SYNTHESIS OF NUCLEOSIDE ANALOGUES

BY

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The Synthesis of Chiral Nucleoside Analogues

by Peter Lloyd Armstrong BSc (Hons)

ABSTRACT

A basic introduction to a variety of nucleoside derivatives is described along with a selection of recent syntheses of the said compounds.

Initial studies on the synthesis of the key furan based intermediate N-2,5-dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)furanyl trichloroacetamide which when hydrolysed to the free amine would yield a simple route to a variety of nucleoside derivatives. The synthesis was performed via the use of an aza-Claisen rearrangement on 1,4-anhydro-2-deoxy-5,6-o-isopropylidene-D-arabino-hex-1-enitol employing trichloroacetonitrile. This reaction proceeded to the desired amide in a facile manner, with excellent yield without the need for thermal rearrangement of the intermediate imidate. Initial efforts to hydrolyse this compound to the free amine proved inconclusive and this reaction was still being optimised at the close of the work.

The Claisen rearrangement of 1,4-anhydro-2-deoxy-5,6-o-isopropylidene-D-arabino-hex-1-enitol employing dimethylacetamide dimethylacetal proceeded successfully to produce an amide useful as an intermediate to the synthesis of furan C-nucleosides.

The key carbocyclic allylic alcohol intermediate 5-methoxymethylcyclopent-2-enol was synthesized via a six step synthesis in racemic form from the ethylene-acetal of 2-methoxymethylcyclopentanone but attempts at deprotection of the methyl ether proved unsuccessful. Attempts to repeat this synthesis using protecting groups other than methyl ether failed at an early stage. The aza-Claisen rearrangement of this allylic alcohol with trichloroacetonitrile proceeded in good yield to cis-N-methoxymethylcyclopent-2-enyltrichloroacetamide. This amide was easily acid hydrolysed to the amine hydrochloride which was subsequently used to synthesize a variety of purine based nucleosides.

5-Methoxymethylcyclopent-2-enol underwent the Claisen rearrangement with both dimethylacetamide dimethylacetal and triethylorthoacetate with the latters product showing promise as a useful intermediate to carbocylic C-nucleosides.

CONVENTIONS

A hashed line		denotes an α-configuration
A solid tapered line		denotes a ß-configuration
A wavy line		denotes either an unknown or unspecified configuration

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1. NUCLEOSIDES: AN INTRODUCTION

1.1 NUCLEOSIDES- Background of Medicinal Uses

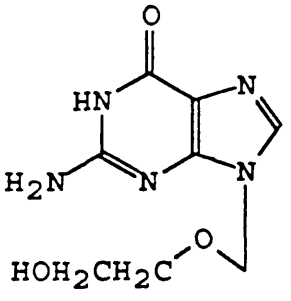
For a number of years it has been well established that nucleosides and their analogues show activity against a variety of physiological ailments. The main areas in which they have been of greatest use are as anti-cancer and antiviral agents.

Viral infections account for about 60 percent of all illnesses in developed countries. This is in contrast to the 15 percent attributable to bacterial infections. There are obviously many varieties of virus which include Herpes simplex virus (HSV) types 1 and 2, the cause of 'cold sores', encephalitis and eye and genital infections and Varicella zoster virus (VZV), the cause of chicken pox and shingles. Epstein-Barr virus (EBV) causes mononucleosis which is better known as glandular fever. To combat this variety of viral infections, numerous classes of compound have been tested of which nucleosides and their analogues have been found to be particularly useful as agents against a wide spectrum of disorders.

An example of a particularly interesting nucleoside analogue is acyclovir (1) which is an effective and selective inhibitor of HSV replication with very low toxicity against host animals[1]. It is manufactured by

the Wellcome Foundation and is now also used in conjunction with AZT for the treatment of Acquired Immune Deficiency Syndrome (AIDS).

Cyclocytidine hydrochloride (2)[2] is effective in the treatment of leukemia L1210 and is also a wide spectrum antiviral. 5-Fluorouridine (5-FU) (3) is at present used in the treatment of solid tumours such as gastrointestinal and breast tumours[3] and 2'-fluoro-5-iodo-aracytosine (FIAC) (4) is highly active against various strains of HSV 1 and 2[4]. FIAC is in fact slightly more active against HSV 1 than acyclovir but it is slightly more toxic to the normal cells. A compound which shows strikingly strong inhibitory effects on influenza and parainfluenza virus replication which has been licensed for use in humans in a variety of countries is ribavarin (5) [5,6].



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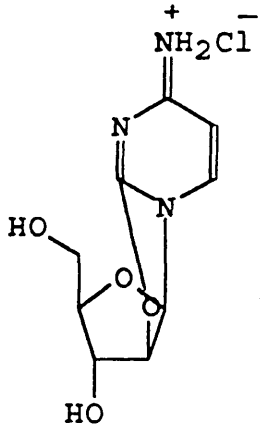

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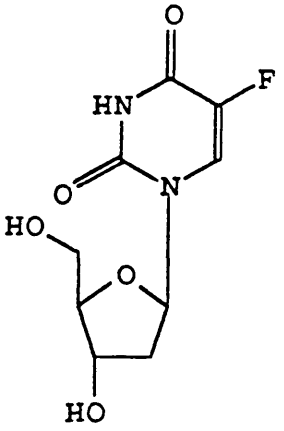

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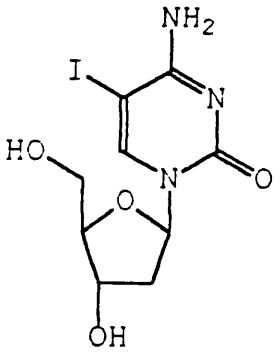

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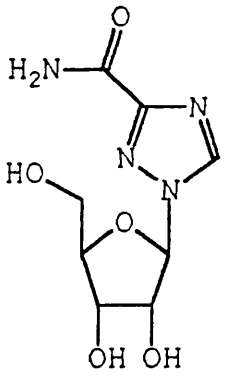


(5)

Research into the use of nucleosides as pharmaceuticals has however taken off in recent years after it was discovered that some are potent inhibitors of Human Immunodeficency Virus (HIV). It is this virus which, it is thought, produces the fatal disorder of AIDS. The following account explains in more depth the use of nucleosides as antiviral agents, taking HIV as the example virus. Throughout the text reference will be made to antiviral activity and this will imply anti-HIV activity; however, many of the compounds also show a wide spectrum of antiviral activity.

1.2 INTRODUCTION TO HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Research into novel antiviral compounds has become one of the biggest growth areas in science in recent years and this is due, mainly, to the spread of the fatal

disease Acquired Immune Deficiency Syndrome (AIDS). Within the scientific community there is still some speculation as to the exact causes of the syndrome, but, the consensus of opinion lies with one theory. It is thought that a retrovirus[7,8] replicates within the immune system of the host leading to the destruction of $T4^+$ cells. It is this drastic reduction in the host's $T4^+$ cell count which is the cause of AIDS[9]. This retrovirus is the third such virus to be detected which affects the human population and as such has been termed Human T-Lymphotropic Virus 3 (HTLV-3) but this is now better recognised by its more recent name of Human Immunodeficiency Virus (HIV)

The retrovirus HIV once within a host's body infects in a most subtle way. The virus first recognises a receptor site on the $T4^+$ cell and binds to it. Next by a fusion process the virus deposits its contents consisting of a strand of viral RNA (vRNA) and the ingenious enzyme viral reverse transcriptase within the host cell. Within the $T4^+$ cell the vRT uses vRNA from HIV as a template to form a strand of viral DNA (vDNA). A double strand of vDNA is then generated and this inserts itself into the $T4^+$ cell's chromosomes. No effect on the host cell is noticed until cell replication occurs. With the vDNA inserted into the parent cell, the new cell replicants produced are genetically altered and can now no longer

perform their assigned immune system function. The human host therefore, slowly loses its ability to combat disease due to the depletion of functioning $T4^+$ cells. At this point viral and bacterial ailments which, to a healthy human, are easily combated now become life threatening without the use of drugs and so common disorders such as influenza are thus often fatal to a patient with AIDS. It has also been shown that HIV infection leads to dementia and loss of intellectual functioning of the host.

The life cycle of HIV would appear to allow various areas at which to disrupt it and so arrest its fatal effects[10]. As the virus binds to the target cell antibodies to the virus or cell receptor could be employed. The viral RNA must be transcripted to a strand of DNA by the enzyme reverse transcriptase and so inhibitors to this enzyme would disrupt the life cycle of HIV. The virus also goes through a budding stage and it is known from other viruses that interferons can help prevent this stage from occurring. Other areas of the life cycle of HIV which appear to show opportunities at which to disrupt it include the integration of DNA into the host genome, expression of the viral genes and the degradation of viral RNA in the RNA-DNA hybrid.

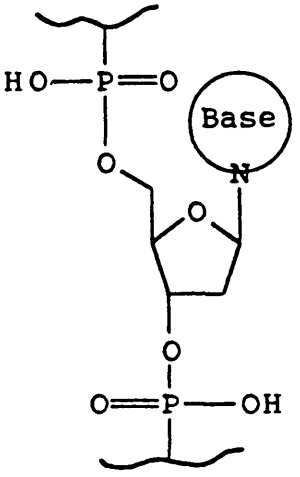
Possibly the most obvious link which could be disturbed by chemical means is the use by HIV of the vDNA producing enzyme vRT. vRT is unique to HIV and is not found naturally within the human body and therefore, if an inhibitor which was totally selective for vRT could be found it would in no way effect the normal bodily functions of the human host. A large majority of the work in the medicinal chemistry field has therefore been concentrated in the production of vRT inhibitors.

Obviously within the human body there are many thousands of vitally important enzymes all of which, along with vRT, are merely complex protein strands. The greatest therapeutic difficulty encountered for the medicinal chemist is to produce a drug which inhibits vRT but also does not interfere with those closely related, important, natural human enzymes. Any reaction of the drug with these human enzymes could lead to side effects which might be pernicious. One vital enzyme often affected by these vRT inhibitors is DNA polymerase alpha and this manifests itself as the side effects of leukopenia and anaemia. The therapeutic and hence synthetic aim is therefore to produce inhibitors which are highly selective for vRT leaving the patient free from any harmful side effects.

1.3 vRT INHIBITORS; Structure and Mode of Action

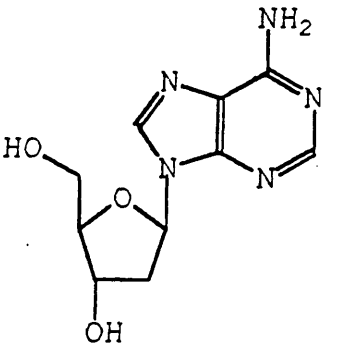
In order to inhibit vRT, compounds must be found which either block the active site of the enzyme to vRNA, or affect the sequencing of the vDNA chain by direct or indirect means. The usual substrate for vRT is vRNA, which is a long chain nucleotide with the general structure shown (Figure 1).

Figure 1



An obvious choice as an inhibitor might therefore appear to be a simple nucleoside as this has the correct structure to enter and block the active site of vRT to the approach of its true substrate vRNA. One such compound might be thought to be the naturally occurring nucleoside 2′-deoxyadenosine (6). As the name implies however, 2′-deoxyadenosine is a member of the deoxynucleoside family of compounds, the normal building blocks of DNA. Hence the vRT is able to utilize it in

the construction of its own vDNA chain and no vRT inhibition is seen.



(6)

Simple changes in chemical functionality at certain carbons around the *sugar* ring can however infer inhibitor qualities and the main change found to be effective was to have carbons 2 and 3 (C2′ and C3′) free from hydroxyl (OH) groups. The hydroxyl groups on the sugar ring at these positions form phosphate bonds which link one nucleotide to another in a DNA chain. In analogues without hydroxyls at C2′ and C3′ this link is unable to be formed and DNA chain growth is terminated. This gives us the class of compounds known as 2′,3′-dideoxynucleosides and these have been found to be potent inhibitors of vRT '*in vitro*'. Following this argument it might be thought that removal of the hydroxyl at C5′ would also infer inhibition of vRT however, removal or replacement of the C5′ hydroxyl leads to a complete loss of activity. This is because the C5′ is now no longer

available for phosphorylation and this stage is very important, being performed by the host cells own kinase enzymes. Nucleosides in their C5′ unphosphorylated form are not active and it is impossible to administer the drug in the phosphorylated form as it cannot be absorbed by the bodily cells. Therefore, the C5′ hydroxyl must be present to allow kinases to phosphorylate the absorbed drug into its active state which can then inhibit vRT.

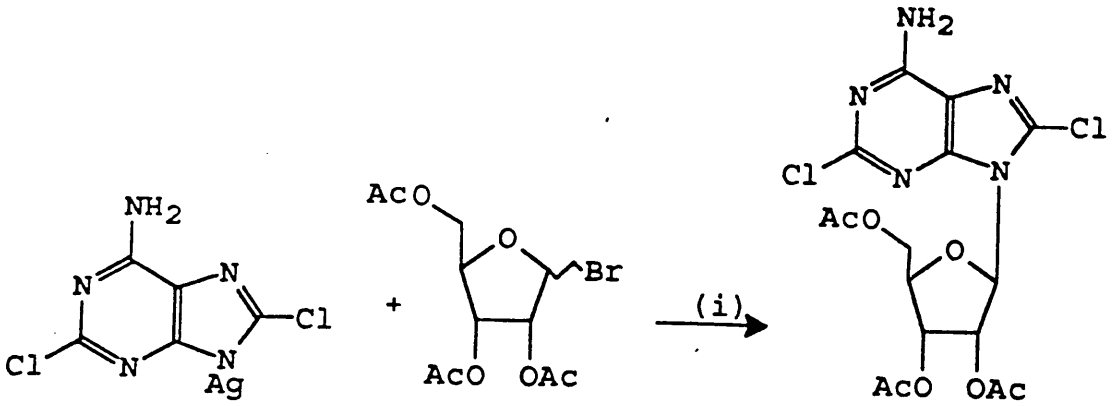
This inhibition can be by two main means, competitive inhibition and chain termination. In competitive inhibition the drug triphosphate binds to the vRT active site, in preference to vRNA. Due to the lack of hydroxyls at C2′ or C3′ the enzyme cannot use it as a substrate to initiate chain growth and thus production of vDNA is arrested. For chain termination to occur the drug triphosphate must first be incorporated into the growing vDNA chain. When the vRT attempts the next link, from the inhibitor nucleoside, it cannot due to the lack of the necessary hydroxyl at C2′ or C3′. The growing vDNA chain is thus terminated and the life cycle of HIV is blocked. It is usual that compounds which inhibit vRT exhibit both competitive inhibition and chain termination as their modes of action.

1.4 NUCLEOSIDES

1.4.1 Classical Syntheses

The term "nucleoside" initially was a reference to the pyrimidine and purine N-glycosides derived from nucleic acids. The common structural characteristic of all these compounds is the presence of a carbohydrate group, usually 2-ß-deoxy-D-ribofuranose or ß-D-ribofuranose, linked to a heterocyclic base.

The first nucleoside to be synthesized in the laboratory was 7-ß-D-glucopyranosyltheophylline by Fischer and Helferich when they condensed tetra-o-acetyl-α-D-glucopyranosyl bromide with the silver salt of theophylline in refluxing xylene[11,12]. The first synthesis of a more important nucleoside, adenosine (7), was by Todd and his co-workers[13] using the methodology of Fischer and Helferich. The silver salt (8) reacts with the ribose derivative (9) in refluxing xylene and reduction, followed by reaction with ammonia yields adenosine (7). Two improvements over this silver salt technique were introduced by Davoll and Lowy[14] who firstly reduced the basicity of the purine by acylation of the amino group and secondly made use of a chloromercury salt instead of the silver salt. Such a purine is shown (10).



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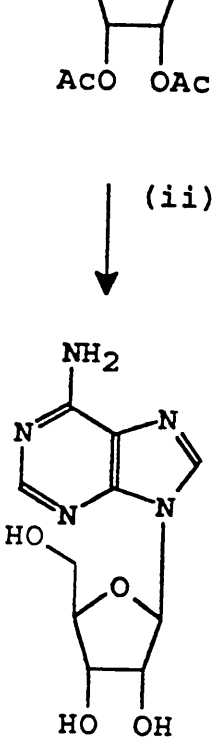
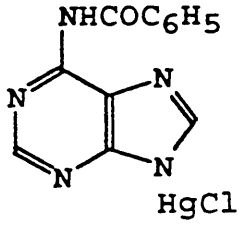


(7)

Reagents: (i) xylene/ reflux, (ii) a) reduction, b) NH_3/ EtOH



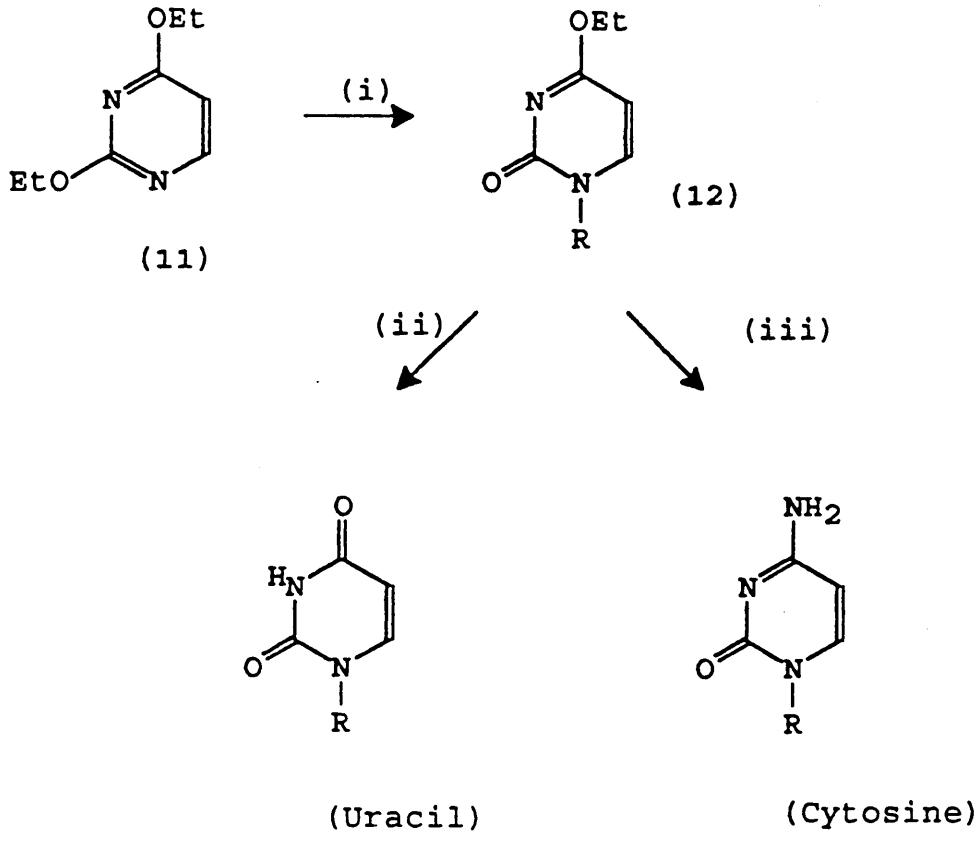
(10)

The silver salt mechanism of Fischer is also applicable to the pyrimidine nucleoside analogues. Mercury salts of pyrimidines have also been successfully used in a number of cases but both of these methods had obvious drawbacks synthetically. The silver salt technique was expensive and the use of highly toxic mercury made both routes poor for larger scale syntheses and so other more viable routes were therefore obviously required.

Hilbert and Johnson discovered a method of synthesizing pyrimidine nucleosides by the reaction of a dialkoxypyrimidine (11) with an alkyl halide (RX) which affords 4-alkoxy-N'-alkyl-2-pyrimidones (12). These products can then be easily reacted to give either uracil or cytosine nucleosides as shown (Scheme 1). The same methodology using a poly-o-acylsugar halide as the alkyl halide component is referred to as the classical Hilbert-Johnson synthesis of N-glycosides[15] and this became the first general method for the preparation of pyrimidine nucleosides.

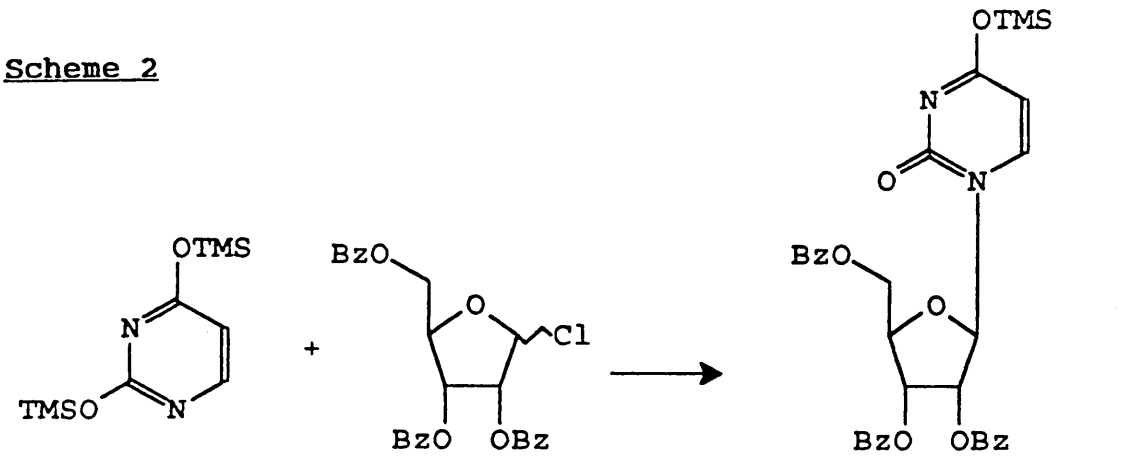
The next major advancement in nucleoside synthesis came with the developments in organosilicon chemistry. Birkofer et al[16] used trimethylsilylated (TMS) bases in preference to the older dialkoxy derivatives (Scheme 2).

Scheme 1



Reagents: (i) RX, (ii) HCl/EtOH, (iii) NH_3/EtOH

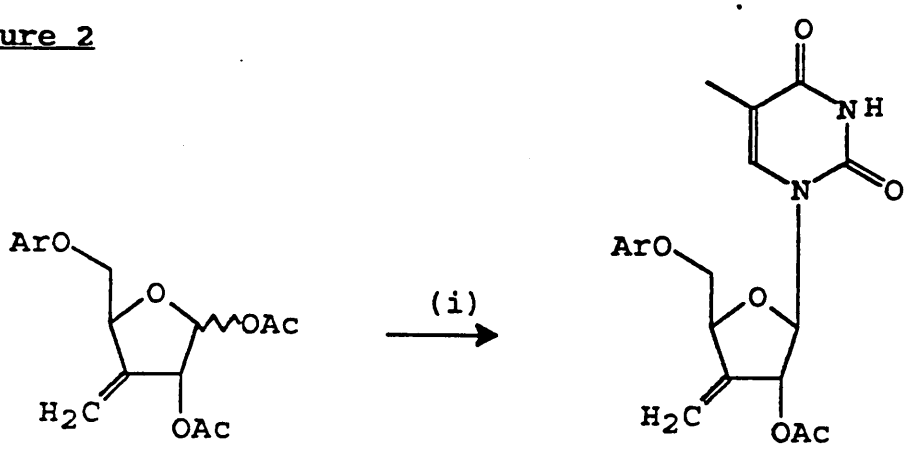
Scheme 2

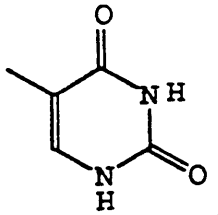


uridine/cytidine

This type of methodology is now the typical synthetic route to both purine and pyrimidine nucleosides and the synthesis has been further advanced by the use of various conditions and reagents such as the use of hexamethyldisilazane and trimethylsilytriflate[17,18]. (Figure 2)

Figure 2

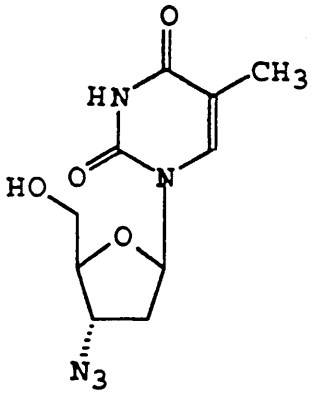




Reagents: (i) , Me_3SiCl, hexamethyldisilazane, $Me_3SiOSO_2CF_3$, 60^{O}, 2 hours

1.4.2 Compounds of Current Interest

As has already been stated the main interest at present is in the class of compounds known as 2',3'-dideoxynucleosides[19] many of which have shown promising anti-retroviral activity *'in vitro'* . Of these compounds the market leader for AIDS treatment is 3'-azido-3'-deoxythymidine (13).

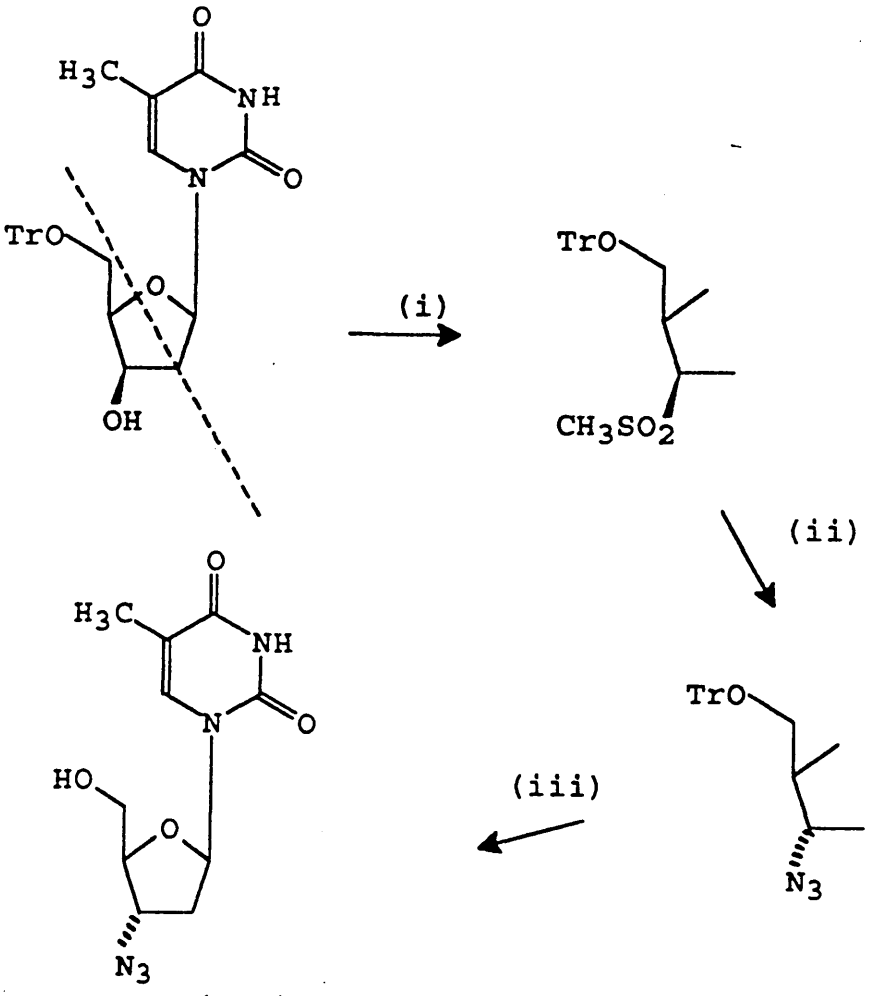


(13)

It is manufactured by the Wellcome Foundation Limited and is better known as either AZT, zidovudine or its UK brand name Retrovir. AZT was synthesized over 20 years ago by Horwitz et al[20] employing the classical Hilbert-Johnson nucleoside synthesis[15] to produce the thymidine derivative which could then be reacted to yield AZT (13) (Scheme 3).

It was not until ten years later that Ostertag et al[21] discovered that AZT was indeed an active antiretroviral but due to its toxicity[22] no useful medical application was apparent. With the advent of HIV/AIDS, AZT was re-evaluated and it exhibited vigorous inhibition of HTLV-3 replication '*in vitro*'.

Scheme 3



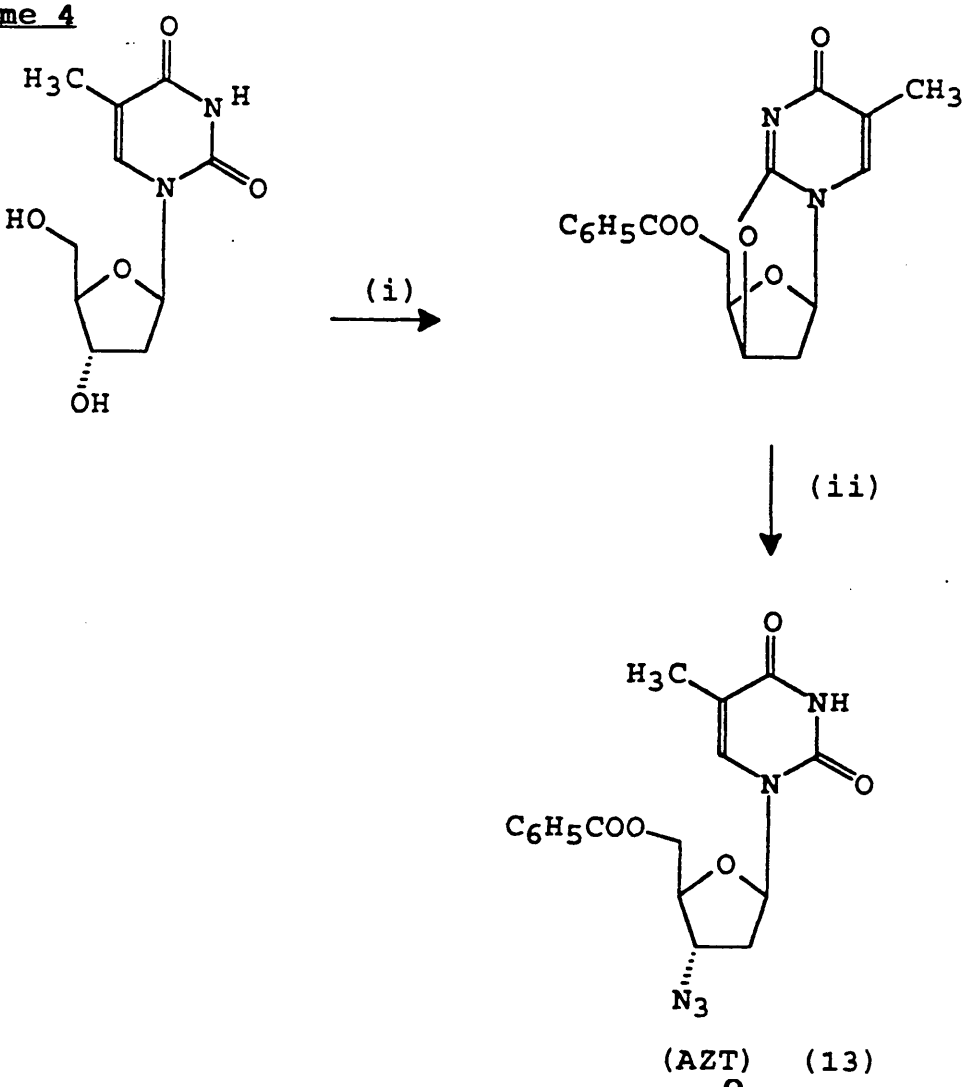
(AZT) (13)

Reagents: (i) methanesulfonyl chloride/ 0^{o}/ 16 hr/ pyridine, (ii) LiN_3/ 3hrs/ 100^{o}/ N_2/ DMF, (iii) $CHCl_3$ HCl/ 0^{o}/ 1 hr

More recent methods of AZT synthesis still stem from thymidine starting materials and one such route is to first produce a 2',3'-anhydro thymidine derivative using a one-pot reaction from thymidine[23] (Scheme 4). The isolated product is then treated with lithium

azide[24,25] under nitrogen with heating, subsequent deprotection of the benzoate ester yields the required product AZT.

Scheme 4



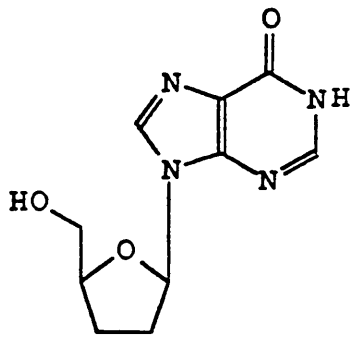
(AZT) (13)

Reagents: (i) a) DIAD/ PPh_3/ benzoic acid/ 22°/ DMF b) PPh_3/ DIAD, (ii) LiN_3/ DMF

The mode of action of AZT[10] is similar to that of other 2',3'-dideoxynucleosides in that it acts as both a competitive inhibitor and a chain terminator. However, AZT has signifiant advantages over other drugs in its

class. As has been previously stated, HIV affects the brain and central nervous system leading to types of dementia and AZT is the only antiretroviral compound known at present which can enter the brain and help prevent this neurological damage caused by HIV. The drawbacks of AZT are that it is highly toxic (particularly to bone marrow) and is quickly metabolised or excreted by the body and a further problem which has surfaced more recently is the emergence of AZT resistant strains of HIV.

With this resistance problem at hand other 2',3'-dideoxynucleosides have been synthesised and one compound of great interest is 2',3'-dideoxyinosine (ddI) (14)[25].

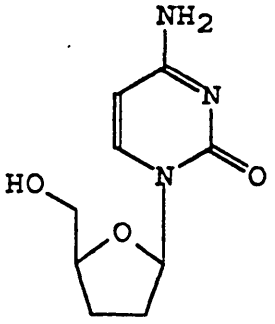


(14)

This compound has been found to be an antiretroviral '*in vivo*' and has recently been ratified as a prescribed drug for the treatment of AIDS in the USA. At present it is only available to patients who either did not respond

to or who were unable to use AZT.

Other compounds with the 2′,3′-carbon positions saturated with hydrogen have also shown promising results of which two compounds of particular interest are 2′,3′-dideoxycytosine (ddC)[18] (15) and 3′-deoxy-2′,3′-didehydrothymidine (d4T)[17] (16).



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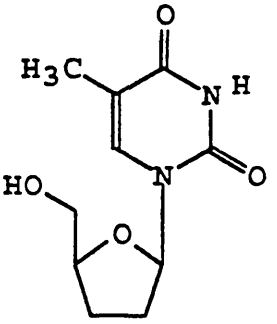
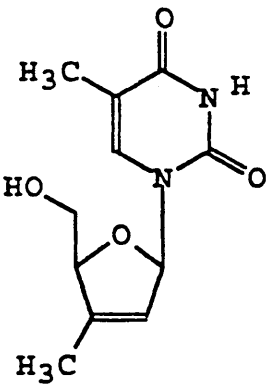
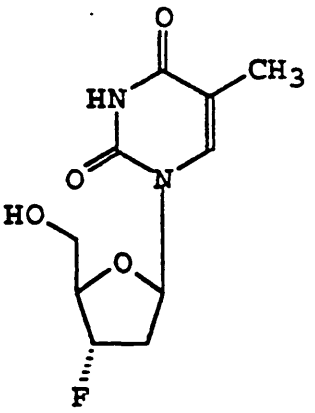


(16)

Other series of compounds which have shown promising initial biological results have been the modified analogues of AZT and d4T, fluorothymidine[42] (FLT) (17) and 2′-deoxy-2′,3′-didehydro-3′-methylthymidine[17] (18). FLT is equipotent '*in vitro*' but 10 times more effective '*in vivo*' than AZT. This has been shown experimentally using the monkey infected with SIV as a model. A particularly interesting aspect of (18) was the unsaturation at C2′ and C3′ as this is a modification which has led to a series of compounds with antiretroviral activity.



(18)



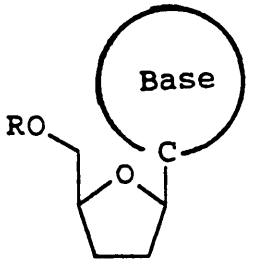
(17)

All the 2',3'-dideoxynucleosides do however have a common drawback which has led to the search for new classes of antiretrovirals. This is that being so closely related, structurally, to the normal building blocks of RNA/DNA they are prone to destruction by the human bodily enzymes. These enzymes attack the link between C1' of the pentacyclic sugar ring and the nitrogen of the attached heterocyclic base (i.e. the -O-C-N- linkage). Therefore the new classes of antivirals, although retaining an overall nucleoside type skeleton must dispense with this -O-C-N- glycosidic link, which is so easily disrupted.

1.5 C-NUCLEOSIDES

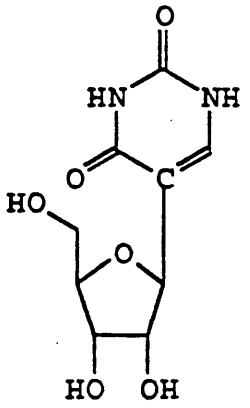
This class of antivirals have the apparent advantage over normal nucleosides in that they do not contain the enzymatically degradable -O-C-N- linkage. They are in the form shown (Figure 3) with the sugar C1′ being bonded to a carbon in the heterocyclic base as opposed to a nitrogen.

Figure 3



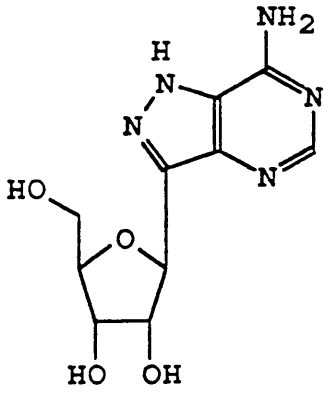
As can be seen there is now an -O-C-C- series of bonds rather than -O-C-N- glycosidic link and this new arrangement is far more stable to enzymatic degradation. Consequently this category of nucleoside, it was hoped, could be more potent antivirals than the 2′,3′-dideoxynucleoside analogues.

The first naturally occurring C-nucleoside to be identified was 5-ß-D-ribofuranosyluracil (pseudouridine) (19) which is an important fragment of tRNA.

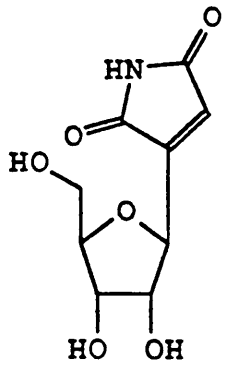


(19)

A number of interesting C-nucleosides have since been isolated and synthesized in the laboratory of which two of the most important have been formycin (20) and showdomycin (21). Formycin was first isolated in the Institute of Microbial Chemistry, Tokyo from *Nocardia interforma* during a screening for antitumour activity[26] in 1964 and has both significant antiviral and antitumour activity. The first of these formycins to be synthesized in the laboratory was the analogue oxoformycin (22) by Farkas and Sorm[27].



