Studies in the Chemistry of Glutarimides.

Robert J. Young Wadham College, Oxford.

D. Phil., Hilary Term 1988.

Abstract

This thesis describes investigations made into the chemistry of C-4 substituted glutarimides. It develops two contrasting approaches to this goal, which reflect the previous synthetic interests in the area. The glutarimides made were screened for potential agrochemical actions at Shell Research Centre, Sittingbourne.

The anti-Leukemia alkaloid sesbanimide has prompted much recent work into the formation of glutarimides attached to functionalised precursors. This chemistry was developed by the formation of a glutarimide from C-5 of *xylo*dialdofuranose, using standard methods. Wittig extension of the aldehyde, followed by Michael addition of malonate and dealkoxycarbonylation gave a glutarate diester; this was converted to the glutarimide *via* an anhydride. A glutarimide was similarly constructed from a β-ribose residue, forming an analogue of the β-C-nucleosides. An approach to the epimeric α-*ribo*-glutarimide was also made. The α- and β-*ribo*aldehydes, from which the glutarimides were elaborated, were each formed stereospecifically by the ring contractions of a pyranose triflate.

Synthetic interest towards the so-called glutarimide antibiotics has centred around the elaboration of a side chain attached to a pre-formed glutarimide. The common precursors in this work were glutarimides attached via C-4 to β-acetyl functions. The corresponding side chain in this work was activated, in a novel manner, by the formation of a stabilized ylid at that centre. Wittig reactions between this ylid and a number of carbonyl compounds were achieved. Some of these Wittig products were elaborated further; a number of simple heterocycles were thus formed, attached to glutarimide *via* a 1-carbon extension. Using a carbohydrate derived side chain an attempt to form a glutarimide attached to a shikimate-related residue was made, by means of an intramolecular aldol cyclisation.

An *N*-substituted glutarimide was formed in a novel reaction between an iminophosphorane and glutaric anhydride.

Many of these synthetic glutarimides exhibited some biological activity.

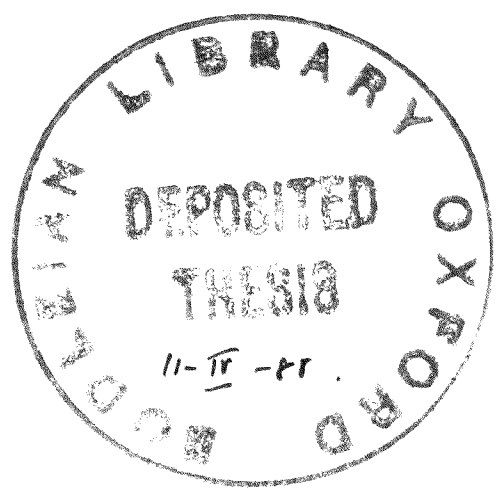
Studies in the Chemistry of Glutarimides

by

Robert J. Young,

Wadham College,

Oxford.



Hilary Term 1988

A Thesis submitted for partial fulfilment of

the requirements for the degree of D. Phil.

To Arf and Mochyn.

A small token of the enormous debt of gratitude which I owe them.

After all, without them, none of this would have been at all possible.

Quotes from the Perkin.

I might have spent long hours in search of that witty *(sic)* and humorous quote to brighten up this dull tome. But I need look no further than the walls of that colourful laboratory to find my inspiration.

"Rob, Tell Rob if you see him that there are two, indeed three Robs in my life,
... and they're all more important to me than him."
GWJF, June '86.

"I do it once a year...
...June and December."
PEH, Dec. '87.

"D_2O is like water."
Mighty, May '86.

"Water has a sharp NMR peak, when it is dry."
RJY, Jan. '87.

"You'll even believe a man can fly."
an excited NGR,
"Isn't that next week when you prop against Bucket."
in reply, FXW, Oct '87.

"Sharks are stupid, they're reptiles."
RJL, Dec '87.

The secret to the meaning of life? (for carbohydrate chemists)
"Ah, beer ish made flom floor ingledients...
Barley, Hopsh, Yeasht, and...um...ah!... diashetone glucoshe!
SKN, Sept '86.

Acknowledgements

The personal acknowledgements in this thesis are many and varied: not only do I wish to thank those directly involved with the project, but also the many people who have made the past two and a bit years so special. Thank you all!

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All of the technical staff in the D.P., for such a great service, in spite of the devilish compounds I have sometimes presented them. I hate to single out but, Elizabeth McGuinness, Val Lamburn and Robin Aplin did me most proud.

Terry Haig, for some useful discussions.

Laurence Harwood for the lone of his laser link.

Jo Peach, Chunder Baird and Geoff Austin, for cracking Goofy's identity.

The many inmates of the Perkin for so much. What a bunch to work with. Where would the world be without them (answers on a postcard please?). I can give thanks in so many ways: Paulos, for losing bets; Mighty, for being himself; Rob for being so wide; Bharat "it's O.K.;" Liza for Daffy and friends; Irving Fryer, for inspiration (nothing could be so bad); Hacker, for letting me know that Somerset still exists; Francis, for telling me the cricket scores; Roy, for reminding me it's tea-time (Greetings Gilbert, although how could you say thanks for that pea you serve); Nigel, well, we have to tease somebody...; Namgoong, for the bananas; Pedro, for some software; Son, for nearly a pint of Guinness for every spectrum I ran for him...
And all the others too, It's been good...

Chris, Nigel, Fiona and Francis, fer tranzlatin this fesis vrom zummerzet.

A lot of others in the D.P., for making it a brighter place.

Steve Evans, Steve Beasley and Yuppie Vince, who made work at Shell just so much the bongie.

To the Great Philosophers, so many thanks, for the companionship, hindrance, hoovering of food, tolerance, *ad infinitum*. -especially over the past few months, when I've been an ugly shadow of my former self. Is my status now confirmed?

John Page, for convincing me what a stout programme *Write Now* is.

Sam Spade, for dogging me last term, to add to the pain of this tome...

And all those I've forgotten...

Contents

Abstract

Quotes from the Perkin

Acknowledgements

Contents

Abbreviations i

A note on nomenclature ii

General Introduction

- Outline 1
- Natural Occurance and Actions of Glutarimides 2
- The Glutarimide Antibiotics 4
- Sesbanimide 6
- References 9

Section A: Formation of Glutarimides from functionalised precursors 10

- *Summary* 11

Introduction

- Previous Synthetic work 12
- Synthesis of C-Nucleoside precursors 23

Results and discussion

- 1) Construction of glutarimide from C-5 of *xylo*furanose 29
- 2) Synthesis of β-*ribo* glutarimide 37
- 3) Approach to α-*ribo* glutarimide 47

Experimental

General Experimental Procedures 54

- 1) Construction of glutarimide form C-5 of xylofuranose 56
- 2) Synthesis of β-*ribo* glutarimide 64
- 3) Approach to α-*ribo* glutarimide 74

References 81

Section A1: Synthesis of *N*-substituted glutarimides from azides 84

Section B: Synthesis and Reactions of an activated substituted glutarimide.89

Summary 90

Introduction

Previous synthetic work 91

Development of novel activation 96

Results and Discussion

1) Synthesis of 4-(carboxymethyl)-glutarimide) 100

2) Formation of glutarimide attached to a stabilized ylid 103

3) Wittig chemistry with the glutarimide-ylid 108

4) Synthesis of glutarimides attached to simple heterocycles 110

5) Approach to glutarimide-shikimate adduct 117

Experimental

1) Synthesis of 4-(carboxymethyl)-glutarimide) 127

2) Formation of glutarimide attached to a stabilized ylid 130

3) Wittig chemistry with the glutarimide-ylid 133

4) Synthesis of glutarimides attached to simple heterocycles 137

5) Approach to glutarimide-shikimate adduct 144

References 151

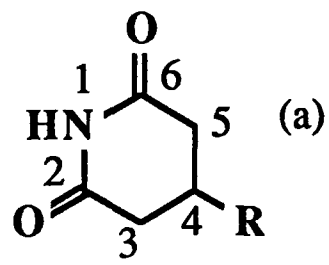
Appendix: Biological Screening, procedures and full results. 153

Abbreviations

Ac	Acetyl
Bu	Butyl
Bn	Benzyl
Δ	Heated at reflux temperature
DCM	Dichloromethane
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
E	*Entgegen, Trans* double bond substitution
Et	Ethyl
Me	Methyl
J	^{1}H NMR Coupling Constant
P	Protecting Group
Ph or Ø	Phenyl
Pr	Propyl
[Si]	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulphonyl (forming *Triflates*)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	Thin Layer Chromatography
Ts	Toluenesulphonyl (*Tosyl*)
Z	*Zusammen, Cis* double bond substitution

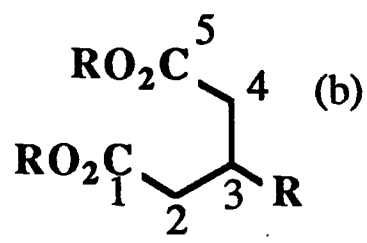
A note on nomenclature.

The glutarimide (piperidine-2,6-dione) is given first priority in numbering; numbered, like all heterocycles from the heteroatom (a).



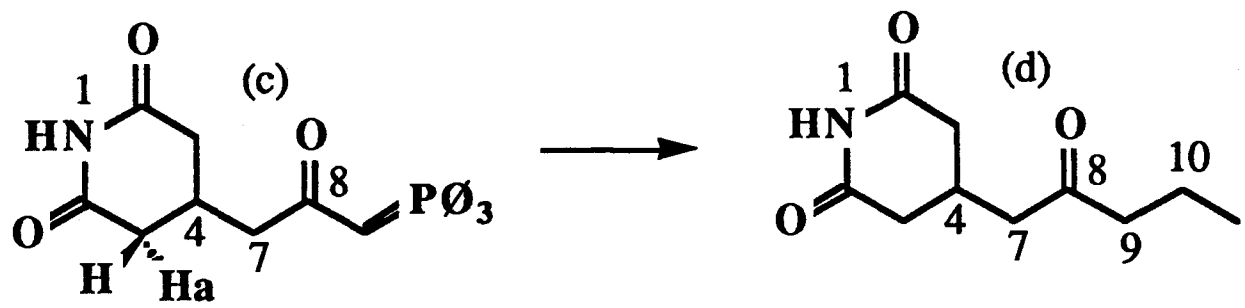
(a)

Sugars are named as such until a Michael reaction, the product of which is described as a glycosylated glutarate (pentane-1,5-dioate) (b). In glutarates and their anhydrides it should be noted that C-3 becomes C-4 of the glutarimide (a).



(b)

In Wittig reactions with the glutarimide ylid (c) the side chain is numbered sequentially (starting at C-7) from the point of attachment to glutarimide (d).



Positions in secondary rings in products are numbered as X'. The superscript H-X^{a} is used to denote one of two diastereotopic protons.

INTRODUCTION

Outline

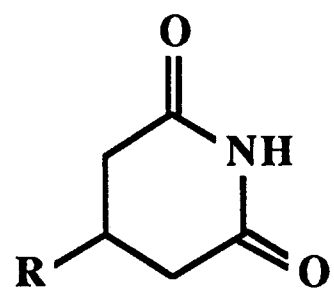
This thesis describes investigations made into the synthesis of compounds containing 4-substituted glutarimides.

The layout is largely divided into two sections which develop the contrasting philosophies employed. The first section discusses the synthesis of the glutarimide ring from suitably functionalised precursors; the second looks at the introduction of the glutarimide by means of a pre-formed activated derivative. In each section the use of carbohydrates as chiral templates for enantiospecific syntheses was employed.[1]

Many of the compounds synthesised which included a glutarimide ring in their structure have been screened for agrochemical activity at Shell Research Centre, Sittingbourne. The results of these tests are given in the text; a more detailed analysis is given in the appendix. At a later date some of the glutarimides will be given preliminary screens for potential anti-cancer properties.

Natural Occurance and Actions of Glutarimides.

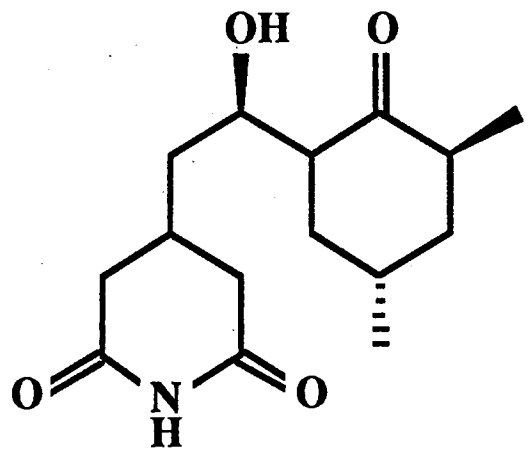
Glutarimide (2,6 piperidinedione) is the trivial name given to the cyclic imide derived from glutaric (1,5 pentanedioic) acid.



Glutarimide, substituted at C-4

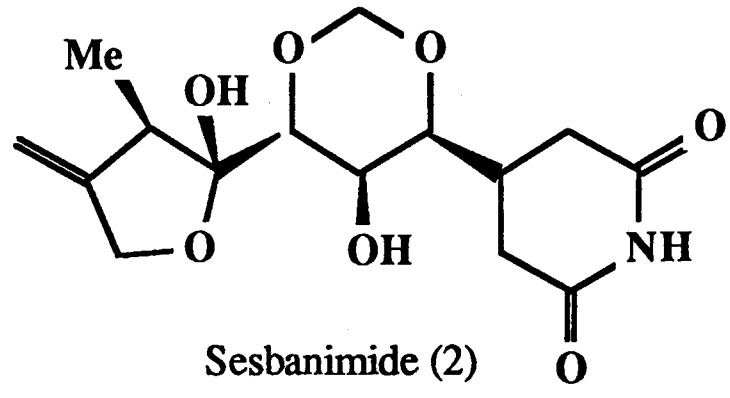
In this thesis the studies were concerned with glutarimides substituted at C-4. Not only does this simplify the chemistry (by virtue of the symmetry not creating any stereochemical problems) but it also produces substitution analogous to that found in the naturally occuring glutarimides.

In nature 4-substituted glutarimides have been most commonly encountered in the well-characterised family of antibiotics structurally related to cycloheximide (1).[2]



Cycloheximide (1)

The isolation and structure elucidation of the unique glutarimide-containing alkaloid sesbanimide (2) by Powell and co-workers[3,4] proved to be a watershed for interest in glutarimide chemistry. Sesbanimide possesses not only an interesting and challenging structure for synthesis but it also exhibits potent anti-tumour activity.



Sesbanimide (2)

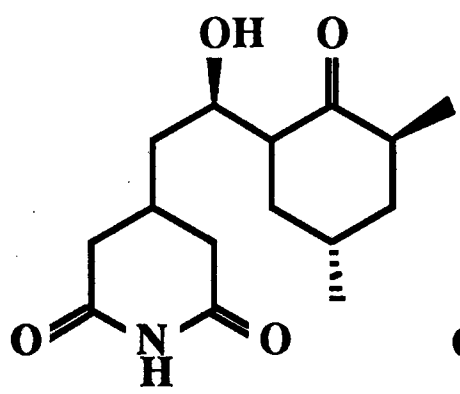
This project arose from common interests in glutarimides. In the course of microbial broth extractions at Shell, cycloheximide (1) and structural relatives were commonly encountered;[5] whilst work had been pursued in Oxford on the first published approach to sesbanimide (1).[6] During this work on sesbanimide problems were encountered with the formation of glutarimide rings: known literature methods employed harsh conditions, inappropriate for the construction of highly functionalised intermediates. The potent action of glutarimide antibiotics makes them potentially useful agrochemicals, but their inherent phyto- and cytotoxicity limits their effectiveness. Some synthetic analogue might perhaps possess only part of this broad spectrum of activity. Thus with academic interest in the synthesis of glutarimides and commercial interest in their biological applications a collaborative programme was pursued.

The two sections of this thesis roughly reflect synthetic interest in the two major areas of glutarimide chemistry: work on sesbanimide is appropriate to section A, whilst methods used on the cycloheximide family are developed in section B.

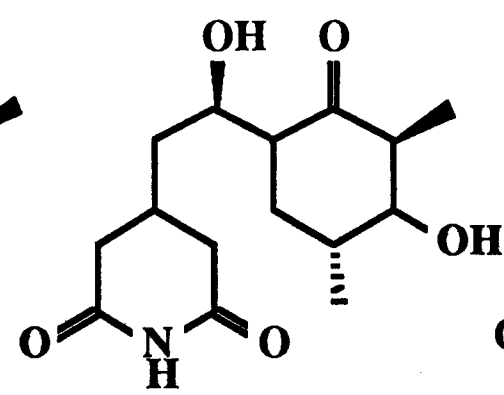
The Glutarimide Antibiotics

Cycloheximide (1) was the first of the so-called glutarimide antibiotics to be discovered, isolated from a streptomycin-producing strain of *Streptomyces griseus*.[7] A feature of the biological action of cycloheximide was that although it displayed little or no activity against the usual pathogenic bacteria associated with streptomycin action, it was most effective in the inhibition of the growth of many fungi.

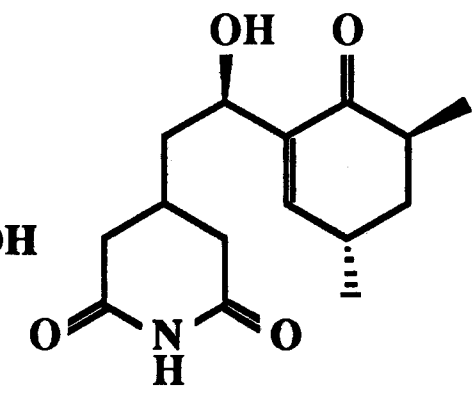
Since cycloheximide (1) was first isolated further work on *Streptomyces* broth extracts has established the identity and activity of about twenty close analogues of this compound, collectively known as the glutarimide antibiotics.[2] These componds are either diastereomeric to cycloheximide or have a closely related structure as typified by such componds as steptovitacin B (3), inactone (4), actiphenol (5), and the acyclic streptimidone (6).



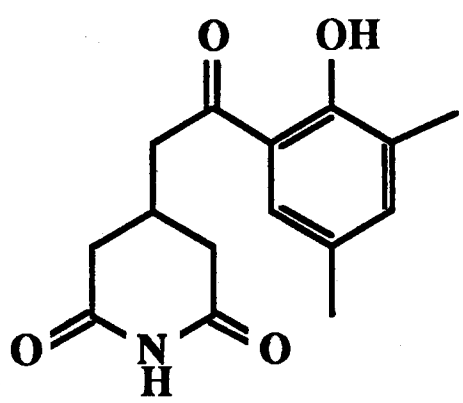
Cycloheximide (1)



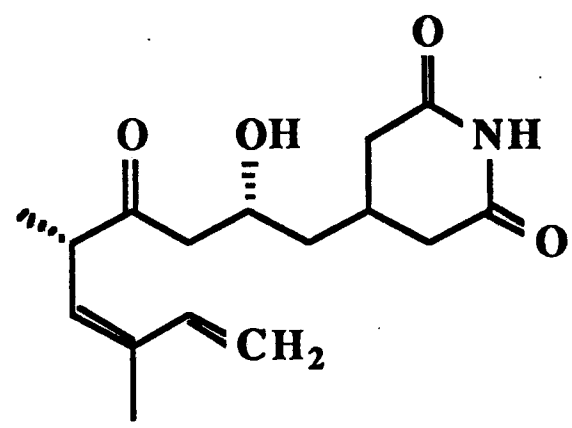
Streptovitacin B (3)



Inactone (4)



Actiphenol (5)



Streptimidone (6)

Although none of these analogues display quite the same degree of activity as cycloheximide itself, several types do show quite marked actions of a similar type: notably the streptovitacins (cycloheximides with an extra ring hydroxyl) and streptimidones (in which the cyclohexanone ring remains unclosed).

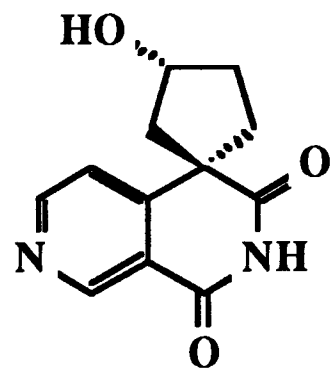
The spectrum of action of these antibiotics is quite remarkable: whilst prokaryotic systems are uninhibited, a wide range of eukaryotes are highly sensitive, notably against fungi and including activity against tumours.[8] Such a broad spectrum of activity however has limited their usefulness as selective biocides. Despite the potent fungicidal action of cycloheximide it has been of little commercial interest due to its high phytotoxicity. The practical uses of such compounds have therefore been restricted to cases where the pathogen is extremely susceptible, or where the treated parts are insensitive to the applied compound.[9] Cycloheximide's current commercial interest is as a plant growth regulant to stimulate the abscision of citrus fruits.[10]

Biological studies of the glutarimide antibiotics and their derivatives[8] have led to the formulation of some structure-activity correlations: three most important structural features are i) the ketone carbonyl group, ii) the imide nitrogen, and iii) the hydroxyl at C-8. None of these features have been removed or substituted without almost complete loss of biological activity. Changes in the configuration of the cyclohexanone ring also greatly influence these actions.

Given the close structural similarity of the active compounds it is reasonable to propose a common mode of action: this has been extensively studied for cycloheximide and some modifications.[8] This has been shown to occur by interference with protein synthesis in the ribosomes, primarily by the inhibition of polypeptide chain elongation. There is also evidence of cycloheximide acting as an inhibitor of nucleic acid synthesis.[8]

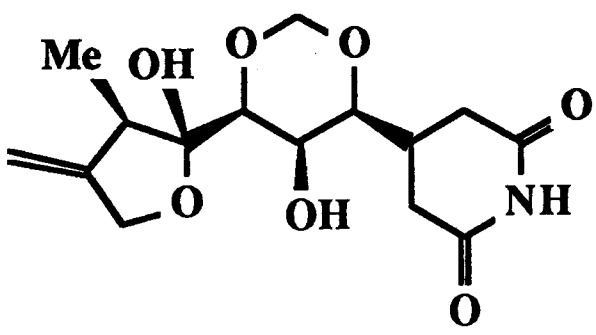
Sesbanimide and Structural Relatives.

In 1979 Powell and co-workers[11] isolated the unique alkaloid sesbanine (7) in cytotoxic extracts from the seeds of *Sesbania drummondii*. This compound was initially thought to be active in the P338 Leukemia screen; but later studies on a more highly purified sample precluded this result.[12]

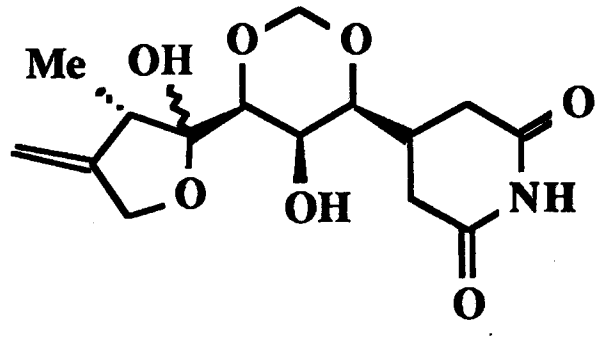


Sesbanine (7)

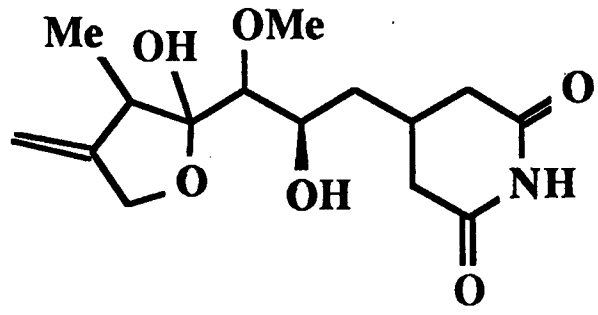
The activity in the P338 leukemia screen was later traced by the same workers to another unique alkaloid in the extract, identified as (+)-sesbanimide A (2);[3] synthesis later showed this to be the correct absolute configuration.[13] The relative configuration was demonstrated by an X-ray crystal structure.



(+)-Sesbanimide A (2)



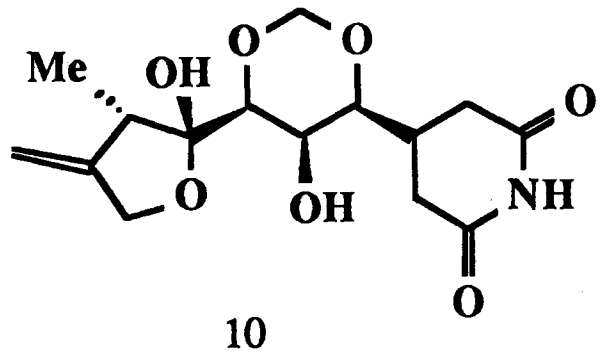
(+)-Sesbanimide B (8)



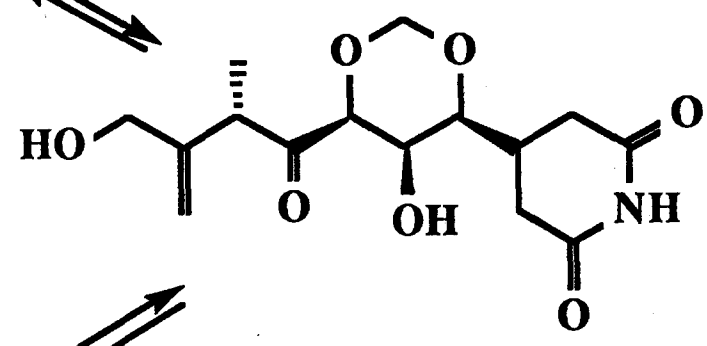
Sesbanimide C (9)

Two further alkaloids of related structure were also isolated and identified, corresponding to sesbanimide B (8) and sesbanimide C (9).[4] These componds each possessed a glutarimide ring linked by an oxygenated carbon fragment to a similar hemiketal; sesbanimide B being a diastereomer of sesbanimide A.

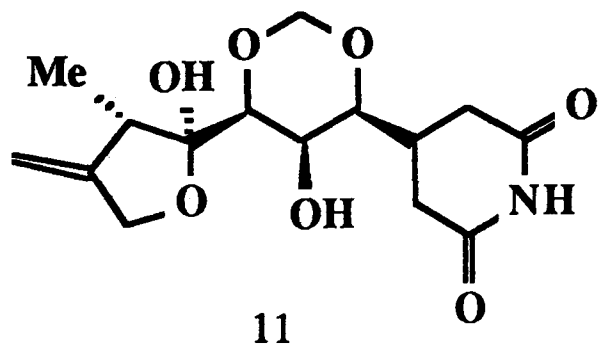
In the crystal structure of sesbanimide A the configuration of the cyclic hemiketal was established; this was also the form in NMR studies carried out in non-polar solvents (such as chloroform).[4,14] In more polar solvents solvents evidence appeared for a dynamic equilibrium between (2) and its anomer; steric factors being responsible for the predominance of (2). In the case of sesbanimide B these factors have been altered and the lactol ring exists in solution as a dynamic equilibrium between the two anomers (10) and (11), mediated by the γ-hydroxy ketone (12). The structure of sesbanimide B was assigned on the basis of comparative NMR studies with sesbanimide A.



10



12



11

The antitumour activity of these compounds was demonstrated against P338 lymphocytic and K210 lymphoid leukemia cells *in vivo* (mice); and against human cancer cells (KB type) *in vitro*. The results for sesbanimide A were achieved at a tenth

of the concentration required for similar activity with sesbanimide B and sesbanimide C. This was however at a substantially lower level than that found for the anti-tumour actions of streptoviatacin A.[15]

References, Introduction

1 S. Hanessian, 'Total Synthesis of Natural Products, The Chiron Approach,' Pergamon, Oxford, 1983.

2 F. Johnson, *Fortschr. Chem. Org. Naturst.*, 1971, **29**, 140.

3 R.G. Powell, C.R. Smith, D. Weisleder, G.K. Matsumoto, J. Clardy and D.Weisleder, *J. Am. Chem. Soc.*, 1983, **105**, 3739.

4 R.G. Powell, C.R. Smith and D. Weisleder, *Phytochemistry*, 1984, **23**, 2789.

5 J.R. Bearder, S.V. Evans, S.C. Beasley, personal communications.

6 G.W.J. Fleet and T.K.M. Shing, *J. Chem. Soc., Chem. Commun.*, 1984, 835.

7 B.E. Leach, J.H. Ford and A.J. Whiffen, *J. Am. Chem. Soc.*, 1947, **69**, 474.

8 E.F Gale, E. Cundliffe, P.E. Reynolds, M.H. Richmond and M.J. Waring, 'The Molecular Basis of Antibiotic Action,' 2nd.Ed., Wiley, New York, 1981, p. 502.

9 J. Dekker, Antibiotics in 'Fungicides,' D.C. Torgeson Ed., 1969, p. 579.

10 T. Misato and K. Yoneyama, Agricultural antibiotics in 'Advances in Acricultural Microbiology,' N.S. Subba Rao Ed., Butterworth Scientific, 1982, p. 465.

11 R.G. Powell, C.R. Smith, D. Weisleder, D.A. Muthard and J. Clardy, *J. Am. Chem. Soc.*, 1979, **101**, 2784.

12 R.G. Powell and C.R. Smith, *J. Nat. Prod.*, 1981, **44**, 86.

13 M.J. Wanner, N.P. Willard, G-J Koomen and U.K. Pandit, *J. Chem. Soc., Chem. Commun.*, 1986, 396.

14 C.P. Grost-Allman, P.S. Steyn, R. Vleggaar and N. Grobbelaar, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1311.

15 A personal communication to the authors of reference 3.

Section A

Formation of Glutarimides from Functionalised Precursors.

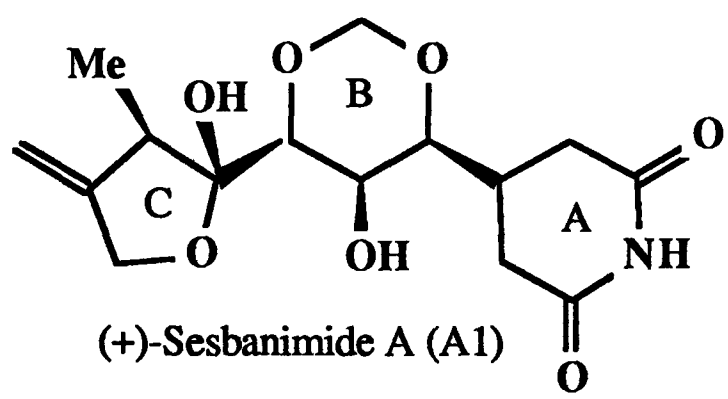
Summary, Section A.

This section of the thesis investigates methods for the synthesis of 4-substituted glutarimides from functionalised precursors. Interest in the chemistry of sesbanimide has prompted much research in this field. The methods employed develop these recent advances in the formation of glutarimides attached to carbohydrates. To this end a glutarimide was synthesized from C-5 of xylose. As the result of a novel formation of α and β C-nucleoside precursors, the synthesis of a glutarimide attached to each epimeric ribose residue was pursued. This was successfully achieved for the β-glutarimide, whilst an approach was made to the epimeric α-compound.

INTRODUCTION

Previous Syntheses of Glutarimides by Elaboration of Functionalised Precursors.

The discovery of the glutarimide sesbanimide A (A1) stimulated much interest by virtue of its potent biological actions. It also represented a great challenge for the synthetic chemist with it having a novel tricyclic structure linked by single bonds. Indeed, until the first enantiospecific synthesis appeared,[1] the absolute configuration was unknown.

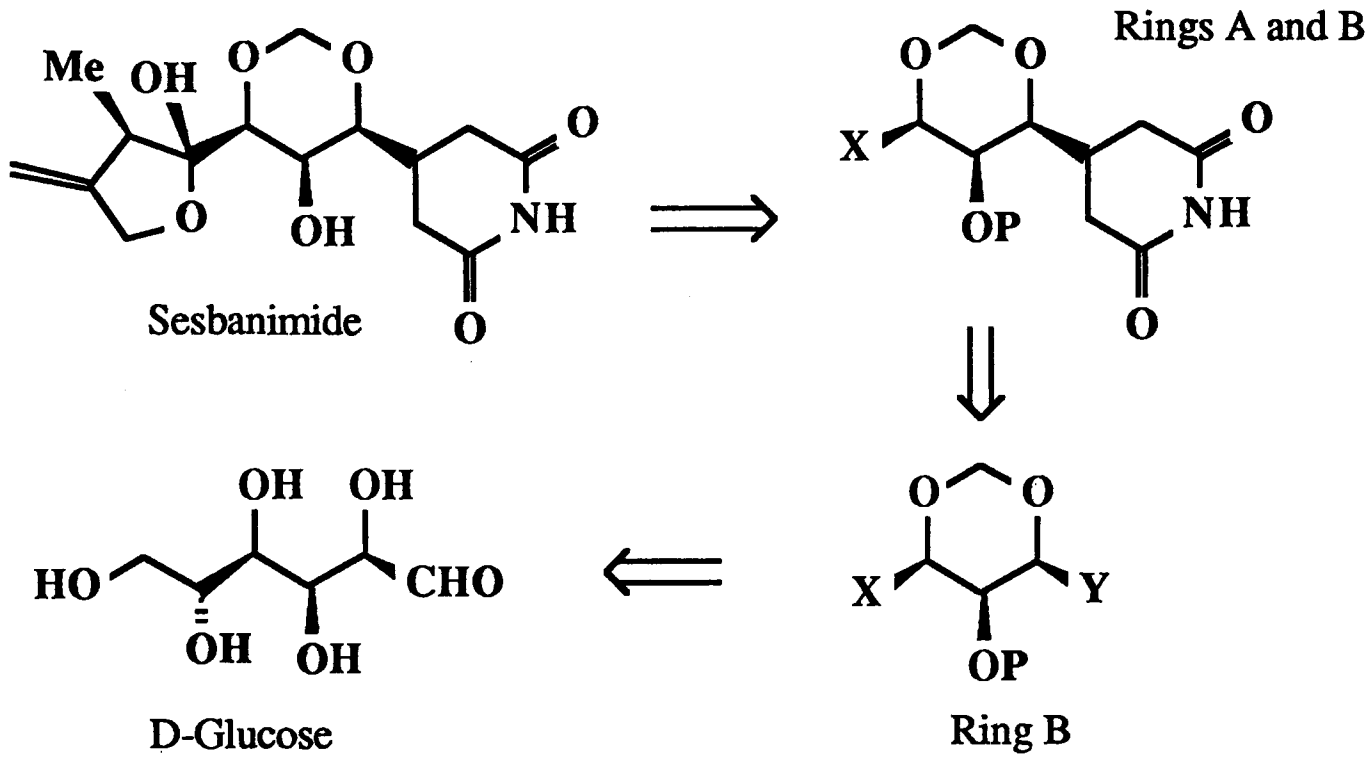


(+)-Sesbanimide A (A1)

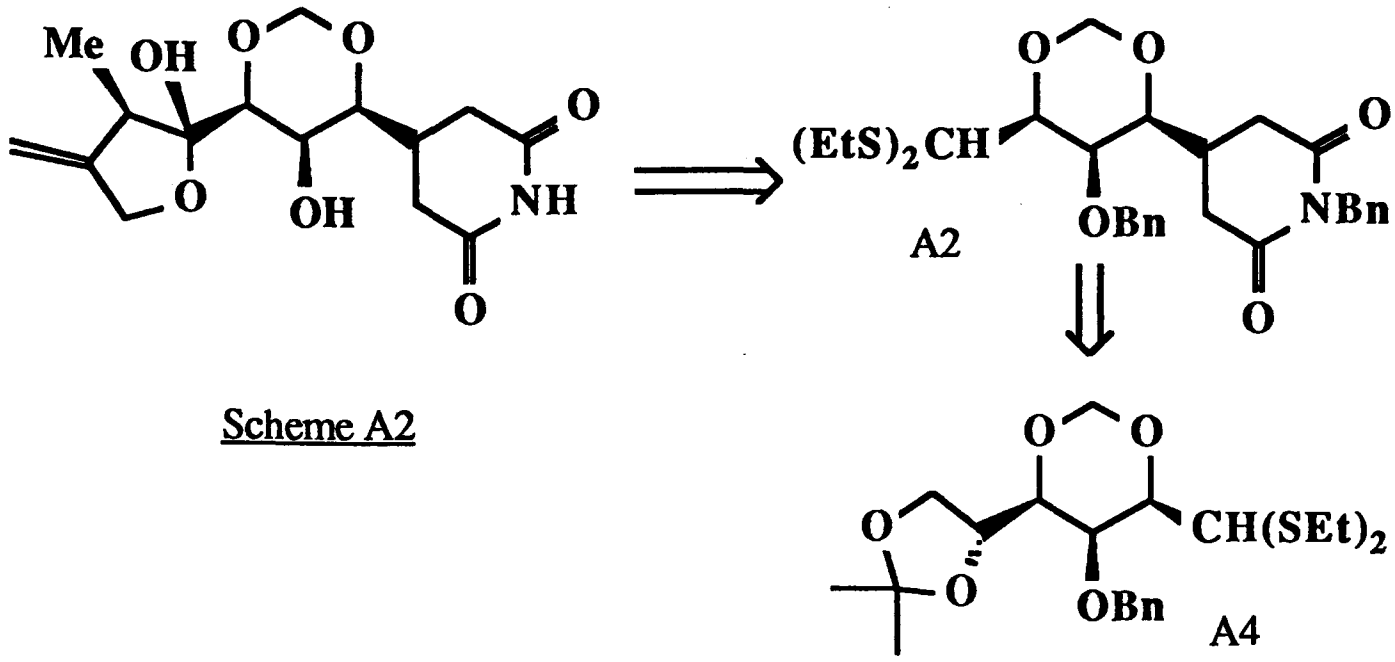
Approaches to the synthesis of sesbanimide prompted much work on the construction of glutarimide itself; this apparently quite simple functionality was surprisingly difficult to form, especially without the use of comparitively harsh conditions.[2] By the use of such methods the yields were uniformly low (10-40%), typically relying on the dehydration of ammonium glutarates[3] or pyrolysis of glutaramic acids.[4]

Fleet and Shing[5] published the first approach to the synthesis of Sesbanimide A in a paper which set the precedent for the subsequent approaches: the B ring was constructed from a chiral pool precursor (D-glucose); the glutarimide (ring A) was constucted next; leaving appropriate functionality to introduce the sensitive lactol (ring C) in some final step (Scheme A1).

Scheme A1



This paper described the synthesis of the enantiomeric dithioacetals (A2 and A3) from a common intermediate (A4), which would allow elaboration to either enantiomer of sesbanimide A (Scheme A2).



Scheme A2

The common intermediate (A4) was effectively a doubly-masked symmetrical dialdehyde (Figure A1). The two aldehydes were distinguished by their protecting groups, which were each sensitive to different conditions, thus allowing their exclusive removal. The elaboration of each aldehyde to a glutarimide was described in the paper; the value of the resulting enantiomeric intermediates (A2 and A3) as sesbanimide synthons was demonstrated in later total syntheses which used similar intermediates (*vide infra*).

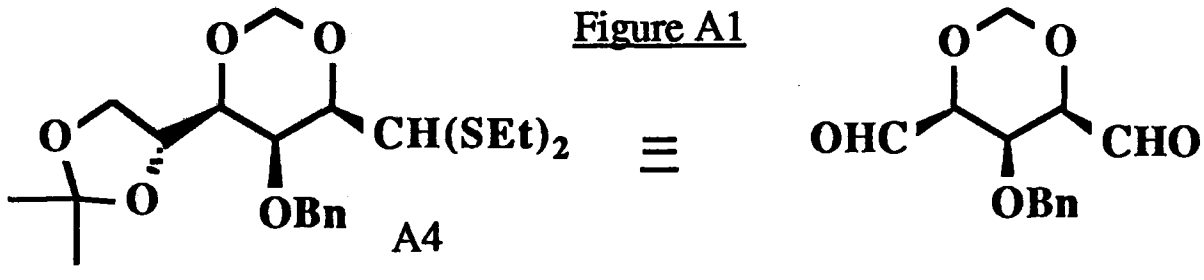
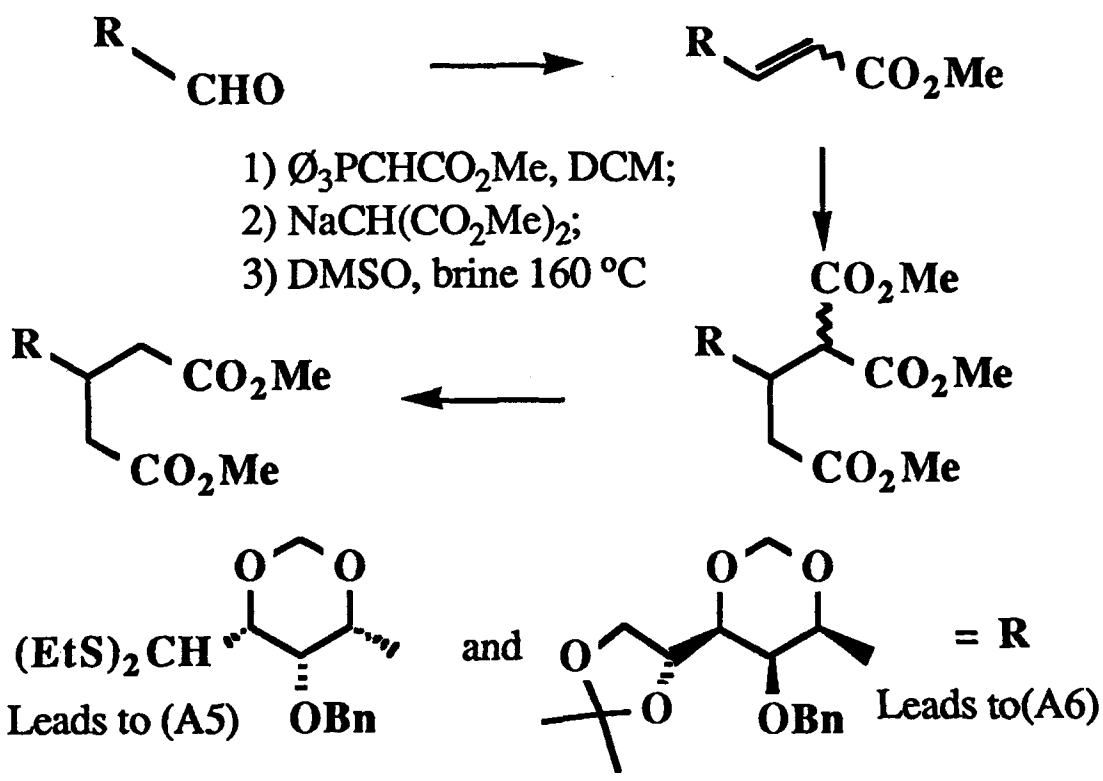


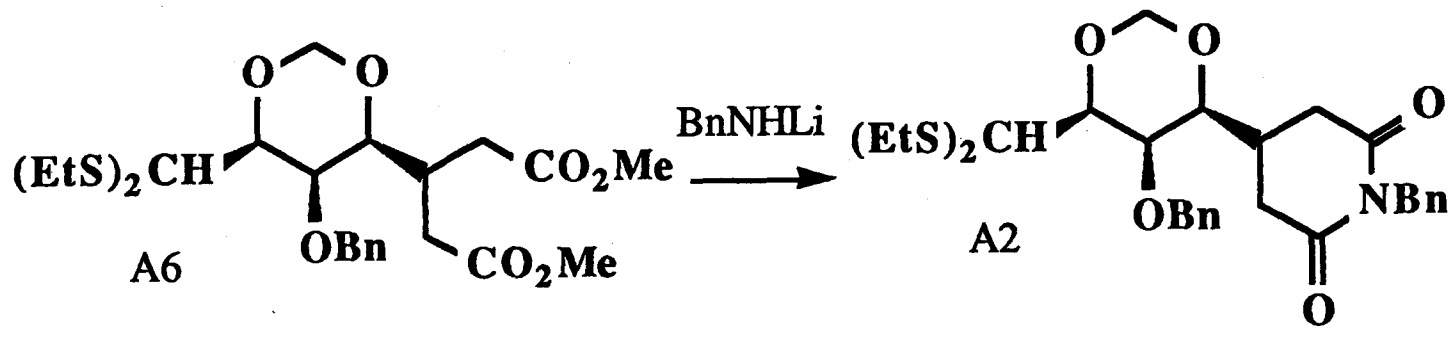
Figure A1

The glutarimide ring was approached in the same way for each enantiomer by conversion of the two distinct deprotected aldehydes to glutarate diesters. This was achieved by Wittig olefination, followed by Michael addition of dimethyl malonate and subsequent Krapcho[6] demethoxycarbonylation (Scheme A3). This gave (A5) directly. Its enantiomer (A6) was synthesized by conversion of the protected diol to the required dithioacetal at this stage.

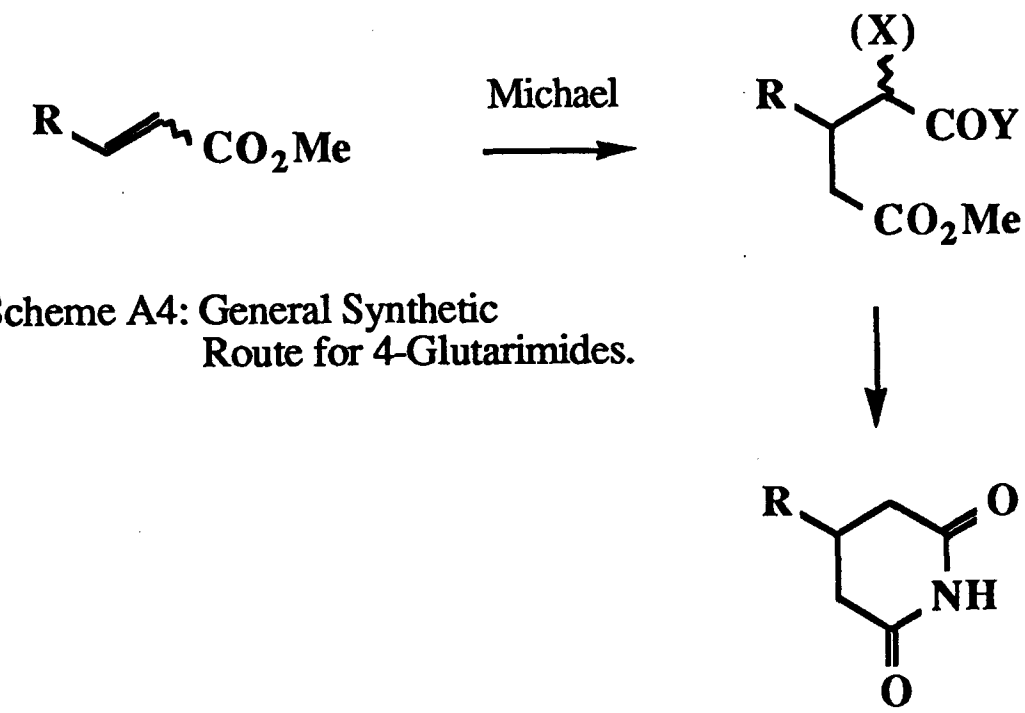
Scheme A3



Conversion of the glutarate diesters (A6 and A5) to the glutarimides (A2 and A3 respectively) was not an easily accomplished reaction: low (30%) yields of these *N*-benzyl substituted enantiomers were isolated on treatment of the diesters with lithium benzylamide at low temperature. This represented the best yield, established from a variety of closure attempts.

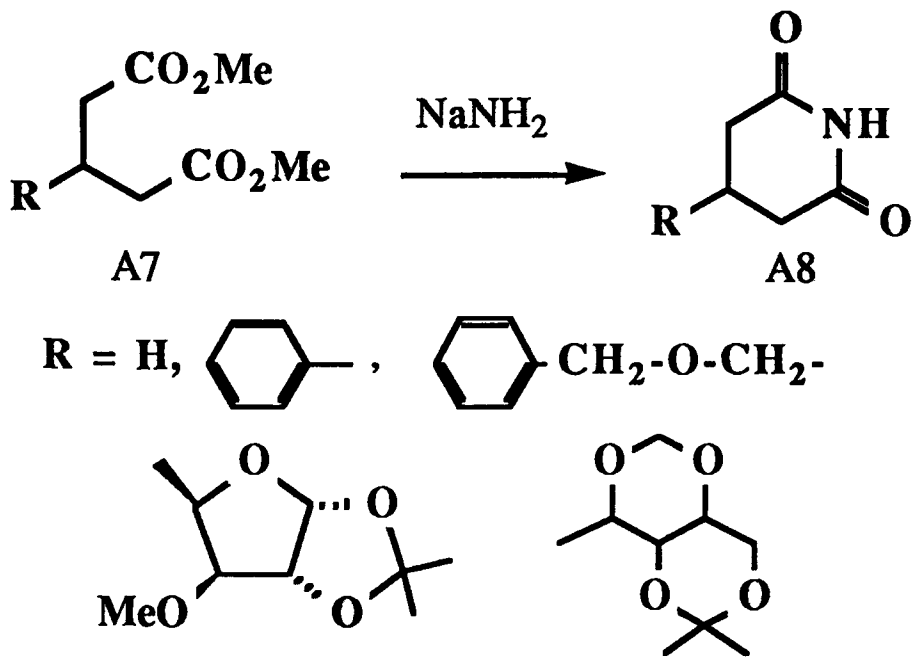


The construction of the glutarimide ring by some novel approach was to be a major feature of the subsequent work on sesbanimide synthesis and indeed the subject of other papers devoted solely to that topic. In this discussion of these studies it can be seen that the basic chemistry is the same: a glutarate is first synthesized from an enoate in the way previously discussed, the key step being a Michael reaction. This glutarate is subsequently closed to a glutarimide; the differences are in the execution of this closure, dependent on the substitution of the nucleophile used in the Michael addition, as shown in Scheme A4.

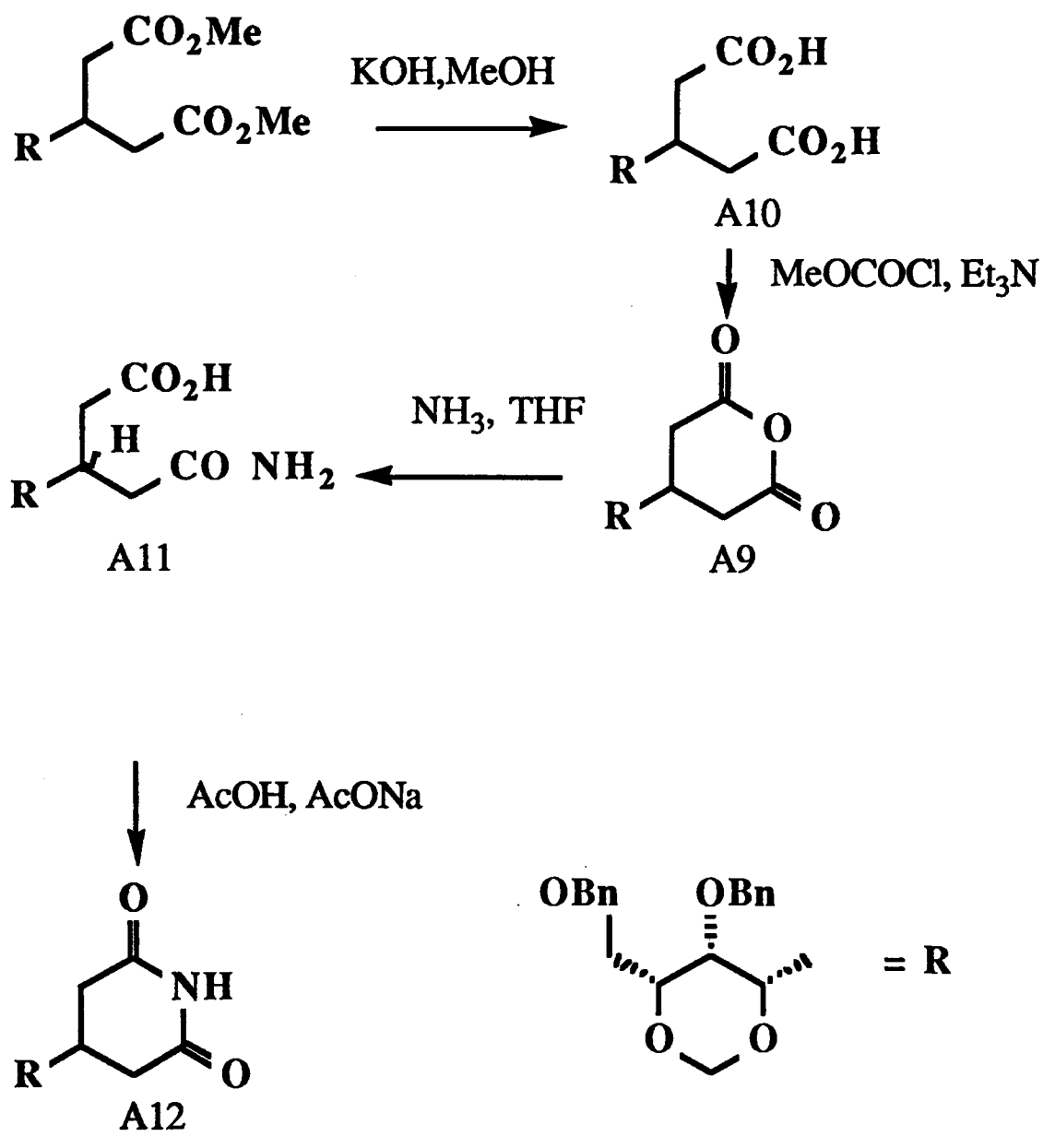


Scheme A4: General Synthetic Route for 4-Glutarimides.

In a general approach to the synthesis of glutarimides, Kinoshita and Clardy[7] closed several 3-substituted dimethyl glutarates (A7) to the corresponding 4-substituted glutarimides (A8) by treatment with sodamide in liquid ammonia in the presence of iron (III) chloride giving yields of 45 to 85%. These glutarimides included carbohydrates amongst their substituents, appropriate to sesbanimide synthesis. Each glutarate was synthesized from an aldehyde by the usual Wittig, Michael, then Krapcho procedure.



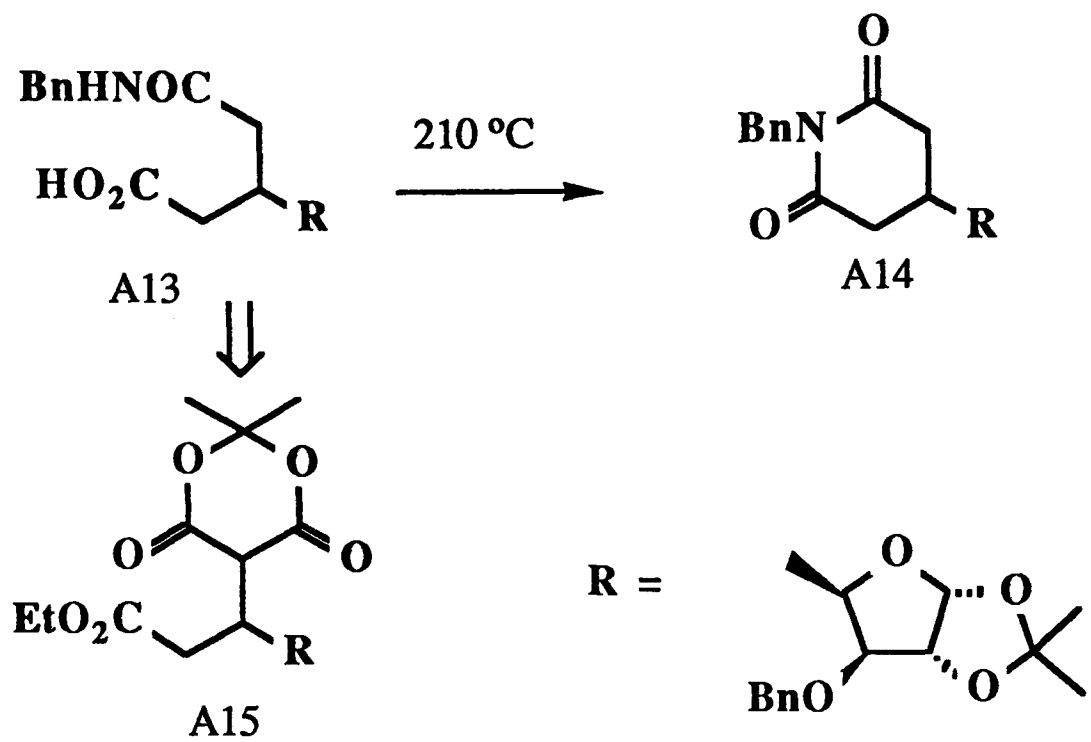
Terashima and co-workers in their approach to sesbanimide[8] (leading to the first synthesis of natural (+)-sesbanimide A[9]) synthesized a glutarate diester attached to the B-ring in the usual 3-step sequence form the appropriately substituted aldehyde (with improved overall yield). In their conversion to the glutarimide, instead of using the Kinoshita/Clardy philosophy of employing a more reactive nucleophile to make the nitrogen-carbon bonds, they activated the carbonyl substitution towards nucleophilic attack. After forming the anhydride (A9), *via* the diacid (A10), nitrogen was simply introduced by its opening with ammonia forming a diastereomeric mixture of the acid/amides (A11). This was readily closed to the glutarimide (A12) by warming in acetic anhydride buffered with sodium acetate, in 52% overall yield. A similar philosophy of activation using a mixed anhydride was reported by Watt, Fitz and Kometani.[12] This led to the formation of glutarimides substituted only at nitrogen.



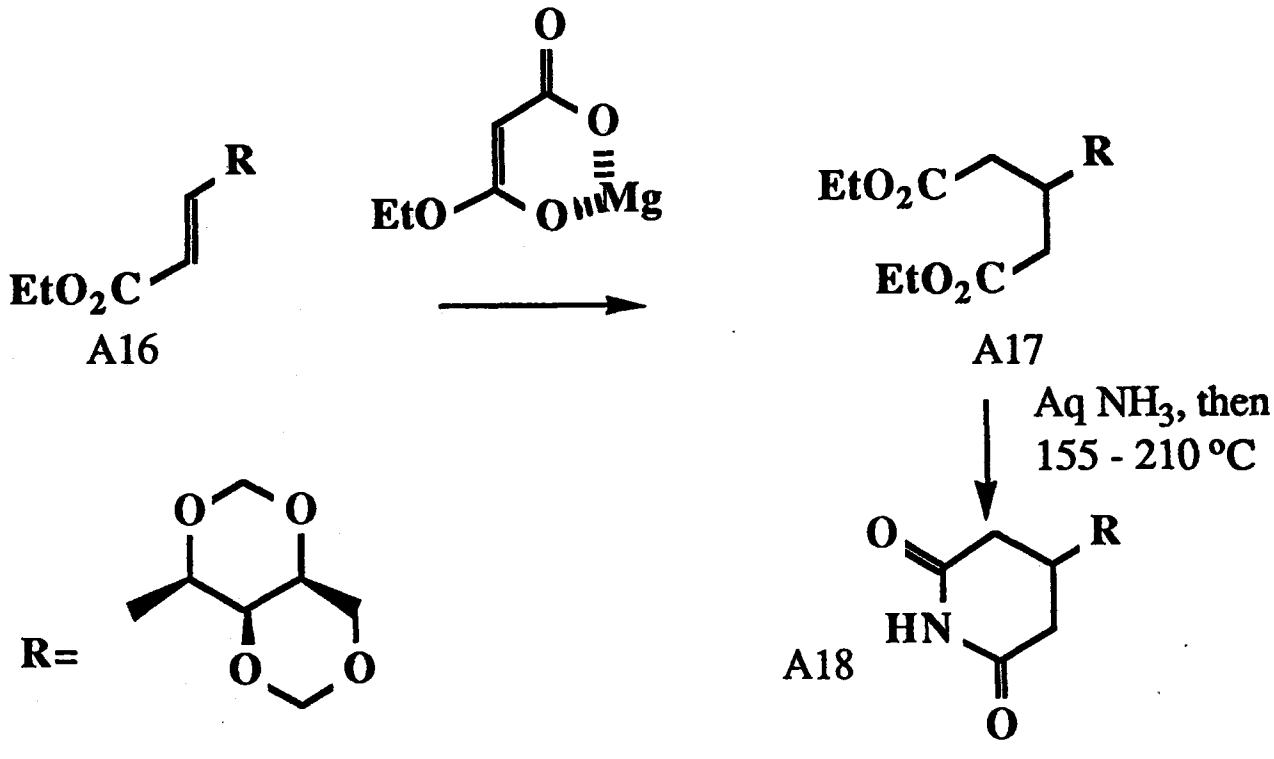
Two methods were published using more old-fashioned pyrolysis methods, forming glutarimide-substituted sesbanimide synthons, with high yields quoted for the imide formation.

