SYNTHESIS OF CARBOCYCLIC ANALOGUES OF C-NUCLEOSIDES AND
SYNTHETIC STUDIES TOWARDS CEPHAM DERIVATIVES AND
THEIR AZA ANALOGUES.

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Preface

The content of this thesis includes, "Synthesis of carbocyclic analogues of C-nucleosides (Part I)" and "Synthetic studies towards cepham derivatives and their aza analogues (Part II)".

Each part is indexed separately with a listing of subheadings in the text, and has an independent numbering system.
Synthesis of Carbocyclic Analogues of C-nucleosides

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Abstract

The synthesis of various intermediates for the preparation of carbocyclic analogues of C-nucleosides is described. The carbocyclic analogues of D,L-sho-domycin, D,L-pyrazofurin A, D,L-6-azapseudouridine, and D,L-4-thio-6-azapseudouridine were synthesized. The cyclization of hydrazones, semicarbazones and thiosemicarbazones to pyrazoles, 6-azauracils and 4-thio-6-azauracils, and the photochemical isomerization of hydrazones and semicarbazones was investigated. Important intermediates for the synthesis of carbocyclic analogues of 2-deoxy and 3-deoxy C-nucleosides were prepared. The carbocyclic analogue of D,L-2-deoxy-pyrazofurin A was synthesized.
Synthèse d'Analogues Carbocycliques des C-Nucléosides

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Résumé

La synthèse de plusieurs intermédiaires pour la préparation d'analogues carbocycliques des C-nucléosides est décrite. L'analogues carbocycliques de la D,L-showdomycine, D,L-pyrazofurine A, D,L-6-azapseudouridine et la 4-thio-6-azapseudouridine ont été préparés. La cyclization d'hydrazones, semicarbazones et thiosemicarbazones aux pyrazoles, 6-azauracils et 4-thio-6-azauraciles, et l'isomerization photochimique d'hydrazones et semicarbazones a été investigé. Intermédiaires importants pour la synthèse d'analogues carbocycliques des C-nucléosides 2-déoxy et 3-déoxy ont été préparés. L'analogue carbocyclique de la D,L-2-deoxypyrazofurine A a été préparé.
To my parents

who have done so much for me
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Introduction

In recent years there has been a growing interest in C-nucleosides, a new class of compounds characterized by a carbon-carbon bond between the sugar moiety and the heterocyclic base.

A number of naturally occurring C-nucleosides have been isolated to date. These are pseudouridine (1), formycin (2), formycin B (3), oxoformycin B (4), showdomycin (5), pyrazofurin A (pyrazomycin) (6), and oxazinomycin (minimycin) (7).

\( X = \text{NH} \) (1)  
\( X = \text{O} \) (7)
The fact that these compounds and some related analogues exhibited antiviral, antibacterial and antitumor activity stimulated their syntheses as well as that of various analogues.

The first attempts at the synthesis of C-nucleosides, involved carbon-carbon bond formation between the sugar moiety and the heterocyclic base. The next development was to introduce an appropriately functionalized carbon side chain with the correct stereochemistry, on which the heterocyclic base could be built. However, practically all syntheses described, involved the use of D-ribose or some other preformed sugar moiety.

Recently, stereospecific total syntheses, independent of natural ribose, have produced many C-nucleosides, opening the way to other related compounds.

Pseudouridine and related compounds.

Pseudouridine, the first C-nucleoside isolated, is present in transfer-RNA and was first synthesized in low yield by Shapiro and Chambers by the condensation of 2,3,5-tri-O-benzyloxy-D-ribofuranosyl chloride (8) with 5-lithio-2,4-dimethoxypyrimidine, and later in 18% yield by the condensation of 2,4:3,5-di-O-benzyldene-aldehydo-D-ribose (10) and 2,4-di-t-butoxy-5-lithiopyrimidine (11).
Because of the importance of pseudouridine as a constituent of RNA, many related compounds have been synthesized and their properties studied. For instance, 2,4-benzylxoy-5-lithiopyrimidine has been condensed with different sugar moieties, namely D-arabinose, D-xylose, and D-ribose to give compounds (12, 13, and 14).
Bobek et al.\textsuperscript{10} reported a synthesis of 6-azapseudouridine (17) from 6-pseudouridine. Reductive ozonolysis of 2',3',5'-tri-O-acetyl pseudouridine (15), followed by treatment of the resulting ketone with thiosemicarbazide and subsequent cyclization with sodium hydroxide afforded (16) which was treated with methyl iodide and acid to give 6-azapseudouridine (17).

Oxazinomycin (7), isolated recently by Sasaki et al.\textsuperscript{11}, showed antitumor and antiviral activities. The synthesis of this compound has not been reported to date. The synthesis of model compounds (18, 19), based on addition reaction of ketone to chlorosulfonyl isocyanate, was reported by Rasmussen and Hassner\textsuperscript{12}.
Pyrazolopyrimidine nucleosides

The pyrazolopyrimidine antibiotics are represented by formycin (2), formycin B (3) and oxoformycin B (4). Formycin, isolated in 1964\textsuperscript{13}, inhibits tumor cells, bacteria, fungi and viruses and it is the most effective analogue to replace adenosine. Formycin B, isolated in 1965\textsuperscript{14}, is less toxic than formycin and inhibits influenza virus. Oxoformycin B, isolated in 1968\textsuperscript{15}, does not inhibit the growth of any organism that has been tested to date, but it is a competitive inhibitor of N'-methyl nicotinamide\textsuperscript{1}. Acton et al.\textsuperscript{16} reported the synthesis of formycin B using a 1,3-dipolar addition reaction of diazo sugar (20) with dimethylacetylenedicarboxylate. The two carbomethoxy groups were selectively functionalized and treatment of this compound with dinitrogen tetroxide and sodium acetate gave the 4-azido-3-carboxy pyrazole (23).
Curtius rearrangement of (23), cyclization in formamide and hydrogenation afforded formycin B (3).

Farkas and Sorm\textsuperscript{17} synthesized oxoformycin B (4) in a similar manner by converting compound (22) into the azide (25), followed by Curtius rearrangement.

Farkas and Sorm\textsuperscript{17} also synthesized an analogue of oxoformycin B using the intermediate (21).
Conversion of this diester into the dihydrazide (26) and cyclization by acid afforded pyrazolopyridazine (27), which was debenzylation to the oxoformycin analogue (28).

Pyrazofurin A (pyrazomycin) and related compounds

Pyrazofurin A (6), isolated from the culture filtrate of a strain of streptomycetes candidus by Williams et al. in 1969, has been shown to be a strong inhibitor of orotidylic acid decarboxylase. It is also a potent antiviral agent. The structure of pyrazofurin A has been reported to be 3(5)-β-D-ribofuranosyl-4-hydroxypyrazole-5(3)-carboxamide and was confirmed by C\textsuperscript{13}nmr, by mass spectral analysis, and by synthesis.
The synthesis involved the condensation of the keto ester (29) with benzylhydrazinoacetic acid to form the hydrazone (30). Five additional steps were necessary to obtain pyrazofurin A (6) in very low yield.

\[ \text{(29) } R=\text{Ac} \quad \rightarrow \quad \text{(30)} \quad \rightarrow \quad \text{(6)} \]

Ramjeesingh\textsuperscript{22} reported a synthesis of a deoxy pyrazolic nucleoside from isopropylidene-2,5-anhydroallose (31). Reaction with carboethoxymethylene-triphenylphosphorane afforded the unsaturated ester (32) which on treatment with diazomethane underwent a 1,3-dipolar cycloaddition to the pyrazoline (33). Dehydrogenation with bromine and treatment with excess methanolic ammonia gave (34). Almost at the same time, Moffatt et al.\textsuperscript{23} described the preparation of (34) using a similar scheme.
Furthermore, the syntheses of many pyrazolic analogues have been reported in recent years. Tronchet et al.\textsuperscript{24-25} described the syntheses of pyrazoles (35,36) bearing aromatic substituents. The amino analogue (37) of pyrazofurin A was made for biological testings, starting from natural formycin B\textsuperscript{26}. 

![Chemical structures](image)

**Showdomycin and related compounds**

The glycosyl nucleoside antibiotic showdomycin was first isolated from Streptomyces showdoensis by Nishimura\textsuperscript{27}. On the basis of spectroscopic studies, chemical transformation, and ultimately X-ray crystallographic examination, showdomycin was shown to be 2-(β-D-ribofuranosyl)maleimide (5)\textsuperscript{28-30}. Showdomycin has antibacterial and antitumor activities\textsuperscript{1}.

A synthesis of showdomycin was reported by Kalvoda et al.\textsuperscript{31}. It involved, as the key intermediate, the keto ester (29).
The keto ester (29) was treated with carbomethoxymethylene-triphenylphosphorane to afford a cis-trans mixture of compound (38). Five additional steps were necessary to obtain showdomycin in low yield.

Moffatt et al.\textsuperscript{32} reported an improved method, which also involved the keto ester (39) as the key intermediate. Reaction of this keto ester (39) with carbamoylmethylene-triphenylphosphorane led directly to the tribenzyl ether of showdomycin (40). Debenzylatation with boron trichloride afforded showdomycin (5).
Recently, a synthesis of 3-methylshowdomycin (41) was published by Moffatt et al., using the condensation of 1-carbamoylethylidenedimethylphenylphosphorane with the keto ester (39). This compound showed a marked reduction of antibacterial activity with respect to showdomycin itself.

\[
\begin{align*}
(39) & \quad R = \text{Bn} \\
(41) & \quad R = \text{Bn}
\end{align*}
\]

Schwartz and Lerner tried to synthesize the N-substituted analogue (43) of showdomycin, but attempts to cleave the acetyl groups in (42) led to destruction of the maleimide ring.

\[
\begin{align*}
(42) & \quad R = \text{Ac} \\
(43) & \quad R = \text{Ac}
\end{align*}
\]
Carbocyclic nucleosides

In addition to C-nucleosides, another sub-class of nucleosides have been synthesized, namely, the carbocyclic nucleoside analogues.

Schaeffer et al.\textsuperscript{35-36} reported the synthesis of a series of substituted cyclopentyl and cyclohexyl derivatives of 6-substituted purines and 9-cycloalkyl adenine derivatives.

Murdock and Angier\textsuperscript{37-38} synthesized various cyclopentyl-thymines (44,45,46), but none were active.

![Chemical structures](44), (45), (46)

The most interesting carbocyclic nucleoside is aristeromycin (47). This compound was synthesized\textsuperscript{19} prior to its isolation from natural sources\textsuperscript{40}, and it is the only naturally occurring carbocyclic nucleoside isolated to date. Aristeromycin regulates the growth of plants and is active against the blast disease of rice plants.
Aristeromycin was synthesized by Shealy and Clayton in the following way. Exo-cis-hydroxylation of norbornadiene (48), followed by acetylation and oxidative cleavage gave (50). The amide prepared from the anhydride of (50) was subjected to a Hoffman rearrangement, followed by a lithium aluminum hydride reduction. The resulting amino alcohol (51) was condensed with 5-amino-4,6-dichloropyrimidine to give (52). Ring closure with triethyl orthoformate, and treatment with ammonia gave aristeromycin (47).
Shealy et al. \(^1\) in 1973 reported the synthesis of the 8-azaadenosine analogue (53), its monophosphate (54) and its cyclic monophosphate (55) which proved to be cytotoxic to cells in culture.

Recently, Playtis and Fissekis reported the synthesis of carbocyclic analogues of 2',3',-dideoxypseudouridine (56, 57)\(^2\).

The aim of this project is to synthesize carbocyclic analogues of showdomycin and pyrazofurin A, and of related 2-deoxy C-nucleosides.
Chapter I

Synthesis of carbocyclic analogues of D,L-showdomycin and D,L-pyrazofurin A.

Our approach for the synthesis of carbocyclic analogues of C-nucleosides required compounds of the general type (58), where Y was a suitably functionalized side chain on which the base nucleus could be built.

Several important intermediates (59,60,61) had been prepared by Reader in our laboratory. Among others, keto esters of type (61) appeared to be the most promising intermediates in the synthesis of carbocyclic analogues of showdomycin (62) and pyrazofurin A (63).

In this chapter, the synthesis of carbocyclic analogues of showdomycin and pyrazofurin A via the keto ester will be described:

![Chemical structures](58) (R=CHO) (60) (R=CHO) (61) (R=CH₂OCPH₃)

(59) R'=H, Y=CHO, (61) R=CH₂OCPH₃

R=C(CH₃)₂
I-1 Preparation of keto esters (79,80,81)

The synthesis of the trityl protected keto ester (61) was developed by Reader. Reader also demonstrated that the trityl protecting group was of limited use because of its instability to reactions used in hydrazone formation.

The starting point of his synthesis was the Diels-Alder adduct (66) which was prepared by condensation of trans-3-bromoacrylic acid (65) and cyclopentadiene in benzene in 65% yield. This compound exists as almost exclusively the endo-carboxylate isomer\(^6\).\(^7\)

The acid (66) was esterified with diazomethane in essentially quantitative yield. This method involved an expensive reagent and was not suitable in preparing a large amount of the ester. Instead the acid was esterified with methanol and a catalytic amount of p-toluenesulfonic acid. The methyl ester (67) could be distilled at 90-92°C/1.2 mmHg.

The methyl ester was oxidized with 30% hydrogen peroxide and a catalytic amount of osmium tetroxide\(^6\) to give a crystalline diol (68) in 50% yield. The diol was converted to its acetonide (69) with acetone and a catalytic amount of p-toluenesulfonic acid in quantitative yield. Hydrogen bromide was eliminated from the isopropylidene derivative by treatment with 1,5-diazabicyclo(5.4.0)undec-5-ene (DBU)\(^7\).
The desired olefinic ester (70) was obtained in quantitative yield.

Ozonolysis of olefinic ester (70) in methylene chloride at -78°C gave an oily ozonide, which was smoothly reduced with dimethyl sulfide to give the aldehyde keto ester (60). The aldehyde keto ester exists as a mixture of the open form (60a) and the closed hydrated form (60b).

Treatment of the crude product with lithium tri-t-butoxyaluminum hydride in tetrahydrofuran gave diol ester (71) as an oil in 65% yield.

Since the trityl protecting group used by Reader was not suitable for our purpose, we decided to selectively block the primary hydroxy group using other protecting groups.

Our first attempt was to prepare diol mono-p-nitrobenzoate (74), which should be stable under the reaction conditions used to form the hydrazone.

Treatment of diol (71) with 1 equiv. of p-nitrobenzoyl chloride in pyridine and methylene chloride gave at least two products and unreacted starting material according to the nmr spectrum and t.l.c. The crude product was separated on silica gel plates using chloroform as an eluant. From the nmr spectral data, the structure of the less polar, minor product (30%) was assigned to the di-p-nitrobenzoate (73).
Its nmr spectrum showed all protons at the expected position. The proton at C-6, C-4 and C-3 appeared as a multiplet at 4.4 ppm, whereas the proton at C-1 appeared as a quartet at 5.2 ppm, due to the fact the di-p-nitrobenzoate (73) was a mixture of epimers at that position. The nmr spectrum of the more polar, major product (50%) indicated that it consisted of a mixture of mono-p-nitrobenzoate (74) and (75) in ratio of 4:1. The presence of latter was determined by integration of the proton signal at 5.2 ppm.

We therefore turned our attention to much more bulky, and therefore hopefully more selective reagents such as pivaloyl chloride or t-butyldimethylchlorosilane.

Treatment of diol (71) with 1 equiv. of pivaloyl chloride in pyridine and methylene chloride gave an oily compound. Purification of the crude product on silica gel plates using ethyl ether as an eluant gave the desired product (76) in 80% yield.
Its nmr spectrum showed a doublet (2H) at 4.10 ppm, a multiplet (3H) at 4.2-4.6 ppm, a singlet (3H, COOMe) at 3.80 ppm and a broad peak (1H, OH) at 2.8-3.0 ppm. The absence of a signal below 5.0 ppm indicated that the desired product (76) had formed. Its ir spectrum showed absorptions at 1745 cm\(^{-1}\) for the carbonyl functions and at 3520 cm\(^{-1}\) for the hydroxy group.

We thought it would be interesting to see whether t-butyldimethylchlorosilane would show the same type of selectivity as pivaloyl chloride, in particular since removal of a pivaloyl group might not be compatible with the maleimide ring of showdomycin.

Treatment of diol (71) with 1 equiv. of t-butyldimethylchlorosilane and 2.5 equiv. of imidazole in dimethylformamide, followed by purification on silica gel plates using ethyl ether as an eluant gave an oily compound in 80% yield. Its nmr spectrum showed a multiplet (3H) at 4.1-4.8 ppm, a doublet (2H) at 3.73 ppm, a singlet (3H, COOMe) at 3.82 ppm and a broad peak (1H, OH) at 3.1 ppm. From the nmr spectral data,
we were unable to find whether the desired product (77) had formed or not.

In order to establish the structure of this compound, the compound was converted with acetic anhydride and pyridine to an oily acetate in quantitative yield. Its nmr spectrum showed a multiplet (1H) at 5.1 ppm, indicative of the formation of the desired acetate (78). We could therefore conclude that the protection of diol with t-butyldimethylchlorosilane have given the desired product (77).

Because of the nature of the protecting groups, it seemed to be advisable to carry out the oxidation of the secondary alcohol function at neutral pH. Oxidation with sodium periodate and ruthenium dioxide\(^3\) appeared to be a promising method for our purpose.

![Chemical Structures](79) (79) ![Chemical Structures](80) (80)
Treatment of (77) in carbon tetrachloride and water with sodium periodate, a catalytic amount of ruthenium dioxide and a small amount of sodium bicarbonate to keep the pH between 6 and 7 gave the oily keto ester (79) in essentially quantitative yield. Its nmr spectrum showed a multiplet (1H) at 4.8 ppm, a doublet of doublets (1H) at 4.40 ppm, a singlet (3H, COOME) at 3.83 ppm, and a quartet (2H) at 3.50 ppm. These peaks at 4.8, 4.40 and 3.50 ppm were assigned to H-2, H-3 and H-5 protons respectively.

Its ir spectrum showed carbonyl absorptions at 1770 and 1750 cm$^{-1}$. Furthermore, its mass spectrum showed a molecular ion peak at m/e 372 and other major peaks at m/e 357 (M$^+$-CH$_3$), at m/e 313 (M$^+$-COOME) and at 257 (M$^+$-t-butyldimethylsilyl).

An attempt to purify the keto ester (79) on silica gel plates led to its decomposition. However, the crude keto ester was pure enough to give satisfactory microanalysis data.

Similarly, oxidation of the pivaloyl protected alcohol (76) to the keto ester (80) was achieved in essentially quantitative yield by using sodium periodate-ruthenium dioxide. This compound was fully identified by its spectral data.
It was then also decided to explore the possibility of oxidative cleavage of olefinic ester (70) to the acid keto ester (81), which might be a useful intermediate for the synthesis of carbocyclic analogues of C-nucleosides.

\[
\begin{align*}
(70) & \quad \rightarrow \quad (81) \quad X=O \\
(81a) & \quad \text{and} \quad (82) \quad X=\text{NNHCONH}_2
\end{align*}
\]

Oxidation of olefinic ester (70) with potassium permanganate and sodium periodate gave the crude acid keto ester (81) in 85% yield. Its nmr spectrum showed a singlet (3H,COOME) at 3.80 ppm and a broad peak (1H,COOH) at 9.0 ppm. These data indicated the presence of (81) rather than (81a), although the latter could not be rigorously excluded. This compound also appeared to decompose on silica gel plates and was further characterized as its semicarbazone derivative (82).
The synthesis of showdomycin (5) was originally accomplished by Kalvoda et al. Their scheme was rather lengthy and cumbersome and required a six-step sequence for conversion of the keto ester into showdomycin.

Recently, an improved method was published by Moffatt et al., also involving, as the key intermediate, the keto ester. In their paper they described the following features:

(i) the reaction of carbamoylmethylenetriphenylphosphorane with the keto ester (83) gave cis-oriented isomer (84) and trans-oriented isomer (85); (ii) cis-oriented intermediate then underwent spontaneous cyclization to the maleimide (86); (iii) steric effect in the substituent R controlled the ratio of cis and trans-oriented isomer.

\[ \text{COOMe} \quad \rightarrow \quad \text{CONH}_2 \quad \text{CONH}_2 \]

\[ \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \]

(83) (84) (85)

\[ \text{(86)} \]
Since it is known that showdomycin is very unstable in base\(^2\), we decided to use (79) instead of (80) as an intermediate since the pivaloyl group can not be easily removed under non-alkaline condition.

The keto ester (79) was treated with 1 equiv. of carbamoylmethylene-triphenylphosphorane\(^5\) in chloroform at room temperature for 3 hours. The reaction gave a single major product, which was less polar than the keto ester (79), together with a considerable amount of polar products. Purification of the crude product on silica gel plates using hexane and ethyl ether (2:1) gave the crystalline product (87) in 75\% yield.

\[
\begin{align*}
(79) & \quad \xrightarrow{\text{Ph}_3P=\text{CHCONH}_2} \quad (87) \\
\end{align*}
\]

Its nmr spectrum showed a broad peak (1H,NH) at 8.2 ppm and a multiplet (1H, vinyl proton) at 6.25 ppm. The ir spectrum showed absorptions at 1780 and 1730 cm\(^{-1}\) for the carbonyl functions and at 1630 cm\(^{-1}\) for the double bond.
Furthermore, this compound showed an absorption at 226 nm in the uv. No attempts were made to identify the more polar products.

Completion of the synthesis of a carbocyclic analogue of showdomycin then only required removal of the protecting groups.

Treatment of (87) with tetraethyl ammonium fluoride in tetrahydrofuran led to decomposition of the maleimide ring. It has been reported that fluoride ion in aprotic solvent is a very strong base, which explains the decomposition of the maleimide ring under the reaction conditions.

The solution to this problem involved acid hydrolysis of the butyldimethylsilyl and isopropylidene group at the same time. Treatment of (87) with 50% aqueous trifluoroacetic acid for 30 minutes gave a crystalline product, m.p. 171-172°C, in 80% yield. Spectral data and microanalysis data were consistent with the structure of (62).

Furthermore, this compound was fully identified by its mass spectrum. It has been reported that the mass spectra of the C-nucleoside antibiotics show a characteristic parent peak at B+30 (B=heterocyclic base). This B+30 has been assigned to the heterocyclic base plus a protonated formyl group which results from fragmentation of the sugar. This information may be considered diagnostic in the structural elucidation of carbon linked nucleoside derivatives.
The mass spectrum of (62) showed a molecular ion peak at m/e 227, base peaks at m/e 124 and m/e 125, which correspond to B+27 and B+28, and other major peaks at m/e 228 (M⁺+1), at m/e 209 (M⁺−H₂O) and at m/e 191 (M⁺−2H₂O).

In most of the carbocyclic analogues of C-nucleosides examined later on⁵⁸, the B+27 and B+28, and sometimes B+27 peak alone, have been found and they probably occur from fragmentation of the cyclopentane ring. It should be pointed out that the mass spectrum of (87) showed major peaks at m/e 124 and m/e 125 but with a significant reduction in relative intensity.

\[
\begin{align*}
\text{m/e 227} & \quad \text{m/e 124} & \quad \text{m/e 125} \\
\text{(B+27)} & \quad \text{(B+28)} \\
\end{align*}
\]
I-3 Synthesis of a carbocyclic analogue of D,L-pyrazofurin A

Earlier work in our laboratory and elsewhere showed that the 4-hydroxy-3-carboxamide pyrazoles could be synthesized from pyruvate ester derivatives. In order to study the spectral characteristics of the hydrazone and pyrazole, the cyclization reaction was first carried out on readily available methyl pyruvate hydrazone (88).

\[
\begin{align*}
\text{COOMe} & \quad \text{CH}_3 \\
\text{N} & \quad \text{NHCH}_2\text{COOMe} \\
(88) & \quad \rightarrow \\
\text{HO} & \quad \text{C} \quad \text{COOMe} \\
\text{CH}_3 & \quad \text{N} \\
(89)
\end{align*}
\]

The hydrazone (88) had, in its ir spectrum, ester absorption peaks at 1745 and 1715 cm\(^{-1}\) and a C=N absorption at 1605 cm\(^{-1}\). Its nmr spectrum showed a broad peak (1H, NH) at 6.3 ppm and the uv spectrum showed an absorption at 273 nm.

Cyclization of hydrazone (88) with sodium methoxide in boiling methanol for 2 hours gave the pyrazole (89) in 30% yield. Its uv spectrum showed \(\lambda_{\text{max}}\) at 225 and 275 nm in 0.1N HCl and \(\lambda_{\text{max}}\) at 237 and 317 nm in 0.1N NaOH. The characteristic bathochromic shift is due to the formation of the enolate ion. Its ir spectrum showed carbonyl absorption
peaks at 1720 and 1690 cm\(^{-1}\) in chloroform, which provide evidence for a keto-enol equilibrium\(^6\).

\[
\begin{align*}
\text{(90a)} & & \text{(90b)}
\end{align*}
\]

The pivaloyl-protected keto ester (80) was treated with ethyl hydrazinoacetate hydrochloride and sodium acetate in aqueous methanol at room temperature and following purification on silica gel plates gave an oily hydrazone (90) in 87\% yield. Its nmr spectrum showed broad peaks (total 1H,NH) at 10.2 and 6.8 ppm, multiplets (8H) at 4.0-4.8 ppm and a singlet (3H,COOME) at 3.77 ppm.

It was quite interesting that the NH-proton signals appeared at 10.2 and 6.8 ppm in ratio of 2:1, while the NH proton of (88) gave a broad peak at 6.3 ppm. This fact could be an indication of the presence of geometrical isomers even if a singlet at 3.77 ppm for the methyl ester group was observed. We concluded that the proton signal at 10.2 ppm represented the NH proton of the syn isomer (90b), for reasons which will be discussed later in this chapter.
The hydrazone (90) showed, in its ir spectrum, broad carbonyl absorptions at 1740 cm\(^{-1}\) and a C=N absorption at 1580 cm\(^{-1}\) and also an absorption at 287 nm in the uv spectrum.

We were unable to separate these geometrical isomers on silica gel plates.

Without separation of a mixture of geometrical isomers, the hydrazone (90) was treated with sodium methoxide in boiling methanol for 2 hours. The nmr spectrum of the crude product was not clean and indicated partial hydrolysis of the pivaloyl group and conversion of the ethyl ester group into the methyl ester group. The uv spectrum showed very weak bathochromic shift when going from acidic to alkaline solution and t.l.c. showed many spots. Because of these difficulties, we were unable to separate the desired product.

We therefore decided to use the t-butyldimethylsilyl protected keto ester (79) instead of the pivaloyl protected keto ester (80).
Condensation of the keto ester (79) with ethyl hydrazinoacetate hydrochloride and sodium acetate in aqueous methanol gave an oily hydrazone (91) in 89% yield, which also existed as a mixture of geometrical isomers in roughly equal amounts according to its nmr spectrum. Spectral data of this compound were similar to those of (90).

Without separation of the mixture of geometrical isomers, treatment of hydrazone (91) with sodium methoxide in boiling methanol for 2 hours gave the desired product (92) as a crystalline compound in 40% yield, after purification on silica gel plates using ethyl ether and chloroform (5:1) as an eluant. Its ir spectrum showed absorption peaks at 1720 and 1690 cm\(^{-1}\) in chloroform, which indicated keto-enol equilibrium, with prevailing enol form and its uv spectrum showed \( \lambda_{\text{max}} \) at 230 and 275 nm in 0.1N HCl and \( \lambda_{\text{max}} \) at 240 and 320 nm in 0.1N NaOH.
Treatment of (92) with ammonia in methanol at room temperature for a week gave the amide (93) as a foam in 85% yield. Spectral data as well as microanalysis data were consistent with the structure assigned. Furthermore, this compound was fully characterized by its mass spectrum.

The mass spectrum of the amide (93) showed a fragmentation pattern with several important peaks. The most important peaks were found to be associated with the substituent CONH$_2$ and OH of the heterocyclic moiety. The elimination of ammonia from the hydroxycarboxamide group proceeded via a favorable 6-membered transition state as depicted below.

This process was also observed in the mass spectrum of pyrazofurin A.

![Chemical Structure]

\[ m/e \ 396 \ (M^+ - CH_3) \quad m/e \ 379 \ (M^+ - CH_3 - NH_3) \]
The same type of fragmentation resulting in the elimination of methanol from the hydroxycarbomethoxy group in (92) was also observed.

(92)

\[
\text{m/e 411 (M}^+\text{-CH}_3) \quad \text{m/e 379 (M}^+\text{-CH}_3\text{-CH}_3\text{OH)}
\]

Completion of the synthesis of a carbocyclic analogue of pyrazofurin A then only required removal of the protecting groups from (93).

Treatment of (93) with 50\% aqueous trifluoroacetic acid at room temperature for 30 minutes gave the desired product (63) as a crystalline compound in 80\% yield.

Spectral data and microanalysis data were consistent with structure assigned. Its mass spectrum again showed a base peak at m/e 168 (B+27).
It had been mentioned that the cyclization of the hydrazone to the pyrazole proceeded in 40% yield only, and that the hydrazone seemed to consist of a mixture of the syn and the anti isomer in a ratio of 2:3. It occurred to us that the low yield of cyclization might be due to the fact that only the syn isomer could cyclize. Since it had been briefly shown by Ouellet\(^6\) that the syn isomer and the anti isomer could be interconverted by irradiation with uv light at the appropriate wavelength, we decided to study the cyclization of the pure syn and anti hydrazones.

Attempts to separate geometrical isomers of hydrazone (91) on silica gel plates in various solvents were unsuccessful owing to similar r.f. values. We were however able to separate these isomers with high pressure liquid chromatography on a silica gel column using 0.5% isopropyl alcohol in methylene chloride.

The first fraction showed, in its nmr spectrum, a triplet for the NH proton at 10.2 ppm and an absorption at 1700 cm\(^{-1}\) for the methyl ester group in its ir spectrum, whereas the second fraction showed a triplet at 6.6 ppm and an absorption at 1720 cm\(^{-1}\). Furthermore, the first fraction showed an uv maximum at 300 nm, whereas the second fraction showed an uv maximum at 275 nm.
We assigned to the first fraction the syn geometry (91b) based on the following reasons. It is obvious that the syn isomer (91b) can have intramolecular hydrogen bonding, but the anti isomer (91a) can not. Intramolecular hydrogen bonding between the carbonyl group of the methyl ester and the NH proton may explain the existence of the NH proton at lower field and also a slight decrease in the absorption frequency of the carbonyl group.

We mentioned briefly that steric effect in the substituent R might control the ratio of geometrical isomers. We therefore considered the possibility of the same type of steric control. When the substituent R is a small methyl group, the formation of the hydrazone may proceed exclusively so as to place two bulkiest substituents (COOME, NHCH₂COOEt)
in a stable trans relationship. On the other hand, with the keto ester (79) the bulky cyclopentane ring becomes the major steric influence.

We therefore concluded that the keto ester (79) gave a mixture of the syn and the anti hydrazone, while methyl pyruvate gave exclusively the anti isomer. The compound assigned the anti geometry showed in many respects similar spectral data as methyl pyruvate hydrazone (88).

Since we successfully separated a mixture of geometrical isomers of (91), we wanted to see whether the anti isomer (91a) cyclized to form a pyrazole ring or not. Each isomer was separately treated with sodium methoxide in boiling methanol for 2 hours. The uv spectrum showed that both isomers had undergone cyclization to form the pyrazole ring and t.l.c. spots of crude products were same with both isomers. This result proved that anti→syn interconversion had occurred under the reaction conditions.

