SYNTHESIS OF D,L-2'-EPI-SHOWDOMYCIN AND -PYRAZOFURIN A AND OF D,L-2'-DEOXYSHOWDOMYCIN

A THESIS

BY

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Synthesis of D,L-2'-Epi-Showdomycin and -Pyrazofurin A and of D,L-2'-Deoxyshowdomycin

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Abstract

Unambiguous syntheses of 5-carbomethoxy-2-exo-3-endo-di-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene and 5-carbomethoxy-2-exo-3-endo-di-methoxymethyloxy-7-oxabicyclo [2.2.1] hept-5-ene, useful intermediates for the preparation of C-nucleosides, were devised. These intermediates were converted to α-keto esters, from which D,L-arabino epimers of showdomycin and pyrazofurin A were synthesized.

2-Exo-acetoxy-5-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene was also transformed to the corresponding keto ester, which was converted to D,L-2'-deoxyshowdomycin. Important intermediates for the synthesis of C-nucleosides were prepared.

Synthèse de la D,L-2'-épi-Showdomycine et -Pyrazofurin A et de la D,L-2'-Déoxyshowdomycine

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Résumé

La synthèse de la 5-carbométhoxy-2-exo-3-endo-di-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] heptène-5 et de la 5-carbométhoxy-2-exo-3-endo-di-méthoxyméthyloxy-7-oxabicyclo [2.2.1] heptène-5, des intermédiaires importants dans la préparation de C-nucléosides, a été réalizée. Ces intermédiaires ont été transformés en α-céto esters, a pratir des quelles les épimères D,L-arabino de la showdomycine et de la pyrazofurine A furent synthetisés.

La 2-exo-acétoxy-5-carbométhoxy-7-oxabicyclo [2.2.1] heptène-5 aussi été transformée en céto-ester, qui ensuite fut converti en 2'-déoxyshowdomycine. De nombreux intermédiaires importants pour la synthèse de C-nucléosides ont été préparés.

To my mother and sisters

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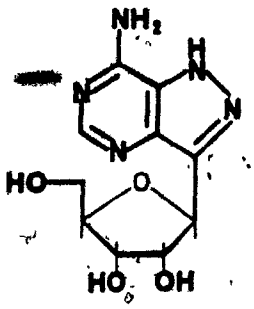
Introduction

During the past decade, a great number of nucleoside components of the nucleic acids have been isolated. The utility of analogues of the naturally occurring nucleic acids components as biochemical tools and as therapeutic agents justifies expansion of the term "nucleoside" from its original definition which was concerned with the carbohydrate derivatives of purines and pyrimidines obtained by hydrolysis of the nucleic acids. The term "nucleoside" includes all those compounds of synthetic or natural origin which contain a heterocyclic base linked, through nitrogen (N-nucleoside) or carbon (C-nucleoside), to the C-1 position of a sugar. A number of important recent reviews on the subject are available.[1,2,3]

A relatively new group of naturally occurring nucleosides exhibiting important biological activities has been isolated recently. They are the C-nucleoside antibiotics, formycin (1), formycin B (2), showdomycin (3), pyrazofurin A (pyrazomycin A) (4), and oxoformycin B (5). Also belonging to this class of compounds is the most recently isolated oxazinomycin (6), a close analogue of pseudouridine (7). All, except pseudouridine and oxoformycin B, possess a variety of antibiotic properties and many exhibit anticancer and antiviral activities. These biological properties, together with their unique structural feature, a C-C linkage between the heterocycle and the sugar

have elicited many efforts directed toward the synthesis of such compounds or analogues thereof. Their biological, biochemical properties and chemical syntheses will be discussed.



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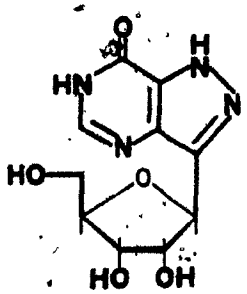

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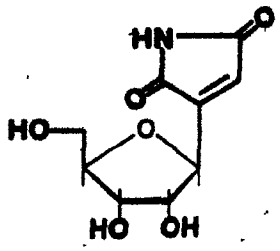

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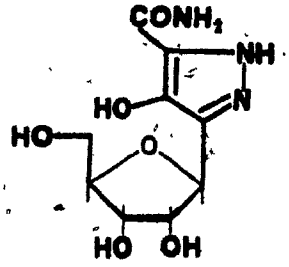

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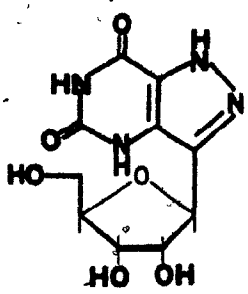

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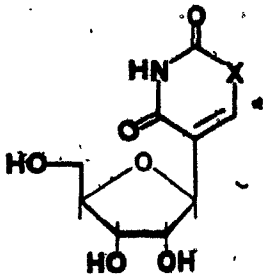


(6) X=O
(7) X=NH

(1) Biological and biochemical properties of C-nucleosides

Biological activity of C-nucleosides has been observed in a wide range of organisms. Aspects on the chemistry and biochemistry of C-nucleosides have been reviewed by Suhadolnik[1].

Showdomycin (3) is a broad spectrum antibiotic. It is active against Ehrlich ascites tumor cells.[5] It inhibits growth, protein and DNA synthesis, and the transport of sugar and amino acids in Escherichia coli.[6] It appears that the maleimide aglycon moiety of showdomycin is an active alkylating agent which is especially active towards the sulfhydryl group of enzymes.[7] Due to the structural resemblance to uridine this antibiotic acts also as a uridine antagonist.[7]

Pyrazofurin A (4) shows antiviral activity against rhinovirus, measles, herpes simplex, and vaccinia viruses in culture cells.[8] The observation of specific reversal of its antiviral activity by uridine and uridine monophosphate points to pyrimidine biosynthetic pathways as a possible vulnerable site of growth inhibition. Uridine reversal of pyrazofurin A activity suggests orotidylic acid decarboxylase inhibition as a probable mode of action.[9]

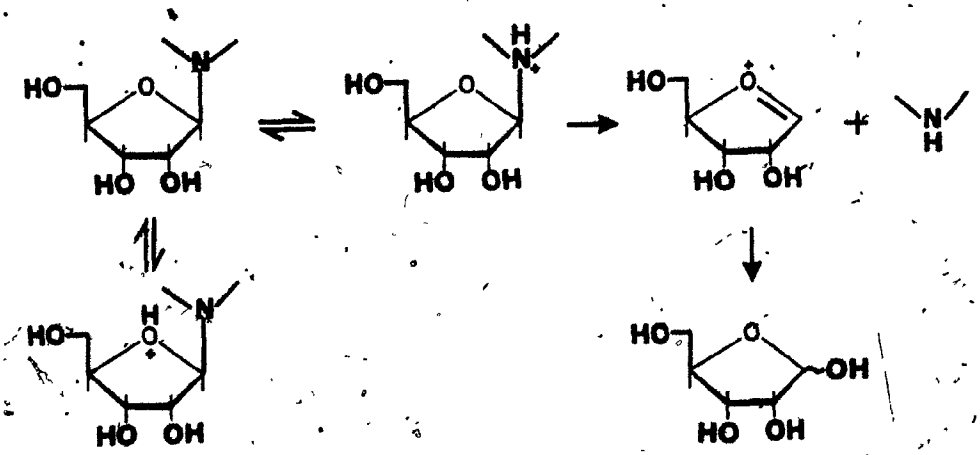
Formycin (1), an analogue of adenosine, inhibits many aspects of purine metabolism in chemotherapeutically sensitive Ehrlich ascites tumor cells including the leukaemia L1210 and influenza A viruses.[10]

Formycin B (2), an inosine analogue, is produced from formycin by the action of adenosine deaminase.[11] Agricultural potential against rice plant disease caused by Xanthomas oryzae has been noted.[12]

Another survey dealing with C-nucleoside research includes

a discussion of the relationship between nucleoside conformation and biological activities by Ward and Reich.[13] Due to the increased bond length of the C-C glycosidic linkage in C-nucleoside compared to the C-N bond in N-nucleoside, the rotational barrier about this linkage is lowered and the C-nucleoside can assume the suitable conformation for interaction with the active site.

The glycosyl bond of C-nucleosides shows an increased stability towards chemical and enzymatic attack relative to their N-nucleoside counterparts. Protonation on the oxygen or nitrogen atom of N-nucleosides leads to C-N bond cleavage to give the free base and free sugar.[14] Since C-nucleoside is more stable in this respect, it should exhibit a prolonged activity.



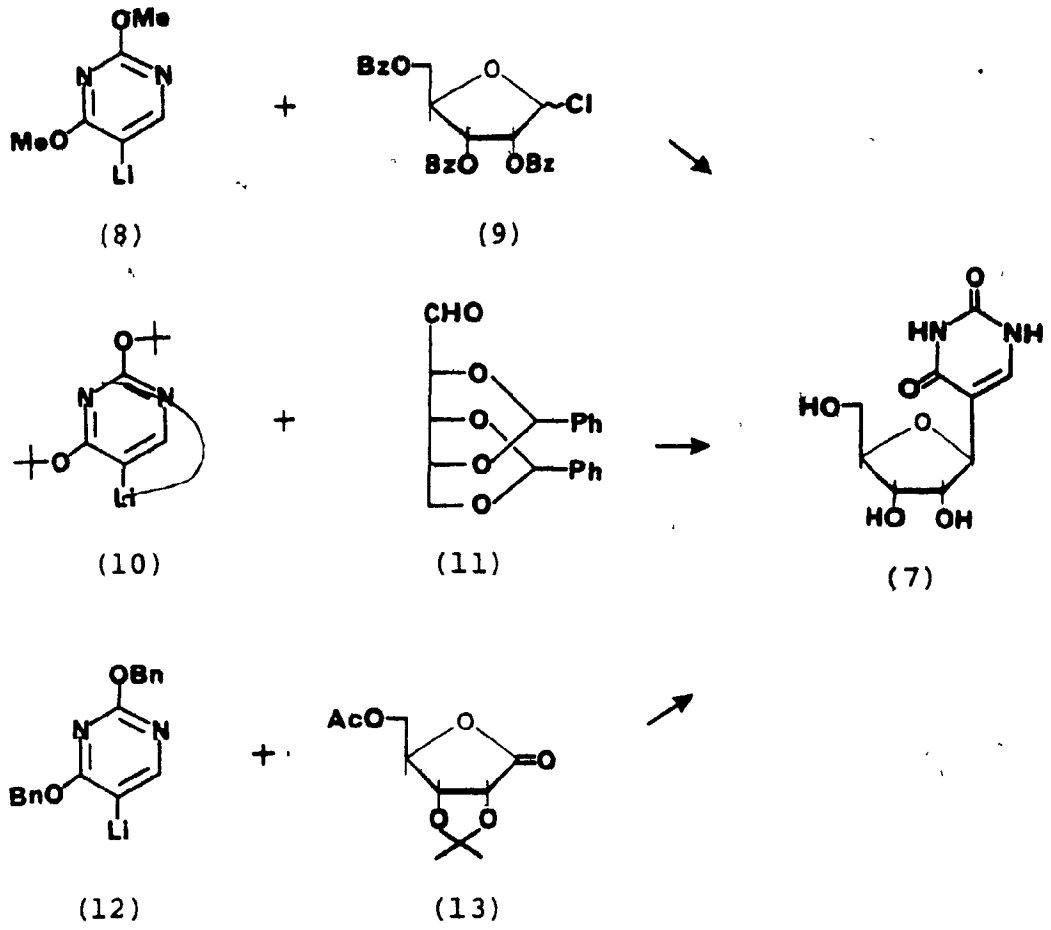
In spite of a great deal of efforts to develop antiviral agents of C-nucleoside, no medical usefulness has thus far been demonstrated for members of C-nucleoside class. The preparation of additional C-nucleosides by synthesis or by modification of naturally available materials, together with a detailed understanding of structure-activity relationships, will assist in the realization of the therapeutic potential of this versatile class of agents. For the chemist, these relationships will suggest a general approach for the preparation of C-nucleoside antibiotics.

(2) Syntheses of C-nucleosides

(a) Pseudouridine, oxazinomycin and related compounds

Pseudouridine (7), 5-β-D-ribofuranosyl uracil, was discovered in 1951 as a nucleotide in an alkaline hydrolyzate of calf liver RNA.[15] Its structure was determined in 1959[16] and the structural assignment for it has been reviewed.[17] The chemistry[18] and biochemistry[19] have been reviewed and its n.m.r.,[20] c.m.r.,[21] and mass[22] spectra have been reported in detail.

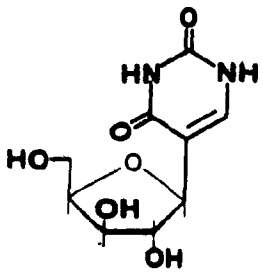
Pseudouridine has been synthesized by a number of investigators. In the first reported synthesis by Shapiro and Chambers,[23] 2,4-dimethoxy-5-lithium-pyrimidine (8) was condensed with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride (9). After



removal of the protecting groups, the natural product was obtained in 2% yield. The yield of pseudouridine was improved up to 18% by condensation of 2,4-di-tert-butoxy-5-lithio-pyrimidine (10) with 2,4:3,5-di-O-benzilidene-aldehydo-D-ribose (11).[24,25] Another synthesis involves the reaction of 2,4-dibenzyloxy-5-lithiopyrimidine (12) with 5-O-acetyl-2,3-O-isopropylidine-D-ribolactone (13). Reduction and acid hydrolysis gave a 10% yield of pseudouridine.[26]

Many related compounds have been synthesized and their

properties studied. When the above pyrimidine (12) was allowed to react with the 2,3:4,5-di-O-isopropylidene-aldehydo derivatives of D-xylose, D-arabinose, and D-ribose, the following products (14,15,16,17) were obtained.[27]



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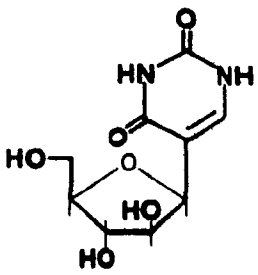

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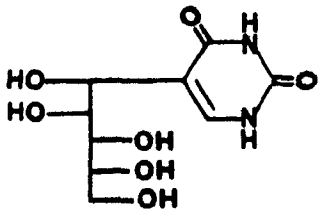

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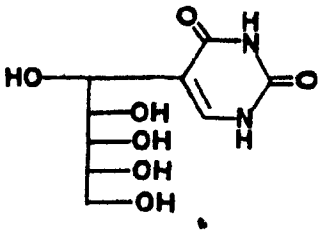
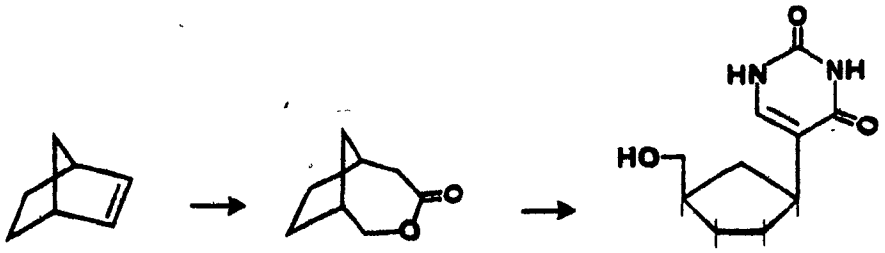


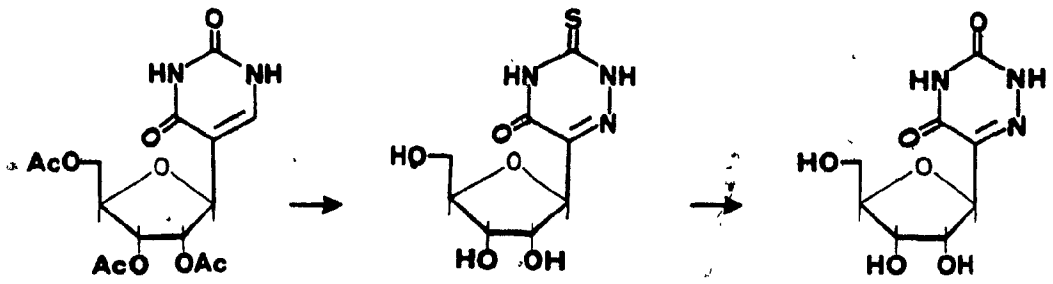
(17)

A carbocyclic analogue of 2',3'-dideoxypseudouridine (20) has been prepared by a multistep synthesis starting from norbornylene (18) and proceeding via the key intermediate, the lactone (19).[28]



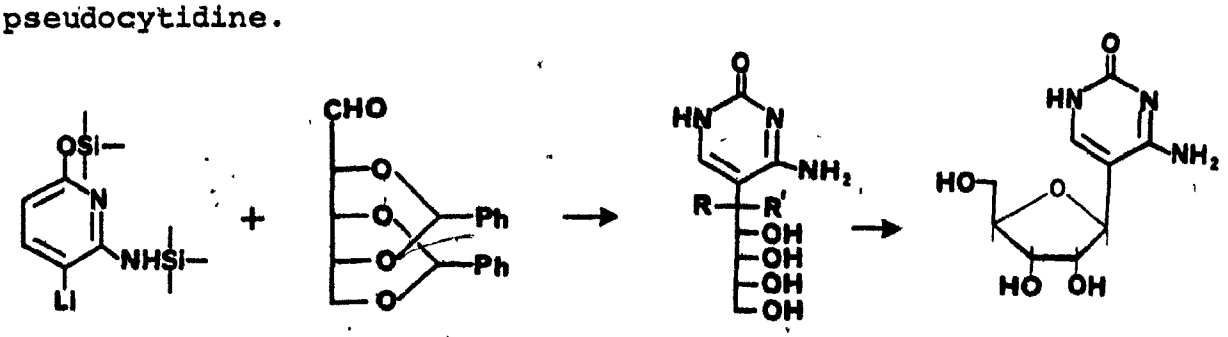
(18) (19) (20)

In a series of papers, Bobek et al. published the syntheses of 6-azapseudouridine[29] and its analogue[30]. For example, reductive ozonolysis of 2',3',5'-tri-O-acetyl-pseudouridine (21), followed by treatment with thiosemicarbazide and cyclization, gave the 6-azathiouracil derivative (22). Methylation with methyl iodide and acid hydrolysis yielded 6-azapseudouridine (23).



(21) (22) (23)

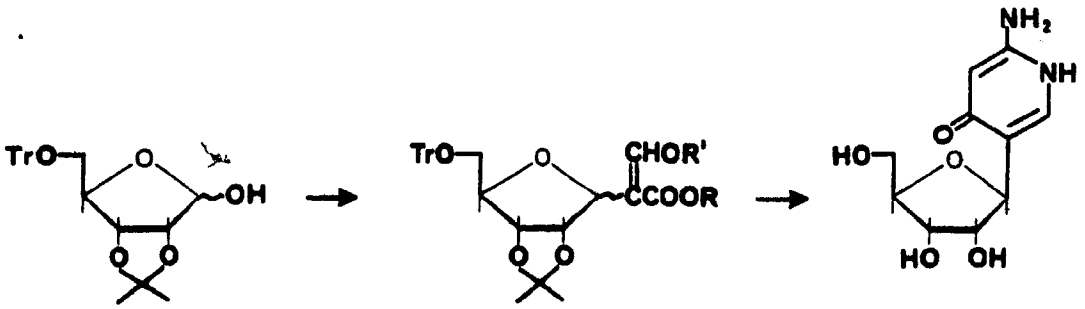
Recently the synthesis of pseudocytidine (28) was reported by David et al.[31] Reaction of (24) with 2,4:3,5-di-O-benzylidene-D-ribose (25) and hydrolysis with acetic acid produced (26) and (27). Treatment of the mixture with sodium nitrite and acetic acid afforded pseudouridine (7) and its α-anomer, while cyclization of the mixture with 1N hydrochloric acid yielded pseudocytidine.



(24) (25) (26) R=OH, R'=H (28)

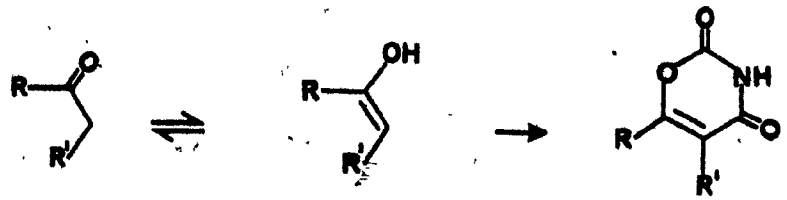
(27) R=H, R'=OH

Fox and co-workers[32] reported a synthesis of pseudoisocytidine (31) from the D-ribose derivative (29). The key intermediate, the 2-(D-ribofuranosyl)-2-formylacetate derivative (30) (R=alkyl, H), was converted to the sodium enolate (R=Na) which was treated with guanidine and sodium methoxide to afford (31) after removal of the protecting groups.



(29) (30) (31)

Oxazinomycin (6) was isolated by Sasaki et al.[33] It showed antitumor and antiviral activities. The synthesis of this compound has not been reported to date. The synthesis of model heterocycles (32,33), based on addition reaction of a ketone to chlorosulfonyl isocyanate, was reported by Rasmussen et al.[34]

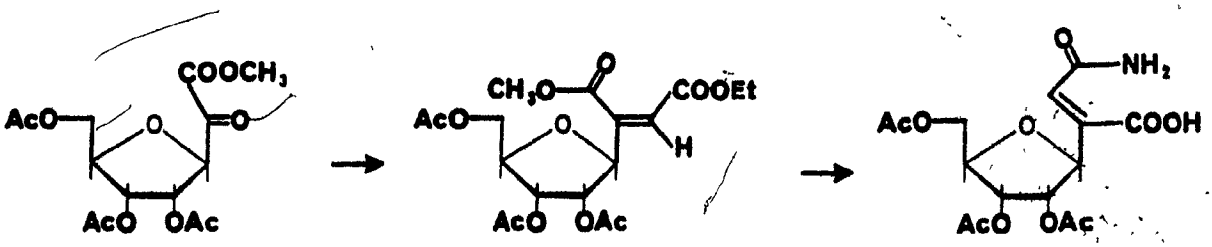


(32) R=Ph, R'=CH_3
(33) R=CH_3, R'=Ph

(b) Showdomycin and related compounds

The C-glycosyl nucleoside antibiotic showdomycin (3) was first isolated from Streptomyces showdoensis by Nishimura et al.[35] Its structure was confirmed as 2-(β-ribofuranosyl) maleimide.[36] Its n.m.r.,[37] c.m.r.,[21] and mass[38] spectra have been reported.

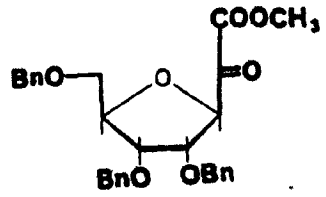
The first synthesis of showdomycin has been briefly reported by Kalvoda et al.[39] It involved, as the key intermediate, the keto ester (34) which was prepared via ozonolysis of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene. The keto ester was condensed with carboethoxymethylenetriphenylphosphorane to give the maleate ester (35). Five additional steps via the maleamide (36) were necessary to obtain showdomycin.



(34) (35) (36)

Trumnlitz et al.[40] has demonstrated that the key intermediate, the keto ester of type (34), possesses great potential for the synthesis of C-nucleosides. They reported a much simplified, two-step conversion of the keto ester into showdomycin via the reaction of methyl 3,6-anhydro-4,5,7-tri-

0-benzyl-D-allo-heptulosonate (37) with carbamoylmethylene-triphenylphosphorane (38) followed by debenzylation of the resulting maleimide (39).



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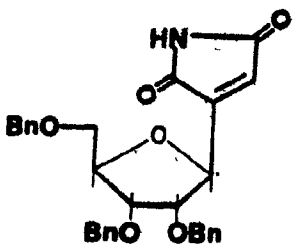

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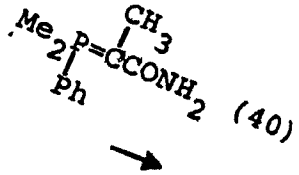

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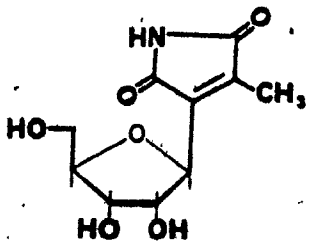


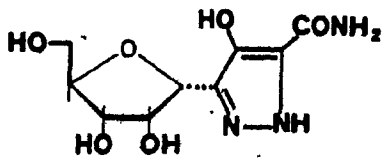
(41)

They extended the above synthetic route for the preparation of 3-methylshowdomycin (41) via the corresponding reaction with 1-carbamoylethylidenedimethylphenylphosphorane (40).[41]

(c) Pyrazofurin A and related compounds

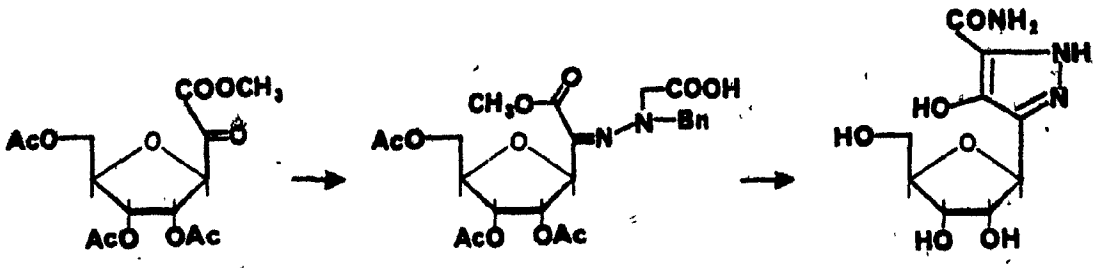
The pyrazolic C-nucleoside pyrazofurin A, 3-(1'-β-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxamide (4), was

isolated from fermentation of a strain of Streptomyces candidus.[42] This organism has yielded a second factor, which was identified as the α-anomer, pyrazofurin B (42).[43] The c.m.r.[44] and mass[45] spectra of pyrazofurin A have been reported.



(42)

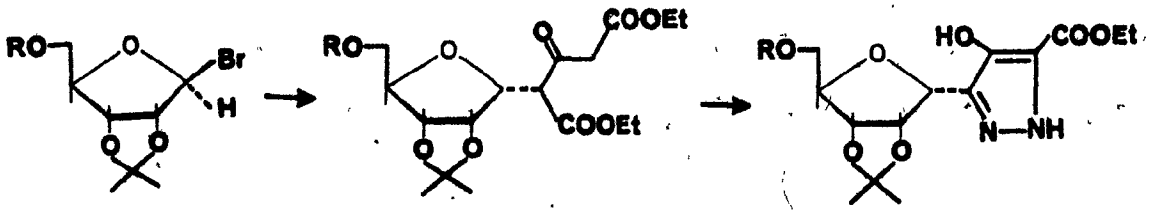
The first synthesis of pyrazofurin A has been reported by Farkas et al.[46] Condensation of the keto ester (34) with 1-benzylhydrazinoacetic acid gave the hydrazone (43). Five further steps yielded pyrazofurin A (4) in low yield.



(34) (43) (4)

Bernado et al.[47] has described a new synthetic route which allowed the preparation of both anomers (4,42). Reaction of the β-D-ribosyl bromide (44) with diethyl 1,3-acetonedicarboxylate afforded the diethyl ester (45). Diazotization of (45) with

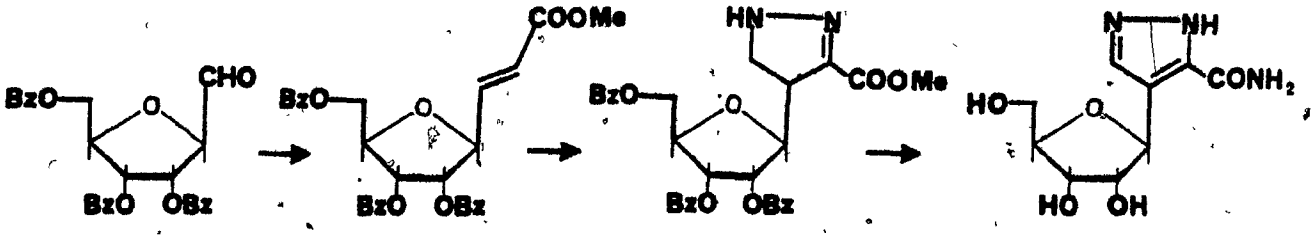
p-toluenesulfonyl azide followed by treatment with sodium ethoxide produced the 4-hydroxypyrazole (46). Ammonolysis and hydrolysis completed the synthesis of (4) and (42).



(44) (45) (46)

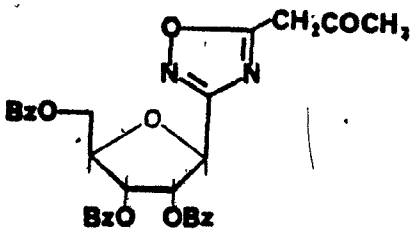
$R=COC_6H_4NO_2$-p

In recent years, the syntheses of many pyrazolic and isoxazolic analogues of C-nucleoside have been reported. Moffatt and co-workers[48] reported the synthesis of 4-(β-D-ribofuranosyl) pyrazole. Condensation of the 2,5-anhydro-D-allose (47) with the appropriate phosphorane gave the unsaturated ester (48) which upon treatment with diazomethane underwent a 1,3-dipolar cycloaddition to give the pyrazoline (49). Dehydrogenation with chlorine and ammonolysis gave the pyrazole (50).



(47) (48) (49) (50)

Just and Ramjeesingh[49] also described the preparation of the pyrazole (50) starting from a non-carbohydrate source. Moffatt's group[50] also reported the syntheses of 3-β-D-ribofuranosyl-1,2,4-oxadiazole (51) and 3-β-D-ribofuranosyl-pyrazole (52).



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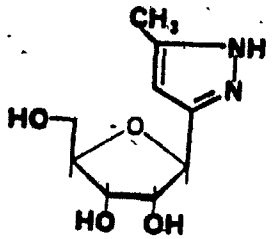

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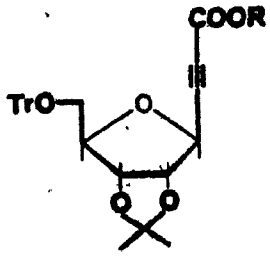
Fox's group[51] reported the synthesis of triazole and pyrazole C-nucleosides via 1,3-dipolar cycloaddition reactions on the triple bond of the C-glycosyl acetylene (53). 1,3-Dipolar addition of (53) with trimethylsilyl azide and diazomethane followed by ammonolysis gave the triazole (54) and pyrazole (55).



