Synthetic Studies towards
Griseusin A

A thesis presented in partial fulfilment

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ABSTRACT

This thesis presents the synthesis and attempted functionalization of the unsaturated ring system of the naturally occurring pyranonaphthoquinone antibiotic griseusin A **88**. Unsaturated spiroketals **333,334** were constructed *via* the addition of 2-trimethylsilyloxyfuran **189** to quinone **328**. Initial work using acetylenic quinone **321** afforded a pentacyclic product **323**, wherein an unanticipated third Michael reaction occurred due to the phenolic hydroxyl group cyclizing onto the α,β-unsaturated ketone moiety. Altering the reaction conditions gave trimethylsilyl analogue **325**, where the final Michael reaction abstracted not a proton (**323**) but a trimethylsilyl cation liberated from **189**. Naphthoquinone **328**, bearing a 2-alkenyl side chain rather than an acetylene, was synthesized using similar methodology to **321** and subsequently converted to furonaphthofuran adduct **330**. Ceric ammonium nitrate oxidative rearrangement of **330** produced diol **332**, which was then cyclized to spiroketals **333,334** under a variety of conditions. The isomer ratio **333:334** resulting from these conditions was determined by high field ^{1}H nmr spectroscopy.

With the two spiroketals **333,334** in hand, efforts were directed towards the functionalization of the C3'-C4' double bond. Osmium tetraoxide catalytic dihydroxylation of model olefin **345** gave diol **353**, where approach of the reagent was from the opposite face to that required for griseusin A **88**. Selective acetylation of the less hindered hydroxyl group was however achieved, giving **354**.

The Woodward-Prevost reaction of olefin **345** formed the iodoacetates **367-369**. Attempts to displace the iodine from the major diaxial iodoacetate **368** gave a complex mixture. Iodoacetate **387** was then prepared wherein the iodine and acetate positions were reversed, treatment of which with silver acetate afforded the fragmentation products **401** and **402**. The minor diequatorial iodoacetate **367** gave, like its stereoisomer **368**, a complex mixture when subjected to displacement conditions. Only iodoacetate **410**, formed from **367**, produced spiroketal hydroxyacetates as hoped for, however both of these had the opposite stereochemistry at C-4 and C-5 to that desired. One of these two hydroxyacetates (**354**) had also been isolated from the selective acetylation of diol **353**.

Several attempts using a variety of reaction conditions were made in an effort to force **333,334** to react with osmium tetraoxide. It was found that the functional groups present in **333**, **334**, **336**, **330** and **323** were incompatible with this reagent. Ketone **327** was the only compound that successfully underwent *syn*-hydroxylation, affording diols **419** and **420**. Use of cetyltrimethylammonium permanganate as an hydroxylation reagent for **333,334** afforded **423** and **421** rather than **343** and **344**, where reaction had occurred at the C5a-C11a double bond.

The difficulty in introducing the oxygenated substituents onto the O1'-C6' spiroketal ring was proposed to be overcome by synthesizing naphthoquinone **430**. The protected hydroxyl groups at C-2' and C-3' in this compound would possess the correct stereochemistry for elaboration to the hydroxyl and acetate groups at C-3' and C-4' respectively in griseusin A **88**.

Towards this end, the synthesis of the required naphthalene precursor (**432**) was undertaken *via* an enantioselective aldol condensation of imide **435** with (*R*)-aldehyde **437**. **435** was formed from (*R*)-phenylalanine and 2-(benzyloxy)acetyl chloride **439** and reacted with **437** using stannous triflate and tetramethylethylenediamine. The major product **452**, possessing the desired 2',3'-*anti* stereochemistry, was protected and the auxiliary reductively removed to give alcohol **459**. Oxidation of **459** using *tetra-n-*propylammonium perruthenate gave aldehyde **434**, ready to be coupled to the Grignard reagent (**498**) of trimethoxybromide **433**.

Trials using heptanal and various organometallic reagents found *n*-butyllithium to be the reagent of choice for generating the anion (in this case the lithiate, **500**) of **433**. With the optimum time determined, the coupling of **500** with **434** was undertaken but yielded only the debrominated compound **499**. The basicity of **500** and the hindrance at the carbonyl group of **434** were cited as possible reasons for this result, and attempts were made to "soften" the anion. Unfortunately both magnesium bromide and ceric chloride failed to produce the desired products **503,504**.

CONTENTS

ABBREVIATIONS

2D	=	two dimensional
aq.	=	aqueous
amu	=	atomic mass units
av	=	average
ax	=	axial
BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	=	boiling point
n-Bu, Bu^n	=	n-butyl
Bu^t	=	*tert*-butyl
Bz	=	benzyl
CAN	=	ceric ammonium nitrate
cat.	=	catalytic
CD	=	circular dichroism
cm^3	=	cubic centimetres (ml)
CoA	=	coenzyme A
conc.	=	concentrated
COSY	=	correlation spectroscopy
CSA	=	camphor sulphonic acid
CTAP	=	cetyltrimethylammonium permanganate
D	=	deuterium
DBN	=	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
decomp.	=	decomposed
deg	=	degree
DEPT	=	distortionless enhancement by polarization transfer
DIBAL	=	diisobutylaluminium hydride
dil.	=	dilute
DMAP	=	4-dimethylaminopyridine
DME	=	dimethoxyethane/ethylene glycol dimethyl ether
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulphoxide
ds	=	diastereoselection
ee	=	enantiomeric excess

18C6	=	1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6 ether)
eq	=	equatorial
equiv.	=	equivalents
FAB	=	fast atom bombardment
h	=	hour
[H]	=	reduction
HETCOR	=	heteronuclear correlation spectroscopy
hplc	=	high pressure liquid chromatography
hrms	=	high resolution mass spectrometry
imid	=	imidazole
IR	=	infra-red
J	=	nmr coupling constant (hertz)
LDA	=	lithium diisopropylamide
MCPBA	=	*meta*-chloroperbenzoic acid
mg	=	milligrams
min	=	minutes
mm^3	=	cubic millimetres (μl)
mmol	=	millimoles
mol	=	moles
MOM	=	methoxymethyl
m.p.	=	melting point
ms	=	mass spectrometry
NADH	=	reduced nicotinamide adenine dinucleotide
NADPH	=	reduced nicotinamide adenine dinucleotide phosphate
NBA	=	*N*-bromoacetamide
NMO	=	4-methylmorpholine *N*-oxide
nmr	=	nuclear magnetic resonance
NOE	=	nuclear *O*verhauser effect
[O]	=	oxidation
OAc	=	acetate
ORD	=	optical rotatory dispersion
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PMB	=	*p*-methoxybenzyl
PPTS	=	pyridinium *p*-toluenesulphonate
Pr^i	=	isopropyl

PTC	=	phase transfer catalyst
py	=	pyridine
R_f	=	distance travelled by compound÷distance travelled by solvent on TLC plate
RT	=	room temperature
s	=	seconds
t	=	time
TBAF	=	tetrabutylammonium fluoride
TBDMS	=	*tert*-butyldimethylsilyl
TES	=	triethylsilyl
Tf	=	trifluoromethanesulphonyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TLC	=	thin layer chromatography
TMEDA	=	*N,N,N',N'*-tetramethylethylenediamine
TMS	=	trimethylsilyl
TPAP	=	*tetra-n*-propylammonium perruthenate
Tr	=	trityl (Ph_3C)
TsOH	=	*p*-toluene sulphonic acid (tosic acid)
UV	=	ultra-violet
var.	=	variety
wt.	=	weight

CHAPTER 1

Introduction

1.1 Pyranonaphthoquinone Antibiotics - Isolation, Structure and Biological Activity

The class of compounds known as the pyranonaphthoquinone antibiotics are isolated from various strains of bacteria and fungi, the majority being microbial in origin. The basic skeleton of these antibiotics is the naphtho[2,3-c]pyran-5,10-dione ring system (figure 1), with some members of the family containing an additional γ-lactone ring fused to the dihydropyran moiety as the basic subunit.
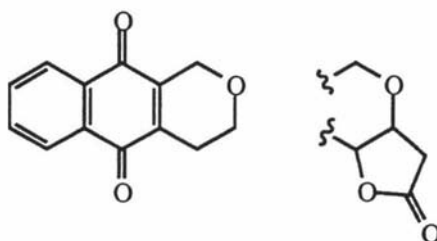
Figure 1

This family of antibiotics has been shown to exhibit activity against a variety of gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity (*vide infra*). In addition, they have been proposed to act as bioreductive alkylating agents, that is, compounds which become potent alkylating agents after they undergo a reduction *in vivo*.[1,2]

According to the postulated mechanism,[1] simple quinones may function as alkylating agents *in vivo via* quinone methides (scheme 1). For a pyranonaphthoquinone antibiotic (scheme 2), this would involve reduction of the naphthoquinone moiety to a hydroquinone **1** followed by ring opening of the γ-lactone, initiated by the hydroxyl group on the naphthalene ring. A similar opening of the pyran ring generates the *bis*-enone **2**, which is susceptible to Michael addition by an appropriate nucleophile. In the event that the attacking nucleophile was a nitrogenous base of a nucleic acid, there exists the possibility that these antibiotics may form adducts such as **3** with DNA. Such properties render these antibiotics interesting and worthwhile synthetic targets, and with some of the more recently discovered examples being structurally quite complex, they provide significant synthetic challenges.

Scheme 1

Scheme 2
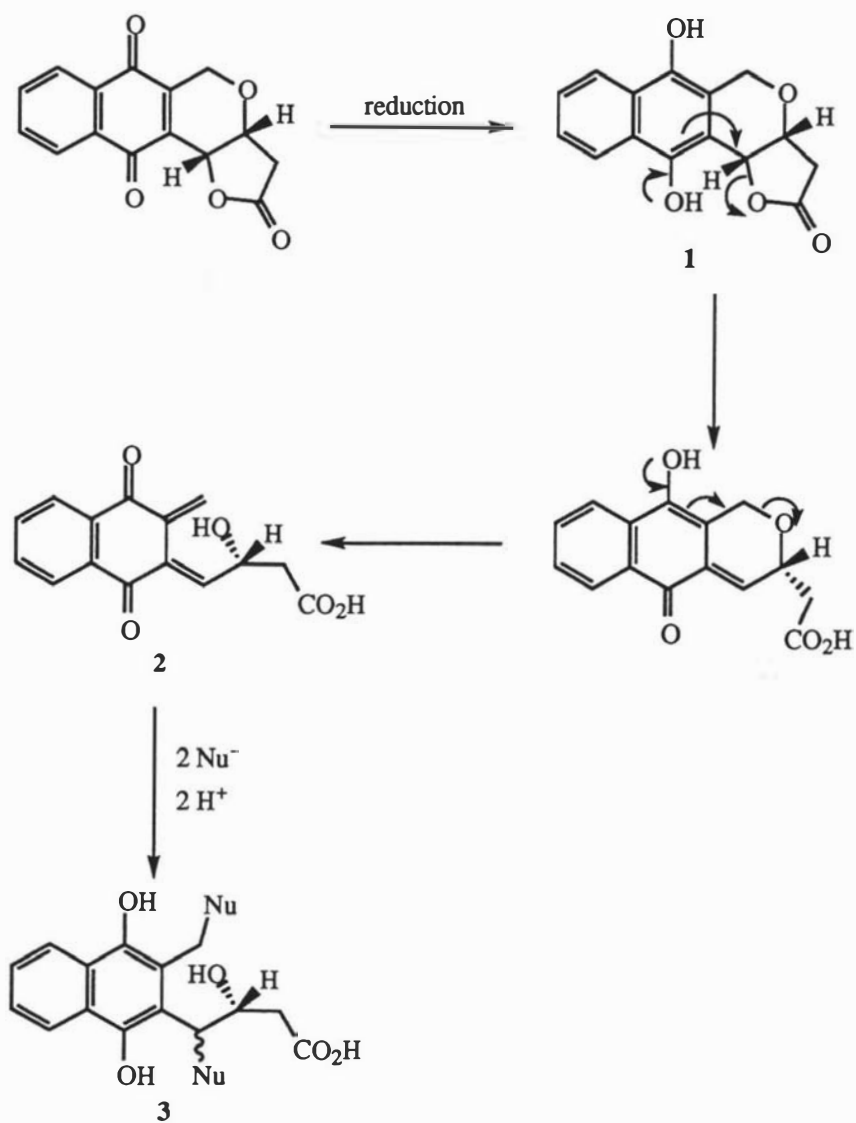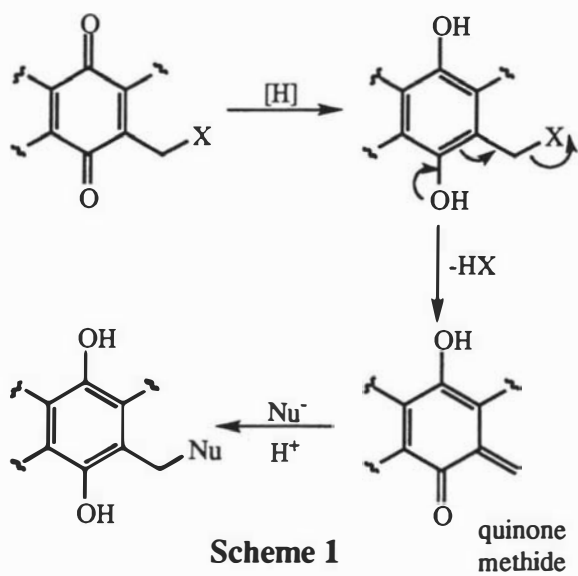
1.1.1 Simple and Fusarium Derived Quinones

The simplest example of a compound containing the naphthopyrandione subunit is psychorubrin **4**, which bears only an additional hydroxyl group at C-3. Psychorubrin **4** was isolated[3] from *Psychotria rubra*, a plant used in Chinese folk medicine, and exhibits significant cytotoxicity against KB tumour cells. Naphthoquinone derivatives of **4** which were potential Michael acceptors *via* extended conjugation were prepared and all had greater cytotoxic properties, however a hydroxyl group reduced *in vitro* activity.[3]

4
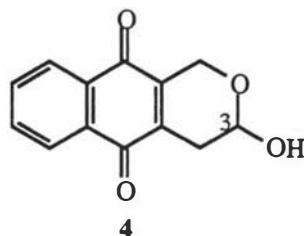
Eleutherin **5** was found[4] in the rhizomes of a member of the iris family, *Eleutherine bulbosa*, and its structure determined[5,6] by extensive chemical degradation and analysis of the fragments. These findings were confirmed later by X-ray crystallography[7] and ^{1}H nmr data.[8] The methyl group at C-1 is more stable in a pseudo-axial position in **6** (versus both methyl groups pseudo-equatorial in **5**) as it is further removed from the neighbouring carbonyl group.[9] Also obtained from *E. bulbosa* was isoeleutherin **6**[10] which is epimeric about C-3 and thus has the configuration (1*R*,3*R*). Eleutherin **5** and isoeleutherin **6** are additionally found in *E. americana*[11] and *E. subaphylla*,[12,13] the latter being a medicinal plant found in Vietnam. Eleutherin **5** shows some activity[6] against *Pyococcus aureus* and *Streptococcus haemolyticus A*, and weak activity against *Bacillus subtilis*.[14] Extracts of *E. bulbosa* have been used as antifertility agents in Haiti[15] and eleutherin **5** from *E. americana* used as a coronary vasodilating agent to treat heart diseases such as angina pectoris.[11,16]

5   **6**
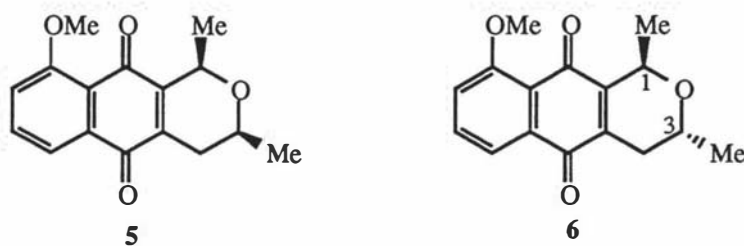
Other compounds similar to the eleutherins have been isolated from various natural sources. The seeds of *Karwinskia humboldtiana* (Rhamnaceae), a desert plant found in northern Mexico and southern Texas yielded[17] 7-methoxyeleutherin **7** and 6-

hydroxy-7-methoxyeleutherin **8**, which were found in the non toxic fraction of the seed extract.[18] The structure of **8** was deduced spectroscopically, with the assumption that the C-methyl groups were *cis*-diequatorial by analogy with cometabolite **7**.[17]
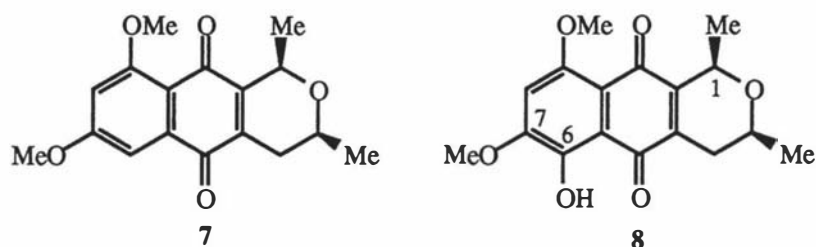
Species of the fungal genus *Fusarium* produce naphthazarinoid pigments, many of which have received attention because of their antibiotic, insecticidal and phototoxic properties[19] (naphthazarins are 5,8-dihydroxynaphthoquinones). Fusarubin **9**, a red pigment was isolated[20] from *Fusarium solani*, a common soil fungus in citrus groves and shown[21] to be identical to oxyjavanicin, isolated earlier[22] from *Fusarium javanicum*. The name fusarubin was retained as the structure of **9** was elucidated using this.[23] Fusarubin has also been isolated from *F. martii*[24] and other species.[25]

9 : R=H
12 : R=Et
19 : R=Me
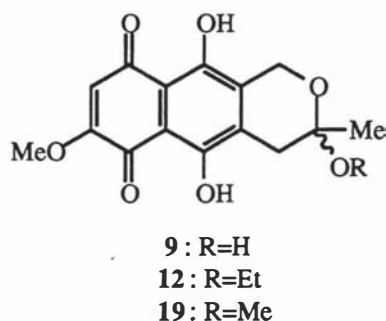
Fusarubin **9** equilibrates with an open chain form (scheme 3) and is therefore optically inactive. In addition, the quinol and quinone rings of the pigment can undergo prototopic exchange, giving rise to four possible tautomeric forms unless the process is prevented by ether formation.[26] Ring substitution influences tautomerism and results in a decrease of at least one of these species: the tautomer normally encountered is that depicted by **9** as this is favoured by electronic factors.[27,28]

Two diastereomeric dihydrofusarubins A and B, **10** and **11**, were isolated[29] from *F. solani* cultures. These are not strictly pyranonaphthoquinones but they are of considerable interest as the precursors of fusarubin **9** and related cometabolites. From chemical shift comparisons and *J* values,[29] 8-H is present in a phenolic rather than a quinone ring, and the ketal ring systems have 4a-H and 10a-H antiperiplanar in **10** and

4

synclinal in **11** (relative stereochemistry illustrated). Conformational free energy calculations[29] supported the hydroxyl group at C-3 being axial, thereby gaining stability
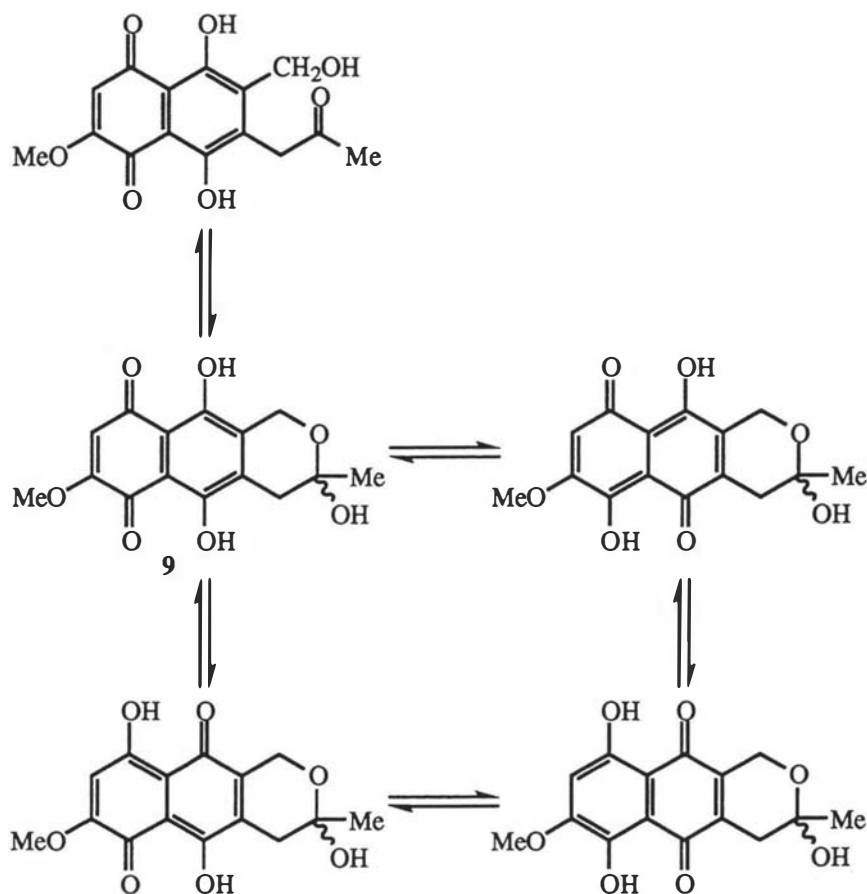
Scheme 3

due to the anomeric effect,[30] however there are several conflicting reports as to the configuration at C-3, C-4a and C-10a.[29,31,32] Both dihydrofusarubins are not very stable and can be transformed into numerous compounds, for example under alkaline conditions air oxidizes each of them to fusarubin **9**,[29] the tautomer of fusarubin initially formed subsequently rearranging. Additionally, **10** and **11** were produced[33] by *F. martii*.

10 : R=H
13 : R=Et
20 : R=Me

11 : R=H
14 : R=Et

5
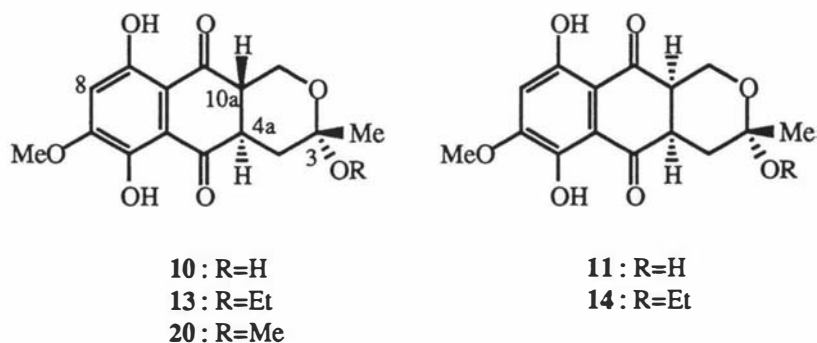
Also from *F. solani* were isolated[34] fusarubin ethyl acetal **12** and the diastereomeric dihydrofusarubin ethyl acetals **13** and **14** and their structures determined[31,35] by spectroscopic methods, chemical interconversion and comparison with previously isolated pigments. A natural ethyl acetal such as **12-14** is unusual and may be due to metabolic ethanol, although biological ethylation is more likely responsible.[31] **13** was also isolated from *F. martii*[33] along with various other acetals of fusarubin **9** and dihydrofusarubin A **10**, and it was suggested[29,33] that as only the dihydrofusarubins and their derivatives were formed when an acidic pH was maintained in the culture, they were the sole true metabolites of *F. martii*, with other fusarubins being derived from such precursors.

A new dihydrofusarubin ethyl acetal **15** was isolated[36] from *Nectria haematococca* (the sexual state of *F. solani*) after epoxidation of anhydrofusarubin **16** (*vide infra*) revealed the presence of another metabolite with the same R$_f$ value. Data obtained showed it to be very similar to **13**, differing only in the configuration at C-3.
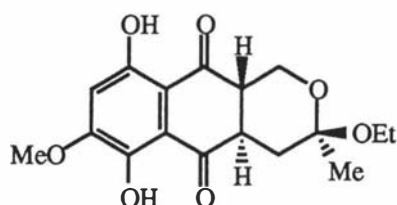
15

Anhydrofusarubin **16** was obtained[37] from root isolates of *F. solani* infected citrus trees exhibiting blight symptoms, but had been identified previously from the dehydration of fusarubin **9**.[20,23,27] It was also found along with **9** and other related pigments in cultures of *Neocosmospora vasinfecta* and *N. africana*.[38]
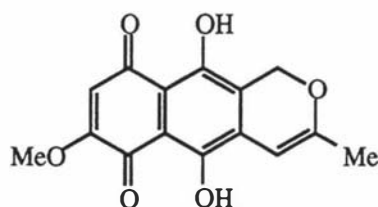
16

Further pyranonaphthoquinone pigments have been obtained[39] from another *Fusarium* species, *F. oxysporum*. 9-*O*-Methylfusarubin **17** and 9-*O*-methylanhydrofusarubin **18** were discovered in isolates of diseased fibrous citrus roots. The major pigment isolated was **17** with **18** and other naphthazarins being present in lesser amounts. 9-*O*-Methylfusarubin **17** was also isolated[40] from *F. moniliforme*, a major parasite of several

grain crops in humid or sub-humid zones.[41] The methyl acetal of **17** was also isolated from *F. oxysporum*[39] and *F. moniliforme*[42] but considered to be an artefact of methanol usage during workup.[39]

17   **18**
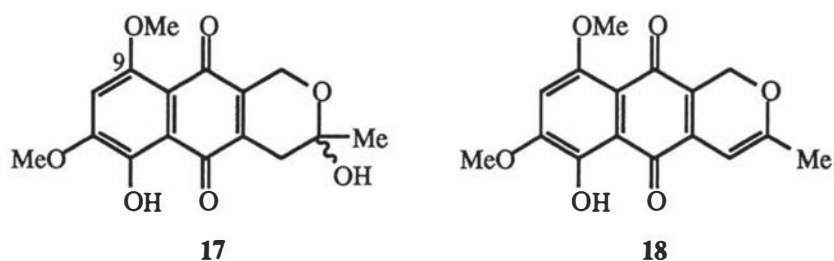
Isolation and identification of eleven naphthoquinones produced by *F. solani* was carried out by Tatum and Baker,[43] two of which, fusarubin methyl acetal **19** and dihydrofusarubin A methyl acetal **20** had not previously been reported as metabolites of *F. solani* (**19** had been formed earlier[20] from fusarubin **9** *via* acid and methanol). It was also reported that fusarubin **9** was a true metabolite of some strains of *F. solani* and not merely a conversion product of **10** and **11** under oxidative[29] or alkaline[31] conditions. This conflicts with results[33] obtained for the ethyl and methyl acetals of fusarubin (**12,19**) and dihydrofusarubin A (**13,20**) (*vide supra*).

In addition to the above examples, *O*-demethylanhydrofusarubin **21** was obtained[44] from *Gibberella fujikuroi* (*F. moniliforme*) and anhydrofusarubin lactone **22**[45] from *Nectria haematococca*, along with eight previously identified pigments. The structure of **21** was determined[44] by spectroscopy and methylation to give anhydrofusarubin **16**. No signal corresponding to the protons at C-1 were found for **22**, and 4-H and the hydroxyl of one phenolic group were deshielded with respect to **21**.[45] The methoxy was located as shown by analogy with cometabolites.

21   **22**
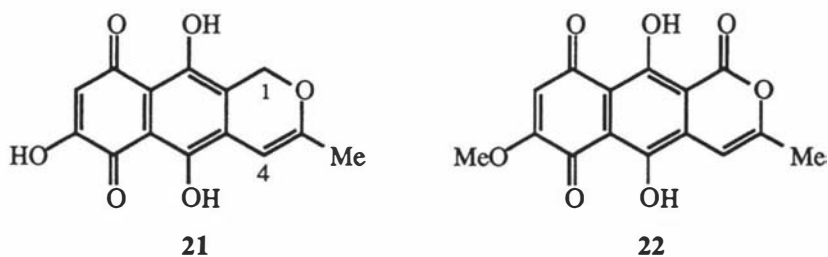
7-*O*-demethyl-6-deoxyfusarubin **23** and its anhydro derivative **24** were isolated[46] from a double mutant of *N. haematococca*. The compounds were identified on the basis of physiochemical data by comparison with known substances. The same group also isolated[47] 6-deoxyfusarubin **25** and 6-deoxyanhydrofusarubin **26** from a similar *Nectria* double mutant.

7

23 : R=H
25 : R=Me

24 : R=H
26 : R=Me
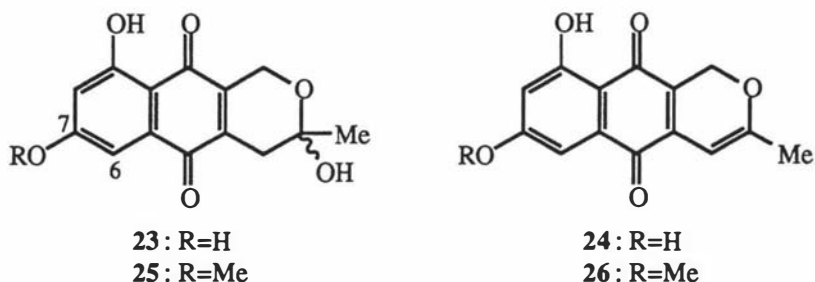
Quinone **27** was isolated[48] from *F. solani* as a major product from several runs on silica gel plates of crude pigment extracts. The proposed structure was based on nmr and mass spectral data of **27** and several derivatives of **27**. In various solvents 1-H and 1-OH exhibited differing ^{1}H nmr chemical shifts, and treatment with acid and methanol gave the corresponding methyl acetal. **27** was also reported shortly thereafter as isolated[49] from *N. haematococca* and named anhydrofusarubin lactol (compare **22**).

27
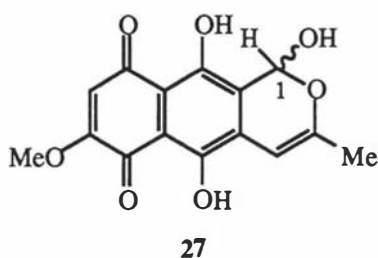
Torula herbarum cultures provided[50] herbarin **28** and anhydroherbarin **29** which differ from the *Fusaria* derived compounds detailed above in the arrangement and type of oxygenated substituents around the naphthoquinone nucleus.[50,51] The methoxy groups were assigned to positions 7 and 9 (versus 6 and 8) on biogenic grounds. Anhydroherbarin **29** does not appear to be an artefact, given that it can be formed by dehydration of **28**. Herbarin methyl acetal **30** was also obtained[52] from *T. herbarum*, and, like **28** and **29** its structure determined by spectroscopic means.[52]

28 : R=H
30 : R=Me

29
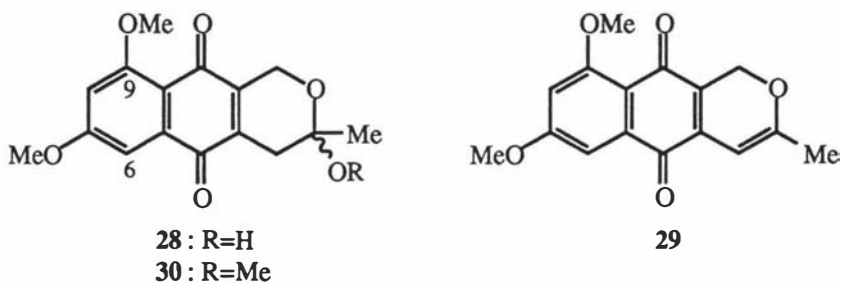
Marticin **31** and isomarticin **32**, isolated[24] from *F. martii*, differ from previous *Fusaria* structures by the presence of an additional C$_3$ chain forming a carboxylic acid substituted 1,3-dioxane. They are diastereomeric about C-2 and C-6[53] and not merely C-

8

4 as first thought,[24,43] 32 forming 31 *via* protonation and ketonization[53] after exposure to acidic silica.[43] In marticin 31 the dioxane ring adopts a predominantly chair conformation (figure 2) whereas in isomarticin 32 the favoured conformation can be represented as a twist boat, *J* values from ^{1}H nmr data[53] fully supporting these structures when compared to 2-alkyl-1,3-dioxanes.[54] The structures depicted (31,32) represented either enantiomer[53] until a later paper[32] used optical rotatory dispersion (ORD) data[55] to assign the absolute configuration for 31 as (2*S*,4*R*,6*R*) and (2*R*,4*R*,6*S*) for 32.
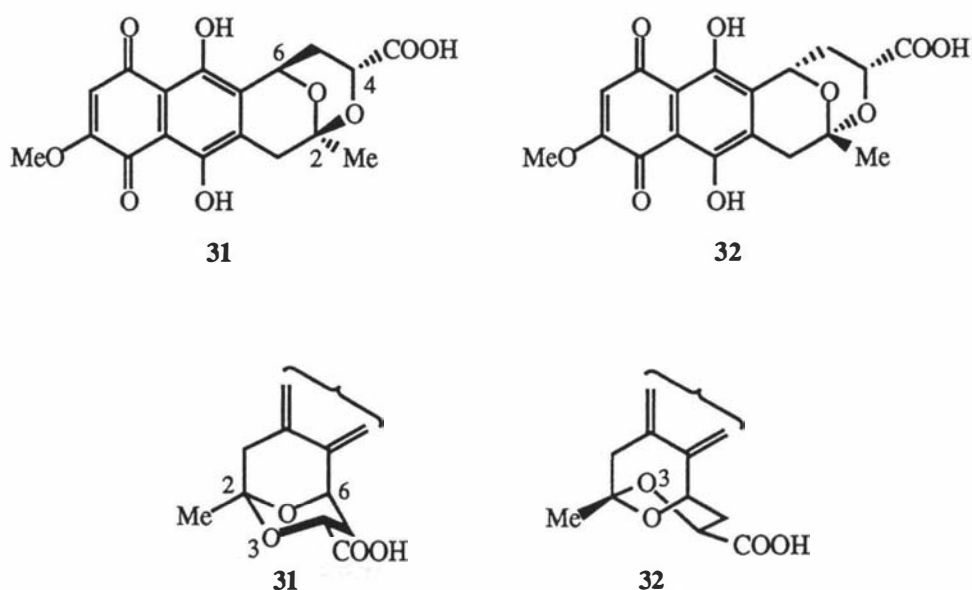
Figure 2

Twenty two naphthoquinone compounds isolated or derived from culture extracts of *F. solani* and *F. oxysporum* were examined for antimicrobial activity.[56] Fifteen exhibited antibiotic activity against *Staphylococcus aureus* and twelve were active against *Streptococcus pyogenes*. Six inhibited the plant pathogen *Corynebacterium poinsettiae*, however only weak antifungal activity was noted. Differing *Fusarium* strains produce these naphthazarin pigments in varying amounts and ratios - a correlation between toxin formation *in vitro* and pathogenicity has been noted.[57]

Fusarubin 9 has been reported to have antimicrobial activity against the yeast *Saccharomyces cerevisiae*,[58] the gram-positive bacteria *Streptomyces albus*,[58] *Mycobacterium phlei*,[22a] *Bacillus subtilis*[58,59] and *Staphylococcus aureus*,[22a,59] as well as phytotoxic[37,57] and antitumour[60] properties. 9 also inhibits cell division,[37] however it shows no activity against fungi and is only weakly toxic to gram-negative bacteria and moderately toxic to higher plants.[57]

The dihydrofusarubins 10 and 11 were found to behave as antibiotics towards the yeast *Candida albicans* and gram-positive bacteria *Bacillus subtilis, Streptococcus faecalis* and *Streptomyces albus*, however no activity was noted for gram-negative

bacteria.[58] This resistance of gram-negative species might be related to a lower permeability of the bacterial cell wall to *Fusarium* pigments.[42] **10** and **11** cause chlorosis and membrane disruption in citrus seedlings, and impair water and electrolyte balance.[61,62]

Fusarubin ethyl acetal **12** and dihydrofusarubin ethyl acetals **13** and **14** were shown to have antibacterial and antifungal activity, but at relatively low levels. Their activity increased according to the following sequence: fungi, yeasts and gram-negative bacteria, gram-positive bacteria, acid-fast bacteria.[34] The methyl acetals of fusarubin and dihydrofusarubin A (**19** and **20**) showed moderate cytostatic activity against mouse leukemia L1210 culture cells as well as moderate antibiotic activity against gram-positive bacteria and fungi.[33] Herbarins **28-30** are weakly antibacterial and antifungal: of the microorganisms tested, *Bacillus subtilis, B. mycoides* and *Pythium debaryanum* were most sensitive.[63]

The marticins **31** and **32** are the most phytotoxic of the naphthazarin group,[53,59,64-66] the difference in structure afforded by the 1,3-dioxane ring versus other members being proposed to account for this. They have been reported to be quite toxic to tomatoes and peas[65] with extensive damage to plant tissue at 8-30 mg/kg,[59] toxicity being increased by low pH (at high pH, *F. decemcellulare* produced[67] a dimeric naphthoquinone aurofusarin **33** with concomitant absence of monomeric pigments such as fusarubin **9** and anhydrofusarubin **16**). Isomarticin **32** was rapidly detected in pea shoots after application (versus other naphthazarin toxins which were only transported poorly), and after 4h the compound was distributed equally throughout the plant.[38] Hence some of its potency[61,62] lies in the ease of translocation throughout the plant tissue. The main mechanism of action of the marticins in tissues of higher plants remains to be determined, inhibition of malate or citrate dehydration in the citric acid cycle is possible.[57] Organellar membrane disruption (for example chloroplasts) has been observed for isomarticin **32** as well as enhanced permeability of pea tissue and increased electrolyte leakage of pea seeds.[68,69]

33

10
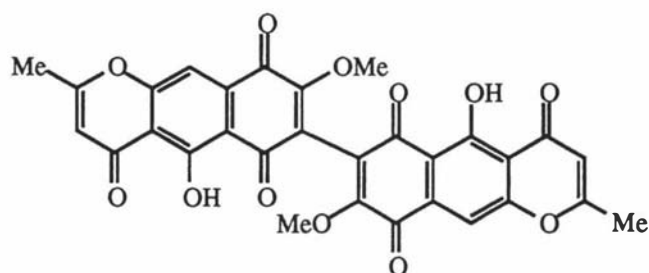
Naphthoquinones interfere in various ways with the metabolism of microorganisms and higher plants, for example by inhibition of the anaerobic decarboxylation of pyruvate (an α-keto acid) through a reaction with coenzyme thiamine pyrophosphate.[70] This enzyme hindrance gives rise to retarded seed germination and root growth in plants, however the inhibition of bacterial growth and in particular the destruction of tissues of higher plants depends on other mechanisms of action. The mechanism of phytotoxic effects of fungal naphthoquinone metabolites may be due to disturbances in metabolism resulting from intracellular oxidation of NADH and NADPH, the formation of toxic oxygen species such as superoxide and hydrogen peroxide (*via* electron transfer by pigments from reduced enzymes to oxygen[71]), or semiquinone forms of the pigments inhibiting metabolism of DNA, RNA and other biopolymers.[72] Quinone pigments have been suggested to bind close to NADH and ferricyanide sites on a mitochondrial reductase enzyme and thus disrupt cellular processes.[73]

The mechanism of resistance of *F. decemcellulare* to naphthazarin pigment metabolites has been studied.[74] Data from spectroscopic analysis suggested that resistance was based on two mechanisms: the increase in the intracellular content of superoxide dismutase (*vide supra*) and pigment transformation by C-7 methoxy group demethylation, the *O*-demethyl derivatives being unable to be reduced by electron transport enzymes due to a decrease in their redox potential.[74]

Naphthazarin toxicity is reduced by certain metal ions[59,64,75] and organic acids,[64,75] the degree of detoxification varies with the toxin and the compound added. From *Pisum* (pea) trials, copper ions are most beneficial and nullify the effects of the phytotoxic marticins **31** and **32** against bacteria and higher plant tissues.[57] This detoxification is probably due to the compounds chelating with the multivalent metals.[26]

1.1.2 Monomeric Quinones

Thysanone **34** was isolated[76] from *Thysanophora penicilloides* after screening of fungal extracts. The skeletal system was assembled based on long range 2D nmr experiments, and the structure and relative stereochemistry confirmed by single crystal X-ray analysis of the monomethyl ether.[76] **34** inhibits the human rhinovirus 3C-protease enzyme and so is a possible chemotherapeutic agent for the common cold.

34
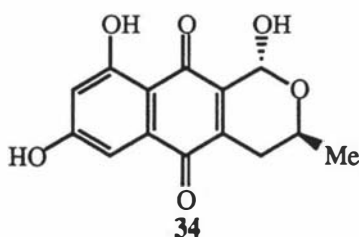
Ventiloquinones A-E, **35-39**, and G **40** were isolated[77] from the acetone extract of the root bark of an Indian plant, *Ventilago maderaspatana*. They are structurally similar to the eleutherins, with variations in the type and arrangement of oxygenated substituents about the terminal aromatic ring. Comprehensive spectroscopic data and comparison with eleutherins **5** and **6** allowed structure assignment for this group of compounds. **35** and **36** have a 1,3-dioxolane ring fused to the aromatic ring, with **36** being the dimethyl derivative of **35**. Comparison of **35** and **36** with eleutherin **5** [1]H nmr data showed excellent agreement, establishing the *cis* stereochemistry of the methyl groups across the pyran ring and revealing no benzenoid or quinonoid protons. Methylation of **35** gives **36** and demethylation of them both results in the same naphthazarin, also confirming the structure as illustrated. Ambiguity exists however as to the positions the methoxy and hydroxyl group occupy about the benzene ring of **35**.
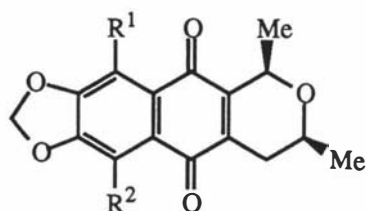
	R[1]	R[2]
A 35	OH(OMe)	OMe(OH)
B 36	OMe	OMe
M 42	OH	OH
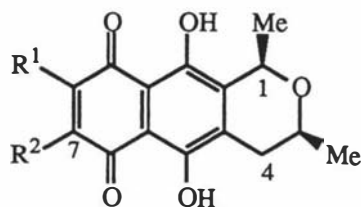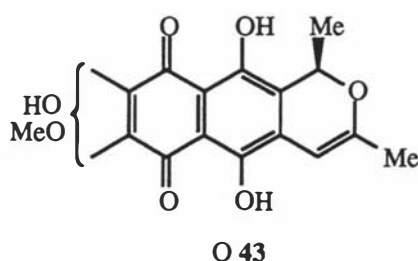
	R[1]	R[2]
C 37	OH(OMe)	OMe(OH)
D 38	OMe	OMe
G 40	H	OH
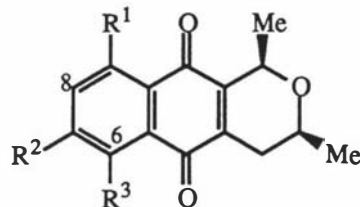
	R[1]	R[2]	R[3]
E 39	OMe	OMe	OMe
L 41	OH	OMe	H

Ventiloquinones C **37** and D **38** both possess a naphthazarin nucleus, with **38** being the dimethyl derivative of **37**. The ^{1}H nmr spectrum of **37** showed a mixture of two isomers whose Rf values were too close to permit separation, and thus *both* structures depicted are correct (versus one only for **35**). Diazomethane methylation[78] of **37** gave **38**: using dimethyl sulphate/potassium carbonate resulted in two tetramethoxy compounds, due to

the tautomerism inherent in the naphthazarin system.[27,28] Ventiloquinone C **37** is also found in *V. bombaiensis*.[79]

Ventiloquinone E **39** has ^{1}H nmr data resembling 6-hydroxy-7-methoxyeleutherin **8**. The position of the β-methoxy group is   established as C-7 and is preferred on biogenic grounds. The chemical shift of the aromatic proton indicates it is located between two oxygen functions. *J* values for G **40** between 1-H and 4-H are smaller than those of **39**, attributable to the partial benzenoid character of the adjacent ring.[28] The position of the β-hydroxyl group at C-7 is again assumed. Attempts to synthetically correlate **39** and **40** were unsuccessful[77] due to epimerization during *peri*-demethylation of **39** with boron tribromide (*vide infra*), but later workers[80] produced the methyl ether of **40** from **39** with aluminium trichloride.

The root bark of *V. goughii*[81a] produced ventiloquinones L **41**, M **42** and O **43**, while Fijian *V. vitiensis*[81b] gave **41** and **42**. As with **35-40**, extensive nmr analysis and comparison with known compounds allowed structure determination for these quinones. The biosynthetically unlikely 6-hydroxy-8-methoxy isomer was ruled out for L **41** by the formation from **41** of 7-methoxyeleutherin **7** by methylation. **41** has also been reported[82] in *Araliorhamnus vaginata* (Rhamnaceae). **42** has a structure very similar to both **35** and **36** which contained a naphthazarin nucleus. No benzenoid or quinonoid protons were noted, and methylation of **42** gave **36**. Ventiloquinone O **43** is very similar to **37**, a 3H singlet at δ4.14 locating the methoxy group adjacent to an hydroxyl on the quinone ring.[28] Unlike the previous ventiloquinones, **43** is an anhydro derivative as evidenced by ^{1}H nmr data for pyran ring protons versus anhydrofusarubin **16**.

Kalafungin **44** was isolated[83] from the fermentation broth of *Streptomyces tanashiensis* and preliminary studies (UV, IR, $[\alpha]_D$) carried out. The structure of **44** and relative configuration at the three stereocentres was determined by X-ray crystallography.[84] Chemical modifications[85] of **44** and comparison of ^{1}H nmr data of these derivatives confirmed the structure as postulated. The absolute stereochemistry of **44** was found[85] to be (3a*R*,5*R*,11b*R*) by comparison of optical rotatory dispersion (ORD) curves[5,86] and ^{1}H nmr data[8] of eleutherin **5** and isoeleutherin **6**. **44** has also been isolated[87] from an alkalophilic actinomycete *Nocardia dassonvillei*, a rare case where the producing organism is not of the genus *Streptomyces*.

44
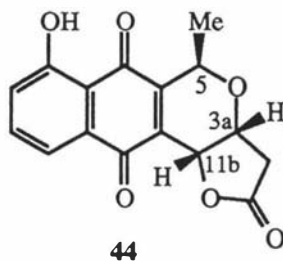
Kalafungin **44** was shown to be inhibitory *in vitro* against a variety of pathogenic fungi, yeasts, protozoa and both gram-positive and gram-negative bacteria.[88] It was also found to inhibit platelet aggregation[89] and showed a strong cytotoxicity against L5178Y mouse leukemic cells *in vitro*.[87] Its antithelmintic activity[90] was affected by various natural sugars, with glucose increasing potency. Reduction potentials of various compounds including **44** were measured,[91] and the possible relation of these to its mode of action (*via* oxyradicals, refer page 11) discussed.

A variant of kalafungin **44**, named tetrahydrokalafungin **45**, was isolated[92] from a wild type strain of *Streptomyces tanashiensis* and also bacterial mutants that did not produce **44**. A gene cluster coding for kalafungin biosynthesis was introduced into the microorganisms and the transformants then produced not only kalafungin **44** and dihydrokalafungin **46** (*vide infra*) but also **45**. Structural analysis (UV, ms, nmr etc) determined that the C4a-C10a double bond had been saturated in this compound (**45**) which was less coloured than **46**.

45

YS-02931K-β/dihydrokalafungin/
4-deoxykalafunginic acid **46**
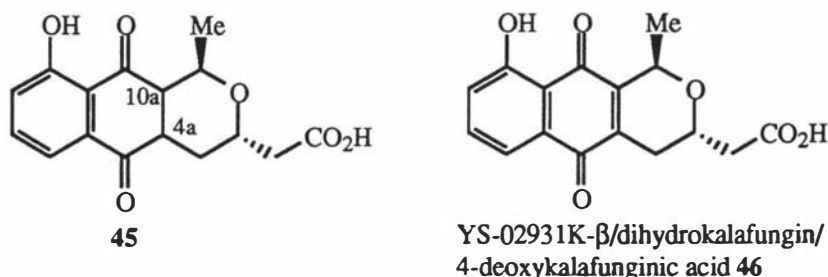
Nanaomycins A **47**,[93,94] B **48**,[93,94] C **49**[95] and D **50**[96] and E **51**[97] were isolated from *Streptomyces rosa* var. notoensis, a soil borne bacterium. An infra-red spectrum indicated A **47** and B **48** contained a quinone group[93] and it was found that **47** and **48** could be interconverted in alkaline solution. A UV spectrum of **47** suggested a juglone moiety as did the IR spectrum, which showed a hydrogen bonded quinone carbonyl group and a free carboxylic acid.[98] Methylation of **47** using methyl iodide/silver(I)oxide gave a dimethyl derivative **52**, confirming the presence of a phenolic hydroxyl group and a carboxyl group in the molecule. The dihydropyran ring and substituents were established by ^{1}H nmr comparison, again with eleutherin **5**,[8] the C-1 methyl and the C-3 acetic acid groups being axial and equatorial respectively.[98] The hydroxyl group was placed at C-9 versus C-6 based on the results of a ^{13}C nmr labelling experiment.[98]
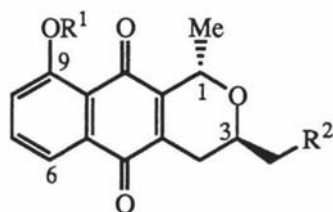
nanaomycin A **47** : R^1=H, R^2=CO$_2$H

nanaomycin C **49** : R^1=H, R^2=CONH$_2$

52 : R^1=Me, R^2=CO$_2$Me

nanaomycin αA **53** : R^1=H, R^2=CO$_2$Me

nanaomycin βA **56** : R^1=H, R^2=CH$_2$OH
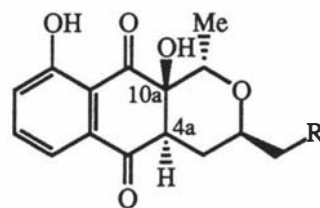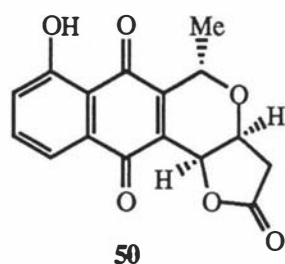
nanaomycin B **48** : R=CO$_2$H

nanaomycin αB **54** : R=CO$_2$Me
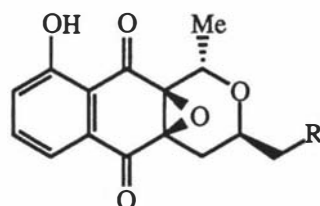
nanaomycin E **51** : R=CO$_2$H

nanaomycin αE **55** : R=CO$_2$Me

nanaomycin βE **57** : R=CH$_2$OH

50

Nanaomycins B **48** and E **51** are C4a,C10a-dihydroderivatives of A **47**. The UV spectrum of B **48** indicated the C4a-C10a bond was saturated, and the ^{13}C nmr chemical shifts of C-4a and C-10a had moved considerably upfield. In cold dilute sodium hydroxide, B **48** could be converted to A **47**, confirming the structure as resulting from the *trans* addition of water across the double bond. The orientation and stereochemistry about the dihydropyran ring was determined as for **47** by ^{1}H nmr and decoupling experiments.[98] Nanaomycin E **51** is the epoxy derivative of A **47**. The molecular formula (*via* hrms) indicated one more oxygen than **47**, and the ^{13}C nmr shifts of C-4a,10a were, like **48**, upfield of **47**. This combined with higher wavenumbers in the quinone IR spectrum suggested a 2,3-epoxy-1,4-naphthoquinone.[97] Various chemical transformations of **51** certified the structure as an epoxide (scheme 4).

Nanaomycin C **49** is the amide of A **47**. Elemental analysis and mass spectrometry showed a nitrogen atom, and due to the molecules neutrality an amide was suspected. The ^{1}H nmr spectrum for **49** was nearly identical to **47** except for the absence of a CO$_2$H proton, instead a broad NH$_2$ signal was present. Nanaomycin D **50** possessed the same characteristics as kalafungin **44**, but the circular dichroism (CD) spectrum displayed a negative Cotton effect,[55] showing it to be enantiomeric to kalafungin **44**.[96] From this and the chemical transformations described (scheme 4) the absolute configurations could be assigned to **47-49**. D **50** can be envisaged as resulting from the closing of the -CH$_2$CO$_2$H side chain of nanaomycin A **47**.

15
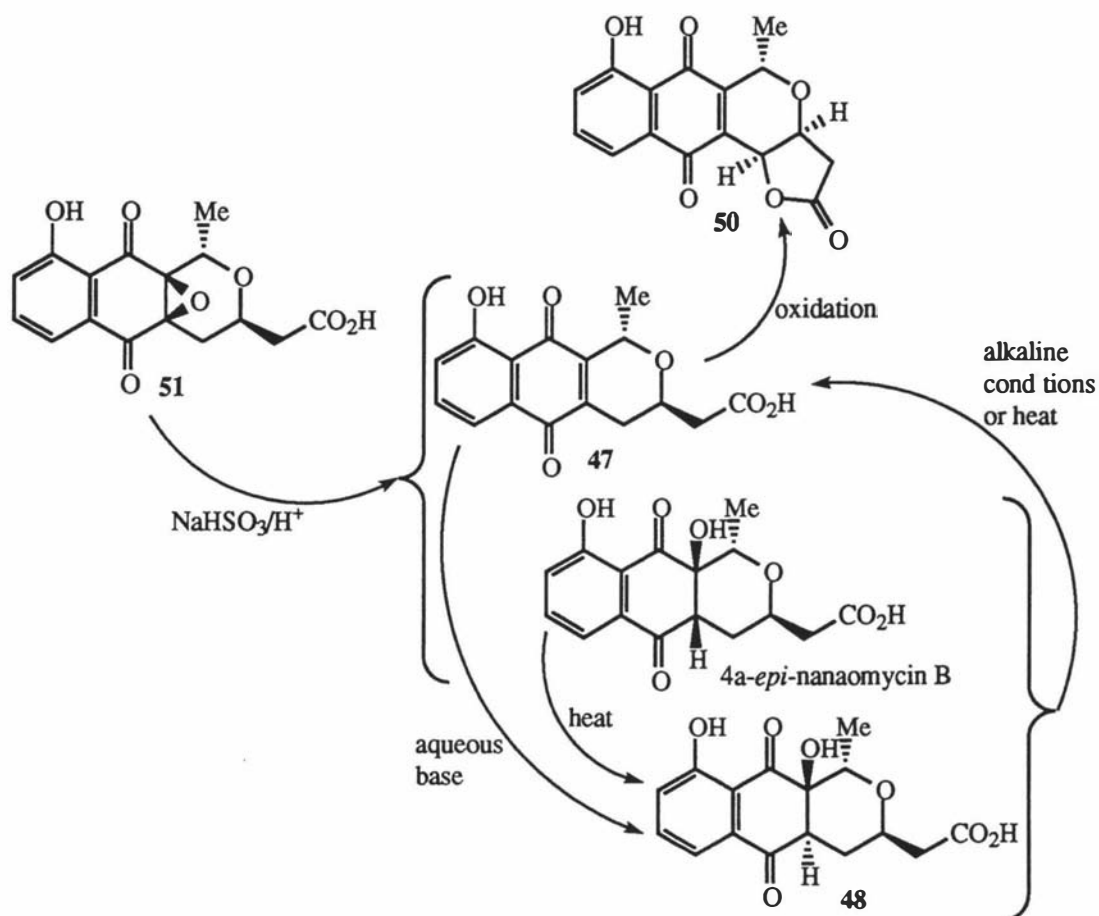
Scheme 4

Nanaomycins A **47** and B **48** inhibit mainly mycoplasmas, fungi and gram-positive bacteria.[93] It is possible that **48** itself has no activity, instead being activated by non-enzymatic conversion to **47**.[94] **47** has been combined with L-cysteine.HCl for a stable antimicrobial topical application,[99] used to treat bovine dermatophytosis,[100] and attached to porphyrins to form fluorescent chromophores for the treatment and diagnosis of cancer.[101]

Nanaomycin E **51** has a weaker antimicrobial activity against gram-positive bacteria than **47**.[97] **49** has a similar spectrum of activity to **47** and **48** but is weaker than **47** against fungi and mycoplasmas.[96] Derivatives of **47** and **48** synthesized from isolated material[98] indicated that the phenolic hydroxyl and the carboxylic acid group were important for antimicrobial activity. Acetylation of the phenolic hydroxyl group did not affect potency against bacteria tested, however methylation destroyed it. The methyl ester of **47** (**53**) showed reduced activity.[98] Nanaomycins A **47**, D **50**, kalafungin **44** and some synthetic analogues were tested[102] against various microorganisms for antibacterial properties, the results showing that the naphthoquinone and lactone portions were required for strong activity.

16

The mode of action of nanaomycin A **47** against gram-positive bacteria was investigated[103] and found to be *via* interference with cytoplasmic membranes and inhibition of oxidative phosphorylation, with secondary inhibitory effects upon protein, nucleic acid and cell wall peptidoglycan biosynthesis. In a gram-negative marine bacterium, it was found[104] that **47** and **50** were reduced by the enzyme systems of the organism, and these reduced forms were quickly autoxidized by molecular oxygen to give superoxide radicals (**50** was found to be more effective than **47**). Thus the antibacterial activities of the two nanaomycins under study were correlated to their ability to produce $O_2^{\underline{\cdot}}$ at the cell membrane.

Fermentation of a *Nocardia* species produced[105-107] YS-02931K-β **46**, the enantiomer of nanaomycin A **47** (**46** is also known as dihydrokalafungin - *vide supra*). **46** exhibited high antimicrobial activity against gram-positive bacteria,[105] for example *Bacillus subtilis*, as well as dermaphytes[105] and fungi.[107]

OS-3966-A, a compound with the same structure (stereochemistry unspecified) as nanaomycin A **47** was produced[108] by an aerobic culture of *Streptomyces rosa* notoensis, and was effective against mycoplasmas and gram-positive bacteria,[108] as well as skin disorders in cattle.[109] OS-3966-B[110] was also isolated along with OS-3966-A and had the molecular formula $C_{16}H_{16}O_7$. It had chemical characteristics and biological activity very similar to that of OS-3966-A, a benzoisochromanquinone structure being likely for this compound.

Five new nanaomycin type antibiotics were produced[111] by a new soil isolate from Yonago city in Japan. A strain of *Streptomyces rosa* var. notoensis (strain OM-173), which differed from the original bacterium only in culture characteristics, yielded OM-173 αA **53** (page 15), αB **54**, αE **55**, βA **56** and βE **57**. The components were active against mycoplasmas and to a lesser extent fungi,[111] however all displayed weaker activity than nanaomycin A **47**. Bioactivity results for **53** and **56** indicated that, as noted earlier, modification of the carboxyl group (to CO_2Me) lowers antimicrobial activity. A later patent[112] detailed the production of OM-173β_1 from the same microorganism, which possessed the same structure as **56** but unspecified chirality. Nanaomycins A **47** and βA **56** were produced[113] from *Streptomyces roseofulvus*, an organism known to produce deoxyfrenolicin **58** and frenolicin B **59** (*vide infra*). Thus two types of benzoisochromanquinone antibiotics with opposite configurations at C-1 and C-3 were produced by the same organism.

The frenolicins **58-60** were obtained from various *Streptomyces* species and are similar in structure to kalafungin **44** but bear a propyl group instead of a methyl at C-1. Frenolicin **60** was isolated[114] from *Streptomyces fradiae* and the structure deduced from physical data.[115,116] Acetate, methyl and dimethyl derivatives of **60** indicated a nanaomycin-type structure with a phenolic hydroxyl group and a free carboxylic acid.

Hydrogenation and reoxidation of **60** produced a compound which was named deoxyfrenolicin **58**, the ease of this transformation suggesting a juglone-2,3-epoxide moiety. A mass spectrum of **60** showed a M-43 peak characteristic of an *n*-propyl group, and ^{1}H nmr revealed the substituents about the dihydropyran ring from splitting patterns and δ-values. Coupling constants showed 1-H to be pseudo-equatorial and 3-H pseudo-axial. The change in the ^{1}H nmr signal for 1-H upon acetylation of the phenolic hydroxyl group indicated substitution at C-9 versus C-6, the signal for C-4 protons remaining unchanged. The epoxide ring stereochemistry (figure 3) was found from the readily formed *trans*-diaxial chlorohydrin **61**, which reformed **60** upon base treatment. The ^{1}H nmr spectrum of **61** still showed 3-H to be axial, thus the epoxide ring and 3-H in **60** were *trans* to each other. It was suggested[32] that the frenolicins have a (1*S*,3*R*) configuration due to the coproduction of nanaomycin A **47** and deoxyfrenolicin **58** (*vide supra*), despite the opposite signs of their respective Cotton effects.[55]
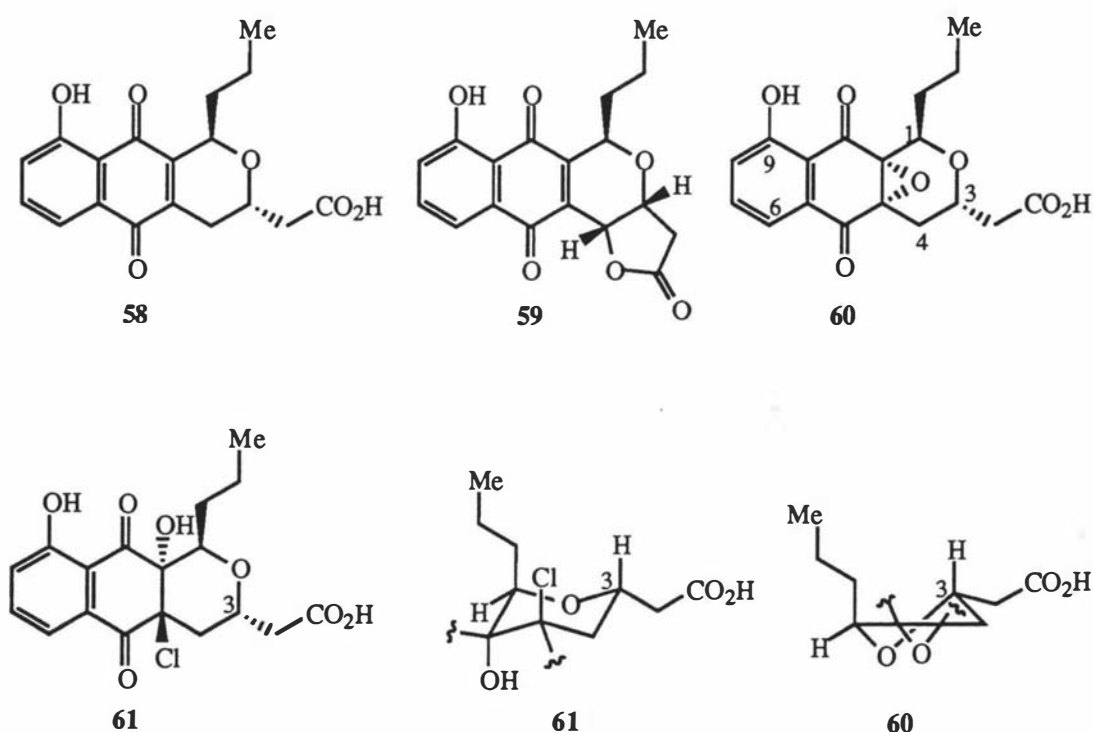
Figure 3

Frenolicin B **59** was isolated from *S. roseofulvus*[117] along with deoxyfrenolicin **58** (previously prepared[115,116] from frenolicin **60**). Spectroscopic data for **59** indicated a structure very similar to **58**, but with **59** being less polar than **58** and the IR spectrum not showing a carboxylic acid group, a lactone ring was suggested. Conversion of **58** to **59** by aerial oxidation in pyridine overnight, in a manner analogous to nanaomycin A **47** and D **50** (*vide supra*), confirmed the structure proposed.

18

Frenolicin **60** shows weak antibacterial activity.[116] Deoxyfrenolicin **58** exhibits significant inhibitory activity *in vitro* against a variety of fungi including ringworm infections in guinea pigs.[115] **58** and **59** are active against mycoplasmas and fungi with **59** showing greater inhibition against fungi and **58** greater inhibition against mycoplasmas.[117] **59** is an excellent anticoccidial agent in poultry[118] (as shown by numerous patents filed), comparable to some of the polyether antibiotics[119] and has been used as a growth promotant in swine.[120] A synergistic composition comprising **59** and a polyether antibiotic had a much higher efficacy against the poultry paramecium *Eimeria tenella* than either component alone.[121] Some derivatives[118,122] of **59** were also shown to be good coccidiostats. **59** strongly inhibits platelet aggregation,[89] more so than selected other members of the pyranonaphthoquinones. Deoxyfrenolicin **58** was devoid of anticoccidial activity,[118] however it stimulated sugar utilization in isolated adipose (fat) cells[123] and significantly inhibited tyrosine hydroxylase activity in rats.[124]

The arizonins **62-67** differ from the simpler antibiotics like kalafungin **44** and frenolicin **60** in that they possess a 7,8-dioxygenated nucleus. They were isolated[125,126] from the fermentation broth of *Actinoplanes arizonaensis*, and vary from one another by the degree and position of *O*-methylation on the aromatic ring, and whether the aliphatic portion of the molecules is present as a γ-lactone or acyclic methyl ester.
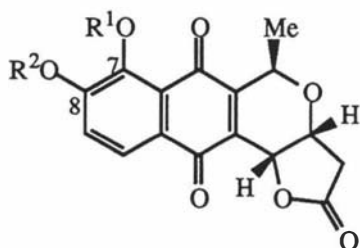
Arizonin A1 **62** : R^1=Me, R^2=H   Arizonin A2 **65** : R^1=Me, R^2=R^3=H
Arizonin B1 **63** : R^1=H, R^2=Me   Arizonin B2 **66** : R^1=H, R^2=Me, R^3=H
Arizonin C1 **64** : R^1=R^2=Me   Arizonin C3 **67** : R^1=R^2=R^3=Me

Arizonin B1 **63** was found by ^{1}H nmr comparison with kalafungin **44** to have close structural similarity. NOE experiments on **63** established the relative stereochemistry about the aliphatic portion of the molecule and placed the methoxy group at C-8. A COSY experiment determined the relative orientation of the hydroxynaphthoquinone to the aliphatic system as **63** and not **68**. The absolute stereochemistry for **63** was determined by a comparison of ORD curves with nanaomycin D **50** and kalafungin **44**, B1 **63** matching **44**.[125]
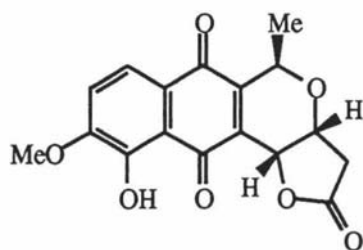
68

Arizonin A1 **62** is isomeric with B1 **63** (*via* hrms) and the ^{13}C nmr spectrum indicated neither quinone carbonyl was hydrogen bonded to an hydroxyl group, hence structure **62** was assigned. This was confirmed by a single crystal X-ray diffraction analysis.[125] A2 **65** was found to possess two methoxy groups and varied in the aliphatic carbon signals (^{13}C nmr) from A1 **62**. This, coupled with an IR spectrum showing an ester functionality versus a γ-lactone led to **65**. Arizonin C1 **64** had a molecular formula established by hrms, two methoxy groups present in nmr spectra and a γ-lactone in an IR spectrum, leading to structure **64**. Arizonin C3 had four methoxy peaks in the ^{1}H nmr and an ester group in the IR spectrum, indicating structure **67**.

The arizonins were found to exhibit antimicrobial activity against pathogenic strains of gram-positive bacteria,[126,127] two members in particular (**62, 63**) exhibiting moderate to potent *in vitro* activity.

Medermycin **69** was isolated[128] as a monohydrochloride from a strain of *Streptomyces tanashiensis* and the structure shown[128-130] to contain the same skeleton as kalafungin **44**, with an amino sugar moiety on the naphthoquinone nucleus at C-8. However Tanaka *et al.* later reported the isolation[131] and structure[132] of lactoquinomycin, and suggested that medermycin **69** could be an isomer of lactoquinomycin on the basis of their apparent different physiochemical properties and biological activities. The synthesis of **69** by Tatsuta *et al.*[133] allowed samples of natural and synthetic **69** to be compared directly with lactoquinomycin. All three materials were shown to have identical physiochemical and spectral data, confirming the structural identification of both antibiotics. In the case of lactoquinomycin,[132] FAB mass spectrometry indicated an MH$^+$ ion of 458 and UV and IR spectra suggested a derivative of juglone. Comparison of ^{1}H nmr data with that of kalafungin **44** revealed one of the aromatic positions was substituted. *J* value data along with coupling between the phenolic hydroxyl group and 2'-H showed C-8 to be the attachment point. The sugar structure was elucidated by ^{1}H nmr comparison with related compounds.[134]

Medermycin **69** is highly active against gram positive organisms,[131] including many species of *Staphylococcus* and *Bacillus*,[128] however all gram negative bacteria tested showed little or no response as did fungi.[128] **69** was effective against neoplastic cells *in vitro*, antibiotic resistant cell lines of L5178Y lymphoblastoma and Ehrlich
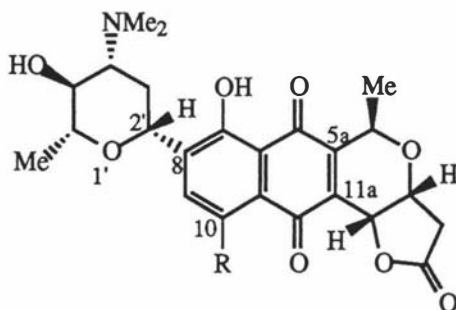
medermycin/lactoquinomycin/lactoquinomycin A **69** : R=H
medermhodin A **72** : R=OH

carcinoma in mice.[131] It also showed 50% inhibition of human leukemia K 562 cells.[135] Platelet aggregation is inhibited by medermycin **69**,[89] as is the biosynthesis of DNA, RNA and protein in cells.[136] This latter effect[136] is due to superoxide radical generation by **69** in cell lysate, as discussed previously for the naphthazarins.[71,72]

S. tanashiensis IM8442T produced[137] a novel antibiotic together with lactoquinomycin **69**. **69** was the major component isolated and the name lactoquinomycin A adopted to distinguish it from the new material, designated lactoquinomycin B **70**. Detailed spectroscopic studies, including high field ^{1}H and ^{13}C nmr spectroscopy and comparison with **69**, elucidated **70** as the epoxide derivative of **69**. Physiochemical properties of **70** were similar to **69**, however large upfield shifts in the C-5a and C-11a ^{13}C nmr signals versus **69** and the change in chemical shifts for 3a-H and 11b-H, coupled with the molecular formula containing an extra oxygen (mass spectrometry), suggested an epoxide between C-5a and C-11a in a manner similar to frenolicin **60**. The stereochemistry about these centres has yet to be determined.

70
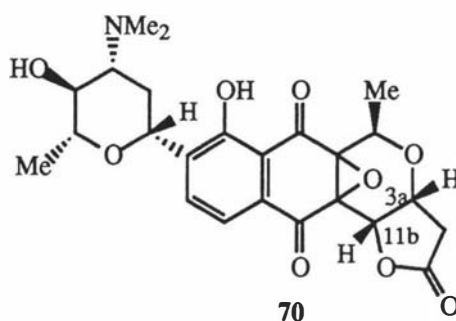
Lactoquinomycin B **70** inhibited gram-positive bacteria but possessed no significant activity against fungi.[137] It showed cytotoxicity against a range of human and murine tumour lines and was more effective against adriamycin and bleomycin resistant cell sublines than the parental cell line.[137]

Development of molecular cloning systems in *Streptomyces* has allowed the isolation of biosynthetic genes from these microorganisms.[138,139] Transfer of gene

21

sequences coding for actinorhodin **71** biosynthesis (*S. coelicolor*, see pages 27 and 51) into a medermycin **69** producer (*Streptomyces* AM-7161) resulted in production[129,140] of the novel hybrid antibiotics mederrhodin A **72** and mederrhodin B **73**. Field desorption mass spectrometry and elemental analysis revealed **72** to be hydroxymedermycin. The position of the hydroxyl group was determined to be C-10 by UV and ^{1}H nmr studies.[129,140] Mederrhodin B **73** was oxidized by various means to give a product with the same spectral properties as **72**,[129] in a manner similar to the conversion of nanaomycin A **47** to D **50**, thus confirming its structure as **73**.

73
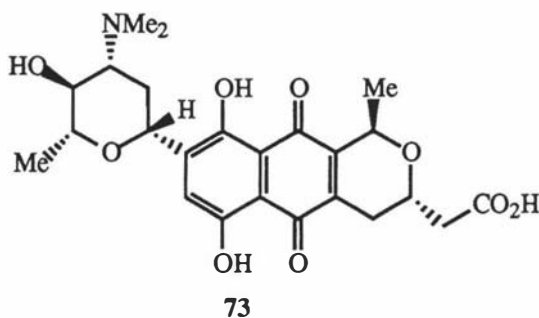
Mederrhodin A **72**, although active against gram-positive bacteria, was less active than medermycin **69**, however both compounds shared similar activities against gram-negative rod bacteria.[129] **72** was a poor inhibitor of platelet aggregation[89] versus **69**, and mederrhodin B **73** was inactive against all bacteria tested.[129]

An antifoliate structurally related to medermycin **69** was found[141] in a soil isolate and termed AM-8402. From spectroscopic analysis it was determined to possess a nanaomycin D **50** moiety and a deoxy sugar, and inhibited a reductase enzyme in bacteria but showed no antitumour activity.[141] An antibiotic termed K-73A was produced by *S. tanashiensis* K-73[142a,b] and *Streptomyces* KW-75[142c] and separated from the crude complex of antibiotics (designated K-73) *via* crystallization. K-73A was a basic compound isolated as the hydrochloride salt, and had the molecular formula $C_{24}H_{29}NO_8$,[142b,c] analogous to a dihydromedermycin derivative, however no structure was proposed. It was effective against several gram-positive bacteria (*Staphylococcus, Sarcina, Bacillus* and *Shigella*[142b,c]) and has been used as an anticoccidial agent.[142d]

The antibiotic granaticin **74** and related compounds have been isolated from several species of *Streptomyces*, and are distinguished by the attachment of two oxygen containing heterocycles at each side of a naphthazarin nucleus. Granaticin **74** (granaticin A or litmomycin[143]) has been isolated from *S. olivaceus*,[144] *S. violaceoruber*,[145] *S. litmogenes*[143] and *S. thermoviolaceus* WR-141,[146,147] and identified by nmr and chemical degradation studies[148] as well as X-ray crystallography.[149] The structure is

shown upside down versus previous isochromanquinones in keeping with the majority of
the published work on **74** and its analogues (save for biosynthetic data, see page 48).
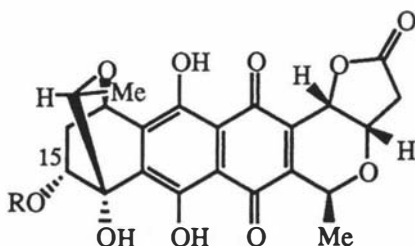
Granaticin/Granaticin A/Litmomycin/Granatomycin C **74**: R=H
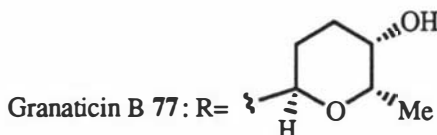
Granaticin B **77**: R=

The naphthazarin based structure was determined by UV spectroscopy, the colour
of an alkaline solution of **74** and the absence of aromatic protons, which indicated the
central portion was flanked by side chains or rings. Ozonolysis and diazomethane
methylation of derivatives of **74** yielded two fragments whose structures (figure 4) were
indicative of being derived from granaticin **74**, the two fused heterocycles being a 2-
oxabicyclo[2.2.2]oct-5-ene system and a pyrano-γ-lactone ring. The former structure is
present in the simpler quinone sarubicin A **75**.[150] The points of attachment of the
oxabicyclo ring to the aromatic nucleus were resolved by X-ray crystallographic
analysis[149] of a tri-*O*-acetylmono-iodo-*O*-acetyl derivative **76** of granaticin, which also
confirmed previous findings.
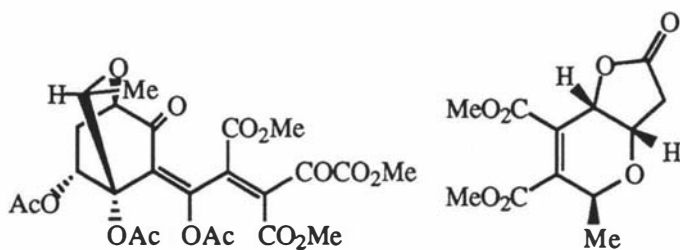
Figure 4
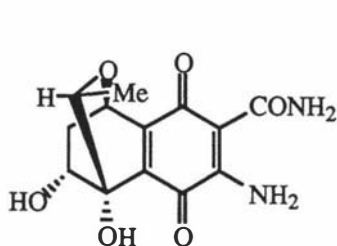
Sarubicin A/U-58,431 **75**
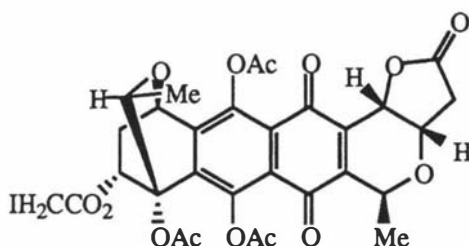
76

Granaticin B **77** was isolated (along with **74**) from *S. violaceoruber*[145,151] and actinomycete *globispororoseus granaticus* var. nov,[152] and upon acid hydrolysis gave granaticin **74** and L-rhodinose.[145] Repeating this procedure on granaticin B tetraacetate provided the compound used for X-ray structure determination (*vide supra*), and as the iodoacetoxy group was located at C-15, **77** was shown to be the α-15-L-rhodinoside of **74**.[145]

Dihydrogranaticin **78** has been produced by *S. thermoviolaceus* WR-141[147] and *S. lateritius*[153] (*vide infra*). Mass spectral and analytical data showed two extra hydrogens in the molecule versus **74**, and chemical interconversion of **74** and **78** by hydrogenolysis and oxidation confirmed dihydrogranaticin as the open chain form **78**. Also obtained[147] were two related anthraquinone pigments **79** and **80**, which can be thought of as arising by opening of the ether bridge in the oxabicyclo moiety. The upfield portions of the ^{1}H nmr spectrum for each pigment were nearly identical to that of the dihydropyran-γ-lactone fragment of **74**.[147] Dihydrogranaticin B **81** was found[154] as a minor constituent along with **74** and **78** in culture extracts of *S. violaceoruber*, the material being identical to that produced by platinum catalysed hydrogenolysis of **77**.
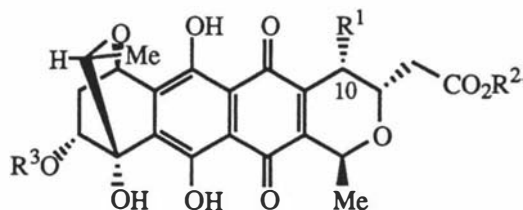
Dihydrogranaticin **78** : R^1=R^2=R^3=H
Granaticinic acid **82** : R^1=OH, R^2=R^3=H
Granaticinic acid methyl ester **84** : R^1=OH, R^2=Me, R^3=H
Dihydrogranaticin methyl ester **83** : R^1=R^3=H, R^2=Me
10-deoxy-10S-(N-acetylcysteinyl)-granaticinic acid **85** : R^2=R^3=H, R^1=
Dihydrogranaticin B **81** : R^1=R^2=H, R^3=
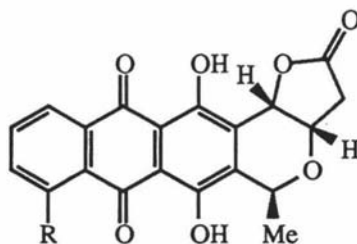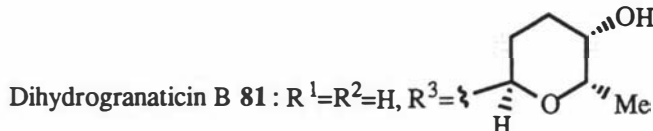
79 : R=COCH$_3$
80 : R=CHOHCH$_3$

Streptomyces sp. XT-11989 produced[155] a mixture of granaticin **74** and granaticinic acid **82**. The acid differs from dihydrogranaticin **78** by an hydroxyl group at C-10 and rapidly lactonizes to form granaticin **74**. **82** was also isolated[156] from *S. lateritius*, along with granatomycins A[153,157] (dihydrogranaticin methyl ester **83**), C[153,157] (granaticin **74**) and D[153,157] (dihydrogranaticin **78**). Granaticinic acid **82** and its methyl ester **84** comprise granatomycins B and E.[156,158] Structures were determined[153,156] by UV, IR and nmr spectroscopy and elemental analysis.

S. violaceoruber, under prolonged culture, produced[159] granaticinic acid **82** and a new compound 4-deoxy-4-*S*-(*N*-acetylcysteinyl)-granaticinic acid **85**, with concomitant loss of the granaticin **74** originally formed. The metabolites were identified by chromatography and spectral analysis. Dihydrogranaticin **78** and granaticinic acid **82** are minor pigments often associated with granaticin **74** in cultures. A number of new granaticin-type antibiotics were obtained[160,161] from *S. lateritius*, two of which were identified as granaticin B **77** and dihydrogranaticin B **81**.

A novel compound, dihydrogranatirhodin **86** was produced[140] by a genetically altered *Streptomyces violaceoruber* organism. It is the C-9 epimer of dihydrogranaticin **78**, having the same configuration at this carbon as actinorhodin **71**.

86
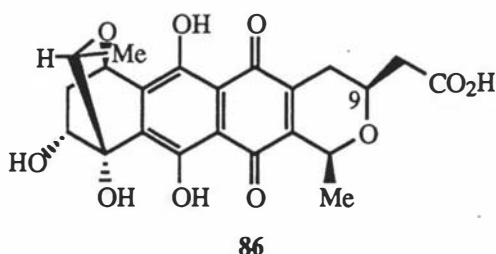
Granaticin **74** is highly active against gram-positive bacteria and protozoa and exhibits some activity against P-388 lymphocytic leukemia in mice and cytotoxicity against KB cells.[143,162] **74** has been reported to inhibit RNA synthesis[156] and to a lesser extent DNA and protein synthesis,[163-167] interact with enzymes containing a sulphydryl group[168] and exert strong activity against Ehrlich carcinoma cells.[168] Granaticin B **77** is active against gram-positive organisms,[151,160] shows inhibition of various transplanted tumours in rodents[166] and inhibits the synthesis of RNA in *Bacillus subtilis*.[169] Dihydrogranaticin **78** and its methyl ester **83** inhibit viruses, mycobacteria and both gram-positive and gram negative bacteria,[157] this antibacterial activity also being possessed by dihydrogranaticin B **81**.[160] Most of the derivatives of **74** inhibit RNA synthesis.[156]

A unique isochromanquinone antibiotic, Sch 38519 **87** was isolated[170] from a *Thermomonospora* species. The UV spectrum resembled closely that of medermycin **69**

and granaticin **74**, as did a portion of the IR spectrum, which indicated the presence of a five membered lactone ring. A ^{1}H nmr and COSY experiment revealed the familiar pyran γ-lactone portion of a benzoisochromanquinone, and ^{13}C nmr pointed to the presence of a C-C linked sugar moiety. Absolute stereochemistry was defined unequivocally by X-ray analysis[170] of the corresponding hydrochloride salt. Biological testing showed **87** inhibits the aggregation of human platelets, and is also active against both gram-positive and gram-negative bacteria.[170,171]

87
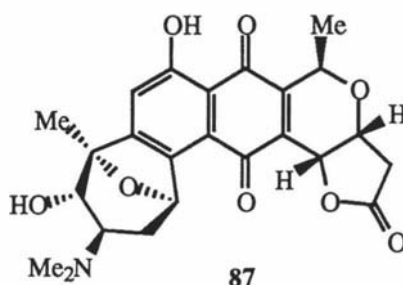
Griseusins A **88** and B **89** were isolated[172] from a soil sample collected in Peru innoculated with *Streptomyces griseus* K-63, and are unique within the family of pyranonaphthoquinone antibiotics in containing a 1,7-dioxaspiro[5.5]undecane ring system fused to a juglone moiety. A UV spectrum showed the presence of a 1,4-naphthoquinone chromophore,[172] IR and ^{1}H nmr spectra showed a γ-lactone ring and detailed nmr work ([1]H *J* values especially) established the structure and stereochemistry of the aliphatic portion of the molecules.[173] Griseusin B **89** was more polar than A **88** and an IR spectrum indicated a -CH$_2$CO$_2$H group rather than a γ-lactone. **89** was oxidized in pyridine upon exposure to air to **88** thus confirming the relationship between the two molecules.
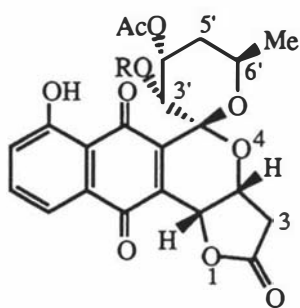
Griseusin A **88** : R=H
3'-O-α-D-forosaminyl-(+)-griseusin A**92** :

R= (structure)

89

26
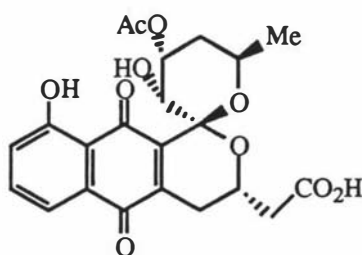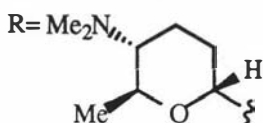
The structures originally assigned[173] to **88** and **89** were based on circular dichroism (CD) curves, which suggested the chirality of the dihydropyran rings was opposite to that of an actinorhodin derivative.[174,175] Following the synthesis[176] of deoxy analogue **90** of griseusin B **89**, whose CD spectrum was essentially the mirror image of natural **89**, Tsuji *et al.*[177] determined the structure of a dibromo derivative **91** of griseusin A **88**, and showed its correct absolute configuration to be (1*R*,3*R*,4*R*,3'*R*,5'*R*,6'*R*). Thus the previous CD spectra for **88** and **89** were not merely influenced by the chirality of the dihydropyran ring but also the conformation of the spiroketal ring system.[177] A recently isolated variant of griseusin A **88** is 3'-*O*-α-D-forosaminyl-(+)-griseusin A **92**,[178] the extra ring of which versus **88** bears a close resemblance to the aminopyran ring of medermycin **69** (page 20).

90   91
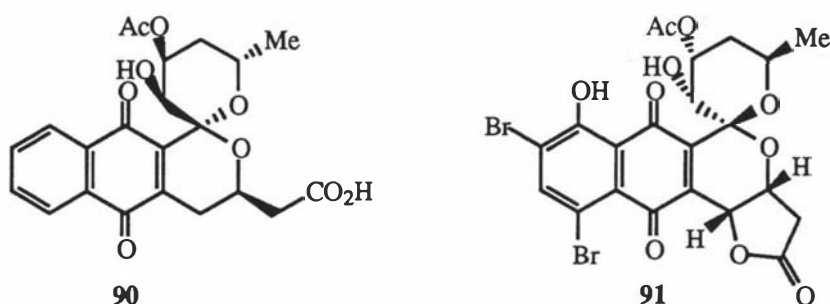
The griseusins are moderately active against gram-positive bacteria *in vitro*[172,178] and this, combined with their structural uniqueness and proposed bioreductive alkylating ability[1,2] has made the synthesis of griseusin A **88** the basis of this thesis.

1.1.3 Dimeric Quinones

Dimeric isochromanquinones exhibit the usual stereochemical features for each half of the molecule, but in addition contain a point of attachment and in several cases exhibit tautomerism, where a quinone moiety is fused to a quinol.

A number of actinomyces produce "litmus like" pigments[179] which were the earliest known isochromanquinones. The actinorhodins **71,93-97** are dimers whose members usually bear a quasi-axial methyl group *trans* to an equatorial acetic acid side chain at C-3, this side chain being able to form a γ-lactone ring. Different combinations of the two molecular halves and their point of attachment to each other can result in many possible structures, of which six occur naturally and are classed as actinorhodins.[32]

71 : R=H

α- 93 : R=H   β- 94 : R=Pr^i γ- 95 : R=H
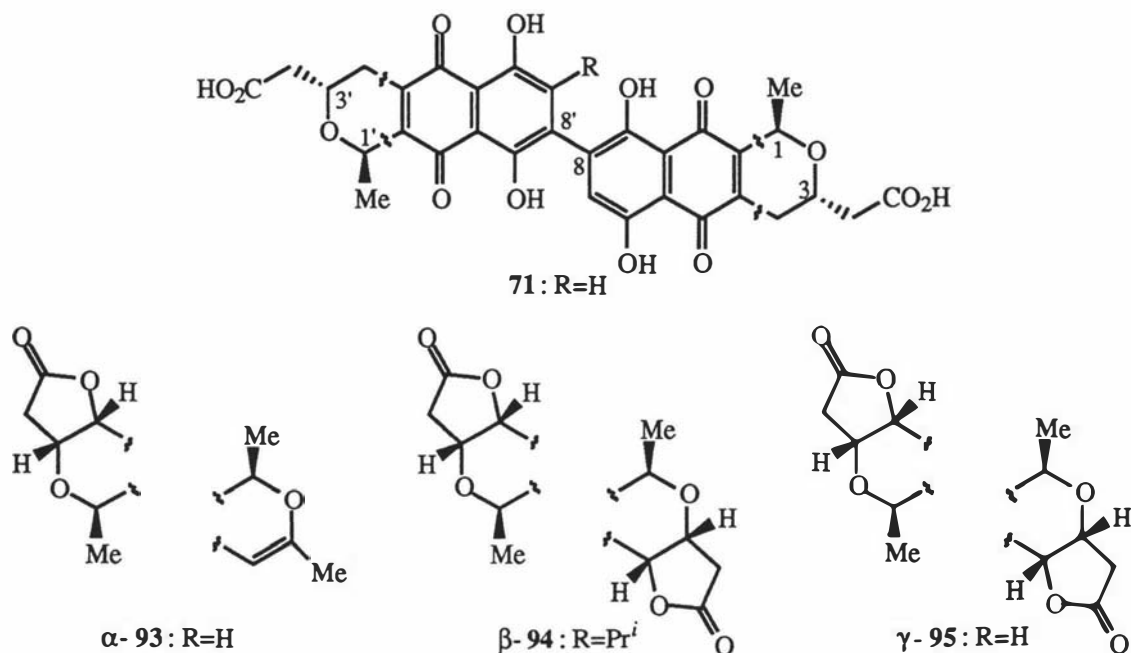
Actinorhodin **71** was isolated[180,181] as a red pigment from the mycelia of an actinomyces species (later specified as *Streptomyces coelicolor*[182]). Actinorhodin **71** is present in the mycelium largely as the almost colourless hydroquinone proto-actinorhodin **98**, which is readily oxidized to **71**.[182] It's indicator properties (blue in alkali, red in acid) gave the first clue as to the structure of **71**. This colour change, coupled with a UV spectrum very similar[183] to that of binaphthazarin **99** *and* chemical modifications[181-183] of **71**, indicated actinorhodin possessed a dimeric structure.

98   99
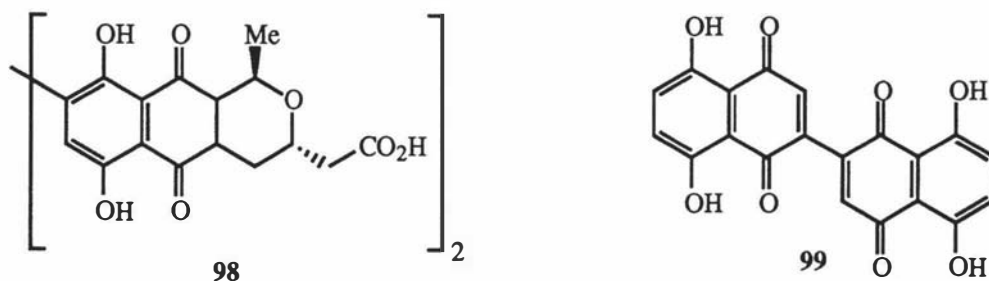
A key step in subsequent structural elucidation was the discovery[183] of a new reaction by which actinorhodin **71** could be cleaved by diazomethane. 2,2'-binaphthoquinone **100** upon treatment[184,185] with diazomethane in dioxane/ether gave the bis adduct **101** (scheme 5), the orientation of which was established.[184] In the presence of excess reagent, **101** was rapidly oxidized *via* a radical anion process[184] to the benzindazole quinones **102** and **103**, in a similar manner to 1,4-naphthoquinone.[184,186] The driving force for this central carbon-carbon bond cleavage is the formation of two mesomerically stabilized products.[187]

28
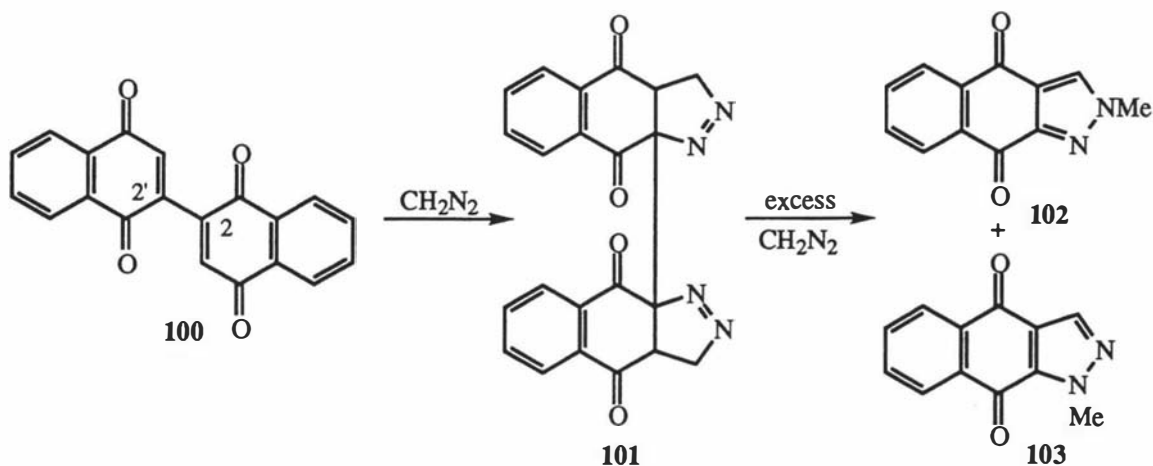
Scheme 5

The structure of actinorhodin **71** was determined[187,188] by extensive chemical degradation[183,188-190] and mass spectral studies.[187] Diazomethane treatment of actinorhodin dimethyl ester tetraacetate gave, after hydrolysis and reesterification, a single homogeneous optically active benzindazolequinone **104** (equation 1), showing that the two halves of **71** had the same structure and configuration, and were linked symmetrically.[187] The structural arrangement of the Me, CO_2H and C_4H_6O fragments attached to the biquinone nucleus was elucidated by alkaline hydrogen peroxide oxidation of actinorhodin **71**[188] and proto-actinorhodin **98**[187] to the tricarboxylic acid **105**, lactic acid **106** and β-hydroxyglutaric acid **107** (equation 2), and actinorhodin diethyl ester[174] to **105**. The conformation of the dihydropyran ring and absolute configuration of the asymmetric centres (1R,1'R,3S,3'S) were determined[174,187] by ^{1}H nmr and optical rotatory dispersion spectra respectively, with the triacid **105** showing C-1 and C-1' of **71** to be (R). The tautomerism associated with actinorhodin **71** has been explored[32,187,191] (*vide infra*) and the point of dimerization studied.[192] Actinorhodin **71** has also been isolated[193] from *S. lividans*.

71 dimethyl ester tetraacetate

Equation 1

29
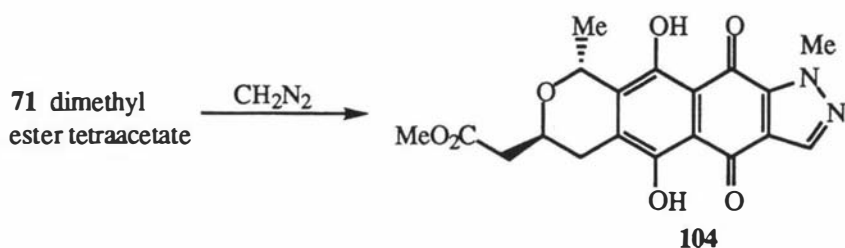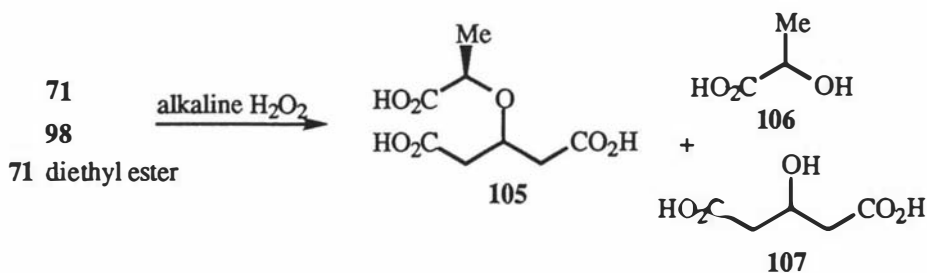
Equation 2

Other actinorhodin congeners obtained from *S. coelicolor* were α- **93**,[194] β- **94**,[194] γ- **95**[194] (page 28), and δ- **96**[194] and ε-*iso*-actinorhodin **97**[194] (*vide infra*). **93** shows one half corresponding to **95** and the other containing an unsaturated moiety, ^{1}H nmr signals agreeing well with anhydrofusarubin **16**. **95** is the dilactone of **71**, with the ^{1}H nmr spectrum showing the molecule to be symmetrical. The 8-8' linkage of **95** was established by the diazomethane degradative procedure discussed earlier which, like **71**, produced indazolequinone **104**. The actinorhodin-like half of **97** is recognized[194] to be connected at C-7 and not C-8 as it is in **71**.[190,192] This mistakenly dimerized product accumulates at an early stage and is not processed further by enzymes. Thus **97** should reflect an early precursor in actinorhodin biosynthesis (see page 51). The halves of δ-actinorhodin **96** are connected not only by a direct carbon-carbon bond but also by a lactone, forming another six membered ring in the middle of the molecule.

δ- **96**

ε-*iso*- **97**
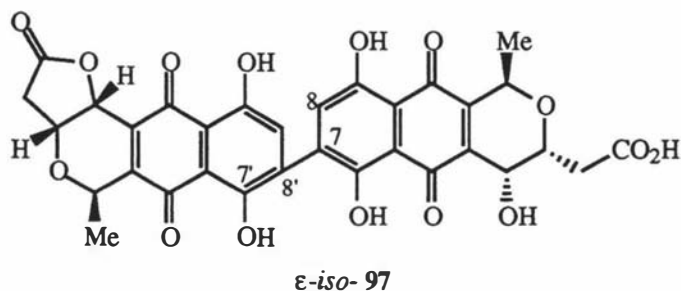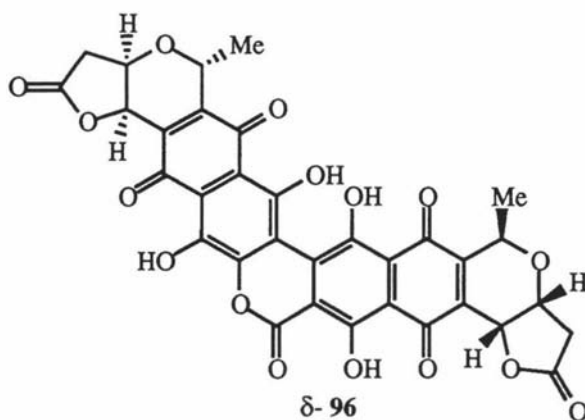
The tautomer illustrated for actinorhodin and its derivatives (**71, 93-97**) is that which appears in the majority of the literature (**a**, figure 5), and is used to maintain consistency with isochromanquinones depicted elsewhere in this work. The dominant form[32] (**b**, figure 5), however, has the quinone and quinol rings reversed such that the pyran ring is fused to the quinol. The major tautomer of granaticin **74** is also **b**, figure 5.
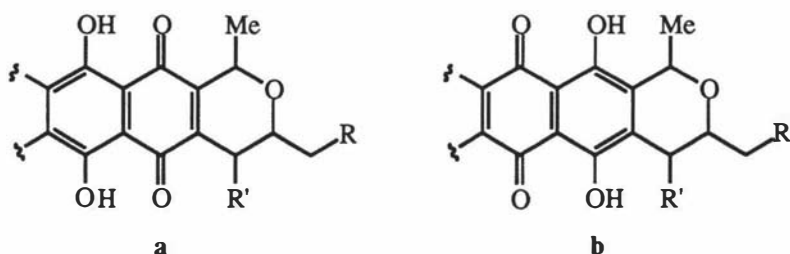
Figure 5

Little has been noted about the biological activity of the actinorhodins: actinorhodin **71** itself exhibits activity against *Staphylococcus aureus*.[181]

Crisamicin A **108** was isolated[195] as the major biologically active component of an antibiotic complex produced by a microorganism *Micromonospora purpureochromogenes* subspecies halotolerans, that was found in a Philippines mud sample. The mass spectrum indicated a molecular formula of $C_{32}H_{22}O_{12}$, and as the ^{13}C and ^{1}H nmr spectra[196] consisted of 16 and 11 signals respectively, crisamicin A **108** was determined to consist of two identical halves. A juglone-type chromophore was inferred by UV and IR spectra and the ^{1}H nmr data was nearly identical with that of kalafungin **44**.

108
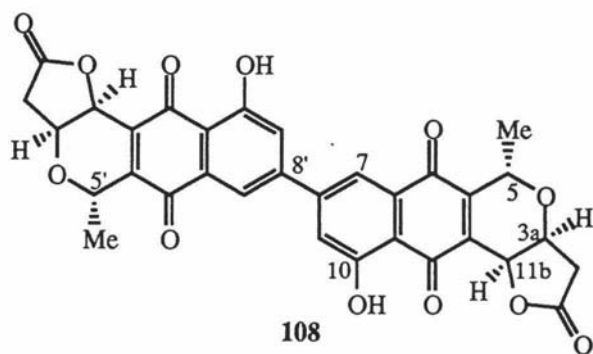
Conversion of **108** into the free acid and subsequent lactone ring closure as well as analysis of chemical derivatives confirmed the structure. The point of dimerization and the position of the hydroxyl group in **108** were determined to be C-8 and C-10 respectively, by shift differences between 4-OH and 4'-OH in the hydrolytically ring opened methyl ether derivative **109**. These differences would not be as pronounced if the

31

structure of crisamycin A **108** was analogous to that of ether **110**, where the connection point and hydroxyl group are C-7 and C-9 respectively (the equivalent of C-9 and C-7 in **108**), and 4,4'-OH are in essentially identical surroundings. The hydroxyl groups position in **108** differs from kalafungin **44** and nanaomycin D **50** and indeed most other isochromanquinones. The absolute configuration of **108** was shown to be (3aS,3a'S,5S,5'S,11bS,11b'S) by comparison of Cotton effects in the ORD curves of **44** and **50**.[196]

109

110
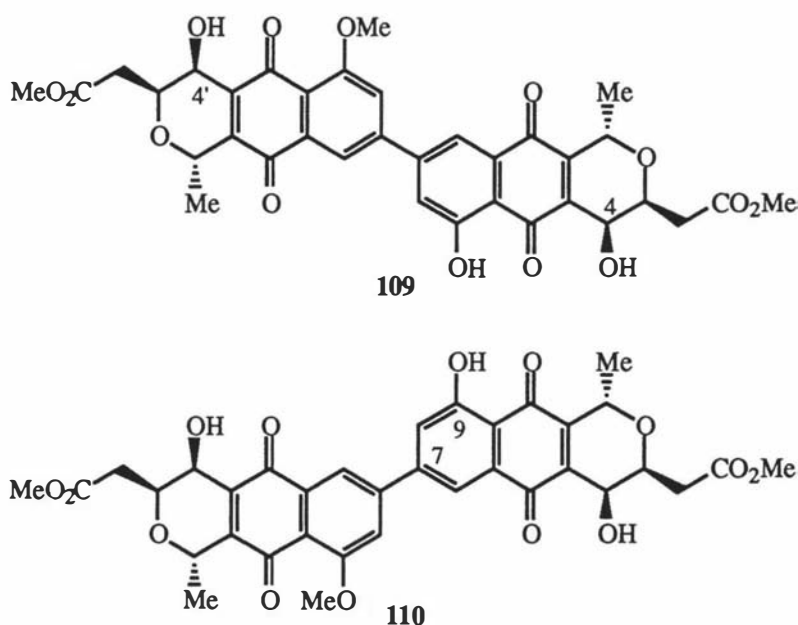
From the antibiotic complex detailed above crisamycin C **111** was also isolated.[197] The hrms peak corresponding to MH[+] was 16 amu higher than **108**, suggesting the two antibiotics differed by one oxygen atom. [1]H and ^{13}C nmr data, as well as labelled feeding experiments, showed **111** to be the C5a'-C11a' epoxide derivative of crisamicin A **108** (compare deoxyfrenolicin **58** and frenolicin **60**, page 18).

