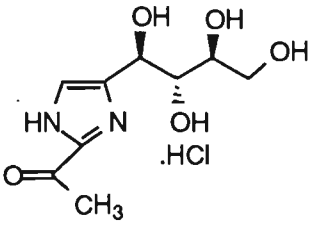
249



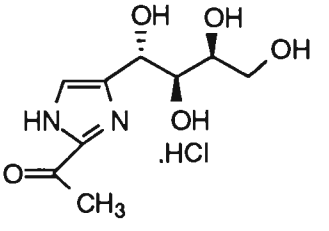
250



251



252



253

In summary, THI (**245**) and its seven optical isomers (**246**, **248-253**) were synthesised and isolated as their hydrochoride salts. The total synthesis of each isomer was carried out from a central imidazole core.

CHAPTER 5

CONCLUSION AND FUTURE WORK

This study has provided a large number of structural analogues of the THI molecule. The immunological assessment of these new compounds should provide information as to the importance of the tetrahydroxybutyl side-chain and its associated stereochemistry on the biological activity of THI and assist in evaluating its mode of action. A total of 13 analogues were synthesised as part of this study, including THI itself and its seven stereoisomers (Figure 5.1). All 13 molecules were constructed *via* a total synthesis starting from 1-ethoxymethyl-4-iodoimidazole. The most effective way to produce the THI analogues was to introduce the butyl side-chain *via* a Stille coupling reaction and then introduce the hydroxyl groups by the Sharpless AD reaction.

In general, each reaction of the synthetic protocols used proceeded efficiently to give the target molecules in good to excellent yields. One exception was the addition of the acetyl moiety to the C2 imidazole position, in which α-proton abstraction from the acetylating agent lead to the target methyl ketone being isolated in modest to good yields and a recovery of the starting imidazole. The other problem step was the AD reaction on (Z)-alkenes which gave diols of low optical purity, despite numerous attempts employing a number of different chiral ligand systems and altering the alkene substituents to assist OsO_4 attack.

Current and future work being carried out in these laboratories involves the synthesis of fluorescein and biotin labelled THI for cell binding studies. Analogues incorporating different heteroaromatic ring systems are also being developed to assess the biological significance of the imidazole ring system. These results and those

from the *in-vivo* and *in-vitro* testing of the THI analogues presented here will be reported elsewhere.

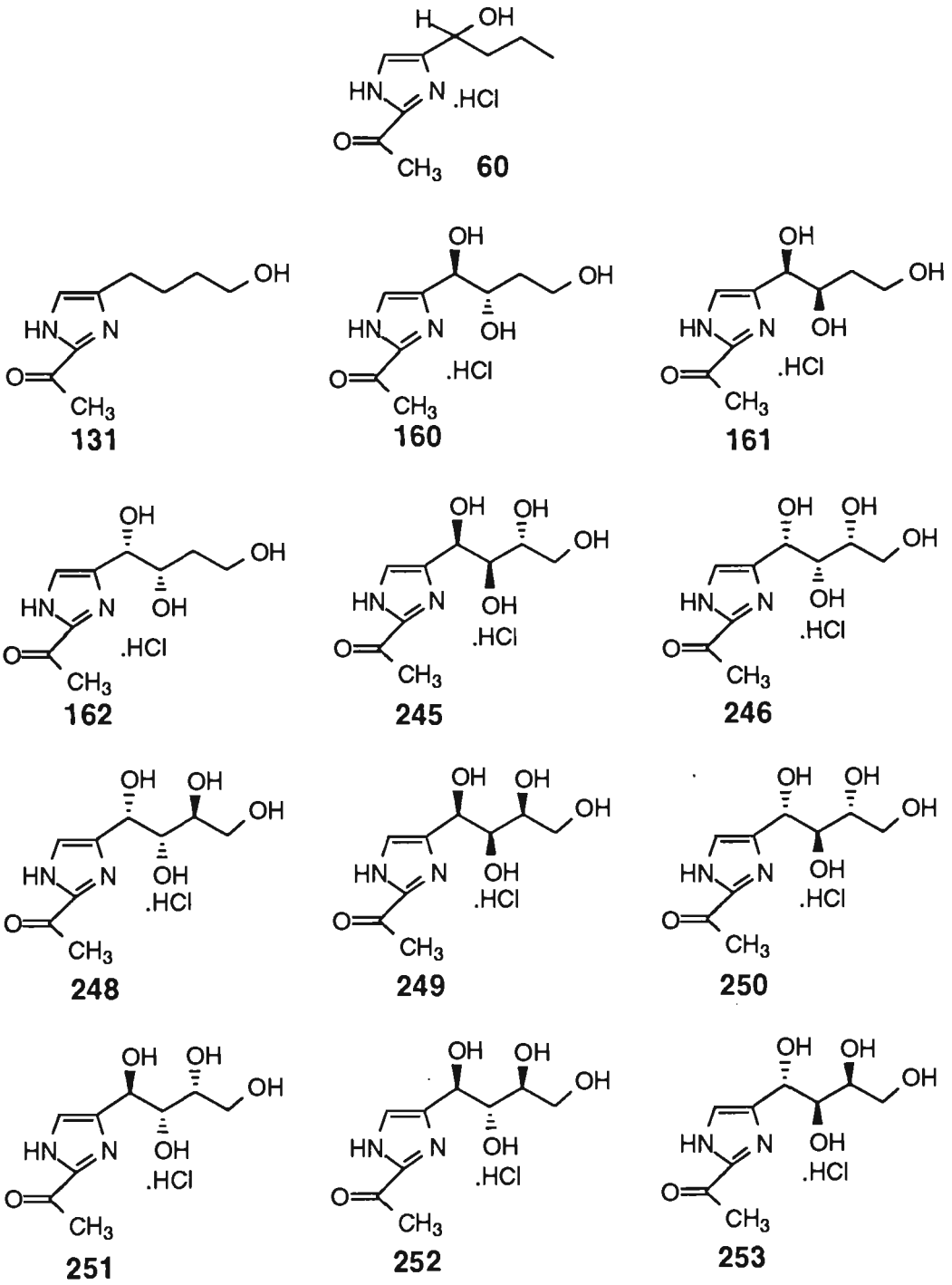


Figure 5.1 Summary of THI analogues synthesised

CHAPTER 6

EXPERIMENTAL

6.1 General Procedures

Melting points were determined on a Gallenkamp hot-stage apparatus and are uncorrected.

Infrared spectra were recorded on a BioRad Fourier Transform Infrared Spectrometer model FTS-7 as mulls in nujol or as neat liquids.

Optical rotations were recorded with a JASCO, DIP-370, Digital Polarimeter in analytical reagent (AR) grade solvents. Specific rotations ($[\alpha]_D$) are reported in degrees per decimeter, with the concentration (c) given in grams per 100 mL in the specified solvent.

^1H NMR spectra were recorded on the following instruments: JEOL FX 90Q F. T. NMR Spectrometer operating at 90 MHz, Varian Unity 400 F. T. NMR Spectrometer operating at 400 MHz, and Varian Unity 300 F. T. NMR Spectrometer operating at 300 MHz. Chemical shifts are reported as δ values in parts per million (ppm). Tetramethylsilane (TMS) was used as the nominal standard for all spectra recorded in deuterated chloroform (0.00 ppm). Proton spectra recorded in d_3-acetonitrile were referenced against the central solvent peak (1.95 ppm). Proton spectra recorded in CD_3OD were referenced against the central residual methyl solvent peak (3.55 ppm). For proton spectra recorded in D_2O, chemical shifts were referenced against the residual solvent peak (4.75 ppm). Data are recorded as follows: chemical shift (δ), integrated intensity, multiplicity (**s**: singlet, **d**: doublet, **t**: triplet, **q**: quartet, **m**: multiplet,

dd: doublet of doublets, etc. **b**: indicates some degrees of broadening in the signal), coupling constant(s) (Hz) and assignment (first order analyses of spectra were attempted where possible and, consequently, chemical shifts and coupling constants for multiplets may only be approximate).

A number of compounds containing imidazole H2 and H5 protons resulted in signals in the ^{1}H NMR spectrum which displayed non-equivalent coupling constants due to instrument limitations. Differences in the olefinic coupling constants were also observed in the ^{1}H NMR signals for H1' and H2' in certain 4-(1'-butenyl)imidazole derivatives, although these too should have been equivalent.

Chemical shifts are reported to three significant figures except where this is insufficient to distinguish peak sets within a molecule or between diastereoisomers. In such cases the chemical shifts are reported to four significant figures.

Two dimensional NMR experiments were carried out using the following instruments: Varian Unity 400 F.T. and Varian Unity 300 F.T. The pulse sequences used were homonuclear ($^{1}H/^{1}H$) correlation spectroscopy (COSY) and heteronuclear ($^{1}H/^{13}C$) correlation spectroscopy (HETCOR).

^{13}C NMR were recorded on a JEOL FX 90Q F.T. NMR Spectrometer (22.5 MHz), a Varian Unity 400 F.T. NMR Spectrometer (100 MHz) and a Varian Unity 300 F.T. NMR Spectrometer (75.6 MHz). The internal reference for ^{13}C NMR spectra was the central peak of

$CDCl_3$ (δ 77.0 ppm), and the central peak of $\underline{C}D_3CN$ (1.3 ppm). For carbon spectra run in D_2O a small quantity of methanol was used as an internal standard (49.0 ppm). Distortionless enhancement by polarisation transfer (DEPT) was used in the assignment of carbon spectra.

Low resolution mass spectra were recorded on a VG Quattro triple quadrupole mass Spectrometer. The protonated molecular ion ($M+H^+$), if present, significantly high mass ions and the more intense low mass ions are reported. Data are presented in the following order: *m/z* value, fragmented ion and relative intensity as a percentage of the base peak.

Microanalyses were performed by the Microanalytical Service Unit, Australian National University, Canberra or the Microanalytical Service Unit, Queensland University, Queensland.

Analytical thin layer chromatography (TLC) was conducted on plastic sheets coated with Merck Kieselgel 60 F_{254} at a 0.2 mm thickness. Preparative layer chromatography was conducted on glass plates coated with Merck Kieselgel 60 F_{254} at a 1.0 mm thickness. The developed plates were visualised under shortwave ultraviolet light. Column chromatography was conducted on silica gel absorbent using Fluka Kieselgel 60 (0.063-0.2 mm) as the absorbent and analytical reagent (AR) grade solvents as indicated.

The High Performance Liquid Chromatography (HPLC) was carried out using a Waters pump model 510 and a Waters μ Porasil column, (particle size 10 μm, pore size 125 Å, dimensions 25 mm x 100

mm). The U.V. detector was a Waters series 450 variable wavelength detector operating at 254 nm.

Solvents and reagents used in these reactions were purified according to well established procedures.[246] Tetrahydrofuran (THF) and diethyl ether were dried over sodium metal and purified by distillation from a purple suspension of sodium/benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), chloroform, acetonitrile, *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride and stored over molecular sieves (4Å) under nitrogen. Methanol was purified by distillation from magnesium methoxide.

All reactions, particularly reactions involving *n*-BuLi, Grignard reagents, LDA or NaH, were performed in glassware that had been oven-dried and cooled in a desiccator prior to use and under an anhydrous nitrogen atmosphere. All organic extracts were dried with anhydrous $MgSO_4$ and after filtration of these solutions, the bulk of the solvent was removed on a Buchi rotary evaporator. The last traces of solvent were removed under high vacuum.

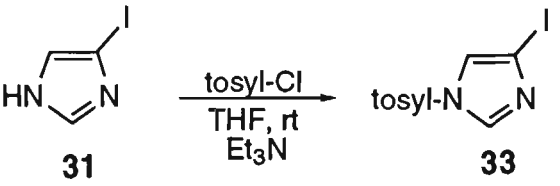
Molecular modelling was performed using the CVFF force field parameters of Insight II, Version 2.3.0., Biosym Tecnologies, San Diego, C.A.

The following known compounds were synthesised *via* reported literature procedures: 2,4,5-triiodoimidazole **30**,[107] 4(5)-iodo imidazole **31**,[108] 4-iodo-1-tritylimidazole **32**,[125] 1-tritylimidazole **37**,[125] 1-diethoxymethylimidazole **44**,[120] 1-ethoxymethylimidazole

46,[121] bis(acetonitrile)palladium(II) chloride[238] and tetrakis(triphenylphosphine)palladium(0).[247]

6.2 Experimental Chapter 2

4-Iodo-1-tosylimidazole (33)



31 **33**

To a solution of 4(5)-iodoimidazole **31** (2.0 g, 10.3 mmol) and *p*-toluenesulfonyl chloride (1.97 g, 10.3 mmol) in anhydrous THF (40 mL) under N_2 was added triethylamine (1.04 g, 10.3 mmol) and the solution was stirred at rt for 24 h. Solid triethylammonium chloride was removed by filtration, the filtrate was diluted with CH_2Cl_2 (50 mL), washed with water (20 mL), dried ($MgSO_4$) and the solvent removed. Recrystallisation from ethanol gave the title compound as a white solid (2.80 g, 78%), mp 146-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, J = 1.2 Hz, H2); 7.83 (2H, d, J = 8.4 Hz, Ar-H2,6); 7.38 (2H, d, J = 8.4 Hz, Ar-H3,5); 7.37 (1H, d, J = 1.2 Hz, H5); 2.46 (3H, s, CH_3).

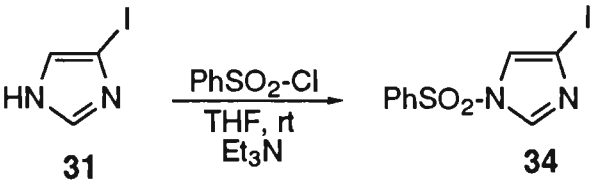
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8 (C2); 137.6 (Ar-C1); 134.2 (C5); 130.6 (Ar-C2,6); 127.5 (Ar-C3,5); 122.3 (Ar-C4); 85.2 (C4); 21.8 (CH_3).

MS (ES+ve) *m/z* 349 ($M+H^+$, 100%); 278 (52%); 155 ($tosyl^+$, 22%).

IR (nujol) 1176 (S=O); 1138 (S=O); 1076; 679 cm^{-1}.

Anal. calcd for $C_{10}H_9N_2O_2SI$: C, 34.50; H, 2.61; N, 8.05. Found: C, 34.48; H, 2.52; N, 7.90.

1-Benzenesulfonyl-4-iodoimidazole (34)



31 34

To a solution of 4(5)-iodoimidazole **31** (3.0 g, 15.5 mmol) and benzenesulfonyl chloride (2.74 g, 15.5 mmol) in anhydrous THF (40 mL) under N_2 was added triethylamine (1.57 g, 15.5 mmol) and the solution was stirred at rt for 16 h. The mixture was filtered and the solvent removed. Recrystallisation from ethanol gave the title compound as a white solid (4.85 g, 78%), mp 124-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 8.4 Hz, Ar-H2,6); 7.90 (1H, t, J = 1.2 Hz, H2); 7.75-7.71 (1H, m, Ar-H4); 7.63-7.58 (2H, m, Ar-H3,5); 7.40 (1H, t, J = 1.2 Hz, H5).

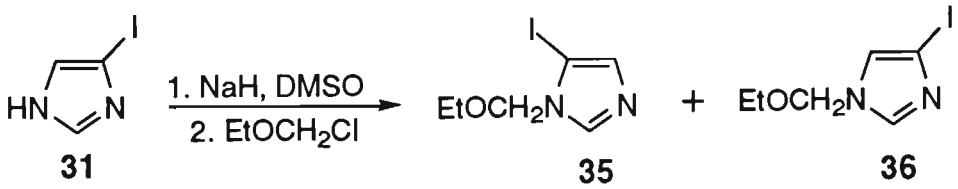
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (C2); 137.1 (Ar-C1); 135.2 (C5); 129.9 (Ar-C2,6); 127.4 (Ar-C3,5); 122.3 (Ar-C4); 85.4 (C4).

MS (ES+ve) *m/z* 335 ($M+H^+$, 100%); 141 ($PhSO_2^+$, 22%).

IR (nujol) 3140; 1175 (S=O); 1143 (S=O); 1072; 920 cm^{-1}.

Anal. calcd for $C_9H_7N_2O_2SI$: C, 32.35; H, 2.11; N, 8.38. Found: C, 32.39; H, 2.07; N, 8.44.

1-Ethoxymethyl-5-iodoimidazole (35) and 1-ethoxymethyl -4-iodoimidazole (36)



31 35 36

To a solution of 4(5)-iodoimidazole **31** (4.0 g, 20.6 mmol) in anhydrous DMSO (20 mL) was added NaH (0.54 g, 22.7 mmol) and the mixture was stirred at 80 °C under N_2 for 2 h. Chloromethyl ethyl ether (2.34 g, 24.7 mmol) in DMSO (4 mL) was added and the solution was stirred for a further 2 h at 80 °C. The mixture was then cooled to rt, poured into a 5% aqueous solution of $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to leave a black oil which was purified by column chromatography (30% ethyl acetate / hexane) to give the protected imidazoles **35** (260 mg, 5%) and **36** (2.44 g, 47%) as light yellow oils. The 1,4- and 1,5-isomers were distinguished *via* ^{1}H NMR 1D nOe experiments (section 2.1).

35: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, s, H2); 7.15 (1H, s, H4); 5.28 (2H, s, CH_2); 3.49 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2$); 1.20 (3H, t, J = 6.8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (C2); 137.3 (C4); 76.3 (C5); 69.4 (CH_2); 64.2 ($CH_3\underline{C}H_2$); 14.6 (CH_3).

MS (ES+ve) *m/z* 253 ($M+H^+$, 100%); 59 ($EtOCH_2^+$, 8%).

36: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, J = 1.2 Hz, H2); 7.14 (1H, d, J = 1.2 Hz, H5); 5.24 (2H, s, CH_2); 3.45 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2$); 1.19 (3H, t, J = 6.8 Hz, CH_3).

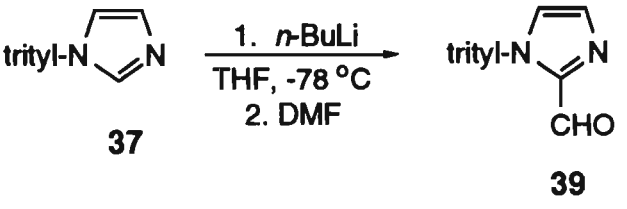
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C2); 124.3 (C5); 82.6 (C4); 76.2 (CH_2); 64.5 ($CH_3\,\underline{C}H_2$); 14.6 (CH_3).

MS (ES+ve) *m/z* 253 ($M+H^+$, 100%); 59 ($EtOCH_2^+$, 8%).

IR (neat) 3101; 2975; 2880; 1473; 1388; 1218; 1107; 933 cm^{-1}.

HRMS calcd for $C_6H_9N_2OI$ 251.9760, found 251.9757.

2-Formyl-1-tritylimidazole (39)



37 39

To a solution of 1-tritylimidazole **37** (1.0 g, 3.2 mmol) in anhydrous THF (40 mL) at 0 °C under N_2 was added *n*-BuLi in hexanes (3.87 mmol) and the solution was stirred for 30 min at 0 °C. DMF (0.94 g, 2.9 mmol) was then added and the mixture was stirred for 30 min at rt and then poured into water (15 mL). The phases were separated and the organic extract was dried ($MgSO_4$) and concentrated. Recrystallisation from ethyl acetate / cyclohexane gave the title imidazole as a white solid (790 mg, 73%), mp 183-184 °C, (lit.[115] mp 189-190 °C).

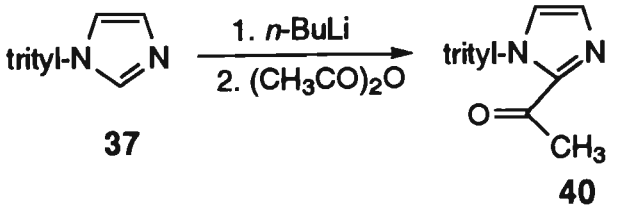
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, s, CHO); 7.33-7.31 (9H, m, trityl Ar-H3,4,5); 7.29 (1H, d, J = 1.2 Hz, H4); 7.13-7.10 (6H, m, trityl Ar-H2,6); 7.02 (1H, dd, J = 0.4, 0.8 Hz, H5).

MS (ES+ve) *m/z* 243 (Ph_3C^+, 100%).

MS (ES-ve) *m/z* 95 ($C_4H_3N_2O^-$, 100%).

^{1}H NMR was consistent with that reported in the literature.[115]

2-Acetyl-1-tritylimidazole (40)



37 40

To a solution of 1-tritylimidazole **37** (1.0 g, 3.2 mmol) in anhydrous THF (40 mL) at 0 °C under N_2 was added *n*-BuLi in hexanes (3.87 mmol) and the solution stirred for 30 min before the addition of acetic anhydride (0.99 g, 9.68 mmol). The reaction was stirred for a further 30 min at rt and then poured into water (15 mL). The phases were separated and the organic phase was dried ($MgSO_4$) and concentrated to leave a red oil. Purification by column chromatography (35% ethyl acetate / hexane) gave the title compound as a cream solid (0.33 g, 29%), plus starting imidazole (0.33 g). An analytical sample was recrystallised from ethanol, mp 129-130 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (9H, m, trityl Ar-H3,4,5); 7.14 (1H, d, J = 1.2 Hz, H4); 7.08-7.05 (6H, m, trityl Ar-H2,6); 7.03 (1H, d, J = 1.6 Hz, H5); 2.32 (3H, s, CH_3).

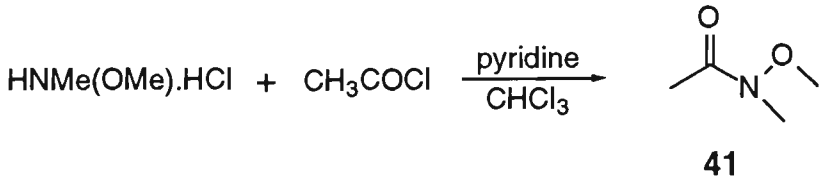
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 186.9 (C=O); 145.6 (C2); 142.8 (Ar-C1); 129.9 (Ar-C2,6); 128.7 (C4); 127.9 (C5); 127.5 (Ar-C3,5); 127.2 (Ar-C4); 77.8 ($\underline{C}Ph_3$); 27.9 (CH_3).

MS (ES+ve) *m/z* 353 ($M+H^+$, 20%); 243 (CPh_3, 100%).

IR (nujol) 1703 (C=O); 1190; 1102; 983 cm^{-1}.

Anal. calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 82.21; H, 5.83; N, 7.87.

N-Methoxy-*N*-methylacetamide (41)



41

N,O-Dimethylhydroxyamine hydrochloride (4.0 g, 41 mmol) and acetyl chloride (2.89 g, 33 mmol) were dissolved in anhydrous chloroform (400 mL) and the solution was cooled to 0 °C.[118] Pyridine (6.89 g, 87.1 mmol) was added and the mixture stirred for 1 h at rt. The solvent was removed *in vacuo* and the residue partitioned between a sat. aqueous solution of NaCl containing 5% HCl and a 1:1 mixture of ether and dichloromethane. The phases were separated and the aqueous solution extracted twice with ether / CH_2Cl_2 (1:1). The combined extracts were dried ($MgSO_4$) and the solvent was removed to leave a light yellow oil. Bulb-to-bulb distillation (67 °C/20 mmHg) gave the title compound as a clear oil (3.14 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s, OCH_3); 3.19 (3H, s, NCH_3); 2.13 (3H, s, CH_3CO).

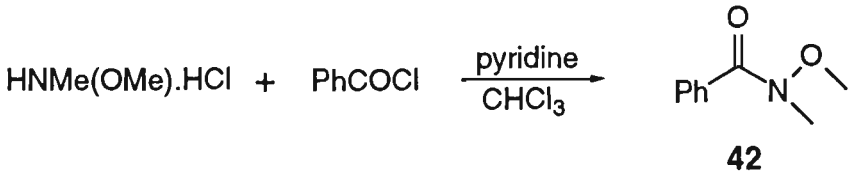
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.7 (C=O); 61.0 (OCH_3); 32.2 (NCH_3); 19.6 ($CO\underline{C}H_3$).

MS (ES+ve) *m/z* 104 ($M+H^+$, 100%).

IR (neat) 2947; 1657 (C=O); 1383; 1188; 957 cm^{-1}.

HRMS calcd for $C_4H_9NO_2$ 103.0633, found 103.0601.

N-Methoxy-*N*-methylbenzamide (42)



42

Using the procedure described above for the synthesis of **41**, compound **42** was obtained as a clear oil, (yield=98%) after purification by bulb-to-bulb distillation (75 °C/0.5 mmHg).

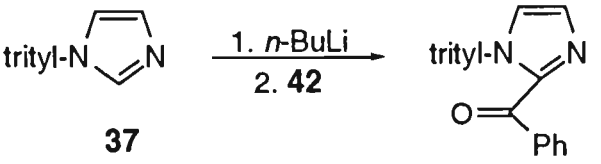
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (2H, m, Ar-H2,6); 7.47-7.38 (3H, m, Ar-H3,4,5); 3.56 (3H, s, OCH_3); 3.36 (3H, s, CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 170.0 (C=O); 134.3 (Ar-C1); 130.4 (Ar-C4); 128.0 (Ar-C2,6); 127.9 (Ar-C3,5); 60.9 (OCH_3); 33.8 (CH_3).

MS (ES+ve) *m/z* 166 ($M+H^+$, 100%); 80 (35%).

IR (neat) 2934; 1653 (C=O); 1375; 1208; 990 cm^{-1}.

2-Benzoyl-1-tritylimidazole (43)



37 **43**

To a solution of 1-tritylimidazole **37** (1.0 g, 3.23 mmol) in anhydrous THF (25 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (3.55 mmol) and the reaction stirred for 1 h at -78 °C. Amide **42** (640 mg, 3.88 mmol) was then added and the reaction stirred for 90 min at 0 °C and then quenched with a sat. aqueous solution of NH_4Cl (10 mL). The phases were separated and the organic phase was dried ($MgSO_4$) and concentrated to leave a thick black syrup. Purification by column chromatography (35% ethyl acetate / hexane), gave the title compound as a light yellow solid (0.84 g, 63%), mp 203-204 °C.

^{1}H NMR, In part (400 MHz, $CDCl_3$) δ 7.69-7.67 (3H, m, Ar-H3,4,5); 7.43-7.49 (2H, m, Ar-H2,6); 7.31-7.22 (9H, m, trityl Ar-H3,4,5); 7.19-7.17 (6H, m, trityl Ar-H2,6).

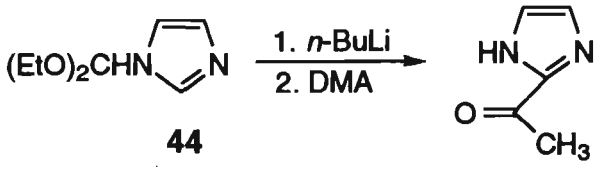
^{13}C NMR, In part (100 MHz, $CDCl_3$) δ 183.2 (C=O); 144.9 (C2); 142.6 (trityl Ar-C1); 137.5 (Ar-C1); 132.0 (C4); 130.2 (Ar-C2,6); 130.1

(trityl Ar-C2,6); 127.7 (Ar-C3,5); 127.5 (trityl Ar-C3,5); 127.1 (Ar-C4); 126.2 (C5); 77.4 ($\underline{C}Ph_3$).

MS (ES+ve) *m/z* 415 ($M+H^+$, <1%); 243 (Ph_3C^+, 100%); 173 ($C_3H_2N_2COPh^+$, 95%).

IR (nujol) 1655 (C=O); 1205; 1128 cm^{-1}.

2-Acetylimidazole (45)



44 **45**

To a solution of 1-diethoxymethylimidazole **44** (1.0 g, 5.88 mmol) in anhydrous THF (25 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (6.47 mmol) and the reaction warmed to rt and stirred for 1 h. The reaction was then cooled to -78 °C, DMA (1.54 g, 17.65 mmol) added and the reaction was stirred for 30 min before warming to rt. The reaction mixture was poured into water (10 mL), the phases were separated and the organic extract was dried ($MgSO_4$) and concentrated. Purification by column chromatography (50% ethyl acetate / hexane) gave the title compound as a white solid (250 mg, 39%), mp 130-132 °C, (lit.[120] mp 136-137 °C).

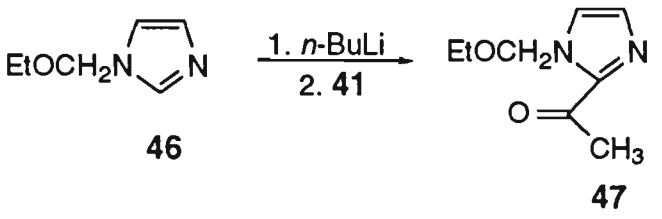
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, H4,5); 2.68 (3H, s, CH_3).

^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (2H, s, H4,5); 2.55 (3H, s, CH_3).

MS (ES+ve) *m/z* 111 ($M+H^+$, 100%).

^{1}H NMR data were consistent with that reported in the literature.[120]

2-Acetyl-1-ethoxymethylimidazole (47)



46 47

To a solution of 1-ethoxymethylimidazole **46** (1.0 g, 7.94 mmol) in anhydrous THF (15 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (8.73 mmol) and the resulting black solution was stirred for 1 h. Amide **41** (1.23 g, 11.9 mmol) in THF (5 mL) was added slowly and the reaction was stirred for 1 h at -78 °C and then for 1 h at rt. Water (5 mL) was then added and the phases were separated and the organic extract was dried ($MgSO_4$) and concentrated to leave a thick black syrup. Purification by column chromatography (20% ethyl acetate / hexane) gave the title compound as a light tan oil (400 mg, 40%). An analytical sample was purified by bulb-to-bulb distillation (85 °C/0.1 mmHg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, d, *J* =1.2 Hz, H4); 7.18 (1H, d, *J* = 1.2 Hz, H5); 5.78 (2H, s, CH_2); 3.53 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2$); 2.67 (3H, s, $COCH_3$); 1.19 (3H, t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7 (C=O); 142.8 (C2); 129.5 (C4); 124.7 (C5); 77.0 (CH_2); 64.9 ($CH_3\underline{C}H_2$); 27.3 ($CO\underline{C}H_3$); 14.8 (CH_3).

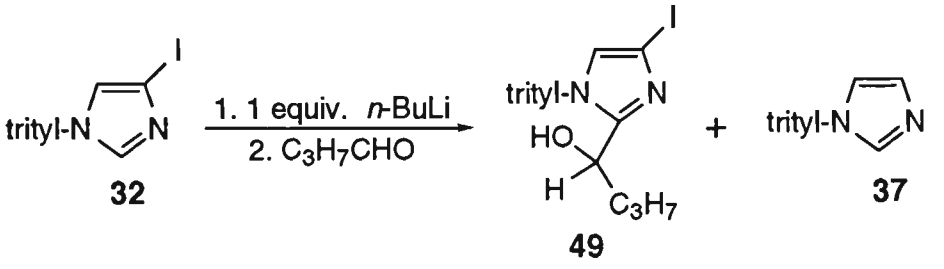
MS (ES+ve) *m/z* 169 ($M+H^+$, 100%); 161 (24%); 59 ($EtOCH_2^+$, 21%).

IR (neat) 3111; 2978; 2932; 1682 (C=O); 1409; 1112-1095 (COC); 635 cm^{-1}.

HRMS calcd for $C_8H_{12}N_2O_2$ 168.0899, found 168.0913.

Reaction of Iodoimidazole 32 with *n*-BuLi and Butanal

i) Stoichiometric *n*-BuLi. 1-Tritylimidazole (37) and 2-(1'-hydroxy-1'-butyl)-4-iodo-1-tritylimidazole (49)



To a solution of iodoimidazole **32** (1.0 g, 2.29 mmol) in anhydrous THF (20 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (2.29 mmol) and the solution was stirred for 45 min at -78 °C. Freshly distilled butanal (180 mg, 2.52 mmol) was added and the reaction was stirred for a further 45 min at -78 °C. The mixture was then warmed to rt and a sat. aqueous solution of NH_4Cl was added. The phases were separated and the organic solution was dried ($MgSO_4$) and concentrated. Purification by column chromatography (45% ethyl acetate / hexane) gave 1-tritylimidazole **37** (220 mg, 31%, mp 215-216 °C) as a light yellow solid and 2-(1'-hydroxy-1'-butyl)-4-iodo-1-tritylimidazole **49** (350 mg, 30%, mp 176-177 °C) as a white solid.

37: ^{1}H NMR In part (400 MHz, $CDCl_3$) δ 7.47 (1H, t, *J* =1.2 Hz, H2); 7.35-7.32 (9H, m, trityl Ar-H3,4,5); 7.15-7.12 (6H, m, trityl Ar-H2,6); 7.02 (1H, t, *J* = 1.2 Hz, H4); 6.83 (1H, t, *J* = 1.2 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (Ar-C1); 139.0 (C4); 129.8 (Ar-C2,6); 128.3 (C4); 128.0 (Ar-C3,5); 127.2 (Ar-C4); 121.7 (C5); 75.2 ($\underline{C}Ph_3$).

MS (ES+ve) *m/z* 311 ($M+H^+$, 11%); 243 (CPh_3^+, 100%).

IR (nujol) 1200; 1074; 1031; 908; 745 cm^{-1}.

49: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.33 (9H, m, trityl Ar-H3,4,5); 7.18-7.15 (6H, m, trityl Ar-H2,6); 6.76 (1H, s, H5); 3.95-3.90 (1H, m, C$\underline{H}$OH); 1.52-1.42 (1H, m, CHOHC$\underline{H}_A$H$_B$); 1.28-1.20 (1H, m, CHOHCH$_A\underline{H}_B$); 0.77-0.68 (1H, m, C$\underline{H}_A$H$_B$CH$_3$); 0.53 (3H, t, J = 7.2 Hz, CH$_3$); 0.36-0.28 (1H, m, CH$_A\underline{H}_B$CH$_3$).

^{13}**C NMR** (100 MHz, $CDCl_3$) δ 155.5 (C2); 149.1 (Ar-C1); 129.7 (Ar-C2,6); 128.3 (Ar-C3,5); 128.2 (Ar-C4); 125.9 (C5); 79.5 (C4); 75.6 ($\underline{C}$Ph$_3$); 67.3 (CHOH); 38.3 (CHOH$\underline{C}$H$_2$); 19.1 ($\underline{C}$H$_2$CH$_3$); 13.5 (CH$_3$).

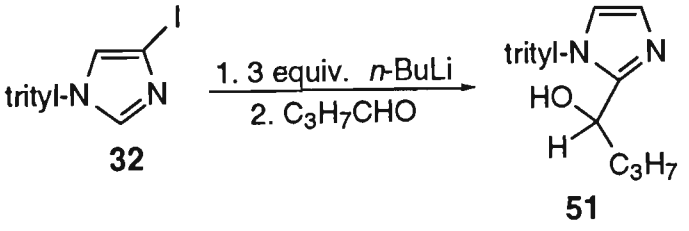
MS (ES+ve) *m/z* 509 (M+H$^+$, 8%); 267 (M-CPh$_3^+$, 18%); 243 (CPh$_3^+$, 100%).

IR (nujol) 3309 (OH, b); 1219; 1109; 946 cm^{-1}.

Anal. calcd for $C_{26}H_{25}N_2OI$: C, 61.43; H, 4.96; N, 5.51. Found: C, 61.88; H, 5.34; N, 5.53.

ii) Excess *n*-BuLi.

2-(1'-Hydroxy-1'-butyl)-1-tritylimidazole (51)



32 **51**

The reaction described above was repeated using 3 molar equivalents of *n*-BuLi in hexanes (6.87 mmol) and 3.1 molar equivalents of butanal (0.51 g, 7.10 mmol). Purification by column chromatography (30% ethyl acetate / hexane) gave 2-(1'-hydroxy-1'-butyl)-1-tritylimidazole **51** as a white solid (310 mg, 31%), mp 187-188 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (9H, m, trityl Ar-H3,4,5); 7.19-7.17 (6H, m, trityl Ar-H2,6); 7.00 (1H, d, J = 1.6 Hz, H4); 6.72 (1H, d, J = 1.6 Hz, H5); 4.00-3.97 (1H, m, C<u>H</u>OH); 1.53-1.44 (1H, m, CHOHC<u>H</u>$_A$H$_B$); 1.32-1.23 (1H, m, CHOHCH$_A$<u>H</u>$_B$); 0.82-0.73 (1H, m, C<u>H</u>$_A$H$_B$CH$_3$); 0.55 (3H, t, J = 7.2 Hz, CH_3); 0.46-0.38 (1H, m, CH$_A$<u>H</u>$_B$CH$_3$).

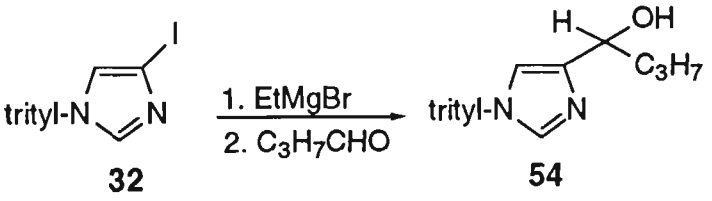
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 153.4 (C2); 142.7 (Ar-C1); 129.9 (Ar-C2,6); 128.1 (Ar-C3,5); 128.0 (Ar-C4); 126.0 (C5); 120.8 (C4); 75.1 (<u>C</u>Ph$_3$); 67.4 (CHOH); 38.5 (CHOH<u>C</u>H$_2$); 19.2 (<u>C</u>H$_2$CH$_3$); 13.6 (CH_3).

MS (ES+ve) *m/z* 383 ($M+H^+$, 17%); 243 (CPh_3^+, 61%); 83 (41%); 74 (100%).

IR (nujol) 3198 (OH, b); 1497; 1235; 1114 cm^{-1}.

Anal. calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.54; H, 7.23; N, 7.38.

4-(1'-Hydroxy-1'-butyl)-1-tritylimidazole (54)



32 54

To a solution of iodoimidazole **32** (3.0 g, 6.70 mmol) in anhydrous CH_2Cl_2 (27 mL) was added EtMgBr in ether (7.60 mmol) and the mixture was stirred for 30 min at rt. Freshly distilled butanal (0.55 g, 7.60 mmol) was then added and the solution was left to stir for 16 h before quenching with a sat. aqueous solution of NH_4Cl (10 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined extracts were dried ($MgSO_4$) and concentrated to leave a light yellow solid. Recrystallisation from

toluene gave the title compound as a white solid (1.79 g, 68%), mp 142-144 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 1.6 Hz, H2); 7.34-7.32 (9H, m, trityl Ar-H3,4,5); 7.14-7.12 (6H, m, trityl Ar-H2,6); 6.70 (1H, dd, *J* = 0.4, 1.2 Hz, H5); 4.63 (1H, t, *J* = 6.8 Hz, C<u>H</u>OH); 1.80-1.74 (2H, m, CHOHC<u>H$_2$</u>); 1.46-1.26 (2H, m, C<u>H$_2$</u>CH$_3$); 0.92 (3H, t, *J* = 7.2 Hz, CH_3).

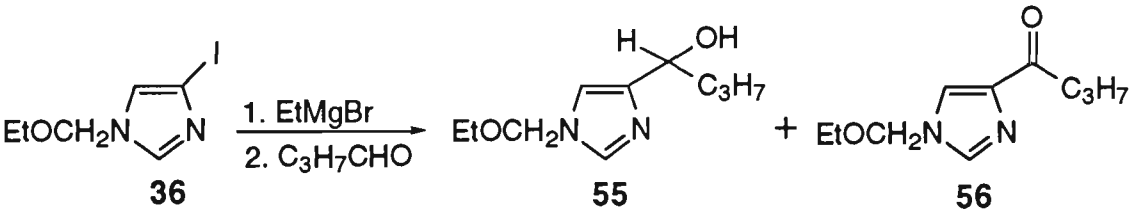
^{13}C NMR, In part (22.5 MHz, $CDCl_3$) δ 144.7 (C2); 142.5 (Ar-C1); 138.6 (C4); 129.8 (Ar-C2,6); 128.0 (Ar-C3,5); 117.3 (C5); 75.4 (<u>C</u>Ph$_3$); 68.4 (CHOH); 39.2 (CHOH<u>C</u>H$_2$); 18.9 (<u>C</u>H$_2$CH$_3$); 13.9 (CH_3).

MS (CI+ve) *m/z* 258 (16%); 243 (Ph_3C^+, 100%); 180 (15%); 165 (73%); 141 ($C_7H_{13}N_2O^+$, 43%); 123 (100%).

IR (nujol) 3174 (OH, b); 1152; 1018; 710 cm^{-1}.

Anal. calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.49; H, 7.08; N, 7.29.

1-Ethoxymethyl-4-(1'-hydroxy-1'-butyl)imidazole (55) and 1-ethoxymethyl-4-(1'-oxo-1'-butyl)imidazole (56)



36 55 56

Using the procedure described above for the synthesis of **54** and iodoimidazole **36**, compound **55** was obtained as a cream solid, (yield=70%, mp 57-59 °C) and the ketone 1-ethoxymethyl-4-(1'-oxo-1'-butyl)imidazole **56** as a tan oil (yield=10%) after purification by column chromatography (50% ethyl acetate / hexane).

55: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 0.8 Hz, H2); 6.94 (1H, s, H5); 5.24 (2H, s, EtOC<u>H$_2$</u>); 4.68 (1H, t, *J* = 6.4 Hz, C<u>H</u>OH); 3.45

(2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.61 (1H, s(b), OH); 1.85-1.79 (2H, m, $CHOHC\underline{H}_2$); 1.55-1.35 (2H, m, $C\underline{H}_2CH_3$); 1.19 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.96 (3H, t, J = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6 (C2); 136.8 (C4); 114.5 (C5); 76.2 ($EtO\underline{C}H_2$); 68.1 (CHOH); 64.3 ($CH_3\underline{C}H_2O$); 39.0 ($CHOH\underline{C}H_2$); 18.9 ($\underline{C}H_2CH_3$); 14.7 ($\underline{C}H_3CH_2O$); 13.9 (CH_3).

