AN APPROACH TO THE SYNTHESIS OF AZACYCLIC C-NUCLEOSIDES

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AN APPROACH TO THE SYNTHESIS OF AZACYCLIC ANALOGUES OF C-NUCLEOSIDES

A Thesis

by

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Submitted to the Faculty of Graduate Studies

at McGill University

in partial fulfilment of the requirements

for the degree of

Doctor of Philosophy

Department of Chemistry

McGill University

Montréal, Québec

September, 1976

"The organic chemist is often shocked to find that nature has preceeded him in the synthesis of an analogue of naturally occurring nucleic acid precursors and derivatives."

from:

'Antagonists and Nucleic Acids' by M. Earl Balis in 'Frontiers of Biology' Vol. 10, ed. by A. Neuberger and E. L. Tatum, North Holland Publishing Co., Amsterdam (1968).

To my parents,
who have done so much for me

To Linda,
who has done everything for me

AN APPROACH TO THE SYNTHESIS OF AZACYCLIC ANALOGUES OF C-NUCLEOSIDES

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ABSTRACT

Several important multi-substituted pyrrolidine intermediates for the synthesis of azacyclic C-nucleoside analogues were prepared. An azacyclic analogue of showdomycin, a naturally occurring C-nucleoside, was easily produced from a pyrrolidine containing an α-ketoester substituent. This pyrrolidine is also a potential intermediate for the elaboration of other heterocyclic systems. Structural and stereochemical assignments of these products and their 8-azabicyclo(3.2.$1^{1,5}$)-octane precursors were made by proton magnetic resonance (p.m.r.) spectroscopy.

Une Approche vers la Synthèse d'Analogues Azacycliques de C-Nucléosides

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Résumé

Plusieurs intermédiaires pyrrolidiniques polysubstitués, utiles pour la synthèse d'analogues azacycliques de C-nucléosides, ont été préparés. Un analogue azacyclique de la showdomycine, un C-nucléoside naturel, a été synthétisé aisément à partir d'une pyrrolidine qui contient un substituant α-cétoester. Cette pyrrolidine est également un intermédiaire potentiel pour la préparation d'autres systèmes hétérocycliques. Les structures et la stéréochimie de ces produits et de leurs précurseurs 8-azabicyclo(3.2.$1^{1,5}$)octane ont été déterminées par résonance magnétique nucléaire (R.M.N.).

ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. George Just for his continuous encouragement and advice throughout the present work.

I also wish to thank the National Research Council of Canada for financial support in the form of a Postgraduate Scholarship (1974-1976).

Grateful acknowledgements are made to:

My wife, Linda, for technical, financial, psychological and emotional support, and for typing the manuscript.

Aria Schifman for proofreading and correcting the manuscript, and for many helpful discussions.

Bob E. Robert Zamboni for his knowledge of organic chemistry and distillation technique, and for his good-natured disposition.

Frank (The Burner) Rothwell, for recording the mass spectra.

All my other co-workers, past and present, for their continuous friendship, and sometimes helpful discussions.

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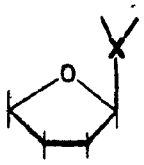
Chapter 1

a. Introduction

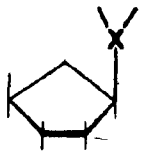
Nucleosides, the important constituents of the nucleic acids DNA and RNA, are compounds of the glycosylamine type in which the aglycone is a purine or pyrimidine base, and the sugar component is the D-ribofuranose or 2-deoxy-D-ribofuranose moiety. In recent years, the term 'nucleoside' has come to include natural and synthetic N-glycosides wherein the aglycone portion is a heterocyclic base (*1*). Analogues in which the C-1 of the sugar residue is bonded to a carbon atom of the heterocyclic base are referred to as 'C-nucleosides' (*2*)[1], and many naturally occurring C-glycosyl nucleosides have been isolated[2]. Particularly interesting are the more recently discovered naturally occurring C-ribosyl nucleosides[2], which will be discussed in detail in this paper.



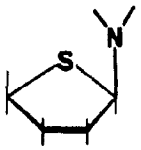
(*1*) X = N

(*2*) X = C

The fact that many nucleosides and C-nucleosides exhibited antiviral, antibacterial and antitumor activity[1,2,3,4] stimulated the synthesis of many nucleoside analogues, in the hope that slight modifications of the nucleoside structure would cause changes in the chemotherapeutic index, or in the toxicity, of the compounds investigated. Accordingly, carbocyclic analogues of nucleosides (3)[5,6] and of C-nucleosides (4)[7,8], wherein the ribofuranosyl ring oxygen is replaced by a methylene group, were synthesized. Thiacyclic nucleoside analogues (5)[8,9] have also been extensively investigated.



(3) X = N
(4) X = C



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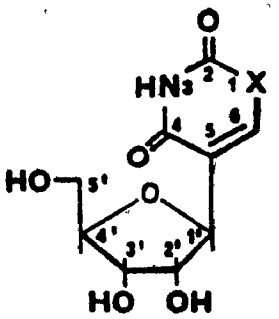
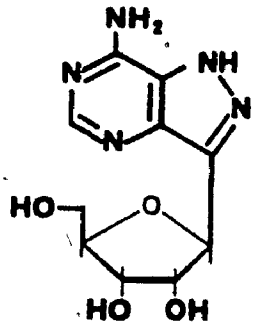
b. Biological and Biochemical Properties of C-Ribofuranosyl Nucleosides

The synthesis and properties of N-nucleosides have been thoroughly examined over the years[1,11], and since 1952, when the first C-nucleoside was identified[12], many such carbo-

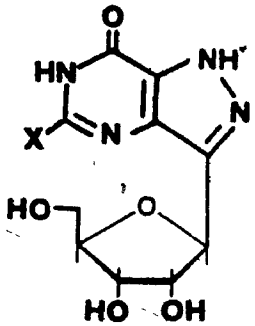
hydrates have appeared in the literature[12,13]. The more recently discovered C-ribofuranosyl nucleosides have especially interesting properties. These modified nucleosides are: pseudouridine (*6*), formycin A (*7*), formycin B (*8*) or laurusin, oxoformycin B (*9*), showdomycin (*10*), pyrazomycin (*11*) or pyrazofurin A, and oxazinomycin (*12*) or minimycin.



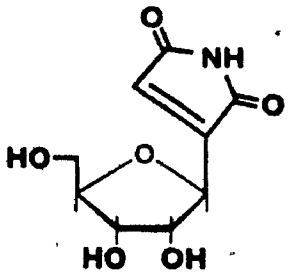
(*6*) X = NH
(*12*) X = O



(*7*)



(*8*) X = H
(*9*) X = OH



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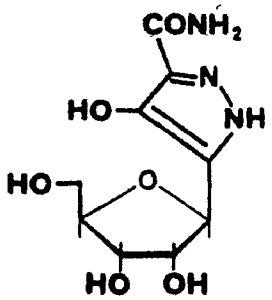
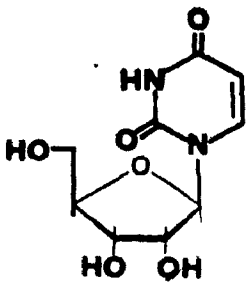


(*11*)

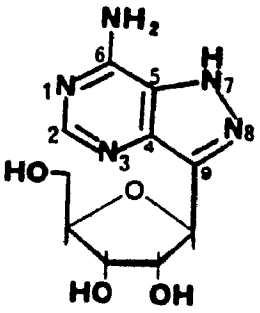
(*i*) Pseudouridine and oxazinomycin: Pseudouridine (*6*)[14], 5-(β-D-ribofuranosyl)uracil, is a structural isomer of uridine (*6a*) and a normal constituent of t-RNA. Its chemical[15] and biochemical[16] properties have been reviewed, and it has proved to be the only member of this class of compounds that does not display medicinally important biological properties. Oxazinomycin (*12*) is the most recently isolated[17] C-ribosyl nucleoside. It displayed some antitumor and antiviral activity.



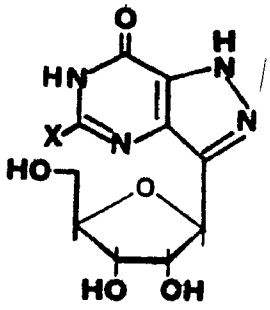
(*6a*)

(*ii*) The Formycin C-Nucleosides: The three pyrazolopyrimidine C-nucleosides are structural analogues of adenosine, inosine and xanthosine. Formycin A (*7*)[18] inhibits the growth of mouse leukemia L-1210, Yoshida rat sarcoma cells, bacteria, fungi and viruses[1,19,20]. It is also the most effective analogue to replace adenosine[21]. Tumor cells which lack adenosine kinase have been found to be resistant to formycin A, indicating that the kinase plays a key role in the mode of action of formycin A.

Formycin B (*8*)[22] does not inhibit animal tumors, but it does inhibit multiplication of influenza A_1 virus. It also inhibits a pathogenic bacterium for rice plant disease caused by *X. oryzae*[22a]. The type of substituent on position 7 of the pyrazolo(4.3-d)-pyrimidine ring is in large part responsible for the biological activities of these nucleosides[1]. Oxoformycin B (*9*)[1] is a competitive inhibitor of N'-methyl nicotinamide, but does not inhibit the growth of any organism tested to date.



(*7*)



(*8*) X = H
(*9*) X = OH

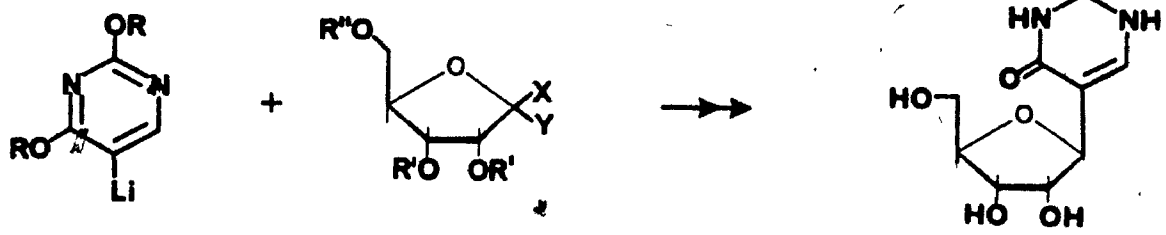
(*iii*) Showdomycin: This nucleoside antibiotic was first isolated from *Streptomyces showdoensis*[24], and its structure has been shown to be 2-(β-D-ribofuranosyl)maleimide (*10*)[4,25]. It is a broad spectrum antibiotic, displaying significant antibacterial and antitumor activities[1,24]. It shows remarkable activity against Ehrlich ascites tumor in mice and HeLa cells[24,26]. The numerous biochemical studies carried out with showdomycin have been reviewed by Suhadolnik[1].

(*iv*) Pyrazofurin A: Pyrazomycin was isolated from *Streptomyces candidus*, and its structure has been determined to be 3(5)-ribofuranosyl-4-hydroxy-pyrazole-5(3)-carboxamide (*11*)[1]. It is a potent antiviral agent both *in vitro* and *in vivo*, and an interesting anti-tumor drug[27]. Pyrazomycin is a strong inhibitor of orotidylic acid decarboxylase, and is an antagonist of uridine metabolism[1].

c. Chemical Syntheses of C-Nucleosides and Related Compounds

The interesting biological properties of the C-glycosyl nucleosides have made them important targets for chemical synthesis. Closely related analogues have also been prepared and their properties scrutinized, in the hope of gaining insight into the mode of action of C-nucleosides.

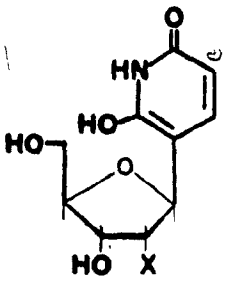
The synthesis of pseudouridine (*6*) has been achieved through carbon-carbon bond formation between a 5-lithiopyrimidine *13* and a suitably activated ribose (e.g. *14* and *15*)[28,29,30]. These



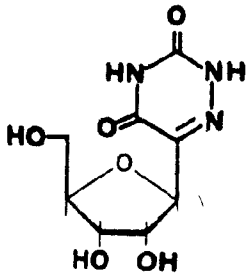
(*13*) (*14*) X, Y = H, Cl (*15*) XY = O (*6*)

approaches were similar to those employed for the synthesis of N-nucleosides, and in general afforded poor yields. Arabino- and xylofuranosyl analogues of pseudouridine were also made *via* direct condensation[31].

Many other analogues have been prepared, the most important of which are shown below. Deazauridine analogues *16* and *17* were investigated[32] as potential inhibitors of thymidylate synthetase. Bobek *et al*[33] synthesized 6-azapseudouridine (*18*) from 2',3',5'-tri-O-acetyl-pseudouridine, and other 6-azauracil derivatives were similarly made from the thiosemicarbazones of L-xylo, D-arabino and D-ribo-hexulosonic acids[34].

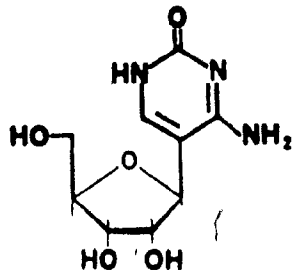


(*16*) X = OH
(*17*) X = H



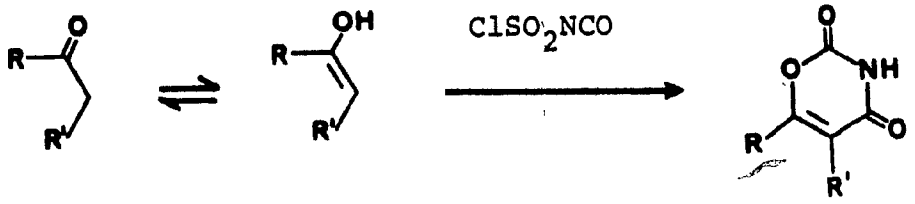
(*18*)

David and Lubideau[35] reported the synthesis of 5-β-D-ribofuranosylcytosine (*19*) (pseudocytidine) and of its α-anomer. Deamination with sodium nitrite converted each isomer to the corresponding pseudouridine at C-1.



(19)

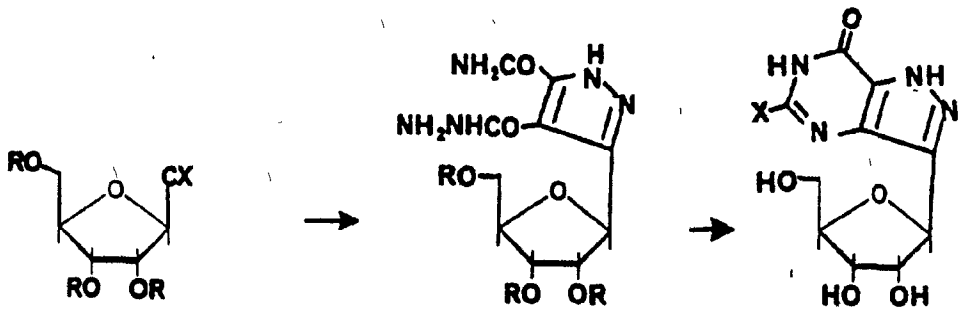
The synthesis of compounds related to oxazinomycin (12) was accomplished[36] *via* the addition reaction of ketones to chlorosulphonylisocyanate:



(20) R = Ph, R' = Me
(21) R = Me, R' = Ph
(12) R = H, R' = β-D-ribofuranosyl

A more versatile route to C-glycosyl nucleosides involves the preparation of appropriately C_1-functionalized derivatives of 2,5-anhydro-D-allose or 2,5-anhydro-D-allitol (22), a compound already containing the desired carbon-carbon bond, from which C_1 can be elaborated into a variety of heterocycles. This approach permits the formation of anomerically pure C-glycosides.

Bobek *et al*[37] transformed the cyano derivative *22a* into the diazo sugar *22b* in six steps, and *22b* was converted to formycin B (*8*)[38] and oxoformycin B (*9*)[37,39] *via* initial cycloaddition to dimethyl acetylenedicarboxylate. Oxoformycin B was prepared by Curtius rearrangement and cyclization of the 3-carbamoyl compound *23*; this same intermediate underwent a similar sequence of reactions to produce formycin B.

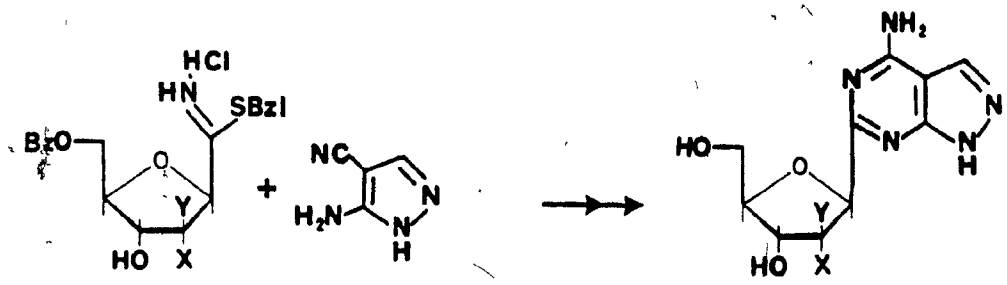


(*22a*) R = CH_2Ph, X = N
(*22b*) R = CH_2Ph, X = HN_2

(*23*) R = CH_2Ph

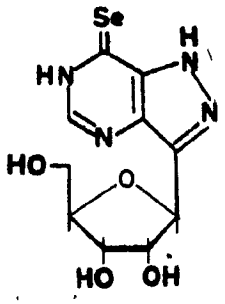
(*8*) X = H
(*9*) X = OH

Kunimoto *et al*[40] found that replacement of the amino group in formycin A (*7*) by a thiol or methyl thiol group produced analogues which inhibited influenza virus. Igolen *et al*[41] synthesized analoges of formycin A by the direct condensation of pyrazole *24* with benzyl thioformidates *25*. Deblocking with methanolic ammonia afforded the pyrimidines *26* and *27* in good overall yield.



(25) (24) (26) Y = H, X = OH
(27) Y = OH, X = H

Many other analogues of the formycin C-nucleosides have been prepared, including the seleno-congener *28* of formycin B[42], the D-arabino epimer *29* of oxoformycin B[43], and two other interesting analogues of oxoformycin B, pyrazolopyridazines *30*[39] and *31*[38].



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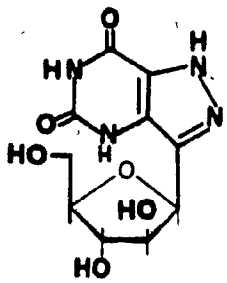

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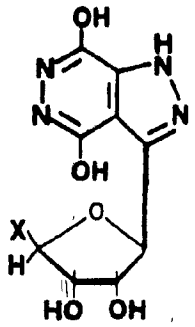
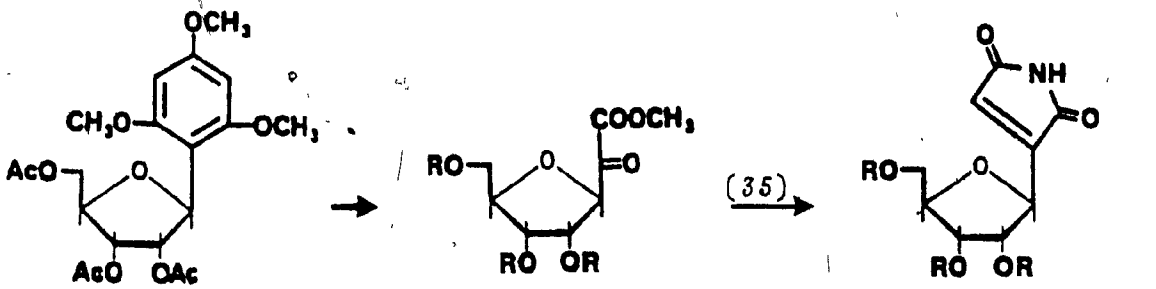


(30) X = CH_2OH, R = H
(31) X = H, RR = $C(CH_3)_2$

Showdomycin (*10*) was first synthesized[44] in six steps from the α-ketoester *33*. The critical step was the ozonolysis of 1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene (*32*) to the α-ketoester *33* required for construction of

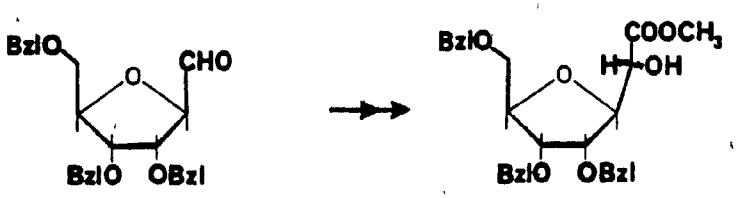
the heterocyclic ring. This method was soon improved upon by Trummlitz and Moffatt[45]. They reacted a similar ketoester, methyl 3,6-anhydro-4,5,7-tri-O-benzyl-D-*allo*-heptulosonate (*34*) with carbamoylmethylenetriphenylphosphorane (*35*) to produce directly the crystalline tribenzyl ester *36*. Pure showdomycin (*10*) was obtained by debenzylation with boron trichloride. The key intermediate *34* had been obtained by oxidation



(*32*) (*33*) R = $COCH_3$; (*34*) R = CH_2Ph; (*36*) R = CH_2Ph; (*10*) R = H

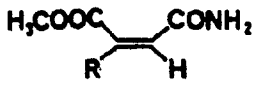
(*35*) $Ph_3P{=}CHCONH_2$

of methyl heptonates *38*; which were prepared from the readily available 3,4,6-tri-O-benzyl-2,5-anhydro-D-allose (*37*)[46].



(*37*) (*38*)

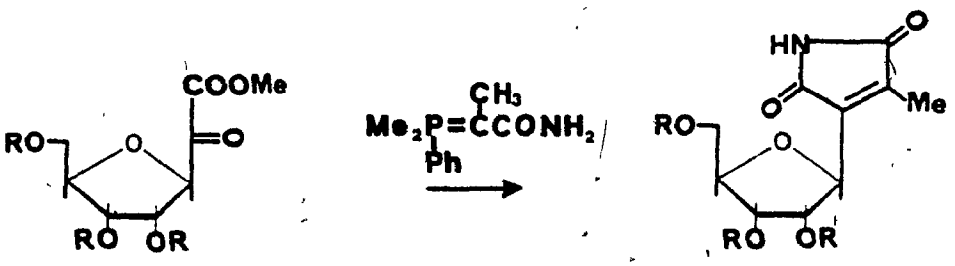
The important heterocyclic ring-forming reaction (*34* → *35* → *36*) was explained by spontaneous cyclization of an intermediate *cis*-maleamic ester *34a* to the corresponding maleimide. Alternatively, the cyclization could have taken place at the level of the betaine precursor of *34a*. The formation of the preponderant *cis*-oriented intermediate was due simply to steric



(*34a*)

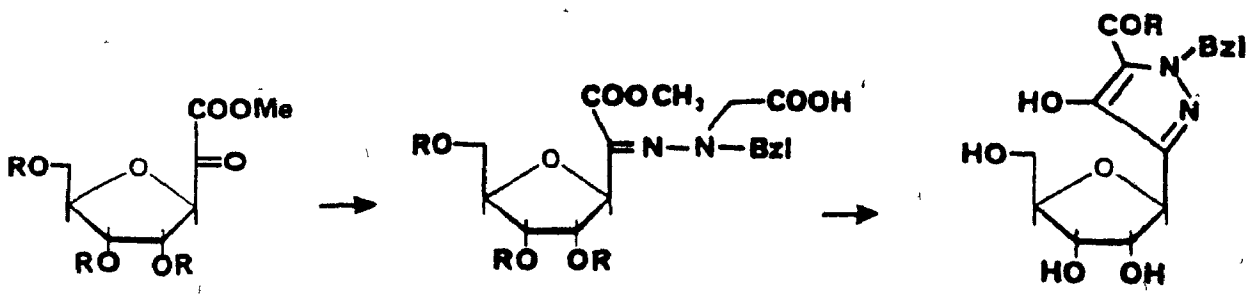
factors[45]. This led to the conclusion that the reaction of α-ketoesters with carbamoylmethylenetriphenylphosphorane provides a direct route to 2-substituted maleimides providing that the substituent R attached to the ketoester (i.e. RCOCOOMe) is reasonably bulky.

More recently, Moffatt *et al*[47] synthesized 3-methylshowdomycin (*39*) by the condensation of their ketoester *34* with 1-carbamoylethylidenedimethylphenylphosphorane. The product displayed a marked reduction of antibacterial activity with respect to showdomycin itself.



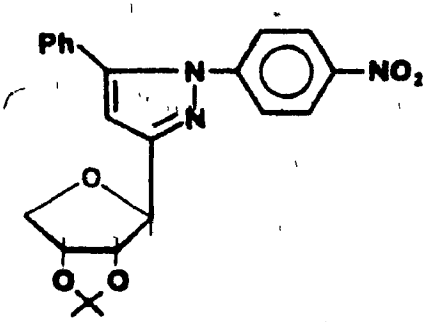
(*34*) R = CH_2Ph (*39*) R = H

Farkas *et al*[48] synthesized pyrazomycin in low yield from the same α-ketoester *33* that they utilized for the production of showdomycin. They reacted the ester with (1-benzyl-hydrazine)-acetic acid to produce the hydrazone *40*, which underwent ring closure and base-catalyzed methanolysis to yield the 4-hydroxypyrazole *41*. Treatment with methanolic ammonia afforded amide *42*, and hydrogenolytic debenzylation yielded crystalline pyrazomycin (*11*) in poor overall yield.

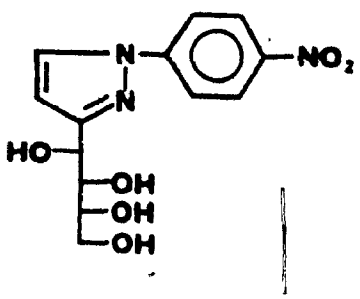


(*33*) R = $COCH_3$ (*40*) R = $COCH_3$ (*41*) R = OCH_3
(*42*) R = NH_2

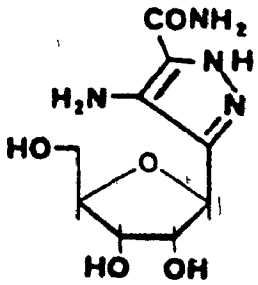
Tronchet *et al*[49] have reported the synthesis of pyrazolic analogues containing aromatic substituents (*43* and *44*). An amino analogue *45*[2] of pyrazomycin was also made for biological testing.



(*43*)

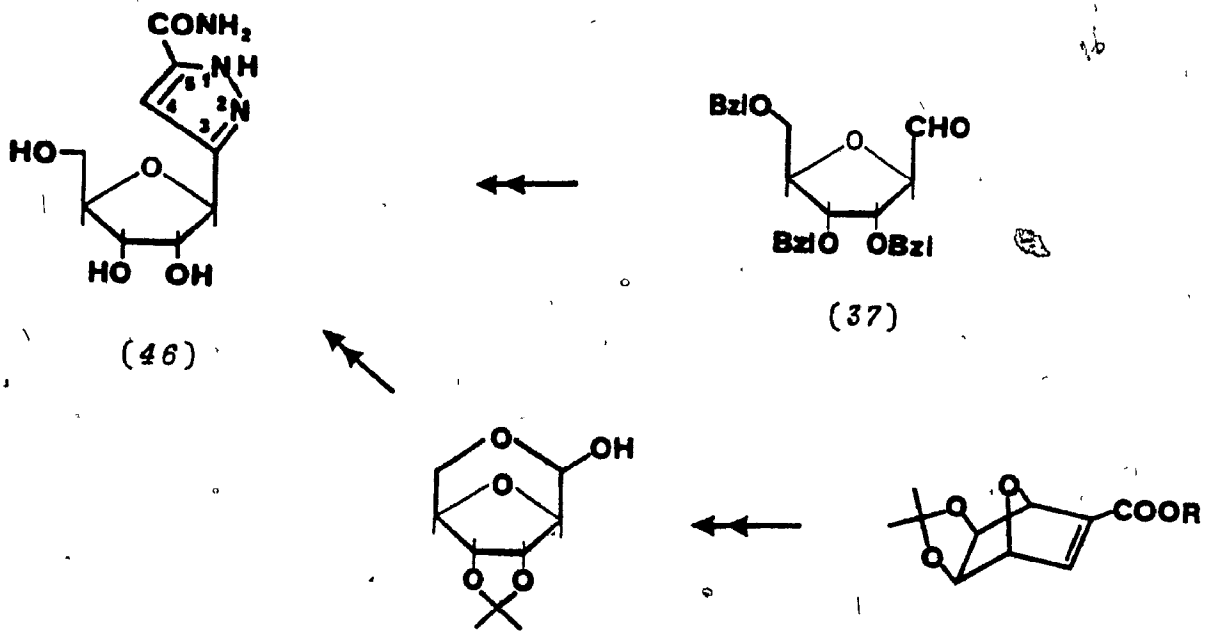


(*44*)



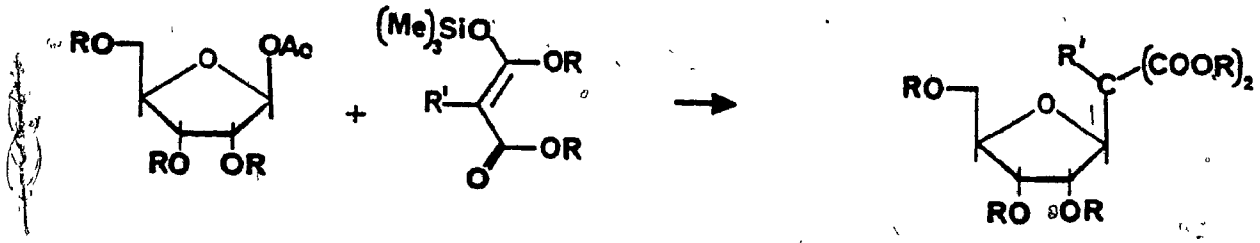
(*45*)

The deoxy pyrazolic C-nucleoside *46* has been prepared[50] from 3,4,6-tri-O-benzyl—2,5-anhydro-D-allose (*37*), and also from 3,4-O-isopropylidene-2,5-anhydro-D,L-allose (*47*)[51], which was synthesized from non-sugar precursors (*48*)[52]. Both of these approaches are versatile routes to C-nucleosides. The hemiacetal *47* has been used in our laboratory to produce several C-glycosides and related derivatives[53], and Moffatt *et al*[45,50] independently utilized the open form *37* to synthesize showdomycin (*10*) (p. 11), 3-methylshowdomycin (*39*) (p. 13), the deoxy pyrazole *45* (p. 14), and several other 4-(β-D-ribofuranosyl)-pyrazoles[50].



(46) (37) (47) (48)

Hanessian[54] has reported a new method of anomeric C-functionalization involving the reaction of acetate *49* with derivatives of O-silyl-enol ethers *50* in the presence of a Lewis acid. In addition, valuable progress has been made in the direct, Lewis acid-catalyzed C-ribosylation of aromatic and heteroaromatic systems[55,56].

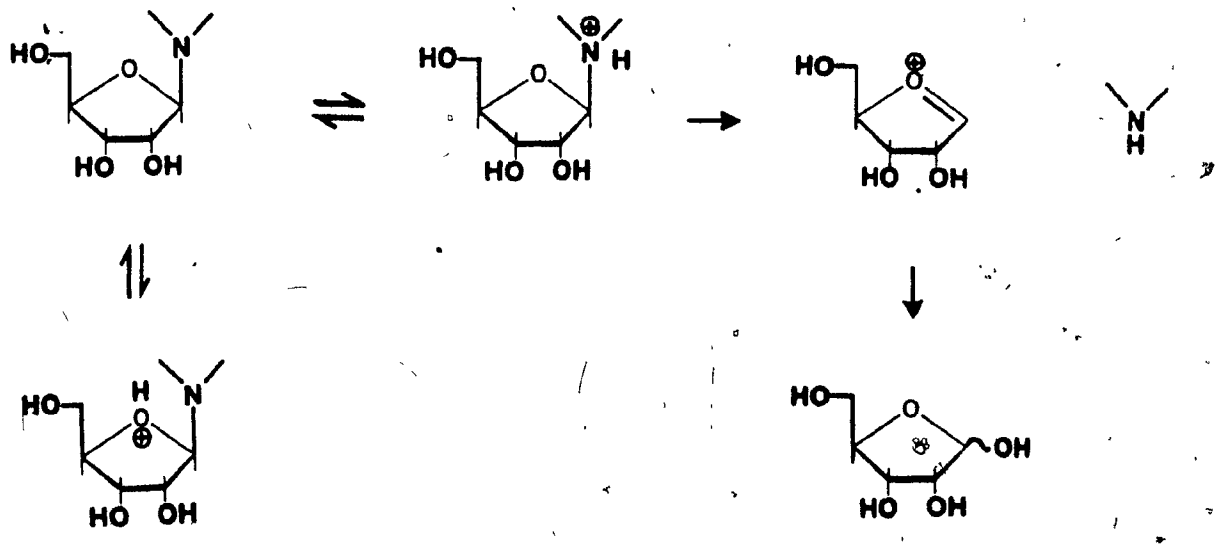


(49) (50) (51)

But despite these and other[57,58] attempts to achieve a 'general' route to C-nucleosides and their analogues, no such procedure has been developed to date. Hopefully, the preparation of other C-nucleosides, together with a detailed understanding of structure-activity relationships, will assist in the realization of the therapeutic potential of this class of compounds.