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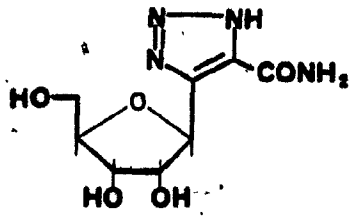

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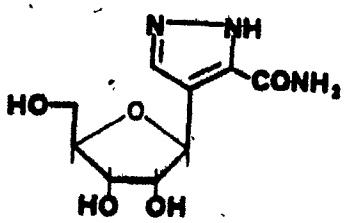
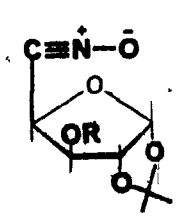


(55)

Other workers have also utilized the C-glycosyl acetylenes to prepare simple triazole,[52] pyrazole,[53] and isoxazole[54] C-nucleosides via 1,3-dipolar cycloaddition reactions.

In a series of recent papers, Tronchet and co-workers have published synthetic approaches to C-nucleosides in which 1,3-dipolar cycloaddition of sugar derivatives such as (56) and (57) with acetylenes led to isoxazoles[55] and pyrazoles[56] respectively and in which the intramolecular cyclization of (58) gave 3-β-D-erythrofuranosyl-1-p-nitrophenylpyrazole.[57]



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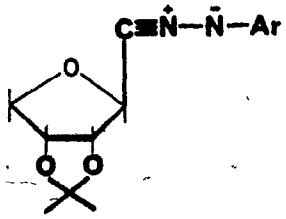

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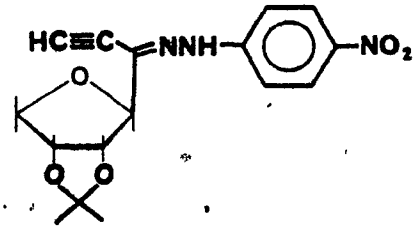
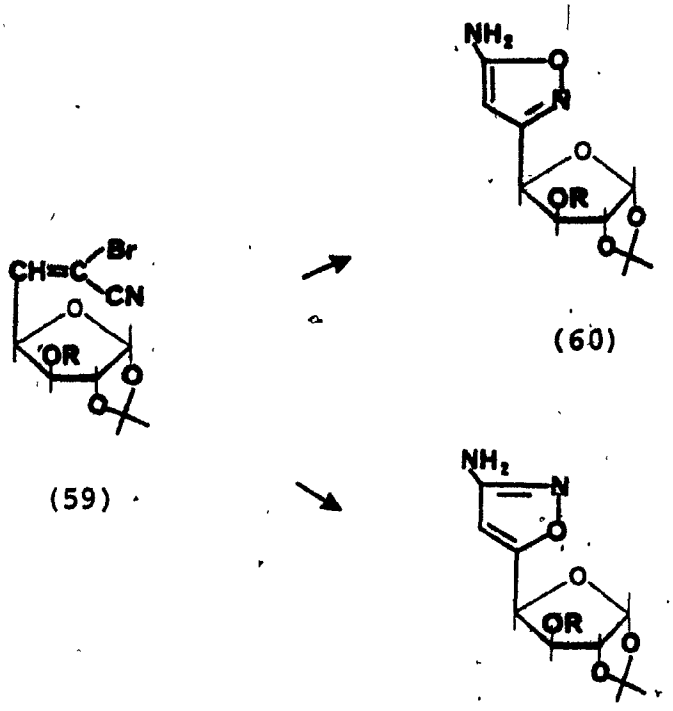


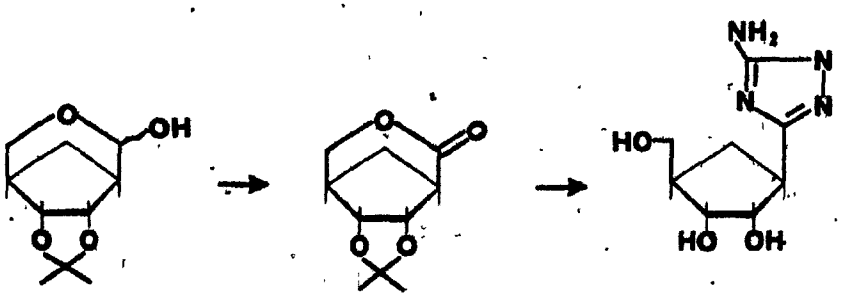
(58)

They have also prepared a variety of C-1' functionalized C-glycosyl derivatives, potential intermediates for the preparation of C-nucleosides.[58] In a further extension of the above work, they prepared the olefin sugars (59) by a Wittig reaction. Treatment of (59) with hydroxylamine and hydroxyurea gave the amino-3-glycosyl-5-isoxazole (60) and amino-3-glycosyl-5-isoxazole (61) respectively.[59]



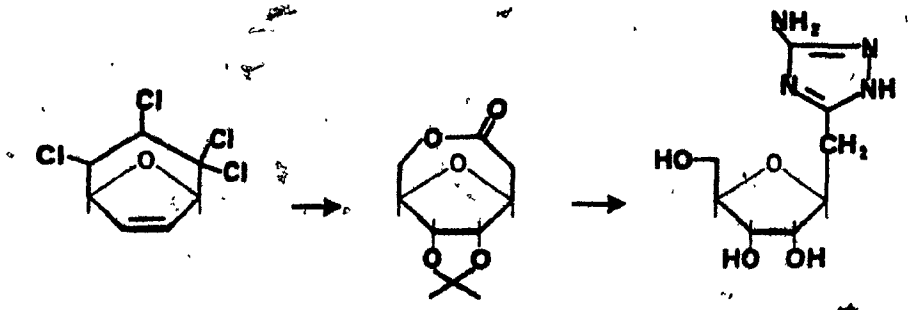
(59) (60) (61)

Just's group[60] has reported another key intermediate, the hemiacetal (62). Oxidation with Collins reagent or Fetizon's reagent gave the lactone (63) which was condensed with aminoguanidine. Hydrolysis with trifluoroacetic acid produced the triazole C-nucleoside (64).



(62) (63) (64)

A triazole homo-C-nucleoside was prepared by Gensler et al.[61] via similar route. They prepared the lactone (66) in five steps from the tetrachlorobicyclo compound (65). Condensation of (66) with aminoguanidine and hydrolysis gave the 3-amino-1,2,4-triazole (67).



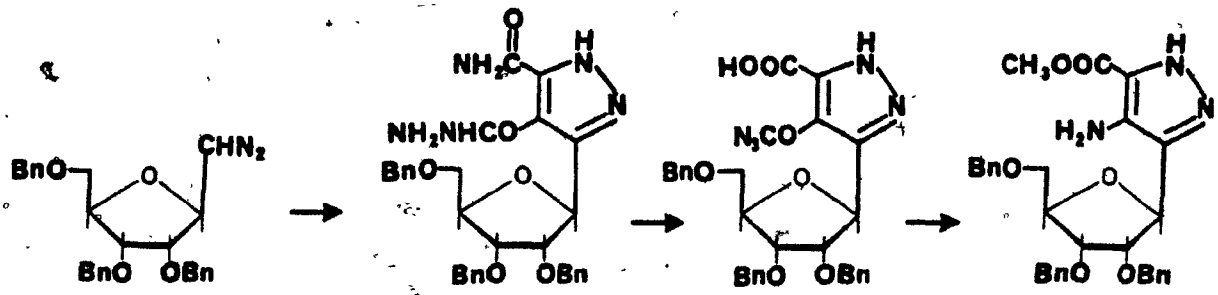
(65) (66) (67)

(d) Formycin and related compounds

Formycin (1) was isolated by Hori et al.[62] from the culture filtrates of Norcardia interforma. Koyama and Umezawa[63] isolated a second antibiotic, formycin B (2), from N. interforma. The x-ray analysis,[64] n.m.r. and u.v.,[65] c.m.r.,[66] and mass[37] spectra of formycin and formycin B have been reported.

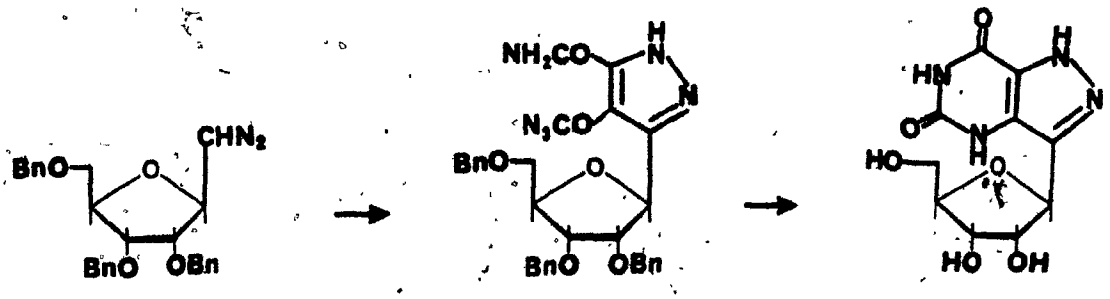
Acton et al.[67] reported the synthesis of formycin B via 1,3-dipolar addition of the diazosugar (68) to dimethyl acetylenedicarboxylate. Ammonolysis and treatment with hydrazine afforded the hydrazide (69) which was converted to the

4-azido-3-carboxy pyrazole (70). After a Curtius rearrangement and methylation, treatment of (71) with formamide and hydrogenation afforded formycin B (2).



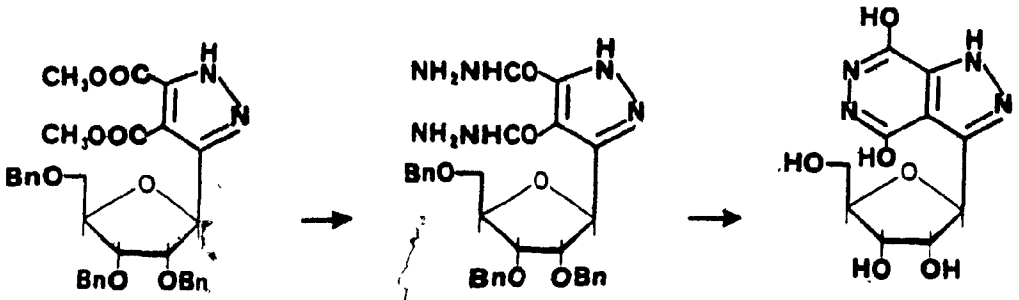
(68) (69) (70) (71)

Farkas and Sorm[68] synthesized oxoformycin B (5) by transforming the compound (68) into the azide (72), followed by heating in tert-butanol and debenzylation with sodium in liquid ammonia.



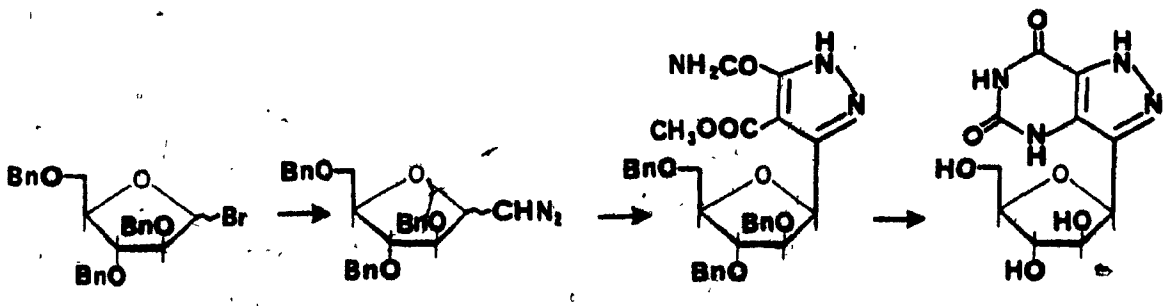
(68) (72) (5)

They also reported the synthesis of an analogue of oxoformycin B using the intermediate (68). Conversion of (68) into the diester (73) and treatment with hydrazine afforded the hydrazide (74). The acid-catalyzed cyclization and debenzylation led to the oxoformycin analogue (75).[68]



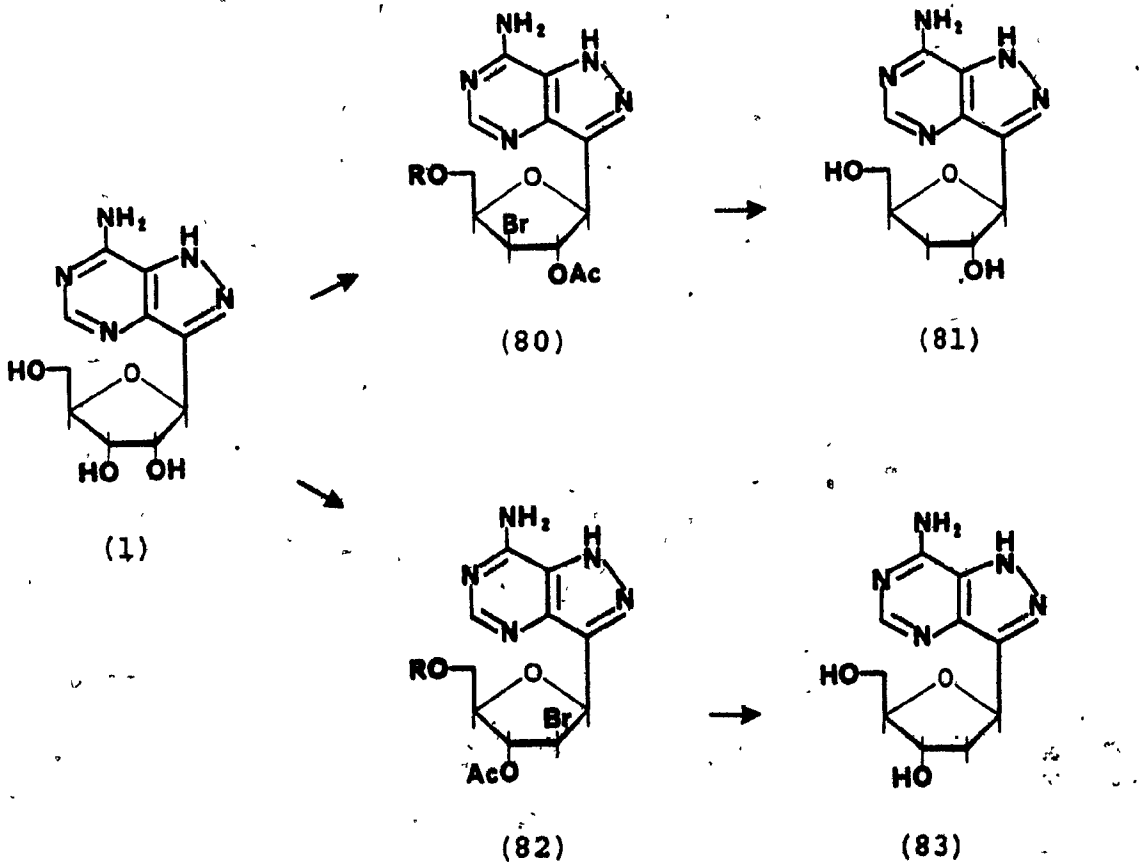
(73) (74) (75)

Acton et al.[69] described the synthesis of the D-arabino epimer (79) of oxoformycin and its α-anomer. 2,3,5-Tri-O-benzyl-D-arabinofuranosyl bromide (76) was converted to the 1-diazo sugar (77). Dipolar addition to dimethylenedicarboxylate and selective ammonolysis afforded the 4-ester-5-carboxamide (78). Hydrazinolysis, Curtius raction, and debenzylation as described before yielded β-D-arabino epimer (79).



(76) (77) (78) (79)

Moffatt's group[70] has reported the synthesis of 3'-deoxy- and 2'-deoxyformycin by chemical modification of formycin. The reaction of formycin with 2-acetoxy isobutyryl bromide gave both 2'-O-acetyl-3'-bromo-3'-deoxy-β-D-ribofuranosyl (80) and 3'-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl nucleosides (82). Treatment with ammonia and catalytic hydrogenolysis of the appropriate compounds gave 2'-deoxyformycin (83) and 3'-deoxyformycin (81).



R=Me_2(OAc)CCO

In summary, the methods described above for the synthesis of C-nucleosides can be classified into three general types as follows:

(1) The conversion of some available C-nucleosides to prepare new ones.

(2) Direct condensation of suitably blocked sugar derivatives with appropriate heterocyclic bases.

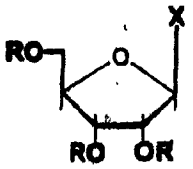
(3) The multistep elaboration of the desired heterocycle from a C-glycosyl derivative functionalized at the C-1' position.

Since the third approach to date has been less explored and more versatile, this method was chosen for the preparation of C-glycosyl nucleosides. In this thesis, approaches to the synthesis of the arabino and 2'-deoxy epimers of the C-nucleosides showdomycin and pyrazofurin A have been studied.

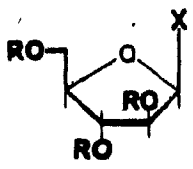
Chapter I

Synthesis of 5-carbomethoxy-2-exo-3-endo-di-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene

Considerable effort has been made over the past several years to develop rational schemes for the synthesis of C-glycosyl nucleosides. A perhaps more versatile and successful approach to date involves the multistep elaboration of the desired heterocyclic system from a C-glycosyl derivative (84) functionalized at the C-1' substituent. Since the carbon-carbon bond joining the sugar moiety and heterocycle is already present, this route permits the formation of anomerically pure C-glycosides.



(84)



(85)

a, X = $COCO_2CH_3$

b, X = CHN_2

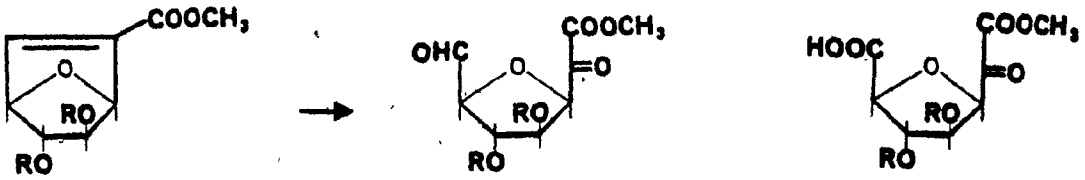
c, X = CHO

d, X = C≡C-COOR

As part of a programme to synthesize C-nucleosides, we were interested in developing a method to prepare arabinose derivatives (85).

The synthesis of C-nucleoside requires intermediates of type (85) which is as yet not readily available. The olefin

ester (86) having the proper stereochemistry could be a precursor of such an intermediate, because oxidative cleavage of the double bond would result in the formation of the desired sugar bearing the proper functional group at the C-1' position (87,88). The oxidative cleavage has, in fact, been utilized in several total syntheses in our laboratory.



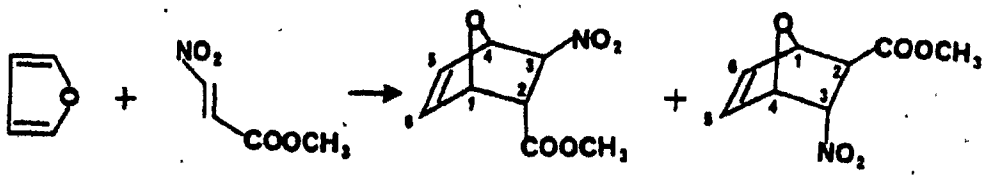
(86) (87) (88)

This chapter details the preparation and stereochemistry of the olefin ester (86). The rigid structure of the 7-oxabicyclo [2.2.1] heptyl skeleton will offer a logical starting point for the synthesis of such compounds.

The 7-oxabicyclo [2.2.1] heptyl system has been employed in synthetic[71] and mechanistic[72] organic chemistry as well as applied chemistry.[73] The most straightforward approach to the construction of the 7-oxabicyclo [2.2.1] hept-5-ene framework takes advantage of the Diels-Alder reaction between furan and a suitable dienophile. Unfortunately, due to the aromatic character of furan[74] and the strain of the bicyclo system[75], the cycloadducts are rather prone to undergo reverse Diels-Alder reactions. Consequently only with the use of very reactive

dienophiles can respectable yield of product be attained. For example, it was reported that five weeks are required to obtain a 39% yield of 2-cyano-7-oxabicyclo [2.2.1] hept-5-ene from furan and acrylonitrile.[76] Likewise, the cycloadduct from furan and methyl acrylate is produced in less than 20% yield after a month or more.[77] The following results may therefore be of interest in connection with the chemistry of the intensively investigated norbornanes and norbornenes.

Treatment of methyl β-nitroacrylate[78] (89) with an excess of furan at room temperature overnight gave in quantitative yield a mixture of the isomeric adducts[4,10] from which the endo-nitro adduct (91) was obtained crystalline and the exo-nitro adduct (90) as an oil. Exo-nitro/endo-nitro ratio of the adducts was calculated to be about 1/2 by n.m.r. spectroscopy.



(89) (90) (91)

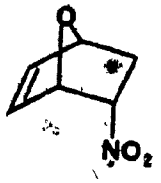
Separation of the adducts allowed for complete analysis of the n.m.r. spectra of the isomers. The C-2 protons in the endo- and exo-isomers showed considerable difference in chemical shift and multiplicity. The C-2 endo proton of the

endo-nitro adduct was observed as a doublet at δ 3.23 ($J_{2,3}$=2 Hz). The corresponding C-2 exo proton of the exo-nitro adduct appeared as a multiplet at δ 3.90. The large difference in chemical shift (0.67 ppm) is probably the result of a deshielding effect of the 7-oxygen or a difference in shielding effect of the olefinic bond.[79] The C-5 and C-6 protons had different chemical shifts in the endo-nitro adduct, and each proton was observed as a quartet of an ABX system, while the C-5 and C-6 protons in the exo-nitro adduct showed a broad singlet. Chemical shifts and coupling constants are given in experimental part.

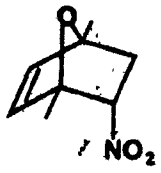
Since the endo/exo ratio in Diels-Alder reaction often depends on the reaction conditions, we examined the equilibration of the 2-carbomethoxy-3-nitro-7-oxabicyclo [2.2.1] hept-5-ene in order to gain some insight into the distribution of products. The mixture of furan and methyl β-nitroacrylate was sealed in an n.m.r. tube and maintained at 45° by means of water bath. The C-3 proton of the exo-nitro isomer and C-2 proton of the endo-nitro isomer were monitored. A one-proton doublet at δ 3.23 (J=2 Hz) appeared first and increased in intensity while a second resonance at δ 4.82 (d, J=2 Hz) appeared at a slower rate. After 8 hr the δ 3.23 resonance reached a maximum and started to decrease, whereas the δ 4.82 resonance continued to increase. After approximately 4 days the relative intensities of the two resonances remained constant. The equilibrium

constant (exo-nitro/endo-nitro) was calculated to be about 2 at 45° from the integrated areas of the δ 3.23 and 4.82 resonances. The total yield of the adducts was approximately 80% at the temperature examined. The mole fraction of both adducts decreased with increasing temperature.

Konig and co-workers[80] reported the similar result that the endo-nitro isomer (92,93) predominated in early stages of the Diels-Alder reactions of furan or 2,5-dimethyl furan with nitroethylene.

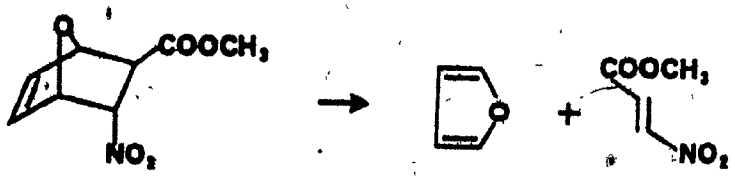


(92)



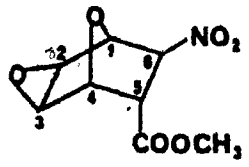
(93)

Pyrolysis of the endo-nitro adduct (91) at 110°/10 mm Hg smoothly yielded methyl β-nitroacrylate (89) due to the relative instability of [4+2] adducts from furan and dienophiles.

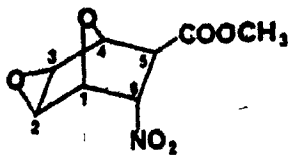


(91) (89)

Prolonged treatment of the adducts (90,91) with m-chloroperbenzoic acid[81] proceeded stereoselectively to afford the exo-epoxides (94,95) respectively. The products showed a sharp i.r. band at 858 cm^{-1}, which was in agreement with absorption of numerous other compounds containing fused epoxide rings.[82] It is known that epoxidation in bicycloheptenes and 7-oxabicycloheptenes occurs from the less hindered exo side.[83]



(94)



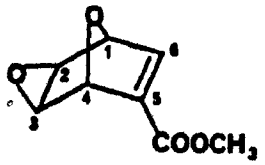
(95)

The structure and stereochemistry of the epoxides were also determined by n.m.r. spectroscopy. The J values in 7-oxabicyclo [2.2.1] hept-5-ene are well established.[79] J between cis protons is quite large (about 8 Hz) compared with about 4 Hz found for the trans proton. Although the bridgehead proton couples with the exo proton with a J of 4 Hz, it fails to couple with the endo proton. Similar features are observed in the norbornyl system.[84]

By analogy, the n.m.r. spectra of the epoxides were interpreted as follows. We would expect that the low field proton α to the nitro group in the compound (94) would appear as a doublet, and in (95) as a quartet or a triplet (X part of

AMX system). As shown in Table 1, we found that the C-6 proton appeared as a doublet (J=4 Hz) in (94) and as a quartet (J=4 Hz) in (95). This interpretation was substantiated by spin-spin decoupling. Irradiation of the C-6 proton of (95) caused the doublet for the C-1 proton to collapse to a singlet. Bridgehead C-1 and C-4 protons showed differences in multiplicity based on dihedral angle dependent $J_{1,6}$ and $J_{4,5}$ coupling constants. The C-2 and C-3 protons were seen as a quartet of an AB system. No assignment of the C-2 and C-3 protons was made.

In order to get additional proof for their structures, the epoxides (94,95) were treated with diazabicyclo [5.4.0] undec-5-ene (DBU)[85] in refluxing methylene chloride to give the D,L-olefin epoxide (96).



(96)

Its n.m.r. spectrum showed an AB quartet centered at δ 3.55 for the C-2 and C-3 protons. The signal from the C-1 proton which coupled with the C-6 proton appeared as a doublet at δ 4.88 with J=2 Hz. A singlet at δ 5.00 represented the C-4 proton. These arguments support the concept of exo approach

Table I

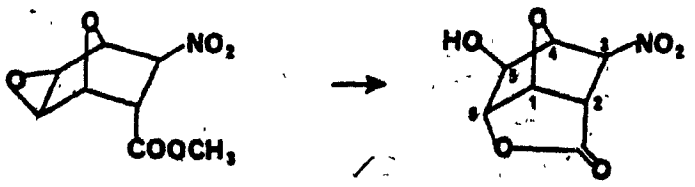
Chemical Shifts and First-Order Coupling Constants for the Epoxides

Compounds	H-1	H-2 (3)	H-3 (3)	H-4	H-5	H-6	OCH_3
	5.10 s	3.63 d	3.73 d	4.88 d	3.93 q	5.25 d	3.73 s
(94)	$J_{1,6}=0$	$J_{2,3}=4$	$J_{3,2}=4$	$J_{4,5}=4$	$J_{5,6}=4$	$J_{6,5}=4$	
	$J_{1,2}=0$	$J_{2,1}=0$	$J_{3,4}=0$	$J_{4,3}=0$	$J_{5,4}=4$	$J_{6,1}=0$	
(95)	4.93 d	3.43 d	3.53 d	4.83 s	3.76 d	5.53 q	3.70 s
	$J_{1,6}=4$	$J_{2,3}=4$	$J_{3,2}=4$	$J_{4,5}=0$	$J_{5,6}=4$	$J_{6,5}=4$	
	$J_{1,2}=0$	$J_{2,1}=0$	$J_{3,4}=0$	$J_{4,3}=0$	$J_{5,4}=0$	$J_{6,1}=4$	

Spectra are recorded at 60 MHz in DMSO-d_6. Chemical Shifts are given in δ, coupling constants in Hz.

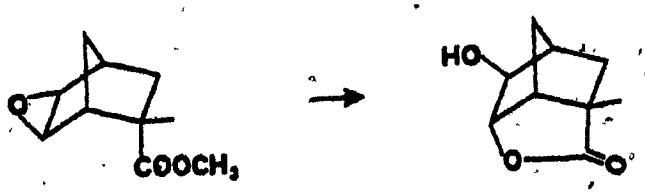
of peracid on the 7-oxabicyclo [2.2.1] heptene system. The correctness of the above assignment will be further proven by the lactonization of (94). Since a number of halosugars have been prepared by cleavage of sugar epoxides, this compound could also provide the precursor for halosugars. For example, methyl 5-O-acetyl-2-bromo-2-deoxy-β-D-xylofuranoside and methyl 5-O-acetyl-3-bromo-3-deoxy-β-D-arabinofuranoside were prepared by cleavage of a sugar epoxide by magnesium bromide.[86]

Treatment of the endo-carbomethoxy epoxide (94) with acetic acid and hydrochloric acid at 90° for 2 hr provided the desired hydroxy lactone (97) in 60% yield.



(94) (97)

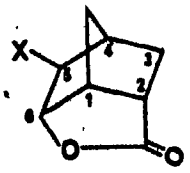
The 2,6 rather than the 2,5 regioselectivity of lactonization was also observed in analogous compound (98), for the product (99) of which a rigorous structure proof exists.[87]



(98) (99)

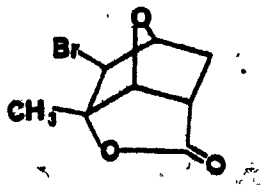
The exo-carbomethoxy epoxide (95) did not lactonize under the conditions as described above, thus confirming the stereochemistry of (94) and (95) assigned previously.

The n.m.r. spectrum of γ-lactones in the bicyclo [2.2.1] heptyl series are of special interest because the bicyclo system with its rigid structure has served as a substrate for the generation and evaluation of numerous mechanistic hypotheses in modern organic chemistry. The characteristic features will be discussed here.