In order to support our results, we wanted to examine the cyclization behaviour of the syn isomer of methyl pyruvate hydrazone. We previously pointed out that there was no indication of the presence of the geometrical isomers.

The hydrazone (88a) was irradiated in methanol at 254 nm for 2 days. This reaction was followed by uv spectroscopy. The uv maximum shifted from 275 to 290 nm, and the nmr spectrum
of the crude product showed broad peaks at 10.0 and 6.6 ppm in a ratio of 4:1. Separation on silica gel plates using chloroform as an eluant gave the pure syn isomer (88b) as an oil in 70% yield.

\[ \text{COOMe} \quad \rightarrow \quad \text{COOMe} \quad \rightarrow \quad \text{HO} \quad \text{COOMe} \]

(88a) \quad (88b) \quad (89)

The hydrazone (88b) showed, in its nmr spectrum, a broad peak at 10.2 ppm for the NH proton and absorptions at 1690 cm\(^{-1}\) (COOMe), and at 1570 cm\(^{-1}\) (C=N) in its ir spectrum. Furthermore, the uv spectrum showed an absorption at 295 nm. These spectral data were very similar to those of the syn-hydrazone (91b).

Treatment of the syn-hydrazone (88b) with sodium methoxide gave the pyrazole (89) in 35% yield, which was almost the same result as when using the anti-hydrazone (88a).

Since it is impossible for the anti isomer to cyclize, our results clearly showed that anti-syn interconversion had occurred during the reaction.
Biological Testings

Preliminary evaluation of the carbocyclic analogues of D,L-showdomycin and D,L-pyrazofurin A failed to show any activity against 15 strains of bacteria and four strains of fungi up to levels as high as 256 mcg/ml. Nine viral strains, including both DNA and RNA types, were not significantly affected by these drugs in tissue culture.

In a special plaque reduction assay against a vaccinia virus challenge, slight activity was noted for both compounds, but only at levels substantially higher than those required for pyrazofurin A to exhibit an equivalent effect. This latter study is summarized on the next page.

We are indebted to Dr. D. C. DeLong and Dr. G. E. Gutowski, Lilly Laboratories, Indianapolis, for carrying out the above tests.
### Plaque Reduction % Inhibition of Plaques

<table>
<thead>
<tr>
<th>Mcg/mL</th>
<th>100</th>
<th>50</th>
<th>25</th>
<th>12</th>
<th>6</th>
<th>3</th>
<th>1.5</th>
<th>0.35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Carbocyclic Analogue of D,L-Showdomycin</strong></td>
<td>100</td>
<td>26</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>The Carbocyclic Analogue of D,L-Pyrazofurin A</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>45</td>
<td>38</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td><strong>Pyrazofurin A</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

- **Virus:** Vaccinia
- **Cell Line:** BSCI

**Note:** The table shows the percentage inhibition of plaques at different concentrations of the compounds.
Chapter II

Synthesis of carbocyclic analogues of D,L-6-azapseudouridine and D,L-4-thio-6-azapseudouridine

The uracil base has been extensively investigated because it is an important nucleic acid constituent. The aza analogues of uracil have attracted the attention of numerous research groups on the basis of their similarity to the natural nucleosides.

In this chapter, the synthesis of carbocyclic analogues of D,L-6-azapseudouridine (94) and D,L-4-thio-6-azapseudouridine (95) will be described.
II-1. Synthesis of a carbocyclic analogue of D,L-6-aza-pseudouridine

Previous work showed the synthetic importance of the \(\alpha\)-keto ester to build a 1,2,4-triazine ring system. It has been reported\(^6\) that semicarbazones (96) of \(\alpha\)-keto acids or \(\alpha\)-keto esters are cyclized under the influence of aqueous sodium hydroxide directly to (97) in variable yield.

\[
\begin{align*}
\text{COOR'} & \quad \rightarrow \\
\text{R} & \quad \text{N} - \text{NHCONH}_2 \\
(96) & \quad (97)
\end{align*}
\]

The reaction is normally carried out at 100°C. Higher yields are obtained by working at room temperature, but the reaction then often takes several months. The cyclization proceeds best with semicarbazones with a higher alkyl or even better an aryl or aralkyl group in the \(\alpha\)-position\(^6\). Furthermore, with the semicarbazones of lower \(\alpha\)-keto acid the reaction proceeds with some difficulty or, in case of pyruvic acid\(^6\), not at all.

Bougault\(^5\) observed that the thiosemicarbazone (98) of pyruvic acid underwent a high yield cyclization resulting in the formation of (99).
Replacement of the sulfur atom with oxygen atom then allowed him to prepare 6-azathymine (100). In contrast with the cyclization of semicarbazones of α-keto acids, the cyclization of thiosemicarbazones proceeds consistently with substantially higher yield. The cyclization of the thiosemicarbazones has therefore served as the basis for the synthesis of 6-azauracils.

Our first approach involved the cyclization of semicarbazone rather than thiosemicarbazone derivative.

The keto ester (79) was treated with semicarbazide hydrochloride and sodium acetate at room temperature overnight. Following purification on silica gel plates using ethyl acetate as an eluant, an oily semicarbazone (101) was obtained in 90% yield.
Its nmr spectrum showed two single peaks of the methyl ester group at 3.8 ppm and two broad singlets of the NH proton at 9.6 and 11.3 ppm, which would be indicative of the presence of geometrical isomers in roughly equal amounts. Its uv spectrum showed an absorption at 265 nm. We were unable to separate these isomers on silica gel plates.

The mixture of geometrical isomers was treated with sodium methoxide in boiling methanol for 2 hours to give a minor product with a polarity less than that of (101) and a major product with same polarity as (101) on silica gel plates using ethyl ether and chloroform (5:1) as an eluant.

The nmr spectrum of less polar, minor product (102) clearly showed the disappearance of the methyl ester group and the presence of two acidic protons at 10.0-11.0 ppm. Its mass spectrum showed a molecular ion peak at m/e 397, a base peak at m/e 282 (M⁺−t-butyldimethylsilyl group) and
other major peaks at m/e 382 (M⁺-CH₃) and at m/e 340 (M⁺-C(CH₃)₃). Furthermore, its uv spectrum showed characteristic absorptions of 6-azauracils at 265 nm in 0.1N HCl and 255 nm in 0.1N NaOH.

The nmr spectrum of a major product showed a broad singlet (1H,NH) at 9.6 ppm, a broad peak (2H,CONH₂) at 6.0 ppm and a singlet (3H,COOMe) at 3.83 ppm. The nmr spectral data indicated that the major product was the anti isomer (101a). Its ir spectrum was almost the same as that of a mixture of geometrical isomers, while its uv spectrum showed an absorption at 262 nm. At this point, above results suggested to us that one of geometrical isomers, the syn isomer, had undergone cyclization to form 1,2,4-triazine ring, while the anti isomer did not. These observations attracted our attention.

We therefore decided to investigate these findings in detail with the semicarbazone of methyl pyruvate as a model compound. In order to simplify the discussion, the relevant spectral data of the syn and the anti isomers of the hydrazone, the semicarbazone and the thiosemicarbazone are summarized on the next page.

The semicarbazone of methyl pyruvate (103a) was easily prepared by treatment of methyl pyruvate with semicarbazide in essentially quantitative yield. Its nmr spectrum showed a broad singlet (2H,CONH₂) at 6.4 ppm, a broad singlet (1H,NH)
<table>
<thead>
<tr>
<th>Syn isomer</th>
<th>Anti isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hydrazone (91)</td>
<td></td>
</tr>
<tr>
<td>Nmr: δ 10.2 ppm</td>
<td>6.6 ppm (NNHCH₂)</td>
</tr>
<tr>
<td>Ir : 1700 cm⁻¹</td>
<td>1720 cm⁻¹ (COOME)</td>
</tr>
<tr>
<td>Uv : λₘₐₓ = 300 nm</td>
<td>λₘₐₓ = 275 nm</td>
</tr>
<tr>
<td>2. Semicarbazone (101)</td>
<td></td>
</tr>
<tr>
<td>Nmr: δ 11.3 ppm</td>
<td>9.6 ppm (NNHCO)</td>
</tr>
<tr>
<td>Ir : 1700 cm⁻¹</td>
<td>1720 cm⁻¹ (COOME)</td>
</tr>
<tr>
<td>Uv : λₘₐₓ = 272 nm</td>
<td>λₘₐₓ = 263 nm</td>
</tr>
<tr>
<td>3. The mixture of geometrical isomers of thiosemicarbazone (108)</td>
<td></td>
</tr>
<tr>
<td>Nmr: δ 12.1 and 9.2 ppm</td>
<td></td>
</tr>
<tr>
<td>Ir : 1710 and 1730 cm⁻¹</td>
<td></td>
</tr>
<tr>
<td>Uv : λₘₐₓ = 315 and 273 nm</td>
<td></td>
</tr>
</tbody>
</table>
at 9.9 ppm and two singlets at 3.77 and 2.08 ppm for the methyl groups. Its ir spectrum showed a carbonyl absorption at 1730 cm⁻¹, while uv spectrum showed an absorption at 262 nm.

Overall, spectral data were similar to those of (101a). According to our assumption, this compound was the anti isomer (103a).

As mentioned previously, the semicarbazone of pyruvic acid or its ester could not be cyclized with sodium methoxide in methanol, while its acid was cyclized with sodium ethoxide in ethylene glycol (b.p. 198°C) at reflux for 15 hours. These results suggested to us that the semicarbazone of pyruvic acid or its ester would exist as the anti isomer and so it did not cyclize easily, while conversion of the anti into the syn isomer might occur under reaction conditions attempted in the latter case.

We next considered the possibility of conversion of the anti (103a) into the syn isomer (103b) by photolysis. The anti isomer (103a) was irradiated at 254 nm in methanol for 2 days. The reaction was followed by uv spectroscopy, which indicated that there was a slight shift of
the absorption maximum from 262 to 265 nm. The nmr spectrum of the crude product showed a broad singlet at 10.8 and 6.6 ppm for the NH and the CONH₂ respectively and also there was an indication of the presence of the starting material to the extent of 10%. Separation on silica gel plates using ethyl acetate as an eluant gave the crystalline syn isomer (103b) in 80% yield. Its ir spectrum showed a carbonyl absorption at 1695 cm⁻¹ and the uv spectrum showed an absorption at 265 nm.

\[ \text{The syn isomer (103b) was treated with sodium methoxide in methanol at room temperature. After adding sodium methoxide, a white precipitate was formed in less than 10 minutes. Its nmr spectrum in D₂O clearly showed the disappear-} \]
ance of the methyl ester group. This compound was assigned to structure (104), namely, the sodium salt of the desired azathymine. Acidification of (104) gave a crystalline 6-azathymine (100) in 75% yield. Its ir spectrum showed very sharp carbonyl absorptions at 1730 and 1680 cm$^{-1}$ and the uv spectrum showed absorptions at 261 nm in 0.1N HCl and at 246 nm in 0.1N NaOH, which were in agreement with reported values.

The above results showed conclusively that the isomer (103b) was the syn isomer since it underwent cyclization under reaction conditions, whereas the anti isomer (103a) did not, and also that cyclization took place before acidification.

We were able to separate the geometrical isomers of the semicarbazone (101) with high pressure liquid chromatography. Separation was carried out with a silica gel column using 0.5% methanol in methylene chloride as an eluant.
The first fraction was the syn isomer (101b), whereas the second fraction was the anti isomer (101a). Furthermore, the spectral data of the second fraction were identical with those of the major product which was recovered after treating with sodium methoxide.

\[
(101a) \rightarrow \text{COOMe} \rightarrow (101b) \rightarrow (102)
\]

The anti isomer (101a) was irradiated at 254 nm in methanol for 2 days. The reaction was followed by uv spectroscopy. The change of the absorption maximum from 263 to 271 nm was observed. Spectral data were identical with those of the syn isomer (101b).

Treatment of this compound with sodium methoxide gave the desired product (102) in 80\% yield.

The results obtained can be summarized as follows: (i) the syn isomer underwent a cyclization reaction under mild conditions to form the triazine ring, whereas the anti isomer did not; (ii) the cyclization reaction took place
under basic condition before acidification; (iii) anti-syn isomerization did not take place under the reaction conditions attempted; (iv) the anti isomer could be converted into the syn isomer on irradiation at 254 nm.

Treatment of (102) with 50% aqueous trifluoroacetic acid at room temperature for 20 minutes gave (94) in 80% yield. Its ir and uv spectrum were consistent with (94). Its mass spectrum showed molecular ion peaks at m/e 243 and m/e 244 (M⁺+1), a base peak at m/e 207 (M⁺-2H₂O) and other major peaks at m/e 225 (M⁺-H₂O), m/e 140 (B+28) and m/e 139 (B+27).

Careful examination of the nmr spectrum of the semicarbazone (82) of the keto ester acid (81) revealed that it existed almost exclusively as the syn isomer. Its nmr spectrum showed a broad singlet at 11.2 ppm, a broad peak at 10.2-11.0 ppm for the NH and the COOH proton and
a singlet at 3.80 ppm for the methyl ester group.

The semicarbazone (101) and the hydrazone (91) of the keto ester (79) are a mixture of geometrical isomers, probably because of steric factors. The exception in (82) is probably due to hydrogen bonding. One possibility is depicted below.
Treatment of semicarbazone (82) with sodium methoxide in boiling methanol for 1 hour gave the crystalline cyclized product (105) in 80% yield. Its ir spectrum showed broad carbonyl absorptions at 1700-1730 cm\(^{-1}\) because of overlapping of absorptions of the CONH groups and the COOH group. Its uv and mass spectrum as well as microanalysis data were consistent with (105). This finding confirmed the idea that the syn isomer of semicarbazones cyclize without difficulty.

\[
\begin{align*}
\text{(105)} & \quad \rightarrow \quad \text{(106)}
\end{align*}
\]

The next step involved the reduction of carboxylic acid to the primary alcohol. Treatment of acid (105) with diborane in tetrahydrofuran afforded the alcohol (106) in 90% yield. Its ir spectrum showed absorptions at 3400-3550 cm\(^{-1}\) and 3300 cm\(^{-1}\) for the OH and the NH groups and at 1730 cm\(^{-1}\) and at 1700 cm\(^{-1}\) for the carbonyl groups, and its uv spectrum showed absorptions at 265 nm in 0.1N HCl and at 255 nm in
0.1N NaOH like all previous compounds containing the same triazine system, indicating the heterocyclic moiety to be stable to diborane.

Treatment of (106) with 90% aqueous trifluoroacetic acid at room temperature for 10 minutes gave the final product (94) in 75% yield. This compound was identical in all respects with (94), obtained by a different route.

II-2 Synthesis of a carbocyclic analogue of D,L-4-thio-6-azapseudouridine

As mentioned previously, it is known that the thiosemicarbazone of methyl pyruvate and pyruvic acid cyclize readily under basic condition. Therefore, we realized that there was a significant difference of behaviours between thiosemicarbazones and semicarbazones of α-keto esters.

\[
\begin{align*}
&\text{COOMe} \\
&\text{CH}_3\text{N} = \text{NHCNSNH}_2 \\
\rightarrow & \text{COOMe} \\
&\text{CH}_3\text{N} = \text{NHCNSNH}_2 \\
&\text{S} \\
&\text{NH} \\
&\text{N}\text{H} \\
&\text{CH}_3
\end{align*}
\]

(107a)   (107b)   (99)

Considering the steric effect between COOMe and NHCSNH₂, and spectral data (IR and NMR), we could assume that the thiosemicarbazone of methyl pyruvate exist almost exclusively
as the pure anti isomer (107a). When the thiosemicarbazone (107a) was treated with excess sodium methoxide at room temperature overnight, the uv spectrum indicated that the reaction mixture consisted of the cyclized product (99) and the starting material. The reaction went to completion in 3 hours at reflux. The anti isomer (107a) must therefore be isomerized to the syn isomer (107b), which underwent cyclization to form (99).

![Chemical structures](image)

Treatment of the keto ester (79) with thiosemicarbazide at reflux overnight gave the corresponding thiosemicarbazone (108) in 86% yield. The nmr spectrum showed two singlets for the methyl ester group at 3.75 and 3.80 ppm, and two peaks for the NH proton at 12.1 and 9.2 ppm, which would be indicative of the presence of a mixture of geometrical isomers. Furthermore, its ir spectrum showed two carbonyl absorptions at 1730 and 1710 cm⁻¹. The geometrical isomers could not be separated on silica gel plates.
We decided to see whether both isomers would cyclize or not, which would tell us whether the anti isomer isomerized to the syn isomer.

The mixture of geometrical isomers was treated with sodium methoxide in boiling methanol for 3 hours. The nmr spectrum of the crude product clearly showed the disappearance of the methyl ester group and its uv spectrum showed absorption maximums at 258 nm in 0.1N NaOH and 269 nm in 0.1N HCl, which were in agreement with reported values. According to these results, we could conclude that both isomers of the thiosemicarbazone (108) underwent cyclization.

Treatment of (109) with 50% trifluoroacetic acid gave the final product, namely, a carbocyclic analogue of D,L-4-thio-6-azapseudouridine. The spectral data were consistent with structure of (95).
Chapter III

Synthesis of a carbocyclic analogue of D,L-2-deoxypyrazofurin A

Since we could successfully synthesize carbocyclic analogues of D,L-showdomycin and D,L-pyrazofurin A, our next aim was to synthesize 2-deoxy carbocyclic C-nucleosides, specifically the carbocyclic analogue of D,L-2-deoxypyrazofurin A (110).

Our first goal was to prepare a useful intermediate readily available in large amounts from which we could synthesize various 2-deoxy carbocyclic analogues of C-nucleosides.

Olefinic ester (111) was considered the key intermediate. Oxidative or reductive cleavage of the double bond would give a substituted cyclopentane (112,113) ready for transformation into carbocyclic analogues of C-nucleosides.

\[
\begin{align*}
(110) & \quad (111) & \quad (112) Y=CHO \\
(113) & \quad Y=COOH
\end{align*}
\]
Our first approach involved hydroboration of the double bond in olefin (67) to introduce the hydroxy group. It has been reported\textsuperscript{71} that hydroboration of norbornyl systems proceeds via predominant exo attack. We expected that hydroboration of olefin (67) would give two compounds (114,115) which could hopefully be separated.

\[ \text{Br} \quad \text{COOMe} \quad \rightarrow \quad \text{Br} \quad \text{COOMe} \quad + \quad \text{Br} \quad \text{COOMe} \]

(67) \quad (114) \quad (115)

Olefin (67) was treated with 1.1 hydride equiv. of diborane in tetrahydrofuran in an ice bath for 1 hour and then oxidized with alkaline hydrogen peroxide at 35-45\textdegree C.\textsuperscript{72} The \textit{nmr} spectrum of the crude product indicated that there were two singlets around 3.7 ppm, which could be assigned to the methyl group of methyl esters, and a small peak at 7.1 ppm corresponding to an olefinic proton. Two singlets of the methyl ester group could be explained by the presence of two compounds, probably isomers. The presence of an olefinic proton could be explained by partial elimination of hydrogen.
bromide due to the strong base used in forming the alcohol. All experimental results indicated that the crude product consisted of three compounds at least. We were unable to separate the compounds on silica gel plates due to partial elimination of hydrogen bromide during purification.

In order to avoid partial elimination of hydrogen bromide during oxidation with alkaline hydrogen peroxide, we repeated the alkaline oxidation of the intermediate borane at 0°C instead of 35-45°C. According to the nmr spectrum, there was no indication of the presence of elimination product. Two signals in the nmr spectrum, corresponding to two methyl esters, were still observed.

Distillation separated the crude products (first fraction: 49-52°C/0.7 mmHg and second fraction: 126-130°C/mmHg).

The nmr spectrum of the first fraction showed a singlet (3H, COOMe) at 3.63 ppm, two broad singlets (each 1H) at 2.4 and 2.0 ppm and a multiplet (7H) at 1.0-1.6 ppm. There was no deuterium oxide exchangeable proton and also no indication of the presence of H-3 proton which generally appeared above 4.0 ppm. Its ir spectrum showed no absorption peak above 3000 cm⁻¹ for the hydroxy group. Furthermore, its mass spectrum showed a molecular ion peak at m/e 152 and other major peaks at m/e 137, m/e 121 and m/e 97. There were no characteristic peaks due to the presence of isotopes of a bromine atom.
From all spectral data, we concluded that there was no hydroxy group and that a bromine atom had been lost. The following structure (117) is proposed on the basis of spectral data and of mechanistic considerations. We thought it was very likely that the intermediate (116) underwent intramolecular displacement to give (117) as depicted below.

\[
\begin{align*}
\text{(116)} & \quad \rightarrow \quad \text{(117)}
\end{align*}
\]

The same type of elimination reaction has been reported as shown below.\(^3\)

The nmr spectrum of the second fraction obtained in the hydroboration reaction showed a multiplet (1H) at 4.2 ppm, a singlet at 3.73 ppm, and a broad singlet (1H, OH) at 2.4 ppm. Its ir spectrum showed absorptions at 1740 cm\(^{-1}\) for the methyl ester group and at 3200-3600 cm\(^{-1}\) for the hydroxy group.
Furthermore, its mass spectrum showed molecular ion peaks at m/e 248 and m/e 250 and a base peak at m/e 169 (M+ - Br). From the spectral data, we could however not differentiate between the two structures, although (114) seemed more likely in view of the formation of the tricyclic compound (117), which was presumably formed in case of (115).

In order to prove the structure of (114), we examined the nmr spectrum using (119) by spin-decoupling to decide the position of the hydroxy group. We thought irradiation of H-4 proton would cause a collapse of endo H-5 proton in case of (115). Otherwise, this would have provided evidence for (114).

Treatment of the alcohol (114) with acetic anhydride and a catalytic amount of pyridine gave the acetate (118), which was contaminated with (119) to the extent of 10% due to partial elimination of hydrogen bromide by pyridine. This difficulty could be solved by using a catalytic amount of p-toluenesulfonic acid instead of pyridine.
Treatment of (118) with DBU in ethyl ether in an ice bath gave an oily olefinic acetate (119) in essentially quantitative yield. Its ir spectrum showed absorptions at 1740 cm\(^{-1}\) for the carbonyl groups and at 1620 cm\(^{-1}\) for the double bond. Its nmr spectrum showed a doublet (1H, J=4 Hz) at 7.12 ppm, a multiplet (1H) at 4.7 ppm, a singlet (3H, COOMe) at 3.74 ppm and two broad singlets at 3.26 and 3.00 ppm.

![Chemical Structure](image)

(119)

Decoupling the broad singlet at 3.00 ppm caused only the doublet at 7.12 ppm to collapse to a singlet. Therefore, the two broad singlets at 3.26 and 3.00 ppm were assigned to H-1 and H-4 respectively. Decoupling the broad singlet at 3.26 ppm and the multiplet at 4.7 ppm did not show any significant changes of proton signals in the nmr spectrum. These results could be explained considering the conformation of norbornene systems.

The exo-bridgehead dihedral angle is around 40°, whereas the endo-bridgehead dihedral angle is around 80°\(^\text{o}^\text{a}\). Therefore, we can expect the significant difference between coupling constant of endo (J=0 Hz) and of exo protons (J=3.0\(\pm\)5.0 Hz) with the adjacent bridgehead hydrogen.
We concluded that spin-decoupling could not give any information on the position of the hydroxy group, while we confirmed that hydroboration of olefin (67) had proceeded via an exo attack.

\[
\text{(114)} \quad \rightarrow \quad \text{(120)} \quad \rightarrow \quad \text{(121)}
\]

Treatment of the alcohol (114) with 1 equiv. of p-nitrobenzoyl chloride and 1.3 equiv. of pyridine gave a crystalline p-nitrobenzoate (120) in 70% yield. Elimination of hydrogen bromide by treatment with DBU gave the crystalline desired product (121) in 94% yield.

Since the structure of (114) could not be established by spin decoupling experiments, we thought we could establish it by lactonization of mesylate (122).

\[
\text{(114)} \quad \rightarrow \quad \text{(122)} \quad \rightarrow \quad \text{(123)}
\]
Treatment of alcohol (114) with mesyl chloride and triethylamine in methylene chloride gave the mesylate (122) in quantitative yield. The mesylate was then gently heated in formic acid for 2 hours. The nmr spectrum of the crude product clearly showed the disappearance of the methyl ester group and of the mesylate group. Its ir spectrum showed a carbonyl absorption at 1790 cm\(^{-1}\) for the lactone. Furthermore, this compound (123) was characterized by a mass spectrum and microanalysis.

This data conclusively established the structure of a major product as (114), and strengthened the structure assignment for the tricyclic compound (117).

The olefinic acetate (119) could be an important intermediate in the synthesis of various 3-deoxy carbocyclic analogues of C-nucleosides should the need ever arise. However, this approach was abandoned because our original plan was to synthesize 2-deoxy carbocyclic analogues of C-nucleosides.

![Chemical Structures](124) \rightarrow \rightarrow \text{(125)}

We next considered the possibility of removing the hydroxy group at C-6 either by displacing the corresponding mesylate by hydride, or by reduction of the corresponding ketone.
Ouellet\textsuperscript{61} described the synthesis of alcohol (124) from which the desired mesylate or the ketone should be readily obtainable.

\[ \text{COOH} \quad \rightarrow \quad \text{RO} \quad \rightarrow \quad \text{+CO} \]

(66) \quad (126) \quad R=H \quad (128)

(127) \quad R=CHO

\[ \text{+CO} \quad \rightarrow \quad \text{+CO} \]

(130) \quad (129) \quad (124)

The olefin (66) was treated with 30\% hydrogen peroxide in formic acid to give the hydroxy lactone (126) and its formate (127) as a byproduct. (127) probably arose from opening of the epoxide with formic acid or subsequent formylation of the alcohol.

Treatment of the lactone (126) with pivaloyl chloride and pyridine gave a crystalline pivalate (128) in essentially quantitative yield.

The next step involved the opening of lactone ring to give olefinic alcohol (124). Treatment of (128) with 1 equiv. of sodium methoxide in methanol gave (124) in 80\% yield. This resulted in the elimination of hydrogen bromide.
as well as opening of lactone ring. (124) was also obtained by treatment of (128) with DBU or triethylamine in methanol. The latter required boiling for 24 hours, whereas the former was carried out at room temperature for 1 hour.

Oxidation of (124) with Jones reagent gave the corresponding ketone (129) in essentially quantitative yield. Its nmr spectrum was consistent with the structure of (129). Furthermore, its ir spectrum showed two different carbonyl absorptions at 1780 cm$^{-1}$ for the ketone group and at 1740 cm$^{-1}$ for the methyl ester group.

The ketone (129) was treated with zinc and hydrogen chloride gas in anhydrous ethyl ether, a modified Clemensen reduction method, in an ice bath. The nmr spectrum of the crude product showed the disappearance of the olefinic proton. Similarly, treatment of (129) with zinc and hydrogen chloride gas in acetic anhydride caused the reaction mixture to turn dark brown. There was no indication of the presence of an olefinic proton.

An attempt using tosylhydrazine and sodium cyanoborohydride was also unsuccessful.

Since we were unable to convert (129) into (125), we considered the possibility of displacement of mesylate (130) by a powerful nucleophile. It has been reported that superhydride (lithium triethylborohydride) is one of the most powerful nucleophiles available for displacement of halides.
Mesylate (130) was prepared from (124) with mesyl chloride and triethylamine and it was then treated with 1 hydride equiv. of superhydride in tetrahydrofuran at room temperature for 12 hours.

\[
\begin{align*}
\text{Mesylate (130)} & \quad \rightarrow \\
\text{(130)} & \quad \rightarrow \\
\text{(131)} & 
\end{align*}
\]

The nmr spectrum of the crude product showed a multiplet (2H) at 4.6-5.0 ppm, a singlet (3H,COOMe) at 3.80 ppm, a singlet (3H,SO₂CH₃) at 3.1 ppm, and a broad peak (1H) at 3.0-3.2 ppm. Its ir spectrum indicated that an absorption at 1620 cm⁻¹ for the double bond disappeared and its mass spectrum showed a molecular ion peak at m/e 348. From these spectral data, we assigned to this compound the corresponding norbornane structure (131). Unfortunately, we were unable to confirm the configuration of the carbomethoxy group in (131) from its nmr spectrum because of overlapping of H-2 proton with the mesyl group and a complex spectrum at 1.6-2.6 ppm.

Since our attempts were unsuccessful, we considered the possibility of avoiding intramolecular displacement of
the exo bromine atom in (117) by the simple device of synthesizing the known endo bromo compound and repeating the hydroboration reaction with it.

\[
\begin{align*}
\text{(64)} & \quad \text{+} & \quad \text{(132)} & \quad \rightarrow & \quad \text{(133) } R=H \\
& & & & \quad \text{(134) } R=\text{CH}_3
\end{align*}
\]

The cis-\(\beta\)-bromoacrylic acid (132) was prepared with propiolic acid and hydrobromic acid at 80°C. The trans isomer was a major product at higher temperature (100°C). The trans isomer crystallized out from the reaction mixture, whereas the cis isomer was soluble in water.

Condensation of cis-\(\beta\)-bromoacryic acid with cyclopentadiene in benzene gave the Diels-Alder adduct (133) in 65% yield. The compound was almost exclusively the endo carboxylate isomer\(^{14-15}\). The acid (133) was esterified with a catalytic amount of p-toluenesulfonylic acid and methanol in quantitative yield.

The methyl ester (134) was treated with 1.1 hydride equiv. of diborane in tetrahydrofuran in an ice bath and was oxidized with alkaline hydrogen peroxide in an ice bath for 30 minutes.
As we anticipated, there was no indication of the presence of the tricyclic compound (117). Distillation at 125-127°C/0.6 mmHg gave alcohol (135,136) in 85% yield. Spectral data were consistent with the structure of either of the two alcohols.

Although this compound was well characterized by spectral data, it was not clear whether (135), (136) or a mixture of these two compounds was present. Therefore, we decided to prepare the olefinic acetate by acetylation of the alcohol, followed by elimination of hydrogen bromide, and to compare the olefinic acetate with (119) whose structure was established previously.

Alcohol was protected as an acetate with acetic anhydride and pyridine in essentially quantitative yield: The nmr spectrum showed a singlet at 3.7 ppm for the methyl ester group and a singlet at 2.0 ppm for the acetate group.

The product seemed to be a pure compound according to nmr, t.l.c. and v.p.c. When the alcohol was treated with
acetic anhydride in pyridine, there was no indication of the presence of olefinic acetate due to the elimination of hydrogen bromide.

![Chemical structure diagram]

When the bromo acetate (137, 138) was treated with DBU in ethyl ether in an ice bath, and even at room temperature, the starting material was recovered unchanged.

Treatment of bromo acetate (137, 138) with DBU in methylene chloride at reflux for 2 hours gave the olefinic acetate (139, 119) in 85% yield. Its nmr spectrum showed two doublets at 7.1 and 6.8 ppm in a ratio of 1:2, whereas the nmr spectrum of (119) showed a doublet at 7.1 ppm.

Therefore, we concluded that hydroboration of (134) gave a mixture of (135) and (136). The desired product (135) was present to the extent of 65% according to the nmr spectrum.