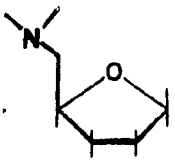
d. Carbocyclic analogues of Nucleosides and C-Nucleosides

Many nucleosides which are effective agents in inhibiting the growth of malignant cells become ineffective *in vivo* because they are rapidly destroyed by enzymatic cleavage into a purine or pyrimidine and a carbohydrate moiety[1,59,60]. The glycosidic C-N bond is readily cleaved by acid hydrolysis as depicted below:



The glycosidic C-C bond of C-nucleosides, however, is more stable towards chemical and enzymatic hydrolysis due to suppression of the normal C-N bond cleavage. Furthermore, this substitution causes a slight increase in the length of the glycosyl bond - 1.55 Å vs. 1.47 Å on the average[61] - which gives C-nucleosides almost free rotation about that bond[62]. This enables them to assume the most suitable conformation for interactions with enzymes.

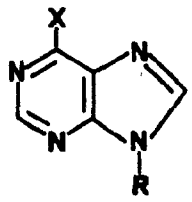
Many so-called 'reversed' nucleosides *52*, which also do not possess the normal linkage between the nitrogen of the base and the anomeric carbon of the sugar, have been investigated. These compounds are also more stable with respect to hydrolytic cleavage. A number of reversed nucleosides have been synthesized[63,64,65], and recently, two patents have been filed which listed several reversed nucleosides as antiviral and anticancer drugs[66,67].



(*52*)

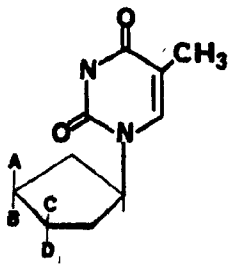
Another series of compounds, wherein a carbon atom replaces the ribofuranosyl ring oxygen, has also been investigated. The resulting carbocyclic nucleoside analogues contain a normal C-N bond at the C-1' position, which should not be subject to the action of nucleoside phosphorylases or hydrolases or otherwise broken easily. This substitution causes only a slight distortion of the ring[68], producing analogues which have the same steric size as furanosyl nucleosides. These compounds have the potential, therefore, either to mimic or antagonize the function of naturally occurring nucleosides and nucleotides.

In the continuing search for anticancer agents, Shaeffer *et al*[69,70] prepared purines *53* attached to the cyclopentyl or cyclohexyl rings. They prepared carbocyclic analogues of 6-substituted purines and some 9-cycloalkyl adenine derivatives which were interesting as adenosine deaminase inhibitors[71]. In general, however, no startling improvement in biological activity was found when compared to the activities of the corresponding furanosyl nucleosides[72].



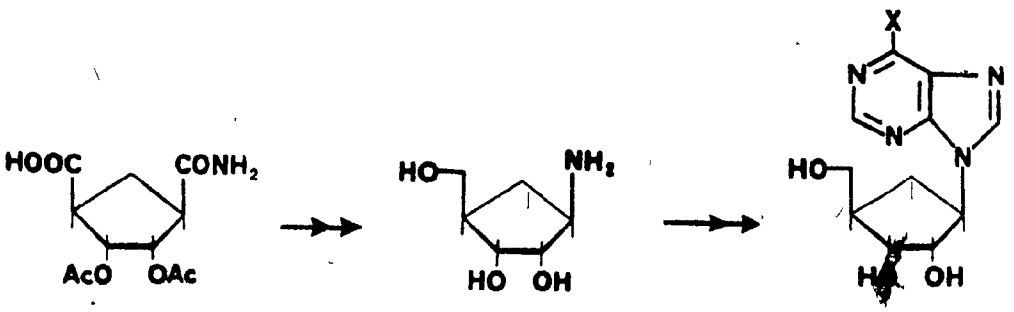
(*53*) R = cyclopentyl, cyclohexyl, monohydroxycyclopentyl, monohydroxycyclohexyl.

Murdock and Angier[73] prepared numerous cyclopentyl analogues (e.g. *54*-*56*) of thymidine, including the cyclopentane isostere *54* of thymidine itself. None of these showed any activity against a wide variety of bacteria and fungi[74]. Several products were also tested against three mouse tumors with negative results[75].



(*54*) A = CH_2OH, B = H, C = H, D = OH
(*55*) A, B = H, OH; C, D = H, OH
(*56*) A, B = COOH, H; C, D = H, OH

The carbocyclic analogue of adenosine, aristeromycin (*59a*) was synthesized as the racemic mixture by Shealy and Clayton[76] and its optically active (-) form was subsequently isolated by Kusaka *et al*[77]. It is the only naturally occurring carbocyclic nucleoside discovered to date. A rigid norbornene ring was utilized for the synthesis of cyclopentanes *57* and *58* of known geometric configuration. In this way, the racemic forms of the carbocyclic analogues *59* of adenosine, inosine, 6-mercaptopurine ribonucleoside and 6-(methylthio)purine ribonucleoside were synthesized[68] from (±)-4β-amino-2α,3α-dihydroxy-1β-cyclopentanemethanol (*58*). Similarly, the carbocyclic analogues of

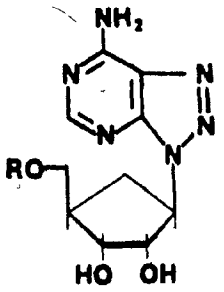


(57) (58) (59a) X = NH_2; (59b) X = OH; (59c) X = SH; (59d) X = SCH_3

2'-deoxy-adenosine and 3'-deoxy-adenosine (cordicepin) were made from *exo*-5-norbornen-2-ol acetate[78].

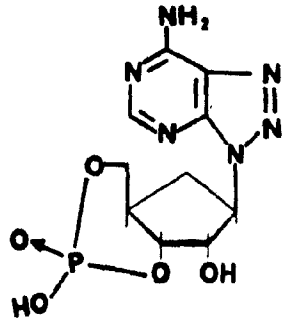
Aristeromycin displayed considerable antitumor activity[68], and was not toxic to mice or killifish[77]. It was not inhibitory against yeast, pathogenic fungi and bacteria except for the acid-fast bacteria[77], but numerous studies[77,79,80] have indicated that aristeromycin can act as an inhibitor by interfering with many processes in the cell, besides causing inhibition by its conversion to the 5'-phosphate. Aristeromycin also controls the growth of plants and is active against the blast disease of rice plants.

Shealy *et al*[81] have also synthesized the 8-azadenosine analogue *60*, its monophosphate *60a*, and its cyclic monophosphate *61*: all proved to be cytotoxic to cells in culture.



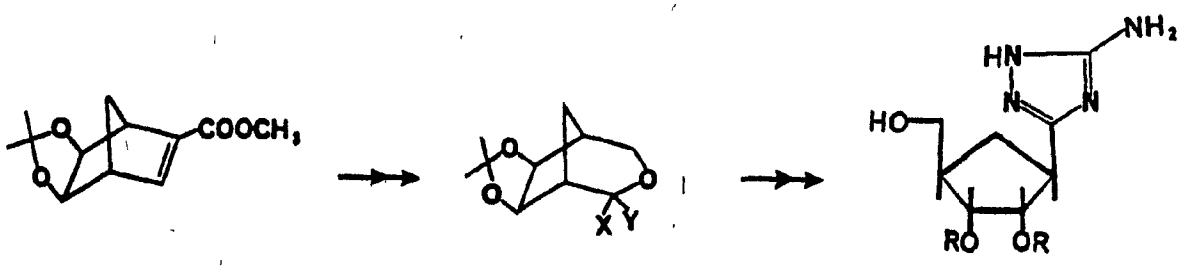
(60) R = H

(60a) R = HO–P(=O)(OH)–



(61)

Fissekis and Markert[82] synthesized various 5-(hydroxycyclopentane)pyrimidines bearing structural similarities to carbocyclic C-nucleosides, but Reader[7,8] was the first to synthesize a carbocyclic analogue *65* of a C-nucleoside. The synthesis involved the production of the unsaturated methyl ester *62*, conversion to the lactol *63*, and oxidation to the lactone *64*. Condensation with aminoguanidine bicarbonate afforded the triazole *65*.



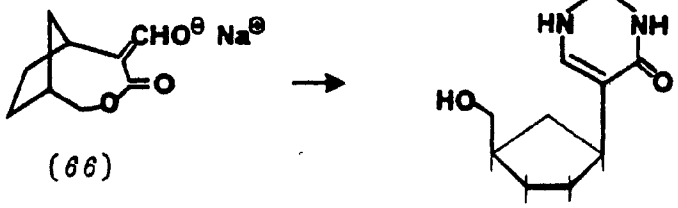
(62)

(63) X, Y = H, OH

(64) XY = O

(65)

More recently, Playtis and Fissekis[83] obtained a carbocyclic analogue *68* of 2',3'-dideoxypseudouridine. The sodium enolate *66*, obtained in good yield from the corresponding lactone, was condensed with thiourea to produce the 2-thiouracil *67* in poor yield; the latter was converted quantitatively to the uracil *68*.

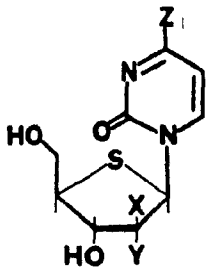


(*66*)

(*67*) X = S
(*68*) X = O

e. Thiacyclic and Azacyclic Nucleoside Analogues

The synthesis and characterization of monosaccharides with a ring heteroatom other than oxygen has also been of general interest for several years. It has been shown that sugar analogues[84,85], nucleoside analogues[86,87] and certain nucleotide analogues[88] having sulphur replacing the ring oxygen atom of the sugar have interesting and intriguing biological properties, among which is low toxicity[85]. Biological investigations of 5-thio-D-glucopyranose[84,85] and pyrimidine nucleosides *69* of

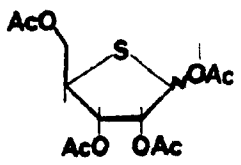


(*69a*) X,Y = H,OH; Z = OH

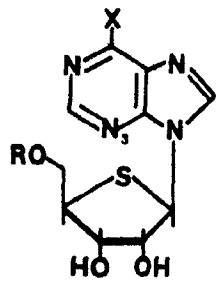
(*69b*) X = H; Y = OH; Z = NH_2

4-thio-β-D-ribofuranose and 4-thio-β-D-arabinofuranose[86] indicated the potential usefulness of these sugars and sugar derivatives as possible chemotherapeutic agents and as analogues of naturally occurring metabolites.

The synthesis of 9-(4'-thio-β-D-ribofuranosyl)adenine (*71*) and its 5'-phosphate (*72*) has been accomplished[88] from the sugar *70*. It was noted that the adenine ring of these analogues had a more restricted movement about the C-N glycosyl bond than that of adenosine, because of electronic repulsion between the nonbonding electrons of the nitrogen at the 3-position of the heterocycle and the ring sulphur.



(*70*)



(*71*) R = H, X = NH_2

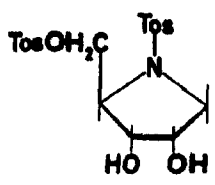
(*72*) R = $HO-\overset{\overset{O}{\|}}{\underset{OH}{\underset{|}{P}}}-$, X = NH_2

(*73*) R = H, X = Cl, SH, H, $N(Me)_2$

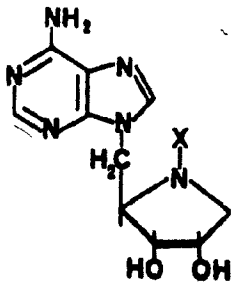
Bobek *et al*[87] prepared and studied the activities of 4'-thio derivatives (*71*, *73*) of several 6-substituted purine nucleosides. They found that, depending on the test system used, the potency of the thioribosyl nucleosides was greater or smaller than that of the ribosyl analogue, when determined *in vitro* with *Streptococcus faecum*, *E. coli*, Leukemia L-1210 and Ehrlich ascites cells.

In general, thiacyclic nucleoside analogues have proved to be useful tools in elucidating the biochemistry of the naturally occurring compounds.

Recently, Nair and Walsh[89] reported the synthesis of the first 'reversed' amino nucleoside, 1-(6-aminopurin-9-yl)-2,5-anhydro-1,2-dideoxy-2-amino-D,L-ribitol *76*, which is really a homo nucleoside analogue. The synthetic imino acid dehydroproline was reduced and hydroxylated to produce the pyrrolidine sugar *74*, which was coupled directly with the sodium salt of adenine to give the tosylated compound *75* as a stable crystalline compound. The detosylated nucleoside *76* was found to be extremely unstable and difficult to handle.



(*74*)



(*75*) R = p-$CH_3C_6H_4SO_2$
(*76*) R = H

Aim of the Project

The aim of the present work was to synthesize azacyclic analogues of C-nucleosides. More specifically, we hoped to produce the azacyclic analogues of showdomycin and pyrazomycin (pyrazofurin A), two C-nucleosides which exhibit very interesting biochemical and biological activities. This project to synthesize azacyclic precursors of C-nucleosides was part of a general program initiated in our laboratory to synthesize C-nucleoside analogues.

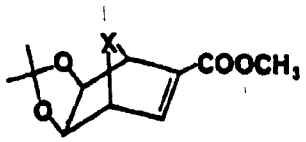
Chapter 2

Synthetic Studies with 7-azabicyclo(2.2.1)norborn-2-enes

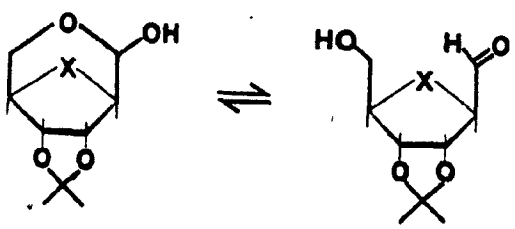
a. Introduction

Compounds of type *77* have been converted to nucleoside analogues in reasonable yields via the ketoester *78*[90] or protected 2,5-anhydro-D,L-allose analogues *79a*[52,91] and *79b*[7]. Ketoester *78* has also been used as the key intermediate in the synthesis of showdomycin[44] and pyrazomycin[48].

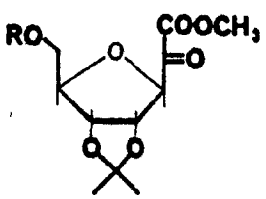
Unsaturated esters *77a* and *77b* have been synthesized by the Diels-Alder reaction of furan or cyclopentadiene with methyl β-nitroacrylate or *trans*-bromoacrylic acid respectively, followed by



(*77a*) X = O
(*77b*) X = CH_2

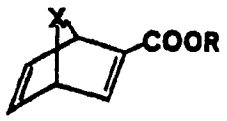


(*79a*) X = O
(*79b*) X = CH_2



(*78*)

hydroxylation, protection and subsequent elimination of nitrous or hydrobromic acid with 1,5-diazabicyclo(5.4.0)undec-5-ene (DBU). Methyl or ethyl propiolate ($H-C\equiv C-CO_2R$) were not used as the dienophiles because they produced adducts *80* that were difficult to hydroxylate. In fact, Reader[8] reported that *80c* (2-carbethoxybicyclo(2.2.1)hepta-2,5-diene) polymerized under the free radical conditions used for the hydroxylation (osmium tetroxide - 30% hydrogen peroxide). Polymerization of such bicyclo(2.2.1)heptadienes occurs readily with a variety of initiators[92].

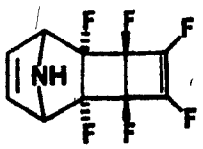


(*80a*) $X=O$, $R=CH_3$
(*80b*) $X=CH_2$, $R=CH_3$
(*80c*) $X=CH_2$, $R=CH_2CH_3$

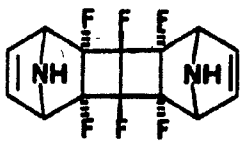
We planned to follow these routes closely in our first attempt to synthesize azacyclic intermediates. We intended to react a pyrrole with the more reactive methyl β-nitroacrylate and eventually produce an olefin ester wherein $X=N-R$. However, because of the aromaticity of the pyrrole ring, cycloadditions with N-substituted pyrroles are in general much slower and require harsher conditions than the corresponding reactions of furan or cyclopentadiene. Withdrawal of π electron density from the nitrogen by an electron-withdrawing group increases the diene

character of the pyrrole; thus it is more reactive towards dienophiles, while ring positions are rendered less susceptible to electrophilic attack. Furthermore, increasing the electron-withdrawing efficiency of the substituent reduces the susceptibility of the adduct towards a retro-reaction[93].

Pyrroles do not generally participate in Diels-Alder reactions with olefinic dienophiles. To our knowledge, only the very reactive hexafluoro-Dewar benzene is known to react with pyrrole, giving the 1:1 and 1:2 adducts *81* and *82*[94].

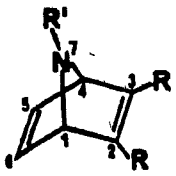


(*81*)



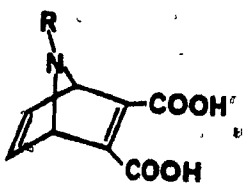
(*82*)

On the other hand, at the start of our work several symmetrical acetylenic dienophiles were known to react with pyrroles to produce the 7-azabicyclo(2.2.1)hepta-2,5-diene system *83*: acetylenedicarboxylic acid[93,95,96,97], dimethyl acetylenedicarboxylate (DMAD)[93,98,99], benzyne[100], tetrafluorobenzyne[101], and tetrachlorobenzyne[102]. These reactions were successful only with N-substituted pyrroles. For example, pyrrole itself and benzyne afforded 2-phenylpyrrole[103]. More recently, only one more dienophile, hexafluorobut-2-yne, has been condensed with pyrroles[104,105].



(83)

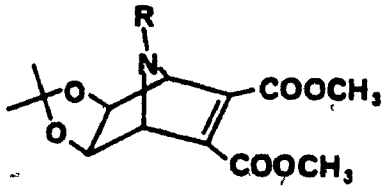
Of all the dienophiles, the reagent that would most readily and conveniently produce adducts structurally close to 77 was DMAD. Its adducts are generally more stable than those of its closest analogue, acetylenedicarboxylic acid. In fact, attempted esterification of two 7-azabicyclo(2.2.1)heptadiene-2,3-dicarboxylic acids 84a and 84b with diazomethane in mild conditions led to decomposition liberating the corresponding pyrroles[106,96]. Furthermore, the reaction between DMAD and N-carbomethoxypyrrole[107] had been catalyzed by a Lewis acid, aluminum trichloride, resulting in a much higher yield of the desired adduct under the right conditions[98] than any other reaction.



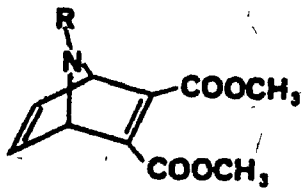
(84a) R = CH_2Ph
(84b) R = COOMe

All of our preliminary attempts to condense methyl β-nitroacrylate with N-carbomethoxypyrrole met with failure. No reaction occurred even when the pyrrole was heated six hours in toluene with excess dienophile. Reactions catalyzed by aluminum trichloride led to an intractable mixture of products.

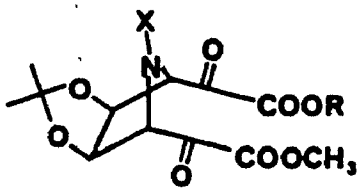
Accordingly, several approaches were envisioned wherein the key intermediate would be the symmetrical diester *86*. It was hoped that this compound could be obtained by hydroxylation and protection of the Diels-Alder adduct *85*, and that it could be converted to a diketoester *87* or an α-ketoacid α-ketoester *88*. Ideally, an oxidative decarboxylation of *88* would lead to an acid α-ketoester or an aldehyde α-ketoester, and these two could then be converted to compounds similar to ketoester *78* or anhydroallose *79* by methods developed in our laboratories[8,108,109].



(*86*)



(*85*)



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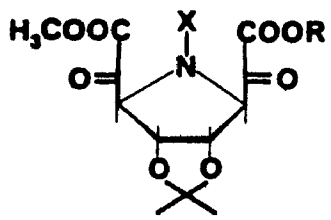
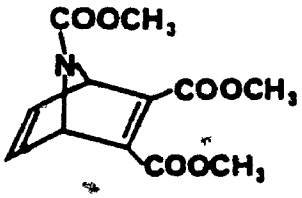


(*87*) R = CH_3

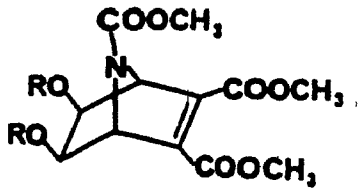
(*88*) R = H

b. N-Carbomethoxy-7-azabicyclo(2.2.1)norborn-2-enes

The most readily available precursor to a molecule of type *86* was N-carbomethoxy-7-azanorbornadiene *89*, prepared in 90% yield by a Diels-Alder reaction of DMAD and N-carbomethoxy-pyrrole catalyzed by five equivalents of aluminum trichloride[98]. Hydroxylation of this adduct with a catalytic amount of osmium tetroxide in the presence of 30% hydrogen peroxide[110] produced a low yield of crude diol *90*. This was converted to its oily isopropylidene derivative *91* with 2,2-dimethoxypropane, acetone and p-toluenesulphonic acid in 23% overall yield based on *89*.



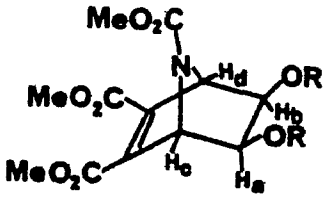
(*89*)

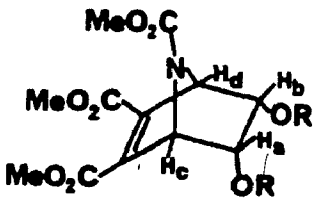


(*90*) R = H

(*91*) RR = $C(CH_3)_2$

The *exo-cis* stereochemistry of the diol and its acetonide was substantiated by the p.m.r. of *91*, which showed a singlet for protons H_a and H_b, as well as a singlet for H_c and H_d. Thus, no coupling was observed between H_a and H_c, nor between H_b and H_d. In *91*, the dihedral angle between H_a and H_c or H_b and H_d is estimated to be about 80-90° from a consideration of molecular models, whereas if H_a and H_b were *exo*-protons (*91a*), the angle would be about 30-40°. Thus, ignoring neighboring group





(*91*) RR = $C(CH_3)_2$ (*91a*) RR = $C(CH_3)_2$

electronegativity effects[111], the Karplus curve[112] predicts very weak or nonexistant coupling in *91* between H_a and H_c, but a coupling constant of about 7 Hz for structure *91a*. Since H_a and H_b appear as a singlet, the *exo-cis* stereochemistry of *91* is confirmed. In fact, the p.m.r. spectra of other 7-azabicyclo(2.2.1)-heptane derivatives[113] exhibit virtually no spin-spin coupling between the bridgehead protons and *endo* protons at C-2 and C-3 ($J<1$ Hz), indicating that the dihedral angle between the C-H bonds is usually about 80° in such compounds. The observable coupling of *exo*-protons at C-2 and C-3 with H_c and H_d however, has proved very useful for the assignment of *exo* or *endo* stereochemistry[113,114]. The same situation applies to bicyclo(2.2.1)-heptane[115], 7-thiabicyclo(2.2.1)heptane[116] and 7-oxabicyclo(2.2.1)-heptane[117] derivatives, which clearly have very similar geometry.

Since the hydroxylation proceeds via a cyclic osmate ester of the diol[118], steric considerations for this intermediate strongly suggested that the hydroxylated compounds had the *exo-cis* configuration, since there should be less interference between

the osmium tetroxide and the nitrogen bridge than between the reagent and the two carbon bridge. Furthermore, this argument seems to be valid when other substituents are attached to the nitrogen, since H_a and H_b will appear as a singlet when the substituent is the acetyl or even the bulky tosyl group.

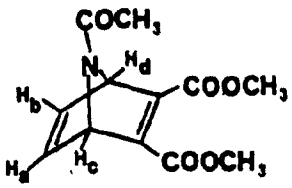
When *91* was ozonized at -78° and the ozonide reduced at low temperature with dimethyl sulphide[119] in an attempt to produce a diketoester of type *87*, a complex mixture of products was obtained. Similar attempts to oxidize *91* with ruthenium dioxide - sodium periodate[120] led to several products. The ozonide of *91* was unstable and showed broad peaks in its p.m.r. spectrum even when freshly prepared. Thus, it was decided to investigate a similar approach with other nitrogen-protecting groups, in the hope that one could be found that would confer stability to the bicyclic system during the oxidation steps.

Hence, the electron-withdrawing acetyl group was investigated, as well as the very stable, bulky p-toluenesulphonyl (tosyl) group.

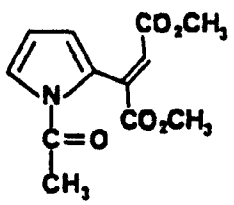
c. N-Acetyl-7-azabicyclo(2.2.1)norborn-2-enes

The N-acetyl adduct *92* was prepared in a manner analogous to that used to produce the N-carbomethoxy derivative *89*. The highest yield (65%) was obtained when equimolar amounts of N-acetyl pyrrole[121] and DMAD were reacted in methylene chloride in the presence of a fivefold excess of aluminum trichloride. A 10%

yield of the 2-substituted pyrrole *93* was also obtained. The latter is believed to be formed from a Michael type addition[122], and compounds like it have commonly been isolated from both thermal reactions[95,96,123] and catalyzed reactions[98] of other pyrroles with acetylenedicarboxylic acid or DMAD. Our products were completely purified by chromatography on silica gel, and the stereochemistry of side product *93* was determined from its p.m.r. spectrum*. A fuller discussion will be presented when discussing the side product obtained when the substituent on the nitrogen is the tosyl group.



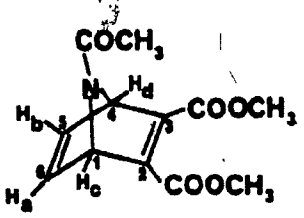
(*92*)



(*93*)

The p.m.r. of adduct *92* did not display the typical coupling of the bridgehead protons with the vinylic protons noted in normal 7-azabicyclo(2.2.1)heptadienes containing identical substituents at C-2 and C-3. Instead of two 2H-triplets expected from a degenerate A_2X_2 system, protons H_c and H_d of *92* displayed two equal intensity signals in deuteriochloroform at 5.60 and 5.78 p.p.m., and a multiplet resembling a quartet at 5.55 in carbon tetrachloride; H_a and H_b displayed a broad

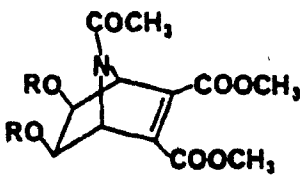
* Prinzbach *et al*[93] could only obtain a semi-pure Diels-Alder adduct *92* in 45% yield from a thermally catalyzed reaction using a twentyfold excess of DMAD.

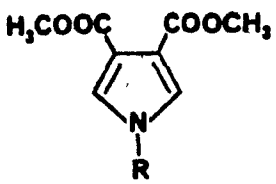


(92)

multiplet in each solvent at approximately 7.2 p.p.m. These absorptions are well downfield of usual bridgehead proton resonances[93], and are a result of restricted rotation about the N-CO bond[124], which makes hydrogen atoms H_c and H_d nonequivalent. From the coalescence temperature[125] a normal amide rotational barrier was determined, and in fact *92* displays a normal amide absorption at 1685-1690 cm^{-1} in its i.r. spectrum.

Hydroxylation of *92* with osmium tetroxide - hydrogen peroxide afforded a poor yield of crude diol *94*. This was converted to its crystalline diacetate *95a* in 25% overall yield, and to its oily isopropylidene derivative *95b* in 20% yield. In all cases a substantial amount (20%) of the retro Diels-Alder product, 3,4-dicarbomethoxy-N-acetylpyrrole (*96*), was isolated from the hydroxylation step. A reaction temperature of 5° lowered this yield by about 5%. Similar products, such as 3,4-dicarbomethoxy-N-carbomethoxypyrrole (*96a*) and the N-tosylpyrrole *96b*, have routinely been obtained from the thermal decomposition of the corresponding adducts[93,107].





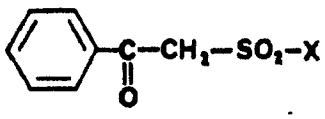
(*94*) R = H
(*95a*) R = $COCH_3$
(*95b*) RR = $C(CH_3)_2$

(*96*) R = $COCH_3$
(*96a*) R = COOMe
(*96b*) R = tosyl

Unfortunately, attempted oxidations of either *95a* or *95b* with either ozone or ruthenium tetroxide led to multiple products. The N-acetyl singlet in the p.m.r. was converted to several smaller peaks, indicating that the oxidation of the N-acetyl moiety had occurred.

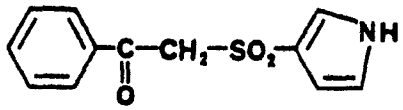
d. The phenacylsulphonamido protecting group

Another N-protecting group which is easily attached to and removed (Zn, CH_3COOH, H^+) from amines[132] was investigated: the phenacylsulphonamido function. Phenacylsulphonyl chloride *98* was prepared from its acid *97*[133] and reacted with one equivalent



(*97*) X = OH
(*98*) X = Cl

of pyrrole and 1.5 equivalents of triethylamine at -40° in methylene chloride. The crystalline product obtained in 20% yield was not the expected N-phenacylsulphonylpyrrole however, but the 3-substituted pyrrole *99*. Modifications of this procedure did not change the result of this reaction. Reactions of the chloride *98* with potassium pyrrole led to a low yield of several products. The unusual substitution at the 3 position of pyrrole was perhaps due to the high reactivity of phenacyl-sulphonyl chloride *98*.



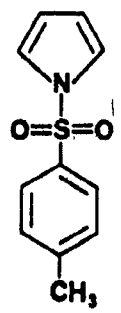
(*99*)

The structure of *99* was confirmed by the presence of a strong band at 3350 cm^{-1} in the i.r. spectrum, indicating a free pyrrole N-H, and a typical p.m.r. pattern for a 3-substituted pyrrole: an exchangeable (D_2O) proton at about 7.6 p.p.m., and one-proton multiplets at 6.18, 6.67 and 7.00. 3-n-Propyl pyrrole displays an exchangeable proton at about 7.8, and one-proton multiplets at 6.13, 6.55 and 6.70[134].

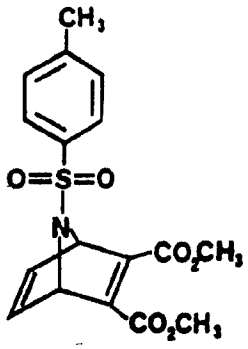
e. p-Toluenesulphonamido-7-azabicyclo(2.2.1)norborn-2-enes

Potassium pyrrole[126] was reacted with p-toluenesulphonyl chloride at room temperature, producing N-(p-toluenesulphonyl)pyrrole (*100*) in 55% yield. The latter was condensed with

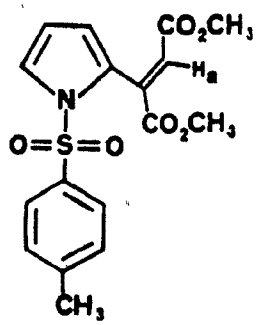
excess DMAD to give a 30% yield of the Diels-Alder adduct *101*[93]. Alternately, several attempts were made to carry out an aluminum trichloride - catalyzed cycloaddition with equimolar amounts of addends and varying amounts of catalyst. The highest yield of the desired adduct was obtained when a fivefold excess of $AlCl_3$ was used: 60% adduct and 40% 2-substituted pyrrole *102*. A 3:1 $AlCl_3$:addends ratio afforded *102* almost exclusively in over 80% yield; a 7:1 ratio yielded roughly equivalent amounts of the two products. Unfortunately, the products could not be separated easily from each other: fractional crystallizations failed, and separation by chromatography was difficult because the R_f values were almost coincident. Complete separation could only be accomplished on a smaller scale by preparative t.l.c. (p.l.c.). Thus, for large scale preparations the thermally catalyzed reaction[93] was used, and the non-reacted addends were recovered off the column used for the work-up and recycled.