(100)

X=I, Br, OTs, OAc, D



(101)

The n.m.r. spectra of γ-lactones in several bridged bicyclo [2.2.1] heptane derivatives (100) have been analyzed in detail by Moriarty et al.[88] They observed the following results: (a) the vicinal coupling constant $J_{1,6exo}$ ($J_{1,2exo}$) is around 5 Hz; (b) $J_{4,5endo}$ ($J_{4,3endo}$) is 0.5 Hz; (c) $J_{5endo,6exo}$ is 0 Hz; (d) the C-1 proton appears at a lower field position relative to the C-2 proton which is attached to the carbon atom bearing the carbonyl group of the lactone. The reason for the unexpected reversal in the chemical shifts of

these protons is that the C-1 proton is located in the region of maximum deshielding. The same conclusion was reached by n.m.r. study of the γ-lactone of 7-oxabicyclo [2.2.1] heptane (101).[89]

By analogy with the spectra of similar lactones, we were able to interpret the n.m.r. spectra of the hydroxylactone (97). The signal of the C-1 proton is split into a triplet at δ 5.60 (J=5 Hz) due to coupling with the C-2 and C-6 protons. The downfield shift of about 0.7 ppm for the C-1 proton compared to the C-4 proton in compound (94) is probably due to the deshielding effect of the lactone carbonyl group discussed above. A doublet was observed at δ 4.63 ($J_{6,1}$=5 Hz) for the C-6 proton. Like the C-6 proton, the C-2 proton showed a doublet at δ 3.63 ($J_{2,1}$=5 Hz). The remaining protons gave singlets at δ 4.10 (H-5), 5.25 (H-4), and 5.33 (H-3). An exchangeable proton was found at δ 3.36. Spin-spin decoupling substantiated our interpretation (see Fig. 1). Upon irradiation of the C-1 proton, the original doublets for the C-2 and C-6 protons collapsed to singlets. Decoupling the doublet for the C-6 proton collapsed the triplet for the C-1 proton to a doublet. Therefore, the C-1 proton coupled with with the C-2 and C-6 protons.

The i.r. spectrum of (97) showed a strong absorption at 1800 cm^{-1} for the γ-lactone. Moriarty et al.[90] explains that abnormally high carbonyl stretching frequency is attributable to dipolar destabilization between the lactone dipole and

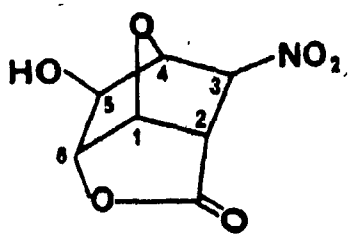
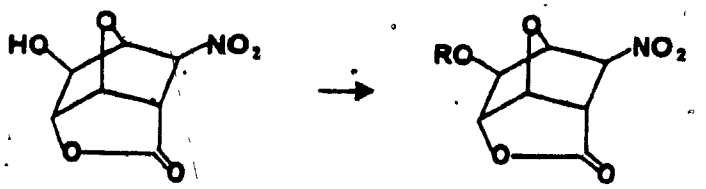


Fig. 1. Downfield portion of the n.m.r. spectrum of compound (97) at 100 MHz in $(CD_3)_2CO$.

the dipole of C-OH bond in ground state. This compound was also completely identified by mass spectrometry and elemental analysis.

In order to increase the yield of the hydroxy lactone (97), a direct lactonization from the Diels-Alder adduct was attempted. It was reported that methyl bicyclo [2.2.1] hept-5-ene-2-carboxylate underwent oxidative lactonization using formic acid and hydrogen peroxide.[91] In our case, treatment of the exo-nitro adduct (90) with formic acid and hydrogen peroxide at 45-50° overnight gave only the corresponding epoxide (94).



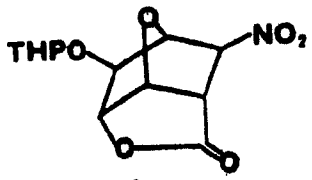
(97) (102) R=Ac

(103) R=THP

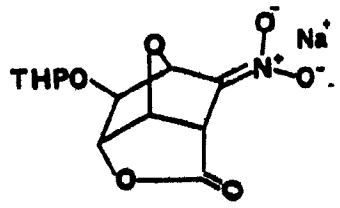
Attempts to acylate the hydroxy lactone (97) with acetic anhydride or pivaloyl chloride in pyridine failed, leading to decomposition products. However, acetylation using acetic anhydride and p-toluenesulfonic acid monohydrate gave the crystalline acetate (102) in 70% yield. The characteristic downfield shift[92] of about 0.7 ppm for the C-5 proton in compound (102) compared to the C-5 proton in compound (97) confirmed the previous assignment of the C-5 proton in the hydroxy lactone.

The hydroxy lactone (97) was found to react rapidly with dihydropyran in the presence of p-toluenesulfonic acid in acetone to give the tetrahydropyranyl ether (103). Examination of the product by t.l.c. revealed the presence of approximately equal amounts of isomers at the new epimeric center generated.

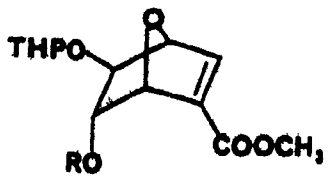
Attempts to transform the lactone (103) into the unsaturated ester (105) using one or more equivalents of sodium methoxide in methanol, the conditions which had cleanly converted the bromolactone in the bicyclo [2.2.1] heptane series to an analogous compound[93] failed because of the formation of the sodium salt (104) and a mixture of several unknown products. There are numerous reports that the sodium salt formation of the nitro compounds occurs rapidly by sodium methoxide[94]



(103)



(104)



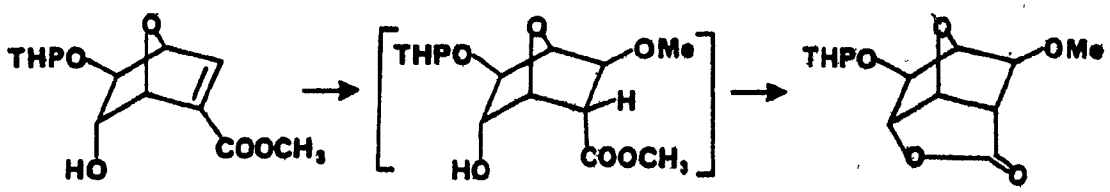
(105) R=H

(106) R=Ac

However, treatment of the lactone (103) with DBU or triethylamine in methanol under reflux afforded the olefin ester (105) as an oil accompanied by varying amounts of the methoxy lactone (108), m.p. 134-136°. The n.m.r. spectrum of the olefin ester showed a one-proton doublet at δ 7.17 (J=2 Hz) for the vinyl proton which coupled with the bridgehead proton. A sharp three-proton singlet appeared at δ 3.76 for the methyl ester. The i.r. spectrum showed a strong carbonyl absorption for the ester carbonyl at 1720 cm^{-1} and no absorption for the nitro group. The olefin ester (105) was characterized as its acetate (106).

The structure of the side product was derived from its i.r. spectrum which indicated the presence of a lactone carbonyl absorption at 1800 cm^{-1} and its n.m.r. spectrum which showed a methoxy group at δ 3.40 and the absence of vinyl proton. The yield of the side product was found to increase with an excess of DBU and longer reaction time. Therefore, it was obvious that the olefin ester (105) was transformed to the methoxy lactone, presumably via the corresponding carbomethoxy alcohol (107) with subsequent relactonization. Some spectroscopic and t.l.c. evidence for the formation of this intermediate could be obtained, but it could not be isolated in a pure state. The stereochemistry of exo-methoxy and exo-hydrogen of the intermediate is presumably the consequence of intitial attack from the more accessible exo-side of the 7-oxabicyclo

[2.2.1] heptene ring followed by thermodynamic exo-protonation of the resulting enolate. This type of conjugated addition of nucleophiles to the norbornadienes also proceeds smoothly and stereoselectively under basic conditions.[35]



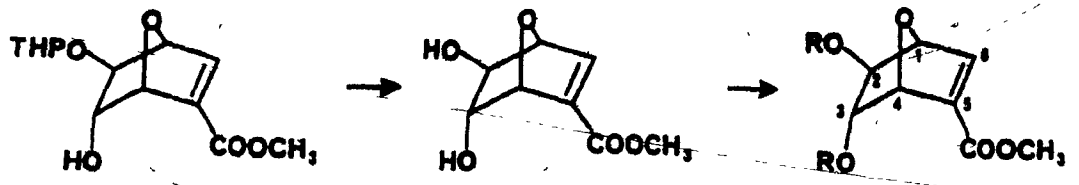
(105) (107) (108)

At this point, it became apparent that the tetrahydropyranyl protecting group obscured the n.m.r. spectra of (103) and (105) enough to make some of the assignments doubtful.

In conceiving a synthetic route to showdomycin itself or analogues we must bear in mind that, while this compound is very stable under acidic conditions,[35,36] it is very labile in base, owing to a rapid Michael type of addition of the 5'-hydroxy group to the maleimide double bond.[36] In view of this alkaline instability of the final product, we decided to use tert-butyldimethylsilyl group for the protection of our sugar moiety. It is known that tert-butyldimethylsilyl ethers are stable to aqueous alcoholic base under normal conditions and removal of the silyl protecting group can be accomplished using tetra-n-butyl ammonium fluoride or acetic

acid.[96] Therefore, this group appeared to be suitable for carrying out the subsequent reaction.

After hydrolysis of the tetrahydropyranyl ether (105) with aqueous acetic acid or 0.1N hydrochloric acid in methanol, the resulting diol (109) was directly silylated with tert-butyldimethylsilyl chloride and imidazole in dimethylformamide[96] at room temperature for 24 hr, giving the disilyl olefin ester (110) in low yield.



(105) (109) (110) R=$Si(CH_3)_2C(CH_3)_3$

(111) R=Ac

(112) R=$COC(CH_3)_3$

The n.m.r. analysis of the product (see Fig. 2) showed that the stereochemistry of the C-2 exo- and C-3 endo-hydroxy groups we planned to introduce had been retained. The assignment of resonances corresponding to the bridgehead C-1 and C-4 protons was straightforward. The expected larger value of $J_{4,3}$=4 Hz over $J_{1,6}$=2 Hz was of diagnostic value here, and was consistent with a number of 7-oxabicyclo [2.2.1] hept-5-ene in our series. The C-4 proton appeared as a doublet at δ4.85 (J=4 Hz) and the C-1 proton resonated as a doublet at δ 4.62 (J=2 Hz).

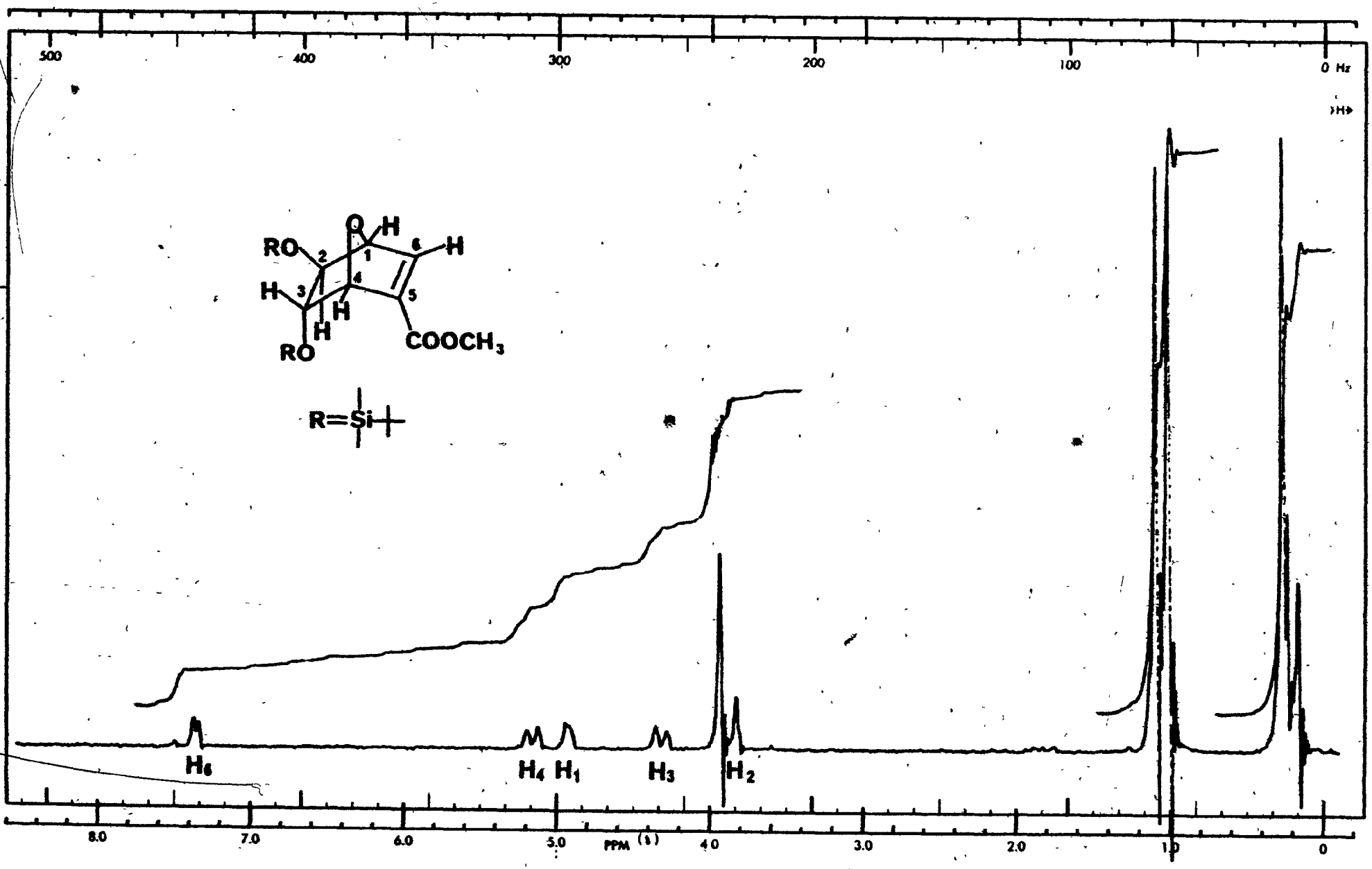


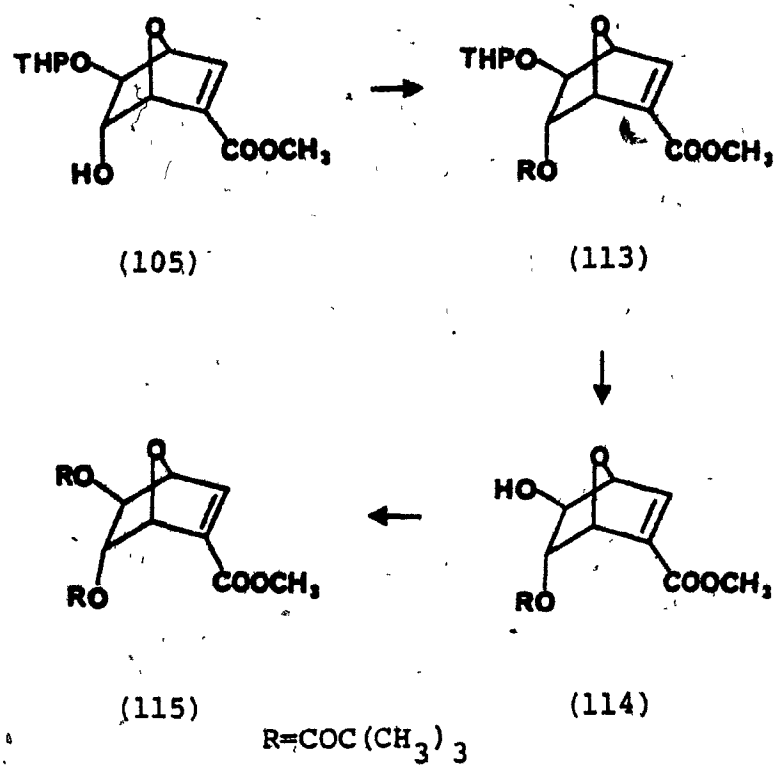
Fig. 2. The n.m.r. spectrum of compound (110) in $CDCl_3$.

The C-6 proton which coupled with the C-1 proton appeared as a doublet at δ 7.02 (J=2 Hz). The C-3 proton appeared as a doublet at δ 4.02 (J=4 Hz) due to coupling with the bridgehead C-4 proton. The C-2 proton occurred as a singlet at δ 3.54 since there was no coupling between C-2 endo and C-3 exo protons. Reasonable consistency prevailed for the relative chemical shifts and coupling constants of structurally related compounds. Further proof of the above assignment was made by spin-spin decoupling. Decoupling the doublet at δ 7.02 caused only the doublet at δ 4.62 to collapse to a singlet. Irradiation of the doublet at δ 4.85 collapsed the doublet at δ 4.02 to a singlet. Therefore, spin-decoupling readily distinguished the C-1 proton from the C-4 proton.

The diol (109) was also transformed into its diacetate (111) and dipivalate (112).

The n.m.r. spectrum of the dipivalate (112) showed similarity to that of the disilyl olefin ester (110). The C-4 proton appeared as a doublet at δ 5.23 ($J_{4,3}$=4 Hz) due to coupling with the C-3 proton at δ 5.03 ($J_{3,4}$=4 Hz). The C-1 proton coupled with the C-6 proton at δ 7.21 ($J_{6,1}$=2 Hz) to give a doublet at δ 4.94 ($J_{1,6}$=2 Hz). The C-2 proton appeared as a singlet at δ 4.52 as expected. Methyl ester and pivalate protons were observed as singlets at δ 3.74, 1.23 and 1.10 respectively.

To get further proof for the correct stereochemistry of trans relationship of hydroxyl function, the olefin ester (105)



(105) (113)

(115) (114)

$R=COC(CH_3)_3$

was converted to the dipivalate as follows. Treatment of the olefin ester with pivaloyl chloride and pyridine afforded the pivaloyl olefin ester (113). Hydrolysis of the tetrahydropyranyl ether of (113) with aqueous acetic acid gave the hydroxy olefin ester (114). Once again, the hydroxyl function of (114) was protected as its pivalate (115). After pivalation, the C-2 proton of (114) was shifted downfield by 0.8 ppm, thus confirming the previous assignment of the C-2 proton in compound (112). This compound was identical in all respects (n.m.r., i.r.) with (112) obtained from the diol (109).

The above method allows the synthesis of differently substituted olefin esters which are acid- and base-stable. The only disadvantage in our synthetic route toward the olefin

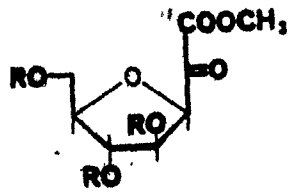
ester was the introduction and deprotection of the tetrahydropyranyl protecting group. In order to avoid this unnecessary step, the hydroxyl group of the hydroxy lactone (97) was protected as tert-butyldimethylsilyl ether or methoxymethyl ether. These reactions will be discussed in chapter II.

Chapter II

Synthesis of 2,5-anhydro-D,L-glucose derivatives

(1) Synthesis of methyl 2-(2β,3α-dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (128) and methyl 2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (137)

It has been demonstrated over the past several years that the furanosyl α-keto esters (84a) are very useful as intermediates for the synthesis of the C-nucleosides, showdomycin and pyrazofurin A. Our first synthetic goal was to synthesize the key intermediate, α-keto ester (116). Here, the ready conversion of the olefin ester into the keto ester will be described.

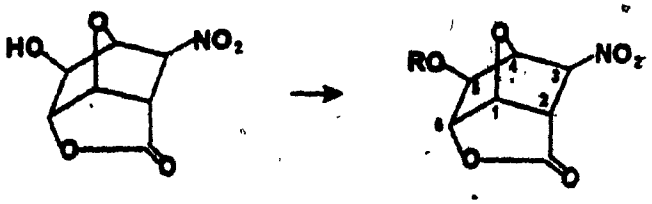


(116)

The synthetic route for the preparation of the olefin ester with proper stereochemistry was well established in chapter I. The reaction sequence was repeated in simplified

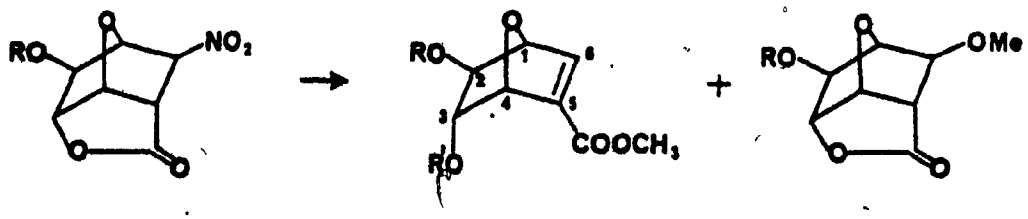
manner to improve yields.

The hydroxy lactone (97) was converted into its tert-butyldimethylsilyl ether (117) by reaction with tert-butyldimethylsilyl chloride and imidazole according to the procedure of Corey et al.[96] The crystalline product, m.p. 112-113°, was obtained in 90% yield. This process seems to proceed via N-tert-butyldimethylsilylimidazole, the conjugated acid of which can be expected to be very reactive silylating agent. The silyl ether (117) was completely identified by its n.m.r. spectrum. The bridgehead C-1 proton appeared as a triplet at δ 5.51 (J=5 Hz) due to coupling with the C-2 and C-6 protons. Another bridgehead C-4 proton resonated as a singlet at δ 4.84 because of no coupling with adjacent endo protons. Two doublets at δ 3.76 and 4.58 with J=5 Hz were assigned to the C-2 and C-6 protons, both of which coupled with the C-1 proton. The $J_{2exo,3endo}$ and $J_{5endo,6exo}$ were too small to identify. Two singlets at δ 4.00 and 5.14 represented the C-5 and C-3 protons. The tert-butyl and dimethyl protons were observed as singlets at δ 0.95 and 0.16 respectively.



(97) (117) R=$Si(CH_3)_2C(CH_3)_3$

Treatment of the lactone (117) with DBU in refluxing methanol for 1 hr gave the hydroxy olefin ester (118), resulting from opening the lactone followed by elimination of nitrous acid. After ready separation by column chromatography on silicic acid, the fast moving side product (119) was isolated while the slower moving hydroxy olefin ester (118) was obtained as an oil in 84% yield. This product was also obtained when the lactone was refluxed with triethylamine in methanol for 6 hr.



(117) (118) R'=H (119)

(120) R'=COC(CH$_3$)$_3$

R=Si(CH$_3$)$_2$C(CH$_3$)$_3$ (121) R=R'

In the n.m.r. spectrum of (118), one proton doublet appeared at δ 7.08 (J=2 Hz) corresponding to the vinyl proton which coupled with the C-1 proton at δ 4.75 (J=2 Hz). An exchangeable proton was observed at δ 3.37. The chemical shift of the C-2 endo proton at δ 3.66 was shifted to higher field by 0.34 ppm than that of the corresponding proton in the lactone (117). This may be explained in terms of the diamagnetic anisotropy of the carbon-carbon double bond. The resonances due to the C-4 and C-3 protons gave doublets

(J=5 Hz) at δ 5.01 and 4.13 respectively.

The side product was shown by n.m.r. and i.r. to be the methoxy lactone (119), which probably arose by the same mode of reaction as already discussed in chapter I.

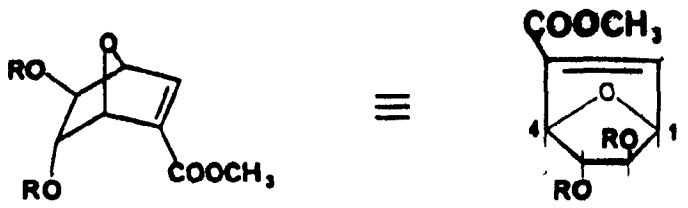
The hydroxy olefin ester was well characterized as its pivalate (120).

Because of easy removal of the protecting groups at the final stage, it was decided to block the hydroxyl group of (118) as its tert-butyldimethylsilyl ether by the above method. However, silylation proceeded in an unpredictable manner, providing the disilylation product (121) with m.p. 90-91° in low yield. No pure material was isolated from the by-products. Conventional silylating techniques using, for example, excess silyl chloride in pyridine or sodium hydride in tetrahydrofuran were unpromising.

The spectral data (i.r., n.m.r.) of (121) was identical with those of the compound (110), which was prepared by different route (see chapter I). The above method of synthesis makes the confirmation of the olefin ester unambiguous, and the structure of the product is further supported by n.m.r. spectroscopy.

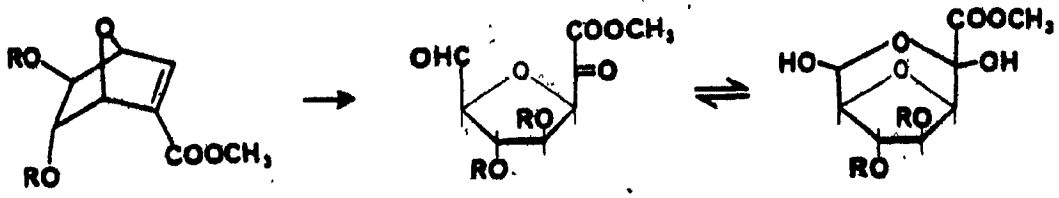
So far, we clearly established the stereochemistry of the 2- and 3-hydroxyl groups. Also, the potential aglycon moiety of the C-1 position and potential hydroxymethyl function of the C-4 position which will be elaborated later on should be

cis to each other, because this stereochemistry was already defined at the Diels-Alder reaction stage. Therefore, our approach will provide an unambiguous synthesis of the β-anomer of the final product.



(121)

Oxidation of the olefin ester (121) with ruthenium tetroxide[97] over a short period of time permitted the isolation of the aldehydo keto ester (122) as a major product with m.p. 81° in 48% yield after column chromatography. The n.m.r. spectrum clearly indicated the presence of a free aldehyde function. One aldehydic proton was observed at δ 9.13 and a good elemental analysis was obtained.



(121) (122) (123)

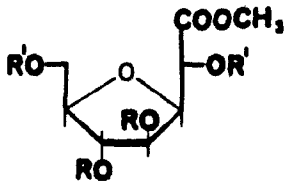
R=Si(CH$_3$)$_2$C(CH$_3$)$_3$

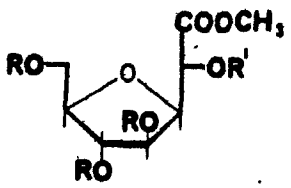
* No absolute stereochemistry is implied in the drawing.

Ozonolysis of the olefin ester (121) followed by reductive work-up with dimethyl sulfide[98] gave a quantitative yield of the aldehydo keto ester (122) in a few instances. This compound was identical in all respects (n.m.r., i.r., m.p.) with the compound previously obtained. In most cases, the reductive ozonolysis afforded a mixture of the aldehydo keto ester (122) and the hydrated hemiacetal (123) in quantitative yield without purification.

Selective reduction of the aldehydo keto ester (122) to the keto ester (128a) was attempted with zinc borohydride.[99] In spite of numerous attempts, no selectivity in the reduction of the aldehydo group was observed and the diol (124) was obtained as a major product in 30% yield. Reduction with diborane-tetrahydrofuran complex[100] yielded the diol as a major product in 45% yield. Reduction with lithium tri-tert-butoxy-aluminum hydride[101] gave the diol in 60% yield. The diol was fully characterized as its diacetate (125). Its n.m.r. spectrum showed two three-proton singlets at δ 2.03 and 2.10 for the acetates. It should be pointed out that we did not know whether the diol (124) and the diacetate (125) would be a pure isomer or a mixture of isomers at C-2.

Since there was no selectivity in the reduction of aldehydo group of (122), it was decided to protect selectively the primary hydroxyl group, and to oxidize the secondary hydroxyl group of the diol (124).





(124) R'=H

(125) R'=Ac

(126) R'=H

(127) R'=Ac

$R=Si(CH_3)_2C(CH_3)_3$

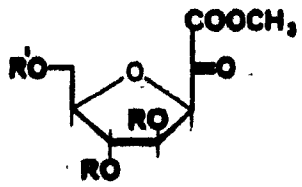
Ogilvie and co-workers[102] reported that tert-butyldimethylsilyl chloride reagent is selective for the 5'-hydroxy group in thymidine in the presence of 3'-hydroxy function. We therefore determined whether tert-butyldimethylsilyl chloride would show similar selectivity in our system.

Thus, the reaction of the diol (124) with one equivalent of the tert-butyldimethylsilyl chloride and 2.5 equivalents of imidazole in dimethylformamide gave the hydroxy ester (126) in 94% yield after purification by a column of alumina using hexane-ethyl ether. Its n.m.r. spectrum showed an exchangeable proton at δ 2.96. From the n.m.r. spectral data, we were unable to know whether the desired product (126) was formed or not.

In order to establish the structure of this compound, the silylated hydroxy ester (126) was converted to its acetate (127). In its n.m.r. spectrum, the C-2 proton of the hydroxy ester (126) was shifted downfield by about 0.8 ppm, which indicated that the acetate group was attached to a secondary alcohol

function. We could therefore conclude that protection of the diol with the silyl chloride led to the desired product (126). Since for our purpose a distinction between two possible isomers of the hydroxy ester was unnecessary, we decided to abandon the separation and assignment of configuration.

At this point, we looked for an oxidation procedure to generate the structural features of a keto ester on which an aglycon moiety could be built. Because of the nature of the acid-labile protecting groups, the oxidation of the secondary alcohol function should be carried out at neutral conditions. Oxidation with sodium periodate-ruthenium dioxide[97] appeared to be a promising method. Oxidation of the hydroxy ester (126) to the keto ester (128) was achieved in good yield by using ruthenium dioxide-sodium periodate in carbon tetrachloride and water with vigorous stirring. The pH was kept between 6 and 7 by the addition of a sodium bicarbonate solution.



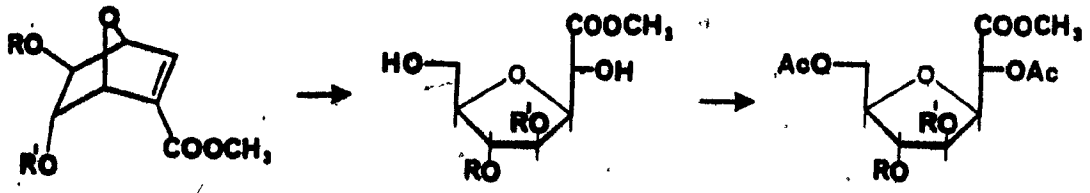
(128) R=R'=$Si(CH_3)_2C(CH_3)_3$

(128a) R=$Si(CH_3)_2C(CH_3)_3$, R'=H

Attempts to purify the product by either column or preparative thin layer chromatography on silicic acid led to decomposition. It is known that the α-keto ester-containing compounds are extremely labile and partial decomposition on silicic acid occurs.[40,41] The oxidation step itself, however, appeared to be quite clean. Since a small amount of impurities did not interfere with subsequent steps (see chapter III), we routinely prepared the keto ester prior to use and treated it without further purification. Following spectral data were highly supportive of its structure. The i.r. spectrum showed strong absorption bands at 1730 and 1750 cm^{-1}. In the n.m.r. spectrum the expected doublet appeared at δ 5.06 (J=5 Hz) for the C-1' proton due to coupling with the C-2' proton.

Because of the low yield of the second silylation encountered at one stage in this sequence (118→121), the above reaction sequence was repeated starting with 5-carbomethoxy-3-endo-pivaloyloxy-2-exo-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene (120).