Our next problem was to separate these isomers. It was impossible to separate these isomers on silica gel plates or on a silica gel column. Distillation was equally inappropriate for the separation of the two isomers.
The first approach was based on treatment of the mixture of acetates (137,138) with formic acid, which should perhaps lead to lactonization of isomer (138), but not of isomer (137), thus perhaps permitting a separation.

\[
\begin{align*}
\text{AcO} & \quad \text{Br} \\
\text{COOMe} & \\
\text{Br} & \quad \text{AcO} \\
\text{COOMe} & \\
\end{align*}
\]

(137)  \quad (138)

The mixture of acetates was treated with formic acid at 100°C for 2 hours. Its nmr spectrum indicated that a broad doublet at 5.7 ppm, which is apparently a proton adjacent to the acetate group in (138), had considerably decreased, whereas a doublet at 5.3 ppm did not change. However, (138) was still present to the extent of 20% according to the nmr spectrum. Its ir spectrum had carbonyl absorptions at 1790 and 1750 cm\(^{-1}\). After 4 hours, there was no more (138). But there was a considerable amount of hydrolysis of the acetate group giving the corresponding formate (140).

Separation on silica gel plates using chloroform as an eluant gave the desired acetate (137) in 40% yield.

Treatment of (137) with DBU in methylene chloride for 2 hours at reflux gave the olefinic acetate (139) in
essentially quantitative yield. Its nmr spectrum showed a doublet at 6.8 ppm, whereas the nmr spectrum of (119) showed a doublet at 7.1 ppm. Although we could separate our desired product, we felt this was not suitable to prepare a large amount of starting material on silica gel plates, and the reaction was not clean.

Our second approach involved separation of the p-nitrobenzoates of alcohols (135,136).

Treatment of alcohol with p-nitrobenzoyl chloride and pyridine gave a crystalline compound in quantitative yield. Extensive efforts were made to separate these isomers using fractional crystallization with various solvents. Fortunately, (142) crystallized from carbon tetrachloride and petroleum ether (b.p. 60-80°C) (7:3) in 45% yield, whereas (143) crystallized from chloroform and petroleum ether (1:1) in 25% yield.

\[
\begin{align*}
R^3 & = \text{COC}_{6}^6\text{H}_{4}\text{NO}_{2}^{2}-p \\
(142) & \\
(143) & 
\end{align*}
\]
The nmr spectra of substituted norbornanes and substituted norbornenes are of special interest for structural and stereochemical assignments, and so the characteristic features will be briefly described here.

The nmr spectrum of (142) had a broad doublet at 5.67 ppm and a doublet of doublets at 4.67 ppm. It appeared reasonable to us to assign these two peaks to the endo H-5 and the exo H-3 respectively. The exo H-3 proton is expected to exhibit vicinal couplings with the exo H-2 and the bridgehead H-4 proton. Furthermore, H-1 and the exo H-3 conforms to a W arrangement and therefore is expected to exhibit long range coupling. From the nmr spectrum, we observed J=12, 4 Hz.

On the basis of literature reports, $J_{\text{2exo-3exo}}$ should be 12 Hz and $J_{\text{3exo-4}}$ should be 4 Hz. On the other hand, it seemed that the long range coupling constant ($J_{\text{3exo-1}}$) was too small to be detected. Similarly, the endo H-5 is expected to exhibit vicinal couplings ($J_{\text{5endo-6endo}}$, $J_{\text{5endo-6exo}}$, $J_{\text{5endo-4}}$) and a long range coupling ($J_{\text{7b-5endo}}$).

Since it is known that $J_{\text{5endo-6endo}}$ is the largest, it appeared reasonable to us to assign 5 Hz to $J_{\text{5endo-6endo}}$. Furthermore, according to our knowledge, it seemed that couplings of the proton pairs endo H$_5$-exo H$_6$, H$_4$-endo H$_5$, and H$_7$-endo H$_5$ cause broadening of peaks. We could not identify these coupling constants in its nmr spectrum.
The endo H-3 proton in (120) was observed at 4.3 ppm, whereas the exo H-3 proton in (143) was observed at 4.7 ppm. This result confirms a down field shift of exo protons signals relative to endo protons in substituted norbornanes.

Furthermore, a doublet of doublets at 3.40 ppm (J=12, 4 Hz) was observed in (143), whereas there was no separation due to overlapping of H-4, H-1 and exo H-2 proton in (142). The bridgehead H-1 and H-4 proton are expected to exhibit vicinal couplings and long range couplings. However, J=12 Hz appeared too large for vicinal couplings with the bridgehead protons and long range couplings. Therefore, a doublet of doublets at 3.40 ppm was assigned to the endo H-2 proton with vicinal coupling constants $J_{2\text{exo}-3\text{exo}} = 12$ Hz and $J_{2\text{exo}-1} = 4$ Hz. We could not detect long range coupling constants ($J_{2\text{exo}-6\text{exo}}$, $J_{2\text{exo}-4}$) from its nmr spectrum.

Treatment of (142) with DBU in methylene chloride for 2 hours at reflux gave olefinic p-nitrobenzoate (144) in quantitative yield. Its nmr spectrum had a singlet (4H, aromatic)
at 8.25 ppm, a doublet (1H, J = 4 Hz, C=CH) at 7.00 ppm, a multiplet (1H, H-5) at 5.10 ppm, a singlet (3H, COOMe) at 3.80 ppm, a broad peak (2H, H-1 and H-4) at 3.3 ppm and a broad singlet (4H, H-6 and H-7) at 1.9 ppm.

(121) was prepared in the same way from (143).

Its nmr spectrum was identical with that of (121), which was prepared from (120).
III-2 Synthesis of a carbocyclic analogue of D,L-2-deoxy-pyrazofurin A

We already established the structure of (144), where the p-nitrobenzoate group was at 5 position with exo configuration.

Since we successfully synthesized a carbocyclic analogue of pyrazofurin A, we decided to follow a similar scheme to synthesize its 2-deoxy analogue.

Ozonolysis of (144) in methylene chloride at -78°C, followed by a mild reduction with dimethyl sulfide afforded the crude aldehyde keto ester (145). Its nmr spectrum indicated the presence of a mixture of the open form (145a) and the closed hydrated form (145b) in a ratio of 1:3.

Since we knew there was almost no selectivity in the reduction of the aldehyde and the ketone group from our previous experience with (60), the crude product was treated with 2 hydride equiv. of diborane in tetrahydrofuran.
Diol (146) was obtained in 40% yield after purification on silica gel plates. We thought that the poor yield presumably resulted from the water of the closed hydrated form (145b). When we used 4 hydride equiv. of diborane, there was an indication of the presence of triol (147) according to integration of the methyl ester group in the nmr spectrum of the crude product.

Because of these difficulties, we decided to remove water as an azeotropic mixture from the closed hydrated form in refluxing benzene. After the crude product was azeotroped in benzene for 2 hours, its nmr spectrum showed an increase in the size of the aldehyde proton, which indicated the presence of the open form to the extent of 70%.

Treatment of this product with 2 hydride equiv. of diborane gave diol (146) in 60% yield after purification. However, we were unable to remove completely water because longer reflux time led to decomposition of the aldehyde keto
ester. The open aldehyde keto ester (145a) seemed to be very sensitive to water and easily converted to its hydrated form.

Treatment of the crude product with lithium tri-t-butoxyaluminum hydride did not give satisfactory results.

Therefore, we decided to cleave the double bond with potassium permanganate and sodium periodate.

Treatment of (144) with potassium permanganate and sodium periodate gave the corresponding keto ester acid (148) in 90% yield. The nmr spectrum of the crude product showed a singlet for the methyl ester at 3.90 ppm, a singlet for the p-nitrobenzoate group at 8.2 ppm and a broad singlet for the carboxylic acid at 10.8 ppm, which indicated the presence of the open form. We were unable to purify this compound due to its instability to silica gel.

Since we obtained the keto ester acid (148) as the open form, we considered the possibility of selective reduction of the carboxylate group in the presence of the keto ester group.
It has been reported that carboxylic acids are reduced selectively to the corresponding alcohols in the presence of ester and keto functional groups by diborane in tetrahydrofuran.

The keto ester acid (148) was treated with 3 hydride equiv. of diborane in tetrahydrofuran in an ice bath. The nmr spectrum of the crude product showed a broad doublet at 4.2 ppm, which should result from the proton adjacent to the secondary hydroxy group due to the formation of diol. Therefore, we realized there was no selectivity between the carboxylate group and the keto group. Purification of the crude product on silica gel plates gave diol (146) in 60% yield. The less polar byproduct was obtained in 20% yield, but we were unable to assign its structure from the nmr spectrum. It is not clear if this byproduct is the result of decomposition of the unstable keto ester (149) on silica gel plates. Treatment of (148) with 4 hydride equiv. of diborane gave diol in 80% yield after purification.
This diol was furthermore characterized as its diacetate (150). Its nmr spectrum showed a singlet for the methyl ester group at 3.80 ppm and two singlets for the diacetate group at 2.20 and 2.07 ppm.

It should be pointed out that we do not know whether the diol (146), the diacetate (150) and following silyl protected alcohol (151) would be a pure isomer or a mixture of isomers. It seemed to be one isomer according to its nmr spectrum and t.l.c.

Since our original plan was to oxidize the hydroxy methyl ester after protection of the diol to the corresponding keto ester, we decided to abandon further studies for the assignment of configuration.

We already knew the t-butyldimethylchlorosilane had shown selectivity in the protection of diol (71) and that it had some advantages over the pivaloyl group. Therefore, we chose t-butyldimethylchlorosilane to protect the primary hydroxy group in diol (146).

(151) R=COC₆H₄NO₂·p
Treatment of diol (146) with 1 equiv. of t-butyldimethylchlorosilane and 2.5 equiv. of imidazole in dimethylformamide at room temperature for 24 hours gave an oily monosilyl derivative (151) in 83% yield. Its nmr spectrum showed a multiplet (1H) at 4.1 ppm and a broad peak for the hydroxy group at 3.1 ppm, which should disappear after oxidation.

The hydroxy ester (151) was oxidized with ruthenium dioxide and sodium periodate to afford the keto ester (152) in essentially quantitative yield. Its nmr spectrum showed the disappearance of a multiplet at 4.1 ppm and of a broad peak at 3.1 ppm.

Treatment of the keto ester (152) with ethyl hydrazinoacetate hydrochloride and sodium acetate gave the hydrazone (153) in 88% yield. According to the nmr spectrum, the NH proton appeared at 10.2 and 6.4 ppm in a ratio of 2:1, which was an indication of the presence of geometrical isomers. Our previous work with the hydrazone (91) and the semicarbazone (101) indicated that the syn isomer existed to the extent of 75%.
Since we knew from previous work that both isomers cyclized to form the pyrazole ring, the mixture of geometrical isomers was treated with sodium methoxide at reflux for 2 hours. The desired pyrazole (154) was obtained in 20% yield. Its nmr spectrum showed the disappearance of the p-nitrobenzoate group and its uv spectrum was in agreement with reported values^{21}.

\[
\text{CONH}_2
\]

(155) \[\rightarrow\] (110)

Treatment of (154) with ammonia in methanol at room temperature for a week gave the amide (155) in 80% yield. Spectral data were consistent with the structure of (155).

Hydrolysis of the t-butyldimethylsilyl protecting group with 50% aqueous trifluoroacetic acid afforded the 2-deoxy carbocyclic analogue of pyrazofurin A (110). Its mass spectrum showed a molecular ion peak at m/e 241, major peaks at m/e 224 (M\(^+\)-NH\(_3\)), m/e 223 (M\(^+\)-H\(_2\)O), and m/e 206 (M\(^+\)-H\(_2\)O-NH\(_3\)), and a base peak at m/e 153 (B+27).
Contributions to knowledge

The synthesis of carbocyclic analogues of D,L-showdomycin, D,L-pyrazofurin A, D,L-6-azapseudouridine, and D,L-4-thio-6-azapseudouridine was accomplished. Important intermediates for the synthesis of carbocyclic analogues of C-nucleosides were prepared. The use of t-butyldimethylchlorosilane and pivaloyl chloride as selective protecting groups for the primary hydroxy group in the presence of the secondary hydroxy group was demonstrated.

The geometrical isomers of hydrazones and semicarbazones were separated and characterized by spectral data. The anti isomers of hydrazones and semicarbazones could be converted to the corresponding syn isomers by photolysis.

The important intermediate (144) was prepared, from which a carbocyclic analogue of D,L-2-deoxypyrazofurin A was synthesized.

In addition, many new compounds were prepared and characterized.
Experimental

Melting points were determined on a Gallenkamp block and are uncorrected.

Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 eV using a direct insertion probe. Nmr spectra were recorded on Varian T-60 and HA-100 spectrophotometers using tetramethysilane as an internal standard. Doublets, triplets, and quartets in the nmr spectral data were recorded as the centre of the peaks. Ir spectra were obtained on a Unicam SP-1000 and a Perkin-Elmer PE-257 infrared spectrophotometer. Uv spectra were recorded using a Unicam SP-800 spectrophotometer.

The photolysis were carried out in quartz tubes using a Rayonet photochemical reactor equipped with lamps with maximum output at 2537 A.

Analytical thin layer chromatography was performed on silica gel coated plastic plates (Eastman Kodak) and on a preparative scale on silica gel (Merck UV254, 366) coated glass plates. Woelm alumina (neutral) and silica gel were used for column chromatography. Separation of a geometrical isomers was carried out with a preparative silica gel/column using an Altek Model 300 liquid chromatography.

Microanalysis were carried out by C. Daessle, Montreal and Heterocyclic Chemical Corporation, Missouri.
Chapter I

3-Exo-bromobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (66)

Freshly distilled cyclopentadiene (37 ml) was added to trans-β-bromoacrylic acid (5.0 g) dissolved in 37 ml of benzene. The solution was refluxed for 1.5 hours and then stripped of solvent and excess cyclopentadiene. Petroleum ether (60-80°C) (20 ml) was added to the residue to help crystallization and evaporated under reduced pressure. After 50 ml of petroleum ether was added to the residue, the reaction mixture was kept in a refrigerator overnight, filtered and washed with petroleum ether.

Yield: 4.80 g (67%), m.p. 133-134°C (lit. 134°C)

Nmr (CDCl₃): δ 1.97 (q, J=10 Hz, 2H), 3.2-3.4 (m, 3H), 4.14 (m, 1H, CHBr), 6.4 (b.s, 2H, CH=CH), 10.8 (b.s, 1H, COOH).

Ir (KBr): 3450 (OH), 1720 (C=O) cm⁻¹.

3-Exo-bromo-2-endo-carbomethoxybicyclo[2.2.1]hept-5-ene (67)

Acid (66) (5.0 g) and p-toluenesulfonic acid (50 mg) were dissolved in 50 ml of methanol. The solution was refluxed for 12 hours and evaporation to near dryness under reduced pressure was followed by the addition of 30 ml of methylene chloride. The solution was washed with 0.5M sodium bicarbonate,
dried over sodium sulfate and then evaporated to dryness in vacuo. Distillation at 90-92°C/1.2 mmHg gave 5.0 g (94%) of the corresponding methyl ester.

Nmr (CDCl₃): δ 1.93 (q, J=10 Hz, 2H), 3.1-3.4 (m, 3H), 3.73 (s, 3H, COOMe), 4.13 (m, 1H, CHBr), 6.3 (b.s, 2H, CH=CH).

Ir (film): 1745 (C=O) cm⁻¹.

3-Exo-bromo-2-endo-carbomethoxy-5,6-exo-dihydroxycyclo[2.2.1]heptane (68)

Ester (67) (5.20 g) and osmium tetroxide (15 mg in 3 ml of t-butanol) were dissolved in 100 ml of ethyl ether. Hydrogen peroxide (30%, 2.7 ml) was added in five lots over five hours and the reaction mixture was then stirred at room temperature for additional 12 hours. Evaporation under reduced pressure followed by the addition of ether gave, on cooling, a white crystalline product.

Yield: 2.98 g (50%), m.p. 144-145°C.

Ir (KBr): 3430/3290 (OH), 1735 (C=O) cm⁻¹.
3-Exo-bromo-2-endo-carbomethoxy-5,6-exo-(dihydroxy-di-O-isopropylidene)-bicyclo[2.2.1]heptane (69)

The diol (68) (5.0 g) was added to 80 ml of reagent acetone containing 10 ml of 2,2-dimethoxypropane. p-Toluene-sulfonic acid (20 mg) was added and the solution was stirred at room temperature for 1 hour. Evaporation to near dryness was followed by addition of 40 ml of methylene chloride. The organic solution was washed twice with 0.5M sodium bicarbonate and once with saturated salt solution. The methylene chloride solution was dried over sodium sulfate and evaporated to dryness in vacuo to give the isopropylidene derivative (69) as an oil in essentially quantitative yield.

Nmr (CDCl₃): δ 1.23 (s,3H), 1.41 (s,3H), 1.8-1.9 (m,2H), 2.6 (m,2H), 3.2 (m,1H), 3.75 (s,3H), 4.0-4.2 (m,3H)

Ir (film): 1740 (C=O), 1390/1380 cm⁻¹ (acetoneide).

2-Carbomethoxy-5,6-exo-(dihydroxy-di-O-isopropylidene)-bicyclo[2.2.1]hept-2-ene (70)

The crude product (5.0 g) obtained from above reaction was dissolved in anhydrous ether (100 ml) and 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU) (5 ml), was added dropwise with cooling in an ice bath and vigorous stirring of the ether solution.
After all the DBU had been added, the solution was stirred for 30 minutes, the white precipitate was filtered off and the filtrate washed several times with 0.5M hydrochloric acid and once with saturated salt solution. Drying over sodium sulfate and evaporation gave a pale yellow oil which crystallized on standing.

Yield: 3.12 g (85%), m.p. 60-62°C.

Nmr (CDCl$_3$): 6 1.35 (s, 3H), 1.53 (s, 3H), 1.95 (q, J=9 Hz, 2H), 3.0 (m, 1H), 3.7 (b, s, 1H), 3.75 (s, 3H), 4.3 (b, s, 2H), 6.97 (d, J=4 Hz, 1H).

Ir (KBr): 1720 (C=O), 1600 (C=C), 1390 cm$^{-1}$.

Methyl-2-(2a,3a-dihydroxy-di-O-isopropylidene-48-aldehyde-cyclopent-18-yl)-glyoxylate (60)

The olefinic ester (70) (2.0 g) was dissolved in 50 ml of dry methylene chloride, cooled to -78°C in a dry ice-acetone bath, and treated with ozone at the rate of 7 m moles of ozone per hour. The reaction was continued until the blue color persisted. The temperature of the solution was allowed to rise to room temperature and excess of ozone was removed by passing nitrogen. The solution was cooled to -78°C in a dry ice-acetone bath and dimethyl sulfide (3ml) was added. The solution was stirred and allowed to come slowly to room
Stirring was continued for a total of 4 hours. The methylene chloride solution was washed three times with saturated salt solution. Drying over sodium sulfate and evaporation gave the oily aldehyde keto ester (60) in essentially quantitative yield.

Nmr (CDCl₃): δ 1.3-1.5 (m, 6H), 1.8-3.2 (m, 4H), 3.7-4.0 (m, 4H), 4.4-5.3 (m, 4H), 9.7 (s, 1H, CHO).

Ir (CHCl₃): 3300-3500 (OH), 1740 cm⁻¹ (C=O).

Methyl-2-(2α,3β-dihydroxy-di-α-isopropylidene-4β-hydroxy-methylcyclopent-1β-yl)-glycolate (71)

The aldehyde keto ester (60) (1.20 g) was dissolved in 100 ml of freshly distilled tetrahydrofuran. With cooling in an ice bath and stirring, lithium tri-t-butoxyaluminum hydride (4.80 g, 4.0 hydride equiv.) was added. The solution was stirred in an ice bath for 2 hours and at room temperature for 10 hours under a nitrogen atmosphere. A solution of 5.0 g of ammonium sulfate in 10 ml of water was added, with stirring in an ice bath, over a 20 minute period. The reaction mixture was stirred for another 30 minutes and it was filtered through celite. The filtrate was evaporated to near dryness under reduced pressure and ethyl acetate was then added to the residue. The solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to give diol (71) as a pale yellow oil. The crude product was purified
by chromatography on silica gel plates using ethyl ether as an eluant.

Yield : 850 mg (70%).

\[
\text{Nmr (CDCl}_3\text{)}: \delta 1.30 (s, 3H), 1.50 (s, 3H), 1.6-2.7 (m, 4H), 3.2 (b.s, 2H, OH), 3.67 (d, J=6 Hz, 2H, CH}_2\text{OH), 3.80 (s, 3H, COOMe)}, 4.0-4.8 (m, 3H).
\]

\[
\text{Ir (film): 3200-3600 (OH), 1745 (C=O), 1390, 1380 cm}^{-1}.
\]

\[
\text{Mass (120°): m/e. 245 (M}^+\text{-CH}_3), 229 (M}^+\text{-OCH}_3), 213 (M}^+\text{-CH}_3\text{-CH}_3\text{OH), 185, 167.}
\]

Analysis: Calculated for C\text{12}_2H\text{20}O\text{6}: C, 55.37; H, 7.75.

Found: C, 55.48; H, 7.43.

**Methyl-2-(2a, 3a-dihydroxy-di-o-isopropylidene-46-pivaloyloxy-methylcyclopent-18-yl)-glycolate (76)**

The diol (71) (300 mg) was dissolved in 10 ml of methylene chloride and 0.5 ml of pyridine. A solution of pivaloyl chloride (110 mg, 1 equiv.) in 15 ml of methylene chloride was slowly added to the reaction mixture in an ice bath. The solution was stirred for 2 hours in an ice bath, overnight at room temperature and then evaporated to dryness under reduced pressure. The residue was taken up in 30 ml of chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was purified by chromatography on silica
gel plates using ethyl ether as an eluant.

Yield: 310 mg (80%).

Nmr (CDCl₃): δ 1.23 (s, 9H, COC(CH₃)₃), 1.30 (s, 3H), 1.45 (s, 3H), 1.6-2.6 (m, 4H), 2.8-3.0 (b, 1H, OH), 3.80 (s, 3H, COOMe), 4.10 (d, J=6 Hz, CH₂-O), 4.2-4.6 (m, 3H).

Ir (film): 3520 (OH), 1745 (C=O), 1395, 1385 cm⁻¹.

Mass (150°): m/e 344 (M⁺), 329 (M⁺-CH₃), 313 (M⁺-OCH₃), 259 (M⁺-CO(CCH₃)₃), 229, 197.

Analysis: Calculated for C₁₇H₂₈O₇: C, 59.28; H, 8.19.

Found: C, 59.07; H, 8.35.

Methyl-2-(2α,3α-dihydroxy-di-0-isopropylidene-4β-t-butyldimethylsiloxymethylcyclopent-1β-yl)-glycolate (77)

The diol (71) (1.020 g), t-butyldimethylchlorosilane (600 mg, 1 equiv.) and imidazole (635 mg, 1 equiv.) were dissolved in 5 ml of dimethylformamide. The solution was stirred at room temperature for 24 hours and evaporated under reduced pressure to remove most of solvent. The residue was taken up in 20 ml of methylene chloride. The solution was washed with water, dried over sodium sulfate and then evaporated to dryness in vacuo. The residue was a pale yellow oil and purification on silica gel plates using ethyl ether as an eluant gave a colorless oil.

Yield: 1.152 g (80%).
Nmr. (CDCl₃): 6 0.05 (s, 6H, Si(CH₃)₂), 0.90 (s, 9H, Si(CH₃)₃),
1.30 (s, 3H), 1.50 (s, 3H), 1.6-2.7 (m, 4H),
3.1 (b.s, 1H, OH), 3.73 (d, J=5 Hz, 2H, SiO-CH₂),
3.82 (s, 3H, COOMe), 4.1-4.8 (m, 3H).

Ir (film): 3350-3600 (OH), 1740 (C=O), 1395, 1385 cm⁻¹.

Analysis: Calculated for C₁₈H₃₄O₆Si: C, 57.75; H, 9.09.
Found: C, 57.33; H, 9.31.

Preparation of the acetate (78) from (77)

The compound (77) (110 mg) was dissolved in 1 ml of
pyridine and 1 ml of acetic anhydride. The solution was stirred
at room temperature overnight and evaporated to near dryness
under reduced pressure. The crude product was purified
by chromatography on a silica gel plate using chloroform as
an eluant to give an oily acetate in quantitative yield.

Nmr (CDCl₃): 6 0.05 (s, 6H), 0.90 (s, 9H), 1.30 (s, 3H), 1.50
(s, 3H), 1.6-2.7 (m, 4H), 2.17 (s, 3H, OCOCH₃),
3.70 (d, J=5 Hz, 2H, SiO-CH₂), 3.80 (s, 3H), 4.4
(m, 2H), 5.1 (m, 1H, CO-CH=OCOCH₃).

Ir (CHCl₃): 1760/1750 (C=O), 1395, 1385 cm⁻¹.

Mass (150°C): m/e 416 (M⁺), 401 (M⁺-CH₃), 359 (M⁺-C(CH₃)₃), 301.

Analysis: Calculated for C₂₀H₃₆O₇Si: C, 57.69; H, 8.65.
Found: C, 57.37; H, 8.67.
Methyl-2-(2α,3α, dihydroxy-di-8-isopropylidene-4β-t-butyl-dimethylsiloxymethylcyclopent-1β-yl)-glyoxylate (79)

To a mixture of sodium periodate (480 mg), sodium bicarbonate (30 mg) and ruthenium dioxide (20 mg) in 20 ml of water was added a solution of the silyl protected alcohol (77) (425 mg) in 20 ml of carbon tetrachloride. The reaction mixture was vigorously stirred at room temperature for about 4 hours. The end of the reaction was indicated by a change of color from black to yellow or blackish yellow. The carbon tetrachloride layer was separated and the aqueous layer was extracted twice with carbon tetrachloride. A few drops of isopropyl alcohol were added to the combined carbon tetrachloride extracts with vigorous stirring and the ruthenium dioxide formed was removed by filtration. The carbon tetrachloride solution was washed with water, dried over sodium sulfate and then evaporated to dryness in vacuo. The crude product was a colorless oil.

Yield: 390 mg (92%).

Nmr (CDCl₃): δ 0.05 (s, 6H), 0.87 (s, 9H), 1.30 (s, 3H), 1.47 (s, 3H), 1.5-2.8 (m, 4H), 3.50 (q, J=5 Hz, 2H, SiOCH₂), 3.83 (s, 3H, COOMe), 4.40 (d, d, J=6, 4 Hz, 1H), 4.8 (m, 1H).

Ir (film): 1770/1750 (C=O), 1490, 1480, 1395, 1385 cm⁻¹.

Mass (200°): m/e 372 (M⁺), 357 (M⁺-CH₃), 315 (M⁺-C(CH₃)₃), 313 (M⁺-COOMe), 257 (M⁺-t-butyldimethylsilyl).
Analysis: Calculated for C_{18}H_{32}O_{6}Si: C, 58.06; H, 8.60.
Found: C, 57.78; H, 8.86.

Methyl-2-(2a,3a-dihydroxy-di-0-isopropylidene-4β-pivaloyloxy-
methylcyclopent-18-yl)-glyoxylate (80)

This keto ester (80) was prepared in the same way as (79).

Nmr (CDCl₃): 8 1.23 (s,9H,COC(CH₃)₃), 1.32 (s,3H), 1.50 (s,3H),
1.6-2.7 (m,4H), 3.88 (s,3H,COOMe), 4.03 (q,J=4 Hz,
2H,CH₂-OCO), 4.43 (d,d,J=6.4 Hz,1H), 4.83 (m,1H).
Ir (CHCl₃): 1750/1740 (C=O), 1495, 1470, 1395, 1385 cm⁻¹.

Methyl-2-(2a,3a-dihydroxy-di-0-isopropylidene-4β-carboxy-
cyclopent-18-yl)-glyoxylate (81)

A mixture of sodium periodate (2.78 g) and potassium
permanganate (100 mg) in 30 ml of pH 7 phosphate buffer
solution and the olefinic ester (670 mg) in 30 ml of acetone
was stirred at room temperature for 3 hours. The reaction
mixture was filtered through celite and the residue on celite
was washed with chloroform. The filtrate was extracted three
times with chloroform. The organic solution was washed with
saturated salt solution, dried over sodium sulfate and evaporated
to give the crude keto ester acid (690 mg) as an oil in
85% yield.
Preparation of its semicarbazone (82) from (81)

The keto ester (81) (190 mg), semicarbazide hydrochloride (78 mg) and sodium acetate (58 mg) were dissolved in 10 ml of methanol and 5 ml of water. The solution was stirred at room temperature overnight and then evaporated under reduced pressure to remove most of methanol. The reaction mixture was extracted three times with methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulfate and then evaporated to dryness to give the semicarbazone (210 mg), which was recrystallized from ethyl ether.

Yield: 180 mg (78%), m.p. 141-143°C.

Nmr (CDCl₃): δ 1.30 (s,3H), 1.47 (s,3H), 2.2-2.5 (m,2H), 2.8-3.0 (m,1H), 3.2-3.5 (m,1H), 3.80 (s,3H,COOMe), 4.67 (m,1H), 5.10 (m,1H), 6.0-6.8 (b,2H,CONH₂), 10.2-11.0 (b,1H), 11.2 (b.s,1H).

Irf (KBr): 3480, 3250-3400, 2500-2700, 1720 (C=O), 1580 (C=N), 1470, 1390 cm⁻¹.

Uv (MeOH): 271 nm (log ε 3.92).
2-((2',α,3'-α-dihydroxy-di-0-isopropylidene-4'β-t-butylidimethyl-siloxymethylcyclopent-1'β-yl)-maleimide (87)

The keto ester (79) (850 mg) and carbamoylmethylene-triphenylphosphorane (730 mg, 1 equiv.) were dissolved in 10 ml of dry chloroform. The solution was stirred at room temperature for 4 hours. The solvent was then evaporated and the residue was chromatographed on silica gel plates using cyclohexane and ethyl ether (2:1) to give an oil (Rf=0.8) which crystallized on standing.

Yield: 660 mg (76%), m.p. 64-65°C.

Nmr (CDCl₃): 6 0.05 (s,6H), 0.90 (s,9H), 1.30 (s,3H), 1.50 (s,3H), 1.7-2.6 (m,3H), 2.8-3.4 (m,1H), 3.67 (d, J=4 Hz,2H,CH₂-OSi), 4.25-4.65 (m,2H), 6.25 (m,1H,C=CH), 8.2 (b,s,1H,NH).

Ir (CHCl₃): 3440 (NH), 1780/1730 (C=O), 1630 (C=C), 1385 cm⁻¹.

Uv (MeOH): 226 nm (log ε 3.98).

Mass (160°): m/e 381 (M⁺), 366 (M⁺-CH₃), 324 (M⁺-C(CH₃)₃), 266, 249, 296, 125 (B+28), 124 (B+27).

Analysis: Calculated for C₁₉H₃₁O₅Si: C, 59.84; H, 8.14; N, 3.67. Found: C, 59.81; H, 8.38; N, 4.02.
2-(2'-α,3'-α-dihydroxy-4'β-hydroxymethylcyclopent-1'β-yl)-maleimide (62).

The compound (87) (920 mg) was dissolved in 4 ml of trifluoroacetic acid and 4 ml of tetrahydrofuran. The solution was stirred for 30 minutes and the solvent was then evaporated under reduced pressure. The residue was chromatographed on silica gel plates using ethyl acetate and acetone. The product was recrystallized from ether-hexane.

Yield: 420 mg (80%), m.p. 171-172°C.