111
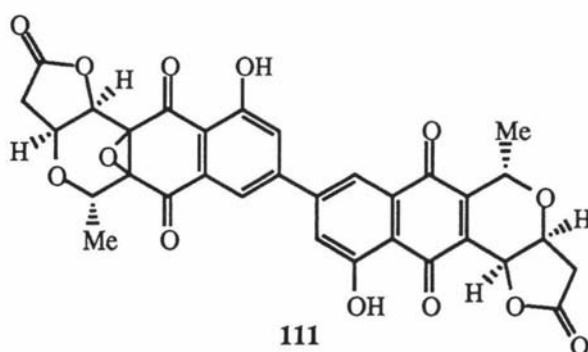
Crisamicin A **108** exhibits *in vitro* activity against gram-positive bacteria, B16 murine melanoma cells and viruses,[196] including herpes simplex, but shows little or no

activity towards gram-negative bacteria or fungi.[195] Crisamicin C **111** was found to be a more potent antibiotic than crisamicin A **108** but shared the same spectrum of antimicrobial activity.[197] The antibiotic complex from which **108** and **111** are isolated has been reported to have antitumour and antiviral activity.[198]

A dimeric ventiloquinone **112** was isolated[81a] along with monomeric examples (page 12) from *Ventilago goughii*. Mass spectrometry showed high molecular weight peaks which suggested a dimer. The ^{1}H nmr and NOE experiments showed a part structure like ventiloquinone L **41** and decoupling experiments provided evidence for a fragment corresponding to earlier examples,[77] for example C **37** and D **38**. The section linking these two structures was conceivably an epoxide (figure 6), analogous to frenolicin **60**, but was excluded by the ^{13}C nmr spectrum in favour of an oxetane. The proposed structure **112** accommodates the part structures detailed and agrees with salient features of the nmr and ms data. A seemingly more likely structure based on two isochromanquinone units is **113** but this does not correlate with the mass spectral data nor some nmr experiments.[81a]

epoxide   oxetane
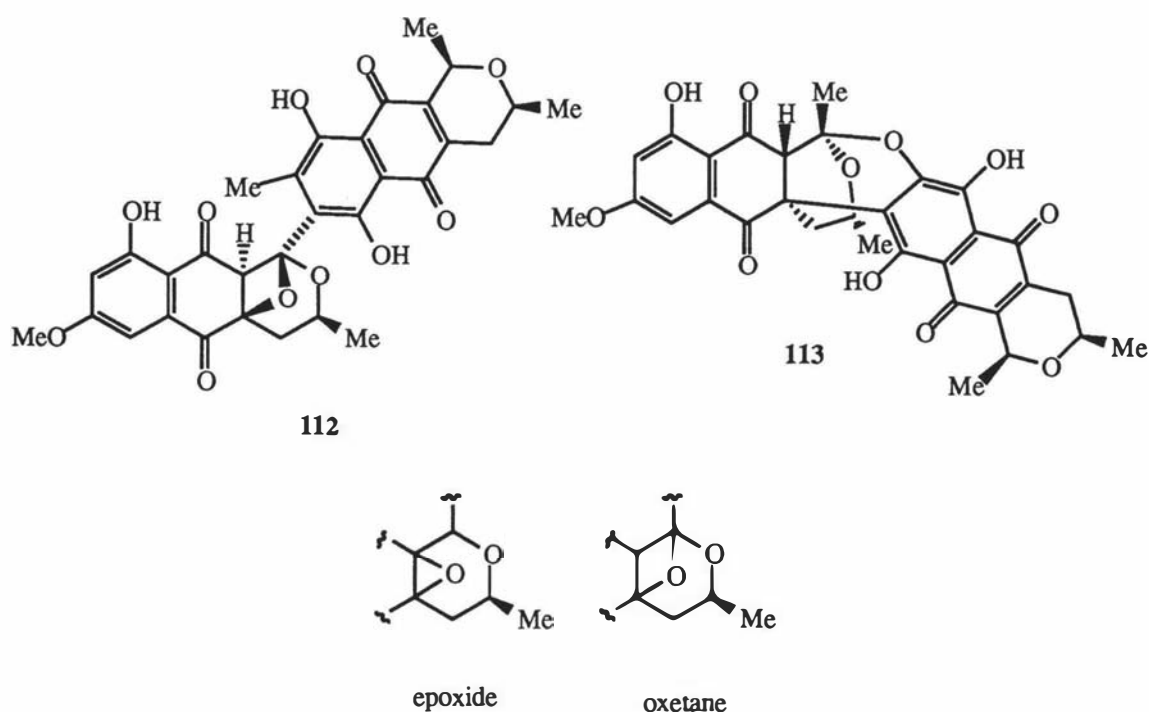
Figure 6

Dimeric naphtho[2,3-c]pyrans constitute molecules of the aphid pigments, a group of compounds extensively investigated by Todd *et al.*[199] Initial studies[200] showed an interrelationship *via* pH change between several highly coloured forms of the pigment, which was termed protoaphin. Such colour transformations in solution of related pigments had been noted previously.[201] Protoaphin-*fb* **114**[202] and protoaphin-*sl* **115**[203]

were isolated[202-204] from the haemolymph of bean and willow aphids (*Aphis fabae* and *Tuberolachnus salignus*) respectively. These brown-yellow coloured substances are hygroscopic, water soluble, acidic and appreciably ionized at physiological pH, forming violet-red anions which are chiefly responsible for the dark colour of the insect. **114** and **115** also show redox properties.

Protoaphin-*fb* **114** : R^1=OH, R^2=H
Protoaphin-*sl* **115** : R^1=H, R^2=OH
Deoxyprotoaphin **123** : R^1=R^2=H
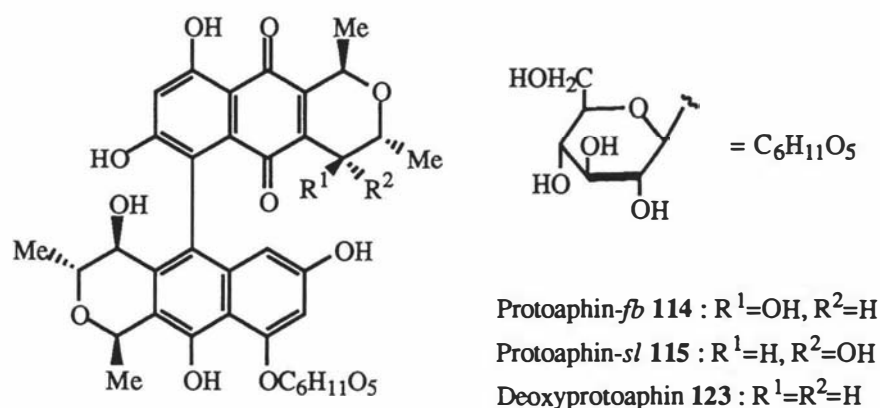
Protoaphins are present in the haemolymph of living insects accompanied by an enzyme which, after death, rapidly converts them into an unstable, sugar free yellow fluorescent xanthoaphin (figure 7). On keeping (oxidation) or more rapidly in the presence of acid or alkali, these form orange chrysoaphins, and a final transformation results in red erythroaphins, the stable end product of this sequence of reactions.[205]

Protoaphin-*fb* **114** $C_{36}H_{38}O_{16}$ Protoaphin-*sl* **115**

Xanthoaphin-*fb* $C_{30}H_{26}O_{10}$ Xanthoaphin-*sl*-1
Xanthoaphin-*sl*-2

Chrysoaphin-*fb* $C_{30}H_{24}O_{9}$ Chrysoaphin-*sl*-1
Chrysoaphin-*sl*-2
Chrysoaphin-*sl*-3

Erythroaphin-*fb* **121** $C_{30}H_{22}O_{8}$ Erythroaphin-*sl*
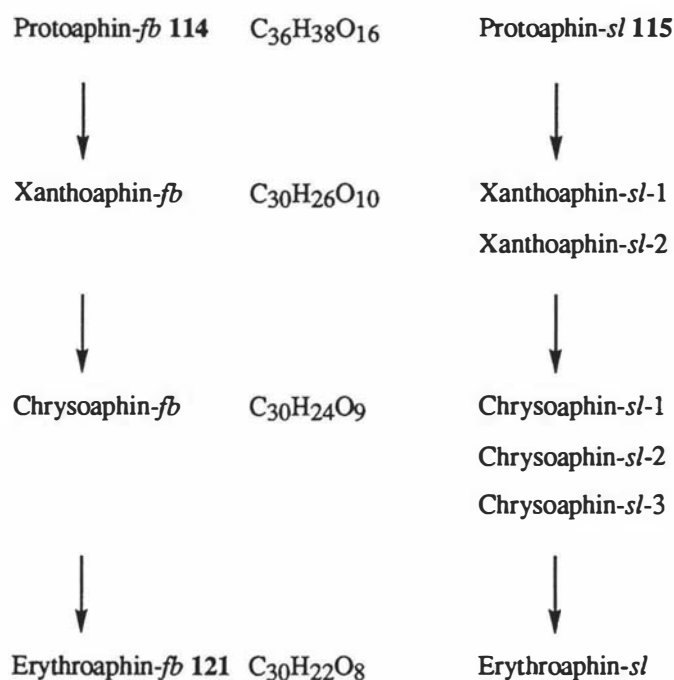
Figure 7

Prolonged reduction[206] of a neutral aqueous solution of **114** followed by aerial oxidation gave two products, an orange acidic quinone ("quinone A" **116**, $C_{15}H_{14}O_6$) and a colourless glucoside ("glucoside B" **117**, $C_{21}H_{26}O_{10}$). Hydrolysis of the glucoside yielded D-glucose and an intractable aglucone. The combined properties of the two fragments **116** and **117** were almost identical with **114**, indicating that it consisted of these two parts effectively insulated from another. UV and IR spectra of **116** suggested a 5,7-dihydroxy-1,4-naphthoquinone and methylation/acetylation found three hydroxyl groups.[206] Chromic acid oxidation[206] gave *D,D*-(+)-dilactic acid **118** of known absolute stereochemistry, and ^{1}H nmr data[8,207] showed a *trans*-diaxial arrangement for 3-H and 4-H, so quinone A was formulated as **116**. The X-ray crystal structure of **116**[208a] and its 7-*O*-methyl e̶t̶h̶e̶r̶[208b] were later obtained and confirmed what was proposed chemically, including the chirality of all asymmetric centres in the molecule.

Quinone A **116** : R^1=OH, R^2=R^3=H

119 : R^1=OH, R^2=H, R^3=$C_6H_{11}O_5$

Quinone A' **122** : R^1=R^3=H, R^2=OH

Deoxyquinone **124** : R^1=R^2=R^3=H

117

120

118
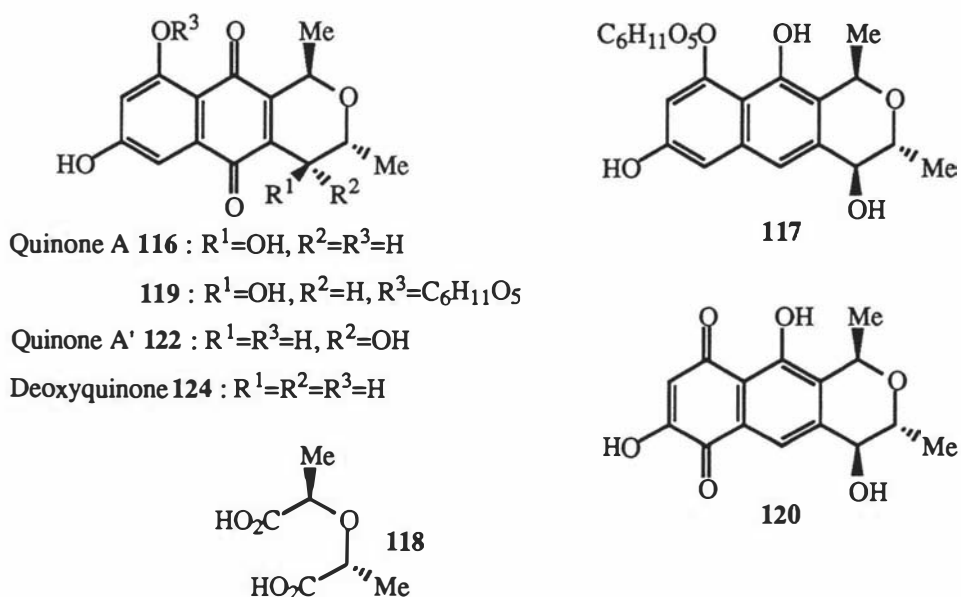
Spectroscopically glucoside B **117** appeared to be a hydroxylated naphthalene, and on oxidation afforded two naphthoquinones. One was a glucoside which was easily hydrolysed to **116** and therefore was **119**, the other quinone was found to be **120**. The β-configuration of the sugar moiety in **117** was evident from the use of a β-specific enzyme to effect hydrolysis.[206] From this detailed structure determination, and knowing that it is transformed into erythroaphin-*fb* **121**, the framework of protoaphin-*fb* **114** could be assigned.

121
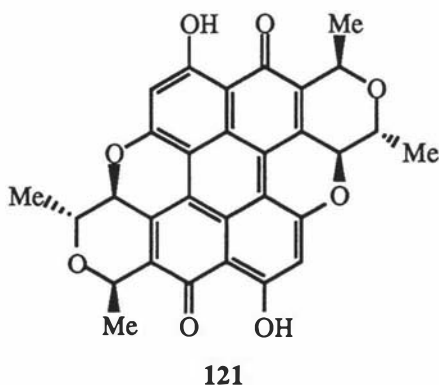
The separate chromophoric properties of the fragments can thus be understood. A similar process with protoaphin-*sl* **115** gave quinone A' **122** which differed only in the configuration about C-4, the *cis* relationship of the relevant protons being confirmed.[206] Both **116** and **122** epimerize to a mixture of both compounds upon anaerobic base treatment.[209] Formation of the protoaphins *in vivo* involves a coupling reaction between the two halves which can be done *in vitro* with ease.[210] The transformations xanthoaphin→chrysoaphin→erythroaphin (figure 7) are simple dehydrations, but the initial conversion of protoaphins to xanthoaphins involves hydrolysis of the glucosidic link, condensation of a quinone carbonyl group with the aglucone and the formation of two hemiketal linkages (equation 3).
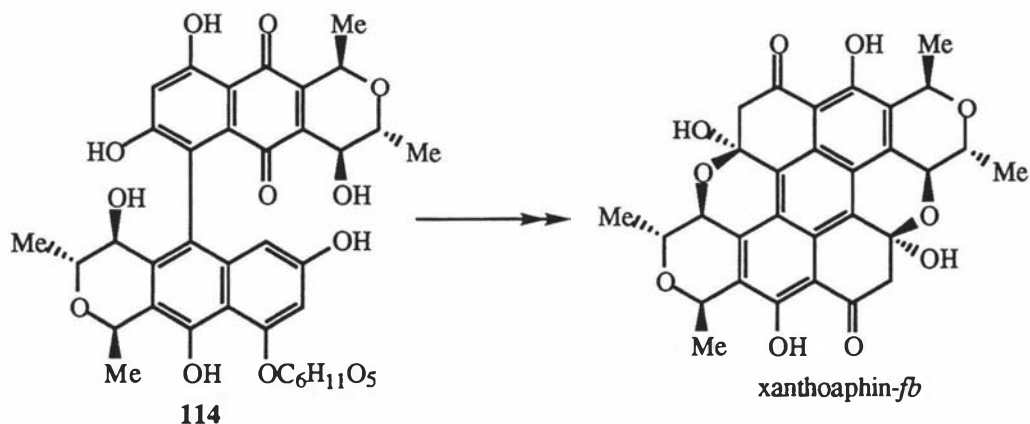
Equation 3

In the course of surveying a considerable number of aphid species, a new protoaphin deoxyprotoaphin **123** was obtained.[211] This new component was found in *Dactynotus* species and mass spectrometry and analytical data were consistent with a protoaphin lacking an hydroxyl group. Mild hydrolysis (*vide supra*) gave deoxyquinone **124** and glucoside B **117**, therefore deoxyprotoaphin had the structure **123**. An extract of *A. fabae* converted **123** into the corresponding chrysoaphin, therefore it was likely that

the configuration about the binaphthyl linkage and the absolute configuration of the naphthalenic halves were the same as in **114**.

Aphids of *Dactynotus jacae* L. contain a distinct group of pigments termed dactynaphins,[205,212] and like the aphins they occur in the living insects as glucosides. They are enzymatically converted into a mixture consisting chiefly of the isomeric, interconvertible rhodo- **125** and xanthodactynaphins-*jc*-1 **126**. Smaller quantities of a similar pair of isomers, rhodo- **127** and xanthodactynaphins-*jc*-2 **128** are also present. The dactynaphin structures above were determined by degradative experiments coupled with spectroscopic studies, and resemble the protoaphins (**114,115,123**) in consisting of two naphthalenic units coupled together, but differ in that coupling is effected through carbon-oxygen rather than carbon-carbon bonds.[209] One of the two structures illustrated is thought to represent the rhododactynaphins but their close similarity did not permit unequivocal differentiation.[209] Dactynaphins-*jc*-2 differ from the -*jc*-1 isomers in lacking a benzylic hydroxyl group, and contain the same non-aromatic portion as isoeleutherin **6**. Protodactynaphin-*jc*-1 **129** was later found[213] and is converted by hydrolysis (loss of glucose) into a mixture of rhodo- **125** and xanthodactynaphins-*jc*-1 **126**. It is presumed to exist in the living insect in the form of a xantho↔rhodo equilibrium: in solution the xantho- compound **129** was the predominant isomer.[213] Pure samples of protorhododactynaphins-*jc*-1 **130** and -*jc*-2 **131** were characterized later by Cameron *et al*.,[211] the -*jc*-2 series not being isolated earlier[213] due to the limited methods available for fractionation at the time.
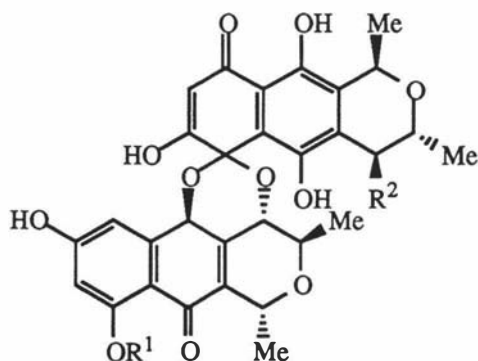
Xanthodactylnaphin-*jc*-1 **126** : R^1=H, R^2=OH

Xanthodactylnaphin-*jc*-2 **128** : R^1=R^2=H

Protoxanthodactynaphin-*jc*-1 **129** : R^1=$C_6H_{11}O_5$, R^2=OH

Protoxanthodactynaphin-*jc*-2: R^1=$C_6H_{11}O_5$, R^2=H
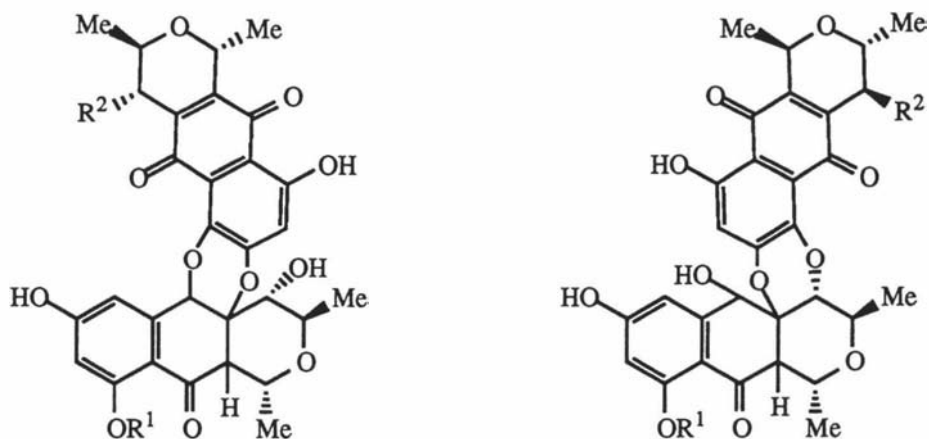
Rhododactylnaphin*jc*-1 **125** : R^1=H, R^2=OH

Rhododactylnaphin*jc*-2 **127** : R^1=R^2=H

Protorhododactylnaphin*jc*-1 **130** : R^1=C$_6$H$_{11}$O$_5$, R^2=OH

Protorhododactylnaphin*jc*-2 **131** : R^1=C$_6$H$_{11}$O$_5$, R^2=H

A somewhat more complex dimer is phenocyclinone **132**, a red pigment isolated[214] from the mycelium of *Streptomyces coelicolor*. The nucleus is a pentaphenediquinone to which is fused (unsymmetrically) on both sides the same ring system. Alternatively, **132** may be thought of as a naphthazarin pyran-γ-lactone tetracyclic ring system, found in for example granaticin **74**, fused either side of a methyl benzene moiety (compare with β- **94** and δ-actinorhodin **96**). ^{1}H nmr data of **132** in comparison with related chromophores, and coupling constants about the pyran ring, led to its structure assignment as **132**. The absolute stereochemistry was undetermined and the choice between the four possible directions of annellation of the two dihydropyran rings is based on biosynthetic arguments[214] (see page 58, section 1.2.3).
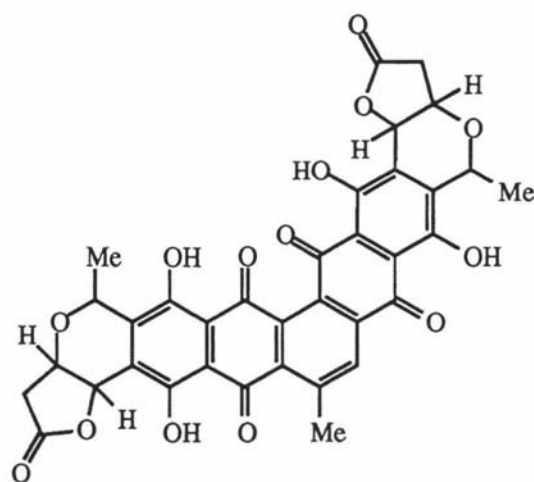
132

The naphthocyclinones **133-140** are a series of closely related pigments which were isolated from cultures of *Streptomyces arenae*. The naphthocyclinones are unsymmetrical dimers in which one of the benzoisochromane units has been modified into an aryl ketone moiety. The naphthazarin chromophore is connected to this aryl ketone *via* two carbon-carbon bonds to give a bicyclo[3.2.1]octadienone system.

α-Naphthocyclinone **133**[215] is an orange dye whose structure, along with others of the group, was determined by a combination of chemical modification, degradation and extensive spectroscopic data of various derivatives. Other members are β- **134**[175] and γ-naphthocyclinone **135**,[175] red pigments isolated along with **133** from *S. arenae* mycelium, and β-naphthocyclinone chlorohydrin **136**, β-naphthocyclinone epoxide **137**, γ-iso- **138**, δ- **139** and ε-naphthocyclinone **140**, discovered by Krone and Zeeck.[216]

α- **133**

β- **134**

γ- **135**

β chlorohydrin **136**

β epoxide **137**

γ-iso **138**

δ- **139**
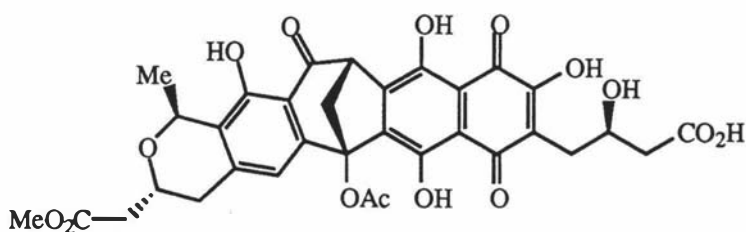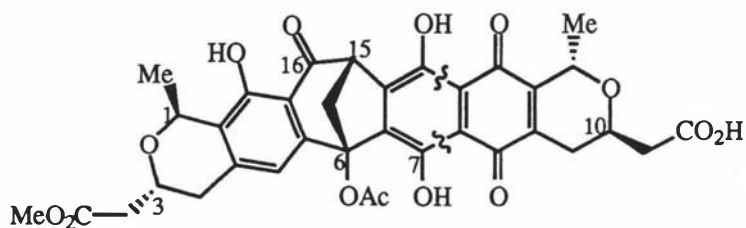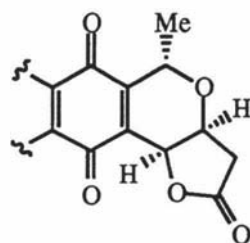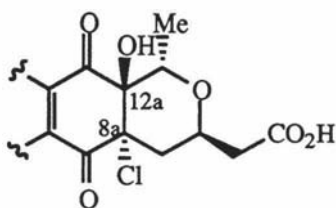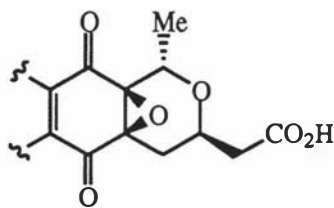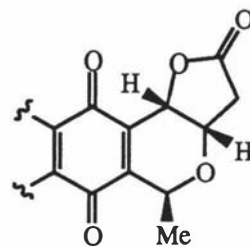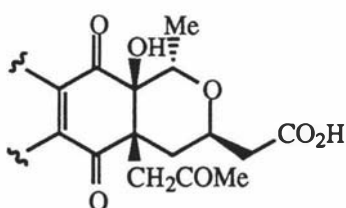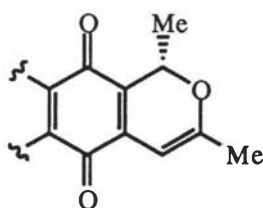
ε- **140**

Chromic acid oxidation of α-naphthocyclinone **133** to **141** (equation 4) and diazomethane degradation of the cyclized α-naphthocyclinone furan derivative **142** to **143, 144** and **145** (scheme 6) established the carbon skeleton. The acetoxy group of **134** was assigned to C-6 rather than C-15 as upon reduction of the C-16 carbonyl group to an alcohol, 16-H appeared as a doublet coupled to 15-H. An acetoxy group at C-6 also explains deshielding of one of the bridging methylene protons and resistance to acetylation of 7-OH.[175] Strong support for the bicyclo[3.2.1]octadienone skeleton was obtained by diazomethane degradation, in a manner analogous to that used for actinorhodin structure elucidation (page 29). When applied to deacetyl-β-naphthocyclinone (**134**: OH in place of OAc) the diazomethane reaction products obtained[175,217] were quinones **145** and **146** and the *seco*-naphthocyclinone **147** (scheme 7), in which the two halves of the molecule are still linked by a single bond. The six membered keto ring of the bicyclooctadienone system is now a quinone ring (refer scheme 6). The *trans* stereochemistry of the dihydropyran ring of **134** and **135** was confirmed by CD spectra of the degradation products.[175]
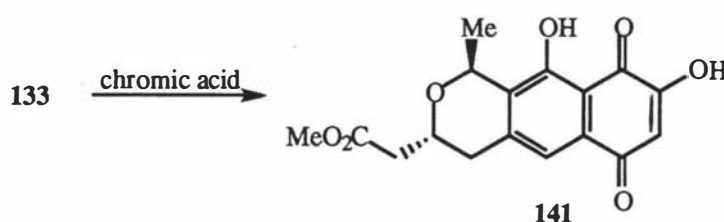
Equation 4

γ-naphthocyclinone **135** is a lactone derivative of β-naphthocyclinone **134** (see nanaomycins A **47** and D **50**). Its structure was determined[175] along with **134**, and confirmed by crystallographic analysis[217] which showed the configuration of the central bicyclo[3.2.1]octadienone ring to be (6R,15S). A fold angle of 110° exists between the two planar halves of the molecule. **135** can be derived from **134** by oxidation in aqueous methanol or UV irradiation.[216]

Three of the more recently isolated compounds, β-naphthocyclinone chlorohydrin **136**, β-naphthocyclinone epoxide **137** and δ-naphthocyclinone **139** contain the molecular skeleton of β-naphthocyclinone **134**. In **136** and **137** the C8a-C12a double bond has been opened to create two new sp[3] centres, in a manner similar to nanaomycin B **48** and frenolicin **60** respectively, whereas **139** is an hydroxy ketone derivative of **134**. **137** undergoes several interesting transformations[216] *via* irradiation and chemical processes, these reactions helping to confirm the structures assigned.

γ-isonaphthocyclinone **138** was separated from the isomeric γ-naphthocyclinone **135** by the use of silica gel impregnated with L-(+)-tartaric acid. Examination of spectroscopic data (including circular dichroism) showed the absolute configuration at all
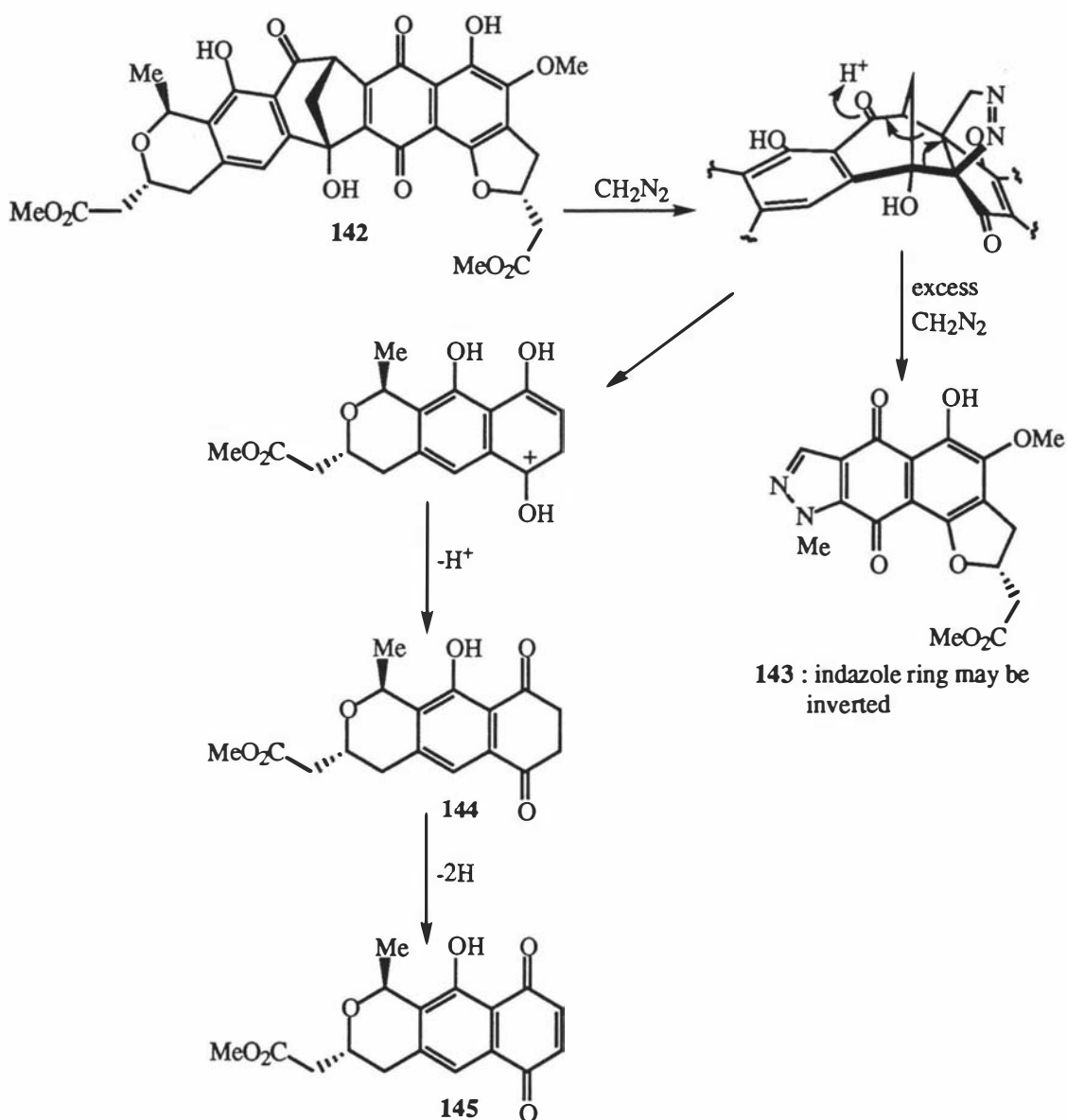
Scheme 6

centres to be the same as **135**, with **138** being a structural isomer where the pyrano-γ-lactone ring is inverted. The isomers could be distinguished by diazomethane degradation, in which the initial cycloaddition occurred in different directions. The halves of γ-isonaphthocyclinone **138** are connected unsymmetrically, which is notable with regard to the biosynthesis (see page 58). There is some ambiguity over the stereochemistry of the Me group on the unsaturated dihydropyran ring of ε-naphthocyclinone **140**, with doubling of certain proton and carbon signals noted.

Detailed work on the ^{13}C nmr and circular dichroism spectra of the naphthocyclinones has been accomplished,[32] and the dominant tautomer for β- 134, γ- 135, γ-iso- 138 and ε-naphthocyclinone 140 and their derivatives determined (a: figure 5, page 31). Several compounds related to granaticin 74 and actinorhodin 71 also favour this tautomer.[32]
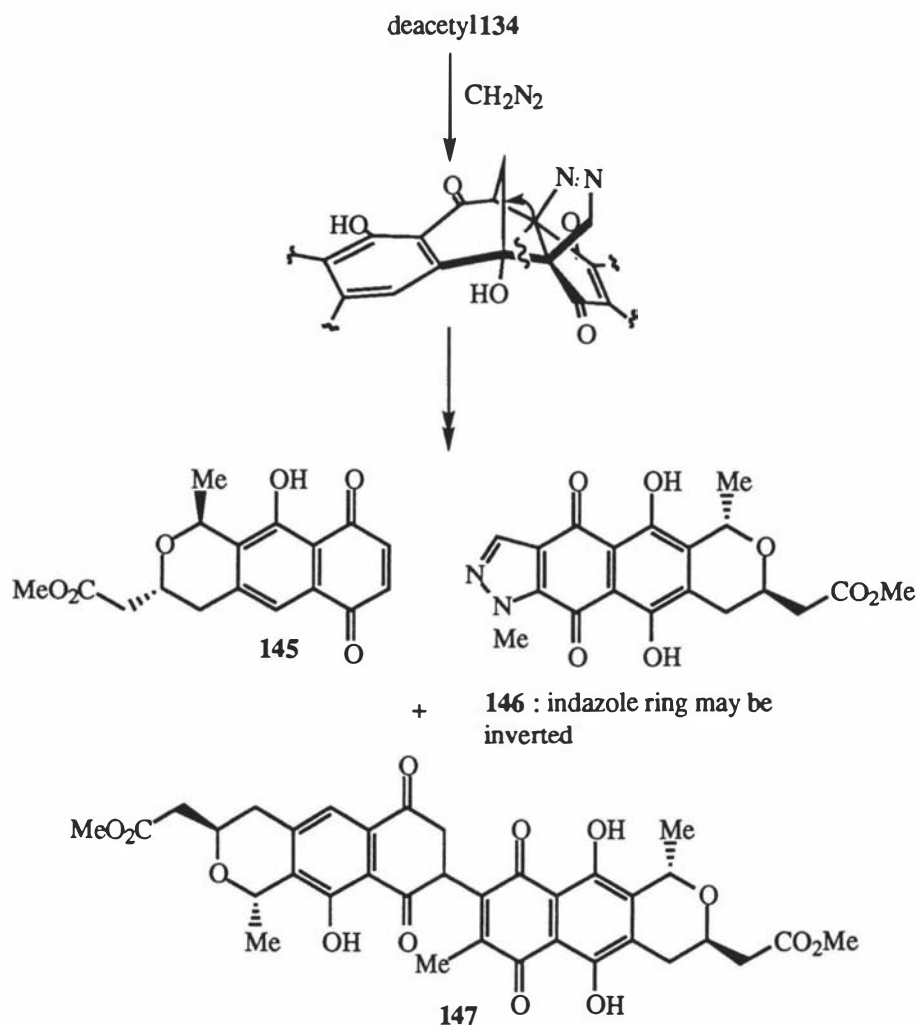
Scheme 7

The biological activities of some of the naphthocyclinones have been investigated. β- 134 and γ-naphthocyclinone 135 were found to be inhibitory against gram-positive bacteria[175] with the suggestion that this activity required a minimum structure (figure 8), since 133 was inactive and the only member of the three (133-135) studied to have a second unit (or half) with only 14 carbons. Derivatives of these and other naphthocyclinones were tested[216] against *Staphylococcus, Proteus* sp. and *E. coli*, with several analogues of β- 134, γ- 135 and δ-naphthocyclinone 139 displaying marked activity in these trials.[216]

42
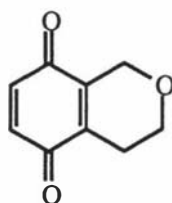
Figure 8

1.2 Pyranonaphthoquinone Biosynthesis

Pyranonapthoquinones are a sizeable family of antibiotics generally sharing the common structural element of a disubstituted tricyclic benzoisochromane skeleton (figure 9). Additional common features are oxygen functions at the positions indicated, a quinone function in one aromatic ring and the absence of an oxygen function at C-9. This substituted benzoisochromane skeleton represents a biosynthetic product common to all members of this class and is built up from acetate/malonate units *via* a polyketide pathway.[218-220] A numbering system which emphasizes the biosynthetic relationships between these members is utilized for this section (1.2) and differs from that used to name these compounds, however it provides consistency when discussing equivalent positions in molecules based around this molecular framework.
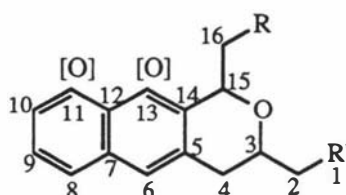
Figure 9

The hydrogens at the two common chiral centres, C-3 and C-15, are in a *trans* relationship. Streptomycetes can produce either compounds of 15*R* (kalafungin **44**, actinorhodin **71**) or 15*S* configuration {granaticin **74**, nanaomycins (**47-51**), naphthocyclinones (**133-140**)}. In at least one case[113] the same culture has been observed to produce members of both enantiomeric series (refer page 17). The benzoisochromane antibiotics can be categorized into simple monomers, C-16 modified monomers (for example frenolicins), carbohydrate modified monomers, and dimers.

For the sake of convenience and clarity, distinct monomers (R-CO$_2^-$) are generally shown in the biosynthetic schemes of the pyranonaphthoquinones noted rather than activated coenzyme A thioester intermediates (R-COSEnz), which are the true enzyme bound species present prior to cyclization and release (see figure 10).

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1.2.1 Simple Monomers

Fusarubins

The pattern of ^{13}C and [2]H (D) incorporations from singly (◊ or •) and doubly labelled (━) acetate into the dihydrofusarubins **10** and **11** from *Fusarium solani*[221] was consistent with seven uniformly incorporated acetate units forming a single chain heptaketide, although the results did not establish which of several possible routes gives the final arrangement. Two examples are given in scheme 8. The methyl group on the dihydropyran ring of **10,11** had a ^{2}H content considerably lower than its precursor [2-^{13}C,2-[2]H3]acetate methyl group, indicating considerable exchange during incorporation as a result of interconversion between acetate and malonate(^-O_2C-CH_2-CO_2^-, figure 10). This methyl group and C-3 comprise the "starter" acetate unit which initiates formation of the polyketide chain. Thus the polyketide is probably formed by linear head to tail condensation of the "starter" acetate and six malonate units.

Scheme 8
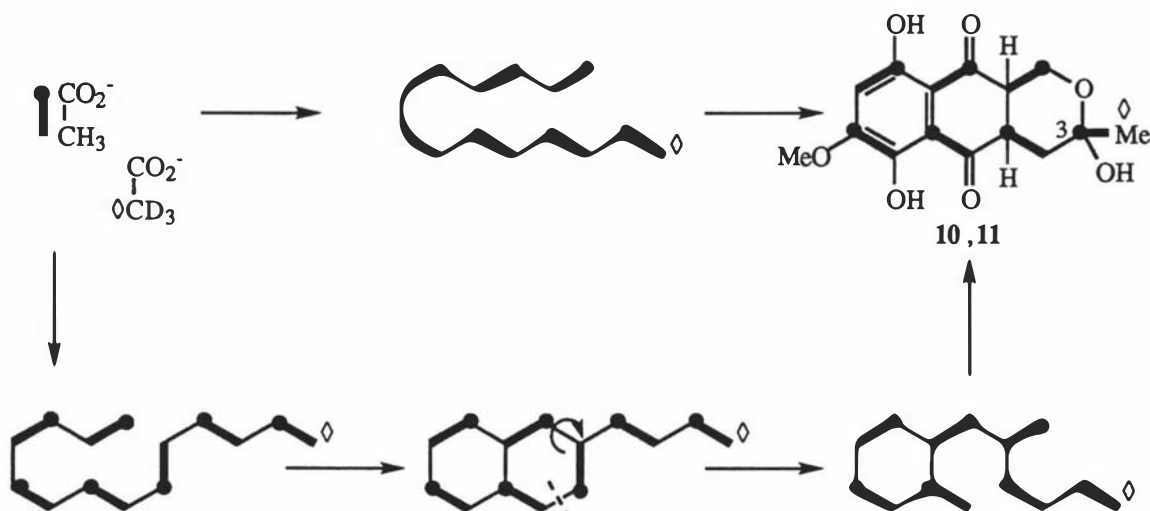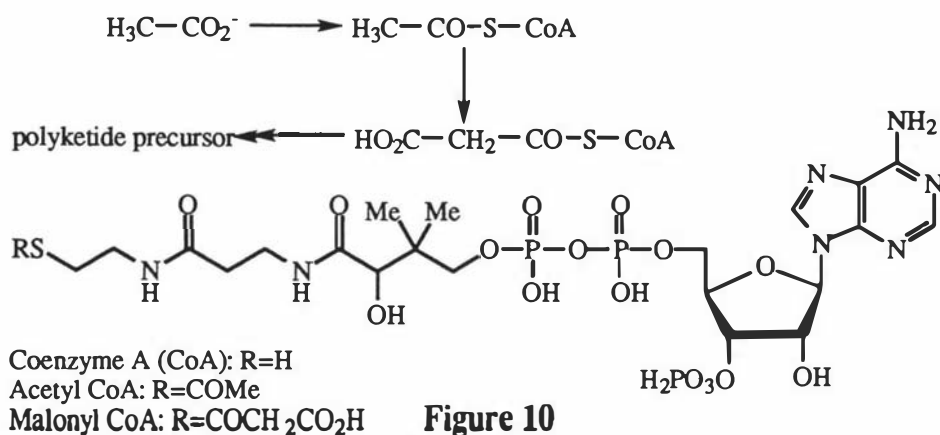
Coenzyme A (CoA): R=H
Acetyl CoA: R=COMe
Malonyl CoA: R=COCH$_2$CO$_2$H   **Figure 10**

In the same manner, incorporation of $[1\text{-}^{13}C]$acetate into 5-deoxyanhydrofusarubin **148** also indicated a heptaketide origin for this molecule[222] (equation 5).
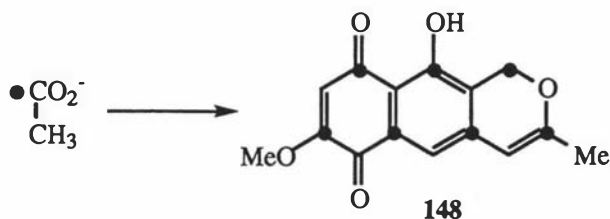
Equation 5

Incorporation of labelling from $[1,2\text{-}^{13}C]$- and $[2\text{-}^{13}C]$acetate into marticin methyl ester **149** (equation 6) established a heptaketide origin for the fusarubin moiety, and the tricarboxylic acid (Krebs) cycle as the biogenic source of the remaining C_3 fragment.[26,53,223] $[2\text{-}^{13}C]$acetate enhanced the ^{13}C nmr signals of two adjacent carbon atoms which correspond to succinate $\{^-O_2C\text{-}(CH_2)_2\text{-}CO_2^-\}$, both atoms derived from C-2 of acetate after one or more passages through the Krebs cycle.[223] While primitive precursors and a biosynthetic scheme for the polyketide moiety have been established, much less is known about the biogenetic interrelationships between naphthoquinone pigments from *Fusaria*. Few studies have been carried out on the sequence of naphthoquinone production by investigating the metabolites formed at time intervals, and of these, different results were obtained for different fungal strains and growing media.[19]
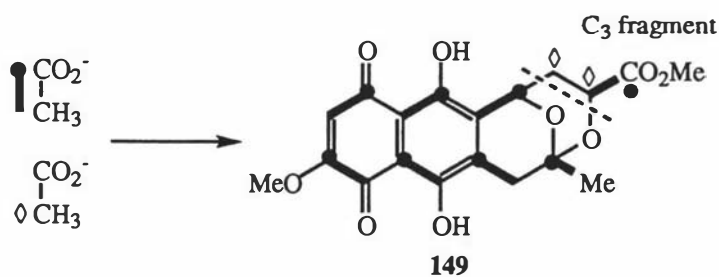
Equation 6

A proposed[19,48] biosynthetic sequence for fusarubin **9** and related naphthoquinones is illustrated (scheme 9), where the aromatic acid **150** formed from heptaketide **151** is reduced first to an aldehyde, then a primary alcohol before cyclization to fusarubin **9**. Another sequence[31] (scheme 10) follows a similar pathway, oxidation occurring later in the reaction order.

45

Scheme 9
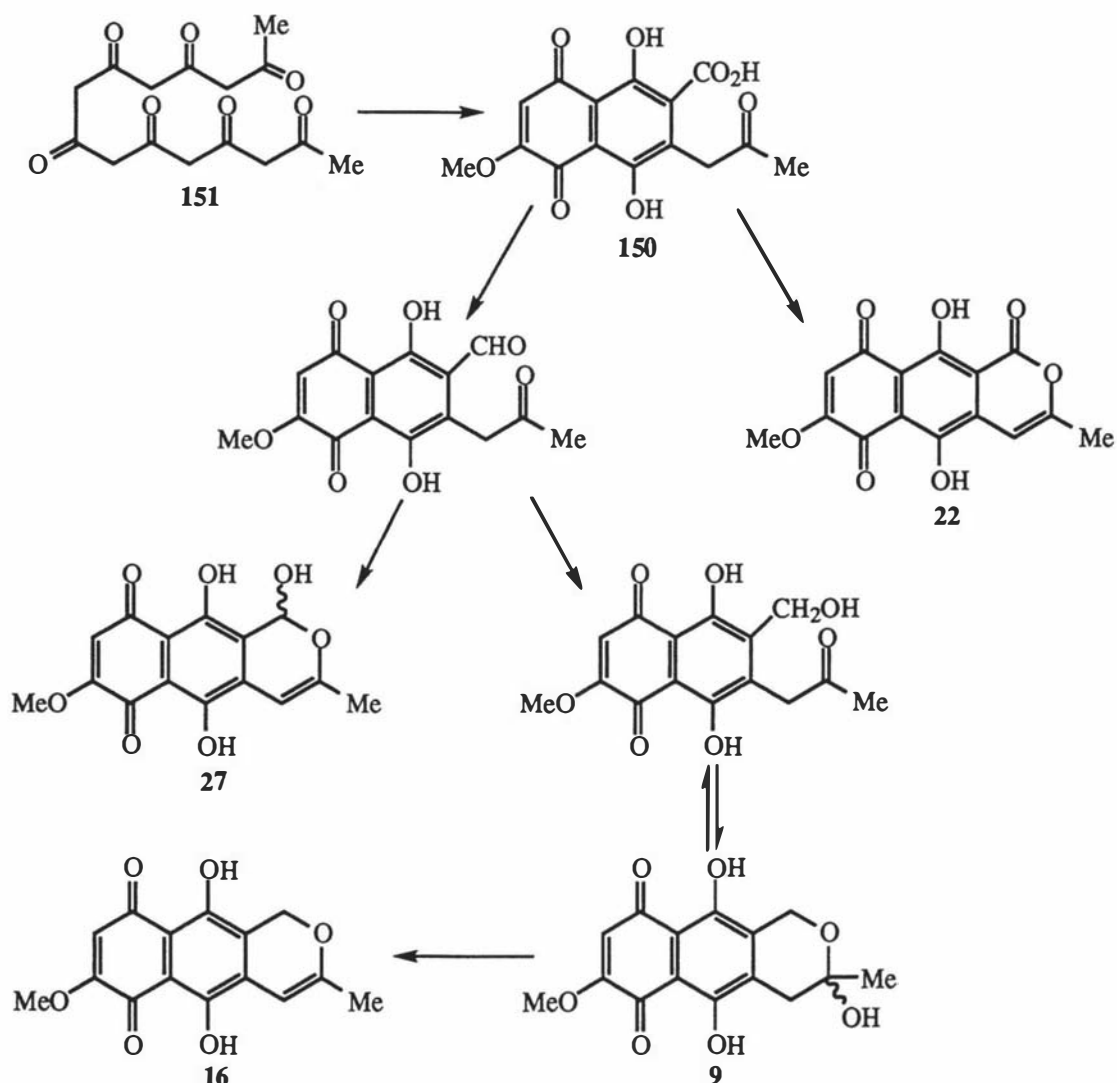
Nanaomycins

One of the first tracer studies on isochromane biosynthesis was carried out in connection with the structure elucidation of nanaomycins.[98] Sodium [1-^{13}C]acetate fed to the fermentation medium of *Streptomyces rosa* var. notoensis produced nanaomycin A **47** which displayed eight enhanced signals by ^{13}C nmr spectroscopy. The labelling pattern (equation 7) was in accord with eight acetate monomers making up the antibiotic skeleton. The phenolic hydroxyl group was attached to a ^{13}C enriched carbon and therefore positioned at C-11 and not C-8 (biosynthetic numbering).

Equation 7

46
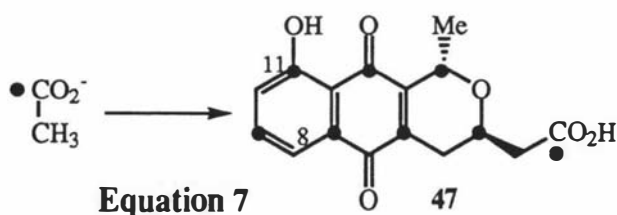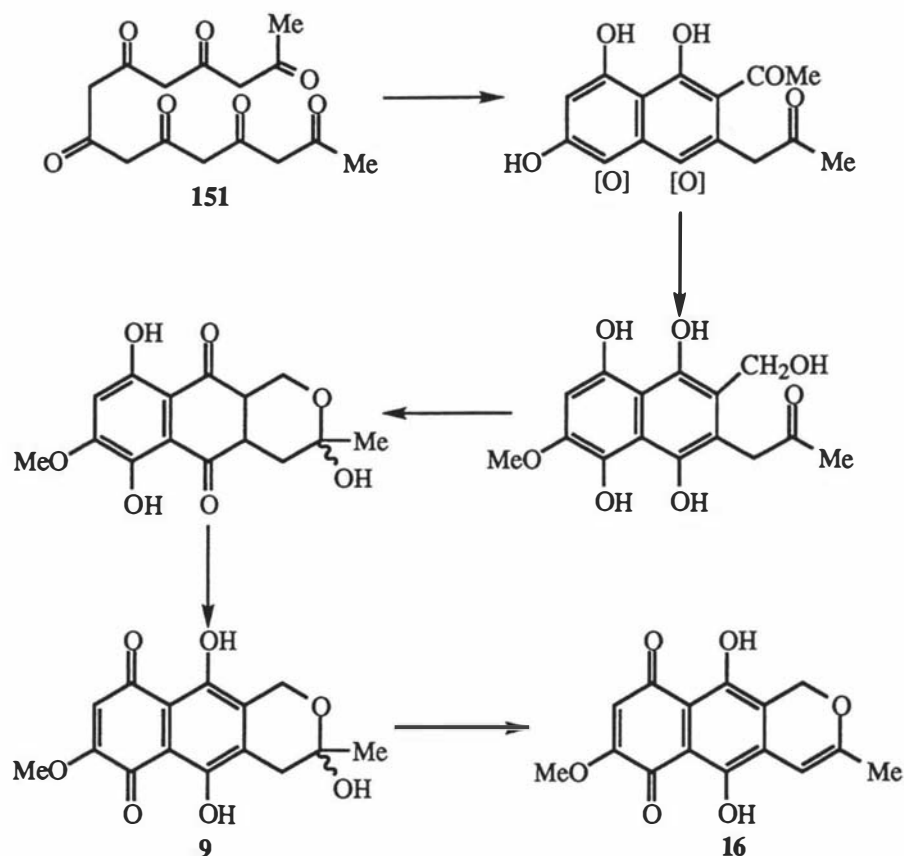
Scheme 10

The biosynthetic relationship amongst the various nanaomycins was studied[224] using the fatty acid synthase inhibitor cerulenin[225] to inhibit *de novo* polyketide (**152**) formation (scheme 11). Cultures of *S. rosa notoensis* were incubated with individual nanaomycins and their transformations to other nanaomycins monitored over time. These experiments revealed that the biosynthetic reaction sequence was conversion of D→A→E→B. As these compounds also undergo chemical interconversion (scheme 4), non-enzymatic transformations were studied as well. All three enzymatic conversions were demonstrated in cell free systems,[226,227] with the enzyme catalysing the first of these, nanaomycin D reductase, being purified and studied in detail. It was found that nanaomycin D **50** is converted to a hydroquinone derivative by the enzyme plus NADH under anaerobic conditions, and that nanaomycin A **47** is then formed nonenzymatically through intramolecular electron transfer.[227] The epoxidation of **47** to nanaomycin E **51** is catalysed by a mixed function monooxygenase requiring NADPH and oxygen.[228] The reductive epoxide opening requires NADH or NADPH and was the first example of such an enzymatic reaction.[228]

47
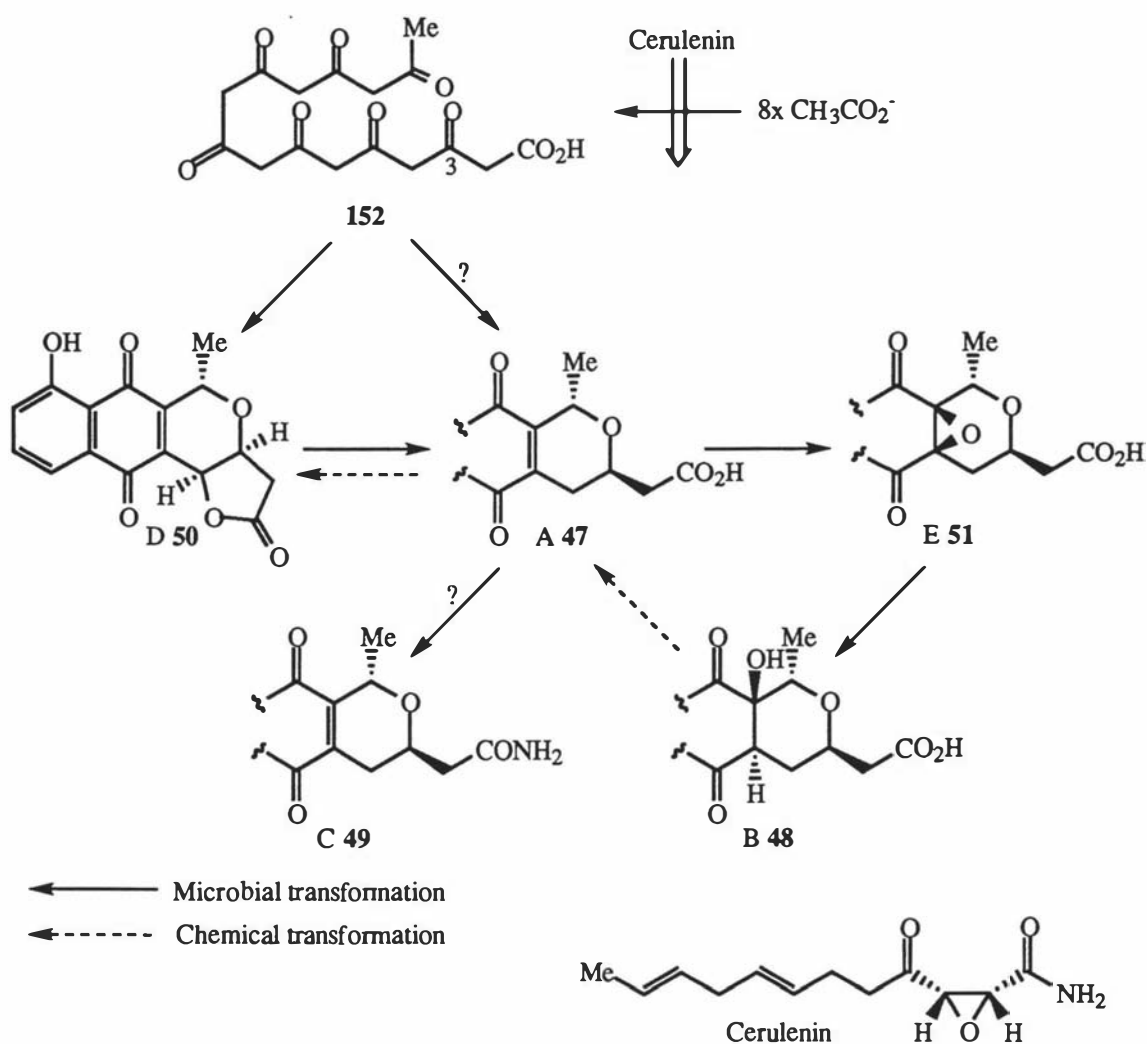
Scheme 11

1.2.2 Carbohydrate Modified Monomers

The question as to whether granaticin **74** was derived entirely from acetate or has a mixed acetate/carbohydrate origin was investigated by two laboratories.[154,229] Both showed that only carbons 1-16 and not carbons 1'-6' (equation 8) were enhanced by the labelled acetate, thus **74** had a mixed biosynthetic origin. Further information on the mode of assembly was found[220] by following the fate of methyl hydrogens and acetate carboxyl oxygens. Using $[2-^{13}C,^{2}H_3]$acetate resulted in incorporation of one atom of deuterium each at C-2 and C-4 (equation 9) suggesting that C-2 of the polyketide chain goes through an intermediate stage of a methine carbon, resulting in the replacement of one deuterium by hydrogen. C-16 carried two not three atoms of deuterium which may be due to rapid equilibrium between acetyl-CoA and malonyl-CoA (figure 10, page 44), or the starter unit may be malonyl-CoA rather than acetyl-CoA. The resulting polyketide would have to be decarboxylated stereospecifically prior to release from the enzyme.

Incorporation of ^{18}O (†) from $[1\text{-}^{13}C,^{18}O_2]$acetate at C-1, 11 and 13 and in the pyran ring was observed, with the pyran oxygen shown to be provided by the C-3 carbonyl group of the polyketide **152** (scheme 11).
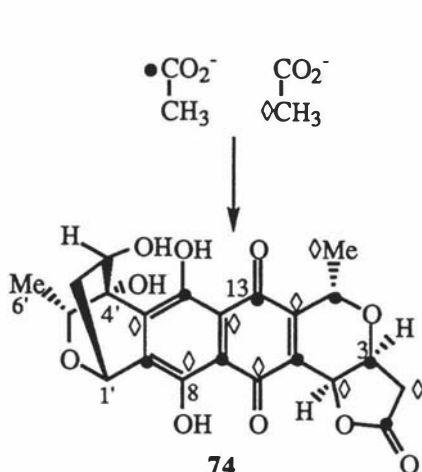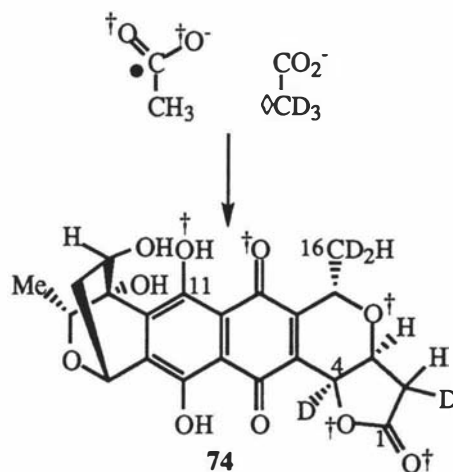
Equation 8   **Equation 9**

As the six carbon bridged moiety was not labelled by acetate, a hexose derived from glucose was a likely alternative. Feeding experiments[154] with glucose labelled in various positions by ^{14}C and tritium (^3H) gave granaticin **74** without a decrease in the $^3H/^{14}C$ ratio, pointing to intact incorporation and retention of both 1'-H (H^a) and 2'-H (H^b) of glucose (equation 10). In contrast, 3'-H (c) and 5'-H (e) were eliminated in the conversion, as shown by doubly labelled glucose samples. This conversion from glucose to the 2,6-dideoxyhexose moiety of **74** involves the removal of the oxygen functionality at C-2' and C-6' and is accompanied by migration of 4'-H (d) to C-6'. These results are characteristic of the glucose oxidoreductase reaction[218] and implicate it as the first specific step in the conversion of glucose to granaticin based on precedent in other streptomycetes.[220] Detailed mechanisms for this transformation (equation 10) have been proposed.[154,218]
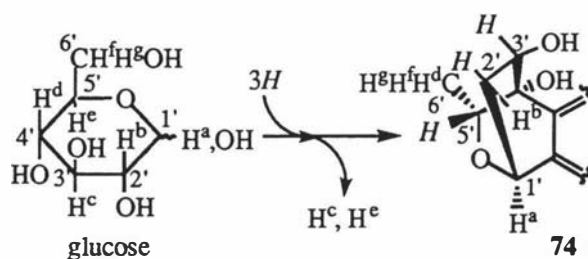
Equation 10

In the attachment of the sugar moiety (in the form of a nucleotide derivative **153**) to the aromatic ring, the regiospecificity of the annelation may be due to two

49

sequences[154] (scheme 12). The first bond formed may be a C-glycosidic linkage between C-1' of the sugar **153** and C-9 (biosynthetic numbering) of an aglycone **154**, followed by an aldol-type condensation between C-10 and the carbonyl group (C-4') of the boat form of **155**. Regiospecificity may be due to recognition of the substitution pattern of the aromatic moiety by the enzyme forming the glycosidic bond. Alternatively, the initial bond is one between C-4' of the sugar **153** and C-10 of nanaomycin A **47**. Subsequent hydroxylation at C-8 and formation of a C-glycosidic bond (between C-9 and C-1' in **156**) completes the structure. The second pathway is favoured as the stereochemistry of the pyran ring can be altered without loosing the regiospecificity of the sugar attachment (refer dihydrogranatirhodin **86**[138-140], page 25). Feeding ^{14}C labelled kalafungin **44** and nanaomycin D **50** did not result in any isotope incorporation into granaticin **74**.[218]
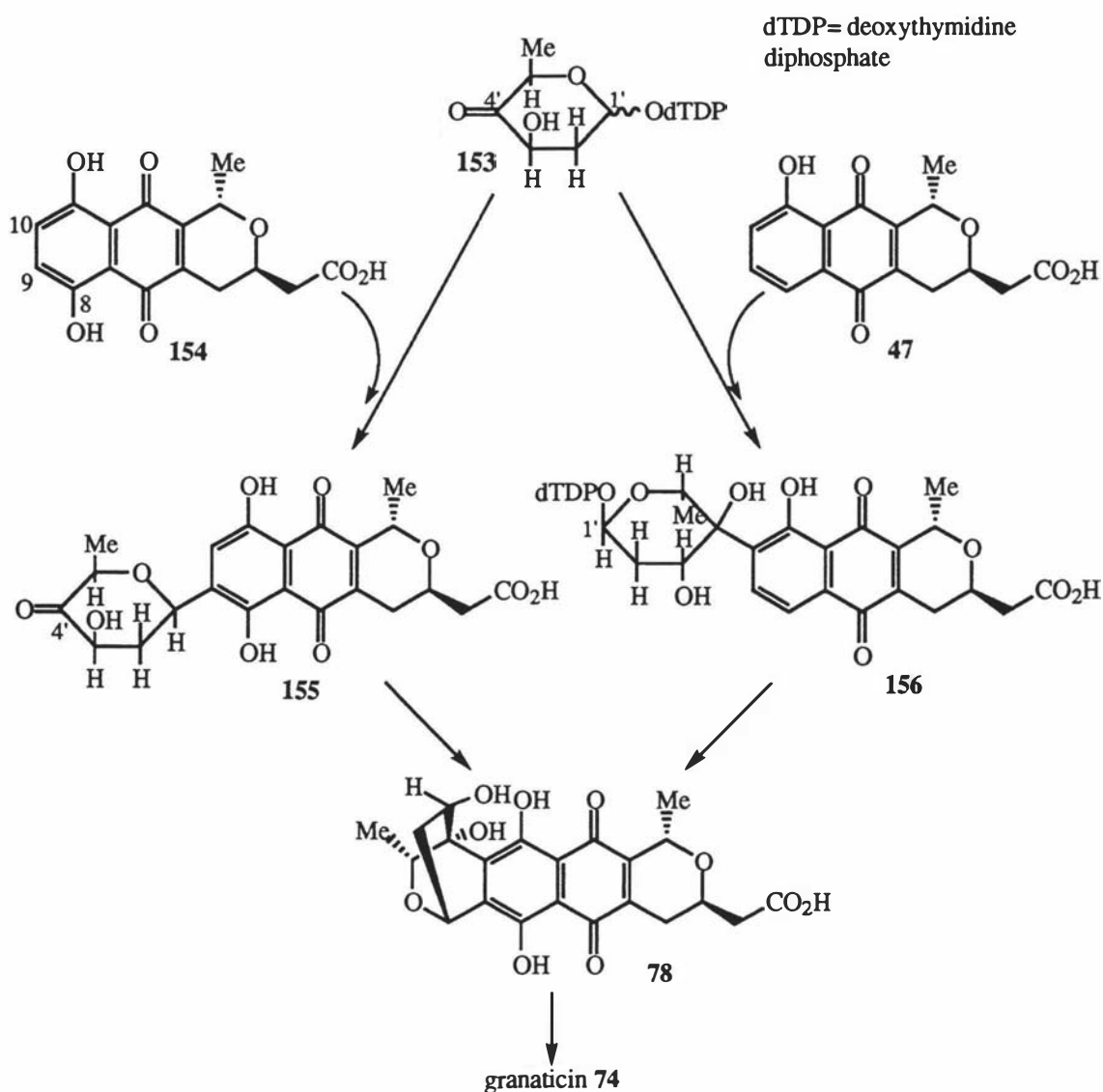
Scheme 12

Contrary to the nanaomycin series, the biosynthetic sequence for granaticin **74** proceeds from the ring opened dihydro form **78** to the lactone (scheme 13). This was established by following the appearance of the two compounds in culture over time,[147,154] and by observing unidirectional conversion of **78** to **74** in cerulenin inhibited cultures[220] and in cell free extracts of *S. violaceoruber*.[147] Whether the enzyme process proceeded *via* a direct cyclization mechanism or by benzylic hydroxylation at C-4 followed by ring closure with loss of water was determined[154] by incubation of the organism under an $^{18}O_2$ atmosphere. Consistent with the mechanism illustrated in scheme 13, no ^{18}O was incorporated into **74** yet the enzymatic reaction was retarded when an atmosphere of argon was used.[154]
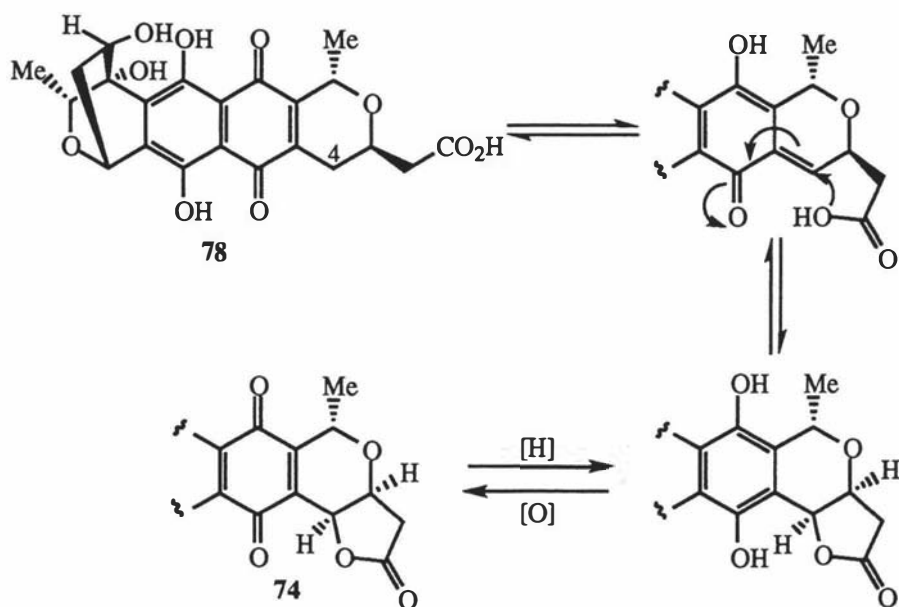
Scheme 13

1.2.3 Dimers

Actinorhodins

The biosynthesis of actinorhodin **71** was proposed early on[187] to come from polyketide precursor **152** (scheme 14), a series of steps leading to **157** which then oxidizes/dimerizes to **71**. The first ^{13}C feeding experiments[192] with *S. coelicolor* using variously labelled acetates and the diacetyl methyl ester of actinorhodin confirmed this acetate/polyketide pathway. Each monomer of the final product was shown to comprise eight intact acetate units (equation 11). The ambiguity from synthetic work over whether the two monomeric units were connected at C-9 or C-10 was solved by these[192] bioenrichment studies. The only sp^2 carbon bearing a directly bonded hydrogen atom

arose from C-1 of an acetate molecule, thus identifying it as C-9 and placing the point of dimerization at C-10.
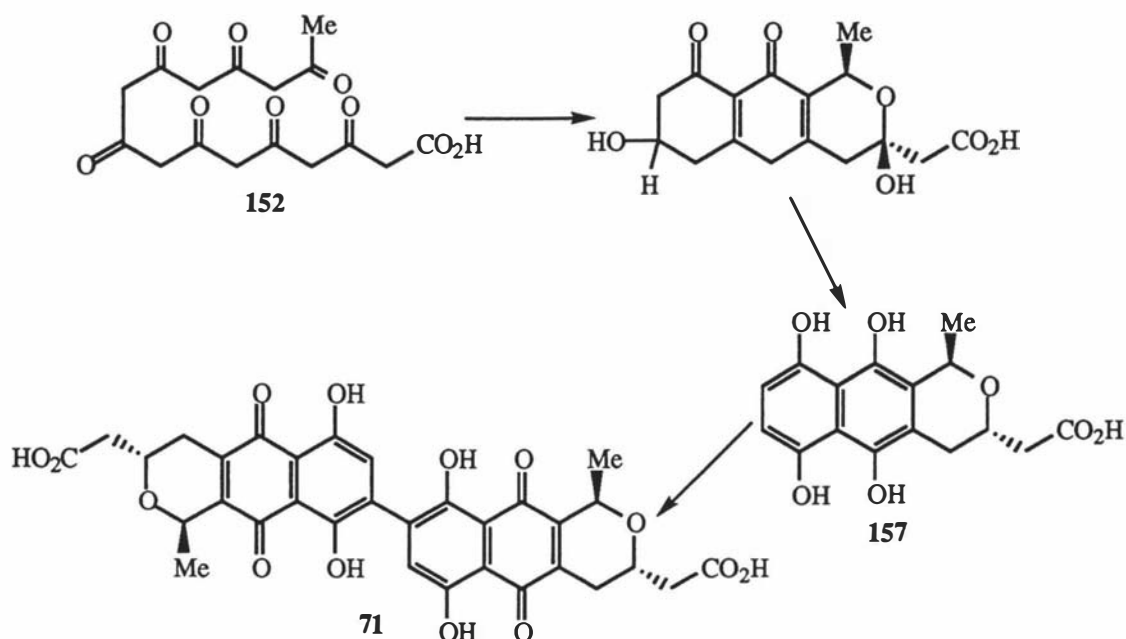
Scheme 14
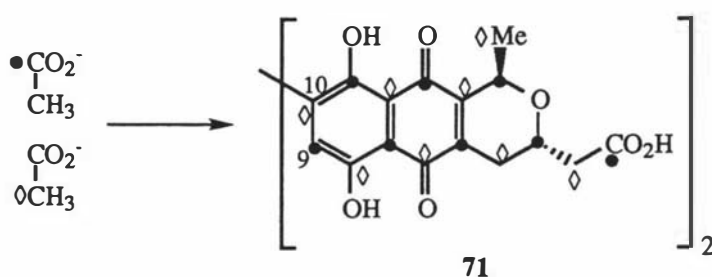
Equation 11

Actinorhodin biosynthesis has been extensively studied[230] by genetic techniques, with *S. coelicolor* being the most characterized member of the genus. Following the establishment of an extensive gene map for this organism, seventy six mutants of *S. coelicolor*, blocked in the biosynthesis of **71**, were isolated[231] and placed into seven groups or classes (figure 11). These groupings were based primarily on where in the biosynthetic pathway they were blocked. Two precursors of **71** that class V (subclass B_1 and B_{135}) could not metabolize were **158** and kalafungin **44** respectively[232,233] (scheme 15). Based on these structures and that of **159** (transformation blocked in class IV), as well as mechanistic extrapolations, a hypothetical pathway of actinorhodin biosynthesis was completed.

Scheme 15
Numbers over arrows indicate those classes unable to effect that transformation

152

postulated B$_{40}$ intermediate

B$_{17}$ intermediate 159

postulated B$_{22}$ intermediate

B$_1$ intermediate 158 ("yellow pigment")

dihydrokalafungin 46

160

actinorhodin 71

kalafungin 44

53

$$\xrightarrow{\text{I, III}} \xrightarrow{\text{VII}} \xrightarrow{\text{IV}} \xrightarrow{\text{VI}} \xrightarrow{\text{V}} \mathbf{71}$$

Mutant Class	Type Strain	Number in Class
I	B78	13
II	2377	26
III	B41	7
IV	B17	5
V	B1	21
VI	B22	2
VII	B40	2
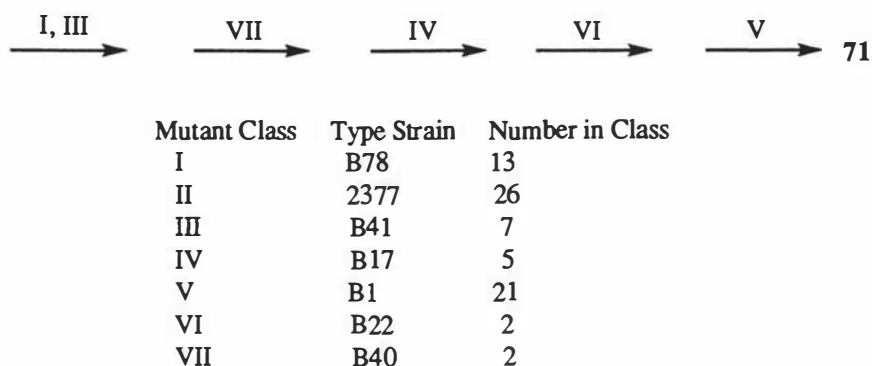
Figure 11

In particular it was proposed that dimerization occurs at the stage of dihydrokalafungin **46** or kalafungin **44** and that the introduction of the C-8 hydroxyl groups (to **160**) is the final step of the reaction sequence. This accounts for the complete regiospecificity of the process {only a linkage through carbons 10 and 10' (biosynthetic numbering) is formed in nature}, which does not require an enzyme that is selective as to the exact structure and stereochemistry at a remote site of its substrate {the various actinorhodins (**71, 93-97**) have differing end fragments and stereochemistries}. Potential biosynthetic pathways to **71** have been proposed and a racemic synthesis of the enantiomer of actinorhodin modelled on these.[234] The common intermediate **161** (scheme 16) can yield **71** by several means, depending on the order of the transformations. In three sequences out of four, hydroxylation is again the final step.

A class VII mutant accumulated copious amounts of a novel sixteen carbon compound mutacin **162**[231] (scheme 17) which although not a precursor of **71**, is related to its biosynthetic pathway. The structure of **162** was correctly determined[235] based on X-ray diffraction and nmr data. [1,2-$^{13}C_2$] labelling revealed its formation from eight intact molecules of acetate in a pattern corresponding to actinorhodin **71**. It is thought to result by a differing mode of cyclization of the open chain polyketide precursor **163**, derived from **152** after reduction at C-9. Mutacin **162**, unusually, may be present as a racemate, which raises interesting questions with regard to enzymatic processes.

Studies[236] showed that the early stages in the biosynthesis of kalafungin **44** in *S. tanashiensis* and actinorhodin **71** biosynthesis in *S. coelicolor* were similar, but the entire pathway in these two *Streptomyces* was not identical. It has been suggested[237] that *S. coelicolor* is misclassified and in reality belongs to the species *S. violaceoruber*, which is known[145] to produce granaticin **74** (refer page 22).
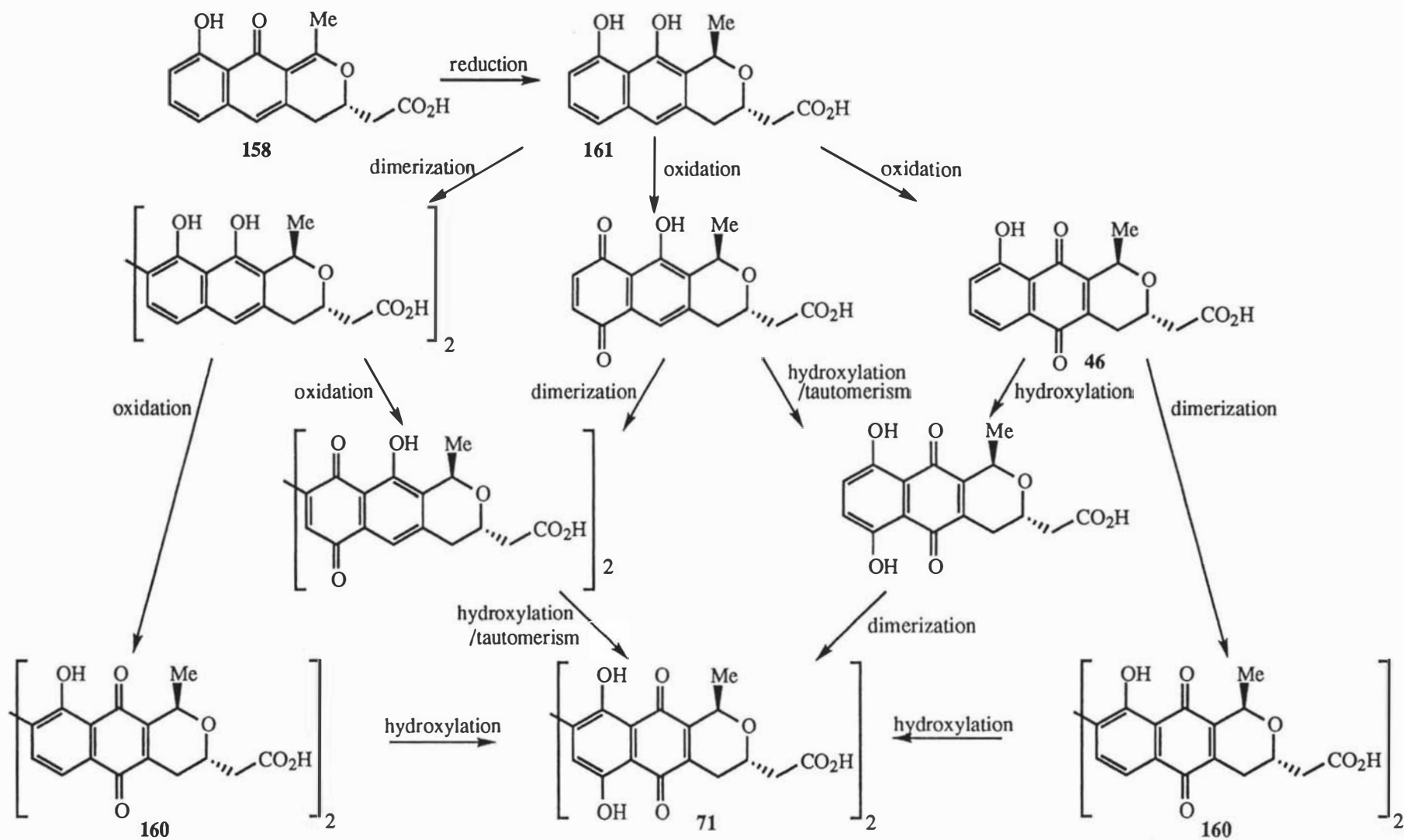
Scheme 16
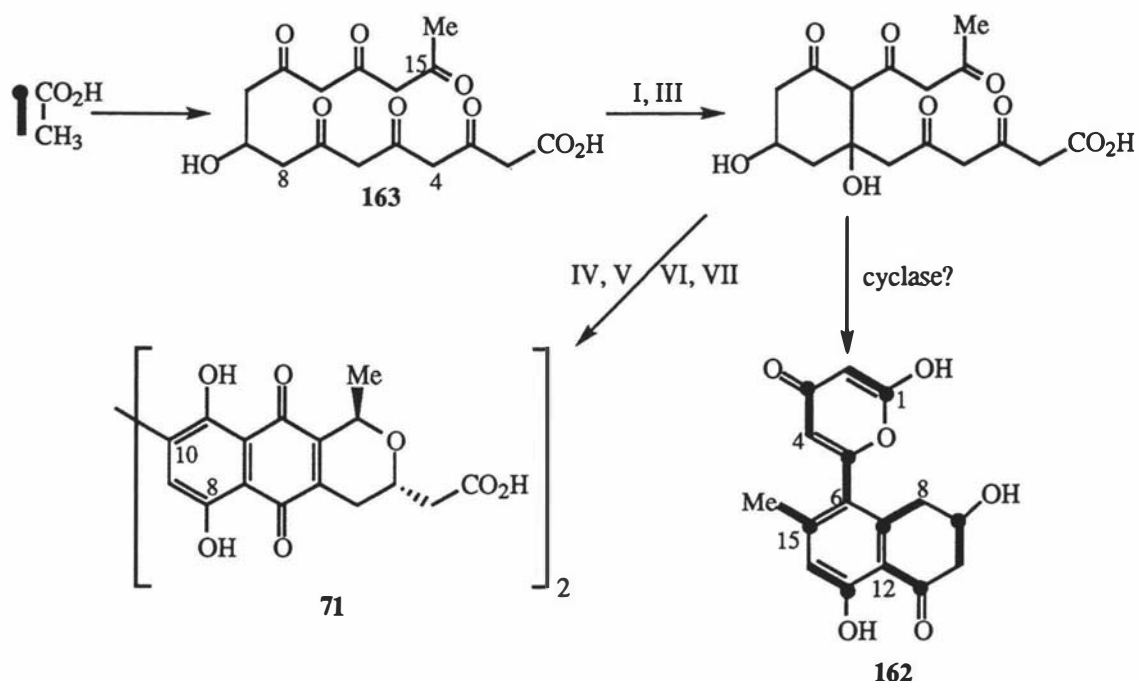
Scheme 17

Crisamycins

As with actinorhodin **71** a polyketide pathway was established for the biosynthesis of crisamicin A **108**[197,238] and C **111**.[239] Using [1-^{13}C]- and [2-^{13}C]acetate the position of linkage and location of the phenolic hydroxyl groups in **108** was determined by ^{13}C nmr enhancement, as was the epoxide position in **111**.

Aphins

Formation of the protoaphins, like other dimeric compounds, clearly involves the coupling of two similar residues. Two possible routes can be envisaged: the precursors are formed in the host plant then ingested by insects and coupled to form pigments, or both synthesis and coupling are carried out in the insect. The second case seems more likely, given that no aphin precursors have been isolated from host plants, and organic substances present in plants (fats, flavanoids) are not transmitted to insects in phloem sap. The pattern of oxygenation in units on which aphid pigments are based is consistent with biosynthesis *via* the acetate/malonate pathway.[199] A biosynthetic pathway is partly illustrated in figure 7: this has been expanded (scheme 18) to show principal biosynthetic precursors and chemical transformation products.[205] Octaketide **152** cyclizes to aglucone **164** which is functionalized to produce both monomeric units (quinone and glucoside) that go to make up the protoaphins. Fusion of the two protoaphin halves leads to the complex planar pigments, dehydration causing the final transformations (refer page 36).

Quinone A **116** : R^1=OH, R^2=R^3=H

Quinone A' **122** : R^1=R^3=H, R^2=OH

? Deoxyquinone **124** : R^1=R^2=R^3=H

Glucoside B **117**

aglucone B **164**

Protoxanthodactynaphin*jc*-1 **129**
Protoxanthodactynaphin*jc*-2

Xanthodactylnaphin*jc*-1 **126**
Xanthodactylnaphin*jc*-2 **128**

Protorhododactynaphin*jc*-1 **130**
Protorhododactynaphin*jc*-2 **131**

Rhododactynaphin*jc*-1 **125**
Rhododactynaphin*jc*-2 **127**

Protoaphin-*fb* **114** : R^1=OH, R^2=H
Deoxyprotoaphin **123** : R^1=R^2=H
Protoaphin-*sl* **115** : R^1=H, R^2=OH

Xanthoaphin-*fb*   Xanthoaphin-*sl*-1 ◄── Xanthoaphin-*sl*-2

Chrysoaphin-*fb*   Chrysoaphin-*sl*-2   Chrysoaphin-*sl*-1

Erythroaphin-*fb* **121**   Erythroaphin-*sl* ◄── Chrysoaphin-*sl*-3

Scheme 18

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Phenocyclinone

A biosynthesis of phenocyclinone **132** was postulated[214] to involve the condensation of two polyketide chains, one an octaketide **152** and the other a C_{19} nonaketide **165** containing one propionate instead of an acetate unit (scheme 19). However in view of the production of both actinorhodin **71** and **132** from *S. coelicolor*, the formation of a dimer from two C_{16} units (**152**) and insertion of a three carbon moiety **166** is more plausible.
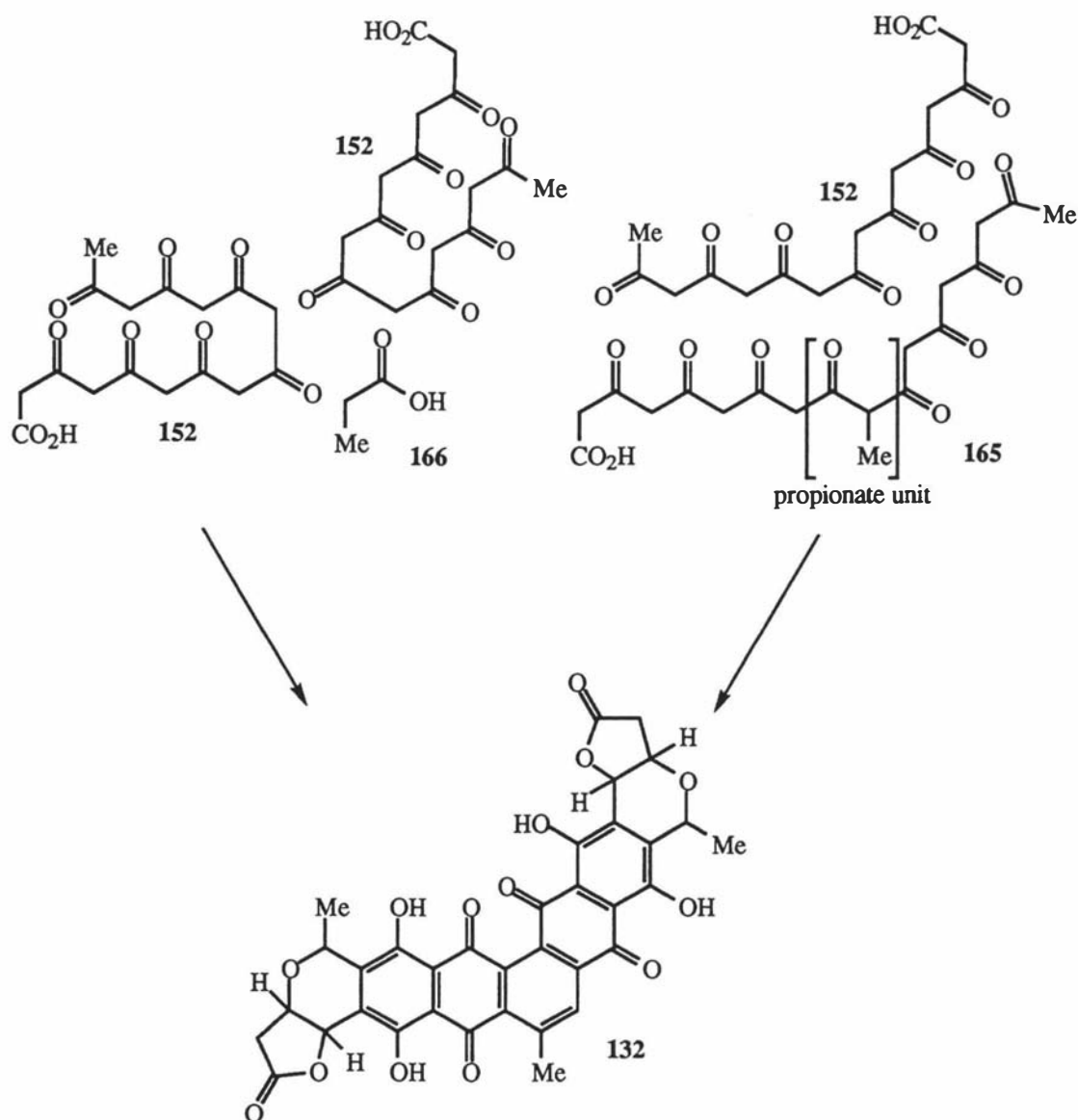
Scheme 19

Naphthocyclinones

The use of [1-^{13}C]- and [2-^{13}C]acetate and diethyl [2-^{13}C]malonate gave the enrichment pattern (equation 12) for α-naphthocyclinone **133**.[240] All carbons atoms of **133** originate from acetate in the alternating labelling pattern predicted by the polyketide

pathway. α-Naphthocyclinone contains only fourteen carbons in the "right hand" portion and could have arisen from two different monomers, one a normal C_{16} unit and the other a C_{14} polyketide. The co-occurrence of β- **134** and γ-naphthocyclinone **135** suggests however that all three are derived by dimerization of two C_{16} units, followed in the case of **133** by loss of two carbon atoms. An additional acetate moiety gives rise to the acetoxy group. The involvement of two polyketide chains follows particularly from the finding that two directly connected carbons in the centre of the molecule (C-10 and C-10', equation 12) are both derived from C-2 of acetate.
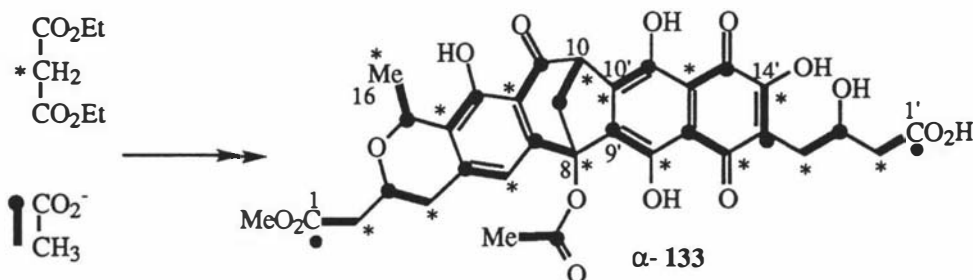
Equation 12

A possible mechanism for the dimerization of two monomers to give the naphthocyclinone systems was proposed[175] (scheme 20). Based on unsymmetric quinone dimers being less common than symmetric ones, it was suggested that the condensation of two monomeric units occurs at an early stage and leads to a symmetric non-quinoid dimer, which is then modified differently in each of the two halves. If this modification led to an intermediate such as **167**, reduction of one of the quinone moieties followed by phenol-carbonyl addition would give an aryl ketone structure **168** as in the naphthocyclinones. Labelling data (equation 12) is in accord with this but initial dimerization involving two differently modified monomeric precursors cannot be ruled out.

A detailed study of the interconversions among naphthocyclinones in *S. arenae* has been carried out.[241] Individual naphthocyclinones (**133-135, 137**) were prepared in ^{14}C labelled form by biosynthesis from [1-^{14}C]acetate then fed individually to cultures of *S. arenae*. Radioactivity distribution after metabolism indicated the biosynthetic reaction sequence shown in scheme 21. The main sequence γ- **135**→β- **134**→β-epoxide **137**→α-naphthocyclinone **133** parallels that seen in the nanaomycin series (D **50**→A **47**→E **51**→B **48**: scheme 11, page 48) rather than that found for granaticin (**78**→**74**: scheme 13, page 51). The lactone ring of **135** undergoes reductive ring opening to **134**, which is then epoxidized to **137**. Side reactions of **134** and **137** lead to δ-naphthocyclinone **139** and β-naphthocyclinone chlorohydrin **136** respectively. The main route of metabolism however involves conversion of the epoxide **134** and/or chlorohydrin **136** of β-naphthocyclinone

59
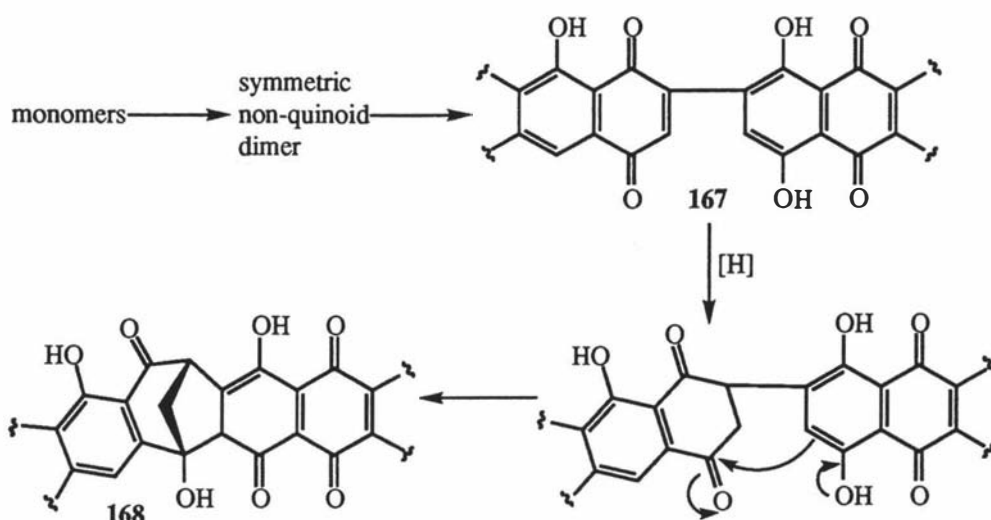
Scheme 20

to α-naphthocyclinone **133**. This reaction has chemical precedent, as both **134** and **136** upon photolysis and hydrolysis give **133**.[216] The conversion of **134** to **139** is obscure and nothing is known about the source of the additional three carbon atoms. α-naphthocyclinone **133** is further transformed into the corresponding acid **169**, the end product of the pathway.

The "monomer" **145**, a degradation product of the naphthocyclinones[175,215] (scheme 6, refer page 41) and the corresponding "dimer" **170** were fed to the producing organism in radiolabelled form. **145** was incorporated into the naphthocyclinones approximately four times more efficiently than **170**, suggesting that **145** may serve as a precursor of the "left hand" half of the naphthocyclinones. The incorporation difference also suggests that dimerization occurs either at the stage of a product derived from **145**, or involves **145** and another monomeric unit to give an unsymmetrical dimer unit.

145

170

γ- **135** : R=Me

β- **134** : R=Me

β chlorohydrin **136** : R=Me

β epoxide **137** : R=Me

δ- **139** : R=Me

α- **133** : R=Me

———▶ firmly established

----▶ probably occurring

α-naphthocyclinone acid **169** : R=H

Scheme 21

61
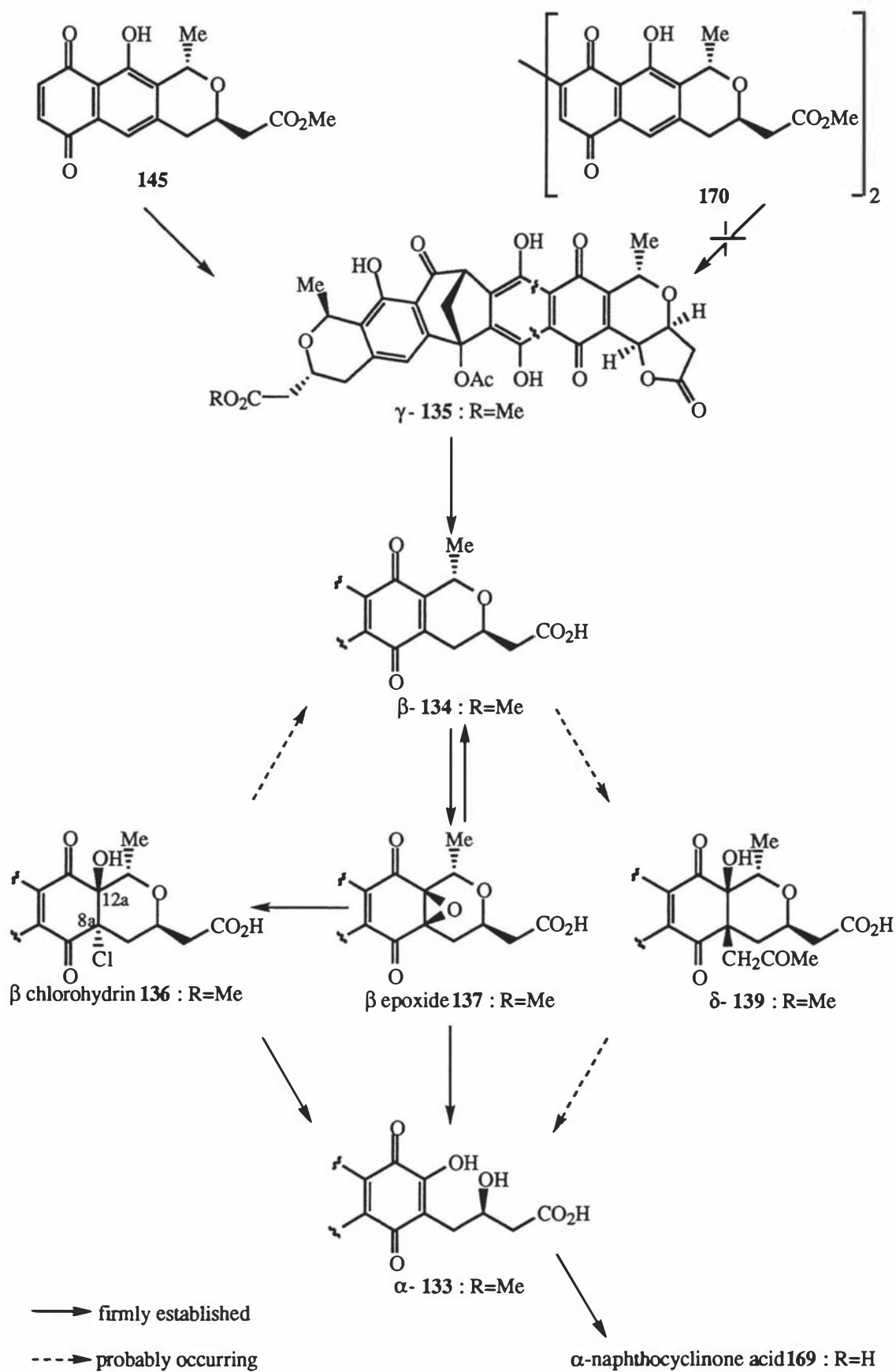
Pyranonaphthoquinones not detailed in section 1.2 have not been subject to such close biosynthetic scrutiny and are presumed to have origins identical to the above mentioned compounds. For example, the biosynthesis of griseusin A **88** itself is stated[242] to begin with a 20 carbon chain, formed by successive condensation of short chain carboxylic acids. The carbon chain is subsequently cyclized and modified to give the final structure. Other monomers such as medermycin **69** with a C-10 modified structure (figure 9, page 43) are no doubt similarly constructed by a myriad of "post-polyketide" modifications.[243]

1.3 Related Syntheses of Pyranonaphthoquinones

1.3.1 Conjugate Addition to Quinones

Addition of 2-*tert*-butoxyfuran **171**

The main approaches to the pyranonaphthoquinone antibiotics based on conjugate additions to activated quinones have made use of butenolide anion equivalents as the nucleophilic component. Methodology developed by Kraus *et al.*[244] made use of 2-*tert*-butoxyfuran **171** as such an anion equivalent. Addition of **171** to 2-acetyl-1,4-naphthoquinone **172** (scheme 22) gave Michael adduct **173** which was reductively methylated *in situ* to afford **174**.[245] Hydride reduction to alcohol **175** and deprotection of the *tert*-butoxy group gave a mixture of β, γ-unsaturated butenolide **176** and cyclized product **177** (2.7:1 ratio). Remaining **176** was isomerized to the "unmasked" α, β-butenolide **178** and cyclized *in situ* using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Oxidative demethylation of **177** gave **179** and (±)-7-deoxykalafungin **180** as a mixture of epimers. No stereocontrol at C-5 was exercised in this approach, however epimerization to the natural configuration is achieved with anhydrous acid. The generality of the key addition step was probed and it was found that under no conditions, including lewis acid catalysis, would furan **171** react with *unactivated* quinones (no electron withdrawing substituent).

In a similar manner naphthoquinone **181** was transformed[246] into pyranonaphthoquinone **182** as a *single* isomer (5-Me *trans* to the lactone ring), deprotection of which by BCl₃ gave a racemic mixture comprising kalafungin **44** and nanaomycin D **50**. The addition of **171** to **181** took 24 hours versus rapid reaction for **172**, and deprotection/cyclization was effected more easily for the methoxy analogue of **175**. This sequence provides a very direct route to the target compounds but has modest overall yield.
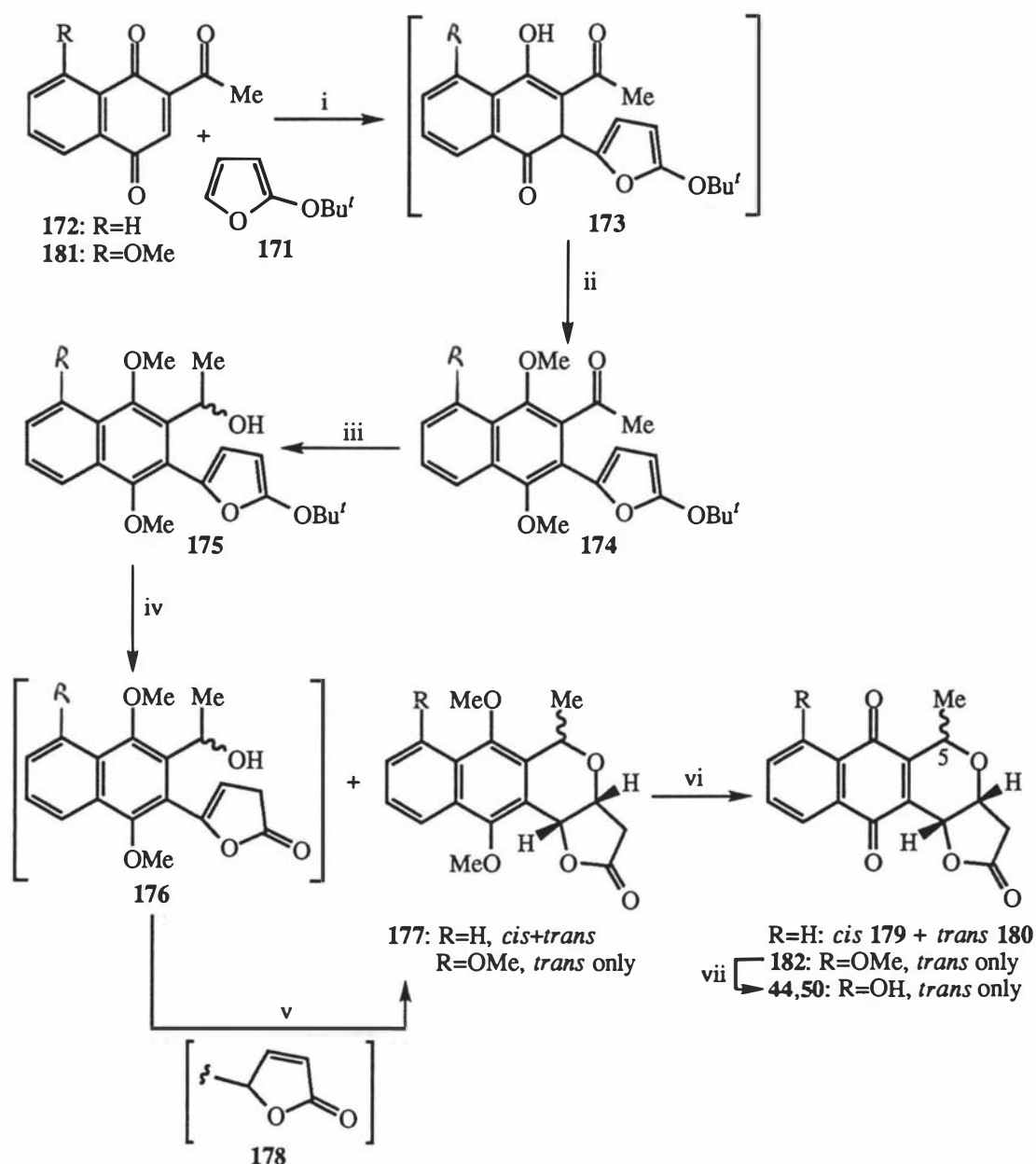
Reagents and Conditions: (i) PhCH$_3$, -78°C to RT; (ii) Me$_2$SO$_4$, K$_2$CO$_3$, Me$_2$CO, reflux; (iii) LiAlH$_4$, Et$_2$O, -10°C, N$_2$; (iv) CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0°C to RT, N$_2$; (v) DBU or DBN, C$_6$H$_6$, RT; (vi) AgO, THF, 6N HNO$_3$; (vii) BCl$_3$, CH$_2$Cl$_2$, -78°C.

Scheme 22

A close analogue of granaticin **74** was elaborated[247] by addition of **171** to advanced intermediate **183** (scheme 23). Quinone **183** was generated from the corresponding dimethyl ether, and gave **184** after Michael addition of **171** and subsequent methylation. Reduction of the acetyl group gave a diastereomeric mixture of carbinols **185** which were subjected to a deprotection/cyclization sequence, giving four diastereomeric pyranlactones (*trans:cis* 4:1). From this mixture, *trans*-**186** was isolated and oxidized to **187**, the diol functionality requiring protection as an acetonide or

63

carbonate before the oxidation. The oxabicyclic system could not withstand O-demethylation conditions and so (±)-granaticin **74** was not realized by this route.
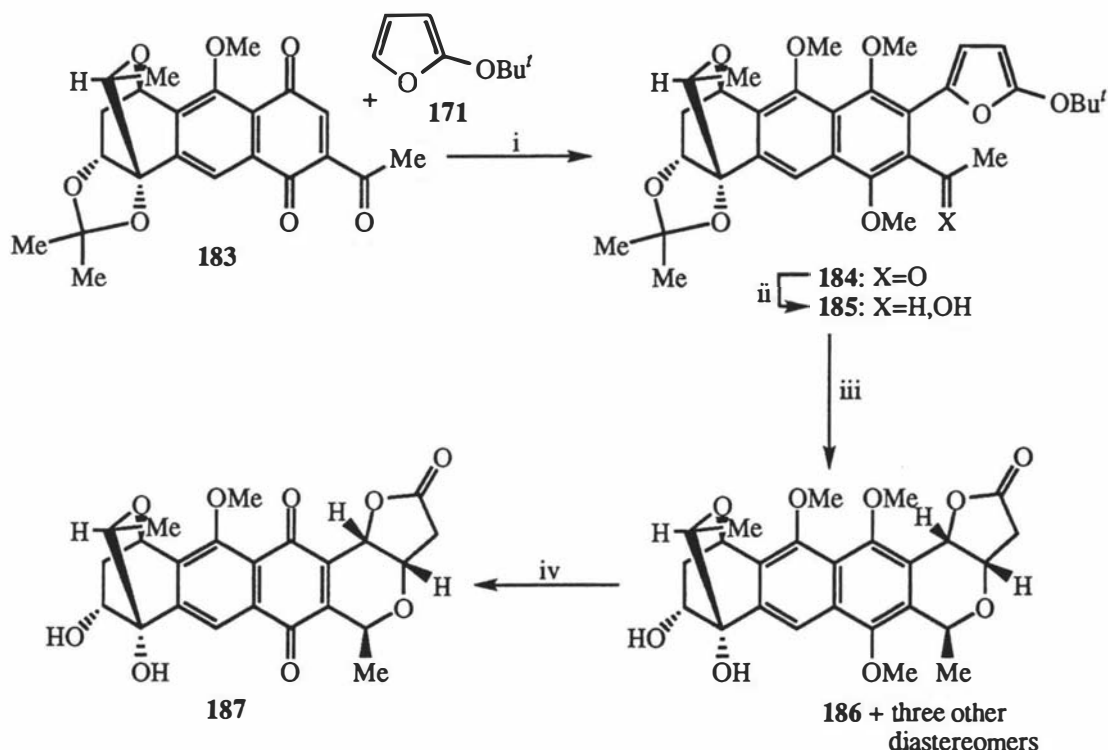
Reagents and Conditions: (i) a: Me $_2$CO, -70 to -10°C; b: Me $_2$SO$_4$, K$_2$CO$_3$, reflux; (ii) LiAlH $_4$, Et$_2$O, -50 to -30°C; (iii) a: TsOH (cat.), MeCN, RT; b: DBU, PhCH$_3$ /CH$_2$Cl$_2$, -10°C; (iv) a: protection; b: aq. CAN, MeCN, RT; c: TsOH (cat.), MeCN, RT.