Reductive ozonolysis of the olefin ester (120) with dimethyl sulfide in methylene chloride led to a number of unidentified products. In the n.m.r. spectrum, the pivalate group showed many singlets and also, t.l.c. indicated the presence of many compounds. Without purification, the resulting mixture was treated with lithium tri-tert-butoxyaluminum hydride in tetrahydrofuran at 0° for 5 hr to give, after

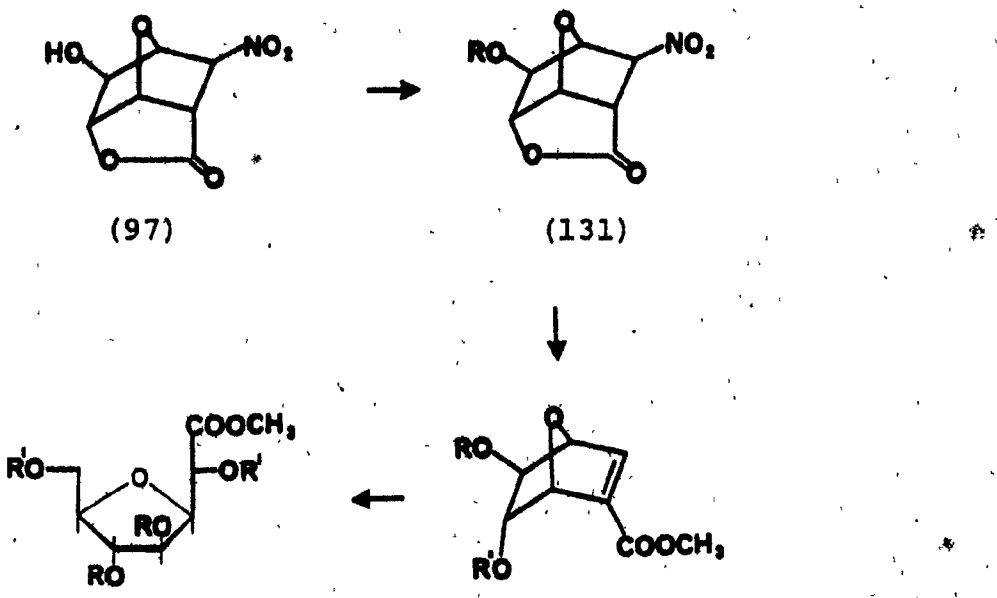


(120) (129) (130)

R=$Si(CH_3)_2C(CH_3)_3$ R'=$COC(CH_3)_3$

chromatography on silicic acid, a 30% yield of the diol (129) from the olefin ester. The diol was transformed to its diacetate (130). The structure of this product (130) was clear from the n.m.r. spectrum. The reason of the low yield of the diol is probably that the pivalate group interacts with the hydroxyl group generated in the ozonolysis-reduction sequence. Ouellet[93] encountered the same problem in the carbocyclic nucleoside series.

Therefore, we sought another suitable protecting group. Methoxymethyl ether was chosen because of the readily available reagent (dimethoxymethane) at low cost and clean reaction with short reaction time. The hydroxy lactone (97) was treated with dimethoxymethane and phosphorus pentoxide[103] in tetrahydrofuran at room temperature for 1.5 hr to give the crystalline product (131) with m.p. 154-155° in almost quantitative yield. The compound was identified by its n.m.r. spectrum which was quite similar to those of other γ-lactones of 7-oxabicyclo [2.2.1]



(97) (131)

(134) R'=H
(135) R'=Ac

(132) R'=H
(133) R=R'

$R=CH_2OCH_3$

heptanes available in this series. The methoxy protons appeared as a singlet at δ 3.06 and methylene protons ($-OCH_2O-$) gave rise to resonance at δ 4.43 as a singlet. All other protons showed the same multiplicity as other γ-lactones (97,117).

Reaction of the lactone (131) with DBU in refluxing methanol gave the hydroxy olefin ester (132) in 68% yield after purification by column chromatography on silicic acid. This compound was also obtained by treatment of the lactone (131) with triethylamine in refluxing methanol for 8 hr.

Treatment of the hydroxy olefin ester (132) with dimethoxymethane and phosphorus pentoxide in chloroform produced a 84% yield of the olefin ester (133). In the n.m.r. spectrum the endo- and exo-methoxy protons appeared as singlets at δ 3.36

and 3.42 respectively. The vinyl proton gave a doublet at δ 7.15 (J=2 Hz) as in other 7-oxabicyclo [2.2.1] heptenes. Bridgehead C-1 and C-4 protons showed differences in coupling constants and chemical shifts. While the C-4 proton at δ 5.12 (J=4 Hz) coupled with the C-3 proton at δ 4.20 (J=4 Hz), the C-1 proton gave a doublet at δ 4.99 with a smaller coupling constant (J=2 Hz). The C-2 proton showed a singlet at δ 3.66. The relative chemical shifts and coupling constants were in accord with those of the disilyl olefin ester (121). The i.r. spectrum showed strong absorptions for the conjugated ester carbonyl (1730 cm^{-1}) and conjugated double bond (1625 cm^{-1}).

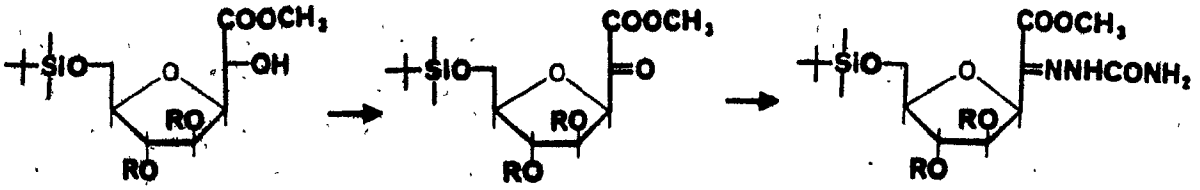
An advantage of the methoxymethyl ether over other protecting groups is that the product can be easily identified by n.m.r. spectroscopy and has no chiral center. This protecting group was satisfactory to accomplish the synthesis of 2'-epi-showdomycin.

Ozonolysis of the olefin ester (133), followed by treatment with dimethyl sulfide and reduction of the resulting aldehydo keto ester-obtained in part as its hydrate- with 4 equivalents of lithium tri-tert-butoxyaluminum hydride, gave the diol (134). The diol was obtained in 59% yield by purification on t.l.c. plates. Acetylation of the diol (134) afforded the diacetate (135).

We already knew that tert-butyldimethylsilyl chloride had shown selectivity in the protection of the diol (124).

Treatment of the diol (134) with 1 equivalent of tert-butyldimethylsilyl chloride and 2.5 equivalents of imidazole in dimethylformamide gave the oily monosilyl derivative (136) in 85% yield.

The keto ester (137) was obtained in good yield when the hydroxy ester (136) was subjected to the same conditions utilized for the preparation of the keto ester (128) from the hydroxy ester (126). In agreement with the keto ester structure, the i.r. spectrum showed two carbonyl absorption bands at 1735 and 1760 cm^{-1}. Nevertheless, the proof of the structure was accomplished by treatment of the keto ester with semicarbazide and obtaining semicarbazone derivative (138) in 60% yield.



(136) (137) (138)

R=CH_2OCH_3

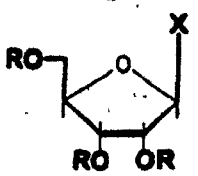
Its i.r. spectrum showed a strong absorption at 1590 (C=N), 1625 ($CONH_2$) and 1725 cm^{-1} (C=O). The u.v. spectrum (λ_{max}^{EtOH} 270 nm) substantiated the formation of the semicarbazone. In the n.m.r. spectrum, two broad singlets at δ 9.63 and 10.53 (half proton each) indicated that a 1:1 mixture of geometric

isomers had been formed. The lower field NH proton resonance reflects the anticipated deshielding effect of the proximate carbonyl group of the syn configuration.[105]

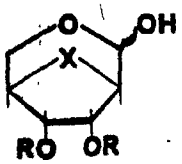
The α-keto ester (137) was the initial synthetic goal of this project. It was obtained from the exo-nitro adduct (90) in an overall yield of 6.5% in 8 steps. The keto ester met the stereochemical requirement for our synthesis, the 4β-tert-butyldimethylsiloxymethyl group being cis to the keto ester function.

(2) Synthesis of 3,4-di-O-methoxymethyl-2,5-anhydro-D,L-glucose

Another type of C-glycosyl derivative which has received much attention recently is represented by the 2,5-anhydro sugars (139,140), from which triazole, pyrazole, and isoxazole C-nucleosides are prepared by Witting reactions and 1,3-dipolar additions as shown in the introduction. Therefore, we investigated the synthesis of 2,5-anhydroglucose such as (141).

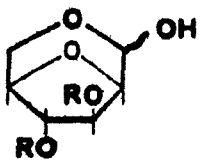


(139) X=CHO



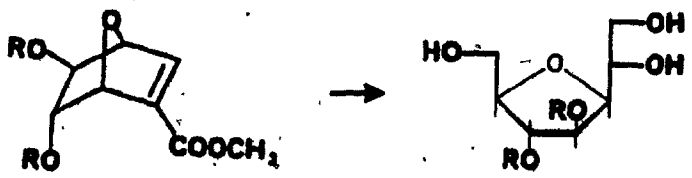
(140a) X=O

(140b) X=CH_2

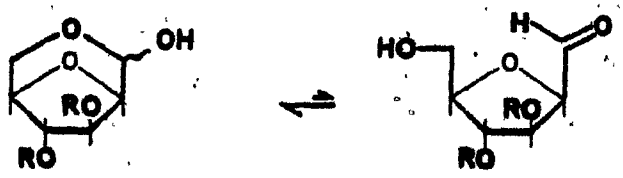


(141)

Ozonolysis of the olefin ester (133) in methylene chloride at low temperature led to an ozonide. In order to prepare the triol (142), the resulting ozonide was treated with sodium borohydride in isopropanol at 0° for 1 hr followed by refluxing for 2 hr. The reaction mixture was then acidified with aqueous acetic acid and evaporated, leaving a white solid which was directly submitted to periodate cleavage in water for 1 hr. By this method, the 2,5-anhydro-D,L-glucose (144) was obtained in 37% yield based on the olefin ester. The product existed in the hemiacetal form as shown. The structural proof for this product was derived form the fact that no aldehydic proton could be detected in the n.m.r. spectrum and no carbonyl absorptions were observed in the i.r. spectrum.



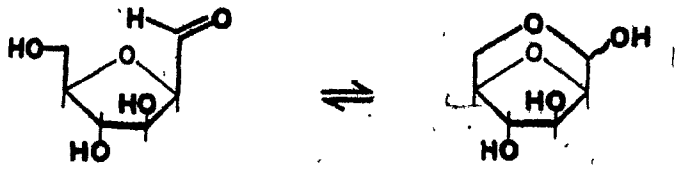
(133) (142)



(144) (143)

$R=CH_2OCH_3$

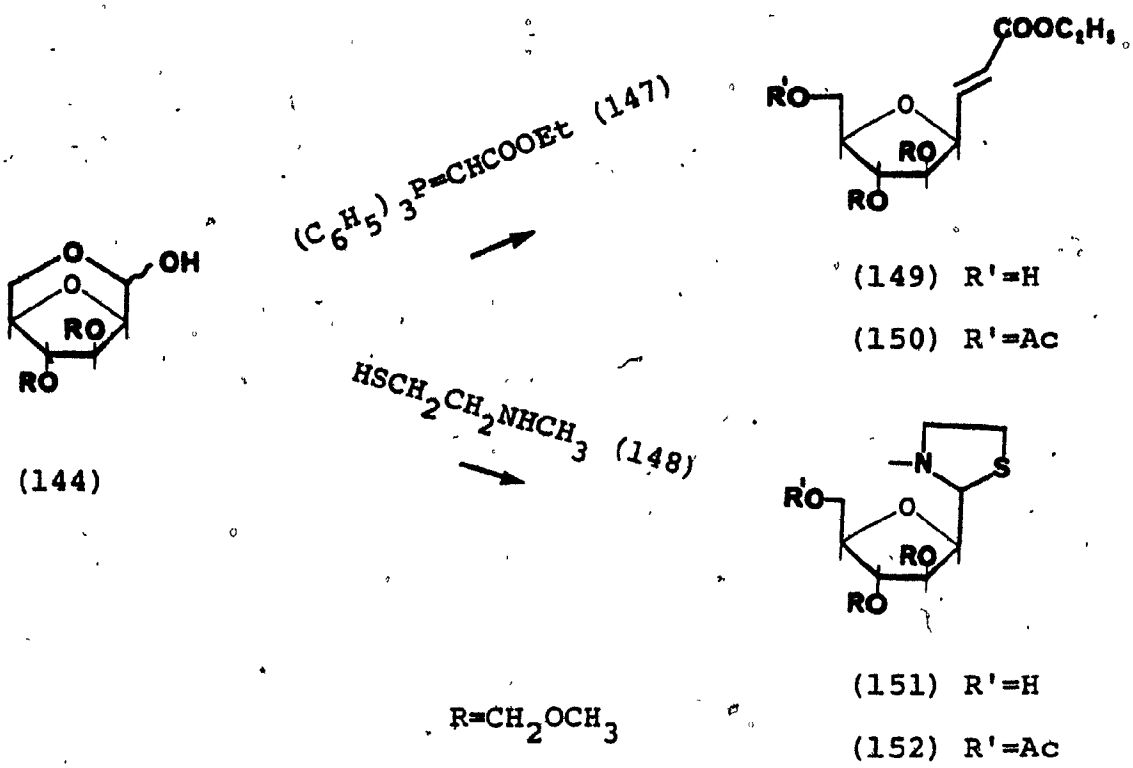
Inspection of molecular models of the 2,5-anhydroaldohexoses reveals that, when the carbonyl group and the primary alcohol group on C-6 are cis-disposed, the formation of a 1,6-hemiacetal is possible without much strain. Defaye[106] pointed out that the formation of an intramolecular hemiacetal (146) in 2,5-anhydroaldehydo-D-glucose (145) could occur easily. In terms of entropy, the hemiacetal formation is much more favorable here. In ordinary hemiacetal formation two molecules, the alcohol and aldehyde, must be tied down, and there is a considerable loss of freedom of motion. In internal hemiacetal formation, only one molecule is involved and much less loss of freedom occurs since only some rotational freedom becomes restricted.[107]



(145) (146)

In order to get further proof of the structure of (144) the hemiacetal (144) was subjected to the following Wittig reaction.

Without any further purification the hemiacetal was condensed with carboethoxymethylenetriphenylphosphorane (147) in methylene chloride at room temperature for 4 hr.



Following chromatography on alumina, the α,β-unsaturated ester (149) was obtained in 79% yield as a homogeneous syrup. Examination by n.m.r. spectroscopy showed that the α,β-unsaturated ester was the pure trans isomer, the C-2 and C-3 protons appearing as sharp doublets of doublets at δ 5.98 and 6.85 with $J_{2,3}$=14 Hz characteristic of a trans/olefin.[108] The above reaction conditions were similar to those used in the condensation of 2,5-anhydro-D-allose with carbomethoxymethylene-triphenylphosphorane.[48] The fact that the product was only trans isomer can be explained if we consider the structure of the intermediate betaine.[109] The threo structure leading to the trans isomer is probably more stable than the erythro which leads to the cis olefin. Similar condensation of 2,5-anhydro-

D-allose (140a) with the above phosphorane gave only the trans olefin ester.[110]

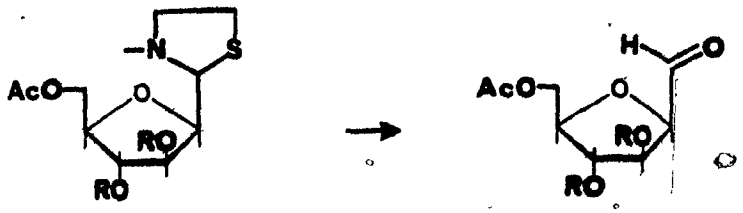
Acetylation of (149) gave the oily acetate (150) in 89% yield after purification by chromatography on alumina.

Since the carboethoxy substituent activates the double bond, the olefin ester is expected to be a good dipolarophile.[111] The utility of this type of compounds as precursors to C-nucleosides has been demonstrated by 1,3-dipolar cycloaddition with diazomethane by other workers.[48,49]

In connection with the synthesis in our laboratory of a series of C-nucleosides, it has been shown that 2,5-anhydro-D-allose (140a) does not readily react with unstable Wittig reagents, for example methylenetriphenylphosphorane.[112] Since this lack of reactivity severely curtails the synthetic utility, we therefore decided to prepare the precursor to the free aldehyde of type (139) which could be a more versatile intermediate. The approach involves three steps: (1) ring opening of the hemiacetal by formation of a suitable derivative of the potential aldehyde; (2) protection of the primary alcohol function; (3) generation of the free aldehyde.

Reaction of the 2,5-anhydro-D,L-glucose (144) with N-methylthioethanolamine (148)[113] in benzene gave the thiazolidine derivative (151). Without purification or further examination the product was directly converted to its acetate derivative (152) in 77% yield from the hemiacetal. This compound

was stable enough to be purified by preparative thin layer chromatography. Since cleavage of the thiazolidine group with one equivalent of mercuric chloride in tetrahydrofuran-water generally gives the free aldehyde;[114] this material would provide precursor to the free aldehyde (153). The thiazolidine derivatives have been shown to be versatile precursors to C-nucleosides in our laboratory![112] No further work has been done with (152).



(152) (153)

R=CH_2OCH_3

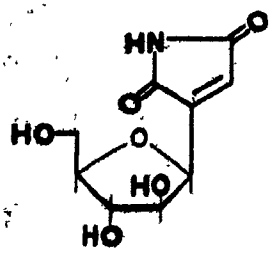
Chapter III

Synthesis of D,L-2'-epi-showdomycin and D,L-2'-epi-pyrazofurin A

(1) Synthesis of D,L-2'-epi-showdomycin

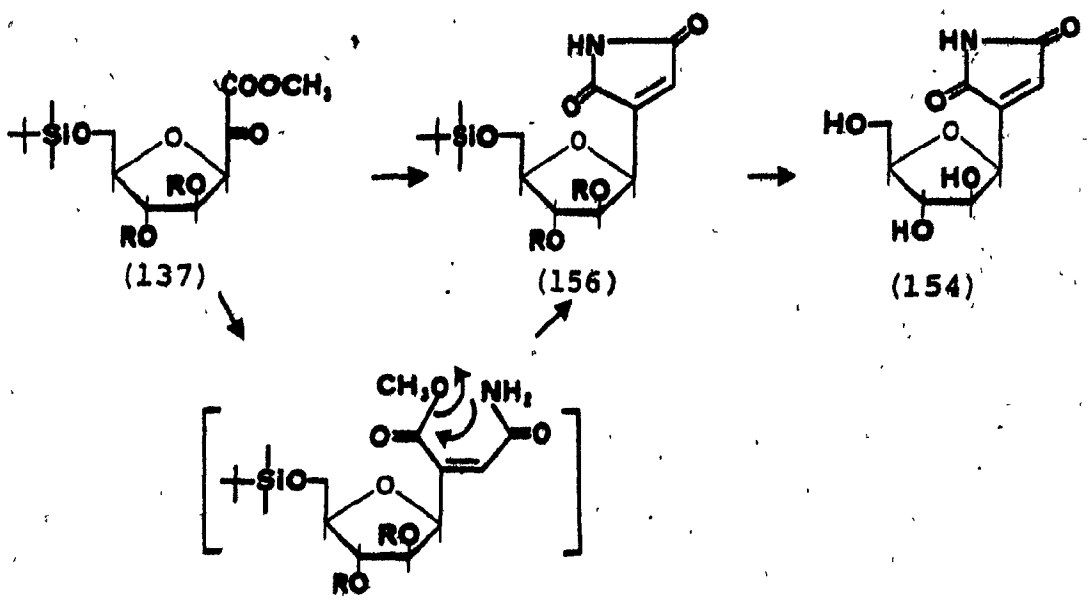
The first synthesis of showdomycin (3) has been briefly reported by Kalvoda et al.[39] It involved, as the key intermediate, keto ester of type (84a). The conversion of the keto ester required a six-step sequence. Recently, Moffatt and co-workers[40] reported a much simplified two-step conversion of the keto ester into showdomycin via the reaction of the keto ester with carbamoylmethylenetriphenylphosphorane.

The synthetic route developed by Moffatt seems capable of extension to the preparation of D,L-2'-epi-showdomycin (154).



(154)

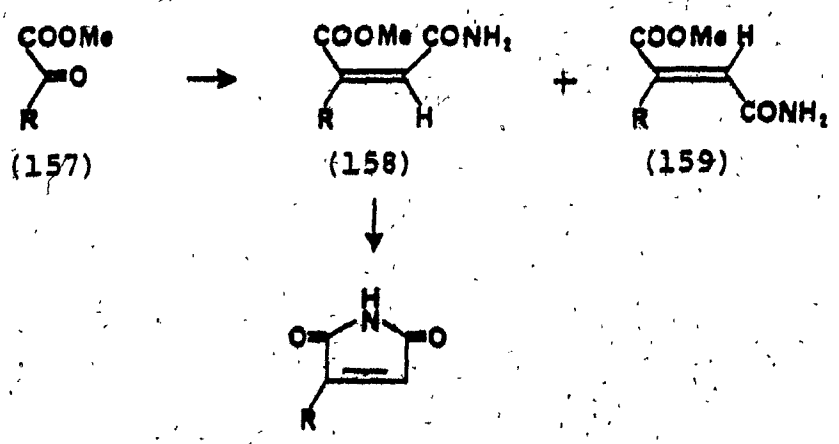
The keto ester (137) reacted with one equivalent of carbamoylmethylenetriphenylphosphorane (38)[115] in chloroform at room temperature for 2 hr. The reaction gave a single major product together with considerable amounts of polar by-products.



Purification of the crude product by chromatography on silica gel plates using hexane-ethyl ether (1:1) gave the maleimide (156) in an overall yield of 40% from the hydroxy ester (136). The n.m.r. spectrum of this substance clearly showed the disappearance of the methyl ester group and the presence of a single NH proton at δ 8.08 and a vinyl proton at δ 6.39. The i.r. spectrum showed characteristic absorption bands at 1790 and 1740 cm^{-1} for the carbonyl function and at 1655 cm^{-1} for the olefinic bond. In the mass spectrum, the molecular ion peak was found at m/e 431 and other major peaks at m/e 400 (M^+-OCH_3) and 374 ($M^+-C(CH_3)_3$). Furthermore, the u.v. spectrum revealed the typical maleimide chromophore having absorption maximum at 222 nm (log ε 4.2). These can be explained by

spontaneous cyclization of an intermediate cis-oriented maleamic acid ester (155) to the corresponding maleimide. It could not be ruled out that cyclization occurred at the betaine level preceding actual formation of (155).

No pure materials were isolated from the polar by-products which contained triphenylphosphine oxide. It is not clear whether these by-products are result of decomposition of the labile keto ester, to a general instability towards nucleophiles of the maleimide ring, or to further reaction of (156) with the phosphorane (38).



Moffatt and co-workers[40] examined this cyclization reaction of methyl pyruvate and methyl phenylglyoxylate with the phosphorane (38) and obtained the following results: (1) the reaction of carbamoylmethylenetriphenylphosphorane with the keto ester (157) produces the cis-oriented maleamate (158)

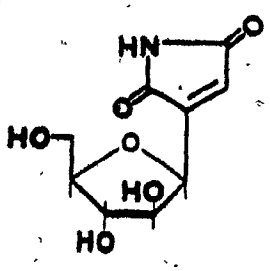
and trans-oriented fumaramate (159): (2) the cis-oriented maleamate undergoes spontaneous cyclization to the maleimide (160): (3) the ratio of cis- and trans-oriented isomers is controlled by the substituent R. From the above results they concluded that the reaction of α-keto esters (157) with (38) provides a direct route to 2-substituted maleimide providing that the substituent R is reasonably bulky.

Completion of the synthesis of D,L-2'-epi-showdomycin then only required removal of the protecting groups. Treatment of (156) with 80% aqueous trifluoroacetic acid led to the simultaneous removal of both tert-butyldimethylsilyl and methoxymethyl groups. Subsequent purification on silica gel plates gave crystalline D,L-2'-epi-showdomycin (154), m.p. 170-171° in 60% yield. The u.v. spectrum of product showed an absorption at 222 nm and the molar extinction coefficient (log ε 4.36) was also in accord with that of the known showdomycin,[16] thus confirming the structure of the aglycon moiety of (154). The i.r. data and elemental analysis were consistent with the structure assigned. Furthermore, this compound was fully identified by its mass spectrum.

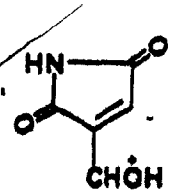
The past few years have witnessed the usefulness of mass spectrometry in the structural elucidation of C-nucleosides.[18,45] There is a striking difference in the fragmentation pattern of C-nucleoside antibiotics as compared to nucleosides possessing a C-N bond linkage. The base peak observed for a number of

C-nucleosides occurs at B+30 in contrast to the usual nucleosides where the B+1 or B+2 normally occurs as the predominant peak (B is the heterocyclic base). This B+30 peak has been assigned to the aglycon plus a protonated formyl group which results from fragmentation of the sugar.

The mass spectrum of D,L-2'-epi-showdomycin (154) was quite typical of other C-nucleosides and showed a minor molecular ion peak at m/e 229 and an abundant peak at m/e 211 corresponding to loss of water from the molecular ion. The base peak was found at m/e 126 (B+30) (161) where B was the heterocyclic aglycon. The B+30 peak is strongly suggestive of a formyl type residue attached to the base. Comparison of the major peaks of showdomycin[38] with those of (154) revealed considerable similarity in the fragmentation pattern.



m/e 229



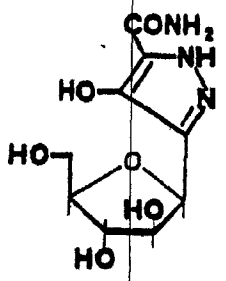
(161)

m/e 126 (B+30)

The overall view of our synthetic route indicated that it afforded a direct and reasonably efficient method for the synthesis of D,L-2'-epi-showdomycin, the overall yield being 1.6% based on the exo-nitro adduct (90).

(2) Synthesis of D,L-2'-epi-pyrazofurin A

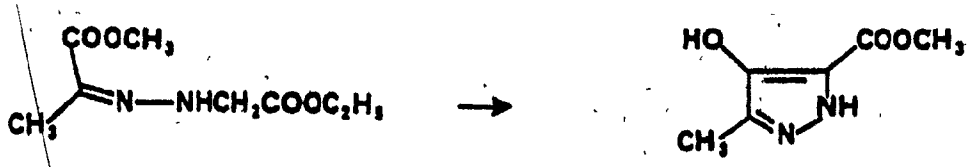
The considerable medical potential of pyrazofurin A due to its antiviral and antitumor activities has made it a interesting target for chemical synthesis. The synthesis of pyrazofurin A has been reported by Farkas et al.[16] and Bernado et al.[17] In this section, the synthesis of D,L-2'-epi-pyrazofurin A (162) will be described.



(162)

Of the various methods available for the synthesis of the 4-hydroxy pyrazole,[116] the condensation of the keto ester with ethyl hydrazinoacetate, followed by Dieckmann reaction of the resulting hydrazone, appeared to be most applicable for our purpose.

With this in mind, the model system was investigated. Methyl pyruvate reacted with ethyl hydrazinoacetate to form the corresponding hydrazone (163) as a solid with m.p. 59-60°. Its i.r. spectrum showed ester carbonyl absorption bands at 1750 and 1725 cm^{-1} and a C=N absorption peak at 1590 cm^{-1}. Its n.m.r. spectrum showed a multiplet at δ 5.96 for the NH

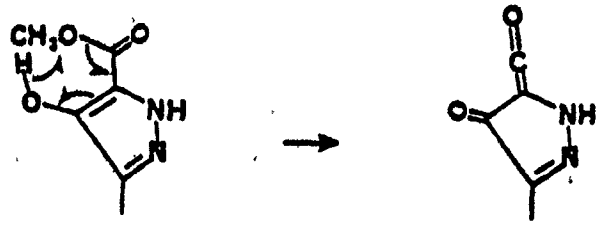


(163) (164)

proton and the u.v. spectrum showed an absorption at 275 nm (log ε 4.04).

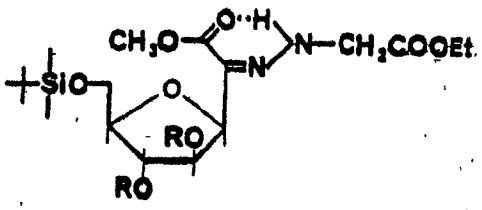
Intramolecular cyclization of the hydrazone (163) using methanolic sodium methoxide under refluxing conditions for 2 hr gave the 4-hydroxy pyrazole (164) in 33% yield. Its u.v. spectrum showed the typical 4-hydroxypyrazole chromophore[117] having λ_{max} at 227 (log ε 3.74) and 276 nm (log ε 3.67) in 0.1N HCl and λ_{max} at 239 (log ε 3.79) and 319 nm (log ε 3.80) in 0.1N NaOH. The above bathochromic shift is due to the formation of the enolate ion. Its i.r. spectrum in chloroform showed two carbonyl absorption bands at 1720 and 1690 cm^{-1}, which provided evidence for a keto-enol equilibrium in chloroform solution![117] Furthermore, the mass spectrum displayed the characteristic McLafferty rearrangement for a 4-hydroxy pyrazole![45] The elimination of the methanol was assumed to proceed via a favorable 6-membered transition state as depicted below. This was also supported by a metastable peak at m/e 98.5 which was calculated from 156→124. The above spectral characteristics

of the hydrazone and the 4-hydroxy pyrazole will be quite useful during the synthesis of 2'-epi-pyrazofurin A.

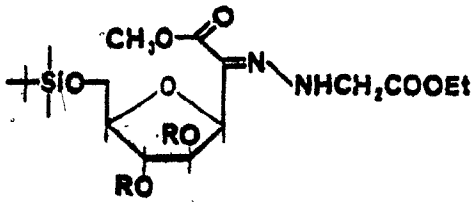


m/e 156 m/e 124

In a direct application of the above model studies to our scheme, the keto ester (137) was treated with ethyl hydrazinoacetate hydrochloride and sodium acetate in aqueous methanol at room temperature to give an oily hydrazone (165,166) in 88% yield after purification on silica gel plates. This compound showed the i.r. absorption bands at 1675, 1715 (C=O), and 1590 cm^{-1} (C=N) and a characteristic u.v. absorption at λ_{max} 287 nm. In the n.m.r. spectrum, the NH proton resonance appeared at δ 9.15 and 9.50 in a ratio of 1:1. This fact is



(165)

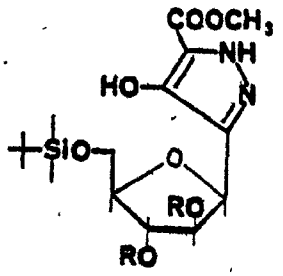


(166)

R=CH_2OCH_3

an indication of the presence of geometrical isomers.[105] Lower field resonance of the NH proton at δ 9.50 in the syn isomer (165) is to be attributable to deshielding effect of internal hydrogen bonding.[105] All attempts to separate these geometrical isomers were unsuccesful.