IR (KBr): 3420/3300/3200 (OH,NH), 1775/1730 (C=O), 1630 cm⁻¹.

UV (MeOH): 228 nm (logε 3.92).

Mass (200°): m/e 228 (M⁺+1), 227 (M⁺), 210 (MH⁺-H₂O), 209 (M⁺-H₂O), 191 (M⁺-2H₂O), 180, 179, 125 (B+28), 124 (B+27).

Analysis: Calculated for C₁₀H₁₃O₅N: C, 52.86; H, 5.77; N, 6.17.

Found: C, 53.28; H, 5.54; N, 6.45.
Preparation of methyl pyruvate hydrazone (88a)

Methyl pyruvate (1.02 g), methyl hydrazinoacetate hydrochloride (1.68 g, 1.2 equiv.) and sodium acetate (990 mg, 1.2 equiv.) were dissolved in 15 ml of methanol and 5 ml of water. The solution was stirred at room temperature for 6 hours. The solution was evaporated under reduced pressure. The residue was taken up in 20 ml of chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. Yield: 1.62 g (86%), m.p. 70-72°C.

Nmr (CDCl₃): δ 2.03 (s, 3H, CH₃C=N), 3.73 (s, 3H, COOMe), 3.80 (s, 3H, COOMe), 4.2 (b.s., 2H, NHCH₂COOMe), 6.3 (b.s., 1H, NHCH₂).

Ir (CHCl₃): 3300 (NH), 1745/1715 (C=O), 1605 cm⁻¹ (C=N).

Uv (MeOH): 273 nm (log ε 4.11).

3(5)-Carbomethoxy-4-hydroxy-5(3)-methylpyrazole (89)

To a solution of hydrazone (88a) (420 mg) in 5 ml of methanol was added 0.63M sodium methoxide (6.8 ml, 2.5 equiv.). The solution was refluxed for 4 hours and evaporated under reduced pressure. The residue was taken up in 10 ml of water, acidified with 0.5M hydrochloric acid and then extracted three times with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and evaporated to dryness in vacuo.
The crude product was chromatographed on silica gel plates using chloroform as an eluant (R_f = 0.6).

Yield: 102 mg (30%), m.p. 140-142°C.

Nmr (CDCl_3): \( \delta \) 2.2 (s, 3H, CH_3), 3.8 (s, 3H, COOMe), 8.4 (b, 2H, NH and OH).

Ir (CHCl_3): 3200-2500, 1720/1690 (C=O), 1640 cm\(^{-1}\).

Uv: \( \lambda_{\text{max}} \) = 225 (log\( \varepsilon \) 3.75) and 275 nm (log\( \varepsilon \) 3.65) in 0.1N HCl.

Conversion of the anti isomer (88a) into the syn isomer (88b)

The hydrazine (88a) (320 mg) was dissolved in 20 ml of methanol. The solution was irradiated for 2 days at 254 nm. The solvent was evaporated under reduced pressure and the crude product was chromatographed on silica gel plates using chloroform as an eluant for the separation. The syn isomer was an oil (R_f = 0.7).

Yield: 225 mg (70%).

Nmr (CDCl_3): \( \delta \) 2.00 (s, 3H, CH_3C=N), 3.67 (s, 3H, COOMe), 3.70 (s, 3H, COOMe), 4.13 (d, J=6 Hz, 2H, NHCH\(_2\)COOMe), 10.2 (b, 1H, NNHCH\(_2\)).

Ir (CHCl_3): 3300 (NH), 1750/1690 (C=O), 1570 cm\(^{-1}\) (C=N).

Uv (MeOH): 295 nm (log\( \varepsilon \) 3.97).
Preparation of pyrazole (89) from the syn hydrazone (88b)

The syn hydrazone (88b) was treated with sodium methoxide at reflux for 4 hours. After usual work-up and separation on silica gel plates, the pyrazole (89) was obtained in 35% yield. Spectral data (nmr, ir and uv) were identical with those of (89) which was obtained from the anti hydrazone (88a).

Preparation of its hydrazone (90) from (80)

To a solution of the keto ester (80) (105 mg) in 5 ml of methanol and 2 ml of water were added ethyl hydrazinoacetate hydrochloride (56 mg, 1.2 equiv.) and sodium acetate (30 mg). The solution was stirred at room temperature overnight and evaporated under reduced pressure to remove most of methanol. The reaction mixture was extracted with methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to dryness in vacuo. Purification on silica gel plates using chloroform as an eluant gave the oily hydrazone (90) (118 mg) in 87% yield.

Nmr (CDCl3): 6 1.2-1.6 (m, 18H, acetonide, bivalate, COOCH₂CH₃), 1.7-2.8 (m, 3H), 3.0-3.5 (b, 1H), 3.77 (s, 3H, COOMe), 4.0-4.8 (m, 8H), 6.8 (b, 0.3H, NH), 10.2 (0.7H, NH).

Ir (CHCl₃): 3300 (NH), 1740 (C=O), 1580 (C=N), 1395, 1385 cm⁻¹.
Preparation of its hydrazone (91) from (79)

The ketoester (79) (720 mg), ethyl hydrazinoacetate hydrochloride (450 mg, 1.5 equiv.) and sodium acetate (240 mg, 1.5 equiv.) were added in 15 ml of methanol and 5 ml of water. The solution was stirred at room temperature overnight. The solution was evaporated under reduced pressure to remove most of methanol and 20 ml of chloroform was added to the reaction mixture. The chloroform solution was washed with water, dried over sodium sulfate and then evaporated to dryness in vacuo. The crude product was purified by chromatography on silica gel plates using ethyl ether as an eluant. Yield: 850 mg (89%).

Nmr (CDCl₃): 0.05 (s,6H), 0.90 (s,9H), 1.1-1.7 (m,9H, O-CH₂CH₃, acetonide), 1.8-2.4 (m,3H), 3.0-3.3 (m,1H), 3.5-3.9 (m,5H, COOMe, SiO-CH₂), 4.0-4.9 (m,6H), 6.90 (t, J=5 Hz, 0.6H, NH), 10.2 (t, J=5 Hz, 0.4H, NH).

Ir (CHCl₃): 3300 (NH), 1750/1700 (C=O), 1580 (C=N) cm⁻¹.

Uv (MeOH): 287 nm (logε 3.93).

Mass (160°): m/e 472 (M⁺), 457 (M⁺-CH₃), 441 (M⁺-OCH₃), 415 (M⁺-C(CH₃)₃), 357 (M⁺-t-butyldimethylsilyl group) 257, 169.
Analysis: Calculated for C_{22}H_{40}O_7N_2Si: C, 55.93; H, 8.33; N, 5.93. Found: C, 55.98; H, 8.68; N, 6.06.

A mixture of geometrical isomers (230 mg) was separated using high pressure liquid chromatography on a silica gel column using 0.5% isopropyl alcohol in methylene chloride at 460 pounds per square inch.

The first fraction: The syn isomer (9lb)
Yield: 120 mg (55%).
Nmr (CDCl_3): δ 0.05 (s,6H), 0.90 (s,9H), 1.10-1.53 (m,9H), 1.67-2.40 (m,3H), 3.0-3.3 (b,1H), 3.53 (q,J=5 Hz,SiO-CH_2), 3.77 (s,3H,COOMe), 4.0-4.7 (m,6H), 10.2 (t,J=5 Hz,1H,NH).
Ir (CHCl_3): 3300 (NH), 1750/1700 (C=O), 1560 cm\(^{-1}\) (C=N).
Uv (MeOH): 300 nm (logε 3.88).

The second fraction: The anti isomer (9la)
Yield: 100 mg (45%).
Nmr (CDCl_3): δ 0.05 (s,6H), 0.90 (s,9H), 1.1-1.6 (m,9H), 1.8-2.3 (m,3H), 2.8-3.1 (b,1H), 3.4-3.8 (m,5H, COOMe,SiO-CH_2), 6.9-4.7 (m,6H), 6.6 (t,J=5 Hz, 1H,NH).
Ir (CHCl_3): 3300 (NH), 1750/1720 (C=O), 1585 cm\(^{-1}\) (C=N).
Uv (MeOH): 275 nm (logε 3.95).
3(5)-(2',α,3'α-dihydroxy-0-isopropylidene-4'β-t-butyldimethyl-siloxymethylcyclopent-1',8'-yl)-5(3)-carbomethoxy-4-hydroxy-pyrazole (92)

To a solution of a mixture of geometrical isomers of hydrazone (91) (340 mg) in 10 ml of methanol was added 0.63M sodium methoxide (3.2 ml, 3 equiv.). The solution was refluxed for 2 hours and evaporated under reduced pressure. The residue was taken up in 10 ml of water, acidified with 0.5M hydrochloric acid and then immediately extracted three times with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, evaporated to dryness and followed by chromatography on silica gel plates using ethyl ether and chloroform (5:1) as an eluant ($R_f=0.8$). The product was crystallized from petroleum ether (60-80°C) and ethyl ether.

Yield: 120 mg (40%), m.p. 153-154°C.

Nmr (CDCl$_3$): δ 0.05 (s,6H), 0.90 (s,9H), 1.30 (s,3H), 1.47 (s,3H), 1.9-2.4 (m,3H), 3.1-3.5 (m,1H), 3.67 (b,d,J=4 Hz, SiO-CH$_2$), 3.90 (s,3H,COOMe), 4.3-4.9 (m,2H), 8.80-9.25 (b,2H,NH,OH).

Ir, (KBr): 3420, 1715 (C=O), 1580, 1470 cm$^{-1}$.

(UV: $\lambda_{max}$=230 (log$\varepsilon$ 3.62) and 275 nm (log$\varepsilon$ 3.50) in 0.1N HCl.

(UV: $\lambda_{max}$=240 (log$\varepsilon$ 3.80) and 320 nm (log$\varepsilon$ 3.93) in 0.1N NaOH.)
Mass (160°): m/e 426 (M⁺), 411 (M⁺-CH₃), 379 (M⁺-CH₃-CH₃OH), 337 (M⁺-C(CH₃)₃-CH₃OH), 311 (M⁺-t-butyl-dimethylsilyl), 279 (M⁺-t-butyldimethylsilyl-CH₃OH), 249, 219, 169 (B+28), 168 (B+27).

Analysis: Calculated for C₂₀H₃₄O₆N₂Si: C, 56.34; H, 7.98; N, 6.57. Found: C, 56.59; H, 7.69; N, 6.71.

3(5)-(2'a,3'a-dihydroxy-0-isopropylidene-4'-8-t-butyldimethyl-siloxymethylcyclopent-1'-8-yl)-5(3)-carboxamide-4-hydroxypyrazole(93)

Pyrazole (92) (340 mg) was dissolved in 20 ml of methanol saturated with ammonia. The flask was well stoppered and allowed to stand for a week. The methanol was evaporated to dryness under reduced pressure and the crude product was chromatographed on silica gel plates using ethyl ether as an eluant to give a foam.

Yield: 280 mg (85%).

Nmr (CDCl₃): 6 0.05 (s, 6H), 0.90 (s, 9H), 1.35 (s, 3H), 1.58 (s, 3H), 1.8-2.7 (m, 3H), 3.1-3.4 (m, 1H), 3.73 (b, s, J=4 Hz, 2H, SiO-CH₂), 4.4-4.9 (m, 2H), 6.7-7.2 (b, 2H, CONH₂), 9.5-10.2 (b, 2H, NH, OH).

Ir (CHCl₃): 3540/3480/3440 (NH, OH), 1680/1630 (C=O), 1590 cm⁻¹.

Uv: λ_max=226 (log ε=3.78) and 270 nm (log ε 3.63) in 0.1N HCl.

λ_max=238 (log ε 3.58) and 312 nm (log ε 3.79) in 0.2N NaOH.
Mass (180°): m/e 411 (M⁺), 396 (M⁺-CH₃), 379 (M⁺-CH₃-NH₃), 354 (M⁺-C(CH₃)₃), 337 (M⁺-C(CH₃)₃-NH₃), 296, 279, 153 (B+27), 136 (B+27-NH₃).

Analysis: Calculated for C₁₉H₃₃O₅N₃Si; C, 55.47; H, 8.03; N, 10.22. Found: C, 55.48; H, 8.32; N, 10.08.

3(5)-(2′α,3′α-dihydroxy-4′8-hydroxymethylcyclopent-1′8-yl)-5(3)-carboxamide-4-hydroxypyrazole (63)

Amide (93) (440 mg) was dissolved in 5 ml of 50% aqueous trifluoroacetic acid. The solution was stirred at room temperature for 30 minutes and evaporated to dryness in vacuo. The crude product was crystallized from ethyl ether and ethanol.

Yield: 240 mg (80%), m.p. 216-218°C.

IR (KBr): 3450/3000-3400 (OH,NH), 1680/1630 (C=O), 1540 cm⁻¹.

Mass (210°): m/e 257 (M⁺), 240 (M⁺-NH₃), 239 (M⁺-H₂O), 222 (M⁺-H₂O-NH₃), 221 (M⁺-2H₂O), 191, 182, 154 (B+28), 153 (B+27), 137 (B+28-NH₃), 136 (B+27-NH₃).

UV: λ max = 226 (log ε 3.81) and 270 nm (log ε 3.63) in 0.1N HCl. λ max = 235 (log ε 3.71) and 311 nm (log ε 3.93) in 0.1N NaOH.

Analysis: Calculated for C₁₀H₁₅O₅N₃; C, 46.69; H, 5.88; N, 16.34. Found: C, 47.09; H, 6.01; N, 16.14.
Chapter II

Methyl-2-((2α,3α-dihydroxy-di-O-isopropylidene-4β-t-butyldimethyl-siloxymethylcyclopent-1β-yl)-glyoxylate semicarbazone (101)

The keto ester (79) (290 mg), semicarbazide hydrochloride (135 mg, 1.5 equiv.) and sodium acetate (100 mg, 1.5 equiv.) were dissolved in 10 ml of methanol and 5 ml of water. The solution was stirred at room temperature overnight and then evaporated under reduced pressure to remove most of methanol. The reaction mixture was diluted with 5 ml of water and extracted with methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulfate and then evaporated to dryness in vacuo. Purification on silica gel plates using ethyl acetate as an eluant gave an oily semicarbazone (101) (300 mg) in 90% yield.

Nmr (CDCl₃): 0.05 (s, 6H), 0.90 (s, 9H), 1.33 (s, 3H), 1.4-2.5 (m, 6H), 3.0-3.4 (m, 1H), 3.5-3.9 (m, 5H, COOMe, Si-O-CH₂), 4.3-4.9 (m, 2H), 6.0 (b, 2H, CONH₂), 9.6 (b.s, 0.4H, NHCO), 11.3 (b.s, 0.6H, NHCO).

Ir (CHCl₃): 3540/3430/3400 (NH); 1720 (C=O), 1580 (C=N), 1470, 1395, 1385 cm⁻¹.

Uv (EtOH): 265 nm (logε 4.00).

Analysis: Calculated for C₁₉H₃₅O₆N₃Si: C, 53.15; H, 8.16; N, 9.79; Found: C, 52.97; H, 8.04; N, 9.49.
A mixture of geometrical isomers was separated using high pressure liquid chromatography on a silica gel column using 0.5% methanol in methylene chloride as an eluant at 920 pounds per square inch.

The first fraction: The syn isomer (101b)
Yield: 40%

Nmr (CDCl₃): δ 0.05 (s,6H), 0.90 (s,9H), 1.33 (s,3H), 1.53 (s,3H), 1.7-2.5 (m,3H), 3.1-3.5 (m,1H), 3.67 (b,d,J=4 Hz, SiO-CH₂), 3.87 (s,3H, COOMe), 4.3-4.8 (m,2H), 5.8 (b,2H,CONH₂); 11.3 (b,s,1H, NNHCO).

IR (CHCl₃): 3540/3420/3300 (NH), 1700 (C=O), 1570 (C=N) cm⁻¹.

UV (MeOH): 272 nm (logɛ 4.01).

The second fraction: The anti isomer (101a)
Yield: 60%

Nmr (CDCl₃): δ 0.05 (s,6H), 0.90 (s,9H), 1.30 (s,3H), 1.58 (s,3H), 1.7-2.4 (m,3H), 3.0-3.4 (m,1H), 3.73 (b,d,J=4 Hz,2H), 3.83 (s,3H, COOMe), 4.3-4.9 (m,2H), 6.0 (b,2H,CONH₂), 9.6 (b,s,NNHCO).

IR (CHCl₃): 3540/3440/3360 (NH), 1720 (C=O), 1570 cm⁻¹.

UV (MeOH): 263 nm (logɛ 4.06).
6-(2',3'-dihydroxy-di-0-isopropylidene-4'-β-t-butylidimethyl-siloxymethylcyclopent-1'-β-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (102)

To a solution of a mixture of geometrical isomers of semicarbazone (101) (430 mg) in 10 ml of methanol was added 0.63M sodium methoxide (3.2 ml, 2 equiv.). The solution was refluxed for 2 hours and evaporated under reduced pressure. The residue was taken up in 10 ml of water, acidified with 0.5M hydrochloric acid and immediately extracted three times with ethyl acetate. The ethyl acetate solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was separated by chromatography on silica gel plates using ethyl ether and chloroform (5:1) as an eluant.

Major Product (R_f=0.5): 215 mg (50%).
Spectral data (nmr,ir,uv) were identical with those of (101a) which was separated using high pressure liquid chromatography.

Minor product (102) (R_f=0.7): 120 mg (30%).

Nmr (CDCl_3): δ 0.05 (s,6H), 0.90 (s,9H), 1.33 (s,3H), 1.53 (s,3H), 1.53 (s,3H), 1.7-2.7 (m,3H), 3.10-3.85 (m,3H), 4.2-4.6 (m,1H), 4.6-5.1 (m,1H), 10.0-11.0 (b and b.s,2H,NHCONH).
Ir (CHCl₃): 3420, 3380, 3100-3300, 1730/1710 (C=O), 1600 (C=N), 1470, 1460, 1395, 1385 cm⁻¹.

Uv: \( \lambda_{\text{max}} = 265 \text{ nm (log} \varepsilon 3.78) \) in 0.1N HCl.
\( \lambda_{\text{max}} = 255 \text{ nm (log} \varepsilon 3.70) \) in 0.1N NaOH.

Mass (150°): m/e 397 (M⁺), 382 (M⁺-CH₃), 340 (M⁺-C(CH₃)₃), 282 (M⁺-t-butyldimethylsilyl), 140 (B+28), 139 (B+27).

Analysis: Calculated for C₁₈H₃₁O₅N₅Si: C, 54.37; H, 7.87; N, 10.57. Found: C, 54.18; H, 8.01; N, 10.61.

Preparation of semicarbazone of methyl pyruvate (103a)

To a solution of methyl pyruvate (1.02 g) in 20 ml of methanol was slowly added a solution of semicarbazide hydrochloride (1.22 g, 1.1 equiv.) and sodium acetate (900 mg, 1.1 equiv.) in 10 ml of water. The solution was stirred at room temperature for 1 hour, the white precipitate was filtered off and washed several times with methanol.

Yield: 1.40 g (88%), m.p. 198-200°C.

Nmr (CDCl₃): 6 2.08 (s,3H₂CH₃-C), 3.77 (s,3H,COOMe), 6.4 (b.s, 2H,CONH₂), 9.9 (b.s,1H,NNHCO).

Ir (KBr): 3540, 3400, 3300-3000, 1730 (COOMe), 1690 (CONH₂), 1595 (C=N), 1450 cm⁻¹.

Uv (MeOH): 262 nm (log} \varepsilon 4.39).
Conversion of the anti semicarbazone (103a) into the syn semicarbazone (103b)

The anti semicarbazone (103a) (210 mg) was dissolved in 20 ml of methanol. The solution was irradiated at 254 nm for 2 days and separated by chromatography on silica gel plates using ethyl acetate as an eluant ($R_f=0.85$). Yield: 160 mg (80%), m.p. 128-130°C.

Nmr (CDCl₃): δ 2.07 (s,3H), 3.77 (s,3H), 6.6 (b.s,2H,CONH₂), 10.8 (b.s,1H,NNH).

Irr (KBr): 3440, 3300, 1695 (C=O), 1600, 1450 cm⁻¹.

Uv (MeOH): 265 nm (logε 4.37).

6-Methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (6-azathymine) (100)

The syn semicarbazone (103b) (140 mg) was added to 3.0 ml of 0.63M (2.1 equiv.). The solution was stirred at room temperature for 30 minutes. The formation of a white precipitate was observed after stirring a few minutes. Without filtration of the white precipitate, the reaction mixture was neutralized with Dowex 50W-X8(H). The resin was filtered and the solvent was evaporated to dryness in vacuo. The crude product was crystallized from ethyl ether. Yield: 85 mg (75%), m.p. 209-211°C (lit. 210-212°C).
Nmr (d-DMSO, external TMS): \( \delta 2.03 \) (s, 3H, CH₃), 9.0-11.0 (b, 2H, NHCONH).  

Ir (KBr): 3280, 3200, 1730/1680 (C=O), 1620 (C=N), 1480 cm⁻¹.  

Uv: \( \lambda_{max} = 261 \) nm (log ε 3.73) in 0.1N HCl.  
\( \lambda_{max} = 246 \) nm (log ε 3.67) in 0.1N NaOH.

**Preparation of sodium salt (104)**

The syn semicarbazone (103b) (100 mg) was added to 1.2 mL of 0.63M sodium methoxide (1.2 equiv.). The solution was stirred at room temperature for 10 minutes, the white precipitate was filtered off and washed with 1 mL of methanol. Drying in vacuo gave sodium salt (45 mg) in 48% yield. Its uv spectrum was identical with (100) and the nmr spectrum in D₂O showed a singlet at 2.10 ppm for the methyl group.

**Conversion of (101a) into (101b)**

The anti semicarbazone (101a) (120 mg) was dissolved in 20 mL of methanol. The solution was irradiated at 254 nm for 2 days and evaporated to dryness in vacuo to afford the syn semicabazole (101b) in essentially quantitatively yield. Spectral data (nmr, ir and uv) were identical with those of (101b) which was separated using high pressure liquid chromatography.
Preparation of (102) from the syn semicarbazone (101b)

To a solution of the syn isomer (101b) (110 mg) obtained from above reaction in 5 ml of methanol was added 0.8 ml of 0.63M sodium methoxide (2 equiv.). The solution was refluxed for 2 hours and evaporated under reduced pressure. The residue was taken up in 10 ml of water. The resulting solution was acidified with 0.5M hydrochloric acid and extracted three times with ethyl acetate. The ethyl acetate solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give (102) (81 mg) in 80% yield. Spectral data (nmr, ir and uv) were identical with those of (102) which obtained from (101).

6-(2\''a,3\''a-dihydroxy-4\'b-hydroxymethylcyclopent-1\'b-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (94)

To a solution of (102) (180 mg) in 5 ml of methanol was added 5 ml of 50% aqueous trifluoroacetic acid. The solution was stirred at room temperature for 20 minutes and evaporated to dryness in vacuo. The crude product was crystallized from methanol and ethyl ether.

Yield: 85 mg (75%), m.p. 184-186°C.

Ir (KBr): 3480/3250/3150 (OH, NH), 1735/1690 (C=O), 1620, 1470 cm\(^{-1}\).

Uv: \(\lambda_{\text{max}} = 265\) nm (log\(e\) 3.80) in 0.1N HCl.
\(\lambda_{\text{max}} = 254\) nm (log\(e\) 3.74) in 0.1N NaOH.
Mass (200°): m/e 244 (M^+1), 243 (M^+), 225 (M^+ -H_2O), 207 (M^+ -2H_2O), 196, 194, 178, 140 (B+28), 139 (B+27).

Analysis: Calculated for C_9H_{13}O_5N_3: C, 44.44; H, 5.39; N, 17.28.
Found: C, 44.38; H, 5.19; N, 17.02.

6-(2'a,3'a-dihydroxy-di-0-isopropylidene-4'B-carboxycyclopent-1'B-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (105)

Semicarbazone (82) (420 mg) was dissolved in 20 ml of methanol containing sodium (100 mg, 3.3 equiv.). The solution was refluxed for 1 hour and evaporated under reduced pressure. The residue was taken up in 10 ml of water. The solution was acidified with 0.5M hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was crystallized from ethyl ether.

Yield: 300 mg (80%), decomposed above 180°C.

IR (KBr): 3350-3600, 3150-3300, 1700-1740 (C=O), 1620 (C=N), 1390 cm^{-1}.

UV: \lambda_{max} = 265 \text{ nm} (\text{log} \epsilon 3.62) \text{ in 0.1N HCl.}
\lambda_{max} = 254 \text{ nm} (\text{log} \epsilon 3.60) \text{ in 0.1N NaOH.}

Mass (180°): m/e 297 (M^+), 283 (M^+ -CH_3), 239, 222, 210, 140 (B+28), 139 (B+27).

Analysis: Calculated for C_{12}H_{15}O_6N_3: C, 48.48; H, 5.09; N, 14.14.
Found: C, 48.30; H, 5.15; N, 14.47.
6-(2'α,3'α-dihydroxy-di-0-isopropylidene-4'β-hydroxymethyl-
cyclopent-1'β-yl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (106)

To a solution of acid (105) (120 mg) in 5 ml of freshly
distilled tetrahydrofuran was added 0.6 ml of 1 molar diborane
(1.5 equiv.) in tetrahydrofuran in an ice bath. The solution
was stirred for 2 hours in an ice bath under nitrogen atmos-
phere. A few drops of water were added and solvents were
evaporated. Boric acid was removed by several coevaporations
with methanol under reduced pressure. Purification of the
crude product by chromatography on silica gel plates using
ethyl acetate as an eluant gave the desired alcohol (106)
(95 mg), which decomposed at above 250°C, in 83% yield.

IR (KBr): 3400-3500/3300 (OH,NH), 1730/1700 (C=O) cm⁻¹.
Uv: \( \lambda_{max} = 265 \text{ nm (log } ε 3.70 \text{) in } 0.1\text{N HCl.} \)
\( \lambda_{max} = 254 \text{ nm (log } ε 3.57 \text{) in } 0.1\text{N NaOH.} \)
Mass (150°); m/e 268 (M⁺-CH₃), 230, 225, 140 (B+28), 139 (B+27).
Analysis: Calculated for C₁₂H₁₇O₅N₃: C, 50.88; H, 6.05;
N, 14.83. Found: C, 51.02; H, 6.09; N, 15.19.
Preparation of (94) from (106)

Compound (106) (140 mg) was dissolved in 5 ml of 90% aqueous trifluoroacetic acid. The solution was stirred at room temperature for 5 minutes and evaporated to dryness in vacuo. The crude product was crystallized from methanol and ethyl ether to give the crystalline compound (94) (90 mg) in 75% yield. Spectral data (ir and uv) and m.p. were identical with those of (94), obtained from (102).

Preparation of thiosemicarbazone (107) of methyl pyruvate

Methyl pyruvate (2.06 g) and thiosemicarbazide (1.83 g, 1 equiv.) were dissolved in 30 ml of 80% aqueous methanol. The solution was stirred at room temperature for 30 minutes. The precipitate was filtered and washed several times with methanol.

Yield: 3.50 g (78%), m.p. 137-138°C.

Nmr (DMSO, external TMS): 2.0 (s,3H,CH₃-C), 3.7 (s,3H,COOMe), 7.6 (b.s,1H), 8.5 (b.s,1H), 10.6 (b,1H).

Ir (Nujol): 3540, 3250, 3180; 1730 (C=O), 1640 (C=N) cm⁻¹.
6-Methyl-3-thiooxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (99)

A solution of the thiosemicarbazone (107) (285 mg) in 6.6 ml of 0.63M sodium methoxide (2 equiv.) was refluxed for 3 hours, cooled and acidified with concentrated hydrochloric acid. The precipitate was filtered.
Yield: 155 mg (70%), m.p. 219-220 (lit. 218-219).

Uv: \( \lambda_{\text{max}} = 272 \text{ nm (log} \epsilon \text{ 4.27) in } 0.1\text{N HCl} \)
\( \lambda_{\text{max}} = 265 \text{ nm (log} \epsilon \text{ 4.22) in } 0.1\text{N NaOH} \).

Methyl-2-(2a,3a-dihydroxy-di-O-isopropylidene-4\beta-t-butyldimethylsiloxymethylcyclopent-1\beta-yl)-glyoxylate thiosemicarbazone (108)

To a solution of the keto ester (79) (530 mg) in 20 ml of methanol was added thiosemicarbazide (150 mg, 1.1 equiv.). The reaction mixture was refluxed overnight and evaporated to near dryness under reduced pressure. The residue was taken up in 20 ml of chloroform. The solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was purified on silica gel plates using ethyl ether as an eluant.
Yield: 545 mg (86%).

Nmr (CDCl\textsubscript{3}): 6 0.05 (s,6H), 0.9 (two s,9H), 1.2-2.8 (m,10H), 3.4-3.8 (m,5H), 4.2-4.6 (b,2H), 4.9-5.1 (b,1H), 7.0-7.2 (b,1H), 9.2 (b.s,0.5H), 12.1 (b.s,0.5H).
Ir (CHCl₃): 3540, 3400, 3300, 1730/1710 (C=O), 1580 (C=N), 1480, 1395, 1385 cm⁻¹.

Uv (MeOH): 273 nm (logε 3.78) and 315 (logε 3.68).

Mass (195°): m/e 445 (M⁺), 430 (M⁺-CH₃), 388 (M⁺-C(CH₃)₃), 386, 356, 330, 298.

6-(2'a,3'a-dihydroxy-di-o-isopropylidene-4'b-t-butyldimethyl-siloxy-cyclopent-1'β-yl)-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (109)

To a solution of the thiosemicarbazone (108) (200 mg) in 5 ml of methanol was added 0.8 ml of 0.63M sodium methoxide (1.1 equiv.). The solution was refluxed for 3 hours and evaporated under reduced pressure. After adding 10 ml of water, the solution was acidified with 0.5N hydrochloric acid and then extracted three times with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and evaporated to dryness in vacuo. Purification of the crude product on silica gel plates using chloroform and ethyl ether (1:2) as an eluant gave the desired product (109) (146 mg) as an oil in 76% yield.

Nmr (CDCl₃): ⁶ 0.05 (s,6H), 0.93 (s,9H), 1.43 (s,3H), 1.67 (s,3H), 1.8-2.7 (b,3H), 3.3-3.9 (m,3H), 4.4-4.7 (m,1H), 4.9-5.2 (m,1H), 10.7-12.2 (b,2H).
Ir. (CHCl₃): 3420, 3380, 3200-3300, 1710, 1610, 1530 cm⁻¹.

Uv: \( \lambda_{\text{max}} = 215 \, (\log \varepsilon 3.91) \) and 269 nm \((\log \varepsilon 4.18)\) in 0.1N HCl.
\( \lambda_{\text{max}} = 224 \, (\log \varepsilon 4.11), \, 258 \, (\log \varepsilon 4.07) \) and 310 nm
\((\log \varepsilon 3.60)\) in 0.1N NaOH.

Mass (185°): m/e 389 \((M^+ - \text{CH}_3)\), 356 \((M^+ - C(CH_3)_3)\), 298 \((M^+ - \text{t-butyldimethylsilyl})\), 280, 206.

6-\((2'\alpha,3'\alpha\text{-dihydroxy-4'β-hydroxymethyl-1'β-yl})-3\text{-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (95)\)}

To a solution of (109) (110 mg) in 2 ml of tetrahydrofuran was added 5 ml of 50% aqueous trifluoroacetic acid. The solution was stirred at room temperature for 30 minutes and evaporated to dryness in vacuo. The crude product was crystallized from methanol and ethyl ether.