Scheme 23

Addition of 2-trimethylsilyloxyfuran **189**

Brimble *et al.*[248-255] have undertaken a program of pyranonaphthoquinone synthesis based on a furonaphthofuran annulation coupled with a ceric ammonium nitrate (see section 2.3, page 99) oxidative rearrangement. Early work[248,249] directed towards the fish antifeedant panacene **188**[256] looked at the uncatalysed addition of 2-trimethylsilyloxyfuran **189** (see section 2.1.5, page 84) to C-2 activated quinones (scheme 24). A facile entry to the *cis*-3a,8b-dihydrofuro[3,2-b]benzofuran-2(3*H*)-one[248,249] and *cis*-6b,9a-dihydrofuro[3,2-b]naphtho[2,1-d]furan-8(9*H*)-one[248,250,251] ring systems was achieved by this procedure.

R=CO₂Me, COMe, SOPh, CO₂CH₂CCl₃,
CO₂CH₂COPh, SPh, Cl, H

dihydrofuro[3,2-b]benzofuran system

172 : R=H
181 : R=OMe   189

190 : R=H
191 : R=OMe

dihydrofuro[3,2-b]naphtho[2,1-d]furan
system
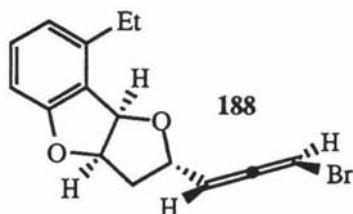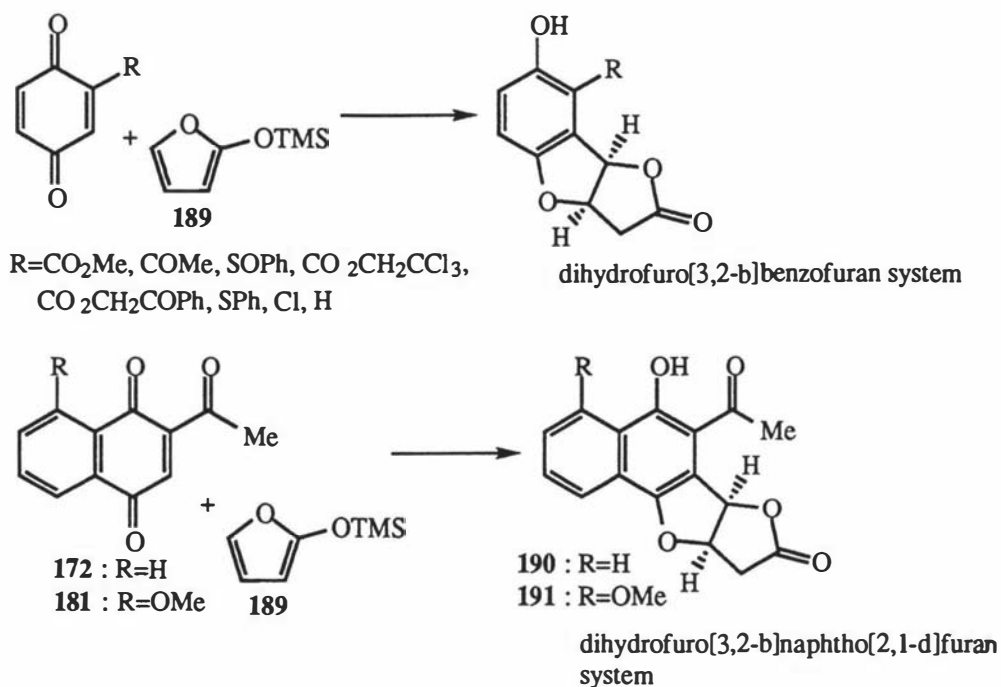
Reagents and Conditions: MeCN, 0 °C, N₂, RT, MeOH.

Scheme 24

From the products isolated, it was envisaged that after initial 1,4-addition of **189** *ortho* to the activating group (R) on the quinone ring, aromatization, followed by a second 1,4-addition of the resulting phenoxy group onto the neighbouring butenolide moiety had occurred, providing the desired heterocycle (scheme 25). For a detailed discussion of this mechanism see section 2.2, page 87.

R'=H (benzoquinone),
-C₄H₄- (naphthoquinone)
R=activating group
(usually ketone)
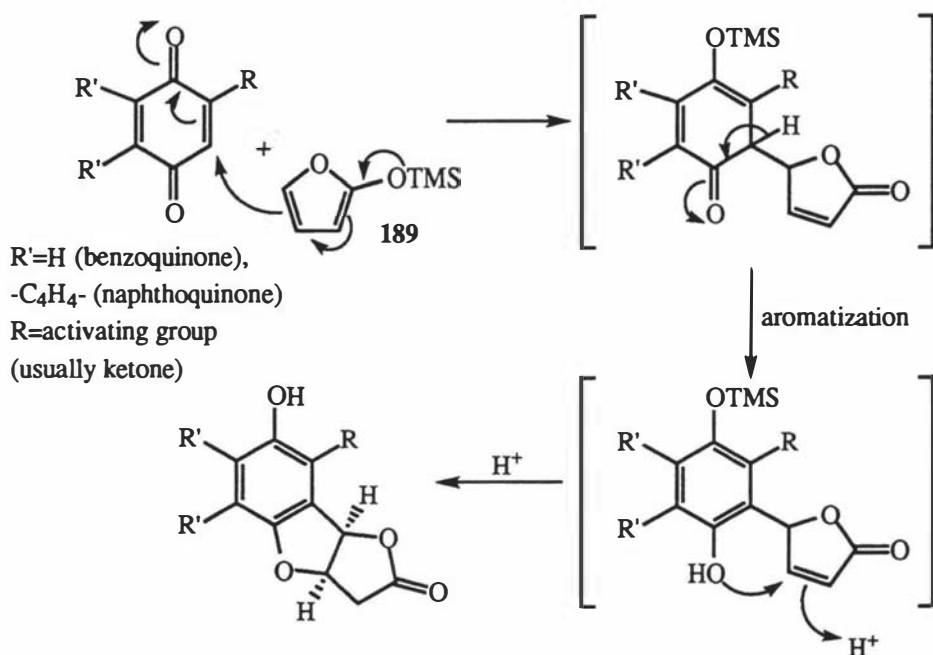
aromatization

Scheme 25

65

Whilst the 1,4-addition of various nucleophiles to quinones had been demonstrated,[245,257-260] the potential of this addition-aromatization sequence for generating the furofuran ring system had not been realized. 1,4-Addition of 2-(*tert*-butoxy)furan 171[245] (*vide supra*) did not result in formation of a butenolide moiety and subsequent cyclization, due to the robust nature of the *tert*-butoxy group. Thus, the use of a silyloxyfuran, being more labile than an alkoxyfuran, encouraged butenolide formation and subsequent ring closure.

There were few examples of such furofuran ring systems occurring naturally, however it was found that a rearrangement could be effected to form the more common γ-pyranolactone, as found in the pyranonaphthoquinone family of antibiotics, and a synthesis of racemic kalafungin 44 was completed (scheme 26). Castagnoli *et al.*[261] had reported that ceric ammonium nitrate in aqueous acetonitrile could be used to oxidize hydroquinone methyl ethers to their corresponding quinones (equation 13), this method being used to generate the quinones used in our 2-trimethylsilyloxyfuran 189 additions.[248-255] On the basis of this reaction it was proposed that the furo[3,2-b]naphtho[2,1-d]furans so formed (190,191, schemes 24 and 26), as cyclic ethers of a hydroquinone, should also undergo an analogous oxidative dealkylation to afford β-hydroxylactones 192,193 (scheme 26). Subsequent nucleophilic attack of the hydroxyl group onto the methyl ketone would then give rise to a pyranlactone (194,195).

R^1=H, Me, OMe

R^2=H, Me, CH_2OH, RCONHR'
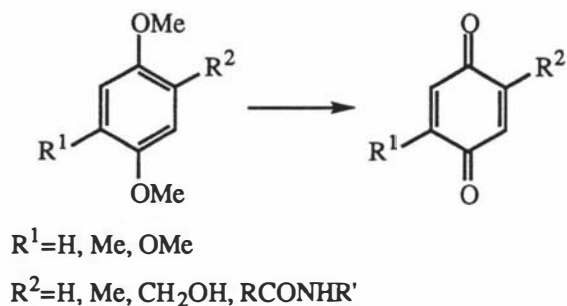
*Reagents and Conditions:*MeCN, H_2O, CAN, RT.

Equation 13

Addition of an aqueous solution of ceric ammonium nitrate (2 equivalents) to methyl ketone adducts 190,191 produced[250,251] the anticipated pyranonaphthoquinones 194,195 (scheme 26). Using the method of Kraus *et al.*[262] the hemiketals were reduced to ethers 179,196, with a *cis* relationship between the alkyl groups at C-5 and C-3a. With (±)-*epi*-7-deoxykalafungin 179 and (±)-*epi*-7-*O*-methylkalafungin 196 synthesized, subsequent treatment of 196 with *excess* boron tribromide effected both epimerization at C-5 and deprotection of the methyl ether to afford a mixture of kalafungin 44 and

nanaomycin D **50**.[263] An attempt to similarly rearrange/transform the analogous benzofuran adducts (scheme 24) was poor yielding and produced polymeric material.[249]

190 : R=H
191 : R=OMe

192: R=H
193: R=OMe

194 : R=H
195 : R=OMe

179 : R=H
196 : R=OMe

(±)-**44**
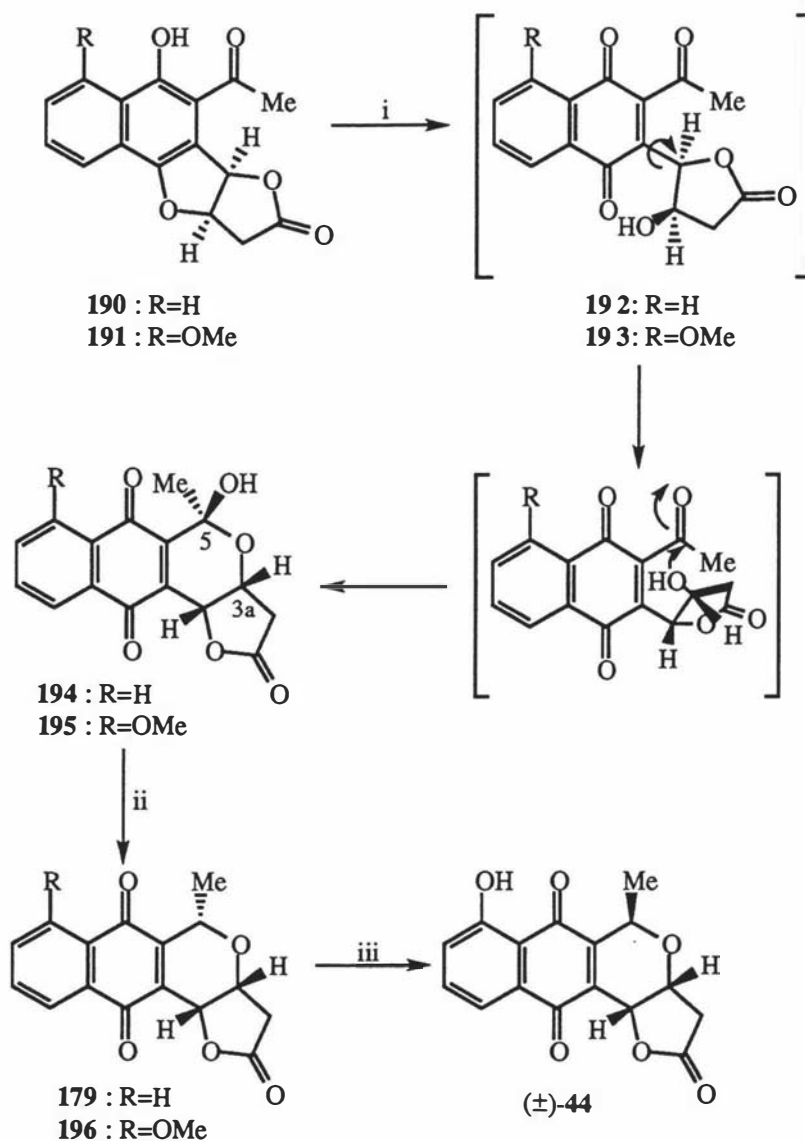
Reagents and Conditions:(i) aq. CAN, MeCN, RT; (ii) CH$_2$Cl$_2$, -78°C, N$_2$, TFA, Et$_3$SiH, RT; (iii) BBr$_3$ (excess), CH$_2$Cl$_2$, -78°C to RT.

Scheme 26

The methodology demonstrated by the synthesis of **179** and **196**[250,251] was later applied to the arizonins[254] and the frenolicins.[255] A synthesis of (±)-5-*epi*-arizonin B1 **197** and (±)-5-*epi*-arizonin C1 **198** was accomplished[254] by starting with the appropriately substituted naphthoquinone **199** (scheme 27). Treatment of bromotosylate **200** with butyllithium in the presence of furan, followed by ring opening of the resultant dihydrofuran gave 7,8-dimethoxynaphthalen-1-ol **201**. The acetate of this underwent Fries rearrangement to naphthol **202** using boron trifluoride etherate. Silver(II) oxide

oxidation of **202** gave quinone **199**, which was transformed to hemiketal **203** by previously described methods.[251] Reduction *via* axial hydride delivery[262] afforded (±)-5-*epi*-arizonin C1 **198**, selective demethylation of which gave (±)-5-*epi*-arizonin B1 **197**.
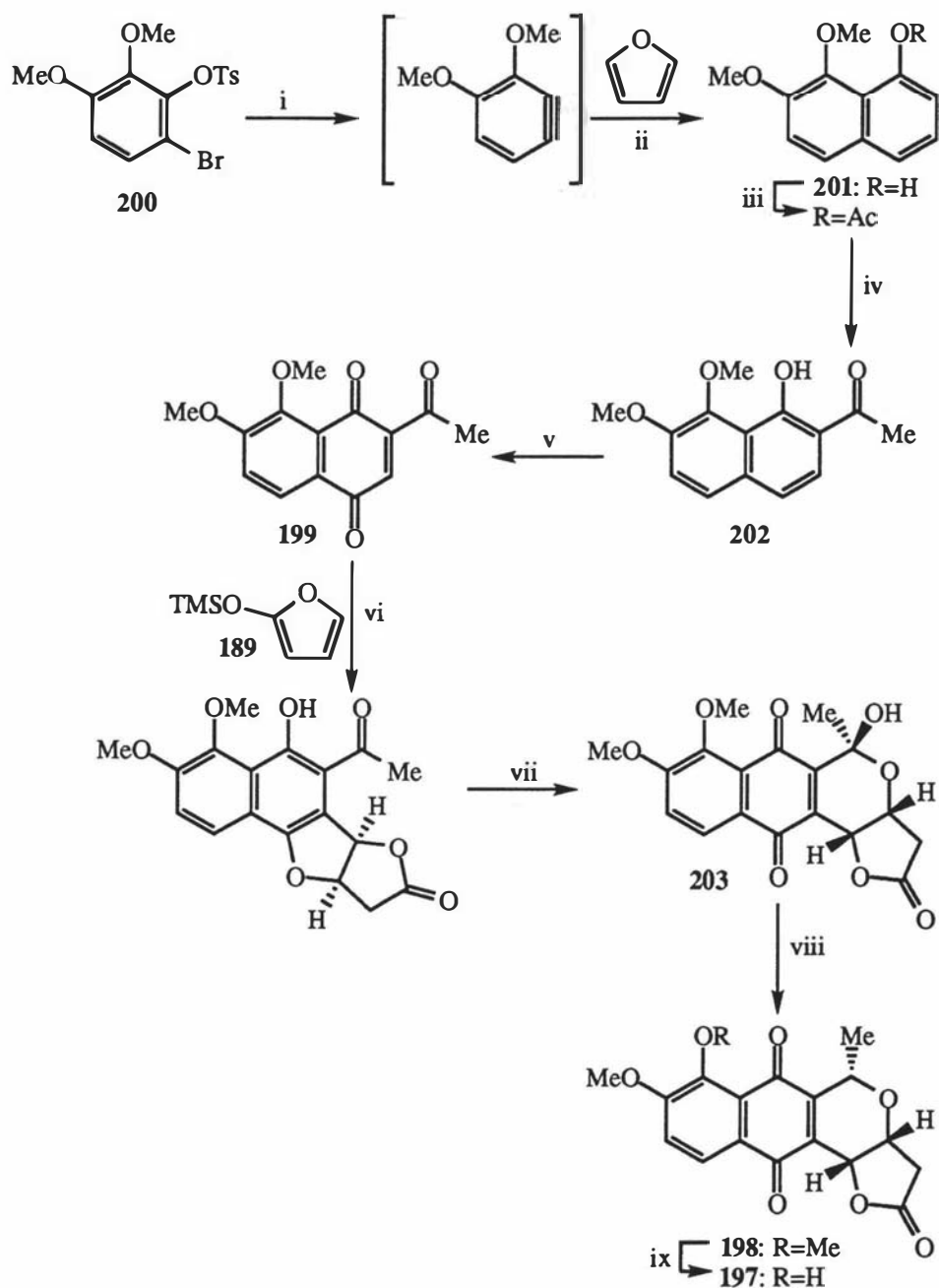
Reagents and Conditions: (i) Bu^{n}Li, THF, -78°C; (ii) conc. HCl, MeOH, reflux; (iii) Ac$_2$O, Et$_3$N, DMAP (cat.), CH$_2$Cl$_2$; (iv) BF$_3$.Et$_2$O, 95°C; (v) AgO, dioxane, conc. HNO$_3$, RT; (vi) MeCN, 0°C, N$_2$; (vii) aq. CAN (2 equiv.), MeCN, RT; (viii) Et$_3$SiH, TFA, RT; (ix) BBr$_3$ (2 equiv.), CH$_2$Cl$_2$, -78°C to RT.

Scheme 27

68

In the synthesis[255] of (±)-frenolicin 60, hydrogenation followed by demethylation provided the desired *trans*-compound 204 (scheme 28). Adduct 205, containing a butanoyl moiety, was formed from the addition of 189 to naphthoquinone 206. Oxidative rearrangement of 205 then furnished hemiketal 207. Attempts to reduce 207 by triethylsilane/trifluoroacetic acid[262] were complicated by decomposition of the resulting product 208, the instability of which was suggested to be due to the large propyl substituent being *cis* to the methylene group of the γ-lactone, creating unfavourable 1,3-interactions.

The successful conversion of 207 to (±)-58 was achieved by hydrogenation over palladium on charcoal to give the crude carboxylic acid, which was methylated to aid isolation. Deprotection of the *cis*-methyl ester 209 to the corresponding naphthol using boron tribromide also effected epimerization at C-1, resulting in formation of *trans*-naphthol ester 204. Hydrolysis of 204 then gives[264,265] (±)-deoxyfrenolicin 58.
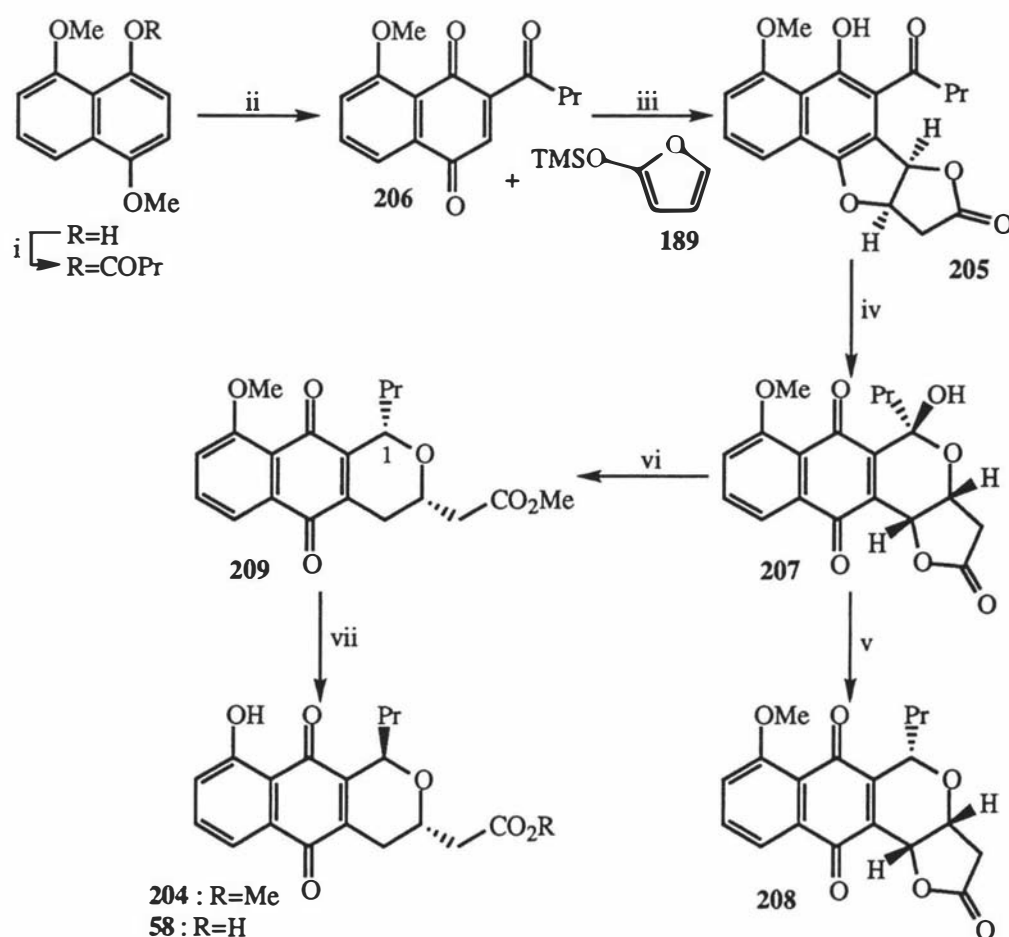
Reagents and Conditions: (i) (Pr^{n}CO)$_2$O, py, RT; (ii) 120 °C, BF$_3$.Et$_2$O; (iii) MeCN, 0 °C, N$_2$, MeOH, RT; (iv) aq. CAN (2 equiv.), MeCN, RT; (v) Et$_3$SiH, TFA, -78 °C to RT; (vi) a: Pd/C (cat.), EtOAc, H$_2$, RT; b: CH$_2$N$_2$, Et$_2$O, RT; (vii) BBr$_3$ (10 equiv.), CH$_2$Cl$_2$, -78°C to 0°C.

Scheme 28

This hydrogenation/deprotection sequence developed for the synthesis of (±)-deoxyfrenolicin was also employed[255] to prepare (±)-nanaomycin A **47** from hemiketal **195** (scheme 26, page 67).

The pentacyclic ring system (**210**) of griseusin A **88** was synthesized[252,253] along with **211** using the furonaphthofuran annulation and ceric ammonium nitrate oxidative rearrangement of Brimble *et al*. Assembly of the initial furo[3,2-b]naphtho[2,3-d]furan **212** required the synthesis of naphthoquinone **213** (scheme 29), derived from the corresponding dimethyl ether **214**. Thus condensation of the lithium acetylide of **215**[266] with 1,4-dimethoxy-2-naphthalenecarboxaldehyde **216**[260,267] afforded an isomeric mixture of alcohol **217**. Oxidation[268] using activated manganese dioxide[268b,269] gave almost quantitatively ketone **218**, which was hydrogenated over palladium on charcoal affording **214**, then oxidatively demethylated to produce quinone **213**.

Addition of 2-trimethylsilyloxyfuran **189** to **213** gave furofuran adduct **212** as a 1:1 isomeric mixture (^{1}H nmr spectroscopy) that was inseparable by flash chromatography. Rearrangement of the isomeric mixture of adducts and concomitant deprotection of the *tert*-butyldimethylsilyl group was accomplished by the use of excess ceric ammonium nitrate (eight equivalents). Treatment of the corresponding diol **219** with camphorsulphonic acid under reflux afforded a 2:1 ratio of the two spiroketal isomers **210** and **211**, both as racemic mixtures, that in this case were easily separated by flash chromatography. The isomer **210** in which the fused γ-lactone ring occupies an equatorial position at C-3a is favoured over isomer **211** (figure 12), where this methylene group (occupying a pseudo-axial position) exhibits unfavourable steric interactions with the oxygen atom O-1'. Due to the 1,3-diaxial arrangement of O-1' and 3a-H in **210**, 3a-H resonated further downfield in this isomer than in **211**, thus supporting the assigned structures.

Figure 12

Reagents and Conditions: (i) **215**, THF, -78 °C, Bu^{n}Li, -78 to -60 °C, then **216**; (ii) excess MnO$_2$, CH$_2$Cl$_2$, RT; (iii) H$_2$, 5% Pd/C (cat.), EtOAc, RT; (iv) aq. CAN (1.9 equiv.), MeCN, RT; (v) MeCN, 0 °C, N$_2$, RT, MeOH; (vi) aq. CAN (8 equiv.), MeCN, RT; (vii) CH$_2$Cl$_2$, CSA (cat.), reflux.

Scheme 29

71
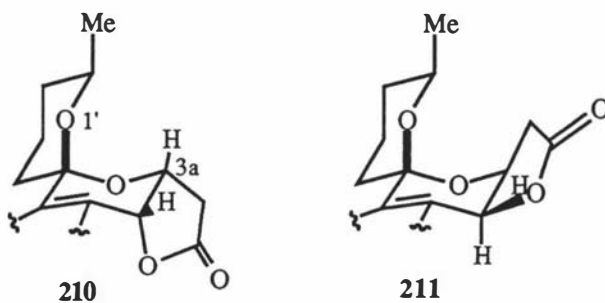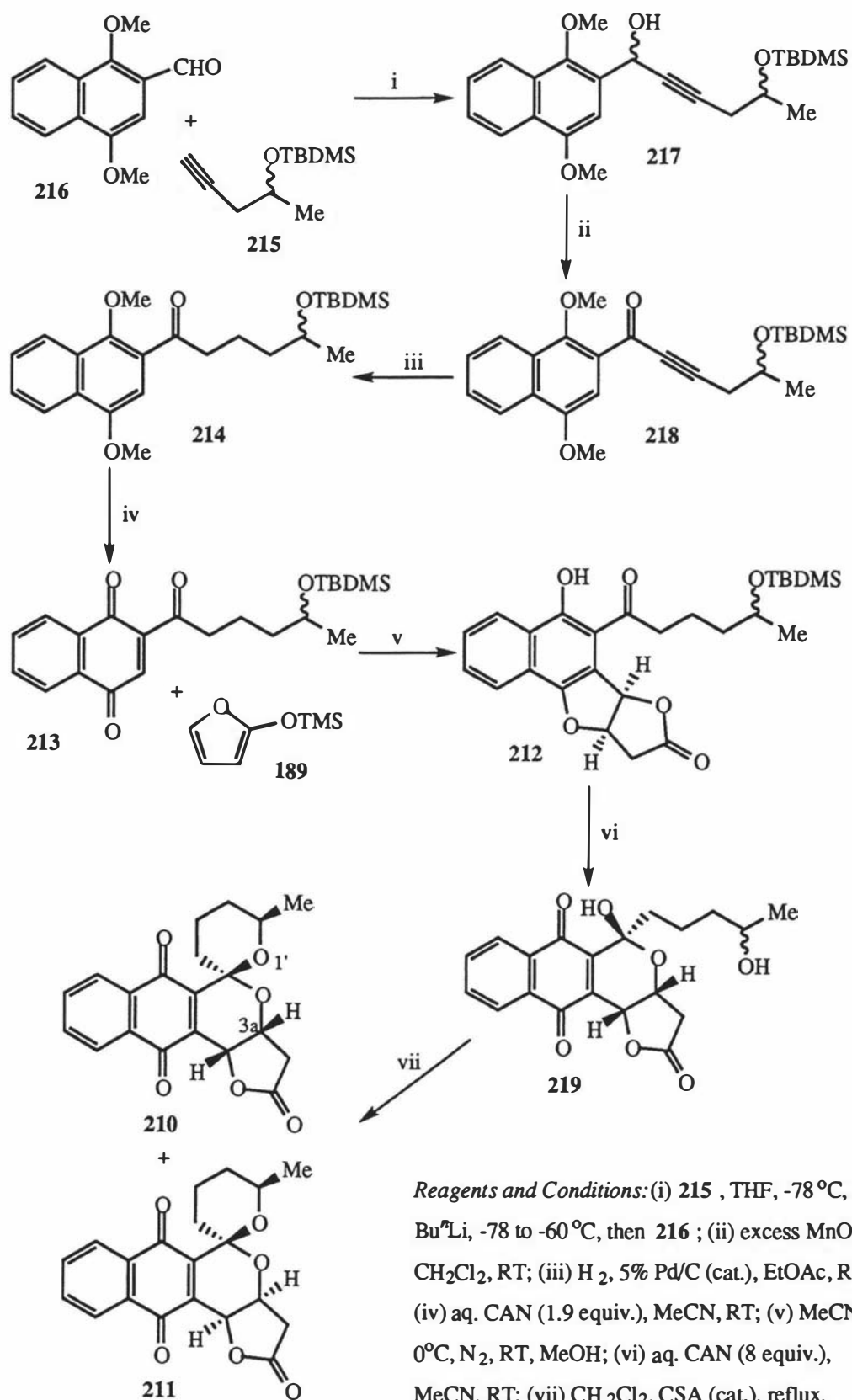
1.3.2   1,7-Dioxaspiro[5.5]undecane Conformations

The conformations of 1,7-dioxaspiro[5.5]undecanes, as present in griseusin A **88** have been studied in depth,[270-273] and three factors observed to influence the preferred conformation: steric factors, anomeric[30] and related effects, and intramolecular hydrogen bonding or chelation.[274] Ring substituents prefer to reside in equatorial positions, however this is balanced against the stabilization gained by the anomeric effect in tetrahydropyrans. Predictions as to molecular shape are more tenuous when one of these preferences is compromised.

Taking an unsymmetrical disubstituted example, there are four possible all-chair conformers corresponding to independent inversion of each ring (scheme 30). The most stable conformer for an *unsubstituted* molecule (X=Y=H) is **I**, where the thermodynamic anomeric effect is maximized. This heavy preference for C-O bonds to have axial orientations has a profound effect on spiroketal conformation, as evidenced by naturally occurring examples and thermodynamic acid catalysed spirocyclizations.[274]
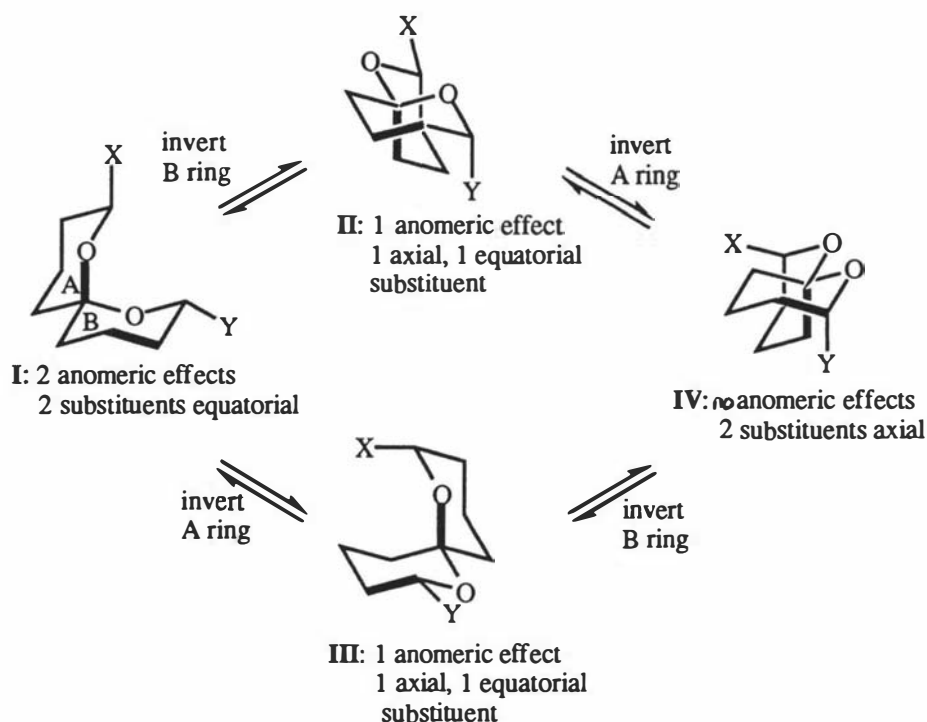
Scheme 30

Early work with spiroketals proceeded on the assumption that the configuration of the spiro carbon of natural products corresponded to the thermodynamically most stable form, available by acid-promoted spirocyclization. This was generally found to be correct, X-ray structures revealing the majority of molecules residing in predictable conformations, in which steric effects were minimized and anomeric effects maximized.

72

Many synthetic strategies have taken advantage of the generality and predictability in formation of 1,7-dioxaspiro[5.5]undecanes,[274] the inherent thermodynamic bias in acetals and related structures having been studied extensively by Deslongchamps.[270-273] With the anomeric effect influencing conformation in a "regular and predictable" manner, "confident synthesis planning may be based on an anomerically driven ring closure under thermodynamic conditions"[274] (scheme 29 and 57).

1.3.3 Cyclization of 3-(2-hydroxyalkyl)naphthalenes

A synthesis by Yoshii *et al.*[275] of spiroketal **210** (*vide supra*) was based on the intramolecular cyclization of a 3-(2-hydroxyalkyl)naphthalene bearing a 1-oxoalkyl group at C-2. 2-Allyl-3-bromo-1,4-dimethoxynaphthalene   **220**[276,277] was alkylated with the methoxymethyl (MOM) ether of 5-hydroxyhexanal (scheme 31) to give carbinol **221**, which was oxidized to the corresponding ketone **222**. Addition of hypobromous acid (generated *in situ*) to the allyl group gave a crude bromohydrin **223** (a δ,δ'-dihydroxyketone) which underwent deprotection and concomitant intramolecular ketalization when heated with acid. The resulting isomeric spiroketals **224** and **225** were formed in a 1:1 ratio, the mixture being treated with sodium cyanide to form nitriles **226** and **227** respectively (3:2 ratio). **227**, however, could be isomerized to **226** under the conditions of nitrile formation, the transformation occurring through β-elimination and addition of the cyanomethyl side chain associated with C-3 (equation 14).

Equation 14
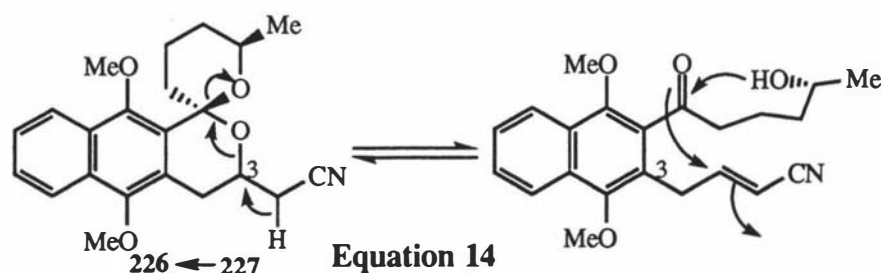
Of four possible diastereomers theoretically possible from this synthesis, **a** and **c** (figure 13) are the major spiroketals produced given that the ketal functionality is formed under thermodynamic control, and taking into account nonbonding interactions and anomeric effects.[274] As **a** and **c** were more stable than their counterparts **b** and **d**, and as **a** is more stable than **c**, spiroketals **224,226** were assigned to structure **a** and **225,227** to structure **c**.

Hydrolysis of **226** produced acid **228**, which was readily oxidized to quinone **229** using ceric ammonium nitrate. The γ-lactone ring was formed by aerial oxidation in pyridine to give the target compound **210**.

Reagents and Conditions: (i) Bu^{n}Li, -78 °C; (ii) PCC, RT; (iii) aq. NBA, HClO$_4$, 0°C; (iv) 10% HCl, 50 °C; (v) NaCN, DMF, 80°C; (vi) KOH, H$_2$O$_2$, 40°C; (vii) CAN, RT; (viii) O$_2$, py, RT.
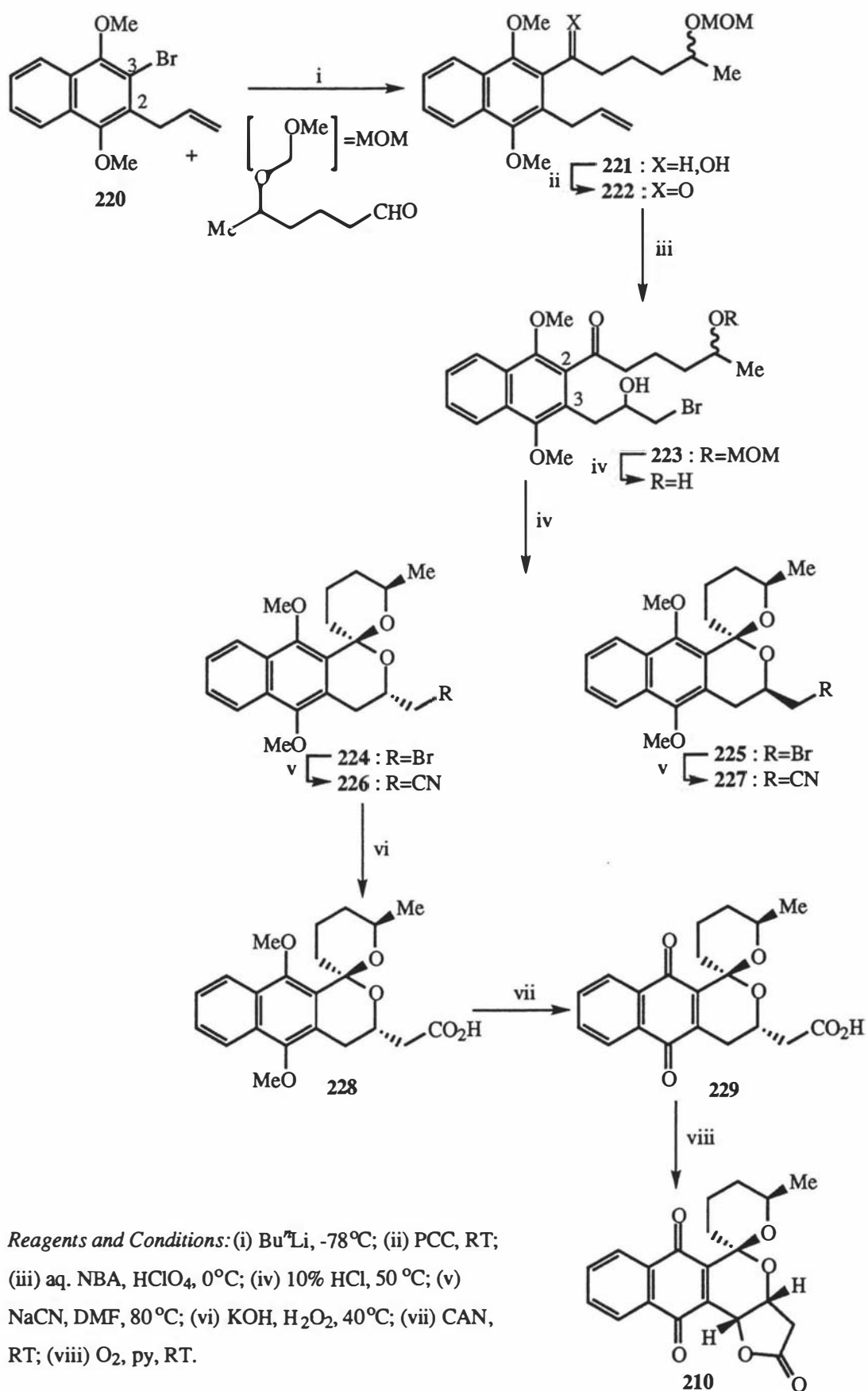
Scheme 31

Figure 13

R=Br, CN
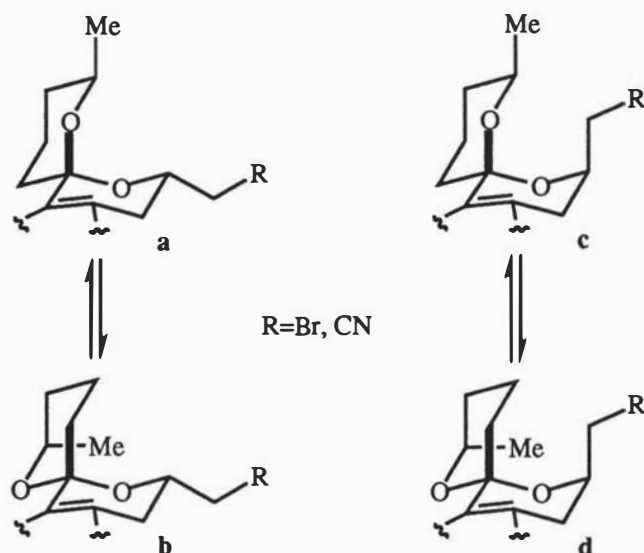
(+)-9-Deoxygriseusin B **90** was later synthesized[176] (scheme 32) based on the above methodology and also that used in the synthesis of racemic nanaomycin A **47** and the eleutherins **5,6**.[276,277] A chiral carbohydrate precursor **230** was used to construct the spiro system, the synthesis of which (**230**) began with 6-deoxy-3,5-O-isopropylidene-L-gulono-γ-lactone **231** [278] (scheme 33). The hydroxyl group of **231** was protected as a methoxymethyl ether before reduction of the lactone to produce diol **232**. Selective benzoylation and deoxygenation by Bartons method[279] {(iv) and (v), scheme 33} gave **233** accompanied by monobenzoate **234**. Saponification of **233** followed by Swern oxidation[280-282] gave the desired aldehyde **230**.
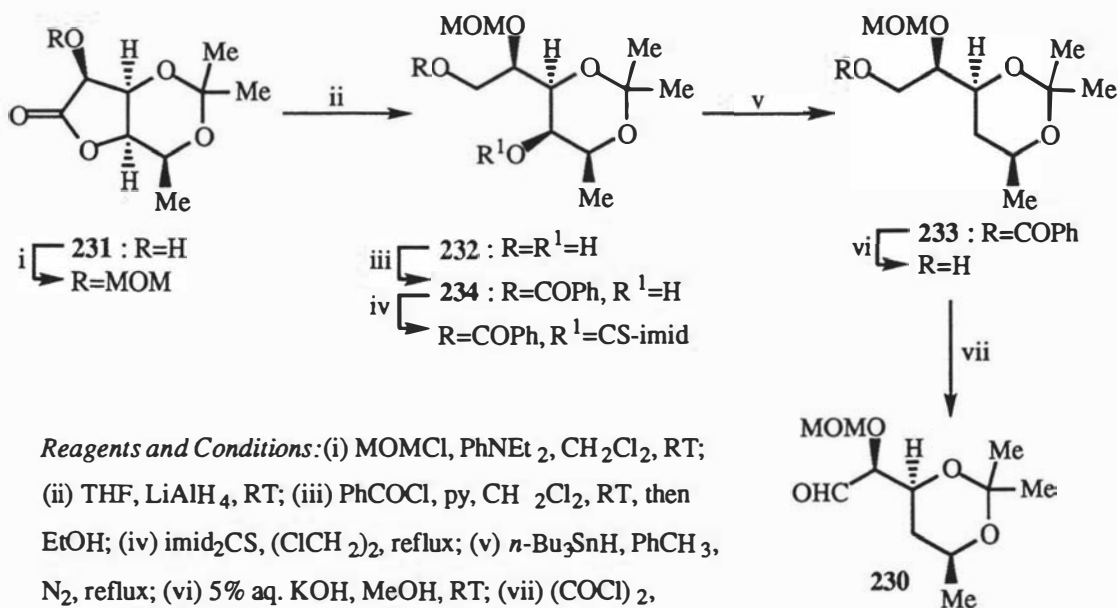
Reagents and Conditions: (i) MOMCl, PhNEt$_2$, CH$_2$Cl$_2$, RT; (ii) THF, LiAlH$_4$, RT; (iii) PhCOCl, py, CH$_2$Cl$_2$, RT, then EtOH; (iv) imid$_2$CS, (ClCH$_2$)$_2$, reflux; (v) *n*-Bu$_3$SnH, PhCH$_3$, N$_2$, reflux; (vi) 5% aq. KOH, MeOH, RT; (vii) (COCl)$_2$, CH$_2$Cl$_2$, -60°C, DMSO, then alcohol, Et$_3$N, -60°C to RT.

Scheme 33

The pyranonaphthoquinone moiety was synthesized from allyl naphthalene **220**,[275] derived from 2-bromonaphthoquinone by allylation and reductive methylation. Lithiation and coupling of **220** to aldehyde **230** (scheme 32, *vide infra*) gave the epimeric alcohols **235** which were oxidized to ketone **236**. Construction of the dioxaspiro ring system from this point was closely modelled on earlier work.[275] Reaction of **236** with hypobromous acid and selective removal of the acetonide group from the side chain led to a 1:1 mixture of epimeric bromoketals **237**, from which nitriles **238,239** were formed in a 2.2:1 ratio respectively. Again, the displacement conditions used {see (**v**), scheme 31} favoured the conversion of **239** to **238**, where the side chain was *trans* to the spiroketal ring oxygen atom.

The nitriles **238,239** were inseparable but the corresponding acetates were easily separated to allow stereochemical assignment. From spin-spin coupling constants between vicinal protons, each isomer had the same conformation of the spiroketal ring as the natural griseusins **88,89**. This was only possible for 1*S*,3*R* and 1*S*,3*S* configurations (figure 14), as the others would experience severe steric hindrance associated with ring substituents. Also, the configurations at C-1 and C-3 should have been established by equilibration (as in equation 14). **238** was assigned as having the cyanomethyl group equatorial, in line with the previous equilibration results.[275]

238 acetate: 1*S*,3*R*   239 acetate: 1*S*,3*S*
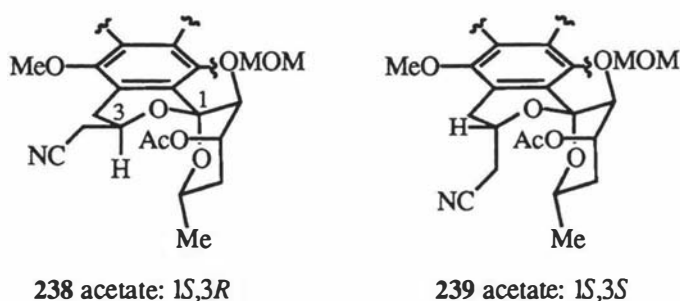
Figure 14

Hydrolysis of **238,239** with ethanolic KOH in the presence of hydrogen peroxide gave acid **240** as a single stereoisomer, epimerization of **239** to the more stable (*R*) configuration at C-3 giving **238** (scheme 32). An initial attempt to complete the synthesis *via* oxidative demethylation of **240**, lactone ring formation and acetylation failed, with only intractable material being obtained when initial removal of the MOM group was attempted. Thus **240** was first acetylated and the methoxymethyl group removed. Oxidative demethylation of **241** then furnished (+)-9-deoxygriseusin B **90**.

As noted earlier (page 27), the circular dichroism spectrum of **90** was found[176] to be the mirror image of naturally occurring griseusin B **89**, thus showing the natural configuration to be 1*R*,3*S* and not 1*S*,3*R* (as in the acetate of **238**, figure 14).

220   **230**

ii ⎡ **235** : X=H,OH
   ⎣ **236** : X=O

237

238   **239**

Reagents and Conditions:(i) THF, -78 °C, N$_2$, Bu^{n}Li, **230** ; (ii) CH$_2$Cl$_2$, PCC, RT; (iii) Me$_2$CO, 0°C, 2.7M HClO$_4$, NBA; (iv) 10% HCl, RT; (v) NaCN, DMF, 70 °C; (vi) EtOH, 30% aq. KOH, 30% aq. H$_2$O$_2$, 40°C then reflux, 0°C, then 10% HCl; (vii) Ac$_2$O, py, RT; (viii) 10% HCl, DME, 50 °C; (ix) THF, AgO, 6M HNO$_3$, RT.

vii ⎡ **240** : R^1=MOM, R^2=H
     ⎣ R^1=MOM, R^2=Ac
viii ⎣ **241** : R^1=H, R^2=Ac

Scheme 32

90

77
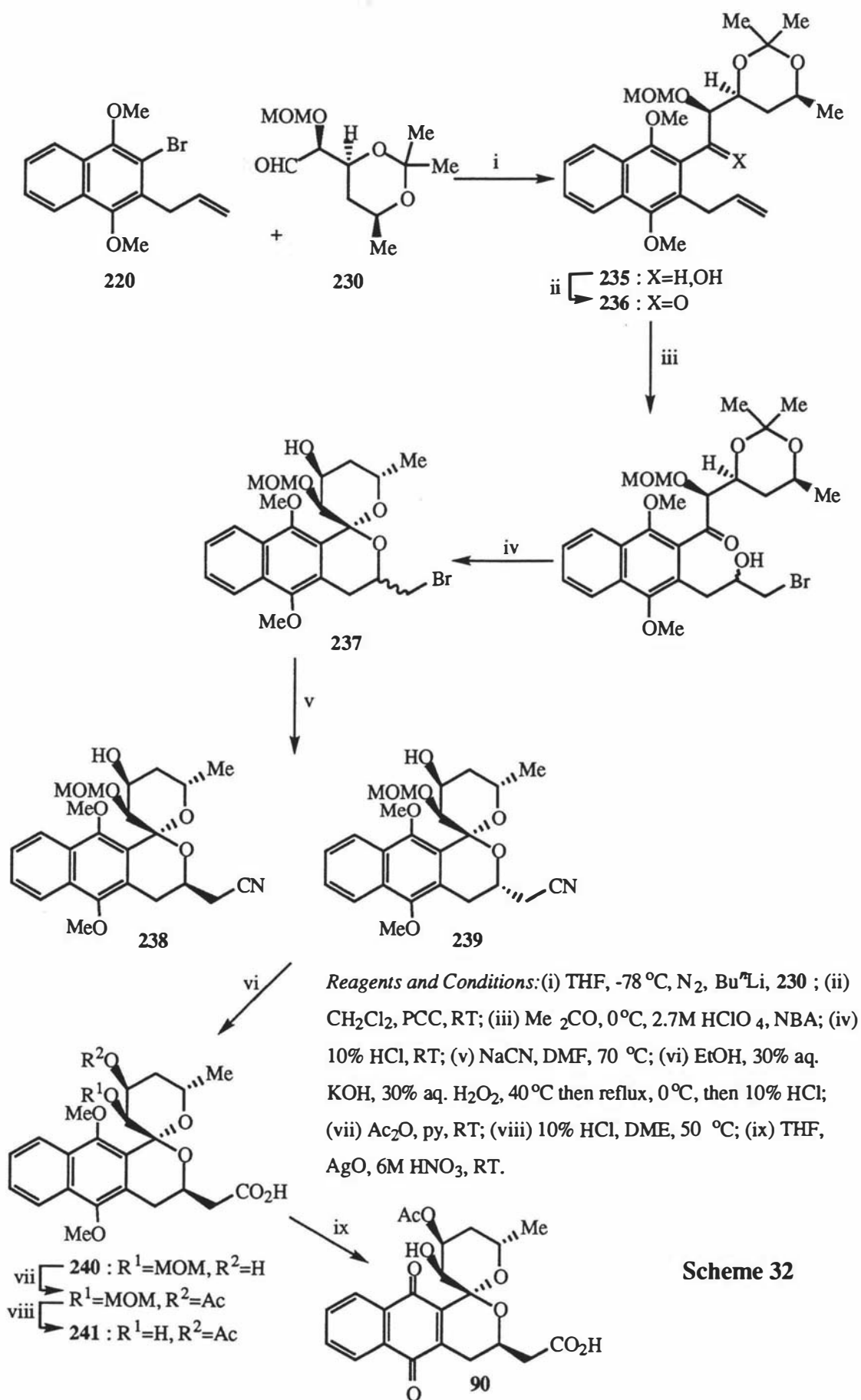
The enantiomers of **88** and **89**, (+)-griseusin A **242** and B **243**, were finally synthesized[283] by the same research group, using methods developed previously.[176,275] The initial starting materials were allylnaphthalene **244**, with a methoxy group at C-5, and aldehyde **230** (scheme 34). Lithiated coupling of these two components and oxidation furnished naphthyl ketone **245** (refer scheme 32 for reaction conditions), however intramolecular ketalization of the corresponding bromohydrin could not be achieved under a variety of conditions. This was presumed to be due to the steric hindrance associated with the *peri* methoxy groups, hence the two phenolic groups were incorporated into an isopropylidene moiety in allyl naphthalene **246** (scheme 35).
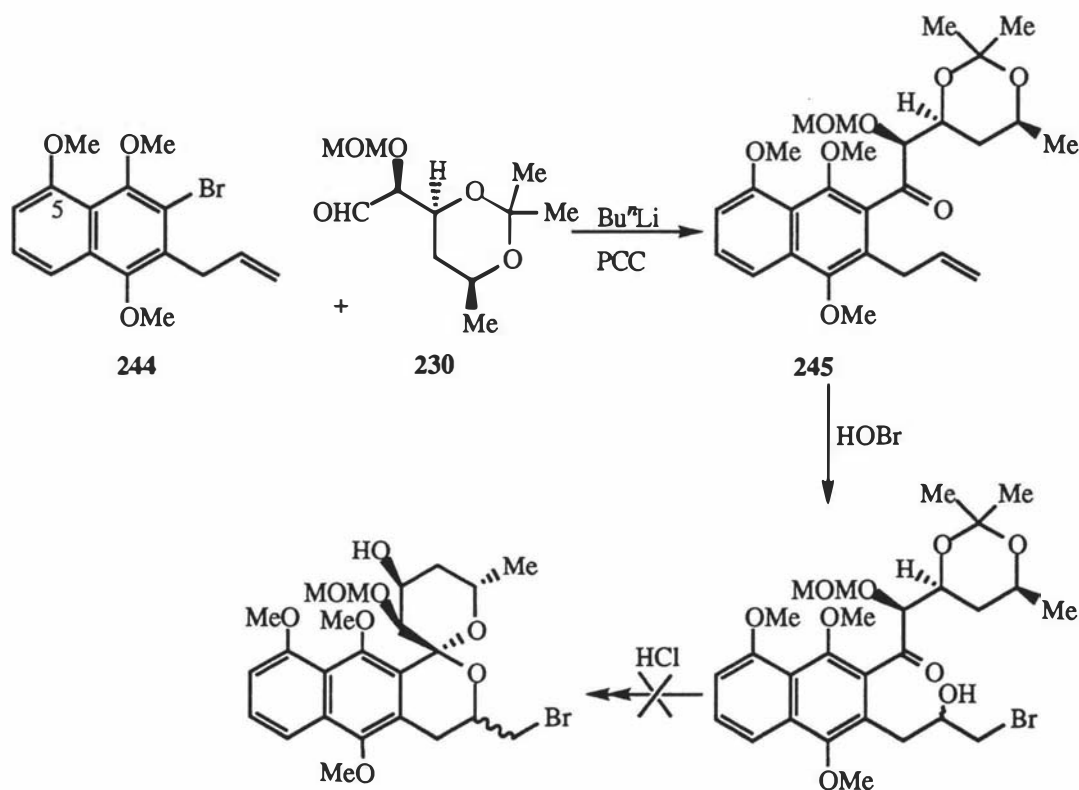
Scheme 34

Coupling of **246** with **230** gave the required carbinols **247**, which were carried through the synthetic sequence as for **235** (scheme 32), resulting in the formation of carboxylic acid **248** as a single epimer (scheme 35). Silver(II) oxidation produced the corresponding quinone as well as deprotecting the phenol group giving (+)-griseusin B **243**, aerial oxidation then providing the lactone ring of (+)-griseusin A **242**.
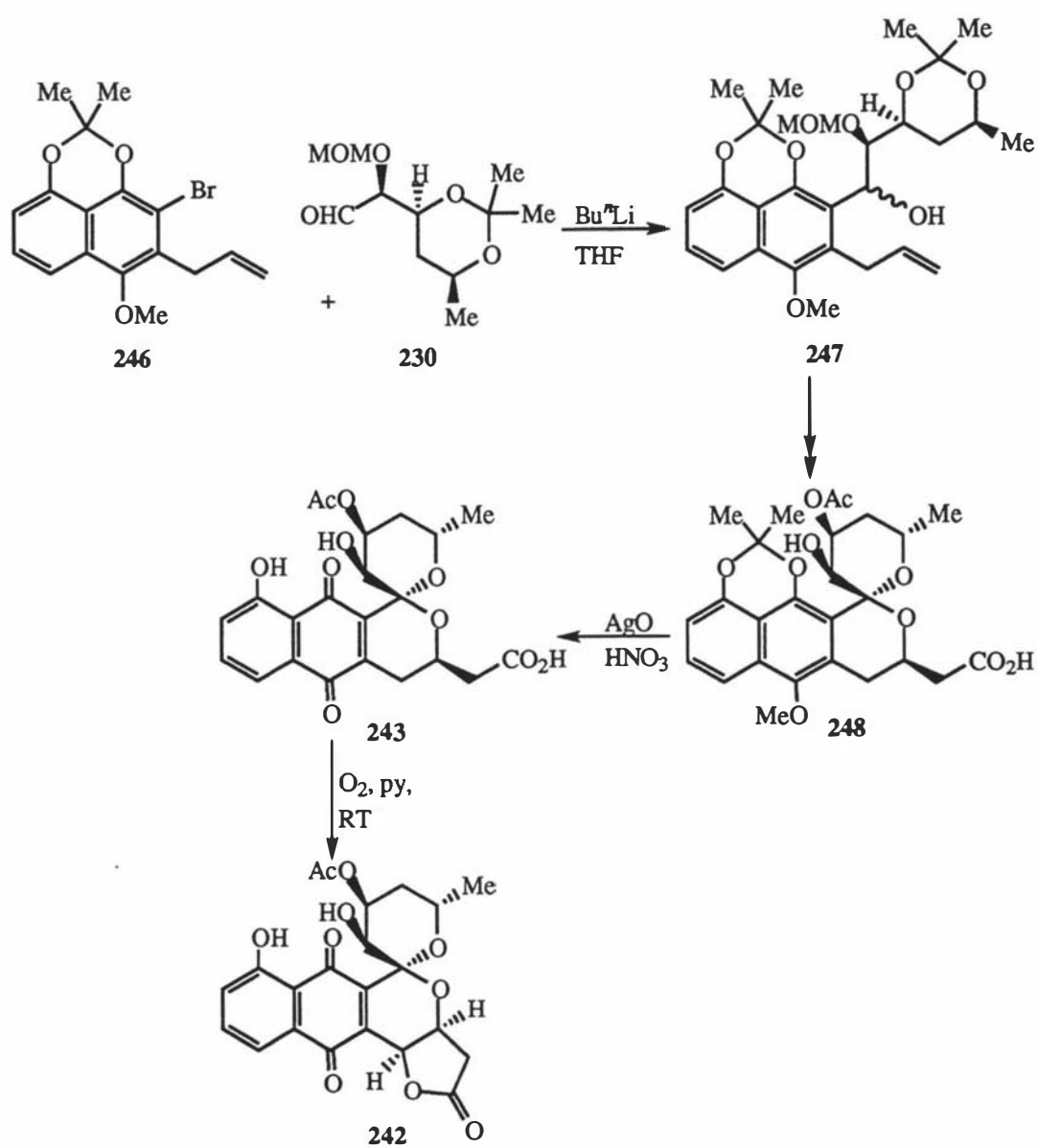
Scheme 35

CHAPTER 2

Synthesis of Pyranonaphthoquinone Spiroketals 333 and 334

2.1 Conjugate Addition of Enol Ethers to α,β-Unsaturated Carbonyl Compounds

In the present work, the addition of 2-trimethylsilyloxyfuran **189** to activated quinones provides an entry to pyranonaphthoquinone antibiotics. The intermediate adduct (furonaphthofuran) is thought to result from a tandem 1,4-addition (sections 1.3.1 and 2.2.1, pages 62 and 87). Thus silyl enol ethers and their 1,4-addition (Michael reaction) to α,β-unsaturated carbonyl compounds, in particular *p*-quinones, is relevant to this work. Similarly, the oxidant used to generate the quinones is also of importance, and thus an overview of these topics is presented in this chapter.

2.1.1 Quinones as Michael Acceptors

The large variation in electron density values about a quinone molecule inevitably invokes a wide spectrum of chemical reactivity. The main characteristic feature of quinones and their derivatives is the tendency to form energetically favoured aromatic or semiquinone systems. The vast majority of the reactions of quinones can be characterized as 1,4-reductive additions of the Michael type (scheme 36: see also section 2.1.2, page 81). The hydroquinone product **249**, formed by protonation/tautomerism of the initial adduct **250** is susceptible to oxidation by air, added oxidant or the quinone starting material.[259,284] In some cases the counter-ion is not a proton but another electrophile, and the nature of these new substituent(s) introduced determines subsequent chemistry. The presence of the phenolic hydroxyl group in **249** as a result of the nucleophilic addition can also lead to further reactions (*vide infra*).[259,284]
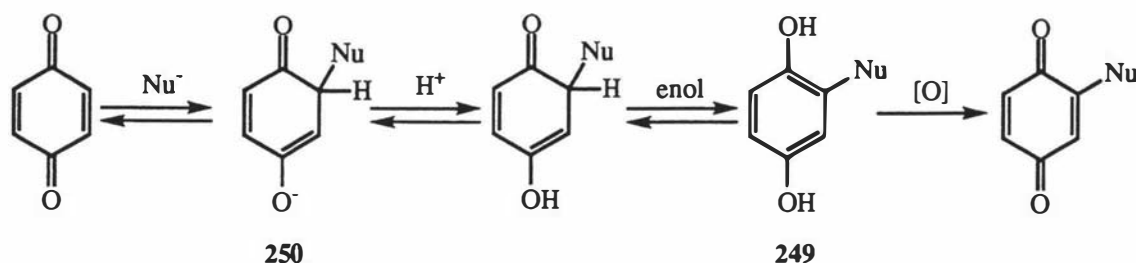
Scheme 36

Early efforts[257] in this area focussed on the conjugate addition of synthetically useful nucleophiles such as enols to electron deficient quinones and their subsequent cyclization to furans (scheme 37). Addition and substitution reactions of quinones have been reviewed.[259,285]
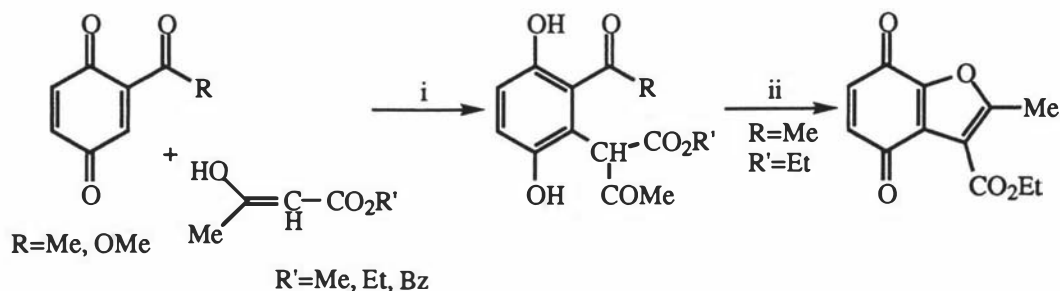
Reagents and Conditions: (i) PhMe, RT; (ii) Me$_2$CO, H$_2$SO$_4$.

Scheme 37

2.1.2 The Michael Reaction

Compounds containing electron withdrawing groups add in the presence of bases to α,β-unsaturated molecules. This is called the Michael reaction and involves conjugate addition.[286a] The net result is HY addition to the multiple bond (equation 15, Y=ZCH⁻Z'), however the mechanism is 1,4-nucleophilic addition to the α,β-unsaturated moiety. Because of the greater susceptibility of triple bonds to nucleophilic attack[286b] (see section 2.4.2, page 101), it is possible for nonactivated alkynes to be substrates in 1,4-additions. Michael reactions utilizing trialkylsilyloxy-substituted heterocyclic aromatic compounds and their synthetic applications have been reviewed.[287]
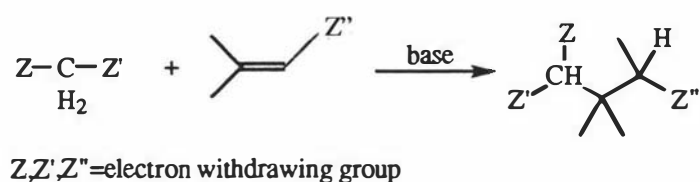
Z,Z',Z"=electron withdrawing group

Equation 15

2.1.3 Silyl Enol Ethers as the Nucleophilic Component

Silyl enol ethers (figure 15) were developed in 1958[288] as precursors for specific enolates.[289] Their usefulness now far surpasses this due to ease of preparation, clean reactions and mildness of desilylation. They combine a reasonable level of reactivity with high selectivity.[289]
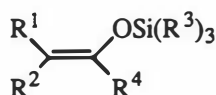
Figure 15

Conjugate addition of silyl enol ethers to α,β-unsaturated carbonyl compounds is now frequently used in synthesis, with both silyl enol ethers and silyl ketene acetals (*vide infra*) being added to a variety of electrophiles.[289] For example, fused angular aromatic ring systems related to angucyclinones were assembled[290] by reaction of the silyl enol ether of cyclohexane-1,3-dione with either acetylbenzoquinone or 2-acetyl-1,4-naphthoquinone **172**, followed by base mediated cyclization (scheme 38).

172 : R=H
181 : R=OMe

enolization/H⁺
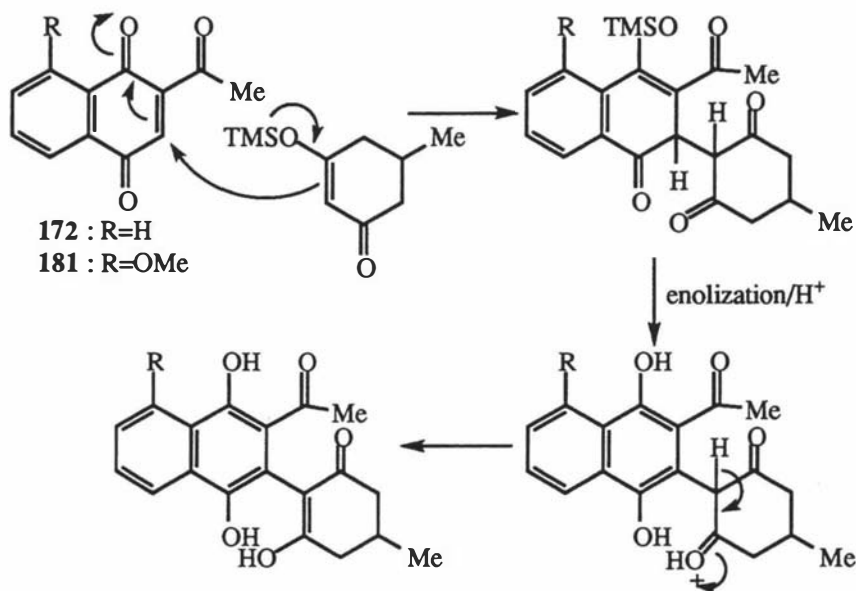
Reagents and Conditions: -20°C to RT.

Scheme 38

Lewis acid catalysed alkylation of silyl enol ethers (the Mukaiyama reaction[289]) has been used for Michael additions to various quinones and their derivatives with trityl salts as catalyst. Alkylation proceeded under extremely mild conditions[291] to afford, in the case of benzoquinone and the silyl enol ether derived from butyraldehyde, adduct **251** stereoselectively (scheme 39). The initial product **252** tautomerized to **253**, the phenol group of which cyclized onto the aldehyde carbonyl to form **254**. Deprotection of the silyl group then gave **251**. The trimethylsilyl group from the enol ether is placed on the phenoxide anion after Michael addition to the quinone, in a similar manner to that proposed in the 2-trimethylsilyloxyfuran **189** addition (scheme 25, page 65). These trimethylsilyl intermediates were not however isolated. A later patent used this method in the preparation of benzofurans as drug intermediates.[292] With phenyl substituted silyl enol ethers such as **255** (equation 16), dehydration took place to give furan **256**.[291]

Scheme 39

Reagents and Conditions: (i) CH $_2$Cl $_2$, TrClO $_4$
(cat.), -45°C; (ii) 5:1 THF:1M HCl.
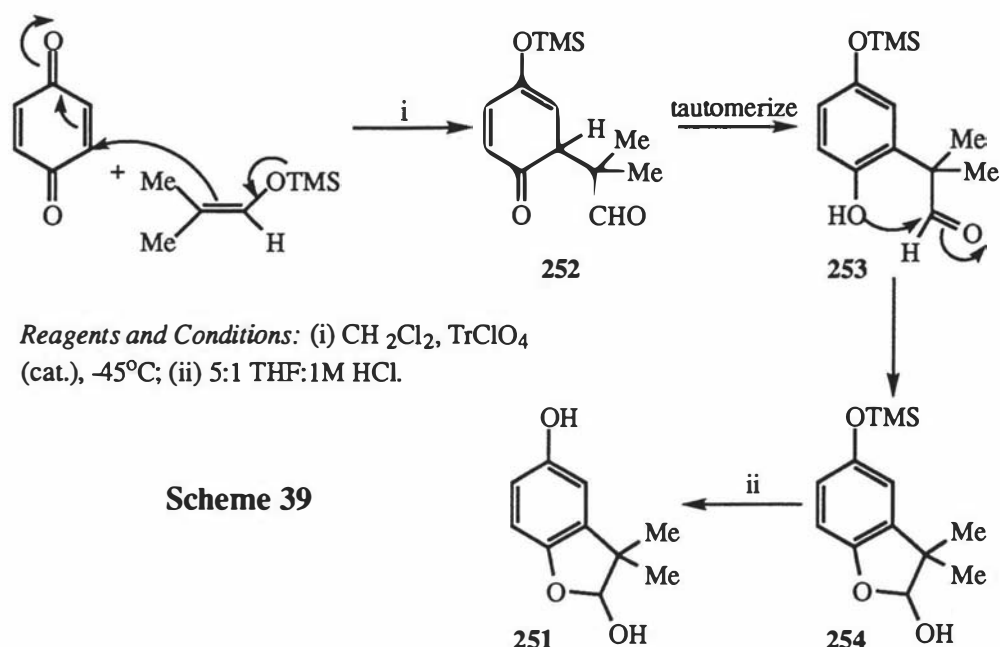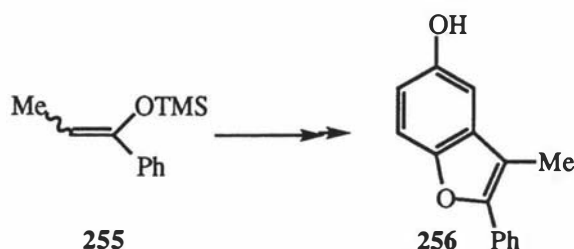
Equation 16

2.1.4 Silyl Ketene Acetals as the Nucleophilic Component

O-Silylated ketene acetals[293] also react with various electrophiles, including α,β-unsaturated carbonyl compounds as Michael acceptors. These Michael-type additions proceed in the absence of a Lewis acid using acetonitrile as solvent.[294] In the example given (equation 17) the trimethylsilyl group of the silyl enol ether is transposed to the carbonyl oxygen, thus *O*-trimethylsilyl ether **257** is actually isolated due to the ring not being aromatic and thus the TMS group being less labile (compare **254**, scheme 39).
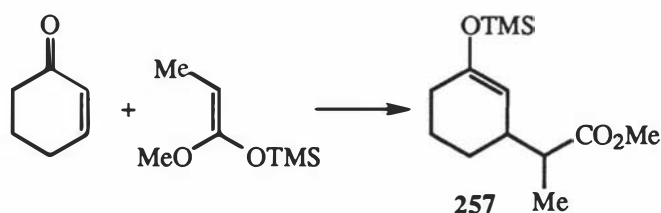
Reagents and Conditions: MeCN, 55°C.

Equation 17

2.15   1-Silyloxybutadienes as the Nucleophilic Component

Dienolate anions such as **a** (figure 16), obtained by the action of bases on α,β-unsaturated carbonyl compounds are well known to react with electrophiles at the α-position under kinetically controlled conditions.[293] The finding that 1-silyloxybuta-1,3-dienes **b** (figure 16) react preferentially at the γ-position with electrophiles extended their synthetic utility. Silyloxy-substituted buta-1,3-dienes have also found widespread use in Diels-Alder reactions.[293] 2-Trimethylsilyloxyfuran **189** is primarily a cyclic 1-silyloxybutadiene, but can also be categorized as a silyl ketene acetal.
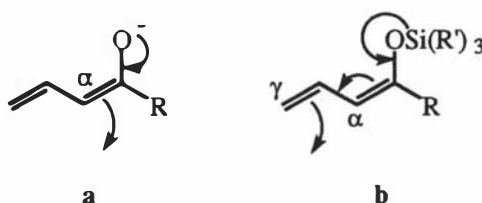
Figure 16

Alkylation of unsaturated compounds by silyloxybutadienes has been used in many syntheses.[293,295] In particular 2-trimethylsilyloxyfuran **189**,[296,297] besides being used in 1,4-additions to activated quinones (refer section 1.3.1, page 64), has been stereoselectively combined with aldehydes by Casiraghi and Rassu *et al.*[298a-c] in syntheses of pyranuronic acid,[298a] octapyranose[298b] and dideoxyheptose derivatives.[298c] Also, addition to imines has been used by this same group for iminoalditols[298d] and quinolizidines[298e] (this last example is illustrated in equation 18).
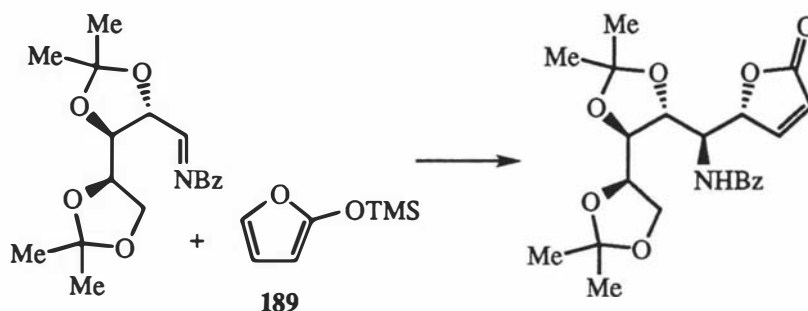
Reagents and Conditions: CH_2Cl_2, -85°C, $BF_3.Et_2O$.

Equation 18

In other syntheses, **189** has been employed in: formation of a macrocyclic antibiotic {(i), scheme 40},[299] mitomycin A and C intermediates (ii)[300] (compare equation 17), the formation of sugar acetonides (iii),[301] a synthesis of a mitomycin C-type antibiotic (iv),[302] *epi*-Swainsonine analogues (v),[303] tetrahydrofuran podands

84

(vi)[304a] and related tetrahydrofuran-based acetogenins (vii),[304b] and styryllactones (viii).[305] The majority of these examples involve addition to aldehydes {(i), (iii), (iv), (viii)} or an imine {(v)}, however substitution by **189** {for example (vi) and (vii), scheme 40} has also been effected.[306] (+)-Goniofufurone[307,308] **258** (equation 19) was synthesized by adding **189** to aldehyde **259**, the final product possessing the same *cis* fused ring system as our furofuran adducts (section 1.3.1).

Reagents and Conditions: (i) CH_2Cl_2, -78°C, $Ti(OPr^i)_2Cl_2$.

(+)-Goniofufurone **258**
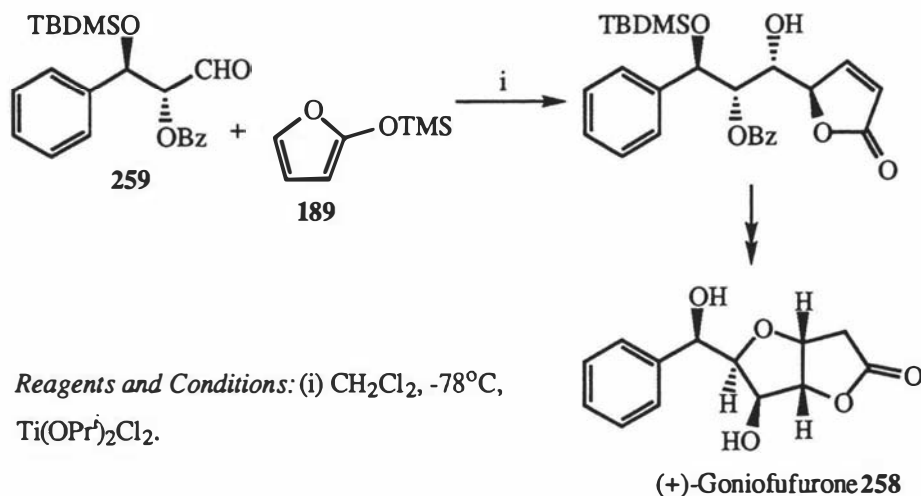
Equation 19

Michael reactions followed by successive sigmatropic rearrangements have been reported[309] involving **189**. Highly electrophilic polyquinones (for example quinizarin **260**) react without the need for catalysis at their internal (most electron deficient) double bond to give, in the case of **260**, adduct **261** (equation 20). Enolization followed by cyclization onto the butenolide moiety was not possible in this case due to the presence of the fused right hand ring.
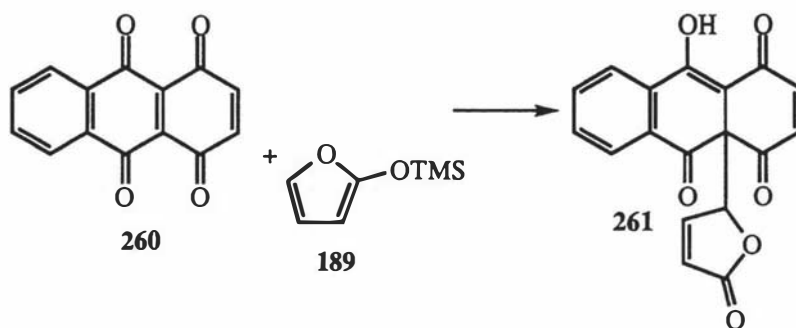
Reagents and Conditions: CH_2Cl_2 or THF, 0°C.

Equation 20
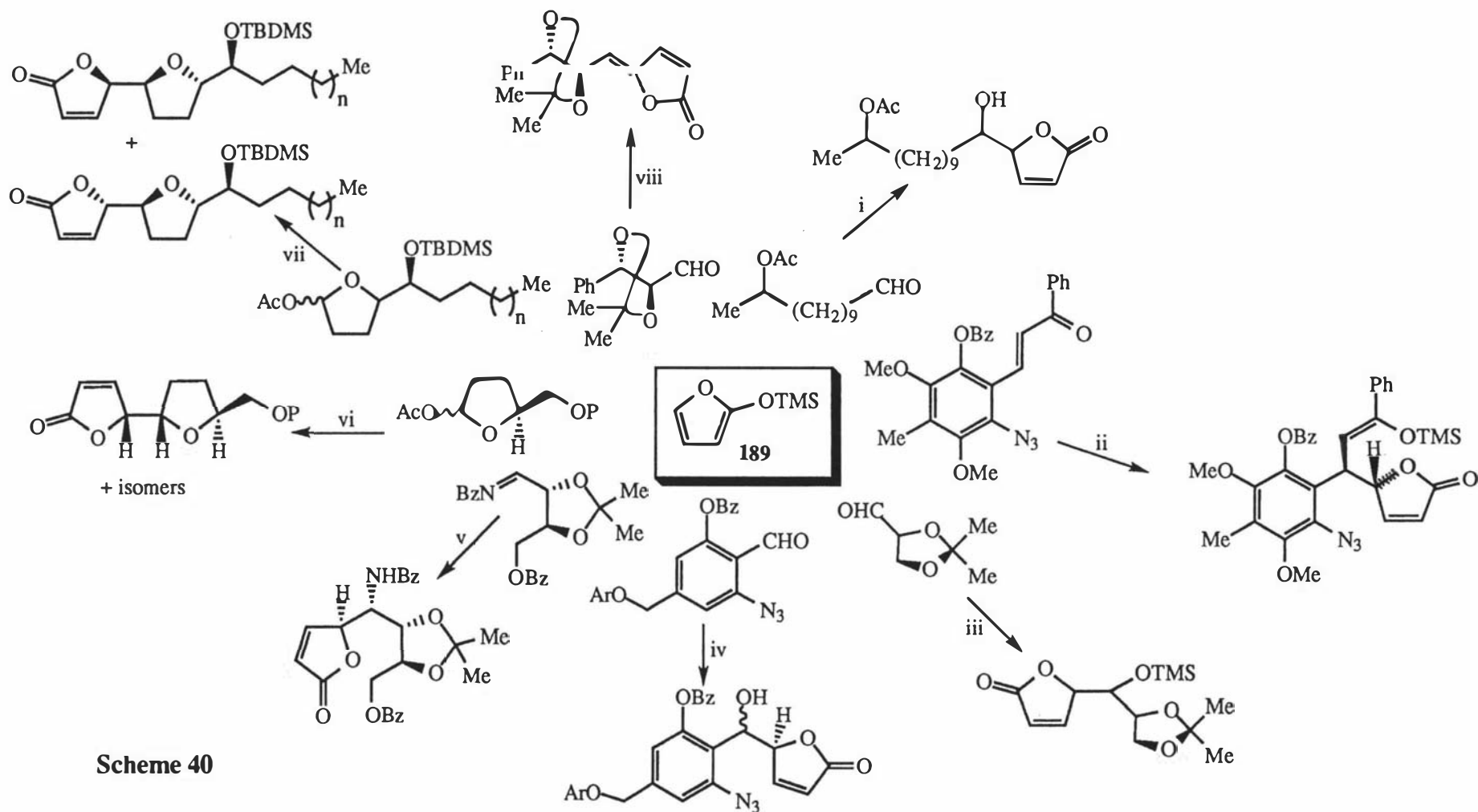
Scheme 40

Reagents and Conditions: (i) CH$_2$Cl$_2$, SnCl$_4$, -78°C to RT; (ii) THF, -78 °C, Bu$^n_4$NF; (iii) CH$_2$Cl$_2$, -90°C, BF$_3$.Et$_2$O; (iv) CH$_2$Cl$_2$, -78°C, SnCl$_4$ (0.01 equiv.); (v) CH$_2$Cl$_2$, -85°C, BF$_3$.Et$_2$O; (vi) CH$_2$Cl$_2$, -78°C, BF$_3$.Et$_2$O; (vii) Et$_2$O, 0°C, Ph$_3$CClO$_4$ (cat.); (viii) a: BF$_3$.Et$_2$O; b: Et$_3$N, Ac$_2$O.

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2.1.6 Other Cyclic and Acyclic Acetals as the Nucleophilic Component

Two examples of Michael addition to quinones that do *not* involve silyl enol ethers, but rather cyclic ketene acetals have been mentioned previously (section 1.3.1) in the context of pyranonaphthoquinone synthesis (schemes 22 and 23, pages 63 and 64). 1,4-Addition of 2-*tert*-butoxyfuran **171** to naphthoquinones **172**,[245] **181**[246] and **183**[247] (scheme 41) affords adducts **173, 262** and **184** respectively, which are key intermediates in the synthesis of pyranonaphthoquinone antibiotics.
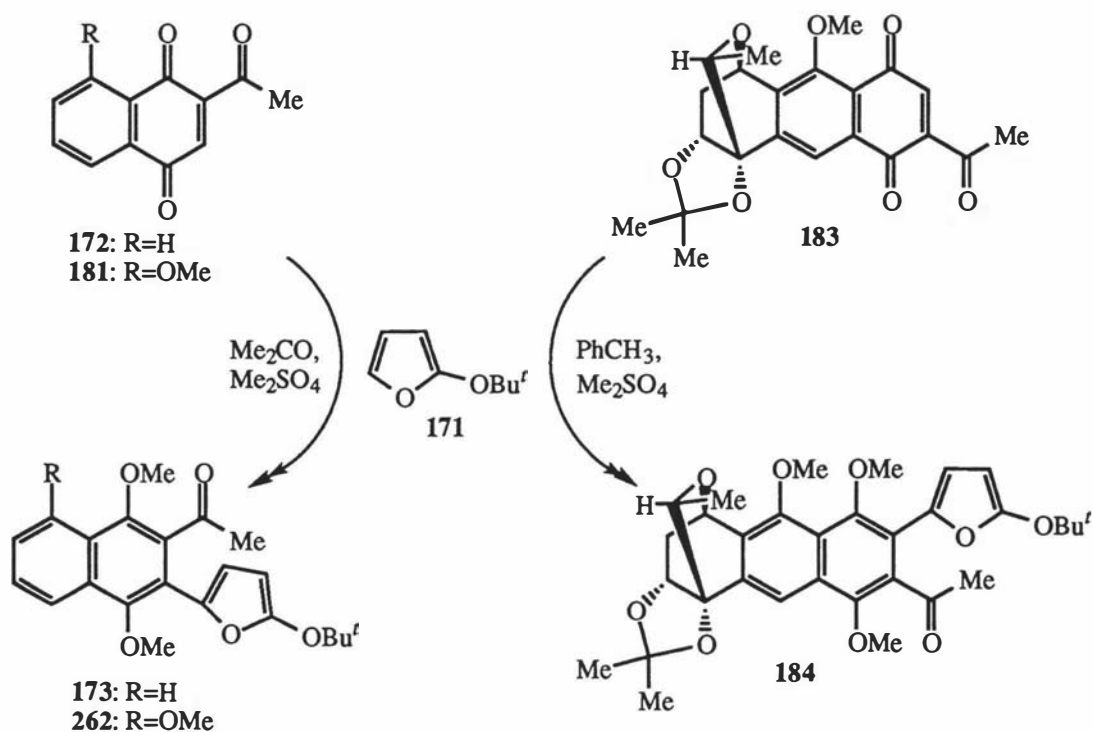
Scheme 41

2.2 Furofuran Annulation: a Mechanistic Discussion

2.2.1 Via *Michael Addition*

The stereochemical outcome of an intramolecular Michael addition analogous to that used to construct the furo[3,2-b]naphtho[2,1-d]furan ring system (scheme 24, page 65) has been investigated by Rupprecht *et al.*[310] The work described by these authors offered a mechanistic insight into the furofuran annulation reaction used in the present study. Earlier work[310] had shown that ferric nitrate oxidation of functionalized hexahydrodibenzofuran **263**, formed by acid mediated rearrangement of Diels-Alder adduct **264**,[310] was accompanied by β-elimination to yield quinone **265** (scheme 42). **265** reclosed (*via* Michael addition) to the same isomer of **263** upon reduction to the

corresponding hydroquinone **266**, however the stereochemistry of the ring junction was not unambiguously assigned. The intermediate that underwent elimination was probably **267**, which is comparable to β-hydroxylactones **192,193** (scheme 26, page 67).
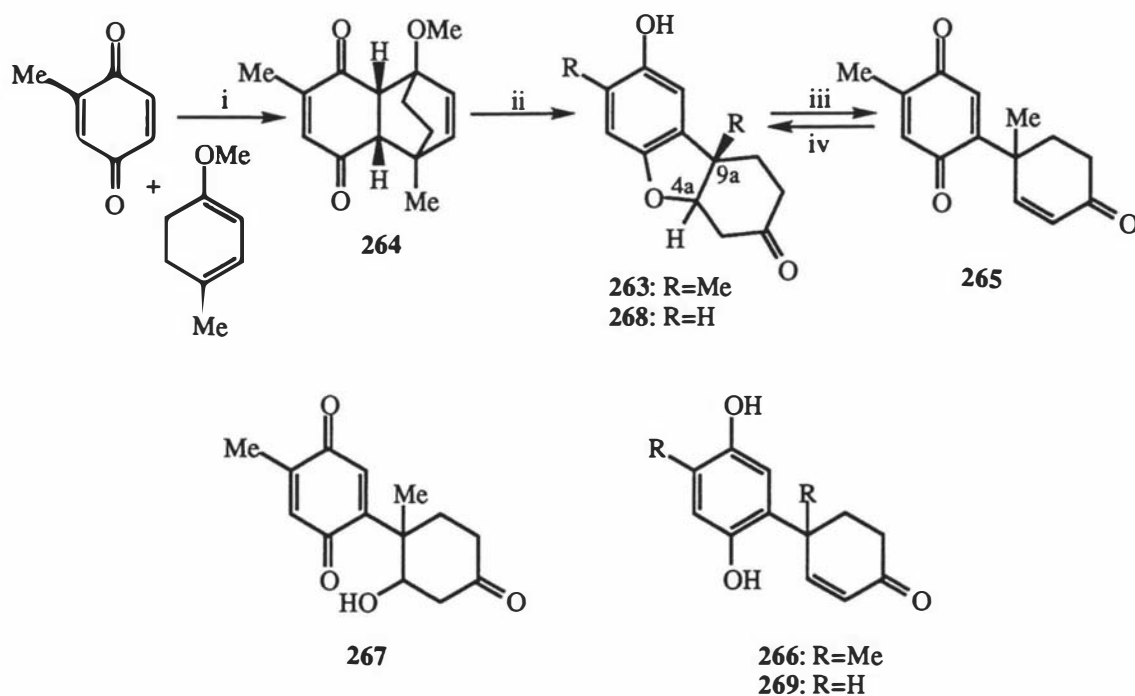
Reagents and Conditions: (i) C $_6$H$_6$, reflux; (ii) HCl/aq. EtOH; (iii) Fe(NO $_3$)$_3$; (iv) H $_2$, Pd/C (cat.).

Scheme 42

Molecular modelling studies[310] on (±)-**268b** (*trans*-**268**, figure 17) indicated a very strained system not likely to be produced by Michael reaction (**269→268**, scheme 42). Theoretical arguments (empirical energy calculations) also supported these studies,[310] suggesting that the *trans* isomer was at least 3 kcalmol^{-1} higher in energy than either the chair or boat form of the thermodynamically more stable *cis* isomer **268a** (figure 17). Confirmation of the *cis* structure of **268** (**268a**) was achieved by an X-ray crystal structure[310] which clearly showed the geometry at the ring junction.
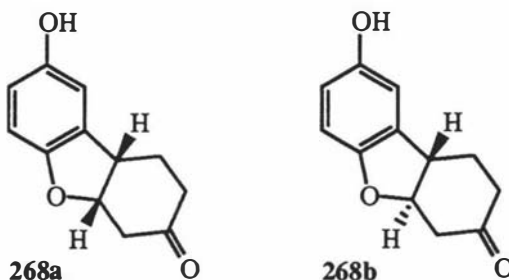
Figure 17

In contrast to the above use of a cyclic α,β-unsaturated Michael acceptor, it was found that intramolecular 1,4-addition of *acyclic* (*E*)-acrylate **270** (scheme 43) afforded *trans*-2,3-dihydrobenzofuran **271**. Formation of *cis*-**272** from *trans*-**271** by oxidation and catalytic reduction allowed ^{1}H nmr comparison of bridgehead proton shifts with **273**. **272** could also be converted to **273** by heating with catalytic piperidine in methanol, proving that the *trans* isomer was in fact the thermodynamic product.

Reagents and Conditions: (i) piperidine, MeOH, reflux *or* neat, RT, 2 months; (ii) DDQ, C$_6$H$_6$, reflux; (iii) H$_2$, Pd/C (cat.), MeOH; (iv) piperidine (cat.), MeOH, reflux; (v) H$_2$, Pd/C (cat.), EtOAc.
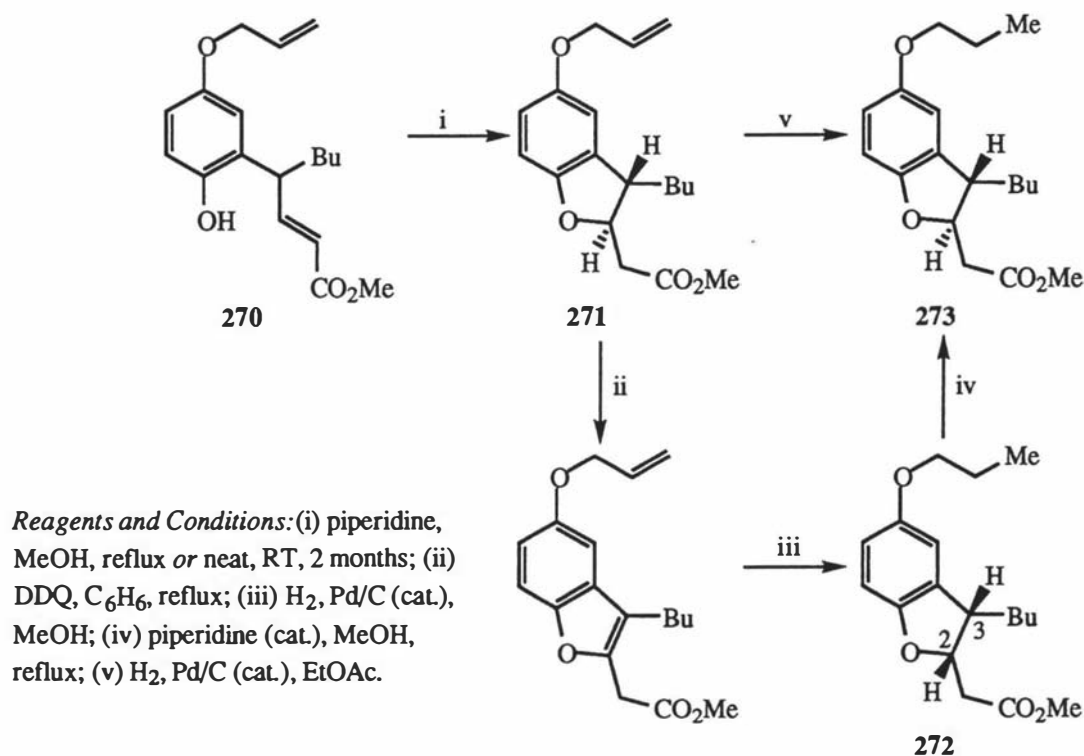
Scheme 43

Thus the nature of the α,β-unsaturated carbonyl compound used as the Michael acceptor controls the stereochemical outcome of the intramolecular Michael addition of the hydroquinone moiety. In cyclic systems[310] the product is a *cis* hexahydrodibenzofuran (**269**→**268a**), whilst in acyclic systems a thermodynamic *trans* 2,3-disubstituted 2,3-dibenzofuran is formed (**270**→**271**).

The results obtained for our furofuran annulation[248-255] follow this pattern in that only *cis* furonaphthofuran adducts, represented by **274**, are formed in the addition of 2-trimethylsilyloxyfuran **189** to naphthoquinones (scheme 44: refer also scheme 24, page 65). The butenolide intermediate **275** has a terminal *cyclic* α,β-unsaturated moiety, which, as with the hexahydrodibenzofurans forms a *cis* ring junction upon intramolecular cyclization. Also, the strained, high energy system that would be produced from a *trans* fusion is unfavourable and "unlikely to form readily in the Michael ring closure step".[310]
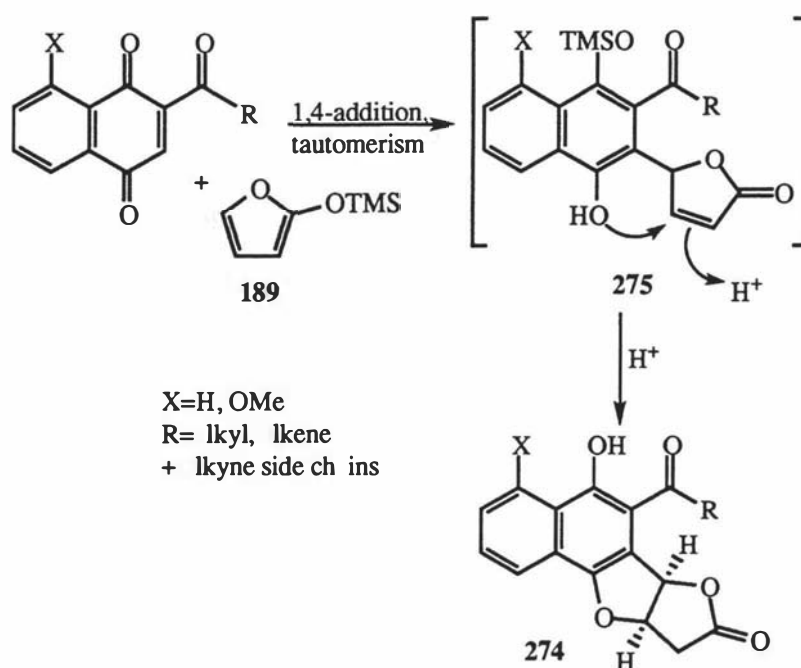
Scheme 44

Molecular model studies on intermediates such as **275** (scheme 44) show that regardless of the stereochemistry at the initial naphthalene-butenolide junction (C-5'), *trans* fusion is not possible (figure 18). When the phenolic hydroxyl group is in close proximity to C-4' of the butenolide (by rotation about the C5'-C3 bond), it sits either above or below the plane of the five-membered ring and on the *opposite* face to the existing butenolide proton at C-5'. Thus the resulting Michael addition gives only a *cis* adduct.
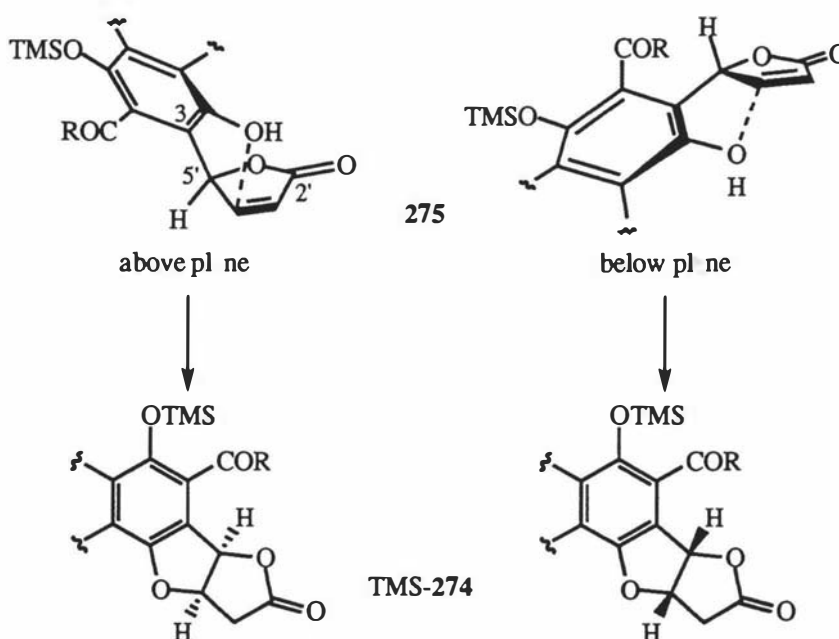
Figure 18

In the first steps of a racemic synthesis of the angucycline antibiotic rabelomycin, Michael addition to a naphthoquinone resulted in the formation of a furonaphthofuran-type adduct[311] (scheme 45). The fused silyloxyfurans **276,277** (**276=189** fused to a cyclohexane ring) were combined with juglone **278** to give not a benzo[a]anthraquinone as anticipated, but, in the case of **276** three products, **279, 280** and **281**. The three products formed were the result of an initial 1,4-addition of the nucleophile to C-3 of the quinone. This was in agreement with the frontier orbital model proposed by Houk *et al*.[312] which predicted the most electrophilic site for a quinone bearing an electron withdrawing group at C-2 to be C-3 (figure 19).[¥]
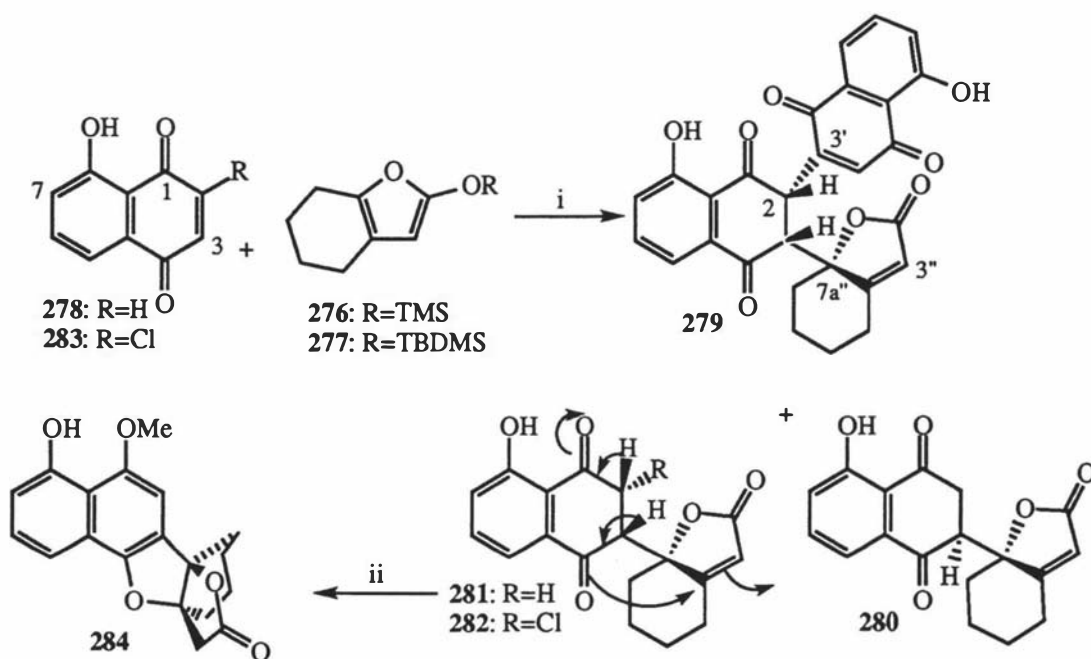
Reagents and Conditions: (i) CH$_2$Cl$_2$, RT; (ii) EtOH, aq. NaOH, Me$_2$SO$_4$, reflux.

Scheme 45
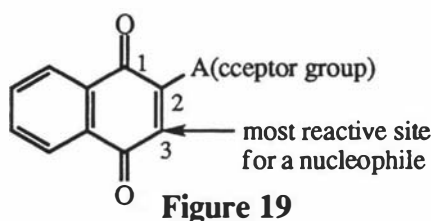
Figure 19

[¥] The numbering in scheme 45 has been altered to match that used by Houk *et al*.[312] in figure 19. In reality, the carbon labelled as C-2 in **279** is actually C-3, and thus C-7a" is attached to C-2 and C-3' to C-3.

Bis-adduct **279** results from a tandem Michael reaction in which the initially formed enolate adds to another molecule of juglone, followed by air oxidation of the less substituted juglone moiety. ^{1}H nmr spectra of **279** and **282** showed no measurable coupling between 2-H and 3-H (either numbering system - footnote[¥]), suggesting an approximately orthogonal orientation of the hydrogen atoms. No catalyst was required in the addition of **276** to either **278** or **283**, and the more stable *tert*-butyldimethylsilyl ether **277** (with **278**) gave the same three products as did **276**. The chlorojuglone **283** gave only **282** upon reaction with **276**.

In an attempt to use the major Michael adduct in a stepwise cycloaddition, **281** was treated[311] with dimethyl sulphate under basic conditions, which resulted in monomethoxy adduct **284** in which the intermediate phenolate had added in a Michael-type reaction to the enone system of **281**, identical to the formation of our furonaphthofuran adducts (scheme 25, page 65). The ring system of **284** contains the framework of the furonaphthofuran ring system, with the cyclohexane moiety of **276** fused to give a tricyclic ring junction.

A further insight into the mechanism of our 1,4-addition was gained when intermediate **285** was obtained from the synthesis[251] of kalafungin **44** analogues. This less soluble product was isolated in 5% yield along with **190** (scheme 24, page 65). Cyclization of butenolide **285** to the desired adduct was however easily achieved through the addition of methanol, the cyclization monitored by UV spectroscopy. A similar intermediate **286** was also obtained from early work directed towards the griseusin A **88** ring system.[253]

285   190   286
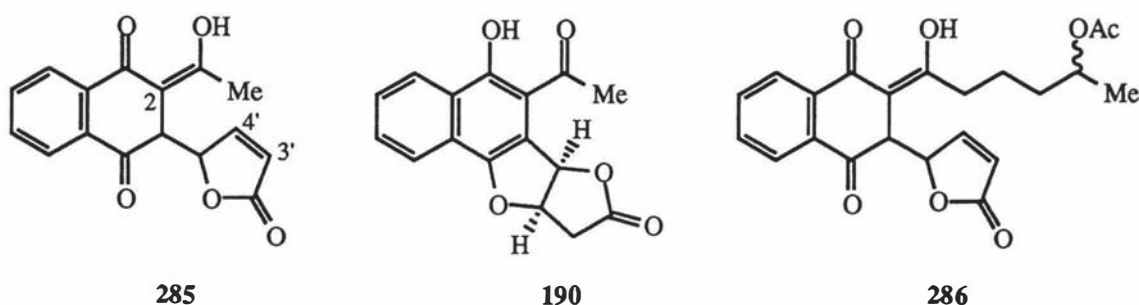
2.2.2   Via *Diels-Alder Fragmentation*

The construction of the furonaphthofuran ring system as a basis for our syntheses of pyranonaphthoquinones has been thought to occur by 1,4-addition of the silyloxyfuran butadiene **189** to an activated naphthoquinone, followed by Michael reaction of a phenolic intermediate tautomer onto a butenolide moiety (scheme 25). An alternative mechanism *via* a Diels-Alder pathway can however be proposed (scheme 46). This

alternative mechanism is based on the reported fragmentation/rearrangement of Diels-Alder adducts of activated quinones under acidic conditions[313-315] (*vide infra*).