Without separation of the mixture of geometrical isomers, the hydrazone (165,166) was treated with sodium methoxide in boiling methanol for 2 hr. The n.m.r. spectrum of the crude product was not clear and t.l.c. showed many spots. The u.v. spectrum showed very weak bathochromic shift from acidic to alkaline solution.



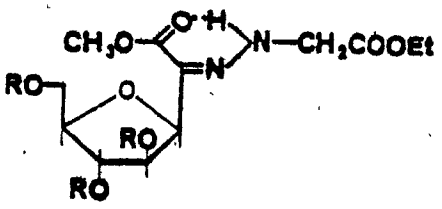
(167) R=CH_2OCH_3

Only a trace amount of the 4-hydroxy pyrazole (167) was isolated by chromatography on silica gel plates. Its u.v. spectrum showed λ_{max} at 228 and 278 nm 0.1N HCl and λ_{max} at 235 and 323 nm in 0.1N NaOH, which was definite proof for the formation of the 4-hydroxy pyrazole. No major product was isolated.

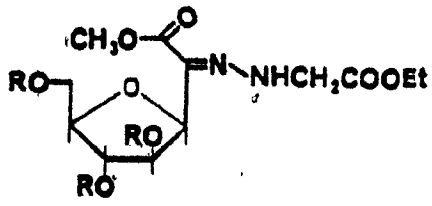
We mentioned briefly that steric effect in the substituent R of the keto ester might control the ratio of geometrical

isomers of the hydrazone. We therefore thought that introduction of the bulky protecting group into 2'-hydroxy group of the sugar might cause the syn isomer to predominate owing to additional steric factors. It was decided to use the tert-butyldimethylsilyl protected keto ester (128) instead of the methoxymethyl protected keto ester (137).

Condensation of the keto ester (128) with ethyl hydrazinoacetate hydrochloride and sodium acetate in aqueous methanol gave an oily hydrazone (168,169) in 72% yield after purification on silica gel plates. According to the n.m.r. spectrum, the NH proton appeared at δ 9.30 and 10.36 in a ratio of 1:2, which indicated the presence of geometrical isomers with predominating syn isomer (168) as expected.



(168)

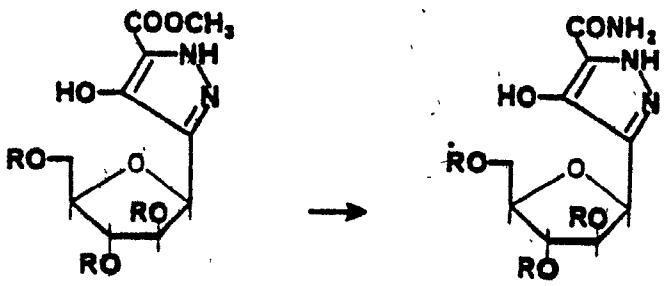


(169)

R=Si(CH$_3$)$_2$C(CH$_3$)$_3$

Without separation of the mixture of geometrical isomers because of close R_f value in various solvent systems, treatment of the hydrazone (168,169) with sodium methoxide in boiling methanol for 4-5 hr gave the 4-hydroxy pyrazole (170) as an oil in 20% yield after purification on silica gel plates

using ethyl ether as eluent. In agreement with the pyrazole structure, the i.r. spectrum of (170) showed strong absorption peaks at 1725 and 1690 cm^{-1} in chloroform which indicated keto-enol equilibrium with prevailing enol form. The u.v. spectrum of (170) in ethanol showed λ_{max} at 230 (log ε 3.72) and 275 nm (log ε 3.58) in 0.1N HCl and λ_{max} at 243 (log ε 3.58) and 320 nm (log ε 3.75) in 0.1N NaOH.

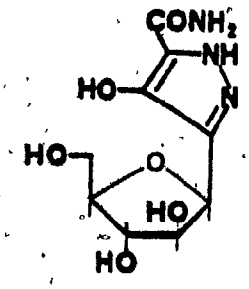


(170) (171)

R=$Si(CH_3)_2C(CH_3)_3$

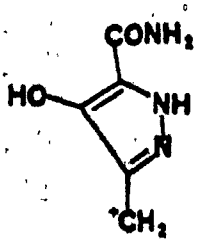
The reaction of the 4-hydroxy pyrazole (170) with methanolic ammonia at room temperature required 7 days to reach completion, and the 5-carboxamide (171) was obtained in 80% yield. Its n.m.r. spectrum showed the presence of NH_2 protons at δ 6.20 and the loss of the methyl ester group, which was confirmed by the absence of the carbonyl absorption above 1700 cm^{-1} in the i.r. spectrum. The strong absorption owing to the carbonyl group of amide was observed at 1675 cm^{-1}.

Completion of the synthesis of D,L-2'-epi-pyrazofurin A then only required removal of the protecting groups from (171).

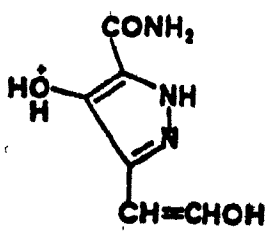


(162)

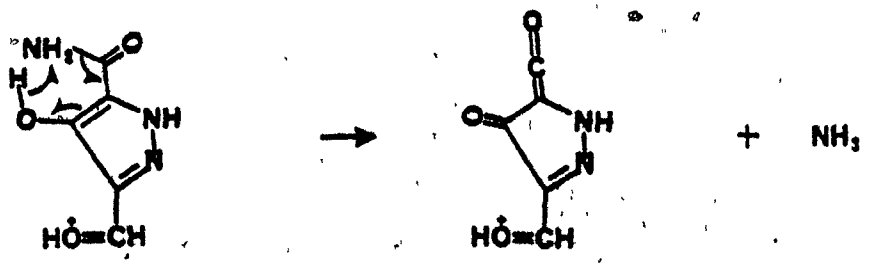
Treatment of (171) with 50% aqueous trifluoroacetic acid at room temperature for 30 min gave the final product (162) as a crystalline compound, m.p. 195-196°, in 75% yield. Spectral data and elemental analysis were consistent with the structure assigned. This compound was fully identified by its mass spectrum. The molecular ion of m/e 259 and base peak at m/e 156 (B+30) which is characteristic in C-nucleosides were observed. The minor ion of m/e 241 and 223 were due to the loss of one and two moles of water respectively, probably from the carbohydrate portion. The peaks at m/e 140 and 170 corresponding to normal nucleoside fragmentation reactions were also observed.



m/e 140



m/e 170



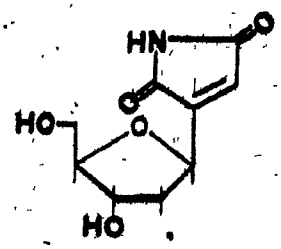
m/e 156 m/e 139

Another diagnostic fragment ion was m/e 139 which arose from the elimination of NH_3 from the hydroxycarboxamido grouping via a 6-membered transition state as shown above. These fragment ions are a direct result of the juxtaposition of the exocyclic hydroxy and carboxamido groups of the aglycon.

Chapter IV

Synthesis of 2-(3α-hydroxy-4β-hydroxymethyl-furan-1β-yl) maleimide (D,L-2'-deoxyshowdomycin)

In the previous chapter in this series we described routes for the stereochemically controlled synthesis of functionalized C-glycosides of general structure of (116) which open pathways to heterocyclic systems. Included in the above work was a facile synthesis of the nucleoside, D,L-2'-epi-showdomycin, via the reaction of the keto ester with carbamoylmethylene-triphenylphosphorane followed by deprotection of the resulting maleimide. This synthetic route seems capable of extension to the preparation of D,L-2'-deoxyshowdomycin (172) via the corresponding reaction of the suitable keto ester with the phosphorane.



(172)

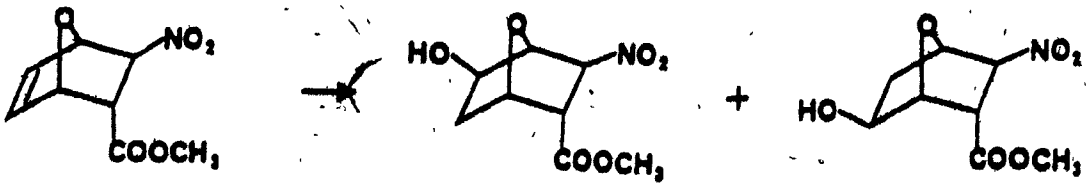
In this chapter, the synthesis of D,L-2'-deoxyshowdomycin,

which is based on a similar reaction scheme and in which olefin ester of type (183) is a key intermediate, will be presented.

The most frequently encountered route for the hydration of carbon-carbon double bond with high regio- and stereo-specificities involves hydroboration-oxidation procedure. Hydroboration proceeds by anti-Markownikoff cis addition from the less hindered side of the double bond.[118] Since hydroboration-oxidation of the norbornene proceeds to give exo-norborneol almost exclusively;[119] this method seems most applicable to our 7-oxabicyclo [2.2.1] heptene system.

Hydroboration of the exo-nitro adduct (90) with borane-tetrahydrofuran complex and oxidation of the resulting organoborane with alkaline hydrogen peroxide[120] were unsatisfactory.

However, hydroboration of (90) with diborane in tetra-hydrofuran at 0°, followed by oxidation with triethylamine N-oxide dihydrate in refluxing tetrahydrofuran as reported by Kabalka;[121] resulted in the formation of the isomeric mixture of the alcohols (173,174) in 42% yield after chromatography on silicic acid. Its n.m.r. spectrum showed two sharp singlets around δ 3.70 which could be assigned to the methyl ester group. These two singlets of the methyl ester group indicated the presence of a mixture of two isomers. The n.m.r. spectrum of a number of more polar unidentified products contained two



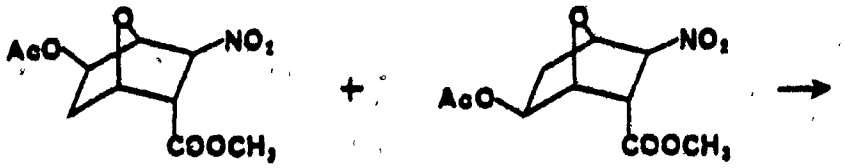
(90) (173) (174)

sets of doublets for a vinyl proton at δ 6.92 and 7.03 which must arise from the nitrous acid elimination product caused by triethylamine generated in the reaction. No pure compound was isolated. Although Kabalka et al.[121] obtained best results in diglyme or xylene, no improvement of yield of the alcohol was made in our case.

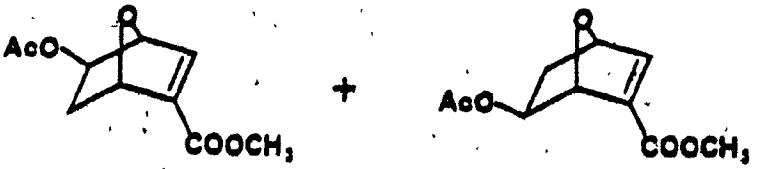
Since hydrogen peroxide oxidation proceeds with clean retention of configuration of the organoborane,[122] we can predict that the above oxidation will take the same course to give exo configuration of alcohol. Indeed, the structure of the reaction products are fully in accord with this prediction.

The resulting isomeric alcohols (173,174) could not be separated by either distillation or chromatography. Without separation, direct acetylation of the alcohol using acetic anhydride and p-toluenesulfonic acid monohydrate afforded the acetates (175,176) in good yield. All attempts to separate both isomeric acetates failed. It is interesting to note

here that acetylation with acetic anhydride in pyridine was unsatisfactory as already mentioned in chapter I.



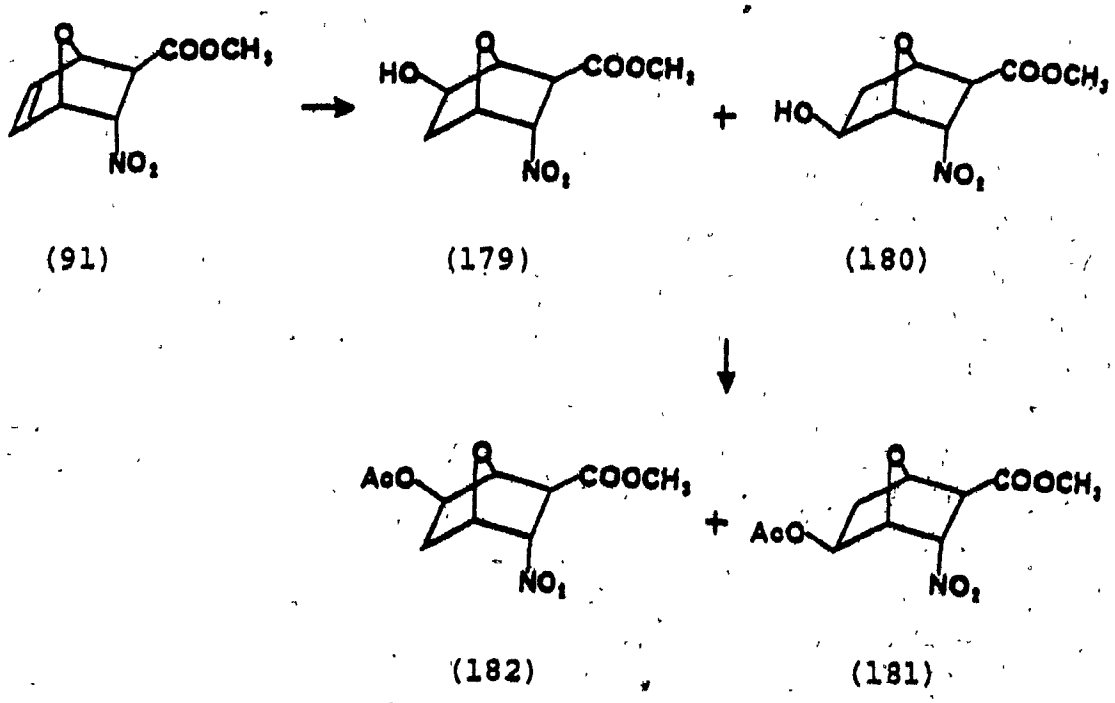
(175) (176)



(177) (178)

In the hope that two isomers might be separated at the next stage, the acetates (175,176) were treated with DBU in methylene chloride under reflux for 1 hr to give the olefin esters (177,178). The products consisted of a 1:1 mixture of isomers according to the n.m.r. spectral data. Two doublets (J=2 Hz) having half a proton intensity each were found at δ 6.92 and 7.03 for the vinyl protons. Once again, the two isomers could not be separated.

The above synthetic route was repeated starting with the endo-nitro adduct (91). Hydroboration of (91) and oxidation of the resulting borane with triethylamine N-oxide dihydrate, under conditions identical to those described above, gave the isomeric alcohols (179,180) which were obtained in 46% yield after column chromatography on silicic acid.



(91) (179) (180)

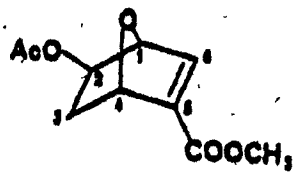
(182) (181)

Without separation of the isomers the mixture of the alcohols was converted into the acetates by reaction with acetic anhydride and p-toluenesulfonic acid monohydrate in 82% yield. Both isomers were found in approximately equal amounts. This conclusion was based on the n.m.r. spectral data where the acetate protons of isomers had different chemical shift at δ 2.00 and 2.03. This observation indicated that hydroboration of the olefin led to a 50:50 distribution of isomeric boranes.

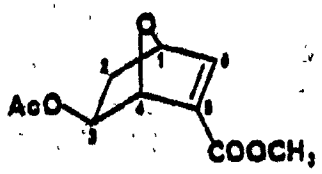
It was possible to separate the two isomers by fractional crystallization from hexane-carbon tetrachloride. One isomer, m.p. 113-114°, was later identified to be the 5-acetate (181) and the other, m.p. 67-68°, to be the 6-acetate (182). At

this stage, we were unable to confirm the structure by n.m.r. spectroscopy. Therefore, we continued the next sequence of our synthetic route.

Elimination of nitrous acid from the 5-acetate (181) by means of 1,5-diazabicyclo [5.4.0] undec-5-ene in refluxing methylene chloride gave the 2-acetate olefin ester (183) in 91% yield. Using the same conditions as above, nitrous acid elimination from the 6-acetate afforded, after chromatography, a good yield of the 3-acetate olefin ester (184). Both isomers had virtually identical i.r. and mass spectra but different n.m.r. spectra. The assignments for the isomers (183,184) were based on the n.m.r. data for these compounds.



(183)



(184)

In the n.m.r. spectrum of the 2-acetate (183) (see Fig. 3), the C-4 proton gave a doublet at δ 5.16 (J=4 Hz) due to coupling with the C-3 exo proton. A doublet for the C-6 proton at δ 6.92 resulted from $J_{6,1}$=2 Hz. Decoupling of the C-6 proton readily allowed identification of the C-1 proton at δ 5.00

(J=2 Hz) because irradiation of the doublet for the C-6 proton collapsed the doublet for the C-1 proton to a singlet. The C-2 proton signal was split into a doublet of doublets with $J_{2,3endo}$=6 Hz and $J_{2,3exo}$=2 Hz (X part of AMX). The C-3 proton appeared as a complex multiplet at δ 1.73-2.20. Remaining two singlets for the carbomethoxy and acetyl protons were found at δ 3.70 and 2.03 respectively.

In the case of the 3-acetate (184) (see Fig. 4), a singlet for the C-4 proton could be expected since there is no coupling between the C-4 proton and C-3 endo proton. In fact, a one-proton singlet overlapped with a one-proton multiplet at δ 4.90-5.10. Irradiation of the multiplet collapsed a doublet for the C-6 proton at δ 7.03 (J=2 Hz) to a singlet. Therefore, it was obvious that a singlet arose from the C-4 proton and a multiplet from the C-1 proton which coupled with the C-6 and C-2 protons. Like the C-2 endo proton in the 2-acetate, the C-3 endo proton showed a doublet of doublets with $J_{3,2endo}$=6 Hz and $J_{3,2exo}$=2 Hz.

The separation of the isomers and the synthesis of the olefin ester (183) was a key step toward a keto ester as shown in chapter II. Our approach so far provided an unambiguous synthesis of the desired olefin ester (183) where the acetate group at C-2 position had exo configuration.

Since we succesfully synthesized an analogue of showdomycin (2'-epi-showdomycin), we decided to follow a similar scheme to

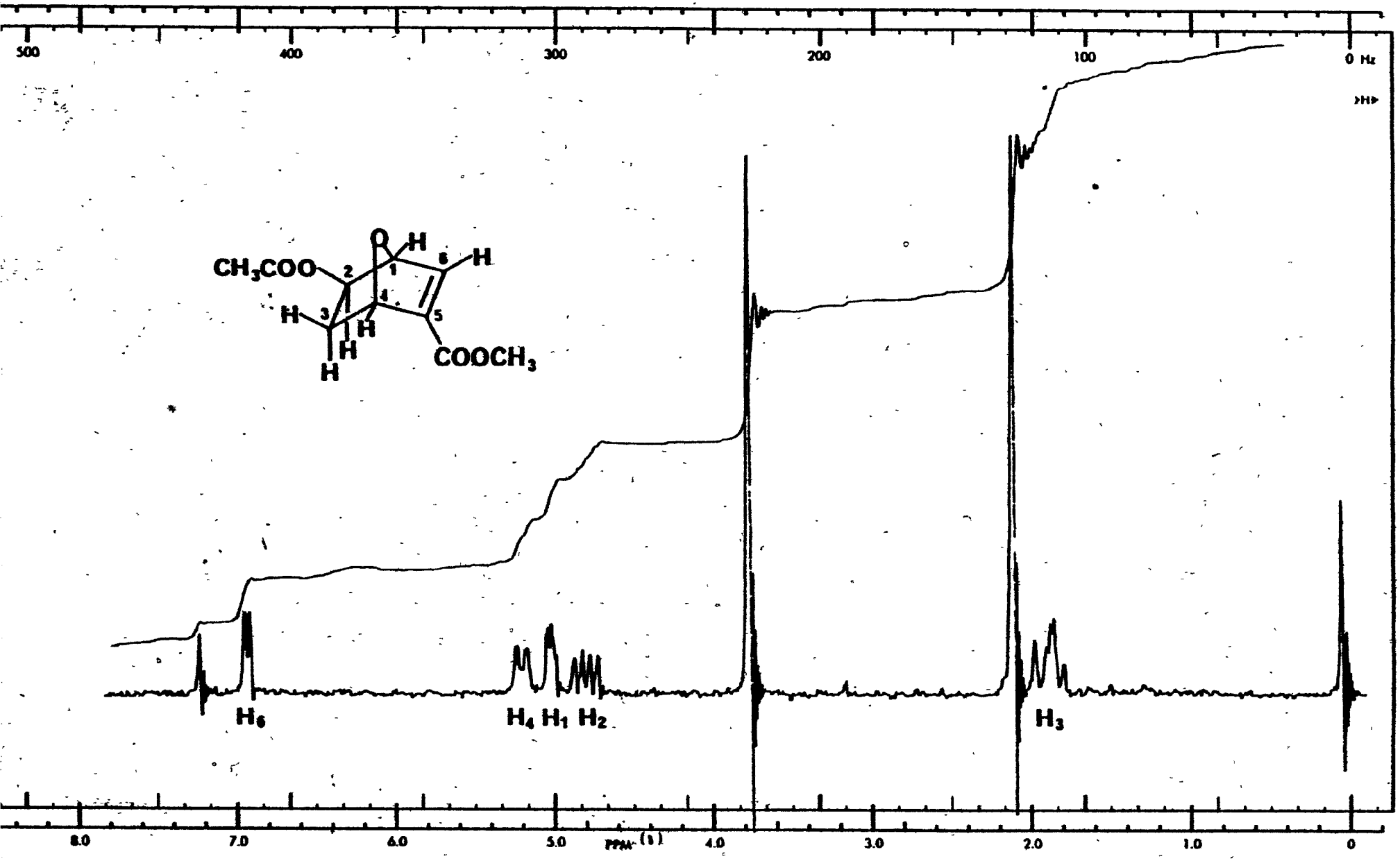


Fig. 3. The n.m.r. spectrum of compound (183) in $CDCl_3$.

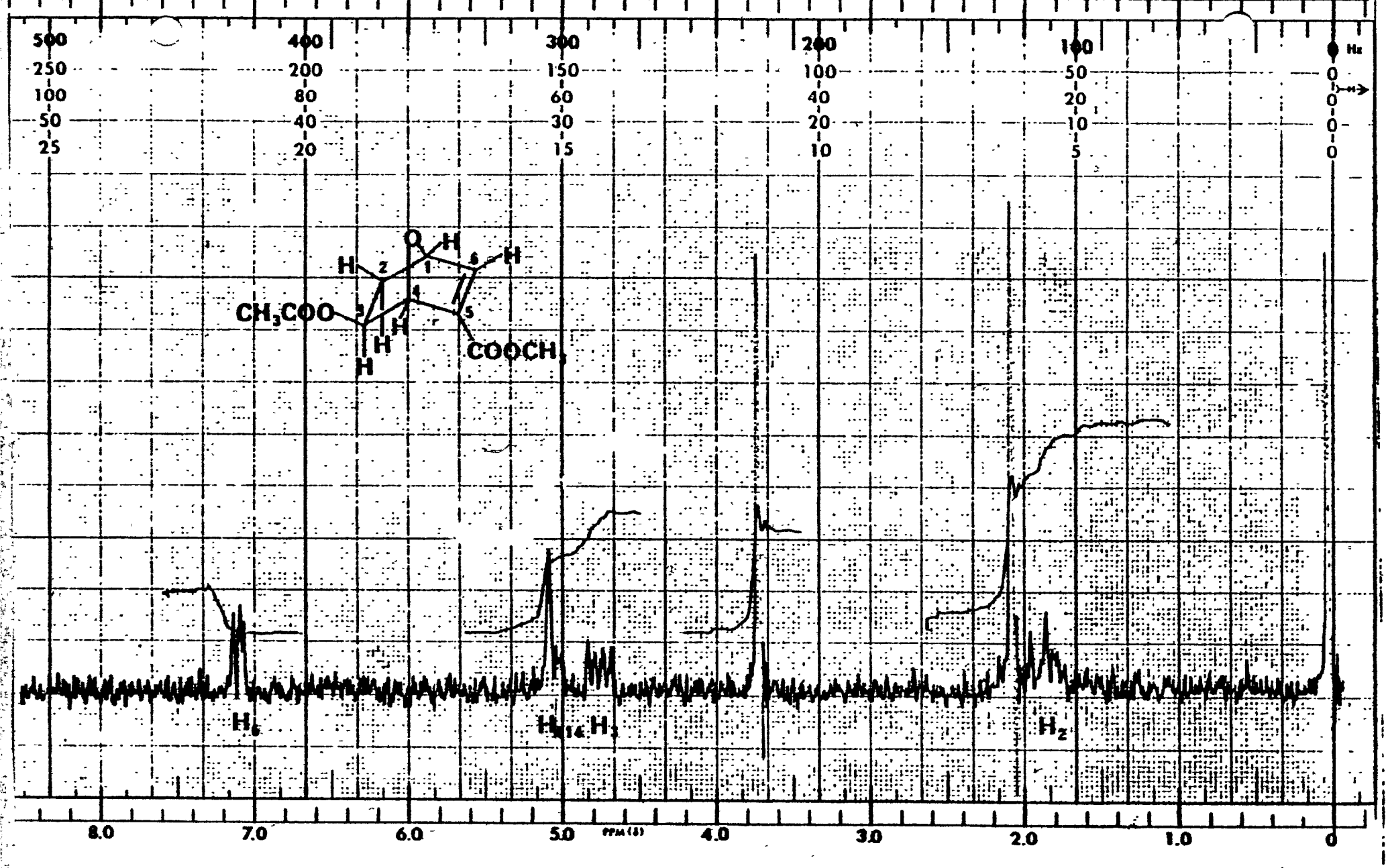
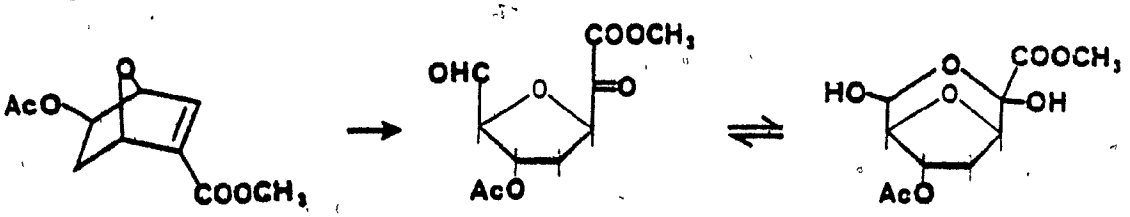


Fig. 4. The n.m.r. spectrum of compound (184) in $CDCl_3$.

synthesize 2'-deoxyshowdomycin.

Ozonolysis of the olefin ester (183) in methylene chloride at low temperature, followed by mild reduction with dimethyl sulfide, afforded the crude aldehydo keto ester (185). Its n.m.r. spectrum indicated the presence of the open form (185a) and the hydrated form (185b) in a ratio of 1:3.

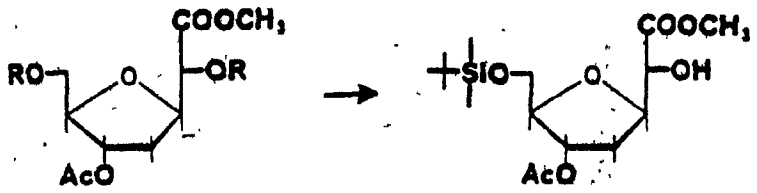


(183) (185a) (185b)

Since we knew that there was no selectivity in reduction of the aldehyde and the ketone group from our previous experience with (122), the aldehydo keto ester was treated with 4 equivalents of lithium tri-tert-butoxyaluminum hydride in tetrahydrofuran at 0° for 4 hr to give the diol ester (186) in 62% yield after column chromatography on silicic acid. The structure of the diol ester was confirmed by acetylation. Elemental analysis, n.m.r., and mass spectra of the triacetate (187) fully supported that structure.

Selective silylation of the diol ester (186) with one equivalent of tert-butyldimethylsilyl chloride and imidazole in dimethylformamide at room temperature for 20 hr provided

the hydroxy ester (188) in 77% yield after purification by column chromatography on silicic acid.



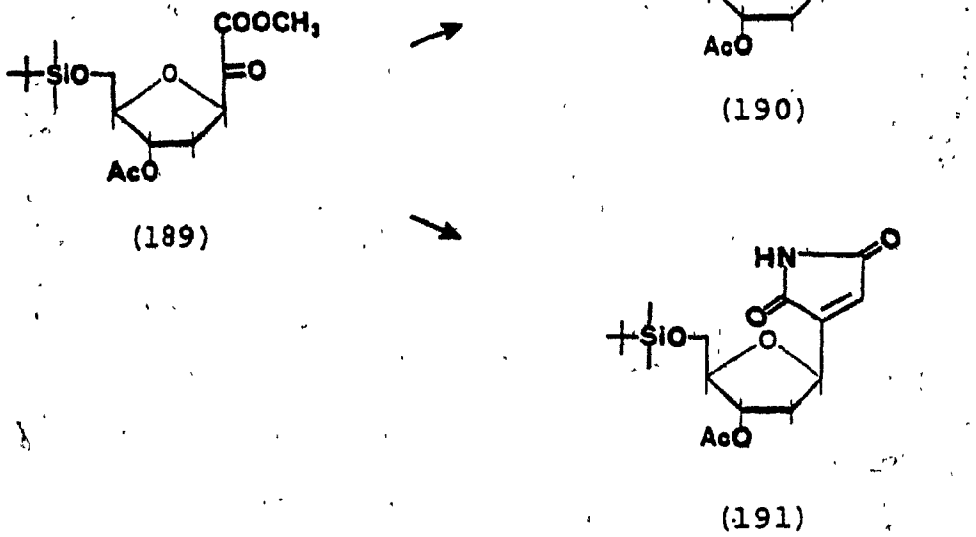
(186) R=H (188)

(187) R=Ac

Our original plan was to oxidize the hydroxy ester to the corresponding keto ester and then treat the latter with carbamoylmethylenetriphenylphosphorane.