MS (ES+ve) *m/z* 199 ($M+H^+$, 100%); 181 ($M-OH^+$, 14%).

IR (nujol) 3160 (OH, b); 1160; 1110; 1030; 970; 810; 670 cm^{-1}.

56: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 1.2 Hz, H2); 7.62 (1H, d, J = 1.2 Hz, H5); 5.33 (2H, s, $EtOC\underline{H}_2$); 3.49 (2H, q, J = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.96 (2H, t, J = 7.2 Hz, $COCH_2$); 1.76 (2H, septet, J = 7.6 Hz, $CH_2C\underline{H}_2CH_3$); 1.20 (3H, t, J = 6.8 Hz, $\underline{C}H_3CH_2O$); 1.00 (3H, t, J =7.6 Hz, CH_3).

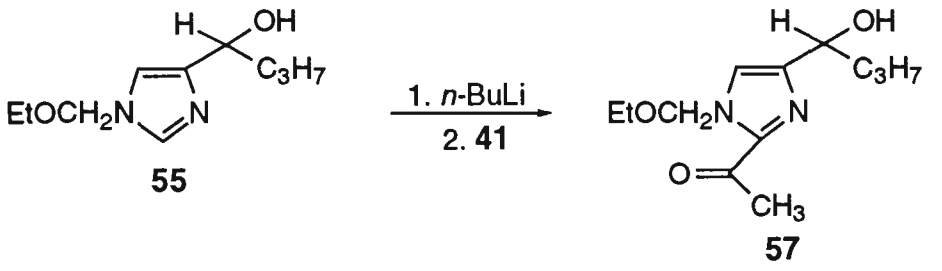
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O); 142.5 (C2); 137.2 (C4); 122.7 (C5); 76.6 ($EtO\underline{C}H_2$); 64.7 ($CH_3\underline{C}H_2O$); 40.6 ($CO\underline{C}H_2$); 17.4 ($\underline{C}H_2CH_3$); 14.5 ($\underline{C}H_3CH_2O$); 13.7 (CH_3).

MS (EI+ve) *m/z* 197 ($M+H^+$, 26%); 169 (84%); 154 (100%); 138 (46%); 127 (65%); 96 (65%); 84 (56%).

IR (neat) 3115; 2964; 2932; 2876; 1675 (C=O); 1534; 1168; 1107 cm^{-1}.

HRMS calcd for $C_{10}H_{16}N_2O_2$ 196.1212, found 196.1208.

2-Acetyl-1-ethoxymethyl-4-(1'-hydroxy-1'-butyl) imidazole (57)



55 **57**

To a solution of imidazole **55** (0.80 g, 4.04 mmol) in anhydrous THF (10 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (8.84 mmol) and the solution was stirred for 1 h. Amide **41** (1.04 g, 10.1 mmol) in THF (5 mL) was slowly added and the solution was stirred for 1 h at -78 °C and then for 2 h at rt. The mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were dried ($MgSO_4$), concentrated and purified by column chromatography (30% ethyl acetate / hexane, then pure methanol after elution of the acetylated product) to give the title compound as a tan oil (200 mg, 21%), plus the starting alcohol **55** (580 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, s, H5); 5.75 (2H, s, $EtOC\underline{H}_2$); 4.72 (1H, s(b), $C\underline{H}OH$); 3.54 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.73 (1H, s(b), OH); 2.65 (3H, s, $COCH_3$); 1.84-1.78 (2H, m, $CHOHC\underline{H}_2$); 1.57-1.38 (2H, m, $C\underline{H}_2CH_3$); 1.20 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.97 (3H, t, *J* = 7.4 Hz, CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 190.8 (C=O); 146.2 (C2); 142.1 (C4); 120.5 (C5); 77.1 ($EtOC\underline{H}_2$); 68.2 (CHOH); 64.9 ($CH_3\underline{C}H_2O$); 39.4 ($CHOH\underline{C}H_2$); 27.3 ($CO\underline{C}H_3$); 18.7 ($\underline{C}H_2CH_3$); 14.8 ($\underline{C}H_3CH_2O$); 13.8 (CH_3).

MS (ES+ve) *m/z* 241 ($M+H^+$, 25%); 223 ($M-OH^+$, 63%); 181 ($M-EtOCH_2^+$, 19%); 165 (19%); 59 ($EtOCH_2^+$, 22%); 42 (100%).

IR (neat) 3408 (OH, b); 2959; 2933; 2873; 1680 (C=O); 1457; 1387; 1353; 1108; 953; 803 cm^{-1}.

HRMS calcd for $C_{12}H_{20}N_2O_3$ 240.1474, found 240.1466.

4-(1'-(*t*-Butyldimethylsilyloxy)-1'-butyl)-1-ethoxymethyl imidazole (58)

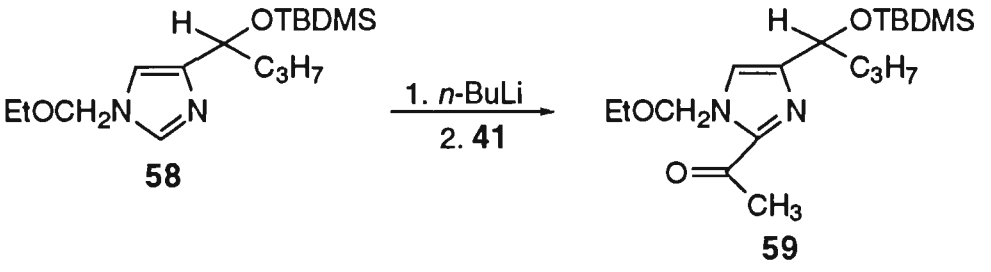
A solution of imidazole (600 mg, 8.89 mmol) and TBDMS-Cl (670 mg, 4.44 mmol) in anhydrous DMF (4 mL) was cooled to 0 °C and set stirring under N_2. Imidazole **55** (790 mg, 3.99 mmol) in anhydrous DMF (4 mL) was then added and the mixture was stirred for 48 h at rt. The solution was then diluted with ether (50 mL), washed with water (3 x 10 mL), dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography (40% ethyl acetate / hexane) gave the title compound as a pale oil (870 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 1.2 Hz, H2); 6.90 (1H, d, J = 0.8 Hz, H5); 5.23 (2H, s, $EtOC\underline{H}_2$); 4.75 (1H, t, J = 5.6 Hz, CHOSi); 3.42 (2H, dq, J = 1.2, 7.2 Hz, $CH_3C\underline{H}_A\underline{H}_BO$); 1.77-1.72 (2H, m, CH_2); 1.43-1.21 (2H, m, $C\underline{H}_2CH_3$); 1.17 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.92-0.86 (12H, m, $C(CH_3)_3$, CH_3); 0.06; -0.04 (2 x 3H, 2 x s, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (C4); 136.3 (C2); 114.8 (C5); 76.2 ($EtO\underline{C}H_2$); 70.2 (CHOSi); 64.1 ($CH_3\underline{C}H_2O$); 40.9 ($\underline{C}H_2CH_2CH_3$); 25.9 ($C(\underline{C}H_3)_3$); 18.5 ($\underline{C}H_2CH_3$); 18.2 ($\underline{C}(CH_3)_3$); 14.7 ($\underline{C}H_3CH_2O$); 14.1 (CH_3); -4.7; -4.9 ($Si(CH_3)_2$).

HRMS calcd for $C_{15}H_{29}N_2O_2Si$ ($M-CH_3$) 297.1998, found 297.2007.

2-Acetyl-4-(1'-(*t*-butyldimethylsilyloxy)-1'-butyl)-1-ethoxymethylimidazole (59)



58 59

To a solution of imidazole **58** (0.66 g, 2.12 mmol) in anhydrous THF (5 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (2.54 mmol) and the solution left to stir for 1 h. Freshly distilled amide **41** (306 mg, 2.97 mmol) in anhydrous THF (5 mL) was added dropwise and the mixture was stirred for 1 h at -78 °C and then for 1 h at rt. The solution was diluted with CH_2Cl_2 (30 mL) and washed consecutively with a 5% aqueous solution of $NaHCO_3$ (10 mL) and water (10 mL). The solution was then dried ($MgSO_4$) and the solvent was removed to leave a dark red oil. Purification by column chromatography (20% ethyl acetate / hexane) gave the title compound as a yellow oil (390 mg, 52%).

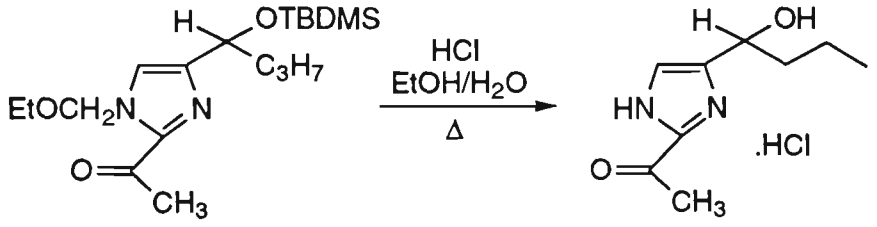
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (1H, s, H5); 5.75 (1H, d, J_{AB} = 10 Hz, $EtOC\underline{H}_AH_B$); 5.71 (1H, d, J_{AB} = 10.4 Hz, $EtOCH_A\underline{H}_B$); 4.79-4.76 (1H, m, CHOSi); 3.54-3.48 (2H, m, $CH_3C\underline{H}_2O$); 2.64 (3H, s, $COCH_3$); 1.75-1.70 (2H, m, $C\underline{H}_2CH_2CH_3$); 1.44-1.37 (2H, m, $C\underline{H}_2CH_3$); 1.18 (3H, dt, J = 0.8, 7.2 Hz, $C\underline{H}_3CH_2O$); 0.94-0.90 (12H, m, $C(CH_3)_3$, CH_3); 0.08; -0.03 (2 x 3H, 2 x s, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (C=O); 147.9 (C4); 141.7 (C2); 121.1 (C5); 77.1 ($EtO\underline{C}H_2$); 70.1 (CHOSi); 64.8 ($CH_3\underline{C}H_2O$); 41.0

($\underline{C}H_2CH_2CH_3$); 27.4 ($CO\underline{C}H_3$); 25.8 ($C(\underline{C}H_3)_3$); 18.4 ($\underline{C}H_2CH_3$); 18.2 ($\underline{C}(CH_3)_3$); 14.8 ($\underline{C}H_3CH_2O$); 14.1 (CH_3); -4.7; -4.9 ($Si(CH_3)_2$).

HRMS calcd for $C_{17}H_{31}N_2O_3Si$ ($M-CH_3$) 339.2104, found 339.2115.

2-Acetyl-4-(1'-hydroxy-1'-butyl)imidazolium chloride (60)



59 **60**

Imidazole **59** (350 mg, 0.99 mmol) was dissolved in 1:1 ethanol / H_2O (8 mL) and conc. HCl (5 mL) and the solution was heated at reflux for 1 h. The solvent was removed and the residue dissolved in water and washed with ether (4 x 10 mL). The water was removed *in vacuo* to give the title salt as a thick tan oil (150 mg, 69%).

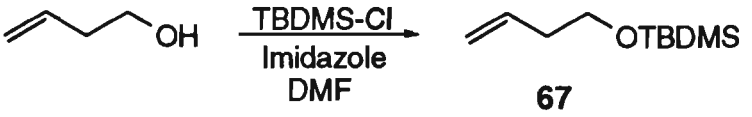
^{1}H NMR (400 MHz, D_2O) δ 7.52 (1H, s, H5); 4.87 (1H, t, J = 6.8 Hz, $C\underline{H}OH$); 2.63 (3H, s, $COCH_3$); 1.81-1.75 (2H, m, $C\underline{H}_2CH_2CH_3$); 1.40-1.23 (2H, m, $C\underline{H}_2CH_3$); 0.85 (3H, t, J = 7.2 Hz, CH_3).

^{13}C NMR (100 MHz, D_2O) δ 184.8 (C=O); 139.7 (C4); 139.3 (C2); 118.5 (C5); 64.8 (CHOH); 37.8 ($CHOH\underline{C}H_2$); 26.5 ($CO\underline{C}H_3$); 18.0 ($\underline{C}H_2CH_3$); 13.0 (CH_3).

MS (ES+ve) *m/z* 183 ($M+H^+$, 100%); 166 ($C_9H_{14}N_2O^+$, 21%).

HRMS calcd for $C_9H_{15}N_2O_2$ 183.1134, found 183.1138.

4-(*t*-Butyldimethylsilyloxy)-1-butene (67)



67

A solution of imidazole (11.8 g, 173.3 mmol) and TBDMS-Cl (11.5 g, 76.2 mmol) in anhydrous DMF (40 mL) was cooled to 0 °C and set to stir under an N_2 atmosphere. 3-Buten-1-ol (5.0 g, 69.3 mmol) was added dropwise and the solution was stirred at rt for 16 h. The solution was then diluted with ether (120 mL) and washed with water (3 x 20 mL). The ether phase was dried ($MgSO_4$) and concentrated to give a light yellow oil. Purification by vacuum distillation (64 °C/20 mmHg) gave the title compound as a clear oil (11.85 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.75 (1H, m, CH); 5.08-4.99 (2H, m, $C\underline{H}_2$=CH); 3.64 (2H, t, J = 6.8 Hz, CH_2O); 2.29-2.23 (2H, m, $C\underline{H}_2CH_2O$); 0.88 (9H, s, $C(CH_3)_3$); 0.04 (6H, s, 2 x CH_3).

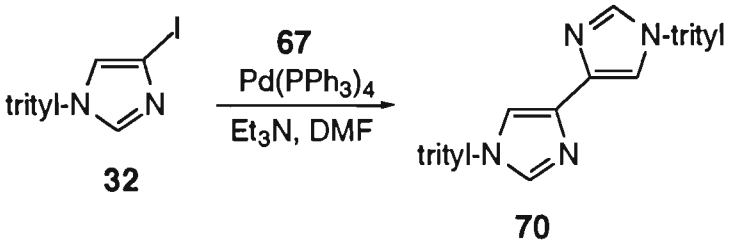
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (C2); 116.2 (C1); 62.8 (C4); 37.5 (C3); 25.9 ($C(\underline{C}H_3)_3$); 14.1 ($\underline{C}(CH_3)_3$); -5.3 (2 x CH_3).

MS (ES+ve) *m/z* 187 ($M+H^+$, 100%); 174 (32%); 156 (32%); 83.0 (66%).

IR (neat) 3079 (=CH_2); 1639 (C=C); 1471; 1256; 1100 cm^{-1}.

Anal. calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found C, 64.73; H, 12.24.

1,1'-Bitrityl-4,4'-bisimidazole (70)



32 70

A solution of iodoimidazole **32** (1.02 g, 2.30 mmol), alkene **67** (860 mg, 4.60 mmol), triethylamine (0.47 g, 4.60 mmol) and $Pd(Ph_3P)_4$ (100 mg, 8.7 x 10^{-5} mol) in anhydrous DMF (5 mL) under N_2 in a sealed, thick walled tube and was stirred at 100 °C for 24 h. The mixture was filtered to collect the precipitated solids and the filtrate was added to a 5% aqueous solution of $NaHCO_3$ (10 mL) and refiltered. The combined solids were washed with water and then acetone to give a cream solid. Recrystallisation from chloroform / toluene (1:1) gave the title compound as a white solid (0.52 g, 73%), mp 279-280 °C (decomp.). Extraction of the aqueous phase with dichloromethane gave no identifiable olefinated product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 1.6 Hz, H2,2'); 7.32-7.29 (18H, m, 6 x Ar-H3,4,5); 7.28 (2H, d, *J* = 1.6 Hz, H5,5'); 7.19-7.17 (12H, m, 6 x Ar-H2,6).

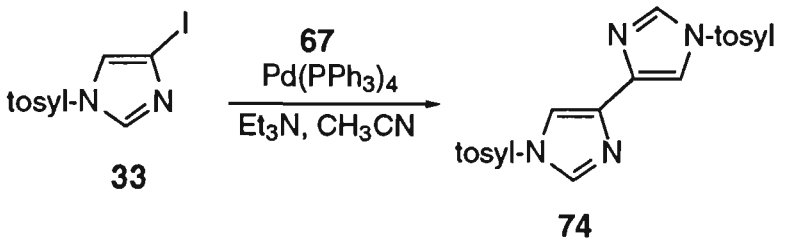
^{13}C NMR In part (22.5 MHz, $CDCl_3$) δ 142.7 (C2,2'); 138.9 (Ar-C1); 136.7 (C4,4'); 129.9 (Ar-C2,6); 128.0 (Ar-C3,5); 127.9 (Ar-C4); 117.1 (C5,5').

MS (ES+ve) *m/z* 619 ($M+H^+$, 61%); 241 (Ph_3C^+, 100%); 82 (61%); 58 (89%).

IR (nujol) 1216; 1185; 1079; 910; 745; 702; 665 cm^{-1}.

HRMS calcd for $C_{44}H_{34}N_4$ 618.2783, found 618.2778.

1,1'-Bitosyl-4,4'-bisimidazole (74)



A solution of iodoimidazole **33** (0.4 g, 1.15 mmol), triethylamine (0.174 g, 1.72 mmol), alkene **67** (0.43 g, 2.30 mmol) and $Pd(Ph_3P)_4$ (53 mg, 4.6 x 10^{-5} mol) in anhydrous acetonitrile (4 mL) under N_2 in a sealed, thick walled tube was stirred at 100 °C for 18 h. The mixture was filtered to collect the precipitated dimer. The filtrate was washed with a 5% aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and then concentrated to leave a black solid. Purification by column chromatography (45% ethyl acetate / hexane) gave additional dimer as a cream solid (combined solids: 140 mg, 55%), mp 219-220 °C (decomp). An analytical sample was recrystallised from ethanol.

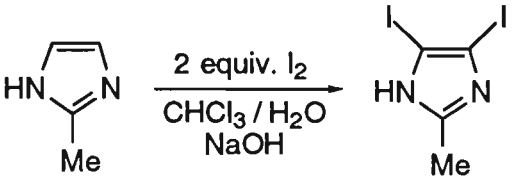
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 1.2 Hz, H2,2'); 7.82 (4H, d, *J* = 8.8 Hz, 2 x Ar-H2,6); 7.60 (2H, d, *J* = 1.2 Hz, H5,5'); 7.33 (4H, d, *J* = 8.4 Hz, 2 x Ar-H3,5); 2.42 (6H, s, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (C2,2'); 138.1 (C5,5'); 136.7 (Ar-C1); 134.7 (C4,4'); 130.4 (Ar-C2,6); 127.5 (Ar-C3,5); 113.4 (Ar-C4); 21.7 (CH_3).

MS (ES+ve) *m/z* 443 ($M+H^+$, 100%); 279 (27%); 102 (57%).

Anal. calcd for $C_{20}H_{18}N_4O_4S_2$: C, 54.29; H, 4.10; N, 12.66. Found: C, 54.00; H, 4.11; N, 12.51.

4,5-Diiodo-2-methylimidazole



A solution of 2-methylimidazole (10.0 g, 0.122 mol) in a 2M aqueous solution of NaOH (300 mL) was added to a solution of iodine (61.9 g, 0.241 mol) in chloroform (300 mL). The two phase system was stirred at rt until the chloroform phase became clear (approx. 3 h). The phases were separated and, using $Na_2S_2O_3$ to prevent colouration, the aqueous phase was neutralised with acetic acid. The precipitated solid was filtered and recrystallised from acetonitrile to give the title compound as a white solid (26.05 g, 64%), mp 180-185 °C (decomp.).

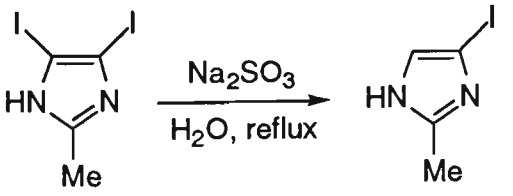
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s, CH_3).

MS (FAB) *m/z* 335 ($M+H^+$, 47%); 209 ($C_4H_4N_2I+H^+$, 28%); 185 (100%); 100 (74%).

IR (nujol) 1550; 1185; 1020; 968 cm^{-1}

Anal. calcd for $C_4H_4N_2I_2$: C, 14.39; H, 1.21; N, 8.39. Found: C, 14.13; H, 1.03; N, 8.10.

4(5)-Iodo-2-methylimidazole



4,5-Diiodo-2-methylimidazole (20.0 g, 60 mmol) and Na_2SO_3 (60 g) were dissolved in 30% aqueous ethanol (1.0 L) and the solution was heated at reflux for 24 h. Ethanol was removed *in vacuo* and the precipitated solid filtered, washed with water and dried to give the title compound as a white powder (8.1 g, 65%) of sufficient purity (^{1}H NMR and TLC analysis) to render recrystallisation unnecessary, mp 141-142 °C. An analytical sample was recrystallised from ethanol.

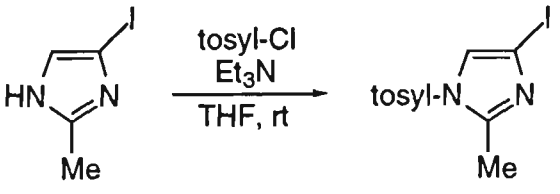
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, s, H5); 2.45 (3H, s, CH_3).

MS (CI+ve) *m/z* 209 ($M+H^+$, 100%); 122 (13%); 100 (26%).

IR (nujol) 3130; 1567; 1167; 1108; 841; 763 cm^{-1}.

Anal. calcd for $C_4H_5N_2I$: C, 23.10; H, 2.42; N, 13.47. Found: C, 23.04; H, 2.42; N, 13.21.

4-Iodo-2-methyl-1-tosylimidazole (75)



75

To a solution of 4(5)-iodo-2-methylimidazole (4.0 g, 19.2 mmol) and tosyl chloride (3.67 g, 19.2 mmol) in anhydrous THF (50 mL) under N_2 was added triethylamine (1.95 g, 19.2 mmol) and the solution was stirred for 24 h. The reaction was filtered and the filtrate was diluted with chloroform (100 mL) and then washed with water (30 mL), dried ($MgSO_4$) and evaporated to dryness. Recrystallisation from ethanol gave the title compound as white needles (5.47 g, 79%), mp 115-116 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.4 Hz, Ar-H2,6); 7.49 (1H, d, *J* = 1.6 Hz, H2); 7.38 (2H, d, *J* = 8.4 Hz, Ar-H3,5); 2.51 (3H, s, CH_3); 2.46 (3H, s, Ar-CH_3).

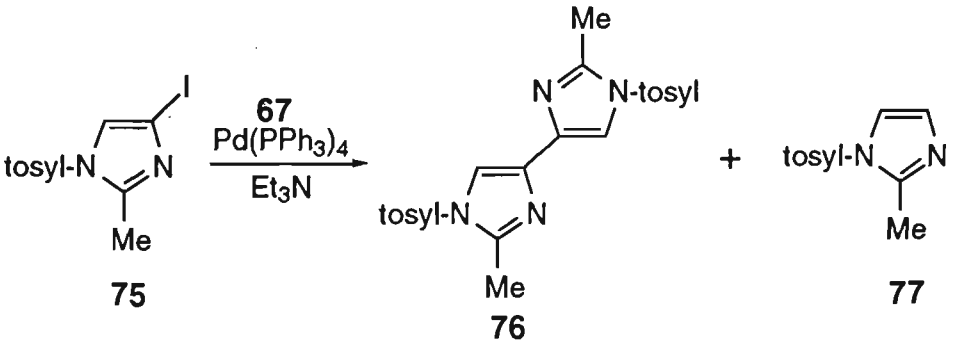
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 147.3 (C2); 146.4 (C5); 134.6 (Ar-C1); 130.4 (Ar-C2,6); 127.5 (Ar-C3,5); 124.1 (Ar-C4); 82.0 (C4); 21.6 (CH_3); 14.8 (CH_3).

MS (ES+ve) *m/z* 363 ($M+H^+$, 16%); 272 (22%); 244 (66%); 208 (46%).

IR (nujol) 3146; 1530; 1321; 1159 (S=O); 1097; 989; 659 cm^{-1}.

Anal. calcd for $C_{11}H_{11}N_2O_2SI$: C, 36.48; H, 3.06; N, 7.73. Found: C, 36.63; H, 2.85; N, 7.51.

2,2'-Dimethyl-1,1'-ditosyl-4,4'-biimidazole (76) and 2-methyl-1-tosylimidazole (77)



Solvent	*Catalyst*	*Yield %*	
		76	*77*
Acetonitrile	$Pd(PPh_3)_4$	40	31
Acetonitrile	$Pd(OAc)_2/P(o\text{-}tol)_3$	20	11
DMF	$Pd(PPh_3)_4$	19	23
Acetonitrile*	$Pd(PPh_3)_4$	37	46

* No Alkene used, Iodoimidazole **75** only.

A general reaction procedure: A solution of iodoimidazole **75** (0.5 g, 1.38 mmol), alkene **67** (0.39 g, 2.07 mmol), triethylamine (0.21 g, 2.07 mmol) and $Pd(Ph_3P)_4$ (64 mg, 5.5 x 10^{-5} mol) in anhydrous acetonitrile (4 mL) was degassed with a stream of argon gas, sealed in a thick walled tube under N_2 and stirred at 100 °C in the dark for 48 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (40% ethyl acetate / hexane) to give the title dimer as a white solid (130 mg, 40%, mp 230-231 °C), plus reduced 2-methyl-1-tosylimidazole **77** (100 mg, 31%, mp 75-76 °C).

76: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (4H, d, *J* = 8.4 Hz, 2 x Ar-H2,6); 7.71 (2H, s, H2,2'); 7.33 (4H, d, *J* = 8.4 Hz, 2 x Ar-H3,5); 2.56 (6H, s, 2 x CH_3); 2.43 (6H, s, 2 x Ar-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3 (C2,2'); 146.1 (C5,5'); 134.9 (Ar-C1); 134.6 (C4,4'); 130.3 (Ar-C2,6); 127.4 (Ar-C3,5); 114.9 (Ar-C4); 21.7 (2 x Ar-$\underline{C}H_3$); 15.2 (2 x CH_3).

MS (ES+ve) *m/z* 471 ($M+H^+$, 100%).

IR (nujol) 1308; 1190; 1162 (S=O); 1092; 990; 811; 665 cm^{-1}

Anal. calcd for $C_{22}H_{22}N_4O_4S_2$: C, 56.15; H, 4.71; N, 11.91. Found: C, 56.41; H, 4.67; N, 11.76.

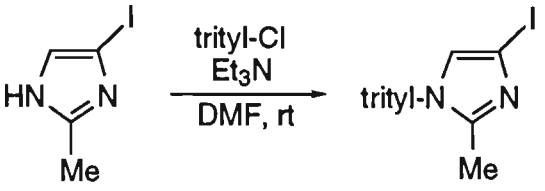
77: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.4 Hz, Ar-H2,6); 7.41 (1H, d, *J* = 2.0 Hz, H5); 7.35 (2H, d, *J* = 8.0 Hz, Ar-H3,5); 6.89 (1H, d, *J* = 1.6 Hz, H4); 2.51 (3H, s, CH_3); 2.45 (3H, s, Ar-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2 (C2); 136.4 (Ar-C1); 134.7 (C4); 131.2 (C5); 130.3 (Ar-C2,6); 127.2 (Ar-C3,5); 117.3 (Ar-C4); 21.5 (Ar-CH_3); 14.9 (CH_3).

MS (ES+ve) *m/z* 237 ($M+H^+$, 100%); 155 ($tosyl^+$, 74%).

IR (nujol) 1593; 1175; 1151 (S=O); 1047; 844; 813; 674 cm^{-1}.

4-Iodo-2-methyl-1-tritylimidazole (78)



78

To a solution of 4(5)-iodo-2-methylimidazole (3.0 g, 14.4 mmol) and trityl chloride (4.02 g, 14.4 mmol) in anhydrous DMF (30 mL) under N_2 was added triethylamine (1.46 g, 14.4 mmol) and the solution was stirred at rt for 24 h. The solution was poured into ice / water (150 mL) and the precipitated solid was collected by gravity filtration. Recrystallisation from ethyl acetate / cyclohexane gave the title compound as a white crystalline solid (4.34 g, 67%), mp 194-195 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (9H, m, 3 x Ar-H3,4,5); 7.13-7.11 (6H, m, 3 x Ar-H2,6); 6.76 (1H, s, H5); 1.64 (3H, s, CH_3).

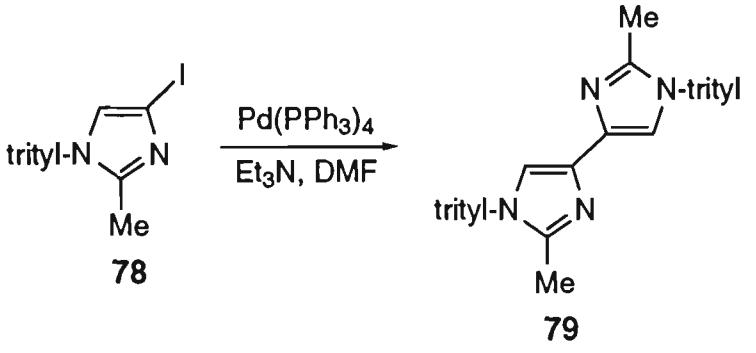
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (C2); 141.7 (Ar-C1); 129.8 (Ar-C3,5); 128.1 (Ar-C2,6); 128.0 (Ar-C4); 126.7 (C5); 78.5 (C4); 75.4 ($\underline{C}Ph_3$); 17.1 (CH_3).

MS (ES+ve) 451 ($M+H^+$; 21%); 243 (CPh_3, 100%); 102 (12%).

IR (nujol) 1217; 742; 701; 667 cm^{-1}.

Anal. calcd for $C_{23}H_{19}N_2I$: C, 61.35; H, 4.25; N, 6.22. Found: C, 61.10; H, 4.23; N, 6.03.

2,2'-Dimethyl-1,1'-dityrityl-4,4'-biimidazole (79)



A solution of iodoimidazole **78** (4.00 g, 8.89 mmol), triethylamine (1.80 g, 17.8 mmol) and $Pd(Ph_3P)_4$ (510 mg, 0.44 mmol) in anhydrous DMF (15 mL) was degassed with a stream of argon, sealed in a thick walled tube under N_2 and stirred at 110 °C in the dark for 48 h. The mixture was cooled to rt, filtered to collect the precipitated dimer and the filtrate was diluted with a 5% aqueous solution of $NaHCO_3$ (30 mL) and refiltered. The collected solids were washed with H_2O and cold acetone to give the title compound as a light tan solid (1.81 g, 63%), mp 250-252 °C (decomp.). Compound **79** was found to be only sparingly soluble in most common organic solvents.

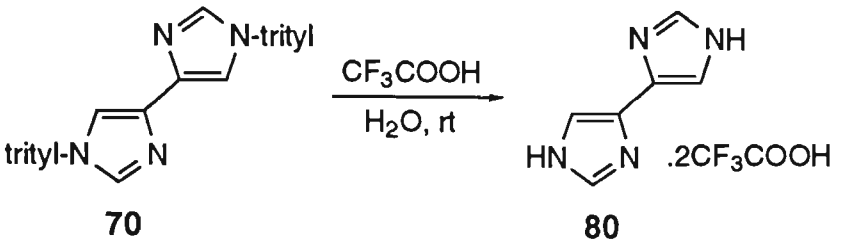
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (18H, m, 6 x Ar-H3,4,5); 7.22 (2H, s, H5,5'); 7.18-7.16 (12H, m, 3 x Ar-H2,6); 1.61 (6H, s, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1 (C2,2'); 142.5 (Ar-C1); 134.0 (C4,4'); 130.1 (Ar-C3,5); 128.0 (Ar-C2,6); 127.7 (Ar-C4); 116.8(C5,5'); 75.0 ($\underline{C}Ph_3$); 17.4 (2 x CH_3).

MS (ES+ve) *m/z* 647 ($M+H^+$, 5%); 589 (12%); 343 (14%); 325 (11%); 243 (Ph_3C^+, 100%).

HRMS calcd for $C_{46}H_{38}N_4$ 646.3096, found 646.3006.

4,4'-Biimidizolium bis(trifluoroacetate) (80)



70 **80**

A solution of biimidazole **70** (1.4 g, 2.25 mmol) in 60% trifluoroacetic acid / H_2O (60 mL) was stirred at rt for 6 h. Precipitated triphenylmethanol was removed by filtration and the solution was concentrated *in vacuo* to leave a yellow oil. The oil was washed with cold acetonitrile to give the title salt as a white solid (560 mg, 60%), mp 203-204 °C.

^{1}H NMR (400 MHz, D_2O) δ 8.12 (2H, s, H2,2'); 7.83 (2H, s, H5,5').

^{13}C NMR (100 MHz, D_2O) δ 163.9 (q, $^2J_{C\text{-}F}$ = 35.7 Hz, $CF_3\underline{C}OO$); 135.4 (C2,2'); 120.7 (C4,4'); 118.0 (C5,5'); 116.4 (q, $J_{C\text{-}F}$ = 290.5 Hz, CF_3).

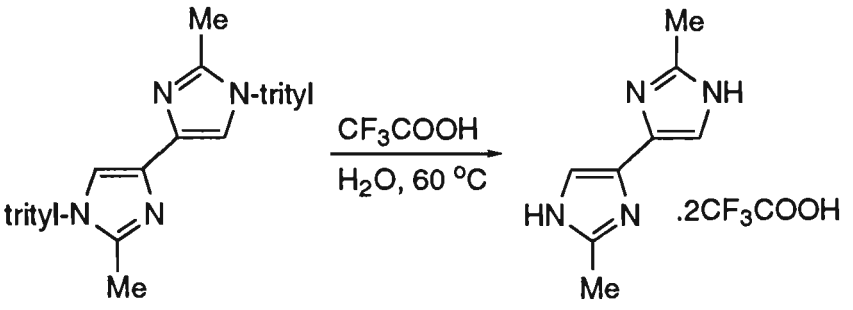
MS (ES+ve) *m/z* 135 ($C_6H_7N_4^+$, 100%); 60 (60%).

MS (ES-ve) *m/z* 113 (CF_3COO^-, 94%); 69 (CF_3^-, 100%).

IR (nujol) 3159-2243 (NH^+, b); 1653 (COO^-); 1190-1150 (CF_3); 842 cm^{-1}.

Anal. calcd for $C_{10}H_8N_4O_4F_6$: C, 33.16; H, 2.22; N, 15.47. Found: C, 33.13; H, 2.25; N, 15.86.

2,2'-Dimethyl-4,4'-biimidizolium bis(trifluoroacetate) (81)



79 **81**

A suspension of biimidazole **79** (1.5 g, 2.32 mmol) in 60% trifluoroacetic acid / H_2O (100 mL) was heated at reflux for 4 h. The reaction was cooled to rt, filtered to remove triphenylmethanol and the solvent was removed to leave a yellow oil. The oil was washed with a small mount of cold acetonitrile to give the title salt as a light cream powder (567 mg, 63%), mp 227-228 °C (decomp.).

^{1}H NMR (400 MHz, D_2O) δ 7.59 (2H, s, H5,5'); 2.66 (6H, s, 2 x CH_3).

^{13}C NMR (100 MHz, D_2O) δ 163.0 (q, $^2J_{C\text{-}F}$ = 35.4 Hz, $CF_3\underline{C}OO$); 146.4 (C2,2'); 120.2 (C4,4'); 116.5 (C5,5'); 116.46 (q, $J_{C\text{-}F}$ = 289.8, CF_3); 10.8 (2 x CH_3).

MS (ES+ve) *m/z* 163 ($C_8H_{11}N_4^+$, 100%); 82 ($C_8H_{12}N_4^{2+}$, 58%).

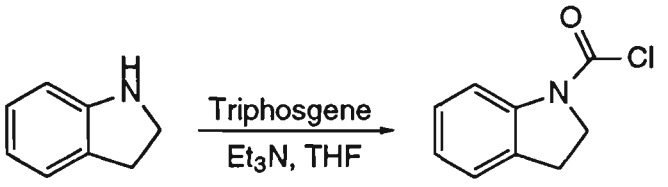
MS (ES-ve) *m/z* 275 ($CF_3CO_2C_8N_{10}N_4^-$, 4%); 113 (CF_3COO^-, 60%); 69 (CF_3^-, 100%).

IR (nujol) 1653 (COO^-); 1186-1150 (CF_3); 665 cm^{-1}.

Anal. calcd for $C_{12}H_{12}N_4O_4F_6$: C, 36.93; H, 3.10; N, 14.36. Found C, 36.99; H, 3.17; N, 14.53.

6.3 Experimental Chapter 3

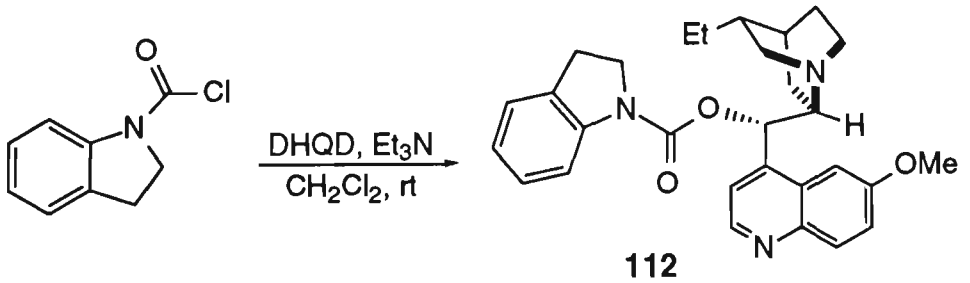
Indolinyl-carbamylchloride



To a solution of indoline (9.0 mL, 80 mmol) and triethylamine (22 mL, 160 mmol) under N_2 was added triphosgene (8.16 g, 27.5 mmol) in anhydrous THF (90 mL) dropwise over a 30 min period. A white solid precipitated immediately and gas was evolved. The solution was stirred rapidly for 3 h at rt and then filtered. The solids were washed with hexane and the combined filtrates evaporated *in vacuo* to give a tan solid (7.30 g, 95%) which was used immediately in the following ligand derivatisation reactions.

MS (ES+ve) *m/z* 265.4 ($M+H^+$, 27%); 74 (100%).

Dihydroquinidinecarbamylindoline (DHQD-IND, 112)



112

Dihydroquinidine (DHQD) (3.26 g, 10 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) and triethylamine (5.5 mL, 39 mmol) at rt under N_2. Indolinyl-carbamylchloride (3.60 g, 12.8 mmol) was dissolved in CH_2Cl_2 (20 mL) and added dropwise to the stirred

solution *via* a pressure equalising dropping funnel. The solution was stirred at rt for 24 h until complete by TLC and then washed with a sat. aqueous solution of NaCl (3 x 25 mL). The aqueous washings were re-extracted with CH_2Cl_2 (3 x 25 mL) and the combined extracts were dried ($MgSO_4$) and concentrated to give a thick syrup. Purification by column chromatography (60:35:5 ethyl acetate / hexane / triethylamine) gave the title compound as an off-white solid (4.00 g, 85%). A small portion was purified further by recrystallisation from 10% ethyl acetate / hexane for use in the dihydroxylation reactions, mp 128-129 °C, $[\alpha]_D^{25}$ -42.0° (*c* 0.87, $CHCl_3$).

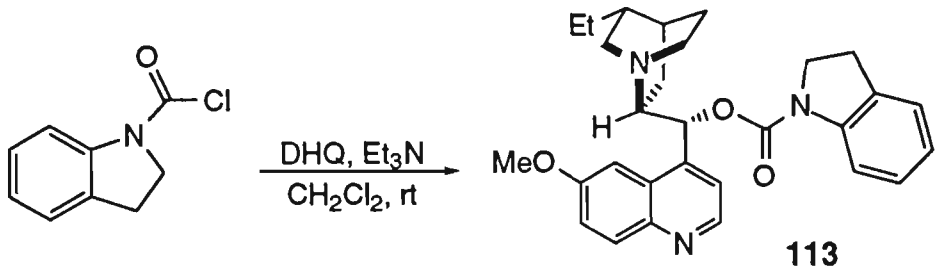
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (1H, d, *J* = 4.4 Hz); 8.00 (1H, d, *J* = 9.2 Hz); 7.80 (1H, d, *J* = 7.2 Hz); 7.51 (1H, s); 7.40-7.34 (2H, m); 7.16 (2H, d, *J* = 7.2 Hz); 6.97-6.95 (1H, m); 6.57 (1H, d, *J* = 8.0 Hz); 4.16-4.09 (1H, m); 3.97 (3H, s); 3.42-3.35 (1H, m); 3.19-3.15 (2H, m); 2.95-2.89 (1H, m); 2.78-2.70 (3H, m); 1.88-1.76 (3H, m); 1.58-1.47 (6H, m); 0.92-0.89 (3H, m).

^{13}C NMR In part (75.6 MHz, $CDCl_3$) δ 157.83; 147.50; 144.86; 144.40; 131.77; 127.54; 124.64; 122.90; 121.76; 118.88; 114.84; 101.73; 74.40; 59.60; 55.56; 50.76; 49.82; 47.51; 37.54; 27.32; 26.15; 25.45; 11.97.

MS (ES+ve) *m/z* 472 ($M+H^+$, 100%).

Anal. calcd for $C_{29}H_{33}N_3O_3$: C, 73.86; H, 7.05; N, 8.91. Found: C, 74.17; H, 7.22; N, 8.84.

Dihydroquininecarbamylindoline (DHQ-IND, 113)



113

The title compound was synthesised using the procedure described above for the preparation of DHQD-IND, using dihydroquinine (DHQ) and a reaction time of 48 h. Purification by column chromatography (60:35:5 ethyl acetate / hexane / triethylamine) gave the title compound as a white solid (4.22 g, 90%). A small portion was purified further by recrystallisation from ethyl acetate for use in the dihydroxylation reaction, mp 188-189 °C, $[\alpha]_D^{25}$ +106.8° (*c* 0.94, $CHCl_3$).