Scheme 46

190 : X=H, R=Me
274 { 191 : X=OMe, R=Me
212: X=H, R=C$_{11}$H$_{25}$OSi
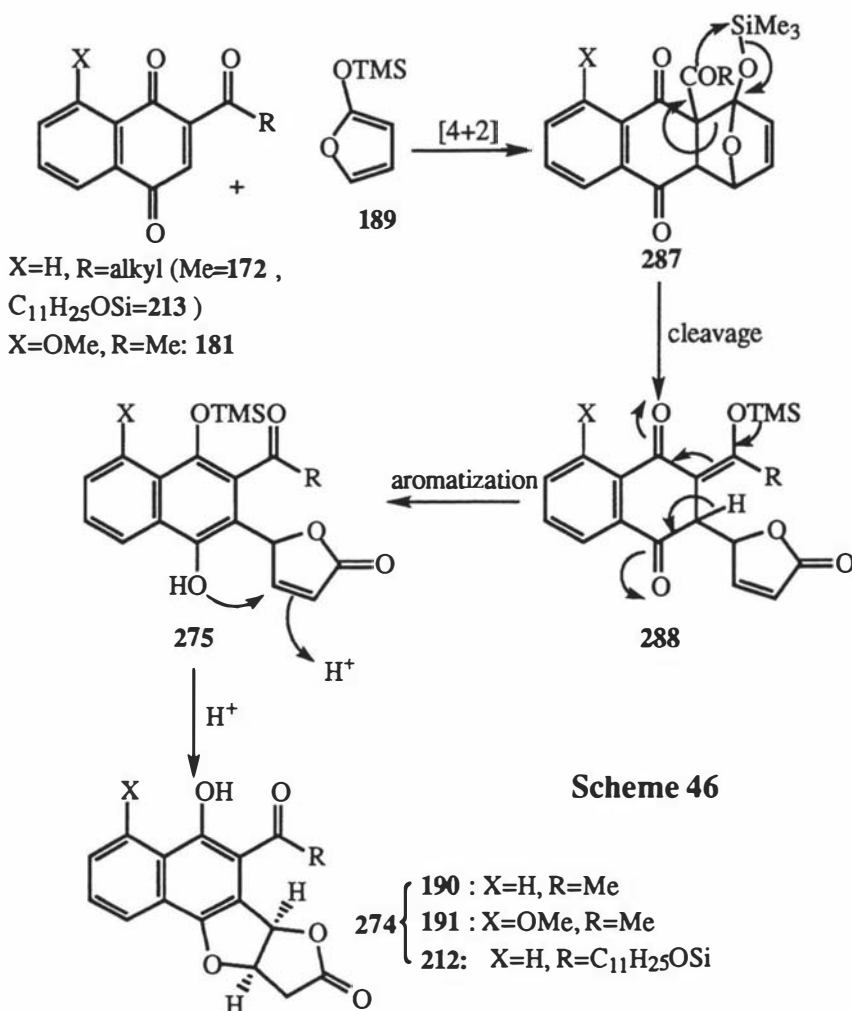
A [4+2] addition of **189** to a functionalized naphthoquinone gives adduct **287** (scheme 46). Cleavage of the "4a-5" carbon-carbon bond (*vide infra*) gives **288**, which upon enolization provides a phenolic hydroxyl group (**275**) that is free to cyclize onto the incumbent butenolide moiety giving adduct **274**. The butenolide intermediates **285,286** (*vide supra*), isolated from earlier work directed towards (±)-kalafungin **44**[251] and (±)-griseusin A **88**,[253] are analogous to **288** (after acid hydrolysis) and could therefore arise *via* this alternate mechanism.

Among the broad structural variety of Diels-Alder adducts obtained from using quinones as the dienophile, compounds such as **289-292** (scheme 47) are unique because of their propensity to undergo selective cleavage of one of the two carbon-carbon bonds generated in the cycloaddition reaction to afford rearranged products. The first example of this was reported by Birch *et al.*[316] Thus bond cleavage of, for example, adduct **292** with tetrabutylammonium fluoride (a retro-Claisen reaction) afforded naphthofuran

93

derivative **293**, which has been used in the synthesis of naturally occurring quinones.[262,317,318] The construction of an alkaloid skeleton[319] and aromatic steroids[320] has been based on similar methodology.

289: R=H
290: R=OMe

from R=H

from R=OMe

(reference 316)

291

294

(reference 321)

292

293

(reference 262)
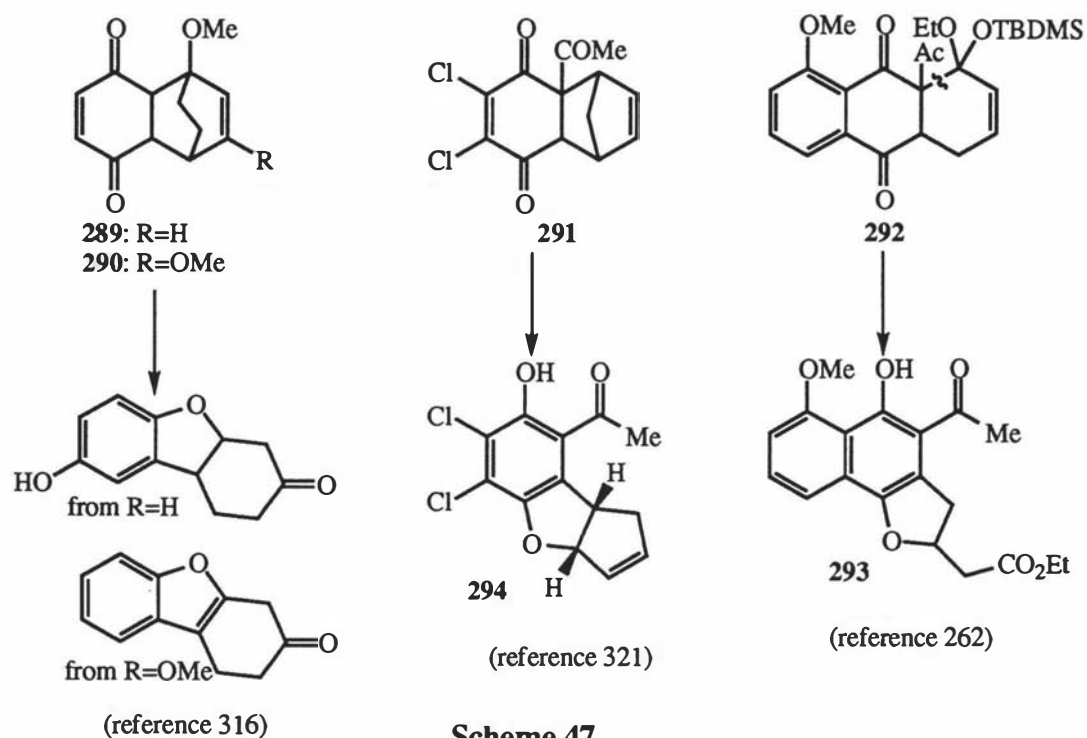
Scheme 47

According to the mechanism proposed[321] the methoxy and acetyl substituents on these adducts favour the required bond fission by resonance stabilisation of the ionic intermediates, as illustrated for adduct **291→294** (scheme 48).

291

294

Scheme 48

94
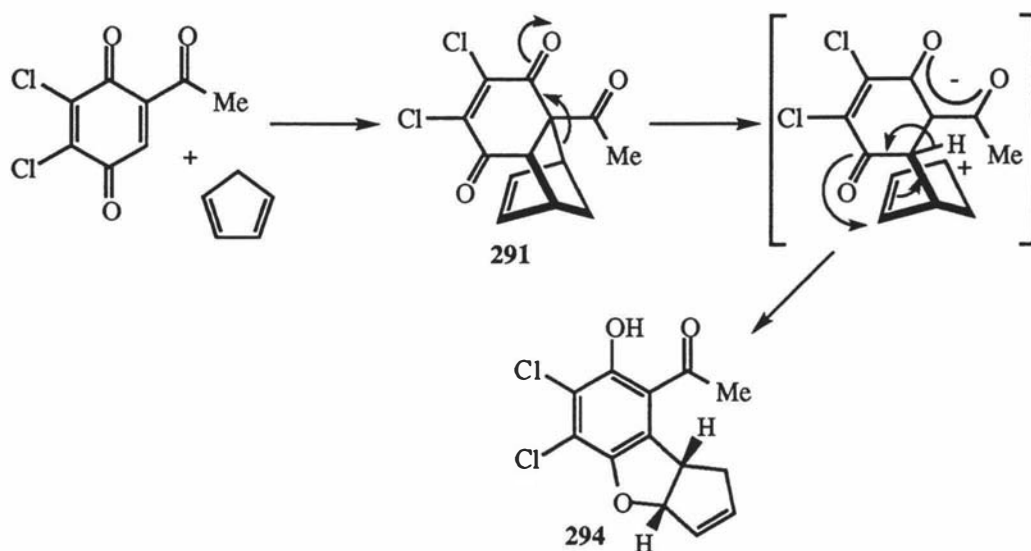
In studies toward rabelomycin analogues, **295** and related adducts in acidic media were studied.[314] The results indicated that conversion of the Diels-Alder adduct **295** to dihydrobenzofuran **296** (scheme 49) was initiated by hydrolysis of the silyl ether to the corresponding alcohol **297**, fission of the 4a-5 carbon-carbon bond, and cyclization of the resulting arylcrotonaldehyde intermediate **298**.
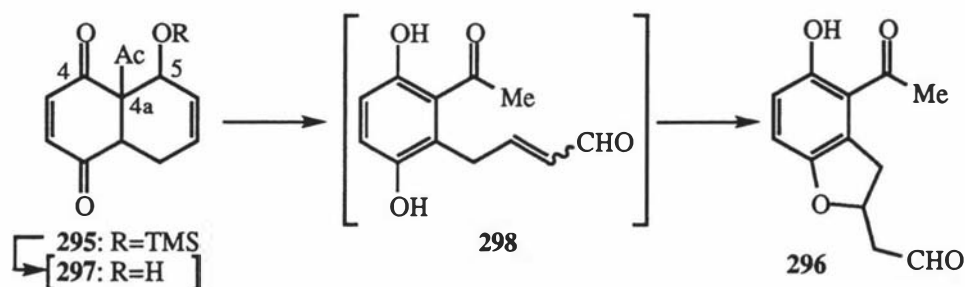
Reagents and Conditions: H_2O/THF (1:9), 1.3M HCl, RT.

Scheme 49

Alcohol **299** was transformed to the corresponding dihydrobenzofuran **300** when its purification was attempted by flash chromatography using chloroform as eluent (equation 21).[314] In the case of adduct **301** (a mixture of diastereomers, equation 22), aromatization by enolization of the cyclohexenedione moiety is prevented due to angular substitution at both C-4a and C-8a. Acid treatment of **301** afforded the corresponding alcohol **302**, however attempts to effect the desired rearrangement were problematic.[314] When alcohol **302** was filtered through silica gel using chloroform stabilized with 1% ethanol the product **303** (initially[313] assigned structure **304**, but later[314] revised to **303**) was produced. Use of ethanol-free chloroform did not result in formation of **303**, thus the presence of an alcohol was essential to effect the rearrangement.
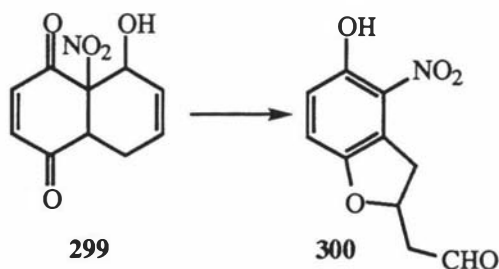
Reagents and Conditions: $CHCl_3$, silica gel.

Equation 21
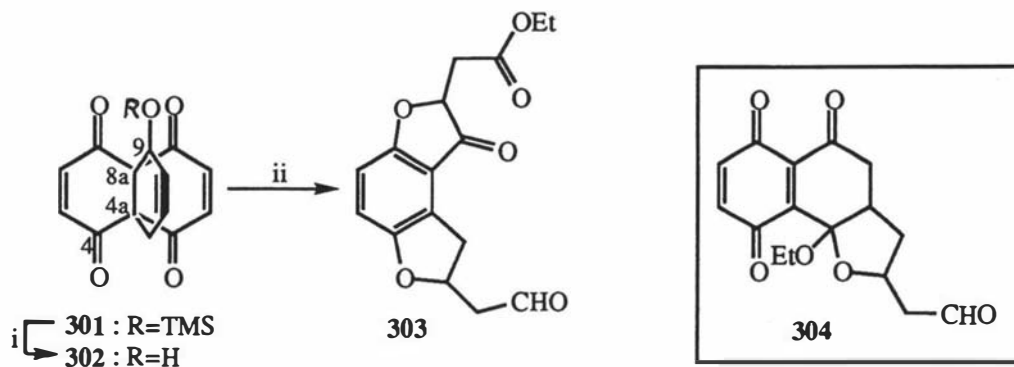
Reagents and Conditions:(i) H_2O/THF (1:9), 1.3M HCl, RT; (ii)
$CHCl_3$, silica gel, purify or $EtOH/CHCl_3$ (1:3), silica gel, stir.

Equation 22

The formation of **303** can be explained by the following sequence (scheme 50).[314] Hemiacetal formation of the C-5 carbonyl with ethanol is followed by acid catalysed 8a-9 carbon-carbon bond cleavage and concomitant enolization. 4a-5 Carbon-carbon bond fission and subsequent cyclization of the newly formed phenoxide anion onto the acyclic double bond then results in dihydrofuran formation. Finally, Michael addition of the phenolic hydroxyl group of the dihydrobenzofuran gives benzodifuran **303**.

Scheme 50

96
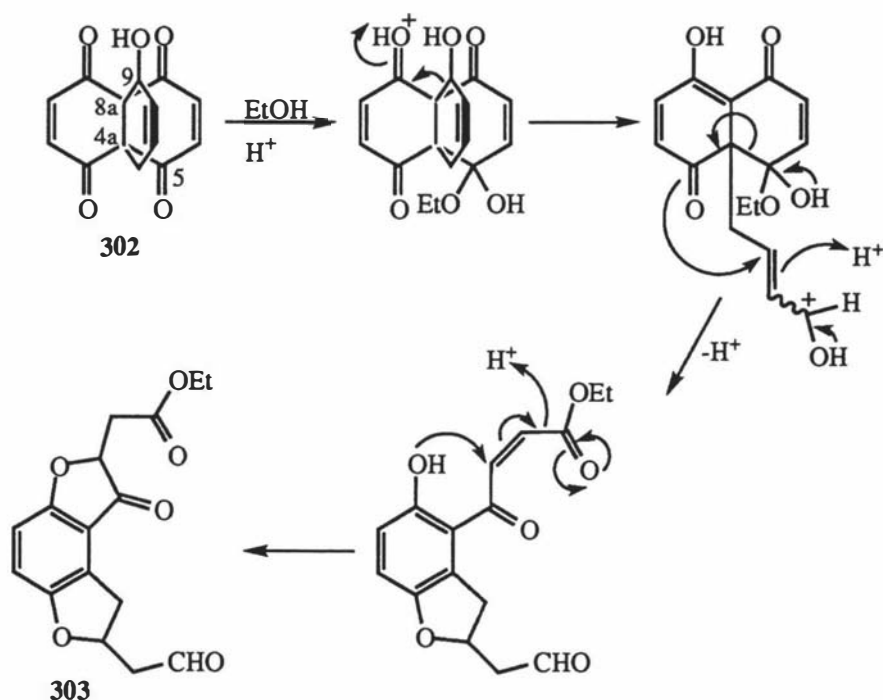
The analogous naphtho derivative (**305**) of **303** was formed[315] in small amounts from **306** (equation 23), the major product being uncyclized naphthofuran **307**. These two compounds affirmed the pathway illustrated in scheme 50.
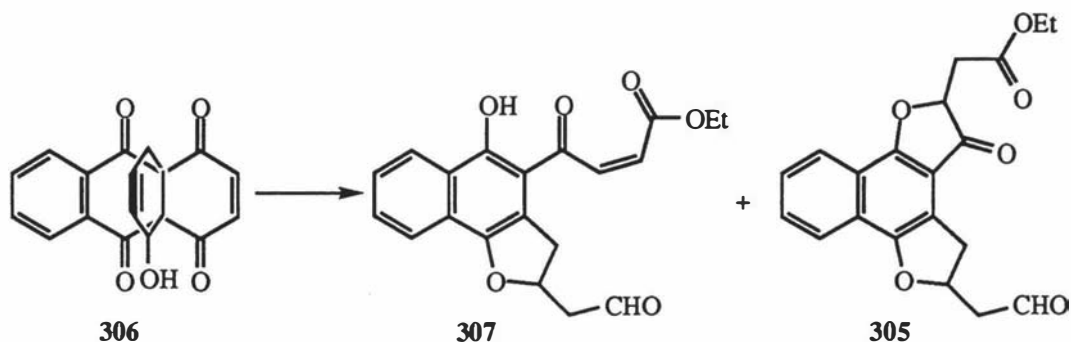
Reagents and Conditions: silica gel, 1:1 EtOH:CHCl$_3$, stir, RT, 10 days.

Equation 23

Reaction of 1,1-bis(O,O-substituted) dienes (for example **189**) with quinones has been considered to proceed by Michael-type additions on the basis of the reaction of similar O-silylated ketene acetals (refer section 2.1.4, page 83), and because no Diels-Alder adducts have been observed as intermediates. The above examples, however, demonstrate that formation of these Diels-Alder adducts is often followed by facile carbon-carbon bond fission to give rearranged products, and hence this two step process (scheme 46, page 93) cannot be excluded as an alternative mechanism, as opposed to a direct Michael addition (scheme 25, page 65).

Dihydrobenzofurans **308** have also been synthesized using acyclic azadienes. Thus, a Michael addition of C-3 of these 1-azadienes to benzoquinone yielded upon ring closure intermediate **309** (scheme 51).[322] Boron trifluoride etherate was used in this case to mediate the Michael addition.
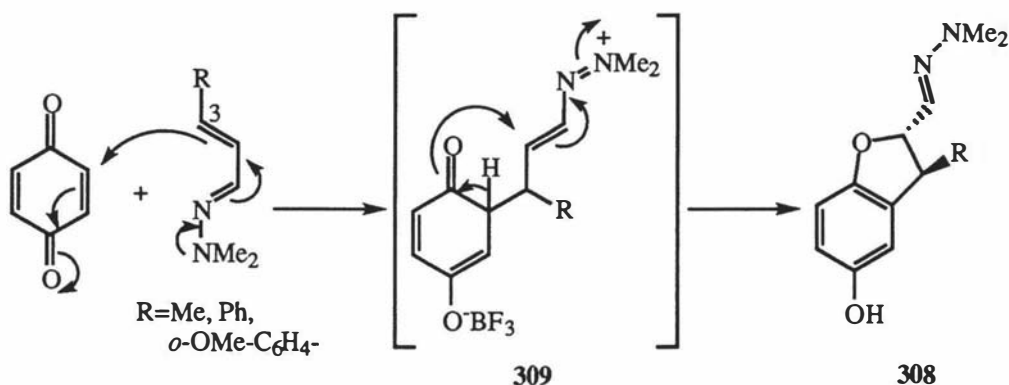
Reagents and Conditions: CH$_2$Cl$_2$, BF$_3$.Et$_2$O.

Scheme 51

97

Cycloaddition of azadiene **310** to quinones (scheme 52) afforded furoquinoline derivatives **311** through a [3+2] process, together with the [4+2] cycloadducts **312,313**.[322,323] 5-Methoxy-1,4-naphthoquinone **314** formed regioisomer **315** (equation 24), where nucleophilic addition of C-3 of the α,β-unsaturated hydrazone **310** had occurred at the more electron deficient carbon of the quinone (C-3). This [3+2] process forming furoquinolines appears to invalidate the hypothesis[314] (scheme 50, *vide supra*) of a carbon-carbon bond fission of [4+2] cycloadducts giving rise to furan derivatives.

Reagents and Conditions:(i) CH₂Cl₂, 0 °C, TFA (1.5 equiv.), RT, then **310** , stir; (ii) deoxygenated PhMe, no H⁺.
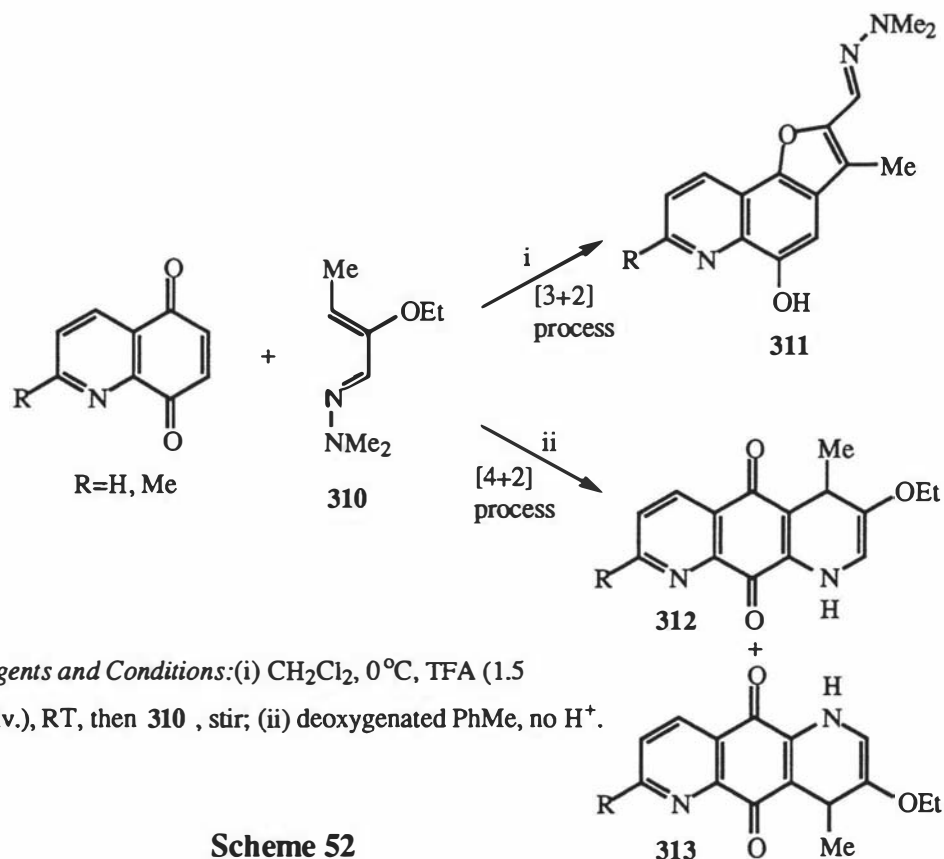
Scheme 52
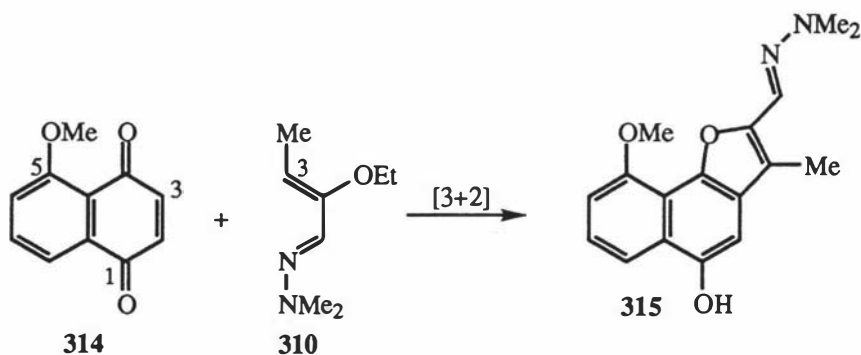
*Reagents and Conditions:*CH₂Cl₂, 0 °C, TFA (2 equiv.), RT, then **310** , stir.

Equation 24

Based on the examples cited above it can be concluded that the precise mechanism of the addition of silyloxydienes to activated quinones remains unclear. It may well be that some reactions proceed *via* a direct Michael addition, whilst others proceed *via* a Diels-Alder fragmentation pathway.

2.3 The use of Ceric Ammonium Nitrate in the Formation of Quinones

Ceric ammonium nitrate is a reagent used extensively by Brimble *et al.*[248-255] in the synthesis of pyranonaphthoquinone antibiotics. Firstly, it is critical to the formation of the initial furonaphthofuran adduct, in that the naphthoquinone required for reaction with 2-trimethylsilyloxyfuran **189** is formed *via* oxidation of the corresponding hydroquinone dimethyl ether. Secondly, CAN is used to effect oxidative rearrangement of the furo[3,2-b]naphtho[2,1-d]furan ring system to the furo[3,2-b]naphtho[2,3-d]pyran system present in the antibiotic natural products (scheme 26, page 67).

Oxidation of *p*-alkoxynaphthalene derivatives to the corresponding naphthoquinones has been accomplished using a variety of (acidic) oxidizing agents,[324] including nitric acid,[324] silver(II) oxide[325,326] and nitric acid impregnated manganese dioxide.[327] Silver(II) oxide is broader in its application but relatively expensive.

Cerium(IV) compounds as oxidants have been known for some time[328] and represent the most notable oxidant amongst the lanthanides. In particular, ceric ammonium nitrate {diammonium hexakis(nitrato-O-)cerate, $(NH_4)_2Ce(NO_3)_6$, CAN} has been utilized extensively for a variety of oxidative transformations.[268a,329] Ce(IV) is a very powerful one electron oxidant: neutral organic species form cation radicals which undergo rapid oxidation by electron transfer, the fate of these reactive radical intermediates determining the nature of the oxidation products isolated.

Oxidation of simple aromatic compounds with cerium(IV) compounds gives quinones (equation 25), however complicated mixtures result if substituted or unsymmetrical substrates are employed. Selective side chain oxidations of arenes can be carried out with CAN, aldehydes being formed from methyl substituted aromatics (equation 26). Radical substitution and addition reactions[330] have also been carried out using CAN, rather than employing the reagent in an oxidative capacity.

Reagents and Conditions:$Ce(SO_4)_2.2(NH_4)_2SO_4$, dil H_2SO_4.
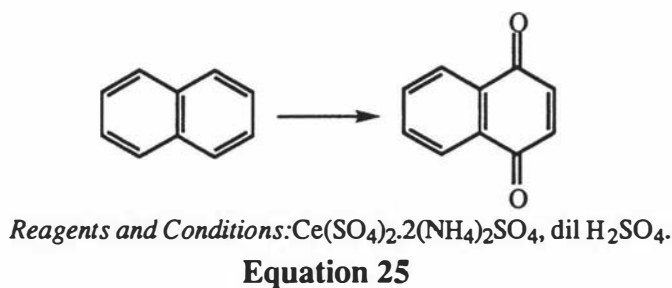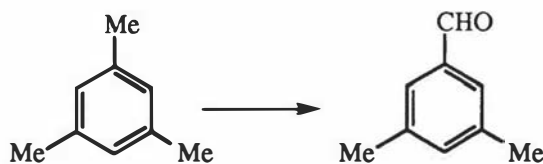
Equation 25

Reagents and Conditions: 50% AcOH, CAN, 80°C.

Equation 26

Hydroquinones are very readily oxidized to quinones by Ce(IV),[331] with silica supported reagents aiding the efficiency of the process.[332] Systems using stoichiometric oxidants and Ce(IV) as catalytic oxidant have also been developed to alleviate the need to use large quantities of cerium salts for a reaction (equation 27). The selectivity and mildness of CAN is demonstrated by the acid sensitive functional groups tolerated, including a *tert*-butoxycarbonyl group and *tert*-butyldimethylsilyl ether (section 1.3.1, pages 64 and 70).
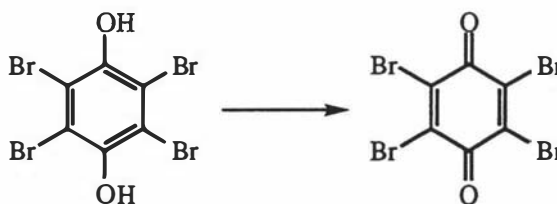
Reagents and Conditions: aq. MeCN, CAN (cat.), $NaBrO_3$, RT.

Equation 27

Oxidative demethylations of hydroquinone monomethyl or dimethyl ethers (for example equation 13,[261] page 66) are achieved readily with Ce(IV) oxidants, the more electron rich ring being preferentially oxidized (all other factors being equal).[329] In this capacity ceric ammonium nitrate has been used in the total synthesis of several natural products. For simple *p*-quinone formation, the oxidation is best performed in the presence of an amine carboxylic acid[333] which complexes with the metal ion. A comparison of CAN and silver(II) oxide indicated that yields were higher with the former.[333]

A mechanistic investigation[261] into the oxidation of *p*-methoxyarenes showed that the resultant quinone carbonyl oxygens are derived from water, hence the oxidation must proceed by aryl-oxygen bond cleavage with the net formation of the quinone and two moles of methanol (scheme 53).

100

Me, OMe, Me / Me, Me, OMe   → $2Ce^{4+}$ / $2H_2O^\dagger$ → [HO† OMe, Me, Me, Me, Me, HO$_\ddagger$ OMe] → Me, O†, Me / Me, Me, O†

$+ 2H^+ + 2Ce^{3+}$ → $+ 2MeOH$
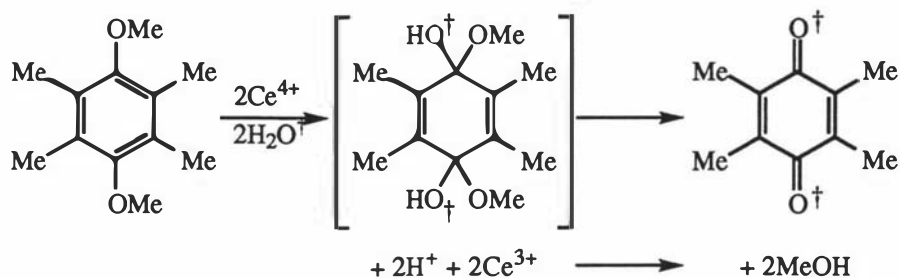
Scheme 53

2.4 Synthesis of Unsaturated Spiroketals 333,334

2.4.1 Retrosynthetic Analysis

Given the successful outcome of earlier work[252,253] (scheme 29, page 71) in constructing the ring system of griseusin A **88**, a retrosynthesis was proposed whereby the substituents on the spiroketal ring would be introduced *via* a double bond (scheme 54). This unsaturated intermediate **316** could be formed by hydrogenation and cyclization of acetylenic hemiketal **317**, which in turn could be produced by ceric ammonium nitrate oxidative rearrangement of furo[3,2-b]naphtho[2,1-d]furan **318**. Adduct **318** would be formed from the key addition of 2-trimethylsilyloxyfuran **189** to acetylenic quinone **319**, wherein the hydroxyl group was protected as a *tert*-butyldimethylsilyl ether[334-336] (scheme 54). This protecting group had been used successfully in the synthesis[252,253] of saturated spiroketals **210** and **211** (scheme 29).

2.4.2 Synthesis of Pentacycle 323

Initial effort focussed on the synthesis of (±)-7-deoxygriseusin A **320**, due to the more ready availability of the corresponding deoxyquinone **321** compared to methoxy-substituted analogue **319**. It was also important to establish the proposed synthesis using less expensive racemic material before introducing the appropriate chirality at C-5'. Attention therefore turned to the synthesis of quinone **321** (scheme 55).

The first two steps in the synthesis of **321** (*n*-BuLi coupling and oxidation) were carried out as described previously (scheme 29), ketone **218** being obtained in 83% yield over these two steps. Oxidative demethylation of **218** using ceric ammonium nitrate proved troublesome, presumably due to the presence of unsaturation at C-2' of the side chain, given that the saturated analogue **214**[252,253] was easily converted to quinone **213** (scheme 29). In this case, CAN resulted in a mixture of **321** and **218** (scheme 55) with the unreacted ketone being recovered after the furofuran annulation step. Silver(II)

101

griseusin A **88** : R=OH
(±)-7-deoxygriseusin A **320** : R=H

316

318

317

319 : R=OMe
321 : R=H, C-5'=(*R*,*S*)

189
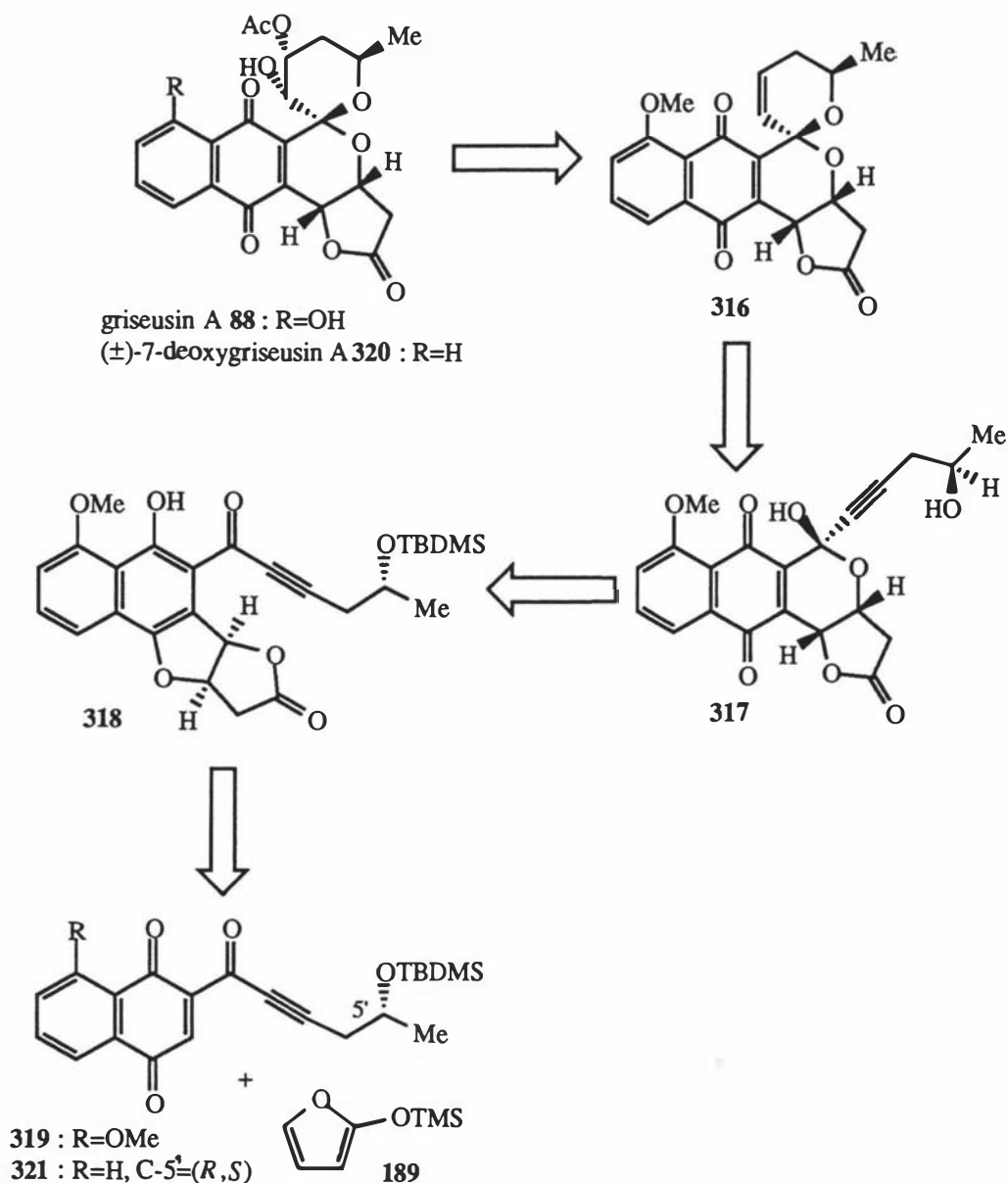
Scheme 54

oxide[325,326] on the other hand furnished quinone **321** with no major contaminants, but the reaction was less predictable and was therefore used to produce material (**321**) suitable for *rapid* data collection.

Addition of 2-trimethylsilyloxyfuran **189** (approximately 1.5 equivalents) to **321** produced not the expected furonaphthofuran adduct **322**, but pentacyclic adduct **323** as a 1:1 mixture of diastereomers (¹H nmr spectroscopy) and in 37-39% yield (over two steps). High resolution mass spectrometry established the molecular formula as $C_{26}H_{30}O_6Si$. The ¹H nmr spectrum exhibited a doublet of triplets at δ_H 5.61 and a doublet at δ_H 6.98, assigned to the bridgehead protons 9a-H and 12a-H respectively. The magnitude of the 9a,12a coupling constant (5.7 Hz) was in agreement with that found in analogues[248,249] of panacene **188**[256] (5.7-6.2 Hz) and goniofufurone **258**[338] (5.9 Hz),

102
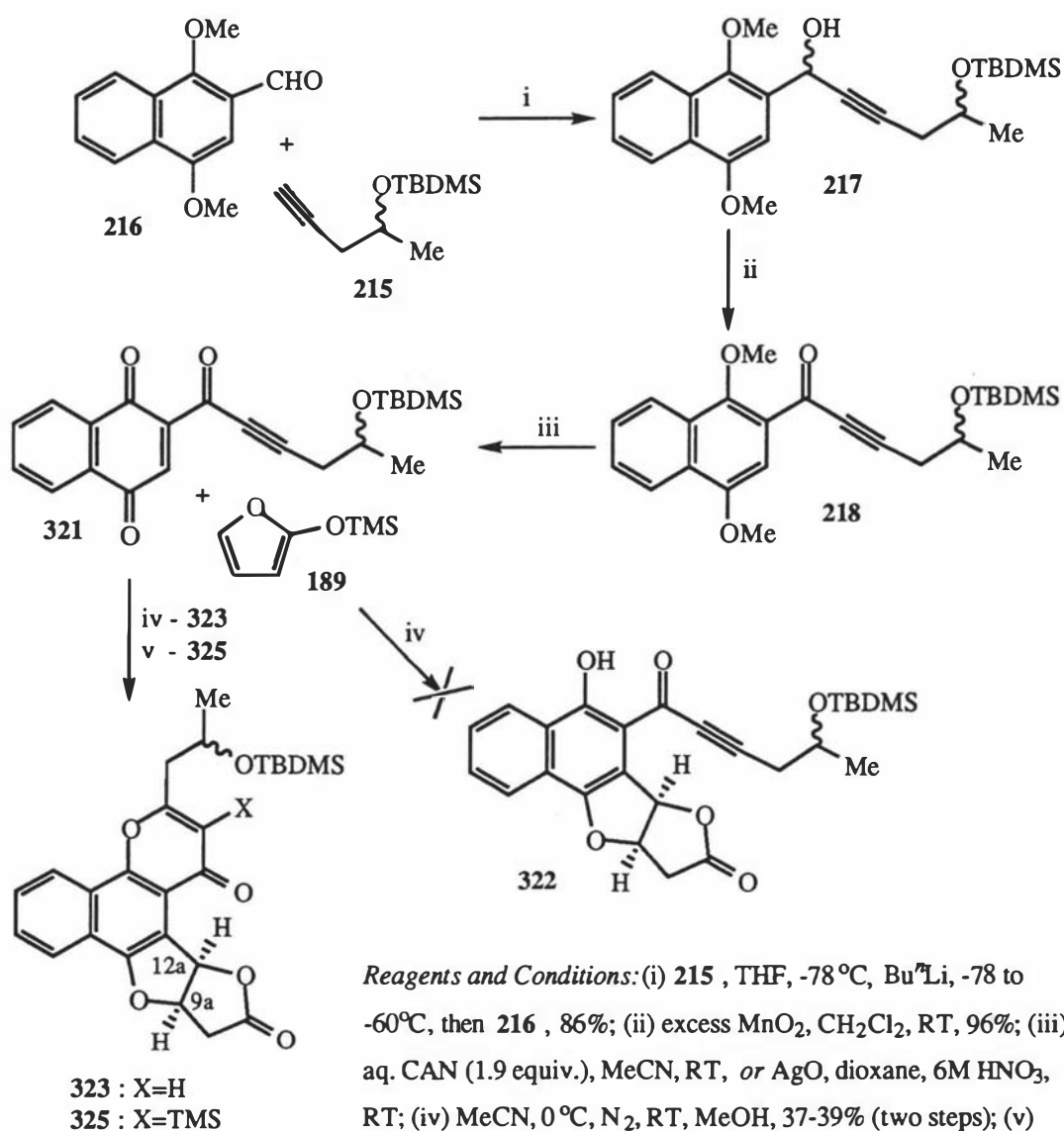
Reagents and Conditions: (i) **215**, THF, -78 °C, Bu^{n}Li, -78 to -60°C, then **216**, 86%; (ii) excess MnO$_2$, CH$_2$Cl$_2$, RT, 96%; (iii) aq. CAN (1.9 equiv.), MeCN, RT, *or* AgO, dioxane, 6M HNO$_3$, RT; (iv) MeCN, 0 °C, N$_2$, RT, MeOH, 37-39% (two steps); (v) MeCN, 0°C, N$_2$, extra **189**, RT, MeOH, 35% (two steps).

Scheme 55

and indicated *cis* fusion of the two furan rings.[§] The more unusual and strained *trans* fusion of these rings is found in a decomposition product of a coumarin,[340] where the bridgehead coupling constant was only 2 Hz.

The absence of a resonance at approximately δ_H 15 together with no absorbance in the infra-red spectrum at 3600-3100 cm^{-1} suggested that the expected phenolic hydroxyl group (**322**) was not present. Disappearance of the absorbance for the acetylene group at approximately 2235 cm^{-1} and the appearance of a singlet in the vinylic region of the ^{1}H nmr spectrum (δ_H 6.35) indicated replacement of the acetylene moiety by a

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[§] Confirmation of a similar *cis*-lactone was obtained by a positive NOE between the bridgehead hydrogens.[339]

vinylic group. The ^{13}C nmr lacked the acetylene carbon resonances, these being replaced by signals 30-70 ppm downfield, consistent with a change to sp^2 hybridization. From these results and COSY and HETCOR spectra[341,342] it was concluded that an additional six membered ring was present, and **323** was assigned the structure shown. Adduct **322** was not observed in the reaction mixture, attesting to the speed[286b] of the additional cyclization to form **323** (scheme 56).
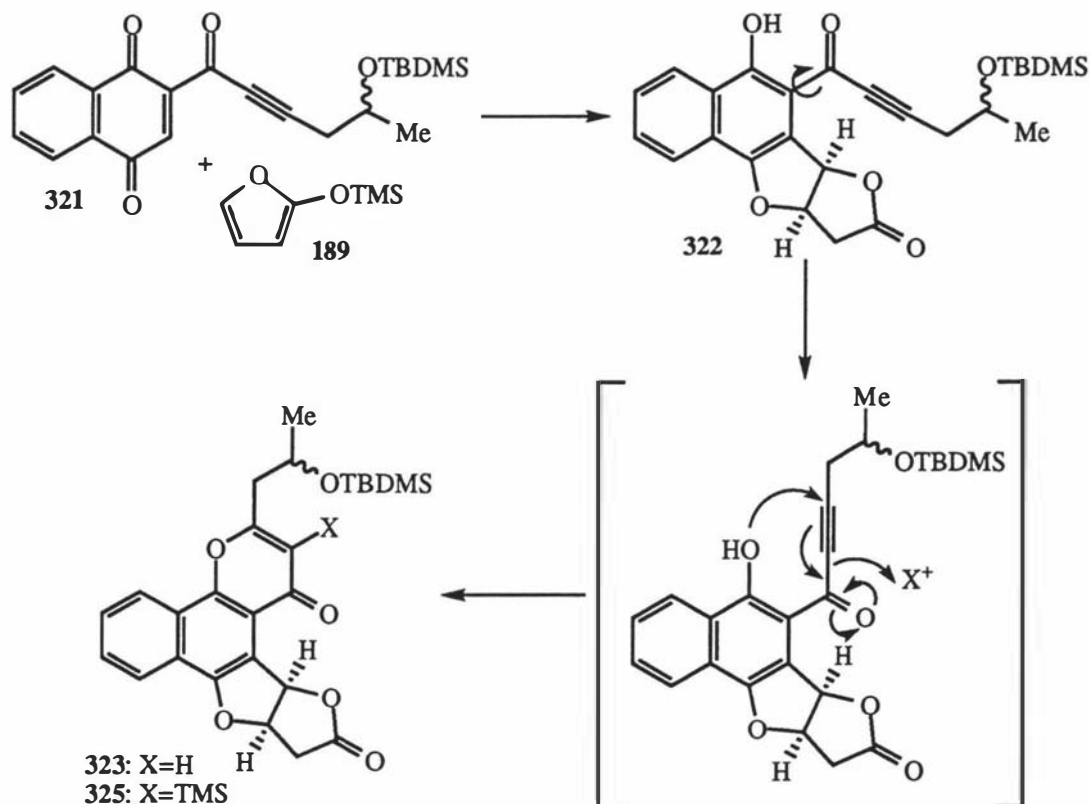
Scheme 56

The similarity between the formation of pentacycle **323** and that of **303** (scheme 50, page 96) and **305** (equation 23, page 97) is notable. In both cases a phenolic hydroxyl group cyclizes onto an α,β-unsaturated ketone (as part of a side chain) to give a new fused ring. The formation of a six membered ring in the case of **323** versus a five membered ring for both **303** and **305** must be influenced by the lack of a second carbonyl group also alpha to the triple bond in **322**.

The upper right hand quadrant of pentacycle **323** bears a close resemblance to several natural products, such as chromones[343] and the kidamycin (or pluramycin) antibiotics[344] (figure 20). Also, polyketide type aromatic natural products such as **324** have been made by biogenically modelled routes.[345]

104
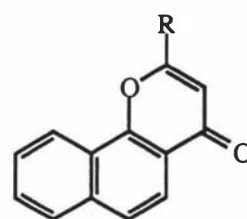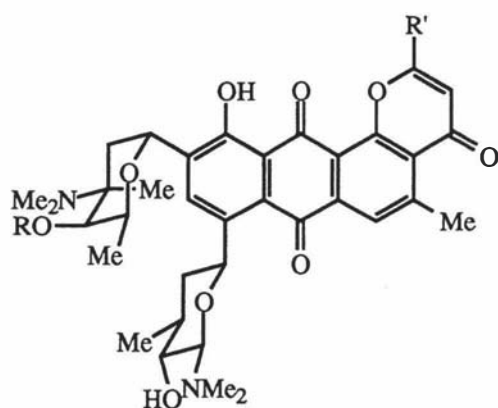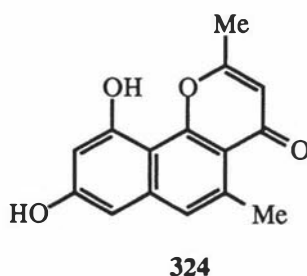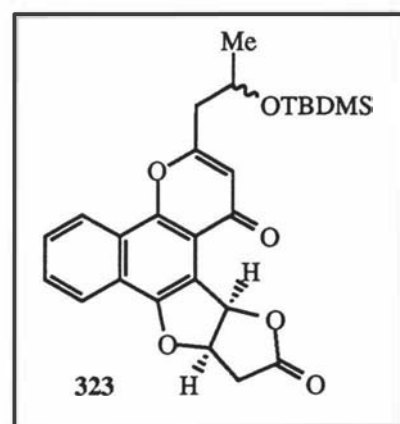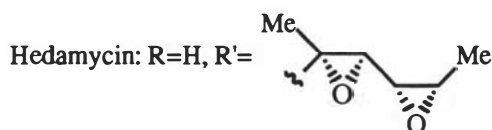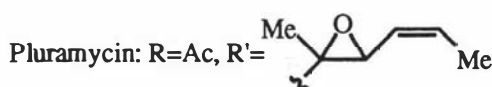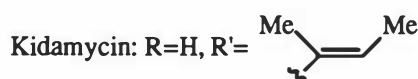
Figure 20

If the amount of 2-trimethylsilyloxyfuran **189** was increased approximately twofold without a concomitant increase in the amount of solvent then a new compound, identified as *C*-trimethylsilyl pentacycle **325** (scheme 55) was formed in 35% yield along with **323** (39%) (both as a 1:1 mixture of diastereomers). The relative R_f values (1:1 hexane-ethyl acetate) of **323** and this new compound (0.57 versus 0.74 respectively) suggested the formation of a less polar material. The ^{1}H nmr spectrum supported the formation of the same pentacyclic ring system as observed in **323**, and the IR spectrum also showed the presence of the same functional groups in the molecule. The proton spectrum did however lack the resonance for the C-2 vinylic proton at δ_H 6.35, and the signals assigned to 1'-CH$_2$ and OSi*Me*$_2$Bu^t were split for **325** whilst they were equivalent in **323**. Hence the structural difference appeared to involve this upper portion of the molecule.

The resonances for $OSiMe_2Bu^t$ in the ^{1}H nmr spectrum of **325** were shifted upfield by approximately 0.25 ppm compared to the position (δ_H 0) in **323**, these protons obviously experiencing increased shielding. A singlet was also observed at δ_H 0.41 which integrated for nine protons and was assigned as a trimethylsilyl group. HETCOR data linked this singlet to a carbon resonance at δ_C 1.40, the chemical shift value confirming a silane moiety. The absence of a vinylic proton in **325** (*vide supra*) and C-2 resonating 7 ppm downfield compared with **323** were consistent with the trimethylsilyl group being located at C-2. The high resolution mass spectrum exhibited a molecular ion at *m/z* 538.2201, equal to the molecular formula assigned to **325**, and a base peak at *m/z* 481 corresponded to loss of the *tert*-butyl group. The formation of **325** can be rationalized in that attack by the multiple bond on a trimethylsilyl cation rather than a proton occurs in the second Michael reaction, this being presumably due to the increased concentration of **189** in the reaction mixture (scheme 56).

2.4.3 Synthesis of Furofuran Adduct 330

Due to the unexpected cyclization taking place to form **323** a new synthetic strategy was developed (scheme 57). It was hoped that with a double bond in the side chain, rather than the more reactive[286b] acetylene group, the unwanted second Michael addition could be avoided or at least retarded. The double bond would provide the necessary unsaturation in order to elaborate the substituents on the spiroketal ring in the later stages of the synthesis.

Semi-hydrogenation of **217** over Lindlar catalyst afforded *cis*-olefin **326** in 92% yield. The main evidence for formation of the *cis*-alkene came from the ^{1}H nmr spectrum which exhibited vinylic protons at δ_H 5.58-5.69 and 5.83-5.92. Subsequent oxidation of alcohol **326** to the α,β-unsaturated ketone **327** proved to be difficult. A variety of reagents[268] were tried before a suitable method was found. Activated manganese dioxide,[268b,269] which was successfully used in the conversion[252,253] of **217** to **218** (scheme 29, page 71), required long reaction times and heating under reflux, and resulted in formation of the "double" dehydrogenation product **218** from **326**. Barium permanganate,[346,347] sulphur trioxide-pyridine,[348] Swern conditions,[280-282] $RuCl_2(PPh_3)_3$,[349] Fetizons reagent,[268c,350-352] pyridinium chlorochromate (PCC)[268d,353-355] and pyridinium dichromate (PDC)[268d,356] all proved unsatisfactory, giving poor yields or a complex mixture of products. Reversing the order of these two reactions and initially effecting hydrogenation of **218** to **327** did not circumvent the problem, as the hydrogenation step required more time and catalyst and afforded **327** in only a 64% yield, together with unreacted **218** and several other unidentified products.

Reagents and Conditions: (i) H$_2$, EtOAc, Lindlar catalyst, RT, 92%; (ii) CH$_2$Cl$_2$, NMO, 4A, TPAP (cat.), N$_2$, RT, 83%; (iii) MeCN, aq. CAN (1.9 equiv.), RT, 92%; (iv) MeCN, 0 °C, N$_2$, **330** 55%, **331** 7%; (v) MeOH, RT; (vi) MeCN, aq. CAN (2 equiv.), RT, 55%; (vii) MeCN, aq. CAN (8 equiv.), RT, 64%; (viii) MeCN, 40% aq. HF, RT, 46%; (ix) CH$_2$Cl$_2$, CSA, reflux, 52%.
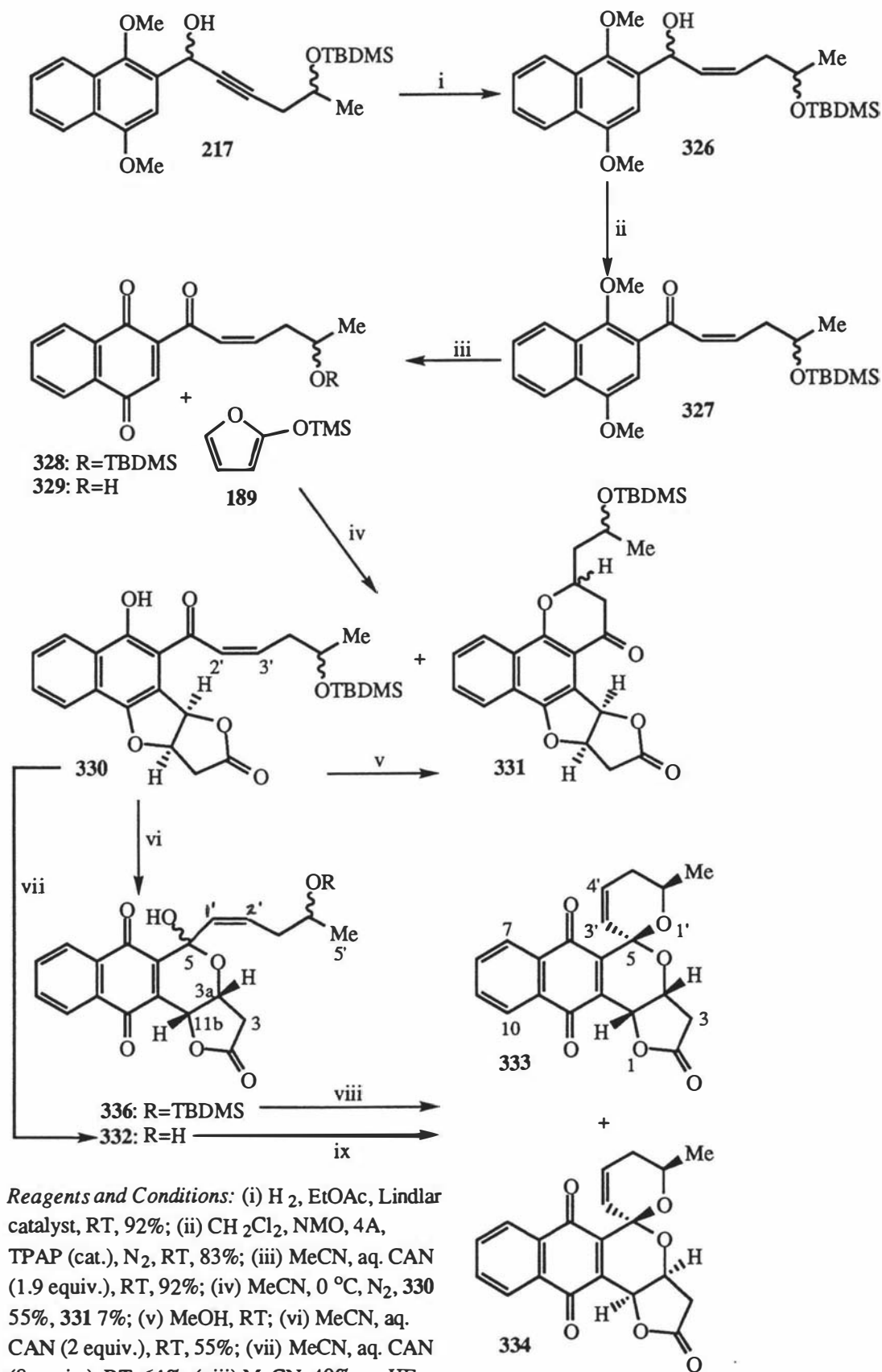
Scheme 57

107

The oxidation of **326** to **327** was solved by using *tetra-n*-propylammonium perruthenate (TPAP), a mild, catalytic oxidant developed by Ley and Griffith *et al.*[357-359] Treatment of **326** with TPAP and co-oxidant *N*-methylmorpholine *N*-oxide, using *twenty two* times the amount of dichloromethane suggested gave ketone **327** cleanly in 83% yield, which was isolated in essentially pure form simply by filtering the reaction mixture through a silica gel pad. Using the solvent volume suggested[358] for **326** (2 cm^3/mmol) gave a lower yield of **327** and produced other products with very similar R_f values. The amount of catalyst was doubled to allow the reaction to reach completion quickly and avoid side products, given the increased volume of solvent.

With the desired ketone **327** in hand, oxidative demethylation proceeded smoothly and in high yield (92%) to furnish quinone **328**. The optimum conditions were found to be 1.9 equivalents of ceric ammonium nitrate combined with the minimum quantity of water required to dissolve the cerium salt. Not adhering to these conditions resulted in a darkening of the reaction mixture and the concomitant appearance of a spot with a lower R_f, assumed to be the deprotected quinone **329** (scheme 57). In related work by us,[360] an hydroxyquinone such as **329** did not undergo the required furofuran annulation and was thus undesirable. A similar situation was experienced[322] in the addition of an azadiene to juglone **278**, in that formation of "tar products" in the attempted Michael addition was attributed to the hydroxyl group on the quinone (compare equation 24, page 98). In our case, the problem could have been due to complex formation of the secondary alcohol liberated with the ceric ion.[331] Alcohols may also undergo direct oxidation, fragmentation, or both processes with ceric ammonium nitrate, depending on their structure.[331]

In all later oxidations using CAN, Florisil was used to separate the oxidant from the product. This helped prevent the unwanted second cyclization from occurring, which was found to be promoted by both residual CAN and flash silica.

Addition of 2-trimethylsilyloxyfuran **189** to **328** under the usual conditions (0°C, MeCN, N$_2$) afforded a mixture of adduct **330** and pentacycle **331** in 55 and 7% yield respectively (scheme 57). The maximum yield of the desired adduct **330** was obtained when the reaction was worked up quickly and methanol was not added. Long reaction times in particular resulted in complete conversion to **331**. If Florisil was not used to remove residual CAN from quinone precursor **328**, then its presence promoted the second cyclization (*vide supra*). The mechanism of formation of **331** from **330** is analogous to that shown for **323** from **322** (scheme 56, page 104).

Adduct **330** was identified from its ^{1}H nmr spectrum by a resonance for a phenolic hydroxyl group at δ_H 14.79, vinylic protons at δ_H 6.39-6.54 and 7.07, and the similarity of the protons in the side chain to ketone **327**. For **331**, whose spectral data closely resembled **323**, there was no hydroxyl signal in the ^{1}H nmr and the vinylic

protons 2'-H and 3'-H in **330** were replaced by signals at δ_H 2.75-2.86 and 4.79-4.88 respectively as a result of sp^3 hybridisation at these positions in **321**. The carbonyl stretch in the infra-red spectrum shifted from 1630 (**330**: α,β-unsaturated ketone) to 1684, 1675 cm^{-1} for **331**. The formation of another asymmetric centre in **331** was indicated by the increased complexity of the nmr spectrum, in that multiple signals were observed for many groups. Adduct **330** was formed as a 1:1 mixture of diastereomers (^{1}H nmr).

2.4.4   Synthesis of Naphthopyran Diol 332

With furonaphthofuran **330** in hand it now remained to effect oxidative rearrangement of this tetracyclic system to that present in the pyranonaphthoquinone antibiotic griseusin A **88**.

Treatment of **330** with an excess of ceric ammonium nitrate (8 equivalents, scheme 57) afforded the furo[3,2-b]naphtho[2,3-d]pyran **332**, wherein oxidative rearrangement (scheme 26, page 67) was accompanied by loss of the silyl protecting group. This loss was previously observed in earlier work on the saturated ring system of **88**.[252,253] The product was isolated in 64% yield after purification by flash chromatography.[361] The yield for this step was significantly lower than the analogous reaction in the saturated series (87% for **212**→**219**, scheme 29, page 71), suggesting that lower yields were obtained upon CAN treatment of molecules possessing unsaturated side chains.

The ^{1}H nmr spectrum of **332** revealed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **330**. The coupling constant between the bridgehead protons was markedly reduced, from 5.9 to 2.9 Hz, reflecting the 6,5 ring fusion now in place. This coupling constant, $J_{3a,11b}$ 2.9 Hz, matched those obtained for the analogous protons in griseusin A **88** and B **89**.[173] The sharp resonance for the phenolic peak in **330** (^{1}H nmr) was replaced by two broad resonances at δ_H 4.72-4.83 and 6.00-6.22. The ^{13}C nmr spectrum reflected the loss of the carbonyl group at δ_C 196.0, and the presence of additional signals at δ_C 92.7 (average of two) was consistent with a lactol carbon (C-5).

The assignment of 3-H^A and 3-H^B was made for **332** (and later furonaphthopyrans, *vide infra*) upon examination of the vicinal coupling between 3-H and 3a-H (figure 21). One of the methylene protons at C-3 which resonated at δ_H 2.75 (av) in **332** exhibited only a large geminal coupling {J_{gem} 17.7 Hz (av)}, whereas the other proton at δ_H 3.00 (av) appeared as a double doublet from additional vicinal coupling to 3a-H ($J_{3a,3}$ 4.8 Hz). Using the Karplus equation[362] and molecular models, the methylene proton which lacked any 3,3a coupling would have a dihedral angle of approximately 90° and was designated as 3-H^A. 3-H^B almost eclipses 3a-H when viewed

along the C3-C3a bond axis and the *J* value (4.8 Hz) was commensurate with this (compare 2-H and 3-H of **279** and **282**, scheme 45, page 91).

Determination of 3-H^A and 3-H^B View along C3-C3a bond axis
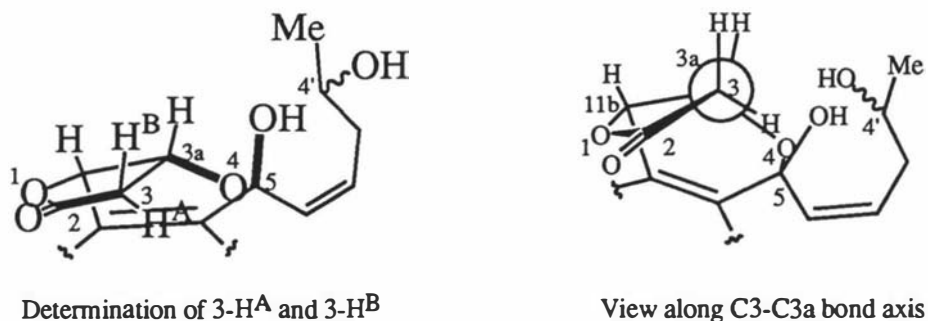
Figure 21

^{1}H nmr spectroscopy established that diol **332** was in fact a mixture of diastereomers due to the presence of four chiral centres. Whilst the relative stereochemistry of the bridgehead protons at C-3a and C-11b has been established to be *cis*, a diastereomeric mixture results due to lack of control of stereochemistry at the anomeric carbon C-5. By comparison, saturated diol **219** (scheme 29, page 71) was isolated as a 1:1 mixture of diastereomers, where the relative configuration between C-5 and C-3a/C-11b was fixed through presumably steric and anomeric effects. Having an unsaturated side chain in some way makes the configuration adopted by **219** less energetically favourable, and so a diastereomeric *mixture* results for **332**.

2.4.5   *Synthesis of the Spiroketal Ring System of 333,334*

<u>From Diol **332**</u>

Having synthesized diol **332** the remaining step required to construct the griseusin A **88** framework involved cyclization to form the spiroketal ring. This transformation was based on our earlier synthesis[252,253] of the ring system of griseusin A, in which C1'-C2' saturated diol **219** was converted to spiroketals **210,211** (scheme 29). Thus diol **332** was treated with camphor sulphonic acid under gentle reflux to afford spiroketals **333,334** in a 3:2 ratio (^{1}H nmr, scheme 57). The two spiroketals were inseparable by flash chromatography but were readily separated by high pressure liquid chromatography[363] (hplc), which confirmed the 3:2 isomeric ratio. The ^{1}H nmr spectrum of the isomeric mixture of spiroketals (figure 22) was readily interpreted due to most of the resonances from the individual isomers being distinguishable.

The assignment of structure **333** to the major isomer was based on the spiroketal functionality being formed under thermodynamic control, and that maximal stability is

110

Figure 22

(italicized protons represent *both* spiroketals)

7-H
10-H

8-H
9-H

CHCl₃

11b-H*
11b-H

4'-H

3'-H

3a-H* 3a-H

6'-H*

6'-H

3-H^B
*3-H^B

*3-H^A
3-H^A

5'-CH₂*

5'-CH₂*

5'-CH₂

H₂O

Me*

Me

111
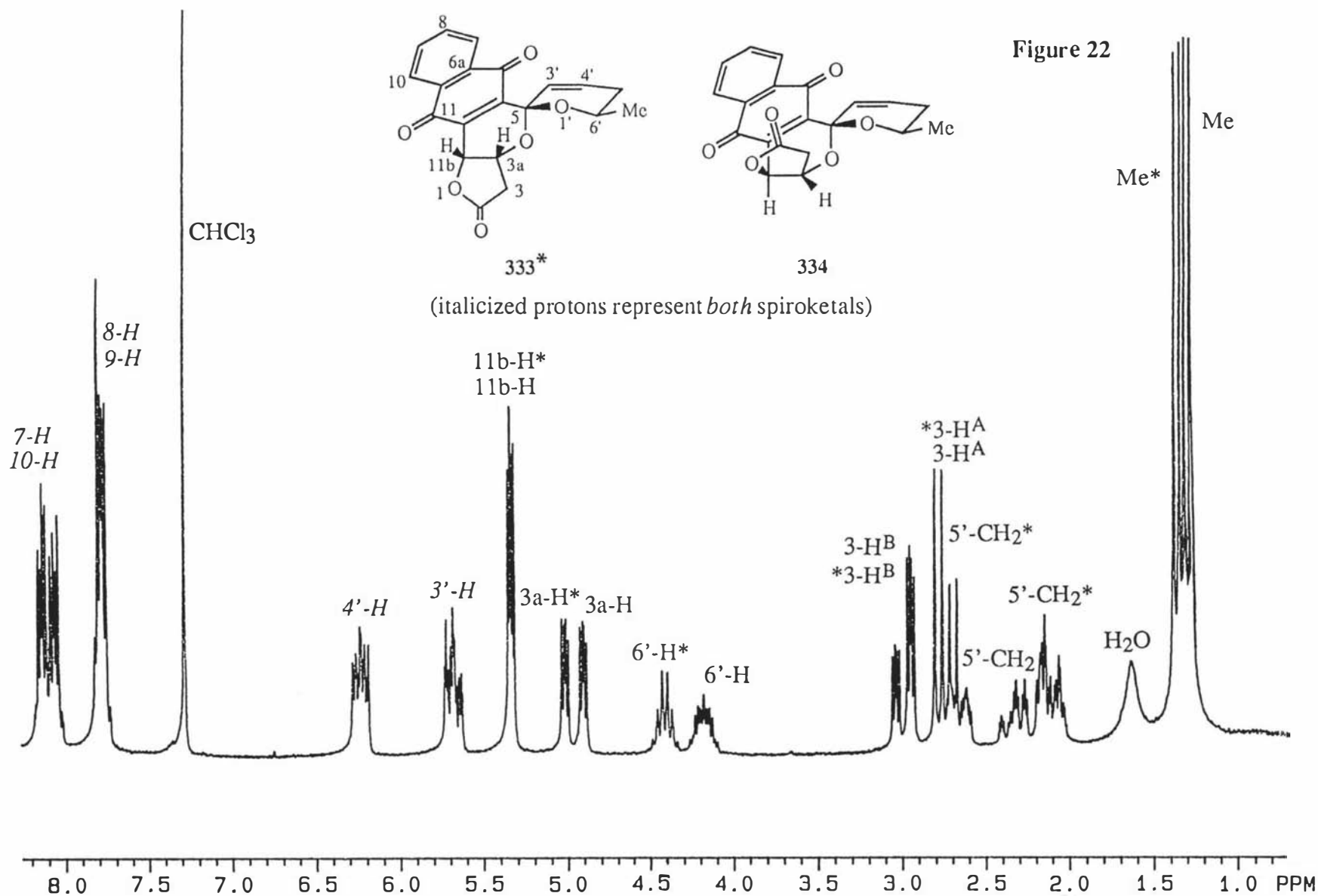
gained through the anomeric effect[30] when the oxygen atom of each pyran ring occupies a position axial with respect to the C-O bond of the adjacent ring.[270-273]

In the case of spiro[5.5]systems, the *bis*-axial arrangement of spiro C-O bonds (section 1.3.2, page 72) is commonly observed in *both* saturated and unsaturated systems[274] (figure 23).

avermectin B_{1a} and B_{2a} okadaic acid
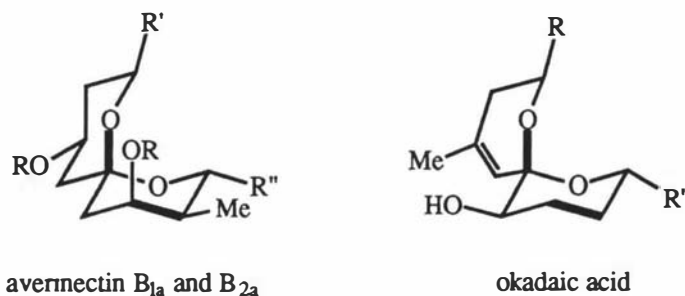
Conformations of Spiroketal Substructures from Various Natural Products

Figure 23

Comparison of the ^{1}H nmr chemical shifts for **333** and **334** supported the assigned structures (figure 24). Thus, spiroketal **334** exhibited a double doublet at δ_H 4.90 assigned to the bridgehead proton 3a-H, whilst for spiroketal **333** this same proton resonated as a double doublet further downfield at δ_H 5.01. The deshielding of 3a-H in this latter isomer is attributed to the 1,3-diaxial interactions between 3a-H and O-1'. [1]H nmr chemical shift differences and relative positions between **333** and **334** were generally the same as between saturated isomers **210** and **211** (figure 12, page 70).
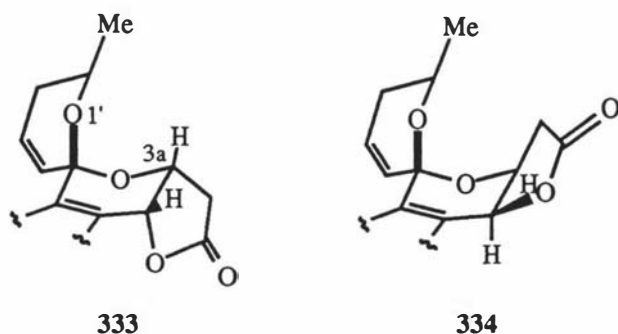
333   334

Figure 24

If the CAN mediated oxidative rearrangement of **330** was left for an extended period of time, the mildly acidic conditions effected cyclization of diol **332** to spiroketals **333,334** as well as isomerization of the starting material to the *trans*-diol **335** (R_f 0.36 versus **332** 0.47, 1:2 hexane-ethyl acetate). Due to the inability of diol **335** to cyclize and

form a six membered ring, formation of this unwanted by-product was prevented by short reaction times.

335
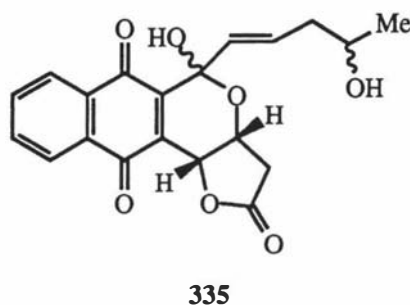
From Silyl Ether 336

The intermediate hemiketal **336** (scheme 57, page 107) with the *tert*-butyldimethylsilyl group still present could be formed from adduct **330** if only two equivalents of ceric ammonium nitrate were used to rearrange the carbon skeleton. This compound was isolated as a glassy solid in 55% yield and as a mixture of stereoisomers.

Stepwise deprotection of silyl ether **336** to alcohol **332** using CAN was much less efficient than direct conversion of **330** to **332**. Formation of **332** from **336** was only effected in 33% yield along with the *trans*-diol **335**. Alternative desilylating agents such as tetrabutylammonium fluoride,[335,336] trifluoroacetic acid and AcOH/THF/H$_2$O[336] resulted in decomposition or a complex mixture, however success was finally realized with aqueous hydrofluoric acid.[364]

Addition of HF to an acetonitrile solution of **336** gave predominantly spiroketals **333,334**, the acidity of the reaction causing *in situ* cyclization of **332** as it formed (use of py-HF or Et$_3$N-HF did not prevent the cyclization and also led to decomposition of **336**). From the differing peak integrations of the spiroketal mixture obtained using either ceric ammonium nitrate or hydrofluoric acid, a definitive assignment of ^{1}H nmr signals belonging to the spiroketal isomers was made (figure 22, page 111). In the present case, use of HF in acetonitrile resulted in an isomeric ratio which was reversed from that obtained with CAN, in that spiroketal **334** was favoured over **333** (**333:334** = 3:7).

The differing isomeric ratios obtained may be attributed to the spiroketal ring being formed under thermodynamic conditions using ceric ammonium nitrate, whilst when hydrofluoric acid is used the reaction proceeds under kinetic control. In an analogous reaction, a [6,5] spiroketal was formed during the synthesis of calyculin A[365] by treatment of an acyclic *bis*-triethylsilyl ether with aq. HF. It was noted that the origin of the preference for formation of the less stable kinetic spiroketal was not readily apparent from the available data, due to a lack of information about the order of ring

forming steps during the spirocyclization process. Equilibration studies on spiroketals **333** and **334** are discussed further in section 2.4.6 (page 115).

A similar one step desilylation/cyclization process[366] for avermectin B2a precursors using HF-pyridine in tetrahydrofuran produced the corresponding kinetic cyclization product **337** (scheme 58). When there was substitution at C-25 (R'≠H) the use of a *tert*-butyldimethylsilyl group led to complex mixtures since the methoxy ketal underwent hydrolysis and fragmentation before the C-25 hydroxyl group was freed and able to cyclize onto the incipient carbocation. Hence the difficulty noted above in forming **332** (and thus **333,334**) from **336** by ceric ammonium nitrate or AcOH/THF/H₂O is not unexpected given the close similarity between the relevant portion of these avermectin precursors and **336**.

Reagents and Conditions: HF-pyridine, py, THF (1:3:6), RT.

Scheme 58

kinetic isomer **337**   thermodynamic isomer
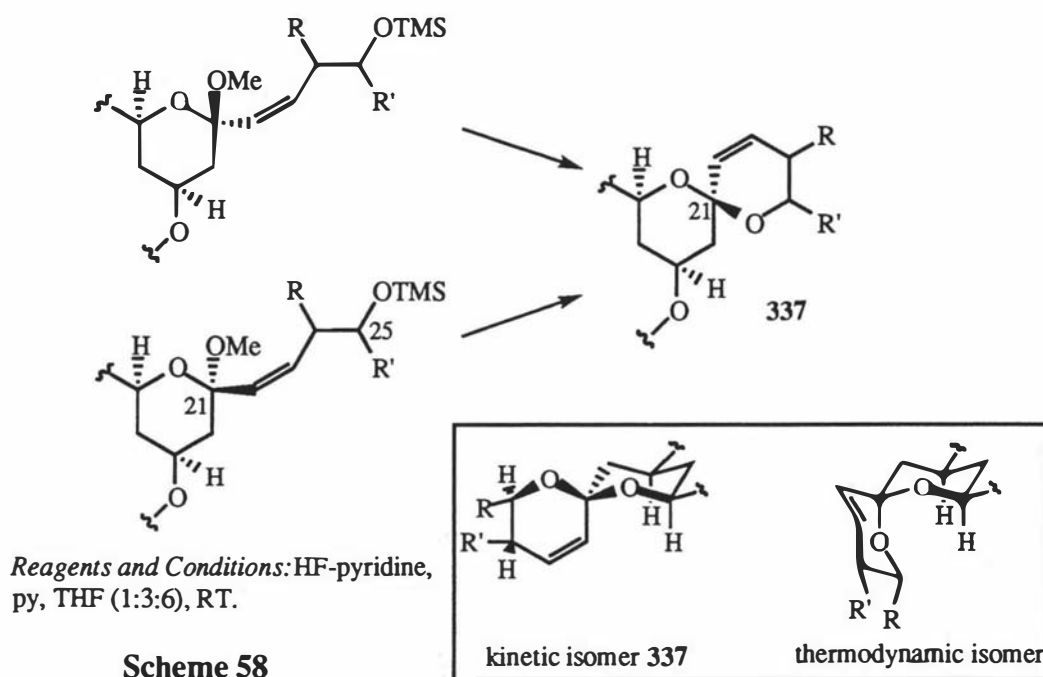
Via Attempted Rearrangement of Pentacycles **323** and **331**

The oxidative rearrangement of the two pentacyclic adducts **323** and **331** was pursued as an alternative route to the griseusin A ring system. It was hoped that rearrangement and cyclization of, for example, **323**, would lead to **338** and **339**, analogues of the natural product (scheme 59). However repeated attempts to carry out even the first part of this transformation yielded only a complex mixture of products, characterized by fluorescent material and a broad baseline smear (TLC). ¹H nmr investigation of this material revealed no structures identifiable with the starting pentacycle, and the IR spectrum displayed markedly broader bands for carbonyl and hydroxyl group absorbances. Treating this crude material with camphor sulphonic acid in order to cyclize any triol **340** that may have been present was unsuccessful. Similar

results were obtained with the saturated pentacycle **331**, where it was hoped that the lack of a double bond would not complicate the oxidation (refer page 109).

Reagents and Conditions: (i) MeCN, aq. CAN (8 equiv.), RT; (ii) CH₂Cl₂, CSA, reflux.
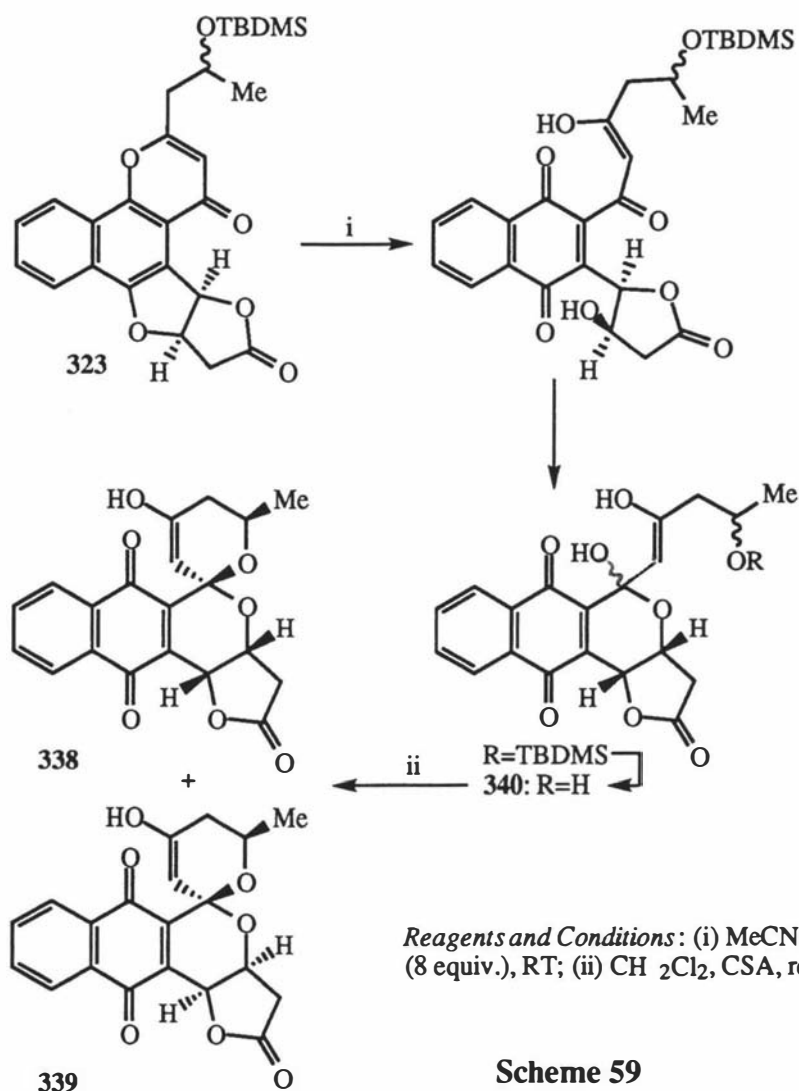
Scheme 59

2.4.6 Equilibration of Spiroketals 333,334

The key unsaturated spiroketal required for the synthesis of racemic 7-deoxygriseusin A **320** had been prepared as a 3:2 (**333**:**334**) diastereomeric mixture (scheme 57, page 107). In contrast to their saturated analogues **210** and **211**[252,253] (ratio 2:1), spiroketals **333** and **334** were inseparable by flash chromatography, however they were separable by hplc (refer page 110). Although the major isomer **333** had the same relative stereochemistry between C-3a and C-5 as required for griseusin A **88**, improvement to the isomeric ratio was desirable, therefore alternative acidic conditions were investigated to effect the construction of the spiroketal ring and increase the amount of **333** produced versus **334**.

As the two saturated analogues **210** and **211** had been made previously, this material was available with which to probe isomer ratios. In an enantioselective synthesis of Talaromycins A and B,[367] trifluoroacetic acid in dichloromethane was used to isomerize the spirocentre in **341** to give the more stable isomer **342** (scheme 60), with all substituents equatorial. This procedure (using benzene as solvent) was tried with **211**, the saturated analogue of **334**, the result being complete and clean conversion of **211** to **210** under reflux in *ca.* 2.5 hours[ø] (scheme 61 and table 1). This confirmed that **210** was the thermodynamic product from the spirocyclization.[252,253]
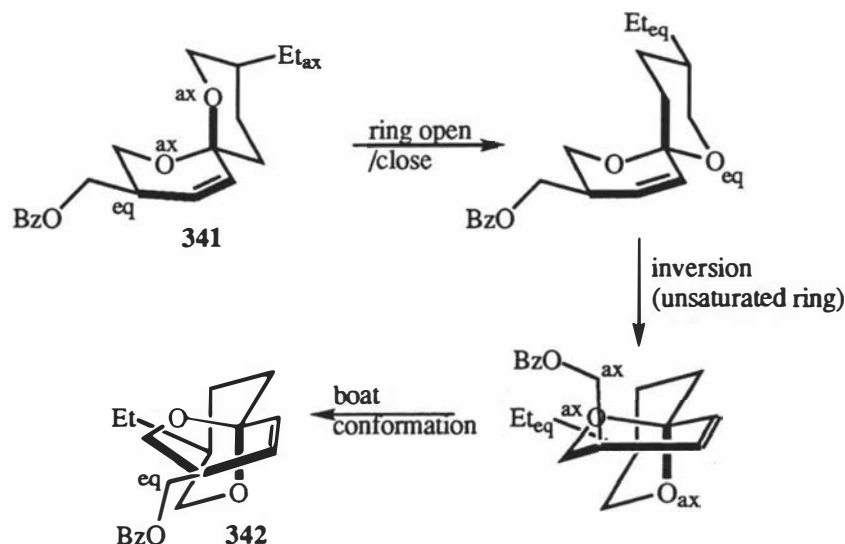
Reagents and Conditions: TFA, CHCl₃.

Scheme 60
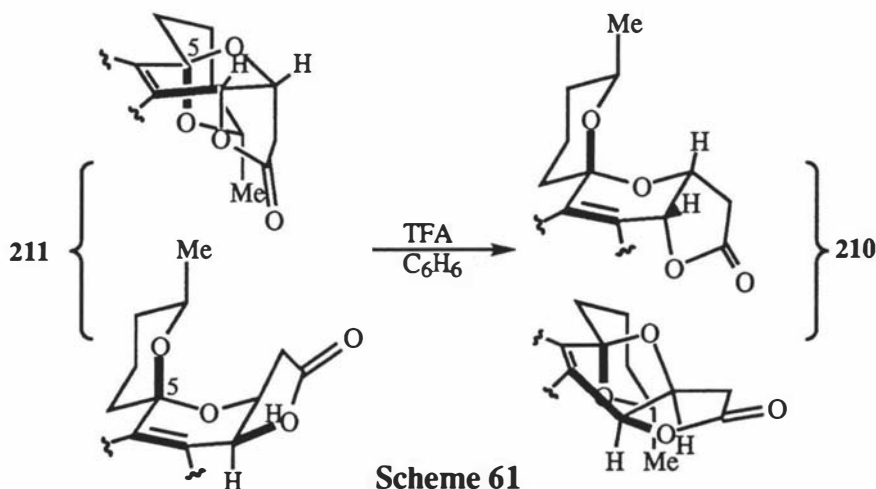
Scheme 61

[ø] **210** was inert to the reagent.

Turning then to a mixture of **333** and **334**, the same procedure unexpectedly changed the isomer ratio (**333:334**) from 8:10 to 5:10 in a similar period of time with 90% recovery of material (table 1). After about 5 hours the ratio had become 4:10 by ^{1}H nmr integration, however only 60% of the original material remained (a similar loss of material had been noted in the equilibration of spiroketals with TFA/CH$_2$Cl$_2$[368]). The decrease in recovered starting material (**333,334**) suggested that decomposition on prolonged treatment with acid was occurring, the decreasing amount of **333** indicating that it was more prone to the acid conditions. This instability of **333** contrasts with its saturated analogue **210** which was inert to the reaction conditions used (footnote$^\emptyset$, page 116). The conversion of **333** *to* **334** was opposite to that seen for the saturated compounds where the *less* abundant HF isomer **211** was transformed to the *more* abundant CAN isomer **210** (scheme 61), and appears contrary to the earlier cited Talaromycin example (scheme 60).

starting material	isomer ratio	conditions	yield (%)	isomer ratio
diol **332**	mixture	CSA, CH$_2$Cl$_2$, reflux	64	3:2 **333:334**
silyl ether **336**	mixture	HF, MeCN, RT	46	3:7 **333:334**
diol **219**	1:1	CSA, CH$_2$Cl$_2$, reflux	64	2:1 **210:211**
spiroketals **333,334**	8:10 **333:334**	TFA, C$_6$H$_6$, reflux, 2.5 h	90	5:10 **333:334**
spiroketals **333,334**	8:10 **333:334**	TFA, C$_6$H$_6$, reflux, 5 h	60	4:10 **333:334**
spiroketal **211**	-	TFA, C$_6$H$_6$, reflux	100	**210**

Table 1

It is possible that the CAN isomer **333** is decomposing faster than the HF isomer **334**, however the ratio change from 8:10 to 5:10 is too dramatic to be accounted for if *only* **333** decomposed, given that the amount of recovered starting material fell by only 10%.

CHAPTER 3

Hydroxylation of 1,7-Dioxaspiro[5.5]undec-4-enes

3.1 *syn*-Hydroxylation of Spiroketal 345 using Osmium Tetraoxide

3.1.1   *Choice of Model System*

Having successfully synthesized unsaturated spiroketals **333** and **334**, the introduction of the hydroxyl groups to the double bond of the terminal pyran ring, as required for griseusin A **88**, was then investigated. It was envisaged that an osmium tetraoxide *syn*-hydroxylation would afford separable (±)-diols **343** and **344**. One of the hydroxyl groups of **343** could then be selectively acetylated at C-4' as in **88** (scheme 62). Due to scarcity of material and the need to examine the stereochemical outcome of the proposed hydroxylation reaction, a model bicyclic spiroketal **345** was used instead of **333,334**.
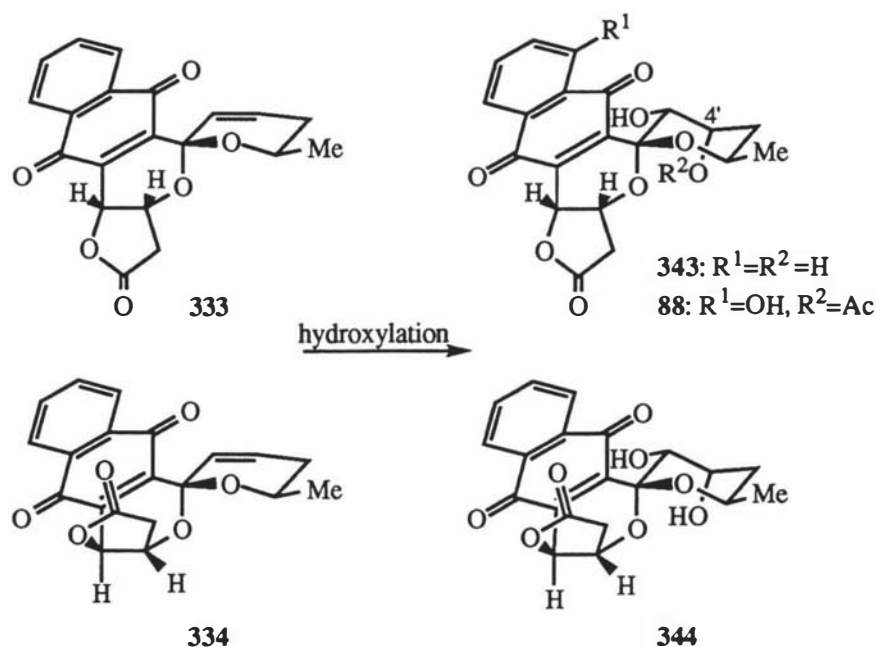
Scheme 62

Spiroketal **345** has been prepared previously by Brimble *et al.*[369,370] for allylic oxidation studies, and also by others[371,372] in the synthesis of related 1,7-dioxaspiro[5.5]undec-4-enes. It was chosen as a model for the proposed hydroxylation reaction due to ease of preparation,[274] availability, and close similarity to the spiroketal

portion of **333,334**. Also, the results gathered would be interesting given that: (i) no examples of *syn*-hydroxylation of spiroketals had been reported (although a highly stereoselective osmylation of an unsaturated chiral acetal had been published[373]), (ii) the level of asymmetric induction for (Z)-disubstituted olefins using chiral tertiary amine ligands was unsatisfactory[374] compared with (E)-mono- and disubstituted olefins (this problem has now been addressed by Sharpless *et al.*[375,376]), and (iii) both steric and heteroatom factors[377] would influence the results.

345   **333,334**
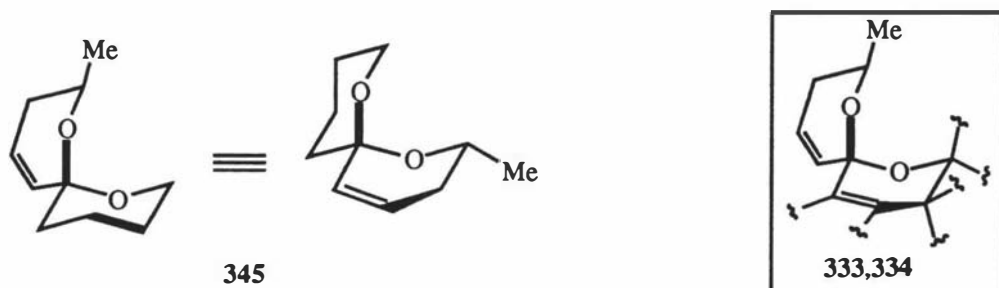
3.1.2   Osmium Tetraoxide

By way of its effectiveness, mildness and versatility, osmium tetraoxide has continued to be the method of choice for the *syn*-hydroxylation[268e,378] of olefins since this reaction was discovered.[379] Initially, the reaction was conducted in a stoichiometric fashion in the absence of secondary oxidants[380] and surmised to proceed *via* an intermediate osmium(VI) ester **346** (equation 28), similar to the analogous potassium permanganate oxidation.[381] Such esters can exist in a variety of monomeric and dimeric forms, and as *cis* and *trans* isomers. **346** undergoes reductive or oxidative hydrolysis to yield the required diol and an insoluble osmium salt or regenerated OsO_4 respectively.

346
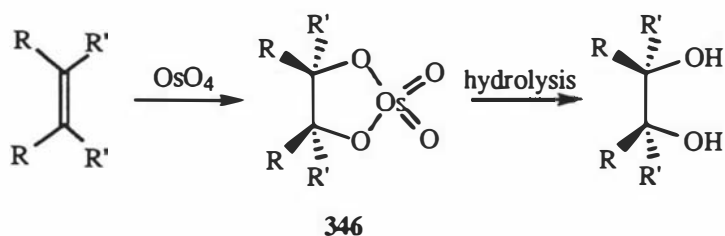
Equation 28

Formation of these osmate ester complexes is accelerated by the addition of a tertiary amine, in particular pyridine, to the reaction mixture[380b] (osmium tetraoxide has a tetrahedral structure and forms very stable five-coordinate trigonal bipyramidal adducts with *N*-donors). This acceleration[382] is thought to be due to coordination of the base to the metal centre, forming a more reactive osmium amine complex **347** (isolable[380b]) and

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thereby increasing the rate of reaction of OsO₄ with the olefin. Although the osmate ester-amine complex was more difficult to hydrolyse, this stoichiometric system remained the method of choice until 1980, mainly due to its mildness and generality.

347
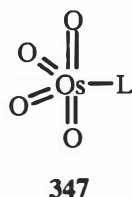
Catalytic methodology has for the most part superseded using osmium tetraoxide in molar equivalents, due to the cost and toxicity of the reagent. Many secondary oxidizing agents have been employed,[268e,378,383-385] including metal (for example barium) chlorates, hydrogen peroxide, *tert*-butyl hydroperoxide, oxygen, sodium periodate, sodium hypochlorite, diphenyl selenoxide and amine *N*-oxides.

The mechanism[268e,386] of *syn*-hydroxylation has generally been thought to proceed *via* a concerted [3+2] cycloaddition process involving attack on oxygen (path a, scheme 63).[380,387] An alternative (stepwise) proposal[388,389] was that the weak nucleophile C=C would be expected to attack the more electropositive osmium centre of the Os=O bond, rather than the oxygen (path b). This [2+2] cycloaddition would produce an organoosmium(VIII) intermediate (osmaoxetane) **348**, rearrangement by reductive insertion of the Os-C bond in to an Os=O bond giving **349** (the last step being facilitated by coordination of ligands).
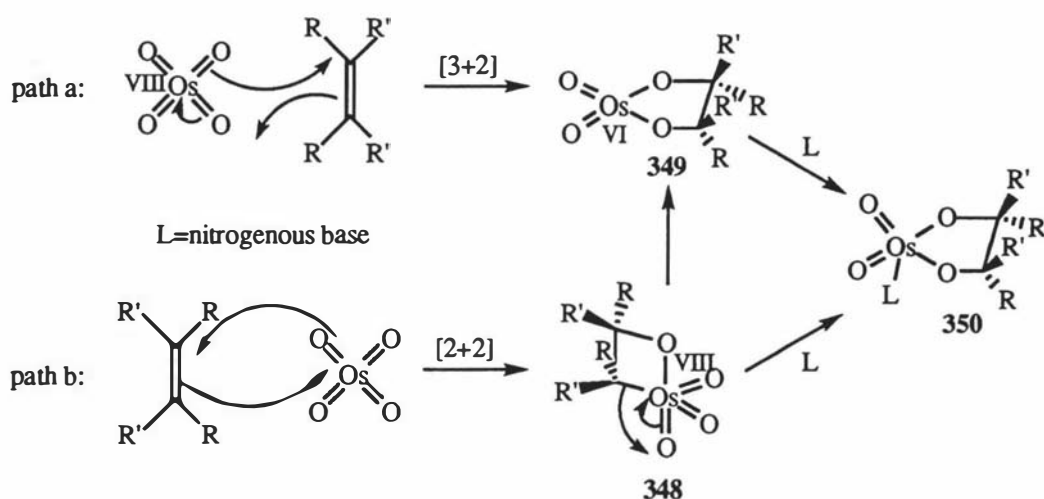
Scheme 63

The simplicity of path a leading to **349** is appealing, however severe angle strain would exist in this structure. By contrast **348** should be substantially less strained due to the longer Os-C and Os-O bonds. Coordination of a ligand *prior* to reaction with the

120

olefin would mean [3+2] cycloaddition could however proceed directly to **350**.[388] Later work[390,391] using 1,1-diphenylethene favoured the "oxametallacyclobutane" model of Sharpless (path b, scheme 63).

Facial selectivity in the approach of the osmium to a π-system can be directed by steric factors and by interactions between a heteroatom and the reagent.[377] The selectivity observed in the reactions of double bonds is the result of a subtle interplay of steric and electronic factors. In particular, the nature and role of electronic effects is far from being definitively assessed.[392]

The development of asymmetric dihydroxylation, pioneered by Sharpless, began with cinchona alkaloid derivatives dihydroquinidine acetate **351** and dihydroquinine acetate **352**.[389] From this point, the search for new ligands to afford better enantiomeric excess (ee) and the exploration of the processes leading to π-face differentiation has culminated in a one-pot procedure for asymmetric dihydroxylation (AD-mix: see section 4.7.3, page 205) and a detailed knowledge about "two-cycle" mechanisms and intermediate structures.[376,393]
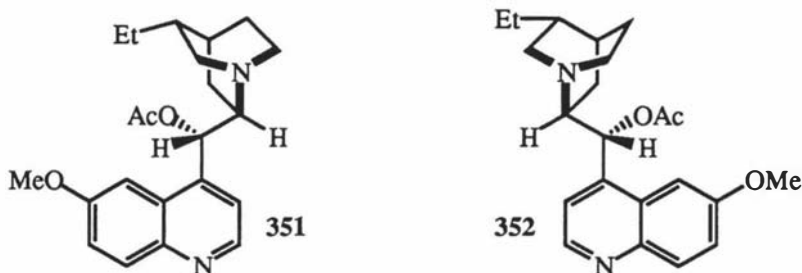
3.1.3 Formation of Diol 353 and Acetates 354 and 355 using Osmium Tetraoxide

Using a catalytic amount of osmium tetraoxide and N-methylmorpholine N-oxide[394,395] alkene **345** underwent smooth hydroxylation in 80% yield to give exclusively *syn*-diol **353** (scheme 64).[396,397] With the removal of unsaturation from the methyl substituted ring it was assumed that **353** would adopt the predicted[274] "all chair" conformation illustrated, with the methyl group equatorial and the ring oxygens axial.[270-273] The methine proton 4-H in **353** resonated at δ_H 4.06 as a double double doublet with coupling constants $J_{4ax,3ax}$ 11.7, $J_{4ax,3eq}$ 5.1 and $J_{4ax,5eq}$ 3.3 Hz, whilst 5-H resonated at δ_H 3.49 as a doublet, $J_{5eq,4ax}$ 3.3 Hz (table 2). The magnitude of $J_{4,5}$ (3.3 Hz) and the large diaxial coupling (11.7 Hz) between one C-3 proton and 4-H clearly established that 4-H and 5-H occupied axial and equatorial positions respectively. The downfield position of 4-H with respect to 5-H was consistent with 4-H and the C6-O7 bond being 1,3-diaxial.[398] From a HETCOR spectrum, the carbon bearing the proton resonating at δ_H 3.49 resonated at δ_C 72.2 and was downfield of the carbon at δ_C 66.1, which was linked

to the proton at δ_H 4.06. C-5 would be expected to be downfield of C-4 by virtue of being next to the spiro carbon, thus the HETCOR spectral data confirmed the assignments made based on vicinal coupling constants.
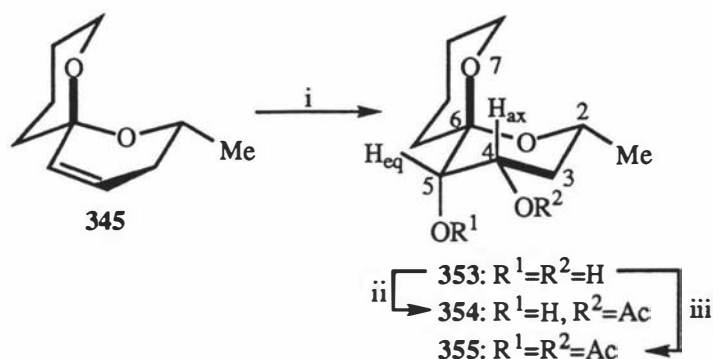
Reagents and Conditions: (i) aq. Me$_2$CO, NMO, OsO$_4$ (cat.), RT, 80%; (ii) CH$_2$Cl$_2$, Ac$_2$O, Et$_3$N, RT, 91%; (iii) CH$_2$Cl$_2$, Ac$_2$O, Et$_3$N, DMAP (cat.), RT, 85%.

Scheme 64

Selective acetylation of the least hindered equatorial hydroxyl group at C-4 afforded **354** in 91% yield (scheme 64). It was necessary to effect the acetylation in the absence of the catalyst 4-dimethylaminopyridine (DMAP) to prevent formation of diacetate **355**. In the ^{1}H nmr spectrum of **354** (table 2) 5-H resonated at δ_H 3.58-3.63, similar to this same proton in **353** (δ_H 3.49), however 4-H appeared downfield at δ_H 5.25 thus confirming acetylation at this carbon. The coupling constants for this latter multiplet (δ_H 5.25, $J_{4ax,3ax}$ 11.7, $J_{4ax,3eq}$ 5.1 and $J_{4ax,5eq}$ 2.9 Hz) confirmed that 4-H adopted an axial position in the molecule.

The methine proton at C-2 of **354** resonated as a quartet double doublet at δ_H 3.83, the coupling constants $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.6 Hz demonstrating that 2-H was axial, a fact not apparent in the ^{1}H nmr spectrum of **353** where C*H*Me appeared as a multiplet and the coupling constants were not defined. Irradiation of the C-2 methyl group (δ_H 1.25) in **354** collapsed the C*H*Me signal to a double doublet, $J_{2ax,3ax}$ 11.0 and $J_{2ax,3eq}$ 2.6 Hz, showing clearly the axial position occupied by 2-H in this (and the other) spiroketals, and thus the equatorial position of the methyl group. The three spiroketals (monoacetate **356** is included in table 2 for comparison with **354** and will be discussed later this chapter) all displayed a diagnostic[398,399] peak at m/z 101 in the mass spectra, assigned to the molecular fragment C$_5$H$_9$O$_2$. This molecular ion was not seen under electron impact (EI) conditions, however use of a "softer" ionization method (LSIMS: see section 5.1, page 209) afforded molecular ions (at high resolution) corresponding to the molecular formula proposed in each case.

Spiroketal	_CH_Me	Me	3-CH$_2$	4-H	5-H	OH	8-CH$_2$	9-CH$_2$	10-CH$_2$	11-CH$_2$	Ac
353	3.67-3.81, m	1.23, d, 6.6	1.36-2.02, m	4.06, ddd, 11.7, 5.1, 3.3	3.49, d, 3.3	2.35, br.s 2.45, br.s	3.57-3.61, m	1.36-2.02, m	1.36-2.02, m	1.36-2.02, m	-
354	3.83, qdd, 6.2, 12.4, 2.6	1.25, d, 6.2	1.51-2.04, m	5.25, ddd, 11.7, 5.1, 2.9	3.58-3.63, m	1.51-2.04, m	3.58-3.63, m	1.51-2.04, m	1.51-2.04, m	1.51-2.04, m	2.08, s
356	3.80, qdd, 6.4, 12.8, 2.4	1.27, d, 6.4	1.33-1.90, m	4.18-4.29, m	4.93, d, 3.3	1.99-2.06, br.s	3.59, dd, 8.3, 3.1	1.33-1.90, m	1.33-1.90, m	1.33-1.90, m	2.14, s
355	3.88, qdd, 6.2, 12.4, 2.9	1.28, d, 6.2	1.49-1.81, m	5.32, ddd, 11.9, 5.3, 2.9	5.05, d, 2.9	-	3.58-3.63, m	1.49-1.81, m	1.49-1.81, m	1.49-1.81, m	1.98, s 2.13, s

Table 2

Data in table recorded at 270 MHz in CDCl$_3$ and listed as δ_H, multiplicity and _J_ value(s) (Hz)
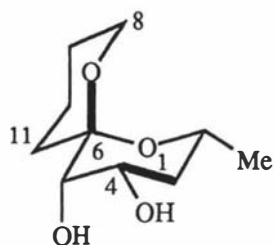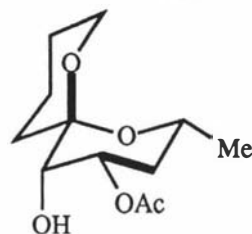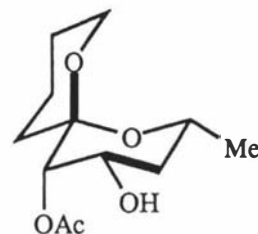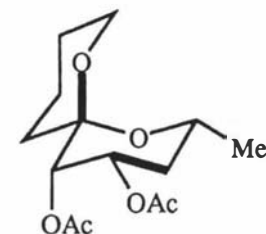
353   354   356   355

The stereochemistry assigned to this series of spiroketals (**353-355**) is that where the hydroxyl group (and hence the derived acetate) at C-5 is exclusively axial and *anti* to the C-O bond of the neighbouring tetrahydropyran ring. No evidence for the formation of the diastereomeric product **357** was observed upon examination of the high field ^{1}H nmr spectrum of the crude reaction product, nor after acetylation of **353** to give either **354** or **355**. The highly stereoselective nature of the reaction was significant in that the steric environment about the double bond of **345** was not thought to overly favour approach from the α-face (figure 25). The addition of other electrophiles such as peroxy acids and *tert*-butyl hypochlorite to related 1,7-dioxaspiro[5.5]undec-4-enes[274,400,401] (see section 3.2.3, page 137) were much less stereoselective, although the preferred face of attack by the electrophile was the same as that observed in the present case for osmylation. The same degree of selectivity to osmylation as displayed by **345** was observed for a range of similar spiroketal olefins (table 3).[396,397]

357

Figure 25

An attempt was made to synthesize the desired diol with the opposite configuration at C-4 and C-5. The use of dihydroquinidine 4-chlorobenzoate as an external chiral amine ligand[402] was unsuccessful in changing the result of the reaction, and its dihydroquinine antipode was not available for comparison at the time this work was undertaken.

3.1.4 Kishi's Allylic Oxidation Rule

The selective attack of OsO_4 seen for **345** could be rationalized in terms of the model proposed by Kishi *et al.*[403-405] for allylic systems. From an extensive study of the oxidation of allylic alcohols it was concluded that the relative stereochemistry between the pre-existing hydroxyl or alkoxy group and the adjacent newly introduced hydroxyl group of the major product in all cases was *anti*. An empirical model (based upon ground state conformational effects and an implied stereoelectronic π-facial bias) was proposed whereby the eclipsed conformation **a** (figure 26), favoured over **b** and **c** due to

124

olefin	diol/hydroxyacetate	yields
		R=H, 78% R=Ac, 89%
		R=H, 73% R=Ac, 84%
		59%
		61%

Table 3

less steric crowding of R^4, was preferentially approached at the olefin face opposite to the pre-existing hydroxyl or alkoxy group (assuming structure **a** is reflected in the transition state).