Yield: 50 mg (72%), m.p. 163-165°C.

Ir (KBr): 3480, 3280, 3100, 1705, 1610, 1560 cm⁻¹.

Uv: \( \lambda_{\text{max}} = 215 \, (\log \varepsilon 3.96) \) and 269 nm \((\log \varepsilon 4.20)\) in 0.1N HCl.
\( \lambda_{\text{max}} = 224 \, (\log \varepsilon 4.11), \, 258 \, (\log \varepsilon 4.08) \) and 310 nm
\((\log \varepsilon 3.52)\) in 0.1N NaOH.

Mass (190°): m/e 259 \((M^+)\), 241 \((M^+ - \text{H}_2\text{O})\), 223 \((M^+ - 2\text{H}_2\text{O})\),
212, 210, 156 \((B+28)\), 155 \((B+27)\).
Chapter III

3-Exo-bromo-2-endo-carbomethoxy-6-exo-hydroxybicyclo[2.2.1]heptane (114) and 3-Endo-carbomethoxytricyclo[2.2.1.0]heptane (117)

To a solution of olefin ester (67) (9.80 g) in 20 ml of tetrahydrofuran was added 16 ml of 1.0 molar diborane (1.1 hydride equiv.) in tetrahydrofuran in an ice bath and the reaction mixture was stirred for 1 hour under a nitrogen atmosphere. The excess diborane was destroyed by adding a few drops of water. The trialkylborane was oxidized by the addition to the stirred reaction mixture of 15 ml of 3N sodium hydroxide, followed by the dropwise addition of 15 ml of hydrogen peroxide in an ice bath. The reaction mixture was stirred for an additional 30 minute, saturated with sodium chloride and then the tetrahydrofuran layer formed was separated and washed with saturated salt solution. The organic layer was dried over sodium sulfate and evaporated to near dryness under reduced pressure. Distillation gave 4.80 g of alcohol (114) (126-130°/0.7 mmHg) and 2.21 g of tricyclic compound (117) (49-52°/0.7 mmHg).

Major product (114):

Nmr (CDCl₃): δ 1.2-2.0 (m, 4H), 2.4 (b.s, 1H, OH), 2.57 (m, 2H), 3.2 (m, 1H), 3.7 (b, 1H), 3.73 (s, 3H, COOMe), 4.2 (m, 1H).
Ir (film): 3200-3600 (OH), 1740 (C=O) cm$^{-1}$.

Mass (150°): m/e 250, 248 (M$^+$, Br$^{91}$, Br$^{79}$), 219/217 (M$^+$-OCH$_3$), 169 (M$^+$-Br), 137.

Minor product (117):

Nmr (CDCl$_3$): $\delta$ 1.0-1.6 (m, 7H), 2.0 (b, 1H), 2.4 (b.s, 1H),
3.63 (s, 3H, COOMe).

Ir (film): 1740 (C=O) cm$^{-1}$.

Mass (60°): m/e 152 (M$^+$), 121 (M$^+$-OCH$_3$), 120 (M$^+$-CH$_3$OH),
93 (M$^+$-COOMe).

3-Exo-bromo-2-endo-carbomethoxy-6-exo-acetoxybicyclo[2.2.1]heptane (118)

Alcohol (114) (270 mg) was dissolved in 5 ml of acetic anhydride. After the addition of p-toluenesulfonic acid (10 mg), the solution was stirred at room temperature overnight and evaporated to near dryness under reduced pressure.

The residue was taken up in 20 ml of methylene chloride and washed with 0.1M sodium bicarbonate solution. The methylene chloride solution was dried over sodium sulfate and evaporated to give an oily acetate in quantitative yield.

Nmr (CDCl$_3$): $\delta$ 1.2-2.2 (m, 4H), 2.00 (s, 3H, OCOCH$_3$), 2.45-2.80 (m, 2H), 3.0-3.3 (m, 1H, CHCOOMe), 3.75 (s, 3H, COOMe), 4.1-4.3 (m, 1H), 4.4-4.6 (m, 1H).

Ir (film): 1750/1730 (C=O), 1440, 1360 cm$^{-1}$. 
Mass (110°): m/e 292, 290 (M⁺,Br₂⁺,Br⁺), 261/259 (M⁺-OCH₃), 232/230 (M⁺-CH₃COOH), 211 (M⁺-Br), 179 (M⁺-Br-CH₃OH), 150 (M⁺-Br-CH₃COOH).

Analysis: Calculated for C₁₁H₁₅O₄Br: C, 45.36; H, 5.15; Br, 27.48. Found: C, 45.54; H, 5.39; Br, 27.60.

2-Carbomethoxy-6-exo-acetoxybicyclo[2.2.1]hept-2-ene (119)

To a solution of acetate (118) (320 mg) in 20 ml of anhydrous ethyl ether was slowly added DBU (300 mg) in an ice bath, washed twice with 10 ml of 0.1M hydrochloric acid and once with saturated salt solution. The ether solution was dried over sodium sulfate and evaporated to give an oily olefinic ester (119).

Yield: 250 mg (90%).

Nmr (CDCl₃): 6 1.2-2.2 (m,4H,H₅ and H₇), 2.04 (s,3H,OCOCH₃), 3.00 (b.s,1H,H₄), 3.26 (s,1H,H₁), 3.74 (s,3H,COOME), 4.7 (m,1H,H₆), 7.12 (d,J=4 Hz,C=CH).

Ir (CHCl₃): 1740 (C=O), 1620 (C=C), 1440, 1370 cm⁻¹.

Mass (90°): m/e 210 (M⁺), 179 (M⁺-OCH₃), 178, (M⁺-CH₃OH), 169 (M⁺-CH₃CO), 168, 150, 136.
3-Exo-bromo-2-endo-carbomethoxy-6-exo-p-nitrobenzoyloxy-
bicyclo[2.2.1]heptane (120)

Alcohol (114) (500 mg), p-nitrobenzoyl chloride (380 mg, 1 equiv.) and pyridine (210 mg, 1.3 equiv.) were dissolved in 10 ml of methylene chloride. After stirring at room temperature, the solution was washed three times with water and once with saturated salt solution. The methylene chloride solution was dried over sodium sulfate and evaporated to give a crystalline compound. The compound obtained was re-crystallized from carbon tetrachloride and petroleum ether. Yield: 560 mg (70%), m.p. 141-143°C.

Nmr (CDCl₃): δ 1.4-2.2 (m, 4H), 2.6-3.0 (m, 2H), 3.2-3.4 (m, 1H, CHCOOMe), 3.80 (s, 3H, COOMe), 4.2-4.4 (m, 1H, CHBr), 4.8-5.0 (m, 1H, CH-OCO), 8.3 (s, 4H, COC₆H₄NO₂-p).

Ir (KBr): 1740 (C=O), 1620, 1555 cm⁻¹.

Mass (180°): m/e 399, 397 (M⁺,Br⁰,Br⁷), 377/375 (M⁺-CH₃OH), 318 (M⁺-Br), 249/247 (M⁺-COC₆H₄NO₂-p).

2-Carbomethoxy-6-exo-p-nitrobenzoyloxybicyclo[2.2.1]hept-2-ene (121)

p-Nitrobenzoate (120) was treated with DBU in the same way as (119) from (118). The yield was essentially quantitative. m.p. 62-63°C.
To a cooled solution of alcohol (114) (788 mg) and triethylamine (358 mg, 1.1 equiv.) in 15 ml of methylene chloride in a dry ice bath was added dropwise mesyl chloride (400 mg, 1.1 equiv.) in 10 ml of methylene chloride. The reaction mixture was stirred for an additional hour in a dry ice bath and then poured into 10 ml of water. The methylene chloride solution was washed twice with water, dried over sodium sulfate and evaporated to give the mesylate as an oil.

Yield: 870 mg (94%).

Nmr (CDCl₃): δ 1.2-2.2 (m, 4H), 2.3-2.9 (b, 2H), 3.00 (s, 3H, OSO₂CH₃), 3.27 (m, 1H), 3.70 (s, 3H, COOMe), 4.1-4.2 (m, 1H, CHBr), 4.3-4.5 (m, 1H, CH-OSO₂).

Ir (film): 1745 (C=O), 1460, 1380 cm⁻¹.

Mass (200°): m/e 296, 294 (M⁺,Br⁸¹,Br⁷⁹), 248, 215 (M⁺-Br), 150.
3-Exo-bromo-6-endo-hydroxybicyclo[2.2.1]heptane-2-endo-carboxylic acid γ-lactone (123)

Mesylate (122) (320 mg) was dissolved in 10 ml of formic acid. The solution was gently heated at 60-65°C for 2 hours and evaporated under reduced pressure to remove most of formic acid. The residue was taken up in 20 ml of ethyl acetate. The solution was washed twice with 0.5M sodium bicarbonate solution, once with saturated salt solution. The ethyl acetate solution was dried over sodium sulfate and evaporated to give an oily lactone. The crude product was purified by chromatography on silica gel plates using chloroform as an eluant.

Yield: 188 mg (80%).

Nmr (CDCl₃): δ 1.2-2.4 (m,4H), 2.7 (b,1H), 2.9-3.0 (m,1H), 3.1-3.3 (m,1H), 4.2 (b.s,1H), 4.6-4.9 (m,1H).

Ir (CHCl₃): 1790 (C=O), 1370, 1320 cm⁻¹.

Mass (110°): m/e: 218, 216 (M⁺,Br⁸,Br⁷), 137 (M⁺-Br), 109 (M⁺-Br-CO).

Analysis: Calculated for C₈H₉O₂Br: C, 44.24; H, 4.15; Br, 36.82.

Found: C, 44.28; H, 4.32; Br, 37.07.
3-Exo-bromo-5-exo-6-endo-dihydroxybicyclo[2.2.1]heptane-2-
endo-carboxylic acid γ-lactone (126)

To a mixture of olefin (66) (10.0 g) in 50 ml of 98% formic acid at 50°C was slowly added 40 ml of 30% hydrogen peroxide over a period of 2 hour. The resulting solution was stirred for one additional hour at 50°C and evaporated under reduced pressure. The residue was taken up in 40 ml of chloroform. The solution was washed twice with 0.5M sodium bicarbonate solution, with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was crystallized from chloroform and hexane. Evaporation of the filtrate left an oil that contained the hydroxy formate (127) as a byproduct.

Yield: 6.4 g (60%).

Nmr (CDCl₃): δ 2.2 (b.s,2H), 2.6 (b.s,1H), 2.7 (b.s,1H), 2.9-3.2 (m,2H), 3.7 (b.s,1H), 4.0 (b.s,1H), 4.4 (m,1H).

Ir (Nujol): 3420 (OH), 1780 (C=O) cm⁻¹.

The hydroxy formate (127): 2.1 g (20%).

Nmr (CDCl₃): δ 2.2 (b.2H), 2.9-3.1 (m,2H), 3.34 (m,1H), 4.16 (s,1H,CHBr), 4.5-4.7 (m,2H), 8.05 (s,1H,CHO).

Ir (CHCl₃): 1730/1780 (C=O) cm⁻¹.
To a solution of alcohol (126) (5.0 g) in 10 ml of pyridine was added pivaloyl chloride (3.1 g, 1.2 equiv.). The reaction mixture was stirred overnight at room temperature and evaporated under reduced pressure. The residue was taken up in 20 ml of chloroform. The chloroform was washed with 0.5N hydrochloric acid, washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give the crystalline pivalate.

Yield: 6.33 g (93%), m.p. 114-115°C.

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\text{Nmr (CDCl}_3\text{): } \delta 1.18 (s, 9H, C(\text{CH}_3)_3), 2.15 (q, J=12 \text{ Hz}, 2H), 2.8 \text{ (b.s,1H), 3.0 (b.s,1H), 3.2-3.3 (m,1H), 4.1 \text{ (b.s,1H), 4.4-4.6 (m,2H).}}
\]

\[
\text{Irr (Nujol): 1790/1740 (C=O) cm}^{-1}.
\]

2-Carbomethoxy-5-exo-pivaloyloxy-6-endo-hydroxybicyclo[2.2.1]hept-2-ene (124)

To a solution of lactone (128) (470 mg) in 20 ml of methanol was added DBU (450 mg, 2 equiv.). The solution was stirred at room temperature for 1 hour and the methanol was evaporated under reduced pressure. The residue was taken up in 20 ml of methylene chloride.
solution was washed with 0.5N hydrochloric acid, once with saturated salt solution, dried over sodium sulfate and evaporated to give an oily unsaturated alcohol (124) (350 mg) in 90% yield. Nmr (CDCl₃): δ 1.17 (s,9H), 1.8 (b.s,2H,CH₂), 2.9-3.1 (b,1H), 3.2-3.4 (b,1H), 3.6 (b.s,1H,OH), 3.77 (s,3H, COOME), 4.1-4.3 (m,2H), 7.08 (d,J=4 Hz,1H,C=CH). Ir (film): 3480 (OH), 1730 (C=O), 1610 (C=C) cm⁻¹.

Opening of lactone (128) with sodium methoxide

To a solution of lactone (128) (1.0 g) in 10 ml of methanol was added 8.0 ml of 0.40M sodium methoxide (1 equiv.) and the solution was stirred at room temperature for 1 hour. The solution was evaporated under reduced pressure and the residue was taken up in 10 ml of methylene chloride. The methylene chloride solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo to give an oily unsaturated alcohol in 80% yield which spectral data (nmr,ir) were identical with those of (124).

Opening of lactone (128) with triethylamine and methanol.

A solution of lactone (128) (240 mg) in 20 ml of methanol and 1 ml of triethylamine was refluxed for 24 hours. After usual work-up, the oily desired product was obtained in 90% yield. Spectral data (ir and nmr) were identical with those of (124).
2-Carbomethoxy-5-exo-pivaloyloxy-6-oxo-bicyclo[2.2.1]hept-2-ene (129)

To a solution of alcohol (124) (450 mg) in 20 ml of acetone in an ice bath, was slowly added chromic acid oxidizing solution (Jones reagent). The addition was continued until the orange color of oxidizing reagent persisted for about 1 hour. The excess oxidizing reagent was destroyed by the addition of a small amount of isopropyl alcohol. The reaction mixture was decanted and the residual green salts were washed with acetone. Cautiously, sodium bicarbonate was added to the solution with stirring until the pH of reaction mixture was neutral. The suspension was filtered through celite and the residue was washed with acetone. The combined acetone solutions were evaporated under reduced pressure. The residue was taken up in 20 ml of chloroform. The chloroform solution was washed with water, once with saturated salt solution, dried over sodium sulfate and evaporated to give the corresponding ketone (129) which crystallized on standing.

Yield: 430 mg (95%), m.p. 74-75°C.

Nmr (CDCl₃): δ 1.17 (s, 9H, C(CH₃)₃), 2.1-2.7 (m, 2H, H₇), 3.1-3.4 (m, 2H, H₁, H₄), 3.13 (s, 3H, COOMe), 4.67 (b.s, 1H, H₅), 7.20 (d, J=3 Hz, 1H, C=CH).

Ir (CHCl₃): 1780/1740 (C=O), 1610 (C=C), 1490, 1470 cm⁻¹.

Mass (90°): m/e 266 (M⁺), 235 (M⁺-OCH₃), 209 (M⁺-C(CH₃)₃).
2-Carbomethoxy-5-exo-pivaloyloxy-6-endo-mesyloxybicyclo[2.2.1]hept-2-ene (130)

To a solution of alcohol (124) (700 mg) and triethylamine (480 mg, 2.2 equiv.) in 10 ml of methylene chloride in a dry ice bath was dropwise added mesyl chloride (300 mg, 1.1 equiv.) in 5 ml of methylene chloride. The reaction mixture was stirred for 1 hour, washed three times with water, dried over sodium sulfate and evaporated to give an oily mesylate (130). The crude product was purified through silica gel column eluting with chloroform.

Yield: 840 mg (90%).

Nmr (CDCl₃): δ 1.17 (s, 9H), 1.9-2.2 (m, 2H, H₇), 3.17 (s, 3H, SO₂CH₃), 3.0-3.3 (b, 1H), 3.5-3.7 (b, 1H), 3.87 (s, 3H, COOMe), 4.67 (b, s, 1H), 5.10 (b, d, J=4 Hz, 1H, H₆), 7.20 (d, J=3 Hz, 1H, C=CH).

Ir (film): 1740 (C=O), 1615 (C=C), 1380 cm⁻¹.

Mass (150°): m/e 346 (M⁺), 261 (M⁺-COC(CH₃)₃), 243, 229.

2-Carbomethoxy-5-exo-pivaloyloxy-6-endo-mesyloxybicyclo[2.2.1] heptane (131)

To a solution of mesylate (130) (340 mg) in 5 ml of tetrahydrofuran was added 1 molar superhydride (1.1 ml, 1.1 hydride equiv.) in tetrahydrofuran. The reaction mixture
was stirred at room temperature overnight under a nitrogen atmosphere. After adding water, the reaction mixture was evaporated under reduced pressure and extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo.

Yield: 320 mg (93%).

Nmr (CDCl₃): δ 1.2 (s, 9H), 1.6-2.6 (m, 6H, H₇, H₃, H₁, H₄), 3.0-3.2 (b, 1H, H₂), 3.1 (s, 3H, OSO₂CH₃), 3.8 (s, 3H, COOMe), 4.6-5.0 (m, 2H, H₅, H₆).

Ir (CHCl₃): 1730 (C=O), 1490, 1470 1380 cm⁻¹.

Mass (130°): m/e 348 (M⁺), 317 (M⁺-OCH₃), 270, 248, 187.

3-Endo-bromobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid (133)

To a solution of 30.0 g of cis-β-bromoacrylic acid in 250 ml of benzene was added freshly distilled cyclopentadiene (200 ml). The resulting solution was refluxed for 1.5 hours and then evaporated to remove benzene and excess of cyclopentadiene. Petroleum ether (60-80°C) (50 ml) was added to the residue to help crystallization and evaporated under reduced pressure. After 150 ml of petroleum ether was added to the residue, the reaction mixture was kept in a refrigerator overnight, filtered and washed with petroleum ether.

Yield: 28.0 g (65%), m.p. 175-177°C, (lit. 155-179°C).
Nmr (CDCl₃): δ 1.52 (q, J=10 Hz, 2H, CH₂), 3.0-3.3 (m, 3H), 4.60 (d.d, J=10, 4 Hz, 1H, CHBr), 6.15 (m, 1H), 6.46 (m, 1H), 10.2 (b.s, 1H, COOH).

Ir (Nujol): 3200-2500 (OH), 1710 (C=O) cm⁻¹.

3-Endo-bromo-2-endo-carbomethoxybicyclo[2.2.1]hept-5-ene (134)

Acid (133) (21.0 g) and p-toluenesulfonic acid (200 mg) were dissolved in 200 ml of methanol. The solution was refluxed overnight. Evaporation to near dryness was followed by the addition of 50 ml of ethyl acetate. The ethyl acetate solution was washed twice with 0.5M sodium bicarbonate, with saturated salt solution, dried over sodium sulfate and then evaporated to dryness in vacuo. Distillation at 92-94°C/1.5 mmHg gave the methyl ester (134) (21.2 g) in 95% yield.

Nmr (CDCl₃): δ 1.53 (q, J=10 Hz, 2H, CH₂), 3.0-3.3 (m, 3H), 3.74 (s, 3H, COOMe), 4.66 (d.d, J=10, 4 Hz, 1H, CHBr), 6.2 (m, 1H), 6.6 (m, 1H).

Ir (film): 1740 (C=O) cm⁻¹.
A mixture of 3-endo-bromo-2-endo-carbomethoxy-5-exo-hydroxybicyclo[2.2.1]heptane (135) and 3-endo-bromo-2-endo-carbomethoxy-6-exo-hydroxybicyclo[2.2.1]heptane (136)

To methyl ester (134) (10.6 g) in 20 ml of tetrahydrofuran was added 18 ml of 1 molar diborane (1.1 equiv.) in tetrahydrofuran in an ice bath. The solution was stirred under a nitrogen atmosphere in an ice bath for 1 hour and then excess diborane was destroyed by adding a few drops of water. The trialkylborane was oxidized by the addition to the stirred reaction mixture of 15 ml of 3N sodium hydroxide, followed by the dropwise addition of 15 ml of hydrogen peroxide in an ice bath. The reaction mixture was stirred for an additional hour and then saturated with sodium chloride and the tetrahydrofuran layer formed was separated. The organic layer was washed with saturated salt solution, dried over sodium sulfate and evaporated to near dryness under reduced pressure. Distillation at 124-126°C/0.6 mmHg gave 9.70 g of a mixture of two alcohols in 85% yield.

Nmr (CDCl₃): δ 1.2-2.3 (m, 3H), 2.6-3.5 (m, 5H), 3.80 (s, 3H, COOMe), 4.2-5.0 (m, 2H).

Ir (film): 3200-3600 (OH), 1740 (C=O), 1450 cm⁻¹.

Mass (150°): m/e 250, 248 (M⁺,Br⁺¹,Br⁻⁷⁹), 219/217 (M⁺-OCH₃), 169 (M⁺-Br), 137 (M⁺-Br-CH₃OH), 109.
A mixture of 3-endo-bromo-2-endo-carbomethoxy-5-exo-acetoxybicyclo[2.2.1]heptane (137) and 3-endo-bromo-2-endo-carbomethoxy-6-exo-acetoxybicyclo[2.2.1]heptane (138)

A mixture of alcohols (4.60 g) was dissolved in 5 ml of acetic anhydride and 2 ml of pyridine. The solution was stirred at room temperature overnight and evaporated under reduced pressure to remove solvents. The residue was taken up in 30 ml of methylene chloride and the solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. Distillation at 112-115°C/0.8 mmHg gave 4.07 g of a mixture of acetates in 90% yield.

Nmr (CDCl₃): δ 1.3-1.9 (m, 3H), 2.0 (s, 3H, OCOCH₃), 2.1-3.3 (m, 4H), 3.7 (s, 3H, COOMe), 4.6 (m, 1H, CHBr), 5.3 and 5.7 (two b.s, 1H, CHOCH₂).  

Ir (film): 1740 (C=O), 1430, 1360 cm⁻¹.

A mixture of 2-carbomethoxy-5-exo-acetoxybicyclo[2.2.1]hept-2-ene (139) and 2-carbomethoxy-6-exo-acetoxybicyclo[2.2.1]-hept-2-ene (119)

To a solution of acetates (3.20 g) in 20 ml of methylene chloride was added DBU (3.20 g, 2 equiv.) and the reaction mixture was refluxed for 2 hours. The solution was washed three times with 0.5N hydrochloric acid, once with saturated
salt solution, dried over sodium sulfate and evaporated to
dryness in vacuo. Distillation at 106-108°C/0.8 mmHg gave
1.97 g of a mixture of olefinic esters in 85% yield.

\text{Nmr (CDCl}_3\text{):} \delta 1.5-1.8 (m, 4H), 2.0 (s, 3H, OCOCH}_3\text{), 3.0 (b, 1H),
3.2 (b, 1H), 3.7 (s, 3H, COOMe), 4.5-4.8 (m, 1H, CH-OCOCH}_3\text{), 6.8 and 7.1 (two d, 1H, C=CH)\).

\text{Ir (film):} 1740 (C=O), 1610 (C=C), 1460, 1390 cm\(^{-1}\).

3-Endo-bromo-2-endo-carbomethoxy-5-exo-acetoxybicyclo[2.2.1]
heptane (137)

A mixture of acetates (137, 138) (250 mg) was dissolved
in 10 ml of formic acid and the resulting solution was
refluxed for 4 hours (bath temperature:110°C). The solution
was evaporated under reduced pressure to remove formic acid.
After adding 20 ml of methylene chloride, the solution was
washed with 0.5M sodium bicarbonate solution, dried over
sodium sulfate and evaporated to dryness in vacuo. The residue
was separated on silica gel plates using chloroform as an
eluant (R\(_f\)=0.75) to give (137) (100 mg) in 40% yield.

\text{Nmr (CDCl}_3\text{):} \delta 1.3-1.9 (m, 3H), 2.00 (s, 3H, OCOCH}_3\text{), 2.2-3.2
(m, 4H), 3.64 (s, 3H, COOMe), 4.58 (d, d, J=12.4 Hz, 1H, CHBr), 5.30 (b, d, J=5 Hz, 1H, CH-OCOCH}_3\text{)\).

\text{Ir (film):} 1740 (C=O), 1430, 1360 cm\(^{-1}\).
Acetate (137) was treated with DBU in methylene chloride at reflux for 2 hours and then usual work-up gave olefinic acetate (139) in essentially quantitative yield.

Nmr (CDCl$_3$): $\delta$ 1.6-1.8 (b, 4H), 2.0 (s, 3H), 3.0 (b.s, 1H), 3.2 (b.s, 1H), 3.7 (s, 3H), 4.6-4.8 (m, 1H, CH$_2$OCO), 6.8 (d, $J=4$ Hz, 1H, C=CH).

Ir (film): 1740 (C=O), 1610 (C=C), 1460, 1390, 1360 cm$^{-1}$.

3-Endo-bromo-2-endo-carbomethoxy-5-exo-p-nitrobenzoyloxybicyclo[2.2.1]heptane (142) and 3-Endo-bromo-2-endo-carbomethoxy-6-exo-p-nitrobenzoyloxybicyclo[2.2.1]heptane (143)

Alcohols (135,136) (910 mg) and p-nitrobenzoyl chloride (680 mg, 1 equiv.) were dissolved in 2 ml of pyridine and 10 ml of methylene chloride. After stirring at room temperature overnight, the solution was evaporated under reduced pressure to remove most of pyridine. The residue was taken up in 20 ml of chloroform. The chloroform solution was washed with water, with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo to give a crystalline compound in essentially quantitative yield. Major product (142) was recrystallized from carbon tetrachloride and petroleum ether (60-80°C) (7:3).
Yield: 650 mg (45%), m.p. 151-153°C.

Nmr (CDCl$_3$): $\delta$ 1.2-2.2 (m, 3H), 2.5-3.4 (m, 4H), 3.77 (s, 3H, COOME), 4.67 (d.d, J=12, 4 Hz, 1H, CHBr), 5.67 (b.d, J=5 Hz, 1H, CH-OCO), 8.33 (s, 4H, COC$_6$H$_4$NO$_2$-p).

Ir (KBr): 1740 (C=O), 1610, 1540 cm$^{-1}$.

Mass (170°): m/e 399, 397 (M$^+$, Br$^{81}$, Br$^{79}$), 367/365 (M$^+$-CH$_3$OH), 318 (M$^+$-Br), 286 (M$^+$-Br-CH$_3$OH), 249/247 (M$^+$-COC$_6$H$_4$NO$_2$-p).

Analysis: Calculated for C$_{16}$H$_{16}$O$_6$NBr: C, 48.24; H, 4.05; N, 3.52. Found: C, 48.47; H, 4.20; N, 3.56.

Minor product (143) was recrystallized from chloroform and petroleum ether (60-80°C) (1:1).

Yield: 360 mg (25%), m.p. 101-103°C.

Nmr (CDCl$_3$): $\delta$ 1.4-2.3 (m, 4H), 2.8 (m, 2H), 3.40 (d.d, J=12, 4 Hz, 1H, COOME), 3.77 (s, 3H, COOME), 4.70 (d.d, J=12, 4 Hz, 1H, CHBr), 6.27 (b.d, J=5 Hz, 1H, CH-OCO), 8.33 (s, 4H, COC$_6$H$_4$NO$_2$-p).

Ir (KBr): 1740/1730 (C=O), 1610, 1540 cm$^{-1}$.

Mass (190°): m/e 399, 397 (M$^+$, Br$^{81}$, Br$^{79}$), 367/365 (M$^+$-CH$_3$OH), 318 (M$^+$-Br), 286 (M$^+$-Br-CH$_3$OH), 249/247 (M$^+$-COC$_6$H$_4$NO$_2$-p).
2-Carbomethoxy-5-exo-p-nitrobenzoyloxybicyclo[2.2.1]hept-2-ene (144)

To a solution of p-nitrobenzoate (142) (310 mg) in 20 ml of methylene chloride was added DBU (200 mg, 1.8 equiv.) and the reaction mixture was refluxed for 2 hours. The reaction mixture was washed with three times with 0.5N hydrochloric acid and once with saturated salt solution. Drying over sodium sulfate and evaporation gave a crystalline compound. Yield: 220 mg (90%), m.p. 118-119°C.

Nmr (CDCl₃): 1.6-2.2 (b, 4H, H₆, H₇), 3.3 (b, 2H, H₁, H₄), 3.80 (s, 3H, COOMe), 5.10 (m, 1H, H₅), 7.00 (d, J=4 Hz, 1H, C=CH), 8.25 (s, 4H, COC₆H₄NO₂-p).

Ir (KBr): 1740 (C=O), 1610, 1540 cm⁻¹.

Mass (250°): m/e 317 (M⁺), 286 (M⁺-OCH₃), 247, 215 150.

Analysis: Calculated for C₁₆H₁₅NO: C, 60.56; H, 4.77; N, 4.41.
Found: C, 60.51; H, 5.04; N, 4.51.

2-Carbomethoxy-6-exo-p-nitrobenzoyloxybicyclo[2.2.1]hept-2-ene (121)

(143) was treated with DBU as above to give (121) in 85% yield. Spectral data (nmr and ir) and m.p. were identical with those of (121), which was prepared from (120).
Methyl-2-(3a-p-nitrobenzoyloxy-48-aldehydocyclopent-18-yl)-glyoxyxlate (145)

The olefinic ester (144) (220 mg) was dissolved in 40 ml of dry methylene chloride, cooled to -78°C in a dry ice-acetone bath, and treated with ozone at the rate of 7 mmoles of ozone per hour. The reaction was continued until the blue color persisted. The temperature of the solution was allowed to rise to room temperature and excess of ozone was removed by passing nitrogen. The solution was cooled to -78°C in a dry ice-acetone bath and dimethyl sulfide (0.2 ml) was added. The solution was stirred and allowed to come slowly to room temperature. Stirring was continued for a total 4 hours. The methylene chloride solution was washed three times with saturated salt solution. Drying over sodium sulfate and evaporation gave the oily aldehyde keto ester (242 mg) in quantitative yield.

Nmr (CDCl₃): 6 1.6-3.4 (b, 7H), 3.8-4.2 (m, 4H), 5.4-5.9 (b, 2H), 8.3 (s, 4H), 9.8 (s, 0.3H, CHO).

Ir (CHCl₃): 3300-3600 (OH), 1730 (C=O), 1620, 1550 cm⁻¹.
Methyl-2-(3α-p-nitrobenzoyloxy-4β-hydroxymethylcyclopent-1β-yl)-glycolate (146)

The crude aldehyde keto ester (145) (320 mg) was dissolved in 50 ml of dry benzene. The water was removed as an azeotropic mixture in refluxing benzene for 2 hours and the solution was evaporated to dryness in vacuo. To a solution of this product in 5 ml of tetrahydrofuran in an ice bath was added 0.60 ml of 1 molar diborane (2 hydride eq.) in tetrahydrofuran. The solution was stirred for 1 hour in an ice bath under a nitrogen atmosphere, a few drops of water was added and then evaporated to dryness in vacuo. Separation of the crude product on silica gel plates using ethyl acetate and chloroform (1:1) as an eluant gave the oily diol in 60% yield (R_f = 0.4).