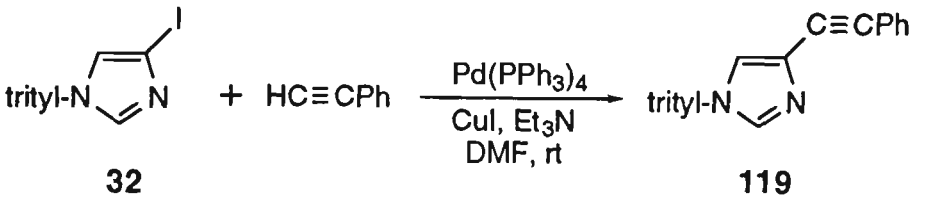
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 4.8 Hz); 8.01 (1H, d, *J* = 9.2 Hz); 7.80 (1H, d, *J* = 7.6 Hz); 7.52 (1H, s); 7.40-7.35 (2H, m); 7.16 (2H, d, *J* = 6.8 Hz); 6.97-6.96 (1H, m); 6.58 (1H, s(b)); 4.16-4.09 (1H, m); 3.97 (3H, s); 3.48-3.40 (1H, m); 3.23-3.16 (2H, m); 3.05 (1H, dd, *J* = 10.0, 13.6 Hz); 2.70-2.64 (1H, m); 2.38-2.34 (1H, m); 1.96-1.61 (4H, m); 1.48-1.34 (4H, m); 0.86 (3H, t, *J* = 7.6 Hz).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 157.93; 152.15; 147.49; 144.90; 144.09; 131.81; 127.56; 124.65; 122.93; 121.79; 118.82; 114.82; 101.67; 74.83; 59.29; 58.36; 55.67; 47.51; 42.59; 37.55; 28.61; 27.78; 27.52; 25.39; 12.12.

MS (ES+ve) *m/z* 472 ($M+H^+$, 100%).

Anal. calcd for $C_{29}H_{33}N_3O_3$: C, 73.86; H, 7.05; N, 8.91. Found: C, 74.30; H, 7.20; N, 8.83.

4-(2'-Phenylethynyl)-1-tritylimidazole (119)



32 **119**

A solution of iodoimidazole **32** (1.0 g, 2.29 mmol), phenylacetylene (0.35 g, 3.44 mmol), triethylamine (2.32 g, 22.9 mmol), CuI (45 mg, 0.23 mmol) and $Pd(Ph_3P)_4$ (132 mg, 0.11 mmol) in anhydrous DMF (15 mL) under N_2 was stirred at rt for 16 h. The reaction mixture was poured into water (150 mL) and filtered to collect the precipitated product. Recrystallisation from 1:1 ethyl acetate / chloroform gave the title compound as a white solid (450 mg, 47%), mp 244-245 °C.

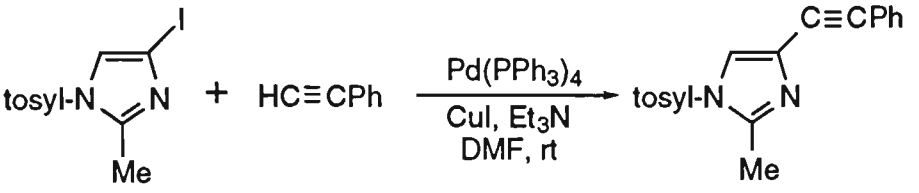
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (2H, m, Ar-H2,5); 7.44 (1H, d, *J* = 1.2 Hz, H2); 7.37-7.35 (9H, m, trityl-H3,4,5); 7.31-7.29 (3H, m, Ar-H3,4,5); 7.16-7.14 (6H, m, trityl-H2,6); 7.11 (1H, d, *J* = 1.6 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (trityl Ar-C1); 139.1 (C2); 131.4 (trityl Ar-C4); 129.7 (trityl Ar-C2,6); 128.22 (Ar-C2,6); 128.19 (Ar-C3,5); 128.16 (trityl Ar-C3,5); 127.99 (Ar-C4); 125.6 (C4); 123.4 (C5); 123.2 (Ar-C1); 89.3 (C≡CPh); 83.2 (C≡CPh); 75.8 (CPh_3).

MS (ES+ve) 411 ($M+H^+$, 2%); 243 (CPh_3^+, 100%).

IR (nujol) 1297; 1107; 979; 865; 742; 701; 665 cm^{-1}.

2-Methyl-4-(2'-phenylethynyl)-1-tosylimidazole (120)



75 **120**

A solution of iodoimidazole **75** (0.8 g, 2.21 mmol), phenylacetylene (0.35 g, 3.44 mmol), triethylamine 2.32 g, 22.9 mmol), CuI (45 mg, 0.23 mmol) and $Pd(Ph_3P)_4$ (132 mg, 0.11 mmol) in anhydrous DMF (10 mL) under N_2 was stirred at rt for 16 h. The reaction mixture was poured into water (150 mL) and the aqueous solution extracted with chloroform (3 x 150 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a dark oil. Purification by column chromatography (22% ethyl acetate / hexane) gave the title compound as a light orange solid (490 mg, 69%). An analytical sample was recrystallised from ethyl acetate to give a white solid, mp 123-124 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.4 Hz, tosyl Ar-H2,6); 7.62 (1H, s, H5); 7.51-7.49 (2H, m, Ar-H2,5); 7.38 (2H, d, *J* = 8.0 Hz, tosyl Ar-H3,5); 7.34-7.32 (3H, m, Ar-H3,4,5); 2.53 (3H, s, CH_3); 2.46 (3H, s, CH_3).

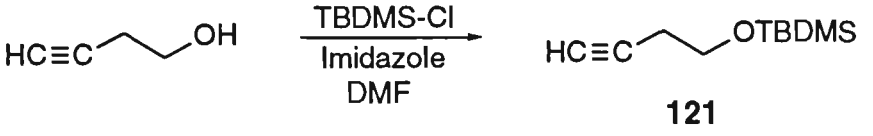
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 146.4 (C2); 145.9 (C5); 134.6 (tosyl Ar-C1); 131.6 (Ar-C2,6); 130.4 (tosyl Ar-C2,6); 128.5 (Ar-C4); 128.3 (Ar-C3,5); 127.5 (tosyl Ar-C3,5); 123.6 (tosyl Ar-C4); 122.5 (Ar-C1); 122.1 (C5); 90.7(C≡CPh); 81.2(C≡CPh); 21.8 (CH_3); 15.0 (CH_3).

MS (ES+ve) *m/z* 337 ($M+H^+$, 100%); 182 (M-tosyl$^+$, 7%).

IR (nujol) 1316; 1191; 1172 (S=O); 1095; 993; 812; 759; 668 cm^{-1}.

Anal. calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.65; H, 4.84; N, 8.24.

4-(*t*-Butyldimethylsilyloxy)-1-butyne (121)



121

A solution of imidazole (8.57 g, 126 mmol) and TBDMS-Cl (9.47 g, 62.8 mmol) in anhydrous DMF (35 mL) was cooled to 0 °C under an N_2 atmosphere. 3-Butyn-1-ol (4.0 g, 57.1 mmol) was added dropwise and the solution was stirred at rt for 16 h. The solution was then diluted with ether (120 mL) and washed with water (3 x 30 mL). The ether phase was dried ($MgSO_4$) and concentrated to give a pale oil. Purification by vaccum distillation (70 °C/10 mmHg) gave the title silyl ether as a clear oil (9.90 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (2H, t, J = 7.2 Hz, CH_2O); 2.40 (2H, dt, J = 2.4, 7.2 Hz, CH_2); 1.96 (1H, t, J = 2.4 Hz, HC≡); 0.89 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, 2 x CH_3).

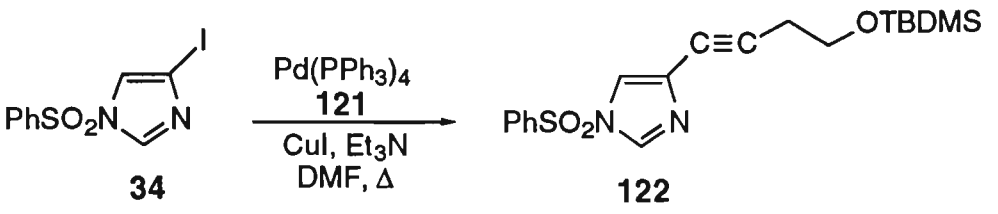
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 81.5 (C2); 69.2 (C1); 61.7 (C4); 25.6 ($C(CH_3)_3$); 22.8 (C3); 18.3 ($C(CH_3)_3$); -5.3 (2 x CH_3).

MS (CI+ve) *m/z* 170 (M-CH_3^+, 4%); 128 (M-^{t}Bu, 58%); 110 (12%); 98 (83%).

IR (neat) 3313 (HC≡); 2120 (C≡C); 1472; 1256; 1115 cm^{-1}.

HRMS calcd for $C_9H_{17}OSi$ (M-CH_3^+) 169.1049, found 169.1047.

1-Benzenesulfonyl-4-(4'-(*t*-butyldimethylsilyloxy)but-1'-ynyl)imidazole (122)



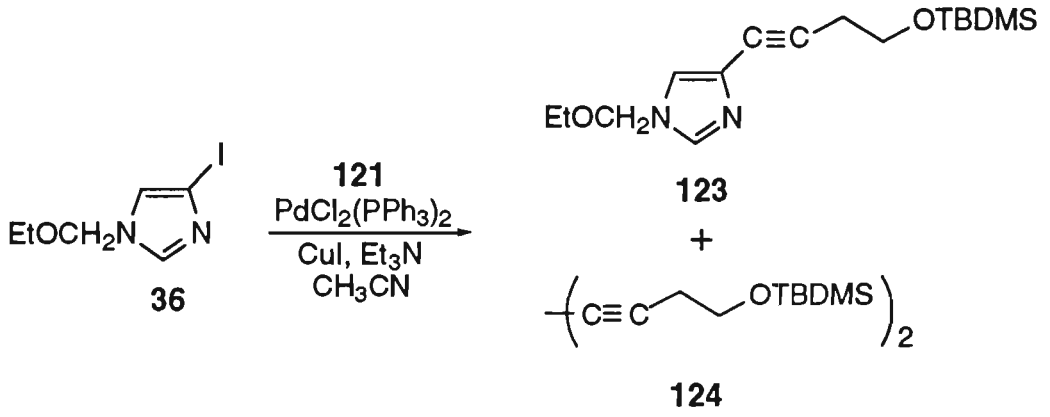
A solution of iodoimidazole **34** (1.0 g, 2.99 mmol), alkyne **121** (0.77 g, 4.49 mmol), triethylamine (3.03 g, 29.9 mmol), CuI (57 mg, 0.3 mmol) and $Pd(Ph_3P)_4$ (132 mg, 0.15 mmol) in anhydrous DMF (10 mL) under N_2 was stirred at 70 °C for 5 h. The reaction mixture was poured into water (100 mL) and the aqueous solution was extracted with chloroform (3 x 150 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a black oil. Purification by column chromatography (20% ethyl acetate / hexane) gave the title compound as a light yellow solid (780 mg, 72%), mp 67-69 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 0.8 Hz, H2); 7.93-7.92 (2H, m, Ar-H2,6); 7.72-7.68 (1H, m, Ar-H4); 7.61-7.56 (1H, m, Ar-H3,5); 7.33 (1H, d, *J* = 0.8 Hz, H5); 3.78 (2H, t, *J* = 7.2 Hz, CH_2); 2.58 (2H, t, *J* = 7.2 Hz, CH_2); 0.89 (9H, s, $C(CH_3)_3$); 0.06 (6H, s, 2 x CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.7 (C2); 136.1 (C4); 135.0 (Ar-C1); 129.9 (Ar-C2,6); 127.5 (Ar-C4); 127.4 (Ar-C3,5); 119.6 (C5); 89.5 ($\underline{C}\equiv CCH_2$); 73.3 ($C\equiv\underline{C}CH_2$); 61.4 ($CH_2O$); 25.9 ($C(\underline{C}H_3)_3$); 23.7 ($CH_2$); 18.3 ($\underline{C}(CH_3)_3$); -5.3 (2 x CH_3).

MS (ES+ve) 391 ($M+H^+$, 100%).

4-(4'-(*t*-Butyldimethylsilyloxy)but-1'-ynyl)-1-ethoxy methylimidazole (123) and 1,8-di(*t*-butyldimethyl silyloxy)-3,5-octadiyne (124)



A solution of iodoimidazole **36** (0.5 g, 1.98 mmol), alkyne **121** (0.55 g, 2.98 mmol), triethylamine (2.00 g, 19.8 mmol), CuI (40 mg, 0.21 mmol) and $PdCl_2(Ph_3P)_2$ (70 mg, 0.1 mmol) in anhydrous acetonitrile (10 mL) was degassed with a stream of argon and the solution was heated at reflux for 3 h. The solution was cooled to rt, poured into H_2O (80 mL) and the aqueous solution was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed to leave a red oil. Purification by column chromatography (55% ethyl acetate / hexane) gave the title compound **123** (242 mg, 40%) as a tan oil, plus the dialkyne 1,8-di(*t*-butylbismethylsilyloxy)-3,5-octadiyne **124** as a dark oil. (380 mg, 35%). An analytical sample of **124** was purified by bulb-to-bulb distillation (117 °C/0.5 mmHg) to give a pale oil.

123: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, J = 1.2 Hz, H2); 7.13 (1H, d, J = 1.2 Hz, H5); 5.23 (2H, s, CH_2); 3.81 (2H, t, J = 7.6 Hz, CH_2OSi); 3.43 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2$); 2.62 (2H, t, J = 7.6 Hz, $C\underline{H}_2CH_2OSi$); 1.18 (3H, t, J = 6.8 Hz, CH_3); 0.90 (9H, s, $C(CH_3)_3$); 0.08 (6H, s, $Si(CH_3)_2$).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 136.9 (C2); 125.5 (C4); 121.6 (C5); 86.9 ($\underline{C}\equiv C CH_2$); 76.3 ($EtO\underline{C}H_2$); 74.8 ($C\equiv\underline{C}CH_2$); 64.6 ($CH_3\underline{C}H_2$); 61.8 ($CH_2OSi$); 25.8 ($\underline{C}(CH_3)_3$); 23.7 ($\underline{C}H_2CH_2OSi$); 18.2 ($\underline{C}(CH_3)_3$); 14.5 ($CH_3$); -5.4 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 309 ($M+H^+$, 100%).

IR (neat) 2929; 2856; 1490; 1357; 1254; 1107 (Si-OR); 838 cm^{-1}.

HRMS calcd for $C_{15}H_{25}N_2O_2Si$ ($M-CH_3$) 293.1685, found 293.1676.

124: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (4H, t, J = 7.2 Hz, 2 x CH_2OSi); 2.46 (4H, t, J = 7.2 Hz, 2 x CH_2); 0.89 (18H, s, 2 x $C(CH_3)_3$); 0.07 (12H, s, 2 x $Si(CH_3)_2$).

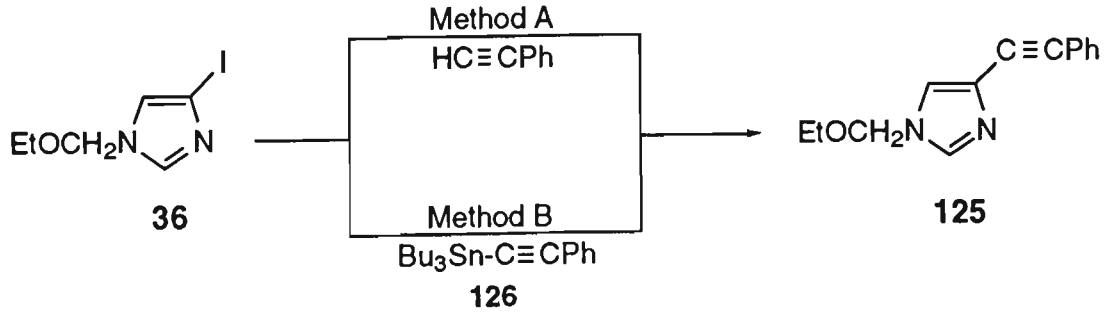
^{13}C NMR (100 MHz, $CDCl_3$) δ 74.5 (C4,5); 66.3 (C3,6); 61.5 (C1,8); 25.8 ($C(\underline{C}H_3)_3$); 23.6 (C2,7); 18.3 ($\underline{C}(CH_3)_3$); -5.4 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 367 ($M+H^+$, 100%); 309 ($M-{}^tBu^+$, 74%); 279 (22%).

IR (neat) 2930; 2856; 1471; 1255; 1108 (Si-O); 838; 776; 665 cm^{-1}.

HRMS calcd for $C_{19}H_{35}O_2Si_2$ ($M-CH_3$) 351.2175, found 351.2174.

1-Ethoxymethyl-4-(2'-phenylethynyl)imidazole (125)



Method A: A solution of iodoimidazole **36** (0.5 g, 1.98 mmol), phenylacetylene (0.30 g, 2.98 mmol), triethylamine (2.0 g, 19.8 mmol), CuI (38 mg, 0.2 mmol) and $Pd(Ph_3P)_4$ (115 mg, 0.1 mmol) in anhydrous acetonitrile (10 mL) under N_2 was heated at reflux for 3

h. The solution was then cooled to rt and poured into H_2O (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography (50% ethyl acetate / hexane) gave the title compound as a tan oil (190 mg, 42%).

Method B: A solution of iodoimidazole **36** (0.5 g, 1.98 mmol), (phenylethynyl)tributylstannane **126** (0.78 g, 1.98 mmol) and $Pd(Ph_3P)_4$ (115 mg, 0.1 mmol) in anhydrous THF (10 mL) under N_2 was heated to reflux for 3 h. The mixture was then cooled to rt and poured into H_2O (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography (50% ethyl acetate / hexane) gave the title compound as a tan oil (310 mg, 69%).

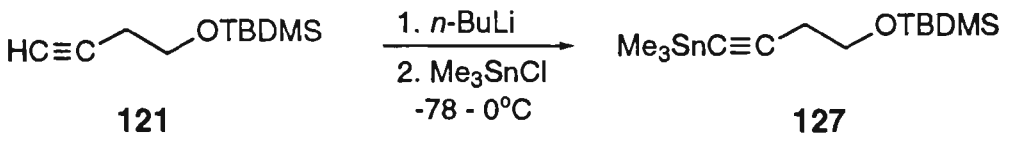
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 1.2 Hz, H2); 7.54-7.52 (2H, m, Ar-H2,6); 7.34-7.32 (3H, m, Ar-H3,4,5); 7.30 (1H, d, *J* = 1.2 Hz, H5); 5.27 (2H, s, EtOC$\underline{H_2}$); 3.47 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H_2}O$); 1.20 (3H, t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.3 (C2); 131.4 (Ar-C2,6); 128.1 (Ar-C3,5); 128.0 (Ar-C4); 125.2 (C4); 123.1 (C5); 89.1 ($\underline{C}$≡CPh); 82.8 (C≡$\underline{C}$Ph); 76.4 (EtO$\underline{C}H_2$); 64.5 ($CH_3\underline{C}H_2O$); 14.5 (CH_3).

MS (ES+ve) 227 ($M+H^+$, 100%); 197 ($M-Et^+$, 6%); 183 ($C_{12}H_{11}N_2^+$, 10%); 59 ($EtOCH_2^+$, 20%); 42 (42%).

HRMS calcd for $C_{14}H_{14}N_2O$ 226.1106, found 226.1114.

1-[4-(*t*-Butyldimethylsilyloxy)]butynyltrimethylstannane (127)



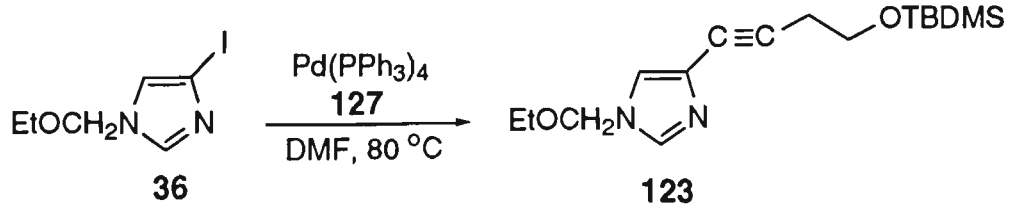
121 **127**

To a solution of the alkyne **121** (3.0 g, 16.30 mmol) in anhydrous THF (10 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (17.93 mmol) and the reaction stirred for 10 min at -78 °C and 20 min at 0 °C. Trimethyltin chloride (3.40 g, 19.56 mmol) in THF (5 mL) was then added dropwise and LiCl precipitated out immediately. The mixture was stirred for 30 min at 0 °C and 16 h at rt. The mixture was diluted with CH_2Cl_2 (40 mL) and the solution was washed with H_2O (15 mL) and then a sat. aqueous solution of NaCl (15 mL) and dried ($MgSO_4$). The solvent was removed to leave a light yellow oil. Purification by bulb-to-bulb distillation (65 °C/0.5 mmHg) gave the title stannane as a clear oil (4.84 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (2H, t, J = 7.2 Hz, CH_2OSi); 2.45 (2H, t, J = 7.2 Hz, $C\underline{H_2}CH_2O$); 0.893 (9H, s, $C(CH_3)_3$); 0.26 (9H, s, ^2J (^{119}Sn, H) = 60.4 Hz, ^2J (^{117}Sn, H) = 58.0 Hz, $Sn(CH_3)_3$); 0.07 (6H, s, $Si(CH_3)_2$).

HRMS calcd for $C_{13}H_{29}SiO^{120}Sn$ 349.1011, found 349.1011.

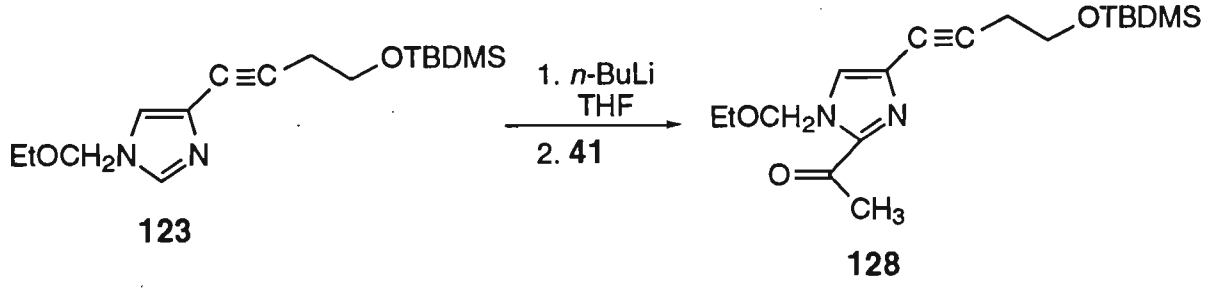
Synthesis of 123 *via* Stille coupling



36 **123**

A solution of iodoimidazole **36** (0.5 g, 1.98 mmol), stannane **127** (1.03 g, 2.97 mmol) and $Pd(Ph_3P)_4$ (229 mg, 0.20 mmol) in anhydrous DMF (8 mL) was degassed with a stream of argon gas and sealed in a thick walled tube under N_2. The solution was then stirred for 24 h at 80 °C. The dark mixture was diluted with ethyl acetate (40 mL) and filtered and the filtrate was washed with H_2O (2 x 15 mL), dried ($MgSO_4$) and concentrated to give a dark oil. Purification by column chromatography (50% ethyl acetate / hexane) gave the alkyne **123** as a tan oil (360 mg, 59%).
Spectral data were identical with that presented for **123** above.

2-Acetyl-4-[4'-(*t*-butyldimethylsilyloxy)but-1'-ynyl]-1-ethoxymethylimidazole (128)



123 **128**

To a solution of imidazole **123** (400 mg, 1.30 mmol) in anhydrous THF (4 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (2.73 mmol) and the reaction left to stir for 1 h at -78 °C. A solution of the amide **41** (0.35 g, 3.25 mmol) in THF (5 mL) was added dropwise and the mixture was stirred for 1 h at -78 °C and then for 1 h at rt. The mixture was diluted with CH_2Cl_2 (15 mL) and the solution was washed with a 5% aqueous solution of $NaHCO_3$ (6 mL), dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Purification by column chromatography (10% ethyl acetate / hexane) gave the title compound as a tan oil (220 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, s, H5); 5.75 (2H, s, $EtOC\underline{H}_2$); 3.82 (2H, t, *J* = 7.2 Hz, CH_2OSi); 3.53 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$); 2.67 (3H, s, $COC\underline{H}_3$); 2.64 (2H, t, *J* = 7.2 Hz, $C\underline{H}_2CH_2OSi$); 1.20 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.91 (9H, s, $C(CH_3)_3$); 0.09 (6H, s, $Si(CH_3)_2$).

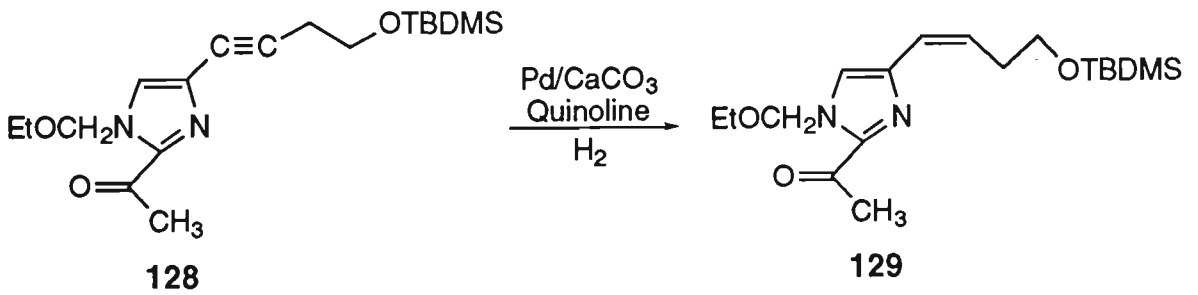
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4 (C=O); 141.9 (C2); 127.0 (C5); 124.9 (C4); 87.8 ($\underline{C}\equiv CCH_2$); 77.3 ($EtO\underline{C}H_2$); 73.9 ($C\equiv\underline{C}CH_2$); 65.0 ($CH_3\underline{C}H_2O$); 61.5 ($CH_2OSi$); 27.3($CO\underline{C}H_3$); 25.8 ($C(\underline{C}H_3)_3$); 23.6 ($\underline{C}H_2CH_2O$); 18.2 ($\underline{C}(CH_3)_3$); 14.7 ($\underline{C}H_3CH_2O$); -5.4 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 351 ($M+H^+$, 100%); 317 (6%); 289 (16%).

IR (neat) 3131; 2928; 2856; 2247 (C≡C); 1683 (C=O); 1456; 1254; 1108 (Si-O); 838 cm^{-1}.

HRMS calcd for $C_{17}H_{27}N_2O_3Si$ ($M-CH_3$) 335.1791, found 335.1758.

(*Z*)-2-Acetyl-4-[4'-(*t*-butyldimethylsilyloxy)but-1'-enyl]-1-ethoxymethylimidazole (129)



128 **129**

To a mixture of imidazole **128** (1.00 g, 2.86 mmol), 10% Pd on $CaCO_3$ (160 mg) and quinoline (370 mg, 2.86 mmol) was added a solution of ethyl acetate / hexane (1:1, 15 mL). The mixture was stirred under a H_2 atmosphere for 90 min then filtered and concentrated *in vacuo*. Purification by column chromatography (2% ethyl acetate / hexane) gave the (Z)-alkene **129** as a tan oil (840 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, s, H5); 6.37 (1H, dt, J = 11.6, 1.6 Hz, Imid-C<u>H</u>=CH); 5.77 (2H, s, EtOC<u>H</u>$_2$); 5.75 (1H, dt, J = 11.6, 7.2 Hz, CH=C<u>H</u>); 3.77 (2H, t, J = 6.8 Hz, CH_2OSi); 3.54 (2H, q, J = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.73 (2H, dq, J = 2.0, 6.8 Hz, C<u>H</u>$_2CH_2OSi$); 2.67 (3H, s, $COCH_3$); 1.20 (3H, t, J = 7.2 Hz, C<u>H</u>$_3CH_2O$); 0.90 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, $Si(CH_3)_2$).

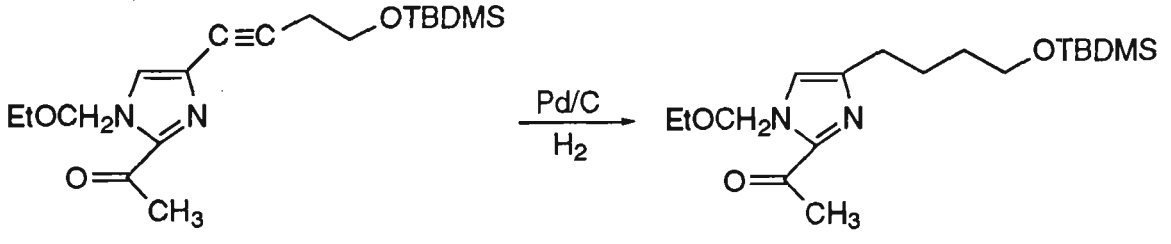
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0 (C=O); 142.0 (C2); 139.9 (<u>C</u>H=CHCH$_2$); 129.4 (C4); 123.4 (CH=<u>C</u>HCH$_2$); 121.7 (C5); 77.04 (EtO<u>C</u>H$_2$); 64.9 ($CH_3\underline{C}H_2O$); 62.6 (CH_2OSi); 32.9 (<u>C</u>H$_2$CH$_2$OSi); 27.4 (CO<u>C</u>H$_3$); 25.9 (C(<u>C</u>H$_3$)$_3$); 18.3 (<u>C</u>(CH$_3$)$_3$); 14.9 (<u>C</u>H$_3$CH$_2$O); -5.3 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 353 ($M+H^+$, 100%); 316 (20%); 288 (55%).

IR (neat) 2955; 2929; 2856; 2366; 2342; 1680 (C=O); 1458; 1254; 1104 (Si-O); 836; 776 cm^{-1}.

HRMS calcd for $C_{17}H_{29}N_2O_3Si$ ($M-CH_3$) 337.1947, found 337.1933.

2-Acetyl-4-[4'-(*t*-butyldimethylsilyloxy)-1'-butyl]-1-ethoxymethylimidazole (130)



128 **130**

To a mixture of the alkyne **128** (220 mg, 0.63 mmol) and 10% Pd on carbon (40 mg) was added ethyl acetate (10 mL) and the mixture set to stir under a H_2 atmosphere for 16 h. The mixture was filtered through a bed of celite and the filtrate was concentrated to give the title compound as a tan oil (210 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, s, H5); 5.74 (2H, s, $EtOC\underline{H}_2$); 3.65 (2H, t, *J* = 6.4 Hz, CH_2OSi); 3.53 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.63 (2H, t, *J* = 8.0 Hz, Imid-$C\underline{H}_2$); 2.65 (3H, s, $COCH_3$); 1.79-1.56 (4H, m, $(C\underline{H}_2)_2CH_2O$); 1.19 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.89 (9H, s, $C(CH_3)_3$); 0.05 (6H, s, $Si(CH_3)_2$).

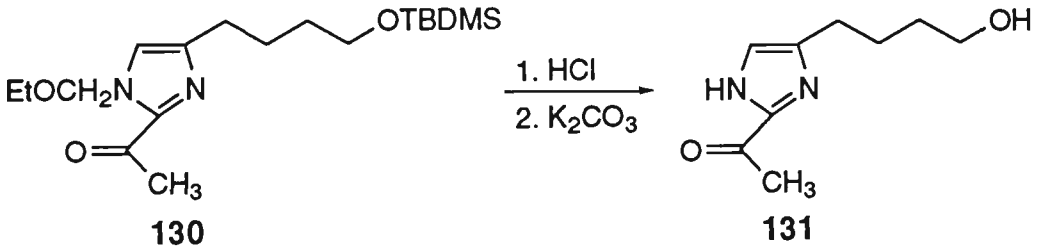
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7 (C=O); 143.8 (C2); 142.0 (C4); 121.4 (C5); 76.9 ($EtO\underline{C}H_2$); 64.8 ($CH_3\underline{C}H_2O$); 62.9 (CH_2OSi); 32.4 (Imid-$\underline{C}H_2$); 28.1 (CH_2); 27.4 ($CO\underline{C}H_3$); 25.9 ($C(\underline{C}H_3)_3$); 25.5 (CH_2); 18.3 ($\underline{C}(CH_3)_3$); 14.9 ($\underline{C}H_3CH_2O$); -5.3 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 355 ($M+H^+$, 100%).

IR (neat) 2930; 2856; 1678 (C=O); 1457; 1256; 1105 (Si-O); 837; 775 cm^{-1}.

HRMS calcd for $C_{18}H_{34}N_2O_3Si$ 354.2338, found 354.2342.

2-Acetyl-4-(4'-hydroxybutyl)imidazole (131)



130 **131**

Imidazole **130** (120 mg, 0.34 mmol) was dissolved in a mixture of ethanol / H_2O (1:1, 10 mL) and conc. HCl (5 mL) was added. The solution was heated to reflux for 1 h, then cooled to rt and the ethanol was removed *in vacuo*. Solid K_2CO_3 was added to the aqueous solution until the evolution of CO_2 gas ceased and the solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried ($MgSO_4$), and the solvent was removed.

Recrystallisation from ethyl acetate / hexane gave the title compound as an orange solid (50 mg, 81%), mp 84-85 °C.

^{1}H NMR (400 MHz, D_2O/DCl) δ 7.48 (1H, s, H5); 3.63 (2H, t, J = 6.4 Hz, CH_2OH); 2.83 (2H, t, J = 7.2 Hz, Imid-C$\underline{H_2}$); 2.70 (3H, s, $COCH_3$); 1.79-1.72 (2H, m, C$\underline{H_2}CH_2O$); 1.63-1.55 (2H, m, CH_2).

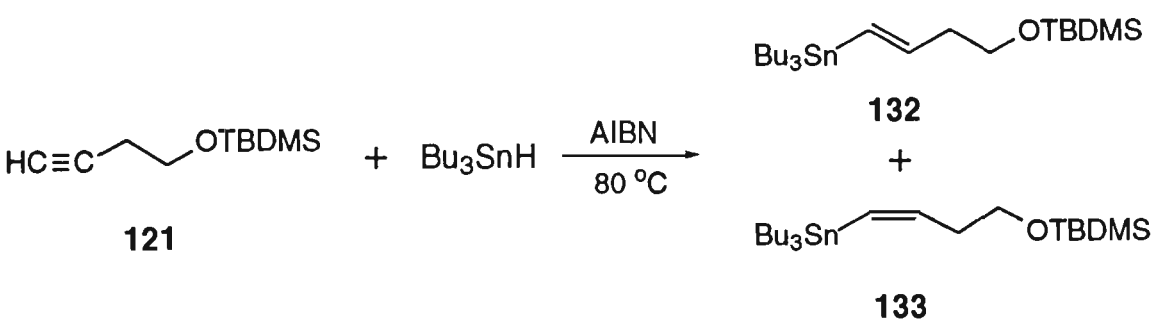
^{13}C NMR (100 MHz, D_2O/DCl) δ 184.6 (C=O); 138.5 (C2); 137.7 (C4); 118.9 (C5); 61.2 (CH_2OH); 30.5 ($\underline{C}H_2CH_2OH$); 26.2 ($CO\underline{C}H_3$); 24.4 (Imid-CH_2); 23.9 (CH_2).

MS (ES+ve) *m/z* 183 ($M+H^+$, 100%); 165 (12%).

HRMS calcd for $C_9H_{14}N_2O_2$ 182.1055, found 183.1055.

Anal. calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.25; H, 7.98; N, 15.39.

(*E*)-1-[4-(*t*-Butyldimethylsilyloxy)]but-1-enyltributyl stannane (132) and (*Z*)-1-[4-(*t*-butyldimethylsilyloxy)] but-1-enyltributylstannane (133)



Reaction Temp.	*Ratio 132/133*
80 °C	81:19
95 °C	89:11
120 °C	90:10

A mixture of the alkyne **121** (2.2 g, 12.0 mmol) and a catalytic amount of AIBN was stirred at 80 °C under an N_2 atmosphere. Tributyltin hydride (3.16 g, 10.9 mmol) was then added and the reaction was stirred at 80 °C for 3 h to give a quantitative yield of a mixture of the stannanes **132** and **133** as a clear oil (ratio **132**:**133** = 81:19).

132: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97-5.95 (2H, m, C<u>H</u>=C<u>H</u>, *J* (Sn, H) = 77.6 Hz); 3.67 (2H, t, *J* = 6.8 Hz, CH_2O); 2.36 (2H, ddt, *J* = 2.0, 3.2, 6.8 Hz, C<u>H</u>$_2$CH_2O); 1.52-1.25 (18H, m, 3 x (C<u>H</u>$_2$)$_3$CH_3); 0.90-0.85 (18H, m, C(CH_3)$_3$, 3 x CH_3); 0.05 (6H, s, Si(C<u>H</u>$_3$)$_2$).

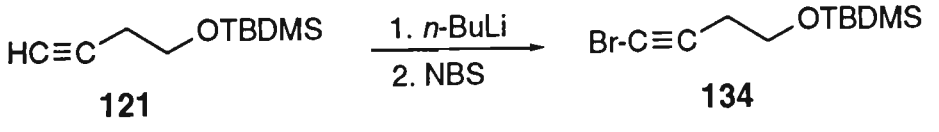
MS (ES-ve) 449* (M-Et$^-$, 47%); 415* (100%); 379* (79%).

HRMS calcd for $C_{22}H_{49}OSi^{120}Sn$ 477.2574, found 477.2585.

* ^{120}Sn peak only reported.

133: ^{1}H NMR (400 MHZ, $CDCl_3$) δ 6.51 (1H, dt, *J* = 6.8, 12.8 Hz, Sn CH=C<u>H</u>); 5.89 (1H, dt, *J* = 1.2, 12.4 Hz, Sn C<u>H</u>=CH); 3.64 (2H, t, *J* = 7.2 Hz,CH_2O); 2.27 (2H, dq, *J* = 1.2, 6.8 Hz, C<u>H</u>$_2$CH_2O); 1.52-1.25 (18H, m, 3 x (C<u>H</u>$_2$)$_3$CH_3); 0.90-0.85 (18H, m, C(CH_3)$_3$, 3 x CH_3); 0.06 (6H, s, Si(CH_3)$_2$).

1-Bromo-4-(*t*-butyldimethylsilyloxy)-1-butyne (134)



121 **134**

To a solution of the alkyne **121** (2.0 g, 10.9 mmol) in anhydrous THF (10 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (11.4 mmol) and the solution was stirred for 10 min at -78 °C and 20 min at 0 °C. The solution was syringed into a stirred slurry of *N*-

bromosuccinimide (4.06 g, 22.8 mmol) in THF (10 mL) at -78 °C and the mixture was stirred at -78 °C for 20 min. The reaction was then stirred at 0 °C for 3 h and at rt for 2 h to complete reaction. The mixture was diluted with CCl_4 and then filtered. The filtrate was concentrated to give an orange oil. Purification by fractional distillation (70 °C/0.5 mmHg) gave the title compound as a clear oil (2.40 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (2H, t, J = 7.2 Hz, CH_2O); 2.42 (2H, t, J = 7.2 Hz, CH_2); 0.90 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, 2 x CH_3).

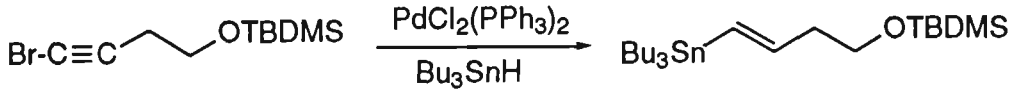
^{13}C NMR (100 MHz, $CDCl_3$) δ 77.4 (C2); 61.4 (C4); 39.1 (Br-C≡); 25.8 ($C(\underline{C}H_3)_3$); 24.0 (C3); 18.3 ($\underline{C}(CH_3)_3$); -5.3 (2 x CH_3).

MS (CI+ve) *m/z* 263* ($M+H^+$, 11%); 241* (31%); 197 (100%).

HRMS calcd for $C_{10}H_{19}OSi^{79}Br$ 263.0467, found 263.0460.

* ^{79}Br isotope peak only reported.

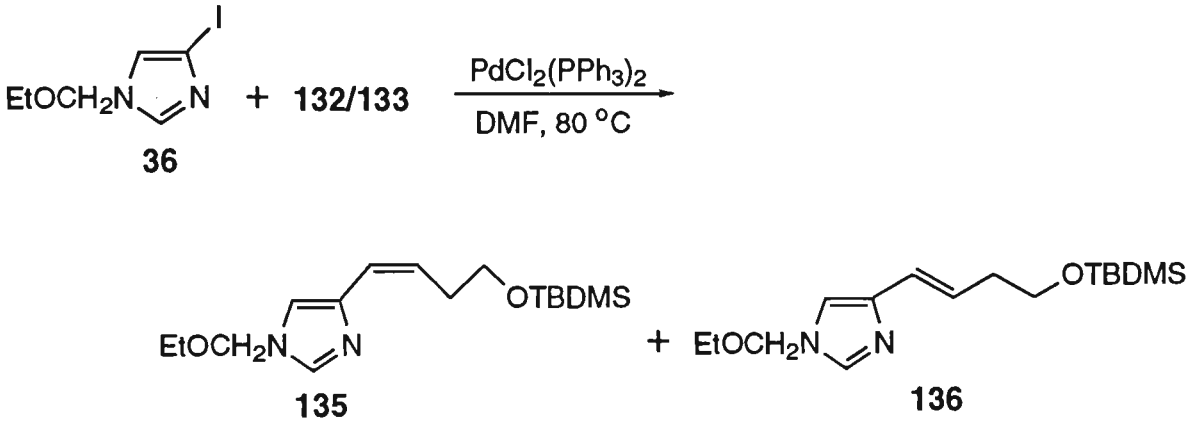
Synthesis of the (*E*)-vinylstannane 132 from the bromoalkyne 134



134 **132**

To a solution of the alkyne **134** (2.38 g, 9.05 mmol) and $PdCl_2(Ph_3P)_2$ (120 mg, 0.18 mmol) in anhydrous THF (15 mL) under N_2 was added dropwise tributyltin hydride (5.27 g, 18.1 mmol) and the resulting orange solution stirred for 1 h at rt. The solution was concentrated to give an orange oil. Purification by fractional distillation (92 °C/0.1 mmHg) gave the (*E*)-stannane **132** as a clear oil (3.14 g, 73%).