Shibuya[11] closed the acid amide (A13) to the *N*-benzyl glutarimide (A14) in 87% yield; interestingly he did not use a Wittig extension in the formation of the glutarate, instead employing a condensation of the required aldehyde with Meldrum's acid, followed by Michael addition of the lithium anion of ethyl acetate to give (A15). Esterification and decarboxylation were achieved by heating (A15) in the presence of 4-nitrophenol and copper powder in acetonitrile; the amide was selectively formed *in situ*

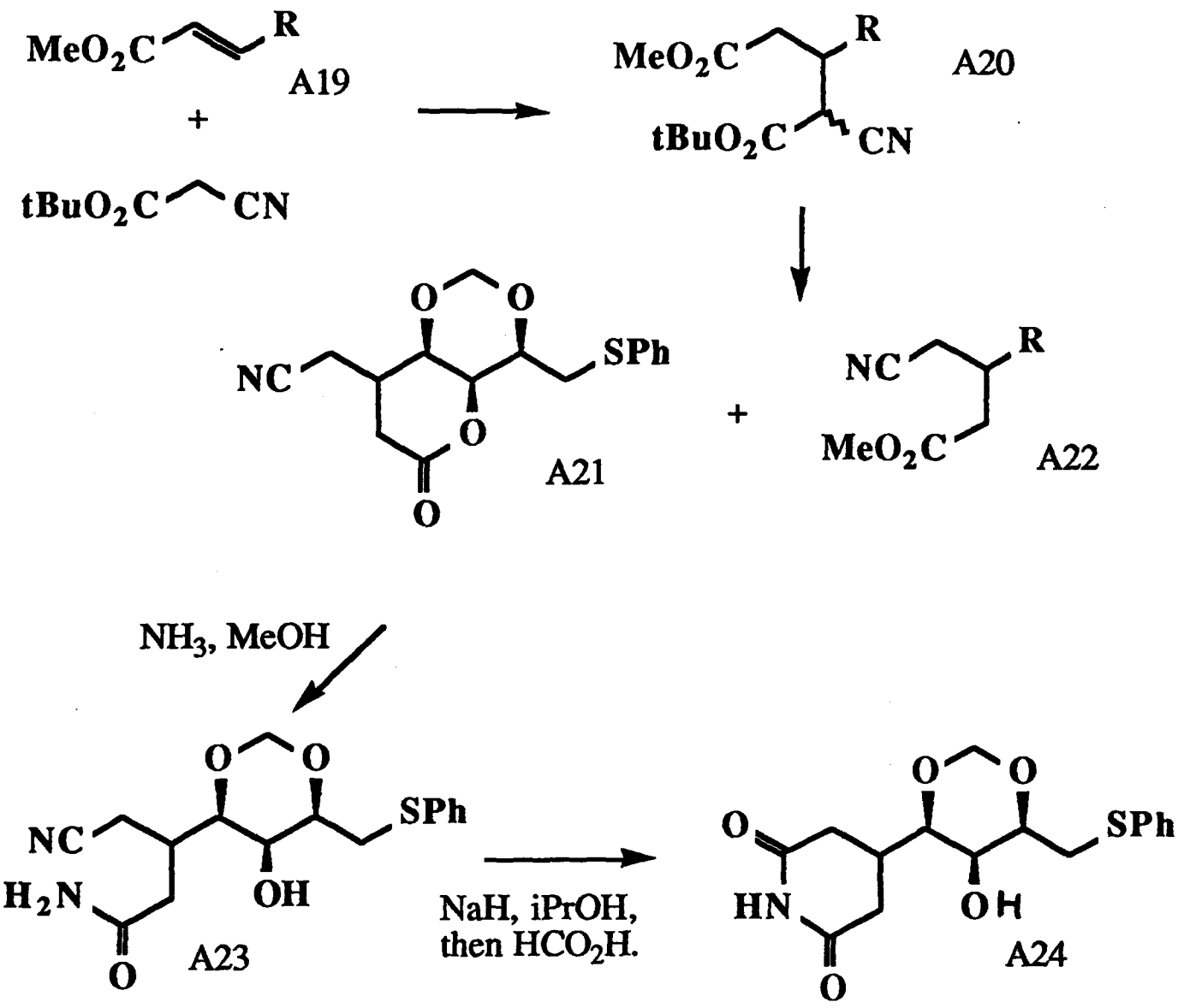
using benzylamine/triethylamine. The acid amide (A13) was formed on base hydrolysis, in 70% overall yield from the aldehyde.



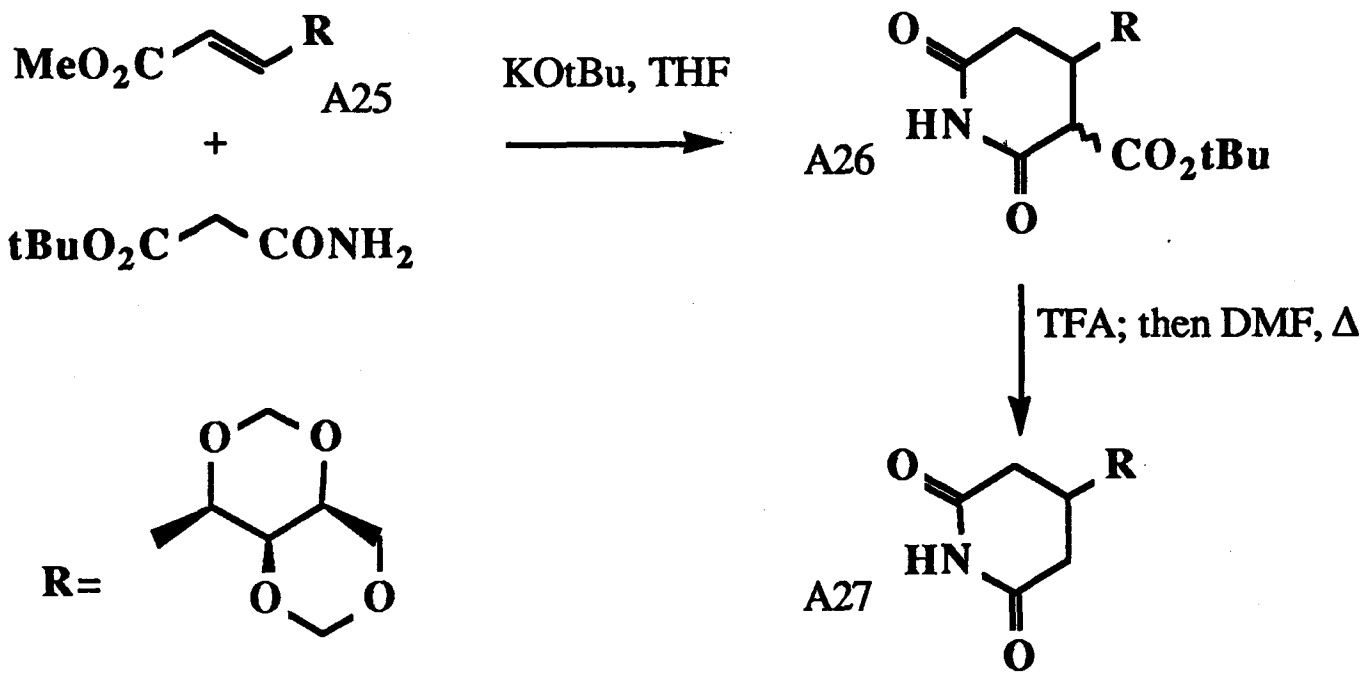
The approach of Schlessinger and Wood[12] took the enoate (A16) through to the glutarate (A17) in one pot by Michael addition then decarboxylation, using the magnesium salt of monoethyl malonate (77% yield). Hydrolysis to the ammonium glutarate followed by pyrolysis[13] gave the glutarimide (A18) in 68% yield. This intermediate was converted into the enantiomer of natural sesbanimide A.



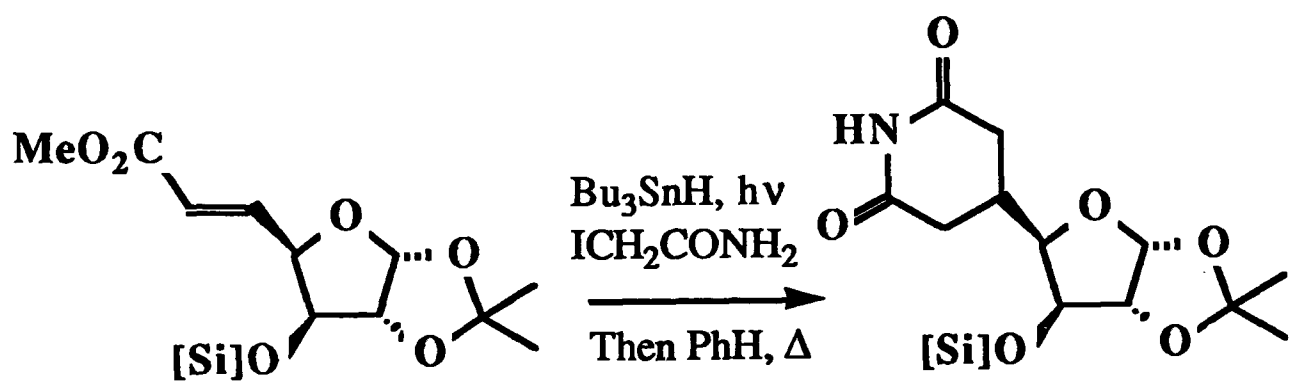
Modifying the Michael nucleophile was a theme developed in the approach of Rousch and Michaelides,[14] the only published route to sesbanimide which does not use a carbohydrate to establish the configuration of ring-B. Starting from an enoate (A19), they employed Michael addition of *tert*-butyl cyanoacetate to give (A20), followed by the Krapcho[6] procedure, which gave a mixture of the lactone (A21) and ester (A22). Ammonolysis of these to the amide (A23) was followed by closure to the glutarimide (A24) by treatment with sodium *iso*propoxide in *iso*propanol, followed by a mild formic acid hydrolysis[15] giving an 80% yield over the three steps.



Pandit and co-workers[16] used a similar modified Michael reaction with great success whereby in one pot the enoate (A25) was converted to the glutarimide (A26). This was achieved by sequential Michael addition followed by cyclisation (prompted by the addition of a second equivalent of base) using *tert*-butyl carbamoylacetate. Hydrolysis of the *tert*-butyl ester followed by decarboxylation by warming in DMF gave the glutarimide (A27) in 78% yield from (A25). Using such chemistry, first the enantiomer,[1] and subsequently the natural (+)-sesbanimide A,[17] were both synthesised by this group; the former synthesis first confirmed the absolute configuration of the natural product.



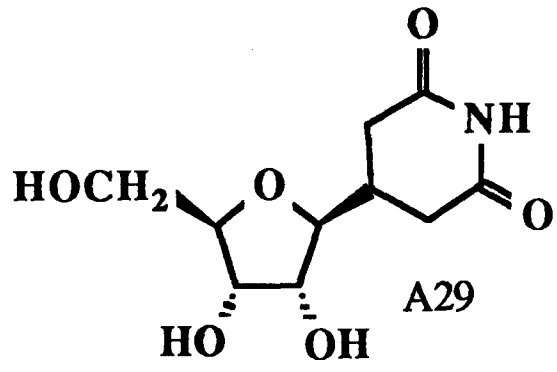
This summary of closure methods is completed by that of Just and co-workers.[18] Their method is similar to that described by Pandit,[16] in that a glutarimide is synthesised from an enoate in one pot. However, rather than using a base catalysed Michael reaction, the two carbon fragment attached to nitrogen was introduced by the 1,4 free radical addition of iodoacetamide. This was followed by cyclisation, achieved by refluxing the product in toluene, which gave up to a 64% overall yield, using various enoates. The product (A28) is similar to the sesbanimide synthon (A14) of Shibuya.[11]



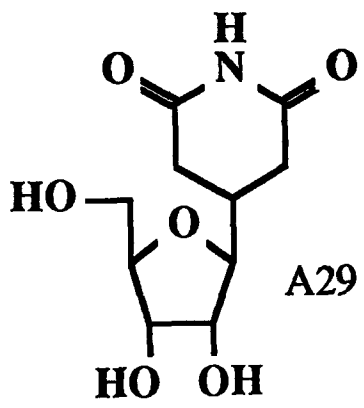
A28

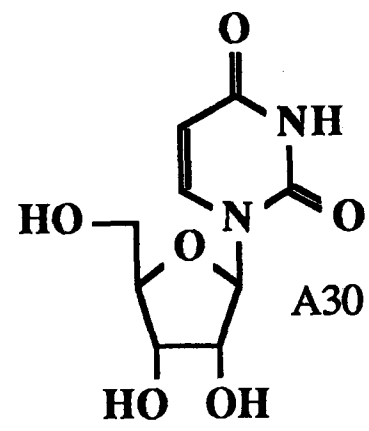
Synthesis of Glutarimide-C-Nucleoside Precursors.

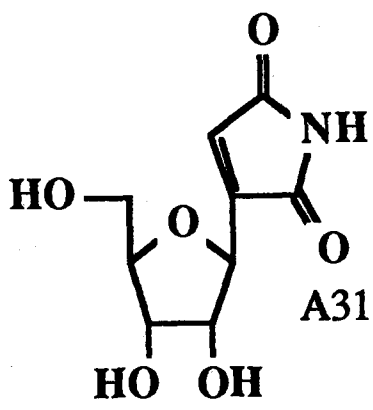
At the outset of the project the formation of the β-glutarimide-C-nucleoside analogue (A29) was regarded as a potentially very interesting goal both for synthesis and biological testing.

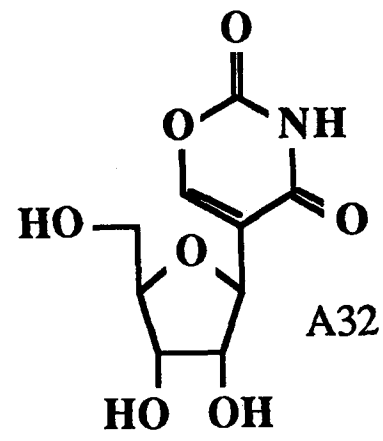


The structure of this compound is not only a glutarimide attached to an oxygenated side branch (an analogy with the glutarimide antibiotics) but it is also very close to that of nucleosides and C-nucleosides. Uridine (A30), one of the nucleosides found in ribose nucleic acid, and the C-nucleosides showdomycin (A31) and oxazinomycin (A32) serve to illustrate this structural relationship.

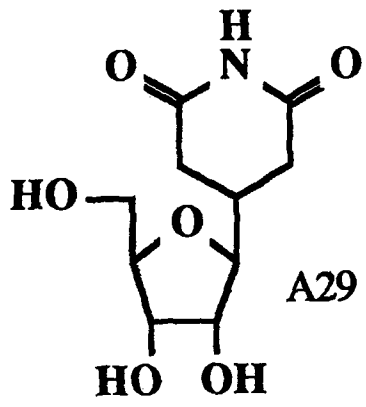




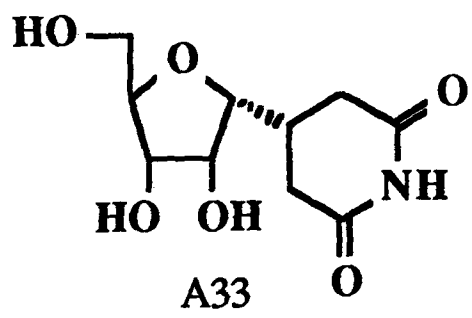




Nucleoside is the generic name given to a group of glycosylated nitrogen heterocycles.[19] A C-nucleoside has this heterocyclic base attached to the carbohydrate *via* a carbon-carbon, rather than the normal nitrogen-carbon, linkage. A number of the naturally occuring C-nucleosides have interesting biological activity.[20] For example showdomycin (A31) and oxazinomycin (A32) exhibit anti tumour and antibacterial actions.[21] Some other C-nucleosides have been shown to be antiviral.[22] Due to these therapeutic actions there has been considerable interest in the synthesis of nucleosides and their analogues.[23] Showdomycin (A31), β-ribose-substituted maleimide, is one such well-studied compound.[24] This differs from (A29) only by unsaturation and one less carbon. However the spectrum of activity of (A29) might be expected to be different from that of showdomycin, since the latter acts by alkylation of thiol groups.[21] Important features are retained though: the nucleoside structure would enable (A29) to penetrate cells easily,[25] whilst the ribose to carbon, rather than ribose to nitrogen, bond increases resistance to enzymatic degredation.[26]



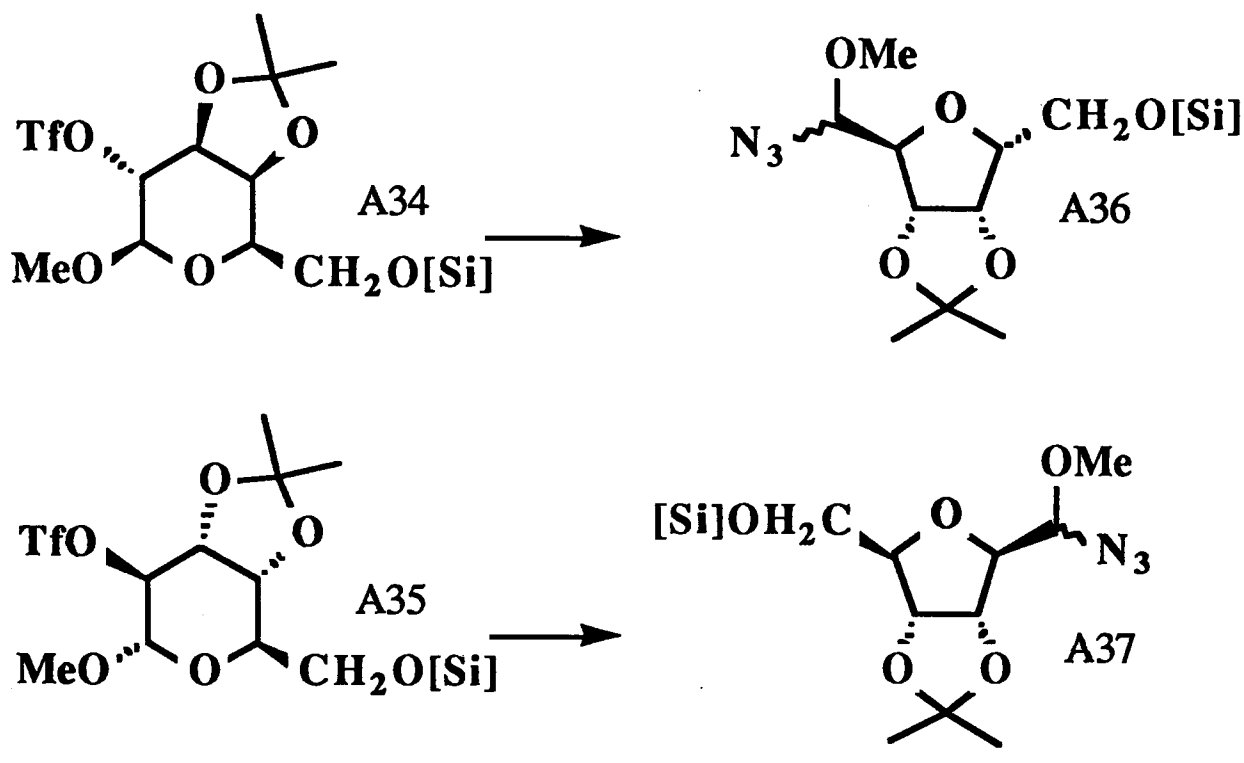
A29



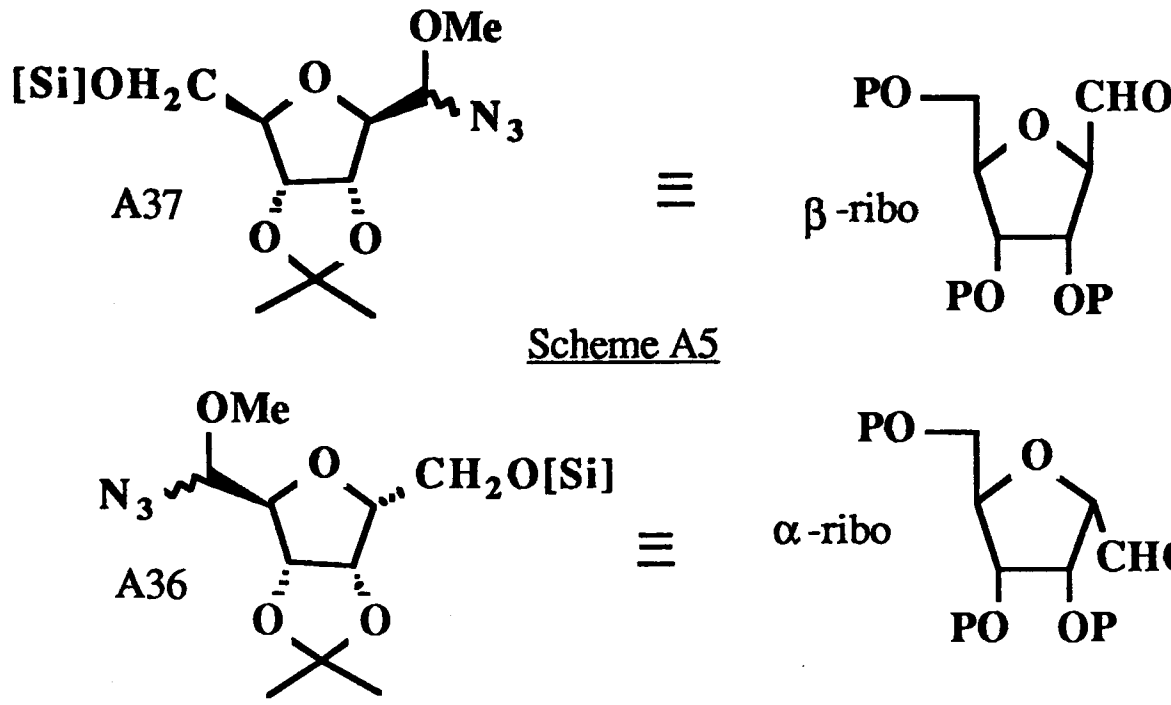
A33

Work published from within the group by Fleet and Seymour[27] proved very important towards the realization of this goal. This offered a stereospecific route to the required β-*ribo*-glutarimide (A29). The epimeric α-*ribo*-glutarimide (A33), would also be readily accessible by similar chemistry published in the same paper.

In this work ring contractions of the *galacto*-pyranoside (A34) and *altro*-pyranoside (A35) gave the alkoxy azides (A36) and (A37) respectively as diastereomeric mixtures about C-1 in high overall yield in each case.



These intermediates were effectively protected ribose residues with a one carbon extension from the anomeric position locked in the α or β configuration. Deprotection and adjustment of oxidation levels would give the riboses with this extension as an aldehyde (Scheme A5). β-C-nucleosides have been constructed from such an intermediate.[25] Glutarimides can also be elaborated from aldehydes, as has already been demonstrated (*vide supra*).



Scheme A5

The originally intended procedure had been for displacement of the triflate ester at C-2 of the α-galactoside by azide, a well-established reaction with corresponding glucosides.[28] Instead this resulted in the not unprecedented[29] ring contraction, to give the azides (A36) in high yield. This contraction, which worked for both the α and β anomers, was set up by the anti-periplanar arrangement of the excellent leaving group to the migrating bond in the ground state chair conformation (Figure A2).

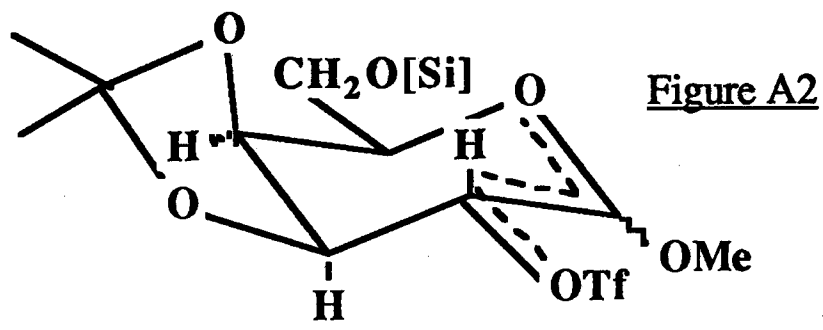
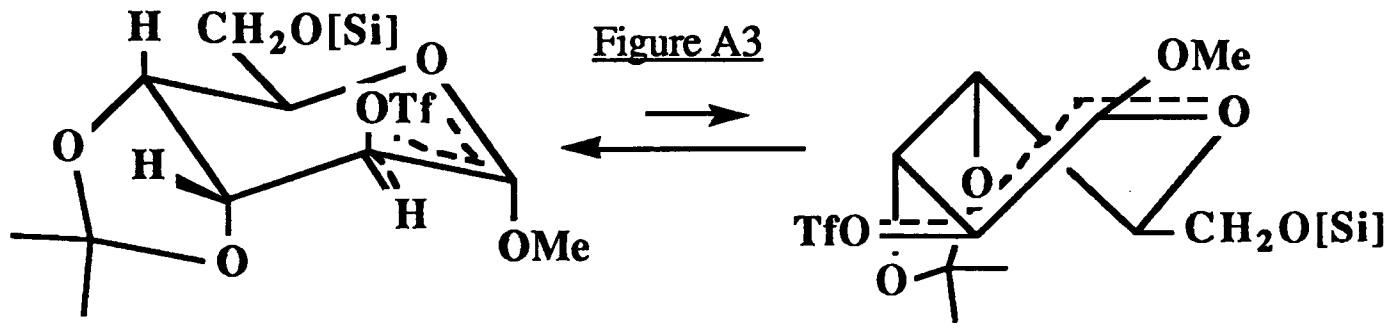


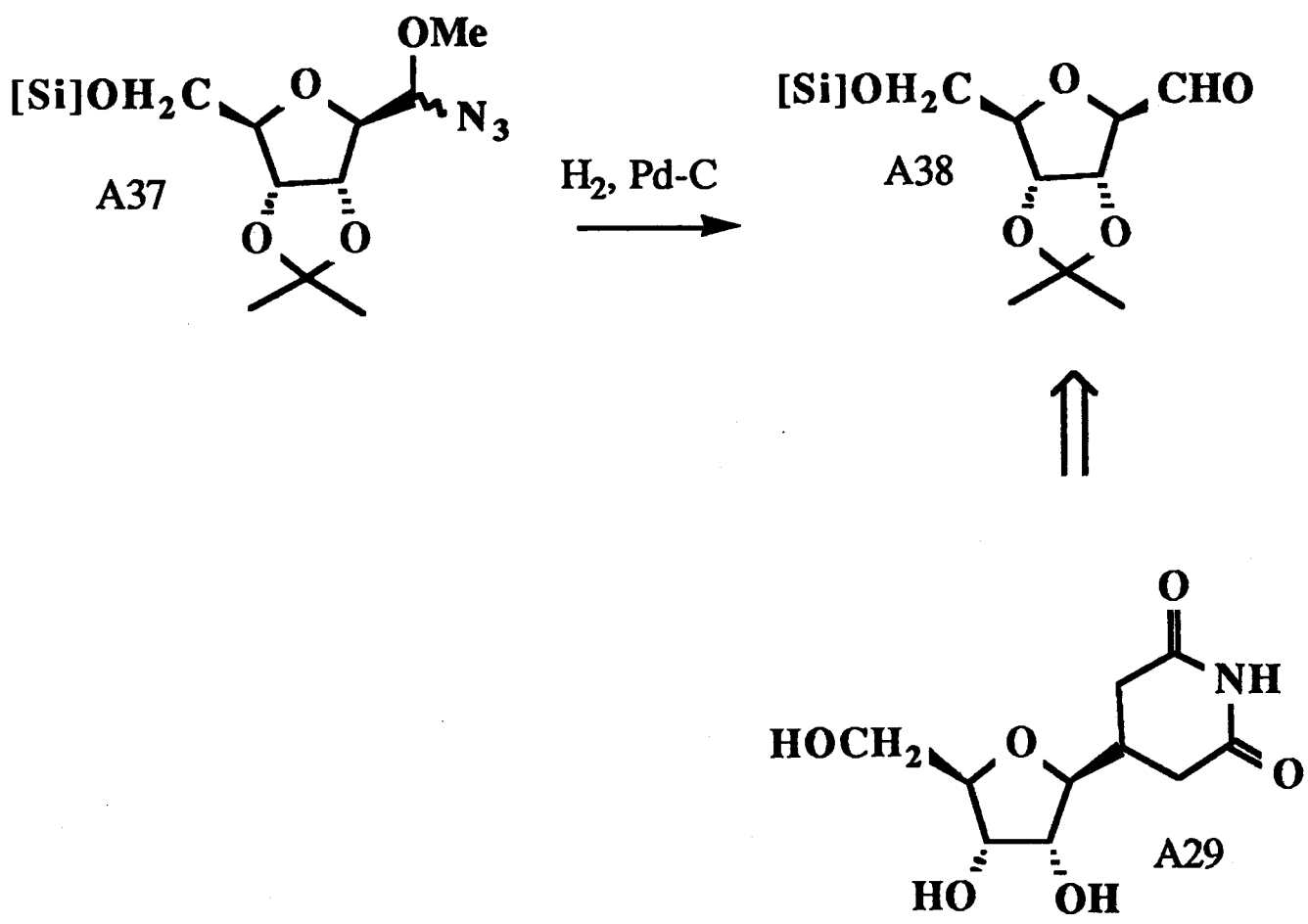
Figure A2

The more interesting chemistry, attempted as a consequence of the previous reaction, was that from the *altro*pyranoside (A35), giving the precursor (A37) with the configuration appropriate for synthesis of the natural β-C-nucleosides. The contraction itself was more remarkable and unprecedented. In the ground state chair configuration (anchored by the bulky 6-*O*-silyl protection) the triflate and migrating bond were not in an anti-periplanar arrangement. Reaction would have to be preceded by a change to a

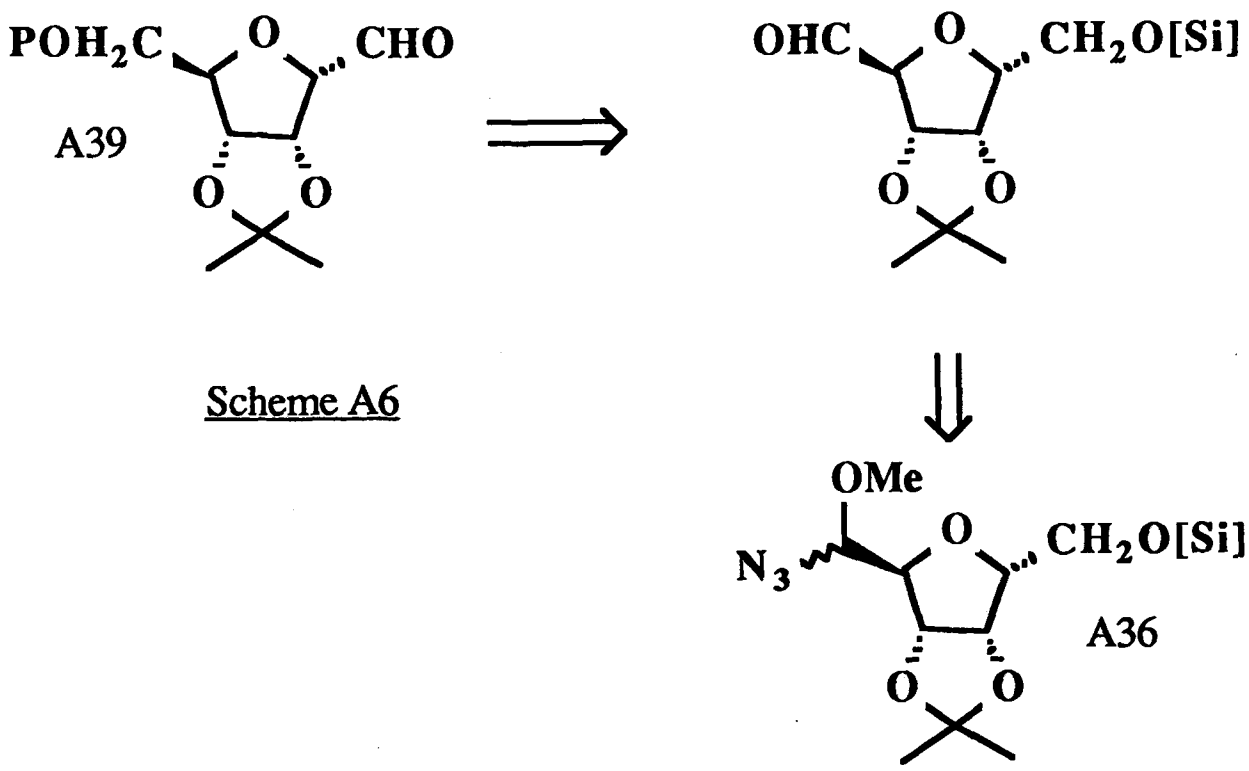
twist boat conformation to achieve this, whilst keeping the bulky silyl substituent in a favourable orientation (Figure A3). Nevertheless this contraction was accomplished cleanly with a similarly excellent yield to the *galacto* analogue.



In order to form the required β-glutarimide an aldehyde in the β-ribose configuration was required: in this case the molecule was already substituted in the required manner, so once the aldehyde (A38) was unmasked the glutarimide of (A29) could be directly constructed by an accomplished method.



To form an α-nucleoside from (A36), an adjustment in the oxidation levels of the exocyclic carbons would first have to be made. This would give an aldehyde, attached in the α-configuration, at C-1' of ribose (Scheme A6). Again, from this aldehyde (A39), the glutarimide of (A33) could be constructed in the same way as it had been in the earlier formation of a glutarimide from C-5 of xylose.

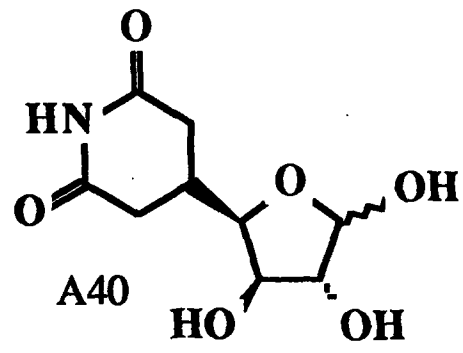


Scheme A6

Results and Discussion.

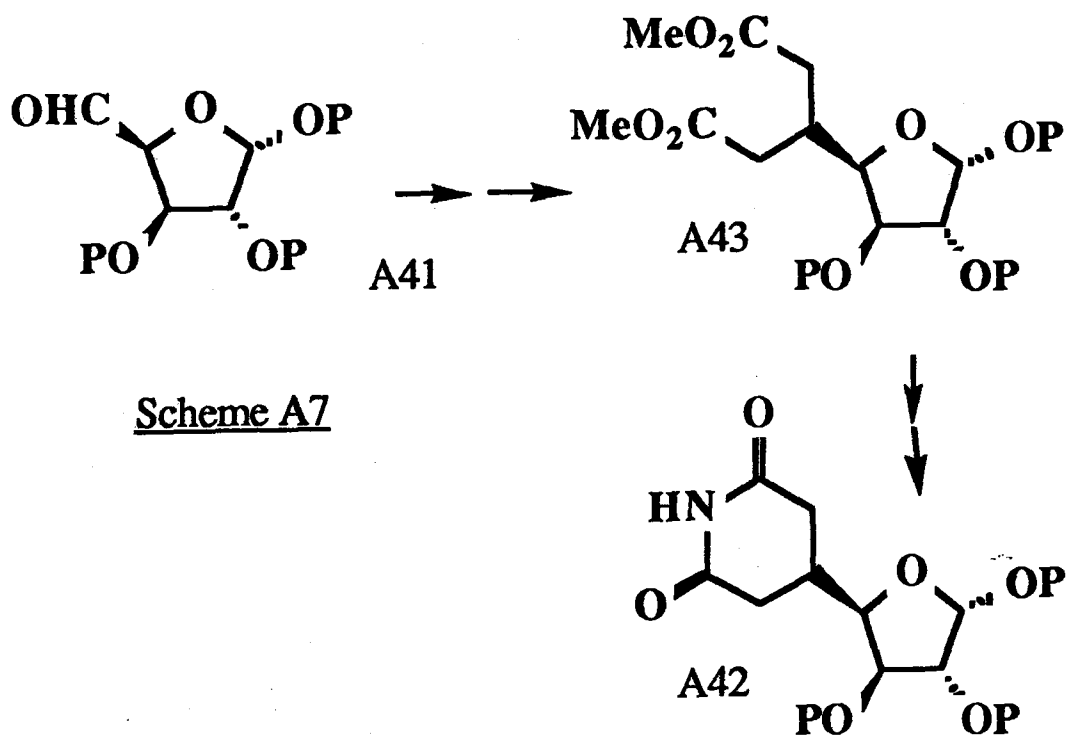
1) Construction of glutarimide from C-5 of *Xylo*furanose.

This section describes the synthesis of a glutarimide attached through C-4 to a fragment derived from D-Xylose (A40), using the typical construction and closure methods described in the introduction.



Retrosynthetic Analysis.

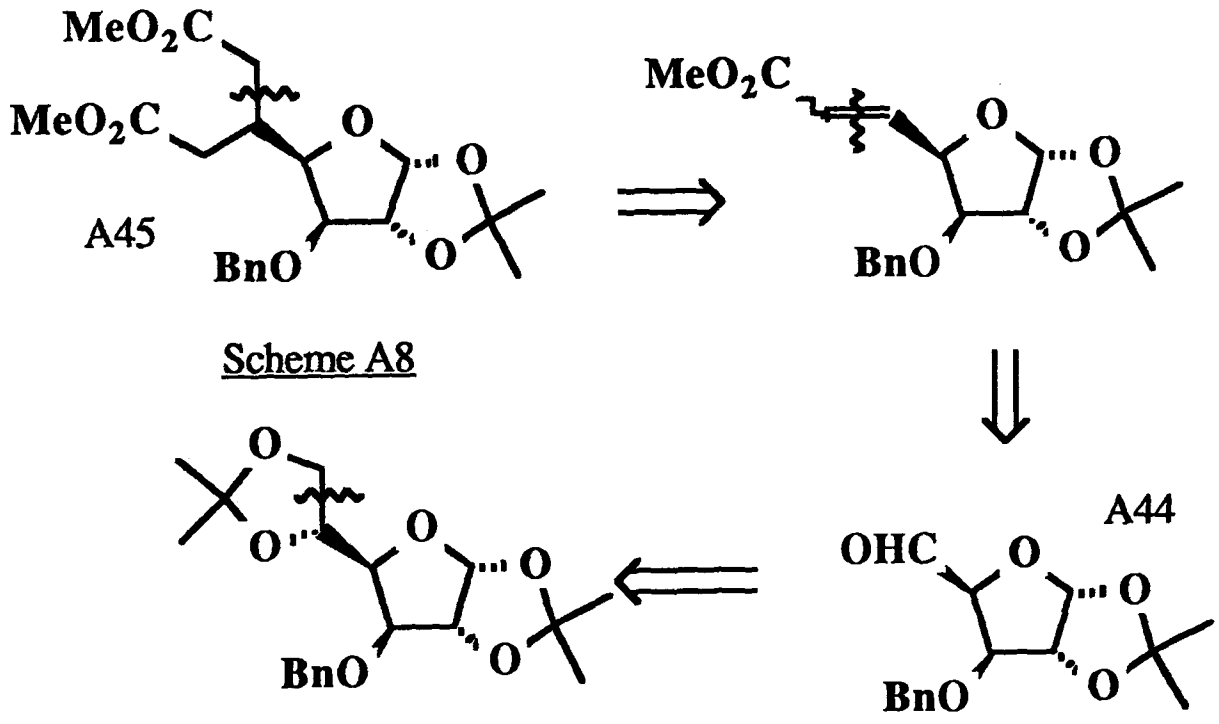
When this research was started two of the methods described in the introduction for the closure of a glutarimide from glutarate diester by milder chemistry had already appeared in the literature.[7,8] Thus the initial target was to elaborate C-5 of dialdo*xylo*furanose (A41) to the glutarimide (A42) formed *via* the diester (A43) by the application of such methodology (Scheme A7).



Scheme A7

This would give rise to a glutarimide attached to a sugar unit which might possess some interesting biological properties; the characterised active natural products have the glutarimide substituted at C-4 by an oxygenated side branch. Despite the recent reports of the synthesis of protected versions of this compound as a sesbanimide synthon (with *N*-protection of the imide),[11] and in model studies (with alternative 3-O protection),[7,18] no results from biological screens have been reported.

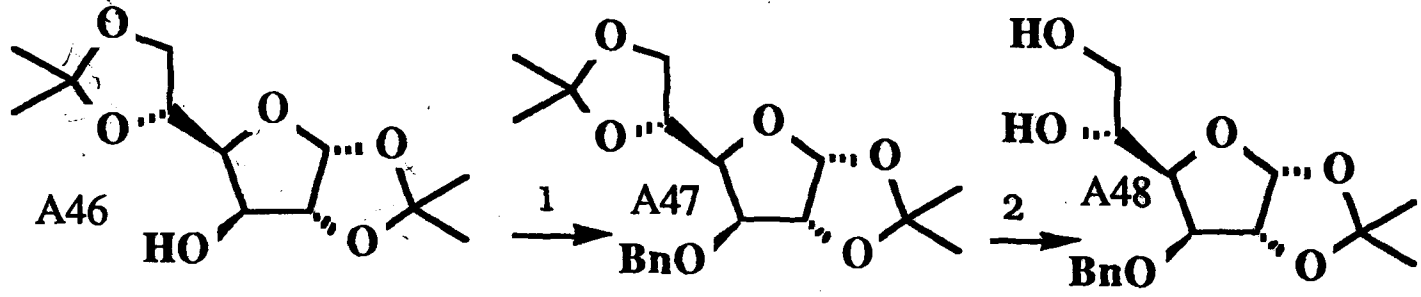
The synthesis of the glutarate diester was to be executed using chemistry similar to that performed in the sesbanimide work,[5] but using the protected xylofuranose (A44) rather than the B-ring of sesbanimide itself. The retrosynthetic analysis to the formation of the diester (A45), is outlined in Scheme A8.



Scheme A8

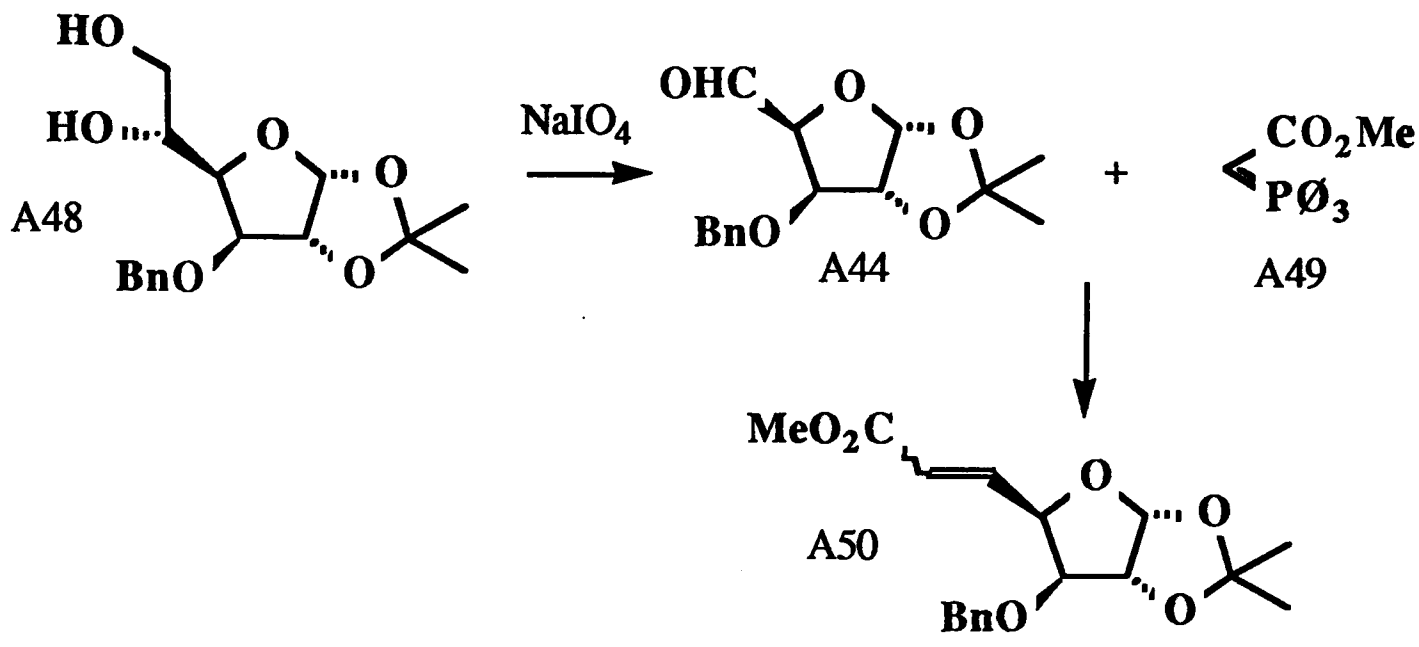
a) Synthesis of the Glutarate Diester.

The required starting material for the synthesis was thus diacetone glucose (A46), a common starting point in enantiospecific syntheses from carbohydrates.[30] Protection of the free hydroxyl at C-3 was achieved by refluxing the sodium alkoxide (formed by deprotonation of diacetone glucose with sodium hydride) with benzyl bromide in dry THF in the presence of tetrabutylammonium iodide.[31] After work-up the resulting oil was co-evaporated with benzene to remove remaining benzyl bromide, after which it was used crude in the next step. The 5,6-acetonide was selectively removed under mild acid hydrolysis conditions; achieved by stirring the diacetonide (A47) in a dilute methanolic solution of hydrochloric acid. This gave the diol (A48) in 90% overall yield from (A46).

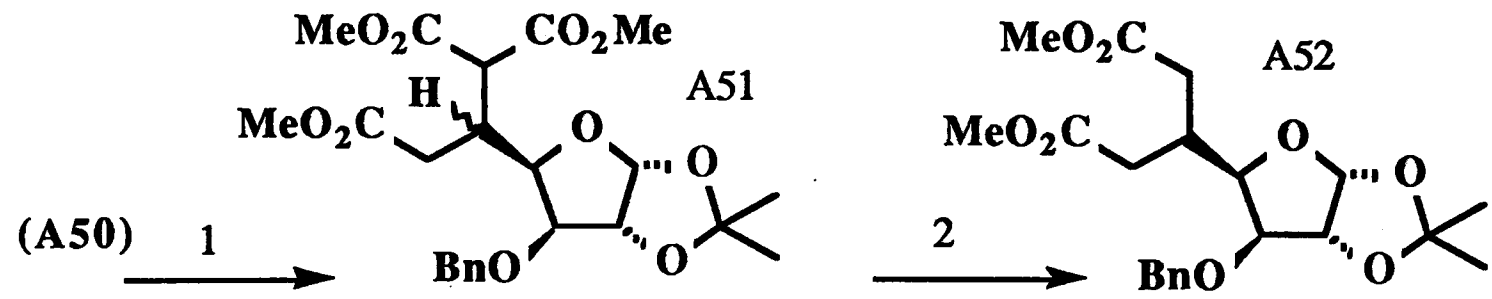


1 NaH, BnBr, Bu_4NI, THF; 2 HCl, MeOH

Oxidative cleavage of the 5,6 bond to give the *xylo*dialdofuranose (A44) was accomplished cleanly using sodium periodate in aqueous methanol. This compound was not isolated, but after suitable work-up was reacted in dichloromethane with the stabilised ylid carbomethoxymethylenetriphenylphosphorane (A49) at room temperature, affording a mixture of the diastereomeric enoates (A50) in 88% overall yield, in a 4:3 (*E*:*Z*) mixture by NMR {$J_{\alpha-\beta}$ 16.0 Hz (*E*), 12.0 Hz (*Z*)}. The compounds did not need to be separated since the stereochemistry was of no consequence in the next step.



Conversion of the enoates to a glutarate diester was carried out in the usual two-stage process of Michael reaction[33] with dimethyl malonate to give the triester (A51); followed by Krapcho demethoxycarbonylation,[6] which formed the required glutarate diester (A52).

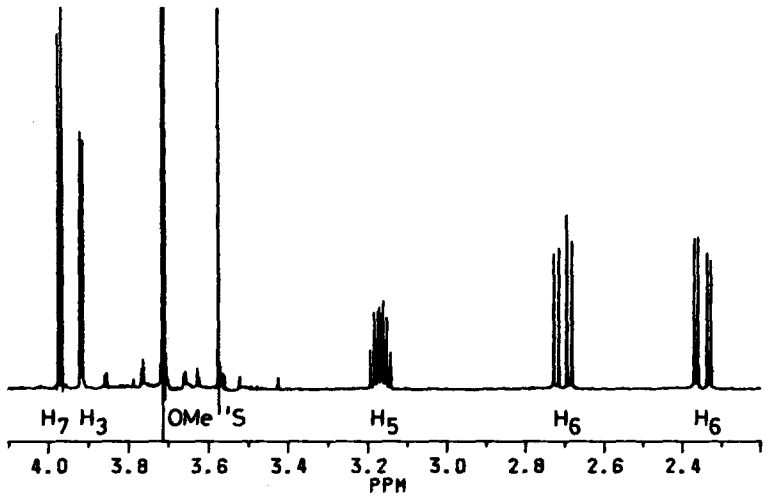


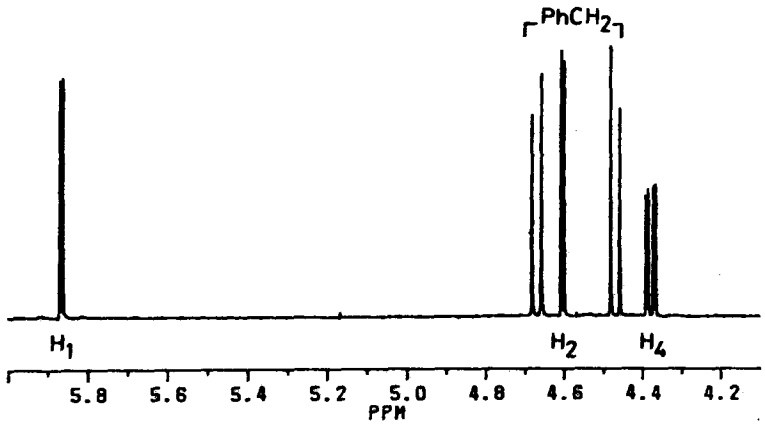
1 $H_2C(CO_2Me)_2$, MeONa, MeOH 2 DMSO, brine, 160 °C

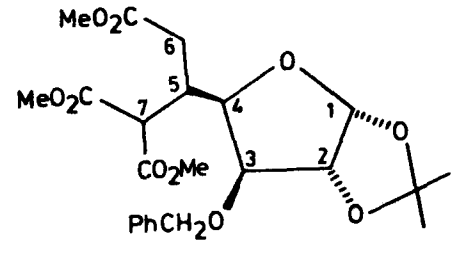
The Michael reaction was executed by refluxing the enoates (A50) with dimethylmalonate in methanol, using fresh prepared sodium methoxide as the base. After initial problems the triester (A51) was produced in multi-gram amounts in 65% yield; rigorous drying of the solvent and all reagents was found to be necessary to achieve good yields. The triester was formed as a mixture of diastereomers at C-6, but predominantly one, which was selectively crystallized from ether-hexane as fine white needles. Both the single diastereomer and the mixture gave similar yields of the product in the subsequent step, when the asymmetry of that particular chiral centre was

removed. Evidence for the mixture (about 15:1) was seen in both the ^{1}H and ^{13}C NMR spectra; the proton spectrum of the single compound showed quite remarkable separation of signals; this was used as an illustrative example for homonuclear 2-D coupling in Andrew Derome's recent book[34] (Figure A4).

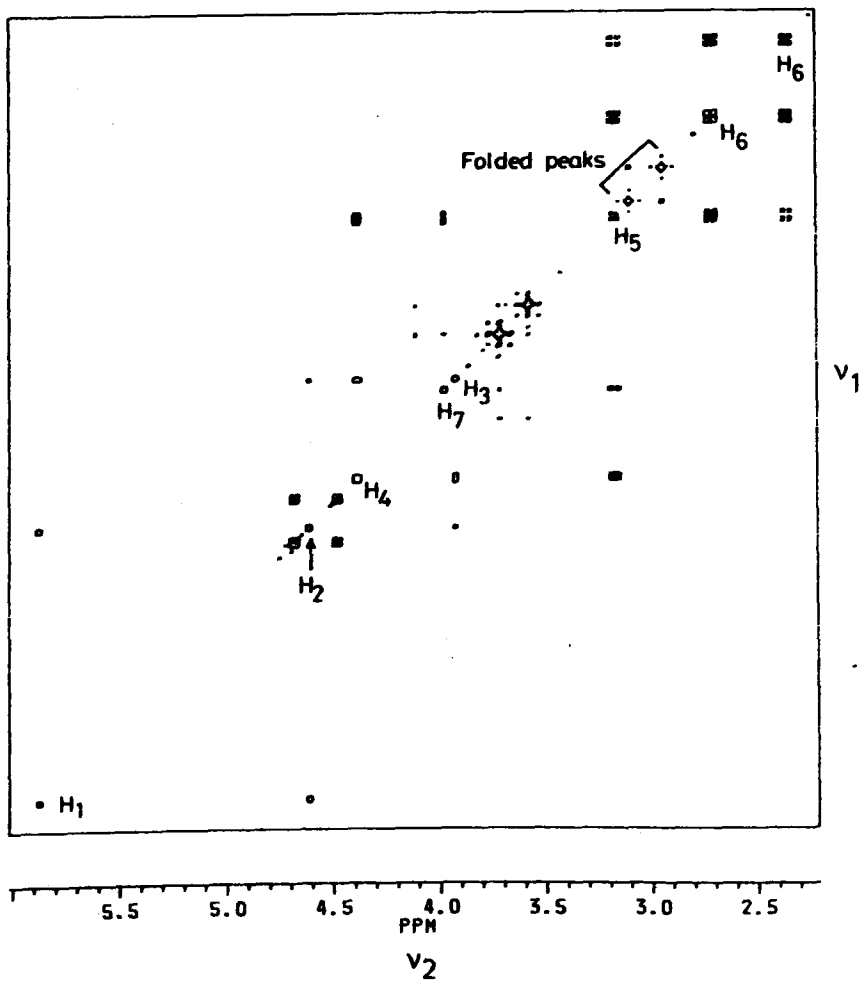
Figure A4: 500 MHz ^{1}H NMR and COSY-45 Spectra of A51. (AED's numbering).







A51

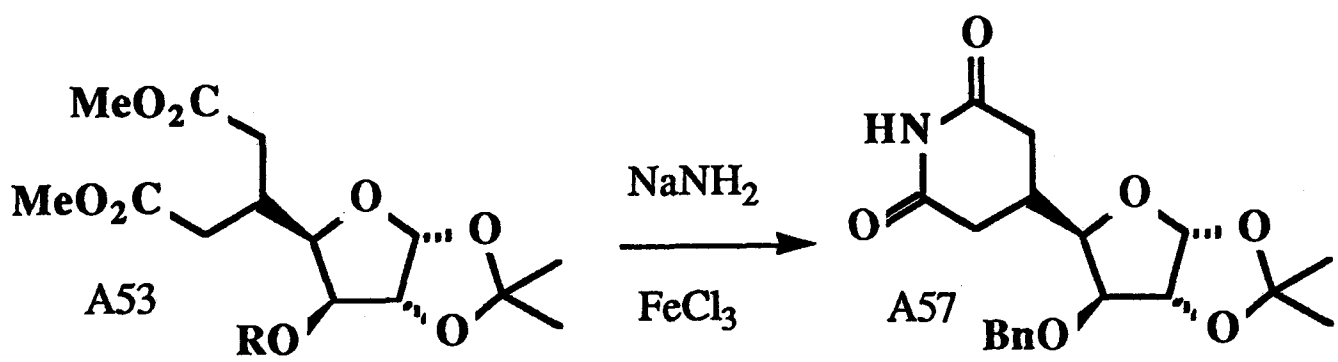


Demethoxycarbonylation using the Krapcho procedure[6] was smoothly accomplished by heating the triester (A51) at 160 ^{o}C in DMSO containing a few drops of brine. After removal of the solvent, requiring heating on a high vacuum rotary evaporator, purification by flash chromatography gave an 87% yield on 2.8 g.

b) Conversion of the Glutarate Diester into a Glutarimide

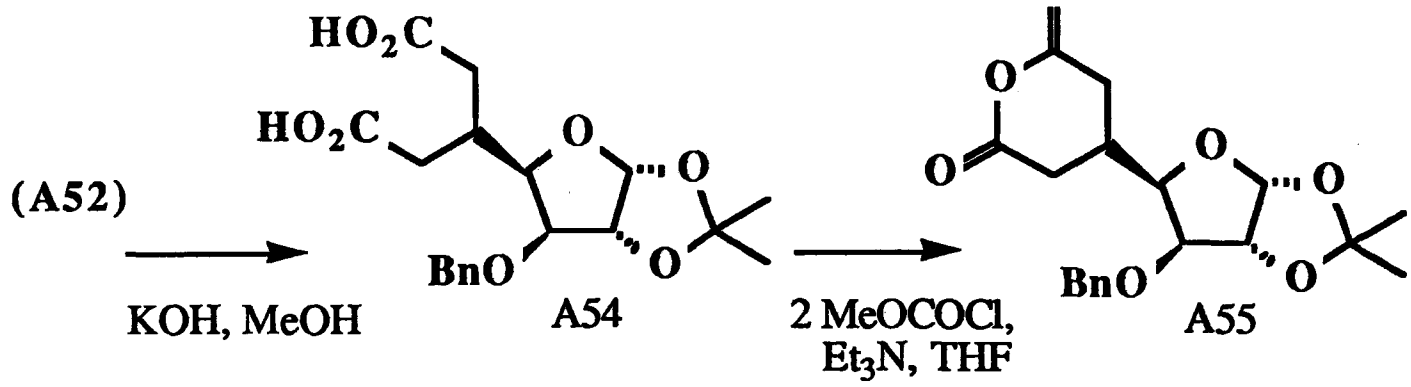
The conversion of the C-3 substituted glutarate diester to the glutarimide was now the goal of the research, so attempts at the literature procedures were made.

