RADICAL REACTIONS IN ORGANIC SYNTHESIS

A Thesis

by

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Dedicated to my wife Blanca, and daughter Jessica

Chemistry Ph.D.

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ABSTRACT

The 4-substituted glutarimide required for the synthesis of sesbanimide (53) was obtained by free radical addition of iodoacetamide onto the α,β-unsaturated ester (81) mediated by tributyltin; the lactol ring C was prepared by the analogous free radical cyclization of the α-bromo-dipropargyl ketal 73.

The syntheses of tricyclic carbapenems involved appropriately substituted monocyclic azetidinone precursors. Free radical 5-exo cyclizations led to the relatively unstable benzo carbapenems 116, 119 and 120. The 6-exo mode, however, afforded stable benzo carbacephems 125, 127, 132 and 133.

β-Bromo- and α,α-dibromoazetidinones were converted stereoselectively to the α-alkylazetidinones 149 and 153, or to β-alkylazetidinones 151, 154 and 159 by a free radical addition onto olefins 148 or allyltributyltin.

Chimie Ph.D.

LES REACTIONS RADICALAIRES EN SYNTHESE ORGANIQUE

de

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RÉSUMÉ

La synthèse du sesbanimide (53) requiert la préparation d'un glutarimide substitué en position 4, lequel est préparé par l'addition radicalaire de l'iodoacétamide sur l'ester α,β-insaturé (81) en présence de tributyl d'étain. Une réaction radicalaire analogue, soit la cyclisation du cétal de l'α-bromodipropargyle sert à préparer le cycle C de ce produit.

Des précurseurs d'azétidinones monocycliques convenablement substitués sont nécessaires à la synthèse de carbapénèmes tricycliques. Les cyclisations radicalaire 5-exo ont donné les benzocarbapénèmes 116, 119, et 120, lesquels sont relativement instables. Par contre, les benzocarbacéphèmes stables 125, 127, 132 et 133 ont été obtenus à partir des cyclisations radicalaires 6-exo.

La synthèse stéréoselective des α-alcoylazétidinones 149 et 153 où des β-alcoylazétidinones 151, 154, et 159 à partir des azétidinones α-bromées et α,α-dibromées correspondantes est effectuée par addition radicalaire sur les oléfines 148 ou sur l'allyltributyl d'étain.

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GLOSSARY OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
b	broad
Bn	benzyl
bp	boiling point
Bu	butyl
t-Bu	tert-butyl
^{13}C nmr	carbon-13 nuclear magnetic resonance
cat	catalytic
cm	centimeter
d	doublet
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DDQ	2,3-dicyano-5,6-dichloroquinone
eq	equivalent
Et	ethyl
g	gram
h	hour
hplc	high performance liquid chromatography
^{1}H nmr	proton nuclear magnetic resonance
ir	infrared
J	coupling constant
M	Molar
m	multiplet
m-CPBA	meta-Chloroperbenzoic acid

MBn	para-Methoxybenzyl
Me	methyl
min	minute
ml	milliliter
mp	melting point
mmol	millimole
ms	mass spectra
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-BrPh	ortho-Bromophenyl
Ph	phenyl
ppm	parts per million
q	quartet
s	singlet
sec	second
t	triplet
THF	tetrahydrofuran

TABLE OF CONTENTS

PREFACE

The formation of carbon-carbon bonds is regarded as the core of organic synthesis. Such processes are almost invariably performed by a "two electron" union of nucleophiles and electrophiles. With exception of biradical processes such as possibly the Diels - Alder[1] or photochemical cycloaddition reactions, the free radical "one electron" method of forming carbon-carbon bonds in organic synthesis was extremely rare until a decade ago.

Radical reactions are widespread in occurence and very important. For instance, most reactions initiated by light such as photosynthesis involve radicals. Most halogenations, explosions, combustions, polymerizations and pyrolyses are radical processes. Free radical reactions occur in most cases at a diffusion-controlled rate and are still viewed by many organic chemist to be an unpredictable, uncontrollable and essentially an unreliable reaction for use in a multistep synthesis of a complex natural product.

Within the last five years, the use of free radicals in organic synthesis has been rapidly expanding. This is mainly due to the developments of free radical chain processes mediated by metals. Carbon radicals can be generated under mild conditions from a variety of functional groups and attack alcohols, amines and carboxyl groups so slowly that these functionalities can be tolerated without protection. Carbon radicals also exhibit high chemo- and regioselectivity. Furthermore, chiral centers adjacent to radicals easily

survive. β-Scissions of radicals are less pronounced than those of anions, and radical rearrangements are less common than those of cations.

In this dissertation, chain reactions mediated by tributyltin radical are applied towards some model studies in the synthesis of a natural antitumor compound, Sesbanimide A (Chapter II), and towards the stereoselective synthesis of highly strained tricyclic azetidinones (Chapter III), and 6-alkylpenicillanates and monocyclic 3-alkylazetidinones (Chapter IV). In the last chapter, an interesting correlation that was observed on examining the proton and carbon-13 spectra of some cis- and trans-azetidinones is described.

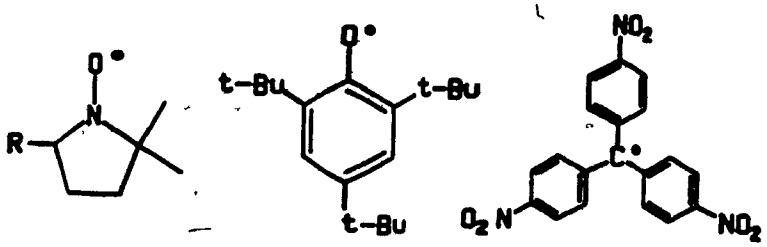
CHAPTER I : INTRODUCTION

Definition of a free radical

A free radical is an atom or molecule which possesses one or more unpaired electrons. Such species may be monoatomic such as halogen atoms or alkali metals and certain metallic ions (1) or organic molecules in which an unpaired electron can be

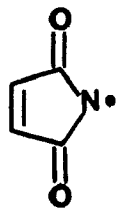
$$Cl\cdot \quad , \quad Br\cdot \quad , \quad Na\cdot \quad , \quad Li\cdot \quad , \quad R_2B\cdot \quad , \quad Fe^{3+} \quad , \quad Cu^{2+} \qquad (1)$$

can be located at a carbon or heteroatom site (2). Free radicals with an unpaired electron on phosphorus, sulfur, and



(2)

nitrogen are known, as well as free radicals from trisubstituted group IV metal compounds (equation 3). These examples are just illustrative of a variety of species which are classified as free radicals.

$$(EtO)_3\overset{O}{\overset{\|}{P}}\cdot \quad , \quad t\text{-}BuS\cdot \quad , \quad R_3Sn\cdot \quad , \quad R_3Ge\cdot \quad , \quad \text{  } \qquad (3)$$

History of Free Radicals

The term "free radical" was first introduced by Lavoisier[2] in 1789, denoting a group of atoms that retained their identity through a series of chemical reactions. In the early 1800's this term was modified to describe part of a molecule which was also capable of independent, separate existence, i.e., the methyl moiety in the ethane molecule. This term took reality when Davy et. al.[3] claimed the preparation of the ammonium radical in 1810, and Gay-Lussac[4] in 1815 discovered cyanogen which was thought to be a free radical (CN). Kolbe[5], in the electrolyses of fatty acids in solution obtained gases which were interpreted to be free radicals (equation 4). Frankland[6] also obtained a gas which he believed to be "free ethyl" by reacting ethyl iodide with zinc in a sealed tube (equation 5). By the mid nineteenth century, other radical

$$2\ C_2H_4O_2 + H_2O \longrightarrow \underset{\text{"Free methyl"}}{2\ CH_3} + 2\ CO_2 + H_2 \qquad (4)$$

$$C_2H_5I + Zn \longrightarrow \underset{\text{"Free ethyl"}}{C_2H_5} + ZnI \qquad (5)$$

species such as cinnamyl, cetyl, cacodyl and benzoyl were also claimed to have been isolated. However, by 1860, when gas-density measurements could be accurately determined for establishing molecular weights, it was realized that species assumed to be radicals were actually molecules. For example, reactions thought to have produced free methyl or ethyl radicals (equation 4 and 5), were identified as ethane or butane

respectively. In fact, the above experiments most likely did produce the claimed radicals as transient species, but because of their short lifetimes they were not detected and and only their dimers were isolated.

With the advent of the valence theory around 1860, most chemist became convinced of the quadrivalency of the carbon atom, bringing to a halt any further attempts to isolate or detect organic free radicals throughout the end of the nineteenth century.

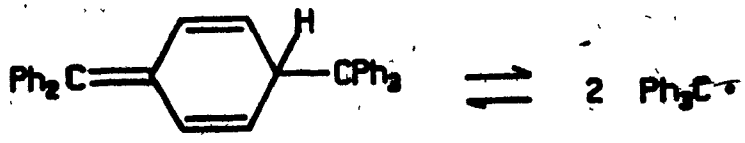
At the turn of the century, the re-discovery of free radicals came about by accident. Moses Gomberg[7], a Russian-born chemist working at the University of Michigan in 1900, reported the unexpected existence of the trityl radical when he attempted to prepare hexaphenylethane from the reaction of triphenylmethyl chloride with either silver or zinc dust in benzene (equation 6). Instead of the stable hexaphenylethane expected, he obtained a yellow solution which reacted rapidly with air (oxygen), iodine and other reagents resulting in decolorization of the solution.

$$Ph_3C\text{-}Cl + Ag^0 \longrightarrow Ph_3C^{\bullet} + AgCl \quad (6)$$

However, when the trityl radical was isolated in the pure form as colorless crystals, it was found to have a molecular weight corresponding to hexaphenylethane. Since cleavage of carbon-carbon bonds by mild reagents such as oxygen or iodine was considered highly unlikely, Gomberg concluded that hexaphenylethane dissociated into free radicals in solution. This conclusion was not easily accepted by chemists in general, but was amply supported by subsequent work. Picard[8] showed that the yellow solution obtained did not follow Beer's law, the colour deepening with dilution. Wieland[9] in 1911, prepared tetraphenylhydrazine which also was claimed to dissociate in solution (equation 7).

$$Ph_2N\text{-}NPh_2 \rightleftharpoons 2\ Ph_2N\cdot \qquad (7)$$

Only recently[10] (1968) has the structure of the trityl dimer been reinvestigated and found not to be hexaphenylethane, but instead compound 1 in equilibrium with the trityl radical, with $K = 2 \times 10^{-4}$ M in benzene at room temperature. Interestingly, Gomberg's original task of preparing hexaphenylethane, it seems, has never been accomplished.



1

Transient free radicals were beginning to be proposed as intermediates in many reactions throughout the next few decades mainly as a result of Paneth and Hofeditz's work[11] in 1929 when they demonstrated the existence of transient alkyl radicals in the gas phase. When tetramethyllead was passed down a heated tube with a stream of nitrogen, a mirror of lead deposited at the point where the tube was heated (point a, see Figure 1) and ethane gas was produced. However in the presence

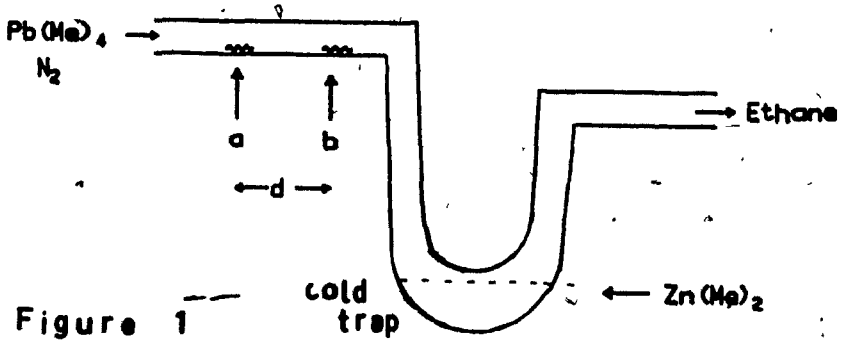


Figure 1

of a zinc mirror at point b somewhat downstream from the point of heating, the zinc mirror was gradually removed producing dimethylzinc (equation 8). By varying the distance between point a and b, the lifetimes of the alkyl radicals were deduced to be around 10^{-3} sec at 2 mm Hg.

$$Pb(CH_3)_4 \longrightarrow 4\ CH_3\cdot + Pb \longrightarrow 2\ CH_3CH_3 \qquad (8)$$
$$\downarrow\ 2\ Zn$$
$$2\ Zn(CH_3)_2$$

In a review in 1937, Hey and Waters[12], explained the products of a range of reactions in solution by free radical mechanisms. During the same year, Kharasch and Mayo[13] rationalized the anti-Markovnikov addition of hydrogen bromide to unsaturated hydrocarbons by postulating that they underwent an addition by a free radical chain process in the presence of light or peroxides (Scheme 1). The production of bromine

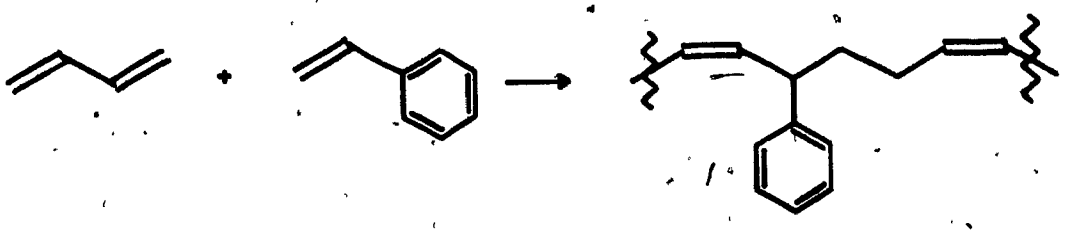
$$HBr \longrightarrow Br\cdot$$

$$Br\cdot + CH_2{=}CHCH_2Br \longrightarrow BrCH_2\dot{C}HCH_2Br$$

$$HBr + BrCH_2\dot{C}HCH_2Br \longrightarrow BrCH_2CH_2CH_2Br + Br\cdot$$

Scheme 1

radicals induced by light or the decomposition of peroxide, initiated a chain sequence which was a prototype of what was to become known as a free radical chain reaction. Also in the same year, Flory[14] proposed a radical mechanism for the addition polymerization process and described the kinetics of radical polymerization of vinyl monomers. The development[15] of synthetic polymers during the second world war, such as synthetic rubber from styrene and butadiene (equation 9), the invention of Neoprene (equation 10), polyethylene and other plastics, made free radical chemistry achieve industrial importance. However, during the 1930-1950 period, free radicals were not universally accepted as respectable reaction intermediates.



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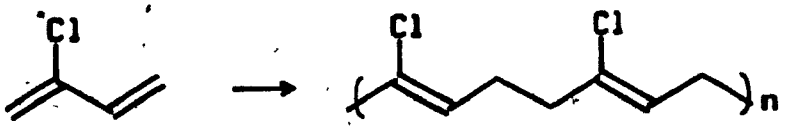

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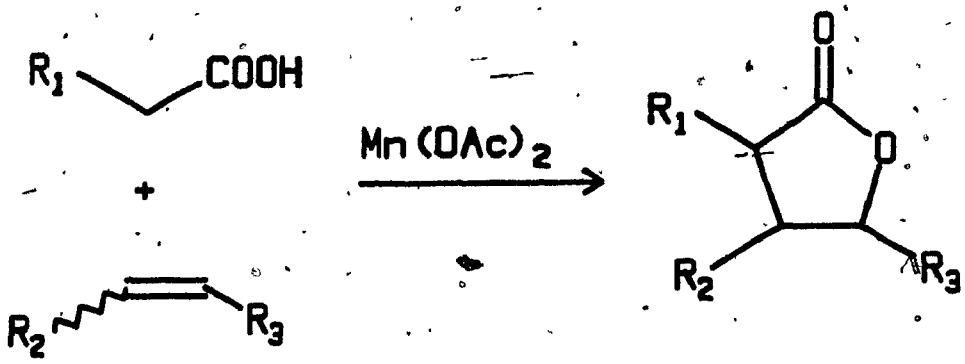
The advent of spectroscopic methods, especially electron spin resonance spectroscopy (ESR), proved beyond any reasonable doubt the existence of transient free radicals even with life-times as short as micro or nano seconds.

Since the 1950's, with the availability of ESR spectroscopy, the field of radical chemistry has received renewed attention. Novel systems for the free radical carbon - carbon bond formation using metals such as tributyltin hydride[16] (equation 12) or redox reactions using transition metals such as manganese[17] (equation 11) have been developed. Although free radical chain reactions have thus been known for many years, their application in organic synthesis has only recently been exploited.



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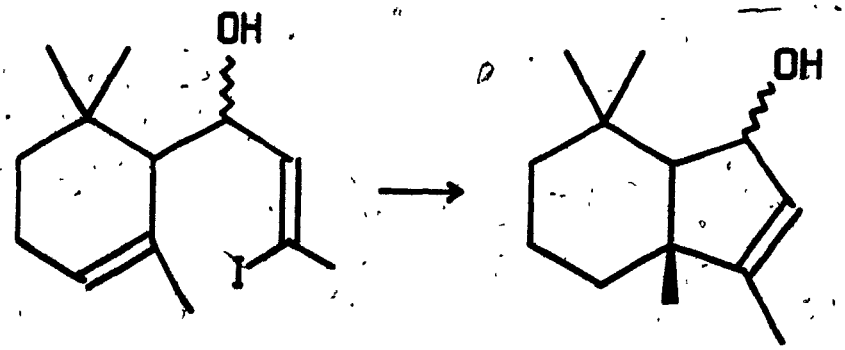

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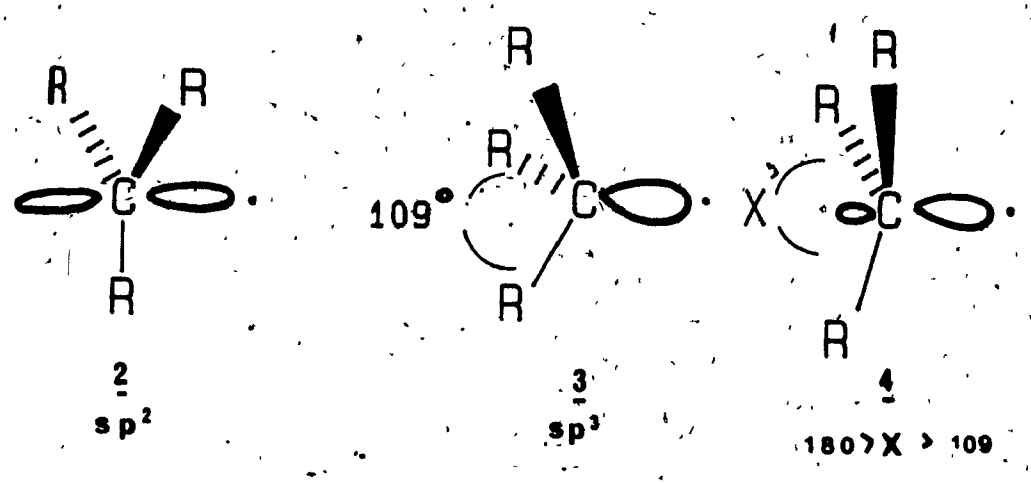
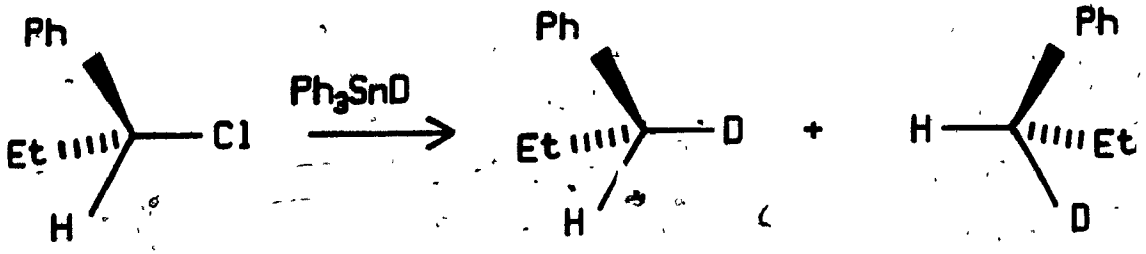
Structure of Alkyl Free Radicals

Several stable conformations for an organic free radical can be envisioned. The central carbon atom could be planar (sp^2), similar to a carbonium ion, with an additional unpaired electron occupying the p_z-orbital (2). Alternatively, it could adopt a tetrahedral structure (3) similar to carbanions (sp^3), or a shallow pyramidal structure in which the unpaired electron contains some s character, that is a hybrid between the p and sp^3 geometry (4). This latter structure would result in a dissymmetric distribution of electron density.



Chemical methods have undoubtably shown that formation of radicals in an assymmetric molecule results in epimerization[18] (equation 13), which is consistent with either a planar (2) or a shallow pyramidal structure with rapid inversion (equation 14).



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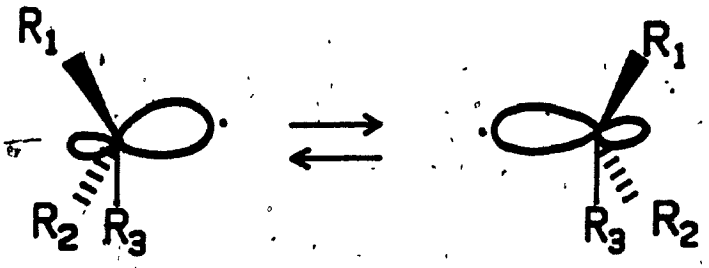

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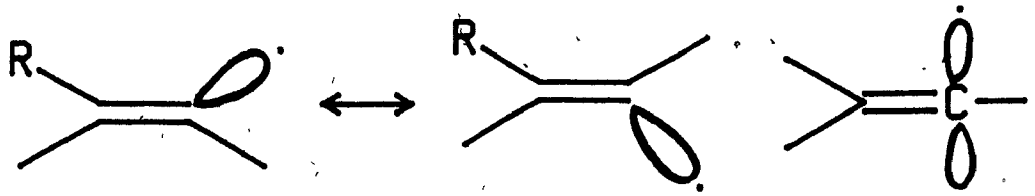
ESR and IR spectroscopic studies have demonstrated that the simple methyl radical possesses a planar or very shallow pyramidal structure at low temperature with about a 5° deviation from planarity, and that the energy barrier between the planar and the shallow pyramidal structure is very low[19]. Substitution of the hydrogens with alkyl substituents favours the adoption of the shallow pyramidal structure. The geometry of the radical is further affected by electronegative groups such as fluorine and oxygen, which can stabilize the radical by π-donation. Increasing the number of fluorine substituents on the central carbon radical, for example, results in a progressive increase of distortion from planarity.

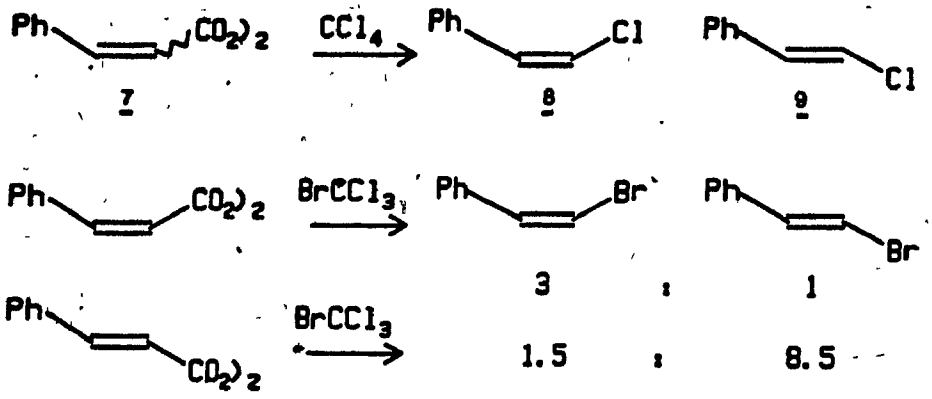
Structure of vinylic Radicals

Vinylic radicals can either adopt a bent geometry with the unpaired electron in a sp^2 orbital (5), or a linear structure with the odd electron in a p-orbital (6).



5 6

ESR studies[21] are consistent with the bent geometry and the possibility of rapid inversion of the two isomeric radicals (5), the barrier of inversion being ca. 8 KJ/mole. Experimental studies[22,23] confirm rapidly inverting bent structures. For instance, heating either cis- or trans-dicinnamoyl peroxide 7 in carbon tetrachloride give the same mixture of E and Z - chlorostyrene 8 and 9. This can be explained by involvement of either a planar or rapidly inverting bent intermediate radical. When bromotrichloro methane is used as the solvent (scheme 2), the ratio of the products is slightly different for the cis or trans precursors. The latter can only be rationalized by postulating that the reaction of the bent radical intermediate with the more reactive bromotrichloromethane competes with inversion of the radical intermediates 5 (R = Ph).



Scheme 2

Stability of organic radicals

In the free radical halogenation of alkanes, the ease of hydrogen abstraction to give the alkyl radical follows the order $CH_4 < 1^o < 2^o < 3^o$. The experimental activation energies[24] E_{act} (Table 1) indicate a decrease in E_{act} paralleled by an increase in the rate of reaction in this series. The bond dissociation energies[25] also decrease with decreasing activation energy (Table 2).

The above order for the ease of formation can be rationalized by assuming that the radical Y is more nucleophilic than a simple alkyl radical and that the polar factor plays a role in stabilizing the transition state by way

Table 1 Energies of Activation, Kcal/Mole

$$R{-}H + X\cdot \longrightarrow R\cdot + H{-}X$$

R	X = Cl	X = Br
CH_3	4	18
1°	1	13
2°	0.5	10
3°	0.1	7.5

Table 2 Bond-Dissociation Energies (kcal/mol)[a]

Bond	D.E	Bond	D.E.
$CH_3{-}H$	104	$HOCH_2{-}H$	92
$CH_3CH_2{-}H$	98	$CH_3\overset{O}{\overset{\|}{C}}CH_2{-}H$	92
$(CH_3)_2CH{-}H$	94.5	$N{\equiv}CCH_2{-}H$	86
$(CH_3)_3C{-}H$	91	$CH_3\overset{O}{\overset{\|}{C}}O{-}O\overset{O}{\overset{\|}{C}}CH_3$	30
$CH_2{=}CH{-}H$	104	$(CH_3)CO{-}OH$	44
$CH_2{-}CH{-}H$ (cyclopropyl)	101	$F{-}F$	38
$PhCH_2{-}H$	85	$Cl{-}Cl$	58
$CH_2{=}CHCH_2{-}H$	85	$Br{-}Br$	46
$F_3C{-}H$	106	$I{-}I$	36
$Cl_3C{-}H$	96	$H{-}F$	136
$C_2H_5{-}F$	106	$H{-}Cl$	103
$C_2H_5{-}Cl$	81	$H{-}Br$	87.5
$C_2H_5{-}Br$	69	$H{-}I$	71
$C_2H_5{-}I$	53		

a. Data taken from J. A. Kerr, *Chem. Rev.* 66, 465 (1966), and S. W. Benson, *J. Chem. Ed* 42, 502 (1965).

of contributing structures (equation 15). Therefore, the greater stabilizing ability of the R group results in a lower amount of energy needed to form the radical.

$$R\text{-}X \quad + \quad Y\cdot \longrightarrow \left[R^{\delta+} \cdots\cdots X \cdots\cdots Y^{\delta-} \right] \qquad (15)$$

X = H , Cl, Br etc...

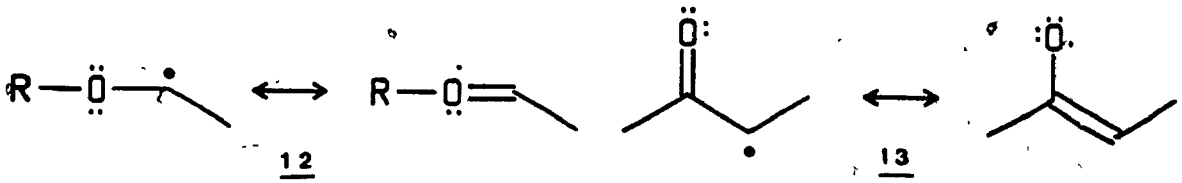
The stabilities of carbon centered radicals follow the same order as that of carbocations (16), the vinyl and aryl radicals being the least stable with very short half-lives (10^{-10} to 10^{-8} sec). Stability of radicals then increases with the

$$Ph\cdot\ ,\ CH{=}CH\cdot \ <\ CH_3\cdot \ <\ R_1CH_2\cdot \ <\ R_2CH\cdot \ <\ R_3C\cdot \ <\ RCH{=}CH{-}\dot{C}HR \ <\ RC{\equiv}C{-}\dot{C}H_2 \qquad (16)$$

number of substituents. Allyl and benzyl radicals are stabilized by π-conjugation. A noteworthy exception is in the propargyl radical, which is found to be 4.5 times more stable than the allyl radical, the ethynyl group with its sp hybridization being more electron attracting than the vinyl group (sp^2).

Heteroatom substituents such as oxygen 12 or halogens also stabilize radicals to some degree through π-donation.

Electron withdrawing alpha substituents such as carbonyl (13) and thiocarbonyl functions or nitriles are also known to stabilize the radical through π- resonance. Furthermore radicals are extremely stabilized by adjacent electron withdrawing and electron releasing functions in molecules such as 14. This mutual reinforcement of the two substituent effects on the radical is known as capto-dative stabilization[26].



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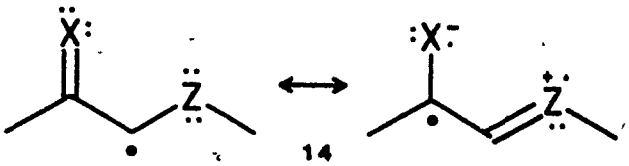
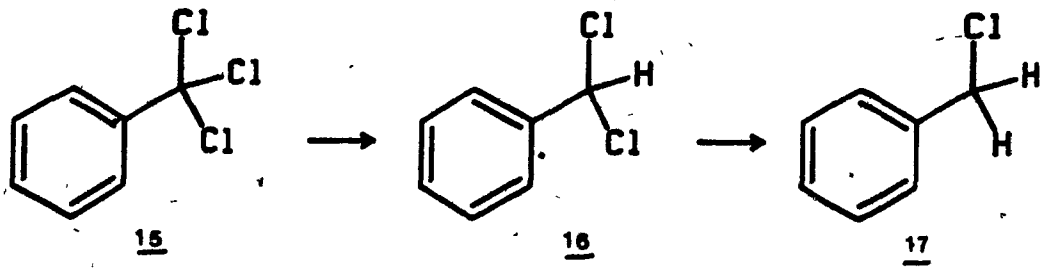


14

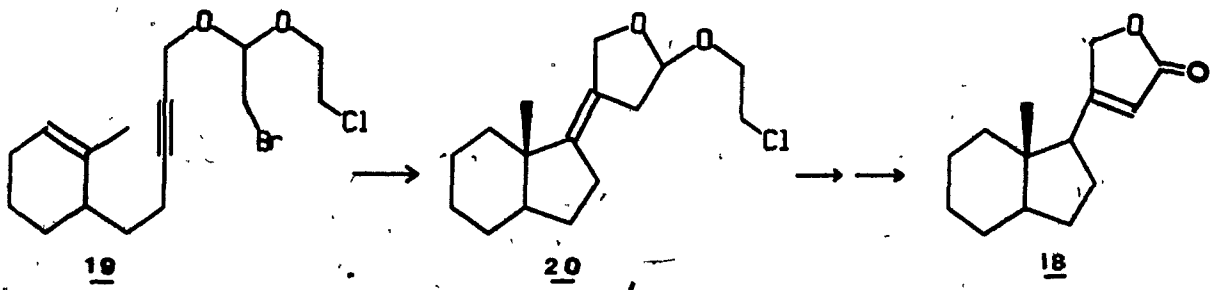
The ease of radical formation is also dependent upon the nature of the covalent C-X bond to be broken. In the carbon-halogen series, the bond dissociation energy decreases along the series chlorine, bromine and iodine (Table 2), and thus a lower amount of energy is needed to form the alkyl radical in this series. For instance, the tributyltin radical abstracts the halide atom from n-butyl chloride at 120°C, from n-butyl bromide at 80°C and from n-butyl iodide at 40°C.