(*100*)

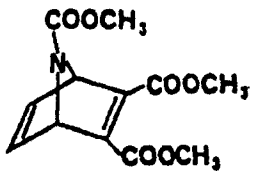


(*101*)

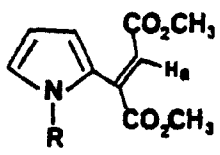


(*102*)

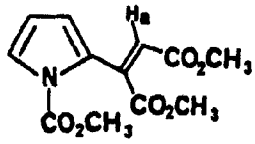
The structure of *102*, like that of *93*, was determined from its p.m.r. spectrum. The most revealing proton was H_a; this olefinic proton displayed a singlet at δ 7.33 (*102*) and δ 6.93 (*93*) p.p.m. respectively. The chemical shift for this proton was 6.96 when R = COOMe (*103*)[98], and in dimethyl fumarate it displayed a singlet at 6.86. Conversely, in dimethyl maleate it appeared at 6.16 and in *104*[98] at 6.36. The p.m.r. spectra of our side products clearly indicated that their structures were those of fumarates *93* and *102*.



(*89*)



(*93*) R = $COCH_3$
(*102*) R = tosyl
(*103*) R = COOMe

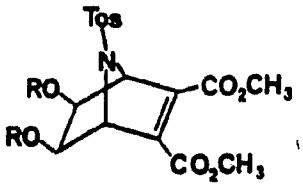


(*104*)

The stereochemistry of *93* and *102* could be predicted from the work of Bansal *et al*[98]. In their experiments involving the $AlCl_3$-catalyzed addition of DMAD to N-carbomethoxypyrrole, when the $AlCl_3$:addends ratio was 1:1, a higher reaction temperature (40°) favoured the synthesis of the Diels-Alder adduct *89* and inhibited side reactions producing fumarate *103* and maleate *104*. A threefold increase in the $AlCl_3$ concentration not only raised the yield of adduct *89* from 54 to 76% but also caused

total isomerization of maleate *104* to fumarate *103*. When the ratio was 5:1, the yield of *89* was about 90%. Independent experiments established that *104* was isomerized to fumarate *103* but that neither compound was interconvertible with the adduct *89* in the presence of $AlCl_3$. Thus it was expected that a fivefold excess of $AlCl_3$ and a reaction temperature of 40° in the present work would lead only to fumarate side products. Furthermore, fumarates are usually the major 2-substituted pyrrole side products in thermally catalyzed reactions.

The adduct *101* was hydroxylated in the usual manner to diol *105*, and the crude product was converted to the crystalline acetonide *106a* in over 50% overall yield. The diol was also characterized as its diacetate *106b*. This was by far the easiest and most productive conversion of a Diels-Alder adduct to a protected *exo-cis* diol.



(*105*) R = H
(*106a*) RR = $C(CH_3)_2$
(*106b*) R = $COCH_3$

The first attempts to oxidize the olefinic diesters *106a* and *106b* to a diketoester with ozone met with failure, because both starting materials proved to be completely inert

to electrophilic attack by O_3 at low temperatures. No reaction occurred until the temperature for the ozonolysis was raised above 0°; even then, prolonged treatment afforded some unreacted material plus a mixture of other products, probably due to oxidation of the aromatic moiety. The olefinic absorption at 1650 cm^{-1} in the i.r. spectrum was especially useful for following the reactions.

The double bond in *106a* and *106b* was clearly unreactive towards electrophilic attack because of deactivation due to delocalization of its electron density onto the carbomethoxy groups, and possibly steric interference from the bulky tosyl group. Fortunately however, *106a* reacted smoothly with ruthenium tetroxide, a powerful oxidant, generated by the action of sodium periodate on ruthenium dioxide in an acetone - water solvent system at room temperature[120]. The diester was converted cleanly to the diketoester hydrate *107* in over 50% yield. The latter was a powder which could be recrystallized from methylene chloride-carbon tetrachloride, but its p.m.r. spectrum (fig. 1) showed a sharp singlet exchangeable with D_2O at 4.50 p.p.m. Duplicate analyses confirmed the presence of one molecule of water in the solid. This 'water of hydration' could not be removed from the compound even with prolonged heating at 50° *in vacuo*. Furthermore, because of the simplicity of the p.m.r. spectrum, the product probably existed in the form shown on the next page (*107a*) wherein the two hydroxyl groups display the *exo-cis* stereochemistry which would result in a more stable conformation than if

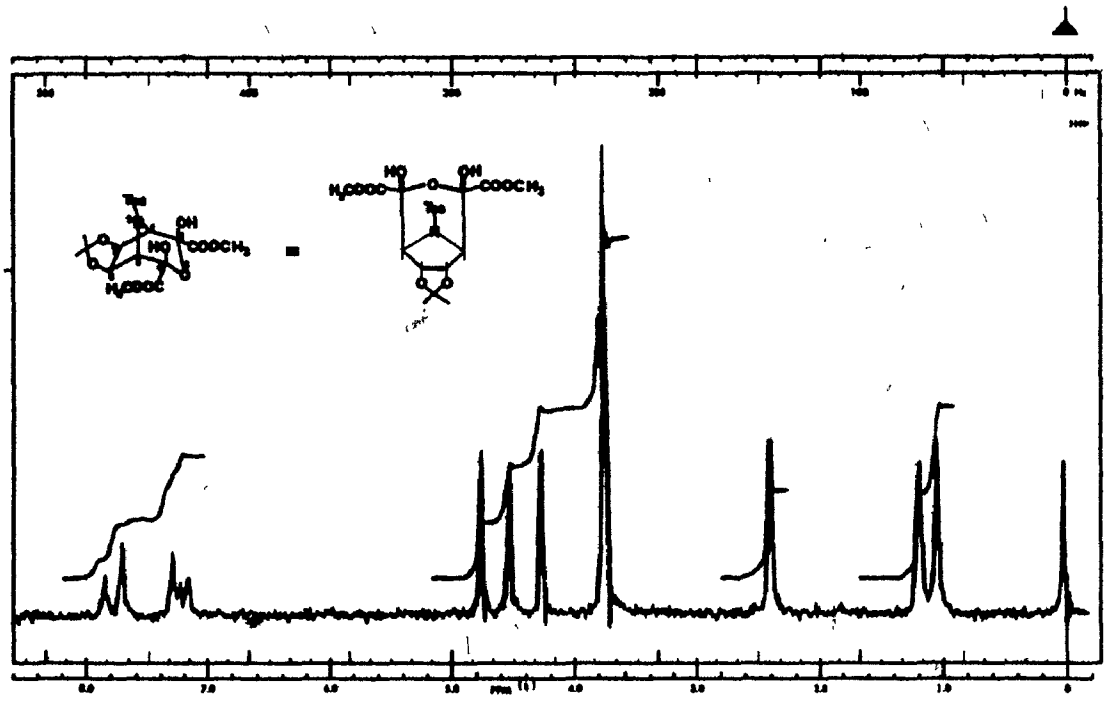
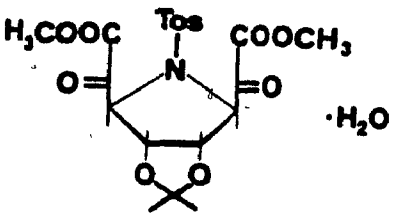
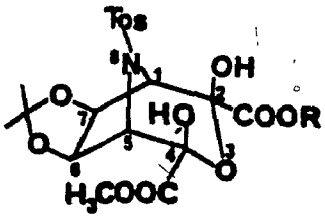


Figure 1. P.m.r. spectrum of diketoester hydrate *107* in deuteriochloroform.



(*107*)



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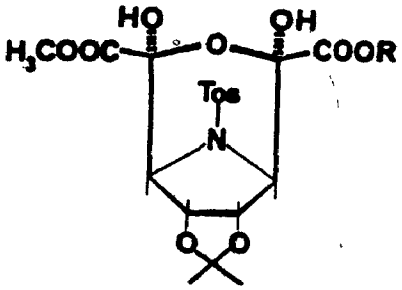
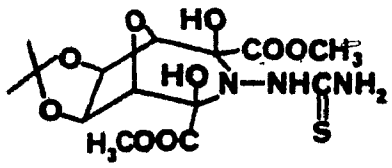


(*107a*) R = CH_3
(*109*) R = H
(isomeric mixture)

the carbomethoxy groups were *exo-cis*. The latter arrangement would be unstable due to the large, destabilizing 1,3-diaxial interaction between the two carbomethoxy groups in the six-membered morpholine ring. This conclusion is similar to that reached by Martel[109] for a closely related bicyclic system (*108*).

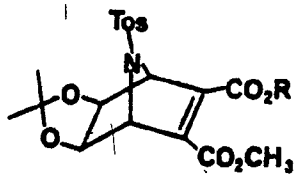


(*108*)

Selective hydrolysis of *107* with one equivalent of sodium hydroxide in THF - water afforded the solid acid-ester *109* in 60% yield. Again the analysis and spectral data indicated the presence of one molecule of water tied up in the solid

product. Thus an important intermediate for our final steps had been produced.

The reverse sequence leading to *109*, namely selective hydrolysis of unsaturated diester *106a* to acid-ester *110* and subsequent oxidation, was not successful. The hydrolysis did proceed smoothly to the unsaturated acid-ester *110* in 70% yield, but all oxidations with ruthenium tetroxide gave intractable products. The oxidations were all buffered to pH 6-7 with KH_2PO_4 - NaOH to prevent the pH of the reaction from dropping too low and destroying the isopropylidene group, with subsequent cleavage of the resulting diol. But all oxidations yielded a poor recovery of a mixture of acidic compounds.



(*106a*) R = CH_3
(*110*) R = H

The p.m.r. spectrum of *110* in acetone-d_6 displayed several interesting absorptions (fig. 2), the most notable of which was a broad acid proton peak at about 6.4 p.p.m. This can only be accounted for by assuming that the carboxylic acid hydroxyl of *110* attacks the neighboring methyl ester and forms a stable orthoester-type adduct *110a* in a very polar solvent,

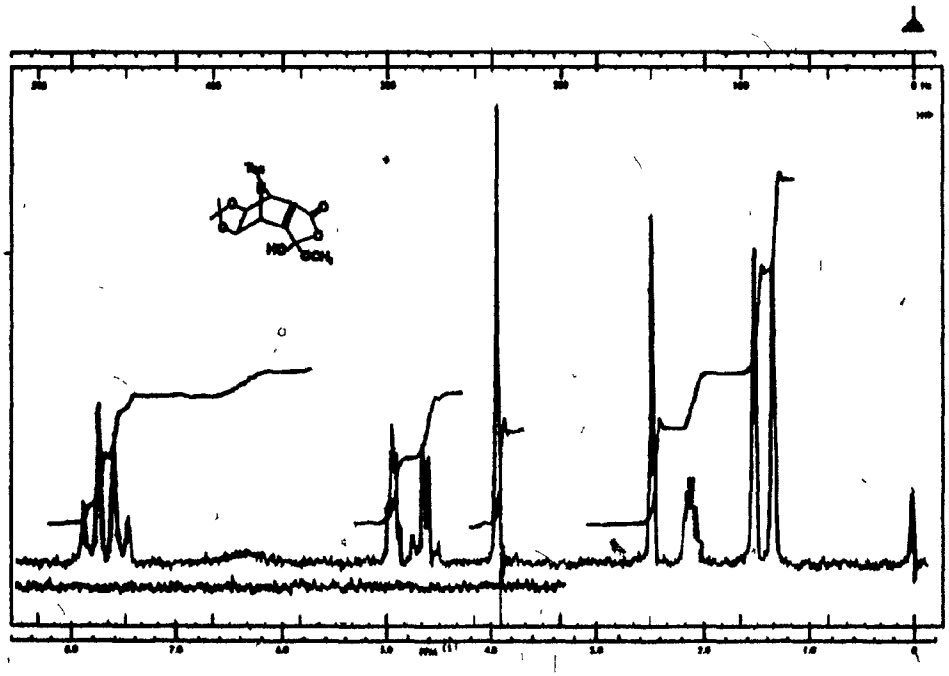
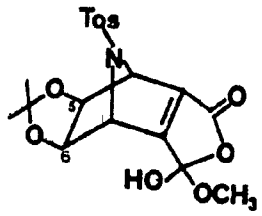


Figure 2. P.m.r. spectrum of unsaturated acid *110* in acetone-d_6. Lower scan is 500 Hz offset.

since in deuteriochloroform *110* exhibited a normal broad acid absorption at 9.1 p.p.m. Two 'quartets' representing the bridge-head protons and the *endo* hydrogens at C-5 and C-6 were also present.

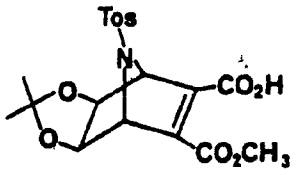


(*110a*)

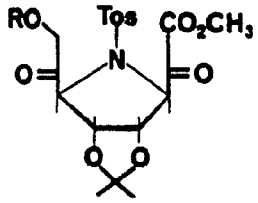
The crucial step, oxidative decarboxylation of *109*, could not be accomplished cleanly. Attempted reactions with lead tetraacetate in acetic acid and water[127] led to a mixture of products. This reagent is the preferred oxidant for α-hydroxy acids, and it is known to cleave α-ketoacids effectively in the presence of protic solvents. The p.m.r. spectra of our crude products showed that the acid-sensitive isopropylidene group of *109* was not destroyed, but the rest of the absorption pattern was complicated, and t.l.c. showed several products. Reaction with benzoic anhydride and pyridine, reagents reportedly able to decarboxylate α-ketoacids[128] to aldehydes under mild conditions, did not yield any aldehydic products. This indicates that the ketoacid *109* (p.42) was not formed even under these dehydrating conditions. A final attempt to decarboxylate *109* with

sodium periodate in an acetone - acetic acid - water solvent system[129], a method which had been successful with α-hydroxy acids, also yielded an intractable mixture.

Since all attempts to decarboxylate *109* smoothly were not successful, it was decided to try to reduce the acid function of *110*, protect the resulting alcohol, and oxidize the olefin to the ketoester *111* or its hydrate. We hoped to cleave the deprotected α-hydroxy ketone to an acid, and hence produce an acid ketoester.

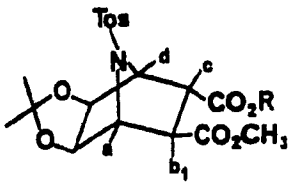


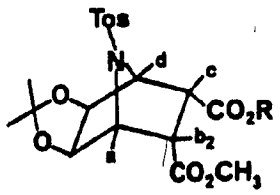
(*110*)



(*111*)

However, reduction of *110* with borane - tetrahydrofuran, a reagent that reacts very quickly and selectively with most acids[130], led exclusively to reduction of the electron-deficient olefinic linkage. A near quantitative yield of a mixture of acids *112* and *113* was obtained upon work-up with water and methanol. Of course, this type of reduction was not unexpected, but it was hoped that some normal reduction of the acid to an alcohol would occur.





(*112*) R=H, m.p. 109-113° (*113*) R=H, m.p. 57-61°

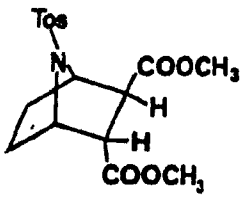
(*114*) R=CH_3 (*115*) R=CH_3

The stereochemistry of the two products was determined from their p.m.r. spectra and those of their methyl esters *114* and *115*, which were obtained by methylation with etheral diazomethane. To begin with, there are pronounced differences in the multiplicity of the signals arising from an *endo* proton or an *exo* proton at C-2 or C-3. As mentioned previously, there is a dihedral angle of about 80° between a bridgehead proton and an *endo* proton at C-2 or C-3. Also, an angle of about 120° exists between protons b and c when they are *trans*, whereas when they are *cis* it becomes almost 0°. Again ignoring the small influence of a neighboring electronegative atom on the coupling constant of vicinally coupled protons[111], the Karplus curve[112] predicts the following torsion angle dependent coupling constants: $J_{a\text{-}b_1} \simeq 0$ Hz, $J_{a\text{-}b_2} \simeq 7$ Hz, $J_{c\text{-}b_1} \simeq 5$ Hz, $J_{c\text{-}b_2} \simeq 10$ Hz and $J_{d\text{-}c} \simeq 7$ Hz. Hence one would expect a doublet ($J_{c\text{-}b_1} \simeq 5$ Hz) for *endo* proton b_1 of a *trans* structure, and a broad triplet ($J_{c\text{-}b_1} \simeq 5$ Hz, $J_{d\text{-}c} \simeq 7$ Hz)

for its proton c.

Furthermore, in a *trans* structure there is a considerable difference in chemical shifts between an *endo* and an *exo* proton. This is due mainly to the deshielding effect of the 7-nitrogen and its protecting group on the latter hydrogen with respect to its effect on the former. For example, the difference between the *exo* and *endo* proton at C-2 and C-3 respectively in *116* was 0.55 p.p.m.[113] : δ 3.55 p.p.m. vs. δ 3.00 p.p.m.

The *trans* stereochemistry of the minor acid product *112* (30% yield) was easily determined from the presence of an *endo* proton doublet ($J \simeq 6$ Hz) at δ 2.97 p.p.m. in deuteriochloroform (3.53 in pyridine-d_5), and an *exo* proton multiplet at 3.93 (a triplet with $J \simeq 6$ Hz at 4.43 in pyridine-d_5). The positions and multiplicities of other peaks in the spectra were consistent with the *trans* structure. The *endo-cis* structure of the major product *113* (65% yield) was similarly established by the absence of any *endo* proton absorption in its p.m.r. spectrum. Protons b_2 and c appeared as a two proton multiplet at 3.47 p.p.m. in *113* (acetone-d_6) and at about 3.7 in *115* (deuteriochloroform). The acid peak appeared at 6.9 p.p.m. in acetone-d_6, and this indicated that the acid-ester actually existed in the closed form *113a* in a polar solvent. Also, a comparison of the p.m.r. spectra of *112* and *114* in pyridine-d_5 showed that the newly formed carbomethoxy methyl group appeared slightly upfield with respect to the original ester function (3.66 vs. 3.80 p.p.m.).



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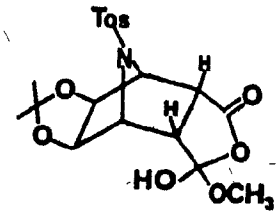


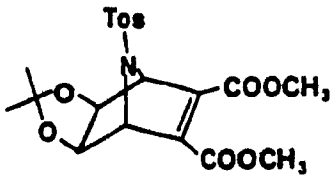
(113a)

These absorptions were similar to those of *116*, wherein the two carbomethoxy methyls appeared at 3.61 and 3.70 p.p.m. in deuteriochloroform[113]. This clearly indicated that the acid functionality of *112* was in the *endo* orientation. A clear explanation of the reduction mechanism is not yet available.

No attempt was made to oxidatively decarboxylate the *trans* acid *112* with lead tetraacetate - iodine and then dehydroiodinate the resulting iodo ester with DBU to an unsaturated ester of type *77* (p. 26), since Martel[52,109] reported that the desired ester *77a* was produced in low yield from an analogous transoid system.

The deactivation of the COOR groups attached to the olefinic bond towards reduction was further demonstrated when an attempt was made to reduce the diester functions of *106a* with lithium aluminum monoethoxide hydride[131] to an unsaturated diol. The reagent is generally utilized for reductions of conjugated esters where saturation of the ethylenic link is a complicating

factor. It converts unsaturated esters to primary allylic alcohols. In the present work, extended reaction times and excess reagent still afforded a substantial amount of unreacted *106a* together with a mixture of products.



(*106a*)

In conclusion, since no clean decarboxylations could be carried out, and because in general the yields in all these attempts were poor, it was obvious that attempts utilizing the Diels-Alder reactions of substituted pyrroles with DMAD would have to give way to a more productive, straightforward approach. The whole general approach involving 7-azabicyclo(2.2.1)heptadienes was unsatisfactory, so a different bicyclic system was sought as the starting point for the synthesis of azacyclic C-nucleoside analogues.

f. Summary and Conclusion

The aluminum trichloride - catalyzed Diels-Alder reactions of N-substituted pyrroles with dimethyl acetylene-

dicarboxylate seem to be generally more useful than the corresponding thermally - catalyzed reactions. Lewis acids cause an enormous increase in the rate of adduct formation, thereby permitting the use of lower temperatures and shorter reaction times. The addends and adduct have been shown to complex with Lewis acids[135], and the formation of the adduct is irreversible, in contrast to thermal reactions, due to the formation of a strong adduct - Lewis acid complex. The catalyst may also deactivate the pyrrole ring to electrophiles while enhancing its reactivity as a diene[136]. Thus, by the use of $AlCl_3$, the low yield of 7-azanorbornadienes reported by Prinzbach *et al*[93] can be improved considerably, mainly because the complications of a thermally - catalyzed reaction (high reaction temperatures for long periods, retro Diels-Alder reactions, etc.) are eliminated.

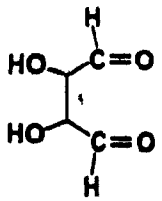
The toluenesulphonamido protecting group proved to be the most stable of the three investigated towards hydroxylation and oxidation, and it had the added advantage of producing crystalline products. However, even when the tosyl group was attached to the nitrogen bridge, the yields of all the important reactions were below 70%. Even so, the main complication preventing the clean formation of an acid ketoester was the presence of a water molecule bonded in the very heart of the reacting species. Clearly, a novel approach towards the synthesis of azabicyclic C-nucleosides was required.

Chapter 3

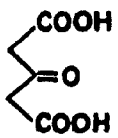
Synthesis of a Key Intermediate for the Production of Azacyclic C-Nucleosides

a. Introduction

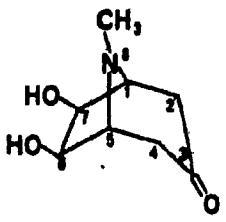
A bicyclic system very closely related to the azabicyclo(2.2.1)hept-2-ene structure is the azabicyclo($3.2.1^{1,5}$)-octane skeleton. The *exo-cis* diol of tropinone, teloidinone (*119*), had been synthesized by a modified Robinson tropane synthesis[137,138] from *meso*-tartaraldehyde *117*, acetonedicarboxylic acid *118* and methylamine in connection with other work on tropane alkaloids. Such a compound seemed well suited for our purposes of synthesizing a key bicyclic intermediate for the production of azacyclic C-nucleosides. The desired *exo-cis* diol moiety was built in, and *119* could be produced readily from inexpensive reagents. We hoped to convert the basic, symmetrical



(*117*)

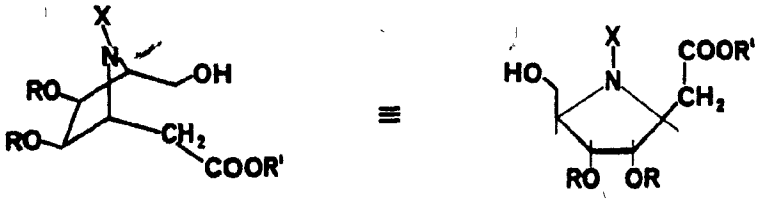


(*118*)

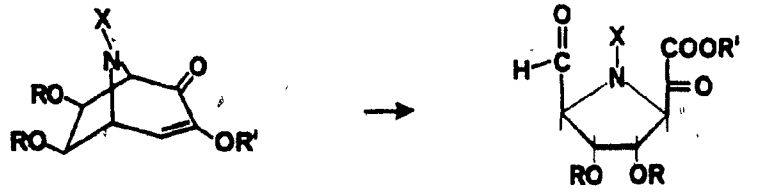


(*119*)

ketone structure of *119* to a nonsymmetrical intermediate such as a lactone or an α-diketone. Once this differentiation had been accomplished, the bicyclic system could be ruptured to produce potentially useful products such as *120* (from the lactone) or *122* (via oxidative opening of the diketone enolate *121*).



(*120*)

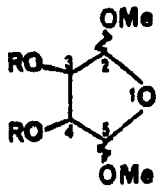


(*121*) (*122*)

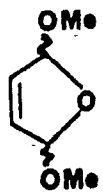
Compound *122* is an aldehyde α-ketoester, one of the desired, elusive products that we could not obtain from aza-bicyclo(2.2.1)hept-2-enes. Also, ester *120* could be useful for synthesizing another important intermediate, an α-ketoester. Several other possibilities existed wherein teloidinone *119* could be transformed to useful intermediates, all based on the reactive, versatile nature of its ketonic function. It was thus chosen as the starting point for our second general approach towards azacyclic C-nucleoside analogues.

b. 7-Azabicyclo(3.2.1^{1,5})octane Derivatives

The synthesis of teloidinone as effected by Sheehan and Bloom[137] involved the condensation of acetonedicarboxylic acid *118*, methylamine and *meso*-tartaraldehyde *117* at pH 5.2. The dialdehyde was prepared by acid hydrolysis of its cyclic acetal, *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (*124*), which in turn was produced by hydroxylation of 2,5-dimethoxy-2,5-dihydrofuran *123* with potassium permanganate. While following this scheme, we have made several improvements. To begin with, the tedious hydroxylation procedure has been replaced by a very simple, straightforward modification of the method used by Gagnaire and Vottero[139], affording the mixture of diols *124* in 43% yield. This mixture was characterized as the diacetate *125*, m.p. 90-2°, the p.m.r. spectrum of which displayed a six proton singlet for the acetate methyls at δ 2.09 p.p.m., a second six proton singlet at 3.46 for the methoxy groups, and



(*124*) R = H
(*125*) R = $COCH_3$

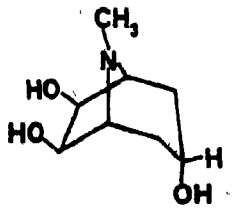


(*123*)

two two-proton multiplets at 5.14 and 5.24 p.p.m. It also gave a satisfactory elemental analysis. The conditions for acid hydrolysis of acetal *124* with hydrochloric acid, and subsequent Robinson synthesis in a pH 5 aqueous buffer, were not altered substantially. However, the extended continuous extraction technique[137,138] used for the isolation of teloidinone was replaced by an extractive technique that afforded virtually the same yield of product in a considerably shorter time period. Recrystallized teloidinone, of sufficient purity for the next step, was recovered in over 40% yield.

The stereochemistry at C-2 and C-5 of the acetal *124* is not important, because once the methyl acetal structure is hydrolyzed, the resulting dialdehyde is a symmetrical compound. However, the *exo-cis* diol stereochemistry of teloidinone *119* is essential, and it has been confirmed that when the condensation is effected under 'simulated physiological conditions'[137,138] as in the present work, teloidinone is the sole product isolated. No trace of the other possible isomer, also a *meso* form, was detected. The definitive proof for the stereochemistry of *119* was its conversion to teloidine *126*[138], tropan-3α,6β,7β-triol*. Since *126* formed a lactone salt with ethyl iodoacetate[142] whose chloride *127* resisted periodate oxidation, and any tropane formed from *meso*-tartaraldehyde must have *cis*-oriented groups, teloidine was thus a 6β,7β-tropandiol.

* According to convention[140,141], the functional groups *cis* to the N-methyl bridge are designated as β, while the *trans* ones are designated as α, as in steroids. Thus teloidinone is 6β,7β-dihydroxy tropan-3-one.



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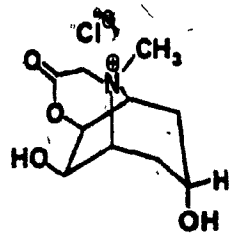
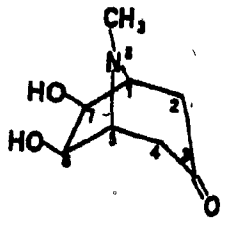


(127)

Our p.m.r. spectrum of teloidinone produced further proof of this *exo* stereochemistry: the 6α, 7α protons displayed a two proton singlet, reminiscent of the *endo* C-5, C-6 protons of azabicyclo(2.2.1)hept-2-enes. A similar stereochemical explanation of the weak or nonexistant coupling between the 6α, 7α protons and the bridgehead protons led us to conclude that the C-6 and C-7 hydrogens in teloidinone (*119*) are indeed in the *endo*, or α, orientation. This stereochemistry is of course expected in view of the fact that α (*endo-cis*) hydroxyl groups would be subject to considerable steric interference from the six-membered piperidone ring of teloidinone in its favoured chair conformation.



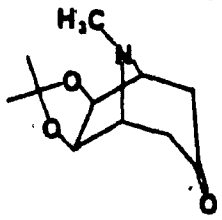
(119)

Because of their simplicity, Robinson-type syntheses have been utilized in a majority of known attempts to synthesize various tropane alkaloids. A more recent synthesis employed the iron nonacarbonyl promoted cyclocoupling reaction between α,α,α',α'-tetrabromoacetone and N-carbomethoxypyrrole to eventually produce *128* in approximately 60% yield based on the pyrrole[143]. While this approach seemed to be more fruitful than

(*128*)

the classical procedure, in our hands the yield of the cycloaddition was lower than reported. Furthermore, the next required step, hydroxylation of *128* to an *exo-cis* diol, did not seem very attractive due to the generally low yields of such conversions (Chapter 2). Overall then, it seemed that the older technique was more applicable in our case, since the required stereochemistry was already present in the initial product, whereas *128* would probably afford only a fair yield of diol.

Teloidinone was converted to its highly crystalline isopropylidene derivative *129* with acetone and concentrated



(129)

hydrochloric acid in 90% yield by a slight modification of the known procedure[144] . The p.m.r. spectrum of both this acetonide (fig. 3) and teloidinone displayed a singlet for the tertiary 6α, 7α protons, and a multiplet for the four protons closest to the ketone that is typical of the N-methyl azabicyclo(3.2.1^{1,5})-octan-3-one system. These compounds exhibit a four proton multiplet from δ 2.0 to 2.9 p.p.m. that resembles very closely an AB quartet (fig. 3). The upper field 'doublet' at 2.34 and 2.06 p.p.m. represents the more shielded α protons at C-2 and C-4, and the large separation between these broad singlets is due to geminal coupling between the α and β protons. The lower field 'doublet' representing the two β protons that are deshielded by the nitrogen bridge, is further split by the bridgehead protons. Observable coupling occurs only between bridgehead protons and β-oriented protons due to geometrical considerations; virtually no coupling is expected with α-oriented protons.

At this point, it was decided that the oxidation-prone

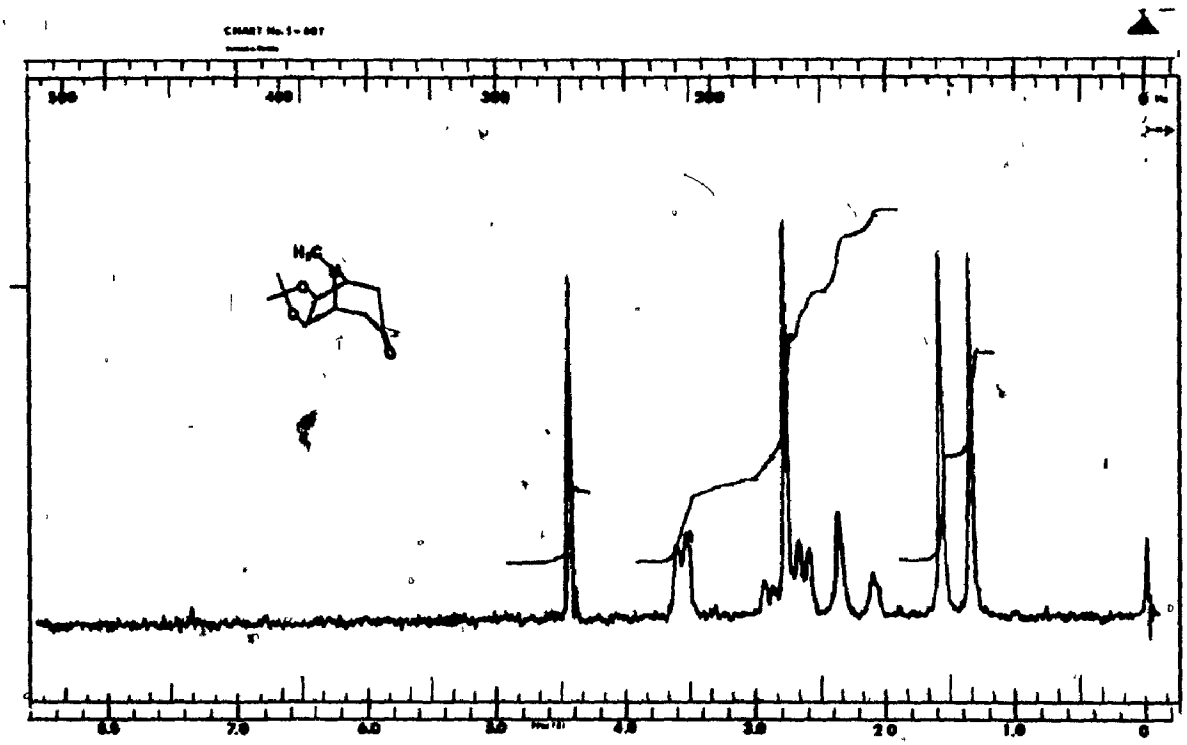


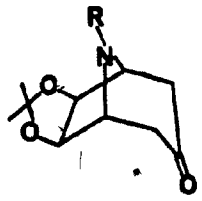
Figure 3. P.m.r. spectrum of teloidinone acetonide (128) in carbon tetrachloride.