Firstly the procedure of Kinoshita and Clardy[7] was tried. This involved the use of sodamide in liquid ammonia, to which a solution of the diester (A52) was added in dry THF, catalysed by iron (III) chloride. Despite the similarity of this diester (A53, R= Bn) to that quoted in the paper (A53, R= Me) only small quantities (<10%) of the required glutarimide (A57) were isolated. This may have been due to side reactions prompted by the removal of the benzyl group under the reaction conditions: the removal of such protection by iron (III) chloride has recently been reported.[35]

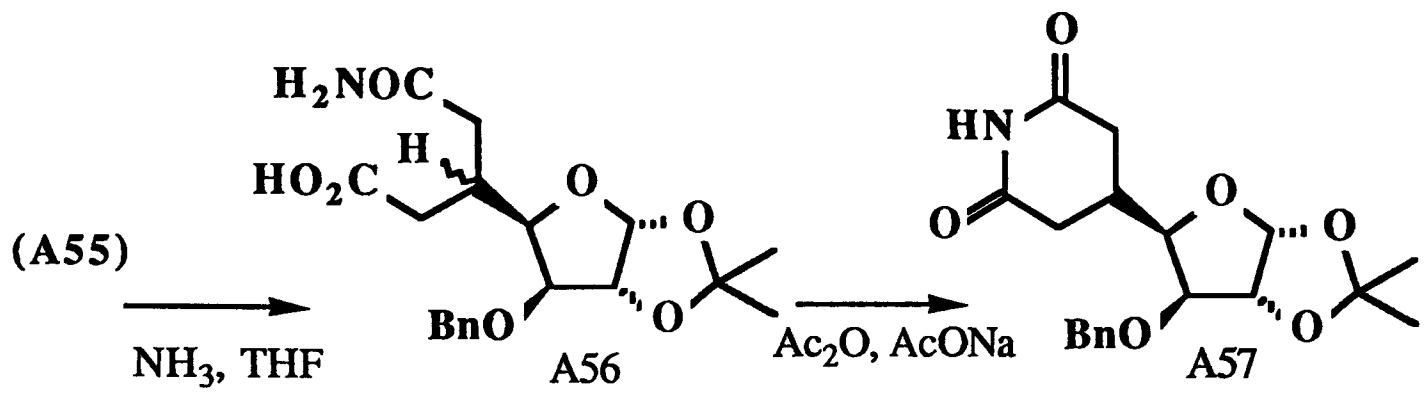


The procedure of Terashima and co-workers[8] was followed in the subsequent closure attempt. This was found to work in this case, with an improvement on the reported overall yield, quoted for their synthesis of glutarimide as the A ring of sesbanimide. Since the report did not appear with full experimental details the actual procedure represents the optimum conditions found for this system.

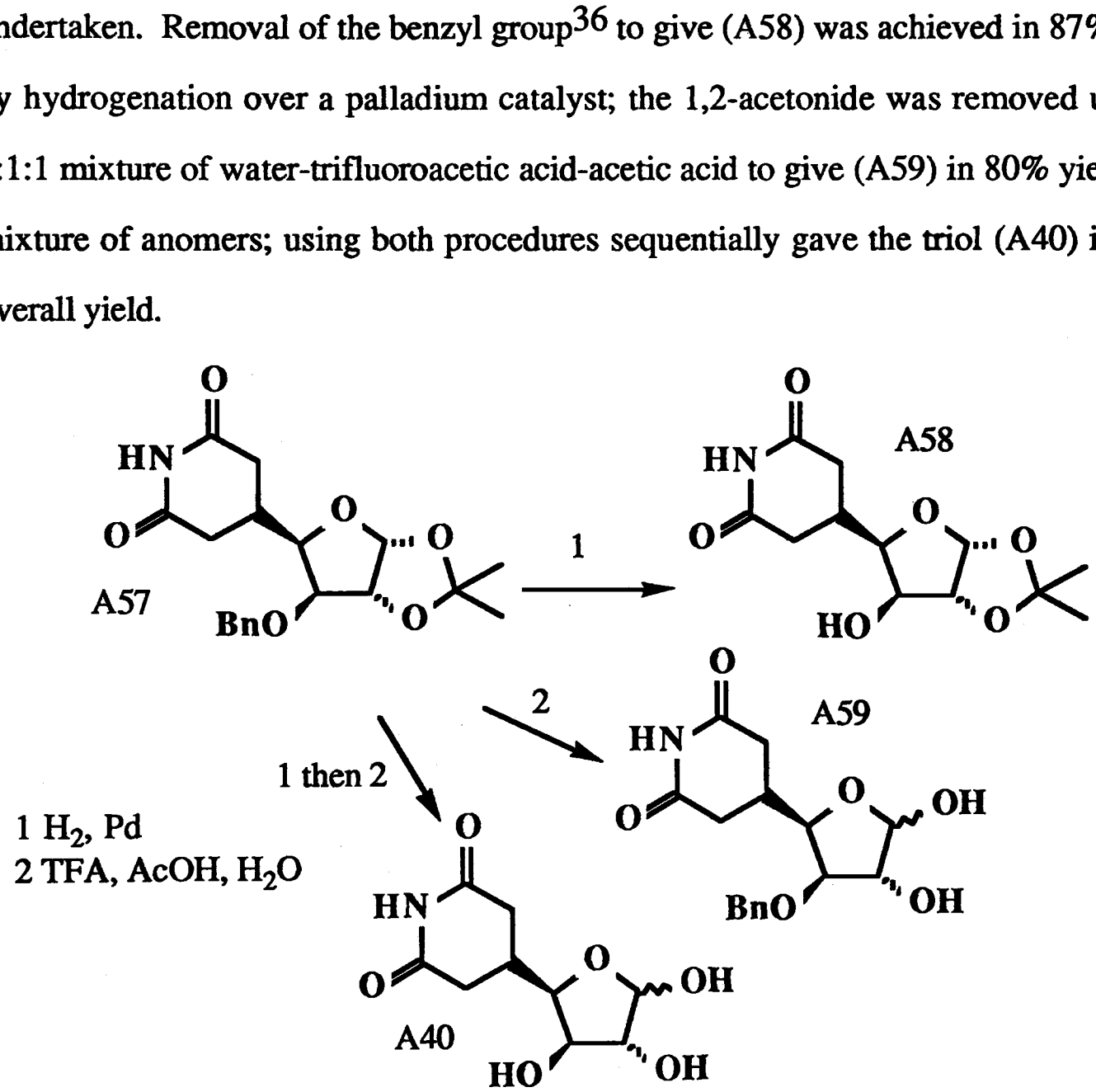
Firstly the diester (A52) was hydrolysed to the diacid (A54) using 1N methanolic KOH; the work-up was achieved by acidification with dilute aqueous HCl (0.1 N) followed by extraction of the resulting solution with chloroform. This material (characteristic ν_{max} 1 710 cm^{-1}) was taken through to the anhydride (A54) *via* a mixed anhydride formed using methyl chloroformate and triethylamine in dry THF at 0 °C. After extraction into ethyl acetate, evaporation and recrystallization from the same solvent gave the anhydride in quantitative yield (ν_{max} 1 810 and 1 760 cm^{-1}).



This more active glutaric acid derivative was then opened by bubbling ammonia through a cooled (0 °C) THF solution to give a diastereomeric mixture of the acid-amide (A56) (ν_{max} 1 700, 1 660 cm^{-1}). After evaporation of the THF and residual ammonia the remaining oil was heated at 100 °C in acetic anhydride buffered with sodium acetate, to afford the glutarimide (A57) in up to 71% yield after flash chromatography, on a two gram scale. Crystallisation (ethyl acetate-hexane) gave a white solid, (^{13}C NMR δ 171.34 and 171.83, s, C=O; ^{1}H NMR, δ 8.05, 1H, brs, NH).



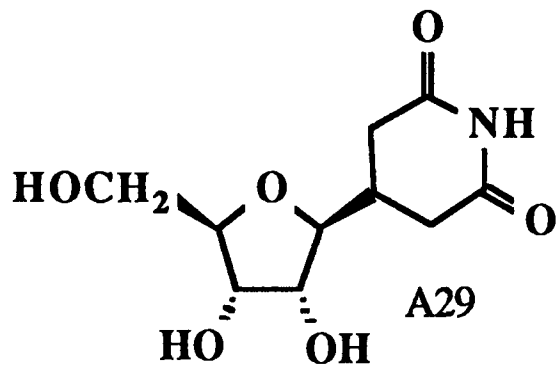
To achieve the synthesis of the target compound and to provide a range of samples for biological screening selective deprotections of the sugar hydroxyls were undertaken. Removal of the benzyl group[36] to give (A58) was achieved in 87% yield by hydrogenation over a palladium catalyst; the 1,2-acetonide was removed using a 1:1:1 mixture of water-trifluoroacetic acid-acetic acid to give (A59) in 80% yield as a mixture of anomers; using both procedures sequentially gave the triol (A40) in 70% overall yield.



In the agrochemical screens the compounds showed a small degree of herbicidal activity, decreasing in effectiveness with the number of free hydroxyl groups. The triol (A40) and the debenzyl alcohol (A58) showed a small degree of fungicidal control.

2) Synthesis of β-*ribo*-glutarimide.

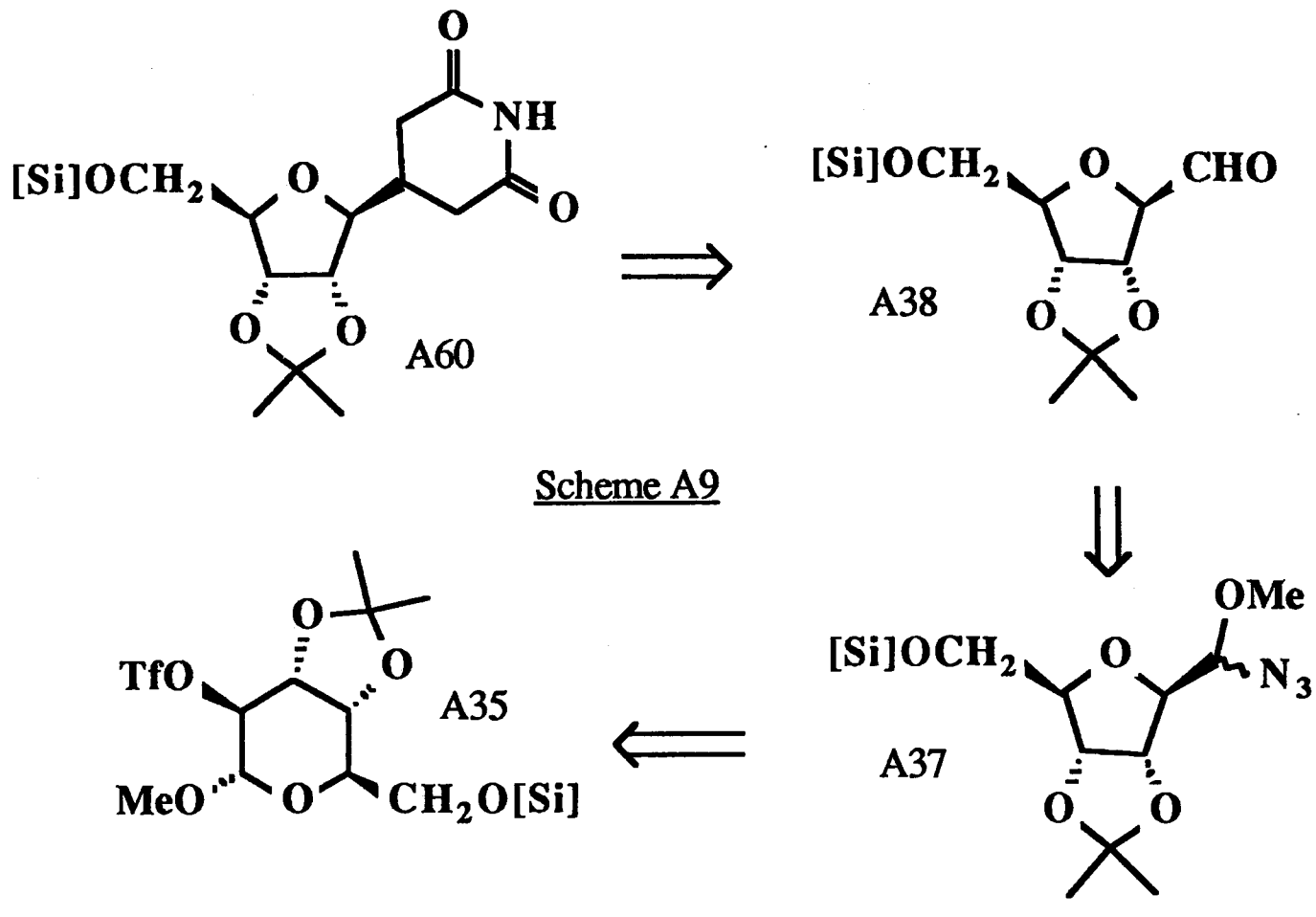
This section describes the synthesis of a glutarimide attached through C-4 to a β-ribose residue (A29) , utilising the novel contraction reported by Fleet and Seymour.[27]



A29

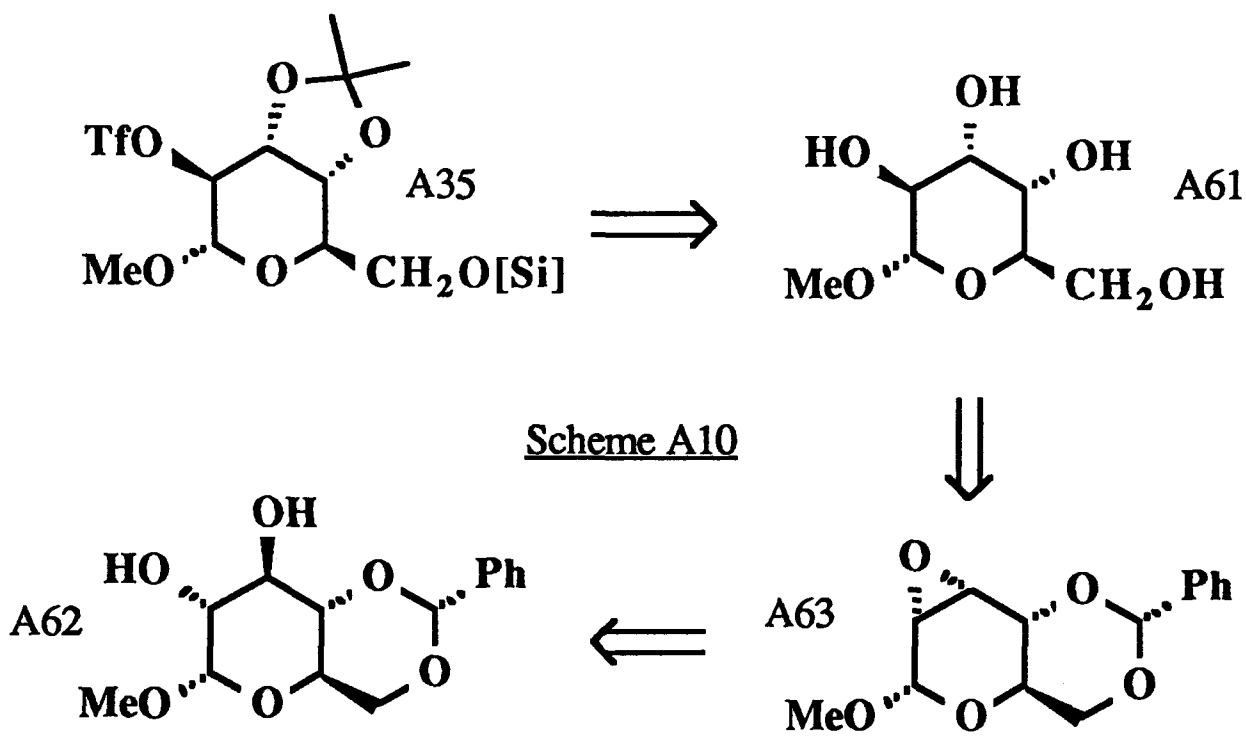
Retrosynthetic Analysis.

The key intermediate in this enantiospecific synthesis was the alkoxy-azide (A37), formed by ring-contraction of the *altro*pyranoside-triflate (A35). Deprotection of (A37) afforded the aldehyde (A38) which could be converted to the glutarimide (A60) (Scheme A9) using procedures executed in the analogous synthesis of a glutarimide from C-5 of dialdo*xylo*furanose.



Scheme A9

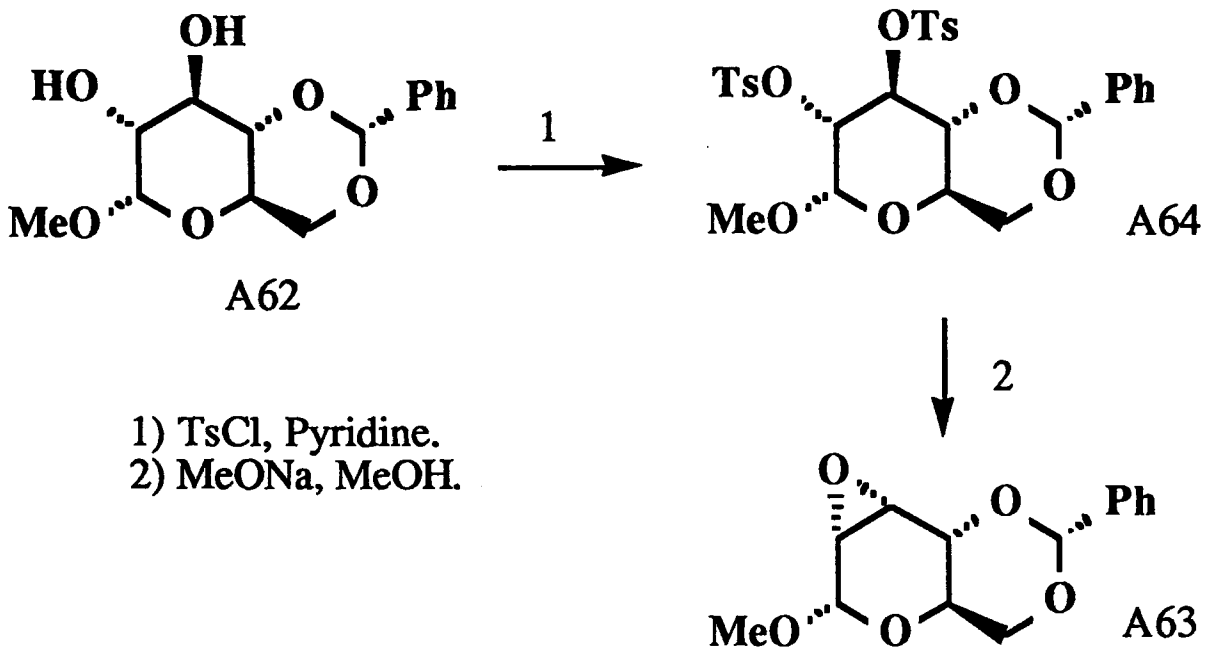
The *altro*pyranoside (A35) was itself derived from methyl-α-D-*altro*pyranoside (A61), a prohibitively expensive substrate commercially, despite its relatively easy synthesis *via* a double inversion of the α-D-*gluco*pyranoside (A62) by ring opening of the epoxide (A63) (Scheme A10).[37]



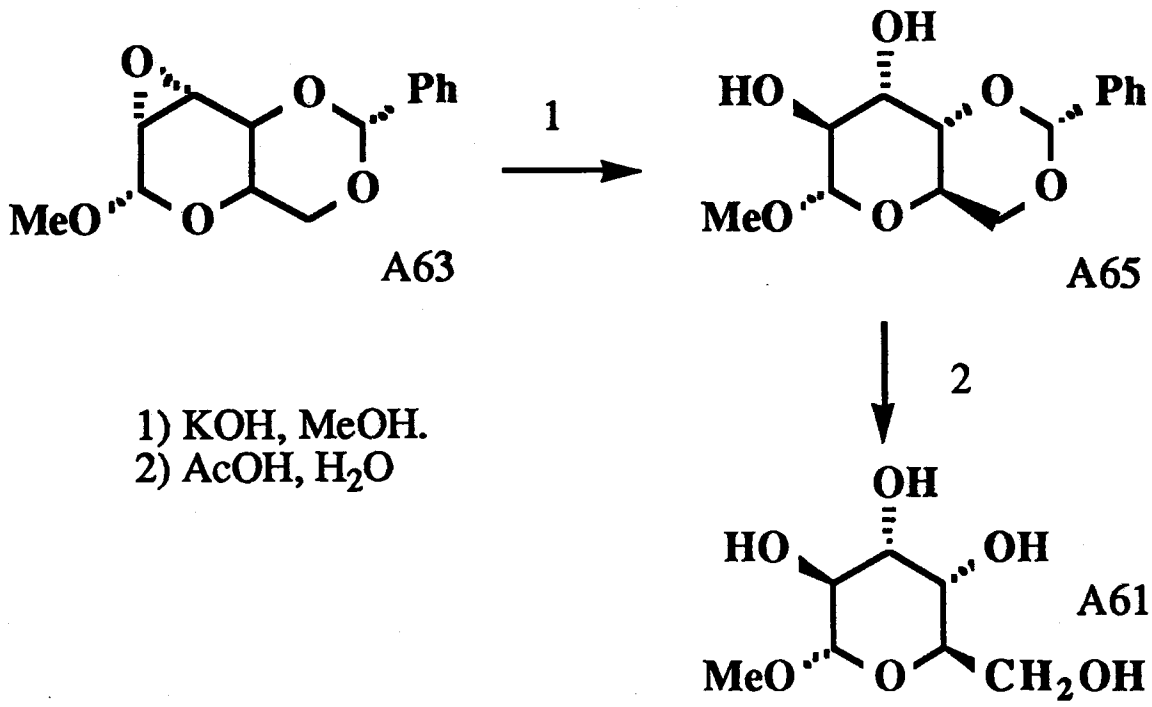
Scheme A10

a) Double inversion sequence to the *altro*pyranoside.

The opening step of the inversion sequence was formation of the ditosyl diester of Methyl-4,6-*O*-benzylidene-α-D-*gluco*pyranoside (A62), which was achieved in 83% yield by stirring (A62) with tosyl chloride in dry pyridine at room temperature for 4 days. On treatment of the ditosylate (A64) with freshly prepared sodium methoxide (5 equivalents) in dry methanol the more reactive ester at C-2 was initially hydrolysed. The second tosylate ester at C-3 was subsequently displaced by the resulting alkoxide, thus forming the required *allo*epoxide (A63). This was executed in 94% yield.

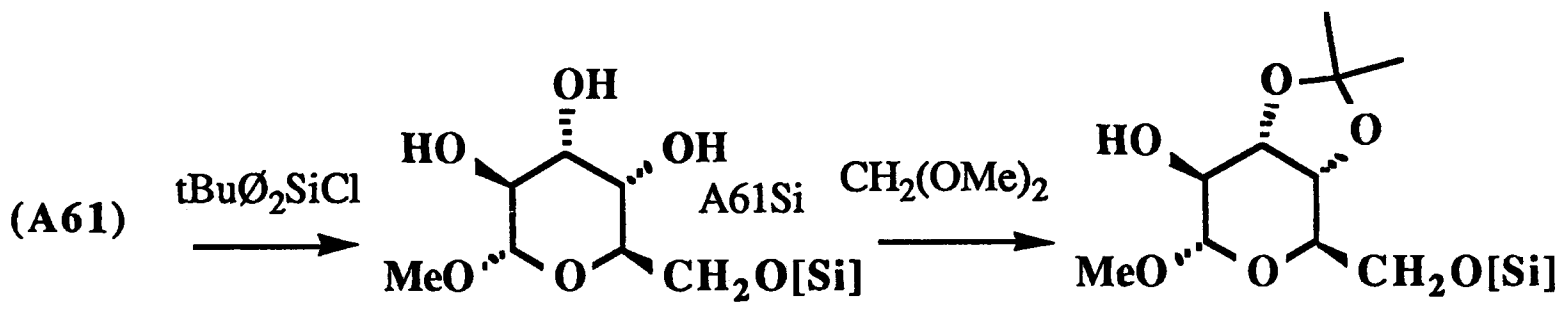


Ring-opening of the epoxide (A63) was achieved by refluxing with aqueous potassium hydroxide for 2 days whence all of the sugar had dissolved. This afforded the protected altrose (A65) in 86% yield through a *trans* diaxial opening. Removal of the 4,6-benzylidene protection was accomplished by stirring (A65) in a 60% aqueous solution of acetic acid, co-removal of solvents and benzaldehyde afforded Methyl-α-D-*altro*pyranoside (A61) as a crude oil; purified only by several co-evaporations with benzene and prolonged drying *in vacuo*.

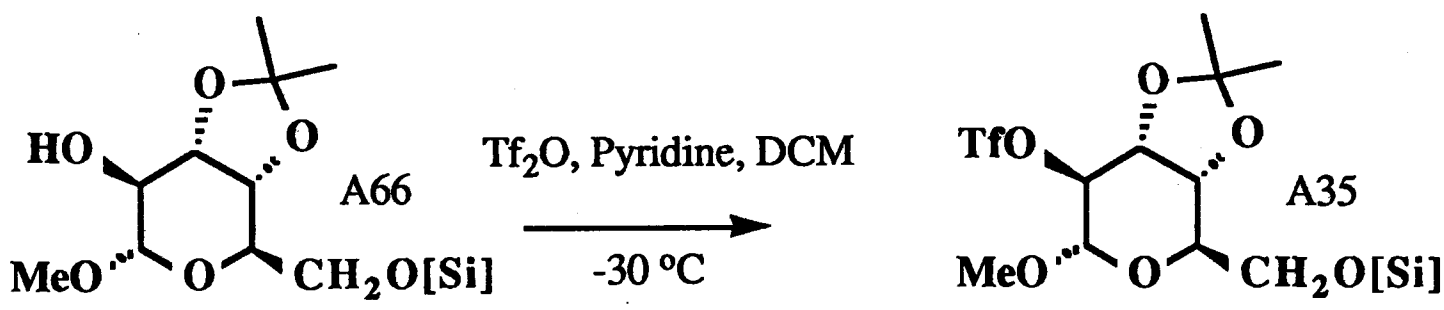


b) Protection through to Ring Contraction.

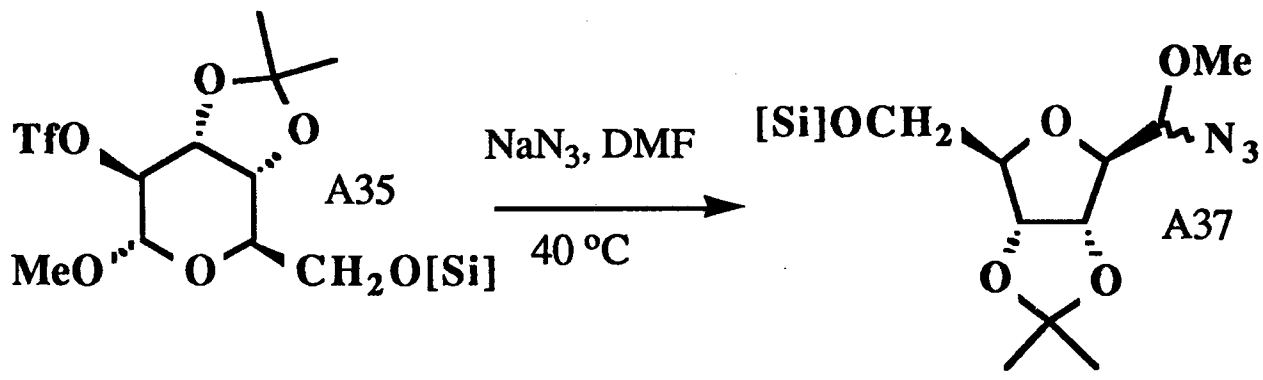
Selective silylation of the primary hydroxyl of the altroside was achieved by treatment of the crude material from the debenzylation with 2 equivalents of imidazole and 1.2 equivalents of *tert*-butyldiphenylsilyl chloride in dry DMF, which gave the monosilyl ether (A61Si) in 82% overall yield for the two steps. Reaction of this triol with 2,2-dimethoxypropane in acetone (pH adjusted to 4 with 10-camphorsulphonic acid) completed the required protection by formation of the *cis*-3,4-acetonide (A66) in 84% yield.



Conversion of the remaining free hydroxyl into its triflate ester was smoothly achieved by stirring (A66) in dry dichloromethane with 2 equivalents of pyridine at -30 ^{o}C and addition of 1.2 equivalents of triflic anhydride. After a suitable work up the crude triflate (A35) was usually used as such in the next stage; however this compound was relatively stable and was purified by flash chromatography during one attempt, giving a 90% yield.

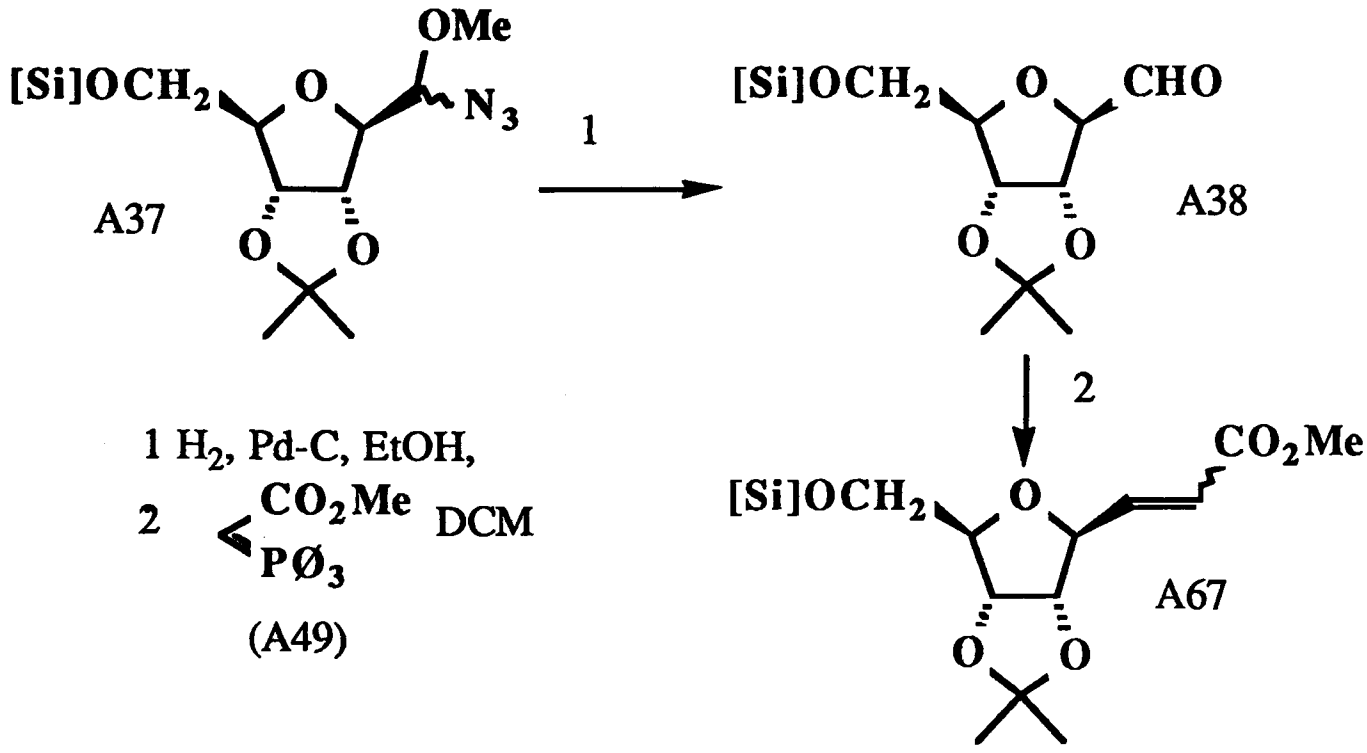


The ring contraction was then performed by treatment of the triflate (A35) with 2.5 equivalents of sodium azide in dry DMF and warming overnight at 40 °C. This produced the diastereomeric alkoxy azides (A37) in 93% yield for the two steps on a large (10 g) scale: no other products were observed. Since the mixed stereochemistry was lost in the subsequent step there was no value in separating these very close running diastereomers, a 3:1 ratio by integration of the methoxy singlet.



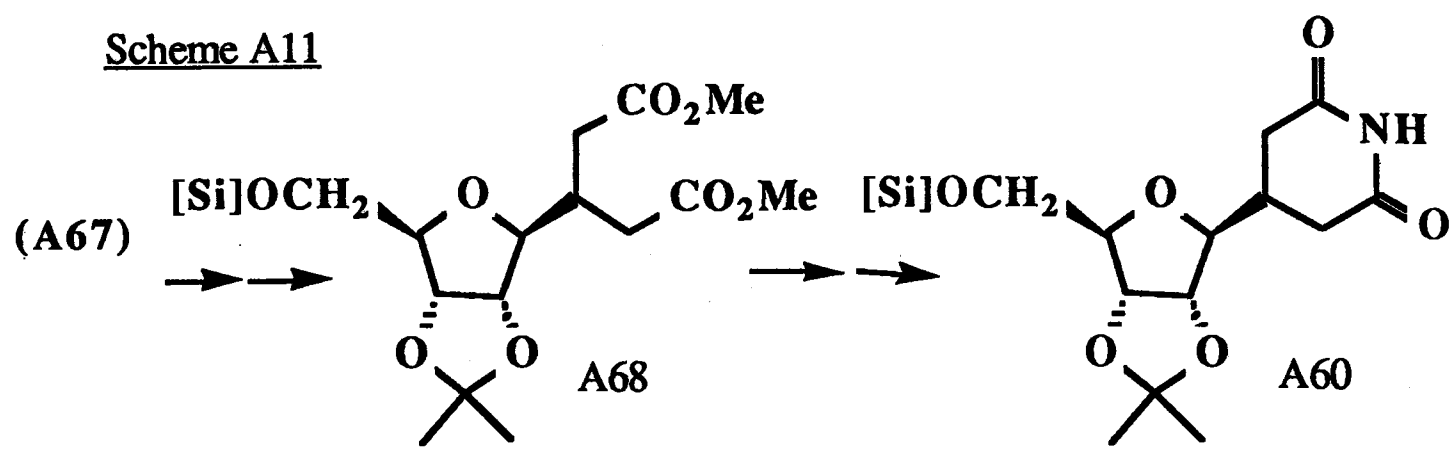
c) Wittig Extension and Glutarimide Formation.

The next required steps in the synthesis were unmasking of the aldehyde and its Wittig extension. The former had previously been performed on a gram scale; in this work it was repeated on ten times that scale, the latter had been achieved on 50 mg, so a considerable scale-up was required. Thus the azides (A37) were dissolved in ethanol, to which was added a little water and some 10% palladium on carbon, ensuing hydrogenation for 45 minutes deprotected the aldehyde (A38), giving an 81% yield after purification by flash chromatography. The Wittig reaction with the stabilized ylid (A49) was achieved by stirring the two reactants for 48 h at room temperature in dichloromethane. Enoates (A67) were isolated in 62% yield as a mixture of diastereomers, inseparable by flash chromatography (7:1 *E*:*Z*, by NMR, $J_{\alpha-\beta}$ 15.7 Hz, *E*; $J_{\alpha-\beta}$ 11.8 Hz, *Z*): the product of this reaction had been incorrectly reported as the single *Z* isomer.[27]



The glutarimide was now to be constructed by the method which had already been achieved in a similar system: familiarity with the chemistry made it the route of choice. The newer literature methods either did not offer any significant enhancement in yield, or a step employed conditions which were incompatible with the protecting groups. Thus the required steps were Michael addition of dimethyl malonate followed by decarboxymethylation to form the glutarate diester (A68), then imide formation using the Terashima procedure[8] to give (A60) (Scheme A11).

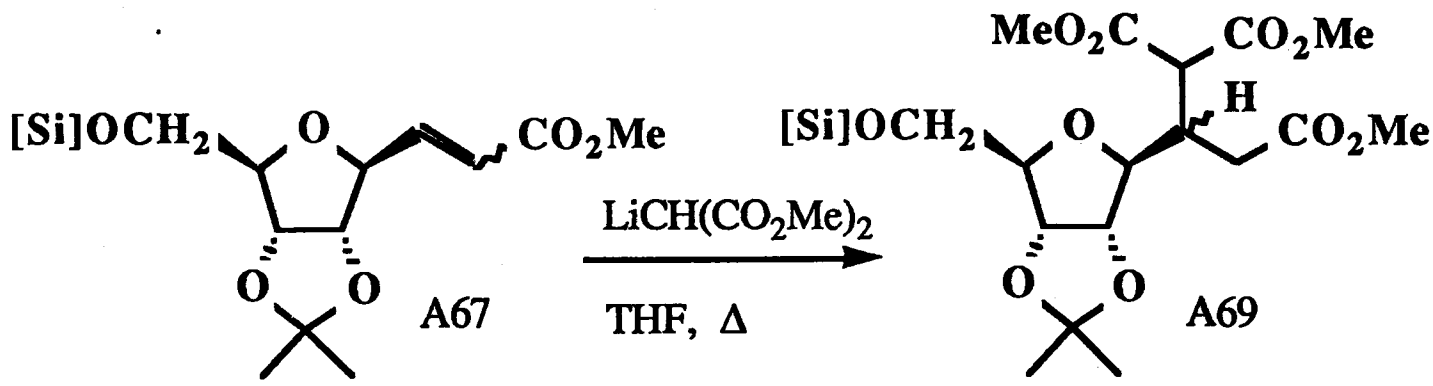
Scheme A11



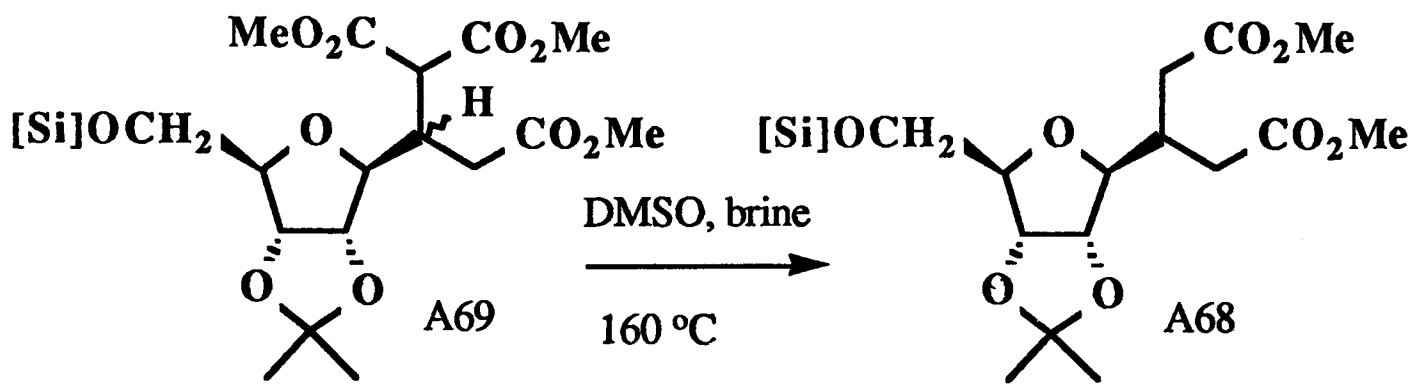
The ensuing Michael reaction held up progress on the route considerably; despite the close structural similarities to the intermediate previously synthesized and other synthons in the various sesbanimide studies.

Initially the conditions employed in the successful synthesis of (A69) were tried, namely refluxing the enoate in dry methanol with dimethyl malonate and a catalytic amount of sodium methoxide. The required product was only ever seen as a minor impurity in a mass spectrum of the single isolated product, which was an adduct formed by the addition of one mole of methanol. This was isolated in around 10 to 15% yield along with about 50% of recovered enoate. Secondly an attempt was made at the high yielding procedure reported by Terashima;[8] this employed the addition of the sodium-stabilized anion of dimethyl malonate: 3 equivalents of sodium hydride were reacted with 3.2 equivalents of dimethyl malonate, to which the enoate was added in the presence of 0.1 equivalents of tetrabutylammonium bromide in dry THF. Initially this gave a respectable yield (75%) of the desired Michael product (A69) on a 50 mg scale, but this was found to neither scale up, nor was it repeatable in any comparable yields on that scale.

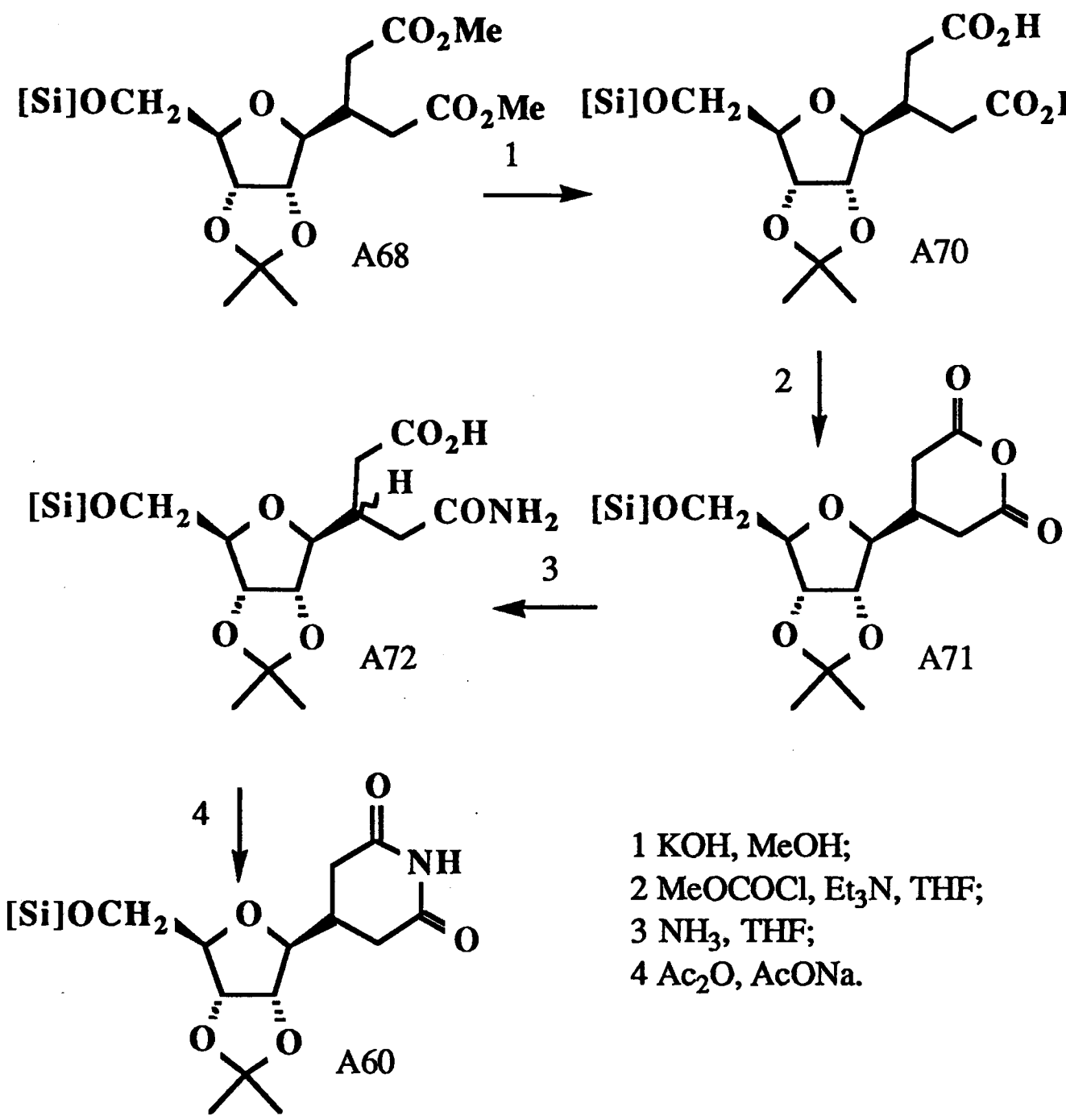
However the addition of the corresponding lithium-stabilized anion was achieved in a good yield (64%), which could be repeated on a reasonable scale (2.9 g). The lithium-stabilized anion was thus generated at -50 ^{o}C by the addition of butyl lithium (1.5 M solution in hexane) to dimethylmalonate in dry THF. On warming to room temperature the enoates (A67) were added, subsequently the reaction was refluxed for 36 hours. On purification by flash chromatography the product was found to co-run with the excess dimethyl malonate, which was removed by warming *in vacuo*, giving (A69) as a colourless syrup, a mixture of diastereomers at C-2.



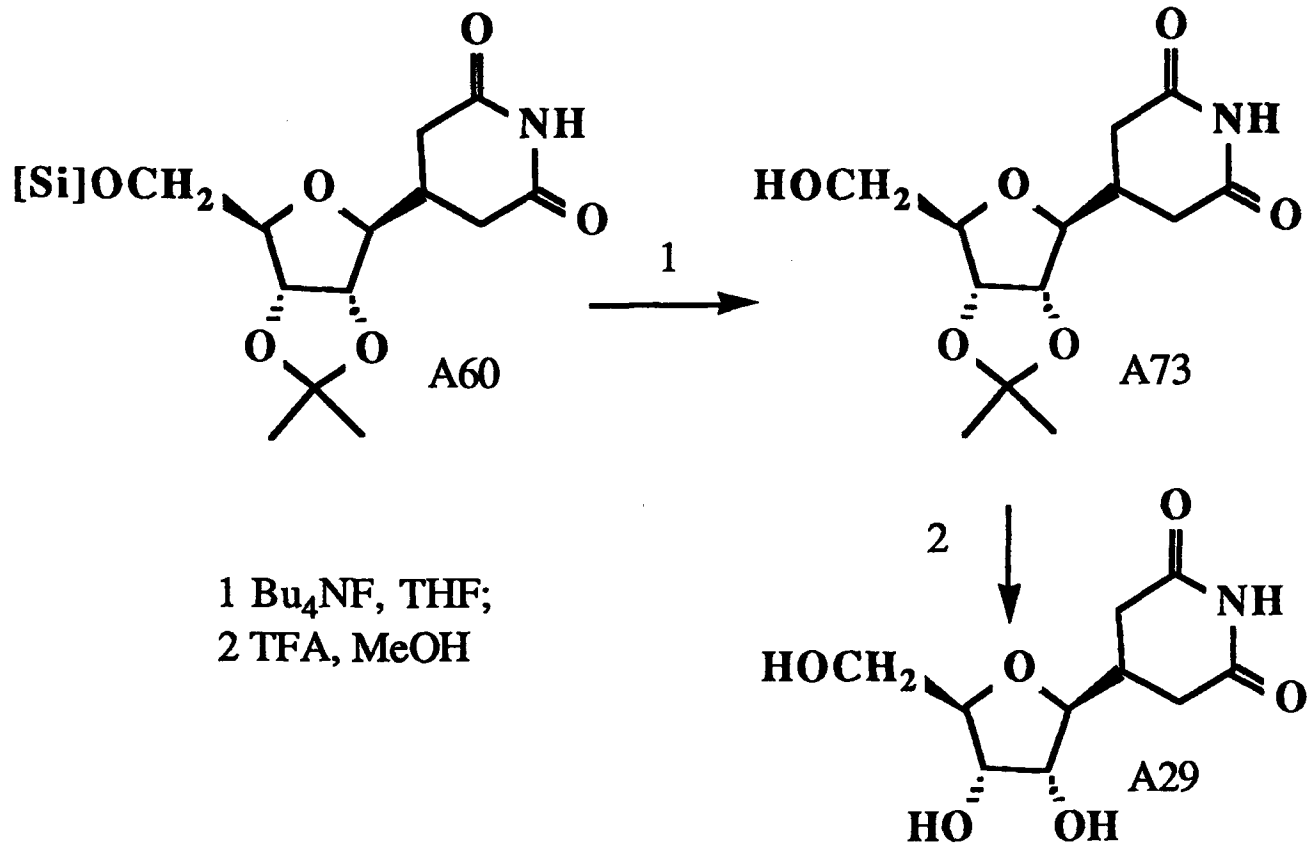
Conversion of the triester (A69) to the diester (A68) by the Krapcho method[6] again worked well, forming 1.73 g in 82% yield. Interestingly this compound had a zero rotation under the standard conditions.



The four steps to convert this diester to the glutarimide were carried out as before by the Terashima procedure,[8] without purification of the intermediates. Diester (A68) was hydrolysed to the diacid (A70) using 1M methanolic KOH as before: this was carefully monitored by t.l.c. and found to be virtually complete within ten hours; if left for longer the overall yield was significantly reduced. The acidification in the work-up was this time performed using acetic acid, due to the sensitivity of the silyl protection to mineral acids. The anhydride (A71) was formed in the same way (triethylamine/methyl chloroformate in dry THF) yielding about 90% of the anhydride, contaminated by a little of the diester (A68) by NMR. Ring opening of the anhydride with ammonia (bubbled through a THF solution of (A71) at 0 °C for one hour) to yield the diastereomeric acid-amides (A72) was followed by evaporation and subsequent closure to the glutarimide (A60) by warming in acetic anhydride buffered by sodium acetate. The overall yield for the four steps was 40%, producing 120 mgs in several batches.



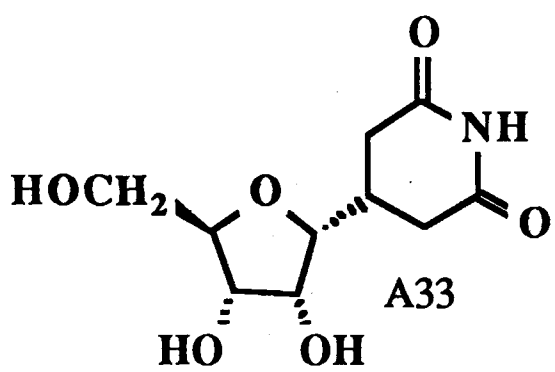
Deprotection of the silyl group was achieved in 86% yield by stirring (A60) with tetrabutylammonium fluoride in THF to produce the alcohol (A73). The acetonide was subsequently removed by stirring a methanolic solution of (A73) with trifluoroacetic acid. This gave the fully deprotected nucleoside (A29) in about 80% yield, but by the time of writing this compound had not been fully characterized.



Unfortunately this potentially very interesting glutarimide, with various degrees of hydroxyl protection, had not been screened for biological activity at the time of writing.

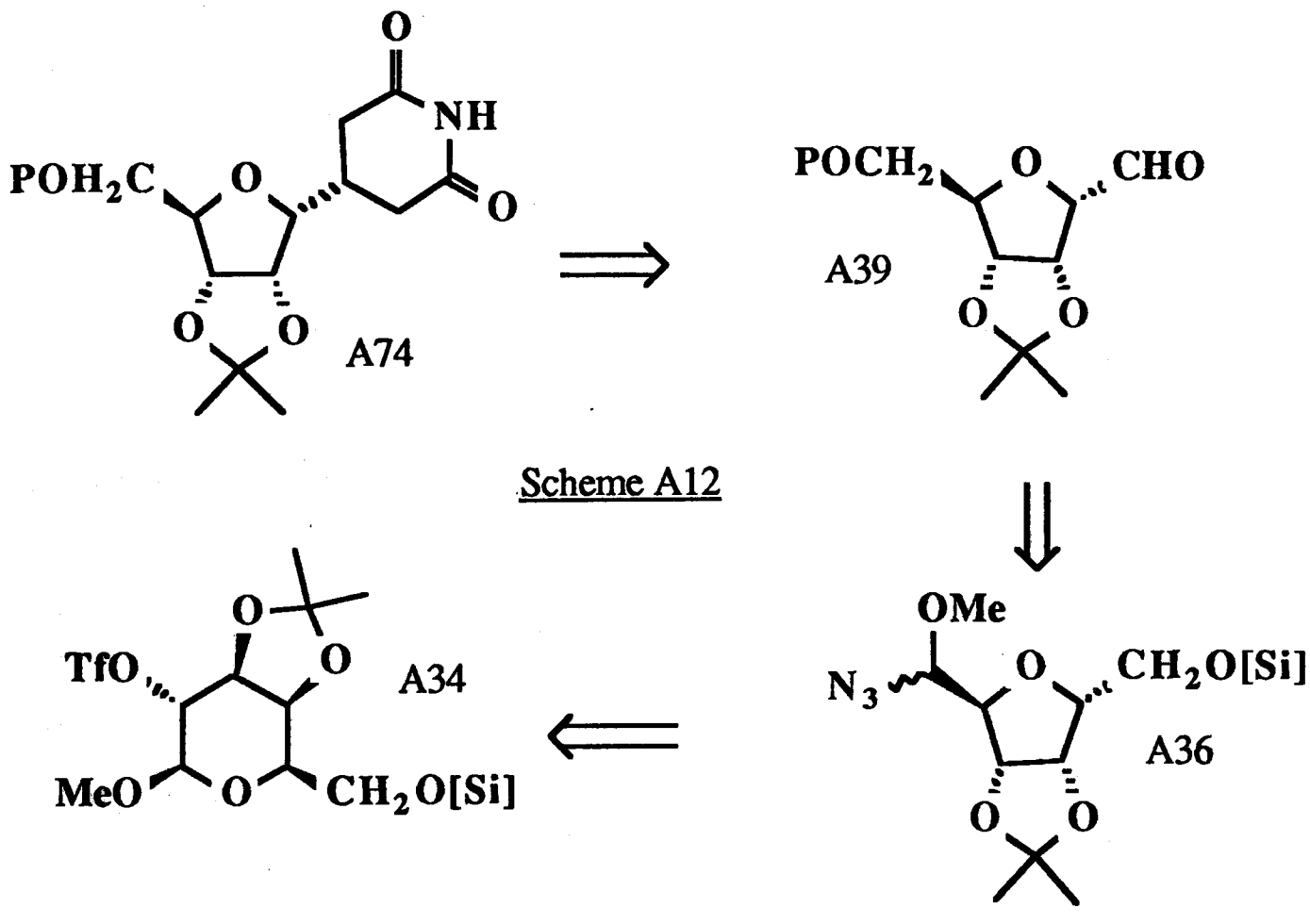
3) Approach to the Synthesis of α-*ribo*-gluatarimide.

This section describes the approch to the formation of a glutarimide attached through C-4 to an α-ribose fragment (A33) using similar methodology to that employed in the previous section.



Retrosynthetic Analysis.

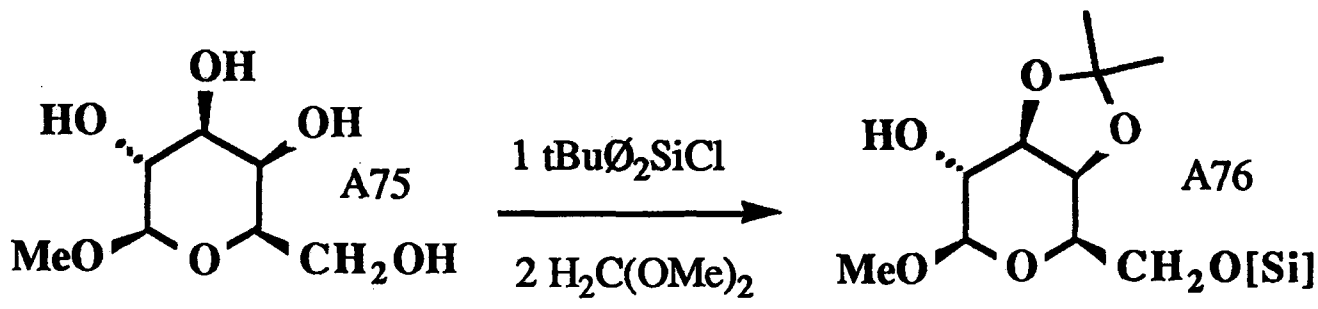
The key intermediate in this enantiospecific route was the alkoxy-azide (A36) formed by ring contraction of the *galacto*pyranoside triflate (A34) (Scheme A12).



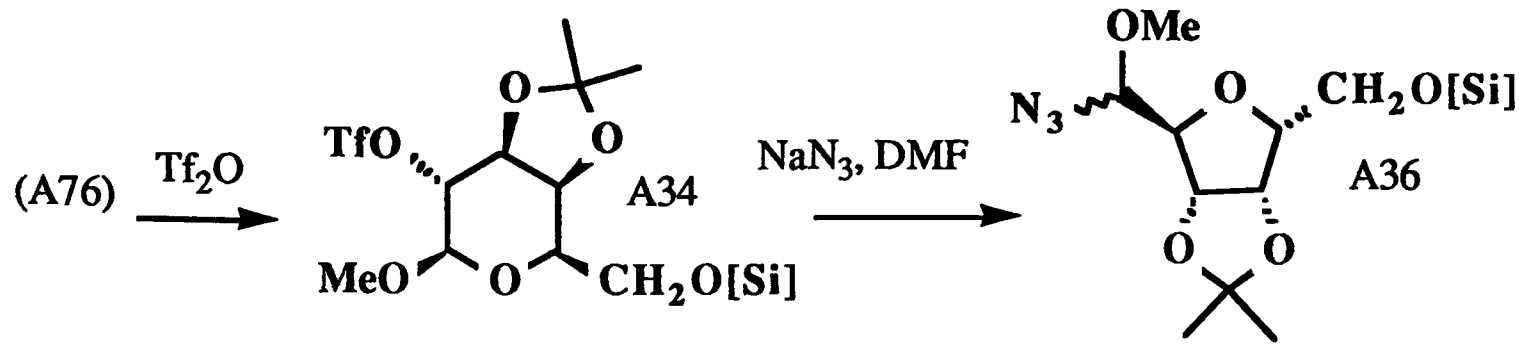
It can be seen that the α-*ribo* aldehyde (A39), required for the synthesis of the glutarimide (A74), does not quite possess the required substitution directly available from (A36). This can be simply achieved by a sequence of deprotection, reduction and protection of C-5', followed by deprotection and oxidation of the carbon attached α to C-1'.

a) Protection through to ring contraction.

In the analogous way to the altrose series, selective primary silylation of methyl-β-D-galactofuranoside (A75) was achieved by reaction of the commercially available material in dry DMF with 2 equivalents of imidazole and 1.2 equivalents of *tert*-butyldiphenylsilyl chloride, giving the monosilyl ether (A75Si) in 75% yield. Reaction of this triol with 2,2-dimethoxypropane in acetone (pH adjusted to 4 with 10-camphorsulphonic acid) completed the required protection by formation of the *cis*-3,4-acetonide (A76) in 85% yield.



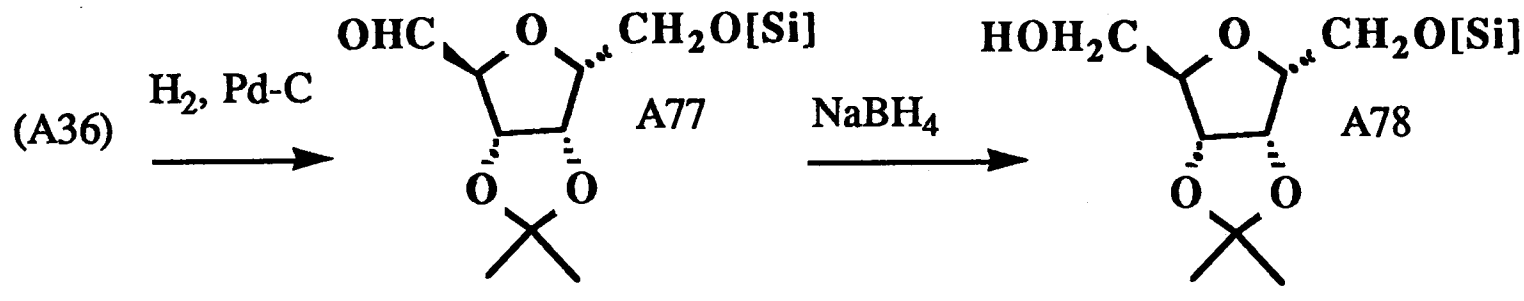
Triflation was also achieved in the same manner as for the diastereomeric *altro*pyranoside (2 equivalents of pyridine at -30 °C in dry dichloromethane, then addition of 1.2 equivalents of triflic anhydride). After work-up the similarly stable triflate (A34) was treated directly with sodium azide in dry DMF at 40 °C, which afforded the more easily separable diastereomeric azides (A36) in 82% overall yield, with no sign of any other products even on a large (6 g) scale.



b) Adjustment of Oxidation levels and Wittig extension.