From a synthetic point of view, the various substituent effects on the generation of an organic radical can lead to very useful applications. For example, benzotrichloride 15 can be reduced stepwise to benzal chloride 16 and to benzyl chloride 17 with tributyltin hydride[27].



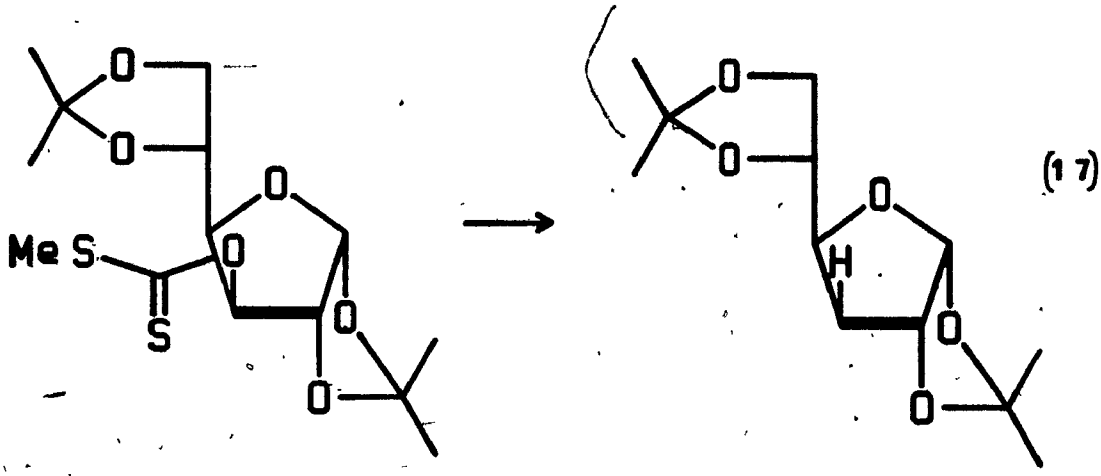
15 16 17

A more elegant example is the synthesis of butenolide 18. The tributyl tin radical abstracts the bromine from 19 at 80°C, leaving the less reactive carbon-chlorine bond intact. The alkyl radical formed then undergoes intramolecular cyclizations to give the tricyclic compound 20, which is then transformed to the butenolide by standard methods[28].



19 20 18

Organic free radicals can also be generated from other compounds such as xanthates, imidazolylthiocarbonates, thiophenols, thiopyridines, and nitro alkanes (equations 17 to 19) at different rates, making free radical reactions highly chemoselective[29,30,31].



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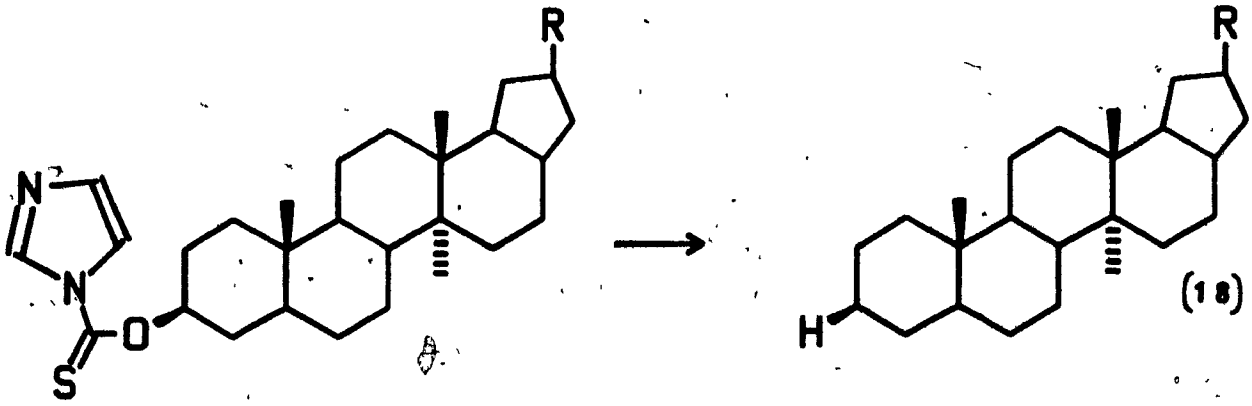

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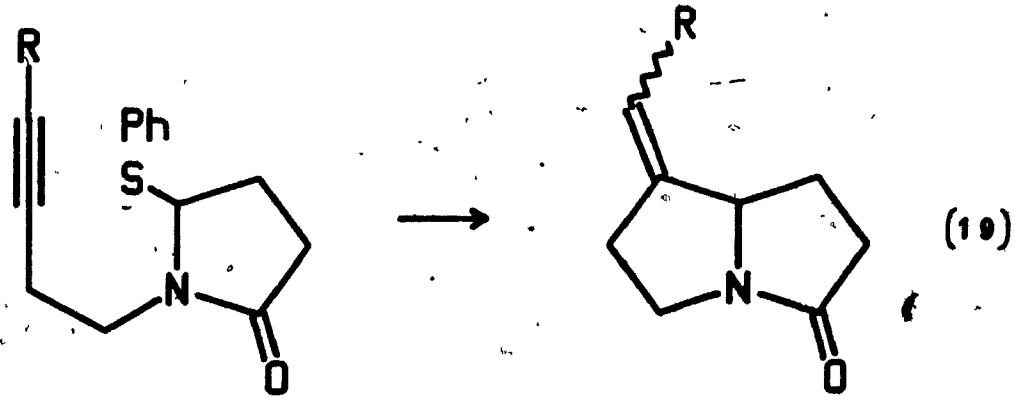


(19)

Catalytic Chain Reaction

There are two types of initiations of a free radical chain reaction (equation 20 and 21): the free radical reaction which is generated by the homolysis of a covalent bond and, less commonly, by an electron transfer process (Redox reactions).

$$A\text{-}B \longrightarrow A^{\bullet} + B^{\bullet} \qquad (20)$$

$$A\text{-}B + e \longrightarrow A^{\bullet} + B^{-} \qquad (21)$$

Homolysis by thermal or photochemical reactions

A free radical chain reaction involves the generation of a catalytic amount of radicals from an initiator, a series of propagation steps and finally, termination by coupling or disproportionation (equation 22 to 26).

$$In \longrightarrow A^{\bullet} \qquad (22)$$

$$A^{\bullet} + B\text{-}C \longrightarrow A\text{-}B + C^{\bullet} \qquad (23)$$

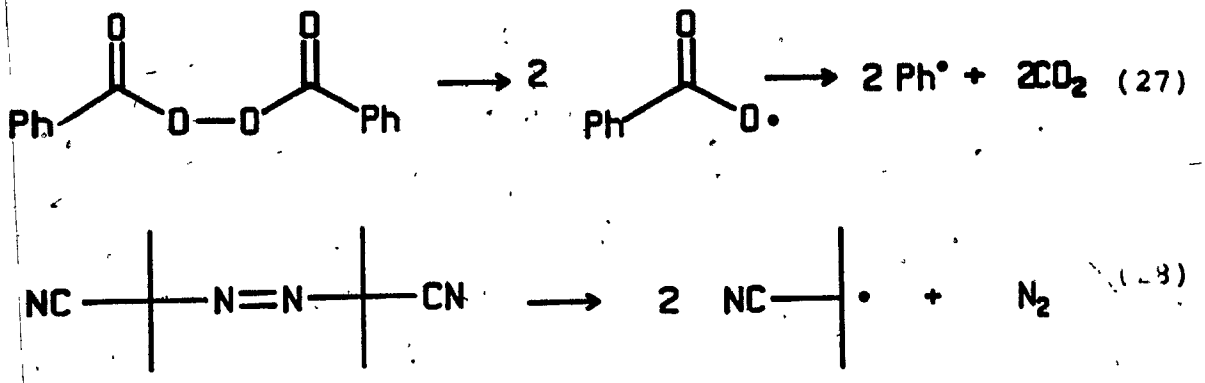
$$C^{\bullet} + B\text{-}C \longrightarrow C\text{-}B + C^{\bullet} \qquad (24)$$

$$C^{\bullet} + D{=}E \longrightarrow C\text{-}D\text{-}E^{\bullet} \qquad (25)$$

$$C^{\bullet} + C^{\bullet} \longrightarrow C\text{-}C \qquad (26)$$

The radicals are generated by the absorption of energy either by photolysis at ambient temperature or by the thermal decomposition of initiators. Radical initiators contain a weak oxygen-oxygen linkage such as benzoylperoxide (equation 27), or

contain an azo moiety such as azobisisobutyronitrile (equation 28) which decomposes into nitrogen and alkyl radicals.



There are a variety of initiators that generate radicals thermally at or above room temperature, and it is practical to choose a compound with a half-life comparable to the reaction time at the temperature needed. Figure 2, shows a plot of half-life versus temperature for some commonly used initiators[32].

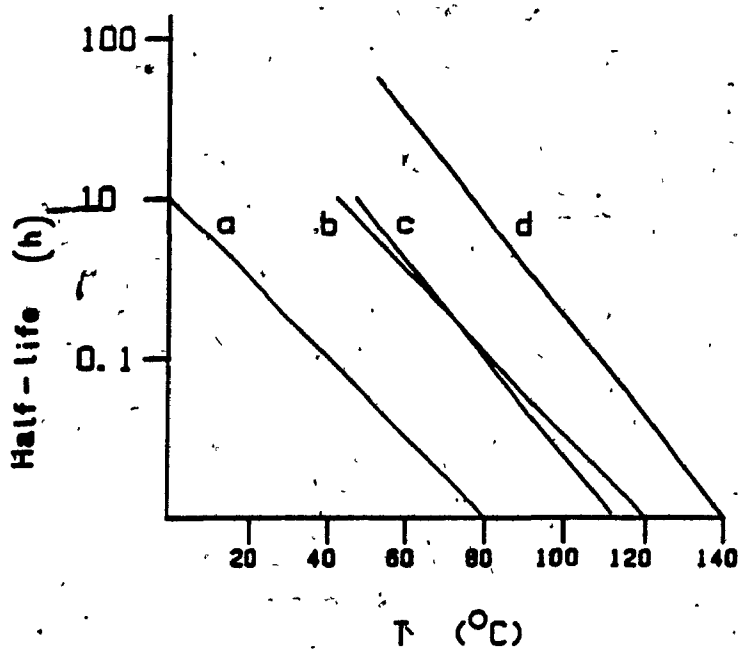


Figure 2. Half-lives for the decomposition of some common initiators. (a) di-t-bu peroxyoxalate; (b) AIBN; (c) $S_2O_8^{2-}$; (d) Benzoyl peroxide

A wide variety of radical propagators are used, such as the bromine radical in the bromination of an alkene (page 8) or the tin radical (Sn·) in the cyclization of an alkylhalide (equation 12). In the formation of carbon-carbon bonds, the halogen, nitrogen, phosphorus and most organosulfur radicals cannot be used since they react with carbon radicals to give an adduct. However other free radical chain propagators such as organosilicon[33] ($R_3Si·$), organogermanium[34] ($R_3Ge·$), organotin[16] ($R_3Sn·$), organolead[35] ($R_3Pb·$), or t-butyl sulfur [36] do not usually interfere by adduct formation with carbon radicals and behave ideally as intermediates.

The overall reaction of the free radical process involving an alkylhalide and an organometallic hydride to give the corresponding reduction product and organometallic halide is given in equation 29.

$$R\text{-}X + M\text{-}H \longrightarrow R\text{-}H + M\text{-}X \qquad (29)$$

The bond dissociation energies for group IV organometallic compounds[36] are shown in Table 3. Focussing on the difference in dissociation energy between the metal-hydride and metal-halide bonds, it can be seen that there is a favourable enthalpy change for reactions involving the organogermanium, organotin or organolead. However, it is less pronounced for organosilicon. The temperature required for the reaction in equation 29 to proceed is about 60 to 80°C for tin, germanium

or lead, and about 160-170°C for silicon. Furthermore the corresponding organosilyl halides are

Table 3. Bond dissociation energies*, Me_3M-X, (Kcal/mol) of compounds Me_3MX.

X	M				
	C	Si	Ge	Sn	Pb
H	105	90	82	74	62
Br	71	94	104	85	-
Cl	84	111	116	101	-
OH	92	126	-	110	-

* Data obtained from reference 36.

strong Lewis acids, which are known to cleave quite resistant functional groups such as ethers or esters at high temperature[37]. However, if the above reactions (equation 29) are performed at ambient temperature by photolysis, then organosilanes can be very practical. The organogermanium and organolead hydrides are considerably more expensive than organotin hydrides and have not been studied very extensively. The most commonly used reagents for the free radical chain reactions in organic synthesis are thus trialkyltin hydrides, and they are the only metal hydrides used in the present work.

The first report[38] on the reduction of an alkyl halide with an organotin hydride appeared thirty years ago. It was

soon followed by several mechanistic investigations[39], and it is now accepted that this reduction proceeds by a free radical chain process. A typical free radical chain cycle is depicted in Figure 3. A catalytic amount of initiator (usually AIBN) abstracts a hydrogen radical from tributyltin hydride generating the tributyltin radical species 21. The tin radical then abstracts a bromine radical from the alkyl halide 22 resulting in the formation of the organic radical 23 which in turn can do either of the following: it can abstract a hydrogen radical from tributyltin hydride to give the reduction product 24 and regenerate the tin radical species 21. Alternatively, if an unsaturated moiety such as 25 is present, the organic radical can undergo an intramolecular cyclization yielding the organic radical 26. Abstraction of a hydrogen radical from tributyltin hydride gives the cyclic product and regenerates the tin radical species 21.

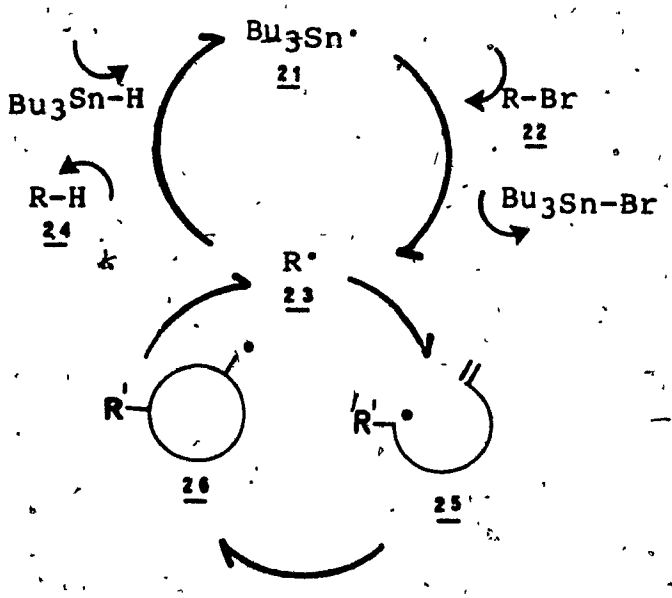


Figure 3

The former pathway leading to reduction 24 will be favoured by a high concentration of tributyltin hydride (< 0.1 M). If the cyclized product is desired, low concentration (0.02 M R_3SnH) and/or very slow addition of tributyltin hydride will favour the intramolecular cyclization as the predominant pathway.

Redox reactions

A redox reaction involves an oxidation-reduction process generally of a transition metal such as cobalt[40], silver[41], copper[42], mercury[43] or manganese[17]. A typical example is the use of cobaloxime as the catalyst (Figure 4). The Co^{1+} 27 generates the organic radical 28 and is oxidized in the process to the Co^{2+} state. The organic radical may undergo various propagation processes and then finally abstracts a hydrogen radical from the solvent. The Co^{2+} species is then reduced with sodium borohydride back to its original Co^{1+} valency. Since the organic synthetic chemist usually prefers mild conditions, these redox type reactions are not as popular as the free radical chain reactions discussed previously.

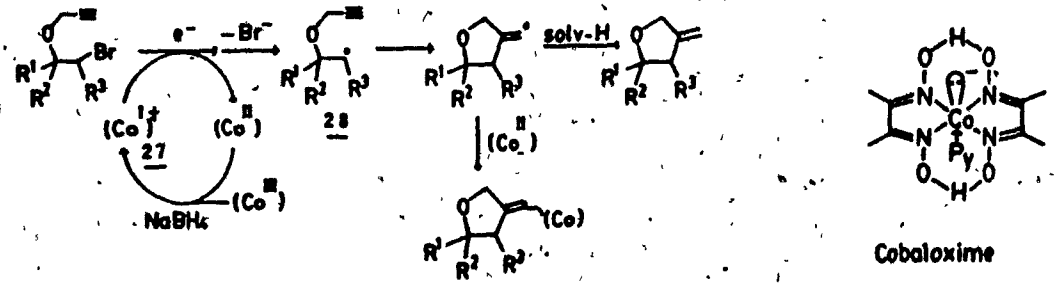


Figure 4

Kinetic analysis of the free radical chain reaction

Using 1-bromohex-5-ene and tributyltin hydride with catalytic AIBN , the kinetic analysis of a typical free radical chain reaction can be easily derived from the sequence below[44] (equation 30 to 35).

Initiation:

$$\text{AIBN} \xrightarrow{k_1} \text{In}\cdot$$

$$\text{In}\cdot + \text{Sn-H} \xrightarrow{k_2} \text{In-H} + \text{Sn}\cdot \qquad (30)$$

Propagation:

$$\text{Sn}\cdot + \text{Br-R} \xrightarrow{k_3} \text{Sn-Br} + \text{R}\cdot \qquad (31)$$

$$\text{R}\cdot + \text{Sn-H} \xrightarrow{k_4} \text{Sn}\cdot + \text{R-H} \qquad (32)$$

$$\text{R}\cdot \xrightarrow{K_5} \text{R'}\cdot + \text{Sn-H} \xrightarrow{k_4} \text{Sn}\cdot + \text{R'-H} \qquad (33)$$

Termination:

$$\text{Sn}\cdot + \text{Sn}\cdot \xrightarrow{k_t} \text{Sn-Sn} \qquad (34)$$

$$\text{R}\cdot + \text{R}\cdot \xrightarrow{k_t} \text{R-R} \qquad (35)$$

The overall rate of reaction can be expressed as:

$$\text{rate} = -\frac{d[\text{AIBN}]}{dt} = \frac{d[\text{Sn-Br}]}{dt} = \frac{-d[\text{R-Br}]}{dt} = \frac{d[\text{Sn-H}]}{dt} \qquad (36)$$

Assuming a steady state approximation, the rate of initiation can be set to equal the rate of termination, and assuming equation 35 to be the dominant rate constant for termination we obtain:

$$k_1[\text{AIBN}] = k_t[\text{R}\cdot]^2 \qquad (37)$$

At a low concentration of tributyltin hydride, the intramolecular cyclization (k_5) is favoured and the rate determining propagation step becomes k_4.

$$\text{rate} = k_4 [\text{Sn-H}] [\text{R}\cdot] \qquad (38)$$

substituting [R·] in equation 38 with 37, gives

$$\text{rate} = k_4 [\text{Sn-H}] \frac{k_1}{k_t} [\text{AIBN}] \qquad (39)$$

in which the overall rate is proportional to the square root of the rate of chain initiation and thus not very sensitive to the initiator concentration.

For carbon radicals, the rate constant for termination in most cases is diffusion controlled, with $k_t = 10^9\ M^{-1}\,sec^{-1}$. Usually the radical concentration during the chain reaction (propagation steps) initiated by the catalytic amount of AIBN is *ca.* 10^{-6} mole/l and inserting these values in equation 40,

$$\frac{\text{rate of propagation}}{\text{rate of termination}} = \frac{k_4 [\text{Sn-H}] [\text{R}\cdot]}{K_t [\text{R}\cdot]^2} > 1 \qquad (40)$$

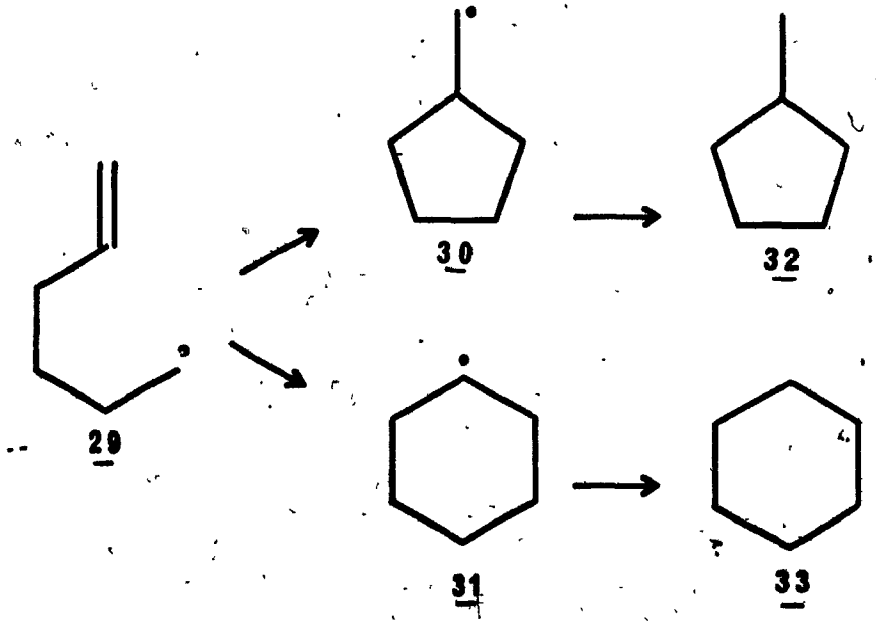
$$K_4 > \frac{(10^9)\ (10^{-6})^2}{(10^{-2})\ (10^{-6})} > 10^3\ M^{-1}sec^{-1}$$

it can be estimated that k_4 must be greater than $10^3\ M^{-1}\text{-}sec^{-1}$. Usually, k_4 and k_5 are far greater ($10^6\ M^{-1}\text{-}sec^{-1}$). Furthermore, since the homolysis of aliphatic amines (N-H) , alcohols

(O-H) and carbonyl moieties takes place with rate k smaller than 10^2 M^{-1}-sec^{-1} (at room temperature), these functionalities are attacked so slowly by carbon radicals, that they need not be protected during the cou se of the reaction which is invaluable in organic synthesis.

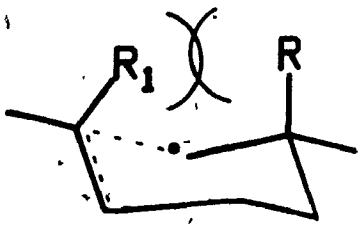
Intramolecular ring closure

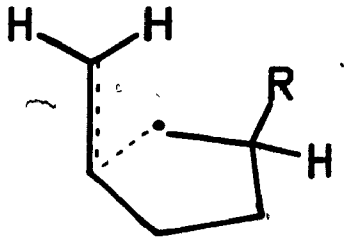
The ring closure of the hexenyl radical[45] 29 can result in the formation of the methylcyclopentane radical 30 (5-exo addition) and/or in the formation of the cyclohexane radical 31 (6-endo ring closure). Thermodynamically, the secondary radical 31 is more stable than the primary radical 30. However, the major product obtained at 80°C is methylcyclopentane[45] (32/33 = 98/2). Futher investigation revealed that the mode of ring closure was irreversible under these conditions and that no resonance hybrid was involved[46], ie. that 30 and 31 are discrete species.



The 5-exo-process proceeds in a highly regioselective fashion to give the thermodynamically less stable product. Several explanations for this have been put forward. Baldwin's vector approach analysis[47] indicates that the trajectory for the incoming radical onto the unsaturated moiety to give the ring closure, will proceed through the least amount of distortion in bond angle and distance. Accordingly, for the cyclization onto a double bond (trigonal system), the 3 and 4 endo-mode is disfavoured whereas the 3 to 7 exo- processes as well as the 5 to 7 endo-processes are favoured. However, the exo-mode of addition predominates over the endo-process. For cyclization onto a triple bond (digonal system), the 3 to 5 endo-modes are disfavoured and so are the 3 to 4 exo-modes. The 5 to 7 exo- and the 6 and 7 endo-modes are favoured and the exo-mode of addition predominates over the endo-process.

A second explanation has been provided by Julia[48]. In this hypothesis, he considered the most favourable transition state for ring formation of the two radical intermediates 34 and 35. The unfavourable non-bonding interaction between the pseudo-axial proton at C-2 and the syn-proton at C-6 should destabilize the transition state 34 with respect to 35,

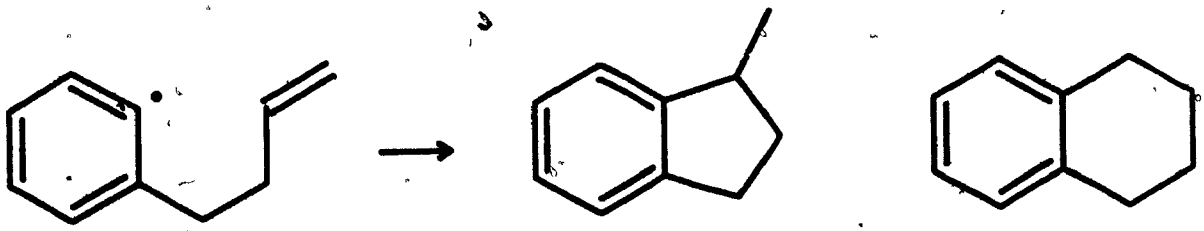




34 R = H
36 R = CH_3

35

resulting in a more favourable 5-exo-cyclization. Further support for this is the cyclization of the radical **36** where the syn-methyl group induces severe non-bonded interactions affording only the 5-membered product[49]. However, the cyclization of the alkenylaryl radical **37**, in which there is no pseudo-axial proton at C-2 in the transition state, gives regiospecifically formation of the 5-exo product[50].



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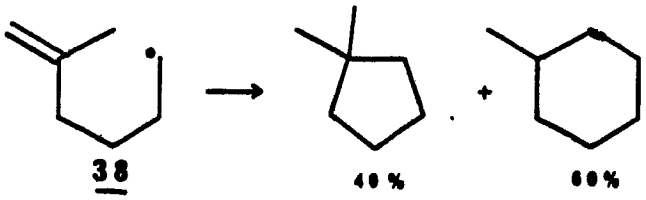
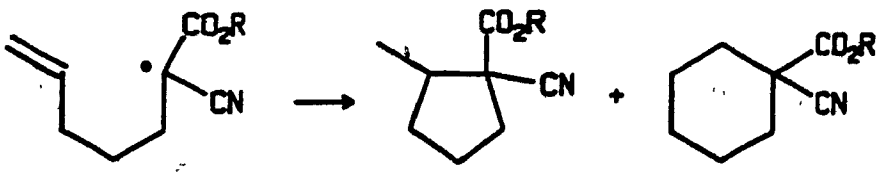
A number of theoretical treatments[51] support Baldwin's vector analysis approach for the alkyl radical's attack on the olefin being the dominant interaction. The transition complex for the incoming nucleophilic radical on an olefinic bond involves overlap of the occupied 2p orbital with one lobe of the vacant π^* orbital creating a fractional positive charge, wheras the incoming radical becomes negatively charged (Fig 5). This transition complex, can be be more easily attained for the 5-exo-ring closure 35, where the required amount of distortion of centres is lower than that of the 6-endo-mode 34.

The favoured exo-ring closure becomes disfavoured, as expected, with increasing the chain length, and the preference of the exo-mode decreases in the series 1-buten-3-yl, 1-penten-4-yl, 1-hexen-5-yl, 1-hepten-6-yl and 1-octen-7-yl. Thus, the difference between the transition state for the exo- and endo-ring processes become smaller for the larger flexible rings.

There are some notable exception to the above rules. For example, the 5-methyl-5-hexenyl radical 38 and the 2-cyano-radical 39 give predominantly the endo-product. However, the



38 40% 60%



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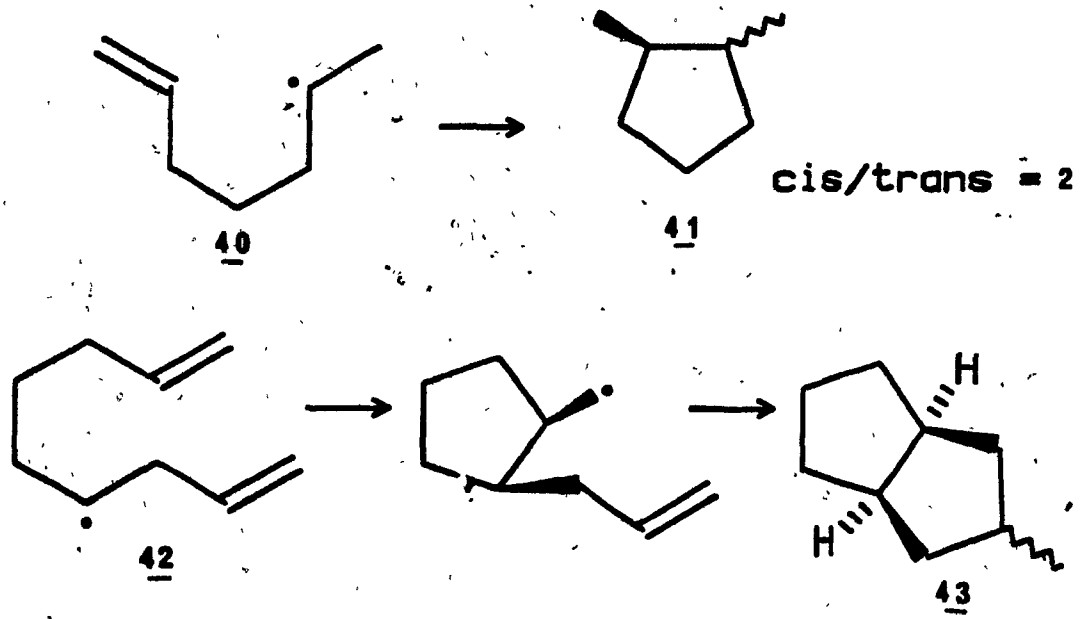
kinetic data[52] show that the 6-endo-cyclization is not enhanced, but because of steric interaction, it is the rate of the 5-exo-cyclization which is greatly retarded.

More interesting than their regiospecificity is the stereospecificity of the cyclization reactions. For instance, the cyclization of 2-heptenyl radical 40 gave predominantly the cis diastereomer 41[53], and similarly the acyclic radical 42 gave the cis-fused bicyclic compound 43 as the major diastereomer[54]. The preferential formation of the cis isomers



most probably results from the favourable electrostatic interaction of the dipolar transition states (Figure 5). An alternative explanation[55] has been ascribed to the effects of orbital symmetry.