(Z)-4-[4'-(*t*-Butyldimethylsilyloxy)but-1'-enyl]-1-ethoxy methylimidazole (135) and (*E*)-4-[4'-(*t*-butyldimethylsilyl oxy)but-1'-enyl]-1-ethoxymethylimidazole (136)



A solution of iodoimidazole **36** (2.63 g, 10.4 mmol), stannanes **132/133** (5.2 g, 10.9 mmol, ratio **132:133** = 81:19) and $PdCl_2(Ph_3P)_2$ (370 mg, 0.53 mmol) in anhydrous DMF (30 mL) was degassed with a stream of argon and sealed in a thick walled tube under N_2. The solution was then stirred in the dark at 80 °C for 24 h. The mixture was diluted with ethyl acetate (200 mL) and the solution was washed with a half sat. aqueous solution of NaCl (3 x 80 mL), dried ($MgSO_4$) and concentrated to leave a dark oil. Purification by column chromatography (40% ethyl acetate / hexane) gave **135** (145 mg, 5%) and **136** (1.64 g, 51%) as yellow oils.

135: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, s, H2); 7.06 (1H, s, H5); 6.38 (1H, dt, J = 1.6, 11.6 Hz, Imid-C<u>H</u>=CH); 5.64 (1H, dt, J = 7.2, 12.0 Hz, CH=C<u>H</u>); 5.26 (2H, s, EtOC<u>H</u>$_2$); 3.76 (2H, t, J = 6.8 Hz, CH_2OSi); 3.46 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.67 (2H, dq, J = 1.6, 6.8 Hz, $C\underline{H}_2CH_2O$); 1.19 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.90 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (C2); 136.6 (Imid-$\underline{C}$H=CH); 127.1 (C4); 122.5 (C5); 117.2 (CH=$\underline{C}$H); 76.2(EtO$\underline{C}H_2$); 64.3 ($CH_3\underline{C}H_2O$); 62.6 ($\underline{C}H_2OSi$); 32.9 ($\underline{C}H_2CH_2OSi$); 25.9 ($C(\underline{C}H_3)_3$); 18.3 ($\underline{C}(CH_3)_3$); 14.7 ($\underline{C}H_3CH_2O$); -5.3 ($Si(CH_3)_2$).

MS (CI+ve) *m/z* 311 ($M+H^+$, 48%); 295 ($M-CH_3^+$, 11%); 253 ($M-{}^tBu^+$, 100%); 197 (71%); 179 (38%); 166 (46%).

136: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 1.2 Hz, H2); 6.90 (1H, d, *J* = 1.6 Hz, H5); 6.33-6.31 (2H, m, $C\underline{H}$=$C\underline{H}$); 5.22 (2H, s, EtOC$\underline{H}_2$); 3.71 (2H, t, *J* = 7.2 Hz, CH_2O); 3.43 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.42-2.37 (2H, m, $C\underline{H}_2CH_2O$); 1.18 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.90 (9H, s, $C(CH_3)_3$); 0.06 (6H, s, $Si(CH_3)_2$).

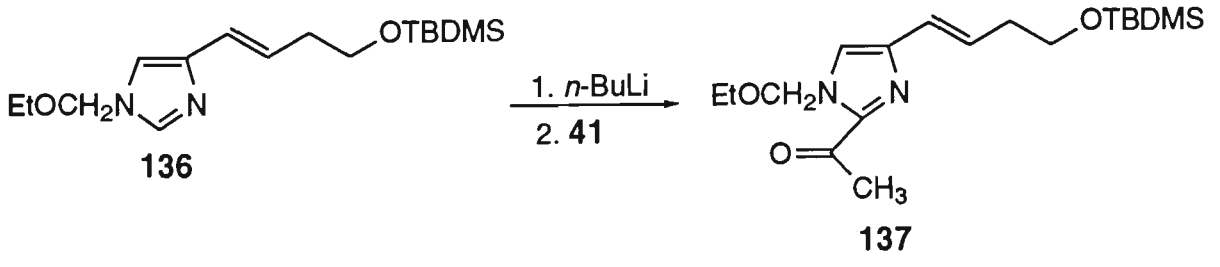
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (Imid-CH=$\underline{C}$H); 137.1 (C2); 126.1 (C4); 123.0 (C5); 115.1 (Imid-$\underline{C}$H=CH); 76.2 (EtO$\underline{C}H_2$); 64.2 ($CH_3\underline{C}H_2O$); 63.0 (CH_2O); 36.5 ($\underline{C}H_2CH_2O$); 25.9 ($C(\underline{C}H_3)_3$); 18.3 ($\underline{C}(CH_3)_3$); 14.6 ($\underline{C}H_3CH_2O$); -5.3 ($Si(\underline{C}H_3)_2$).

MS (ES+ve) *m/z* 311 ($M+H^+$, 100%); 288 (14%).

IR (neat) 2954; 2929; 2856; 1361; 1257; 1105; 909; 836; 733 cm^{-1}.

HRMS calcd for $C_{16}H_{30}N_2O_2Si$ 310.2076, found 310.2091.

(*E*)-2-Acetyl-4-[4'-(*t*-butyldimethylsilyloxy)but-1'-enyl]-1-ethoxymethylimidazole (137)



To a solution of the alkene **136** (2.0 g, 6.45 mmol) in anhydrous THF (10 mL) under N_2 at -78 °C was added *n*-BuLi in hexanes (7.74 mmol) and the resulting black solution stirred for 1 h at -78 °C. A solution of the freshly distilled amide **41** (930 mg, 9.03 mmol) in anhydrous THF (5 mL) was added slowly and the resulting solution stirred for 1 h at -78 °C and a further 1 h at rt. The mixture was then diluted with CH_2Cl_2 (40 mL), washed with a 5% aqueous solution of $NaHCO_3$ (15 mL), dried ($MgSO_4$) and concentrated to give a black oil. Purification by column chromatography (40% ethyl acetate / hexane) gave the title compound as a tan oil (1.43 g, 63%), plus starting alkene **136** (0.42 g).

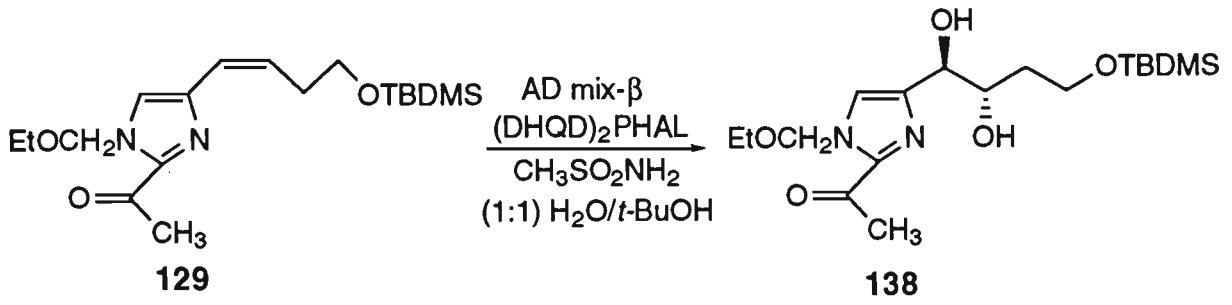
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (1H, s, H5); 6.44-6.33 (2H, m, C<u>H</u>=C<u>H</u>); 5.75 (2H, s, $EtOCH_2$); 3.74 (2H, t, J = 7.2 Hz, CH_2OSi); 3.53 (2H, q, J = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.67 (3H, s, $COCH_3$); 2.46-2.41 (2H, m, $C\underline{H}_2CH_2OSi$); 1.19 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.91 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, $Si(CH_3)_2$.

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (C=O); 142.3 (C2); 140.7 (Imid-<u>C</u>H=CH); 128.1 (C4); 122.7 (C5); 120.9 (CH=<u>C</u>H); 77.0 ($EtO\underline{C}H_2$, over $CDCl_3$); 64.8 ($CH_3\underline{C}H_2O$); 62.8 (CH_2OSi); 36.4 ($\underline{C}H_2CH_2OSi$); 27.3 ($CO\underline{C}H_3$); 25.9 ($C(\underline{C}H_3)_3$); 18.3 ($\underline{C}(CH_3)_3$); 14.8 ($\underline{C}H_3CH_2O$); -5.3 ($Si(CH_3)_2$).

MS (CI+ve) *m/z* 353 ($M+H^+$, 13%); 337 ($M-CH_3^+$, 6%); 307 ($M-EtO^+$, 15%); 295 ($M-{}^tBu^+$, 65%); 207(22%).

HRMS calcd for $C_{18}H_{32}N_2O_3Si$ 352.2182, found 352.2177

(1'*R*,2'*S*)-2-Acetyl-4-[1',2'-dihydroxy-4'-(*t*-butyldimethyl silyloxy)]-1'-butyl-1-ethoxymethylimidazole (138)



129 **138**

A representative AD procedure: To a mixture of AD mix-β (0.8 g) and $(DHQD)_2PHAL$ (18 mg, 2.28 x 10^{-5} mol) in H_2O (3 mL) and *t*-BuOH (2 mL) was added methanesulfonamide (108 mg, 1.34 mmol) with stirring. The 2-phase system was then cooled to 0 °C and the (*Z*)-alkene **129** (200 mg, 0.57 mmol) in *t*-BuOH (1 mL) was added in one addition. The mixture was stirred at 0 °C for 3 days until the reaction was complete by TLC analysis. Na_2SO_3 (1.7 g) was then added at 0 °C and the mixture was warmed to rt and left to stir for 1 h. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 12 mL). The combined extracts were washed with a 2M aqueous solution of KOH (15 mL), then dried ($MgSO_4$) and the solvent was removed to leave a yellow oil. Purification by column chromatography (35% ethyl acetate / hexane) gave the title compound as a light yellow oil (160 mg, 73%, ee= 26%).

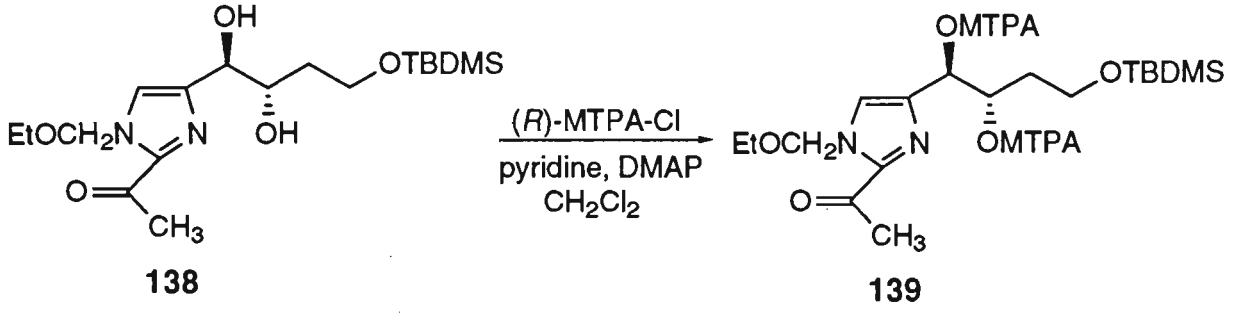
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, s, H5); 5.75 (2H, s, $EtOC\underline{H}_2$); 4.64 (1H, t, *J* = 5.2 Hz, $C\underline{H}OH$); 4.32 (1H, d, *J* = 2.8 Hz, OH); 4.05-4.00 (1H, m, CHOH); 3.94-3.84 (2H, m, CH_2OSi); 3.74 (1H, d, *J* = 4.8 Hz, OH); 3.55 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.63 (3H, s, $COCH_3$); 1.86-1.81 (2H, m, $C\underline{H}_2CH_2OSi$); 1.20 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.91 (9H, s, $C(CH_3)_3$); 0.10 (6H, s, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (C=O); 143.4 (C2); 141.7 (C4); 122.2 (C5); 77.2 ($EtO\underline{C}H_2$); 74.4 (CHOH); 70.8 (CHOH); 65.0 ($CH_3\underline{C}H_2O$); 61.2 (CH_2OSi); 34.6 ($\underline{C}H_2CH_2O$); 27.3 ($CO\underline{C}H_3$); 25.8 ($C(\underline{C}H_3)_3$); 18.1 ($\underline{C}(CH_3)_3$); 14.8 ($\underline{C}H_3CH_2O$); -5.5 ($Si(CH_3)_2$).

MS (ES+ve) *m/z* 387 ($M+H^+$, 100%); 332 (7%).

HRMS calcd for $C_{18}H_{35}N_2O_5Si$ 387.2314, found 387.2307.

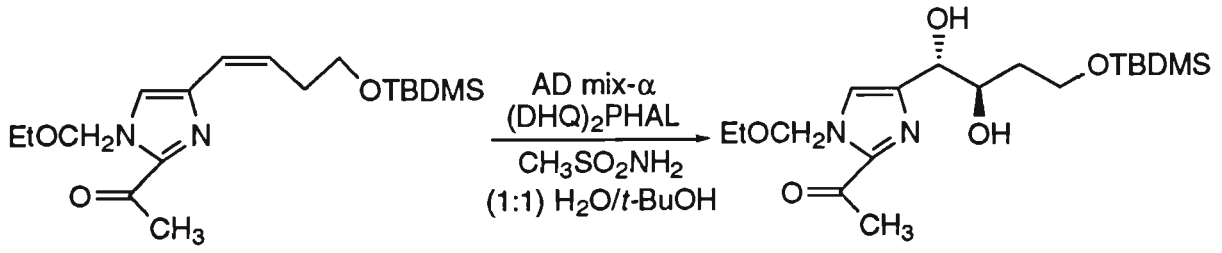
(1'*R*,2'*S*)-2-Acetyl-4-[1',2'-di-(*S*)-(α-methoxy-α-(trifluoromethyl)phenylacetyloxy)-4'-(*t*-butyldimethylsilyloxy)]-1'-butyl-1-ethoxymethylimidazole (139)



A representative procedure: To a solution of the diol **138** (20 mg, 5.2 x 10^{-5} mol) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (MTPA-Cl) (30 mg, 1.22 x 10^{-4} mol) in anhydrous CH_2Cl_2 (1 mL) was added pyridine (0.5 mL) and a catalytic quantity of *N,N*-dimethylaminopyridine. The solution was stirred for 24 h at rt and was then diluted with ether (6 mL). The solution was washed consecutively with cold aqueous solutions of 5% HCl (3 mL), sat. Na_2CO_3 (3 mL) and H_2O (3 mL) and then dried ($MgSO_4$). The solvent was removed to leave a pale oil which was taken into $CDCl_3$. ^1H NMR analysis showed the major diastereomer **139** to be present in 26% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.21 (10H, m, 2 x Ar-H2-6); 7.11 (1H, s, H5); 6.35 (1H, d, *J* = 3.2 Hz, H1'); 5.73 (1H, dt, *J* = 8.0, 4.0 Hz, H2'); 5.60 (2H, ABq, *J* = 9.6 Hz, $EtOC\underline{H}_A\underline{H}_B$); 4.34 (2H, dq, *J* = 1.6, 7.2 Hz, CH_2OSi); 3.54-3.31 (8H, m, 2 x OCH_3, $CH_3C\underline{H}_2O$); 2.57 (3H, s, $COCH_3$); 1.97-1.62 (2H, m, $C\underline{H}_2CH_2OSi$); 1.07 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.81 (9H, s, $C(CH_3)_3$); -0.04; -0.06 (2 x 3H, 2 x s, $Si(CH_3)_2$). **MS** (ES+ve) *m/z* 819 ($M+H^+$, 49%); 705 (34%); 80 (100%).

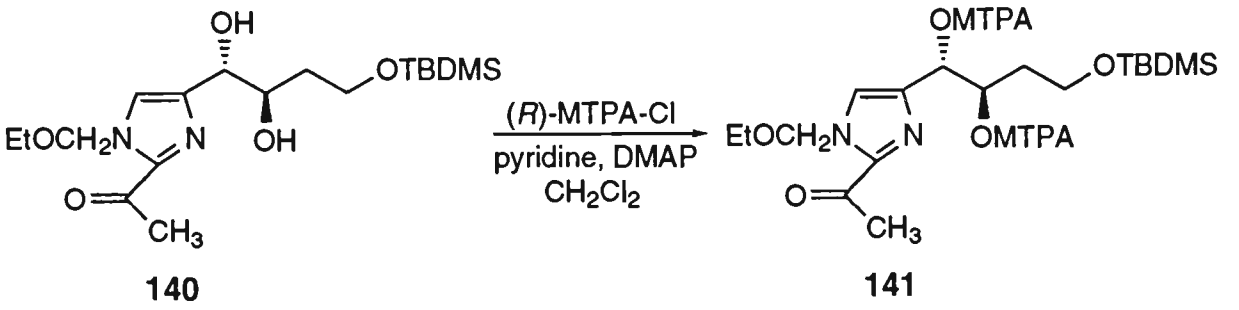
(1'*S*,2'*R*)-2-Acetyl-4-[1',2'-dihydroxy-4'-(*t*-butyldimethyl silyloxy)]-1'-butyl-1-ethoxymethylimidazole (140)



129 **140**

Using the general procedure described above for the synthesis of **138**, compound **140** was obtained as a thick pale oil after purification by column chromatography (35% ethyl acetate / hexane), yield=56%, ee=8%. Spectral data were identical to that of **138**.

(1'*S*,2'*R*)-2-Acetyl-4-[1',2'-di-(*S*)-(α-methoxy-α-(trifluoro methyl)phenylacetyloxy)-4'-(*t*-butyldimethylsilyloxy)]-1'-butyl-1-ethoxymethylimidazole (141)

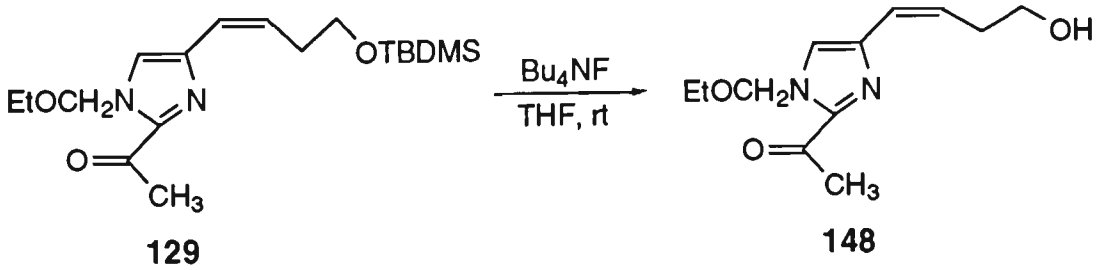


140 **141**

Using the general procedure described above for the synthesis of **139**, the diester **141** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **141** to be present in 8% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.19 (10H, m, 2 x Ar-H2-6); 6.63 (1H, s, H5); 6.30 (1H, d, *J* = 2.8 Hz, H1'); 5.78 (1H, dt, *J* = 8.0, 3.6 Hz, H2'); 5.50 (2H, s, $EtOC\underline{H}_2$); 4.32 (2H, dq, *J* = 1.6, 7.2 Hz, CH_2OSi); 3.52-3.29 (8H, m, 2 x OCH_3, $CH_3C\underline{H}_2O$); 2.51 (3H, s, $COCH_3$); 1.97-1.62 (2H, m, $C\underline{H}_2CH_2OSi$); 1.10 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.78 (9H, s, $C(CH_3)_3$); -0.06; -0.08 (2 x 3H, 2 x s, $Si(CH_3)_2$).

(*Z*)-2-Acetyl-4-(4'-hydroxybut-1'-enyl)-1-ethoxymethyl imidazole (148)



129 **148**

A solution of the silyl ether **129** (0.75 g, 2.13 mmol) and Bu_4NF (1.11 g, 4.26 mmol) in THF (10 mL) was stirred at rt for 75 min.

The solution was diluted with ethyl acetate (30 mL) and washed consecutively with a sat. aqueous solution of NaCl (10 mL) and H_2O (10 mL). The aqueous washings were re-extracted with ethyl acetate (20 mL) and the combined extracts were dried ($MgSO_4$) and concentrated to leave a thick oil. Purification by column chromatography (35% ethyl acetate / hexane) gave the title alcohol as a yellow oil (400 mg, 79%).

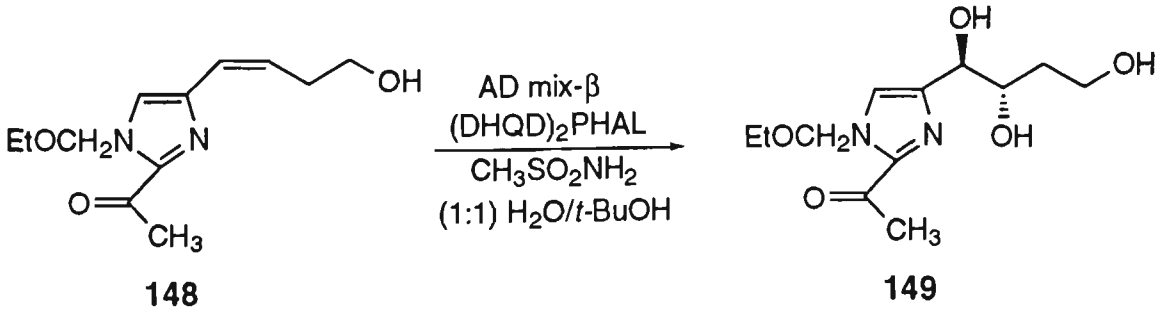
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, s, H5); 6.45 (1H, d, J = 11.6 Hz, Imid-C<u>H</u>=CH); 5.88-5.80 (1H, m, Imid-CH=C<u>H</u>); 5.77 (2H, s, EtOC<u>H</u>$_2$); 4.34 (1H, s (b), OH); 3.89-3.84 (2H, m, C<u>H</u>$_2$OH); 3.56 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.81-2.75 (2H, m, C<u>H</u>$_2$CH$_2$OH); 2.67 (3H, s, $COCH_3$); 1.21 (3H, t, J = 7.2 Hz, C<u>H</u>$_3$CH$_2$O).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (C=O); 141.3 (C2); 139.1 (Imid-<u>C</u>H=CH); 129.9 (C4); 123.3 (Imid-CH=<u>C</u>H); 121.8 (C5); 76.95 (EtO<u>C</u>H$_2$); 64.9 ($CH_3\underline{C}H_2O$); 61.9 (CH_2OH); 31.8 (<u>C</u>H$_2$CH$_2$OH); 27.3 ($CO\underline{C}H_3$); 14.6 (<u>C</u>H$_3$CH$_2$O).

MS (ES+ve) *m/z* 239 ($M+H^+$, 100%); 197(18%); 102 (9%); 59 (17%).

HRMS calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1315.

(1'*R*,2'*S*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl)-1-ethoxymethylimidazole (149)



148 **149**

Using the general procedure described above for the synthesis of **138**, compound **149** was obtained as a white solid after purification by column chromatography (10% methanol / ethyl acetate), yield=75%, mp 83-84 °C, ee=26%.

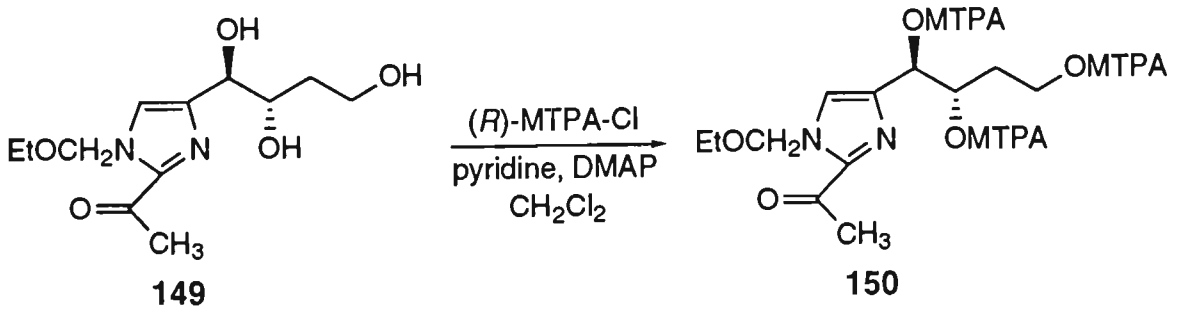
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, s, H5); 5.76 (2H, s, $EtOC\underline{H}_2$); 4.65 (1H, d, *J* = 5.6 Hz, Imid-C<u>H</u>OH); 4.12-4.04 (1H, m, C<u>H</u>OH); 3.96-3.86 (2H, m, $C\underline{H}_2OH$); 3.56 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.64 (3H, s, $COC\underline{H}_3$); 1.87-1.74 (2H, m, $C\underline{H}_2CH_2OH$); 1.21 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2 (C=O); 142.8 (C2); 141.7 (C4); 122.6 (C5); 77.1 ($EtO\underline{C}H_2$); 73.5 (Imid-<u>C</u>HOH); 71.0 (CHOH); 65.1 ($CH_3\underline{C}H_2O$); 59.8 ($\underline{C}H_2OH$); 34.0 ($\underline{C}H_2CH_2OH$); 27.2 ($CO\underline{C}H_3$); 14.7 ($\underline{C}H_3CH_2O$).

MS (ES+ve) *m/z* 294 ($M+Na^+$, 100%); 139 (100%); 102 (65%).

Anal. calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.65; H, 7.53; N, 10.02.

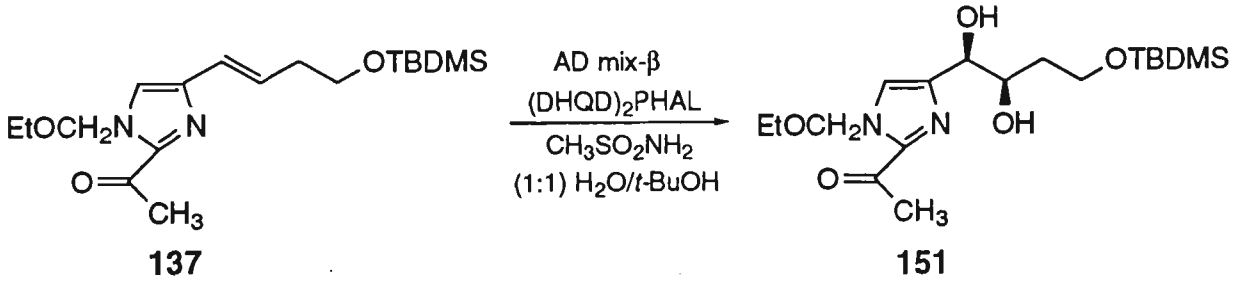
(1'*R*,2'*S*)-2-Acetyl-4-[1',2',4'-tri-(*S*)-(α-methoxy-α-(trifluoromethyl)phenylacetyloxy)]-1'-butyl-1-ethoxy methylimidazole (150)



Using the general procedure described above for the synthesis of **139**, the triester **150** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **150** to be present in 26% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.28 (15H, m, 3 x Ar-H2-6); 7.16 (1H, s, H5); 6.30 (1H, d, *J* = 3.2 Hz, H1'); 5.66 (2H, ABq, *J* = 10.4 Hz, $EtOC\underline{H}_A\underline{H}_B$); 5.71-5.61 (1H, m, H2'); 4.27-4.19 (2H, m, CH_2OSi); 3.61-3.40 (11H, m, 3 x OCH_3, $CH_3C\underline{H}_2O$); 2.57 (3H, s, $COCH_3$); 2.10-1.87 (2H, m, $C\underline{H}_2CH_2OSi$); 1.34 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$).

(1'*R*,2'*R*)-2-Acetyl-4-[1',2'-dihydroxy-4'-(*t*-butyldimethyl silyloxy)]-1'-butyl-1-ethoxymethylimidazole (151)



137 **151**

Using the general procedure described above for the synthesis of **138**, compound **151** was obtained as a thick yellow syrup after purification by column chromatography (40% ethyl acetate / hexane), yield=65%, ee=99%, $[\alpha]_D^{25}$ -13.7° (*c* 2.85, $CHCl_3$).

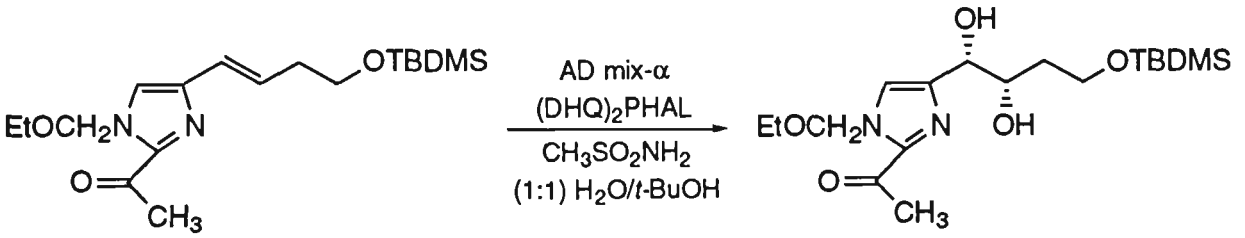
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, s, H5); 5.75 (2H, ABq, *J* = 10.8 Hz, $EtOC\underline{H}_A\underline{H}_B$); 4.61 (1H, dd, *J* = 4.0, 5.6 Hz, Imid-C<u>H</u>OH); 4.16 (1H, dt, *J* = 4.0, 7.2 Hz, C<u>H</u>OH); 4.01 (1H, d, *J* = 3.2 Hz, OH); 3.91-3.88 (2H, m, CH_2OSi); 3.55 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 3.50 (1H, d, *J* = 6.4 Hz, OH); 2.64 (3H, d, *J* = 0.4 Hz, $COC\underline{H}_3$); 1.91-1.78 (2H, m, $C\underline{H}_2CH_2OSi$); 1.20 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.91 (9H, s, $C(CH_3)_3$); 0.10; 0.09 (2 x 3H, 2 x s, $Si(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (C=O); 143.3 (C2); 141.8 (C4); 122.2 (C5); 77.02 ($EtO\underline{C}H_2$); 73.0 (Imid-<u>C</u>HOH); 70.8 (CHOH); 64.9 (CH_3CH_2O); 61.0 ($\underline{C}H_2OSi$); 35.0 ($\underline{C}H_2CH_2OSi$); 27.2 ($CO\underline{C}H_3$); 25.7 ($C(\underline{C}H_3)_3$); 18.0 ($\underline{C}(CH_3)_3$); 14.7 ($\underline{C}H_3CH_2O$); -5.65; -5.67 ($Si(CH_3)_2$).

MS (CI+ve) *m/z* 387 ($M+H^+$, 100%); 371 ($M-CH_3^+$, 12%); 329 ($M-{}^tBu^+$,10%).

HRMS calcd for $C_{18}H_{35}N_2O_5Si$ 387.2315, found 387.2326.

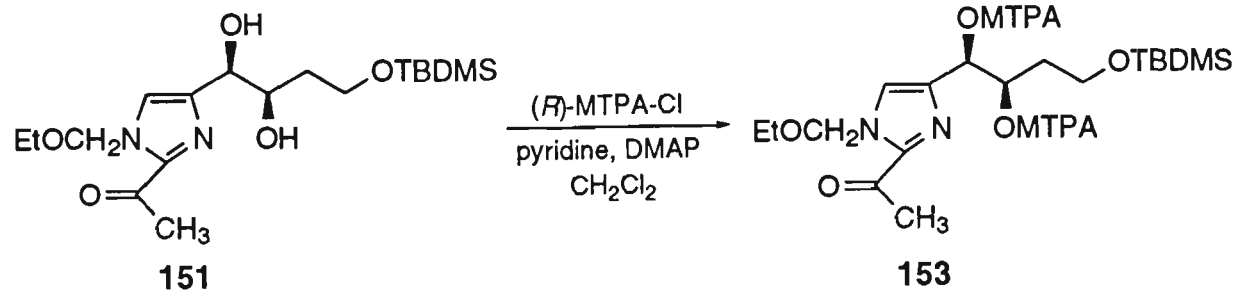
(1'*S*,2'*S*)-2-Acetyl-4-[1',2'-dihydroxy-4'-(*t*-butyldimethyl silyloxy)]-1'-butyl-1-ethoxymethylimidazole (152)



137 **152**

Using the general procedure described above for the synthesis of **138**, compound **152** was obtained as a thick yellow syrup after purification by column chromatography (40% ethyl acetate / hexane), yield=56%, ee=98%, $[\alpha]_D^{25}$ +13.3° (*c* 2.45, $CHCl_3$). Spectral data were identical to that of **151**.

(1'*R*,2'*R*)-2-Acetyl-4-[1',2'-di-(*S*)-(α-methoxy-α-(trifluoro methyl)phenylacetyloxy)-4'-(*t*-butyldimethylsilyloxy)]-1'-butyl-1-ethoxymethylimidazole (153)



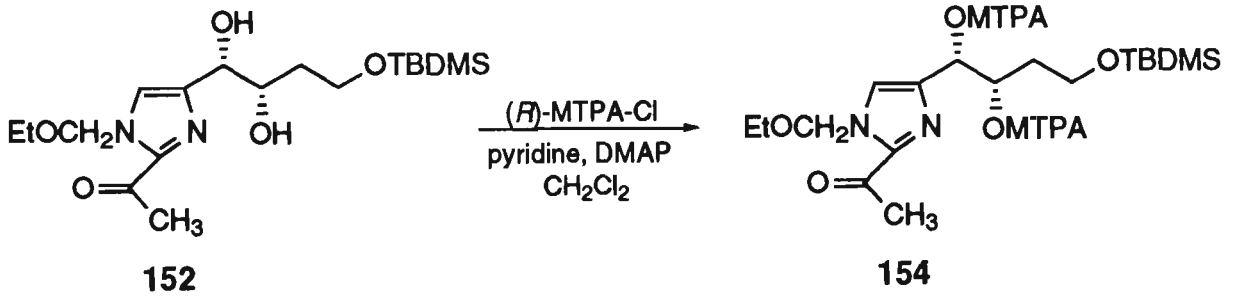
151 **153**

Using the general procedure described above for the synthesis of **139**, the diester **153** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **153** to be present in 99% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (2H, m, 2 x Ar-H4); 7.40-7.28 (8H, m, 2 x Ar-H2,3,5,6); 6.85 (1H, s, H5); 6.24 (1H, d, J = 3.6 Hz, H1'); 5.79 (1H, dt, J = 3.2, 6.4 Hz, H2'); 5.68 (1H, d, J_{AB} = 10.4 Hz, $EtOCH_A\underline{H}_B$); 5.42 (1H, d, J_{AB} = 10.4 Hz, $EtOCH_A\underline{H}_B$); 3.71-3.61 (2H, m, CH_2OSi); 3.52 (3H, s, OCH_3); 3.40 (2H, q, J = 6.8 Hz, $CH_3C\underline{H}_2O$); 3.37 (3H, s, OCH_3); 2.49 (3H, s, $COCH_3$); 1.93-1.88 (2H, m, $C\underline{H}_2CH_2OSi$); 1.31 (3H, t, J = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.90 (9H, s, $C(CH_3)_3$); 0.05 (6H, s, $Si(CH_3)_2$).

MS (ES+ve) *m/z* 819 ($M+H^+$, 81%); 586 (100%); 351 (29%); 189 (40%).

(1'*S*,2'*S*)-2-Acetyl-4-[1',2'-di-(*S*)-(α-methoxy-α-(trifluoro methyl)phenylacetyloxy)-4'-(*t*-butyldimethylsilyloxy)-1'-butyl]-1-ethoxymethylimidazole (154)



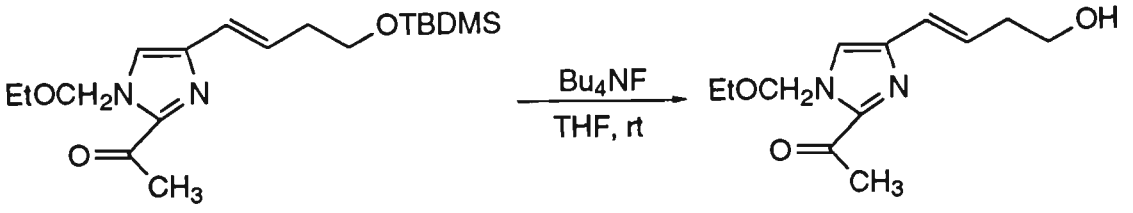
152 **154**

Using the general procedure described above for the synthesis of **139**, the diester **154** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **154** to be present in 98% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (2H, m, 2 x Ar-H4); 7.39-7.28 (8H, m, 2 x Ar-H2,3,5,6); 6.90 (1H, s, H5); 6.29 (1H, d, J = 3.6 Hz, H1'); 5.89 (1H, dt, J = 3.6, 6.4 Hz, H2'); 5.65 (1H, d, J_{AB} = 10.4 Hz,

EtOC$\underline{H}_A H_B$); 5.55 (1H, d, J_{AB} = 10.0 Hz, EtOC$H_A\underline{H}_B$); 3.65-3.53 (2H, m, CH_2OSi); 3.50; 3.43 (2 x 3H, 2 x s, 2 x OCH_3); 3.39 (2H, q, J = 6.8 Hz, $CH_3C\underline{H}_2O$); 2.55 (3H, s, $COCH_3$); 1.87-1.82 (2H, m, $C\underline{H}_2CH_2OSi$); 1.13 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.89 (9H, s, $C(CH_3)_3$); 0.035; 0.028 (2 x 3H, 2 x s, $Si(CH_3)_2$).

(*E*)-2-Acetyl-4-(4'-hydroxybut-1'-enyl)-1-ethoxymethyl imidazole (155)



137 **155**

A solution of the silyl ether **137** (700 mg, 1.99 mmol) and Bu_4NF (1.04 g, 3.98 mmol) in THF (10 mL) was stirred at rt for 75 min. The dark solution was then diluted with ethyl acetate (30 mL) and washed consecutively with a sat. aqueous solution of NaCl (10 mL) and H_2O (10 mL). The aqueous washings were extracted with ethyl acetate (2 x 20 mL), the combined extracts were dried ($MgSO_4$) and concentrated to leave a thick dark oil. Purification by column chromatography (50% ethyl acetate / hexane) gave a light yellow oil which solidified on standing (350 mg, 74%), mp 80-81°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, s, H5); 6.43-6.41 (2H, m, C$\underline{H}$=C$\underline{H}$); 5.75 (2H, s, EtOC$\underline{H}_2$); 3.80-3.75 (2H, m, $C\underline{H}_2OH$); 3.53 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.68 (3H, s, $COCH_3$); 2.51-2.67 (2H, m, $C\underline{H}_2CH_2OH$); 1.59 (1H, t, J = 5.6 Hz, OH); 1.19 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$).

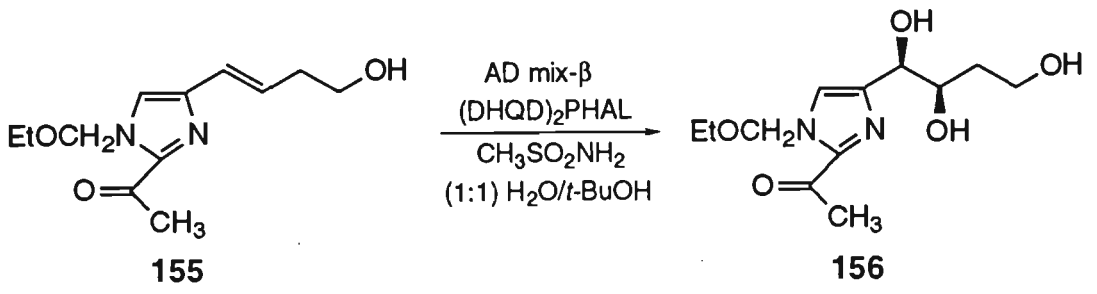
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0 (C=O); 142.3 (C2); 140.4 (Imid-$\underline{C}$H=CH); 127.6 (C4); 123.7 (C5); 121.3 (CH=$\underline{C}$H); 77.1 (EtO$\underline{C}H_2$); 64.9

($CH_3\underline{C}H_2O$); 61.8 ($\underline{C}H_2OH$); 36.2 ($\underline{C}H_2CH_2OH$); 27.4 ($CO\underline{C}H_3$); 14.8 ($\underline{C}H_3CH_2O$).

MS (ES+ve) *m/z* 239 ($M+H^+$, 100%), 197 (15%).

Anal. calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.66; H, 7.82; N, 11.58.

(1'*R*,2'*R*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl)-1-ethoxymethylimidazole (156)



155 **156**

Using the general procedure described above for the synthesis of **138**, compound **156** was obtained as a white solid after purification by column chromatography (10% methanol / ethyl acetate), yield=79%, ee=95%, mp 102-103 °C, $[\alpha]_D^{26}$ -11.2° (*c* 1.35, MeOH).

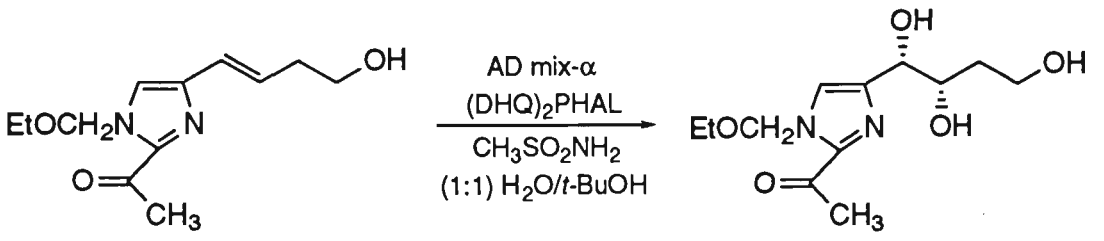
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, s, H5); 5.76 (2H, ABq, *J* = 10.4 Hz, $EtOC\underline{H}_A\underline{H}_B$); 4.54 (1H, dd, *J* = 4.0, 7.2 Hz, Imid-C$\underline{H}$OH); 4.21-4.16 (1H, m, C$\underline{H}$OH); 3.92-3.89 (2H, m, C$\underline{H}_2$OH); 3.87 (1H, d, *J* = 2.8 Hz, CHO$\underline{H}$); 3.56 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 3.50 (1H, d, *J* = 5.2 Hz, CHO$\underline{H}$); 3.10-3.08 (1H, m, $CH_2O\underline{H}$); 2.64 (3H, s, $COCH_3$); 2.01-1.92 (1H, m, $C\underline{H}_AH_BCH_2OH$); 1.84-1.77 (1H, m, $CH_A\underline{H}_BCH_2OH$); 1.21 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$).