(20)



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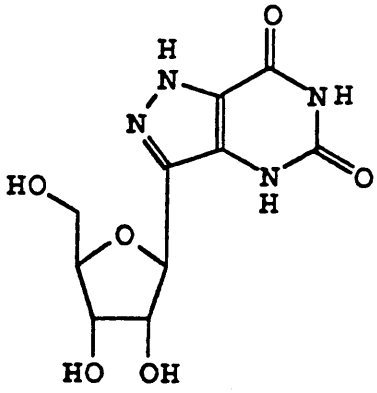


(22)

Since this synthesis many analogues have been developed and much work has been perfomed in this area by Buchanan et al[28].

Probably the largest volume of work in the C-nucleoside field has been on the compound showdomycin[29,30] which was initially discovered by a research group at the Shionogi Research Laboratory led by Nishimura[31] in 1964 by isolation from *Streptomyces showdoensis*. Showdomycin exhibited antiviral activity *'in vitro'* and is also active against gram-positive and gram-negative bacteria and tumours. The synthesis of the compound has usually been tackled by one of two routes. Either D-ribose is used, which leads to optically active showdomycin, or furan is employed to derive the ribose unit by cycloaddition followed by stereoselective hydroxylation.

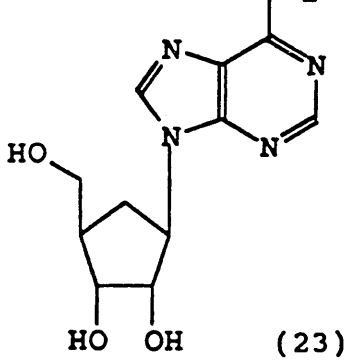
The area of using C-nucleosides for the treatment of HIV is of interest due to the stability of the -O-C-C- series of bonds. However, as yet no compound in this class has been discovered which shows any significantly useful anti-HIV activity. Due to this fact, the majority of work in the anti-HIV field has continued in the areas of nucleoside analogues and the newer carbocyclic nucleosides.

1.6 CARBOCYCLIC NUCLEOSIDES

1.6.1 Background and Synthesis

Both nucleosides and C-nucleosides are found occurring naturally in the human body with the advantage of the C-nucleosides being their stability to bodily enzymes. Unfortunately, as yet, no potent anti-HIV compound has been discovered in the latter class of molecules. With the drawbacks in these two fields scientists took the next obvious step towards a new series of compounds and this step was to alter the nucleoside framework by replacing the oxygen atom of the furan sugar ring with a methylene group so producing a cyclopentane analogue. It was hoped that this step would maintain the stability towards enzymes shown by C-nucleosides yet keep the high activity of the nucleosides.

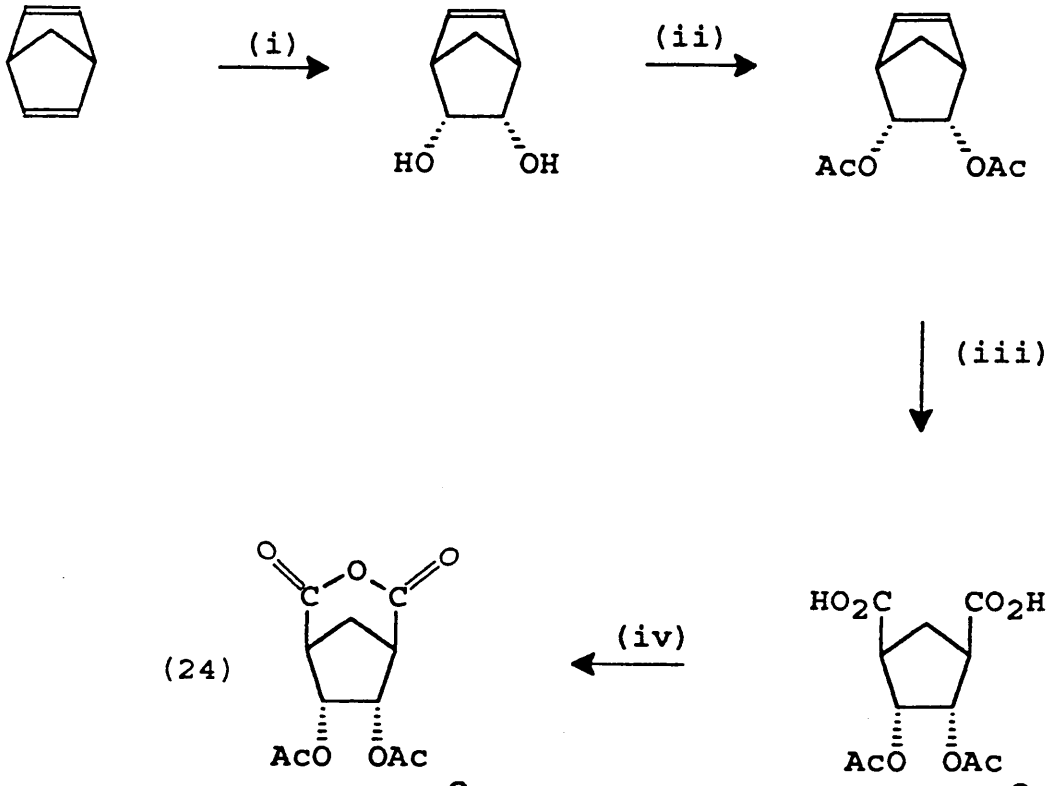
The early inventive work in this field was attempted by Shealy and Clayton[32] who initially synthesized racemic carbocyclic analogues of the adenosine, inosine, 6-mercaptopurine and 6-(methylthio)purine nucleosides. Their first synthesis was that of carbocyclic adenosine (23).



(23)

Biological studies showed (23) to be highly cytotoxic and that it was a substrate for both kinase and deaminase enzymes. Shealy's synthesis used norbornadiene as the starting material which by a 4 step process (scheme 5) produced 2 α ,3 α -diacetoxy,1ß,4ß-cyclopentanedicarboxylic acid anhydride (24).

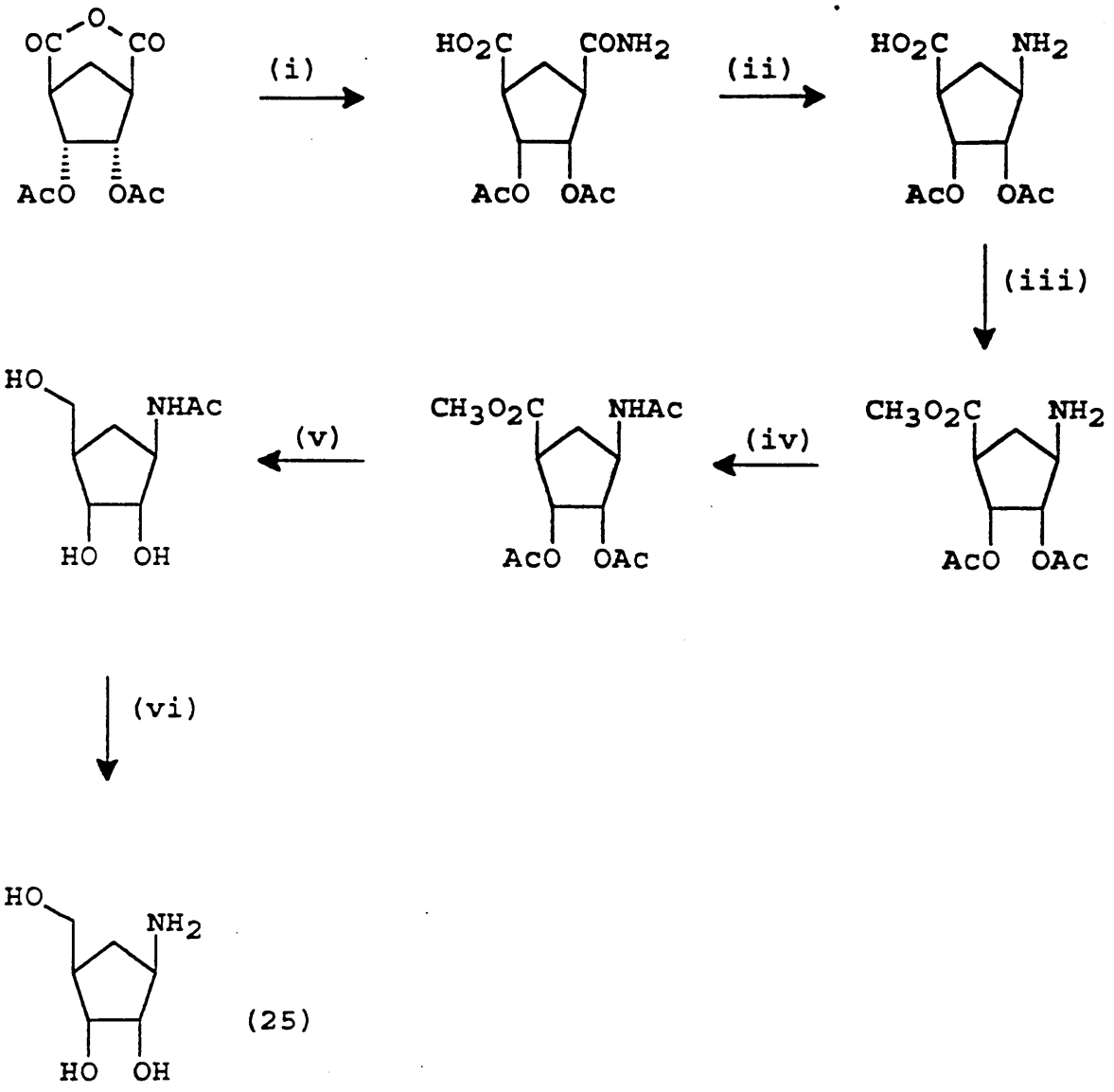
Scheme 5



Reagents: (i) $KMnO_4$/ -70^O, (ii) acetic anhydride/ -70^O to 22^O, (iii) $NaMnO_4$/ CO_2, (iv) ethoxyacetylene

Ring opening of the acid anhydride to yield the acid-amide functionality was followed by 5 further steps which ultimately led to the key intermediate (25) (±)-4ß-amino,2 α ,3 α -dihydroxy-1ß-cyclopentanemethanol (scheme 6).

Scheme 6

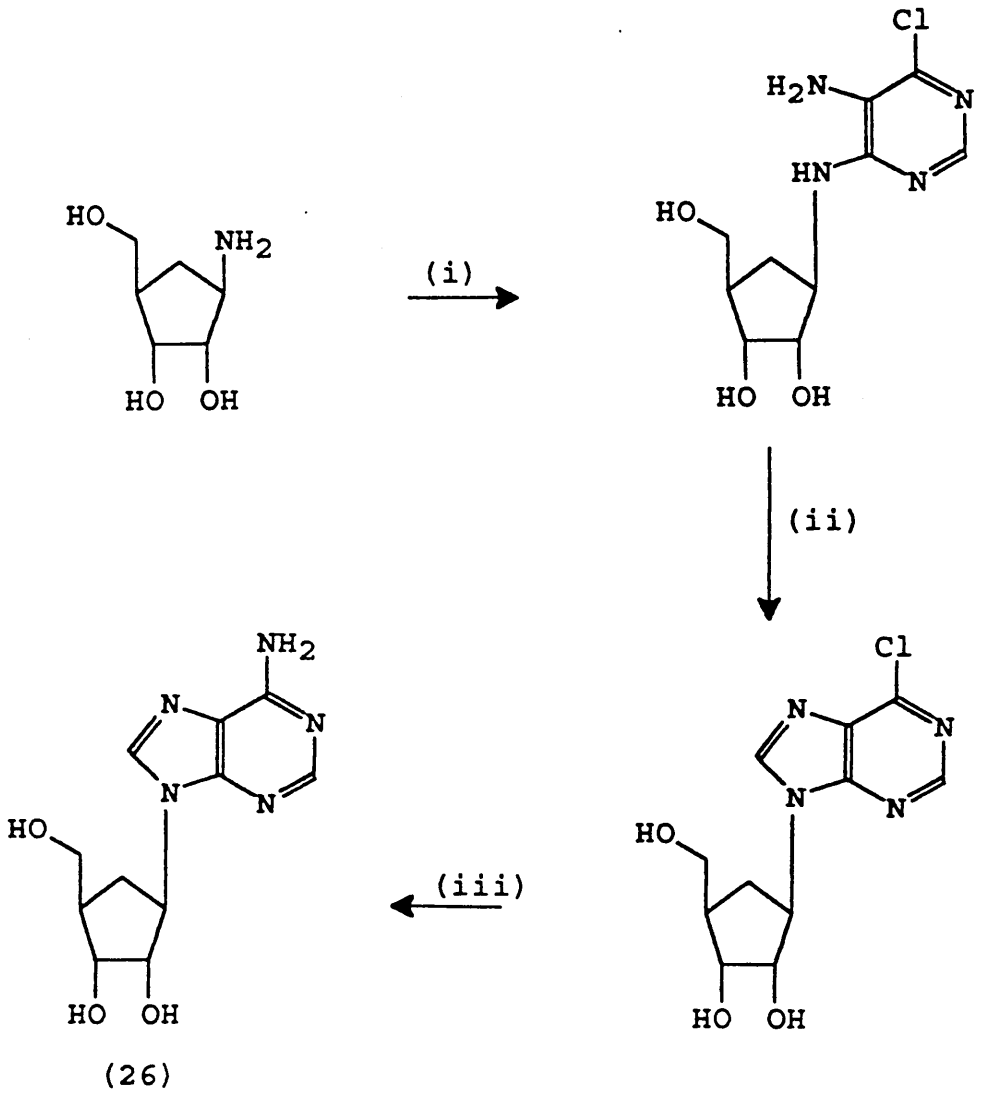


(25)

Reagents: (i) NH_3 (g)/ 5^o, (ii) Br_2/ NaOH, (iii)CH_3OH HCl (g), (iv) acetic anhydride/ pyridine, (v) $LiBH_4$/ 40^o (vi) a) carbon/ HCl, b) NH_3

From the key amine intermediate (25), well published methods for the synthesis of the base moiety were applicable. To furnish carbocyclic adenosine Shealy reacted the amine (25) with 5-amino-4,6-dichloropyrimidine which followed by ring closing with triethyl orthoformate and amination in liquid ammonia gave the compound (26) (scheme 7).

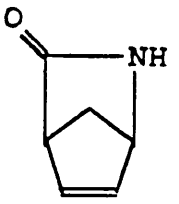
Scheme 7



(26)

Regents: (i) 5-amino-4,6-dichloropyrimidine/ butanol/ Et_3N, (ii) $HC(OEt)_3$/ H^+, (iii) NH_3

These early routes were too lengthy to allow rapid analogue preparation and the next step forward was made by Daluge and Vince[33] by their use of the compound 2-azabicyclo[2.2.1]hept-5-ene-3-one (27). Here they reported the synthesis of carbocyclic arabinosyladenine which showed promising antiviral and antitumour activity. Kam et al[34] furthered this work utilising (27) to produce a series of amine intermediates which were extremely useful for carbocyclic nucleoside synthesis.



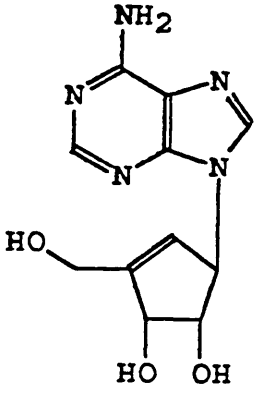
(27)

This lactam (27) has since become the basic starting material for a large volume of work in this field as it is readily available in chiral form and therefore gives an easy introduction to the synthesis of chirally pure carbocyclic nucleosides.

1.6.2 Compounds of Current Interest

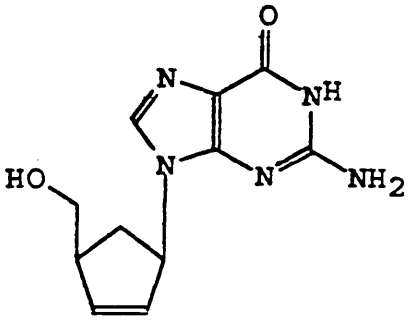
One initially very interesting compound was neplanocin-A (28). The neplanocins were first isolated from a cell culture in 1979[35] and neplanocin-A demonstrated superior antitumour activity[36]. The first

total synthesis of this compound in chiral form was by a group at the University of Tokyo[37] followed a few months later by Marquez[38] who employed a vastly different method.



(28)

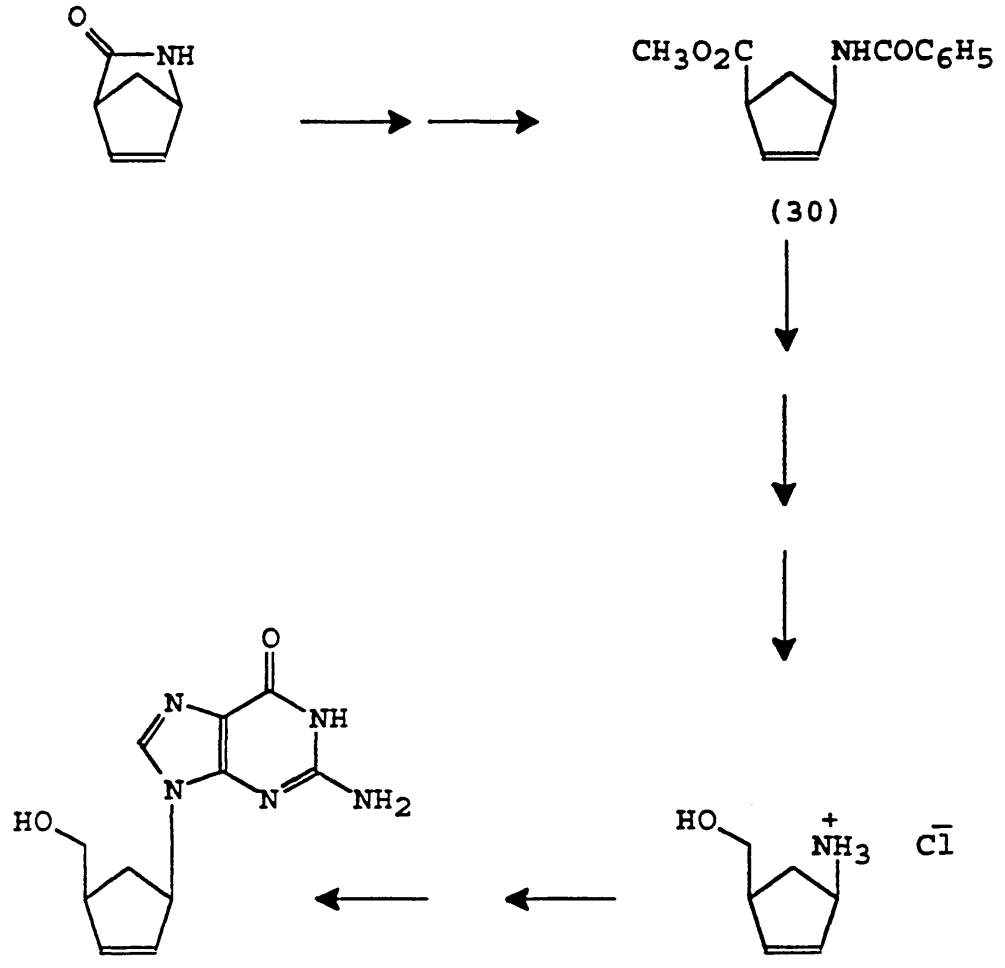
A vigorous worker in this field of carbocyclic nucleosides has been Roberts[39-41]. He has produced many elegant papers dealing with carbocyclic syntheses and recently his group have produced some interesting carbocyclic AZT analogues[42] which have shown anti-HIV activity. Probably the most useful compound dealt with by Roberts has however been carbovir (29) which has recently been put forward as a possible chemotherapeutic agent for the treatment of patients infected by HIV.



(29)

Roberts and his co-workers have synthesized chirally pure carbovir by two distinctly different routes[43] of which the first employed a linear approach starting from the chirally pure (-)-lactam (27). Ring opening of the lactam was followed by protection of the acid and amine to generate (30) (scheme 8). Reduction of the ester and hydrolysis of the amide allowed reaction with 2-amino-4,6-dichloropyrimidine and four further well known reactions led to the final product; (-)-carbovir (29).

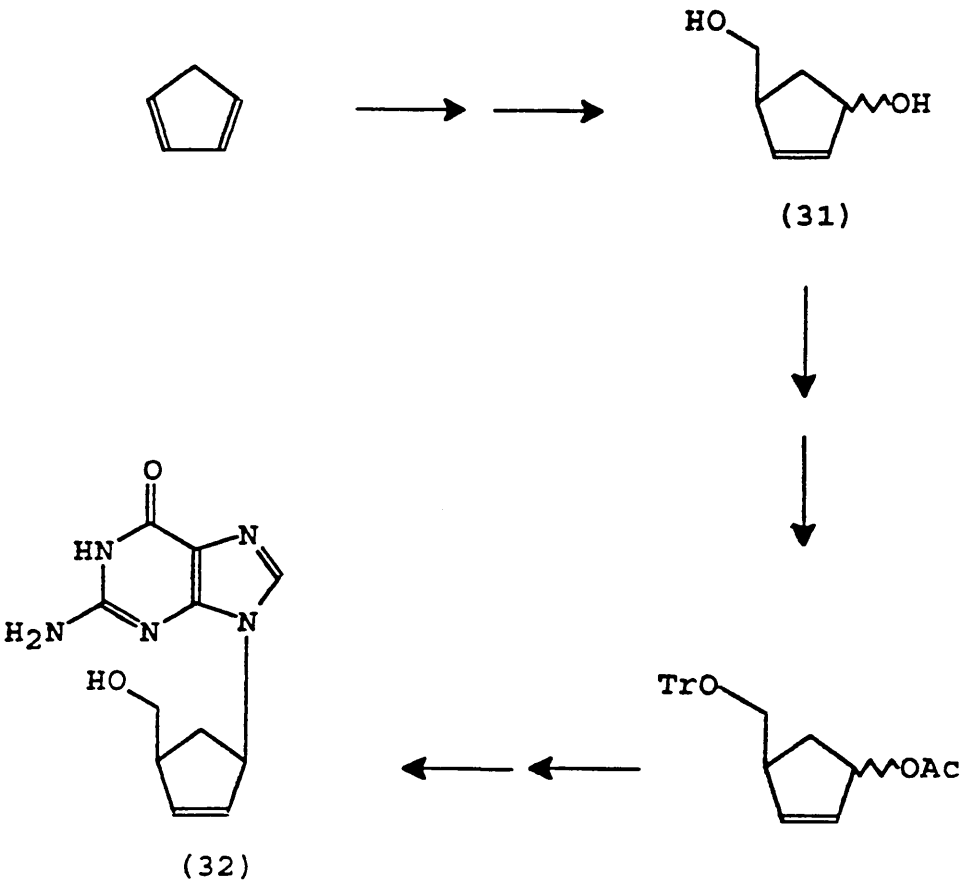
Scheme 8



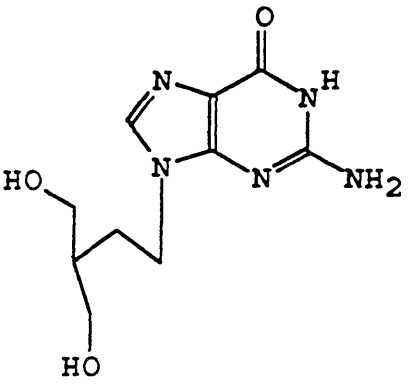
(Carbovir)

The second method employed a convergent approach where reaction of cyclopentadiene with formaldehyde and formic acid followed by treatment with base gave a mixture of (±)-4-*cis*-hydroxycyclopent-2-enylmethanol isomers (31). Protection of the primary alcohol as the trityl ether and subsequent enzymatic acetylation of the secondary alcohol with *Pseudomonas fluorescens* lipase as catalyst furnished the optically pure ester. Reaction of this ester with 2-amino-6-chloropyrimidine, sodium hydride and palladium tetrakis(triphenylphosphine) and subsequent hydrolysis with base produced the optically active (+)-carbovir (32) (scheme 9).

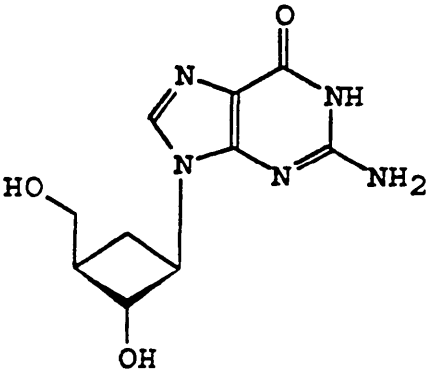
Scheme 9



Within the last few years some extremely novel carbocyclic mimics of nucleosides have been developed and the following examples have replaced the cyclopentane ring with a variety of groups. In penciclovir (33) a branched alkyl chain is used and this compound is highly active against herpes simplex virus types 1 and 2. The isomeric compound (34)[44] has also been shown to exhibit potent antiviral activity, where a cyclobutyl ring has replaced the original cyclopentyl.



(33)



(34)

Both Norbeck et al[45] and Green et al[46] have replaced the cyclopentane with a cyclopropyl ring but as yet none of these compounds has shown any marked antiviral activity.

1.6.3 Carbocyclic C-Nucleosides

This area has not been particularly well investigated in comparison with the other classes of compounds already mentioned and this is probably in the main due to the

decreased activity of C-nucleosides as compared with nucleosides. However, if a compound existed which was active in this class it would have the excellent property of being highly stable to enzymatic attack. Saksena[47] has described a route to carbocyclic C-nucleosides but as yet none of the products synthesized have shown interesting antiviral activity.

1.7 INITIAL AIMS OF THE RESEARCH PROJECT

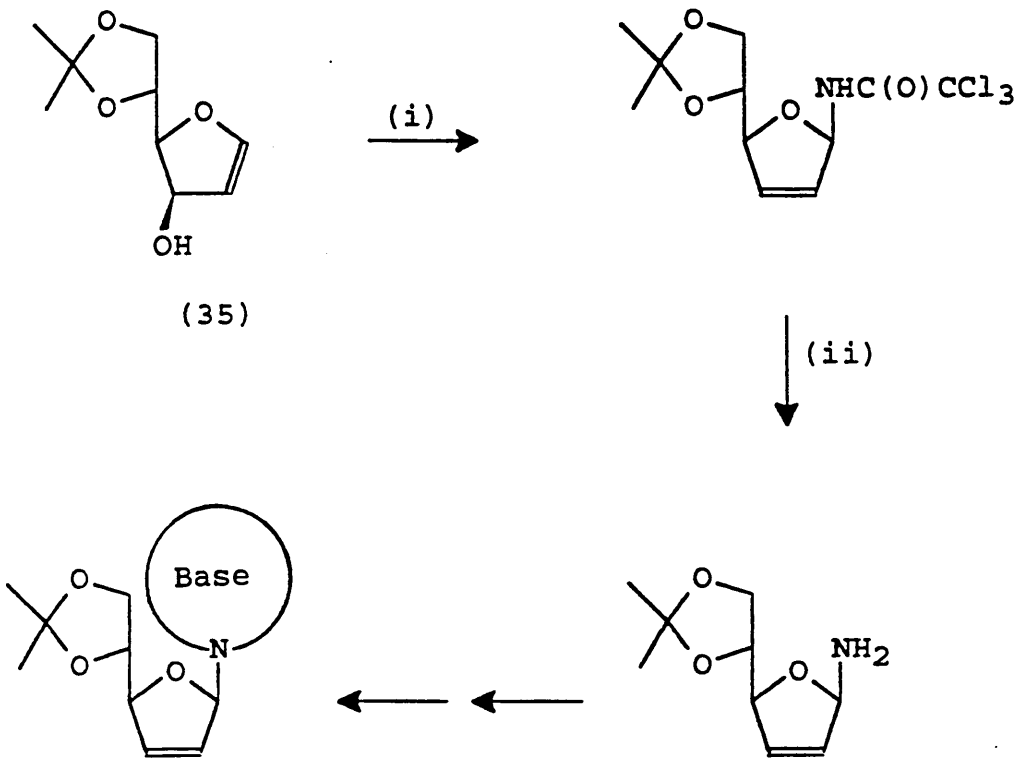
In simple terms the purpose of the project was to develop new routes to the four classes of nucleoside analogues already mentioned (nucleosides, C-nucleosides, carbocyclic nucleosides and carbocyclic C-nucleosides) ultimately in chiral form. These routes would involve the use of either an intramolecular Claisen or aza-Claisen rearrangement to establish the correct general stereochemistry. It was hoped that any nucleoside analogues synthesized would be submitted for biological testing by the collaborating body, the Wellcome Foundation Limited.

Routes to 2',3'-dideoxynucleosides

The fundamental reaction was to be an aza-Claisen rearrangement[48] on the glycal (35) which was readily

available via a three step synthesis. The trichloroacetamide could then be hydrolysed to the free amine as shown in scheme 10 and the desired heterocyclic base could subsequently be formed by well published methods using the amine as a *'synthetic handle'*.

Scheme 10

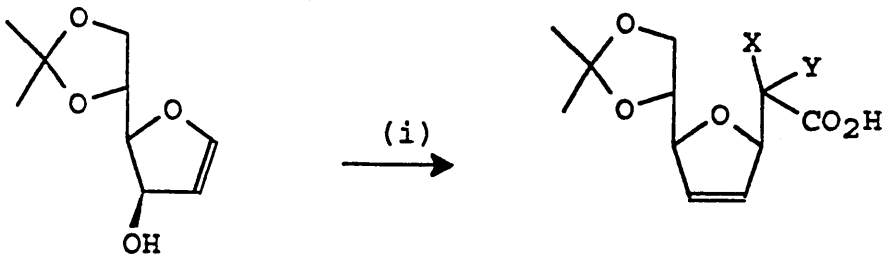


Reagents: (i) a) Cl_3CCN/ 0^{o}, b) $Hg(OCOCF_3)_2$
(ii) NaOH/ EtOH

Route to C-Nucleosides

Again the glycal (35) was to be used as the precursor. The glycal was to be reacted in a Claisen rearrangement as described by Ireland et al[49] and shown in figure 4.

Figure 4



(35)

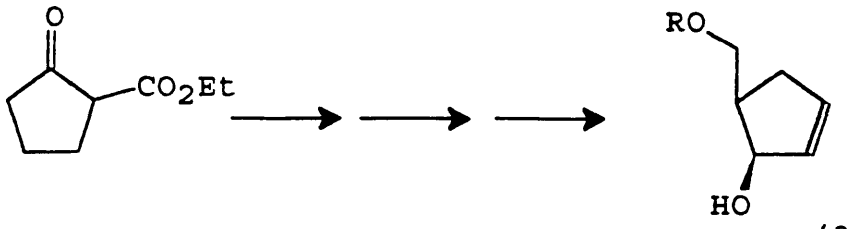
Reagents: (i) a) XCYHCOCl, b) LDA, c) Me_3SiCl, d) heat

Variation of X and Y to SPh or OMe could provide a useful '*synthetic handle*' upon which to build the required heterocyclic base.

Route to Carbocyclic and Carbocyclic C-Nucleosides

Analogous Claisen and aza-Claisen rearrangements to those shown in scheme 10 and figure 4 could be employed in the carbocyclic series. Firstly however the cyclopentane allylic alcohol (36) required for these rearrangements would have to be prepared and this was to be achieved using a modified method previously outlined by Paulsen and Maaß[50] (Figure 5).

Figure 5



(36)

This route leads to the required cyclopentane allylic alcohol as a racemate but the desired chiral form could be isolated via a variety of techniques.

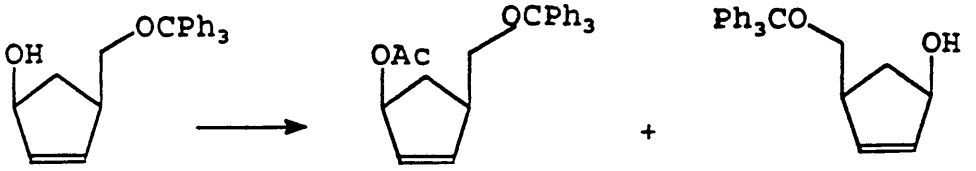
Three techniques are widely used both in industry and academia. The classical method and one which is particularly useful when dealing with large scale reactions is a resolution in which the reaction of the racemate with an optically pure carboxylic acid. This would produce a pair of diastereomeric esters which could then be separated by physical techniques such as chromatography or recrystallization.

The second method could be to employ an enzymatic resolution somewhere in the synthesis. This technique employs an enzyme which will effect a reaction on only one of the enantiomers of the compound being used. A good example of this is the use by Roberts[43] of '*Pseudomonas fluorescens*' lipase with vinyl acetate to react with the racemic alcohol (37) (Figure 6). Only the (+)-form of the starting alcohol is reacted on by the enzyme to yield an acetate (38) which can then be isolated by physical methods, thus procuring the molecule in chiral form. It would certainly appear possible to use this methodology to isolate chirally pure material from the allylic alcohols (36).

The third method would be to employ one of the new

range of chiral reducing agents for reducing a ketone such as R- or S-Alpine hydride, which are borane derivatives. Chiral reducing agents react with a pro-chiral material generating an excess of one of the optically active forms. A distinct advantage of this method is that unlike the previous two methods, where 50% of the starting material is wasted, a majority is employed in preferentially producing one chiral form.

Figure 6



(37) (+) (38) (-)

CHAPTER 2

FURAN BASED NUCLEOSIDES AND C-NUCLEOSIDES

2.1. Background - Synthesis

2.2. Synthesis of the Furan Allylic Alcohol (35)

2.3. Claisen Rearrangements

2.3.1. Background

2.3.2. Claisen Rearrangements on Furan Allylic Alcohol (35)

2.4. Aza-Claisen Rearrangements

2.4.1. Background

2.4.2. Aza-Claisen Rearrangements on the Furan Allylic Alcohol (35)

2.5. Use of Glycal (35) and its Ferrier Rearranged Derivative (42)

2.6. Summary and Future Work

2. FURAN BASED NUCLEOSIDES AND C-NUCLEOSIDES

2.1 BACKGROUND- Synthesis

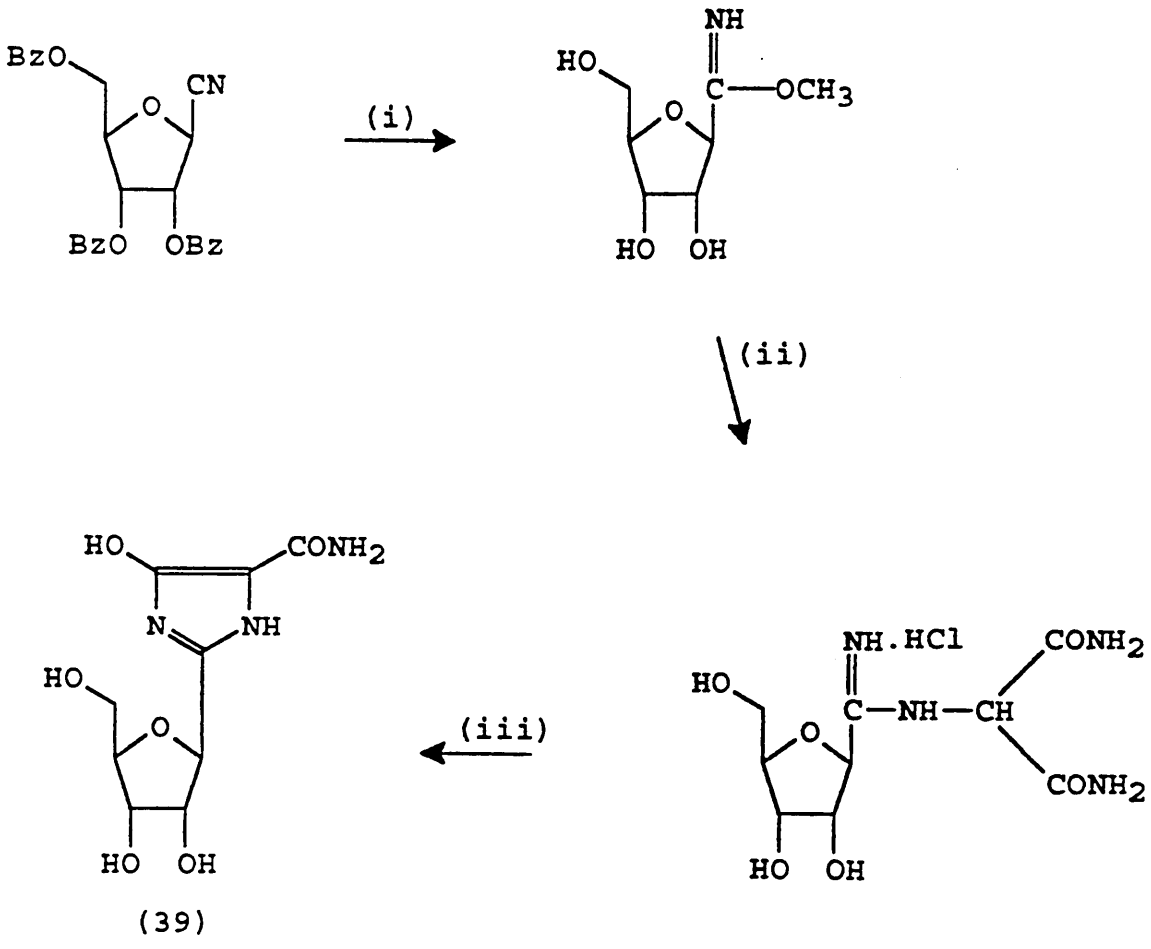
As has been previously stated the above classes of compound are of great interest for use as pharmaceuticals, mainly in the fields of antiviral and anticancer medicine. From naturally occurring furan nucleosides it has been possible to synthesize a variety of novel analogues which have shown enhanced medicinal activity, some of which have been mentioned earlier in this text such as AZT (13), FLT (17) and ddI (14). The recent rapid development of nucleosides as pharmaceutical agents has arisen due to their selective inhibition of viral enzymes and they have shown activity against a variety of viral infections such as HIV, VZV and HSV types 1 and 2.

The classical synthesis of nucleosides has already been outlined earlier in chapter 1. There are two distinct methods of synthesis, namely a convergent approach or a linear route.

In the field of nucleoside synthesis the linear approach has been mainly used in routes to C-nucleosides. A linear synthesis is one in which the entire target molecule is built up in consecutive small steps and has

the main disadvantage of producing relatively poor overall yields of a target molecule over a long multi-step synthesis. However, for the production of C-nucleosides this has proven to be the main method of synthesis. This linear approach is shown well by Poonian and Nowoswiat[51] (Scheme 11) in their synthesis of the C-nucleoside analogues of the immunosuppressive and antiviral agent bredinin[52] (39).