Figure 26

125
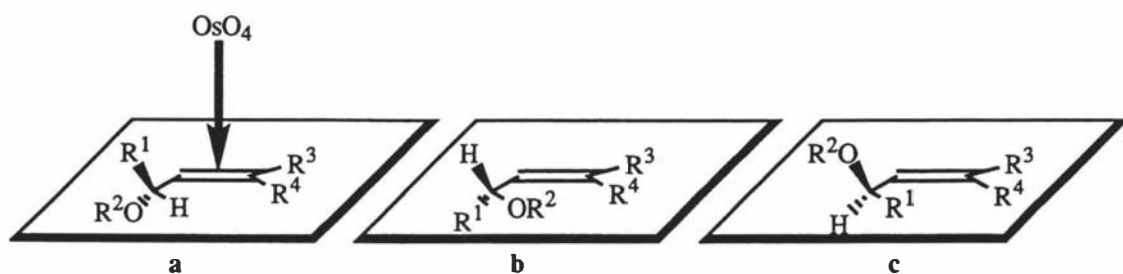
Stereoselectivity was reportedly higher for *cis* olefins which supported this conformational argument, as preference for **a** over **b** and **c** would be more significant for *cis* rather than *trans* olefins (both cyclic and acyclic systems gave the same results when studied). In the case of **345**, the cyclic nature of the molecule and the stabilizing anomeric effect holds the molecule in the conformation illustrated, and thus approach of the electrophile is from the face opposite to the C6-O7 bond (figure 27).
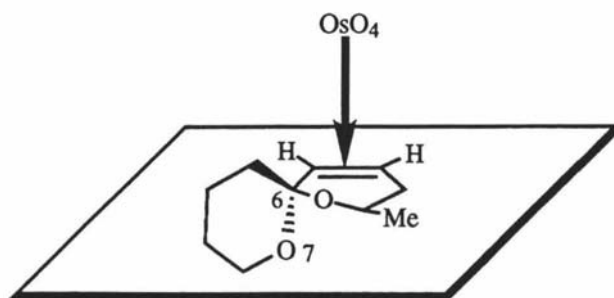
Figure 27

Analogous results have been observed in the osmylation of α,β-unsaturated esters,[406] γ-hydroxy-α,β-unsaturated esters[407] and pyranoses.[408] This empirical rule has also been noted in the conversion of aliphatic 1,6-dialdehydes to *cis* cyclohexane diols,[409] but results to the contrary using cyclobutenes have been reported.[392] Explanations for this reaction selectivity have been proposed[410] and the topic of stereoselective electrophilic additions to olefins discussed.[392,411,412] However, the "factors are difficult to evaluate because the mechanism of osmylation is not well defined"[411] (refer section 3.1.2, page 119). In a study using chiral 1,1-disubstituted allylic olefins,[410] the observed enhanced diastereoselectivity could be explained by both the Vedejs and Houk models[410] but not by the Kishi model.

Earlier work[413-415] involving unsaturated pyrans treated under stoichiometric conditions (stoichiometric conditions produced[403-405] higher stereoselectivity than did catalytic methods) gave results in agreement with the proposed allylic model. Olefin **358** gave only **359** when treated[414] with OsO$_4$ in pyridine (equation 29), with both new substituents on the opposite face of the ring to the allylic methoxy group. The same result was found when the allylic alkoxy group was fused to the pyran ring as in **360** (equation 30).[415] Other work[413] showed the interplay of steric factors, the "allylic rule" and solvent effects (scheme 65).

358 → **359**
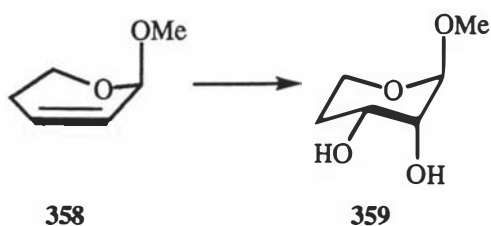
Reagents and Conditions: OsO$_4$, py, RT.

Equation 29

360
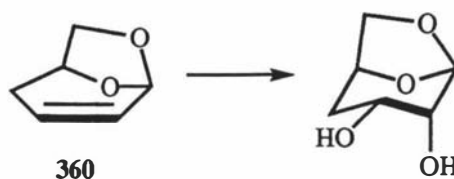
Reagents and Conditions: OsO$_4$, py or dioxane, RT.

Equation 30
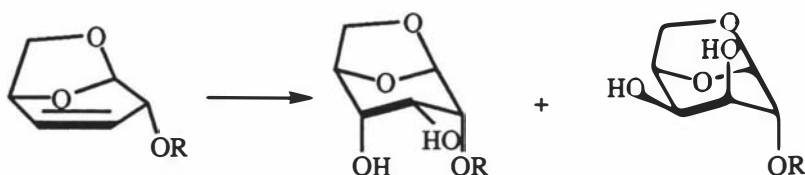
Reagents and Conditions: OsO$_4$, py or dioxane, RT.

R	solvent		yield	
H	pyridine	36%		30%
H	dioxane	51%		27%
Ac	pyridine	60%		32%
Ac	dioxane	88%		8%
Me	pyridine	23%		58%
Me	dioxane	49%		46%

Scheme 65

Upon conclusion of the current work,[396] *exocyclic* hydroxylation of a related spiroketal was reported.[416] Using the same catalytic methodology[394] olefin **361** was transformed to **362** (equation 31), wherein osmylation had proceeded from the olefin face opposite to the C-O bond of the second ring. The double bond in this case is not allylic to a C-O bond therefore steric effects may play the dominant role in stereochemistry determination.

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361   362
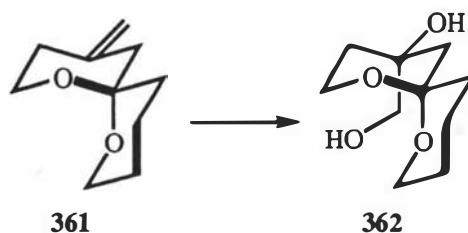
Reagents and Conditions: aq. Me₂CO, OsO₄ (cat.), NMO, RT.

Equation 31

3.1.5 Summary

Although the stereochemical outcome of the hydroxylation of **345** by osmium tetraoxide {**353**: figure 28 and scheme 64, page 122} was opposite to that required for the synthesis of griseusin A **88**, it proved to be highly stereoselective. This selectivity should allow the formation of acyclic compounds of known relative configuration by conversion[274,417] of these hydroxyspiroketals to open-chain derivatives. It was also found that the least hindered hydroxyl group at C-4 could be selectively acetylated (**353**→**354**, figure 28), a key requirement for the synthesis of griseusin A **88** based upon the advanced diol intermediate **343** (scheme 62, page 118).

353: R=H
354: R=Ac   88
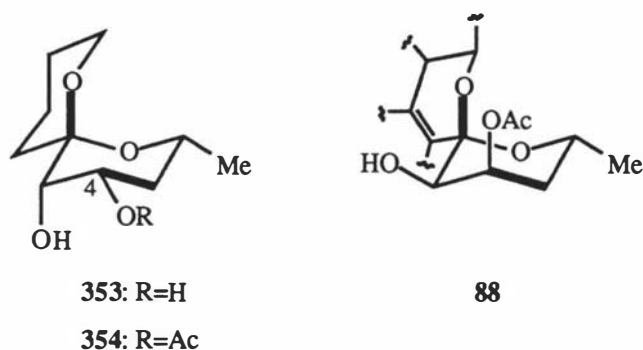
Figure 28

At this point, alternative methods were sought to effect *syn*-hydroxylation of olefin **345** from the required β-face (figure 25, page 124). Methodology developed would then be applied to the hydroxylation of the spiroketal system **333,334** as required for the synthesis of griseusin A **88** (scheme 62).

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3.2 *syn*-Hydroxylation of Spiroketal 345 using Iodine and Silver Acetate in Aqueous Acetic Acid

3.2.1   The Woodward-Prevost Reaction

In view of the inability of osmium tetraoxide to effect *syn*-hydroxylation of our model olefin **345** from the now recognized more hindered upper face (and therefore spiroketals **333,334**), another method was sought to achieve this and so produce **357** {and thus eventually **343** (scheme 62, page 118)}. Attention therefore turned to the Woodward-Prevost or Woodward *syn*-hydroxylation reaction.[381,418] This involves hydroxylation of an olefin using iodine and silver acetate in wet acetic acid to give *cis* glycols (scheme 66).

357

Woodward-Prevost Reaction
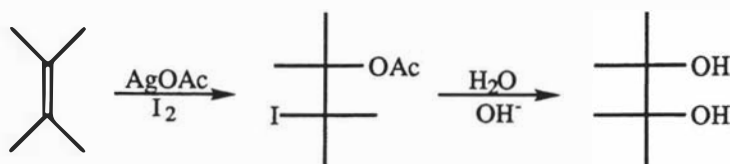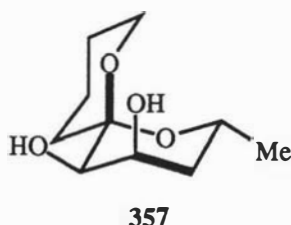
Scheme 66

The mechanism[419,420] involves addition of I⁺, in the form of a silver stabilized acyl hypoiodite or "Simonini complex" **363**,[421] to the least hindered face of an olefin (scheme 67). Nucleophilic attack of acetate onto one of the two carbons forming the iodonium ion **364** gives a *trans*-iodoacetoxy derivative **365**. Conversion of this to the final product has been probed[422] by ^{18}O labelling of a 1,2-benzyloxy halide, which confirmed the presence of a cyclic acetoxonium ion intermediate such as **366**, formed by anchimeric assistance of the acetate group of **365** combined with the powerful affinity of silver ion for iodide. Addition of water to **366** cleaves the five membered ring and the resulting hydroxyacetate can be hydrolysed to give a *cis* diol.
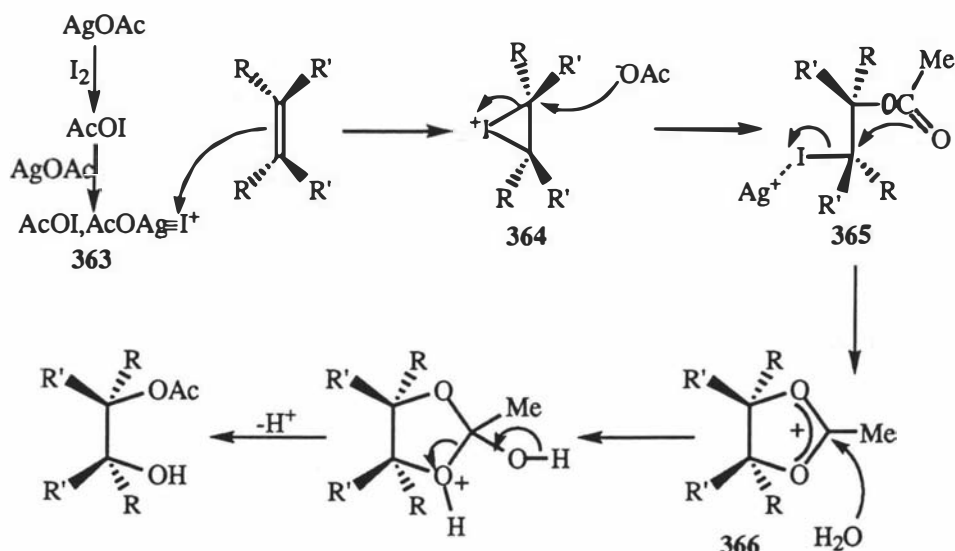
Scheme 67

It was hoped that treatment of **345** with I_2/AgOAc/aq. AcOH would result in overall *syn*-hydroxylation to afford diol **357** with the opposite stereochemistry to that obtained using OsO_4.

3.2.2 Preparation of Iodoacetates 367, 368 and 369

Reaction of olefin **345** with iodine and silver(I) acetate in aqueous acetic acid[420] gave products of lower R_f (hexane-ethyl acetate 4:1) in a ratio of 4:11:3 (**367:368:369**, equation 32). These were initially thought to be hydroxyacetates but their infra-red spectra were devoid of hydroxyl groups, and their mass spectra exhibited molecular peaks at m/z 354 suggesting they were in fact the "intermediate" *trans* iodoacetates from the reaction (scheme 66 and **365**, scheme 67). The structure of each compound was assigned on the basis of detailed ^{1}H nmr chemical shift and coupling constant analysis (see page 133).

It was expected that only two products, **367** and **368**, arising from the reversible formation of iodonium ions would be formed. **367** results from approach of "I^+" to the *more* hindered upper face of the double bond of **345** (path b, scheme 68), followed by attack of AcO^- at C-4. This presumably less stable *cis*-iodonium ion **370**$^\approx$ would be expected to react more rapidly with the nucleophile (AcO^-) than the *trans* isomer **371**, however this is countered by the high energy twist-boat conformation **372** that is required

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$^\approx$ *cis* is used to describe the iodine being on the same side of the methyl-substituted spiroketal ring relative to the C6-O7 bond.

to be adopted by **370** in order to facilitate a pseudo-diaxial alignment of the two substituents, and thus the formation of **367**.[423]

345

367 + **368** + **369**

(4 : 11 : 3)
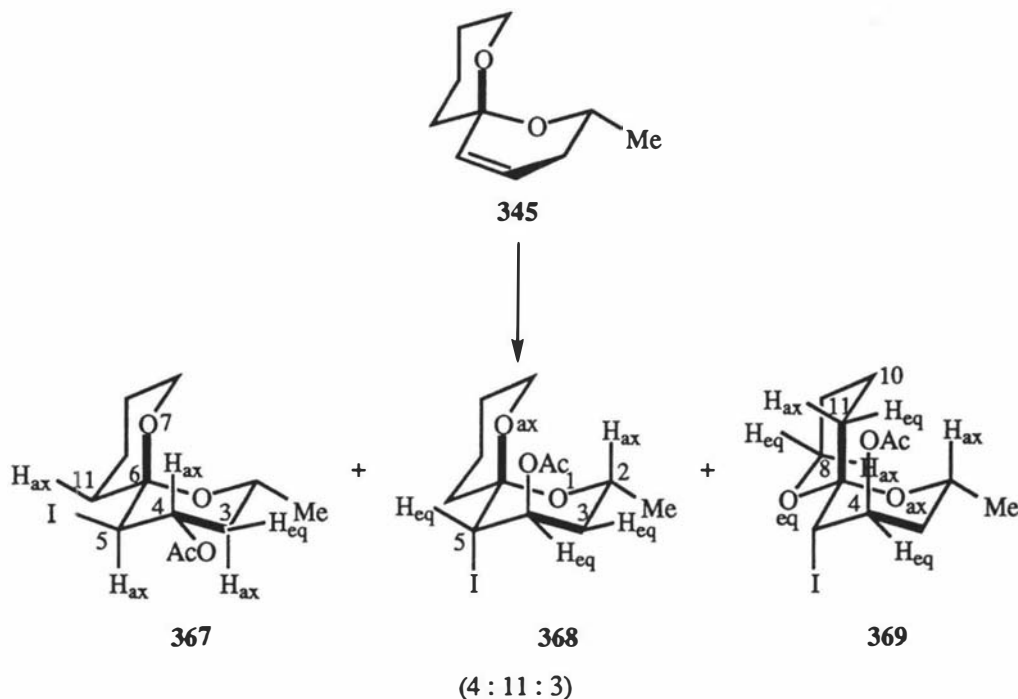
Reagents and Conditions: aq. AcOH, AgOAc, then I_2 (portionwise), RT, **367** 16%, **368** 43%, **369** 12%.

Equation 32

368 should be and was the predominant isomer as it results from approach of "I+" to the *less* hindered face of the double bond (path a, scheme 68). Antiparallel approach of AcO⁻ at C-4 is somewhat hindered in **371** by the second ring and it should react more slowly than **370**, nevertheless **368** is the major product as the antiparallel opening is easily accommodated by a favourable, low energy chair conformation **373**.

In both cases, high steric hindrance to attack at C-5 from the second ring results in a strong preference for attack of AcO⁻ at C-4 and thus powerful regiocontrol. This control is also attributable to the inductive electron withdrawing effect of two oxygen atoms attached to the spiro carbon C-6. The resultant increased positive charge character at the carbon alpha to the spiro centre (C-5) would favour positive charge development/onium ion intermediates at the β-carbon (C-4), and hence subsequent reaction with nucleophiles at this site. Thus **367** is formed from **370** in preference to **374**, which also suggests that the second stage of the reaction (AcO⁻ attack) is kinetically controlled. The opening of oxirane rings analogous to iodonium ions **370** and **371** is discussed later this chapter with reference to the Furst and Plattner rule[424] (section 3.2.5, page 141).

131
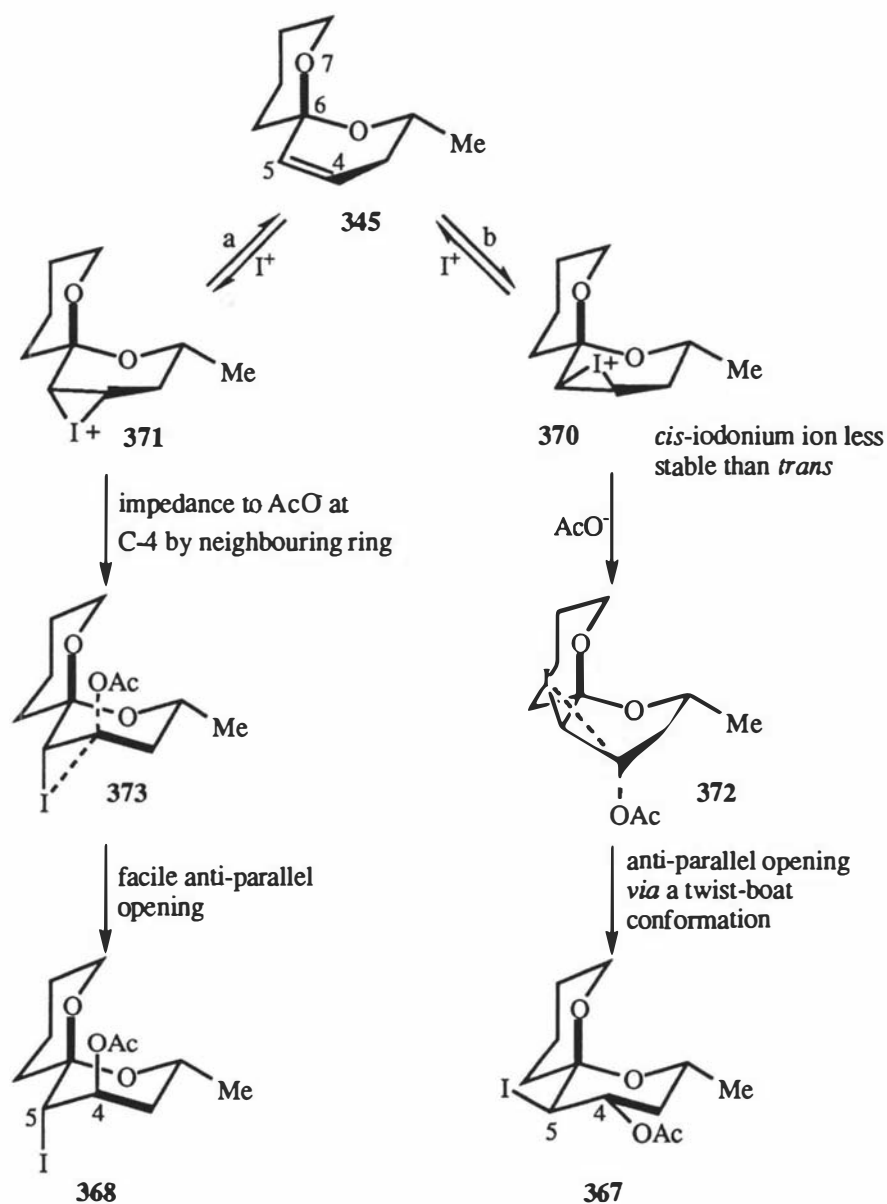
Scheme 68

In summary, the overall process is controlled firstly by the relative rates of attack of I⁺ *cis* and *trans* to the C6-O7 bond, secondly by steric factors/substituent effects influencing nucleophilic attack at C-4 of the iodonium ion, and thirdly by the conformation adopted in iodonium ion ring opening.

374
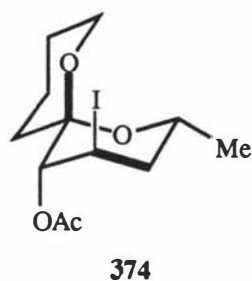
The ^{13}C nmr spectrum for all three iodoacetates could be assigned using DEPT 90 and 135 techniques and by comparison to ^{13}C nmr data reported for related spiroketals.[370,397,401] The signals for a given iodoacetate carbon (with the exception of C-5) were within a range of 5 ppm and therefore very consistent. C-4 (equation 32) resonated at approximately δ_C 72 versus C-5 at δ_C 31-40, showing attack of the strongly electron withdrawing acetoxy group at C-4 of the iodonium ion in each case.

In all three compounds **367-369** the carbons resonating between δ_C 71.6-74.1, which were clearly bonded to an acetoxy group (as evidenced by the chemical shift), exhibited HETCOR spectra correlation to double double doublets in the range δ_H 5.22-5.31. The methine carbons resonating between δ_C 31.8-39.5 correlated with the doublets between δ_H 3.77-4.27, these two connections establishing that the CHI proton was located at C-5 and the CHOAc proton at C-4.

The *trans*-diaxial coupling between 4-H and 5-H in iodoacetate **367** was particularly significant in assigning the relative stereochemistry between these two protons. 4-H resonated as a double double doublet at δ_H 5.31 ($J_{4ax,5ax}$ 11.0 Hz, $J_{4ax,3ax}$ 11.0 and $J_{4ax,3eq}$ 5.1 Hz) and 5-H as a doublet at δ_H 3.77, $J_{5ax,4ax}$ 11.0 Hz (table 4). The magnitude of these coupling constants clearly established that 4-H and 5-H adopted axial positions.

The CHOAc proton (4-H) in **367** appeared further downfield than both its vicinal counterpart 5-H and 4-H in **368** *and* **369**. This was due to it being not only geminal to an acetoxy group but also 1,3-diaxial to O-7 of the neighbouring ring. The methylene group at C-3 resonated at δ_H 1.47-1.90 in **367**, deshielded compared to **368** (δ_H 1.28-1.87), as the acetoxy group by being equatorial bisected these two protons. This same acetoxy group was axial and directed away from 3-CH$_2$ in **368**. The C-11 axial proton of **367** (J_{gem} 13.0, $J_{11ax,10ax}$ 13.0 and $J_{11ax,10eq}$ 4.4 Hz) was split out from the equatorial one and shifted downfield as it was 1,3-*syn* to the equatorial iodine atom at C-5.

The coupling constants for 4-H and 5-H in **368** suggested assignment of these protons to equatorial positions, in that vicinal coupling constants were all equal to 2.2 Hz. 5-H resonated as a double doublet at δ_H 4.27 (figure 29), further downfield than the same proton in **367** (δ_H 3.77) due to the proximity of CHI to both 4-OAc and O-7. The observation of a double doublet for 5-H (versus a doublet in **367**) was attributed to long range W-coupling[425] between 5-H$_{eq}$ and 3-H$_{eq}$, further confirming the equatorial position of 5-H. 4-H resonated at δ_H 5.23 in **368**, upfield of its position in **367** (δ_H 5.31) as it is not 1,3-diaxial to O-7. The position of 2-H in **368** (δ_H 4.11) was substantially downfield of **367** (δ_H 3.81-3.96), consistent with 2-H in **368** being 1,3-diaxial to *both* 4-OAc and O-7 (and further evidence for the acetoxy group being axial). Moreover, the coupling constants for 2-H in **368** ($J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.0 Hz) confirmed the axial position of 2-H not only in **368** but also in iodoacetate **367**.

Spiroketal	CHMe	Me	3-H_{eq}	3-H_{ax}	CHI	CHOAc	OAc	8-CH_2	9-CH_2	10-CH_2	11-H_{eq}	11-H_{ax}
367	3.81-3.96, m	1.21, d, 6.2	1.47-1.90, m	1.47-1.90, m	3.77, d, 11.0	5.31, ddd, 11.0, 11.0, 5.1	2.09, s	3.51-3.74, m	1.47-1.90, m	1.47-1.90, m	2.02-2.06, m	2.27, ddd, 13.0, 13.0, 4.4
368	4.11, qdd, 6.2, 12.4, 2.0	1.25, d, 6.2	1.28-1.87, m	1.28-1.87, m	4.27, dd, 2.2, 2.2	5.23, ddd, 2.2, 2.2, 2.2	2.05, s	3.56-3.63, m	1.28-1.87, m	1.28-1.87, m	2.08-2.17, m	2.28, ddd, 14.7, 11.6, 3.3
369	3.91-4.05, m	1.27, d, 6.2	1.42-2.11, m	1.42-2.11, m	4.27, d, 3.7	5.22, ddd, 3.7, 3.7, 3.7	2.14, s	3.66-3.74, m (eq) 3.91-4.05, m (ax)	1.42-2.11, m	1.42-2.11, m	2.24-2.33, m	1.42-2.11, m

Table 4

Data in table recorded at 270 MHz in CDCl$_3$ and listed as δ_H, multiplicity and J value(s) (Hz)
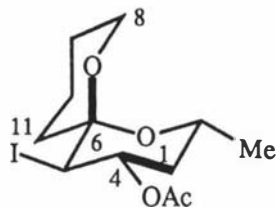
367
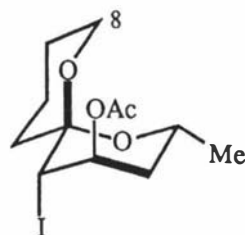
368
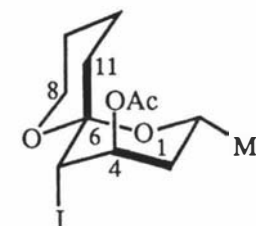
369

Figure 29
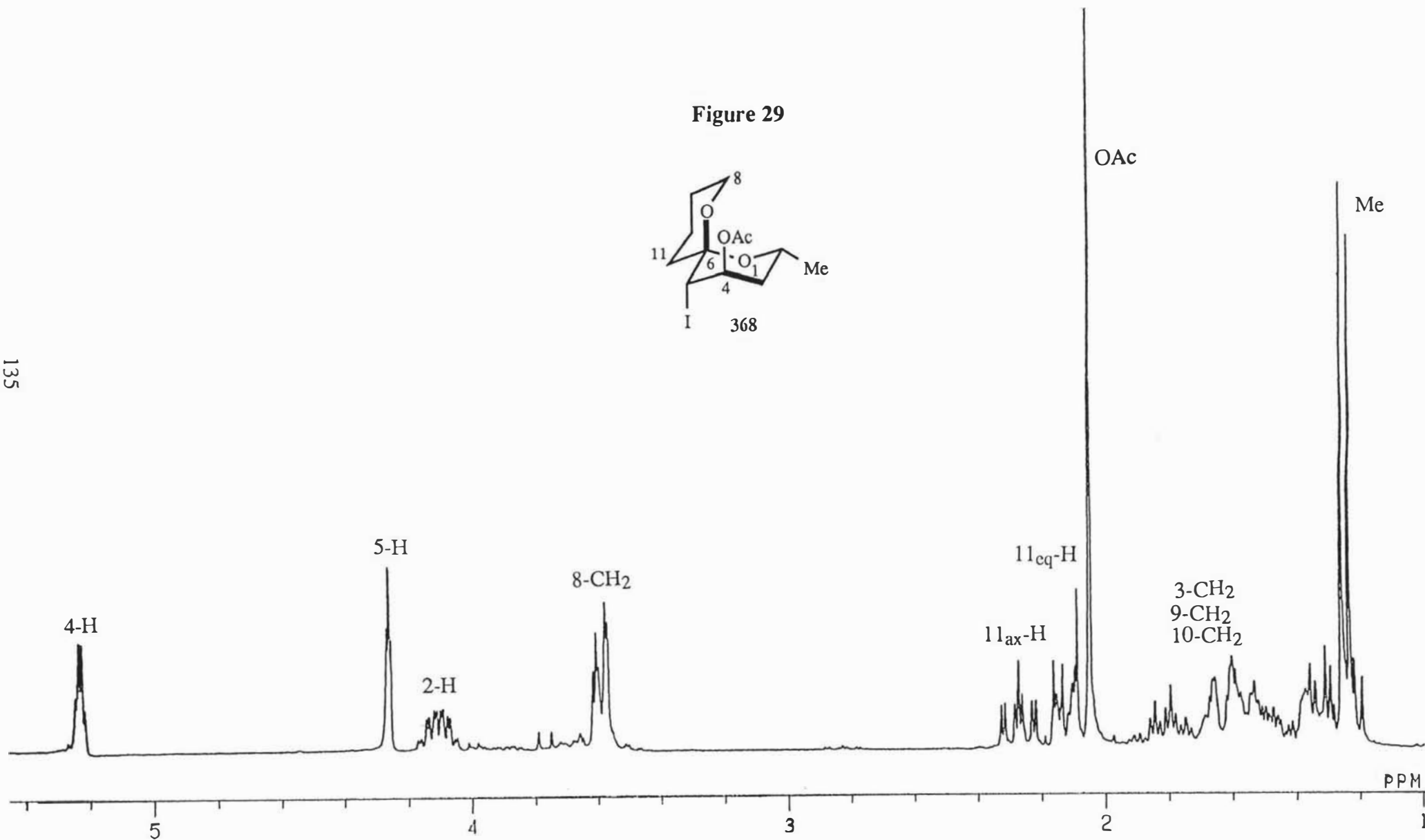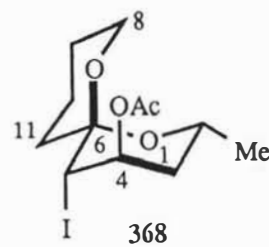
The third (and somewhat unexpected) minor iodoacetate **369** isolated from the attempted Woodward-Prevost reaction was assigned using 2D nmr techniques. **369** exhibited almost identical δ_H and J values for 4-H and 5-H as was observed for iodoacetate **368**, indicating a diaxially substituted first ring. Noticeably, however, the C-2 proton (C*H*Me) resonated at δ_H 3.91-4.05, very similar to **367** (δ_H 3.81-3.96) and further upfield than the same proton in **368** (δ_H 4.11). This suggested that unlike **368**, 2-H in **369** was only 1,3-diaxial to *one* oxygen atom rather than two, and this was pivotal in determining its structure. The C-8 methylene group in **369** was resolved into individual resonances for the axial and equatorial protons, and each was downfield compared to both **367** (δ_H 3.51-3.74) and **368** (δ_H 3.56-3.63), which were unresolved. The methylene groups 9-CH_2 and 10-CH_2 in **369** were downfield of **368** (δ_H 1.42-2.11 versus 1.47-1.90 respectively). These observations suggested a different stereochemistry at the unsubstituted second ring.

Based on known transformations in spiroketals[274] structure **369** was proposed, wherein the second ring of **368** had undergone a ring opening followed by closure from the opposite face of C-6, *via* the intermediacy of   planar   cation **375** (scheme 69).
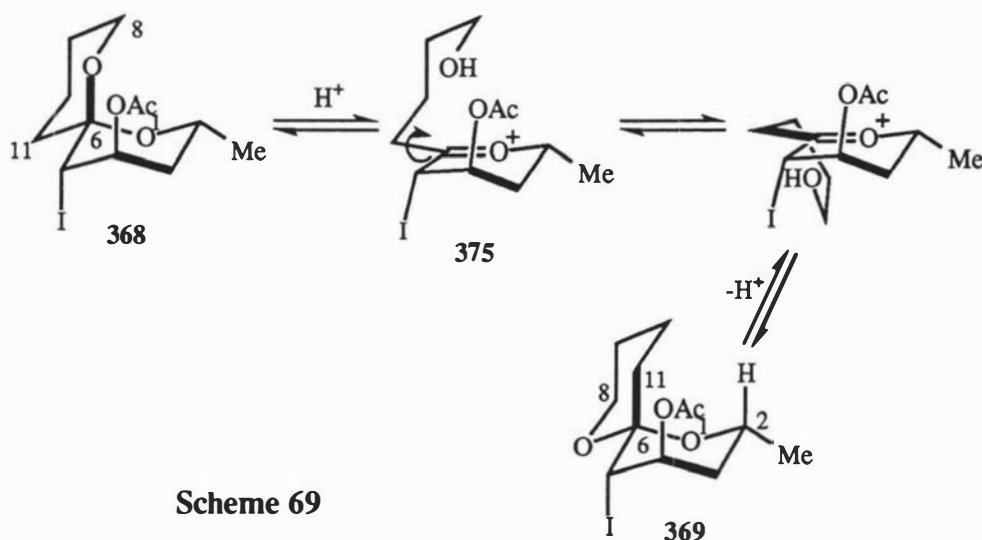
Scheme 69

Thus the data for 8, 9 and 10-CH_2 in **369** could be correlated with this "inverted" structure. 2-H is only 1,3-diaxial to the 4-OAc group and therefore has a similar chemical shift to that of **367** (1,3-diaxial to only O-7). The 8-H multiplet at δ_H 3.66-3.74 was assigned as the equatorial proton, with the axial proton resonating at δ_H 3.91-4.05 as it was now 1,3-diaxial to O-1 (refer equation 32, page 131). 11-H_{eq} in **369** was assigned as δ_H 2.24-2.33 from the line shape apparent in the multiplet and by work with models, which showed this proton to be very close to 4-OAc and O-1. Its axial counterpart resonated within the δ_H 1.42-2.11 multiplet.

By undergoing this transformation (**368→369**) a stabilizing anomeric effect[30] at the spiro centre was lost however 4-OAc and O-7 were no longer 1,3-diaxial (11-CH$_2$ and 4-OAc were the groups now placed in this sterically unfavourable arrangement). Thus the driving force for this transformation may well be associated with the change in overall dipole moment observed when **368** rearranges to **369**.

The reaction time was varied in order to see if this would have any effect on the 4:11:3 product ratio for **367:368:369**. It was found that the ratio did not alter, regardless of the reaction time allowed (15 min - 24 h), which suggested that the ratios observed were established rapidly and did not fluctuate.

3.2.3 Addition of Electrophiles to Related Compounds

Addition of other electrophiles to spiroketal olefins similar to **345** proceed with high regiospecificity but modest stereoselectivity. Electrophilic chlorohydroxylation of spiroketals **376**[426] and **377**[401] afforded only isomers in which the halogen was attached to the carbon alpha to the spirocentre (scheme 70). In the case of **377**, "the lack of stereocontrol observed presumably reflects conformational, steric and electronic effects peculiar to this system".[401] Similar results were obtained in an oxymercuration-demercuration reaction.[367,427]
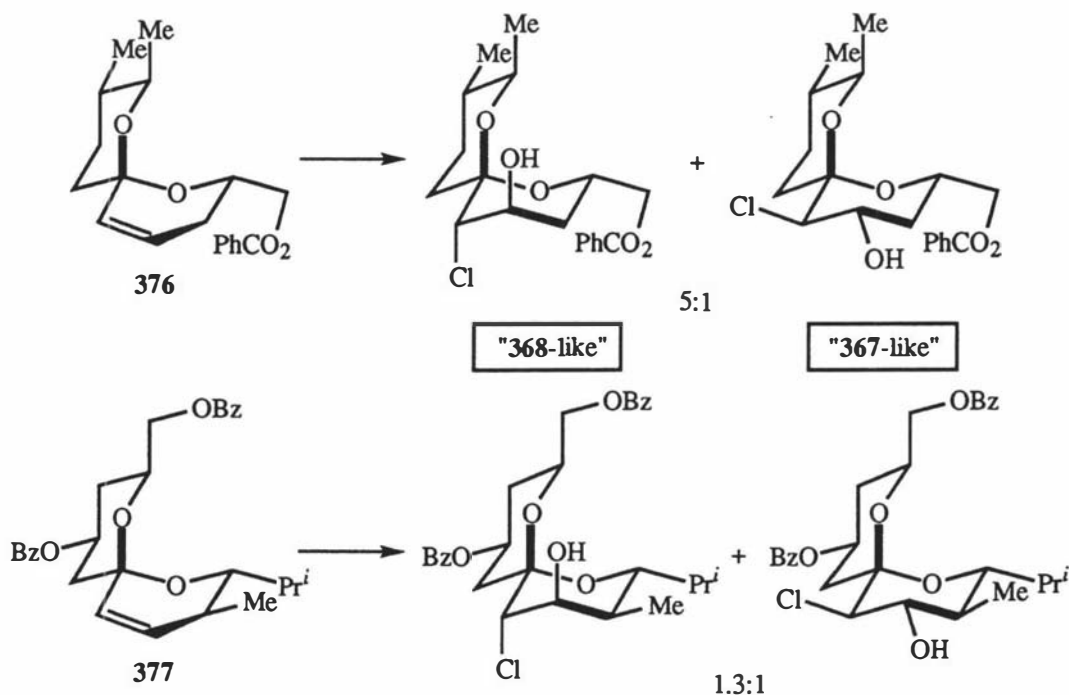
Reagents and Conditions: Bu^{t}OCl, aq. Me$_2$CO, RT.

Scheme 70

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For glycal additions, below plane approach is the preferred mode of attack by electrophilic reagents in the absence of overriding steric effects. The facial selectivity observed for these compounds was also found[428] to be dependant upon the structure of the nucleophile. Axial alkoxy groups have a powerful effect and direct the electrophile to the opposite face of the double bond (equation 33). This "allylic alkoxy effect" as discussed earlier (section 3.1.4, page 124) reinforces the preferential formation of **368** (from **345**), in that the electrophile "I$^+$" approaches from the face opposite to the C6-O7 bond.

R^1=H, R^2=OBz; **a:b** = 1:10
R^1=OBz, R^2=H; **a:b** = 12:1
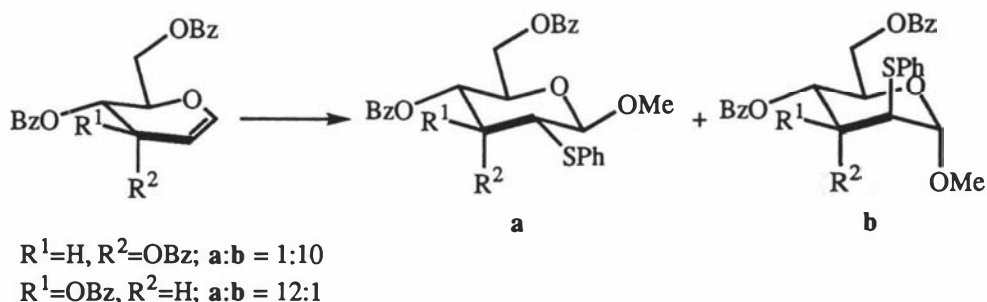
Reagents and Conditions: CH$_2$Cl$_2$, -60°C, SbCl$_3$, MeOH.

Equation 33

3.2.4 Attempted Acetoxonium Ion Formation from 368

The fact that iodoacetates **367-369** were easily isolated indicated that there was some hindrance to the acetoxy group displacing the iodine to form the corresponding acetoxonium ion (**366**: scheme 67, page 130), which may then form hydroxyacetate products. This was highlighted by comparison of our result (equation 32, page 131) with a cyclohexane system (scheme 71).[423] In this example, iodoacetates **378** and **379** underwent facile solvolysis in AgOAc/AcOH at room temperature for 24 hours giving the corresponding hydroxyacetates. Diols **380-382**[429] were formed by the Woodward-Prevost reaction of olefin **383** followed by reduction of the corresponding hydroxyacetates (equation 34), thus the intermediate *iodoacetates* were not even isolated in this case. Intermediate iodoacetates have been isolated from dry Prevost reactions using silver(I) or thallium(I) acetate,[423] and wet and dry conditions with bismuth(III) acetate.[430,431]

Since **367** *did* form in the Woodward-Prevost reaction of **345**, this suggests that the upper face of **345** is not completely hindered to electrophilic attack as was observed in the earlier osmylation reaction (scheme 64, page 122). A possible reason for this difference is the disparity in bulk between the two electrophiles.

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378 OAc   23:36:36

379   58:21
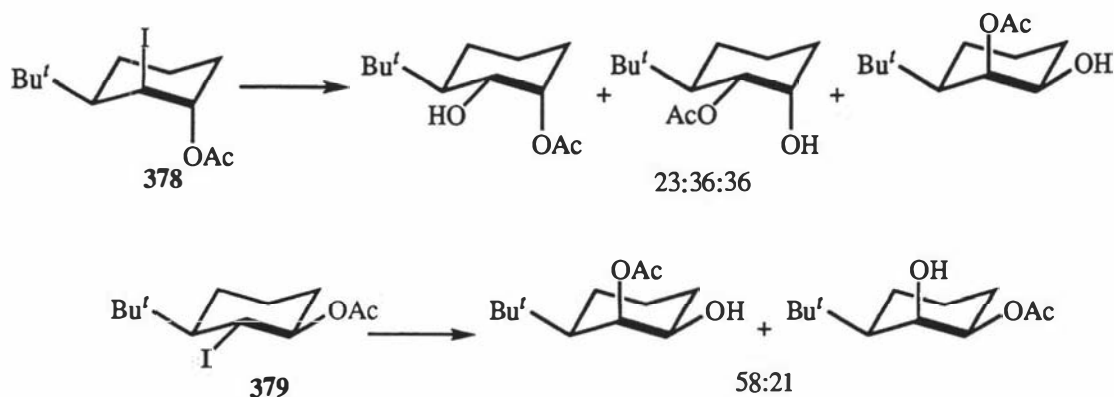
Reagents and Conditions: AgOAc, AcOH, RT.

Scheme 71

383	380	381	382
	85%	14%	1%
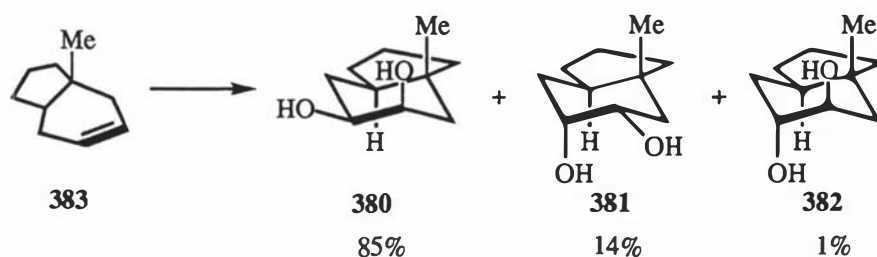
Reagents and Conditions: a: I_2, AgOAc, AcOH; b: LiAlH$_4$.

Equation 34

The relative stabilities of the three compounds in cold storage, as evidenced by decomposition to iodine and other components, was found to be **367 > 369 > 368**. This decomposition was accelerated in chlorinated solvents and at room temperature. **367** is predicted to be the most stable isomer in that it has the maximal number of anomeric effects (two) and the iodine and acetoxy substituents are equatorial. **369** has one anomeric effect at the spiro centre and both substituents are axial, whereas **368** has two anomeric effects and both substituents axial but exhibits unfavourable O7↔4OAc 1,3-diaxial interactions. These interactions may well be the cause behind the apparent lower relative stability of **368** versus **369**.

The inability of the acetoxy group in any of the three iodoacetates **367-369** to anchimerically displace the iodine atom using this Woodward-Prevost methodology was further highlighted when harsher conditions were applied. Iodoacetate **368** was treated with various silver reagents[432] (AgOAc, AgBF$_4$) in a variety of aqueous solvents (AcOH, DMF, DMSO, MeOH) under reflux in order to give acetoxonium ion **384** and thus the monoacetates of **357**, namely **385** and **386** (scheme 72). These conditions, however, resulted in decomposition of the starting material. The crude reaction mixtures were examined by ^{1}H nmr spectroscopy and in several cases up to four acetate peaks

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were observed, with the CHI proton still in evidence. Most signals were complicated and broader than those of the starting material. Hence it appeared that the attempted displacement of iodine from **368** resulted in isomerization *without* loss of the iodine.

Scheme 72

88
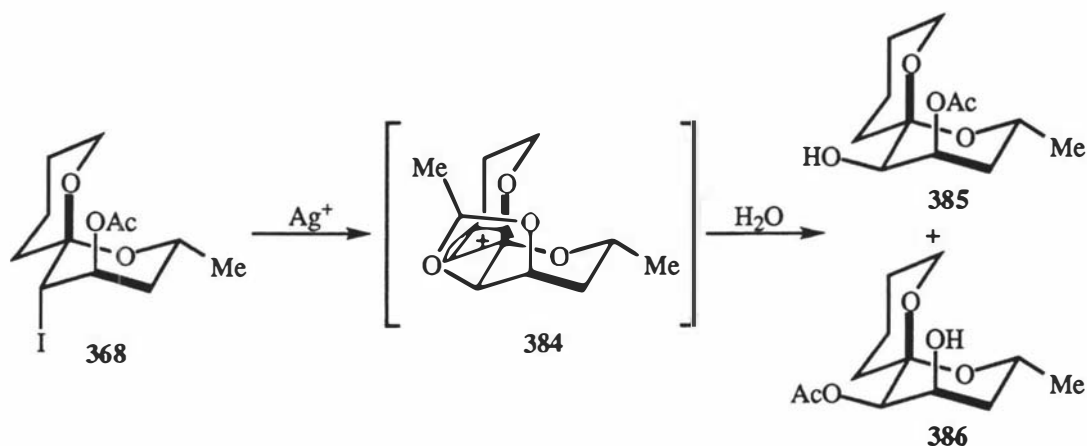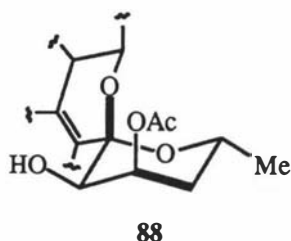
Intramolecular displacement of the iodine in **368** *and* **367** was also attempted by refluxing the initial reaction mixture after allowing the iodoacetates to form. However the number of products involved and their behaviour (R_f) on silica rendered monitoring of the reaction by TLC difficult. It was therefore easier to work with the individual compounds. By using this approach, any products formed could be directly attributed to *one* starting material.

It was possible that the steric demands about the iodine[433,434] were too great due to the halogen being attached to a secondary carbon atom (itself part of a neopentyl-like structure), and also the proximity of the neighbouring ring. As well, electronegative α-substituents (the acetoxy group and two ketal oxygens in this case) contribute to resistance to S_N2 (and S_N1) displacement. This is due to unfavourable electronic effects associated with the necessary development of partial positive charge at C-5, and the development of adverse dipolar interactions in the transition state for intramolecular displacement[435] (illustrated for **368**, figure 30). Thus it was decided to reverse the positions of the iodine and acetoxy groups and attempt the silver assisted displacement

140

with iodoacetate **387**, in the hope that this would afford acetoxonium ion **384** (scheme 73) more easily.
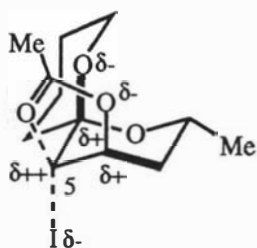
Figure 30
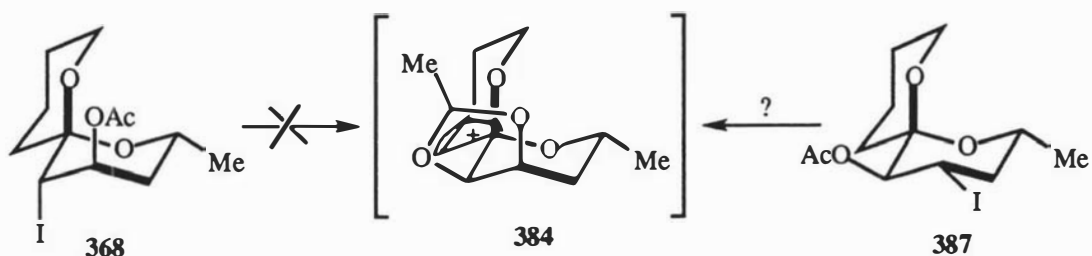
Scheme 73

3.2.5 Synthesis of Iodoacetate 387

<u>Synthesis of Epoxide **388**</u>

Diequatorial iodoacetate **387** was envisaged to be prepared from **368** *via* epoxide **388** (scheme 74). Selective opening of **388** by lithium iodide would give iodohydrin **389** which could then be acetylated to give **387**.

Reagents and Conditions: (i) DMSO/THF, N_2, 18C6, KO_2, 46%; (ii) THF, LiI, RT to -50 °C, N_2, **368** , then $BF_3.Et_2O$, 86%; (iii) CH_2Cl_2, Ac_2O, Et_3N, DMAP (cat.), RT, 95%.

Scheme 74

141
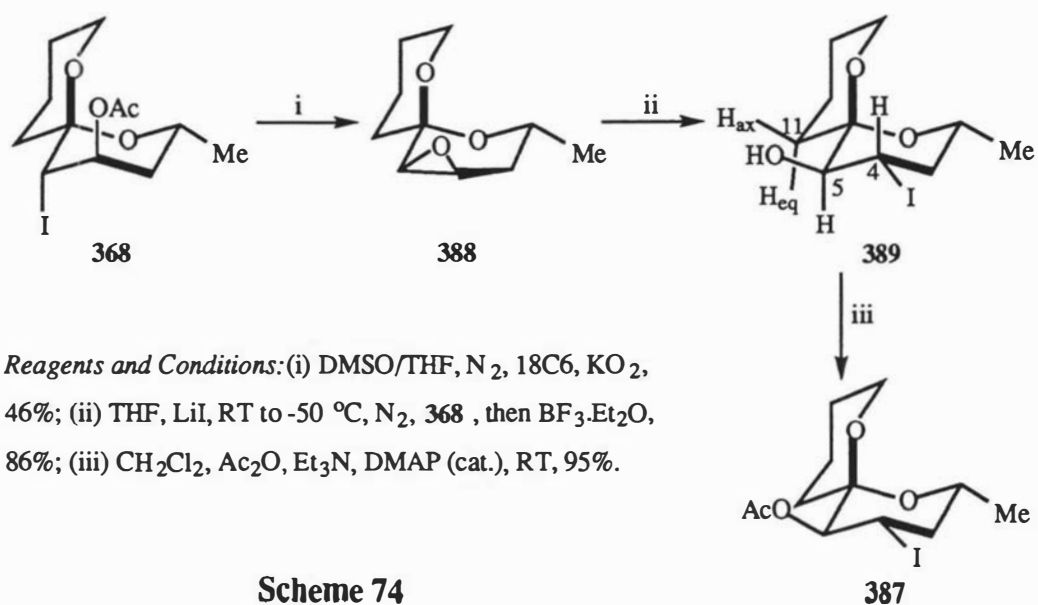
Treatment of **368** with potassium superoxide[436,437] in THF/DMSO in the presence of 18-crown-6 ether[436,438,439] gave the desired epoxide **388** but in poor yield (46%, scheme 74).[∞] The formation of an epoxide was evident by the enhanced volatility (pungency) of the isolated reaction product. The infra-red spectrum lacked a carbonyl group due to the loss of the acetate, instead there was a strong C-O stretch at 793 cm^{-1}. The mass spectrum confirmed the absence of iodine in the molecule, with the molecular ion at m/z 185 due to MH$^+$ ($C_{10}H_{17}O_3$). The two oxirane ring protons resonated in the ^{1}H nmr spectrum as a multiplet at δ_H 3.33-3.38 (4-H) and a doublet at δ_H 3.09 ($J_{5,4}$ 4.0 Hz) for 5-H (figure 31). These assignments were made on the basis of signal multiplicity and comparison with similar spiroketal epoxides (for example **390**, figure 31).[400,401] Epoxide **388** was also prepared as the minor isomer in the reaction of **345** with *meta*-chloroperbenzoic acid (see section 3.2.7, page 151).

	388	**390**
4-H	3.33-3.38 m	3.18 m
5-H	3.09 d J 4.0 Hz	3.18 m
11$_{eq}$-H	2.03 ddd J 14.3, 2.2, 2.2 Hz	2.30 ddd J 12.2, 4.4, 1.5 Hz
11$_{ax}$-H	1.49-1.93 m	1.56 dd J 11.6, 11.6 Hz
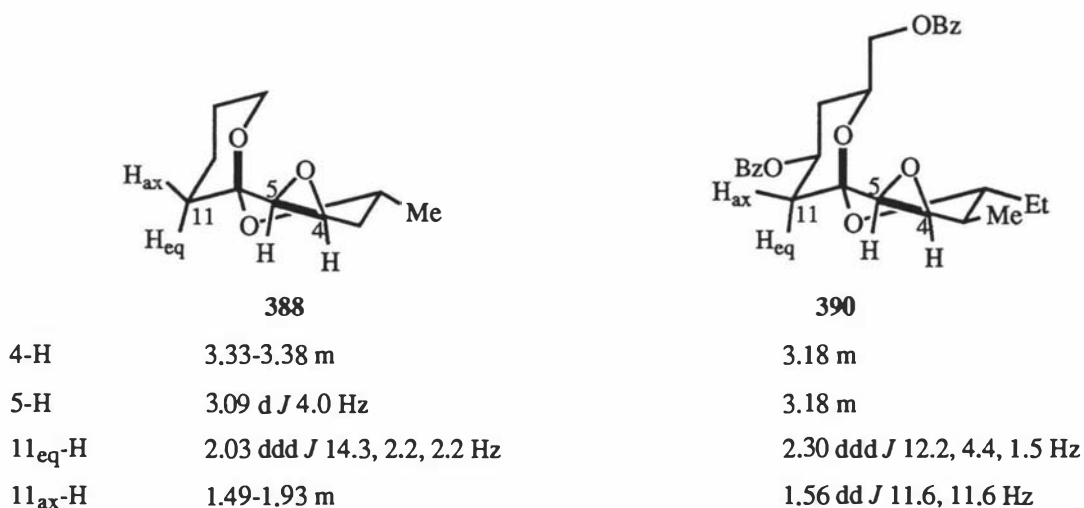
Figure 31

Formation of Iodohydrin **389**

With epoxide **388** in hand, it was regio- and stereoselectively opened[441] by lithium iodide/boron trifluoride etherate[440] to give diequatorial iodohydrin **389** in 86% yield (scheme 74). **388** adopts a twist-boat conformation[442] before nucleophilic attack of I$^-$ occurs from the pseudo-axial position of the lower face at C-4 to give **391** (scheme 75: compare **372**, scheme 68). Reversion to the more stable chair conformation then gives

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∞ Earlier work by Brimble *et al.*[440] had used potassium superoxide to displace iodine (by OH) from a tricyclic spiroketal, however this was not feasible for **368** due to the presence of the base-sensitive acetate group. The ensuing reaction (anchimeric displacement by O$^-$) was nevertheless convenient as a means to generate epoxide **388**.

diequatorial **389**. Preferential positive charge formation at C-4 (refer page 131, 140) raises the energy of the diaxial transition state that would lead to **392**.
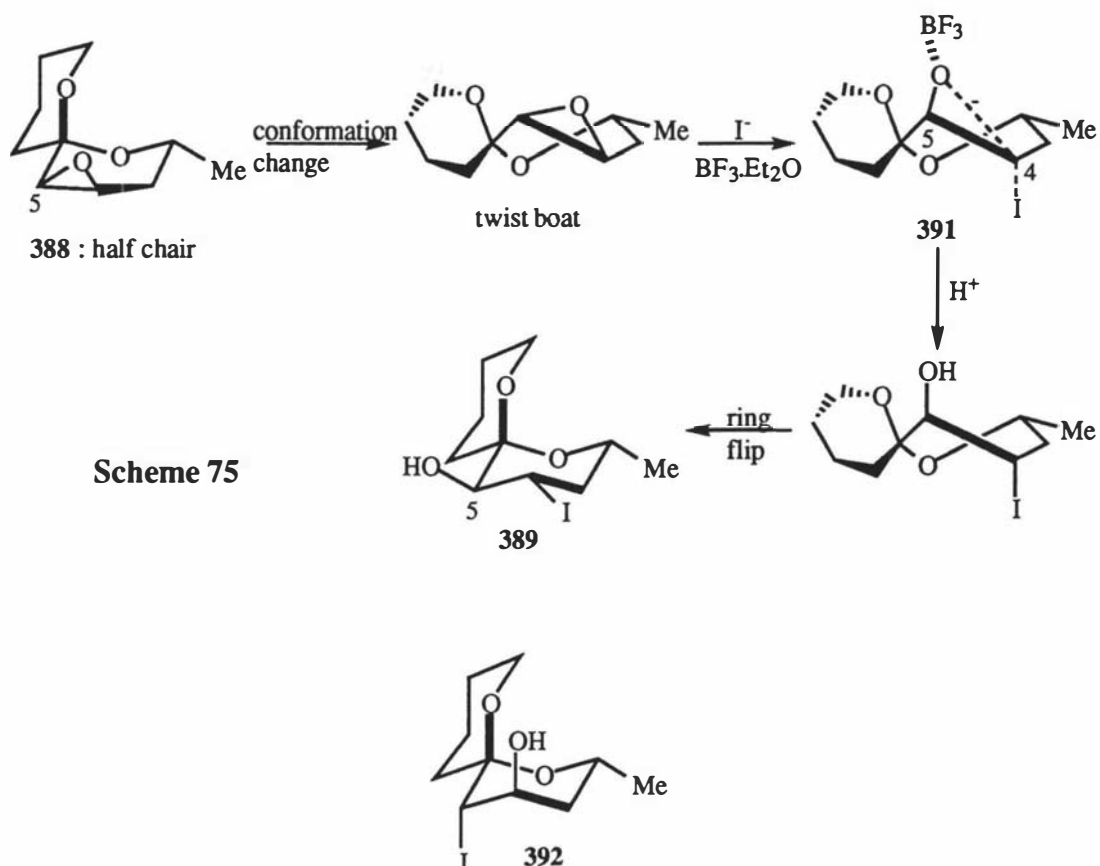
Scheme 75

A strong hydroxyl stretch at 3556-3212 cm^{-1} in the IR spectrum together with peaks in the mass spectrum at m/z 313 (MH$^+$) and 185 (MH-HI) indicated that iodohydrin **389** had been formed (scheme 74). The multiplicity and coupling constants of 4-H and 5-H in the ^{1}H nmr spectrum indicated the relative stereochemistry of the iodine and hydroxyl groups on the spiroketal ring. 4-H resonated at δ_H 4.39 as a double double doublet, $J_{4ax,5ax}$ 10.4, $J_{4ax,3ax}$ 12.7 and $J_{4ax,3eq}$ 4.8 Hz, and 5-H as a double doublet at δ_H 3.39, $J_{5ax,4ax}$ 10.4 and $J_{5ax,OH}$ 9.2 Hz, confirming that the iodine and hydroxyl groups occupied equatorial positions. 11_{ax}-H in **389** was deshielded versus 11_{eq}-H by being 1,3-*syn* to 5-OH, which itself was coupled to 5-H (J 9.2 Hz), implying a slow rate of exchange of the OH proton. The δ_C values for C-4 and C-5 (32.2 and 78.3 respectively) supported the location of the hydroxyl group at C-5, these chemical shift values being essentially the reverse of iodoacetate **367** (refer page 133).

Opening of Oxirane Rings[441]

Aside from the examples given below, in most epoxides the oxirane ring generally opens to give 1,2-diaxial product(s). This has been formalized as the Furst and

143

Plattner rule[424] and was initially developed from work on steroidal epoxides, since which it has been applied to a wide range of compounds. The twist-boat transition state which leads to diequatorially opened epoxides has been noted,[401] for example in the treatment of epoxide **390** (figure 31) with 5% perchloric acid to give the *trans*-diequatorial diol **393** (scheme 76).[400,401] Epoxide **394** on the other hand formed the expected *trans*-diaxial diol **395** by antiparallel opening of the ring.
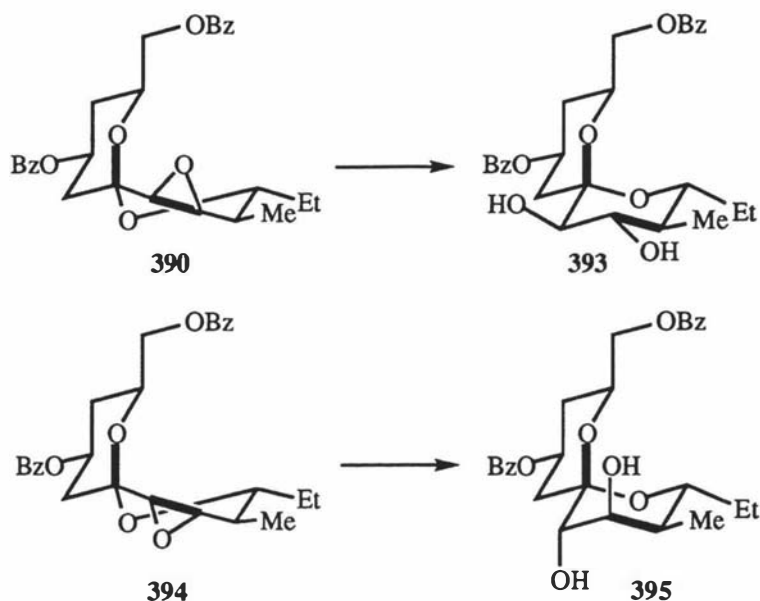
Reagents and Conditions: THF, 5% aq. HClO$_4$, 55°C.

Scheme 76

Reduction of *trans*-epoxide **396** with lithium aluminium hydride proceeded in an antiperiplanar manner to afford diaxial alcohol **397** (scheme 77), whereas the *cis*-epoxide **398** underwent reduction *via* a twist-boat transition state[423] to afford diequatorial alcohol **399**. Cyclic epoxides have also been opened with strong regiocontrol by aminolysis (R$_2$NH, LiClO$_4$) and azidolysis (NaN$_3$, LiClO$_4$).[443]
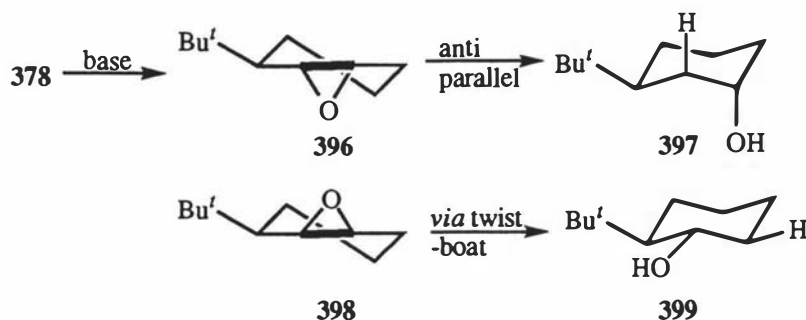
Reagents and Conditions: C$_6$H$_6$, {(MeOCH$_2$CH$_2$O)$_2$AlH$_2$}Na (RedAl), RT then reflux.

Scheme 77

<u>Alternative Halohydrin Syntheses</u>

One of several alternative one-pot conversions of epoxides to halohydrins involved[444] the use of triphenylphosphine and iodine in anhydrous dichloromethane. Halohydrin formation was reportedly immediate and nearly quantitative in all cases examined. Oxirane bridge cleavage in conformationally rigid epoxides by this procedure was found to be stereoselective, leading only to the product resulting from *anti* opening of the ring (scheme 78). This parallels general epoxide opening under acidic conditions.

R=H, Bu'
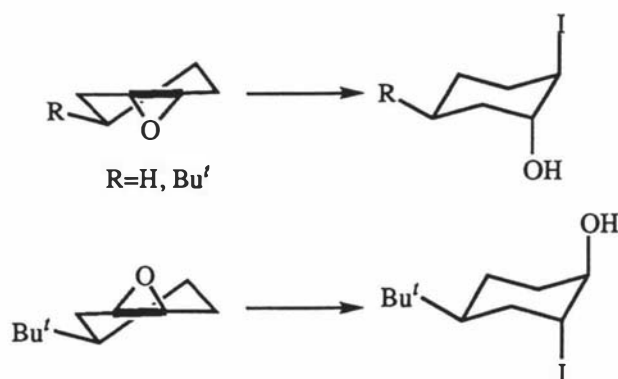
Reagents and Conditions: CH_2Cl_2, I_2, RT, add PPh$_3$, then epoxide.

Scheme 78

A procedure[445] similar to our LiI/BF$_3$.Et$_2$O method[440] was later reported using lithium halides and acetic acid/tetrahydrofuran {(i), equation 35}. The reaction was mild, convenient and compatible with a wide range of functional groups. Another closely related procedure[446] detailed opening of epoxides by α-halogenoalkyllithiums, using boron trifluoride etherate to activate the process at low temperatures {(ii), equation 35}. This gave the corresponding 1,2-trichloro alcohols in good yield with the same regio and stereoselectivity observed with LiX/AcOH/THF.[445] In this latter work[446] tetrahydrofuran itself was ring opened by the carbenoid species Li$^+$CCl$_3^-$ and Li$^+$CHCl$_2^-$, hence it was less tolerant of diverse functionality (R, equation 35).

In scheme 78 and equation 35, the least hindered face and position respectively of the oxirane ring was attacked by the halide (X$^-$).

i: R=alkyl, aryl etc   i: X=Cl, Br, I
ii: R=alkyl   ii: X=CCl$_3$, CHCl$_2$
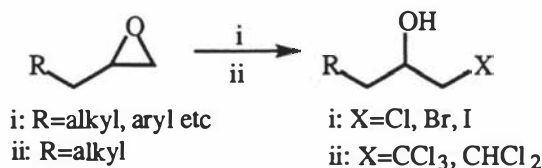
Reagents and Conditions:(i) AcOH/THF, LiX, RT;
(ii) LiX, THF, CHCl$_3$, -95°C, then BF$_3$.Et$_2$O, -65°C.

Equation 35

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If not for the conformational rigidity of the 1,7-dioxaspiro[5.5]undecane system present in **388**, the lithium cation from LiI may have influenced[447] the regioselectivity of the oxirane opening and led to differing products. This is illustrated for the structurally similar epoxide **400** of 2-benzyloxy-5,6-dihydro-2*H*-pyran.[447c]

400

3.2.6 Attempted Displacement of Iodine from Iodoacetate 387

<u>Isolation of Acyclic Esters **401** and **402**</u>

Acetylation of **389** under standard conditions gave iodoacetate **387** (scheme 74, page 141), where the iodine was now on the least hindered carbon atom (C-4 versus C-5) and set up for displacement by the acetate at C-4 from above the ring. Treatment of **387** with silver(I) acetate in refluxing aqueous acetic acid gave two less polar products. This reaction initially looked promising, however extensive spectroscopic analysis (including 2D techniques) showed the compounds to be *acyclic* esters **401** and **402** (equation 36), arising from ring fragmentation.

387

401

+

402

354
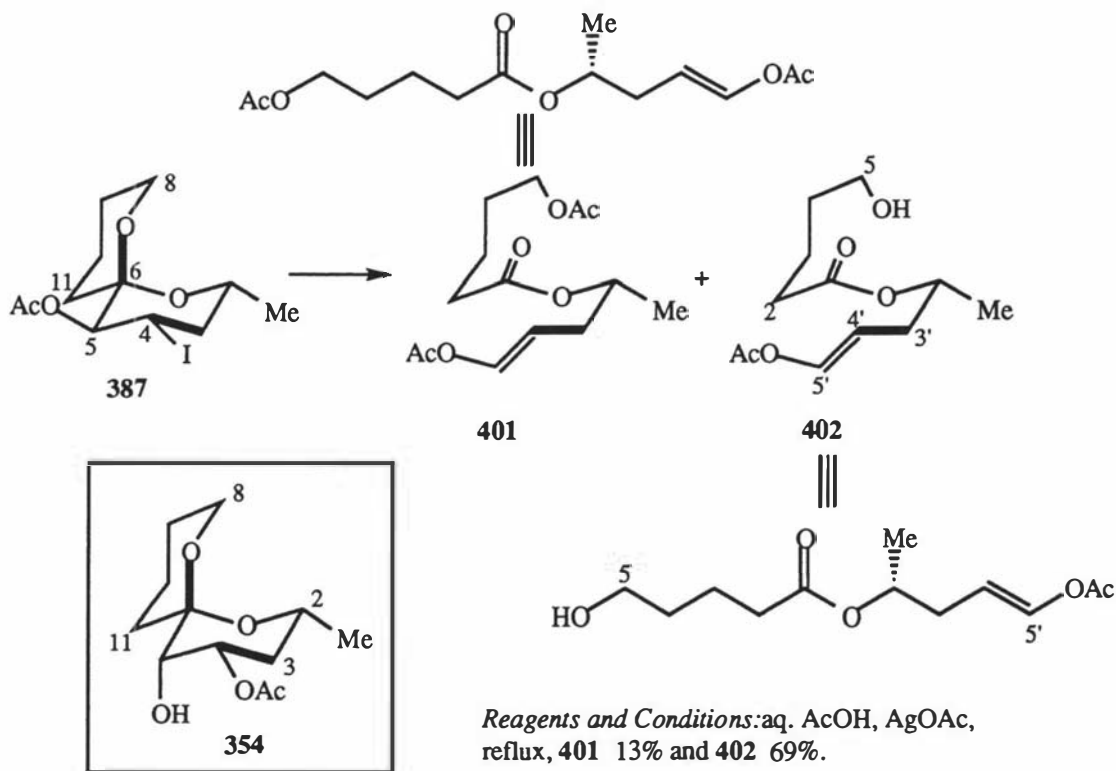
*Reagents and Conditions:*aq. AcOH, AgOAc, reflux, **401** 13% and **402** 69%.

Equation 36

The mass spectrum of both **401** and **402** gave molecular ions consistent with the desired hydroxyacetates **385,386** (scheme 72, page 140) and their corresponding diacetate **403** respectively. The infra-red spectrum for **402** showed the presence of an acetate and hydroxyl group, however there was also another carbonyl stretch and a vinylic absorbance at 1676 cm^{-1}. The presence of a double bond in **402** was confirmed by the ^{1}H nmr spectrum which displayed two doublet of triplets at δ_H 5.36 and δ_H 7.10, assigned to 4'-H and 5'-H respectively (analogous to 4-H and 5-H in **387**). The stereochemistry about the double bond was established as *trans* from the magnitude of the vinylic coupling constant 12.5 Hz.[448] The C=C stretch at 1676 cm^{-1} in the infra-red spectrum also indicated specifically a *trans* double bond for **401** and **402**.

403
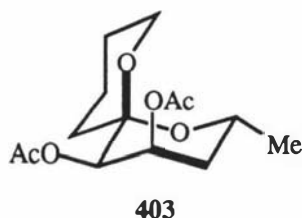
Other notable differences in the ^{1}H nmr spectra of **402** compared with a *cyclic* hydroxyacetate such as **354** were: (i) CHMe (2'-H) was now a quartet of triplets (δ_H 4.94, J 6.2 Hz), as the C-3' protons were no longer resolved (from loosing their rigid axial and equatorial positions), (ii) 3'-CH$_2$ resonated further downfield (δ_H 2.24) from being allylic in **402**, (iii) 5-CH$_2$ (8-CH$_2$ in **354**) was a triplet, J 6.2 Hz, (iv) 2-CH$_2$ (11-CH$_2$ in **354**) resonated downfield as a triplet at δ_H 2.33, J 7.1 Hz, consistent with being adjacent to the newly formed ester group, (v) the signal at approximately δ_C 98 from the spiro centre had disappeared and there was a new carbonyl signal at δ_C 173.2, and (vi) two ^{13}C signals at δ_C 109.8 (C-4') and 137.4 (C-5') replaced C-4 and C-5 at approximately 70 ppm (**354**).

It was inferred that **401** was the acetate of **402** (formed by the weakly acetylating reaction conditions), and this was supported by the presence of a second acetyl group in the ^{1}H nmr spectrum as well as the downfield shift of 5-CH$_2$ from δ_H 3.65 in **402** to δ_H 4.07 in **401**.

The observation that fragmentation of **387** had occurred rather than iodine displacement (as proposed in scheme 73) suggested the acetoxy group was unable to "come across" the top face of the spiroketal to form acetoxonium ion **384**. Interestingly, the tetrahydropyranyl ether of **389** was treated with KO$_2$/THF/DMSO/18C6, conditions used to form **388** from **368** (scheme 74), and *still* the iodine was unable to be displaced. Thus it appeared that steric and electronic factors strongly prevented displacement of iodine from the top face of the 1,7-dioxaspiro[5.5]undecane ring.

147

The Mechanism of Conversion of **387** to **401** and **402**

The mechanism proposed for the observed fragmentation (equation 36) is shown in scheme 79. The driving force for this reaction is the affinity of iodine for silver ion, the subsequent elimination of silver iodide being accompanied by the breaking of the C5-C6 bond giving rise to resonance stabilized carbocation **404** (compare **375** of scheme 69, page 136). Water present in the reaction mixture then attacks the carbocation, which, after loss of a proton affords **405**. Fission of the C6-O7 bond and proton transfer between the hydroxyl group and the remaining ring oxygen atom produces **402**. **401** is then formed by acetylation of **402**.

Scheme 79
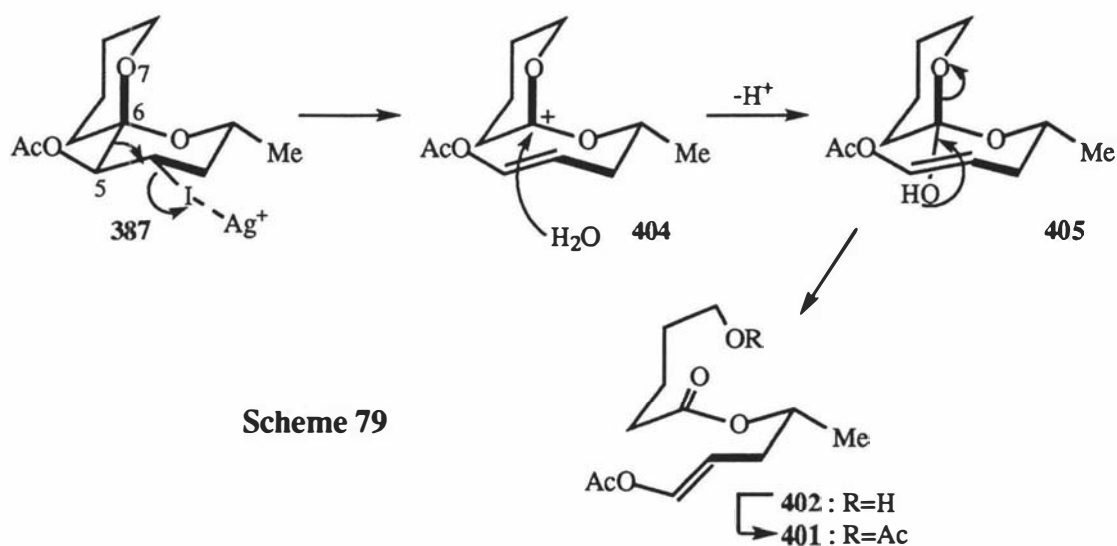
The axial orientation of key bonds in the transformation of **387** to **402** aid the rearrangement proposed. The C5-C6 and C4-I bonds are antiperiplanar in **387** (**a**, figure 32) and so molecular orbitals (C5-C6, C4-I σ^*) are aligned correctly for C4-C5 double bond formation (**b**, figure 32). Thus the opening of the first ring and concomitant loss of AgI is enhanced. A similar ease of elimination was noted for a diaxial bromospiroketal **406** (scheme 80).[449] The diequatorial epimer **407** was unable to access the high energy conformation conducive to elimination (compare scheme 68, page 132). Thus, in the case of the analogous unsubstituted bromospiroketal **408**, ring opening with lithium diisopropylamide (LDA) proceeded *via* path a (scheme 81). In this case the C-H bond was antiperiplanar to the C-O$_a$ bond thereby facilitating the ring cleavage.

Figure 32

Br

Me ... **O** ... **H** ... **O** ... **Me**

406

$\xrightarrow{\text{Bu}^t\text{OK}}_{\text{DMSO}}$

Me ... **O** ... **O** ... **Me**

$\xleftarrow{\quad\times\quad}$

H ... **Me** ... **O** ... **H** ... **O** ... **Br** ... **Me**

407

Scheme 80

Li⁺ ⁻N(Pr^i)₂

Br ... **O** ... a ... b ... **O** ... **H**

408

$\xrightarrow{a}$ HO ... **Br** ... **O**

$\xrightarrow{\quad\times\quad b\quad}$ **Br** ... **O** ... OH

Scheme 81
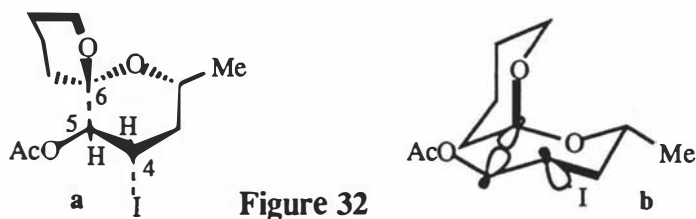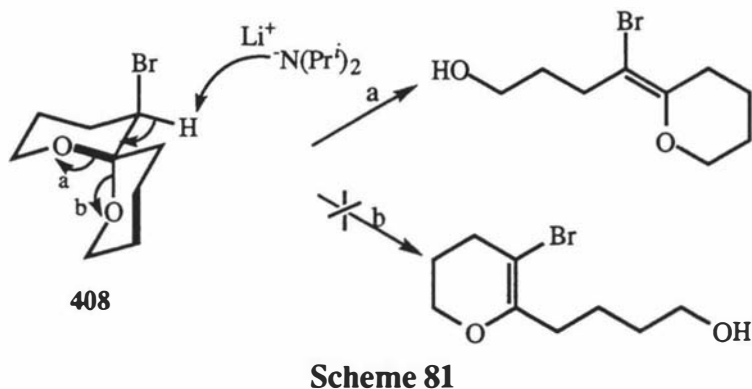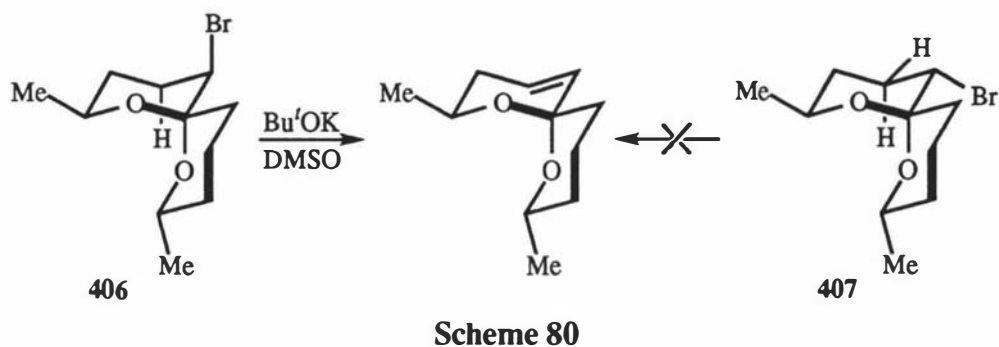
This fragmentation of **387** to **401** and **402** represents a synthesis of acyclic compounds of known relative configuration from a cyclic compound. This procedure[274,417] is also possible for the diols made by osmium tetraoxide *syn*-hydroxylation of 1,7-dioxaspiro[5.5]undec-4-enes (refer table 3, page 125).

<u>Synthesis of Aldehyde **409**</u>

In an effort to deprotect **402** and so form a diol which could then be used to form a crystalline derivative, **402** was subjected to mild hydrolysis with potassium carbonate in methanol. However, this afforded aldehyde **409** (equation 37). The mass spectrum gave a molecular ion at m/z 203 (MH⁺). A carbonyl peak in the infra-red spectrum was observed at lower wavenumbers (1735-1701 cm⁻¹) versus **402**, which together with a weak C-H stretch at 2727 cm⁻¹ suggested the presence of an aldehyde group. 3'-CH₂ in the ¹H nmr spectrum of **409** shifted upfield to δ_H 1.89-1.94 compared with its position at δ_H 2.24 in **402**, as it was no longer allylic. The other major differences were the absence of vinylic peaks at δ_H 5.36 (4'-H) and 7.10 (5'-H), and the appearance of a triplet of doublets at δ_H 2.50 ($J_{4',3'}$ 7.3 and $J_{4',5'}$ 1.4 Hz) and a triplet at δ_H 9.77 ($J_{5',4'}$ 1.4 Hz), assigned to 4'-CH₂ and 5'-CHO respectively. The ¹³C nmr spectrum lacked a vinyl group (formerly δ_C 109.8 and 137.4 for C-4' and C-5' in **402**) and acetate groups (δ_C 168.2 and 20.7), instead showing the presence of an aldehydic carbonyl at δ_C 201.5.

149
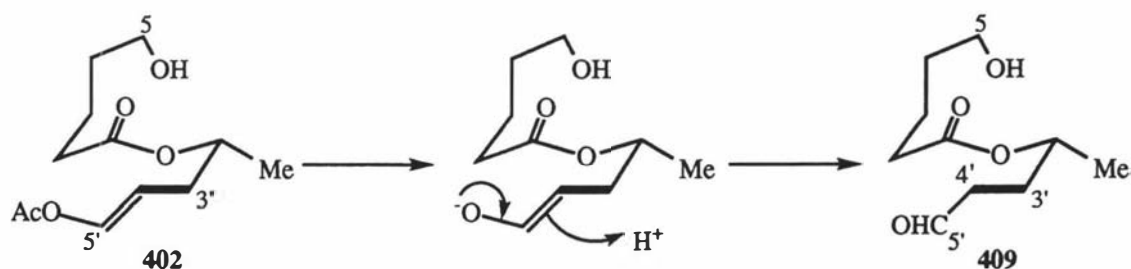
Equation 37

Having been unsuccessful in making hydroxyacetates **385** and **386** from either **368** *or* **387** (scheme 82, refer also schemes 72 and 73), it was decided to complete the structure/reactivity picture being built up by investigating the silver-catalysed reaction of **410**, which was regioisomeric with **368**. The results of this study would then indicate whether formation of the acetoxonium ion *by a C-5 OAc group* on the *lower* face of the molecule (**411**, scheme 83) would be any easier than from C-4 of the lower face or C-4/C-5 of the top face, the last three not being achieved to date (page 140 and scheme 82).

Scheme 82

150

Reagents and Conditions: aq. AcOH, AgOAc, reflux. **354** 21% and **356** 74%.
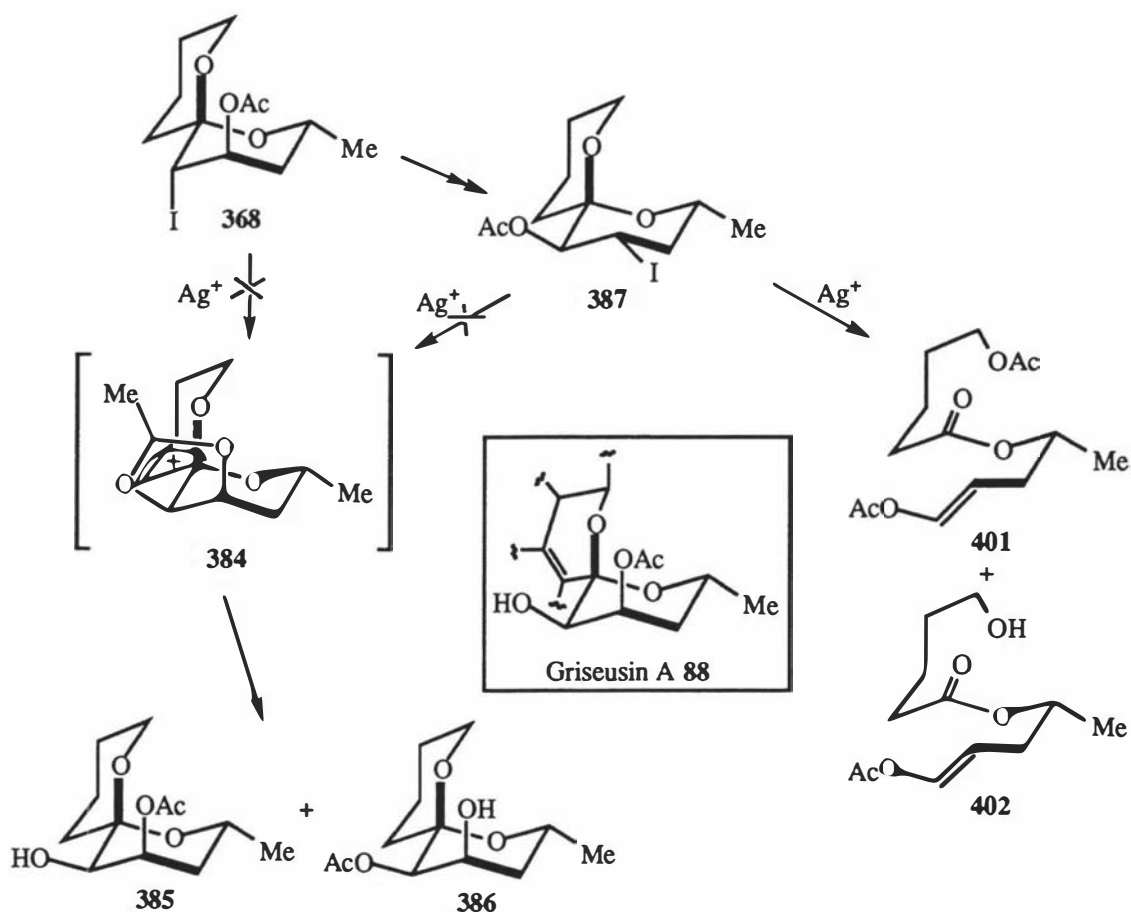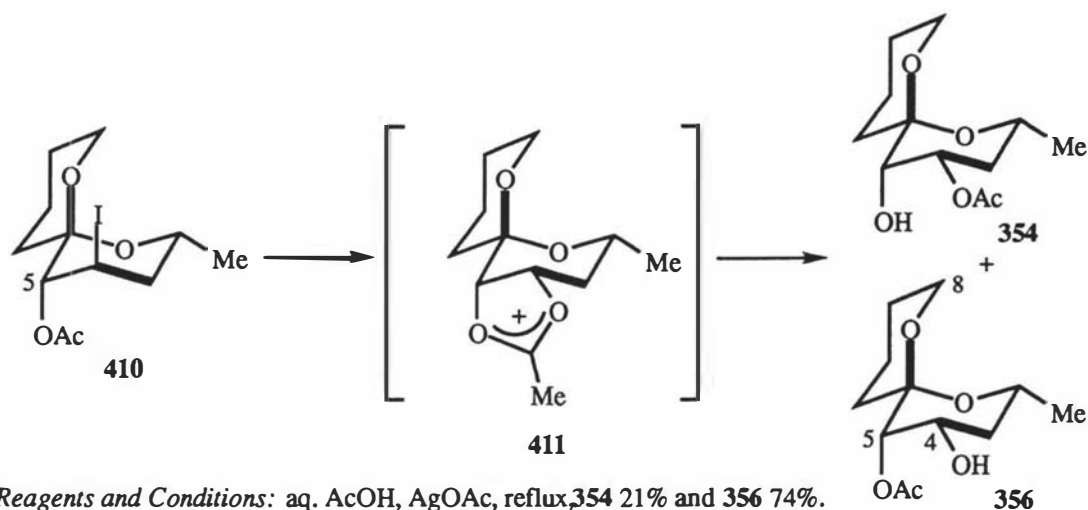
Scheme 83

3.2.7   Synthesis and Reaction of Iodoacetate **410**: Production of Hydroxyacetates **354** and **356**

Formation of Iodoacetate **410**

It was anticipated that **410** could be prepared from **367** (scheme 84) in a manner analogous to that of **387** from **368** (scheme 74, page 141). Treatment of **367** with potassium superoxide gave epoxide **412**, the ^{1}H nmr data of which was comparable to an analogous epoxide **394**[400,401] (figure 33). 4-H in **412** resonated as a double doublet, $J_{4,3eq}$ 5.6 and $J_{4,5}$ 3.6 Hz, since no coupling was present between 4-H and pseudo-axial 3-H due to a dihedral angle of approximately 90°.[362] 4-H in the analogous epoxide **394** resonated as a doublet, $J_{4,5}$ 4.0 Hz, and showed no coupling to pseudo-axial 3-H which confirmed the result for **412**. Long range W-coupling[425] (0.6 Hz) was also observed in **412** between 5-H and 3-H$_{eq}$ (figure 33), providing further evidence for the assignment of the epoxide ring as *anti* to the C6-O7 bond.

Bromohydrin **413**[450] was converted to epoxide **388** (using sodium hydride) in 46% yield. It is of note that this was the same percentage yield obtained for the conversion of **368** to **388** by KO$_2$ (scheme 74), yet **412** was formed from diequatorial **367** in 79% yield. The poorer yield of **388** from these *diaxial* compounds (**368**, **413**) suggests resistance to formation of bridged species (acetoxonium ions or oxirane rings) across the top face of such molecules.

151
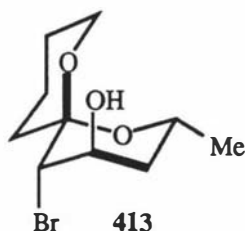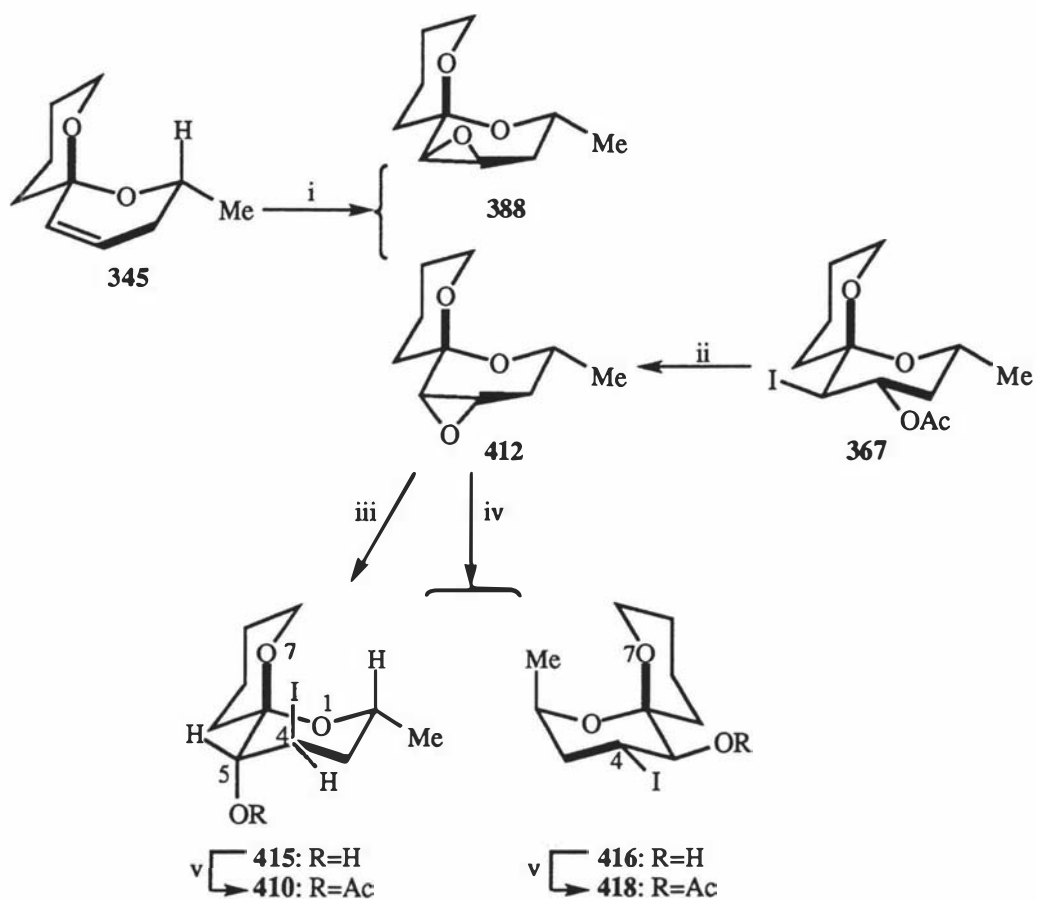
Reagents and Conditions: (i) CH$_2$Cl$_2$, 0°C, MCPBA, RT, **388** 29% and **412** 38%; (ii) DMSO/THF, N$_2$, 18C6, KO$_2$, 74%; (iii) THF, LiI (1.5 equiv.), RT to -50 °C, N$_2$, **412**, then BF$_3$.Et$_2$O (10.5 equiv.), 91%; (iv) less THF, LiI (1.1 equiv.), RT to -50 °C, N$_2$, **412**, then BF$_3$.Et$_2$O (2.0 equiv.), **415** 49% and **416** 39%; (v) CH$_2$Cl$_2$, Ac$_2$O, Et$_3$N, DMAP (cat.), RT, **410** 89%, **418** 85%.

Scheme 84

	412	394
4-H	3.32 dd $J_{4,3eq}$ 5.6, $J_{4,5}$ 3.6 Hz	3.00 d J 4.0 Hz
5-H	2.80 dd $J_{5,4}$ 3.6, $J_{5,3eq}$ 0.6 Hz	2.94 d J 4.0 Hz
11$_{eq}$-H	1.48-1.97 m	2.39 ddd J 12.4, 4.4, 1.5 Hz
11$_{ax}$-H	1.48-1.97 m	1.60 dd J 11.8, 11.8 Hz

Figure 33

152

A superior preparation of epoxides **388** and **412** was achieved by epoxidation of olefin **345** using *meta*-chloroperbenzoic acid[451,452] {(i), scheme 84}. Although this afforded epoxide **412** in approximately half the yield (38%) to that obtained *via* **367** (74%), the simplicity of the procedure meant it was the method of choice to prepare both epoxides rather than the two-step method from olefin **345**.[453] Comparison of **388** and **412** made by MCPBA epoxidation of **345** with samples obtained from treatment of iodoacetates **368** and **367** respectively with potassium superoxide showed them to be identical. Addition of sodium acetate to the epoxidation reaction mixture lowered epoxide yields (23% **388** and 25% **412**) and resulted in incomplete reaction of **345**. An attempt to effect epoxidation of **345** by using iodine and pyridinium dichromate[454] gave only baseline material (TLC).

Attempts to alter the ratio of **388:412** produced by epoxidation in favour of **388** (and hence **387** for previous work, scheme 74) by using solvents such as hexane, benzene and acetic acid[455] were unsuccessful. Either no reaction was observed (hexane) or the resulting epoxides were difficult to isolate[456] due to their volatility. Epoxidation of a related spiroketal olefin **414** by MCPBA gave a 1:1.6 ratio of **390** (figure 31, page 142) to **394** (figure 33) in 91% yield.[400,401] This compared well with the 1:1.3 ratio of **388:412** in 67% combined yield (scheme 84).

414
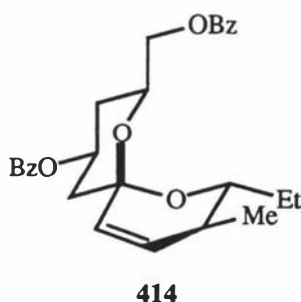
Lithium iodide opening of epoxide **412** proceeded regio- and stereoselectively to give diaxial iodohydrin **415** in good yield {(iii), scheme 84}. Formation of **415** by *trans*-diaxial opening of the epoxide ring at C-4 accounts for the selectivity observed in the reaction. The stereochemistry assigned to **415** was evident from the ^{1}H nmr spectrum. C*H*Me resonated at δ_H 4.07-4.19 and was deshielded compared to the same proton in **389** (δ_H 3.77), consistent with being 1,3-diaxial to both 4-I and O-7. 4-H resonated upfield at δ_H 4.29-4.33, compared with δ_H 4.39 for **389**, as it was now equatorial and not deshielded by 1,3-diaxial O-7. 5-H of **415** resonated as a double doublet at δ_H 3.76 ($J_{5eq,OH}$ 8.4 and $J_{5eq,4eq}$ 2.9 Hz), downfield from that observed in **389** (δ_H 3.39, $J_{5ax,4ax}$ 10.4 and $J_{5ax,OH}$ 9.2 Hz) due to its proximity to 4-I and O-7.

Unexpected Formation of Iodohydrin 416

If the amount of tetrahydrofuran used in the epoxide ring opening of **412** was halved, and only two mole equivalents of boron trifluoride etherate used, then two iodohydrins **415** and **416** were formed (scheme 84). The additional product was in fact an iodohydrin, as shown by a molecular ion at m/z 313 (MH$^+$) in the mass spectrum, and by the infra-red spectrum which displayed a strong hydroxyl stretch at 3589-3172 cm^{-1}. The ^{1}H nmr spectrum of **416** exhibited a double double doublet at δ_H 4.61, the coupling constants $J_{4ax,5ax}$ 9.9, $J_{4ax,3ax}$ 13.0 and $J_{4ax,3eq}$ 4.4 Hz establishing that 4-H occupied an axial position analogous to the same proton in **389**. 5-H resonated at δ_H 3.40 as a double doublet, $J_{5ax,OH}$ 9.9 and $J_{5ax,4ax}$ 9.9 Hz, thus it too was axial. The main difference between **416** and **389** was the position of the doublet assigned to the methyl group, which resonated in **416** at δ_H 1.40 and was deshielded compared with its position in both **389** (δ_H 1.18) and **415** (δ_H 1.26). 4-H was also downfield by comparison with **389** (δ_H 4.39) and **415** (δ_H 4.29-4.33). These two observations suggested that CHI and the methyl group were 1,3-diaxial to the neighbouring ring oxygen O-7. A ring opening had therefore occurred to obtain this stereochemistry.

It was proposed that the unsubstituted ring of **415** had, under the acidic conditions used, undergone ring opening followed by closure from the opposite face of the substituted ring to give **417** (scheme 85). A ring flip of the substituted ring from one chair conformation to the other then occurs, placing the iodo and hydroxyl groups in more stable equatorial positions, with the methyl group assuming an axial orientation. As all these compounds are in fact racemic, **416** represents both mirror images depicted in scheme 85 (the left hand enantiomer is easier to examine when comparing nmr data with **389** and **415**). Formation of **416** occurred when the amount of solvent, LiI and BF$_3$.Et$_2$O used were decreased (the overall effect being a reduction in reagent concentrations).

Thus, the modification to reaction conditions used may well reflect a change in reaction control, from kinetic to thermodynamic conditions. The driving force in formation of **416** once the inversion of the spiro centre has occurred is presumed to be the restoration of the original two anomeric effects, as well as having the two large groups (I, OH) equatorial.

Formation of 354 and 356 by Silver Acetate Treatment of 410

Acetylation of **415** under standard conditions (Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$) gave **410** cleanly in 89% yield (scheme 84). **410** was then subjected to the displacement conditions used successfully in the formation of **401** and **402** from **387**. This resulted in the formation of two hydroxyacetates identified as **354** and **356** (scheme 83, page 151). The structure of **354** was determined by comparison with a sample of the same compound prepared by osmylation of **345** (refer section 3.1.3, page 121). **356** was

inversion of
spiro centre

ring
flip

Me

415

417

mirror
plane

416
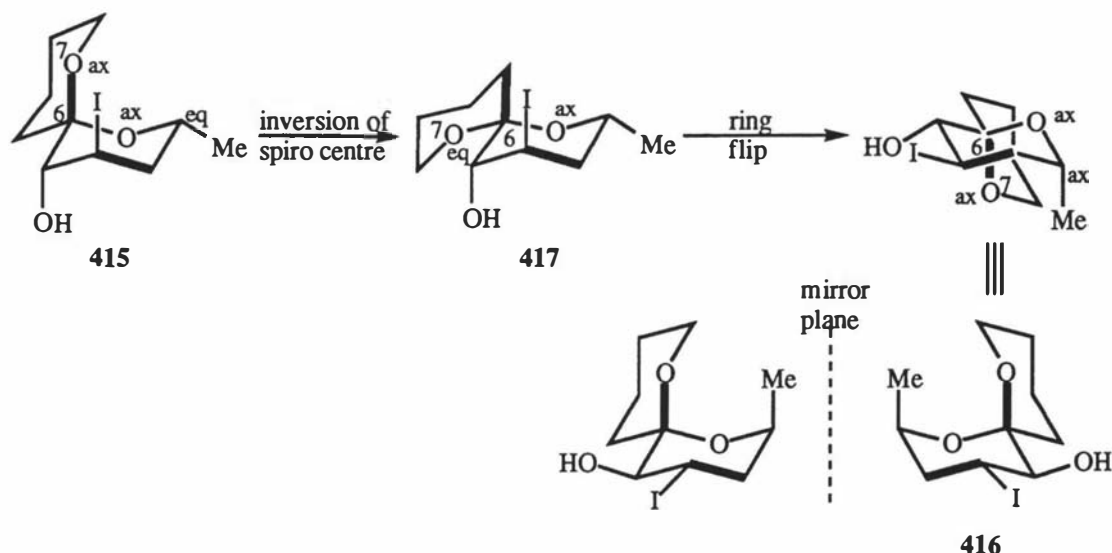
Scheme 85

spectroscopically very similar to **354** (table 2, page 123). 4-H resonated as a multiplet in the ^{1}H nmr spectrum of **356** at δ_H 4.18-4.29, which was similar to **353** at δ_H 4.06 but greatly upfield of **354** at δ_H 5.25. Thus the hydroxyl group was placed at C-4. The chemical shift for 5-H, which resonated as a doublet at δ_H 4.93 ($J_{5eq,4ax}$ 3.3 Hz), indicated that the OAc group was attached to C-5 and compared well to the 5-H doublet present in **355** (δ_H 5.05, $J_{5eq,4ax}$ 2.9 Hz). **356** had a lower R_f value than **354**, consistent with the hydroxyl group being less shielded by the rest of the molecule than in **354**. By being exposed, the hydroxyl group can interact more strongly with silica gel and **356** is therefore more polar.

A mixture of **354** and **356** was acetylated under standard conditions (*vide supra*) affording a single product, spectroscopic data (IR, ^{1}H, ^{13}C) for which was identical to diacetate **355**. Towards completion of the acetylation only **354** was present by TLC. The slower reactivity of **354** towards acetylation was consistent with its hydroxyl group being more hindered than that of **356**.

418 (scheme 84, page 152) was treated with silver acetate, however a mixture of products resulted that did not resemble **401, 402** or **418** and hence the reaction was not explored further.

3.2.8 Summary

Although the desired formation of hydroxyacetates **385** and **386** (scheme 82, page 150), which possess the oxygenated substituents about the 1,7-dioxaspiro[5.5]undecane ring as required for griseusin **88** was not achieved, nevertheless study of the Woodward-Prevost reaction of **345** provided valuable information on the stereoelectronic effects

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affecting attempted displacements of iodoacetates. In respect to the displacement reactions undertaken, the following paragraph from work on deoxy halogenosugars[457] is relevant to the results obtained (table 5, refer also sections 3.2.4, 3.2.6 and 3.2.7). *"Many displacement reactions suffer, however, from one or more of the following limitations: (a) destructively vigorous reaction conditions, (b) inability to effect displacement in certain situations, particularly when the leaving group is attached to a secondary carbon, (c) competing elimination reactions, and (d) molecular rearrangements"*.
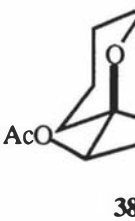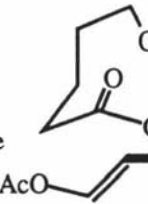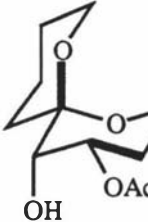
Table 5

3.3 *syn*-Hydroxylation Attempts with Naphthalene and Quinone Olefins

3.3.1 *Attempts to Hydroxylate Synthetic Pyranonaphthoquinones*

With the failure of both osmium tetraoxide and the Woodward-Prevost reaction to successfully introduce the required substituents on the correct face of the unsaturated spiroketal ring of model olefin **345**, it was nevertheless decided to attempt the hydroxylation of **333** and **334** in order to synthesize analogues of griseusin A **88**. It was possible that the presence of the naphthoquinone functionality could alter the outcome of the hydroxylation reaction, and if so, spiroketal **345** was too simplistic a model for olefins **333,334**.

Treatment of **333,334** with NMO/OsO$_4$[394] resulted in no reaction after six hours. Addition of more catalyst and oxidant and leaving the reaction overnight also produced no change. Upon TLC analysis and subsequent work up, the reaction gave 56% recovery of the starting material, suggesting that the procedure was somewhat destructive to the naphthoquinone starting material.

Given that steric and electronic effects *not* present in **345** were apparently retarding reaction of **333** and **334**, a trimethylamine *N*-oxide/pyridine system used for hindered olefins[458,459] was tried. This resulted in a 60% recovery of starting material.$^\Omega$ Stoichiometric conditions[413-415] using dioxane as solvent (rather than pyridine as quinones were found to be sensitive to bases - refer earlier) followed by flash chromatography with methanol as eluent afforded a small amount of orange solid. This exhibited hydroxyl and quinone carbonyl groups in the infra-red spectrum but no γ-lactone carbonyl group, suggesting this ring may have been opened. The ^{1}H nmr spectrum did not exhibit the characteristic resonances attributable to bridgehead protons and other salient features of the ring system, indicating these had also been destroyed.

Due to the apparent incompatibility of spiroketals **333,334** to the osmylation reaction, the hydroxylation of precursors to these quinones was investigated (table 6). Naphthopyrantrione **336**, whose (acyclic) double bond should have been relatively unhindered compared with **333,334** produced a lower R$_f$ (TLC) yellow solid, albeit in very low yield. This proved difficult to examine spectroscopically, the results of which were disappointing. Adduct **330** produced products of *higher* R$_f$, also in poor yield. Treatment of pentacycle **323** with OsO$_4$ did not result in any substantial product after two

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$^\Omega$ Reaction times for catalytic osmylations can be as much as fifty times shorter in the presence of the additive methanesulphonamide,[460] which may have allowed isolation of some material from this reaction.

333

OsO$_4$
-catalytic/hindered
-stoichiometric

complex mixture of both starting material and
very polar fluorescent products
- C=O and OH present by IR but no γ-lactone
  ring by ^{1}H nmr

334

336

OsO$_4$
-catalytic
-stoichiometric

no reaction and loss of
starting material

330

OsO$_4$
-catalytic
-stoichiometric

complex baseline mixture
- ^{1}H nmr shows ring system
  destroyed
- IR shows evidence of OH
  group(s)

323

OsO$_4$
-catalytic

no identifiable products

Table 6

158

days under catalytic conditions. The results obtained for the attempted hydroxylation of **333/334**, **336**, **330** and **323** are summarized[œ] in table 6.