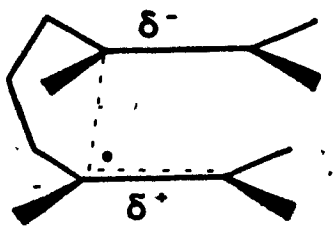


Figure 5

Intermolecular addition

The bimolecular addition of a carbon radical onto an unsaturated alkyl moiety is considerably slower than the corresponding intramolecular cyclization. The unfavourable entropy effect for bimolecular additions can be compensated for by using an electron withdrawing group on the olefin (Michael acceptor) in order to lower the activation enthalpy of the free radical addition. The rate of hydrogen abstraction from the organotin hydride by a carbon radical is about 10^6 M^{-1}-sec^{-1}, and the intermolecular addition of the radical onto an electrophilic olefin such as acrylonitrile or methyl acrylate is equally ca. 10^6 M^{-1}-sec^{-1}. In order to favour carbon-carbon bond formation over reduction, an excess (10 to 20 eq.) of the electrophilic olefin is necessary. Figure 6 outlines the catalytic cycle for intermolecular addition reactions. The radical species 44 adds onto the terminal bond of the electro-

philic olefin exclusively, due to the thermodynamic stability of the radical intermediate 45 formed. Adduct 45 is stabilized by the electron withdrawing substituent (Y) and thus much less nucleophilic. The rate of addition of 45 to an electrophilic olefin is approximately 10^2 M^{-1} sec^{-1} and it is therefore trapped by tributyltin hydride to give the product before it can dimerize (or polymerize) with the excess electrophilic olefin. One condition which is therefore required in the intermolecular free radical reaction, is that the nucleophilic alkyl radical 44 must be considerably less stable than adduct 45.

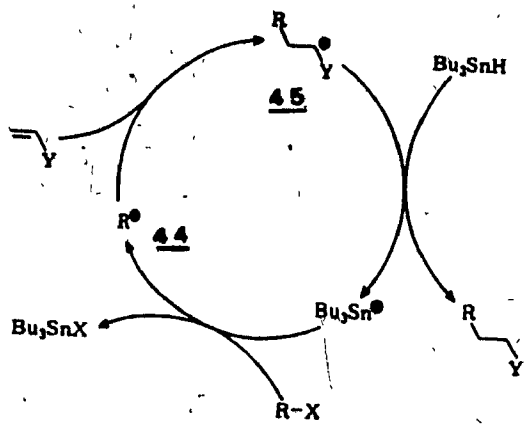
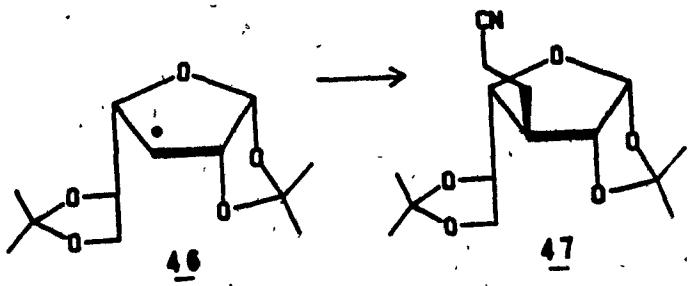


Figure 6

The stereochemistry of the intermolecular addition is found to be controlled by both steric (equation 41) and electronic (equation 42) factors of the incoming radical[56,57]. Thus, the sugar radical 46 adds acrylonitrile substrate from the less hindered side of the furanose ring, to give exclusively the adduct 47. Alternatively, the glucose acetal 48 adds to the acrylonitrile to give the more constrained diastereomer 49,



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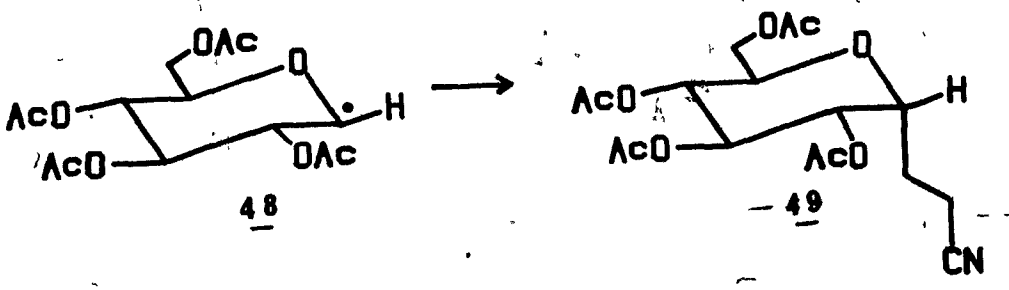
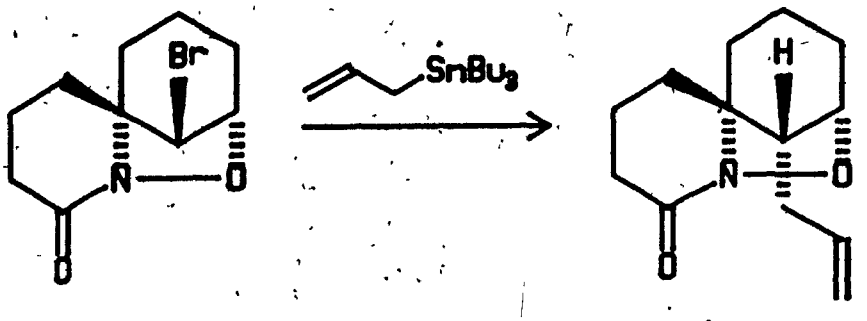


(42)

probably because of the anomeric effect which stabilizes the intermediate radical in the axial form.

The major side product encountered in the above intermolecular reactions is the direct abstraction of a hydrogen radical from tributyltin hydride, resulting in reduction of the organic radical. One method to avoid this byproduct is by using organotin compounds such as allyltributyltin[58] (equation 43) or tributyltin acrylate[59] (equation 44), which act as both olefinic substrate and tin radical chain propagators. These have been used stoichiometrically to trap alkylradicals and give adducts in high yields. In this S_H2 reaction, the radical adds onto the allyltin substrate 50 to give intermediate radical 51 which then generates the tin radical propagator 52 by disproportionation (Figure 7).



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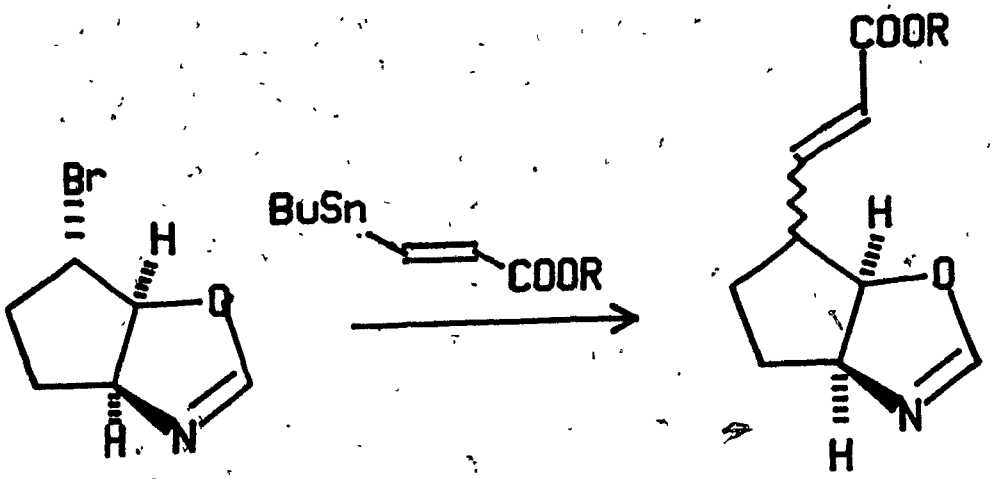

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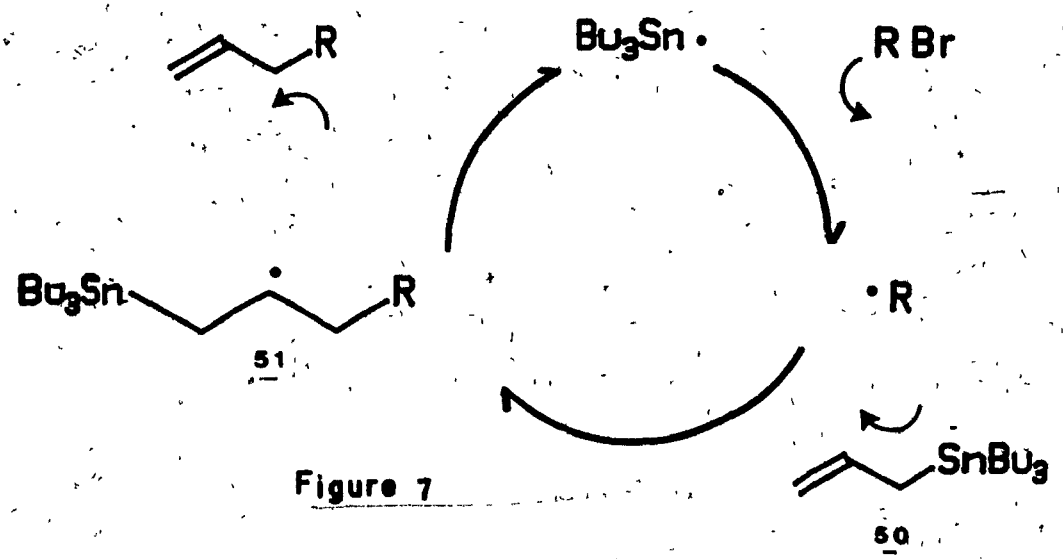
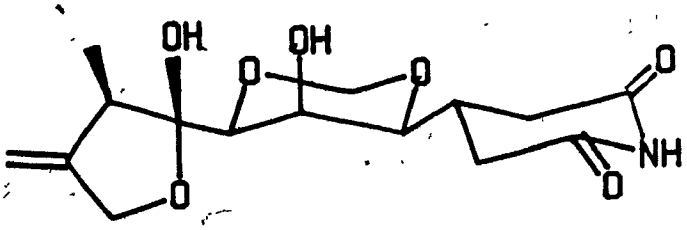


Figure 7

CHAPTER II : MODEL STUDIES TOWARDS THE SYNTHESIS OF SESBANIMIDE

Introduction

Sesbanimide A (53), is a potent antitumor agent isolated from the seeds of Sesbania drummondii[60] and Sesbania punicea[61] in low yields (10^{-5} %). Its tricyclic structure is novel with respect to the three rings linked together by single bonds. It has shown remarkable activity against leukemia in mice and notable inhibitory activity in the growth of human cancer cells in vitro[62]. The relative stereochemistry of sesbanimide A was determined by X-ray crystallographic analysis, but the absolute stereochemistry has only been established recently through its synthesis. Pandit and coworker[63a], followed by Schlessinger and Wood[63b], independently reported the synthesis of (-)-sesbanimide 54. Subsequently, Terashima and Matsuda[64], synthesized (+)-sesbanimide 53, and through comparison of rotation with the authentic alkaloid determined the absolute configuration of the natural product to be (+)-sesbanimide 53.



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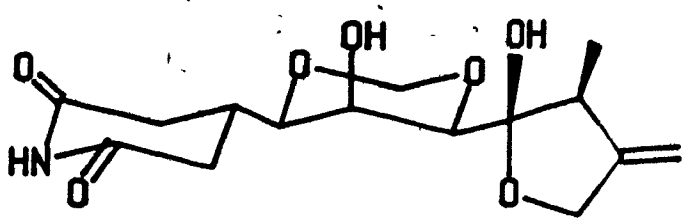

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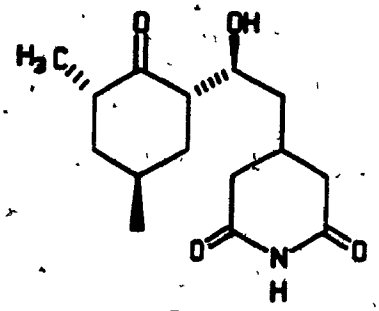
Sesbanimide has also been the target of several model studies pertaining in particular to the lactol and glutarimide rings[65], the latter ring being a widespread moiety in glutarimide antibiotics[67] such as cycloheximide (55), and protomycin (56).



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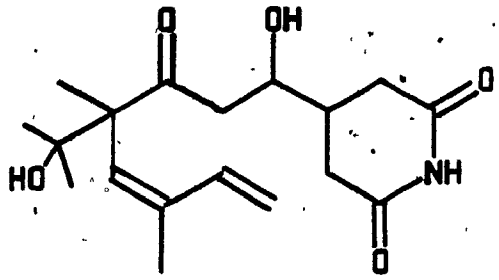

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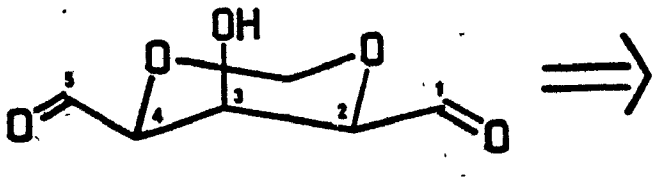
Most approaches reported in the literature derive the central ring B (57), from appropriately protected glucose 58 or the related pentose having the same relative stereochemistry at C-2, C-3, and C-4 where C-1 and C-5 are masked aldehydes[67]. From these potential aldehydes, the lactol (ring A) and glutarimide (ring C) can then be constructed leading to both enantiomers of sesbanimide.



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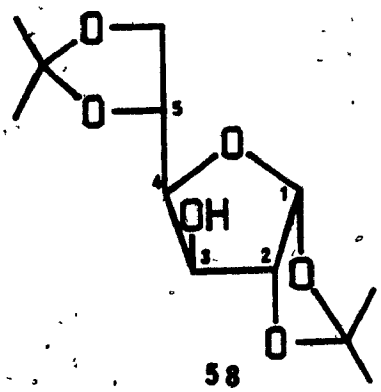
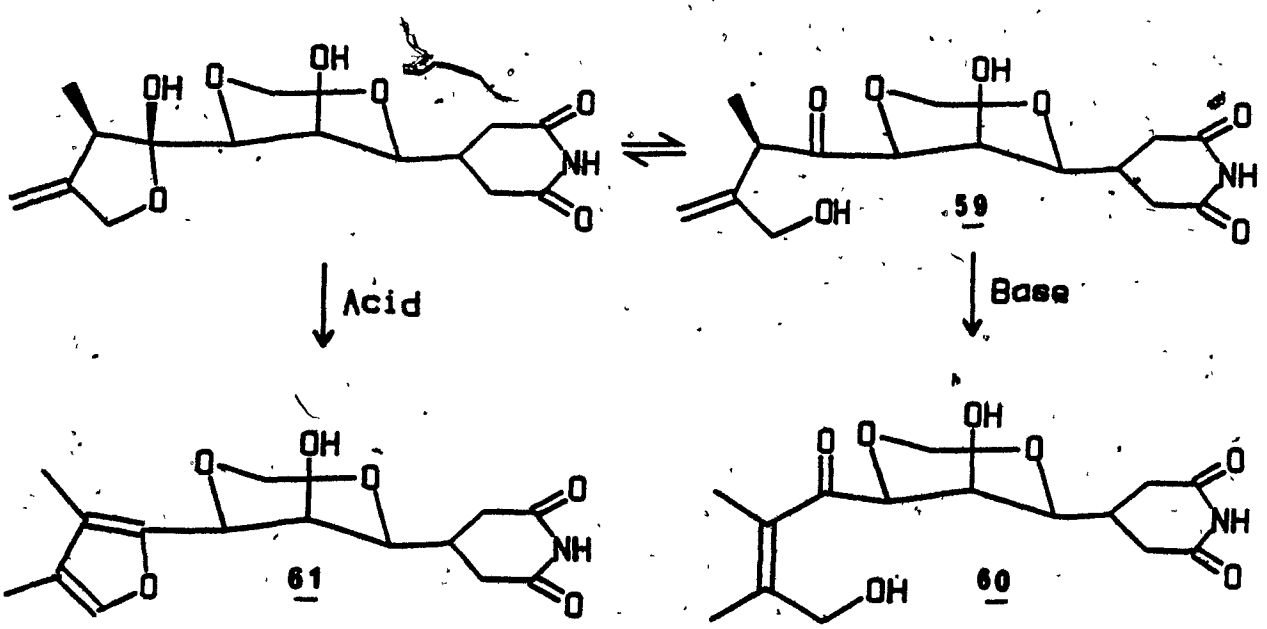


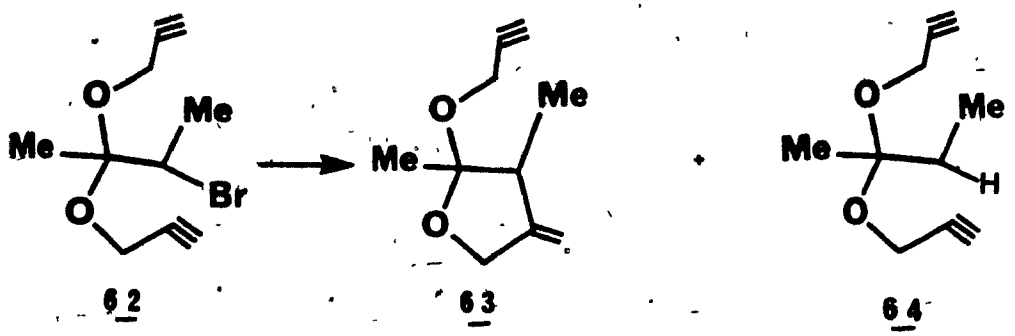
58

In solution, the lactol ring of sesbanimide is in equilibrium with the corresponding hydroxy ketone 59. The hydroxy ketone is very base labile, resulting in the isomerization of the double bond to the more stable conjugated system 60. In strong acid, it rearranges to the furan 61 with loss of water[68].



Model Study towards the Synthesis of Lactol Ring A

The strategy we envisaged for the synthesis of the lactol (ring A) moiety, was a mild free radical cyclization of an alkyl halide onto an acetylenic bond via a 5-exo-dig-process. (Scheme 2). Commercially available 3-bromo-2-butanone was thus ketalized with an excess of propargyl alcohol and catalytic p-toluenesulfonic acid at 60°C overnight to give the ketal 62 in 80 % yield. Cyclization of 62 in boiling benzene containing 1.1 eq of tributyltin hydride and AIBN (cat), gave after five hours, a 57 % yield of the cyclic ketal 63 together with some product of reduction 64 (15 %).

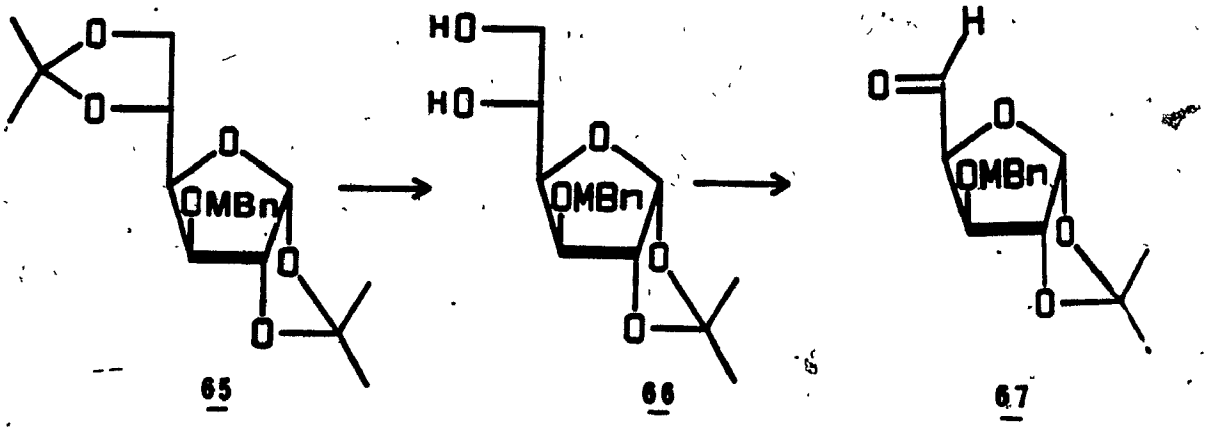


62 63 64

Scheme 2

In order to test this sequence on a more complex substrate, and ascertain the usefulness of the recently described p-methoxybenzyl protecting group[69], we next proceeded to transform the commercially available 1,2:5,6-diacetone glucose 58 into the bromo-ketone 70. Protection of the 3-hydroxy group of 58 with p-methoxybenzyl chloride and tetrabutylammonium iodide gave a 95 % yield of 65. Hydrolysis of the 5,6-acetal moiety of

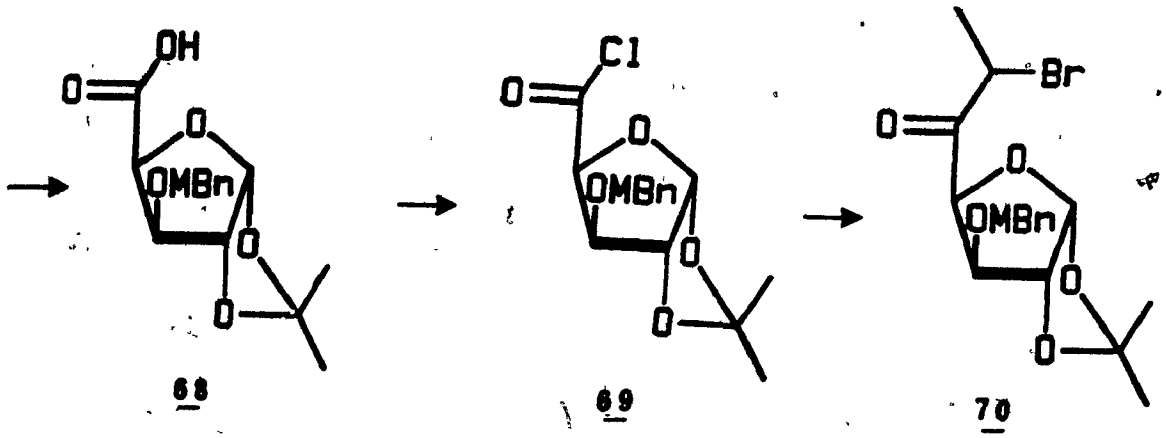
65 with 70% aqueous acetic acid then gave 87 % of the diol 66. The direct transformation of diol 66 to the acid 68 using sodium periodate and potassium permanganate proved to be difficult. The p-methoxybenzyl protecting group was oxidized giving mixtures of debenzylated diol, aldehyde and acid. In retrospect, this is not surprising since the p-methoxybenzyl functionality can be removed using a mild oxidant such as dicyanodichloroquinone (DDQ). The diol 66 was then oxidized with sodium periodate to give the aldehyde 67 as a crystalline product in 90 % yield.



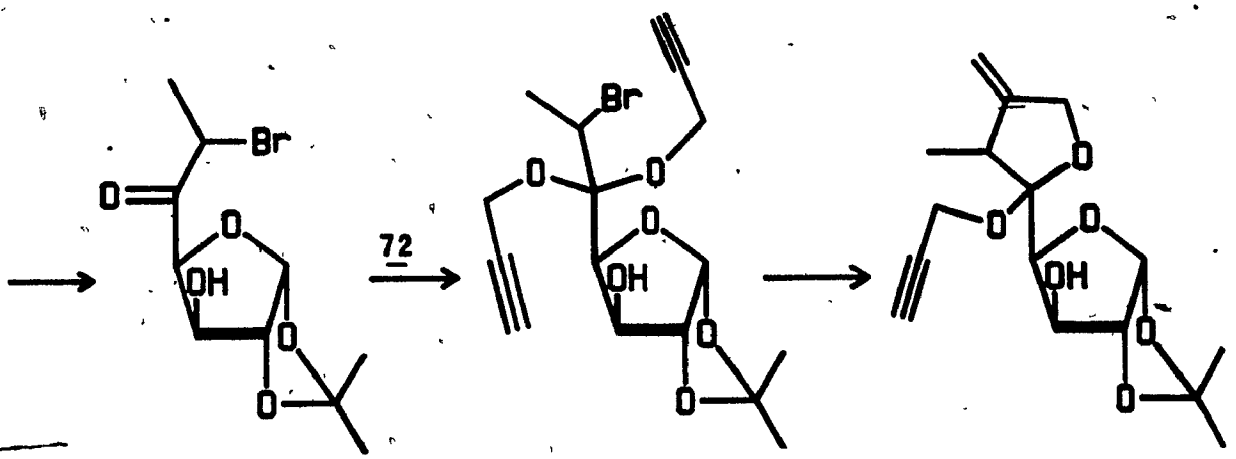
65 66 67

After investigation of several oxidants, it was found that silver (I) or silver (II) oxides transformed the aldehyde 67 to the acid 68 in 85 % yield. Treatment of the sodium or triethylamine salt of the acid 68 with oxalyl chloride at -10°C in methylene chloride, gave the corresponding acid chloride 69. This acid chloride (69) was then treated with excess diazoethane at 0°C (24 h), followed by addition of an excess of

pyridinium hydrobromide to afford the bromo-ketone 70 as an 8 to 1 mixture of diastereomers (36 %), which were separated by flash chromatography. Ketalization of 70 with propargyl alcohol

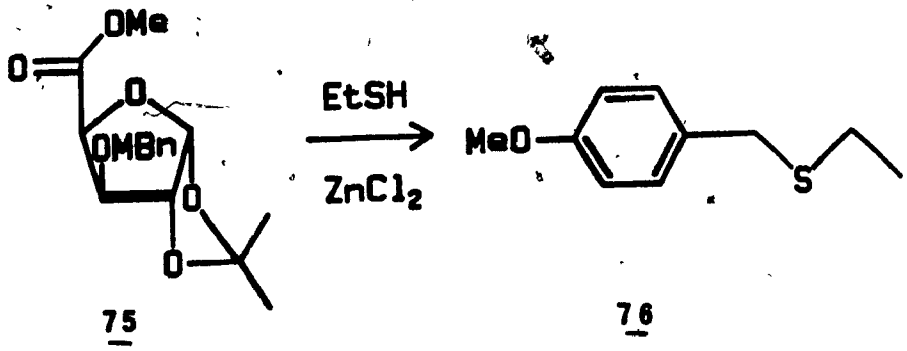


also proved to be difficult. Using several acid catalysts such as p-toluenesulfonic acid, acidic resin or chlorotrimethylsilane resulted in hydrolysis of the ketal and p-methoxybenzyl moieties. The p-methoxybenzyl protecting group was therefore removed with DDQ to give a 91 % yield of the alcohol 71. Cross ketalization of 71 with the dipropargyl ketal of acetone 72 and acidic resin, then afforded 27% of the ketal 73. Finally, radical cyclization of 73 in 0.02 M boiling benzene with 1.1 eq of tributyltin hydride and AIBN (cat) gave after 5 h the cyclic ketal 74 (56 %). This radical cyclization was performed using the major diastereomer derived from 70, and gave only one detectable diastereomer of 74. The radical cyclization thus proceeded stereoselectively. However, we were unable to ascertain its stereochemistry by nmr and mass spectrometry. This cyclic ketal can, in principle, be converted by mild hydrolysis to the lactol ring.



71 73 74

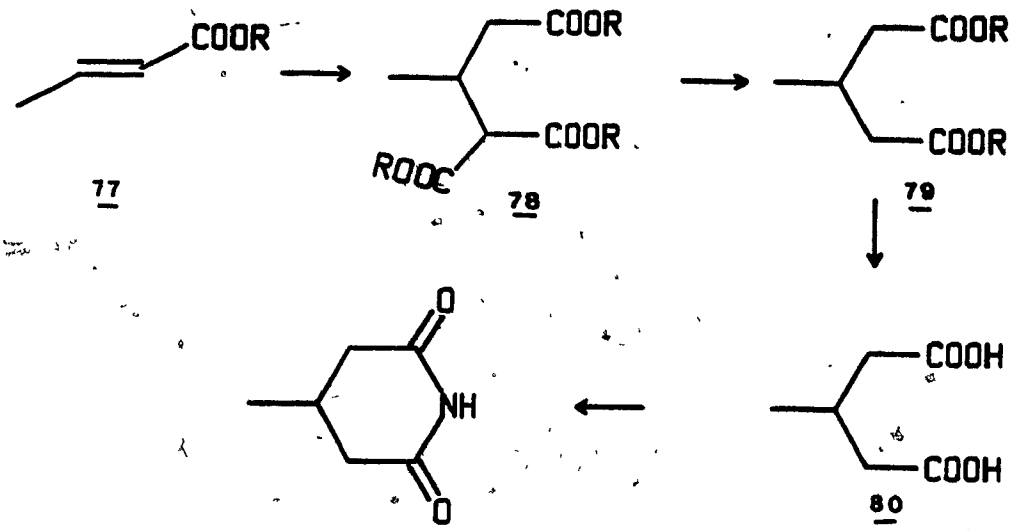
Since the p-methoxybenzyl protecting group seemed to be unstable to acid catalyzed ketalization procedures, we investigated its stability to the thio-ketalization procedure which we were expecting to use to construct the middle ring B of sesbanimide from the glucose derivative. When the methyl ester 75 was treated with ethanethiol in the presence of catalytic amounts of zinc chloride, both ketalization at C-1 and cleavage of the ether at C-3 occurred to give the corresponding p-methoxybenzyl thioethyl ether 76. Although the p-methoxybenzyl protecting group is reported to be stable to aqueous acid or base, we found that it is unstable to Lewis acid promoted ketalization and probably esterification procedures.



75 76

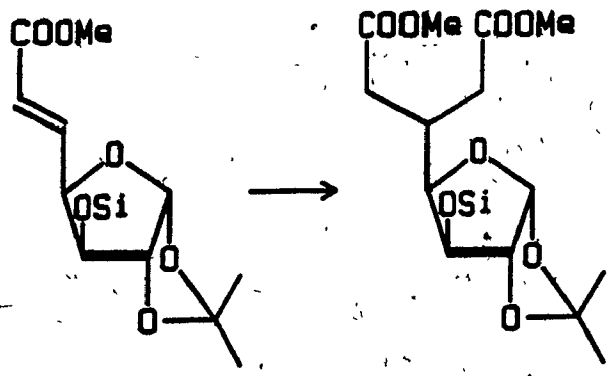
Model Studies towards the Synthesis of 4-Substituted Glutarimide

Recent interest in the total synthesis of sesbanimide, has led to numerous model studies on the construction of the 4-substituted glutarimide rings[67,68,70]. All of these approaches are modifications of a well known method starting from an α,β-unsaturated ester 77, which can easily be obtained from a corresponding aldehyde by a Wittig reaction. The ester 77 is treated with the potassium or sodium salt of diethyl malonate, and the resulting triester 78 decarbomethoxylated with sodium chloride at 160°C in dimethylsulfoxide/water to give the diester 79. Hydrolysis with lithium hydroxide yields the diacid 80, which upon heating to 165°C with 2 to 4 equivalents of urea gives the glutarimide in reasonable overall yields[71] (Scheme 3). Since this procedure, or its modifications is quite cumbersome, we sought a different approach involving a free radical reaction.