Scheme 11

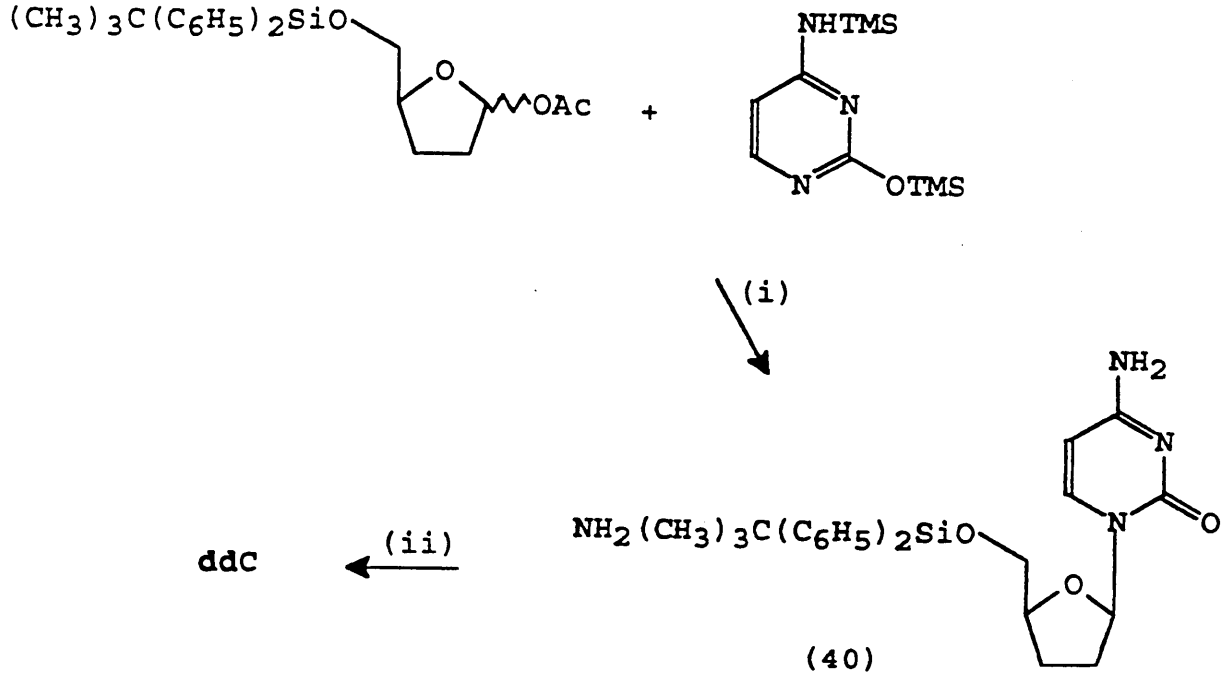


(39)

Reagents: (i) $NaOCH_3$, (ii) $(NH_2CO)_2CHNH_2.HCl$/ DMSO (iii) H_2O/ heat

This scheme shows very well a linear synthesis with the heterocycle being built onto the sugar moiety in a three step process.

For the production of nucleosides, mainly the convergent approach is utilised as it has the advantage that yields of the target molecule are significantly higher than for a comparative linear synthesis. The classical syntheses of nucleosides discussed previously employ this convergent methodology where the final molecule is built up by reacting together large, previously synthesized portions of the target compound. This method can be seen in the synthesis of ddC and CNT by Okabe et al[18].



Reagents: (i) Lewis acid, CH_2Cl_2, (ii) a) H^+ b) HO^-

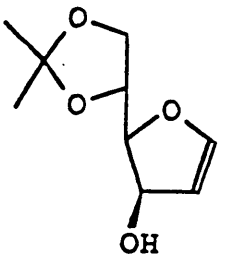
As can be seen the two main portions of the nucleoside, the sugar and base, are reacted together in one step to produce (40) in a typical convergent synthesis.

The initial aims of the research project were to employ Claisen and aza-Claisen rearrangements on a suitable allylic alcohol. These reactions would lead to compounds containing synthetic '*handles*' with the correct relative stereochemistry for heterocyclic base synthesis. Therefore, it was initially envisaged that a linear approach would be used for the overall synthesis of the nucleoside analogues but for this approach to be applicable a suitable allylic alcohol had first to be found. Once synthesized the allylic alcohol would have the desired rearrangements performed on it.

2.2 SYNTHESIS OF THE FURAN ALLYLIC ALCOHOL (35)

The furan allylic alcohol (35) derived from D-mannose appeared to be ideal for the purposes of the project as, being derived from a sugar, it was chiral and it also contained an interesting isopropylidene protecting group. As can be seen from previous examples the majority of nucleoside analogues contain a simple single primary alcohol at the C5′ position. The isopropylidene group in

the mannose derived compounds could be deprotected to generate the diol and from this functionality numerous reactions could be performed preferentially on either the primary or secondary alcohols to instil novelty into any final nucleoside analogues synthesized.

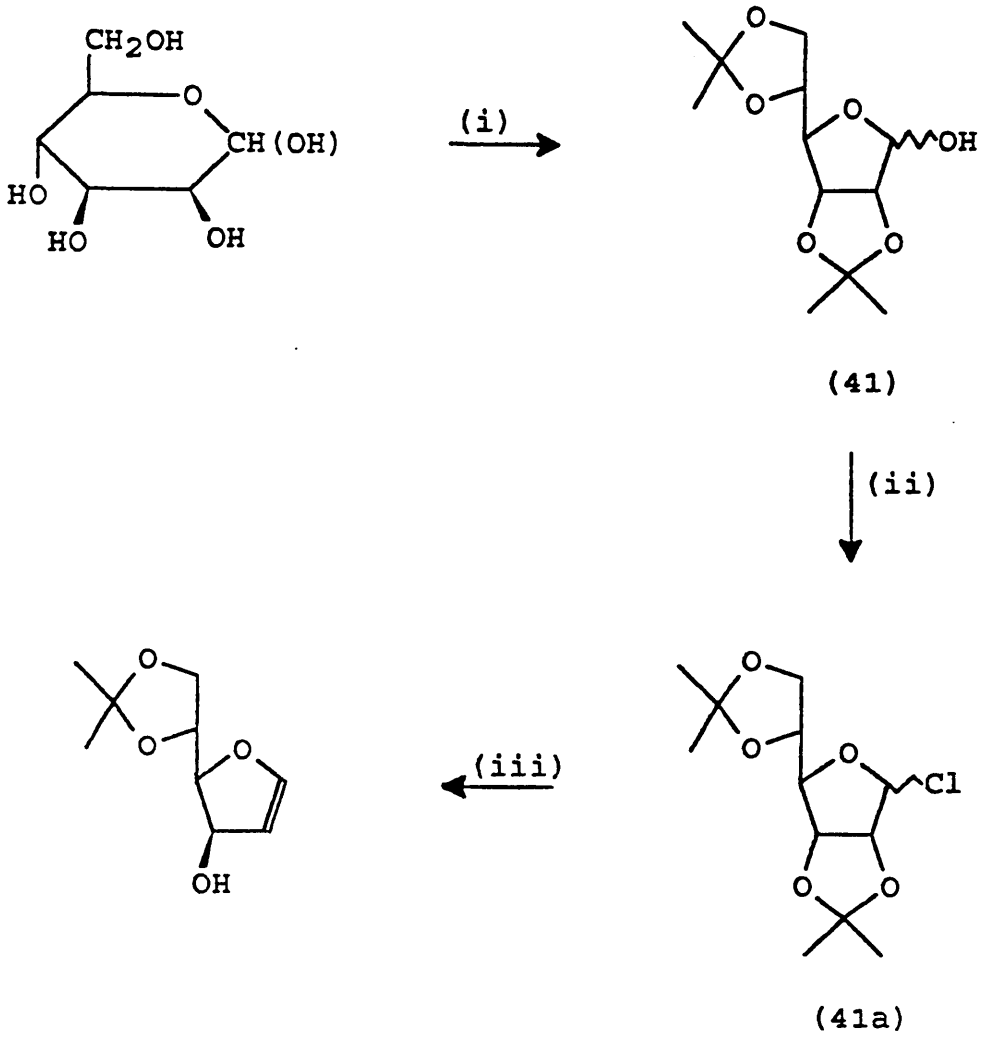


(35)

This compound (35) was synthesized by a three step procedure from D-mannose (Scheme 12). Refluxing D-mannose with concentrated HCl in acetone[53] furnished, after recrystallization, the alcohol (41) in excellent yield (85%). ^{1}H NMR confirmed the product as the desired ring closed hemi-acetal (41). Particularly indicative was the singlet and doublet witnessed at 1.36-1.46 delta which correlated for the 12 hydrogens of the two isopropylidene protecting groups. The alcohol was then chlorinated in CCl_4 containing a molar equivalent of Ph_3P[53] and this reaction produced the glycosyl chloride in good yield as an orange liquid (70.4%). Complete disappearance of the starting material was established by the lack of any OH stretching frequency in the IR spectrum of the crude product. It should be noted that the yield of this reaction was very dependent upon the

quality of the solvent employed. Use of CCl_4 which had not been dried thoroughly led to significant drops in yield and so before each new reaction was commenced the required amount of CCl_4 was freshly distilled into the reaction vessel. Difficulties were also encountered during the work up of this reaction as following filtration and concentration under reduced pressure a thick, sticky mixture of product and $Ph_3P=O$ was left. Isolation of the product from this mixture proved very difficult. The solution to this problem was to perform a series of semi-concentrations and subsequent filtrations of the precipitated $Ph_3P=O$ thus leading to the production of a reasonably pure sample of glycosyl chloride. Although ^1H NMR still showed the presence of $Ph_3P=O$ (<10%) this proved to have no effect on the next stage of the reaction scheme and so was ignored. The third and final stage in the synthesis was a reductive elimination on the glycosyl chloride by lithium wire in liquid ammonia[49]. This reaction worked extremely well and always gave good yields of the crude glycal which was easily purified by column chromatography. This product's structure was confirmed by spectral analysis. IR data showed the reappearance of an OH stretching peak at 3200-3550 cm^{-1} and the ^1H NMR spectrum contained all the desired signals including the indicative OH at 2.45 ppm and the olefin multiplets at 5.15 and 6.50 ppm.

Scheme 12

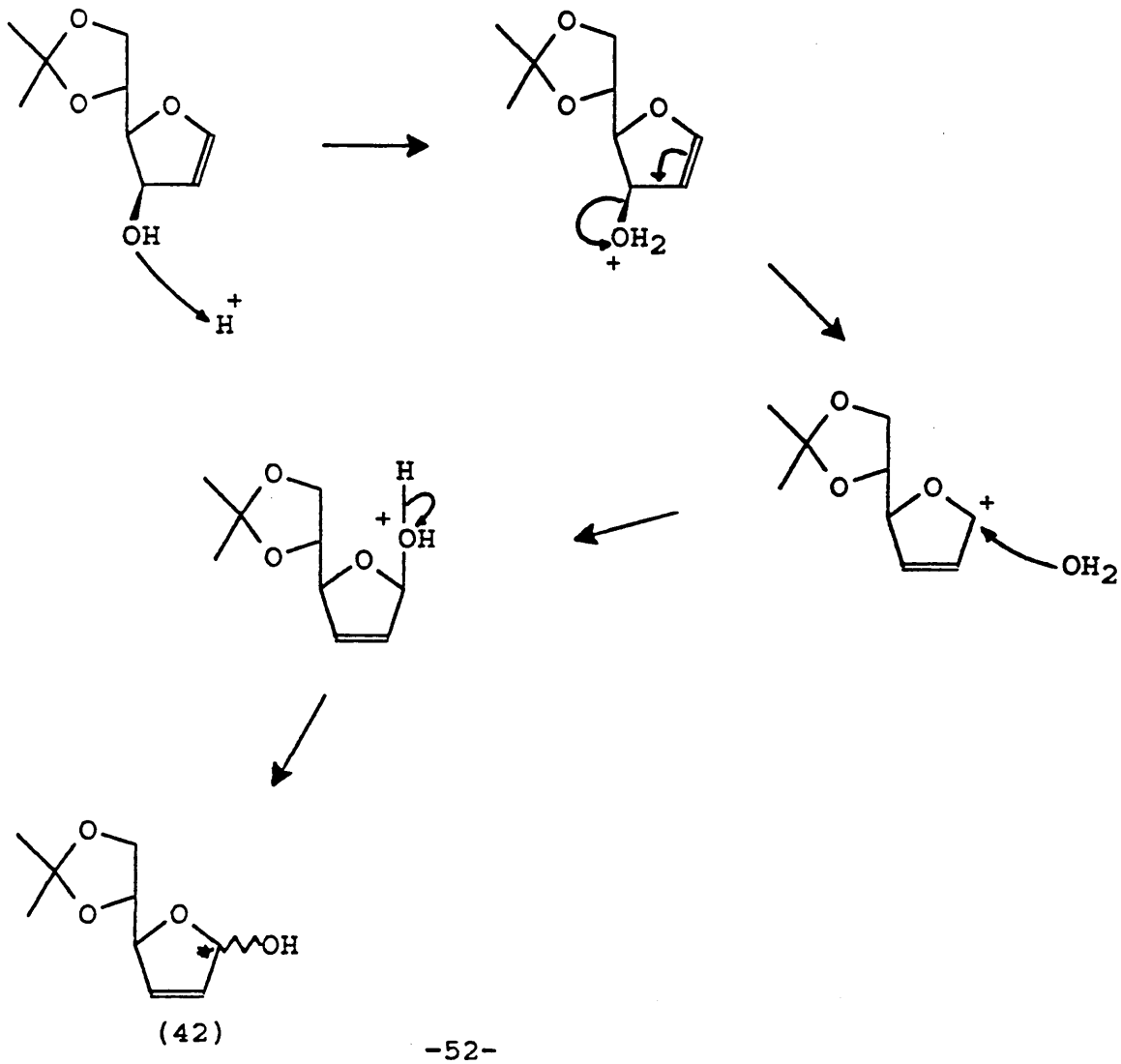


Reagents: (i) H^+/ acetone, (ii) Ph_3P/ CCl_4
(iii) Li (m)/ NH_3 (l)

An important experimental procedure during the chromatography was the addition of 2% Et_3N to the mobile phase. Without this added base the glycal (35) was unstable to the acidity of the silica stationary phase, undergoing an important and well known reaction termed

the Ferrier rearrangement. This led to the production of the hemi-acetal (42) (Scheme 13) which contained undefined stereochemistry around the anomeric carbon *. This Ferrier product (42) was isolated from chromatographic columns run on the crude glycal (35) without the addition of Et_3N. The structure of (42) was subsequently confirmed by spectral data. With this important fact in mind the desired furan allylic alcohol (35) was thus available in multi-gramme quantities for use in Claisen and aza-Claisen rearrangements.

Scheme 13

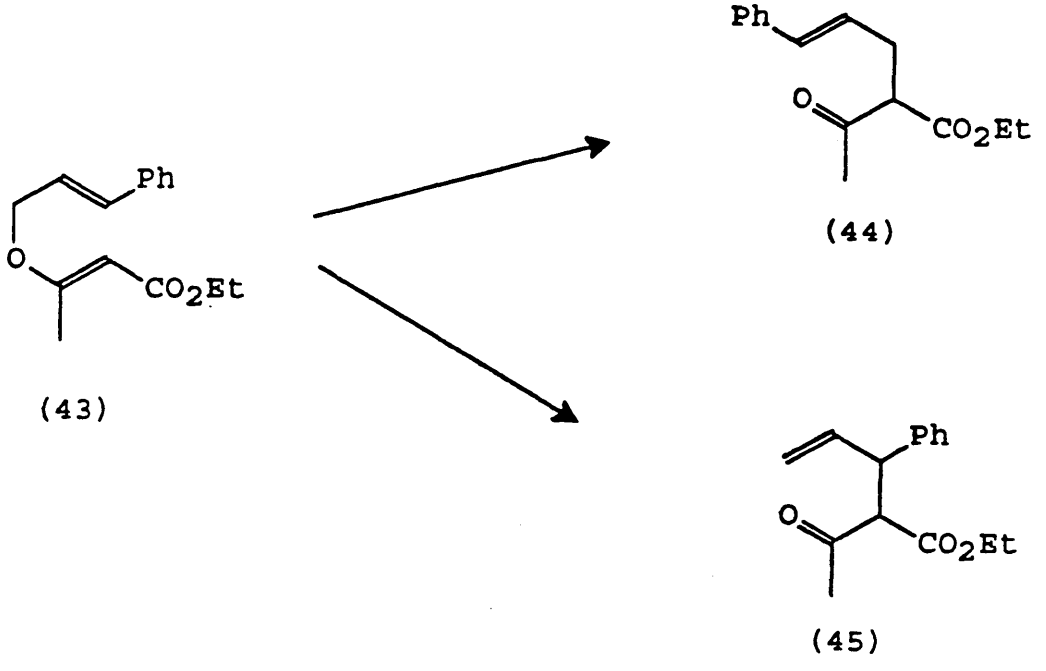


(42)

2.2 CLAISEN REARRANGEMENTS

2.2.1 Background

The Claisen rearrangement[54] has wide applicability in a variety of organic syntheses and was first described by Ludwig Claisen[55] in 1912. However, it was not until 20 years later that two groups investigated the aliphatic rearrangement noted by Claisen using the model compound ß-cinnamyloxycrotonate (43). Bergmann and Corte[56] employed Claisen's conditions using ammonium chloride catalyzed exchange of cinnamyl alcohol with ethyl 3-ethoxy-2-crotonate for the formation of (43). Lauer and Kilburn[57] used sodium cinnamylate and ethyl ß-chlorocrotonate to form (43).

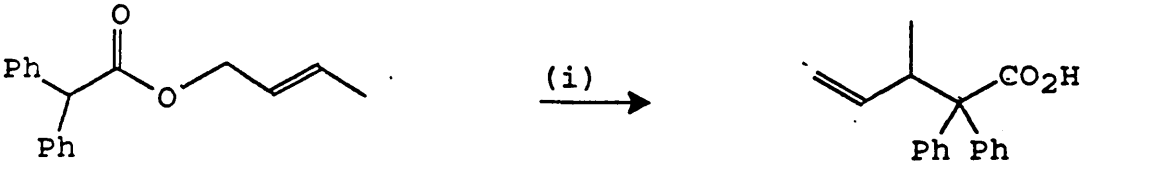


(43) (44) (45)

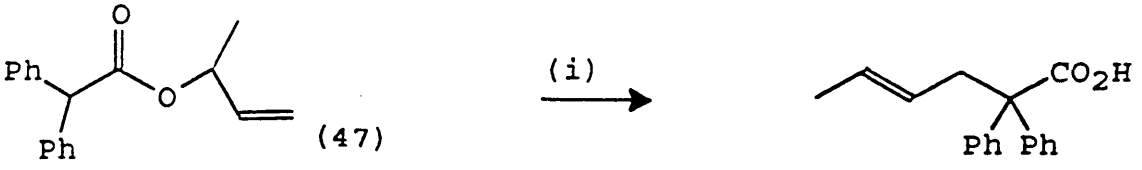
The rearrangement step was performed by both groups with ammonium chloride as catalyst. Bergmann and Corte obtained both (44) and (45) whereas only the desired rearranged product (45) was observed by Lauer and Kilburn.

The first practical example of the preparation of gamma-delta-unsaturated carboxylic acids using the aliphatic Claisen rearrangement was by Arnold et al[58] in 1949 (Figure 7).

Figure 7



(46)

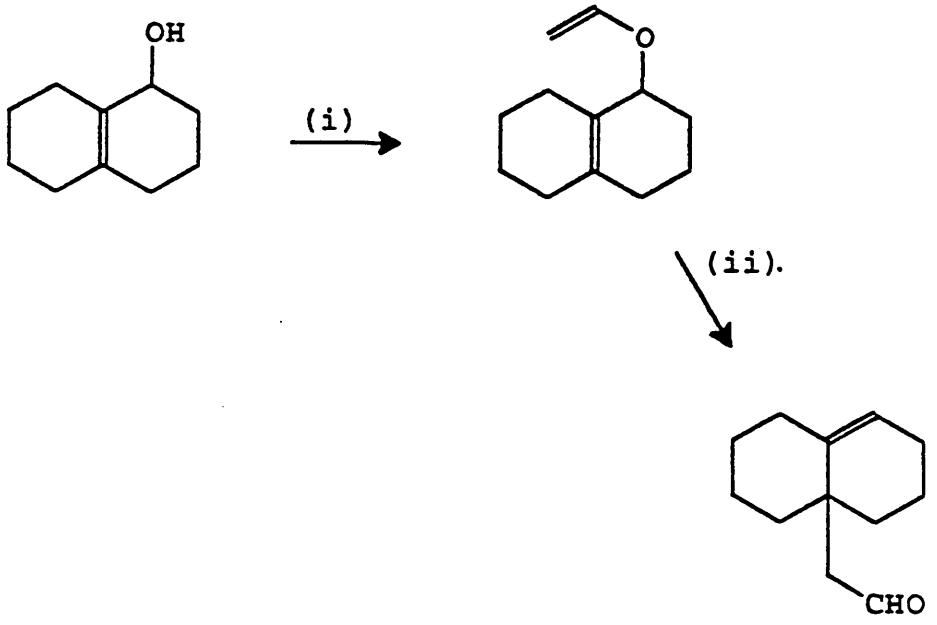


(47)

Reagents: (i) $C_6H_2(Me)_3MgBr$/ Et_2O

The rearrangement was performed on (46) and (47) using mesitylmagnesium bromide at ambient temperatures. A variation of this method was the use of sodium hydride as the base in refluxing toluene[58a]. Important for our project was the work of Burgstahler and Nordin[59] who were able to demonstrate that the Claisen rearrangement

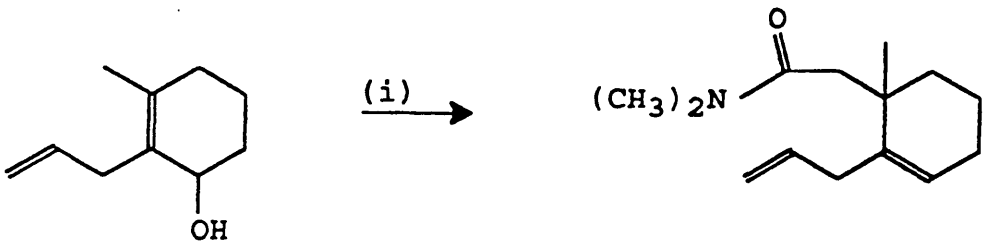
was successful in a system where at least one of the double bonds was contained within a ring.



Reagents: (i) $ROCH{=}CH_2$/ $Hg(OAc)_2$, (ii) heat

While exploring the chemistry of triethyloxonium fluoroborate Meerwein et al[61] discovered a route to N,N-dimethylformamide diethyl acetal. Eschenmoser[62] took this class of compounds and reacted them with allylic alcohols to produce, after rearrangement, gamma,delta-unsaturated amides. This rearrangement of amide acetals has since become a very useful synthetic tool. Buchi et al[63] employed this reaction in the production of a range of alkaloid derivatives and more recently Jenkins and his co-workers[64] used the amide acetal rearrangement in the synthesis of 2,3,3-trisubstituted cyclohexenes (Figure 8).

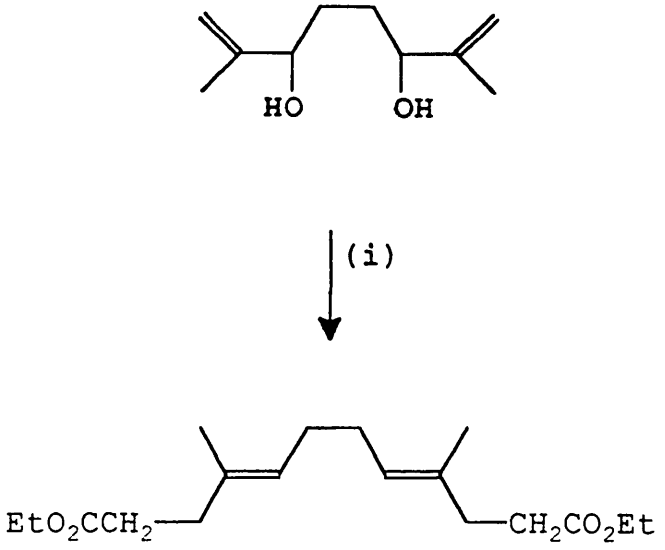
Figure 8



Reagents: (i) $MeC(OMe)_2NMe_2$/ heat

A very useful and simple addition to the array of Claisen rearrangements was discovered by Johnson et al[65] when his group investigated the acid catalyzed exchange and subsequent rearrangement of ethyl orthoacetate with allylic alcohols to yield gamma,delta-unsaturated esters (Figure 9). This has since become a widely published method[66] with many uses in organic synthesis[67].

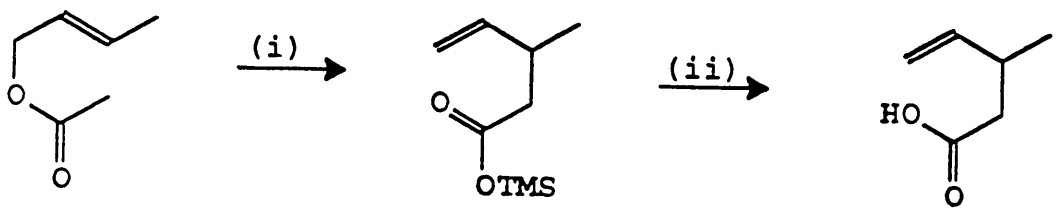
Figure 9



Reagents: (i) $MeC(OEt)_3$/ propionic acid/ 138^{O}/ 3 hrs

An interesting breakthrough occurred with the publication of Ireland's[60] work in this field where he used lithium dialkylamide bases to produce ester enolates which could undergo rearrangement at ambient temperatures (Scheme 14). Both the enolates and their O-silyl ketene acetals underwent facile rearrangement to yield gamma,delta-unsaturated acids.

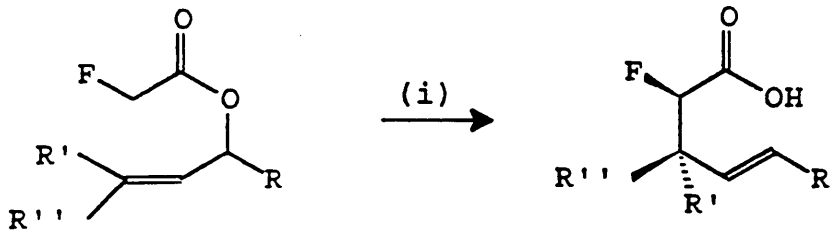
Scheme 14



Reagents: (i) LICA/ TMSCl, (ii) H_3O^+

A variation of Ireland's work was performed by Welch[68] when he produced allyl fluoroacetates which upon deprotonation with LDA and silylation with TMSCl underwent the Claisen rearrangement yielding α-fluoro carboxylic acids (Figure 10).

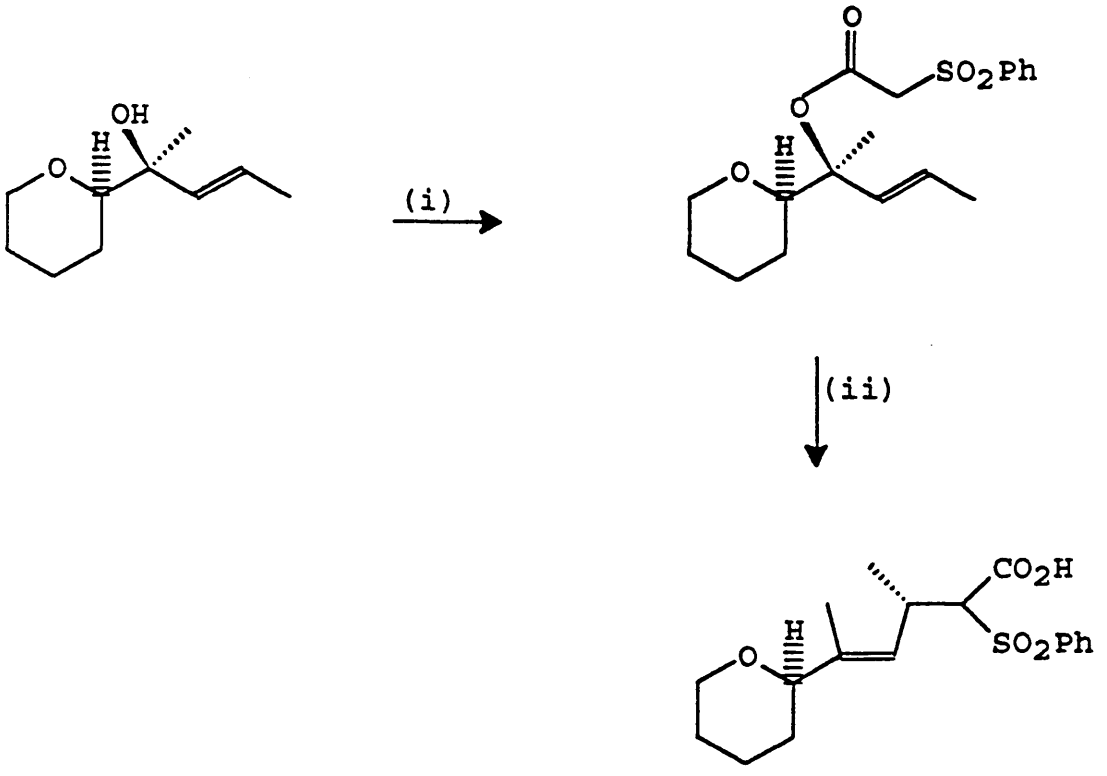
Figure 10



Reagents: (i) a) LDA, b) TMSCl, c) H_2O

Davidson and his co-workers[69] also used a variant of the Ireland ester-Claisen rearrangement in their synthesis of the antifungal agent ambruticin. They produced tertiary sulphone esters and used them to prepare gamma,delta-unsaturated sulphones in a highly stereocontrolled manner (scheme 15).

Scheme 15

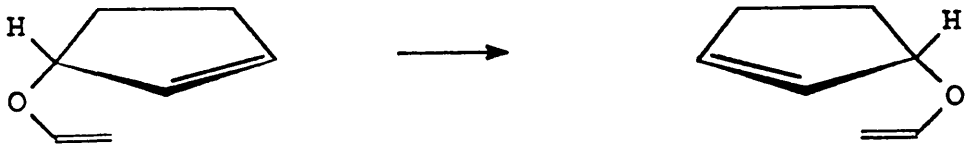


Reagents: (i) pyridine/ $CHCl_3$/ $(PhSO_2CH_2C(O))_2O$
(ii) LDA/ TMSCl

Claisen rearrangements are classified as [3,3] sigmatropic reactions which are highly exothermic, concerted pericyclic reactions with a characteristic negative entropy. The exact structure of the transition

state encountered during the rearrangement is still open to some speculation but it must obviously involve a high degree of resonance stabilisation. These highly ordered transition states effect a reliable transfer of stereochemistry from starting materials to products such as the asymmetric induction observed with chiral substrates as shown in figure 11.

Figure 11

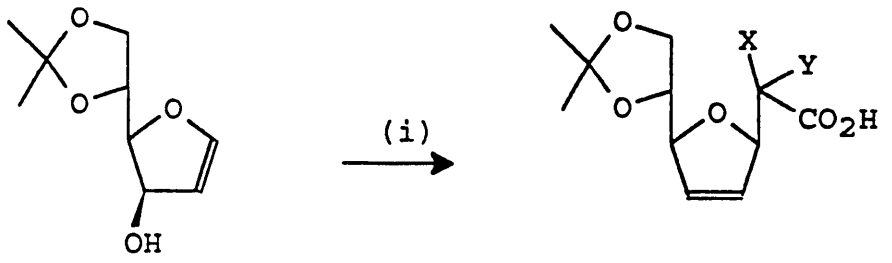


It is also important to note that the primary chiral centre is destroyed during the rearrangement in what is termed a self-immolative process.

2.3.2 Claisen Rearrangements on Furan Allylic Alcohol (35)

For the research project it was decided that a variant of the Ireland-ester Claisen rearrangement would be employed. Ireland had previously used acid chlorides to furnish the desired ester for rearrangement (Figure 12) where X and Y are CH_3 or H.

Figure 12



(35)

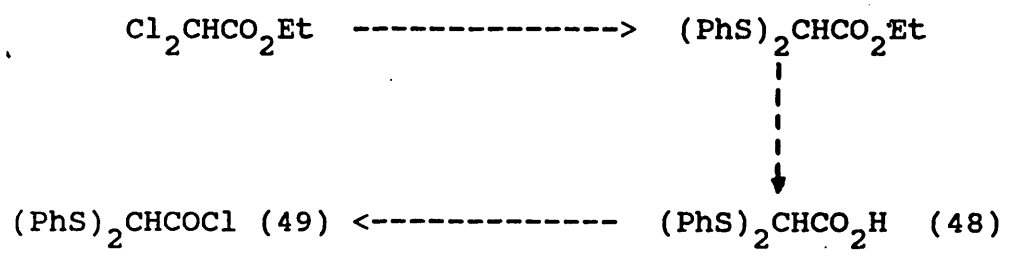
Reagents: (i) a) XYCHCOCl, b) LDA, c) TMSCl, d) heat

The acid side chain produced would appear to be a useful synthetic *'handle'* for a linear synthetic build up of the required heterocyclic base moeity. Its suitability would however be enhanced by replacing the X and Y groups with something more useful synthetically, such as OMe or SPh. With these groups attached a route becomes available to an α-ketoester side chain which is

known to be useful in the synthesis of C-nucleosides such as showdomycin[70].

Firstly the desired bis(phenylthio) acid chloride (49) was formed in a three step process (Scheme 16).

Scheme 16

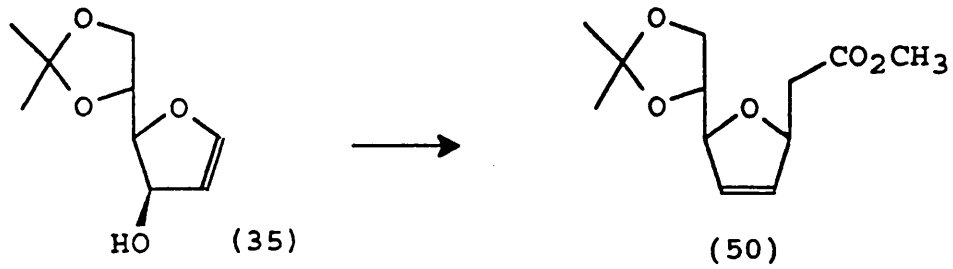


The first two steps were trivial and gave the acid (48) as a white solid in good yield (73%) which exhibited the characteristic OH stretching peak for a carboxylic acid in the IR spectrum covering the region 2500-3300 cm^{-1}. The next stage was the chlorination of the acid to produce the desired acid chloride. Initial reactions using the classical reagent of thionyl chloride proved unsuccessful with the final compound decomposing during the isolation procedure of vacuum distillation. The main breakdown product of this thermal decomposition was rather unexpectedly PhSSPh. The mechanism of this rearrangement is unknown but it must involve considerable molecular fragmentation. This structure was confirmed by ^1H NMR, IR and MS analysis of the solid isolated from the distillation. Employing the milder reagent oxalyl

chloride in dry CH_2Cl_2 gave a crude product whose spectral data showed it was substantially the desired acid chloride. In the IR spectrum of the acid (48) the carbonyl peak occurred at 1690-1730 cm^{-1} whereas no such peak was witnessed in the data for the acid chloride crude product. Only the expected and desired C=O peak at 1750-1820 cm^{-1} indicative of acid chlorides was present. The ^1H NMR spectrum of the crude material only contained signals at 4.85 and 7.2 ppm correlating to the CH and aromatic groups expected and no contaminant peaks were observed. No attempt was made to purify this product by distillation because of worries about decomposition, but it could be purified by rapid column chromatography. The acid chloride both crude and purified, was used in a modified ester Claisen rearrangement employing Ireland's conditions[49]. Numerous attempts at the reaction all yielded complex mixtures, with no single major product being formed. Column chromatography of these crude reaction mixtures allowed isolation of the various products observed. No attempt was made to assign a structure to each compound, merely a comparison was made with the expected data for the desired product. Unfortunately none of the compounds isolated from the mixture was the required branched acid product.

Due to the rather disappointing results achieved with the Ireland-ester Claisen rearrangements attention was

focussed onto other methods of obtaining the desired products. The obvious choice at first appeared to be Johnson's[65] acid catalzed ethyl orthoacetate rearrangement and this reaction was attempted employing trimethyl orthoacetate as both substrate and solvent with propionic acid as the catalyst.



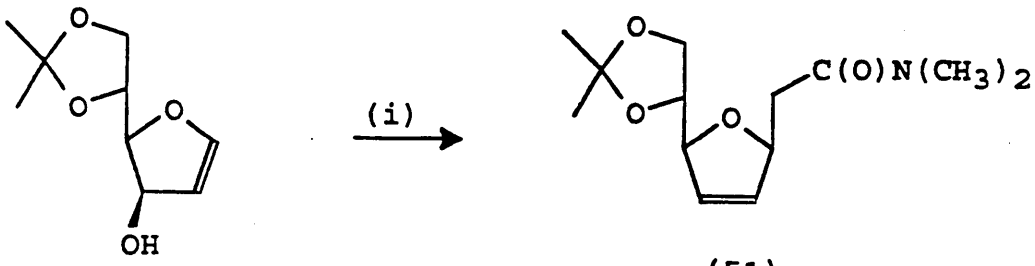
Reagents: (i) $MeC(OMe)_3$/ propionic acid

The single product obtained after 3 hours reflux was not the desired methyl ester (50) as ^1H NMR analysis and comparison with previous recorded spectra showed the product to be the Ferrier rearranged alcohol (42). This compound was subsequently stable to the reaction conditions employed, showing no tendency to undergo a Claisen rearrangement itself.

The Johnson-Claisen rearrangement could not therefore, be used in the furan system compounds due to the acidic conditions required for reaction. A method of Claisen rearrangement was thus required which employed non-acidic conditions and the obvious choice was an amide

acetal rearrangement. Dimethylacetamide dimethylacetal was reacted with the allylic alcohol (35) in refluxing o-xylene (Figure 13).