Nmr (CDCl_3): δ 1.2-2.8 (m, 6H), 3.3 (b.s, 2H, OH), 3.70 (d, J=5 Hz, 2H, CH_2OH), 3.83 (s, 3H, COOMe), 4.23 (d, J=4 Hz, 1H, CO-CH-OH), 5.3 (b, 1H, CH-OCO), 8.27 (s, 4H).

Ir (CHCl_3): 3650-3200 (OH), 1740 (C=O), 1620, 1550 cm⁻¹.

Mass (200°): m/e 353 (M⁺), 294 (M⁺-COOMe), 276 (M⁺-H_2O-COOMe), 203 (M⁺-COC_6H_4NO_2-P), 168, 150.

Analysis: Calculated for C_{16}H_{19}O_8N: C, 54.39; H, 5.42; N, 3.96.

Found: C, 54.09; H, 5.58; N, 3.84.
Methyl-2-(3α-p-nitrobenzoyloxy-4β-carboxycyclopent-1β-yl)-
glyoxylate (148)

A mixture of sodium periodate (1.80 g, 4.5 equiv.) and potassium permanganate (100 mg) in 15 ml of pH 7 phosphate buffer and olefinic ester (144) (600 mg) in 20 ml of acetone was stirred at room temperature for 4 hours. The reaction mixture was filtered through celite and the residue was washed with acetone. The filtrate was extracted with chloroform. The organic solution was washed with water, with saturated salt solution. Drying over sodium sulfate and then evaporation gave an oily compound (620 mg) in 90% yield.

Nmr (CDCl₃): 2.0-3.0 (m, 5H), 3.2 (m, 1H), 3.90 (s, 3H, COOMe), 5.6 (m, 1H, CH-OCO), 8.20 (s, 4H), 10.8 (b.s, 1H, COOH).

Ir (CHCl₃): 3500-3100 (OH), 1750 (C=O), 1630, 1550 cm⁻¹.

Mass (180⁰): m/e 320 (M⁺-COOH), 306 (M⁺-COOMe), 215 (M⁺-COC₆H₄NO₂-p), 167, 150.

Preparation of diol (146) from the keto ester acid (148)

To a cooled solution of keto ester acid (148) (250 mg) in 10 ml of tetrahydrofuran in an ice bath was added 1.00 ml of 1.0 molar diborane (4.6 hydride equiv.) in tetrahydrofuran. The reaction mixture was stirred in an ice bath for 1 hour.
A few drops of water was added and solvents were evaporated. Purification on silica gel plates using chloroform and ethyl acetate (1:1) as an eluant gave an oily compound in 80% yield. Spectral data (nmr and ir) and r.f. value were identical with those of (146) which was obtained from (145).

**Preparation of diacetate (150) from (146)**

Diol (146) (85 mg) was dissolved in 2 ml of pyridine and 0.5 ml of acetic anhydride. The solution was stirred at room temperature overnight and evaporated under reduced pressure. Purification on a silica gel plate using chloroform and ethyl acetate (1:1) as an eluant gave an oil in 93% yield.

Nmr (CDCl₃): δ 1.2-3.0 (m, 6H), 2.07 (s, 3H, OCOCH₃), 2.20 (s, 3H, OCOCH₃), 3.80 (s, 3H, COOMe), 4.23 (d, J=5 Hz, 2H, CH₂CO), 5.00 (d, J=4 Hz, 1H, CO-CH-OCO), 5.33 (m, 1H, CH-OCO), 8.27 (s, 4H).

Ir (CHCl₃): 1750/1740 (C=O), 1620, 1550 cm⁻¹.

Mass (140°): m/e 406 (M⁺-OCH₃), 394 (M⁺-CH₃CO), 378 (M⁺-COOMe), 276, 211.
Methyl-2-(3α-p-nitrobenzoyl oxy-4β-t-butyldimethylsiloxy methyl- cyclopent-18-yl)-glycolate (151)

Diol (146) (320 mg), t-butyldimethylchlorosilane (150 mg, 1.1 equiv.) and imidazole (155 mg, 2.5 equiv.) were dissolved in 5 ml of dimethylformamide. After stirring at room temperature for 24 hours, the solution was evaporated under reduced pressure to remove most of dimethylformamide. The residue was taken up in 30 ml of chloroform. The chloroform solution was washed three times with water, dried over sodium sulfate and evaporated to dryness in vacuo. Purification on silica gel plates using chloroform and ethyl acetate (2:1) gave an oily compound (350 mg) in 83% yield.

Nmr (CDCl₃): δ 0.05 (s,6H,Si(CH₃)₂), 0.85 (s,9H,Si-C(CH₃)₃), 1.3-2.6 (m,6H), 3.1 (b.s,1H,OH), 3.66 (d,J=4 Hz, CH₂=OSi), 3.77 (s,3H,COOMe), 4.1 (m,1H,CO-CH-OH), 5.3 (m,1H,CH-OCO), 8.23 (s,4H).

Ir (CHCl₃): 3650-3100 (OH), 1740 (C=O), 1620, 1540 cm⁻¹.

Mass (200°): m/e 467 (M⁺), 410 (M⁺-C(CH₃)₃), 408 (M⁺-COOMe), 243, 224, 213, 150.

Analysis: Calculated for C₂₂H₃₃O₃NSi: C, 56.52; H, 7.12; N, 3.00. Found: C, 56.53; H, 7.34; N, 3.04.
Methyl-2-(3α-p-nitrobenzoyloxy-4β-t-butyldimethylsiloxyethyl-cyclopent-1β-yl)-glyoxylate (152)

Sodium periodate (280 mg, 2.2 equiv.) and ruthenium dioxide (20 mg) were dissolved in 20 ml of water. The pH of the mixture was controlled between 6 and 7 by the addition of a small amount of sodium bicarbonate (20 mg). The solution of the hydroxy ester (151) (280 mg) in 30 ml of carbon tetrachloride was added to the mixture, with vigorous stirring, at room temperature. The end of the reaction, after about 4 hours, was indicated by a change in color from black to yellow. The carbon tetrachloride layer was separated, washed with water, and ruthenium dioxide was removed by the addition of a few drops of isopropyl alcohol and filtered. The carbon tetrachloride solution was dried over sodium sulfate and evaporated to dryness in vacuo to give the keto ester in 93% yield as an oil.

Nmr (CDCl₃): 6 0.05 (s, 6H), 0.93 (s, 9H), 1.4-2.8 (m, 6H), 3.70 (b, 2H, CH₂-Si), 3.87 (s, 3H, COOMe), 5.3 (m, 1H), 8.23 (s, 4H).

Ir (CHCl₃): 1740 (C=O), 1620, 1550 cm⁻¹.

Mass (200°): m/e 465 (M⁺), 408 (M⁺-C(CH₃)₃), 406 (M⁺-COOMe), 379, 300 (M⁺-CH₃-CO₆H₄NO₂-p), 224.
Preparation of hydrazone (153) from (152)

The keto ester (152) (280 mg), ethyl hydrazinoacetate hydrochloride (108 mg) and sodium acetate (60 mg) were dissolved in 10 ml of methanol and 2 ml of water. The reaction mixture was stirred at room temperature overnight, evaporated under reduced pressure to remove most of methanol and then extracted twice with methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. Purification on silica gel plates using chloroform and ethyl acetate (3:1) as an eluant gave the hydrazone (300 mg) in 88% yield as an oil.

Nmr (CDCl₃): δ 0.05 (s,6H), 0.90 (s,9H), 1.27 (t, J=7 Hz,3H, OCH₂CH₃), 1.5-2.7 (m,6H), 3.7 (b,2H,CH₂-O-Si), 3.77 (s,3H,COOMe), 4.0-4.6 (m,4H,NHCH₂-COOCH₂CH₃), 5.3 (m,1H,CH-OCO), 6.4 (t, J=4 Hz,0.3H,NH), 8.20 (s,4H,COCl₆H₄NO₂-P), 10.2 (t, J=4 Hz,0.7H,NH).

Ir (CHCl₃): 3250-3650 (NH), 1740/1720 (C=O), 1620, 1550 cm⁻¹.

Uv (MeOH): 266 nm (logε 3.93) and 290 nm (logε 3.74).

Mass (200°): m/e 565 (M⁺), 550 (M⁺-CH₃), 508 (M⁺-C(CH₃)₃), 490, 398.

Analysis: Calculated for C₂₆H₃₉O₅N₃Si: C, 55.21; H, 6.95; N, 7.43. Found: C, 55.40; H, 6.98; N, 7.20.
3(5)-(3'-α-hydroxy-4'-β-t-butyldimethylsiloxymethylcyclopent-1'-β-yl)-5(3)-carbomethoxy-4-hydroxypyrazole (154)

To a solution of hydrazone (153) (570 mg) in 10 ml of methanol was added 0.63M sodium methoxide (3.5 ml, 2.2 equiv.). The reaction mixture was refluxed for 2 hours, evaporated under reduced pressure, acidified with 0.1N hydrochloric acid after 10 ml of water was added to the residue and then extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and evaporated to dryness in vacuo. Separation on silica gel plates using ethyl ether as an eluant gave an oil (75 mg) in 20% yield (R_f=0.4).

Nmr (CDCl_3): δ 0.07 (s,6H), 0.93 (s,9H), 1.5-2.5 (m,5H), 3.3-3.9 (m,3H), 3.93 (s,3H,COOMe), 4.3 (m,1H), 6.6 (b,2H,OH,NH).

Ir (CHCl_3): 3460, 1720/1~90 (C=O), 1590 cm⁻¹.

Uv: λ max = 228 (logε 3.28) and 275 nm (logε 3.66) in 0.1N HCl.

λ max = 238 (logε 3.87) and 320 nm (logε 3.91) in 0.1N NaOH.

Mass (160°): m/e 370 (M⁺), 355 (M⁺-CH₃), 339 (M⁺-OCH₃), 338 (M⁺-CH₃OH), 313 (M⁺-C(CH₃)₃), 295, 281 (M⁺-CH₃OH-C(CH₃)₃), 221, 189, 169.
3(5)-(3'α-hydroxy-4'β-t-butyldimethylsiloxymethylcyclopent-1'β-yl)-5(3)-carboxamide-4-hydroxypyrazole (155)

The pyrazole (154) (150 mg) was added to 10 ml of methanol saturated with ammonia. The solution was allowed to stand at room temperature for a week. Evaporation and following purification on a silica gel plate using ethyl acetate as an eluant gave an amide (115 mg) in 80% yield as a foam.

IR (CHCl₃): 3580/3440 (OH,NH), 1690/1630 (C=O) cm⁻¹.

UV: \( \lambda_{max} = 220 \) (logε 3.77) and 268 nm (logε 3.57) in 0.1N HCl
\( \lambda_{max} = 235 \) (logε 3.69) and 315 nm (logε 3.69) in 0.1N NaOH.

Mass-(210°): m/e 355 (M⁺), 298 (M⁺ - C(CH₃)₃), 281 (M⁺ - NH₃ - C(CH₃)₃), 250, 206 189, 154 (B+28), 157 (B+27).

Analysis: Calculated for C₁₆H₂₉O₄N₃Si: C, 54.08; H, 8.17; N, 11.83. Found: C, 54.19; H, 8.24; N, 11.60.

3(5)-(3'α-hydroxy-4'β-hydroxymethylcyclopent-1'β-yl)-5(3)-carboxamide-4-hydroxypyrazole (110)

To a solution of the amide (155) (140 mg) in 2 ml of methanol was added 2 ml of 50% aqueous trifluoroacetic acid. The solution was stirred at room temperature for 30 minutes and then evaporated under reduced pressure. The crude product was crystallized from methanol and ethyl ether.
Yield: 58 mg (60%), m.p. 138-141°C.

IR (KBr): 3100-3600 (OH, NH), 1690/1640 (C=O) cm⁻¹.

UV: \[ \lambda_{\text{max}} = 220 \text{ (log } e 3.76) \text{ and } 268 \text{ nm (log } e 3.64) \text{ in } 0.1 \text{N HCl.} \]

\[ \lambda_{\text{max}} = 235 \text{ (log } e 3.77) \text{ and } 314 \text{ nm (log } e 3.90) \text{ in } 0.1 \text{N NaOH.} \]

Mass (170°): m/e 241 (M⁺), 224 (M⁺-NH₃), 223 (M⁺-H₂O),

206 (M⁺-NH₃-H₂O), 193, 154 (B+28), 153 (B+27), 137 (B+28-NH₃), 136 (B+27-NH₃).
Bibliography

75. Reference 46, p. 142.
Synthetic Studies Towards Cepham Derivatives
And Their Aza Analogues

Abstract

Several synthetic approaches for the synthesis of cepham derivatives and their aza analogues were investigated. The use of the oxazolidine protecting group and of the thiazolidine group, and the stability of the thiazolidine group to nucleophilic attack were demonstrated. Ring opening reactions of 2-phenyl-4-heteromethylene-5-oxazolone were studied. In addition, several important intermediates were prepared and characterized.
Etudes synthétiques vers les dérivés cépham et leurs analogues azotiques

Résumé

Plusieurs schémas synthétiques pour la synthèse de dérivés cépham et leurs analogues azotiques ont été investigés. L'emploi des groupements protecteurs oxazolidine et thiazolidine, et la stabilité du groupement thiazolidine vers l'attaque nucléophile, ont été démontres. Les réactions qui ouvrent le 2-phényl-4-hétérométhylène-5-oxazolone ont été étudiés. Plusieurs intermédiaires importants ont aussi été préparés et caractérisés.
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Introduction

\( \beta \)-Lactams are four-membered heterocyclic compounds of the type (1) containing nitrogen as the hetero atom. Although the first \( \beta \)-lactam was recognized by Staudinger in 1907, \( \beta \)-lactams as a class acquired importance only after it was established that penicillin (2) contained a \( \beta \)-lactam unit as a structural feature.\(^2\)

\[
\begin{align*}
(1) & \quad R-CO-NH-\overset{\text{N}}{\text{O}}-\overset{\text{S}}{\text{CH}}_3 \quad \overset{\text{COOH}}{\text{COOH}} \\
(2) & \quad H \quad H \\
& \quad H \quad H \\
& \quad H \quad H
\end{align*}
\]

The structure of penicillin had hardly been elucidated when Brotzu in 1945 discovered what turned out to be another \( \beta \)-lactam producing cephalosporium species near a sewage outlet in the sea off Sardinia.

Abraham and Newton\(^4\) carried out a detailed examination of all the antibiotics produced by this cephalosporium species. In 1955 they isolated from the cultures of a mold, cephalosporium acremonium, a new antibiotic substance which they called cephalosporin C (3). The structure was determined by the same workers\(^5\) in 1961 and confirmed by Hodgkin and Maslen\(^6\)
by means of X-ray analysis.

Much work was done between 1940 and 1945 on the chemical synthesis of penicillins but without much success.

In meantime, single step fermentation processes had become sufficiently developed so as to make any multistep chemical synthesis noncompetitive. This was not true, however, for the cephalosporin series of β-lactam antibiotics. Therefore, the total synthesis of cephalosporin C and its derivatives seemed very worthwhile.

The total synthesis of a derivative of cephalosporin C (4), which has no biological activity, was reported by Heymes et al. in 1966.

The most successful stereospecific total synthesis of cephalosporin C and cephalothin was reported by R. B. Woodward in his Nobel address in 1965.

Using L-cysteine (5) as the starting point ensured the correct absolute stereochemistry at 7 position of cephalosporin C.
L-cysteine (5) was protected with an acetonide function and then reacted with t-butoxy carbonyl chloride to give (6). The acid (6) was esterified with diazomethane and then reacted with dimethyl azodicarboxylate to afford (7).

Oxidation of (7) with lead tetractate followed by treatment with sodium acetate in methanol produced the trans hydroxy compound (8). Treatment of the mesylate of (8) with azide, followed by reduction with aluminum amalgam in methanol gave the desired cis amino-ester (9).

The γ-lactam was formed using triisobutyl aluminum and this resulting compound condensed with preformed dialdehyde (10).
to give (11). From (11) the amino-aldehyde (12) was produced by treatment with trifluoroacetic acid. Then, acylation of the amino group, reduction of the aldehyde with diborane followed by acetylation of the resulting hydroxy group and isomerization of the double bond in pyridine gave the ester (13a) which could be converted to free acid (13) by reaction with zinc in 90% aqueous acetic acid.

Recently, Christensen et al. and independently Edward et al. reported the total synthesis of the cephalosporin derivatives. Their methods are based on the well-known cycloaddition reaction of ketenes with imines, a procedure originally
adapted to the preparation of penicillin analogues by Bose.¹¹

A number of review articles and monographs¹²⁻¹⁸ have
dealt with other synthetic approaches and with the chemistry
and biological activity of the cephalosporin antibiotics.

Cephalosporins and penicillins seem to have similar modes
of action, interfering with bacterial cell wall synthesis.¹⁹⁻²¹
Cephalosporins, however, have some characteristics that in
many cases make them more useful than penicillins. They are,
like penicillins, non-toxic, but they are also more acid stable,
and more chemical variations are possible. Perhaps the greatest
disadvantage, however, is that they are much more expensive
than penicillins.

In recent years there has been a growing interest in
oxacepham derivatives (14), carbacepham derivatives (15) and
aza analogues of cepham derivatives (16), new classes of
compounds characterized by replacement of sulfur by oxygen,
carbon and nitrogen atom respectively.

![Chemical structure](image)

(14) X=O
(15) X=CH₂
(16) X=NH
In 1968, Sheehan\textsuperscript{22} reported the synthesis of a new series of oxygen analogues (17) of the cepham ring system.

A partial synthesis of the oxacephem derivative (18) from penicillin derivative was also reported in 1974 by S. Wolfe\textsuperscript{23}.

\begin{center}
\begin{tikzpicture}
\node (17) [draw] {17};
\node (18) [right of=17, draw] {18};
\end{tikzpicture}
\end{center}

Recently, Christensen\textsuperscript{24-25} published the successful total synthesis of oxacephalothin (14a) and carbacephalothin (15a). Biological tests indicated that the gram-positive antibacterial activity of oxacephalothin is about the same as that of cephalothin, but its gram-negative activity is doubled. Also, it turned out that carbacephalothin is biologically active.

\begin{center}
\begin{tikzpicture}
\node (14a) [draw] {14a};
\node (15a) [right of=14a, draw] {15a};
\end{tikzpicture}
\end{center}

(14a) $X=O$

(15a) $X=CH_2$
Concerning aza analogues of cepham derivatives, S. Wolfe\textsuperscript{26} reported the conversion of a penicillin derivative to 1-aza-6-epidethiocepham (19) and Bose\textsuperscript{27} described the synthesis of several novel aza analogues (20,21) of cepham by reaction of N-acylated 1,4,5,6-tetrahydropyrimidine with acid chloride in the presence of triethylamine.

\begin{align*}
(19) & \quad \text{R'}=\text{N}_3 \\
(20) & \quad \text{R'}=\text{CH}_2\text{N}_3, \text{R'}=\text{N}_3 \\
(21) & \quad \text{R'}=\text{COCH}_2\text{OPh}, \text{R'}=\text{NH}_2
\end{align*}
Outline of the project

In 1962, Ugi\textsuperscript{20} reported a new method to synthesize a penicillin analogue (26) by treatment of the imine acid (22) with an isonitrile (24) in a two phase system consisting of water and petroleum ether. He indicated that in aqueous media, the imine acid (22) is in equilibrium with the zwitter ion (23), which reacts with an isonitrile to form the bicyclic adduct (25), and that this adduct rearranges to the penicillin analogue (26).

This approach to penicillins was not used any further because of the wrong stereochemistry of the carboxamide group introduced in (26). We decided to use an analogous scheme to prepare cepham derivatives and their aza analogues,
in which the stereochemical problem is resolved by the eventual introduction of a double bond.

The main features of the proposed scheme are shown below.

\[ (24) \]

\[ \text{(27) } X=S \quad \text{(30) } X=S \]
\[ \text{(28) } X=O \quad \text{(31) } X=O \]
\[ \text{(29) } X=\text{NH} \quad \text{(32) } X=\text{NH} \]

This thesis describes part of a project dealing with synthetic approaches towards cepham derivatives, oxacephem derivatives and their aza analogues.

In chapter I and chapter II, synthetic approaches towards cepham derivatives and their aza analogues will be described.
Since our attempts to synthesize cepham derivatives, oxacephem derivatives and their aza analogues using the Ugi reaction were unsuccessful, we decided to explore the possibility of preparing the key intermediates (33, 34, 35) which will provide cepham derivatives, opening the way to their analogues, by using the acid chloride-imine method.

Therefore, attempts to prepare the important intermediate (35) will be briefly described in chapter III.
Chapter I

Synthetic studies towards cepham derivatives using the Ugi reaction

Attempts to synthesize cepham derivatives were made by Rossy\textsuperscript{29} and Rosebery\textsuperscript{30}.

The starting point of the synthesis was D-mannitol from which the diacetin (40) was prepared in 30\% yield using known procedures\textsuperscript{31–32}. From the diacetin (40), glyceraldehyde (41) was prepared by cleavage of the vicinal diol with lead tetraacetate in benzene. Treatment of (41) with formaldehyde and potassium carbonate in aqueous methanol gave the dioxane (42). Treatment of the dioxane (42) with N-methylethanolamine in refluxing benzene rapidly led to the alcohol (43). The alcohol (43) was converted to the mesylate (44) by treatment with mesyl chloride and triethylamine.

\[
\begin{align*}
\text{(39)} & \quad \text{(40)} & \quad \text{(41)}
\end{align*}
\]
Repeating the whole reaction sequences, we found that the mesylate (44) was contaminated with the dimesylate (45) in variable amounts (10-50%). The structure of (45) was assigned based on its microanalytical and nmr spectral data.

Since the mesylate (45) must be derived from the diol (46), we concluded that the diol had been formed by a Cannizzaro reaction occurring during the work-up of the dioxane (42), which had involved removal of methanol from water in the presence of formaldehyde and potassium carbonate.

In order to avoid this problem, and since the formation of the dioxane (42) could also take place in an aqueous medium, it was desirable to perform the cleavage reaction with aqueous periodate.
Düpre\textsuperscript{13} prepared the glyceraldehyde acetonide (41) by treatment of (40) with sodium periodate in pH 6 phosphate buffer solution. Without isolation of glyceraldehyde acetonide, it was treated with aqueous formaldehyde and potassium carbonate to afford the dioxane (42) in 81\% yield from the diacetonide (40).

Treatment of the dioxane (42) with N-methylethanolamine, followed by mesylation led to the mesylate (44) in essentially quantitative yield.

This new procedure eliminated the formation of the dimesylate (45) as a byproduct, and allowed for the synthesis of the mesylate (44) in large quantities and in a reproducible manner.

The next reaction involved condensation of the mesylate (44) with sodium thiol (48).

Sodium thiol (48) was obtained from ethoxymethylene-oxazolone (47)\textsuperscript{14} by treatment with 1 equiv. of sodium hydrosulfide in methanol for 3 minutes in an ice bath in 85\% yield.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{N} \\
\text{C}_6\text{H}_4\text{O} & \quad \text{S} \\
\text{(47)} & \quad \text{(48)}
\end{align*}
\]
Treatment of the mesylate (44) with sodium thiol (48) in butanone afforded oxazolidine oxazolone (49) in 50% yield after purification. This relatively low yield apparently resulted from an attack of the sodium thiol (48) on the labile oxazolidine protecting group of the mesylate. This was confirmed by exchanging the oxazolidine group for the thiazolidine group.

Chung\textsuperscript{15} had prepared thiazolidine mesylate (51) by treatment of the dioxane (42) with N-methylthiethanolamine,\textsuperscript{36} followed by mesylation of the resulting alcohol (50).
Displacement of the thiazolidine mesylate (51) with sodium thiol (48) gave thiazolidine oxazalone (52) in 88% yield.

The hydrolysis of the oxazolidine protecting group in (49) to give the corresponding aldehyde (53) in 80% yield was carried out by treatment of (49) with 50% aqueous acetic acid for 30 minutes at room temperature. This compound was also obtained from thiazolidine oxazalone (52) by treatment with 1 equiv. of mercuric chloride in aqueous tetrahydrofuran at room temperature for 30 minutes.

Attempts to convert the aldehyde oxazalone (53) to the aldehyde acid (54) were unsuccessful. The hydrolysis reaction was followed by UV spectroscopy. The thiomethylene-oxazolone (53) has a characteristic UV absorption at 360 nm.
Upon hydrolysis of (53) to the acid-amide (54), the uv maximum should shift to the absorption characteristic of a benzamide and \( \beta \)-thio-substituted enone, namely about 225 nm and 285 nm. However, when the hydrolysis was carried out in aqueous sodium hydroxide, a rapid shift of the 360 nm absorption to 330 nm was observed after which there was no further change. The 330 nm absorption is characteristic of the hydroxymethyleneoxazolone salt (55). When milder bases such as aqueous sodium bicarbonate or carbonate were used to open the oxazolone, similar results were observed.

Therefore, displacement of the thio substituent of the oxazolone by hydroxide ion must have taken place.

Because of difficulties in opening the oxazolone ring, we considered the possibility of conversion of aldehyde-oxazolone (53) into (56) which might open easily by mild bases to give our desired imine acid (27).

![Structural formulas](image)

Treatment of (53) with 1 equiv. of ammonia in methylene chloride did not give the desired product. Instead, amino-methyleneoxazolone (57) was obtained in 60% yield.
The spectral data were identical with those of an authentical sample which was prepared from ethoxymethyleneoxazolone (47) by treatment with ammonia.

Rosebery had been able to open the oxazolone ring in (52) with a catalytic amount of triethylamine in methanol to give the corresponding methyl ester (58) in quantitative yield. The ester formation was complete in less than 10 minutes at room temperature. The methyl ester (58) showed the desired uv absorption at 226 nm and 287 nm.

Since Rosebery had shown that the methyl ester (58) could be obtained in a reproducible manner, we investigated the reaction of the oxazolone (52) with other alcohols. We discovered that the oxazolone (52) reacted with primary alcohols such as benzyl alcohol and β,β,β-trichloroethanol to give the corresponding esters, but did not react with secondary or tertiary alcohols. This gave us only a limited number of esters from which to choose.
We first decided to investigate the hydrolysis of the methyl ester (59). Treatment of (58) with 50% aqueous acetic acid gave the aldehyde methyl ester (59) in 90% yield.

Attempts to hydrolyze the methyl ester from (59) under various conditions were unsuccessful.

Therefore, we prepared the imine ester (60) from (59) by treatment with ammonia. The uv absorption at 285 nm characteristic of the 8-thiosubstituted-α,β-unsaturated ester, which should disappear upon ring closure, was observed to disappear. On the other hand, a small absorption at 275 nm appeared. Probably this uv absorption was due to the formation of β-amino-α,β-unsaturated ester (61) due to partial substitution by ammonia.

Extensive efforts to hydrolyze the imine ester (60) to the imine acid (27) were made under various conditions without much success. Because of difficulties of separation and the complexity of the spectral data, we could not identify the resulting products.
Therefore, we turned our attention to another ester, namely trichloroethyl ester, that could be removed more easily under mild conditions.

Treatment of oxazolidine oxazolone (49) with $\beta,\beta,\beta$-trichloroethanol and triethylamine at room temperature gave the trichloroethyl ester (62) in quantitative yield. The aldehyde ester (63) was obtained in 95% yield by treatment of (62) with 50% aqueous acetic acid.

The aldehyde ester (63) was treated with zinc in 90% aqueous acetic acid in an ice bath for 2 hours. Longer reaction time resulted in partial hydrolysis of the acetonide group. The nmr spectrum of the crude product showed the disappearance of the trichloroethyl ester group, a singlet
for the aldehyde proton at 9.5 ppm and a broad peak for the acid proton at 9.0-9.6 ppm. Microanalysis data were not consistent with the structure of (54), probably due to contamination with zinc salts. The oxygen analogue (54a) of our aldehyde acid has been reported to decompose rapidly in less than 30 minutes on standing at room temperature\textsuperscript{41}.

Without purification, the aldehyde acid (50) was treated with ammonia in methylene chloride or anhydrous ethyl ether in an attempt to prepare the imine acid (27). Upon conversion of (54) into (27), the uv spectrum should show the disappearance of the absorption at 280 nm. However, only a slight shift of the maximum to 270 nm was observed. After acidification, the uv spectrum of the crude product showed an absorption at 280 nm.

\[
\begin{align*}
\text{(27)} & \quad \text{NH-C-Ph} \\
\text{(64)} & \quad \text{C-\(\text{OH}_{\text{CH}_2\text{CCl}_3}\)} \\
\end{align*}
\]

Since we were unable to prepare the imine acid (27) from the aldehyde acid (54), we decided to prepare the imine ester (64).
The condition used by Rosebery for the formation of the imine ester, namely saturated ammonia in dimethoxyethane at room temperature for 3 hours, appeared to result in the partial displacement of the trichloroethyl ester group by ammonia.

In order to avoid this problem, the aldehyde ester (63) was treated with 1 equiv. of ammonia in tetrahydrofuran at room temperature for 2 hours. Spectral data of the product obtained were in agreement with the structure of (64).

The imine ester (64) was treated with zinc in 90% aqueous acetic acid in an ice bath for 2 hours. The spectral data (nmr and ir) of the crude product clearly showed the disappearance of the trichloroethyl ester group. However, the nmr spectrum and t.l.c. were not clean and the mass spectrum did not give any useful information.

It is known that compounds of this type are very unstable because of the lability of the imine function and the ease with which they are decarboxylated.

The products of decomposition of the imine ester (64) were not investigated any further, but are most likely analogous to the products of decomposition obtained for the corresponding oxygen analogue by Grozinger. The pathways of decomposition are outlined on the next page.
Because of this instability, we performed the hydrolysis and the subsequent Ugi reaction without isolating the intermediate imine acid. The ir spectrum of the crude product obtained in numerous runs showed a weak carbonyl absorption at 1730 cm$^{-1}$ and the mass spectrum did not give a correct molecular ion peak and characteristic $\beta$-lactam fragmentation peaks.

In summary, the failure of this approach is probably due to decomposition of the imine acid under reaction conditions and polymerization of the imine acid during the Ugi reaction.$^{13}$

This scheme was abandoned at this point.
Chapter II

Synthetic studies towards aza analogues of cepham derivatives

In order to synthesize aza analogues of cepham derivatives, we decided to prepare the imine acid (29) from readily available oxazolidine mesylate (44) in a similar to that manner described in chapter I. Although the hydrolysis of (59) had not proceeded well, it was expected that replacement of S by NH would give a more stable system, since it would be a vinylogous carbamate rather than a vinylogous thiocarbonate.

The immediate objective was to obtain the amine (66). The first approach involved the reaction of oxazolidine mesylate (44) with an azide anion, followed by reduction of the corresponding azide (65) to the amine (66).

When the oxazolidine mesylate (44) was treated with lithium azide in methanol at reflux for 24 hours, the crude product consisted of two compounds. The major product was crystallized from petroleum ether (60-80°C) in 60% yield.
Since the oxazolidine protecting group was not stable to silica gel, we were unable to purify the minor product.

When the major product was treated with 50% aqueous acetic acid, no reaction occurred, which told us that the compound was not our desired product (65). Microanalysis data indicated that it was an isomer of (65). Its nmr spectrum showed a singlet (1H) at 5.2 ppm, a multiplet (7H) at 2.0-3.0 ppm, and two singlets at 1.37 and 1.50 ppm for the acetonide group.