Scheme 3

The use of excess olefinic substrates to trap organic radicals yielding the corresponding 1,4- addition products has been well documented. In order to make this reaction synthetically useful for the formation of 4-substituted glutarimides, we studied conditions for the addition of organic radicals generated *in situ* with tributyltin hydride, using as a model substrate the silylated glucose 81 to obtain either the corresponding diester or glutarimide directly. Thus, when the α,β-unsaturated ester 81[72] and a twenty fold excess of methyl bromoacetate were heated to 80°C with a catalytic amount of AIBN and slow addition of tributyltin hydride over a 15 h period, a 30 % yield of the glutarate 82 was obtained with recovery of over 60% of the starting material. Removal of the stannanes and recycling the crude reaction/product employing the same conditions yielded 56 % diester 82 and 8 % starting material.

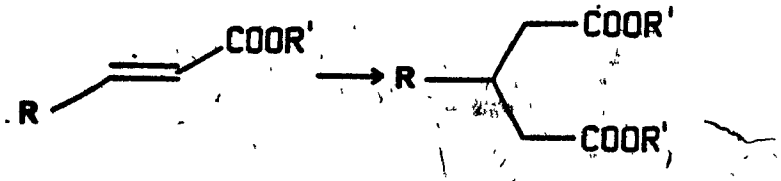


81 82

$Si{=}SiPh_2$ +

It should be noted that on more rapid addition of tributyltin hydride, or on dilution with solvent, the yield of 82 was vanishingly small.

Addition of methyl bromoacetate to methyl acrylate (83) or methyl crotonate (84) in benzene using the conditions described, gave 85% and 77 % yield of glutarate 85 and 86 without recycling.



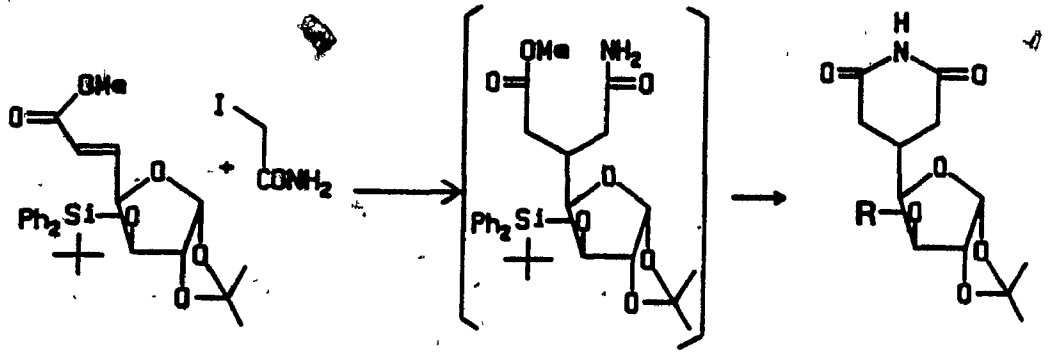
83 R = H 85 R = H

84 R = CH_3 86 R = CH_3

R' = CH_3

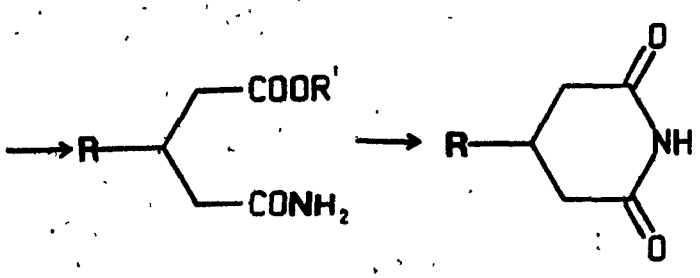
More interestingly, when the above reaction was carried out with excess iodoacetamide as the radical precursor, 81 as the unsaturated ester component, and the mixture irradiated

with a tungsten lamp at 80 - 90°C, a mixture of amido ester 87 and glutarimide 88 was obtained after recycling once. Further heating of this mixture at 120°C gave 64 % of glutarimide 88, with a 5 % recovery of 81. Higher yields could be obtained by cyclizing the isolated amido ester 87 by known methods[73]. A similar glutarimide derivative (88 R = Bn) has been converted to the A/B rings of sesbanimide[67b].



81 87 88

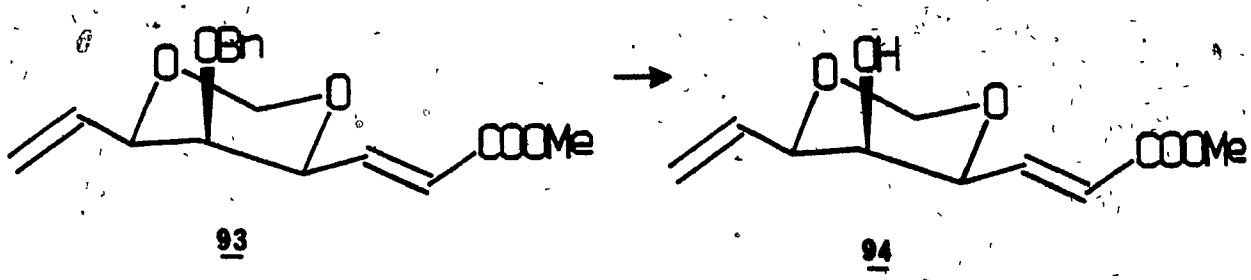
The iodoacetamide addition to methyl acrylate or crotonate gave similar mixtures of amido esters 89 and 90 and glutarimide 91 and 92 in 87 and 85 % combined yield respectively. Further heating provided glutarimides 91 and 92 in good yield without recycling. In all of these reactions, none of the 1,2-addition product was detected.



89 R=H
90 R=CH_3

91 R=H
92 R=CH_3

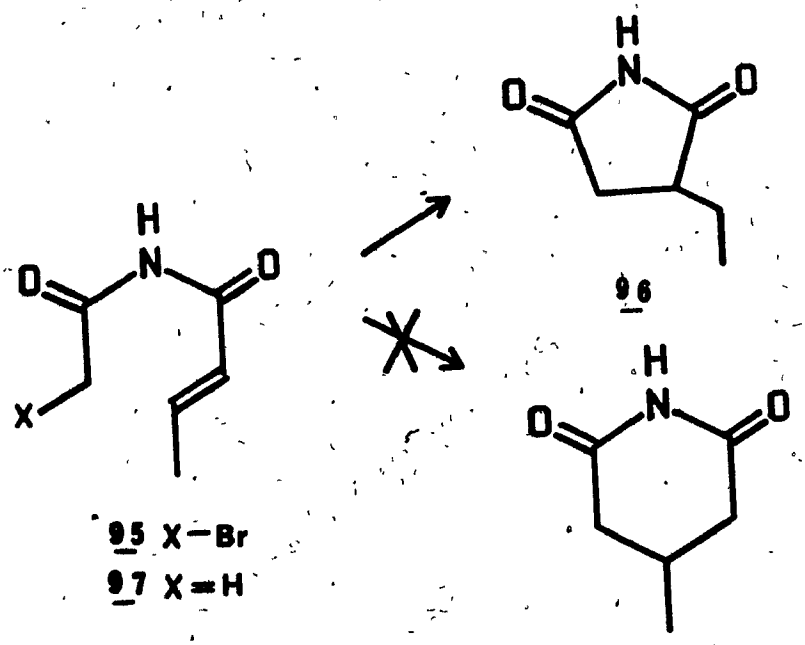
When the above iodoacetamide procedure was carried out on substrate[74] 93, containing the protected middle ring of sesbanimide, the expected glutarimide was not obtained. Instead it resulted in the cleavage of the benzyl ether protecting group. Further investigation showed that treatment of substrate 93 with an excess of iodoacetamide at 80°C for several hours, resulted in deprotection giving the alcohol 94. This indicates that the iodoacetamide as the solvent most likely forms some hydroiodic acid which is responsible for the cleavage of the benzyl ether group. This is not altogether surprising, as other Lewis acids such as BF_3 at 0°C are known to cleave the benzyl ether functionality[75].



93 94

2-Substituted Succinimides by Free Radical Cyclization

Since the 5-exo-trig intramolecular cyclization is generally favoured over the alternate 6-endo-process, we investigated the outcome for the free radical cyclization of 95. However, in this case the kinetically favoured 5-exo-mode may be outweighed by the thermodynamically favoured 1,4-addition (6-endo-ring closure) onto the unsaturated imide. The imide 95, obtained from crotonamide and bromoacetic anhydride[72], gave exclusively 2-ethyl succinimide 96 derived from a 5-exo-trig addition of the radical to the olefinic bond, with some product of reduction 97. During the course of this investigation, Clive and Beaulieu[76] reported that the intramolecular cyclization of a series of unsaturated esters also gave exclusively the 5-exo-ring closure. Interestingly, recent investigation by Porter and coworkers[77] have shown that the intramolecular cyclization of larger rings containing an unsaturated ketone, gave the 1,4-cycloaddition product exclusively.



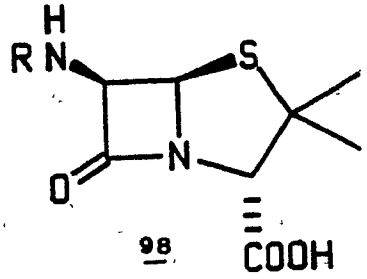
95 X=Br
97 X=H

96

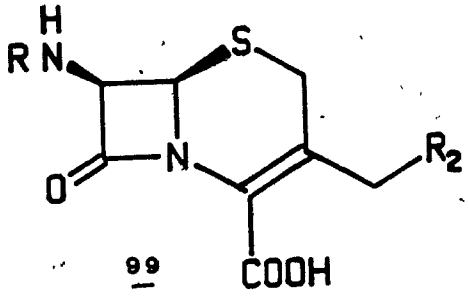
CHAPTER III : SYNTHESIS OF TRICYCLIC AZETIDINONES BY INTRAMOLECULAR CYCLIZATION

Introduction

Some common features of the classical β-lactam antibiotics such as penicillin 98 and cephalosporin 99, are the cis configuration of the azetidinone ring, an amidic side chain at the 5 or 6 position and a carboxylic acid at the 3 or 4 position respectively, and a fused second ring which engenders enough strain on the β-lactam linkage as to make it more reactive than its monocyclic counterpart 100. A method of measuring the strain and hence lability of this amide bond is through infrared spectroscopy. Monocyclic azetidinones exhibit the lactam frequency at 1715 to 1720 cm^{-1}, whereas the more strained bicyclic azetidinone exhibits a higher amide frequency at about 1765 cm^{-1}.



98



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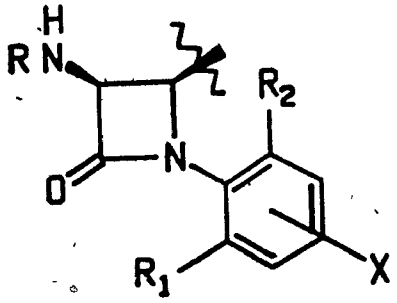
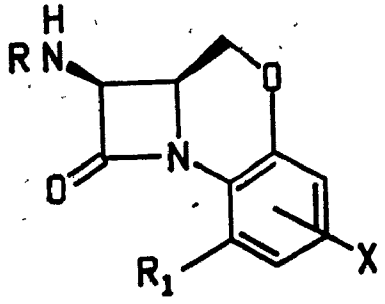


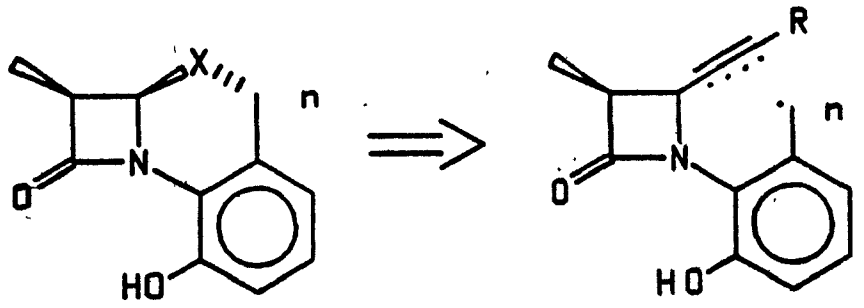
100



101

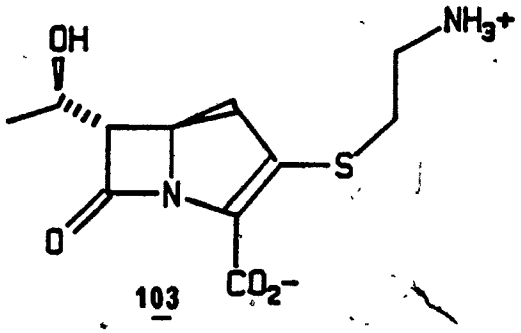
During the past decade, there has been considerable interest[81,82] in preparing tricyclic azetidinones of the type 101, where the double bond and carboxylic acid moiety of cephalosporin 99 is replaced by a phenolic group. Whereas the monocyclic precursors, 100 were devoid of any activity, some of the corresponding tricyclic azetidinones showed weak antibacterial activity against some Gram negative species[83,84]. With the encouragement of these results, we decided to prepare the more strained tricyclic azetidinones 102 (n= 0,1). The carbapenem 102 (n=0) is somewhat similar to the recently described β-lactam antibiotic thienamycin (103), except that a phenolic group replaces the α, β -unsaturated carboxylic acid function of 103. The synthesis of thienamycin or carbacephems 102 (n=1) were previously achieved by ionic methods[85]. In view of the known instability of tricyclic carbacephems towards acids and nucleophilic reagents, we sought for a free radical method for their synthesis[86].

As suitable precursors for the intramolecular free radical annelation yielding 102, the radicals were generated either beta (n=0) or gamma (n=1) to the nitrogen atom of the azetidinone 104, and a phenyl substituent (R) was chosen so that the exo-mode of addition should be favoured over the endo-process. Similar free radical cyclizations yielding bicyclic azetidinones have been described elsewhere.[87]



102 n = 0, 1
X = C, S, O

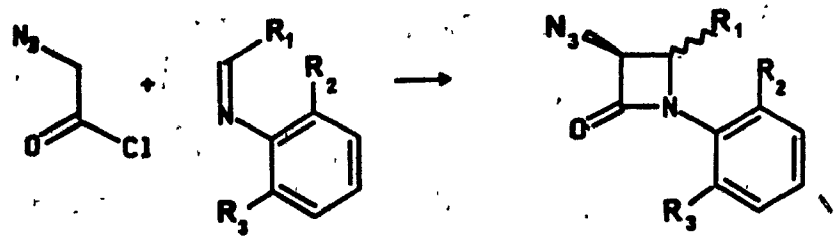
104



103

Results and Discussion

The monocyclic azetidinones 105 -109, were prepared by the known methods[83], involving the condensation of an appropriate Schiff base with azidoacetyl chloride in the presence of equimolar amounts of triethylamine (Scheme 4, Table 4). Reduction of the azide substituent using hydrogen sulfide and triethylamine followed by acylation of the amine intermediate with phenylacetyl chloride and triethylamine gave fair to good yields of the expected amido azetidinones 110 - 114.



105 - 109

Scheme 4

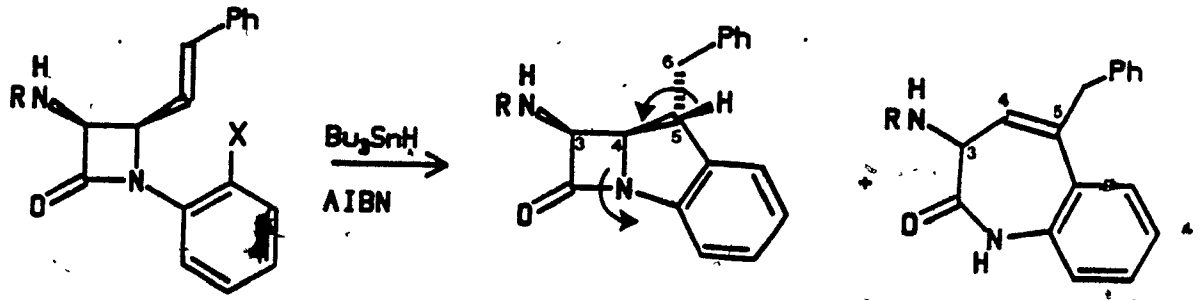
Table 4. Azido-azetidinones from the condenzation of a Schiff base with azido acetylchloride.

	R_1	R_2	R_3	% Yield cis	% Yield trans
105	CH=CHPh	Br	H	48	32
106	C≡CPh	Br	H	35	35
107	CH=CHPh	CH_2OSi	H	85	-
108	CH=CHPh	CH_2OSi	OBn	90	-
109	C≡CPh	CH_2OSi	H	87	-

Si = t-$BuSiMe_2$

Free radical cyclization of 110 (0.02 M in refluxing benzene) with slow addition of tributyltin hydride and catalytic AIBN over a 20 hr period under an inert atmosphere, gave the reduction product 115 (15 %), tricyclic azetidinone 116 (5 %) and the azepinone 117 (35 %) together with some starting material, after separation using a neutral silica hplc

column. The configuration of 116 was assigned, based on its coupling constant of 8 Hz (J_{H4-H5}), by analogy with diastereomers 125 and 134 discussed below. When this tricyclic benzo carbapenem 116 was placed in an nmr tube ($CDCl_3$), it decomposed within a week, and 117 was isolated as the major product. Due to the instability of 116 in solution, the free radical annelation of 110 was repeated using 1,5 eq of tributyltin hydride over a shorter period of time (3 hr). After evaporation of the solvent, the crude residue was redissolved in carbon tetrachloride, and 116 precipitated as colorless crystals (24 %). The infrared spectrum of 116 displayed the azetidinone carbonyl frequency at 1805 cm^{-1}, which is



110 X = Br

115 X = H

R = BnCO

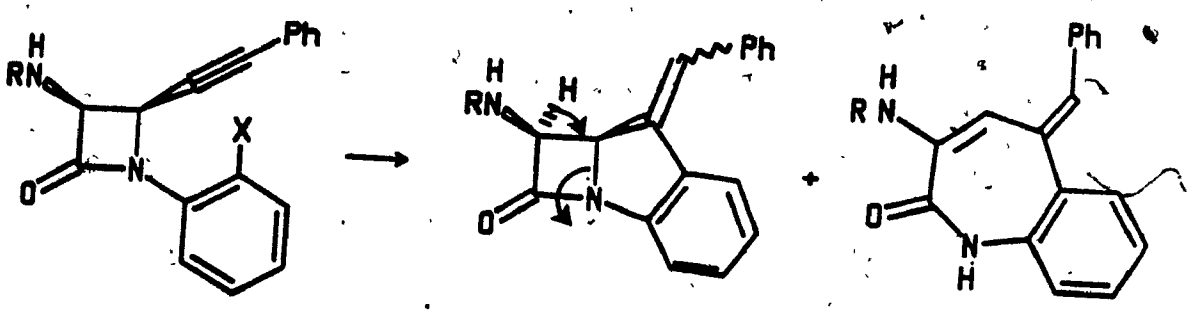
116

117

considerably higher than for less strained bicyclic azetidinones such as cephalosporanic acid (1765 cm^{-1}). The decomposition of 116 to 117 most likely resulted via proton abstraction at C_5 with double bond formation at C_4-C_5 and ring opening at the C_4-N position to give 117 which is closely related to diazepam (see arrows, 116). In order to avoid this decomposition, we decided to carry out the next experiment on a propargyl azetidinone 111, where the resulting product 119/120

lacks the C_5 proton.

Thus, the free radical cyclization of 111 gave two tricyclic azetidinones 119 and 120 in a 4:3 ratio as a crystalline mixture (31 %), mp 140 to 145 °C. Also, the reduction product 118 (27 %), some starting material and several decomposition products were obtained. The mixture of 119 and 120 did not survive chromatography using various types of silica and only 120 was recovered partially when neutral silica gel was used. Attempts to recrystallize this mixture also failed, giving decomposition in solution within a few days. From this decomposed mixture was isolated the azepinone 121 which most likely resulted via proton abstraction at C_3 forming a double bond at C_3-C_4 and ring opening at N-C_4 of the azetidinone rings 119 and 120, The infrared spectra of 119/120 showed the azetidinone carbonyl frequency vibration at 1824 cm-1.

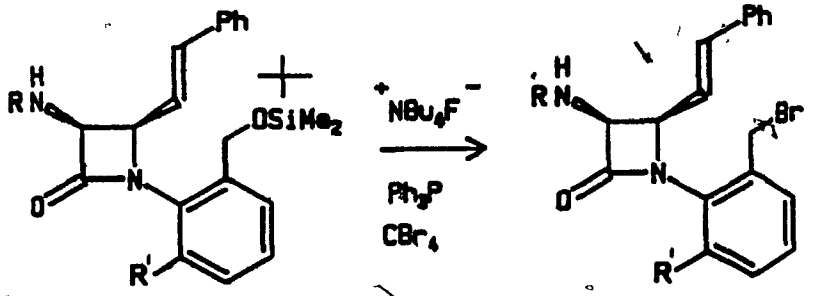


111 X=Br
118 X=H

119/120

121

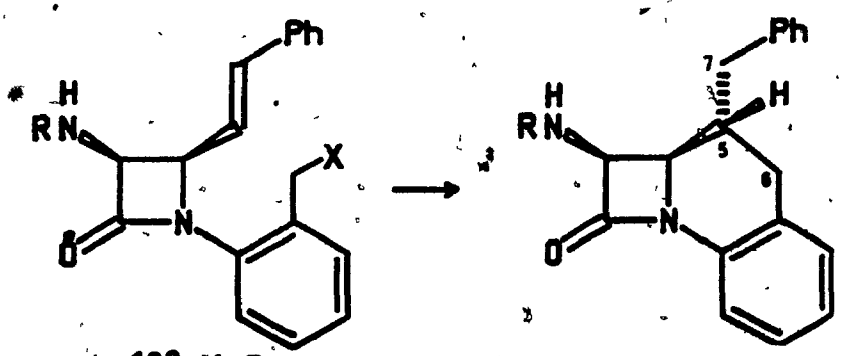
Since the benzo carbapenems obtained were found to be unstable in solution, we next investigated the formation of the somewhat less strained benzo carbacephems 102 (n=1). Desilylation of 112 or 113 using tetrabutylammonium fluoride followed by bromination of the corresponding alcohol with triphenylphosphine and carbon tetrabromide , gave good yields of the bromo azetidinone 122 and 123 respectively.



112 R'=H
113 R'=OBn

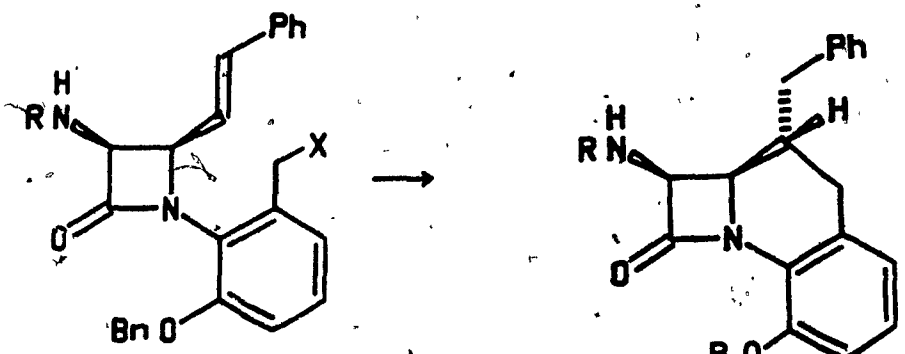
122 R'=H
123 R'=OBn

Free radical cyclization of 122 gave some reduction product 124 and 65 % of tricyclic benzo carbacephem, mp 256 °C, exclusively as the less crowded diastereomer 125. The infrared spectrum showed the azetidinone carbonyl absorption at 1755 cm $^{-1}$. This tricyclic product resulting from a 6-exo addition was found to be highly stable in solution. Similarly,



122 X=Br
124 X=H

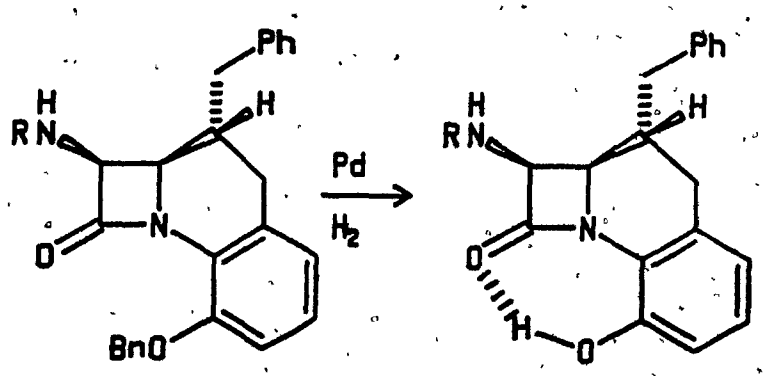
125



123 X = Br
126 X = H

127

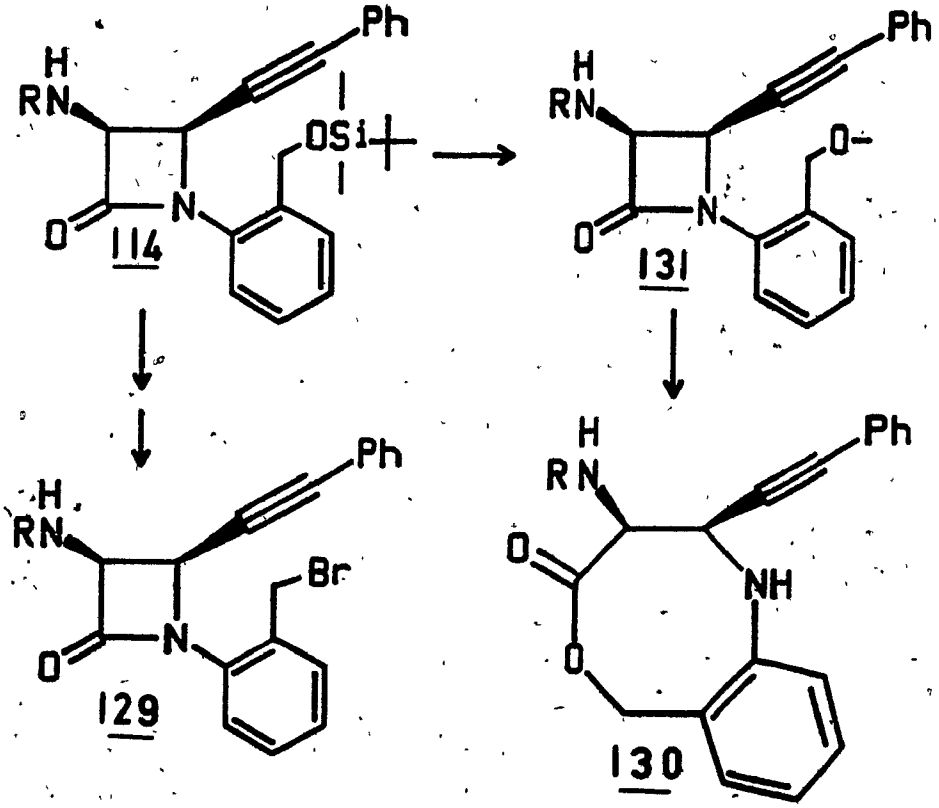
free radical cyclization of 123 gave the reduction product 126 and a good yield of the analogous tricyclic azetidinone 127 (70%), mp 273°C, which displayed the infrared carbonyl vibration at 1770 cm^{-1}. Hydrogenolysis of 127 using palladium on charcoal in DMF afforded an almost quantitative yield of the tricyclic phenol 128, which displayed the carbonyl frequency at lower wavenumbers , 1715 cm^{-1}, due to H-bonding



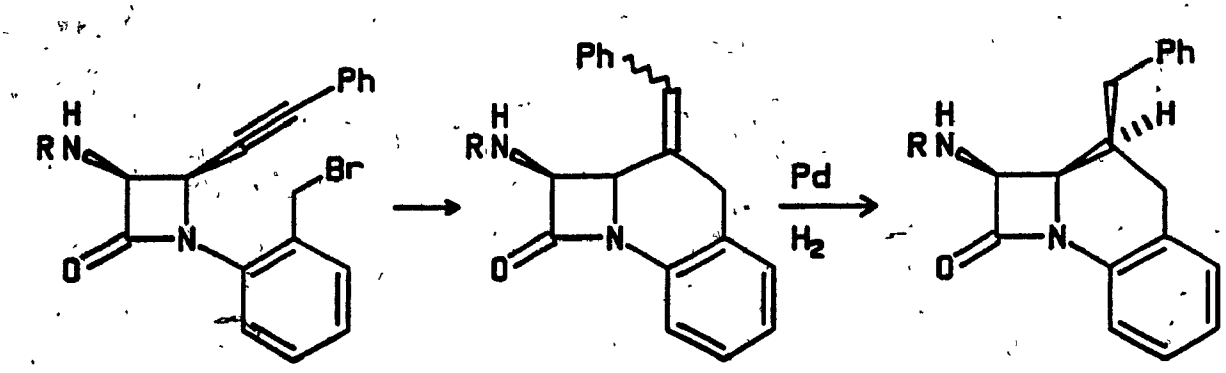
127 128

of the phenol proton with the azetidinone carbonyl. The presence of the azetidinone was proven by silylation with Me_3SiCl/Et_3N, which gave a product where the azetidinone frequency reverted to its expected position at 1773 cm^{-1}. In both of the above cyclizations, no diastereomer of 125/127 or 7-endo-cyclization product was detected.

Desilylation of the azetidinone 114 with tetrabutylammonium fluoride gave a very low yield of the expected alcohol. The major byproduct formed was an eight membered lactam 130, which most likely resulted by nucleophilic ring opening of the intermediate azetidinone 131. The silyl group was therefore removed using 20% trifluoroacetic acid, and the corresponding alcohol brominated using triphenylphosphine and carbontetra bromide to afford the bromo azetidinone 129 in good yield.



The free radical cyclization of 129, gave the 6-exo-intramolecular cyclization products as a 1:1 mixture of geometric isomers in over 75 % combined yield. These tricyclic azetidinones 132 and 133 were easily separated by flash chromatography and their structures assigned unambiguously by nOe nmr experiments. The tricyclic azetidinones 132 and 133, mp 189 and 196 °C respectively, were found to be soluble in most organic solvents and stable in solution. Interestingly the more sterically crowded Z isomer 133 displayed a slightly higher azetidinone carbonyl frequency at 1753 cm^{-1} as compared to 1748 cm^{-1} for 132. Hydrogenation of either 132 or 133 using platinum black as catalyst, reduced the exocyclic double bond from the less hindered side to give the more crowded tricyclic benzo carbacephem 134 as the only product, mp 236-237 °C. The coupling constant between H-4 and H-5 was found to be 3 Hz, distinctly smaller than for its diastereomer 125 (10 Hz). The infrared spectrum showed the carbonyl frequency at 1768 cm^{-1}



129 132/133 134

which was, not surprisingly, 13 wavenumbers higher than its less constrained diastereomer 125. A different perspective of the product for this reduction (132/133 to 134), as well as its diastereomer 125 is shown in Figure 8.