3.3.2 Preparation of Naphthalene Diols 419 and 420

Isolation of Two Diols from the Osmylation Reaction of 327

Given the unsuccessful attempts to hydroxylate the immediate precursors to pyranonaphthoquinones **333** and **334**, it was decided to investigate the osmium tetraoxide reaction of vinylic ketone **327**. Catalytic hydroxylation[394] of **327** proceeded cleanly to give two products, identified as diols **419** and **420** (equation 38). This suggested that the previous reactions (table 6) were impeded by the presence of the furonaphthofuran and furonaphthopyran ring systems as most other functionality present in **336**, **330** and **323** was also present in **327**, and an anthracycline with quinone and dimethyl ether moieties underwent catalytic (NMO) hydroxylation.[461]

- each diol structure represents a pair of enantiomers
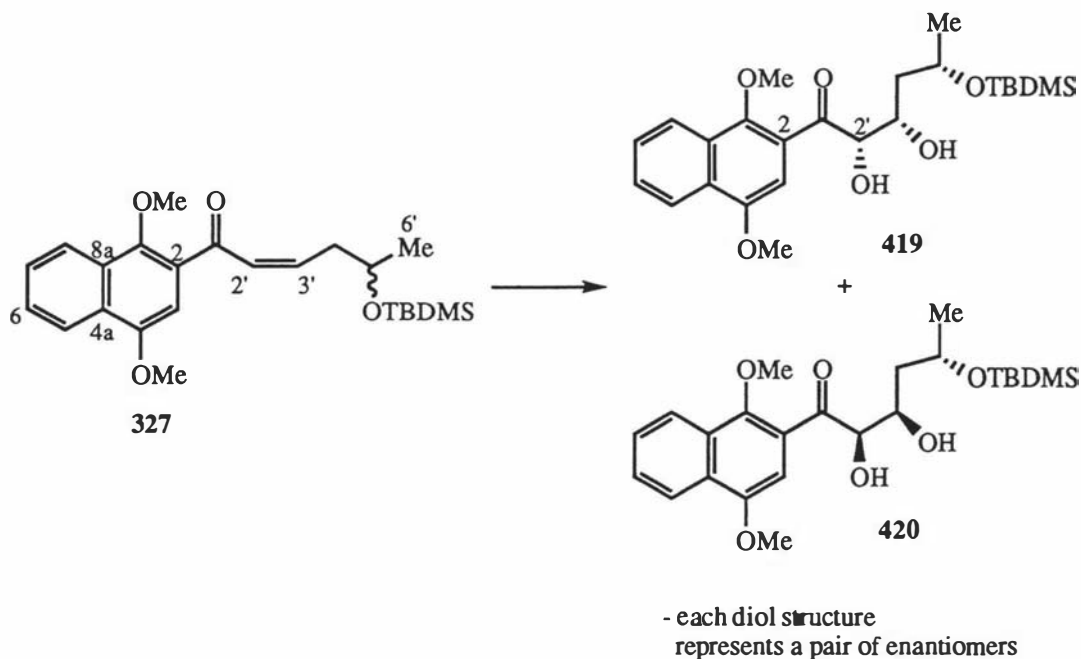
Reagents and Conditions: aq. Me$_2$CO, NMO, OsO$_4$ (cat.), RT, **419** 26% and **420** 34%.

Equation 38

Assigning the nmr spectra of both diols and hence their respective structures relied heavily on the two dimensional nmr techniques[341,342] COSY and HETCOR. The diols had similar R$_f$ values and were isolated as oils in approximately the same amounts

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[œ] At the end of these reactions active OsO$_4$ was still present in the reaction mixture.

159

(26% and 34%). **419** was found to be less stable than **420**. The slight excess of diol **420** (34%) versus **419** (26%) may well be ascribed to decomposition of **419** upon purification. The infra-red spectrum of both diols exhibited a large hydroxyl stretch at approximately 3600-3200 cm^{-1} and a carbonyl stretch at 1664 cm^{-1}, the latter having shifted from 1643 cm^{-1} in **327**, consistent with the loss of the C2'-C3' double bond. All ^{1}H nmr signals from the side chain of **419** and **420** were shifted to some extent upfield relative to **327** (table 7), indicating loss of the double bond. The vinylic protons at δ_H 6.45 and 7.15 in **327** were absent from the spectra of **419** and **420**, and were replaced by several multiplets at δ_H 2.9-5.5 due to the formation of the 1,2-diol moiety. The ^{13}C nmr spectrum displayed large upfield shifts for C-2' and C-3' due to their conversion from sp^2 to sp^3 carbons.

The individual peaks in the ^{1}H nmr spectra were assigned by 2D methods as mentioned earlier, with many of the peaks having no measurable coupling constants with which to link them to other protons. Determining the structures for the two diols was done by analysing chemical shift differences of key protons, based on the molecules having the conformation shown in figure 34 (given that the side chain is acyclic and conformationally mobile, despite some degree of hydrogen bonding being probable - figure 35).

Figure 34

Figure 35

160

Diol /Olefin	SiMe$_2$	Bu^t	Me	4'-CH$_2$	3'-OH	2'-OH	3'-H	2'-H	5'-H	4-OMe	1-OMe	3-H	6,7-H	5,8-H
419	-0.04, s -0.01, s	0.79, s	0.99, d, 5.9	A: 1.21-1.32, m B: 1.57-1.68, m	3.30, d, 4.4	3.87-4.17, m	3.87-4.17, m	5.32-5.40, m	3.87-4.17, m	3.87-4.17, m	3.87-4.17, m	6.97, s	7.61-7.66, m	8.12-8.16, m 8.28-8.31, m
420	-0.13, s -0.09, s	0.55, s	1.00, d, 6.2	A: 1.03-1.14, m B: 1.49-1.72, m	2.93, d, 5.7	3.89-4.12, m	4.22-4.33, m	5.45, dd, 6.2, 2.9	3.89-4.12, m	4.02, s	3.97, s	6.97, s	7.60-7.64, m	8.13-8.17, m 8.24-8.28, m
327	0.09, s	0.90, s	1.22, d, 6.2	2.78-3.02, m	-	-	6.45, dt, 11.7, 7.3	7.15, dt, 11.7, 1.8	4.00-4.07, m	4.01, s	3.87, s	7.05, s	7.56-7.60, m	8.16-8.19, m 8.23-8.27, m

Table 7

Data in table recorded at 270 MHz in CDCl$_3$ and listed as δ_H, multiplicity and J value(s) (Hz)
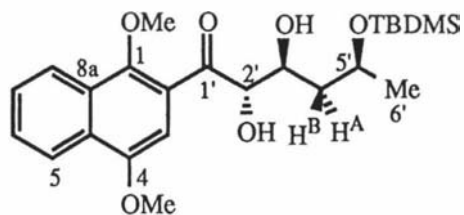
419
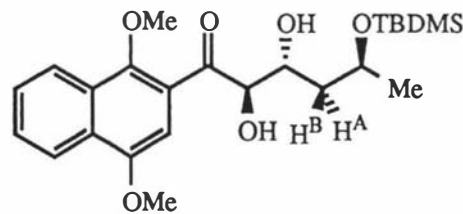
420
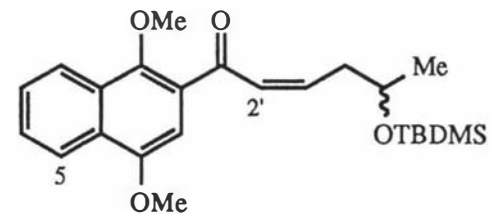
327

3'-H in **420** (**a**, figure 34) resonated further downfield (δ_H 4.22-4.33) compared to that of **419** (δ_H 3.87-4.17), consistent with the fact that in **420** 3'-H is *both* 1,2-*syn* to the 2'-hydroxyl group and 1,3-*syn* to the 5'-*O-tert*-butyldimethylsilyl group. In **419** (**c**, figure 34), 3'-H is only 1,2-*syn* to 2'-OH. The 3'-hydroxyl proton in **419** resonates further downfield (at δ_H 3.30) than its counterpart in **420** (δ_H 2.93), in keeping with it being 1,3-*syn* to the 5'-*O-tert*-butyldimethylsilyl group. The SiMe$_2$ and Bu^t groups resonate further downfield in **419** than those in **420**, as in the former molecule the silyl moiety is 1,3-*syn* to the 3'-hydroxyl group. Both 2'-H and 2'-OH are in similar environments for both molecules and their δ_H values reflect this (table 7).

Assignment of the 4-CH$_2$ resonances was carried out in a similar manner. 4'-H^A in **420** (**b**, figure 34) is 1,2-*syn* to 3'-OH, whereas 4'-H^B is 1,2-*syn* to the 5'-*O-tert*-butyldimethylsilyl group and 1,3-*syn* to 2'-OH. Hence the resonance at δ_H 1.03-1.14 was assigned to 4'-H^A and 1.49-1.72 to 4'-H^B. In **419** (**d**, figure 34) the downfield resonance (δ_H 1.57-1.68) was ascribed to 4'-H^B, which is both 1,2-*syn* to 3'-OH and 5'-OTBDMS. This close proximity to two oxygen atoms means 4'-H^B in **419** is deshielded with respect to both its geminal proton (4'-H^A of **419**) and 4'-H^B of **420** (table 7).

A means to more definitively assign structure to the diastereomeric diols **419** and **420** could be accomplished by making a cyclic derivative and examining the ring coupling constants. A benzylidene acetal[462] is commonly used for 1,2- and 1,3-diols, a 1,3-acetal being formed preferentially in the case of a molecule containing both a 1,2- and a 1,3-diol. Such derivatives (figure 36) should allow structure determination from a combination of chemical shifts, splitting patterns and *J* values.[365,463-465] The most favoured conformations are illustrated, the other possible conformation in each case having two groups axial (one of which is the large(st) naphthalene moiety) and thus unfavourable 1,3-diaxial interactions.
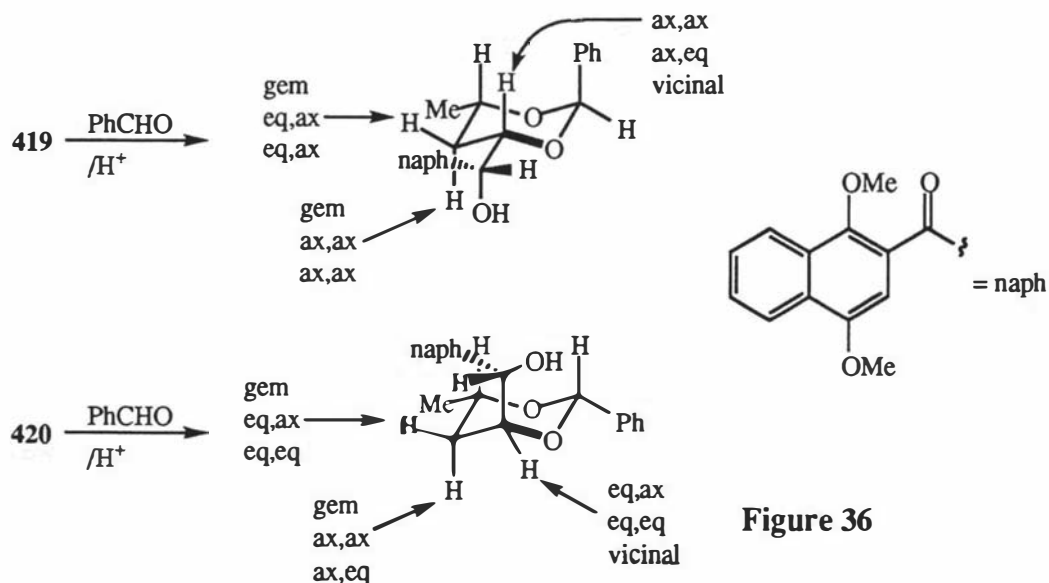
Figure 36

3.3.3 Use of MnO₄⁻: Synthesis of Spiroketal Diols **421** and **423**

Having determined the limitations of using osmium tetraoxide to effect *syn*-hydroxylation, attention then turned to the use of an alternative reagent, namely potassium permanganate. The mechanism of permanganate oxidation is thought to involve a cyclic ester intermediate, much like osmium tetraoxide (equation 28, page 119). It has been well documented[381,466,467] that this reagent is a somewhat harsh oxidant, in certain cases the diols formed are cleaved and/or oxidized further. It was hoped that this harsher reagent would effect some reaction at the C3'-C4' double bond of **333,334**.

Reactions involving $KMnO_4$ are usually carried out in basic, aqueous solution which was not appropriate for olefins **333,334**. An improvement on this method involves the use of phase-transfer catalysis, which increases oxidation yields by allowing partitioning of the substrate into an organic solvent. Initial attempts with such a system[468-470] using **333,334** failed, with only baseline material (TLC) being formed from the starting naphthoquinones. Varying dilution and stirring rates[471,472] did not aid in isolating any useful material from the reaction.

Other means to improve $KMnO_4$ oxidations involve the use of permanganate salts that are soluble in organic solvents, thereby removing the need for an aqueous phase or basic conditions. Triphenylmethylphosphonium permanganate[473] is one such reagent, with improved yields being reported compared to the use of $KMnO_4/H_2O$. A more recent reagent which resulted in higher yields for a wider variety of olefins was cetyltrimethylammonium permanganate (CTAP), $C_{16}H_{33}NMe_3^+MnO_4^-$.[474] Reaction of alkenes at room temperature in dichloromethane with CTAP provided the corresponding diols in good yield. Other quaternary ammonium permanganate salts have been prepared but were used for oxidation rather than hydroxylation purposes.

Treatment of **333,334** with CTAP in dichloromethane at room temperature produced a more polar spot (TLC) for which the infra-red spectrum had an hydroxyl stretch at 3861-3369 cm⁻¹. The ¹H nmr spectrum, however, showed that both 3'-H and 4'-H were still present, therefore the C3'-C4' double bond had not been hydroxylated. Further evidence that a reaction had occurred somewhere else in the molecule was apparent by the observation of new hydroxyl signals at δ_H 3.64-3.81, 4.42 and 4.46 in the ¹H nmr spectrum, subsequent acetylation of the hydroxylation products resulting in the loss of these resonances. All the aromatic protons were still present in the new compounds and the chemical shifts for C-6a and C-10a had not significantly changed, therefore it was concluded that the C5a-C11a double bond had reacted with CTAP. This was supported by the upfield shift of C-5a and C-11a from approximately δ_C 144 (5a) and 136 (11a) in **333,334** to δ_C 82, consistent with conversion of sp² carbons to oxygen-substituted sp³ carbons.

Both the ^{1}H and ^{13}C nmr spectra indicated that only *two* diastereomers were present (as an inseparable mixture) out of a possible four, hence the reagent had effected dihydroxylation *stereoselectively*. High resolution mass spectrometry afforded a molecular ion at *m/z* 386.0962, consistent with the molecular formula $C_{20}H_{18}O_8$.

Molecular modelling studies[475] performed on **333,334** predicted that isomer **334** would be approached by the CTAP reagent from the lower face of the C5a-C11a double bond, the upper face being sterically very hindered by both the lactone and the spiroketal ring (figure 37). This lower face approach would give diol **421**.

334
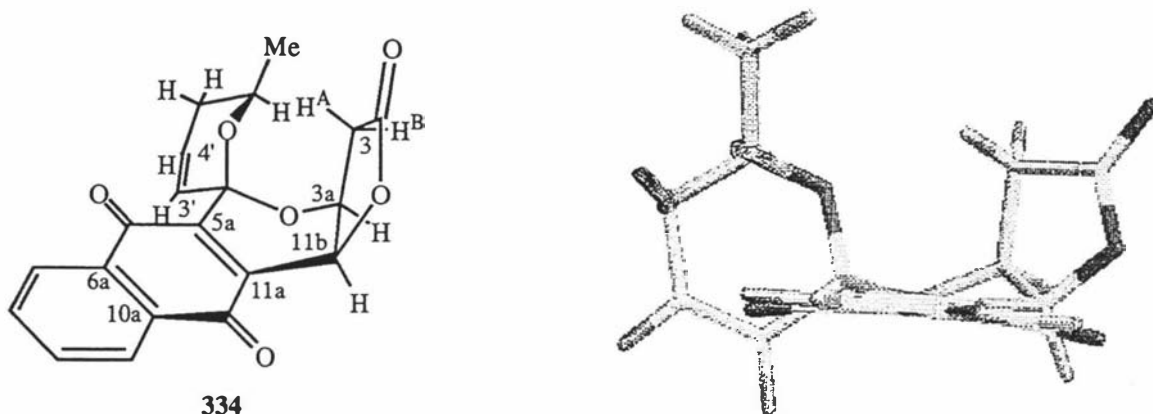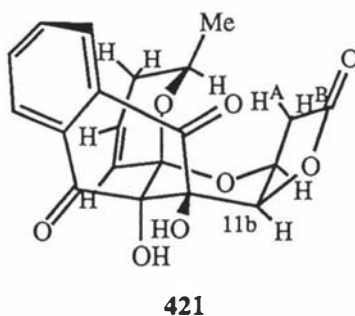
Figure 37

421

Approach of the hydroxylation reagent to the C5a-C11a double bond in spiroketal **333** was more difficult to predict (figure 38). There seems little difference in gross steric bulk between the pyran and the lactone, however the lactone moiety by its position does appear to shield the lower face more effectively than the pyran ring does the upper. It may be that the position of the oxygen atoms on the bottom face, however, allows for better complexation of the CTAP prior to reaction. Thus the situation for **333** was less clear, and therefore the assignment of a structure to the diol obtained from **333** was difficult.

333
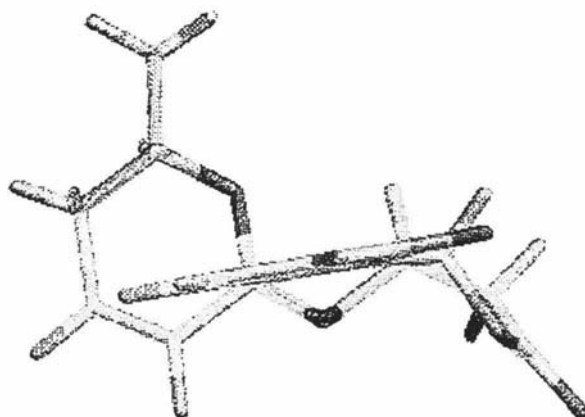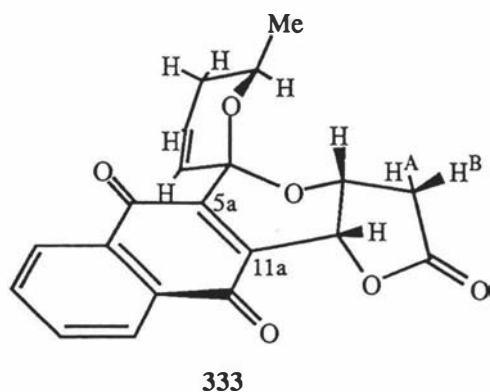
Figure 38

If the diol obtained from **333** resulted from CTAP approaching from the lower face of the double bond (**422**, figure 39) then the chemical shifts for the spiroketal ring protons (3'-H to 6'-H) should be similar to those of **421**, given that both molecules have the large aromatic moiety in the same position with respect to the spiroketal ring. The effect of the lactone ring being "down" or *anti* to the C5-O1' bond (**422**) versus "up" or *syn* to C5-O1' in **421** should be comparable to the δ_H difference observed between **333** and **334** for the spiroketal ring protons 3'-H to 6'-H. Examination of the ^{1}H nmr spectrum of the two diols showed large differences between the signals for both 6'-Me and 6'-H, approximately 0.3 and 0.5 ppm respectively. These values were much greater than would reasonably be expected if structure **422** were the other product and only the lactone ring position distinguished it from **421** {δ_H differences between **333** and **334** were approximately 0.05 ppm (6'-Me) and 0.23 ppm (6'-H)}. Thus it appeared that **423** (figure 39) was the diol formed along with **421**, **423** arising by approach of CTAP from the upper face of the C5a-C11a double bond of **333**.

422: R=H
426: R=Ac

423: R=H
425: R=Ac

Figure 39

165
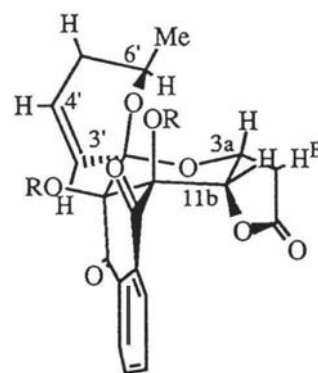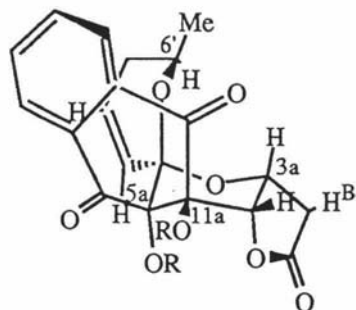
Most of the protons in the ^{1}H nmr spectra for the spiroketal diols were upfield by at least 0.2 ppm compared to resonances in the two starting olefins **333** and **334**. This shielding may be due to the (now) out of plane aromatic ring having an effect on the aliphatic portion of the molecule. This would be more pronounced in **422** where most protons are in close proximity to/"in the shadow of" the aromatic ring. The differences in line shape (a sharp singlet versus a broad multiplet) of the hydroxyl protons in the two diols suggested dissimilar hydrogen bonding environments, more likely in **423** than **422**. A more definitive assignment of structure for the diol formed from **333** will require larger amounts of material in order to separate the two diols (for example by hplc) and carry out further *individual* 2D nmr work.

Given the small amount of material available, the diol mixture was acetylated to see if the corresponding δ_H changes could help in deciding which structure (**423** or **422**) was correct for the CTAP product of **333**. The diols underwent smooth acetylation (Ac$_2$O, CH$_2$Cl$_2$, Et$_3$N, DMAP) to give two diacetates, **424**, and either **425** or **426** (figure 39).

424
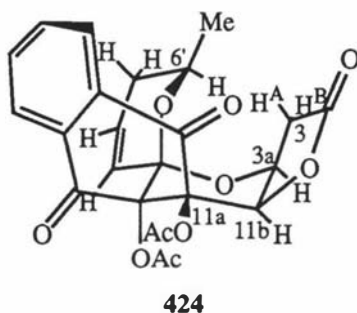
The mass spectrum exhibited an M$^+$ peak at m/z 470.1221 which was consistent with the molecular formula C$_{24}$H$_{22}$O$_{10}$. The hydroxyl protons were absent from the ^{1}H nmr spectrum and were replaced by three singlets at δ_H 2.18, 2.19 and 2.20 (the first peak having twice the intensity of the other two). Most protons had shifted downfield in this transformation, especially 11b-H, which experienced the greatest shift of δ_H 5.38, 5.41 to δ_H 5.91, 5.93. Such a large chemical shift difference between diols and diacetates for this proton suggested that **423** (figure 39) was the other diol product in the CTAP reaction. 11b-H would be most affected by the conversion of an hydroxyl to an acetoxy group if it was 1,2-*syn* to an OH group, as in **423** and **425**. In **422** 11b-H is 1,2-*anti* to the neighbouring OH group. Also, for diacetates **424** and **425**, one would expect a negligible difference in the chemical shift for 11b-H since it has a similar electronic environment. This is indeed the case, with δ values of 11b-H for the two diacetates only 0.03 ppm apart (δ_H 5.91, 5.93).

Both 3a-H and 6'-Me were shifted downfield upon conversion of the diols to the diacetates (approximately 0.15 ppm each). For 3a-H this was consistent with the acetate groups (especially 11a-OAc) being on the same side of the molecule as this proton, providing more evidence that dihydroxylation of the C5a-C11a double bond of **333** resulted in formation of diol **423** (figure 39).

3.3.4 Summary

Based on the results obtained from the dihydroxylation of spiroketals **333,334**, it appeared that hydroxyl groups on the spiroketal ring as required for griseusin A **88** would have to be put in place before assembly of the ring itself. Once constructed, an unsaturated spiroketal ring such as that found in **333,334** resists hydroxylation, to the extent that other sources of unsaturation about the molecule (C5a-C11a) react instead. This lack of reactivity is thought to be mainly steric in nature, though electronic factors are no doubt also involved.[392] No other methods[476] of hydroxylation were considered to be viable and so a new approach was sought based on information gleaned on the reactivity of **333,334** towards hydroxylation to date.

CHAPTER 4

Stereoselective Aldol Approach to Naphthalene 432

4.1 New Strategy and Retrosynthesis

4.1.1 Previous Work

Chapter two described the synthesis of unsaturated spiroketals **333** and **334**, the major isomer **333** envisaged as providing an entry to racemic 7-deoxygriseusin A **320** *via* functionalization of the C3'-C4' double bond (scheme 86). This proposed methodology was discounted in chapter three as several attempts to introduce the required oxygenated substituents to bicyclic model compound **345** and both **333,334** failed. This was attributed to both steric and electronic factors, the latter two compounds producing as a result diols **423,421** (pages 164 and 165) rather than **343,344** (scheme 62, page 118). Beside this difficulty in placing substituents around the terminal spiroketal ring once it was formed, yields for the unsaturated series of compounds were consistently lower than those obtained for earlier saturated work.[252,253] Also, all the additions of 2-trimethylsilyloxyfuran **189** to naphthoquinones were not stereoselective[477] and hence the desired spiroketal isomer **333** was formed with significant amounts of the diastereomer **334**.

4.1.2 Alternative Retrosynthesis based on an Aldol Condensation

In order to address the three deficiencies cited above an alternative retrosynthetic strategy for Griseusin A **88** was devised (scheme 87). It was envisaged that griseusin A **88** would be derived from the corresponding methyl ether **427**, which can be assembled by acid catalysed spirocyclization of triol **428**. **428** in turn may be formed by the well precedented ceric ammonium nitrate oxidative rearrangement of adduct **429**. Adduct **429** would then result from addition of 2-trimethylsilyloxyfuran **189** to quinone **430**, with the chirality present in **430** hopefully conferring a degree of selectivity to this addition. The quinone would be derived from alcohol **431** (by oxidation to **432** then oxidative demethylation), the alcohol being formed *via* addition of the Grignard reagent derived from bromide **433** to chiral aldehyde **434**.
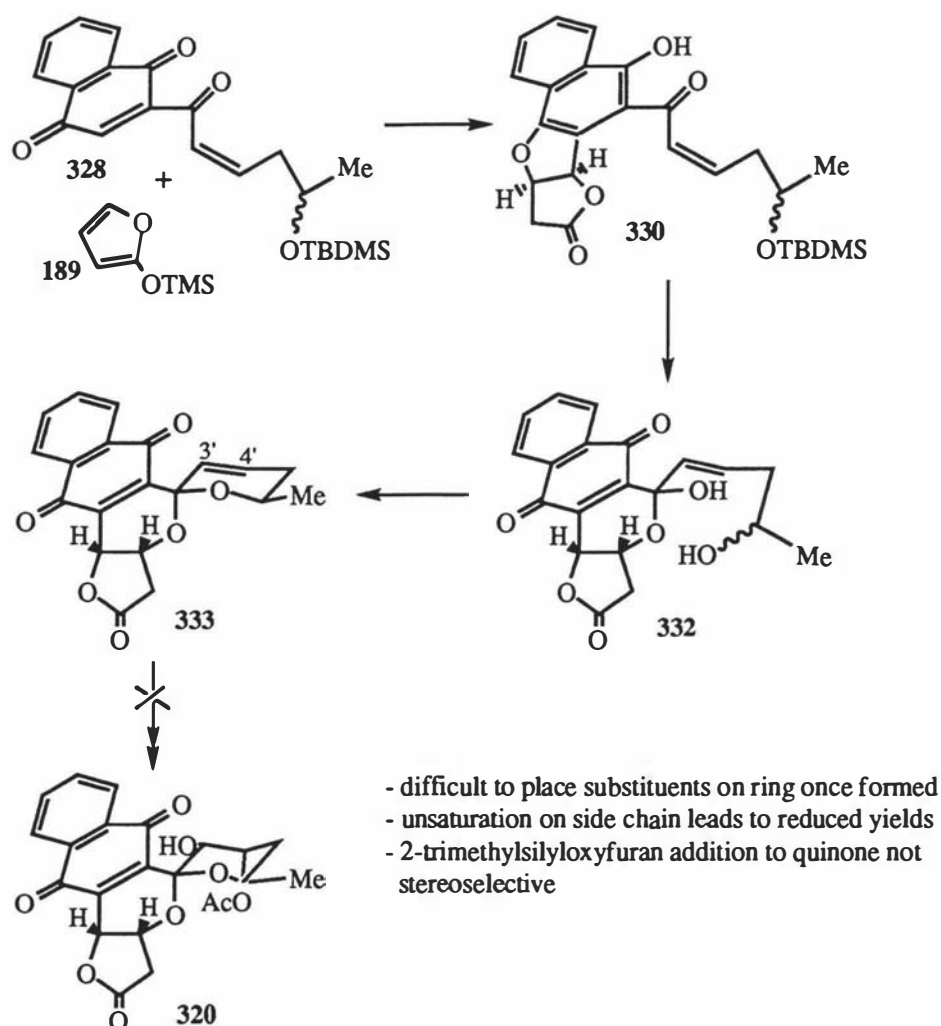
Scheme 86

Construction of aldehyde **434** with the correct 2,3-*anti* stereochemistry is based on work by Evans *et al.*[478] which reported the addition of isobutrylaldehyde to the tin(II) enolate of benzyloxy imide **435**, giving a 63% yield of *anti* aldol product **436** (equation 39). Using this methodology, it was therefore envisaged that aldehyde **434** would be formed *via* an *anti*-selective aldol condensation of the tin(II) enolate of imide **435** with aldehyde **437** (scheme 87).
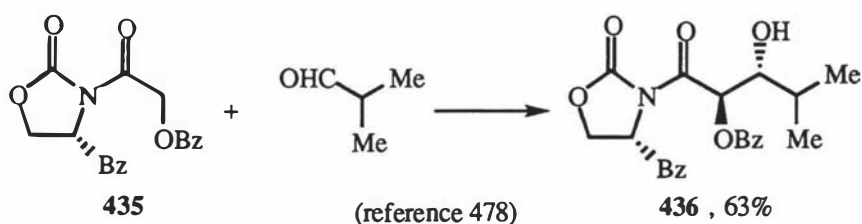
Reagents and Conditions: Sn(OTf)$_2$, CH$_2$Cl$_2$, -78°C, Et$_3$N, TMEDA.

Equation 39

169

Scheme 87

170
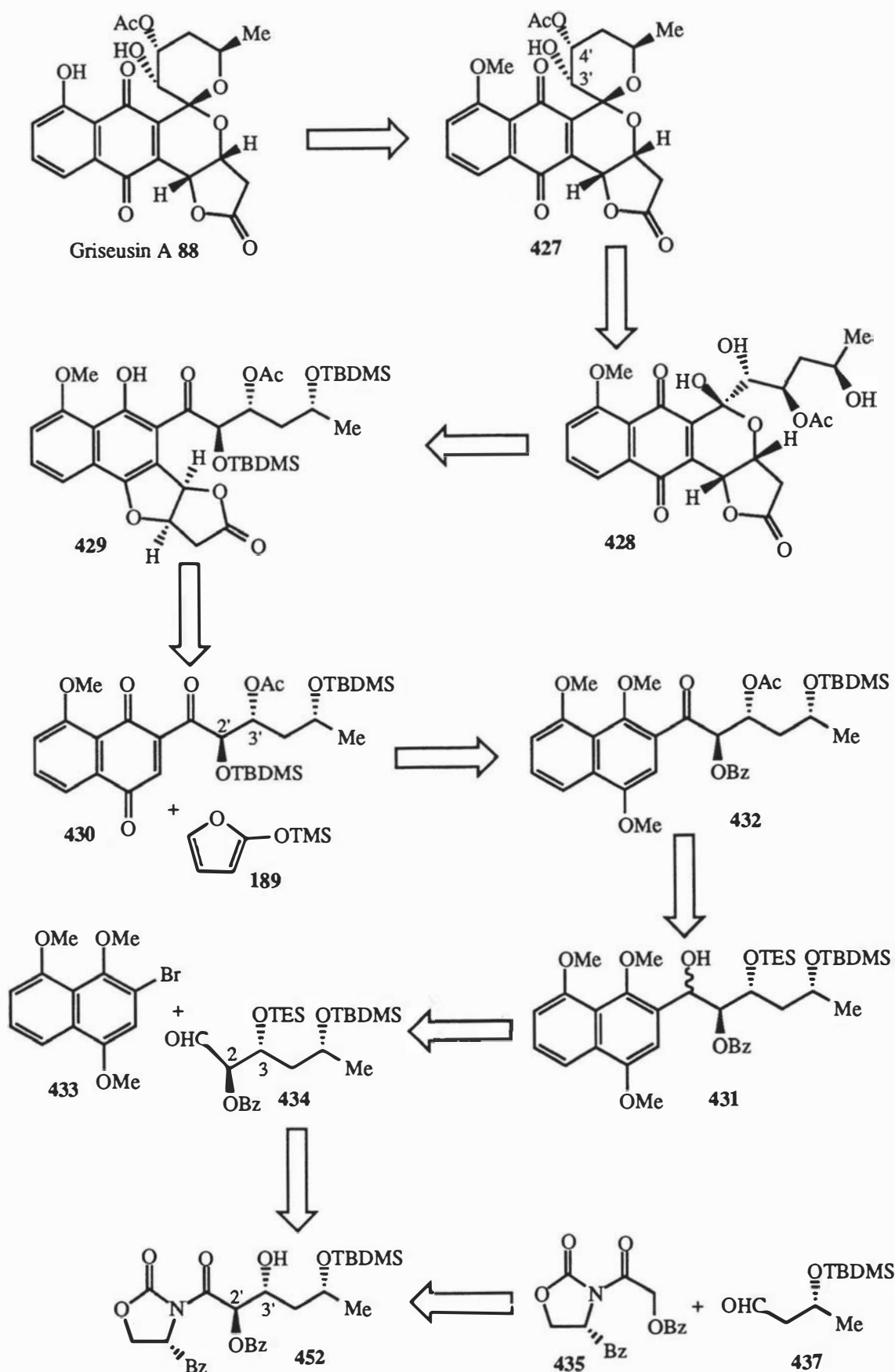
4.2 Synthesis of Reactants for the Aldol Condensation

4.2.1 Synthesis of Imide 435

Imide **435** was formed by the low temperature alkylation of the lithiate of **438** with acid chloride **439**[479] (scheme 88). Oxazolidinone **438**[480] was prepared from (R)-phenylalanine **440** by reduction to the amino alcohol **441** followed by heating with diethyl carbonate. Due to the lower cost of (S)-phenylalanine, initial work to optimize conditions for the synthesis of **435** was carried out using this material.

Reagents and Conditions: (i) THF, NaBH$_4$, 0°C, N$_2$, BF$_3$.Et$_2$O, 0°C to reflux, 81%; (ii) (EtO)$_2$CO, K$_2$CO$_3$, 135°C, 80%; (iii) THF, **438**, -78°C, N$_2$, Bu^{n}Li, -20°C then -78°C, **439**, 84%.
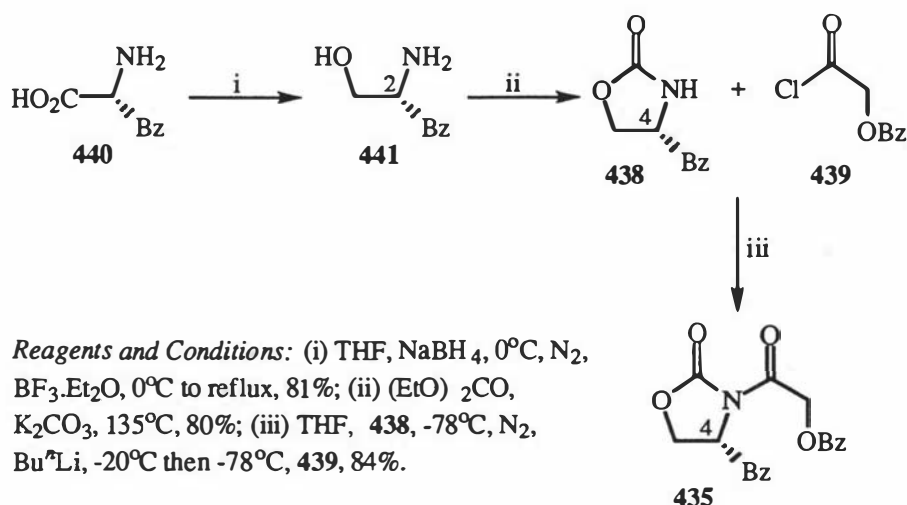
Scheme 88
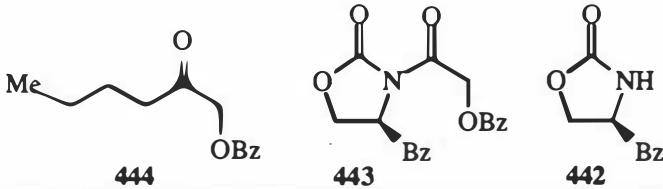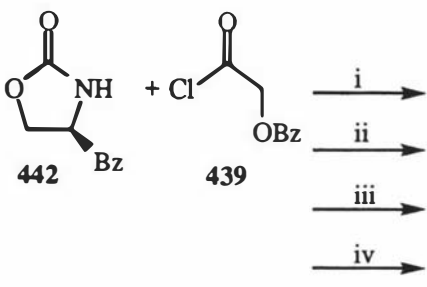
The reduction of amino acids to amino alcohols can be carried out by a variety of reagents, in particular three (BH$_3$.Me$_2$S, NaBH$_4$ and LiAlH$_4$) were shown[481] not to cause any significant degree of racemization. Sodium borohydride and lithium aluminium hydride however afforded poor yields of the (S)-amino alcohol and so attention turned to the use of diborane.[480,482] Due to difficulties with obtaining the borane-methyl sulphide complex it was decided to generate diborane *in situ*[483-485] (equation 40)[486,487] for the reduction of the amino acid.[488,489] Sodium borohydride was chosen as the hydride source[490] for diborane generation due to its ease of handling, stability and cost. The use of diglyme (2-methoxy ethyl ether) as a solvent was avoided and tetrahydrofuran[491] used instead to ensure ease of isolation of the very polar amino alcohol.

$$3BH_4^- + 4BF_3 \longrightarrow 2B_2H_6 + 3BF_4^-$$

$$3RCO_2H + BH_3 \longrightarrow (RCO_2)_3B + 3H_2 \xrightarrow{2BH_3} 3(RCH_2OBO) \xrightarrow{3H_2O} 3RCH_2OH + 3B(OH)_3$$
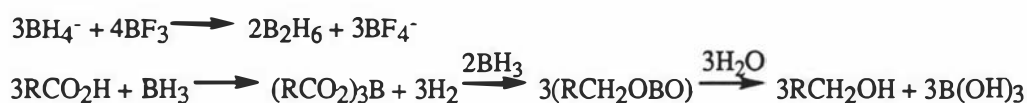
Equation 40

The boron salts were removed at the completion of the reaction by dissolving the crude material in dichloromethane and washing well with water, then filtering the dried solution through Celite to trap any further precipitated salts. The melting point and optical rotation ($[\alpha]_D$) values obtained for **441** {as compared with the (2S)-enantiomer[480]} showed that this isolation procedure was effective, and the yield (81%) was comparable to that obtained by using borane-methyl sulphide itself.[480,482]

Formation of oxazolidinone **438** was carried out using diethyl carbonate and potassium carbonate.[480,482] It then remained to effect N-alkylation of **438** with acid chloride **439**. Generation of the anion of **442** {(S)-**438**} at -78ºC with n-BuLi (one equivalent) followed by addition of **439** and warming to room temperature[492] afforded the (4S)-N-acyl oxazolidinone **443** in only 10% yield {(i), table 8}, with the major product **444** resulting from attack of butyllithium on the acid chloride. Formation of the anion at -25ºC and quenching the reaction, again at room temperature, gave a slightly improved yield of **443** {34%, (iii)}. The optimal procedure {(iv), table 8} was found to be generation of the anion at -20ºC, recooling the reaction to -78ºC then addition of **439**, followed by quenching *still at -78ºC*. This procedure resulted in an 84% yield of imide **435** when applied to (4R)-oxazolidinone **438**, the m.p. and nmr data for which was in agreement with the literature values for the (S)-enantiomer **443**.[480]

	444	**443**	**442**
i	33%	10%	0%
ii	0%	0%	51%
iii	0%	34%	0%
iv	0%	77-79%	0%

Reagents and Conditions: (i) -78 ℃, 30 min., **439**, RT; (ii) -78 to -25 ℃, 30 min., -78℃, **439**, RT; (iii) -78 to -20 ℃, 30 min., -78℃, **439**, RT; (iv) 78 to -20 ℃, 30 min., -78℃, **439**.

Table 8

The use of a phenylalaninol derived oxazolidinone has been found to be superior[493] to other common oxazolidinones {derived from (S)-valinol and (4R,5S)-norephedrine}, and also offers the advantages of a higher degree of crystallinity

combined with a chromophore for TLC/HPLC analysis that does not interfere with upfield ^{1}H nmr resonances (important when using silyl protecting groups - see section 4.5.1, page 193).

4.2.2 Stannous Trifluoromethanesulphonate

Stannous trifluoromethanesulphonate was prepared from $SnCl_2$ and trifluoromethanesulphonic acid according to the method of Mukaiyama et al.[494] and stored under argon in a dessicator until required. It was transferred rapidly to the reaction flask under a stream of argon[480] and heated under high vacuum before use. The diastereoselection obtained with these aldol reactions was noted[495] to be dependant on the quality of $Sn(OTf)_2$ used, with the reagent predicted to have a shelf life of approximately six months under the storage conditions described above.

4.2.3 Aldehyde 437

Aldehyde **437** was prepared from *tert*-butyldimethysilyl protected ester **445** (scheme 89).[496-499] The starting (*R*)-hydroxy ethyl ester **446** was purchased (section 5.1, page 209), however it can be synthesized in high enantiomeric purity by yeast reduction[500] or more conveniently *via* asymmetric hydrogenation[501] of a β-keto ester using BINAP.[502] Racemic material was initially used to develop the procedures shown in scheme 89 and the experimental section (5.2, page 244).

Reagents and Conditions: (i) DMF, 0 °C, N_2, TBDMSCl, imid, RT, 85%; (ii) Et$_2$O, LiBH$_4$, N_2, add **445**/MeOH, reflux, 91%; (iii) CH$_2$Cl$_2$, NMO, 4A, TPAP (cat.), N_2, RT, 81%.
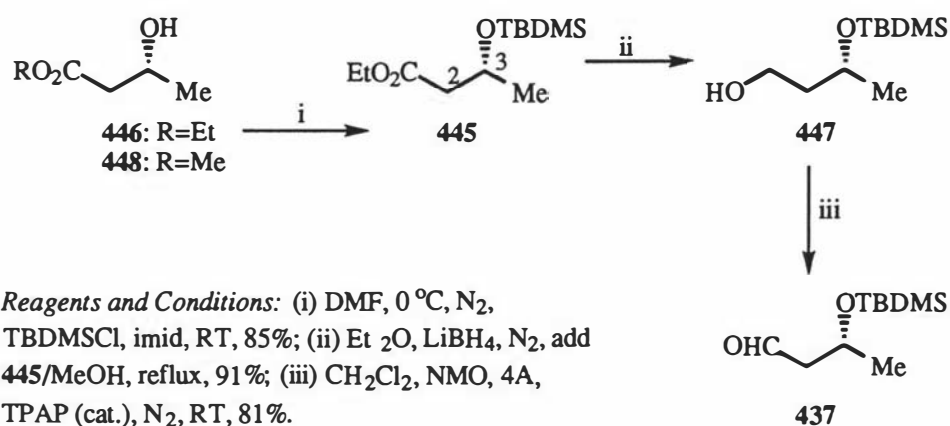
Scheme 89

One[498,499] of the two syntheses involving these compounds (**437,445,447**) used diisobutylaluminium hydride[503,504] (DIBAL) to reduce **445** to **447** before oxidation to **437**. Generally, DIBAL can be used to reduce esters to the corresponding aldehydes without effecting subsequent reduction to the alcohol. Thus it has been reported that **437**

could be formed in 97% yield from (3R)-(-)-methyl 3-hydroxybutyrate **448** by *tert*-butyldimethylsilyl protection and DIBAL reduction.[505] The structurally similar achiral aldehyde **449** was also prepared[506] cleanly from an hydroxy ester in the same manner (equation 41). Another aluminium reagent, sodium bis(2-methoxyethoxy)aluminium (Red-Al), produced **437** (exclusively) from the *tert*-butyldimethylsilyl ether of **448**.[507] However reduction of this same TBDMS-protected methyl ester with DIBAL, as reported in the synthesis of a polyene macrolide,[508] afforded a 71% yield of **437** and 28% yield of **447**. (2S,3S)-**450** also "could not be efficiently reduced directly to the aldehyde" {(2S,3S)-**449**, equation 41} using DIBAL, and required[509] a two step procedure which involved lithium borohydride reduction followed by Swern oxidation.[280-282]

$$ \text{EtO}_2\text{C} \overset{\text{OR}}{\underset{\underset{\text{Me}}{|}}{\overset{3}{\underset{2}{\text{Me}}}}} \quad \xrightarrow{\text{ii}} \quad \text{OHC} \overset{\text{OTBDMS}}{\underset{\underset{\text{Me}}{|}}{\overset{1}{\underset{2}{\text{Me}}}}} $$

i ⌐ R=H
 └➤ **450**: R=TBDMS

449
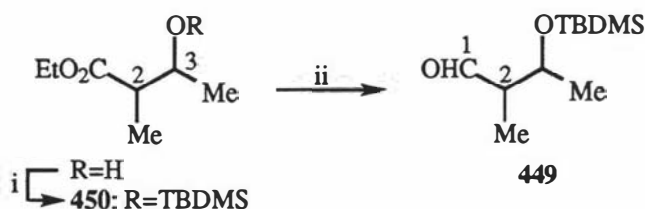
Reagents and Conditions:
reference 506-(2R,S, 3R,S): (i) TBDMSCl, imid, DMF, 0 °C; (ii) PhMe, -78 °C, DIBAL.
reference 509-(2S, 3S): (i) TBDMSCl, imid, DMF, DMAP; (ii) a: LiBH$_4$, THF; b: DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$.

Equation 41

Despite the conflicting accounts on the reduction of esters with DIBAL, the reduction of racemic **445** was carried out with this reagent and produced *solely* racemic **447**. The yield was low due to the work up being complicated by flocculent aluminium residues, despite the use of Rochelle salt (potassium sodium tartrate) to complex the metal cations. Because of this difficulty lithium borohydride was employed as reductant,[496,497,509,510] and this produced racemic **447** and ultimately **447** itself in 91% yield (scheme 89).

With alcohol **447** in hand the oxidation to **437** was undertaken. The previous synthesis of **437**[498,499] used pyridinium chlorochromate, this procedure showing no detectable epimerization. Swern conditions employed in the production of (2S,3S)-**449**[509] also did not result in epimerization of the product. Nevertheless, in the present work, TPAP (*tetra-n*-propylammonium perruthenate, refer section 2.4.3, page 108) was determined as the preferred reagent for oxidation of **447** to **437**. Due to the clean

production of the aldehyde (**437**) and its instability upon storage[¶] no further purification was undertaken once the crude material was isolated. Notably, flash chromatography of aldehyde **449** resulted in "considerable oxidative loss of material", and the compound was "very prone to oxidation by air".[506] Aldehyde **437** was thus synthesized and isolated an hour or less before being required for the aldol reaction, with a solution in (dry) THF being made up immediately prior to introduction to the ensuing reaction.

It was interesting to note that the optical rotation recorded for **437** produced *via* TPAP was somewhat higher than that formed[499] by pyridinium chlorochromate {-17.90 (TPAP) versus -14.4 (PCC)}, suggesting that PCC led to partial racemization of the aldehyde. **437** was purified further by kugelrohr distillation (75°C/4 mmHg) but the magnitude of the rotation did not significantly alter (although the yield dropped considerably to approximately 60%). Use of a higher oven temperature (>110°C) resulted in material with an $[\alpha]_D$ of -15.43.

4.3 The Aldol Coupling

4.3.1   *Formation of the Three Aldol Diastereomers 451,452,453*

Following the procedure detailed in the supplemental material[512] to reference 478, reaction of the stannous enolate of imide **435** (generated with Et₃N and Sn(OTf)₂ at -78°C) with aldehyde **437** in the presence of TMEDA for 2 h gave an 83% yield of aldol products **451**, **452** and **453** in a 1:16:4 ratio (equation 42). This result was comparable to the analogous aldol products **436**[478] (60% yield with 24% other diastereomers) and **454**[365] (63% yield and 19% other diastereomers) (table 9, page 179). Separation by flash chromatography was difficult due to the similar R_f values of the three isomers. A hexane-ethyl acetate (4:1) eluent resulted in optimal separation of the isomers, however the lower aldol product **453** was often eluted together with unreacted imide **435**. The imide reclaimed from the reaction exhibited no change in optical purity and so was able to be recycled in later reactions.[493] Use of one equivalent of aldehyde versus 1.2[512] did not alter the yield or ratio of products and so was adopted to conserve material (**437**).

[¶] After two weeks refrigeration 38% of the original material had been lost and the remaining compound exhibited multiple signals in the ¹H nmr spectrum. Once formed as a solution in ether, racemic **437** "was used immediately without further purification".[511]
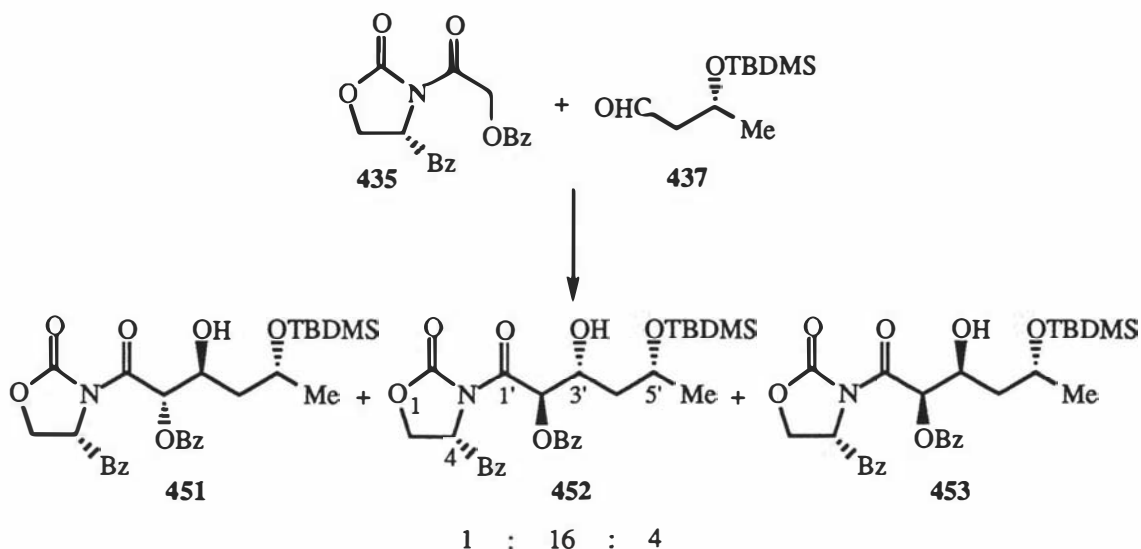
Reagents and Conditions: Sn(OTf)$_2$, CH$_2$Cl$_2$, RT, N$_2$, Et$_3$N, -78°C, **435**, then TMEDA, then **437**; **451** 4%, **452** 62%, **453** 17%, **435** 29%.

Equation 42

As imide **435** was recovered from the reaction, the temperature at which the enolate was formed and at which the aldehyde added was raised from -78 to -60°C (compare alkylation of **442**, page 172). This led to a slight increase in the total yield (86%) and no imide was recovered from the reaction, however the reaction diastereoselectivity decreased substantially (**451:452:453** = 1:25:18).[513]

4.3.2 Structure Elucidation of the Major Aldol Product 452

<u>[1]Hnmr Spectroscopy and Product Comparison</u>

All three products **451-453** gave molecular ions at *m/z* 528 (MH$^+$), consistent with the molecular formula C$_{29}$H$_{41}$NO$_6$Si. The infra-red spectra of all three products exhibited O-H absorptions between 3629 and 3278 cm^{-1} and C-O stretches at approximately 1105 cm^{-1}. The stereochemistry assigned to the major aldol product **452** was based on literature precedent[365,478,512] and was supported by the magnitude of the 2'-3' vicinal coupling constant, which was similar to that observed for analogous *anti* aldol products[365,478,512] (table 9). Full assignment of the proton and carbon nmr spectra were aided by COSY and DEPT experiments.

The ^{1}H nmr spectrum of **452** (figure 40) displayed a *tert*-butyldimethylsilyl group and two benzyl groups (Ar-H), features of both **435** and **437** in this and the two other reaction products indicating a successful coupling. 4'-CH$_2$ resonated as two distinct double double doublets at δ_H 1.67 and 1.94 in **452**, upfield of the corresponding protons (2-CH$_2$) in **437** which resonated at δ_H 2.40-2.59. This change in chemical shift was

Figure 40

452

177
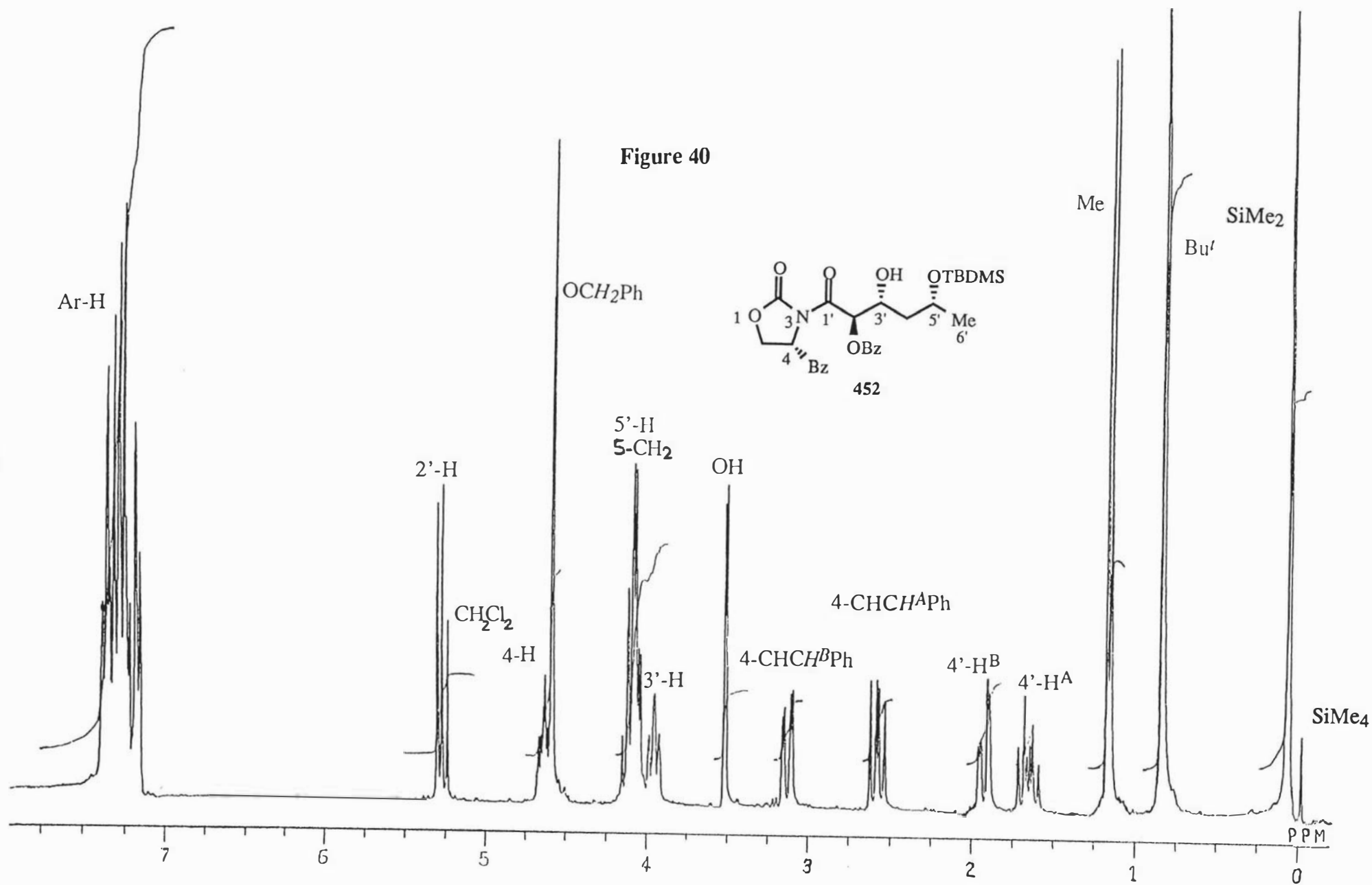
indicative of these protons being adjacent to an sp^3 centre (CHOH) rather than an sp^2 centre (C=O). The difference between 4'-H^A and 4'-H^B in **452** reflects the conformation adopted by the side chain and helped to affirm the structure proposed. The new hydroxyl group appeared as a doublet at δ_H 3.54, $J_{OH,3'}$ 2.2 Hz, whilst a multiplet at δ_H 3.94-4.01 was assigned to 3'-H.

2'-H (CHOBz) of *anti* isomer **452** resonated as a doublet at δ_H 5.31, the chemical shift and coupling constant (*J* 7.7 Hz) both similar to the analogous proton in aldol products **436**[512] and **454**[365] (table 9) which were formed under essentially the same reaction conditions. Proof of stereochemical assignment for **436** was obtained[512] by reduction and conversion to a 1,3-acetonide and examining the vicinal coupling constants. The absolute configuration was determined by conversion to D-α-hydroxyisovaleric acid **455**.[512] The relative stereochemistry of **454** was proven by conversion to an *N*-methylpyrrolidinone derivative **456** for which NOE difference measurements and relevant coupling constants established the stereochemistry.[365,512] Given the similarity in chemical shift and coupling constant of 2'-H in **452** with the same proton in **436** and **454**, the stereochemistry between 2'-H and 3'-H was confidently taken to be *anti*. However, it remained to be established whether the major *anti* aldol product was **452** or **451**, that is, whether 3'-H was *syn* or *anti* to 5'-H.

455   456
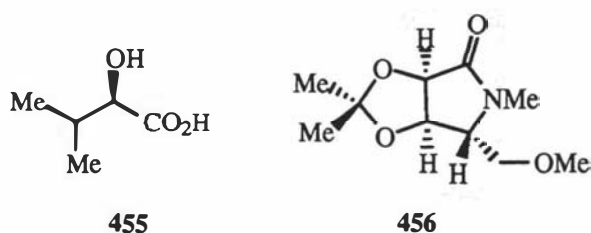
^{13}C nmr Acetonide Work

Confirmation$^\Sigma$ of the absolute stereochemistry at C-2'/C-3' in the major aldol product **452** was obtained by examining the *^{13}C* nmr spectrum of an acetonide derivative (^{1}H nmr coupling constants can also be used[463-465]). Extensive analysis of alternating polyol chains using 1,3-diol acetonides found a strong correlation between ^{13}C resonances of acetonide carbons and diol relative stereochemistry.[515-517] *Syn* and *anti* polyols exhibit distinct δ_C ranges for the methyl and ketal carbons within 95% confidence limits[517] (figure 41). In order to make use of this method to establish the

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Σ ^{1}H nmr spectroscopy alone cannot be relied on as a definitive analytical tool in establishing relative stereochemistry in conformationally mobile systems such as **451-453**.[514]

Product	SiMe₂	Buᵗ	Me	4'-Hᴬ	4'-Hᴮ	CHC*H*ᴬPh	CHC*H*ᴮPh	3'-OH	3'-H
452ᵃ	0.08, s	0.86, s	1.18, d, 6.2	1.67, ddd, 14.3, 9.7, 9.7	1.94, ddd, 14.3, 3.8, 1.6	2.60, dd, 13.6, 9.9	3.15, dd, 13.6, 3.3	3.54, d, 2.2	3.94-4.01, m
436ᵇ	-	-	0.88, d, 6.8 1.00, d, 7.0	2.12, m	-	2.62, dd, 13.4, 9.9	3.22, dd, 13.5, 3.2	1.92, d, 9.3	3.70, m
454ᶜ	-	-	2.86, s (*N*Me)	4.34, m	-	2.94, dd, 13.9, 8.1	3.11, dd, 13.9, 3.7	not listed	4.02, dd, 6.9, 5.2
451ᵃ	0.08, s 0.10, s	0.90, s	1.21, d, 6.2	1.68-1.86, m	1.68-1.86, m	2.65, dd, 13.2, 9.9	3.31, dd, 13.2, 3.3	3.23, d, 4.5	4.14-4.34, m
453ᵃ	0.05, s	0.87, s	1.19, d, 6.2	1.58, ddd, 14.3, 7.1, 2.2	1.78-1.94, m	2.72, dd, 13.6, 9.9	3.27, dd, 13.6, 3.3	2.83, d, 6.2	4.09-4.28, m

ᵃData recorded at 270 MHz in CDCl₃ and listed as δ_H, multiplicity and *J* value(s) (Hz)
ᵇRecorded at 500 MHz in CDCl₃[478] ᶜRecorded at 500 MHz in d₆-DMSO at 125°C[365]

Table 9

452

436

454

451

453

Product	5-CH₂	5'-H	OC*H*ᴬAr	OC*H*ᴮAr	4-H	2'-H	Ar-H	OMe
452ᵃ	4.01-4.17, m	4.01-4.17, m	4.61, s	4.61, s	4.53-4.69, m	5.31, d, 7.7	7.17-7.41, m	-
436ᵇ	4.17, m	see Me	4.52, d, 11.5	4.55, d, 11.5	4.70, m	5.36, d, 8.5	7.10-7.40, m	-
454ᶜ	4.19, dd, 8.9, 3.3 4.28, dd, 8.9, 8.0	A: 3.62, dd, 10.9, 4.6 B: 3.68, dd, 10.9, 8.6	4.42, d, 11.4 (C₆H₄OMe) 5.07, d, 12.9 (Ph)	4.46, d, 11.4 (C₆H₄OMe) 5.09, d, 12.9 (Ph)	4.64, m	5.35, d, 6.9	6.87, m 7.21-7.36, m	3.22, s 3.76, s
451ᵃ	4.00-4.14, m	4.14-4.34, m	4.61, s	4.61, s	4.48-4.66, m	5.28, d, 5.9	7.21-7.40, m	-
453ᵃ	4.09-4.28, m	4.09-4.28, m	4.54, d, 11.7	4.75, d, 11.7	4.63-4.78, m	5.17, d, 2.9	7.19-7.42, m	-
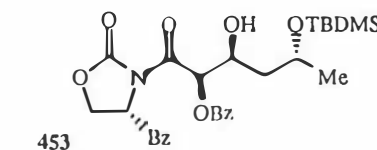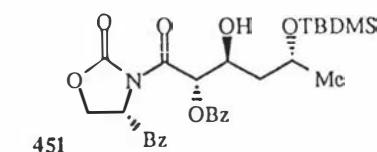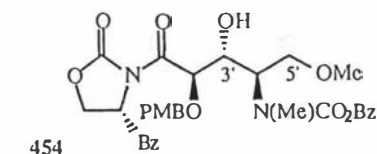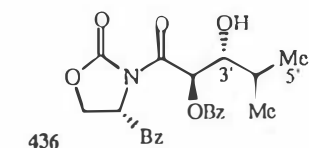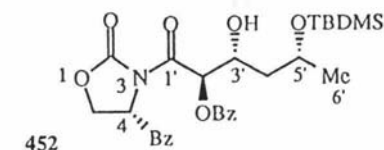
relative stereochemistry at C-3' and C-5', the synthesis, protection and spectroscopic analysis of acetonide **457** was undertaken (scheme 90). Deprotection[336] of **452** with hydrofluoric acid in acetonitrile gave baseline material (TLC), whilst use of tetrabutylammonium fluoride afforded a complex mixture. Use of pyridinium p-toluenesulphonate in ethanol[518] was slow and low yielding, however some material assumed to be **458** was obtained. Treatment of this with p-toluene sulphonic (tosic) acid in acetone gave only numerous unidentified products.

Figure 41

Reagents and Conditions: (i) HF, MeCN, RT; (ii) TBAF, THF, RT; (iii) PPTS (cat.), EtOH, RT; (iv) TsOH (cat.), Me $_2$CO, RT.
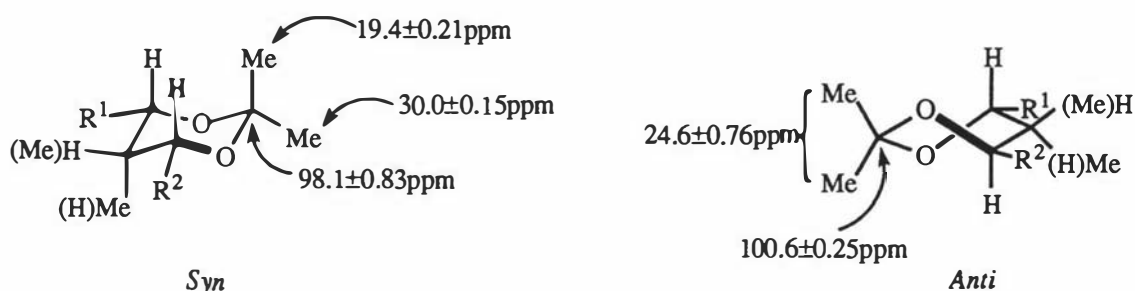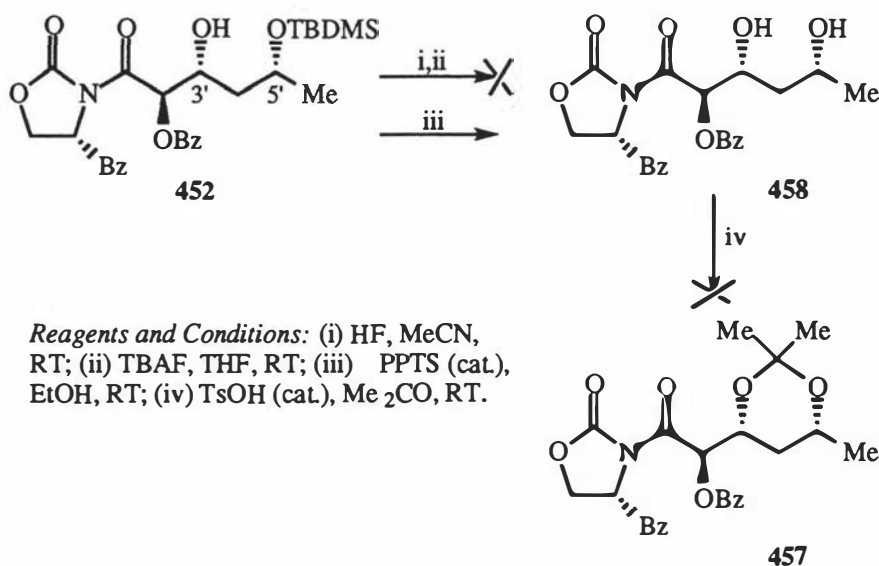
Scheme 90

As the oxazolidinone auxiliary was thought to be complicating matters it was reductively removed using lithium borohydride. Acetylation of the resultant alcohol (**459**, scheme 91: see also scheme 98, page 194) followed by treatment with pyridinium p-toluene sulphonate in ethanol afforded diol **460**. This was converted after isolation to an acetonide in 93% crude yield using tosic acid and acetone. The ^{13}C nmr spectrum of **461** displayed methyl resonances at δ_C 19.6 and 30.1 and a ketal resonance at δ_C 98.6, which was consistent with data for a *syn*-diol derived acetonide (figure 41). Thus 3-H and 5-H

in **461** were *syn* to each other, which in turn established that the absolute stereochemistry at C-3' in **452** was (*R*), as the configuration at C-5' was derived from (*R*)-aldehyde **437**. Thus the 2',3' coupling constant (which indicated an *anti* relationship between 2'-H and 3'-H, *vide supra*) showed the configuration at C-2' in **452** to also be (*R*).

Reagents and Conditions: (i) Ac$_2$O, CH$_2$Cl$_2$, Et$_3$N, DMAP (cat.), RT; (ii) PPTS (cat.), EtOH, RT; (iii) TsOH (cat.), Me$_2$CO, RT.
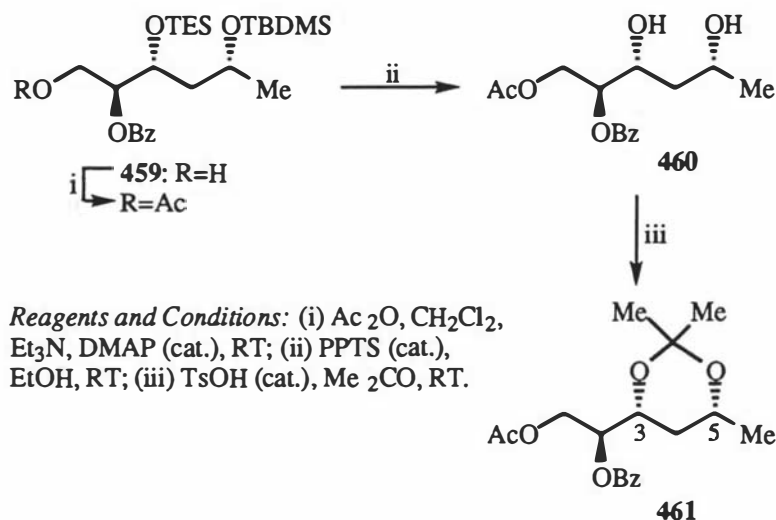
Scheme 91

4.3.3 Structural Assignment of 451 and 453

The next most abundant product **453** from the aldol reaction was assigned as the 2',3'-*syn* isomer that would have predominated using normal Evans'[480,495] /Mukaiyama[494] aldol methodology. It was produced in 17% yield and in a ratio (with **452**) similar to that reported for the *syn* and *anti* thiazolidine-2-thiones **462** and **463**[519] (figure 42: see also equation 43, page 182). The structure was confirmed by comparison with **464**[520] (figure 42), in that the chemical shift (δ_H 5.17) and coupling constant (*J* 2.9 Hz) for 2'-H in **453** (table 9) was nearly identical to the analogous proton in this imide.
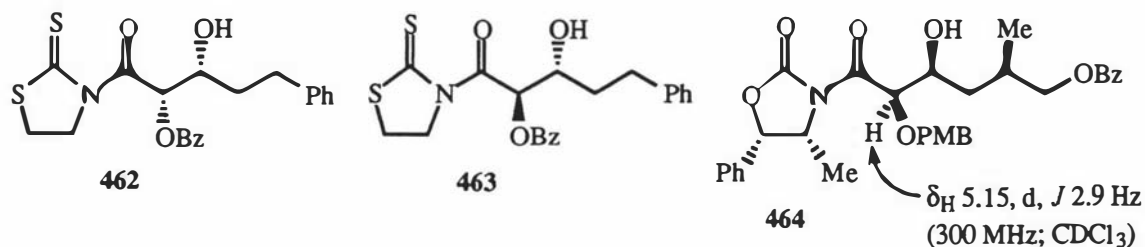
Figure 42

In the least polar minor isomer **451**, 2'-H resonated at δ_H 5.28 with a coupling constant of 5.9 Hz (table 9), which was similar to **452** and quite different from **453**, suggesting a 2',3'-*anti*, 3',5'-*anti* stereochemistry for **451** (equation 42, page 176).

4.4 The Outcome of the Sn(II)/TMEDA Mediated Aldol Reaction

4.4.1 *Origin of the* Anti *Aldol Reaction Employed in the Synthesis of 452*

In the original paper by Mukaiyama and Iwasawa,[519] stereocontrol of the tin(II) aldol reaction was achieved by coordination of the diamine tetramethylethylenediamine (TMEDA) with a divalent tin enolate. Thus the controlling element was external and not covalently bonded to the reactants. 3-(2-Benzyloxyacetyl)thiazolidine-2-thione **465** in the presence of *N*-ethylpiperidine and β-phenylpropanal gave varying ratios of racemic *syn* and *anti* stereoisomers **462** and **463**, depending on whether TMEDA was added to the enolate (equation 43). Essentially, with TMEDA the ratios were reversed and the *anti* isomer **463** was obtained as the main product (74:26→17:83 *syn:anti*).

*Reagents and Conditions:*CH$_2$Cl$_2$, -78°C,
Sn(OTf)$_2$, *N*-ethylpiperidine.

Equation 43
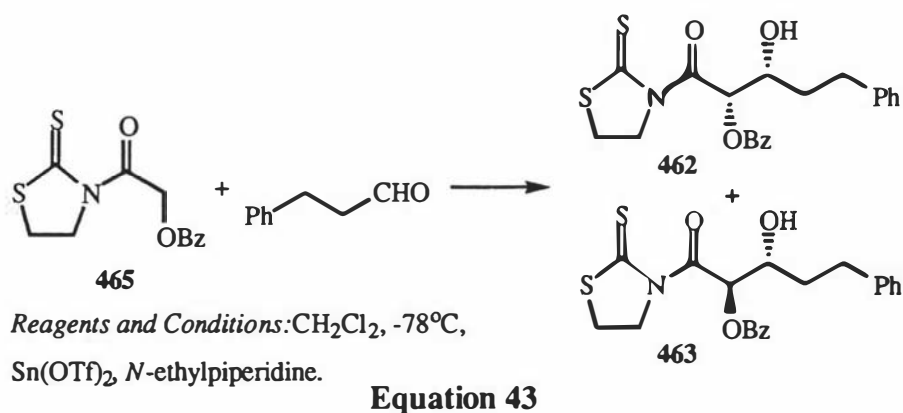
It was suggested[519] that stereoselection was determined by the fact that coordination of TMEDA changes the coordination pattern of the divalent tin enolate from tetrahedral to octahedral, which causes the transition state to alter from a chair- to a boat-type. Interestingly, aromatic aldehydes gave predominantly the *anti* isomer with or without TMEDA (see section 4.4.3, page 185). Use of (*S*)-diamine **466** as a ligand gave >90% ee values for the aldol products so formed.[519]
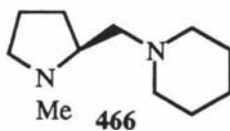
Based on these results Evans *et al.*[365,478] synthesized *anti* aldol products **436** and **454** (table 9) in the synthesis of calyculin A. In these cases, *internal* absolute stereocontrol was achieved by the use of well known[521,522] chiral oxazolidinone enolates. It was remarked[365] that "a detailed understanding of the details of this reaction awaits further study".

4.4.2 The Aldol Reaction - an Overview

Of the transition states proposed for nucleophilic addition to carbonyls,[523-525] the pericyclic Zimmerman-Traxler model[525] has been the most popular and widely applied primarily due to its success as the best available predictive tool for aldol stereoselectivity. Diastereoselection[526-528] can be explained by the hypothesis that the reaction proceeds *via* a preferred chair-like transition state[529] involving co-operative metal ion ligation of both the enolate and carbonyl substrates[530] (scheme 92).

The stereochemical outcome of this cyclic transition state reaction is generally rationalized in terms of the geometry of the starting enolate, which is dependant on the steric bulk of the enolate group R_1 (figure 43). When R_1 is large the (*Z*)-enolate is favoured as there is unfavourable steric interaction between R_1 and R_2 in the transition state leading to the (*E*)-enolate. Enolate geometry is also dependant upon the reaction conditions (either kinetic or thermodynamic control[531]), with the stereoisomer formed under kinetic conditions being critically dependant on the geometry of the starting enolate {(*Z*) giving *syn* and (*E*) giving *anti* products, scheme 92}.

Using the (*Z*)-enolate the Zimmerman-Traxler model accounts for formation of the *syn* product. However, which of the two possible *syn* products is formed depends on the two modes of approach of the enolate to the enantiotopic faces of the aldehyde. If one considers the two transition states (**a** and **b**) leading to the two *syn* aldol products **467** and **468** (figure 44), in **a** the small group (R_S) has less steric repulsion with the metal ligands (L) than does the large group (R_L, **b**) and hence the former is favoured, leading to the *syn* isomer indicated (**467**).

Figure 44

183
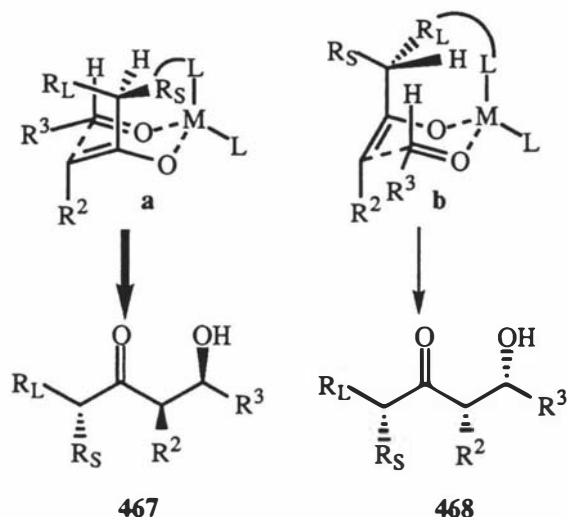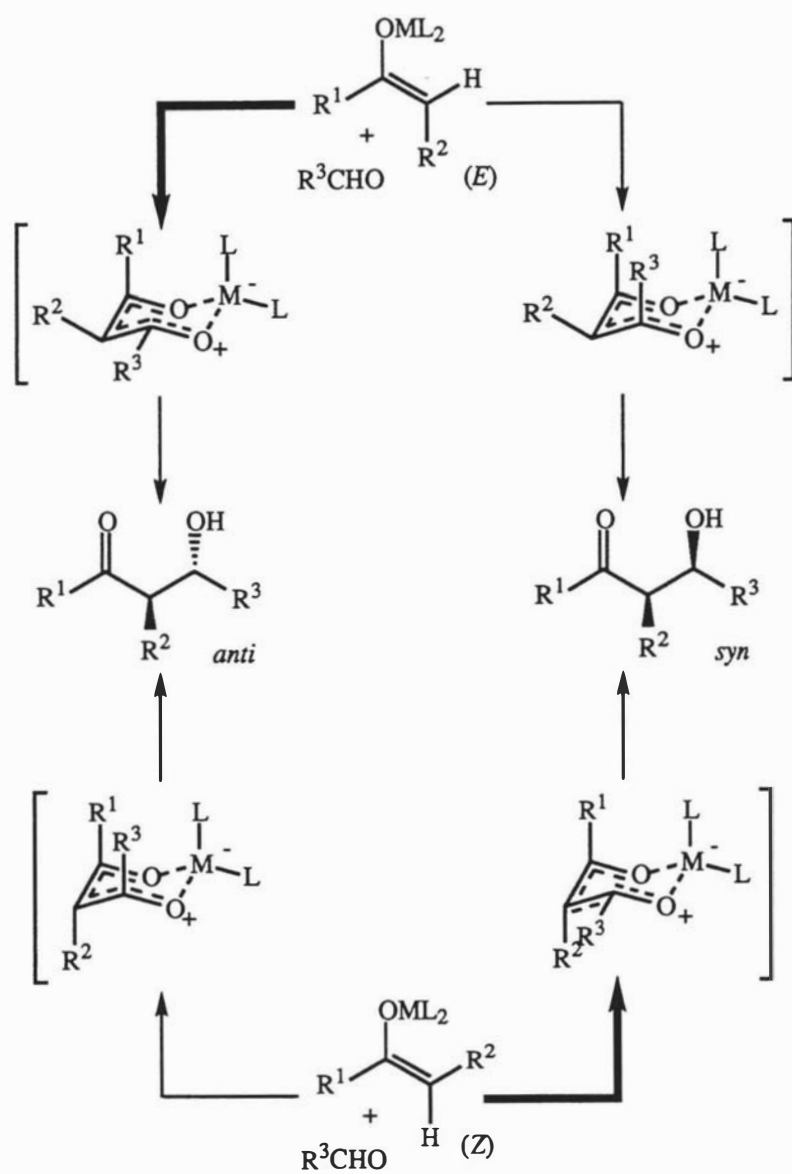
Scheme 92
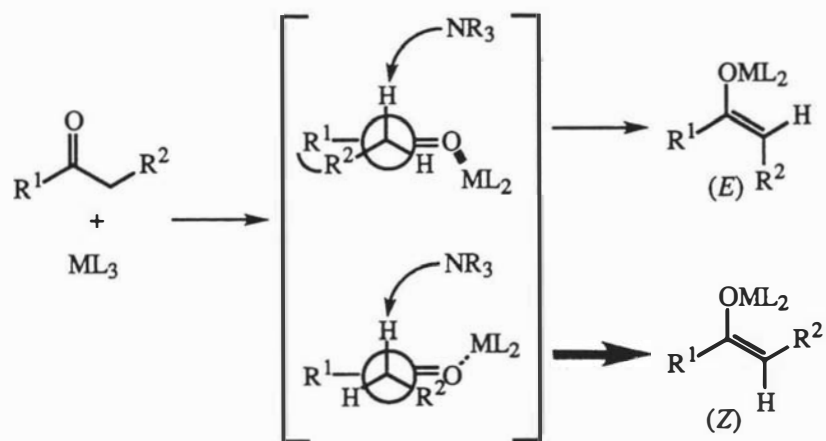
Figure 43

In an analogous way oxazolidinone **435** forms part of an enolate structure with transition state **a** favoured over **b** (figure 45), and thus the *syn* product **453** {**469**: R^2=OBz, R^3=(*R*)-CH$_2$CH(OTBDMS)Me - refer equation 42, page 176} is rationalized as occurring *via* transition state **a**. Aldol product **453** has the stereochemistry expected from the normal Evans' aldol reaction using an enolate (boron or tin) derived from a (4*R*)-oxazolidinone such as **435**. Accounting for the formation of the major non-Evans *anti* aldol product **452** (equation 42) was however more difficult.
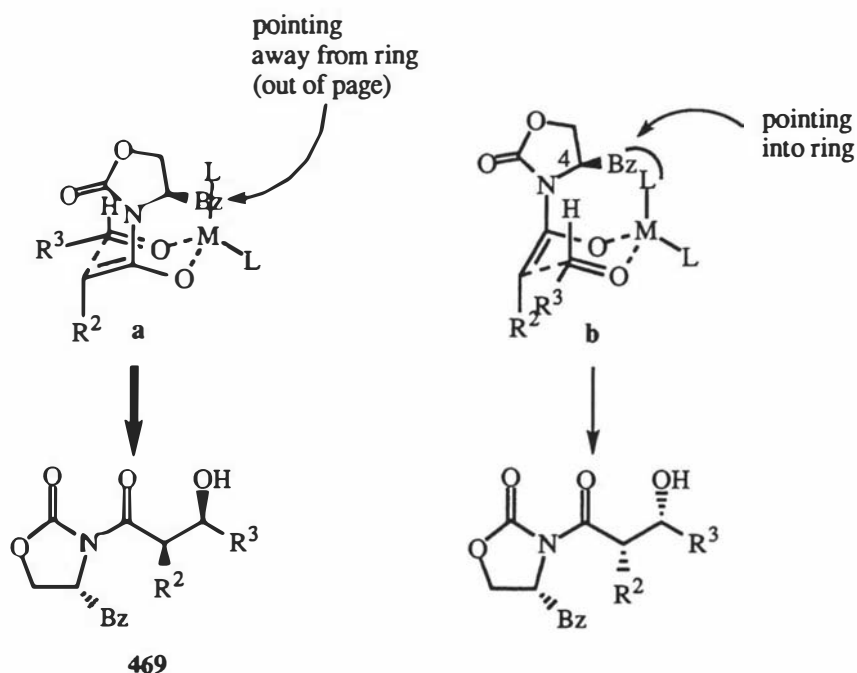
Figure 45

4.4.3 *(Z)-Enolate* Anti *Aldol Transition States*

An investigation[514] into the conditions that induce the aldol reaction of *N*-(haloacetyl)-2-oxazolidinones and aromatic aldehydes to yield predominantly *anti* adducts (scheme 93) provided valuable insights into why the *anti* product **452** was formed using Sn(II)/TMEDA in the present study.

The aldol reaction of the (*Z*)-enolates of (4*S*)-(1-methylethyl)-2-oxazolidinone showed a strong propensity to proceed *via* transition state **470** when non-coordinating cations were used[514] {(i) and (ii), scheme 93}. From **470**, *syn* adducts **471** were formed as the main products with aromatic aldehydes benzaldehyde and **472** (refer transition state **b**→**468**, figure 44). However, in one instance where aldehyde **472** (which has a phenyloctyl group at the *ortho* position) rather than benzaldehyde was used in conjunction with Sn(II), *anti* isomer **473** was the major aldol product {(iii)}. This reversal in selectivity was enhanced by the use of the more sterically demanding

185

M=B, Sn(II), Ti
(non-chelating metals)
L=OTf,: (Sn(II)), Bu (B),
Cl (Ti)

474

i,ii

iii

470

479

471-*syn*

473-*anti*

477-*syn*

475-*anti*

480

478

normal route for
aliphatic aldehydes

iv,v

476

M=Li, Zn, Sn(IV)
(chelating metals)
L=THF (Li), Cl (Zn),
Bu^n {Sn(IV)}
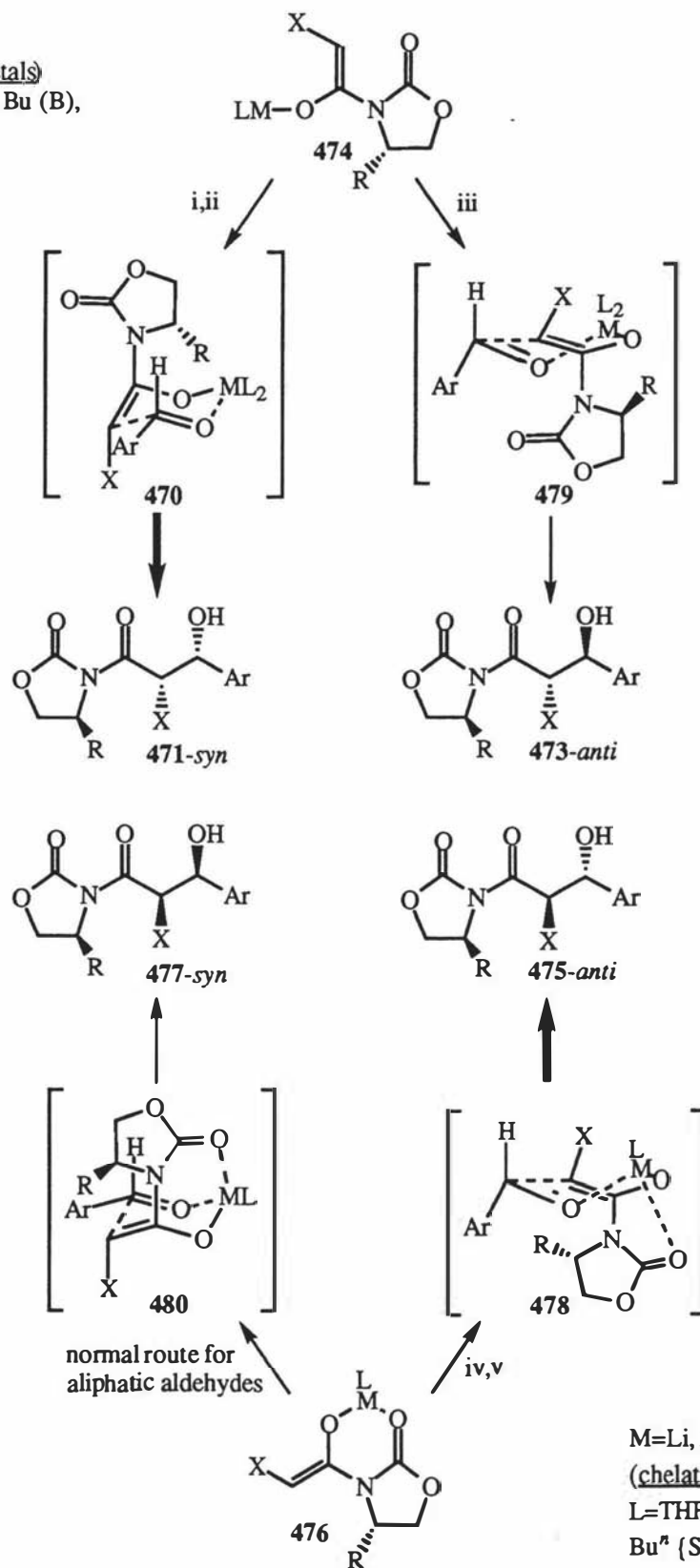
(i) M=B, Sn(II), Ti, X=F, Cl, Br, R=Pr ^{i}, aldehyde=PhCHO; (ii) M=B, Ti, X=Br, R=Pr ^{i},
aldehyde=**472**; (iii) M=Sn(II), X=Br, R=Pr ^{i}, Ph, aldehyde=**472**; (iv) M=Li, Zn, Sn(IV), X=F,
Cl, Br, R=Pr ^{i}, aldehyde=PhCHO; (v) M=Li, Zn, Sn(IV), X=Br, R=Pr ^{i}, aldehyde=**472**.

Scheme 93

186

auxiliary derived from phenylglycine (**474**: R=Ph) rather than the valinol based compound (R=Pr^i).

Anti products represented by **475** were the major products when chelating metals (enolate **476**) were used in conjunction with benzaldehyde and **472** {(iv) and (v), scheme 93 - note also reference 519}. As only the configuration at the β-carbon of **475** had changed relative to the corresponding *syn* isomers (**477**), expected for aliphatic aldehydes, epimerization during the reaction at the α-carbon *or* reactions involving (*E*)-enolates were ruled out.
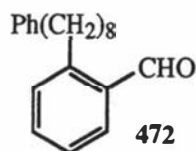
In order to account for the formation of *anti* adducts **475** from (Z)-enolates using chelating metals and benzaldehyde {(iv) and (v), scheme 93} as opposed to **473** when using non-chelating Sn(II) with aldehyde **472** {(iii)}, the twist-boat transition states **478** and **479** were respectively proposed. It was assumed that the (Z)-enolates and not the (*E*)-enolates were the principal reactants. In further support of these transition states (**478**, **479**), there was little discernible difference in diastereoselectivity between oxazolidinones with differing halogen substituents.[514] The *anti* isomers, therefore, most probably resulted from *reversal of the aromatic aldehyde enantiofacial selectivity.*

A purely steric explanation for the formation of *anti* products when using aromatic aldehydes and chelating metals was dismissed when a more sterically demanding aliphatic aldehyde (with a lithium enolate) gave predominantly *syn* aldol products analogous to **471** and **477**. The shift in product stereochemistry for a Sn(II) enolate (from **471** to **473** when using **472** instead of benzaldehyde, scheme 93) was attributed to increased unfavourable steric interactions in the chair transition state **470**. These interactions mean transition state **479** becomes favoured and can compete effectively with **470** to give *anti* products **473**. This steric effect exerted by the aldehyde substituent compares with the formation of **462** and **463**[519] (equation 43, page 182) where diamine TMEDA was the causal agent in the stereochemical change. Ultimately, an aldehyde's inherent steric and electronic properties determine which of its faces (*re* or *si*) reacts (aliphatic aldehydes have previously been shown[513] to react only through chair-like transition states **470** or **480**).

The reversal in selectivity of the aldol condensation illustrated by this work[514] {*anti* products from (Z)-enolates} has been reported[532-540] and tentatively explained using boat-like transition states[534-540] (for example scheme 94[540]), and by the possibility

57-80% yield, 89-97% ee
R=Pr, Pr^i, Bu^t, CH$_2$=CH,
CH$_2$=CMe, Ph

88% ds, 95% ee
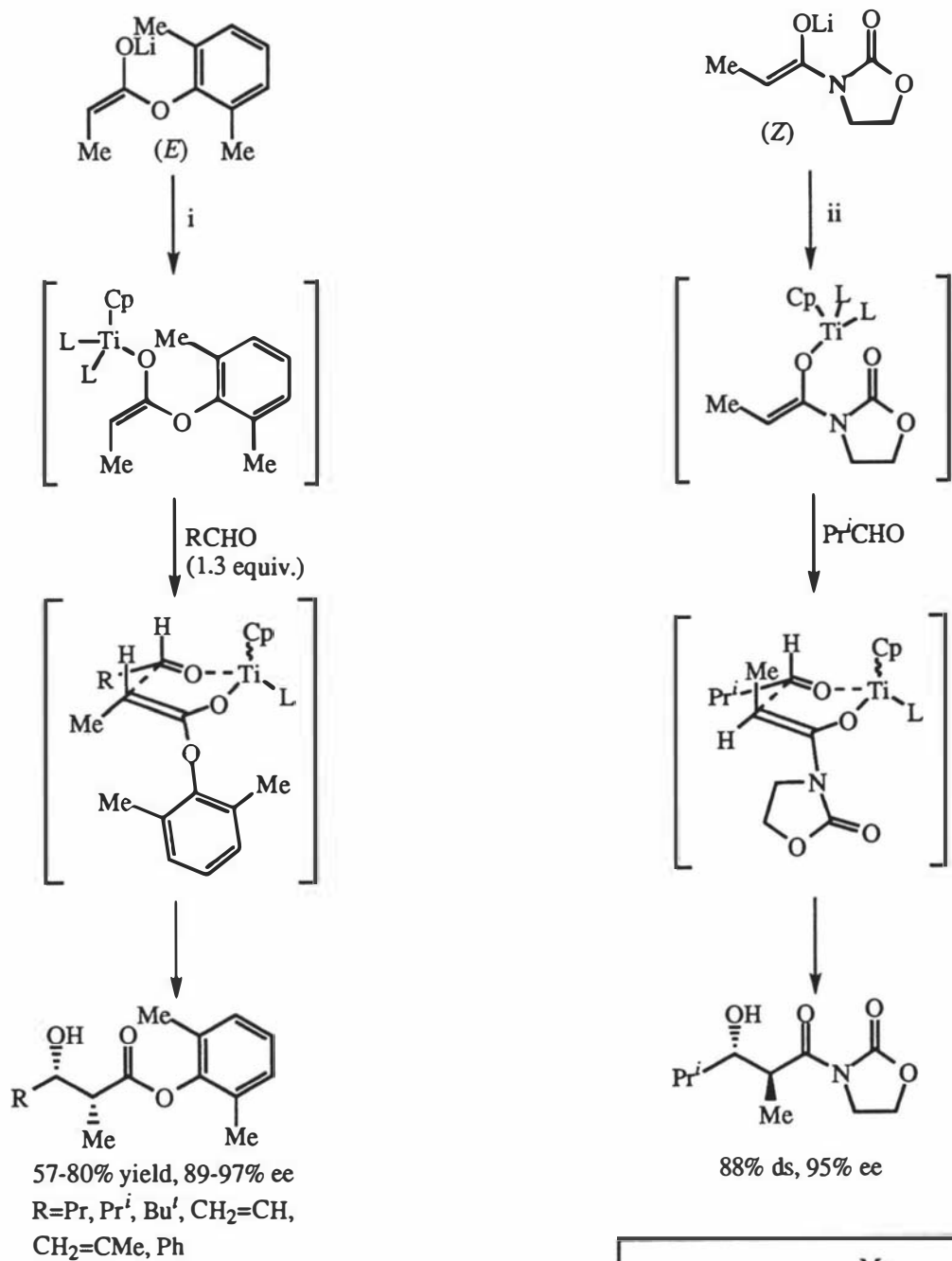
Reagents and Conditions: (i) Et$_2$O, -78°C, TiCpL$_2$Cl
(1.25 equiv.), 24 h; (ii) THF, -78 °C, TiCpL$_2$Cl (1.25
equiv.), 24 h.

Scheme 94
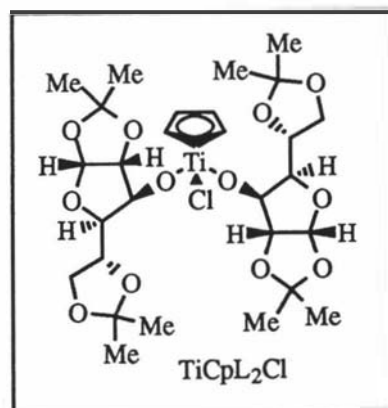
of enolate isomerization[540] (scheme 95). There is evidence to suggest that the energy differences between a chair transition state as represented by the Zimmerman-Traxler model and a boat (or twist-boat) transition state (which also leads to a reversed aldehyde enantiofacial selectivity) are so small as to make minor reaction variables very crucial in determining the final product stereochemistry. In some cases[541,542] the twist-boat transition state has been found to be of lower energy than that of the chair. Conceivably, the boat transition state pathway under certain conditions could be energetically favoured, as in the case of aromatic titanocene (Z)-enolate **481** where a chair transition state competes with the favoured boat transition state (scheme 95).[540]

8-23% yield, 55-99% ee   27-68% yield, 94-98% ee

R=Pr, Pr^i, Bu^t,
CH$_2$=CH, CH$_2$=CMe
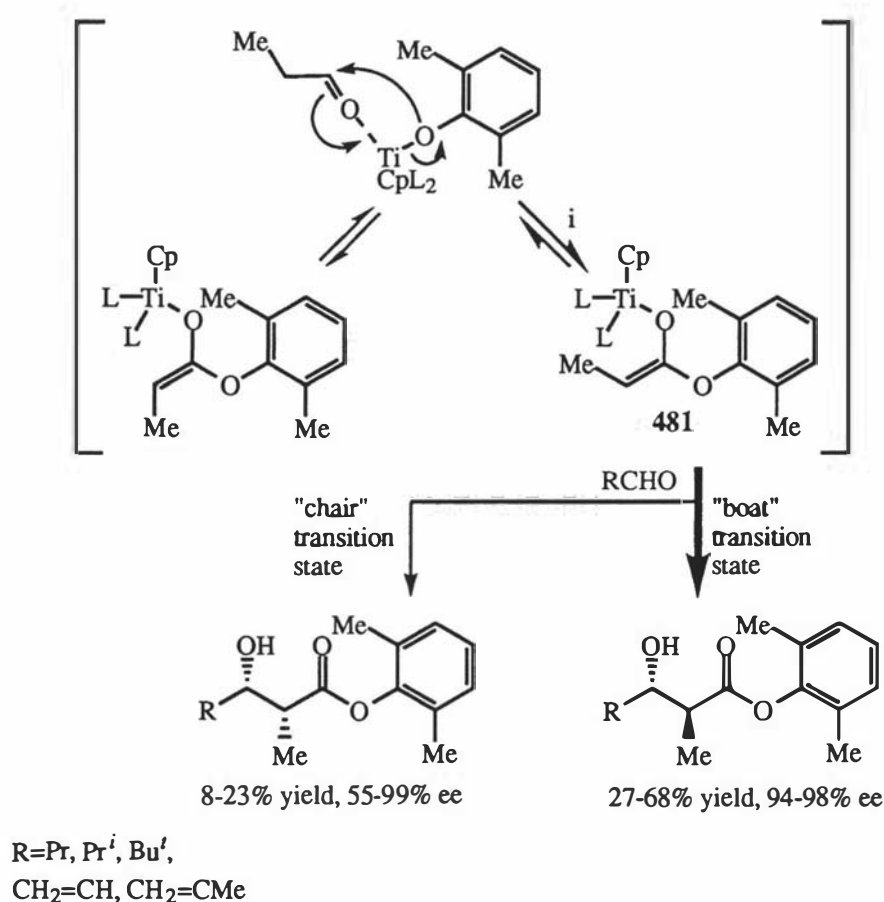
Reagents and Conditions: (i) -78 °C, 24 h, then -25 to -30 °C, 4 h, -78 °C.

Scheme 95

4.4.4 The Anti Aldol Reaction of 435 with 437 using Sn(OTf)$_2$/TMEDA

The Evans' *syn* Aldol Reaction

Generation of the (Z)-enolate from (4S)-oxazolidinone **482** (**443**: X=OBz) using Sn(OTf)$_2$[494] and N-ethylpiperidine, and subsequent reaction with an aldehyde, led to the formation of *syn* aldol products with high selectivity[543] (scheme 96[480,495]). The sense of asymmetric induction in these reactions is directly analogous to the stereochemical outcome of related boron enolates[521] {scheme 92 and figure 43, ML$_2$=Sn(:)OTf}, and stands in contrast to observations which suggest the opposite sense of induction for similar stannous enolates.[544,545]
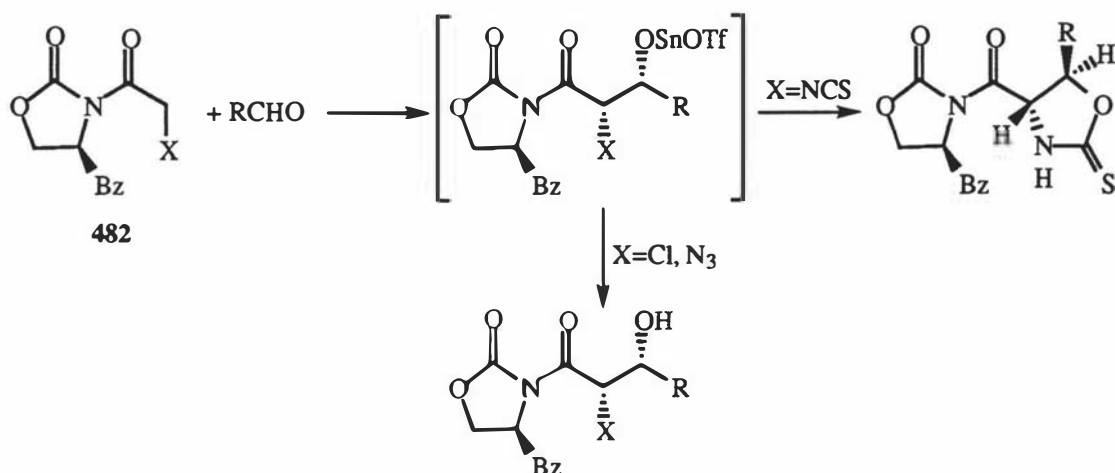
Reagents and Conditions: THF, -78 °C, Sn(OTf)$_2$, N-ethylpiperidine.

Scheme 96

Tin(II) Coordination Patterns

Tin(II) compounds in general have a coordination number of four and a tetrahedral-type geometry. There are atoms at three corners of the tetrahedron and a lone pair of electrons at the fourth.[546,547] A pentagonal bipyramid or complex eight coordinate structure is also possible for tin(II) compounds,[546] the former being portrayed in cyclic transition states involving Sn(II) (figure 46).[548,549]

(reference 548)　　**Figure 46**　　(reference 549)
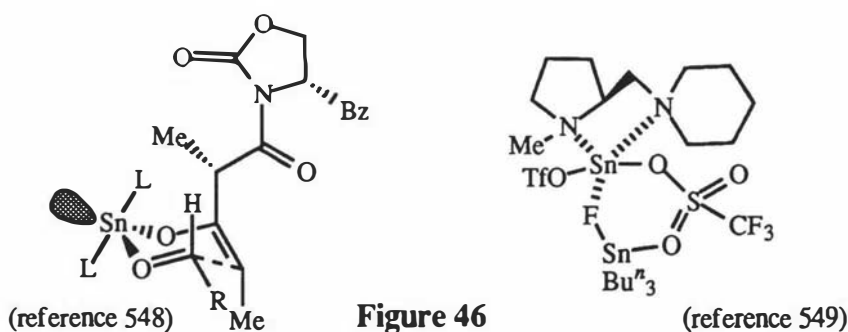
The Formation of **452**

The use of a β-chiral aldehyde combined with a chiral enolate in the present work (double asymmetric induction[550]) was not expected to be problematic, even if the two compounds formed a "mis-matched" pair, as a chiral centre covalently attached to the enolate has more effect than a detached incoming chiral reagent. Also, Evans' reagents have such a high facial preference that they totally overwhelm the modest facial preferences of most chiral aldehydes.[æ]

In the formation of the three aldol products **451-453** (equation 42, page 176), the *anti* product **452** is preferentially formed over the normal Evans' *syn* product **453**. Given the suggestion[519] that there may be a change in the coordination pattern of the tin upon addition of the tetraamine TMEDA to the reaction (minor reaction variables being crucial in determining product stereochemistry[514]), together with known data[546,548,549] on tin(II) coordination patterns *and* work described earlier by several groups,[514,540] it is proposed that the aldol reaction used in the present work proceeds *via* a boat-like transition state **b**[Δ] (figure 47). Transition state **b** becomes more favourable than the chair-like structure **a**[547] (analogous to **a** of figure 44), and thus **452** is the major isomer produced.

Bidentate TMEDA in some fashion favours the transition state where the face of aldehyde **437** approached by the Sn(II) enolate derived from **435** is *si* rather than *re*. Transition state **a** is therefore higher in energy than **b** (figure 47), possibly due in part to unfavourable gauche interaction between OBz and R. *That is, the diastereofacial selectivity of aliphatic aldehyde 437 was reversed by the addition of TMEDA to the aldol reaction under study (equation 42) without the addition of any amine,[514] in a manner analogous to the selectivity change illustrated in scheme 93 (470→479) for the condensation of a C-4 epimeric N-(haloacetyl)-2-oxazolidinone with a sterically bulky aromatic aldehyde.* How this change in selectivity is brought about by TMEDA remains open to interpretation, with further details from Evans *et al.* about this reaction[365,478] having yet to be published.

[æ] A recent study[551] on double stereodifferentiating aldol reactions noted that a β-heteroatom could act as the main stereochemical determinant even if the α-substituent was mis-matched.

[Δ] The exact nature and number of coordinated species about the tin atom is unclear.

453 - major product expected from
normal Evans' *syn* reaction

452 - major product from
Sn(II)/TMEDA reaction (equation 42)
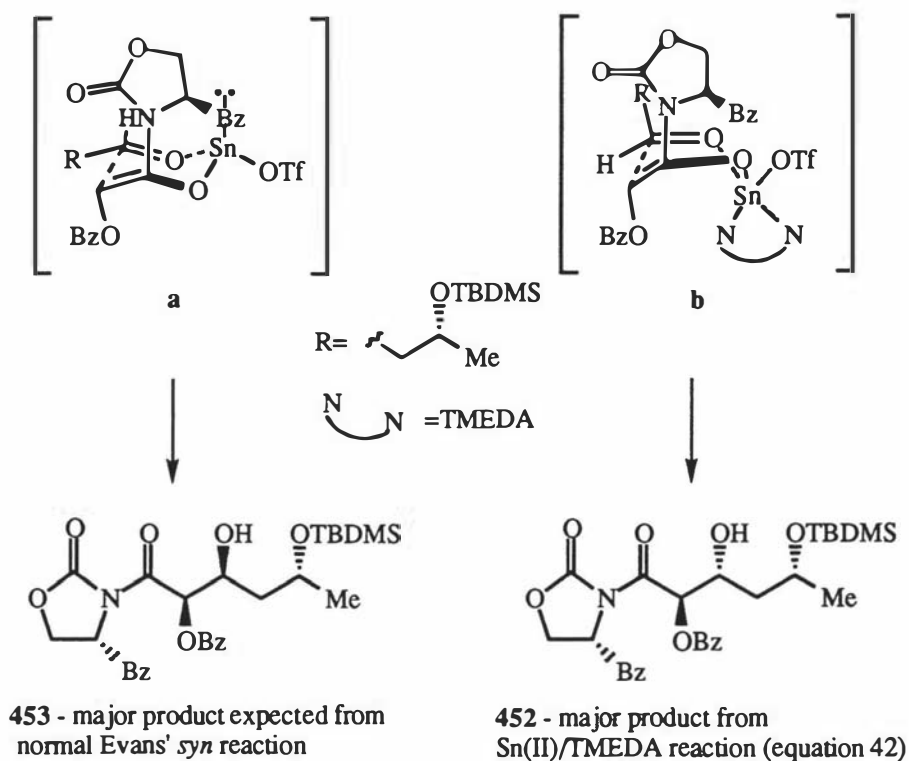
Figure 47

In boat-like transition state **b** (figure 47) the enolate attacks the *si* face of aldehyde **437**. The alternative boat-like transition state **483** {which like **a** (figure 47) leads to *syn* product **453**} is higher in energy than **b** due to unfavourable gauche interaction between OBz and R (and also presumably higher in energy than **a** due to the latters chair conformation).