There are two possible structures (68,69) for this compound. Since it is known \(^{45-46}\) that oxazolidines containing a secondary amine function exist in part as the tautomeric Schiff base, it could be assumed that oxazolidine mesylate (44) may exist to a small extent as the immonium ion (44a).

\[
\begin{align*}
(44) & \quad \rightarrow \quad [\text{structure}] \quad \rightarrow \quad (67) \\
(44a) & \quad \rightarrow \quad [\text{structure}] \quad \rightarrow \quad (68) \\
(67) & \quad \rightarrow \quad (67a) \\
(69) & \quad \rightarrow \quad (68) 
\end{align*}
\]
Reaction of the immonium ion with the azide anion might give an intermediate which may be expected to cyclize to give (69). However, the nmr spectral data of the major product did not fit the structure of (69), but (68). The product (68) was perhaps formed by attack of the tertiary amine on the mesylate, followed by ring opening by the azide anion or by attack of (67a) by the azide anion, although other reaction paths cannot be rigorously excluded.

When the oxazolidine mesylate (44) was treated with sodium azide in butanone, the crude product also consisted of two compounds. The major product was the desired oxazolidine azide (65) which had been the minor product when using lithium azide in methanol.

The crude product was treated with 50% aqueous acetic acid in an attempt to prepare the aldehyde azide (70). The nmr spectrum of the crude product indicated the presence of the aldehyde azide (70) to the extent of 70%. It was not further purified because it could not easily be separated from its byproduct.
In a second approach to prepare the amine (66), the crystalline oxazolidine phthalimide (71) was obtained in 80% yield by treatment of (44) with potassium phthalimide in dimethylformamide or dimethylsulfoxide.

To establish the structure of (71), this compound was treated with 50% aqueous acetic acid to give the aldehyde phthalimide (72). Its nmr spectrum showed a singlet (6H) at 1.4 ppm for the acetonide group, a doublet and a singlet (4H) at 4.0-4.4 ppm, a multiplet (4H) at 7.8 ppm for the phthalimide group and a singlet (1H) at 9.8 ppm for the aldehyde proton.

It was therefore concluded that the displacement of the mesylate with potassium phthalimide gave the desired product (71) without attacking of the oxazolidine protecting group by the phthalimide anion.

An attempt to obtain the amine (66) from (71) with anhydrous hydrazine in ethanol was unsuccessful due to partial cleavage of the oxazolidine protecting group.
Treatment of oxazolidine phthalamide (71) with 2 equiv. of n-propyl amine in ethanol at 50°C for 24 hours gave the corresponding amine (66) in 50% yield after separation on alumina plates.

Because of the lability of the oxazolidine protecting group, it was decided to use thiazolidine mesylate (51), which had just become available.

Displacement of the thiazolidine mesylate (51) with an azide anion gave only the desired product (73) in methanol or butanone in quantitative yield. Treatment of (51) with potassium phthalamide gave (75) in 81% yield.

\[
\begin{align*}
\text{(73)} & \quad \rightarrow \quad \text{(74)} & \quad \leftarrow \quad \text{(75)}
\end{align*}
\]

The thiazolidine azide (73) was reduced with stannous chloride to give the thiazolidine amine (74) in 70% yield. The thiazolidine amine (74) was also obtained by treatment of (75) with n-propyl amine in ethanol.
The next step involved the condensation of ethoxymethyleneoxazolone (47) with the amine (74).

Treatment of the amine (74) with (47) in ethanol gave the thiazolidine oxazolone (76) in 85% yield. Its uv spectrum showed an absorption at 354 nm, which is characteristic of a β-substituted-aminomethyleneoxazolone.

In order to obtain the benzamide acid (77), the thiazolidine oxazolone (76) was treated with sodium hydroxide in aqueous dioxane. The reaction was followed by uv spectroscopy. We could anticipate that the uv maximum at 350 nm should shift to the absorption characteristic of a benzamide and a β-aminosubstituted enone, namely about 225 nm and 280 nm.
But a shift of the 350 nm absorption to 330 nm was observed after which there was no further change. The absorption at 330 nm is characteristic of hydroxymethyleneoxazolone (55). Furthermore, when (76) was treated with methanol in the presence of triethylamine, only starting material was recovered even after prolonged heating.

We could see a significant difference between β-amino-substituted oxazolone (76) and β-thiosubstituted oxazolone (49). It presumably results from the fact that the nitrogen atom is more highly conjugated with the oxazolone ring than the sulfur atom, resulting in a lessened reactivity of the oxazolone ring toward methanol.

The next approach involved the addition of ammonia to the aldehyde oxazolone (79) to afford (80). Treatment of the thiazolidine oxazolone (76) with mercuric chloride in aqueous tetrahydrofuran at room temperature for 30 minutes gave the aldehyde oxazolone (79) in 90% yield.

When the aldehyde oxazolone (79) was treated with ammonia,
a rapid shift of 352 to 344 nm was observed after which there was no further change. No further studies were made to identify the product, but it is very likely that the product obtained is aminomethyleneoxazolone (57).

\[
\begin{align*}
\text{(81) } & \quad \text{NH}_2 \\
\text{(82) } & \quad \text{C}_4\text{H}_4\text{O} \\
\text{(83) } & \quad \text{C}_2\text{H}_4\text{N}_2
\end{align*}
\]

As an alternative route to prepare the benzamide ester (78) or the benzamide acid (77), we considered the possibility of condensation of the amine (74) with α-benzamido-β-ethoxyacrylic ester (82).

(82) was prepared from the ethoxymethyleneoxazolone (47) by treatment with methanol in the presence of triethylamine.

The feasibility of the scheme was studied with cyclohexyl amine as a model amine. When (82) was treated with cyclohexyl amine, no reaction occurred.

Since we knew that ethoxymethyleneoxazolone (47) reacted with amines at the β-position, we decided to replace the benzamide group with a more strong electron withdrawing group such as the phthalimide group.

We therefore synthesized α-phthalimide-β-methoxy acrylic ester (85) using known procedures.\(^{\text{52}}\)
Phthaloylglycine benzyl ester was formylated with benzyl formate and sodium hydride to benzyl-2-phthalimido-3-hydroxy-acrylate (84), and the methoxy acrylate (85) was prepared in quantitative yield by treatment of (84) with diazomethane.

As a preliminary study, the methoxy acrylate (85) was treated with cyclohexyl amine to afford the desired product (86) in 80% yield. Its nmr spectrum indicated the disappearance of the methoxy group and presence of the NH proton at 3.3 ppm.

Treatment of the thiazolidine amine (74) with 1 equiv. of the methoxy acrylate (85) in ethanol at room temperature overnight gave the thiazolidine ester (87) in 52% yield.
Its ir spectrum showed absorptions at 3420 cm\(^{-1}\) for the amine group, at 1795 and 1730 cm\(^{-1}\) for the carbonyl groups, and at 1650 cm\(^{-1}\) for the double bond. Furthermore, its uv spectrum showed an absorption at 282 nm; which is a characteristic absorption for an \(\beta\)-amino-substituted acrylic ester.\(^{39}\)

\[
\begin{align*}
&\text{CH=CHCOOCH}_2\text{Ph} \quad \text{R=phthalimido} \\
&\text{CH=CHCOOCH}_2\text{Ph} \\

(88) &\rightarrow (89)
\end{align*}
\]

Treatment of the thiazolidine ester (87) with mercuric chloride in aqueous tetrahydrofuran gave the aldehyde ester (88) in 90% yield. Spectral data were consistent with the structure of (88).

At this point we wanted to prepare the corresponding imine ester (89) from the aldehyde ester (88).

The aldehyde ester (88) was treated with 1 equiv. of ammonia in tetrahydrofuran at room temperature overnight. Its uv spectrum did not change even when treating with excess ammonia and its ir spectrum was almost identical with that of aldehyde ester (88). Apparently, the reaction did not go in the desired way.
Since we were unable to prepare the desired imine ester (88), and the overall project to synthesize cepham derivatives and oxacephem derivatives using the Ugi reaction were unsuccessful, we abandoned this approach.

Because of the considerable efforts spent in developing the synthesis of the mesylate (44,51), it was decided to try to convert this intermediate to a tetrahydropyrimidine of type (91), which would then be reacted with a ketene to provide a β-lactam. Synthetic work towards this objective is described in chapter III.
Chapter III

Preliminary studies towards the synthesis of the key intermediate, the tetrahydropyrimidine derivative

The first immediate objective was to obtain the tetrahydropyrimidine (91) via the diamine (90) as depicted below.

\[
\begin{align*}
\text{(44) } X &= O \\
\text{(51) } X &= S
\end{align*}
\]

In the first attempt, the protecting group of the oxazolidine mesylate (44) was hydrolyzed by the usual procedure using acetic acid. The aldehyde mesylate (92) was treated with sodium cyanide and ammonium chloride in methanol saturated with ammonia at room temperature for 5 days.

\[
\begin{align*}
\text{(92)} & \quad \text{(93)} & \quad \text{(94)}
\end{align*}
\]
The nmr spectrum of the crude product indicated it to be a mixture of (93) and (94). Attempts at purification by the formation of a hydrogen bromide salt resulted in the formation of the crystalline hydrogen bromide of (94). The filtrate was proven to contain cyanohydrin mesylate (93) by comparison with an authentic sample prepared by treatment of aldehyde mesylate (92) with sodium cyanide and ammonium chloride in methanol at room temperature for 1 hour.

It is known \(^5\) that the cyanohydrin compound can be converted into the corresponding cyanoamine by treatment with ammonia.

The cyanohydrin mesylate (93) was treated with saturated ammonia in methanol in pressure bottle at 60°C for 2 days. The reaction mixture turned to black. After usual work-up, the crude product was obtained in 30% yield. Its nmr spectrum indicated the existence of cyanohydrin mesylate to the extent of 20% and partial disappearance of the mesylate group. No pure products could be isolated.

Since the mesylate function in (93) was labile to ammonia, we decided to work with the aldehyde azide (70), which was prepared from the thiazolidine azide (73).

Treatment of the aldehyde azide (70) with sodium cyanide and ammonium chloride in methanol saturated with ammonia at room temperature for 3 days gave almost exclusively the cyanohydrin azide (95).

* With the help of Mr. T. J. Liak
Its nmr spectrum showed two singlets at 4.50 and 4.67 ppm, which is an indication of the presence of the cyanohydrin azide (95). This compound was further characterized as its acetate (96). The nmr spectrum of acetate (96) showed all protons at the expected positions and its ir spectrum showed a carbonyl absorption at 1770 cm\(^{-1}\) for the acetate group.

Treatment of cyanohydrin azide (95) with saturated ammonia in methanol in pressure at 80\(^\circ\)C for 2 days gave the cyanoamine azide (97) in 20% yield after purification. Its nmr spectrum showed a broad deuterium oxide exchangeable peak at 2.0 ppm for the amine group and a multiplet for the proton adjacent to the cyano group and the amine group at 3.7 ppm.
Its ir spectrum showed characteristic absorptions for the primary amine at 3380 and 3440 cm\(^{-1}\).

It seemed that compounds (93,95) containing the mesylate or the azide function decomposed under reaction conditions necessary to form the cyanoamine compounds (94,97).

From these experiments, it is obvious that cyanohydrin formation is more rapid than cyanoamine formation.

The mode of formation of cyanoamines from aldehydes is still not elucidated with complete certainty. The following mechanism has been proposed\(^{54-55}\).

\[ R\text{-C}=O \rightleftharpoons R\text{-C}_\text{CN} \]
\[ \text{OH} \rightleftharpoons R\text{-CH}_2\text{NH} \]
\[ \text{OH} \rightleftharpoons R\text{-C}_\text{NH}_2 \]

Since we were unable to obtain the desired cyanoamine compounds in good yield, we considered forming the imine first, and adding to it sodium cyanide.
We decided to use benzyl amine to afford cyanobenzylamine (100,102), which could be converted into the diamine (90) by hydrogenolysis.

Aldehyde mesylate (92) was treated with 1 equiv. of benzyl amine and anhydrous magnesium sulfate in methylene chloride at room temperature for 2 hours. The nmr spectrum of the crude product indicated that the carbinol amine (98) had been formed.

\[
\begin{align*}
(98) \quad R=\text{OMs} & \quad \rightarrow \quad (99) \quad R=\text{OMs} \\
(101) \quad R=\text{N}_3 & \quad \rightarrow \quad (100) \quad R=\text{OMs} \\
(102) \quad R=\text{N}_3
\end{align*}
\]

Removing the water as an azeotropic mixture in refluxing benzene for 2 hours, the desired imine (99) was obtained in essentially quantitative yield. The imine (99) showed, in its ir spectrum, the C-N absorption peak at 1680 cm\(^{-1}\) and a multiplet for the imine proton at 7.8 ppm in the nmr spectrum.

Treatment of the imine (99) with sodium cyanide and ammonium chloride gave the cyanobenzylamine mesylate (100) in 90% yield.
Its nmr spectrum showed the disappearance of the imine proton at 7.8 ppm and the presence of the NH proton at 2.1 ppm. Furthermore, the mesylate group appeared as two singlets at 3.00 and 3.04 ppm in a ratio of 2:1 due to the fact that two isomers were present in the product.

Similarly, the cyanoamine azide (102) could be prepared from the aldehyde azide (70). Spectral data were consistent with the structure of (102).

Hydrogenolysis of cyanoamine mesylate (100) using palladium on charcoal in acetic acid led to a mixture of products. Although the nmr spectrum of the crude product showed the disappearance of the benzyl group, we were unable to isolate the desired product.

Attempts to use cyanobenzylamine azide (102) were also unsuccessful.

Since we could not prepare the desired diamine (90) by using hydrogenolysis of the cyanoamine compounds (100, 102), we repeated the cyanoamine reaction in absolute ethanol instead of methanol.

Treatment of aldehyde azide (70) with sodium cyanide and ammonium chloride in absolute ethanol saturated with ammonia for 2 days at 50°C gave the cyanoamine azide (97) in 70% yield. Spectral data were identical with those of (97) which was obtained from the cyanohydrin azide (95).
Hydrogenation of cyanoamine azide (97) with palladium on charcoal in absolute ethanol at 1 atmosphere led only to complex mixtures in which there appeared to be no major product. This probably results from the instability of diamine (90) generated from the reaction mixture, or the possibility of reduction of the cyano group. We therefore decided to repeat the hydrogenation in acetic acid by using 1 equiv. of hydrogen gas. The ir spectrum of the crude product showed the disappearance of the azide peak and t.l.c. indicated that the crude product was the acetic acid salt of diamine (103). The spectral data of the diamine diacetate (103) were compatible with the structure assigned, without however conclusively proving the structure.

Since it became obvious that the total synthesis of aza analogues of cepham derivatives could not be brought to an end in a short time, the work was stopped at this point.
Contributions to knowledge

Several synthetic sequences for the synthesis of cepham derivatives and their aza analogues were investigated.

An improved procedure for the preparation of oxazolidine mesylate starting D-mannitol was developed.

The use of the oxazolidine protecting group and of the thiazolidine group, and the stability of the thiazolidine group to nucleophilic attack were demonstrated.

Ring opening reactions of 2-phenyl-4-thiomethylene-5-oxazolone and 2-phenyl-4-alkoxymethylene-5-oxazolone and 2-phenyl-4-aminomethylene-5-oxazolone were studied.

Several new compounds were prepared and characterized.
Chapter 1

Preparation of mannitol diacetonide (40)

D-mannitol (200 g) was suspended in a mixture of acetone (1.5 l) and dimethoxypropane (180 g). p-Toluenesulfonic acid monohydrate (0.6 g) was added and the suspension was stirred at room temperature for 90 minutes. Unreacted mannitol (90-100 g) was removed by filtration and the filtrate shaken with anhydrous potassium carbonate (50 g) until it was colorless. The potassium carbonate was removed by filtration and the filtrate evaporated to dryness in vacuo. The semi-solid residue was transferred to an Erlenmeyer flask containing petroleum ether (b.p. 60-80°C) (3.5 l). The mixture was then heated to boiling with vigorous stirring until almost all the solid had dissolved. The mixture was allowed to settle for 5 minutes, decanted, and allowed to crystallize at room temperature. The product was removed by filtration, washed well with cold petroleum ether and allowed to dry. Yield: 42 g (30%), m.p. 119-121°C (lit. 119°C).

Preparation of glyceraldehyde acetonide (41)

The procedure of Baer and Fischer was followed. The product was a colourless oil and distilled at 55-58°C/22 mmHg (lit. 35-42°C/8-11 mmHg).
Yield: 80%

Nmr (CDCl₃): δ 1.43, 1.49 (each s, 6H), 3.8-4.3 (m, 3H), 9.7 (s, 1H, CHO).

Ir (film): 3450 (OH), 1725 (C=O), 1260, 1220 cm⁻¹.

Preparation of dioxane (42) from (41)

The procedure of Rossy was followed using glyceraldehyde acetonide (41), formaldehyde and potassium carbonate in aqueous methanol. We found, however, this product was contaminated with an impurity.

Direct preparation of dioxane (42) from mannitol diacetonide (40)

Mannitol diacetonide (40) (24 g) was dissolved in 400 ml of pH 6 phosphate buffer solution and sodium periodate (20.4 g) was added. The reaction mixture was stirred at room temperature for 30 minutes and then followed by the addition of 75 ml of 40% formaldehyde and a solution of potassium carbonate (23 g) in 70 ml of water. The solution was stirred overnight at room temperature and extracted three times with methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to dryness in vacuo. The crystalline product was pure enough for further use.

Yield: 28.3 g (81%), m.p. 89-90°C.
Preparation of oxazolidine alcohol (43)

The dioxan (42) (25 g), prepared directly from mannitol diacetonide (40), was dissolved in 500 ml of benzene and N-methylethanolamine (20.7 g, 2.1 equiv.) was added. The reaction mixture was heated until the benzene distilled slowly. The distillate was cloudy. After 350 ml of benzene had been collected, the distillate contained no more water and the benzene was removed by evaporation under reduced pressure. The residue was distilled under high vacuum and the fraction boiling at 100-103°C/0.5 mmHg was collected. Yield: 24.9 g (86%).

Nmr (CDCl₃): δ 1.45 (s, 6H), 2.60 (s, 3H, N-CH₃), 2.5-2.9 (m, 1H), 3.2-3.6 (m, 1H), 3.7-4.4 (m, 8H).
Ir (film): 3600-3300, 2810, 1470, 1380 cm⁻¹.

Preparation of oxazolidine mesylate (44)

The oxazolidine alcohol (43) (27.6 g) was dissolved in a mixture of methylene chloride (250 ml) and triethylamine (19.4 g, 1.5 equiv.). The solution was cooled in a dry ice bath and
freshly distilled mesyl chloride (16.2 g, 1.1 equiv.) in 50 ml of methylene chloride was added dropwise over a period of 2 hours with good stirring. The reaction mixture was then poured into ice water. The methylene chloride layer was washed with water, dried over sodium sulfate, and evaporated to dryness in vacuo. The crude product was recrystallized from petroleum ether (60-80°C).

Yield: 33.7 g (90%), m.p. 83-84°C.

Nmr (CDCl₃): δ 1.45 (s,6H), 2.50 (s,3H,N-CH₃), 2.5-2.9 (m,1H), 3.00 (s,3H,OSO₂CH₃), 3.0-3.3 (m,1H), 3.6-4.4 (m,7H).

Ir (KBr): 2820, 1475, 1380 cm⁻¹.

Separation of dimesylate (45) from the crude mesylation product

After mesylation of the impure oxazolidine alcohol (43), prepared from the impure dioxane (42), the pure oxazolidine mesylate (44) was separated by recrystallization of the crude product from petroleum ether (60-80°C). The residue was then passed through an alumina column using methylene chloride and ethyl ether (1:1) as an eluant and solvents were evaporated. The resulting solid was recrystallized from petroleum ether and methylene chloride (1:1). m.p. 67-68°C.

Nmr (CDCl₃): δ 1.47 (s,6H), 3.08 (s,6H,two SO₂-CH₃), 3.98 (s,2H, OCH₂), 4.25 (s,4H,two CH₂-OSO₂).
Ir (KBr): 2950, 1495, 1470, 1395, 1385 cm\(^{-1}\).

Analysis: Calculated for C\(_9\)H\(_{18}\)O\(_8\)S\(_2\): C, 34.28; H, 5.96; S, 20.23.

Found: C, 34.11; H, 5.81; S, 20.34.

Preparation of thiazolidine alcohol (50)

This compound was prepared from dioxane (42) and N-methyl-ethanethiolamine in the same way as oxazolidine alcohol (43) from dioxane (42).

Yield: 90%, b.p. 127-130°C/0.2 mmHg.

Nmr (CDCl\(_3\)): \(\delta\) 1.45 (s, 6H), 2.50, 2.56 (each s, 3H, N-CH\(_3\)), 2.8-3.2 (m, 4H, N-CH\(_2\)CH\(_2\)-S), 3.4-3.9 (m, 5H), 4.20, 4.25 (each s, 1H, N-CH-S).

Ir (film): 3460, 2810, 1470, 1390 cm\(^{-1}\).

Preparation of thiazolidine mesylate (51)

This compound was prepared in the same way as oxazolidine mesylate (44) from (43).

Yield: 95%, m.p. 65-66°C.

Nmr (CDCl\(_3\)): \(\delta\) 1.45 (s, 6H), 2.50, 2.55 (each s, 3H, N-CH\(_3\)), 2.8-3.2 (m, 4H), 3.06 (s, 3H, SO\(_2\)-CH\(_3\)), 4.0-4.4 (m, 5H).

Ir (KBr): 2810, 1455, 1390, 1380 cm\(^{-1}\).
Preparation of 2-phenyl-4-thiomethylene-5-oxazolone sodium salt (48)

To a stirred ice cooled suspension of 2-phenyl-4-ethoxy-methylene-5-oxazolone (47) (5.0 g) in 10 ml of methanol was added sodium hydrosulfide (1.3 g, 1 equiv.). The reaction mixture turned red and the undissolved material went into solution almost immediately. The solution was stirred for 3 minutes in an ice bath and then poured into dioxan (80 ml) heated to 70°C. The clear red solution was cooled in an ice bath until precipitation of the bright yellow sodium thiol was complete. The product was removed by filtration, washed twice with ethyl ether and dried in vacuo.
Yield: 4.9 g (95%), m.p. 245-247°C (decomp.).
Nmr (D₂O): δ 7.35-8.10 (m, 5H, aromatic), 9.14 (s, 1H, C=CH).

Preparation of 4-(((2',2''-dimethyl-4''-(3''-methyloxazolidine-2''-yl)-dioxolan-4''-yl)methyl)thio)methylene)-2-phenyl-5-oxazolone (49)

To a solution of oxazolidine mesylate (44) (1.20 g) in 30 ml of butanone was added sodium thiol (48) (1.20 g, 1.3 equiv.). The reaction mixture was refluxed for 1.5 hours under a nitrogen atmosphere, allowed to cool and filtered.
The dark brown filtrate was evaporated to dryness in vacuo. The residue was taken up in 2 ml of chloroform and the solution was passed through a column of alumina (10 g, Woelm, Act.1) using chloroform and ethyl ether (1:1) as an eluant. A total of 50 ml of eluant was collected and evaporated to dryness in vacuo. The pale yellow residue was crystallized from ethyl ether. Yield: 0.82 g (50%), m.p. 127-129°C.

Nmr (CDCl₃): δ 1.4 (s,6H), 2.15 (s,3H,NC₃), 2.4-2.8 (m,1H), 3.0-4.0 (m,7H), 4.1 (s,1H,N-CH=O), 7.3-8.3 (m,6H,C=CH,aromatic).

Ir (KBr): 1780 (C=O), 1635 (C=N) cm⁻¹.

Uv (MeOH): 360 nm (logε 4.66)

Preparation of 4-(((2',2'-dimethyl-4'-((3'-methylthiazolidine-2''-yl)-dioxolan-4'-yl)methyl)thio)methylene)-2-phenyl-5-oxazolone (52)

To a solution of thiazolidine mesylate (51) (520 mg) in 20 ml of butanone was added sodium thiol (450 mg, 1.2 equiv.). The reaction mixture was refluxed for 2 hours under a nitrogen atmosphere, allowed to cool and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified through a column of silica gel using chloroform and ethyl ether (1:1) as an eluant. After purification the crude product was a pale yellow oil.
Yield: 620 mg (88%).

Nmr (CDCl$_3$): δ 1.45 (s,6H), 2.50, 2.56 (each s,3H, NCH$_3$), 3.0-3.4 (m,4H), 3.5-3.8 (m,2H), 4.0-4.3 (m,2H, O-CH$_2$), 4.5 (m,1H, N-CH-S), 7.6-8.0 (m,4H), 8.3' (m,2H).

Ir (CHCl$_3$): 1780 (C=O), 1640 (C=N) cm$^{-1}$.

Uv (MeOH): 360 nm (logε 4.65).

Mass (230°): m/e 420 (M$^+$).

Analysis: Calculated for C$_{20}$H$_{24}$O$_4$N$_2$S$_2$: C, 57.14; H, 5.71; N, 6.67; S, 15.24. Found: C, 57.20; H, 5.63; N, 6.46; S, 14.78.

Preparation of 2,2-dimethyl-4-(((5'-oxo-2'-phenyl-2'-oxazolidine-4'-ylidene)methyl)thiomethyl)-1,3-dioxolane-4-carboxaldehyde (53)

Oxazolidine oxazolone (49) (0.90 g) was dissolved in 10 ml of 50% aqueous acetic acid. The solution was allowed to stand at room temperature for 30 minutes, then diluted with 20 ml of water and extracted three times with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was crystallized from ethyl ether.

Yield: 0.61 g (80%), m.p. 80-81°C.

Nmr (CDCl$_3$): δ 1.5 (s,6H), 3.5 (s,2H$_2$CH$_2$-S), 4.2 (q, J=10 Hz, 2H, O-CH$_2$-C), 7.2-8.2 (m,6H), 9.8 (s,1H, CHO).
Ir (KBr): 1780/1740 (C=O), 1630 (C=N) cm⁻¹.

Uv (MeOH): 360 nm (logε 4.63).

Analysis: Calculated for C₁₇H₁₇O₅NS: C, 58.79; H, 4.93; N, 4.03; S, 9.23. Found: C, 59.03; H, 4.82; N, 4.23; S, 9.25.

Preparation of aldehyde oxazolone (53) from (52)

To a solution of thiazolidine oxazolone (52) (410 mg) in 20 ml of 60% aqueous tetrahydrofuran was added mercuric chloride (290 mg, 1.05 equiv.). The solution was stirred at room temperature for 30 minutes. The precipitate was filtered off and the filtrate was extracted with chloroform. The organic solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo to give the aldehyde oxazolone (290 mg) in 86% yield. Spectral data (nmr, ir and uv) and m.p. were identical with those of (53) which was prepared from (49).

Preparation of 2-phenyl-4-aminomethylene-5-oxazolone (57)

Ethoxymethyleneoxazolone (47) (350 mg) was dissolved in 10 ml of ethanol and ammonia was passed into the solution for 5 minutes. The yellow precipitate was filtered and washed with ethanol.
Yield: 240 mg (80%), m.p. 213-215°C (lit. 1213-215°C).

IR (KBr): 3420, 1730, 1680, 1620, 1590 cm\(^{-1}\).

UV (MeOH): 342 nm (log\(_e\) 4.43).

Reaction of aldehyde oxazolone (53) with ammonia

To a solution of the aldehyde oxazolone (340 mg) in 5 ml of methylene chloride was added 2.5 ml of 0.44M ammonia in methylene chloride (1.1 equiv.). The solution was allowed to stand at room temperature for 30 minutes and evaporated to dryness in vacuo. After adding 5 ml of methanol, the reaction mixture was filtered. The product was recrystallized from methanol to give (57) in 60% yield.

Spectral data (ir and uv) and m.p. were identical with those of (57), which was obtained from above reaction.

Preparation of 2-benzamido-3-(((2',2'-dimethyl-4'-3',3'-dioxolan-2'-yl)methyl)thio)acrylic acid methyl ester (58) from oxazolidine oxazolone (49)

The oxazolidine oxazolone (49) (0.50 g) was suspended in 10 ml of methanol. Triethylamine (0.2 ml) was added and the reaction mixture was allowed to stir at room temperature for 1 hour. The methanol and triethylamine were then evaporated under reduced pressure and the residue was completely dried under high vacuum.
Yield: 0.54 g (100%).

Nmr (CDCl₃): 6 1.45 (s, 6H), 2.50 (s, 3H), 2.4-2.9 (m, 1H), 3.0-
3.4 (m, 3H), 3.6-4.0 (m, 4H), 3.80 (s, 3H, COO⁻Me)
4.1 (s, 1H), 7.3-8.0 (m, 7H).

Ir (CHCl₃): 3420, 1710 (C=O), 1690 (N-C=O), 1390, 1380 cm⁻¹.

Uv (MeOH): 287 nm (log ε 4.27) and 226 nm (log ε 4.11)

Preparation of 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-
dioxolan-4'-yl)methyl)thio)acrylic acid methyl ester (59)

The oxazolidine methyl ester (58) (270 mg) was dissolved
in 10 ml of 50% aqueous acetic acid. The reaction mixture
was stirred at room temperature for 1 hour, diluted with.
20 ml of water and the mixture was extracted with chloroform.
The chloroform layer was washed with water, dried over sodium
sulfate and evaporated to dryness in vacuo to give a foam.
Yield: 210 mg (90%).

Nmr (CDCl₃): 6 1.45 (s, 6H), 3.1 (q, J=15 Hz, 2H, CH₂-S), 3.70
(s, 3H, COO⁻Me), 4.05 (q, J=10 Hz, 2H, CH₂-O),
7.2-8.0 (m, 7H, aromatic, C=CH, NH)

Ir (CHCl₃): 3310, 1735/1720 (C=O), 1670 (N-C=O) cm⁻¹.

Uv (MeOH): 287 nm (log ε 4.25) and 226 nm (log ε 4.12).
Preparation of \( \alpha \)-benzamido-2,2-dimethyl-1,3-dioxa-7-thia-9-aza(spiro) [4,5]dec-9-ene-8-acetic acid methyl ester (60) from the aldehyde methyl ester (59)

To a solution of aldehyde ester (59) (1.0 g) in 10 ml of tetrahydrofuran was added 4.0 ml of 0.60M ammonia (1.1 equiv.) in tetrahydrofuran. The solution was allowed to stand at room temperature for 2 hours and evaporated to dryness in vacuo to give a white solid in quantitative yield. m.p. 125-127°C.

Nmr (CDCl₃): δ 1.45 (s, 6H), 2.75 (q, J=10 Hz, 2H, CH₂-S), 3.80 (s, 3H, COOME), 3.8-4.4 (m, 2H, O-CH₂-C), 4.9-5.4 (m, 2H, N-C=S, CO-NH), 6.8-8.0 (m, 7H).

Ir (KBr): 3340, 1750 (C=O), 1650, 1660 cm⁻¹.

Uv (MeOH): 224 nm (logε 4.17), shoulder at 275 (logε 3.40)

Analysis: Calculated for C₁₈H₂₂N₂O₅S: C, 57.14; H, 5.82; N, 7.41; S, 8.47. Found: C, 56.90; H, 6.05; N, 7.25; S, 8.30.