N-methyl group would have to be replaced by one that would be stable to acid, base and oxidation in order for the sequence we had in mind to succeed. A good choice seemed to be an N-carbalkoxy group, which was stable to the aforementioned conditions. For example, it was known that N-methyl tertiary amines could be converted to N-carbethoxy urethanes (i.e. carbamates) with ethyl chloroformate[145,146,147,148], and it had been reported that such groups were reducible by lithium aluminum hydride to the original amines[145], or were converted to the free secondary amines under strong alkaline[147,148] or milder acid[146a] conditions. Several benzyl[145], phenyl[145,147,148] and 2,2,2-trichloroethyl[149] carbamates have also been reported. These can be cleaved under milder, more selective conditions.

Since we did not want to place too bulky a group on the nitrogen bridge for our initial studies, it was decided that the smaller members of the alkyl chloroformate family would be used. When teloidinone acetonide *129* was reacted in toluene with a twentyfold excess of ethyl chloroformate in a modified von Braun demethylation, an 85% yield of the crystalline ethyl urethane *130* was obtained. Its infrared spectrum clearly indicated the presence of a new urethane or carbamate carboxyl absorption at $\nu_{C=O}$ 1705 cm^{-1}, very close to the ketone peak at 1720 cm^{-1}, and the N-methyl singlet in the p.m.r. spectrum of *129* was replaced by an ethyl quartet - triplet system at δ 4.15 and 1.27 p.p.m. respectively.

Although no reference was found in the literature

pertaining to the analogous reaction with methyl chloroformate, a similar reaction of the acetonide at 90° with this reagent produced a fair yield of methyl urethane *131*, plus an unexpected side product which began to precipitate out of solution almost immediately upon warming the reagents. When the reaction was carried out at a lower temperature (60°), both conversions were more sluggish, but a higher yield of urethane was produced. Under optimum conditions, a 75% yield of *131* and a 15-20% yield of the precipitate were obtained in a reasonable time period.



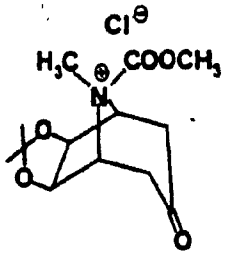
(*130*) R = COOEt, m.p. 77-78°
(*131*) R = COOMe, m.p. 123-123.5°

The p.m.r. spectrum of the N-carbomethoxy derivative *131* displayed a three proton singlet at 3.79 p.p.m. ($NCOOCH_3$), a broad two proton multiplet at 4.52 for the bridgehead protons, and a singlet at 4.47 for the C-6 and C-7 α protons. Also, the four protons next to the carbonyl now appeared as a single broad multiplet centered at 2.56 p.p.m., very similar to the spectrum of the ethyl carbamate *130*. The structure of this multiplet differed from that of the N-methyl amine *129* because electron

density from the nitrogen is delocalized onto the urethane carbonyl. Hence the electron density of the non-bonded lone pair on the nitrogen of amine *129* is no longer present to cause a large difference in chemical shifts between the α and β protons at C-2 and C-4. With this deshielding effect gone, the four protons appear as a single broad multiplet.

Both demethylations are quite different from the reaction of ethyl chloroformate with tropinone *132*, which was reported to produce the N-carbethoxy derivative smoothly in 95% yield[148]. Obviously steric hindrance from the isopropylidene group caused the reactions in the present work to proceed much more slowly, probably by interfering considerably with the formation of the normal intermediate salt for such demethylations (e.g. *133*).

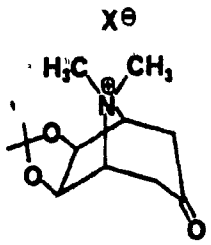
(*132*)



(*133*)

The nature of the side product produced concomitantly with *131* was difficult to establish. Its solubility in water indicated a salt structure, and a test with silver nitrate produced an almost equimolar weight of silver chloride. This same

test was just as positive once the salt had been recrystallized from methanol - ether. Its p.m.r. spectrum (fig. 4) in D_2O was extremely similar to that of teloidinone acetonide (fig. 3), except for the presence of an extra three proton singlet. This led us to suspect initially that it might be the chloride *133*. However, its infrared spectrum clearly showed the presence of a single, sharp carbonyl band at 1730 cm^{-1}, most reasonably assigned to a ketone. Hence we suspected that this compound might be the methochloride *134*. Micro-analytical data confirmed this suspicion, but the mass spectrum of *134* did not display the expected molecular ion at m/e 261.5. Instead, a molecular ion at m/e 225, resulting from a Hoffman elimination, appeared.



(*134*) X = Cl
(*135*) X = I

Proof for this structure was obtained when *134* was demethylated back to teloidinone acetonide *129* in very poor yield with 1,5-diazabicyclo (2.2.2)octane in dimethylformamide[151]. Also, the methiodide *135* was prepared from teloidinone acetonide and methyl iodide with difficulty; its i.r. and p.m.r. spectra were similar to that of the methochloride *134*, and its mass spectrum was identical to that of *134*. Further proof was later produced

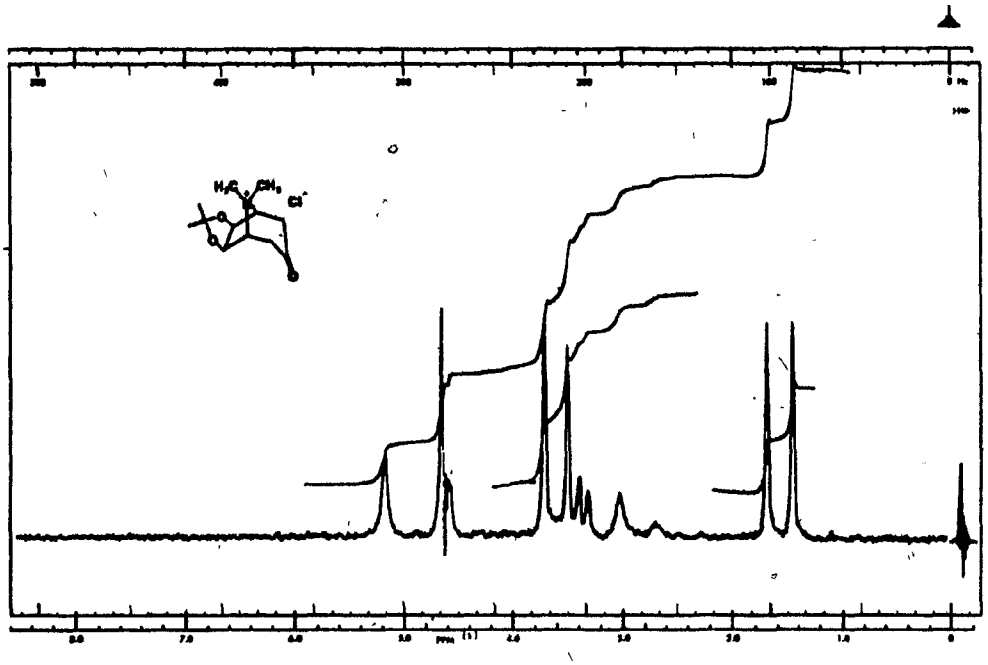


Figure 4. P.m.r. spectrum of methochloride *184* in D_2O (external TMS). Addition of one drop of trifluoroacetic acid shifts solvent absorption (at 4.7 p.p.m.) downfield, revealing a broad doublet at 4.65 p.p.m.

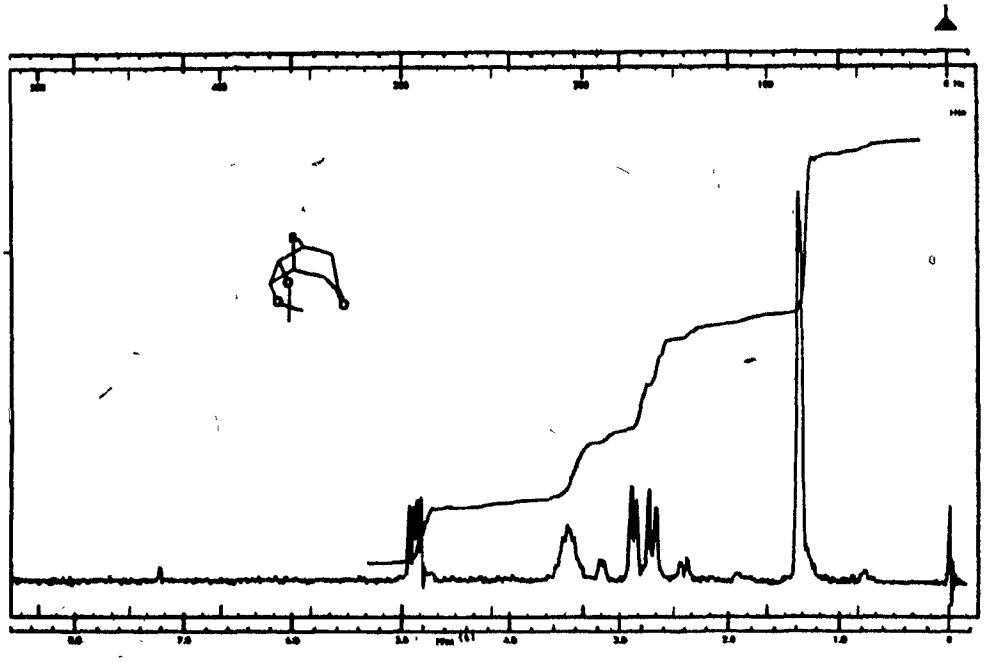
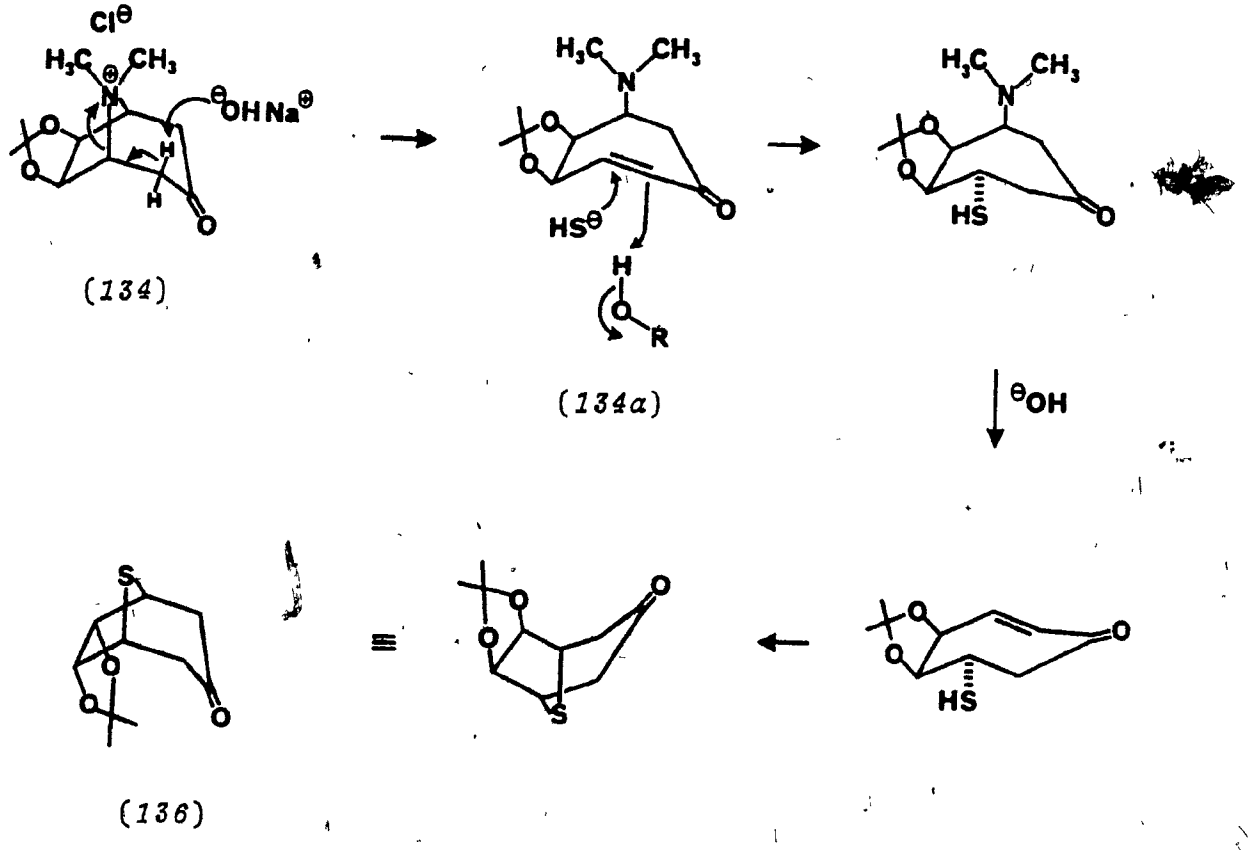


Figure 5. P.m.r. spectrum of 5-thiateloidinone acetonide *186* in deuteriochloroform.

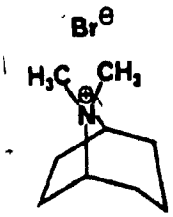
when *134* was reacted with excess sodium sulphide ($Na_2S.9H_2O$) in ethanol - water to form the interesting 6α,7α-dihydroxy-O-isopropylidene-8-thiatropan-3-one *136*, a nicely crystalline compound, in over 50% yield. The reversal in stereochemistry at C-6 and C-7 is easily explainable if one assumes that a double displacement of the nitrogen bridge occurs, as shown below. Sodium hydroxide is produced in the aqueous medium, and probably initiates the sequence of reactions by a β-elimination leading to the α,β-unsaturated ketone *134a* [141]. This is followed by attack by HS^-, the presumed active nucleophile, from the less hindered α side of the bicyclic system. Further interaction as displayed below converted the salt to *136*.



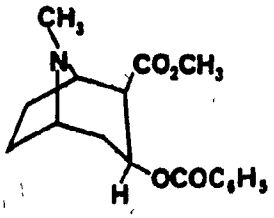
(*134*) (*134a*) (*136*)

The structure of *136* was confirmed by its p.m.r. spectrum (fig. 5), which displayed several important differences from the *exo*-acetonides examined thus far. To begin with, the two methyl peaks of the isopropylidene group now had almost the same chemical shift, in marked contrast to previous cases (viz. figs. 3 and 4). Also, the tertiary protons at C-6 and C-7 now appeared as a quartet, probably due to coupling with the adjacent bridgehead protons plus longer range coupling with the opposite bridgehead protons, i.e. $J_{H\text{-}C\text{-}C\text{-}C\text{-}H} \simeq 2.5$ Hz and $J_{H\text{-}C\text{-}C\text{-}H} \simeq$ 4 Hz. Finally, the four protons closest to the carbonyl appeared as a symmetric octet (2.4-3.2 p.p.m.), since *both* the α and β protons at C-2 and C-4 could couple with the bridgehead protons, as well as experience geminal coupling.

It is not clear by what mechanism methochloride *134* was formed. Although analogous methobromides have been isolated from von Braun demethylations using cyanogen bromide[152], it was concluded that they arose simply by interaction of starting material with the methyl bromide produced as a byproduct. For example, under the conditions used to demethylate tropane[153], nearly half of it was converted to the quarternary salt *137*. With cocaine (*138*), demethylation was the predominant reaction, and only some cocaine methobromide was formed[154]. At first glance, this does not seem to be the case in the present work, because no methochloride was isolated in the reaction of teloidinone acetonide with ethyl chloroformate, even though methyl chloride



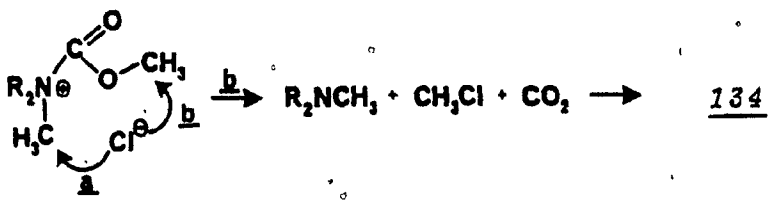
(137)



(138)

must also have been formed for the reaction to proceed to completion. There seems to be no valid reason why the starting material should react with methyl chloride in one case but not in another experimentally similar one.

The most plausible explanation probably involves the alternate reaction b shown below wherein the chloride anion attacks the urethane methyl of the intermediate *133* in an S_n^2 displacement[145]. Carbon dioxide and methyl chloride are formed concomitantly in close proximity to the regenerated starting material, hence the two latter compounds might interact at this



(133)

stage. When ethyl chloroformate is used, however, this competitive reaction is suppressed, and the chloride anion attacks the N-methyl group of the intermediate *133* exclusively. Now, when we attempted to produce the methochloride *134* by reacting teloidinone acetonide *129* with methyl chloride, a very slow reaction occurred in warm benzene. It is clearly a slow process. Accordingly, there is a strong possibility that path b may actually be much faster than path a, but because of the slow interaction between starting material and methyl chloride, a relatively minor amount of chloride *134* was isolated. Thus, while there is virtually no chance of starting material reacting with the small amount of methyl chloride produced in one case, there is ample opportunity for it to form the salt *134* in the other case, because starting material and methyl chloride may be continuously generated at a rate faster than urethane formation.

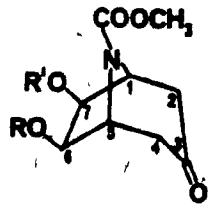
The temperature dependence of the product composition may now be explained. As the temperature is raised, either the rate of reaction between starting material and methyl chloride is enhanced, or the rate of path b is increased at a greater rate than the competing path a. Hence a greater yield of side product is isolated at a higher reaction temperature.

Attempts to Form an α-Diketone

Reactions of symmetrical, cyclic ketones with selenium dioxide are known to afford fair yields of α-diketones only

when excess starting material is employed[155]. In our case, the attempted oxidation of N-carbomethoxyteloidinone acetonide (*131*) to an α-diketone with selenium dioxide[155] in dioxane - water led to an intractable mixture.

Another attempt to synthesize an α-diketone involved the formation of an α-hydroxy ketone and subsequent oxidation. The method of McKillop *et al*[156] for converting ketones to their α-hydroxy derivatives, involving the use of thallium trinitrate trihydrate ($Tl(NO_3)_3.3H_2O$) and nitric acid in acetic acid, was the mildest procedure. Thus the acid-labile isopropylidene group of N-carbomethoxyteloidinone acetonide (*131*) was converted to the diacetate before it was subjected to hydroxylation. However, some difficulty was encountered in this transformation. If an aqueous solution containing more than 60% trifluoroacetic acid was used for the deprotection at a reaction temperature above 70°, a substantial amount of a monotrifluoroacetyl derivative was formed together with the diol *139*. This was isolated as the 6β-acetoxy-7β-trifluoroacetoxy-N-carbomethoxyteloidinone (*141*) after normal acetylation with pyridine and acetic anhydride. The i.r. spectrum of *141* displayed a trifluoroacetyl absorption at $\nu_{C=O}$ 1800 cm^{-1}, an acetyl peak at 1760, and both the urethane and ketone carbonyl bands at 1720 cm^{-1}. Its p.m.r. spectrum showed a single acetate resonance at δ 2.07 p.p.m., and a quartet for the chemically different protons at C-6 and C-7. The crystalline diacetate *140* was isolated as the major product (60% yield) only when a more dilute acidic solution was used for the



(*131*) $RR' - C(CH_3)_2$

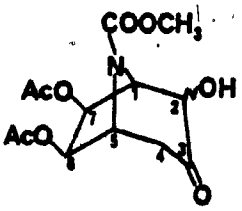
(*139*) $R = R' = H$

(*140*) $R = R' = COCH_3$
m.p. 156-159°

(*141*) $R = COCH_3$, $R' = COCF_3$

hydrolysis at a lower temperature. If we had required the diacetate *140* in higher yields or in larger amounts, dilute hydrochloric acid would have been the reagent of choice, but this was not necessary. The p.m.r. spectrum of *140* clearly showed a six proton acetate singlet at δ 2.03, and a singlet at 5.02 for the C-6 and C-7 protons.

The diacetate was converted to the powdery α-hydroxy ketone *142* in 40% yield with thallium trinitrate trihydrate[156]. This product displayed two distinct acetate absorptions at $\nu_{C=O}$ 1780 and 1760 cm^{-1} in its infrared spectrum (KBr disk), as well



(*142*) m.p. 160-161.5°

as two urethane peaks at 1720 and 1705, plus an α-hydroxy ketone carbonyl band at 1650. The latter is below usual ketonic absorptions due to internal hydrogen bonding. In solution, the urethane peaks coalesced to a single absorption at 1720 cm^{-1}. The sharp singlet for the N-carbomethoxy methyl group in the p.m.r. spectrum (fig. 6) clearly showed that only one of the two possible isomers at C-2 was isolated. Two chemically different acetate methyls were also displayed at 2.06 and 2.15 p.p.m., as well as a two proton multiplet at 2.70 for the C-4 hydrogens adjacent to the ketone. A hydroxyl proton absorption under the multiplets at about 5.4 was determined when a drop of trifluoroacetic acid shifted it downfield, and caused a change in the structure and integration of the multiplets (inset, fig. 6). The exact stereochemistry at C-2 could not be determined because its tertiary proton appeared in the midst of the multiplets. The broad doublet at 4.60 p.p.m. was due to the bridgehead proton at C-5, since the two bridgehead hydrogens in the diacetate *140* appeared as a broad multiplet at 4.5 p.p.m.

Attempted oxidation of the α-hydroxy ketone *142* to a diketone by means of the standard reagent for such transformations, cupric diacetate monohydrate in methanol and/or acetic acid[157], afforded mainly unreacted starting material even after prolonged treatment. Reaction of *142* with dimethylsulphoxide-acetic anhydride[158], a mixture very useful for oxidation of hindered alcohols, yielded mainly recovered starting material.

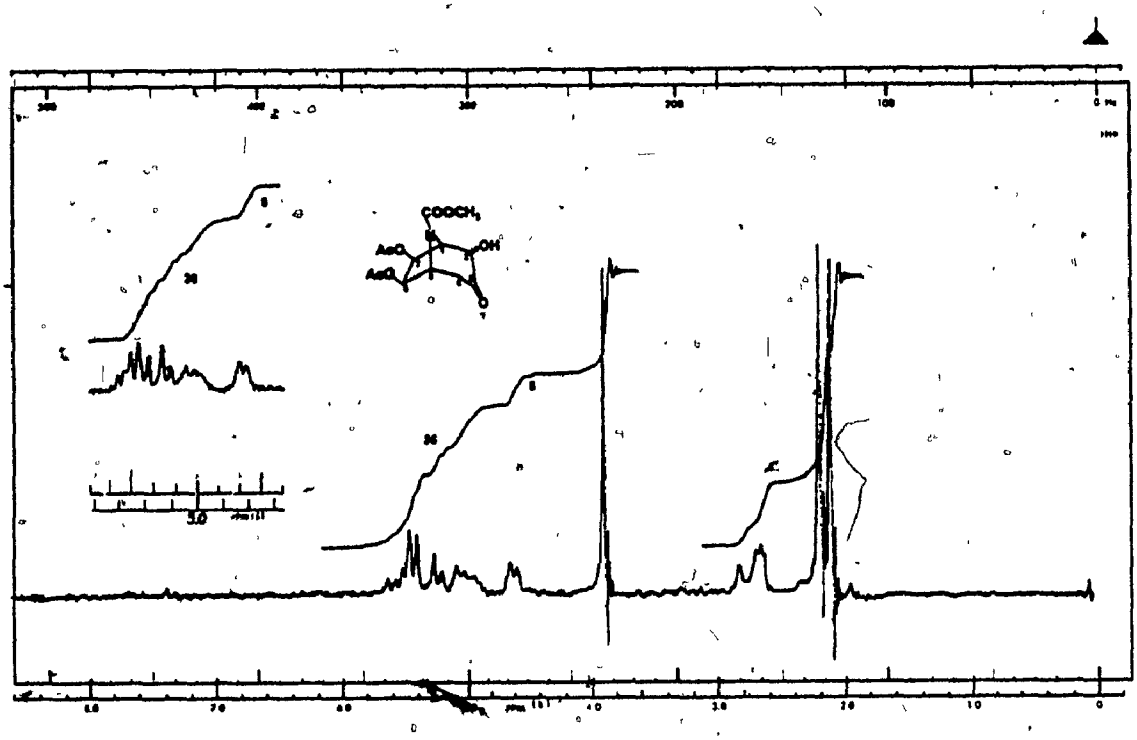
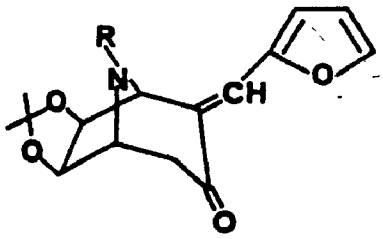


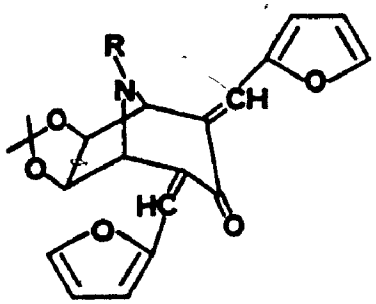
Figure 6. P.m.r. spectrum of α-hydroxy ketone *1d2* in deuteriochloroform. Inset shows effect of addition of one drop of trifluoroacetic acid.

A similar attempt with pyridinium chlorochromate[159] in methylene chloride failed. Even exposure to ruthenium dioxide - potassium periodate in a carbon tetrachloride - water two phase system[160] did not effect a clean oxidation. It is believed that the hydroxyl function is exceptionally unreactive due to steric screening caused by the N-carbomethoxy group, regardless of whether the hydroxyl group at C-2 is α or β. In one case the carbomethoxy group could prevent the formation of the alcoholate ester intermediate, while in the other, it could prevent abstraction of the tertiary proton at C-2. This interference adds to the normal unreactivity of a cyclic α-hydroxy ketone towards oxidation.

A direct formation of an olefinic bond adjacent to the carbonyl group at C-3 was considered next. We intended to synthesize the monofurfuryl derivatives *143* in the hope that oxidative cleavage would yield an α-diketone in a minimum of steps. Unfortunately, reaction of the ketones in ethanol with one equivalent of furfuraldehyde[161] and aqueous sodium hydroxide at 0-5° afforded a 45-50% yield of the yellow, highly crystalline 2,4-disubstituted derivatives *144* and *145*. It appeared that the monofurfuryl intermediates reacted even faster than the original ketones due to conjugation effects, since no trace of the monosubstituted ketones was found. Several modifications in temperature and amounts of reagents used did not change the nature of the products. When a twofold excess of furfuraldehyde was used, the recrystallized di-substituted derivative *145* was



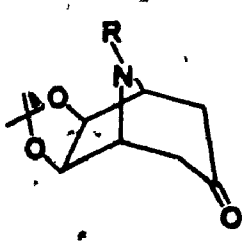
(*143*)



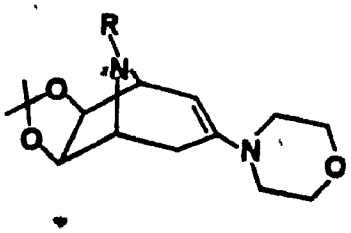
(*144*) R = CH_3
(*145*) R = COOMe

recovered in over 80% yield.

In our last attempt to convert the symmetrical ketones *129*, *130* and *131* to unsymmetrical α-diketones, the morpholine enamines of these ketones were prepared with the aid of titanium tetrachloride [162]. Of the enamines, *146* was a semi-crystalline compound obtained in nearly quantitative yield before recrystallization, while *147* and *148* were oils isolated in 75 and 95% yield respectively. All three proved to be quite unstable. Indeed, when 100 mg of *146* was recrystallized from reagent petroleum ether (60-80°), almost 40% of the enamine was reconverted to starting material.

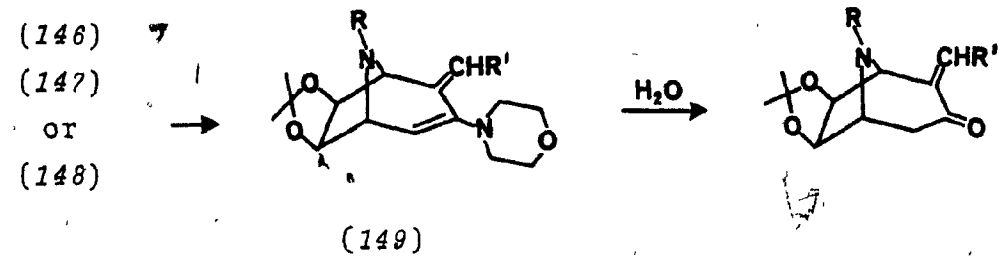


(*129*) R = CH_3
(*130*) R = COOMe
(*131*) R = COOEt



(*146*) R = CH_3 m.p. 100-101°
(*147*) R = COOMe
(*148*) R = COOEt

We hoped to convert the enamines to unsaturated enamines of type *149* by the method of Birkofer *et al*[163]. The latter could then be hydrolyzed easily to α,β-unsaturated ketones[163]. However, when the enamines were reacted with isobutyraldehyde under the same conditions used by Birkofer *et al*, a mixture of products was always obtained.



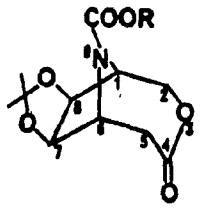
(149)

c. Synthesis of Key Intermediates via Lactonization

Since all our attempts to form an α-diketone failed, we turned our attention to a more straightforward method of converting the symmetrical materials to unsymmetrical, synthetically useful products: lactonization of the C-3 ketone. We hoped to convert the two urethanes *130* and *131* to their respective lactones, which would be excellent starting points for the final modifications to azacyclic ribofuranosyl analogues. Baeyer-Villiger oxidation of the N-carbomethoxy derivative *131* with m-chloroper-

benzoic acid and a small amount of 2,4,6-tri(t-butyl)phenol (a radical inhibitor) in 1,2-dichloroethane[164] was optimized after several runs by conveniently following the reaction by gas chromatography. A Hewlett-Packard 700 Laboratory Chromatograph was employed, using standard SE-30 Ultraphase and Chromosorb W support. The reaction thus monitored showed the complete disappearance of starting ketone after 20-22 hours when it was carried out at 60° with a 2.5-fold excess of peracid and 20 mg of inhibitor. The latter is essential when operating above room temperature for extended periods, because it prevents the thermal decomposition of the peracid[164].

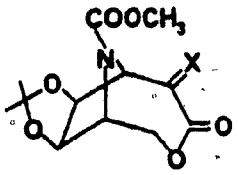
A 60% yield of the crystalline D,L-lactone *150* was isolated. Its infrared spectrum clearly showed the presence of a strong lactone peak at $\nu_{C=O}$ 1755 cm^{-1}, and the p.m.r. spectrum displayed a clean quartet for the C-7 and C-8 protons at 4.7 p.p.m.