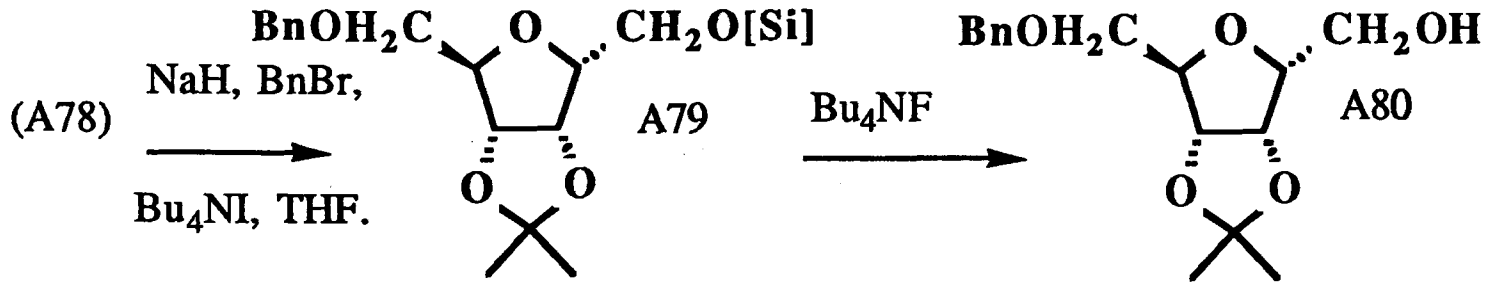
Formation of the required α-*ribo* aldehyde (A39) from the methoxy azides (A36) required an adjustment in the oxidation level of each exocyclic carbon. It was best accomplished at this early stage by first deprotection, reduction then protection of C-5', followed by deprotection and oxidation of the carbon attached α to C-1'. Nothing would have been gained by employing each of the diastereomeric methoxy azides as synthons, which was a possibility, only to form a common intermediate at a later stage.

On hydrogenation of the azides (A36) in ethanol over 10% palladium on charcoal the aldehyde (A77) was unmasked cleanly in 90% yield after chromatography. Reduction by sodium borohydride in aqueous methanol gave the alcohol (A78) as the major product in 76% yield.

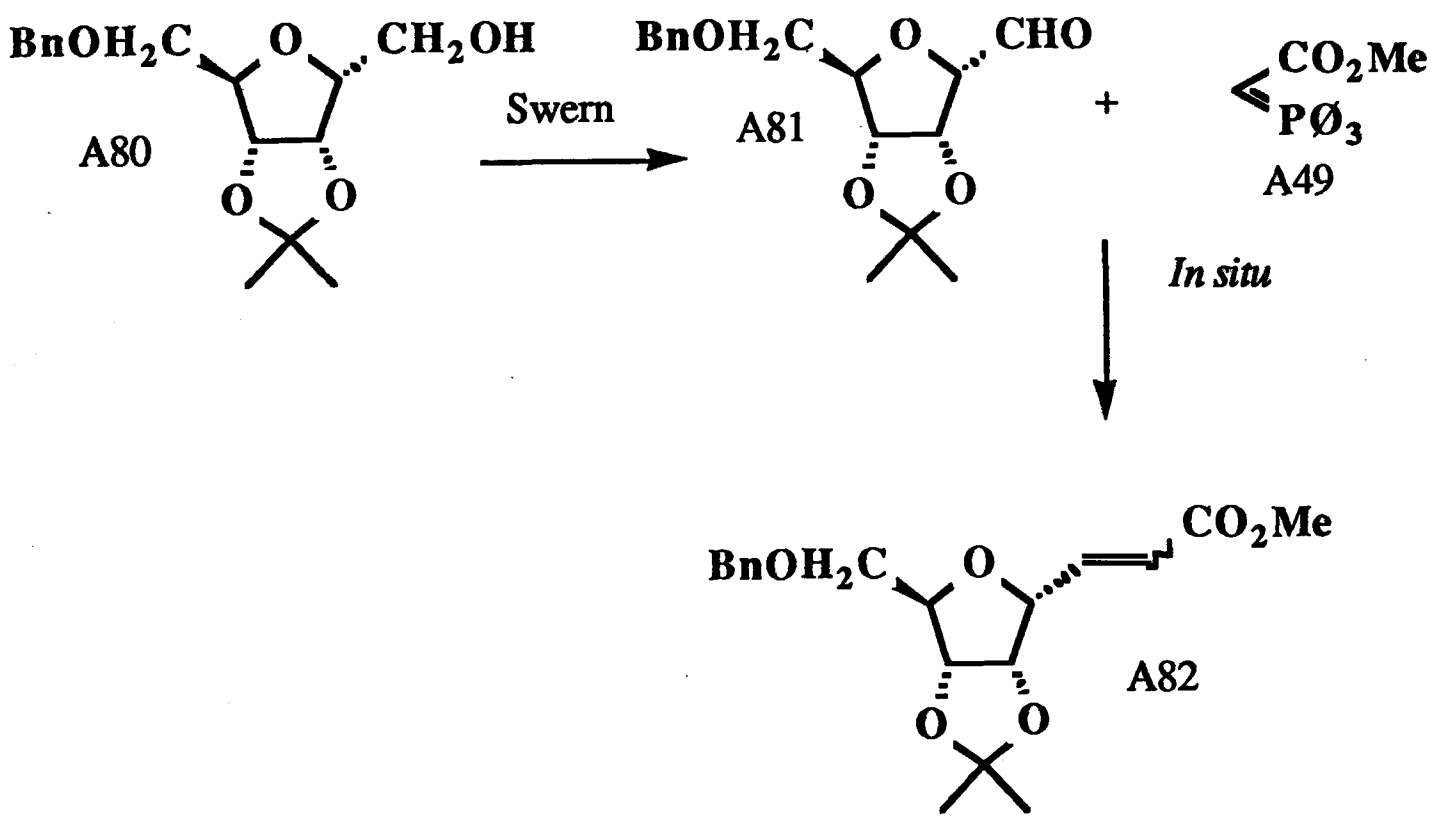


Protection of (A78) by benzylation (Sodium hydride in THF to form the alkoxide, then addition of benzyl bromide in the presence of tetrabutylammonium

iodide) was accomplished cleanly to form fully protected 2,5-anhydro-talitol (A79) in 78% yield. The subsequent removal of the silyl group (tetrabutylammonium fluoride in THF) gave the mono-deprotected talitol (A80), with the required configuration and protection, in 90% yield.



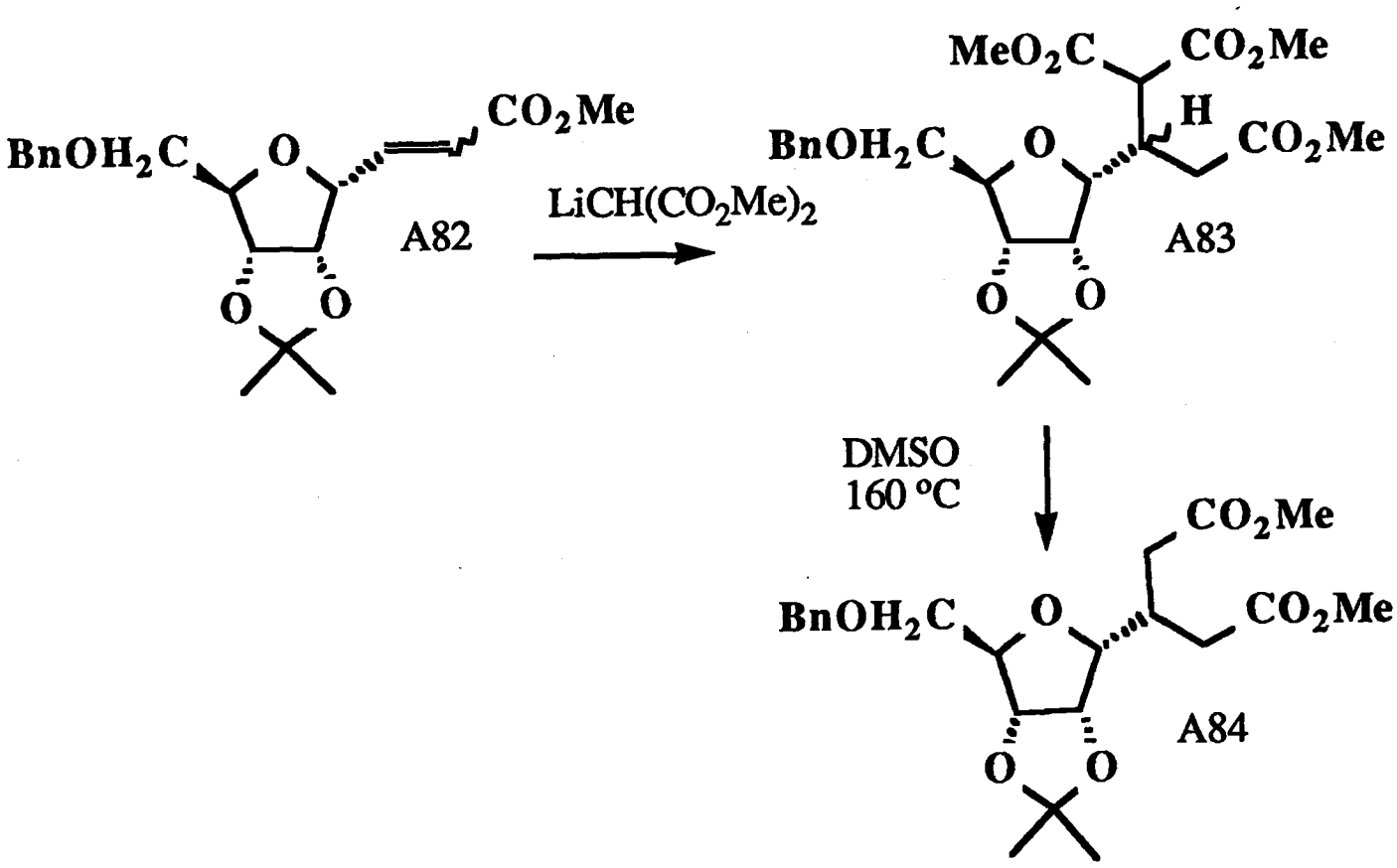
The free alcohol (A80) was oxidized to the aldehyde (A81) using the Swern procedure[38] (dimethyl sulphoxide/oxalyl chloride in dichloromethane at -78 ^{o}C, followed by triethylamine). The aldehyde (A81) was not isolated, but reacted *in situ* with the stabilised ylid (A49), giving the enoates (A82) as a partially seperable mixture of geometric isomers in 75% overall yield on a 1 g scale (~1:1 *E*:*Z*, by NMR, $J_{\alpha-\beta}$ 15.8 Hz, *E*; $J_{\alpha-\beta}$ 11.7 Hz, *Z*).



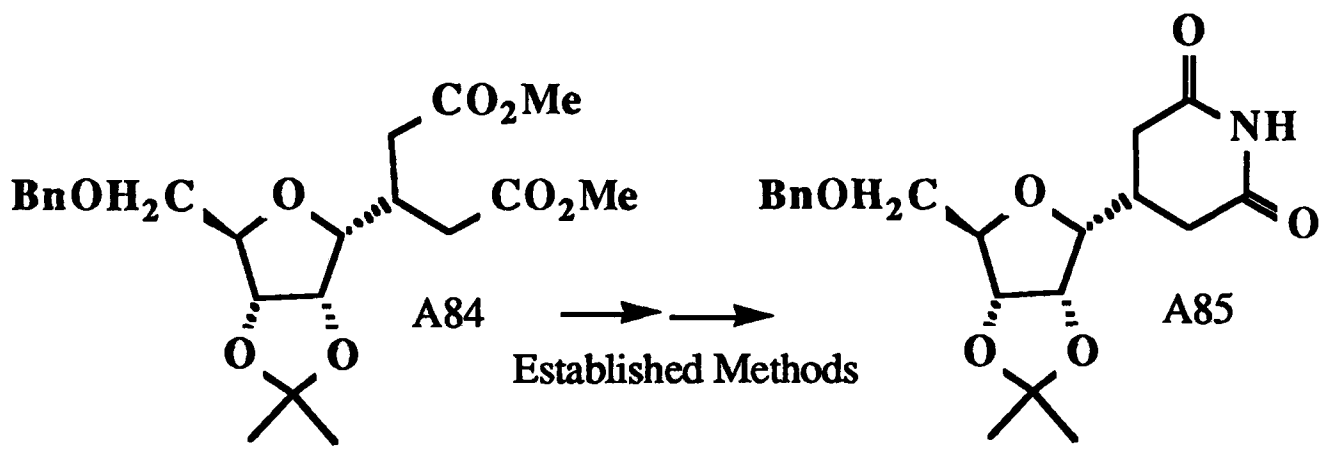
c) Conversion to Glutarate Diester.

In a similar fashion to the β-ribo case, the Michael addition of dimethyl malonate to the enoates (A82) proved a difficult reaction; it was this step which prevented the successful completion of the synthesis.

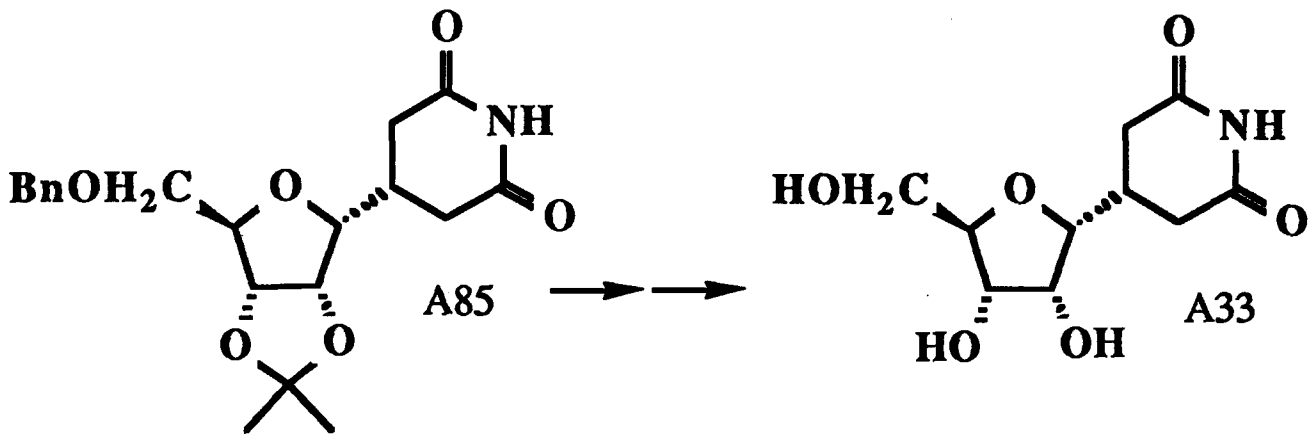
In attempts to perform this reaction both the use of sodium methoxide in methanol (with no success) and sodium hydride/tetrabutylammonium bromide in THF (low, <15% yield of desired product) were tried. However using the previously more reliable lithium malonate method a 26% yield of the triester (A83) was isolated. This compound, a mixture of diastereomers, was characterized and converted to the desired diester (A84) in 46% yield, using the usual Krapcho conditions, albeit on a very small scale.



A single attempt was made with this small amount of the diester (A84) to form the glutarimide (A85) in the usual way following the Terashima procedure;[8] however none of the required compound was isolated as a result of these reactions.



With the work achieved on this route to form the enoates (A82) in good yield, and the characterisation of the triester (A83) and diester (A84), a little further research into the Michael reaction should permit successful completion of the synthesis by formation of the required glutarimide (A33) by suitable deprotection of (A85).



EXPERIMENTAL

General Procedures

Infra-Red ($\nu_{max.}$) spectra were recorded on a Perkin-Elmer 297 instrument, calibrated with 1 602 cm^{-1} of polystyrene.

Ultra-Violet ($\lambda_{max.}$) spectra were recorded on a Perkin-Elmer 555 instrument, extinction coefficients (ε) quoted in $dm^3mol^{-1}cm^{-1}$.

Proton Nuclear Magnetic Resonance (^1H NMR) spectra were recorded on one of several instuments: Perkin-Elmer R24B (60 MHz), Varian Gemini (200 MHz), Bruker WH300 (300 MHz), Nicolet QE-300 (300 MHz), or Bruker AM500 (500 MHz). The high field machines were referenced to residual proton signals of the solvents (δ_H $C\underline{H}Cl_3$ = 7.27; dimethyl sulphoxide = 2.54 ppm). All spectra were recorded at 300 MHz machine unless otherwise stated. (In both carbon and proton spectra multiplicities are given by: s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, and br signifies a broad resonance).

Carbon-13 (^{13}C NMR) spectra were recorded on either a Bruker AM250 (62.9 MHz), or a Varian Gemini (50.0 MHz) instument, using solvent peaks as reference: (e.g. deuterochloroform centre peak δ_C 77.00 ppm and dimethylsulphoxide δ_C 39.70 ppm. All spectra are in deuterochloroform on the AM250, unless otherwise stated. Multiplicities were assigned by off-resonance decoupling on the AM250, or using the DEPT sequence on the Gemini.

Melting Points (m.p.) were recorded on a Koffler Hot Stage. Temperatures, which are corrected, are quoted in degrees Celcius, ^oC.

Mass Spectra (m/z) were recorded on V.G. 16F or 30F or a ZAB 1F spectrometer, in conjunction with a V.G. data system 2050, using a variety of techniques: electron impact (E.I.), desorption chemical ionization (D.C.I.), chemical ionization (C.I.), alternate CI/EI (ACE) fast atom bombardment (FAB).

Optical Rotations $[\alpha]_D$, were recorded on a Perkin-Elmer 241 polarimeter, with concentrations quoted in g/100 ml.

Microanalyses were carried out on a Carlo Erba 1106 elemental analizer.

Thin Layer Chromatography (t.l.c.) was performed on glass pre-coated silica-gel (F_{254}) plates (Merck). Silica plates were visualised by U.V. light and acid charring (5% sulphuric acid in methanol; or ceric sulphate/ammonium molybdate in 5% aqueous sulphuric acid).

Preparative Thin Layer Chromatagraphy, (p.l.c.), was carried out on 20x20 cm plates covered with an F_{254} silica adsorbent 1 and 2 mm thick (Merck).

Column Chromatography: routine purifications were carried out by "flash chromatography", as described in *J.Org.Chem.*, 1978, **43**, 2923; using Merck 40-60 μm flash silica gel.

Dry Column Chromatography: was carried out as described in *Aldrichimica Acta*, 1985, **18(I)**, 25, using Merck 60H silica gel.

Solvents: Benzene and toluene were dried over sodium wire. Hexane refers to the petroleum fraction boiling at about 67 °C, distilled before use. Tetrahydrofuran was dried by refluxing with sodium and benzophenone and distilling under nitrogen. *N,N*- Dimethyl formamide was distilled from calcium hydride under reduced pressure. Pyridine was refluxed over, distilled from and stored over potassium hydroxide. Dichloromethane was distilled from calcium hydride. Methanol was refluxed with and distilled from magnesium methoxide.

Reagents: sugars were purchased from the Sigma Chemical Company, most other chemicals were obtained from the Aldrich Chemical Company. 4-DMAP and tetrabutylammonium cyanide were bought from Fluka.

1,2;5,6-Di-*O*-isopropylidene-3-*O*-benzyl-α-D-glucofuranose (A47)

Sodium hydride (50% dispersion in oil, 5.28g, 110 mmol, 1.1 equivalents) was washed with three 20 ml portions of hexane under nitrogen, then suspended in 30 mls of dry THF. Diacetone glucose (26.10g, 100 mmol) in dry THF (240 ml) was added with cooling over 1 h. After this hour at 0°C tetrabutylammonium iodide (0.6g, 1.6 mmol) and benzyl bromide (13.0 ml, 1.1 eq) were added and the resulting mixture refluxed for 45 min when t.l.c. (1:1 ether/hexane) revealed completion. (Starting material Rf 0.15, product Rf 0.50). After cooling the solution was filtered with silica topped with celite and the cake washed x3 with ether. Solvents were removed and the resulting syrup was co-distilled with benzene to remove any benzyl bromide impurities. The *benzyl ether* (A47) was used directly in the next stage as this crude syrup.

1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-glucofuranose (A48)

The crude benzyl ether (A47) was all dissolved in 10% aqueous methanol (200 mls) containing 1.1 ml of concentrated hydrochloric acid and stirred for 24 h at room temperature. T.l.c. then revealed completion (2:1 ether/hexane, Product Rf 0.20, Starting material Rf 0.70). The mixture was neutralised by careful addition of 880 ammonia, solvents partially reduced, and the residue partitioned between ethyl acetate/water. The dried ($MgSO_4$) organic layer was evaporated and purified on a dry column eluted by a gradient of ethyl acetate/hexane to give the *diol* (A48) (28.0 g, 90% from diacetone glucose). $[\alpha]_D^{20}$ -54.2° (*c*, 1.43 in $CHCl_3$) (lit,[32] -46.4° c,4.98 in $CHCl_3$), ν_{max} ($CHCl_3$) 3 420 (OH) cm^{-1}, ^1H NMR ($CDCl_3$) 1.33 and 1.50 (each 3H, s, Me), 1.90 and 2.40 (each 1H, br, exchange-D_2O, OH), 3.70 and 3.82 (each 1H, dd, J_{gem} 11.4 Hz, 6/6'-H), 4.03 (1H, m, 5-H), 4.10 (2H, m, 3-H and 4-H), 4.64 (1H,

d, *J* 3.8 Hz, 2-H), 4.55 and 4.74 (each 1H, d, *J* 11.8 Hz, CH_2Ph), 5.95 (1H, d, *J* 3.8 Hz, 1-H), 7.30 (5H, m, ArH).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose-(1,4) (A44)

To the diol (A48) (8,15 g, 26.3 mmol) in vigorously stirred methanol (100 ml), was added sodium periodate (8.56 g, 40 mmol). Water was added until the mixture became turbid and this was stirred at room temperature for 3 h when t.l.c. (1:1 ethyl acetate/hexane) revealed a clean reaction (Product Rf 0.45, starting material Rf 0.20). The ensuing suspension was filtered through celite, concentrated and dissolved in 80 ml of dichloromethane, which was washed twice with water, dried ($MgSO_4$) and evaporated to dryness.

The resulting crude syrup was reacted directly in the next stage without further purification.

3-*O*-Benzyl-5-*C*-carbomethoxymethylene-1,2-*O*-isopropylidene-5-anhydro-α-D-*xylo*furanose (A50)

The crude aldehyde (A44) in 40 ml of dichloromethane was stirred under nitrogen together with (carbomethoxymethylene)triphenylphosphorane (12.3 g, 36.8 mmol) added in one portion in a further 30 ml of dichloromethane. This mixture was stirred at room temperature for 72 h. Concentration of the sample followed by dry column chromatography (2:1 ether/hexane) produced a mixture of geometric isomers (4:3 *E*:*Z* by NMR) which could be separated by flash chromatography (1:1 ether/hexane, *Z*, Rf 0.5; *E*, Rf 0.4). The geometric mixture of the enoates, a colourless syrup, was used in the next step. (7.68 g, 88% over 2 steps). n_{max} (film) 1 720 (C=O), 1 660 (C=C) cm^{-1}, ^1H NMR ($CDCl_3$) (*Z* isomer) 1.34 and 1.48 (3H, s, Me), 3.70 (3H, s, OMe), 4.27

(1H, d, 3-H), 4.43 and 4.43 (1H, dd, CH_2Ph), 4.63 (1H, d, 2-H), 5.75 (1H, m, 4-H), 5.95 (1H, dd, *J* 12 Hz, a-CH), 6.03 (1H, d, 1-H), 6.79 (1H, dd, *J* 12 Hz, b-CH), 7.25 (5H, m, Ar-H); for *E* isomer 5.82 and 6.79 (each 1H, dd, *J* 16 Hz); m/z (DCI, NH_3) 352 ($M+NH_4^+$) 335 (100%, $M+H^+$).

Dimethyl-2-methoxycarbonyl-3-(*4*-3-O-benzyl-1,2-di-O-isopropylidene-α-D-*xylo*furanosyl)-pentane-1,5-dioate (A51)

To the geometric mixture of enoates (A50) (4.01 g, 12.0 mmol) in rigorously dried methanol (50 ml) under nitrogen was added dimethyl malonate (5.50 ml, 4.0 equivalents, stored over molecular sieves) and freshly prepared sodium methoxide in methanol (1N solution, 0.25 ml). After refluxing the mixture for 4 h the reaction was quenched by the addition of 50 ml of 1N aqueuous KH_2PO_4. This was extracted with three 100 ml portions of chloroform and dried ($MgSO_4$). After concentration flash chromatography and evaporation yielded the triester as a white solid (3.64 g, 65%). In some column fractions white needles, m.p. 82-83 ^0C, were deposited, which appeared (by NMR) to be a single diastereomer.$[\alpha]_D^{20}$ -49.8° (*c* 1.09 in $CHCl_3$); ν_{max} ($CHCl_3$) 1 740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.31 and 1.47 (each 3H, s, Me), 2.34 and 2.70 (each 1H, dd, 4/4a-H), 3.16 (1H, m, 3-H), 3.57, 3.71, and 3.72 (each 3H, s, OMe), 3.92 (1H, d, 3'-H), 3.96 (1H, d, 2-H), 4.37 (1H, dd, 4'-H), 4.61 (1H, d, 2'-H), 4.68 and 4.46 (each 1H, d, CH_2Ar), 5.86 (1H,d, 1'-H), 7.30 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.45 and 26.77 (q, Me), 32.68 (t, 4-C), 34.28 (d, 3-C), 51.15 (d, 2-C), 51.54 52.07 52.33 (q, OMe), 71.42 (t, CH_2Ar), 80.03 81.25 81.76 (d,2'-C, 3'-C and 4'-C), 104.64 (d, 1'-C), 111.74 (s, isopropylidene), 127.72, 127.90, and 128.38 (d, Ar), 137.08 (s, Ar), 168.72, 169.34, and 172.24 (s, C=O); m/z (DCI, NH_3) 484 ($M+NH_4^+$) and 467 (100%, $M+H^+$); (Found C, 59.28, H 6.48, $C_{23}H_{30}O_{10}$ requires

C, 59.22, H, 6.48%).

Dimethyl-3-(*4*-3-O-benzyl-1,2-di-O-isopropylidene-α-D-*xylo*furanosyl)-pentane-1,5-dioate (A52)

The triester (A51) (2.84 g) was taken up in 35 ml of dimethyl sulphoxide to which was added 10 drops of brine. This solution was heated at 160 °C under nitrogen for 6 h when t.l.c. (1:1 ether/hexane) revealed no starting material (Rf 0.25) and one product (Rf 0.40). Removal of the solvent was facilitated using a high vacuum pump with a cold finger trap, which produced a brown sludge. This was purified by flash chromatography, which yielded the *diester* (A52) as a colurless oil (2.17 g, 87%). $[\alpha]_D^{20}$ -43.2° (*c*, 1.18 in $CHCl_3$); ν_{max} (film) 1 735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.32 and 1.48 (each 3H, s, Me), 2.30 to 2.85 (5H, m, 2/2a/3/4/4a-H), 3.61 and 3.63 (each 3H, s, OMe), 3.87 (1H, d, 3'-H), 4.21 (1H, dd, 4'-H), 4.58 (1H, d, 2'-H), 4.48 and 4.72 (each 1H, d, CH_2Ph), 5.90 (1H, d, 1'-H), 7.30 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.27 and 26.67 (q, Me), 31.10 (d, 3-C), 34.46 and 34.65 (t, 2-C and 3-C), 51.30 and 51.38 (q, OMe), 71.47 (t, CH_2Ph), 80.82, 81.22, and 81.82 (d, 2'-C, 3'-C, and 4'-C), 104.54 (d, 1'-C), 111.46 (s, isopropylidene-C), 127.81, 127.93, and 128.40 (d, Ar), 137.04 (s, Ar), 172.19 and 172.75 (s, C=O); m/z (DCI, NH_3) 409 (100%, $M+H^+$); (Found C, 61.69, H, 7.09, $C_{21}H_{28}O_8$ requires C, 61.75, H, 6.91%).

3-(*4*-3-O-Benzyl-1,2-di-O-isopropylidene-α-D-*xylo*furanosyl)-pentane-1,5-dioic acid (A54)

The diester (A52) (0.52 g, 1.27 mmol) was dissolved in 20 ml of 1N KOH in methanol and stirred at room temperature for 72 h, when t.l.c. (1:9 EtOH/$CHCl_3$, plus a few drops of AcOH) revealed no starting material (Rf 0.80) with a streak at low Rf.

The pH was then adjusted to 3 by the addition of dilute hydrochloric acid (1N), from which the diacid was extracted with two 50 ml portions of chloroform. The white foam obtained after drying ($MgSO_4$) and evaporation to dryness was used without further purification in the next stage. ν_{max} ($CHCl_3$), 3 400 br (OH), and 1 710 (C=O) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 10.8 (2H, s, exchange-D_2O, CO_2H).

3-(*4*-3-O-Benzyl-1,2-di-O-isopropylidene-α-D-*xylo*furanosyl)-pentane-1,5-dioic anhydride (A55)

The diacid (A54) was dissolved in 15 ml of dry THF under nitrogen and cooled to 0 °C. To this solution was added methyl chloroformate (0.14 ml, 1.8 mmol) and triethylamine (0.18 ml, 1.27 mmol), and the mixture maintained at this temperature for 2 h. Over the next hour ambient temperature was reached and the solvent then removed *in vacuo*. The residue was taken up in 50 ml of ethyl acetate, washed twice with water, dried ($MgSO_4$) and evaporated to give a white solid (460 mg, 100% from A52). Recrystallisation (EtOAc) gave white prisms, m.p. 124-125 °C. $[\alpha]_D^{20}$ -64.7° (*c*, 1.35 $CHCl_3$); ν_{max} ($CHCl_3$) 1 810 and 1 760 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 and 2.48 (each 3H, s, Me), 2.34 and 2,58 (each 2H, m, 3/3a/5/5a-H), 3.10 (1H, m, 4-H), 3.88 (2H, m, 3'-H and 4'-H), 4.65 (1H, d, 2'-H), 4.44 and 4.74 (each 1H, d, CH_2Ph), 5.92 (1H, d, 1'-H), 7.34 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.04 and 26.66 (s, Me), 28.24 (d, 4-C), 32.56 and 32.94 (t, 3-C, and 5-C), 71.77 (t, CH_2Ph), 81.09, 81.41 and 81.67 (d, 2'-C, 3'-C, and 4'-C), 104.79 (d, 1'-C), 111.87 (s, isopropylidene), 128.04, 128.45 and 128.75 (d, Ar), 136.52 (s, Ar), 165.60 and 165.87 (s, C=O); m/z (DCI, NH3) 363 (45%, $M+H^+$), 91 (100, $C_7H_7^+$), (Found C, 62.73, H, 6.12, $C_{19}H_{22}O_7$ requires C, 62.97, H, 6.12%).

4-(*4*-3-O-benzyl-1,2-di-O-isopropylidene-α-D-*xylo*furanosyl)-piperidine,2,6-dione

(A57).

The anhydride (A55) (1.09 g, 3.0 mmol) was dissolved in 50 ml of dry THF and cooled to 0°C. A stream of ammonia was bubbled through this solution for 1 h, after which excess ammonia was allowed to evaporate and the solvent removed *in vacuo*. The crude mixed *acid-amide* (A56) [characterised by its IR spectrum, ν_{max} 1 700 (acid C=O) and 1 660 (amide C=O) cm^{-1}] was dissolved in acetic anhydride (40 ml) containing sodium acetate (1.24 g, 15.0 mmol). This mixture was heated at 100 °C for 20 min, then cooled and concentrated. Flash chromatography (5% ethanol in chloroform) gave a crude syrup which was crystallised from ethyl acetate-hexane yielding a white solid (0.77 g, 71%), m.p. 136-137 °C; $[\alpha]_D^{20}$ -73.8° (*c*, 1.21 in $CHCl_3$); ν_{max} ($CHCl_3$) 1 730, 1 710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.34 and 1.49 (each 3H, s, Me), 2.14 to 2.66 (4H, m, 3/3a-H and 5/5a-H), 2.95 (1H, m, 4-H), 3.87 (2H, m, 3'-H and 4'-H), 4.68 (1H, d, 2'-H), 4.46 and 4.72 (each 1H, d, CH_2Ph), 5.92 (1H, d, 1'-H), 7.35 (5H, m, ArH), 8.05 (1H, br, exchanges-D_2O, NH); ^{13}C NMR ($CDCl_3$), 26.03 and 26.63 (q, Me), 29.48 (d, 2-C), 33.99 (t, 5-C), 34.89 (t, 3-C), 71.25 (t, CH_2Ar), 80.91, 81.53, and 81.94 (d, 2'-C, 3'-C, and 4'-C), 104.73 (d, 1'-C), 111.69 (s, actetonide), 127.96, 138.53, and 128.69 (d, Ar), 136.61 (s, Ar), 171.34 and 171.83 (s, C=O); m/z (DCI, NH_3), 379 ($M+NH_4^+$, 100%), and 362 ($M+H^+$, 45); (Found C, 63.29; H, 6.54; N, 3.65; $C_{19}H_{23}O_6N$ requires C, 63.14; H, 6.41; N, 3.88%).

4-(*4*-1,2-Di-O-isopropylidene-α-D-*xylo*furanosyl)-piperidine,2,6-dione (A58)

The benzylether (A57) (400 mg) was dissolved in 40 ml of ethanol, to which was added about 50 mgs of Palladium black. This was stirred under an atmosphere of

hydrogen for 24 h, when t.l.c. (10% EtOH in $CHCl_3$) revealed completion (ether Rf 0.8, alcohol Rf 0.5). After filtration through a celite plug concentration afforded a white solid, recrystallised from ethanol (260 mg, 87 %). M.p. 200- 202 °C, $[\alpha]_D^{20}$ - 31,4° (*c* 0.51, chloroform); ν_{max} (Nujol) 3 410 (OH), 3 200 (NH), and 1 690 (C=O) cm-1; ^{1}H NMR (MeOD-d3) 1.29 and 1·43 (each 3H, s, Me), 2.38 to 2.82 (5H, m, 3/3a/4/4a/5-H), 3.85 (1H, dd, J_{3-4} 2.6 Hz, 4'-H), 4.06 (1H, d, J_{3-4} 2.6 Hz, 3'-H), 4.48 (1H, d, J_{1-2} 3.7 Hz, 2-H), 5.85 (1H, d, J_{1-2} 3.7 Hz, 1'-H); ^{13}C NMR (DMSO-d6) 26.22 and 26.85 (q, Me), 29.31 (d, 3-C), 33.60 (t, 3-C), 35.11 (t, 5-C), 72.92 (d, 3'-C), 82.64 and 85.19 (d, 2'-C, and 4'-C), 104.25 (d, 1'-C), 110.66 (s, acetonide), 172.88 and 173.03 (s, glut C=O); m/z (DCI, NH_3), 289 ($M+NH_4^+$, 100 %), 272 ($M+H^+$ 55);. (Found C, 53.35; H, 6.58; N, 5.02; $C_{12}H_{17}NO_6$ requires C, 5 .13; H, 6.32; N, 5.16 %).

4-(*4*-3-O-Benzyl-D-*xylo*furanosyl)-piperidine,2,6-dione (A59)

The acetonide (A57) (400 mg) was. dissolved in 20 ml of 1:1:1 trifluoroacetic acid: acetic acid: water, and stirred for 24 h at room temperature, when t.l.c. (10% EtOH in $CHCl_3$) revealed a clean reaction (lactol, two close spots Rf 0.2). The solvents were removed under reduced pressure to give solid which was recrystallized from methanol, (270 mg, 80%). M.p. 100-101 °C; ν_{max} (Nujol) 3 400 (OH), 3 200 (NH), and 1 690 (C=O) cm-1; ^{1}H NMR (MeOD d-3) (mixture of anomers) 2.41 to 2.85 (5H, M, 3/3a/4/5/5a-H)), 3.85 to 4.15 (3H, m, 2'/3'/4'-H), 4.40 to 4.75 (2H, m, CH_2Ph), 5.08 and 5.28 (1H, both d, 1-H α and β), 7.20 (5H, m, Ar-H), m/z (DCI, NH_3), 340 ($M+NH_4^+$, 80 %), 322 ($M+H^+$ 30), 91 (100); (Found C, 57.98; H, 6.47; N, 3.97; $C_{16}H_{19}O_6N$.MeOH requires C, 57.79; H, 6.51; N, 3.96 %).

4-(*4*-D-*Xylo*furanosyl)-piperidine,2,6-dione (A40)

The acetonide (A58) (160 mg) was dissolved in 15 ml of 1:1:1 trifluoroacetic acid: acetic acid: water, and stirred for 24 h at room temperature, when t.l.c. (10% EtOH in $CHCl_3$) revealed completion (starting material Rf 0.5, product Rf 0). The solvents were removed under reduced pressure to give solid which was recrystallized from methanol, (120 mg, 85%). M.p. 196-197 °C; ν_{max} (Nujol) 3 410 (OH), 3 200 (NH), and 1 690 (C=O) cm^{-1}; ^1H NMR (D_2O) (mixture of anomers) 2.25 to 2.70 (5H, m, 3/3a/4/5/5a-H), 3.25 to 4.05 (3H, m, 2'/3'/4'-H), 4.98 and 5.25 (1H, both d, 1-H $\underline{\alpha}$ and β); (Found C, 45.0; H, 6.46; N, 5.32; $C_9H_{13}NO_6$.MeOH requires C, 45.6; H, 6.46; N, 5.32 %).

Methyl-4,6-*O*-Benzylidene-2,3-di-*O*-*p*-toluenesulphonyl-α-D-glucofuranoside (A64).

Using the literature method,[37] Methyl-4,6-benzylidene-α-D-glucofuranoside (Sigma) (19.75 g, 70 mmol) was vigorously stirred for 4 days at room temperature with *p*-toluenesulphonyl chloride in 150 ml of dry pyridine under dry nitrogen. The mixture was poured onto 500 ml of cracked ice which was extracted with 3x 200 ml portions of dichloromethane when most of the ice had melted. The combined organic fractions were cooled with a generous amount of cracked ice and washed with two iced portions of 6N HCl. This was followed by further washing by saturated aqueous $NaHCO_3$, saturated $CuSO_4$ (2x), water, and brine. After drying with $MgSO_4$ the solvent was evaporated to yield a syrup, which gave a white solid on trituration with ether; this solid was collected and washed with further portions of ether. Concentration of the mother liquor afforded a second crop of solid which was treated in a similar manner, giving a combined yield of 34.14 g, (83%). M.p. 146-148 °C, lit.[37] 147-148 °C; $[\alpha]_D^{20}$ +14.7° (*c* 1.59, chloroform), lit[37] +12° (*c* 6.0, chloroform); 1H NMR ($CDCl_3$) 2.26, 2.46 (each 3H, s, Me), 3.42 (3H, s, OMe), 3.51 (1H, t, 4-H), 3.67 (1H, t, 6-H), 3.85 (1H, m, 5-H), 4.25 (1H, dd, 6'-H), 4.44 (1H, dd, 2-H), 5.10 (1H, t, 3-H), 5.15 (1H, d, 1-H), 5.29 (1H, s, benzylidine-H), 6.92 (2h, d, Ar-H), 7.35 (7H, m, Ar-H), 7.64, 7.84 (each 2H, d, Ar-H).

Methyl-2,3-anhydro-4,6-*O*-benzylidene-α-D-allofuranoside (A63).

Using a slightly modified literature method,[37] the ditosylate (A64) (29.50 g, 50 mmol) was dissolved in 400 ml of dry dichloromethane under dry nitrogen and cooled with ice. A solution of sodium methoxide, freshly prepared by dissolving sodium (5.75 g, 250 mmol) in dry methanol (150 ml) was added to this and the

mixture stirred at room temperature for 48 h, when t.l.c. (1:1 ethyl acetate/hexane) revealed no further starting material (Rf 0.8), with one product (Rf 0.5). The solution was diluted with 200 ml of water; the dichloromethane separated, and the aqueous layer extracted with two 200 ml portions of dichloromethane. The combined organic fractions were washed with 100 ml of water and 100 ml of brine, dried ($MgSO_4$), and concentrated under reduced pressure. This produced a white solid which was filtered and washed with ether, producing 12.40 g, 94 %, which was a single compound by NMR. M.p. 202-203 ^oC, lit[37] about 200 ^oC; $[\alpha]_D^{20}$ +145^o, (*c*, 2.0, $CHCl_3$), lit[37] +140^o (*c* 2.0, chloroform); ^1H NMR ($CDCl_3$) 3.49 (3H, s, Me), 3.52 (2H, m, 2/3-H), 3.70 (1H, t, 6'-H), 3.97 (1H, d, 4-H), 4.10 (1H, m, 5-H), 4.25 (1H, dd, 6'-H), 4.90 (1H, d, 1-H), 5.58 (1H, s, benzylidene-H), 7.39 (5H, m, Ar-H).

Methyl-4,6-*O*-Benzylidene-α-D-altropyranoside (A65)

A solution of 11.00 g (197 mmol) of potassium hydroxide in 280 ml of water was refluxed with the epoxide (A63) (8.65 g, 32.8 mmol) until all of the latter had dissolved (48 h). This solution was cooled, then partially neutralised with 6N sulphuric acid (25.0 ml, 0.75 eq) and filtered to remove a small amount of solid residue. This aqueous solution was then extracted with 250, 150, and 2x 100 ml portions of dichloromethane, which were combined and backwashed with brine. This brine was added to the aqueous fraction which was then exhaustively extracted with seven further 100 ml portions of dichloromethane until tlc revealed no further product (Rf 0.4, 9:1 EtOH:$CHCl_3$). After a brine wash all fractions were combined and concentrated in vacuo, yielding a white crystalline solid (7.93 g, 86%). M.p 168-170 ^oC, Lit$ 169-170 ^oC. $[\alpha]_D^{20}$ +116.4^o (*c* 2.0, $CHCl_3$), lit[37] +115^o (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) 2.25 (1h, d, OH), 2.95 (1H, d, OH), 3.46 (3H, s, OMe), 3.80-4.44 (6H, m, 2/3/4/5/6/6'-H), 4.68 (1H, s, 1-H), 5.54 (1H, s, benzylidene), 7.42

(5H, m, Ar-H).

Methyl-α-D-altropyranoside (A61)

A solution of 7.90 g (29.0 mmol) of the benzylidene-altroside (A65) was dissolved in 150 ml of glacial acetic acid diluted with 100 ml of water. This was stirred at room temperature for 36 h,when t.l.c. (9:1 EtOH:$CHCl_3$) revealed no starting material (Rf 0.4) with other material on the baseline. The solvents were removed under reduced pressure and the residue co-evaporated with three 100 ml portions of dry benzene. After drying on a high vacuum line for several hours the *altroside* (A61) was used without further purification in the next stage.

Methyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-altropyranoside (A61Si).

Tert-Butylchlorodiphenylsilane (9.0 ml, 35.0 mmol) was added dropwise, with stirring, to a solution of the crude methyl-α-D-altropyranoside (30) (29.0 mmol) and imidazole (3.95 g, 58.0 mmol) in dry dimethylformamide (150 ml), under an atmosphere of nitrogen at room temperature. After 2 hours t.l.c. (10% ethanol/chloroform) showed absence of starting material (Rf 0) and presence of one product (Rf 0.6). The dimethylformamide was removed and the residue dissolved in chloroform (250 ml). The resulting solution was washed successively with dilute aqueous hydrochloric acid (0.1 M, 2x 250 ml) water (2x 250ml), and brine (50 ml), then dried ($MgSO_4$),filtered and evaporated to a clear syrup. Purification by dry column chromatography (EtOAc/hexane) gave the silyl ether (31) as a colourless syrup (10.26 g, 82% over two steps). ^1H NMR ($CDCl_3$) 1.09 (9H, s, CMe_3), 3.30, 2.72, 2.28 (3H, br, OH), 3.44 (3H, s, MeO), 4.07-3.70 (6H, m, 2-H, 3-H, 4-H, 5-H, 6-H, 6'-H), 4.69 (1H, s, 1-H), 7.8-7.3 (10H, m, ArH).

Methyl-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-α-D-altropyranoside (A66).

The silyl ether (A61Si) (10.26 g) was dissolved in a 9:1 mixture of acetone to 2,2-dimethoxypropane. 10-Camphorsulphonic acid was added to adjust pH to 4 . After 2 hours t.l.c. (10% ethanol/chloroform) showed no starting material. The solution was neutralized by addition of saturated aqueous ammonia and the solvent removed. The resulting syrup was dissolved in 200 ml of chloroform which was washed with water, then brine and dried ($MgSO_4$). Filtration and evaporation, followed by flash chromatography (1:1 ether/hexane) gave the *acetonide* (A66) as a colourless syrup (9.40 g, 84%). ^1H NMR 1.09 (9H, s, CMe_3), 1.49, 1.34 (6H, 2s, acetonide), 2.75 (1H, d, OH), 3.49 (3H, s, MeO), 3.94-3.77 (4H, m, 2-H, 5-H, 6-H, 6'-H), 4.24, 4.12 (each, 1H, t, 3-H, 4-H), 4.58 (1H, d, 1-H), 7.8-7.3 (10H, m, ArH).

Methyl-6-*O*-*tert*-butyldiphenylsilyl-4,3-*O*-isopropylidene-2-*O*-trifluoromethanesulphonyl-α-D-altropyranoside (A35).

Dry pyridine (3.22 ml, 39.8 mmol) was added to a solution of the alcohol (A66) (9.40 g, 19.9 mmol) in dry dichloromethane (250 ml) stirred under nitrogen. Trifluoromethanesulfonic anhydride (4.04 ml, 24.0 mmol) was added to the mixture at -30°C. The reaction was maintained between -20°C to -30°C for one hour, when t.l.c. (50% ether/hexane) showed absence of starting material (Rf 0.2) and a single product (Rf 0.8). The reaction mixture was allowed to warm to room temperature and was quenched with methanol (10 ml). The resulting solution was washed with water, saturated sodium bicarbonate solution, saturated copper sulphate (x2), water, brine, then dried ($MgSO_4$), filtered and evaporated without heating. The product was

usually used directly in the next step, although purification was achieved by flash chromatography (5% ether/hexane) to give the *triflate* (A35) as a clear syrup in some cases (90% yield). ^{1}H NMR 1.09 (9H, s, CMe_3), 1.51, 1.36 (6H, 2s, acetonide), 3.48 (3H, s, MeO), 4.84-3.81 (7H, m, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, 6'-H), 7.8-7.3 (10H, m, Ar-H).

2,5-Anhydro-1-azido-6-*O*-tert-(butyldiphenyl)silyl-3,4-*O*-isopropylidine-1-*O*-methyl-D-allitol (A37).

The crude triflate (A35) (from 29.9 mmol) was dissolved in dry dimethylformamide (250 ml) and sodium azide (3.40 g, 50.0 mmol) was added. The mixture was stirred at 40°C under nitrogen for fifteen hours when t.l.c (20% ether/hexane) showed absence of starting material and two products (Rf 0.55 and 0.6). The solvent was evaporated and the residue partitioned between ether and brine. The aqueous layer was further washed with ether; the combined organic washings were dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography gave a miture of the diastereomeric *azides* (A37) (9.25 g, 93% over two steps). ^{1}H NMR of mixture ($CDCl_3$) 1.10 (9H, CMe_3), 1.40, 1.60 (3H, s, Me), 3.45 and 3.55 (total 3H, each s, OMe), 3.80 (2H, m, 6/6^a-H), 4.15 (2H, m, 2/5-H), 4.45 (1H, m, 3-H), 4.70 (2H, m, 1/4-H)

2,5-Anhydro-6-*O*-tert-butyldiphenylsilyl-3,4-*O*-isopropylidine-D-allose (A37).

The diastereomeric mixture of azides (A37) (9.25 g) was dissolved in ethanol containing a few drops of water, to which 10% palladium on charcoal (about 200 mg) was added. This suspension was then stirred under hydrogen at atmospheric pressure and room temperature. After 1 hour t.l.c. (40% ether/hexane) showed a single product

(Rf 0.3). The reaction mixture was then filtered through a celite plug, which was well washed with ethanol and the solvent evaporated. The residue was purified by flash chromatography (40% ether/hexane) yielding the *aldehyde* (A38) as a clear oil (6.64g, 81%). This was used directly in the next step.

1-(*E*-*C*-Carbomethoxymethylene)-2,5-anhydro-6-*O*-*tert*-butyldiphenylsilyl-1-deoxy-3,4-*O*-isopropylidene-D-allitol (A67)

To the aldehyde (A38) (6.64g, 15.1 mmol) in 300 ml of dichloromethane was added the ylid (A49) in one portion. This was stirred for 72 h when t.l.c. showed no further aldehyde (Rf 0.3, 2:3 ether/hexane) and one major product (Rf 0.7). The solvent was removed and the residue purified by flash chromatography (2:3 ether/hexane). This gave the *enoates* (A67) as a mixture of geometric isomers (7:1 E:Z, 4.14 g, 62%). ^{1}H NMR ($CDCl_3$) (*E*) 1.07 (9H, s, CMe_3), 1.36, 1.57 (each 3H, s, Me), 3.74 (3H, s, OMe), 3.78 (2H, m, 6/6'-H), 4.17 (1H, dd, 5-H), 4.52 (2H, m, 2/3-H), 4.72 (1H, dd, $J_{3,4}$ 6.1 Hz, 4-H), 6.17 (1H, dd, *J* 15.8 Hz, α-CH), 7.04 (1H, dd, β-CH), 7.37 to 7.71 (10H, m, Ar-H); n.b. Z, 5.83 and 6.30 (each 1H, dd, *J* 11.8 Hz, CH)

Dimethyl-2-methoxycarbonyl-3-(5'-*t*butyldiphenylsilyl-2',3'-*O*-isopropyilidene-β-D-ribofuranosyl)-pentane-1,5-dioate (A69)

To a solution of dimethyl malonate (2.70 ml, 23.2 mmol) in dry THF cooled to -50 ^{o}C under nitrogen was added a solution of n-Butyl lithium in hexane (1.6 N, 11.7 ml). This was stirred for 20 min after which a solution of the diasteromeric enoates (A67) (2.90 g, 5.80 mmol) was added in 25 ml of dry THF. The temperature was allowed to rise to room temperature, a condensor fitted, and the mixture subsequently refluxed for 36 h. After this time had elapsed only a trace of starting material remained (Rf

0.6) with one major product (Rf 0.5). The reaction was quenched with 50 ml of 1M aqueous KH_2PO_4. This was extracted with 3x 100 ml portions of chloroform, which were combined, washed with brine, dried, and evaporated. The mixture was partially purified by flash chromatography (1:4 ether/hexane eluant), to give a mixture of the *triester* (A69) and co-running dimethyl malonate. The later was removed by high vacuum rotary evaporation, leaving a colourless oil which was a mixture of the possible diastereomers by NMR (2.33 g, 64 %). ν_{max} (film) 1 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.05 (9H, s, CMe_3), 1.30, 1.60 (3H, s, Me), 2.60-3.05 (3H, m, 2/4/4a-H), 3.60-3.80 (12H, m, 3x OMe, 5'/5'a/3-H), 4.00 (2H, m, 1'/4'-H), 4.45 (1H, m, 2'-H), 4.65 (1H, m, 3'-H); m/z 646 ($M+NH_4^+$, 55%), 629 ($M+H^+$, 10), 551 ($M+H^+$-PhH, 100); (Found C, 62.86; H, 7.07; $C_{33}H_{44}O_{10}Si$ requires, C, 63.10; H, 7.07 %).

Dimethyl-3-(5'-*t*butyldiphenylsilyl-2',3'-*O*-isopropyilidene-β-D-ribofuranosyl)-pentane-1,5-dioate (A68)

To a solution of the triester (A69) (2.33g) in dimethyl sulphoxide (100 ml) was added 0.5 ml of brine. This mixture was heated at 160 °C for 5h when t.l.c. (1:4 ether /hexane) revealed absence of starting material (Rf 0.2), and one product (Rf 0.1). The solvent was then removed by high vacuum rotary evaporation and the residue partitioned between chloroform and water (100 ml of each). The chloroform was washed with brine, dried, and evaporated, leaving a caramel which was purified by flash chromatography, giving a colourless syrup (1.73 g, 82%). $[\alpha]_D^{20}$ 0.00 (c 1.18, chloroform); ν_{max} (Film) 1 735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) 1.06 (9H, s, Me), 1.33, 1.52 (3H, s, Me), 2.43 to 2.63 (5H, m, 2/2a/3/4/4a-H); 3.64, 3.66 (3H, s, OMe), 3.76 (1H, m, 1'-H), 4.00 (1H, m, 4'-H), 4.39 (1H, t, $J_{2',3'}$ 6.5 Hz, 2'-H), 4.66 (1H, dd, 3'-H), 7.30-7.80 (10H, m, Ar-H); ^{13}C NMR 19.22 (s, CMe_3), 25.57 (q, Me),

26.60 (q, Me_3), 27.50 (q, Me), 34.57, 34.83 (t, 3/5-C), 35.24 (d, 4-C), 51.48, 51.56 (q, OMe), 63.90 (t, 5'-C), 81.65, 82.94, 83.82, and 85.10 (d, 1'/2'/3'/4'-C), 114.46 (s, acetonide), 127.68, 129.71, 135.61 (d, Ar-H), 133.22 (s, Ar), 172.49 and 172.67 (s, C=O); m/z (DCI, NH_3) 588 ($M+NH_4^+$, 28%), 571 ($M+H^+$, 10), 493 ($M+H^+$-PhH, 100%); (Found C, 65.23; H, 7.60; $C_{31}H_{42}O_8Si$ requires, C, 65.23; H, 7.42 %).

3-(5'-*t*Butyldiphenylsilyl-2',3'-*O*-isopropyilidene-β-D-ribofuranosyl)-pentanedioic anhydride (A71).

The diester (A68) (325 mg, 0.88 mmol) was stirred in 5 ml of 1M KOH in methanol for 8 h, after which there was no starting material by t.l.c. (Rf 0.5, 1:1 ether/hexane). The solution was acidified with acetic acid, and the solution diluted with water (20 ml). The resulting suspension was extracted with chloroform, backwashed with brine, dried ($MgSO_4$) and evaporated. The crude *acid* (A70) was taken up in dry THF (5 ml) to which was added triethylamine (78 ml, 0.88 mmol) and methyl chloroformate (55 ml, 1.0 mmol). The resulting suspension was stirred for 3 h at 0 °C after which it was evaporated. The residue was partitioned between water/ethyl acetate, dried and evaporate. The crude *anhydride* (A71) was used in this form (about 300 mg of material). ν_{max} 1 810, 1 760 cm $^{-1}$; ^{1}H NMR (200 MHz, $CDCl_3$) 1.05 (9H, s, CMe_3), 1.35, 1.55 (3H, s, Me), 2.40-2.90 (5H, m, 2/2a/3/4/4a-H), 3.65 (1H, m, 1'-H), 3.85 (3H, m, 5'/5'a/4/-H), 4.35 (1H, t, 2'-H), 4.70 (1H, dd, 3'-H), 7.40-7.80 (10H, m, Ar-H).

4-(5'-*t*Butyldiphenylsilyl-2',3'-*O*-isopropyilidene-β-D-ribofuranosyl)-piperidine-2,6-dione (A60).

The crude anhydride (A71) was dissolved in dry THF cooled with ice, and ammonia bubbled through this solution for 1 h. The solution was evaporated and the crude *acid-amide* (A72) dissolved in 5 ml of acetic anhydride. Sodium acetate (250 mg, 5 eq) was added and the mixyure heated under nitrogen at 100 °C for 25 min. The solvent was removed and the residue partitioned between water and brine. On evaporation and subsequent chromatographic purification, the glutarimide (A60) was obtained as a viscous oil, 119 mg, 40%. $[\alpha]_D^{20}$ -15° (*c* 0.94, chloroform); ν_{max} (KBr) 3 200 (NH) and 1 700 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.06 (9H, s, Me), 1.35, 1.82 (3H, s, Me), 2.25-2.76 (5H, m, 3/3a/4/5/5a-H), 3.65 (1H, t, $J_{1',2'}$ 6.2 Hz), 3.80 (2H, m, 5'/5'a-H), 4.04 (1H, m, 4'-H), 4.35 (1H, t, 2'-H), 4.71 (1H, dd, $J_{2',3'}$ 3.6 Hz, 3'-H), 7.35 to 7.45 (10H, m, Ar-H); ^{13}C NMR 19.12 (s, CMe_3) 25.37 (q, Me), 26.74 (q, Me), 26.74 (s, CMe_3), 27.38 (q, Me), 33.72 (t, 3-C), 33.96 (d, 4-C), 34.04 (t, 5-C), 63.69 (t, 5'-C), 81.57, 82.79, 84.27, 85.80 (d, 1'/2'/3'/4'-C), 114.88 (s, acetonide), 127.97, 130.10, 135.77 (d, Ar-H), 133.27 (s, Ar), 171.84, 172.06 (s, C=O); m/z 541 ($M+NH_4^+$, 12%), 466 ($M+H^+-Me_2CO$, 35), 446 ($M+H^+-PhH$, 100); (Found C, 66.66; H, 7.38; N, 2.39; $C_{29}H_{37}O_6NSi$ requires C, 66.51; H, 7.12; N, 2.39%).

4-(2',3'-*O*-Isopropyilidene-β-D-ribofuranosyl)-piperidine-2,6-dione (A73)

To the silyl ether (A71) (112 mgs, 0.21 mmol) in THF (5 ml) was added tetrabutylammonium fluoride (1M solution in THF, 0.26 ml). After 4 hours no starting material (Rf 0.5 1:1 ethyl acetate/hexane) remained and one product observed (Rf 0.4, EtOAc). The solvent was removed and purification achieved by flash chromatography, to yield the *alcohol* (A73) as a white solid on trituration with ether (51.3 mg, 84%). M.p 114/115 °C; $[\alpha]_D^{20}$ -40.0° (*c*, 0.59, in $CHCl_3$); ν_{max} (KBr) 3 300 (OH), 3 200 (NH), and 1 690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.33, 1.52 (3H,s,

Me), 2.45 to 2.80 (6H, m, 3/3^{a}/4/5/5^{a}-H and OH), 3.75 (3H, m, 1'/5'/5'^{a}-H), 4.03 (1H, m, 4'-H), 4.40 (m, 2'-H), 4.70 (1H, m, 3'-H), 8.74 (1H, brs, NH); ^{13}C NMR 25.23, 27,25 (q, Me), 33.03 (d, 4-C), 33.20, 34.65 (t, 3/5-C), 62.45 (t, 5'-C), 81.29, 82.52, 84.52, 86.49 (d, 1'/2'/3'/4'-C), 115.15 (s, acetonide), 172.39, 173.59 (s, C=O); m/z (DCI, NH_3) 286 ($M+H^+$, 85%), 303 ($M+NH_4^+$, 100); (Found C, 54.90; H, 6.76; 4.64; $C_{13}H_{19}NO_6$ requires C, 54.73; H, 6.71; N, 4.91%).

4-(β-D-ribofuranosyl)-piperidine-2,6-dione (A29)

To the alcohol (A73) (20.0 mg) in methanol (2 ml) was added trifluoroacetic acid (1 ml). After one hour at room temperature the starting material had disappeared (Rf 0.5, EtOAc), with one major product (Rf 0.3, 1:9 MeOH/EtOAc). The solvents were removed and the residue columned using the same solvent system, to yield the *nuceoside* (A29) as a syrup (13.8 mg, 80%). ^{1}H, NMR (MeOD-d3) 2.30 to 2.70 (5H, m, 3/3a/4/5/5a-H), 3.50-3.95 (6H, m, 1'/2'/3'/4'/5'/5'a-H), m/z (DCI, NH_3) 263 ($M+NH_4^+$, 100%).