Preparation of 2-benzamido-3-(((2',2'-dimethyl-4'-o-oxazolidine-2'-yl)-1',3'-dioxolan-2'-yl)methyl)thio)acrylic acid 888-trichloroethyl ester (62) from (49)

The oxazolidine oxazolone (49) (500 mg) was suspended in 5 ml of 888-trichloroethanol and triethylamine (0.2 ml) was added. The reaction mixture was stirred at room temperature for 3 hours. The excess trichloroethanol and triethyl-
amine were then removed by distillation under reduced pressure but the trace of trichloroethanol was contaminated with the product. The analytical sample was obtained by passing through a column of alumina (Woelm Act.1) using ethyl ether as an eluant.

Yield: 620 mg (90%).

Nmr (CDCl₃): δ 1.40 (s, 6H), 2.43 (s, 3H, NCH₃), 2.5-2.9 (m, 1H), 3.0-3.4 (m, 3H), 3.5-4.3 (m, 5H), 4.8 (b.s, 2H, OCH₂CCl₃), 7.2-8.0 (m, 7H).

Ir (CHCl₃): 3320, 2810, 1730 (≈'O), 1670 (N-C=O)

Mass (200°): m/e 552 (M⁺)

Uv (EtOH): 289 (log ε 4.18) and 228 nm (log ε 4.25)

Analysis: Calculated for C₂₂H₂₇N₂O₆SCl₃: C, 47.73; H, 4.88; N, 5.06; S, 5.78; Cl, 19.17. Found: C, 48.06; H, 5.13; N, 5.35; S, 5.97; Cl, 19.21.

Preparation of 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)thio)acrylic acid βββ-trichloroethyl ester (63) from (62)

The oxazolidine trichloroethyl ester (62) (280 mg) was dissolved in 10 ml of 50% aqueous acetic acid. The solution was stirred at room temperature for 30 minutes, diluted with 30 ml of water and extracted three times with methylene chloride. The methylene chloride solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo.
Yield: 238 mg (95%).

Nmr (CDCl$_3$): $\delta$ 1.5 (6H), 3.3 (q, $J$=13 Hz, 2H, $CH_2$-S), 4.2 (q, $J$=10 Hz, 2H, $C-O-CH_2$), 4.95 (s, 2H, $CH_2CCl_3$), 7.4-8.1 (m, 7H), 9.95 (s, 1H, CHO).

Ir (CHCl$_3$): 3340, 1750/1740 (C=O), 1680 (N-C=O), 1610 cm$^{-1}$.

Uv (MeOH): 289 (log$\varepsilon$ 4.19) and 228 nm (log$\varepsilon$ 4.20).

Mass (290°): m/e 495 (M$^+$).

Analysis: Calculated for C$_{19}$H$_{20}$O$_6$NSCl$_3$: C, 46.00; H, 4.03; N, 2.82; S, 6.45; Cl, 21.47. Found: C, 45.69; H, 4.27; N, 3.02; S, 6.48; Cl, 21.79.

Preparation of 2-benzamido-3-(((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)thio)acrylic acid (54) from (63)

To a solution of the aldehyde ester (63) (750 mg) in 10 ml of 90% aqueous acetic acid was added zinc (200 mg). The reaction mixture was stirred in an ice bath for 2 hours and filtered. The filtrate was extracted with ethyl acetate. The ethyl acetate solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo to give a foam.

Yield: 440 mg (80%).

Nmr (CDCl$_3$): $\delta$ 1.50 (s, 6H), 3.26 (q, $J$=13 Hz, 2H, $CH_2$-S), 4.20 (q, $J$=10 Hz, 2H, $CH_2$-O), 7.4-8.2 (m, 7H), 9.5 (s, 1H, CHO), 9.0-9.6 (b, 1H, COOH).

Ir (CHCl$_3$): 3400, 2500-2900, 1720, 1680 cm$^{-1}$.
Preparation of α-benzamido-2,2-dimethyl-1,3-dioxa-7-thia-9-aza(spiro)[4,5]dec-9-ene-8-acetic acid βββ-trichloroethyl ester (64) from (63)

To a solution of the aldehyde ester (63) (114 mg) in 5 ml of tetrahydrofuran was added 6.2 ml of 0.107 M ammonia (1.1 equiv.) in tetrahydrofuran. The solution was allowed to stand at room temperature for 2 hours and evaporated to dryness in vacuo to give a foam in quantitative yield.

Nmr (CDCl₃): δ 1.45 (s, 6H), 2.6-3.0 (b, 2H, CH₂-S), 3.8-4.4 (m, 2H, CH₂-O), 4.80 (s, 2H, CH₂CCl₃), 4.8-5.2 (m, 2H), 7.2-8.0 (m, 7H).

Irr (CHCl₃): 3420, 1770 (C=O), 1670 (N-C=O), 1620, 1610 cm⁻¹.

Mass (220°): m/e 494 (M⁺).

Analysis: Calculated for C₁₉H₂₁N₂O₅SCl₃: C, 46.06; H, 4.24; N, 5.65; S, 6.46; Cl, 21.41. Found: C, 45.80; H, 4.43; N, 5.39; S, 6.26; Cl, 21.69.
Preparation of 4-methyl-6-(2',2'-dimethyl-1',3'-dioxolan)-7-triazo-perhydro-1,4-oxazepine (68)

The oxazolidine mesylate (44) (602 mg) was dissolved in 30 ml of 0.9M methanolic lithium azide solution. The solution was refluxed for 24 hours and evaporated under reduced pressure. The residue was taken up in 30 ml of ethyl ether and 20 ml of water. The ethyl ether solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was recrystallized from petroleum ether (60-80°C).

Yield: 300 mg (60%), m.p. 48-49°C.

Nmr (CDCl₃): δ 1.37 (s,3H), 1.50 (s,3H), 2.47 (s,3H,N-CH₃), 2.5-3.0 (m,4H), 3.7-4.4 (m,4H), 5.20 (s,1H).

Ir (KBr): 2120 (N₃), 1480, 1390, 1325 cm⁻¹.

Mass (125°): m/e 242 (M⁺).

Analysis: Calculated for C₁₀H₁₈N₄O₃: C, 49.59; H, 7.45; N, 23.13. Found: C, 49.85; H, 7.56; N, 22.94.

Reaction of oxazolidine mesylate (44) with sodium azide in butanone

To a solution of oxazolidine mesylate (210 mg) in 20 ml of
butanone was added sodium azide (190 mg, 4 equiv.).
The reaction mixture was refluxed for 24 hours, was allowed
to cool and filtered. The filtrate was evaporated under
reduced pressure and the residue was taken up in 20 ml of
chloroform. The chloroform solution was washed with water,
dried over sodium sulfate and evaporated to give the crude
product (154 mg) in 90% yield as an oil.

\[ \text{Nmr (CDCl}_3) : 6 \quad 1.37 \ (s, 3H), \ 1.47 \ (s, 3H), \ 2.3-2.8 \ (m, 4H), \]
\[ 3.0-3.4 \ (m, 2H), \ 3.5-4.2 \ (m, 6H), \ 5.2 \ (s, 0.2H). \]

Preparation of oxazolidine phthalimide (71)

To a solution of oxazolidine mesylate (44) (256 mg) in
15 ml of dimethylformamide was added potassium phthalimide
(320 mg). The reaction mixture was gently heated at 60-70°C
for 2 days. After the addition of 40 ml of chloroform to
the reaction mixture, the resulting mixture was poured into
100 ml of water. The chloroform layer was washed with 1N
sodium hydroxide, with water, dried over sodium sulfate and
evaporated to dryness in vacuo. The crude product was
recrystallized from petroleum ether (60-80°C).

Yield: 240 mg (80%), m.p. 102-103°C.

\[ \text{Nmr (CDCl}_3) : 6 \quad 1.1-1.6 \ (m, 6H), \ 2.60 \ (s, 3H, N-CH}_3), \ 2.4-2.7 \ (m, 1H), \]
\[ 3.1-3.5 \ (m, 1H), \ 3.6-4.4 \ (m, 7H), \ 7.6-8.0 \ (m, 4H, phthalimide). \]
Ir (KBr): 2900, 1780/1735 (C=O), 1470, 1420, 1390 cm⁻¹.
Mass (110°): m/e 346° (M⁺).

**Preparation of aldehyde phthalimide (72)**

The oxazolidine phthalimide (71) (130 mg) was dissolved in 10 ml of 50% aqueous acetic acid. The solution was stirred at room temperature for 30 minutes and followed by the addition of 10 ml of water. The resulting solution was extracted with methylene chloride. Drying over sodium sulfate and evaporation to dryness in vacuo gave the aldehyde phthalimide (72) (94 mg) in 87% yield as an oil.

Nmr (CDCl₃): 1.43 (s, 6H), 4.03 (d, J=2 Hz, 2H), 4.20 (s, 2H), 7.6-8.1 (m, 4H), 9.83 (s, 1H, CHO).

Ir (CHCl₃): 2900, 1780/1735 (C=O), 1470, 1390, 1380 cm⁻¹.

**Preparation of oxazolidine amine (66) from (71)**

To a solution of oxazolidine phthalimide (71) (260 mg) in 10 ml of absolute ethanol was added n-propyl amine (97 mg, 2.2 equiv). The solution was gently heated at 50-60°C for 24 hours, evaporated under reduced pressure, followed by the addition of 10 ml of petroleum ether (60-80°C) and filtered. The amine was separated on alumina plates using ethyl acetate as an eluant (Rₚ=0.3).
Preparation of thiazolidine azide (73) from (51)

To a solution of thiazolidine mesylate (160 mg) in 10 ml of butanone was added sodium azide (150 mg, 4 equiv.). The reaction mixture was refluxed for 24 hours, allowed to cool and filtered. The filtrate was evaporated under reduced pressure and the residue was taken up in 20 ml of chloroform. The solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give the thiazolidine azide (110 mg) in 83% yield as an oil.

\[
\text{Nmr (CDCl}_3\text{): } \delta 1.50 \text{ (s, 6H), 2.4-2.7 \text{ (m, 3H), 2.8-3.1 \text{ (m, 4H, N-CH}_2\text{-CH}_2\text{-S), 3.60 (d, } J=2 \text{ Hz, 2H, CH}_2\text{-N}_3\text{), 3.8-4.3 \text{ (m, 2H, O-CH}_2\text{-C), 4.41 (q, } J=8 \text{ Hz, 1H, N-CH-S).}}
\]

\[
\text{Ir (film): 2940, 2900, 2820, 2120 (N}_3\text{), 1470, 1395, 1380 cm}^{-1}.
\]

Preparation of thiazolidine phthalimide (75) from (51)

This compound was prepared from (51) in the same way as (71) from (44).
Yield: 81%, m.p. 110-112°C.

Nmr (CDCl₃): 6 1.30 (d, 3H), 1.60 (d, 3H), 1.80 (d, 3H, N-CH₃), 3.0-3.6 (m, 4H, N-CH₂-CH₂-S), 4.0-4.9 (m, 5H, O-CH₂-C, CH₂-NC=O, N-CH-S), 7.6-8.1 (m, 4H, phthalamide).

Irr (KBr): 1780/1740 (C=O) cm⁻¹.

Mass (180°): m/e 362 (M⁺).

Analysis: Calculated for C₁₈H₂₂N₂O₄S: C, 59.67; H, 6.08; N, 7.73; S, 8.84. Found: C, 59.79; H, 5.88; N, 7.88; S, 8.89.

Preparation of thiazolidine amine (74) from (73)

To a solution of the thiazolidine azide (73) (140 mg) in 2 ml of ethanol in an ice bath was added a solution of stannous chloride dihydrate (130 mg) in 2 ml of 3N sodium hydroxide. The reaction mixture was stirred in an ice bath 15 minutes, diluted with 5 ml of water and then extracted three times with methylene chloride. The methylene chloride layer was washed with water, with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. Yield: 88 mg (70%).

Nmr (CDCl₃): 6 1.50 (s, 6H), 1.8-2.1 (b, 2H, NH₂), 2.50 (d, 3H, N-CH₃), 2.8-3.4 (m, 6H, N-CH₂-CH₂-S, CH₂-N), 3.9 (b.s, 2H, O-CH₂-C), 4.4 (s, 1H, N-CH-S).

Mass (170°): m/e 232 (M⁺).
Preparation of thiazolidine amine (74) from (75)

This compound was prepared from (75) in the same way as oxazolidine amine (66) from oxazolidine phthalimide (71). The product was separated through a column of silica gel using ethyl acetate as an eluant. The amine was obtained in 80% yield. The nmr spectral data were identical with those of (74) which was obtained from (73).

Preparation of 4-(((2',2'-dimethyl-4'-(3''-methylthiazolidine-2''-yl)-dioxolan-4'-yl)methyl)amino)methylene)-2-phenyl-5-oxazolone (76)

To a solution of thiazolidine amine (74) (130 mg) in 10 ml of ethanol was added ethoxymethyleneoxazolone (47) (120 mg, 1 equiv.). The solution was gently heated at 60°C for 5 minutes and then evaporated to dryness in vacuo to give the thiazolidine oxazolone (76) in 85% yield as an oil after passing through a silica gel column using ethyl acetate.

Nmr (CDCl₃): δ 1.57 (s,6H), 2.67, 2.73 (each s,3H,N-CH₃), 3.0-3.6 (m,5H,N-CH₂-CH₂-S, NH), 3.8-4.1 (m,2H,CH₂-NH-C=C), 4.1-4.4 (m,2H,O-CH₂-C), 4.5-4.7 (m,1H,N-CH-S), 7.2-8.2 (m,6H).

Irr (CHCl₃): 3420 (NH), 2880, 2820, 1740 (C=O), 1670, 1620 cm⁻¹.

Uv (EtOH): 354 nm (log ε 4.28).
Preparation of 2,2-dimethyl-4-(((5'-oxo-2'-phenyl-2'-oxazolidine-4'-ylidene)methyl)(amino)methyl)-1,3-dioxolane-4-carboxaldehyde (79) from (76)

To a solution of thiazolidine oxazolone (76) (400 mg) in 10 ml of 60% aqueous tetrahydrofuran was slowly added mercuric chloride (280 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was extracted three times with ethyl ether and the organic solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was purified by passing through a column of silica gel using ethyl ether as an eluant.

Yield: 303 mg (90%).

Nmr (CDCl$_3$): 6 1.57 (s, 6H), 3.4-4.6 (m, 5H, NH, O-CH$_2$-C, CH$_2$-N), 7.2-8.2 (m, 6H, aromatic, C=CH), 9.67 (s, 1H, CHO).

Ir (CHCl$_3$): 2920, 1750 (C=O), 1680, 1620 cm$^{-1}$.

Uv (EtOH): 354 nm ($\log \varepsilon$ 4.30).

Mass (230°): m/e 330 (M$^+$).

Preparation of benzyl-2-phthalimido-3-hydroxyacrylate (84)

The procedure of Sheehan and Johnson$^{52}$ was followed, and the pale yellow solid was recrystallized from ethanol and water (1:1).
Yield: 42%, m.p. 149-150°C (lit. 153-154°C).

Nmr (DMSO-d$_6$): 5.1 (s,2H,CH$_2$), 7.23 (s,5H,phenyl), 7.8-8.2 (m,5H,phthalimide,C=CH), 11.6 (b,1H,OH).

Ir (KBr): 3500-3100, 1800/1740/1730 (C=O), 1680 cm$^{-1}$.

Preparation of benzyl-2-phthalimido-3-methoxyacrylate (85)

Diazomethane in ether (about 0.4M solution) was added dropwise to a stirred solution of hydroxyacrylate (84) (420 mg) in 20 ml of anhydrous ethyl ether, until a faint yellow color persisted. The excess of diazomethane was destroyed by the addition of a few drops of acetic acid. The ether solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give the methoxy acrylate (85) as an oil in essentially quantitative yield.

Nmr (CDCl$_3$): 4.0 (s,3H,OCH$_3$), 5.4 (s,2H,CH$_2$), 7.5 (s,5H,phenyl), 7.8-8.2 (m,5H).

Ir (CHCl$_3$): 1800/1730 (C=O), 1680 cm$^{-1}$.

Preparation of benzyl-2-phthalimido-3-cyclohexylaminoacrylate (86)

To a solution of the methoxy acrylate (85) (240 mg) in 10 ml of absolute ethanol was added cyclohexyl amine (80 mg, 1.1 equiv.). The solution was gently heated at 60°C for 30 minutes and evaporated to near dryness under reduced pressure. The residue was purified by passing through a column of silica gel using ethyl acetate as an eluant.
Yield: 230 mg (80%).

Nmr (CDCl$_3$): $\delta$ 1.0-2.3 (b, 11H, cyclohexyl), 3.3 (b, 1H, NH), 5.4 (s, 2H, CH$_2$), 7.6 (s, 5H, phenyl), 7.8-8.4 (m, 5H).

Ir (CHCl$_3$): 3420 (NH), 1800/1735 (C=O), 1660 cm$^{-1}$.

Preparation of benzyl 2-phthalimido-3-((2',2'-dimethyl-4'-(3'-methylthiazolidine-2''-yl)-1',3'-dioxolan-4''-yl)methyl) amino)acrylate (87).

The thiazolidine amine (74) (228 mg) and the methoxy acrylate (85) (322 mg, 1 equiv.) were dissolved in 20 ml of ethanol. The solution was stirred at room temperature overnight and then evaporated to dryness in vacuo. The residue was chromatographed on silica gel plates using ethyl ether as an eluant ($R_f = 0.5$).

Yield: 274 mg (52%).

Nmr (CDCl$_3$): $\delta$ 1.40 (s, 6H), 2.32, 2.37 (each s, 3H, N-CH$_3$), 2.6-3.0 (m, 4H, N-CH$_2$-CH$_2$-S), 3.4-4.0 (m, 5H, O-CH$_2$-C, C-CH$_2$-NH-C), 4.2 (b, s, 1H), 5.2 (s, 2H, CH$_2$C$_6$H$_5$), 7.3 (s, 5H, phenyl), 7.6-8.0 (m, 5H, phthalimide, C=CH)

Ir (CHCl$_3$): 3420 (NH), 2850, 1795/1730/1720 (C=O), 1650 cm$^{-1}$.

Uv. (EtOH): 221 nm (log$\epsilon$ 4.13) and 282 nm (log$\epsilon$ 4.09).

Mass (220°): m/e 537 (M$^+$).
Preparation of benzyl 2-phthalimido-3-((4'-formyl-2',2'-dimethyl-1',3'-dioxolan-4'-yl)methyl)amino)acrylate (88)

To a solution of thiazolidine benzyl ester (87) (160 mg) in 10 ml of 80% aqueous tetrahydrofuran was added mercuric chloride (105 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 1 hour, filtered and evaporated under reduced pressure. After adding 10 ml of water, the reaction mixture was extracted three times with ethyl ether. The ether solution was dried over sodium sulfate and evaporated to dryness in vacuo. The product was purified by passing through a column of silica gel using ethyl acetate as an eluant. Yield: 125 mg (90%).

Nmr (CDCl₃): δ 1.4 (d, 6H), 3.2-3.8 (b, 3H, C-CH₃-NH-C), 3.9-4.1 (m, 2H, O-CH₂-C), 5.1 (s, 2H, CH₂C₆H₅), 7.2 (d, 5H), 7.6-8.0 (m, 5H, phthalimide, C=CH), 9.7 (d, 1H, CHO).

Ir (CHCl₃): 3250-3450, 1790/1730/1720 (C=O), 1660, 1650 cm⁻¹.

Uv (EtOH): λ 221 nm (log ε 4.15) and 282 nm (log ε 4.13).

Mass (280°): m/e 464 (M⁺).
Preparation of aldehyde mesylate (92)

The oxazolidine mesylate (44) (1.20 g) was dissolved in 10 ml of 50% aqueous acetic acid. The solution was stirred at room temperature for 30 minutes, then diluted with 10 ml of water and extracted three times with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give the aldehyde mesylate in 80% yield as an oil.

Nmr (CDCl₃): δ 1.40, 1.50 (each s, 6H), 3.09 (s, 3H, SO₂CH₃), 4.07 (q, J=8 Hz, 2H, O-CH₂-C), 4.36 (s, 2H, CH₂-OSO₂), 9.60 (s, 1H, CHO).

Ir (film): 1725 (C=O), 1450, 1390, 1380 cm⁻¹.

Preparation of a mixture of cyanoamine mesylate (94) and cyanohydrin mesylate (93) from aldehyde mesylate (92)

To a solution of aldehyde mesylate (480 mg) in 30 ml of absolute methanol saturated with ammonia were added sodium cyanide (120 mg, 1.2 equiv.) and ammonium chloride (160 mg, 1.5 equiv.). The flask was then well stoppered and allowed to stand at room temperature for 5 days. The resulting brown solution was evaporated under reduced pressure. The residue
was taken up in 20 ml of ethyl acetate and 10 ml of water. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate solutions were washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was dissolved in 10 ml of anhydrous ethyl ether. Hydrogen bromide gas was passed into the ether solution in a dry ice bath and the precipitate was filtered. The precipitate was suspended in 10 ml of chloroform and the saturated bicarbonate solution added to a stirred solution. The chloroform layer was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to afford the cyanoamine mesylate (94) (160 mg) in 30% yield. The filtrate was washed with saturated bicarbonate solution, washed with water, dried over sodium sulfate and evaporated to afford the cyanohydrin mesylate (93) (240 mg) in 45% yield.

Cyanoamine mesylate (94):

Nmr (CDCl₃): δ 1.50 (s, 6H), 1.7-2.1 (b, 2H, NH₂), 3.06 (s, 3H, SO₂CH₃), 3.7-4.4 (m, 5H).

Ir (film): 3420/3360 (NH₂), 2260 (CN) cm⁻¹.

Mass (120°): m/e 264 (M⁺).

Cyanohydrin mesylate (93):

Nmr (CDCl₃): δ 1.43, 1.54 (each s, 6H), 3.10 (s, 3H, SO₂CH₃), 4.2 (b.s, 1H, OH), 3.9-4.4 (m, 4H, two O-CH₂), 4.50, 4.63 (each s, 1H, CN-CH-OH).

Ir (film): 3600-3200 (OH), 2280 (CN) cm⁻¹.
Preparation of cyanohydrin mesylate (93) from (92)

To a solution of aldehyde mesylate (120 mg) in 10 ml of methanol were added sodium cyanide (50 mg, 2 equiv.) and ammonium chloride (80 mg, 3 equiv.). The solution was stirred at room temperature for 1 hour and evaporated under reduced pressure. The residue was taken up in 20 ml of ethyl acetate and 10 ml of water. The ethyl acetate solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo to give the cyanohydrin mesylate in quantitative yield. Spectral data (nmr and ir) were identical with those of (93) which was prepared from above reaction.

Preparation of aldehyde azide (70) from (73)

To a solution of thiazolidine azide (73) (240 mg) in 10 ml of 60% aqueous tetrahydrofuran was slowly added mercuric chloride (290 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 30 minutes and filtered. The filtrate was extracted with chloroform and the organic solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. The product was purified by passing through a column of silica gel using chloroform as an eluant.
Yield: 112 mg (65%).

Nmr (CDCl₃): δ 1.50, 1.57 (each s, 6H), 3.2-3.6 (m, 2H, CH₂N₃), 4.00 (q, J=10 Hz, 2H, CH₂-O), 9.57 (s, 1H, CHO).

Ir (CHCl₃): 2150 (N₃), 1730 (C=O) cm⁻¹.

Preparation of cyanohydrin azide (95) from (70)

To a solution of aldehyde azide (610 mg) in 40 ml of absolute methanol saturated with ammonia were added sodium cyanide (200 mg, 1.2 equiv.) and ammonium chloride (230 mg, 1.3 equiv.). The flask was then well stoppered and allowed to stand at room temperature for 3 days. The resulting solution was evaporated under reduced pressure. The residue was taken up in 20 ml of chloroform and 10 ml of water. The chloroform solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. Yield: 560 mg (80%).

Nmr (CDCl₃): δ 1.50 (s, 6H), 3.4-3.9 (m, 3H, OH, CH₂N₃), 3.9-4.2 (m, 2H, CH₂-O), 4.50, 4.67 (each s, 1H, CN-CH-OH).

Ir (film): 3600-3200 (OH), 2150 (N₃) cm⁻¹.

Preparation of its acetate (96) from (95)

To a solution of cyanohydrin azide (95) (100 mg) and triethylamine (80 mg, 1.5 equiv.) in 5 ml of dry methylene chloride was added acetyl chloride (51 mg, 1.2 equiv.) in
3 ml of dry methylene chloride in a dry ice bath. The reaction mixture was stirred for 1 hour, washed with water, dried over sodium sulfate and evaporated to give the acetate as an oil in essentially quantitative yield.

Nmr (CDCl$_3$): $\delta$ 1.50 (s,6H), 2.10 (s,3H,COCH$_3$), 3.6-3.8 (m,2H,CH$_2$N), 3.9-4.2 (m,2H,CH$_2$-O), 5.40, 5.56 (each s,1H,CN-CH-OCO).

IR (CHCl$_3$): 2140 (N$_3$), 1770 (C=O), 1470 cm$^{-1}$.

Preparation of cyanoamine azide (97) from (95)

Ammonia was passed into the solution of cyanohydrin azide (75) (340 mg) in 20 ml of methanol in pressure bottle for 10 minutes. The bottle was then well stoppered and allowed to keep at 80°C for 2 days. The resulting black solution was evaporated under reduced pressure. The solution was filtered through celite and then separated the chloroform layer. The chloroform solution was washed with saturated salt solution, dried over sodium sulfate and evaporated to dryness in vacuo. The product was purified by passing through a column of silica gel using ethyl acetate as an eluant. After purification, the product was obtained in 20% yield as an oil.

Nmr (CDCl$_3$): $\delta$ 1.50 (s,6H), 1.8-2.4 (b,2H,NH$_2$), 3.4-3.6 (m,2H,CH$_2$N$_3$), 3.7 (m,1H,CN-CH-NH$_2$), 3.9-4.2 (m,2H,CH$_2$-O).
**Preparation of cyanoamine azide (97) from aldehyde azide (70)**

To a solution of aldehyde azide (930 mg) in 50 ml of absolute ethanol saturated with ammonia in pressure bottle were added sodium cyanide (295 mg, 1.2 equiv.) and ammonium chloride (345 mg, 1.3 equiv.). The bottle was then well stoppered and allowed to keep at 50°C for 2 days. After usual work-up, the product was obtained in 70% yield as an oil. Spectral data (nmr and ir) were identical with those of (97) which was prepared from (95).

**Preparation of benzylamino alcohol (98) from (92)**

To a solution of aldehyde mesylate (92) (150 mg) in 10 ml of dry methylene chloride were added benzyl amine (75 mg, 1.1 equiv.) and anhydrous magnesium sulfate (300 mg). The reaction mixture was stirred at room temperature for 2 hours. The mixture was filtered and the filtrate was evaporated to give the amino alcohol as an oil in quantitative yield. Spectral data (nmr and ir) were as follows:

**Nmr (CDCl₃):**
- 1.40 (s, 6H)
- 2.3-2.6 (b.s, 2H, NH, OH)
- 2.95 (s, 3H, SO₂CH₃)
- 3.6-4.6 (m, 7H)
- 7.20 (s, 5H, phenyl)

**Ir (CHCl₃):**
- 3600/3200-3400 (OH, NH)
- 1470, 1380 cm⁻¹.
Preparation of benzylimine mesylate (99) from (98)

The amino alcohol (98) obtained from above reaction was dissolved in 30 ml of dry benzene. The water was removed as an azeotropic mixture at reflux for 2 hours and the benzene was evaporated to dryness in vacuo. The product was obtained as an oil in essentially quantitative yield.

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\text{Nmr (CDCl}_3\text{): }\delta 1.42, 1.53 \text{ (each s,6H), } 2.90 \text{ (s,3H,SO}_2\text{CH}_3),
\]
\[
3.9-4.2 \text{ (m,2H,O-CH}_2\text{-C), } 4.35 \text{ (s,2H,CH}_2\text{-SO}_2),
\]
\[
4.6 \text{ (b.s,2H,CH}_2\text{C}_6\text{H}_5), \ 7.20 \text{ (s,5H,phenyl),}
\]
\[
7.7 \text{ (m,1H,CH=NH).}
\]

\[
\text{Ir (CHCl}_3\text{): } 3300-3500, 1640 (\text{C=NH}) \text{ cm}^{-1}.
\]

Preparation of cyanobenzylamine mesylate (100) from (99)

To a solution of imine (99) (210 mg) in 20 ml of absolute methanol were added sodium cyanide (70 mg, 2 equiv.) and ammonium chloride (120 mg, 3 equiv.). The solution was stirred at room temperature overnight and evaporated to near dryness under reduced pressure. The residue was taken up in 20 ml of chloroform and 10 ml of water. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was purified on silica gel plates using ethyl acetate as an eluant.
Yield: 200 mg (90%).

Nmr (CDCl₃): δ 1.50 (s, 6H), 1.8-2.2 (b, 1H, NH), 3.00, 3.04 (each s, 3H, SO₂CH₃), 3.6-4.6 (m, 7H), 7.25 (s, 5H).

Ir (CHCl₃): 3340 (NH), 1410, 1380 cm⁻¹.

Mass (130°): m/e 364 (M⁺).

Preparation of benzylimine azide (101) from (70)

To a solution of aldehyde azide (70) (200 mg) in 20 ml of dry methylene chloride was added benzyl amine (120 mg, 1.1 equiv.). The solution was stirred at room temperature for 2 hours and evaporated to near dryness under reduced pressure. The residue was taken up in 30 ml of dry benzene. The water was removed as an azeotropically mixture at reflux for 2 hours and the solution was evaporated to dryness in vacuo. The crude product was obtained as an oil in quantitative yield.

Nmr (CDCl₃): δ 1.44, 1.52 (each s, 6H), 3.3-3.6 (m, 2H, CH₂N₃), 3.8-4.2 (m, 2H, O-CH₂), 4.5 (b, s, 2H, CH₂C₆H₅), 7.2 (s, 5H), 7.6 (m, 1H, CH=N).

Preparation of cyanobenzylamine azide (102) from (101)

To a solution of imine (101) (270 mg) in 20 ml of absolute methanol were added sodium cyanide (100 mg, 2 equiv.) and ammonium chloride (160 mg, 3 equiv.). The solution was stirred at room temperature overnight and evaporated to near
dryness. The residue was taken up in 20 ml of chloroform and 10 ml of water. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness in vacuo. The crude product was purified on silica gel plates using ethyl acetate as an eluant.

Yield: 252 mg (85%).

Nmr (CDCl₃): δ 1.40 (s,6H), 1.8-2.1 (b,1H,NH), 3.3-3.5 (m,2H, CH₂N₃), 3.6-4.2 (m,5H), 7.2 (s,5H).

Ir (CHCl₃): 3440 (NH), 2120 (N₃), 1470, 1390, 1380 cm⁻¹.

Mass (100°): m/e 301 (M⁺).

Hydrogenation of cyanobine azide (97)

The cyanobine azide (97) (100 mg) was dissolved in 10 ml of acetic acid and 5% palladium on charcoal (10 mg) was added. Hydrogen gas (11.0 ml, 1 equiv.) was passed into the reaction mixture at 1 atmosphere for 2 hours. The reaction mixture was filtered and the filtrate evaporated to dryness in vacuo. The crude product was obtained in quantitative yield as a pale brown oil.

Nmr (CD₃OD): δ 1.27, 1.33 (each s,6H), 1.83 (s,4H), 3.2-4.4 (m,5H).

Ir (film): 3160, 2400-2900, 1700, 1540, 1390, 1380 cm⁻¹.
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