(*150*) R = CH_3; m.p. 117-8°
(*151*) R = CH_2CH_3

A similarly monitored Baeyer-Villiger oxidation of the ethyl carbamate *130* proceeded much more slowly. Even with a greater excess of peracid and a higher reaction temperature, the conversion to an oily product mixture which consisted mainly of lactone *151* by p.m.r. and mass spectroscopy was not as good as with methyl urethane *131*. The only explanation for this phenomenon must be that the longer, bulkier ethyl chain of the N-carbethoxy compound *130* stretches out over its 4-piperidone ring[141] and covers the ketone at C-3, thus blocking the approach of the peracid. This finding precludes the use of the more easily removable benzyl, phenyl or 2,2,2-trichloroethyl groups.

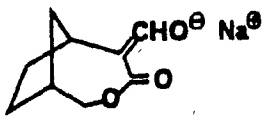
It was known that lithium diisopropylamide converted esters into their enolate salts at low temperature[165]. Carboxylation of the α-anions of esters with carbon dioxide had produced malonic acids[166]. Moreover, Grieco and Hiroi[167] had converted lactones to their enolates with lithium diisopropylamide, and quenching with carbon dioxide also afforded malonic acid derivatives. The latter were then decarboxylated in diethylamine-aqueous formaldehyde to form α-methylene lactones in good yields[167]. Since α-methylene lactones can in principle be oxidized to their α-keto derivatives, we applied the method of Grieco and Hiroi to lactone *150*, in the hope of producing the α-methylene lactone *150a*, from which α-keto lactone *152* would be prepared.



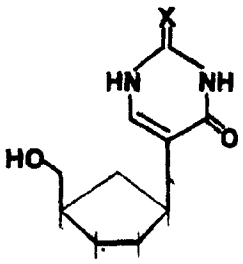
(150a) X = CH_2
(152) X = O

The lactone *150* was reacted with lithium diisopropylamine in tetrahydrofuran[168] at -78°, and the resulting α-anion was quenched with dry carbon dioxide. The crude malonic acid thus produced was treated with diethylamine - aqueous formaldehyde, followed by sodium acetate - acetic acid[167]. However, a mixture of products was obtained in every attempt, probably due to ring opening of the bicyclic system.

A similar attempt to functionalize the α-position of lactone *150* with sodium hydride and methyl formate[83] (i.e. formylation of the enolate) also led to an intractable mixture. A similar carbocyclic compound *66* had been obtained in good yield from its lactone by Playtis and Fissekis[83]. Condensation of the sodium salt with thiourea had produced the 2-thiouracil *67* in very poor yield, and the latter was converted quantitatively to the uracil *68*, a carbocyclic analogue of 2',3'-dideoxypseudouridine (Chapter 1). Other attempts to functionalize our lactone with sodium hydride and furfuraldehyde or isobutyraldehyde also failed.

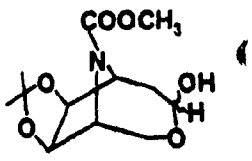


(66)

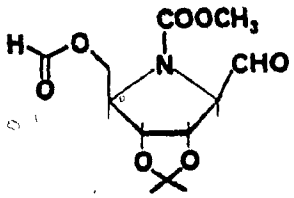


(67) X = S
(68) X = O

Another completely different approach, beginning with the lactone but leading to an interesting aldehyde, was tried. It was hoped that the lactone *150* could be reduced selectively to the hemiacetal *153* with diisobutylaluminum hydride (DIBAL). Elimination of water would lead to a vinyl ether, and ozonolytic ring opening followed by reductive work-up according to the procedure of Frehel and Deslongchamps[169], would readily afford the aldehyde-formate *154*.

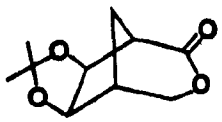


(153)



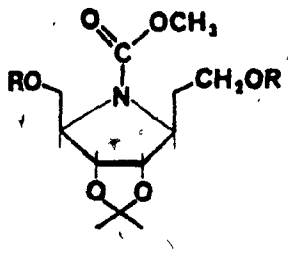
(154)

DIBAL was known to reduce lactones smoothly to the hemiacetal stage[170], and Faure[171] had used it for this purpose with a lactone (*155*) similar to ours. However, since DIBAL was also known to reduce urethanes to the N-methyl amines at room temperature[172], the temperature of our reaction could not be



(*155*)

raised above 5-10°. Thus, when the reaction was carried out with one equivalent of DIBAL in dry toluene under nitrogen at -10° for 2 hours, a mixture of products was recovered, of which the starting material was one component. Alterations of these experimental conditions did not produce significant amounts of hemiacetal. When a 2.5-fold excess of DIBAL was used at 5° for 3 hours, the major product was the completely reduced diol *156*, recovered as a clear, colorless oil in 30% yield. The structure of the reduction product was confirmed by conversion to its diacetate *157*. The i.r. spectrum of the diol displayed a strong alcoholic band peaking at 3470 cm^{-1} (ν_{O-H}), and a urethane carbonyl at $\nu_{C=O}$ 1700. Its p.m.r. spectrum contained a urethane methyl resonance at δ 3.68 p.p.m.,

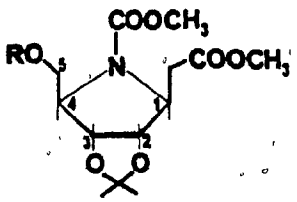


(*156*) R = H
(*157*) R = $COCH_3$

isopropylidene methyls at 1.26 and 1.41, and several broad multiplets. The mass spectrum clearly displayed peaks for the molecular ion (m/e 275) and for losses of methyl (260), hydroxyl (258) and methoxyl (244) radicals. The p.m.r. spectrum of the diacetate contained two distinct acetyl methyls at δ 2.02 and 2.05 p.p.m., and its mass spectrum showed peaks for loss of methyl (m/e 344), acetyl (300), CH_3COOCH_2 (286) and $CH_3COOCH_2CH_2$ (272) fragments.

At this time, it was decided to open the lactone ring of *150* and attempt to convert the resulting ester to intermediates which could be converted to azacyclic nucleoside analogues. The lactone was reacted at room temperature with 1.1 equivalents of sodium methoxide in methanol to produce the hydroxy methyl ester *158* in near quantitative yield. Attempts to cleave the bicyclic lactone under milder conditions, such as triethylamine in anhydrous methanol[171], led to complete recovery of the starting material. The alcoholic function of *158* was protected with tert-butyldimethylsilyl chloride[173],

yielding the oily silyl ether *159* in greater than 85% yield based on lactone *150*. The urethane moiety was completely unchanged, and no appreciable decomposition of the bicyclic structure occurred under the mild conditions employed. All spectra and analytical data supported the structure of *159*. Most notably, the lactone peak in the i.r. spectrum of *150* was replaced by



(*158*) R = H
(*159*) R = Si

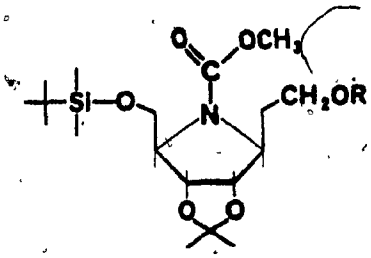
an ester absorption at $\nu_{C=O}$ 1740 or 1750 cm^{-1} in alcohol *158* or silyl ether *159* respectively, and a new methyl ester peak coincident with the urethane methyl resonance appeared in the p.m.r. spectrum. The silyl ether moiety displayed a six proton dimethylsilyl singlet at 0.14 p.p.m. and a nine proton tert-butylsilyl singlet at 0.96 p.p.m. In the mass spectrum of *159*, fragmentations characteristic of a tert-butyldimethylsilyl ether were noted. Besides peaks representing a loss of methyl (m/e 402) and methoxide (m/e 386) radicals, strong peaks for the loss of the tert-butyl (m/e 360, $M^+ - 57$), tert-butyldimethylsilyl (m/e 302, $M^+ - 115$) and $Me_3C(CH_3)_2SiOCH_2$ (m/e 272, $M^+ - 145$) fragments were observed. The three latter fragmentations are

found in all the mass spectra of such silyl ethers.

As will be seen shortly, this intermediate possessed the stability necessary for conversion to a more ractive intermediate, upon which a heterocyclic ring could be formed *via* a cycloaddition.

d. Attempts to form a Terminal Olefin

The first sequence involved the reduction of the methyl ester to an alcohol, conversion of the hydroxyl function to a good leaving group, and then formation of an olefin by elimination. The latter compound might be an extremely useful dipolarophile for the production of such heterocyclic bases as isoxazolines, pyrazolines or pyrazoles [171]. Alternately, it could be cleaved oxidatively to an aldehyde, thus producing the protected open form of the azacyclic analogue of 2,5-anhydroallose. The silyl ester *159* was accordingly selectively reduced over a period of two days with excess diborane in THF, and the alcohol *160* was isolated in nearly 70% yield. This was converted quantitatively to the mesylate *161* with methanesulphonyl chloride and triethylamine in methylene chloride. Besides the urethane methyl singlet at δ 3.62 p.p.m., the p.m.r. spectrum of *161* displayed a methanesulphonyl methyl absorption at 2.93 and a broad



(*160*) R = H

(*161*) R = SO_2CH_3

multiplet representing the saturated methylene group (CH_2-CH_2-OMs) at 1.97 p.p.m. Characteristic mesylate absorptions at 1365 and 1180 cm^{-1} were present in its i.r. spectrum, as well as a urethane carbonyl band at 1710 cm^{-1}.

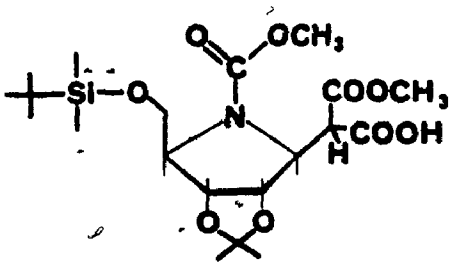
Unfortunately, all attempts to eliminate methanesulphonic acid from *161* failed. When it was treated with excess pyridine or triethylamine, no reaction occurred, even at elevated temperatures. Heating with 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) or DBU[174] for prolonged periods also yielded no olefin.

Since dehydrotosylations have occasionally been reported to proceed more smoothly and in higher yield than the corresponding dehydromesylations[175,176], and we hoped to obtain a crystalline derivative of alcohol *160*, several attempts were made to tosylate the hydroxyl group. However, little reaction occurred, even at elevated temperatures. Considerable steric interference from the large tert-butyldimethylsilyl ether at the 5-position may prevent the desired conversion. At this time our concurrent

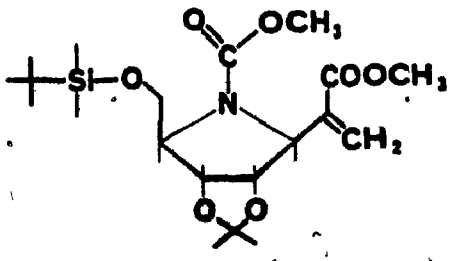
investigation towards the synthesis of an α-ketoester produced a breakthrough, so the present approach was abandoned. However, it is felt that elimination of methanesulphonic acid from *161* even with the strongest bases, such as potassium tert-butoxide (KO^tBu), would not proceed in high yield. A study on the reaction of primary and secondary aryl and alkyl sulphonates with potassium tert-butoxide in DMSO[177] clearly showed that sulphonate esters of normal primary alcohols or primary alcohols containing α-alkyl substituents gave 20-30% alkenes and 30-70% t-butyl ethers of the alcohols; under identical conditions, the alkyl benzenesulphonates of cyclohexanol and cyclopentanol were converted to the corresponding alkenes in about 80% yield. Snyder[178] noted the same difference between cyclohexyl benzenesulphonate and n-octyl benzenesulphonate. These facts, plus the unreactivity of mesylate *161* towards DBN and DBU, made this general approach unsatisfactory.

e. Synthesis of Methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyldimethylsiloxymethyl-N-carbomethoxypyrrolydin-1β-yl)-malonate (*162*), acrylate (*163*) and glyoxylate (*164*)

Our other option was to convert ester *159* to an α-ketoester. Methyl ester *159* was reacted under a nitrogen atmosphere with one equivalent of lithium diisopropylamide in THF[168] at -78°. This was allowed to warm up to -30°, and anhydrous carbon dioxide was bubbled through the solution containing the enolate. The resulting malonic acid *162* was not isolated; the crude product was reacted directly with aqueous formaldehyde and diethylamine, followed by further heating with sodium acetate and glacial acetic acid. The α-methylene methyl ester *163* was isolated by silica gel chromatography as a clear, colorless oil in over 80% yield based on ester *159*. The p.m.r. spectrum of



(*162*)

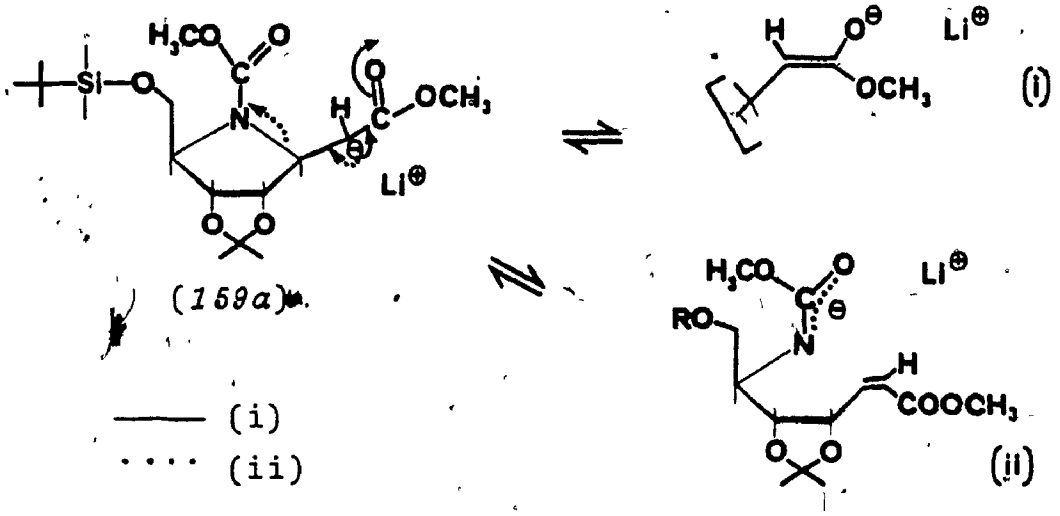


(*163*)

the product displayed two well separated olefinic multiplets at δ 6.10 and 5.70 p.p.m., two carbomethoxy methyls at 3.72 and 3.60 as well as gem-dimethyl singlets at 1.45 and 1.29 p.p.m. The i.r. spectrum of this compound exhibited a strong, broad carbonyl band between 1735 and 1720 cm^{-1}, and a weaker olefinic absorption at 1650. Its mass spectrum displayed easily discernible peaks for loss of methyl (m/e 414) and methoxide (m/e 398) radicals, as well as the strong peaks characteristic of the fragmentation of a tert-butyldimethylsilyl ether (m/e 372, $M^+ - Me_3C$, etc.).

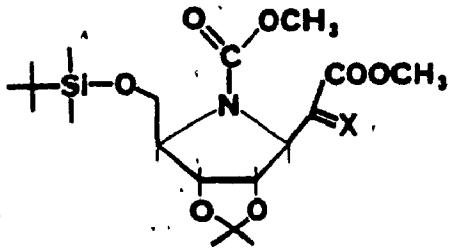
The conversion from saturated methyl ester to α-methylene ester *163* warrants close scrutiny, since the stereochemistry of the unsaturated ester will also be that of the α-keto-ester and thus of all nucleoside analogues derived from the latter by condensation. The important aspect of this sequence is that there is the possibility of destroying the 'anomeric'* purity of the C-1 position of the azaribofuranosyl ring. That is, the intermediate enolate lithium salt *159a* can exist not only in the common form *i*, but there is the possibility that ring opening to *ii* may occur. Consequent ring reclosure could produce a mixture of anomers or, indeed, only the reversed α anomer wherein the -CHCOOMe branch is *cis* to the isopropylidene group but *trans* to the bulky silyl ether. The fact that the solution containing the enolate was never warmed above -30° minimizes

* While it is not strictly correct to denote the C-1 position here as anomeric, it is convenient since it refers to the anomeric position of normal nucleosides.



the possibility of this occurring. Furthermore, in the p.m.r. spectrum of the α-methylene ester *163*, the difference in chemical shifts between the gem-dimethyl singlets was 0.16 p.p.m. (1.45 - 1.29), identical to the difference noted for the saturated ester *159* (1.46 - 1.30). We expect this difference to be nearly zero for the α-anomer of *163* (viz. the spectrum of the thio compound *136* on p. 61a). Since the stereochemistry of ester *159* is known, because it was derived by ring opening of a saturated, bicyclic lactone under mild conditions, the desired β-configuration at C-1 is probably correct. The analysis of the p.m.r. spectrum of the protected azacyclic showdomycin analogue (Chapter 4) will confirm this conclusion.

Ozonolysis of the methylene linkage of *163* at -78° in dry ethyl acetate, followed by reductive work-up with dimethyl sulphide[119], afforded the crude α-ketoester *164* (methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyldimethylsiloxymethyl-N-carcomethoxypyrrolidin-1β-yl)-glyoxylate). Both the i.r. and p.m.r. spectra showed the complete disappearance of the terminal alkene structure. However, two pairs of gem-dimethyl singlets were noted in the p.m.r. spectrum in an approximate 2:1 ratio, indicating



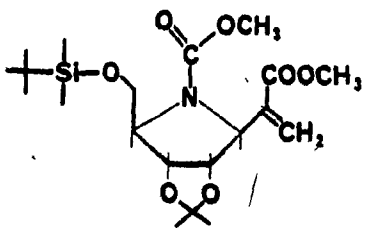
(*163*) X = CH_2
(*164*) X = O

that the desired product constituted, at best, no more than two-thirds of the total mixture. Unfortunately, *164* could not be purified by conventional methods: it would not crystallize out of the mixture of products, and it proved to be unstable towards chromatographic separations, like several other very closely related ribofuranosyl α-ketoesters[45,179]. The quality of the crude product was not improved when other solvents were used for the ozonolysis. When a small amount of starting material was ozonized in dry methylene chloride, virtually identical spectra were obtained, whereas when dry methanol was utilized, broader peaks in the i.r. and p.m.r. spectra characterized the mixture. Thus the crude product obtained with ethyl acetate as solvent had to be used directly in the next step.

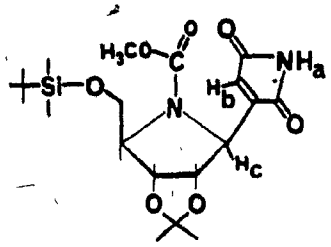
Chapter 4

Synthesis of an Azacyclic Analogue of Showdomycin, 2-(2'α,3'α-Dihydroxy-4'β-hydroxymethyl-N-carbomethoxypyrrolidin-1'β-yl) maleimide

The crude α-ketoester mixture obtained by ozonolysis and reduction of olefinic ester *163* was condensed directly with carbamoylmethylenetriphenylphosphorane[45] in dry chloroform at room temperature. The crystalline azacyclic showdomycin analogue *165* was isolated by preparative chromatography on silica gel plates in 40% yield based on *163*. Its structure was assigned, based on the following data: its i.r. spectrum (fig. 7), which clearly displayed maleimide-type carbonyl absorptions at ν 1787, 1738, 1722, 1655 cm^{-1} (C=O, C=C) extremely similar to those of



(*163*)



(*165*) m.p. 88-89°

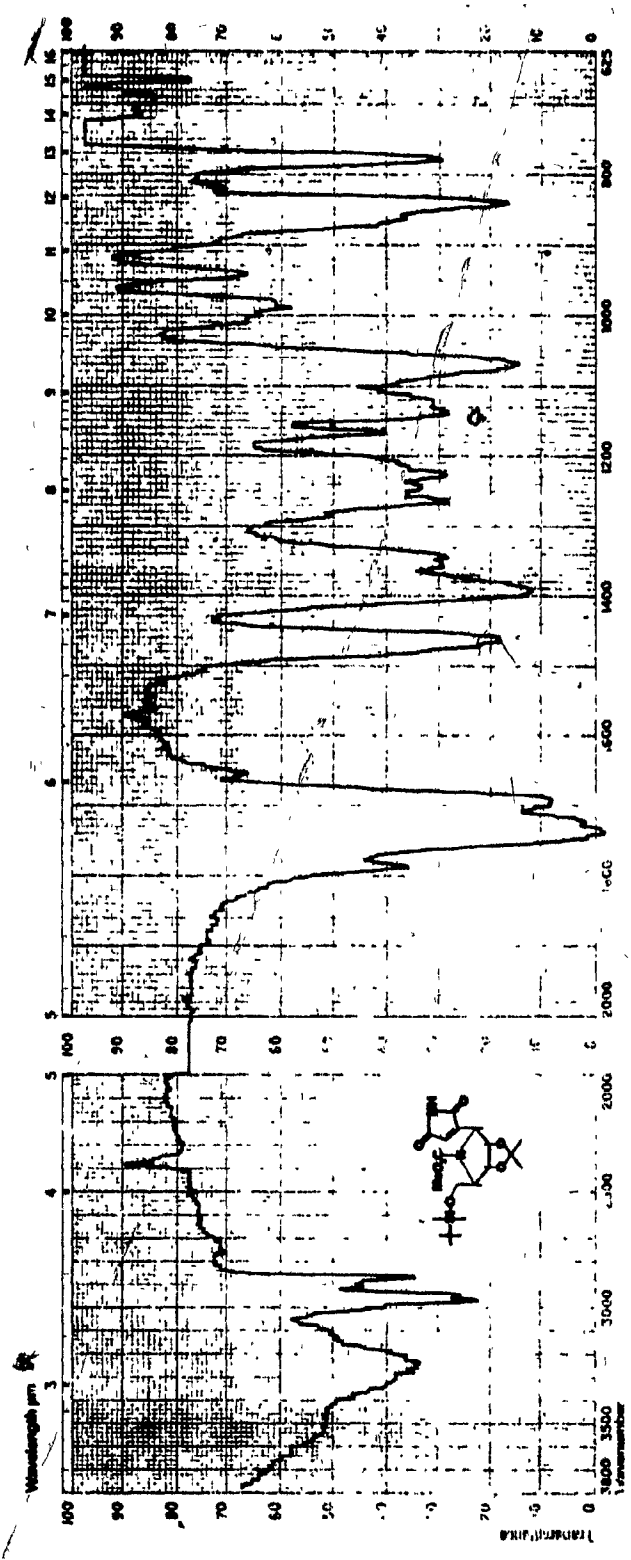


Figure 7. Infrared spectrum (KBr pellet) of the blocked azacyclic analogue *144* of showdomycin.

citraconimide (3-methyl maleimide)[180] and of showdomycin itself (1775, 1725, 1705, 1645 cm^{-1})[180]. The only difference was the presence of a carbamate carbonyl peak at ~1695 cm^{-1}. The maleimide N-H was further identified as a broad band at 3250 cm^{-1} (water in the KBr pellet caused broadening). Its ultraviolet spectrum in absolute ethanol displayed a maximum absorption at 221.3 nm (ε 18000, log ε 4.25) and a small inflection at about 275 nm (ε 1000, log ε 3.0) almost identical to that of showdomycin itself, which showed a λ_{max} at 222 nm (log ε 4.1) and a shoulder at about 285 nm (log ε 2.8) in 95% ethanol[180]. Citraconimide displayed these absorptions at 220 (log ε 3.84) and 275 nm (log ε 2.17). Microanalytical data confirmed the empirical formula, and the mass spectrum clearly showed a peak at m/e 425 ($M^+ - CH_3$) and typical silyl ether fragmentations at m/e 383 ($M^+ - Me_3C$) and 325 ($M^+ - Me_3C(CH_3)_2Si$). Finally, a thorough examination of the p.m.r. spectrum in deuteriochloroform (fig. 8) confirmed the stereochemical assignments. A broad, exchangeable (D_2O) one proton multiplet at δ 8.06 p.p.m. was assigned to the acidic imide N-$\underline{H}_a$ proton, and a triplet ($J \simeq 2$ Hz) at 6.25 represented the olefinic proton $\underline{H}_b$ which was coupled to both the imide proton and the tertiary proton $\underline{H}_c$. Triacetyl showdomycin displayed similar absorptions at 8.0 and 6.6 p.p.m. ($J \simeq 1.5$ Hz) in deuteriochloroform[180]. Our vinyl proton absorption collapsed to a sharp doublet upon addition of heavy water or upon irradiation at δ 4.90. The latter indicated that the

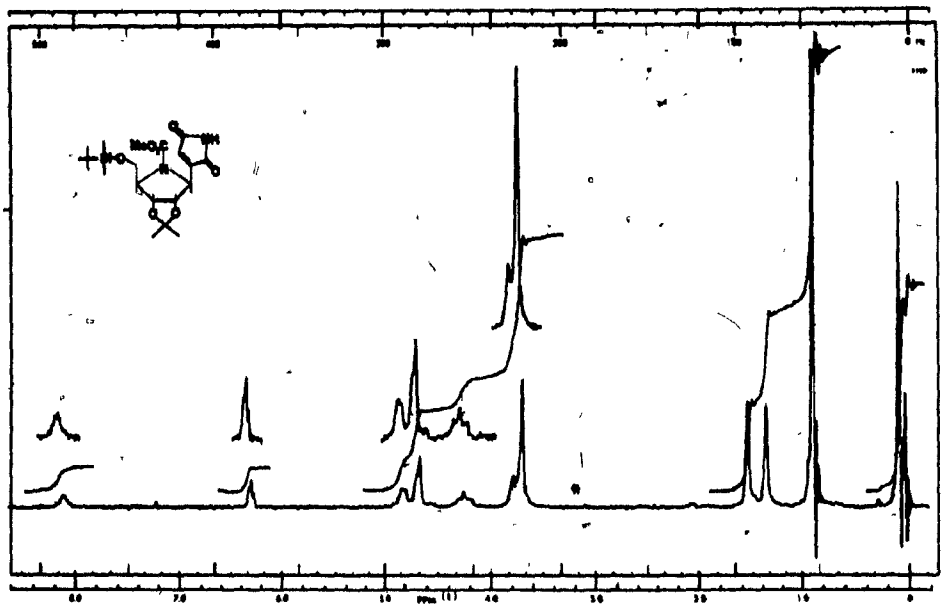


Figure 8. P.m.r. spectrum of the blocked azacyclic analogue *166* of showdomycin in deuteriochloroform.

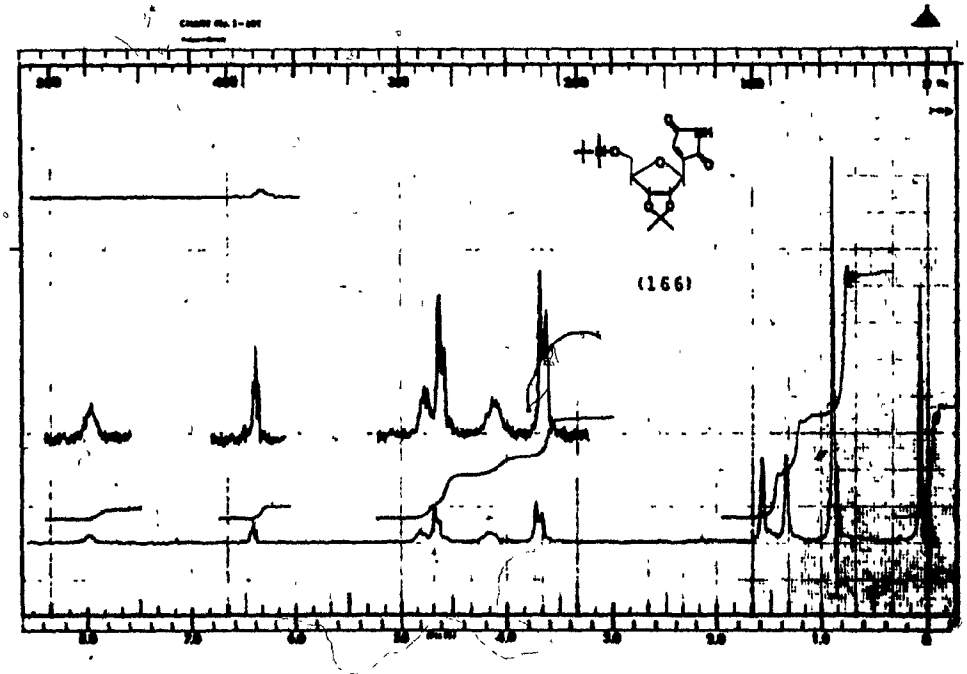


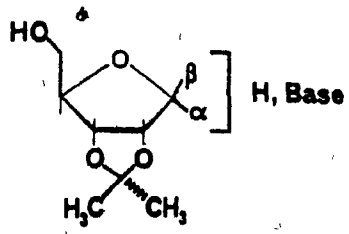
Figure 9. P.m.r. spectrum of blocked showdomycin (*166*) in deuteriochloroform. Top scan is 100 Hz offset.

multiplet centered at δ 4.90 was due to $\underline{H}_c$. However, when the triplet due to $\underline{H}_b$ was irradiated, the multiplet due to $\underline{H}_c$ did not collapse to a doublet as expected, probably due to the fact that it appears very close to other peaks and hence may mask absorption due to another proton.

A comparison of our spectrum with that of similarly protected showdomycin *166* (fig. 9), prepared independently in our laboratory[181], shows that the two spectra are virtually superimposable, with the sole exception of the extra N-carbomethoxy methyl resonance in fig. 8. The three proton multiplets between δ 4.5 and 4.9 p.p.m. in either case represent the 1'α,2'β and 3'β hydrogens, and the broad multiplet centered at about 4.2 is due to the 4'α proton. The two proton multiplets at about 3.7 p.p.m. are caused by the two C-5' protons ($C\underline{H}_2$-O-Si). The three proton singlet at δ 3.66 p.p.m. in fig. 8 is, of course, the urethane methyl absorption ($R_2NCOOC\underline{H}_3$). The two silyl ether singlets appear at exactly the same position in both spectra (0.9 and 0.07 p.p.m.), and the positions of the isopropylidene methyls is only slightly different: δ 1.52 and 1.33 p.p.m. in fig. 8 vs. δ 1.58 and 1.36 in fig. 9.

The remarkable similarity between the two spectra indicates that substitution of a protected nitrogen for the oxygen atom of the ribofuranosyl ring causes very little distortion of the ring. Furthermore, the carbomethoxy group does not seem to interact substantially with the heterocyclic base.

Confirmation of the 'anomeric' configuration of our azacyclic D,L-ribofuranoside was also obtained from the p.m.r. spectrum. Imbach *et al*[182] have recently studied the p.m.r. spectra of many α and β-D-ribofuranosides whose alcoholic functions at the 2' and 3' positions were protected with an isopropylidene group. They reported that in a total of fifty-one cases the difference Δδ between the chemical shifts corresponding to the two methyl groups of this 2,2-dimethyl dioxolane system fell into the following limits: α anomers: $\Delta\delta \leq 0.10$ p.p.m. (average value: 0.03); β anomers: $\Delta\delta \geq 0.18$ p.p.m. (average value: 0.20)..

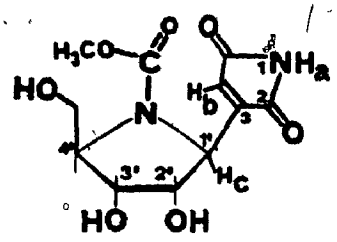


It was concluded[182] that, since the isopropylidene group rigidly maintains the conformation of the ribofuranosyl ring, the diamagnetic anisotropy of the base should influence the difference in chemical shift of the methyl groups. In the case of the β anomer the base should not influence the isopropylidene group much; however, in the α case, the base is close

to the dioxolane ring and hence should influence one of the methyl groups more than the other. Thus a decrease is noted for $\Delta\delta$. This hypothesis is in accord with the fact that isopropylidene methyl absorptions appear at higher field for α anomers than for β anomers[182].

Thus, if we disregard the relatively minor stereochemical distortion imposed on the ribofuranosyl ring by substituting a nitrogen atom for the ring oxygen atom - a difference we nevertheless hope may cause marked changes in biochemical or biological activity - the above data can be utilized here for a configurational assignment. The difference in chemical shifts is 0.22 p.p.m. for the protected showdomycin (fig. 9) and 0.18 p.p.m. for the azacyclic analogue (fig. 8); these values definitely indicate that both compounds are the β anomers.