Methyl-6-*O*-tert-butyldiphenylsilyl-β-D-galactopyranoside (A75Si).

Tert-Butylchlorodiphenylsilane (9.36 ml, 36.0 mmol) was added dropwise, with stirring ,to a solution of methyl β-D-galactopyranoside (26) (5.82 g, 30.0 mmol) and imidazole (4.49 g, 66.0 mmol) in dry dimethylformamide (80 ml), under an atmosphere of nitrogen at room temperature. After 3 hours TLC (5% ethanol in chloroform) showed absence of starting material (Rf 0) and presence of one product (Rf 0.3). The dimethylformamide was removed and the residue dissolved in chloroform (100 ml). The resulting solution was washed successively with dilute aqueous hydrochloric acid (0.1M, 2x100 ml), water (2x 100ml), and brine (100 ml), then dried (NMgSO4), filtered and evaporated to a clear syrup. Purification by dry column chromatography (hexane/ethyl acetate) gave the *silyl ether* (A75Si), (9.72 g, 75%) as a colourless syrup. ^{1}H NMR ($CDCl_3$) 1.06 (9H, s, CMe_3), 2.88-4.48 (13H, m, 3 OH, MeO, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, 6'-H), 7.35-7.73 (10H, m, ArH).

Methyl-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (A76).

The triol (A75Si) (6.56 g, 15.2 mmol) was dissolved in a 9:1 mixture of acetone and 2,2-dimethoxypropane. 10-Camphorsulphonic acid was added to adjust pH to 4 . After 2 hours t.l.c. showed the reaction to be complete. The solution was neutralized by addition of saturated aqueous ammonia solution and the solvents removed. The resulting syrup was dissolved in chloroform and washed with water and brine. The chloroform layer was dried ($MgSO_4$), filtered and evaporated to a syrup. This was purified by flash chromatography to give the *acetonide* (A76) as a colourless syrup (6.09 g, 85%). ^{1}H NMR ($CDCl_3$) 1.07 (9H, s, CMe_3), 1.36, 1.52 (6H, 2s, acetonide), 2.45 (1H, d, OH), 3.53 (3H, s, MeO), 3.54-4.30 (7H, m, 1-H, 2-H, 3-H, 4-H, 5-H, 6-

H, 6'-H), 7.27-7.44 (10H, m, ArH).

2,5-Anhydro-1-azido-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidine-1-O-methyl-D-talitol (A36).

Dry pyridine (0.36 ml, 4.6 mmol) was added to a solution of the acetonide (A76) (6.09 g, 12.9 mmol) in dry dichloromethane stirred under an atmosphere of dry nitrogen. Trifluoromethanesulfonic anhydride (2.62 ml, 15.5 mmol) was added to the mixture at -30°C. The reaction was maintained between -20°C and -30°C for one hour, when t.l.c (1:1 ether:hexane) showed absence of starting material (Rf 0.2)and a single product (Rf 0.8). The reaction mixture was allowed to warm to room temperature and was quenched with methanol (10 ml). The resulting solution was washed with water, saturated sodium bicarbonate solution, saturated copper sulphate solution (x2), water, brine, then dried ($MgSO_4$), filtered and evaporated without heating. The crude *triflate* (A34) was dissolved in dry dimethylformamide (150 ml) and sodium azide (2.20 g, 33.0 mmol) added. The mixture was stirred at 40°C under nitrogen for fifteen hours. T.l.c. showed absence of starting material and two products (Rf 0.5 and 0.6, 1:4 ether/hexane). The solvent was evaporated and the residue partitioned between dichloromethane and brine. The aqueous layer was further washed with dichloromethane. The combined organic washings were dried ($MgSO_4$), filtered and evaporated. The diastereomeric azides (A36) were partially separated by flash chromatography (gradient elution 5%-10% ether/hexane) to give 5.29 g product (82% yield) in 3:1 ratio of more polar to less polar azides. *Less polar*, $[\alpha]_D^{20}$ -28.3° (*c*, 1.17 in CH_2Cl_2); ν_{max} (film) 2100 cm^{-1}; ^1H NMR 1.07 (9H, s, CMe_3), 1.39, 1.32 (6H, 2s, isopropylidine), 3.51 (3H, s, MeO), 3.96, 3.87 (each 1H, d, 6-H, 6'-H, $J_{6,6'}$ 10.5, $J_{5,6}$ 6.3 Hz), 4.05 (1H, dd, 2-H), 4.17 (1H, m, 5-H), 4.48 (1H,

d, 1-H, $J_{1,2}$ 4.2 Hz), 4.72 (1H, dd, 4-H, $J_{4,5}$ 4.3 Hz), 4.81 (1H, dd, 3-H, $J_{2,3}$ 1.4, $J_{3,4}$ 6.1 Hz), 7.8-7.3 (10H, m, ArH).; *More Polar*, $[\alpha]_D^{20}$ +53.5 (*c*, 1.17 in CH_2Cl_2); ϖ_{max} (film) 2100 cm^{-1}; ^1H NMR 1.07 (9H, s, CMe_3), 1.38, 1.31 (6H, 2s, acetonide), 3.52 (3H, s, MeO), 3.94, 3.86 (each 1H, dd, 6-H,6'-H), 4.67, 4.16 (5H, m, 1-H, 2-H, 3-H, 4-H, 5-H), 7.8-7.3 (10H, m, ArH).

2,5-Anhydro-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidine-D-talose (A77).

The diastereomeric azides (A36) (1.92 g) were dissolved in ethanol (100 ml) and a few drops af water. 10% palladium on charcoal was added to the solution which was then stirred under hydrogen at atmospheric pressure and room temperature. After 1 hour t.l.c. (40% ether/hexane) showed a single product (Rf 0.2). The reaction mixture was filtered through a celite plug which was well washed with ethanol and the solvent evaporated. The residue was purified by flash chromatography (40% ether/hexane) to give the *aldehyde* (A77) (1.54 g, 90%) which was used directly in the next stage.

2,5-Anhydro-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidine-D-talitol (A78).

The aldehyde (A77) (1,54 g, 3.50 mmol) was dissolved in 9:1 methanol/water cooled to 0 °C. Sodium borohydride (266 mg, 7.0 mmol) was added to the solution which was stirred at room temperature for 25 min. T.l.c (60% ether/hexane) showed one major product (R_f 0.3). Excess ammonium chloride was then added to the reaction mixture and the solvent removed. The residue was dissolved in chloroform and washed with water and brine. The organic layer was dried, filtered and evaporated. The product was purified by flash chromatography to give *talitol* (A79) as a colourless syrup (1.17 g, 76%). ^1H NMR ($CDCl_3$) 1.08 (9H, s, CMe_3), 1.40, 1.32 (3H, s, Me), 1.8 (1H, brs, OH), 3.57 (2H, d, 1-H, 1'-H), 4.13-3.88 (4H, m, 2-H, 5-H,

6-H, 6'-H), 4.73, 4.59 (each 1H, dd, 3-H, 4-H), 7.8-7.3 (10H, m, ArH).

2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-6-*O*-benzyl-3,4-isopropylidine-D-talitol (A79).

To a suspension of sodium hydride (50 % dispersion in oil, 0.14 g, 6.90 mmol) in 50 ml of dry THF under nitrogen cooled to 0 °C was added the alcohol (A78) (1.17 g, 2.65 mmol, in 50 ml dry THF) in a dropwise manner. After stirring for 20 min tetrabutylammonium iodide (93 mg, 0.27 mmol) and benzyl bromide (0.35 ml, 2.92 mmol) were added and the mixture subsequently stirred at room temperature for 14 h. T.l.c (3:2 ether/hexane) showed no starting material (Rf 0.3) and one major product (Rf 0.9). The solvents were removed and the residue coevaporated with benzene, before purification by flash chromatography (3:7 ether/hexane). This afforded the benzyl ether (A79) in 78% yield (1.09 g), as a colourless syrup. ^{1}H NMR 1.90 (9H, s, CMe_3), 1.33, 1.42 (3H, s, Me), 3.57 (2H, m, 1/1^a-H), 3.95 (2H, m, 6/6^a-H) 4.23 (2H, m, 2/5-H), 4.55 (2H, m, $ArCH_2$), 4.80 (2H, m, 3/4-H), 7.20 to 7.80 (15H, m, Ar-H); m/z (DCI, NH_3) 550 ($M+NH_4^+$, 60%), 91 (100).

2,5-Anhydro-6-*O*-benzyl-3,4-isopropylidine-D-talitol (A80).

To the silyl ether (A79) (1.08 g, 2.05 mmol) in THF (80 ml) was added tetrabutylammonium fluoride (1M soluotion in THF, 2.55 ml). After stirring at room temperature for 2 h completion was apparent by t.l.c. (Silyl ether Rf 0.8, 2:5 ether/hexane, prod Rf 0.05). The solvent was removed *in vacuo* and the residue purified by flash chromatography, to yield the alcohol (A80) as a colourless syrup (0.54 g, 90%). $[\alpha]_D^{20}$ -14.8° (*c*, 0.81, chloroform); 1H NMR ($CDCl_3$) 1.33, 1.41 (3H, s, Me), 2.30 (1H, brs, OH), 3.58 (2H, dd, 1/1^a-H), 3.87 (2H, m, 6/6^a-H) 4.22

(2H, m, 2/5-H), 4.50 (2H, m, $ArCH_2$), 4.81 (2H, m, 3/4-H), 7.35 (5H, m, Ar-H); m/z (DCI, NH_3) 294 ($M+H^+$, 95%) 312 ($M+NH_4^+$, 100); (Found C, 65.23; H, 7.89; $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.54%).

6-*O*-Benzyl-1-*E*-*C*-(carbomethoxymethylene)-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-talitol (A82)

To a solution of dimethyl sulphoxide (1.16 g, 15 mmol) in dry dichloromethane (50 ml) at -78 °C was added oxalyl chloride (0.65 ml, 7.5 mmol). This was stirred at that temperature for 10 min, then the alcohol (A81) was added in 50 ml of dichloromethane, and the combined solutions stirred for a further 10 min. Triethylamine (4.12 ml, 30 mmol) was then added, and after a further 15 minutes at -78 °C the stabilized ylid (A49) (3.75 g, 11 mmol) was added. The solution was allowed to warm to room temperature and kept there for 4 h. T.l.c. then showed only two spots, the two geometric *enoates* (A82) (Rf 0.6 and 0.5, 2:1 ether/hexane). These were partially separarted by flash chromatography to afford the *E* isomer as a white solid on crystallization from ether (Combined yield, about 1:1 ratio, 0.97 g, 78%). M.p. 54/55 °C, $[\alpha]_D^{20}$ -78.0° (*c*, 0.41, chloroform), ν_{max} 1 720 and 1 680 cm^{-1}; 1H NMR ($CDCl_3$), 1.37, 1.46 (3H, s, Me), 3.61 (2H, m, 6/6a-H), 3.75 (3H, s, OMe), 4.26 (1H, m, 5-H), 4.54 (1H, dd, CH_2Ph) 4.84 (3H, m, 2/3/4-H), 6.14 and 6.97 (each 1H, dd, *J* 15.8 Hz, olefinics), 7.32 (5H, m, Ar-H); (N.b. 5.93 and 6.32, dd, *J* 11.7 Hz, *Z*); ^{13}C NMR 26.13, 25.13 (q, Me) 51.50 (q, OMe), 71.80, 73.65 (t, 6-C, and CH_2Ph), 81.64, 82.94, 83.23, 83.48 (d, 2/3/4/5-C), 112.97 (s, acetonide), 122.17 (d, a-CH), 127.52, 127.82, 128.49 (d, Ar-H), 138.05 (s, Ar), 143.02 (d, b-CH), 166.54 (s, C=O); m/z 349 ($M+H^+$, 100%), 312 ($M+NH_4^+$, 25); (Found C, 65.46; H, 6.98; $C_{19}H_{24}O_6$ requires, C, 65.50; H, 6.94%).

Dimethyl-2-methoxycarbonyl-3-(5'-benzyyl-2',3'-*O*-isopropyilidene-α-D-ribofuranosyl)-pentane-1,5-dioate (A83)

To a solution of dimethyl malonate (0.14 ml, 0.90 mmol) in dry THF cooled to -50 °C under nitrogen was added a solution of n-Butyl lithium in hexane (1.6 N, 0.96 ml). This was stirred for 20 min after which a solution of the diasteromeric enoates (A67) (105 mg, 0.30 mmol) was added in 5 ml of dry THF. The temperature was allowed to rise to room temperature, a condensor fitted, and the mixture subsequently refluxed for 22 h. After this time had elapsed only a trace of starting material remained (Rf 0.5) with one major product (Rf 0.4). The reaction was quenched with 5 ml of 1M aqueous KH_2PO_4. This was extracted with 3x 10 ml portions of chloroform, which were combined, washed with brine, dried, and evaporated. The mixture was purified by flash chromatography (1:4 ether/hexane eluant) to give the *triester* (A69) as a colourless oil, which was a mixture of the possible diastereomers by NMR (37.4 mg, 26%). ν_{max} 1 735 cm^{-1}; ^1H NMR 1.30, 1.45 (3h, s, Me), 2.75 (2H, m, 4/4^a-H), 3.20 (1H, m, 3-H), 3.55 (2H, m, 5'/5'^{a}-H), 3.70, 3.80, 3.85 (3H, s, OMe), 4.00 (1H, d, 2-H), 4.20 (2H, m, 1'/4'-H), 4.80 (2H, m, 2'/3'-H), 7.37 (5H, m, Ar-H); m/z 481 ($M+H^+$, 100%), 498 ($M+NH_4^+$, 10).

Dimethyl--3-(5'-benzyl-2',3'-O-*i*sopropyilidene-α-D-ribofuranosyl)-pentane-1,5-dioate (A84)

To a solution of the triester (A83) (37.0 mg) in dimethyl sulphoxide (5 ml) was added 1 drop of brine. This mixture was heated at 160 oC for 5h when t.l.c. (1:1 ether /hexane) revealed absence of starting material (Rf 0.2), and one product (Rf 0.3). The solvent was then removed by high vacuum rotary evaporation and the residue partitioned between chloroform and water (10 ml of each). The chloroform was

washed with brine, dried, and evaporated, leaving a caramel which was purified by flash chromatography, giving a colourless syrup (15.0 mg, 48%). $[\alpha]_D^{20}$ -15.8° (*c* 0.53, chloroform); ν_{max} (Film) 1 735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.32, 1.50 (3H, s, Me), 2.28 to 2.50 (5H, m, 2/2a/3/3a-H), 3.50 (2H, d, 5'/5'a-H), 3.64, 3.65 (3H, s, OMe), 4.05 (1H, dd, $J_{1',2'}$ 3.7 Hz, 1'-H), 4.16 (1H, t, 4'-H), 4.50 (2H, m, CH_2Ph), 4.70 (1H, dd, $J_{2',3'}$ 6.1 Hz, 2'-H), 4.77 (1H, dd, 3'-H), 7.32 (5H, m, Ar-H); ^{13}C NMR 25.04 (q, Me), 26.33 (q, Me), 34.59, 35.09 (t, 3/5-C), 32.79 (d, 4-C), 51.41, 51.48 (q, OMe), 70.92, 73.47 (t, 5'-C, CH_2Ph), 81.26, 82.60, 82.61, and 83.32 (d, 1'/2'/3'/4'-C), 112.45 (s, acetonide), 127.46, 129.67, 128.43 (d, Ar-H), 138.02 (s, Ar), 172.80 and 173.07 (s, C=O); m/z (DCI, NH_3) 440 ($M+NH_4^+$, 32%), 423 ($M+H^+$, 100%).

References, Section A.

1 M.J. Wanner, N.P. Willard, G-J Koomen and U.K. Pandit, *J. Chem. Soc., Chem. Commun.,* 1986, 396.

2 a) M.K. Hargreaves, J.G. Prichard and H.R. Dave, *Chem. Rev.,* 1970, **70**, 439; b) O.H. Wheeler and O. Rosado, in 'The Chemistry of Amides,' S. Patai and J. Zabicky Eds, Wiley, New York, 1970, p. 335.

3 a) G.B. Hoey and C.T. Lester, *J. Am. Chem. Soc.,* 1951, **73**, 4473; b) B.C. Lawes, *ibid.,* 1960, **83**, 6413; c) H.k. Hall Jr. and A.K. Schneider, *ibid.,* 1958, **80**, 6409; d) W. Schneider and H. Goetz, *Arch. Pharmaz.,* 1961, **294**, 506.

4 a) D.D. Phillips, M.A. Acitelli and J. Meinwald, *J. Am. Chem. Soc.,* 1957, **79**, 3517; b) G. Paris, L. Berlinquet and R. Gaudry, *Org. Syn.,* 1963, **4**, 496; c) I. Murakoshi, E. Kidoguchi, M. Nakamura, J. Haginiwa, S. Ohmiya, K. Hiashiyama and H. Otsumata, *Phytochem.,* 1981, **20**, 1725.

5 G.W.J. Fleet and T.K.M. Shing, *J. Chem. Soc., Chem. Commun.,* 1984, 835.

6 A.P. Krapcho, *Synthesis,* 1982, 805, 893.

7 T. Kinoshita, K. Okamato and J. Clardy, *Synthesis,* 1985, 402.

8 F. Matsuda, M. Kawasaki and S. Terashima, *Tetrahedron Lett.,* 1985, **26**, 4639.

9 F. Matsuda and S. Terashima, *Tetrahedron Lett.,* 1986, **27**, 3407.

10 T. Kometani, T. Fitz and D.S. Watt, *Tetrahedron Lett.,* 1986, **27**, 919.

11 M. Shibuya, *Heterocycles,* 1985, **23**, 61.

12 R.H. Schlessinger and J.L. Wood, *J. Org. Chem.,* 1986, **51**, 2621.

13 A.S. Bailey and R. Robinson, *J. Chem. Soc.,* 1950, 1375.

14 W.R. Roush and M.R. Michaelides, *Tetrahedron Lett.,* 1986, **27**, 3353.

15 J.C. Bottaro and E.A. Berchtold, *J. Org. Chem.,* 1980, **45**, 1176.

16 M.J. Wanner, G-J Koomen and U.K. Pandit, *Heterocycles,* 1984, **22**, 1483.

17 M.J. Wanner, N.P. Willard, G-J Koomen and U.K. Pandit, *Tetrahedron,* 1987, **43**, 2549.

18 G. Sacripante, C. Tan and G. Just, *Tetrahedron Lett.,* 1985, **26**, 5643.

19 R.J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley-Interscience, New York, 1970.

20 S. Nakamura and H. Kondo, *Heterocycles,* 1977, **8**, 583.

21 R.J. Suhadolnik, 'Nucleoside as Biological Probes,' Wiley, New York, 1979.

22 S. Hanessian and A.G. Pernet, *Adv. Carbohydr. Chem. Biochem.,* 1976, **33**, 111.

23 a) B.K. Bhattacharya, M.I. Lim, B.A. Otter and R.S. Klein, *Tetrahedron Lett.,* 1986, **27**, 815; b) S Nitsuma, K. Kato, T. Takita and H. Umezewa, *Ibid.,* 1985, **26**, 5785.

24 A.G.M. Barrett, H.B. Broughton, S.V. Attwood and A.A.L. Gunatilika, *J. Org. Chem.,* 1986, **51**, 495, and cited references.

25 J.G. Buchanan, *Prog. Chem. Nat. Prod.,* 1983, **44**, 243.

26 J. Goodchild, 'The Biochemistry of Nucleoside Antibiotics,' in "'Topics in Antibiotic Chemistry,' P.G. Sammes, Ed., E. Horwood, Chichester, 1982, p. 99.

27 G.W.J. Fleet and L.C. Seymour, *Tetrahedron Lett.,* 1987, **28**, 3015.

28 a) G.W.J. Fleet, M.J. Gough and T.K.M. Shing, *Tetrahedron Lett.,* 1984, **25**, 4029; b) G.W.J. Fleet and P.W. Smith, *Tetrahedron,* 1987, **43**, 979.

29 F. Mahmoud, E. Sayed Ahmed, S. David and J-M, Vatele, *Carbohydr. Res.,* 1986, **155**, 19.

30 T.D. Inch, *Tetrahedron,* 1984, **40**, 3161.

31 S. Czernecki, C. Georgoulis and C. Provelenghiou, *Tetrahedron Lett.,* 1976, **17**, 3535.

32 M.L. Wolfrom and S. Hanessian, *J. Org. Chem.,* 1962, **27**, 1800.

33 E.D. Bergmann, D. Ginsburg and R. Pappo, *Org. React.,* 1959, **10**, 179.

34 A.E. Derome, 'Modern NMR Techniques for Cheistry Research,' Pergamon, Oxford, 1987, p. 233.

35 M.H. Park, R. Takeda and K. Nakanishi, *Tetrahedron Lett.*, 1987, **28**, 3823.

36 T.W. Greene, 'Protective Groups in Organic Synthesis,' Wiley, New York, 1981.

37 N.K. Richtmeyer in 'Methods in Carbohydrate Chemistry,' R.L.Whistler and M.L. Wolfram, Eds, Academic Press, New York, 1962, **I**, p.105.

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

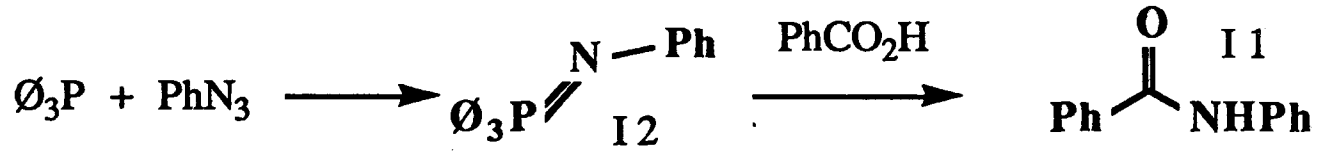
Section A1

Synthesis of N-substituted glutarimides from azides.

Introduction

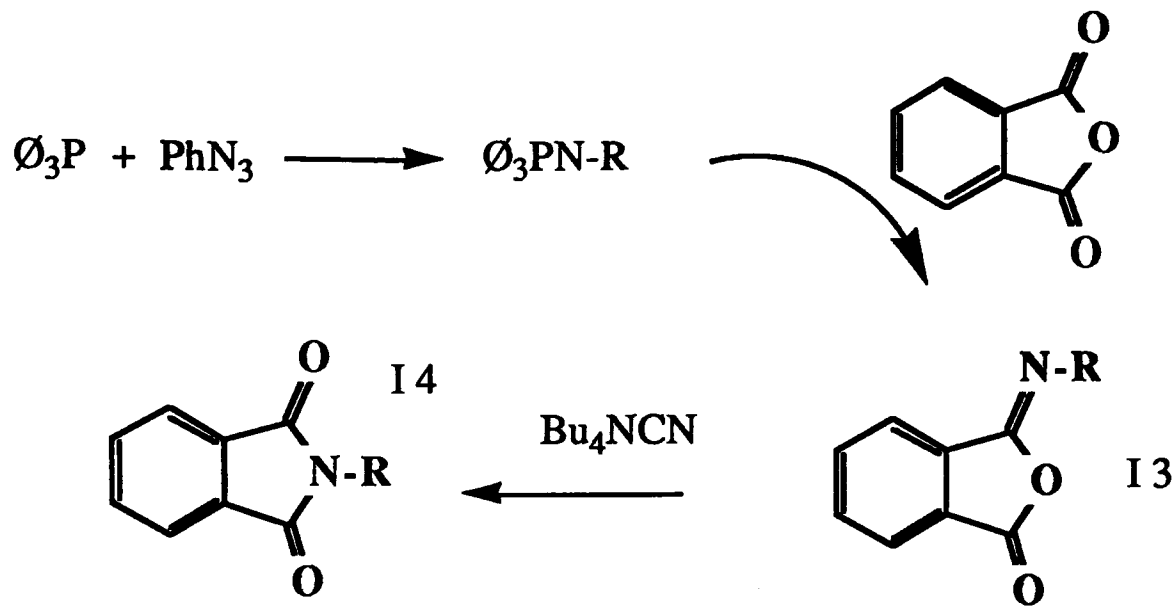
At the outset of the project one of the areas of investigation was to have been consideration of novel mild methods of glutarimide closure. This was somewhat precluded by the activity towards the synthesis of sesbanimide.

An original idea had been to approach the synthesis of a glutarimide by reaction of a glutarate derivative, a diester or the anhydride, with an iminophosphorane. The formation of the latter type of compound, from triphenylphosphine and an azide, has been a well-studied reaction.[1] From such an intermediate the formation an amide (I 1), by reaction of benzoic acid with the iminophosphorane (I 2) derived from phenyl azide, has been reported.[2]



The publication by Garcia and co-workers[3] of their novel method of introducing substituted amines was the prompt for an attempt to be made.

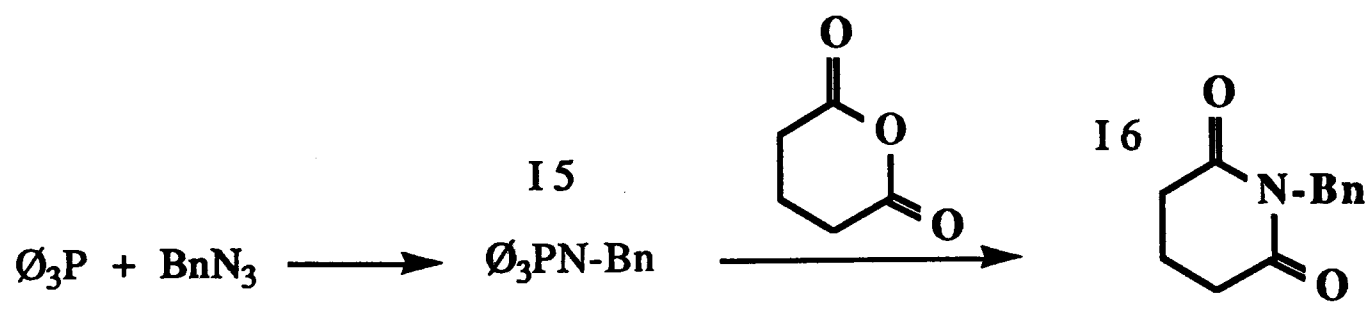
The Garcia method was to take an azide (a variety were quoted in the paper) and to react this with triphenylphosphine in dry dichloromethane to form the iminophosphorane. The addition to this of freshly sublimed phthalic anhydride resulted in the formation of the *iso*imide (I 3), which in the presence of tetrabutylammonium cyanide was isomerised to the phthalimide (I 4). This was accomplished in good yields for a number of different azides. Its versatility as a general method of introducing a protected primary amine function was demonstrated by the facile deprotection to the free amine using hydrazine.



Results and Discussion

The synthesis of *N*-Benzyl Glutarimide was achieved by this reaction.

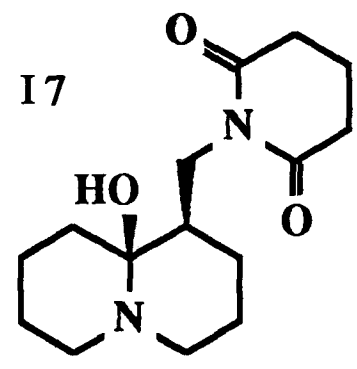
On treatment of a solution of benzyl azide in dichloromethane with triphenylphosphine vigorous evolution of nitrogen was observed. This was due to the formation of the iminophosphorane (I 5). Glutaric anhydride and tetrabutylammonium cyanide were added to this, and the only product ever isolated was the required *N*-Benzyl Glutarimide (I 6). The procedure was never properly quantified: 71% was the highest yield isolated, although typically 50 to 55% resulted from the various reaction times and equivalents of reagents employed. A similar yield of the glutarimide was isolated when the procedure was repeated without the cyanide.



The best evidence for the identity of the compound (I 6) was shown by ^{13}C NMR: the symmetry of the glutarimide ring resulted in it only exhibiting 3 peaks in the broadband decoupled spectrum.

Interest in this reaction was somewhat curtailed by other developments in the project. This work may yet prove more productive since *N*-substituted glutarimides are not unknown in nature, the lupinine alkaloid lamprolobine (I 7) and structural relatives have recently been characterized.[4]

I 7



Experimental

To a solution of benzyl azide (266 mg, 2.0 mmol) in dry dichloromethane at room temperature under nitrogen, was added triphenylphosphine in 2 ml of the same solvent. This was accompanied by the vigorous evolution of a gas. To this solution was added freshly recrystallized glutaric anhydride (114 mg, 1.0 mmol) and tetrabutylammonium cyanide (27.0 mgs, 0.1 mmol) in a further 2 ml of dichloromethane. The mixture was stiired for 14 h, when t.l.c. (neat dichloromethane) showed only one product (Rf 0.6). The mixture was evaporated and columned with neat dichloromethane to yield *N-Benzyl Glutarimide* (I 6) as an oil, which crystallized on standing. M.p. 48-49 ^{o}C; ν_{max} (film) 1 720, 1 680 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) 1.95 (2H, q, 4-CH_2), 2.60 (4H, t, 3/5-CH_2), 4.90 (2H, s, CH_2Ph), 7.25 (5H, m, Ar-H); ^{13}C NMR 17.03 (t, 4-C), 32.84 (t, 3/5-C), 47.62 (t, CH_2 Ph), 126.88, 128.28, 129.15 (d, Ar-C), 137.31 (s, Ar-C), 172.33 (s, C=O); m/z (EI) 203 (M^+, 100%); (found C, 70.65; H, 6.46; N, 7.11: $C_{12}H_{12}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%)

References

1 a) Y.G. Gololobov, I.N. Zhmurova and L.F. Kasukhin, *Tetrahedron,* 1978, **37**, 437; b) R.A. Abramovitch and E.P. Kyba, in 'The Chemistry of the Azide Group,' S. Patai, Ed., Interscience, New York, 1971, p.294.

2 L. Horner and A. Gross, *Annalen.,* 1955, **591**, 117.

3 J. Garcia, J. Vilarrasa, X. Bordas and A. Banaszek, *Tetrahedron. Lett.,* 1986, **27**, 639.

4 K.A. Asres, W.A. Gibbons, J.D. Phillipson and P. Mascagni, *J. Nat. Prods.,* 1986, **49**, 117.

Section B

Synthesis and Reactions of an Activated Substituted Glutarimide.

Summary, Section B.

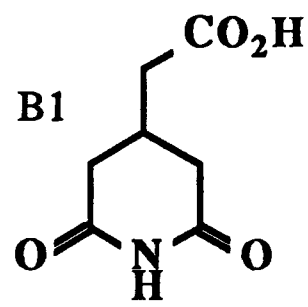
This section of the thesis develops methods for the synthesis of 4-substituted glutarimides starting from a precursor which has a reactive centre on the chain extension from glutarimide. This is a development of the chemistry which has been used in the synthesis of cycloheximide and its structural relatives. To this end a substituted ylid was formed and characterized.

Starting from the ylid, a number of different substituted glutarimides were formed by Wittig chemistry. Many of these products had appropriate substitution for further elaboration, formation of simple heterocyclic compounds attached to glutarimide illustrated this. Using a carbohydrate-derived aldehyde in a Wittig reaction resulted in an approach to a glutarimide attached to a shikimate-type residue.

INTRODUCTION

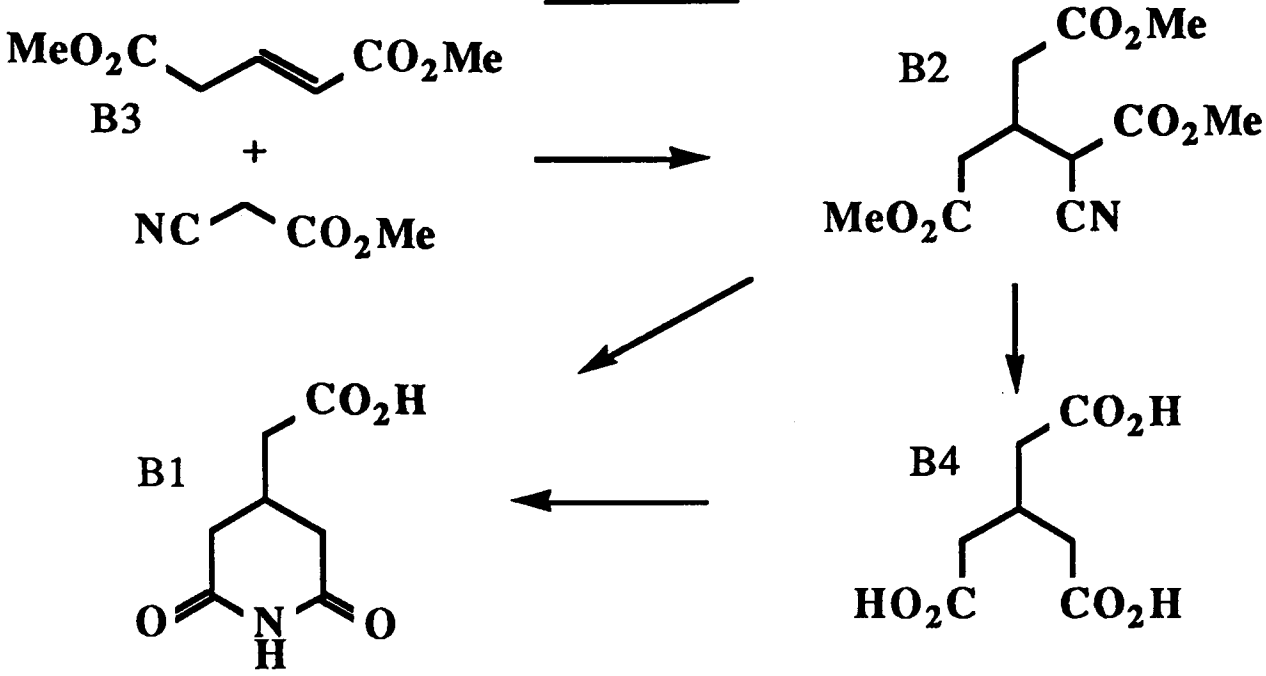
Previous synthetic work using substituted glutarimides

In common with their biological actions, the chemistry of the glutarimide antibiotics, and indeed their analogues and homologues too, has been well studied and documented.[1] The key compound common to all of the synthetic work in the area is the glutarimide (B1) attached through C-4 to acetic acid.



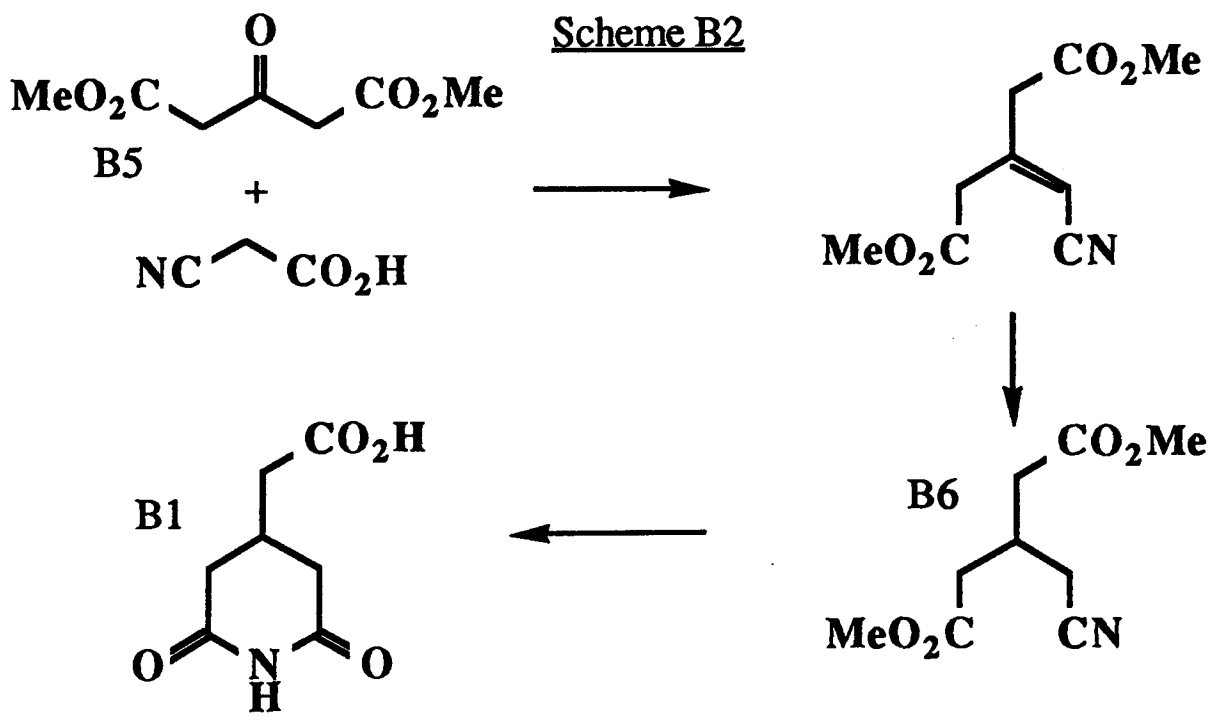
4-(Carboxymethyl)-glutarimide (B1) was first prepared by Phillips, Acitelli, and Meinwald[2] *via* the intermediate (B2), the product from the Michael addition of methyl cyanoacetate to dimethylpentenedioate (B3). Controlled acid hydrolysis of (B2), a somewhat capricious reaction, produced low yields of (B1). This procedure was somewhat improved upon by Lawes,[3] who hydrolysed (B2) to methane triacetic acid (B4), which gave better yields of (B1) on pyrolysis of its ammonium salt (Scheme B1).

Scheme B1

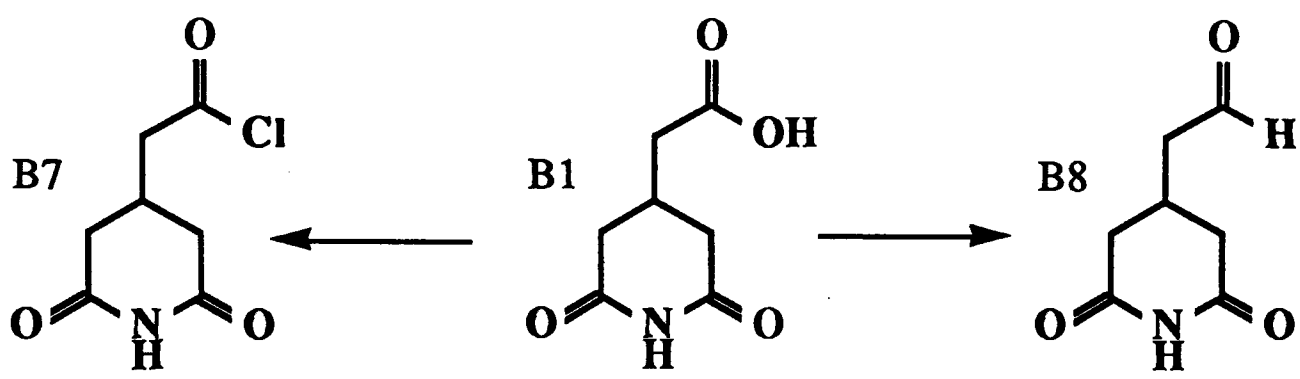


Independent work by Johnson[4] and Egawa[5] afforded (B1) in both increased and more consistent yields. The key step was the Cope condensation between dimethylacetonedicarboxylate (B5) and cyanoacetic acid; which, on hydrogenation of the intermediate olefin, gave the saturated nitrile (B6) in good overall yield. On boiling (B6) with aqueous acid the required glutarimide (B1) was thus formed in high yield, and on a large scale (Scheme B2).

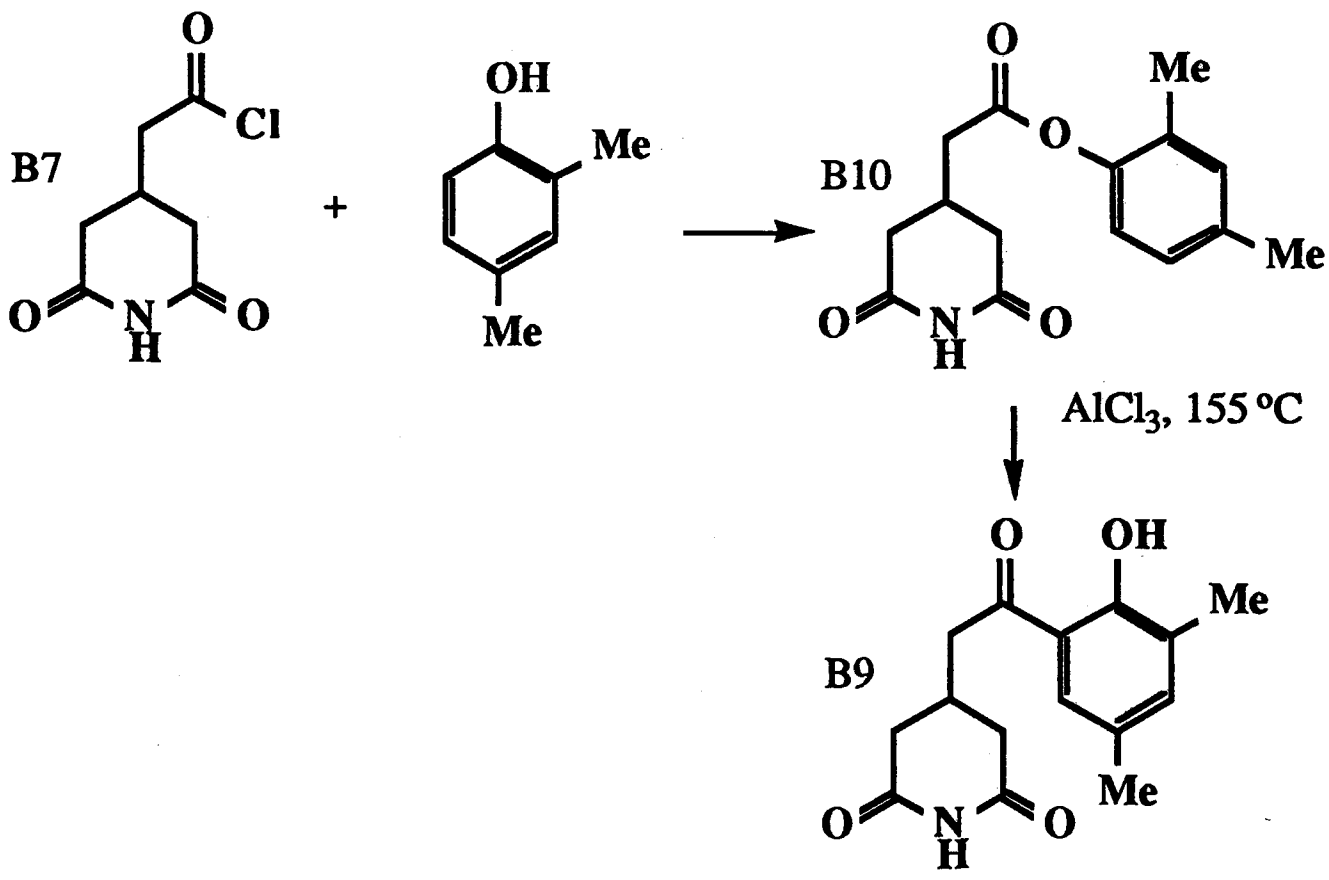
Scheme B2



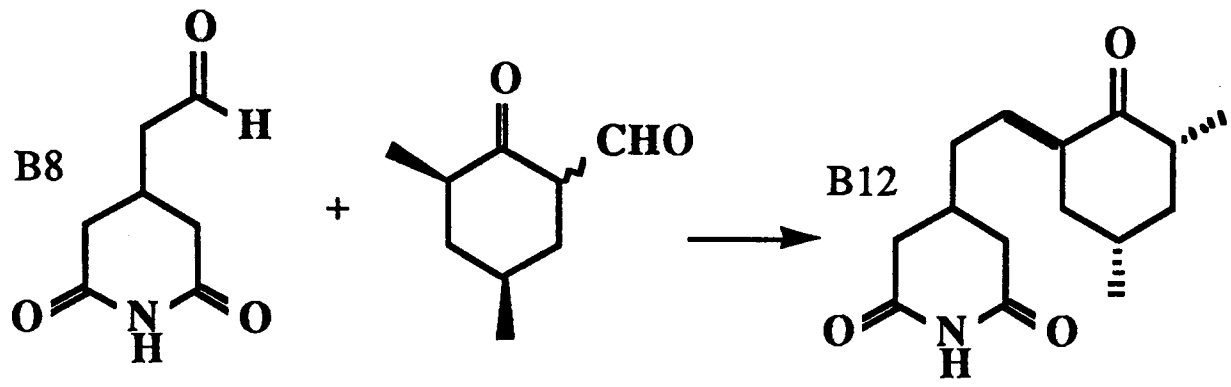
The utility of the acid (B1) as a synthetic reagent was realized by its ready conversion by treatment with thionyl chloride to its acid chloride (B7), and to the corresponding aldehyde (B8) by catalytic reduction.[2]



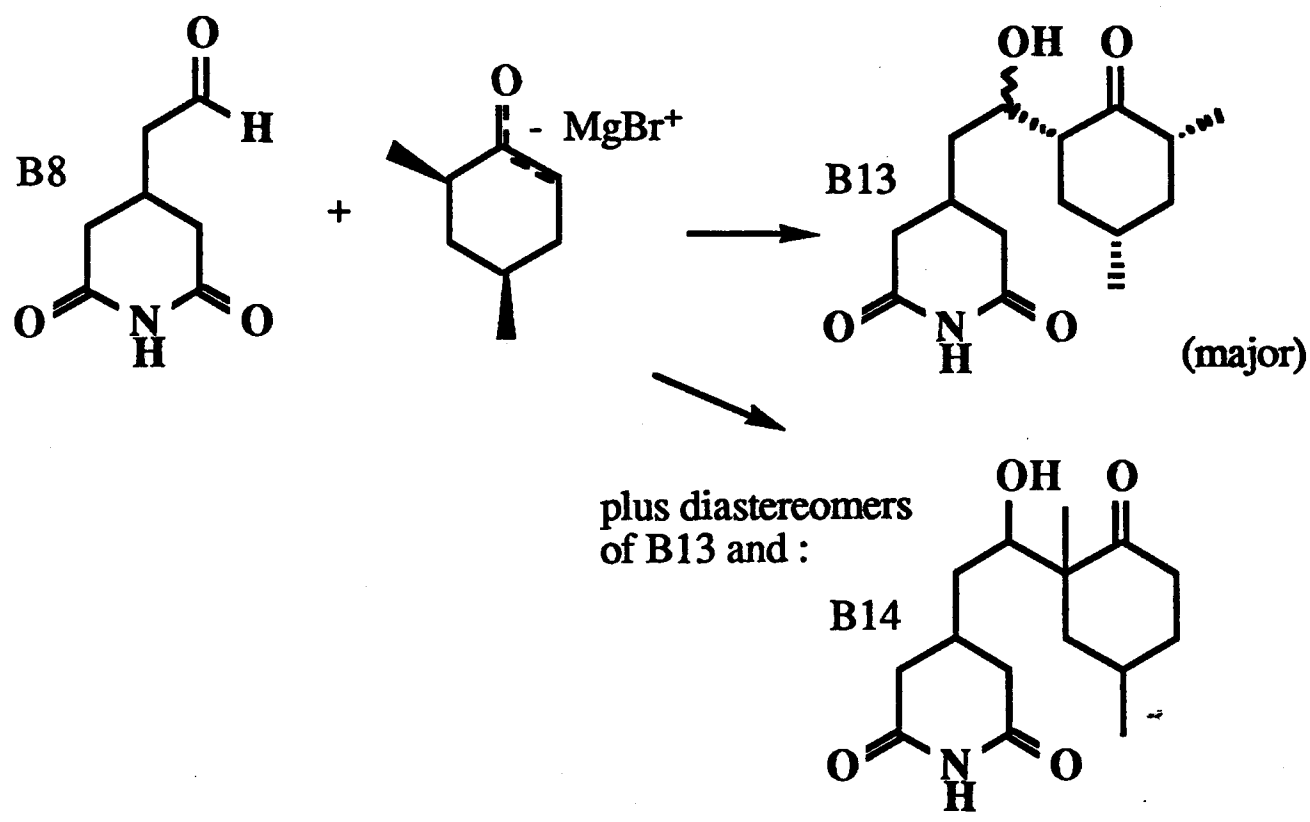
Johnson[4] reported the synthesis of the naturally-occuring actiphenol (B9) *via* a Fries rearrangement of the ester (B10), prepared by acylation of 2,4-dimethylphenol with the acid chloride (B7).



The use of the aldehyde (B8) as a synthon for cycloheximide (B11) and its structural relatives was first shown by Lawes,[3] who synthesised anhydroisocycloheximide (B12) by condensing (B8) with 2-hydroxymethylene-2,4-dimethylcyclohexanone in an aldol reaction driven by potassium carbonate.

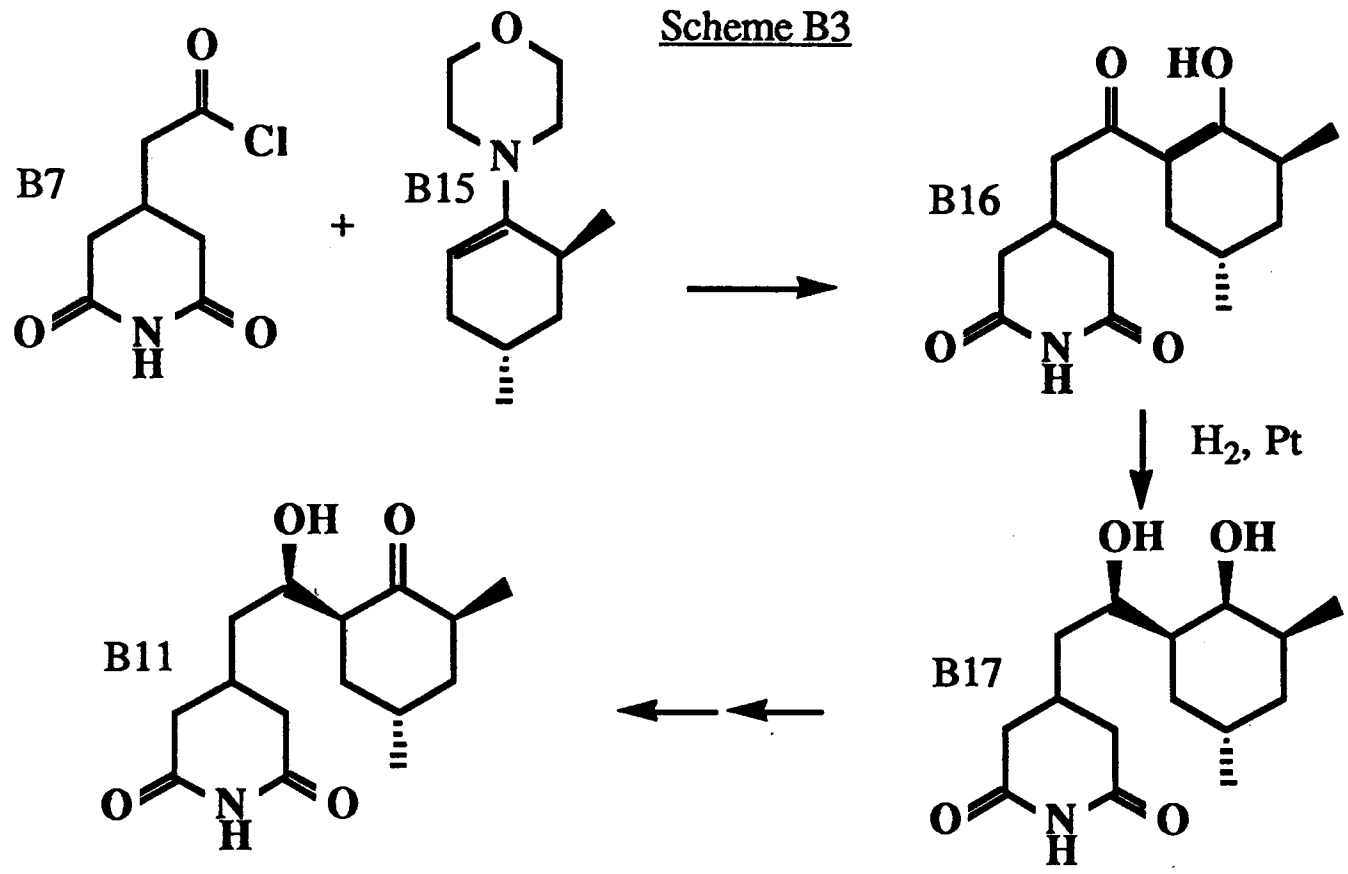


The successful synthesis of (B12) led to the synthesis of cycloheximide diastereomers by using metal-mediated condensations; Johnson[6] and Egawa[7] independently published the synthesis of neocycloheximide (B13). This was the major isolated product of the Nielsen condensation between the aldehyde (B8) and the bromomagnesium salt of *cis*-2,4-dimethylcyclohexanone; other products were shown to be either diastereomers of (B13) or to be based upon the *gem*-cycloheximide structure (B14).



The total synthesis of cycloheximide itself was to prove rather more tricky, since stereospecifically controlled ways of intoducing functionality were required. In their approach Johnson and co-workers[8] used the enamine (B15) as a key chiral intermediate, affording (B16) with the correct stereochemistry as a result of acylation by the acid chloride (B7). Reduction by catalytic hydrogenation led to the diol (B17), which possessed the same stereochemistry as cycloheximide (B11) itself. Elaboration to the target was accomplished by selective protection of the acyclic alcohol, followed by oxidation and subsequent deprotection (Scheme B3).

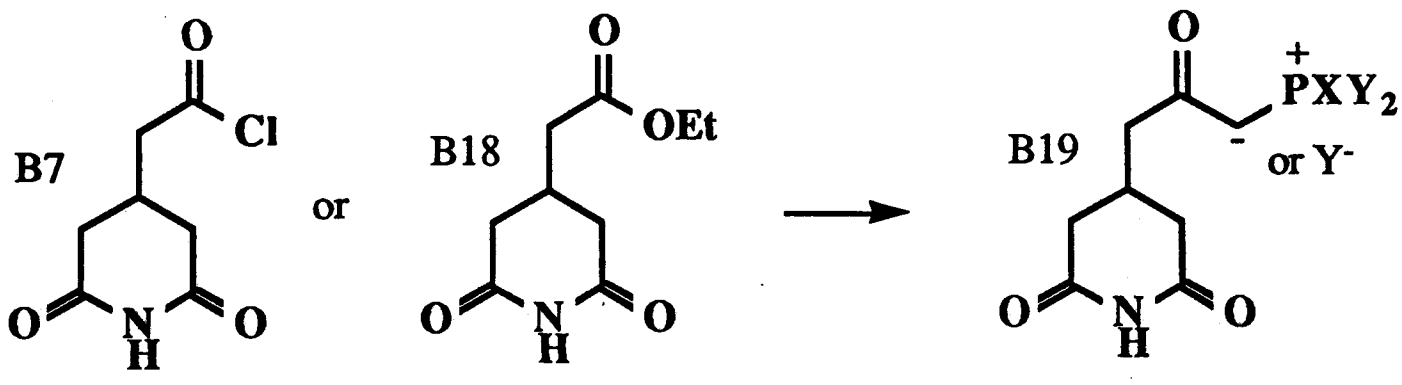
Scheme B3



The type of chemistry described is typical of that pursued in the synthesis of these antibiotics; Johnson's paper[1] provides a good review of this work. The potency of some of these antibiotics, which is somewhat negated by their broad spectrum of action, has led to the synthesis of many analogues in the search for a more desirable spectrum of activity; relatively recent work on the synthesis of various new diastereomers of cycloheximide[9] and streptovitacin,[10] using modified aldol chemistry with various chiral cyclohexanones, illustrates the continued interest in this field.

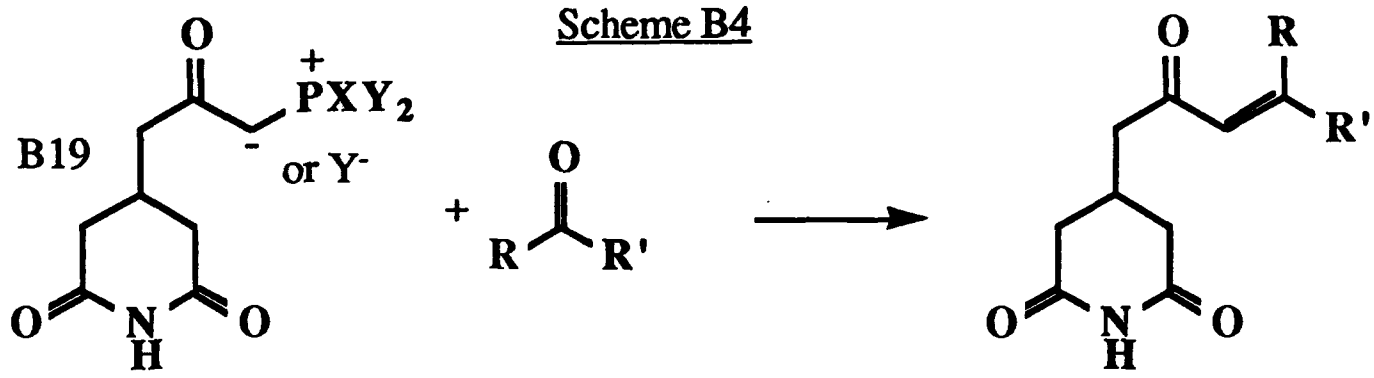
Development of Novel Activation.

In the work discussed so far it has been illustrated that by forming a glutarimide with an activated side-chain at the beginning of a synthesis, further relatively simple chemistry can give rise to interesting compounds. In forming the glutarimide at such a stage, the reaction can then be achieved on a large scale and in good yields despite the harsh conditions required. Since the resulting compounds possess the basic structural features of the cycloheximide family of antibiotics they often have interesting biological activity: by utilisation of these intermediates a range of analogues have been quite simply constructed. However since the chemistry of the acid (B1) and its derivatives has already been well studied it was decided to look for some other substitution on the side chain which would be inherently reactive towards further elaboration of the molecule by simple methods. Activation in such a potentially versatile intermediate could be derived from suitable phosphorus substitution of the side-chain. The goal of this work was thus to achieve acylation of some phosphorous stabilized anion by either the acid chloride (B7) or the corresponding ester (B18), to give a doubly stabilized intermediate corresponding to (B19).