^{13}C NMR (100 MHz, CD_3OD) δ 191.5 (C=O); 144.8 (C2); 143.0 (C4); 124.7 (C5); 78.1 ($EtO\underline{C}H_2$); 72.7 ($\underline{C}HOH\underline{C}HOH$); 65.8 ($CH_3\underline{C}H_2O$); 60.0 ($\underline{C}H_2OH$); 36.7 ($\underline{C}H_2CH_2OH$); 27.4 ($CO\underline{C}H_3$); 15.2 ($\underline{C}H_3CH_2O$).

MS (CI+ve) *m/z* 256 ($M-CH_3^+$, 13%); 237 (26%); 209 (26%); 197 (64%); 139 (100%).

Anal. calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.65; H, 7.53; N, 10.02.

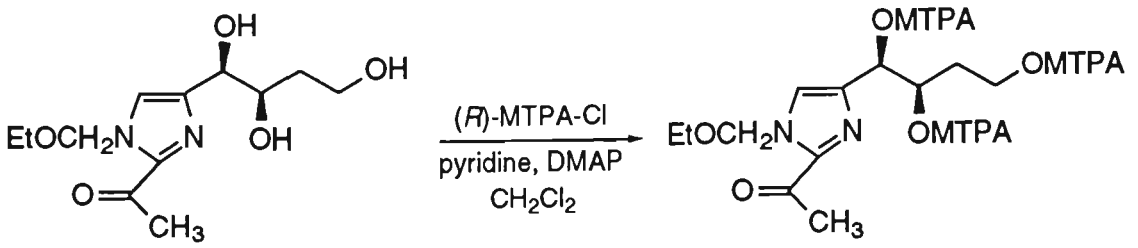
(1'*S*,2'*S*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl)-1-ethoxymethylimidazole (157)



155 **157**

Using the general procedure described above for the synthesis of **138**, compound **157** was obtained as a white solid, after purification by column chromatography (10% methanol / ethyl acetate), yield=76%, ee=90%, mp 102-103 °C, $[\alpha]_D^{26}$ +11.7° (*c* 1.3, MeOH). Spectral data were identical to that of **156**.

(1'*R*,2'*R*)-2-Acetyl-4-[1',2',4'-tri-(*S*)-(α-methoxy-α-(trifluoromethyl)phenylacetyloxy)]-1'-butyl-1-ethoxy methylimidazole 158



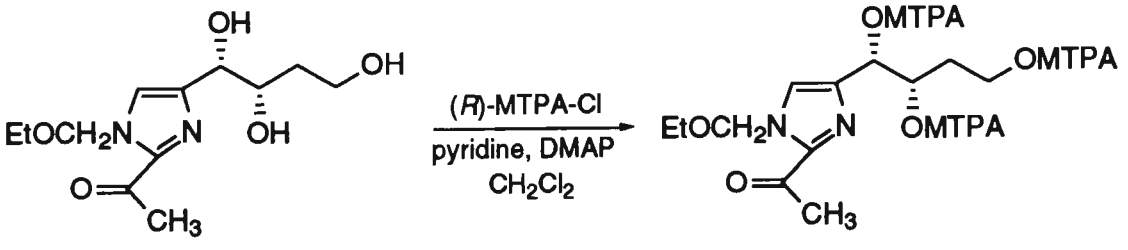
156 **158**

Using the general procedure described above for the synthesis of **139**, the triester **158** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **158** to be present in 95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.29 (15H, m, 3 x Ar-H2-6); 6.86 (1H, s, H5); 6.09 (1H, d, J = 3.3 Hz, H1'); 5.71-5.66 (1H, m, H2'); 5.68 (1H, d, J_{AB} = 10.2 Hz, EtOC$\underline{H}_A$H$_B$); 5.46 (1H, d, J_{AB} = 10.2 Hz, EtOCH$_A\underline{H}_B$); 4.37-4.09 (2H, m, CH_2OSi); 3.55 (3H, d, J = 1.2 Hz, OCH_3); 3.50 (3H, d, J = 0.9 Hz, OCH_3); 3.42 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 3.35 (3H, s, OCH_3); 2.46 (3H, s, $COCH_3$); 2.10-2.05 (2H, m, $C\underline{H}_2CH_2OSi$); 1.14 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$).

MS (ES+ve) *m/z* 921 (M+H$^+$, 100%); 688 (35%); 555 (24%).

(1'*S*,2'*S*)-2-Acetyl-4-[1',2',4'-tri-(*S*)-(α-methoxy-α-(trifluoromethyl)phenylacetyloxy)-1'-butyl]-1-ethoxy methylimidazole (159)



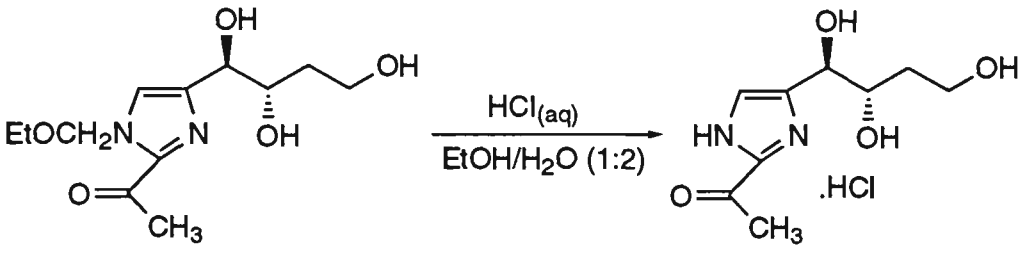
157 **159**

Using the general procedure described above for the synthesis of **139**, the triester **159** was obtained as a pale oil. ^{1}H NMR analysis in $CDCl_3$ showed the major diastereomer **159** to be present in 90% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.29 (15H, m, 3 x Ar-H2-6); 6.89 (1H, s, H5); 6.18 (1H, d, J = 4.5 Hz, H1'); 5.79 (1H, dt, J = 7.8, 4.8 Hz, H2'); 5.58 (2H, ABq, J = 10.2 Hz, EtOC$\underline{H}_A\underline{H}_B$); 4.27-4.09 (2H, m, CH_2OSi); 3.55 (3H, d, J = 1.2 Hz, OCH_3); 3.450; 3.446 (2 x 3H, 2 x s, 2 x

OCH_3); 3.40 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.51 (3H, s, $COCH_3$); 2.10-1.91 (2H, m, $C\underline{H}_2CH_2OSi$); 1.13 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$).

(1'*R*,2'*S*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl) imidazolium chloride 160



149 **160**

A representative deprotection procedure: To a solution of the triol **149** (110 mg, 0.40 mmol) in ethanol / H_2O (1:1, 8 mL) was added conc. HCl (4 mL). The mixture was heated at reflux for 1 h, cooled to rt and the ethanol removed *in vacuo*. The aqueous solution was washed with ether (3 x 5 mL) then concentrated and the sample dried under high vacuum at ca. 60 °C for 2 h to give the title compound as a hydroscopic, glassy yellow solid (94 mg, 93%). An analytical sample was recrystallised from ethanol / acetonitrile, mp 129-131 °C.

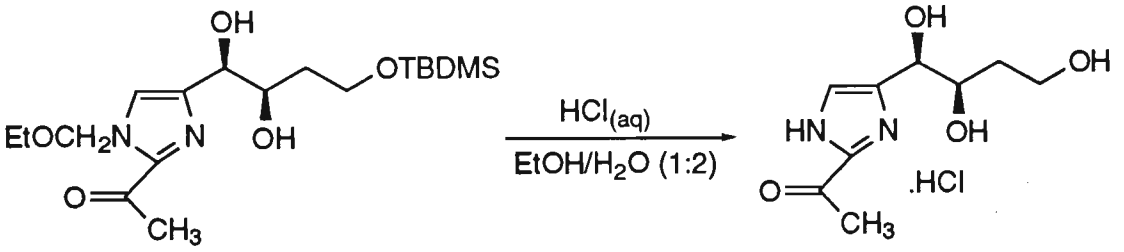
^{1}H NMR (400 MHz, D_2O/DCl) δ 7.56 (1H, s, H5); 4.78 (1H, d, J = 5.2 Hz, Imid-C$\underline{H}$OH); 3.96 (1H, ddd, J = 2.8, 5.6, 10.0 Hz, C$\underline{H}$OH); 3.67-3.63 (2H, m, $C\underline{H}_2OH$); 2.63 ($COCH_3$); 1.82-1.70 (1H, m, $C\underline{H}_AH_BCH_2OH$); 1.49-1.40 (1H, m, $CH_A\underline{H}_BCH_2OH$).

^{13}C NMR (100 MHz, D_2O/DCl) δ 185.2 (C=O); 139.8 (C2); 136.7 (C4); 119.8 (C5); 70.4 (Imid-$\underline{C}$HOH); 68.9 (CHOH); 58.2 (CH_2OH); 34.4 ($\underline{C}H_2CH_2OH$); 26.3 ($CO\underline{C}H_3$).

MS (ES+ve) *m/z* 215 ($M+H^+$, 100%); 197 ($M-H_2O^+$, 59%); 179 ($M-2H_2O^+$, 47%).

Anal. calcd for $C_9H_{15}N_2O_4Cl.1/3H_2O$: C, 42.11; H, 6.15; N, 10.91. Found: C, 42.32; H, 6.18; N, 10.61.

(1'*R*,2'*R*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl) imidazolium chloride 161



151 **161**

Using the general procedure described above for the synthesis of **160**, compound **161** was obtained as a tan solid, yield=98%, mp 236-242 °C (decomp.), $[\alpha]_D^{23}$ -9.6° (*c* 1.80, H_2O).

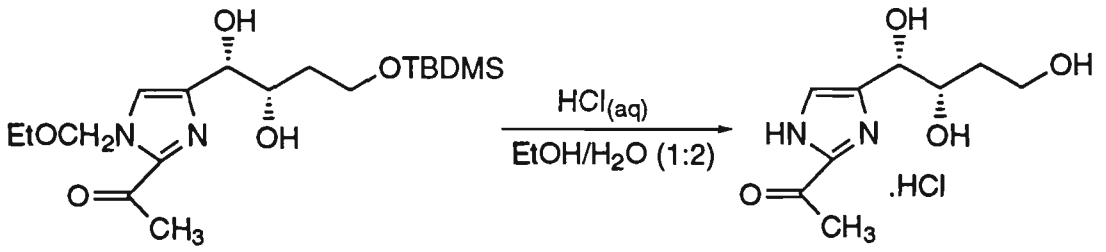
^{1}H NMR (400 MHz, D_2O) δ 7.46 (1H, s, H5); 4.73 (1H, d, *J* = 4.4 Hz, Imid-C<u>H</u>OH); 3.84 (1H, dd, *J* = 4.0, 14 Hz, C<u>H</u>OH); 3.57-3.52 (2H, m, C<u>H</u>$_2$OH); 2.53 (3H, s, CH_3); 1.64-1.46 (2H, m, C<u>H</u>$_2$$CH_2OH$).

^{13}C NMR (100 MHz, D_2O) δ 184.7 (C=O); 139.4 (C2); 137.0 (C4); 119.3 (C5); 70.1 (Imid-<u>C</u>HOH); 68.3 (CHOH); 58.2 (CH_2OH); 34.2 (<u>C</u>H_2CH_2OH); 26.4 (CH_3).

MS (ES+ve) *m/z* 215 ($C_9H_{15}N_2O_4^+$, 100%); 197 (15%).

HRMS calcd for $C_9H_{15}N_2O_4$ 215.1032, found 215.1043.

(1'*S*,2'*S*)-2-Acetyl-4-(1',2',4'-trihydroxy-1'-butyl) imidazolium chloride 162

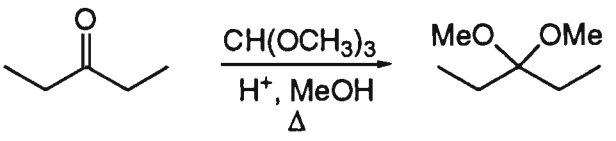


152 **162**

Using the general procedure described above for the synthesis of **160**, compound **162** was obtained as a tan solid, yield=97%, $[\alpha]_D^{23}$ +9.8° (*c* 1.50, H_2O). Spectral data were identical to that of **161**.

6.4 Experimental Chapter 4

3,3-Dimethoxypentane



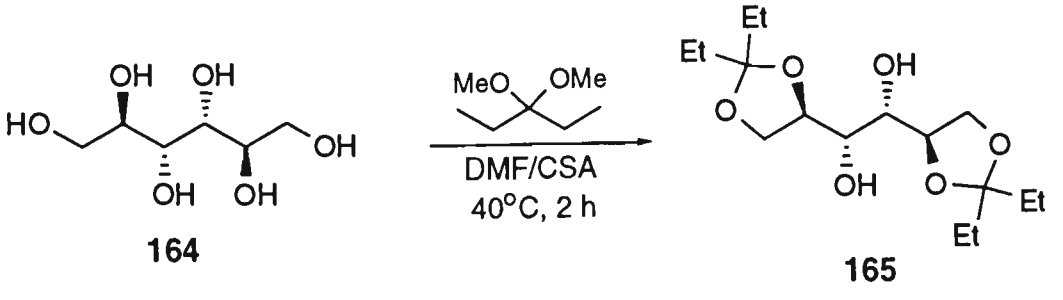
A solution of 3-pentanone (36.2 g, 0.42 mol), trimethyl orthoformate (46.5 g, 0.438 mol) and *p*-toluenesulfonic acid (catalytic) in anhydrous methanol (90 mL) under N_2 was heated to reflux for 5 h. The reaction was cooled to rt, solid sodium bicarbonate was added and the mixture was stirred at rt for 15 min. The reaction was then filtered. Methanol and methyl formate were removed *in vacuo* and the remaining oil was fractionally distilled at atmospheric pressure (bp > 110 °C) to give the title compound as a clear liquid (31.66 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (6H, s, 2 x OCH_3); 1.60 (4H, q, J = 7.6 Hz, 2 x CH_2); 0.82 (6H, t, J = 7.6 Hz, 2 x CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 103.8 (C3); 47.2 (OCH_3); 24.1 (C2,4); 8.0 (C1,5).

MS (CI+ve) *m/z* 103 (M-Et$^+$, 100%); 101 (M-OCH_3^+, 90%); 100 (41%).

1,2,5,6-Di-O-(3-Pentylidene)-D-mannitol (165)



164 165

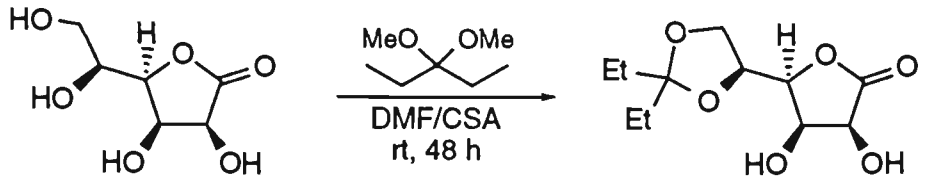
To a slurry of D-mannitol **164** (15.0 g, 82.2 mmol) in anhydrous DMF (38 mL) and camphorsulfonic acid (0.58 g) at 40 °C was added 3,3-dimethoxypentane (22.8 g, 0.173 mmol) dropwise over a 10 min period and the solution was left to stir for 3 h. Triethylamine (0.5 g) was added, the solution was stirred for 10 min at rt and the DMF was then removed *in vacuo*. The residual oil was dissolved in ethyl acetate (200 mL), washed with a half sat. aqueous solution of NaCl (2 x 135 mL) and dried ($MgSO_4$). The solvent was removed to leave a thick oil which solidified as a white solid. The solid was dried under high vacuum for 2 h at ca. 60 °C to give 23.70 g of crude product which was determined to be 95% pure by ^1H NMR using a measured amount of CH_2Cl_2 as an internal standard (22.52 g, 86%). An analytical sample was recrystallised from 20% ethyl acetate / hexane, mp 87-89 °C (lit.[207] mp 97.1-98.1 °C), $[\alpha]_D^{28}$ +10.1° (*c* 5.0, MeOH), (lit.[207] $[\alpha]_D$ +7.1°, *c* 5.0, MeOH).

^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.13 (4H, m, 2 x H1,6); 3.91 (2H, dd, *J* = 6.0, 8.0 Hz, H3,4); 3.78 (2H, t, *J* = 6.0 Hz, H2,5); 2.56 (2H, d, *J* = 6.8 Hz, 2 x OH); 1.70-1.58 (8H, m, 4 x $C\underline{H}_2CH_3$); 0.89; 0.91 (2 x 6H, 2 x t, *J* = 7.6 Hz, 4 x CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 113.2 ($\underline{C}Et_2$); 76.3 (C2,5); 71.6 (C1,6); 67.4 (C3,4); 29.6 (2 x $\underline{C}H_2CH_3$); 28.9 (2 x $\underline{C}H_2CH_3$); 8.15 (2 x CH_3); 7.99 (2 x CH_3).

MS (CI+ve) *m/z* 319 ($M+H^+$, 12%); 289 ($M-Et^+$, 30%); 271 (8%); 233 ($M-C_5H_{10}O^+$, 33%); 203 (85%); 185 (21%); 159 ($C_8H_{15}O_3^+$, 19%); 147 (73%); 129 ($C_7H_{13}O_2^+$, 100%); 111 (100%).

5,6-O-(3-Pentylidene)-L-gulono-1,4-lactone (167)



166 167

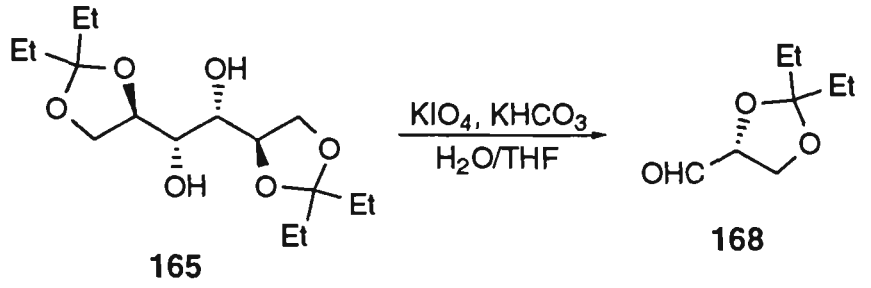
To a slurry of L-gulono-1,4-lactone **166** (25 g, 140 mmol) in anhydrous DMF (125 mL) containing camphorsulfonic acid (0.5 g) was added 3,3-dimethoxypentane (30.0 g, 228 mmol). The mixture became homogeneous after approximately 1 h, and was stirred vigorously for 48 h at rt. The solvent was then removed *in vacuo* to leave a thick oil. A large stirring bar was added to the hot oil and toluene (375 mL) was added with vigorous stirring. After approximately 5 min the solution thickened to give a viscous gel which was cooled to 0 °C. The gel was filtered and the filter cake was washed with cold toluene. The resulting white solid was then dried for 3 h under high vacuum to give the title compound (25.3 g, 73%), $[\alpha]_D^{27}$ +33.4° (*c* 1.06, CH_3OH), (lit.[207] $[\alpha]_D$ +34.4°, *c* 0.978, CH_3OH). An analytical sample was recrystallised from acetone mp 145-146 °C (lit.[207] mp 149.7-150.8 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (1H, ddd, *J* = 5.6, 7.2, 12.4 Hz, C<u>H</u>CH_2O); 4.49-4.47 (1H, m, C<u>H</u>OCO, lactone); 4.43-4.38 (2H, m, C<u>H</u>(OH)C<u>H</u>(OH)); 4.24 (1H, dd, *J* = 7.2, 8.4 Hz, C<u>H</u>$_A$H$_B$O); 3.90 (1H, dd, *J* = 7.2, 8.4 Hz, CH$_A$<u>H</u>$_B$O); 1.73-1.64 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 0.93-0.89 (6H, m, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.02 (C=O); 112.82 (<u>C</u>Et$_2$); 81.26 (<u>C</u>OHCO); 75.40 (CH_2<u>C</u>H); 70.21 (CH_2); 69.18 (COH); 64.94 (<u>C</u>HCHOH); 29.11; 28.84 (2 x <u>C</u>H$_2$CH$_3$); 8.14; 7.90 (2 x CH_3).

MS (EI-ve) *m/z* 245 ($M-H^-$, 39%); 159 (11%); 127 ($C_7H_{11}O_2^-$, 100%).

2,3-O-(3-Pentylidene)-D-glyceraldehyde (168)



165 168

To a slurry of KIO_4 (14.32 g, 62.3 mmol) and $KHCO_3$ (0.57 g, 5.7 mmol) in H_2O (100 mL) was added a solution of **165** (18.0 g, 56.6 mmol) in THF (40 mL) dropwise over a 10 min period. The reaction was left to stir vigorously for 3 h at rt. The solution was cooled to 0 °C then filtered and the filter cake was washed with ethyl acetate (20 mL). The filtrate was warmed to rt, the aqueous phase was saturated with solid NaCl and the layers were separated. The aqueous layer was extracted a second time with ethyl acetate (40 mL) and the combined extracts were dried ($MgSO_4$) and concentrated to leave a pale oil (19.4 g). Distillation (61 °C/5 mmHg) (lit.[207] 68-72 °C/6 mmHg) gave the title aldehyde as a clear oil (12.60g, 70%), $[\alpha]_D^{28}$ +76.3° (*c* 1.06, toluene) (lit.[207] $[\alpha]_D^{28}$ +80.1°, *c* 0.166, toluene).

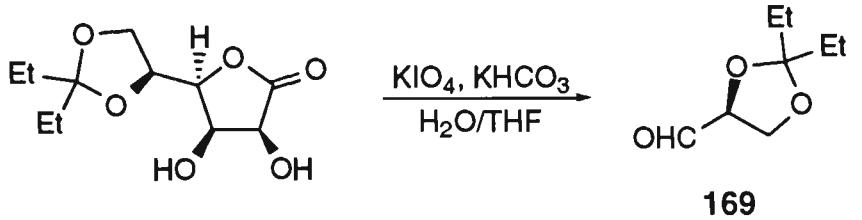
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, d, *J* = 2.0 Hz, CHO); 4.39 (1H, ddd, *J* = 2.0, 5.2, 7.6 Hz, H2); 4.18 (1H, dd, *J* = 7.6, 8.4 Hz, H_A3); 4.06 (1H, dd, *J* = 5.2, 8.0 Hz, H_B3); 1.75-1.65 (4H, m, 2 x $C\underline{H}_2CH_3$); 0.96; 0.92 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 201.3 (CHO); 115.1 ($\underline{C}Et_2$); 79.9 (C2); 65.5 (C3); 29.2; 28.7 (2 x $\underline{C}H_2CH_3$); 7.93; 7.77 (2 x CH_3).

MS (CI+ve) *m/z* 159 ($M+H^+$, 36%); 129 ($M-Et^+$, 100%).

IR (neat) 3449(b); 2974; 2941; 2883; 1735 (C=O); 1464; 1361; 1173; 1083; 913 cm^{-1}.

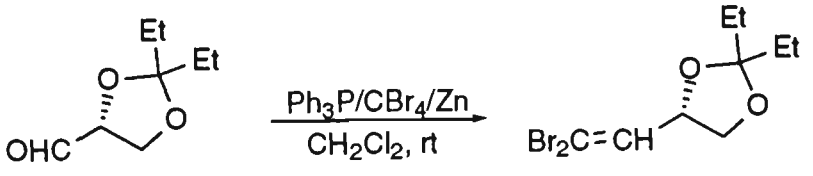
2,3-O-(3-Pentylidene)-L-glyceraldehyde (169)



167 169

Using the procedure described above for the synthesis of **168**, the title compound was obtained as a clear oil (72%) after distillation (85 °C/10 mmHg, lit.[207] 43-44 °C/0.3 mmHg), $[\alpha]_D^{23}$ -74.8° (*c* 1.18, toluene), (lit.[207] $[\alpha]_D$ -79.4°, *c* 1.18, toluene). Spectral data were identical to that of **168**.

(4*S*)-2,2-Diethyl-4-(2',2'-dibromoethenyl)-1,3-dioxolane (172)



168 172

A mixture of triphenylphosphine (26.56 g, 101.3 mmol), carbon tetrabromide (33.58 g, 101.3 mmol) and zinc dust (6.62 g, 101.3 mmol) were suspended in anhydrous CH_2Cl_2 (200 mL) and the mixure was stirred for 24 h under N_2. The aldehyde **168** (5.16 g, 32.7 mmol) was then added and the mixture was stirred for a further 24 h. The mixture was diluted with hexane (800 mL),

filtered and the insoluble residue taken into CH_2Cl_2 (100 mL). The CH_2Cl_2 solution as then diluted with hexane (400 mL) and filtered. The combined filtrates were washed with sat. aqueous NH_4Cl (400 mL), H_2O (300 mL) and dried ($MgSO_4$). The solvent was removed to give a light yellow oil of essentially pure olefin (8.90g, 87%), $[\alpha]_D^{28}$ +6.8° (*c* 1.18, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (1H, d, *J* = 7.2 Hz, C<u>H</u>=CBr_2); 4.72 (1H, dd, *J* = 6.4, 7.6 Hz, H4); 4.21 (1H, dd, *J* = 6.4, 8.4 Hz, H_A5); 3.63 (1H, t, *J* = 7.6 Hz, H_B5); 1.65 (2 x 2H, p, *J* = 7.6 Hz, 2 x C<u>H</u>$_2$$CH_3$); 0.93; 0.89 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3).

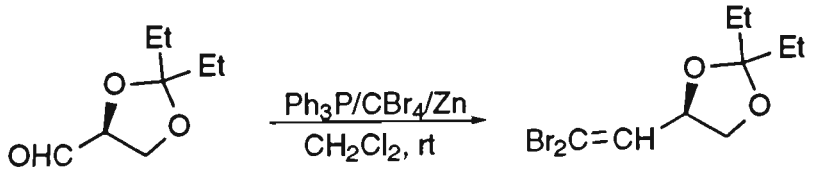
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9 (CBr_2); 113.4 (C2); 92.4 (<u>C</u>H=CBr_2); 76.3 (C4); 68.2 (C5); 29.59; 29.35 (2 x <u>C</u>H_2CH_3); 8.07; 7.96 (2 x CH_3).

MS (CI+ve) *m/z* 315 ($M+H^+$, 6%); 285 ($M-Et^+$, 70%); 229 ($C_4H_5OBr_2^+$, 20%); 215 ($C_3H_3OBr_2^+$, 31%); 160 (100%); 119 (100%); 107 (100%).

IR (neat) 2971; 2938; 2880; 1718; 1616; 1458; 1172; 1078; 915; 808; 665 cm^{-1}.

HRMS calcd for $C_9H_{15}{}^{79}Br_2O_2$ 312.9440, found 312.9446.

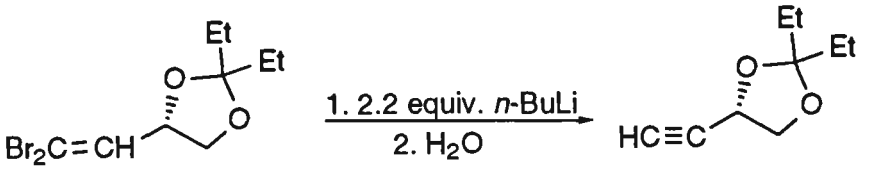
(4*R*)-Diethyl-4-(2',2'-dibromoethenyl)-1,3-dioxolane (173)



169 173

Using the procedure described above for the synthesis of **172**, the title compound was obtained as a light yellow oil (77%), $[\alpha]_D^{25}$ -6.4° (*c* 1.05, $CHCl_3$). Spectral data were identical to that of the **172**.

(4*S*)-2,2-Diethyl-4-ethynyl-1,3-dioxolane (174)



172 **174**

To a solution of alkene **172** (6.88 g, 22.1 mmol) in anhydrous THF (50 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (48.7 mmol). The solution was stirred for 1 h at -78 °C and then for 1 h at ambient temperature. Water (15 mL) and hexane (60 mL) were added and the phases were separated. The aqueous phase was extracted with hexane (15 mL) and the combined extracts were washed with H_2O (10 mL) and dried ($MgSO_4$). The solvent was removed to leave an orange oil which was purified by bulb-to-bulb distillation (61 °C/6 mmHg) to give the title dioxolane as a clear oil (2.36 g, 69%), $[\alpha]_D^{27}$ +44.1° (*c* 0.75, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, ddd, *J* = 2.0, 6.4, 8.0 Hz, H4); 4.18 (1H, dd, *J* = 6.4, 8.0 Hz, H_A5); 3.89 (1H, dd, *J* = 6.8, 8.0 Hz, H_B5); 2.49 (1H, d, *J* = 2.0 Hz, C≡C<u>H</u>); 1.74; 1.63 (2 x 2H, 2 x q, *J* = 7.6 Hz, 2 x $C\underline{H}_2CH_3$); 0.94; 0.89 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3).

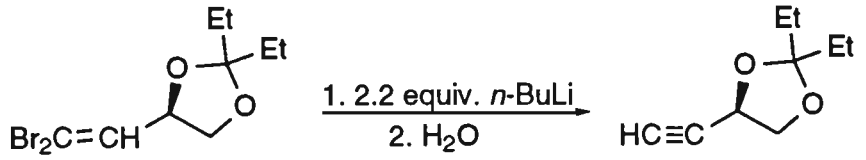
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 114.5 (C2); 81.3 (HC≡<u>C</u>); 73.8 (C4); 70.3 (C5); 65.5 (H<u>C</u>≡C); 29.6; 29.3 (2 x $\underline{C}H_2CH_3$); 8.1; 7.8 (2 x CH_3).

MS (CI+ve) *m/z* 155 ($M+H^+$, 26%); 125 ($M-Et^+$, 100%); 87 (96%).

IR (neat) 3300 (HC≡C); 2972; 2940; 2883; 1464; 1355; 1172; 1079; 912; 665 cm^{-1}.

HRMS calcd for $C_9H_{15}O_2$ 155.1072, found 155.1070.

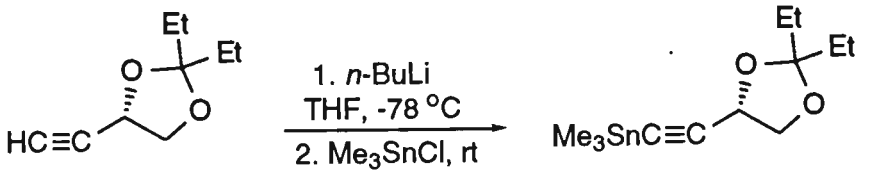
(4*R*)-2,2-Diethyl-4-ethynyl-1,3-dioxolane (175)



173 175

Using the procedure described above for **174**, the title compound was obtained as a clear oil (76%) after bulb-to-bulb distillation (85 °C/10 mmHg), $[\alpha]_D^{26}$ -38.3° (*c* 1.75, $CHCl_3$). Spectral data were identical to that of **174**.

(4*S*)-2,2-Diethyl-4-(trimethylstannylethynyl)-1,3-dioxolane (177)



174 177

To a solution of alkyne **174** (1.0 g, 6.5 mmol) in anhydrous THF (5 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (7.15 mmol). The reaction was stirred for 10 min at -78 °C and 20 min at 0 °C. A solution of trimethyltin chloride (1.60 g, 7.80 mmol) in THF (5 mL) was then added dropwise. The solution was stirred for 35 min at 0 °C and then warmed to rt and left to stir for 16 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed consecutively with H_2O (10 mL) and sat. aqueous NaCl (10 mL) and then dried ($MgSO_4$). The solvent was removed to leave a thick black oil. Bulb-to-bulb

distillation (104 °C/0.5 mmHg) gave the title stannane as a fluorescent green oil (1.23 g, 60%), $[\alpha]_D^{27}$ +24.4° (*c* 1.3, $CHCl_3$).

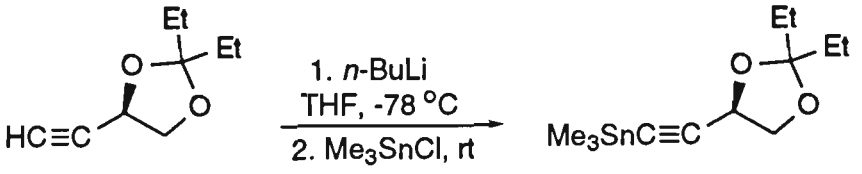
^{1}H NMR (400MHz, $CDCl_3$) δ 4.70 (1H, dd, *J* = 6.4, 7.6 Hz, H4); 4.16 (1H, dd, *J* = 6.4, 8.0 Hz, H_A5); 3.83 (1H, t, *J* = 8.0 Hz, H_B5); 1.74; 1.62 (2 x 2H, 2 x q, *J* = 7.6 Hz, 2 x $C\underline{H}_2CH_3$); 0.94; 0.89 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3); 0.289 (9H, s, ^2J (^{117}Sn, H) = 58.0 Hz, ^2J (^{119}Sn, H) = 60.4 Hz, $Sn(CH_3)_3$).

MS (EI+ve) *m/z* 289* (M-Et$^+$, 51%); 217* (31%); 165* ($SnMe_3^+$, 100%).

HRMS calcd for $C_{10}H_{17}O_2{}^{120}Sn$ 289.0250, found 289.0241.

* ^{120}Sn isotope peak.

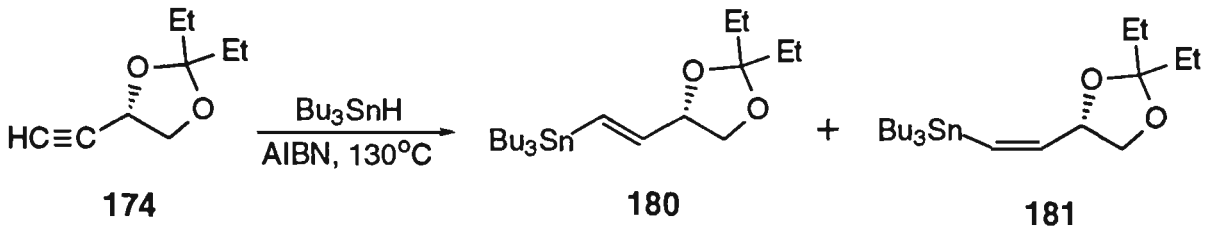
(4*R*)-2,2-Diethyl-4-(trimethylstannylethynyl)-1,3-dioxolane (179)



175 **179**

Using the procedure described above for the synthesis of **177**, the title compound was obtained as a bright green oil (59%) after bulb-to-bulb distillation, $[\alpha]_D^{26}$ -23.4° (*c* 0.97, $CHCl_3$). Spectral data were identical to that of **177**.

(4*S*)-(*E*)-2,2-Diethyl-4-(2'-tributylstannylethenyl)-1,3-dioxolane (180) and (4*S*)-(*Z*)-2,2-Diethyl-4-(2'-tributyl stannylethenyl)-1,3-dioxolane (181)



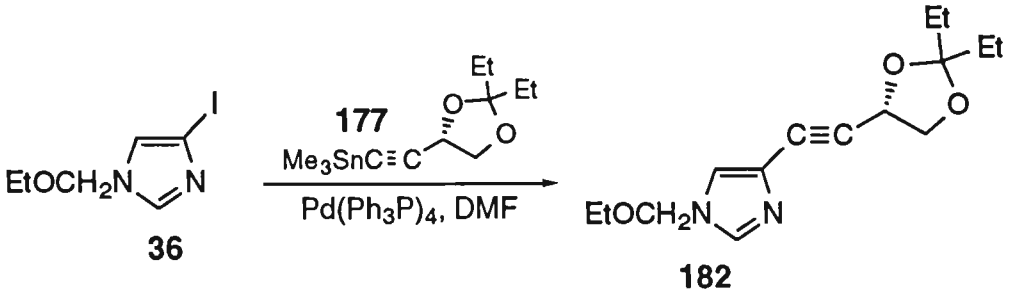
174 **180** **181**

A mixture of freshly distilled alkyne **174** (1.2 g, 7.79 mmol), Bu_3SnH (2.50 g, 8.57 mmol) and a catalytic amount of AIBN under argon was sealed in a thick walled reaction vessel and set to react at 130 °C for 2.5 h. The solution was then cooled to rt and the solution evaporated *in vacuo*. Purification by bulb-to-bulb distillation (125 °C/0.01 mmHg) gave a mixture of the title stannanes as a clear oil (2.94 g, 85%, **180**:**181** = 81:19).

180: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.31 (1H, dd, *J* = 0.8, 19.2 Hz, $Bu_3SnC\underline{H}$=CH); 5.94 (1H, dd, *J* = 6.4, 18.8 Hz, CH=C$\underline{H}$); 4.49-4.43 (1H, m, H4); 4.10 (1H, dd, *J* = 6.0, 8.0 Hz, H_A5); 3.56 (1H, t, *J* = 8.0 Hz, H_B5); 1.71-1.62 (4H, m, 2 x $C\underline{H}_2CH_3$); 1.52-1.25 (18H, m, 9 x CH_2); 0.98-0.87 (15H, m, 5 x CH_3).

181: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.44 (1H, dd, *J* = 8.4, 12.4 Hz, Bu_3SnCH=C$\underline{H}$); 6.19 (1H, d, *J* = 12.4 Hz, CH=C$\underline{H}$); 4.28-4.23 (1H, m, H4); 4.04 (1H, dd, *J* = 6.0, 7.6 Hz, H_A5); 3.58 (1H, t, *J* = 8.0 Hz, H_B5); 1.71-1.62 (4H, m, 2 x $C\underline{H}_2CH_3$); 1.52-1.25 (18H, m, 9 x CH_2); 0.98-0.87 (15H, m, 5 x CH_3).

(3'*S*)-4-[3',4'-O-(3'-Pentylidine)-3',4'-dihydroxybut-1'-ynyl]-1-ethoxymethylimidazole (182)



A solution of trimethylstannane **177** (0.80 g, 2.53 mmol), iodoimidazole **36** (0.76 g, 3.03 mmol) and $Pd(Ph_3P)_4$ (290 mg, 0.25 mmol) in anhydrous DMF (10 mL) in a thick walled reaction vessel was degassed with a stream of argon. The vessel was sealed and the solution was stirred at 80 °C for 24 h in the dark. The resulting dark solution was then cooled to rt, diluted with ethyl acetate (50 mL) and filtered. The filtrate was washed with a half sat. aqueous solution of NaCl (2 x 20 mL) then dried ($MgSO_4$) and concentrated to give a dark oil. Purification by column chromatography (50% ethyl acetate / hexane) gave the title compound as a tan oil (405 mg, 58%), $[\alpha]_D^{29}$ +18.0° (*c* 5.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 1.2 Hz, H2); 7.24 (1H, d, *J* = 1.6 Hz, H5); 5.26 (2H, s, EtOC$\underline{H}_2$); 4.92 (1H, t, *J* = 6.8 Hz, C≡CC$\underline{H}$); 4.22 (1H, dd, *J* = 6.4, 8.0 Hz, C≡CCH-C$\underline{H}_A$H$_B$); 3.97 (1H, t, *J* = 7.6 Hz, C≡CCH-CH$_A\underline{H}_B$); 3.44 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 1.76; 1.65 (2 x 2H, 2 x q, *J* = 7.6 Hz, 2 x $C\underline{H}_2CH_3$); 1.18 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2O$); 0.95; 0.91 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3).

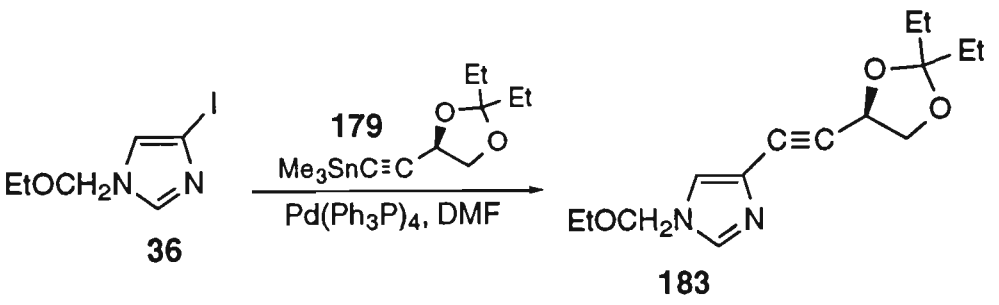
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.1 (C2); 124.2 (C4); 122.9 (C5); 114.1 ($\underline{C}Et_2$); 86.2 (Imid-$\underline{C}$≡C); 77.2 (Imid-C≡$\underline{C}$); 76.3 (EtO$\underline{C}H_2$); 70.1 (CH); 66.1 (CH_2); 64.4 ($CH_3\underline{C}H_2O$); 29.5; 29.2 (2 x $\underline{C}H_2CH_3$); 14.5 ($\underline{C}H_3CH_2O$); 8.0; 7.7 (2 x CH_3).

MS (ES+ve) *m/z* 279 ($M+H^+$, 100%); 193 ($M-C_5H_{10}O^+$, 14%); 59 ($EtOCH_2^+$, 8%); 42 ($C_3H_6^+$, 63%).

IR (neat) 2973; 2937; 2881; 2238 (C≡C); 1493; 1355; 1107; 1078; 913; 752 cm^{-1}.