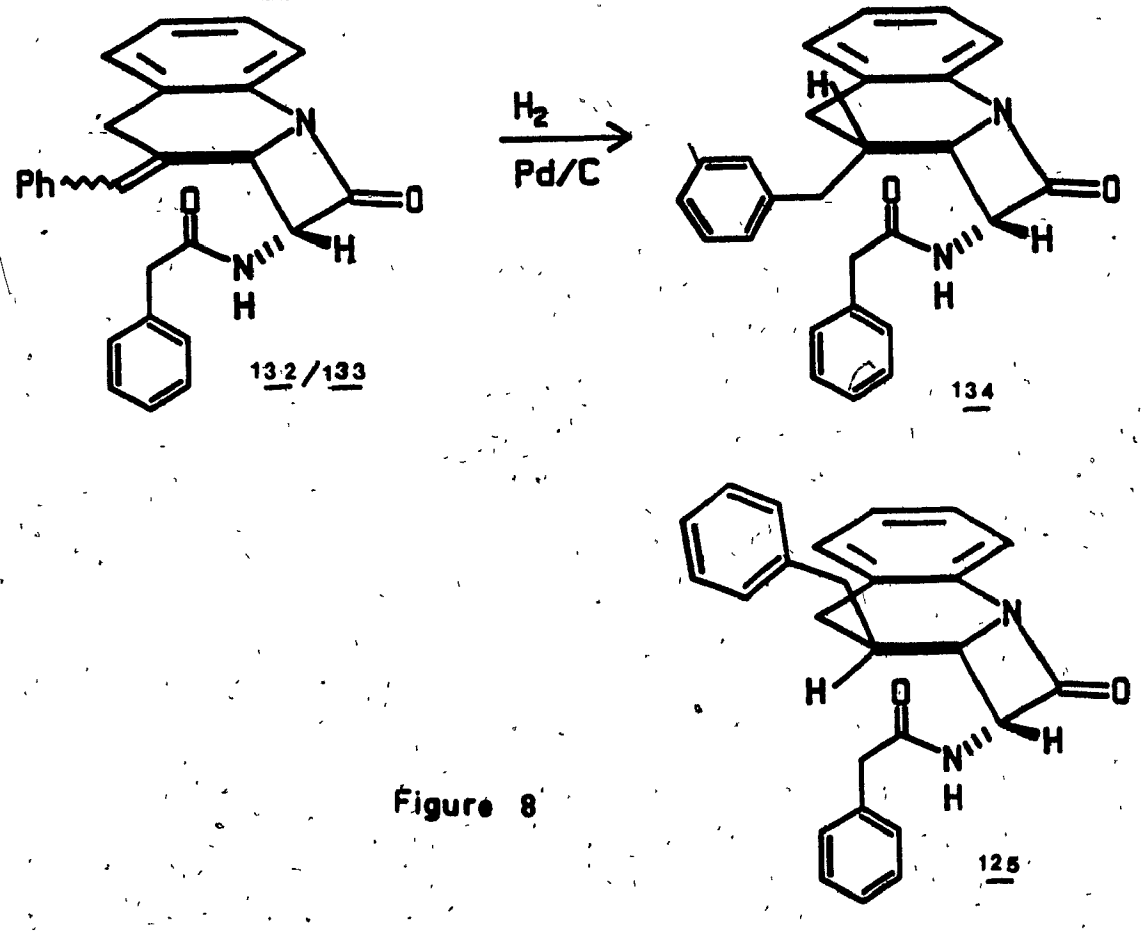
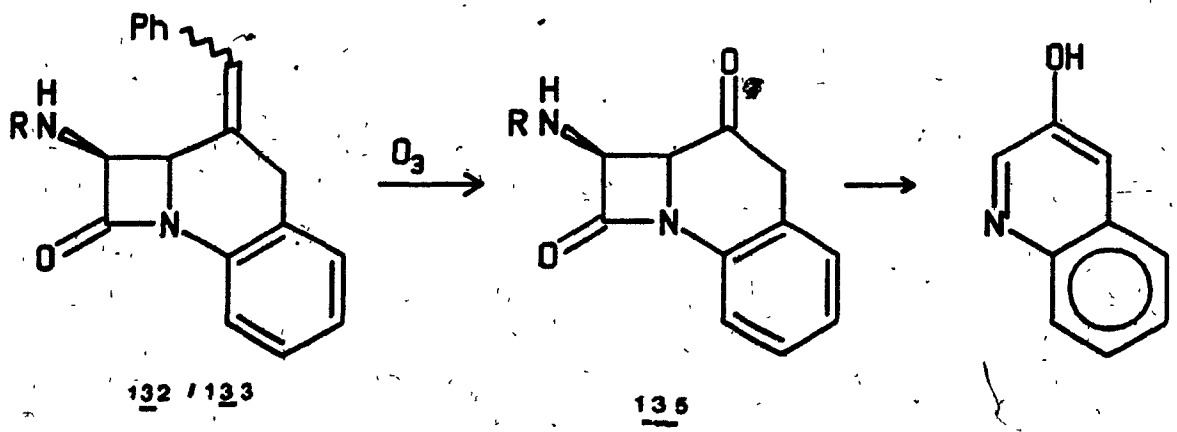


Figure 8

Finally, a mixture of 132 and 133 was ozonolyzed to give the corresponding ketone 135 in good yield. Its infrared spectrum showed the azetidinone frequency at 1793 cm^{-1} and the ketone absorption at 1722 cm^{-1}. This ketone was considerably less stable than its olefinic precursor, and slowly decomposed on silica gel.

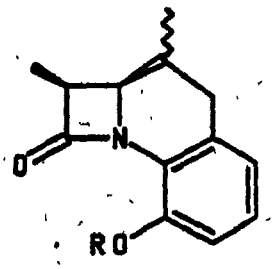


132 / 133 135

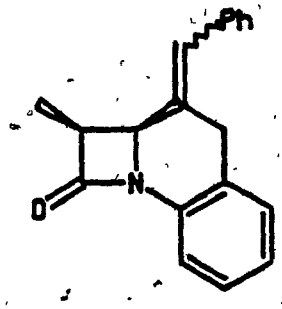
Conclusion

Overall, the infrared data indicate a trend of higher instability as the azetidinone carbonyl frequency increases from 1748 to 1824 cm^{-1} (Scheme 5), and that the more constrained diastereomer or regioisomer display a higher β-lactam frequency. Azetidinones with the lactam frequency above 1780 were found to be very unstable. Since a phenolic moiety with close proximity to the azetidinone carbonyl was found to stabilize the lactam linkage through hydrogen bonding, it would be interesting to prepare the hydroxyl derivative of carbapenem 116. By analogy with 128, it should absorb at 1780 cm^{-1}.

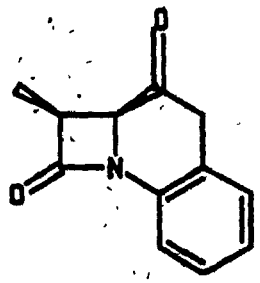
The reactions carried out establish the usefulness of a radical process for the carbon-carbon bond formation in strained azetidinones. These free radical reactions also give good stereochemical control in the intramolecular cyclization onto an olefinic bond.



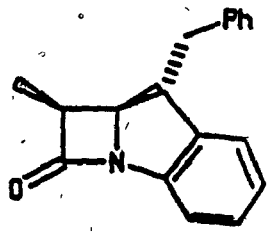
1755 , 1788



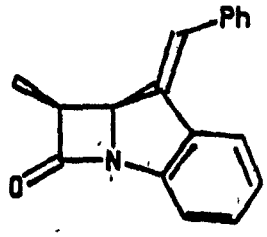
1748 , 1753



1793



1805



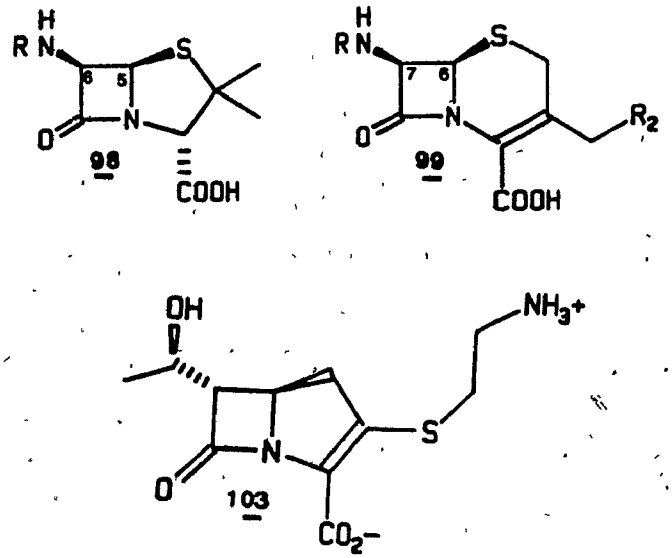
1824

Scheme 5

CHAPTER IV : STEREOSELECTIVE SYNTHESIS OF -ALKYLAZETIDINONES BY FREE RADICAL CHAIN REACTIONS

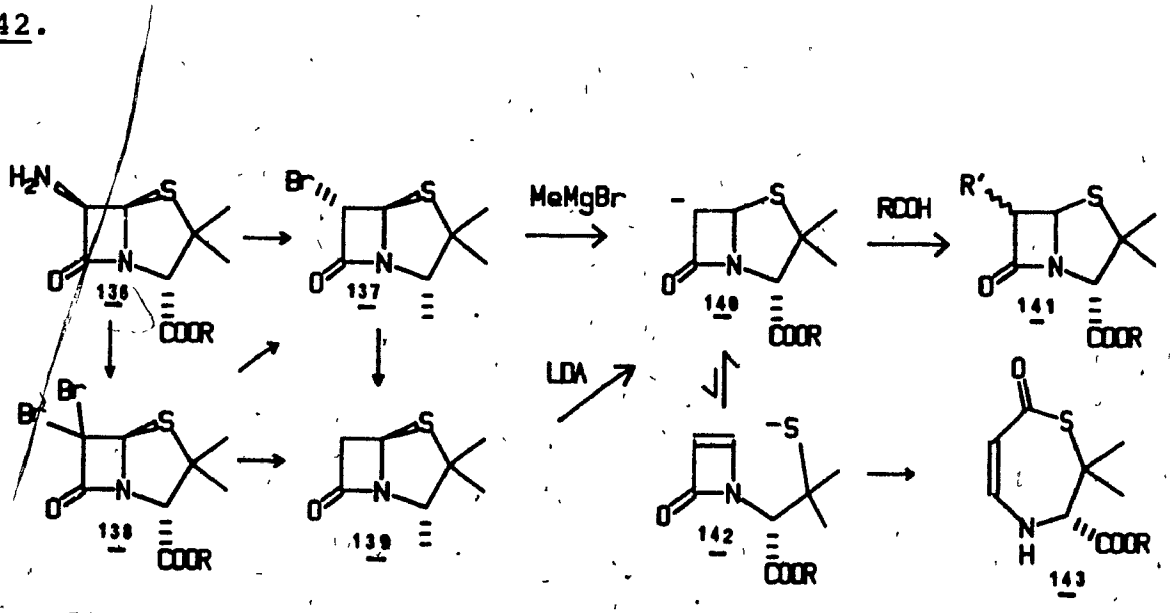
Introduction

The discovery of thienamycin 103 as a β-lactam antibiotic has revolutionized the accepted structure-activity concept with respect to configuration around the azetidinone ring and the nature of the side chain of the azetidinone moiety. The introduction of an analog of 103 as a medicinal agent has led to renewed interest in the modification of earlier antibiotics such as penicillins 98 and cephalosporins 99 at the 6- and 7-position respectively[88,89].



Replacement of the amide in 98 and 99 by an alkyl group is usually carried out in the following way. Diazotization of 136 with sodium nitrite and sulfuric acid, followed by bromination with either sodium bromide or bromine gives 137 or 138 respectively. These bromo-derivatives can then be reduced to the dihydropenicillin 139. Metallation of 137 with methyl-

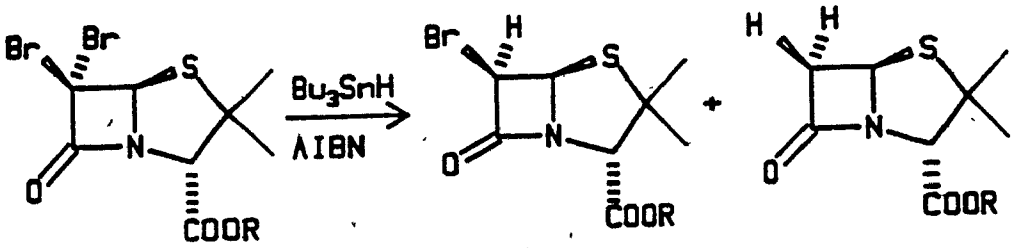
magnesium bromide or lithiation of 139 with lithium diisopropylamine then gives the 6-alkylpenicillins 141, after quenching with the appropriate aldehyde. The products obtained are usually a diastereomeric mixture with some epimerization at the C-5 position of 141 resulting from an equilibrium of 140 with 142 via β-cleavage. In fact, the major side product from the above reaction is found to be 143, which results from the sulfide addition onto the carbonyl moiety of the intermediate 142.



The widespread use of electrophilic olefins to trap carbon radicals generated from alkyl halides by a free radical chain mechanism[91], prompted us to investigate the suitability of 6-bromo- or 6,6-dibromopenicillanates as precursors for such trapping experiments.

Results and Discussions

The 6 α-bromo- and 6,6-dibromopenicillanic acids were prepared from 6 α-aminopenicillanic acid (6-APA) by known methods[92,93] and transformed to their benzhydryl esters 144 and 145 respectively in good yields. Reduction of the dibromopenicillanate 145 with an equimolar amount of tributyltin hydride gave 6 β-bromopenicillanate 146 as the only diastereomer together with the reduction product 147. This latter type of reaction was well investigated by Manhas et. al.[94], who proposed that the radical intermediate formed at C-6 abstracted the proton from the bulky tributyltin hydride from the less hindered side of the azetidinone giving the cis-bromo isomer.

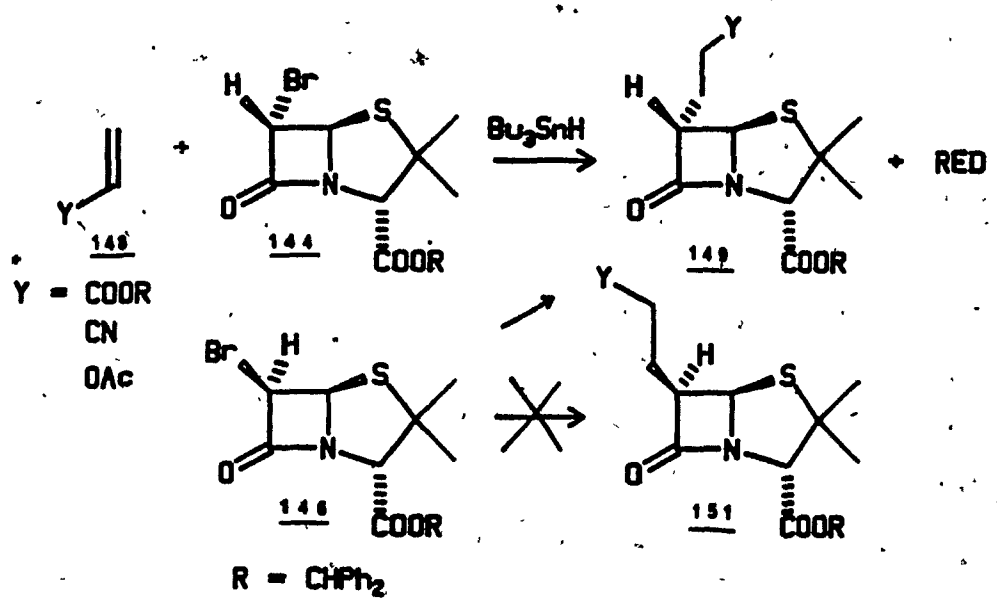


145 146 147

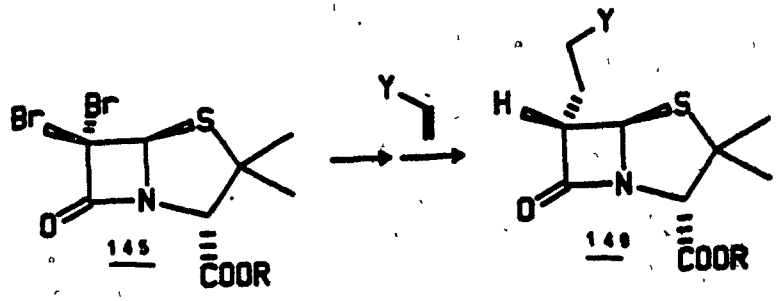
R = $CHPh_2$

When an 0.1 M benzene solution of cis- or trans- 6-bromo-penicillanate 146 or 144 and the olefin 148 (15 - 20 eq) was treated at 80°C, with tributyltin hydride over a 5 to 6 h period, 30 to 35 % reduction product 147 and 40 to 67 % of trans-penicillanate 149 were obtained (Method A, Table 5).

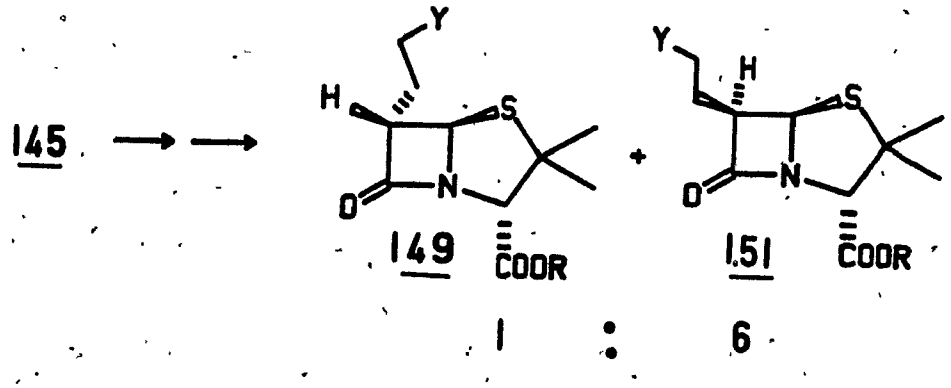
Smaller amounts of olefin 148 or faster addition of the tin hydride, reduced the yield of alkylated product 149 and enhanced the formation of 147.



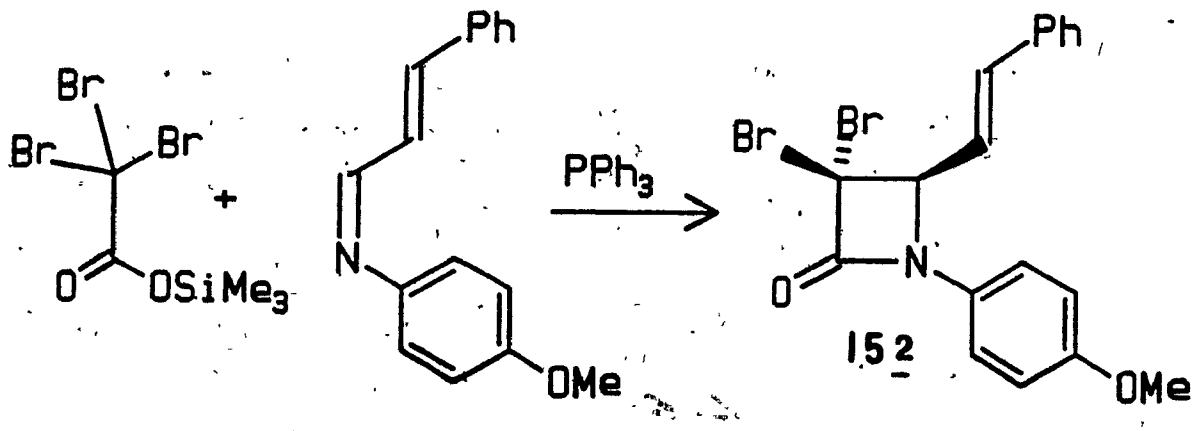
The 6,6-dibromopenicillanate 145 can be directly transformed to the trans product 149 in a one pot procedure by first refluxing a solution of 145 with tributyltin hydride (2 h), followed by addition of the olefin (15 - 20 eq) and slow addition of tributyltin hydride over a 5 h period, giving similar overall yields (Method B).



Treatment of 6,6-dibromopenicillanate 145 with excess olefin and slow addition of tributyltin hydride over a 5 h period, followed by evaporation of the excess olefin and solvent, gave after further reflux (2 h) with 1.2 eq of tributyltin hydride, 40 to 55 % reduction product and 35 to 47 % of the cis-penicillanate 151 as the major diastereomer (Method C).



Similarly the 3,3-dibromo azetidinone 152, prepared from the tribromosilyl ester and corresponding Schiff base with triphenylphosphine (Scheme 6), was converted by method A to the trans-product 153 (46%) exclusively, and via method C to the cis-product 154 (44 %) as the major diastereomer (6 :1).



Scheme 6

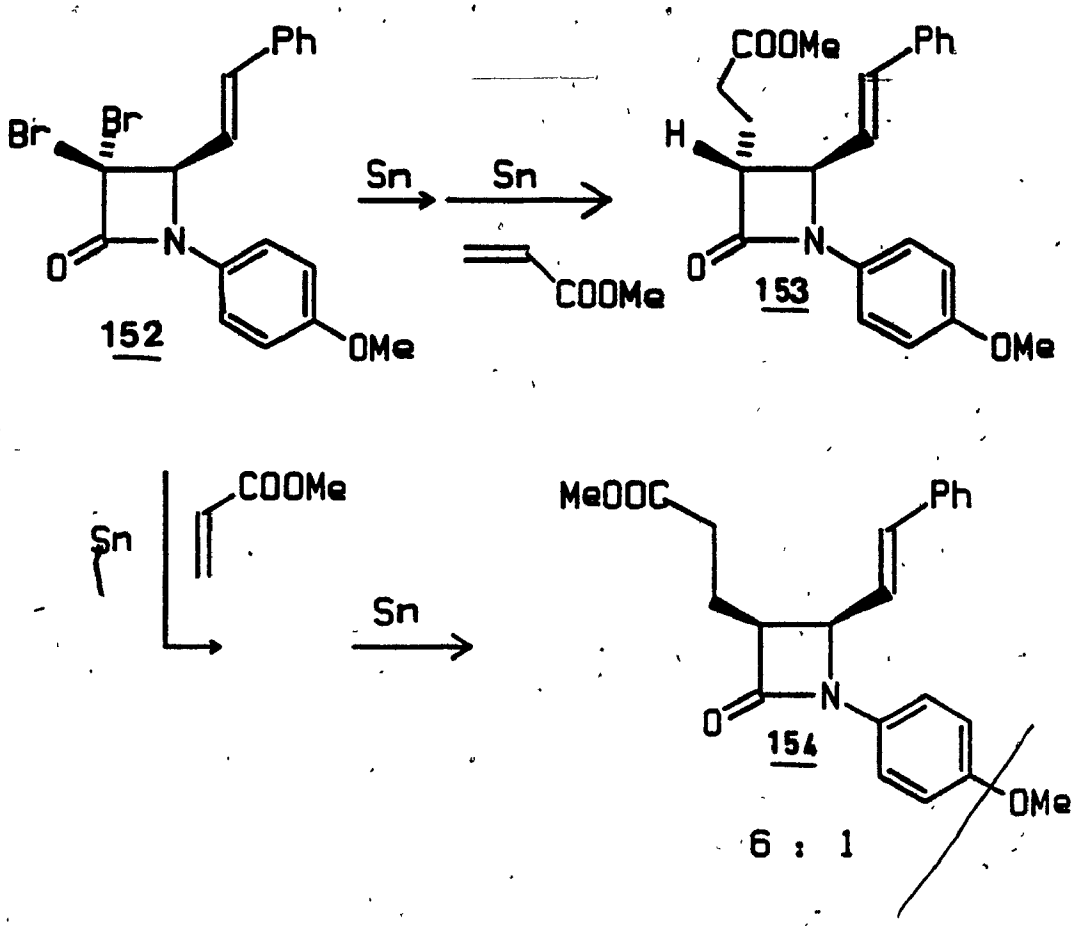
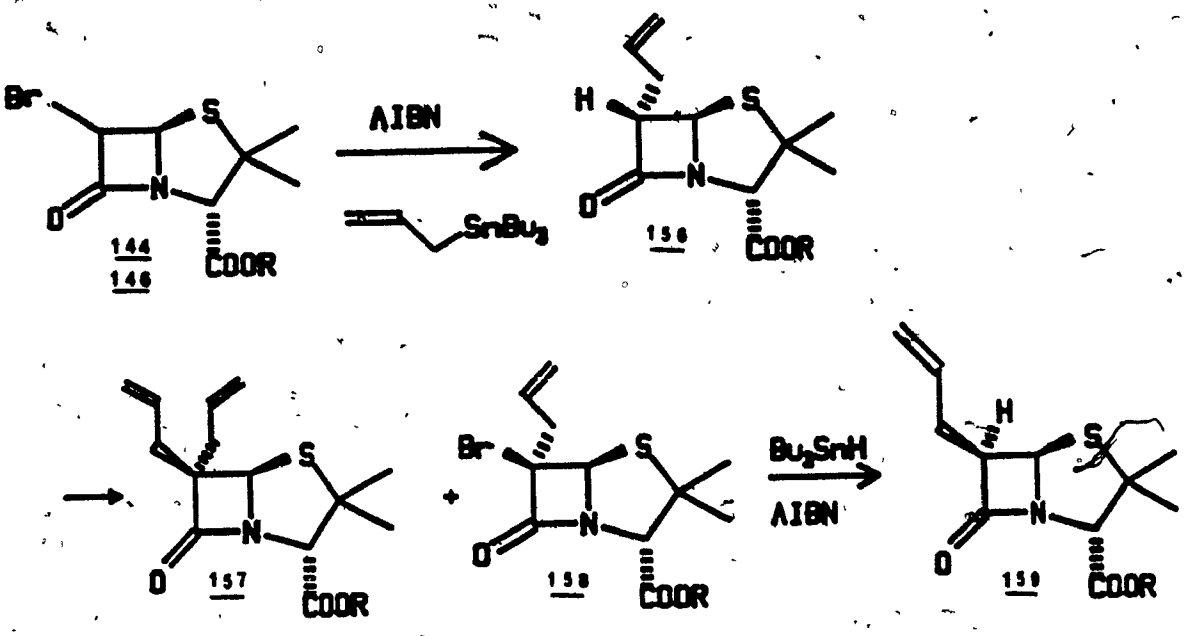


Table 5. Reaction of bromopenicillanates with olefins 148.

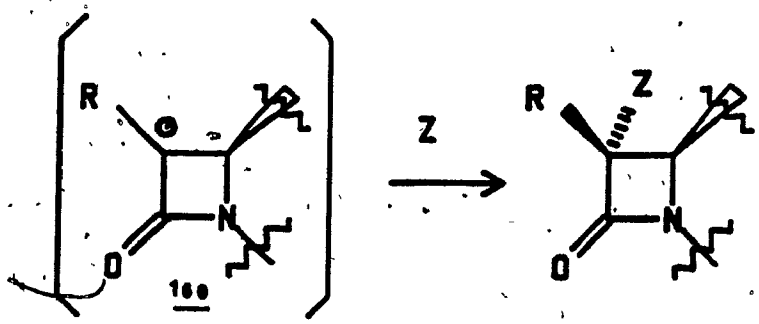
entry	substrate	olefin 148	method	Yield % 149 trans	151 cis
a	144	=-CN	A	67	-
b	145	=-CN	B	48	-
c	146	=-CN	C	8	47
d	144	=-COOMe	A	55	-
e	146	=-COOMe	C	6	44
f	144	=-OAc	A	43	-
g	146	=-OAc	C	5	35

In all of the above free radical reactions, the use of tributyltin hydride gave considerable amounts of reduction product 147 or 155. In order to avoid this major side reaction, we investigated the use of allyltributyltin which acts as both the olefinic substrate and tin radical chain propagator (S_H2)[95].

Using either the cis- or trans-6-bromopenicillanate with allyltributyltin (3 eq) and 15 % of azobisisobutyronitrile (AIBN) in toluene at 65°C gave 95 % of the 6α-allylpenicillanate 156 (95 %) as the only detectable diastereomer after 45 minutes. Reaction of 6,6-dibromopenicillanate 145 with allyltributyltin (2.2 eq) and AIBN (15 %) gave the 6 β-bromo,6α-allylpenicillanate 158 (60 %), 6,6-diallylpenicillanate 157 (22 %) and starting material (18 %) after 25 minutes at 80°C in toluene. Longer reaction time gave higher amounts of 157. Reduction of this mixture using tributyltin hydride transformed 158 into the 6 β-allylpenicillanate 159 as the only diastereomer in high yield. The stereochemistry of 158 was established by nOe ^1H nmr experiment. Also, the above reactions did not proceed in the presence of a radical scavenger such as 2,6-di-t-butyl-4-methylphenol (BHT), confirming a radical mechanism.

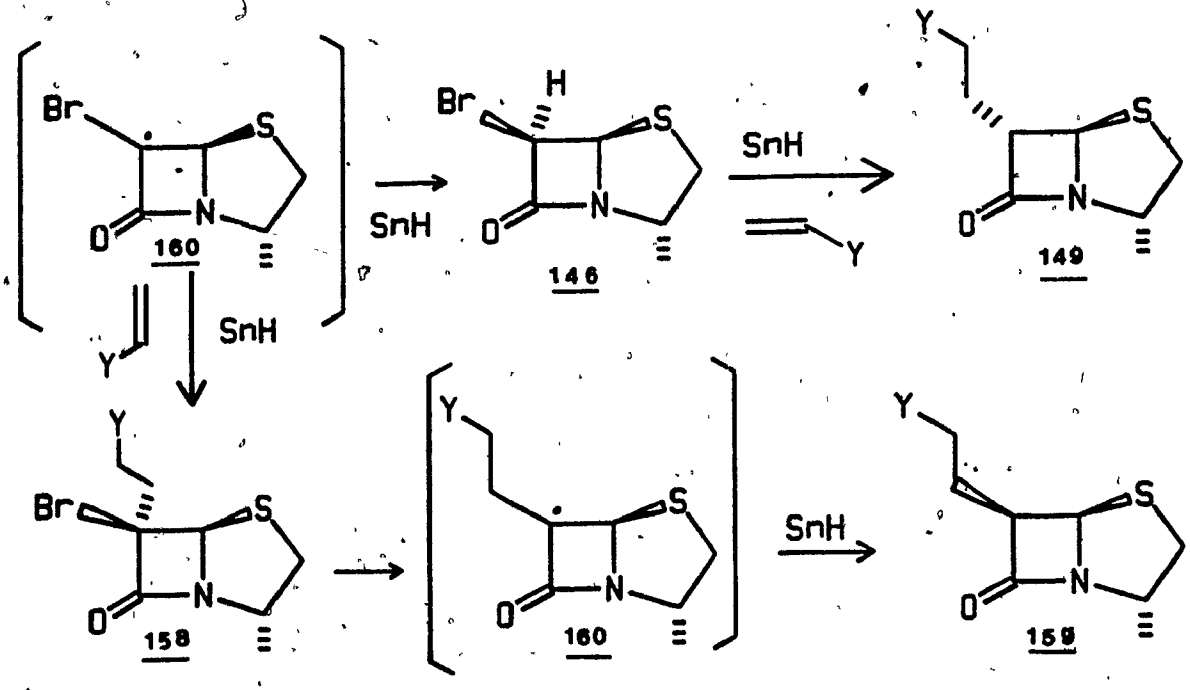


The reaction time for the above S_{H2} process was observed to be much faster than that obtained from simple alkyl halides and allyltributyltin (8 hrs at 80°C)[96]. The rate of conversion of 145 to 158 was about three times faster[97] than that of 144 to 156. Since a bromine substituent will stabilize the radical intermediate 160 more than an alkyl or hydrogen substituent, we can therefore postulate that the rate of reaction increases with an increase in radical stabilization for the above S_{H2} process.