Several different methods were examined for the oxidation of the hydroxy ester (188) to the keto ester, methyl 2-(3α-acetoxy-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (189). Ruthenium dioxide-sodium periodate method which was succesfully used in the previous series failed. Using dimethylsulfoxide-dicyclohexylcarbodiimide (DMSO-DCC) with dichloroacetic acid as the proton source[122] the hydroxy ester was converted to the keto ester (189) in low yield within 1 hr at room temperature. The crude product contained some dicyclohexylurea and dicycloacetyl-N,N'-dicyclohexylurea, both known by-products of the oxidation reaction using dichloroacetic acid. No attempts to remove the by-products

were made because of the known instability of the α-keto esters. The proof of the structure of the keto ester (189) was accomplished by direct condensation of the crude keto ester with carboethoxymethylenetriphenylphosphorane in methylene chloride at room temperature for 2 hr and obtaining the maleate (190) in 44% yield. The maleate (190) was considered to have the cis diester structure by analogy with results with other workers.[39,40] The n.m.r. spectrum of (190) showed a doublet at δ 6.03 (J=2 Hz) for the vinyl proton which coupled with the C-1' proton.



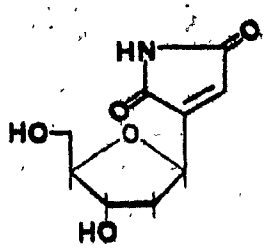
(189) (190) (191)

Because of the low yield of the keto ester, another oxidation method was investigated. When the oxidation of the hydroxy ester (188) was carried out using dimethylsulfoxide-

acetic anhydride[123] at room temperature overnight, better results were obtained. Without any purification the resulting keto ester (189) gave upon condensation with carboethoxymethylenetriphenylphosphorane the corresponding maleate (190) in [illegible]ield. This compound was identical in all respects wit[illegible] compound obtained from DMSO-DCC oxidation and condensation of the above phosphorane.

The keto ester (189) obtained by oxidation with dimethylsulfoxide-acetic anhydride was treated with 1 equivalent of carbamoylmethylenetriphenylphosphorane in chloroform at room temperature for 2 hr. The reaction gave a single major product together with a considerable amount of polar products. By chromatography of the products on silica gel plates, the maleimide (191) was isolated in an overall yield of 38% from the hydroxy ester (188). In agreement with the maleimide structure, this product showed a strong u.v. absorption characteristic for the maleimide chromophore at 222 nm in ethanol. The i.r. spectrum showed a broad absorption at 3420 cm^{-1} (NH) and the typical absorptions at 1780, 1740, 1725, and 1655 cm^{-1} (C=O, C=C). In the mass spectrum the major peak was found at m/e 312 (M^+-$C(CH_3)_3$). The n.m.r. spectrum displayed a single NH proton at δ 8.20 and a vinyl proton at δ 6.55.

The protected 2'-deoxyshowdomycin (191) was subjected to treatment with 0.1N methanolic hydrochloric acid at room temperature for 26 hr to remove the acetyl and silyl groups.



(172)

Subsequent purification by a column of silicic acid using acetone-ethyl acetate (3:7) led to crystalline D,L-2'-deoxy-showdomycin (172), m.p. 122-124°, in 68% yield. Kalvoda[39] and Nakagawa et al.[36] used the same conditions to remove the acetyl groups of 2',3',5'-tri-O-acetyl-showdomycin. The mass spectrum clearly indicated the complete removal of the protecting groups. Molecular ion was found at m/e 213 (M^+) and major fragment corresponding to loss of water from the molecular ion at m/e 195 (M^+-H_2O). The u.v. spectrum showed an absorption at 222 nm (log ε 4.18) like showdomycin and 2'-epi-showdomycin and the molar extinction coefficient was also in accordance with the known examples, thus confirming the structure of the aglycon moiety of (172). Furthermore, the elemental analysis confirmed the purity of the final product.

The synthetic route described seems to be quite simple and straightforward. Therefore, the present method would appear to offer an interesting route to analogues and homologues of showdomycin. By extension of the above work to the preparation

of other type of 2-substituted carbamoylmethylene ylides it would appear possible to develop syntheses of various 2,3-substituted maleimides.

Contributions to knowledge

The equilibration of the isomeric 2-carbomethoxy-3-nitro-7-oxabicyclo [2.2.1] heptenes was accomplished. The tert-butyldimethylsilyl group as a selective protecting group for the primary hydroxyl group adds great versatility to the available protecting groups for C-nucleoside synthesis.

Synthetic routes for the stereochemically controlled preparation of functionalized C-glycosides, the keto ester (128,137,189) and 2,5-anhydro-D,L-glucose (144), which open pathways to heterocyclic systems, were developed. Facile syntheses of D,L-2'-epi-showdomycin, D,L-2'-epi-pyrazofurin A, and D,L-2'-deoxyshowdomycin were accomplished from the keto esters. Valuable intermediates for the synthesis of C-nucleosides were prepared.

The information obtained from the mass spectra of the above C-nucleosides would be useful for the structural elucidation of C-nucleoside antibiotics.

Many new compounds were prepared and characterized.

Experimental Section

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

N.m.r. spectra were obtained on a Varian T-60 or HA-100 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Values given for the coupling constants are first order. Mass spectra were obtained on an AEI-MS-902 mass spectrometer using the direct sample inlet system with 70 eV ionization energy at the indicated temperature. I.r. spectra were obtained on a Unicam SP-1000 or Perkin-Elmer PE-257 infrared spectrometer. U.v. spectra were recorded using a Unicam SP-800 spectrometer.

Analytical thin layer chromatography was done using silica gel coated plastic plates (Eastman Kodak) and preparative thin layer chromatography using 20x20 cm glass plates coated with a 1 mm layer of Brinkmann $HF_{254,366}$. Woelm alumina (act. III) and silicic acid (act. III) were used for column chromatography unless otherwise specified.

Elemental anlayses were performed by C. Daessle, Montreal or Heterocyclic Chemical Corporation, Missouri.

Chapter I

Methyl β-nitroacrylate (89)[78]

To a solution of methylacrylate (86 g, 1 mole) and iodine (254 g, 1 mole) in ethyl ether (1000 ml) at 0° was introduced nitrogen dioxide (46 g, 1 mole) over a period of 1 hr under nitrogen. The reaction mixture was stirred for an additional 2 hr under nitrogen. The ether solution was washed with a saturated sodium thiosulfate solution, aqueous sodium bicarbonate, water, and dried over sodium sulfate. Evaporation of the solvent left 168 g of methyl 3-nitro-2-iodopropionate as a brown oil. Without purification, this compound was directly used. To a stirred suspension of anhydrous sodium acetate (53 g, 0.65 mole) in ethyl ether (0.5 l) was added dropwise methyl 3-nitro-2-iodopropionate (168 g, 0.65 mole) at room temperature. The reaction mixture was refluxed for 1 hr. Filtration of sodium iodide and evaporation to dryness left a dark brown oil which after crystallization from methanol-ice afforded 65 g (75%) of (89) as a yellow solid with m.p. 36-38° (lit. 38°).

I.r. (neat): 1730 (C=O), 1540 (NO_2), 1645 cm^{-1} (C=C).
N.m.r. ($CDCl_3$): δ 3.91 (s, 3H), 7.15 (d, 1H), 7.80 (d, 1H).

2-Endo-carbomethoxy-3-exo-nitro-7-oxabicyclo [2.2.1] hept-5-ene (90) and 2-exo-carbomethoxy-3-endo-nitro-7-oxabicyclo [2.2.1] hept-5-ene (91)

A mixture of methyl β-nitroacrylate (89) (131 g, 1 mole) and furan (272 g, 4 mole) was stirred overnight at room temperature. Evaporation of excess furan gave 189 g (95%) of the isomeric mixture (90,91) as a yellow oil.

One isomer, the endo-nitro adduct (91), was crystallized from ethyl ether, giving 113 g (56%) with m.p. 66-67°.

I.r. (KBr): 1730 (C=O), 1540 (NO_2), 870 cm^{-1} (C-N).

N.m.r. ($CDCl_3$): δ 3.23 (d, 1H, $J_{2,3}$=2 Hz, H-2), 3.82 (s, 3H, OCH_3), 5.39 (d, 1H, $J_{1,6}$=2 Hz, H-1), 5.43-5.70 (s+m, 2H, H-3, H-6), 6.40 (dd, 1H, $J_{6,5}$=6 Hz, $J_{6,1}$=2 Hz), 6.76 (dd, 1H, $J_{5,6}$=6 Hz, $J_{5,4}$=2 Hz).

The filtrate contaminated with (91) was concentrated to dryness. Chromatography of the residue on a column of silicic acid using chloroform gave 57 g (29%) of (90) as an oil.

I.r. (neat): 1735 (C=O), 1525 (NO_2), 870 cm^{-1} (C-N).

N.m.r. ($CDCl_3$): δ 3.75 (s, 3H, OCH_3), 3.90 (dd, 1H, $J_{2,1}$=4 Hz, $J_{2,3}$=2 Hz, H-2), 4.82 (d, 1H, $J_{3,2}$=2 Hz, H-3), 5.32 (d, 1H, $J_{1,2}$=4 Hz, H-1), 5.50 (s, 1H, H-4), 6.55 (b.s, 2H, H-5, H-6).

5-Endo-carbomethoxy-6-exo-nitro-2,3-exo-epoxido-7-oxabicyclo [2.2.1] heptane (94)

(a) To a solution of (90) (3.03, 15 mmole) in methylene chloride (50 ml) was added dropwise a solution of 85% m-chloroperbenzoic acid (3.66 g, 17 mmole) in methylene chloride (50 ml). Stirring was continued for 2 days at room temperature. The reaction mixture was washed with 10% sodium sulfite and 5% sodium bicarbonate solution, water, and finally with brine. Drying over sodium sulfate and evaporation gave 2.44 g (74.4%) of (94) as an oil which was crystalled from methanol, m.p. 109-110°.

I.r. (KBr): 1745 (C=O), 1550 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 3.46 (q, 2H, J=4 Hz, H-2, H-3), 3.82 (s, 3H, OCH_3), 4.00 (q, 1H, J=4 Hz, H-5), 4.76-5.03 (m, 2H, H-4, H-6), 5.10 (s, 1H, H-1).

Mass (170°): m/e 215 (M^+), 169 (M^+-NO_2), 109 ($M^+-COOCH_3-HNO_2$).

Anal. Calcd. for $C_8H_9NO_6$: C, 44.65; H, 4.17; N, 6.51.

Found: C, 44.66; H, 4.34; N, 6.68.

(b) A mixture of (90) (199 mg, 1 mmole) and 30% hydrogen peroxide (0.9 ml) in 98% formic acid (5 ml) was stirred overnight at 50° and evaporated to dryness. The residue was dissolved in chloroform, washed with 0.1N sodium bicarbonate solution and with water, dried and evaporated.

The residue was purified by chromatography on a silica gel plate using benzene-ethyl acetate (1:1), giving 71 mg of (94) as an oil which was crystallized from methanol with m.p. 109-110°. The spectral data (i.r., n.m.r., m.s.) were identical with those of the product obtained as abovd.

5-Exo-carbomethoxy-6-endo-nitro-2,3-exo-epoxido-7-oxabicyclo [2.2.1] heptane (95)

To a solution of (91) (2.02 g, 10 mmole) in methylene chloride (40 ml) was added by protions a solution of 85% m-chloroperbenzoic acid (2.49 g, 14 mmole) in methylene chloride (40 ml). The mixture was stirred for 2 days at room temperature. Excess peracid was then destroyed by addition of 10% sodium sulfite solution. The organic phase was washed with 5% aqueous sodium bicarbonate and water and dried over magnesium sulfate. Solvent removal left an oil which was crystallized from ethyl ether. Recrystallization from chloroform-hexane gave 1.31 g (60%) of (95) with m.p. 100-101°.

I.r. (KBr): 1740 (C=O)\ 1550 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 3.30-3.60 (m, 3H, H-2, H-3, H-5), 3.80 (s, 3H, OCH_3), 4.80 (s, 1H, H-4), 4.88 (d, 1H, $J_{1,6}$=5 Hz, H-1), 5.42 (q, 1H, J=4 Hz, H-6).

Mass (130°): m/e 215 (M^+), 184 (M^+-OCH_3), 169 (M^+-NO_2), 109 ($M^+-COOCH_3-HNO_2$).

Anal. Calcd. for $C_8H_9NO_6$: C, 44.65; H, 4.17; N, 6.51.
Found: C, 44.54; H, 4.44; N, 6.77.

5-Carbomethoxy-2,3-exo-epoxido-7-oxabicyclo [2.2.1] hept-5-ene (96)

A solution of (95) (319 mg, 1.48 mmole) and DBU (281 mg, 1.77 mmole) in methylene chloride (10 ml) was refluxed for 40 min. The mixture was diluted with methylene chloride, washed with 0.1N hydrochloric acid three times, water, and evaporated to dryness. The crude product was purified by passing it through a column of silicic acid using chloroform. Crystallization of the major product from carbon tetrachloride-hexane gave 152 mg (61%) of (96) with m.p. 76-77°.

I.r. (KBr): 1700 (C=O), 1595 cm^{-1} (C=C).
N.m.r. ($CDCl_3$): δ 3.48 (d, 1H, J=3.5 Hz, H-2(3)), 3.62 (d, 1H, J=3.5 Hz, H-3(2)), 3.75 (s, 3H, OCH_3), 4.88 (d, 1H, J=2 Hz, H-1), 5.00 (s, 1H, H-4), 7.26 (d, 1H, J=2 Hz, H-6).
Mass (120°): m/e 168 (M^+), 153 (M^+-CH_3), 139, 136 (M^+-CH_3OH).
Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80.
Found: C, 57.37; H, 4.85.

Using the same conditions described above, (94) was transformed to (96) identical in all respects with the compound obtained from (95).

5-Exo-6-endo-dihydroxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (97)

A solution of (94) (3.12 g, 15 mmole) in acetic acid (20 ml), hydrochloric acid (10 ml), and water (10 ml) was heated at 90-95° for 2 hr. After cooling to room temperature, the solvents were evaporated in vacuo to dryness and the residue was coevaporated with ethanol. The black residue was dissolved in hot acetone and treated with charcoal. The filtrate was concentrated to afford a yellow oil. Crystallization from acetone-chloroform gave 2.34 g (60%) of (97) with m.p. 170-171°.

I.r. (KBr): 3500 (OH), 1800 (lactone C=O), 1575 cm^{-1} (NO_2).

N.m.r. ($(CD_3)_2CO$): δ 3.36 (b.s, 1H, OH), 3.63 (d, 1H, $J_{2,1}$=5 Hz, H-2), 4.10 (s, 1H, H-5), 4.63 (d, 1H, $J_{6,1}$=5 Hz, H-6), 5.25 (s, 1H, H-4), 5.33 (s, 1H, H-3), 5.60 (t, 1H, J=5 Hz; H-1).

Anal. Calcd. for $C_7H_7NO_6$: C, 41.79; H, 3.48; N, 6.96.

Found: C, 41.66; H, 3.75; N, 7.17.

5-Exo-acetoxy-6-endo-hydroxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (102)

A mixture of (97) (165 mg) and acetic anhydride (2 ml) containing one equivalent of p-toluenesulfonic acid monohydrate was stirred at room temperature for 30 min. The resulting solid was collected by filtration and washed with cold water to give 139 mg (70%) of analitically pure (102) with m.p. 198-200°.

I.r. (KBr): 1800 (lactone C=O), 1745 (C=O), 1560 cm^{-1} (NO_2).

N.m.r. (DMSO-d_6): δ 2.08 (s, 3H, $COCH_3$), 3.62 (d, 1H, $J_{6,1}$=5 Hz, H-6), 4.82 (d, 1H, $J_{2,1}$=5 Hz, H-2), 4.98 (s, 1H, H-5), 5.36 (s, 1H, H-3), 5.62 (t, 1H, J=5 Hz, H-1), 5.83 (s, 1H, H-4).

Mass (210°): m/e 243 (M^+), 196 (M^+-NO_2), 155, 109.

Anal. Calcd. for $C_9H_9NO_7$: C, 44.44; H, 3.70; N, 5.76.

Found: C, 44.24; H, 3.73; N, 5.41.

6-Endo-hydroxy-3-exo-nitro-5-exo-tetrahydropyranyloxy-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (103)

To a solution of (97) (1.0 g, 5 mmole) and p-toluenesulfonic acid (10 mg) in acetone was added dihydropyran (2 ml). The mixture was stirred at room temperature for 4 hr and then evaporated, leaving a solid residue. Recrystallization from

acetone-hexane gave 1.21 g (85%) of (103) with m.p. 123-124°.

I.r. (KBr): 1800 (lactone C=O), 1560 (NO_2), 1040 cm^{-1}.

N.m.r. ($(CD_3)_2CO$): δ 1.57 (m, 6H, $(CH_2)_3$), 3.33-3.57 (m, 3H), 3.90 (s, 1H), 4.36-4.70 (m, 2H), 5.03 (b.s, 2H), 5.23 (t, 1H, J=4 Hz).

Anal. Calcd. for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.26; N, 4.91.
Found: C, 50.43; H, 5.47; N, 5.12.

5-Carbomethoxy-3-endo-hydroxy-2-exo-tertrahydropyranyloxy-7-oxabicyclo [2.2.1] hept-5-ene (105) and 6-Endo-hydroxy-3 exo-methoxy-5-exo-tetrahydropyranyloxy-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (108)

(a) A solution of (103) (336 mg, 1.18 mmole) and DBU (205 mg, 0.13 mmole) in methanol-methylene chloride (1:1) (10 ml) was refluxed for 45 min. The solvents were then evaporated and the residue was dissolved in chloroform, washed with 0.1N hydrochloric acid three times and water, dried over sodium sulfate and evaporated. The residue was applied on silica gel plates using chloroform. Elution of the major, more polar band gave 220 mg (70%) of (105) as an oil.

I.r. ($CHCl_3$): 3480 (OH), 1720 (C=O), 1625 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.68 (m, 6H, $(CH_2)_3$), 2.70 (b.s, 1H, OH), 3.65 (m, 2H), 3.76 (s, 4H), 4.25 (d, 1H, J=4 Hz),

4.76 (m, 1H), 5.00-5.08 (m, 2H), 7.17 (d, 1H, J=2 Hz, C=CH).

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71.
Found: C, 57.65; H, 6.58.

Elution of the minor, less polar band gave 45 mg (14%) of (108) with m.p. 134-136°.

I.r. (KBr): 1800 cm^{-1} (lactone C=O).

N.m.r. ($CDCl_3$): δ 1.66 (m, 6H), 2.73 (d, 1H, J=4 Hz), 3.40 (s, 3H, OCH_3), 3.50-4.00 (m, 4H), 4.56 (d, 1H, J=4 Hz), 4.67-4.90 (m, 2H), 5.36 (t, 1H, J=5 Hz).

Mass (160°): m/e 270 (M^+), 238 (M^+-CH_3OH).

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.71; H, 6.71.
Found: C, 57.82; H, 6.71.

(b) A solution of (103) (285 mg, 1 mmole) and triethylamine (167 mg, 1 mmole) in methanol-methylene chloride (1:1) (10 ml) was refluxed for 8 hr. The solvents were evaporated to dryness and residue was dissolved in chloroform, washed with dilute hydrochloric acid and water. The organic phase was dried over sodium sulfate and evaporated. Chromatography of the residue on a column of silicic acid using chloroform gave 176 mg (65%) of (105) as an oil.

3-Endo-acetoxy-5-carbomethoxy-2-exo-tetrahydropyranyloxy-7-oxabicyclo [2.2.1] hept-5-ene (106)

A solution of (105) (91 mg) and acetic anhydride (1 ml) in pyridine (2 ml) was stirred overnight at room temperature. The mixture was then evaporated to dryness in vacuo. The residue was dissolved in chloroform and washed with water. The dried organic phase was evaporated and purified by chromatography on a silica gel plate using ethyl ether, giving 70 mg (67%) of (106) as an oil which solidified on standing with m.p. 81-82°.

I.r. ($CHCl_3$): 1740 (C=O), 1625 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.69 (m, 6H, $(CH_2)_3$), 1.96 (s, 3H, CH_3CO), 3.47 (m, 1H), 3.76 (s+m, 5H), 4.76 (b.s, 1H), 4.96-5.33 (m, 3H), 7.17 (d, 1H, J=2 Hz).

Mass (145°): m/e 312 (M^+), 281 (M^+-OCH_3), 228 ($M^+-O(CH_2)_4CH$).

Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46.

Found: C, 57.47; H, 6.49.

5-Carbomethoxy-2-exo-3-endo-di-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene (110)

A solution of (105) (1.8 g, 6.67 mmole) in methanol (10 ml) and 0.1N hydrochloric acid (10 ml) was stirred overnight at room temperature. After evaporation to dryness in vacuo, the resulting compound (109) was treated with tert-butyldimethylsilyl chloride (3.04 g, 20 mmole) and imidazole (1.36 g, 20 mmole) in dry dimethylformamide (10 ml) at 45° for 24 hr. The mixture was evaporated to dryness and the residue was dissolved in chloroform, washed with water three times, dried over sodium sulfate, and evaporated. Chromatography of the residue on a column of silicic acid using hexane-methylene chloride (2:3) gave 1.14 g (41%) of (110) as an oil which solidified on standing with m.p. 90-91°.

I.r. (KBr): 1738 (C=O), 1630 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 0.10 (s, 12H, $2Si(CH_3)_2$), 0.83 (s, 9H, $C(CH_3)_3$), 0.90 (s, 9H, $C(CH_3)_3$), 3.54 (b.s, 1H, H-2), 3.64 (s, 3H, OCH_3), 4.02 (d, 1H, $J_{3,4}$=4 Hz, H-3), 4.62 (d, 1H, $J_{1,6}$=2 Hz, H-1), 4.85 (d, 1H, $J_{4,3}$= 4 Hz, H-4), 7.02 (d, 1H, $J_{6,1}$=2 Hz, H-6).

Anal. Calcd. for $C_{20}H_{38}O_5Si_2$: C, 57.97; H, 9.18.

Found: C, 57.88; H, 9.27.

5-Carbomethoxy-2-exo-3-endo-diacetoxy-7-oxabicyclo [2.2.1] hept-5-ene (111)

After hydrolysis of the tetrahydropyranyl ether (105) as prepared for (110), the resulting diol (109) (76 mg) was stirred overnight at room temperature with acetic anhydride and pyridine. Following evaporation the residue was chromatographed on a silica gel plate using methylene chloride. Crystallization from hexane-carbon tetrachloride gave 80 mg (73%) of (111) with m.p. 78-79°.

I.r. ($CHCl_3$): 1755, 1735 (C=O), 1625 cm^{-1} (C=O).

N.m.r. ($(CD_3)_3CO$): δ 1.98 and 2.14 (s, 3H, each, $COCH_3$), 3.77 (s, 3H, OCH_3), 4.63 (b.s, 1H), 4.96-5.37 (m, 3H), 7.28 (d, 1H, $J_{6,1}$=2 Hz).

Mass (120°): m/e 270 (M^+), 239 (M^+-OCH_3), 227 (M^+-CH_3CO), 167, 127, 102, 43.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22.

Found: C, 53.62; H, 5.43.

5-Carbomethoxy-2-exo-3-endo-dipivaloyloxy-7-oxabicyclo [2.2.1] hept-5-ene (112)

The crude diol (109) (155 mg, 0.83 mmole) was treated with pivaloyl chloride (1 ml) and pyridine (2 ml). The reaction mixture was stirred overnight at ambient temperature and evaporated to dryness. The residue was dissolved in chloroform, washed with 0.1N hydrochloric acid and water, dried over sodium sulfate. After solvent removal purification of the residue by chromatography on silica gel plates using methylene chloride afforded 182 mg (72%) of (112) as a homogeneous syrup.

I.r. ($CHCl_3$): 1750, 1735 (C=O), 1630 cm^{-1}.

N.m.r. ($CDCl_3$): δ 1.10 and 1.23 (s, 9H, each $C(CH_3)_3$), 3.74 (s, 3H, OCH_3), 4.52 (b.s, 1H, H-2), 4.94 (d, 1H, $J_{1,6}$=2 Hz), 5.03 (d, 1H, $J_{3,4}$=4 Hz), 5.23 (d, 1H, $J_{4,3}$=4 Hz), 7.21 (d, 1H, $J_{6,1}$=2 Hz).

Mass (100°): m/e 354 (M^+), 339 (M^+-CH_3), 323 (M^+-OCH_3), 228.

Anal. Calcd. for $C_{18}H_{26}O_7$: C, 61.00; H, 7.40.

Found: C, 59.88; H, 7.64.

5-Carbomethoxy-3-endo-pivaloyloxy-2-exo-tetrahydropyranyloxy-7-oxabicyclo [2.2.1] hept-5-ene (113)

A mixture of (105) (61 mg, 0.23 mmole) and pivaloyl chloride (0.5 ml) in pyridine (1 ml) was stirred overnight at room temperature. The mixture was evaporated to dryness and the residue was dissolved in chloroform, washed with 0.1N hydrochloric acid and water. The organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed on a column of silicic acid using methylene chloride, giving 67 mg (85%) of (113) as an oil.

I.r. ($CHCl_3$): 1760, 1750 (C=O), 1630 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.15 (s, 9H, $C(CH_3)_3$), 1.33-1.90 (m, 6H, $(CH_2)_3$), 3.33-4.00 (s+m, 6H), 4.85 (m, 1H), 4.90-5.33 (m, 3H), 7.12 (d, 1H, J=2 Hz).

5-Carbomethoxy-2-exo-hydroxy-3-endo-pivaloyloxy-7-oxabicyclo [2.2.1] hept-5-ene (114)

A solution of (113) (67 mg, 0.19 mmole) in acetic acid-water-tetrahydrofuran (6:3:2) (11 ml) was stirred overnight at room temperature. After evaporation to dryness in vacuo, the residue was chromatographed on a column of silicic acid using chloroform, giving 43 mg (84%) of (114) as an oil.

I.r. ($CHCl_3$): 3450 (OH), 1625 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.10 (s, 9H, $C(CH_3)_3$), 3.00 (b.s, 1H, OH), 3.60 (b.s, 1H, H-2), 3.70 (s, 3H, OCH_3), 4.66 (d, 1H, $J_{4,3}$=4 Hz, H-4), 4.90 (d, 1H, $J_{1,6}$=2 Hz, H-1), 5.20 (d, 1H, $J_{3,4}$=4 Hz, H-3), 7.10 (d, 1H, $J_{6,1}$=2 Hz, H-6).

5-Carbomethoxy-2-exo-3-endo-dipivaloyloxy-7-oxabicyclo [2.2.1] hept-5-ene (115)

A solution of (114) (43 mg) and pivaloyl chloride (0.5 ml) in pyridine (1 ml) was stirred overnight at room temperature. After usual work-up the residue was chromatographed on a column of neutral alumina using chloroform, giving 56 mg (100%) of (115) as an oil. The n.m.r. and i.r. spectra were superimposable with those of the compound(112) obtained from the diol (109).

Chapter II

6-Endo-hydroxy-3-exo-nitro-5-exo-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (117)

To a solution of (97) (2.01 g, 10 mmole) in tetrahydrofuran (20 ml) and dimethylformamide (20 ml) was added tert-butyldimethylsilyl chloride (2.26 g, 15 mmole) and imidazole (1.90 g, 25 mmole). The reaction mixture was stirred at room temperature for one day. After evaporation of the solvent the residue was dissolved in ethyl acetate, washed with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid (40 g) using methylene chloride, giving 2.84 g (90%) of (117) as an oil which was crystallized from hexane with m.p. 112-113°

I.r. (Nujol): 1800 (lactone C=O), 1560 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 0.16 (s, 6H, $Si(CH_3)_2$), 0.95 (s, 9H, $C(CH_3)_3$), 3.76 (d, 1H, $J_{2,1}$=5 Hz, H-2), 4.00 (s, 1H, H-5), 4.58 (d, 1H, $J_{6,1}$=5 Hz, H-6), 4.84 (s, 1H, H-4), 5.14 (s, 1H, H-3), 5.51 (t, 1H, J=5 Hz, H-1).

Mass (150°): m/e 315 (M^+), 258 ($M^+-C(CH_3)_3$).

Anal. Calcd. for $C_{13}H_{21}NO_6Si$: C, 49.52; H, 6.67; N, 4.44.
Found: C, 49.77; H, 6.87; N, 4.56.

5-Carbomethoxy-3-endo-hydroxy-2-exo-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene (118) and 6-Endo-hydroxy-3-exo-methoxy-5-exo-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (119)

(a) To a stirred refluxing solution of DBU (635 mg) in methylene chloride-methanol (1:1) (30 ml) was added dropwise a solution of (117) (1.22 g, 3.8 mmole) in methylene chloride (15 ml). The mixture was refluxed for an additional 15 min. After evaporation of the cooled solution the residue was dissolved in chloroform, washed with dilute hydrochloric acid and water, dried over sodium sulfate, and evaporated. The residue was chromatographed on a column of silicic acid using chloroform, giving 976 mg (84%) of the more polar compound (118) as a colorless syrup.

I.r. ($CHCl_3$): 3500 (OH), 1725 (C=O), 1620 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 0.13 (s, 6H, $Si(CH_3)_2$), 0.97 (s, 9H, $C(CH_3)_3$), 3.37 (b.s, 1H, OH), 3.66 (s, 1H, H-2), 3.76 (s, 3H, OCH_3), 4.13 (d, 1H, $J_{3,4}$=5 Hz, H-3), 4.75 (d, 1H, $J_{1,6}$=2 Hz, H-1), 5.01 (d, 1H, $J_{4,3}$=5 Hz, H-4), 7.08 (d, 1H, $J_{6,1}$=2 Hz, H-6).

The less polar compound (119) (62 mg) was also obtained.

I.r. ($CHCl_3$): 1800 cm^{-1}.

N.m.r. ($CDCl_3$): δ 0.15 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $C(CH_3)_3$), 2.67 (d, 1H, J=5 Hz), 3.33 (s, 3H, OCH_3), 3.62 (s, 1H), 3.68 (s, 1H), 4.30-4.50 (m, 2H), 5.63 (m, 1H).

Anal. Calcd. for $C_{13}H_{24}O_5$: C, 60.00; H, 9.23.

Found: C, 59.95; H, 9.34.

(b) A solution of (117) (316 mg, 1 mmole) and triethylamine (167 mg, 1.1 mmole) in methanol (10 ml) was refluxed for 6 hr. The mixture was then evaporated to dryness. The residue was dissolved in chloroform and washed with water. The organic phase was dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on a column of silicic acid using chloroform afforded 230 mg (72%) of (118) as a colorless oil.