483

Most other *anti* aldol reactions that have been reported use titanium, zinc or zirconium (*E*)-enolates. Heathcock *et al.*[528,552] proposed an open transition state model to account for results favouring *anti* products using two equivalents of Bu_2BOTf (scheme 97). The excess Bu_2BOTf acted as a Lewis acid and the resulting reactive complex **484** has the aldehyde reacting *via* its *si* face, producing the *anti* isomer. It was suggested[514] however that the role of the open transition state in the case of *N*-(haloacetyl)-oxazolidinones (scheme 93) was minimal. 0.5 equivalents of $SnCl_4$[528] also led to *anti*

products, but the amount of Sn(OTf)$_2$ used in the present study (1.5 equivalents, see page 249) preclude this open transition state as a possibility.

484
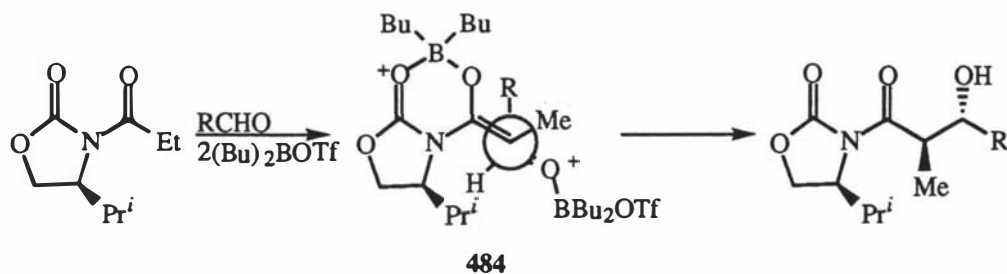
Scheme 97

4.5 Formation of Highly Functionalized Aldehyde 434

4.5.1 Choice of an Hydroxyl Protecting Group for 452

The hydroxyl group in the desired *anti* isomer **452** needed to be protected for conversion to aldehyde **434**, which was required to react with the Grignard reagent derived from bromide **433** (scheme 87). The protecting group chosen needed to be stable to reduction, oxidation[553] and other likely conditions needed to form **431** (scheme 87, page 170). The triethylsilyl group[554,555] was decided upon from consideration of such conditions[556,557] and by noting a very similar triethylsilyl protection/deprotection regime used in the synthesis of an immunosupressant.[520]

Silylation using triethylsilyl trifluoromethanesulphonate and 2,6-lutidine gave **485** cleanly and in high yield (scheme 98). Successful protection of the hydroxyl group was evidenced by the disappearance of the absorbance at 3589-3280 cm^{-1} in the infra-red spectrum. In the ^{1}H nmr spectrum the hydroxyl proton at δ_H 3.54 was replaced by resonances at δ_H 0.58 and 0.92 due to the triethylsilyl protons. 4'-CH$_2$ in **485** was no longer two distinct protons and the 5'-H and 5-H$_2$ resonances coalesced with the signal for 3'-H (3'-H was distinct from the former two groups in **452**). The mass spectrum interestingly exhibited a peak at *m/z* 756, higher than the molecular ion peak at *m/z* 642. This mass corresponded to *bis*-TES olefin **486**, which was proposed to have formed under the energetic (EI) conditions of the spectrometer.

486
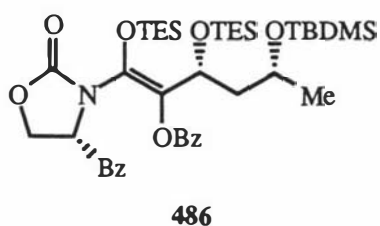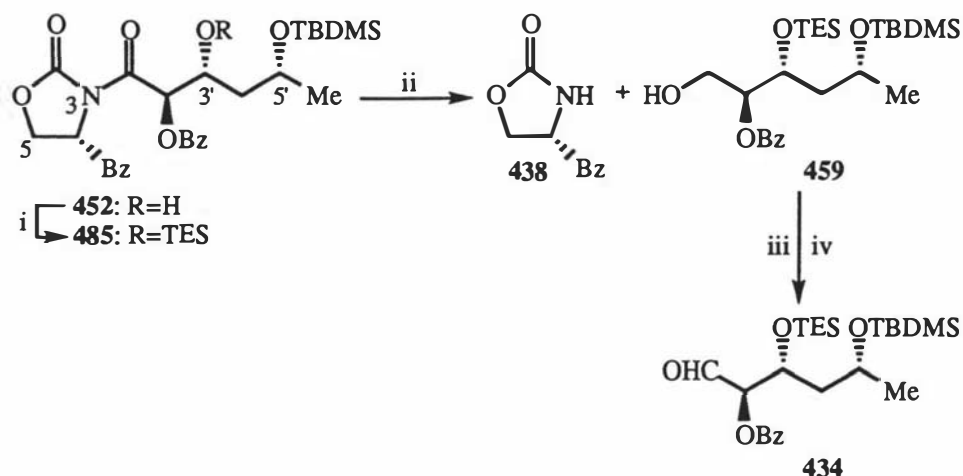
Reagents and Conditions: (i) CH$_2$Cl$_2$, 0°C, N$_2$, TESOTf, 2,6-lutidine, RT, 88%; (ii) THF, 0°C, N$_2$, LiBH$_4$, RT, **459** 82% and **438** 71%; (iii) CH$_2$Cl$_2$, NaOAc, 4A sieves, PCC, N$_2$, RT, 84%; (iv) CH$_2$Cl$_2$, NMO, 4A sieves, 0°C, N$_2$, then TPAP (cat.), RT, 81%.

Scheme 98

4.5.2 Reductive Removal of the Chiral Auxiliary

The removal of the chiral auxiliary from aldol products (imides) can lead to an acid, alcohol or amide, depending on what transformation is to be carried out subsequently and the requirements of the substrate. In our case it was thought simplest to reduce **485** to an alcohol then oxidize to the desired aldehyde **434**.

Treatment of **485** with lithium borohydride in tetrahydrofuran[365,512,522] gave alcohol **459** and auxiliary **438** in 82 and 71% yield respectively (scheme 98). The optical rotation ($[\alpha]_D$) displayed by the reclaimed auxiliary was unchanged and so it was able to be recycled. Amide **487**, which could be formed by *endocyclic* carbonyl attack[†] was not evident in this reduction even though other similarly crowded imides were not removed as cleanly.[560,562] An "interplay of electronic and steric factors" dictates the degree of carbonyl selectivity.[558]

487
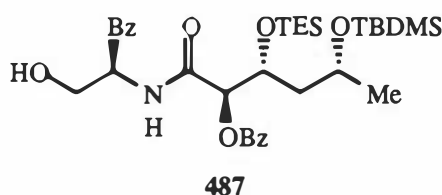
[†] Several reagents/methods are available to aid removal of auxiliaries from imides where the reactivity of the exocyclic carbonyl group has been suppressed: (LiOBz),[522,558] (LiO$_2$H),[559] (LiBH$_4$/H$_2$O)[560] and (BzSLi).[561]

The appearance of an hydroxyl stretch at 3659-3167 cm^{-1} in the infra-red spectrum and a resonance at δ_H 2.51-2.69 in the ^{1}H nmr spectrum, together with an ion at m/z 469 in the mass spectrum all supported the successful reductive removal of the chiral auxiliary. All signals in both ^{1}H and ^{13}C nmr spectra previously due to the auxiliary were absent. C*H*OBz moved upfield {δ_H 5.40 (**485**) to 3.44-3.50} in the reduction product **459** since it was now alpha to a methylene rather than a carbonyl group. A broad singlet at δ_H 3.80 was assigned to the C*H$_2$*OH group. The number of signals in the aromatic region (δ_C 127-139) of the ^{13}C nmr spectrum was halved, and there were no peaks past δ_C 138.4, confirming that all carbonyl groups had been removed or reduced.

The stability of **459** to prolonged storage was not great, with a sample that had been kept at approximately 2°C for six weeks showing signs of isomerization. The ^{1}H nmr spectrum of this stored material had dual signals for the methyl and the SiMe$_2$ resonances, the C*H*OBz multiplet and OC*H$_2$*Ph doublets were each more complex and the C*H*OTES multiplet was broader. The ^{13}C nmr spectrum displayed three "duplicated" signals (C-2, C-4 and C-5), and a spurious peak at δ_C 15.3. Thus alcohol **459** was prepared within two weeks of being required for use in the subsequent oxidation.

4.5.3 Oxidation Methods Forming 434

Oxidation of **459** to the corresponding aldehyde **434** (scheme 98) was carried out using TPAP (refer sections 2.4.3 and 4.2.3) because of its simplicity, speed and the fact that "oxidation of substrates with labile α-centres proceeds without racemization".[358] This last point was highlighted in the synthesis of calyculin A[365] where aldehyde **488** was formed by Swern oxidation of **489** (equation 44) with approximately 30% racemization {the substitution of diisopropylethylamine (Hunig's base) for triethylamine circumventing the problem in this case}.
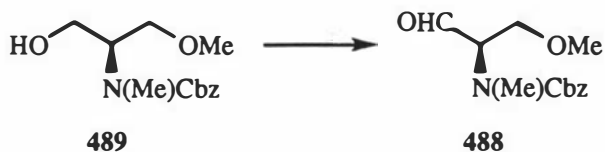
Reagents and Conditions: (COCl)$_2$, DMSO, Pr$^i_2$NEt, -78 to -50°C.

Equation 44

489 was "racemization prone",[365] and as **434** also isomerized over time (refer footnote¶, page 175) it was not stockpiled but made as demand required. PCC was also tried as an alternative method of oxidation since no epimerization at C-3 of pyranoside **490** occurred[355] when using this reagent (equation 45). The optical rotations of the

aldehyde samples (**434**) prepared by these two reagents were compared and it was found that the material obtained using TPAP had a consistently higher value ($[\alpha]_D$=+14.64) than the material obtained using PCC ($[\alpha]_D$=+12.35).
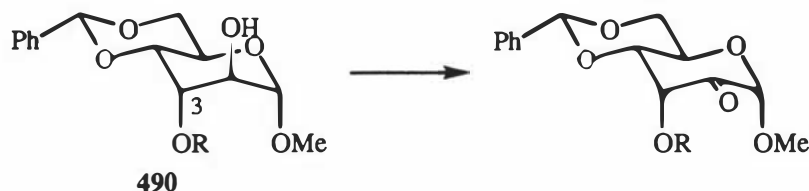
Reagents and Conditions: PCC, CH$_2$Cl$_2$, RT.

Equation 45

434 was identified by the carbonyl absorbance at 1736 cm^{-1} and the aldehydic C-H stretches at 2737 and 2703 cm^{-1} in the IR spectrum. The aldehyde proton resonated in the ^{1}H nmr spectrum as a doublet at δ_H 9.69, $J_{1,2}$ 2.6 Hz, and 2-H (C*H*OBz) shifted from δ_H 3.44-3.50 (**459**) to δ_H 3.73 (**434**). The ^{13}C nmr spectrum exhibited a resonance at δ_C 204.0, consistent with formation of an aliphatic aldehyde.

*4.5.4   Mosher Ester Analysis of Aldehyde **434***

The extent of racemization/epimerization occurring in an oxidation reaction can be determined by reduction of the carbonyl compound (aldehyde) to an alcohol followed by Mosher[563] esterification. This method has been used successfully for both aldehyde **488**[365] (equation 44) and **491**,[564] and so was applied to **434**. Lithium borohydride reduction (LiBH$_4$, THF, 0°C) followed by esterification {(R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, CCl$_4$, Et$_3$N} gave only a 46% yield of the ester and 10% recovered alcohol **459**. As the technique relies on *all* the substrate reacting the procedure was tried again with less solvent but still the conversion was problematic and so this method was not pursued. Other methods[565-567] to effect esterification could be attempted in the future as required.

491
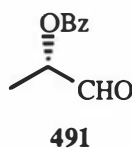
4.6 The Grignard Addition of Aldehyde 434 and Bromide 433

4.6.1 Formation of 433

The synthesis of bromide **433**, as required for the Grignard coupling with **434** (scheme 87, page 170), followed a similar reaction sequence as used for related naphthoquinones[568] and daunomycinone precursors,[569] however certain steps {(i), (iii) and (v), scheme 99} employed different reagents. The Baeyer-Villiger reaction in particular was carried out using a selenium dioxide/hydrogen peroxide system as this was found to be (overall) higher yielding than *meta*-chloroperbenzoic acid[568,569] (the reported[568] yield of 77% for **492** from **493** was not able to be matched, with 43% being the best yield obtained with MCPBA). Hydrolysis of the resulting formate (acetone/dil. HCl) was much cleaner using this SeO$_2$ method and the product (**492**) was collected by filtration rather than purified by flash chromatography.

Bromination was complicated, with the amount of bromine needing to be strictly controlled in order that poly bromination did not occur. Also, the starting material **492** had to be pure for the reaction to be successful (both literature procedures[568,569] quoted greater than 90% crude yield for this step). Methylation of **494** using Me$_2$SO$_4$/KOH/aq. DMSO gave **433**, and was higher yielding than the one literature method which used THF/NaH/MeI.[569] The spectroscopic data for trimethoxybromide **433** agreed with the literature data,[569] thus confirming the regiochemistry of the bromination.
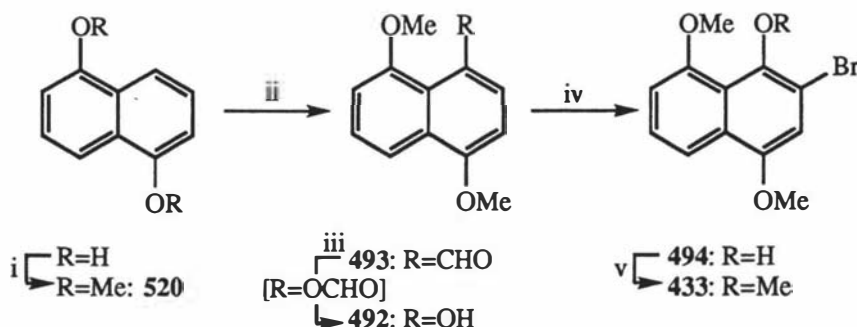
Reagents and Conditions: (i) THF/DMSO, 0 °C, Me$_2$SO$_4$, then aq. KOH, 0°C to RT, 81%; (ii) DMF/PhMe, 0 °C, N$_2$, POCl$_3$, 0°C to reflux, 87%; (iii) a: CH$_2$Cl$_2$, SeO$_2$, 30% H$_2$O$_2$, (Bu^n)$_4$NHSO$_4$ (cat.), RT; b: Me$_2$CO, 10% HCl, reflux, 80% over two steps; (iv) CCl$_4$, Br$_2$, RT, 72%; (v) THF/DMSO, 0 °C, Me$_2$SO$_4$, then aq. KOH, 0°C to RT, 68%.

Scheme 99

4.6.2   Developing Grignard Methodology using Heptanal

There was precedent for the proposed coupling of aldehyde **434** and bromide **433** using a Grignard reagent,[570] in that regioisomeric bromide **495** was coupled to oxazole **496** (equation 46) using magnesium in tetrahydrofuran.[571] However for the most part, butyllithiums were used to metallate similar bromides for subsequent coupling to carbonyl compounds (table 10).[283,277,572-574] In order to establish suitable reaction conditions in the present work, heptanal was initially studied instead of the valuable chiral aldehyde **434**.
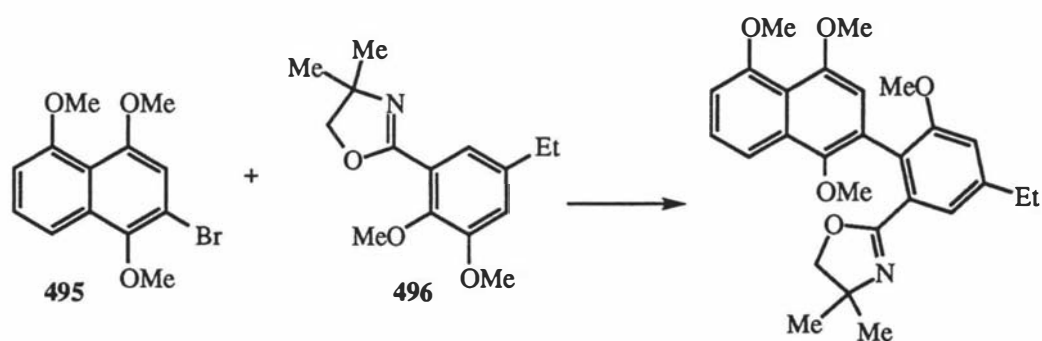
Reagents and Conditions: THF, **495**, Mg, I_2, reflux, then **496**.

Equation 46

Initial attempts to synthesize alcohol **497**, using clean magnesium turnings in tetrahydrofuran to generate the metallated trimethoxynaphthalene **498**[575] (scheme 100) were generally unsuccessful, the more polar product obtained after addition of heptanal was in fact 1,4,5-trimethoxynaphthalene **499**[576-578] {(i), scheme 100}. This product arises *via* proton abstraction by **498** after its formation, despite examples where refluxing[571] (equation 46) and long reaction times[574] (equation 47) produced carbanions that subsequently reacted successfully. In subsequent experiments the time **498** was left to form was decreased from approximately 1 to 0.4 h, the temperature once the reaction had been initiated (iodine, heat) was kept strictly at or below room temperature, and activated magnesium[579] was used to speed up anion formation. However these measures still failed to produce any useful amount of the desired alcohol **497**.[a]

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[a] **497** was identified by its relatively simple nmr spectra, strong hydroxyl stretch in the infra-red spectrum and correct molecular weight by mass spectrometry. **499** was identified by comparison with published data.[578]

198
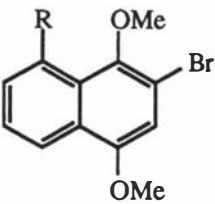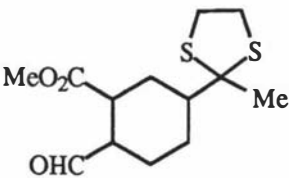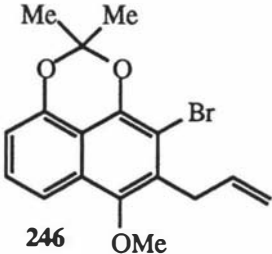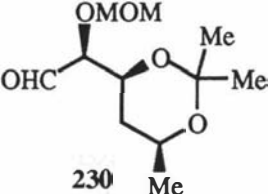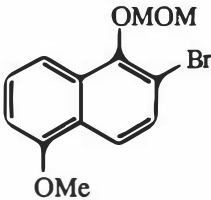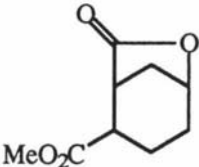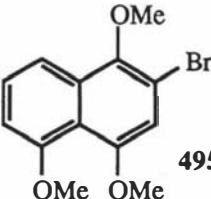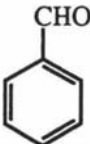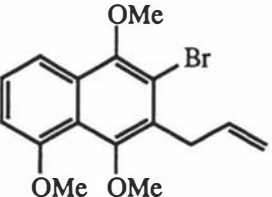
entry	bromide	carbonyl compound	reaction conditions
1	R, OMe, Br, OMe R=H, OMe (433)	MeO₂C, S, S, Me, OHC	Et₂O, N₂, -78°C, BuⁿLi (1.1 equiv.), then aldehyde -78°C to RT; reference 572.
2	Me, Me, O, O, Br, 246, OMe	OMOM, Me, OHC, O, Me, O, 230, Me	THF, -78°C, BuᵗLi (1.1 equiv.); reference 283.
3	OMOM, Br, OMe	O, O, MeO₂C	DME, -25°C, BuᵗLi (2.0 equiv.); reference 573
4	OMe, Br, 495, OMe, OMe	CHO	THF, -78°C, BuᵗLi (2.1 equiv.); reference 574
5	OMe, Br, OMe, OMe	MeCHO	THF, -78°C, BuⁿLi (1.0 equiv.); reference 277

Table 10

Reagents and Conditions: (i) THF, Mg, RT, N$_2$; (ii) THF, -78 °C, N$_2$, Bu^{n}Li (1.0 equiv.),
497 79%, **499** 8%.

Scheme 100

Reagents and Conditions: THF, Mg, RT, 2 h, then silane, reflux.

Equation 47

Thus it appeared that carbanion **498** formed slowly, but that once formed it was basic enough to abstract a proton from the solvent before the carbonyl compound was added. Difficulties such as this had been noted with regioisomeric bromide **495** (equation 46, page 198), its reaction with magnesium proceeding slowly even at elevated temperatures.[574] Deuterium oxide quenching studies with the Grignard reagent of **495** showed that protonation was occurring either from traces of water in the solvent or the solvent (THF) itself. From this result it was observed that "while it is known that strongly basic anions such as *n*-butyllithium or trityllithium will deprotonate tetrahydrofuran, it is surprising that the Grignard reagent of **495** is basic enough to do so at temperatures near and above 0°C".[574]

Due to the difficulty in determining *when* the Grignard reagent had completely formed, and so prevent either or both **499** and **433** being isolated upon subsequent work up, the procedure was modified and the carbanion generated using *n*-butyllithium[580] at low temperature {(ii), scheme 100}. Thus it was hoped that formation of **500** could be

200

achieved by rapid halogen-metal exchange, and the aldehyde then added quickly {more in line with reference 572 (entry 1, table 10)}. Also, at this much lower temperature the anion **500** would be less reactive and so less prone to abstract a hydrogen from the solvent (forming **499**). The results of varying the time (t) between alkyl lithium and heptanal addition are given in table 11 and illustrated in graph 1.

Time (s)	% 499	% 497
43	12	64
65	10	68
85	8	79
105	30	67
120	30	62
135	25	45
158	33	50
180	58	24

(% yield of **497** is *not* based on the amount of **499** recovered from the reaction)

Table 11
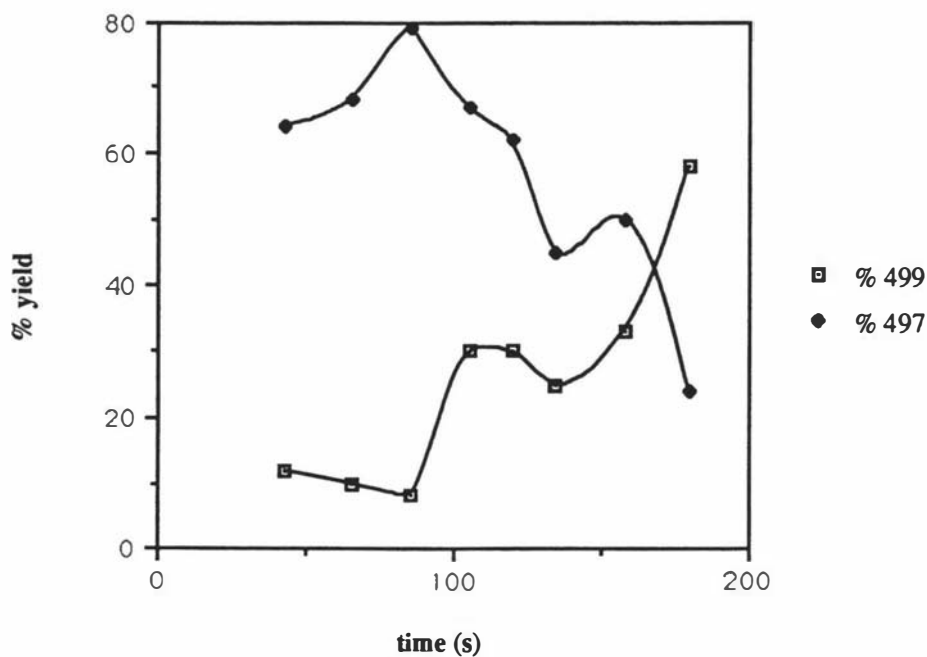
Time Elapsed between addition of *n*-BuLi to **433** and addition of heptanal *vs* % yield of **497,499**

Graph 1

The initial trials at about t=180 seconds gave predominantly trimethoxynaphthalene **499**, further experiments at shorter time intervals giving varying amounts of bromide **433**, alcohol **497** and **499**. The fact that no bromide was detected/isolated after a short time interval (t=43 s) indicated metallation was near instantaneous. The rise in percentage yield of **499** from approximately t=85 seconds showed the carbanion present to be increasingly protonated, even at the low (-78°C) temperature used throughout the reaction. Thus it appeared that the optimum time at which to add the carbonyl compound after generation of the aryllithium was 85 seconds.

4.6.3 Attempted Coupling of Aldehyde **434** and Bromide **433**

Armed with this knowledge (*vide supra*), the actual coupling of **433** with functionalized aldehyde **434** was attempted. Using the optimized conditions developed with heptanal (**433**, THF, -78°C, *n*-BuLi, 85 s, then **434**) gave naphthalene **499** as the major product, together with recovered aldehyde **434** and trace amounts of the diastereomeric alcohols **501** and **502** resulting from (excess) butyllithium attack on **434**.
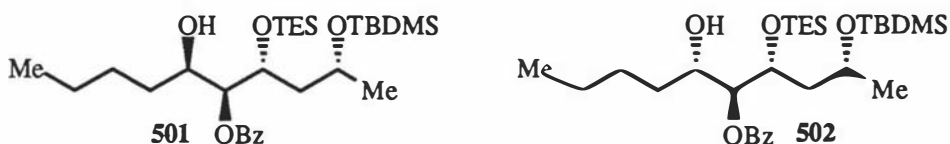
These two alcohols both exhibited a molecular ion at m/z 525 (MH$^+$) in the mass spectra, and the infra-red spectra showed hydroxyl absorbances at 3225-3640 cm^{-1}. This confirmed the addition of a butyl group to aldehyde **434**. The ^{1}H nmr spectra displayed several differences compared to **434**: (i) the OCH_2Ph protons were shifted further apart (by approximately 0.2 ppm), (ii) CHOTES was split into two essentially defined multiplets, and (iii) CHOBz now resonated as a double doublet, J 7.1, 2.5 Hz, as a consequence of the CHOTES *and* CHOH proton.

In only one attempt was there any evidence for formation of the desired compounds **503** and **504**. In this reaction (THF, -78°C, *n*-BuLi, 85 s), a very small amount of material was isolated which ran just above **499** (TLC). Mass spectrometry of this new material gave a molecular ion at m/z 684.3869 which was correct for $C_{38}H_{60}O_7Si_2$ (684.3878). The ^{1}H nmr spectrum exhibited three methoxy peaks, together with resonances for OCH_2Ph and CHOSi. Oxidation of this product using manganese dioxide gave a less polar material that exhibited an m/z peak at 682.3711, consistent with oxidation of an alcohol (**503,504**) to a ketone (**505**). Thus, whilst the oxidation of **503,504** was not problematic, unfortunately the anion coupling of aldehyde **434** was far from satisfactory.

OMe OMe OH OTES OTBDMS

OBz

OMe **503**

OMe OMe OH OTES OTBDMS

OBz

OMe **504**

OMe OMe O OTES OTBDMS

OBz

OMe **505**
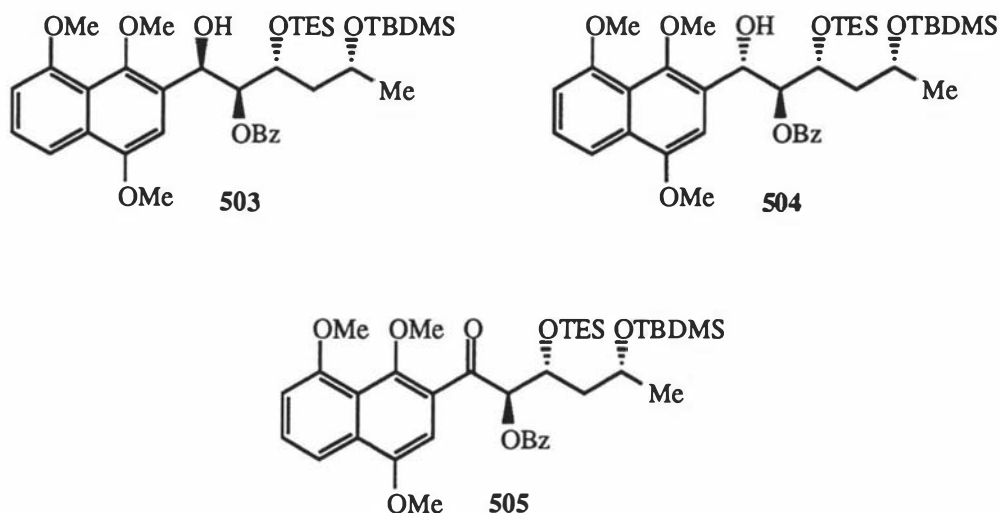
In order to soften the anion **500** (scheme 100, page 200) and so avoid protonation (**499**) by solvent molecules *or* aldehyde **434**, two approaches were tried. The first approach involved transmetallation of the organolithium **500** with magnesium,[581] by the addition of magnesium bromide[582] to **500** at t=60 s, followed by **434** at t=85 s. It was hoped that metal exchange would allow anion **498** to form rapidly and then react with **434**, before gaining a proton from the reaction. Again, however, the predominant compounds upon work up were **434** and **499**, with a trace amount of bromide **433**. A similar attempt with **495** and aldehyde **506** (refer equation 47, page 200) failed to result in alkylation.

The lack of reactivity at the carbonyl group of **434** was postulated to be due to steric constraints about this centre preventing approach of the metallated aromatic (**498** or **500**) such that proton abstraction was favoured. Also, the presence of three electron donating methoxy substituents about the naphthalene ring was thought to increase the basicity of the aryl anions. In an effort to make the carbonyl group of **434** more electrophilic and so attractive to **500**, and also "soften" **500** to reduce its basicity, cerium chloride was employed.[583,584]

Organocerium reagents have been noted for preventing unwanted side reactions[585] in coupling reactions by their electrophilic nature and it was hoped such assistance would be rendered here. However, only trace amounts of material in addition to **499** were isolated, one of the additional products by mass spectrometry exhibiting a molecular ion consistent with **507** (compare **486**, page 193).

OTES OTBDMS

OHC

OBz

Me

507
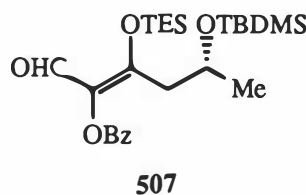
4.7 Future Work

With the failure of a lithium, magnesium or cerium-based anion approach to **431** and **432** (scheme 87, page 170), other options for the future synthesis of these compounds are suggested below.

4.7.1 Transmetallation with Differing Metals

Other metals besides magnesium and cerium could be used to effect transmetallation of anion **500** in an effort to encourage reaction with **434**. For example, the use of copper[586] and tin[587] could be explored. In addition, samarium iodide[588] could be used to couple **433** and **434** in a radical "samarium Grignard reaction". Changing the solvent to those that would coordinate less with metals (toluene, hexane) may reduce the reactivity of **500**, however solubility could be a problem in these cases.

4.7.2 Alternatives to Aldehyde 434

A Weinreb amide[589-592] **508** (scheme 101) could be formed from imide **485** (or **452**, transamination being "critically assisted by the free hydroxyl group"[365]), as opposed to reduction of **485** to alcohol **459** and then oxidation to **434** (scheme 98, page 194). The coupling of the anion of bromide **433** with **508** may be easier than with an aldehyde moiety {a similarly hindered amide **509** reacted with vinyl bromide **510** (equation 48)[593,594]}, and the resulting product **511** (scheme 101) does not require an oxidation step at this point (as does **431**). Use of a Weinreb amide would also reduce the acidity of the methine proton alpha to the carbonyl group, which may be the source of protonation of the aryl anions **498** and **500** (or the aldehyde proton itself).

Reagents and Conditions: (i) MeONHMe.HCl, CH$_2$Cl$_2$, 0°C, AlMe$_3$ (2.0 M in PhMe), RT to -10°C, **485** or **452**; (ii) THF, -78°C, Bu^{n}Li.
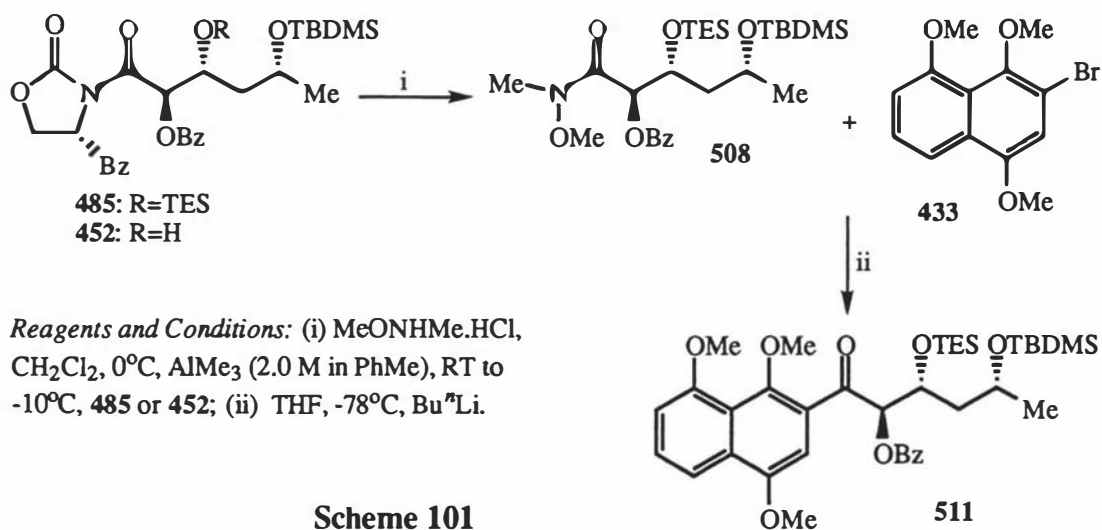
Scheme 101
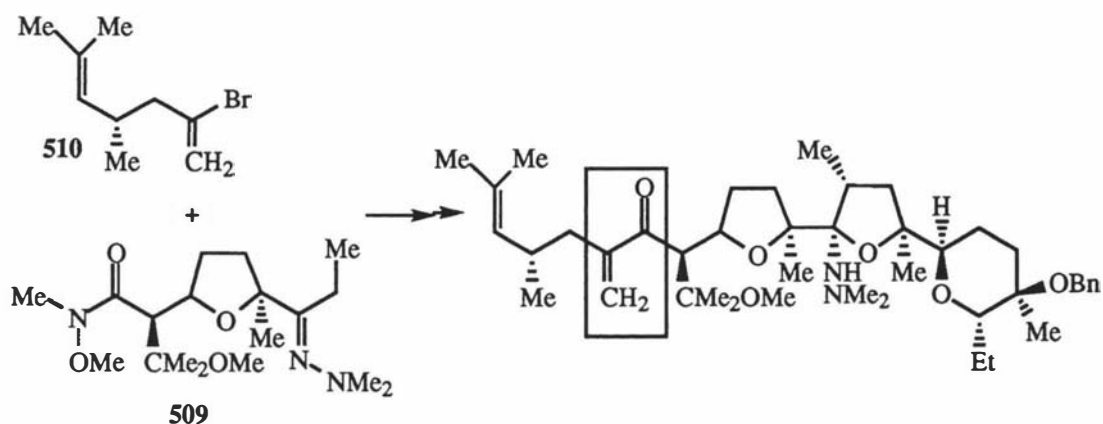
Reagents and Conditions: Bu^{t}Li, Et$_2$O, -78 to 0°C.

Equation 48

4.7.3 Asymmetric Dihydroxylation

An alternative route to ketone **432** (scheme 87) can been proposed using the asymmetric dihydroxylation procedure developed by Sharpless.[376,393] Treatment of *cis* keto-olefin **512** (scheme 102) with AD-mix α {(DHQ)$_2$-PHAL **513**[460]} buffered with sodium bicarbonate to avoid epimerization[595] should afford diol **514** according to the mnemonic model proposed (figure 48).[375] Using this approach the spiro ring substituents of griseusin A **88** are already attached to the naphthalene moiety and hence the problems experienced in attempting to add the oxygenated functionality later (chapter 3), or in the coupling of aryl anions **498,500** with aldehyde **434** (section 4.6.3, page 202) are circumvented.

Reagents and Conditions: (i) AD-mix α {K$_2$OsO$_2$(OH)$_4$, (DHQ)$_2$-PHAL **513** , K$_3$Fe(CN)$_6$, K$_2$CO$_3$}, H$_2$NSO$_2$Me, NaHCO$_3$, Bu^{t}OH/H$_2$O.

Scheme 102

327: R=H, C-5'=(R,S)
512: R=OMe, C-5'=(R)

Figure 48

(DHQ)₂PHAL **513**

(hydroquinine 1,4-phthalazinediyl diether)

DHQ-IND **515**

{(9-O-indolinylcarbamoyl)dihydroquinine}
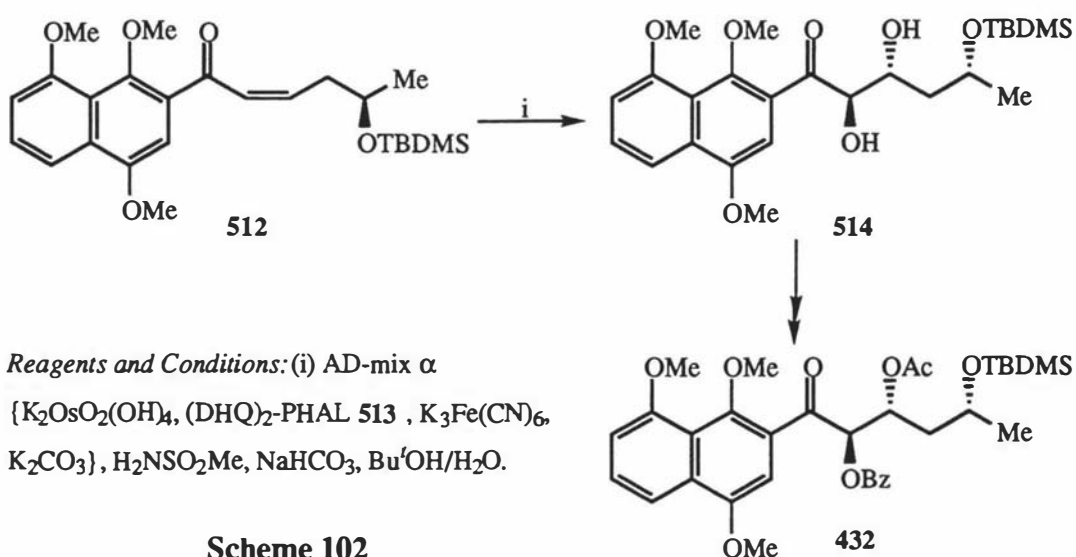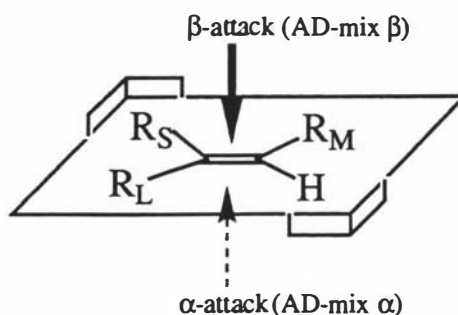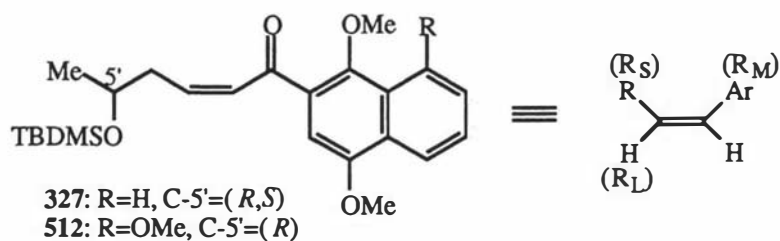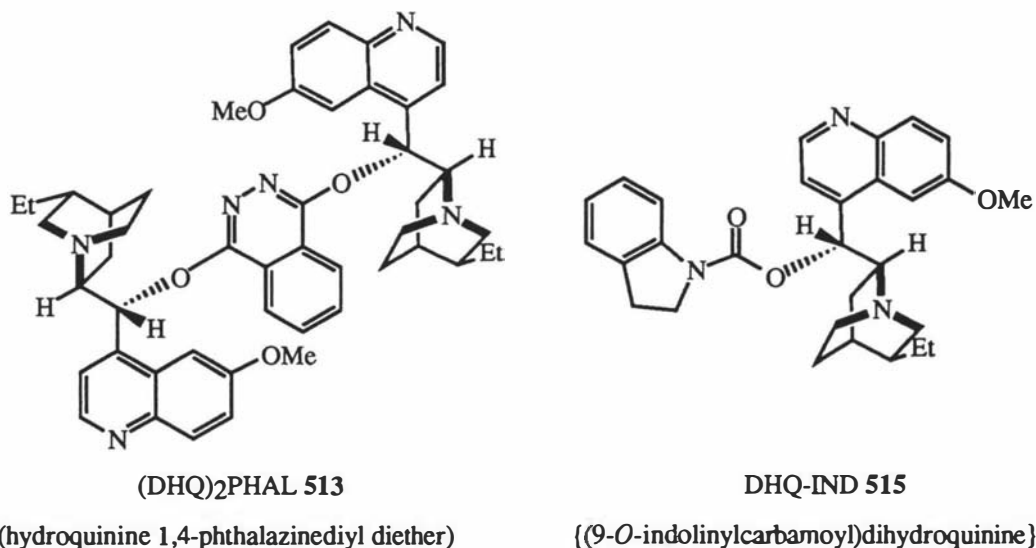
Carbamate ligand **515** has proven[375] to be the best ligand for *cis*-disubstituted olefins, with the predominant enantiomer obtained having an absolute configuration consistent with figure 48. Aliphatic functionalized alkenes however still give ee values somewhat below their aromatic counterparts. The phthalazine ligand has the convenience of being incorporated into a ready made mixture (AD-mix) with oxidant and catalyst, but the indolinyl ligand can be used with components added separately to the reaction.

The appropriate chirality at C-5' in **512** could be introduced following the procedure for (*S*)-acetylene **516**[596,597] (scheme 103), formed from chiral propylene oxide **517**.[598] Coupling of aldehyde **518** and (*R*)-**516** (**518** formed from **433** by anion reaction

with DMF *or* Duff formylation[599] of **492**), in a manner similar to **216** and **215** (refer scheme 29, page 71), would give after oxidation **512**. Dihydroxylation and selective protection[600] of **512** would then afford **432** (scheme 102).

Reagents and Conditions: (i) HC≡CLi.H$_2$N(CH$_2$)$_2$NH$_2$, NH$_3$;
(ii) TBDMSCl, DMF, imid.
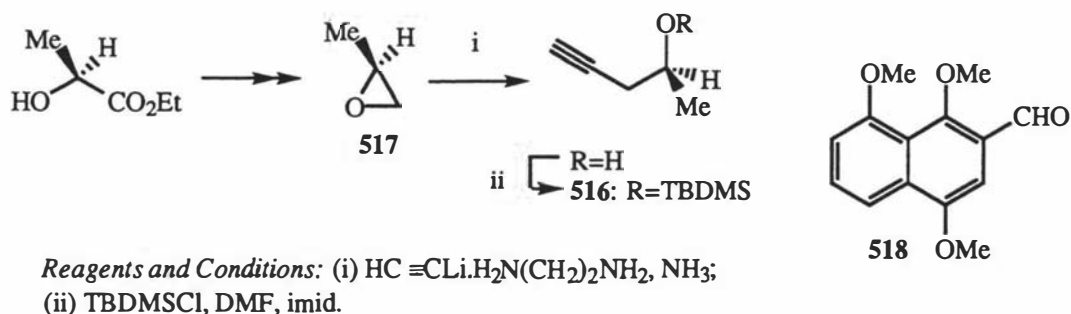
Scheme 103

4.7.4 Protecting Group Changes

A di-*tert*-butylsilylene group[601] could be used once **452** was formed to protect both C-2' and C-3' (as **519**) through the proposed synthesis (scheme 87 *or* 101) to avoid excessive protecting group manipulations. Also, the transformation **514**→→**432** (scheme 102) requires selective protection of two secondary hydroxyl groups.
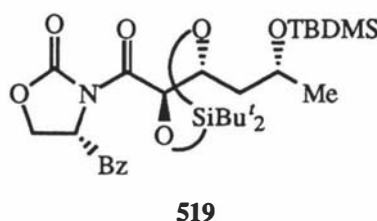
519

4.7.5 Making the Michael Addition Enantioselective

If the second Michael addition that results in the furofuran ring system does not produce the desired isomer starting from quinone **430** (scheme 87, page 170) then a chiral additive such as *Cinchona* alkaloids[602] (refer page 121) could be used to obtain the required enantioselectivity.

CHAPTER 5

Experimental

5.1 General Details

All new (that is, unlisted or inadequately characterized in Chemical Abstracts) compounds have been written in *italics* where first reported with complete spectral data.

Melting points were determined using a Kofler hot stage apparatus and are uncorrected.

Elemental analyses were carried out by the microanalytical laboratory, University of Otago, Dunedin.

Optical rotations were measured on an Optical Activity AA-100 or a Perkin Elmer 241 polarimeter in the solvent and at the temperature and concentration (g/100 cm^3) indicated. Specific rotations are given in 10^{-1}.deg.cm^2.g^{-1}. Readings were taken using the 589.3 nm sodium line and a 1 dm cell.

Infra-red spectra were recorded using a Pye Unicam SP3-200S, BIO-RAD FTS-7, BIO-RAD FTS 40V or a Perkin Elmer 1600 Fourier Transform infra-red spectrophotometer. Compounds were prepared as nujol mulls, thin films or solutions (in the solvent specified) between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad.

^{1}H nuclear magnetic resonance spectra were recorded on a Bruker AC 200 (200 MHz), JEOL GX270 (270 MHz) or Bruker AM 400 (400 MHz) spectrometer at ambient temperature. Data is expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br.s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, dt = doublet of triplets, q = quartet, qdd = quartet double doublet, sextet or m = multiplet), coupling constant (*J* Hz) and assignment.

^{13}C nuclear magnetic resonance spectra were recorded on a Bruker AC 200 (50.3 MHz), JEOL GX270 (67.8 MHz) or Bruker AM 400 (100.6 MHz) spectrometer at

ambient temperature with complete proton decoupling. Data is expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT135 and DEPT90 experiments[603]) and assignment. Where an inseparable mixture of stereoisomers was obtained, resonances for a given proton or carbon are grouped together when a definitive assignment of the individual peaks to a particular stereoisomer could not be made.

Low resolution mass spectra were recorded on a VG70-250S or a VG70-SE double focusing magnetic sector mass spectrometer operating with an ionization potential of 70eV (EI, CI) or 20keV (LSIMS). High resolution mass spectra were recorded at a nominal resolution of 5000 or 10,000 as appropriate. Major fragmentations are given as percentages relative to the base peak intensity and assigned where possible. Ionization methods employed were (i) electron impact (EI), (ii) liquid secondary ion mass spectrometry (LSIMS) using cesium as secondary ion, and (iii) chemical ionization (CI) with ammonia as reagent gas. Matrices used for LSIMS sample preparation were 4-nitrobenzyl alcohol (NBA) and a 5:1 mix (v/v) of dithiothreitol:dithioerythritol (DTDE).

Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualized by ultra-violet fluorescence or by staining with iodine, ninhydrin in ethanol or vanillin in methanolic sulphuric acid.

Flash chromatography was performed according to the procedure of Still *et al.*[361] using Merck Kieselgel 60 or Riedel-de Haen Kieselgel S silica gel (both 230-400 mesh) with the indicated solvents.

Concentration "in vacuo" or "at reduced pressure" refers to concentration using a rotary evaporator connected to a water aspirator. Removal of residual solvent or volatile reagents where desired was achieved by evacuation (0.1-0.01 mm Hg) with a high stage oil vacuum pump.

1,4-Naphthoquinone, (±)-pent-4-yn-2-ol, 2-(trimethylsilyloxy)furan **189**, 1,5-dihydroxynaphthalene, ethyl (*R*)-(-)-3-hydroxybutyrate **446** and (*R*)-phenyl alanine **440** were purchased from Aldrich Chemical Company and purified as necessary. *n*-Butyllithium was obtained as a solution in hexanes (nominal concentration 1.6 or 2.5 mol dm^{-3}) and the concentration determined before use by titration according to the method of Lipton *et al.*[604] Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego.[605] Ether refers to diethyl ether, hexane refers to *n*-hexane (b.p. 65-

69°C), dioxane refers to 1,4-dioxane and brine refers to saturated aqueous sodium chloride solution.

Unless otherwise noted, low temperature reactions were carried out in oven dried glassware under a dry inert atmosphere. Reactions monitored by TLC and not given a completion time were generally finished in 0.5-4 h. Temperatures from -78°C to -20°C were obtained by either a dry ice/acetone or liquid nitrogen/acetone bath. Room temperature refers to approximately 20°C.

The format adopted in presenting experimental data (section 5.2) is that recommended by the Journal of the Chemical Society, Perkin Transactions 1, in its "Instructions for Authors (1995)": *J. Chem. Soc., Perkin Trans. 1,* 1995, vii.

5.2 Compound Data

1,4-Dimethoxy-2-naphthalenecarboxaldehyde **216**

The title compound **216** (3.551 g, 55% over two steps) was prepared from 1,4-dimethoxynaphthalene (4.806 g, 30.1 mmol) according to the procedure of Uno[260] as pale yellow needles, m.p. 118.0-119.0°C (lit.,[260] m.p. 118-119°C). The ^{1}H nmr spectrum was in agreement with that reported in the literature.[260]

216
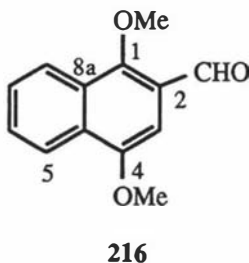
(±)-2-tert-Butyldimethylsilyloxypent-4-yne **215**

To a solution of (±)-pent-4-yn-2-ol (5.00 g, 59 mmol) and *N,N*-dimethylformamide (63 cm^3) at 0°C under a calcium chloride drying tube was added *tert*-butyldimethylsilyl chloride (8.96 g, 59 mmol) and imidazole (19.87 g, 292 mmol). The reaction mixture was warmed to room temperature and then stirred 30 h, poured into ether (100 cm^3) and washed with water (3 x 45 cm^3). The aqueous washings were re-extracted with ether (20 cm^3) and the combined organic phases dried over sodium sulphate. Removal of the solvent at reduced pressure yielded a pale yellow liquid which upon distillation afforded the *title compound* **215** (10.88 g, 92%) as a colourless liquid, b.p. 170-172°C/760 mmHg [Found: (M-H)$^+$, 197.2256. C$_{11}$H$_{22}$OSi requires (*M*-H), 197.2269]; υ_{max} (film)/cm^{-1} 3315s (*H-C*≡C), 2130w (C≡C) and 1085s (C-O); δ_H (200 MHz; CDCl$_3$) 0.05(2) (6H, s, SiMe$_2$), 0.87 (9H, s, Bu^t), 1.21 (3H, d, *J* 6.1, Me), 1.94 (1H, t, $J_{5,3}$ 2.7 Hz, HC≡C), 2.19 (1H, ddd, J_{gem} 16.5, $J_{3,2}$ 7.0 and $J_{3,5}$ 2.7 Hz, 3-H), 2.33 (1H, ddd, J_{gem} 16.5, $J_{3',2}$ 5.7 and $J_{3',5}$ 2.7 Hz, 3-H') and 3.86-4.01 (1H, m, CHOSi); δ_C (50.3 MHz; CDCl$_3$) 2.1, 2.2 (CH$_3$, SiMe$_2$), 18.1 (C, *C*Me$_3$), 23.2 (CH$_3$, C-1), 25.8 (CH$_3$, C*Me$_3$*), 29.4 (CH$_2$, C-3), 67.5 (CH, C-2), 69.7 (CH, C-5) and 81.8 (C, C-4); *m/z* (EI) 197 (M-H, 58), 97 (M-C$_4$H$_9$OSi, 26), 85 (M-C$_5$H$_9$OSi, 45), 71 (M-C$_6$H$_{11}$OSi, 63), 57 (C$_4$H$_9$, 100) and 43 (CH$_3$CO, 56).

211
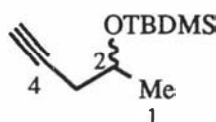
215

(1'R*,5'R*)- *and* (1'R*,5'S*)-2-(5-tert-*Butyldimethylsilyloxy-1-hydroxyhex-2-ynyl*)-1,4-*dimethoxynaphthalene* **217**

To a solution of (±)-2-*tert*-butyldimethylsilyloxypent-4-yne **215** (1.32 g, 6.65 mmol) in dry tetrahydrofuran (20 cm^3), cooled to -78°C under an atmosphere of nitrogen, was added *n*-butyllithium (4.90 cm^3 of a 1.50 mol dm^{-3} solution, 7.32 mmol). After *ca.* 1 h, during which time the reaction temperature was raised to -60°C, a solution of 1,4-dimethoxy-2-naphthalenecarboxaldehyde **216** (1.08 g, 4.99 mmol) in dry tetrahydrofuran (10 cm^3) was added. The reaction was quenched after a further 1 h by the addition of saturated aqueous ammonium chloride (5 cm^3). Following extraction with ether (2 x 15 cm^3) the organic layer was washed with water (2 x 7 cm^3) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a yellow oil, which upon purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent afforded the *title compound* **217** (1.79 g, 86%) as a yellow oil and as a 1:1 mixture of stereoisomers (^{1}H nmr) (Found: C, 69.8; H, 8.6. $C_{24}H_{34}O_4Si$ requires C, 69.5; H, 8.3%); υ_{max} (film)/cm^{-1} 3600-3130s (OH) and 2240w (C≡C); δ_H (270 MHz; CDCl$_3$) 0.04 (6H, s, SiMe$_2$), 0.86, 0.87 (9H, s, Bu^t), 1.23 (3H, d, *J* 5.9 Hz, Me), 2.34-2.43 (2H, m, CH$_2$C≡C), 2.74-2.85 (1H, m, CHOSi), 3.97 (3H, s, 1-OMe), 4.00 (3H, s, 4-OMe), 5.98 (1H, br.s, C*H*OH), 7.01 (1H, s, 3-H), 7.45-7.57 (2H, m, 6-H and 7-H), 8.01-8.05 (1H, m, 5-H or 8-H) and 8.21-8.24 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -4.7, -4.8 (CH$_3$, SiMe$_2$), 18.1 (C, *C*Me$_3$), 23.4 (CH$_3$, C-6'), 25.8(CH$_3$, C*Me$_3$*), 29.8 (CH$_2$, C-4'), 55.6 (CH$_3$, 4-OMe), 60.1 (CH, C-1'), 63.1 (CH$_3$, 1-OMe), 67.5 (CH, C-5'), 81.8, 84.4 (C, C-2', C-3'), 102.2 (CH, C-3), 122.0, 122.5 (CH, C-5, C-8), 125.8, 126.7 (CH, C-6, C-7), 126.6 (C, C-2), 128.3, 129.2 (C, C-4a, C-8a) and 146.3, 152.3 (C, C-1, C-4); *m/z* (EI) 414 (M$^+$, 14), 357 (M-C$_4$H$_9$, 24), 298 (19), 159 (C$_8$H$_{19}$OSi, 22), 119 (100), 75 [(CH$_3$)$_2$SiOH, 84] and 73 (74).
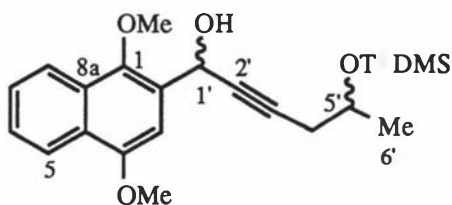
217

(±)-2-(5-tert-*Butyldimethylsilyloxy-1-oxohex-2-ynyl*)-1,4-*dimethoxynaphthalene* **218**

A mixture of (1'R*,5'R*)- and (1'R*,5'S*)-2-(5-*tert*-butyldimethylsilyloxy-1-hydroxyhex-2-ynyl)-1,4-dimethoxynaphthalene **217** (959 mg, 2.31 mmol) and activated manganese dioxide (1.10 g, 13 mmol) in dichloromethane (30 cm^3) was stirred vigorously at room temperature until all starting material had disappeared (TLC). The suspension was filtered through a Celite pad and the solvent removed under reduced pressure to give a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (4:1) as eluent, to give the *title compound* **218** (915 mg, 96%) as a yellow oil (Found: C, 69.8; H, 8.0. $C_{24}H_{32}O_4Si$ requires C, 69.9; H, 7.8%); υ_{max} (film)/cm^{-1} 2235s (C≡C) and 1647s (C=O); δ_H (270 MHz; CDCl$_3$) 0.10 (6H, s, SiMe$_2$), 0.89 (9H, s, Bu^t), 1.36 (3H, d, *J* 6.2 Hz, Me), 2.56-2.74 (2H, m, CH$_2$C≡C), 4.02 (3H, s, 1-OMe), 4.04 (3H, s, 4-OMe), 4.11-4.18 (1H, m, CHOSi), 7.29 (1H, s, 3-H), 7.59-7.65 (2H, m, 6-H and 7-H) and 8.22-8.27 (2H, m, 5-H and 8-H); δ_C (67.8 MHz; CDCl$_3$) -4.7, -4.8 (CH$_3$, SiMe$_2$), 18.1 (C, *C*Me$_3$), 23.6 (CH$_3$, C-6'), 25.8 (CH$_3$, C*Me*$_3$), 30.3 (CH$_2$, C-4'), 55.7 (CH$_3$, 4-OMe), 64.1 (CH$_3$, 1-OMe), 67.1 (CH, C-5'), 83.7 (C, C-2'), 92.5 (C, C-3'), 102.5 (CH, C-3), 122.5, 123.8 (CH, C-5, C-8), 125.6 (C, C-2), 127.2, 128.5 (CH, C-6, C-7), 129.1, 129.6 (C, C-4a, C-8a), 151.5, 153.4 (C, C-1, C-4) and 176.4 (C, C-1'); *m/z* (EI) 412 (M$^+$, 12), 355 (M-C$_4$H$_9$, 67), 296 (M-C$_6$H$_{16}$OSi, 100), 215 (M-C$_{11}$H$_{21}$OSi, 27), 148 (20), 73 (57) and 57 (C$_4$H$_9$, 7).
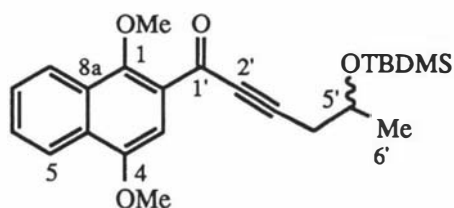
218

(±)-2-(5-tert-*Butyldimethylsilyloxy-1-oxohex-2-ynyl*)-1,4-*naphthoquinone* **321**

Using Ceric Ammonium Nitrate
A solution of ceric ammonium nitrate (921 mg, 1.67 mmol) in water (7 cm^3) was added dropwise to a vigorously stirred solution of (±)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-dimethoxynaphthalene **218** (364 mg, 0.88 mmol) in acetonitrile (49 cm^3) at room temperature. After 0.25 h the reaction mixture was diluted with dichloromethane (57 cm^3), washed with water (2 x 36 cm^3) and dried over sodium sulphate. Evaporation of the solvent at reduced pressure afforded a mixture (317 mg) of

the *title compound* **321** and ketone **218** [*ca.* 1:1 (TLC)] as an orange oil. The mixture was used in the subsequent step without any attempt to separate the two components.

Using Silver(II) Oxide and Nitric Acid

To (±)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-dimethoxynaphthalene **218** (12 mg, 0.029 mmol), silver(II) oxide[606] (14 mg, 0.11 mmol) and 1,4-dioxane (1.3 cm^3) was added dropwise 6 mol dm^{-3} nitric acid (29 mm^3). The suspension was vigorously stirred until no starting material could be detected by TLC (*ca.* 1 min), poured into dichloromethane (3 cm^3) and washed with water (2 x 1 cm^3). The organic phase was dried over sodium sulphate and the solvent evaporated under reduced pressure to give the *title compound* **321** (15 mg) as an orange oil [Found: (M+2H)$^+$, 384.1733. $C_{22}H_{26}O_4Si$ requires (*M*+2H), 384.1757]; υ_{max} (film)/cm^{-1} 2216s (C≡C) and 1670br,s (C=O, quinone and α,β-unsaturated ketone); δ_H (200 MHz; CDCl$_3$) 0.06 (6H, s, SiMe$_2$), 0.86 (9H, s, Bu^t), 1.27 (3H, d, *J* 6.1 Hz, Me), 2.55-2.60 (2H, m, CH$_2$C≡C), 3.98-4.16 (1H, m, CHOSi), 7.32 (1H, s, 3-H), 7.64-7.84 (2H, m, 6-H and 7-H) and 8.02-8.16 (2H, m, 5-H and 8-H); *m/z* (EI) 384 (M+2H, 4), 327 (M+2H-C$_4$H$_9$, 10), 325 (M-C$_4$H$_9$, 12) and 75 [(CH$_3$)$_2$SiOH, 74]. The crude material was used in the next step without further purification.
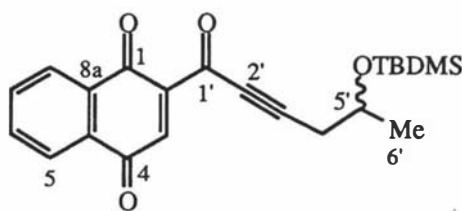
321

(9aR*,12aR*,2'R*)- *and* (9aR*,12aR*,2'S*)-3-(2-tert-*Butyldimethylsilyloxypropyl*)-9a,12a-*dihydro*-1H-*furo*[2",3":4',5']*furo*[3',2':3,4]*naphtho*[1,2-b]*pyran*-1,11(10H)-*dione* **323**

Reaction of quinone **321** *prepared by ceric ammonium nitrate*

A solution of 2-trimethylsilyloxyfuran **189** (109 mg, 0.70 mmol) in acetonitrile (3.3 cm^3) was added dropwise to an ice cooled mixture (*ca.* 1:1) of (±)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-naphthoquinone **321** and ketone **218** (317 mg combined mass), in acetonitrile (39 cm^3), under an atmosphere of nitrogen. After 1 h, the reaction was left to warm to room temperature and then methanol (5 cm^3) was added. After a further 30 h, the solvent was removed under reduced pressure to give an orange oil, which was purified by flash chromatography using hexane-ethyl acetate (1:1) as

eluent to afford ketone **218** (173 mg, 48%) and the *title compound* **323** [84 mg, 39% over two steps (based on unreacted **218**)] as a pale yellow oil and as a 1:1 mixture of stereoisomers (^{1}H nmr). Trituration using ether gave a white solid, m.p. 186.5-188.5°C (Found: C, 67.15; H, 6.8. $C_{26}H_{30}O_6Si$ requires C, 66.9; H, 6.5%); υ_{max} (film)/cm^{-1} 1776s (C=O, γ-lactone), 1654s, 1634s (C=O, α,β-unsaturated ketone) and 1597m (C=C); δ_H (270 MHz; CDCl$_3$) 0.00 (6H, s, SiMe$_2$), 0.80, 0.81 (9H, s, Bu^t), 1.32 (3H, d, J 6.2 Hz, Me), 2.84 (2H, d, $J_{1',2'}$ 5.1 Hz, 1'-CH$_2$), 3.18 (2H, d, $J_{10,9a}$ 4.0 Hz, 10-CH$_2$), 4.26-4.41 (1H, m, CHOSi), 5.61 (1H, dt, $J_{9a,12a}$ 5.7 and $J_{9a,10}$ 4.0 Hz, 9a-H), 6.35 (1H, s, 2-H), 6.98 (1H, d, $J_{12a,9a}$ 5.7 Hz, 12a-H), 7.74-7.79 (2H, m, 6-H and 7-H), 8.07-8.10 (1H, m, 5-H or 8-H) and 8.45-8.49 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -5.0, -4.6 (CH$_3$, SiMe$_2$), 18.0 (C, CMe$_3$), 24.0 (CH$_3$, C-3'), 25.7 (CH$_3$, CMe$_3$), 35.6 (CH$_2$, C-10), 44.6, 44.7 (CH$_2$, C-1'), 66.8, 67.1 (CH, C-2'), 83.1 (CH, C-9a), 84.6 (CH, C-12a), 110.9 (C, C-12b), 113.2, 113.4 (CH, C-2), 117.3 (C, C-12c), 122.7, 122.8, 122.9, 123.0 (CH, C-5, C-8), 126.4 (C, C-4b, C-8a), 128.8, 129.4 (CH, C-6, C-7), 149.3 (C, C-8b), 155.4 (C, C-4a), 165.7, 165.9 (C, C-3), 174.5 (C, C-11) and 177.4 (C, C-1); *m/z* (EI) 466 (M$^+$, 4), 422 (M-CO$_2$, 4), 409 (M-C$_4$H$_9$, 100), 365 (M-CO$_2$-C$_4$H$_9$, 30) and 75 [(CH$_3$)$_2$SiOH, 25].

Reaction of quinone **321** *prepared by silver(II) oxide*

A solution of 2-trimethylsilyloxyfuran **189** (9.0 mg, 0.058 mmol) in acetonitrile (0.3 cm^3) was added dropwise to an ice cooled solution of crude (±)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-naphthoquinone **321** (15 mg), in acetonitrile (1.8 cm^3), under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (0.4 cm^3) added. After a further 30 h, the solvent was removed under reduced pressure to give an orange oil which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford the *title compound* **323** (5.0 mg, 37% over two steps) as a 1:1 mixture of stereoisomers (^{1}H nmr).

323

(9aR*,12aR*,2'R*)- *and* (9aR*,12aR*,2'S*)-2-*Trimethylsilyl*-3-(2-tert-*butyldimethylsilyloxypropyl*)-9a,12a-*dihydro*-1H-*furo*[2",3":4',5']*furo*[3',2':3,4]*naphtho*[1,2-b]*pyran*-1,11(10H)-*dione* **325**

A solution of 2-trimethylsilyloxyfuran **189** (65 mg, 0.41 mmol) in acetonitrile (1.8 cm^3) was added dropwise to an ice cooled mixture (79 mg) of ($\pm$)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-naphthoquinone **321** and ketone **218** in acetonitrile (10 cm^3) under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (1.2 cm^3) added. After stirring 30 h, the solvent was removed under reduced pressure to give an orange oil, which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford ketone **218** (22 mg, 24%), pentacycle **323** [29 mg, 39% over two steps (based on unreacted **218**)] and the *title compound* **325** [30 mg, 35% over two steps (based on unreacted **218**)] as a pale yellow solid and as a 1:1 mixture of stereoisomers (^{1}H nmr), m.p. 188.5-190.5°C (Found: M$^+$, 538.2201. C$_{29}$H$_{38}$O$_6$Si$_2$ requires M, 538.2207); υ_{max} (film)/cm^{-1} 1781s (C=O, γ-lactone), 1643w (C=O, α,β-unsaturated ketone) and 1618m (C=C, vinylic); δ_H (270 MHz; CDCl$_3$) -0.24, -0.23, -0.01, 0.00 (6H, s, 2'-OSiMe$_2$), 0.41 (9H, s, 2-SiMe$_3$), 0.75 (9H, s, Bu^t), 1.32(2) (3H, d, J 5.9 Hz, Me), 2.87, 2.89 (1H, dd, J_{gem} 13.9 and $J_{1',2'}$ 7.0 Hz, 1'-H^A), 3.04, 3.07 (1H, dd, J_{gem} 13.9 and $J_{1',2'}$ 8.4 Hz, 1'-H^B), 3.16 (2H, d, $J_{10,9a}$ 3.8 Hz, 10-CH$_2$), 4.37-4.53 (1H, m, CHOSi), 5.56 (1H, dt, $J_{9a,12a}$ 5.9 and $J_{9a,10}$ 3.8 Hz, 9a-H), 6.95, 6.96 (1H, d, $J_{12a,9a}$ 5.9 Hz, 12a-H), 7.71-7.77 (2H, m, 6-H and 7-H), 8.05-8.08 (1H, m, 5-H or 8-H) and 8.43-8.47 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -4.9, -4.7 (CH$_3$, 2'-OSiMe$_2$), 1.40(2)(CH$_3$2-SiMe$_3$), 17.9 (C, CMe$_3$), 24.3 (CH$_3$, C-3'), 25.6 (CH$_3$, C*Me*$_3$), 35.5 (CH$_2$, C-10), 44.1 (CH$_2$, C-1'), 67.7, 68.2 (CH, C-2'), 82.9 (CH, C-9a), 84.7(2) (CH, C-12a), 110.7, 110.8 (C, C-12b), 115.9(2) (C, C-12c), 120.1, 120.2 (C, C-2), 122.6, 122.8, 122.9 (CH, C-5, C-8), 126.2 (C, C-4b, C-8a), 128.6, 129.2 (CH, C-6, C-7), 149.1(2) (C, C-8b), 155.1 (C, C-4a), 168.7, 168.9 (C, C-3), 174.6, 174.7 (C, C-11) and 181.4, 181.5 (C, C-1); m/z (EI) 538 (M$^+$, 18), 481 (M-C$_4$H$_9$, 100), 391 (18), 343 (34) and 73 [(CH$_3$)$_3$Si, 62].
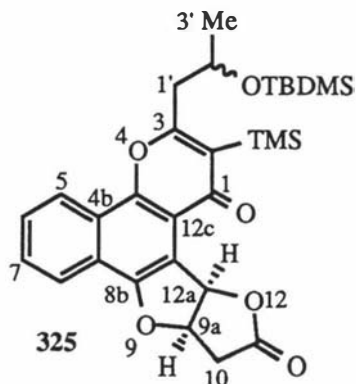
(2'Z)-(1'R*,5'R*)- and (1'R*,5'S*)-2-(5-tert-*Butyldimethylsilyloxy-1-hydroxyhex-2-enyl)-1,4-dimethoxynaphthalene* **326**

To (1'R*,5'R*)- and (1'R*,5'S*)-2-(5-*tert*-butyldimethylsilyloxy-1-hydroxyhex-2-ynyl)-1,4-dimethoxynaphthalene **217** (1.364 g, 3.29 mmol) dissolved in ethyl acetate (45 cm^3) was added Lindlar catalyst (120 mg). The reaction vessel was flushed with hydrogen from a reservoir and the contents stirred at room temperature for 0.5 h. After removal of the catalyst by filtration through a Celite pad the filtrate was concentrated at reduced pressure to give a yellow oil. Purification by flash chromatography, using hexane-ethyl acetate (4:1) as eluent gave the *title compound* **326** (1.261 g, 92%) as a yellow oil and as a 1:1 mixture of stereoisomers (^{1}H nmr) (Found: C, 69.2; H, 8.5. $C_{24}H_{36}O_4Si$ requires C, 69.2; H, 8.7%); υ_{max} (film)/cm^{-1} 3700-3060m (OH) and 1635w (C=C, vinylic); δ_H (270 MHz; CDCl$_3$) 0.07, 0.08, 0.09 (6H, s, SiMe$_2$), 0.90, 0.91 (9H, s, Bu^t), 1.18, 1.22 (3H, d, J 6.2 Hz, Me), 2.22-2.65 (2H, m, =CHCH_2), 2.90, 2.94 (1H, br.s, OH), 3.89-4.02 (1H, m, CHOSi), 3.91, 3.92 (3H, s, 1-OMe), 4.00 (3H, s, 4-OMe), 5.58-5.69 (1H, m, =CHCH$_2$), 5.83-5.92 (1H, m, CH=CHCH$_2$), 6.03 (1H, d, J 7.7 Hz, CHOH), 6.94, 6.95 (1H, s, 3-H), 7.44-7.56 (2H, m, 6-H and 7-H), 8.01-8.04 (1H, m, 5-H or 8-H) and 8.21-8.24 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -4.6, -4.5 (CH$_3$, SiMe$_2$), 18.2 (C, CMe$_3$), 23.3, 24.0 (CH$_3$, C-6'), 25.7, 25.9 (CH$_3$, CMe_3), 37.4, 38.1 (CH$_2$, C-4'), 55.5 (CH$_3$, 4-OMe), 62.6 (CH$_3$, 1-OMe), 64.2, 64.8 (CH, C-1'), 68.2, 68.6 (CH, C-5'), 101.7, 101.8 (CH, C-3), 121.9, 122.3 (CH, C-5, C-8), 125.3, 126.5 (CH, C-6, C-7), 126.1 (C, C-2), 128.3, 129.7 (C, C-4a, C-8a), 131.1, 131.5 (CH, C-2'), 133.6, 134.0 (CH, C-3') and 146.1, 152.2 (C, C-1, C-4); *m/z* (EI) 416 (M$^+$, 23), 398 (M-H$_2$O, 7), 326 (11), 284 (M-C$_6$H$_{16}$OSi, 10), 201 (26), 159 (C$_8$H$_{19}$OSi, 20), 119 (100), 75 [(CH$_3$)$_2$SiOH, 54] and 57 (C$_4$H$_9$, 8).
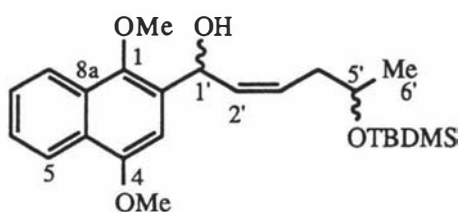
326

*(2'Z)-(±)-2-(5-tert-*Butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-dimethoxynaphthalene* **327**

To a mixture of (2'Z)-(1'R*,5'R*)- and (1'R*,5'S*)-2-(5-*tert*-butyldimethylsilyloxy-1-hydroxyhex-2-enyl)-1,4-dimethoxynaphthalene **326** (199 mg, 0.48 mmol), 4-

methylmorpholine *N*-oxide (84 mg, 0.72 mmol) and powdered 4A molecular sieves (240 mg) in dichloromethane (20 cm^3), under an atmosphere of nitrogen, was added *tetra-n*-propylammonium perruthenate (15 mg, 10 mol %). The reaction was stirred until no starting material was visible (TLC). Filtration of the reaction mixture through a glass frit and then a silica gel pad, followed by concentration of the filtrate at reduced pressure afforded a yellow oil. Purification by flash chromatography, using hexane-ethyl acetate (95:5) as eluent gave the *title compound* **327** (164 mg, 83%) as a yellow oil (Found: C, 69.6; H, 8.1. C$_{24}$H$_{34}$O$_4$Si requires C, 69.5; H, 8.3%); υ_{max} (film)/cm^{-1} 1643s (C=O) and 1594m (C=C, vinylic); δ_H (270 MHz; CDCl$_3$) 0.09 (6H, s, SiMe$_2$), 0.90 (9H, s, Bu^t), 1.22 (3H, d, *J* 6.2 Hz, Me), 2.78-3.02 (2H, m, =CHC*H$_2$*), 3.87 (3H, s, 1-OMe), 4.00-4.07 (1H, m, CHOSi), 4.01 (3H, s, 4-OMe), 6.45 (1H, dt, *J*$_{3',2'}$ 11.7 and *J*$_{3',4'}$ 7.3 Hz, =CHCH$_2$), 7.05 (1H, s, 3-H), 7.15 (1H, dt, *J*$_{2',3'}$ 11.7 and *J*$_{2',4'}$ 1.8 Hz, C*H*=CHCH$_2$), 7.56-7.60 (2H, m, 6-H and 7-H), 8.16-8.19 (1H, m, 5-H or 8-H) and 8.23-8.27 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -4.7, -4.4 (CH$_3$, SiMe$_2$), 18.1 (C, *C*Me$_3$), 23.9 (CH$_3$, C-6'), 25.9 (CH$_3$, C*Me$_3$*), 39.7 (CH$_2$, C-4'), 55.7 (CH$_3$, 4-OMe), 64.2 (CH$_3$, 1-OMe), 68.3 (CH, C-5'), 102.6 (CH, C-3), 122.4, 123.1 (CH, C-5, C-8), 123.2 (C, C-2), 127.1, 127.6 (CH, C-6, C-7), 128.3, 128.7 (C, C-4a, C-8a), 128.9 (CH, C-2'), 145.4 (CH, C-3'), 151.2, 151.8 (C, C-1, C-4) and 193.0 (C, C-1'); *m/z* (EI) 414 (M$^+$, 37), 357 (M-C$_4$H$_9$, 82), 298 (M-C$_5$H$_{12}$OSi, 52), 283 (M-C$_6$H$_{15}$OSi, 37), 267 (M-C$_7$H$_{19}$OSi, 75), 215 (M-C$_{11}$H$_{23}$OSi, 46), 159 (C$_8$H$_{19}$OSi, 32), 133 (60), 117 (34), 75 [(CH$_3$)$_2$SiOH, 36], 73 (100) and 57 (C$_4$H$_9$, 10).
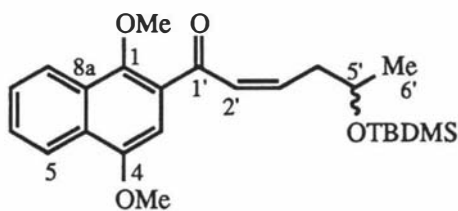
327

(2'*Z*)-(±)-2-(5-tert-*Butyldimethylsilyloxy-1-oxohex-2-enyl*)-1,4-*naphthoquinone* **328**

A solution of ceric ammonium nitrate (510 mg, 0.93 mmol) in water (4 cm^3) was added dropwise to a vigorously stirred solution of (2'*Z*)-(±)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-dimethoxynaphthalene **327** (203 mg, 0.49 mmol) in acetonitrile (30 cm^3) at room temperature. After 0.25 h, the reaction mixture was diluted with dichloromethane (30 cm^3), washed with water (2 x 20 cm^3) and dried over sodium sulphate. After removal of residual oxidant by filtration through a Florisil pad the filtrate

was concentrated at reduced pressure to give the *title compound* **328** (173 mg, 92%) as an orange oil [Found: $(M+2H)^+$, 386.2053. $C_{22}H_{28}O_4Si$ requires $(M+2H)$, 386.1913]; υ_{max} (film)/cm^{-1} 1669 (C=O, quinone and α,β-unsaturated ketone) and 1613 (C=C, vinylic); δ_H (270 MHz; CDCl$_3$) 0.07, 0.08 (6H, s, SiMe$_2$), 0.89 (9H, s, Bu^t), 1.20 (3H, d, *J* 6.2 Hz, Me), 2.83-2.94 (2H, m, =CHCH_2), 4.03 (1H, sextet, *J* 5.9 Hz, CHOSi), 6.50-6.68 (2H, m, CH=CHCH$_2$), 7.12 (1H, s, 3-H), 7.78-7.82 (2H, m, 6-H and 7-H) and 8.08-8.14 (2H, m, 5-H and 8-H); *m/z* (EI) 386 (M+2H, 5), 329 (M+2H-C$_4$H$_9$, 8), 327 (M-C$_4$H$_9$, 12), 285 (12), 254 (M+2H-C$_6$H$_{16}$OSi, 8), 215 (13), 186 (M+2H-C$_{11}$H$_{23}$OSi, 10), 159 (C$_8$H$_{19}$OSi, 60), 115 (23), 75 [(CH$_3$)$_2$SiOH, 100] and 73 (88).
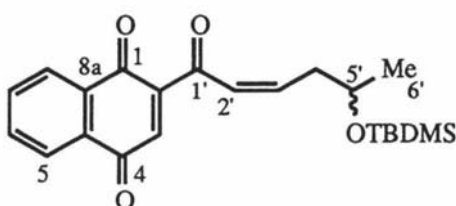
328

(2'Z)-(6bR*,9aR*,5'R*)- *and* (6bR*,9aR*,5'S*)-6-(5-tert-*Butyldimethylsilyloxy*-1-*oxohex*-2-*enyl*)-6b,9a-*dihydro*-5-*hydroxyfuro*[3,2-b]*naphtho*[2,1-d]*furan*-8(9H)-*one* **330**

A solution of 2-trimethylsilyloxyfuran **189** (138 mg, 0.88 mmol) in acetonitrile (4.5 cm^3) was added dropwise to an ice cooled solution of (2'Z)-($\pm$)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-naphthoquinone **328** (173 mg, 0.44 mmol), in acetonitrile (23 cm^3), under an atmosphere of nitrogen. After 0.5 h the solvent was removed under reduced pressure to give an orange oil, which was then purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford:

(i) the *title compound* **330** (111 mg, 55%) as an orange semi-solid and as a 1:1 mixture of stereoisomers (^{1}H nmr). Trituration using hexane-ether (4:1) produced an orange solid, m.p. 108.0-110.0°C (Found: C, 66.5; H, 6.7. $C_{26}H_{32}O_6Si$ requires C, 66.6; H, 6.9%); υ_{max} (film)/cm^{-1} 3670-3090w (OH), 1785br,s (C=O, γ-lactone), 1630s (C=O, α,β-unsaturated ketone) and 1572br,s (C=C); δ_H (200 MHz; CDCl$_3$) 0.05, 0.07 (6H, s, SiMe$_2$), 0.87, 0.88 (9H, s, Bu^t), 1.19, 1.20 (3H, d, *J* 6.1 Hz, Me), 2.61-2.88 (2H, m, =CHCH_2), 3.03-3.32 (2H, m, 9-H and 9-H'), 3.96-4.19 (1H, m, CHOSi), 5.44 (1H, ddd, $J_{9a,6b}$ 5.9, $J_{9a,9}$ 5.9 and $J_{9a,9'}$ 2.7 Hz, 9a-H), 6.35 (1H, d, $J_{6b,9a}$ 5.9 Hz, 6b-H), 6.39-6.54 (1H, m, =CHCH$_2$), 7.07 (1H, dt, $J_{2',3'}$ 12.0 and $J_{2',4'}$ 1.7 Hz, CH=CHCH$_2$), 7.57-7.79 (2H, m, 2-H and 3-H), 7.88-7.99 (1H, m, 1-H or 4-H), 8.45-8.56 (1H, m, 4-H or 1-H) and 14.79 (1H, s, OH); δ_C (67.8 MHz; CDCl$_3$) -4.8, -4.5 (CH$_3$, SiMe$_2$), 18.1 (C, CMe$_3$),

23.5, 24.0 (CH$_3$, C-6'), 25.8 (CH$_3$, CMe_3), 35.6 (CH$_2$, C-9), 39.7, 39.8 (CH$_2$, C-4'), 67.9, 68.2 (CH, C-5'), 81.2 (CH, C-9a), 85.6 (CH, C-6b), 110.1 (C, C-6), 111.2 (C, C-6a), 122.1, 125.3 (CH, C-1, C-4), 124.5, 128.3 (C, C-4a, C-10b), 127.9 (CH, C-2'), 128.4, 130.5 (CH, C-2, C-3), 144.7, 145.5 (CH, C-3'), 150.5 (C, C-10a), 160.7 (C, C-5), 174.1 (C, C-8) and 196.0 (C, C-1'); m/z (EI) 468 (M$^+$, 34), 411 (M-C$_4$H$_9$, 53), 367 (M-C$_4$H$_9$-CO$_2$, 20), 336 (M-C$_6$H$_{16}$OSi, 17), 295 (M-C$_9$H$_{21}$OSi, 18), 268 (M-C$_{11}$H$_{24}$OSi, 17), 159 (C$_8$H$_{19}$OSi, 100), 95 (38), 73 (87) and 43 (CH$_3$CO, 39).
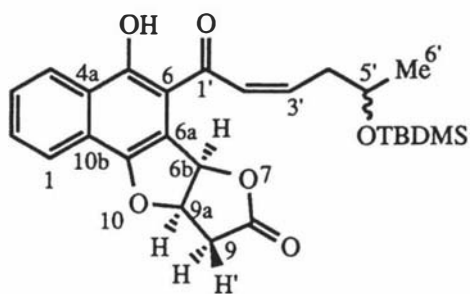
330

(ii) (3R*,9aR*,12aR*,2'R*)-, (3R*,9aR*,12aR*,2'S*)-, (3S*,9aR*,12aR*,2'R*)- *and* (3S*,9aR*,12aR*,2'S*)-3-(2-tert-*Butyldimethylsilyloxypropyl*)-2,3,9a,12a-*tetrahydro*-1H-*furo*[2",3":4',5']*furo*[3',2':3,4]*naphtho*[1,2-b]*pyran*-1,11(10H)-*dione* **331** (15 mg, 7%) as a white solid and as a mixture of stereoisomers (^{1}H nmr), m.p. 131.0-133.0°C (Found: C, 66.7; H, 7.1. C$_{26}$H$_{32}$O$_6$Si requires C, 66.6; H, 6.9%); ν_{max} (CHCl$_3$)/cm^{-1} 1780s (C=O, γ-lactone) and 1684s, 1675s (C=O, aryl ketone); δ_H (270 MHz; CDCl$_3$) 0.08, 0.09(2), 0.010(2) (6H, s, SiMe$_2$), 0.81, 0.82, 0.89, 0.90 (9H, s, Bu^t), 1.27, 1.30 (3H, d, J 6.1 Hz, Me), 1.72-2.32 (2H, m, 1'-CH$_2$), 2.75-2.86 (2H, m, 2-CH$_2$), 3.14 (2H, d, $J_{10,9a}$ 4.0 Hz, 10-CH$_2$), 4.14-4.28, 4.33-4.45 (1H, m, CHOSi), 4.79-4.88 (1H, m, 3-H), 5.48-5.54 (1H, m, 9a-H), 6.74(2), 6.79 (1H, d, $J_{12a,9a}$ 5.9 Hz, 12a-H), 7.60-7.72 (2H, m, 6-H and 7-H), 7.94-7.97 (1H, m, 5-H or 8-H) and 8.26-8.32 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -4.8, -4.3 (CH$_3$, SiMe$_2$), 17.9, 18.1 (C, CMe$_3$), 23.6, 23.7, 24.6 (CH$_3$, C-3'), 25.8 (CH$_3$, CMe_3), 35.7 (CH$_2$, C-10), 42.9, 43.0, 43.1, 43.2 (CH$_2$, C-2), 44.3, 44.4, 45.0, 45.2 (CH$_2$, C-1'), 64.2, 65.0 (CH, C-2'), 75.8, 77.2 (CH, C-3), 82.1, 82.3 (CH, C-9a), 85.1 (CH, C-12a), 111.4, 111.5, 111.9 (C, C-12b, C-12c), 122.4, 124.2 (CH, C-5, C-8), 127.0, 127.1, 127.2 (C, C-4b, C-8a), 127.9, 128.0, 129.9 (CH, C-6, C-7), 152.2(2), 152.4 (C, C-8b), 155.6(2), 156.0 (C, C-4a), 174.8(2) (C, C-11) and 191.4, 191.6 (C, C-1); m/z (EI) 468 (M$^+$, 47), 411 (M-C$_4$H$_9$, 97), 367 (M-C$_4$H$_9$-CO$_2$, 15), 343 (100), 297 (23), 262 (28), 212 (19), 182 (21), 162 (84), 132 (C$_6$H$_{16}$OSi, 20), 113 (26), 73 (31) and 31 (34).
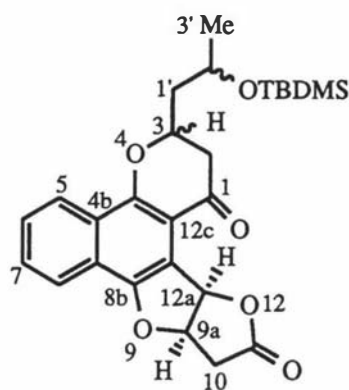
331

(1'Z)-(3aR*,5R*,11bR*,4'R*)-, (3aR*,5R*,11bR*,4'S*)-, (3aR*,5S*,11bR*,4'R*)- *and* (3aR*,5S*,11bR*,4'S*)-3,3a,5,11b-*Tetrahydro-5-hydroxy-5-(4-tert-butyldimethylsilyloxypent-1-enyl-2H-furo*[3,2-b]*naphtho*[2,3-d]*pyran-2,6,11-trione* **336**

A solution of ceric ammonium nitrate (175 mg, 0.32 mmol) in water (1 cm^3) was added dropwise to a solution of naphthofuranone **330** (78 mg, 0.16 mmol) in acetonitrile (10 cm^3) at room temperature, and the reaction stirred until no starting material could be detected (TLC). The reaction mixture was poured into dichloromethane (17 cm^3), washed with water (5 cm^3) and dried over sodium sulphate. The solution was filtered through a Florisil pad and the solvent evaporated under reduced pressure to give an orange solid. Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent gave the *title compound* **336** (43 mg, 55%) as a glassy yellow solid and as a mixture of stereoisomers (^{1}H nmr), m.p. 64.5-67.5°C (Found: C, 64.7; H, 6.9. C$_{26}$H$_{32}$O$_7$Si requires C, 64.4; H, 6.7%); υ_{max} (CH$_2$Cl$_2$)/cm^{-1} 3671-3122w (OH), 1794s (C=O, γ-lactone), 1671s (C=O, quinone) and 1594m (C=C); δ_H (400 MHz; CDCl$_3$) 0.10, 0.11, 0.12(2), 0.15 (6H, s, SiMe$_2$), 0.91(3) (9H, s, Bu^t), 1.22, 1.27 (3H, d, J 6.1 Hz, Me), 2.07-3.05 (2H, m, =CHCH$_2$), 2.66, 2.73 (1H, d, J_{gem} 17.6 Hz, 3-H^A), 2.95, 2.97 (1H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 5.0 Hz, 3-H^B), 3.95-4.08 (1H, m, CHOSi), 4.96, 5.03 (1H, dd, $J_{3a,3B}$ 5.0 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.30(2) (1H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 5.67-6.09 (2H, m, CH=CHCH$_2$), 7.75-7.85 (2H, m, 8-H and 9-H) and 8.06-8.15 (2H, m, 7-H and 10-H); δ_C (100.6 MHz; CDCl$_3$) -4.8, -4.2 (CH$_3$, SiMe$_2$), 14.1, 18.1, 22.7 (C, CMe$_3$), 23.7, 24.5, 29.3, 29.7 (CH$_3$, C-5'), 25.7, 25.8, 26.0 (CH$_3$, CMe_3), 36.4, 37.4, 40.0, 40.2 (CH$_2$, C-3'), 36.6, 37.6, 38.4, 38.6 (CH$_2$, C-3), 65.7, 66.4 (CH, C-3a), 68.4, 69.6 (CH, C-4'), 68.9, 69.1 (CH, C-11b), 92.5, 93.9 (C, C-5), 126.4, 126.7 (CH, C-7, C-10), 130.9, 131.3 (C, C-6a, C-10a), 131.8 (CH, C-1'), 131.8, 132.7 (CH, C-2'), 134.1, 134.4, 134.6, 134.8 (CH, C-8, C-9), 140.0, 140.9 (C, C-11a), 144.8, 144.9, 145.7 (C, C-5a), 174.3,

174.4 (C, C-2) and 182.2, 183.2, 183.5, 183.6 (C, C-6, C-11); *m/z* (EI) 483 (M-H, 0.3), 469 (M-CH$_3$, 1), 440 (M-CO$_2$, 2), 427 (M-C$_4$H$_9$, 46), 409 (13), 383 (M-CO$_2$-C$_4$H$_9$, 40), 339 (10), 295 (24), 265 (10), 159 (M-C$_8$H$_{19}$OSi, 74), 115 (25), 103 (14), 95 (8), 75 [(CH$_3$)$_2$SiOH, 77], 73 (100), 69 (8) and 43 (CH$_3$CO, 9).
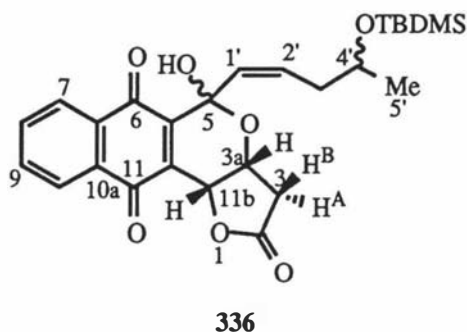
336

(1'Z)-(3aR*,5R*,11bR*,4'R*)-, (3aR*,5R*,11bR*,4'S*)-, (3aR*,5S*,11bR*,4'R*)- *and* (3aR*,5S*,11bR*,4'S*)-3,3a,5,11b-*Tetrahydro-5-hydroxy-5-(4-hydroxypent-1-enyl)2H-furo*[3,2-b]*naphtho*[2,3-d]*pyran-2,6,11-trione* **332**

A solution of ceric ammonium nitrate (282 mg, 0.51 mmol) in water (0.8 cm^3) was added dropwise to a solution of naphthofuranone **330** (30 mg, 0.064 mmol) in acetonitrile (3.5 cm^3) at room temperature, and the reaction mixture stirred until no starting material could be detected (TLC, *ca.* 10 min). The reaction was poured into ethyl acetate (8 cm^3), washed with water (2 x 4 cm^3) and dried over sodium sulphate. The solution was filtered through a Florisil pad and the solvent evaporated under reduced pressure to give an orange solid that was purified by flash chromatography, using hexane-ethyl acetate (1:2) as eluent, to afford the *title compound* **332** (15 mg, 64%) as a yellow solid and as a mixture of stereoisomers (^{1}H nmr), m.p. 91.0-95.0°C (Found: C, 64.6; H, 4.9. C$_{20}$H$_{18}$O$_7$ requires C, 64.9; H, 4.9%); υ_{max} (film)/cm^{-1} 3591-3072s (OH), 1787s (C=O, γ-lactone), 1667s (C=O, quinone) and 1592m (C=C); δ_H (270 MHz; CDCl$_3$) 1.23 (1H, d, *J* 6.6 Hz, Me), 1.25 (1H, d, *J* 7.0 Hz, Me), 1.30 (0.5H, d, *J* 6.2 Hz, Me), 1.32 (0.5H, d, *J* 7.0 Hz, Me), 2.10-2.68 (2H, m, =CHC*H$_2$*), 2.73, 2.76 (1H, d, *J*$_{gem}$ 17.6 Hz, 3-H^A), 2.99 (0.5H, dd, *J*$_{gem}$ 17.6 and *J*$_{3B,3a}$ 4.8 Hz, 3-H^B), 3.00 (0.5H, dd, *J*$_{gem}$ 17.8 and *J*$_{3B,3a}$ 4.8 Hz, 3-H^B), 3.84-4.04 (1H, m, C*H*OH), 4.72-4.83 (1H, br.s, OH), 4.99, 5.00 (1H, dd, *J*$_{3a,3B}$ 4.8 and *J*$_{3a,11b}$ 2.9 Hz, 3a-H), 5.30(2) (1H, d, *J*$_{11b,3a}$ 2.9 Hz, 11b-H), 5.67-5.85 (1H, m, C*H*=CHCH$_2$), 5.87-6.00 (1H, m, =C*H*CH$_2$), 6.00-6.22 (1H, br.s, OH), 7.73-7.82 (2H, m, 8-H and 9-H) and 8.02-8.13 (2H, m, 7-H and 10-H); δ_C (67.8 MHz; CDCl$_3$) 22.9, 23.2, 23.8, 28.6 (CH$_3$, C-5'), 36.3, 37.1, 40.0 (CH$_2$, C-3'), 36.6, 38.6, 38.8, 39.1 (CH$_2$, C-3), 66.5, 66.9 (CH, C-3a), 66.9, 68.2 (CH, C-4'), 68.7, 69.0 (CH, C-11b), 92.3, 93.1 (C, C-5),

126.4, 126.5, 126.6(2) (CH, C-7, C-10), 130.5, 130.7 (CH, C-1'), 131.1(2), 131.9, 132.1 (C, C-6a, C-10a), 132.7, 133.3 (CH, C-2'), 134.0, 134.1, 134.3, 134.4, 134.6, 134.7 (CH, C-8, C-9), 139.3 (C, C-11a), 145.5, 145.8 (C, C-5a), 174.7, 175.4 (C, C-2) and 182.4, 182.7, 183.0, 183.3 (C, C-6, C-11); m/z (EI) 370 (M$^+$, 6), 354 (M-H$_2$O, 100), 308 (M-H$_2$O-CO$_2$, 21), 295 (61), 286 (M-C$_5$H$_8$O, 48), 249 (36), 225 (24), 199 (13), 162 (27), 139 (15), 105 (17), 77 (14) and 43(CH$_3$CO, 27).
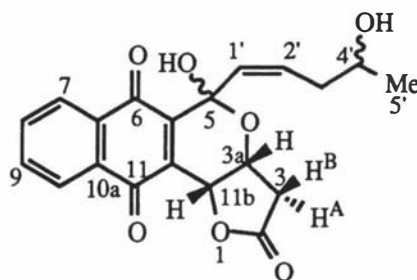
332

(3aR*,5S*,11bR*,6'R*)-3a,11b,5',6'-*Tetrahydro-6'-methylspiro[5H-furo[3,2-*b]*naphtho[2,3-d]pyran-5 ,2'-[2H]pyran]-2,6,11(3H)-trione* **333** *and*
(3aS*,5S*,11bS*,6'R*)-3a,11b,5',6'-*Tetrahydro-6'-methylspiro[5H-furo[3,2-*b]*naphtho[2,3-d]pyran-5 ,2'-[2H]pyran]-2,6,11(3H)-trione* **334**

Using camphorsulphonic acid

To a solution of naphthopyrantrione **332** (36 mg, 0.097 mmol) in dichloromethane (5 cm^3) was added a catalytic quantity (*ca.* 2 mg) of camphorsulphonic acid. The reaction was heated gently at reflux until no starting material was visible (TLC). Removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (1:1) as eluent to give the *title compounds* **333** and **334** (18 mg, 52%) as a yellow solid and as a 3:2 (**333*:334**) mixture of stereoisomers (^{1}H nmr), m.p. 229.0-233.0°C (Found: C, 67.8; H, 4.9. C$_{20}$H$_{16}$O$_6$ requires C, 68.2; H, 4.6%); υ_{max} (film)/cm^{-1} 1791s (C=O, γ-lactone), 1672s (C=O, quinone) and 1595w (C=C); δ_H (270 MHz; CDCl$_3$) 1.30 (1.2H, d, J 6.2 Hz, Me), 1.35* (1.8H, d, J 6.6 Hz, Me), 2.02-2.17*, 2.26-2.40, 2.60-2.72* (2H, m, 5'-CH$_2$), 2.71* (0.6H, d, J_{gem} 17.6 Hz, 3-H^A), 2.76 (0.4H, d, J_{gem} 17.7 Hz, 3-H^A), 2.98 (0.4H, dd, J_{gem} 17.7 and $J_{3B,3a}$ 4.7 Hz, 3-H^B), 2.99* (0.6H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 4.9 Hz, 3-H^B), 4.08-4.24 (0.4H, m, 6'-H), 4.31-4.47* (0.6H, m, 6'-H), 4.90 (0.4H, dd, $J_{3a,3B}$ 4.7 and $J_{3a,11b}$ 3.1 Hz, 3a-H), 5.01* (0.6H, dd, $J_{3a,3B}$ 4.9 and $J_{3a,11b}$ 3.0 Hz, 3a-H), 5.32* (0.6H, d, $J_{11b,3a}$ 3.0 Hz, 11b-H), 5.33 (0.4H, d, $J_{11b,3a}$ 3.1 Hz, 11b-H), 5.63-5.71 (1H, m, 3'-H), 6.19-6.26 (1H, m, 4'-H), 7.73-7.80 (2H, m, 8-H and 9-H) and 8.02-8.15 (2H, m, 7-H and 10-H); δ_C (67.8

MHz; CDCl$_3$) 21.0, 21.5 (CH$_3$, CH$_3$), 29.7, 31.1 (CH$_2$, C-5'), 36.6 (CH$_2$, C-3), 65.9, 68.9 (CH, C-6'), 66.3, 66.6 (CH, C-3a), 69.0 (CH, C-11b), 91.5, 92.6 (C, C-5), 125.6, 125.7 (CH, C-3'), 126.4, 126.6 (CH, C-7, C-10), 127.6, 129.2 (CH, C-4'), 131.3, 132.2, 133.3 (C, C-6a, C-10a), 134.0, 134.1, 134.5 (CH, C-8, C-9), 135.5, 136.2 (C, C-11a), 144.0, 144.5 (C, C-5a), 174.1, 174.3 (C, C-2) and 181.5, 182.3, 183.1, 183.3 (C, C-6, C-11); m/z (EI) 352 (M$^+$, 22), 324 (M-CO, 93), 307 (M-CO$_2$H, 97), 295 (M-CO-C$_2$H$_5$, 75), 279 (M-CO$_2$-C$_2$H$_5$, 34), 251 (M-C$_5$H$_9$O$_2$, 29), 238 (M-C$_6$H$_{10}$O$_2$, 29), 212 (29), 182 (M-C$_8$H$_{10}$O$_4$, 29), 162 (100), 132 (26), 113 (30), 95 (13), 70 (25), 43 (CH$_3$CO, 26) and 31 (46).

Using hydrofluoric acid

To a solution of naphthopyrantrione **336** (18.0 mg, 0.037 mmol) in acetonitrile (3 cm^3) was added dropwise a solution of 40% aqueous hydrofluoric acid (0.10 cm^3) in acetonitrile (1.0 cm^3) until no starting material could be detected (TLC). The reaction mixture was poured into ethyl acetate (5 cm^3), washed with water (2 x 3 cm^3) and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (1:1) as eluent to give the *title compounds* **333** and **334** (6.2 mg, 46% over two steps) as a 3:7 (**333**:**334**) mixture of stereoisomers (^{1}H nmr).
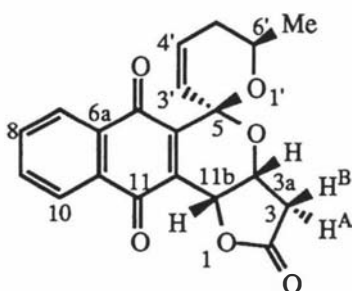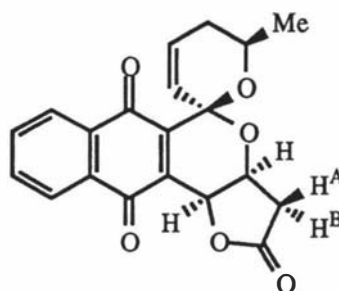
333   334

(2R*,6S*)-2-*Methyl*-1,7-*dioxaspiro[5.5]undec-4-ene* **345**

The title compound **345** (2.518 g, 60%) was prepared from (±)-2-trimethylsilyloxypent-4-yne (3.905 g, 25.0 mmol), *n*-butyllithium (17.9 cm^3 of a 1.54 mol dm^{-3} solution, 27.5 mmol) and δ-valerolactone (3.010 g, 30.0 mmol) according to the procedure of Brimble *et al.*[370] as a colourless liquid. The ^{1}H and ^{13}C nmr spectra were in agreement with that reported in the literature.[370,372]

345
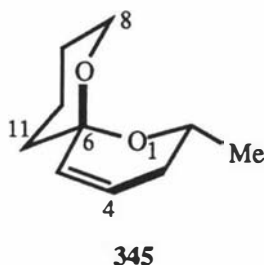
(2R*,4S*,5S*,6S*)-2-*Methyl*-1,7-*dioxaspiro[5.5]undecane-4,5-diol* **353**

To a mixture of (2R*,6S*)-2-methyl-1,7-dioxaspiro[5.5]undec-4-ene **345** (110 mg, 0.65 mmol), 4-methylmorpholine *N*-oxide (91 mg, 0.78 mmol) and water (164 mg, 9.10 mmol) in acetone (0.8 cm^3) was added osmium tetraoxide (0.33 cm^3 of a 2.5 wt. % solution in *tert*-butyl alcohol, 0.05 equiv.). The reaction mixture was stirred at room temperature for 16 h, then sodium dithionite (453 mg, 2.60 mmol), Florisil (100 mg), water (328 mg, 18.2 mmol) and acetone (3 cm^3) were added and the resultant suspension stirred for 0.5 h. After drying with sodium sulphate the suspension was filtered through a short column of silica gel and the column washed with acetone (30 cm^3). The solvent was removed under reduced pressure and the residue purified by flash chromatography, using hexane-ethyl acetate (1:1) as eluent to give the *title compound* **353** (106 mg, 80%) as a colourless oil (Found: C, 59.3; H, 8.8. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%); υ_{max} (film)/cm^{-1} 3693-3015s (OH) and 1099m (C-O); δ_H (270 MHz; CDCl$_3$) 1.23 (3H, d, J 6.6 Hz, Me), 1.36-2.02 (8H, m, 3, 9, 10 and 11-CH$_2$), 2.35 (1H, br.s, OH), 2.45 (1H, br.s, OH), 3.49 (1H, d, $J_{5eq,4ax}$ 3.3 Hz, 5$_{eq}$-H), 3.57-3.61 (2H, m, 8-CH$_2$), 3.67-3.81 (1H, m, C*H*Me) and 4.06 (1H, ddd, $J_{4ax,3ax}$ 11.7, $J_{4ax,3eq}$ 5.1 and $J_{4ax,5eq}$ 3.3 Hz, 4$_{ax}$-H); δ_C (67.8 MHz; CDCl$_3$) 18.2 (CH$_2$, C-10), 21.1 (CH$_3$, Me), 25.0 (CH$_2$, C-9), 31.6 (CH$_2$, C-11), 35.9 (CH$_2$, C-3), 60.4 (CH$_2$, C-8), 63.8 (CH, C-2), 66.1 (CH, C-4), 72.2 (CH, C-5) and 98.0 (C, C-6); *m/z* (EI) 203 (MH$^+$, 0.3), 185 (MH-H$_2$O, 0.5) and 101 ($C_5H_9O_2$, 100). Upon prolonged refrigeration at approximately 2°C the oil formed a colourless solid, m.p. 74.5-78.0^{o}C.