R = H, Br, alkyl

The mechanism of the reaction must involve a radical intermediate such as 160 which either adds onto an olefinic bond or abstracts the hydrogen from tributyltin hydride, from the less hindered side of the azetidinone moiety. The minor diastereomer 149 (or 154) formed from method C, most likely results from some reduction of 145 to 146, which then adds onto olefin 148 (Scheme 7).



Scheme 7

Conclusion

In summary, the tributyltin mediated addition of a 3-azetidinyl or 6-penicillanyl radical to allyltributyltin or electrophilic olefins 148, constitute a mild and stereoselective method for introducing alkyl side-chains to azetidinones.

CHAPTER V : PROTON AND CARBON-13 NUCLEAR MAGNETIC RESONANCE STUDIES OF T- AND C- AZETIDINONES

Introduction

A number of techniques have been put forward for use in the configurational analysis of azetidinones. If both carbon-3 and carbon-4 bear proton substituents, ^{1}H nmr spectroscopy, in most instances, makes the distinction between T and C arrangements of H-3 and H-4 possible*. For polysubstituted azetidinones, however, no such fast and generally applicable spectroscopic technique appears available. Using ^{1}H nmr spectroscopy, the interpretation of chemical shift values[98] and nOe measurements[99] have provided reliable results only in selected cases, so that chemical degradation of polysubstituted compounds was necessary[100]. X-ray crystallography hinges on the availability of crystals and is both costly and time consuming[101]. Using ^{13}C nmr spectroscopy, ^{1}H - ^{13}C long range coupling constants have been measured[102], but ^{13}C chemical shift values of azetidinones have only been interpreted for substituent effects[103].

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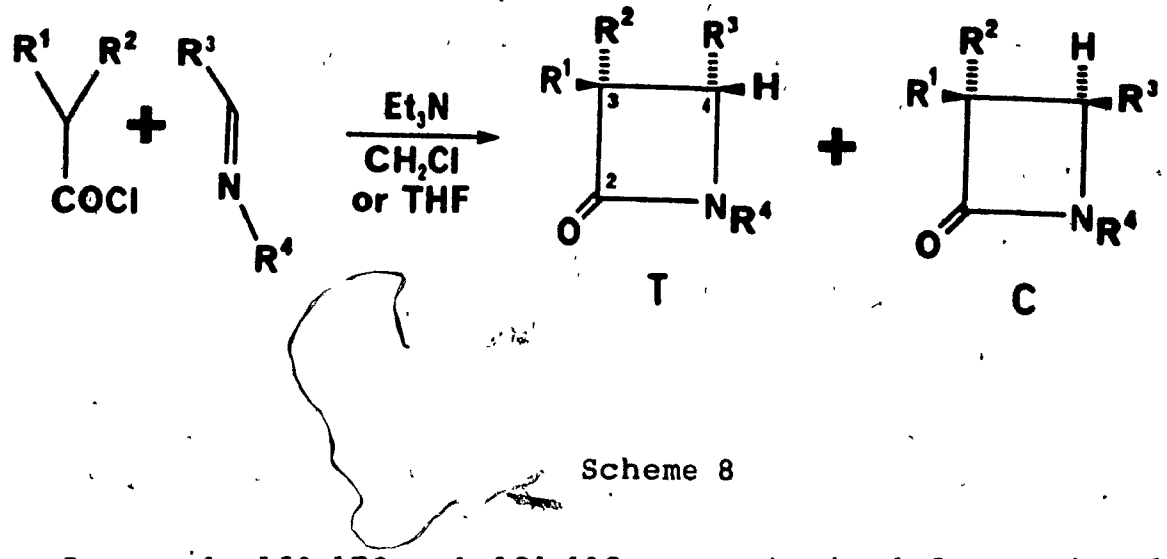
* The R and S designation for the C (cis) and T (trans) azetidinone pairs are listed in their corrosponding Table (6-11)

In carbohydrate chemistry, ^{1}H and ^{13}C nmr chemical shift information has been used for many years for conformational analysis[104,105], and the data of Perlin and Koch[106] indicate that the net shielding of ^{13}C nuclei of isomeric cyclohexane derivatives increases additively with an increase in repulsive non-bonding interaction within the molecules. However, studies of this kind have not been undertaken using azetidinones as substrates.

This chapter describes the effect of T/C isomerism, i.e., changes in conformational strain on the chemical shift values both of azetidinone ring carbon atoms (^{13}C nmr) and of protons attached to the azetidinone nucleus.

Results and discussions

The azetidinones under investigation were prepared in the course of projects described in chapters three and four, and were synthesized *via* the reaction of an acid chloride and a suitable Schiff base in the presence of triethylamine (Scheme 8). In general, mixtures of isomers were obtained, with the ratio of isomers being dependant upon the Schiff base and the solvent used[107], and both isomers were isolated by column chromatography. The T and C configuration of the azetidinone was determined from the coupling constants observed at H_3 and H_4 of the azetidinone nucleus, i.e., J= 2-3 Hz for the T isomer and J= 4-5 Hz for the C isomer.



Scheme 8

Compounds 169,170 and 181,182 were obtained from Bristol-Myers and Eli Lilly respectively. The polysubstituted azetidinones 183 to 190 were prepared by a method analogous to the one described above, and their T and C configuration assigned unambiguously from nOe studies, which were made possible by the favourable methyl substituent at carbon-3.

Monocyclic azetidinones bearing a proton at carbon-3:

Table 6, lists the ^{13}C chemical shift values for the azetidinone ring carbon atoms, together with the sums of the chemical shift values for carbon-2, carbon-3 and carbon-4, calculated in order to investigate a potential Perlin-Koch type relationship. Table 7, shows the corresponding ^{1}H chemical shift values.

The carbonyl resonance (carbon-2) proved to be the least affected by T/C isomerism of all the three ring carbon resonances, with differences in chemical shift values between corresponding T and C isomers of ca. 0.6 ppm. The carbon-2 resonances for T isomers were found either downfield or upfield of the resonances for corresponding C isomers. For both carbon-

Table 6: ^{13}C nmr chemical shifts of 3,4-disubstituted azetidinones.

		T/C	R_1	R_2	R_3	R_4	C-2	C-3	C_4	C_{ring}
161	(2R,3R) and (2S,3S)	T	N_3	H	CH=CHPh	o-BrPh	162.1	70.35	64.94	297.4
162	(2S,3R) and (2R,3S)	C					163.0	67.69	62.93	293.7
163	(2R,3R) and (2S,3R)	T	N_3	H	C≡CPh	o-BrPh	161.8	71.43	53.76	287.0
164	(2S,3R) and (2R,3S)	C					162.4	67.46	53.46	283.3
165	(2R,3R) and (2S,3R)	T	NHCOBn	H	CH=CHPh	o-BrPh	164.4	65.28	59.46	289.1
166	(2S,3R) and (2R,3S)	C					163.9	63.37	59.35	286.6
167	(2R,3R) and (2S,3R)	T	NHCOBn	H	C≡CPh	o-BrPh	164.5	64.30	53.73	282.6
168	(2S,3R) and (2R,3S)	C					165.5	59.22	53.62	278.4
169	(2S,3R)	T	OH				172.6	69.14	58.12	299.9
170	(2R,3R)	C	$MeCHCH_2$	H	$SCPh_3$	$^tBuSiMe_2$	171.9	64.23	60.68	296.8
171	(2S,3R) and (2R,3S)	T	H	Ph	Ph	p-MeOPh	165.0	65.15	63.80	294.0
172	(2S,3S) and (2R,3R)	C					164.1	64.93	62.99	292.0

Table 7: ^1H nmr chemical shifts of 3,4-disubstituted azetidinones.

		T/C	R_1	R_2	R_3	R_4	H-3	H-4	H_{3+4}
161	(2R,3R) and (2S,3S)	T	N_3	H	CH=CHPh	o-BrPh	4.86	4.93	9.79
162	(2S,3R) and (2R,3S)	C					5.33	5.06	10.4
163	(2R,3R) and (2S,3R)	T	N_3	H	C≡CPh	o-BrPh	5.15	4.85	10.0
164	(2S,3R) and (2R,3S)	C					5.52	4.90	10.4
165	(2R,3R) and (2S,3R)	T	NHCOBn	H	CH=CHPh	o-BrPh	4.81	4.97	9.78
166	(2S,3R) and (2R,3S)	C					5.31	5.45	10.8
167	(2R,3R) and (2S,3R)	T	NHCOBn	H	C≡CPh	o-BrPh	4.99	5.23	10.2
168	(2S,3R) and (2R,3S)	C					5.75	5.48	11.2
169	(2S,3R)	T	OH $MeCHCH_2$	H	$SCPh_3$	$^tBuSiMe_2$	3.38	4.06	7.45
170	(2R,3R)	C					3.14	4.32	7.46
171	(2S,3R) and (2R,3S)	T	H	Ph	Ph	p-MeOPh	4.26	4.90	9.16
172	(2S,3S) and (2R,3R)	C					4.18	4.83	9.01

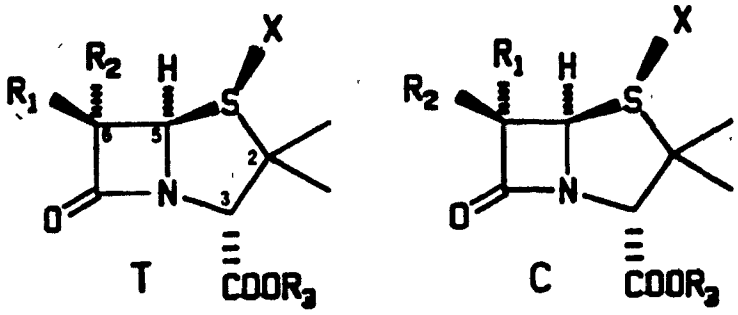
3 and carbon-4, the T isomer resonances were detected downfield from their corresponding C isomer resonance, with maximum downfield shifts of 5.1 (carbon-3) and 1.0 (carbon-4) ppm. We noted that carbon-3 resonances invariably displayed larger downfield shifts than carbon-4 resonances and, thus, subtracting the chemical shift values for carbon-4 from that of carbon-3 yielded numerical values which were consequently larger for T isomers than for C isomers, by an average value of 3.2 ppm. Similarly, the sums of the chemical shift values for carbon-2, carbon-3 and carbon-4 proved to be larger for T isomers than for corresponding C isomers, as postulated by a Perlin - Koch type relationship.

Contrary to the pattern observed for the resonance for carbon-3 and carbon-4 in ^{13}C nmr, in the ^{1}H nmr spectra both H-3 and H-4 resonances for T isomers were generally found upfield of the resonances for corresponding C isomers. Accordingly, the sums of the chemical shift values of H-3 and H-4 resonances were smaller for T than for corresponding C isomers. The presence of two phenyl substituents at carbon-3 and carbon-4 (171,172) caused exceptional chemical shift values for both the H-3 and H-4 resonances.

Bicyclic azetidinones :

Tables 8 and 9 list the ^{13}C and ^{1}H nmr chemical shift values, respectively of the T and C isomers of penicillanates 173 to 182. The chemical shift values for azetidinone carbon-5 and carbon-6, in general, exhibit the same trend as observed in the carbon-3 and carbon-4 resonances of monocyclic azetidinones

(Table 6) with differences in chemical shift values between the T and C isomers being more pronounced at carbon-6. The sums of the chemical shift values for carbon-5 and carbon-6 were



consistently larger for the T isomers than the corresponding C isomers of penicillanates 173 to 180. However, the presence of a sulfoxide group (beta) in the T/C pair of penicillanates 181 and 182, caused exceptional chemical shift values for carbon-5, resulting in only a small difference between the sums of the chemical shift values for the ring carbon resonances for the T/C pair. A similar trend was found when the sums of all the ^{13}C chemical shift values for all the carbon resonances were considered. On closer examination, it was found that the amide carbonyl resonance for the C*isomer (182) was 5 ppm downfield from the corresponding resonance for the T isomer. A possible explanation for this, may be the shielding cone of the sulfoxide group (beta) which can influence the amide substituent in 182 by dipolar, H-bonding or anisotropic interaction.

Table 8: ^{13}C nmr chemical shifts of penicillanates.

		T/C	R_1	R_2	R_3	X	C-5	C-6	C_{6+5}	C_{ring}	C_n
173	(5R,6S)	T	CH_2CH_2COOMe	H	$CHPh_2$	-	66.48	60.74	166.9	294.2	1940
174	(5R,6R)	C					66.96	52.42	167.0	286.5	1931
175	(5R,6S)	T	CH_2CH_2COOMe	H	CH_3	-	66.62	60.53	168.4	295.5	995.5
176	(5R,6R)	C					66.27	53.16	168.6	288.0	985.2
177	(5R,6S)	T	CH_2CH_2CN	H	$CHPh_2$	-	66.04	59.89	166.8	292.7	1815
178	(5R,6R)	C					66.35	52.51	166.8	285.6	1805
179	(5R,6S)	T	$CH_2CH=CH_2$	H	$CHPh_2$	-	69.73	60.62	167.0	297.4	1942
180	(5R,6R)	C					66.70	53.17	167.2	287.1	1931
181	(5R,6S)	T	$NHCOCH_2OPh$	H	CH_3	O	77.96	64.85	168.2	311.0	1459
182	(5R,6R)	C					76.52	66.46	168.2	311.3	1465

Table 9: ^1H nmr chemical shifts of penicillanates.

		T/C	R_1	R_2	R_3	X	H-5	H-6	H_{6+5}	H_n
173	(5R,6S)	T	CH_2CH_2COOMe	H	$CHPh_2$	-	5.07	3.35	8.42	31.1
174	(5R,6R)	C					5.47	3.65	9.12	31.6
175	(5R,6S)	T	CH_2CH_2OAc	H	$CHPh_2$	-	5.13	3.36	8.49	31.2
176	(5R,6R)	C					5.46	3.67	9.13	31.8
177	(5R,6S)	T	CH_2CH_2CN	H	$CHPh_2$	-	5.13	3.40	8.53	27.7
178	(5R,6R)	C					5.51	3.69	9.20	28.2
179	(5R,6S)	T	$CH_2CH=CH_2$	H	$CHPh_2$	-	5.15	3.38	8.53	36.4
180	(5R,6R)	C					5.44	3.68	9.12	36.8
181	(5R,6S)	T	$NHCOCH_2OPh$	H	CH_3	O	5.08	5.41	10.5	26.3
182	(5R,6R)	C					5.03	6.09	11.1	27.o

For the ^1H chemical shift values (Table 9), on the other hand, the sums of the chemical shift values of H-3 and H-4 resonances were larger for the C isomer than for corresponding T isomers.

3,4-Trisubstituted azetidinones:

The replacement of a proton at C-3 by a methyl group (183-190) reduced the range of chemical shift values for the C-2 resonance for T and C isomers, with differences in chemical shift values between the T and C isomers averaging 0.1 ppm. The C-3 resonances for the T isomers of T/C pairs were detected both upfield or downfield of the C-3 resonances for the corresponding C isomers, and no consistent pattern was observed. C-4 resonances for the T isomers, however, were without exception located upfield of the corresponding C isomer resonances, with the average value of the upfield shift being 2.1 ppm. Interestingly, the sums of the chemical shifts of the C-2, C-3 and C-4 resonances were smaller for the T isomers than for the C isomers. In contrast to the strong influence of an additional substituent at C-3, removal of the N-substituent (187,188 to 189,190) did not have a similar effect, with the ring carbon resonances for both the T and the C isomers undergoing chemical shift changes of similar magnitudes, thus resulting in retention of the general pattern of their chemical shift values.

Table 10: ^{13}C nmr chemical shifts of 3,4-trisubstituted azetidinones.

		T/C	R_1	R_2	R_3	R_4	C-2	C-3	C-4	C_{ring}
183	(2S,3S) and (2R,3R)	T	N-phthaloyl	CH_3	CH=CHPh	p-MeOPh	163.5	70.49	65.00	299.0
184	(2R,3S) and (2S,3R)	C					163.4	69.61	66.47	299.4
185	(2S,3S) and (2R,3R)	T	PhO	CH_3	CH=CPh	p-MeOPh	165.1	90.97	65.59	321.6
186	(2R,3S) and (2S,3R)	C					165.1	89.09	68.07	322.3
183	(2S,3R) and (2R,3S)	T	Ph	CH_3	Ph	p-MeOPh	168.6	67.06	62.62	298.3
184	(2R,3R) and (2S,3S)	C					168.6	68.85	64.76	302.3
183	(2S,3R) and (2R,3S)	T	Ph	CH_3	Ph	H	172.4	64.11	63.66	300.1
184	(2R,3R) and (2S,3S)	C					172.5	66.64	65.4	304.5

Analogously to that observed for the C-4 resonances, the proton chemical shift values for the T and C isomers were reversed in 3,4 trisubstituted azetidinones, and the H-4 resonances (Table 11) for the T isomer was downfield of the H-4 resonances of the corresponding C isomer. With similar consistency, the resonance for the methyl substituent at C-3 was detected upfield for the T isomer.

Conclusion

Analysis of the ^{13}C and ^{1}H nmr spectra for T/C pairs of azetidinones showed that both the ^{13}C chemical shift values and the ^{1}H chemical shift values for azetidinones 161 to 172 and 183 to 190, or penicillanates 173 to 182, differ distinctly for pairs of T and C isomers. This may provide an additional analytical tool for use in configurational analysis particularly in the case of polysubstituted azetidinones.

Table 11: ^1H nmr chemical shifts of 3,4-trisubstituted azetidinones.

		T/C	R_1	R_2	R_3	R_4	H-4	C_3-CH_3	H_{4+Me}
183	(2S,3S) and (2R,3R)	T	N-phthaloyl	CH_3	CH=CHPh	p-MeOPh	4.94	1.91	6.85
184	(2R,3S) and (2S,3R)	C					4.71	2.17	6.88
185	(2S,3S) and (2R,3R)	T	PhO	CH_3	CH=CPh	p-MeOPh	4.86	1.65	6.51
186	(2R,3S) and (2S,3R)	C					4.63	1.72	6.35
183	(2S,3R) and (2R,3S)	T	Ph	CH_3	Ph	p-MeOPh	5.21	1.23	6.44
184	(2R,3R) and (2S,3S)	C					5.03	1.92	6.95
183	(2S,3R) and (2R,3S)	T	Ph	CH_3	Ph	H	4.93	1.16	6.09
184	(2R,3R) and (2S,3S)	C					4.75	1.86	6.61

CONTRIBUTION TO KNOWLEDGE

1. Free radical addition of methyl bromoacetate onto α, β-unsaturated esters 81, 83 and 84 gave exclusively the 1,4 Michael adducts 82, 85 and 86 respectively in high yields.
2. Analogously, 4-substituted glutarimides 91, 92, and 88 were obtained in good yields using iodoacetamide as the radical precursor.
3. Tricyclic carbapenems 116, and 119/120 were obtained by free radical cyclization of an appropriate monocyclic N-substituted azetidinone. These strained tricyclic azetidinones were found to be unstable in solution, and to exhibit exceptionally high β-lactam infrared frequency.
4. Tricyclic carbacephems 125, 127 and 132/133 were synthesized analogously and found to be much more stable. Hydrogenolysis of 127 gave the tricyclic phenol carbacephem 129 which gave an unusually low β-lactam frequency resulting from hydrogen bonding, wheras ozonolysis of 132/133 gave the keto tricyclic carbacephem 135, which was less stable than the above tricyclic carbacephems, but more stable than the benzo cabapenems.
5. A stereoselective method for the syntheses of cis- and trans-6-alkylpenicillanates 149 and 151 respectively, was developed using a free radical chain reaction. Similarly, N-substituted monocyclic cis- and trans-3-alkylazetidinones 153 and 154 respectively, were synthesized.

Experimental

The nmr spectra were recorded on a Varian XL-200 or XL-300 spectrometer using TMS as internal standard and chloroform as the solvent (unless otherwise specified). The chemical shift (δ) and coupling constant (J) are quoted in ppm and Hertz respectively, and their assignments were determined unambiguously by decoupling, nOe or 2D experiments when necessary. The infrared spectra (ir, νmax) were recorded on a Perkin Elmer 297 and the values quoted in cm^{-1}. Mass spectra (ms) were obtained on HP 5984A or Dupont 21-482B mass spectrometers, ion source 250° and 70 eV electron impact, direct inlet; m/z (assignment, relative intensity). Melting points were determined on a Gallenkamp block and are uncorrected. Column chromatography was performed using Woelm Silica 32 - 63 micron size.

Experimental : (Chapter II)

3-Bromo-2,2-bis(O-propargyl) butane62

3-Bromo-2-butanone (1.0 g, 6.6 mmole), propargyl alcohol (5.6 g, 100 mmol) and trimethylsilyl chloride (2.5 g, 23 mmol) were stirred overnight at room temperature and then heated to reflux for one hour. The mixture was cooled, the solvent removed and the residue azeotropically distilled with toluene (10 ml) to give 610 mg of product (40 %) after distillation; bp 75-80°C at 12 mm-Hg; ^1H nmr ($CDCl_3$): 1.49 (s,3H,CH_1), 1.69(d,3H,C_4-H,J= 5.8), 2.41 (t,2H,C_1'-H), 4.15 (dd,1H,C_3-H,J= 5.8), 4.18 (m,4H,C_3'-H); ms (210°C): 229 (M^+, 0.3), 189 (M^+ - C_3H_3O, 6.8), 91 (M^+ - $C_6H_6O_2$, 13), 65 (28), 43 (100).

Radical cyclization of 62

Tributyltin hydride (500 mg,2.18 mmol), benzene (2 ml) and AIBN (5 mg) were added dropwise over a 5 h period (syringe pump) to dry benzene (40 ml), ketal 62, and AIBN (2 mg) at 80°C under an inert atmosphere. The mixture was cooled, the solvent removed and the residue dissolved in acetonitrile and washed three times with hexanes (30 ml). The solvent was removed to afford the cyclic ketal 63 as an oil; ^1H nmr ($CDCl_3$); 1.11 (d,3H,C_2-H,J= 8), 1.48 (s,3H,CH_3), 1.85 (dd,1H,C_2-H,J= 8), 2.33 (t,1H,C_1'-H,J= 2), 4.17 (d,2H,C_2-H,J= 2), 4.23 (m,2H,CH_2'-H), 4.88 (m,2H,C=CH_2).

3-O(p-methoxybenzyl)-1,2:5,6-di-O-isopropylidene-D-glucofuranose 65

To a stirred suspension of sodium hydride (0.8g, 50% oil dispersion,16 mmole) in 50 ml of dry THF at 10°C under an inert atmosphere, were added diacetone glucose (2.6g, 10 mmole) followed by tetrabutylammonium iodide (0.1 g, 0.3 mmole). After 15 min, p-methoxybenzyl chloride (1.56 g, 10 mmole) was added dropwise, and the mixture was then refluxed for one hour, cooled to room temperature, and the excess sodium hydride neutralized with glacial acetic acid (1 to 2 ml). The solvent was removed, the residue dissolved in ether (100 ml), washed with aqueous sodium bicarbonate (5 %, 50 ml) and and then with brine (50 ml). The organic extract was dried with $MgSO_4$ and the solvent removed to give an oil. The oil dissolved in a mixture of ether and hexanes (1 : 9), and the solution filtered through celite. The solvent was removed to give 3.7 g of product as a pale yellow oil (98 %); ^1H nmr ($CDCl_3$): 1.30, 1.36, 1.40 and 1.48 (s,3H,CH_3), 3.79 (s,3H,OCH_3), 4.0 - 4.50 (m,5H,C_2-H,C_3-H,C_5 and C_6-H), 4.57 (d,1H,C_4-H,J= 3.8), 4.6 (s,2H,CH_2-Ar), 5.9(d,1H,C_1-H,J= 3.6), 6.80 - 7.40 (m,4H,Ar-H).

3-O(p-methoxybenzyl)-1,2-O-isopropylidene- D-glucofuranose 66

Diacetone glucose 65 (0.56 g,1.47 mmole) and acetic acid (70 %, 3 ml) were heated to 70°C for 45 min. The mixture was cooled, dissolved in water (20 ml) and extracted twice with methylene chloride (20 ml). The organic extract was washed with brine (20 ml), dried over $MgSO_4$ and and the solvent removed to

give the diol 18 as an oil (480 mg, 96 %). ^{1}H nmr ($CDCl_3$): 1.32 and 1.48 (s,3H,CH_3), 2.9 - 3.0 (bs,2H,C_5-OH and C_6OH), 3.83 (s,3H,OCH_3), 3.75 - 4.10 (m,3H,C_5-H and C_6-H), 4.13 (s,2H,C_3-H and C_2-H), 4.6 (bs,3H,CH_2-Ar and C_4-H), 5.90 (d,1H,C_1-H,J= 3.8), 6.8 - 7.43 (bs,4H,Ar-H).

3-O(p-methoxybenzyl)-1,2-O-isopropylidene D-glucofuranaldehyde 67

Sodium periodate (17.4g, 81 mmol) and water (100 ml) were added to THF (100 ml) and diol 66 (7.3 g, 22 mmol) at ambient temperature. After 2 h, the precipitate was filtered off, washed with water (50 ml) and ether (50 ml), and the combined filtrate concentrated to half volume under reduced pressure. The product was extracted three times with ether (100 ml), and the organic extracts washed with brine (100 ml) and then dried over $MgSO_4$. The solvent was removed to give 5.6 g (85 %) of aldehyde 67 as a pale yellow oil; ^{1}H nmr ($CDCl_3$): 1.33 and 1.46 (s,3H,CH_3), 3.81 (s,3H.OCH_3), 4.33(d,1H,C_3-H,J= 3.7), 4.45 (d,1H,C_2-H,J= 3.8), 4.56 (dd,2H,OCH_2-Ar,J= 6.4,16), 4.66 (d,1H,C_4-H,J= 3.7), 5.15 (d,1H,C_1-H,J= 3.8), 6.8 - 7.26 (m,4H,Ar-H), 9.20 (2,1H,C_5-H,J=1.8).

3-O(p-methoxybenzyl)-1,2-O-isopropylidene D-furanoic acid 68

A suspension of silver(I)oxide (4.2 g, 18.2 mmol) in aqueous sodium hydroxide (5 %, 30 ml) were added dropwise to THF (30 ml) and aldehyde 67 (5.6 g, 18.2 mmol) at ambient temperature. This exothermic reaction was kept below 30°C. After an additional 2 h of stirring, the precipitate was fltered off and washed with water (50 ml) and THF (50 ml). The

combined filtrate was concentrated to 60 ml under reduced pressure, and then extracted twice with ether (50 ml). The organic extract was discarded, the aqueous fraction acidified with aqueous hydrochloric acid to a pH of 2.0, and extracted twice with ether (50 ml). The organic extract was washed with brine (50 ml), dried over $MgSO_4$ and the solvent removed to give an oil which crystallized on refrigeration. Recrystallization using ether/hexanes gave 4.7 g of colorless product (87 %), mp 96-101 °C; ^1H nmr ($CDCl_3$): 1.34 and 1.46 (s,3H,CH_3), 3.8 (s,3H,OCH_3), 4.26 (d,1H,C_3-H,J= 3.8), 4.5 (s,2H,CH_2), 4.53 (d,1H,C_2-H,J= 3.7), 4.8 (d,1H,C_4-H,J= 3.8), 6.02 (d,1H,C_1-H,J= 3.6), 6.66 - 7.2 (m,4H,Ar-H), 9.32 (bs,1H,O-H). ms (60 °C): 324 (M^+, 1.0), 279 (M^+ - COOH, 4.0), 220 (15), 205 (6), 180 (2.5), 153 (19), 152 (84), 138 (64), 135 (86), 121 (84).

3-O(p-methoxybenzyl)-1,2-O-isopropylidene D-glucofuranoyl chloride 69

Glucofuranoic acid 68 (870 mg, 2,7 mmol) and triethylamine (2.0 ml) were stirred for several min, and the excess triethyl amine removed under reduced pressure. The residue was azeotroped with toluene (10 ml) to give 988 mg (100 %) of pale yellow crystals. This salt was then dissolved in methylene chloride (50 ml), cooled to 0°C, and treated with a dropwise addition of oxallyl chloride (300 mg, 2.8 mmole) under an inert atmosphere. The mixture was then warmed to room temperature and stirred for an additional 30 min. The solvent was removed, the residue dissolved in ether (30 ml) and the precipitate (triethylamine hydrochloride) filtered off. The solvent was

then removed to give the furanoyl chloride as a yellow oil; ^1H nmr ($CDCl_3$): 1.33 and 1.45 (s,3H,CH_3), 3.78 (s,3H,OCH_3), 4.1 (d,1H,C_3-H,J= 3.7), 4.38 (d,1H,C_2-H,J= 3.7), 4.56 (s,2H,OCH_2O), 4.58 (d,1H,C_4-H,J= 3.7), 6.07 (d,1H,C_1-H,J= 3.6), 6.81 - 7.20 (m,4H,Ar-H).

6-Methyl,6-Bromo,5-oxo-3(O-p-methoxybenzyl)-1,2-O-isopropylidene D-glucofuranose 70

Glucofuranoyl chloride 69 (920 mg, 2.68 mmole) was added dropwise to ethereal diazomethane (excess) at 0°C. The resulting mixture was then refrigerated overnight at -5°C. A stream of nitrogen was then passed through the solution until room temperature, in order to remove the excess diazomethane. Pyridinium hydrobromide (8 g, 52 mmol) was added and the mixture stirred for 10 h at room temperature. The excess salt was filtered off, the solvent removed and the residue purified by column chromatography using ether/hexanes as eluant (1.5 : 8.5) to give the bromo-ketone as an 8:1 mixture of diastereomers. The major isomer was purified by flash chromatography giving 70 as colorless crystals (291 mg, 27 %), mp 72-74 °C; ^1H nmr ($CDCl_3$): 1.33 and 1.49 (s,3H,CH_3), 1.60 (d,3H,C_7-H,J= 6.8), 3.80 (s,3H,OCH_3), 4.27 (d,1H,C_3-H,J= 3.7), 4.42 (dd,2H,OCH_2-Ar,J= 11,14.6), 4.58 (d,1H,C_2-H,J= 3.4), 4.83 (dd,1H,C_6-H,J= 6.8), 6.07 (d,1H,C_1-H,J= 3.5), 6.84 - 7.15 (m,4H,Ar-H); ^{13}C nmr ($CDCl_3$): 18.62 (C_7), 26.41 and 26.99 (CH_3), 41.71 (C_6), 55.26 (OCH_3), 72,42 (CH_2), 84.13 (C_2), 84.20 (C_3), 106.24 (C_1), 108.1, 112.55, 128.59, 113.9, 129.6 (Ar-C), 159.6 (C_5); ms (65°C): 414/416 ($M^{+\cdot}$, 0.5), 335 ($M^{+\cdot}$-Br$^\cdot$, 70.7), 277 (31.3), 177 (36.2), 159 (100), 149 (26.7), 175

(20.6), 121 (100); Exact mass (105°C): calcd. for $C_{18}H_{23}O_6$; 335.1494: found; 335.1424 .