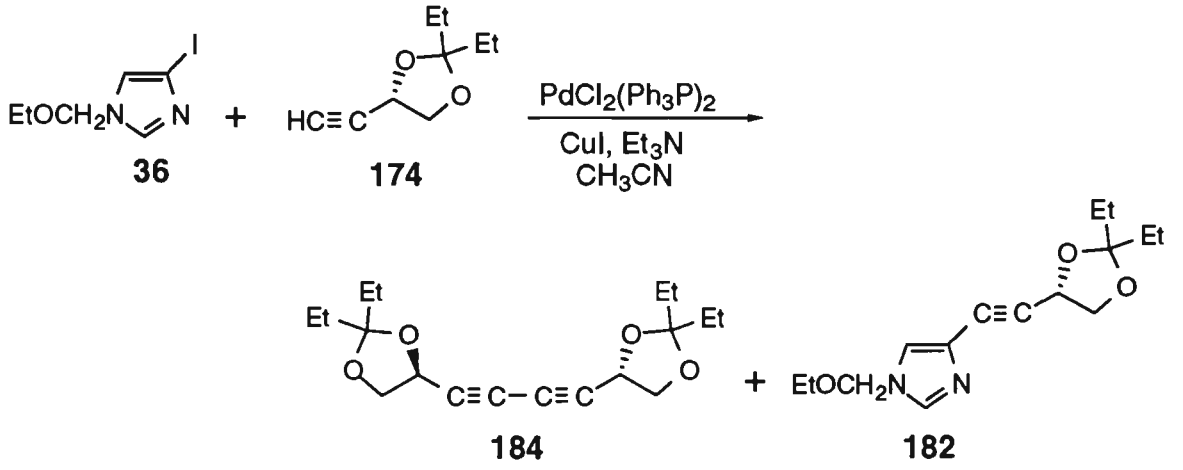
HRMS calcd for $C_{15}H_{22}N_2O_3$ 278.1630, found 278.1626.

(3'*R*)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-ynyl]-1-ethoxymethylimidazole (183)



Using the procedure described above for the synthesis of imidazole **182**, the title compound was obtained as a tan oil (53%) after purification by column chromatography (40% ethyl acetate / hexane), $[\alpha]_D^{23}$ -25.9° (*c* 1.03, $CHCl_3$). Spectral data were identical to that of **182**.

Synthesis of imidazole 182 and (2*S*,7*S*)-1,2,7,8-O-di-(3-pentylidene)-1,2,7,8-tetrahydroxy-3,5-octadiyne (184) *via* palladium(0) / alkyne coupling.



A solution of alkyne **174** (1.83 g, 11.88 mmol), iodoimidazole **36** (3.59 g, 14.26 mmol), CuI (230 mg, 1.21 mmol), $PdCl_2(Ph_3P)_2$ (420 mg, 0.60 mmol) and triethylamine (12.0 g, 0.119 mmol) in anhydrous CH_3CN (20 mL) was degassed using a stream of argon and the solution was heated to reflux for 4 h under N_2. The mixture was then cooled to rt, poured into H_2O (100 mL) and extracted with CH_2Cl_2 (4 x 80 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed to leave a thick black oil. Purification by column chromatography (50% ethyl acetate / hexane) gave the target imidazole **182** (0.76 g, 23%), plus the dialkyne **184** (1.26 g, 69%).

184: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (2H, t, *J* = 6.0 Hz, H2,7); 4.17 (2H, dd, *J* = 6.4, 8.0 Hz, H_A1, H_A8); 3.92 (2H, dd, *J* = 6.4, 8.0 Hz, H_B1, H_B8); 1.73; 1.63 (2 x 4H, 2 x q, *J* = 7.6 Hz, 4 x $C\underline{H}_2CH_3$); 0.94; 0.88 (2 x 6H, 2 x t, *J* = 7.6 Hz, 4 x CH_3).

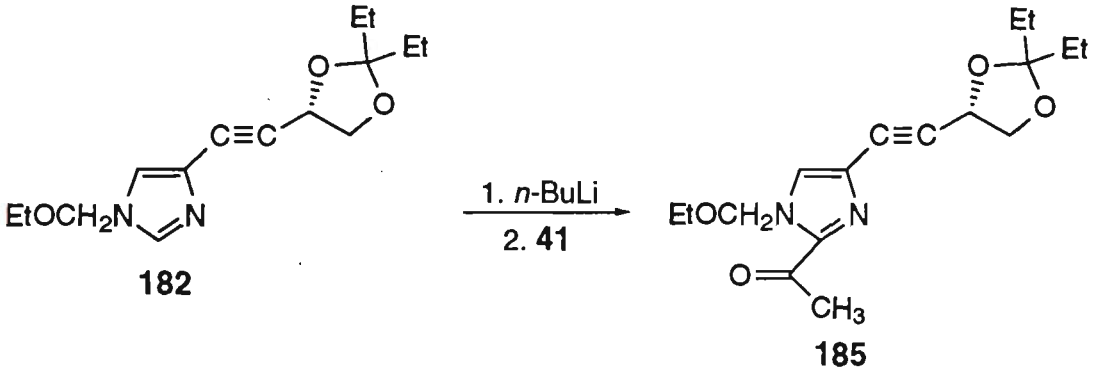
^{13}C NMR (22.5 MHz, $CDCl_3$) δ 114.8 (2 x $\underline{C}Et_2$); 77.2 (C4,5); 69.9 (C2,7); 69.5 (C3,6); 65.9 (C1,8); 29.5; 29.2 (4 x $\underline{C}H_2CH_3$); 8.1; 7.8 (4 x CH_3).

MS (EI+ve) *m/z* 277 ($M-Et^+$, 44%); 217 (10%); 191 (15%); 135 (23%); 87 (31%); 57 (100%).

IR (neat) 2972; 2938; 2881; 2150 (C≡C); 1463; 1336; 1171; 1082; 910; 762 cm^{-1}.

HRMS calcd for $C_{16}H_{21}O_4$ 277.1440, found 277.1446.

(3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-ynyl]-1-ethoxymethylimidazole (185)



To a solution of alkyne **182** (550 mg, 1.98 mmol) in anhydrous THF (5 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (2.37 mmol) and the solution was stirred for 90 min at -78 °C. Freshly distilled amide **41** (0.29 g, 2.77 mmol) in THF (5 mL) was then added dropwise and the reaction mixture stirred for 1 h at -78 °C and then was slowly warmed to rt and stirred for a further 1 h. The mixture was diluted with CH_2Cl_2 (15 mL), washed with a 5% aqueous solution of $NaHCO_3$ (5 mL), dried ($MgSO_4$) and the solvent was removed to leave a black oil. Purification by column chromatography (40% ethyl acetate / hexane) gave the title

compound as a tan oil (310, 67% corrected for recovered starting alkyne), $[\alpha]_D^{29}$ +23.3° (*c* 2.40, $CHCl_3$), plus the starting alkyne **182** (150 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, s, H5); 5.75 (2H, s, EtOC$\underline{H}_2$); 4.93 (1H, t, *J* = 7.2 Hz, C≡CC$\underline{H}$); 4.24 (1H, t, *J* = 7.2 Hz, C≡CCHC$\underline{H}_A$H$_B$); 4.00 (1H, t, *J* = 7.2 Hz, C≡CCHCH$_A\underline{H}_B$); 3.54 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.67 (3H, s, $COCH_3$); 1.77; 1.66 (2 x 2H, 2 x q, *J* = 7.2 Hz, 2 x $C\underline{H}_2CH_3$); 1.20 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.96; 0.92 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH_3).

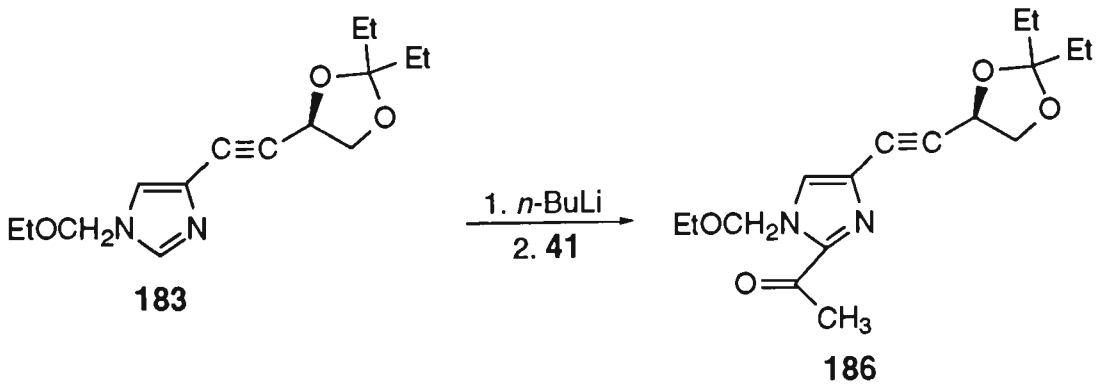
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C=O); 142.3 (C2); 128.1 (C5); 123.8 (C4); 114.4 ($\underline{C}Et_2$); 86.9 (Imid-$\underline{C}$≡C); 78.4 (Imid-C≡$\underline{C}$); 77.6 (EtO$\underline{C}H_2$); 70.1 (CH); 66.2 (CH_2); 65.3 ($CH_3\underline{C}H_2O$); 29.6; 29.3 (2 x $\underline{C}H_2CH_3$); 27.5 ($CO\underline{C}H_3$); 14.8 ($\underline{C}H_3CH_2O$); 8.2; 7.9 (2 x CH_3).

MS (ES+ve) *m/z* 321 ($M+H^+$, 100%).

IR (neat) 2973; 2937; 2881; 2201 (C≡C); 1685 (C=O); 1457; 1352; 1170; 1108; 1079; 913; 764 cm^{-1}.

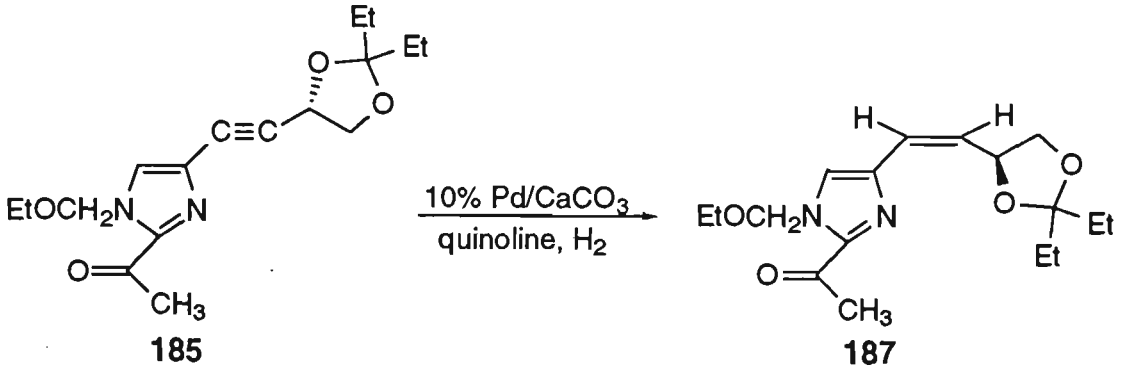
HRMS calcd for $C_{17}H_{24}N_2O_4$ 320.1736, found 320.1749.

(3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-ynyl]-1-ethoxymethylimidazole (186)



Using the procedure described above for the synthesis of the methyl ketone **185**, the title compound was obtained pure as a tan oil (69%), with the starting alkyne (11%) also isolated after column chromatography (20% ethyl acetate / hexane), $[\alpha]_D^{23}$ -32.4° (*c* 1.0, $CHCl_3$). Spectral data were identical to that of **185**.

(3'*S*)-(*Z*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (187)



+ (*E*)-alkene + alkane

To a solution of alkyne **185** (740 mg, 2.31 mmol) and quinoline (300 mg, 2.31 mmol) in hexane (10 mL) was added 10% Pd on $CaCO_3$ (70 mg). The mixture was stirred for 2 h under a H_2 atmosphere until the hydrogenation was complete by ^1H NMR analysis. The mixture was vacuum filtered through a bed of celite and the plug washed thoroughly with ethyl acetate. The filtrate was then concentrated *in vacuo* to give a tan oil which was purified by column chromatography (15% ethyl acetate / hexane) to give the title (Z)-alkene as a tan oil (595 mg, 80%), $[\alpha]_D^{21}$ +18.7° (*c* 0.87, $CHCl_3$). A small amount of the (*E*)-alkene (35 mg, 5%) and over-reduced alkane (30 mg, 4%) were also separately isolated from the column, both as tan oils.

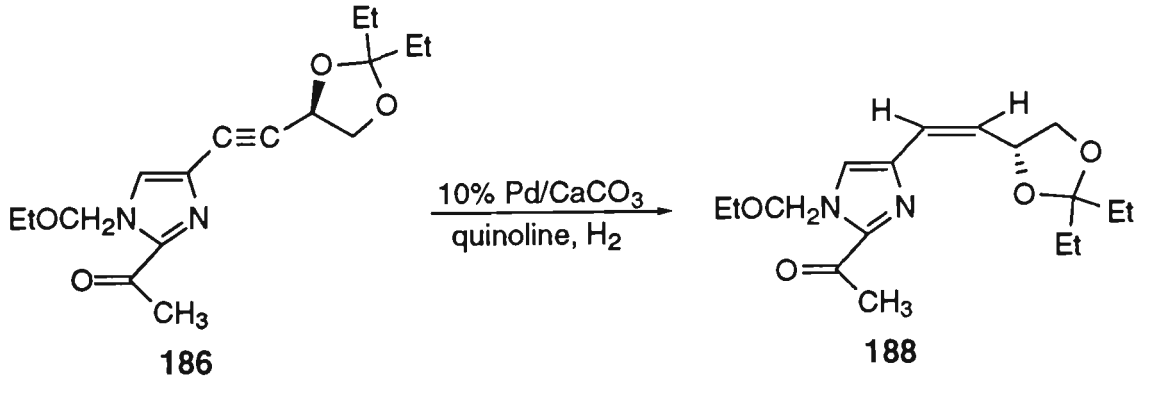
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, s, H5); 6.39 (1H, dd, *J* = 1.2, 7.6 Hz, Imid-C<u>H</u>=CH); 5.79-5.73 (3H, m, Imid-CH=C<u>H</u>, EtOC<u>H</u>$_2$); 5.69-5.64 (1H, m, CH=CHC<u>H</u>); 4.43 (1H, dd, *J* = 6.4, 8.0 Hz, C<u>H</u>$_A$H$_B$O); 3.63 (1H, t, *J* = 8.0 Hz, CH$_A$<u>H</u>$_B$O); 3.54 (2H, q, *J* = 7.2 Hz, CH$_3$C<u>H</u>$_2$O); 2.66 (3H, s, COCH$_3$); 1.72; 1.71 (2 x 2H, 2 x q, *J* = 7.2 Hz, 2 x C<u>H</u>$_2$CH$_3$); 1.20 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$CH$_2$O); 0.97; 0.96 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH$_3$).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 190.8 (C=O); 142.4 (C2); 130.4 (Imid-<u>C</u>H=CH); 139.0 (C4); 124.0 (Imid-CH=<u>C</u>H); 122.1 (C5); 113.1 (<u>C</u>Et$_2$); 77.1 (EtO<u>C</u>H$_2$); 73.9 (CH); 70.2 (CH$_2$); 65.0 (CH$_3$<u>C</u>H$_2$O); 30.04; 29.85 (2 x <u>C</u>H$_2$CH$_3$); 27.2 (CO<u>C</u>H$_3$); 14.8 (<u>C</u>H$_3$CH$_2$O); 8.11; 7.92 (2 x CH$_3$).

MS (ES+ve) *m/z* 323 (M+H$^+$, 100%); 237 (56%).

HRMS calcd for $C_{17}H_{26}N_2O_4$ 322.1892, found 322.1901.

(3'*R*)-(*Z*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (188)



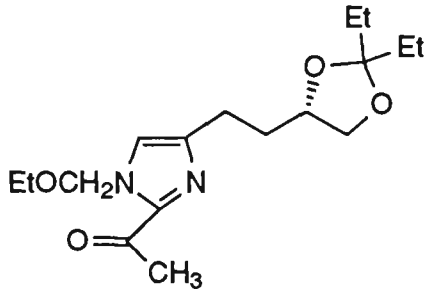
186 **188**

+ (*E*)-alkene + alkane

Using the procedure described above for the synthesis of **187**, the title compound was obtained pure as a tan oil (79%), with the (*E*)-alkene (6%) and over-reduced alkane (7%) also isolated after purification by column chromatography (15% ethyl acetate /

hexane), $[\alpha]_D^{27}$ -16.5° (*c* 0.62, $CHCl_3$). Spectral data were identical to that of **187**.

(3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxy -1'-butyl]-1-ethoxymethylimidazole



The title alkane was isolated during the synthesis of **187** above, $[\alpha]_D^{23}$ +2.9° (*c* 0.43, $CHCl_3$).

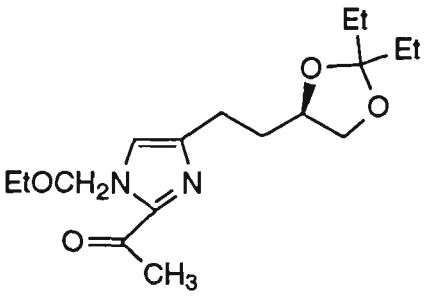
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, s, H5); 5.74 (2H, s, $EtOC\underline{H}_2$); 4.18-4.09 (1H, m, $CH_2C\underline{H}$-O); 4.06 (1H, dd, *J* = 6.0, 7.5 Hz, $C\underline{H}_AH_BO$); 3.57-3.49 (3H, m, $CH_3C\underline{H}_2O$, $CH_A\underline{H}_BO$); 2.82-2.61 (2H, m, Imid-$C\underline{H}_2$); 2.64 (3H, s, $COCH_3$); 2.03-1.88 (2H, m, Imid-$CH_2C\underline{H}_2$); 1.66; 1.62 (2 x 2H, 2 x q, *J* = 7.5 Hz, 2 x $C\underline{H}_2CH_3$); 1.19 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.92; 0.90 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH_3).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 190.7 (C=O); 142.8 (C2); 142.1 (C4); 121.5 (C5); 112.6 ($\underline{C}Et_2$); 76.9 ($EtO\underline{C}H_2$); 75.6 ($CH_2\underline{C}H$-O); 69.9 (CH_2O); 64.8 ($CH_3\underline{C}H_2O$); 32.9 (CH_2); 29.9; 29.7 (2 x $\underline{C}H_2CH_3$); 27.4($CO\underline{C}H_3$); 24.6 (CH_2); 14.8 ($\underline{C}H_3CH_2O$); 8.2; 7.9 (2 x CH_3).

MS (EI+ve) *m/z* 325 ($M+H^+$, 7%); 295 ($M-Et^+$, 72%); 253 (30%); 237 (34%); 207 (52%); 181 (58%); 163 (80%).

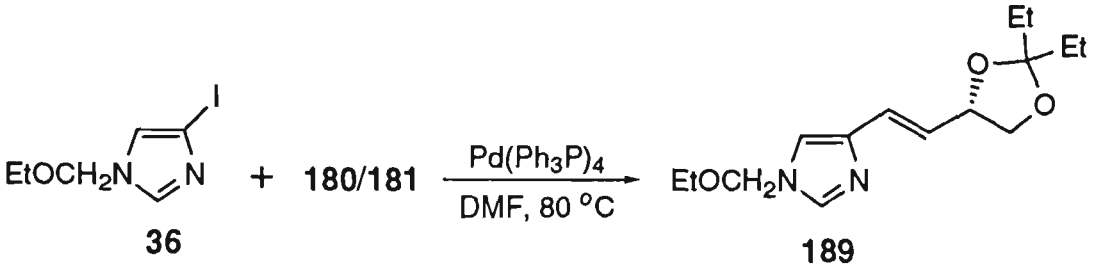
HRMS calcd for $C_{17}H_{28}O_4N_2$ 324.2049, found 324.2041.

(3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxy -1'-butyl]-1-ethoxymethylimidazole



The title alkane was isolated during the synthesis of **188** above, $[\alpha]_D^{27}$ -2.4° (*c* 0.70, $CHCl_3$). Spectral data were identical to that of the (3'*S*) enantiomer.

(3'*S*)-(*E*)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (189)



Run	*Solvent*[a]	*Catalyst*	*Yield (189)*
1	DMF	$Pd(Ph_3P)_4$	26%
2	THF	$Pd(Ph_3P)_4$	28%
3	Acetonitrile	$Pd(Ph_3P)_4$	31%
4	DMF	$Pd_2(dba)_3$, $AsPh_3$, CuI	45%

[a]All reactions carried out in sealed reaction vessels at 80 °C under argon.

A representative procedure: A solution of iodoimidazole **36** (560 mg, 2.22 mmol), stannanes **180/181** (900 mg, 2.02 mmol, **180**:**181** = 81:19) and $Pd(PPh_3)_4$ (230 mg, 2.0 x 10^{-4} mol) in anhydrous DMF (10 mL) in a thick walled tube was flushed with argon, sealed and stirred at 80 °C for 24 h. The reaction was then cooled to rt, diluted with CH_2Cl_2 (60 mL), washed with H_2O (30 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (45% ethyl acetate / hexane) gave the title compound as a tan oil (120 mg, 26%), $[\alpha]_D^{25}$ +18.8° (*c* 3.0, MeOH).

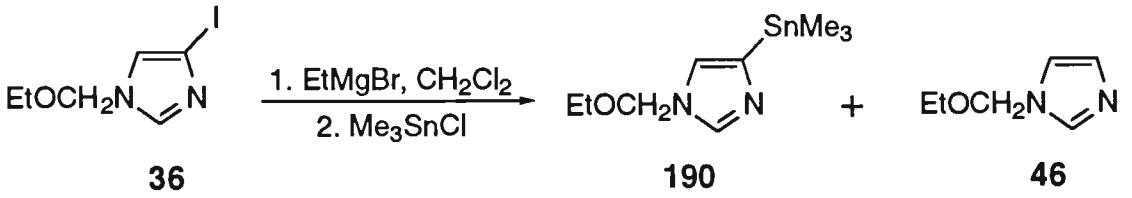
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 1.2 Hz, H2); 6.95 (1H, d, *J* = 1.6 Hz, H5); 6.58 (1H, d, *J* = 15.6 Hz, Imid-C<u>H</u>=CH); 6.31 (1H, dd, *J* = 8.0, 16.0 Hz, CH=C<u>H</u>); 5.24 (2H, s, EtOC<u>H</u>$_2$); 4.67-4.61 (1H, m, CH=CHC<u>H</u>); 4.14 (1H, dd, *J* = 6.0, 8.0 Hz, C<u>H</u>$_A$H$_B$O); 3.65 (1H, t, *J* = 8.0 Hz, CH$_A$<u>H</u>$_B$O); 3.44 (2H, q, *J* = 7.2 Hz, CH$_3$C<u>H</u>$_2$O); 1.73-1.65 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 1.18 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$CH$_2$O); 0.944; 0.935 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 140.0 (Imid-CH=<u>C</u>H); 137.3 (C2); 125.2 (C4); 124.4 (C5); 116.6 (Imid-<u>C</u>H=CH); 112.9 (<u>C</u>Et$_2$); 77.3 (CH=CH<u>C</u>H); 76.0 (EtO<u>C</u>H$_2$); 69.8 (CH$_2$); 64.1 (CH$_3$<u>C</u>H$_2$O); 29.8; 29.6 (2 x <u>C</u>H$_2$CH$_3$); 14.4 (<u>C</u>H$_3$CH$_2$O); 7.9; 7.8 (2 x CH$_3$).

MS (ES+ve) *m/z* 281 ($M+H^+$, 100%).

HRMS calcd for $C_{15}H_{24}O_3N_2$ 280.1787, found 280.1793.

1-Ethoxymethyl-4-(trimethylstannyl)-imidazole (190) and 1-ethoxymethylimidazole (46)



36 **190** **46**

To a solution of iodoimidazole **36** (1.5 g, 5.95 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2 was added EtMgBr in ether (6.55 mmol) and the mixture was stirred for 30 min at rt. The solution was then cooled to 0 °C, trimethyltin chloride (1.43 g, 7.14 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise and the mixture was then warmed to rt and stirred for 2 h. The mixture was then diluted with CH_2Cl_2 (20 mL), washed with a half sat. aqueous solution of NaCl (2 x 10 mL), dried ($MgSO_4$) and the solvent was removed to leave a yellow oil. Purification by bulb-to-bulb distillation (70 °C/0.2 mmHg) gave the title stannane **190** (1.13 g, 66%), plus deiodinated **46** (120 mg, 16%) as clear oils.

46: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, s, H2); 7.10 (1H, s, H4); 7.06 (1H, t, *J* = 1.2 Hz, H5); 5.29 (2H, s, CH_2); 3.45 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2$); 1.19 (3H, t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.3 (C2); 129.9 (C4); 118.7 (C5); 76.1 (CH_2); 64.2 ($CH_3\underline{C}H_2$); 14.6 (CH_3).

MS (ES+ve) *m/z* 127 ($M+H^+$, 100%).

IR (nujol) 3108; 2980; 1221; 1111 (COC) cm^{-1}.

190: ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 0.9 Hz, H2); 7.07 (1H, d, J = 1.2 Hz, H5); 5.29 (2H, s, CH_2); 3.46 (2H, q, *J* = 7.8 Hz, $CH_3C\underline{H}_2$); 1.19 (3H, t, *J* = 6.9 Hz, CH_3); 0.302 (9H, s, ^{2}J (^{117}Sn, H) = 54.6 Hz, ^{2}J (^{119}Sn, H) = 57 Hz, $Sn(CH_3)_3$).

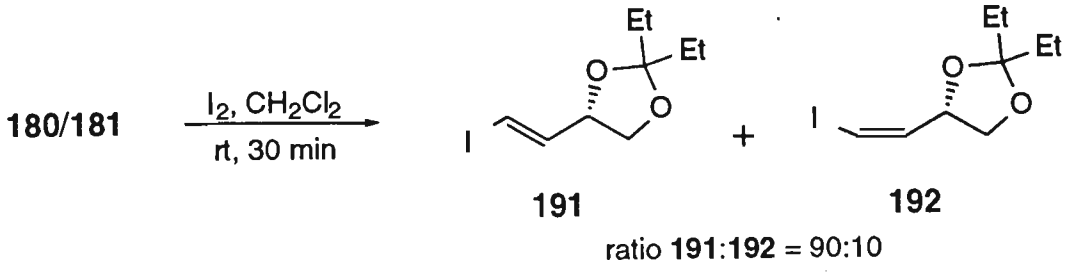
^{13}**C NMR** (75.6 MHz, $CDCl_3$) δ 141.5 (C2); 139.6 (C4, *J* (Sn, C) = 59.5 Hz); 126.5 (C5, *J* (Sn, C) = 109.6 Hz); 75.6 (CH_2); 64.2 ($CH_3\underline{C}H_2$); 14.6 (CH_3); -9.6 ($Sn(CH_3)_3$, *J* (^{117}Sn, C) = 349.9 Hz, *J* (^{119}Sn, C) = 366.0 Hz).

MS (ES+ve) *m/z* 291* ($M+H^+$, 100%).

HRMS calcd for $C_9H_{18}N_2O^{120}Sn$ 290.0440, found 290.0438.

* ^{120}Sn isotope peak.

(4*S*)-(*E*)-2,2-Diethyl-4-(2'-iodoethenyl)-1,3-dioxolane (191) and (4*S*)-(*Z*)-2,2-diethyl-4-(2'-iodoethenyl)-1,3-dioxolane (192)



191 **192**

ratio **191**:**192** = 90:10

To a solution of the trimethylvinyl stannanes **180/181** (2.67 g, 6.10 mmol, **180**:**181** = 81:19) in anhydrous CH_2Cl_2 (10 mL) under N_2 was added iodine (1.47 g, 5.79 mmol) in CH_2Cl_2 dropwise and the mixture stirred for 30 min. The solution was then washed with a sat. aqueous solution of $Na_2S_2O_3$ (10 mL) and the organic extract was concentrated. The residual oil was taken into ether (10 mL) and stirred vigorously with a sat. aqueous solution of KF (10 mL) for 1 h. Precipitated Bu_3SnF was removed by filtration, the layers were separated and the organic extract dried ($MgSO_4$) and

concentrated. Purification by bulb-to-bulb distillation (110 °C/10 mmHg) gave the title vinyliodides as a pale oil (0.9 g, 52%, ratio **191:192** = 90:10).

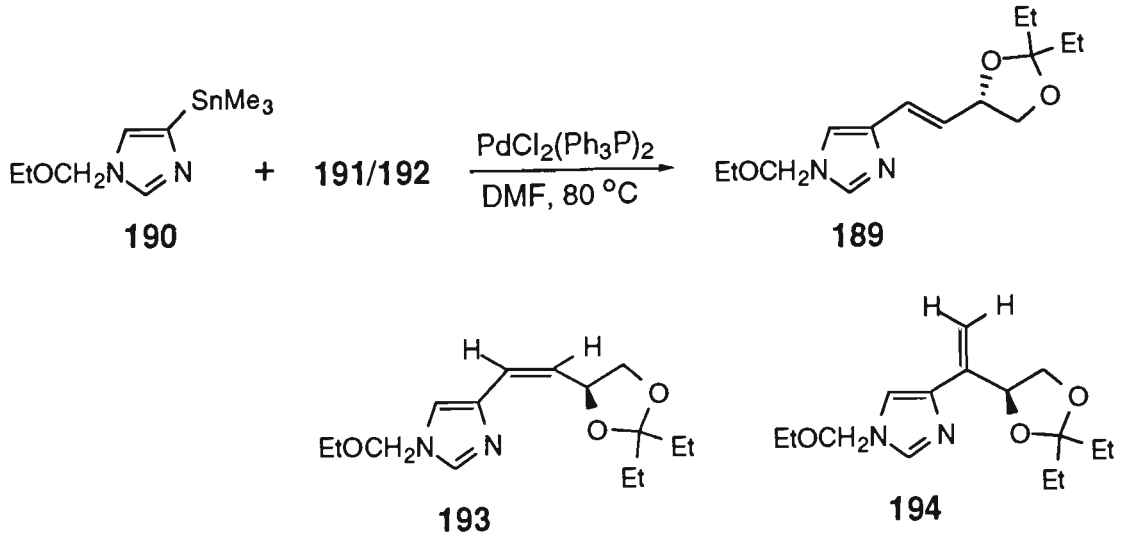
191: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59-6.52 (2H, m, C<u>H</u>=C<u>H</u>); 4.51-4.44 (1H, m, H4); 4.11 (1H, dd, *J* = 6.3, 8.1 Hz, H_A5); 3.60 (1H, t, *J* = 7.8 Hz, H_B5); 1.71-1.60 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 0.96-0.88 (6H, m, 2 x CH_3).

MS (ES+ve) *m/z* 253 ($M-Et^+$, 100%); 179 (16%).

HRMS calcd for $C_7H_{10}O_2I$ ($M-Et^+$) 252.9726, found 252.9727.

192: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48-6.36 (2H, m, C<u>H</u>=C<u>H</u>); 4.82-4.74 (1H, m, H4); 4.25 (1H, dd, *J* = 6.3, 7.8 Hz, H_A5); 4.20 (1H, dd, *J* = 6.6, 8.4 Hz, H_B5); 1.71-1.60 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 0.96-0.88 (6H, m, 2 x CH_3).

(3'*S*)-(*Z*)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (193) and (3'*S*)-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxy-but-2'-enyl]-1-ethoxy methylimidazole (194)

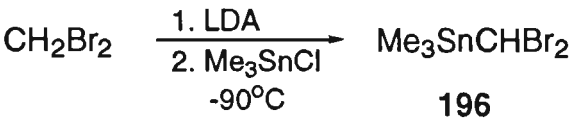


A solution of imidazole **190** (180 mg, 0.62 mmol), vinyliodides **191/192** (207 mg, 0.73 mmol, **191**:**192** = 90:10) and $PdCl_2(PPh_3)_2$ (26 mg, 3.1 x 10^{-5} mol) in anhydrous DMF (2 mL) in a thick walled tube was flushed with argon, sealed and stirred at 80 °C for 8 h. The reaction was then cooled to rt, diluted with CH_2Cl_2 (10 mL), washed with a half sat. aqueous solution of NaCl (2 x 5 mL), dried ($MgSO_4$) and concentrated to leave a yellow oil. Purification by column chromatography (40% ethyl acetate / hexane) gave the desired coupled imidazole **189** (90 mg, 60%), plus **193** (20 mg, 13%) and **194** (10 mg, 7%) as tan oils.

193: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 1.2 Hz, H2); 7.05 (1H, d, *J* = 1.2 Hz, H5); 6.41 (1H, d, *J* = 11.6 Hz, Imid-C<u>H</u>=CH); 5.64 (1H, dd, *J* = 8.0, 11.6 Hz, CH=C<u>H</u>); 5.62-5.52 (1H, m, CH=CHC<u>H</u>); 5.26 (2H, s, EtOC<u>H</u>$_2$); 4.35 (1H, dd, *J* = 6.0, 8.0 Hz, C<u>H</u>$_A$H$_B$O); 3.60 (1H, t, *J* = 8.0 Hz, CH$_A$<u>H</u>$_B$O); 3.45 (2H, q, *J* = 10.8 Hz, $CH_3C\underline{H}_2O$); 1.74-1.67 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 1.19 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$CH$_2$O); 0.953; 0.951 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH_3).

194: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 1.6 Hz, H2); 7.11 (1H, d, *J* = 1.6 Hz, H5); 5.73 (1H, t, *J* = 1.6 Hz, C=C<u>H</u>$_A$H$_B$); 5.45 (1H, t, *J* = 1.6 Hz, C=CH$_A$<u>H</u>$_B$); 5.26 (2H, s, EtOC<u>H</u>$_2$); 5.02-4.98 (1H, m, CH); 4.38 (1H, dd, *J* = 6.4, 8.0 Hz, C<u>H</u>$_A$H$_B$O); 3.66 (1H, dd, *J* = 8.0, 8.4 Hz, CH$_A$<u>H</u>$_B$O); 3.48 (2H, q, *J* = 6.8 Hz, $CH_3C\underline{H}_2O$); 1.80-1.71 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 1.20 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$CH$_2$O); 0.98; 0.97 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH_3).

Dibromomethyltrimethylstannane (196)

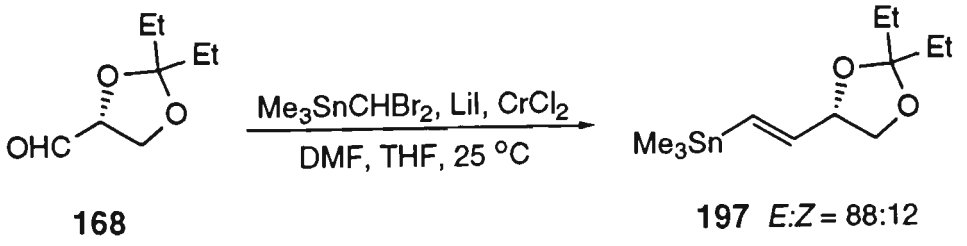


To a solution of LDA (6.32 mmol) in anhydrous THF / ether (1:1, 6 mL) at -90 °C under N_2 was added dropwise a solution of CH_2Br_2 (1.15 g, 6.64 mmol) in THF / ether (1:1, 6 mL). The resulting dark solution was stirred at -90 °C for 15 min. and then trimethyltin chloride (6.32 mmol) in THF / ether (1:1, 12 mL) was slowly added. The resulting light tan solution was warmed to -55 °C, stirred at that temperature for 3 h and then quenched with a 10% aqueous solution of HCl (15 mL). The layers were separated and the aqueous phase was extracted with ether (15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a tan oil. Purification by bulb-to-bulb distillation (64 °C/0.01 mmHg) gave the title stannane as a clear oil (1.55 g, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (1H, s, *J* (Sn,H) = 12.6 Hz, $CHBr_2$); 0.35 (9H, s, ^2J (^{117}Sn,H) = 53.7 Hz, ^2J (^{119}Sn,H) = 56.4 Hz, $Sn(CH_3)_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 28.2 ($CHBr_2$), -8.3 ($Sn(CH_3)_3$).

(4*S*)-(*E*)-2,2-Diethyl-4-(trimethylstannylethenyl)-1,3-dioxolane (197)



168 197 *E*:*Z* = 88:12

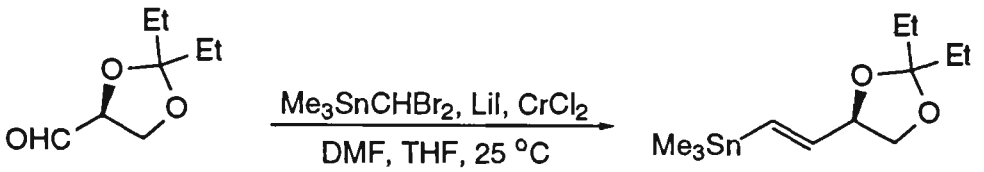
A general procedure: To a stirred slurry of chromium(II) chloride (1.46 g, 11.8 mmol) in anhydrous THF (16 mL) under N_2 was added anhydrous DMF (0.70 g, 11.8 mmol) and the reaction was stirred for 15 min at rt. Alkyne **168** (190 mg, 1.18 mmol) and dibromomethyltrimethylstannane **196** (700 mg, 2.07 mmol) in anhydrous THF (4 mL) were then added and the reaction vessel was wrapped in aluminium foil to exclude light. Lithium iodide (0.63 g, 4.72 mmol) in anhydrous THF (4 mL) was added and the reaction left to stir for 16 h. The mixture was then poured into H_2O (30 mL) and extracted with 40-60 petroleum ether (3 x 30 mL). The combined extracts were washed with H_2O (20 mL) and sat. aqueous NaCl (20 mL) and then dried ($MgSO_4$) and concentrated to leave a light yellow oil. Purification by bulb-to-bulb distillation (78 °C/0.01 mmHg) gave the vinylstannane as a clear oil (300 mg, 80%, ratio *E*:*Z* = 88:12).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (1H, dd, *J* = 0.8, 18.8 Hz, ^2J (^{117}Sn, H) = 76 Hz, ^2J (^{119}Sn, H) = 78 Hz, $Me_3SnC\underline{H}$=CH); 5.95 (1H, dd, *J* = 7.2, 18.8 Hz, ^2J (^{117}Sn, H) = 66.4 Hz, ^2J (^{119}Sn, H) = 70.4 Hz, CH=C$\underline{H}$); 4.49-4.43 (1H, m, CH=CHC$\underline{H}$); 4.10 (1H, dd, *J* = 6.4, 8.0 Hz, C$\underline{H}_A$H$_B$); 3.57 (1H, t, *J* = 8.0 Hz, CH$_A$$\underline{H}_B$); 1.71-1.59 (4H, m, 2 x C$\underline{H}_2$CH$_3$); 1.00-0.88 (6H, m, 2 x CH$_3$); 0.14 (9H, s, ^2J (^{117}Sn, H) = 53.6 Hz, ^2J (^{119}Sn, H) = 56.0 Hz, Sn(CH$_3$)$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 144.5 ($\underline{C}$H=CH); 134.2 (CH=$\underline{C}$H); 113.2 ($\underline{C}$Et$_2$); 80.2 (CH=CH$\underline{C}$H); 67.7 (CH$_2$); 29.96; 29.76 (2 x $\underline{C}$H$_2$CH$_3$); 8.12; 8.05 (2 x CH$_3$); -9.8 (Sn(CH$_3$)$_3$).

HRMS calcd for $C_{12}H_{25}O_2{}^{120}Sn$ 321.0876, found 321.0871.

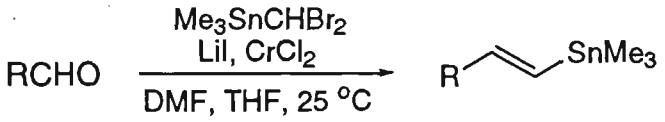
(4*R*)-(*E*)-2,2-Diethyl-4-(trimethylstannylethenyl)-1,3-dioxolane (198)



169 **198** *E:Z* = 94:6

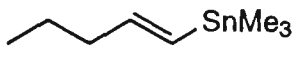
Using the general procedure described above for the synthesis of **197**, the title compound was obtained as a pale oil (85%, *E:Z* = 94:6) after bulb-to-bulb distillation (51 °C/0.1 mmHg). Spectral data were identical to that of **197**.

Synthesis of trimethylvinylstannanes from representative aliphatic aldehydes



Using the general procedure described above for the synthesis of **197**, the following trimethylvinylstannanes were isolated pure after bulb-to-bulb distillation.

1. R = Pr: (1-Pentenyl)trimethylstannane



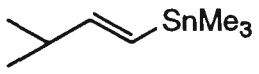
Yield = 77%, *E:Z* = 69:31, bp = 92 °C/20 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, dt, *J* = 5.2, 18.8 Hz, SnCH=C<u>H</u>); 5.92 (1H, d, *J* = 18.8 Hz, SnC<u>H</u>=CH); 2.11 (2H, dt, *J* = 4.8, 7.5 Hz,

CH=CHC<u>H</u>$_2$); 1.47-1.37 (2H, m, C<u>H</u>$_2$CH$_3$); 0.90 (3H, t, J = 7.6 Hz, CH$_3$); 0.10 (9H, s, ^2J (^{117}Sn,H) = 52.8 Hz, ^2J (^{119}Sn,H) = 55.2 Hz, Sn(CH$_3$)$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 149.2 (<u>C</u>H=CH); 128.1 (CH=<u>C</u>H); 39.7 (CH_2); 21.9 (CH_2); 13.7 (CH_3); -9.7 (Sn(CH_3)$_3$).

2. R = ^{i}Pr: (3-Methyl-1-butenyl)trimethylstannane

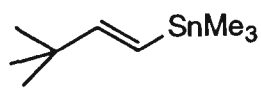


Yield = 82%, *E:Z* = 73:27, bp = 100 °C/20 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (1H, dd, J = 5.2, 19.2 Hz, SnCH=C<u>H</u>); 5.88 (1H, dd, J = 0.8, 18.8 Hz, SnC<u>H</u>=CH); 2.34-2.25 (1H, m, CH), 0.99 (6H, d, J = 6.4 Hz, CH(C<u>H</u>$_3$)$_2$); 0.10 (9H, s, ^2J (^{117}Sn,H) = 52.8 Hz, ^2J (^{119}Sn,H) = 54.8 Hz, Sn(CH_3)$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 156.0 (<u>C</u>H=CH); 124.0 (CH=<u>C</u>H); 35.0 (CH); 21.9 (CH(<u>C</u>H$_3$)$_2$); -9.7 (Sn(CH_3)$_3$).