Figure 13



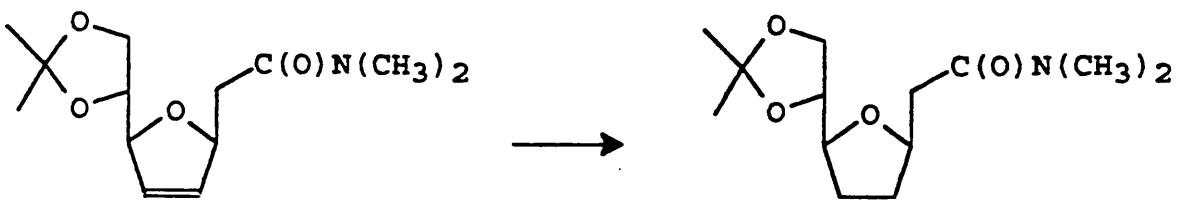
(51)

Reagents: (i) dimethylacetamide dimethylacetal/ o-xylene heat/ 64 hrs

Initially the starting materials were simply added together in one pot and refluxed over 64 hours under a positive pressure of nitrogen. Following removal of the volatiles, TLC of the crude material showed the reaction had proceeded to generate a single product. Column chromatography yielded the pure rearranged amide (51) in 71% yield as a clear colourless gum. No OH peak was visible in the IR spectrum thus confirming complete disappearance of the starting alcohol (35) and the appearance of a C=O peak at 1679 cm^{-1} suggested the presence of an amide functionality. Characteristically in the ^{1}H NMR spectrum the presence of a singlet at 2.0 ppm for the amide methyl groups and a shift of the olefin signals fromm 5.15 and 6.50 ppm to 5.95 and 6.1 ppm

confirmed that the desired rearrangement had taken place. Further experimentation attempting to both enhance the yield and shorten the reaction time was subsequently undertaken involving the use of a trap to remove the methanol produced during the rearrangement. Due to Le Chateliers principle this should have enhanced the yield but results obtained proved inconclusive. Future work could involve the use of better methods of methanol removal such as employing a soxhlet extractor filled with $CaCl_2$ which again should help enhance the yield. The rearranged amide appeared to contain all the qualities required for use as an intermediate in novel C-nucleoside synthesis. The synthetic *'handle'* side chain was present to allow heterocyclic base synthesis and the isopropylidene protecting group had the possibilities for a variety of interesting substituents to be made available. Finally the unsaturation between C2' and C3' might be extremely useful for the addition of a variety of functionalities. For instance, in order to produce another series of compounds in this area, one simple reaction was to reduce the double bond by hydrogenation employing a palladium on charcoal catalyst. This reaction was performed (Figure 14) and led to the saturated amide (52) being isolated in 88% yield. This compound (52) could prove useful in producing a series of 2',3'-dideoxy nucleoside analogues.

Figure 14



(51) (52)

Reagents: (i) Pd/C H_2

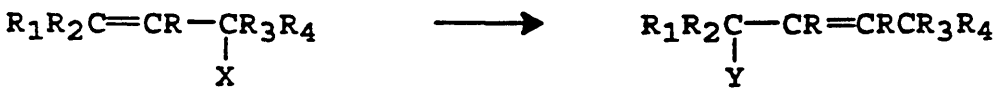
2.4 AZA-CLAISEN REARRANGEMENTS

2.4.1 Background

As has been previously shown the Claisen rearrangement has proved a useful method for the production of intermediates in the synthesis of C-nucleosides. Although of interest, the C-nucleosides are not as biologically active in most cases as nucleosides. A method of producing a sugar with a synthetic '*handle*' suitable for nucleoside synthesis could therefore prove extremely useful and such a reaction would appear to be what is commonly termed as the aza-Claisen or hetero-Claisen rearrangement.

Prior to 1974 a generally useful method for the 1,3 transposition of oxygen and nitrogen functions was not available (Figure 15, X=OH, Y=NR_2)

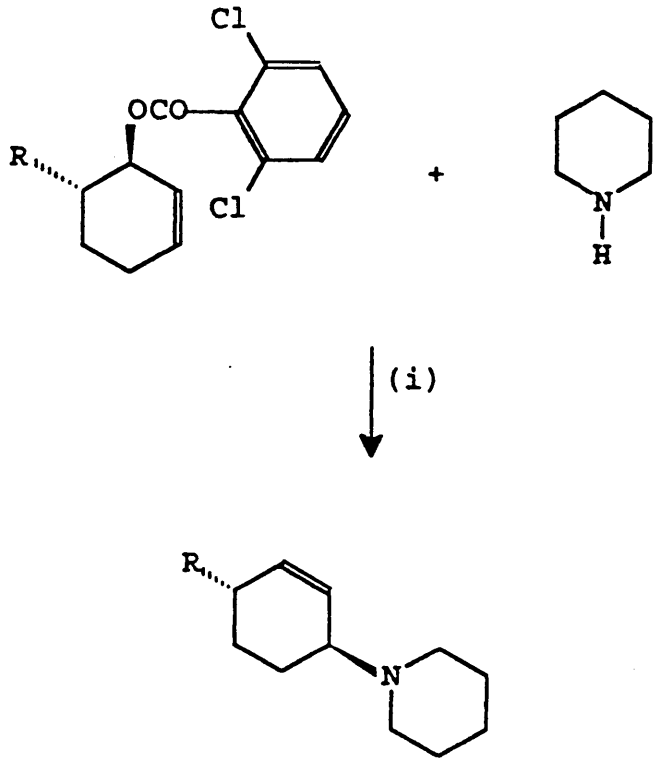
Figure 15



This is exactly the reaction which was required if the furan allylic alcohol (35) was to produce a useful intermediate for nucleoside synthesis. The reaction shown in figure 15 would have wide applicability in a variety of organic syntheses. Methods prior to 1974 for effecting this rearrangement all had serious drawbacks. The S_N2 reaction of allylic alcohol derivatives with amines can be successful but it relies on direct displacement being precluded by steric and other factors[71](Figure 16).

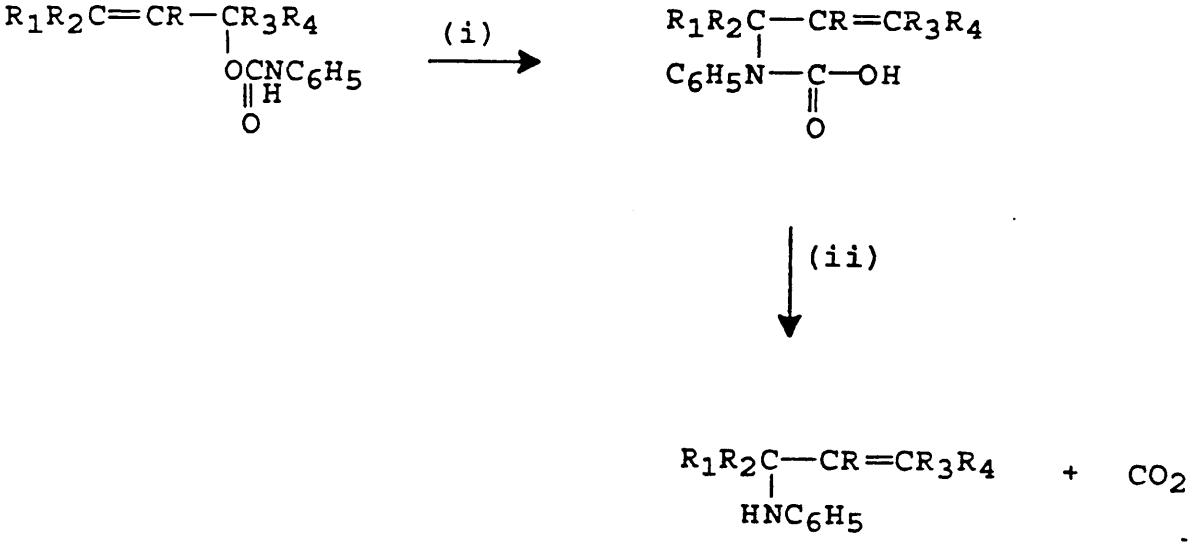
One of the most applicable processes was the base-catalyzed thermal rearrangement of allylic phenyl urethanes at 200-240^{o}C (Scheme 17) but a drawback of this process is that always ionization (S_Ni) occurs and thus even in the best cases significant amounts of unrearranged compounds are isolated.

Figure 16



Reagents: (i) 130^{O}

Scheme 17

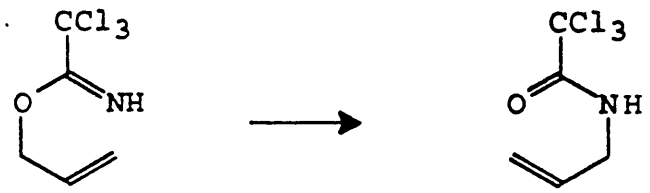


Reagents: (i) 200-240^{O}, (ii) base/ heat

Another method of interest was the rearrangement of N-phenylformimidates[72] and allylic N-phenylbenzimidates[73] at 200-250°C to yield the corresponding amides. This again had serious problems in that the yields to the required imidate intermediate are moderate and also the high temperatures needed to effect the rearrangement could disrupt the structure of the amides produced.

With this lack of a generally applicable method for O to N transposition in mind, a breakthrough occured in 1974 with the publication of a paper by Overmann[74]. In this paper he reported the facile [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates to afford the corresponding trichloroacetamides (Figure 17). This synthetic operation results in the much sought after 1,3 transposition of alcohol and nitrogen functions.

Figure 17



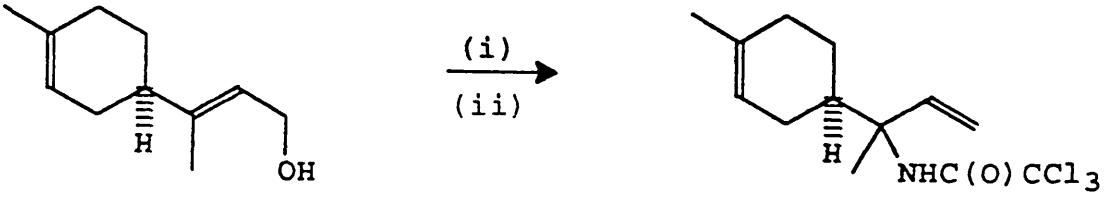
Overmann first prepared the intermediate allylic trichloroacetimidates from the corresponding alcohol and trichloroacetonitrile in almost quantitative yield and subsequently these imidates were easily thermally rearranged within a few hours in a high boiling solvent

such as m-xylene to furnish the desired trichloroacetamide product. A further interesting point was the observation that added mercuric salts often catalysed the rearrangement quite appreciably. The trichloroacetyl group could then be easily hydrolytically removed to yield the free amine. The great advantages over any previous method for 1,3 O to N transposition included the much lower temperatures required to effect the rearrangement and the ease of removal of the trichloroacetyl group to yield the free amine.

This important reaction has since been used in a variety of syntheses. Overmann himself employed it in the production of the interesting natural alkaloid intermediate 1-azaspiro[5,5]undec-7-en-2-one[75] (scheme 18).

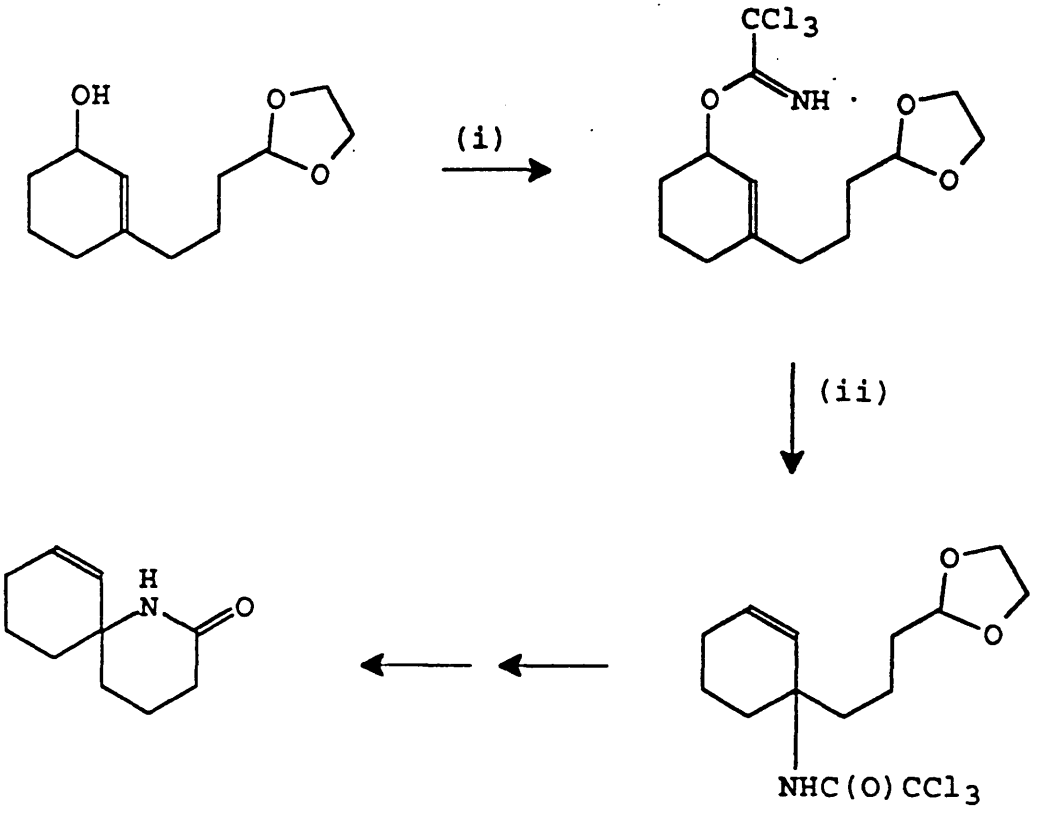
More recently Ichikawa[76] required the use of the aza-Claisen rearrangement as the crucial step in the synthesis of aminobisabolanes (Figure 18).

Figure 18



Reagents: (i) a) NaH/ Cl_3CCN, (ii) toluene/ reflux

Scheme 18



Reagents: (i) NaH/ Cl_3CCN/ 0^{o}, (ii) hexane/ 69^{o}/ 4-5 days

Even though the conditions for the trichloroacetimidate synthesis are fairly mild, yields of the final acetamide

after rearrangement are still sometimes only modest. This is due to competing decomposition of the imidate in the refluxing solvent, as compared with the desired rearrangement.

Savage and Thomas[77] attempted to further eliminate this problem by the use of trifluoroacetonitrile instead of trichloroacetonitrile. [3,3] Rearrangements of allylic imidates are accelerated by the addition of electron-withdrawing substituents on the imidate carbon and therefore, by replacing chlorine with the more highly electro-negative element fluorine, they hoped for and achieved the effect of allowing the rearrangement to occur under even milder conditions. The only drawback for this method was that it employed trifluoro-acetonitrile, which was more expensive than trichloroacetonitrile and as a gas was more difficult to handle in the laboratory.

2.4.2. Aza-Claisen Rearrangements on the Furan Allylic Alcohol (35)

For the basis of the project it was decided to employ Overmann's methodology[78] using trichloroacetonitrile as opposed to the more expensive trifluoro derivative.

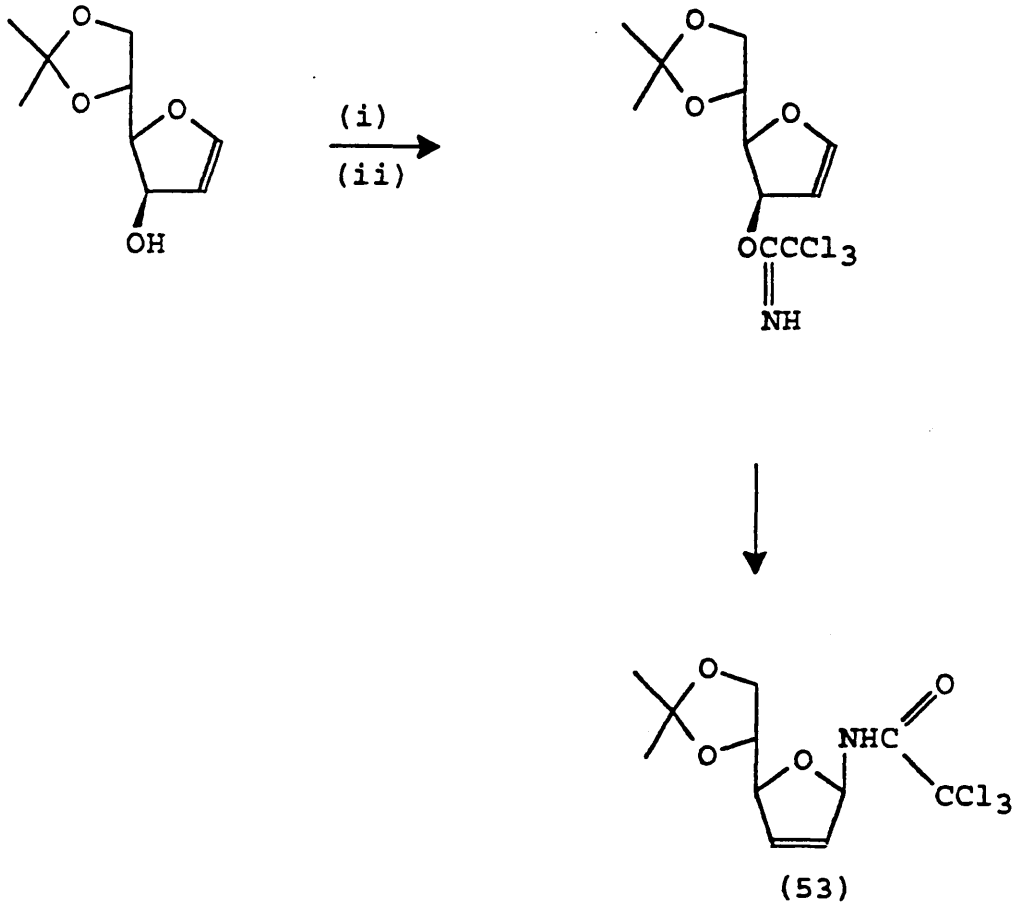
A clear colourless solution of the furan allylic alcohol (35) in dry ether was treated with a 0.1 mole

equivalent of sodium hydride to produce the reactive alkoxide. After a period of twenty minutes hydrogen evolution had ceased and the bright orange clear liquid was transferred via syringe to a solution of trichloroacetonitrile (1 mole equivalent) at $0^{o}C$. Subsequent work up yielded a pale green liquid which crystallised upon standing and was presumed to be the trichloroacetimidate product. However, IR examination of this solid did not show the expected characteristic strong C=N str at 1660 cm^{-1}, instead a peak at 1720 cm^{-1} was observed. This unknown solid was dissolved in dry toluene and refluxed to see if any rearrangement/reaction occurred. No reaction was observed and after work up and recrystallization the pure white crystalline solid isolated was analysed more closely. The appearance of a peak in the IR spectrum at 1720 cm^{-1} led to the possibility that this correlated for the C=O stretching frequency expected in the desired trichloroacetamide product. This would signify that the intermediate imidate had rearranged in a facile manner to the trichloroacetamide (53) under the reaction conditions employed (Scheme 19).

Analysis by proton NMR, mass spectrometry and micro analysis confirmed the structure of the white solid as that of the coveted trichloroacetamide (53). In the ^{1}H NMR spectrum the shift of the olefin signals from 5.15

and 6.50 ppm to 6.15 and 6.45 ppm indicated the rearrangement had indeed occurred and this was confirmed by the EI-MS of the solid which contained a molecular ion at 330 mass units as required for (53).

Scheme 19



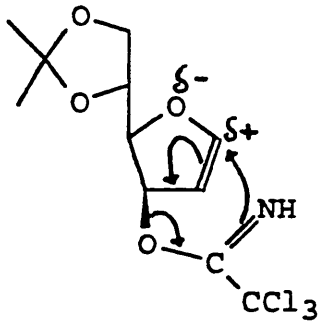
(53)

Reagents: (i) NaH, (ii) Cl_3CCN/ 0^{O}

The yield of the reaction was modest (48%) but this still compared favourably with similar rearrangements attempted by other groups. The explanation for this novel facile rearrangement could be due to two possible reasons.

Firstly the ring nature of the furan helps place the functional groups of the intermediate imidate into the correct spatial arrangement for rearrangement to occur. The main driving force for the reaction however is probably the fact that the furanose oxygen polarises the single bond with carbon (Figure 19) thus making nucleophillic attack on that carbon more favourable.

Figure 19



Further experimentation showed that the reaction worked equally well with anywhere up to 1 mole equivalent of sodium hydride with little effect on the overall yield. A further benefit discovered was that impure glycal (35) could be employed again with little or no effect on the yield. The reaction is however fairly water sensitive and it was discovered that the use of ether freshly distilled from $LiAlH_4$ had a marked positive effect on the yield. Thus by following these guidelines the reaction yield was optimised to 78% and so the

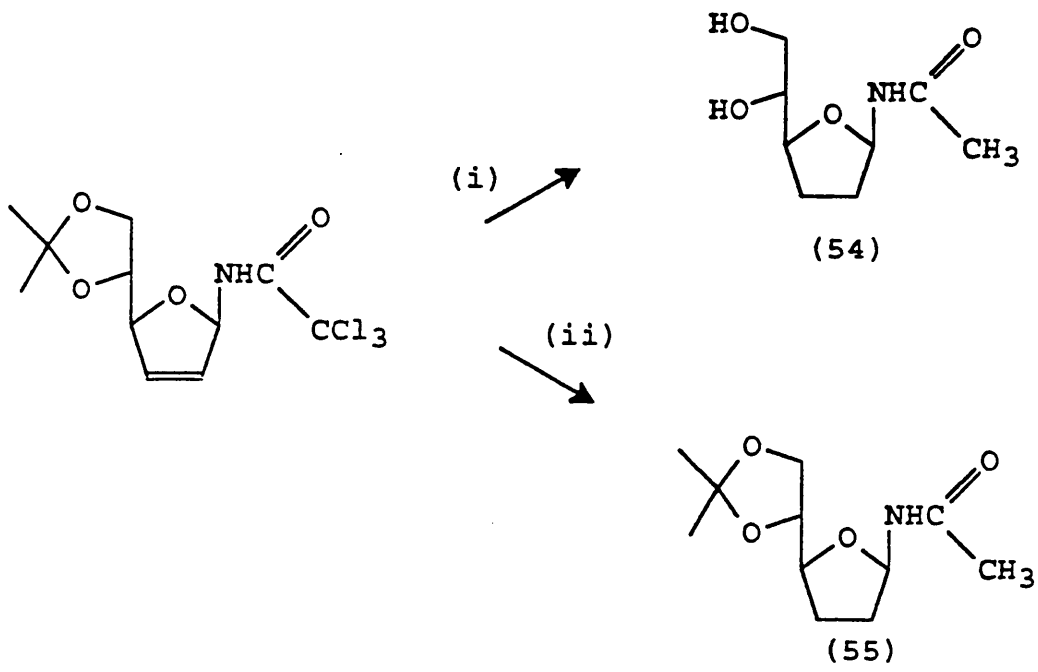
trichloroacetamide (53) became easily available in multi-gramme quantities.

The next stage of the reaction scheme, the hydrolysis of the trichloroacetyl group to the free amine, appeared rather trivial. From this amine a variety of well published methods are available for the linear synthesis of the required heterocyclic bases. Following Overmann's method[78] it was therefore attempted to hydrolyse (53) with aqueous NaOH in ethanol at room temperature. After 36 hours the starting material had been consumed leaving a product lying on the baseline of the TLC plate. Even by employing highly polar solvents such as methanol this product spot could only be moved to Rf=0.10. Initial IR and proton NMR analysis appeared to suggest that the desired free amine had not been produced. A variety of reaction conditions were attempted in order to produce the amine with the quantity of NaOH used appearing to have no affect on the reaction as did alteration of the reaction temperature.

After much experimentation it was decided that the amine was probably unstable and not isolable under the reaction conditions being employed. Hydrogenating the double bond of the trichloroacetamide (53) was thought to be a useful way of lowering the reactivity of the amine produced by hydrolysis. Initially the hydrogenation was

attempted using Pd on charcoal as catalyst and ethyl acetate as the solvent. These conditions produced a highly polar product which was extremely difficult to isolate. IR analysis of this polar compound showed both O-H str. and C=O str peaks which appeared to suggest that the isopropylidene protecting group had been cleaved. This was confirmed by proton NMR by the loss of the signals for this group at 1.35 and 1.42 ppm and thus this spectral analysis showed the compound produced was the diol-acetamide (54). The Pd catalyst had not only hydrogenated the olefin as required but also the trichloroacetyl group had been hydrogenolysed to the acetamide which was confirmed by the loss of the chlorine isotope pattern in the EI-MS and by the appearance, in the proton NMR, of a signal for the amide methyl group at 2.1 ppm. The HCl produced during this hydrogenolysis was sufficient to facilitate the cleavage of the isopropylidene protecting group leaving the diol. The next hydrogenation was therefore performed with Adams' catalyst (PtO), a milder hydrogenating agent and with Et_3N added to the solvent to react with any free HCl. The resultant product (55) from this procedure was isolated in good yield (89%) and again showed hydrogenolysis of the trichloroacetyl group but this time the isopropylidene had remained intact. The amide (55) still presented difficulties for its use in the synthesis of the desired free amine. This was due to the

difficulty in hydrolysing the amide without the use of acidic conditions which would disrupt the molecule's structure.



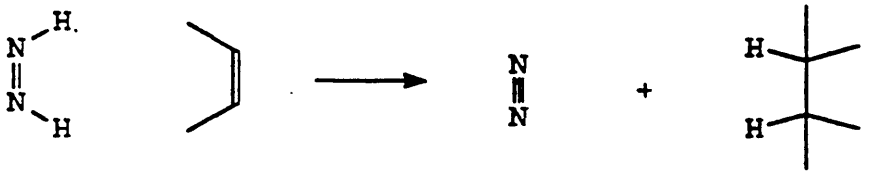
Reagents: (i) Pd/C H_2, (ii) PtO/ H_2/ Et_3N

If the trichloroacetamide was to prove a useful intermediate for nucleoside synthesis either methods for the non-acidic hydrolysis of (55) or ways of reducing the olefin of (53) specifically with no accompanying hydrogenolysis would need to be found.

Two olefin specific reducing agents are diimide and Wilkinson's catalyst. Diimide (NH=NH) is formed from N_2H_4 and an oxidising agent as both its syn and anti forms, although only the syn form reduces the double

bond, probably in part via a cyclic mechanism (Figure 20).

Figure 20



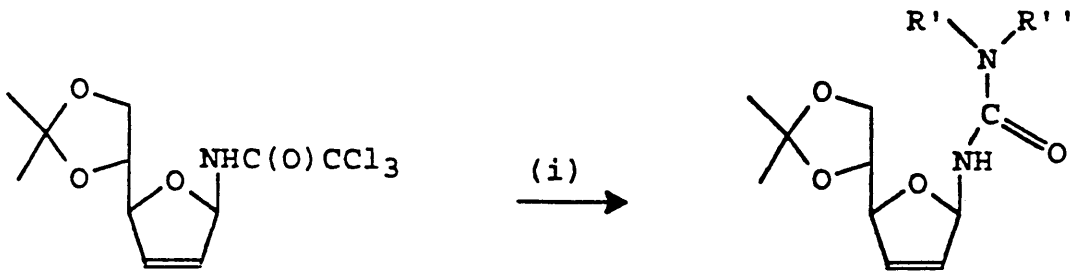
The addition is stereospecifically syn and takes place, in general, from the least hindered side of the double bond. As can be seen from its mode of action a diimide would be unable to effect the undesired side reaction of trichloroacetyl hydrogenolysis.

Wilkinson's catalyst (chlorotris(triphenylphosphine)-rhodium, $RhCl(Ph_3P)_3$) is known to catalyze the hydrogenation of many olefinic compounds without disturbing such groups as COR, COOR, NO_2 and CN present in the same molecule. This reagent is a homogeneous catalyst and can be employed in a variety of organic solvents. Both Wilkinson's catalyst and diimide could therefore be employed to attempt the specific reduction of the olefin in order to produce the desired saturated trichloroacetamide. Unfortunately due to lack of time neither of these methods were actually tested.

Due to the lack of success in isolating the free

amine it was decided to seek other methods of employing the trichloroacetamide (53) to produce nucleoside analogues. An initial thought was that nucleophilic attack at the amide carbonyl might induce the displacement of the trichloroacetyl as a leaving group. This would be of extreme interest if the nucleophile could be of a type which would produce an urea derivative (Figure 21)

Figure 21



(53)

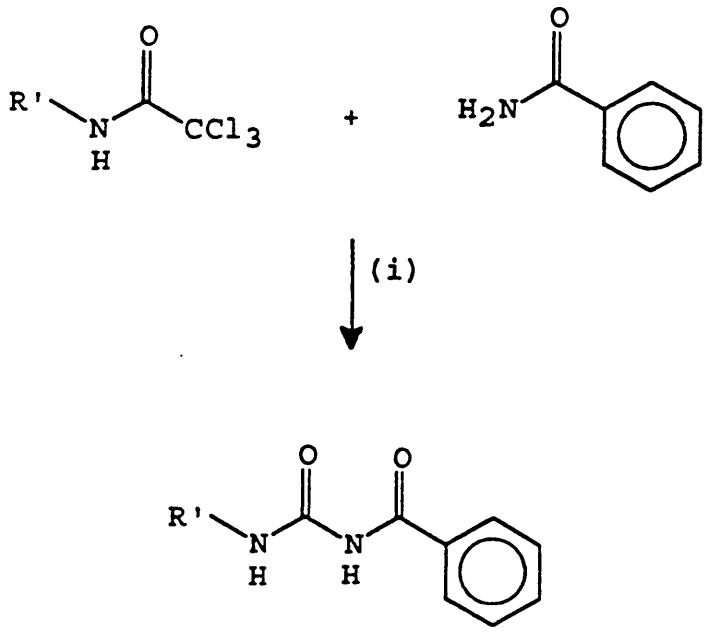
Reagents: (i) HNR'R''

Ureas have often been used as building blocks for the synthesis of heterocyclic pyrimidine bases. Initial experimentation using sodamide in dry THF did not show any reaction, possibly due to the lack of solubility of sodamide in THF. A variety of reaction conditions such as varying the quantity of sodamide employed and the temperature of the mixture appeared to make no apparent difference to the reaction outcome. In a subsequent reaction the trichloroacetamide (53) was dissolved in dry THF and gaseous ammonia was bubbled through the stirred

mixture, but reaction for 48 hours at room temperature led only to recovery of starting materials. Similarly (53) was dissolved in ethanol and conc. ammonia was added and the reaction vessel stoppered. After 48 hours removal of the volatile components gave the crude material as a complex mixture from which the desired product was not isolated.

An interesting paper by Antanassova et al[79] appeared to show a use for trichloroacetamides which was of great relevance to this work of urea derivative synthesis. Antanassova and his co-workers reacted trichloroacetamides with carboxamides in the presence of excess powdered NaOH in DMSO to yield acylureas (Figure 22) via their in situ generated isocyanates. This would appear to show an easy route to the synthesis of urea analogues potentially useful in the synthesis of nucleoside derivatives. Only very tentative initial experimentation has been performed using this method with the trichloroacetamide (53) being reacted with the model compound benzamide to yield a complex mixture of products. Further work is needed in this interesting area in order to assess its viability as a route to urea intermediates useful for nucleoside analogue synthesis.

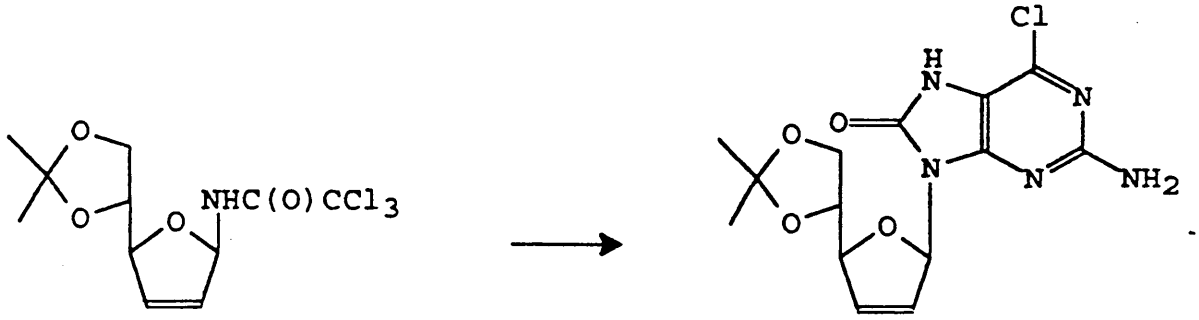
Figure 22



Reagents: (i) DMSO/ NaOH/ 80^{O}

A possible method of purine heterocyclic base synthesis would be that described numerous times in literature as the reaction between an amine and a dichloropyrimidine derivative[80]. Although the free amine was not available at present an attempt was made to perform this reaction on the trichloroacetamide (53) (Figure 22) by trapping the intermediate amine in situ.

Figure 22



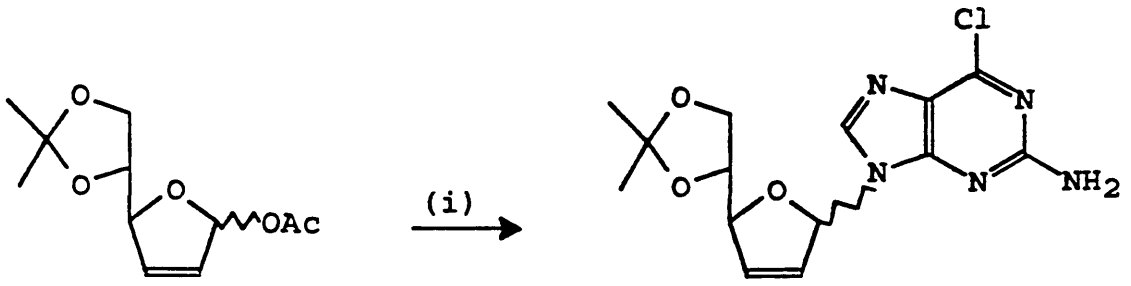
Following 36 hours reflux all the starting material had been consumed leaving a mixture of starting pyrimidine and baseline material by TLC. Analysis by IR, proton NMR and EI-MS failed to aid in the elucidation of the product/s formed by this reaction.

2.5 Use of Glycal (35) and its Ferrier Rearranged Derivative (42)

The product of the Ferrier rearrangement, the cyclic hemi-acetal (42), has been mentioned previously in this report and was formed by acid catalysis during a trimethyl orthoacetate Claisen rearrangement of the glycal (35). If the glycal (35) or its rearranged derivative (42) could be reacted to produce their acetyl derivatives a number of possibilities become applicable for the convergent synthesis of nucleoside analogues. One obvious method would be to employ the reaction of (56) with a purine heterocyclic base in the presence of a Pd catalyst[43] (Figure 23).

Initial attempts to produce the acetate of glycal (35) employing ^{n}butyllithium and distilled acetyl chloride were unsuccessful with starting material and an unknown product being recovered. Reaction of the glycal

Figure 23



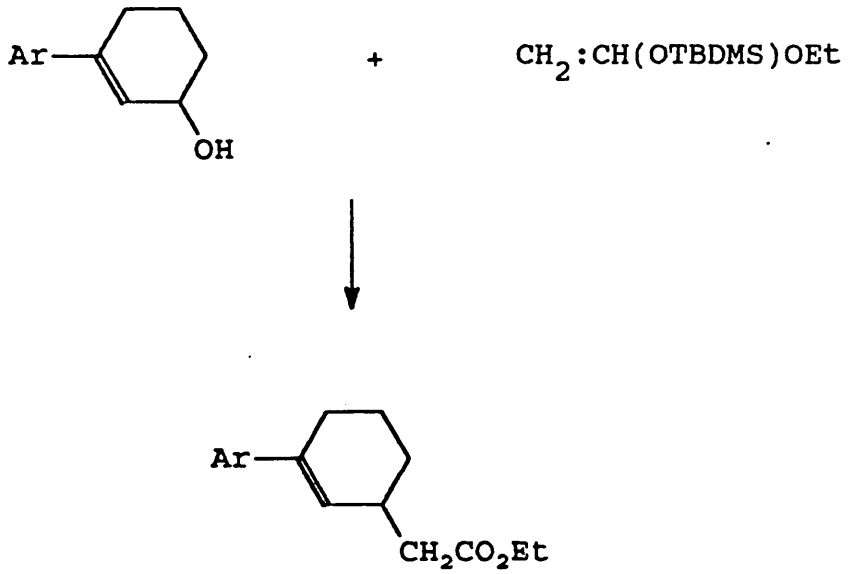
(56)

Reagents: (i) 2-amino-6-chloropurine/ NaH/ $Pd(PPh_3)_4$

(35) with acetic anhydride in pyridine with DMAP as catalyst led, after 54 hours at room temperature, to recovery of starting materials. Refluxing this mixture overnight and removal of all the volatiles produced a black gum which showed signs (IR; C=O str.) that the acetate had been formed. However, TLC and proton NMR appeared to show that this was probably a minor product only. Unfortunately due to a lack of time no further work was possible in this area.

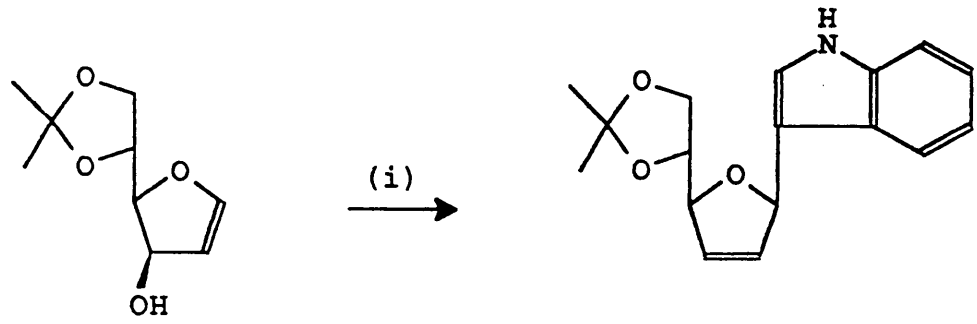
A very recent paper by Pearson and Schkeryantz[81] describes the nucleophilic displacement reactions of allylic alcohols and their acetates in the presence of $LiClO_4$ (Figure 24). If the nucleophile employed could for instance be a silylated pyrimidine or purine base this would be a novel and simple route to a range of nucleoside analogues.

Figure 24



An initial reaction using this methodology was attempted employing glycal (35) with indole as the model nucleophile, in the presence of $LiClO_4$ (Figure 25).

Figure 25



Reagents: (i) $LiClO_4$/ indole

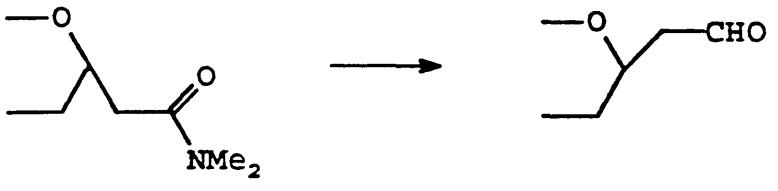
After 12 hours at room temperature TLC showed no reaction had occurred and upon work-up only starting materials were recovered. It would be hoped that if the acetate of the glycal could be isolated this might prove to be more

successful. If reaction was shown to take place with a model nucleophile this method could prove very useful in nucleoside synthesis. A change in nucleophile to a silylated pyrimidine or purine base could prove to be both a novel and easy route to a range of nucleoside derivatives.