5-Carbomethoxy-3-endo-pivaloyloxy-2-exo-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene (120)

A mixture of (118) (320 mg, 1 mmole) and pivaloyl chloride (1 ml) in dry pyridine (5 ml) was stirred overnight at room temperature and then evaporated to dryness in vacuo. The mixture was coevaporated with toluene as a chaser, dissolved in chloroform, and washed with 5% hydrochloric acid and water.

The dried organic phase was evaporated and the residue was chromatographed on a column of silicic acid (120) using ethyl ether-hexane (1:1), giving 300 mg (89%) of (120) as a syrup that solidified on standing with m.p. 48-49°.

I.r. (neat): 1760, 1750 (C=O), 1630 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.13 (s, 9H, $C(CH_3)_3$), 3.72 (s, 3H, OCH_3), 3.80 (b.s, 1H), 4.80 (b.s, 1H), 4.88 (d, 1H, J=5 Hz), 5.25 (d, 1H, J=5 Hz), 7.28 (d, 1H, J=2 Hz).

Mass (110°): m/e 369 (M^+-CH_3), 353 (M^+-OCH_3), 327 ($M^+-C(CH_3)_3$), 258, 201.

Anal. Calcd. for $C_{19}H_{32}O_6Si$: C, 59.35; H, 8.39.
Found: C, 59.66; H, 8.28.

5-Carbomethoxy-2-exo-3-endo-di-tert-butyldimethylsiloxy-7-oxabicyclo [2.2.1] hept-5-ene (121)

A mixture of (118) (1.14 g, 3.8 mmole), tert-butyldimethylsilyl chloride (1.44 g, 9.5 mmole) and imiazole (610 mg, 8.9 mmole) in dimethylformamide (20 ml) was stirred at room temperature for 6 hr and then evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water and with brine, dried over sodium sulfate, and evaporated. The resulting syrup was chromatographed on a column of silicic acid using ethyl

ether-hexane (1:1), giving 600 mg (51%) of (121) as an oil which solidified on standing with m.p. 90-91°. The product was identical in all respects (n.m.r., i.r., m.p.) with the compound (110) obtained from (105).

Methyl 2-(4β-aldehydo-2β,3α-dihydroxy-2,3-di-O-tert-butyl-dimethylsilyl-furan-1β-yl) glyoxylate (122)

(a) To a solution of (121) (241 mg, 0.58 mmole) in carbon tetrachloride (10 ml) was added ruthenium dioxide dihydrate (20 mg) and a solution of sodium periodate (500 mg) in water (10 ml). The pH of the aqueous layer was controlled between 6 and 7 by the addition of a 30% sodium bicarbonate solution. After 1.5 hr stirring at room temperature, the reaction was terminated by adding a few drops of isopropyl alcohol. Ruthenium dioxide was removed on Celite and the organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform as eluent afforded 125 mg (48%) of (122) which solidified on standing with m.p. 81°.

I.r. ($CHCl_3$): 1770, 1750 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.03 (s, 6H, $Si(CH_3)_2$), 0.16 (s, 6H, $Si(CH_3)_2$), 0.80 (s, 9H, $C(CH_3)_3$), 0.97 (s, 9H, $C(CH_3)_3$),

4.05 (s, 3H, OCH_3), 4.43 (b.s, 2H), 4.82 (d, 1H, J=4 Hz), 5.65 (d, 1H, J=4 Hz), 9.13 (s, 1H).

Anal. Calcd. for $C_{20}H_{38}O_7Si_2$: C, 53.81; H, 8.52.
Found: C, 54.10; H, 8.36.

(b) To a solution of (121) (109 mg) in dry methylene chloride at -78° was bubbled ozone until a blue color was observed. Excess ozone was removed by passing nitrogen while the system was kept at -78° and dimethyl sulfide (0.5 ml) was added. The mixture was allowed to come to room temperature over a period of 5 hr. The solution was then washed with brine three times and dried over magnesium sulfate. Evaporation of the solvent gave 115 mg (98%) of (122) with m.p. 81°. The n.m.r. and i.r. spectra were superimposable with those of the compound prepared above. The melting point was not depressed upon mixture with an above sample.

In most cases, the product existed as a mixture of the free aldehydo keto ester (122) and its hydrate (123).

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-hydroxymethyl-furan-1β-yl) glycolate (124)

(a) After reductive ozonolysis[98] of (121) (386 mg, 0.93 mmole) in methylene chloride, the solution was washed with brine two times, dried, and evaporated. To a solution of the residue in dry tetrahydrofuran (40 ml) was added lithium tri-tert-butoxy-aluminum hydride (954 mg, 3.72 mmole) at 0°. The resulting clear mixture was allowed to warm to room temperature and stirred overnight under nitrogen. A solution of ammonium sulfate (2 g) in water (2 ml) and Celite (1 g) were added to the reaction mixture at 0°. The mixture was stirred for 30 min and finally filtered over a layer of Celite. The residue was washed with tetrahydrofuran. Following evaporation of the solvent the residue was dissolved in ethyl acetate, washed with water, dried, and evaporated. The residue was purified by chromatography on silica gel plates using ethyl ether-hexane (2:1), giving 250 mg (59%) of (124) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1745 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.10 (m, 12H, $2Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 0.90 (s, 9H, $C(CH_3)_3$), 1.96 (b.s, 1H), 2.70 (b.s, 1H), 3.54-4.36 (m, 10H).

Anal. Calcd. for $C_{20}H_{42}O_7Si_2$: C, 53.33; H, 9.33.

Found: C, 53.00; H, 9.17.

(b) Preparation of zinc borohydride[99]

A mixture of anhydrous zinc chloride (4.0 g) with dry ethyl ether (50 ml) was boiled until most of the solid had dissolved. The mixture was allowed to stand at room temperature and the supernant liquid was carefully decanted from insoluble material. The ethereal zinc chloride solution was added dropwise at room temperature to a stirred suspension of sodium borohydride (2.7 g) in dry ethyl ether (150 ml). Stirring was continued overnight. The solids were allowed to settle, and the liquid was removed by filtration. The ethereal solution of zinc borohydride was stored under nitrogen.

(c) Preparation of the doil (124) with zinc borohydride

After reductive ozonolysis of (121) (207 mg, 0.5 mmole) in methylene chloride as above the ethereal zinc borohydride solution (5 ml) was added to a solution of the resulting aldehydo keto ester in dry ethyl ether (10 ml). After stirring at 0° for 0.5 hr, 5 ml of 50% aqueous acetic acid was added and the mixture was stirred for 30 min. The mixture was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate, washed with brine and evaporated. The residue was purified by chromatography on a silica gel plate using hexane-ethyl ether (1:2), giving 68 mg (30%) of (124).

The product was identical with the compound obtained from (a).

(d) Preparation of the diol (124) with diborane

After reductive ozonolysis of (121) (312 mg, 0.75 mmole) in methylene chloride, a solution of the resulting aldehydo keto ester in dry tetrahydrofuran (5 ml) was cooled in an ice bath. Then, a 1M diborane solution (1 ml) was added and stirred for 1 hr at 0°. Excess hydride was carefully destroyed with water. The mixture was diluted with ethyl acetate. The organic phase was washed with brine, dried, and evaporated. Chromatography of the residue on a column of silicic acid using hexane-ethyl ether (1:2) afforded 152 mg (45%) of (124) as an oil. The spectral data (i.r., n.m.r.) were identical with those of the compound obtained from (a).

Methyl 2-O-acetyl-2-(2β,3α-dihydroxy-2,3-di-O-tert-butyl-dimethylsilyl-4β-acetoxymethyl-furan-1β-yl) glycolate (125)

The compound (124) (126 mg) was acetylated with acetic anhydride (1 ml) and pyridine (1.5 ml). The reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in chloroform, washed with dilute hydrochloric acid and water. The organic phase was dried over sodium sulfate and evaporated.

The residue was chromatographed on a column of silicic acid using ethyl ether-hexane (1:2), giving 136 mg (91%) of (125) as an oil which solidified on standing with m.p. 74-77°.

I.r. (KBr): 1755 (C=O), 1240, 1080 cm^{-1}.

N.m.r. ($CDCl_3$): δ 0.13 (m, 12H, $2Si(CH_3)_2$), 0.96 (s, 18H, $2C(CH_3)_3$), 2.03 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 3.90-4.33 (m, 6H), 4.70 and 4.86 (b.s, 0.5H each).

Mass (200°): m/e 519 (M^+-CH_3), 503 (M^+-OCH_3), 477 ($M^+-C(CH_3)_3$).

Anal. Calcd. for $C_{24}H_{46}O_9Si_2$: C, 53.93; H, 8.61.

Found: C, 54.12; H, 8.84.

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glycolate (126)

To a solution of (124) (106 mg, 0.24 mmole) in dimethylformamide (5 ml) were added tert-butyldimethylsilyl chloride (36 mg, 0.24 mmole) and imidazole (40 mg, 0.6 mmole). The mixture was stirred at room temperature for 21 hr. The solvent was evaporated in vacuo and the residue was coevaporated several times with ethyl acetate. The residue was dissolved in chloroform, washed with water, dried, and evaporated. The resulting syrup was chromatographed on a column of neutral alumina using ethyl ether-hexane (1:2), giving 125 mg (94%) of (126) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1730 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.10 (m, 18H, $3Si(CH_3)_2$), 0.92 (m, 27H, $3C(CH_3)_3$), 2.96 (b.s, 1H), 3.30-3.90 (m, 5H), 3.90-4.45 (m, 5H).

Anal. Calcd. for $C_{26}H_{56}O_7Si_3$: C, 55.32; H, 9.93.

Found: C, 55.59; H, 9.84.

Methyl 2-O-acetyl-2-(2β,3α-dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glycolate (127)

The compound (126) (125 mg, 0.22 mmole) was acetylated with acetic anhydride (1.5 ml) and pyridine (1.5 ml). After usual work-up the crude product was chromatographed on a column of alumina using ethyl ether-hexane (1:1) to give 134 mg (100%) of (127) as an oil which solidified on standing with m.p. 68-72°.

I.r. (KBr): 1760 (C=O), 1080, 840 cm^{-1}.

N.m.r. ($CDCl_3$): δ 0.05 (m, 18H, $3Si(CH_3)_2$), 0.87 (b.s, 27H, $3C(CH_3)_3$), 2.06 (s, 3H, $COCH_3$), 3.63 (m, 1H), 3.71 (s, 3H, OCH_3), 3.85-4.33 (m, 5H), 4.70 (b.s, 1/2H), 4.85 (b.s, 1/2H).

Anal. Calcd. for $C_{28}H_{58}O_8Si_3$: C, 55.45; H, 9.55.

Found: C, 55.16; H, 9.32.

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (128)

To a mixture of (126) (416 mg, 0.74 mmole) and ruthenium dioxide dihydrate (20 mg) in carbon tetrachloride (40 ml) was added a solution of sodium periodate (633 mg) in water (40 ml). The pH of the mixture was controlled between 6 and 7 by the addition of 5% sodium bicarbonate solution. After vigorously stirring at room temperature until a yellow color persisted, a few drops of isopropyl alcohol was added to terminate the reaction. Ruthenium dioxide was removed on Celite and the organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated, giving 353 mg of crude (128). The spectral data of the crude product were given.

I.r. ($CHCl_3$): 1750, 1730 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.13 (m, 18H, $3Si(CH_3)_2$), 0.86 (m, 27H, $3C(CH_3)_3$), 3.76-4.00 (m, 5H), 4.13 (m, 1H), 4.33 (m, 1H), 4.53 (b.s, 1H), 5.60 (d, 1H, J=4 Hz).

Methyl 2-(2β-pivaloyloxy-3α-tert-butyldimethylsiloxy-4β-hydroxymethyl-furan-1β-yl) glycolate (129)

To a solution of (120) (176 mg, 0.46 mmole) in methylene chloride at -78° was bubbled ozone until a blue color persisted. Excess ozone was flushed with dry nitrogen and dimethyl sulfide (0.5 ml) was added. The mixture was allowed to rise from -78° to room temperature over a period of 5 hr. The solution was washed with brine, dried over magnesium sulfate, and evaporated. A solution of the residue in dry tetrahydrofuran (10 ml) was treated with lithium tri-tert-butoxyaluminum hydride (369 mg, 1.38 mmole) and the mixture was stirred for 4 hr at 0°. A solution of ammonium sulfate (500 mg) in water (1 ml) and Celite (250 mg) were added to the reaction mixture at 0°. The mixture was stirred for 30 min and filtered over Celite. The residue was washed with tetrahydrofuran. After evaporation of the solvent the residue was chromatographed on a silica gel plate using hexane-ethyl ether, giving 58 mg (30%) of (129) as an oil.

I.r. (neat): 3450 (OH), 1740 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.15 (m, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$), 2.96 (b.s, 1H), 3.60-4.00 (m, 6H), 4.00-4.50 (m, 3H), 4.90-5.28 (m, 2H).

Methyl 2-acetoxy-2-(2β-pivaloyloxy-3α-tert-butyldimethylsiloxy-4β-acetoxymethyl-furan-1β-yl) glycolate (130)

The diol (129) (58 mg, 0.12 mmole) was treated with acetic anhydride (0.5 ml) and pyridine (1 ml). The reaction mixture was stirred overnight at room temperature and evaporated to dryness. The residue was dissolved in chloroform, washed with 0.1N hydrochloric acid and water, dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on a column of silicic acid using ethyl ether-hexane (1:1) as eluent, giving 68 mg (98%) of (130) as an oil.

I.r. ($CHCl_3$): 1745 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.13 (m, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.23 (s, 9H, $C(CH_3)_3$), 2.06 (s, 6H, $2COCH_3$), 3.76 (s, 3H, OCH_3), 3.94-4.16 (m, 4H), 4.03-4.68 (m, 1H), 4.93-5.15 (m, 2H).

Anal. Calcd. for $C_{23}H_{40}O_{10}Si$: C, 54.76; H, 7.93.
Found: C, 54.55; H, 7.83.

6-Endo-hydroxy-3-exo-nitro-5-exo-methoxymethloxy-7-oxabicyclo [2.2.1] heptane-2-endo-carboxylic acid γ-lactone (131)

To a stirred solution of (97) (1.33 g, 6.6 mmole) and methylal (5 ml) in tetrahydrofuran (30 ml) was added phosphorus pentoxide (about 5 g). After stirring for 1.5 hr at room temperature the mixture was filtered and the residue was washed with tetrahydrofuran. The filtrate was combined and evaporated to dryness. The residue was dissolved in ethyl acetate and washed with 5% sodium bicarbonate solution, water, and brine. Evaporation of the dried organic phase gave 1.53 g (93%) of (131) as an analitically pure soild with m.p. 154-155°.

I.r. (KBr): 1800 (lactone C=O), 1560 cm^{-1} (NO_2).

N.m.r. $(CD_3)_2CO$): δ 3.06 (s, 3H, OCH_3), 3.36 (d, 1H, J=5 Hz, CHOCO), 3.86 (s, 1H, $CH_2OC\underline{H}$), 4.40 (d, 1H, J=5 Hz), 4.43 (s, 2H, OCH_2O), 5.23 (s, 2H), 5.50 (t, 1H, J=5 Hz, $OC\underline{H}CHCO$).

Mass (150°): m/e 245 (M^+), 199 (M^+-NO_2).

Anal. Calcd. for $C_9H_{11}NO_7$: C, 44.08; H, 4.52; N, 5.71.

Found: C, 44.22; H, 4.75; N, 5.54.

5-Carbomethoxy-3-endo-hydroxy-2-exo-methoxymethyloxy-7-oxabicyclo [2.2.1] hept-5-ene (132)

To a refluxing solution of DBU (818 mg, 5.38 mmole) in 40 ml of methanol-methylene chloride (1:1) was added dropwise a solution of (131) (1.32 g, 5.38 mmole) in methylene chloride (20 ml). The mixture was refluxed for an additional 30 min. After evaporation of the solvents the residue was dissolved in ethyl acetate, washed with 0.1N hydrochloric acid three times and water, dried over sodium sulfate and evaporated. The residue was chromatographed on a column of neutral alumina using ethyl ether, giving 840 mg (67.8%) of (132) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1730 (C=O), 1625 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 3.36 (s, 3H, CH_2OCH_3), 3.37 (s, 3H, CH_2OCH_3), 3.40-3.60 (b.s, 2H), 4.16 (d, 1H, J=4 Hz), 4.67 (s, 2H, OCH_2O), 4.90 (m, 2H), 7.01 (d, 1H, J=2 Hz, C=CH).

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13.

Found: C, 52.08; H, 6.28.

The same compound (132) was obtained by treatment of (131) with triethylamine in refluxing methanol for 8 hr.

5-Carbomethoxy-2-exo-3-endo-di-methoxymethyloxy-7-oxabicyclo [2.2.1] hept-5-ene (133)

To a stirred solution of (132) (1.3 g, 5.6 mmole) in chloroform (50 ml) were added methylal (10 ml) and approximately 5 g of phosphorus pentoxide. The mixture was stirred at room temperature for 2 hr and poured into 5% sodium bicarbonate solution. The organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on a column of silicic acid using chloroform, giving 1.3 g (84%) of (133) as a homogeneous syrup.

I.r. ($CHCl_3$): 1730 (C=O), 1625 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 3.36 (s, 3H, CH_2OCH_3), 3.42 (s, 3H, CH_2OCH_3), 3.66 (s, 1H), 3.76 (s, 3H, OCH_3), 4.20 (d, 1H, J=4 Hz), 4.66 (q, 2H, OCH_2O, J=3 Hz), 4.76 (s, 2H, OCH_2O), 4.99 (d, 1H, J=2 Hz, C=CHCH), 5.12 (d, 1H, J=4 Hz, CH=C-CH), 7.15 (d, 1H, J=2 Hz, C=CH).

Mass (110°): m/e 259 (M^+-CH_3), 243 (M^+-OCH_3), 213 ($M^+-CH_3OCH_2O$), 148.

Anal. Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62.

Found: C, 52.38; H, 6.53.

Methyl 2-(2β;3α-dihydroxy-2,3-di-O-methoxymethyl-4β-hydroxymethyl-furan-1β-yl) glycolate (134)

To a solution of (133) (327 mg, 1.19 mmole) in methylene chloride at -78° was bubbled ozone until a faintly blue color was observed. Excess ozone was flushed with dry nitrogen while the system was kept at -78° and dimethyl sulfide (0.5 ml) was added. The mixture was allowed to rise to room temperature over a period of 5 hr. The solution was then washed with brine three times, dried over magnesium sulfate and evaporated. To a pre-cooled solution of the residue in freshly distilled tetrahydrofuran (50 ml) at 0° was added lithium tri-tert-butoxyaluminum hydride (1.22 g, 4.8 mmole). The resulting clear solution was then allowed to warm to room temperature and stirred overnight under dry nitrogen. After the usual work-up (see the preparation of (124)), the crude product was purified by chromatography on a column of silicic acid using chloroform, giving 222 mg (60%) of (134) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1745 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 3.33 (s, 3H, CH_2OCH_3), 3.36 (s, 3H, CH_2OCH_3), 3.67-3.96 (m, 6H), 4.06-4.56 (m, 5H), 4.56-4.83 (m, 5H).

Anal. Calcd. for $C_{12}H_{22}O_9$: C, 46.45; H, 7.15.

Found: C, 46.28; H, 7.28.

Methyl 2-acetoxy-2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-acetoxymethyl-furan-1β-yl) glycolate (135)

The compound (134) (73 mg) was acetylated using acetic anhydride (1 ml) and pyridine (1 ml) with stirring overnight at room temperature. After evaporation to dryness chromatography of the residue on a column of silicic acid using ethyl ether-hexane (1:1) gave 84 mg (92%) of (135) as an oil.

I.r. (neat): 1745, 1755 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 2.00 (s, 3H, $COCH_3$), 2.03(s, 3H, $COCH_3$), 3.21 (s, 3H, CH_2OCH_3), 3.24 (s, 3H, CH_2OCH_3), 3.68 (s, 3H, OCH_3), 3.90-4.13(m, 5H), 4.13-4.30 (m, 1H), 4.46 (m, 2H, OCH_2O), 4.50 (s, 2H, OCH_2O), 4.86 (s, 0.5H), 5.0 (s, 0.5H).

Mass (110°): m/e 363 (M^+-OCH_3), 317, 289 ($M^+-COCH_3-CH_3OCH_2OH$).

Anal. Calcd. for $C_{16}H_{26}O_{11}$: C, 48.73; H, 6.60.

Found: C, 48.63; H, 6.88.

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glycolate (136).

A mixture of (134) (169 mg, 0.54 mmole), tert-butyl-dimethylsilyl chloride (82 mg, 0.54 mmole) and imidazole (92 mg, 1.35 mmole) in dimethylformamide (5 ml) was stirred

at room temperature for 18 hr. After evaporation to dryness the residue was dissolved in chloroform and washed three times with water, dried, and evaporated, leaving a syrup. The latter was chromatographed on a column of silicic acid using ethyl ether-hexane (2:1), giving 197 mg (85%) of (136) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1745 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $C(CH_3)_3$), 3.32 (s, 3H, $CH_2OC\underline{H}_3$), 3.36 (s, 3H, $CH_2OC\underline{H}_3$), 3.48 (m, 1H), 3.60-4.00 (m, 6H), 4.08-4.43 (m, 4H), 4.62 (b.s, 4H).

Anal. Calcd. for $C_{18}H_{36}O_9Si$: C, 50.94; H, 8.94.
Found: C, 50.68; H, 8.37.

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (137)

To a solution of (136) (424 mg, 1 mmole) in carbon tetrachloride (40 ml) were added ruthenium dioxide dihydrate (20 mg) and a solution of sodium periodate (856 mg, 4 mmole) in water (40 ml). The pH of the reaction mixture was controlled between 6 and 7 by the addition of a 5% sodium bicarbonate solution. After 6 hr of stirring at room temperature until a yellow color persisted, the reaction was terminated by adding a few drops of isopropyl alcohol. After collection

of the black precipitated solid (RuO_2) on Celite, the organic phase was then washed with water and brine, dried over magnesium sulfate, and evaporated, leaving 359 mg of the crude (137). Attempted purification by chromatography on silicic acid led to partial decomposition and accordingly the material was used directly in the next step. The spectral data of the crude product were given.

I.r. (neat): 1760, 1735 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.08 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 3.13 (s, 3H, $CH_2OC\underline{H}_3$), 3.25 (s, 3H, $CH_2OC\underline{H}_3$), 3.36-3.58 (m, 2H), 3.72 (s, 3H, OCH_3), 3.76 (m, 1H), 4.13 (b.s, 1H), 4.30 (m, 1H), 4.40-4.70 (m, 4H), 5.06 (d, 1H, J=5 Hz).

Methyl 2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate semicarbazone (138)

A solution of the crude keto ester (137) (105 mg, 0.25 mmole), semicarbazide hydrochloride (34 mg, 0.3 mmole), and sodium acetate (27 mg, 0.32 mmole) in methanol-water (4:1) (10 ml) was stirred overnight at room temperature. Methanol was then evaporated and the residue was partitioned

between ethyl acetate and water. The organic phase was washed with water, dried over sodium sulfate, and evaporated. The residue was purified by chromatography on a silica gel plate using chloroform-ethyl acetate (1:1), giving 72 mg (60%) of (138) as an oil.

I.r. ($CHCl_3$): 3570, 3450, 3350 (NH, NH_2), 1725 (C=O), 1625 ($CONH_2$), 1590 cm^{-1} (C=N).

U.v. (λ_{max}^{EtOH}): 270 nm.

N.m.r. ($CDCl_3$): δ 0.10 (d, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $C(CH_3)_3$), 3.15 (d, 3H, $CH_2OC\underline{H}_3$), 3.30 (s, 3H, $CH_2OC\underline{H}_3$) 3.60-3.85 (m, 6H), 4.04 (b.s, 1H), 4.20-4.70 (m, 5H), 5.00 (dd, 1H, J=4 Hz), 5.20-5.90 (m, 2H), 9.63 (b.s, 1/2H), 10.53 (b.s, 1/2H).

Mass (120°): m/e 479 (M^+), 464 (M^+-CH_3), 448 (M^+-OCH_3), 437 ($M^+-NH=C=O$), 422 ($M^+-C(CH_3)_3$), 335, 131, 129, 117, 89, 75, 73, 45.

Anal. Calcd. for $C_{19}H_{37}N_3O_7Si$: C, 47.60; H, 7.72; N, 8.77.
Found: C, 47.91; H, 7.78; N, 8.52.

3,4-Di-O-methoxymethyl-2,5-anhydro-D,L-glucose (144)

To a solution of (133) (230 mg, 0.84 mmole) in methylene chloride was bubbled ozone until a faintly blue color was observed. Excess ozone was flushed with dry nitrogen and evaporation of solvent left a white foam. The resulting ozonide in isopropanol was treated with sodium borohydride (500 mg) at 0° and then refluxed for 4 hr. The solution was then cooled in an ice-bath and stirred with 50% aqueous acetic acid (10 ml) for 30 min and evaporated in vacuo. The residue was coevaporated with ethanol and dissolved in water and stirred with sodium periodate (300 mg) for 1 hr at room temperature. The resulting precipitate was removed by filtration on cotton and the filtrate extracted with chloroform three times. The organic phase was dried over magnesium sulfate. Evaporation of the solvent gave 77 mg (37%) of (144) as a colorless syrup.

I.r. ($CHCl_3$): 3500, 3420 (OH), 2840, 2800 cm^{-1}.

N.m.r. ($CDCl_3$): δ 3.36 (b.s, 6H, $2OCH_3$), 3.56 (b.s, 1H), 3.90 (m, 1H), 3.93-4.27 (m, 3H), 4.36 (m, 2H), 4.27 (m, 4H), 4.98 (b.s, 1H).

Anal. Calcd for $C_{10}H_{18}O_7$: C, 47.99; H, 7.25.

Found: C, 47.65; H, 7.51.

Ethyl trans-3-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-hydroxymethyl-furan-1β-yl) acrylate (149)

To a solution of (144) (144 mg, 0.58 mmole) in methylene chloride (10 ml) was added carboethoxymethylenetriphenylphosphorane (242 mg, 0.69 mmole). After 4 hr of stirring at room temperature, the solvent was evaporated and the residue was partitioned between chloroform and water. The organic phase was dried over sodium sulfate and evaporated. The residue was chromatographed on a column of neutral alumina using chloroform, giving 143 mg (79%) of (149) as a chromatographically homogeneous syrup.

I.r. ($CHCl_3$): 3500 (OH), 1730 (C=O), 1680 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.23 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$), 2.23 (t, 1H, J=6 Hz, OH), 3.26 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.53-4.30 (m, 8H), 4.52 (d, 2H, J=2 Hz), 4.60 (s, 2H), 5.98 (dd, 1H, J=14 Hz, J=2 Hz), 6.85 (dd, 1H, J=14 Hz, J=4 Hz).

Mass (120°): m/e 320 (M^+), 289 (M^+-OCH_3), 243, 230 ($M^+-2CH_3OCH_2$).

Anal. Calcd. for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55.

Found: C, 52.48; H, 7.62.

Ethyl trans-3-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-acetoxymethyl-furan-1β-yl) acrylate (150)

The compound (149) (40 mg, 0.13 mmole) was acetylated using acetic anhydride (1 ml) and pyridine (2 ml). Evaporation to dryness and purification by chromatography on a column of neutral alumina using chloroform gave 40 mg (89%) of (150) as a colorless oil.

I.r. ($CHCl_3$): 1750, 1730 (C=O), 1680 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.27 (t, 3H, J=6 Hz, $CH_2\underline{CH_3}$), 2.06 (s, 3H, $COCH_3$), 3.28 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.90-4.30 (m, 8H), 4.46-4.70 (m, 4H), 6.02 (dd, 1H, J=14 Hz, J=2 Hz), 6.88 (dd, 1H, J=14 Hz, J=4 Hz).

Mass (120°): m/e 362 (M^+), 331 (M^+-OCH_3), 317 (M^+-2CH_3O), 272 ($M^+-2CH_3OCH_2$).

Anal. Calcd. for $C_{16}H_{26}O_9$: C, 53.03; H, 7.23.

Found: C, 53.10; H, 7.32.

N-Methyl 2-(2β,3α-dihydroxy-2,3-di-O-methoxymethyl-4β-hydroxymethyl-furan-1β-yl) thiazolidine (151) and its acetate (152)

To a solution of (144) (77 mg, 0.31 mmole) in dry benzene (15 ml) was added N-methylthioethanolamine (31 mg, 0.34 mmole). The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent the crude product (151) was directly acetylated with acetic anhydride and pyridine. The crude product was purified by chromatography on a column of alumina using chloroform to give 86 mg (77%) of (152) as a colorless oil.

I.r. ($CHCl_3$): 2870, 2830 ($N-CH_3$), 1755 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 2.03 (s, 3H, $COCH_3$), 2.30 and 2.40 (s+s, total 3H), 2.60-3.26 (m, 4H, CH_2CH_2), 3.30 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.90-4.23 (m, 6H), 4.37-4.53 (m, 1H), 4.57-4.76 (m, 4H).

Mass (120°): m/e 365 (M^+), 333 (M^+-CH_3OH), 318 (M^+-CH_2SH), 102.

Anal. Calcd. for $C_{15}H_{27}NO_7S$: C, 49.32; H, 7.40; N, 3.84; S, 8.77.

Found: C, 49.53; H, 7.60; N, 4.08; S, 8.53.

Chapter III

2-(2β,3α-Dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyl-dimethylsiloxymethyl-furan-1β-yl) maleimide (156)

A solution of carbamoylmethylenetriphenylphosphorane (351 mg, 1.07 mmole) and the crude keto ester (137) (450 mg, 1.07 mmole) in dry chloroform (20 ml) was stirred at room temperature for 2 hr. The solvent was then evaporated and the residue was purified by chromatography on silica gel plates using ethyl ether-hexane (1:1), giving 216 (47%) of (156) as an oil.

I.r. ($CHCl_3$): 3460, 3250 (OH, NH), 1790, 1740, 1705 (C=O), 1655 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.82 (s, 9H, $C(CH_3)_3$), 3.20 (d, 3H, J=4 Hz, OCH_3), 3.26 (s, 3H, OCH_3), 3.53-4.10 (m, 3H), 4.13-4.26 (m, 1H), 4.36 (s, 2H, OCH_2O), 4.48 (s, 2H, OCH_2O), 4.72 (m, 1H), 5.10 (m, 1H), 6.39 (m, 1H, C=CH), 8.08 (b.s, 1H, NH).

Mass (120°): m/e 431 (M^+), 400 (M^+-OCH_3), 374 ($M^+-C(CH_3)_3$), 328.

Anal. Calcd. for $C_{19}H_{33}NO_8Si$: C, 52.90; H, 7.66; N, 1.62.