The azacyclic analogue *165* of showdomycin was deblocked with 50% aqueous trifluoroacetic acid, affording the triol *167* in 75% yield after purification by p.l.c. However, the product



(*167*)

failed to crystallize from several mixtures of solvents, including benzene-acetone, a mixture which had been used successfully by Moffatt[45] with showdomycin itself. The u.v. spectrum of our product displayed a maximum absorption in ethanol at 223.7 nm, and a shoulder at 278 nm. The carbonyl absorption region of its i.r. spectrum was similar to that of the protected analogue *165*, and a broad hydroxyl absorption was present at about 3350 cm^{-1}. Its mass spectrum displayed peaks at m/e 268 ($M^+ - H_2O$), 255 ($M^+ - CH_3O$), 237 ($M^+ - CH_3O - H_2O$), 220 (M*, 255 → 237), 205, 117, and 59. The p.m.r. spectrum of *167* in acetone-d_6 is shown in fig. 10. Unfortunately, due to the proximity of the absorptions, no definite assignments could be made, except for : the imide proton H_a at about 9.5 p.p.m., the olefinic proton H_b at 6.6 p.p.m., and the urethane methyl absorption at 3.60 p.p.m.

Biological testing of this compound has not yet been undertaken, but since the p.m.r. spectrum of the blocked azacyclic analogue *165* was so similar to that of analogously blocked showdomycin *166*, it is possible that our analogue may display some activity, since there exists an intimate interconnection between molecular structure, conformation and the biological activities of nucleosides. However, our triol *167* should possess much less freedom of rotation about the C-3' - C-1' bond due to the presence of the N-carbomethoxy group. This increased restriction, relative to showdomycin, upon the range of the torsion angle may prevent the compound from assuming the most desir-

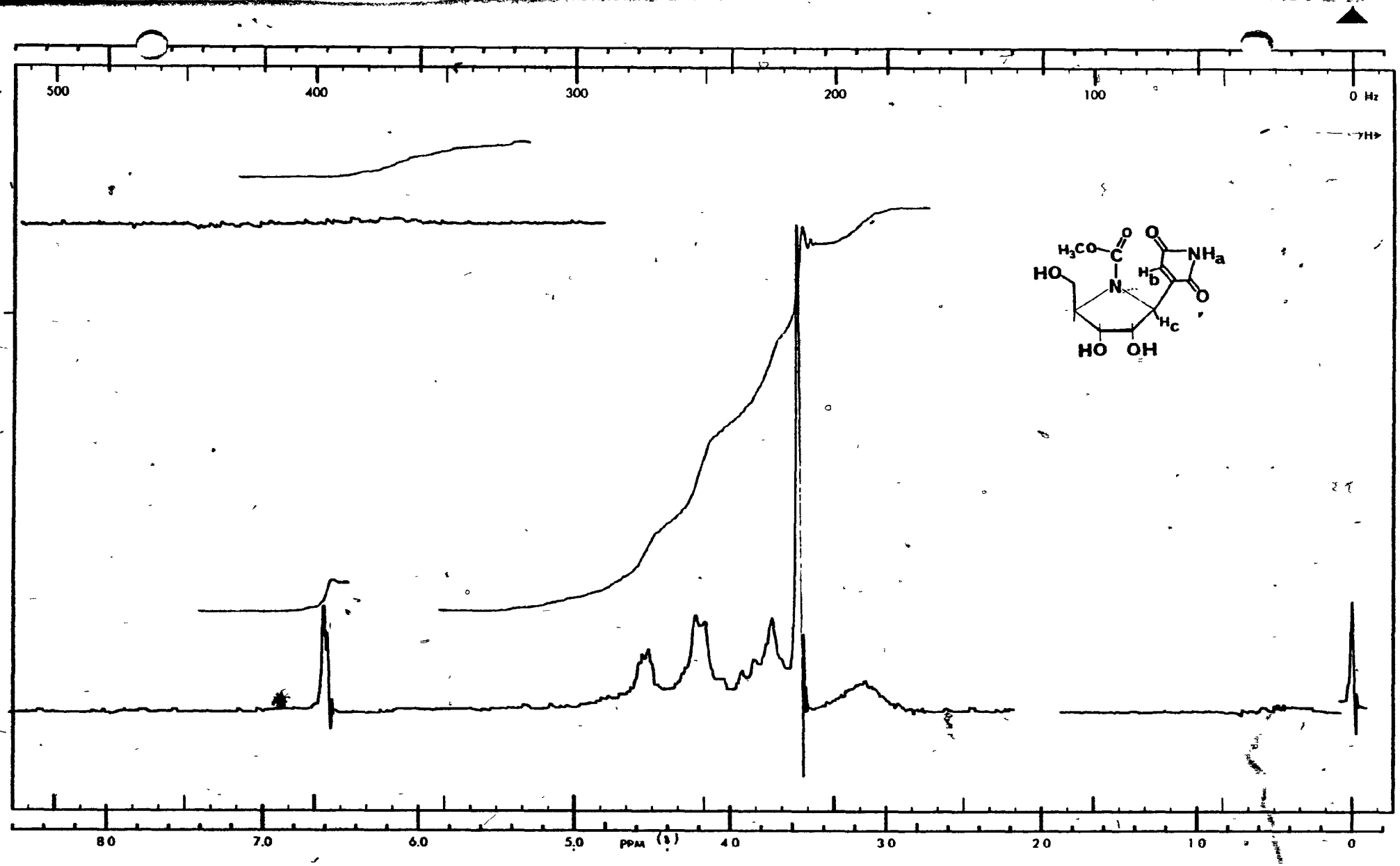
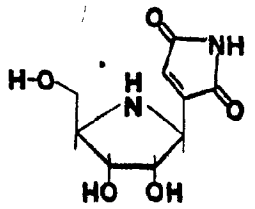


Figure 10. P.m.r. spectrum of deblocked azacyclic showdomycin *167* in acetone-d_6 (external TMS).

able conformation for biological interactions. Accordingly, it was decided to try to remove the urethane protecting group, and to compare the activity of *167* with that of the completely deblocked compound *168*.



(*168*)

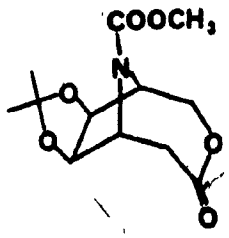
a. Attempted Removal of the N-Carbomethoxy Group

The usual aqueous hydrolytic conditions commonly employed for the removal of N-carbethoxy groups (p. 58) were much too vigorous to be utilized successfully for the clean removal of the N-carbomethoxy group from many of our products. We required a milder, more selective method of removing the urethane moiety and thus generating the free amine.

Although only lithium iodide in refluxing pyridine[183] had been reported to effectively cleave N-carbomethoxy urethanes and methyl esters, various other reagents had been developed for effecting cleavage of the alkyl oxygen bond of hindered methyl esters by nucleophilic displacement of the carboxylate anion from the methyl group. These included: lithium N-propyl mercaptide[184],

lithium iodide in refluxing pyridine, 2,6-lutidene or 2,4,6-collidene[185], lithium iodide in hot DMF[186], potassium tert-butoxide in warm DMSO[187], lithium iodide and sodium cyanide in DMF[188], and sodium cyanide HMPT[189]. Furthermore, boron halides have been used for the cleavage of hindered methyl esters[190] and of tert-butyloxycarbonyl and benzyloxycarbonyl amine protecting groups[191,192].

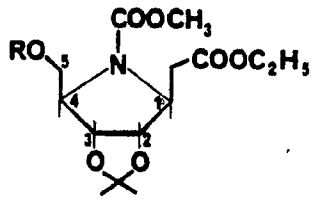
Our first attempts to remove the N-carbomethoxy group from lactone *150* with lithium iodide in DMF[186] or boron tribromide in methylene chloride[192] led to intractable mixtures.



(*150*)

Since the methods described above are quite specific for the cleavage of methyl esters[189], it was decided to form the saturated, stable ethyl ester *169* from lactone *150*, and attempt to selectively remove the N-carbomethoxy group. Accordingly, lactone *150* was reacted with sodium ethoxide in ethanol at -15°, and the resulting alcohol was silylated. A simple chromatographic separation on silica gel afforded the pure oily product *169* in 85% yield, based on *150*. The i.r. spectrum of *169*

displayed two carbonyl absorptions, at 1730 cm^{-1} (ester) and at 1700 (urethane), and all other spectral data supported the proposed structure.



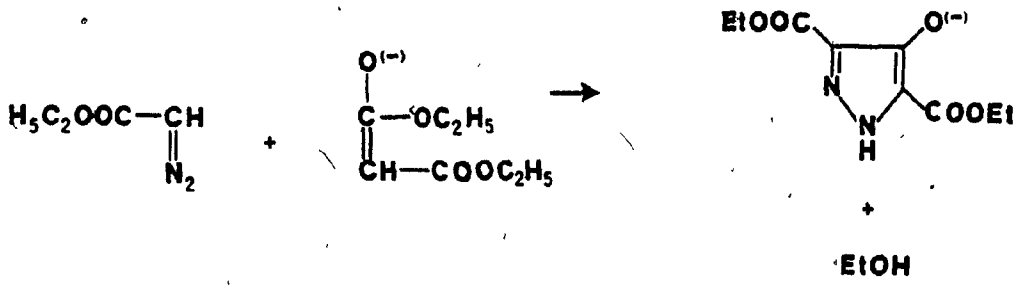
(*169*)

However, when this saturated ester was reacted with potassium tert-butoxide in dimethylsulphoxide[187], extensive decomposition occurred, and very little free amine was recovered. Similarly, when it was reacted with lithium iodide in dimethylformamide under an atmosphere of nitrogen[187], heating for 2-3 hours did cleave the urethane to a significant extent, but it also caused decomposition.

We have been unable to efficiently remove the N-carbomethoxy group from any of our compounds, and as yet a reagent capable of cleaving simple N-carbalkoxy groups has not been reported in the literature.

b. Attempted Synthesis of an Azacyclic Analogue of Pyrazofurin A

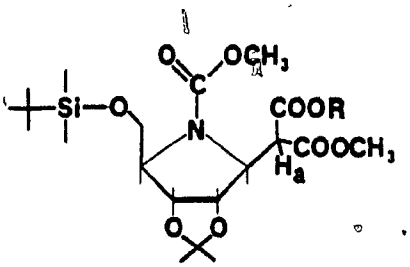
Malonic esters were known to undergo condensation with ethyl diazoacetate in the presence of sodium ethoxide, affording 4-hydroxypyrazoles in fair yields[193]:



This approach seemed superior to the usual methods employed in our laboratory[179] and elsewhere[194]. These methods involved conversion of α-ketoesters to hydrazinoacetates or similar compounds, and subsequent cyclization to hydroxypyrazoles with excess sodium methoxide in very low yield.

Accordingly, the sequence of reactions leading to the azacyclic analogue of showdomycin was modified to produce a malonic ester derivative which might lead to an azacyclic analogue of pyrazomycin. The methyl ester *159* was converted to the crude malonic acid mixture (*162*) as usual, and the latter was methylated with etheral diazomethane[195]. The malonic ester *170* was obtained in 60-65% yield after chromatography on silica gel,

based on ester *159*. The infrared spectrum of the product displayed a malonic ester absorption at $\nu_{C=O}$ 1730 cm^{-1}, and a urethane band at $\nu_{C=O}$ 1700 cm^{-1}. Its mass spectrum contained



(*162*) R = H

(*170*) R = CH_3

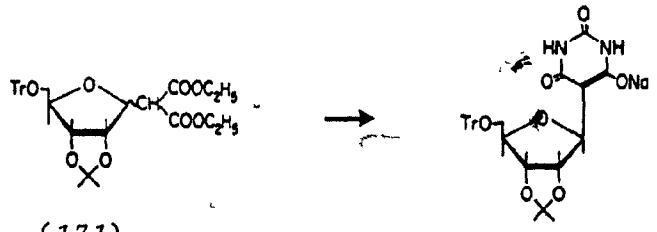
peaks representing loss of CH_3 (m/e 460), CH_3O (444), Me_3C (418) and $Me_3C(Me_2)Si$ (360) fragments, and its p.m.r. spectrum displayed three carbomethoxy singlets, centered at δ 3.65 p.p.m.

When malonic ester *170* was reacted with ethyl diazoacetate and sodium methoxide in methanol at -10° [193,196], no conversion to a 4-hydroxypyrazole occurred. Substantial decomposition of the starting material was noted. Upon repeating this experiment at room temperature, almost complete decomposition of the malonic ester occurred. No trace of a heteroaromatic ring was found.

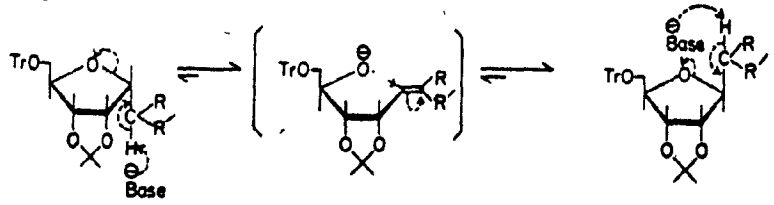
Thus it appears that, while the anion of the malonic ester *170* was most likely easily generated by abstraction of proton H_a, it would not react with ethyl diazoacetate.

This may be due to steric effects, or because the anion decomposes rapidly upon formation.

While the preceding approach was not productive, it should be noted that Ohrui and Fox[59] utilized an anomeric mixture of a similar C-glycoside (*171*) to produce the sodium salt *172* of barbituric acid. They theorized that a plausible mechanism for the conversion of anomeric mixture *171* to predominantly β product *172* was the one shown below:



(*171*) (*172*)

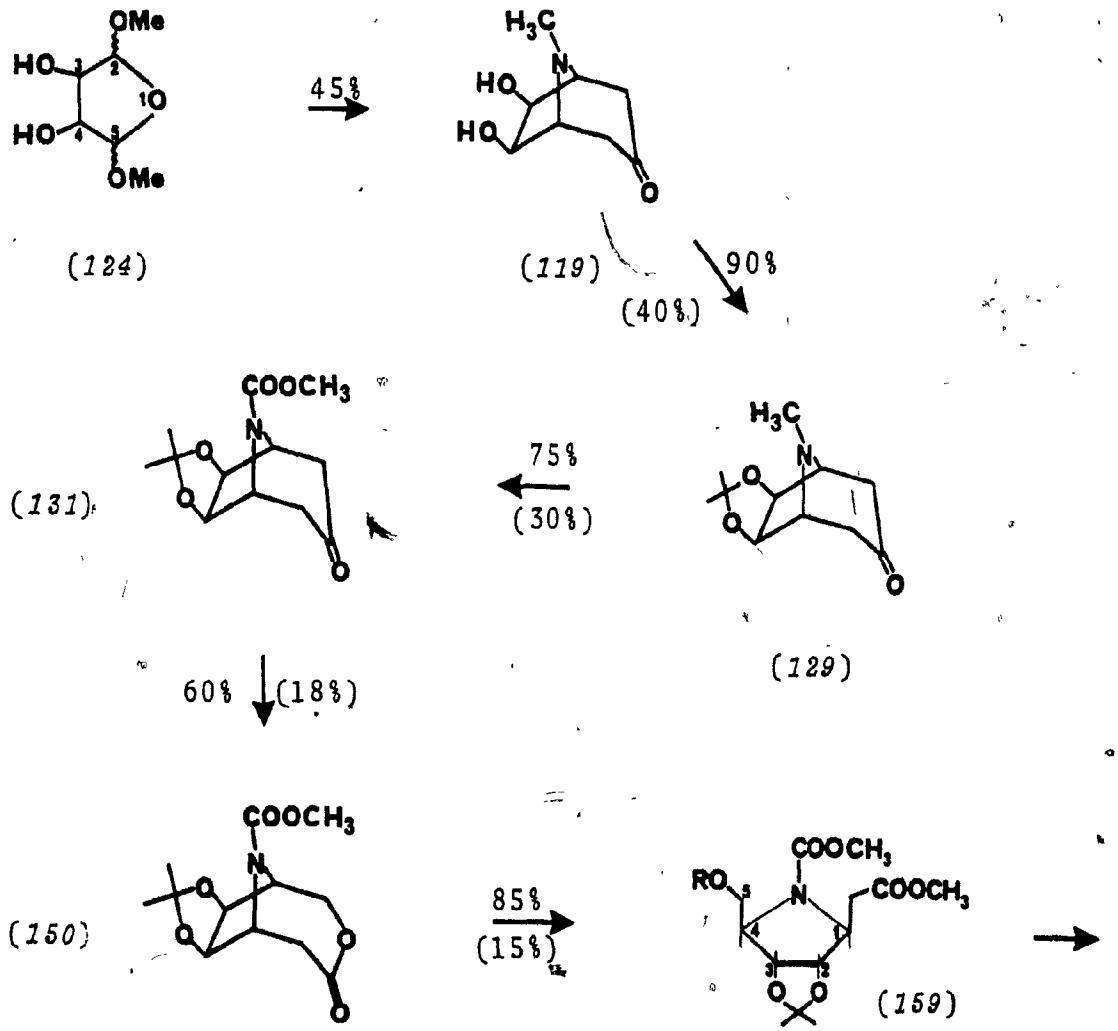


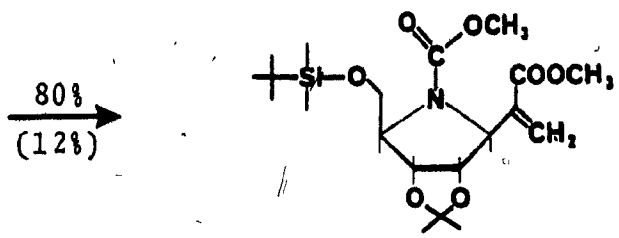
(*171a*)

They concluded that the isopropylidene group would favour the formation of the more thermodynamically stable β ('*trans*') isomer in the equilibrium process and would prevent polymerization (e.g. from *171a*) by favouring the tetrahydrofuran ring structure[197]. Apparently, this conclusion is not valid in the present case.

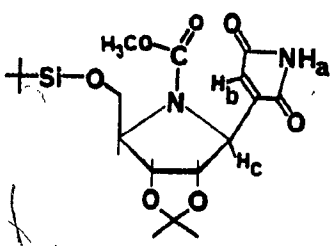
c. Summary and Conclusion

The synthesis of an azacyclic analogue of showdomycin has been accomplished in eight steps from teloidinone *119*. Shown below is a schematic representation of the successful synthesis; above each arrow is the optimum yield for the individual conversion, and beneath the arrow (in brackets) is a cumulative yield, based on the dimethyl acetal *124*.

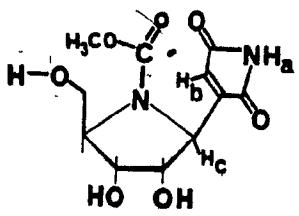




(164)



(165)



(167)

In the course of the present work, several important intermediates for the production of azacyclic analogues of C-nucleosides have been synthesized. Especially important was the α-ketoester *164*, which was converted to an azacyclic analogue of showdomycin in two steps. The ketoester might also be convertible by well-known methods, albeit in low yields, to azacyclic analogues of pyrazomycin[179,194] and of pseudouridine[179]. A second intermediate, the malonic ester derivative *170*, was also produced, and it appears that this compound could be converted to a pseudouridine analogue[59] quite easily in a single step.

We have shown that the N-carbomethoxy group is quite stable towards acids, bases, nucleophiles and electrophiles. In fact, it was too stable to be removed efficiently from any of our intermediates. In order for the present work to be adapted for the production of completely deblocked azacyclic C-nucleoside analogues, either a relatively mild, selective method of cleaving the N-carbomethoxy moiety should be developed, or a different amine protecting group must be utilized.

Contributions to Knowledge

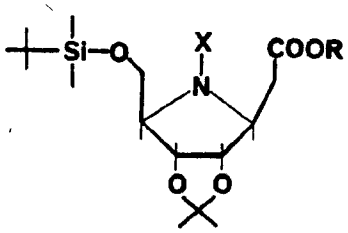
A multi-substituted pyrrolidine containing an α-keto-ester substituent was synthesized, from which an azacyclic analogue of showdomycin was easily formed. This ketoester was produced in good yield from a bicyclic system whose stereochemistry was precisely defined.

Several other pyrrolidine intermediates which could be elaborated into other C-nucleoside analogues were also prepared. Many new 7-azabicyclo(2.2.1)hept-2-enes and 8-azabicyclo-(3.2.1)octanes were synthesized.

Suggestions for Further Study

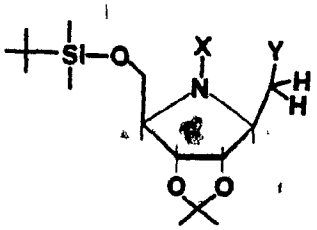
Should the azacyclic C-nucleoside analogues display interesting biochemical or biological activity, further studies should be carried out in three general areas: (1) improvement of the present synthetic scheme, (2) development of a complementary approach, and (3) synthesis of other nucleoside analogues.

(1) Modifications can be envisioned to improve the synthesis of an α-ketoester, for example. An ester of type *173* might be converted to an α-hydroxy ester with lithium diisopropylamine and molybdenum peroxide (MoO_5.Py.HMPA)[198]. Subsequent mild oxidation with either DMSO-DCC[45] or DMSO-acetic anhydride[179a] would effect conversion to an α-ketoester. In a similar approach, an ester of type *173* may be converted in high yield to its α-bromoester derivative[41], and oxidation with DMSO-DCC[199] would then lead to the α-ketoester. These reactions might obviate the need for ozonolytic cleavage, and thus improve the overall yield of an α-ketoester from a saturated ester.

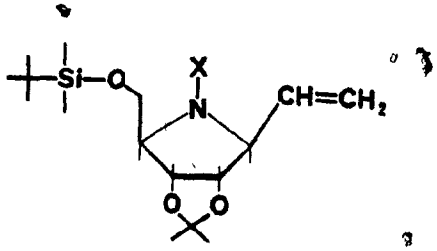


(*173*)

(2) On a different approach, an ester of type *173* could be converted to an amide *174* which could then be reduced selectively (BH_3.THF) [200] to the amine *175*. Oxidation of the latter with hydrogen peroxide or an organic peracid would afford the amine oxide ($Y = CH_2R_2N \rightarrow O$) which could be made to undergo a Cope elimination [201], finally affording the desired terminal olefin *176*. Conversely, the methanesulphonate ester of an alcohol obtained from reduction of ester *173* could be displaced by an amine, and the latter could undergo a Cope elimination. An even higher overall yield might be obtained if that alcohol is converted to a halide, and the latter expulsed by an amine. These ideas may be useful if one desires the terminal olefin as a starting point for 1,3-cycloadditions.

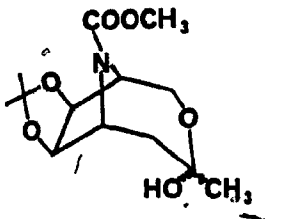


(*174*) $Y = CH_2CONR_2$
(*175*) $Y = CH_2NR_2$



(*176*)

Another suggestion involves reacting the lactone *150* with one equivalent of methyl lithium to produce the hemiketal *177*. Elimination of water and ozonolytic cleavage of the resulting olefin would afford, upon reductive work-up, the aldehyde-acetate *178* [169]. This aldehyde may be a very useful inter-



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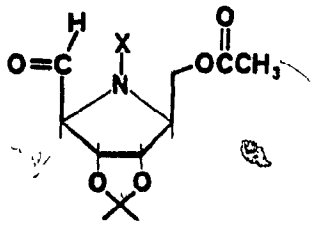
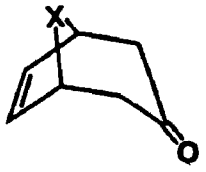


(178)

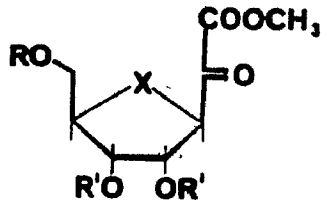
mediate for the synthesis of nucleoside analogues.

(3) The aldehyde used in the Robinson synthesis can be easily modified to contain a *trans*-diol, an epoxide or a single alcoholic function[202]. These would eventually lead to azacyclic nucleosides containing the 2',3'-*trans* diol structure, and the 2'- or 3'-deoxy analogues.

Also, 8-oxabicyclo(3.2.1)oct-6-en-3-one *179* and the carbocyclic analogue *180* have been synthesized in low yield[203], but may be obtained in very high yield by a modification of the diiron nonacarbonyl-catalyzed cycloaddition of Noyori *et al* [143]. It would be interesting to try to hydroxylate these to *exo-cis* diols, and submit the protected diols to the same reactions as in the present work. Lactonization, ring opening and protection, and functionalization at the α-position of the resulting ester would afford the α-ketoesters *181* and *182*. The former has been synthesized in various ways in our laboratory[179a] and elsewhere[44,45], and the latter has also been prepared by Kim[179b]. The octenones *179* and *180* should undergo



(*179*) X = O
(*180*) X = CH_2



(*181*) X = O
(*182*) X = CH_2

catalytic hydroxylation much more smoothly than if a nitrogen bridge were present, since steric interference and oxidative side reactions are no longer a problem. If the ketone moiety interferes with a clean reaction, it could readily be protected and later deprotected in high yield.

EXPERIMENTAL SECTION

Solvents were reagent grade unless otherwise specified. All evaporations were done under reduced pressure (water aspirator) with a bath temperature of 25-45° unless otherwise noted.

Melting points were determined on a Gallenkamp block in open capillary tubes and are uncorrected. Mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 eV using a direct insertion probe. Infrared (i.r.) spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 spectrophotometer. Ultraviolet (u.v.) spectra were obtained on a Unicam SP-800 and a CARY 17 spectrophotometer. Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian T-60 instrument using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts are given in the δ scale in parts per million (p.p.m.). Doublets ('d'), triplets ('t') and quartets ('q') were recorded at the centre of the peaks, and multiplets ('m') as their range of absorption; other abbreviations used: singlet ('s') and broad ('b').

Analytical thin layer chromatography (t.l.c.) was performed on silica gel-coated plates (Eastman Kodak or Machery-Nagel Polygram G) and on a preparative scale (p.l.c.) on silica

gel (Merck $UV_{254,366}$) coated glass plates. Woelm alumina (neutral) and silica gel were used for column chromatography.

Elemental analyses were performed by C. Daessle, Montreal, and Heterocyclic Chemical Corporation, Missouri.

EXPERIMENTAL - CHAPTER 2

2,3-Dimethyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-carbomethoxy-7-azabicyclo(2.2.1)-hept-2-ene-2,3-dicarboxylate (*91*)

To a solution of a 2.20 g (8.14 mmol) of the Diels-Alder adduct *89* in 40 ml ethyl ether and 20 ml acetone was added 3.0 ml of osmium tetroxide solution (1 g OsO_4 in 200 ml purified tert-butanol)[110] and 2.0 ml 30% hydrogen peroxide. After stirring vigorously for 48 h at r.t., t.l.c. (silica gel, methylene chloride) showed the total disappearance of starting material. The reaction was quenched by addition of 20 ml 10% sodium bisulphite, and this aqueous layer was back-extracted with ethyl acetate (2 x 25 ml). The combined organic layers were dried (Na_2SO_4) and evaporated, leaving a yellow oil which was chromatographed on silica gel. Elution with ethyl ether - methylene chloride (1:1) afforded the crude diol as the most polar component of the mixture.

The crude diol was protected by reaction with 20 ml dry acetone and 10 ml 2,2-dimethoxypropane, catalyzed by 10 mg p-toluenesulphonic acid monohydrate. Once the starting diol was completely reacted by t.l.c., the solvents were evaporated off and the residue was purified by chromatography on a silica gel column, eluting with methylene chloride. The resulting clear, colorless oil was obtained in 23% yield, based on the adduct

89; p.m.r. ($CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 3.70 (s, 3H), 3.83 (s, 6H), 4.54 (s, 2H), 5.00 p.p.m. (s, 2H); i.r. (film) 1745 (urethane), 1730 and 1720 (ester), 1640 (C=C), 1390 and 1380 cm^{-1} (gem-dimethyl); mass spectrum m/e 326 ($M^+ - CH_3$), 310 ($M^+ - CH_3O$).

Anal. Calcd. for $C_{15}H_{19}NO_8$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.47; H, 5.38; N, 4.18.

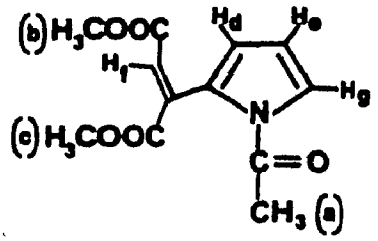
2,3-Dimethyl-N-acetyl-7-azabicyclo(2.2.1)-2,5-heptadiene-2,3-dicarboxylate (*92*)

and

Dimethyl 1-acetyl-2-pyrrolyl fumarate (*93*)

N-acetyl pyrrole (2.20 g, 20 mmol)[121] dissolved in 30 ml dry methylene chloride was added to a solution of 2.85 g (20 mmol) dimethyl acetylenedicarboxylate and 13.4 g (100 mmol) anhydrous aluminum chloride in 170 ml methylene chloride. The mixture was stirred at 45° for 90 min, then cooled in ice. Ice chips were added slowly to quench the reaction, and the organic phase was washed with 100 ml water. Drying (Na_2SO_4) and evaporation left a dark oil which was chromatographed on silica gel. Elution with methylene chloride - benzene (1:1) afforded mainly the side product *93* in about 10% yield; p.m.r. ($CDCl_3$) δ 2.48 (s, 3H_a), 3.66 (s, 3H_b), 3.75 (s, 3H_c), 6.27 (s, H_d), 6.32 (s, H_e), 6.93 (s, H_f), 7.28 p.p.m. (t, H_g, J ≈ 2.5 Hz); i.r. (film) 3160 (pyrrole ring), 1735 (C=O's), 1650

(olefinic C=C), 1640 cm^{-1} (aromatic C=C); mass spectrum m/e 251 (M^+), 220 ($M^+ - CH_3O$), 209 ($M^+ - CH_2{=}C{=}O$), 192 ($M^+ - CH_3COO$).



(93)

Elution with methylene chloride yielded the Diels-Alder adduct as a slightly yellow oil, yield 3.3 g (65%); p.m.r. ($CDCl_3$) δ 1.95 (s, 3H), 3.84 (s, 3H), 5.55 (m, 1H), 5.72 (m, 1H), 7.10 p.p.m. (m, 2H); u.v. (95% EtOH) λ_{max} 210 nm (ε 13000), shoulder 290 nm (ε 1200); i.r. (film) 1735 (diester C=O), 1690 (amide C=O), 1648 cm^{-1} (C=C); mass spectrum m/e 251 (M^+), 225 (M^+ - acetylene), 219, 209 ($M^+ - CH_2{=}C{=}O$), 196.

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18. Found: C, 57.53; H, 5.27.

2,3-Dimethyl *exo-cis*-5,6-diacetoxy-N-acetyl-7-azabicyclo(2.2.1)-hept-2-ene-2,3-dicarboxylate (*95a*)

and

3,4-Dicarbomethoxy-N-acetyl-pyrrole (*96*)

The adduct *92* (2.0 g, 8 mmol) was dissolved in 60 ml ether and 20 ml acetone, and to this was added 2 ml osmium tetroxide solution and 1.5 ml of 30% hydrogen peroxide. When all the starting material had been consumed according to t.l.c., the

reaction was quenched with 20 ml of 10% sodium bisulphite. Back-extraction of the aqueous phase with ethyl acetate (2 x 25 ml), combination of all the organic layers, drying (Na_2SO_4) and evaporation left a yellow oil with a complex p.m.r. spectrum. Passage through a silica gel column, eluting with methylene chloride - acetone (9:1), afforded the main side product *96* as a yellow solid in 20% yield. It was recrystallized from ethyl ether as white crystals, m.p. 84°; p.m.r. ($CDCl_3$) δ 2.57 (s, 3H), 3.80 (s, 6H), 7.75 p.p.m. (s, 2H); i.r. (KBr) 3160 (pyrrole ring), 2980, 1765 (ester C=O), 1715 (amide C=O), 1575, 1540 cm^{-1}; u.v. (95% EtOH) λ_{max} 214 nm (ε 18000), shoulder 222 (ε 16000), shoulder 250 (ε 11000); mass spectrum m/e 225 (M^+), 194 ($M^+ - CH_3O$), 183 (3,4-dicarbomethoxypyrrole), 152, 122, 120.

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.24; H, 4.77; N, 6.01.

Elution with methylene chloride - acetone (1:1) afforded the crude diol *94* in 25% yield; p.m.r. ($CDCl_3$) δ 2.12 (s, 3H), 3.82 (s, 6H), 4.05 (s, 1H), 4.75 (b.s, 2H, exch. with D_2O), 4.84 (m, 1H), 5.23 p.p.m. (m, 1H).