6-Methyl-6-Bromo,5-Oxo-1,2-O-isopropylidene D-glucofuranose 71

Methylene chloride (10 ml) , water (0.5 ml), bromo-ketone 70 (250 mg, 0.60 mmol) and DDQ (200 mg, 0.87 mmol) were stirred at room temperature overnight.The solvent was removed, and the residue dissolved in water (30 ml) and extracted twice with ethyl ether (30 ml). The organic extract was washed with aqueous sodium bicarbonate (5 %, 30 ml), brine (30 ml) and dried over Na_2SO_4. The solvent was then removed to give 225 mg of colorless crystals (99 %), mp 107 °C; ^1H nmr ($CDCl_3$): 1.34 and 1.51 (s,3H,CH_3), 1.72 (d,3H C_7-H,J= 6.8), 2.26 (d,1H,O-H), 4.56 (m,2H,C_2-H and C_3-H), 4.90(dd,1H,C_6-H,J= 6.4,6.8), 4.99 (d,1H,C_1-H,J= 3.2); ms (40 °C): 293 (M^+ - H, 0.8), 279 (M^+ - CH_3, 7.4), 221 (7.2), 219 (7.6), 201 (6.6), 159 (87), 59 (100).

6-Methyl,6-Bromo,5-(dipropargyl ketal)-1,2-O-isopropylidene D-glucofuranose 73

Benzene (2 ml), 2,2-dipropargyl propane 72 (120 mg, 0.79 mmol), bromo-ketone 71 (46 mg, 0.156 mmol) and acidic resin (catalytic) were stirred overnight at ambient temperature, and then 2 h at 60-80 °C. The mixture was cooled, the solvent removed and the residue purified by column chromatography to give 15 mg (25 %) bromo-ketal 73 as a colorless oil; ^1H nmr ($CDCl_3$), 1.39 and 1.50 (s,3H,CH_3)m 1.85 (d,3H,C_7-H,J= 6.8), 2.47 - 2.50 (m,2H,C_3'-H), 2.98 (d,1H,O-H,J=6.2), 4.28 - 4.42 (m,3H,C_6-H,C_2-H and C_3-H), 4.43 - 4.50 (m,5H,C_4-H, C_1'-H), 5.13 (d,1H,C_1-H,J= 3.8); ms (117°C), isobutane (CI): 333/335 (M^+-

C_3H_3O, 100/100), 291 (6.7), 289 (17.2), 279 (27.3), 255 (5.8), 237 (8.6);

Radical cyclization of 73

Tributyltin hydride (14 mg, 0.05 mmol), benzene (3 ml), bromo-ketal 73 (15 mg, 0.039 mmol) and AIBN (catalytic) were refluxed for 5 h. The mixture was cooled and the solvent removed to give a residue which was dissolved in acetonitrile (10 ml) and washed three times with hexanes (10 ml). The solvent was removed and the product was purified by column chromatography to give 6.5 mg (55 %) of cyclic ketal 74 as an oil; ^1H nmr ($CDCl_3$): 1.19 (d,3H,C_{10}-H,J= 7.3), 1.38 and 1.52 (s,3H,CH_3), 1.96 (dd,1H,C_6-H,J= 7.3, 16), 2.39 (t,1H,C_3-H,J= 2), 4.24 (m,2H,C_1-H), 4.24 - 4.27 (m,5H,C_2-H,C_3-H,C_4-H and C_9-H), 4.93 (m,2H,C_{11}-H), 5.12 (d,1H,C_1-H,J= 4); ms (150 °C), isobutane (CI): 383 ($M + H^+$, 2.1), 323 (2.3), 281 (9.2), 216 (13).

Methyl 3-O(p-methoxybenzyl)-1,2-O-isopropylidene D-glucofuranate 75

Ethereal diazomethane (5 %, 30 ml) was added to furanoic acid 68 (100 mg, 0.31 mmol) and ether (20 ml) at 0°C. After 3 h, the excess diazomethane was decomposed with glacial acetic acid (until decolorization) and the solvent removed. The residue was purified by column chromatography to give the methyl furanoate as an oil (98 mg, 94 %); ^1H nmr ($CDCl_3$): 1.32 and 1.47 (s,3H,CH_3), 3.76 (s,3H,$COOCH_3$); 4.24 (d,1H,C_3-H,J= 3.7), 3.81 (s,3H,OCH_3), 4.5 (dd,2H,OCH_2O,J= 5,17), 4.57 (d,1H,C_2-H,J= 3.7), 4.81 (d,1H,C_4-H,J= 3.6), 6.08 (d,1H,C_1-H,J=

3.6), 6.85 - 7.21 (dd,4H,Ar-H); ms (70°), isobutane (C.I.): 339 ($M^+ + H^+$, 2.5), 338 (M^+, 0.8), 280 ($M^+ - CO_2CH_3$, 2.9), 263 (2.0), 121 (100).

Thio-ketalization of 75

Methyl glucofuranoate 75 (100 mg, 0.295 mmol), ethyl-acetate (5 ml), ethanethiol (91 mg, 1.5 mmol) and zinc (II) chloride (5 mg) were stirred at -10° C for 15 min. The mixture was warmed to room temperature, and the solvent removed. Purification of the residue by column chromatography gave 48 mg (89 %) of p-methoxybenzyl thioethyl ether 76 as a pale yellow oil; ^1H nmr ($CDCl_3$): 1.22 (t,3H,CH_3,J= 10), 2.41 (dd,2H,CH_2,J= 10,16), 3.64 (s,2H,Ar-CH_2), 3.76 (s,3H,OCH_3), 6.8 - 7.26 (dd,4H,Ar-H); ms (35°C): 182 (M^+, 32.9), 153 (M^+ - Et, 1.0), 151 (1.4), 122 (22.9), 121 (100), 91 (6.8).

1,2-isopropylidene-3-O-(diphenyl-tertbutyl silyl)-4-glutaryl- D glucofuranose 82

Tributyltin hydride (1.2 g, 4.15 mmol) and AIBN (2 mg) were added dropwise over a 12 h period (syringe pump) to dry benzene (0.5 ml), unsaturated ester 81 (100 mg, 0.207 mmol), methyl bromoacetate (635 mg, 4.15 mmol) and AIBN (2 mg) at 80°C under an inert atmosphere. The mixture was cooled, the solvent removed and the residue dissolved in acetonitrile (30 ml) and washed three times with hexanes. The solvent was removed to give a mixture of glutarate 82 (30 %) and starting material (over 60 %). The mixture was then recycled once using the above conditions to afford 68 mg of glutarate 46 (58 %) and 5 % starting material after purification by column chromatography; ^{1}H nmr ($CDCl_3$): 1.07 (s,9H,Me_3), 1.26 and 1.37 (s,6H,Me_2), 2.37 (d,2H,C_6-H,J= 6.4), 2.70 (ABX,2H,C_7-H,J= 3.8,7.2,16), 2.71 - 3.00 (m,1H,C_5-H), 3.63 and 3.65 (s,3H,OMe), 4.08 (dd,1H,C_4-H,J= 2.5,10), 4.23 (dd,1H,C_3-H,J= 2.5), 4.27 (d,1H,C_2-H,J= 3.8), 5.72 (d,1H,C_1-H,J= 3.8), 7.4 - 7.7 (m,10H,Ar-H); ms (181°C); 525 (M^+ - C_2H_3O, 8.8), 499 (M^+ - C_4H_9, 100), 441 (12), 381 (17), 339 (18), 253 (13), 213 (12); Exact mass (105°C): calcd. for $C_{26}H_{31}O_8Si$ (M^+ - C_4H_9); 499.1788: found; 499.1811 .

Dimethyl glutarate 85

Tributyltin hydride (1.9g, 11.5) and AIBN (2 mg) were added dropwise over a 5 h period to dry Benzene (5 ml), methyl acrylate (100 mg,1.16 mmol), methyl bromoacetate (1.3 g, 11.5 mmol) and AIBN (5 mg) at 80°C under an inert atmosphere. The mixture was cooled , the solvent removed and the residue dissolved in acetonitrile (50 ml) and washed three times with hexanes (50

ml). The solvent was then removed and the residue distilled to give 155 mg (77 %) of glutarate 85 as an oil, bp 96-99°C at 15 mm-Hg. The spectroscopic data (^{1}H nmr and ir) were identical to that previously reported[79a].

Dimethyl 4-methylglutarate 86

Using the same procedure as described for 85, was obtained 75 % yield of methyl 4-methylglutarate 86 with identical physical and spectroscopic data to that previously reported[78].

1,2-isopropylidene-3-O-(diphenyl-tertbutylsilyl)-4-glutarimidyl- D-glucofuranose 88

Tributyltin hydride (1.2 g, 4.15 mmol) was added dropwise over a 12 h period (syringe pump) to unsaturated ester 81 (100 mg, 0.207 mmol) and iodoacetamide (890 mg, 4.15 mmol) at 40°C under an inert atmosphere with irradiation using a tungsten lamp. The mixture was cooled, the solvent removed and the residue dissolved in acetonitrile (30 ml) and washed three times with hexanes. The solvent was removed to give a mixture of glutarimide 87 , amido ester 88 and starting material. The mixture was then recycled once using the above conditions and then heated at 120°C for 3 h to afford 70 mg of glutarimide 88 (67 %) and 10 % starting material after purification by column chromatography; ir (KBr): 1710 (CO), 3250 (N-H); ^{1}H nmr ($CDCl_3$): 1.06 (s,9H,t-butyl), 1.11 and 1.37 (s,3H,Me_3), 2.18 - 3.00 (m,5H,C_5-H,C_6-H and C_7-H), 3.78 (dd,1H,C_4-H,J= 2.4,8.7), 4.19 (d,1H,C_3-H,J= 2.4), 4.35 (d,1H,C_2-H,J= 3.7), 5.80 (d,1H,C_1-H,J= 3.7), 7.37 - 7.80 (m,10H,Ar-H), 7.95 (bs,1H,N-H);

ms (264°C); 452 ($M^{+\cdot} - C_4H_9$, 100), 453 (32.7), 454 (9.8), 394 (8), 353 (14), 322 (9), 274 (14), 199 (32); Exact mass (180°C): calcd. for $C_{24}H_{26}O_6NSi$ ($M^{+\cdot} - C_4H_9$); 452.1529: found; 452.1489 .

Glutarimide 91 and 4-methylglutarimide 92

Using the same procedure as described for the preparation of glutarate 85 and using iodoacetamide instead of methyl bromoacetate, gave after heating to 120°C of the crude mixture for three hours and purification by column chromatography, 87 % of glutarimide 91 and 85 % of 4-methylglutarimide 92. Both physical and spectroscopic data were identical with that previously reported[79b,80].

Hydroxy-unsaturated ester 94

Iodoacetamide (300 mg,1.62 mmol) and the benzyl ether 93 (50 mg, 0.16 mmol) were heated at 80°C for 3 h. The mixture was cooled, dissolved in water (30 ml) and the product extracted with ethylacetate (30 ml), The solvent was removed and the residue purified by column chromatography to give 25 mg (71 %) of alcohol 94 as colorless crystals, mp 104 °C; ^1H nmr ($CDCl_3$): 2.28 (d,1H,O-H, J= 10.5), 3.60 (d,1H,C_5-H,J= 10.5), 3.74 (s,3H,)Me), 4.21 (d,1H,C_6-H,J= 5), 4.35 (dd,1H,C_9-Ha,J= 7.5), 5.19 (d,1H,C_9-Hb,J= 7.5), 5.30 (m,2H,C_8-H), 5.92 (m,1H,C_7-H), 6.13 (dd,1H,C_2-H,J= 2,16), 6.88 (dd,1H,C_1-H,J=4, 16); ms (50°C): 214 ($M^{+\cdot}$, 2.4), 183 ($M^{+\cdot} - CH_3O$, 17.6), 129 (31.9), 128 (36.2), 28 (100).

2-Ethylsuccinimide 96

Tributyltin hydride (510 mg, 1.75 mmol) and AIBN (2 mg) were added dropwise over a 5 h period to N-bromoacetyl crotonamide[72] 95 (300 mg, 1.46 mmol) and dry benzene (40 ml) at 80°C under an inert atmosphere. The solution was cooled, the solvent removed and the residue dissolved in acetonitrile (30) and washed three times with hexanes (30 ml). The solvent was removed and the and the residue purified by column chromatography to afford 121 mg of 2-ethylsuccinimide (65 %) as colorless crystals, mp 76-77°C; Litt.[80] mp 70°C; ms(90°C): 127 ($M^{+\cdot}$, 15), 99 (M^+ - CO, 46), 84 ($M^{+\cdot}$ - C_2HO, 13), 69 (32), 56 (100), 41 (71).

Experimental : (Chapter 3)

The cis-azetidinones 110 and 111 were prepared by a procedure as described for 112[83], 113 and 114[84]. The spectroscopic data for the azido-azetidinones 105 and 106, as well as the trans-azetidinones for 110 and 111 are given in chapter 5.

Bromo azetidinone 110

Prepared in 78 % yield from its corresponding azide; mp 138-139 °C; ir (KBr): 3300 (NH), 1771 (azetidinone), 1654 (amide); ^{1}H nmr ($CDCl_3$): 3.51 (s,2H,CH_2), 5.31 (dd,1H,C_3-H,J= 5.3,8), 5.45 (dd,1H,C_4-H,J= 5.4,8), 5.9 (dd,1H,C_5-H,J= 8,16), 6.15 (d,1H,N-H,J= 8), 6.52 (d,1H,C_6-H,J= 16), 7.03 - 7.51 (m,14 H,Ar-H); ^{13}C nmr ($CDCl_3$): 43.4 (CH_2), 59.9 (C_3), 63.4 (C_4), 117-136 (C_5 C_6 and Ar-C); 165.7 (C_2), 171.4 (amide carbonyl); ms (150 °): 460/462 (M^+,0.6), 284 (M^+ - $C_{10}H_9NO_2$,32), 263 (M^+ - $C_{18}H_{17}NO$,38.8), 197 (40.7), 171 (72.6), 145 (67.6), 91 (100). Exact mass: calcd. for $C_{25}H_{21}O_2N_2Br$: 460.0783; found: 460.0799.

Free radical cyclization of 110

Tributyltin hydride (170mg, 0.55 mmol), AIBN (cat) and dry benzene (3ml) were added to azetidinone 110 (213mg, 0.46 mmol) and dry benzene (20 ml) at reflux temperature during 20 h (syringe pump) under an inert atmosphere. The mixture was cooled to room temperature and the solvent removed. The residual yellow oil was dissolved in acetonitrile (30 ml), washed with hexanes (3 X 30 ml) and the solvent removed. HPLC using isopropanol/hexanes (1:5) as eluent gave starting material and the following products:

Reduction product 115 (15 %); ir (KBr): 1765 (azetidinone), 1657 (amide); ^{1}H nmr ($CDCl_3$): 3.56 (s,2H,CH_2), 4.95 (dd,1H,C_4-H,J= 5,8), 5.53 (dd,1H,C_3-H,J= 5,8), 5.98 (dd,1H,C_5-H,J= 8,16), 6.61 (d,1H,C_6-H,J= 16), 7.01 - 7.44 (m,16H,N-H and Ar-H). Tricyclic benzo carbapenem 116 (5 %); mp 121 °C: ir (KBr): 3305 (NH), 1805 (azetidinone), 1664 (amide); ^{1}H nmr ($CDCl_3$): 2.95 (dd,1H,C_6-Hb,J= 13.8,18), 3.18 (dd,1H,C_6-Ha,J= 6.2,13.8), 3.34-3.45 (m,1H,C_5-H), 3.45 (dd,2H,CH_2,J= 4,16), 4.32 (dd,1H,C_4-H,J= 5,8), 5.39 (dd,1H,C_3-H,J= 5,8), 5.73 (d,1H,N-H,J= 8), 7.05-7.32 (m,14H,Ar-H); ms (260 °C): 382 (M^+,100), 337 (M^+ - 45,56), 247 (M^+ - $BnCONH_2$,96), 207 (M^+ - $C_{10}H_9NO_2$,53.1). Exact mass : calcd. for $C_{25}H_{22}N_2O_2$: 382.1681; found: 382.1734. Azepinone 117 (35 %); ir (KBr): 3290 (NH), 1680 (lactam), 1657 (amide); ^{1}H nmr ($CDCl_3$): 3.63 (s,2H,CH_2CO), 4.31 (dd,2H,CH_2Ar,J= 3,5), 4.56 (d,1H,C_4-H,J= 5.2), 5.68 (dd,1H,C_3-H,J= 5,6), 6.78 (d,1H,N-H,J= 6), 6.93 - 8.0 (m,15H,Ar-H); ms (111°C): 382 (M^+,0.23), 291 (M^+ - Bn,0.3), 207 (M^+ - $C_{10}H_9NO_2$,31.3), 206 (24.4), 130 (100) .

Repeating the above cyclization, except adding 1.5 eq of tributyltin hydride over a 3 h period, gave after evaporation of the solvent and trituration of the corresponding residue with carbon tetrachloride, a precipitate. The crystals were filtered off and washed with hexanes to give 116 (24%) as colorless crystals with identical spectroscopic data as before.

Bromo azetidinone 111

Prepared in 71 % yield from its corresponding azide; mp 151-152 °C as colorless crystals; ir (KBr): 2280 (C≡C): 1741

(azetidinone), 1647 (amide); ^{1}H nmr ($CDCl_3$): 3.65 (s,2H,CH_2), 5.48 (d,1H,C_4-H,J= 5.4), 5.75 (dd,1H,C_3-H,J= 5.4,9), 6.78 (d,1H,N-H,J= 9), 7.11 - 7.6 (m,14H,Ar-H); ^{13}C nmr ($CDCl_3$): 43.46 (CH_2), 53.62 (C_4), 59.22 (C_3), 81.34 (C_5); 90.07 (C_6), 118 - 133 (18C,Ar-C), 165.5 (C_2), 171.22 (amide carbonyl); ms (195°C): 458/460 (M^+,5.7), 283/284 (M^+ - $C_{10}H_9NO_2$,20.8), 175 (M^+ - 283, 5.7).

Free radical cyclization of 111

Tributyltin hydride (150 mg, 0.5 mmol), AIBN (cat) and dry benzene (1 ml) were added to azetidinone 111 (193 mg, 0.42 mmol) and dry benzene (20 ml)at reflux temperature during 5 h (syringe pump) under an inert atmosphere. The mixture was cooled to room temperature and the solvent removed. The residue was dissolved in acetonitrile (30 ml), washed with hexanes (3 X 30 ml) and the solvent removed. Trituration of the residue with carbon tetrachloride/acetonitrile gave the tricyclic azetidinone 119 and 120 as yellow precipitate (4:3 ratio respectively, 31%), mp 140 - 145 °C . From the filtrate was isolated starting material (5%), reduction product 118 (11 %), and the azepinone 121 (27%) after separation by column chromatography using ethyl acetate/hexanes as eluent (1:1).

Tricyclic azetidinone 119; ^{1}H nmr ($CDCl_3$): 3.60 (dd,1H,CH_2,J= 2.5,17), 5.79 (dd,1H,C_3-H,J= 5.9,9.2), 6.00 (d,1H,N-H,J= 9.2), 6.32 (d,1H,C_6-H,J=2.5), 7.07-7.54 (m,14H,Ar-H); ^{13}C NMR ($CDCl_3$): 43.42 (CH_2), 58.34 (C_4), 62.13 (C_3, 126.01 (C_6), 122 - 144 (Ar-C and C_5); 171.00 (C_1), 175.87 (amide carbonyl).

Tricyclic azetidinone 120; ^{1}H nmr ($CDCl_3$): 3.06 (dd,2H,CH_2,J=

17,34), 5.51 (dd,1H,C_4-H,J= 3.3,6), 5.66 (d,1H,N-H,J= 10), 6.10 (dd,1H,C_3-H,J= 6,10), 6.99 (d,1H,C_6-H,J= 3.3), 7.07 - 7.54 (m,14H,Ar-H); ^{13}C nmr ($CDCl_3$): 42.79 (CH_2), 58.02 (C_4); 61.86 (C_3), 123.42 (C_6), 122 - 144 (Ar-C and C_5), 170.32 (C_2), 175.77 (amide carbonyl); ir of 119 and 120 (KBr): 3290 - 3310 (NH), 1824 (azetidinone), 1640-1647 (amide).

Reduction product 118; ir (KBr): 3300 (NH), 1745 (azetidinone), 1649 (amide); ^1H nmr ($CDCl_3$): 3.65 (s,2H,CH_2), 5.03 (d,1H,C_4-H,J= 5), 5.72 (dd,1H, C_3-H,J= 5,8), 6.26 (d,1H,N-H,J= 8), 7.05-7.59 (m,15H,Ar-H); ms (111°C) chemical ionization, isobutane: 381 (M^++H^+, 22.1), 363 (M^+ - BnCO,15.8), 353 (381 - CO,10.1), 206 (M^+ - $C_{10}H_9NO_2$,100), 176 (M^+ - 206,65.7).

Azepinone 121; ^1H nmr ($CDCl_3$): 4.19 (s,2H,CH_2CO), 6.86 - 7.50 (m,11H,Ar-H and C=CH), 8.85 (bs,1H,NH).

Silyl azetidinone 112

Prepared in 49 % yield from its corresponding azide; mp 123 - 124°C (colorless crystals); ir (KBr): 3210 (NH), 1768 (azetidinone), 1645 (amide); ^1H nmr ($CDCl_3$): 0.048 and 0.056 (s,6H,$SiMe_2$), 0.907 (s,9H,t-butyl), 3.67 (s,2H,CH_2CO), 5.18 (2,1H,C_4-H,J= 8), 5.7 (s,2H,CH_2O), 5.71 (dd,1H,C_3-H,J= 5,10), 6.3 (d,1H,N-H,J= 10), 7.1 - 7.5 (m,14H,Ar-H); ms (175°C): 524 (M^+,0.1), 467 (M^+ - t-butyl,1.9), 349 (M^+ - $C_{10}H_9NO_2$,1.7), 292 (26.1).

Bromo azetidinone 122

Tetrabutylammonium fluoride (4.69 g, 17 mmol) and THF (5 ml) were added to azetidinone 112 (5.0 g, 9.5 mmol) and 150 ml of dry THF at 0°C under a nitrogen atmosphere. After 30

minutes, water (2 ml) was added and the solvent removed. The residue was then purified by flash chromatography using ethylacetate/hexanes (1:1) as eluent to give the alcohol as colorless crystals (72%); mp 174-175°C; ir (KBr) ν_{max}: 1756 (azetidinone), 1660 (amide); ^{1}H nmr ($DMSOd_6$): 3.34 (s,2H,CH_2CO), 4.52 - 4.56 (bs,1H,O-H), 4.53 (s,2H,CH_2-O), 4.82 (dd,1H,C_4-H,J= 5,86), 5.25 (dd,1H,CH_3-H,J= 5,8), 6.05 (dd,1H,C_5-H,J= 8,16), 6.40 (d,1H,C_6-H,J= 16), 6.8 - 7.28 (m,19H,Ar-H), 8.26 (d,1H,N-H,J= 8); ms (230°C): 410 ($M^{+\cdot}$ - $2H^+$,2.6), 333 (410 - Ph,3.3), 320 ($M^{+\cdot}$ - Bn - $^{\circ}H^+$,50.1).

To the above alcohol (700 mg,1.7 mmol) and dry methylene chloride (100 ml) at 0°C under a nitrogen atmosphere were added carbon tetrabromide (560 mg) followed by a slow addition of triphenylphosphine (430 mg,1.97 mmol). After 3 h of stirring, the solution was allowed to warm up to room temperature, and purified by column chromatography using ethyl acetate/hexanes (1:3) to give the azetidinone 122 as colorless crystals (62.5%) after recrystalization from ethylacetate/hexanes; mp 123 - 124°C ; ir (KBr): 3310 (NH), 1744 (azetidinone), 1644 (amide); ^{1}H nmr ($CDCl_3$): 3.60 (s,2H,CH_2-O), 4.72 (dd,2H,CH_2Br,J= 10.4,22), 5.02 (dd,1H,C_4-H,J= 5,8.2), 5.55 (dd,1H,C_3-H,J= 5,8), 6.08 (dd,1H,C_5-H,J= 8.2,16), 6.38 (d,1H,N-H,J= 8), 6.64 (d,1H,C_6-H,J= 16), 7.1 - 7.34 (m,14H,Ar-H); ms (305 °C): 474/476 (M^+,4/3.9), 395 ($M^{+\cdot}$ - Br·,33), 394 (M^+ - HBr,100), 317 ($M^{+\cdot}$ - Ph - HBr,70.5), 275 ($M^{+\cdot}$ - HBr - BnCO,43.7), 220 ($M^{+\cdot}$ - $C_{10}H_9NO_2$ - Br·,45), 263 ($M^{+\cdot}$ - $C_{18}H_{17}NO$,17).

Bromo azetidinone 123

Prepared as described for 122. The alcohol was obtained in 65 % yield from 113 as colorless crystals, mp 163°C; ^{1}H nmr ($CDCl_3$): 3.50 (s,2H,CH_2CO), 4.12 (dd,1H,O-H,J= 4,8), 4.64 and 4.82 (dd,2H,CH_2-O,J= 8,12 and 4,12), 5.08 (s,1H,$PhCH_2Ar$), 5.13 (dd,1H,C_4-H,J= 5,8), 5.24 (dd,1H,C_3-H,J= 5,8), 6.07 (dd,1H,C_5-H,J= 8,16), 6.40 (d,1H,C_6-H,J= 16), 6.80 (d,1H,N-H,J= 8), 6.9 - 7.39 (m,13H,Ar-H); ms (200°C): 518 (M^+,0.1), 343 (M^+ - $C_{10}H_9NO_2$,0.9), 263 (M^+ - $C_{15}H_{13}NO_3$,42.7), 175 (M^+ - NC_4,3.0). Azetidinone 123 was obtained as colorless crystals in 81 % yield from the above alcohol; mp 145 - 146°; ir (KBr): 3270 (NH), 1758 (azetidinone), 1656 (amide); ^{1}H nmr ($CDCl_3$): 3.56 (s,2H,CH_2CO), 4.66 (dd,2H,CH_2Br,J= 10,10.1), 5.05 (s,2H,$PhCH_2Ar$), 5.12 (dd,1H,C_4-H,J= 5,8), 5.41 (dd,1H,C_3-H,J= 5.8), 5.96 (bd,1H,N-H,J= 8), 6.09 (dd,1H,C_5-H,J= 8,16), 6.42 (d,1H,C_6-H,J= 16), 6.88 - 7.39 (m,18H,Ar-H); ms (285°C): 580/582 (M^+,0.8/0.7), 501 (M^+ - Br,38.4), 500 (M^+ - HBr,100), 423 (M^+ - HBr - Ph,30), 381 (M^+ - HBr - BnCON,19.9).

Bromo azetidinone 129

Starting from silyl azetidinone 114, the alcohol was obtained in 51 % yield as colorless crystals using 20% trifluoroacetic acid as described in reference 83; mp 184-185°C; ir (KBr): 3305 (NH), 1768 (azetidinone), 1650 (amide); ^{1}H nmr ($DMSOd_6$): 3.29 (s,1H,O-H), 3.61 (s,2H,CH_2CO), 4.69 (s,2H,CH_2-O), 5.23 (d,1H,C_4-H,J= 5), 5.50 (dd,1H,C_3-H,J= 5,8), 7.08 - 7.46 (m,15H,Ar-H and N-H); ms (208°C) chemical ionization, isobutane: 411 (M^+ + 1,19.4), 319 (M^+ + 1 - $C_{10}H_9NO_2$,9.1).

Exact mass (208°): calcd. for $C_{26}H_{22}N_2O_3$: 410.1629; found: 410.1685 .

Azetidinone 129 was obtained in 63 % yield from the above alcohol as colorless crystals; mp 135-136°; ir (KBr): 3290 (NH), 1755 (azetidinone), 1666 (amide); ^1H nmr ($CDCl_3$): 3.69 (s,2H,CH_2CO), 4.64 (dd,2H,CH_2Br,J= 10,18), 5.21 (d,1H,C_4-H,J= 5), 5.75 (dd,1H,C_3-H,J= 5,8), 6.30 (d,1H,N-H,J= 8), 7.05 - 7.51 (m,14H,Ar-H); ms (195°): 472/474 (M^+,0.3), 343 (M^+ - Br·,1.8), 392 (M^+ - Bn,1.8), 392 (M^+ - HBr,5.8), 218 (M^+ - Br· - $C_{10}H_9NO_2$,56.8), 217 (41.2), 175 (28.2).

Radical cyclization of 122.

Tributyltin hydride (442 mg, 1.52 mmol), AIBN (cat.) and benzene (5 ml) were added to azetidinone 122 (600 mg, 1.27 mmol) and dry benzene (55 ml) at reflux temperature during 10 h under an inert atmosphere. The mixture was cooled to room temperature and the precipitate filtered off and washed with hexanes to give the azetidinone 125 (340 mg, 68%) as colorless crystals. From the filtrate, after the usual work-up and column chromatography, was recovered the reduction product 124 (12 %) using ethylacetate/hexanes as eluent.

Benzo carbacephem 125; mp 256°C; ir (KBr): 3290 (NH), 1755 (azetidinone), 1642 (amide); ^1H nmr (Pyridine-d_5,60°C): 1.95 (m,1H,C_5), 2.19 (dd,1H,C_6-Hc,J= 10,13), 2.32 (dd,1H,C_7Ha,J= 15,13), 2.59 (dd,1H,C_7-Hb,J= 4,15), 2.97 (dd,1H,C_6-Hd,J= 4,13), 3.74 (dd,1H,C_4-H,J= 5,10), 3.82 (s,2H,CH_2CO), 5.96 (dd,1H,C_3-H,J= 5,9), 6.99 - 7.63 (m,14H,Ar-H), 9.91 (d,1H,N-H,J= 9); ^{13}C nmr (dmso-d_6): 30.45 (C_7), 32.32 (C_5) 36.85 (C_6), 42.11

(CH_2Ph), 56.77 (C_4), 58.56 (C_3), 117 - 138.3 (Ar-C), 165.68 (C_2), 170.57 (amide carbonyl); ms (225°C): 396 (M^+,2.2), 305 (M^+ - Bn,2.1), 277 (M^+ - BnCO,6.6), 222 (M^+ + 1 - $C_{10}H_9NO_2$,35.7), 175 (1.9), 77 (100). Exact mass : calcd. for $C_{26}H_{24}O_2N_2$: 396.1837 ; found: 396.1830 .