Found: C, 52.68; H, 7.76; N, 1.49.

2-(2β,3α-Dihydroxy-4β-hydroxymethyl-furan-1β-yl) maleimide (154)

A solution of (156) (212 mg, 0.5 mmole) in a mixture of trifluoroacetic acid-water-tetrahydrofuran (4:1:1) (12 ml) was stirred at room temperature for 4 hr. After evaporation to dryness in vacuo the residue was chromatographed on a silica gel plate using ethyl acetate (R_f=0.35). Crystallization from acetone-hexane gave 68 mg (60%) of (154) with m.p. 170-171°.

I.r. (KBr): 3470, 3280, 3110, 3070, 2710 (NH,OH,CH), 1775, 1735, 1720, 1700 (C=O), 1625 cm^{-1} (C=C).

U.v. (λ_{max}^{EtOH}): 222 nm (log ε 4.36).

Mass (170°): m/e 229 (M^+), 211 (M^+-H_2O), 180, 140 ($M^+-HOCHCH_2B$), 127 (B+31), 126 (B+30), 110, 87, 85, 69, 57, 55, 45, 44, 43, 32, 31, 28 (B is maleimide).

Anal. Calcd. for $C_9H_{11}NO_6$: C, 47.16; H, 4.80; N, 6.15.
Found: C, 47.05; H, 4.75; N, 6.08.

Preparation of the hydrazone (163) from methyl pyruvate

A mixture of methyl pyruvate (879 mg, 8.61 mmole), ethyl hydrazinoacetate hydrochloride (1.60 g, 10.3 mmole) and sodium acetate (917 mg, 11.2 mmole) in methanol-water (6:1) (35 ml) was stirred overnight at room temperature. Methanol was evaporated and the residue was partitioned between ethyl acetate and water. The dried organic phase was evaporated, leaving a solid residue. Recrystallization from carbon tetrachloride-petroleum ether (30-60°) gave 1.66 g (95%) of (163) with m.p. 59-60°.

I.r. ($CHCl_3$): 3360 (NH), 1750, 1725 (C=O), 1590 cm^{-1} (C=N).

N.m.r. ($CDCl_3$): δ 1.21 (t, 3H, J=6 Hz, $CH_2\underline{CH_3}$), 1.93 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.90-4.30 (m, 4H), 5.96 (m, 1H, NH).

U.v. (λ_{max}^{EtOH}): 275 nm (log ε 4.04).

Mass (70°): m/e 202 (M^+), 171 (M^+-OCH_3), 129, 97.

Anal. Calcd. for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.86.

Found: C, 47.57; H, 7.29; N, 13.89.

3(5)-Carbomethoxy-4-hydroxy-5(3)-methyl pyrazole (164)

A mixture of (163) (577 mg, 2.86 mmole) and methanolic sodium methoxide (10 ml of 0.2N) was refluxed for 4 hr. After evaporation of methanol the residue was dissolved in water and acidified with dilute hydrochloric acid to pH 3 and extracted with ethyl acetate three times. The dried organic phase was evaporated, leaving a solid residue. Recrystallization from acetone-hexane gave 149 mg (33%) of (164) with m.p. 141-143°.

I.r. (KBr): 3420, 3200-2500 (NH and OH), 1720 (C=O), 1590 (C=N), 1445, 1480 cm^{-1}.

N.m.r. (pyridine-d_5): δ 2.33 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 8.23 (s, 2H, OH and NH).

U.v. (λ_{max}^{EtOH}): 227 (log ε 3.74) and 276 nm (log ε 3.67) in 0.1N HCl.

239 (log ε 3.79) and 319 nm (log ε 3.80) in 0.1N NaOH.

Mass (150°): m/e 156 (M^+), 124 (M^+-CH_3OH), 156, 124.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94.

Found: C, 45.93; H, 5.30; N, 18.15.

Preparation of the hydrazone (165,166) from (137)

To a solution of the keto ester (137) (157 mg, 0.37 mmole) in methanol-water (6:1) (14 ml) were added ethyl hydrazinoacetate hydrochloride (86 mg, 0.56 mmole) and sodium acetate (49 mg, 0.59 mmole). The reaction mixture was stirred overnight at room temperature. Most of methanol was evaporated and the residue was partitioned between chloroform and water. The organic phase was washed with water, dried over sodium sulfate and then evaporated to dryness in vacuo. The residue was purified by chromatography on silica gel plates using ethyl ether, giving 172 mg (38%) of the geometric isomers of the hydrazone (165,166) as an oil.

I.r. ($CHCl_3$): 3350 (NH), 1760, 1710 (C=O), 1590 cm^{-1} (C=N).

N.m.r. ($CDCl_3$): δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 1.27 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$), 3.23-3.60 (m, 6H, $2CH_2O\underline{CH_3}$), 3.68-4.00 (m, 6H), 4.00-4.69 (m, 5H), 4.70-5.00 (m, 5H), 5.90 (m, 1H), 9.15 (m, 0.5H, NH), 9.50 (m, 0.5H, NH).

U.v. (λ_{max}^{EtOH}): 287 nm.

Mass (160°): m/e 522 (M^+), 507 (M^+-CH_3), 491 (M^+-OCH_3), 465 ($M^+-C(CH_3)_3$), 433.

Anal. Calcd. for $C_{22}H_{42}N_2O_{10}Si$: C, 50.57; H, 8.05; N, 5.36.
Found: C, 50.52; H, 7.85; N, 5.28.

3(5)-(2β,3α-Dihydroxy-2,3-di-O-methoxymethyl-4β-tert-butyl-dimethylsiloxymethyl-furan-1β-yl)-5(3)-carbomethoxy-4-hydroxypyrazole (167)

To a solution of the geometric isomers of the hydrazone (165,166) (117 mg, 0.22 mmole) in dry methanol (5 ml) was added 0.2N methanolic sodium methoxide (2 ml, 0.4 mmole). The reaction mixture was refluxed for 2 hr and then evaporated under reduced pressure. The residue was dissolved in water (5 ml) and acidified with 0.1N hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on a silica gel plate using ethyl ether as eluent. The compound (5 mg) with R_f=0.5 showed the characteristic u.v. absorption of the 4-hydroxypyrazole (167).

U.v. (λ_{max}^{EtOH}): 228 and 278 nm in 0.1N HCl.
235 and 323 nm in 0.1N NaOH.

Preparation of the hydrazone (168,169) from(128)

To a solution of the keto ester (128) (353 mg, 0.63 mmole) in methanol-water (15:2) (17 ml) were added ethyl hydrazino-acetate hydrochloride (123 mg, 0.8 mmole) and sodium acetate (74 mg, 0.9 mmole). The reaction mixture was stirred overnight at room temperature and evaporated to remove most of methanol.

The residue was partitioned between chloroform and water. The organic phase was dried over sodium sulfate and evaporated. Purification of the crude product on silica gel plates using chloroform-ethyl acetate (5:3) gave 299 mg (72%) of the hydrazone (168,169) as an oil.

I.r. ($CHCl_3$): 3400, 3250 (NH), 1740, 1690 (C=O), 1550 cm^{-1} (C=N).

N.m.r. ($CDCl_3$): δ 0.05-0.30 (m, 18H, $3Si(CH_3)_2$), 0.87-1.10 (m, 27H, $3C(CH_3)_3$), 1.33 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$), 3.75 (s, 3H, OCH_3), 3.76-4.50 (m, 9H), 5.10 (m, 1/3H), 5.33 (m, 2/3H), 9.30 (m, 1/3H, NH), 10.36 (t, 2/3H, NH).

U.v. (λ_{max}^{EtOH}): 287 nm (log ε 3.80).

Mass (120°): m/e 663 (M^+), 648 (M^+-CH_3), 632 (M^+-OCH_3), 618 ($M^+-OCH_2CH_3$), 606 ($M^+-C(CH_3)_3$), 505, 473, 301.

Anal. Calcd. for $C_{30}H_{62}N_2O_8Si_3$: C, 54.34; H, 9.42; N, 4.22.
Found: C, 54.41; H, 9.29; N, 4.07.

<u>3(5)-(2β,3α-Dihydroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl)-5(3)-carbomethoxy-4-hydroxypyrazole (170)</u>

To a solution of a mixture of the isomeric hydrazone (168,169) (421 mg, 0.64 mmole) in dry methanol (10 ml) was added methanolic sodium methoxide (2 ml of 0.2M). The solution

was refluxed for 4-5 hr and evaporated to dryness. The residue was taken up in 10 ml of water, acidified with 0.1N hydrochloric acid and then immediately extracted with ethyl acetate three times. The organic phase was dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel plates using ethyl ether, giving 84 mg (20%) of (170) as an oil.

I.r. ($CHCl_3$): 3420 (OH), 1725 (C=O), 1690 (C=O), 1610 (C=N), 1460 cm^{-1}.

N.m.r. ($CDCl_3$): δ 0.10-0.20 (m, 18H, $3Si(CH_3)_2$), 0.73-0.90 (m, 27H, $3C(CH_3)_3$), 3.56-4.50 (m, 8H), 5.10 (d, 1H, J=2.5 Hz).

U.v. (λ_{max}^{EtOH}): 230 (log ε 3.72) and 275 nm (log ε 3.58) in 0.1N HCl.

243 (log ε 3.58) and 320 nm (log ε 3.75) in 0.1N NaOH.

Mass (160°): m/e 601 (M^+-CH_3), 585 (M^+-OCH_3), 559 ($M^+-C(CH_3)_3$), 527 ($M^+-CH_3OH-C(CH_3)_3$), 427, 355, 299, 261.

Anal. Calcd. for $C_{28}H_{56}N_2O_7Si_3$: C, 54.55; H, 9.09; N, 4.54.

Found: C, 54.37; H, 9.18; N, 4.43

3(5)-(2β,3α-Dihyroxy-2,3-di-O-tert-butyldimethylsilyl-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl)-5(3)-carboxamide-4-hydroxypyrazole (171)

A solution of (170) (154 mg, 0.25 mmole) in saturated methanolic ammonia (10 ml) was stored at room temperature for 7 days. Evaporation of the solvent and chromatography of the residue on a silica gel plate using chloroform afforded 120 mg (80%) of (171) as a foam.

I.r. ($CHCl_3$): 3480, 3380, 3200 (OH, NH), 1680, 1620 (C=O), 1590 cm^{-1}.

U.v. (λ_{max}^{EtOH}): 227 (log ε 3.75) and 270 nm (log ε 3.64) in 0.1N HCl.
235 (log ε 3.67) and 310 nm (log ε 3.83) in 0.1N NaOH.

Mass (200°): m/e 545 (M^+-$C(CH_3)_3$), 489, 478, 462, 388.

Anal. Calcd. for $C_{27}H_{55}N_3O_6Si_3$: C, 53.82; H, 9.14; N, 6.98.
Found: C, 53.93; H, 8.98; N, 7.12.

3(5)-(2β,3α-Dihydroxy-4β-hydroxymethyl-furan-1β-yl)-5(3)-carboxamide-4-hydroxypyrazole (162)

A solution of (171) (102 mg, 0.17 mmole) in 50% aqueous trifluoroacetic acid (5 ml) was stirred at room temperature for 30 min. The reaction mixture was evaporated to dryness in vacuo, leaving a yellow solid. Recrystallization from acetone-benzene gave 30 mg (72%) of (162) with m.p. 195-196°.

I.r. (KBr): 3540, 3000-3400 (OH and NH), 1650, 1615 (C=O), 1570, 1545, 1480, 1080 cm^{-1}.

U.v. (λ_{max}^{EtOH}): 228 (log ε 3.86) and 269 nm (log ε 3.71) in 0.1N HCl.

232 (log ε 3.72) and 312 nm (log ε 3.89) in 0.1N NaOH.

Mass (200°): m/e 259 (M^+), 242 (M^+-NH_3), 241 (M^+-H_2O), 224 ($M^+-H_2O-NH_3$), 223 (M^+-2H_2O), 211 ($M^+-NH_3-OCH_3$), 170 (BCH=CHOH), 156 (b+30), 140 (BCH_2), 139, 124, 123, 60, 56, 54, 45, 44, 43, 42, 41 (B is the heterocyclic base).

Anal. Calcd. for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21.

Found: C, 41.71; H, 5.37; N, 15.92.

Chapter IV

A mixture of 2-endo-carbomethoxy-5-exo-hydroxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane (173) and 2-endo-carbomethoxy-6-exo-hydroxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane (174)

To a solution of (90) (654 mg, 3.3 mmole) in dry tetrahydrofuran (10 ml) was added 2 ml of 1M diborane (2 mmole) and the reaction mixture was stirred at 0° for 2.5 hr under nitrogen. Following evaporation to dryness in vacuo, a solution of the residue and triethylamine N-oxide dihydrate (368 mg, 3.3 mmole) in tetrahydrofuran (15 ml) was heated under reflux for 2.5 hr. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with 0.1N hydrochloric acid, water, and brine. The organic phase was dried over sodium sulfate and evaporated. The residue was chromatographed on a column of silicic acid using chloroform, giving 300 mg (42%) of the isomeric mixture of the alcohols (173, 174) as an oil.

I.r. ($CHCl_3$): 3620, 3450 (OH), 1755 (C=O), 1570 cm^{-1} (NO_2).
N.m.r. ($CDCl_3$): δ 1.46-2.33 (m, 2H), 2.83 (m, 1H), 3.66-4.16 (m, 5H), 4.63-5.30 (m, 3H).

A mixture of 5-exo-acetoxy-2-endo-carbomethoxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane (175) and 6-exo-acetoxy-2-endo-carbomethoxy-3-exo-nitro-7-oxabicyclo [2.2.1] heptane (176)

Treatment of a mixture of the isomeric alcohols (173, 174) (218 mg, 1.1 mmole) with acetic anhydride (2 ml) and one equivalent of p-toluenesulfonic acid monohydrate, under conditions identical to those described for the preparation of (181,182), gave 194 mg (75%) of the isomeric mixture of the acetates (175,176) as an oil.

I.r. ($CHCl_3$): 1740 (C=O), 1560 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 1.70-2.33 (m, 5H), 3.70-3.96 (m, 4H), 4.55-5.23 (m, 4H).

Mass (120°): m/e 260 (M^++1), 228 (M^+-OCH_3), 213 (M^+-NO_2), 169, 43.

Anal. Calcd. for $C_{10}H_{13}NO_7$: C, 46.33; H, 5.06; N, 5.40.
Found: C, 46.36; H, 5.20; N, 5.35.

A mixture of 2-exo-acetoxy-5-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene (177) and 3-exo-acetoxy-5-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene (178)

A solution of the isomeric mixture of the acetates (175,176) (260 mg, 1 mmole) and DBU (161 mg, 1.1 mmole) in

methylene chloride (20 ml) was heated under reflux for 1.5 hr. The mixture was diluted with methylene chloride, washed with 0.1N hydrochloric acid and water, dried over sodium sulfate and evaporated. The residue was chromatographed on a column of silicic acid using chloroform-hexane (3:1), giving 174 mg (82%) of the isomeric mixture of the olefin ester (177,178) as an oil.

I.r. ($CHCl_3$): 1725, 1710 (C=O), 1610 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.70-2.20 (s+m, 5H, $COCH_3$ and CH_2), 3.70 (s, 3H, OCH_3), 4.76 (m, 1H), 4.90-5.20 (m, 2H), 6.92(d, 1/2H, J=2 Hz), 7.03 (d, 1/2H, J=2 Hz).

Mass (120°): m/e 212 (M^+), 197 (M^+-CH_3), 181 (M^+-OCH_3), 169 (M^+-COCH_3), 152 (M^+-CH_3COOH).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70.
Found: C, 56.47; H, 5.40.

<u>A mixture of 2-exo-carbomethoxy-5-exo-hydroxy-3-endo-nitro-7-oxabicylo [2.2.1] heptane (179) and 2-exo-carbomethoxy-6-exo-hydroxy-3-endo-nitro-7-oxabicyclo [2.2.1] heptane (180)</u>

A solution of (91) (858 mg, 4.3 mmole) in dry tetrahydrofuran (10 ml) was cooled to 0° by means of an ice-water bath. To the reaction mixture was added 3 ml of 1M diborane solution (3 mmole) in tetrahydrofuran and stirred for 2.5 hr under

nitrogen. After evaporation to dryness in vacuo the residue and triethylamine N-oxide dihydrate (658 mg, 4.3 mmole) were dissolved in dry tetrahydrofuran (20 ml). The reaction mixture was heated under reflux for 2.5 hr. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with 0.1N hydrochloric acid, water and with brine, dried and evaporated. Chromatography of the residue on a column of silicic acid using chloroform afforded 416 mg (46%) of the isomeric mixture of the alcohols (179,180) as an oil.

I.r. ($CHCl_3$): 3650, 3500 (OH), 1735 (C=O), 1578 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 1.33-2.40 (m, 2H, CH_2), 2.90 (m, 1H), 3.26 (m, 1H), 3.73 (s, 3H, CH_3), 4.03 (m, 1H), 4.60-5.10 (m, 2H), 5.10-5.30 (m, 1H).

Anal. Calcd. for $C_8H_{11}NO_6$: C, 44.24; H, 5.11; N, 6.45.
Found: C, 44.35; H, 5.10; N, 6.78.

<u>A mixture of 5-exo-acetoxy-2-exo-carbomethoxy-3-endo-nitro-7-oxabicyclo [2.2.1] heptane (181) and 6-exo-acetoxy-2-exo-carbomethoxy-3-endo-nitro-7-oxabicyclo [2.2.1] heptane (182)</u>

A mixture of the isomeric alcohols (179,180) (504 mg, 2.32 mmole) and acetic anhydride (4 ml) containing one equivalent of p-toluenesulfonic acid monohydrate was stirred

overnight at room temperature. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform, washed with water and dried over sodium sulfate. Following evaporation of the solvent chromatography of the residue on a column of silicic acid using chloroform afforded 495 mg (82%) of the isomeric mixture of the acetates (181,182) as an oil.

One isomer, the 5-acetoxy heptane (181), was crystallized from hexane-carbon tetrachloride to give 220 mg with m.p. 113-114°.

I.r. (KBr): 1735 (C=O), 1550 cm^{-1} (NO_2).

N.m.r. ($CDCl_3$): δ 1.70-2.60 (M, 5H, $COCH_3$ and CH_2), 3.36 (d, 1H, J=4 Hz), 3.70 (s, 3H, OCH_3), 4.70-5.03 (m, 3H), 5.30 (m, 1H).

Mass (120°): m/e 228 (M^+-OCH_3), 213 (M^+-HNO_2), 171, 153, 128, 43.

Anal. Calcd. for $C_{10}H_{13}NO_7$: C, 46.33; H, 5.06; N, 5.40.
Found: C, 46.53; H, 5.26; N, 5.43.

Upon evaporation the residue contaminated with (181) was chromatographed on a column of silicic acid using chloroform-hexane (1:1), giving 121 mg of the 6-acetoxy heptane (182) as an oil at the expense of both isomers. The product solidified on standing with m.p. 67-68°.

I.r. (KBr): 1735 (C=O), 1550 cm^{-1} (C-NO_2).

N.m.r. ($CDCl_3$): δ 1.70-2.30 (m, 5H, $COCH_3$ and CH_2), 3.37 (d, 1H, J=4 Hz), 3.70 (s, 3H, OCH_3), 4.70-5.06 (m, 3H), 5.20 (m, 1H).

Mass (120°): m/e 228 (M^+-OCH_3), 213 (M^+-HNO_2), 169, 127, 81.

Anal. Calcd. for $C_{10}H_{13}NO_7$: C, 46.33; H, 5.06; N, 5.40.

Found: C, 46.23; H, 5.30; N, 5.21.

2-Exo-acetoxy-5-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene (183)

A solution of (181) (605 mg, 2.34 mmole) and DBU (444 mg, 281 mmole) in methylene chloride (20 ml) was refluxed for 1.5 hr. The mixture was diluted with methylene chloride, washed with 0.1N hydrochloric acid and water, dried, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform-hexane (3:1) afforded 453 mg (91%) of (183) as an oil which solidified on standing with m.p. 62-63°.

I.r. (KBr): 1725, 1710 (C=O), 1610 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.73-2.20 (s+m, 5H, $COCH_3$ and CH_2), 3.70 (s, 3H, OCH_3), 4.76 (q, 1H, J=3 Hz, H-2), 5.00 (d, 1H, $J_{1,6}$=2 Hz, H-1), 5.16 (d, 1H, $J_{4,3exo}$=4 Hz, H-4), 6.92 (d, 1H, $J_{6,1}$=2 Hz, H-6).

Mass (120°): m/e 212 (M^+), 181 (M^+-OCH_3), 169 (M^+-$COCH_3$), 152 (M^+-CH_3COOH), 137, 127, 109.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70.
Found: C, 56.45; H, 5.36.

3-Exo-acetoxy-5-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene (184)

A mixture of (182) (189 mg, 0.73 mmole) and DBU (122 mg, 0.8 mmole) in methylene chloride was heated under reflux for 1.5 hr. After usual work-up chromatography of the residue on a column of silicic acid using chloroform-hexane (3:1) gave 108 mg (70%) of (184) as an oil which was crystallized from hexane-carbon tetrachloride with m.p. 119-120°.

I.r. (KBr): 1725, 1710 (C=O), 1610 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 1.70-2.10 (s+m, 5H, $COCH_3$ and CH_2), 3.70 (s, 3H, OCH_3), 4.75 (q, 1H, J=3 Hz, H-3), 4.90-5.10 (s+m, 2H, H-4 and H-1), 7.03 (d, 1H, $J_{6,1}$=2 Hz, H-6).

Mass (120°): m/e 197 (M^+-CH_3), 181 (M^+-OCH_3), 169 (M^+-COCH_3), 152 (M^+-CH_3COOH), 127, 95, 43.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70.
Found: C, 56.46; H, 5.58.

Methyl 2-(3α-acetoxy-4β-hydroxymethyl-furan-1β-yl) glycolate (186)

To a solution of (183) (483 mg, 2.28 mmole) in dry methylene chloride at -78° was bubbled ozone until a blue color persisted. Excess ozone was flushed with nitrogen and dimethyl sulfide (0.5 ml) was added. The reaction mixture was allowed to come to room temperature over a period of 5 hr. The solution was then washed with brine three times, dried over magnesium sulfate and evaporated. To a solution of the residue (185) in dry tetrahydrofuran (20 ml) at 0° was added lithium tri-tert-butoxyaluminum hydride (2.3 g, 9.1 mmole). The reaction mixture was stirred at 0° for 5 hr and a solution of ammonium sulfate (1.5 g) in water (2 ml) was added. After filtration over a layer of Celite and evaporation, the residue was dissolved in ethyl acetate, washed with water, dried, and evaporated. The residue was chromatographed on a column of silicic acid using chloroform-ethyl acetate (1:2), giving 349 mg (62%) of (186) as an oil.

I.r. ($CHCl_3$): 3500 (OH), 1750 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 1.73-2.56 (s+m, 5H, $COCH_3$ and $OCHCH_2$), 3.43-4.16 (m, 7H), 4.16-4.80 (m, 3H), 5.10 (m, 1H).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50.
Found: C, 48.49; H, 6.28.

Methyl 2-acetoxy-2-(3α-acetoxy-4β-acetoxymethyl-furan-1β-yl) glycolate (187)

The diol (186) (157 mg) was acetylated with acetic anhydride (1 ml) and pyridine (2 ml). After the usual work-up chromatography of the crude product on a column of silicic acid using chloroform-hexane (1:1) afforded 149 mg (70%) of (187) as an analitically pure oil.

I.r. (neat): 1745 cm^{-1} (C=O), no hydroxyl group.
N.m.r. (CCl_4): δ 1.80-2.70 (m, 11H, $3COCH_3$ and $OCHCH_2$), 3.63 (m, 3H, OCH_3), 3.76-4.06 (m, 3H), 4.30 (m, 1H), 4.73-5.06 (m, 2H).
Mass (110°): m/e 332 (M^+), 301 (M^+-OCH_3), 273 (M^+-CH_3COO), 259, 201, 152, 81.
Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07.
Found: C, 50.38; H, 6.26.

Methyl 2-(3α-acetoxy-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glycolate (188)

To a solution of (186) (242 mg, 0.98 mmole) in dimethylformamide (5 ml) was added tert-butyldimethylsilyl chloride (148 mg, 0.98 mmole) and imidazole (166 mg, 2.45 mmole). The reaction mixture was stirred at room temperature for 20 hr. The solvent was evaporated in vacuo. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a column of silicic acid using chloroform gave 276 mg (77%) of (188) as an oil.

I.r. (neat): 3450 (OH), 1740 cm^{-1} (C=O).

N.m.r. ($CDCl_3$): δ 0.13 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $C(CH_3)_3$), 1.76-2.53 (s+m, 5H, $COCH_3$ and $OCHCH_2$), 3.23 (m, 1H), 3.53-3.97 (m, 6H), 4.10-4.46 (m, 2H), 5.03 (m, 1H).

Anal. Calcd. for $C_{16}H_{30}O_7Si$: C, 53.04; H, 8.29.

Found: C, 53.27; H, 8.05.

Methyl 2-(3α-acetoxy-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) glyoxylate (189) and 1-Methyl-4-ethyl 2-(3α-acetoxy-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) maleate (190)

(a) A solution of (188) (136 mg, 0.38 mmole) and acetic anhydride (1 ml) in dry dimethylsulfoxide (4 ml) was stirred overnight at room temperature. The mixture was diluted with chloroform and washed with a aqueous sodium bicarbonate solution, water, and brine. Evaporation of the dried organic phase gave the crude keto ester (189). To a solution of the resulting keto ester (189) in methylene chloride (10 ml) was added carboethoxymethylenetriphenylphosphorane (132 mg, 0.38 mmole). After 2 hr of stirring at room temperature, the reaction mixture was evaporated to dryness. Chromatography of the residue on a column of silicic acid using chloroform afforded 138 mg (86% from the hydroxy ester (188)) of (190) as an oil.

I.r. ($CHCl_3$): 1745 (C=O), 1675 cm^{-1} (C=C).

N.m.r. ($CDCl_3$): δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 1.25 (t, 3H, J=7 Hz, $CH_2\underline{CH_3}$), 1.70-2.23 (s+m, 5H, $COCH_3$ and $OCH\underline{CH_2}$), 3.50-3.63 (m, 2H), 3.66 (s, 3H, OCH_3), 3.86 (m, 1H), 4.03 (q, 2H, J=6 Hz, OCH_2), 4.60 (m, 1H), 5.00 (m, 1H), 6.03 (d, 1H, J=2 Hz, C=CH).

Mass (120°): m/e 373 ($M^+-C(CH_3)_3$), 313, 267, 253.

Anal. Calcd. for $C_{20}H_{34}O_8Si$: C, 55.81; H, 7.91.

Found: C, 55.92; H, 7.78.

(b) To a solution of (188) (272 mg, 0.76 mmole) and dicyclohexylcarbodiimide (206 mg, 1 mmole) in dry dimethylsulfoxide (1 ml) and benzene (1 ml) was added dichloroacetic acid (0.04 ml, 0.5 mmole) at 0°. After 30 min at room temperature the mixture was cooled to 0° and a concentrated aqueous solution of oxalic acid (80 mg) was added. The mixture was kept at room temperature for 20 min, diluted with ethyl acetate and then the precipitate was filtered. The filtrate was washed five times with water and the organic phase was dried over Linde 4A Molecular Sieve and evaporated to a syrup. The latter was dissolved in ethanol and a small amount of dicyclohexylurea was removed by filtration. Evaporation of the solvent left the keto ester (189) as a syrup that was contaminated by minor amounts of dicyclohexylurea and N-dichloroacetyl-N,N'-dicyclohexylurea. To a solution of the crude (189) in methylene chloride (10 ml) was added carboethoxymethylenetriphenylphosphorane (264 mg). After 2 hr at room temperature the mixture was evaporated to dryness. The residue was chromatographed on a column of silicic acid using chloroform, giving 142 mg (44% from (188)) of (190) as an oil. Spectral data (n.m.r., i.r.) were identical with those of the above compound.

2-(3α-Acetoxy-4β-tert-butyldimethylsiloxymethyl-furan-1β-yl) maleimide (191)

A mixture of (188) (152 mg, 0.42 mmole) and acetic anhydride (1 ml) in dry dimethylsulfoxide (4 ml) was stirred overnight at room temperature. The mixture was diluted with chloroform and washed with a aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over magnesium sulfate and evaporated to dryness, leaving the crude keto ester (189) as an oil which was contaminated with minor amounts of impurities. Without any further purification this material was directly used in the next step. A solution of the resulting keto ester and carbamoylmethylenetriphenylphosphorane (121 mg, 0.38 mmole) in dry chloroform was stirred at room temperature for 2 hr. The solvent was then evaporated. The residue was chromatographed on a silica gel plate using ethyl ether-hexane (1:1), giving 58 mg (38% from hydroxy ester (188)) of (191) as an oil.

I.r. ($CHCl_3$): 3420 (NH), 1780, 1740, 1725 (C=O), 1645 cm^{-1} (C=C).
U.v. (λ_{max}^{EtOH}): 222 nm
N.m.r. ($CDCl_3$): δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 1.70-2.76 (s+m, 5H, $COCH_3$ and $OCH\underline{CH}_2$), 3.70-3.90 (m, 2H), 4.10 (m, 1H), 4.83-5.23 (m, 1H), 5.33 (m, 1H), 6.55 (t, 1H, C=CH), 8.20 (m, 1H, NH).
Mass (120°): m/e 312 ($M^+-C(CH_3)_3$), 253, 129, 117, 75, 73.

Anal. Calcd. for $C_{17}H_{27}NO_6Si$: C, 55.28; H, 7.32; N, 3.79.
Found: C, 55.12; H, 7.35; N, 3.68.

2-(3α-hydroxy-4β-hydroxymethyl-furan-1β-yl) maleimide (172)

A solution of (191) (102 mg, 0.28 mmole) in 0.1M methanolic hydrochloric acid (15 ml) was stirred at room temperature for 29 hr. After evaporation to dryness, chromatography of the residue on a column of silicic acid using acetone-ethyl acetate (3:7) afforded 40 mg (68%) of (172) as an oil which was crystallized from acetone-benzene with m.p. 122-124°.

I.r. (KBr): 3510, 3320, 3280, 3100 (OH, NH), 1770, 1700 (C=O), 1640 cm^{-1} (C=C).

U.v. (λ_{max}^{EtOH}): 222 nm (log ε 4.18).

Mass (170°): m/e 214 (M^++1), 213 (M^+), 195 (M^+-H_2O), 182, 165, 153, 136, 124, 81, 53, 44, 43, 39, 31, 29.

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57.
Found: C, 50.85; H, 5.40; N, 6.64.

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