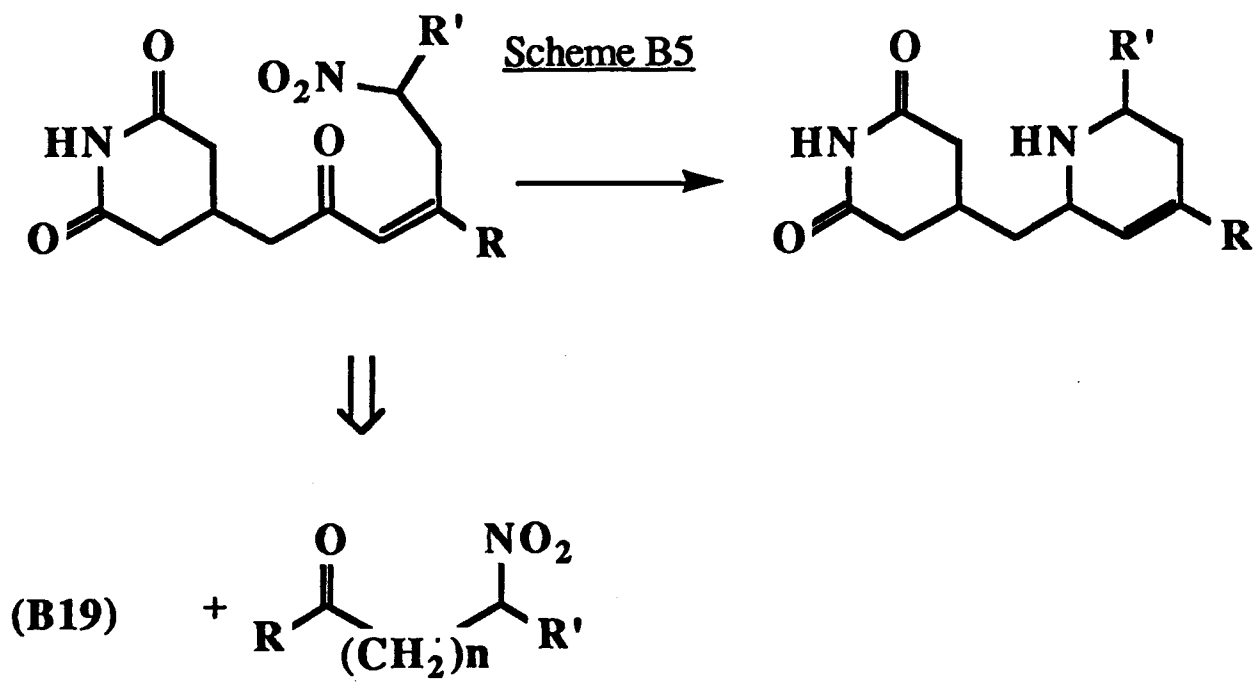
From such an intermediate Wittig[11] or Wadsworth-Emmons[12] type chemistry would be simple to execute (Scheme B4), giving rise to any number of potential adducts in one controlled step from substituted carbonyl compounds.

Scheme B4

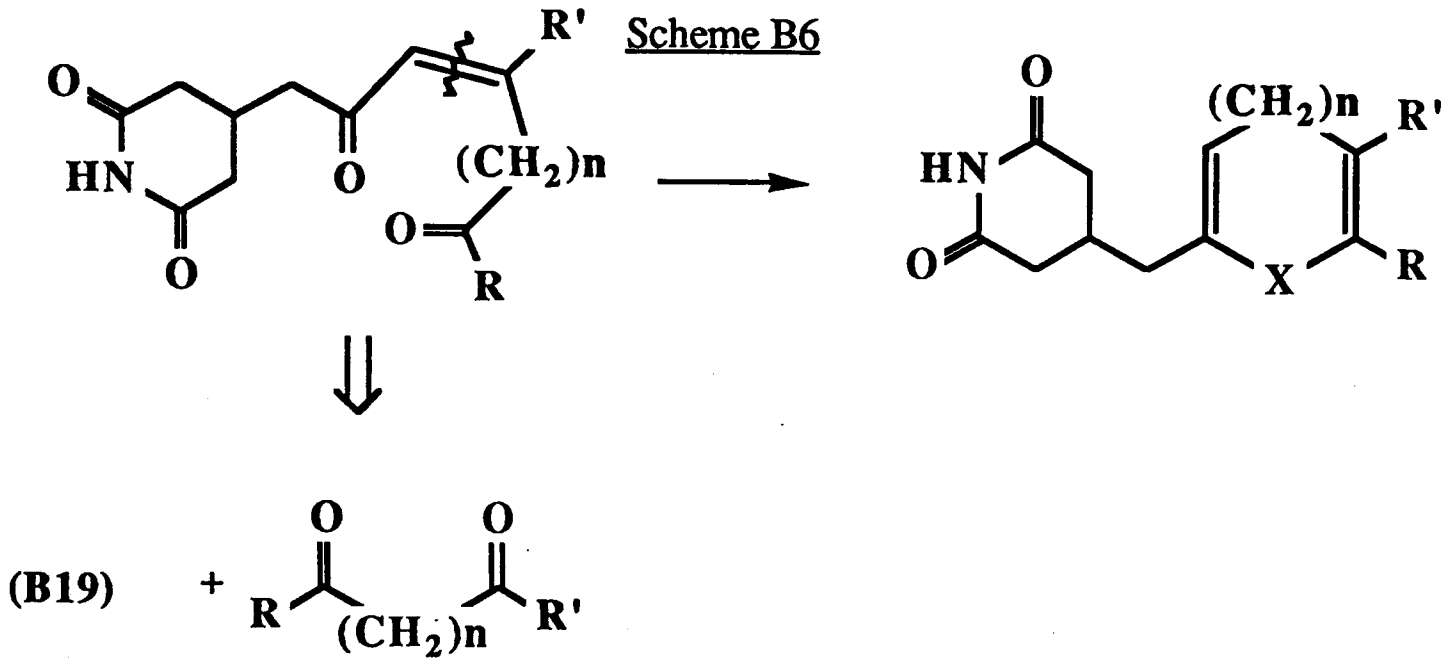


The formation by such a reaction of an α,β-unsaturated ketone, itself functionality reactive towards further substitution, demonstrates the utility of such an intermediate. For example, using the ketone functionality an intramolecular reductive amination is possible from a suitably substituted precursor (Scheme B5).

Scheme B5



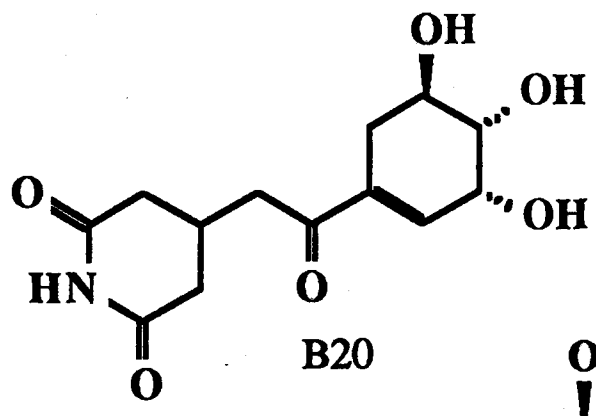
Developing the chemistry shown in Scheme B4 reaction of the ylid (B29) with suitable dicarbonyls gives rise to the possibility of forming glutarimides linked to a variety of heterocycles. The products, themselves dicarbonyls, are the classic synthons for 5 and 6 ring heteroaromatics (Scheme B6).[13]



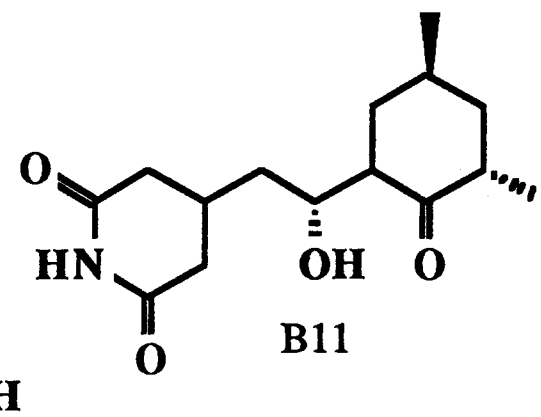
Scheme B6

(B19) +

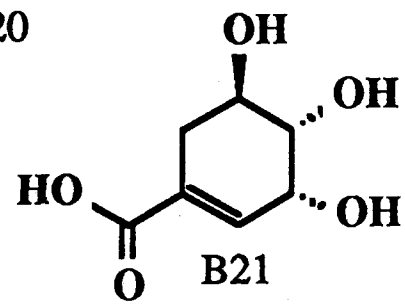
The phosphorus substitution would open up the possibility of forming the potentially very interesting glutarimide-shikimate derivative (B20), which shows some structural similarity to cycloheximide (B11). Shikimic acid is itself (B21) an important natural metabolite in the biosynthesis of aromatic amino acids and their structural relations.[14]



B20



B11

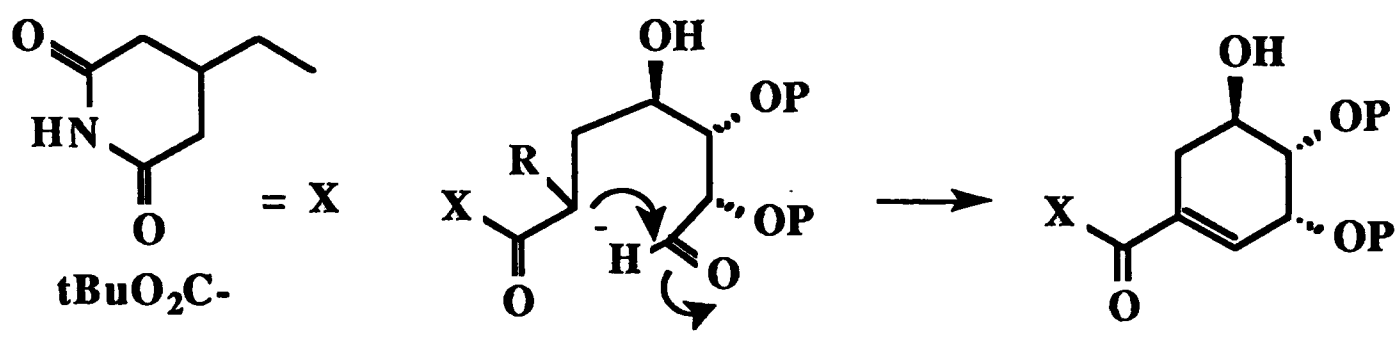


B21

The chemistry to form this compound was to be based on the key intramolecular cyclisation (Figure B1, R, unknown), of the type first published by Fleet, Shing, and Warr[15] in their enantiospecific synthesis of shikimic acid. This paper proposed general

methods for the enantiospecific synthesis of polyhydroxylated cyclohexenes: the Wadsworth -Emmons reaction[12] (R = $^{+}PO(OMe)_2$) was achieved; proposals were made for potential Wittig[11] (R = $^{+}P\emptyset_3$), Doebener[16] (R = CO_2H), and aldol[17] (R = H) chemistry. Such chemistry had been further investigated within the group by the synthesis of several diastereomers of shikimic acid.[18]

Figure B1

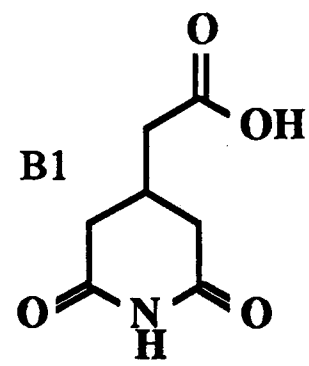


From a biological point of view even the simple olefins formed from the phosphorus-substituted compound are of potential biological interest since they possess similar structural features to the natural and synthetic glutarimides with known actions; such as a 4-substituted glutarimide ring attached to a side chain with oxygen at the 2-position. Consequently the Wittig products and their derivatives were all to be screened at Shell.

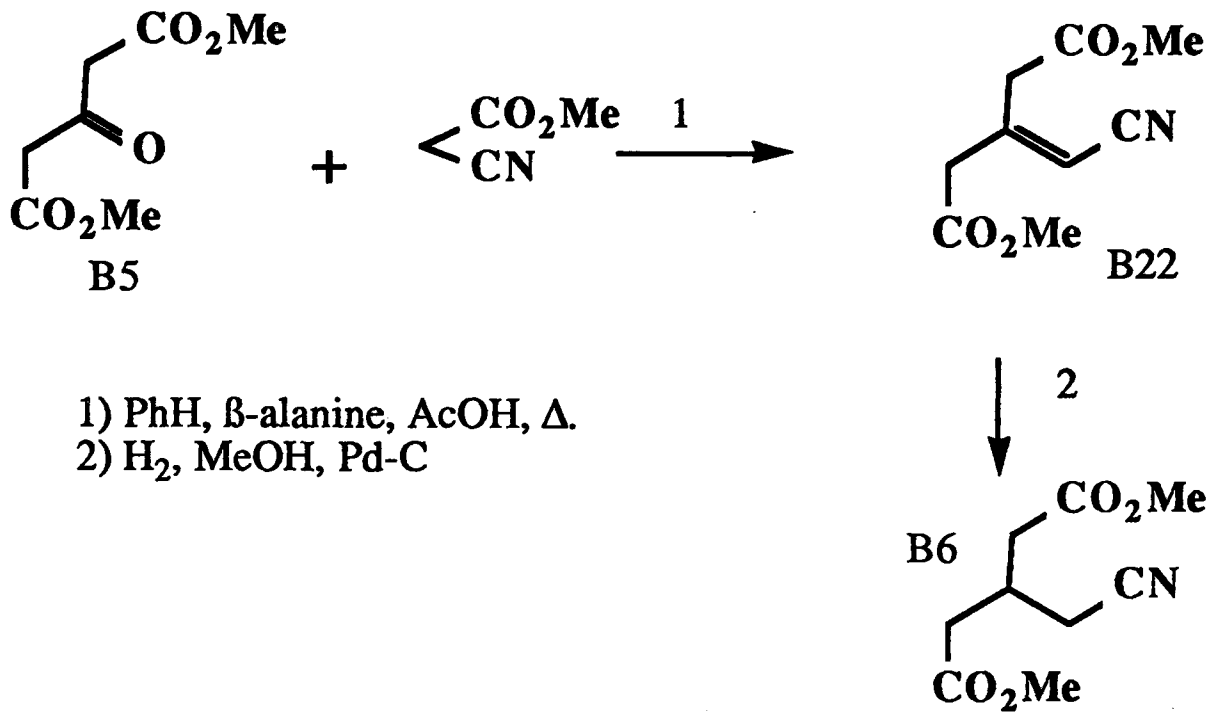
Results and Discussion

1) Synthesis of 4-(carboxymethyl)-glutarimide and Derivatives.

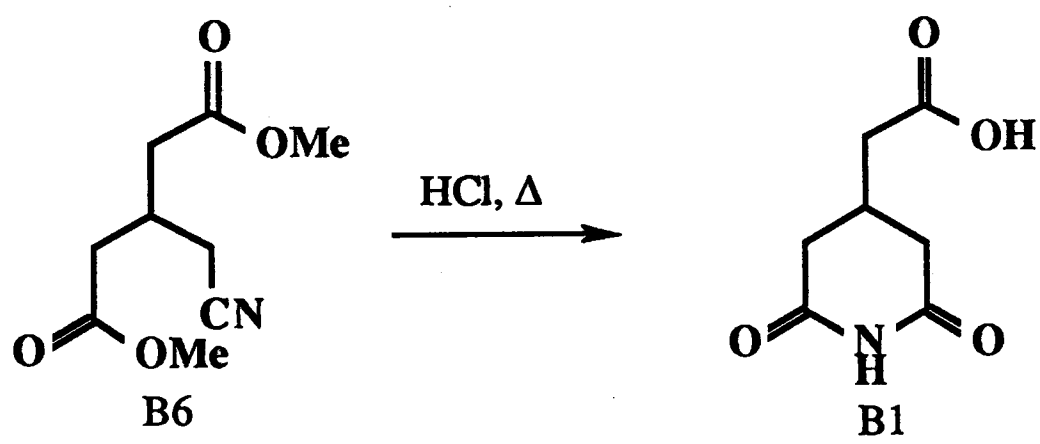
4-(Carboxymethyl)-glutarimide (B1) was readily synthesized in tens of grams by following a combination of the literature methods of Johnson[4] and Egawa;[5] this was a comparable scale to that published by the latter author, Johnson's work was on an industrial scale producing kilograms of material.



The Cope condensation between dimethylacetonedicarboxylate (B5) and cyanoacetic acid was achieved on a 100g scale by refluxing the reactants in benzene/acetic acid (10:1) with a Dean-Stark water extractor in the presence of a catalytic amount of β-alanine. The reaction was continued until no further water was being removed (20 h); after work-up, the liquid olefin (B22) was purified by distillation giving an 85% yield. Subsequent hydrogenation (50% solution in methanol, 10% palladium on charcoal catalyst) followed by filtration through a silica plug gave the saturated cyanodiester (B6) in 95% yield.

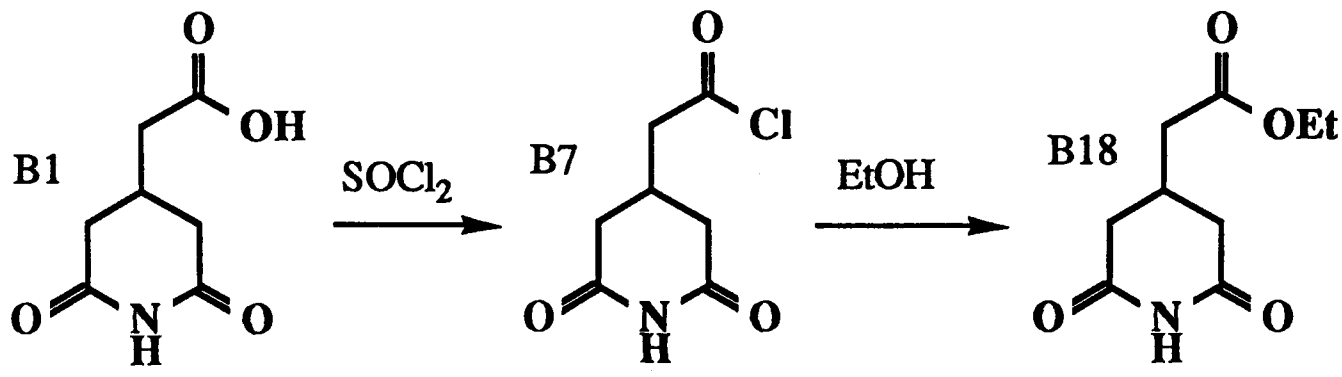


Conversion to 4-(carboxymethyl)-glutarimide (B1) was achieved by refluxing (B6) with concentrated hydrochloric acid for one hour. On removal of the solvents a white sludge resulted; this was dissolved in boiling acetone, then filtered to remove ammonium chloride impurities. After a reduction in volume, refrigerated storage yielded several crops of white cystals. Tens of grams were produced in this way in 40 to 70% yield.

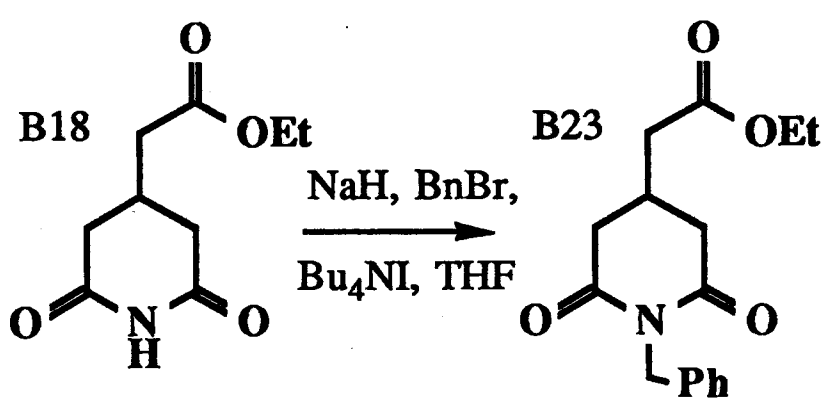


To form the acid chloride (B7) the acid was refluxed with thionyl chloride until it had all dissolved, after which the solvent was removed by rotary evaporation. This afforded a remarkably crystalline material (translucent prisms) which was washed with

a little dry benzene and used in this form; the procedure was repeated each time that the material was required. The corresponding ethyl ester (B18) was formed by stirring the acid chloride in dry ethanol at room temperature until it had all dissolved; concentration gave a white solid which was recrystallized from ethanol.

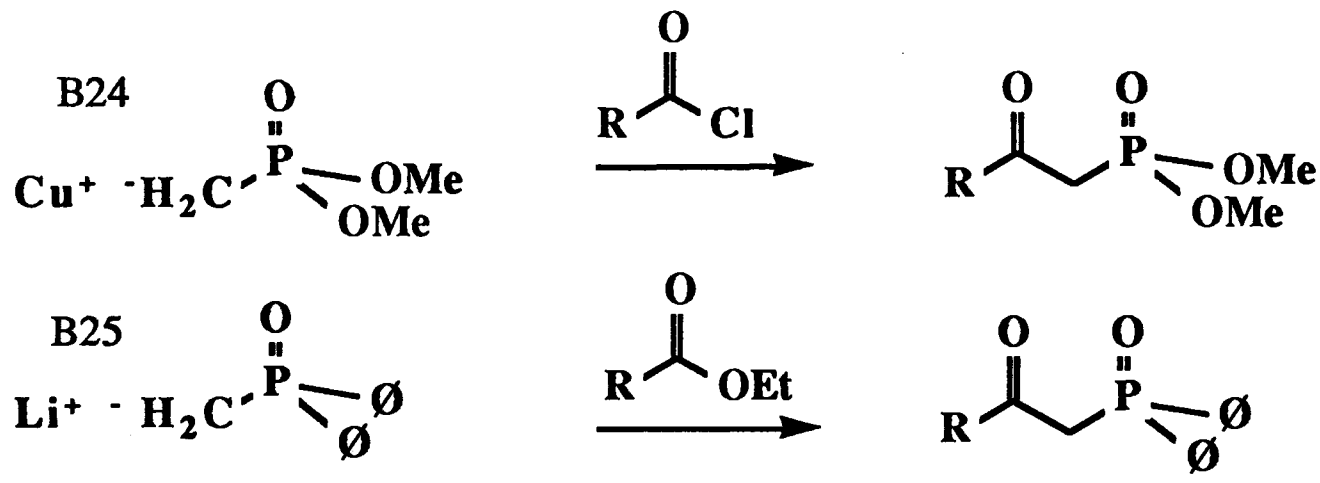


The ester (B18) was also formed with the imide nitrogen protected. This was achieved, in an unoptimised 37% yield, by deprotonation with sodium hydride and treatment with benzyl bromide, to form the *N*-benzyl glutarimide (B23).



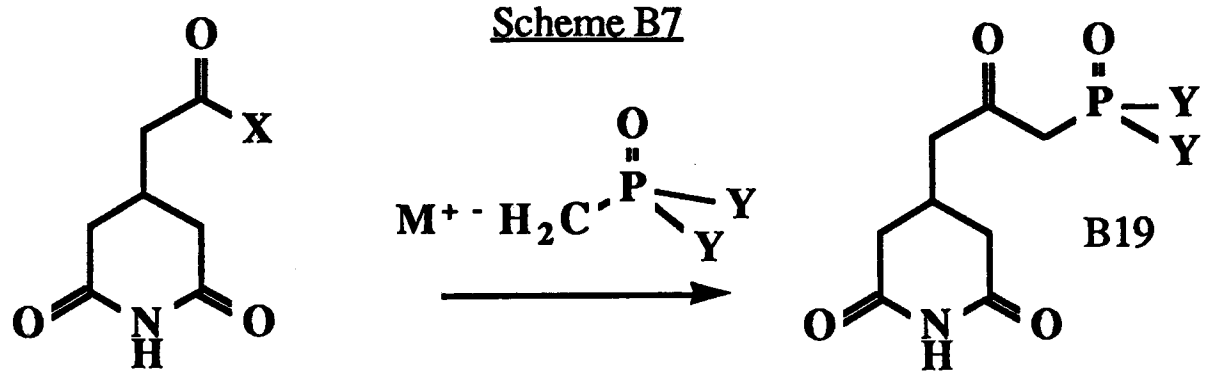
2) Formation of a glutarimide attached to a stabilized ylid.

General methods appear in the literature for the acylation of α-anions to phosphorus. These include the reaction of α-anions of phosphonates (B24) with acid chlorides, mediated by the copper (I) cation;[19] and the reaction of esters with phosphine oxides (B25), mediated by a lithium cation.[20]



The investigation of analogous chemistry with the acid chloride (B7) and the ester (B18) was therefore pursued. By such a method, formation of the required phosphorous synthon (B19) could be accomplished (Scheme B7).

Scheme B7



The employment of both glutarimide synthons (plus the ester with benzyl protection of the imide nitrogen) with a number of different cations, resulted in no tangible product being isolated from these reactions. Each time a deeply coloured intractable tar was isolated. The reaction was attempted by forming the anion of

dimethyl methylphosphonate {$MeP(O)(OMe)_2$} or methyl diphenylphosphine oxide {$MeP(O)Ø_2$} in THF at low temperature and subsequent addition of the acylating agent in THF. No problems were encountered when ethyl acetate was added, as a model compound, to the lithium anion of both phosphorus compounds. The various combinations tried are summarised in Table B1. The failure of this reaction was probably due to the ring opening of the glutarimide at some stage. A reaction has been reported in which a glutarimide is opened by a Grignard reagent.[21]

Table B1: Combinations used in the attempted acylation reactions.

Reactions carried out in dry THF.

DMP is dimethyl methylphosphonate; *DPPO* is diphenylphosphine oxide.

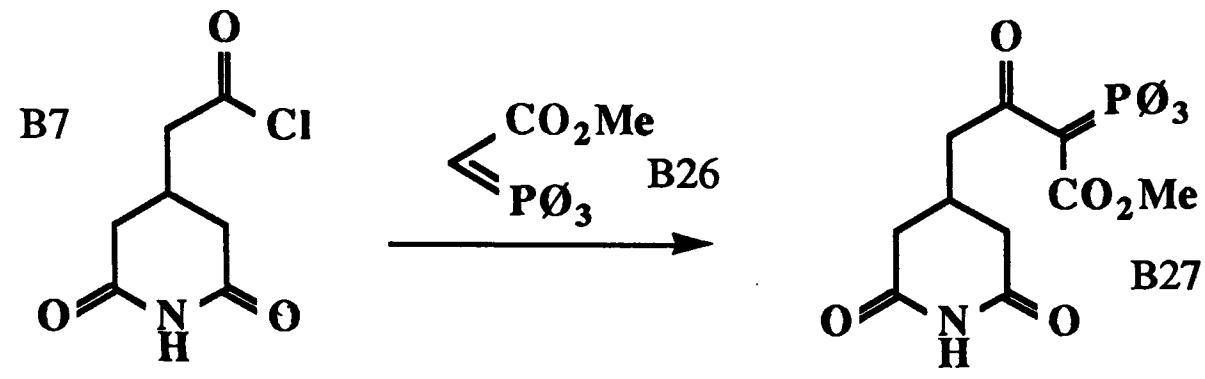
No products of interest were isolated.

Counter Ion (equivalents)	Temperature (°C)	P Substitution	Acyl-X
Na^+, 2.2, 1.1	0, 25	DMP	Cl (B7)
Li^+, 3.3, 1.1	-78	DMP	Cl (B7)
Li^+, 2.2, 1.1	-78	DPPO	Cl (B7)
Cu^+, 3.0, 1.1	-78	DMP	Cl (B7)
Cd^{2+}, 2.0	25	DMP	Cl (B7)
Li^+, 3.3, 1.1	-78	DMP	OEt (B18)
Li^+, 2.2, 1.1	-78	DPPO	OEt (B18)
Li^+, 2.2, 1.1	-78	DPPO	*N*-Bn,OEt (B23)

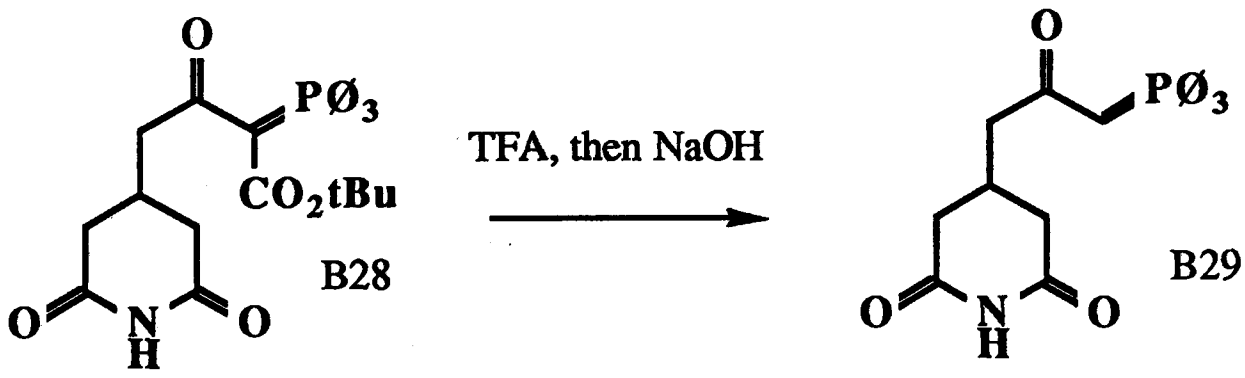
N.b. $DPPO^-Li^+$ plus EtOAc a 90% yield of required product was isolated.

DMP^-Li^+ plus EtOAc a 70% yield of required product was isolated.

A successful acylation of an α-anion to phosphorus was achieved however, on reaction of the acid chloride (B7) with the stabilized ylid (B26) in THF, giving the triply substituted product (B27)

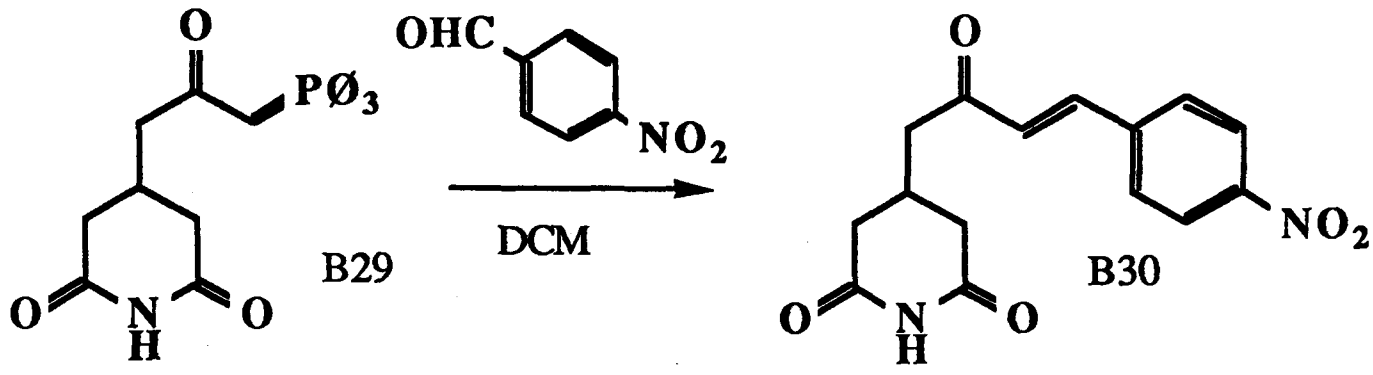


This compound itself was not particularly interesting; the ylid was unreactive, a consequence of both carbonyl groups giving a degree of extra stability (*vide infra*). This was overcome by acylation of the ylid (B26) with a *tert*-butyl rather than a methyl ester. Acidic hydrolysis of the resulting ester (B28), followed by decarboxylation, yielded the mono-substituted ylid (B29) after a basic wash in the work-up.



The identity of this compound was first established by its successful Wittig reaction with 4-nitrobenzaldehyde to give (B30). This used the crude chloroform extract of the hydrolysis/decarboxylation, dissolved in dry dichloromethane, along with the aldehyde. After stirring overnight a suspension was observed; this was obviously neither starting material nor triphenylphosphine oxide. On filtration and drying this was characterized as the *E* enone (B30) ($J_{\alpha-\beta}$ 15.8 Hz), isolated in 63% yield over the two steps. Amazingly no other purification was required to obtain a microanalytical

result within the required ± 0.3 tolerance (Found, C, 59.40; H, 4.69; N, 9.52; $C_{15}H_{14}N_2O_5$ requires C, 59.60;H, 4.67;N, 9.27%).



Subsequent research showed that the ylid (B29) could be purified by flash chromatography. From the resulting syrup, trituration with ether afforded a white solid, which was quite stable at room temperature.

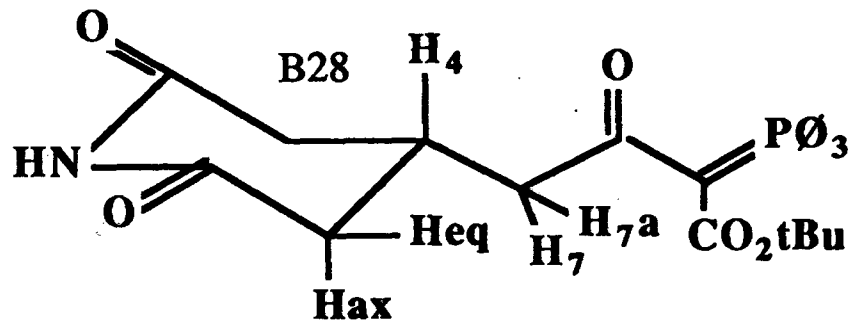
To consolidate on the achieved ylid formation, methods of improving the yields and increasing the scales of the reactions were investigated. After various modifications, the yield of the acylation reaction to form (B28) was increased to 90%, producing up to 40 g. Addition of 4-*N*,*N*-dimethylaminopyridine to the reaction mixture was the key factor which increased this yield. Purification was accomplished by dry column chromatography.

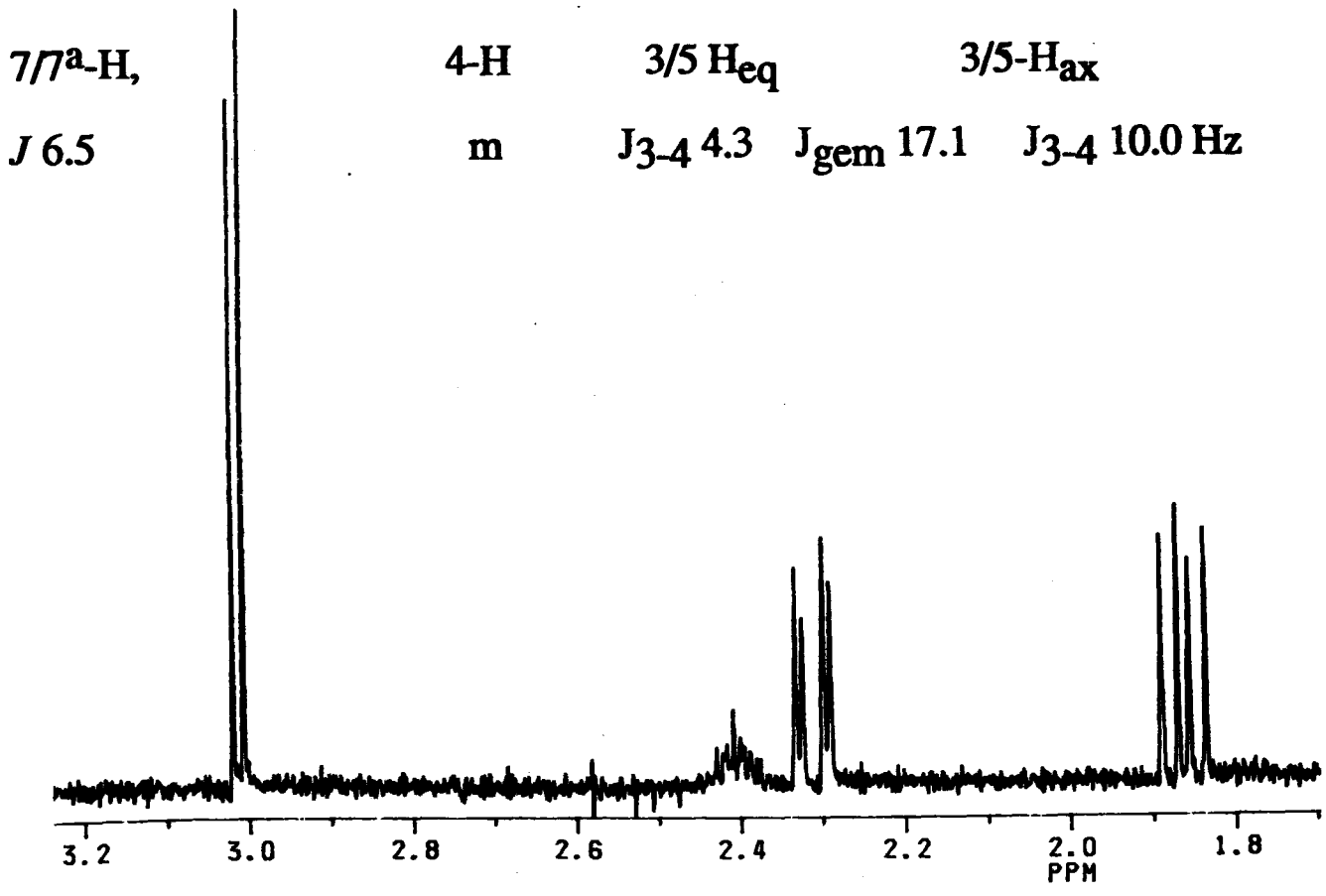
Hydrolysis followed by decarboxylation to give (B29) was best performed by warming the *tert*-butoxy ylid (B28) in neat trifluoroacetic acid for 2 hours, and including a sodium hydroxide wash in the work-up. Subsequent purification by flash chromatography and trituration yielded up to 70% of (B29). This ylid was stable at room temperature, and indeed relatively so at over 100 ^{o}C, as shown in later Wittig reaction attempts.

The 300 MHz proton NMR spectrum of the glutarimide ring protons of this compound, like those of (B27 and B1), had a splitting pattern which did not have an obvious fine structure. It was expected to be relatively simple, since C-3 and C-5 were equivalent in the carbon-13 spectrum. This would be expected from such an achiral

glutarimide; the two methylene carbon signals in the spectrum of cycloheximide were quite close, and the protons were fully assignable.[22] This splitting pattern was similar for many further products. At 500 MHz the picture became clarified, especially when the spectrum was run in d-6 benzene, as exemplified by the ylid (B28) (Figure B1). Two double doublets (each 2H, representing the diastereotopic axial and equatorial protons of C-3 and C-5), a multiplet (H-4), and a doublet due to the enantiotopic protons at C-7 were shown. As would be expected, this pattern was seen in all of the products derived from the ylid (B29), only the relative positions of the peaks were changed.

Figure B1: 500 MHz spectrum of B28 in C_6D_6.(*J* in Hz)

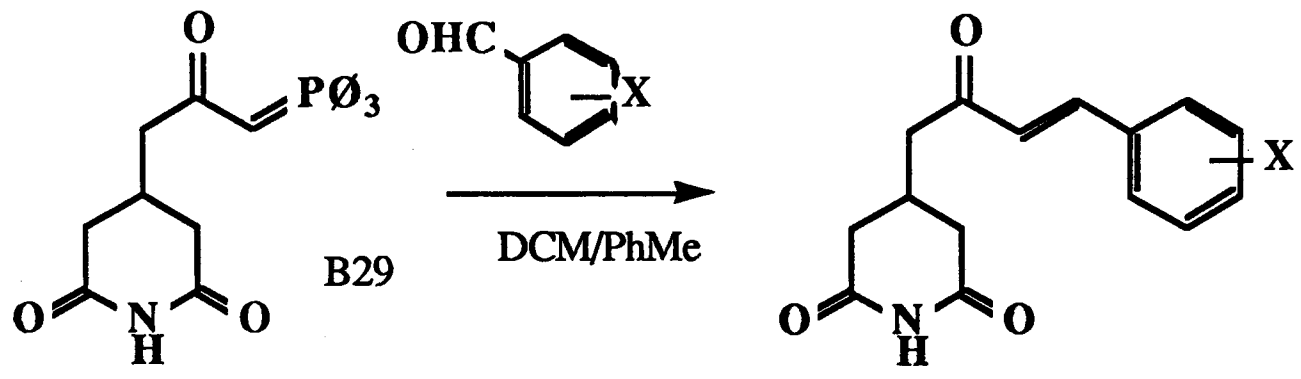




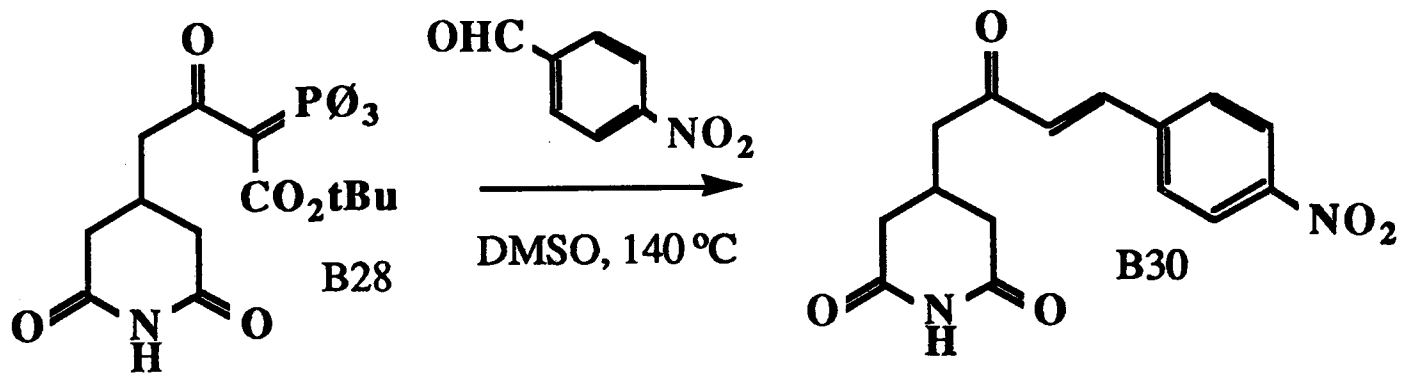
3) Wittig Chemistry with the Glutarimide-Ylid.

As a result of the successful formation of the Wittig adduct with 4-nitrobenzaldehyde, with very simple execution and purification, it was decided to look at reactions with a range of such aldehydes (Scheme B8).

Scheme B8: Wittig Reactions with Ylid B29 and Various substituted Benzaldehydes



The chemistry was first repeated on the same aldehyde however, but using the dicarbonyl ylid (B28). This was followed by NMR, initially in CD_2Cl_2, but subsequently in d-6 DMSO, when it became obvious that heating was required. On heating for 14h at 140 °C a product was eventually formed. This was identical to (B30), derived from the deprotected ylid (B29); only the *E* isomer was present.



With the reactive ylid (B29) the chemistry was repeated for a number of substituted benzaldehydes. In each case a similar conclusion was reached. Stirring the aldehyde with the ylid (B29) in either dichloromethane at room temperature, or toluene when warming was required, resulted in deposition of the *E* enoate in good yield. Purification was not required, each compound gave a satisfactory microanalysis result

by simply drying by suction. Results are summarised in Table B2.

Table B2. Reactions of Ylid (B29) with Substituted Benzaldehydes.

Substituent	Number	Temp./ °C	Solvent	Yield / %	M.p. / °C
4-NO_2	(B30)	25	DCM	62	239-240
2-OH	(B31)	25	DCM	95	214-215
2-F	(B32)	100	PhMe	77	180-181
3-CF_3	(B33)	100	PhMe	74	158-159
4-OMe	(B34)	100	PhMe	55	173-174
(2-Pyridyl)	(B35)	100	PhMe	88	214-215

In biological screens these compounds did not show an activity, with the exception of a trace of fungicidal contol for the 2-fluoro derivative.

As a result of this successful formation of Wittig adducts from relatively simple aldehydes the chemistry developed in the next section investigates the chemistry resulting from carbonyls which have substitution appropriate for further elaboration of the attached functionality.

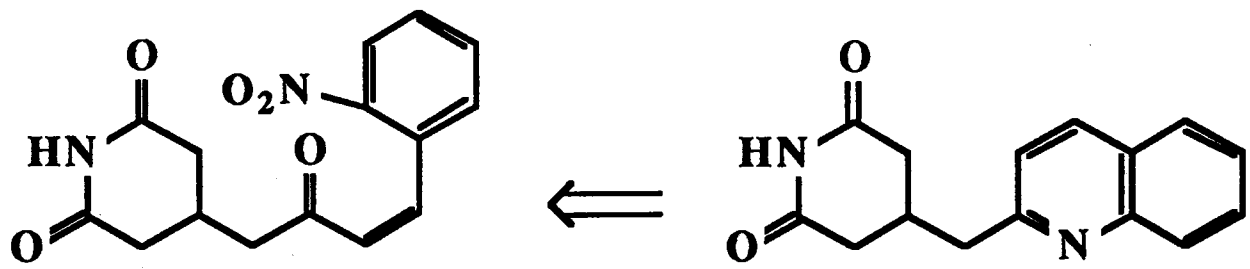
4) Synthesis of glutarimides attached to simple heterocycles.

In this section Wittig extensions of the ylid (B29) were made with various substituted carbonyl compounds. The configurations of the resulting side chains were designed in a way such that closure to various heterocylic compounds could be easily achieved by simple methods.

a) Synthesis of Quinoline

Retrosynthetic Analysis.

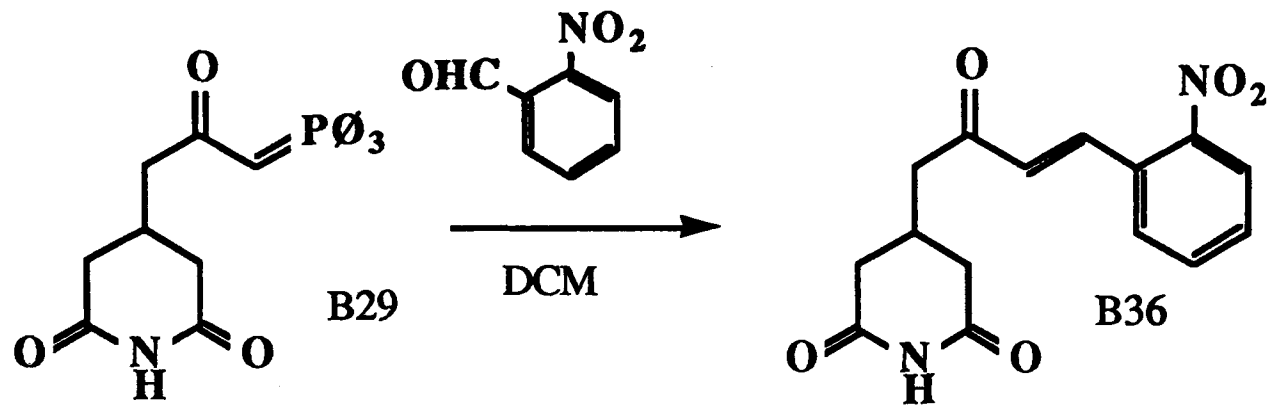
The Wittig reaction of the ylid (B29) with 2-nitrobenzaldehyde, gives rise to an intermediate (B36) with stabilized nitrogen functionality δ to a carbonyl group. This is the required synthon for the closure of a 6-membered nitrogen heterocycle; reduction and cyclisation would give rise to the quinoline (B37).



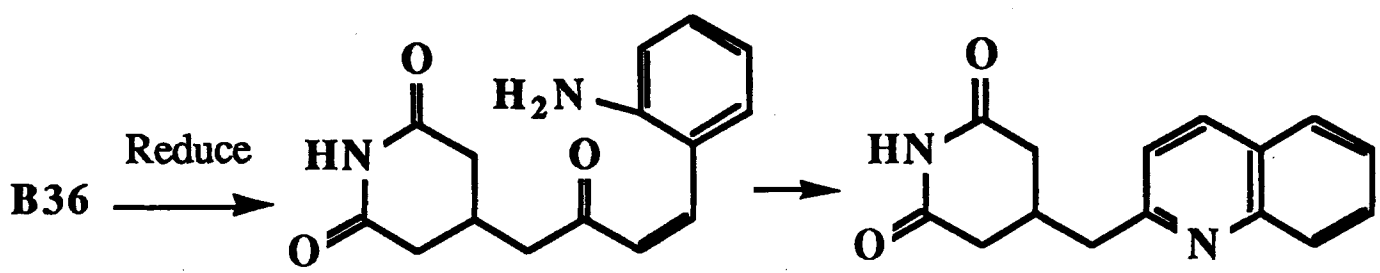
B36 B37

Wittig reaction, reduction/cyslisation.

Formation of the enone (B36) was accomplished as before by stirring the ylid (B29) and 2-nitrobenzaldehyde in dichloromethane for 48h. Filtration of the product yielded 91% of the single *E* enone.



The closure of such compounds to quinolines has been well studied.[23] The most convenient reduction method for this compound appeared to be hydrogenation. Other reduction methods might have resulted in reaction with the glutarimide.[24]



B37

Thus the enone (B36) was hydrogenated in ethanol (requiring a large volume due to the low solubility) over a palladium on charcoal catalyst. This resulted in a mixture of products, the major one of interest being the required quinoline. The tricky separation was achieved by two successive preparative t.l.c. elutions. On crystallisation (EtOH), the amount of quinoline (B37) isolated represented a 20% yield. The conditions of the reaction were not optimised, but the potential for forming 6-membered nitrogen heterocycles by such methodology was thus demonstrated.

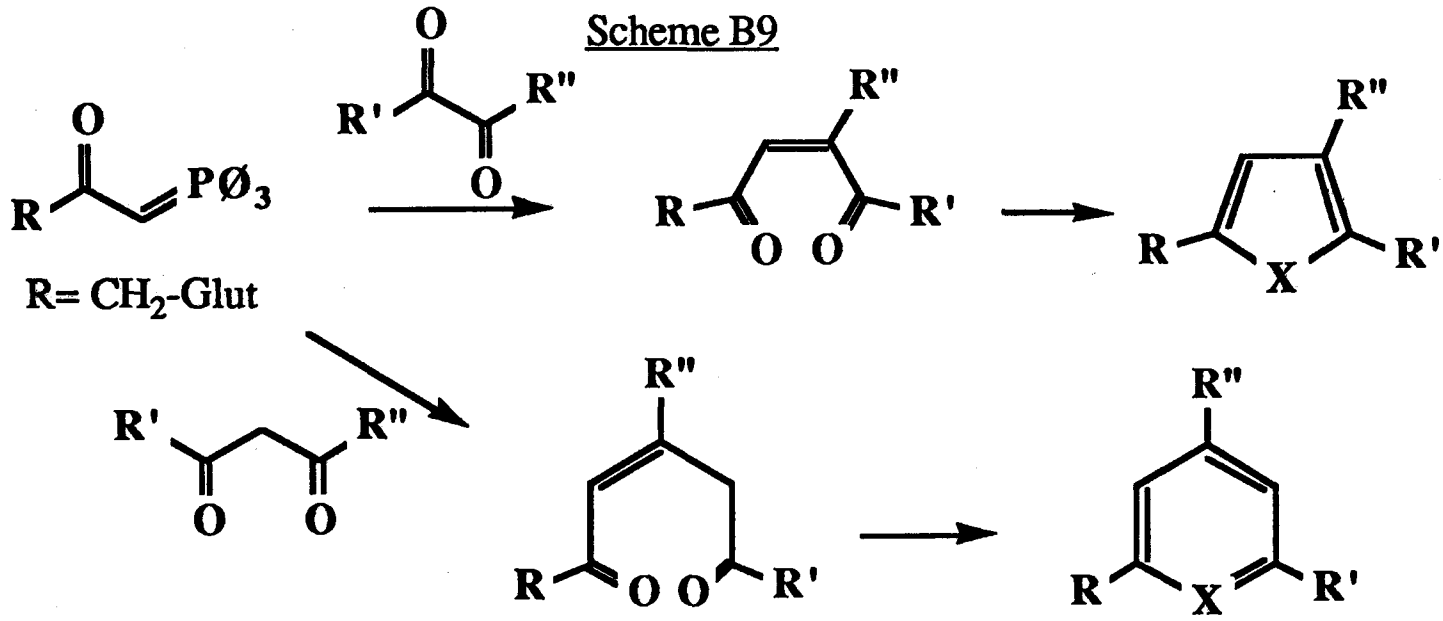
This compound showed a small degree of anti-fungal activity.

b) Synthesis of Simple Heterocycles form Diketones.

Retrosynthetic Analysis

To form the precursors of five and six ring heterocycles, the appropriate 1,2- or 1,3-dicarbonyl compound was required for the Wittig step. Closure of the resultant 1,4- or 1,5-dicarbonyl compound to the heterocycle would follow, by the use of standard procedures[13] (Scheme B9).

Scheme B9

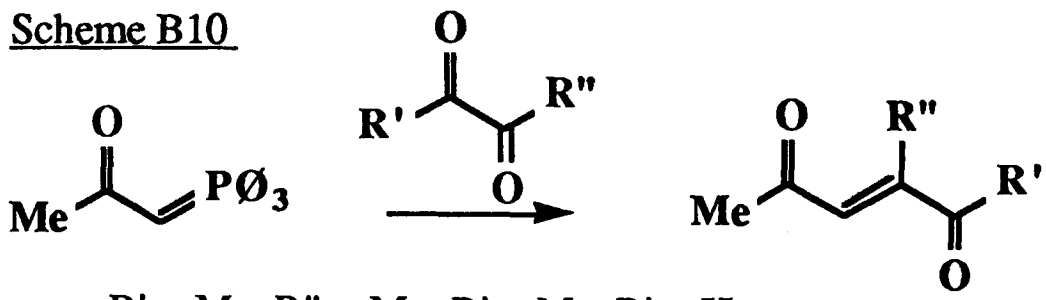


i) Synthesis of Dicarbonyls.

After initially achieving no reaction between the ylid (B29) and a some dicarbonyl compounds, a series of studies were first conducted on a model system. Thus acetylmethylene triphenylphosphorane (B38) was reacted with the dicarbonyls, to find the required conditions, before the glutarimide-ylid (B29) was committed. Using a variety of conditions a reaction could still not be achieved with a 1,3-dicarbonyl (neither pentane-2,4-dione, nor methyl 3-oxo-butanoate). The acidity of the methylene α to two carbonyls was probably the limiting factor. However using 1,2 dicarbonyls a successful reaction was achieved by using DMF as a solvent. This worked for butane-

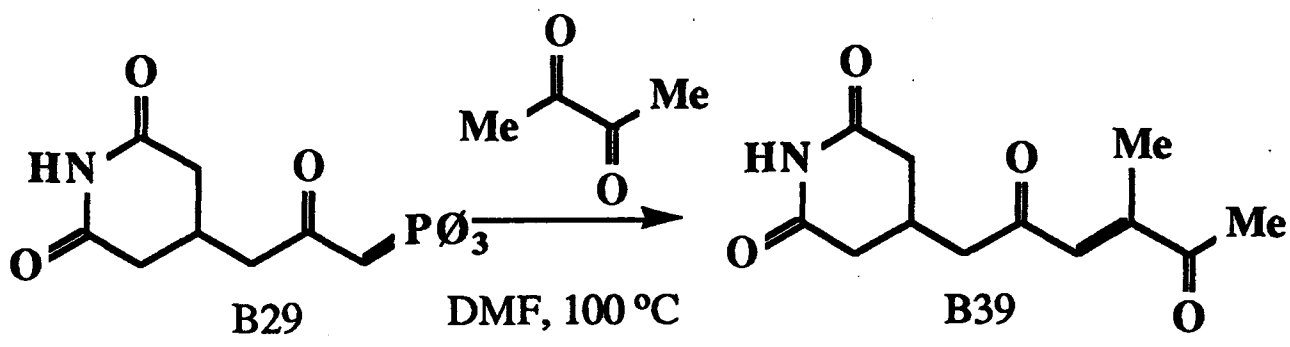
2,3-dione, 2-oxo-propanal and ethyl 2-oxopropanoate (Scheme B10). On completion, partitioning of the mixture between water and ether gave rise to a crude NMR spectrum of the product plus triphenylphosphine oxide.

Scheme B10

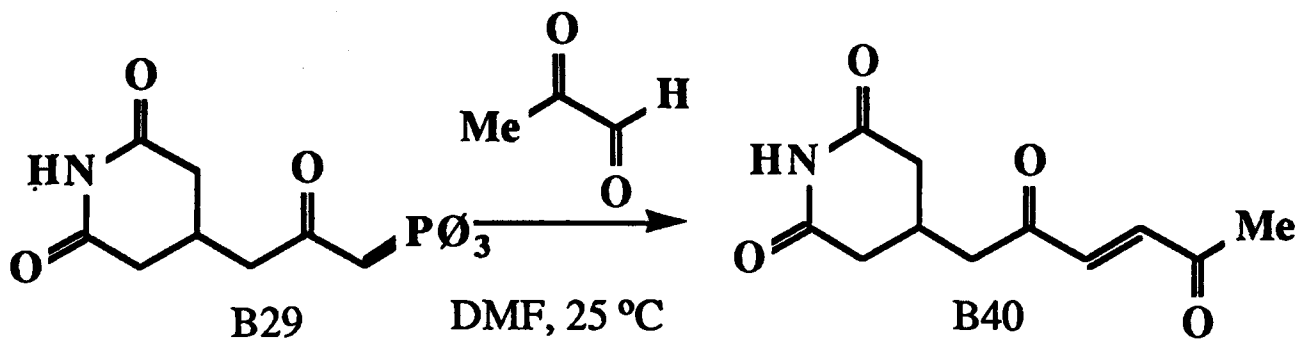


R' = Me, R" = Me; R' = Me, R' = H;
R' = OEt, R" = Me.

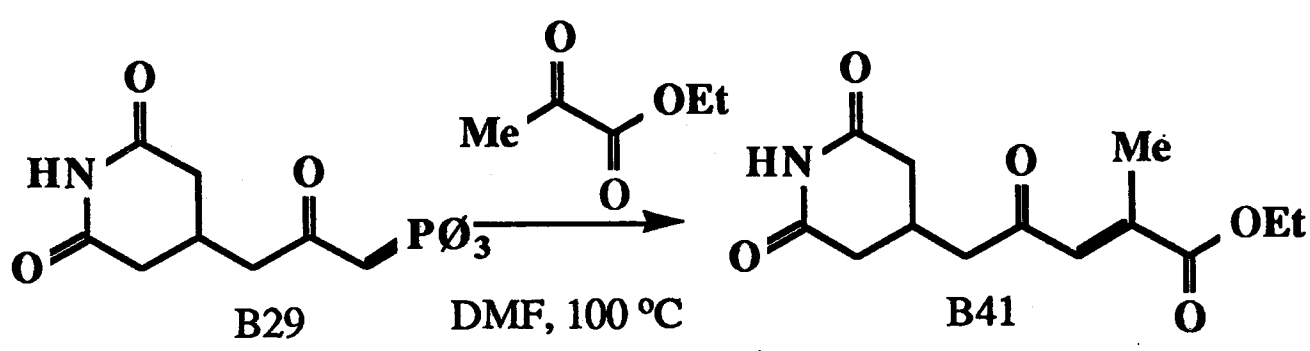
Using the glutarimide ylid, warming at 100 °C with an excess of butane-2,3-dione gave rise to the dienone (B39). This could not be separated from triphenylphosphine oxide by chromatography, but the *E* isomer could be crystallised from the crude mixture, giving a 65% isolated yield. The ^{1}H NMR spectrum of the mixture showed a ratio of 4:1 *E*:*Z*, based on the respective integrals of the olefinic signal at δ 6.56 and 5.96.



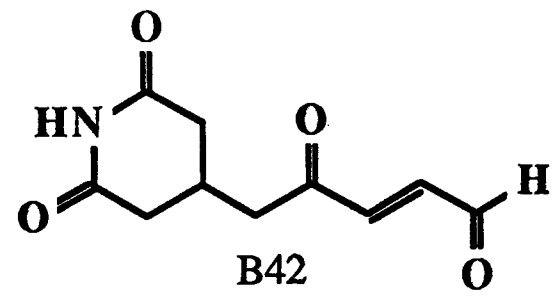
In a similar fashion the dienone (B40) was formed from 2-oxo-propanal by reaction in DMF at room temperature. This compound was separable from triphenylphosphine oxide by flash chromatography, as an *E,Z* mixture (5:1 by NMR, ratio of *AB* quartets at δ 6.83 and 6.32 respectively). The *E* isomer could be crystallized from this mixture as fine white needles.



The reaction was also successfully achieved with ethyl 2-oxopropanoate to yield the ester (B41). This was again inseparable from triphenylphosphine oxide, but the *E* isomer was crystallized in 90% yield. This compound showed a degree of antifungal activity.