3. R = ^{t}Bu: (2,2-Dimethyl-1-butenyl)trimethylstannane

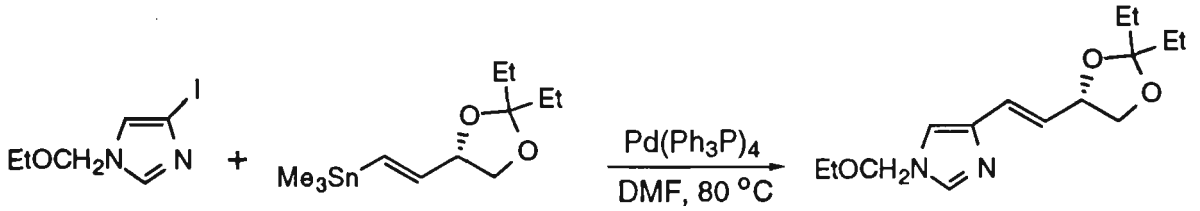


Yield = 60%, *E:Z* = 84:16, bp = 111 °C/20 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (1H, d, J = 18.8 Hz, ^2J (^{117}Sn,H) = 48.8 Hz, ^2J (^{119}Sn,H) = 52.4 Hz, SnC<u>H</u>=CH); 5.84 (1H, d, J = 19.2 Hz, ^3J (^{117}Sn,H) = 57.2 Hz, ^3J (^{119}Sn,H) = 60.8 Hz, SnCH=C<u>H</u>); 1.00 (9H, s, C(CH_3)$_3$); 0.07 (9H, s, ^2J (^{117}Sn,H) = 50.8 Hz, ^2J (^{119}Sn,H) = 53.2 Hz, Sn(CH_3)$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 159.5 (<u>C</u>H=CH); 120.9 (CH=<u>C</u>H); 29.2 (C(<u>C</u>H$_3$)$_3$); 28.7 (<u>C</u>(CH$_3$)$_3$); -9.7 (Sn(CH_3)$_3$).

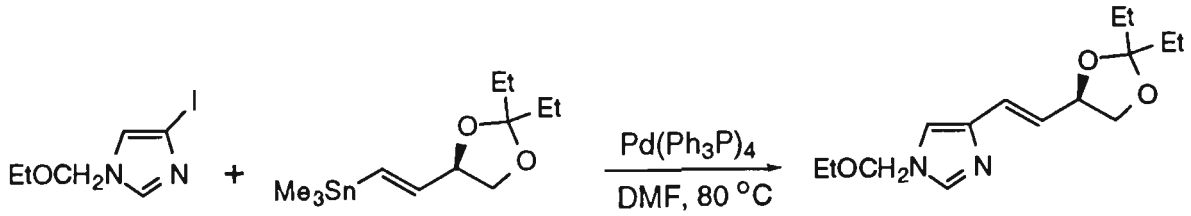
Synthesis of 189 *via* the trimethylvinylstannane 197



36 **197** **189**

A solution of trimethylvinylstannane **197** (100 mg, 0.314 mmol), iodoimidazole **36** (87 mg, 3.45 x 10^{-4} mol) and $Pd(Ph_3P)_4$ (20 mg, 1.73 x 10^{-5} mol) in anhydrous DMF (2.5 mL) in a thick walled reaction vessel was flushed with argon and then sealed and left to stir at 80 °C in the dark for 24 h. The solution was then cooled to rt and diluted with CH_2Cl_2 (10 mL) and washed with half sat. aqueous solution of NaCl (2 x 5 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (40% ethyl acetate / hexane) gave the title alkene as a tan oil (64 mg, 83%).

(3'*R*)-(*E*)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (201)

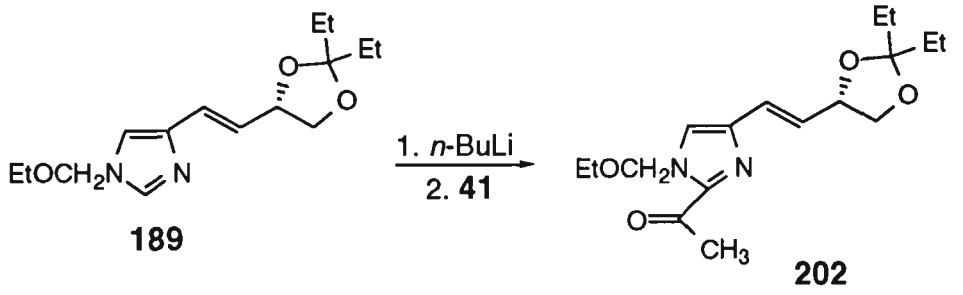


36 **198** **201**

Using the procedure described above for the synthesis of **189**, the title compound was obtained as a dark tan oil (46%) after purification by column chromatography (35% ethyl acetate /

hexane), $[\alpha]_D^{25}$ -18.3° (*c* 0.82, MeOH). Spectral data were identical to that of **189**.

(3'*S*)-(*E*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (202)



To a solution of the alkene **189** (345 mg, 1.23 mmol) in anhydrous THF (5 mL) at -78 °C under N_2 was added *n*-BuLi in hexanes (1.48 mmol) and the solution left to stir for 1 h at -78 °C. Freshly distilled amide **41** (180 mg, 1.72 mmol) in anhydrous THF (5 mL) was then added dropwise and the reaction mixture was stirred for 1 h at -78 °C and then for 1 h at rt. CH_2Cl_2 (20 mL) was added and the solution was washed with a 5% aqueous solution of $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (15% ethyl acetate / hexane) gave the title methyl ketone as a tan oil (255 mg, 65%).

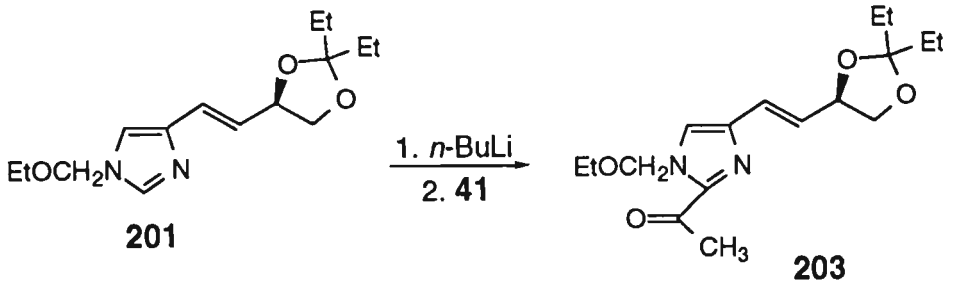
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, s, H5); 6.61 (1H, d, *J* = 15.6 Hz, Imid-C<u>H</u>=CH); 6.37 (1H, dd, *J* = 7.2, 15.6 Hz, CH=C<u>H</u>); 5.75 (2H, s, EtOC<u>H</u>$_2$); 4.69-4.62 (1H, m, CH=CHC<u>H</u>); 4.16 (1H, dd, *J* = 6.0, 8.1 Hz, C<u>H</u>$_A$H$_B$O); 3.66 (1H, t, *J* = 8.1 Hz, CH$_A$<u>H</u>$_B$O); 3.53 (2H, q, *J* = 6.9 Hz, CH$_3$C<u>H</u>$_2$O); 2.68 (3H, s, COCH$_3$); 1.75-1.65 (4H, m, 2 x C<u>H</u>$_2$CH$_3$); 1.19 (3H, t, *J* = 6.9 Hz, C<u>H</u>$_3$CH$_2$O); 0.96; 0.94 (2 x 3H, 2 x t, *J* = 7.5 Hz, 2 x CH$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 190.9 (C=O); 142.6 (C2); 139.5 (C4); 127.2 (Imid-CH=CH); 124.0 (C5); 122.2 (CH=CH); 113.3 (CEt_2); 77.14; 77.10; 69.9 ($CHCH_2$); 64.9 (CH_3CH_2O); 29.94; 29.67 (2 x CH_2CH_3); 27.3 ($COCH_3$); 14.8 (CH_3CH_2O); 8.1 (2 x CH_3).

MS (CI+ve) *m/z* 332 (M^+, 21%); 293 ($M-Et^+$, 24%); 277 ($M-EtO^+$, 16%); 265 ($M-EtOCH_2^+$, 11%); 236 (30%); 177 (68%); 161 (100%).

HRMS calcd for $C_{17}H_{26}N_2O_4$ 322.1892, found 322.1891.

(3'*R*)-(*E*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (203)

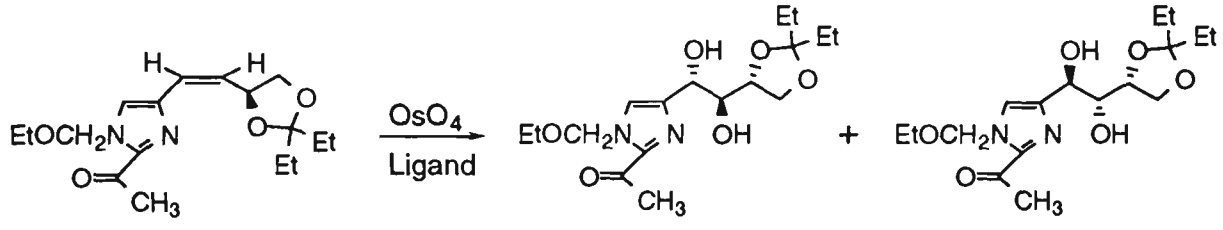


201 **203**

Using the procedure described above for the synthesis of **202**, the title compound was obtained pure as a light tan oil (72%) after purification by column chromatography (15% ethyl acetate / hexane) with the starting alkene (19%) also recovered, $[\alpha]_D^{26}$ -39.0° (*c* 0.92, $CHCl_3$). Spectral data of **203** were identical to that of **202**.

General AD procedure for chiral ligand evaluation on the (Z)-alkene 187:

(1'*S*,2'*S*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (219) and (1'*R*,2'*R*,3'*R*)-2-acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (220)



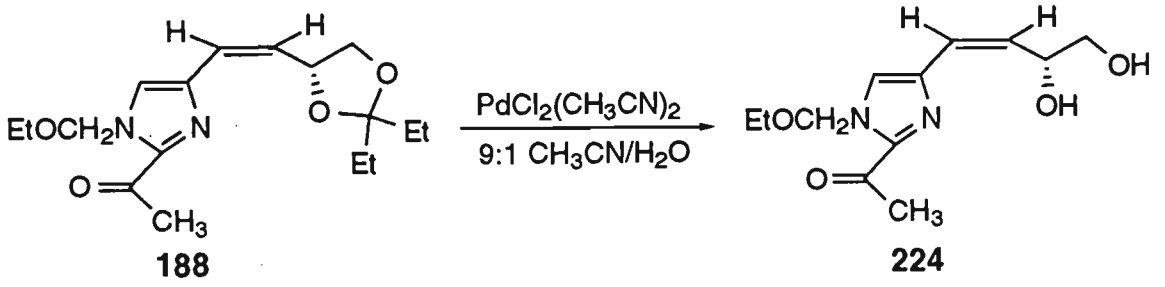
187 **219** **220**

Ligand	*ratio 219 : 220*
none	2.1 : 1
$(DHQD)_2PHAL$	1.7 : 1
$(DHQ)_2PHAL$	1 : 2.0
$(DHQD)_2PYR$	1.2 : 1
$(DHQ)_2PYR$	2.0 : 1
DHQD-IND	1.6 : 1
DHQ-IND	3.2 : 1

A mixture of K_3FeCN_6 (61 mg, 1.86×10^{-4} mol), K_2CO_3 (26 mg, 1.86×10^{-4} mol), methanesulfonamide (18 mg, 1.86×10^{-4} mol), $K_2OsO_4.2H_2O$ (0.7 mg, 2.4×10^{-6} mol) and 5 mol % of the chiral ligand was slurried in H_2O (0.8 mL) and cooled to 0 °C. The (Z)-alkene **187** (20 mg, 6.21×10^{-5} mol) in *t*-BuOH (0.8 mL) was then added in a single addition and the two phase system was stirred for 16 h until the reaction was complete by TLC analysis. Sodium

sulfite (200 mg) was added, the reaction was warmed to rt and stirred for 1 h. Water (3 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined extracts were washed with a 2M aqueous solution of KOH (5 mL), dried ($MgSO_4$) and concentrated. Purification by preparative layer chromatography (50% ethyl acetate / hexane) gave a mixture of diastereomeric tetraols **219** and **220** which were taken into $CDCl_3$ for ^1H NMR analysis. Spectral data for **219** and **220** are given below.

(3'*R*)-(*Z*)-2-Acetyl-4-[3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (224)



188 **224**

A solution of the (Z)-alkene **188** (76 mg, 2.36 mmol) and $(CH_3CN)_2PdCl_2$ (6 mg) in acetonitrile / H_2O (9:1, 4 mL) was heated to reflux for 2 h until TLC analysis showed the absence of starting material. The solution was then concentrated *in vacuo* and the residue was dissolved in ethyl acetate and washed through a plug of silica with excess ethyl acetate. The solvent was removed to leave the title diol as an orange oil (46 mg, 77%), $[\alpha]_D^{25}$ +82.2° (*c* 0.46, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, s, H5); 6.42 (1H, dd, *J* = 1.5, 6.0 Hz, Imid-C<u>H</u>=CH); 5.83-5.74 (1H, m, CH=C<u>H</u>); 5.77 (2H, s, EtOC<u>H</u>$_2$);

4.76-4.69 (1H, m, C<u>H</u>OH); 3.80-3.70 (2H, m, C<u>H</u>$_2$OH); 3.56 (2H, q, J = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.67 (3H, s, $COCH_3$); 1.21 (3H, t, J = 7.2 Hz, CH_3).

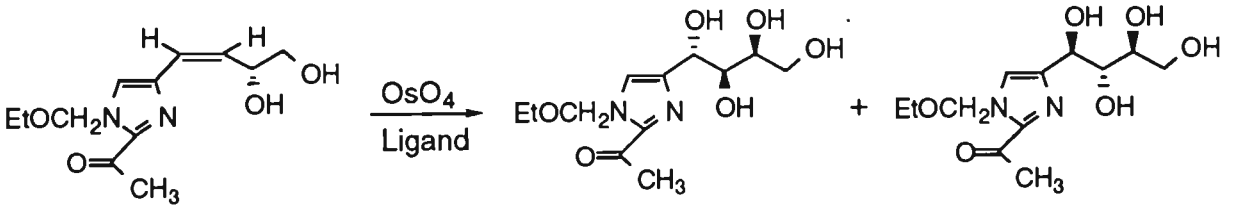
^{13}C NMR (75.6 MHz, $CDCl_3$) δ 190.0 (C=O); 141.8 (C2); 138.6 (C4); 131.5 (<u>C</u>H=CH); 124.1 (CH=<u>C</u>H); 121.7 (C5); 77.4 ($EtO\underline{C}H_2$); 69.1 (CHOH); 66.1 (CH_2); 65.3 (CH_2); 27.4 ($CO\underline{C}H_3$); 14.8 ($\underline{C}H_3CH_2O$).

MS (ES+ve) *m/z* 255 ($M+H^+$, 100%); 238 ($M-OH^+$, 17%).

HRMS calcd for $C_{11}H_{15}N_2O_3$ ($M-CH_2OH$) 223.1082, found 223.1088.

General AD procedure for chiral ligand evaluation on the (*Z*)-alkene 224:

(1'*S*,2'*S*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl)-1-ethoxymethylimidazole (225) and (1'*R*,2'*R*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl)-1-ethoxy methylimidazole (226)



224 **225** **226**

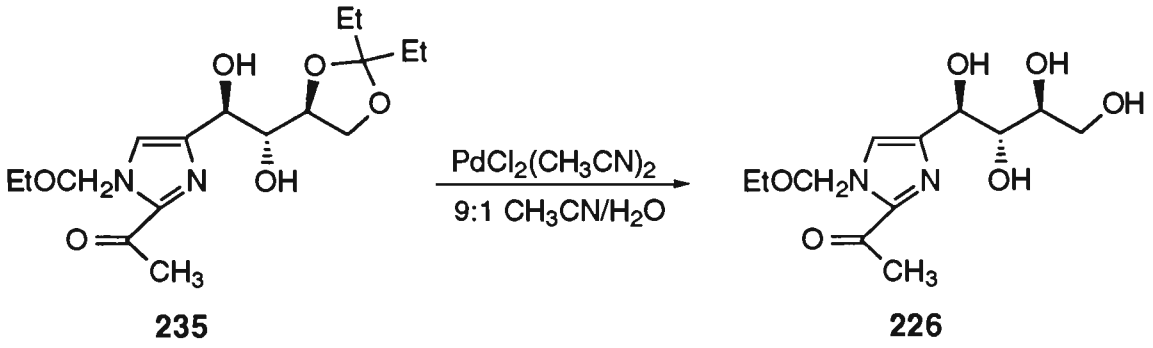
Ligand	*ratio 225:226*
none	1.2 : 1
$(DHQD)_2PHAL$	1 : 1.1
$(DHQ)_2PHAL$	1 : 3.5
$(DHQD)_2PYR$	1.4 : 1
$(DHQ)_2PYR$	1.3 : 1
DHQD-IND	1.2 : 1
DHQ-IND	1 : 1

A mixture of K_3FeCN_6 (78 mg, 2.36 x 10^{-4} mol), K_2CO_3 (33 mg, 2.36 x 10^{-4} mol), methanesulfonamide (15 mg, 2.36 x 10^{-4} mol), $K_2OsO_4.2H_2O$ (0.9 mg, 3.14 x 10^{-6} mol) and 5 mol % chiral ligand was slurried in H_2O (1.0 mL) and cooled to 0 °C. The (Z)-alkene **224** (20 mg, 7.87 x 10^{-5} mol) in *t*-BuOH (1.0 mL) was then added in a single addition and the two phase system stirred for 3 days until the reaction was complete by TLC analysis. Sodium sulfite (200 mg) was added and the reaction was warmed to rt and stirred for 1 h. A sat. aqueous solution of NaCl (2 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 4 mL) and ethyl acetate (2 x 4 mL). The combined extracts were washed with a 2M aqueous solution of KOH (5 mL), dried ($MgSO_4$) and concentrated. Purification by preparative layer chromatography (10% methanol / ethyl acetate) gave a mixture of diastereomeric tetraols **225** and **226** which were taken into deuterated acetone for ^1H NMR analysis.

225: ^1H NMR (300 MHz, d^6-acetone) δ 7.48 (1H, s, H5); 5.78-5.77 (2H, m, EtOC$\underline{H}_2$); 4.76 (1H, d, *J* = 7.2 Hz, Imid-C$\underline{H}$OH); 3.91-3.62 (4H, m, (C$\underline{H}$OH)$_2$C$\underline{H}_2$OH); 3.535 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$); 2.545 (3H, s, $COCH_3$); 1.13 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2O$).

226: ^1H NMR (300 MHz, d^6-acetone) δ 7.48 (1H, s, H5); 5.78-5.77 (2H, m, EtOC$\underline{H}_2$); 4.85 (1H, d, *J* = 5.4 Hz, Imid-C$\underline{H}$OH); 3.91-3.62 (4H, m, (C$\underline{H}$OH)$_2$C$\underline{H}_2$OH); 3.544 (2H, q, *J* = 6.9 Hz, $CH_3C\underline{H}_2O$); 2.548 (3H, s, $COCH_3$); 1.13 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2O$).

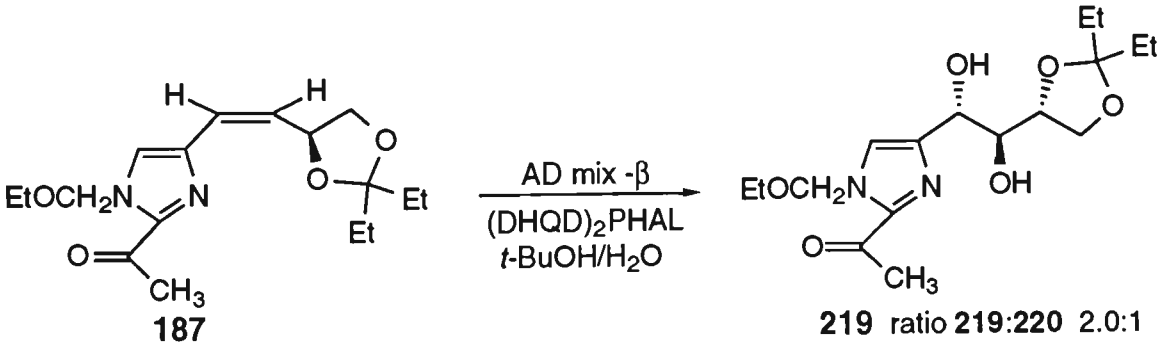
Confirmation of the stereochemical assignments for 225 and 226



235 **226**

A solution of the tetraol **235** (35 mg, 9.8 x 10^{-5} mol) and $PdCl_2(CH_3CN)_2$ (6 mg) in acetonitrile / H_2O (9:1, 4 mL) was heated to reflux for 2 h. The solution was then cooled to rt, filtered through a bed of silica with excess MeOH and concentrated. The resulting orange residue was taken into deuterated acetone for ^1H NMR analysis. The ^1H NMR spectra was identical to that of **226** synthesised from the alkene **224** *via* the AD reaction above.

(1'*S*,2'*S*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (219)



187 **219** ratio **219**:**220** 2.0:1

A general AD procedure for alkenes using AD mix-β:

Into a 25 mL round bottom flask was added AD mix-β (1.09 g), $(DHQD)_2PHAL$ (24 mg, 3.09 x 10^{-5} mol), $K_2OsO_4.2H_2O$ (2.8 mg, 9.75 x

10^{-6} mol) and methanesulfonamide (147 mg, 1.55 mmol). The reagents were dissolved in H_2O (4 mL) and *t*-BuOH (2 mL) and the solution cooled to 0 °C. The (*Z*)-alkene **187** (250 mg, 7.76 x 10^{-4} mol) in *t*-BuOH (2 mL) was added in a single addition and the reaction was allowed to stir for 48 h at 0 °C until complete by TLC. Sodium sulfite (1.2 g) was then added, the reaction was warmed to rt and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (4 x 5 mL) and ethyl acetate (5 mL) and the combined extracts were washed with a 2M aqueous solution of KOH (7 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (40% ethyl acetate / hexane) gave the title compound as a pale yellow oil (200 mg, 72%). The ratio of **219**:**220** was 2.0:1 from ^{1}H NMR analysis.

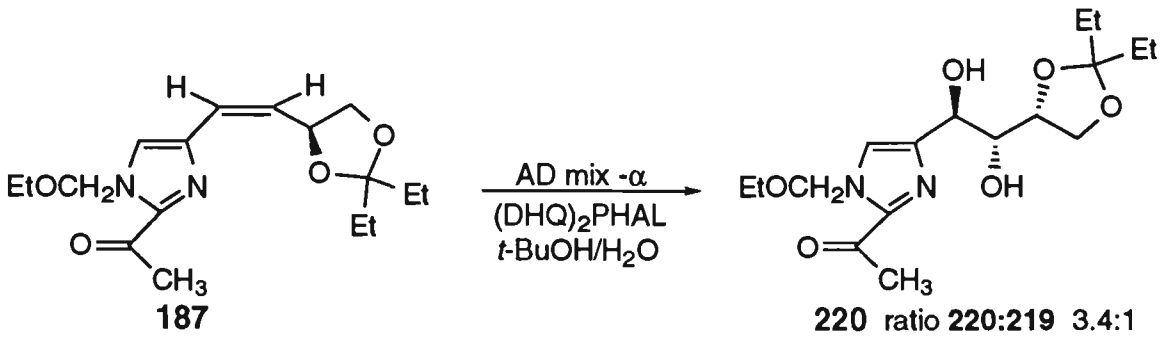
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, s, H5); 5.77 (2H, d, *J* = 2.4 Hz, EtOC$\underline{H}_2$); 4.82 (1H, dd, *J* = 4.0, 6.4 Hz, Imid-C$\underline{H}$OH); 4.56 (1H, d, *J* = 4.0 Hz, CHO$\underline{H}$); 4.23-4.18 (1H, m, C$\underline{H}_A$H$_B$O); 4.04-3.98 (1H, m, C$\underline{H}$OH); 3.85-3.73 (2H, m, CH$_A\underline{H}_B$O, C$\underline{H}$); 3.66 (1H, d, *J* = 3.6 Hz, CHO$\underline{H}$); 3.561 (2H, q, *J* = 7.2 Hz, CH$_3$C$\underline{H}_2$O); 2.62 (3H, s, COCH$_3$); 1.74-1.59 (4H, m, 2 x C$\underline{H}_2$CH$_3$); 1.207 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$O); 0.926; 0.881 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH$_3$).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 190.3 (C=O); 142.8 (C2); 141.7 (C4); 122.4 (C5); 113.8 ($\underline{C}$Et$_2$); 77.8 (CH); 77.4 (EtO$\underline{C}$H$_2$); 75.5 (CHOH); 69.4 (CHOH); 68.2 (CH$_2$); 65.2 (CH$_3\underline{C}$H$_2$O); 29.6; 29.0 (2 x $\underline{C}$H$_2$CH$_3$); 27.3 (CO$\underline{C}$H$_3$); 14.8 ($\underline{C}$H$_3$CH$_2$O); 8.13; 8.05 (2 x CH$_3$).

MS (ES+ve) *m/z* 357 (M+H$^+$, 100%).

HRMS calcd for $C_{15}H_{23}N_2O_6$ 327.1556, found 327.1556.

(1'*R*,2'*R*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3', 4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (220)



A general AD procedure for alkenes using AD mix-α:
Into a 25 mL round bottom flask was added AD mix-α (1.09 g), $(DHQ)_2PHAL$ (24 mg, 3.09 x 10^{-5} mol), $K_2OsO_4.2H_2O$ (2.8 mg, 9.75 x 10^{-6} mol) and methanesulfonamide (147 mg, 1.55 mmol). The reagents were dissolved in H_2O (4 mL) and *t*-BuOH (2 mL) and the solution was then cooled to 0 °C. The (*Z*)-alkene **187** (250 mg, 7.76 x 10^{-4} mol) in *t*-BuOH (2 mL) was added in a single addition and the reaction was allowed to stir for 48 h at 0 °C until complete by TLC analysis. Sodium sulfite (1.2 g) was then added, the reaction was warmed to rt and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (4 x 5 mL) and ethyl acetate (5 mL) and the combined extracts were washed with a 2M aqueous solution of KOH (7 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (40% ethyl acetate / hexane) gave the final product as a pale yellow oil (200 mg, 72%). The ratio of **220**:**219** was 3.4:1 from ^1H NMR analysis.

^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, s, H5); 5.76 (2H, d, *J* = 7.2 Hz, EtOC$\underline{H}_2$); 4.76 (1H, t, *J* = 6.0 Hz, Imid-C$\underline{H}$OH); 4.32-4.27 (1H, m, C$\underline{H}_A$H$_B$O); 4.04-3.98 (1H, m, C$\underline{H}$OH); 3.85-3.73 (2H, m, CH$_A\underline{H}_B$O, C$\underline{H}$); 3.547 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$); 3.28 (1H, d, *J* = 6.8 Hz, OH); 3.21

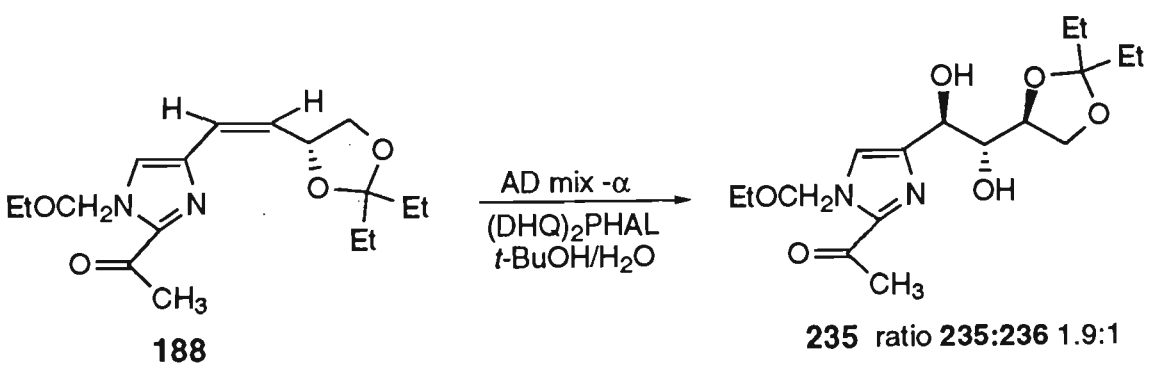
(1H, d, J = 6.4 Hz, OH); 2.643 (3H, s, $COCH_3$); 1.74-1.60 (4H, m, 2 x $C\underline{H}_2CH_3$); 1.200 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2O$); 0.929; 0.880 (2 x 3H, 2 x t, J = 7.2 Hz, 2 x CH_3).

^{13}C NMR (75.6 MHz, $CDCl_3$) δ 190.6 (C=O); 142.7 (C2); 142.0 (C4); 122.1 (C5); 113.1 ($\underline{C}Et_2$); 77.3 ($EtO\underline{C}H_2$); 76.0 (CH); 73.5 (CHOH); 69.8 (CHOH); 66.5 (CH_2); 65.2 ($CH_3\underline{C}H_2O$); 29.6; 27.0 (2 x $\underline{C}H_2CH_3$); 27.3 ($CO\underline{C}H_3$); 14.8 ($\underline{C}H_3CH_2O$); 8.13; 8.05 (2 x CH_3).

MS (ES +ve) *m/z* 357 ($M+H^+$, 100%).

HRMS calcd for $C_{15}H_{23}N_2O_6$ 327.1556, found 327.1546.

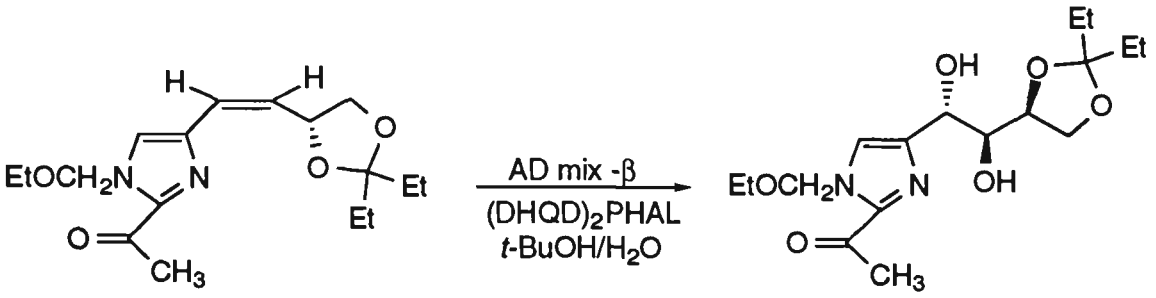
(1'*R*,2'*R*,3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (235)



188 **235** ratio **235:236** 1.9:1

Using the general procedure described above for the synthesis of **220**, except that the (*Z*)-alkene **188** (225 mg, 6.98 x 10^{-4} mol) was used, the title compound was obtained as a pale yellow oil (235 mg, 95%) after purification by column chromatography (40% ethyl acetate / hexane). The ratio of **235**:**236** was 1.9:1 from ^{1}H NMR analysis. Spectral data of **235** were identical to that of **219**.

(1'*S*,2'*S*,3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (236)

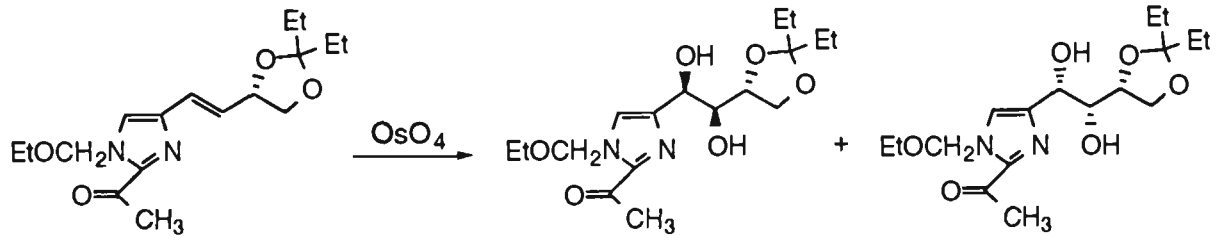


188 **236** ratio **236:235** 1:1.1

Using the general procedure described above for the synthesis of **219**, except that (*Z*)-alkene **188** (225 mg, 6.98 x 10^{-4} mol) was used, the title compound was obtained as a pale yellow oil (225 mg, 91%) after purification by column chromatography (40% ethyl acetate / hexane). The ratio of **236**:**235** was 1:1.1 from ^{1}H NMR analysis. Spectral data of **236** were identical to that of **220**.

Dihydroxylation of the (*E*)-alkene 202 in the absence of a chiral ligand:

(1'*R*,2'*S*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (238) and (1'*S*,2'*R*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxy methylimidazole (239)

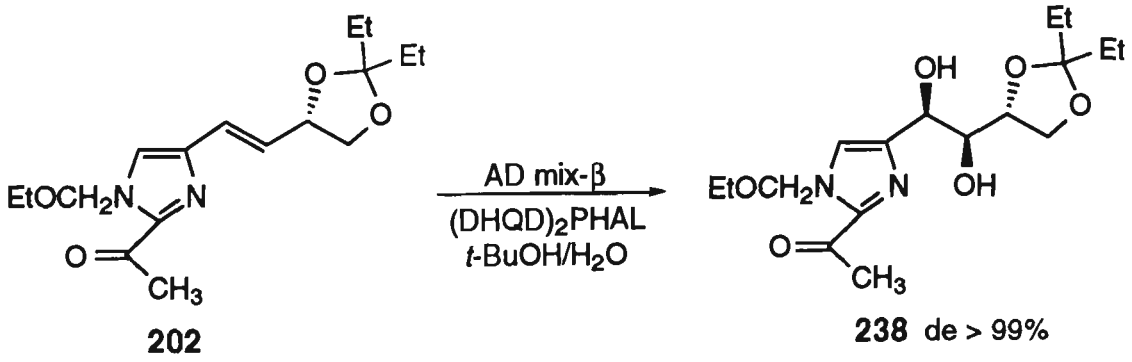


202 **238** **239**

ratio **238**:**239** = 3.5:1

To a solution of the (*E*)-alkene **202** (20 mg, 6.21 x 10^{-5} mol) in *t*-BuOH / H_2O (1:1, 2 mL) was added $K_3Fe(CN)_6$ (62 mg, 1.86 x 10^{-4} mol), K_2CO_3 (26 mg, 1.86 x 10^{-4} mol), methanesulfonamide (12 mg, 1.2 x 10^{-4} mol) and $K_2OsO_4.2H_2O$ (1 mg, 3.48 x $^{-6}$ mol) and the solution cooled to 0 °C and stirred vigorously for 3 days until complete by TLC analysis. Sodium sulfite (200 mg) was added and the reaction was warmed to rt and stirred for 1 h. The mixture was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (4 x 5 mL) and the combined extracts were washed with a 2M aqueous solution of KOH (6 mL), dried ($MgSO_4$) and concentrated. The residue was purified by preparative layer chromatography (50% ethyl acetate/hexane) and the diastereomeric mixture taken into deuterated acetone for ^1H NMR analysis. The ratio of **238**:**239** was 3.5:1 from ^1H NMR analysis. Spectral data for **238** and **239** are given below.

(1'*R*,2'*S*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (238)



202 **238** de > 99%

Using the general procedure described above for the synthesis of **219**, except that the (*E*)-alkene **202** (70 mg, 2.17 x 10^{-4} mol) was used and additional osmium catalyst excluded, the title compound was obtained as a thick pale oil (62 mg, 80%, de > 99%) after

purification by column chromatography (50% ethyl acetate / hexane), $[\alpha]_D^{23}$ +3.7° (*c* 2.10, MeOH).

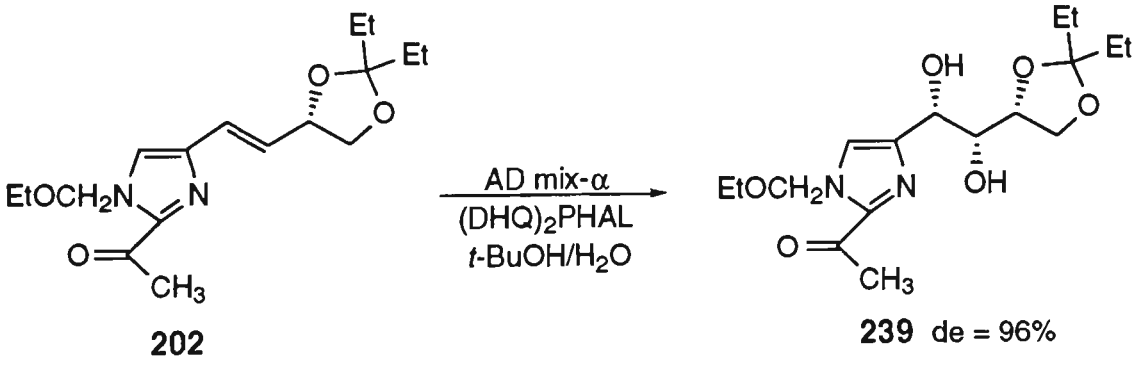
^{1}H NMR (400 MHz, d^6-acetone) δ 7.48 (1H, d, *J* = 0.4 Hz, H5); 5.77 (1H, d, J_{AB} = 10.4 Hz, EtOC$\underline{H}_A$H$_B$); 5.74 (1H, d, J_{AB} = 10.4 Hz, EtOCH$_A\underline{H}_B$); 4.84 (1H, d, *J* = 2.0 Hz, Imid-C$\underline{H}$OH); 4.23 (1H, dd, *J* = 6.4, 13.2 Hz, CH-O); 4.08 (1H, dd, *J* = 6.0, 8.0 Hz, C$\underline{H}_A$H$_B$O); 3.91 (1H, dd, *J* = 6.4, 8.0 Hz, CH$_A\underline{H}_B$O); 3.85 (1H, dd, *J* = 2.4, 7.6 Hz, C$\underline{H}$OH); 3.53 (2H, q, *J* = 6.8 Hz, CH$_3$C$\underline{H}_2$O); 2.53 (COCH$_3$); 1.66-1.56 (4H, m, 2 x C$\underline{H}_2$CH$_3$); 1.12 (3H, t, *J* = 6.8 Hz, C$\underline{H}_3$CH$_2$O); 0.89; 0.86 (2 x 3H, 2 x t, *J* = 7.6 Hz, 2 x CH$_3$).

^{13}C NMR (75.6 MHz, d^6-acetone) δ 190.6 (C=O); 145.1 (C2); 142.6 (C4); 124.0 (C5); 113.2 (C$\underline{C}$Et$_2$); 77.5 (EtO$\underline{C}$H$_2$); 76.4 (CH-O); 75.6 (CHOH); 68.7 (Imid-$\underline{C}$HOH); 68.2 (CH$_2$O); 65.1 (CH$_3\underline{C}$H$_2$O); 29.4; 29.0 (2 x $\underline{C}$H$_2$CH$_3$); 27.2 (CO$\underline{C}$H$_3$); 15.1 ($\underline{C}$H$_3$CH$_2$O); 8.5; 8.3 (2 x CH$_3$).

MS (ES+ve) *m/z* 379 (M+Na$^+$, 100%).

HRMS calcd for $C_{17}H_{28}N_2O_6$ 356.1947, found 356.1942.

(1'*S*,2'*R*,3'*R*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (239)



202 **239** de = 96%

Using the general procedure described above for the synthesis of **220**, except that the (*E*)-alkene **202** (70 mg, 2.17 x 10^{-4} mol) was used and additional osmium catalyst excluded, the title compound

was obtained as a thick pale oil (52 mg, 67%, de = 96%) after purification by column chromatography (50% ethyl acetate / hexane), $[\alpha]_D^{23}$ +4.4° (*c* 2.40, MeOH).

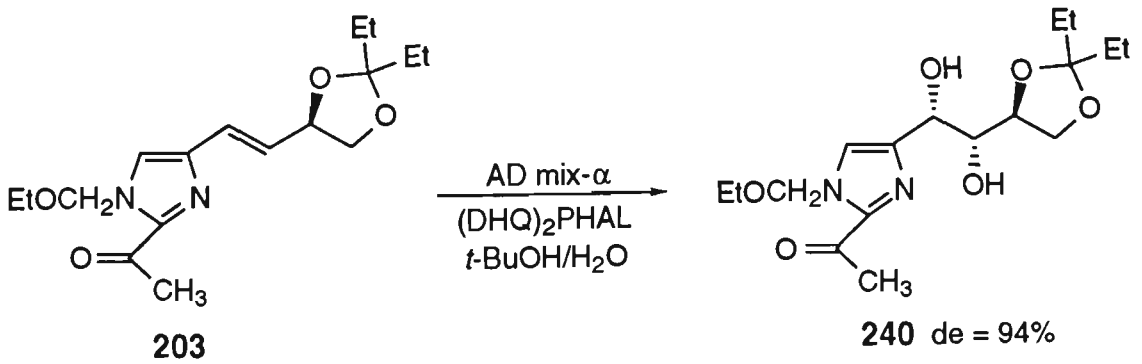
^{1}H NMR (400 MHz, d^6-acetone) δ 7.47 (1H, s, H5); 5.73; (2H, ABq, *J* = 10.4 Hz, EtOC$\underline{H}_A\underline{H}_B$); 4.72 (1H, d, *J* = 4.4 Hz, Imid-C$\underline{H}$OH); 4.25 (1H, s(b), Imid-CHO$\underline{H}$); 4.21 (1H, ddd, *J* = 5.2, 6.8, 11.2 Hz, CH-O); 3.97 (1H, dd, *J* = 6.4, 8.0 Hz, C$\underline{H}_A$H$_B$O); 3.96-3.92 (1H, s(b), OH); 3.84-3.77 (2H, m, C$\underline{H}$OH, CH$_A\underline{H}_B$O); 3.52 (2H, q, *J* = 7.2 Hz, CH$_3$C$\underline{H}_2$O); 2.54 (3H, s, COCH$_3$); 1.66-1.54 (4H, m, 2 x C$\underline{H}_2$CH$_3$); 1.15 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$O); 0.88; 0.84 (2 x 3H, 2 x t, *J* = 7.2 Hz, 2 x CH$_3$).