2.6 Summary and Future Work

The Claisen amide-acetal rearrangement of the glycal (35) works well but little work has been attempted in its uses as a precursor to C-nucleosides. A possible route for its use is discussed by Tulshian and Fraser-Reid[67] whereby the amide is reduced with $Li(OEt)_3AlH$ to produce an aldehyde functionality (Figure 26). From this aldehyde a number of possibilities for C-nucleoside base build up are available.

Figure 26



Reagents: (i) $Li(OEt)_3AlH$

The aza-Claisen rearrangement on the glycal (35) has produced interesting results in so much that the rearrangement is facile under the reaction conditions employed. Typically refluxing in a suitable solvent is required to effect the rearrangement step. Unfortunately little success has been forthcoming in the hydrolysis of this amide to produce the free amine which would be an intermediate of great use in nucleoside analogue synthesis. Certainly areas which require much greater examination are the use of trichloroacetamides to produce urea derivatives and the reduction of the double bond of trichloroacetamide (53) by reagents such as Wilkinson's catalyst and diimide in an attempt to moderate the reactivity of the free amine and thus permit its isolation. Czernecki's paper would seem to be an extremely interesting one concerning the reaction of trichloroacetamides to produce urea derivatives which could prove very useful as intermediates in nucleoside synthesis.

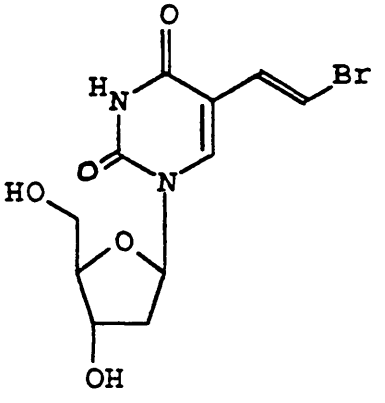
Finally in this furan area is the use of the glycal (35) or its Ferrier rearranged product (42) as their acetate derivatives. As yet the acetates have not been isolated but with further experimentation using acetic anhydride and DMAP in refluxing pyridine it should be possible to furnish the desired product. The use of these acetates in conjunction with $LiClO_4$ and a silylated

heterocyclic base could provide a quick and easy method of chiral nucleoside synthesis. As previously discussed these acetates could also be employed in the more standard reaction with a chlorinated heterocyclic base in the presence of a Pd catalyst to furnish a nucleoside derivative. A further possible use for the glycal (35) is highlighted in a paper by Farr and Daves[95]. The glycal alcohol is initially protected as the t-butyl-diphenylsilyl ether. Subsequent reaction of this silyl protected compound with the mercury salt of a heterocyclic base in the presence of palladium acetate catalyst produced an interesting C-nucleoside derivative.

3.0 CARBOCYCLIC NUCLEOSIDES

3.1 Introduction

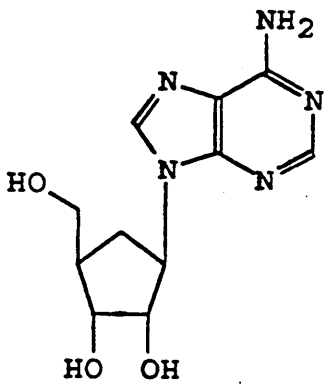
The major disadvantage of furan based nucleoside analogues as antiviral agents is their instability to degradative enzymatic fission in the body. An example of this is shown by the antiviral compound E-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) (57) which is removed from the blood stream within two hours of administration.



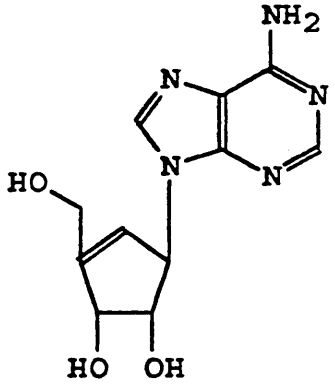
(57)

As has been previously stated it is the glycosidic -O-C-N- linkage between the sugar and base moieties which is enzymatically hydrolysed and therefore alterations of the sugar or base entities would hopefully produce nucleoside analogues that exert interesting and powerful biological activity. Replacement of the furanose oxygen atom for instance with a methylene group would produce

the range of cyclopentane analogues better known as carbocyclic nucleosides. The hydroxy and base groups occupy the same positions, have the same spatial relationships and may be expected to assume the same conformations as their nucleoside analogues. Thus the carbocyclic derivatives have the potential either to mimic or antagonize the functions of the naturally occurring nucleosides and nucleotides. The other major advantage of these carbocyclic analogues is that they no longer contain the -O-C-N- linkage which is so easily degraded by bodily enzymes. The carbon-nitrogen bond joining the heterocyclic base to the cyclopentane ring should be comparable in stability to that of a simple alkyl derivative and so should be less susceptible to this enzymatic degradation. A further possible advantage is that carbocyclic nucleosides offer the possibility of being more selective antiviral agents than their nucleoside analogues. This is due to the more stringent substrate requirements of the mammalian kinase enzymes as compared with those of the virally coded enzymes of infected cells. The majority of carbocyclic nucleosides are synthetic in nature but several of natural origin have been discovered such as (-)-aristeromycin (58) and (-)-neplanocin (59).



(58)

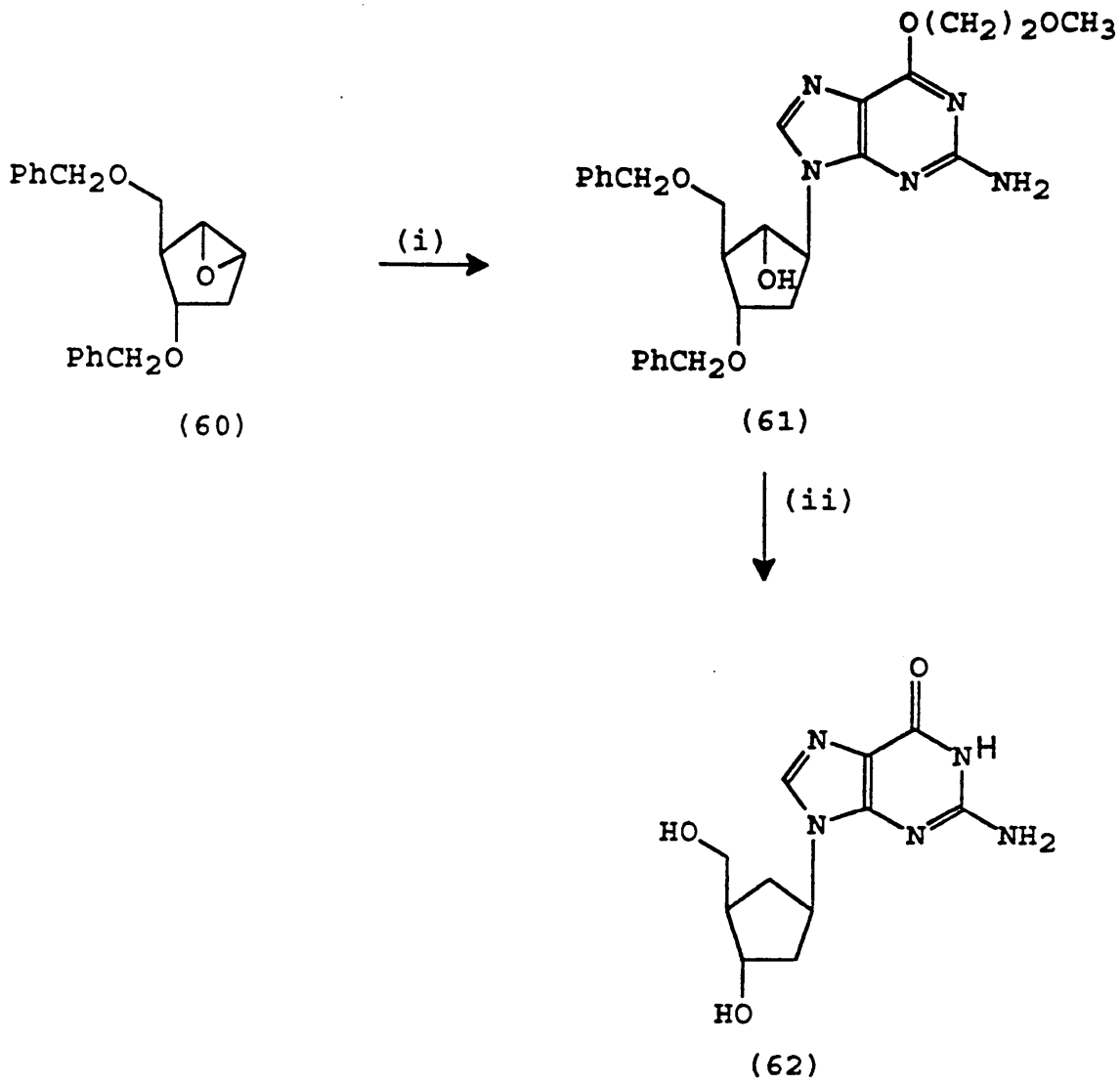


(59)

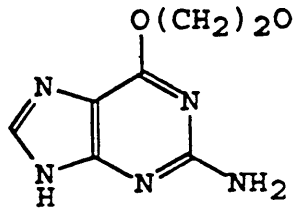
Recently carbaoligonucleotides have been prepared for the first time[82] and for their synthesis a reasonable supply of enantiomerically pure carbocyclic nucleosides is required. The synthesis of such a supply requires a different methodology to that used in classical nucleoside synthesis due to the lack of an acetal moiety. A variety of other methods for carbocyclic nucleoside synthesis have been employed such as the initial work by Shealy and Clayton[32] who constructed the heterocyclic base from an amino group positioned on the cyclopentane ring. Another useful method of synthesis is the direct displacement of a suitable leaving group located at C1 by a base. A further strategy uses nucleophilic opening of an epoxide by base from which carbanucleoside connection and generation of a hydroxy group is accomplished simultaneously. This methodology has been used by Roberts[41] for opening the epoxide (60) with 2-amino-6-

methoxypurine in DMF at 145°C using lithium hydride as a catalyst to produce (61). Deoxygenation and deprotection of (61) yielded the carbocyclic nucleoside 2'-deoxyguanosine (62) (Scheme 20).

Scheme 20

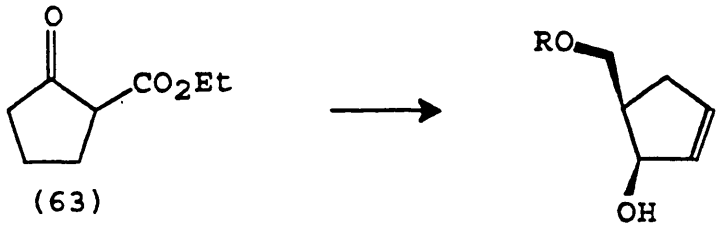


(60) (61) (62)

Reagents: (i) 

(ii) a) H_2 Pd/C, b) HCl/ 80°

Similarly to the work in the furan system the first synthetic objective for this section was the production of suitable allylic alcohol upon which the Claisen and aza-Claisen rearrangements could be performed. It was decided that a modified method of Paulsen and Maaß[50] would lead to such a useful carbocyclic allylic alcohol of the general structure (63)



(63) (36)

3.2 Synthesis of Carbocyclic Allylic Alcohol (36)

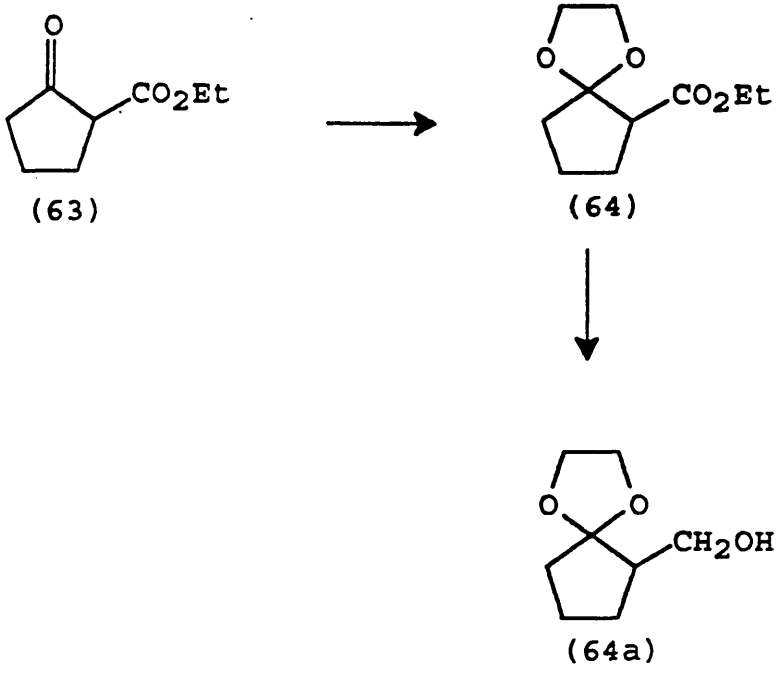
The initial reaction in the scheme (scheme 21) was the protection of an ß-ketoester as its ethylene ketal. Classically this reaction is performed with ethylene glycol and tosic acid employing benzene as the solvent but due to the high toxicity of benzene it was thought prudent to substitute this for the less harmful alternative of toluene. Early reactions using Dean-Stark apparatus for capture of the water azeotrope gave rather

unpromising results as the crude product isolated after work up was a black viscous liquid which contained a complex mixture of products. Purification of this crude mixture by distillation did not give the pure product and the yields obtained were substantially lower than was to be expected (25% as compared with literature 56%). Column chromatography also proved ineffective as a method of purification and so the initial commercially supplied ethyl ester (63) was substituted with laboratory synthesized methyl ester analogue. Reactions using this methyl ester provided comparable results to the ethyl ester.

A model reaction was thus tried employing the exact conditions cited by Paulsen and Maaß which meant using the undesired solvent benzene. After base work-up the crude product appeared as a clear pale green liquid. Analysis by ^{1}H NMR, IR and MS showed the mixture to contain almost solely the desired ketal product (64). Particularly characteristic was the appearance, in the ^{1}H NMR spectrum, of a singlet correlating for the 4 hydrogens of the ketal protecting group. The only contaminant was a slight amount of benzene and this was easily removed by distillation which also allowed isolation of the ketal (64) as a clear colourless liquid in excellent yield (76%). However, for general use in the synthetic scheme 21 it was unnecessary to purify this

ketal, as the crude material was sufficiently pure for use in the next reaction. It is presumed that the failure of the ketalization in toluene was due to the higher reaction temperature required, in comparison with benzene.

Scheme 21



(63) (64) (64a)

The next synthetic step was to reduce the ethyl ester to its primary alcohol with $LiAlH_4$, a reaction which was easily performed on a large scale in dry ether at 0^oC. Typically the work-up of a $LiAlH_4$ reaction involves the use of acid to aid dissolution of the lithium and aluminium salts in aqueous medium from which the desired product may be isolated by solvent extraction. This was not possible in this scheme as the ketal would have been hydrolysed under the acidic conditions employed, a

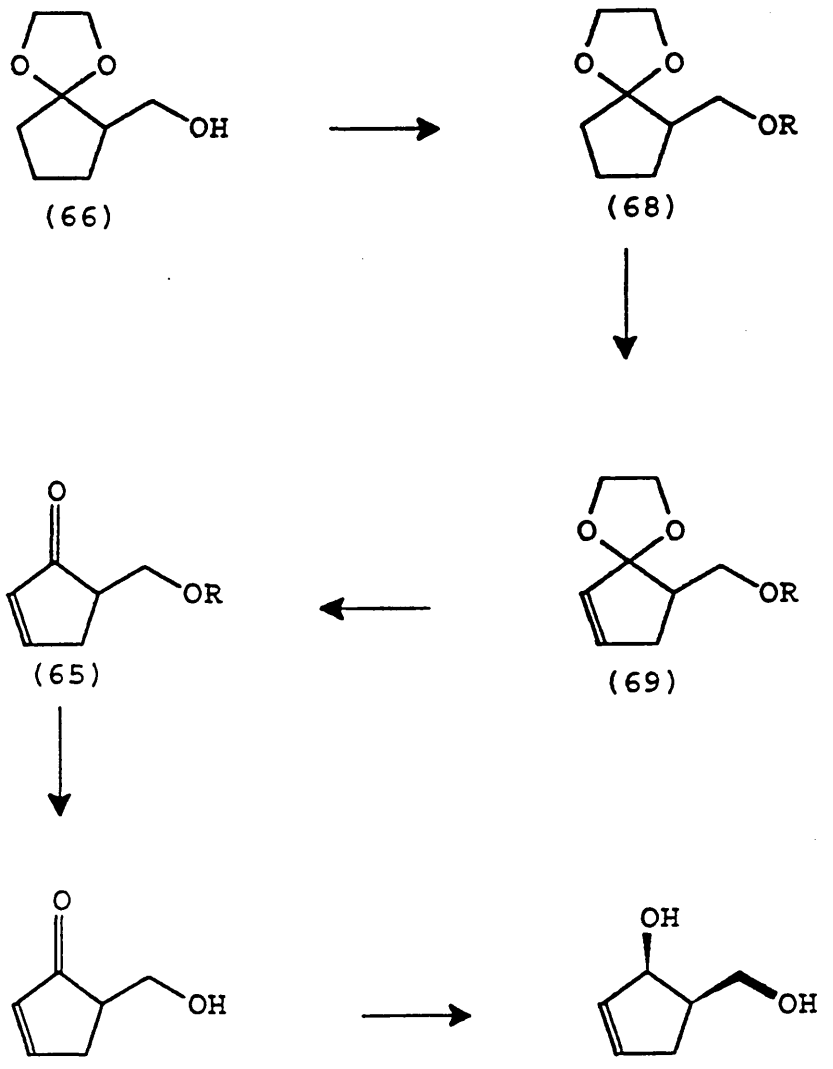
problem which was solved by the addition of a molar equivalent of NaOH. This NaOH precipitated out the unwanted salts and so subsequent filtration and careful washing of the filtrate yielded the crude alcohol as a clear colourless liquid in virtually quantitative yield (98%). IR analysis confirmed the reaction had gone to completion by the total disappearance of the C=O str at 1725 cm^{-1} due to the ester and the subsequent appearance of the expected O-H str. at 3250-3600 cm^{-1} of the product alcohol. No further purification of this compound was necessary.

It was the next four steps of the reaction pathway which were to prove the most crucial in the production of the final allylic alcohol (36) (scheme 22). Protection of the primary alcohol was to be followed by a bromination/dehydrobromination procedure to insert the double bond allylic to the ethylene ketal. Deprotection of the ketal with acid would furnish the α,β-unsaturated ketone (65) which by a simple reduction would thus provide the final desired allylic alcohol (36) product.

The first step therefore was the protection of the primary alcohol of (66) which was important as it would have serious effects on later stages of the synthesis. It was hoped that a rather bulky group could be used to

protect the alcohol which would subsequently sterically

Scheme 22

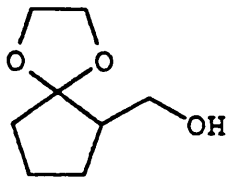


direct the hydride attack, during the final ketone reduction onto the lower face of the cyclopentane ring. This would therefore produce the desired cis configuration of alcohol to protecting group. A variety of bulky protecting groups exist and one obvious choice was trityl (triphenylmethyl ether), but the usefulness of

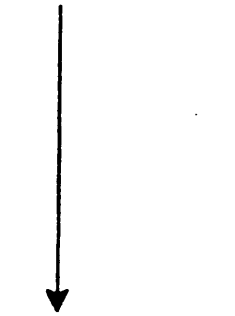
this group was questionable as its stability to the acidic ketal deprotection was unknown. Therefore a more suitable acid stable functionality was required and other possible protecting groups of use would include esters or one of the range of silicon moieties such as the particularly useful bulky tert-butyldiphenylsilyl group.

The primary alcohol of (66) was thus reacted to produce compounds with a wide variety of protecting groups attached (Figure 27).

Figure 27



(66)

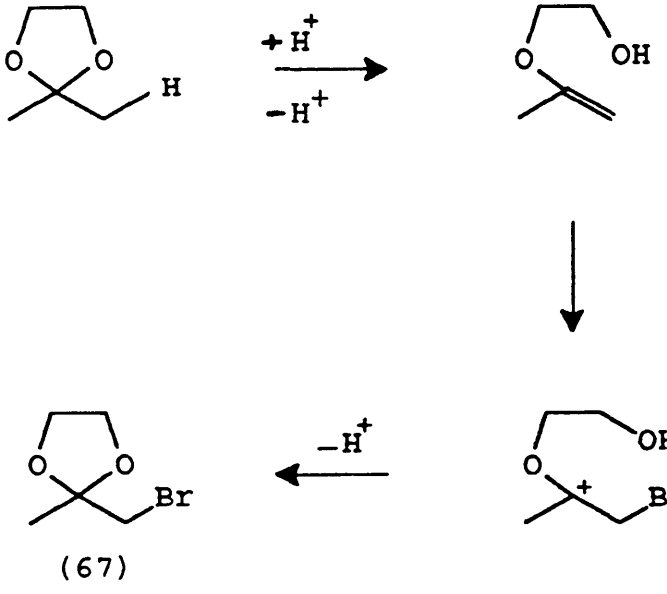


(68)

when R= Me compound=68a

The bromination/dehydrobromination reaction was to possibly prove the most crucial in the reaction pathway. The ketal which had already protected the ketone from attack by $LiAlH_4$ now took on its next crucial role in the bromination mechanism. Bromination/dehydrobromination alpha to a naked carbonyl is a somewhat finnicky reaction and so this type of reaction is best handled via the ketal of the carbonyl. The ketal of an enolizable ketone readily forms the related enol ether in the presence of a catalytic amount of acid. This enol ether is very labile to electrophillic attack and so not surprisingly bromine will react with it instantaneously ultimately leading to the α -bromoketal (67) (scheme 23).

Scheme 23



(67)

Garbisch[83c] has shown that further addition of a second bromine onto the same carbon is not possible

without much harsher reaction conditions. A particular advantage of using ketals is that dehydrobromination can easily be achieved with a variety of strong bases. The dehydrobromination of an α-bromocarbonyl is on the other hand open to many damaging side reactions and so with this knowledge an initial reaction was performed using the methyl ether protected compound (68). Ethylene glycol was used as the solvent for the reaction but during the addition of the bromine it was not possible to maintain the light straw colouration discussed by Paulsen and Maaß at the temperature of $<20^{o}C$. Isolation of the α-bromoketal intermediate product was followed immediately by dehydrobromination with anhydrous NaOMe in dry DMSO. ^{1}H NMR analysis of the crude product showed the appearance of a trace amount of olefinic material by the appearance of multiplet signals at 5.67 and 6.06 ppm. and subsequent purification by column chromatography furnished the desired allylic ketal in poor yield (10%). Following this disappointing result a variety of reaction conditions were employed in an attempt to optimize the reaction yield. This optimization initially entailed monitoring the effect, if any, of altering the contact time of the bromine with the methyl ether (68). Thus reactions were carried out where the methyl ether was left stirring with bromine for periods ranging from 10 minutes to 2 hours. This variable seemed to have surprisingly little effect on the overall yield of the

reaction. Other variables observed included the rate of bromine addition and the temperature at which volatiles were removed during isolation of the intermediate bromo-ketal (67). The rate of addition of bromine had little effect on the yield, but, the concentrating temperature did have a dramatic effect. At temperatures $<15^{0}$ all the bromide formed remained intact but as the temperature rose above 20^{0} substantial decomposition of this intermediate occurred, leading to poor yields of the final alkene product. The most important point noted was however, that the bromination often required an initial amount of heating ($>45^{o}C$) to initiate the reaction. Once this initiation had occurred it was possible to add the bromine so as to keep the light yellow colouration throughout the addition as required. This initiation with heat led to a great enhancement and better reproducibility in the yields of (69) obtained. Substituting NaOH in EtOH for anhydrous NaOMe in DMSO made for a far easier experimental procedure and little derogatory effect on the yield was noticed. Thus by isolating the bromide at low ($<20^{0}$) temperatures and initiation with a little heat the reaction was optimized to an adequate yield of 68%.

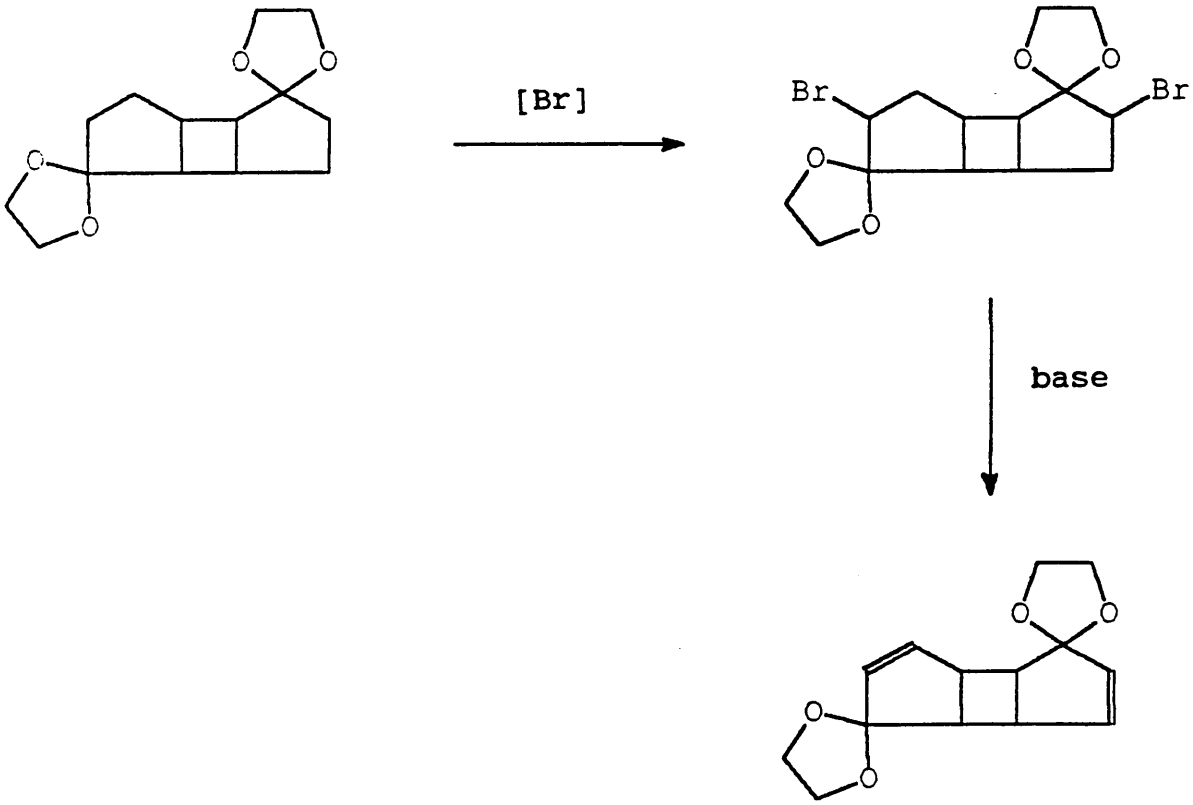
With the bromination/dehydrobromination reaction optimized using the methyl ether (68), a variety of the other protected compounds synthesized were reacted under

the same conditions. When using TBDMS and TBDPS protected alcohols no bromine decolourization could be noted when employing ethylene glycol as solvent and following the subsequent dehydrobromination a complex mixture of products was isolated. The benzoate and pivaloate esters produced similar results. In the case of the pivaloate ester however some olefinic compound was isolated from the dehydrobromination stage and its strucure confirmed by ^{1}H NMR, IR and MS analysis. This reaction only produced the desired product when $^{t}BuOK$ had been substituted for anhydrous NaOMe. The yield was poor (<15%) and subsequent reactions gave a variety of yields ranging from 0% to 15% and thus the reaction was disregarded for use in the synthetic scheme 22. Other compounds also tried were the benzyl ether, the monomethoxymethyl ether and the trityl ether. Reaction of these compounds merely led to recovery of starting materials with no olefinic material isolated.

A possible reason for this lack of reaction and/or poor yields with a variety of the protected alcohols was the insolubility of the starting materials in ethylene glycol. Even with vigorous stirring the compounds were still visible as large globules rather than the required fine dispersion. Three different methods were thus employed to determine if it was this solubility factor which was determining the lack of reaction. Two of the

methods are closely related in that they employ compounds which when dissolved in a suitable solvent act as free bromine. The use of pyridinium hydrobromide perbromide[84] was first cited by Djerassi and Scholz[85] for the α-bromination of steroid ketones. More recently Eaton[83b,86] has employed it in a variety of syntheses where ethylene ketals have been used as intermediates for bromination/dehydrobromination reactions (scheme 24). Pyridinium hydrobromide perbromide is a useful brominating agent as it is a stable and crystalline salt which can, in contrast to bromine, be weighed out accurately on a micro or semi-micro scale.

Scheme 24

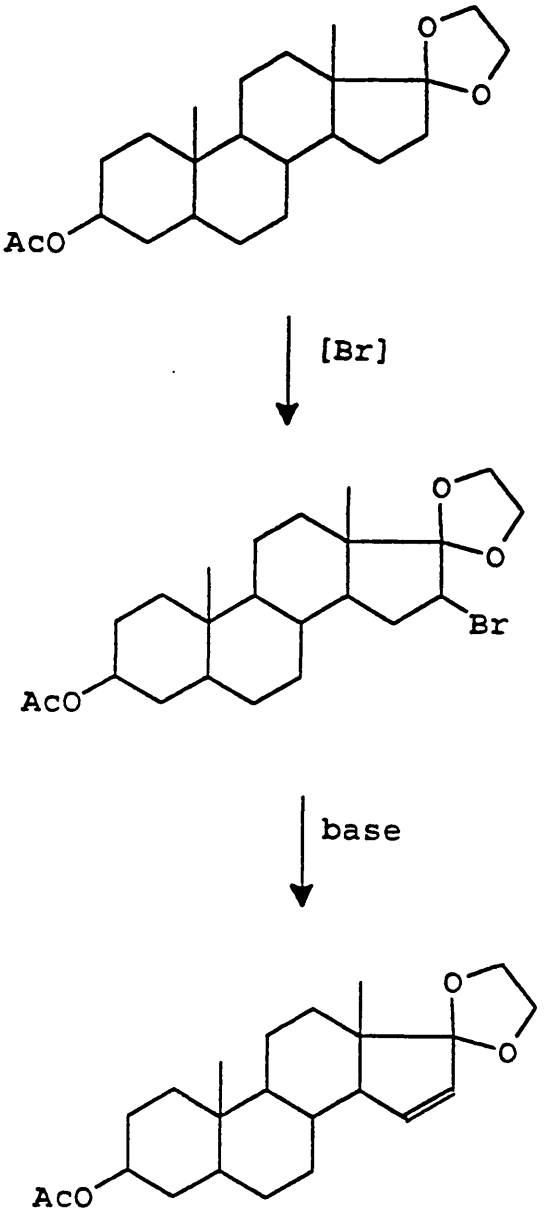


Initial brominations of the methyl ether compound (68a) in dry THF and subsequent dehydrobromination with ^{t}BuOK led to yields comparable with those previously obtained using bromine and NaOMe. Reaction with the silyl and ester protected alcohols was therefore attempted but in all cases a mixture of products was isolated with no double bond character being observed in the proton NMR spectrum.

The second alternative bromination attempted was closely related to the method previously discussed with the compound trimethylammonium tribromide being used in dry THF. This methodology was employed by Marquet[87] to brominate alpha to ethylene ketals during a steroid synthesis (scheme 25). Again this reagent gave good results when used in conjunction with the methyl ether (68) but complex mixtures where obtained when either the silyl or ester protected compounds were used.

Finally brominations were carried out using elemental bromine employing dry THF as the solvent as opposed to ethylene glycol. An initial difficulty encountered with this method was that accurate measurement of the mass or volume of bromine to be used was very difficult on a small scale. This subsequently led to a variety of products being formed, possibly due to over or under

Scheme 25



bromination caused by incorrect amounts of bromine being added.

A further reason for the failure of the bromination/dehydrobromination reactions on all but the methyl ether was almost certainly related to the stability of the

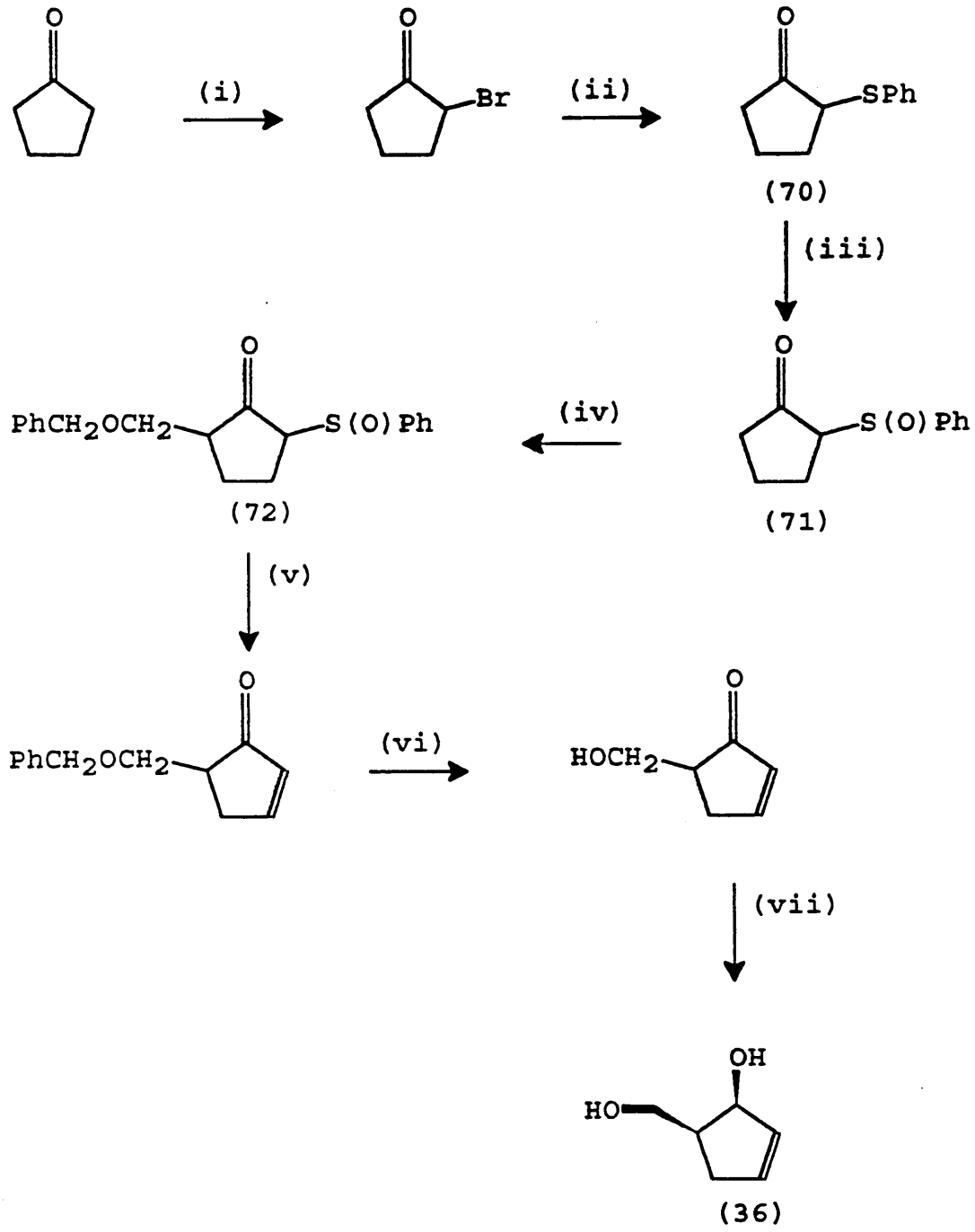
protecting groups to pH. The silyl and ester protected compounds are not stable to strong base and so the groups would have been cleaved during the dehydrobromination step leaving the reactive alkoxide. Acid work-up of this crude mixture could lead to isolation of the alcohol which would be of great use later in the reaction scheme. Unfortunately due to a lack of time it was not possible to investigate this idea further.

Due to the setbacks encountered in the production of a suitably protected allylic alcohol (36) by the modified Paulsen and Maaß approach an entirely different method for its synthesis was evaluated (scheme 26).

Cyclopentanone was employed as a cheap and readily available starting material. A single bromination alpha to the ketone was achieved by the use of cupric bromide in chloroform/ethyl acetate (1:1 mixture)[92] and the α-bromoketone produced was then used in its crude state for the next step which involved the displacement of the bromine by nucleophilic attack of a phenylthio (PhS^-Na^+) functionality. The α-phenylthioketone (70) was thus isolated in 73% yield as a clear, colourless, pungent oil. Confirmation of the product as the desired structure was undertaken by ^1H NMR analysis. The spectrum contained the indicative multiplet signal at 7.15 ppm correlating to the 5 aromatic hydrogens, also

the multiplet signal for the single hydrogen alpha to the

Scheme 26



Reagents: (i) $CuBr_2$/ $CHCl_3$/ EtOAc, (ii) PhS^-Na^+
(iii) $NaIO_4$, (iv) a) LDA, b) $PhCH_2OCH_2Cl$, (v) heat
(vi) [H], (vii) [hydride]

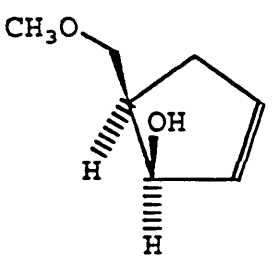
carbonyl and phenylthio had shifted as would be expected from 4.15 ppm for the bromoketone to 3.50 ppm. Reaction of this phenylthio (70) with $NaIO_4$[93] (1 mole equivalent) gave the sulphoxide derivative (71) as a pale yellow solid (81%). This reaction was easily monitored by TLC due to the dramatic drop in Rf for the sulphoxide product as compared with the sulphide starting material. The reason for synthesizing the sulphoxide was so that at a later point the double bond functionality could be inserted into the ring by thermal elimination of the suphoxide group which followed by reduction of the ketone would produce an allylic alcohol of the desired type. The next step in the synthesis was crucial to the overall production of the allylic alcohol (36). Grieco and Pogonowski[94] had used the sulphoxide (71) to produce compounds with a functionality alpha to the ketone but on the opposite side to the sulphoxide. This was achieved by synthesizing the dianion using LDA and reacting this nucleophile with a suitable electrophilic reagent. Employing this methodology it was thought that substitution of a benzyl chloromethyl ether for the chlorobenzene employed by Grieco could lead to the interesting compound (72) (scheme 26) which would contain both a benzyl protected alcohol and a ketone functionality. These groups in combination with the sulphoxide would give a compound which contains all the functionalities desired for the production of the allylic

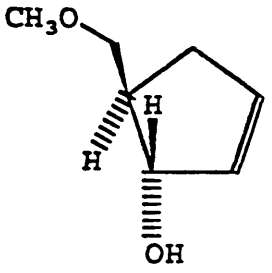
alcohol required. Numerous attempts at this reaction led only to recovered starting materials and a few minor unknown products.