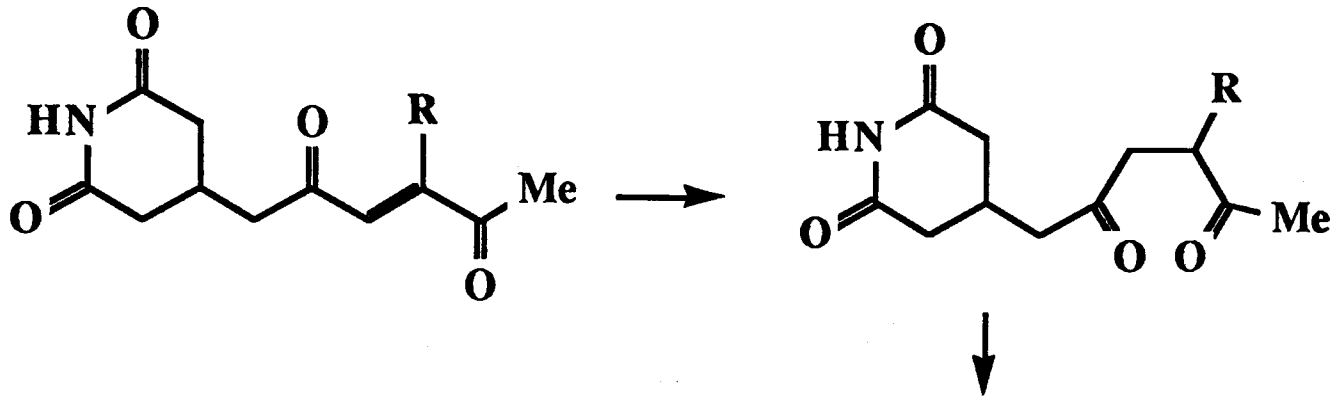


In a crude extract from the reaction of the ylid (B29) with glyoxal under similar conditions, there was evidence for some of the required aldehyde (B42) by NMR. However this mixture soon turned into an intractable gum, so the reaction was not pursued.



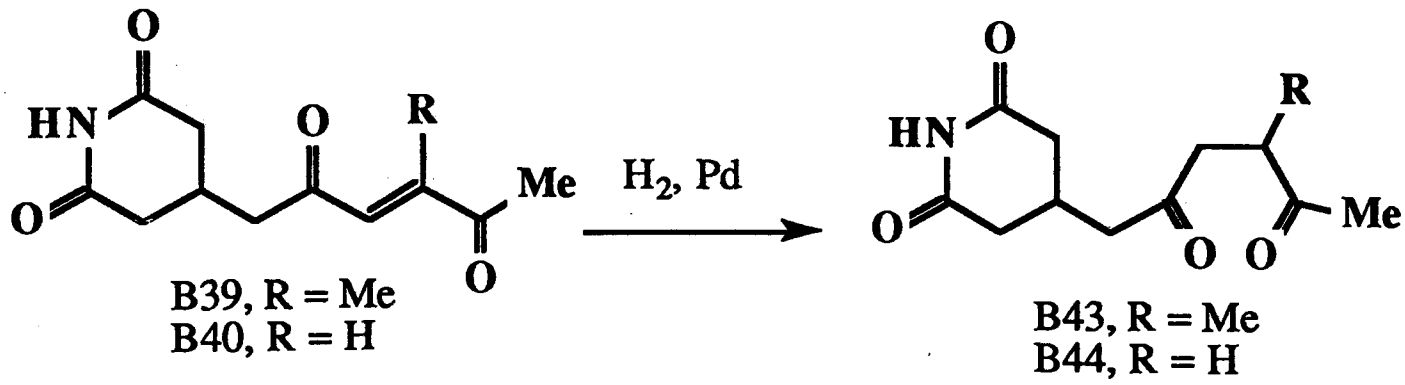
ii) Reduction and Subsequent Cyclisation to Heterocycles.

The conversion of the two ketones (B39 and B40) into five ring heterocycles first required reduction of the double bond (Scheme B11).



Scheme B11

This was achieved smoothly for each by hydrogenation over palladium in ethanol. The reaction was complete in 20 minutes and subsequent purification gave both the dimethyl (B43) and the monomethyl (B44) diketones as white needles in high yield.

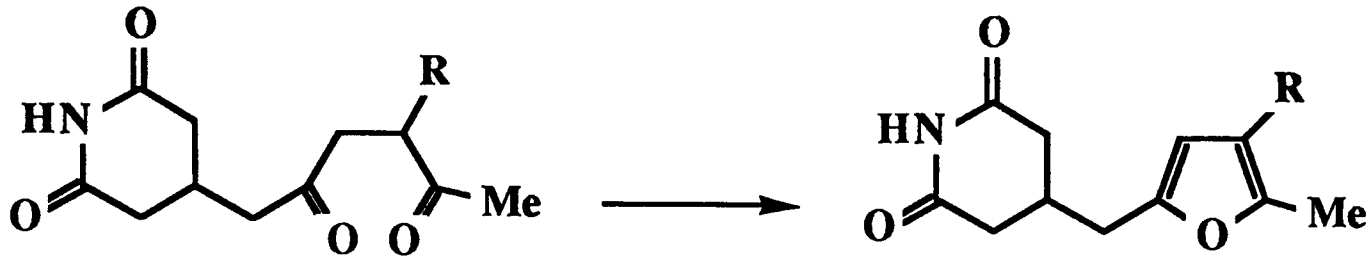


B39, R = Me
B40, R = H

B43, R = Me
B44, R = H

The utility of these diketones as synthons for glutarimide-substituted heterocycles was demonstrated by the conversion of each one into both a furan and an *N*-benzyl pyrrole.

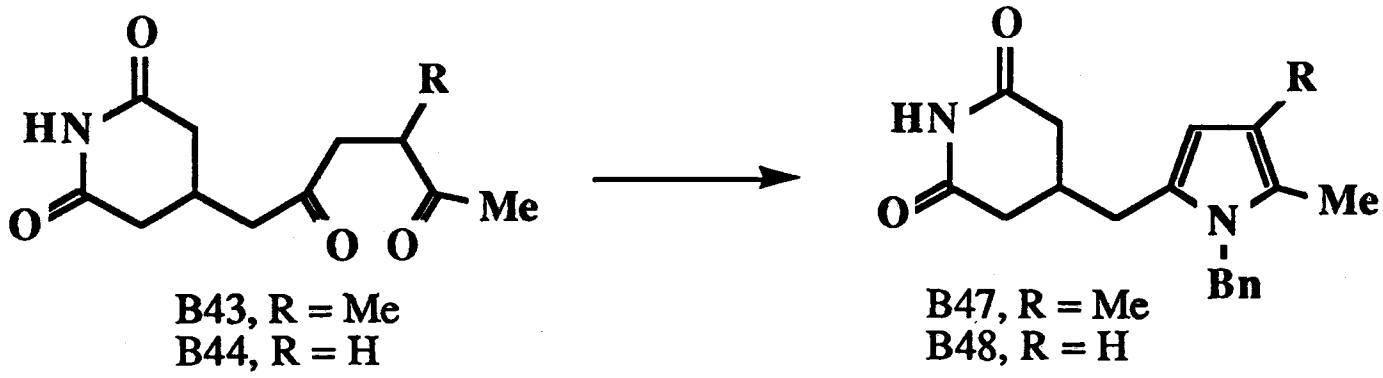
The furan was closed by a standard Paal-Knoor modification,[25] by cyclisation with *para*-toluenesulphonic acid in toluene. Thus the dimethyl furan (B45) and the methyl furan (B46) were formed in 93 and 48% yields respectively.



B43, R = Me
B44, R = H

B45, R = Me
B46, R = H

The pyrroles were formed by the Paal-Knoor method[26] too, achieved by refluxing the diketones with benzylamine in benzene. Yields of the dimethyl (B47) and methyl (B48) *N*-benzyl pyrroles were 90 and 78%.



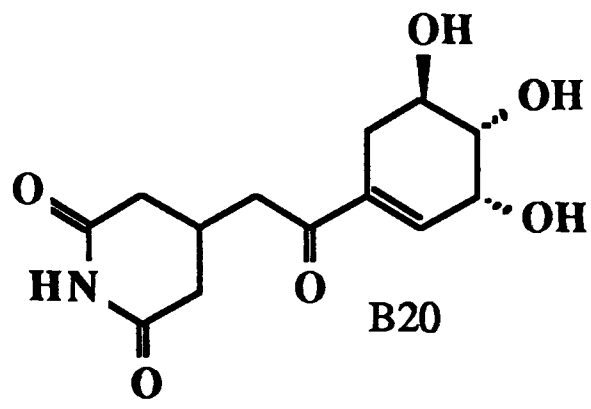
B43, R = Me
B44, R = H

B47, R = Me
B48, R = H

The three of these heteocycles screened (monomethyl furan was omitted) each displayed some anti-fungal control.

Approach to the Synthesis of Glutarimide-Shikimate adduct.

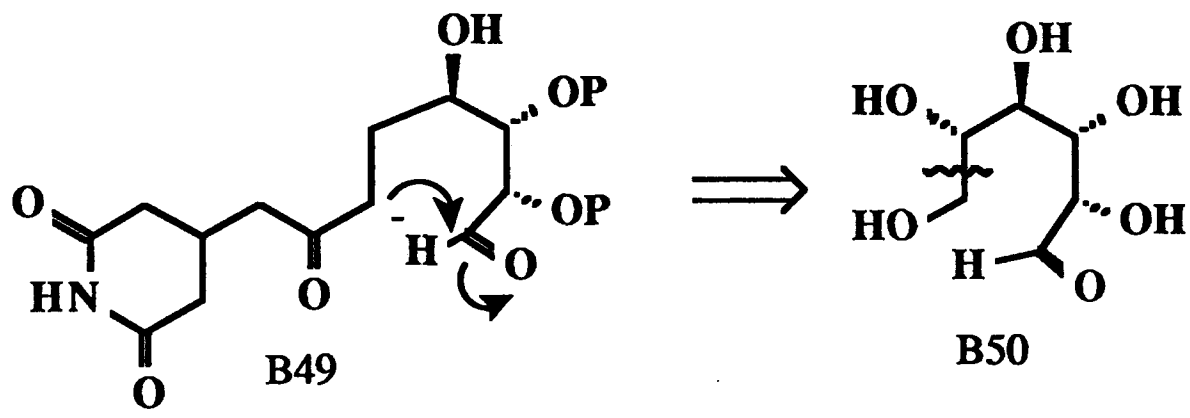
This section describes an approach to the glutarimide-shikimate (B20), using the cyclisation method by which Fleet, Shing and Warr synthesized shikimic acid.[15]



B20

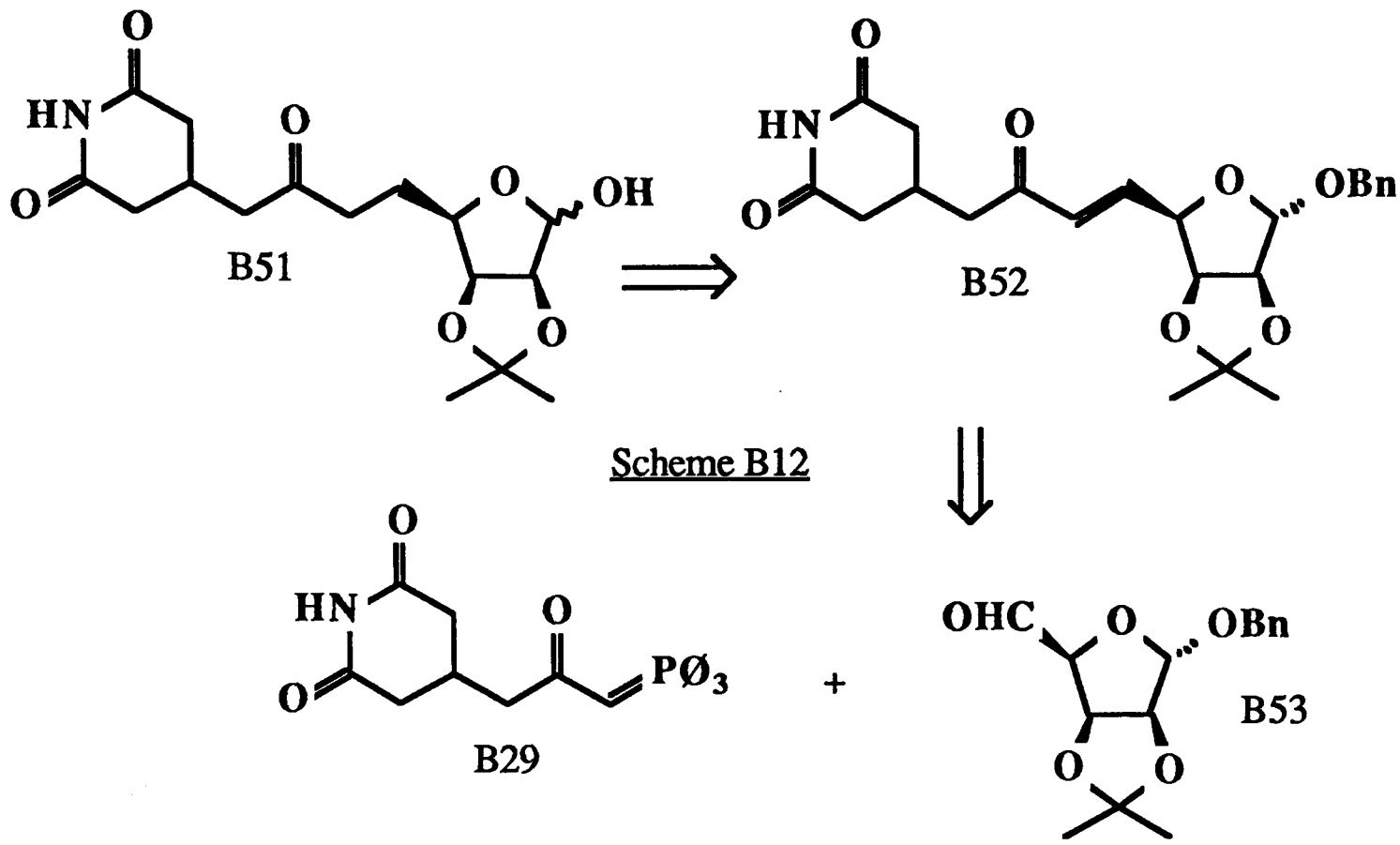
Retrosynthetic Analysis

The required cyclisation to the cyclohexene could be achieved by an aldol condensation of a γ-hydroxy aldehyde (B49). Since the desired stereochemistry of the hydroxylated cyclohexene ring in the target was the same as shikimic acid itself the required chiron would be derived from D-mannose (B50).

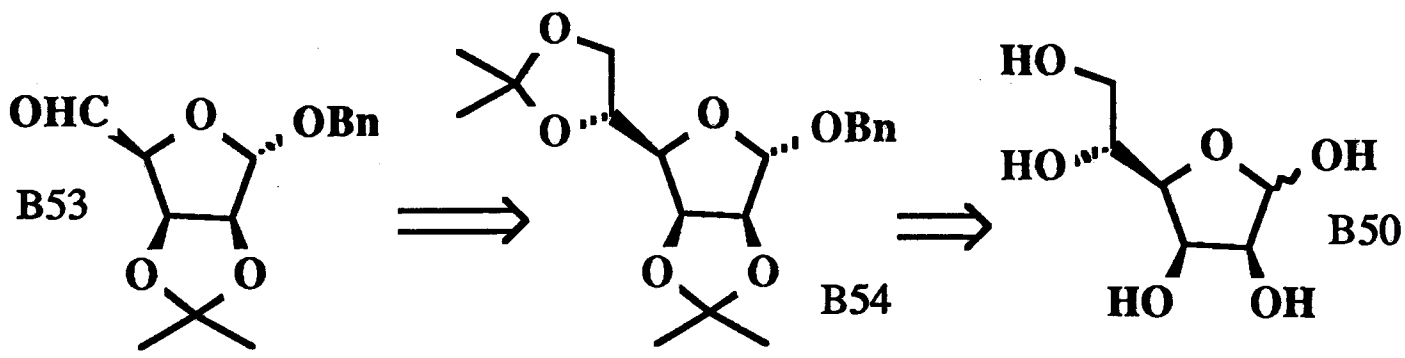


The lactol (B51), the cyclic form of the required γ-hydroxy aldehyde, could be derived from the enone (B52), the result of a Wittig reaction between the ylid (B29) and the appropriate dialdofuranoside. This could be achieved in one pot (by hydrogenation) with benzyl protection of the anomeric hydroxyl; it can thus be seen that the

dialdo*lyxo*furanoside (B53) is the required synthon (Scheme B12).

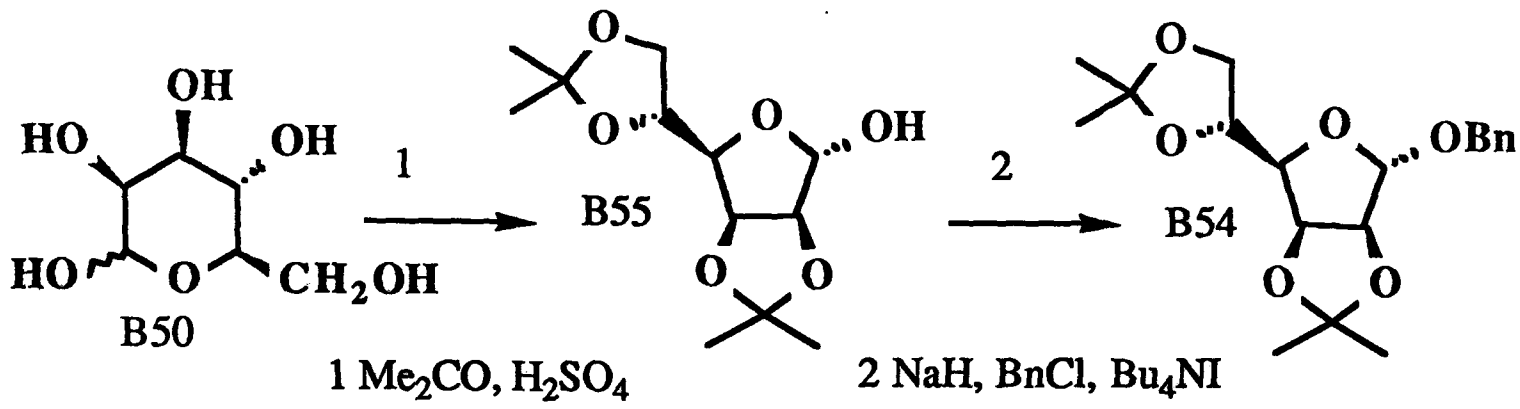


The dialdo*lyxo*furanoside (B76) is readily available from D-mannose (B50) *via* the diacetonide (B54).[27]

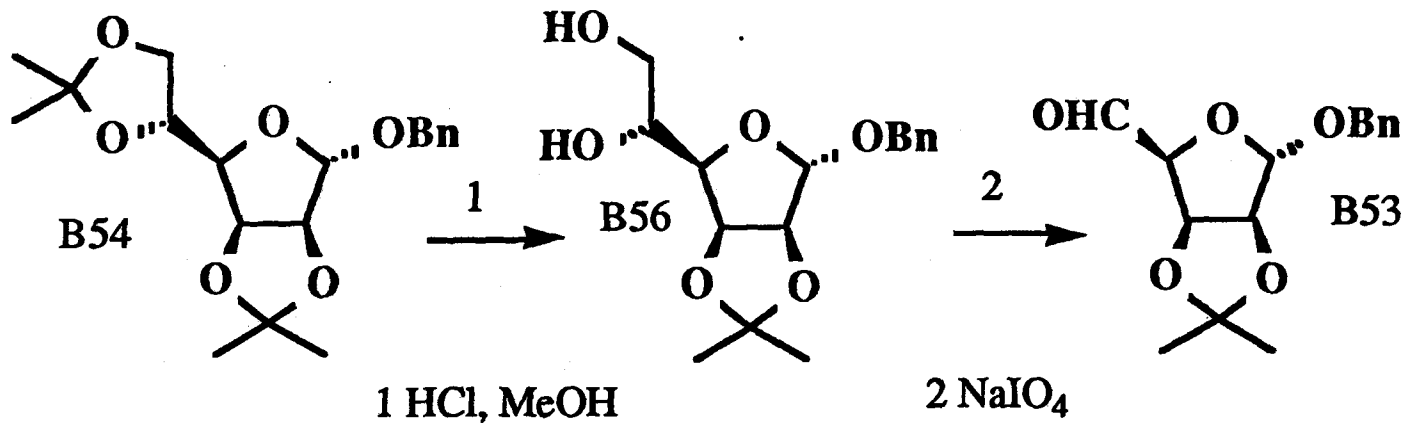


a) Synthesis of the Lactol.

Diacetone mannose (B55)[28] was prepared in 93% yield by stirring a suspension of D-mannose in acetone with concentrated sulphuric acid until all of the sugar had dissolved: refluxing the solution after the pH had been raised with sodium carbonate gave the single (α) anomer. The anomeric hydroxyl was then benzylated in the usual way[27] by stirring the sodium alkoxide with benzyl chloride in DMF to give the benzylfuranoside (B54), taken *en masse* to the next stage.

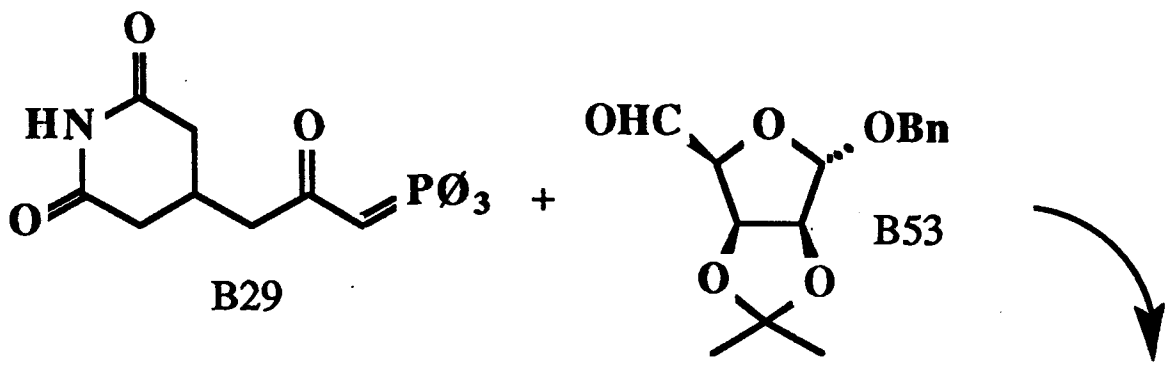


Removal of the 5,6 acetonide was selectively achieved by stirring the diacetonide (B54) in dilute methanolic HCl, affording the diol (B56) in 80% yield for the two steps from diacetone mannose. This was readily oxidatively cleaved to the aldehyde (B53) using sodium periodate in aqueous methanol.



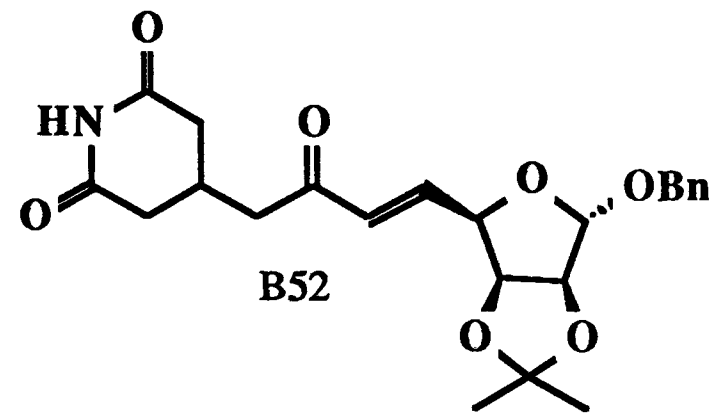
The Wittig reaction was executed by adding the ylid (B29) to a solution of the crude aldehyde (B53) in dry dichloromethane. The temperature was raised to reflux for

48 h, after which the reaction was complete. This gave the enones (B52) in a 6:1 ratio (*E*:*Z*, by NMR, $J_{\alpha-\beta}$ 15.7 Hz, *E*; $J_{\alpha-\beta}$ 11.8 Hz, *Z*). Triphenylphosphine oxide co-ran with the products, so the mixture was inseparable by column chromatography. However by dissolving the crude syrup in hot ethanol several crops of crystals of the pure *E* isomer could be recovered on standing, representing a 65% isolated yield from the diol (B56). In production the enone (B52) was partially purified by a flash column, followed by crystallization, which would give about 50% yield of the pure compound. Hydrogenation of the remaining mixture resulted in the recovery of material, since the resulting lactol (B51) was separable from triphenylphosphine oxide.



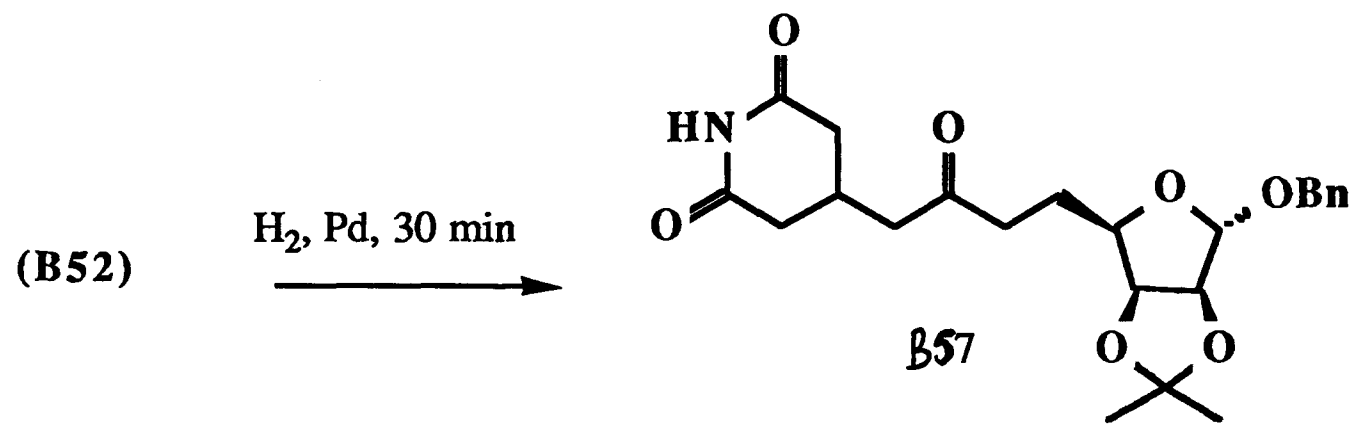
B29 +

B53

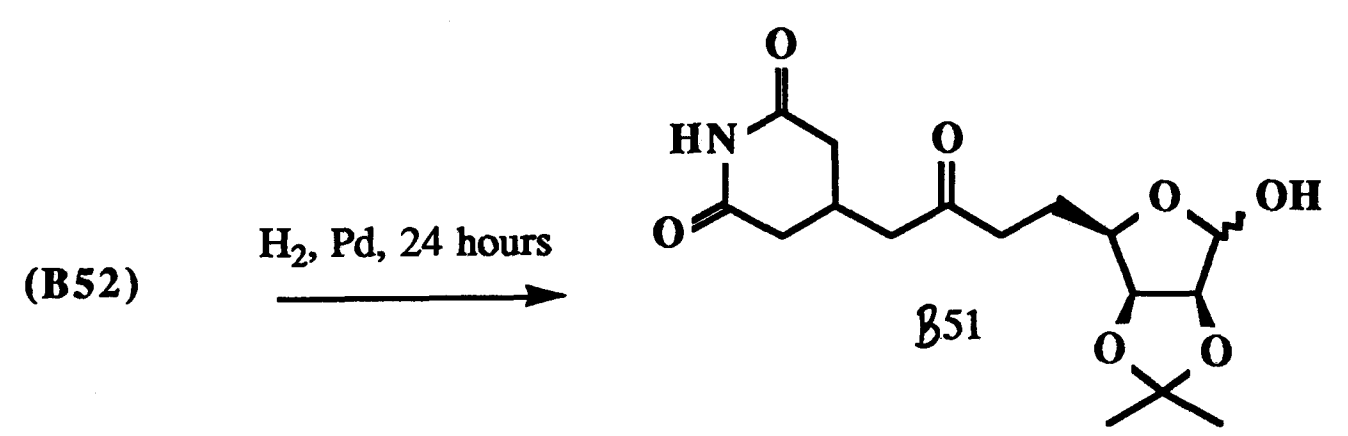


B52

Investigations into the hydrogenation of (B52) (using a suspension of palladium black in ethyl acetate/ethanol co-solvents) showed that the unsaturation was removed rapidly to form the ketone (B57), which was indistinguishable by Rf from the starting enone. When the reaction was stopped after 30 minutes the ketone (B57) was isolated in quantitative yield after removal of the catalyst and solvent (fine white needles on recrystallization from ethanol).



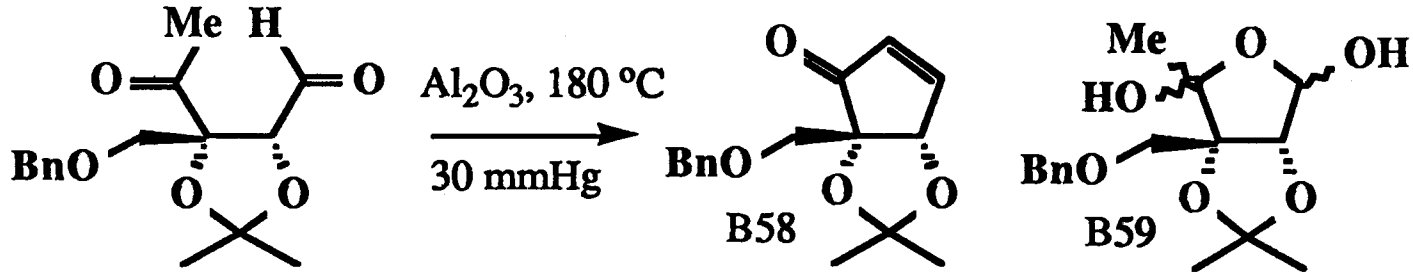
The benzyl protection of the anomeric hydroxyl was subsequently removed by hydrogenation under the same conditions for 24 hours.[29] This gave the lactol (B51) as a mixture of anomers, the α-anomer being predominant. On recrystallization (from ethanol) the α-anomer was selectively deposited, this was shown in the NMR spectrum of freshly dissolved crystals (in chloroform or benzene); anomerisation occured after a few hours.



Each of these compounds containing a glutarimide i.e. enone (B52), ketone (B57), and lactol (B51) were screened at Shell: the two benzyl furanosides each showed a degree of fungicidal activity. As was the case for their achiral relations derived from Wittig chemistry, the NMR spectra of these compounds showed the two diastereotopic centres of the glutarimide ring to be magnetically equivalent.

b) Attempted aldol cyclisation

The formation of aldol products from intramolecular cyclisations of 1-6 dicarbonyl compounds is a reasonably well documented procedure.[17] A number of polyhydroxylated cyclohexenes had been formed by Wadsworth-Emmons chemistry from various suitably substituted sugar lactols.[18] However the precedent for intramolecular aldol cyclisations of carbohydrates was not good. A successful reaction in the literature, forming cyclopentenone (B58), was executed after many attempts, employing a variety of conditions.[30] The formation of the bis hemiketals (B59) was one side-reaction competing with the desired closure. The authors described the many failures as "somewhat surprising, and to say the least frustrating."



In this work the aldol condensation proved to be a great problem as well. Even after the employment of a wide range of conditions (Table B3), the required product {either the enone (B60) or aldol (B61)} was not identified (Scheme B13). Either an intractable gum or starting material were isolated from such reactions.

Scheme B13, required aldol cyclisation.

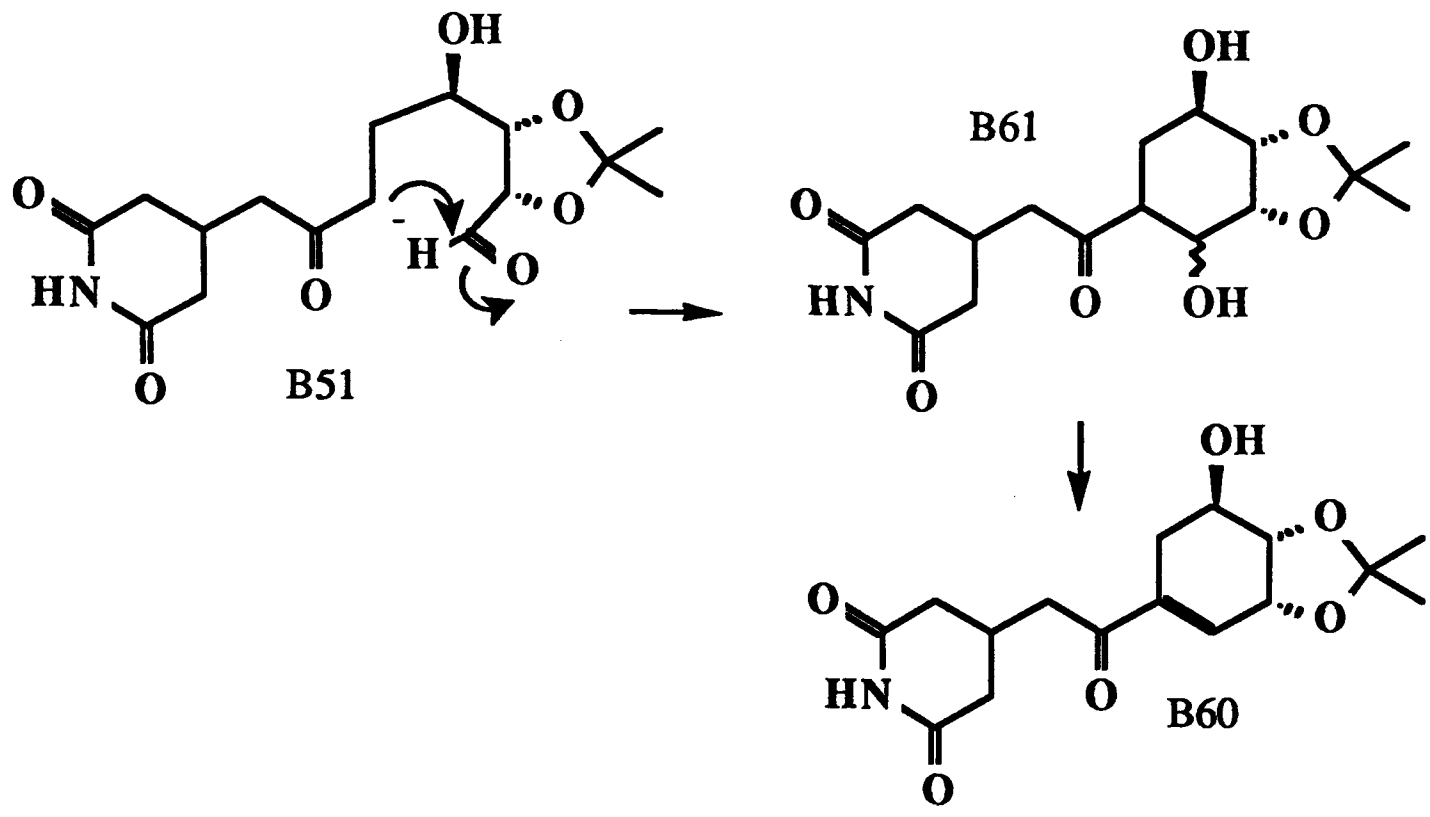
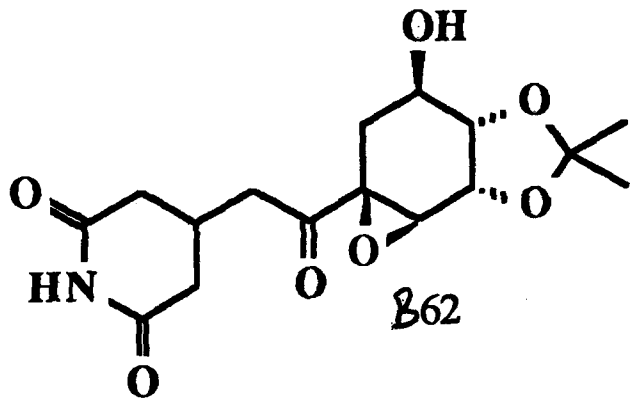


Table B3, Summary of reagents tried to affect the aldol cyclisation.

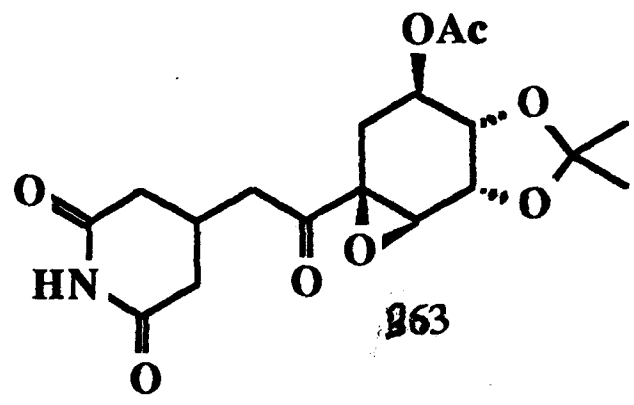
(*Result* refers to the ammount of lactol recovered)

Base	Solvent	Temperature (^{o}C)	Result
NaOMe	MeOH	25 to reflux	nil
NaH	THF	25 to reflux	nil
KOH	MeOH	25	nil
Al_2O_3	PhMe	reflux	all
Al_2O_3	none	100	little
Al_2O_3	1,4 dioxan	reflux	all
KOtBu	THF	25	nil
NaOAc	THF	reflux	most
NaOAc	MeOH	25 to reflux	most

A large effort was put into this work due the isolation and characterization of the epoxide (B62) from one set of conditions employed. This product must have been derived from either the enone (B60) or the aldol (B61) by oxidation of the intermediate. Refluxing the lactol (B51) with potassium carbonate in dry benzene in the presence of 18-crown-6 for 6 days resulted in the isolation of a 48% yield of this epoxide, allowing for recovered starting material. No other products were isolated. Originally, the identity was unknown: mass spectral and microanalytical data were inconsistent with the required product by virtue of an extra oxygen. On treatment of (A62) with acetic anhydride in dichloromethane in the presence of pyridine, only the monoacetate (A63) could be formed. The configuration was eventually solved by an X-Ray crystal structure (Figure B2). This product might itself have interesting biological properties: senepoxides and crotepoxides (epoxidised carbocycles derived from the shikimate pathway) have some interesting biological actions.[31]

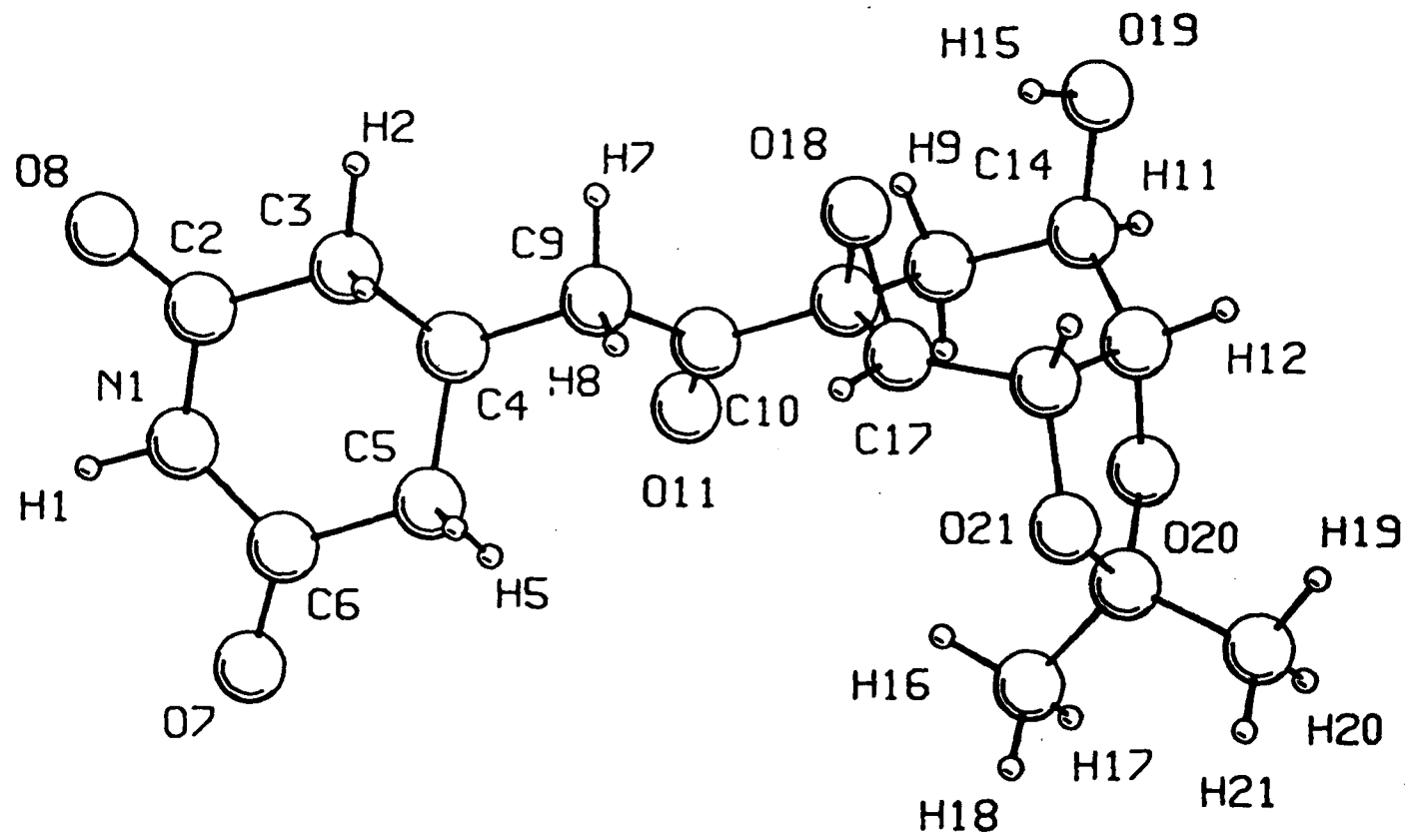


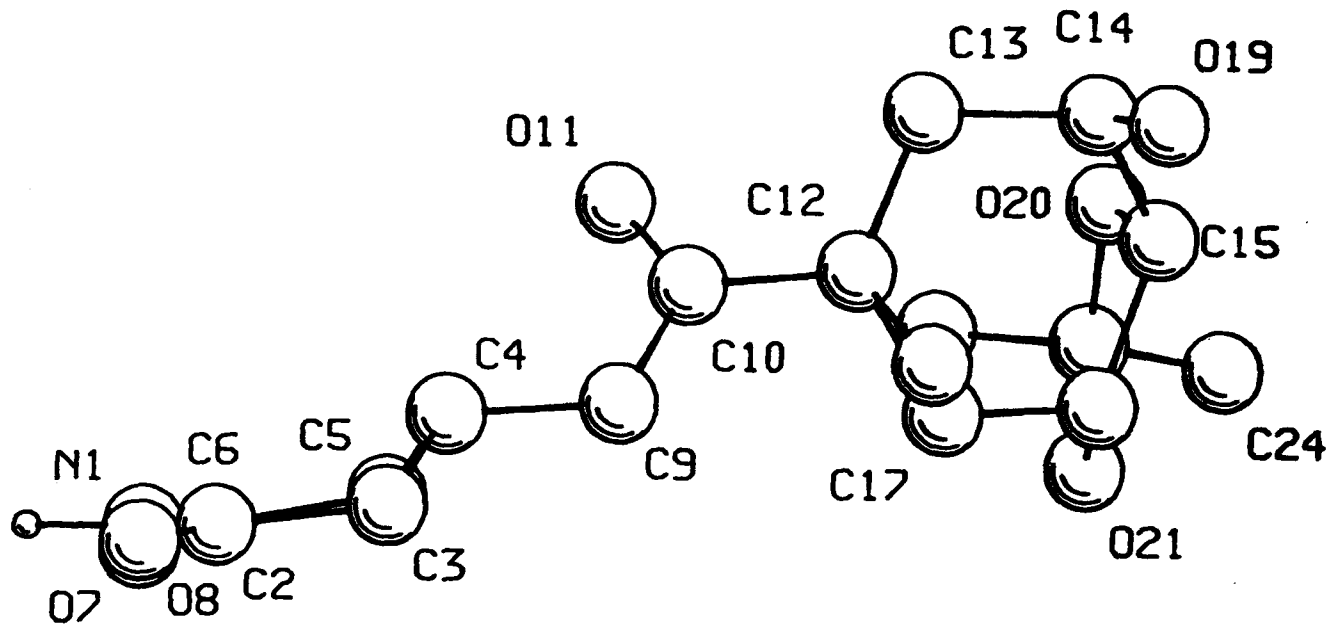
B62



B63

Figure B2: X-Ray crystal structure of the epoxide (B62).





EXPERIMENTAL

Dimethyl-3(cyanomethylene)-pentane-1,5-dioate (B22).

Using the literature method,[4,5] to a solution of dimethyl-3-oxo-pentanedioate (100g, 0.58 mol) in benzene (100 ml) were added cyanoacetic acid (53.7g, 0.63 mol), b-alanine (3.50g, 40 mmol), and glacial acetic acid (15.0 ml). This solution was heated in an oil bath at 140-150 ^{o}C under a Dean-Stark water extractor for 11 h after which time a further 1.5 g of b-alanine and 5.0 ml of glacial acetic acid were added. After 18 h no further water was extracted, so the solution was then allowed to cool and a further 100 ml of benzene was added. This organic phase was washed successively with water, 5% aqueous $NaHCO_3$, water, and brine, then dried over $MgSO_4$. The benzene was removed *in vacuo* and the residue distilled to yield the olefin (B22) as a colourless liquid (92.0 g, b.p. 124-128 ^{o}C, 0.1 mm Hg, 86%); ν_{max} (Neat film) 2 220 (CN), 1 725 (C=O), and 1 620 (C=C) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) 3.30 (2H, s, CH_2), 3.55 (2H, s, CH_2), 3.70 (6H, s, Me), 5.50 (1H, s, olefinic-H).

Dimethyl-3-(cyanomethyl)-pentane-1,5-dioate (B6).

To a solution of the olefin (B22) (92.0 g, 0.48 mol) in methanol (200 ml) was added 2 g of 10% Palladium on activated charcoal. This suspension was stirred under an atmosphere of hydrogen until 11.5 l(0.48 mol) of the gas had been consumed. The catalyst was filtered on a celite cake, which was washed with several portions of methanol. After removal of the solvent *in vacuo*, the residue was purified by a silica filtration eluted with ether. Concentration by rotary evaporation followed by application of a little pump pressure yielded the saturated *cyanodiester* (B6) as a colourless oil (86.5 g, 95%); ν_{max} (Neat film) 2 220 (CN), and 1 720 (C=O) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) 2.50 (5H, m), and 3.70 (6H, s, Me).

4-(Carboxy-methyl)-piperidine-2,6-dione (B1)

The cyano-diester (B6) (38.7 g) was mixed with 160 ml of concentrated hydrochloric acid and the resulting mixture heated at 85-90 ^{o}C for 45 min. The aqueous acid was removed using a cold finger trap first with water pump, and subsequently with lower pressure. The residue was dissolved in boiling acetone, filtered to remove ammonium chloride impurities, and then partially reduced in volume. From this acetone solution repeated crops of white crystals were collected on refrigerated storage. Yield 12.5 g, 40%. M.p. 174-6 ^{0}C (Lit.,[5] 176-176.5 ^{o}C), ν_{max} (Nujol) 1 720 (acid C=O), and 1 680 (glut C=O) cm^{-1}; ^{1}H NMR (D_2O) 2.30 (4H, m, 3-H, 5-H, 7-H and 7'-H), 2.50 (1H, m, 4-H), 2.65 (2H, dd, 3'-H, and 5'-H); ^{13}C NMR (DMSO-d6) 27.02 (d, 4-C), 37.22 (t, 3-C, and 5-C), 38.60 (t, 7-C), 173.00 (s, acid C=O), 173.20 (s, glut C=O).

4-(Chlorocarbonyl-methyl)-piperidine-2,6-dione (B7)

The acid chloride was freshly prepared each time it was required by refluxing the acid (B1) in thionyl chloride until all had dissolved (Typically 5 ml per mmol). The thionyl chloride was then removed *in vacuo* and the highly crystalline (white rhombic crystals) acid chloride collected rapidly by suction and washed with a little dry benzene. M.p. 135-136 ^{0}C (lit.,[5], 135-136 ^{o}C); ν_{max} 1 815 (C=OCl) and 1 700 (C=O glut) cm^{-1}. The acid chloride was then reacted in this state.

4-(Ethoxycarbonyl-methyl)-piperidine-2,6-dione (B18).

The acid chloride (B7) (2.0 g) was stirred in dry ethanol for about 30 min when it had all dissolved. The ethanolwas removed and the *ester* (B18) recrystallized from the ensuing sludge, in >90% yield. M.p. 71-72 ^{o}C, ν_{max} (KBr) 3 300 (OH) 1 725, 1 700 cm^{-1}; ^{1}H, NMR ($CDCl_3$) 1.15 (3H, t, Me), 2.30 (2H, d, 7/7^{a}-H), 2.40 (3H, m, 3/4/5-

H) 2.55 (2H, dd, $3^a/5^a$-H), 4.15 (2H, q, CH_2Me), 8.04 (1H, brs, NH); ^{13}C NMR 14.15 (q, Me), 27.04 (d, 4-C), 37.16 (t, 3/5-C), 34.45 (t, 7-C), 60.63 (t, CH_2-O) 170.50 (s, C=O), 171.51 (s, glut C=O); m/z (DCI, NH_3) 217 ($M+NH_4^+$, 100%).

N-Benzyl-4-(Ethoxycarbonyl-methyl)-piperidine-2,6-dione (B23).

The ester (B18) (199 mg, 1.0 mmol) was suspended in dry THF (5 ml) under nitrogen. To this was added sodium hydride (50% suspension in oil (52.8 mgs, 1.1 mmol) whilst cooling with ice. After stirring for 20 min benzyl bromide (0.12 ml, 1.1 mmol) and tetrabutylammonium iodide (10 mg, 0.05 mmol) were added. The mixture was stiired at room temperature overnight, after which t.l.c showed one product of higher mobility (Rf 0.6 1:1 EtOAc/hexane) than staring material (Rf 0.2). The solvent was removed, and the residue co-evaporated with benzene before it was columned (1:1 EtOAc/hexane) to yield the N-*benzyl* glutarimide as a colourless oil, 105 mg, 37%. ν_{max} 1 735 and 1 700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1,20 (3H, t, Me), 2.30 (2H, dd, 7/7a-H), 2.45 (2H, dd, $3/3^a$-H), 2.85 (3H, m, $3^a/5^a$/4-H), 4.15 (2H, q, CH_2Me), 4.95 (2H, s, CH_2Ph), 7.30 (5H, m, Ar-H); ^{13}C NMR 14.13 (q, Me), 26.16 (d, 4-C), 38.36 (t, 3/5-C), 38. 85 (t, 7-C), 42.77 (t, CH_2Ph), 60.86 (t, CH_2-O) 127.43, 128.35 128.73 (d, Ar-C), 137.06 (s, Ar-C), 170.75 (s, C=O), 171.14 (s, glut C=O); m/z (DCI, NH_3) 289 (M^+, 55%), 91 (100) (Found, C, 66.36; H. 6.74; N, 4.82; $C_{16}H_{19}NO_4$ requires, C, 66.42; H, 6.62; N, 4.84%).

(Carbo*tert*butoxy)methylenetriphenylphosphonium bromide.

*Tert*Butyl α-bromoacetate (19.5 g, 0.1 mol) was added dropwise over 1 h to a solution of triphenyl phosphine (27.6 g, 0.105 mol) in dry benzene (150 ml) which was cooled with a water bath to maintain a temperature of below 40 °C. The solution was left to stir overnight by which time a thick precipitate of the phosphonium salt had formed. This solid was collected by vacuum filtration and washed with hexane. A little pump

pressure was then applied to complete drying. Yield 43.87 g, 96%, m.p. 177-179 °C (lit.,[32] 177 °C).

(Carbo*tert*butoxy)methylenetriphenylphosphorane.

The phosphonium salt (43.74 g) was suspended in 800 ml of water, to which was added a few drops of phenolphthalein, followed by sodium hydroxide pellets until the colour turned pink. 800 ml of benzene was added and the mixture stirred vigorously for 3 h, by which time all of the solid had dissolved. The layers were then allowed to separate and the benzene fraction retained. This was washed with water and brine then dried with $MgSO_4$. Concentration, which gave a solid, followed by an ether wash and drying *in vacuo* yielded the stabilised *ylid* as a white powder (32.05 g, 89%), m.p. 153-154 °C (lit.,[33] 154-156 °C).

4-(3-Carbo*tert*-butoxymethylene-2-oxo-3-triphenylphosphoranylidene-propyl)-piperidine-2,6-dione (B28)

The freshly prepared acid chloride (B7) (15.15 g, 80 mmol) dissolved in 600 ml of dry THF was added to a vigorously stirred solution of the ylid (46.40 g, 125 mmol) and *N,N*-dimethylaminopyridine (10.76 g, 88 mmol) in a further 1.5 l of dry THF. A white suspension formed immediately, and this was vigorously stirred at room temperature for 14 h. The suspension was filtered directly through a celite capped thin silica plug which was well washed with ethyl acetate. Solvents were evaporated *in vacuo*, and the residue purified by filtration through a bigger silica plug. Evaporation gave a white solid (37.50 g, 88%). Recrystallization from ethyl acetate gave white needles, m.p. 218-219 °C.

ν_{max} (KBr disc) 3 200 (NH), 1 740 (C=O, ester), 1 725, 1 695, and 1 645 (C=O) cm^{-}

1; ^{1}H NMR ($CDCl_3$) 1.05 (9H, s, Me), 2.25 (2H, dd, 3-H, 5-H), 2.65 (3H, m, 3'-H, 4-H, 5'-H), 3.00 (2H, d, 7-H), 7.40 to 7.70 (15H, m, ArH), 7.95 (1H, brs, NH); [N.b.the glutarimide peaks of this spectrum were fully assigned by running the spectrum at 500 MHz in benzene-*d*6; 1.85 (2H, dd, J_{gem} 17.1 Hz, J_{trans} 10.0 Hz, 3-H, 5-H), 2.31 (2H, dd, J_{gem} 17.1 Hz, J_{cis} 4.3 Hz, 3'-H, 4'-H), 2.40 (1H, m, 4-H), 3.00 (2H, d, J 6.5 Hz, 7-H and 7'-H)]; ^{13}C NMR ($CDCl_3$) 27.22 (d, 4-C), 28.04 (q, Me), 37.68 (t, 3-C, and 5-C), 44.27 and 44.17 (t, coupled to ^{31}P, 7-C), 77.25 (d, in BB and CW spectra, C-α to P), 78.85 (s, $\underline{C}Me_3$), 126.50 (d, Ar quaternary), 128.66, 132.79, and 132.95 (d, Ar), 172.64 (s, C=O glut), 193.45 (s, C=O); m/z (FAB+) 530 (MH^+); (Found C, 70.25; H, 6.26; N, 3.09; P, 5.70; $C_{31}H_{32}NO_5P$ requires C, 70.31; H, 6.09; N, 2.65; P, 5.85%).

4-(2-Oxo-3-triphenylphosphoranylidene-propyl)-pipreidine-2,6-dione (B29)

The *tert*butoxycarbonyl ylid (B28) (37.50 g) was dissolved in trifluoroacetic acid (350 ml), and the resulting solution warmed at 60 °C for 2 h. The acid was removed *in vacuo* and the residue dissolved in chloroform. This solution was succesively washed with water, 1N sodium hydroxide, water, and brine. After drying ($MgSO_4$) and concentration the residue was purified on a flash column eluted with a gradient of ethanol in chloroform (1 to 10%). A clear syrup resulted which could was triturated with ether to form a white solid, m.p. 191-192 °C, (18.11 g, 60%). ν_{max} (KBr) 3 200 (NH) and 1 700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.40 (4H, m, 3/4/7/7a-H), 2.75 (3H, m, 3a/4/5a-H), 7.70 to 7.50 (16H, m, Ar-H and H-9), 7.95 (1H, brs, NH); ^{13}C NMR 27.91 (d, 4-C), 37.47 (t, 3/5-C), 45.50 and 45.25 (each t, 7-C, with coupling to ^{31}P), 53.70 (dd (d in BB), 9-C), 127.0 (d (BB and CW), Ar-C), 128.6, 132.01, 132.88 (d, Ar-CH), 172.66 (s, glut C=O), 188.65 (s, C=O); m/z (FAB+) 430 (MH^+, 100%),

(Found C, 72.56; H, 5.58; N, 3.05; P,7.14; $C_{26}H_{24}NO_3P$ requires C, 72.71; H, 5.63; N, 3.26; P, 7.22%).

Wittig reactions with the ylid (B29) and substituted benzaldehydes; *general reaction scheme:*

The ylid (B29) was stirred in either dichloromethane or toluene under nitrogen. To this solution was added the aldehyde (1.1 equivalents) by syringe (either neat or dissolved in the same solvent) and the mixture was stirred at the relevant temperature until t.l.c. (10% ethanol in chloroform) revealed completion when no trace of the ylid (Rf 0.5) remained. Cooling (if needed) and simple filtration followed by vacuum drying produced the *4-(4-phenyl-2-oxo-but-3-enyl)-piperidine-2,6-dione,* which was in each case found to be of micro-analytical purity. Further crops of crystals were sometimes collected by evaporation of the filtrate, followed by washing of the residue with cold toluene, and collection by suction.

4-Nitrobenzaldehyde (30)

Solvent: Dichloromethane; Time 14 h; Room temperature; 63% yield. Buff needles, m.p. 239-240 °C. ν_{max} (KBr disc) 3 200 (NH), 1 720, 1 680 (C=O), and 1 610 (C=C) cm^{-1}; ^1H NMR (DMSO d-6), 2.35 (2H, dd, 3-H, and 5-H), 2.60 (3H, m, 3^a-H, 4-H, and 5^a-H), 2.80 (2H, d, 7/7^a-H), 7.05 and 7.75 (both 1H, d, *J* 15.8 Hz, olefinics), 8.15 (4H, ABq, Ar-H), 10.75 (1H, brs, NH); ^{13}C NMR (DMSO d-6), 25.97 (d, 4-C), 37.13 (t, 3-C, and 5-C), 44.69 (t, 7-C), 124.13 and 129.65 (d, Ar), 130.16 (d, α-CH), 138. 89 (d, β-CH), 141,12, and 148.27 (s, Ar), 173.03 (s, C=O, glut), 198.47 (s, C=O); m/z (EI), 302 (M^+ 100%); (Found C, 59.40; H, 4.69; N, 9.52; $C_{15}H_{14}N_2O_5$ requires C, 59.60; H, 4.67; N, 9.27%).

2-Hydroxybenzaldehyde (B31)

Solvent: Dichloromethane; Time 48 h; Room temperature, 95% yield. White powder, m.p. 214-215 ^{o}C. ν_{max} (KBr disc) 3 220- 3 080 (br, NH and OH), 1 710 and 1 690 (C=O), and 1 600 (C=C) cm^{-1}; 1H NMR (DMSO d-6), 2.31 (2H, dd, 3-H and 5-H), 2.55 (3H, m, 3^{a}-H, 4-H, and 5^{a}-H), 2.74 (2H, d, 7/7^{a}-H), 6.86 (d, *J* 16.4 Hz, α-CH), 7.60 to 6.80 (4H, m, Ar-H), 7.78 (1H, d, *J* 16.4 Hz, β-CH), 10.72 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 26.11 (d, 4-C), 37.16 (t, 3/5-C), 44.44 (t, 7-C), 116.39, 119.59 (d, Ar-C), 121.04 (s, Ar-C), 125.86 (d, α-CH), 128.79, 132.01 (d, Ar-C), 138.03 (d, β-CH), 157.20 (s, Ar-COH), 173.12 (s, glut C=O), 198.40 (s, C=O); λ_{max} (EtOH) 255 (6 280), 264 (5 600) and 295 (3 210) nm; m/z (DCI, NH_3) 274 ($M+H^+$, 100%); (Found C, 66.01; H, 5.41; N, 5.05; $C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53; N, 5.13%).