^{13}C NMR (100 MHz, d^6-acetone) δ 190.6 (C=O); 144.2 (C2); 142.7 (C4); 124.2 (C5); 113.0 (C$\underline{C}$Et$_2$); 77.9 (CH-O); 77.5 (EtO$\underline{C}$H$_2$); 74.5 (CHOH); 70.4 (Imid-$\underline{C}$HOH); 67.0 (CH$_2$); 65.0 (CH$_3\underline{C}$H$_2$O); 30.4; 30.0 (2 x $\underline{C}$H$_2$CH$_3$); 27.2 (CO$\underline{C}$H$_3$); 15.1 ($\underline{C}$H$_3$CH$_2$O); 8.3 (2 x CH$_3$).

MS (ES+ve) *m/z* 379 (M+Na$^+$, 100%).

HRMS calcd for $C_{17}H_{28}N_2O_6$ 356.1947, found 356.1942.

(1'*S*,2'*R*,3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (240)

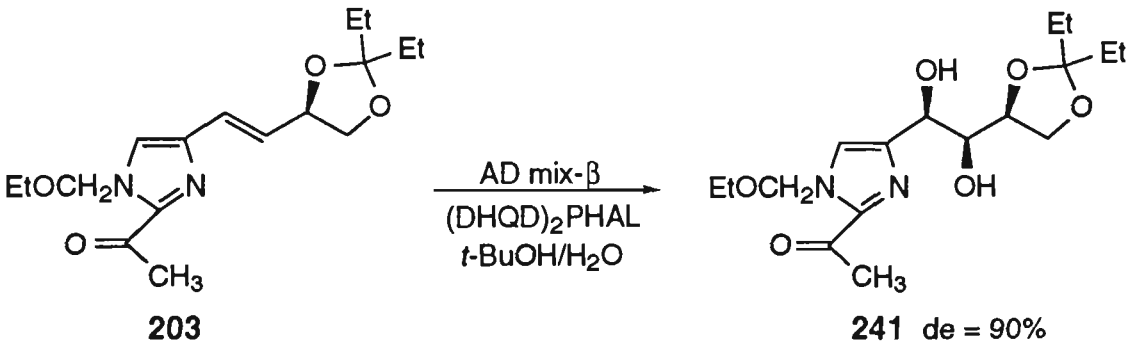


203 **240** de = 94%

Using the general procedure described above for the synthesis of **220**, except that the (*E*)-alkene **203** (150 mg, 4.66 x 10^{-4} mol) was used and additional osmium catalyst excluded, the title compound

was obtained as a thick pale oil (130 mg, 78%, de = 94%) after purification by column chromatography (45% ethyl acetate / hexane), $[\alpha]_D^{23}$ -3.3° (*c* 1.3, MeOH). Spectral data were identical to that of **238**.

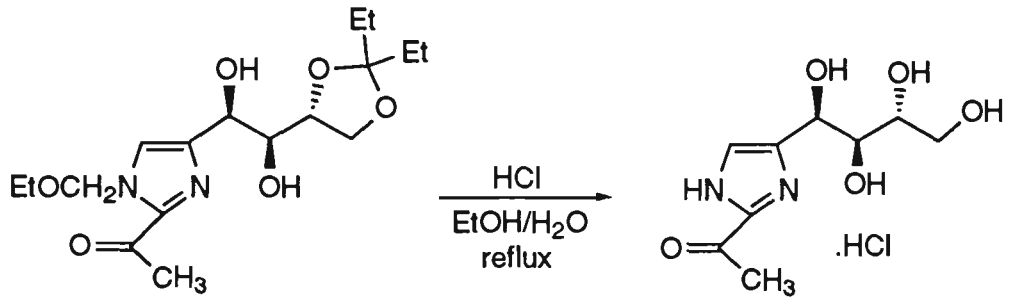
(1'*R*,2'*S*,3'*S*)-2-Acetyl-4-[3',4'-O-(3'-pentylidene)-1',2',3',4'-tetrahydroxy-1'-butyl]-1-ethoxymethylimidazole (241)



203 **241** de = 90%

Using the general procedure described above for the synthesis of **219**, except that the (*E*)-alkene **203** (150 mg, 4.66 x 10^{-4} mol) was used and additional osmium catalyst excluded, the title compound was obtained as a pale oil (155 mg, 93%, de = 90%) after purification by column chromatography (45% ethyl acetate / hexane), $[\alpha]_D^{23}$ -5.3° (*c* 1.55, MeOH). Spectral data were identical to that of **239**.

(1'*R*,2'*S*,3'*R*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (245)

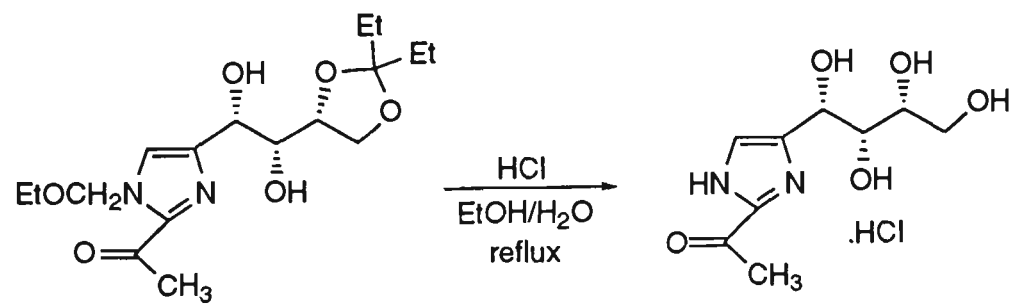


238 **245**

Using the general procedure described above for the synthesis of **160**, compound **245** was obtained as a tan solid in quantitative yield (100%). A small amount of decomposition of the tetraol had occurred, with repeated attempts to purify the compound by ion exchange, silica and alumina chromatography unsuccessful.

^{1}H NMR (300 MHz, D_2O) δ 7.60 (1H, s, H5); 5.21 (1H, s, Imid-C<u>H</u>OH); 3.83-3.60 (4H, m, 2 x C<u>H</u>OH, C<u>H$_2$</u>OH); 2.66 (3H, s, $COCH_3$).

(1'*S*,2'*R*,3'*R*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (246)



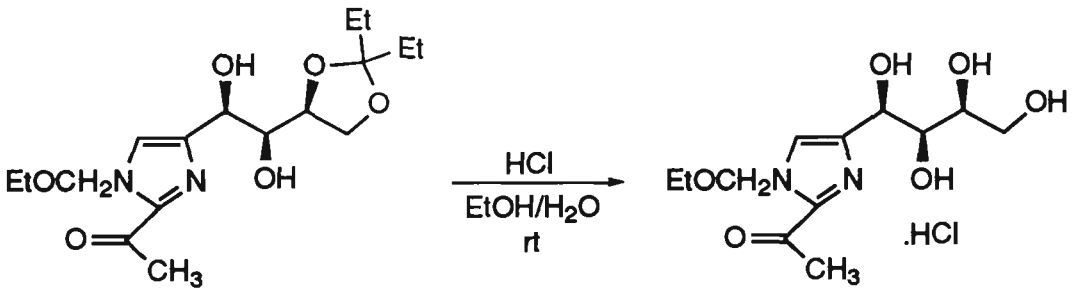
239 **246**

Using the general procedure described above for the synthesis of **160**, compound **246** was obtained as a tan solid in quantitative

yield (100%). A small amount of decomposition of the tetraol had occurred.

^{1}H NMR (400 MHz, D_2O) δ 7.60 (1H, s, H5); 5.04 (1H, d, *J* = 5.2 Hz, Imid-C<u>H</u>OH); 3.84-3.58 (4H, m, 2 x C<u>H</u>OH, C<u>H$_2$</u>OH); 2.65 (3H, s, $COCH_3$).

(1'*R*,2'*S*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl)-1-ethoxymethylimidazolium chloride (247)

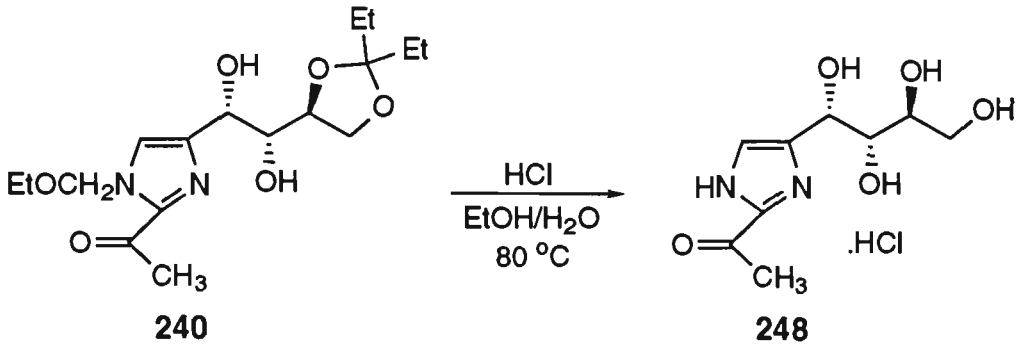


241 **247**

To a solution of imidazole **241** (16 mg, 0.045 mmol) in ethanol / H_2O (1:1, 8 mL) was added conc. HCl (4 mL) and the solution stirred at rt. A small portion of the reaction mixture was removed after a 30 min period and concentrated to dryness. ^{1}H NMR analysis in D_2O of the resulting residue showed a complete removal of the pentylidene protecting group, with the ethoxymethyl moiety still intact. The tetraol was then treated for a further 5.5 h at rt and the reaction was monitored regularly by ^{1}H NMR analysis. Removal of the ethoxymethyl group was not achieved after this time at an ambient reaction temperature.

^{1}H NMR (300 MHz, D_2O) δ 7.78 (1H, s, H5); 5.72 (2H, s, EtOC<u>H$_2$</u>); 4.97 (1H, d, *J* = 4.8 Hz, Imid-C<u>H</u>OH); 3.78-3.76 (1H, m, C<u>H</u>OH); 3.59-3.50 (5H, m, C<u>H</u>, C<u>H$_2$</u>, $CH_3C\underline{H_2}O$); 2.61 (3H, s, $COCH_3$); 1.04 (3H, t, J = 7.2 Hz, CH_3).

(1'*S*,2'*R*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (248)



240 **248**

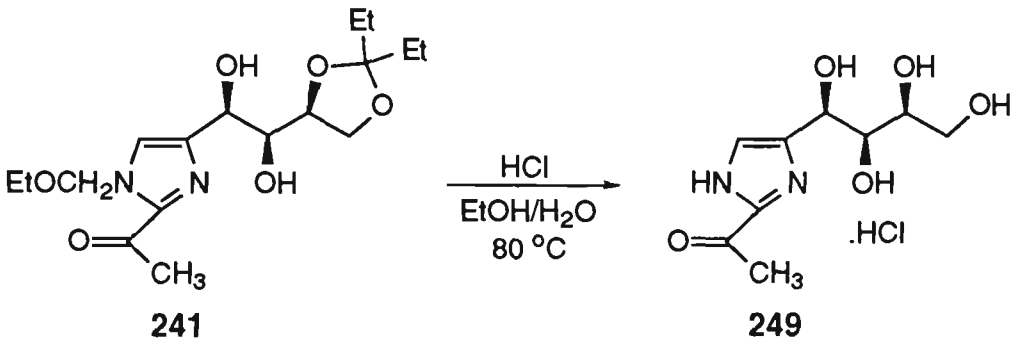
A general deprotection procedure: To a solution of imidazole **240** (120 mg, 3.37 x 10^{-4} mol) in ethanol / H_2O (1:1, 8 mL) was added conc. aqueous HCl (4 mL) and the reaction stirred at 80 °C for 90 min. The solution was then cooled to rt, filtered and concentrated by freeze drying to give the title compound as a glassy yellow solid (90 mg, 100%), mp 174-178 °C (decomp), $[\alpha]_D^{27}$ +14.9° (*c* 0.70, H_2O).

^{1}H NMR (300 MHz, D_2O) δ 7.60 (1H, s, H5); 5.21 (1H, s, Imid-C<u>H</u>OH); 3.82-3.61 (4H, m, 2 x C<u>H</u>OH, C<u>H$_2$</u>OH); 2.66 (3H, s, $COCH_3$).

^{13}C NMR (100 MHz, D_2O) δ 187.2 (C=O); 141.7 (C2); 140.2 (C4); 121.6 (C5); 75.2; 73.1; 67.3 (3 x CHOH); 65.4 (CH_2OH); 28.9 (CH_3).

MS (ES+ve) *m/z* 231 ($M+H^+$, 100%); 213($M-OH^+$, 64%); 200 ($M-CH_2OH^+$, 23%).

(1'*R*,2'*S*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (249)



241 **249**

Using the general procedure described above for the synthesis of **248**, the title compound was obtained as a light tan solid after concentration by freeze drying (95%), $[\alpha]_D^{26}$ -11.3° (*c* 0.70, H_2O).

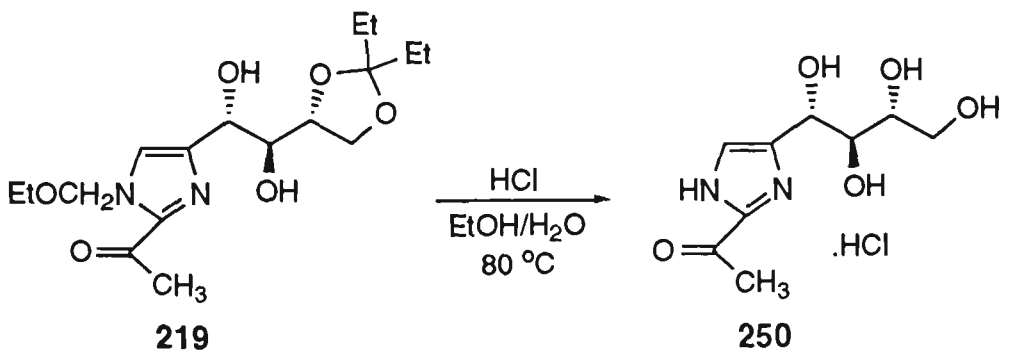
^{1}H NMR (300 MHz, D_2O) δ 7.61 (1H, s, H5); 5.04 (1H, d, *J* = 4.8 Hz, Imid-C<u>H</u>OH); 3.83-3.57 (4H, m, 2 x C<u>H</u>OH, C<u>H</u>$_2$OH); 2.64 (3H, s, $COCH_3$).

^{13}C NMR (75.6 MHz, D_2O) δ 184.7 (C=O); 139.4 (C2); 136.6 (C4); 119.5 (C5); 72.7; 71.3; 66.1 (3 x CHOH); 62.5 (CH_2OH); 26.4 (CH_3).

MS (LSIMS+ve) *m/z* 231 ($M+H^+$, 100%).

HRMS calcd for $C_9H_{15}N_2O_5$ 231.0981, found 231.0975.

(1'*S*,2'*S*,3'*R*)-2-Acetyl-4-(1',2',3,'4'-tetrahydroxy-1'-butyl) imidazolium chloride (250)



219 **250**

Using the general procedure described above for the synthesis of **248**, the title compound was obtained as a light tan solid after concentration by freeze drying (85%), mp 161-168 °C (decomp).

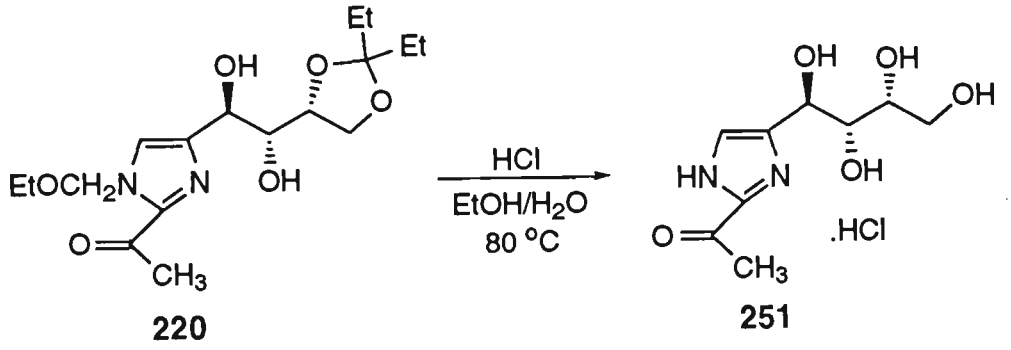
^{1}H NMR (300 MHz, D_2O) δ 7.61 (1H, s, H5); 5.12 (1H, d, *J* = 4.8 Hz, Imid-C<u>H</u>OH); 3.95-3.56 (4H, m, 2 x C<u>H</u>OH, C<u>H$_2$</u>OH); 2.65 (3H, s, $COCH_3$).

^{13}C NMR (75.6 MHz, D_2O) δ 184.6 (C=O); 139.1 (C2); 135.6 (C4); 119.7 (C5); 72.9; 71.8; 65.9 (3 x CHOH); 62.5 (CH_2OH); 26.4 (CH_3).

MS (ES+ve) *m/z* 231 ($M+H^+$, 100%); 213 ($M-H_2O^+$, 24%).

HRMS calcd for $C_9H_{15}N_2O_5$ 231.0981, found 231.0976.

(1'*R*,2'*R*,3'*R*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (251)



220 **251**

Using the general procedure described above for the synthesis of **248**, the title compound was obtained as a light tan solid (90%) after concentration by freeze drying, mp 168-174 °C (decomp).

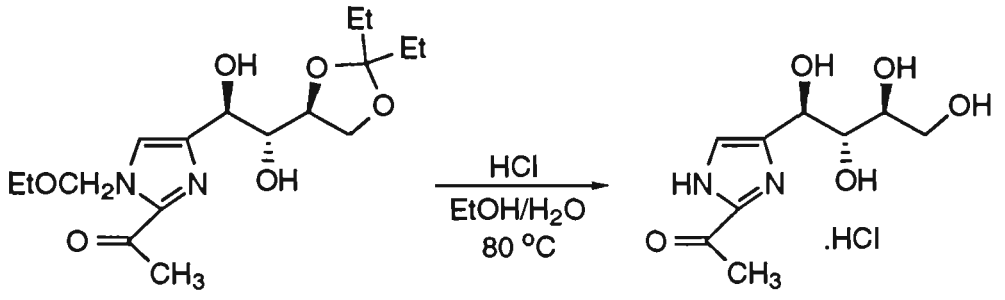
^{1}H NMR (300 MHz, D_2O) δ 7.60 (1H, s, H5); 4.89 (1H, d, *J* = 8.4 Hz, Imid-C<u>H</u>OH); 3.92-3.60 (4H, m, 2 x C<u>H</u>OH, C<u>H$_2$</u>OH); 2.64 (3H, s, $COCH_3$).

^{13}C NMR (75.6 MHz, D_2O) δ 184.6 (C=O); 139.1 (C2); 137.4 (C4); 119.5 (C5); 72.2; 69.9; 65.0 (3 x CHOH); 62.8 (CH_2OH); 26.4 (CH_3).

MS (ES-ve) *m/z* 229 ($M-H^-$, 100%).

HRMS calcd for $C_9H_{15}N_2O_5$ 231.0981, found 231.0970.

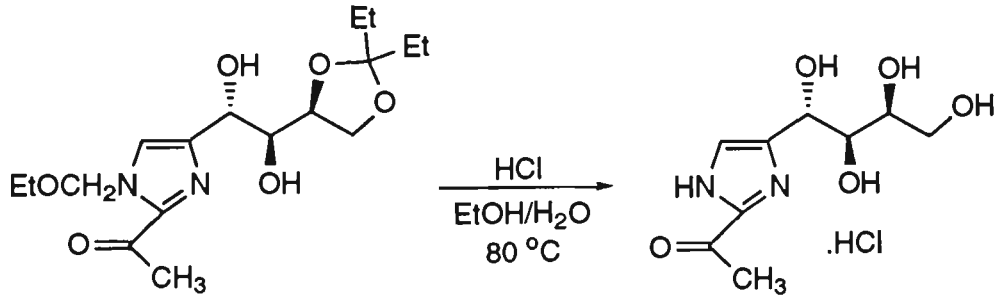
(1'*R*,2'*R*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (252)



235 **252**

Using the general procedure described above for the synthesis of **248**, the title compound was obtained as a light tan solid after concentration by freeze drying (85%), mp 177-182 °C (decomp). Spectral data were identical to that of **250**.

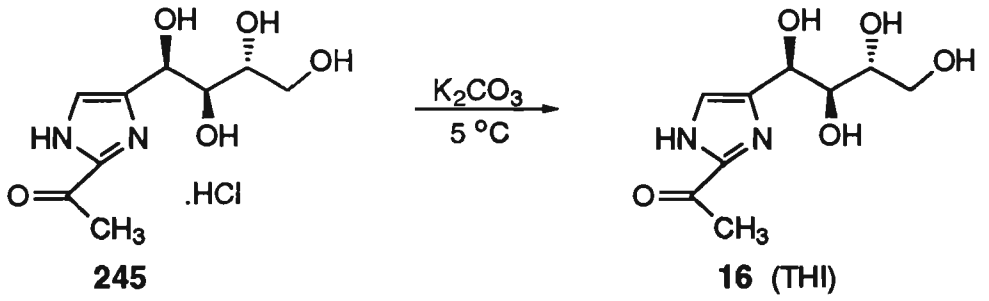
(1'*S*,2'*S*,3'*S*)-2-Acetyl-4-(1',2',3',4'-tetrahydroxy-1'-butyl) imidazolium chloride (253)



236 **253**

Using the general procedure described above for the synthesis of **248**, the title compound was obtained as a light tan solid after concentration by freeze drying (92%), mp 154-157 °C (decomp). Spectral data were identical to that of **251**.

(1'*R*,2'*S*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetrahydroxy-1'-butyl)imidazole (THI) (16)



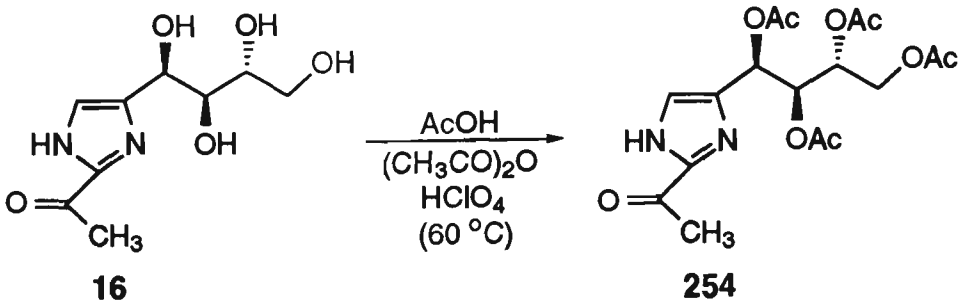
245 **16** (THI)

To a solution of the imidazolium salt **245** (155 mg, 0.59 mmol) in H_2O (3 mL) was added solid K_2CO_3 (82 mg, 0.59 mmol). The solution was then cooled to near freezing for 3 days and the precipitated THI collected after centrifuging the solution. The precipitate was washed with H_2O to remove salts and then dried under high vacuum to give the title compound as a light yellow solid (33 mg, 24%), mp 240-244 °C (lit.[86] mp 232-233 °C), $[\alpha]_D^{23}$ -14.9° (*c* 0.09, H_2O) (lit.[86] $[\alpha]_D^{25}$ -12°, *c* 1.17, 1N HCl).

^{1}H NMR (300 MHz, D_2O/DCl) δ 7.30 (1H, s, H5); 4.91 (1H, s, Imid-C<u>H</u>OH); 3.51-3.32 (4H, m, (C<u>H</u>OH)$_2$C<u>H$_2$</u>OH); 2.35 (3H, s, $COCH_3$).

Spectral data were identical to that of an authentic sample of THI.[87]

(1'*R*,2'*S*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (254)



16 **254**

A general acetylation procedure:

1. From authentic THI:[87] To a stirred solution of acetic anhydride (3.0 mL) and glacial acetic acid (5.0 mL) was added THI **16** (200 mg, 0.87 mol). A perchloric acid/acetic anhydride catalyst was added (4 drops, prepared by addition of 1.0 g of 70% $HClO_4$ to 2.3 g acetic anhydride at 0 °C) and the reaction was stirred for 1 h at 60 °C. The mixture was poured into H_2O / ice (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a thick tan oil. Recrystallisation from ethyl acetate gave the title compound as a white powder (190 mg, 55%), mp 153-154 °C, $[\alpha]_D^{24}$ -22.6° (*c* 0.58, CH_3CN).

2. From THI synthesised in this project: Using the general procedure descibed above, THI synthesised in this study was converted to the tetraacetate. Purification by preparative layer chromatography (60% ethyl acetate / hexane) gave the title compound as a white solid (47%), $[\alpha]_D^{24}$ -20.0° (*c* 0.09, CH_3CN). Spectral data were identical to that of the tetraacetate synthesised from authentic THI above.

^{1}H NMR (400 MHz, CD_3CN) δ 7.27 (1H, s, H5); 6.05 (1H, d, *J* = 4.8 Hz, Imid-C<u>H</u>OAc); 5.56 (1H, dd, *J* = 5.2, 7.2 Hz, Imid-CHOAcC<u>H</u>OAc); 5.18 (1H, ddd, *J* = 2.8, 5.6, 8.8 Hz, C<u>H</u>OAcCH$_2$OAc); 4.25 (1H, dd, *J* = 3.2, 12.4 Hz, C<u>H</u>$_A$H$_B$OAc); 4.11 (1H, dd, *J* = 6.0, 12.4 Hz, CH$_A$<u>H</u>$_B$OAc); 2.51 (3H, s, $COCH_3$); 2.04; 2.02; 2.00; 1.98 (4 x 3H, 4 x s, 4 x OAc).

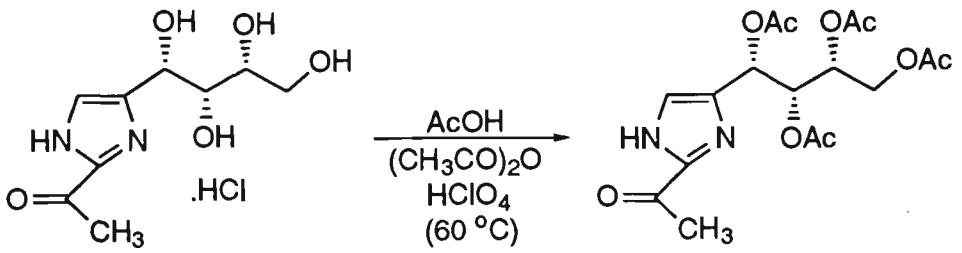
^{13}C NMR (100 MHz, CD_3CN) δ 188.7 (C=O); 170.3; 169.7; 169.6; 169.5 (4 x C=O); 145.0 (C2); 138.5 (C4); 120.2 (C5); 70.8; 68.7; 67.5 (3 x <u>C</u>HOAc); 61.5 (<u>C</u>H$_2$OAc); 24.7 (CO<u>C</u>H$_3$); 20.00; 19.93; 19.88; 19.86 (4 x OAc).

MS (ES+ve) *m/z* 399 ($M+H^+$, 100%); 339 ($M-AcO^+$, 71%).

HRMS calcd for $C_{17}H_{23}N_2O_9$ 399.1402, found 399.1398.

Anal. calcd for $C_{17}H_{22}N_2O_9$: C, 51.26; H, 5.57; N, 7.03. Found: C, 51.09; H, 5.66; N, 6.65.

(1'*S*,2'*R*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (255)



246 **255**

Using the general procedure described above for the synthesis of **254**, the title compound was obtained as a glassy solid after purification by preparative layer chromatography (60% ethyl acetate / hexane).

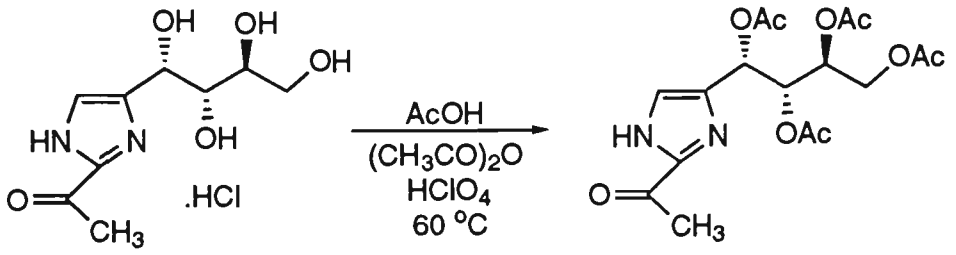
^{1}H NMR (400 MHz, CD_3CN) δ 7.29 (1H, s, H5); 5.98 (1H, d, J = 8.4 Hz, Imid-C<u>H</u>OAc); 5.70 (1H, dd, J = 3.6, 8.0 Hz, Imid-CHOAcC<u>H</u>OAc); 5.01 (1H, ddd, J = 3.6, 5.2, 8.8 Hz, Imid$(CHOAc)_2C\underline{H}OAc$); 4.18 (1H, dd, J = 5.2, 11.6 Hz, $C\underline{H}_AH_BOAc$); 4.00 (1H, dd, J = 6.4, 11.6 Hz, $CH_A\underline{H}_BOAc$); 2.52 (3H, s, $COCH_3$); 2.08; 2.05; 2.00; 1.96 (4 x 3H, 4 x s, 4 x OAc).

^{13}C NMR In part (100 MHz, CD_3CN) δ 181.7 (C=O); 170.2; 169.8 (2 x C=O); 169.7 (2 x C=O); 145.1 (C2); 71.2; 68.7; 68.2 (3 x <u>C</u>HOAc); 61.6 ($\underline{C}H_2OAc$); 24.7 ($CO\underline{C}H_3$); 20.1; 20.0; 19.9; 19.8 (4 x OAc).

MS (ES+ve) *m/z* 399 ($M+H^+$, 100%); 339 ($M-AcO^+$, 82%).

HRMS calcd for $C_{17}H_{23}N_2O_9$ 399.1402, found 399.1409.

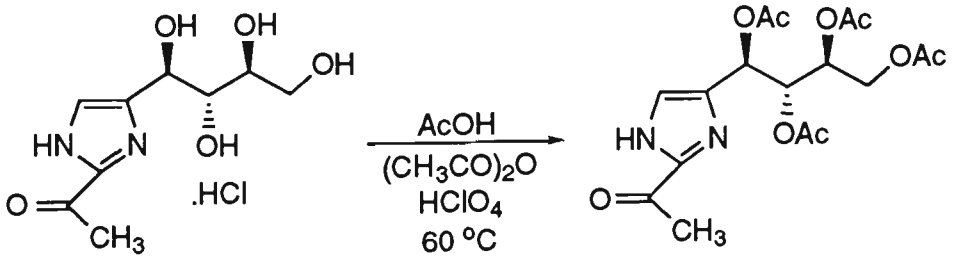
(1'*S*,2'*R*,3'*S*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (256)



248 **256 + 257**

Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **256** and **257** was obtained as a tan solid (71%, ratio **256**:**257** = 5.3:1) after purification by preparative layer chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer, $[\alpha]_D^{24}$ +19.4° (*c* 0.06, CH_3CN). Spectral data were identical to that of **254**.

(1'*R*,2'*R*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (257)



252 + 253 **257 + 256, 258, 259**

Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **256-259** was obtained from acetylation of a mixture

of **252** and **253** as a cream solid (47%, ratio **257**:**256**:**259**:**258** = 3.8:1.9:2.2:1.0) after purification by preparative layer chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer.

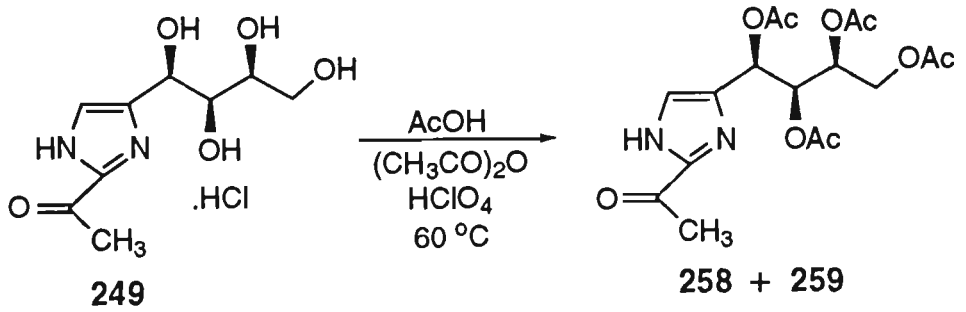
^{1}H NMR (300 MHz, CD_3CN) δ 7.31 (1H, s, H5); 6.01 (1H, d, *J* = 5.1 Hz, Imid-C<u>H</u>OAc); 5.61 (1H, dd, *J* = 5.1, 6.3 Hz, Imid-CHOAcC<u>H</u>OAc); 5.12 (1H, ddd, *J* = 3.0, 6.0, 9.3 Hz, Imid(CHOAc)$_2$C<u>H</u>OAc); 4.34 (1H, dd, *J* = 3.3, 12.3 Hz, C<u>H</u>$_A$H$_B$OAc); 4.13 (1H, dd, *J* = 6.0, 12.3 Hz, CH$_A$<u>H</u>$_B$OAc); 2.49 (3H, s, $COCH_3$); 2.05; 2.01; 2.00; 1.99 (4 x 3H, 4 x s, 4 x OAc).

^{13}C NMR (75.6 MHz, CD_3CN) δ 188.7 (C=O); 170.37; 169.62; 169.61; 169.60 (4 x C=O); 144.7 (C2); 138.6 (C4); 119.7 (C5); 70.4; 69.5; 68.9 (3 x <u>C</u>HOAc); 61.6 (<u>C</u>H$_2$OAc); 24.6 (CO<u>C</u>H$_3$); 20.09; 20.06 (2 x OAc); 19.88 (2 x OAc).

MS (ES+ve) *m/z* 399 ($M+H^+$, 78%); 339 ($M-AcO^+$, 100%).

HRMS calcd for $C_{17}H_{23}N_2O_9$ 399.1402, found 399.1389.

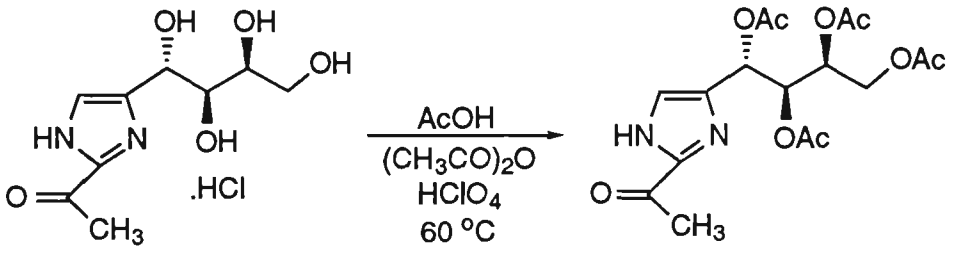
(1'*R*,2'*S*,3'*S*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (258)



Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **258** and **259** was obtained as a cream solid (93%, ratio **258**:**259** = 1.3:1) after purification by preparative layer

chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer. Spectral data were identical to that of **255**.

(1'*S*,2'*S*,3'*S*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (259)



253 + 252 **259 + 256, 257, 258**

Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **256-259** was obtained from acetylation of a mixture of **253** and **252** as a cream solid (37%, ratio **259**:**258**:**257**:**256** = 2.8:1.0:3.1:1) after purification by preparative layer chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer.

^{1}H NMR (300 MHz, CD_3CN) δ 7.29 (1H, s, H5); 5.89 (1H, d, *J* = 7.8 Hz, Imid-C<u>H</u>OAc); 5.62 (1H, dd, *J* = 3.9, 7.8 Hz, Imid-CHOAcC<u>H</u>OAc); 5.42 (1H, ddd, *J* = 4.8, 6.9, 8.4 Hz, Imid(CHOAc)$_2$C<u>H</u>OAc); 4.20 (1H, dd, *J* = 4.5, 12.0 Hz, C<u>H</u>$_A$H$_B$OAc); 4.11 (1H, dd, *J* = 6.6, 11.7 Hz, CH$_A$<u>H</u>$_B$OAc); 2.50 (3H, s, $COCH_3$); 2.03; 2.01; 1.99; 1.94 (4 x 3H, 4 x s, 4 x OAc).

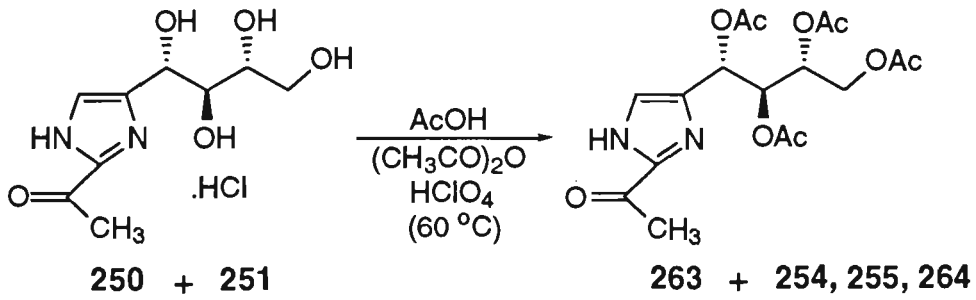
^{13}C NMR (75.6 MHz, CD_3CN) δ 188.7 (C=O); 170.3; 169.9, 169.6; 169.5 (4 x C=O); 144.8 (C2); 139.1 (C4); 119.9 (C5); 70.9; 68.5; 67.4

(3 x CHOAc); 62.2 ($\underline{C}H_2OAc$); 24.6 ($CO\underline{C}H_3$); 20.1; 19.9 (2 x OAc); 19.8 (2 x OAc).

MS (ES+ve) *m/z* 399 ($M+H^+$, 57%); 339 ($M-AcO^+$, 100%).

HRMS calcd for $C_{17}H_{23}N_2O_9$ 399.1402, found 399.1407.

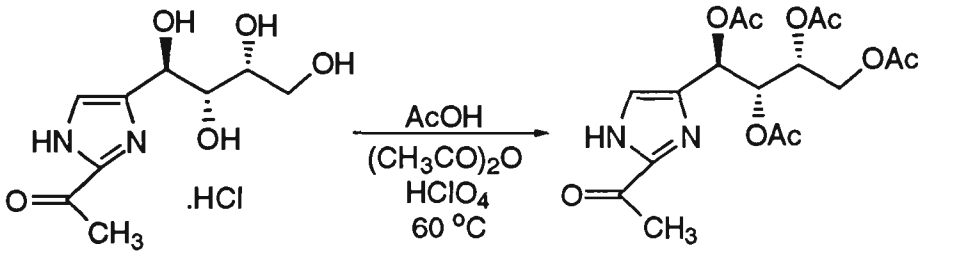
(1'*S*,2'*S*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (263)



250 + 251 **263 + 254, 255, 264**

Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **254**, **255**, **263** and **264** was obtained from acetylation of a mixture **250** and **251** as a cream solid (65%, ratio **263**:**254**:**264**:**255** = 6.3:1.7:3.0:1) after purification by preparative layer chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer. Spectral data were identical to that of **257**.

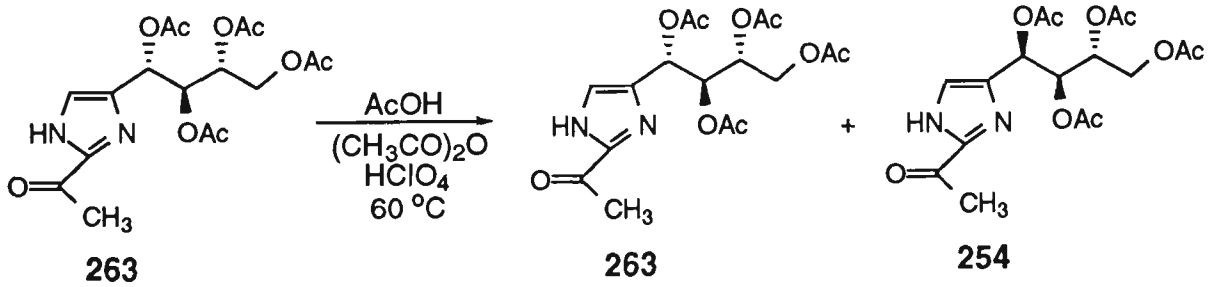
(1'*R*,2'*R*,3'*R*)-2-Acetyl-4(5)-(1',2',3',4'-tetraacetoxy-1'-butyl)imidazole (264)



251 + 250 **264 + 254, 255, 263**

Using the general procedure described above for the synthesis of **254** and a reaction time of 6 h at 60 °C, a mixture of the tetraacetates **254**, **255**, **263** and **264** was obtained from acetylation of a mixture **251** and **250** as a cream solid (63%, ratio **264**:**255**:**263**:**254** = 4.0:2.7:1.1:1) after purification by preparative layer chromatography (60% ethyl acetate / hexane). HPLC separation of the diastereomers (30% ethyl acetate / hexane) gave the title compound as a single diastereomer. Spectral data were identical to that of **259**.

Epimerisation of the tetraacetate 263 at C1' to give 254



263 **263** **254**

Using the general procedure described above for the synthesis of **254**, the tetraacetate **263** (20 mg, 5.0 x 10^{-5} mol) was retreated for 6 h at 60 °C. The mixture was poured into H_2O / ice (10 mL) and

extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give a tan oil. The oil was purified by preparative layer chromatography (60% ethyl acetate / hexane) and the resulting solid taken into CD_3CN. ^1H NMR analysis showed the tetraacetates **263** and **254** to be present in a 2.5:1 ratio, with the latter tetraacetate formed from **263** *via* epimerisation at C1'.

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