The diol was acetylated overnight with pyridine and acetic anhydride, and the residue left upon evaporation of the solution was chromatographed on a silica gel column, eluting with methylene chloride. The clear, colorless, oily product was obtained in 20% yield based on *92*. It slowly crystallized, and it was recrystallized from ethyl ether, m.p. 95-96°; p.m.r. ($CDCl_3$)

δ 2.09 (s, 9H), 3.85 (s, 6H), 5.00 (s, 2H), 5.00 (m, 1H), 5.33 p.p.m. (m, 1H); i.r. (film) 3020, 2975, 1765-1755 (acetate), 1740 (ester), 1685-1680 (amide), 1655 cm^{-1} (C=C); u.v. (95% EtOH) λ_{max} 220 nm (ε 5000); mass spectrum m/e 369 (M^+), 338 ($M^+ - CH_3O$).

Anal. Calcd. for $C_{16}H_{19}NO_9$: C, 52.03; H, 5.19; N, 3.79. Found: C, 52.05; H, 5.06; N, 3.98.

2,3-Dimethyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-acetyl-7-azabicyclo(2.2.1)-hept-2-ene-2,3-dicarboxylate (*95b*)

The crude diol *94* was also converted to the isopropylidene derivative by reaction with acetone, 2,2-dimethoxypropane, and a catalytic amount of p-toluenesulphonic acid monohydrate. The residue left by evaporating the solution to dryness was chromatographed on a silica gel column. Elution with methylene chloride afforded the pure oily acetonide in 15% overall yield; p.m.r. ($CDCl_3$) δ 1.34 (s, 3H), 1.43 (s, 3H), 2.10 (s, 3H), 3.86 (s, 6H), 4.60 (s, 2H), 4.95 (d, 1H, J=2 Hz), 5.44 p.p.m. (d, 1H, J=2 Hz); i.r. (film) 1740-1735 (esters), 1675 (amide), 1645 (C=C), 1390 and 1383 cm^{-1} (gem-dimethyl); mass spectrum m/e 310 ($M^+ - CH_3$), 196, 194, 193, 152, 100, 85.

Anal. Calcd. for $C_{15}H_{15}NO_7$: C, 55.38; H, 5.89; N, 4.31. Found: C, 55.17; H, 5.68; N, 4.22.

3-Phenacylsulphonyl pyrrole (*99*)

Phenacyl sulphonyl chloride *98* (2.19 g, 10 mmol) [133]

dissolved in 50 ml anhydrous ethyl ether was added dropwise with stirring to a solution of 0.67 g (10 mmol) freshly distilled pyrrole and 1.5 g (15 mmol) triethylamine in 25 ml ether at -35° (dry ice/acetone). After 1 h the reaction mixture was allowed to warm up to r.t., then stirred vigorously for 2 h. The precipitate was filtered off, and the filtrate was washed with dilute hydrochloric acid (2 x 25 ml), 10% sodium bicarbonate (25 ml) and 15 ml water. The organic phase was dried (Na_2SO_4) and evaporated, and the yellow residue was recrystallized from chloroform as white crystals, m.p. 134-134.5°; yield 15%; p.m.r. (acetone-d_6) δ 4.88 (s, 2H), 6.18 (m, 1H), 6.67 (m, 1H), 7.00 (m, 1H), 7.3-7.6 (b.m, 4H, 3 aromatic protons from phenyl ring and 1H exchangeable with D_2O), 7.75 (d, 1H, J≃2 Hz), 7.91 p.p.m. (d, 1H, J≃2 Hz); i.r. (KBr) 3350 (pyrrole N-H), 1685 (C=O), 1605 (aromatic C=C), 1585 (aromatic C=C), 1538 cm^{-1}; u.v. (95% EtOH) λ_{max} 248 nm (ε 16500), 211 (ε 16200); mass spectrum m/e 249 (M^+), 185 ($M^+ - SO_2$), 130 ($C_4H_4NSO_2$), 105 (C_6H_5CO).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.42; N, 5.62; S, 12.75. Found: C, 57.47; H, 4.52; N, 5.89; S, 12.99.

N-(p-toluenesulphonyl)-pyrrole (*100*)

Potassium pyrrole (20 g, 0.19 mol)[126] was suspended in 100 ml dry toluene, and to this was added a solution of 36 g (0.19 mol) p-toluenesulphonyl chloride in 100 ml toluene dropwise with vigorous stirring over a period of 30 min. The mixture was stirred

overnight, then filtered. The filtrate was evaporated to dryness, leaving a dark solid which was recrystallized from methanol as white crystals, m.p. 102-103° (lit[93] 103°), yield 23 g (55%). The p.m.r. spectrum was identical to that obtained in ref. 93.

2,3-Dimethyl N-(p-toluenesulphonyl)-7-azabicyclo(2.2.1)-2,5-heptadiene-2,3-dicarboxylate (*101*)

and

Dimethyl 1-(p-toluenesulphonyl)-2-pyrrolyl fumarate (*102*)

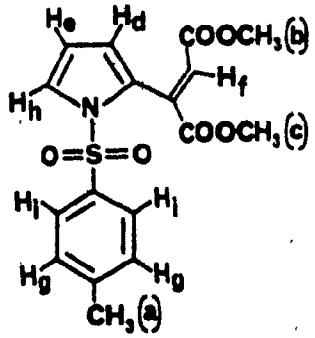
A solution of 2.21 g (0.01 mol) N-(p-tosyl)-pyrrole *100* in 10 ml dry methylene chloride was added to one of 6.70 g (0.05 mol) anhydrous aluminum chloride and 1.42 g (0.01 mol) dimethyl acetylenedicarboxylate in 90 ml methylene chloride dropwise with stirring. After stirring at 40° for 90 min, ice was added and the organic layer was washed with 50 ml water. Drying (Na_2SO_4) and evaporation left a yellow solid, m.p. 128-132° (lit[93] 146° for pure adduct). The p.m.r. and t.l.c. of this solid showed the presence of the two products *101* and *102* in a 3:2 ratio. Attempted separation by chromatography failed, as did all fractional crystallizations; complete separation could only be accomplished by preparative t.l.c. on silica gel, eluting with chloroform - benzene (1:1). The m.p., p.m.r., and u.v. of the Diels-Alder adduct were identical to those obtained by Prinzbach[93]; i.r. (KBr) 1750 and 1735 and 1720 (C=O's), 1648

(C=C of unsaturated diester), 1605 cm^{-1}; mass spectrum m/e 363 (M^+), 337 (M^+ - acetylene), 221 (N-(p-tosyl)-pyrrole), 208, 155, 91.

The side product was recrystallized from carbon tetrachloride, m.p. 159-160°; p.m.r. ($CDCl_3$) δ 2.48 (s, $3H_a$), 3.54 (s, $3H_b$), 3.95 (s, $3H_c$), 6.45 (m, H_d, H_e), 7.24 (s, H_f), 7.46 (X_2, $2H_g$), 7.53 (b.s, H_h), 7.93 p.p.m. (A_2, $2H_i$); i.r. (KBr) 3160 (pyrrole ring), 1745-1730 (C=O's), 1655, 1650, 1600 cm^{-1}; mass spectrum m/e 363 (M^+), 304 (M^+ - CH_3COO), 240, 239, 208.

Anal. Calcd. for $C_{17}H_{17}NO_6S$: C, 56.20; H, 4.68; N, 3.86. Found: C, 56.07; H, 4.61; N, 3.72.

A similarly catalyzed reaction using a threefold excess of aluminum chloride produced the side product in high yield; a sevenfold excess yielded roughly equal portions of adduct and side product.



(102)

2,3-Dimethyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluenesulphonyl)-7-azabicyclo(2.2.1)-hept-2-ene-2,3-dicarboxylate (*106a*)

To a solution of 1.0 g (2.74 mmol) of adduct *101* in 30 ml anhydrous ether and 20 ml acetone was added 2 ml osmium tetroxide solution and 1 ml 30% hydrogen peroxide. The resulting solution was stirred vigorously at r.t. and monitored by t.l.c. (silica gel, methylene chloride - benzene 1:1). After 60 h, the reaction mixture became clear and yellow, and t.l.c. showed the complete disappearance of starting material. The reaction was quenched with 20 ml 10% sodium bisulphite, and this aqueous layer was back-extracted with 25 ml ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated, leaving an orange oil; p.m.r. ($CDCl_3$) δ 2.24 (s, 3H), 3.65 (s, 6H), 3.86 (s, 2H), 4.45 (b.s, 2H, exch. with D_2O), 4.68 (s, 2H), 7.10 (X_2, 2H), 7.50 p.p.m. (A_2, 2H); i.r. (film) 3450 (O-H), 1735 (C=O), 1650 (C=C of unsaturated diester), 1600 cm^{-1} (aromatic C=C).

The crude diol was dissolved in 25 ml dry acetone, and 10 ml 2,2-dimethoxypropane and 10 mg p-toluenesulphonic acid monohydrate was added. Once t.l.c. (silica gel, methylene chloride) showed complete conversion to the protected product having R_f=0.8, the solution was evaporated to dryness, and the solid residue was recrystallized from methylene chloride - ether, m.p. 182.5°. The yield was 50% (0.5 g) based on *101*; p.m.r.

($CDCl_3$) δ 1.28 (s, 3H), 1.47 (s, 3H), 2.39 (s, 3H), 3.72 (s, 6H), 4.42 (s, 2H), 4.80 (s, 2H), 7.25 (X_2, 2H), 7.67 p.p.m. (A_2, 2H); i.r. (KBr) 1735 and 1725 (C=O's), 1645 (C=C of unsaturated diester), 1603 (aromatic C=C), 1390 and 1380 cm^{-1} (gem-dimethyl); u.v. (95% EtOH) λ_{max} 227 nm (ε 17000); mass spectrum m/e 422 ($M^+ - CH_3$), 378 ($M^+ - CH_3COO$), 337 (3,4-dicarbomethoxy-N-(p-tosyl)-pyrrole), 306.

Anal. Calcd. for $C_{20}H_{23}NO_8S$: C, 54.92; H, 5.30; N, 3.20; S, 7.32. Found: C, 54.64; H, 5.03; N, 3.10; S, 7.51.

2,3-Dimethyl *exo-cis*-5,6-diacetoxy-N-(p-toluenesulphonyl)-7-azabicyclo(2.2.1)-hept-2-ene-2,3-dicarboxylate (*106b*)

The crude diol was converted to the diacetate with pyridine - acetic anhydride in the usual way. Also, the isopropylidene derivative *106a* (97 mg, 0.22 mmol) was dissolved in 5 ml 50% aq. trifluroacetic acid and stirred for 5 min, then the solution was evaporated to dryness, using benzene as chaser. The crude diol was converted to the same diacetate in the usual way. Recrystallization of the product from chloroform - ether afforded 80 mg (70%) white crystals, m.p. 165-6°; p.m.r. ($CDCl_3$) δ 2.12 (s, 6H), 2.40 (s, 3H), 3.71 (s, 6H), 4.90 (s, 4H), 7.25 (X_2, 2H), 7.68 p.p.m. (A_2, 2H); i.r. (KBr) 1745 (acetate), 1728 (C=O of unsaturated diester), 1652 (C=C of unsaturated diester), 1605 cm^{-1} (aromatic C=C); mass spectrum m/e 481 (M^+), 450 ($M^+ - CH_3O$), 422 ($M^+ - CH_3COO$).

2,4-Dihydroxy 2,4-dicarbomethoxy *exo-cis*-6,7-dihydroxy-O-isopropylidene-N-(p-toluenesulphonyl)-3-oxa-8-azabicyclo(3.2.1^{1,5})-octane (*107a*)

Sodium metaperiodate (4.1 g, 19.0 mmol) and ruthenium dioxide hydrate[120] (40 mg) were dissolved in a potassium dihydrogen phosphate - sodium hydroxide buffer solution (75 ml, pH 6), and to this was added dropwise a solution of 2.07 g (4.75 mmol) of unsaturated diester *106a* in 75 ml acetone. After 2 h, another 500 mg periodate was added, and after 4 h, a final 400 mg was added. After a total of 4.5 h, 10 ml isopropanol was added, and the mixture was filtered through a bed of Kieselguhr. The solid was washed well with chloroform, and the combined filtrates were evaporated to remove the organic solvents. The remaining aqueous solution was extracted with 3 x 100 ml chloroform. Drying (Na_2SO_4) and evaporation left a solid which was recrystallized from methylene chloride - carbon tetrachloride, m.p. 213-215°; yield 1.2 g (55%); p.m.r. ($CDCl_3$) δ 1.03 (s, 3H), 1.18 (s, 3H), 2.39 (s, 3H), 3.74 (s, 6H), 4.24 (s, 2H), 4.50 (s, 2H, exch. with D_2O), 4.72 (s, 2H), 7.23 (X_2, 2H), 7.78 p.p.m. (A_2, 2H); i.r. (KBr) 3400 and 3320 (O-H), 1763, 1754, 1738, 1607 (aromatic C=C), 1389 cm^{-1}; u.v. (95% EtOH) λ_{max} 233 nm (ε 16000); mass spectrum m/e 472 ($M^+ - CH_3$), 457 ($M^+ - CH_2{=}O$), 454 ($M^+ - CH_3 - H_2O$), 414.

Anal. Calcd. for $C_{20}H_{23}NO_{10}S$: C, 51.17; H, 4.94; N, 2.98; S, 6.83. Calcd. for $C_{20}H_{25}NO_{11}S$: C, 49.28; H, 5.17; N, 2.87;

S, 6.58. Found: C, 49.79, 49.66; H, 5.20, 5.10; N, 2.97; S, 6.61.

2,4-Dihydroxy 4-carbomethoxy *exo-cis*-6,7-dihydroxy-O-isopropylidene-N-(p-toluenesulphonyl)-3-oxa-8-azabicyclo(3.2.1^{1,5})-octane-2-carboxylate (*109*)

The hydrated diester *107a* (685 mg, 1.40 mmol) was dissolved in 10 ml tetrahydrofuran, and to this was added slowly 15.0 ml of 0.10N sodium hydroxide. The reaction was followed by t.l.c. until the total disappearance of starting material (22 h). The tetrahydrofuran was evaporated off under reduced pressure, and the resulting aqueous suspension was extracted with 10 ml ethyl acetate to remove impurities. It was then cooled in ice, acidified to pH 3.5 with 3% hydrochloric acid and extracted with 15 ml ethyl acetate. Re-acidification and extraction was repeated three more times, and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The oily residue solidified when triturated with methylene chloride, and recrystallization from ethyl acetate - carbon tetrachloride afforded 400 mg (60%) of light white powder, m.p. 186-189°; p.m.r. (pyridine-d_5) δ 1.30 (s, 3H), 1.65 (s, 3H), 2.28 (s, 3H), 3.60 (s, 3H), 4.67 (q, 2H), 5.35 (q, 2H), 7.15 (X_2,2H), 8.06 p.p.m. (A_2, 2H) acid proton under solvent absorption; i.r. (KBr) 3420 and 3340 (O-H), 1765 (ester), 1750 (acid), 1395 and 1385 cm^{-1} (gem-dimethyl); mass spectrum m/e 442 ($M^+ - CH_3O$), 439, 425, 410, 295.

Anal. Calcd. for $C_{19}H_{23}NO_{11}S$: C, 48.20; H, 4.90; N, 2.96. Found: C, 48.49; H, 5.03; N, 3.25.

2-Methyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluene-sulphonyl)-7-azabicyclo(2.2.1)hept-2-ene-2,3-dicarboxylate (*110*)

The unsaturated diester *106d* (1.378 g, 3.16 mmol) was dissolved in 40 ml tetrahydrofuran, and to this was added slowly 31.6 ml of 0.10N NaOH. The hydrolysis was followed by t.l.c., using silica gel and methylene chloride. After a short time, all the diester was consumed, and the tetrahydrofuran was evaporated off under reduced pressure. The resulting aqueous mixture was neutralized to pH 7 with 3% hydrochloric acid and extracted with 25 ml ethyl acetate to remove neutral impurities. It was then cooled in ice, acidified to pH 3.5, and extracted with 25 ml ethyl acetate. The pH of the solution rose; thus it was cooled, re-acidified to pH 3 and extracted again. This procedure was repeated once more. The combined organic extracts were dried (Na_2SO_4) and evaporated, leaving a yellow oil. The product could be crystallized from either ethyl ether or chloroform - carbon tetrachloride, m.p. 192-193°; yield 900 mg (70%); p.m.r. (acetone-d_6) δ 1.34 (s, 3H), 1.54 (s, 3H), 2.49 (s, 3H), 3.94 (s, 3H), 4.63 (q, 2H), 4.92 (m, 2H), 6.34 (b.m, 1H, position varies with concentration), 7.54 (X_2, 2H), 7.80 p.p.m. (A_2, 2H); p.m.r. ($CDCl_3$) δ 1.28 (s, 3H), 1.52 (s, 3H), 2.42 (s, 3H), 3.96 (s, 3H), 4.40 (s, 2H), 4.95 (s, 2H), 7.29 (X_2, 2H), 7.65 (A_2, 2H),

9.10 p.p.m. (b.m, 1H, exch. with D_2O); i.r. (KBr) 2800-2700 (acid), 1745 (ester C=O), 1695 (acid C=O), 1633 (C=C of unsaturated di-ester), 1607 (aromatic C=C), 1392 and 1383 cm^{-1} (gem-dimethyl); u.v. (acetonitrile) λ_{max} 230 nm, shoulder 255; mass spectrum m/e 408 ($M^+ - CH_3$), 306, 292.

Anal. Calcd. for $C_{19}H_{21}NO_8S$: C, 53.90; H, 5.00; N, 3.31; S, 7.56. Found: C, 53.64; H, 5.06; N, 3.51; S, 7.47.

2-Methyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluene-sulphonyl)-7-azabicyclo(2.2.1)heptane-2-*endo*-3-*exo*-dicarboxylate (*112*)

and

2-Methyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluene-sulphonyl)-7-azabicyclo(2.2.1)heptane-2,3-*endo*-dicarboxylate (*113*)

A solution of unsaturated acid ester *110* (690 mg, 1.63 mmol) in 30 ml dry tetrahydrofuran was cooled to 0° in a dry 3-neck 100 ml round-bottomed flask equipped with septum, stop-cocks and mercury bubbler and flushed with nitrogen. Borane - tetrahydrofuran solution (1.65 ml, 1.0M) was added dropwise. The temperature was allowed to rise to r.t., and the solution was stirred 1 h. The reaction was quenched with water (5 ml) and evaporated to dryness. Co-evaporation with methanol (3 x 15 ml) left a semi-solid residue which was recrystallized from chloro-form - carbon tetrachloride, affording 210 mg (30% yield) of the *trans*-isomer *112* as a light white powder, m.p. 109-113°; p.m.r.

($CDCl_3$) δ 1.11 (b.s, 6H), 2.47 (s, 3H), 2.97 (d, 1H, J ≃ 6 Hz), 3.85 (s, 3H), 3.93 (m, 1H), 4.37 (s, 2H), 4.60 (m, 2H), 7.30 (X_2, 2H), 7.85 (A_2, 2H), 9.35 p.p.m. (b.s, 1H, exch. with D_2O); p.m.r. (pyridine-d_5) δ 1.25 (s, 3H), 1.40 (s, 3H), 2.30 (s, 3H), 3.53 (d, 1H, J ≃ 6 Hz), 3.84 (s,3H), 4.43 (t, 1H, J ≃ 6 Hz), 4.84 (q, 2H), 5.06 (m, 2H), 7.47 (X_2, 2H), 8.30 p.p.m. (A_2, 2H), acid proton under solvent absorption; i.r. (KBr) 2800-2500 (broad, acid), 1755 (ester C=O), 1720 and 1705 (acid C=O), 1610 cm^{-1}; mass spectrum m/e 410 ($M^+ - CH_3$), 394 ($M^+ - CH_3O$), 270, 252.

Anal. Calcd. for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29; S, 7.54. Found: C, 53.38; H, 5.31; N, 3.16; S, 7.61.

Evaporation of the filtrate and addition of excess carbon tetrachloride yielded 450 mg (65% yield) of the *cis*-isomer *113* as a white powder, m.p. 57-61°; p.m.r. (acetone-d_6) δ 1.18 (s, 6H), 2.43 (s, 3H), 3.47 (m, 2H), 3.63 (s, 3H), 4.29 (m, 2H), 4.70 (q, 2H), 6.9 (b.m, 1H), 7.32 (X_2, 2H), 7.80 p.p.m. (A_2, 2H); i.r. and mass spectra similar to the *trans*-isomer.

2,3- Dimethyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluene-sulphonyl)-7-azabicyclo(2.2.1)heptane-2-*endo*-3-*exo*-dicarboxylate (*114*)

and

2,3-Dimethyl *exo-cis*-5,6-dihydroxy-O-isopropylidene-N-(p-toluene-sulphonyl)-7-azabicyclo(2.2.1)heptane-2,3-*endo*-dicarboxylate (*115*)

Methylation of the two acids was accomplished by dissolving in a 1:1 mixture of ethyl ether - tetrahydrofuran and adding

etheral diazomethane (approximately 0.3M) dropwise until the yellow colour persisted. Stirring 2 h at r.t. and evaporation to dryness afforded quantitative yields of the diesters as clear, colorless oils. P.m.r. of *trans*-diester *114* ($CDCl_3$) δ 1.17 (b.s, 6H), 2.42 (s, 3H), 2.93 (d, 1H, J ≃ 6 Hz), 3.82 (s, 6H), 3.7-4.6 (m's, 5H), 7.39 (X_2, 2H), 7.92 p.p.m. (A_2, 2H); its p.m.r. spectrum in pyridine-d_5 displayed singlets at 1.25 and 1.37 (3H each, gem-dimethyl), a doublet for the *endo* proton (J ≃ 6 Hz) at 3.40, a singlet at 3.66 (*endo*-COOMe), a singlet at 3.80 (*exo*-COOMe), and a triplet (J ≃ 6 Hz) at 4.25 p.p.m. for the *exo* proton.

P.m.r. of *cis-endo*-diester ($CDCl_3$) δ 1.20 (b.s, 6H), 2.45 (s, 3H), 3.76 (s, 6H), 3.76 (m, 2H), 4.37 (m, 2H), 4.73 (s, 2H), 7.36 (X_2, 2H), 7.90 p.p.m. (A_2, 2H).

EXPERIMENTAL - CHAPTER 3

Cis-3,4-Dihydroxy-2,5-dimethoxytetrahydrofuran (*124*)

To a solution of 34.0 g (0.26 mol) 2,5-dimethoxy-2,5-dihydrofuran in 250 ml acetone and 450 ml water cooled in an ice-salt bath was added 48 g (0.33 mol) powdered potassium permanganate in several lots with vigorous stirring. After the final addition, the suspension was stirred 1 h at 2-5°. Heating to 50°for 20 min converted the colloidally dissolved manganese dioxide to a flocculent precipitate. This was removed by filtration through a bed of Celite, and the precipitate was further washed with 100 ml acetone. The combined filtrates were evaporated under reduced pressure, and the residue was triturated with absolute ethanol. The resulting white solid was filtered off, and the filtrate was distilled *in vacuo*. The product was obtained as a viscous, colorless liquid, b.p. 120-130° (2 mm); yield 18.4 g (43%). Gagnaire and Vottero[139] obtained a 45% yield in a similar procedure, and they reported the p.m.r.; i.r. (film) 3430 (OH), 2960, 1140, 1035, 1000 cm^{-1}.

After storage at r.t. for one day, the product was completely crystalline; m.p. 59-62° (lit[140] 65-67°)

Cis-3,4-Diacetoxy-2,5-dimethoxytetrahydrofuran (*125*)

Diol *124* was acetylated with pyridine and acetic anhydride

as usual, and the crude product was purified by passage through a silica gel column eluting with benzene ether (10:1). The diacetate was obtained as a white solid, m.p. 90-2°; p.m.r. (acetone-d_6) δ 2.09 (s, 6H), 3.46 (s, 6H), 5.14 (b.s, 2H), 5.24 p.p.m. (m, 2H); i.r. ($CHCl_3$) 1760, 1380, 1110 cm^{-1}; mass spectrum m/e 218 ($M^+ - CH_2O$).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50. Found: C, 48.60; H, 6.74.

6β,7β-Dihydroxytropan-3-one (Teloidinone) (*119*)

The hydrolysis of acetal *124* (6.50 g, 39.6 mmol) was accomplished by warming to 50° with 40 ml 1N hydrochloric acid for 30 min. The methanol formed was removed by distillation under reduced pressure, and the resulting yellow, aqueous solution of *meso*-tartaric aldehyde was cooled and adjusted to pH 5 by addition of 5N sodium hydroxide. This solution was added to a buffer solution of 55 g citric acid monohydrate and 537 ml 1.0N sodium hydroxide. Then 17.1 g (109.6 mmol) acetonedicarboxylic acid was dissolved in 75 ml water, adjusted to pH 5 with 5N sodium hydroxide, and added to the buffer solution. Finally, 4.76 g (70.5 mmol) methylamine hydrochloride dissolved in the minimum amount of water was added. The light yellow solution was stirred at r.t. for three days. The product was isolated in one of two ways: (a) the solution was saturated with potassium carbonate and extracted continuously with ether

for a minimum of four days. The crystalline teloidinone separated from the ether extract, and it was collected daily. Concentration of the ether afforded a little more product. The total yield was 3.0 g (44%), m.p. 183-5° with decomposition (lit[137] 188-9° for the crude). (b) The solution was concentrated under reduced pressure to a volume of 150 ml and washed with 100 ml ethyl acetate to remove impurities. It was then saturated with potassium carbonate and extracted with ethyl acetate (10 x 100 ml). The organic solvent was recycled and used to extract several reactions. The brown solid obtained by evaporating off the ethyl acetate was recrystallized from ethanol, m.p. 180-2°; yield 45%; p.m.r. (DMSO-d_6, ext. TMS) δ 2.08 (b.s, 0.67H), 2.36 (b.s, 1.33H), 2.76 (s, 3H), 2.80 (m, 1.33H), 2.98 (m, 0.67H), 3.45 (m, 2H), 3.90 (s, 2H), 4.90 p.p.m. (b.m, 2H, exch. with D_2O); i.r. (KBr) 3490 and 3100 (O-H), 2980, 1725 (C=O), 1145, 980, 760 cm^{-1}; mass spectrum m/e 171 (M^+), 111.

6β,7β-Dihydroxy-O-isopropylidene-tropan-3-one (Teloidinone acetonide) (*129*)

To a suspension of 4.71 g (27.5 mmol) teloidinone *119* in 500 ml acetone was added 19.0 ml conc. hydrochloric acid with vigorous stirring. This mixture was stirred at r.t. for 20 h, by which time it had become a clear, yellow solution. It was then neutralized by bubbling in anhydrous ammonia (to pH 8-9), and the resulting ammonium chloride filtered off. The precipitate

was washed with another 100 ml acetone, and the filtrates were evaporated to dryness *in vacuo*. The yellow solid residue was recrystallized from petroleum ether (60-80°); the product was obtained as white needles, m.p. 84-86° (lit[144] 87-90°). The yield was 5.25 g (90%) in three crops; p.m.r. ($CDCl_3$) δ 1.34 (s, 3H), 1.55 (s, 3H), 2.06 (b.s, 0.67H), 2.34 (b.s, 1.33H), 2.61 (d, 1.33H), 2.75 (s, 3H), 2.87 (d, 0.67H), 3.55 (m, 2H), 4.42 p.p.m. (s, 2H); i.r. (KBr) 3025, 2980, 2945, 1720 (C=O), 1395 and 1390 (gem-dimethyl), 1220, 1080, 1055, 873 cm^{-1}; mass spectrum m/e 211 (M^+), 196 ($M^+ - CH_3$).

6β,7β-Dihydroxy-O-isopropylidene-N-carbethoxy tropan-3-one (*130*)

Freshly distilled ethyl chloroformate (6.2 ml, 76.3 mmol) was added to a solution of 805 mg (3.8 mmol) of teloidinone acetonide *129* in 15 ml dry toluene. This solution was heated to gentle reflux for 30 h, then evaporated to dryness under reduced pressure. The solid residue was recrystallized from petroleum ether (60-80°) - ether, affording an 85% yield of white crystals, m.p. 77-78°; p.m.r. ($CDCl_3$) δ 1.23 (s, 3H), 1.27 (t, 3H), 1.40 (s, 3H), 2.48 (b.m, 4H), 4.15 (q, 2H), 4.40 (s, 2H), 4.46 p.p.m. (b.m, 2H); i.r. (KBr) 1720 (ketone), 1705 (urethane), 1395 and 1385 cm^{-1} (gem-dimethyl); mass spectrum m/e 269 (M^+), 254 ($M^+ - CH_3$), 169, 168.

Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.82; H, 7.09; N, 5.22.

6β,7β-Dihydroxy-O-isopropylidene-N-carbomethoxy tropan-3-one (*131*)

Freshly distilled methyl chloroformate (29.6 ml, 0.384 mol) was added to a solution of 4.05 g (0.0192 mol) of teloidinone acetonide *129* in 50 ml dry benzene. This solution was warmed to 60° and stirred for 20 h. Then the white precipitate (methochloride *134*) was filtered off, and the filtrate was evaporated to dryness. The white solid residue was recrystallized from anhydrous ether, m.p. 123-123.5°. Further crops were obtained by adding petroleum ether (30-60°) until the solvent was a 1:1 mixture. Total yield 3.6 g (75%) in four crops; p.m.r. ($CDCl_3$) δ 1.30 (s, 3H), 1.46 (s, 3H), 2.56 (b.m, 4H), 3.79 (s, 3H), 4.47 (s, 2H), 4.52 p.p.m. (b.m, 2H); i.r. (CCl_4) 2980, 2950, 2890, 1730 (C=O's), 1460, 1395 and 1385 cm^{-1} (gem-dimethyl); mass spectrum (150°) m/e 255 (M^+), 240 ($M^+ - CH_3$), 155, 154.

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.34; H, 6.66; N, 5.52.

Evaporation of the last filtrate left 275 mg (6.3%) unreacted starting material.

6β,7β-Dihydroxy-O-isopropylidene-tropan-3-one methochloride (*134*)

The side product isolated above was quite pure, and it was obtained in 17% yield (875 mg). An analytical sample was prepared by dissolving in methanol and adding anhydrous ether until

partial reprecipitation had occurred, then cooling; m.p. 168-170° with charring; p.m.r. (D_2O) δ 1.53 (s, 3H), 1.79 (s, 3H), 2.80 (b.s, 0.67H), 3.14 (b.s, 1.33H), 3.43 (d, 1.33H), 3.60(s, 3H), 3.70 (b.m, 0.67H), 3.80 (s, 3H), 4.70 (d, 2H), 5.25 p.p.m. (b.s, 2H); i.r. (KBr) 3120, 3025, 3005, 2950, 1730 (C=O), 1395 (gem-dimethyl), 1215, 1160, 1065 cm^{-1}; mass spectrum (150°) m/e 225 (M^+ - HCl, Hoffman elimination), 210 (M^+ - HCl - CH_3), 167.

Anal. Calcd. for $C_{12}H_{20}NO_3$: C, 55.06; H, 7.70; N, 5.35. Found: C, 55.01; H, 7.52; N, 5.07.

Regeneration of Teloidinone Acetonide (*129*) from methochloride *134*

The methochloride *134* (262 mg, 1mmol) and 1,4-diazabicyclo(2.2.2)octane (224 mg, 2 mmol) were dissolved in 5 ml DMF and heated to reflux under nitrogen for 3 h. Water (25 ml) was added, and this solution was extracted with 50 ml benzene. The organic layer was dried (Na_2SO_4) and evaporated, leaving a brown semi-solid which was chromatographed on a short alumina column, eluting with ether. The product was recovered as yellowish crystals, identical to teloidinone acetonide (*129*) by i.r. and t.l.c.; yield: 30 mg (14%).

6β,7β-Dihydroxy-O-isopropylidene-tropan-3-one methiodide (*135*)

Teloidinone acetonide *129* (86 mg, 0.42 mmol) was dissolved in 10 ml dry benzene in a glass pressure bottle. Methyl iodide (1 ml) was added, and the solution was heated to 80° for 24 h.

The mixture was then cooled, and the yellowish precipitate was collected; yield 43 mg; m.p. 186-189° with charring. The p.m.r. spectrum of this methiodide in D_2O-acetone-d_6 was similar to that of methochloride *134*; i.r. (KBr) 1750 cm^{-1} (C=O); the mass spectrum (200°) was almost exactly identical to that of *134*, displaying a molecular ion at m/e 225 (M^+ - HI, Hoffman elimination).