Reduction product 124; ir (KBr): 3305 (NH), 1740 (azetidinone), 1675 (amide); ^1H nmr ($CDCl_3$): 2.32 (s,3H,CH_3), 3.50 (s,2H,CH_2CO), 4.92 (dd,1H,C_4-H,J= 5,8), 5.56 (dd,1H,C_3-H,J= 5,8), 6.15 (dd,1H,C_5-H,J= 8,16), 6.56 (d,1H,C_5-H,J= 16), 6.92 - 7.57 (m,15H,Ar-H and N-H); ms (100°C): 396 (M^+,3.2), 395 (5.7), 305 (M^+ - Bn,1.8), 277 (M^+ - BnCO,6.0), 221 (M^+ - $C_{10}H_9NO_2$,33), 222 (100).

Radical cyclization of 123

Tributyltin hydride (72 mg, 0.25 mmol), AIBN (cat) and benzene (1.5 ml) were added to azetidinone 123 and dry benzene (10 ml) at reflux temperature during 5 h (syringe pump) under an inert atmosphere. After a further 3 h at the same temperature, the reaction mixture was cooled to room temperature whereby a white precipitate formed. The precipitate was filtered off and washed with hexanes to give azetidinone 127 (39 mg, 70%) as colorless crystals. The solvent was removed to give an oily residue which after the usual work up and purification by column chromatography (ethylacetate/hexanes 1:1) gave the reduction product 126 (12 %).

Tricyclic benzo carbacephem 127; mp 273-274°C; ir (KBr): 3282 (NH), 1770 (azetidinone), 1655 (amide); ^1H nmr (Pyridine-d_5): 2.25 - 2.4 (m,3H,C_5-H C_7-Ha and C_6-HC), 2.63 (dd,1H,C_7-H_6,J= 1.2,14), 2.98 (dd,1H,C_6-Hd,J= 1.2,10), 3.69 (dd,2H,C_4-

H,J= 5,10.2), 3.81 (s,2H,CH_2CO), 5.17 (dd,2H,CH_2-O,J= 12,22), 5.97 (dd,1H,C_3-H,J= 5,9), 6.84 - 7.7 (m,14H,Ar-H), 9.97 (d,1H,N-H,J= 9); ms (273°C): 502 (M^+,0.96), 411 (M^+ - Bn,4.5), 383 (M^+ - BnCO,1.6), 328 (M^+ + 1 - $C_{10}H_9NO_2$,100), 148 (M^+ - 328,0.5). Exact mass (270°): calcd. for M^+ - Bn, $C_{26}H_{23}O_3N_2$: 411.171; found: 411.171.

Reduction Product 126; ir (KBr): 3278 (NH), 1748 (azetidinone), 1650 (amide); ^1H nmr ($CDCl_3$): 2.33 (s,3H,CH_3), 3.50 (s,2H,CH_2CO), 4.95 (dd,1H,CH_4-H,J= 5,8), 5.06 (dd,2H,$PhCH_2$-O,J= 12,16), 5.38 (dd,1H,C_3-H,J= 5,8), 5.95 (dd,1H,C_5-H,J= 8,16), 6.17 (d,1H,N-H,J= 8), 6.44 (d,1H,C_6-H,J= 16), 6.75 - 7.39 (m,18H,Ar-H); ms (282°C): 502 (M^+,2.7), 411 (M^+ - Bn,4.5), 327 (M^+ - $C_{10}H_9NO_2$,21.3), 328 (41.9), 237 (17.1).

Phenol carbacephem 128

Azetidinone 127 (25 mg), ethanol (5 ml) and dimethylformamide (2.5 ml) were hydrogenated with palladium on charcoal (2.5 mg, 10%) until 2.5 ml of hydrogen had been absorbed. The mixture was filtered and the solvent removed. Recrystallization from hot ethyl acetate and precipitation with hexanes gave quantitative yield of azetidinone 128 as colorless crystals; mp 282 - 283°C ; ir (KBr): 3420 (b,OH), 3280 (NH), 1715 (azetidinone), 1658 (amide); ^1H nmr (Pyridine-d_5): 2.35 - 2.47 (m,3H,C_5-H C_6-Hc and C_7-Ha), 2.71 (d,1H,C_7-Hb,J= 12), 3.01 (d,1H,C_6-Hd,J= 10), 3.78 (dd,1H,C_4-H,J= 5,9.2), 3.85 (s,2H,CH_2CO), 5.02 (bs,1H,OH), 5.95 (dd,1H,C_3-H,J= 5,9), 6.87 - 7.49 (m,14H,Ar-H), 9.98 (d,1H,N-H,J= 9); ms (220°C): 412 (M^+,2.9), 293 (M^+ - BnCO,5.5), 237 (M^+ - $C_{10}H_9NO_2$,15.5), 238

(100). Exact mass (260°C): calcd. for $C_{26}H_{24}O_3N_2$: 412.1786 ; found: 412.1835 .

Lactam 130

Using the procedure as described for 122, the lactam 130 was obtained in 70% yield as colorless crystals, mp 177 - 178°C; IR (KBr): 3415 (b,N-H), 1739 (CO_2), 1668 (amide): ^1H nmr: 3.65 (s,2H,CH_2CO), 4.05 (d,1H,N-H,J =7.5), 4.68 (dd,1H,C_8-H,J= 3,7.5), 5.45 (dd,1H,C_7-H,J= 3,7.4), 5.06 (d,1H,C_4-Ha,J= 13,), 5.58 (d,1H,C_4-Hb,J= 13), 6.97 (d,1H,N-H,J= 7.4), 7.02 - 7.40 (m,14H,Ar-H): ^{13}C nmr ($CDCl_3$): 43.61 (C_{13}), 53.03 (C_8), 58.25 (C_7), 68.15 (C_4), 83.50 (C_9), 88.54 (C_{10}), 121.7 - 145.2 (Ar-C), 170.48 (CO_2), 170.59 (amide carbonyl); Exact mass (195°C): calcd. for $C_{26}H_{22}O_3N_2$; 410.1629: found; 410.1685.

Free radical cyclization of 129

Tributyltin hydride (125 mg, 0.42 mmol), AIBN (cat) and benzene (2 ml) were added to azetidinone 129 (170 mg, 0.36 mmol) and dry benzene (18 ml) at reflux temperature during 12 h (syringe pump) under an inert atmosphere. The mixture was cooled to room temperature and the solvent removed. The residue was dissolved in acetonitrile (30 ml), washed with hexanes (3 X 30 ml) and the solvent removed. Column chromatography using ethylacetate/hexanes as eluent gave the following products: Tricyclic azetidinone 132 (37%); E-isomer; mp 189°C (colorless crystals); ir (KBr): 3305 (NH), 1748 (azetidinone), 1690 (amide); ^1H nmr ($CDCl_3$): 3.30 (dd,2H,C_7-H,J= 16,30), 3.47

(s,2H,CH_2CO), 4.78 (d,1H,C_4-H,J= 5), 5.77 (d,1H,N-H,J= 8), 5.78 (dd,1H,C_3-H,J= 5,8), 6.60 (s,1H,C_6-H), 6.96 - 7.41 (m,14H,Ar-H); ms (270°C): 394 (M^+,0.7), 275 (M^+ - BnCO,0.6), 260 (M^+ - BnCONH,0.93), 221 (M^+ - $C_{10}H_9NO_2$,18.2), 220 (100). Exact mass (270°C): calcd. for $C_{26}H_{26}O_2N_2$: 394.1681; found: 394.1695.

Tricyclic azetidinone 133 (38%): Z-isomer, mp 196°C; ir (KBr): 3260 NH); 1753 (azetidinone), 1655 (amide); ^1H nmr ($CDCl_3$): 3.60 (s,2H,CH_2CO), 3.63 (dd,2H,C_7-H,J= 19,28), 4.62 (d,1H,C_4-H,J= 5), 5.64 (dd,1H,C_3-H,J= 5,8), 6.04 (d,1H,N-H,J= 8), 6.29 (s,1H,C_6-H), 7.06 - 7.44 (m,14H,Ar-H); ms (269°C): 394 (1.6), 260 (11), 275 (0.9), 221 (21.7), 220 (100), 219 (19.6). Exact mass : calcd. 394.1681; found: 394.1710.

Tricyclic Benzo carbacephem 134

A mixture of azetidinones 132 (10 mg) and 133 (10 mg), ethyl acetate (5 ml) and ethanol (3 ml) was added platinum black (3 mg). The mixture was stirred at room temperature under a hydrogen atmosphere, overnight. The mixture was filtered off and the solvent removed. The residue was purified by flash chromatography using ethylacetate/hexanes as eluent to give, after recrystalization from chloroform/carbon tetrachloride, the tricyclic azetidinone 134 as colorless crystals (25 %); mp 237°C; ir (KBr): 3305 (NH), 1768 (azetidinone), 1641 (amide); ^1H nmr ($CDCl_3$): 1.91 - 2.04 and 2.36 - 2.65 (m,5H,C_5-H C_6-H and C_7-H), 3.65 (dd,2H,CH_2CO,J= 2.5,6), 4.25 (dd,1H,C_4-H;J= 3,5), 5.41 (dd,1H,C_3-H,J= 5,6), 6.01 (d,1H,N-H,J= 6), 6.7 - 7.5 (m,14H,Ar-H); ms (220°C): 396 (M^+,2.1), 305 (M^+ - Bn,1.7), 277 (M^+ - BnCO,23.1), 262 (M^+ - $BnCONH_2$,20), 222 (M^+ + H -

$C_{10}H_9NO_2$,14.2), 175 (14.4). Exact mass : calcd. for $C_{26}H_{24}O_2N_2$: 396.1837; found: 396.1758 .

Tricyclic keto-azetidinone 135

A mixture of azetidinones 132 (10 mg) and 133 (10 mg), methanol (2 ml) and dichloromethane (2 ml) at -78°C was ozonized for 5 min. The light blue solution was stirred for 15 minutes, and a stream of nitrogen was passed through the solution for 15 minutes. Dimethylsulfide (excess) was added and the mixture left overnight at room temperature. The solvents were removed and the residue purified by column chromatography using ethylacetate/hexanes (1:1) to give the ketone 135 as a yellow oil (75 % yield); ir (neat): 3160 (NH), 1793 (azetidinone), 1722 (ketone), 1647 (amide); 1H nmr ($CDCl_3$): 3.55 (dd,1H,C_6-Ha,J= 1.8,22), 3.56 (s,2H,CH_2CO), 4.06 (d,1H,C_6-Hb,J= 22), 4.06 (dd,1H,C_4-H,J= 1.8,5.7), 4.74 (dd,1H,C_3-H,J= 5.7,7.2), 6.05 (d,1H,N-H,J= 7.2), 7.17 - 7.39 (m,9H,Ar-H); ms (148°C) chemical ionization, isobutane: 321 (M^+ + 1,48.4), 320 (M^+,2.7), 319 (14.7), 304 (321 - 17,38.8), 303 (321 - 18,48.3), 176 (14.6), 146 (M^+ + 1 - $C_{10}H_9NO_2$,100).

Experimental : (Chapter IV)

Benzhydryl 6,6-Dibromopenicillanate 145

Diphenyldiazomethane (1.5 g, 7.7 mmol) and ethyl acetate (50 ml) were added dropwise to a mixture of 6,6-dibromopenicillanic acid (2.7 g, 7.6 mmol) and ethyl acetate (50 ml) at room temperature . The mixture was stirred overnight and the excess diphenydiazomethane was destroyed with a dropwise addition of acetic acid until the red solution decolorized to faint yellow. The product was then purified by flash chromatography to give 3.4 g (87 %) of product as colorless crystals, mp 155-157 °C; ir (KBr): 1795 (CO_2), 1754 (azetidinone); ^1H nmr: 1.31 and 1.56 (s,3H,CH_3), 4.87 (s,C_3-H,1H), 6.09 (s,1H,C_5-H), 7.28 (s,1H,CO_2CH), 7.40 - 7.66 (m,10H,Ar-H); ms (175 °C): 523/525/527 ($M^{+\cdot}$, 0.5/1.0/0.5), 444/446 ($M^{+\cdot}$, 0.4/0.4), 167(100), 152(209) 114 (18.3). Exact mass (205°C): calcd. for $C_{21}H_{19}NO_3SBr_2$: 524.9433 ; found : 524.9424 .

Benzhydryl 6 α-Dibromopencillanate 144

Using the same procedure as above, 6α-dibromopenicillanic acid was converted to the benzhydryl ester in 83 % yield as light yellow crystals, mp 94 - 96 °C; ir (KBr): 1787 and 1749 (CO); ^1H nmr: 1.27 and 1.66 (s,3H,CH_3), 4.62 (s,1H,C_3-H), 5.33 (d,1H,C_5-H,J= 4), 5.59 (d,1H,C_6-H,J= 4), 6.94 (s,1H,COOCH), 7.33 - 7.37 (bs,10H,Ar-H); ms (130°C): 445/447 ($M^{+\cdot}$, 1.7), 366 ($M^{+\cdot}$ - Br·,0.3), 234/236 ($M^{+\cdot}$ - $C_{14}O_2H_{11}$, 6.0), 167 (100), 152 (10.8), 114 (23.8). Exact mass (130°C); calcd. for

$C_{21}H_{20}NO_3SBr$: 447.0328; found: 447.0355 .

Benzhydryl 6 β-Dibromopenicillanate 146

6,6-dibromopenicillanate 145 (100 mg, 0.22 mmol), benzene (10 ml) and tributyltin hydride (91 mg, 0.31 mmol) were heated to 65°C under a nitrogen atmosphere for 5 h. The solvent was removed, the residue dissolved in 30 ml of acetonitrile and washed three times with hexanes (30 ml). The solvent was then removed and the residue purified by column chromatography using ethyl acetate - hexanes (1 : 5) as eluant to give 19 mg of 6,6-dihydropenicillanate 147 (27 %) and 70 mg of 6β-bromopenicillanate 146 (73 %) as colorless oils;

6β-Dibromopenicillinate 146; ir (CCl_4): 1792 and 1751 (CO); ^1H nmr: 1.30 and 1.60 (s,3H,CH_3), 4.66 (s,1H,C_3-H), 4.78 (d,1H,C_5-H,J= 2), 5.45 (d,1H,C_6-H,J= 2), 6.94 (s,1H,COOCH), 7.26 - 7.46 (bs,10H,Ar-H); ms (108°C): 445/447 (M^+, 0.1), 307/309 (5.6), 197 (10), 188 (76.3), 184 (67.1), 167 (45.5), 105 (100).

6,6-dihydropenicillanate 147; ^1H nmr: 1.23 and 1.49 (s,3H,CH_3), 3.03 (dd,1H,C_6-H,J= 2, 16), 3.52 (dd,1H,C_6-H ,J= 4, 16), 4.54 (s,1H,C_3-H), 5.27 (dd,1H,C_5-H,J= 2, 4), 6.91 (s,1H,COOCH), 7.31 - 7.34 (bs,10H, Ar-H).

N-(p-methoxyphenyl)-3,3-dibromo-4-styrylazetidinone 152; ir (CCl_4): 1782 (azetidinone) ; ^1H nmr : 3.76 (s,3H,OCH_3), 5.08 (d,1H,C_4-H,J= 8), 6.18 (dd,1H,C_5,J= 8, 16), 6.85 (s,1H,C_6-H,J= 16), 6.91 - 7.49 (m,9H,Ar-H) ; ms (175 °C): 435/437/439 (M^+,1.2/2.6/1.3), 356/358 (M^+· - Br·, 3.6/3.7), 286/288/290 (M^+· - $C_8H_7O_2N$), 14/36/21), 249 (16.9), 237 (M^+· - C_2OBr_2), 149 (M^+· - $C_{10}H_8Br_2$, 52.4), 134 (27.5), 128 (100). Exact mass (185°C);

calcd. for $C_{18}H_{15}NO_2Br_2$: 436.9454 ; found : 436.9452.

General procedure for the reaction of 144, 145 or 146 with olefins:

Method A

Benzhydryl 6 α-bromopenicillanate 144 (200 mg, 0.45 mmol), dry benzene (5 ml) and methyl acrylate (0.58 g, 6.7 mmol) were refluxed under a nitrogen atmosphere. To this mixture was added tributyltin hydride (157 mg, 0.54 mmol), benzene (2 ml) , AIBN (2 mg) and methyl acrylate (380 mg, 4.5 mmol) over a 5 to 6 h period (syringe pump). After the addition, the mixture was refluxed for 2 h and then cooled to room temperature. The solvent and excess methyl acrylate was removed. The residue was dissolved in acetonitrile (50 ml) and washed three times with hexanes (50 ml). The solvent was then removed and the residue purified by chromatography using ethyl acetate - hexanes (1 : 4) as eluant giving of benzhydryl 6 α-(2'-carbomethoxyethyl)-penicillanate 149d (132 mg, 65 %) as colorless crystals, mp 84-85 °C.

Method B

Benzhydryl 6,6-dibrompenicillanate 145 (200 mg, 0.38 mmol), benzene (4 ml) and tributyltin hydride (115 mg, 0.40 mmol) were heated at 65°C under nitrogen for 5h. To this mixture was then added acrylonitrile (424 mg, 7.6 mmol) followed by a dropwise addition of tributyltin hydride (155 mg, 0.53 mmol), benzene (1 ml) and AIBN (2mg) over a 5 to 6 h period. The mixture was cooled to room temperature and the solvent

removed. The residue was dissolved in acetonitrile (50 ml) and washed three times with hexanes (50 ml). The solvent was then removed and the residue purified by chromatography using ethyl acetate - hexanes (1 : 4) as eluant giving 91 mg of benzhydryl 6 α-(2'-cyanomethoxythyl)-penicillanate 149a (48 %) as an oil. Crystalization with carbon tetrachloride and hexanes gave colorless product, mp 132°C.

Method C

Benzhydryl 6,6-dibromopenicillanate 145 (200 mg, 0.38 mmol), benzene (4 ml), and acrylonitrile (424 mg, 7.6 mmol) were heated under a nitrogen atmosphere. To this mixture was added dropwise tributyltin hydride (115 mg, 0.40 mmol), benzene (1 ml) and AIBN (2 mg) over 5 to 6 h (syringe pump). The mixture was cooled and the solvent and excess acrylonitrile removed. The residue was dissolved in benzene (10 ml), treated with tributyltin hydride (155 mg, 3.8 mmol) , AIBN (2 mg) and refluxed for 3 h under a nitrogen atmosphere. The mixture was cooled to room temperature and the solvent removed. The residue was dissolved in acetonit-rile (50 ml) and washed three times with hexanes (50 ml). The solvent was then removed and the residue purified by chromatography using ethyl acetate - hexanes (1 : 4) as eluant giving the benzhydryl 6 β-(2'-cyanomethoxyethyl)-penicillanate 151c (74mg, 47 %) as an oil.

Benzhydryl 6α-(2'-cyanoethyl)penicillanate 149a; ir (CCL_4): 2249 (CN), 1740 - 1785 (b,CO); ^1H nmr: 1.26 and 1.62 (s,3H,CH_3), 2.22 (m,2H,$C_{1'}$-H_2), 2.54 (dt,2H,C_9-H_2,J= 3, 7), 3.40 (dt,1H,C_6-H,J= 2, 7), 4.58 (s,1H,C_3-H), 5.13 (d,1H,C_7-H,J=

2), 6.94 (s,1H,OCH), 7.35 (bs,10H,Ar-H); ^{13}C nmr : 15.30 ($C_{2'}$), 24.65 ($C_{1'}$), 26.06 and 32.98 (CH_3), 59.89 (C_6), 65.68 (C_2), 66.04 (C_5), 69.70 (C_3), 78.42 (C_{10}), 118.53 (CN), 126 - 139 (Ar-C), 166.78 (C_7), 172.55 (CO_2) ; ms (190 °C): 420 (M^+,8.0), 380 (M^+,6.0), 209 (M^+,9.2), 168 (41.9), 167 (100), 166 (45.7), 165 (61.8). Exact mass (190 °C): calcd. for $C_{24}H_{24}O_3N_2S$: 420.1507 ; found: 420.1547 .

Benzhydryl 6 β-(2'-cyanoethyl)-penicillanate 151c; ir (CCl_4): 2248 (CN), 1742 and 1775 (b,CO); ^1H nmr: 1.26 and 1.60 (s,3H,CH_3), 2.17 (m,2H,$C_{2'}$-H), 2.50 (t,2H,$C_{2'}$-H), 3.69 (dt,1H,C_6-H,J= 4, 8), 4.50 (s,1H,C_3-H), 5.51 (d,1H,C_5-H,J= 4), 6.94 (s,1H,COOCH), 7.31 - 7.36 (m,10H,Ar-H); ^{13}C nmr: 15.00 ($C_{2'}$), 22.47 ($C_{1'}$), 26.30 and 32.50 (CH_3), 52.51 (C_6), 64.99 (C_2), 66.35 (C_5), 69.19 (C_3), 78.40 ($CHPh_2$), 118.54 (CN), 127 - 139 (Ar-C), 166.78 (CO_2), 173.59 (C_7) .

Benzhydryl 6 α-(2'-carbomethoxyethyl)-penicillanate 149d; ir (CCl_4): 1736 - 1770 (b,CO); ^1H nmr : 1.24 and 1.61 (s,3H,CH_3), 2.16 (m,2H,$C_{2'}$-H), 2.50 (m,2H,$C_{1'}$-H), 3.35 (dt,1H,C_6-H,J= 2, 8), 3.68 (s,3H,$COOCH_3$), 4.55 (s,1H,C_3-H), 5.07 (d,1H,C_5-H,J= 2), 6.93 (s,1H,COOCH), 7.26 - 7.36 (m,10H,Ar-H); ^{13}C nmr : 26.06 and 33.00 (CH_3), 23.86 ($C_{1'}$), 31.36 ($C_{2'}$), 51.77 (OCH_3), 60.74 (C_6), 65.49 (C_2), 66.48 (C_5), 69.64 (C_3), 78.26 (OCH), 127 - 139.7 (Ar-C), 166.95 (C_7), 172.79 and 173.78 (CO_2) ; ms (85°C): 453 (M^+, 0.2), 371 (M^+, 3.4), 279 (7.3), 227 (27.6), 198 (13.1), 194 (65.9), 167 (88.4), 149 (65.3) . Exact mass (100°C): calcd. for $C_{25}H_{27}O_5NS$: 453.1609 ; found: 453.1610.

Benzhydryl 6 β-(2'-carbomethoxyethyl)-penicillanate 151e; ir (CCl_4): 1734 - 1771 (b,CO); ^1H nmr : 1.29 and 1.66 (s,3H,CH_3), 2.10 (m,1H,C_1'-H), 2.37 (m,1H,C_2'-H), 3.65 (m,1H,C_6-H), 3.71 (s,3H,OCH_3), 4.50 (s,1H,C_3-H), 5.47 (d,1H,C_5-H,J= 4), 6.95 (s,1H,OCH), 7.30 -7.40 (m,10H,Ar-H); ^{13}C nmr: 26.35 and 32.16 (CH_3), 25.79 (C_1'), 31.49 (C_2'), 51.71 (OCH_3), 52.42 (C_6), 64.57 (C_2), 66.96 (C_5), 69.34 (C_3), 78.21 (OCH), 127 - 139.3 (Ar-C), 167.04 (C_7), 173.11 and 174.69 (CO_2) .

Benzhydryl 6 α-(2'-acetoxyethyl)-penicillanate 149f; ir (CCl_4): 1740 and 1772 (CO) ; ^1H nmr : 1.24 and 1.61 (s,3H,CH_3), 2.03 (s,3H,$COCH_3$), 2.19 (m,2H,C_1'-H), 3.36 (dt,1H,C_6-H,J= 2, 6), 4.18 (m,2H,C_2'-H), 4.56 (s,1H,C_3-H), 5.13 (d,1H,C_7-H,J= 2), 6.92 (s,1H,OCH), 7.26 - 7.36 (m,10H,Ar-H); ^{13}C nmr: 26.05 and 33.02 (CH_3), 20.83 ($CO\underline{C}H_3$), 27.66 (c_1'), 59.13 (C_6), 61.98 (C_9), 65.46 (C_2), 66.58 (C_5), 69.61 (C_3), 78.26 (OCH), 126.9 - 139.2 (Ar-C), 166.93 (C_7), 170.83 (CO_2), 173.50 (C_3'); ms (110 °C): 453 (M^+, 1.6), 425 (M^+ - CO, 0.9), 325 (M^+ - $C_6H_8O_3$, 1.8), 244 (5.1), 188 (34), 168 (39), 167 (100).

Benzhydryl 6β-(2'-acetoxyethyl)-penicillanate 151g; ir (CCl_4): 1741 and 1772 (CO); ^1H nmr: 1.24 and 1.63 (s,3H,CH_3), 2.04 (s,3H,$COCH_3$), 2.18 (m,2H,C_1'-H), 3.67 (m,1H,C_5-H), 4.13 (m,2H,C_2'-H), 4.49 (s,1H,C_3-H), 5.46 (d,1H,C_6-H,J= 4.5), 6.93 (s,1H,OCH), 7.24 - 7.37 (m,10H,Ar-H).

N-(p-methoxyphenyl)-3α-(2'carbomethoxyethyl)-4-styrylazetidinone 153; ir (KBr): 1742 (CO); ^1H nmr: 2.21 (t,2H,C_1'-H), 2.56 (m,2H,C_2'-H), 3.13 (dt,1H,C_3-H,J= 2, 8), 3.69 (s,3H,CO_2CH_3),

3.77 (s,3H,OCH_3), 4.33 (dd,1H,C_4-H,J= 2,8), 6.29 (dd,1H,C_5-H,J= 8, 16), 6.76 (d,1H,C_6-H,J= 16), 7.24 - 7.45 (m,9H,Ar-H).; ms (85°C) : 365 (M^+,1.2), 313 (4), 281 (18), 280 (22), 149(73), 130 (100). Exact mass (85°C): calcd. for $C_{22}H_{23}O_4N$: 365.1627; found; 365.1644 .

N-(p-methoxyphenyl)-4-styryl-azetidinone 155; ir (CCl_4): 1740 (CO); ^1H nmr: 2.93 (dd,1H,C_3-H,J= 2, 16), 3.41 (dd,1H,C_3-H,J= 4, 16), 3.77 (s,3H,OCH_3), 4.64 (m,1H,C_4-H), 6.31 (dd,1H,C_5-H,J= 8, 16), 6.83 (d,1H,C_6-H,J= 16), 7.23 - 7.45 (m,(H,Ar-H); ms, (85°): 279 (M^+,1.0), 237 (M^+ - C_3H_2O,7.0), 172 (2.6), 149 (50.8), 130 (100), 129 (33.8).

Benzhydryl 6α-allylpenicillanate 156

Benzhydryl 6-bromopenicillanate 144 or 146 (50 mg, 0.11 mmol), toluene (0.4 ml), allyltributyltin (74 mg 0.22 mmol) and AIBN (2.4 mg) was warmed to 65°C under a nitrogen atmosphere for 45 minutes. The solvent was removed and the residue worked up as before giving 43 mg (95 %) of product as a colorless oil; ir (neat): 1750 (azetidinone), 1772 (CO_2); ^1H nmr: 1.24 and 1.62 (s,3H,CH_3), 2.58 (m,2H,C_1'-H), 3.38 (dt,1H,C_6-H,J= 2, 7), 4.57 (s,1H,C_3-H), 5.09 - 5.19 (m,3H,C_6-H and C_3'-H), 5.79 (m,1H,C_2'-H), 6.93 (s,1H,COOCH2), 7.26 ; ^{13}C nmr : 26.12 and 33.17 (CH_3), 32.33 (C_1'), 60.62 (C_6), 65.56 (C_2), 66.03 (C_3), 69.73 (C_5), 78.28 (OCH), 117.77 (C_3'), 127 - 139 (Ar-C), 133.53 (C_2'), 167.02 (C_7), 173.96 (CO_2); ms (95°C) : 407 (M^+,10.5), 379 (M^+ - CO, 1.0), 326 (M^+ - C_5H_5O, 1.9), 240 (3.0), 168 (48.2), 167 (100), 165 (31.0), 114 (32.3) ; Exact mass

(105°C): calcd. for $C_{24}H_{25}O_3NS$: 407.1555 ; found 407.1562 .

Benzhydryl 6β-allyl 159 and 6,6-diallylpenicillanate 157

Benzhydryl 6,6-dibromopenicillanate 145 (53 mg, 0.10 mmol), toluene (0.4 ml), allyltributyltin (64 mg, 0.20 mmol) and AIBN (2.4 mg) was warmed to 65°C under a nitrogen atmosphere for 45 minutes. The solvent was removed and the residue dissolved in acetonitrile (15 ml) and washed with hexanes (20 ml). The solvent was removed to give a mixture of 6α-allyl,6β-bromopenicillanate 158 and 6,6-diallylpenicillanate 157 which could not be separated by column chromatography. To the above mixture was then added tributyltin hydride (44 mg, 0.15 mmol), benzene (10 ml) and AIBN (cat) and refluxed for 2 h. The mixture was cooled to room temperature and the solvent removed. After the usual work up and column chromatography, 30 mg of 6β-allylpenicillanate 159 and 9 mg of 157 was obtained as colorless oils.

Benzhydryl 6β-allylpenicillanate 159; ir (neat): 1749 (azetidinone), 1773 (CO_2); ^1H nmr: 1.25 and 1.62 (s,3H,CH_3), 2.53 (t,2H,$C_{1'}$-H,J= 8), 3.68 (dt,1H,C_6-H,J= 4,8) 4.48 (s,1H,C_3-H), 5.05 - 5.12 (m,2H,$C_{3'}$-H), 5.44 (d,1H,C_5-H,J= 4), 5.75 (m,1H,$C_{2'}$-H), 6.94 (s,1H,COOCH), 7.26 - 7.34 (m,10H,Ar-H); 13C nmr: 26.45 and 31.78 (CH_3), 29.80 ($C_{2'}$), 53.17 (C_6), 64.22 (C_2), 66.70 (C_5), 69.17 (C_3), 78.22 (OCH), 117.12 ($C_{3'}$), 127 - 139 (Ar-C), 133.74 ($C_{2'}$), 167.20 (C_7), 175.06 (CO_2); ms (115°C) , chemical ionization, ammonia : 425 ($M + NH_4^+$, 0.4), 392 (M^+ - 15, 0.2), 391 (0.8), 168 (14), 167 (100).

Benzhydryl 6,6-diallylpenicillanate 157; ir (neat): 1730 -1780 (b,CO) ; ^1H nmr: 1.24 and 1.61 (s,3H,CH_3), 2.53 (m,4H,C_2'-H), 4.48 (s,1H,C_3-H), 5.11 - 5.19 (m,5H,C_5-H and C_2'-H) 5.81 (m,2H,C_2'-H), 6.92 (s,1H,OCH), 7.25-7.35 (m,10H,Ar-H); ^{13}C nmr: 26.23 and 32.55 (CH_3), 34.71 and 37.36 (C_1'), 61.49 (C_6), 64.40 (C_2), 68.26 (C_5), 71.03 (C_3), 78.15 (OCH), 119.19 and 119.31 (C_3'-H), 127.4-139.4 (Ar-C), 131.76 and 132.38 (C_2'), 166.95 (C_7), 175.85 (CO_2); ms (95°C): 447 (M^+, 0.2), 408 (M^+ - C_3H_4, 0.7), 407 (2.4), 326 (3.0), 240 (1.9), 196 (2.3) 168 (35.6), 167 (100), 152 (12.3). Exact mass (100°C): calcd. for $C_{27}H_{29}O_3NS$: 447.1867; found: 447.1833.

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