Due to the great length of time spent on optimizing the bromination/dehydrobromination reaction and the failure of the new possible scheme (scheme 26) it was decided to continue along the initial reaction pathway (schemes 21/22) using the methyl ether (68). The crude allylic ketal methyl ether (69) was taken and the ketal deprotected by stirring in a mixture of coarse silica and oxalic acid. Column chromatography yielded the α,β-unsaturated ketone (65) in 93% yield. The IR spectrum suggested that the reaction had proceeded as expected by the appearance of a peak at 1710 cm^{-1} which could correlate for the ketone carbonyl. This was further confirmed by the disappearance of the singlet for the ethylene ketal protecting group at 3.96 ppm in the proton NMR. Efforts to then deprotect the methyl ether following Paulsen and Maaß' methodology using TMSI proved unsuccessful with complex mixtures being recovered. Further attempts at ether deprotection employing TMSCl/NaI[88] and ß-bromocatecholborane[89] led to the recovery of starting materials only.

Pressing ahead with the methyl protected α,β-unsaturated ketone, the next step was the reduction of

the ketone to the secondary alcohol (36). This would produce the allylic alcohol functionality required for the Claisen and aza-Claisen rearrangements. The methyl ether was probably not going to be a bulky enough group to direct the reduction in the way desired and initial reductions with $LiAlH_4$ at low temperatures ($<-20^{o}C$) yielded the allylic alcohol (36) as the two epimers in roughly equal amounts which could be separated by column chromatography (97/3 chloroform/methanol).

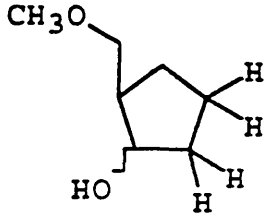




In order to determine which of the two products isolated by the chromatography was the desired cis, ß isomer it was necessary to perform some NOE NMR experiments. NOE and 2D-COSY spectra were also analysed to determine whether any Ferrier type rearrangements had occurred. For the product with the higher Rf value, NOE's were observed between CH_2-5 and CH-1. This established the position of this methylene group as being adjacent to the double bond and thus no Ferrier rearrangement had occurred. Irradiation of H3 gave enhancement of H4 by

approximately 3% and conversely irradiation of H4 enhanced the signal for H3. This result established that H3 and H4 were on the same face of the ring and therefore this product was the desired cis-(ß)-epimer. To further confirm this result NOE and 2D-COSY experiments were performed on the product with the lower Rf. 2D-COSY confirmed that CH_2-5 were coupled to a double bond proton whereas H4 was not. This again confirmed that no Ferrier type rearrangement had arisen. NOE was observed between CH_2-6 and H3 (approx. 1.6%) but not between H4 and H3. This confirms that H4 and H3 are on opposite faces of the ring and therefore this product was the trans-(alpha)-epimer.

^1H NMR (360 MHz/30^oC) also verified the presence of a contaminant in the sample of the ß-epimer which was found to be a by-product of the $LiAlH_4$ reduction of the α,β-unsaturated ketone. Even at the low temperatures employed (<-20^oC) reduction of the ketone was accompanied by saturation of the double bond leading to the fully saturated alcohol (73) which was the contaminant observed.



(73)

Lowering the reaction temperature and use of stoichemetrically correct amounts of $LiAlH_4$ although slightly lessening the degree of saturation did not fully prevent it. Even the best conditions led to approximately 10% saturation and this product was inseparable, by chromatography, from the desired ß-epimer. A further drawback of this $LiAlH_4$ reduction was that no hydride directing effect was witnessed and thus alpha and ß epimers were isolated in similar yields of 28 and 30% respectively.

Due to these problems of saturation combined with poor yield of the desired ß-epimer the use of other reducing agents was assessed. An obvious choice due to its selectivity for the ketone (leaving the double bond unaffected) and steric bulkiness was di-isobutylaluminium hydride (DIBAL)[90]. Reaction of the purified unsaturated ketone (65) in toluene with 1.5 equivalents of DIBAL (1.0 M in hexanes) at $-78^{o}C$ supplied the alcohol as a mixture of epimers in 78% yield. Column chromatography again allowed separation of the epimers giving a yield of 65% for the ß-epimer and 13% for the alpha-epimer and subsequent ^{1}H NMR analysis of the ß-epimer sample showed there to be no saturation of the double bond. DIBAL had proven not only to prevent saturation but also the reduction had been directed in favour of the required ß-epimer due to the bulkiness of

the reducing agent. The use of DIBAL did however have drawbacks which included its relatively high price, the necessity for low temperatures and its difficulty of use on a large scale. This latter difficulty revolved around the work-up procedure of such reactions. After quenching with water and methanol, a thick gelatinous mixture was produced which could be filtered only with difficulty even when hyflo filter aid was employed. In an attempt to obtain the maximum yield an inordinate length of time was required to wash the filter cake thoroughly even on a small scale.

The reducing agent of choice for these α, ß-unsaturated ketone systems within a ring is now $NaBH_4$ and $CeCl_3$ in methanol[90,91]. This reagent is highly selective for ketones at its operating temperature of 0^oC, producing very little (<3%) saturation and when used in conjunction with the α, ß-unsaturated ketone (65) and following purification, the ß-epimer was isolated in 56% and the α-epimer in 24% yield. ^1H NMR verified that very little (<3%) of the saturated by-product had been generated. Although the use of $NaBH_4$ and $CeCl_3$ does not deliver as good a ratio of ß to α epimers as DIBAL this disadvantage is overcome by its ease of use on a large scale and its low cost. Following the extensive use of the $NaBH_4/CeCl_3$ reduction on the unsaturated ketone (65) it was possible to acquire reasonable quantities of the carbocyclic allylic alcohol (36) for

reaction in Claisen and aza-Claisen rearrangements.

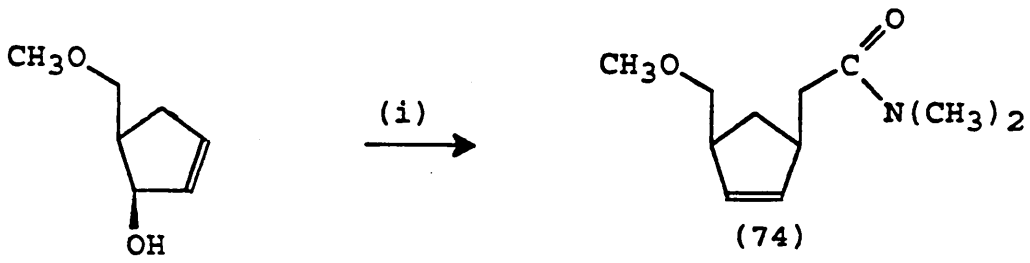
3.3 CLAISEN REARRANGEMENTS

3.3.1 Synthesis and Use of Products

The initial reaction performed on the carbocyclic alcohol (36) was an amide-acetal Claisen rearrangement employing dimethylacetamide dimethylacetal in refluxing o-xylene to furnish the rearranged amide (74) as a clear, pale yellow, viscous liquid in 74% yield (Figure 28). Confirmation of the rearranged amide structure was established by spectral data. The appearance of the C=O peak at 1649 cm^{-1} in the IR spectrum for the amide carbonyl and the shift of the olefin signals in the proton NMR spectrum to 5.80 ppm were both indicative of the desired product. The appearance in the proton NMR of the singlets at 2.95 and 3.00 ppm correlating for the amide methyl groups was further positive evidence that the correct product had been synthesized.

This amide although possibly quite useful as a precursor in the synthesis of carbocyclic C-nucleosides was not as immediately interesting as the ester product from the Johnson type Claisen rearrangement. Because the

Figure 28



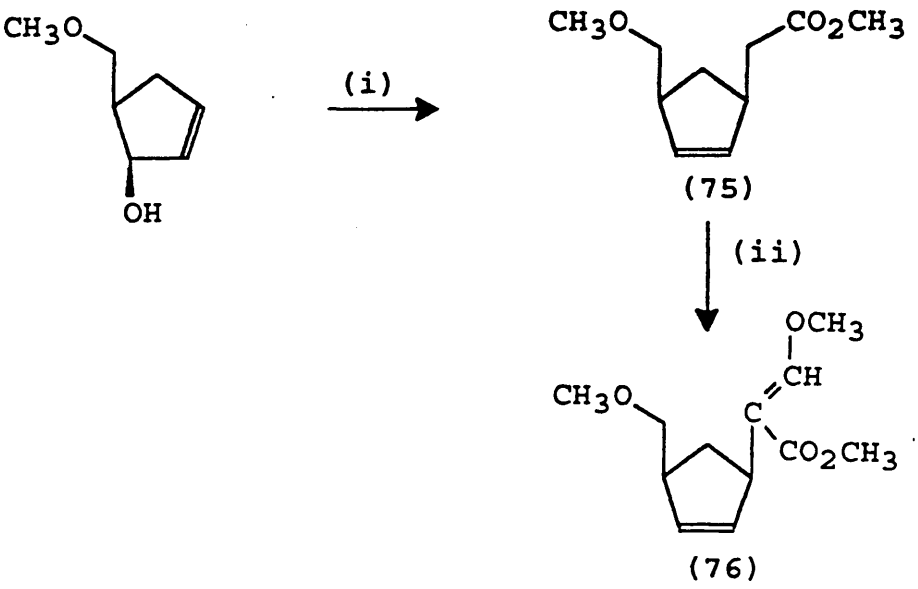
(74)

Reagents: (i) $CH_3C(OCH_3)_2N(CH_3)_2$/ o-xylene/ reflux

molecular framework of the allylic alcohol is now based upon the cyclopentane ring the acid catalyzed Ferrier rearrangement is no longer a concern. The reaction of allylic alcohol (36) and trimethyl orthoacetate using propionic acid as catalyst was thus attempted (Scheme 27) and following 24 hours reflux it was found that the rearrangement had worked well producing, after purification, the ester (75) in 76% yield. Once again the IR spectrum was extremely useful in establishing the generation of the ester (75) by the appearance of the indicative carbonyl C=O peak at 1756 cm^{-1}. FAB-MS also aided in the confirmation of the structure by the identification of the MH^+ signal at 185 mass units. Reaction of this ester (75) with ethyl formate and sodium hydride generated the α, ß-unsaturated ester (76) in poor yield (<10%). Reaction of this ester with base and guanidine should in a single step deliver a carbocyclic C-nucleoside analogue. If this ring closure reaction

worked the previous step would have to be optimized to produce far better yields of the unsaturated ester (76) but unfortunately due to the lack of time it was not possible to investigate this further.

Scheme 27



Reagents: (i)$MeC(OMe)_3$/ propionic acid/ reflux

(ii) a) NaH/ EtOH/ HCOOEt, b) MeI

3.4 AZA-CLAISEN REARRANGEMENTS

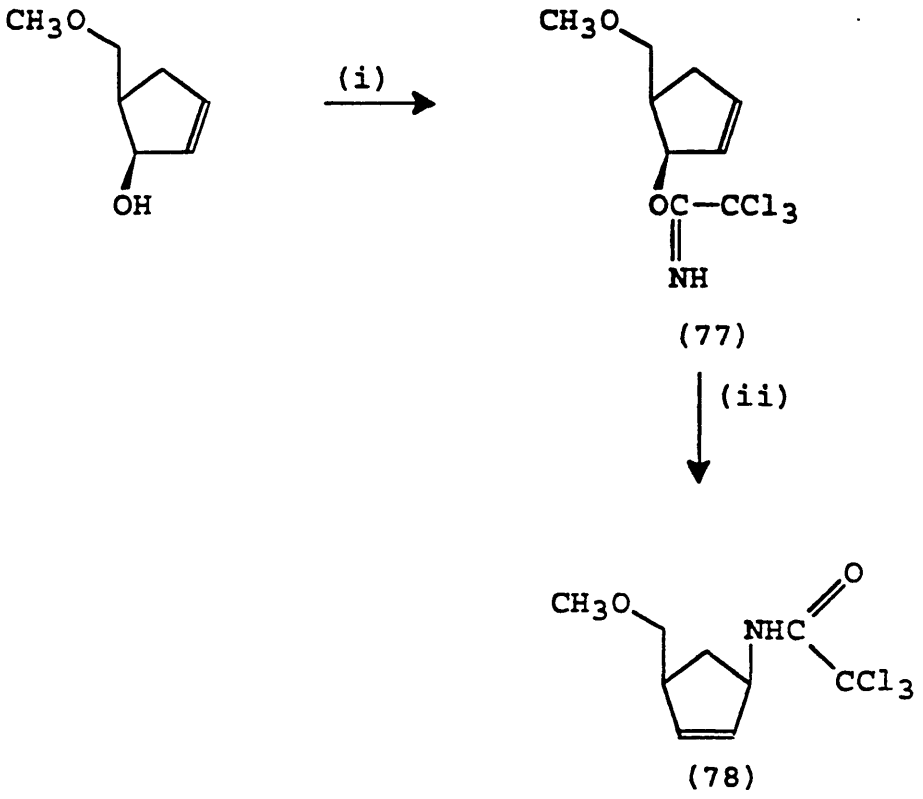
3.4.1 Synthesis and Use of Products

Preliminary reactions on the carbocyclic allylic alcohol (36) using sodium hydrdide, trichloroacetonitrile and sodium dried ether were inconclusive with on occasions some product appearing to be formed yet on

others none being witnessed by IR and TLC analysis. The use of ether dried over $LiAlH_4$, distilled trichloroacetonitrile and flame dried equipment solved this problem. Reaction of the alcohol (36) with 0.1 equivalents of sodium hydride in $LiAlH_4$ dried ether and subsequent addition to distilled trichloroacetonitrile at $0^{o}C$ yielded the trichloroacetimidate intermediate. Unlike the furan system the rearrangement of this imidate to the acetamide was not facile under these reaction conditions and it was necessary to effect the rearrangement in refluxing toluene over a period of up to 8 hours (Scheme 28). The intermediate imidate (77) was water sensitive and was therefore used without further purification for the thermal rearrangement to furnish the crude trichloroacetamide as an orange liquid. Column chromatography permitted isolation of the trichloroacetamide as a pure white solid in good yield (68%) whose structure was confirmed by spectral data. An IR spectrum established the presence of a peak for N-H str. at 3340 cm^{-1} and for C=O str. at 1730 cm^{-1}. ^{1}H NMR further confirmed the presence of the amide by the broad singlet at 7.45 ppm for the amide hydrogen and by a shift in the olefinic signal to 5.7 ppm as would be expected. Agreement between the theoretical and experimentally achieved values for the micro-analysis of the product was the final piece of concurring evidence required to prove the white crystalline solid was the desired

trichloroacetamide (78). This product (78) would appear to be an excellent precursor for the synthesis of carbocyclic nucleosides as hydrolysis of the trichloroacetamide group to the amine would leave a compound onto which heterocyclic bases could easily be built.

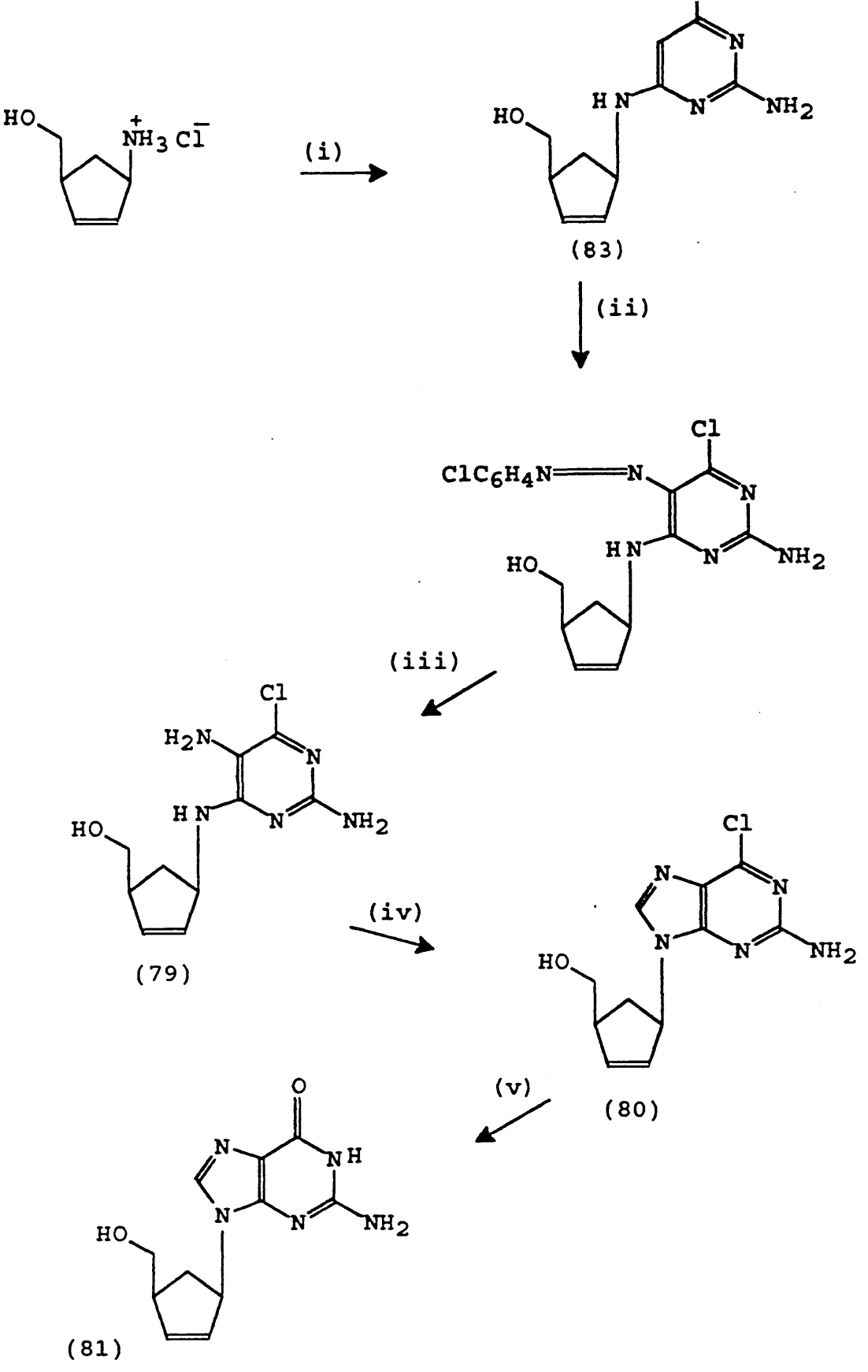
Scheme 28



Reagents: (i) NaH/ Cl_3CCN, (ii) toluene/ reflux

3.4.2 Use of Trichloroacetamide (78) in the Production of Nucleoside Analogues

Overmann's method for the hydrolysis of the trichloroacetamide to the free amine employed 2N NaOH in ethanol at room temperature but in this case the amide (78) reacted to yield a baseline product, by TLC, which was both difficult to work-up and isolate. Fortunately however as there are no longer any acid labile fuunctionalities in the molecule it was possible to hydrolyse the amide (78) in refluxing 2N HCl (scheme 29). This hydrolysis furnished the amine hydrochloride which was used immediately without purification in the next stage of the synthesis. It was this production of the amine hydrochloride that at last gave us an introduction to a variety of reactions which would lead to the formation of purine and pyrimidine bases. The quickest and easiest route to a number of carbocyclic nucleoside analogues appeared to be with the use of a dichloropyrimidine derivative. This methodology would create a series of purine nucleoside analogues and has been employed by Roberts et al[43] who made use of 2-amino-4,6-dichloropyrimidine in the production of carbovir (Scheme 29).



Reagents: (i) 2-amino-4,6-dichloropyrimidine / base
(ii) $4\text{-}ClC_6H_4N_2^+Cl^-$, (iii) Zn/ HOAc,
(iv) $(EtO)_3CH/^2HCl$, (v) NaOH/ reflux

As can be seen the use of 2-amino-4,6-dichloropyrimidine to produce (83) necessitates the formation of an amine functionality at carbon 5 via means of a diazotization followed by reduction with zinc-acetic acid and it is this amine which is vital for ring closure of the pentacyclic ring forming the purine structure. A quicker route to a series of nucleoside analogues would appear to be by substituting the 2-aminopyrimidine with a 5-amino derivative. Obviously carbovir and its analogues would now no longer be initially synthesized due to the lack of an amine functionality at C-2 but an array of other nucleoside analogues would be possible. Lim and Marquez[38] had previously made use of this 5-amino-4,6-dichloropyrimidine during their synthesis of neplanocin A.

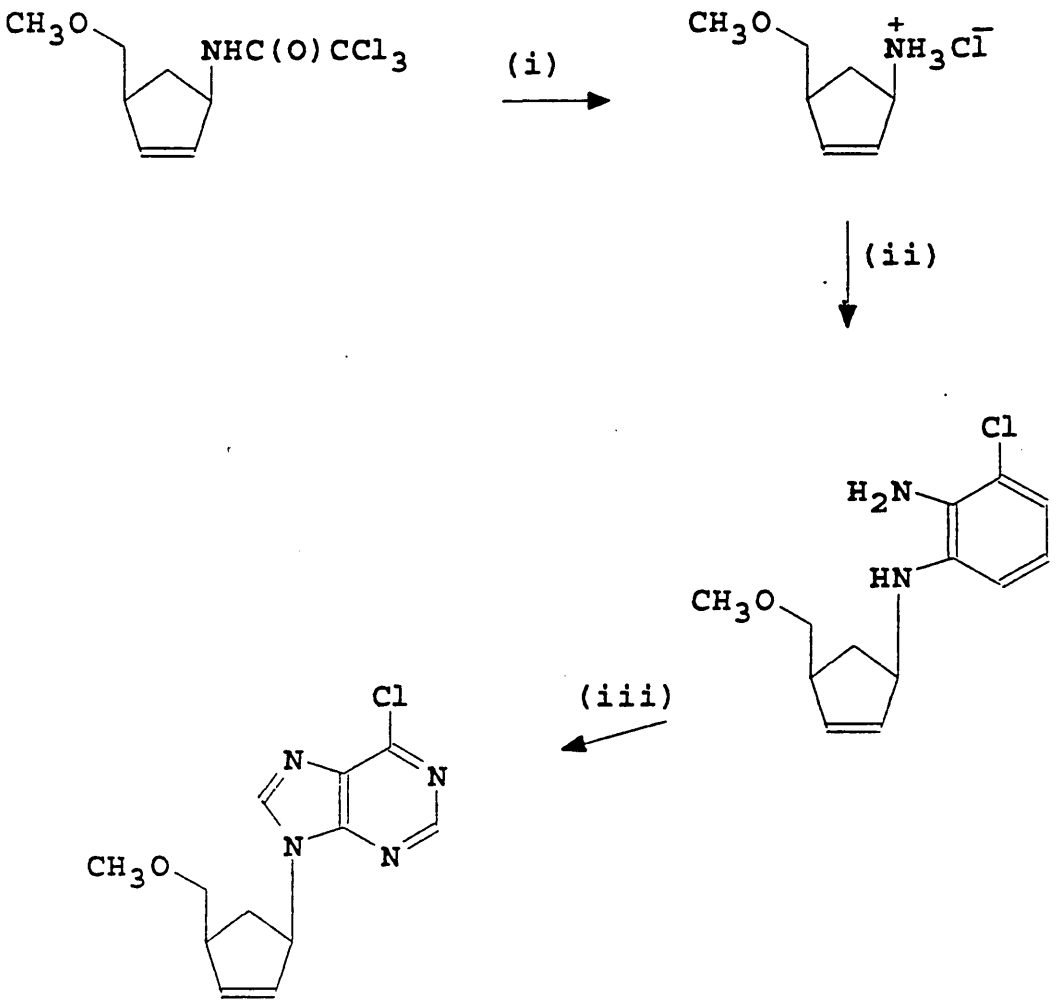
The trichloroacetamide (78) was thus hydrolysed in refluxing 2N HCl and ethanol to generate the desired amine hydrochloride and this product was immediately refluxed in a mixture of n-butanol, diisopropylethylamine and 5-amino-4,6-dichloropyrimidine (2 mole equivalents) for 48 hours to deliver the diamine (79) as white needles (61%) with a melting point of 114-116^{0}. The peaks at 3000-3500 cm-1 and 1630/1590 cm^{-1} in the IR spectrum of this compound (79) corresponded for the amine and C=C/C=N functionalities expected. The molecular ions at 254 and 256 witnessed in the EI-MS of this product established the presence of chlorine as expected. Subsequent

reaction of this diamine (79) with freshly distilled triethyl orthoformate and concentrated HCl at room temperature for 24 hours furnished the ring closed chloropurine analogue (80) whose IR spectrum showed a loss of any amine peaks between 3000 and 3500 cm^{-1}, thus confirming reaction had taken place. Column chromatography yielded (80) as an off-white solid (80%) (Scheme 30).

The diamine (79) could also be used in the production of the triazole compound[80] as shown in figure 29. Synthesis of this compound was accomplished by reaction of (79) with sodium nitrite in an acetic acid/ water mixture at $0^{o}C$ and it appeared as a pale brown solid (73%) whose structure was confirmed by IR and ^{1}H NMR data.

From the chloropurine (80) synthesis of both adenosine and inosine purine nucleoside analogues was possible. Hydrolysis of (80) in gently refluxing 0.3N NaOH yielded, after purification, the dideoxyinosine analogue (81) as an off white solid (66%) (Figure 30) whose structure was confirmed by IR, ^{1}H NMR and HRMS. A particularly characteristic feature of the product was the combination of -OH and C=O stretching frequencies in the IR spectrum, relating to the two isomers.

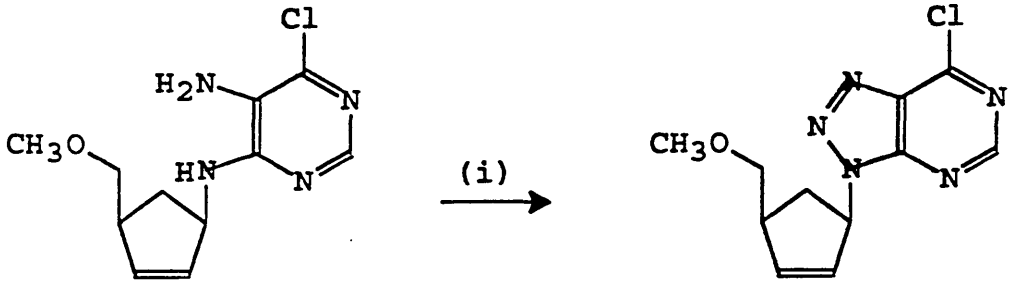
Scheme 30



Reagents: (i) H^+/ EtOH, (ii) 5-amino-4,6-dichloropyrimidine/ $^iPr_2NEt$/ butanol/ reflux, (iii) $(EtO)_3CH$/ HCl then HCl/ H_2O

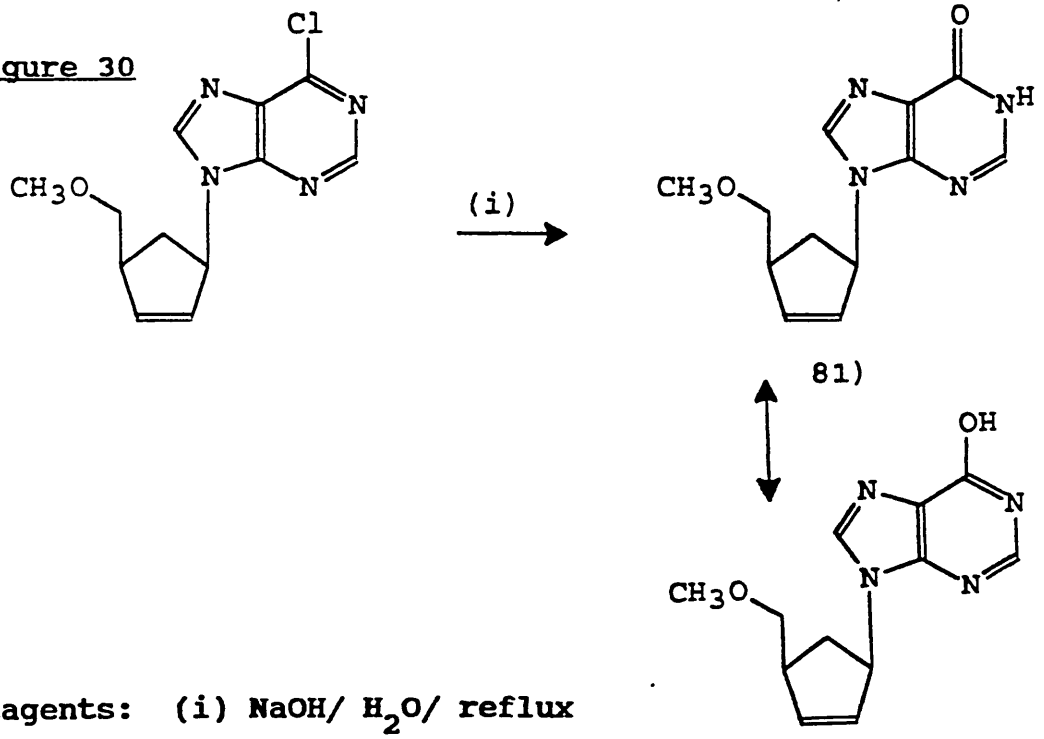
To obtain an adenosine nucleoside analogue it was necessary to react the chloropurine (80) in a closed system with a 2:1 mixture of concentrated ammonia and methanol. 48 hours at 60^oC was followed by purification using rapid micro-column chromatography to furnish the

Figure 29



Reagents: (i) AcOH/ $NaNO_2$

Figure 30

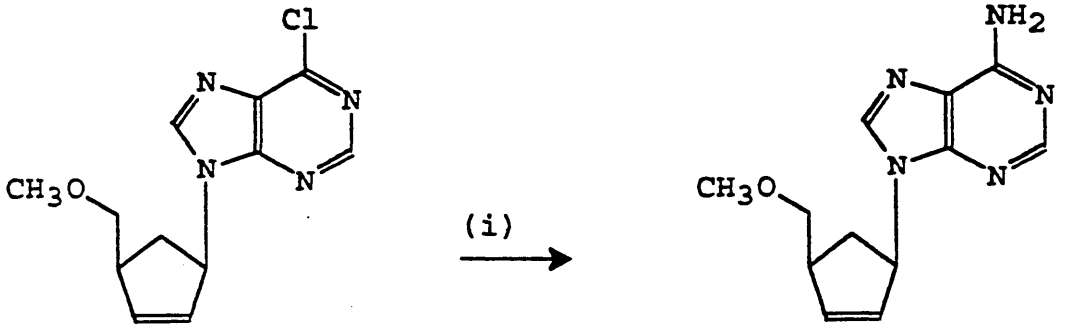


Reagents: (i) NaOH/ H_2O/ reflux

dideoxyadenosine compound (82) (Figure 31) in 60% yield whose IR spectrum showed the expected reappearance of N-H

peaks between 3000 and 3500 cm^{-1}.

Figure 31



(82)

Reagents: (i) NH_3 (conc)/ EtOH

As can be seen therefore a range of carbocyclic nucleoside analogues have been produced which during their linear synthesis have undergone an aza-Claisen rearrangement to gain the correct relative stereochemistry for heterocyclic base build up. All the nucleosides produced so far have been in racemic form only.

3.5 SUMMARY AND FUTURE WORK

The allylic alcohol (36) was produced in a 6 step synthesis from 2-oxocyclopentanecarboxylate ethyl ester. The desired ß-epimer of the alcohol (36) was isolated and its structure confirmed by NOE NMR experimentation.

Further work is however needed in the bromination/ dehydrobromination stage so that protecting groups more useful than the methyl ether could be used. This will mean a more thorough examination of the use of pyridinium hydrobromide perbromide and trimethylammonium tribromide as brominating agents in THF. The protecting group decided upon must be stable to the strong bases employed in the dehydrobromination step. This could mean further evaluation of the trityl and monomethoxymethyl ether protecting groups.

The Claisen rearrangements on the allylic alcohol (36) employing amide-acetals and trimethyl orthoacetate both worked well. The amide functionality has not yet been fully evaluated for its use as a precursor to carbocyclic C-nucleosides. The ester rearranged compound (75) shows much promise as an intermediate to C-nucleosides. Optimization of the ethyl formate reaction to yield the unsaturated ester (76) and subsequent successful reaction of this product with guanidine should produce a carbocyclic C-nucleoside analogue.

The aza-Claisen rearrangement on the alcohol (36) was very water sensitive and all reagents and solvents were scrupulously dried before their use. The overall yield of the rearrangement was good. The use of the

trichloroacetamide (78) has led to the successful synthesis of a number of carbocyclic dideoxy nucleoside analogues in their methyl ether protected form. For these compounds to exhibit biological activity it is almost certain that a method for removing the methyl ether must be found. As has already been stated the nucleoside analogues produced have been racemic. Following biological testing on the racemates it would be necessary to produce optically active species of any compounds which exhibited any biological activity. This would entail the use of the enzymatic or chemical methods employed for separating chiral forms discussed earlier during the introduction to this thesis.

4.1. Materials and Techniques

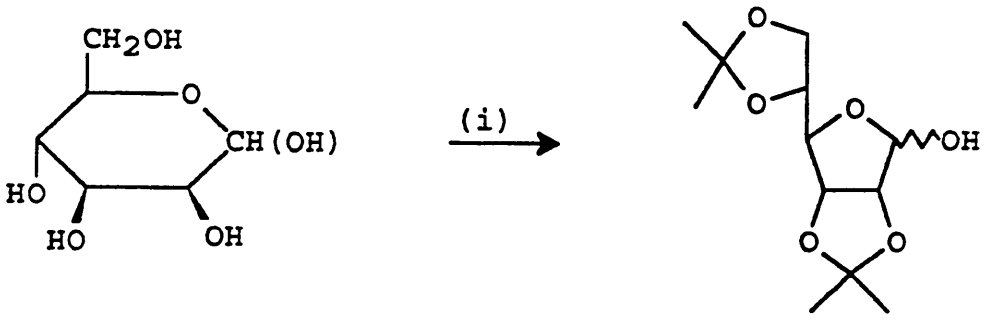
Infrared spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer. ^{1}H nmr spectra were recorded on Bruker 250 MHz, Bruker 200 MHz, Bruker WP80 SY and JEOL PMX 60 SI spectrometers. Samples were prepared in the solvent stated in each method. Microanalyses were determined at the Wellcome Foundation, Beckenham. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Mass spectra were recorded at both the Wellcome Foundation and Sheffield Hallam University.

IR data is given in cm^{-1}. ^{1}H NMR data is given on the ppm scale using tetramethylsilane as the internal reference. Abbreviations used for the form of the signal are as follows ; s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet.

Flash chromatography and column chromatography were performed on Merck 7734 and Merck 7730 silica gel respectively. Thin layer chromatography was performed on Merck 5554 Alufolien Kieselgel $60F_{254}$ plates.

When required anhydrous solvents were prepared according to literature[96]. All reactions requiring inert atmospheres were performed under nitrogen.

2,3:5,6-Di-O-isopropylidene-ß-D-mannofuranose[53] (41)



(41)

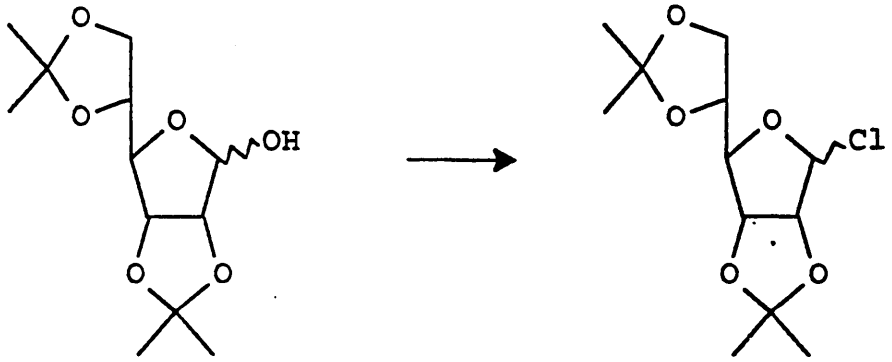
To a solution of concentrated H_2SO_4 (3.8 ml) in acetone (250 ml) was added anhydrous D-mannose (5.50 g, 30.6 mmol). Stirring was commenced and continued with the exclusion of water for 5 hours. The solution was then neutralised by the addition of Na_2CO_3, filtered and the residue washed with hot acetone (100 ml). The combined extracts were then concentrated and the resultant residue was dissolved in dry ether, filtered and precipitated with petrol (3 times volume of ether). The precipitate was isolated and the mother liquor partially evaporated to yield a further portion of product. The combined product portions were recrystallized from petrol to yield pure (41) (6.72 g, 84.6%).

m.p. : 122-124 ^{O}C **Lit. m.p.** : 121-122^{O}C

IR (KBr): 3005-3580 (OH str), 2980, 2930, 2890 (CH str)

^{1}H **NMR** : 1.36-1.46 (s+d, 12H), 3.70 (m, 1H), 4.06-4.90 (m, 6H), 5.27 (s, 1H).

2,3:5,6-Di-O-isopropylidene-S-D-mannofuranosyl chloride[53] (41a)



(41) (41a)

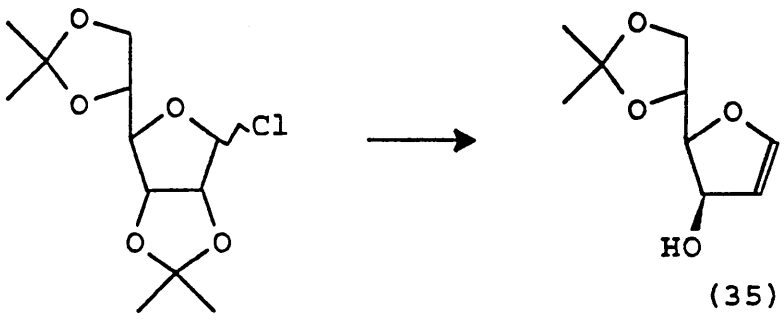
To a slurry of (40) (20.0 g, 76.9 mmol) in dry CCl_4 (100 ml) was added triphenylphosphine (20.3 g, 76.9 mmol). The reaction mixture was then heated under reflux with the exclusion of water for 14 hours. To the solution was added anhydrous lead carbonate (2.0 g) and powdered activated charcoal (1.0 g). The resultant cooled mixture was filtered (hyflo) and the filter cake washed with ice cold CCl_4 (30 ml). The filtrate was concentrated to approximately one third its volume whereupon it was cooled in ice and a further portion of triphenylphosphine oxide precipitated out. After a second filtration (hyflo), the filter cake was washed with ice cold petrol (20 ml) and the filtrate concentrated to yield crude (41a) as a bright orange, clear, viscous liquid. Column chromatography (CH_2Cl_2) yielded pure (41a) as a clear, pale orange, viscous liquid (15.1 g, 70.4%).