353
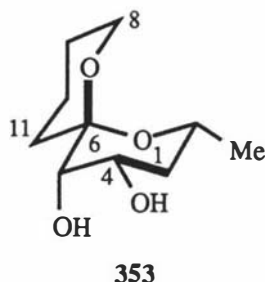
(2R*,4S*,5S*,6S*)-5-*Hydroxy-2-methyl-1,7-dioxaspiro[5.5]undec-4-yl acetate* **354**

To a solution of (2*R**,4*S**,5*S**,6*S**)-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol **353** (89 mg, 0.40 mmol) in dichloromethane (8 cm^3) was added acetic anhydride (0.11 cm^3, 1.12 mmol) followed by triethylamine (0.11 cm^3, 0.79 mmol), and the solution stirred at room temperature until no starting material could be detected (TLC). The solvent was removed at reduced pressure and the residue purified by flash chromatography, using hexane-ethyl acetate (4:1) as eluent, to give the *title compound* **354** (94 mg, 91%) as colourless prisms, m.p. 129.0-130.0°C (Found: C, 59.15; H, 8.0. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.25%); υ_{max} (film)/cm^{-1} 3462s (OH), 1737s (C=O) and 1249s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.25 (3H, d, *J* 6.2 Hz, Me), 1.51-2.04 (9H, m, 3, 9, 10, 11-CH$_2$ and OH), 2.08 (3H, s, OAc), 3.58-3.63 (3H, m, 8-CH$_2$ and C*H*OH), 3.83 (1H, qdd, $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.6 Hz, C*H*Me) and 5.25 (1H, ddd, $J_{4ax,3ax}$ 11.7, $J_{4ax,3eq}$ 5.1 and $J_{4ax,5eq}$ 2.9 Hz, C*H*OAc); δ_C (67.8 MHz; CDCl$_3$) 18.2 (CH$_2$, C-10), 21.0, 21.3 (CH$_3$, 2 x Me), 25.0 (CH$_2$, C-9), 31.5 (CH$_2$, C-11), 32.2 (CH$_2$, C-3), 60.5 (CH$_2$, C-8), 63.8 (CH, C-2), 70.0, 70.4 (CH, C-4, C-5), 98.1 (C, C-6) and 170.2 (C, *C*OMe); *m/z* (EI) 114 (C$_6$H$_{10}$O$_2$, 9), 101 (C$_5$H$_9$O$_2$, 100), 84 (C$_5$H$_8$O, 47), 55 (12) and 43 (CH$_3$CO, 27).

354
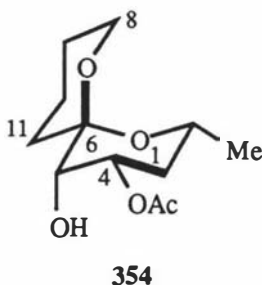
(2R*,4S*,5S*,6S*)-2-Methyl-1,7-dioxaspiro[5.5]undec-4,5-yl diacetate 355

Using the procedure described for the preparation of hydroxyacetate **354**, the *title compound* **355** (28 mg, 85%) was prepared from (2R*,4S*,5S*,6S*)-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol **353** (23 mg, 0.11 mmol), acetic anhydride (31 mm³, 0.32 mmol) and triethylamine (32 mm³, 0.23 mmol), with the addition of 4-dimethylaminopyridine (*ca.* 3 mg) as catalyst. Purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent gave colourless needles, m.p. 112.5-113.0°C (Found: C, 59.0; H, 7.8. $C_{14}H_{22}O_6$ requires C, 58.7; H, 7.7%); υ_{max} (film)/cm^{-1} 1749s (C=O) and 1247m, 1227m (C-O, acetate); δ_H (270 MHz; CDCl₃) 1.28 (3H, d, J 6.2 Hz, Me), 1.49-1.81 (8H, m, 3, 9, 10 and 11-CH₂), 1.98 (3H, s, 4 or 5-OAc), 2.13 (3H, s, 5 or 4-OAc), 3.58-3.63 (2H, m, 8-CH₂), 3.88 (1H, qdd, $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.9 Hz, CHMe), 5.05 (1H, d, $J_{5eq,4ax}$ 2.9 Hz, 5_{eq}-H) and 5.32 (1H, ddd, $J_{4ax,3ax}$ 11.9, $J_{4ax,3eq}$ 5.3 and $J_{4ax,5eq}$ 2.9 Hz, 4_{ax}-H); δ_C (67.8 MHz; CDCl₃) 18.0 (CH₂, C-10), 20.9, 21.0, 21.1 (CH₃, 3 x Me), 24.8 (CH₂, C-9), 31.1 (CH₂, C-11), 32.9 (CH₂, C-3), 60.4 (CH₂, C-8), 64.1 (CH, C-2), 67.8 (CH, C-4), 70.2 (CH, C-5), 97.2 (C, C-6) and 170.1, 170.4 (C, 2 x COMe); *m/z* (EI) 286 (M⁺, 0.3), 143 ($C_7H_{11}O_3$, 21), 126 ($C_7H_{10}O_2$, 22), 114 ($C_6H_{10}O_2$, 9), 101 ($C_5H_9O_2$, 100), 84 (C_5H_8O, 14) and 43 (CH₃CO, 40).
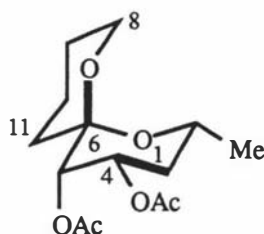
355

5-*Iodo*-2-methyl-1,7-dioxaspiro[5.5]undec-4-yl acetate 367,368,369

To a stirred suspension of (2R*,6S*)-2-methyl-1,7-dioxaspiro[5.5]undec-4-ene **345** (94 mg, 0.56 mmol), silver acetate[420] (280 mg, 1.68 mmol) and water (0.11 cm³, 6 mmol) in glacial acetic acid (10 cm³) was added iodine (171 mg, 0.67 mmol) portionwise over 10 min. The resultant yellow mixture was stirred for 18 h then filtered through a cotton wool plug to remove insoluble material. The filtrate was poured into ether (40 cm³) and washed with water (2 x 7 cm³) and saturated aqueous sodium hydrogen carbonate (7 cm³). The aqueous washings were extracted with ether (7 cm³) and the combined ethereal fractions washed with brine (7 cm³) then dried over sodium sulphate. Removal

of the solvent under reduced pressure gave an orange residue that was purified by flash chromatography, using hexane-ethyl acetate (95:5) as eluent to afford:

(i) (2R*,4S*,5R*,6S*)-*iodoacetate* **367** {32 mg, 16%; R_f 0.39 [hexane-ethyl acetate (9:1)]} as colourless rods, m.p. 49.5-52.5°C (Found: C, 41.1; H, 5.7; I, 36.0. $C_{12}H_{19}O_4I$ requires C, 40.7; H, 5.4; I, 35.8%); υ_{max} (film)/cm^{-1} 1748s (C=O) and 1239s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.21 (3H, d, J 6.2 Hz, Me), 1.47-1.90 (6H, m, 3, 9 and 10-CH$_2$), 2.02-2.06 (1H, m, 11$_{eq}$-H), 2.09 (3H, s, OAc), 2.27 (1H, ddd, J_{gem} 13.0, $J_{11ax,10ax}$ 13.0 and $J_{11ax,10eq}$ 4.4 Hz, 11$_{ax}$-H), 3.51-3.74 (2H, m, 8-CH$_2$), 3.77 (1H, d, $J_{5ax,4ax}$ 11.0 Hz, CHI), 3.81-3.96 (1H, m, CHMe) and 5.31 (1H, ddd, $J_{4ax,5ax}$ 11.0 Hz, $J_{4ax,3ax}$ 11.0 and $J_{4ax,3eq}$ 5.1 Hz, CHOAc); δ_C (67.8 MHz; CDCl$_3$) 18.6 (CH$_2$, C-10), 20.7, 21.2 (CH$_3$, 2 x Me), 24.4 (CH$_2$, C-9), 33.9 (CH$_2$, C-11), 39.5 (CH, C-5), 40.6 (CH$_2$, C-3), 61.2 (CH$_2$, C-8), 63.0 (CH, C-2), 72.5 (CH, C-4), 97.9 (C, C-6) and 169.8 (C, COMe); m/z (EI) 354 (M$^+$, 14), 194 (95), 167 (M-CH$_3$CO$_2$H-HI, 40), 101 (C$_5$H$_9$O$_2$, 100) and 43 (CH$_3$CO, 43).
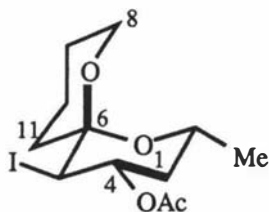
367

(ii) (2R*,4R*,5S*,6S*)-*iodoacetate* **368** {85 mg, 43%; R_f 0.34 [hexane-ethyl acetate (9:1)]} as colourless rods, m.p. 73.0-81.0°C (Found: C, 40.5; H, 5.4; M$^+$, 354.0325. $C_{12}H_{19}O_4I$ requires C, 40.7; H, 5.4%; M, 354.0328); υ_{max} (film)/cm^{-1} 1739s (C=O), 1242s (C-O, acetate) and 1083s (C-O, ether); δ_H (270 MHz; CDCl$_3$) 1.25 (3H, d, J 6.2 Hz, Me), 1.28-1.87 (6H, m, 3, 9 and 10-CH$_2$), 2.05 (3H, s, OAc), 2.08-2.17 (1H, m, 11$_{eq}$-H), 2.28 (1H, ddd, J_{gem} 14.7, $J_{11ax,10ax}$ 11.6 and $J_{11ax,10eq}$ 3.3 Hz, 11$_{ax}$-H), 3.56-3.63 (2H, m, 8-CH$_2$), 4.11 (1H, qdd, $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.0 Hz, CHMe), 4.27 (1H, dd, $J_{5eq,4eq}$ 2.2 and $J_{5eq,3eq}$ 2.2 Hz, CHI) and 5.23 (1H, ddd, $J_{4eq,5eq}$ 2.2, $J_{4eq,3ax}$ 2.2 and $J_{4eq,3eq}$ 2.2 Hz, CHOAc); δ_C (67.8 MHz; CDCl$_3$) 19.6 (CH$_2$, C-10), 21.0, 21.2 (CH$_3$, 2 x Me), 24.3 (CH$_2$, C-9), 31.2 (CH$_2$, C-11), 31.8 (CH, C-5), 38.9 (CH$_2$, C-3), 60.6 (CH$_2$, C-8), 61.8 (CH, C-2), 74.1 (CH, C-4), 96.2 (C, C-6) and 170.5 (C, COMe); m/z (EI) 354 (M$^+$, 5), 295 (M-CH$_3$CO$_2$H, 15), 194 (78), 183 (C$_9$H$_{12}$O$_4$, 43), 167 (C$_9$H$_{12}$O$_3$, 18), 101 (C$_5$H$_9$O$_2$, 67) and 43 (CH$_3$CO, 100).
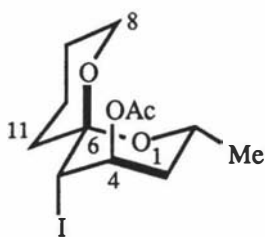
368

(iii) (2R*,4R*,5S*,6R*)-*iodoacetate* **369** {24 mg, 12%; R_f 0.29 [hexane-ethyl acetate (9:1)]} as colourless rods, m.p. 95.5-98.5°C (Found: C, 40.5; H, 5.2; M⁺, 354.0329. $C_{12}H_{19}O_4I$ requires C, 40.7; H, 5.4%; M, 354.0328); υ_{max} (film)/cm⁻¹ 1746s (C=O) and 1242s (C-O, acetate); δ_H (270 MHz; CDCl₃) 1.27 (3H, d, J 6.2 Hz, Me), 1.42-2.11 (7H, m, 3, 9, 10-CH₂ and 11_{ax}-H), 2.14 (3H, s, OAc), 2.24-2.33 (1H, m, 11_{eq}-H), 3.66-3.74 (1H, m, 8_{eq}-H), 3.91-4.05 (2H, m, CHMe and 8_{ax}-H), 4.27 (1H, d, $J_{5eq,4eq}$ 3.7 Hz, CHI) and 5.22 (1H, ddd, $J_{4eq,5eq}$ 3.7, $J_{4eq,3ax}$ 3.7 and $J_{4eq,3eq}$ 3.7 Hz, CHOAc); δ_C (67.8 MHz; CDCl₃) 18.6 (CH₂, C-10), 21.2, 21.4 (CH₃, 2 x Me), 24.7 (CH₂, C-9), 29.0 (CH₂, C-11), 37.8 (CH₂, C-3), 38.0 (CH, C-5), 62.2 (CH₂, C-8), 65.1 (CH, C-2), 71.6 (CH, C-4), 97.8 (C, C-6) and 169.7 (C, COMe); m/z (EI) 354 (M⁺, 12), 295 (MH-CH₃CO₂H, 47), 194 (100), 167 ($C_9H_{12}O_3$, 53), 101 ($C_5H_9O_2$, 79) and 43 (CH₃CO, 72).
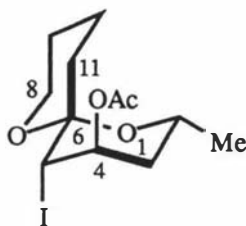
369

(2R*,4R*,5R*,6S*)-4,5-*Epoxy-2-methyl-1,7-dioxaspiro[5.5]undecane* **388**

To a solution of (2R*,4R*,5S*,6S*)-5-iodo-2-methyl-1,7-dioxaspiro[5.5]undec-4-yl acetate **368** (152 mg, 0.43 mmol) in dry dimethyl sulphoxide (10 cm³) and dry tetrahydrofuran (3 cm³) under an atmosphere of nitrogen was added 18-crown-6 (227 mg, 0.86 mmol) followed by potassium superoxide (92 mg, 1.29 mmol). After stirring for 4 h the mixture was poured into ether (83 cm³) and washed with water (3 x 17 cm³). The aqueous washings were extracted with a further volume of ether (33 cm³) and the combined ethereal phases dried over sodium sulphate. Removal of the solvent under reduced pressure gave a clear oil that was purified by flash chromatography, using hexane-ethyl acetate (4:1) as eluent, to give the *title compound* **388** (36 mg, 46%) as a

colourless oil [Found: (MH)$^+$, 185.1187. $C_{10}H_{17}O_3$ requires (MH), 185.1178]; υ_{max} (film)/cm^{-1} 1080m (C-O) and 793s (epoxide C-O); δ_H (270 MHz; CDCl$_3$) 1.16 (3H, d, J 6.2 Hz, Me), 1.49-1.93 (7H, m, 3, 9, 10-CH$_2$ and 11$_{ax}$-H), 2.03 (1H, ddd, J_{gem} 14.3, $J_{11eq,10ax}$ 2.2 and $J_{11eq,10eq}$ 2.2 Hz, 11$_{eq}$-H), 3.09 (1H, d, $J_{5,4}$ 4.0 Hz, 5-H), 3.33-3.38 (1H, m, 4-H), 3.66-3.72 (1H, m, 8$_{eq}$-H) and 3.77-3.89 (2H, m, CHMe and 8$_{ax}$-H); δ_C (67.8 MHz; CDCl$_3$) 18.3 (CH$_2$, C-10), 20.6 (CH$_3$, Me), 25.1 (CH$_2$, C-9), 32.6 (CH$_2$, C-11), 34.7 (CH$_2$, C-3), 51.7 (CH, C-4), 55.1 (CH, C-5), 59.7 (CH, C-2), 60.9 (CH$_2$, C-8) and 93.5 (C, C-6); m/z (LSIMS, DTDE matrix) 185 (MH$^+$, 100), 167 (MH-H$_2$O, 36), 141 (9), 101 (C$_5$H$_9$O$_2$, 12), 85 (11) and 55 (12).

388
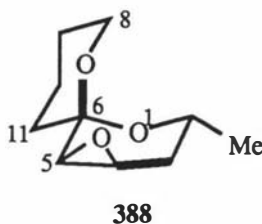
(2R*,4S*,5S*,6S*)-4,5-Epoxy-2-methyl-1,7-dioxaspiro[5.5]undecane **412**

Using the procedure described for the preparation of epoxide **388**, the *title compound* **412** (23 mg, 74%) was prepared from (2R*,4S*,5R*,6S*)-5-iodo-2-methyl-1,7-dioxaspiro[5.5]undec-4-yl acetate **367** (60 mg, 0.17 mmol), 18-crown-6 (90 mg, 0.34 mmol) and potassium superoxide (36 mg, 0.51 mmol) as a colourless oil (Found: C, 65.2; H, 8.6. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.75%); υ_{max} (film)/cm^{-1} 1097s (C-O) and 891s (epoxide C-O); δ_H (200 MHz; CDCl$_3$) 1.15 (3H, d, J 6.3 Hz, Me), 1.48-1.97 (8H, m, 3, 9, 10 and 11-CH$_2$), 2.80 (1H, dd, $J_{5,4}$ 3.6 and $J_{5,3eq}$ 0.6 Hz, 5-H), 3.32 (1H, dd, $J_{4,3eq}$ 5.6 and $J_{4,5}$ 3.6 Hz, 4-H) and 3.59-3.94 (3H, m, 8-CH$_2$ and CHMe); δ_C (67.8 MHz; CDCl$_3$) 17.7 (CH$_2$, C-10), 20.8 (CH$_3$, Me), 25.3 (CH$_2$, C-9), 30.4 (CH$_2$, C-11), 32.2 (CH$_2$, C-3), 50.9 (CH, C-4), 52.8 (CH, C-5), 61.0(2) (CH$_2$, C-8; CH, C-2) and 94.5 (C, C-6); m/z (LSIMS, DTDE matrix) 185 (MH$^+$, 45), 167 (MH-H$_2$O, 29), 113 (38), 85 (38) and 43 (CH$_3$CO, 55).

412
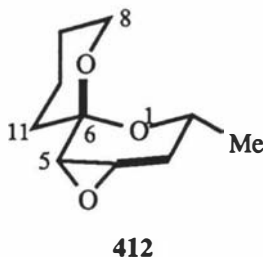
4,5-*Epoxy*-2-*methyl*-1,7-*dioxaspiro*[5.5]*undecane* **412,388**

To a stirred solution of (2R*,6S*)-2-methyl-1,7-dioxaspiro[5.5]undec-4-ene **345** (103 mg, 0.61 mmol) in dichloromethane (4 cm³) at 0°C was added portionwise over two min *m*-chloroperbenzoic acid (276 mg of a 70% w/w sample, 1.12 mmol). After 2 h the reaction was allowed to warm to room temperature and stirred a further 46 h. The solution was poured into ether (50 cm³) and washed with 10% aqueous sodium sulphite (14 cm³) and saturated aqueous sodium hydrogen carbonate (2 x 14 cm³). The aqueous washings were extracted with ether (14 cm³) and the combined organic fractions washed with brine (14cm³) before being dried over sodium sulphate. Removal of the solvent at reduced pressure gave a colourless oil which upon purification by flash chromatography using hexane-ethyl acetate (95:5→4:1) as eluent, gave (i) (2R*,4S*,5S*,6S*)-*epoxide* **412** {43 mg, 38%; R$_f$ 0.48 [hexane-ethyl acetate (4:1)]} and (ii) (2R*,4R*,5R*,6S*)-*epoxide* **388** {33 mg, 29%; R$_f$ 0.31 [hexane-ethyl acetate (4:1)]}, both as colourless oils [for which spectroscopic data was in agreement with that reported on pages 230 (**412**) and 229 (**388**)].

(2R*,4S*,5S*,6S*)-4-*Iodo*-2-methyl-1,7-*dioxaspiro*[5.5]*undecan*-5-*ol* **389**

A suspension of lithium iodide (294 mg, 2.20 mmol) in dry tetrahydrofuran (15 cm³) was cooled to -50°C under an atmosphere of nitrogen. To this was added a solution of (2R*,4R*,5R*,6S*)-4,5-epoxy-2-methyl-1,7-dioxaspiro[5.5]undecane **388** (270 mg, 1.47 mmol) in dry tetrahydrofuran (28 cm³), followed after 0.25 h by boron trifluoride etherate (1.90 cm³, 15.4 mmol). The reaction was stirred at this temperature for 0.5 h, then water (0.7 cm³) added and the mixture warmed to room temperature. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, using hexane-ethyl acetate (95:5→4:1) as eluent gave the *title compound* **389** (393 mg, 86%) as colourless needles, m.p. 82.0-83.0°C (Found: C, 38.65; H, 5.6; I, 40.8. $C_{10}H_{17}O_3I$ requires C, 38.5; H, 5.5; I, 40.65%); υ_{max} (film)/cm⁻¹ 3556-3212m (OH) and 1092br,s (C-O); δ_H (270 MHz; CDCl₃) 1.18 (3H, d, *J* 6.2 Hz, Me), 1.46-1.64 (4H, m, 9-CH₂, 10_{eq}-H and 11_{eq}-H), 1.73-1.92 (1H, m, 10_{ax}-H), 1.98-2.16 (1H, m, 11_{ax}-H), 2.04-2.22 (1H, m, 3_{ax}-H), 2.22 (1H, d, *J* 9.2 Hz, OH), 2.41 (1H, ddd, J_{gem} 13.2, $J_{3eq,4ax}$ 4.8 and $J_{3eq,2ax}$ 2.2 Hz, 3_{eq}-H), 3.39 (1H, dd, $J_{5ax,4ax}$ 10.4 and $J_{5ax,OH}$ 9.2 Hz, C*H*OH), 3.58-3.72 (2H, m, 8-CH₂), 3.77 (1H, qdd, $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.2 Hz, C*H*Me) and 4.39 (1H, ddd, $J_{4ax,5ax}$ 10.4, $J_{4ax,3ax}$ 12.7 and $J_{4ax,3eq}$ 4.8 Hz, C*H*I); δ_C (67.8 MHz; CDCl₃) 18.3 (CH₂, C-10), 20.3 (CH₃, Me), 24.9 (CH₂, C-9), 31.0 (CH₂, C-11), 32.2 (CH, C-4), 46.4 (CH₂, C-3), 61.0 (CH₂, C-8), 66.3

(CH, C-2), 78.3 (CH, C-5) and 97.9 (C, C-6); m/z (LSIMS, DTDE matrix) 313 (MH$^+$, 40), 185 (MH-HI, 100), 153 (27), 135 (48), 103 (30), 101 (C$_5$H$_9$O$_2$, 27) and 85 (27).
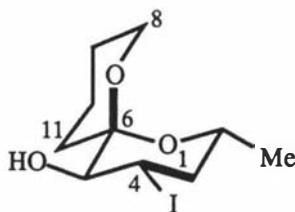
389

(2R*,4R*,5R*,6S*)-4-*Iodo*-2-methyl-1,7-*dioxaspiro*[5.5]*undecan*-5-*ol* 415

The *title compound* **415** (63 mg, 91%) was synthesized using a modification of the procedure described for the preparation of iodohydrin **389**, from (2R*,4S*,5S*,6S*)-4,5-epoxy-2-methyl-1,7-dioxaspiro[5.5]undecane **412** (41 mg, 0.22 mmol), lithium iodide (44 mg, 0.33 mmol) and boron trifluoride etherate (0.30 cm^3, 2.44 mmol). After addition of water and warming to room temperature, the reaction mixture was poured into ether (28 cm^3), washed with water (5 cm^3) and the aqueous washings then extracted with ether (12 cm^3). The combined organic fractions were dried over sodium sulphate and passed through a silica gel pad before the solvent was removed under reduced pressure. The resultant pale yellow solid was purified by flash chromatography using hexane-ethyl acetate (95:5→4:1) as eluent to give the *title compound* **415** (63 mg, 91%) as colourless needles, m.p. 104.0°C (decomp.) [Found: C, 38.45; H, 5.5; (MH)$^+$ 313.0307. C$_{10}$H$_{17}$O$_3$I requires C, 38.5; H, 5.5%; (*M*H) 313.0301]; υ_{max} (film)/cm^{-1} 3420br,s (OH) and 1082m (C-O); δ_H (270 MHz; CDCl$_3$) 1.26 (3H, d, J 6.2 Hz, Me), 1.41-2.08 (8H, m, 3, 9, 10 and 11-CH$_2$), 2.25 (1H, d, J 8.4 Hz, OH), 3.57-3.72 (2H, m, 8-CH$_2$), 3.76 (1H, dd, $J_{5eq,OH}$ 8.4 and $J_{5eq,4eq}$ 2.9 Hz, C*H*OH), 4.07-4.19 (1H, m, C*H*Me) and 4.29-4.33 (1H, m, CHI); δ_C (67.8 MHz; CDCl$_3$) 18.1 (CH$_2$, C-10), 20.7 (CH$_3$, Me), 21.4 (CH, C-4), 24.6 (CH$_2$, C-9), 31.4 (CH$_2$, C-3), 37.1 (CH$_2$, C-11), 60.2 (CH$_2$, C-8), 61.7 (CH, C-2), 71.6 (CH, C-5) and 98.4 (C, C-6); m/z (CI) 330 (MH+NH$_3$, 4), 313 (MH$^+$, 37), 295 (MH-H$_2$O, 36), 185 (MH-HI, 100), 169 (38), 167 (13), 118 (16) and 101 (C$_5$H$_9$O$_2$, 21).
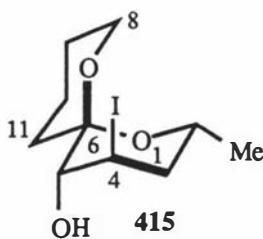
415

(2R*,4R*,5S*,6R*)-4-*Iodo-2-methyl*-1,7-*dioxaspiro*[5.5]*undecan-5-ol* **416**

A suspension of lithium iodide (122 mg, 0.91 mmol) in dry tetrahydrofuran (4.7 cm^3) was cooled to -50°C under an atmosphere of nitrogen. To this was then added a solution of (2*R**,4*S**,5*S**,6*S**)-4,5-epoxy-2-methyl-1,7-dioxaspiro[5.5]undecane **412** (151 mg, 0.82 mmol) in dry tetrahydrofuran (9.5 cm^3), followed after 0.25 h by boron trifluoride etherate (0.20 cm^3, 1.63 mmol). The reaction was stirred at this temperature for 0.5 h, then water (0.4 cm^3) was added and the mixture warmed to room temperature. The solvent was removed under reduced pressure and the residue purified by flash chromatography, using hexane-ethyl acetate (95:5→4:1) as eluent to give iodohydrin **415** (125 mg, 49%) and the *title compound* **416** (99 mg, 39%) as colourless needles, m.p. 64.0-67.0°C (Found: C, 38.45; H, 5.7; I, 41.0. C$_{10}$H$_{17}$O$_3$I requires C, 38.5; H, 5.5; I, 40.65%); υ_{max} 3589-3172s (OH) and 1078s (C-O); δ_H (270 MHz; CDCl$_3$) 1.40 (3H, d, *J* 7.0 Hz, Me), 1.47-1.66 (4H, m, 9-CH$_2$, 10$_{eq}$-H and 11$_{eq}$-H), 1.70-1.89 (1H, m, 10$_{ax}$-H), 2.02 (1H, ddd, J_{gem} 13.0, $J_{11ax,10ax}$ 13.0 and $J_{11ax,10eq}$ 4.6 Hz, 11$_{ax}$-H), 2.35 (1H, ddd, J_{gem} 13.0, $J_{3eq,4ax}$ 4.4 and $J_{3eq,2eq}$ 1.8 Hz, 3$_{eq}$-H), 2.61 (1H, ddd, J_{gem} 13.0, $J_{3ax,4ax}$ 13.0 and $J_{3ax,2eq}$ 5.9 Hz, 3$_{ax}$-H), 2.73 (1H, d, *J* 9.9 Hz, OH), 3.40 (1H, dd, $J_{5ax,OH}$ 9.9 and $J_{5ax,4ax}$ 9.9 Hz, C*H*OH), 3.63-3.73 (1H, m, 8$_{eq}$-H), 3.83-4.06 (2H, m, C*H*Me and 8$_{ax}$-H) and 4.61 (1H, ddd, $J_{4ax,5ax}$ 9.9, $J_{4ax,3ax}$ 13.0 and $J_{4ax,3eq}$ 4.4 Hz, C*H*I); δ_C (67.8 MHz; CDCl$_3$) 18.3 (CH$_2$, C-10), 20.2 (CH$_3$, Me), 24.9 (CH$_2$, C-9), 28.9 (CH, C-4), 32.2 (CH$_2$, C-11), 43.4 (CH$_2$, C-3), 61.5 (CH$_2$, C-8), 70.1 (CH, C-2), 78.4 (CH, C-5) and 98.7 (C, C-6); *m/z* (LSIMS, NBA matrix) 313 (MH$^+$, 35), 273 (27), 246 (35), 185 (MH-HI, 100), 136 (81), 101 (C$_5$H$_9$O$_2$, 92) and 78 (33). For iodohydrin **415** data refer page 232.
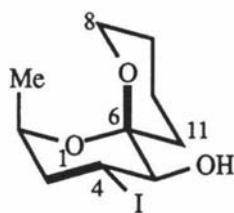
416

(2R*,4S*,5S*,6S*)-4-*Iodo-2-methyl*-1,7-*dioxaspiro*[5.5]*undec-5-yl acetate* **387**

To a solution of (2*R**,4*S**,5*S**,6*S**)-4-iodo-2-methyl-1,7-dioxaspiro[5.5]undecan-5-ol **389** (235 mg, 0.75 mmol) in dichloromethane (11 cm^3) was added acetic anhydride (0.50 cm^3, 3.55 mmol), triethylamine (0.40 cm^3, 2.87 mmol) and a catalytic amount of 4-dimethylaminopyridine (*ca.* 5 mg). The solution was stirred at room temperature until no

starting material was visible (TLC). The solvent was removed under reduced pressure and the residue purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the *title compound* **387** (252 mg, 95%) as colourless needles, m.p. 105.5-107.5°C (Found: C, 40.9; H, 5.6; I, 35.8. $C_{12}H_{19}O_4I$ requires C, 40.7; H, 5.4; I, 35.8%); υ_{max} (film)/cm^{-1} 1747s (C=O) and 1230s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.20 (3H, d, J 6.2 Hz, Me), 1.42-1.63 (5H, m, 9, 11-CH$_2$ and 10$_{eq}$-H), 1.73-1.88 (1H, m, 10$_{ax}$-H), 2.12-2.26 (1H, m, 3$_{ax}$-H), 2.20 (3H, s, OAc), 2.48 (1H, ddd, J_{gem} 13.3, $J_{3eq,4ax}$ 4.8 and $J_{3eq,2ax}$ 2.2 Hz, 3$_{eq}$-H), 3.57-3.76 (2H, m, 8-CH$_2$), 3.83 (1H, qdd, $J_{2ax,Me}$ 6.2, $J_{2ax,3ax}$ 12.4 and $J_{2ax,3eq}$ 2.2 Hz, CHMe), 4.53 (1H, ddd, $J_{4ax,3ax}$ 12.7, $J_{4ax,5ax}$ 11.0 and $J_{4ax,3eq}$ 4.8 Hz, CHI) and 4.96 (1H, d, $J_{5ax,4ax}$ 11.0 Hz, CHOAc); δ_C (67.8 MHz; CDCl$_3$) 18.1 (CH$_2$, C-10), 20.2, 21.3 (CH$_3$, 2 x Me), 24.4 (CH, C-4), 24.7 (CH$_2$, C-9), 31.3 (CH$_2$, C-3), 46.4 (CH$_2$, C-11), 61.1 (CH$_2$, C-8), 66.1 (CH, C-2), 77.5 (CH, C-5), 97.5 (C, C-6) and 170.3 (C, COMe); *m/z* (LSIMS, DTDE matrix) 355 (MH$^+$, 100), 295 (MH-CH$_3$CO$_2$H, 67), 227 (MH-HI, 35), 167(MH-HI-CH$_3$CO$_2$H, 63), 153 (33), 135 (53), 103 (52), 101 (C$_5$H$_9$O$_2$, 38), 85 (72) and 43 (CH$_3$CO, 42).
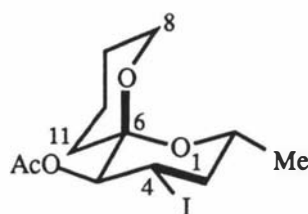
387

(2R*,4R*,5R*,6S*)-4-*Iodo-2-methyl*-1,7-*dioxaspiro*[5.5]*undec*-5-*yl acetate* **410**

Using the procedure described for the preparation of iodoacetate **387,** the *title compound* **410** (76 mg, 89%) was prepared from (2R*,4R*,5R*,6S*)-4-iodo-2-methyl-1,7-dioxaspiro[5.5]undecan-5-ol **415** (75 mg, 0.24 mmol), acetic anhydride (0.16 cm^3, 1.21 mmol) and triethylamine (0.13 cm^3, 0.96 mmol) as colourless rods, m.p. 107.5-110.0°C [Found: C, 40.8; H, 5.7; (MH)$^+$, 355.0418. C$_{12}$H$_{19}$O$_4$I requires C, 40.7; H, 5.4%; (MH), 355.0406]; υ_{max} (film)/cm^{-1} 1749s (C=O) and 1232s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.29 (3H, d, J 6.2 Hz, Me), 1.33-2.04 (8H, m, 3, 9, 10 and 11-CH$_2$), 2.09 (3H, s, OAc), 3.58-3.76 (2H, m, 8-CH$_2$), 4.09-4.23 (1H, m, CHMe), 4.24-4.27 (1H, m, CHI) and 4.96 (1H, d, $J_{5eq,4eq}$ 2.2 Hz, CHOAc); δ_C (67.8 MHz; CDCl$_3$) 17.2 (CH, C-4), 17.9 (CH$_2$, C-10), 20.6, 20.8 (CH$_3$, 2 x Me), 24.6 (CH$_2$, C-9), 31.2 (CH$_2$, C-3), 37.6 (CH$_2$, C-11), 60.1 (CH$_2$, C-8), 61.7 (CH, C-2), 71.3 (CH, C-5), 97.3 (C, C-6) and 169.5 (C,

COMe); m/z (LSIMS, NBA matrix) 355 (MH$^+$, 35), 295 (MH-CH$_3$CO$_2$H, 28), 227 (MH-HI, 33), 155 (C$_8$H$_{12}$O$_3$, 100), 101 (C$_5$H$_9$O$_2$, 17) and 43 (CH$_3$CO, 13).
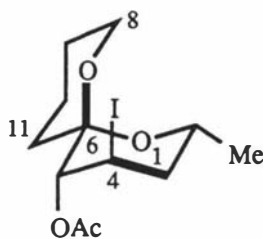
410

(2R*,4R*,5S*,6R*)-4-*Iodo*-2-methyl-1,7-*dioxaspiro*[5.5]*undec*-5-*yl acetate* **418**

Using the procedure described for the preparation of iodoacetate **387**, the *title compound* **418** (51 mg, 85%) was prepared from (2R*,4R*,5S*,6R*)-4-iodo-2-methyl-1,7-dioxaspiro[5.5]undecan-5-ol **416** (53 mg, 0.15 mmol), acetic anhydride (0.12 cm^3, 0.85 mmol) and triethylamine (0.09 cm^3, 0.65 mmol) as colourless rods, m.p. 114.0-114.5ºC [Found: C, 41.1; H, 5.3; I, 36.3; (MH)$^+$, 355.0413. C$_{12}$H$_{19}$O$_4$I requires C, 40.7; H, 5.4; I, 35.8%; (MH) 355.0406]; υ_{max} (nujol)/cm^{-1} 1739s (C=O), 1203s (C-O, ether) and 1230s (C-O, acetate); δ_H (200 MHz; CDCl$_3$) 1.36-1.95 (6H, m, 9, 10 and 11-CH$_2$), 1.43 (3H, d, J 7.0 Hz, Me), 2.20 (3H, s, OAc), 2.43 (1H, ddd, J_{gem} 13.6, $J_{3eq,4ax}$ 4.4 and $J_{3eq,2eq}$ 1.8 Hz, 3$_{eq}$-H), 2.57-2.79 (1H, m, 3$_{ax}$-H), 3.60-3.79 (1H, m, 8$_{eq}$-H), 3.79-4.14 (2H, m, CHMe and 8$_{ax}$-H), 4.72 (1H, ddd, $J_{4ax,5ax}$ 11.2, $J_{4ax,3ax}$ 11.2 and $J_{4ax,3eq}$ 4.4 Hz, CHI) and 5.00 (1H, d, $J_{5ax,4ax}$ 11.0 Hz, CHOAc); δ_C (50.3 MHz; CDCl$_3$) 18.4 (CH$_2$, C-10), 20.7, 21.3 (CH$_3$, 2 x Me), 21.8 (CH, C-4), 25.0 (CH$_2$, C-9), 32.8 (CH$_2$, C-3), 43.9 (CH$_2$, C-11), 61.9 (CH$_2$, C-8), 70.2 (CH, C-2), 78.0 (CH, C-5), 98.5 (C, C-6) and 170.2 (C, COMe); m/z (CI) 355 (MH$^+$, 100), 295 (MH-CH$_3$CO$_2$H, 82), 229 (30), 227 (MH-HI, 53), 167 (MH-HI-CH$_3$CO$_2$H, 55), 165 (55), 118 (40) and 101 (C$_5$H$_9$O$_2$, 100).
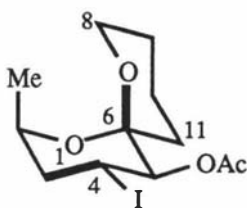
418

(4'E)-5'-*Acetoxypent-4'-en-2'-yl 5-acetoxypentanoate* **401** *and* (4'E)-5'-*Acetoxypent-4'-en-2'-yl 5-hydroxypentanoate* **402**

A mixture of (2R*,4S*,5S*,6S*)-4-iodo-2-methyl-1,7-dioxaspiro[5.5]undec-5-yl acetate **387** (166 mg, 0.47 mmol), silver acetate (157 mg, 0.94 mmol) and water (0.4 cm^3, 23 mmol) in glacial acetic acid (13 cm^3) was heated at reflux for 0.25 h, at the end of which time two products were visible (TLC). The suspension was filtered through a Celite pad, the pad washed with dichloromethane (20 cm^3) and the filtrate dried over sodium sulphate. Removal of the solvent at reduced pressure gave a clear oil that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to give:

(i) *diacetate* **401** {18 mg, 13%; R$_f$ 0.46 [hexane-ethyl acetate (1:1)]} as a colourless oil (Found: C, 58.9; H, 7.8. C$_{14}$H$_{22}$O$_6$ requires C, 58.7; H, 7.7%); υ_{max} (film)/cm^{-1} 3082w (=C-H), 1763-1720s (C=O, ester and 2 x acetate), 1676m (C=C, *trans*) and 1226br,s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.22 (3H, d, J 6.2 Hz, Me), 1.59-1.75 (4H, m, 3 and 4-CH$_2$), 2.05 (3H, s, CH$_2$OAc), 2.12 (3H, s, =CHOAc), 2.22-2.27 (2H, m, =CHCH_2), 2.30-2.35 (2H, m, CH_2COO), 4.07 (2H, t, J 6.2 Hz, CH_2OAc), 4.94 (1H, qt, $J_{2',Me}$ 6.2 and $J_{2',3'}$ 6.2 Hz, CHMe), 5.36 (1H, dt, $J_{4',5'}$ 12.5 and $J_{4',3'}$ 7.7 Hz, =CHCH$_2$) and 7.11 (1H, dt, $J_{5',4'}$ 12.5 and $J_{5',3'}$ 1.3 Hz, =CHOAc); δ_C (67.8 MHz; CDCl$_3$) 19.4 (CH$_3$, C-1'), 20.7 (CH$_3$, 5'-COMe), 21.0 (CH$_2$, C-3), 21.5 (CH$_3$, 5-COMe), 28.0 (CH$_2$, C-4), 33.8 (CH$_2$, C-3'), 34.0 (CH$_2$, C-2), 64.0 (CH$_2$, C-5), 69.9 (CH, C-2'), 109.7 (CH, C-4'), 137.4 (CH, C-5'), 167.4 (C, 5'-COMe), 171.4 (C, 5-COMe) and 172.8 (C, C-1); *m*/*z* (LSIMS, NBA matrix) 287 (MH$^+$, 52), 279 (37), 220 (34), 149 (74), 137 (38), 101 (C$_5$H$_9$O$_2$, 44), 89 (57), 77 (67), 57 (49), 43 (CH$_3$CO, 100) and 29 (36).
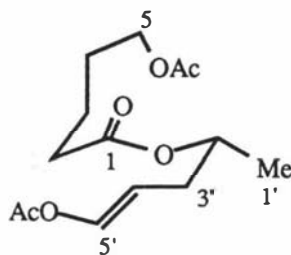
401

(ii) *hydroxyacetate* **402** {79 mg, 69%; R$_f$ 0.32 [hexane-ethyl acetate (1:1)]} as a colourless oil (Found: C, 59.1; H, 8.3. C$_{12}$H$_{20}$O$_5$ requires C, 59.0; H, 8.0%); υ_{max} (film)/cm^{-1} 3082w (=C-H), 3670-3116s (OH), 1755s, 1732s (C=O, ester and acetate), 1676m (C=C, *trans*) and 1221br,s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.22 (3H, d, J 6.2 Hz, Me), 1.55-1.74 (4H, m, 3 and 4-CH$_2$), 2.12 (3H, s, OAc), 2.24 (2H, ddd, $J_{3',4'}$ 7.7, $J_{3',2'}$ 6.2 and $J_{3',5'}$ 1.3 Hz, =CHCH_2), 2.33 (2H, t, J 7.1 Hz, CH_2COO), 3.65 (2H, t, J 6.2

Hz, CH_2OH), 4.94 (1H, qt, $J_{2',Me}$ 6.2 and $J_{2',3'}$ 6.2 Hz, CHMe), 5.36 (1H, dt, $J_{4',5'}$ 12.5 and $J_{4',3'}$ 7.7 Hz, =CHCH$_2$) and 7.10 (1H, dt, $J_{5',4'}$ 12.5 and $J_{5',3'}$ 1.3 Hz, =CHOAc); δ_C (67.8 MHz; CDCl$_3$) 19.5 (CH$_3$, C-1'), 20.7 (CH$_3$, COMe), 21.1 (CH$_2$, C-3), 32.1 (CH$_2$, C-4), 33.8 (CH$_2$, C-3'), 34.2 (CH$_2$, C-2), 62.2 (CH$_2$, C-5), 69.8 (CH, C-2'), 109.8 (CH, C-4'), 137.4 (CH, C-5'), 168.2 (C, COMe) and 173.2 (C, C-1); m/z (LSIMS, DTDE matrix) 245 (MH$^+$, 94), 227 (MH-H$_2$O, 3), 185 (M-CH$_3$CO-H$_2$O, 14), 149 (13), 127 (24), 101 (C$_5$H$_9$O$_2$, 100), 85 (74) and 43 (CH$_3$CO, 25).

402
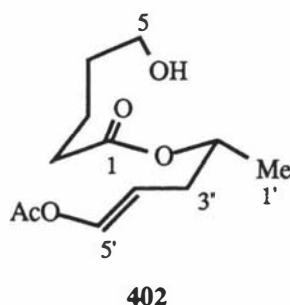
5'-Oxopent-2'-yl 5-hydroxypentanoate **409**

To (4'E)-5'-acetoxypent-4'-en-2'-yl 5-hydroxypentanoate **402** (36 mg, 0.15 mmol) in methanol (2.6 cm^3) was added potassium carbonate (7 mg, 0.051 mmol) and the mixture stirred until no starting material was visible (TLC). The majority of the solvent was removed under reduced pressure and the residual liquid (*ca.* 0.3 cm^3) was subjected to flash chromatography, using hexane-ethyl acetate (1:1) as eluent, to give the *title compound* **409** (24 mg, 82%) as a colourless oil [Found: (MH)$^+$, 203.1288. C$_{10}$H$_{18}$O$_4$ requires (*M*H), 203.1283]; υ_{max} (film)/cm^{-1} 3702-3060s (OH), 2727w (*H-C=O) and 1735-1701s (C=O, ester and aldehyde); δ_H (270 MHz; CDCl$_3$) 1.25 (3H, d, J 6.2 Hz, Me), 1.55-1.82 (4H, m, 3 and 4-CH$_2$), 1.89-1.94 (2H, m, 3'-CH$_2$), 2.32 (2H, t, J 7.3 Hz, CH_2COO), 2.50 (2H, td, $J_{4',3'}$ 7.3 and $J_{4',5'}$ 1.4 Hz, CH_2CHO), 3.66 (2H, t, J 6.2 Hz, CH_2OH), 4.94 (1H, qt, $J_{2',Me}$ 6.2 and $J_{2',3'}$ 6.2 Hz, CHMe) and 9.77 (1H, t, $J_{5',4'}$ 1.4 Hz, CHO); δ_C (67.8 MHz; CDCl$_3$) 20.0 (CH$_3$, C-1'), 21.1 (CH$_2$, C-3), 28.1 (CH$_2$, C-3'), 32.0 (CH$_2$, C-4), 34.1 (CH$_2$, C-2), 40.0 (CH$_2$, C-4'), 62.2 (CH$_2$, C-5), 70.0 (CH, C-2'), 173.3 (C, C-1) and 201.5 (C, C-5'); m/z (CI) 220 (MH+NH$_3$, 2), 203 (MH$^+$, 3), 185 (M-OH, 3), 118 (8), 101 (C$_5$H$_9$O$_2$, 47) and 85 (C$_5$H$_9$O, 100).

409
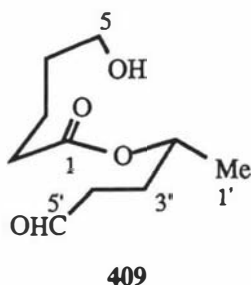
(2R*,4S*,5S*,6S*)-4-*Hydroxy-2-methyl-1,7-dioxaspiro[5.5]undec-5-yl acetate* **356**

Using the procedure described for the preparation of esters **401** and **402**, the *title compound* **356** {31 mg, 74%; R_f 0.50 [hexane-ethyl acetate (1:1)]} was prepared from (2R*,4R*,5R*,6S*)-4-iodo-2-methyl-1,7-dioxaspiro[5.5]undec-5-yl acetate **410** (61 mg, 0.17 mmol) and silver acetate (58 mg, 0.35 mmol). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent afforded a colourless solid, m.p. 81.0-82.5°C (Found: C, 58.7; H, 8.1. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.25%); υ_{max} (film)/cm^{-1} 3647-3107s (OH), 1743s (C=O) and 1245s (C-O, acetate); δ_H (270 MHz; CDCl$_3$) 1.27 (3H, d, J 6.4 Hz, Me), 1.33-1.90 (8H, m, 3, 9, 10 and 11-CH$_2$), 1.99-2.06 (1H, br.s, OH), 2.14 (3H, s, OAc), 3.59 (2H, dd, $J_{8,9ax}$ 8.3 and $J_{8,9eq}$ 3.1 Hz, 8-CH$_2$), 3.80 (1H, qdd, $J_{2ax, e}$ 6.4, $J_{2ax,3ax}$ 12.8 and $J_{2ax,3eq}$ 2.4 Hz, C*H*Me), 4.18-4.29 (1H, m, C*H*OH) and 4.93 (1H, d, $J_{5eq,4ax}$ 3.3 Hz, C*H*OAc); δ_C (67.8 MHz; CDCl$_3$) 18.0 (CH$_2$, C-10), 21.0(2) (CH$_3$, 2 x Me), 24.9 (CH$_2$, C-9), 31.4 (CH$_2$, C-11), 35.8 (CH$_2$, C-3), 60.3 (CH$_2$, C-8), 64.2 (CH, C-2), 65.6 (CH, C-4), 73.1 (CH, C-5), 97.2 (C, C-6) and 171.6 (C, *C*OMe); *m/z* (LSIMS, NBA matrix) 245 (MH$^+$, 100), 227 (MH-H$_2$O, 12), 185 (MH-CH$_3$CO$_2$H, 48), 167 (MH-H$_2$O-CH$_3$CO$_2$H, 12), 143 (14), 137 (23), 101 (C$_5$H$_9$O$_2$, 54), 77 (16), 55 (23) and 43 (CH$_3$CO, 44).

Hydroxyacetate **354** {9 mg, 21%; R_f 0.60 [hexane-ethyl acetate (1:1)]} was also obtained from the reaction (for which physical and spectroscopic data was in agreement with that reported on page 226).

Acetylation of an approximately 1:1 mixture of the two hydroxyacetates **356** and **354** (9 mg, 0.037 mmol) following the procedure described for the formation of diacetate **355**, using acetic anhydride (10 mm^3, 0.052 mmol), triethylamine (11 mm^3, 0.037 mmol) and 4-dimethylaminopyridine (*ca.* 1 mg) gave 9 mg (85%) of diacetate **355**, thus confirming the identities of the two products obtained from iodoacetate **410**.

238

356
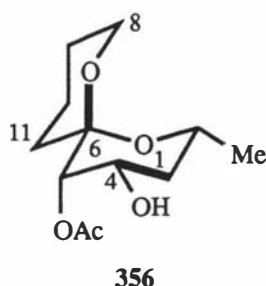
(2'S*,3'S*,5'S*)-2-(5-tert-*Butyldimethylsilyloxy*-1-*oxohexan*-2,3-*diol*)-1,4-
dimethoxynaphthalene **419** *and* (2'R*,3'R*,5'S*)-2-(5-tert-*Butyldimethylsilyloxy*-1-
oxohexan-2,3-*diol*)-1,4-*dimethoxynaphthalene* **420**

The *title compounds* **419** and **420** were prepared following the procedure for diol **353**, from (2'Z)-2-(5-*tert*-butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-dimethoxynaphthalene **327** (49 mg, 0.12 mmol), 4-methylmorpholine N-oxide (17 mg, 0.14 mmol) and osmium tetraoxide(60 mm^3 of a 2.5 wt. % solution in *tert*-butyl alcohol, 0.05 equiv.). Purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent gave:

(i) *diol* **419** {12 mg, 26% based on unreacted **327**; R_f 0.63 [hexane-ethyl acetate (1:1)]} as a colourless oil [Found: (MH)$^+$, 449.2346. $C_{24}H_{36}O_6Si$ requires (MH), 449.2359]; v_{max} (film)/cm^{-1} 3604-3222s (OH), 1663s (C=O) and 1104s (C-O); δ_H (270 MHz; CDCl$_3$) -0.04, -0.01 (6H, s, SiMe$_2$), 0.79 (9H, s, Bu^t), 0.99 (3H, d, J 5.9 Hz, Me), 1.21-1.32 (1H, m, 4'-H^A), 1.57-1.68 (1H, m, 4'-H^B), 3.30 (1H, d, J 4.4 Hz, 3'-OH), 3.87-4.17 (9H, m, 2 x OMe, 2'-OH, 3'-H and CHOSi), 5.32-5.40 (1H, m, 2'-H), 6.97 (1H, s, 3-H), 7.61-7.66 (2H, m, 6-H and 7-H), 8.12-8.16 (1H, m, 5-H or 8-H) and 8.28-8.31 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -5.0, -4.2 (CH$_3$, SiMe$_2$), 17.9 (C, CMe$_3$), 23.9 (CH$_3$, C-6'), 25.7 (CH$_3$, CMe_3), 40.0 (CH$_2$, C-4'), 55.8 (CH$_3$, 4-OMe), 64.5 (CH$_3$, 1-OMe), 68.5 (CH, C-5'), 72.7 (CH, C-3'), 79.9 (CH, C-2'), 101.6 (CH, C-3), 122.6, 123.4 (CH, C-5, C-8), 123.2 (C, C-2), 127.4, 128.3 (CH, C-6, C-7), 128.2, 129.4 (C, C-4a, C-8a), 151.7, 152.2 (C, C-1, C-4) and 202.1 (C, C-1'); m/z (LSIMS, NBA matrix) 449 (MH$^+$, 26), 317 (MH-C$_6$H$_{16}$OSi, 18), 229 (21), 215 (C$_{13}$H$_{11}$O, 100), 159 (C$_8$H$_{19}$OSi, 41), 145 (C$_7$H$_{17}$OSi, 41), 101 (25) and 73 (60).
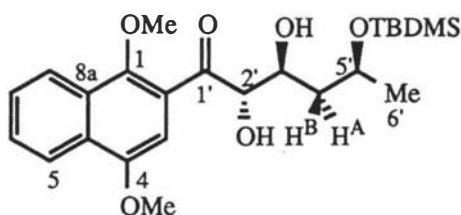
419

(ii) *diol* **420** {16 mg, 34% based on unreacted **327**; R_f 0.51 [hexane-ethyl acetate (1:1)]} as a colourless oil (Found: C, 64.1; H, 8.0. $C_{24}H_{36}O_6Si$ requires C, 64.25; H, 8.1%); υ_{max} (film)/cm^{-1} 3632-3135s (OH), 1665s (C=O) and 1102br,s (C-O); δ_H (270 MHz; CDCl$_3$) -0.13, -0.09 (6H, s, SiMe$_2$), 0.55 (9H, s, Bu^t), 1.00 (3H, d, *J* 6.2 Hz, Me), 1.03-1.14 (1H, m, 4'-H^A), 1.49-1.72 (1H, m, 4'-H^B), 2.93 (1H, d, *J* 5.7 Hz, 3'-OH), 3.89-4.12 (2H, m, 2'-OH and CHOSi), 3.97 (3H, s, 1-OMe), 4.02 (3H, s, 4-OMe), 4.22-4.33 (1H, m, 3'-H), 5.45 (1H, dd, $J_{2',OH}$ 6.2 and $J_{2',3'}$ 2.9 Hz, 2'-H), 6.97 (1H, s, 3-H), 7.60-7.64 (2H, m, 6-H and 7-H), 8.13-8.17 (1H, m, 5-H or 8-H) and 8.24-8.28 (1H, m, 8-H or 5-H); δ_C (67.8 MHz; CDCl$_3$) -5.4, -4.6 (CH$_3$, SiMe$_2$), 17.5 (C, *C*Me$_3$), 23.4 (CH$_3$, C-6'), 25.4 (CH$_3$, C*Me$_3$*), 39.4 (CH$_2$, C-4'), 55.8 (CH$_3$, 4-OMe), 64.4 (CH$_3$, 1-OMe), 65.8 (CH, C-5'), 70.3 (CH, C-3'), 80.4 (CH, C-2'), 101.6 (CH, C-3), 122.6, 123.4 (CH, C-5, C-8), 124.4 (C, C-2), 127.3, 128.3 (CH, C-6, C-7), 128.4, 129.5 (C, C-4a, C-8a), 151.9, 152.3 (C, C-1, C-4) and 201.8 (C, C-1'); *m/z* (LSIMS, NBA matrix) 449 (MH$^+$, 40), 303 (20), 215 (C$_{13}$H$_{11}$O, 100), 203 (28), 159 (C$_8$H$_{19}$OSi, 24), 145 (C$_7$H$_{17}$OSi, 47), 101 (20) and 73 (44).

Ketone **327** (6 mg, 12%) was recovered from the reaction.

420
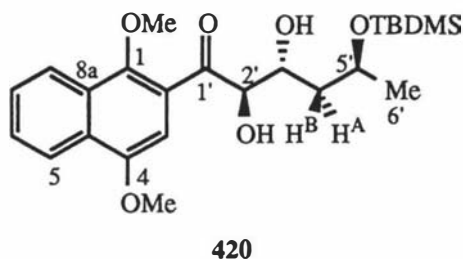
(3aR*,5S*,5aS*,11aR*,11bS*,6'R*)-3a,5a,11a,11b,5',6'-*Hexahydro*-5a,11a-*dihydroxy*-6'-*methylspiro*[5H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-5',2'-[2H]*pyran*]-2,6,11(3H)-*trione* **423** *and* (3aS*,5S*,5aR*,11aS*,11bR*,6'R*)-3a,5a,11a,11b,5',6'-*Hexahydro*-5a,11a-*dihydroxy*-6'-*methylspiro*[5H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-5',2'-[2H]*pyran*]-2,6,11(3H)-*trione* **421**

To a solution of spiroketal olefins **333** and **334** [8.3 mg, 0.024 mmol as a 4:5 (**333:334**) mixture of stereoisomers] in dichloromethane (0.25 cm^3) was added cetyltrimethylammonium permanganate[474] (11.9 mg, 0.030 mmol) and the reaction stirred at room temperature for 3h. Ether (3 cm^3) was added and the suspension dried over sodium sulphate before being filtered through a silica gel pad. After washing the pad with ether (*ca*. 15 cm^3) and removal of the solvent under reduced pressure, the residue was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent, to give

the *title compounds* **423** and **421** (2.1 mg, 27% based on unreacted **333,334**) as a yellow solid and as a 1:1 (**423:421**) mixture of stereoisomers (^{1}H nmr), m.p. 237.0-239.5°C (Found: M$^+$, 386.0962. $C_{20}H_{18}O_8$ requires M, 386.1002); υ_{max} (CH_2Cl_2)/cm^{-1} 3861-3369s (OH), 1785s (C=O, γ-lactone) and 1706s, 1687s (C=O, α-hydroxy aryl ketone); δ_H (270 MHz; CDCl$_3$) 0.68 (1.5H, d, J 6.3 Hz, Me), 0.98 (1.5H, d, J 6.6 Hz, Me), 0.82-0.96, 1.20-1.40, 1.48-1.87 (2H, m, 5'-CH$_2$), 2.73, 2.75 (1H, d, J_{gem} 17.5 Hz, 3-H^A), 2.93(2) (1H, dd, J_{gem} 17.5 and $J_{3B,3a}$ 4.6 Hz, 3-H^B), 3.26-3.40, 3.73-3.89 (1H, m, 6'-H), 3.64-3.81 (1H, m, 2 x OH), 4.42, 4.46 (1H, s, 2 x OH), 4.61, 4.78 (1H, dd, $J_{3a,3B}$ 4.6 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.38, 5.41 (1H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 5.85-5.95 (1H, m, 3'-H), 5.95-6.03 (1H, m, 4'-H), 7.73-7.82 (2H, m, 8-H and 9-H) and 8.02-8.17 (2H, m, 7-H and 10-H); δ_C (100.6 MHz; CDCl$_3$) 19.5, 19.9 (CH$_3$, Me), 29.7, 31.3 (CH$_2$, C-5'), 37.7, 37.8 (CH$_2$, C-3), 66.0, 68.8 (CH, C-6'), 67.8, 68.3 (CH, C-3a), 73.9 (CH, C-11b), 80.7, 81.5, 84.2 (C, C-5a, C-11a), 96.2, 97.0 (C, C-5), 122.3(2) (CH, C-3'), 126.2, 126.5 (CH, C-7, C-10), 127.0, 127.3 (CH, C-4'), 129.2, 130.8 (C, C-6a, C-10a), 133.8, 133.9, 134.9, 135.1 (CH, C-8, C-9), 173.9, 174.0 (C, C-2) and 188.6, 188.7, 196.3, 196.4 (C, C-6, C-11); m/z (EI) 386 (M$^+$, 2), 277 (37), 257 ($C_{14}H_9O_5$, 6), 204 (13), 192 (21), 162 (8), 113 ($C_6H_9O_2$, 100), 95 (15), 85 (56) and 43 (CH$_3$CO, 29).

Unreacted spiroketals **333,334** (1.1 mg, 13%) were recovered from the reaction.
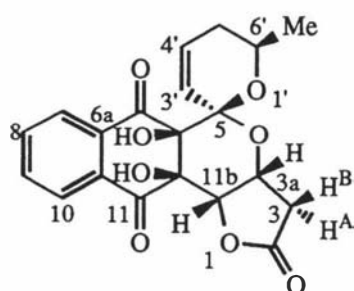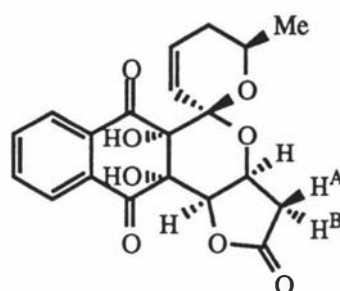
423   **421**

Stannous trifluoromethanesulphonate

The title compound was prepared by an adaptation of the method of Mukaiyama *et al.*[494] After adding the trifluoromethanesulphonic acid (18.7 cm^3, 0.21 mol) to anhydrous tin(II) chloride (12.72 g, 0.21 mol) under an atmosphere of nitrogen, the reaction was heated 21 h then extra acid added (5 cm^3, 0.056 mol) and the mixture heated a further 4 h. The excess acid and volatiles were removed *in vacuo* and the solid washed thoroughly with sodium dried ether (6 x 40 cm^3). The product was dried under reduced pressure at 50°C for 8 h, then stored under argon in a desiccator until required[495] (Found: C, 5.8; F, 27.05; S, 15.3. SnC$_2$F$_6$O$_6$S$_2$ requires C, 5.8; F, 27.35; S, 15.4%).

2-(Phenylmethoxy)acetyl Chloride **439**

The title compound **439** (67.38 g, 78% over two steps) was prepared using a modification of the procedure of Kukla and Fortunato.[479] A greater amount of benzyl alcohol (520 cm^3, 5.02 mol) was used to maintain the fluidity of the reaction mixture, and after addition of sodium hydride (22.00 g, 0.92 mol), ethyl bromoacetate (52 cm^3, 0.47 mol) was added instead of ethyl chloroacetate. After hydrolysis of the ester, the crude carboxylic acid was heated with thionyl chloride (52 cm^3, 0.70 mol) and the resultant acid chloride purified by distillation. The product was obtained as a colourless oil, b.p. 69-71°C/0.15 mmHg (lit.,[607] b.p. 81-83°C/0.6 mmHg); υ_{max} (film)/cm^{-1} 3089w, 3065m and 3032m (Ar-H), 1798br,s (C=O) and 1132s (C-O); δ_C (50.2 MHz; CDCl$_3$) 73.4 (CH$_2$, OCH$_2$Ph), 74.7 (CH$_2$, C-2), 127.9, 128.2, 128.5 [CH, Ph (first and last peak coincidental)], 136.0 (C, OCH$_2$*Ph*) and 171.7 (C, C-1). The ^{1}H nmr data was in agreement with that reported in the literature.[479]

439
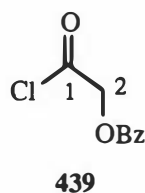
(2R)-2-Amino-3-phenyl-1-propanol **441**

To a suspension of (*R*)-phenylalanine **440** (6.250 g, 37.8 mmol) and sodium borohydride (1.575 g, 41.6 mmol) in dry tetrahydrofuran (25 cm^3) at 0°C under an atmosphere of nitrogen was added dropwise boron trifluoride etherate (6.95 cm^3, 55.5 mmol). The

reaction was stirred 2.5 h at 0°C then heated under reflux for 18 h. After cooling to room temperature, 4 mol dm^{-3} aqueous sodium hydroxide (30 cm^3) was added and the mixture refluxed 1 h. The tetrahydrofuran layer was decanted and the aqueous layer extracted with ethyl acetate (2 x 120 cm^3). The combined organic fractions were dried over sodium sulphate and the solvent removed at reduced pressure to give an oily residue, which was dissolved in dichloromethane (200 cm^3), washed with water (3 x 60 cm^3), brine (60 cm^3) and dried over sodium sulphate. Filtration through a Celite pad followed by removal of the solvent under reduced pressure produced a colourless solid. Recrystallization from hexane-ethyl acetate (1:1) gave the title compound **441** (4.634 g, 81%) as colourless needles, m.p 89.0-92.0°C {lit.,[480] m.p. 89.5-91.5°C [(2S)-enantiomer]}; $[\alpha]_D^{20.0}$ +24.5 (c 2.357, EtOH) {lit.,[480] $[\alpha]_D$ -24.7 (c 1.03, EtOH) [(2S)-enantiomer]}.

441
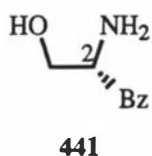
(4R)-4-(Phenylmethyl)-2-oxazolidinone **438**

The title compound **438** (4.587 g, 80%) was prepared following the procedure of Evans and Weber,[480] from (2R)-2-amino-3-phenyl-1-propanol **441** (4.893 g, 32.4 mmol), potassium carbonate (448 mg, 32.4 mmol) and a lesser amount of diethyl carbonate (7.0 cm^3, 60.8 mmol). Recrystallization from hexane-ethyl acetate (4:1) gave colourless needles, m.p. 86.5-88.5°C {lit.,[480] m.p. 87.0-88.5°C [(4S)-enantiomer]}; $[\alpha]_D^{19.5}$ -4.90 (c 2.262, EtOH) {lit.,[480] $[\alpha]_D$ +4.9 (c 1.10, EtOH) [(4S)-enantiomer]}.

438
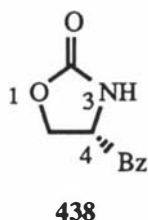
(4R)-3-[2-(Phenylmethoxy)-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone **435**

To (4R)-4-(phenylmethyl)-2-oxazolidinone **438** (4.538 g, 25.6 mmol) in dry tetrahydrofuran (68 cm^3) cooled to -78°C under an atmosphere of nitrogen was added *n*-

butyllithium (17.6 cm^3 of a 1.60 mol dm^{-3} solution, 28.2 mmol). The solution was raised to -20°C over 1.5 h, cooled back to -78°C and 2-(phenylmethoxy)acetyl chloride **439** (5.199 g, 28.2 mmol) in dry tetrahydrofuran (5 cm^3) added slowly. The solution was stirred a further 0.5 h before being quenched by the addition of saturated aqueous ammonium chloride (16 cm^3). Following extraction with dichloromethane (73 cm^3) the organic layer was washed with 1 mol dm^{-3} aqueous sodium hydroxide (24 cm^3), water (24 cm^3) and brine (24 cm^3) before being dried over sodium sulphate. The solvent was removed under reduced pressure to afford a pale yellow oil, which upon purification by flash chromatography using hexane-ethyl acetate (7:3) as eluent gave the *title compound* **435** (6.999 g, 84%) as a colourless crystalline solid (Found: C, 69.9; H, 5.7; N, 4.2. C$_{19}$H$_{19}$NO$_4$ requires C, 70.1; H, 5.9; N, 4.3%); $[\alpha]_D^{20.0}$ -69.57 (c 1.638, CH$_2$Cl$_2$); ν_{max} (nujol)/cm^{-1} 1765s (OC=ON) and 1703s (NC=OC); δ_H (270 MHz; CDCl$_3$) 2.80 (1H, dd, J_{gem} 13.4 and J 9.3 Hz, CHCH^APh), 3.29 (1H, dd, J_{gem} 13.4 and J 3.1 Hz, CHCH^BPh), 4.09-4.29 (2H, m, CH$_2$OCO), 4.57-4.75 (5H, m, CHN, OCH_2Ph and OCH$_2$CO) and 7.13-7.49 (10H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) 37.6 (CH$_2$, CHCH$_2$Ph), 54.6 (CH, C-4), 67.1 (CH$_2$, C-2'), 69.5 (CH$_2$, C-5), 73.3 (CH$_2$, OCH$_2$Ph), 127.3, 127.9(2), 128.4, 128.9, 129.3 [CH, 2 x Ph (last 4 peaks coincidental)], 134.8 (C, CHCH$_2$*Ph*), 137.1 (C, OCH$_2$*Ph*), 153.2 (C, C-2) and 170.0 (C, C-1'); m/z (EI) 326 (MH$^+$, 0.5), 234 (M-CH$_2$Ph, 3), 219 (MH-OCH$_2$Ph, 27), 176 (MH-OCH$_2$Ph-CH$_3$CO, 3), 128 (MH-OCH$_2$Ph-CH$_3$CO-CH$_2$Ph, 14), 91 (CH$_2$Ph, 100) and 65 (10).
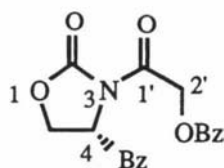
435

(3R)-Ethyl 3-(tert-butyldimethylsilyloxy)butanoate **445**

To a solution of (3*R*)-ethyl 3-hydroxybutanoate **446** (2.705 g, 20.5 mmol) and *N,N*-dimethylformamide (14 cm^3) at 0°C under an atmosphere of nitrogen was added *tert*-butyldimethylsilyl chloride (3.239 g, 21.5 mmol) and imidazole (3.484 g, 51.2 mmol). After 2 h the reaction was left to warm to room temperature and stirred a further 20 h. The solution was poured into ether (100 cm^3), washed with water (3 x 16 cm^3), brine (16 cm^3) then dried over sodium sulphate. Removal of the solvent under reduced pressure gave a clear liquid which upon distillation afforded the title compound **445** (4.294 g,

85%) as a colourless liquid, b.p. 110-111°C/13 mmHg (lit.,[497] b.p. 87-88°C/5 Torr); $[\alpha]_D^{22.0}$ -26.15 (c 4.148, CHCl$_3$) [lit.,[497] $[\alpha]_D^{24.5}$ -25.5 (c 1.16, CHCl$_3$)].

OTBDMS

EtO$_2$C ~~~~ Me
  1   3

445
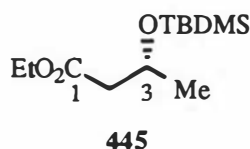
(3R)-3-(tert-*Butyldimethylsilyloxy*)-1-*butanol* **447**

To a stirred suspension of lithium borohydride (396 mg, 18.2 mmol) in dry ether (27 cm^3) under an atmosphere of nitrogen was added a solution of (3R)-ethyl 3-(*tert*-butyldimethylsilyloxy)butanoate **445** (2.990 g, 12.1 mmol) and methanol (0.7 cm^3) in dry ether (6 cm^3) over 1 h. The reaction was heated under reflux until no starting material was visible (infra-red), then cooled in ice and quenched by the addition of 2 mol dm^{-3} aqueous sodium hydroxide (16 cm^3). After 20 min the mixture was allowed to reach room temperature and then poured into ether (72 cm^3). The layers were separated and the aqueous phase extracted with ether (3 x 50 cm^3). The combined organic fractions were washed with brine (40 cm^3), dried over sodium sulphate and the solvent removed under reduced pressure. The clear liquid obtained was distilled to give the title compound **447** (2.257 g, 91%) as a colourless liquid, b.p. 62-63°C/0.1 mmHg (lit.,[497] b.p. 74-80°C/4 Torr); $[\alpha]_D^{22.0}$ -30.18 (c 0.280, CHCl$_3$) [lit.,[497] $[\alpha]_D^{24.5}$ -30.4 (c 1.09, CHCl$_3$)].

OTBDMS

HO ~~~~ Me
   1   3

447
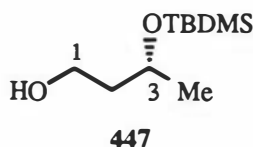
(3R)-3-(tert-*Butyldimethylsilyloxy*)-1-*butanal* **437**

To a solution of (3R)-3-(*tert*-butyldimethylsilyloxy)-1-butanol **447** (1.716 g, 8.40 mmol) in dichloromethane (35 cm^3) under an atmosphere of nitrogen was added 4-methylmorpholine *N*-oxide (1.476 g, 12.60 mmol) and powdered 4A molecular sieves (4.809 g). After 5 min *tetra-n*-propylammonium perruthenate (95 mg, 3.5 mol %) was added and the reaction stirred at room temperature until no starting material was visible (TLC). Filtration of the reaction mixture through a glass frit and then a silica gel pad, followed by removal of the solvent under reduced pressure gave the title compound **437**

(1.376 g, 81%) as a clear liquid [Found: (MH)⁺, 203.1467. $C_{10}H_{22}OSi$ requires (MH) 203.1430]; $[\alpha]_D^{19.6}$ -17.90 (c 0.354, CHCl₃) [lit.,[499] $[\alpha]_D^{16}$ -14.4 (c 1.05, CHCl₃)]; υ_{max} (film)/cm⁻¹ 2723w (H-C=O), 1734s (C=O) and 1134m, 1092m (C-O); δ_C (67.8 MHz; CDCl₃) -5.0, -4.4 (CH₃, SiMe₂), 17.9 (C, CMe₃), 24.1 (CH₃, C-4), 25.7 (CH₃, CMe_3), 52.9 (CH₂, C-2), 64.5 (CH, C-3) and 202.1 (CH, C-1); m/z (LSIMS, NBA matrix) 203 (MH⁺, 7), 187 (16), 159 (MH-CH₂CHOH, 81), 145 ($C_7H_{17}OSi$, 26), 115 ($C_6H_{15}Si$, 38), 103 (23), 89 ($C_4H_9O_2$, 22), 75 ($C_3H_7O_2$, 24) and 73 ($C_3H_5O_2$, 100). The ¹H nmr spectrum was in agreement with that reported in the literature.[499] The crude material was used in the next step without further purification.

437
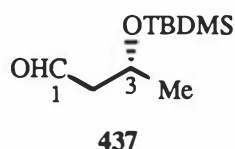
1,5-Dimethoxynaphthalene **520**

To 1,5-dihydroxynaphthalene (5.18 g, 0.03 mol; recrystallized from 50% aqueous ethanol), dimethylsulphoxide (9 cm³) and tetrahydrofuran (17 cm³) at 0°C was added with stirring dimethyl sulphate (11.0 cm³, 0.12 mol). After 10 min potassium hydroxide (13.35 g, 0.24 mol) in water (16.5 cm³) was added dropwise and the resultant suspension stirred for 1 h at 0°C then left to warm to room temperature. The reaction was returned to 0°C then poured into ice water (300 cm³) and the crude product collected by suction filtration, washed with ice cold water (3 x 400 cm³) and dried under reduced pressure. Recrystallization from chloroform afforded the title compound **520** (4.92 g, 81%) as pale yellow needles, m.p. 183.0-184.0°C (lit.,[608] m.p. 183-184°C). The ¹H nmr spectrum was in agreement with that reported in the literature.[569]

520
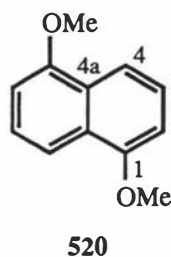
4,8-Dimethoxy-1-naphthalenecarboxaldehyde **493**

The title compound **493** (4.868 g, 87%) was prepared from 1,5-dimethoxynaphthalene **520** (5.234 g, 25.9 mmol) and phosphorus oxychloride (3.2 cm^3, 41.3 mmol) according to the procedure of Rapoport *et al.*[568] Recrystallization from hexane-dichloromethane (4:1) gave cream plates, m.p. 125.0-126.0°C (lit.,[609] m.p. 124-126°C). The ^{1}H nmr spectrum was in agreement with that reported in the literature.[569]

493
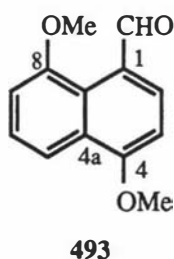
4,8-Dimethoxy-1-naphthalenol **492**

A mixture of 4,8-dimethoxy-1-naphthalene carboxaldehyde **493** (1.00 g, 4.62 mmol), selenium dioxide (478 mg, 4.31 mmol), dichloromethane (17 cm^3) and 30% hydrogen peroxide (4.5 cm^3) was stirred with a catalytic amount (*ca.* 10 mg) of tetrabutylammonium hydrogen sulphate for 30 h at room temperature. The reaction was filtered through a Celite pad and the red filtrate washed with water (5 cm^3). The solvent was removed under reduced pressure and the residue refluxed with acetone (27 cm^3) and 10% aqueous hydrochloric acid (14 cm^3) for 0.5 h. The reaction mixture was cooled to 0°C and the solid collected by suction filtration, washed with water (2 x 50 cm^3) and dried at reduced pressure to give the title compound **492** (755 mg, 80%) as colourless plates, m.p. 158.5-159.0°C (lit.,[568] m.p. 155-156°C). The ^{1}H nmr spectrum was in agreement with that reported in the literature.[569]

492
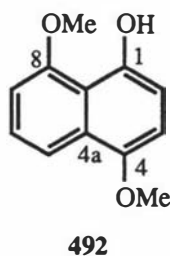
2-*Bromo*-4,8-*dimethoxy*-1-*naphthalenol* **494**

The title compound **494** (243 mg, 72%) was prepared according to the procedure of Rapoport *et al.*[568] from 4,8-dimethoxy-1-naphthalenol **492** (243 mg, 1.19 mmol) and bromine (191 mg, 1.20 mmol). Purification of the crude product by flash chromatography using hexane-ethyl acetate (95:5) as eluent gave colourless needles, m.p. 141.0-143.0°C (decomp.) [lit.,[568] m.p. 141-142°C (decomp.)]. The ^{1}H nmr spectrum was in agreement with that reported in the literature.[568]

494
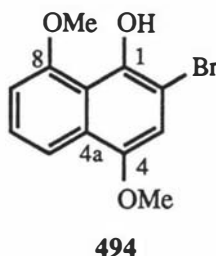
2-*Bromo*-1,4,8-*trimethoxynaphthalene* **433**

To 2-bromo-4,8-dimethoxy-1-naphthalenol **494** (300 mg, 1.06 mmol), dimethylsulphoxide (0.5 cm^3) and tetrahydrofuran (1.0 cm^3) at 0°C was added with stirring dimethyl sulphate (0.15 cm^3, 2.12 mmol). After 10 min potassium hydroxide (238 mg, 4.24 mmol) in water (0.3 cm^3) was added dropwise and the resultant purple solution stirred for 1 h at 0°C, then stirred a further 2 h upon reaching room temperature. The reaction was poured into ethyl acetate (20 cm^3), washed with water (3 x 4 cm^3) and dried over sodium sulphate. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography, using hexane-ethyl acetate (95:5) as eluent, gave the title compound **433** (214 mg, 68%) as a white crystalline solid, m.p. 84.0-85.5°C; υ_{max} (CHCl$_3$)/cm^{-1} 1074s (C-O); δ_C (50.2 MHz; CDCl$_3$) 55.6, 56.1 (CH$_3$, 1-OMe or 4-OMe and 8-OMe), 61.4 (CH$_3$, 4-OMe or 1-OMe), 107.7, 108.7 (CH, C-3, C-7), 113.9 (C, C-2), 114.7 (CH, C-5), 120.9 (C, C-8a), 125.8 (CH, C-6), 127.9 (C, C-4a), 146.4, 151.5 (C, C-1, C-4) and 156.1 (C, C-8); m/z (EI) 298 [M$^+$(^{81}Br), 100], 296 [M$^+$(^{79}Br), 100], 283 [M$^+$(^{81}Br)-CH$_3$, 34], 281 [M$^+$(^{79}Br)-CH$_3$, 34], 202 (92) and 187 (51). The ^{1}H nmr spectrum was in agreement with that reported in the literature.[569]
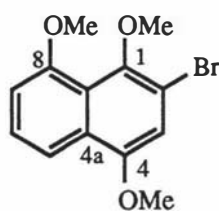
433

3-[5-(tert-*Butyldimethylsilyloxy*)-3-*hydroxy*-1-*oxo*-2-(*phenylmethoxy*)*hexyl*]-4-(*phenylmethyl*)-2-*oxazolidinone* **451,452,453**

To a suspension of stannous trifluoromethanesulphonate (2.123 g, 5.09 mmol) in dry dichloromethane (16.4 cm^3) under an atmosphere of nitrogen was added triethylamine (0.71 cm^3, 5.09 mmol) and the resultant yellow suspension immediately cooled to -78°C. After 5 min, a solution of (4R)-3-[2-(phenylmethoxy)-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone **435** (1.105 g, 3.40 mmol) in dry dichloromethane (5.5 cm^3) was added and the resultant solution stirred at -78°C for 1 h. N,N,N',N'-tetramethylethylenediamine (0.77 cm^3, 5.09 mmol) was then added, followed after 5 min by (3R)-3-(*tert*-butyldimethylsilyloxy)-1-butanal **437** (687 mg, 3.40 mmol) in dry dichloromethane (1.0 cm^3). The reaction mixture was stirred at -78°C for 2 h then poured into a vigorously stirred, ice cooled mixture of 1 mol dm^{-3} aqueous sodium hydrogen sulphate-dichloromethane (1:1, 440 cm^3). After stirring for 5 min the layers were separated and the aqueous layer extracted with dichloromethane (110 cm^3). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (165 cm^3), brine (165 cm^3), dried over sodium sulphate and the solvent removed under reduced pressure. Purification of the pale yellow oil by flash chromatography using hexane-ethyl acetate (4:1) as eluent gave:

(i) (4R,2'S,3'S,5'R)-*aldol adduct* **451** {51 mg, 4% based on unreacted **435**; R$_f$ 0.63 [hexane-ethyl acetate (7:3)]} as a colourless oil (Found: C, 65.9; H, 7.55; N, 2.7. C$_{29}$H$_{41}$NO$_6$Si requires C, 66.0; H, 7.8; N, 2.65%); $[\alpha]_D^{20.8}$ -50.10 (c 1.562, CHCl$_3$); υ_{max} (film)/cm^{-1} 3629-3363m (OH), 1777s (O*C=O*N), 1703s (N*C=O*C), 1395m, 1387m (C-N) and 1111br,m (C-O); δ_H (270 MHz; CDCl$_3$) 0.08, 0.10 (6H, s, SiMe$_2$), 0.90 (9H, s, Bu^t), 1.21 (3H, d, *J* 6.2 Hz, Me), 1.68-1.86 (2H, m, 4'-CH$_2$), 2.65 (1H, dd, J_{gem} 13.2 and $J_{A,4}$ 9.9 Hz, CHC*H^A*Ph), 3.23 (1H, d, *J* 4.5 Hz, OH), 3.31 (1H, dd, J_{gem} 13.2 and $J_{B,4}$ 3.3 Hz, CHC*H^B*Ph), 4.00-4.14 (2H, m, CH$_2$OCO), 4.14-4.34 (2H, m, CHOSi and C*H*OH), 4.48-4.66 (1H, m, CHN), 4.61 (2H, s, OC*H$_2$*Ph), 5.28 (1H, d, $J_{2',3'}$ 5.9 Hz, C*H*OBz) and 7.21-7.40 (10H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) -5.1, -4.5 (CH$_3$, SiMe$_2$), 17.9 (C, *C*Me$_3$), 23.3 (CH$_3$, C-6'), 25.8 (CH$_3$, C*Me$_3$*), 37.6 (CH$_2$, CH*C*H$_2$Ph), 40.8

(CH$_2$, C-4'), 55.1 (CH, C-4), 66.4 (CH$_2$, C-5), 66.6 (CH, C-5'), 69.9 (CH, C-3'), 73.2 (CH$_2$, OCH$_2$Ph), 79.8 (CH, C-2'), 127.2, 127.9, 128.3, 128.5, 128.9, 129.4 [CH, 2 x Ph (last 4 peaks coincidental)], 135.3 (C, CHCH$_2$*Ph*), 137.4 (C, OCH$_2$*Ph*), 153.2 (C, C-2) and 172.0 (C, C-1'); *m/z* (LSIMS, NBA matrix) 528 (MH$^+$, 17), 396 (M-C$_6$H$_{16}$OSi, 11), 304 (11), 286 (17), 178 (C$_{10}$H$_{12}$NO$_2$, 13), 91 (CH$_2$Ph, 100), 75 [(CH$_3$)$_2$SiOH, 14] and 73 (23).
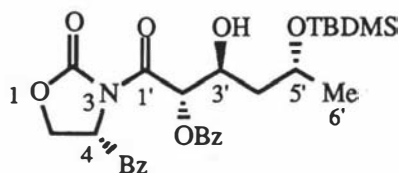
451

(ii) (4R,2'R,3'R,5'R)-*aldol adduct* **452** {789 mg, 62% based on unreacted **435**; R$_f$ 0.56 [hexane-ethyl acetate (7:3)]} as a colourless oil (Found: C, 66.0; H, 7.4; N, 2.6. C$_{29}$H$_{41}$NO$_6$Si requires C, 66.0; H, 7.8; N, 2.65%); $[\alpha]_D^{20.3}$ -56.11 (c 1.788, CHCl$_3$); υ_{max} (film)/cm^{-1} 3589-3280m (OH), 1784s (O*C*=*O*N), 1703s (N*C*=*O*C), 1389m (C-N) and 1105m (C-O); δ_H (270 MHz; CDCl$_3$) 0.08 (6H, s, SiMe$_2$), 0.86 (9H, s, Bu^t), 1.18 (3H, d, *J* 6.2 Hz, Me), 1.67 (1H, ddd, *J*$_{gem}$ 14.3, *J*$_{4'A,3'}$ 9.7 and *J*$_{4'A,5'}$ 9.7 Hz, 4'-H^A), 1.94 (1H, ddd, *J*$_{gem}$ 14.3, *J*$_{4'B,3'}$ 3.8 or 1.6 and *J*$_{4'B,5'}$ 1.6 or 3.8 Hz, 4'-H^B), 2.60 (1H, dd, *J*$_{gem}$ 13.6 and *J*$_{A,4}$ 9.9 Hz, CHC*H^A*Ph), 3.15 (1H, dd, *J*$_{gem}$ 13.6 and *J*$_{B,4}$ 3.3 Hz, CHC*H^B*Ph), 3.54 (1H, d, *J* 2.2 Hz, OH), 3.94-4.01 (1H, m, C*H*OH), 4.01-4.17 (3H, m, CHOSi and CH$_2$OCO), 4.53-4.69 (1H, m, CHN), 4.61 (2H, s, OC*H$_2$*Ph), 5.31 (1H, d, *J*$_{2',3'}$ 7.7 Hz, C*H*OBz) and 7.17-7.41 (10H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) -5.0, -4.2 (CH$_3$, SiMe$_2$), 17.6 (C, *C*Me$_3$), 24.2 (CH$_3$, C-6'), 25.6 (CH$_3$, C*Me$_3$*), 37.7 (CH$_2$, CHCH$_2$Ph), 42.2 (CH$_2$, C-4'), 55.2 (CH, C-4), 66.2 (CH$_2$, C-5), 69.6 (CH, C-5'), 72.6 (CH, C-3'), 72.8 (CH$_2$, OCH$_2$Ph), 78.8 (CH, C-2'), 127.0, 127.8, 128.1, 128.2, 128.6, 129.2 [CH, 2 x Ph (last 4 peaks coincidental)], 135.1 (C, CHCH$_2$*Ph*), 137.1 (C, OCH$_2$*Ph*), 153.3 (C, C-2) and 172.1 (C, C-1'); *m/z* (LSIMS, NBA matrix) 528 (MH$^+$, 18), 396 (M-C$_6$H$_{16}$OSi, 16), 304 (6), 286 (8), 268 (11), 178 (C$_{10}$H$_{12}$NO$_2$, 11), 159 (8), 117 (8), 91 (CH$_2$Ph, 100), 75 [(CH$_3$)$_2$SiOH, 9], 73 (16), 55 (9) and 43 (CH$_3$CO, 8).
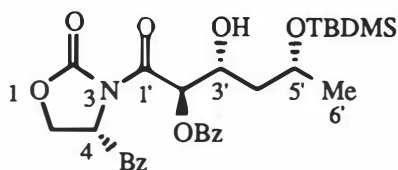
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(iii) (4R,2'R,3'S,5'R)-*aldol adduct* **453** {216 mg, 17% based on unreacted **435**; R_f 0.48 [hexane-ethyl acetate (7:3)]} as a colourless oil (Found: C, 65.7; H, 7.6; N, 2.6. $C_{29}H_{41}NO_6Si$ requires C, 66.0; H, 7.8; N, 2.65%); $[\alpha]_D^{19.0}$ -16.91 (c 5.348, CHCl$_3$); υ_{max} (film)/cm^{-1} 3624-3278m (OH), 1782s (O*C*=*O*N), 1710s (N*C*=*O*C), 1390m (C-N) and 1105br,m (C-O); δ_H (270 MHz; CDCl$_3$) 0.05 (6H, s, SiMe$_2$), 0.87 (9H, s, Bu^t), 1.19 (3H, d, *J* 6.2 Hz, Me), 1.58 (1H, ddd, J_{gem} 14.3, $J_{4'A,3'}$ 7.1 or 2.2 and $J_{4'A,5'}$ 2.2 or 7.1 Hz, 4'-H^A), 1.78-1.94 (1H, m, 4'-H^B), 2.72 (1H, dd, J_{gem} 13.6 and $J_{A,4}$ 9.9 Hz, CHC*H^A*Ph), 2.83 (1H, d, *J* 6.2 Hz, OH), 3.27 (1H, dd, J_{gem} 13.6 and $J_{B,4}$ 3.3 Hz, CHC*H^B*Ph), 4.09-4.28 (4H, m, CHOSi, C*H*OH and CH$_2$OCO), 4.54 (1H, d, J_{gem} 11.7 Hz, OC*H^A*Ph), 4.63-4.78 (1H, m, CHN), 4.75 (1H, d, J_{gem} 11.7 Hz, OC*H^B*Ph), 5.17 (1H, d, $J_{2',3'}$ 2.9 Hz, C*H*OBz) and 7.19-7.42 (10H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) -5.2, -4.5 (CH$_3$, SiMe$_2$), 17.9 (C, *C*Me$_3$), 23.4 (CH$_3$, C-6'), 25.7 (CH$_3$, C*Me$_3$), 37.5 (CH$_2$, CHCH$_2$Ph), 42.0 (CH$_2$, C-4'), 55.6 (CH, C-4), 65.9 (CH, C-5'), 66.7 (CH$_2$, C-5), 69.1 (CH, C-3'), 72.9 (CH$_2$, OCH$_2$Ph), 79.9 (CH, C-2'), 127.3, 128.0, 128.3(2), 128.9, 129.3 [CH, 2 x Ph (last 4 peaks coincidental)], 135.1 (C, CHCH$_2$*Ph*), 137.1 (C, OCH$_2$*Ph*), 153.2 (C, C-2) and 170.6 (C, C-1'); *m/z* (LSIMS, NBA matrix) 528 (MH$^+$, 19), 470 (M-C$_4$H$_9$, 5), 396 (M-C$_6$H$_{16}$OSi, 15), 286 (13), 268 (8), 178 (C$_{10}$H$_{12}$NO$_2$, 11), 159 (7), 117 (9), 91 (CH$_2$Ph, 100), 75 [(CH$_3$)$_2$SiOH, 13] and 73 (21).

Upon prolonged refrigeration at approximately 2°C the oil formed a white solid (needles), m.p. 68.0-71.0°C.

Imide **435** (320 mg, 29%) was recovered from the reaction.
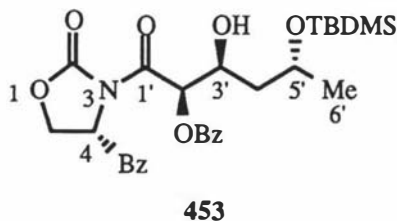
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(4R,2'R,3'R,5'R)-3-[5-(tert-*Butyldimethylsilyloxy*)-1-*oxo*-2-(*phenylmethoxy*)-3-(*triethylsilyloxy*)hexyl]-4-(*phenylmethyl*)-2-*oxazolidinone* **485**

To a solution of (4*R*,2'*R*,3'*R*,5'*R*)-3-[5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-1-oxo-2-(phenylmethoxy)hexyl]-4-(phenylmethyl)-2-oxazolidinone **452** (742 mg, 1.41 mmol) in dry dichloromethane (7.8 cm^3) at 0°C under an atmosphere of nitrogen was added triethylsilyl trifluoromethanesulphonate (0.42 cm^3, 1.86 mmol) followed by 2,6-dimethylpyridine (0.26 cm^3, 2.25 mmol). The resultant solution was allowed to reach room temperature and stirred until no starting material was visible (TLC). The reaction

mixture was poured into dichloromethane (52 cm^3), washed with water (12 cm^3), brine (12 cm^3) then dried over sodium sulphate. Removal of the solvent at reduced pressure afforded a pale yellow oil that was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to give the *title compound* **485** (797 mg, 88%) as a colourless oil (Found: C, 65.4; H, 8.4; N, 2.1. C$_{35}$H$_{55}$NO$_6$Si$_2$ requires C, 65.5; H, 8.6; N, 2.2%); $[\alpha]_D^{21.1}$ -43.75 (c 1.408, CHCl$_3$); υ_{max} (film)/cm^{-1} 1784s (O*C*=O*N*), 1709s (N*C*=O*C*), 1388br,s (C-N) and 1116br,s (C-O); δ_H (270 MHz; CDCl$_3$) 0.01, 0.06 (6H, s, SiMe$_2$), 0.58 [6H, q, *J* 7.9 Hz, Si(C*H$_2$*CH$_3$)$_3$], 0.88 (9H, s, Bu^t), 0.92 [9H, t, *J* 7.9 Hz, Si(CH$_2$C*H$_3$*)$_3$], 1.13 (3H, d, *J* 5.9 Hz, Me), 1.71-1.93 (2H, m, 4'-CH$_2$), 2.55 (1H, dd, J_{gem} 13.4 and J_4 9.9 Hz, CHC*H^A*Ph), 3.13 (1H, dd, J_{gem} 13.4 and J_4 3.3 Hz, CHC*H^B*Ph), 4.00-4.16 (4H, m, 2 x CHOSi and CH$_2$OCO), 4.51-4.67 (3H, m, CHN and OC*H$_2$*Ph), 5.40 (1H, d, $J_{2',3'}$ 7.0 Hz, C*H*OBz) and 7.16-7.43 (10H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) -4.6, -4.5 (CH$_3$, SiMe$_2$), 5.0 (CH$_2$, *C*H$_3$CH$_2$Si), 6.8 (CH$_3$, CH$_3$*C*H$_2$Si), 18.1 (C, *C*Me$_3$), 24.5 (CH$_3$, C-6'), 25.9 (CH$_3$, C*Me$_3$*), 37.9 (CH$_2$, CH*C*H$_2$Ph), 46.0 (CH$_2$, C-4'), 55.6 (CH, C-4), 65.7 (CH, C-5'), 66.1 (CH$_2$, C-5), 70.9 (CH, C-3'), 73.2 (CH$_2$, O*C*H$_2$Ph), 80.9 (CH, C-2'), 127.3, 127.9, 128.3, 128.5, 129.0, 129.4 [CH, 2 x Ph (last 4 peaks coincidental)], 135.3 (C, CHCH$_2$*Ph*), 137.5 (C, OCH$_2$*Ph*), 153.0 (C, C-2) and 172.2 (C, C-1'); *m/z* (LSIMS, NBA matrix) 642 (M$^+$, 4), 612 (7), 584 (M-C$_4$H$_{10}$, 5), 510 (M-C$_6$H$_{16}$OSi, 9), 418 (5), 286 (6), 185 (7), 159 (C$_8$H$_{19}$OSi, 35), 115 (22), 91 (CH$_2$Ph, 100), 73 (47) and 59 (13).
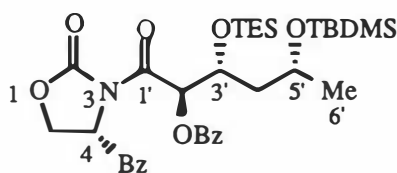
485

(2S,3R,5R)-5-(tert-*Butyldimethylsilyloxy*)-2-(*phenylmethoxy*)-3-(*triethylsilyloxy*)-1-*hexanol* **459**

To a solution of (4*R*,2'*R*,3'*R*,5'*R*)-3-[5-(*tert*-butyldimethylsilyloxy)-1-oxo-2-(phenylmethoxy)-3-(triethylsilyloxy)hexyl]-4-(phenylmethyl)-2-oxazolidinone **485** (214 mg, 0.33 mmol) in dry tetrahydrofuran (13.0 cm^3) at 0°C under an atmosphere of nitrogen was added portionwise over 2 min lithium borohydride (15 mg, 0.69 mmol). The solution was allowed to reach room temperature and stirred *ca*. 3 h then quenched by the addition of water (0.25 cm^3). After 10 min the reaction mixture was poured into ether (25 cm^3), washed with water (7.5 cm^3), brine (7.5 cm^3) and dried over sodium sulphate. Removal of the solvent at reduced pressure gave a clear oil that upon purification by

flash chromatography, using hexane-ethyl acetate (4:1) as eluent gave the *title compound* **459** (128 mg, 82%) as a colourless oil (Found: C, 63.8; H, 10.35. $C_{25}H_{48}O_4Si_2$ requires C, 64.05; H, 10.3%); $[\alpha]_D^{20.1}$ -10.53 (c 1.906, CHCl$_3$); υ_{max} (film)/cm^{-1} 3659-3167m (OH) and 1087br,s (C-O); δ_H (270 MHz; CDCl$_3$); 0.06 (6H, s, SiMe$_2$), 0.65 [6H, q, J 7.7 Hz, Si(CH_2CH$_3$)$_3$], 0.90 (9H, s, Bu^t), 0.98 [9H, t, J 7.7 Hz, Si(CH$_2$CH_3)$_3$], 1.15 (3H, d, J 6.1 Hz, Me), 1.58-1.86 (2H, m, 4-CH$_2$), 2.51-2.69 (1H, br.s, OH), 3.44-3.50 (1H, m, CHOBz), 3.80 (1H, br.s, CH_2OH), 3.89-4.04 (1H, m, CHOTBDMS), 4.04-4.19 (1H, m, CHOTES), 4.62 (1H, d, J_{gem} 11.5 Hz, OCH^APh), 4.70 (1H, d, J_{gem} 11.5 Hz, OCH^BPh) and 7.26-7.46 (5H, m, Ar-H); δ_C (67.8 MHz; CDCl$_3$) -4.6, -4.4 (CH$_3$, SiMe$_2$), 4.9 (CH$_2$, CH$_3$CH$_2$Si), 6.9 (CH$_3$, CH_3CH$_2$Si), 18.0 (C, CMe$_3$), 23.9 (CH$_3$, C-6), 25.9 (CH$_3$, CMe_3), 44.6 (CH$_2$, C-4), 61.1 (CH$_2$, C-1), 65.7 (CH, C-5), 71.0 (CH, C-3), 71.8 (CH$_2$, OCH_2Ph), 81.6 (CH, C-2), 127.6, 127.8, 128.3 [CH, Ph (last 2 peaks coincidental)] and 138.4 (C, OCH$_2$$Ph$); m/z (LSIMS, NBA matrix) 469 (MH$^+$, 6), 411 (M-C$_4$H$_9$, 2), 337 (MH-C$_6$H$_{16}$OSi, 9), 245 (11), 159 (C$_8$H$_{19}$OSi, 30), 115 (13), 91 (CH$_2$Ph, 100), 73 (31) and 59 (9).

Auxiliary **438** (42 mg, 71%) was recovered from the reaction.

459
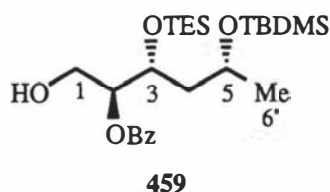
(2R,3R,5R)-5-(tert-*Butyldimethylsilyloxy*)-2-(*phenylmethoxy*)-3-(*triethylsilyloxy*)-1-*hexanal* **434**

Using Pyridinium Chlorochromate

To a mixture of (2S,3R,5R)-5-(*tert*-butyldimethylsilyloxy)-2-(phenylmethoxy)-3-(triethylsilyloxy)-1-hexanol **459** (175 mg, 0.37 mmol), anhydrous sodium acetate (664 mg, 8.09 mmol) and powdered 4A molecular sieves (1.528 g) in dichloromethane (6.2 cm^3), under an atmosphere of nitrogen, was added pyridinium chlorochromate (161 mg, 0.75 mmol). The suspension was stirred until no starting material was visible (TLC) then ether (2 cm^3) and hexane (2 cm^3) were added. After 5 min the reaction was filtered through a silica gel pad and the solvent removed at reduced pressure to give a pale yellow oil. Purification by flash chromatography, using hexane-ethyl acetate (4:1) as eluent gave the *title compound* **434** (164 mg, 84%) as a colourless oil, $[\alpha]_D^{19.3}$ +12.35 (c 1.200, CHCl$_3$).

Using tetra-n-*Propylammonium Perruthenate*

To a mixture of (2*S*,3*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-(phenylmethoxy)-3-(triethylsilyloxy)-1-hexanol **459** (124 mg, 0.26 mmol), 4-methylmorpholine *N*-oxide (46 mg, 0.39 mmol) and powdered 4A molecular sieves (140 mg) in dichloromethane (0.7 cm^3) at 0°C under an atmosphere of nitrogen was added *tetra-n*-propylammonium perruthenate (5 mg, 5 mol %). The reaction was allowed to warm to room temperature and stirred until no starting material was visible (TLC). Filtration of the reaction mixture through a silica gel pad and removal of the solvent at reduced pressure afforded a clear oil. Purification by flash chromatography using hexane-ethyl acetate (4:1) as eluent gave the *title compound* **434** (100 mg, 81%) as a colourless oil (Found: C, 64.4; H, 9.7. C$_{25}$H$_{46}$O$_4$Si$_2$ requires C, 64.3; H, 9.9%); $[\alpha]_D^{22.2}$ +14.64 (c 1.152, CHCl$_3$); υ_{max} (film)/cm^{-1} 2737w, 2703w (*H-C=O*), 1736s (C=O) and 1109br,s (C-O); δ_H (270 MHz; CDCl$_3$) 0.02, 0.03 (6H, s, SiMe$_2$), 0.60 [6H, q, *J* 7.9 Hz, Si(C*H$_2$*CH$_3$)$_3$], 0.87 (9H, s, Bu^t), 0.94 [9H, t, *J* 7.9 Hz, Si(CH$_2$C*H$_3$*)$_3$], 1.12 (3H, d, *J* 6.2 Hz, Me), 1.58-1.85 (2H, m, 4-CH$_2$), 3.73 (1H, dd, $J_{2,1}$ 2.6 and $J_{2,3}$ 2.6 Hz, C*H^A*OBz), 3.86-4.01 (1H, m, C*H*OTBDMS), 4.13-4.24 (1H, m, C*H*OTES), 4.59 (1H, d, J_{gem} 11.6 Hz, OC*H^B*Ph), 4.65 (1H, d, J_{gem} 11.6 Hz, OC*H*Ph), 7.27-7.39 (5H, m, Ar-H) and 9.69 (1H, d, $J_{1,2}$ 2.6 Hz, CHO); δ_C (67.8 MHz; CDCl$_3$) -4.7, -4.4 (CH$_3$, SiMe$_2$), 4.9 (CH$_2$, CH$_3$*C*H$_2$Si), 6.8 (CH$_3$, *C*H$_3$CH$_2$Si), 18.0 (C, *C*Me$_3$), 23.9 (CH$_3$, C-6), 25.8 (CH$_3$, C*Me$_3$*), 44.1 (CH$_2$, C-4), 65.5 (CH, C-5), 71.5 (CH, C-3), 72.7 (CH$_2$, OCH$_2$Ph), 86.2 (CH, C-2), 127.9, 128.4 [CH, Ph (2 and 3 peaks coincidental respectively)], 137.4 (C, OCH$_2$*Ph*) and 204.0 (CH, CHO); *m/z* (CI) 484 (MH$^+$ + NH$_3$, 1), 467 (MH$^+$, 11), 335 (MH-C$_6$H$_{16}$OSi, 100), 235 (15), 215 (11), 203 (24), 159 (C$_8$H$_{19}$OSi, 75), 132 (C$_6$H$_{16}$OSi, 63), 120 (13), 108 (20), 91 (CH$_2$Ph, 80) and 74 (12).

434
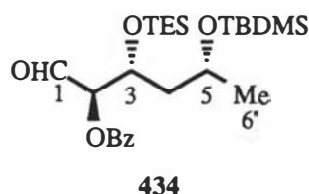
(±)-2-(1-*Hydroxyheptyl*)-1,4,8-*trimethoxynaphthalene* **497**

To 2-bromo-1,4,8-trimethoxynaphthalene **433** (54 mg, 0.18 mmol) in dry tetrahydrofuran (1.35 cm^3) at -78°C under an atmosphere of nitrogen was added *n*-butyllithium (96 mm^3 of a 1.90 mol dm^{-3} solution, 0.18 mmol). After precisely 85 s, heptanal (48 mm^3, 0.34 mmol) was added and the solution then stirred at -78°C for 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (0.5 cm^3), then ether

(2 cm^3) was added and the mixture raised to room temperature. The mixture was poured into ether (20 cm^3) and washed with water (5 cm^3). The aqueous phase was extracted with ether (2 x 10 cm^3) and the combined ethereal extracts washed with brine (10 cm^3) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (4:1) as eluent to afford:

(i) 1,4,5-trimethoxynaphthalene **499** (3 mg, 8%) as a cream solid, m.p. 115.0-117.5°C (lit.,[576] 116-118°C). The ^{1}H and ^{13}C nmr and mass spectral data were in agreement with that reported in the literature.[574]

499
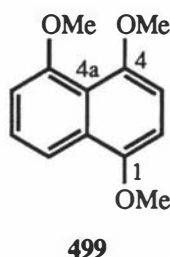
(ii) the *title compound* **497** (47 mg, 79%) as a pale yellow oil (Found: M$^+$, 332.1989. C$_{20}$H$_{28}$O$_4$ requires M, 332.1988); υ_{max} (film)/cm^{-1} 3624-3131br,m (OH) and 1076s (C-O); δ_H (200 MHz; CDCl$_3$) 0.87 (3H, t, J 6.4 Hz, 7'-Me), 1.15-1.48 (6H, m, 4', 5' and 6'-CH$_2$), 1.48-1.70 (2H, m, 3'-CH$_2$), 1.70-1.95 (2H, m, 2'-CH$_2$), 2.04-2.30 (1H, br.s, OH), 3.80 (3H, s, 8-OMe), 3.98 (3H, s, 1-OMe), 4.00 (3H, s, 4-OMe), 5.27 (1H, dd, $J_{1',2'A}$ 7.9 and $J_{1',2'B}$ 5.3 Hz, CHOH), 6.90 (1H, s, 3-H), 6.92 (1H, d, $J_{7,6}$ 8.4 Hz, 7-H), 7.37 (1H, dd, $J_{6,5}$ 8.4 and $J_{6,7}$ 8.4 Hz, 6-H) and 7.86 (1H, dd, $J_{5,6}$ 8.4 and $J_{5,7}$ 1.0 Hz, 5-H); δ_C (50.2 MHz; CDCl$_3$) 14.0 (CH$_3$, C-7'), 22.5 (CH$_2$, C-6'), 26.1 (CH$_2$, C-5'), 29.2 (CH$_2$, C-4'), 31.7 (CH$_2$, C-3'), 38.4 (CH$_2$, C-2'), 55.6, 56.0 (CH$_3$, 1-OMe or 4-OMe and 8-OMe), 62.8 (CH$_3$, 4-OMe or 1-OMe), 68.5 (CH, C-1'), 102.4 (CH, C-3), 106.8 (CH, C-7), 114.7 (CH, C-5), 120.1 (C, C-8a), 125.3 (CH, C-6), 128.1 (C, C-4a), 133.5 (C, C-2), 145.9, 151.7 (C, C-1, C-4) and 155.6 (C, C-8); m/z (EI) 332 (M$^+$, 67), 247 (M-C$_6$H$_{13}$, 100), 232 (M-C$_6$H$_{13}$-CH$_3$, 43), 217 (M-C$_6$H$_{13}$-CH$_3$-CH$_3$, 18) and 43 (CH$_3$CO, 19).

497
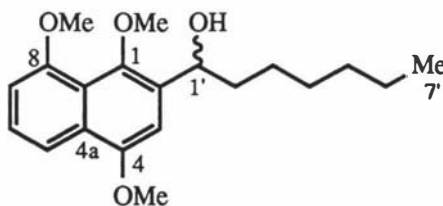
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