2-Fluorobenzaldehyde (B32).

Solvent: Toluene; Time 14 h; 100 ^{o}C, 77% yield. White powder, m.p. 180-181 ^{o}C. ν_{max} (KBr disc) 3 200 (NH), 1 700 and 1 670 (C=O), and 1 625 (C=C) cm^{-1}; 1H NMR (DMSO d-6), 2.34 (2H, dd, 3-H and 5-H), 2.52 (3H, m, 3^{a}-H, 4-H, and 5^{a}-H), 2.82 (2H, d, 7/7^{a}-H), 6.92 (d, *J* 16.5 Hz, α-CH), 7.26 to 7.52 (3H, m, Ar-H), 7.63 (1H, d, *J* 16.5 Hz, β-CH), 7.68 (1H, m, ArH), 10.72 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 25.97 (d, 4-C), 37.11 (t, 3/5-C), 44.65 (t, 7-C), 125.14 (d, α-CH), 116.42, 122.20, 128.83, 129.41, 132.71, 160.91(complex, due to ^{19}F coupling, Ar-C), 134.11 (d, β-CH), 173.00 (s, glut C=O), 198.27 (s, C=O); λ_{max} (EtOH) 280 (14 180), and 206 (13 460) nm; m/z (EI) 275 (M^+); (Found C, 65.43; H, 5.03; N, 4.84; $C_{15}H_{14}NO_3F$ requires C, 65.45; H, 5.13; N, 5.09%).

3-(Trifluoromethyl)-Benzaldehyde (B33).

Solvent: Toluene; Time 14 h; 100 ^{o}C, 74% yield. White powder, m.p. 158-159 ^{o}C.

ν_{max} (KBr disc) 3 200 (NH), 1 700 and 1 670 (C=O), and 1 630 (C=C) cm^{-1}; 1H NMR (DMSO d-6), 2.32 (2H, dd, 3-H and 5-H), 2.50 (3H, m, 3^a-H, 4-H, and 5^a-H), 2.80 (2H, d, 7/7^a-H), 7.04 (d, *J* 16.4 Hz, α-CH), 7.64 (3H, m and d, *J* 16.4 Hz, β-CH, and ArH), 8.03 (2H, m, ArH), 10.74 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 26.05 (d, 4-C), 37.12 (t, 3/5-C), 44.60 (t, 7-C), 124.00 (q, CF_3), 125.20 (d, Ar-C), 126.72 (s, Ar-C), 128.30 (d, α-CH), 129.20 (s, Ar-C), 130.13, 132.12, 135.74, (d, Ar-C), 140.79 (d, β-CH), 172.97 (s, glut C=O), 198.43 (s, C=O); λ_{max} (EtOH) 254 (16 750), and 212 (12 900) nm; m/z (DCI, NH_3) 326 ($M+H^+$, 100%); (Found C, 58.92; H, 4.14; N, 4.18; $C_{16}H_{14}NO_3F_3$ requires C, 59.08; H, 4.34; N, 4.31%).

4-Methoxybenzaldehyde (B34).

Solvent: Toluene; Time 48 h; 100 °C; 55% yield. White powder, m.p. 173-174 °C. ν_{max} (KBr disc) 3 200 (NH), 1 700 (C=O), and 1 600 (C=C) cm^{-1}; 1H NMR (DMSO d-6), 2.30 (2H, dd, 3-H and 5-H), 2.53 (3H, m, 3^a-H, 4-H, and 5^a-H), 2.75 (2H, d, 7/7^a-H),3.79 (3H, s, OMe), 6.90 (d, *J* 16.3 Hz, α-CH), 7.00 (2H, d, Ar-H), 7.58 (1H, d, *J* 16.4 Hz, β-CH), 7.69 (2H, d, Ar-H), 10.72 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 26.20 (d, 4-C), 37.20 (t, 3/5-C), 44.20 (t, 7-C), 55.49 (q, OMe), 114.62 (d, Ar-C), 124.31 (d, α-CH), 127.01 (s, Ar), 130.45 (d, Ar-C), 142.65 (d, β-CH), 161.43 (s, Ar), 173.08 (s, glut C=O), 198.17 (s, C=O); λ_{max} (EtOH) 320 (21 070), 230 (10 300) and 202 (20 380) nm; m/z (FAB$^+$) 288 ($M+H^+$, 100%); (Found C, 66.59; H, 5.97; N, 4.88; $C_{16}H_{17}NO_4$ requires C, 66.59; H, 5.85; N, 4.64%).

2-Pyridinecarboxaldehyde (B35).

Solvent: Toluene; Time 14 h; 100 °C, 88% yield. White powder, m.p. 214-215 °C. ν_{max} (KBr disc) 3 200 (NH), 1 700 and 1 660 (C=O), and 1 625 (C=C) cm^{-1}; 1H NMR (DMSO d-6), 2.33 (2H, dd, 3-H and 5H), 2.55 (3H, m, 3^a-H, 4-H, and 5^a-H),

2.84 (2H, d, 7/7^{a}-H), 7.14 (d, *J* 16.0 Hz, α-CH), 7.42 (1H, m, Ar-H), 7.63 (1H, d, J 16.0 Hz, β-CH), 7.85, 7.90, 8.65 (each 1H, m, ArH), 10.75 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 26.04 (d, 4-C), 37.11 (t, 3/5-C), 44.50 (t, 7-C), 125.09, 124.89 (d, Ar-C), 129.39 (d, α-CH), 137.33,(d, Ar-C), 141.62 (d, β-CH), 150.18 (d, Ar-C), 152.66 (s, Ar-C), 173.00 (s, glut C=O), 198.73 (s, C=O); m/z (FAB+) 259 (MH^+); (Found C, 65.30; H, 5.67; N, 10.52; $C_{14}H_{14}N_2O_3$ requires C, 65.10; H, 5.46; N, 10.85%).

4-(*E*-2-Oxo-4(2-nitrophenyl)-but-3-enyl)-piperidine-2,6-dione (B36)

The ylid (B29) (645 mg, 1.5 mmol) and 2-nitrobenzaldehyde were stirred together in dry dichloromethane (30 ml) at room temperature for 72 h. After this time the enone (B36) had been deposited from the solution, so it was collected by vacuum filtration and dried using pump pressure yielding a white powder (645 mg, 92%). M.p. 214-215 ^{o}C. ν_{max} (KBr disc) 3 200 (NH), 1 700 and 1 680 (C=O) cm^{-1}; ^{1}H NMR (DMSO d-6), 2.83 (2H, dd, 3-H and 5-H), 3.04 (3H, m, 3^{a}-H, 4-H, and 5^{a}-H), 3.29 (2H, d, 7/7^{a}-H),. 7.34 (d, *J* 16.1 Hz, α-CH), 8.16 (1H, t, 4'-H), 8.27 (1H, t, 5'-H), 8.35 (1H, d, *J* 16.1 Hz, β-CH), 8.40 (1H, d, 6'-H), 8.55 (1H, d, 3'-H), 11.23 (1H, brs, NH); ^{13}C NMR (DMSO d-6) 26.38 (d, 4-C), 37.51 (t, 3/5-C), 45.26 (t, 7-C), 125.29 (d, α-CH), 129.71 (d, 4'-C), 130.19 (s, 1'-C), 130.73 (d, 5'-C), 131.52 (d, 6'-C), 134.41 (d, 3'-C), 137.84 (d, β-CH), 149.08 (s, 2'-C), 173.38 (s, glut C=O), 198.53 (s, C=O); λ_{max} (EtOH) 202 (14 200), and 252 (7 790) nm; m/z (CI, CH_4) 303 ($M+H^+$, 100%); (Found C, 59.35; H, 4.58; N, 8.97; $C_{15}H_{14}N_2O_5$ requires C, 59.60; H, 4.67; N, 9.27%).

4-(2-quinolinyl-methyl)-piperidine-2,6-dione (B37)

The enone (B36) (300 mg) was dissolved in 150 ml of ethanol, and about 30 mg of 10% palladium on charcoal was added. The resulting suspension was stirred under an atmosphere of hydrogen for 30 minutes, after which a complex t.l.c. pattern showed one major product (Rf 0.6, 10% ethanol in chloroform), plus many other spots. After removal of the catalyst with the aid of a well washed celite cake the filtrate was concentrated under reduced pressure, leaving an oil which was purified by preparative layer chromatography, using first two plates of 2 mm thickness, followed by four of 1 mm silica layer, eluted by 8% ethanol in chloroform. After extraction of the required

band and evaporation of the solvent the required *quinoline* (B37) was recrystallised from ethanol (48 mg, 19%). M.p. 172-173 ^{o}C; ν_{max} (KBr disc) 3 200 (NH), 1 700 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$), 2.43 (2H, dd, 3-H and 5H), 2.75 (2H, dd, 3^{a}/5^{a}-H), 2.88 (1H, m, 4-H), 3.29 (2H, d, 7/7^{a}-H), 7.25 (1H, d, 3'-H), 7.51 (1H, t, 7'-H), 7.70 (1H, t, 6'-H), 7.79 (1H, d, 5'-H), 8.03 (1H, d, 4'-H), 8.12 (1H, brs, NH); ^{13}C NMR ($CDCl_3$) 30.53 (d, 4-C), 37.61 (t, 3/5-C), 45.57 (t, 7-C), 121.61 (d, 3'-C), 126.37 (d, 6'-C), 127.93 (s, 4a'-C), 127.58 (d, 5'-C), 129.09 and 130.84 (both d, 7'/8'-C), 136.81 (d, 4'-C), 145.05 (s, 8a'-C), 158.10 (s, 2'-C), 171.74 (s, C=O); λ max (EtOH) 207 (27 000), 228 (24 900), 272 (2 800), and 315 (3 420) nm; m/z (CI, CH_4) 255 (M+H^{+}, 100%); (Found C, 71.23; H, 5.55; N, 10.79; $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02%).

4-(*E*-2,5-Dioxo-4-methyl-hex-3-enyl)-piperidine-2,6-dione (B39)

To the ylid (B29) (2.15 g, 5.0 mmol) in 150 ml of dry DMF under nitrogen was added butane-2,3-dione (4.4 ml, 10 eq) in one portion. The resulting mixture was stirred at 100 ^{o}C for 14 h, when t.l.c. revealed no trace of the ylid (Rf 0.5, 10% ethanol in chloroform). The solvent and remaining diketone were co-removed under reduced pressure and the residue chromatographed on silica gel, eluted by a gradient of an ethanol-chloroform mixture (1-10%). The product, which co-ran with triphenylphosphine oxide, was partially crystallized from ethanol as the pure *E* isomer for which the data is given (0.54 g, 46 %). M.p. 138-139 ^{0}C; ν_{max} (KBr) 3 200 (NH), 1 700 (glut C=O) and 1 680 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.18 (3H, s, Me), 2.34 (2H, dd,3/5-H), 2.38 (3H, s, Me), 2.72 (5H, m, 3^{a}/5^{a}/4/7/7^{a}-H) 6.77 (1H, s, 9-H), 8.18 (1H, brs, NH); 13C NMR 13.72 (q, Me), 25.71 (d, 4-C), 26.27 (q, Me), 37.11 (t, 3/5-C), 48.38 (t, CH_2), 129.66 (d, C̲H=C), 148.96 (s, CH=C̲), 171.13 (s, glutarimide C=O), 198.25 and 199.97 (s, C=O); λ_{max} (EtOH) 204 (10 200), and 242 (7 82) nm;

m/z (CI, CH_4) 238 ($M+H^+$, 100%); (Found C, 61.05; H, 6.48; N, 5.75; $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.37; N, 5.90%).

4-(2,5-Dioxo-4-methylhexyl)-piperidine-2,6-dione (B43)

To the dienone (B39) (540 mgs) in ethanol (125 ml) was added about 50 mgs of Palladium black. The resulting suspension was stirred under hydrogen for 30 min when completion was apparent by t.l.c. (Product Rf 0.5, dienone Rf 0.55; 5% EtOH in $CHCl_3$). The catalyst was removed using a celite plug, and after concentration purification was achieved by flash chromatography (5% EtOH in $CHCl_3$). Crystallisation from ethanol yielded white needles, (385 mg, 75 %). M.p. 75-76 °C; ν_{max} (KBr) 3 200 (NH), 1 700 br (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.15 (3H, d, *J* 7.4 Hz, CH_3), 2.21 (3H, s, CH_3), 2.25 to 3.15 (10H, m, 3/3a/5/5a/4/7/7a/9/9a/10-H), 7.99 (1H, brs, NH); ^{13}C NMR 16.46 (q, Me), 25.77 (q, Me), 28.18 (d, 4-C), 37.20 (t, 3/5-C), 42.18 (d,10-C), 45.60 (t, 9-C), 46.68 (t, 3/5-C), 171.47 (s, glut C=O), 206.41 and 210.87 (s, C=0); m/z (CI, CH_4) 240 ($M+H^+$, 100%); (Found C, 60.39,; H, 7.27; N, 5.73; $C_{12}H_{17}N04$ requires C, 60.23; H, 7.16; N, 5.73%).

4-(4,5-dimethylfurfuryl)-piperidine-2,6-dione (B45).

To the diketone (B43) (36.0 mg, 0.15 mmol) in 5 ml of dry toluene was added *para*toluenesulphonic acid (3.0 mg, 0.1 eq), and the mixture stirred for 14 h at 50 °C, after which t.l.c. (10% EtOH in $CHCl_3$), revealed a clean reaction, starting material Rf 0.5, product Rf 0.6. The solvent was removed under reduced pressure and the residue purified by flash chromatography, eluant 5% ethanol in chloroform. This gave the *furan* (B45) recrystallised as fine white needles (EtOH) (30.8 mg, 93%, m.p.

108/9 °C). ν_{max} (KBr) 3 200 (NH), 1 700 (C=O) cm^{-1}; 1H NMR ($CDCl_3$) 1.88 (3H, s, Me), 2.14 (3H, s, Me), 2.32 (2H, dd, 3/5-H), 2.45 (1H, m, 4-H), 2.51 (2H, d, 7/7a-H), 2.69 (2H, m, 3/3a-H), 5.82 (1H, s, 3'-H), 8.32 (1H, brs, NH); ^{13}C NMR 9.72 (q, Me), 11.72 (q, Me), 30.01 9d, 4-C), 32.89 (t, 7-C), 37.30 (t, 3/5-C), 110.85 (d, 3'-C), 114.52 (s, 4'-C), 146.67 (s,2'-C), 148.07 (s, 5'-C), 171.90 (s, C=O); λ_{max} (EtOH) 205 (13 400), and 222 (6 080) nm; m/z (CI, CH_4) 232 ($M+H^+$, 100%).; (Found C, 65.25; H, 6.81; N, 6.00 $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%).

4-(2-(*N*-benzyl-4,5-dimethyl-pyrrolyl)-methyl)-piperidine-2,6-dione (B47).

To a solution of the diketone (B43) (36.0 mg, 0.15 mmol) in 10 ml of dry benzene under nitrogen was added benzylamine (0.16 ml, 1.5 mmol) in one portion. The temperature was raised to reflux for 120 h, when t.l.c. revaeled completion. (Product Rf 0.7, diketone Rf 0.5; 5% EtOH in $CHCl_3$). After removal of the solvent the residue was purified by flash chromatography (solvent as t.l.c), yilding an oil which crystallised ontrituration with ether, 42 mg, 90%. M.p. 111-112 °C; ν_{max} (KBr) 3 200 (NH), 1 700 (C=O) cm^{-1}; 1H NMR ($CDCl_3$) 2.05, 2.04 (3H, s, Me), 2.20 (3H, m, 3/5/4-H), 2.52 (2H, d, 7/7a-H), 2.68 (2H, dd, 3a/5a-H), 4.97 (2H, s, Ch_2-Ph), 5.78 (1H,s, 3'-H), 6.84 (2H, M, Ar-H), 7.28 (3H, m,Ar-H), 7.85 (1H, brs, NH); ^{13}C NMR 9.78, 11.23 (q, Me), 30.35 (d, 4-C), 31.66 (t, 7-C) 37.54 (t, 3/5-C), 46.86 (t, CH_2Ph), 109.01 (d,3'-C), 114.19, 125.10 (s, 2'/5'-C) 124.5 (d, Ar-CH), 126.01 (s, 4'-C), 127.28 128.85 (d, Ar-CH), 138.52 (s, Ar-C 171.80 (s, C=O); λ_{max} (EtOH) 205 (16 600) nm; m/z (FAB+) 311 ($M+H^+$, 25%) 91 (100); (Found C, 73.16; H, 7.34; N, 8.83; $C_{19}H_{22}N_2O_2$ requires C, 73.52; H, 7.15; N, 9.03%).

4-(Ethyl-3-methyl-2-oxo-pent-3-enoyl)-piperidine-2,6-dione (B41).

To the ylid (B29) (645 mg, 1.5 mmol) in 50 ml of dry DMF under nitrogen was added ethyl pyruvate (1.70 ml, 10 eq) in one portion. The resulting mixture was stirred at 100 °C for 14 h, when t.l.c. revealed no trace of the ylid (Rf 0.5, 10% ethanol in chloroform). The solvent and remaining ester were co-removed under reduced pressure and the residue chromatographed on silica gel, eluted by a gradient of an ethanol-chloroform mixture (1-10%). The product, which co-ran (Rf 0.75) with triphenylphosphine oxide, was crystallized from ethanol as the pure *E* isomer (380 mg, 90%). M.p. 104-105 °C. ν_{max} (KBr) 3 200 (NH), 1 700 (glut C=O) and 1 690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), 1.32 (3H, t, $CH_2\underline{CH_3}$), 2.24 (3H, s, Me), 2.33 (2H, dd, 3/5-H), 2.70 (5H, m, 3a/4/5a/7/7a-H), 4.26 (2H, q, $\underline{CH_2}CH_3$), 7.02 (1H, s, =CH), 8.27 (1H, brs, NH); ^{13}C NMR 14.04 (q, Me), 14.51, (q, Me), 25.74 (d, 4-C), 37.14 (t,3/5-C), 48.42 (t, 7-C), 61.72 (t, $O\underline{C}H_2CH_3$), 130.66 (d, 9-C), 142.86 (s, 10-C), 167.09 (s, ester C=O), 171.14 (s, C=O), 197.92 (s, C=O); λ_{max} (EtOH) 204 (15 100) and 235 (10 800) nm; m/z (CI, CH_4) 268 ($M+H^+$, 100%); (Found C, 58.68; H, 6.42; N, 5.22; $C_{13}H_{17}NO_5$ requires C, 58.42; H,6.41; N, 5.24%).

4-(*E*-2,5-dioxo-hex-3-enyl)-piperidine-2,6-dione (B40).

To the ylid (B29) (860 mg, 2.0 mmol) in 100 ml of dry DMF under nitrogen was added 2-oxo-propanal (40% aqueous solution, 1.8 ml, 10 eq) in one portion. The resulting mixture was stirred at room temperature for 14 h, when t.l.c. revealed no trace of the ylid (Rf 0.5, 10% ethanol in chloroform). The solvent was removed under reduced pressure and the residue chromatographed on silica gel, eluted by a gradient of an ethanol-chloroform mixture (0-10%). The product (Rf 0.6), thus separated from triphenylphosphine oxide (Rf 0.7) was crystallised from ethanol as the pure *E* isomer (345 mg,77 %). M.p. 119-120 °C; ν_{max} (KBr) 3 200 (NH), 1 700 (glut C=O) and 1 675 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.61 (3H, s, Me), 2.40 (3H, m, 3/5/4-H), 2.80

(2H, dd, $3^a/5^a$-H), 6.81 and 6.88 (each 1H, d, *J* 16.4 Hz, CH), 8.01 (1H, brs, NH); ^{13}C NMR 25.72 (d, 4-C), 28.38 (q, Me), 37.16 (t,3/5-C), 45.18 (t, 7-C), 136.20, 137.64 (d,9/10-C), 171.28 (s, C=O), 197.16 and 197.36 (s, C=O); λ_{max} (EtOH) 205 (14 500) and 228 (11 500) nm; m/z (DCI, NH_3) 241 ($M+NH_3^+$, 100%).; (Found C, 59.25; H, 5.96; N, 6.11; $C_{11}H_{13}NO_4$ requires C, 59.18; H, 5.87; N, 6.28%).

4-(2,5-Dioxo-hexyl)-2,6-piperidine-2,6-dione (B44)

To the dienone (B40) (180 mgs) in ethanol (70 ml) was added about 50 mgs of Palladium black. The resulting suspension was stirred under hydrogen for 20 min when completion was apparent by t.l.c. (Product Rf 0.6, dienone Rf 0.65; 10% EtOH in $CHCl_3$). The catalyst was removed using a celite plug; after concentration, purification was achieved by recrystallisation from ethanol, giving white needles (175 mg, 95 %). M.p. 75-76 °C; ν_{max} (KBr) 3 200 (NH), 1 700 (glut C=O) and 1 690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 2.19 (3H, s, Me), 2.33 (3H, m, 3/5/4-H), 2.60 to 2.79 (8H, m, $3^a/5^a/7/7^a/9/9^a/10/10^a$-H), 7.95 (1H, brs, NH); ^{13}C NMR 25.84 (q, Me), 29.67 (d, 4-C), 36.42 (t, 9-C),36.44 (t, 10-C), 37.22 (t, 3/5-C) 46.72 (t, 7-C), 171.50 (s, C=O), 206.36 and 206.56 (s, C=O); m/z (DCI, NH_3) 226 ($M+H^+$, 90%) 243 ($M+NH_4^+$, 100); (Found C,58.62; H, 6.82; N, 6.10; $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.72; N, 6.22%).

4-(5-methyl-furfuryl)-piperidine-2,6-dione (B46).

To the diketone (B44) (45.0 mg, 0.20 mmol) in 10 ml of dry toluene was added *para*toluenesulphonic acid (4.0 mg, 0.1 eq), and the mixture stirred for 48 h at 50 °C, after which t.l.c. (5% EtOH in $CHCl_3$), revealed a only a trace of the diketone (Rf 0.4) with one product (Rf 0.6). The solvent was removed under reduced pressure and

the residue purified by flash chromatography, eluant 5% ethanol in chloroform. This gave a colourless oil (20.8 mg, 48%). ν_{max} (film) 3 200 (NH), 1 700 (C=O) cm^{-1}; 1H NMR (CDCl3) 2.25 (3H, s, Me), 2.32 (2H, dd, 3/5-H), 2.50 (1H, m, 4-H), 2.68 (2H, d, J 6.2 Hz, 7/7a-H), 2.72 (2H, dd, 5a/3a-H), 5.87 and 5.95 (each 1H, d, *J* 3.0 Hz, furan-H), 7.96 (1H, brs, NH); 13C 13.49 (q, Me), 30.02 (d, 4-C), 32.99 (t, 3/5-C), 37.31 (t, 7-C), 106.14 and 108.30 (d, 3'-C and 4'-C), 147.20 and 149.00 (s, 2'-C and 5'-C), 171.76 (s, C=O); m/z (DCI, NH_3) 208 ($M+H^+$, 100%).

4-(2-(N-Benzyl-5-methyl-pyrrolyl)-methyl)-piperidine-2,6-dione (B48).

To a solution of the diketone (B44) (45.0 mg, 0.2 mmol) in 10 ml of dry benzene under nitrogen was added benzylamine (0.20 ml, 2.0 mmol) in one portion. The temperature was raised to reflux for 120 h, when t.l.c. revaeled completion. (Product Rf 0.6, diketone Rf 0.5; 5% EtOH in $CHCl_3$). After removal of the solvent the residue was purified by flash chromatography (1 to 5% gradient of EtOH in $CHCl_3$), yielding an oil which crystallized on trituration with ether, 40 mg, 68%. M.p. 134-135 °C; ν_{max} (KBr) 3 200 (NH), and 1 690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 2.16 (3H, s, Me), 2.21 (3H, m,3/4/5-H), 2.54 (2H, d, *J* 6.3 Hz, 7/7a-H), 2.67 (2H, dd, 3a/5a-H), 5.01 (2H, s, CH_2Ar), 5.92 (2H, m, 3'/4'-H), 6.84 (2H, m, Ar-H), 7.28 (3H, m, Ar-H), 7.91 (1H, brs, NH); ^{13}C 12.36 (q, Me), 30.36 (d, 4-C), 31.69 (t, 3/5-C), 37.51 (t, 7-C), 46.73 (t, CH_2Ar), 106.22 and 107.14 (d, 3'/4'-C), 125.36, 127.36 and 128.90 (d, Ar-C), 127.35, and 128.95 (s, 2'/5'-C), 138.20 (s, Ar-C), 171.68 (s, C=O); λ_{max} 206 (15 900) nm; m/z (FAB+) 311 ($M+H^+$, 25%), 91 (100); (Found C, 72.62; H, 7.05; N, 8.99; $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.40%).

2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranose (B55)

To a vigorously stirred suspension of D-mannose (15.0 g, 83.3 mmol) in acetone (AR grade, 200 ml) was added concentrated sulphuric acid (3.5 ml) in one portion. This was stirred at room temperature untiil all of the sugar had dissolved (3 h) after which the solution was carefully neutralised with solid sodium carbonate. The suspension was then filtered through celite and the filtrate removed to suitable apparatus where it was refluxed for 1 h with 0.5 g of sodium carbonate. After cooling the mixture was filtered through a silica plug (well washed with ethyl acetate) and concentrated to a white solid which was recrystallised from hexane. (White needles, m.p. 122-123 °C, (lit,[28] 122-123 °C) (20.15 g, 93%); ^{1}H NMR ($CDCl_3$), 1.33, 1.38, 1.46, and 1.47, (all 3H, s, Me), 4.10 (2H, m, 4-H, and 6-H), 4.20 (1H, dd, 6'-H), 4.40 (1H, m, 5-H), 4.75 (1H, d, 2-H), 4.85 (1H, dd, 3-H), 5.35 (1H, s, 1-H).

Benzyl-2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranoside (B54)

Sodium hydride (50% dispersion in oil, 2.4 g, 50 mmol) was washed with three 10 ml portions of hexane, then suspended in 25 ml of dry DMF under nitrogen. To this suspension was added diacetone mannose (10.4 g, 40 mmol) in a further 25 ml of dry DMF, with benzyl chloride (11.5 ml, 100 mmol), and the mixture stirred at room temperature for one hour. To this mixture was then added 62.5 ml of 1N sodium methoxide in methanol and the mixture refluxed for 30 min. After cooling 100 ml of water was added to the mixture, which was then extracted with 2x 100 ml portions of ether. The ether was subsequently backwashed with water (2x), washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After coevaporation with three 75 ml portions of benzene (to remove excess benzyl chloride), the residue was purified by flash chromatography (4:1 to 2:1 ether-hexane gradient) to give a syrup which was

used as such in the next stage. An analytical sample was crystallized from aqueous methanol. M.p.53-54 ^{o}C, lit,[27] 54-55^{o}C); ^{1}H NMR, ($CDCl_3$), 1.33, and 1.39 (each 3H, s, Me), 1.47 (6H, s, 2x Me), 3.98 (2H, m, 6-H, and 4-H), 4.12 (1H, dd, 6'-H), 4.42 (1H, m, 5-H), 4.67 (1H, d, J 5.9 Hz, 2-H), 4.50 and 4.65 (each 1H, d, J 8.0 Hz, CH_2Ph), 4.81 (1H, dd, J_{2-3} 5.9 Hz, 3-H), 5.09 (1H, s, 1-H), 7.33 (5H, m, Ph).

Benzyl-2,3-*O*-isopropylidene-α-D-mannofuranoside (B56)

The crude diacetonide (B54) was dissolved in 180 ml of methanol, to which was added 3.0 ml of concentrated hydrochloric acid, the solution then diluted to turbidity with distilled water. T.l.c. revealed after 3 h that no starting material remained (Rf 0.8, 1:1 ether-hexane). The solution was then carefully neutralised with 880 ammonia and partially reduced in volume. This mixture was extracted with 150 ml of chloroform which was in turn washed with water (2x) and brine, before drying ($MgSO_4$). Concentration and flash chromatography (2 to 4% gradient of methanol in chloroform) yielded a grainy syrup which was crystallized from ethyl acetate- hexane. (9.92 g, 80% for two steps). M.p. 60-61 ^{o}C lit.[27] 60-61 ^{o}C); ^{1}H NMR ($CDCl_3$) 1.33 and 1.48 (both 3H, s, Me), 2.00 and 2.77 (both 1H, br, OH), 3.68 and 3.82 (each 1H, dd, J_{gem} 11.4 Hz, 6-H, and 6'-H), 4.00 (2H, m, 4-H, and 5-H), 4.51 and 4.63 (each 1H, d, CH_2Ph), 4.67 (1H, dd, J_{2-3} 6.0 Hz, 2-H), 4.86 (1H, dd, J_{2-3} 6.0 Hz, 3-H), 5.13 (1H, s, 1-H), 7.34 (5H, m, Ar).

Benzyl-2,3-*O*-isopropylidene-α-D-lyxo-pentodialdofuranoside-(1,4) (B53)

To the diol (B56) (0.87g, 2.8 mmol) in 25 ml of methanol was added sodium periodate (0.90 g, 0.42 mmol) in 2 ml of water; the reaction was then diluted until turbidity by careful further addition of water. After stirring for one hour t.l.c. (5%

ethanol in chloroform) revealed a clean reaction (product Rf 0.7, Starting material Rf 0.5). The resulting suspension was filtered through a celite plug , well washed with methanol, partially concentrated, and partitioned using 100 ml of chloroform washed with 2x 100 ml of water. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to dryness. Without further purification the aldehyde was carried through to the next step.

4-(*E*-2-oxo-4-(*4*-1-*O*-Benzyl-2,3-*O*-isopropylidene-α-D-lyxofuranosyl)-but-3-enyl)-piperidine-2,6-dione (B52)

The aldehyde (B53) was used, assuming a 90% yield, as the resulting crude syrup which was taken up in 50 ml of dry dichloromethane and added to the ylid (B29) in a further 50 ml of dichloromethane. After 2 days of reflux under nitrogen the reaction was virtually complete by t.l.c. so the solvent was removed and the residue partially pufified by flash chromatography (gradient of 1% to 5% ethanol in chloroform): this resulted in the recovery of 98 mg of starting aldehyde. The product, a 7:1 mixture of geometric isomers by NMR, was virtually inseparable from the triphenylphosphine oxide biproduct by chromatography but careful crystallisation from hot ethanol gave white needles of the E isomer (0.57 g, 65%) m.p. 151-152 ^{0}C. The rest of the required material was best recovered after hydrogenation of the double bond and the benzyl ether (vide supra). (Data for the E isomer) $[\alpha]_D^{20}$ + 5.2^o (c, 1.00, $CHCl_3$); ν_{max} (KBr disc) 3 200 (NH), 1 730 (C=O), 1 690 (C=O), and 1 665 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.32 and 1,46 (each 3H, s, Me), 2.35 (2H, dd, 3/5-H), 2.75 (5H, m, 3a/5a/7/7a/4-H), 4.50 and 4.70 (each 1H, d, J 11.7 Hz, CH_2Ar), 4.65 (1H, m, 4'-H), 4.70 (1H, d, J 3.8 Hz, 2'-H), 4.80 (1H, dd, J_{2-3} 3.8 Hz, J_{3-4} 5.8 Hz, 3'-H), 5.16 (1H, s, 1'-H), 6.38 (1H, dd, J 16.0 and 1.5 Hz, 9-CH), 6.85 (1H, dd, J 16.0 and 5.4 Hz, 10-CH), 7.33 (5H, m, ArH), 8.23 (1H, brs, NH); ^{13}C NMR ($CDCl_3$) (nb, full

assignments of this spectrum with the aid of ^{1}H-^{13}C heteronuclear shift correlation) 24.83 (q, Me), 26.01 (d and q, 4-C, and Me), 37.36 (t, 3/5-C), 44.09 (t, 7-C), 69.21 (t, CH_2Ar), 79.24 (d, 4'-C), 81.10 (d, 3'-C), 85.26 (d, 2'-C), 105.41 (d, 1'-C), 113.11 (s, acetonide), 128.52 and 128.02 (d, Ar), 130.85 (d, 9-CH). 137.03 (d, 10-CH), 171.46 (s, glut C=O), 196.42 (s, C=O); λ_{max} (EtOH) 210 nm (23 450); m/z (ACE, NH_3) 447 ($M+NH_4^+$), and 430 ($M+H^+$); (Found C, 64.57; H, 6.27; N, 3.19; $C_{23}H_{27}NO_4$ requires C, 64.32; H, 6.34; N, 3.26%).

4-(2-oxo-4-(*4*-1-*O*-Benzyl-2,3-*O*-isopropylidene-α-D-lyxofuranosyl)-butyl)-piperidine-2,6-dione (B57)

The enoate (B52) (70 mg) was dissolved in 25 ml of a 3:2 mixture of ethanol-ethyl acetate to which was added 20 mg of Palladium black in the usual manner. The suspension was stirred under an atmosphere of hydrogen for one hour. The resulting ketone (B57) was inseparable from the enone by t.l.c., but it was more reactive towards the molybdate charring reagent. Filtration of the catalyst with the aid of a well washed celite cake, evaporation and recrystallisation (EtOH) gave fine white needles (70 mg, 100%). M.p. 82-83 °C, ν_{max} (KBr) 3 200 (NH), 1 700 br (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.31 and 1.45 (each 3H, s, Me), 2.02 (2H, m, 10/10a-H), 2.27 to 2.78 (9H, m, 3/3a/45//5a/7/7a/9/9a-H), 3.93 (1H, m, 4'-H), 4.48 (1H, d, CHH'Ph), 4.63 (3H, m, CHH'Ph, 2'-H, and 3'-H), 5.04 (1H, s, 1'-H), 1.30 (5H, m, Ar), 8.23 (1H, brs, NH); ^{13}C NMR ($CDCl_3$) 22.67 (t, 10-C), 24.86 and 25.68 (both q, Me), 26.08 (d, 4-C), 37.24 (t, 3-C, and 5-C), 39.83 (t, 7-C), 46.22 (t, 9-C), 69.00 (t, CH_2Ph), 78.94 (d, 4'-C), 80.21 (d, 3'-C), 85.29 (d, 2'-C), 105.16 (d, 1'-C), 112.46 (s, acetonide), 127.79 , 127.90, and 128.46 (all d, Ar), 137.47 (s, Ar), 171.41 (glut C=O), 206.92 (s, C=O); m/z (CI, NH_3) 449 ($M+NH_4^+$), 324 (100%); (Found C, 64.01; H, 6.78; N, 3.08; $C_{23}H_{29}NO_7$ requires C, 64.02; H, 6.77; N, 3.25%).

4-(2-Oxo-4-(*4*-2,3-*O*-isopropylidene-D-lyxofuranosyl)-butyl)-piperidine-2,6-dione (B57)

The enoate (B52) (1.40 g) was dissolved in 250 ml of a 3:2 mixture of ethanol-ethyl acetate to which was added 200 mg of Palladium black in the usual manner. The suspension was stirred under an atmosphere of hydrogen for 48 h, when t.l.c (5% EtOH in $CHCl_3$,) revealed no spot corresponding to the enone (B52) or ketone (B57) (Rf 0.6), and one product (Rf 0.3). After filtration of the catalyst with the aid of a well washed celite cake, evaporation and a short flash column gave a grainy oil. Recrystallisation (EtOH) gave initially fine white needles of only the α-anomer (as shown by the nmr of freshly dissolved material), m.p. 114-115 °C (Total yield 1.02 g, 92%). ν_{max} (KBr) 3 360 (OH), 3 200 (NH), 1 730 (C=O), 1 680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) (a-anomer) 1.32 and 1.45 (each 3H, s, Me), 2.02 (2H, m, 10/10^a-H), 2.32 to 2.80 (9H, m, 3/3^a/4/5//5^a/7/7^a/9/9^a-H), 3.48 (1H, brs, exchanges D_2O, OH), 4.12 (1H, m, 4'-H), 4.60 (1H, d, J_{2-3} 5.9 Hz, 2'-H), 4.65 (1H, m, 3'-H), 5.32 (1H, s, 1'-H), 8.16 (1H, brs, exchanges D_2O, NH), (nb. no significant enhancement of resolution in C_6D_6 at 500 MHz); ^{13}C NMR ($CDCl_3$) 22.57 (t, 10-C), 24.83 and 25.63 (each q, Me), 26.07 (d, 4-C), 37.17 (t, 3-C, and 5-C), 39.36 (t, 9-C), 46.45 (t, 7-C), 78.56 (d, 4'-C), 80.38 (d, 3'-C), 85.82 (d, 2'-C), 100.68 (d, 1'-C), 112.38 (s, acetonide), 172.33 (s, glut C=O), 207.64 (s, C=O); m/z (NH_3, DCI) 342 ($M+H^+$), 324 ($M+H^+$-18, 100%); (Found C, 56.41; H, 6.50, N, 3.91; $C_{16}H_{23}NO_7$ requires C, 56.29; H, 6.79, N, 4.10%).

4-[2-(1'S,2'S,3'S,4'S,5'R)-1',2'-Epoxy-3',4'-5'-trihydroxy-cyclohexyl-2-oxo-ethyl]-piperidine-2,6-dione (B62).

The lactol (B51) (85 mg, 0.25 mmol) was added to dry benzene (50 ml) containing 18-crown-6 (66 mg, 0.25 mmol) and potassium carbonate (104 mg, 0.75 mmol), all under dry nitrogen. The mixture was refluxed for 96 h, after which there remained starting material (Rf 0.3, 5% EtOH in $CHCl_3$), with a single product (Rf 0.5). The solution was filtered, evaporated and then purified by flash chromatography, giving recovered lactol (37 mg) and the epoxide (B62) (23.3 mg, 48%, on recovery of S/M). Crystallization from ethanol gave white needles, m.p. 184-185 ^oC. ν_{max} (KBr) 3 450 (OH) and 1 700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.38 (6H, s, Me) 2.05-2.90 (10H, m, 3/3a/4/5/5a/7/7a/6'/6'a-H and 0H), 3.33 (1H, s, 2'-H), 4.06 (1H, m, 5'-H), 4.34 (1H, t, $J_{3,4}$ 5.5 Hz, 4'-H), 4.65 (1H, d, 3'-H), 8.09 (1H, brs, NH); ^{13}C NMR (heteronuclear correlated) 24.28 (t, 6'-C), 25.35 (q, Me), 25.51 (d, 4-C), 27.53 (q, Me), 37.20 (t, 3/5-C), 39.37 (t, 7-C), 57.53 (d, 2'-C), 63.43 (s, 1'-C), 64.50 (d, 5'-C), 70.60 (d, 3'-C), 74.35 (d, 4'-C), 110.47 (s, acetonide), 170.91 (s, glut C=O), 204.37 (s, C=O); m/z 340 ($M+H^+$, 30%), 357 ($M+NH_4^+$, 100); (Found C, 56.43; H, 6.36; N, 4.07 $C_{16}H_{21}NO_7$ requires C, 56.62; H, 6.24; N, 4.13%).

4-[2-(1'S,2'S,3'S,4'S,5'R)-5'Acetoxy-1',2'-epoxy-3',4'-dihydroxy-cyclohexyl-2-oxo-ethyl]-piperidine-2,6-dione (B63).

The epoxide (B62) (5.0 mg, 0.014 mmol) was dissolved in 1 ml of dry dichloromethane under nitrogen at room temperature. To this was added pyridine (12 µl, 10 eq), and acetic anhydride 4 µl, 2 eq). After one hour no starting material remained (Rf 0.5, 1:10 ethanol/chloroform) with one product (Rf 0.7). The solution was diluted and washed with water, copper sulphate (x2), water, brine, then dried ($MgSO_4$). Filtration through a short silica plug (eluted with the t.l.c. solvent) gave the acetate (B63) as an oil, 5.0 mg. ^1H NMR ($CDCl_3$) 1.37 (6H, s, Me), 2.07 (3H, s, C=OMe), 2.10 to 2.95 (9H, m, 3/3a/4/5/5a/7/7a/6'/6'a-H), 3.24 (1H, s, 2'-H), 4.18

(1H, t, 4'-H), 4.56 (1H, d, $J_{3',4'}$, 3'-H), 5.22 (1H, m, 5'-H), 7.92 (1H, brs, NH); m/z (ACE, NH_3) 382 ($M+H^+$, 30%), 399 ($M+NH_4^+$, 100).

References, Section B.

1 F. Johnson, *Fortschr. Chem. Org. Naturst.*, 1971, **29**, 140.

2 D.D. Phillips, M.A. Acitelli and J. Meinwald, *J. Am. Chem. Soc.*, 1957, **79**, 3517.

3 B.C. Lawes, *J. Am. Chem. Soc.*, 1960, **83**, 6413.

4 F. Johnson, *J. Org. Chem.*, 1962, **27**, 3658.

5 Y. Egawa, M. Suzuki and T. Okuda, *Chem. Pharm. Bull.*, 1963, **11**, 589.

6 F. Johnson, W.D. Gurowitz and N.A. Starkovsky, *Tetrahedron Lett.*, 1962, 1167.

7 Y. Egawa, M. Suzuki and T. Okuda, *J. Antibiotics*, 1961, **14**, 158; *Chem. Pharm. Bull.*, 1963, **11**, 582.

8 F. Johnson, W.D. Gurowitz and N.A. Starkovsky, *J. Am. Chem. Soc.*, 1964, **86**, 118; *Ibid.*, 1966, **88**, 149

9 S. Kudo, T. Oritani and K. Yamashita, *Agric. Biol. Chem.*, 1984, **48**, 2739.

10 S. Kudo, T. Oritani and K. Yamashita, *Agric. Biol. Chem.*, 1985, **49**, 2919.

11 L.D. Cama and B.D. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006.

12 W.S.Wadsworth, *Org. React.*, 1977, **25**, 73.

13 See 'Comprehensive Heterocyclic Chemistry,' A.R. Katritzky and C.W. Rees Eds, Vols 2,3 and 4, Pergamon, Oxford, 1984.

14 a) U. Weiss and J.M. Edwards, 'The Biosynthesis of Aromatic Compounds,' Wiley, New York, 1980; b) E. Haslam, 'The Shikimate Pathway,' Wiley, New York, 1974.

15 G.W.J. Fleet, T.K.M. Shing and S.M. Warr, *J. Chem. Soc., Perkin Trans. I*, 1984, 905.

16 G. Jones, *Org. React.*, 1967, **15**, 204; P.M. Collins, W.G. Overend and T.K.M. Shing, *J. Chem. Soc., Chem. Commun.*, 1982, 297.

17 A.T. Neilsen and W.J. Houlihan, *Org. React.*, 1968, **16**, 47.

18 G.W.J. Fleet and D. Fryer, unpublished results.

19 F. Mathey and P. Savignac, *Tetrahedron,* 1978, **34**, 649; *Synthesis,* 1976, 766.

20 R.S. Torr and S Warren, *J. Chem. Soc. Pak.,* 1979, **1**, 15.

21 O.H. Wheeler and O. Rosado, in 'The Chemistry of Amides,' S. Patai and J. Zabicky Eds, Wiley, New York, 1970, p. 335.

22 P.W. Jeffs and D.J. McWilliams, *J. Am. Chem. Soc.,* 1981, **103**, 6185.

23 G. Jones, 'Synthesis of Quinoline Ring System,' in 'Quinolines, Heterocyclic Compounds, Vol. 32,' Ed. G. Jones, Wiley, New York, 1977.

24 There is precedent for the reduction of glutarimides, see for example:
a) M.K. Hargreaves, J.G. Prichard and H.R. Dave, *Chem. Rev.,* 1970, **70**, 439;
b) R.H. Schlessinger and J.L. Wood, *J. Org. Chem.,* 1986, **51**, 2621.

25 C.W. Bird and G.W.H. Cheeseman, in Ref 13, Vol 4, p. 97.

26 R. Livingstone, in 'Rodd's Chemistry of Carbon Compounds,' 2nd Edition, S. Coffey, Ed., Elsevier, Amsterdam, 1973, IVA, p. 331.

27 J.S. Brimacombe, F. Hunedy and L.C.N. Tucker, *J. Chem. Soc. C,* 1968,1381.

28 'Methods in Carbohydrate Chemistry,' R.L.Whistler and M.L. Wolfram, Eds, Academic Press, New York, 1963, II, p.319.

29 T.W. Greene, 'Protective Groups in Organic Synthesis,' Wiley, New York, 1981.

30 J.P.H. Verheyden, A.C. Richardson, R.S. Bhatt, B.D. Grant, W.L. Fitsch and J.G. Moffatt, *Pure Appl. Chem.,* 1978, **56**, 1363.

31 B. Ganem, *Tetrahedron,* 1978, **34**, 3353.

32 G.F. Griffiths, G.W. Kenner, S.W. McCombie, K.M. Smith and M.J. Sutton, 1976, **32**, 275.

33 P.L. Stotter and K.A. Hill, *Tetrahedron Lett.*,1975, 1679.

APPENDIX

Biological Screening of the Glutarimides.

Results of Miniscreen Analyses at Shell Research Centre, Sittingbourne.

This section summarises the results from the three primary agrochemical screens to which each of the indicated glutarimides was subjected.

Fungicide Tests.

The compound was sprayed as a 1 500 ppm solution in 50% aqueous acetone containing a surfactant. A score of 1 was the result of 50-80% control of the disease; one of 2 represented 90-100% control. Unconfirmed activity.was indicated by *.

Test Fungi were as follows.

Pv_a	*Plasmopara viticola*	Vine Downy Mildew	(antisporulant)
Pv_p	*Plasmopara viticola*	Vine Downy Mildew	(prophylactic)
Bc	*Botrytis cinerea*	Grey Mould	(prophylactic)
Eg	*Erysiphe graminis*	Barley Powdery Mildew	(therapeutic)
Po	*Pyricularia oryzae*	Rice Blast	(eradicant)
Ln	*Leptosphaeria nodorum*	Wheat Glume Blotch	(eradicant)
Pr	*Puccinia recondita*	Wheat Brown Rust	(therapeutic)

Results.

These were the tests in which most activity was seen, a good proportion of compounds showed at least some unconfirmed activity. The groups reflect the synthetic origins of each compound. At least one compound from each group showed some positive result.

Group a) BA1 $Pv_p/1^*$, Eg/1 BA3 Eg/1.

Group b) BA7 $Pv_p/2$, Bc/1^*; BA6 Eg/1^*, Pr/1^*.

Group c) BA8 Eg/1^*.

Group d) BA13 $Pv_p/2$.

Group e) BA16 $Pv_p/1^*$; BA17 Pvp/1^*;

BA18 $Pv_a/1^*$, Pr/1^*; BA19 $Pv_a/1^*$

Herbicide Tests.

The following species were tested in both pre-emergence and foliar tests. Application was achieved by spraying the equivalent of 0.32 Kg/Ha 50% aqueous acetone solution, containing a surfactant (a lower than normal concentration).

Maize	Linseed
Rice	Mustard
Barnyard Grass	Sugar Beet
Oat	Soya

Results

Of all the compounds screened only three showed any sign of herbicidal activity. The numbers represent a combined score for the range of species, each scored out of 10, so these represent a low level of action. There was a degree of selectivity in that only the dicotyledonous species were affected. These three compounds were also screened for Plant Growth Regulatory properties, but no action was observed.

Scores: BA2, 3; BA3 6, BA4 10.

Insecticide Screens

In these tests the compound was sprayed as a 0.2% active ingredient solution in 80% aqueous acetone containing a surfactant. The following species were treated:

Aedes aegypt	Yellow Fever Mosquito
Musca domestica	House Fly
Spodoptera littoralis	Egyptian Cotton Leaf Worm
Tetranychus uriticae	Red Spider Mite

Results

Only one compound, BA7, showed any activity in this screen; showing 60-80% mortality against *Musca domestica.*

Summary of all Results.

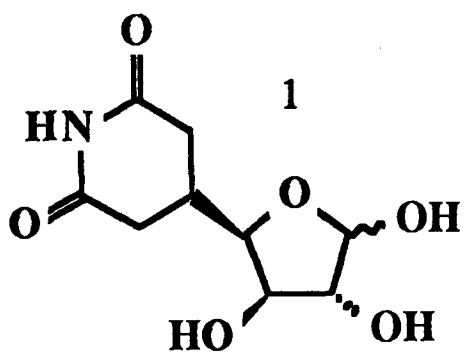
Although many of these compounds exhibited some activity in these primary screens, especially fungicidal, none of this was at a suitable level to warrant further investigation.

Compounds Screened

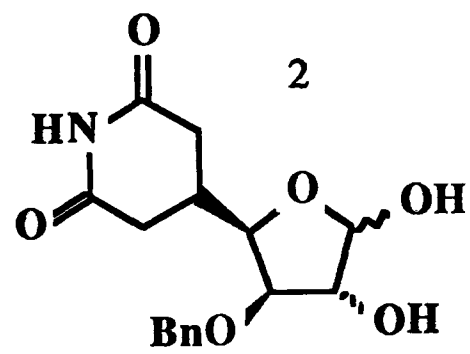
These are grouped according to synthetic origins.

(New numbers, prefixed by BA, in discussion)

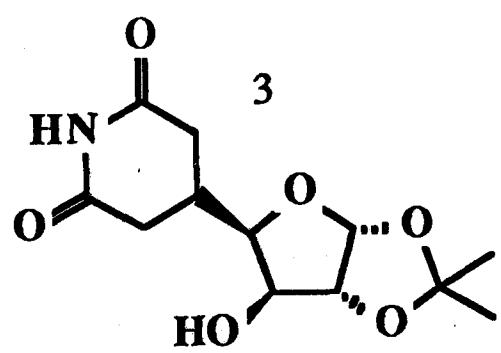
Group a), *Glutarimides attached to D-Xylose.*



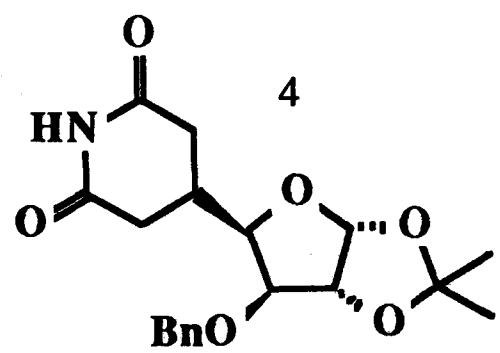
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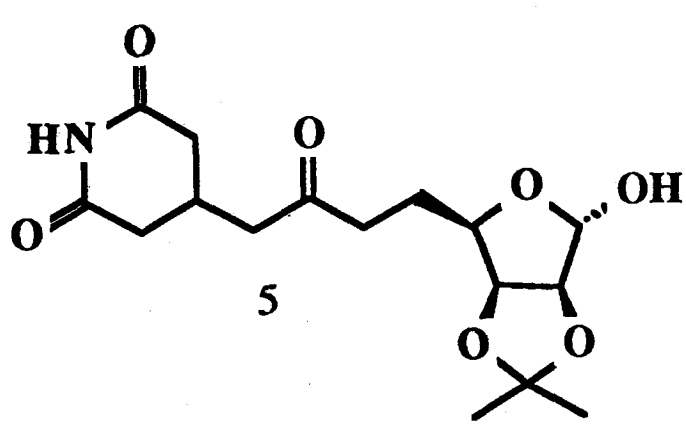


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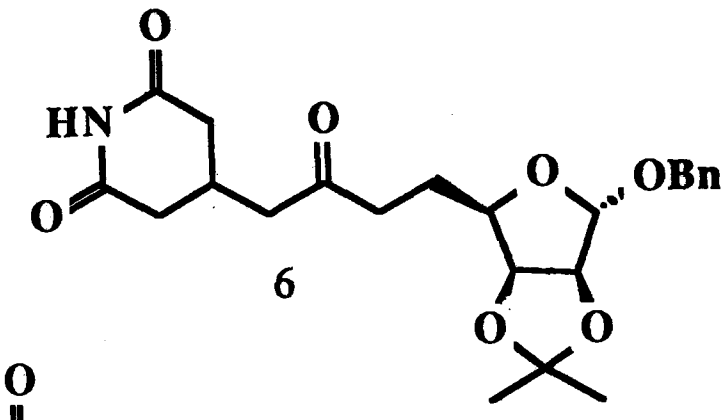


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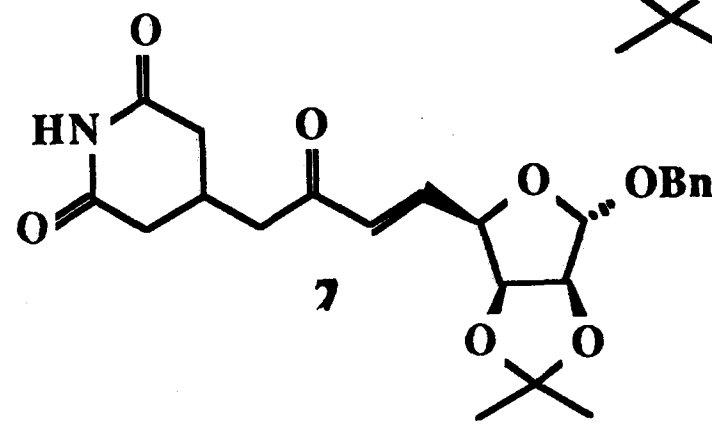
Group b), *Glutarimides attached to D-Lyxose* via *Wittig Chemistry*



5

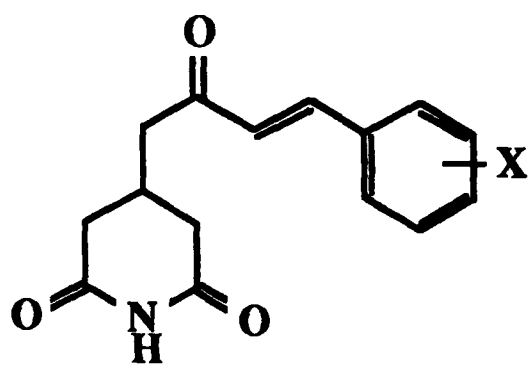


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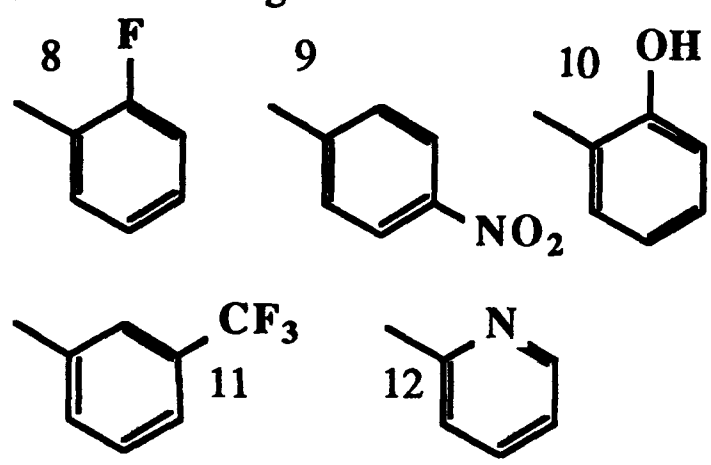


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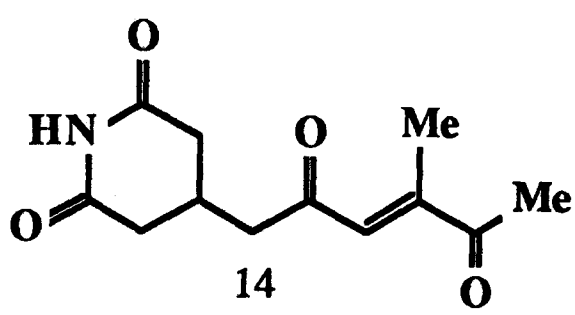
Group c), *Glutarimides attached to aromatic residues* via *Wittig Chemistry*

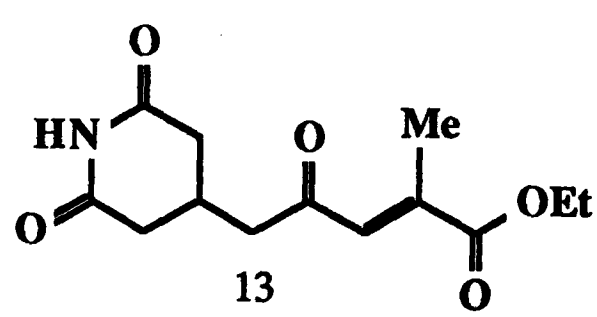


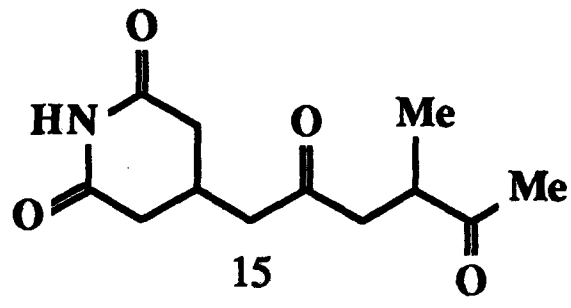
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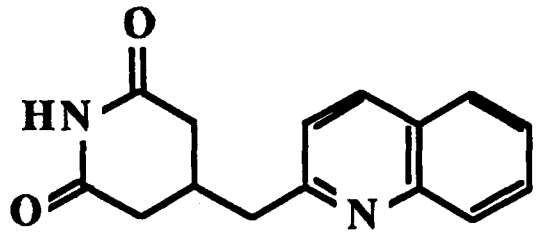
Group d), *Glutarimides attached to a dicarbonyl fragment*



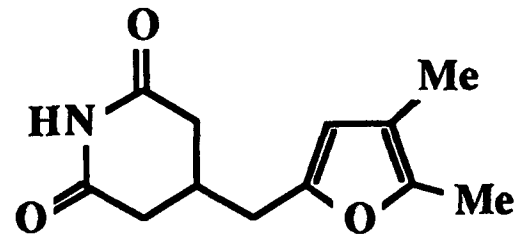




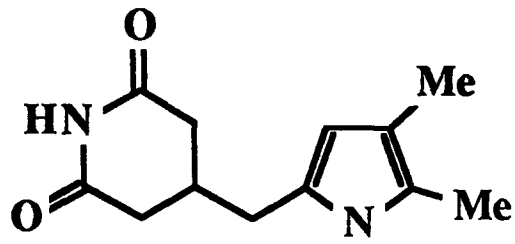
Group e), *Glutarimides attached to simple heterocycles*



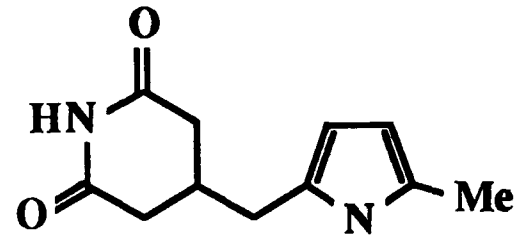
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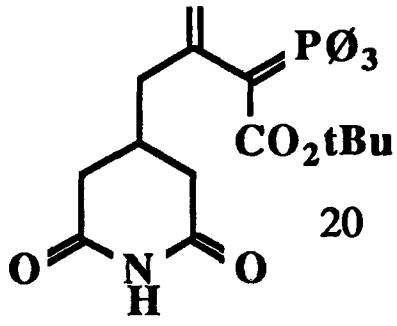


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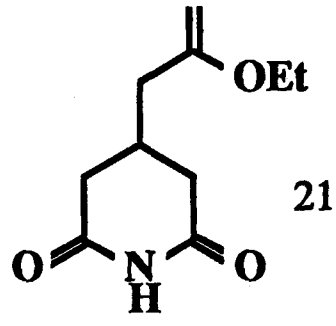


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Group f), *Miscellaneous glutarimides*



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