IR (liquid film): 2990, 2940, 2880 (CH str)

^{1}H NMR ($CDCl_3$) : 1.25-1.55 (s+d, 12H), 3.95-5.05 (m, 6H), 5.98 (s, 1H)

MS (EI) m/z : MH^+ 288, MH^++2 290

1,4-Anhydro-2-deoxy-5,6-o-isopropylidene-D-arabino-hex-1-enitol[49] (35)



(41a) (35)

To a flame dried flask fitted with a flushing dry nitrogen stream, dry ice condenser and seated in a cooling bath (-78 ^{o}C, dry ice/ acetone) was added anhydrous liquid ammonia (500 ml). To this was added lithium wire (2.78 g, 0.38 mol) and the clear colourless liquid turned opaque navy blue. A solution of furanosyl chloride (41a) (18.0 g, 0.065 mol) in dry THF (100 ml) was added dropwise, slowly. The cooling bath was then removed and ammonia reflux allowed for 2½ hours. Anhydrous ammonium chloride (31.2 g, 0.58 mol) was added cautiously and the solution changed to a milk-white

emulsion. This mixture was diluted with ether (400 ml) and transferred to a large conical flask using more ether (200 ml). After standing for 18 hours the resulting ethereal solution was filtered through hyflo filter aid. The filter cake was thoroughly washed with ether (300 ml) and the combined filtrates were concentrated to yield a clear pale green liquid (12.2 g). Column chromatography (60/40; petrol/ethyl acetate + 2% Et_3N) yielded the pure glycal (35) as a clear colourless liquid (9.43 g, 78%).

IR (liquid film): 3200-3550 (OH str), 1640-1680 (C=C str)
^1H NMR ($CDCl_3$) : 1.35 (s, 3H), 1.45 (s, 3H), 2.45 (s, 1H) 3.85-4.60 (m, 4H), 4.9 (m, 1H), 5.15 (m, 1H olefin), 6.5 (m, 1H olefin)
MS (EI) m/z: MH^+ 187.

bis-Phenylthioacetic acid (48)

$$Cl_2CH_2CO_2Et \longrightarrow (PhS)_2CHCO_2H$$

Metallic sodium (4.6 g, 0.20 mol) was dissolved in dry ethanol (200 ml) and thiophenol (23.2 g, 0.20 mol) was added dropwise. After stirring for 30 minutes a

was added dropwise. After stirring for 30 minutes a solution of ethyl dichloroacetate (15.7 g, 0.10 mol) in dry ethanol (25 ml) was added, slowly, and the mixture left stirring for 14 hours. The ethanol was removed along with any residual thiophenol by distillation. The resultant cooled mixture was partitioned between ether (50 ml) and water (100 ml). The ether layer was the re-extracted with water (2 x 25 ml), dried ($MgSO_4$) and concentrated to yield the crude ester as a clear, colourless liquid (23.9 g, 79%).

This crude ester was dissolved in ethanol (100 ml) and to this mixture was added a slight excess of an aqueous solution of sodium hydroxide (3.4 g in 25 ml water). After 4 hours stirring the majority of the ethanol was removed, water (75 ml) was added and the mixture extracted with ether (2 x 20 ml). The aqueous layer was then acidified (approx. pH 2) with conc. HCl and the white crystalline product formed was filtered off, washed with water and dried in vacuo yielding (20.9 g, 96%) of the carboxylic acid (48).

IR (KBr disc) : 2500-3300 (OH str), 1690-1730 (C=O str), 1590,1480 (C=C str)

H NMR ($CDCl_3$): 4.66 (s, 1H), 5.95 (s,br, 1H), 7.1 (m, 10H)

MS (EI) m/z: M^+ 276

bis-Phenylthioacetyl chloride (49)

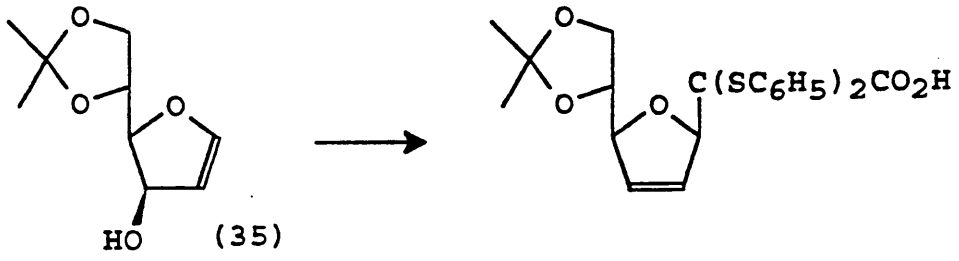
$(PhS)_2CHCO_2H$ ----------> $(PhS)_2CHC(O)Cl$

To a stirred solution of the acid (48) (4.0 g, 14 mmol) in dry dichloromethane (80 ml) at 0^oC under nitrogen was added dry DMF (0.13 ml) and oxalyl chloride (3.8 g, 30 mmol). The reaction was stirred for 14 hours and then concentrated to furnish the crude acid chloride (49) as a dark orange oil (4.10 g). Column chromatography yielded pure (49) as a clear yellow oil (3.55 g, 86%).

IR (liquid film): 3060 (CH str), 1750-1820 (C=O str) 1580, 1490 (C=C str).

^1H NMR ($CDCl_3$) : 4.85 (s, 1H), 7.2 (m, 10H).

Attempted Preparation of 2,5-dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)- α, α , bisphenylthiofuran-2-acetic acid from (35)

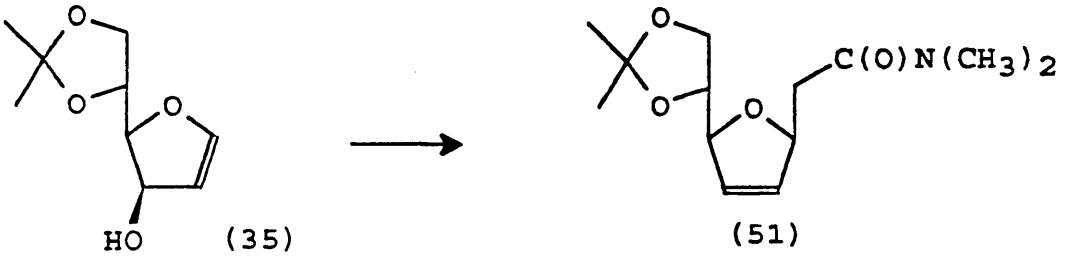


(35)

To a stirred solution of starting alcohol (35) (720 mg, 3.87 mmol) in dry THF (10 ml) at -78°C (dry ice/ acetone) under nitrogen was added n-butyllithium (1.6 M in hexanes) (2.4 ml. 3.90 mmol). After stirring for 15 minutes a solution of the acid chloride (49) (1.08 g, 3.90 mmol) in dry THF (5 ml) was added. After 5 minutes at 0°C the mixture was added dropwise to a stirred solution of LDA (7.8 mmol) in dry THF (10 ml) at -78°C. Ten minutes later the reaction was treated with trimethylsilyl chloride (7.8 mmol) and the reaction allowed to warm to room temperature and stir for a further 1 hour. The mixture was then diluted with 0.5N NaOH (40 ml) and washed with ether (5 ml). The aqueous layer was acidified (pH 2) and extracted with ether (4 x 20 ml). The combined organics were dried ($MgSO_4$) and concentrated to yield a complex mixture of products. Isolation of these components by column chromatography

(50/50; petrol/ethyl acetate) showed that the desired product had not been formed.

2,5-Dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy furan N,N-dimethyacetamide (51)



A flame dried flask was charged with the alcohol (35) (1.00 g, 5.4 mmol), dimethylacetamide dimethylacetal (3.60 g, 27 mmol) and o-xylene (20 ml). The mixture was refluxed under a positive pressure of nitrogen for 48 hours. The solution was then concentrated to yield the crude amide (51) as a dark brown oil (1.45 g). Column chromatography (50/50; petrol/ethyl acetate + 2% Et_3N) provided the pure amide (51) as a clear colourless gum (980 mg, 71%).

FT-IR (liquid film): 2989, 2935, 2905, 2881, 1639 (C=O str), 1067

^{1}H NMR-250 MHz ($CDCl_3$): 1.35 (s, 3H), 1.45 (s, 3H), 2.35-2.80 (m, 2H), 2.95 (s, 2H), 3.05 (s, 3H), 3.95 (m,

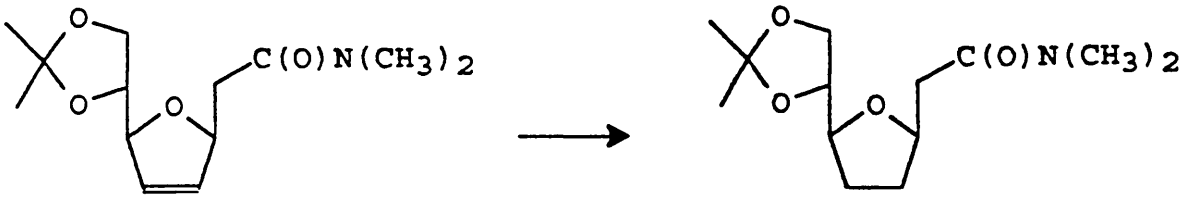
3H), 4.65 (m, 1H), 5.20 (m, 1H), 5.95 (m, 1H olefin), 6.08 (m, 1H olefin).

MS (EI + FAB) m/z: $M-H^+$ 256

Microanalysis found: C, 60.81; H, 8.12; N, 5.27;

$C_{13}H_{21}NO_4$ **requires :** C, 61.16; H, 8.29; N, 5.49.

5-(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxyfuran N,N-dimethylacetamide (52)



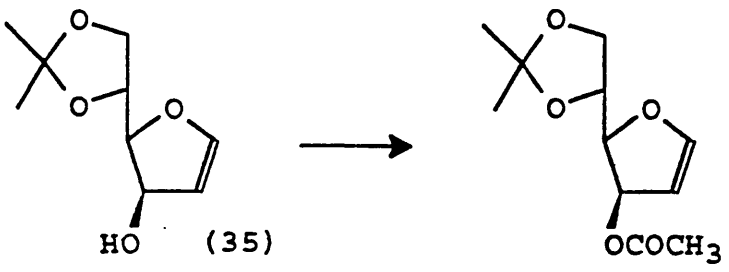
(51) (52)

To the amide (51) (500 mg, 1.96 mmol) in ethanol (5 ml) and triethylamine (1 ml) was added Adams catalyst (PtO) (25 mg) and the reaction was placed under a positive pressure of hydrogen. The catalyst was filtered off and the filter cake washed with ethanol. The combined filtrates were concentrated and the product appeared as a clear pale yellow syrup (420 mg, 84%).

IR (liquid film): 2980, 2920, 2880,1670 (C=O str)

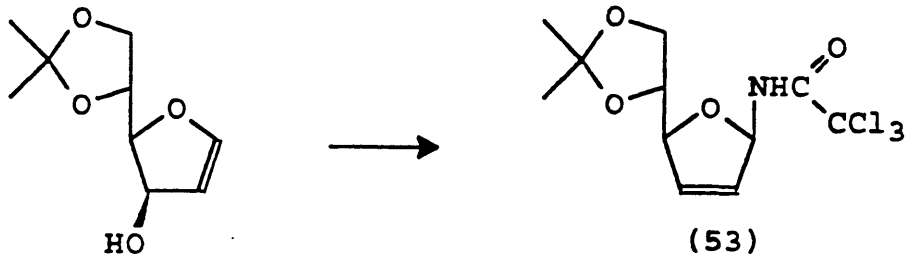
^1H **NMR** ($CDCl_3$)**:** 1.2-1.5 (m, 7H), 1.8-2.2 (m, 3H), 2.4-2.75 (m, 2H), 3.0 (m, 6H), 3.75-4.25 (m, 5H).

Attempted Preparation of 2,5-dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxyfuran acetic acid from (35)



To a flame dried flask was added the alcohol (35) (1.00 g, 5.4 mmol) and dry ether (15 ml). After cooling to 0^{O}C n-butyllithium (3.6 ml, 5.7 mmol) was added dropwise. The reaction was stirred at 0^{O}C for 1 hour after which time a solution of acetyl chloride (460 mg, 5.9 mmol) in dry ether (5 ml) was added dropwise. The cooling bath was removed and stirring continued for 5 hours. The mixture was poured into iced water (50 ml) and the ether separated. The aqueous layer was extracted with ether (4 X 15 ml) and the combined organics were washed with water (2 X 15 ml), dried ($MgSO_4$) and concentrated. This reaction supplied only recovery of starting materials and one minor unknown product.

2,5-Dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-furan trichloroacetamide (53)



(35) (53)

To sodium hydride (215 mg, 5.4 mmol) was added petrol (10 ml) and the oil removed with a pipette. The hydride was then suspended in dry ether (20 ml). To this was added, dropwise, a solution of the alcohol (35) (10.0 g, 54 mmol) in dry ether (20 ml). Stirring was continued for 30 minutes after which time hydrogen evolution had ceased. After cooling to $0^{o}C$ a solution of trichloroacetonitrile (7.8 g, 54 mmol) in dry ether (20 ml) was added dropwise. This mixture was left for 3 hours whereupon the solvents were removed under reduced pressure. A solution of petrol (40 ml) containing 0.1% methanol was added and the mixture shaken vigorously for 1 minute. The resultant solution was filtered by gravity and the process was then repeated twice more. The combined filtrates were concentrated to supply crude (53) as a soft yellow solid (15.9 g). Recrystallization from petrol furnished pure trichloroacetamide (53) as a white crystalline solid (13.9 g, 78 %).

IR (KBr disc): 3320, 3380 (NH str), 1720 (C=O str)

^{1}H NMR-250 MHz ($CDCl_3$): 1.35 (s, 3H), 1.42 (s, 3H), 3.8 (q, 1H), 4.1 (q, 1H), 4.35 (m, 1H), 4.75 (m, 1H), 6.0 (m, 1H), 6.15 (m, 1H), 6.45 (m, 1H), 7.6 (s,br, 1H).

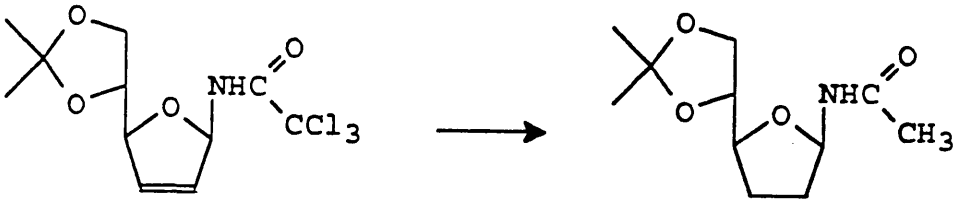
MS (FAB) m/z: MH^+ 330, MH^+ (^{37}Cl) 332,

MH^+ ($-NHCOCCl_3$) 169

Microanalysis found : C, 40.24; H, 4.31; N, 4.03

$C_{11}H_{14}Cl_3NO_4$ requires: C, 39.98; H, 4.27; N, 4.24

2,5-Dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl) furan acetamide (55)



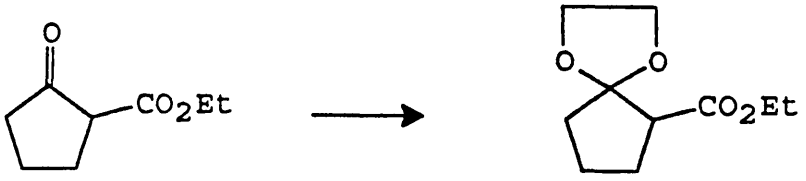
(53) (55)

To the trichloroacetamide (53) (1.00 g, 3.03 mmol) in ethyl acetate (8 ml) and triethylamine (2 ml) was added Adams catalyst (PtO) (50 mg) and the mixture was hydrogenated at room temperature and just above atmospheric pressure. Upon completion of reaction the catalyst was filtered off and the solvent removed under reduced pressure. The product appeared as an orange syrup (620 mg, 89%).

IR (Liquid Film): 3260-3500 (N-H str), 2990, 2960, 2900, 1680 (C=O str)

^{1}H NMR ($CDCl_3$): 1.1-1.7 (m, 4H), 1.4 (s, 3H), 1.5 (s, 3H), 1.95 (s, 3H), 3.8-4.1 (m, 4H), 5.6 (m, 1H) 7.1 (s, br, 1H)

Ethyl 1,4-dioxaspiro [4.4] nonane-6-carboxylate[50] (64)



(63) (64)

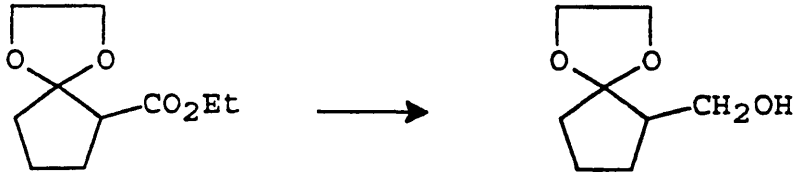
To dry benzene (500 ml) was added ethyl 2-oxocyclopen tanecarboxylate (50.0 g, 0.32 mol), ethylene glycol (49.5 g, 0.80 mol) and p-toluenesulphonic acid (1.5 g, 8.0 mmol). The mixture was refluxed under a Dean-Stark trap with the strict exclusion of water for 48 hours. After cooling to room temperature the sample was washed with 2N NaOH (2 x 120 ml) and water (3 x 50 ml), dried ($MgSO_4$) and concentrated to yield a very pale green liquid. Column chromatography (80/20; petrol/ethyl acetate) gave (64) as a clear colourless liquid (48.4 g, 75.6%).

IR (Liquid film): 1725 (C=O str)

^{1}H NMR ($CDCl_3$): 1.30 (t, 3H J = 7.1Hz)), 1.60-2.30 (m, 6H), 2.30-

2.45 (m, 1H), 3.98 (s, 4H), 4.1 (q, 2H)

1,4-Dioxaspiro [4.4] non-6-ylmethanol (66)



(64) (66)

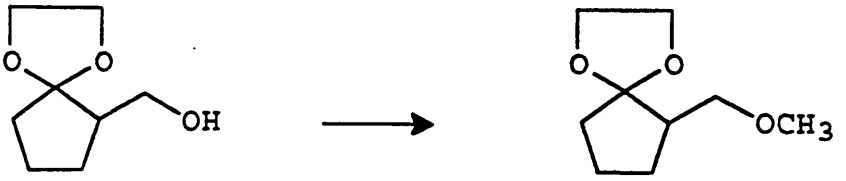
To a suspension of $LiAlH_4$ (9.1 g, 0.24 mol) in dry ether (300 ml) at 0^o was added, dropwise, a solution of (64) (48.4 g, 0.24 mol) in dry ether (200 ml). The solution was stirred for two hours at 0^0 and for a further 14 hours at room temperature. 15% NaOH in saturated Na_2SO_4 (24.8 ml) was added with caution to the ice cooled mixture. The mixture was then filtered and the filter cake washed with ether (500 ml) and the combined ether layers were dried ($MgSO_4$) and concentrated to yield (66) as a clear colourless liquid (36.8 g, 97%) which required no further purification.

IR (Liquid film): 3250-3600 (br, OH str), no C=O str

^{1}H NMR ($CDCl_3$): 1.52-1.98 (m, 6H), 2.04-2.25 (m, 1H),

3.60 (d, 2H, J = 6.2Hz), 3.88 (s, 4H)

6-Methoxymethyl-1,4-dioxaspiro [4.4] nonane (68a)



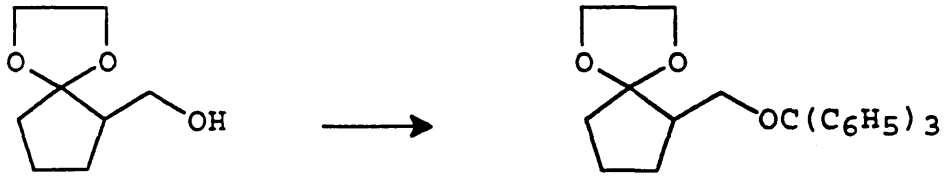
(66) (68a)

To sodium hydride (1.8 g, 45 mmol) was added petrol (25 ml) and the oil removed with a pipette. The hydride was then suspended in dry THF (40 ml) and the alcohol (66) (7.05 g, 41 mmol) was added dropwise as a solution in dry THF (20 ml). After 3 hours at room temperature followed by ice cooling methyl iodide (9.1 g, 64 mmol) was added slowly, dropwise, and stirring was continued for a further 14 hours. After this time iced water (100 ml) was added and the mixture extracted with ether (4 x 50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to yield (68a) as a light orange liquid (5.3 g). Column chromatography (80/20; petrol/ethyl acetate + 2% Et_3N) yielded (68a) as a clear colourless liquid (4.6 g, 84%).

IR (Liquid film): 2965, 2920, 2890 (CH str), 1120 (CH b)

^{1}H NMR ($CDCl_3$) : 1.39-1.99 (m, 6H), 2.22 (m, 1H), 3.30-3.50 (m, 2H), 3.35 (s, 3H), 3.91 (s, 4H)

6-Triphenylmethoxymethyl-1,4-dioxaspiro [4.4] nonane (68b)



(66) (68b)

To a solution of triphenylmethyl chloride (7.05 g, 25.3 mmol) and DMAP (8 mg) in dry pyridine (20 ml) was added a solution of the alcohol (66) (4.3 g, 25.3 mmol) in dry pyridine (10 ml). After stirring at room temperature for 32 hours the reaction mixture was poured into water (100 ml) and the aqueous solution extracted with petrol (4 x 20 ml). The combined petrol layers were washed with water (4 x 20 ml), dried ($MgSO_4$) and concentrated to yield crude (68b) as a light green highly viscous liquid (9.87 g). Column chromatography (90/10; petrol/ethyl acetate + 2% Et_3N) gave pure (68b) as a clear colourless gum which slowly crystallized in the freezer to a pure white solid (7.29 g, 72%).

IR (KBr disc) : 3060, 3090, 2990, 2960 (CH str)

760, 690 (C-H b)

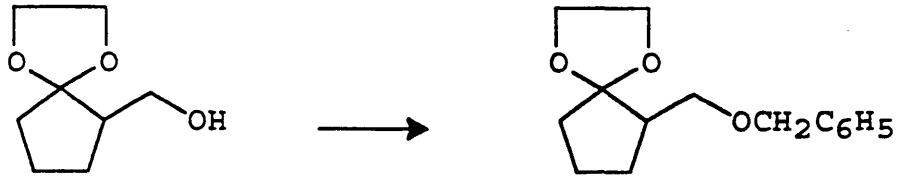
^{1}H NMR ($CDCl_3$): 1.4-2.1 (m, 6H), 2.28 (quin, 1H, J = &&Hz), 3.1 (m, 2H), 3.75 (m, 4H), 7.3 (m, 15H)

MS (FAB) m/z: $M-H^+$ 399.0, CPh_3^+ 243.0, CPh_2^+ 165.0

Microanalysis found: C, 81.05; H, 7.10; O, 11.85

$C_{27}H_{28}O_3$ requires : C, 80.90; H, 7.05; O, 11.98

6-Benzyloxymethyl-1,4-dioxaspiro [4.4] nonane (68c)



(66) (68c)

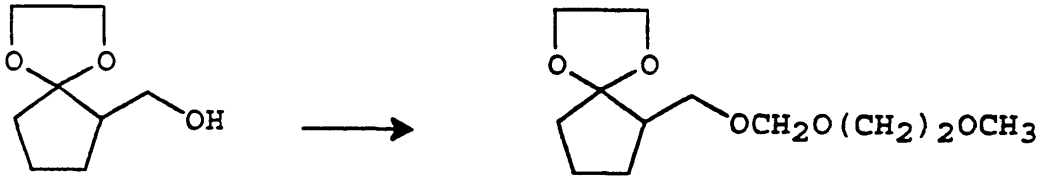
To sodium hydride (1.11 g, 28 mmol) was added petrol (25 ml) and the oil removed with a pipette. The hydride was then suspended in dry THF (40 ml) and the alcohol (66) (4.0 g, 25 mmol) was added dropwise as a solution in dry THF (10 ml). Following 2½ hours at room temperature and 30 minutes at 0^0 a solution of benzyl bromide (4.33 g 25 mmol) in dry THF (15 ml) was added dropwise and the resulting solution was left stirring at ambient temperature for 14 hours. The mixture was then poured into iced water (100 ml) and this aqueous solution was

extracted with ether (5 x 40 ml). The combined organic layers were washed with water (2 x 40 ml), brine (40 ml), dried ($MgSO_4$) and concentrated to yield crude ether (68c) as a very pale green liquid. Column chromatography (90/10; petrol/ethyl acetate + 2% Et_3N) yielded (68c) as a clear colourless liquid (6.01 g, 97%).

FT-IR (Liquid film): 2982, 2930, 1450 wk, 1275 strong, 1117, 714 strong, 680, 770 (C-H b)

^1H NMR ($CDCl_3$): 1.4-2.45 (m, 7H), 3.25-3.6 (m, 2H), 3.75 (s, 4H), 4.4 (s, 2H), 7.15 (s, 5H)

6-Methoxyethoxymethoxymethyl-1,4-dioxaspiro [4.4] nonane (68d)



(66) (68d)

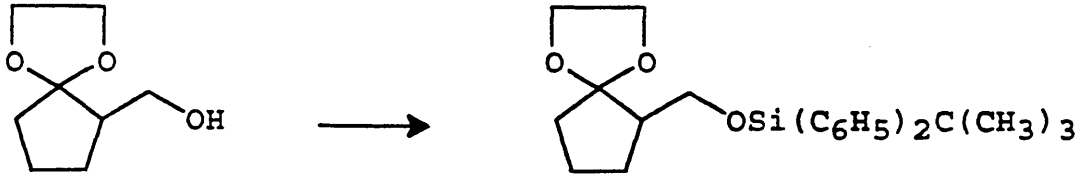
To sodium hydride (310 mg, 7.6 mmol) was added petrol (5 ml) and the oil was removed with a pipette. The hydride was suspended in dry THF (8 ml) and a solution of the alcohol (66) (1.00 g, 6.3 mmol) in dry THF (4 ml) was added dropwise. After 2½ hours at room temperature and

30 minutes at 0^0 a solution of freshly distilled methoxyethoxymethyl chloride (950 mg, 7.6 mmol) in dry THF (4 ml) was added dropwise. After stirring for 24 hours the reaction mixture was poured into iced water (30 ml) and the aqueous layer extracted with ether (5 x 20 ml). The combined ether portions were dried ($MgSO_4$) and concentrated to give crude (68d) as a clear colourless liquid. Column chromatography (50/50; petrol/ethyl acetate + 2% Et_3N) yielded pure (68d) as a clear colourless liquid (1.27 g, 68%).

IR (Liquid film): 2940, 2920, 2870, 1110, 1040

^1H NMR ($CDCl_3$) : 1.45-2.05 (m, 6H), 2.25 (quin, 1H), 3.4 (s, 1H), 3.45-3.75 (m, 6H), 3.90 (s, 4H), 4.7-4.85 (m, 2H)

6-t-Butyldiphenylsilyloxymethyl-1,4-dioxaspiro [4.4] nonane (68e)



(66) (68e)

To dry DMF (15 ml) was added t-butyldiphenylsilyl chloride (1.91 g, 7.0 mmol), imidazole (0.95 g, 13.9

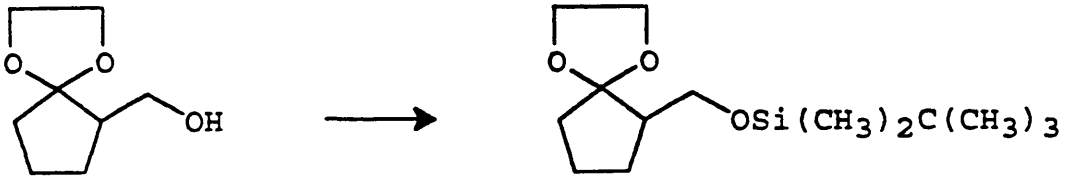
mmol) and the alcohol (66) (1.00 g, 6.3 mmol) and stirring was continued for 48 hours at room temperature with the exclusion of water. The mixture was then poured into water (50 ml) and the aqueous phase was extracted with petrol (4 x 15 ml). The combined organics were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to yield a pale green gum (3.0 g) which was purified by column chromatography (85/15; petrol/ethyl acetate + 2% Et_3N). The desired silyl ether (68e) appeared as a clear colourless gum (2.17 g, 87%).

IR (Liquid film): 3040/3080 wk, 2940, 2860, 1430 wk, 1120 v strong, 780 v strong

^1H NMR ($CDCl_3$) : 1.05 (s, 9H), 1.40-2.38 (m, 7H), 3.33-3.85 (m, 2H), 3.75 (s, 3H), 7.15-7.75 (m, 10H)

MS (FAB) m/z : MH^+ 396

6-t-Butyldimethylsiloxymethyl-1,4-dioxaspiro [4.4] nonane (68f)



(66) (68f)

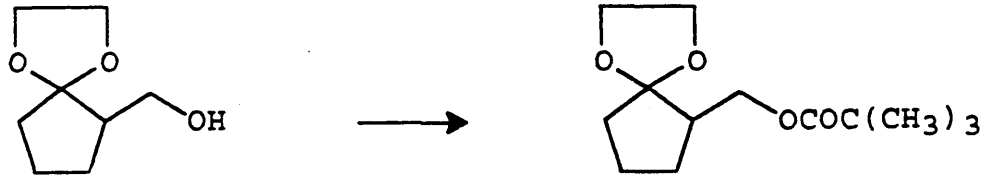
To dry DMF (15 ml) was added the alcohol (66) (1.00 g 6.3 mmol), t-butyldimethylsilyl chloride (1.1 g, 7.2 mmol) and imidazole (0.95 g, 13.9 mmol). After stirring for 48 hours at room temperature with the exclusion of water the mixture was poured into water (50 ml) and the aqueous phase was extracted with petrol (4 x 15 ml). The combined organics were washed with water (3 x 10 ml), dried ($MgSO_4$) and concentrated to yield (68f) as a pale yellow viscous liquid. Column chromatography (85/15; petrol/ethyl acetate + 2% Et_3N) yielded the pure silyl ether as a clear, colourless liquid (1.37 g, 80%).

IR (Liquid film): 2960, 2940, 2870, 2850, 1260, 1120 v strong, 780 v strong

^1H NMR ($CDCl_3$) : 0.0 (s, 6H), 0.8 (s, 9H), 1.4-2.25 (m, 7H), 3.4-3.75 (m, 2H), 3.85 (s, 4H)

MS (FAB) m/z : MH^+ 273

1,4-Dioxaspiro [4.4] non-6-ylmethyl 2,2-dimethyl propanoate (68g)



(66) (68g)

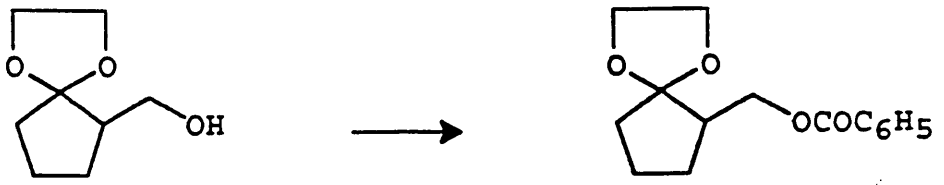
A solution of the alcohol (66) (2.00 g, 12.7 mmol) and dry ether (25 ml) was cooled to 0^0 whereupon ^{n}butyllithium (8.5 ml, 13.5 mmol) was added slowly, dropwise. During this addition a precipitate of lithium alkoxide appeared. After 1 hour at 0^0 a solution of distilled pivaloyl chloride (3.07 g, 12.7 mmol) in dry ether (10 ml) was added dropwise, the cooling bath was then removed and the reaction left at room temperature for a further 3 hours. The mixture was then poured carefully into iced water (75 ml) and the ether layer separated. The remaining aqueous layer was extracted with ether (3 x 25 ml) and the combined organics were washed with water (2 x 20 ml), dried ($MgSO_4$) and concentrated. The crude product appeared as a clear colourless liquid (3.01 g, 98%) and was virtually pure (^{1}H NMR showed >98% purity) and so no further purification was necessary.

IR (Liquid Film): 2950, 2860, 1720 (C=O str), 1280, 1150 v strong

^{1}H NMR ($CDCl_3$) : 1.2 (s, 9H), 1.35-2.5 (m, 7H), 3.80-4.2 (m, 2H), 3.85 (s, 4H)

MS (FAB) m/z : MH^+ 243

1,4-Dioxaspiro [4.4] non-6-ylmethyl benzoate (68h)



(66) (68h)

A solution of alcohol (66) (3.00 g, 19.0 mmol) and dry ether (30 ml) was cooled to 0^0 and ^{n}butyllithium (12.5 ml, 20.0 mmol) was added slowly whereupon a precipitate of lithium alkoxide emerged. After 1 hour at 0^0 a solution of benzoyl chloride (2.67 g, 19.0 mmol) in dry ether (10 ml) was added, the cooling bath was removed and stirring continued for 4 hours. The reaction mixture was then poured into iced water (80 ml) and the ether separated off. The aqueous phase was extracted with ether (3 x 25 ml) and the combined organics were washed with water (2 x 25 ml), dried ($MgSO_4$) and concentrated to yield crude (68h) as an orange liquid (5.22 g) which was purified by column chromatography (85/15; petrol/ethyl acetate + 2% Et_3N) to produce a clear colourless liquid (4.78 g, 96%).

FT-IR : 2983, 2930, 1718 (C=O str v strong), 1275 v strong, 1117, 714

^{1}H NMR ($CDCl_3$) : 1.50-2.11 (m, 6H), 2.48 (quin, 1H)

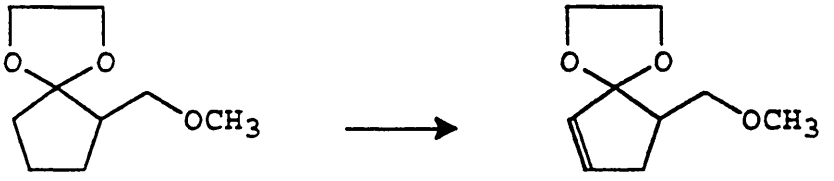
3.90 (s, 4H), 4.35 (m, 2H), 7.50-8.05 (m, 5H)

MS (FAB) m/z : MH^+ 262

Microanalysis found: C, 68.53; H, 6.94; O, 24.53

$C_{15}H_{18}O_4$ requires : C, 68.69; H, 6.92; O, 24.40

6-Methoxymethyl-1,4-dioxaspiro [4.4] non-8-ene (69)



(69)

A. Employing Br_2 and NaOH

To a vigorously stirred mixture of (68a) (20.0 g, 0.12 mol) in ethylene glycol (100 ml) was added bromine (18.5 g, 0.12 mol). Initially 0.5 ml of bromine was added and the mixture was heated to 50^0 until the solution began to decolourize whereupon it was cooled to below 20^0. The remaining bromine was then added at such a rate that the mixture maintained a straw yellow colour. A further 30 minutes after bromine addition was complete the mixture was carefully poured into a vigorously stirring suspension of Na_2CO_3 (29.8 g) in petrol (100 ml). After stirring for 1 hour, water (100 ml) was added and the organic layer separated. The aqueous layer

was extracted with ether (6 x 80 ml) and the combined organic fractions were dried ($MgSO_4$) and concentrated to yield the crude bromide intermediate as a clear, light green liquid (27.8 g) which was used without further purification.

This bromide was immediately dissolved in dry ethanol (150 ml) and NaOH (10 g) was added and the mixture was refluxed with the exclusion of water for 14 hours. After cooling to room temperature the mixture was poured into water (500 ml) and extracted with dichloromethane (6 x 100 ml). The combined dichloromethane layers were dried ($MgSO_4$) and concentrated to produce the crude alkene (69) which was most conveniently used without further purification in the next stage of the reaction pathway. A portion of this sample (1.00 g) was purified by column chromatography (80/20; petrol/ethyl acetate + 2% Et_3N) to yield pure (69) as a clear colourless liquid (810 mg, 63%).

2. Employing Pyridinium Hydrobromide Perbromide and Anhydrous Sodium Methoxide

A solution of methyl ether (68a) (500 mg, 2.91 mmol) and dry THF (12 ml) was cooled to -78^0 (dry ice/ acetone) and pyridinium hydrobromide perbromide (1.02 g, 3.20 mmol) was added in one portion. Stirring was continued until starch-iodide paper showed a negative result. Pyridine (250 mg, 3.20 mmol) was added with

vigorous stirring and after a further 10 minutes the mixture was poured into 10% (aq) Na_2CO_3 solution (10 ml) and subsequently extracted with dichloromethane (4 x 10 ml). The combined organics were washed with water (2 x 20 ml), dried ($MgSO_4$) and concentrated to give the crude product as a clear, dark red liquid (840 mg) and this was used immediately without further purification.

To a suspension of NaOMe (anhy) (490 mg, 9.02 mmol) in dry DMSO (8 ml) at $>20^0$ was added a solution of the bromide crude product (840 mg) in dry DMSO (2 ml). After 4 hours iced water (20 ml) was added and the solution saturated with NaCl and subsequently extracted with petrol (8 x 15 ml). The petrol layers were washed with water (2 x 30 ml), dried ($MgSO_4$) and concentrated which left the crude alkene (69) as a light orange liquid (360 mg) which could be purified by column chromatography (80/20; petrol/ethyl acetate + 2% Et_3N). This gave pure (69) as a clear, colourless liquid (280 mg, 57%).

3. **Employing Phenyltrimethylammonium Tribromide and Anhydrous Sodium Methoxide**

To a solution of (68a) (500 mg, 2.91 mmol) in dry THF (12 ml) at 0^0 was added in one batch phenyltrimethylammonium tribromide (1.15 g, 3.06 mmol). Following two hours with occasional stirring the mixture was poured into a solution of saturated sodium bicarbonate (12 ml)/ 0.1 N sodium thiosulphate (12 ml) and extracted with

ether (4 x 20 ml). The combined ether portions were washed with water (3 x 25 ml), brine (25 ml), dried (Na_2SO_4) and concentrated to produce the crude bromide intermediate as a clear, orange liquid (940 mg) which again was used without further purification.