6α,7α-Dihydroxy-O-isopropylidene-8-thiatropan-3-one (*136*)

Sodium sulphide hydrate ($Na_2S.9H_2O$, 1.04 g, 4.3 mmol) was dissolved in 15 ml ethanol - water (2:1), and to this was added 378 mg (1.44 mmol) methochloride *134* in 15 ml ethanol - water (2:1). The solution was heated 30 min at 50°, then stirred 1 h at r.t. The ethanol was removed under reduced pressure, and the resulting aqueous mixture was extracted with methylene chloride (3 x 15 ml). Drying (Na_2SO_4) and evaporation afforded 200 mg of a yellow solid which consisted of a 6:1 mixture of 8-thiatropan-3-one *136* and teloidinone acetonide *129* by p.m.r. Purification by chromatography on 20 x 20 cm silica gel plates, using ether - hexanes (3:2) as the solvent system, afforded 145 mg (47%) of a white powder, m.p. 114-115.5°. An analytical sample was obtained by recrystallization from petroleum ether (60-80°), m.p. 115.5-116.5°; p.m.r. ($CDCl_3$) δ 1.35, 1.37 (s, s, 6H), 2.40 (d, 0.4H), 2.69 (d, 1.6H), 2.87 (d, 1.6H), 3.16 (d, 0.4H), 3.46 (b.m, 2H), 4.88 p.p.m. (q, 2H); i.r. (KBr) 3000,

2940, 1720 (C=O), 1390 and 1383 cm^{-1} (gem-dimethyl); mass spectrum (130°) m/e 214 (M^+), 199 ($M^+ - CH_3$).

Anal. Calcd. for $C_{10}H_{14}O_3S$: C, 56.07; H, 6.59. Found: C, 56.10; H, 6.53.

6β,7β-Diacetoxy-N-carbomethoxy tropan-3-one (*140*)
and
6β-Acetoxy-7β-trifluoroacetoxy-N-carbomethoxy tropan-3-one (*141*)

N-Carbomethoxy teloidinone acetonide *131* (255 mg, 1 mmol) was dissolved in 5 ml 30% trifluoroacetic acid - water and heated to 55°. The reaction was carried out in a 50 ml flask with no stopper, and it was followed by p.m.r. After 2 h another 0.5 ml trifluoroacetic acid was added, and heating was continued for 2 h more. By this time p.m.r. showed the almost complete disappearance of the isopropylidene group, so the solution was evaporated to dryness, using benzene as chaser. Acetylation was carried out with 1 ml pyridine and 1 ml acetic anhydride for 4 h at r.t. The solution was then evaporated to dryness and passed through a small silica gel column, eluting with methylene chloride. The eluate was evaporated to near dryness, and excess ethyl ether was added to precipitate out the product. The solid was collected, and cooling the filtrate afforded a second crop; total yield 175 mg, 60%; m.p. 157-159°; p.m.r. ($CDCl_3$) δ 2.03 (s, 6H), 2.61 (b.m, 4H), 3.73 (s, 3H), 4.47 (b.m, 2H), 5.02 p.p.m. (s, 2H); i.r. (KBr) 1755-1745 (acetates), 1720-1710 cm^{-1} (urethane and

ketone); mass spectrum (150°) m/e 299 (M^+), 239 ($M^+ - CH_3COO$), 197, 154.

Anal. Calcd. for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73; N, 4.68. Found: C, 52.03; H, 5.51; N, 4.73.

When this same sequence of reactions was carried out with an acid solution that was more than 60% trifluoroacetic acid and heated above 70°, a large amount of 6β-acetoxy-7β-trifluoroacetoxy-N-carbomethoxy tropan-3-one (*141*) was obtained mixed with the desired product; p.m.r. ($CDCl_3$) δ 2.07 (s, 3H), 2.67 (b.m, 4H), 3.80 (s, 3H), 4.57 (b.m, 2H), 5.17 p.p.m. (q, 2H); i.r. ($CHCl_3$) 1800 (trifluoroacetate), 1760 (acetate), 1720 (urethane and ketone), 1460 cm^{-1}; mass spectrum (100°) m/e 353 (M^+), 334 ($M^+ - F$), 322 ($M^+ - CH_3O$).

2-Hydroxy 6β,7β-diacetoxy-N-carbomethoxy tropan-3-one (*142*)

Diacetate *140* (205 mg, 0.685 mmol) was dissolved in 2 ml glacial acetic acid, and a solution of thallium trinitrate trihydrate (400 mg, 0.9 mmol) in 1.3 ml acetic acid was added. Five drops of concentrated nitric acid was then added, and the solution was stirred overnight at r.t. The solid was filtered off, and the filtrate was neutralized with 10% sodium bicarbonate and with solid sodium bicarbonate. The resulting mixture (approx. 35 ml) was allowed to stand at r.t. overnight, then the precipitate was filtered off. The aqueous filtrate was extracted with 3 x 30 ml methylene chloride. Drying ($MgSO_4$) and evaporation

afforded a white foam. This was dissolved in carbon tetrachloride and excess ethyl ether was added. On cooling, 80 mg (38% yield) of a white powder was recovered, m.p. 160-161.5°; p.m.r. ($CDCl_3$) δ 2.06 (s, 3H), 2.15 (s, 3H), 2.70 (m's, 2H), 3.88 (s, 3H), 4.60 (m, 1H), 4.82-5.63 p.p.m. (m's, 5H; 1H at 5.4 moved downfield by CF_3COOH); i.r. (KBr) 1780 and 1760 (acetates), 1720 and 1705 (urethane), 1650 cm^{-1} (α-hydroxy ketone); mass spectrum (155°) m/e 315 (M^+), 314 ($M^+ - H$), 272 ($M^+ - H - CH_2CO$), 235.7 (M*, 314 → 272), 212, 196, 184.

Anal. Calcd. for $C_{13}H_{17}NO_8$: C, 49.52; H, 5.44; N, 4.44. Found: C, 49.38; H, 5.21; N, 4.49.

2,4-Difurfurylidene-6β,7β-dihydroxy-O-isopropylidene tropan-3-one (*144*)

Teloidinone acetonide *129* (422 mg, 2 mmol) was dissolved in 4 ml of 95% ethanol and cooled in ice. A solution of 88 mg (2.2 mmol) sodium hydroxide in 1 ml water was added, followed by a solution of 200 mg (2.1 mmol) freshly distilled furfuraldehyde in 1 ml ethanol. A yellow precipitate was soon formed. The mixture was stirred 30 min, 5 ml water was added, and the precipitate was harvested. The bright yellow product was recrystallized from chloroform - absolute ethanol as yellow crystals in 50% yield, m.p. 218-221° with charring; p.m.r. ($CDCl_3$) δ 1.34 (s, 3H), 1.66 (s, 3H), 2.50 (s, 3H), 4.60 (s, 2H), 4.86 (s, 2H), 6.58 (q, 2H), 6.80 (d, 2H), 7.66 p.p.m. (b.m, 4H); i.r. (KBr) 3160, 3120, 1675

(ketone), 1615, 1590, 1550, 1480 cm^{-1}; mass spectrum (200°) m/e 367 (M^+), 352 ($M^+ - CH_3$), 267, 238.

2,4-Difurfurylidene-6β,7β-dihydroxy-O-isopropylidene-N-carbomethoxy tropan-3-one (*145*)

The same conditions as on the previous page (for *144*) were employed, affording a 45% yield of product as yellow crystals recrystallized from chloroform - absolute ethanol, m.p. 198-202° with charring; p.m.r. ($CDCl_3$) δ 1.33 (s, 3H), 1.53 (s, 3H), 3.70 (s, 3H), 4.66 (s, 2H), 5.96 (b.m, 2H), 6.60 (q, 2H), 6.86 (d, 2H), 7.53 (b.s, 2H), 7.77 p.p.m. (b.m, 2H); i.r. (KBr) 3150, 1715 (urethane), 1680 (ketone), 1620, 1585, 1550 cm^{-1}; mass spectrum (180°) m/e 411 (M^+), 396 ($M^+ - CH_3$), 353, 311, 252.

Anal. Calcd. for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.40. Found: C, 63.97; H, 5.02; N, 3.26.

When this reaction was repeated with a twofold excess of furfuraldehyde, an 81% yield of recrystallized product was obtained.

6β,7β-Dihydroxy-O-isopropylidene-tropan-3-one morpholine enamine (*146*)

Teloidinone acetonide *129* (100 mg, 0.4 mmol) was dissolved in 10 ml dry benzene in a 50 ml 3-neck flask equipped with a drying tube and two septums. This was cooled in ice, and

excess morpholine (0.16 ml, 2 mmol) was added. Then 0.8 ml of a 0.30M solution of titanium tetrachloride[162] in benzene was added, and the ice was allowed to melt. The solution was stirred at r.t. overnight. The originally yellow solution became colorless, and a white precipitate formed. The solid (morpholine hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The resulting semi-solid product was obtained in nearly quantitative yield. An analytical sample was prepared by recrystallization from petroleum ether (60-80°), m.p. 100-101°, but this also caused substantial decomposition of the product, probably due to water in the solvent. P.m.r. ($CDCl_3$) δ 1.16 (s, 3H), 1.32 (s, 0.4H), 1.38 (s, 3H), 1.58 (s, 0.6H), 2.10-2.48 (b,m, 1H), 2.26 (s, 3H, N-$\underline{CH}_3$), 2.64 (m, 4H, $\underline{CH}_2$-N-$\underline{CH}_2$), 3.13 (q, 2H, $\underline{CH}$-N(CH_3)-$\underline{CH}$), 3.52 (m, 4H, $\underline{CH}_2$-O-$\underline{CH}_2$), 4.20 p.p.m. (m, 3H, C=C-$\underline{H}$ and O-$\underline{CH}$-$\underline{CH}$-O); i.r. (KBr) 3070 (C=C-H), 1620 cm^{-1} (C=C); mass spectrum (130°) m/e 280 (M^+), 265 ($M^+ - CH_3$), 221, 179.

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.11; H, 8.48; N, 10.07.

6β,7β-Dihydroxy-O-isopropylidene-N-carbomethoxy tropan-3-one morpholine enamine (*147*)

and

6β,7β-Dihydroxy-O-isopropylidene-N-carbethoxy tropan-3-one morpholine enamine (*148*)

These were prepared in exactly the same way as *146*, in 75 and 95% yield respectively. Both were oils, and both displayed a weak band about 3070 cm^{-1} (C=C-H) in the i.r. spectra, as well as a band at 1710 (urethane) and at 1630 cm^{-1} (C=C). Interestingly, both p.m.r. spectra also displayed a broad singlet at about 1.70 p.p.m. integrating for 0.4H, and a broad singlet at 1.95 integrating for 0.6H, similar to the N-methyl compound *146*. These absorptions are probably due to the α proton at C-4.

7β,8β-Dihydroxy-O-isopropylidene-N-carbomethoxy 3-oxa-9-azabicyclo(4.2.$1^{1,6}$)nonan-4-one (*150*)

Ketone *131* (2.52 g, 9.9 mmol) was dissolved in 60 ml 1,2-dichloroethane, and to this was added 5.0 g (25 mmol) of 85% m-chloroperbenzoic acid and 20 mg 2,4,6-tri(t-butyl)phenol. This mixture was heated to 55° and followed by gas chromatography (Hewlett-Packard 700 Laboratory Chromatograph, SE-30 Ultraphase (10% w/w) with Chromosorb W support in 6' x 1/8" column). After 22 h the starting material had disappeared, and the solution was cooled to -15° for 30 min to precipitate out most of the m-chlorobenzoic acid. The acid was filtered off, and the filtrate was washed successively with cold 10% sodium bisulphite (15 ml), cold 10% sodium bicarbonate (3 x 15 ml) and saturated salt solution (20 ml). The organic phase was dried ($MgSO_4$) and evaporated off, leaving a partially solidified oil. This was dissolved in anhydrous ether and allowed to crystallize

out at -15°, m.p. 117-8°. More product was obtained by adding petroleum ether (30-60°) and cooling, total yield 1.6 g (60%); p.m.r. ($CDCl_3$) δ 1.26 (s, 3H), 1.40 (s, 3H), 2.93 (m, 2H), 3.73 (s, 3H), 4.33 (b.m, 4H), 4.53 (d, 1H), 4.86 p.p.m. (d, 1H); i.r. (CCl_4) 3000, 2960, 1755 (lactone), 1725 (urethane), 1455, 1392 and 1382 cm^{-1} (gem-dimethyl); mass spectrum (150°) m/e 271 (M^+), 256 ($M^+ - CH_3$), 240 ($M^+ - CH_3O$), 214 ($M^+ - CH_3 - CH_2{=}C{=}O$), 179.0 (M*, 256 → 214), 142.

Anal. Calcd. for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.29; H, 6.41; N, 5.11.

3,4-O-Isopropylidene 2β-(2'-hydroxyethyl)-5β-hydroxymethyl-N-carbomethoxypyrrolidine-3α,4α-diol (*156*)

The lactone *150* (184 mg, 0.68 mmol) was dissolved in 5 ml dry toluene and syringed into a 25 ml 3-neck flask equipped with septum, stopcocks and mercury bubbler. The apparatus was flushed with dry nitrogen and cooled to 0°. A solution of diisobutylaluminum hydride (8 ml of a 0.175M solution) was added dropwise over 5 min with a syringe. The reaction was allowed to proceed at 5° for 3 h. Then 1 ml methanol was added, followed by 0.5 ml ethyl acetate. The mixture was filtered through a bed of Kieselguhr, and the filtrate was evaporated to dryness. The resulting oil was chromatographed on silica gel, eluting with ethyl acetate - ethyl ether (1:1). The diol was recovered as a clear, colorless oil in 30% yield; p.m.r. ($CDCl_3$) δ 1.26 (s, 3H),

1.41 (s, 3H), 1.80 (b.m, 2H, $C\underline{H}_2$-CH_2-OH), 3.60 (b.m, 4H), 3.68 (s, 3H), 3.85-4.2 (b.m, 2H), 4.25-4.74 p.p.m. (m's, 2H, O-C$\underline{H}$-C$\underline{H}$-O); i.r. (film) 3470 (O-H), 1700 cm^{-1} (urethane); mass spectrum (120°) m/e 275 (M^+), 260 ($M^+ - CH_3$), 258 (M^+ - HO), 244 ($M^+ - CH_3O$), 200.

3,4-O-Isopropylidene 2β-(2'-acetoxyethyl)-5β-acetoxymethyl-N-carbomethoxypyrrolidine-3α,4α-diol (*157*)

The diol *156* was acetylated overnight with pyridine and acetic anhydride, and work-up as usual afforded the diacetate as a clear, colorless oil which only partly solidified after several weeks; p.m.r. ($CDCl_3$) δ 1.27 (s, 3H), 1.42 (s, 3H), 1.95 (b.m, 2H, $C\underline{H}_2$-CH_2-OAc), 2.02 (s, 3H, $COC\underline{H}_3$), 2.05 (s, 3H, $COC\underline{H}_3$), 3.68 (s, 3H), 3.9-4.35 (b.m, 6H), 4.63 p.p.m. (q, 2H, O-C$\underline{H}$-C$\underline{H}$-O); i.r. (film) 1750 (acetates), 1710 cm^{-1} (urethane); mass spectrum (120°) m/e 344 ($M^+ - CH_3$); 300 ($M^+ - CH_3COO$), 286 ($M^+ - CH_3COOCH_2$), 272 ($M^+ - CH_3COOCH_2CH_2$).

Methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-hydroxymethyl-N-carbomethoxypyrrolidin-1β-yl)-acetate (*158*)

The lactone *150* (2.38 g, 8.8 mmol) was dissolved in 40 ml dry methanol under an atmosphere of dry nitrogen, and to this was added a solution of 223 mg (9.7 mmol) sodium in 20 ml dry methanol. The resulting yellow solution was allowed to

stand at r.t. for 18 h, then cooled in ice and neutralized with 5N hydrochloric acid. The resulting solution was evaporated to dryness, and the residue triturated with methylene chloride. The inorganic salt was filtered off and washed well, and the filtrate was dried ($MgSO_4$) and evaporated to dryness. The oily orange residue (2.4 g) was quite pure by p.m.r., and was used directly in the next step. P.m.r. ($CDCl_3$) δ 1.30 (s, 3H), 1.47 (s, 3H), 2.71 (d, 2H, $C\underline{H}_2COOMe$), 3.50 (b.m, 2H, exch. with D_2O), 3.70 (s, 6H, 2 x $COOC\underline{H}_3$), 3.70 (b.m, 2H), 3.92-4.85 p.p.m. (m's, 4H); i.r. (film) 3480 (O-H), 1740-1710 (C=O's), 1460, 1390 cm^{-1}; mass spectrum (110°) m/e 303 (M^+), 288 ($M^+ - CH_3$), 286 ($M^+ - OH$), 285 ($M^+ - H_2O$), 272 ($M^+ - CH_3O$), 256, 240, 230.

Methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyldimethyl-siloxymethyl-N-carbomethoxypyrrolidin-1β-yl)-acetate (*159*)

The crude alcohol *158* (2.4 g, 8 mmol) was dissolved in dry N,N-dimethylformamide (15 ml), and to this was added 1.6 g (10.5 mmol) tert-butyldimethylsilyl chloride[173] and 1.43 g (21 mmol) imidazole. This solution was stirred at r.t. overnight, then evaporated to dryness *in vacuo*. The residue was partitioned between methylene chloride (35 ml) and water (25 ml), and the organic layer was further washed with water (3 x 20 ml), dried ($MgSO_4$) and evaporated. The crude silyl ether was purified by passage through a short silica gel column, eluting with ethyl ether. The product was obtained as a slightly yellow oil,

yield 3.0 g (85% based on lactone *150*); p.m.r. (CCl_4, ext. TMS) δ 0.14 (s, 6H, dimethylsilyl), 0.96 (s, 9H, tert-butylsilyl), 1.30 (s, 3H), 1.46 (s, 3H), 2.55 (m, 2H, CH_2COOMe), 3.66 (s, 6H, 2 x $COOCH_3$), 3.68 (b.m, 2H), 3.77-4.66 p.p.m. (m's, 4H); i.r. (film) 2960, 1750 (ester), 1720 (urethane), 1460, 1390 cm^{-1}; mass spectrum (100°) m/e 402 ($M^+ - CH_3$), 386 ($M^+ - CH_3O$), 360 ($M^+ - (CH_3)_3C$), 302, 272, 228.

Anal. Calcd. for $C_{19}H_{35}NO_7Si$: C, 54.65; H, 8.45; N, 3.35. Found: C, 54.52; H, 8.27; N, 3.38.

3,4-O-Isopropylidene 2β-(2'-hydroxyethyl)-5β-tert-butyldimethylsiloxymethyl-N-carbomethoxypyrrolidine-3α,4α-diol (*160*)

Ester *159* (526 mg, 1.26 mmol) was dissolved in 10 ml dry tetrahydrofuran in a 50 ml 3-neck flask equipped with septum, stopcocks and mercury bubbler. The apparatus was flushed with nitrogen, cooled to 0°, and 4.2 ml of a 1M borane-THF solution was added with a syringe. The ice was allowed to melt, and the solution was allowed to stand at r.t. for 2 d. Then 1 ml methanol was added, and the solution was evaporated to dryness. Co-evaporation with methanol (2 x 15 ml) left an oily residue which was chromatographed on silica gel. Elution with ethyl acetate - methylene chloride (1:5) recovered unreacted ester, then elution with a 1:1 mixture of the same solvents afforded 350 mg (70% yield) of alcoholic product as a clear, colorless oil; p.m.r. (CCl_4) δ 0.08 (s, 6H, dimethylsilyl), 0.91 (s, 9H, tert-butyl-

silyl), 1.27 (s, 3H), 1.42 (s, 3H), 1.60 (b.m, 2H, CH-$\underline{CH}_2$-CH_2), 3.24-4.17 (b.m's, 7H, 1H exch. with D_2O at about 3.5), 3.60 (s, 3H), 4.24 (b.d, 1H, $\underline{CH}$-O), 4.51 p.p.m. (b.d, 1H, $\underline{CH}$-O); i.r. (film) 3490 (O-H), 1710 and 1695 (urethane), 1460, 1390 cm^{-1}; mass spectrum (95°) m/e 374 ($M^+ - CH_3$), 332 ($M^+ - Me_3C$), 300 ($M^+ - Me_3C - CH_3OH$), 274 ($M^+ - Me_3C(CH_3)_2Si$), 271.0 (M*, 332 → 300).

3,4-O-Isopropylidene 2β-(2'-mesyloxymethyl)-5β-tert-butyldimethyl-siloxymethyl-N-carbomethoxypyrrolidine-3α,4α-diol (*161*)

To a solution of 100 mg (0.257 mmol) of alcohol *160* in 6 ml dry methylene chloride was added 2.35 ml of a 0.167M solution of triethylamine in dry dichloromethane. This solution was cooled to -50° (dry ice - acetone), and 0.92 ml of a 0.32M solution of methanesulphonyl chloride in methylene chloride was added to it dropwise. The solution was allowed to warm up to r.t., then stirred 1 h. It was then washed with 2 x 10 ml cold water. The organic layer was dried ($MgSO_4$) and evaporated, leaving the clear, colorless mesylate in nearly quantitative yield; p.m.r. (CCl_4) δ 0.09 (s, 6H), 0.92 (s, 9H), 1.29 (s, 3H), 1.42 (s, 3H), 1.97 (b.m, 2H), 2.93 (s, 3H, $OSO_2\underline{CH}_3$), 3.60 (b.m, 2H, $\underline{CH}_2OSi$), 3.62 (s, 3H), 3.7-4.6 p.p.m. (m's, 6H); i.r. (film) 1710 (urethane), 1460, 1365 and 1180 cm^{-1} (mesylate); mass spectrum (130°) m/e 410 ($M^+ - Me_3C$), 322 ($M^+ - Me_3C(CH_3)_2SiOCH_2$).

Anal. Calcd. for $C_{19}H_{37}NSO_8Si$: C, 48.80; H, 7.97; N, 3.00. Found: C, 48.52; H, 7.81; N, 2.83.

Methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyldimethyl-siloxymethyl-N-carbomethoxypyrrolidin-1β-yl)-acrylate (*163*)

A three-necked 50 ml flask equipped with a septum, stopcocks and a mercury bubbler was flushed with dry nitrogen and charged with 11.5 ml of a 0.26M solution of lithium diisopropylamine in dry tetrahydrofuran[167]. This was cooled to -78° in an acetone - dry ice bath, and a solution of 1.015 g (2.45 mmol) of ester *159* in 15 ml tetrahydrofuran was added with a syringe over a three minute period. The flask was allowed to slowly warm up to -25°, and then dry carbon dioxide was bubbled into the solution for 10 min *via* a syringe needle. The resulting yellow solution was neutralized to pH 6 with 10% hydrochloric acid, and the precipitated diisopropylamine hydrochloride was filtered off. The filtrate was evaporated to dryness, and the residue was used in the next reaction without further purification.

The crude malonic acid was heated to 50° with 1.3 ml (12.25 mmol) diethylamine and 2.5 ml of 37% aq. formaldehyde for 30 min, then 250 mg sodium acetate and 2.5 ml glacial acetic acid was added. The mixture was heated to 50° for 20 min, then allowed to cool. Water (20 ml) was added, and the aqueous mixture was extracted with methylene chloride (3 x 25 ml). The organic extracts were dried ($MgSO_4$) and evaporated, and the crude product was chromatographed on silica gel. Elution with ether - hexane (2:1) afforded the product as a clear, colorless

oil in 80% yield. An analytical sample was obtained by preparative t.l.c. on a 20 x 20 cm silica gel plate using ether - hexane (1:1) as the solvent system; p.m.r. (acetone-d_6) δ 0.12 (s, 6H), 0.92 (s, 9H), 1.29 (s, 3H), 1.45 (s, 3H), 3.60 (s, 3H), 3.72 (s, 3H), 3.75 (b.m, 1H), 3.83-4.33 (m's, 2H), 4.40-4.85 (m's, 3H), 5.70 (m, 1H, C=C-H), 6.10 p.p.m. (m, 1H, C=C-H); i.r. (film) 2975, 2950, 2875, 1735-1720 (C=O's), 1650 (C=C), 1460, 1390 cm^{-1}; mass spectrum (130°) m/e 414 ($M^+ - CH_3$), 398 ($M^+ - CH_3O$), 372 ($M^+ - (CH_3)_3C$), 360.

Anal. Calcd. for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found: C, 55.65; H, 8.44; N, 3.47.

EXPERIMENTAL - CHAPTER 4

2-(2'α,3'α-Dihydroxy-O-isopropylidene-4'β-t-butyldimethylsiloxymethyl-N-carbomethoxypyrrolidin-1'β-yl)-maleimide (*165*)

The olefin ester *163* (280 mg, 0.65 mmol) was dissolved in 45 ml dry ethyl acetate and treated with ozone at -78°. Dry nitrogen was bubbled through the solution to remove excess ozone, and dimethyl sulphide (0.1 ml, 1.3 mmol) was added. The mixture was stirred for 30 min at -60°, then allowed to warm up to r.t. and stand 5 h. It was washed with 3 x 25 ml of saturated salt solution, dried (Na_2SO_4) and evaporated to dryness. The residue (270 mg) displayed no olefinic absorption in the i.r. spectrum, but appeared impure by p.m.r.

The crude product was dissolved in 10 ml dry chloroform and 208 mg (0.65 mmol) of carbamoylmethylenetriphenylphosphorane[45] was added. The yellow solution was stirred for 3 h at r.t., then evaporated to dryness. The oily residue was separated on 20 x 20 cm silica gel plates using ether - hexane (3:1) as the solvent system, and 150 mg of a clear, colorless oil was recovered. The product was crystallized from ether - hexane, m.p. 88-89° in 40% overall yield based on olefin ester *163*; p.m.r. ($CDCl_3$) δ 0.07 (s, 6H), 0.87 (s, 9H), 1.33 (s, 3H), 1.52 (s, 3H), 3.66 (s, 3H), 3.72 (b.m, 2H), 4.22 (m, 1H), 4.50-4.90 (m's, 3H), 6.25 (t, 1H,

C=C-H), 8.06 p.p.m. (b.m, N-H); i.r. (KBr) 3250 (maleimide N-H), 2970, 2950, 2870, 1787, 1738, 1695 (urethane), 1655 (maleimide C=C), 1460, 1390 cm^{-1}; u.v. (EtOH) λ_{max} 221.3 nm (ε 18000), shoulder ~275 nm (ε 1000); mass spectrum (170°) m/e 425 (M^+ - CH_3), 383 (M^+ - $(CH_3)_3C$), 325 (M^+ - $(CH_3)_3C(CH_3)_2Si$).

Anal. Calcd. for $C_{20}H_{32}N_2O_7Si$: C, 54.52; H, 7.32; N, 6.36. Found: C, 54.54; H, 7.52; N, 6.50.

2-(2'α,3'α-Dihydroxy-4'β-hydroxymethyl-N-carbomethoxypyrrolidin-1β-yl)-maleimide (*167*)

Blocked showdomycin analogue *166* (130 mg, 0.30 mmol) was dissolved in 3 ml of 50% aqueous trifluoroacetic acid. After standing at r.t. for 5 min, the solution was evaporated to dryness. Separation on a 20 x 20 cm silica gel plate, eluting with ethyl acetate, afforded 70 mg (75%) of a clear colorless oil which would not crystallize; p.m.r. (acetone-d_6, external TMS) δ 3.15 (b.m, 2H), 3.60 (s, 3H), 3.65-4.80 (b.m's, 7H), 5.60 (d, 1H), 9.5 p.p.m. (b.m, 1H); i.r. (film) 1780, 1730-1700, 1650 cm^{-1} (C = O, C = C), 3350 cm^{-1} (OH); mass spectrum (150°) m/e 268 (M^+ - H_2O), 255 (M^+ - CH_3O), 237 (M^+ - CH_3O - H_2O), 220 (M*, 255 → 237), 205, 117, 59.

Ethyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyl-dimethyl-siloxymethyl-N-carbomethoxypyrrolidin-1β-yl)-acetate (*169*)

Lactone *150* (1.037 g, 3.84 mmol) was dissolved in 35 ml absolute ethanol and to this was added a solution of 95 mg (4.2 mmol) of sodium in 25 ml ethanol. This was allowed to stand at -15° for 16 h, then neutralized with conc. hydrochloric acid. The resulting salt was filtered off, and the filtrate was evaporated to dryness. The yellow, oily residue was dissolved in 5 ml dimethylformamide, and 700 mg tert-butyldimethylsilyl chloride and 620 mg imidazole were added. This solution was allowed to stand at r.t. overnight, then evaporated *in vacuo*. The residue was partitioned between 35 ml methylene chloride and 25 ml water. The organic layer was further washed with 2 x 20 ml water, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on silica gel, eluting with ethyl ether. The product was recovered as a clear, yellowish oil in 85% yield (1.4 g); p.m.r. ($CDCl_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.25 (t, 3H), 1.30 (s, 3H), 1.44 (s, 3H), 2.68 (b.m, 2H, $C\underline{H}_2COOEt$), 3.66 (s, 3H), 3.7 (b.m, 2H, $C\underline{H}_2OSi$), 4.10 (q, 2H), 3.9-4.3 (b.m, 2H), 4.4-4.7 p.p.m. (m's, 2H, O-C<u>H</u>-C<u>H</u>-O); i.r. (film) 1730 (ester), 1700 (urethane), 1440, 1370 cm^{-1}; mass spectrum (130°) m/e 416 ($M^+ - CH_3$), 400 ($M^+ - CH_3O$), 386 ($M^+ - CH_3CH_2O$), 374 ($M^+ - (CH_3)_3C$), 316, 286, 228.

Anal. Calcd. for $C_{20}H_{37}NO_7Si$: C, 55.66; H, 8.64; N, 3.24. Found: C, 55.39; H, 8.91; N, 3.42.

Methyl-2-(2α,3α-dihydroxy-O-isopropylidene-4β-t-butyldimethyl-siloxymethyl-N-carbomethoxypyrrolidin-1β-yl)-malonate (*170*)

A three-necked 50 ml flask equipped with a septum, stopcocks and a mercury bubbler was flushed with dry nitrogen and charged with 12.5 ml of a 0.44M solution of lithium diisopropylamine in tetrahydrofuran. This was cooled to -78°, and a solution of 1.88 g (4.1 mmol) of methyl ester *159* in 10 ml tetrahydrofuran was added with a syringe over a two minute period. The flask was allowed to warm up to -25°, and then dry carbon dioxide was bubbled into the solution for 10 min *via* a syringe needle. The solution was neutralized with conc. hydrochloric acid, and the resulting salt was filtered off. The filtrate was evaporated to dryness, and the residue was triturated with 30 ml ethyl ether. The last traces of salt were filtered off, leaving an ether solution of malonic acid *162*.

To 15 ml ether was added 3 ml of 40% potassium hydroxide, and this was cooled to 5°. To this, with cooling and stirring, was added 1.0 g powdered nitrosomethylurea[195] in small portions over 2 minutes. The ether layer was decanted and added dropwise to the cooled solution of crude malonic acid *162* in ether. After 1 h at r.t., the solution was evaporated to dryness. Chromatography on a silica gel column, eluting with ether - Hexane (1:1), afforded the product in 60% yield based on methyl ester *159*. P.m.r. spectrum ($CDCl_3$) δ 0.11 (s, 6H), 0.93 (s, 9H), 1.30 (s, 3H), 1.43 (s, 3H), 3.60-3.70 (3 x s, 9H), 3.7-4.3 (m's,

4H), 4.3-4.7 p.p.m. (m's, 3H); i.r. (film) 2920, 2890, 2820, 1730 (malonic ester), 1700 (urethane), 1440, 1375 cm^{-1}; mass spectrum (160°) m/e 460 ($M^+ - CH_3$), 444 ($M^+ - CH_3O$), 418 ($M^+ - Me_3C$), 386 ($M^+ - Me_3C - MeOH$), 360 ($M^+ - Me_3C(Me_2)Si$), 356.5 (M^*, 418 → 386), 228, 189.

Anal. Calcd. for $C_{21}H_{37}NO_9Si$: C, 53.03; H, 7.84; N, 2.95. Found: C, 52.74; H, 8.05; N, 2.98.

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