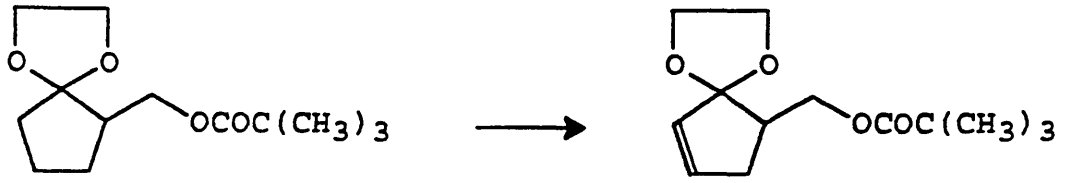
To a suspension of anhydrous NaOMe (600 mg, 11.1 mmol) in dry DMSO (8 ml) at $<20^0$ was added the crude bromide (940 mg) as a solution in dry DMSO (2 ml). Following 4 hours stirring iced water (20 ml) was added and the solution saturated with NaCl. Petrol (8 x 15 ml) was used to extract the crude product and the combined organics were washed with water (2 x 30 ml), dried ($MgSO_4$) and concentrated. The clear, pale green, crude alkene was purified by column chromatography (80/20; petrol/ethyl acetate + 2% Et_3N) yielding pure (69) as a clear colourless liquid (270 mg, 55%)

Analysis of Pure (69)

IR (Liquid film): 1650 (C=C str)

^1H NMR ($CDCl_3$) : 2.16 (m, 1H), 2.56 (m, 2H), 3.37-3.58 (m, 2H), 3.37 (s, 3H), 3.96 (m, 4H), 5.67 (m, 1H olefin) 6.06 (m, 1H olefin)

1,4-Dioxaspiro [4.4] non-8-ene-6-ylmethyl-2,2-dimethylpropanoate from 68g



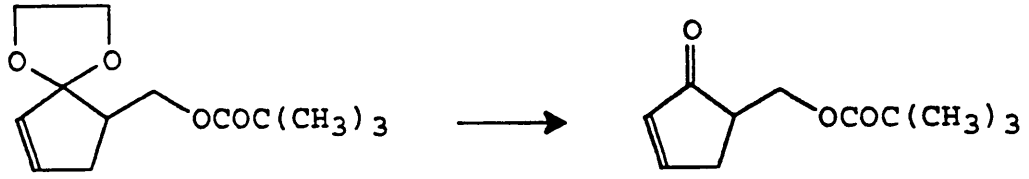
(68g)

To a vigorously stirred mixture of ester (68g) (1.00 g, 4.1 mmol) in ethylene glycol (20 ml) was added an initial amount of bromine (0.05 ml). The mix was heated to 50^0 and left until decolourization was initiated whereupon the reaction was cooled to $<20^0$ and the remainder of the bromine was added at a rate which maintained a straw yellow colour in the reaction pot. After 30 minutes this mixture was slowly poured into a suspension of Na_2CO_3 (1.1 g) in petrol (10 ml) and then allowed to stir for a further 1 hour. Water (25 ml) was then added and the organic phase separated. The aqueous portion was extracted with dichloromethane (6 x 15 ml) and the combined organics were washed with water (2 x 15 ml), dried ($MgSO_4$) and concentrated to yield the crude bromide intermediate as a light amber liquid (990 mg, 3.1 mmol).

To ^tBuOK (350 mg, 3.1 mmol) and dry DMSO (8 ml) was added a solution of the synthesized bromide intermediate

(990 mg, 3.1 mmol) in dry DMSO (4 ml). After 14 hours the mixture was poured into iced water (40 ml) and extracted with petrol (8 x 15 ml). The organic portions were washed with water (2 x 30 ml), dried ($MgSO_4$) and concentrated to give the crude material as a clear, pale green liquid (410 mg). This product was used without purification for the subsequent ketal deprotection reaction.

2-oxocyclopent-3-enylmethyl 2,2-dimethylpropanoate



To a slurry of coarse silica (1.1 g) and dichloromethane (15 ml) was added 10% (aq) oxalic acid (0.11 ml) and the mixture was stirred for 15 minutes after which time a solution of the alkene (410 mg, 1.8 mmol) in DCM (3 ml) was added in a couple of portions. After 1 hour $NaHCO_3$ (40 mg) was added and the reaction stirred for a further 20 minutes. The reaction was then filtered and the filter cake washed thoroughly with DCM (20 ml). The filtrate was dried ($MgSO_4$) and concentrated

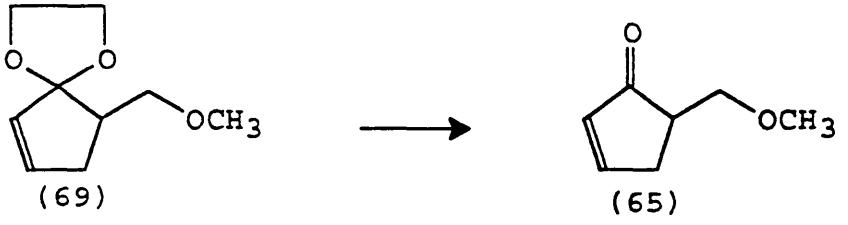
to yield a crude product which was purified by column chromatography (75/25; petrol/ethyl acetate) to isolate pure unsaturated ketone as a clear, colourless liquid (42 mg, 12%).

IR (Liquid film): 1680-1740 (C=Ostr)

^{1}H NMR ($CDCl_3$) : 1.0-1.30 (m, 9H), 2.33-2.8 (m, 3H), 4.15-4.30 (d, 2H), 6.1 (m, 1H olefin), 7.60 (m, 1H olefin)

MS (EI) m/z : MH^+ 197

5-Methoxymethylcyclopent-2-enone



(69) (65)

To a slurry of coarse silica (26.4 g) and dichloromethane (250 ml) was added 10% (aq) oxalic acid (2.7 g) and the mixture was stirred for 15 minutes after which time a solution of the alkene (69) (10.0 g, 59 mmol) in DCM (45 ml) was added in a couple of portions. After 1 hour $NaHCO_3$ (1.1 g) was added and the reaction stirred for a further 20 minutes. The reaction was then

filtered and the filter cake washed thoroughly with DCM (100 ml). The filtrate was dried ($MgSO_4$) and concentrated to yield a crude product which was purified by column chromatography (60/40; petrol/ethyl acetate) to isolate pure unsaturated ketone (65) as a clear, very pale orange liquid (6.90g, 93%).

FT-IR : 2926, 2893, 2845, 2827,1707 (C=O str, v strong) 1121

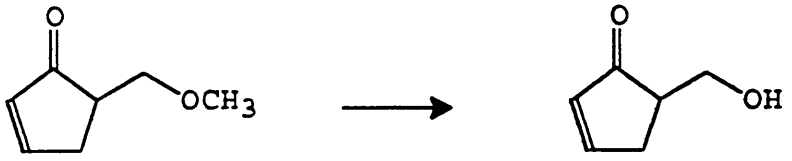
^1H NMR ($CDCl_3$) : 2.40-2.92 (m, 3H), 3.32 (s, 2H), 3.61 (m, 2H), 6.19 (m, 1H olefin), 7.74 (m, 1H olefin)

MS (FAB) m/z : MH^+ 127

Microanalysis found: C, 66.78; H, 8.16; O, 25.24;

$C_7H_{10}O_2$ requires : C, 66.64; H, 7.99; O, 25.38;

Attempted Preparation of 2-Oxocyclopent-3-enyl methanol from (65)



(65)

To the methyl ether (65) (250 mg, 1.98 mmol) was added in turn dry chloroform (4 ml), dry pyridine (60 mg) and freshly distilled trimethylsilyl iodide (622 mg, 3.11

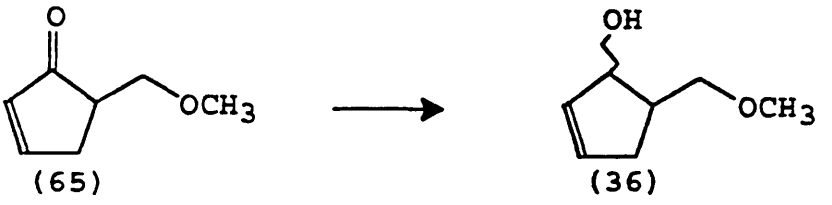
mmol) and the mixture was heated to and kept at 60^0 for 48 hours. Anhydrous methanol (2 ml) was added and the volatiles removed to yield a crude product which by TLC and proton NMR analysis was shown to be a complex mixture of compounds.

Attempted Preparation of 5-Bromoethylcyclopent-2-enone from (65)

(65)

To the methyl ether (65) (500 mg, 3.9 mmol) in DCM (10 ml) was added dropwise ß-bromocatecholborane (0.2 M in DCM) (19.5 ml, 3.9 mmol) and the reaction was left for 14 hours. Water (15 ml) was added and the reaction left for a further 30 minutes after which time it was diluted with DCM (100 ml) and the organic layer separated. The DCM phase was washed with 10% (aq) NaOH (2 x 30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated to yield a product which by TLC and proton NMR analysis was confirmed as recovered starting material only.

5-Methoxymethylcyclopent-2-enol (36)



(65) (36)

A. $LiAlH_4$ reduction

To a slurry of $LiAlH_4$ (455 mg, 12mmol) in dry ether (20 ml) at -20^0 (dry ice/carbon tetrachloride) was added slowly, dropwise, a solution of (65) (2.00 g, 16 mmol) in dry ether (15 ml). After 2 hours 15% (aq) NaOH saturated with Na_2SO_4 (4.2 ml) was cautiously added and the resultant mixture was filtered, the filter cake being thoroughly washed with ether (50 ml). The filtrate was dried ($MgSO_4$) and concentrated to yield crude (36) as a clear, orange mixture of isomers (1.52 g). Column chromatography (97/3; DCM/methanol) permitted separation of the two isomers and yielded the desired ß-alcohol as a clear colourless liquid (610 mg, 30%) with a by-product, saturated alcohol (15%).

B. Diisobutylaluminium hydride reduction

To a solution of ketone (65) (1.00 g, 7.9 mmol) and dry toluene (15 ml) at -78^0 (dry ice/acetone) was added slowly, dropwise, DIBAL (1.0 M in hexanes) (15.9

ml, 15.9 mmol) and the reaction kept at -78^0 for 2 hours. Methanol (10 ml) was carefully added and the mixture allowed to warm to room temperature whereupon water (2 ml) was added and the gelatinous mixture filtered through hyflo filter aid. The filter cake was washed with hot ether (4 x 30 ml) and the filtrate was concentrated to yield crude (36) which was purified by column chromatography (97/3; DCM/methanol) to isolate the desired ß-alcohol (658 mg, 65%) and the α -alcohol (132 mg, 13%) as clear, colourless liquids.

C. $NaBH_4/CeCl_3$ reduction

To a mix of the ketone (65) (1.72 g, 13.4 mmol) and $CeCl_3$ (0.4 M in methanol) (35 ml, 14 mmol) at 0^0 $NaBH_4$ was added portionwise, slowly, so as to keep the reaction temperature below 5^0. After 1 hour water (10 ml) was added and the reaction carefully concentrated to approximately ¼ its volume. A further 100 ml water was added and the aqueous mixture extracted with ether (8 x 30 ml). The combined organic fractions were washed with brine (50 ml), dried ($MgSO_4$) and concentrated. The crude mixture of alcohol isomers was purified by column chromatography (97/3; DCM/methanol) to yield the ß-alcohol (961 mg, 56%) and the α -alcohol (410 mg, 24%) as clear, colourless liquids.

IR (Liquid film): 3250-3600 (br, O-H str),1670 (C=C str)

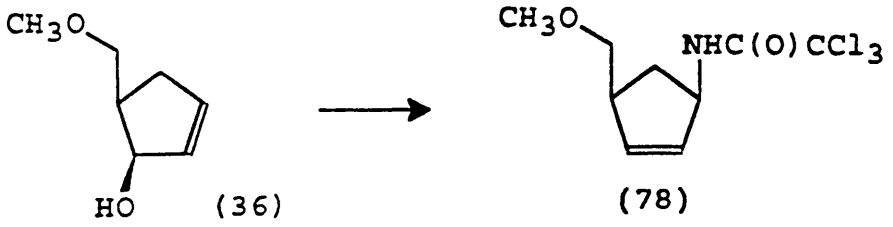
^{1}H NMR-360 MHz ($CDCl_3$) :

ß-Isomer : 2.10-2.42 (m, 2H), 2.52 (m, 1H), 3.39 (m, 3H), 3.58 (m, 2H), 4.83 (d, 1H), 5.84 (m, 1H, olefin) 5.97 (m, 1H, olefin)

α-Isomer : 2.0 (m, 1H), 2.32 (m, 1H), 2.58 (m, 1H), 3.35 (m, 1H), 3.40 (m, 2H), 4.65 (s, 1H), 5.75 (m, 1H olefin), 5.88 (m, 1H, olefin)

MS (FAB) m/z : MH^+ 129, MH^+-31 98

cis-N-4-Methoxymethylcyclopent-2-enyltrichloro-acetamide (78)



To sodium hydride (48 mg, 1.2 mmol) was added petrol (5 ml) and the oil removed with a pipette. The hydride was then suspended in dry ether (8 ml). To this was added, dropwise, a solution of alcohol (36) (1.50 g, 12 mmol) in dry ether (5 ml). Stirring was continued for 15 minutes after completion of hydrogen evolution whereupon the mixture was cooled to 0^0. A separate flask was charged with trichloroacetonitrile (1.73 g, 12 mmol) and

dry ether (8 ml) and cooled to 0^0. The alkoxide solution was then slowly transferred via a syringe into the trichloroacetonitrile mixture and this was left for 2 hours whereupon the solvents were removed under reduced pressure. A solution of petrol (25 ml) containing methanol (0.1%) was added and the mixture shaken vigorously for 1 minute. The resultant solution was filtered by gravity and the process was repeated twice more. The combined filtrates were concentrated to yield the crude intermediate imidate as a clear, light green liquid (3.04 g).

IR (Liquid film): 3500-3000 (No OH str), 3340 (NH str), 1660 (C=N str, v strong)

This crude imidate was, without purification, dissolved in dry toluene and refluxed with the exclusion of water for 6 hours. Cooling and subsequent concentration of the reaction mixture yielded crude (78) as a dark brown viscous liquid which was purified by column chromatography (60/40; petrol/ethyl acetate) to give the desired trichloroacetamide (78) as a white crystalline solid (2.22 g, 68%).

IR (KBr disc) : 3340 (N-H str), 2980, 2940, 2900, 2840, 1730 (C=O str), 1530, 820 strong

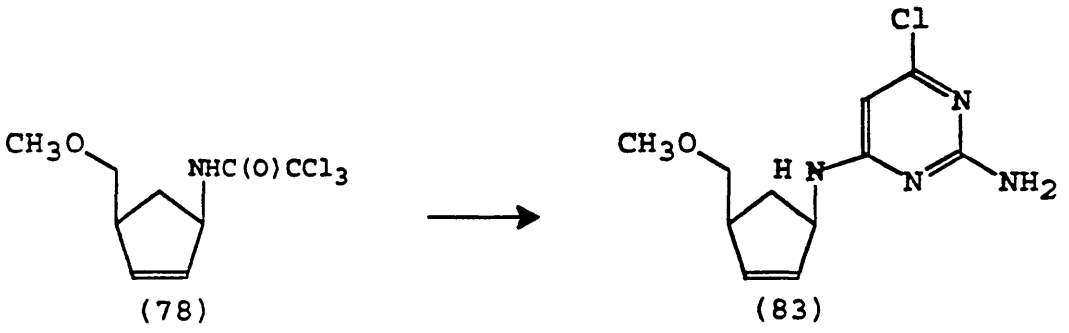
^{1}H NMR ($CDCl_3$) : 1.7 (m, 1H), 2.4 (m, 1H), 3.25-3.45 (m,

3H), 3.30 (s, 3H), 4.80 (m, 1H), 5.7 (m, 2H olefin), 7.45, (s, br, 1H)

Microanalysis found : C, 39.85; H, 4.38; N, 5.09

$C_9H_{12}Cl_3NO_2$ requires : C, 39.66; H, 4.44; N, 5.14

2-Amino-4-chloro-6-(4-methoxymethylcyclopent-2-enyl)amino pyrimidine (83)



(78) (83)

To the trichloroacetamide (78) (1.00 g, 3.7 mmol) was added ethanol (25 ml) and 2N HCl (25 ml) and the mixture refluxed for 54 hours. After solvent removal under reduced pressure n-butanol (45 ml), 2-amino-4,6-dichloro-pyrimidine (2.00 g, 12 mmol) and diisopropylethylamine (15 ml) were added and the mixture refluxed under nitrogen for 36 hours. Following cooling the mix was poured into water (60 ml) and the product extracted with DCM (5 x 150 ml). The combined organics were dried ($MgSO_4$) and concentrated to produce an orange syrup which was purified by column chromatography (50/50; petrol/ ethyl acetate) to yield (83) as an off-white solid

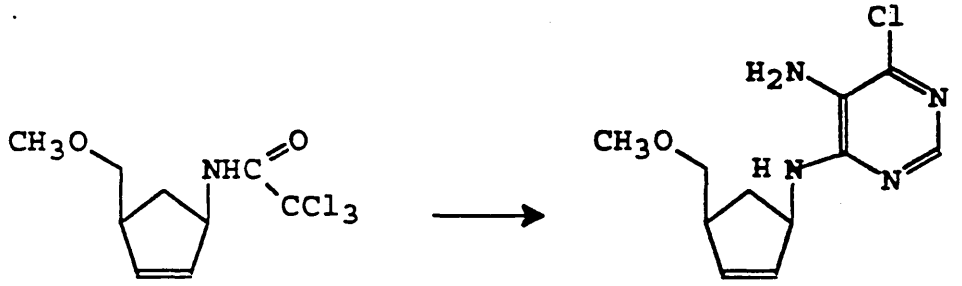
(770 mg, 82%).

m.p. : 106-108°

IR (KBr disc) : 3100-3450 (NH_2 str),
1630/1580 (C=C, C=N str)

^1H NMR ($CDCl_3$) : 1.35 (m, 1H), 2.60 (m, 1H), 3.20-3.50 (m, 3H), 3.30 (s, 3H), 4.85 (s, br, 2H), 5.00 (s, 1H) 5.25-5.60 (m, 2H), 5.65-5.85 (m, 2H olefin)

5-Amino-2-chloro-6-(4-methoxymethylcyclopent-2-enyl) aminopyrimidine (79)



(78) (79)

To the trichloroacetamide (78) (1.00 g, 3.7 mmol) was added ethanol (25 ml) and 2N HCl (25 ml) and the mixture refluxed for 54 hours. After solvent removal under reduced pressure n-butanol (45 ml), 5-amino-4,6-dichloro-pyrimidine (2.00 g, 12 mmol) and diisopropylethylamine (15 ml) were added and the mixture refluxed under nitrogen for 24 hours. Following cooling the mix was poured into water (60 ml) and the product extracted with

DCM (5 x 150 ml). The combined organics were dried ($MgSO_4$) and concentrated to produce crude (79) as a yellow syrup which was purified by column chromatography (50/50; petrol/ethyl acetate) to yield (79) as a pale yellow solid. This product was further purified by recrystallization (petrol/ethyl acetate) to yield pure (79) as white needles (570 mg, 61%).

m.p. : 114-116^0

IR (KBr disc) : 3000-3550 (NH_2 str), 2980, 2940, 2880, 1630/1590 (C=C, C=N str), 1125 v strong

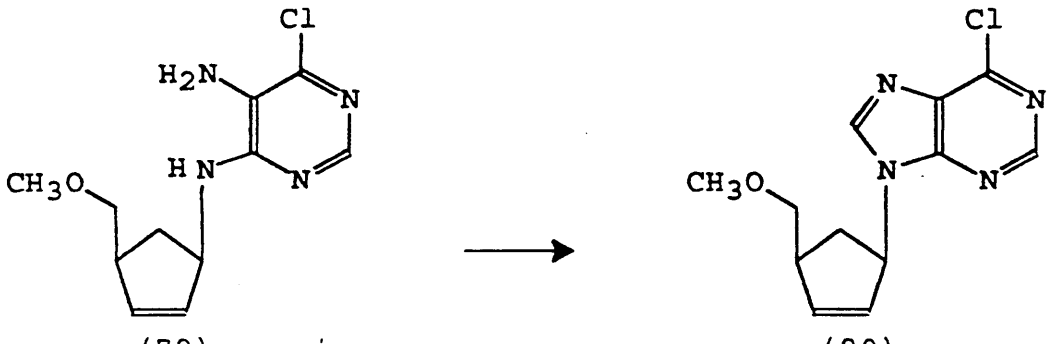
^1H NMR ($CDCl_3$) : 1.35 (m, 1H), 2.60 (m, 1H), 3.20-3.50 (m, 3H), 3.30 (s, 3H), 4.85 (s, br, 2H), 5.00 (s, 1H) 5.25-5.60 (m, 2H), 5.65-5.85 (m, 2H olefin)

MS (EI) m/z : M^+, 254, M^+ (^{37}Cl), 256, MH^+ ($-OCH_3$), 224

H.R.M.S. found : 254.0944

H.R.M.S. requires : 254.0934 (for $C_{11}H_{15}N_4ClO$)

6-Chloro-9-(4-methoxymethylcyclopent-2-enyl)-9H-purine (80)



(79) (80)

To the pyrimidine (79) (400 mg, 1.57 mmol) was added freshly distilled triethylorthoformate (9.5 ml) and c.HCl (0.4 ml) and the mixture was stirred at room temperature for 24 hours. The volatiles were removed and the residue stirred in 0.5 N HCl (15 ml) for 1 hour after which the reaction mix was taken to pH 8 by the careful addition of 1N NaOH. The mixture was again concentrated this time to yield crude (80) as an orange-brown solid (378 mg). Column chromatography (ethyl acetate) yielded (80) as an off-white crystalline solid (332 mg, 80%).

m.p. : $88\text{-}90^0$

IR (KBr disc) : 3100, 3060, 2980, 2920,1630/1590 (C=C, C=N str) 1200, 640

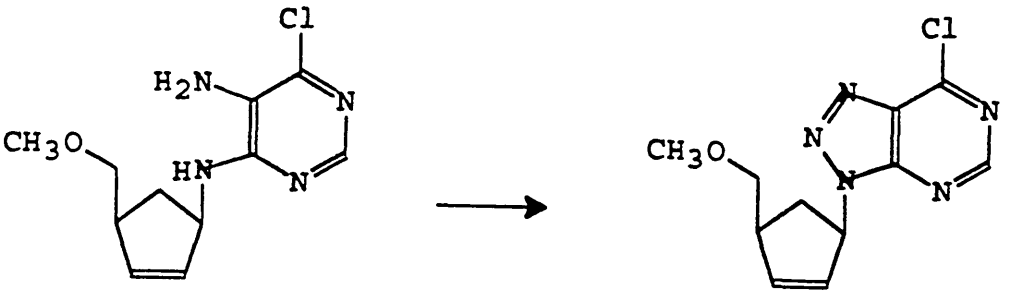
^{1}H NMR ($CDCl_3$) : 1.7 (m, 1H), 2.80 (m, 1H), 3.05 (m,1H), 3.25-3.45 (m, 3H), 3.25 (s, 3H), 5.65 (m, 1H), 5.78 (m, 1H, olefin), 6.15 (m, 1H, olefin), 8.25 (s, 1H), 8.64 (s, 1H)

MS (EI) m/z : M^+, 264, M^+ (^{37}Cl), 266

H.R.M.S. found : 264.0773

H.R.M.S. requires : 264.0777 (for $C_{12}H_{13}N_4ClO$)

7-Chloro-3-(4-methoxymethylcyclopent-2-enyl)-8-azapurine (84)



(79) (84)

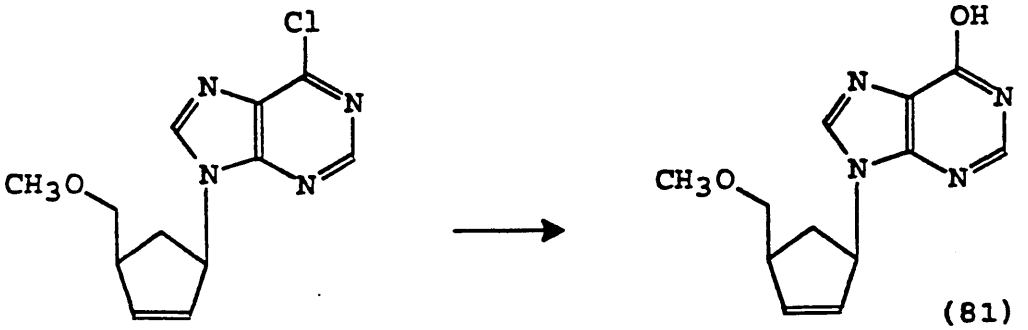
Pyrimidine (79) (100 mg, 0.39 mmol) was dissolved in acetic acid (1.5 ml) and water (2.0 ml) and cooled to 0^0. To this was added a cold solution of sodium nitrite (32 mg, 0.47 mmol). After 2 hours TLC showed complete disappearance of the starting pyrimidine and the reaction mix was poured into water (8 ml). This aqueous phase was extracted with DCM (4 x 5 ml) and the combined organics were washed with 2N NaOH (2 x 5 ml), water (5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated to give a crude light brown crystalline solid. Recrysallization from ethyl acetate/petrol yielded (84) as an off-white crystalline solid (76 mg, 73%).

m.p. : $71-73^0$

IR (KBr disc) : 1630/1590 (C=C, C=N str)

^{1}H NMR ($CDCl_3$) : 2.1 (m, 1H), 2.8 (m, 1H), 3.12 (m, 1H) 3.31 (s, 3H), 3.45 (m, 2H), 5.92 (m, 1H, olefin), 6.08 (m, 1H), 6.2 (m, 1H, olefin), 8.85 (s, 1H)

6-Hydroxy-9-(4-methoxymethylcyclopent-2-enyl)-9H-purine (81)



(81)

The chloropurine (80) (100 mg, 0.378 mmol) was refluxed under nitrogen in 0.3N NaOH (5 ml) for 4 hours. The mixture was then neutralised with 0.5N HCl and concentrated to yield crude (81) as a dark brown liquid which was purified by column chromatography (90/10; DCM/methanol) to give (81) as an off-white solid (61 mg, 66%).

m.p. : $60-62^0$

IR (KBr disc) : 3100-3500 (O-H str), 1710 (C=O str), 1570 (C=C/C=N str)

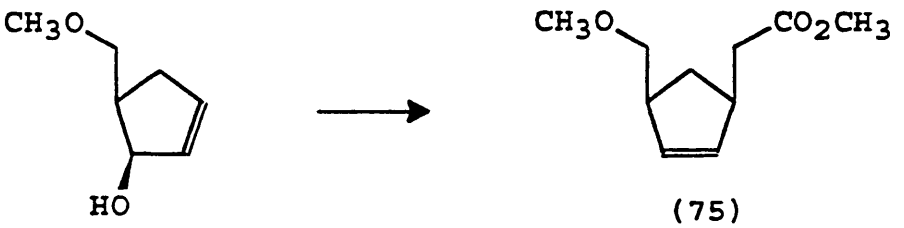
^{1}H NMR ($CDCl_3$) : 1.7 (m, 1H), 2.85 (m, 1H), 3.05 (m, 1H), 3.15-3.50 (m, 2H), 3.25 (s, 3H), 6.0 (m, 1H olefin), 6.15 (m, 1H olefin), 8.15 (s, 1H), 8.50 (s, 1H), 12.8 (s, br, 1H)

MS (EI) m/z : MH^+ 247

H.R.M.S. found : 246.1110

H.R.M.S. requires : 246.1117 (for $C_{12}H_{14}N_4O_2$)

4-Methoxymethylcyclopent-5-enylmethoxyformate (75)



(36) (75)

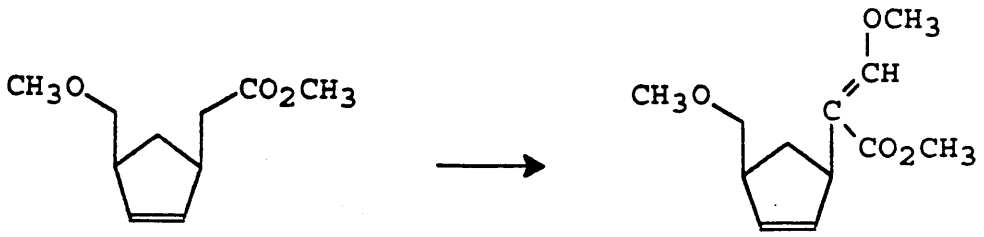
A mixture of the alcohol (36) (1.00 g, 7.9 mmol), trimethyl orthoacetate (15 ml) and propionic acid (0.1 ml) was refluxed under a positive pressure of nitrogen for 18 hours. The solution was then concentrated to yield the crude ester as a light yellow liquid (1.46 g). Column chromatography (90/10; petrol/ethyl acetate) yielded the pure ester (75) as a clear, colourless liquid (1.10 g, 76%).

FT-IR : 2990, 2928, 2876, 2827, 1756 (C=O str), 1244, 1190

^{1}H NMR ($CDCl_3$) : 1.60-2.60 (m, 4H), 2.05 (d, 2H), 3.25-3.45 (m, 2H), 3.35 (s, 3H), 3.65 (s, 3H), 5.75 (s, 2H olefin)

MS (FAB) m/z : MH^+ 185

Methyl-2-(4-methoxymethylcyclopent-2-enyl)-3-methoxy propenoate (76)



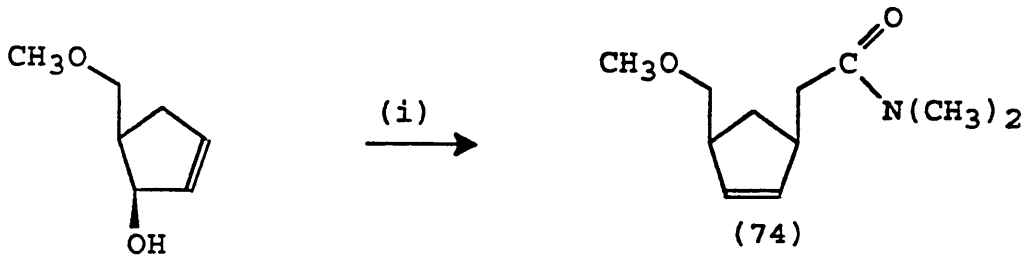
(75) (76)

To sodium hydride (46 mg, 1.15 mmol) was added petrol (2 ml) and the oil removed with a pipette. Dry THF (5 ml), ethanol (4 mg) and the starting ester (75) (200 mg, 1.09 mmol) were added quickly followed by ethyl formate (81 mg, 1.09 mmol). The reaction was left stirring under nitrogen for 12 hours after which time methyl iodide (200 mg, 1.40 mmol) was added. After 4 hours the mixture was concentrated and the residue adsorped onto silica, which was immediately purified by column chromatography (50/50; petrol ethyl acetate) to yield two products. The minor product proved to be the desired di-ene (76) (36 mg, 0.16 mmol).

IR (Liquid film): 3400-3080 (OH str), 1735 (C=O str)

MS (EI) m/z : MH^+ 226

N,N-Dimethyl-(4-methoxymethylcyclopent-2-enyl) acetamide



(36) (74)

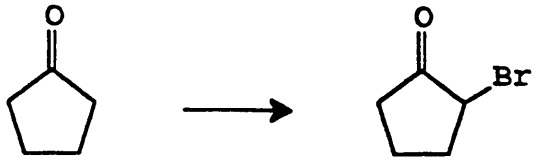
To the alcohol (36) (1.00 g, 7.09 mmol) was added dimethylacetamide dimethylacetal (5.26 g, 39.5 mmol) and o-xylene and this mixture was refluxed under nitrogen for 48 hours. The solution was then concentrated to yield the crude amide as an amber liquid (1.64 g) which was purified by column chromatography (90/10; ethyl acetate/ petrol). The pure amide (74) appeared as a clear, pale yellow liquid (1.15 g, 74%).

FT-IR : 2920, 2893, 2870, 2827,1649 (C=O str), 1396, 1111, 741

^{1}H NMR ($CDCl_3$) : 1.60 (m, 1H), 1.90 (m, 1H), 2.35 (m, 3H), 2.95 (s, 3H), 3.00 (s, 3H), 3.25 (m, 3H), 3.35 (s, 3H), 5.80 (m, 2H olefin)

MS (FAB) m/z : MH^+ 198

2-Bromocyclopentanone

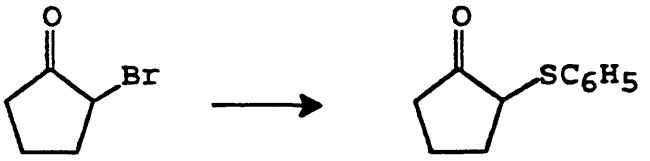


To a refluxing mixture of cyclopentanone (1.0 g, 11.9 mmol), chloroform (10 ml) and ethyl acetate (10 ml) was added over 2 hours, powdered cupric bromide (5.3 g, 23.8 mmol), allowing the green colouration produced to subside before the next addition. After a further 1½ hours the reaction was cooled to room temperature and filtered with the filter cake being washed with chloroform (10 ml). The filtrate was concentrated to give the crude alpha-bromoketone as a dark brown oil. This crude mixture was dissolved in ether (40 ml) and the organic layer washed with water (15 ml), 5% sodium bicarbonate (2 x 15 ml) and brine (15 ml), dried (Na_2SO_4) and concentrated to yield the crude bromoketone as a pale yellow liquid (1.23 g, 63%). This bromoketone was sufficiently pure for use in the next reaction of the proposed scheme 26.

IR (Liquid film): 1690 (C=O str)

^1H NMR ($CDCl_3$) : 2.0-2.55 (m, 6H), 4.15 (m, 1H)

2-Phenylthiocyclopentanone (70)



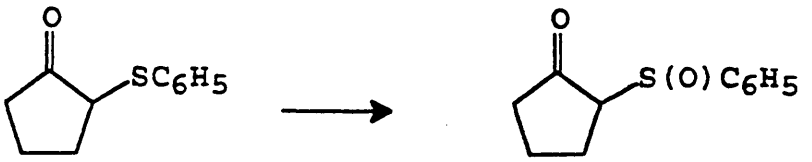
(70)

To dry ethanol (10 ml) was added metallic sodium (140 mg, 6.2 mmol) and the mixture stirred until complete disappearance of any solid. A solution of thiophenol (680 mg, 6.2 mmol) and dry ethanol (5 ml) was added dropwise. After ½ hour a solution of the bromoketone (1.01 g, 6.2 mmol) in dry ethanol (5 ml) was added slowly and the resultant mixture was left for 8 hours. The reaction mixture was poured into iced water (120 ml) and the aqueous phase extracted with ether (3 x 30 ml). The combined organics were washed with water (25 ml), 2N NaOH (25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated to produce crude (70) as a yellow oil (970 mg). Column chromatography (70/30; petrol/ethyl acetate) yielded pure (70) as a clear, colourless, pungent oil (870 mg, 73%).

IR (Liquid film): 3020-3080 (C-H str), 1690 (C=O str) 1580/1500 (C=C str)

^{1}H NMR ($CDCl_3$) : 1.85-2.50 (m, 6H), 3.50 (m, 1H), 7.15 (m, 5H)

2-Phenylsulphinylcyclopentanone (71)



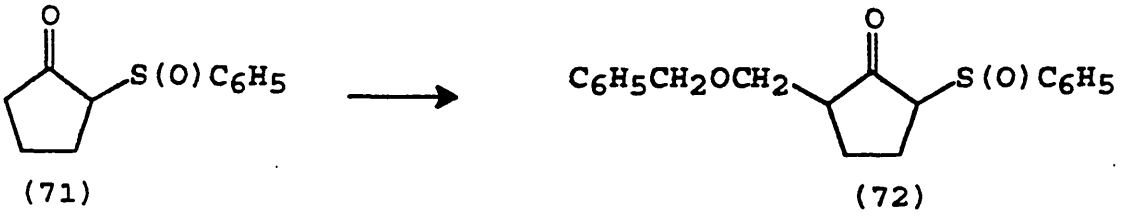
(70) (71)

To a mixture of sulphide (70) 10.6 g, 55.3 mmol) and methanol (125 ml) at 0^0 was added, over 20 minutes, a suspension of $NaIO_4$ (11.83 g, 55.3 mmol) in water (60 ml). After 48 hours at room temperature the reaction mixture was filtered and the filter cake washed with methanol (40 ml). The filtrate was concentrated and the residue dissolved in DCM (50 ml) which was then washed with water (2 x 25 ml). The combined aqueous portions were extracted with DCM (3 x 20 ml) and all the organic phases were dried ($MgSO_4$) and concentrated to give the crude sulphoxide as a deep red liquid (10.23 g). Column chromatography (90/10; ethyl acetate/petrol) yielded the sulphoxide (71) as a pale yellow solid which could be further purified by recrystalization (ethyl acetate/ petrol) to give a white solid (9.32 g, 81%).

IR (KBr Disc) : 3000-3080 (C-H str), 1700 (C=O str), 1590/1490 (C=C str)

^1H NMR ($CDCl_3$): 1.75-2.45 (m, 6H), 3.25 (m, 1H), 7.4 (s, 5H)

Attempted Preparation of 2-Benzyloxymethyl-5-Phenylsulphinylcyclopentanone (72)



(71) (72)

A flame dried flask was charged with diisopropylamine (320 mg, 3.17 mmol) and dry THF (3 ml) and the solution was cooled to -20^0 (dry ice/CCl_4). n-Butyllithium (2.0 ml, 3.17 mmol) was added dropwise and after a further 10 minutes a solution of the sulphoxide (71) (300 mg, 1.44 mmol), HMPA (260 mg, 1.44 mmol) and dry THF (3 ml) was added, slowly. After stirring for 30 minutes a mixture of the benzyloxymethyl chloride (240 mg, 1.50 mmol) in dry THF (2 ml) was added, dropwise and the reaction left for 4 hours. The mix was quenched with 2N HCl (10 ml) and the aqueous phase extracted with DCM (3 x 15 ml). The combined organics were dried (Na_2SO_4) and concentrated to yield a crude product whose NMR spectral analysis confirmed that starting materials only had been recovered.

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As part of this project the author has attended a Biochemistry lecture course at Sheffield University. Various research colloquia given by internal and external speakers at Sheffield Hallam, Sheffield University and the Wellcome Foundation have also been attended.

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